CHAPTER 2

Initiation of Glucose Lowering Therapy in Type 2 Diabetes Mellitus Patients in General Practice
Abstract

*Aim* - Purpose of this study was to investigate determinants for the initiation of glucose lowering therapy in general practice and perspectives of these type 2 diabetes mellitus patients with respect to future glycemic control.

*Methods* - Among incident type 2 diabetic patients in general practice factors associated with initiation of glucose lowering therapy were examined by Cox’ regression analyses. Also the relationship between glucose levels at diagnosis and future glycemic control was investigated.

*Results* - In total, 603 newly diagnosed patients with type 2 diabetes mellitus were included in the study. Of the incident type 2 patients, 319 (53%) started immediately (in the first month following diagnosis) with oral therapy. One, two, and three years after diagnosis of diabetes the cumulative incidences were 71% (CI_{95%}: 66-73%), 75% (CI_{95%}: 71-79%), and 81% (CI_{95%}: 77-84%), respectively. Age, body weight, systolic and diastolic blood pressure, history of cardiovascular disease, or total serum cholesterol values were not associated with time to start of oral drug therapy. Level of hyperglycemia at diagnosis was strongly related to initiation of drug therapy and future glycemic control.

*Conclusion* - This study shows that the initial severity of diabetes, assessed by the degree of hyperglycemia at the time of diagnosis, is a major factor in determining the time to start of pharmacological treatment of diabetes and the likelihood of achieving target levels of glycemic control in the future, independent of glucose lowering strategy.
Introduction

Glycemic control is the cornerstone of the management of type 2 diabetes mellitus. Lifestyle intervention (i.e. proper nutrition, physical exercise) is the first treatment step in patients with only moderate hyperglycemia. Although difficult to achieve, modest weight loss and increased exercise have beneficial effects on glucose values, lipids and blood pressure. In the United Kingdom Prospective Diabetes Study (UKPDS), newly diagnosed adults with type 2 diabetes reduced their average HbA1c level from ~9 to 7% after three months of dietary treatment. When despite implementation of these lifestyle changes the fasting blood glucose target (< 8.0 mmol/l) is not achieved within three months, drug treatment should be considered.

In the UKPDS, glycemic control deteriorated gradually with time, even in the intensively treated patients. This worsening of glycemic control has been attributed to the natural course of type 2 diabetes and lack of efficacy of current hypoglycemic therapy. Recent studies show that early addition of insulin or metformin can significantly improve glycemic control without leading to increased hypoglycemia or weight gain.

However, little is known about the efficacy of treatment of type 2 diabetes patients in daily primary care. Especially, the extent and effectiveness of lifestyle interventions (dietary treatment, increased exercise level) in routine care remains unclear. For instance, in some cases doctors decide to start drug therapy immediately following diagnosis. There is little data on the clinical grounds (patient characteristics) on which general practitioners (GPs) make this decision and the perspectives of these patients with respect to future glycemic control.

The aim of this study was to investigate determinants for the initiation of oral glucose lowering therapy in newly diagnosed type 2 diabetes mellitus patients in general practice.
Patients and Methods

Study setting
This study was performed among patients who received comprehensive primary care from 17 GPs in a Dutch middle-sized town (n=50,574). Detailed clinical information was captured in a single electronic medical record system (Medicom®), whereas information on pharmacy based drug dispensions was registered in a second database (Pharmacom®). Hospital admission and discharge data were available through the PHARMO Record Linkage System. The following data were available for this study: demographic data, medical history, comorbidity (including International Classification of Primary Care (ICPC) codes), diabetic complications, prescriptions and drug dispensions, doctor in attendance (specialist, GP), referrals to specialists, and a ‘medical journal’ (a database-file containing free text, as recorded by the GP in the computer).

To guarantee privacy, all analyses were performed using anonymous records. Regarding medication prescriptions and dispensings, all drugs were coded according to the Anatomical Therapeutic Chemical (ATC) Classification. Hospital diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM codes).

