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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

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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

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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

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Table 1 – Baseline characteristics of type 2 diabetes patients with incident insulin therapy: Disease Analyzer Germany, France, UK.

Variables	Germany (1423 physicians)	France (280 physicians)	UK (680 physicians)
N	9747	702	3936
Age (mean, SD)	68.1 (11.5)[a,b]	65.5 (12.2)[a]	64.5 (11.6)[b]
Sex, males (%)	50.6[b]	52.7	54.2[b]
Diabetes treatment (practice) (years)	11.4 (6.8)[a,b]	8.3 (4.7)[a]	13.3 (6.7)[b]
HbA1c (%)[c]	8.6 (2.1)[b]	8.8 (1.7)	9.7 (2.1)[b]
BMI (kg/m^2)[c]	30.8 (6.0)	30.4 (5.6)	30.8 (6.4)
Sulfonylureas (%)	39.4[a]	32.9[a]	38.6
Metformin	40.5[b]	41.6	44.6[b]
Glinides	4.5[a,b]	10.0[a]	1.2[b]
Acarbose	6.2[b]	2.8	0.8[b]
Glitazones	4.9[b]	6.4	12.7[b]
DPP-4 inhibitors	4.2[b]	5.5	1.4[b]
GLP-1 analogs	0.4[b]	0.8	0.7[b]
Myocardial infarction (%)	8.5[a]	3.6[a]	8.2
Coronary heart disease	35.5[a,b]	17.4[a]	20.8[b]
Heart failure	22.8[a,b]	8.6[a]	5.6[b]
TIA/stroke	9.3[a,b]	1.6[a]	5.5[b]
Hypertension	70.2[a,b]	56.6[a]	48.4[b]
Lipid disorders	43.9[a,b]	32.9[a]	17.3[b]
Peripheral arterial disease	13.2[a,b]	3.1[a]	0.4[b]
Retinopathy	4.0[a,b]	0.3[a]	3.2[b]
Nephropathy	12.1[a]	3.4[a]	12.8
Neuropathy	12.4[a,b]	1.4[a]	1.6[b]

Data are means (SD) or prevalence (%), p-value < 0.05, chi-square tests or age- and sex-adjusted tests (linear or logistic regression models). [a]Germany vs France; [b]Germany vs UK; [c]Subgroups with recorded BMI and HbA1c values (last value before insulin therapy: 0–183 days): $n = 2429$ (Germany), $n = 560$ (France), $n = 2738$ (UK); missing data for HbA1c was found in 2908 (29.8%) patients in Germany, in 98 (14.0%) in France and in 158 (4.0%) subjects in the UK practices.

above-mentioned confounders are shown in Table 2. Among macrovascular outcomes, only patients with newly diagnosed coronary heart disease were significantly more likely to have insulin treatment in all three countries. In addition, newly diagnosed heart failure was significantly associated with onset of insulin therapy.

Among incident microvascular complications, both patients with nephropathy and neuropathy were significantly more likely to have insulin initiated in all three samples. Also incident retinopathy was significantly associated with insulin initiation in Germany and UK. The corresponding hazard ratio for retinopathy for France was also well above 1.0, without statistical significance.

Compared to biguanides (reference group), patients with sulfonylureas, alpha-glucosidase-inhibitors, and glinides were significantly more likely to start with insulin in all three countries (Table 3). Thiazolidinediones were related to a higher likelihood of to have insulin initiated in Germany and UK. On the other hand, patients with DPP-4 inhibitors were less likely to have insulin initiated in all three countries. GLP-1 analogs were not significantly related to insulin treatment in Germany and France, but showed a similar association like DPP-4 inhibitors in UK. Similar results were found when additionally adjusting for BMI, fasting glucose and HbA1c, which were only available for a subgroup of patients (Germany, $n = 2429$; France: $n = 560$; UK, $n = 2738$) (data not shown).

Table 2 – Association of newly diagnosed micro- and macrovascular complications (ICD-10) on the time to insulin initiation in type 2 diabetes patients in primary care (Germany, France, UK; Disease Analyzer database).

Variables	Germany	France	UK
Coronary heart disease	1.20 (1.13–1.28)*	1.54 (1.16–2.05)*	1.47 (1.31–1.66)*
Myocardial infarction	1.15 (1.04–1.27)*	1.05 (0.59–1.86)	1.97 (1.67–2.31)*
TIA/stroke	1.21 (1.11–1.32)*	0.56 (0.25–1.25)	1.13 (0.96–1.32)
Peripheral vascular disease	1.29 (1.20–1.39)*	1.85 (1.09–3.12)*	1.61 (0.94–2.79)
Heart failure	1.45 (1.35–1.55)*	2.54 (1.80–3.58)*	1.72 (1.45–2.03)*
Retinopathy	1.41 (1.25–1.60)*	3.23 (0.79–13.27)	1.38 (1.20–1.60)*
Nephropathy	1.42 (1.32–1.52)*	2.72 (1.37–3.77)*	1.20 (1.11–1.31)*
Neuropathy	1.62 (1.52–1.76)*	2.06 (1.10–3.86)*	1.54 (1.25–1.89)*

Cox regression models with time to insulin (dependent variable) adjusting for age, sex, physician speciality: diabetologist care, private health insurance, diabetes duration, therapy with oral antidiabetic agents and comorbidity (hypertension, lipid disorders).
Data are hazard ratios (95%CI).
* $p < 0.01$.

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Table 3 – Association of oral antidiabetic agents on the time to insulin initiation in type 2 diabetes patients in primary care (Germany, France, UK; Disease Analyzer database).

