International Journal of Cardiology 178 (2015) 292–296

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Risk of cardiovascular disease: The effects of diabetes and anti-diabetic drugs — A nested case–control study

Michael Gejl [a,b,c,g,*,1], Jakob Starup-Linde [c,d,1], Jan Scheel-Thomsen [e], Soeren Gregersen [c], Peter Vestergaard [d,f]

[a] Department of Biomedicine, Aarhus University, Aarhus, Denmark
[b] Centre for Advanced Imaging, The University of Queensland, Brisbane, Australia
[c] Department of Endocrinology and Internal Medicine (MEA), Aarhus University Hospital, Aarhus, Denmark
[d] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[e] Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
[f] Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark
[g] Department of Nuclear Medicine and PET Centre, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

*Article history:*
Received 28 August 2014
Received in revised form 24 October 2014
Accepted 10 November 2014
Available online 12 November 2014

*Keywords:*
Type 2 diabetes mellitus
Cardiovascular disease
Glucagon-like peptide-1
GLP-1
Liraglutide
Biguanides

ABSTRACT

*Aims:* Type 2 diabetes (DM) increases the risk of cardiovascular disease. We investigated the effects of antidiabetic drugs on the composite endpoint (CE) of ischemic heart disease, heart failure or stroke in DM patients.
*Methods:* We conducted a nested case–control study. Cases were DM patients who subsequently suffered from CE; controls were DM patients with no history of CE after DM diagnosis. Using the Danish National Hospital Discharge Register, we included DM patients with information on date of DM diagnosis, date of CE, and comorbidities. From the Central Region of Jutland, Denmark, medication use and biochemical parameters were collected. Logistic regression analyses were conducted and mutually adjusted for comorbidities, pharmaceutical use, and biochemical parameters.
*Results:* 10,073 DM patients were included (65,550 person-years). 1947 suffered from a subsequent CE. CE prior to DM diagnosis (OR = 20.18, 95% CI: 16.88–24.12), neuropathy (OR = 1.39, 95% CI: 1.05–1.85) and peripheral artery disease (OR = 1.31, 95% CI: 1.02–1.69) increased the risk of CE. Biguanides (OR = 0.62 95% CI; 0.54–0.71) and liraglutide (OR = 0.48 95% CI; 0.38–0.62) significantly decreased the risk of CE as did statin treatment (OR = 0.63, 95% CI: 0.54–0.72). DPP-4 inhibitors, insulin and β-cell stimulating agents had neutral effect. When results were adjusted for biochemical risk markers (1103 patients, 7271 person-years, 189 cases), biguanides (OR = 0.54, 95% CI: 0.34–0.87) and liraglutide (OR = 0.32, 95% CI: 0.14–0.70) treatment retained a significant risk reduction. The effect of liraglutide was dose and duration dependent ($p < 0.05$).
*Conclusion:* We have shown an association between the use of biguanides and liraglutide and a reduced risk of CE in DM patients.



## 1. Introduction

The main cause of death in type 2 diabetes mellitus (DM) remains cardiovascular disease [1] and hyperglycemia is associated with increased cardiovascular risk [2]. Intensive blood glucose control reduces microvascular complications, but the protective effect on macrovascular disease and mortality remains disappointing [3]. The beneficial effect of lowering blood glucose to very low levels is controversial as one of the major problems being the increase in the number of hypoglycemic events [4]. As improved prognostic outcome has been reported for some antidiabetic drugs, but not for others despite similar glucose-lowering effects [5], pleiotropic effects beyond the glucose-lowering effect of the drugs may add new dimensions to future treatment recommendations for DM [6].

Native glucagon-like peptide-1 (GLP-1) and GLP-1 analogues are reported to have several significant cardiovascular effects with the potential to reduce the excess mortality and morbidity in patients with DM as well as non-diabetic patients with cardiac disease [6,7]. However, caution is warranted if extrapolating putative beneficial short-term cardiovascular surrogate effects to long-term cardiovascular endpoints and mortality.

The GLP-1 analogues and DPP-4 inhibitors have been available to patients for shorter time than the conventional diabetes medication, and there is only limited and conflicting information on the cardiovascular impact of these agents in real life patients. While clinical outcome studies investigating the cardiovascular effects of GLP-1 based therapies have been initiated, the first two studies on DPP-4 inhibitors, designed to evaluate cardiac safety reported largely neutral outcomes [8,9].

* Corresponding author at: Department of Biomedicine — Pharmacology, Aarhus University, The Bartholin Building, University Park 1240, 8000 Aarhus C, Denmark.
*E-mail address:* mg@farm.au.dk (M. Gejl).
[1] These authors contributed equally to the work and the manuscript.

http://dx.doi.org/10.1016/j.ijcard.2014.11.096
0167-5273/

It remains unknown whether a specific antidiabetic therapy is superior to other drugs in reducing the risk of composite endpoints (CE) in patients with DM. We performed a nested case–control study focusing on the risk of cardiovascular morbidity of the various antidiabetic medications by using data from several registers from Denmark. This study was designed to investigate the association between CE (ischemic heart disease, heart failure and stroke incidence) and previous use of antidiabetic medication with focus on GLP-1 analogues.