Subjects
In the Netherlands, most patients with diabetes mellitus type 2 visit their GP for regular check-ups. They were identified from the registries by International Classification of Primary Care (ICPC-2) codes T90 or T90.2, and/or the description ‘diabetes mellitus type 2’ in their medical records. Data from both primary care and the pharmacy based dispensing records were complete for the period of February 1994 to August 2000 and were considered for the present study.

For the present study we selected all newly diagnosed patients with type 2 diabetes during this period (N=603). Following the Dutch General Practitioners’ Guidelines, treatment of newly diagnosed patients starts with dietary advice and encouragement of physical activity. Oral glucose lowering medication is indicated if target levels of blood glucose are not achieved within 3 months. Drugs of first
choice are sulfonylurea derivatives and, in obese patients (body mass index > 27), metformin. Glycemic control was defined in terms of poor (HbA$_1c$ > 8.5%), acceptable (HbA$_1c$: 7.0-8.5%), and good control (HbA$_1c$ < 7.0%) according to the College of Dutch General Practitioners’ Guidelines.\(^7\)

**Data analysis**

For categorical variables, numbers and percentages and for continuous data means and standard deviations (SD) or standard errors of the mean (± s.e.m.) were calculated. For comparison of continuous variables and categorical variables, we used the Students’ t-test and chi-square test, respectively. The Kaplan-Meier method was used to calculate the cumulative incidence of glucose lowering drug use, defined as: 1 – cumulative survival probability; under the assumption that treatment will be continuous and lifelong after initiation of this medical therapy. We performed log rank tests to assess differences between subgroups.

We compared time to start of oral hypoglycemic drug treatment between four strata of fasting and non-fasting blood glucose levels at diagnosis (FBG and NFBG), defined by quartile cut-off points. Spearman’s correlation coefficient was calculated to study the association between FBG and NFBG levels.

Furthermore, we used Cox’ proportional hazards analyses and controlled for confounding by including covariates (like age, gender, body weight and blood pressure) in the model. We calculated hazard ratios (HR) with corresponding 95% confidence intervals (CI\(_{95\%}\)). Start of oral hypoglycemic therapy was the event of interest, date of censoring was the end of follow-up (death, migration, end of study in August 2000).

With respect to glycemic control, mean differences between FBG and NFBG strata were analyzed using analysis of variance (ANOVA). Additional adjustments for potential confounders (age, gender, duration of diabetes, and body weight) were made by including these as covariates. All analyses were carried out using the statistical package SPSS version 9.0 for Windows.
Table 2.1 General characteristics of newly diagnosed patients with type 2 DM (N=603)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD) or %</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>62.0 (13.5)</td>
<td>603 (100%)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43.4</td>
<td>262</td>
</tr>
<tr>
<td>Diabetes duration* (years)</td>
<td>3.0 (1.9)</td>
<td>603 (100%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.6 (1.5)</td>
<td>317 (53%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.8 (17.8)</td>
<td>303 (50%)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28.9 (5.2)</td>
<td>147 (24%)</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td>8.7 (2.5)</td>
<td>444 (74%)</td>
</tr>
<tr>
<td>Random blood glucose (mmol/l)</td>
<td>10.7 (3.8)</td>
<td>445 (74%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>150.7 (20.6)</td>
<td>407 (67%)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.4 (10.5)</td>
<td>405 (67%)</td>
</tr>
<tr>
<td>Total serum cholesterol (mmol/l)</td>
<td>5.7 (1.0)</td>
<td>373 (62%)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.20 (0.31)</td>
<td>265 (44%)</td>
</tr>
<tr>
<td>Ratio HDL/ Total cholesterol</td>
<td>5.2 (1.5)</td>
<td>249 (41%)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.60 (0.95)</td>
<td>178 (30%)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.54 (2.34)</td>
<td>265 (44%)</td>
</tr>
<tr>
<td>Serum creatinine (mmol/l)</td>
<td>84.1 (23.0)</td>
<td>369 (61%)</td>
</tr>
<tr>
<td>History of cardiovascular disease (%)</td>
<td>21.2</td>
<td>127</td>
</tr>
<tr>
<td>Ischemic heart disease (excl. MI)</td>
<td>11.3</td>
<td>68</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7.1</td>
<td>43</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.6</td>
<td>22</td>
</tr>
<tr>
<td>CVA, TIA</td>
<td>7.0</td>
<td>42</td>
</tr>
<tr>
<td>Switchers to insulin therapy (%)</td>
<td>10.9</td>
<td>66</td>
</tr>
</tbody>
</table>

