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ASSESSING THE LEADER TRIAL: UNDERSTANDING MYOCARDIAL INFARCTION SUBTYPES IN TYPE 2 DIABETES MELLITUS PATIENTS AND THE BENEFICIAL IMPACT OF LIRAGLUTIDE THERAPY.

Satish Kumar Singh[*]
Senior Resident, Department of Medicine, Shree Krishna Medical College & Hospital, Muzaffarpur, Bihar, India.

ABSTRACT.

Background:
Myocardial infarction (MI), often associated with diabetes mellitus (DM), lacks detailed subtype data. Liraglutide, administered to high-risk Type 2 DM individuals, reduced major CV events, including CV mortality, non-fatal MI, and non-fatal stroke, based on the LEADER trial (8,240 participants). It notably lowered MI risk (192 liraglutide vs. 239 placebo). This post-hoc analysis examines MI differences, outcomes, subtypes, and troponin levels in LEADER.

Methods:
LEADER trial data were used to assess MI occurrences in the liraglutide and placebo groups, considering MI subtype, troponin levels, and baseline patient characteristics.

Results:
Reports of 680 MIs (both first and recurrent) were made; the liraglutide group had fewer than the placebo group (259 vs. 321). With liraglutide, the number of MIs linked to CV death was significantly reduced (7 vs. 18 fatal MIs). The majority of MIs with symptoms were spontaneous MIs (418/541) and non-ST-segment elevation MIs (455/541). Baseline data displayed that a greater proportion of MI individuals treated with liraglutide had previously undergone a coronary artery bypass graft, whereas a smaller proportion had peripheral arterial disease in the lower limbs and more than 50% stenosis in different arteries (coronary, carotid, etc.).

Conclusion:
According to this investigation, liraglutide may affect the clinical results of MI and lower the incidence of myocardial infarction in high-risk type 2 DM patients.

Recommendation:
This study supports considering liraglutide therapy for high-risk Type 2 diabetes mellitus patients, especially those with a history of cardiovascular issues or heightened MI risk. Healthcare providers should assess patient risk factors and discuss liraglutide's potential benefits in reducing MI and related major adverse cardiovascular events. Regular troponin level monitoring and MI subtype evaluation can guide personalized treatment. Ongoing research may offer further insights into liraglutide's long-term impact on MI outcomes in Type 2 DM patients.

Keywords: *Myocardial infarction, Type 2 diabetes mellitus, Liraglutide*
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Corresponding author: *Satish Kumar Singh*[*]
Email: *(s.satish38@gmail.com)*
Senior Resident, Department of Medicine, Shree Krishna Medical College & Hospital, Muzaffarpur, Bihar, India.

INTRODUCTION.

Diabetes mellitus (DM) is widely acknowledged as a significant risk factor for coronary heart disease, leading to approximately a two-fold rise in the likelihood of experiencing a myocardial infarction (MI) [1]. Upon a thorough examination, the healthcare provider duly noted an elevated respiratory rate. Nevertheless, there is a scarcity of available data concerning the distribution of MI subtypes among individuals with diabetes mellitus. Liraglutide, which is a synthetic derivative of human glucagon-like peptide-1 (GLP-1), has obtained regulatory approval for therapeutic use in adults with T2 DM [2,3]. The LEADER cardiovascular (CV) outcomes trial was conducted to assess the long-term impact of liraglutide on CV disease outcomes. The clinical trial findings indicate that the administration of liraglutide in conjunction with the standard of care yielded a notable 13% decrease in the occurrence of significant CV events. These events include CV death, non-fatal MI, and non-fatal stroke. This reduction was observed in comparison to the administration of a placebo [4]. In a retrospective study of the Liraglutide Effect and Action in Diabetes:

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Evaluation of Cardiovascular Outcome Results (LEADER) trial, it was observed that patients who were administered liraglutide exhibited a reduced occurrence of myocardial infarction (MI) in comparison to individuals who received placebo [4]. The primary objective of the current post hoc analysis was to elucidate the various subcategories of MI within the LEADER study and to evaluate any discrepancies in the observed subcategories among the consumption of liraglutide and placebo.

METHODS.

Study Design.

The study was conducted at 'institute name'. The LEADER trial was a double-blind, randomized controlled trial with a follow-up period from January 2019 to January 2023.

Study Type:

This study included a prospective analysis.

Ethical consideration.

