Time to insulin initiation and long-term effects of initiating insulin in people with type 2 diabetes mellitus: the Hoorn Diabetes Care System Cohort Study

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Abstract

Objective: The aim of this study was to assess the time to insulin initiation in type 2 diabetes mellitus (T2DM) patients treated with oral glucose-lowering agents and to determine the baseline characteristics associated with time to insulin initiation. This was evaluated in T2DM patients with HbA1c levels consistently $\geq 7.0\%$ during total follow up and in those with fluctuating HbA1c levels around 7.0%.

Design and methods: Prospective, observational study was performed, comprising 2418 persons with T2DM aged ≥ 40 years who entered the Diabetes Care System between 1998 and 2012 with a minimum follow up of at least 3 years, following the first HbA1c level $\geq 7.0\%$. Cox regression analyses were performed to assess the determinants of time to insulin initiation. Data related to long-term effects of insulin initiation were studied at baseline and at the end of follow up using descriptive summary statistics.

Results: Two-thirds of the patients initiated insulin during follow up. The time to insulin varied from 1.2 years (range 0.3–3.1) in patients with HbA1c levels consistently $\geq 7.0\%$ to 5.4 years (range 3.0–7.5) in patients with fluctuating HbA1c levels around 7.0%. Longer diabetes duration (hazard ratio (HR) 1.04 95% CI 1.03–1.05) and lower age (HR 1.00 95% CI 0.99–1.00) at baseline were associated with a shorter time to initiation. More insulin initiators had retinopathy compared with patients that remained on oral glucose-lowering agents during follow up.

Conclusion: The time to insulin initiation was short, and most of the patients with HbA1c levels consistently $\geq 7.0\%$ were initiating insulin. Longer diabetes duration and younger age shortened the time to insulin.

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Introduction

Guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend target HbA1c values of $\leq 7.0\%$ in the majority of type 2 diabetes mellitus (T2DM) patients (1, 2). Not reaching the target HbA1c values of $\leq 7.0\%$ has been shown to increase the risk of diabetes-related

complications (3, 4, 5). Treatment of people with T2DM initially involves lifestyle changes and therapy with oral glucose-lowering agents. In case of an inadequate response to oral glucose-lowering agents, treatment with insulin is indicated (1, 2, 6). Initiating insulin therapy only after persistent high glucose values is a traditional approach (3).

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Evidence suggests that early intensive insulin therapy may slow down the progression of diabetes and reduce the risk of long-term complications through preservation of remaining β -cell function (3, 4, 5). The United Kingdom Prospective Diabetes Study showed that patients who initiated insulin earlier in the course of diabetes had better long-term glucose control than those who remained on the conventional therapy with oral glucose-lowering agents (7).

Studies in patients inadequately responding to oral glucose-lowering agents showed a time to insulin initiation varying between 2 and 8 years (8, 9, 10). However, these studies were retrospective and were generally based on registries from primary care practices (PCPs) prior to 2005. Furthermore, these studies only addressed insulin initiation and not intensification of the oral glucose-lowering treatment. Finally, observational studies on the long-term effects of insulin initiation, with respect to glycaemic control, microvascular complications and mortality, are not available. Three randomized controlled trials (RCTs) reported that a reduction in HbA1c was associated with a reduction in microvascular complications (7, 11, 12). However, these RCTs were performed in relatively healthy T2DM patients (7, 11, 12).

The present prospective, population based study addresses all issues described above and includes annually standardized measurements from people with T2DM during the period between 1998 and 2012.

The aim of this study was to assess the time to insulin initiation in T2DM patients treated with oral glucose-lowering agents and to determine the baseline characteristics associated with time to insulin initiation. This was evaluated in T2DM patients with HbA1c levels consistently $\geq 7.0\%$ and in those with fluctuating HbA1c levels around 7.0% separately. An exploratory aim was to evaluate long-term outcomes, including glycaemic control, microvascular complications and mortality.

