# Type 2 Diabetes Mellitus Treatment Strategies in Primary Care: *Utrecht Diabetes Epidemiology Studies*

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# Type 2 Diabetes Mellitus Treatment Strategies in Primary Care: *Utrecht Diabetes Epidemiology Studies*

Behandelingsstrategieën van type 2 diabetes mellitus in de eerstelijns gezondheidszorg:
*Utrecht Diabetes Epidemiologie Studies*

(met een samenvatting in het Nederlands)

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Imagination is more important than knowledge

*- Albert Einstein*

***Voor papa en mama***

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# Contents

# CHAPTER 1

# Introduction

## Introduction

Diabetes mellitus is defined by chronically increased blood glucose levels, e.g., 'hyperglycemia', and is classified into two major diseases: type 1 and type 2. Type 1 diabetes is defined as the absolute deficiency of insulin secretion and the absence of C-peptide, and type 2 diabetes as the combination of resistance to insulin action and an inadequate compensatory insulin secretory response of the pancreatic beta-cell.[1, 2] Diabetes mellitus affects approximately 5% of the general population. Type 2 diabetes accounts for about 85-90% of all patients with diabetes mellitus.[3]

The prevalence of patients with type 2 diabetes mellitus increases rapidly and will be doubled worldwide in 2010 compared to 1999. In the Netherlands, a prevalence of diabetes mellitus of 8.3% was found in a population of 50-74 year old subjects[4]; the overall prevalence of patients with type 2 diabetes is currently approximately 300,000 and is expected to increase to 400,000 – 500,000 by 2010.[5]

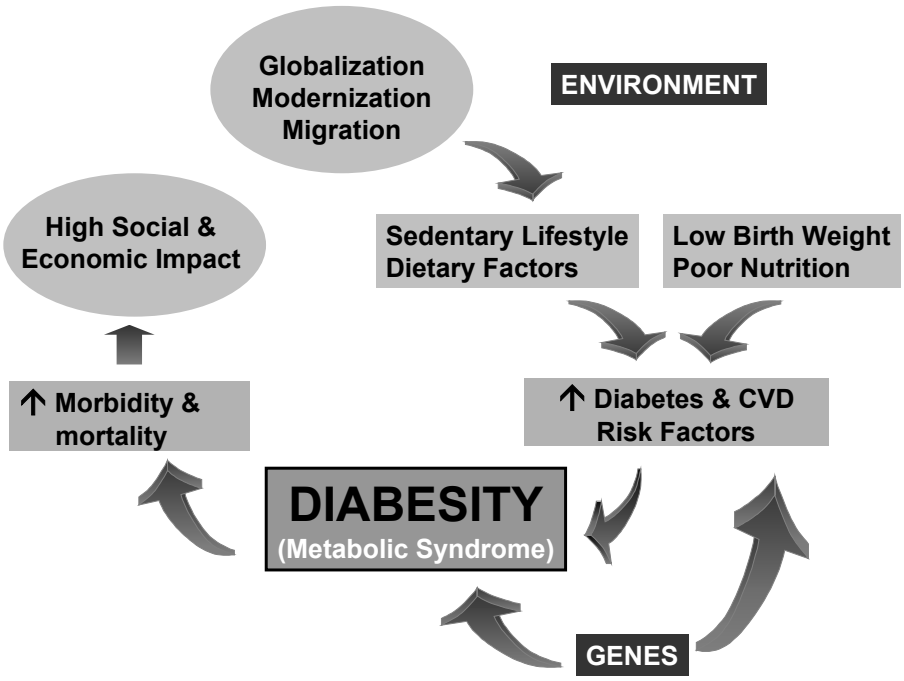


**Figure 1.1** The metabolic syndrome; genes and environment interacting

Changes in lifestyle such as decreased physical activity, increasing obesity and changes in food consumption, and ageing of the population have been implicated in this epidemic.[6] These unfavorable lifestyle habits accompanied by a higher risk for the development of insulin resistance and type 2 diabetes is also referred to as 'diabesity' (*Figure 1.1*).

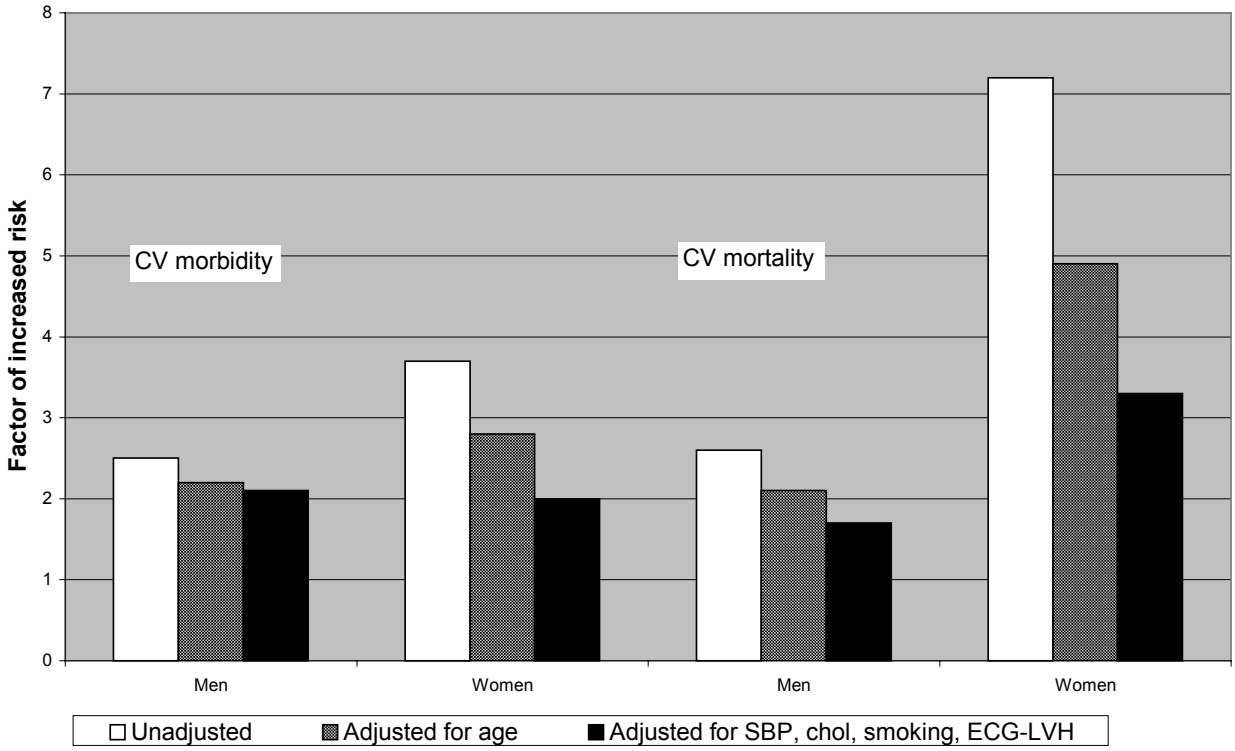


**Figure 1.2** Risk of cardiovascular events in diabetics versus non-diabetics aged 45-74 years. Adapted from the Framingham Study.[13]

Patients with type 2 diabetes have an increased risk of morbidity and mortality from microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (myocardial infarction, stroke, and peripheral vascular disease) complications.[7, 8] Patients with type 2 diabetes have a two- to fourfold increase in cardiovascular risk and 80% of them will eventually develop cardiovascular disease (*Figure 1.2*).[9-13] Part of the increased risk may be explained by the observation that type 2 diabetes mellitus clusters with several other cardiovascular risk factors.[14-16] This clustering of metabolic and cardiovascular disorders has been referred to as

the Insulin Resistance Syndrome (IRS) or metabolic syndrome, including insulin resistance, hyperglycemia, obesity, dyslipidemia, and hypertension.[14, 17]

The pathogenesis of type 2 diabetes mellitus is thought to involve an interaction of environmental factors with genetic susceptibility (*Figure 1.1*).[18, 19] In patients with type 2 diabetes and established fasting hyperglycemia, the rate of basal hepatic glucose production is excessive, despite plasma insulin secretions that are increased. Furthermore, defects in insulin receptor function, insulin receptor-signal transduction pathway, glucose transport and phosphorylation, glycogen synthesis, and glucose oxidation contribute to muscle insulin resistance.[20] Impaired insulin secretion also plays a major role in the pathogenesis of glucose intolerance in patients with type 2 diabetes.[1] Although debate still continues about which defect – insulin resistance or impaired insulin secretion – initiates the cascade of events leading to overt diabetes mellitus, patients with type 2 diabetes mellitus eventually are characterized by defects in both insulin secretion and insulin action.[21]

## The importance of glycemic control in type 2 diabetes mellitus

Aggressive management of hyperglycemia aims to reduce microvascular and/or macrovascular complications in patients with type 2 diabetes. More definitive information on the relation between improved glycemic control and prevention of complications was recently provided by the United Kingdom Prospective Diabetes Study (UKPDS).[22-25] The main purpose of this randomized clinical trial was to investigate whether intensive treatment to control glucose levels in people with newly diagnosed type 2 diabetes is effective in reducing the incidence of clinical complications in a study lasting 20 years. The median follow-up was 10.0 years; during this period a difference in $HbA_{1c}$ values of 0.9 percentage points (7.0% compared with 7.9%, $p< 0.001$) was maintained between the group assigned to intensive therapy (sulfonylureas, insulin, or metformin) and the group assigned to conventional therapy (diet).

The main conclusions of the study were that intensive glucose lowering treatment reduced diabetes-related events ($p= 0.03$), mainly as a consequence of improved

microvascular outcomes (background retinopathy in particular, p= 0.01). There was however only a borderline significant risk reduction in myocardial infarction (-16%, p= 0.052) and no effect on diabetes-related mortality or all-cause mortality in the group receiving intensive treatment.[24]

Results from several other studies have similarly raised the possibility that treatment with agents that increase insulin levels (i.e. sulfonylureas and exogenous insulin) may actually be detrimental.[26-29] Treatments that are effective in lowering glucose levels can have simultaneous effects on other cardiovascular disease risk factors and should be considered when identifying appropriate therapy for individual patients. Sulfonylureas and insulin may cause weight gain and hypoglycemia, but insulin treatment has been shown to improve lipid abnormalities in people with type 2 diabetes.

Metformin can be considered an effective treatment to improve glycemic control in obese type 2 diabetic patients[30, 31] and has a beneficial effect on the diabetic lipid profile that is particularly characterized by low high-density lipoprotein (HDL)-cholesterol concentrations and hypertriglyceridemia.[32, 33]

## Switching therapies in type 2 diabetes patients: a 'normal' course of events?

The UKPDS showed that type 2 diabetes mellitus is a chronic progressive disorder (*Figure 1.3*).[22, 24, 25] After an initial and similar decrease in the $HbA_{1c}$ value with metformin, sulfonylureas, or insulin, the rate of increase in this level was identical to that in the group treated with diet therapy. This important observation emphasizes the need for constant reassessment of the diabetic patient and appropriate adjustment of the therapeutic regimen in order to maintain the desired level of glycemic control.[22]

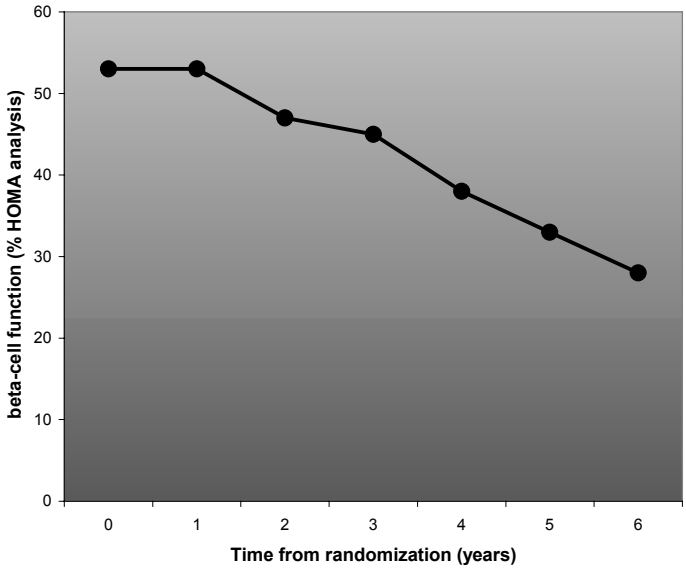


**Figure 1.3** Type 2 diabetes mellitus is a progressive disease: beta-cell function deteriorated to 28% in UKPDS diet-treated patients (adapted from the UK Prospective Diabetes Study Group. Diabetes 1995; 44:1249-1248)

Type 2 diabetes generally affects older people in whom the side effects of improved glycemic control may be less acceptable. On the basis of the results reviewed above, it seems most prudent to reduce blood glucose in patients with type 2 diabetes to levels as close to normal as possible while avoiding symptomatic hypoglycemia. Effective treatment will require the combined use of diet, exercise, oral agents, and insulin.[22]

*Stepwise treatment of type 2 diabetes*

The treatment of type 2 diabetes mellitus includes a number of sequential steps to lower hyperglycemia. These comprise the cornerstone of treatment of type 2 diabetic patients.

According to the Dutch and international guidelines, target levels of glycemic control (capillary whole blood) are as follows[34-36]:

| | Good | Acceptable | Poor |
|---|---|---|---|
| Fasting glucose (mmol/l) | 4-7 | 7-8 | > 8 |
| $HbA_{1c}$ (%) | < 7 | 7-8.5 | > 8.5 |

*Step 1*: Lifestyle recommendations, referral to dietician, after three months checking of blood glucose values.

*Step 2*: After dietary failure, initiate pharmacologic treatment with a sulfonylurea derivative (for instance tolbutamide 500 mg once daily) in patients having a BMI < 27 kg/$m^2$ and with metformin (500 mg once daily) in obese patients (BMI > 27 kg/$m^2$). Start with the lowest dose, increase every 2-4 weeks until target values are achieved.

*Step 3*: If step 2 fails, add metformin or sulfonylurea, respectively. If a patient has contra-indications or suffers from unpleasant side effects: replace the relevant agent with acarbose (50 mg three times daily). Combination therapy of three or even more agents is not recommended.

Eventually, in diabetic patients in whom glycemic control is not achieved with maximal combined oral agent therapy, several options are available[37]: addition of bedtime insulin in combination with oral treatment, switching to a mixed-split insulin regimen, or addition of a third oral agent. If oral treatment fails (secondary failure), addition of or switching to insulin is the final therapeutic option. Self-monitoring of blood glucose takes an important place in this treatment strategy.

According to the Dutch guidelines for type 2 diabetes mellitus patients, 3-monthly and yearly check-ups are recommended. Fasting blood glucose (patients on diet or users of oral hypoglycemic agents) or a glucose curve (users of insulin)

are advised to be determined at the 3-monthly check, whereas blood pressure, fasting blood glucose, $HbA_{1c}$, creatinin, total cholesterol, HDL-cholesterol, and triglycerides are recommended to be performed at the yearly check. Diet and exercise must be emphasized even after pharmacological treatment has begun.

## Insulin therapy in the primary care setting

It is important to recognize that, ultimately, most patients with type 2 diabetes will require treatment with insulin, either alone or in combination with an oral agent to achieve sufficient glycemic control.[38] Numerous studies have shown that excellent glycemic control can be achieved with intensive insulin therapy in patients with type 2 diabetes.[38, 39] Recently, Dandona *et al* suggested even an anti-inflammatory and potential anti-atherogenic effect of insulin.[40] These research results suggested there should be little hesitation about using insulin either alone or in combination with oral agents if glycemic control cannot be attained with oral agents alone.[41-43]

However, most studies of intensive insulin therapy have been carried out in academic settings, using strict (research) protocols with specialty teams devoted to patient care. For instance, Goddijn studied prospectively a cohort of patients referred by general practitioners to an outpatient department for consideration of insulin therapy.[44] In contrast, most primary care physicians do not have specialized training in insulin use and management of its complications, do not have sufficient time to follow up patients at frequent intervals to ensure appropriate adjustment of the insulin dose, and do not have diabetes specialty teams to assist them. Moreover, the diabetes mellitus guidelines of the Dutch College of General Practitioners provide no clear indication when insulin should be given or when a patient should be referred to a specialist.[34]

Hayword and coworkers examined insulin therapy prescribed by general practitioners in a large staff-model health maintenance organization.[45] In 1738 insulin-treated patients with type 2 diabetes the mean decrease in $HbA_{1c}$ value was 0.9 percentage points, and 60% of patients had a $HbA_{1c}$ value that exceeded 8.0% at 2 years. In a parallel cohort, 43% of patients who were taking sulfonylureas had an $HbA_{1c}$ value that exceeded 8.0%. One can raise criticisms about this study, but the results do not indicate any superiority of insulin over sulfonylureas or vice

versa in a primary care setting. Although performed in a randomized clinical trial setting, the UKPDS also failed to show any advantage of insulin over oral agents.[24, 25]

## The general practitioner (GP): a key agent in the dynamics of type 2 diabetes mellitus care

Standards of care for diabetes have been widely disseminated since the late 1980s[36], but primary care providers have been slow to adopt the recommended screening and treatment guidelines. Yet, while there is an extensive literature on patients' beliefs and attitudes that affect adherence to recommended treatment regimens, little is known, by comparison, about GP beliefs and attitudes that may interfere with their adherence to current standards of care. In a study by Larme and Pugh on barriers to guideline implementation, GPs rated diabetes as significantly harder to treat than hypertension and angina pectoris.[46] Explanations for frustrations with diabetes care include the characteristics of the disease itself and the complexity of its management, and a perceived lack of support from society and the health care system for their efforts to control diabetes.[46, 47]

In particular, physicians are weary of treading the fine line between tight control and hypoglycemia. Furthermore, diabetes is harder for GPs to treat than other chronic conditions because its successful management relies to a great extent on lifestyle change, which is largely beyond GP's control.[48] Diabetes treatment is also difficult because although GPs may feel considerable urgency to control diabetes, their patients do not and still think of type 2 diabetes as a 'mild' disease.

In the evaluation of the quality of care the concepts of efficacy and effectiveness are important. Efficacy is the achieved optimal effect under ideal circumstances (randomized clinical trials, experiments) and effectiveness is the maximal attainable effect under everyday circumstances (routine practice). There are several factors explaining the gap between research and practice. Achieving good diabetic control is affected by the doctor's attitude and practices and by the patient's understanding of the disease and the extent to which they will alter their lifestyle in the quest for good blood glucose control. Therefore, both doctor and patient can contribute to increase the effectiveness of diabetes care. In addition, several pharmaceutical care

interventions may help to improve the effectiveness of diabetes care in general [49-52], and cardiovascular risk management in particular.[53, 54]

## UDES framework

The *Utrecht Diabetes Epidemiology Studies* (UDES) were initiated to study the effectiveness of diabetes care and drug therapy outcomes in diabetes (i.e. glycemic control, micro- and macrovascular complications), to evaluate the management of risk factors (i.e. cardiovascular disease, pregnancy, psychiatric disorders, poor compliance), and to investigate innovation in diabetes therapy. For the studies, a database comprising pharmacy, hospital admission and general practitioner data was established to gain more insight in the treatment of diabetes mellitus in daily clinical practice.

Evidence of a drug's efficacy from randomized controlled clinical trials is often obtained in selected patient groups who typically have less comorbidity than the patients who receive these drugs in clinical practice.[55, 56] More insight in the effectiveness of treatment of type 2 diabetes mellitus patients in actual daily practice and the possible extrapolation of artificial trial results may be obtained by using data that are routinely collected in primary care and community pharmacies. As type 2 diabetes commonly coexists with concomitant diseases and risk factors, polypharmacy is often indicated. Optimal pharmacotherapy of these diseases and risk factors is more complicated than the treatment of these conditions without the presence of other diseases.[57] Therefore, observational studies have the advantage to provide us with information about longitudinal effects of treatment.

Moreover, because type 2 diabetes is a chronic, incurable and progressive disorder, constant reassessment of glycemic control and treatment regimen is needed. Switching between therapeutic options (life style intervention, start of oral drug treatment, increasing doses and eventually changeover to insulin) takes an important position in optimizing the treatment of the patient with type 2 diabetes mellitus.

## Outline of the thesis

As outlined in the text above, treatment of type 2 diabetes is (still) far from ideal. Practitioners are in the middle of making constantly decisions having on one hand extensive treatment guidelines, recommendations, et cetera (mostly based on more or less artificial trial results) and on the other hand a care and treatment demanding patient. It is even more complicated, the person by that hand is frequently not feeling or perceiving him/her self as a patient, but because some 'tests' say he or she is, something has to be done.

And current medical evidence says something needs to be done otherwise the risk of both micro- and macrovascular complications will be high. Studying determinants of glucose lowering drug use and their effects may help to explore the gap between clinical practice and evidence (as recommended in guidelines and standards for care of type 2 diabetes). In this thesis, we will meet each other in a number of studies where the treatment of type 2 diabetes mellitus has been assessed with regard to determinants and effects of the hub-and-spoke switching between the individual glucose lowering treatment strategies. The results of these studies will quantify the influence of patient characteristics on changes in glucose lowering treatment strategies. Based on these outcomes a GP can improve the prognosis of her/his diabetic patients by pushing forward the implementation of necessary changes in the individual treatment strategy.

We defined two relevant outcomes in the course of type 2 diabetes treatment strategy:

1. Start of oral drug therapy following life style intervention (diet, exercise);
2. Switch to insulin therapy.

Intermediate changes in glucose lowering therapy were also examined, like intensification of oral drug therapy by increasing doses or combining drugs.

The specific study aims were:

### Start of oral hypoglycemic therapy in type 2 diabetes

To investigate determinants of starting oral glucose lowering drug use in newly diagnosed patients in daily practice (*Chapter 2*).

### Determinants and effects of different strategies in type 2 diabetes therapy

To assess whether more intensive glucose lowering therapy results in adequate glycemic control and if more severe diabetes is associated with more advanced cardiovascular disease or intensified cardiovascular treatment (*Chapter 3*).

To determine the effects of cardiovascular drug treatment and blood pressure levels on glycemic control (*Chapter 4*).

### Switching to insulin therapy: determinants and consequences

To investigate which factors are associated with switching from oral hypoglycemic agents to insulin therapy in general practice (*Chapter 5*).

To assess whether switching to insulin is associated with medication refill compliance of oral hypoglycemic agents (*Chapter 6*).

To study the relationship between use of antipsychotic drugs and switching to insulin therapy (*Chapter 7*).

Finally, several type 2 diabetes treatment strategies and suggestions for further research are discussed in *Chapter 8*.