## 2. Methods

The present study was conducted as a nested case–control study in a cohort of DM patients. Using the Danish National Hospital Discharge Register we initially included all patients diagnosed with DM in the period 1977–2011. The registry covers all inpatient contacts from 1977 until 1994, hereafter also outpatient visits to hospitals, clinics and emergency rooms. It is considered as a nearly complete registration of somatic hospital events in Denmark in a population of relative demographic stability [10]. Approval has been obtained by the Danish Data Protection Agency. This manuscript presents new and unpublished data as part of a larger registry study focusing at associations between diabetes medication and outcomes [11].

Subjects with DM were extracted using ICD10 (E11) and ICD8 (250) codes. We only included patients diagnosed with DM. We rejected patients with 1) an unspecified DM diagnosis, 2) type 1 diabetes diagnosis, 3) both a type 1 DM and a type 2 DM diagnosis, and 4) no information on date of diagnosis. The validity of a diagnosis of DM and of not having DM in general is high [12]. Cases were patients with DM who subsequently suffered from CE; controls were DM patients with no occurrence of CE at a later date than their DM diagnosis.

Cases was identified using the corresponding DI20, DI21, DI22, DI23, DI24, DI25 DI63, DI64, DI50, 41009, 41099, 411xx, 412xx, 413xx, 414xx, 42709–42711, 42719, 433xx, 434xx, and 436xx codes for CE. A case was defined by an event subsequent to DM diagnosis. Only patients with a diagnosis of CE at a later date than the DM diagnosis and after the start of the prescription registry (see below) were included in the case population. CE includes ischemic heart disease, stroke and heart failure. Due to a unique personal identifier it is possible to link the diagnoses to the same individual.

Table 1 presents the evaluated exposure variables along with their respective ICD-codes or ATC-codes.

Comorbidities were extracted from the registry using their corresponding ICD codes. A proxy variable was created for alcohol (alcohol-related diagnoses) and hypertension (the use of anti-hypertensive drugs). Age was defined as the age of the individual at January 1, 2008. All cases were subsequent to this date, thus medication use was first collected from this date. The duration of DM (DM duration) was defined by the time from the date of DM diagnosis to the end of the prescription register, December 31, 2011. From the Central Region of Jutland, Denmark, medication use (yes/no) was collected from a registry. Users were grouped as ever/never users for each pharmaceutical defined by one or more redeemed prescriptions in the period January 1, 2008 to December 31, 2011. Any drug bought are registered with ATC code, dose sold, and sales date for the period January 1, 2008 to December 31, 2011. Only prescription agents and not over the counter drugs are registered. As all sales are registered to the individual who redeemed the prescription, the capture and validity of data are high. Any medication sold is linked to a patient's unique personal identifier, and it is therefore possible to link prescriptions with diagnosis. We only included information on drugs prescribed before the date of any CE diagnosis. Only DM patients with information on medication use are included in the study. A total of 1947 cases were available and 8126 controls were available, all with information on pharmaceutical use. DM patients with no redeemed prescriptions on antidiabetic drugs (e.g. dietary treated) were also included in the analysis. From the Central Region of Jutland, biochemical risk markers (in the period 2008–2012) linked to the same unique personal identifier was extracted. All biochemical analyses were performed in an ISO certified laboratory. Included biochemical analyses were restricted to the time before the date of any CE.

Dose and prescription duration for liraglutide were calculated. Duration was defined as the time between the first redeemed prescription and the date of event (for cases) or before the end of follow up, December 31, 2011 (for controls). Dose was defined as the total daily dose redeemed before the event of CE or before the end of follow up, December 31, 2011 (for controls). Both liraglutide duration and liraglutide dose were grouped in non-users and by 25th centile, 50th centile and 75th centile.

Statistical analysis was done using STATA 8. We used univariate logistic regression to calculate crude odds ratios (OR) and used multivariate logistic regression to calculate the adjusted OR. The DM patients received different combinations of treatment and individual adjustment by usage of other pharmaceuticals including antidiabetics was performed in the model. In the multivariate analysis the following variables were included: previous CE, age, DM duration, gender, atrial fibrillation, hypertension, alcohol related diagnosis, nephropathy, retinopathy, neuropathy, peripheral artery disease, usage of antiarrhythmic drugs, vitamin K antagonists, heparin, pentasaccharide, argatroban, thrombocyte function inhibitors, acetylsalicylic acid, cyclooxygenase 2 inhibitors, nonselective cyclooxygenase inhibitors, buprenorphine, tramadol, oxycodone, morphine, codeine, fentanyl, pethidine, glucocorticoids, bisphosphonates, benzodiazepines, antipsychotics, antiepileptic drugs, statins, antidepressants, insulins, glitazones, DPP-4 inhibitors, liraglutide, exenatide, biguanide, and β cell stimulants. A sensitivity analysis was conducted with the addition of biochemical variables to the model. This model also included HbA1c (%), LDL cholesterol (mmol/l), HDL cholesterol (mmol/l), total cholesterol (mmol/l), triglycerides (mmol/l) and creatinine (μmol/l).