Subjects and methods

Study population

A prospective, observational study was performed using data from the Diabetes Care System in the period between 1998 and 2012, described in detail elsewhere (13, 14). In short, the Diabetes Care System provides diabetes care in the region of West Friesland in The Netherlands, a region with about 200 000 inhabitants that is representative of a Western European population (15).

The Diabetes Care System uses a managed care plan for T2DM with contracted health care providers and is responsible for the quality of diabetes care in the region. Diabetes care encompasses the care provided by a patient's PCP, according to the Dutch treatment guidelines for T2DM (16), the annual assessment as organized centrally by the Diabetes Care Centre for annual review and patient education by the diabetes nurse and dietician. Results of the assessment and protocol-driven therapeutic advice are provided to the patient's PCP (17). Patients are included in the Diabetes Care System 1.45 years (range 0.3–5.3) after the clinical diagnosis.

For each patient, the year of entry was considered as the baseline measurement (T0). The Diabetes Care System maintains anonymized computer records, and the patients were informed of the use of these records for research purposes.

Participants

All 2418 T2DM patients aged 40 years and over (to exclude people with type 1 diabetes), with at least three follow-up moments after the first HbA1c level $\geq 7.0\%$ and with a mean HbA1c level $\geq 7.0\%$ during follow up and not using insulin before entry in the Diabetes Care System, were extracted. Patients that were already using insulin at the baseline measurement were excluded. Participants included in this study had a follow-up period ranging from 3 to 14 years.

Measurements

HbA1c was assessed with a DCCT standardized reversed-phase cation exchange chromatography (HA 8160 analyzer, Menarini, Florence, Italy). HbA1c was detected using a dual-wavelength colorimetric (415–500). The intra-assay coefficient of variation (CV) was 0.6% at a mean level of 4.9%, and the inter-assay CV was 0.8% at a mean level of 5.5%.

Weight and height were measured annually (whilst the patients were barefooted and wearing light clothing). BMI was calculated (weight in kilograms divided by the square of height in meters). Diabetes duration was self-reported and was divided into four groups: a diabetes duration of 0–2, 2–5, 5–10 and 10 years or longer. The diabetes duration was verified at the PCP. Diabetes management differs across PCPs and by the employment of a nurse practitioner (NP) for diabetes management. Therefore, PCP organizations were categorized into three types: i) involvement of an NP in diabetes management

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and the insulin is initiated by the PCP; ii) involvement of an NP and the insulin was initiated by the Diabetes Care System; and iii) no NP and the insulin was initiated by the Diabetes Care System. At any time, the PCP organization has the opportunity to send a patient to the Diabetes Care System for the initiation of insulin. In The Netherlands, patients are obliged to choose a PCP based on the geographical location of the PCP, and they might choose a PCP within a geographical location on the basis of their preferences, e.g. involvement of an NP.

Blood pressure was measured annually. Systolic and diastolic blood pressures were measured on the right arm after 5 min of rest in a seated position with the oscillometric device, Colin 8800C, between 2003 and 2011. After 2011, the oscillometric device, Welch Allyn monitor, was used. Glucose (fasting and 2 h after the oral glucose tolerance test) was measured in venous plasma using the glucose oxidase method (Glucoquant/hexokinase/G6P-DH; Boehringer Mannheim, Mannheim, Germany). Triglycerides, total and HDL cholesterol were determined from fasting blood samples using enzymatic techniques (Boehringer Mannheim). LDL cholesterol was estimated using the Friedewald formula, except in subjects with triglycerides >4.5 mmol/l. Estimated glomerular filtration rate was calculated using the modification of diet in renal disease formula.

