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The impact of new insights and revised practice guidelines on prescribing drugs in the treatment of Type 2 diabetes mellitus

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Aims
The aim of this study was to investigate the impact of new insights and revised guidelines on initial and follow-up treatment with antihyperglycaemic drugs over the period 1998–2003.

Methods
The InterAction Database (IADB), which contains pharmacy dispensing data from 53 community pharmacies in the Northern and Eastern part of the Netherlands, was used in this study. Prevalence and incidence rates of oral antihyperglycaemic drug use were calculated for each year. Follow-up treatment was compared for two cohorts of initial users of oral antihyperglycaemic drugs, starting treatment either 1 year before or 1 year after guideline revision.

Results
The prevalence and incidence rate of oral antihyperglycaemic drug use increased over the study period from 1.8% to 2.4% ($P < 0.001$) and 0.3% to 0.4% ($P = 0.04$). The proportion of metformin as initial treatment increased rapidly in the observation period from 14% to 50% ($P < 0.001$). Initial users of metformin in 2000 received additional treatment with a sulphonylurea in the follow-up period less often compared with those who started metformin in 1998 (46% *vs.* 60%, $P < 0.004$). In contrast, initial users of sulphonylurea in 2000 received additional treatment with metformin more often compared with those who started a sulphonylurea in 1998 (42% *vs.* 36%, $P < 0.008$). The new drugs, thiazolidinediones and meglitinides, were seldom used as initial treatment

Conclusions
New insights and the revision of the practice guideline were followed by a significant increase in both initial and follow-up treatment with metformin among patients with Type 2 diabetes mellitus.

Introduction

Diabetes mellitus is a growing disease largely accounted for an increasing number of people diagnosed with Type 2 diabetes mellitus (T2DM). In the Netherlands, treatment of T2DM is often started by a general practitioner (GP). Changing lifestyle and dietary measures are usually the first step. The second step is pharmacotherapy with an oral blood glucose-lowering drug. In the early

1990s in the Netherlands, as in the rest of the world, there were three groups of oral blood glucose-lowering drugs available, i.e. biguanides, sulphonylureas and α-glucosidase-inhibitors. After 1999, two new groups of drugs, i.e. meglitinides (repaglinide, nateglinide) and thiazolidinediones (rosiglitazone, pioglitazone), became available.

International and national guidelines provide evidence-based recommendations for the treatment of TD2M [1]. In the Netherlands, we have national practice guidelines of the Dutch College of General Practitioners (NHG) [2, 3]. The first NHG guideline for T2DM appeared in 1989 and recommended to start with a short-acting (or weak) sulphonylurea, such as tolbutamide, in all T2DM patients. When the effect of tolbutamide was insufficient, a switch was recommended to a longer-acting (strong) sulphonylurea, such as gliclazide or glibenclamide. The use of metformin was reserved for obese patients with a body mass index (BMI) >30 kg m^{-2}. The biguanide metformin was feared for its risk of lactic acidosis and considered to be contraindicated in patients with renal impairment or cardiovascular complications. The α-glucosidase-inhibitors were judged to be modestly effective, but hampered by a high prevalence of gastrointestinal side-effects and recommended only in combination with other drugs.

In September 1998, the United Kingdom Prospective Diabetes Study (UKPDS) research group published the results of intensified treatment of diabetes and demonstrated the beneficial effects of metformin in overweight T2DM patients [4, 5]. Worldwide, the UKPDS results changed the existing ideas of treating T2DM. In 1999, the NHG guideline was thoroughly revised in line with the results of the UKPDS study. In the revised guideline, a distinction in pharmacological treatment was made for patients with a BMI above and below 27 kg m^{-2} [3]. Lean patients (BMI <27 kg m^{-2}) were advised to start initial treatment with a sulphonylurea, such as tolbutamide or gliclazide. For obese patients (BMI ≥27 kg m^{-2}) the recommendation was to start with metformin. When monotherapy failed, a combination of metformin and sulphonylurea was considered appropriate. The new drugs, meglitinides and thiazolidinediones, were not yet included in this revised guideline.

It is recognized that new guidelines or insights are not always implemented in daily practice [6, 7]. From studies of drug prescription trends conducted in the USA and UK, it has become clear that the use of metformin and thiazolidinediones has increased since 1997 at the expense of especially long-acting sulphonylurea [8–11]. These studies, however, did not provide insight into the treatment steps at the level of the individual patient.

