Liraglutide Mortality Effect on Atrial Fibrillation Patients

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December 4, 2021

Abstract

Introduction: Liraglutide, a glucagon-like peptide 1 receptor agonist (GLP-1) utilized for management of type 2 diabetes mellitus, has been associated with reduced risk of cardiovascular events. However, it is also associated with increased heart rate and reduced heart rate variability. In this study, we investigate the effect of liraglutide in patients with atrial fibrillation (AF). Methods: TriNetX global research network provided aggregate data for this retrospective cohort study of AF patients on liraglutide that were matched to AF patients not on liraglutide from January 1, 2016, through November 13, 2021. Primary outcomes were all-cause mortality, ischemic stroke, hemorrhagic stroke, acute heart failure episode, and acute coronary syndrome episode. Results: 16,214 AF patients on liraglutide were propensity score matched to AF patients not on liraglutide. They were matched for demographics, cardiovascular procedures, cardiovascular medications, hypertension, diabetes, heart failure, ischemic heart disease, and diabetic medications. AF patients on liraglutide were found to have a significantly lower risk of all-cause mortality (HR 0.67, 95% CI 0.631 – 0.711, $p < 0.001$). There was a tendency toward lower risk of stroke, acute heart failure, and acute coronary syndrome but was not statistically significant. Conclusion: Liraglutide is associated with lower risk of all-cause mortality in AF patients. These findings are limited due to the retrospective nature of the study. Further examination is needed of liraglutide effect on mortality in AF patients.

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Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Funding Statement: All authors have no financial disclosures.

Conflict of Interest Statement: All authors have no conflict of interest to report.

Ethics Approval Statement: The study has Western Institutional Review Board (IRB) approval due to the nature of the TriNetX database presenting only aggregate, de-identified data without any exposure of PHI.

Patient Consent Statement: This study was a retrospective study without use of any identifying information and patient consent was waived.

Permission: All material is original research and content. We give permission to reproduce material.

Clinical Trial Registration: None

ABSTRACT

Introduction:

Liraglutide, a glucagon-like peptide 1 receptor agonist (GLP-1) utilized for management of type 2 diabetes mellitus, has been associated with reduced risk of cardiovascular events. However, it is also associated with increased heart rate and reduced heart rate variability. In this study, we investigate the effect of liraglutide in patients with atrial fibrillation (AF).

Methods:

TriNetX global research network provided aggregate data for this retrospective cohort study of AF patients on liraglutide that were matched to AF patients not on liraglutide from January 1, 2016, through November 13, 2021. Primary outcomes were all-cause mortality, ischemic stroke, hemorrhagic stroke, acute heart failure episode, and acute coronary syndrome episode.

Results:

16,214 AF patients on liraglutide were propensity score matched to AF patients not on liraglutide. They were matched for demographics, cardiovascular procedures, cardiovascular medications, hypertension, diabetes, heart failure, ischemic heart disease, and diabetic medications. AF patients on liraglutide were found to have a significantly lower risk of all-cause mortality (HR 0.67, 95% CI 0.631 – 0.711, $p < 0.001$). There was a tendency toward lower risk of stroke, acute heart failure, and acute coronary syndrome but was not statistically significant.

Conclusion:

Liraglutide is associated with lower risk of all-cause mortality in AF patients. These findings are limited due to the retrospective nature of the study. Further examination is needed of liraglutide effect on mortality in AF patients.

1. INTRODUCTION

Liraglutide, a glucagon-like peptide 1 receptor (GLP-1) agonist that has been widely used for treatment of diabetes mellitus type 2, has also been associated with reduced risk for cardiovascular events in addition to lowering systolic blood pressure in patients with diabetes [1]. However, increased heart rate and reduced heart rate variability have been associated with liraglutide in patients with coronary artery disease and diabetes [2]. However, there is no knowledge of the effect of liraglutide on atrial fibrillation (AF) patients. In this study, we examined the effect of liraglutide in the AF patient population.

2. METHODS

In this retrospective cohort study, we reviewed aggregate de-identified data via the TriNetX Research Network from https://live.trinetx.com. Inclusion criteria was: (1) patients having been diagnosed with AF using ICD-10 codes (see Supplemental Table 1), (2) AF diagnosis present for at least one month, and (3) patients being 18 years or older. For the liraglutide cohort, we included (4) patients on liraglutide and (5) that these patients were on liraglutide for at least month as of November 13, 2021. A 1:1 propensity-scored matching was then conducted and controlled for age, gender, race, ethnicity, hypertensive heart disease, diabetes, metabolic diseases, overweight and obesity, genitourinary disease, respiratory disease, atrial fibrillation, ischemic heart disease, neoplasms, heart failure, vascular disease, cerebrovascular disease, rheumatic valvular disease, nonrheumatic valvular disease, cardiovascular procedures, cardiovascular medications, and blood glucose lowering medications.

Statistical analysis was conducted via TriNetX. Categorical variables were compared using chi-square tests while continuous variables were compared utilizing independent sample t-tests. Cox proportioned hazards ratio with 95% confidence intervals (CI) for incidence of all-cause mortality, ischemic stroke, hemorrhagic stroke, acute heart failure episode, and acute coronary syndrome episode were generated after propensity score matching. Kaplan-Meier analysis was conducted to estimate all-cause mortality. Statistical significance was set at $p < 0.05$.

