Contents available at Sciverse ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation

A comparison of duration of first prescribed insulin therapy in uncontrolled type 2 diabetes☆

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ARTICLE INFO

Article history:
Received 9 March 2011
Received in revised form
25 August 2011
Accepted 5 September 2011
Published on line 2 October 2011

Keywords:
Type 2 diabetes
Insulin
Therapy

ABSTRACT

Aims: We investigated whether differences in duration of first insulin use in type 2 diabetes remain after adjustment for potential confounders, and what factors are associated with longer use.

Methods: People prescribed a first insulin (2000–2007) after 2–3 non-insulin glucose lowering treatments (OGLD) were identified from the THIN UK primary care database and grouped by insulin, detemir ($n = 165$), glargine ($n = 1011$) or NPH ($n = 420$). Time from beginning insulin to the prescription of another insulin type or a glucagon-like peptide was compared between insulins in a Cox model adjusting for: demographics, HbA1c, history of vascular complications and cardiovascular risk factors. The strength of association between duration of use and these variables was investigated.

Results: The adjusted hazard ratios compared to glargine for treatment change were 1.58 (95% CI 1.25, 2.00) for detemir and 1.49 (1.25, 1.78) for NPH. Lower mean treatment HbA_{1c} correlated with longer time to a different insulin regimen (Spearman rank correlation −0.30, $p < 0.01$) as were continuing OGLDs, older age, longer time from diagnosis, lower body mass index, lower HbA_{1c}, and no heart failure at baseline.

Conclusions: People who began treatment with glargine and those with better on-treatment HbA_{1c} remained on their first insulin for longer than those who began detemir or NPH.

1. Introduction

A short-term aim of the management of type 2 diabetes is good glycaemic control with a longer-term aim of reducing complications. Initial pharmaceutical treatment is usually with an oral therapy. However, a steady decline in islet β-cell function usually results in progressive hyperglycaemia despite up-titrated treatment. When glycaemic targets are not achieved the physician has an option to commence insulin based treatment or add an additional oral glucose-lowering drug (OGLD). The choice when beginning insulin treatment is usually between human NPH insulin (NPH) injected once or twice daily, a long-acting insulin analogue or a pre-mix preparation. Current UK NICE guidance recommends beginning with NPH but considering long-acting

☆ Presented at International Society for Pharmacoeconomics and Outcomes Research, November 2010.

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Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; HbA_{1c}, glycosylated haemoglobin; MI, myocardial infarction; OGLD, oral glucose-lowering agents; THIN, The Health Information Network; TIA, transient ischaemic attack; UK, United Kingdom; US, United States.

0168-8227/$ – see front matter
doi:10.1016/j.diabres.2011.09.003

analogues or pre-mixed insulin formulations under specified circumstances [1]. Oral therapy is often continued in parallel with insulin as there is evidence that insulin-oral combination therapy is associated with a significantly lower insulin dose and other advantages compared to insulin monotherapy [2].

When glycaemic control continues to deteriorate further despite dose titration, insulin treatment can be intensified further for example by adding meal-time insulin to those on basal insulin (or switching to a pre-mix formulation). Oral agent therapy may also be changed, or more recently a glucagon-like peptide (GLP) added (not currently a licensed indication in Europe).

Although an intensification of insulin regimen is inevitable with time in most people, there are good reasons why the first insulin regimen should be continued as long as possible provided it is efficacious. People on insulin become used to the routine and properties of that insulin (and injection device), and can find change stressful. There may also be new patterns of glucose control and hypoglycaemia with any new regimen, requiring care and precautions on changeover. It is therefore beneficial to be on the first insulin regimen for as long as it is clinically satisfactory.

Recent observational studies have reported differences in the duration of first insulin therapy between the insulin types in type 2 diabetes. Insulin glargine (glargine) appears to have longer duration of use than NPH insulin [3,4], but comparison with insulin detemir (detemir) has given inconsistent results [4,5]. However, follow-up was short and the comparisons were either not adjusted for baseline characteristics, or adjustment was limited and did not include glycaemic control.

The objective of the current study was therefore to investigate if differences in duration of first insulin to time of intensification of therapy between insulin glargine and NPH insulin remained after adjusting for baseline characteristics, to compare the duration of first therapy between insulin glargine and insulin detemir and to understand which patient characteristics were associated with longer duration of therapy.

2. Patients and methods

2.1. Data source

All study populations, prescribing and patient characteristics were identified from the THIN database. In summary, THIN is an observational database comprising electronic primary care records from throughout the UK. Validation studies have shown THIN to be appropriate for use in epidemiology research [6]. Details of demographic and administrative data, primary care diagnoses and prescription treatment are routinely recorded against date in separate files within individual patient records. Details of referrals, secondary care diagnoses and deaths are also captured because of the structure of the health system. Major events from before computerization are added retrospectively. Data on preventive care is routinely recorded including details of an annual diabetic patient review and any interim measurements. Medical events are automatically coded at entry using the Read coding system [7]. The 381 practices included in the present study had electronic links to pathology laboratories so would include test results in the patient records automatically. The protocol was approved by a Cambridgeshire-4 (UK) Ethics Committee.

2.2. Cohort formation and treatment definition

The study population was selected from people with a diagnosis of diabetes who started insulin therapy between 2000 and 2007 from a baseline of two or three OGLDs (Section 6.1.2 of the British National Formulary). The study population comprised those who started glargine, detemir or NPH as a single insulin, had poor glycaemic control (HbA_{1c} >7.5% in the previous 3 months) and were aged 18–80 years. Starting insulin therapy was defined as at least two prescriptions for one insulin type, with no prior history of insulin therapy. All people had to have at least one year of electronic records before and after commencing insulin. People remained in the cohorts whether or not they continued treatment with oral agents. To ensure that long-term insulin therapy was intended, people with a recent history of cancer (diagnosis or treatment) or glucocorticoid therapy or who stopped all insulin therapy during follow-up were excluded.

2.3. Study variables

The primary endpoint was time from the first insulin prescription (index date) to the date of the first prescription of a different insulin or initiation of a GLP-1 mimetic (end date), whether or not the original insulin was then continued. The end date could be at anytime from the index date to the end of the patient record so the length of follow-up varied between patients. Pre-mixed insulin was not included in the study as people who start therapy with this insulin type tend to change insulin dose or regimen rather than type when their glycaemic control deteriorates and so no endpoint would be identified. Any record of hypoglycaemia and HbA_{1c} level between index and end date was also identified.

The following potential confounding variables were accessed as of the index date: age, sex, year of first insulin, duration of diabetes calculated from the earliest record of diagnosis, review or treatment, continuation of OGLD treatment and number of baseline drugs, body mass index (BMI), smoking status, HbA_{1c} and glomerular filtration rate [8,9] in the previous year. Clinical history was also searched for records of hyperlipidaemia, heart failure, hypoglycaemia, vascular disease including myocardial infarction, other ischaemic or coronary artery disease, coronary revascularisation, stroke (ischaemic and unspecified stokes), other cerebral insufficiency/ischaemia, hypertension and microvascular complications (retinopathy, nephropathy or peripheral neuropathy). Hyperlipidaemia included a history of raised lipids either as a diagnosis (hyperlipidaemia or hypercholesterolaemia) or a blood result (total cholesterol:HDL ratio or cholesterol alone) recorded before the index date.

2.4. Statistical analysis

Patients were grouped according to initial insulin, namely glargine, detemir or NPH. Descriptive analyses were followed