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Influence of macro- and microvascular comorbidity on time to insulin initiation in type 2 diabetes patients: A retrospective database analysis in Germany, France, and UK

Karel Kostev[a,*], *Wolfgang Rathmann*[b]

[a] *IMS HEALTH, Frankfurt, Germany*
[b] *Institute of Biometrics and Epidemiology, German Diabetes Center, Duesseldorf, Germany*

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ABSTRACT

Aim: To investigate if micro- and macrovascular co-morbidity has an influence on the time to insulin initiation in type 2 diabetes patients.
Methods: Longitudinal data from general practices in Germany, France and UK (Disease Analyzer) from 1995 to 2009 were analyzed, including 44,440 patients in Germany, 10,148 patients in France, and 25,499 patients in UK with newly diagnosed diabetes (index date). Cox regression was used to investigate the association of newly diagnosed micro- and macrovascular complications (ICD-10) on the time to insulin initiation adjusting for age, sex, antidiabetic therapy, and co-morbidity (hypertension, lipid disorders).
Results: Insulin treatment was started in 9747 (22%) patients in Germany within 10 years after index date (France: $n = 702$, 7%; UK: 3936, 14%). In all three countries, occurrence of microvascular complications was significantly associated with a higher likelihood to have insulin initiated (hazard ratio (HR), 95%CI: neuropathy: Germany 1.6; 1.5–1.8; France: 2.1; 1.1–3.9; UK: 1.5; 1.3–1.9; nephropathy: Germany 1.4; 1.3–1.6; France: 2.7; 1.4–3.8; UK: 1.2; 1.1–1.3). Among macrovascular complications, only coronary heart disease was related to insulin initiation in all three countries (Germany 1.2; 1.1–1.3; France: 1.5; 1.2–2.0; UK: 1.5; 1.3–1.7).
Conclusions: A more rapid progression to insulin therapy was found in patients with microvascular complications.

1. Introduction

Although insulin therapy has been well established as an effective agent to lower HbA_{1c} levels [1], insulin initiation is often considered as an unfavorable step in the treatment of type 2 diabetes, both by patients and their healthcare providers [2]. Known barriers for insulin therapy are hypoglycemia and weight gain along with anxiety over disease progression [3]. This often results in undesirable postponement of insulin therapy.

Recently, a retrospective analysis of patients with type 2 diabetes showed the gap between first instance of oral antidiabetic drug failure and start of insulin therapy to be almost 5 years in 50% of the patients [4]. This primary care database study failed to detect a substantial earlier time to start of

* *Corresponding author at*: CES LifeLink – Epidemiology IMS HEALTH GmbH & Co. OHG, Darmstädter Landstraße 108, 60598 Frankfurt am Main, Germany. Tel.: +49 069 66 04 4878.
E-mail address: kkostev@de.imshealth.com (K. Kostev).
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insulin with the presence of diabetic co-morbidities [4]. In the presence of retinopathy and neuropathy median time to insulin was only slightly lower [4]. Because of the relatively small numbers of individuals with these co-morbidities, this study does not allow conclusive inference about an association between micro- and macrovascular complications and time to insulin.

Another family practice based study from Canada found that 74% of type 2 diabetes patients already had a diabetes-related complication at the time of insulin initiation [5]. Despite knowledge of glycemic targets, general practitioners in this study added insulin late in the course of disease [5]. It has not been specifically investigated if the presence of diabetes-related complications influences the time to insulin initiation in type 2 diabetes patients.

Thus, the aim of the current study was to study the influence of micro- or macrovascular complications on the onset of insulin therapy in type 2 diabetic patients in Germany, France and in UK.

2. Patients and methods

The Disease Analyzer database (IMS HEALTH) assembles drug prescriptions, diagnoses, and basic medical and demographic data directly obtained from the practice computer system of general practitioners [6]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System) and the quality of reported data were monitored by IMS based on a number of criteria (e.g. completeness of documentation, linkage of diagnoses and prescriptions). The sampling methods for the selection of physicians' practices were appropriate to obtain a representative database of primary care practices [6]. Prescription statistics for several drugs were very similar to available data from pharmaceutical prescription reports [6]. The age structures for given diagnoses in Disease Analyzer also agreed well with those from corresponding disease registries [6].