Variables	Germany	France	UK
Sulfonylureas	2.06 (1.94–2.19)*	1.40 (1.14–1.71)*	2.13 (1.96–2.31)*
Glinides	2.31 (2.07–2.58)*	1.98 (1.46–2.69)*	4.77 (3.43–6.62)*
Alpha-glucosidase inhibitors	2.29 (2.00–2.62)*	1.18 (0.70–2.00)	4.37 (2.93–6.50)*
Thiazolidinedione	1.52 (1.34–1.72)*	0.87 (0.61–1.25)	1.87 (1.67–2.10)*
DPP-4 inhibitors	0.58 (0.51–0.67)*	0.42 (0.28–0.61)*	0.50 (0.36–0.68)*
GLP-1 analogs	1.19 (0.79–1.81)	1.21 (0.45–3.52)	0.65 (0.43–0.99)*

Reference group: biguanides.
Cox regression models with time to insulin (dependent variable) adjusting for age, sex, physician speciality: diabetologist care, private health insurance, diabetes duration, macro- and microvascular complications and comorbidity (hypertension, lipid disorders).
Data are hazard ratios (95%CI).
* $p < 0.01$.

4. Discussion

In primary care practices (Germany, France, UK) the diagnosis of a microvascular complication or coronary heart disease was associated with a higher likelihood to have insulin initiated in type 2 diabetes. Patients on oral-glucose antidiabetics were more likely to start insulin therapy except for DPP-4 inhibitor users, who were less likely compared to biguanides to progress to insulin.

Little is known about predictors of insulin therapy in primary care practices. Our findings regarding microvascular complications and insulin initiation are similar to the Translating Research into Action for Diabetes (TRIAD) study [7]. Type 2 diabetes patients in TRIAD who intensified therapy with insulin were more likely to have developed complications (cardiovascular disease, retinopathy, nephropathy, neuropathy) between baseline and follow-up [7]. They were also more likely to be sicker as indicated by a higher Charlson comorbidity index [7]. In US veterans, type 2 diabetes patients with higher comorbidity (Charlson score) were also more likely to have insulin initiated [8]. On the contrary, comorbidity was not related to onset of insulin therapy in another study from the US (Kaiser Permanente) [9]. However, this analysis only included patients with a combination of metformin and sulfonylureas [9]. Over half of these patients continued on the same therapy for 3 years although they failed to maintain an HbA1c level of 8% [9]. This glycemic burden associated with not initiating insulin therapy leads to an increased risk of microvascular complications [10]. Our present primary care study including patients from three European countries indicates that after these complications have developed the likelihood for initiating insulin increases.

Those patients who had insulin initiated had higher prescription prevalence of oral antidiabetic agents (sulfonylureas, metformin, thiazolidinediones, acarbose) [8]. Insulin initiation was more common among patients who received several classes of oral antidiabetics, suggesting that additional oral agents are used before transition to insulin therapy [8]. DPP-4 inhibitors or GLP-1 analogs were not included because the study period was from 1998 to 2006 (before market launch) [8].

In our study, patients with DPP-4 inhibitors were less likely to have insulin initiated compared to biguanide users (reference). In patients with type 2 diabetes who do not achieve the glycemic targets with metformin alone, DPP-4 inhibitors can lower HbA1c in a similar way to sulfonylureas without side effects (hypoglycemia, weight gain) [11]. It has been already stated that these advantages of DPP-4 inhibitors may help to overcome "clinical inertia", which is defined as failure to initiate and to advance therapy in a patient who is not on an evidence-based therapeutic goal [12]. Our study shows that the use of DPP-4 inhibitors may delay the use of insulin in primary care patients.

Current guidelines such as a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes on the management of hyperglycemia in type 2 diabetes recognize that most patients express reluctance to begin insulin therapy [13]. If the general practitioner feels the importance of starting insulin therapy encouragement of the patient usually overcomes such retinence [13]. However, physician attitudes that delay insulin initiation are often similar to those of the patients [10]. Patients and physicians both express their concern about the impact of insulin therapy on social life and work, and side effects, particularly hypoglycemia [14]. Physicians may also delay insulin initiation because of difficulties in training patients to administer insulin and the extra efforts and time for monitoring [8]. Thus, to improve the care of people with diabetes, attitudes of primary care physicians, who treat the majority of type 2 diabetes patients, need to be addressed to overcome "therapeutic inertia".

4.1. *Study limitations*

Retrospective primary care database analyses are in general limited by the validity and completeness of data. In particular, no valid information on onset of type 2 diabetes, diabetes type, change in diagnostic procedures (screening), prescribed daily insulin doses, and important outcome measures (e.g. hypoglycemia) were available in the database. Also assessment of comorbidity relied on ICD codes by primary care physicians only, and results on complications may be biased if some doctors performed diagnostic checks more often and with more accuracy. Data on socioeconomic status and lifestyle-related risk factors (smoking, alcohol, physical activity) was also lacking. Second, HbA1c and fasting glucose values were only available for a subgroup at baseline but not during the course of insulin treatment. Finally, the low prevalence for microvascular complications observed in the present study

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compared to population-based estimates indicated that a substantial number of patients who have such complications were missed.

In conclusion, in primary care practices in three European countries (Germany, France, UK) those type 2 diabetes patients who developed microvascular complications or coronary heart disease were more likely to have insulin initiated.

Conflict of interest statement

KK is an employee of IMS Health and WR has received a consulting fee from IMS Health.

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