Microalbuminuria was considered present if urine albumin-to-creatinine ratio was >2.0 mg/mmol. Retinopathy (fundus photography of both eyes was performed yearly) was measured from 1998 until 2000, with a Kowa Pro Fundus camera with a green filter (Kowa Optical Industry, Torrance, CA, USA). Black and white, 35 mm photographs were taken 30 min after mydriasis with 0.5% tropicamide and 2.5% phenylephrine eye drops. From the beginning of 2000 until 2004, fundus photography of both eyes was performed with a non-mydratic Canon CR5 camera (Canon, Inc., Tokyo, Japan). From 2004, fundus photography of both eyes was performed using a non-mydratic Topcon TRC NW 100 camera (Topcon, Tokyo, Japan). All participants were examined using 45° fundus photographs. One photograph was centered on the macula and the other nasally with one optic disc diameter from the temporal side. All photographs were graded by an experienced ophthalmologist according to the EURODIAB classification score (18). The retinopathy at the end of follow up is calculated for each person at the end of her/his follow-up period. All measurements were performed at the clinical chemistry laboratory at the Westfriesgasthuis in Hoorn (The Netherlands).

Information on current medication use was registered yearly at the annual visit by checking dispensing labels brought by patients with T2DM. Three different groups of oral glucose-lowering agents were defined: metformin, sulfonylurea and other oral glucose-lowering agents. The other oral glucose-lowering agent category contains the following groups of oral glucose-lowering agents: thiazolidinediones, alpha glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, meglitinides and glucagon-like peptide receptor agonists.

Mortality was derived from the municipal administration registries updated every 3 months. Information on the cause of death was retrieved from medical records of general practitioners and from the local hospital.

Statistical analysis

At first, two groups were defined: one group that initiated insulin during follow up and the other remained on oral glucose-lowering agents. Moreover, within these groups, we distinguished patients with HbA1c levels consistently $\geq 7.0\%$ and fluctuating HbA1c levels around 7.0%. Patients with all HbA1c measurements $\geq 7.0\%$ during total follow up were defined as 'consistently $\geq 7.0\%$ ', and patients with HbA1c measurements fluctuating around 7.0% were defined as 'fluctuating around 7.0%'.

Baseline characteristics (i.e. age, sex, BMI, diabetes duration, HbA1c, systolic blood pressure (SBP), fasting glucose, total cholesterol, HDL cholesterol, triglycerides and oral glucose-lowering agents) of the four groups were studied using descriptive summary statistics. Baseline characteristics of insulin initiators vs no insulin initiators were tested for differences with one-way ANOVA and *post hoc* Bonferroni tests for mean levels, with chi-square tests for proportions and Kruskal–Wallis test for median levels in the study population.

The time to insulin initiation was calculated as the time between the first HbA1c level higher than 7.0% and the time to insulin initiation. Mean HbA1c levels over time in the groups were plotted in a graph. The number of oral glucose-lowering agents used at baseline and end of follow up was calculated. If patients were initiating insulin during follow up, the number of oral glucose lowering agents before the initiation of insulin was registered.

A Cox proportional hazards model was used to determine which characteristics at baseline (i.e. BMI, glucose, PCP organization, SBP, HbA1c and diabetes duration) were associated with the timing of insulin initiation. All analyses were adjusted for age and sex. All determinants with *P* values <0.10 were entered

simultaneously using a backward elimination method, leading to a model including only significant ($P < 0.05$) determinants. Before the model was constructed, the proportional hazard assumption, i.e. that the hazard ratio (HR) is constant over time, was tested by comparing estimated log–log survival curves for all covariates. All continuous variables were divided into quartiles to check whether these variables met the proportional hazard assumption. All assessed log–log survival plots graphically showed two parallel lines, indicating no violation of the assumption.

We repeated the Cox regression analysis stratifying HbA1c levels in patients with HbA1c levels consistently $\geq 7.0\%$ and with HbA1c levels fluctuating around $\geq 7.0\%$. Data are presented as HR with a 95% CI. P values lower than 0.05 were considered statistically significant.

Data related to long-term consequences of insulin initiation (mortality, retinopathy and microalbuminuria) were studied at baseline and at the end of follow up using descriptive summary statistics.

Statistical analyses were performed using SPSS for Windows (version 20.0, SPSS, Inc.).

Results

Figure 1 shows the flow chart of the T2DM population analyzed in this study. A total of 8308 persons with T2DM

participated in the Diabetes Care System. For the current study, 2418 T2DM patients with an HbA1c $\geq 7.0\%$ were included.