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# 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.[1-4] In the United Kingdom Prospective Diabetes Study (UKPDS), newly diagnosed adults with type 2 diabetes reduced their average $HbA_{1c}$ level from ~9 to 7% after three months of dietary treatment.[1, 5] 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.[6, 7]

In the UKPDS, glycemic control deteriorated gradually with time, even in the intensively treated patients.[5] This worsening of glycemic control has been attributed to the natural course of type 2 diabetes and lack of efficacy of current hypoglycemic therapy.[5, 8] Recent studies show that early addition of insulin or metformin can significantly improve glycemic control without leading to increased hypoglycemia or weight gain.[1, 8]

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 dispensings was registered in a second database (Pharmacom®). Hospital admission and discharge data were available through the PHARMO Record Linkage System.[9, 10] 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 dispensings, 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.[7] 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)

| Characteristic | Mean (SD) or % | Total number of patients |
|---|---|---|
| Age at onset (years) | 62.0 (13.5) | 603 (100%) |
| Male (%) | 43.4 | 262 |
| Diabetes duration* (years) | 3.0 (1.9) | 603 (100%) |
| $HbA_{1c}$ (%) | 7.6 (1.5) | 317 (53%) |
| Weight (kg) | 83.8 (17.8) | 303 (50%) |
| Body Mass Index ($kg/m^2$) | 28.9 (5.2) | 147 (24%) |
| Fasting blood glucose (mmol/l) | 8.7 (2.5) | 444 (74%) |
| Random blood glucose (mmol/l) | 10.7 (3.8) | 445 (74%) |
| Systolic blood pressure (mmHg) | 150.7 (20.6) | 407 (67%) |
| Diastolic blood pressure (mmHg) | 86.4 (10.5) | 405 (67%) |
| Total serum cholesterol (mmol/l) | 5.7 (1.0) | 373 (62%) |
| HDL cholesterol (mmol/l) | 1.20 (0.31) | 265 (44%) |
| Ratio HDL/ Total cholesterol | 5.2 (1.5) | 249 (41%) |
| LDL cholesterol (mmol/l) | 3.60 (0.95) | 178 (30%) |
| Triglycerides (mmol/l) | 2.54 (2.34) | 265 (44%) |
| Serum creatinine (mmol/l) | 84.1 (23.0) | 369 (61%) |
| History of cardiovascular disease (%) | 21.2 | 127 |
| Ischemic heart disease (excl. MI) | 11.3 | 68 |
| Myocardial infarction | 7.1 | 43 |
| Heart failure | 3.6 | 22 |
| CVA, TIA | 7.0 | 42 |
| Switchers to insulin therapy (%) | 10.9 | 66 |

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; $HbA_{1c}$: glycosylated 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, $CI_{95\%}$: 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).

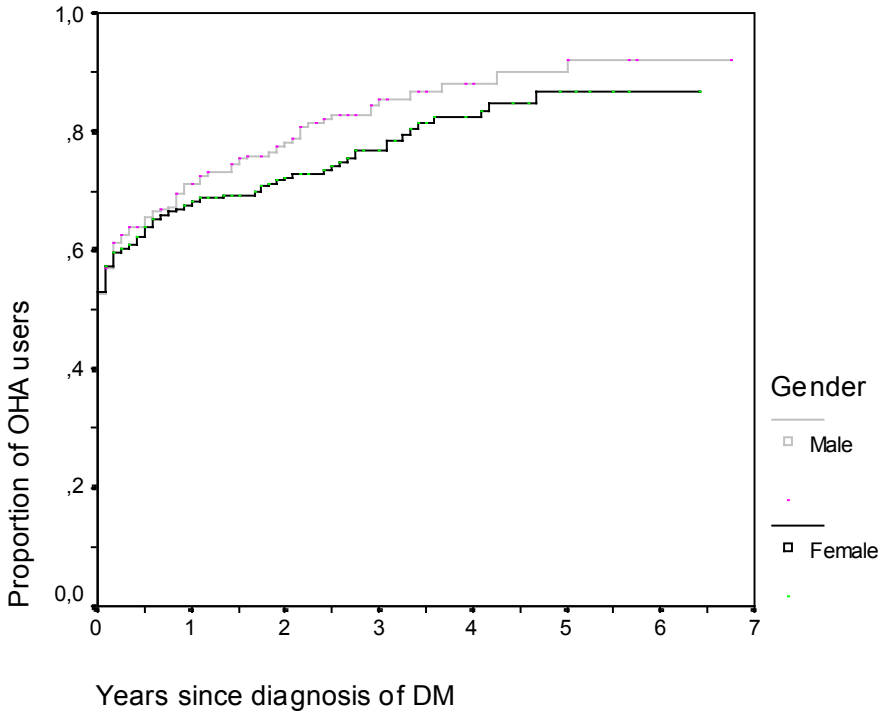



**Figure 2.1** Start of oral hypoglycemic agent (OHA) use after diagnosis of diabetes

*Start of oral hypoglycemic therapy in newly diagnosed patients*

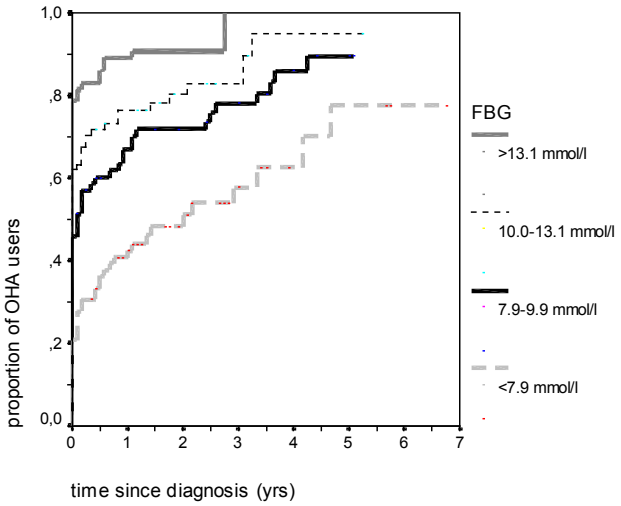
*Figure 2.1* represents the cumulative incidence (Kaplan Meier curve estimate) of glucose lowering drug use in newly diagnosed type 2 diabetes mellitus patients. Of the incident type 2 patients, 319 (53%) started immediately (in the first month following diagnosis) with oral therapy. One, two, and three years after diagnosis of diabetes the cumulative incidences were 71% ($CI_{95\%}$: 66-73%), 75% ($CI_{95\%}$: 71-79%), and 81% ($CI_{95\%}$: 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.

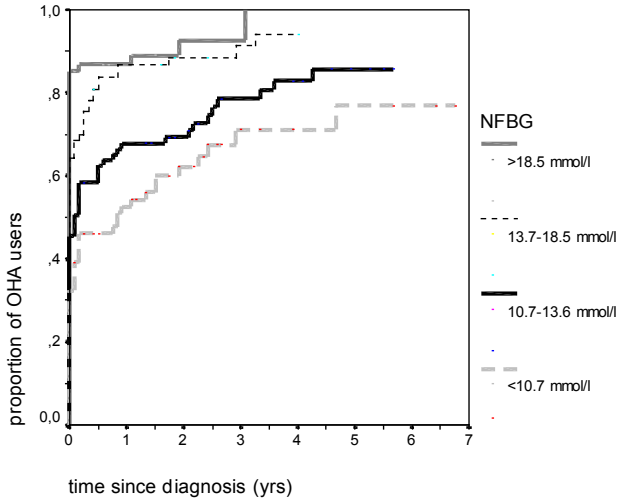
In more than half of the patients (51.8%), tolbutamide was the drug of first choice, followed by a second-generation sulfonylurea (gliclazide, glibenclamide, glimepiride, and glipizide; 30.4%), and metformin (18.2%). Patients who started with metformin weighed significantly more than other patients (97.3±3.0 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.




**2.2 a** Fasting blood glucose and time to drug treatment




**2.2 b** Non-fasting blood glucose and time to drug treatment

**Figure 2.2 a and 2.2** 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 $HbA_{1c}$ 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 $HbA_{1c}$ levels compared to patients who started oral glucose therapy immediately following diagnosis and patients who started oral therapy later; 0.6% points ($CI_{95\%}$: 0.2-1.0) and 0.7% points ($CI_{95\%}$: 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.

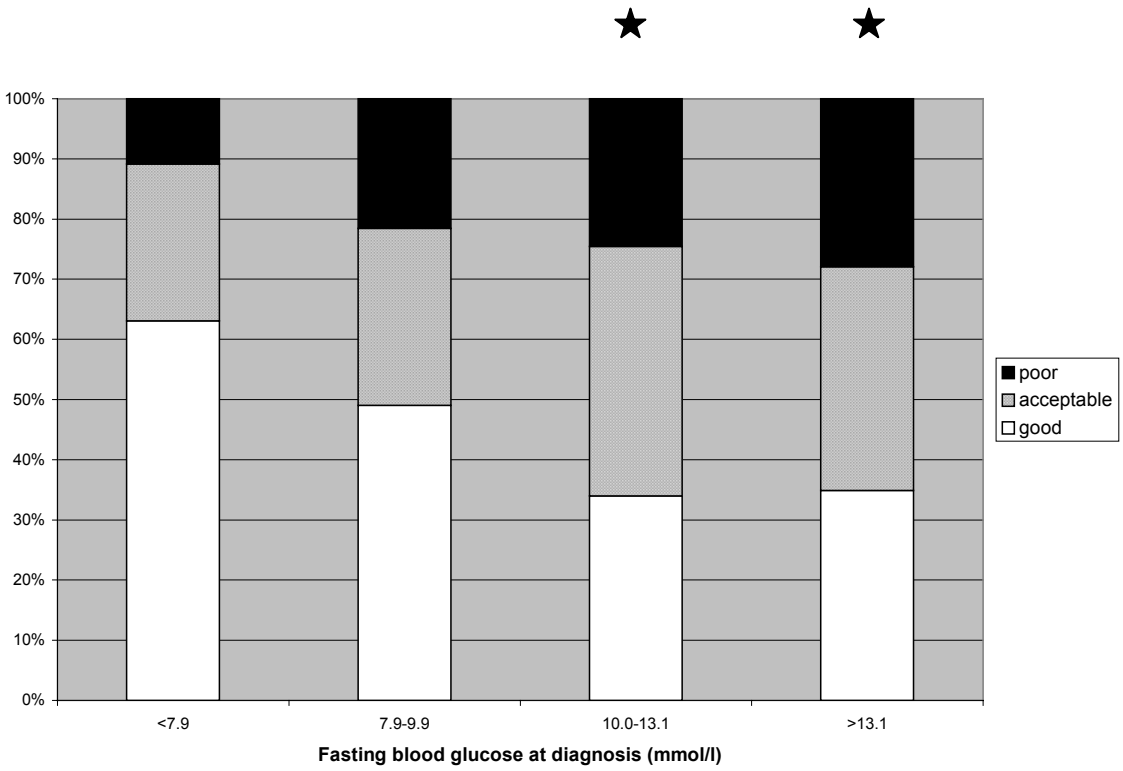



**Figure 2.3** Glucose level at diagnosis and future glycemic control

Asterisks: p< 0.01, metabolic control compared to the first quartile
Definition of glycemic control:
Poor: $HbA_{1c}$ > 8.5%
Acceptable: $HbA_{1c}$ between 7.0-8.5%
Good: $HbA_{1c}$ < 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 $HbA_{1c}$ 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, its 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.[23, 24] Moreover, intentional weight loss in overweight individuals with type 2 diabetes is also associated with substantial reductions in mortality.[25] 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.[7] 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 ($HbA_{1c}$< 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.

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# CHAPTER 3

# Glucose Lowering Therapy and Cardiovascular Risk Management in Type 2 Diabetes Mellitus: a Population-Based Study in General Practice

## Abstract

*Aim* - Glucose lowering therapy in type 2 diabetes includes successive steps, but little is known about control of hyperglycemia and cardiovascular risk factors in daily practice when treatment is intensified. Aim of our study was to investigate whether more intensive glucose lowering therapy results in adequate glycemic control and if more severe diabetes is associated with more cardiovascular disease and/or intensified cardiovascular drug treatment.

*Methods* - In a cross-sectional study, including patients with type 2 diabetes mellitus in general practice, the association between glucose lowering treatment and the occurrence of cardiovascular morbidity and treatment was examined by regression analyses. Four modalities of glucose lowering therapy were compared: dietary treatment only, sulfonylurea (SU) therapy only, metformin (with or without SU), and insulin therapy.

*Results* - In total, 1,072 patients with type 2 diabetes mellitus were included in the study. In only 60-85% of these patients studied in routine primary care, relevant metabolic measurements were available. Fasting plasma glucose and mean $HbA_{1c}$ increased significantly with escalating glucose lowering therapy. The proportion of patients with well-controlled diabetes decreased from 53% (diet only) to 10% (insulin). The overall prevalences of hypertension and hypercholesterolemia were 66% and 71% respectively, among those who had recordings of blood pressure (N=748) and lipid levels (N=647) available. While stepping up hypoglycemic treatment, the prevalence of hypertension increased, and the level of diastolic and systolic blood pressure remained stable. With respect to lipid metabolism and cardiovascular events no notable differences were found between the treatment groups, only the prevalence of heart failure was higher in insulin treated patients.

*Conclusion* - Increased intensity of glucose lowering therapy was significantly associated with poorer glycemic control, higher body weight and increased prevalence of hypertension. Despite deterioration of glycemic control with intensified glucose lowering treatment, control of other metabolic risk factors such as high blood pressure and cholesterol remained stable, probably due to increased prescribing of cardiovascular drug therapy.

## Introduction

People with type 2 diabetes mellitus have a two- to fourfold increased risk of dying of heart disease, and the co-existence of classic risk factors (hypertension, elevated serum cholesterol, and smoking) increases this risk substantially – probably to a greater extent than in nondiabetic individuals.[1-4] In the United Kingdom Prospective Diabetes Study (UKPDS), glycemic control deteriorated progressively over time, even in the intensively treated patients.[5] This worsening of glycemic control has been attributed to the natural course of type 2 diabetes and the eventual lack of efficacy of current hypoglycemic therapy.[6, 7]

Because epidemiological analyses showed a continuous association between the risk of cardiovascular complications, mortality and level of glycemia in diabetes mellitus patients, adequate glycemic control remains very important.[8, 9] This is also emphasized in current type 2 diabetes mellitus guidelines.[10, 11] Glucose lowering therapy currently follows four steps: diet, sulfonylurea derivatives or metformin, combined oral therapy, and eventually insulin. Every next step is initiated when glycemic control is no longer adequate, mostly due to worsening of the disease. If diabetes mellitus is more severe, faster progression of treatment takes place. Because the common aim of glucose lowering therapy is to control hyperglycemia, blood glucose levels should not be different between treatment groups.

It is not yet entirely clear if more severe type 2 diabetes is also related to an increased cardiovascular risk. This would result in increased levels of lipids, blood pressure, body mass index and preferably intensified treatment of cardiovascular disease. However, in the clinical practice of primary care there is often hesitation to intensify drug treatment.[12, 13]

The aim of this study was to investigate whether more intensive glucose lowering therapy results in adequate glycemic control. In addition, we examined if more severe diabetes (assessed by glucose lowering treatment category) was associated with an increased presence of cardiovascular disease or intensified cardiovascular treatment.

## Methods

*Study setting*

This study was performed among patients who received comprehensive primary care from 17 general practitioners (GPs) in a Dutch middle-sized town (n=50,574). All GPs used a single electronic medical record system (Medicom®), which was available for this study, as well as information on drug dispensings from the pharmacist database (Pharmacom®). Hospital admission and discharge data were available through the PHARMO Record Linkage System.[14, 15]

The following data were available: demographic data, medical history, comorbidity (including *International Classification of Primary Care* (ICPC) codes), diabetic complications, drug dispensings, prescribing doctor (specialist, GP), referrals to specialists, and the medical record (a database-file containing free text, as recorded by the GP).

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).

*Subjects*

The total study population consists of all cases with type 2 diabetes mellitus as cared for by the network of collaborating GPs (n=17) during 1992-2000 (n=1,144). In the Netherlands, virtually all patients with diabetes mellitus type 2 visit their GP for regular check-ups. Study subjects were identified from the registries by the use of oral glucose lowering agents or *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 available for the purpose of this study. Subjects in whom the diagnosis of type 2 diabetes remained uncertain, due to incomplete and missing data, were excluded

(N=72). In patients with diagnosed type 2 diabetes but unknown date of diagnosis we relied on January 1990 as a reasonable estimate.

In the analyses the following four categories of glucose lowering therapy were compared: dietary treatment only, sulfonylurea (SU) therapy only, metformin (with or without SU), and insulin therapy (with or without combined oral therapy). The diabetic treatment was defined at the time of the last available (i.e. most recent) measurement of a variable of interest. Therefore, the treatment groups comprise dynamic populations, due to therapeutic changes during course of the disease the actual treatment depends on the moment of the variable measured. Presence of cardiovascular morbidity and treatment was defined on basis of: blood pressure, total serum cholesterol level, fasting plasma glucose, $HbA_{1c}$, total cholesterol/HDL ratio, and body weight.

Hypertension was defined as systolic blood pressure > 140 mmHg (in patients older than 60 years > 160 mmHg) and/or diastolic blood pressure > 90 mmHg[10, 16], or treatment with antihypertensive drugs.

We defined hypercholesterolemia as a total serum cholesterol > 5.0 mmol/l in concordance with the Dutch guidelines[10, 16], or use of lipid lowering drugs. Blood pressure and cholesterol levels were considered controlled if these levels were below the above mentioned cut-off points.

Furthermore, we looked at the management of dyslipidemia, according to the standards of medical care for patients with diabetes mellitus of the American Diabetes Association.[11] Optimal LDL cholesterol levels are < 2.60 mmol/l, optimal HDL cholesterol levels are > 1.15 mmol/l in men and > 1.40 mmol/l in women and desirable triglyceride levels are <1.7 mmol/l.[11, 17]

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.[10] Cardiovascular morbidity included: cerebrovascular disease (including cerebrovascular accidents and transient ischaemic attacks, ICPC codes: K89-K91, ICD-9-CM codes: 430-438), myocardial infarction (ICPC: K75, ICD-9-CM: 410), ischemic heart disease (ICPC: K74, K76, ICD-9-CM: 411-414), and heart failure (ICPC: K77, ICD-9-CM: 428). Hospitalization data were available from January 1992-July 1999, meaning that

from July 1999 until August 2000 we relied on general practitioner's data only to assess the incidence of cardiovascular events.

*Data analysis*

For categorical variables, numbers and percentages and for continuous variables means and standard errors of the mean (s.e.m.) were calculated. For comparison of continuous and categorical variables, we used the Students' t-test and chi-square test, respectively. The association between glucose lowering treatment and cardiovascular risk factors was examined by regression analyses. Depending on the type of outcome variable (continuous or dichotomous), we performed multiple linear or logistic regression, respectively, to estimate regression coefficients and odds ratios (OR) with corresponding 95% confidence intervals (CI). We controlled for potential confounding by age, gender, duration of diabetes, co-morbidity and co-medication.

In the analyses the following four mutually exclusive categories of glucose lowering therapy were compared: dietary treatment only, sulfonylurea (SU) therapy only, metformin (with or without SU), and insulin therapy (with or without combined oral therapy). All analyses were carried out using the statistical package SPSS version 9.0 for Windows.

## Results

In this primary care population (mean age of 61.6±0.4 years and 45% males), the estimated prevalence of (diagnosed) type 2 diabetes mellitus patients was 2.3% (1,144/50,574; $CI_{95\%}$: 2.1-2.4%).

*Table 3.1* shows the general characteristics of the 1,072 patients included in this study. Age at diagnosis of diabetes and duration of disease refer only to patients (N=888) with known date of diagnosis. After imputation (see Methods section) of the missing values with regard to date of diagnosis, the mean age at diagnosis changed slightly to 60.9 ± 0.42 years with an average duration of diabetes of 6.3 ± 0.17 years (N=1,025, 95.6%).

**Table 3.1** General characteristics of patients with type 2 DM (N=1,072)

| Characteristic | Mean or % | Total number of patients |
|---|---|---|
| Age at onset (years) | 61.0 ± 0.45 | 888 (82.8%) |
| Male (%) | 44.1 ± 1.5 | 473/599 |
| Diabetes duration* (years) | 5.7 ± 0.19 | 888 (82.8%) |
| $HbA_{1c}$ (%) | 7.9 ± 0.06 | 573 (53.5%) |
| Weight (kg) | 82.2 ± 0.7 | 523 (48.8%) |
| Body Mass Index ($kg/m^2$) | 28.7 ± 0.36 | 212 (19.8%) |
| Fasting blood glucose (mmol/l) | 8.8 ± 0.09 | 784 (73.1%) |
| Random blood glucose (mmol/l) | 10.8 ± 0.13 | 808 (75.4%) |
| Systolic blood pressure (mmHg) | 152.0 ± 0.73 | 755 (70.4%) |
| Diastolic blood pressure (mmHg) | 86.1 ± 0.36 | 752 (70.1%) |
| Total serum cholesterol (mmol/l) | 5.7 ± 0.04 | 646 (60.3%) |
| HDL cholesterol (mmol/l) | 1.22 ± 0.02 | 450 (42.0%) |
| Total cholesterol/HDL ratio | 5.1 ± 0.12 | 429 (40.0%) |
| LDL cholesterol (mmol/l) | 3.61 ± 0.05 | 305 (28.5%) |
| Triglycerides (mmol/l) | 2.36 ± 0.10 | 447 (41.7%) |
| Serum creatinine (mmol/l) | 87.1 ± 1.12 | 652 (60.8%) |
| History of cardiovascular disease | 27.8 ± 1.4 | 298/774 |
| Ischaemic heart disease (excl. MI) | 15.3 ± 1.1 | 164/908 |
| Myocardial infarction | 9.7 ± 0.9 | 104/968 |
| Heart failure | 5.9 ± 0.7 | 63/1009 |
| CVA, TIA | 10.4 ± 0.9 | 111/961 |

Values are proportions or means ± standard error of the mean (SEM)
* At date of end of study (August 31st 2000) or date of censoring (loss to follow up)
CVA: cerebrovascular accident; $HbA_{1c}$: glycosylated hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MI: myocardial infarction; TIA: transient ischemic attack

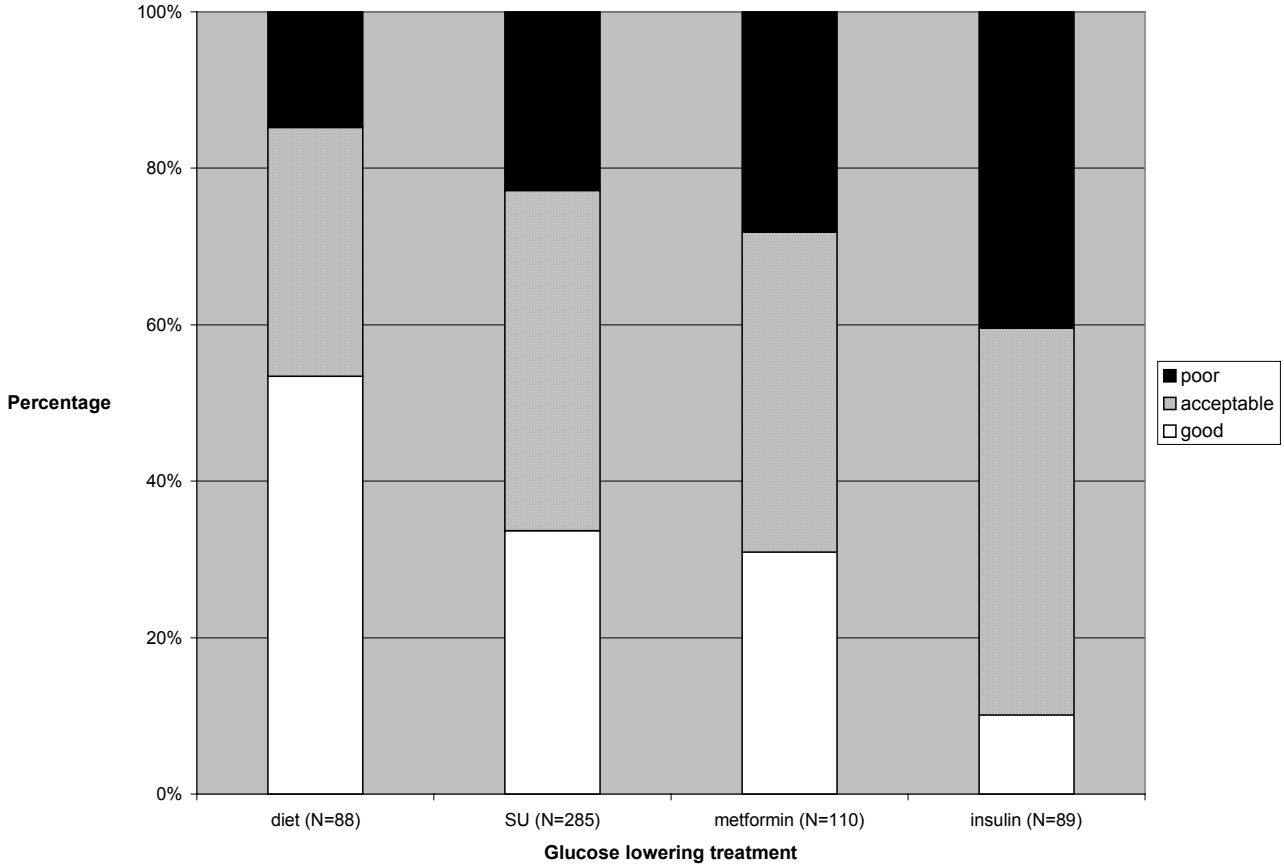


**Figure 3.1** Glycemic control (expressed by $HbA_{1c}$) according to category of glucose lowering treatment

Definition of glycemic control:
Poor: $HbA_{1c} > 8.5\%$
Acceptable: $HbA_{1c}$ between 7.0-8.5%
Good: $HbA_{1c} < 7.0\%$

After a mean duration of 5.7 years (*Table 3.1*), in total 241 (22.5%) patients switched to insulin therapy, and 174 (16.2%) remained on dietary treatment only. In total, 992 (92.5%) patients had at least one of the outcome variables recorded during the study period (after a diagnosis of diabetes).