Therefore, it is not clear to what extent these drugs were prescribed as initial or follow-up treatment. In this study, we investigated the impact of revised insights and guidelines on the prescription trends for initial treatment of T2DM patients as well as for the treatment changes during follow-up.

Methods

The InterAction Database (IADB), containing pharmacy dispensing data from 53 community pharmacies in the Northern and Eastern part of the Netherlands, was used in this study [12, 13]. In the period from 1997 to 2003, the IADB covered a population of approximately 450 000 people. The size of this population increased over the study period but there was no change in age and gender distribution. In the Netherlands, people commonly register with one pharmacy and obtain all their medication from that pharmacy, so that a complete medication history of an individual is available in the pharmacy dispensing records.

The prevalence and incidence rates of oral antihyperglycaemic drug use (ATC code A10B*, Table 1) were calculated per year according to age group (≤ 14 years, 15–39 years, 40–64 years, ≥65 years) and gender. The yearly prevalence rate was calculated by counting the number of patients receiving one or more prescriptions for an oral antihyperglycaemic drug divided by the total number of patients in the database per age and gender group in the respective years. The incidence rate of oral antihyperglycaemic drug use was defined as the number of people who received initial treatment with an oral antihyperglycaemic drug per year.

From the population, we defined patients using antihyperglycaemic drugs as patients being treated for T2DM. In this group, proportions of initial treatment were calculated for every calendar year of the observation period. Initial treatment was defined as the first prescription dispensed for an antihyperglycaemic drug when no antihyperglycaemic drugs had been dispensed in the preceding 6 months (in the Netherlands, drugs are dispensed for a maximum of 3 months). When a patient received two prescriptions for antihyperglycaemic drugs at the date of the initial treatment both prescriptions were counted. χ^2 tests were used to determine differences between proportions.

To investigate changes in treatment during follow-up, we followed two cohorts of initial users over a period of 2.7 years (1000 days). The first cohort started an oral antihyperglycaemic drug in 1998 and the second cohort in 2000, one year before and one year after, respectively, the introduction of the revised NHG guidelines. The cohorts were divided into those starting with metformin

Table 1

Available blood glucose-lowering drugs in the Netherlands

Drug group	ATC – code	Generic name
Insulin	A10A	
Oral blood glucose-lowering drugs		
Biguanides	A10BA02	Metformin
Sulphonylureas (SU)	A10BB01	Glibenclamide
Glyburide (US)	A10BB03	Tolbutamide
	A10BB07	Glipizide
	A10BB09	Gliclazide
	A10BB12	Glimepiride
Combination of metformin and sulphonylurea	A10BD02	Metformin/glibenclamide
α-Glucosidase inhibitors	A10BF01	Acarbose
Thiazolidinediones (TZD)	A10BG02	Rosiglitazone
	A10BG03	Pioglitazone
Other oral blood glucose-lowering drugs	A10BX02	Repaglinide
	A10BX03	Nateglinide

Table 2

Number and characteristics of people using oral antihyperglycaemic drugs

	Population		Users of oral antihyperglycaemic drugs			
	Male	Female	Male		Female	
Year	*n*	*n*	*n*	Age, years	*n*	Age, years
1998	197 077	206 283	3070 (1.6%)	65.4 ± 12.5	4155 (2.0%)	69.8 ± 12.9
1999	210 851	220 847	3464 (1.6%)	64.9 ± 12.5	4526 (2.1%)	69.5 ± 12.9
2000	214 359	222 470	3763 (1.8%)	64.7 ± 12.6	4892 (2.2%)	69.5 ± 13.0
2001	215 713	224 329	4129 (1.9%)	64.7 ± 12.4	5196 (2.3%)	69.4 ± 13.1
2002	218 992	226 000	4523 (2.1%)	64.5 ± 12.7	5458 (2.4%)	69.3 ± 13.0
2003	222 137	229 657	5038 (2.3%)	64.5 ± 12.5	5989 (2.6%)	69.2 ± 13.1

(initial metformin group) and those starting with a sulphonylurea (initial sulphonylurea group). The cohorts were separately evaluated for males and females. Data were analysed using Kaplan–Meier survival (log-rank tested) and Cox proportional hazard analyses. The event in these analyses was the start of another antihyperglycaemic drug (metformin, sulphonylurea or insulin), either in addition to or as a replacement of the initial drug. Survival time was censored for death or moving (loss to follow-up) and follow-up period. Adjustments for age differences (between the cohorts) were made using Cox proportional hazard analyses. All statistical analyses were performed using SPSS 12 statistical software (SPSS Inc., Chicago, IL, USA).