Values are proportions or means, standard deviation (SD) between parentheses
* At date of end of study (August 31st 2000) or date of censoring (loss to follow up)
CVA: cerebrovascular accident; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; TIA: transient ischemic attack
Results

Table 2.1 shows the general characteristics of the 603 newly diagnosed patients included in this study. Regarding metabolic measurements, such as fasting blood glucose and cholesterol measurements, mean values during diabetes are given. In total, 136 patients (23%) remained on dietary treatment only (mean duration of diabetes: 2.1±0.1 years) and 66 (11%) patients switched to insulin therapy after a mean diabetes duration of 1.6±0.2 years. The overall prevalence of (recorded) cardiovascular disease was higher in men compared to women (age-adjusted OR 2.0, CI95%: 1.3-3.0).

A history of ischemic heart disease in general (OR_{adj} 2.4, CI_{95%}: 1.4-3.9), and especially myocardial infarction (OR_{adj} 3.9, CI_{95%}: 1.9-7.8), was more common in males, while females more often suffered from heart failure (OR_{adj} 2.5, CI_{95%}: 0.9-8.3).

![Graph](image)

**Figure 2.1**  Start of oral hypoglycemic agent (OHA) use after diagnosis of diabetes
Start of oral hypoglycemic therapy in newly diagnosed patients

Figure 2.1 represents the cumulative incidence (Kaplan Meier curve estimate) of glucose lowering drug use in newly diagnosed type 2 diabetes mellitus patients. Of the incident type 2 patients, 319 (53%) started immediately (in the first month following diagnosis) with oral therapy. One, two, and three years after diagnosis of diabetes the cumulative incidences were 71% (CI<sub>95%</sub>: 66-73%), 75% (CI<sub>95%</sub>: 71-79%), and 81% (CI<sub>95%</sub>: 77-84%), respectively. The curves show that men started with drug treatment sooner after diagnosis, but this difference was not statistically significant (logrank test statistic: 1.93, p= 0.17). Indeed, 3 years after diagnosis 21% of women and 15% of men were still on dietary treatment only. Patients treated with diet only were slightly more likely to be female than patients who started drug therapy, e.g., 63% versus 55% women, respectively (p= 0.07).

Age, body weight (sex-adjusted), systolic and diastolic blood pressure, history of cardiovascular disease, or total serum cholesterol values were not associated with time to start of oral drug therapy. Furthermore, we compared time to treatment in patients diagnosed before 1999 and since 1999, (introduction of revised guidelines: recommended period to attempt reaching acceptable glycemic control with dietary treatment only reduced to three months instead of six months), but no difference was found.

In more than half of the patients (51.8%), tolbutamide was the drug of first choice, followed by a second-generation sulfonylurea (gliclazide, glibenclamide, glimepiride, and glipizide; 30.4%), and metformin (18.2%). Patients who started with metformin weighed significantly more than other patients (97.3±3.0 versus 83.1±1.4 kg, respectively (p< 0.001)), and were younger at onset of diabetes (56.7±1.4 versus 62.9±0.6 years, respectively (p< 0.001)). Acarbose was prescribed in only 10 patients (2.1%) and 13 patients (2.8%) started oral treatment with two drugs simultaneously, predominantly a combination of metformin and a sulfonylurea.

In 398 patients (66%) fasting and/or non-fasting blood glucose (FBG and NFBG) at diagnosis was recorded in the medical file. Mean FBG and NFBG values were 10.8 (SD 4.0) and 14.6 (5.8), respectively. In a subsample of patients
with both measurements available, fasting and non-fasting blood glucose levels at diagnosis (n=185) showed a moderate correlation (Spearman’s r=0.43, p<0.001). As shown in Figures 2.2a and 2.2b, initiation of hypoglycemic drug therapy was strongly related to glucose level at diagnosis.