With respect to glycemic control ($HbA_{1c}$, fasting -, or random blood glucose), 934 (87.1%) patients had at least one measurement registered. At least one of the variables of the lipid spectrum (total cholesterol, HDL, LDL, or triglycerides) was recorded in 647 (60.1%) patients. Among patients with measurements available, 24%, 38%, 11% and 45% had optimal mean levels with regard to total serum cholesterol, HDL cholesterol, LDL cholesterol and triglycerides, respectively. No differences in (recorded) prevalence of cardiovascular disease in general between both sexes were observed. History of myocardial infarction was more frequent in males (OR 1.7, $CI_{95\%}$: 1.1-2.5), while females more often suffered from heart failure (OR 2.7, $CI_{95\%}$: 1.5-4.8).

*Glycemic control and body weight*

Fasting plasma glucose increased significantly with type of glucose lowering therapy (test for trend: $p<0.001$, *Table 3.2*). In the group treated with diet only, the mean fasting plasma glucose was 7.6±0.3 mmol/l, while in the sulfonylurea, metformin and insulin treated patients glucose levels were 0.8, 1.2, and 1.6 mmol/l higher, respectively. Mean $HbA_{1c}$ levels also differed significantly between treatment groups (*Table 3.2*). *Figure 3.1* shows the glycemic control in the four groups of glucose lowering treatment. For example, the proportion of patients with well-controlled diabetes varied from 53% (dietary treatment) to 10% (insulin therapy).

Patients on metformin and/or insulin therapy were more obese than patients in both other groups, with both a mean body weight of about 85 kg, compared to 80.3 kg in the patients on diet only, and 79.3 kg in sulfonylurea users. This difference was more marked in males than females (*Table 3.2*); male patients using metformin or insulin weighed about 10 kg more.

**Table 3.2** Metabolic and risk factors by category of glucose lowering treatment

| Variable | Diet | SU | Metformin | Insulin | P-value* |
|---|---|---|---|---|---|
| FBG (mmol/l) | 7.6 ± 0.2 | 8.4 ± 0.2 | 8.8 ± 0.3 | 9.2 ± 0.3 | <0.001 |
| $HbA_{1c}$ (%) | 7.1 ± 0.1 | 7.8 ± 0.1 | 8.0 ± 0.2 | 8.4 ± 0.2 | <0.001 |
| Total cholesterol (mmol/l) | 5.7 ± 0.1 | 5.5 ± 0.1 | 5.6 ± 0.1 | 5.5 ± 0.1 | 0.441 |
| Cholesterol/HDL ratio | 5.1 ± 0.2 | 4.8 ± 0.1 | 4.9 ± 0.2 | 5.7 ± 0.9 | 0.223 |
| Hypercholesterolaemia | 71.5% | 66.8% | 76.7% | 76.3% | 0.157 |
| Body weight ♀♀ (kg) | 76.0 ± 1.9 | 75.1 ± 1.7 | 79.2 ± 1.9 | 78.1 ± 4.0 | 0.230 |
| Body weight ♂♂ (kg) | 85.2 ± 1.7 | 83.5 ± 1.4 | 93.6 ± 2.5 | 94.0 ± 3.5 | <0.001 |
| Diastolic BP (mmHg) | 83.2 ± 0.9 | 84.2 ± 0.7 | 85.3 ± 0.8 | 83.8 ± 0.9 | 0.495 |
| Systolic BP (mmHg) | 148.9 ± 2.0 | 150.8 + 1.4 | 147.9 ± 1.7 | 152.5 ± 2.1 | 0.559 |
| Hypertension | 51.2% | 64.0% | 74.4% | 72.3% | <0.001 |

Values are proportions (%) or means ± standard error of the mean (SEM)
* Test for trend
BP: blood pressure; FBG: fasting blood glucose; $HbA_{1c}$: glycosylated hemoglobin; HDL: high-density lipoprotein; SU: sulfonylurea derivative

*Hypertension*

The overall prevalence of hypertension was 66% ($CI_{95\%}$: 63-69%) among those who had recordings of blood pressure available (N=748). When divided by the total study population (denominator), the prevalence was 46% ($CI_{95\%}$: 43-49%). Among these patients with high blood pressure, 13% used no medication, in 43% the blood pressure was adequately controlled by antihypertensives, and 44% were treated but poorly controlled. Type 2 diabetes mellitus patients with recordings available more frequently had a history of cardiovascular disease (30% versus 22%, p= 0.005) than those without registered blood pressure measurements. Diastolic and systolic blood pressure levels were comparable in the treatment groups (*Table 3.2*), but hypertension was significantly related to type of glucose lowering therapy; the adjusted OR (dietary treatment as reference category) was 1.6 ($CI_{95\%}$: 1.0-2.4) in the sulfonylurea treated group, 2.8 ($CI_{95\%}$: 1.7-4.5) in the metformin group, and 2.2 ($CI_{95\%}$: 1.3-3.8) in the group on insulin therapy. Treatment with antihypertensive drugs was more common in the metformin and insulin treated groups compared to the SU and diet treated groups (*Figure 3.2*), also after adjustment for body weight and age.

*Hypercholesterolemia*

About 60% of type 2 diabetes mellitus patients had recordings of total cholesterol in their medical record, among these 646 patients the prevalence of hypercholesterolemia was 71% ($CI_{95\%}$: 67-74%). Total serum cholesterol values were more likely to be available for male (p= 0.04) patients with a younger age at onset of disease (p= 0.02). The proportions of these patients treated with lipid lowering drugs are shown per glucose lowering treatment category in *Figure 3.2*. With respect to the different types of glucose lowering treatment the prevalence of hypercholesterolemia varied between 67% (sulfonylurea treatment) and 77% (metformin). The proportion of patients with known total cholesterol values who were treated with lipid lowering agents was 14% ($CI_{95\%}$: 12-17%).

*Cardiovascular morbidity and events*

Type 2 diabetes mellitus patients on insulin therapy suffered more often from cardiovascular disease compared to dietary and orally treated patients, 35% versus 25% and 26% in both other groups, respectively (OR compared to diet: 1.6, $CI_{95\%}$: 1.0-2.5).

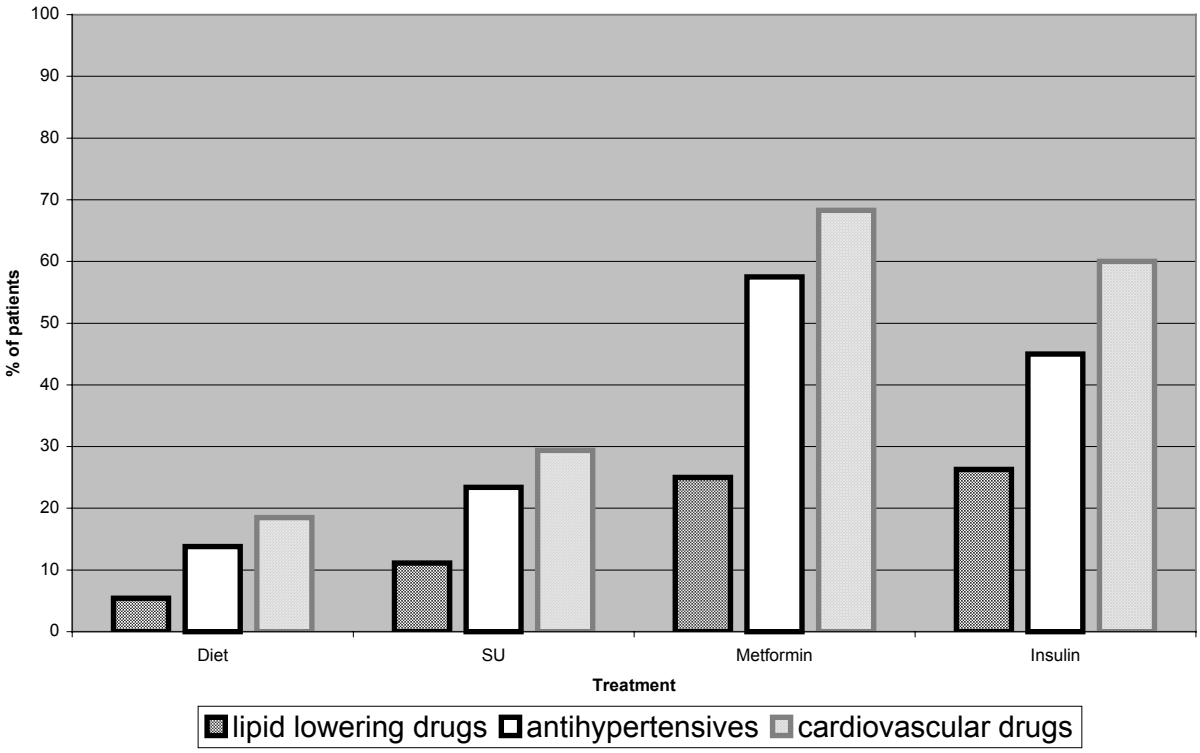


**Figure 3.2** Treatment of cardiovascular risk factors in four strata of glucose lowering therapy

Cardiovascular drugs are defined as: antithrombotics, cardiacs, diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, other antihypertensive drugs (mainly alpha-blockers), and lipid lowering agents (ATC codes B01, C01-C03, C07-C10)

After adjustment for age at diagnosis, duration of disease and gender, this association was no longer significant (OR 1.4, $CI_{95\%}$: 0.8-2.3). When we compared the prevalence of ischemic heart disease, myocardial infarction, cerebrovascular disease, and heart failure separately between the treatment groups, only the presence of heart failure (12%) was significantly higher in insulin treated patients ($OR_{adj}$ 3.6, $CI_{95\%}$: 1.3-9.6). Treatment with any cardiovascular drug was more common in groups treated with metformin and insulin compared to the sulfonylurea and diet treated groups (see also *Figure 3.2*).

## Discussion

In this study we compared metabolic and cardiovascular risk factors and the presence of cardiovascular disease in type 2 diabetes patients according to different glucose lowering treatment regimens: diet only, oral therapy (sulfonylurea and/or metformin) and insulin therapy.

Significant differences across glucose lowering treatment groups were observed for glycemic control (mean fasting glucose and $HbA_{1c}$), body weight (especially in males) and prevalence of hypertension. With respect to lipid metabolism (total serum cholesterol and prevalence of hypercholesterolemia) and cardiovascular events no notable differences were found, only the prevalence of heart failure was higher in insulin treated patients. Treatment with antihypertensive drugs, lipid lowering drugs and cardiovascular drugs was more common in metformin and insulin treated patients compared to sulfonylurea and diet treated patients.

The strength of this study is the use of routinely collected primary care data, which reflect usual clinical practice. Computerized general practice networks provide databases that may fruitfully be used for research, and permit analysis of diagnostic, treatment and prescribing patterns in different patient groups within the population at large. These databases enhance access to health related information of large groups of patients over a long period of time.[18, 19] From other studies, it is known that the sensitivity of general practice registries in identifying patients with diagnosed diabetes exceeds 90%.[20] As patients with type 2 diabetes in

the Netherlands are often cared for exclusively in general practice, comprehensive data are more likely to be obtained from primary care than from hospital care.[21]
In the Netherlands, the prevalence of type 2 diabetes in the age-group 30-74 years is 2.7-3.2% and increases with age (7-8% per year)[22], and the estimated prevalence of 2.3% observed in the present study seems a representative and reliable estimate.[23, 24]

To appreciate the results some aspects of this study need to be addressed. According to the Dutch guidelines for type 2 diabetes mellitus patients, 3-monthly and yearly checks are recommended in type 2 diabetes mellitus patients.[10] Fasting blood glucose levels (patients on diet or users of oral drugs) or glucose daycurves (users of insulin) are advised to be determined at the 3-monthly check, whereas blood pressure, HbA1c, creatinin, total cholesterol, HDL-cholesterol, triglycerides are recommended to be performed at the annual visit. Our study disclosed deficiencies in the general practitioners' information system with regard to several metabolic parameters and anthropometric measurements. In only 60-85% of these primary care patients, relevant metabolic measurements were available.

The substantial lack of cholesterol (40%) and glycemic control recordings (13%) may be partly explained by the fact that patients were referred to the laboratory and that measurements were carried out, but not recorded in the medical file of the patients. This finding is consistent with other studies performed in general practice.[25, 26] Furthermore, general practitioners may have written down measurements only when they varied from normal ranges. This could have led to an overestimation of the number of uncontrolled type 2 diabetes mellitus patients. Therefore it seems that the recorded data were insufficient for optimal care of diabetes patients.

Data on body mass index were also fairly incomplete, largely because height was seldom measured, despite regular weighing. In spite of the incompleteness of the recorded data, our results with regard to level of blood pressure, lipid measurements and glycemic control were equal to a recently performed Dutch trial in general practice[27] and observational studies by Harris and Grant *et al.*[13, 28]

As shown in The Utrecht Diabetes Project[29], standardized data transfer between GP, diabetologist and laboratory might offer an effective infrastructure for shared diabetes care.

Furthermore, in this study while stepping up the glycemic control, simultaneously the treatment of other cardiovascular risk factors was intensified (*Figure 3.2*) with progression of diabetes. While the prevalence of hypertension was significantly higher in more intensively treated patients, levels of diastolic and systolic blood pressure were comparable in the different treatment groups. It is important to mention that due to confounding by indication the metformin treated patients are more obese and therefore comprise high (cardiovascular-) risk patients.[10] In less obese patients, a sulfonylurea is first choice medication, followed by addition of metformin and eventually insulin therapy.[10]

Glycemic control is important in the management of type 2 diabetes and prevention of both micro- and macrovascular complications. Epidemiological analysis of the UKPDS data suggests that 0.5% decrement of $HbA_{1c}$ might translate to an 11.5% reduction in risk of diabetes-related complications.[8] Diabetic subjects already have an atherogenic pattern of risk factors which may be present for many years before onset and may contribute to the risk of macrovascular disease as much as the duration of disease itself.[4, 30, 31] As shown in the UKPDS 61 and Chapter 2 of this thesis, fasting glucose levels at diagnosis are associated with improved future perspectives. People presenting with type 2 diabetes with lower initial glycemia who may be earlier in the course of their disease had fewer adverse clinical outcomes despite similar glycemic progression.[32]

By comparing different modalities of glucose lowering treatment in this observational study, we showed that with intensifying the hypoglycemic treatment, the number of patients treated with cardiovascular drugs increases and glycemic control worsens during course of the disease. With respect to adequate treatment of type 2 diabetes mellitus and its complications this implies that a physician runs the risk of 'locking the stable after the horse has bolted'.

Therefore, it is very important to hold on to the idea of type 2 diabetes as a progressive and complex syndrome instead of a simple disease characterized by hyperglycemia, so that early treatment of risk factors can take place and one steps

in time with the disease. In conclusion, despite deterioration of glycemic control with intensified glucose lowering treatment, control of other metabolic risk factors remained stable, probably due to increased prescription of cardiovascular drugs.

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# CHAPTER 4

# Antihypertensive Medication and Glycemic Control in Patients with Type 2 Diabetes Mellitus

## Abstract

*Aim* - To investigate the association between antihypertensive medication and glycemic control in patients with type 2 diabetes, including the potential modification by glucose lowering therapy.
*Methods* - Type 2 diabetes mellitus patients were identified in general practices in a Dutch middle-sized town from 1994-2000. Comorbidity, laboratory tests, and blood pressure values and information on drug dispensings were obtained from general practitioners' files, pharmacy records, and hospital admission data. Glucose lowering treatment was defined at the moment of the most recent measurement of the variable of interest. Differences in glycemic control (fasting blood glucose and $HbA_{1c}$ values) between users and non-users of antihypertensive medication were compared by analysis of variance.
*Results* - More than one third of the patients used any antihypertensive medication. Users of antihypertensive medication had significantly lower $HbA_{1c}$ values, increased weight and slightly, non-significant, lower fasting glucose values compared to non-users. When adjusting for category of diabetes treatment, duration of diabetes, blood pressure, and body weight, the $HbA_{1c}$ level was even more lower in patients using antihypertensive drugs (difference 0.5 percent-points, $p< 0.05$). The association with glycemic control was present in all categories of diabetes treatment.
*Conclusion* - Our study showed that patients with type 2 diabetes mellitus not using any antihypertensive medication have increased $HbA_{1c}$ levels and lower body weight. This may indicate a subgroup with predominantly beta-cell failure.

## Introduction

In patients with type 2 diabetes mellitus antihypertensive drug treatment decreases both mortality and morbidity.[1-3] A special consideration in diabetic patients is the effect of antihypertensive drugs on glycemic control. For instance, antihypertensive drugs, such as beta-blockers and diuretics, increase insulin sensitivity.[4-6] In randomized intervention studies with different antihypertensive drugs among subjects without diabetes both an increased as well as decreased plasma glucose levels have been reported.[7, 8] Because these effects are not limited to one class of drugs, it may not be a specific drug effect that is independent of blood pressure lowering.

It is not well known if the effects of these drugs on glucose metabolism are also present in patients with type 2 diabetes.[9] In the UKPDS hypertension study, patients treated with atenolol had higher $HbA_{1c}$ levels over the first four years of follow-up than those randomized to captopril (7.5% versus 7.0%, p= 0.004), although during the second four years the levels were the same.[10] The FACET trial compared the effects of fosinopril and amlodipine on serum lipids and diabetes control in hypertensive type 2 diabetes mellitus patients.[11] After 3.5 years, $HbA_{1c}$ levels in both groups did not differ from the baseline values. The glucose values showed a small decrease, which was equal in both groups.

The effects probably differ between patients using different glucose lowering therapy (diet, oral agents, insulin), and may be dependent on the underlying pathophysiologic mechanism of diabetes. Because type 2 diabetes is a heterogeneous disease, the effects might vary considerably in daily clinical practice.

To investigate the associations between antihypertensive medication and glycemic control in patients with type 2 diabetes mellitus, including the potential modification by glucose lowering therapy, we performed an observational study in a population of type 2 diabetes patients treated by general practitioners.

## Patients and Methods

*Study setting*

This study was performed among patients who received comprehensive primary care from 17 general practitioners (GPs) in a Dutch middle-sized town (n=50,574). All GPs used a single electronic medical record system (Medicom®), which was available for this study, as well as information on drug dispensings from the pharmacist database (Pharmacom®). Hospital admission and discharge data were available through the PHARMO Record Linkage System.[12, 13]

The following data were available for this study: demographic data, medical history, comorbidity (including *International Classification of Primary Care* (ICPC) codes), diabetic complications, drug dispensings, prescribing doctor (specialist, GP), referrals to specialists, and the medical journal (a database-file containing free text, as recorded by the GP).

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).

*Subjects*

The study population consists of all cases with type 2 diabetes mellitus as seen by the network of collaborating GPs (n=17) during 1992-2000 (n=1,144). In the Netherlands, most patients with diabetes mellitus type 2 visit their GP for regular check-ups. They were identified from the registries by the use of oral glucose lowering agents or *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 available for the purpose of this study. Subjects in whom the correct diagnosis of type 2 diabetes remained uncertain, due to incomplete and missing data, were excluded

(n=72), as well as patients with no glucose or $HbA_{1c}$ results in their medical files (n=257). Therefore, the study population consisted of 815 patients with fasting blood glucose (n=779) and/or $HbA_{1c}$ (n=572) measurements recorded. In patients with diagnosed type 2 diabetes but unknown date of diagnosis we relied on January 1990 as a reasonable estimate.

*Variables of interest*

In both cohorts of type 2 diabetic patients, patients with fasting blood glucose or $HbA_{1c}$ values recorded in their medical file, respectively, we ascertained differences in metabolic control between users and non-users of antihypertensive medication. We compared most recent (i.e. last available) measurements of blood glucose and $HbA_{1c}$ in both groups. Antihypertensive drug use was classified into the major antihypertensive classes: beta-blockers (C07), angiotensin converting enzyme (ACE) inhibitors (C09), thiazide diuretics (ATC codes C03A, C03B, C03EA), calcium channel blockers (C08), and a remaining category of miscellaneous blood pressure lowering drugs (C02, mainly alpha-blockers).

We defined users of antihypertensives as patients using any blood pressure lowering drugs in the half year preceding the last measurement of the glycemic parameter of interest. Blood pressure was defined at the date of measurement closest to the date of the most recent glycemic variable, but at least within the period from 3 months before until 3 months after this recording, otherwise blood pressure was coded as 'missing'. We also compared glycemic control in users of lipid lowering drugs, defined as patients using any serum lipid lowering drug (ATC group C10) in the half year preceding the last measurement, with glycemic control in non-users. The diabetic treatment was defined at moment of the last available measurement of the variable of interest.

*Data analysis*

For categorical variables, numbers and percentages and for continuous data means and standard deviations were calculated. For comparison of the continuous variables between patients who did and did not use antihypertensive medication, we used the Students' t-test. Analysis of covariance was used to adjust for potential

confounding factors, notably age, gender, duration of diabetes, body weight, and blood pressure. All analyses were performed by SPSS version 10 for Windows.

