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Original article

All-cause mortality in patients with diabetes under glucagon-like peptide-1 agonists: A population-based, open cohort study

K.A. Toulis [a,b,1], W. Hanif [c,1], P. Saravanan [d], B.H. Willis [a], T. Marshall [a], B. Kumarendran [a], K. Gokhale [a], S. Ghosh [c], K.K. Cheng [a], P. Narendran [c,e], G.N. Thomas [a,*], K. Nirantharakumar [a,c,*]

[a] *Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom*
[b] *424 General Military Hospital, Thessaloniki, Greece*
[c] *Diabetes Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom*
[d] *University of Warwick & George Eliot Hospital, Coventry, United Kingdom*
[e] *Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, United Kingdom*

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ABSTRACT

Aim. – The glucagon-like peptide-1 receptor agonist (GLP1a) liraglutide has been described to benefit patients with type 2 diabetes mellitus (T2DM) at high cardiovascular risk. However, there are still uncertainties relating to these cardiovascular benefits: whether they also apply to an unselected diabetic population that includes low-risk patients, represent a class-effect, and could be observed in a real-world setting.

Methods. – We conducted a population-based, retrospective open cohort study using data derived from The Health Improvement Network database between Jan 2008 to Sept 2015. Patients with T2DM exposed to GLP1a ($n = 8345$) were compared to age, gender, body mass index, duration of T2DM and smoking status-matched patients with T2DM unexposed to GLP1a ($n = 16{,}541$).

Results. – Patients with diabetes receiving GLP1a were significantly less likely to die from any cause compared to matched control patients with diabetes (adjusted incidence rate ratio [aIRR]: 0.64, 95% CI: 0.56–0.74, P-value < 0.0001). Similar findings were observed in low-risk patients (aIRR: 0.64, 95% CI: 0.53–0.76, P -value = 0.0001). No significant difference in the risk of incident CVD was detected in the low-risk patients (aIRR: 0.93, 95% CI: 0.83–1.12). Subgroup analyses suggested that effect is persistent in the elderly or across glycated haemoglobin categories.

Conclusions. – GLP1a treatment in a real-world setting may confer additional mortality benefit in patients with T2DM irrespective of their baseline CVD risk, age or baseline glycated haemoglobin and was sustained over the observation period.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP1a) may have a favourable cardiovascular health profile compared to other glucose-lowering medications. Previously, this was extrapolated on the basis of their beneficial effects on weight, blood pressure, endothelial function and myocardial metabolism [1,2]. Recently, this effect has been formally assessed in the LEADER trial [3], in which rates of all-cause mortality, cardiovascular mortality and incident cardiovascular disease (CVD) were shown to be significantly lower in high CVD risk patients with type 2 diabetes mellitus (T2DM) treated with liraglutide. This finding is of major clinical importance when considering the increased risk of cardiovascular and all-cause mortality in patients with T2DM [4].

Notwithstanding the importance of these findings, patients at low risk for CVD were excluded from these trials. Exploring whether the cardio-protective effect associated with the use of liraglutide is applicable in an unselected diabetic population, inclusive of low-risk patients, is of both clinical and research merit. Moreover, whether the reported CVD benefits are intrinsic to

* Corresponding authors. Institute of Applied Health Research, University of Birmingham, PO B15 2TT, Birmingham, UK. Tel.: +44 (0)121 414 8344.
E-mail addresses: gneilthomas@yahoo.co.uk (G.N. Thomas), k.nirantharan@bham.ac.uk (K. Nirantharakumar).
[1] Equal contribution.

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liraglutide or represent a class-effect and thus, applicable to other approved GLP1a class members (exenatide, lisixenatide or dulaglutide), is still unclear. Finally, a potential confirmation of the beneficial CVD findings in a real-world setting (outside of clinical trial setting) would strongly support available trial data.

We therefore conducted a population-based, retrospective open cohort study to explore the additional benefits on mortality and CVD of treatment with GLP1a on a standard, background antidiabetic medication in the general T2DM population and in those at low-risk of CVD.

