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High daily insulin exposure in patients with type 2 diabetes is associated with increased risk of cardiovascular events

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ABSTRACT

Aims: Intensive glucose control, often involving insulin treatment, failed to improve cardiovascular outcomes in several clinical trials. Observational studies reported an association between insulin use and cardiovascular disease (CVD) risk. It has therefore been suggested that insulin adversely affects CVD risk. To investigate the feasibility of this hypothesis, we studied the association between insulin dose and CVD risk in type 2 diabetes.

Methods: A case-control study was conducted of new users of oral antidiabetics who were prescribed insulin, using the Dutch Pharmo database. Cases were hospitalized for a cardiovascular event (CVE) and matched 1:2 to patients who were not hospitalized for a CVE, by sex, age, duration of diabetes and type of oral antidiabetic. Patients were divided into tertiles according to mean daily insulin dose. Conditional logistic regression analyses were used to explore the association between insulin exposure and CVE risk.

Results: We included 836 patients (517 (62%) male, mean age 66 years). After adjusting for available potential confounders, including HbA1c and triglycerides, insulin exposure was positively related to CVE risk (odds ratios for high (≥53.0 U/day) and intermediate (24.3–52.9 U/day) vs. low exposure (≤24.2 U/day): 3.00 [95% confidence interval (CI) 1.70 to 5.28] and 2.03 [95% CI 1.17 to 3.52].

Conclusion: Our findings are in line with the suggestion that high-dose insulin therapy adversely affects CVD risk, but need to be interpreted with caution due to the observational nature of the study. The role of particularly high-dose insulin in the progression of CVD warrants further investigation.

1. Introduction

Patients with type 2 diabetes (T2DM) are at increased risk of cardiovascular disease (CVD) [1]. Hyperglycemia is an established independent predictor of both micro- and macro-vascular disease [2]. Consequently, optimized glucose control is the cornerstone in the treatment of T2DM. Treatment in T2DM typically starts with oral glucose-lowering drugs, whereas insulin is added only if HbA1c targets are not reached.

Although a substantial body of evidence has demonstrated a linear relationship between HbA1c levels and CVD risk, several large-scale intervention studies failed to confirm the anticipated benefit of more stringent HbA1c targets [3–6]. Insulin was often used to achieve these lower HbA1c levels While these trials were not designed to investigate the effects of insulin therapy, post-hoc analyses indicated that both hypoglycemia and the degree of HbA1c lowering could not account for the lack of benefit in patients receiving more intensive treatment [7,8]. This has caused some to speculate on the potential harms of insulin therapy. On the other hand, a reduced risk of myocardial infarction in patients receiving intensive glucose control (consisting of either oral anti-diabetics or insulin) has also been demonstrated, in the United Kingdom Prospective Diabetes Study (UKPDS) [9]. A number of observational studies have reported an association between insulin use and increased CVD risk, which persisted after adjusting for potentially confounding factors including diabetes severity [10–16]. However,

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their results should be interpreted with caution as residual bias is likely to account for some of the observed association. Mechanistically, evidence from *in vitro* and experimental studies revealed several pathways through which insulin may exert direct pro-atherogenic effects, whereas other studies have ascribed cardioprotective effects to insulin [17–20]. These findings have added to the controversy on the potential harms and benefits of insulin therapy in T2DM [17].

Previous observational studies, which indicated an association between insulin exposure and increased CVD risk, did not quantify the relationship in terms of level-of-insulin exposure. Dose-dependency in the association between insulin exposure and CVD risk could lend further support to the concept that insulin therapy *per se* might contribute to CVD risk, and could thereby provide an explanation for the lack of insulin-established HbA1c improvement on CVD risk.

In this study, we investigated whether the level of insulin exposure exhibited a positive association with the risk of subsequent CVD events in patients with new-onset T2DM. To this end, we used a large population-based database, in which pharmacy records were linked to hospital admission data.