The analyzed database period was January 1995–December 2010. The first diabetes diagnosis (ICD: E11) was defined as the index date. All subjects with a first time prescription of insulin (ATC: A10C) were selected. Further inclusion criteria were (i) continuous treatment in the same practice ($\geq$1 visit during the twelve months before index date and $\geq$1 visit each year during at least 1 year after index date, (ii) age at index date above 40 years (mainly type 2 diabetic patients).

Main outcome measure was the initiation of insulin therapy depending on micro- and macrovascular complications recorded in the database after index date (first diagnosis of type 2 diabetes mellitus). Macrovascular complications were determined based on primary care diagnoses (ICD-10 codes) for coronary heart disease (I20, I24, I25), myocardial infarction (I21, I22, I23, I25.2), stroke (I63, I64, G45), peripheral vascular disease (E11.5, E14.5, I73.9) and heart failure (I50). Microvascular complications included retinopathy (E11.3, E14.2), neuropathy (E11.4, E14.4), and nephropathy (E11.2, E14.2, N18, N19). Furthermore, the incidence of diabetic foot complications (foot syndrome, gangrene, ulceration) was analyzed, which was defined based on the original text of the diagnoses in order to detect specific diabetes-related events.

Diagnosed hypertension and lipid disorders were assessed as potential confounders. Demographic data included patient age, sex, health insurance (private/statutory health insurance), and diabetologist care. Data on HbA1c, fasting glucose measurements and body mass index, which were only available in a subgroup, were also analyzed.

Descriptive statistics (means, standard deviations, proportions) are given for the above-mentioned variables separately for all three country samples. Differences in characteristics of patients with incident insulin therapy were assessed using chi-square tests or age- and sex-adjusted tests (linear or logistic regression: Germany vs France; Germany vs UK). A multivariate Cox regression model was fitted with the insulin treatment initiation as dependent variable (up to 10 years after index date) and an indicator variable for specific micro- or macrovascular diagnoses. The proportional hazards assumption was assessed for all analyses. Furthermore, therapy with oral antidiabetic agents (metformin, sulfonylurea, alpha-glucosidase-inhibitors, glinides, gliptines and DPP-4 inhibitors), and potential confounders (age, sex, physician speciality: diabetologist care, private health insurance, diabetes duration), and comorbidity (hypertension, lipid disorders) were included as independent variables. Biguanides were used as the reference group for the associations of the various oral antidiabetic agents with time to insulin initiation. Two sided tests were used and a p-value of <0.05 was considered as statistically significant. All analyses were carried out using SAS 9.2. (SAS Institute, Cary, USA).

3. Results

3.1. *Patient characteristics*

The clinical characteristics of type 2 diabetes patients with incident insulin therapy in primary care practices Germany, France and UK are shown in Table 1. Mean age was slightly higher in Germany than in France or UK ($p < 0.05$). The sex distribution was largely similar, slightly more males were included. Average diabetes treatment in the practices before start of insulin treatment ranged from about 8 years (France) to 13 years (UK). The average recorded body mass index was high in all samples (about 31 kg/m^2), as were the last HbA1c values before insulin treatment. Biguanides were the most frequently used oral antidiabetics in all countries followed by sulfonylureas and glitazones. There were differences in the prevalence of recorded macrovascular complications, which were higher in the German patients than in France and UK. Also hypertension and lipid disorders were more frequently diagnosed in the German practices than in France or UK. Microvascular complications (neuropathy, retinopathy) were more frequently diagnosed in German type 2 diabetes patients than in France or UK. Prevalence of diagnosed nephropathy was similar in Germany and UK, whereas in France a lower prevalence was found.

The results of the multivariable Cox regression analyses on the association of macro- and microvascular complications on the time to insulin initiation after adjusting for the