Figure 2.2 a and 2.2 b  Start of oral hypoglycemic therapy and glucose levels at diagnosis
Time to treatment increased from 0.2 (SD 0.6, FBG > 13.1 mmol/l) to 1.4 years (1.5, FBG < 7.9 mmol/l); test for trend p< 0.001. In a Cox’ regression analysis, adjusted for age at onset of diabetes and gender, this relationship remained statistically significant; HRs were 1.7 (2nd quartile), 2.2 (3rd) and 2.9 (4th), respectively, compared to the group with lowest FBG values. Patients starting immediately with tablets to control their hyperglycemia had higher blood glucose values at diagnosis compared to patients (N=136) who remained on dietary treatment only; fasting blood glucose: 12.3±0.3 versus 8.9±0.4 mmol/l (p< 0.001), non-fasting blood glucose: 16.6±0.5 versus 11.6±0.7 mmol/l (p< 0.001).

Figure 2.3 shows the association between level of hyperglycemia at diagnosis, according to quartiles of fasting blood glucose values, and future glycemic control (most recent HbA1c measurement available, N=193). The association between NFBG at diagnosis and actual glycemic control followed a similar pattern (data not shown, N=177). Glycemic control differed significantly between groups, also after adjustment for age and duration of diabetes (p= 0.016). The lowest quartile (1st quartile: FBG < 7.9 mmol/l) had significantly better control than patients in the 3rd and 4th quartiles. The mean duration of diabetes at the time of this measurement was 2.4 years and did not differ between quartiles. Patients who remained on dietary treatment only had significantly lower HbA1c levels compared to patients who started oral glucose therapy immediately following diagnosis and patients who started oral therapy later; 0.6% points (CI95%: 0.2-1.0) and 0.7% points (CI95%: 0.2-1.2) lower, respectively (adjusted for age, gender and duration of diabetes).

In groups of patients with similar glucose levels at diagnosis (defined by tertiles of FBG and NFBG levels), immediate initiation of glucose lowering medication was not significantly related to future glycemic control. Only, in the highest tertiles (FBG > 11.9 mmol/l and NFBG > 16.2 mmol/l respectively) patients showed a tendency towards better future glycemic control when they immediately started pharmacological treatment. In the highest tertile of FBG, proportions of patients with good, fair and poor control respectively were 32%, 40%, 28% in the ‘immediate starters’ compared to 25%, 25%, 50% in the other patients.
Initiation of insulin therapy was not related to glucose levels at diagnosis, but among switchers to insulin the time to treatment with insulin shortened with increasing blood glucose level, from 2.9 years (NFBG < 11.4 mmol/l) to 1.3 years (NFBG > 16.2 mmol/l); test for trend, p= 0.05, adjusted for age and gender. Patients who switched were younger at diagnosis, 57.8±1.7 versus 62.7±0.6 years (p= 0.001) compared to non-switchers.

**Figure 2.3** Glucose level at diagnosis and future glycemic control

Asterisks: p< 0.01, metabolic control compared to the first quartile
Definition of glycemic control:
Poor: HbA1c > 8.5%
Acceptable: HbA1c between 7.0-8.5%
Good: HbA1c < 7.0%
Discussion

We assessed determinants of initiation of pharmacological glucose lowering treatment in newly diagnosed type 2 diabetes mellitus patients in general practice. Fifty-three percent of the patients started immediately with blood glucose lowering therapy. The strongest predictors of time to drug therapy were fasting and non-fasting blood glucose levels at diagnosis. Also, a tendency to prescribe oral hypoglycemic agents sooner in men than women was shown, although not statistically significant. Furthermore, blood glucose levels at diagnosis of diabetes predicted future glycemic control; patients in the lowest quartiles had significantly lower future HbA1c levels, independent of actual glucose lowering therapy.