Before participation, all patients submitted written informed permission, and all participating centers acquired approval from their institutional review board or ethical committee.

Participants.

The study enrolled 8240 patients diagnosed with T2DM and identified as high-risk candidates for CV events.

Inclusion Criteria.

The inclusion criteria were met by participants who presented with type 2 diabetes mellitus and exhibited a heightened susceptibility to cardiovascular events.

Exclusion Criteria.

Exclusion of patients occurred in cases where they failed to satisfy the predetermined inclusion criteria or exhibited medical conditions that rendered their participation infeasible due to contraindications.

The study employed a comprehensive strategy to identify potential cases of myocardial infarctions (MIs), including those without obvious symptoms (silent MIs). This strategy involved various techniques, including central electrocardiogram (ECG) assessments, investigator-reported adverse events, and systematic searches of adverse events in the Medical Dictionary for Regulatory Activities, all conducted in a blinded manner. All deaths and cerebrovascular events were adjudicated, as well as probable acute coronary syndromes, including MIs, by a clinical research organization and an independent, blinded event adjudication committee. MI episodes were classified by kind and subtype, as well as by fatality or non-fatality. P-values below the threshold of 0.05 were deemed to possess statistical significance.

Statistical Analysis.

The statistical analysis encompassed the utilization of the following methodologies: Poisson regression, which involved adjusting for the individual trial observation time, to facilitate the comparison of observed rates of all myocardial infarctions (MIs). Additionally, the Chi-squared test was employed to compare the cardiovascular history at screening among individuals who experienced one or more MIs during the trial.

RESULTS.

From a cohort of 8240 participants, 6,531 were enrolled in the study and cleared the inclusion criteria. During the clinical trial, a total of 680 myocardial infarctions (MIs), commonly known as heart attacks, were documented among a cohort of 6,531 patients. Among these cases, 192 occurred in the group receiving liraglutide, while 239 were observed in the placebo group. The group administered liraglutide exhibited a reduced incidence of myocardial infarctions (MIs) in comparison to the group receiving a placebo. First MIs accounted for 80% of all MIs, while 18% were recurrent (Table 1).

In the liraglutide group, 83% of participants with an MI had only one, 10% had two, and 3% had more than two MIs. Similarly, in the placebo group, 82% had one MI, 12% had two, and 3% had more than two.
A tendency towards a reduced incidence of fatal myocardial infarctions (MIs) was observed within the cohort receiving liraglutide; nevertheless, this observation failed to achieve statistical significance.

At the outset of the clinical trial, it was noted that a higher proportion of patients who were administered liraglutide had a previous medical history involving coronary artery bypass graft procedures. In contrast, a lower percentage of these patients receiving liraglutide had a history of peripheral artery disease in their lower limbs and more than a fifty percent narrowing of their carotid, coronary, or other arteries compared to the placebo-treated individuals who had experienced heart attacks.
The majority (81%) of all cases of myocardial infarction (MI) presented with symptoms, with 86% classified as non-ST elevation MI (non-STEMI) and 12% as ST-elevation myocardial infarctions (STEMI). There was an observed trend towards a higher occurrence of ST-segment elevation MI (STEMI) events in the liraglutide group; nevertheless,

this observation failed to achieve statistical significance. The occurrence of spontaneous MI (type 1) was observed to be more frequent compared to other types (type 2-5) in both cohorts under investigation.

Additionally, a non-significant inclination was observed towards an increased occurrence of myocardial infarctions (MIs) in individuals with troponin levels equal to or less than five times the upper reference limit within the liraglutide treatment group, as compared to the placebo group. A comparable pattern was noted in myocardial infarctions (MIs) linked to troponin levels that were equal to or less than 10 times the upper reference limit.

Table 1: Each subtype of myocardial infarction and all symptomatic myocardial infarctions.

Variable	Liraglutide, event	Placebo, event
All myocardial infarctions	**259 (100%)**	**321 (100%)**
First	192 (80%)	239 (80%)
Recurrent	57 (18%)	72 (18%)
Symptomatic myocardial infarction	197 (82%)	244 (81%)
Silent myocardial infarction	52 (16%)	67 (17%)
Outcome		
Non-fatal / fatal	242 (94%) / 16 (4%)	293 (92%) / 18 (6%)
Symptomatic myocardial infarctions	**197 (100%)**	**244 (100%)**
ST-segment elevation myocardial infarction / non-ST-segment elevation myocardial infarction	38 (15%) / 149 (83%)	28 (10%) / 206 (88%)
Type		
1 / 2–5	141 (80%) / 46 (18%)	177 (80%) / 57 (18%)
2	33 (13%)	33 (12%)
3	4 (2%)	9 (2%)
4a	3 (1%)	6 (2%)
4b	3 (1%)	6 (2%)
5	0 (0%)	0 (0%)

DISCUSSION.