## Results

The clinical characteristics of the study population are given in *Table 4.1*. Blood pressure and weight were recorded in a small proportion of the patient files, mainly in those patients using blood pressure lowering medication. More than one third of the patients used antihypertensive medication, half of them (52.1%) only one class of drugs (beta-blocker, ACE-inhibitor, Ca-antagonist, or thiazide diuretic). This did not result in optimal controlled blood pressure: the average blood pressure in antihypertensive drug users was 155/87 mmHg, compared to 148/83 mmHg in non-users ($p< 0.01$). Use of antihypertensive medication was not associated with diabetes treatment or recordings of glycemic control (data not shown).

Systolic blood pressure was not associated with glycemic control ($p> 0.2$). A higher diastolic blood pressure was associated with a slightly increased fasting glucose values (regression coefficient 0.035 mmHg/mmolL, $CI_{95\%}$: 0.008-0.061, $p< 0.05$). There was no association between diastolic blood pressure and $HbA_{1c}$.
Patients using antihypertensive medication had significant lower $HbA_{1c}$ values, increased weight and slightly, non-significant, lower fasting glucose values (*Table 4.2*). When adjusting for category of diabetes treatment (diet, sulfonylureas, metformin, insulin), duration of diabetes, blood pressure, and body weight, the $HbA_{1c}$ level was even more lower in patients using antihypertensive drugs (difference 0.5 percent-points, $p< 0.05$).

**Table 4.1** Clinical characteristics at time of glycemic assessment

| | n=779* | n=572† |
|---|---|---|
| Age (years) | 65.9 (13.1) | 65.3 (12.2) |
| Male | 44.3 | 45.8 |
| Weight (kg) | 81.2 (17.6) (n=195) | 83.4 (18.6) (n=127) |
| Diabetes duration (years) | 5.0 (5.0) | 5.2 (4.8) |
| Fasting blood glucose (mmol/l) | 8.5 (3.1) | |
| $HbA_{1c}$ (%) | | 7.8 (1.6) |
| Glucose lowering treatment | | |
| - Diet | 18.0 | 15.4 |
| - Sulphonylureas | 43.8 | 49.8 |
| - Metformin | 20.8 | 19.2 |
| - Insulin | 17.5 | 15.6 |
| Switchers to insulin therapy | 20.3 | 20.6 |
| Lipid lowering medication | 14.6 | 14.3 |
| Systolic blood pressure (mmHg) | 152.0 (23.0) (n=343) | 152.1 (23.2) (n=224) |
| Diastolic blood pressure (mmHg) | 85.1 (11.1) (n=343) | 85.5 (11.4) (n=224) |
| Antihypertensive medications | 39.7 | 34.8 |
| - Beta-blockers | 18.5 | 15.4 |
| - ACE-inhibitors | 23.5 | 20.5 |
| - Thiazide diuretics | 10.9 | 9.1 |
| - Ca-blockers | 10.0 | 9.4 |
| - Miscellaneous drugs | 0.9 | 1.4 |

* Patients with fasting blood glucose values recorded
† Patients with $HbA_{1c}$ values recorded
Values are means with standard deviation between parentheses, or percentages

If the analyses were restricted to patients with hypertension based on blood pressure values (>= 160/95 mmHg), the same associations were found. This was also when the analyses were performed for each general practice separately. The association with glycemic control was present in all categories of diabetes treatment (*Figure 4.1*). The use of lipid lowering medication (93.9% statins) was not associated with glycemic control (*Table 4.2*).

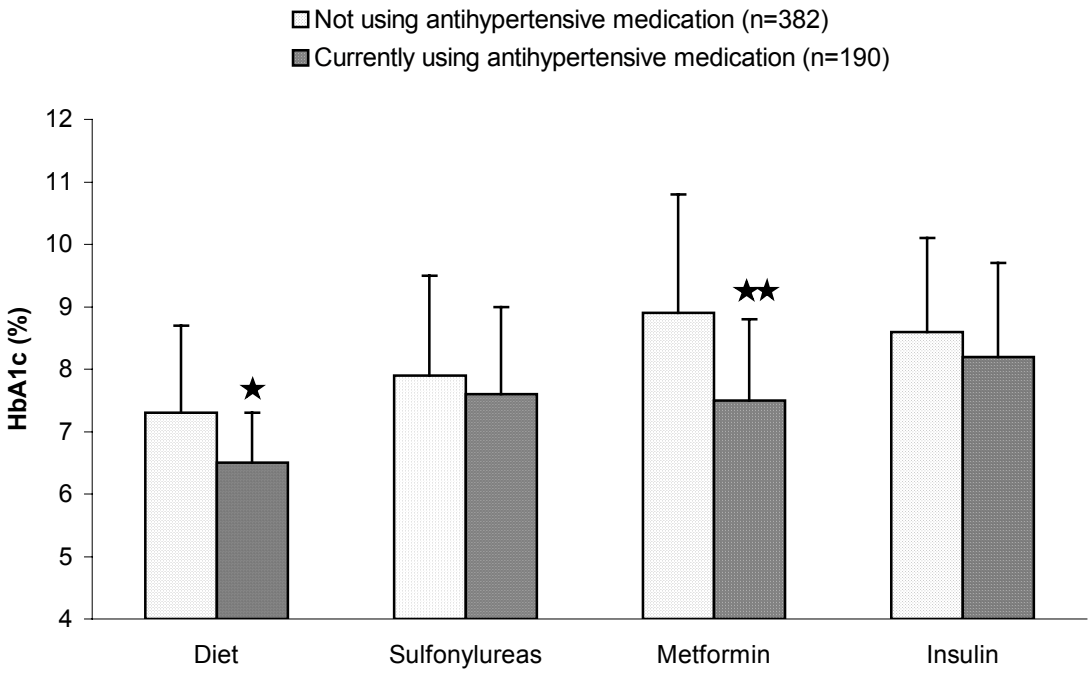


**Figure 4.1** $HbA_{1c}$ by antihypertensive medication use

* p< 0.05, ** p< 0.01

**Table 4.2** Glycemic control by current medication use

| | $HbA_{1c}$ (%) | Fasting glucose (mmol/l) | Weight (kg) |
|---|---|---|---|
| *Currently using antihypertensive medication* | | | |
| - no | 8.0 (1.7) | 8.6 (3.2) | 78.7 (17.0) |
| - yes | 7.6 (1.4)** | 8.5 (3.0) | 85.0 (18.0)* |
| *Currently using lipid lowering medication* | | | |
| - no | 7.8 (1.6) | 8.5 (3.2) | 80.8 (17.4) |
| - yes | 7.9 (1.6) | 8.4 (2.6) | 83.2 (18.9) |

Values are means with standard deviation between parentheses.
* p< 0.05, ** p< 0.01

**Table 4.3** $HbA_{1c}$ and blood pressure by class of antihypertensive medication

| | $HbA_{1c}$%) | Glucose (mmol/l) | Blood pressure (mmHg) |
|---|---|---|---|
| No antihypertensive | 8.0 (0.1) | 8.6 (0.1) | 148/83 (2/1) |
| Beta-blockers | 7.5 (0.3) | 8.0 (0.4) | 150/86 (4/2) |
| ACE-inhibitors | 7.7 (0.2) | 8.5 (0.3) | 155/88 (3/2)* |
| Calcium-antagonists | 8.4 (0.5) | 9.3 (0.9) | 142/80 (7/3) |
| Thiazide diuretics | 7.8 (0.4) | 7.4 (0.5) | 156/85 (8/2) |
| Miscellaneous | 6.9 (0.5) | - † | - † |
| Combinations | 7.5 (0.1)* | 8.5 (0.3) | 158/87 (2/1)** |

† No observations
Values are means with standard error between parentheses
* p< 0.05, ** p< 0.01, compared to no antihypertensive use

The difference in $HbA_{1c}$ was present for all classes, except for calcium-antagonists, of antihypertensive medication, but only reached statistical significance in the largest subgroup of patients using drugs from more than one class (*Table 4.3*). The same associations were found in the four categories of diabetes treatment, but due to small numbers these associations were not statistically significant (data not shown). The fasting glucose levels were slightly lower for all classes of blood pressure lowering drugs, again as well in each stratum of glucose lowering treatment.

Patients using antihypertensive medication started more often with insulin treatment during the follow-up period (23.9% versus 17.9%, $p< 0.05$). However, when adjusting for duration of diabetes the association was no longer present.

## Discussion

In this study we showed that patients using antihypertensive medication had better glycemic control, notably lower $HbA_{1c}$ levels, and increased body weight. This was not explained by differences in diabetes treatment, duration of diabetes, or achieved blood pressure level.

In this observational study, a potential explanation for our findings is that antihypertensive treatment is driven by glycemic control and vice versa (confounding by indication). However, if anything, patients with worse glycemic control are likely to receive more antihypertensive medication, because they are at an increased risk for vascular complications, and are likely to visit the GP more often.

We found an opposite association, so confounding by indication can not explain our results. A more probable explanation might be that both use of antihypertensive medication and better glycemic control are the result of appropriate treatment of patients with diabetes.[14, 15]

However, the absence of an association between lipid lowering medication and $HbA_{1c}$ level does not support this explanation.

Beta-blockers and diuretics increase insulin sensitivity[4, 6], whereas ACE-inhibitors have a potential protective effect on diabetic nephropathy.[16] As a consequence, patients with type 2 diabetes are more likely to switch to ACE-inhibitors, and start more frequently with ACE-inhibitors.[17] In the hypertension sub-study of the UKPDS patients were randomized to captopril or atenolol. Patients given atenolol gained more weight and had higher $HbA_{1c}$ levels in the first half of the study. However, both treatments reduced blood pressure to the same extent and were similarly effective in reducing the risk of macrovascular and microvascular complications of diabetes.[10]

Several studies have shown a positive association between blood pressure and insulin sensitivity.[18, 19] Indeed, the 'metabolic syndrome' includes both insulin resistance and hypertension.[20] A few studies have reported lower glucose or $HbA_{1c}$ levels in type 2 diabetes patients with hypertension (or antihypertensive medication) compared to normotensive diabetes patients, as found in the present study.[21, 22] In the ABCD trial the $HbA_{1c}$ values continuously decreased in all treated diabetes patients during the study.[23] These results are compatible with the hypothesis that type 2 diabetes patients without hypertension are a subgroup of patients with predominant beta-cell failure. Indeed, we found an increased weight in patients using antihypertensive medication.

The strength of our study is the use of routinely collected primary care data, which reflect usual clinical practice. General practice networks provide databases that may fruitfully be used for research.[24] A limitation of this approach is the incompleteness of the data, notably of body weight, which is consistent with other studies performed in general practice.[25]

In conclusion, this study shows that patients with type 2 diabetes mellitus who do not use any antihypertensive medication have increased $HbA_{1c}$ levels. This may indicate that this subgroup has predominantly beta-cell failure.

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# CHAPTER 5

# Factors Associated with Switching from Oral Hypoglycemic Agents to Insulin Therapy

## Abstract

*Aim* - Purpose of our study was to determine factors that are associated with switching from oral hypoglycemic agents to insulin therapy in patients with diabetes mellitus type 2 in general practice.

*Methods* – We performed a longitudinal, observational study in a Dutch general healthcare center. All pharmacologically treated patients with diabetes mellitus type 2 were included (n = 152). Comorbidity, laboratory results and medication use were obtained from the general practitioners' files.

*Results* - A total of 31 (20.4%) patients switched from oral hypoglycemic agents to insulin therapy; they were significantly younger at the onset of diabetes, 50.5 versus 57.7 years. Fasting blood glucose levels and $HbA_{1c}$ values were significantly higher after the switch compared to patients on oral treatment, 10.0 mmol/l versus 8.4 mmol/l and 8.8% versus 7.9%, respectively. Concerning comorbidity, they suffered more frequently from acute myocardial infarction, lipid disorders, depression, retinopathy, and atrial fibrillation. Cardiovascular disease in general was present more often in patients who switched over to insulin, 77.4% versus 52.9% (OR 3.1, $CI_{95\%}$: 1.2-7.6).

*Conclusions* - Patients who switch over to insulin therapy are younger at diagnosis, suffer from more health problems besides diabetes, especially cardiovascular disease, and have worse metabolic control, compared with users of oral hypoglycemic agents.

## Introduction

As type 2 diabetes mellitus (DM) advances, secondary failure of oral hypoglycemic therapy develops as a consequence of progressive loss of beta-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance.[1] The yearly failure rate of this therapy following an optimal initial response is approximately 5% tot 10% and increases with duration of diabetes.[2] If oral treatment initially works but later fails (secondary failure), patients are switched over to insulin therapy.[3-6] The increasing number of patients with type 2 DM and recent insights regarding the importance of strict glycemic control are expected to result in a larger number of type 2 diabetic patients receiving insulin treatment.[3]

Although the results of the United Kingdom Prospective Diabetes Study (UKPDS) underline the importance of good glycemic control[7], many general practitioners (GPs) appear hesitant to switch patients over to insulin therapy.[8] The recently updated diabetes mellitus guidelines of the Dutch College of General Practitioners ('NHG standaard') provide no clear indication when insulin should be given or when the patient should be referred to a specialist.[9, 10]

Only a limited number of studies have investigated which factors are associated with the decision whether or not to convert type 2 DM patients to insulin therapy and none of these were performed in general practice.[11-14] Nevertheless, GPs possess a wealth of information on the health of their patients, and on many aspects of their medical treatment.

Therefore, we compared 'switchers' and 'non-switchers' with respect to patient characteristics, course of the disease, metabolic control and comorbidity, using a GP database.

## Materials and methods

*Population*

This study was carried out among people who were registered in one general healthcare center in Almere, the Netherlands (n=6800). This healthcare center offers all aspects of primary care and is staffed by six GPs. Their practices were of similar size, between 1010 and 1145 patients, and similar in age and sex distribution. All patient information is stored in one database (Medicom®). To guarantee privacy, all analyses were performed using anonymous records.

*Study design*

The study population consisted of all prevalent cases of type 2 DM and all those diagnosed during the study period, from January 1995 until June 1999. So, GPs in our study were still using the first edition of the GPs' guidelines.[9] In the Netherlands, most patients with type 2 DM visit their GP for regular check-ups. They were identified from the register by the use of oral hypoglycemic agents or *International Classification of Primary Care* (ICPC) codes T90 or T90.2, and/or the description 'diabetes mellitus type 2' in their medical record. Subsequently diet-treated patients were excluded (n=46).

Medical treatment starts with a first-generation sulfonylurea (tolbutamide), followed by second-generation sulfonylureas and/or addition of a biguanide or α-glucosidase inhibitors (in obese patients).[9] Diabetes patients are treated according to a locally developed treatment protocol ('Diabetes Care Almere'). Patients should be switched over to insulin therapy if they are on maximized oral medication and still have $HbA_{1c}$ values greater than 8%.

Following the diabetes care protocol, maximum dosages of oral agents are: glibenclamide 15 mg per day, gliclazide 240 mg per day, glipizide 20 mg per day, glimepiride 6 mg per day, and metformin 3000 mg per day.

The protocol included three steps of insulin treatment:

1. a single dose of bedtime (long-acting) insulin plus daytime sulfonylurea therapy;
2. two injections of intermediate-acting insulin;
3. multiple daily injections, combination of short-acting and intermediate-acting insulin.

The following data were obtained from the anonymous patient records: all medication prescriptions, demographic data, comorbidity (defined according to ICPC classification), diabetic complications, doctor in attendance (specialist, GP), referrals to specialists, and the medical journal (a database file containing free text, as written down by the GP).
Regarding medication prescriptions, all drugs were coded according to the *Anatomical Therapeutic Chemical (ATC) Classification*.[15]
We defined 'switchers' as subjects who switched to insulin therapy (ATC code A10A) with or without continuation of oral hypoglycemic medication. Some of the initial patients were already being treated with insulin.

Microalbuminuria was defined as having at least one measurement of urinary albumin concentration higher than 20 mg/l. For other continuous variables (glycosylated hemoglobin ($HbA_{1c}$), fasting plasma glucose, total serum cholesterol, body mass index, et cetera) we calculated a mean yearly value per patient and subsequently a mean value per patient over the whole study period. As we expect poor controlled patients to have more measurements, this approach gives equal weight to each subject.

*Data analysis*
For the comparison of continuous variables and categorical variables between switchers and non-switchers, we used the Student's t-test and chi-square test, respectively. Odds ratios (ORs) and 95% confidence intervals ($CI_{95\%}$) were calculated to compare risks of other diseases and disorders, and drug use for those patients on insulin therapy versus those using oral medication. P-values less than 0.05 were considered statistically significant. We divided the follow-up period of patients who were switched over to insulin therapy into two phases, *before* and *after* the changeover to insulin therapy.

The Kaplan-Meier method was used to calculate the cumulative incidence of switching over to insulin among the cases present in 1995. Survival time was defined as months on oral hypoglycemic treatment. So, the cumulative incidence of switching was calculated as: 1 - cumulative survival probability. All analyses were carried out using the statistical package SPSS, version 9.0 for Windows.
For descriptive variables without further statistical testing, for instance to determine reasons for not switching despite secondary failure of oral treatment, the medical journal as registered by the GP was used.

## Results

*Figure 5.1* shows the number of type 2 diabetic patients, excluding those on dietary treatment only, during the study period. Between 1995 and 1999 there was an increase in the total number of patients diagnosed with type 2 diabetes mellitus; 72 patients in 1995 increasing to 136 patients in 1999. Two of the initial patients enrolled were already on insulin therapy. The estimated prevalence of diabetes mellitus type 2 at June 30th 1999 was 2.1% (136/6510; $CI_{95\%}$ 1.7% - 2.4%).

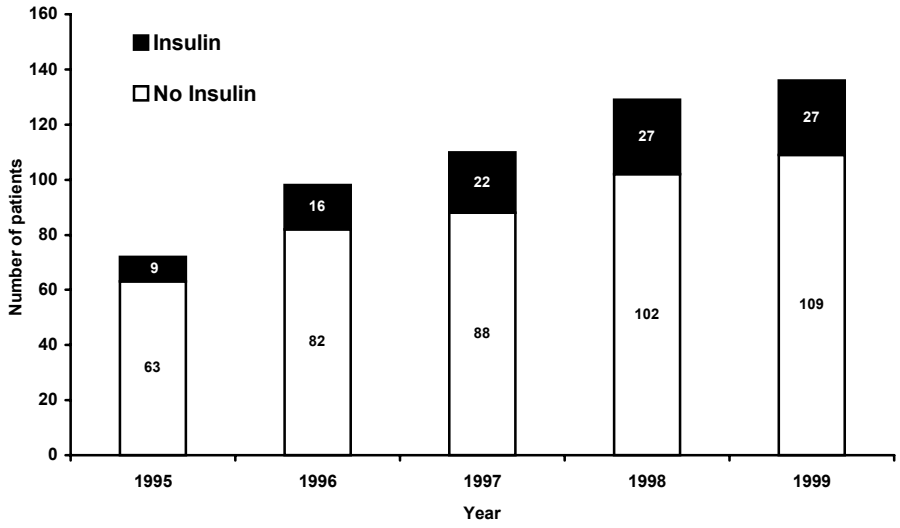


**Figure 5.1** Insulin treatment over time in a healthcare center in Almere

In the study, 79 men and 73 women, aged between 32 and 94 years (mean age 62.8 years), with diabetes mellitus type 2 were enrolled. Their clinical and demographic characteristics are given in *Table 5.1*. During the study period 14 patients died, three in the insulin-requiring group. Two patients moved out of the country in 1997.

**Table 5.1** Characteristics of type 2 diabetic patients

| Variable | N = 152 |
|---|---|
| Age at onset (yrs) | 56.3 ± 1.2 |
| Male (%) | 52.0 ± 4.1 |
| Duration of disease (yrs) | 5.8 ± 0.5 |
| Fasting blood glucose (mmol/l) | 8.7 ± 0.2 |
| $HbA_{1c}$ (%) | 8.0 ± 0.2 |
| Systolic blood pressure (mmHg) | 149.3 ± 1.9 |
| Diastolic blood pressure (mmHg) | 85.2 ± 0.8 |
| Total serum cholesterol (mmol/l) | 5.8 ± 0.1 |
| HDL cholesterol (mmol/l) | 0.7 ± 0.1 |
| Triglycerides (mmol/l) | 1.2 ± 0.1 |
| Body mass index ($kg/m^2$) | 31.6 ± 0.7 |
| Weight (kg) | 85.4 ± 1.5 |

values are proportions or means ± standard error of the mean (SEM)
HDL = high-density lipoprotein; $HbA_{1c}$ = glycosylated hemoglobin

*Conversion to insulin therapy*

Of 152 patients, 31 (20.4%) switched from oral hypoglycemic agents to insulin therapy. The cumulative incidence of switching to insulin treatment among prevalent cases in 1995, with a mean diabetes duration of 5.9 years, was 36% ($CI_{95\%}$ 23%-48%) in June 1999. Before switching, 16 patients (62%) were on the maximum dosage of a sulfonylurea derivative (SU), while 12 (46%) patients used a SU in combination with metformin. Four patients (15%) had an obvious or plausible reason for switching over to insulin without maximizing oral medication in accordance with the guidelines; two had a myocardial infarction, one wished to become pregnant and another patient had no adequate response to oral hypoglycemic agents within 6 weeks. In total 22 patients (75%) were referred to

diabetiologist or were hospitalized at the moment they switched to insulin therapy. After stabilization of their metabolic state, in 18 patients (85%) diabetes care was continued by their GP.

*Reasons for not switching*

Within the study population ten patients did not switch to insulin therapy despite secondary failure of oral hypoglycemic agents, defined by latest $HbA_{1c}$ equal to or greater than 8.0 %, and maximal treatment with oral hypoglycemic agents. Subsequently, we identified reasons for not switching, according to the GP, by examining the medical journal. The main reasons for not switching were: resistance (n=6), hesitation or unwillingness to undergo insulin therapy (n=1), and non-compliance with appointments (n=2) and medication regimen (n=5). Two of these patients were already self-monitoring their blood glucose levels. The reasons for not switching remained unclear in two patients.

*Switchers in comparison to non-switchers*

The differences between type 2 diabetic patients treated with insulin and patients on oral hypoglycemic agents are listed in *Table 5.2*. Patients switching over to insulin therapy, were significant younger at the onset of the disease, and had a shorter duration of diabetes (4.0 versus 4.8 years). At the end of the study period, there was no significant difference in age between the two groups; the mean age for switchers was 60.7 (± 13.1) years, compared to 63.4 (± 14.3) years in the patients who did not switch over to insulin. The fasting blood glucose and $HbA_{1c}$ values of insulin users compared to users of oral hypoglycemic agents were significantly higher after the switch ($p= 0.01$ and $p= 0.02$, respectively).