In the United Kingdom Prospective Diabetes Study, level of hyperglycemia at diagnosis was also associated with poorer prognosis: patients with high glucose levels suffered from more subsequent cardiovascular disease, ischemic heart disease in particular, retinopathy, erectile dysfunction, and showed progressive requirement for multiple therapies.11, 12, 13 Furthermore, it is known that hyperglycemia is independently strongly related to higher mortality and cardiovascular morbidity rates.14-19

Strength of this study is the use of routinely collected primary care data, which reflect usual clinical care. General practice networks provide databases that may fruitfully be used for research. The use of computerized databases permits analyses of diagnostic, treatment and prescribing patterns in different patient groups within the general population. These databases enhance access to health related information of large groups of patients over a long period of time.20, 21 From other studies, it is known that the sensitivity of general practice registries in identifying patients with diagnosed diabetes exceeds 90%.22

Some limitations of this study need to be addressed. In only 66% (398/603) of the patients a blood glucose value at diagnosis was recorded in their medical file. Partly, this can be explained by the fact that a considerable proportion of type 2 diabetes mellitus patients is diagnosed by an accidental finding of increased glucose level in routine laboratory examinations performed in hospitalized patients. Furthermore, data on body weight and body mass index were scarce. The presence
(or absence) of obesity is of great importance in the etiology and treatment spectrum of type 2 diabetes.

Early in the course of the disease when insulin resistance and hyperinsulinemia characterize diabetes, energy restriction not related to weight loss and moderate weight loss (5-10% of body weight) have been shown to improve hyperglycemia. Moreover, intentional weight loss in overweight individuals with type 2 diabetes is also associated with substantial reductions in mortality. While the disease progresses and insulin deficiency becomes the central issue, it may be too late for weight loss to be helpful. According to the Dutch guidelines for type 2 diabetes mellitus patients, pharmacological treatment has to be considered if target levels of glycemic control are not achieved after a dietary treatment period of at least three months. However, the results of this observational study in general practice show that in about half of the patients with type 2 diabetes GPs started drug treatment immediately following diagnosis. Although patients who immediately started with hypoglycemic drugs had higher glucose levels at diagnosis compared to the remaining subjects, GPs’ intentions to deviate from the standard for diabetes care remain unclear. Maybe this reflects doubts among GPs about the effectiveness of very time-consuming lifestyle interventions in the majority of the patients. Furthermore, the presence (or absence) of severe hyperglycemic symptoms in the individual patient is likely to play an important role in making this decision. However, we did not take any subjective measurements, like patients’ complaints, into account. Moreover, lack of financial support and insufficient availability of dieticians may also be important issues. It is also possible that GPs are likely to register patients as having type 2 diabetes at the moment oral hypoglycemic therapy is started, leading to a certain degree of selection bias.

One might expect hyperglycemia to be treated more aggressively in patients with a worse cardiovascular profile or even established cardiovascular disease at diagnosis of diabetes. However, we found time to start of oral glucose lowering therapy not to be associated with a history of cardiovascular disease and cardiovascular risk factors such as body weight, blood pressure, and total serum cholesterol. Maybe there is still lack of awareness among GPs of the importance to
treat diabetes as a multifactorial disease. On the other hand, current targets for glycemia, lipids and blood pressure are attainable in only 50%-70% of individuals with type 2 diabetes.26

We were intrigued by the observation that a small proportion (about 17% after 3 years of diabetes) of the patients remained on dietary treatment only for a long time and nevertheless still achieved good glycemic control (HbA1c < 7.0%). In the UKPDS those patients were termed ‘diet satisfactory’ and excluded from the analysis after the 3-month run-in period. Of the initially 4,075 included newly diagnosed type 2 diabetes patients, after 3 years 357 (11.5%) patients and even after 9 years 115 (8.6%) patients maintained fasting plasma glucose levels < 6.0 mmol/l on diet only.11 The most likely explanation for this observation is that type 2 diabetes may be a curable disease in moderate obese patients who can achieve sufficient weight loss.27-29 Alternatively, part of these patients may have been incorrectly diagnosed as having type 2 diabetes mellitus.

In conclusion, this study shows that the initial severity of diabetes, assessed by the degree of hyperglycemia at the time of diagnosis, is a major factor in determining the time to start of pharmacological treatment of diabetes and the likelihood of achieving target levels of glycemic control in the future, independent of glucose lowering strategy. Furthermore, the findings indicate that more research is needed on the patients who remain on diet only for a long time while achieving good glycemic control.
Chapter 2

References

Initiation of glucose lowering therapy