Baseline characteristics

Table 1 shows baseline characteristics of the four subgroups of T2DM patients. In total, 1474 patients (61.0%) initiated insulin and 944 patients (39.0%) remained on oral glucose-lowering agents during follow up. In total, 555 (23%) patients had HbA1c levels consistently higher than $\geq 7.0\%$ (groups 1A and B), and 1863 (77%) patients had HbA1c levels fluctuating around 7.0% during follow up (groups 2A and B).

Time to insulin

In total, 416 (75%) patients with HbA1c levels consistently higher $\geq 7.0\%$ initiated insulin (group 1A) in a median time of 1.2 years (range 0.3–3.1), and 1058 (56.8%) patients with levels fluctuating around 7.0% initiated insulin (group 2A) in a median time of 5.4 years (range 3.0–7.5).

Insulin initiation vs no insulin initiation

Insulin initiators were younger (60.9 vs 62.0 years), had lower BMI levels (29.9 vs 30.4 kg/m²), higher glucose levels

Figure 1

Flow chart of the included T2DM patients within the Diabetes Care System. At year 1 (T1) are 2418 patients included in the study. After 15 years (T15) 192 patients are still included in the study.

Table 1 Baseline characteristics at entry in the Diabetes Care System of the study population. Data is presented as mean $\pm$ s.d. or median (interquartile range).

	HbA1c consistently $\geq 7.0\%$		HbA1c fluctuating around 7.0%	
	Group 1A	Group 1B	Group 2A	Group 2B
	Insulin initiation	No insulin initiation	Insulin initiation	No insulin initiation
Number of patients	416	139	1058	805
Age (years)	61.2 $\pm$ 10.4	62.5 $\pm$ 11.6	60.8 $\pm$ 10.4*	61.9 $\pm$ 10.5*
Sex (male %)	52.6	51.1	51.1*	57.9*
BMI (kg/m ²)	29.9 $\pm$ 5.5	30.4 $\pm$ 5.3	29.9 $\pm$ 5.6*	30.4 $\pm$ 5.5*
Diabetes duration at entry in Diabetes Care System (years)	2.5 (0.3 – 7.0) [†]	1.2 (0.3 – 4.0) [†]	2.1 (0.4 – 6.6)*	0.8 (0.2 – 2.7)*
HbA1c (mmol/mol)	69 $\pm$ 1.9 [†]	63 $\pm$ 1.5 [†]	65 $\pm$ 1.8	66 $\pm$ 1.8
SBP (mmHg)	141.7 $\pm$ 21.0	143.8 $\pm$ 22.6	142.0 $\pm$ 21.2*	144.0 $\pm$ 20.5*
Fasting glucose (mmol/l)	10.3 $\pm$ 2.8 [†]	9.1 $\pm$ 2.6 [†]	9.8 $\pm$ 3.9*	9.2 $\pm$ 2.4*
Total cholesterol (mmol/l)	5.4 $\pm$ 1.2	5.4 $\pm$ 1.3	5.4 $\pm$ 1.2	5.3 $\pm$ 1.1
HDL cholesterol (mmol/l)	1.19 $\pm$ 0.3	1.21 $\pm$ 0.4	1.20 $\pm$ 0.4	1.20 $\pm$ 0.3
Triglycerides (mmol/l)	2.20 $\pm$ 1.7	2.15 $\pm$ 1.3	2.25 $\pm$ 3.3	2.01 $\pm$ 1.2
Microalbuminuria (%)	21.4	18.0	19.3	19.4
Any retinopathy (%)	15.6	8.1	12.1	9.2
Grade 1 retinopathy (%)	11.0	3.6	8.2	6.6
Grade 2 retinopathy (%)	2.8	3.6	2.2	1.4
Grade 3 retinopathy (%)	1.5	0.9	1.2	0.9
Grade 4 retinopathy (%)	0.3	0.0	0.5	0.3
Metformin use only (%)	16.3 [†]	30.2 [†]	24.4*	35.9*
SU use only (%)	27.6	20.1	24.4*	19.9*
Metformin + SU use only (%)	34.1 [†]	23.7 [†]	20.3*	12.4*
Other combination (%)	4.3	2.2	2.4	1.9
Unknown medication (%)	17.7	23.8	28.5	29.9
Time to insulin (years)	1.2 (0.3 – 3.1) [†]		5.4 (3.0 – 7.5) [†]	
End of follow up				
Follow up (years)	8.8 $\pm$ 3.3 [†]	4.9 $\pm$ 2.4 [†]	8.9 $\pm$ 3.3*	7.1 $\pm$ 3.0*
Metformin use only (%)	25.2 [†]	15.8 [†]	29.4*	18.8*
SU use only (%)	14.4 [†]	1.4 [†]	6.0*	4.0*
Metformin + SU use only (%)	36.3	44.6	36.5*	53.9*
Other combination (%)	3.8	7.2	6.4*	11.7*
Unknown medication (%)	20.3	31.0	21.7	8.8
Long-term consequences				
Microalbuminuria (%)	30.4	25.9	27.7	24.5
Any retinopathy (%)	12.1	12.2	11.3*	6.8*
Grade 1 retinopathy (%)	6.3	8.4	6.7	4.3
Grade 2 retinopathy (%)	2.6	1.5	1.7	1.0
Grade 3 retinopathy (%)	0.8	0.8	0.8	0.5
Grade 4 retinopathy (%)	2.4	1.5	2.1	1.0
Mortality (%)	21.4	27.3	18.0	21.2