**Table 5.2** Insulin users compared to users of oral hypoglycemic agents

| Measure | Insulin therapy (N=31) | | No insulin therapy (N=121) |
|---|---|---|---|
| | *Before switch* | *After switch* | |
| Age at onset (yrs)* | 50.5 ± 2.2 | | 57.7 ± 1.3 |
| Duration of disease (yrs)* | 4.0 ± 1.3 | 2.6 ± 0.2 | 4.8 ± 0.5 |
| Cigarette smokers (%) | 50.0 | | 64.0 |
| Fasting blood glucose (mmol/l)† | 8.8 ± 0.6 | 10.0 ± 0.6 | 8.4 ± 0.2 |
| $HbA_{1c}$ (%)† | 8.5 ± 0.3 | 8.8 ± 0.4 | 7.9 ± 0.2 |
| Total serum cholesterol (mmol/l)‡ | 6.4 ± 0.2 | 5.8 ± 0.2 | 5.7 ± 0.1 |
| Systolic blood pressure (mmHg) | 156.3 ± 6.1 | 155.8 ± 4.9 | 148.1 ± 2.0 |
| Diastolic blood pressure (mmHg) | 86.0 ± 3.1 | 85.5 ± 2.3 | 85.0 ± 0.9 |
| Body mass index ($kg/m^2$)§ | 32.8 ± 2.5 | 31.3 ± 1.6 | 31.8 ± 0.9 |
| Weight (male)§ | 82.3 ± 6.2 | 91.3 ± 3.9 | 88.3 ± 2.3 |
| Weight (female)§ | 95.0 ± 6.3 | 84.1 ± 6.3 | 80.8 ± 2.4 |
| ***Diabetic complications*** | | | |
| Microalbuminuria‖ | 53.8 | | 37.8 |
| Retinopathy* | 19.4 | | 6.6 |
| Neuropathy | 16.1 | | 5.8 |
| Other medical disorders (number)* | 7.0 ± 0.9 | | 4.5 ± 0.3 |

values are proportions or means ± SEM
* p-value < 0.05, insulin users compared to users of oral hypoglycemic agents
† p-value < 0.05, insulin users, after switch, compared to users of oral hypoglycemic agents
‡ p-value < 0.05, insulin users, before switch, compared to users of oral hypoglycemic agents
§ sparse data about BMI and weight before switch (2 and 11 respectively)
‖ urinary albumin concentration ≥ 20 mg/l

Before these patients were converted to insulin therapy they had significantly higher total serum cholesterol levels, 6.4 mmol/l *versus* 5.7 mmol/l (p= 0.04).
Microalbuminuria was present in patients on oral hypoglycemic agents (OHA) about as frequently as in those treated with insulin. But we also found that the urinary albumin concentration was less tested in insulin-treated patient than in those on OHA, 41.9% *versus* 61.2% (OR 0.5, $CI_{95\%}$: 0.2-1.0). Retinopathy and neuropathy were more frequent in insulin-treated patients, although the difference in prevalence of neuropathy was borderline significant; odds ratios were 3.4 ($CI_{95\%}$: 1.1-10.6) and 3.1 ($CI_{95\%}$: 0.9-10.7) respectively.

*Comorbidity*
Comorbidity, defined as a health problem besides diabetes in the GP list, was present in 31 (100%) of the switchers and 106 (87.6%) of the subjects that were not converted to insulin therapy (p= 0.04).
Patients who were converted to insulin therapy had more comorbidity, notably acute myocardial infarction (OR versus non-switchers 3.5, $CI_{95\%}$: 1.3-9.6), depression (OR 14.3, $CI_{95\%}$: 2.7-74.9), disorders in lipid metabolism (OR 2.9, $CI_{95\%}$: 1.1-7.8), and atrial fibrillation (OR 8.8, $CI_{95\%}$: 1.5-50.6). Of borderline significance were the higher frequencies of benign prostate hypertrophy (OR 6.4, $CI_{95\%}$: 1.0-40.0) and chronic obstructive pulmonary disease (OR 4.3, $CI_{95\%}$: 1.0-18.4) in patients on insulin. Cardiovascular disease in general was present more often in the patients that were switched over to insulin therapy, the prevalence was 77.4% versus 52.9% (OR 3.1, $CI_{95\%}$: 1.2-7.6).
All diseases mentioned usually occurred before patients converted to insulin therapy; these percentages varied between 63.6% (acute myocardial infarction) and 100% (benign prostate hypertrophy).

*Co-medication*
Drugs most frequently prescribed besides the hypoglycemic medications were analgesics, non-steroid anti-inflammatory drugs, psycholeptics, antibiotics, and antimycotic drugs. Of the patients on insulin treatment, 83.9% used one or more cardiovascular drug(s), identified as groups B01, C01-C03 and C07-C10 following

the ATC classification, versus 62.8% in subjects on oral treatment only (OR 3.1, $CI_{95\%}$: 1.1-8.6). When we inspected the cardiovascular medication further, patients on insulin used about twice more frequently cardiacs, angiotensin converting enzyme inhibitors, lipid lowering medication and antithrombotic agents, ORs were 2.9, 3.0, 3.2 and 2.5 respectively (*Table 5.3*).

**Table 5.3** Medication use in insulin using versus non-insulin using patients

| Generic name | ATC* | % use | Odds Ratio | [95% CI] |
|---|---|---|---|---|
| Cardiacs | C01 | 45.2 v 22.3 | 2.87 | [1.25 – 6.55] |
| Diuretics | C03 | 41.9 v 28.9 | 1.78 | [0.79 – 4.01] |
| Beta blocking agents | C07 | 35.5 v 28.1 | 1.41 | [0.61 – 3.25] |
| Calcium channel blockers | C08 | 29.0 v 20.7 | 1.57 | [0.64 – 3.83] |
| ACE inhibitors† | C09 | 58.1 v 31.4 | 3.02 | [1.35 – 6.80] |
| Other antihypertensive drugs‡ | C02 | 12.9 v 1.7 | 8.82 | [1.53 – 50.63] |
| Lipid lowering medication | C10 | 38.7 v 16.5 | 3.19 | [1.34 – 7.59] |
| Antithrombotic agents | B01 | 54.8 v 33.1 | 2.46 | [1.10 – 5.49] |
| Antidepressants | N06A | 12.9 v 7.4 | 1.84 | [0.53 – 6.44] |
| Anti-asthmatics | R03 | 35.5 v 25.6 | 1.60 | [0.69 – 3.70] |

* ATC = Anatomical Therapeutic Chemical classification
† ACE = Angiotensin converting enzyme
‡ including for instance antiadrenergic agents (doxazosin), agents acting on arteriolar smooth muscle (hydralazine), serotonin antagonists (ketanserin)

## Discussion

This study describes patients with diabetes mellitus type 2 who switched from oral hypoglycemic agents to insulin therapy in a primary care setting. Several factors potentially associated with the decision to convert to insulin therapy were found, notably: younger age at diagnosis, more comorbidity, worse metabolic control, and use of more cardiovascular medication.

The study population consisted of all prevalent cases of type 2 DM and all those diagnosed during the study period, from January 1995 until June 1999. So, the updated GPs' guidelines on type 2 diabetes mellitus, introduced in 1999, were not implemented in primary care yet.[10] Important changes compared with the earlier edition of the guidelines[9] - used by the GPs in our study - are the shortening of the dietary period from six to three months and the introduction of metformin as first-choice medical therapy in obese patients (body mass index > 27 kg/m$^2$).[10] However, both aspects are not likely to influence the associations we found between some patient characteristics and switching to insulin therapy in type 2 diabetes.

General practice networks provide databases that may fruitfully be used for research. The use of computerized databases permits analysis 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.[16, 17] The sensitivity of general practice registers in identifying patients with diagnosed diabetes exceeds 90%.[18] The prevalence of 2% which we found in this GP population closely approximates the estimated prevalence in the Netherlands.[19, 20] Also, the increase in diabetes is in agreement with the trend reported for the Netherlands. The increase is based on both the ageing of the population and increased awareness of diabetes among GPs.[21] One advantage of using data derived from a healthcare center is the uniform approach to the treatment. GPs and district nurses cooperate closely, following to a local developed treatment protocol. However, the individual physicians all make their own decisions. Because of the strict protocol, the effect of variability will be limited.

Data on body mass index and smoking were very incomplete (available in 27.6% and 43.4% of the patients, respectively). Given the high mean values (*Tables 5.1 and 5.2*) it seems that GPs only record these characteristics in obese and smoking patients. Although most patients are weighed regularly, body height was seldom measured. Our main results did not derive from these variables, so there was no influence on the associations we found.

Secondary failure to treatment with oral hypoglycemic agents is defined as an inadequate glucose-lowering effect of oral drugs after an initial good response.[11-13] Failure implies that the whole treatment strategy failed, not simply the drug treatment.[12] The causes of failure include non-compliance, weight gain, declining beta-cell function, infection, and the use of diabetogenic drugs, such as glucocorticoids, thiazides, and beta-blockers.[11] In our study, the cumulative incidence of switching to insulin therapy was 36% over a 4.5 year period, which is comparable to other studies.[22-24] After nine years of follow-up in the U.K. Prospective Diabetes Study (UKPDS), 30% of the patients had switched over to insulin treatment.[23]

Groop and colleagues concluded that secondary failure to treatment with oral hypoglycemic agents is determined by the disease itself rather than by patient-related factors.[11] The presence of islet cell and thyrogastric antibodies can unmask a distinct group of type 2 diabetic patients with a high risk of secondary drug failure and subsequent insulin dependency.[12] However, this is probably only a small proportion of the patients who become insulin users.

Although experimental studies show that insulin therapy can be save and efficacious in improving glycemic control in type 2 diabetes.[7, 25, 26] little is known about factors determining the decision to use insulin in type 2 DM. In a randomized controlled trial (UKPDS 26), higher failure rates were found in those with higher glucose concentrations, those who were younger, those with lower beta-cell reserve and those randomized to glibenclamide compared with chlorpropamide.[27] In the literature we found no studies that described determinants in type 2 diabetic patients associated with switching over from oral hypoglycemic agents to insulin therapy in *primary care*. Goddijn studied

prospectively a cohort of type 2 diabetic patients referred by general practitioners to an outpatient department for consideration of insulin therapy. As in our study, she found that switchers had a higher $HbA_{1c}$. However, in contrast to our findings, her patients had a lower body mass index and had been taking oral hypoglycemic agents longer.[13] These differences might indicate that GPs wait longer to refer patients for insulin than switching the patients themselves. In addition, the study of Goddijn was performed a few years ago. Since then GPs seem more likely to switch to insulin therapy, probably because of the increased awareness of strict glycemic control.

It is well known that diabetic patients suffer from more (cardiovascular) morbidity than subjects without diabetes.[28, 29] In addition, we found that insulin users suffered more frequently from other diseases besides diabetes. Also the higher frequency of depressive disorders has been described elsewhere. Among other things, depression is associated with poorer medication regimen adherence.[30] Furthermore, 64% to 100% of these disorders developed or occurred in the period before patients converted to insulin, suggesting that the course of the disease in diabetic patients who eventually switch over to insulin therapy is more severe. The younger age of onset and shorter duration of diabetes in these patients further support their increased severity.

The UKPDS has shown that more intensive management aiming for near-normal glucose levels reduces the risk of diabetes-related complications, particularly microvascular disease.[7] This suggests that physicians should be on the alert for patients with secondary failure who should be converted to insulin therapy in time.

Our results suggest that insulin therapy is started after the development of diabetic complications and other comorbidity; in other words, 'one locks the stable after the horse has bolted'.

In conclusion, we found that patients who switch over to insulin therapy due to secondary failure are younger at diagnosis, more frequently suffer from depression, acute myocardial infarction, lipid disorder, atrial fibrillation, and retinopathy and have higher $HbA_{1c}$ and total serum cholesterol values.

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# CHAPTER 6

# Refill Compliance in Type 2 Diabetes Mellitus: a Predictor of Switching to Insulin Therapy?

## Abstract

*Aim* - To assess whether switching to insulin therapy in patients with type 2 diabetes mellitus is associated with medication refill compliance of oral hypoglycemic agents.

*Methods* - The PHARMO Record Linkage System was used as data source for this study. Patients with newly treated type 2 diabetes mellitus were defined as subjects in whom oral hypoglycemic therapy was initiated between 1991 and 1998. We performed a matched case-control study in this cohort. Cases were patients who switched to insulin therapy. Date of switching in the case was defined as the index date. Controls were subjects still on oral therapy on the index date, matched on duration of diabetes and calendar time. We measured the medication refill compliance in the year starting 18 months before the index date and calculated various compliance indices.

*Results* - In total, 411 cases and 411 matched controls were identified. Cases suffered more often from more severe comorbidity and used a higher number of oral hypoglycemic agents and concomitant non-diabetic drugs. The overall compliance rate did not differ significantly between cases and controls, the adjusted OR was 1.3 ($CI_{95\%}$: 0.6-2.8).

After performing multivariate logistic regression modeling, age at onset of diabetes, gender, comedication, combination therapy, and daily dosage frequency, were independently related to switching.

*Conclusion* - We were unable to confirm the hypothesis that noncompliance with treatment is more prevalent in patients with secondary failure. Other variables, like comorbidity and disease-related factors seem to play a more important role in switching to insulin therapy.

## Introduction

Oral hypoglycemic agents are the major treatment for people with type 2 diabetes mellitus. As type 2 diabetes mellitus advances, secondary failure of oral hypoglycemic therapy develops as a consequence of progressive loss of beta-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance.[1, 2] Each of the available oral hypoglycemic agents has limited glucose-lowering efficacy and many patients eventually require insulin to avoid marked hyperglycemia.[3]

Furthermore, other factors, such as severity of the disease itself and younger age at diagnosis, may contribute to disease exacerbations leading to a switch to insulin therapy due to secondary failure.[4, 5]

Noncompliance with prescribed regimens is one of the main causes of poor metabolic control in patients with diabetes.[6] An estimated 10-30% of patients with type 2 diabetes withdraw from their prescribed regimen within 1 year of diagnosis and, of the remainder, nearly 20% administer insufficient medication to facilitate an adequate reduction in blood glucose.[7]

'Compliance' has been defined as an attempt by patients to take their medication each day as prescribed, or the extent to which the patient's actual history of drug administration corresponds to the prescribed regimen.[8] Patients typically take less medication than they have been prescribed. In several studies assessing adherence to glucose lowering regimens, overall compliance rates between 64 and 83% were found for oral hypoglycemic agents.[9-12]

The prescription refill records of centralized pharmacies are a potential source of information about patient compliance. Based on the assumption that a patient cannot be compliant when he has not obtained sufficient medications, *refill compliance* can be measured.[13]

Population-based studies of refill compliance showed that many, if not most, patients fail to continue medication intended for long-term use[14]; therapy discontinuation rates for oral hypoglycemic agents varied between 8 and 16% per year.[10, 15] Noncompliance of oral hypoglycemic agents results in decreased glycemic control, which falsely indicates secondary failure and unjustified initiation of insulin therapy.

The purpose of the present study was to assess whether switching to insulin therapy in patients with type 2 diabetes is associated with medication refill compliance of oral hypoglycemic agents.

## Patients and methods

*Data source*

The PHARMO Record Linkage System (PHARMO RLS) was used as data source for this study. The PHARMO RLS comprises pharmacy dispensing records linked to hospital discharge data of all community-dwelling residents of eight Dutch cities, counting for more than 450,000 patients histories, from 1985 onwards.[16, 17] Drugs are coded according to the *Anatomical Therapeutic Chemical (ATC) Classification*.[18] Because in the Dutch health care system patients are usually designated a single pharmacy to fill their prescriptions independent of prescriber, virtual complete data are available for each subject. These data include sex, date of birth, drug names with ATC codes, dispensing date, total supply, prescribed dosage regimen, prescriber, dates on admission and discharge from hospital, and discharge diagnoses.

*Study subjects*

Patients with newly treated type 2 diabetes mellitus were defined as subjects in whom oral hypoglycemic therapy was initiated between 1991 and 1998. The date of starting oral hypoglycemic treatment was presumed to approximate their date of clinical diagnosis. Patients were eligible for inclusion in the cohort if they received no hypoglycemic medication during 180 days (half a year) preceding the date of starting oral hypoglycemic agent use. Furthermore, patients were only included if they were dispensed at least two consecutive prescriptions of oral hypoglycemic agents.

We performed a matched case-control study, nested in this cohort of patients with type 2 diabetes. Cases were patients initially treated with oral hypoglycemic agents who added or switched to insulin therapy. Date of switching

in the case was defined as the index date for each matched pair. Their medication history of oral hypoglycemic therapy before the switch was at least 18 months. Controls were subjects still on oral therapy on the index date. We matched cases and a similar number of controls on calendar time (quarter of the year) of first prescription of an oral hypoglycemic agent. From the 430 cases who met the inclusion criteria, 16 were excluded because they discontinued their oral therapy in the 18 month-period before the index date. Discontinuation of pharmacotherapy was defined as a gap of at least 365 days (a year) during which the patient used no hypoglycemic agents at all. For three cases, the matching procedure was not successful. Eventually, these additional exclusions left 411 cases and 411 controls for study.

*Medication use*

In general, Dutch pharmacy policy limits the quantity of medications dispensed at one time to a 3-month supply and requires physicians to write new prescriptions at six-month intervals. All prescriptions for oral hypoglycemic agents (sulfonylureas, biguanides, or alpha-glucosidase inhibitors) were retrieved. Both for the cases and controls, we measured the medication refill compliance in the year starting 18 months (a year and a half) before the index date (called 'risk window'), excluding the half-year period before the index date.

Visualized:


The reason we disregarded this 'black period' is because we knew from clinical practice and research experience that this episode just before a switch to insulin is frequently featured by cluttered and erratic drug use patterns, with several oral hypoglycemic agents prescribed at the same time and often an unclear dosage regimen, due to the lack of adequate glycemic control in this period.

With regard to drug regimen characteristics and complexity, three variables were created from the prescription profile of each patient: the average number of doses per day of oral hypoglycemic agents, presence of combination therapy (concomitant use of more than one hypoglycemic agent), and the number of concurrent medications other than hypoglycemic drugs.

*Ascertainment of refill compliance*

The pharmacy data were used to calculate the compliance measure on the basis of an index previously developed and validated by Steiner *et al.*[13] The intended duration of every oral hypoglycemic agent prescription was calculated from details on the dispensing (total amount dispensed and drug regimen). Firstly, we calculated MED_INT (Medication-Interval) for all successive prescriptions during the exposure window. MED_INT is the ratio of days' supply obtained at the beginning of a specific time interval to the days elapsed before the subsequent refill. For a series of refill intervals, an overall measure of compliance, MED_TOT (Medication-Total), was calculated as the total supply of pills dispensed divided by the total number of days elapsed.

Because measures of medication availability may fail to identify clinically meaningful treatment gaps, we also calculated a third compliance index, MED_OUT (Medication-Out). MED_OUT was defined as the total number of days without medications divided by the total days of observation. So, if it comes to perfect compliance, i.e. continuous drug availability, MED_TOT = 1 and MED_OUT = 0. Subsequently, different categories of compliance were created from these continuous indices. A classification of undercompliance ('gap') was given if the patient refilled the prescription more than 7 days after the expected date or MED_INT was < 90%. A classification of overcompliance ('oversupply') was given if the patient refilled the prescription more than 7 days before the expected date or MED_INT was > 110%. Relative over- and undercompliance was assessed by dividing the total number of oversupplies and gaps, respectively, by the total number of dispensings.

Furthermore, we looked at compliance as a dichotomous measure and considered patients to be sufficiently compliant with their treatment when at least

80% of the days in the study period were covered.[19, 20] Since the outpatient pharmacies do not record prescriptions dispensed during an inpatient admission, the number of days spent in the hospital was included in the model to control for possible underestimation of compliance due to hospitalizations.

*Comorbidity*

An individual's morbidity and overall health status was assessed using the chronic disease score (CDS), a validated measure of chronic medical conditions based on medications used.[21-23] The CDS was calculated by assigning scores (0 – 5) to classes of drugs according to the severity of the disease for which they were prescribed during a one-year period, the (hypothetical) maximum total score is 35. Because the study population comprised patients with type 2 diabetes mellitus, the minimum score was 2. For example, a CDS of 7 or more is associated with a fivefold increase in the risk of hospitalization and a tenfold increase in the risk of death.[21]

*Statistical Analysis*

We performed conditional logistic regression analysis to estimate matched odds ratios (ORs) with respect to the different compliance indices for cases compared to controls, and 95% confidence intervals (CIs), using EGRET.[24]

With regard to potential confounding, we controlled for age, sex, drugs regimen characteristics, days of hospitalizations, and comorbidity as measured by the chronic disease score. We used chi-square (categorical variables) and Mann-Whitney (continuous variables) tests to evaluate differences in general characteristics between cases and controls.

Furthermore, we performed multivariate conditional logistic regression analysis to define a model including only strong and/or known predictors of switching to insulin therapy.

## Results

In this nested case-control study, 411 cases (patients who switched to insulin) and 411 matched controls (those who did not switch) were identified in the period from 1991 to 1998. General characteristics are given in *Table 6.1*. There was a borderline significant difference with respect to sex distribution in cases and controls (50% versus 44% males, respectively, p= 0.06). The mean chronic disease score, as an indicator of morbidity and overall health status, was not different in cases and controls (5.7 versus 5.3, p= 0.07). Severe (co)morbidity (CDS> 7) was more prevalent in cases compared to controls (28% versus 18%, p= 0.001). In total, 112 (13.6%) patients were hospitalized during the one-year exposure period, the maximum number of hospitalizations was 6. With respect to concomitant drug use, cases used on average one (not hypoglycemic) drug more than controls (p= 0.004). Cases were about twice more likely to use more than one hypoglycemic agent; 239 (58%) cases received combination therapy, compared to 120 (29%) of the controls (p< 0.001). The most common combination was a second-generation sulfonylurea derivative with metformin (59%), followed by two different sulfonylureas (16%) and a second-generation sulfonylurea with acarbose (12%).

*Table 6.2* presents various ascertained compliance indices in cases and controls. The overall compliance rate (MED_TOT) and MED_OUT did not differ significantly between cases and controls. The crude OR for MED_TOT was 1.5 ($CI_{95\%}$: 0.8-2.8). In addition, after controlling for comorbidity (CDS, hospitalizations), drug regimen characteristics (dosage frequency, combination of oral hypoglycemic therapy, concurrent medication), and patient characteristics (gender, age at onset), the adjusted OR was 1.3 ($CI_{95\%}$: 0.6-2.8). With respect to the different oral hypoglycemic agents, mean compliance rates varied between 96.2% (glimepiride) and 99.3% (acarbose). Compliance was related to frequency of dosage and varied between 98.1% (once or twice daily) and 93.6% (three or more times daily), p= 0.01. When we considered patients sufficiently compliant with an overall compliance rate of at least 80%, 86.1% of the cases and 83.5% of the controls were compliant, this difference was statistically not significant (p= 0.29). Relative overcompliance was more prevalent in cases (32% versus 28%, resp.) with a matched OR of 1.9 ($CI_{95\%}$: 1.0-3.7). With respect to relative undercompliance,

cases and controls were comparable (33% versus 34%, respectively). When compliance was defined as 1-MED_OUT, mean compliance was 85.3±15%.

As presented in *Table 6.3*, the following variables were related to switching: gender, age at onset of diabetes, comedication, combination therapy (simultaneous use of more than one oral hypoglycemic agent), daily dosage frequency. Overcompliance , defined as a mean overall compliance rate higher than 110%, was a borderline significant determinant (p= 0.07).