Results

The prevalence and incidence rate of oral antihyperglycaemic drug use increased in the study period (Table 2, Figure 1A,B). The prevalence rate increased from 1.8% to 2.4% ($P < 0.001$) and this change was similar for males and females (Table 2). The incidence rate increased from 0.3% to 0.4% ($P = 0.04$). The incidence and prevalence rate for the very young (<15 years) was almost zero, and not displayed.

The proportion of metformin as initial treatment showed a large increase from 13.4% in 1998 to 49.9% in 2003 (Figure 2, $P < 0.001$), consequently decreasing the proportion of initial sulphonylurea use. Of the sulphonylureas, the use of gliclazide and glimepiride was unchanged, whereas that of glibenclamide and tolbutamide decreased. The use of other drugs, including acarbose, rosiglitazon, pioglitazon, repaglinide and insulin, was very small as initial treatment. Finally, between 2 and 3% of the patients were given two different antihyperglycaemic drugs as initial treatment.

After 2.7 years, 39% of the patients on initial sulpho-
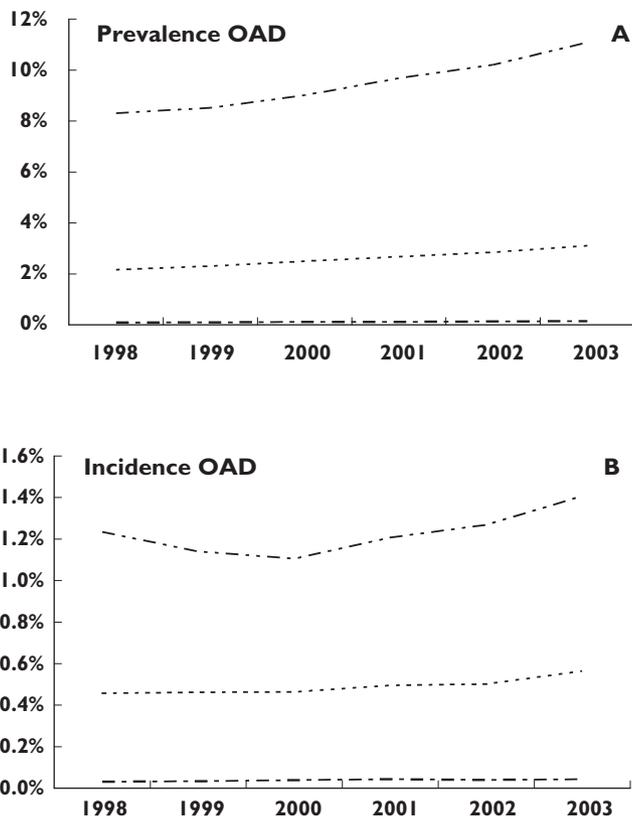
Figure 1

Prevalence (A) and incidence (B) rate of oral antihyperglycaemic drug (OAD) use for three age groups (15–39 years (–·–·), 40–64 years (······), ≥ 65 years (–···–))
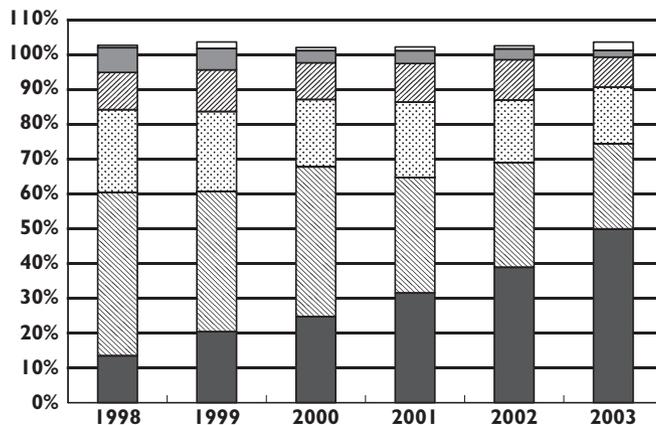
Figure 2

Proportion of initial treatment with oral antihyperglycaemic drugs (drug groups are not mutually exclusive due to 2–3% of patients receiving two drugs at the date of initial treatment). The group 'other' includes acarbose, rosiglitazone, pioglitazone, repaglinide and insulin. Other (☐), glibenclamide (▨), glimepiride (▨), gliclazide (▨), tolbutamide (▨), metformin (■)

nylurea treatment had received follow-up treatment with metformin, whereas 52% of initial metformin users had received follow-up treatment with sulphonylurea. In 20–38% of the patients on initial metformin treatment, follow-up treatment with a sulphonylurea was already started within the first 100 days (Figure 3A,C), whereas follow-up treatment with metformin was more gradual over the whole study period (Figure 3B,D).