*indicates a statistical significant difference in groups 2A vs 2B; [†]indicates a statistical significant difference in groups 1A vs B ($P < 0.05$); [‡]indicates a statistical significant difference in group 1A vs group 2A ($P < 0.001$).

(9.9 vs 9.2 mmol/l) and a longer diabetes duration (2.2 vs 0.9 years) compared to patients that remained on oral glucose-lowering agents.

Intensification of treatment in patients initiating insulin

At baseline, patients in group 1A used one (45.0%), two (37.0) or three (0.5%) oral glucose-lowering agents. During follow up, the number of oral glucose-lowering agents was

increasing. Before the initiation of insulin, 29.8% of these patients were using one oral glucose-lowering agent, 57.5% were using two oral glucose-lowering agents and 1.0% was using three oral glucose-lowering agents. At baseline, patients in group 2A used one (49.1%), two (21.6%) or three (0.8%) oral glucose-lowering agents. In this group, the number of oral glucose-lowering agents increased during follow up. Before the initiation of insulin, patients used one (33.6%), two (43.5%) or three or more (2.4%) oral glucose-lowering agents.

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At the initiation of insulin, 11.1% of the patients in group 1A used only metformin, 18.5% only SU, 54.8% a combination of metformin and sulphonylurea derivatives (SU) and 3.8% another combination of oral glucose-lowering agents. In group 2A, 22.9% of the patients were using only metformin, 10.0% only SU, 40.9% a combination of metformin and SU and 5.7% another combination of oral glucose lowering agents.

Intensification of treatment in patients remaining on oral glucose-lowering agents

During follow up, the PCPs intensified the treatment with oral glucose-lowering agents in groups 1B and 2B (see Table 1). In total, 15.8% of the 139 patients in group 1B used only metformin, 1.4% used only SU, 44.6% used a combination of metformin and SU and 7.2% used another combination of oral glucose lowering agents at the last follow-up moment. Patients in group 2B used only metformin (18.8%) at the last follow-up moment, 4.0% only SU, 53.9% a combination of metformin and SU and 11.7% another combination of oral glucose-lowering agents.

Baseline characteristics associated with time to insulin initiation

Table 2 presents the Cox regression models for the time to insulin initiation in T2DM patients. Longer duration of diabetes (HR 1.04 95% CI 1.03–1.05) and lower age (HR 1.00 95% CI 0.99–1.00) were associated with a shorter time to insulin in T2DM patients. Stratifying patients with HbA1c levels consistently $\geq 7.0\%$ higher glucose levels

(HR 1.10 95% CI 1.06–1.14) at baseline were associated with a shorter time to insulin. In T2DM patients with HbA1c levels fluctuating around 7.0%, longer duration of diabetes (HR 1.04 95% CI 1.03–1.05) at baseline was associated with a shorter time to insulin. PCP organization was not associated with time to insulin initiation in any of the groups.

