

STUDY PROTOCOL

# Does Real World Use of Liraglutide Match its Use in the LEADER Cardiovascular Outcome Trial? Study Protocol

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## ABSTRACT

**Background:** Liraglutide is an injectable therapy to treat type 2 diabetes (T2DM), belonging to the glucagon-like peptide-1 receptor agonist class of drugs. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial established that liraglutide demonstrated glucose-lowering benefits and improved cardiovascular outcomes in those individuals with T2DM at high cardiovascular risk.

**Aims:** The aim of this study is to report the prevalence and characteristics of people treated with liraglutide compared with the LEADER trial. In addition, the remaining portion of the T2DM population will be examined to determine the prevalence of those who meet the inclusion criteria for the LEADER trial but who are not treated with this medication.

**Study Design and Methods:** This is a cross-sectional analysis of routinely collected primary care data on all people with T2DM included in the Royal College of General Practitioners

(RCGP) Research and Surveillance Center (RSC) network database. People with T2DM will be identified from the dataset using a well-established ontological process. Read and other clinical codes will be used to identify people prescribed liraglutide and those at high cardiovascular risk. We will use descriptive statistics to report the characteristics of people with T2DM prescribed liraglutide compared with those of the LEADER trial and the proportion of the wider T2DM cohort that matches the LEADER inclusion criteria. In terms of ethical considerations, this study used pseudonymized data, and was classed as an “Audit of current practice”.

**Planned Outputs:** The results of the study will be submitted for publication in a peer-reviewed journal to report the applicability of the results of the LEADER trial to real-world clinical practice.

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**Keywords:** Cardiovascular diseases; Cross-sectional studies; Diabetes mellitus, type 2; Liraglutide; Medical record systems, computerized

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## INTRODUCTION

Liraglutide is an established injectable therapy, belonging to the glucagon-like peptide-1 (GLP-1) receptor agonist class of drugs, for the treatment of hyperglycemia in people with type 2

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diabetes (T2DM). Like other medications within its class, liraglutide improves glycemic control by stimulating the GLP-1 receptor to produce more insulin, while simultaneously suppressing the secretion of glucagon and prolonging gastric emptying [1, 2]. Clinical trials have demonstrated that liraglutide has various benefits, including reduced glycated hemoglobin (HbA1c), decreased risk of hypoglycemia compared with sulfonylurea, and weight loss [3, 4]. Liraglutide has also been shown to have renoprotective effects and to reduce systolic blood pressure [5–7]. More recently, the effects of liraglutide have been explored in a cardiovascular outcome trial (CVOT).

CVOTs are safety trials for the new classes of drugs used in the management of T2DM. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study was a double-blind randomized controlled trial assessing the cardiovascular effects of liraglutide compared to a placebo, when added to standard care in patients with T2DM [8]. It was also designed to evaluate any inferiority or superiority in terms of cardiovascular benefit.

The study comprised 9340 individuals with T2DM and high cardiovascular disease risk. After a median follow-up of 3.8 years, time-to-event analysis confirmed the liraglutide was associated with a lower rate of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared with placebo. The results of the LEADER trial confirmed not only the non-inferiority of liraglutide with respect to cardiovascular safety but provided evidence of its superiority in terms of cardiovascular outcomes.

Whether these findings translate into real-world clinical practice is unclear. Here we set out the method we will use to determine (1) the current pattern of prescribing liraglutide within a nationally representative general practice network and (2) the prevalence of people with T2DM possessing the same cardiovascular risk profile as those included in the LEADER trial. This will inform the extent to which the findings of the LEADER trial can be generalized to routine clinical practice.

## AIMS AND METHODS

We will perform a cross-sectional analysis of all people with T2DM included in the Royal College of General Practitioners (RCGP) Research and Surveillance Center (RSC) database to identify people prescribed liraglutide and to describe their cardiovascular risk profile. In addition, the proportion of those with a cardiovascular risk profile comparable to that of those included in the LEADER trial will be reported.

### Objectives

The aim of the study is to compare the clinical characteristics of patients prescribed liraglutide with those people included in the LEADER trial. We also aim to identify the proportion of patients in the RCGP RSC database that meet the inclusion criteria for liraglutide as used in the LEADER trial but who are not prescribed this medication.

The primary objectives are:

1. To identify the number of people prescribed liraglutide in UK primary care who meet the inclusion criteria for the LEADER trial.
2. To describe the characteristics of patients taking liraglutide:
  - a. The number of people that meet each of the LEADER inclusion criteria.
  - b. The duration of their diabetes.
  - c. The number of people identified on concurrent oral antihyperglycemic medications or on insulin.
3. To describe the demographic (age, gender, ethnicity, socioeconomic status [SES, using the Index of Multiple Deprivation [9]]) and clinical characteristics (HbA1c, blood pressure, renal function, body mass index, etc.) of people in each of the groups described above.

The secondary objectives are:

4. To identify the number of people in the entire RCGP RSC cohort who meet the inclusion criteria for the LEADER trial.
5. To describe the characteristics of the people with T2DM eligible for the LEADER trial:

- a. The number of people who meet each of the LEADER inclusion criteria.
  - b. The duration of their diabetes.
  - c. The number of those identified on concurrent oral antihyperglycemic medications or on insulin.
6. To describe the demographic (age, gender, ethnicity, SES) and clinical characteristics (HbA1c, blood pressure, renal function, body mass index, etc.) of people in each of the groups described above.

### Data Source

The RCGP RSC is a primary care sentinel network that includes the records from over 200 primary care practices distributed across England covering a population of over 2,000,000 patients. This is a nationally representative sample [10], primarily used for the monitoring of respiratory disease and infections such as influenza for vaccine effectiveness [11–13].