A secondary matched analysis was conducted. Controls were chosen from the cohort based on risk-set sampling, and were matched 3:1 on age and gender. Conditional logistic regression was used with the same variables as above (excluding age and gender).

In the following 'risk' is used synonymous for odds.

**Table 1**
Evaluated exposure variables used in the adjusted, covariate analysis. ICD codes are shown as both ICD10 and ICD8.

| Diabetes mellitus & CE (ICD) |
|---|
| Type 2 diabetes mellitus: DE110, DE111, DE119, 25006, 25007, 25009 |
| CE: DI20, DI21, DI22, DI23, DI24, DI25, DI63, DI64, DI50, 41009, 41099, 411xx, 412xx, 413xx, 414xx, 42709–42711, 42719, 433xx, 434xx,436xx |
| Comorbidities (ICD) |
| Atrial fibrillation (DI48, 42793, 42794), nephropathy (DE102, DE112, 24902, 25002), neuropathy (DE104, DE114, 24903, 25003), retinopathy (DE103, DE113, 24901, 25001), peripheral artery disease (DE105, DE115, 24904, 24905, 25004, 25005), alcohol (DF10, 303) |
| Antidiabetic drugs, antihypertensive drugs, statins, antiarrhythmic drugs (ATC) |
| Insulin (A10A), biguanides (A10BA), β-cell stimulating (A10BB), glitazones (A10BG), DPP-4 inhibitors (A10BH, A10BH01, A10BD07, A10BH02, A10BD08, A10BH03, A10BD10, A10BH05, A10BD11), liraglutide (A10BX07), exenatide (A10BX04), lixisenatide (A10BX10) |
| Antihypertensive drugs (C09, C07A, C08, C02AB, C02AC, C02CA, C02DB, C03C, C03AA, C03D) |
| Statins (C10AA) |
| Antiarrhythmic drugs (C01BD, C01AA, C01BC, C08DA, C01B) |
| Anticoagulants & thrombocyte inhibitors (ATC) |
| B01A, B01AA, B01AB, B01AX, B01AE, B01AF, B01AC, M01A, M01AH05, M01AH01, M01AH04, M01AB08, M01AB01, M01AB05, M01AA01, M01AE01, M01AE17, M01AC06, M01AC02, M01AE02, MAC01, M01AX01, M01AE14, M01AE11, M01AC02, M01AB15, M01AE52, M01AC05) |
| Others (ATC) |
| Opioids (N02AB02, N02AB03, N02AA01, R05DA04, N02AA05, N02AX02, N02AE01, N07BC01), glucocorticoids (H02AB), bisphosphonates (M05BA), antipsychotics (N05A), antiepileptics (N03A), antidepressants (N06A), benzodiazepines N05BA, (N05CD), Aspirin N02BA |

## 3. Results

### 3.1. Population characteristics

Table 2 presents the baseline patient characteristics. Among the population of DM patients in Denmark, 10,073 DM patients contributing a total of 65,550 person-years, had information on comorbidities and

**Table 2**
Baseline characteristics of cases and controls (10,073 patients with DM contributing 65,550 person-years) used in the covariate adjusted analyses.

| | Cases (n = 1947) | Controls (n = 8126) |
|---|---|---|
| Age (y) (mean ± SD) | 65.6 ± 11.5 | 58.1 ± 13.6 |
| DM duration (y) (mean ± SD) | 9.5 ± 6.8 | 6.6 ± 6.2 |
| Males (n) | 1230 | 4306 |
| Females (n) | 717 | 3820 |
| Hypertension (n) | 1605 | 6513 |
| Statins users (n) | 1308 | 6180 |
| Antiarrhythmic drugs (n) | 240 | 437 |
| Nephropathy (n) | 132 | 372 |
| Neuropathy (n) | 108 | 266 |
| Retinopathy (n) | 47 | 169 |
| Peripheral artery disease (n) | 154 | 309 |
| Previous CE (n) | 735 | 289 |
| Atrial fibrillation (n) | 314 | 469 |
| Alcohol (n) | 59 | 277 |
| Insulin users (n) | 835 | 3385 |
| Biguanide users (n) | 1016 | 6162 |
| β-cell stimulating drug users (n) (n) | 601 | 3032 |
| Glitazone users (n) | 21 | 112 |
| DPP-4 inhibitor users (n) | 121 | 921 |
| GLP-1: liraglutide users (n) | 95 | 1293 |
| GLP-1: exenatide users (n) | 51 | 310 |

DM = diabetes mellitus; CE + composite endpoint; n = number; y = years.