Long-term consequences of insulin initiation

At baseline, no differences were found in microalbuminuria and retinopathy between patients initiating insulin compared with patients who remain on oral glucose-lowering agents. At the end of follow up (mean follow up 5.3 year, s.d. 3.4), there were statistically significant more patients with microalbuminuria and retinopathy in insulin initiators compared with patients who remained on oral glucose-lowering agents (microalbuminuria: 28.4 vs 24.7%; retinopathy: 11.6 vs 7.7%). The total mortality ($n=209$ vs $n=279$) in patients who remained on oral glucose-lowering agents was statistically significantly higher compared with patients who initiated insulin during follow up (22.1 vs 18.9%; $P=0.05$). After adjustment for baseline HbA1c, the relationship for microalbuminuria and mortality disappeared, but did not materially changed the results for retinopathy.

No differences were found in microalbuminuria, retinopathy and mortality at baseline and at the end of follow up in patients of groups 1A and B. There were statistically significant more patients in group 2A with retinopathy at the end of follow up compared with patients in group 2B (27.7 vs 24.5%). No differences were found in microalbuminuria and mortality between groups 2A and B.

Table 2 Cox proportional hazard model of the time to insulin in people with T2DM treated with oral glucose-lowering agents.

	HR (95% CI)	P level
Overall population		
Sex (female vs male)	1.06 (0.95–1.18)	0.28
Age (years)	1.00 (0.99–1.00)	<0.001
Diabetes duration (years)	1.04 (1.03–1.05)	0.05
Patients with HbA1c levels consistently $\geq 7.0\%$ (Groups 1A and B)		
Sex (female vs male)	0.96 (0.79–1.17)	0.67
Age (years)	1.00 (0.99–1.01)	0.65
Glucose (mmol/l)	1.10 (1.06–1.14)	<0.001
Patients with fluctuating HbA1c levels around 7.0% (Groups 2A and B)		
Sex (female vs male)	1.10 (0.97–1.24)	0.15
Age (years)	0.99 (0.99–1.00)	0.06
Diabetes duration (years)	1.04 (1.03–1.05)	<0.001

HbA1c levels over time

Figure 2 represents the HbA1c levels over time in the different groups of patients. Group 1B shows the worst course of HbA1c levels over time, with HbA1c levels that remained above 7.6% during the first 10 years of follow up. Patients in group 2B showed HbA1c levels of around 7.2%.

Discussion

Insulin therapy was initiated in 61% of the 2418 included T2DM patients treated with oral glucose-lowering agents during follow up. The time to insulin varied from 1.2 years (range 0.3–3.1) in patients with HbA1c levels consistently $\geq 7.0\%$ to 5.4 years (range 3.0–7.5) in

Figure 2

HbA1c levels over time in the four groups of people with T2DM. The numbers on the X-axis represent the years of follow up of the people with T2DM included in this study.

patients with fluctuating HbA1c levels around 7.0%. Longer duration of diabetes at baseline was associated with a shorter time to insulin initiation. Patients who initiated insulin during follow up had more retinopathy compared with patients who remained on oral glucose-lowering agents during follow up even after adjusting for HbA1c.

To our knowledge, this is the first observational study describing subgroups of people with type 2 diabetes with HbA1c levels consistently $\geq 7.0\%$ and fluctuating HbA1c levels around $\geq 7.0\%$ with a long-term follow up.