UK general practice is suited to this type of study because it is a registration-based system; each patient is registered with a single practice and if they move their data move with them [14]. Each patient also has a unique patient identifier, the National Health Service (NHS) number, which not only facilitates specific patient–data linkage but also the potential for data linkage with other datasets, such as pathology results. Repeat prescription data have been complete since the 1990s following the transition from paper-based to computerized medical records (CMR) in UK primary care, while the coding of chronic disease and laboratory links were standardized in 2004 [15]. We have recently demonstrated our ability to monitor adherence to different classes of therapies using this database [16].

UK primary care CMR data are recorded using the Read classification [17]. The coded data includes patient demographics (age, sex, ethnicity, and SES), diagnosis and processes of care (referrals, annual reviews, care pathways, etc.), prescriptions, and laboratory data. Inclusion of data recording targets in the UK primary care pay-for-performance targets have led to a high level of data completeness in these records,

particularly in the population of people with T2DM [10].

We will use all data collected from primary care practices after 1 January 2016, which will comprise all patients with a T2DM diagnosis who are over the age of 18 years. Within this cohort, we will identify and report the proportion of those with a prescription for liraglutide, and all of those with similar cardiovascular risk/conditions to those of the LEADER trial. The demographic and clinical characteristics of these groups will be reported. Missing data for each variable of interest will also be stated.

In the interests of information governance, the RCGP RSC data is pseudonymized by NHS number. This study was classed as an “Audit of current practice,” and therefore specific ethical approval was not required.

### Data Analysis

People with T2DM will be identified using a two-step process that we have reported in detail elsewhere [18]. This is an ontological-based approach that integrates numerous data elements to enhance case definition [19]. Initially, all people with diabetes are identified using a combination of diagnostic codes, HbA1c and blood glucose test results (two or more that confirm diabetes), and medication use (except metformin). Codes specific to gestational diabetes or other types of secondary diabetes are excluded. People are then categorized by diabetes type (T1DM, T2DM, undetermined diabetes type) using a seven-step algorithm that takes into account previous and current drug therapies used, diagnosis codes specific to diabetes type, and other important clinical characteristics (age and body mass index at diagnosis, and duration of oral anti-hyperglycemic medications).

We will use the high cardiovascular risk inclusion criteria for the LEADER trial to determine prevalence within the T2DM cohort (Table 1). People will be identified with each cardiovascular risk factor using the most similar diagnostic codes, or other codes which determine diagnosis of a risk factor. We will provide a

**Table 1** Inclusion criteria for the LEADER trial taken from the supplementary material provided in the LEADER publication by Marso et al. [8]

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**LEADER trial inclusion criteria**

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T2DM with HbA1c  $\geq$  7%

Cardiovascular disease:  $\geq$  50 years of age and  $\geq$  1 of the following:

Previous myocardial infarction

Previous stroke or transient ischemic attack

Previous coronary, carotid or peripheral arterial revascularization

> 50% stenosis of coronary, carotid, or lower extremity arteries

History of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging or unstable angina with ECG changes

Asymptomatic cardiac ischemia documented by positive nuclear imaging test, exercise test or dobutamine stress echo

Chronic heart failure New York Heart Association class II–III

Chronic renal failure:

eGFR < 60 mL/min/1.73 m<sup>2</sup> (Modification of Diet in Renal Disease formula)

eGFR < 60 mL/min (Cockcroft–Gault formula)

No previous cardiovascular disease group:  $\geq$  60 years and  $\geq$  1 of the following:

Microalbuminuria (ACR) or proteinuria

Hypertension and left ventricular hypertrophy by ECG or imaging

Left ventricular systolic or diastolic dysfunction by imaging

Ankle-brachial index < 0.9

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T2DM Type 2 diabetes mellitus, HbA1c glycated hemoglobin, ECG electrocardiogram, eGFR estimated glomerular filtration rate, ACR albumin:creatinine ratio

complete list of codes and a full description of the process in the final manuscript.

### Statistical Methods

We will use descriptive statistics (percentages, means, standard deviations, etc.) to describe the characteristics of the cohorts. Crude rates of each variable of interest will be reported within each cohort, with 95% confidence intervals.

## STRENGTHS AND LIMITATIONS

A number of strengths of the dataset have been described in the section “Data Source”. The large denominator (> 2 million patients) of this high-quality real-world evidence dataset is a specific strength. We have also previously demonstrated our ability to compare real-world and trial use of another class of medication in diabetes [20], and also to link complex data, in this example pancreatitis, to cases of diabetes [21]. However, given that the minority of people with T2DM are prescribed liraglutide, there may not be enough statistical power to confirm “true differences” between groups.

Another potential limitation is missing data in a patient’s primary care record, whereby a number of patients may have particular conditions that have not been recorded. Nonetheless, the pay for performance scheme (P4P), i.e., the Quality and Outcomes Framework (QOF), implemented in 2004 to incentivize primary care practices to achieve indicator thresholds for the management of chronic diseases [22], has improved data quality in primary care. Additional strengths and limitations found while undertaking the study will be reported in the final version of the manuscript.

## CONCLUSION

This real-world evidence cross-sectional analysis will investigate the prevalence of people with T2DM in a nationally representative primary care population currently prescribed liraglutide and their cardiovascular risk profile; and those

in the wider T2DM population that meet the inclusion criteria for the LEADER trial.

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**Compliance with Ethics Guidelines.** This study is considered to be an “Audit of current practice” when tested against the Health Research Authority (HRA)/Medical Research Council (MRC) “Is my study research” tool and therefore did not require specific ethical approval [23]. In addition, the processes and systems are streamlined to operationalize these studies, as we consistently strive to follow best practices in surveillance and quality improvement [24, 25]. Approval for use of the data was acquired from the RCGP RSC Study Approval Committee.

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