**Table 6.1** General characteristics of the study population

| Variable | | Cases (N=411) | Controls (N=411) | P-value |
|---|---|---|---|---|
| Male sex (%) | | 207 (50%) | 180 (44%) | 0.059 |
| Age at onset* (yrs) | | 59.0 ± 0.6 | 65.0 ± 0.6 | <0.001 |
| Calendar year of onset* | | 1993.9 ± 0.07 | 1993.9 ± 0.07 | … |
| Duration of disease† (yrs) | | 3.5 ± 0.07 | 3.5 ± 0.07 | … |
| Age at switching (yrs) | | 62.5 ± 0.6 | … | … |
| Chronic Disease Score: | | | | |
| | 2 | 95 (23%) | 105 (26%) | 0.416 |
| | 3-5 | 110 (27%) | 120 (29%) | 0.437 |
| | 6-7 | 93 (23%) | 113 (27%) | 0.107 |
| | >7 | 113 (28%) | 73 (18%) | 0.001 |
| Comedication (total number of drugs)‡ | | 8.3 ± 0.3 | 7.0 ± 0.2 | 0.004 |
| Number of hospitalizations‡ | | | | |
| | 0 | 351 (85%) | 359 (87%) | 0.416 |
| | 1 | 40 (10%) | 41 (10%) | 0.907 |
| | >=2 | 20 (5%) | 11 (3%) | 0.099 |
| Drug regimen | | | | |
| 1. Monotherapy | | 172 (41.8%) | 291 (70.8%) | <0.001 |
| OHA§: | Tolbutamide | 34.9 | 50.9 | 0.001 |
| | Glibenclamide | 37.8 | 22.7 | <0.001 |
| | Gliclazide | 18.0 | 19.6 | 0.678 |
| | Glimepiride | 4.1 | 0.3 | 0.003 |
| | Metformin | 5.2 | 5.5 | 0.903 |
| | Acarbose | 0 | 1.0 | 0.182 |
| 2. Combination therapy | | 239 (58.2%) | 120 (29.2%) | <0.001 |
| Number of OHAs§ | | 1.8 (1-4) | 1.3 (1-3) | <0.001 |
| Daily dosage frequency | | 2.1 (1.0-3.7) | 1.9 (1.0-4.0) | <0.001 |

Data are means ± SEM or numbers; variance or percentages between parentheses

* date of first prescription of oral hypoglycemic agent

† at indexdate, i.e. date of switching to insulin therapy of the cases

‡ during the one year period refill compliance was measured

§ OHA: oral hypoglycemic agent, with respect to use of OHAs, percentages are given

**Table 6.2** Compliance indices in cases and controls

| Outcome variable | Cases (N=411) | Controls (N=411) |
|---|---|---|
| Compliance rate (MED_TOT) | 0.98 (0.17-2.39) | 0.96 (0.24-1.55) |
| Compliance category*: <0.70 | 9.2 | 10.0 |
| 0.70-0.89 | 16.3 | 16.5 |
| 0.90-1.10 | 51.6 | 58.4 |
| 1.11-1.30 | 18.2 | 10.7 |
| >1.30 | 4.6 | 4.4 |
| MED_OUT | 0.15 (0-0.86) | 0.14 (0-0.76) |

variance or percentages between parentheses

* with respect to compliance categories, percentages are given

**Table 6.3** Determinants of switching to insulin therapy*

| Variable | OR | $CI_{95\%}$ |
|---|---|---|
| Gender (1=male) | 1.45 | 1.04-2.03 |
| Age at onset (per year) | 0.96 | 0.94-0.97 |
| Comedication (per extra drug)† | 1.08 | 1.04-1.11 |
| Glucose lowering combination therapy (1=yes) | 3.44 | 2.36-5.03 |
| Daily dosage frequency | 1.34 | 1.03-1.74 |
| Undercompliance‡ | 1.07 | 0.72-1.57 |
| Overcompliance‡ | 1.51 | 0.96-2.36 |

* multivariate conditional logistic regression modeling

† number of drugs besides hypoglycemic medication

‡ undercompliance: overall compliance rate< 90%; overcompliance: overall compliance rate > 110%; reference category: overall compliance rate 90-110%

## Discussion

We measured refill compliance with oral hypoglycemic therapy among patients who switched to insulin therapy and those who did not. The finding that compliance was only borderline associated with switching does not support the hypothesis that noncompliance with treatment is more prevalent in patients with secondary failure.

A recent study by Evans *et al* for the DARTS/MEMO collaboration showed similar results, they found in a comparable diabetic population even significantly improved compliance in patients who did commence insulin (100.4% versus 92.9% in non-switchers, $p< 0.001$).[25] Other variables, like patient and drug regimen characteristics seem to play an important role in explaining switching to insulin therapy.

Pharmacy records provide a reliable tool to measure drug exposure when compared with home inventory (e.g., a comparison between the prescribed medication vs. the medication in the patient's home) or pill count.[9, 26] One important advantage is avoidance of any Hawthorne effect (i.e., improvement of performance when the subject is under observation) by assessing compliance retrospectively by review of prescription-refill records.[27] Furthermore, it is known that observational studies of drug exposure can be more accurately estimated from dispensing rather than prescribing data, for example, Beardon *et al* found an overall rate of non-redemption of 5.2% with regard to prescriptions.[28] Paes and his colleagues already proposed that the use of refill data might be especially useful in the community pharmacy setting.[9] One advantage of this method is that pharmacy computers can deliver a signal if the patient is too late for his or her refill.[7] It provides the possibility to monitor a large number of patients without extra investments.

Compared to similar studies, we found a reasonably high overall compliance rate of 97%.[9, 10, 12, 30] For example, Paes *et al* examined the compliance as registered by MEMS® (Medication Event Monitoring System) devices of a group type 2 diabetes mellitus patients.[12] They excluded patients using a weekly dose organizer (a substantial part in an elderly population). They found an overall compliance of 74.8%, but compliance was strongly related to frequency of dosage and varied

between 98% (once daily) and 66% (three times daily). We found that higher complexity of the dosage regimen (more comedication, use of combination therapy and higher number of dosages per day) was also associated with a higher risk of switching.

This finding supports the 'stepping stone theory', intrinsic to secondary failure. Before the ultimate switch to insulin, intermediate steps due to gradually worsening of metabolic control are taken, like raising the doses and addition of other oral hypoglycemic agents. When we defined compliance as 1-MED_OUT, our results were compatible with a study by Venturini[11], mean compliance rates were 85% and 83%, respectively.

Refill compliance measures, however, have inherent limitations. First, and most important, refill compliance measures cannot assess the relationship between the duration of drug action and the timing of doses, which has a critical impact on the efficacy of treatment in diabetes. Studies with reliable compliance assessment have shown that the main error patients make is to take the prescribed dose at longer-than-prescribed intervals – often by hours.[29] Other cons of this method are that nothing can be said about patients getting their refills on time, the cause of noncompliance is unknown and in general the results will overestimate compliance.[9] For instance, it is quite common for a person to cash a repeat prescription several days before they need it for reason of convenience. However, the occurrence of this phenomenon is not expected to be different between cases and controls. Besides that, measures of treatment gaps make the assumption that both embedded and terminal gaps are due to noncompliance by the patient rather than drug discontinuation by the clinician.

Unfortunately, the computerized pharmacy records only provide information on the dosage regimen at the time the prescription is filled, interim changes by the physician remain unobserved. The fact that we did not reveal any difference in compliance rates between cases and controls could be due to interim changes to the drug regimen. Cases are more likely to receive increasing doses in response to their poor glycemic control, resulting in an overestimation of the compliance rate. It is important to realize that if the daily dose changes, so does the duration of supply on hand. For example, if a patient were instructed to double his

daily dose, his residual days' supply would be halved. Hence, the refill compliance measurement would be an overestimation of reality. After all, relative overcompliance was substantially higher in the cases. Nevertheless, the high specificity of refill compliance allows identification of a subset of individuals who cannot be taking enough medication to attain a treatment goal, because they have not obtained enough drugs in the pharmacy.[14]

Within the diabetes literature, the tendency has been to treat adherence and metabolic control as interchangeable constructs.[6, 31] Adherence is one factor, but not the only factor, which may influence a patient's metabolic status only when an effective treatment regimen has been prescribed by the physician.[6] Although early addition of other agents may delay the increasing hyperglycemia, each of the available oral hypoglycemic agents has limited glucose-lowering efficacy and many patients eventually require insulin to avoid marked hyperglycemia (i.e. secondary failure). In the UKPDS, the worsening of glycemic control has been attributed to the natural course of type 2 diabetes and lack of efficacy of current antihyperglycemic therapy.[3] We showed that besides adherence, other, sometimes unchangeable factors (e.g. age and gender) are strong predictors of switching to insulin therapy.

In conclusion, we found that noncompliance in general was not associated with switching to insulin in type 2 diabetic patients. In the near future, it could be useful to explore the relationship between 'timing compliance' (timing of doses) and metabolic control using the MEMS® method. We suggest that other factors independent of a patient's willingness to adhere to a treatment regimen, like disease-related factors, are more relevant in explaining secondary failure in most patients.

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# CHAPTER 7

# Antipsychotic Drugs May Worsen Metabolic Control in Type 2 Diabetes Mellitus Patients

## Abstract

*Aim* - Several studies have indicated that type 2 diabetes mellitus is more common among schizophrenic patients than in the general population. Purpose of the present study was to assess the association between the use of antipsychotic drugs and alterations of glycemic control.

*Methods* - In this cohort study, newly diagnosed patients with type 2 diabetes were selected from the PHARMO Record Linkage System, comprising pharmacy records for all 320,000 residents of six Dutch cities. In total, 2,585 patients with type 2 diabetes were identified as incident oral hypoglycemic agents users between 1991-1997 and had at least two years medication history after diagnosis. Switching from oral hypoglycemic agents to insulin therapy was considered a proxy for deterioration of beta-cell function. We compared the incidence of switching between users of antipsychotic drugs and non-users by performing a Cox's proportional hazards model analysis.

*Results* - Two years after diagnosis we found an increased risk for switching to insulin therapy for users of antipsychotics compared to non-users; the relative hazard (hazard ratio, HR) was 2.0 ($CI_{95\%}$: 1.2 – 3.3), which did not change after adjustment for potential confounders. The risk decreased in the subsequent years after diagnosis.

*Conclusion* - It seems that use of antipsychotics in type 2 diabetes mellitus is associated with switching to insulin therapy (i.e. 'secondary failure'), especially in the first two years of the disease.

## Introduction

Several studies indicate that type 2 diabetes mellitus, impaired glucose tolerance, and insulin resistance are more common among patients with psychiatric disorders, such as major mood disorders and schizophrenia, than among the general population.[1-3] As type 2 diabetes advances, secondary failure of oral hypoglycemic therapy develops as a consequence of progressive loss of beta-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance.[4]

In recent years, case reports have been published describing the emergence of de novo onset of diabetes or worsening of previously well-controlled diabetes after the start of treatment with atypical antipsychotics.[5-10] Those 'novel' antipsychotics are called atypical for their relative lack of the extrapyramidal side effects typical of older, mostly higher dosed antipsychotics.[11, 12] Furthermore, already decades ago it has been reported that conventional neuroleptics, chlorpromazine in particular, may also alter glucose-insulin homeostasis[13, 14] and lead to new cases of diabetes mellitus.[15]

The present study deals with the possible relationship between the use of antipsychotic drugs and worsening of glycemic control in patients with type 2 diabetes mellitus. Switching from oral hypoglycemic agents to insulin therapy is considered a proxy for deterioration of metabolic control. Therefore, we compared 'switchers' and 'non-switchers' with respect to antipsychotic drug use during a period following diagnosis of type 2 diabetes mellitus.

## Patients and Methods

*Data source*

The PHARMO Record Linkage System (PHARMO RLS) was used as data source for this study, comprising pharmacy dispensing records of all community-dwelling residents of six Dutch cities, counting for more than 450,000 patients histories, from 1985 to present.[16, 17] Drugs were coded according to the *Anatomical Therapeutic Chemical (ATC) Classification*.[18] Because in the Dutch health care system ambulatory patients are usually designated a single pharmacy to fill their prescriptions independent of prescriber, virtually complete data are available for each subject. These data include sex, date of birth, drug names with ATC codes, dispensing date, total supply, prescribed dosage regimen, and prescriber. Pharmacy data from January 1991 to June 1999 were obtained for this study, comprising about 320,000 patient histories.

*Study subjects*

In this cohort study, incident patients with type 2 diabetes mellitus were defined as subjects starting their first oral hypoglycemic treatment (ATC code A10B) between 1991 and 1997. Patients were eligible for inclusion if they received no hypoglycemic medication (tablets or insulin) during 180 days (half a year) preceding the date of starting oral hypoglycemic agent use. Furthermore, patients were only included if they were dispensed at least two consecutive prescriptions of oral hypoglycemic agents. Subsequently, we excluded subjects who switched to insulin within 3 months (90 days) after their first prescription of a hypoglycemic agent ('primary failure').

*Study design*

We performed a follow-up study in a subcohort of patients who had at least two years (730 days) of medication history after diagnosis, i.e. first prescription of an oral hypoglycemic agent. Exposure was defined as the usage of antipsychotic drugs (i.e. 'any use'), ATC group N05A (excluding lithium, N05AN), in the two years after the first use of an oral hypoglycemic agent. The event of interest was defined

by switching from oral hypoglycemic agents to insulin therapy (ATC code A10A) with or without continuation of oral hypoglycemic medication. We compared the incidences of switching to insulin therapy between users of antipsychotic drugs and non-users. Atypical antipsychotic drugs included risperidone, clozapine, olanzapine, and quetiapine.[19]

*Data analysis*

For the comparison of continuous variables and categorical variables between users of antipsychotics and non-users, we used the Student's *t*-test and $\chi^2$ test, respectively.

We performed a Cox's proportional hazards model analysis (variable follow-up) in the cohort of all incident type 2 diabetic patients who had at least two years of follow-up. Survival time was from date of first prescription of oral hypoglycemic agents to the day of switching to insulin therapy. Patients who did not switch were censored at the date of leaving the pharmacy (i.e. loss to follow-up) or end of study (July 1999). Use of antipsychotics (dichotomous), age at date of first prescription of oral hypoglycemic agents (years), gender, and calendar year of diagnosis, were time-independent variables.

We adjusted for the use of anticholinergic antiparkinson medication (ATC group N04A), because a higher rate of switching might be expected in patients suffering from extrapyramidal side effects. With regard to other potential confounders, we took into account the use of medication with known side effects on glucose metabolism: corticosteroids for systemic use (H02), beta-blocking agents (C07), and thiazides and loop diuretics (C03, except C03D). Because of the known positive relationship between the prevalence of depressive disorders and type 2 diabetes[20], we also investigated the potential association or interaction between antipsychotics, switching and antidepressants.

Subsequently, we calculated crude and adjusted relative hazards (hazard ratios, HR) with the corresponding 95% confidence intervals ($CI_{95\%}$) for switching to insulin in the users of antipsychotic drugs at several time intervals of follow-up (two, three, four and five years after diagnosis of diabetes mellitus).

## Results

In total 3,001 patients with newly diagnosed type 2 diabetes mellitus were enrolled in the study, their demographic characteristics and some data on drug usage are given in *Table 7.1*.

**Table 7.1** Basic characteristics of patients with type 2 DM

| Variable | N = 3,001 |
|---|---|
| Male sex (%) | 1472 (49.1%) |
| Age at index date* (yrs) | 63.4 (0.24) |
| Duration of disease (yrs) | 4.0 (0.04) |
| Total follow-up time (yrs) | 9.9 (0.05) |
| Insulin therapy (%) | 603 (20.1%) |
| Age at switching† (yrs) | 62.2 (0.54) |
| Duration of disease at date of switching† (yrs) | 2.8 (0.07) |
| *Drug use during diabetes (%)* | |
| Cardiovascular drugs‡ | 2298 (76.6%) |
| Psycholeptic drugs§ | 1435 (47.8%) |
| Antipsychotics\|\| | 248 (8.3%) |
| Atypical antipsychotics¶ | 14 (0.5%) |
| Lithium | 12 (0.4%) |
| Antidepressive agents | 361 (12.0%) |

Data are means with standard error of the mean between parentheses or numbers (with percentages, %)

* date of first prescription of oral hypoglycemic agents

† N = 603 (switchers)

‡ cardiovascular drugs are defined as antithrombotics, cardiacs, diuretics, ß-blockers, calcium channel blockers, ACE inhibitors, other antihypertensive drugs, and lipid lowering agents (ATC codes B01, C01-C03, C07-C10)

§ ATC group N05

|| ATC group N05A (excluding lithium, N05AN)

¶ clozapine, risperidone, olanzapine, or quetiapine

Age at diagnosis varied between 18 and 98 years. Among antipsychotic drug users ('ever use'), 99 (40%) received only one or two prescriptions, 68 (27%) received 3-9 prescriptions, 30 (12%) received 10-19 prescriptions, and 51 (21%) received 20 or more prescriptions. In the baseline cohort, within the total follow-up period only 14 (0.5%) used an atypical antipsychotic drug after the date of first prescribed oral hypoglycemic agent. Antipsychotic drugs most frequently used were haloperidol (Haldol®, 29%), pipamperone (Dipiperon®, 27%), levomepromazine (Nozinan®, 16%), and zuclopenthixol (Cisordinol®, 14%).

A total of 2,585 (86%) patients completed two years of follow-up after the index date (first prescription of oral hypoglycemic agent). They were younger at diagnosis than the remaining 416 subjects, 62.6 versus 69.0 years ($P< 0.001$), they did not significantly differ with respect to gender distribution. These patients were included in the Cox's regression analysis.

*Figures 1a – 1d* show the 'insulin free survival' in antipsychotic users and non-users during the course of time (exposure definition at two, three, four and five years after diagnosis, respectively). For instance, after four years of disease, well over 20% switched to insulin therapy in both groups. Because primary failure was an exclusion criterion, the figures show straight regression lines in both groups during the first three months (i.e. no events). Crude and adjusted HRs are shown in *Table 7.2*. Two years after diagnosis we found an significantly increased risk for switching to insulin therapy for users of antipsychotics compared to non-users; the hazards were 18.4% and 9.3% respectively, and the crude relative hazard (hazard ratio, HR) was 2.0 ($CI_{95\%}$: 1.2 – 3.3). In this two-year period, 236 patients (9.1%) switched to insulin therapy. Adjusted for age at onset and calendar year of first prescription of an oral hypoglycemic agent, the HR was 2.0 ($CI_{95\%}$: 1.2 – 3.3). Additionally, we controlled for concomitant medication (see table comments). Adjustment for differences in gender distribution did not change the results.

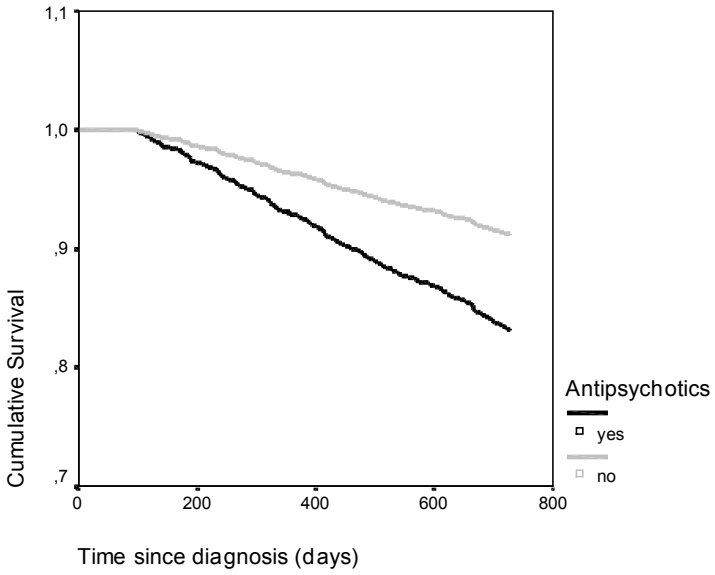


**Figure 7.1 a** Cut-off point at 2 years

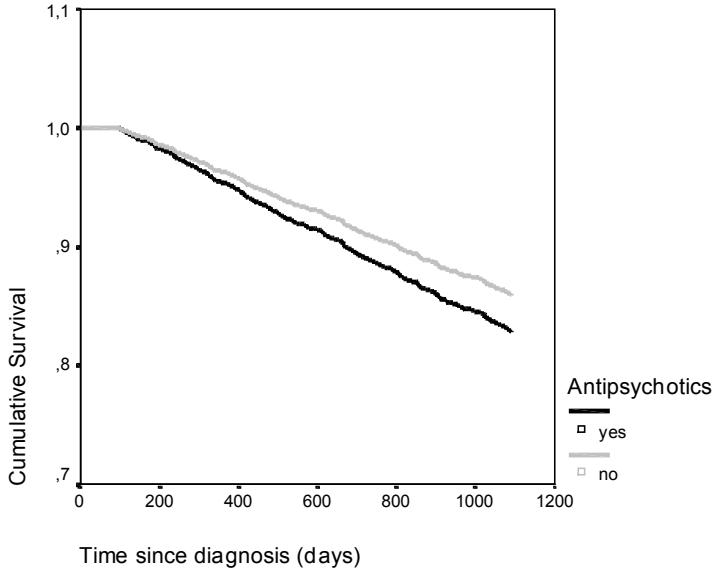


**Figure 7.1 b** Cut-off point at 3 years

**Figure 1a-1d** Switching to insulin therapy by use of antipsychotic drugs after 2, 3, 4, and 5 years respectively

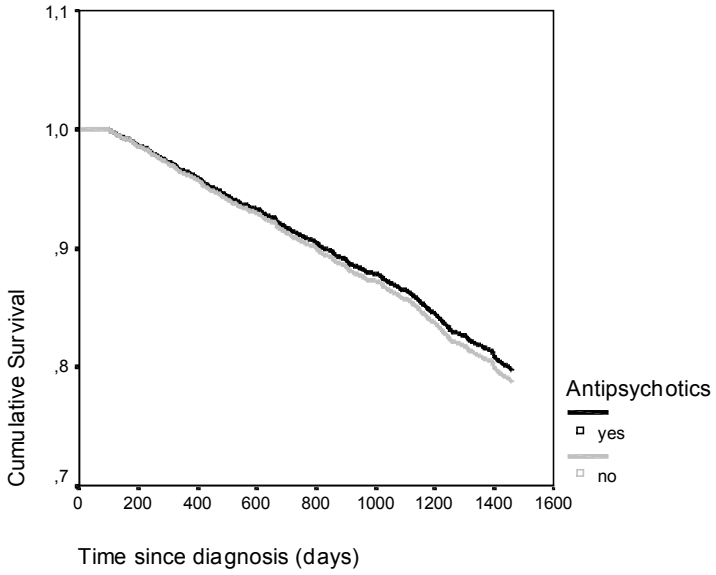


**Figure 7.1 c** Cut-off point at 4 years

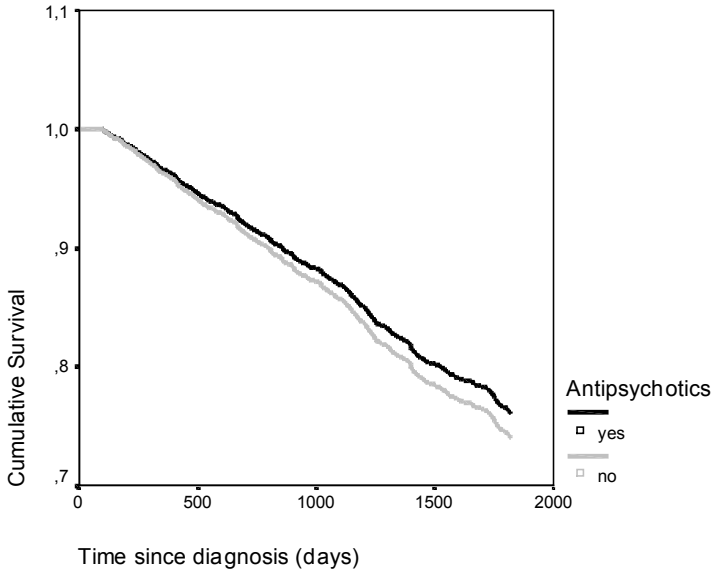


**Figure 7.1 d** Cut-off point at 5 years

*First two years after diagnosis*

Subsequently, we singled out the two-year period after diagnosis. We investigated the degree of continuation of oral hypoglycemic medication after the start of insulin therapy (i.e. combination therapy) in both groups. In non-users of antipsychotics, the oral therapy was continued in about half of the patients (49%), while in users of antipsychotics only 4 out of 16 switchers (25%) were on combined medication regimen. The odds ratio for continuation of oral therapy after switch was 0.4 ($CI_{95\%}$: 0.1 – 1.1), thus borderline significant (p= 0.06).