Especially females in the 2000 cohort on initial metformin treatment were less likely to receive sulphonylurea in the follow-up period compared with the 1998 cohort (Figures 3C, $P = 0.003$). In both year cohorts, 10% of the males and 25% of the females discontinued using metformin after receiving follow-up treatment with a sulphonylurea, which could not be attributed to any differences in prescribed dosages of metformin (data not shown). The initial users of sulphonylurea in the 2000 cohort were more likely to receive metformin compared with the 1998 cohort ($P = 0.007$). No difference was found between males and females (Figure 3B,D). In 10% of the cases, the sulphonylurea was discontinued after follow-up treatment with metformin was started.

Age differences between the cohorts were only small and did not influence the differences found.

At the end of the follow-up period, about 8% of the initial metformin and initial sulphonylurea users had started with insulin (data not shown). No earlier switch to insulin was found between the year or gender cohorts, but there was a difference in discontinuation rates of the initial drug. After receiving insulin, more patients discontinued using the sulphonylurea (70%) compared with metformin (40%) ($P < 0.05$).

Discussion

Based on pharmacy dispensing data, we found an increase in the prevalence and incidence rate of oral antihyperglycaemic drug use over the period 1998–2003. Changes in initial and follow-up prescription rates of individual drugs were largely in agreement with new insights and revised treatment recommendations. The percentage of T2DM patients on initial treatment with metformin increased from 15% in 1998 to 50% in 2003. Furthermore, metformin was added more frequently to initial sulphonylurea treatment in 2000 compared with 1998. The new drugs, thiazolidinediones and meglitinides, were seldom used as initial treatment.

Several studies have addressed changes in pharmacological treatment in diabetes over time. Some did not focus on specific drug treatments [14, 15], included all diabetes mellitus patients [9] or were based on data from the early 1990s [15–17]. Those that did address treatment changes in the period during and after the publi-
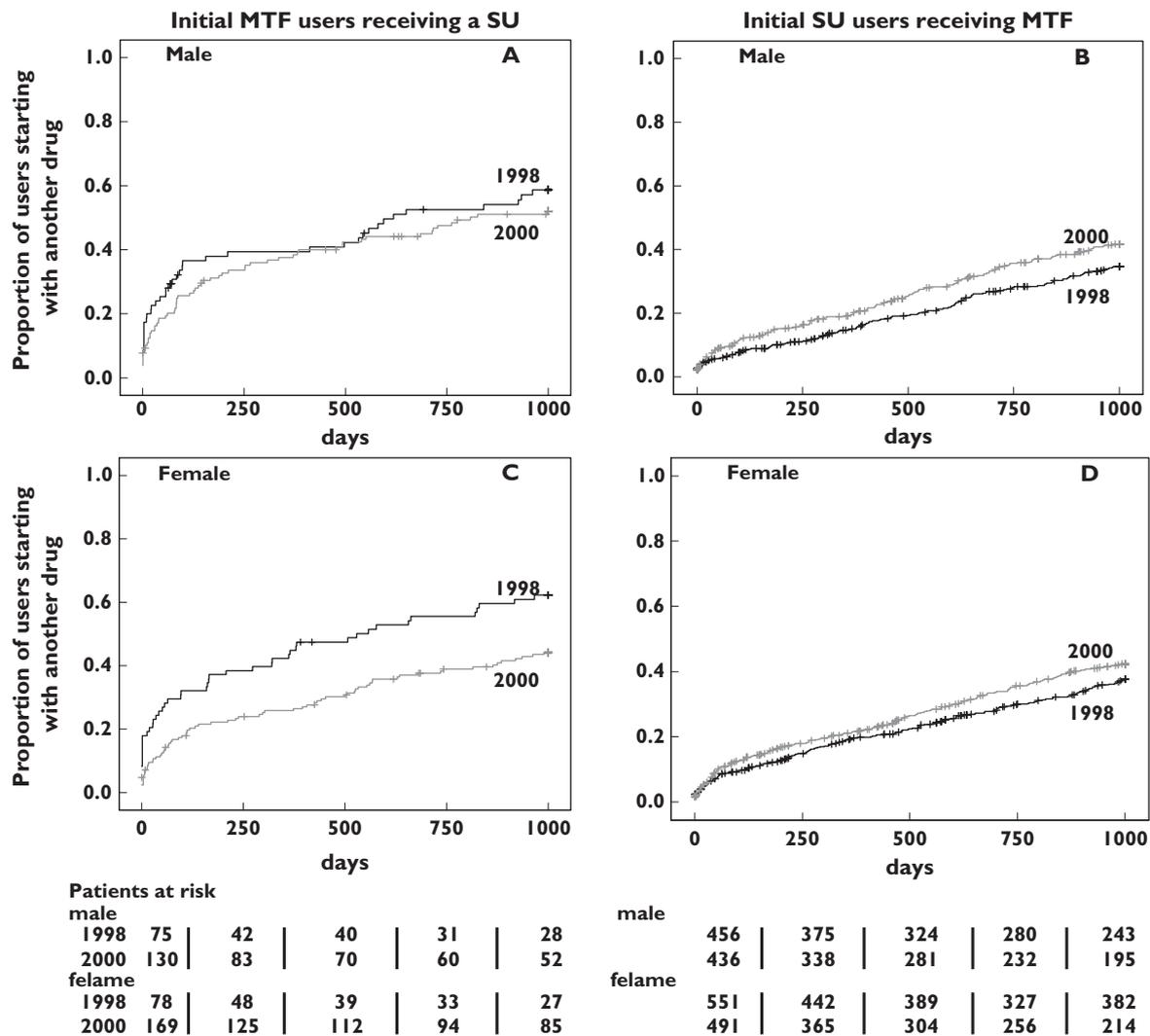
Figure 3