Nichols *et al.* (8) studied the proportion of patients attaining and maintaining the glycemic target of 8.0% treated with oral glucose-lowering agents and the possible initiation of insulin. Even with a less strict target (8.0%) compared to our study, only 41.9% of these patients initiated insulin during a mean follow up of 4.6 years (8). Other studies reported a proportion varying from 40 to 60% of patients that initiated insulin and a time to insulin initiation varying between 2 and 8 years (8, 9, 10, 19). However, these studies did not use the ADA/EASD target level of 7.0%, which impedes the comparison with our results. However, it is clear that even with higher HbA1c target levels, the time to insulin initiation in these populations was longer compared to our study. In an earlier study by our group (20), we showed that managed diabetes care with a central organization and central management of care was statistically significantly associated with a better process of the diabetes care and lower direct costs compared to usual diabetes care. This persisted

after adjustment for differences in patient characteristics at baseline. This could be the explanation that in insulin initiation, this centrally managed diabetes care is the reason for a shorter time to insulin initiation. Thereby, care outcomes and glycemic control of this population are usually better than those in other cohorts (1, 2, 3), and most likely outcomes would be worse in other populations.

Patients that initiated insulin showed more retinopathy compared to patients that remain on oral glucose lowering agents during follow up. The exact reason for this is difficult to explain and needs further elaboration. However, the association between deteriorating glycemic control and an increased risk of microvascular complications was reported by many others before (7, 21). After adjustment for HbA1c, there was no difference in mortality between insulin users and patients that remain on oral glucose-lowering agents. These findings are in accordance with results from the Veteran's Affairs Diabetes Trial (VADT) study. This study found no effect on the mortality rates in T2DM patients initiating insulin compared to T2DM patients that remain on oral glucose-lowering drugs (21).

Observational research is an important complementary approach used to document how drugs are actually used in routine clinical practice; we have to address some limitations of the present study. The data on medication use might be an underestimation (not all medication is known) because information on medication use was obtained on the basis of self-reporting, and no information on the medication dose was available. In the study period of 1998–2012, national guidelines were updated. These guidelines were advocating in 1999 first choice treatment of metformin in patients with a BMI > 27 . In 2006, metformin was first choice treatment for all T2DM patients. This could not have affected the results of our study.

Not all known patient, physician and practice-related reasons for possible delay in the time to initiation of insulin have been measured. For example, we were not able to include patients' psychological insulin resistance, e.g. patients fear of disease progression, needle anxiety, concerns about hypoglycaemia and weight gain, adherence to lifestyle advices and oral glucose-lowering medication (8, 22). Moreover, we were not able to include adherence of PCPs with guidelines. Differences in protocol adherence could influence timely insulin initiation. However, we did not find a statistically significant association of PCP practice organization with timing of insulin initiation. We assume that most PCPs followed the

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agreed regional diabetes protocol, but we could not exclude that PCPs felt resistance against insulin initiation in people with fluctuating values around the glycemic target.

Strengths of this study include the prospective, observational design with a long-term follow up (up to 14 years), the completeness of the dataset and standardized yearly measurements. Furthermore, we described the intensification of the treatment and long-term consequences of insulin initiation. Additionally, the study population was larger ($n=2418$) than most of the previously published studies on this subject. Finally, all patients with T2DM in the described region are referred to the Diabetes Care System; therefore, biased referral of the most complex patients to secondary care is unlikely to have occurred.

Our findings urge additional studies examining the benefits of an earlier initiation of insulin therapy. In addition, further research is needed to understand the clinician, patient and system-related barriers to insulin initiation in order to design strategies targeted at modifying barriers to insulin initiation.

Declaration of interest

R J Heine is an employee and stock holder at Eli Lilly and Company, Indianapolis IN, USA. G Nijpels received unrestricted grants from Novo Nordisk and Sanofi-Aventis and is a member of the advisory board of Eli Lilly. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

R Mast researched the data and wrote the manuscript. I Walraven and A P Danielle Jansen researched the data and reviewed and edited the manuscript. R Mast, G Nijpels, A P Danielle Jansen and J G Hugtenburg conceived and designed the study, researched the data and reviewed and edited the manuscript. G Nijpels, A A W A van der Heijden, S P Rauh, R J Heine, J G Hugtenburg, P J M Elders and J M Dekker reviewed and edited the manuscript. R Mast is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Clinical Study	R Mast and others	Time to insulin in T2DM patients	174:5	571
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