Of the 236 switchers, 14 (7.0%) used antipsychotics during the last two years, compared to 77 (3.3%) of the patients who continued oral hypoglycemic therapy (OR 2.2, $CI_{95\%}$: 1.2 – 4.0). No switch to insulin therapy was seen in any of the 6 patients who used *atypical* antipsychotic drugs.

Use of antipsychotics was strongly associated with use of antidepressants, in users of antipsychotics the prevalence of antidepressant use was 34% versus 7% in non-users (OR 7.5, $CI_{95\%}$: 4.8 – 11.9). After additional adjustment for use of antidepressants, the relationship was still statistically significant (*Table 7.2*).

**Table 7.2** Crude and adjusted hazard ratios ($HR_{crude}$ and $HR_{adj}$) at different time intervals since diagnosis of DM

| Time since diagnosis | $HR_{crude}$ | $HR_{adj}$* | $HR_{adj}$† |
|---|---|---|---|
| 2 years | 2.0 [1.2-3.3] | 2.0 [1.2-3.3] | 1.7 [1.0-3.0] |
| 3 years | 1.2 [0.8-2.0] | 1.3 [0.8-2.1] | 1.2 [0.8-2.0] |
| 4 years | 0.9 [0.6-1.4] | 1.0 [0.7-1.6] | 1.0 [0.7-1.6] |
| 5 years | 0.9 [0.6-1.3] | 1.0 [0.7-1.4] | 1.0 [0.7-1.6] |

95% Confidence intervals between square brackets

* Adjusted for age at onset and calendar of diagnosis

† Additional adjustment for use of ß-blocking agents, diuretics (thiazides and loop-), antiparkinson drugs, antidepressants, and corticosteroids for systemic use

Finally, when we compared the risk of switching to insulin therapy over the total follow-up period between users and non-users of antipsychotics in the first two years after the onset of diabetes, the HR was 1.6 ($CI_{95\%}$: 1.1 – 2.4).

## Discussion

In our study, the use of antipsychotic drugs in type 2 diabetes mellitus was associated with a higher rate of switching to insulin therapy (i.e. 'secondary failure'), especially in the first two years of the disease. This present study strongly indicates that antipsychotic drugs can not only induce diabetes but also cause worsening of glycemic control in patients with already known type 2 diabetes.

In type 2 diabetes the primary underlying defect is probably insulin resistance, with an early phase of normal plasma glucose levels maintained by compensatory hyperinsulinemia. The failure to maintain this compensatory hyperinsulinemia eventually results in loss of glycemic control and development of clinical diabetes. Many studies have reported that diabetes, impaired glucose tolerance, and insulin resistance are more common among patients with schizophrenia and other mental illnesses than among the general population.[1-3, 9, 21] For instance, Mukherjee and colleagues found a 15.8% overall prevalence of diabetes among schizophrenic patients, this prevalence is considerably higher than reported from epidemiological surveys in the general population.[3] Therefore, the possibility remains that diabetes in schizophrenia may result from the use of neuroleptics, rather than the psychiatric disorder itself.[22] Although the exact mechanism of antipsychotic induced diabetes remains obscure, studies by Ardizzone *et al* suggest that atypical drugs may block glucose accumulation directly at the level of the glucose transporter protein in cells derived both from peripheral and brain tissue.[23]

Some limitations of this study need to be addressed, notably the lack of information on important patient factors that predict severity or prognosis of disease, like body mass index, lipids, smoking habits, $HbA_{1c}$, prevalence of diabetic complications, and blood pressure. So the results could be confounded by one of these factors, without the possibility to correct for it. Therefore, differences in switching to insulin therapy may to some extent be explained by metabolic

differences. For instance, type 2 diabetes mellitus is strongly and consistently associated with overweight and obesity. Moreover, weight gain is a well-known side effect of antipsychotic drug use[24, 25], so maybe the weight gain is partly responsible for the worsening of metabolic control rather than the drug itself.[26] Although we cannot examine the possible etiologic causal explanations, this does not weaken the found association between antipsychotic drug use and worsening of glycemic control.

Furthermore, it is important to mention that we studied an elderly population with type 2 diabetes in an outpatient setting. Data were obtained from community pharmacies so patients living in nursing homes, psychiatric institutes, and mental clinics were not included. Elderly patients have various medical grounds for using antipsychotic drugs, for instance: (nocturnal) agitation, the beginnings of dementia, acute psychosis, delirium, bipolar disorder, or schizophrenia. Unfortunately, we had no information on the indication for which the antipsychotic drugs were prescribed. So, we could not link psychiatric diagnoses to switching to insulin therapy directly.

Antipsychotic drugs can be classified, based on their liabilities to induce extrapyramidal side effects (EPS), into two main categories: typical antipsychotics, which are often associated with EPS of both acute and chronic nature and atypical antipsychotics, which cause a significant lower incidence of EPS.[11] In contrast to current belief, we found no difference between atypical and conventional antipsychotic drugs with regard to worsening of glycemic control, but the 'novel' drugs were rarely prescribed and no event of interest was observed in the group of atypical antipsychotic drug users.

We propose that the observed worsening of metabolic control is probably due to pancreatic beta-cell toxicity of antipsychotic drugs. First, the deterioration appears in an early stage of the disease, which suggests that antipsychotic drugs have a quite immediate effect in susceptible subjects. The fact that two, three, four, and five years after the diagnosis of diabetes the corresponding risk for switching in users of antipsychotics compared to non-users changed from 2.0 through 1.2 into 0.9, indicates an acute effect that diminishes in the course of time. This is

strongly in favor of beta-cell toxicity rather than deterioration of insulin resistance, which would cause a more gradual decline in beta-cell function.

Secondly, after the switch to insulin therapy only 25% of the antipsychotic users continued their oral hypoglycemic therapy, which is half the prevalence of combination therapy in non-users. Since the mechanism of action of all oral hypoglycemic agents to a great extent depends on the residual activity of the beta-cell, oral therapy will be ineffective if beta-cell toxicity is the case.

In conclusion, our study suggests that antipsychotics, besides already known diabetogenic effects, can lead to fast deterioration of glycemic control, probably due to beta-cell toxicity. Although many aspects of this relation remain unclear and uncertain, we believe that glycemic control should be monitored more closely in these patients.

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# CHAPTER 8

# General Discussion

## Introduction

This thesis started with a discussion on the gradually and frequently progressive nature of the disease course of type 2 diabetes mellitus, previously named Non-Insulin-Dependent Diabetes Mellitus or adult-onset diabetes. The disease of interest in this thesis is a metabolic disorder characterized by the combination of resistance to the action of insulin and an inadequate compensatory insulin secretory response of the pancreatic β-cell.[1] Biochemical onset invariably precedes clinical diagnosis, and the pancreatic β-cell function and insulin secretory remaining capacity in newly diagnosed patients will differ. Disease control and response to therapy are traditionally evaluated by assessing $HbA_{1c}$ levels. Since the last few years also other risk factors such as blood pressure and serum cholesterol levels are determined. These risk factors reflect intrinsic disease severity as modified by patient self-care behavior and clinical management.

Glycemic control deteriorates further with time as complications ensue, accompanied by progressive requirements for higher doses of hypoglycemic agents.[2, 3] Moreover, many patients end up in a phase where insulin therapy is needed to achieve adequate glycemic control. Hub-and-spokes patterns of patients switching between different treatment scenarios are rather the rule than the exception. Some selected, but typical courses of diabetes in general practice and response to therapy strategies over time are depicted on the facing page (*Figure 8.1*).

In this thesis, treatment courses of type 2 diabetes as been depicted in *Figure 8.1* have been assessed with regard to determinants and effects of switching between different available glucose lowering treatment strategies. We will discuss in this chapter the headlines of our findings, will put them in the perspective of further research and will conclude with some comments on the prospects of UDES. We will address the research value and accessibility of routinely recorded data in health care for scientific purposes.

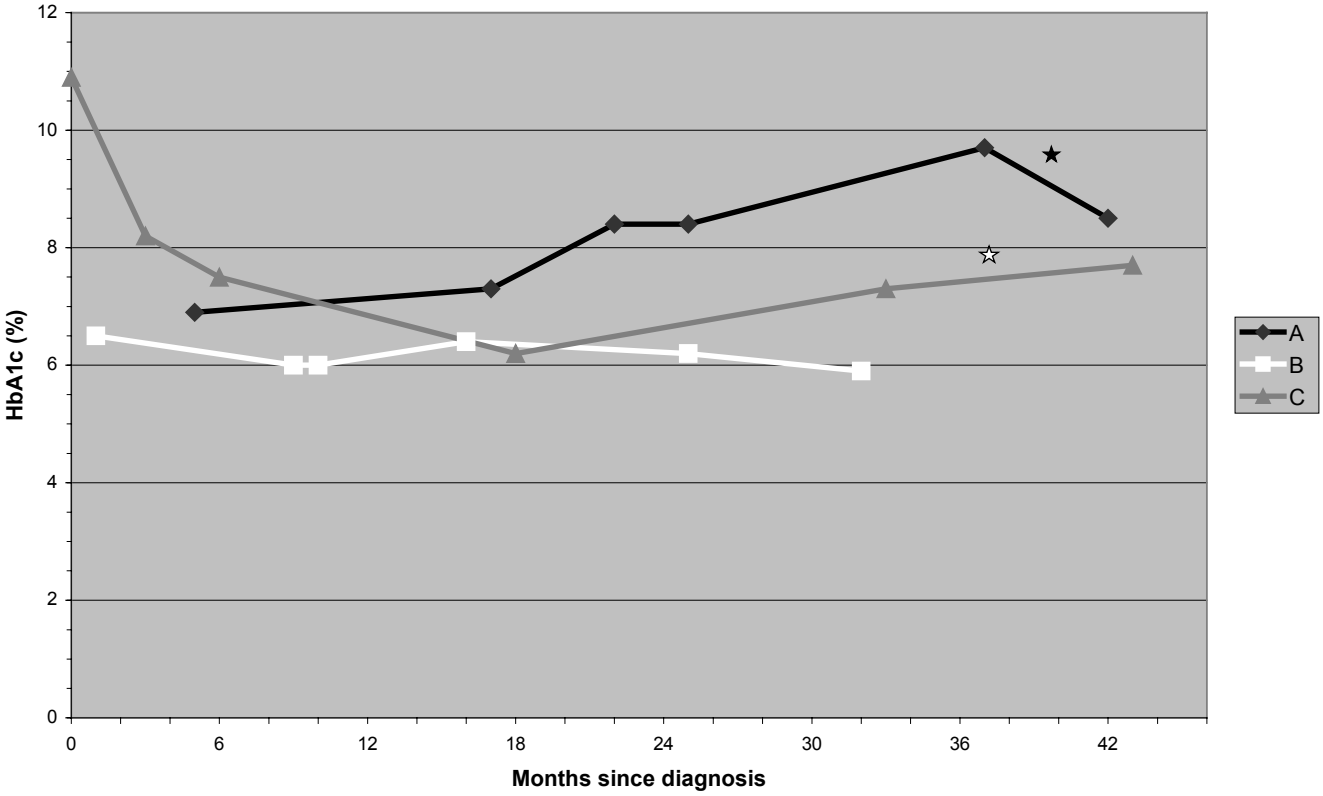


**Figure 8.1** (cases selected from the source population as described in Chapter 2) shows typical glycemic control ($HbA_{1c}$, %) in three female patients with type 2 diabetes mellitus, following different glucose lowering treatment strategies.

Patient A was 57.9 years old (weight 84 kg, height unknown) at onset of diabetes and started immediately with oral therapy, notably tolbutamide. She was treated for dyslipidemia with pravastatin 20 mg once daily. Fasting and non-fasting glucose levels at diagnosis were 9.0 and 20.2 mmol/l. After almost three and a half-year (black asterisk) she switched over to insulin therapy. Patient B, 66.9 years old, with a body mass index of 23.3 kg/m$^2$ and fasting- and non-fasting blood glucose levels of 6.8 and 11.7, respectively, at diagnosis. She had hypercholesterolemia, treated with fluvastatin 40 mg daily, and a cerebrovascular accident in her medical history. She achieved a maximum weight loss of 5 kg (BMI 21.6 kg/m$^2$) and remained stable at a weight of 57 kg (BMI 22.5 kg/m$^2$). This patient had a mean $HbA_{1c}$ value of 6.2% and showed excellent glycemic control on dietary treatment only. Patient C, 54.3 years old, with untreated hypertension, had fasting- and non-fasting glucose levels of 10.8 and 18.8 mmol/l when diagnosed with type 2 diabetes. She started with lifestyle changes but after a good initial response, illustrated by decreasing $HbA_{1c}$, glycemic control deteriorated. She gained weight during course of the disease, increasing from 65 (BMI 24.5 kg/m$^2$) to 67 (25.2 kg/m$^2$) kg. Well over three years since diagnosis oral drug treatment was initiated with glicazide (white asterisk).

## Glucose lowering therapy in general practice: initiation and switching

The first-line therapy modality for type 2 diabetes includes an optimal diet with appropriate weight reduction and exercise accompanied by patient education and self-management. Only when these measures fail to restore adequate glycemic control after a run-in period of at least three months, pharmacologic treatment should be considered.[4, 5] However, in a reaction coming from internal medicine on the Dutch GP guidelines, the reviewer argued in favor of earlier control and consideration of the height of the blood glucose level.[6]

Pharmacological treatment of diabetes may be no more than a surrogate for successful weight loss, the only strategy that offers the prospect of cure.[7, 8] In obese patients with type 2 diabetes, weight loss of 10 kg can achieve greater reductions in $HbA_{1c}$ and fasting glucose than treatment with metformin, and improves control of lipid and blood pressure without the need for additional drug treatment.[9]

However, although diet and exercise can be effective strategies over the short-term, only a few patients obtain substantial long-term benefit.

Early in the course of the disease, insulin resistance and hyperinsulinemia characterize diabetes. But as the disease progresses and insulin deficiency becomes the central issue, it may be to late for weight loss to be helpful. In fact, we doubt whether patients who remain on dietary treatment for years and have adequate and stable glycemic control merit the diagnosis 'type 2 diabetes mellitus', or rather just have relative insulin resistance due to overweight or obesity.

As shown in Chapter 2, a small but substantial part of newly diagnosed type 2 diabetes patients remains on diet only while achieving good glycemic control. This shows that indeed a small proportion of patients is able to 'cure' their diabetes by their lifestyle changes, weight loss in particular. However, it is also possible that the diagnosis was made incorrectly. One could question if these patients have been 'cured' by their lifestyle changes - weight loss in particular - or if the diagnosis was incorrect.

At 3 years after diagnosis of diabetes, approximately 50% of patients will need more than one pharmacological agent because monotherapy does not achieve the target values of $HbA_{1c}$ and by 9 years approximately 75% of patients will need

multiple therapies to achieve FPG concentrations of less than 7.8 mmol/l or $HbA_{1c}$ levels below 7%.[2] It is apparent by 9 years after diagnosis that even with a combination of oral agents a substantial number, possibly the majority, of patients will need the addition of insulin therapy to obtain an $HbA_{1c}$ level below 7%.[2] GPs should not hesitate too long to take this step, because after initial fear or reservation of both patients and doctors, metabolic control and treatment satisfaction increase, while cardiovascular risk decreases.[10-12] The UKPDS showed that in patients with type 2 diabetes, complications of the disease affected quality of life, whereas therapeutic policies shown to reduce the risk of complications had no effect on quality of life.[13] A Dutch study presented similar results, but besides complications also insulin therapy and obesity were independently associated with a lower health-related quality of life.[14] In our study in Chapter 2 we showed that the initial severity of diabetes, assessed by the degree of hyperglycemia, is a major factor in determining the likelihood of achieving target levels of glycemic control in the future, regardless of actual glucose lowering treatment.

We found that increased intensity of glucose lowering therapy was significantly associated with poorer glycemic control, higher body weight and increased prevalence of hypertension (Chapter 3). Despite further deterioration of glycemic control with intensified glucose lowering treatment, control of other metabolic risk factors remained stable, probably due to increased prescribing of cardiovascular drug therapy. These findings are consistent with the results from a review on glycemic control and cardiovascular disease by Wild *et al.* They concluded that control of hypertension and hyperlipidemia are important to reduce risk of cardiovascular disease in people with diabetes and may be more easily achieved than tight glycemic control.[15] In the near future, hopefully more insight regarding the association between blood pressure and glucose lowering therapy and the development of micro-and macrovascoular outcomes in type 2 diabetic patients will be provided by results from the ADVANCE study.[16] ADVANCE is designed to provide reliable evidence on the balance of benefits and risks conferred by blood pressure lowering therapy and intensive glucose control therapy in high-risk diabetic patients, regardless of initial blood pressure or glucose

concentrations. The primary outcomes are, first, the composite of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death and, second, the composite of new or worsening nephropathy or diabetic eye disease.

It is possible that secondary failure of oral hypoglycemic drugs with subsequent insulin requirement may, in fact, be due to poor adherence rather than to β-cell exhaustion. In our study (Chapter 6) we found a relatively high refill prescription rate of 97% compared to other studies. Part of this difference can be explained by difference with regard to methodology in calculation of refill compliance. For instance, in the study by Donnan *et al*, the previous prescription was censored at the start of the new prescription, if a subsequent prescription was refilled before the end of a previous prescription, possibly leading to an underestimation of refill compliance.[17] Although we were unable to proof a relationship between noncompliance – as measured by refill compliance rates - and secondary failure, we still believe that poor adherence is a major obstacle to the benefit of complex drug regimens in the treatment of type 2 diabetes.[18, 19] But other variables like comorbidity and disease related factors seem to play a more important role in switching to insulin therapy (Chapter 5, Chapter 7).

## Subtypes in type 2 diabetes mellitus: individualized treatment strategies based on antibodies or clinical features?

Some patients who present with a clinical picture consistent with type 2 diabetes have autoantibodies similar to those found in type 1 diabetes, and may masquerade as type 2 diabetes if antibody determinants are not made.[20-22] Islet cell autoimmunity, which is characteristic of type 1 diabetes, appears in fact to be present in up to 10-15% of subjects diagnosed clinically with type 2 diabetes. In the UKPDS, it was reported that in patients diagnosed with type 2 diabetes, the presence of autoantibodies to the enzyme glutamic acid decarboxylase (GAD) and cytoplasmic islet cell antibodies (ICA) were a predictor of insulin requirement. In addition, Syed and colleagues found in a subset of type 2 diabetes patients a pronounced activation of acute phase response that seems to be associated with

islet cell autoimmunity.[23] They proposed the identification of a subgroup of type 2 diabetes patients by using autoantibody as well as inflammatory markers. Individualized therapeutic strategies could potentially be instituted sufficiently early in course of the disease and most likely delay the onset of insulin requirement and the complications related with hyperglycemia.[23]

We strongly debate the feasibility of this approach in daily general practice. These laboratory tests are very costly and time-consuming. Furthermore, cost-effectiveness of this secondary screening method is unclear.

As shown in Chapter 2 and Chapter 4, one can also distinguish different groups of patients based on response to glucose lowering therapy or antihypertensive treatment.

Indeed, we would favor a more practical approach based on response to glucose lowering therapy and phenotypical characteristics (e.g. lean versus obese, young versus old) of the patient.[21, 22] In the randomization process of the UKPDS, roughly three types of type 2 diabetic patients were distinguished.[2] First of all, the primary diet failure group, consisting patients with a fasting plasma glucose (FPG) concentration higher than 15 mmol/l or continued symtoms due to hyperglycemia. Secondly, asymptomatic patients with FPG concentrations of 6 to 15 mmol/l during the run-in period of three months of lifestyle recommendation only (mainly dietary advice). The last group, termed diet satisfactory, maintained on diet alone and achieved FPG values below 6 mmol/l and developed no symptoms due to hyperglycemia.

When we apply this categorization to our study, the different subtypes are represented by patient A, C, and B respectively in *Figure 8.1*. For the primary diet failure group (patient A), it seems very important to intensify drug treatment in time, especially timely addition of insulin to the therapeutic regimen.[12, 24] Unfortunately, our results (Chapter 5) suggested that insulin therapy is often started after the development of diabetic complications and other comorbidity; in other words, 'one locks the stable after the horse has bolted'. Patients achieving excellent glycemic control for a long time on dietary treatment only (patient B), were excluded form the analysis in the UKPDS.[2] However, we believe this to be an intriguing patient group that deserves further research (Chapter 2). The 'normal'

type 2 diabetic patient is represented by patient C, who after an initial good response to lifestyle intervention needs pharmacological treatment due to deterioration of the β-cell function. Ultimately, most of these patients will require (addition of) insulin.[2]

## Switching means trouble?

Although overall treatment satisfaction in Dutch patients with type 2 diabetes is very high[14], patients with diagnosed diabetes mellitus type 2 are not being managed optimally (Chapter 3, Chapter 5).[25, 26] In the future, the treatment for diabetes mellitus type 2 must be directed towards the development of treatments tailored to meet the individual patient's needs.[27, 28] We should set targets that are reasonable for individual patients. These targets will be evidence based in so far as they will be derived from the findings of research studies, but they cannot in reality seek to achieve results attained in such artificial circumstances.

Switching indicates trouble because patients who require multiple therapies shortly following diagnosis have a worse prognosis with regard to future glycemic control, accompanied by more (cardiovascular) comorbidity and comedication. Concerning daily practice, the emphasis lays on stepping in time with the disease. Ultimately, efforts to achieve the $HbA_{1c}$ target of 7% will require at least 50% of patients with type 2 diabetes to be treated with insulin, with major resource implications as well as practical challenges.[28] Optimal diabetes treatment is not only switching to oral or insulin therapy, but also adding blood pressure lowering and lipid lowering drugs in time.