Methods

Study design

Population-based, retrospective open cohort study in which patients with T2DM exposed to GLP1a were compared to age, sex, body mass index (BMI), documented duration of T2DM, and smoking status-matched patients with T2DM unexposed to GLP1a.

Source of data

Data were derived from The Health Improvement Network database (THIN). This is a database of anonymised electronic patient records, contributed by general practices (GP) using the Vision computer system. It includes records from over 640 UK GPs (approximately 12 million patients, of which 3.5 million are actively registered).

Study cohort

The study period was set from the 1st Jan 2008 (study start) to 1st Sept 2015 (study end, date of the last data collection). All individuals in the study cohort were required to be registered at their practice at least a year before entry into the study. This decision ensured that:

- these were new (incident prescriptions) as opposed to a patient being continued on a prescription that was initiated in another practice;
- sufficient time for co-morbidities and concomitant medications to be recorded.

Their practice was also required to have been using their computer system (Vision) for at least a year prior to their index date and have an AMR date (an indicator of practice data quality) prior to their index date in order to ensure that the practice was making full use of their system and not under-recording important outcomes.

Exposure

Any subject administered GLP1a at any time point during the observation period was identified and recorded first. Individuals were included in the exposed cohort if they:

- were aged 18+ years at the index date;
- had a diagnosis of T2DM any time before their index date;
- had been initiated treatment with a GLP1a (liraglutide, exenatide, lisixenatide);
- had at least one prescription in four consecutive quarters of a year.

This date (the start of the fourth quarter of consecutive prescriptions) was the index date for each exposed patient. An intention-to-treat approach was followed and exposure was assumed to remain unchanged during the observation period. A description of the observed treatment patterns is provided in the Appendix B.

Selection of the unexposed cohort (controls)

After the completion of the exposed cohort, the identification of the unexposed patients (controls) and matching procedure were applied and by definition, no "control" was exposed to four consecutive quarter of GLP1a. For each exposed patient, up to two unexposed controls were selected from patients registered in a general practice participating into THIN. Controls were required to have a diagnosis of diabetes mellitus before their index date and to be unexposed to GLP1a, and they were:

- individually matched to cases on age at index date (to within one year);
- BMI (to within 2 kg/m^2);
- gender;
- documented duration of diabetes (to within 3 years);
- smoking status.

To avoid immortal time bias, the unexposed cohort was matched at the index date of their respective exposed patients and are assigned the same index as their respective exposed patients.

Follow-up

Exposed and unexposed patients with T2DM were followed up (observation period) from the index date until the first of the following events (exit date): patient died; patient left practice; last data collection from practice; patient diagnosed with any of the following cardiovascular outcomes (myocardial infarction and ischaemic heart disease, stroke and TIA, heart failure). When cardiovascular events were followed by different CVD events or death occurred in the same subject, the observation period was calculated to the first event.

Outcomes

The primary outcome was all-cause mortality (death from any cause during the observation period) in the total study population. A composite CVD measure of myocardial infarction and ischaemic heart disease, stroke and TIA and heart failure served as the secondary outcome in analysis restricted to low-risk population. The low-risk population was defined as the absence of history of any of the CVD outcomes forming the composite described above at baseline. CVD end-points were used as an outcome only in the low-risk subset of the study population (those with no record of myocardial infarction and ischaemic heart disease, stroke and TIA and heart failure before or at index date). This decision was made in order to avoid any bias arising from miscoding between incident and prevalent CVD outcomes. A compound-specific analysis (exploring medication-specific effects in the risk of death from any cause) was also undertaken. The definition of the primary outcome in THIN database has already been validated [5].

Diagnosis of T2DM, myocardial infarction and ischaemic heart disease, stroke and TIA, and heart failure (inclusive of codes suggestive of left ventricular dysfunction) was determined by Read Codes (http://systems.hscic.gov.uk/data/uktc/readcodes). For diabetes, codes indicative of type1 diabetes were not included.

Patient-level covariates

Potential risk modifiers (confounders) were used as model covariates (in addition to matching parameters age, gender, BMI,

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