3. RESULTS

A total of 16,285 AF patients were on liraglutide and 1,557,935 AF patients were not on liraglutide as of November 13, 2021. After propensity score matching, both cohorts had a size of 16,214 patients and their general characteristics can be seen in **Table 1** .

AF patients on liraglutide were found to have a lower risk of all-cause mortality when compared to AF patients not on liraglutide (HR 0.67, 95% CI 0.631 - 0.711, $p < 0.001$). This was further supported with Kaplan-Meier analysis and log-rank test seen in **Figure 1.** It was found that survival probability was higher in patients with AF and liraglutide (66% vs. 63.5%, $p < 0.001$). There also appeared to be a lower risk for ischemic stroke, hemorrhagic stroke, acute heart failure episode, and acute coronary episode, although it did not reach statistical significance (**Table 2**).

4. DISCUSSION

Our findings suggest that use of liraglutide in AF patients was associated with lower risk of all-cause mortality after controlling for comorbidities, cardiovascular medications, diabetic medications, and cardiovascular procedures. With liraglutide, there was a trend towards lower risk of ischemic stroke, hemorrhagic stroke, acute heart failure episode, and acute coronary syndrome episode in these patients, but did not reach statistical significance.

Liraglutide is one of the GLP-1 receptor agonists that has been utilized for treatment of diabetes mellitus and associated with a reduced risk of major cardiovascular outcomes. In the LEADER trial, diabetic patients with increased cardiovascular risk were randomized to liraglutide or placebo and were found to have significantly lower cardiovascular-related and all-cause mortality with liraglutide [1]. However, in patients with reduced ejection fraction, the data has been controversial. In the FIGHT trial there was no significant difference in the number of deaths or heart failure-related hospitalization in patients with reduced left ventricular function on the medication [3]. The LIVE trial found that in patients with reduced left ventricular ejection fraction, liraglutide use was associated with no major change in LVEF, increased heart rate variability, and serious cardiac events including cardiovascular related death, ventricular tachycardia, acute coronary syndrome, worsening heart failure, and atrial fibrillation [4]. There have been reports of increased heart rate with liraglutide possibly due to a direct effect on the sinoatrial node [5,6].

Furthermore, pooled data analysis of multiple trials demonstrated that in diabetic patients, GLP-1 agonists were not associated with increased incidence of atrial fibrillation when compared to placebo [7]. In addition, a meta-analysis of 34 trials found that GLP-1 receptor agonists did not increase the risk of atrial fibrillation [8]. Currently, there have been no studies examining the effect of liraglutide or GLP-1 agonists in atrial

fibrillation patients and their outcomes.

Our study provides large retrospective data on the effect of liraglutide on AF patients and found that liraglutide use is associated with lower mortality risk (HR 0.67, 95% CI 0.631 – 0.711, $p < 0.001$). The mechanism of GLP-1 agonist benefits on atrial fibrillation is still not fully understood. In canine atrial fibrillation models, liraglutide had electrophysiologic effects such as suppressing atrial fibrillation inducibility and conduction velocity. This may contribute to the decreased mortality associated with these patients due to decreased burden of AF. Further studies are needed to examine the mechanism of liraglutide's possible protective effect on atrial fibrillation patients.

There are several limitations to this study. First, these results are based on aggregate data of ICD and CPT codes. We attempted to address these issues by utilizing time constraints to ensure patients had diagnoses and medications for at least one month. In addition, the TriNetX data platform provided the aggregate data and statistical analysis. This limited our abilities to utilize other analytical methods. Lastly, we were unable to control for social factors. Liraglutide may not be as accessible for patients with lower socioeconomic status which may introduce a potential bias. Despite these limitations, this study provides a new potential benefit of liraglutide in AF patients by reducing mortality, as prospective trials on this cohort are lacking.

In 16,214 atrial fibrillation patients, use of liraglutide was associated with lower risk of all-cause mortality. Further studies should be conducted to provide additional evidence for the benefit of liraglutide in patients with atrial fibrillation.

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Table 1. Baseline Characteristics of the AF Patients With and Without Liraglutide Before and After Propensity-Score Matching