The liraglutide group had significantly fewer MIs compared to the placebo group. In the cohort of individuals who experienced a myocardial infarction (MI) during the clinical trial, notable distinctions were observed among those with a prior medical history of peripheral arterial disease, coronary artery bypass graft, affecting the lower extremities, or the presence of greater than 50 percent stenosis in carotid, coronary, or other arterial pathways at the onset of the trial. Nevertheless, it is imperative to exercise caution when interpreting these disparities owing to the limited patient population afflicted with each cardiovascular complication at the commencement of the clinical trial.

The majority of MIs observed in both cohorts exhibited characteristics consistent with non-STEMI and were classified as type 1, indicating a spontaneous occurrence. There were no statistically significant variations observed among the cohorts about myocardial infarctions characterized by distinct outcomes, including non-fatal or fatal MIs, STEMI and non-STEMI, type 1 and type 2–5 MIs, or MIs with elevated or diminished troponin levels.

Nevertheless, notable variations in the numerical representation of MIs were observed among the cohorts under investigation. The precise mechanisms underlying the observed cardiovascular advantages of liraglutide in the LEADER trial remain incompletely elucidated. However, conjecture has been put forth proposing its potential anti-atherogenic properties [5]. The observed phenomenon may be attributed to the beneficial impact of liraglutide on body

wt., lipid profiles, systolic BP, and inflammatory markers [5, 6].

Liraglutide also appears to have a direct effect on the heart muscle, as seen in experiments on mice and humans [7]. In the analyses, there were noticeable trends towards fewer fatal MIs and lower troponin levels in liraglutide-treated patients, which could suggest less severe heart attacks.

CONCLUSION.

In conclusion, the current post hoc analysis has demonstrated that liraglutide exhibits a decrease in the overall occurrence of MI events among persons diagnosed with T2DM who are at a heightened risk. However, no statistically significant variances in the distribution of MI subtypes were observed when comparing different treatment groups. Nevertheless, it is worth noting that there are numerical disparities observed in certain subtypes when comparing treatment cohorts, indicating that liraglutide might exert an influence on the clinical manifestations of MI.

LIMITATIONS OF THE STUDY.

It's important to note that the analyses did not account for competing risks, which could influence the distribution of MI types. If a severe myocardial infarction (MI) resulted in cardiovascular mortality, the prioritization of the analysis would be given to the occurrence of cardiovascular mortality rather than the severe MI. Hence, an intervention aimed at mitigating the occurrence of fatal myocardial infarctions (MIs) may potentially be linked to a concomitant transition towards more acute manifestations of MIs.

RECOMMENDATION.

Based on the findings of this study, it is recommended that liraglutide therapy be considered a valuable addition to the treatment regimen for high-risk Type 2 diabetes mellitus (DM) patients, particularly those with a history of cardiovascular problems or at increased risk of myocardial infarction (MI). Healthcare providers should assess the individual patient's risk factors and, where appropriate, discuss the potential benefits of liraglutide therapy in reducing the incidence of MI and related major adverse cardiovascular events (CV mortality, non-fatal MI, and non-fatal stroke). Additionally, ongoing monitoring of troponin levels and periodic evaluation of MI subtypes can aid in tailoring treatment strategies for better patient outcomes. However, clinical decisions should always be made on a case-by-case basis, taking into account the patient's overall health and treatment goals. Further research and prospective studies may provide additional insights into the long-term impact of liraglutide therapy on MI outcomes in Type 2 DM patients.

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LIST OF ABBREVIATIONS:

DM	:	Diabetes Mellitus
MI	:	Myocardial Infarction
CV	:	Cardiovascular Disease
T2 DM	:	Type 2 Diabetes Mellites
STEMI	:	ST Elevation Myocardial Infarctions
ECG	:	Electrocardiogram

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CONFLICT OF INTEREST.

The authors report no conflicts of interest in this work.

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