Although control of blood glucose levels remains the cornerstone of the treatment of type 2 diabetes mellitus, the high prevalence of concomitant diseases emphasizes that pharmacotherapy in type 2 diabetes mellitus should not be limited solely to this objective. Polypharmacy may be unavoidable. Results from randomized clinical trials indicate that drug treatment of cardiovascular risk factors, such as hypertension and hyperlipidemia, substantially reduce the risk of cardiovascular diseases.[29-32] In the Heart Protection Study on cholesterol lowering therapy in high-risk individuals (including diabetes), allocation to 40 mg simvastatin

daily reduced the rates of myocardial infarction, stroke and revascularization by about one-quarter.[32] Therefore, treatment of cardiovascular morbidity and risk factors should be another key factor in the treatment of type 2 diabetes mellitus.[33] Given the cardiovascular risk profile of type 2 diabetes, up to 10% of patients could require two or three hypoglycemic agents (ultimately including insulin), at least three antihypertensive agents, two hypolipidemic agents, and aspirin.[28]
From a practical point of view, it might be expected that a simple treatment regimen such as once daily therapy would improve adherence, as a study of 91 patients treated with sulfonylureas alone demonstrated, using MEMS devices.[18] The development of combination tablets by the pharmaceutical industry seems to be an important goal for better prognosis and effective prevention of complications in type 2 diabetes.[28] Pharmacotherapy of type 2 diabetes is a complicated task and next steps in management of glycemic control may partly be based on drug history data. Therefore, teamwork between physicians, pharmacist and the diabetic patients themselves is needed.

## UDES: where are we now and future prospects

The Utrecht Diabetes Epidemiology Studies (UDES) were initiated to study the effectiveness of diabetes care and drug outcomes (i.e. glycemic control, micro- and macrovascular complications), to identify the management of risk factors (i.e. cardiovascular diseases, pregnancy, psychiatric disorders, poor compliance), and to study effectiveness of innovation in insulin therapy (fast-acting insulin analogues, computed insulin pen). For the studies, a database comprising pharmacy, hospital admission and general practitioner data was established to gain more insight in the treatment of diabetes mellitus in daily clinical practice.

A major limitation of the use of observational studies in the assessment of intended effects of treatment is confounding by (contra-)indication for treatment.[34, 35] The prescribing of drugs to patients by physicians is by definition not random. For instance, because oral hypoglycemic agents and insulin are generally added as a result of worsening metabolic control, it seems logical that a strong association exists between required intensity of therapy and $HbA_{1c}$ level. Thus, in contrast to

randomized clinical trials, prognoses of differently treated patients are usually not comparable, resulting in a biased estimate of the treatment effect. Epidemiological methods such as matching, restriction and multivariate adjustment can be used to control for confounding. Other methods, such as the use of propensity scores, may help to improve the validity of estimates of effectiveness of drug treatments in observational studies.[36-38]

In the future, research opportunities will be improved within the framework of UDES by not only linking pharmacy, hospital admission and general practice data, but also including laboratory data. Linkage of routine data deriving from different disciplines of health care has great potential for future epidemiological studies and could make an important contribution to the improvement of the quality of diabetes care in general and also makes identification of adverse effects possible. Concerning privacy issues in medical research, weighing of ethical 'costs' and 'benefits' is an essential and productive additional perspective in the design and conduct of epidemiological studies.[39]

UDES has the potential to become one of the well-established research databases comprising routinely collected data (such as the General Practice Research Database[40, 41], MEMO/DARTS[42]). An important added value of the UDES database could be the high representativeness of daily clinical care. In fact, even with regard to data-collection, there were no interventions performed at all.

With regard to future orientation, validation and assessment of the quality of the database are important and also necessary issues.[43] For instance, in the DARTS study, a detailed manual study of relevant records for patients registered with a random sample of eight general practices allowed for validation of the case ascertainment.[42] In view of the quality and validation of the GPRD, only data meeting the minimum standards are added to the research database. Practices that fail to meet the required standards are removed from the database. There have also been several validation studies of the GPRD, confirming that the quality and completeness of the computerized recorded data is high.[40, 43]

Considering validation of the UDES database, we would suggest clinical examination in combination with laboratory testing in a random sample of patients to confirm the medical history of type 2 diabetes, instead of (manual) medical

record searching. Additionally, by this approach one will gain an insight the proportion of possibly cured or incorrectly diagnosed patients.

## Final considerations

In conclusion, based on the studies described in this thesis, the following recommendations for clinical practice and research are given. As a main strategy in diabetes care we would favor physicians to perform distinct individualized treatment strategies in type 2 diabetes mellitus, based on the subgroups defined by clinical characteristics rather than pathophysiological differences. For instance, the uniform approach of a three-month run-in period of dietary treatment, as recommended in the Dutch General Practitioners' guidelines, seems too long in some patients (with primary failure to diet therapy).

Practical recommendations should be based on initial response to glucose lowering therapy and severity of diabetes at diagnosis. Furthermore, validation of the UDES databases is needed in the future, we would recommend clinical examinations in addition to medical record searching.

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# CHAPTER 9

## Summary

Diabetes mellitus is defined by chronically increased blood glucose levels, e.g. 'hyperglycemia'. Patients with type 2 diabetes are characterized by defects in both insulin secretion and insulin action due to insulin resistance and failure of the pancreatic beta-cell function. Reduction of hyperglycemia aims to prevent micro- and/or macrovascular complications in patients with type 2 diabetes, so glucose lowering therapy is the cornerstone of the management of type 2 diabetic patients.
The reality of daily clinical practice may not cohere with the results from randomized clinical trials. Studying determinants of glucose lowering drug use may help to explore the gap between clinical practice and evidence. In this thesis, the treatment of type 2 diabetes mellitus has been assessed with regard to determinants and effects of different glucose lowering strategies.

The first-line therapy modality for type 2 diabetes includes an optimal diet with weight reduction and exercise accompanied by patient education and self-management. According to the Dutch general practitioners' guidelines for type 2 diabetes care, pharmacological treatment has to be considered if target levels of glycemic control are not achieved after a dietary period of at least three months.
Little is known about the clinical grounds on which the general practitioners make the decision to initiate pharmacological therapy and the perspectives of these patients with respect to future glycemic control. In **Chapter 2** we showed that the initial severity of diabetes, assessed by the degree of hyperglycemia at diagnosis, is the major factor in determining the time to start drug treatment and the likelihood of achieving target levels of glycemic control in the future, independent of glucose lowering therapy. Remarkably, a small proportion of the patients remained on dietary treatment only for a long time and still achieved good glycemic control ($HbA_{1c}$ < 7.0 %).
In **Chapter 3** and **Chapter 4**, we studied determinants and effects of different strategies in glucose lowering therapy. Firstly, we assessed whether more intensive glucose lowering therapy resulted in adequate glycemic control. Increased intensity of hypoglycemic therapy was significantly associated with poorer glycemic control, higher body weight and increased prevalence of hypertension. Despite deterioration of glycemic control with intensified treatment, control of other

metabolic risk factors such as high blood pressure and cholesterol remained stable, probably due to increased prescribing of cardiovascular drugs (**Chapter 3**). Furthermore, when focusing on the association between antihypertensive medication, blood pressure and glycemic control (**Chapter 4**), it was shown that patients using antihypertensives had better glycemic control, notably lower $HbA_{1c}$ levels, and increased body weight. We believe that patients with diabetes mellitus who do not use antihypertensive medication comprise a subgroup of patients with predominantly beta-cell failure.

As type 2 diabetes mellitus advances, secondary failure develops as a consequence of progressive loss of beta-cell function and worsening of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance. If oral treatment initially works but later fails, patients need to switch over to insulin therapy. There is little data on factors that are associated with this therapeutic switch. We compared switchers and non-switchers with respect to demographic characteristics, metabolic control, comorbidity, co-medication, and compliance to their oral drug regimen.
In a population of 152 type 2 diabetes mellitus patients in Almere (**Chapter 5**), it was found that patients who switched to insulin were younger at diagnosis, had worse metabolic control and suffered from more health problems besides diabetes. Especially cardiovascular disease was more frequently present among switchers, 77.4% versus 52.9% (odds ratio (OR) 3.1; 95% confidence interval ($CI_{95\%}$): 1.2-7.6). The Dutch PHARMO Record Linkage System was used as data source for the studies performed in **Chapter 6** and **Chapter 7**, The PHARMO RLS comprises pharmacy dispensing records linked to hospital admission data of all community-dwelling residents of eight cities (N~ 450,000) from 1985 onwards. **Chapter 6** describes the results of a matched case-control study; we compared patients who switched to insulin (cases) with patients still on oral therapy on the index date (controls) with respect to refill compliance. 'Compliance' has been defined as an attempt by patients to take their medication each day as prescribed. This was assessed by calculating the extent to which the patient's actual history of drug administration corresponds to the prescribed regimen. The overall

compliance rate did not differ significantly between cases and controls, the adjusted OR was 1.3 ($CI_{95\%}$ 0.6-2.8). So, we were unable to confirm the hypothesis that noncompliance with treatment is more prevalent in patients with secondary failure. In conclusion, cases suffered more often from severe comorbidity (assessed by the Chronic Disease Score) and used a higher number of oral hypoglycemic agents and concomitant non-diabetic drugs. Other comorbidity and disease-related factors that play a role in switching to insulin therapy are illustrated in **Chapter 5** and **Chapter 7**.

Because several studies indicated that type 2 diabetes is more common among schizophrenic patients than in the general population, we examined the association between antipsychotic drugs and alterations of glycemic control (**Chapter 7**). We considered switching from oral hypoglycemic agents to insulin therapy a proxy for deterioration of beta-cell function. Two years after diagnosis we found an increased risk for switching to insulin therapy for those patients using antipsychotics compared to non-users; the hazard ratio (HR) was 2.0 ($CI_{95\%}$: 1.2-3.3). This risk decreased in subsequent years following diagnosis.

The thesis was concluded in **Chapter 8**, where the results of our studies are discussed with a focus on optimizing diabetes treatment strategies based on different subgroups of type 2 diabetic patients that are easily identified based on clinical characteristics rather than pathophysiology. Clinical practice should depend on initial response to glucose lowering therapy and severity of diabetes at diagnosis. Roughly, three types of type 2 diabetic patients were distinguished; the primary diet failure group, the diet satisfactory group and an intermediate group of 'normal' type 2 diabetes patients. Furthermore, we stressed the importance of validation of the UDES database concerning future research purposes.

In conclusion, the studies presented in this thesis show that combining data that are routinely collected in clinical practice can give more insight into treatment of type 2 diabetes. It is important for physicians to set targets that are reasonable for individual patients, the emphasis lays on stepping in time with the disease and the

need for constant reassessment of the diabetic patient accompanied by appropriate therapeutic adjustments. Pharmacotherapy of type 2 diabetes is a complicated task and next steps in management of glycemic control may be partly based on drug history data. Therefore, teamwork between physicians, pharmacists and the diabetic patients themselves is needed.

# CHAPTER 10

# Nederlandse Samenvatting

De aandoening diabetes mellitus wordt gekenmerkt door een chronisch verhoogd glucosegehalte in het bloed, oftewel 'hyperglykemie'. Karakteriserend voor patiënten met type 2 diabetes is dat zij lijden aan een defect in zowel de uitscheiding als de werking van insuline ten gevolge van insulineresistentie en onvoldoende activiteit van de beta-cel in de alvleesklier. Aangezien verlaging van het bloedsuikergehalte in belangrijke mate bijdraagt aan het voorkómen van microvasculaire (retinopathie, nefropathie, neuropathie) en macrovasculaire complicaties (myocardinfarct, herseninfarct, perifeer vaatlijden) vormt glucoseverlagende therapie dé pijler van de behandeling van patiënten met type 2 diabetes.
Mogelijkerwijs stemt de realiteit van de dagelijkse klinische praktijk niet altijd overeen met resultaten zoals deze zijn gevonden in gerandomiseerde klinische onderzoeken (randomized clinical trials, RCTs). Het bestuderen van determinanten van glucoseverlagende therapie kan een goede hulp zijn bij het exploreren en de overbrugging van de verschillen tussen klinische praktijk en aangetoonde experimentele studieresultaten. In dit proefschrift zijn determinanten en effecten van verschillende bloedsuikerverlagende strategieën in het kader van de behandeling van type 2 diabetes mellitus bestudeerd.

De behandelingsmodaliteit van eerste keus bestaat uit een optimaal dieet met gewichtsreductie en stimulering van de lichamelijke activiteit in combinatie met patiënteneducatie en zelfsturing. Volgens de type 2 diabetes mellitus behandelingsstandaard van het Nederlands Huisartsen Genootschap (NHG) moet medicamenteuze therapie worden overwogen als de glykemische streefwaarden niet bereikt worden na behandeling met een dieet gedurende tenminste drie maanden.
Er is weinig bekend omtrent de klinische gronden op basis waarvan huisartsen de beslissing nemen om te starten met farmacologische therapie en ook de toekomstige vooruitzichten van deze patiënten wat betreft verdere glykemische controle zijn onduidelijk.
In **Hoofdstuk 2** hebben we aangetoond dat de initiële ernst van de aandoening, bepaald door de mate van hyperglykemie op het moment dat type 2 diabetes is

gediagnosticeerd, de belangrijkste factor is aangaande de bepaling van de termijn tot het starten van medicamenteuze therapie. Tevens hangt de ernst van de aandoening bij diagnose sterk samen met de waarschijnlijkheid om glucosestreefwaarden te bereiken in het toekomstige beloop van de ziekte, onafhankelijk van de gekozen bloedsuikerverlagende therapie. Opvallend is het feit dat voor een kleine groep patiënten een goede glykemische regulatie ($HbA_{1c}$< 7.0%) haalbaar was ondanks de exclusieve behandeling met een dieet gedurende langere tijd.

In **Hoofdstuk 3** en **Hoofdstuk 4** bestudeerden we determinanten en effecten van verschillende bloedsuikerverlagende behandelingsstrategieën. Allereerst is bepaald in hoeverre intensivering van de glucoseverlagende behandeling resulteerde in een adequate glykemische controle. Een intensievere bloedsuikerverlagende behandeling was significant geassocieerd met een slechtere glykemische controle, een hoger lichaamsgewicht en een verhoogde prevalentie van hypertensie. Ondanks de waargenomen verslechtering van de bloedglucose controle bij een intensievere behandeling bleef de controle van andere metabole risicofactoren zoals hoge bloeddruk en cholesterol stabiel, mogelijk als gevolg van een frequenter voorschrijven van cardiovasculaire medicatie (**Hoofdstuk 3**).

Wanneer de relatie tussen bloeddrukverlagende medicatie, bloeddruk en glykemische regulatie (**Hoofdstuk 4**) nader onder de loep werd genomen, werd bovendien aangetoond dat gebruikers van bloeddrukverlagende medicijnen (antihypertensiva) betere controle van hun bloedglucose bereikten, zij hadden namelijk lagere $HbA_{1c}$ waarden. Daarnaast hadden zij een hoger lichaamsgewicht dan de patiënten die geen antihypertensiva kregen voorgeschreven.

Wij denken dat patiënten met diabetes mellitus die geen bloeddrukverlagende medicatie gebruiken een subgroep vormen bestaande uit patiënten waarbij het falen van de beta-cel op de voorgrond staat.

Wanneer de ziekte type 2 diabetes mellitus voortschrijdt ontwikkelt zich het zogenaamd 'secundair falen' als gevolg van enerzijds progressief functieverlies van de beta-cel en een verergering van de insulineresistentie door het voortdurend te hoge bloedsuikerniveau en de mogelijke ontwikkeling van therapieresistentie ten

aanzien van orale medicatie anderzijds. Patiënten moeten worden overgezet op een behandeling met insuline als orale behandeling in eerste instantie voldoende werkzaam is maar later toch tekortschiet. Weinig is bekend over factoren die samenhangen met deze therapeutische overschakeling.

In een populatie bestaande uit 152 patiënten met type 2 diabetes mellitus in Almere (**Hoofdstuk 5)** toonden we aan dat patiënten die overschakelden naar insuline therapie ('switchers') jonger waren op moment van diagnose, een slechtere metabole controle hadden en bovendien leden zij vaker aan andere gezondheidsproblemen naast diabetes. Switchers presenteerden zich vooral veel vaker met hart- en vaatziekten, 77,4% versus 52,9% (odds ratio (OR) 3,1; 95% betrouwbaarheidsinterval (BI): 1,2-7,6). Voor de studies beschreven in **Hoofdstuk 6** en **Hoofdstuk 7** is als gegevensbron het PHARMO Record Linkage System (RLS) gebruikt, een Nederlandse database die apotheekgegevens en ziekenhuisopnames bevat van ongeveer 450.000 patiënten. **Hoofdstuk 6** beschrijft de resultaten van een zogenaamde case-controle studie; waarbij we de mate van 'refill compliance' vergeleken in patiënten die overschakelden naar insuline therapie (zgn. cases) met patiënten die nog steeds orale therapie (tabletten) gebruikten op de index datum (datum van overschakeling naar insuline in de cases). 'Refill compliance' is een maat voor de therapietrouw ('compliance') en is gebaseerd op apotheekgegevens (afhaaldata van nieuwe medicatie, 'refill') in combinatie met medicatievoorschriften. Een perfecte overeenstemming tussen afleverdata en het voorgeschreven therapieschema resulteert in een 'refill compliance' van 100%. Cases en controles hadden eenzelfde ziekteduur, zij waren gematched op duur van de diabetes. De totale compliancegraad verschilde niet significant tussen cases en controles, de geadjusteerde OR was 1,3 ($BI_{95\%}$: 0,6-2,8). We bleken dus niet in staat om de hypothese te bevestigen dat een gebrek aan therapietrouw leidt tot een snellere overschakeling naar insuline therapie. Concluderend leden cases vaker aan ersntige co-morbiditeit (bepaald aan de hand van de Chronic Disease Score) en zij gebruikten een hoger aantal orale bloedsuikerverlagende middelen en bijkomende niet-diabetische medicijnen. In **Hoofdstuk 5** en **Hoofdstuk 7** worden een aantal

andere ziektegerelateerde factoren en bijkomende aandoeningen (co-morbiditeit) beschreven die een rol spelen bij de overschakeling naar insuline therapie.
Aangezien in verscheidene studies aanwijzingen zijn gevonden voor het feit dat type 2 diabetes vaker voorkomt bij patiënten met schizofrenie dan in de algemene bevolking hebben we het verband tussen het gebruik van antipsychotica en veranderingen in de glykemische regulatie onderzocht (**Hoofdstuk 7**). De overschakeling van orale bloedsuikerverlagende medicatie naar insuline therapie werd beschouwd als een objectieve maat voor verslechtering van de beta-cel functie. We vonden twee jaar na de diagnose van diabetes een verhoogd risico op switchen naar insuline bij patiënten die antipsychotica gebruikten in vergelijking tot niet-gebruikers van deze medicijnen; de hazard ratio (HR, een soort relatief risico) was 2,0 ($BI_{95\%}$: 1,2-3,3). De daaropvolgende jaren na diagnose nam dit risico af.

Tot slot vindt afronding van het proefschrift plaats in **Hoofdstuk 8**, alwaar onze studieresultaten zijn besproken in het licht van optimalisering van diabetes behandelingsstrategieën gebaseerd op verschillende subgroepen type 2 diabetes patiënten die gemakkelijker geïdentificeerd kunnen worden op basis van klinische kenmerken in plaats van de pathofysiologie. De klinische praktijk moet meer afhankelijk zijn van de initiële repons op glucoseverlagende therapie en ernst van diabetes bij de diagnosestelling. Grofweg worden drie typen type 2 diabetes patiënten onderscheiden: allereerst de primaire dieet falers, patiënten waarbij een dieet weinig tot geen effect sorteert, vervolgens de groep waarbij een dieet alleen toereikend is voor een goede glykemische controle en tenslotte een tussenliggende groep bestaande uit 'normale' type 2 diabeten. Bovendien hebben we het belang van validatie van de UDES database benadrukt met betrekking tot toekomstige onderzoeksdoeleinden.

Concluderend laten de in dit proefschrift gepresenteerde studies zien dat het combineren van gegevens die routinematig worden verzameld in de klinische praktijk meer inzicht kan geven in de behandeling van type 2 diabetes. Het is belangrijk dat artsen behandelingsdoelen nastreven die redelijkerwijs haalbaar zijn voor de individuele patiënt, waarbij de nadruk ligt op het in de pas lopen met de

(progressieve) ziekte en de noodzaak tot het constant herbeoordelen van de diabeet, samengaand met geschikte therapeutische aanpassingen.
De juiste farmacotherapie van type 2 diabetes mellitus is een gecompliceerde taak voor behandelaars, opvolgende stappen in de behandeling van glykemische controle kunnen soms gedeeltelijk worden gebaseerd op gegevens omtrent de medicatiehistorie (bijvoorbeeld het effect van eerder gebruikte medicatie). Samenwerking tussen artsen, apothekers en de diabeet zelf is daarom zeer belangrijk.

## List of publications

Spoelstra JA, Stolk RP, Klungel OH, Erkens JA, Rutten GEHM, Leufkens HGM, Grobbee DE. Initation of glucose lowering therapy in type 2 diabetes mellitus in general practice. *Submitted.*

Spoelstra JA, Stolk RP, Klungel OH, Erkens JA, Rutten GEHM, Leufkens HGM, Grobbee DE. Glucose lowering therapy and cardiovascular risk management in type 2 diabetes mellitus: a population-based study in general practice. *Submitted.*

Stolk RP, Spoelstra JA, Klungel OH, Erkens JA, Rutten GEHM, Leufkens HGM, Grobbee DE. Antihypertensive medication and glycemic control in patients with type 2 diabetes mellitus. *Submitted.*

Spoelstra JA, Stolk RP, De Bruyne MC, Erkens JA, Herings RMC, Leufkens HGM, Grobbee DE. Factors associated with switching from oral hypoglycemic agents to insulin therapy. *The Netherlands Journal of Medicine 2002; 60(6): 243-248.*

Spoelstra JA, Stolk RP, Heerdink ER, Klungel OH, Erkens JA, Leufkens HGM, Grobbee DE. Refill compliance: a predictor of switching to insulin therapy? *Pharmacoepidemiology and Drug Safety (in press).*

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- "*Proefschrift*? Wanneer verschijnt dan het èchte?"
- "*Promoveren*, ja, dat willen we allemaal wel…!"

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## Curriculum Vitae

José Astrid Spoelstra was born on February 6th, 1973, in Sneek, the Netherlands. She graduated secondary school in 1991 at the Bogerman College in Sneek. She started Medical School at the University of Groningen and obtained her medical degree in May 1998. In 1998, she worked a few months as a company doctor for the Arbo Management Group in Leeuwarden.
In February 1999, she accepted the opportunity to perform a PhD project at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (supervised by Prof. dr. D.E. Grobbee and Dr. R.P. Stolk) and the Department of Pharmacoepidemiology and Pharmacotherapy, Faculty of Pharmaceutical Sciences, Utrecht University (supervised by Prof. dr. H.G.M. Leufkens and Dr. O.H. Klungel). In June 2001, she obtained a MSc in Clinical Epidemiology at the Netherlands Institute for Health Sciences, Erasmus University Rotterdam.