	Initial Populations	**Initial Populations**	**Initial Populations**	**Propensity Score Matched Populations**	**Propensity Score Matched Populations**	**Propensity Score Matched Populations**
	AF and Liraglutide (n=)	**AF and no Liraglutide** (n =)	**P-Value**	**AF and Liraglutide** (n =)	**AF and no Liraglutide** (n =)	**P-Value**
Age (years) **at Dx of AF** (mean + SD)	65.4 + 10.6	71.3 + 12.8	< 0.0001	65.5 + 10.5	65 + 13.4	< 0.0001
Gender	**Gender**	**Gender**	**Gender**	**Gender**	**Gender**	**Gender**
Male	57.5%	56.6%	0.0202	57.5%	58.9%	0.0093
Female	45.5%	43.4%	0.0208	42.5%	41.1%	0.0087
Unknown	18.7%	26.2%	< 0.0001	18.8%	18.5%	0.4757
Race/Ethnicity	**Race/Ethnicity**	**Race/Ethnicity**	**Race/Ethnicity**	**Race/Ethnicity**	**Race/Ethnicity**	**Race/Ethnicity**
White	78.8%	79.8%	< 0.0001	78.8%	79.6%	0.1325
Black	12.6%	9.2%	< 0.0001	12.6%	11.8%	0.0221
Asian	0.7%	1.3%	< 0.0001	0.7%	0.6%	0.3436
Hispanic/Latino	4.7%	2.9%	< 0.0001	4.7%	4.3%	0.0960
Co-Morbidities	**Co-Morbidities**	**Co-Morbidities**	**Co-Morbidities**	**Co-Morbidities**	**Co-Morbidities**	**Co-Morbidities**
HTN	81.6%	44.2%	< 0.0001	81.6%	79.9%	0.0001
Ischemic Heart Disease	48.3%	23.1%	< 0.0001	48.2%	46.9%	0.0190
Heart Failure	36.8%	15.4%	< 0.0001	36.8%	35.3%	0.0051
Metabolic Diseases	78.5%	40.2%	< 0.0001	78.5%	77.2%	0.0064
Nonrheumatic Mitral Valvular Disease	16.2%	9.1%	< 0.0001	16.2%	15.3%	0.0261

	Initial Populations	**Initial Populations**	**Initial Populations**	**Propensity Score Matched Populations**	**Propensity Score Matched Populations**	**Propensity Score Matched Populations**
Nonrheumatic Aortic Valve Disease	12.2%	7.7%	< 0.0001	12.2%	11.3%	0.0113
Chronic Rheumatic Heart Disease	10.8%	5.9%	< 0.0001	10.8%	9.5%	0.0002
Type 2 Diabetes Mellitus	81.2%	18.3%	< 0.0001	81.1%	81.3%	0.6906
Cerebrovascular Disease	20.8%	12.1%	< 0.0001	20.8%	19.8%	0.0263
Vascular Disease	27.3%	13.8%	< 0.0001	27.3%	26.1%	0.0139
Renal and Genitourinary Disease	64.1%	33.0%	< 0.0001	64.0%	62.7%	0.0145
Respiratory Disease	60.6%	32.5%	< 0.0001	60.5%	58.9%	0.0030
Neoplasms	37.5%	22.3%	< 0.0001	37.5%	37.0%	0.3643
Others	**Others**	**Others**	**Others**	**Others**	**Others**	**Others**
Cardiovascular Procedures	68.6%	40.4%	< 0.0001	68.5%	66.7%	0.0004
Cardiovascular Medications	92.7%	57.7%	< 0.0001	92.7%	93.0%	0.2359
Blood Glucose Lowering Agents	89.5%	24.0%	< 0.0001	89.5%	91.3%	< 0.0001

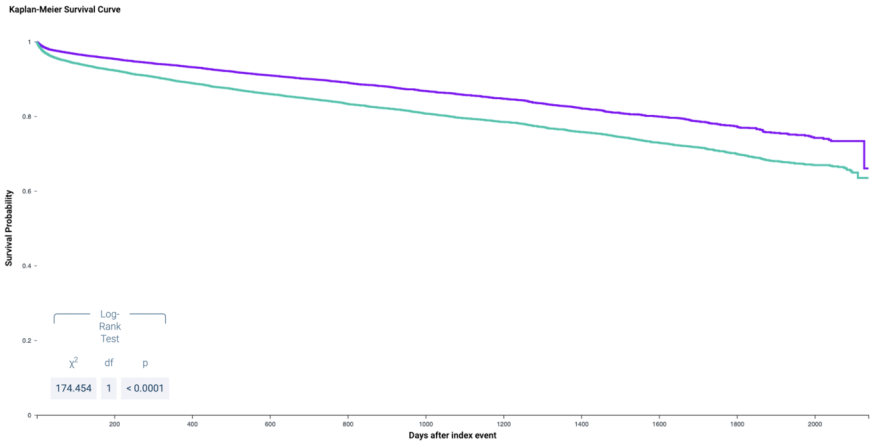
AF = Atrial Fibrillation, Dx = Diagnosis, SD = Standard Deviation, HTN = Hypertension

Table 2. Outcomes of AF Patients With and Without Liraglutide After Propensity-Score Matching

	HR	**95% CI**	**P-Value**
Ischemic Stroke	0.951	0.727 – 1.245	0.9437
Hemorrhagic Stroke	0.944	0.73 – 1.221	0.4496
Acute Heart Failure Episode	0.930	0.865 – 1.001	0.2276
Acute Coronary Syndrome	0.976	0.884 – 1.079	0.3378
All-Cause Mortality	0.670	0.631 – 0.711	< 0.001

HR = Hazards Ratio, CI = Confidence Interval

Figure 1. Kaplan-Meier Survival Curve for Atrial Fibrillation Patients On and Not On Liraglutide



Purple = Atrial Fibrillation patients on Liraglutide

Green = Atrial Fibrillation patients not on Liraglutide