Kaplan–Meier curves showing the changes in treatment after initial treatment with metformin in males (A) and females (B), and with sulphonylurea in males (C) and females (D)

cation of the main UKPDS results showed that metformin use increased after 1997 [8–11]. Our study demonstrates that the rapid increase in metformin use was largely due to the increased use of metformin as initial treatment but also as follow-up treatment for patients started on sulphonylurea, which is in accordance with the revised guideline recommendations in the Netherlands. The fact that the new drugs, marketed after 2000, and α-glucosidase-inhibitors were hardly prescribed as initial treatment is also in agreement with the guideline recommendations. It can, however, be expected that the extension of the registered indications of the thiazolidinediones in Europe in 2004, allowing their use as monotherapy in T2DM patients, will lead to an increased use of these drugs as initial treatment. This

is analogous to the USA, where thiazolidinediones were marketed earlier and had a broader registration at introduction, and where a steep increase in their prescription rates has been reported [8, 11].

Within the group of the sulphonylureas, the prescription of glibenclamide and tolbutamide decreased during the study period. Only the decreased use of glibenclamide is in accordance with the revised guidelines and corresponds with observations in the UK that longer-acting sulphonylureas are increasingly being replaced by shorter-acting drugs [9, 10].

The observation that female patients discontinued metformin more frequently than male patients when receiving follow-up treatment with sulphonylurea is intriguing. We observed no differences in prescribed

dosages for metformin between males and females. The discontinuation rate in females of 25% is much larger than expected from tolerability data of clinical trials, which showed that 10–15% of patients discontinued metformin because of adverse effects [18].

A strength of this study is that the pharmacy dispensing records were linked to individual patients. This made it possible to follow individual drug use over time. Prevalence data give insight only into the percentage of the population exposed to oral antihyperglycaemic drugs in a given period of time. The incidence and follow-up prescription rates give a better insight into the drug preferences of doctors in specific time periods.

The use of a pharmacy dispensing database also has its limitations. Pharmacy databases do not include detailed clinical information. Therefore, it is not known whether the observed prescription rates for metformin fully followed the revised guideline with respect to the prevailing BMI. On the other hand, the proportion of metformin users corresponds to the estimated 60% of T2DM patients that have a BMI >27 kg m^{-2} in the Netherlands [19, 20].

Second, we recognize that there is a small overlap between the two year cohorts, which tends to result in an underestimation.

In conclusion, we found a significant change in the prescribing pattern of oral antihyperglycaemic drugs in patients with T2DM which was in concordance with the publication of the UKPDS results and practice guideline revisions in the Netherlands. This indicates that in this therapeutic area changes in insights and treatment recommendations were quickly transferred into daily clinical practice.

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