2. Methods

2.1. Setting

Data were obtained from the PHARMO Record Linkage System (Pharmo Institute, Utrecht, The Netherlands) which consists of multiple observational databases linked on a patient level. Data characterize more than three million people in The Netherlands. For the purpose of this study, drug prescription data from the community pharmacy database, clinical laboratory measurements from the clinical laboratory register, and hospitalization data from the Dutch national medical register (LMR) were used. Drug dispensing records were coded according to the *Anatomical Therapeutic Chemical (ATC) Classification*, and included data on the date and amount of the drug dispensed, as well as the prescribed dose regimens and duration (Appendix A). Hospitalization records included information on primary and secondary diagnoses (coded according to the *International Classification of Diseases Ninth Revision (ICD 9), Clinical Modification*), admission and discharge dates, and operations and procedures (Appendix A).

2.2. Study design and population

We conducted a nested case-control study within a cohort of individuals who started treatment with oral glucose-lowering drugs (ATC code A10B) between January 1998 and December 2008. Within this cohort, we selected all individuals who were prescribed insulin during follow-up. Individuals were excluded if they had previously received antidiabetic drugs (ATC codes A10A or A10B) or if no information was available prior to the date of first prescription of oral glucose-lowering drugs.

Cases were defined as patients who were hospitalized for a cardiovascular event (CVE) during follow-up, which included ischemic heart disease, ischemic stroke and ischemic peripheral arterial disease. For each case, two controls without a CVE were included. Cases and controls were matched by sex, age at the start of insulin treatment (within three years), duration of antidiabetic therapy (within 120 days), and the type of first oral glucose-lowering drugs (metformin, SU-derivates, other). Follow-up was defined as the time interval between the date of first prescription of insulin and the date at which a CVE occurred or the date at which drug prescription data were no longer available.

Data were obtained on clinical laboratory results, previous hospitalizations, oral glucose-lowering drugs and concomitant drug therapy. Insulin exposure was quantified according to the mean daily exposure, defined as the total units of dispensed insulin divided by the number of days of insulin treatment. Subsequently, patients were divided into insulin exposure tertiles (low, intermediate and high insulin exposure groups). In addition, information was obtained on the type of oral glucose-lowering drugs, concomitantly used antihypertensive drugs and lipid-lowering therapy (see Appendix A for a list of ATC-codes). Subjects were considered to have a cardiovascular history if they had been hospitalized for a CVE prior to the index date (see Appendix A for a list of used ICD-9 codes). Results of laboratory assessments at dates approximating the date of first prescription and the last date of follow-up were retrieved. Measurement values were included if they were obtained within three months (HbA1c), six months (ALAT, creatinine, glomerular filtration rate [GFR]) or 12 months (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C] and triglycerides) before the index date or prior to the last date of follow-up.

2.3. Statistical analyses

Patient characteristics were compared between groups (cases and controls; low-, intermediate- and high insulin exposure) using a mixed-effects model for continuous variables. Differences in dichotomous variables between groups were analyzed by conditional logistic regression.

Conditional logistic regression analysis was used to explore the association between the level of insulin exposure and CVE risk. Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated as crude estimates, using subjects in the lowest exposure tertile as references. Multivariable conditional regression analyses was used to adjust for potential confounders for which information was present in 100% of subjects i.e., gender, age (at initiation of insulin therapy), cardiovascular history, use of antihypertensive and lipid-lowering drugs, duration of insulin therapy, type of oral glucose-lowering drug (i.e., metformin, SU-derivatives, other) and continuation of oral glucose-lowering drugs after starting insulin therapy (Model 1). In addition, we adjusted for HbA1c, LDL-c, HDL-c, GFR and triglycerides at baseline (Model 2). Subsequently, backward stepwise elimination (probability for removal $p > 0.1$) of potential confounders included in Model 2 resulted in Model 3.

Variables that were not normally distributed were log-transformed before statistical analysis. Multiple imputation was performed for missing laboratory values. For each missing value, five imputations were performed, based on age, gender, cardiovascular history, use of antihypertensive agents, lipid-lowering drugs and oral glucose-lowering drugs, lipids, HbA1c, GFR, ALAT and creatinine. These were subsequently combined into one effect estimate. Statistical analyses were performed with SPSS software (version 19.0, Chicago, Illinois, USA).

3. Results

3.1. Study population

A total of 26,258 new users of oral-glucose lowering drugs were identified, of whom 3853 were subsequently prescribed insulin. Of these, 287 (7.4%) experienced a CVE during the follow-up period (cases). These cases were matched to 549 individuals who remained free of CVE (controls).

Clinical characteristics of cases and controls are shown in Table 1. Cases more often had a history of CVD (28% vs. 14%), and