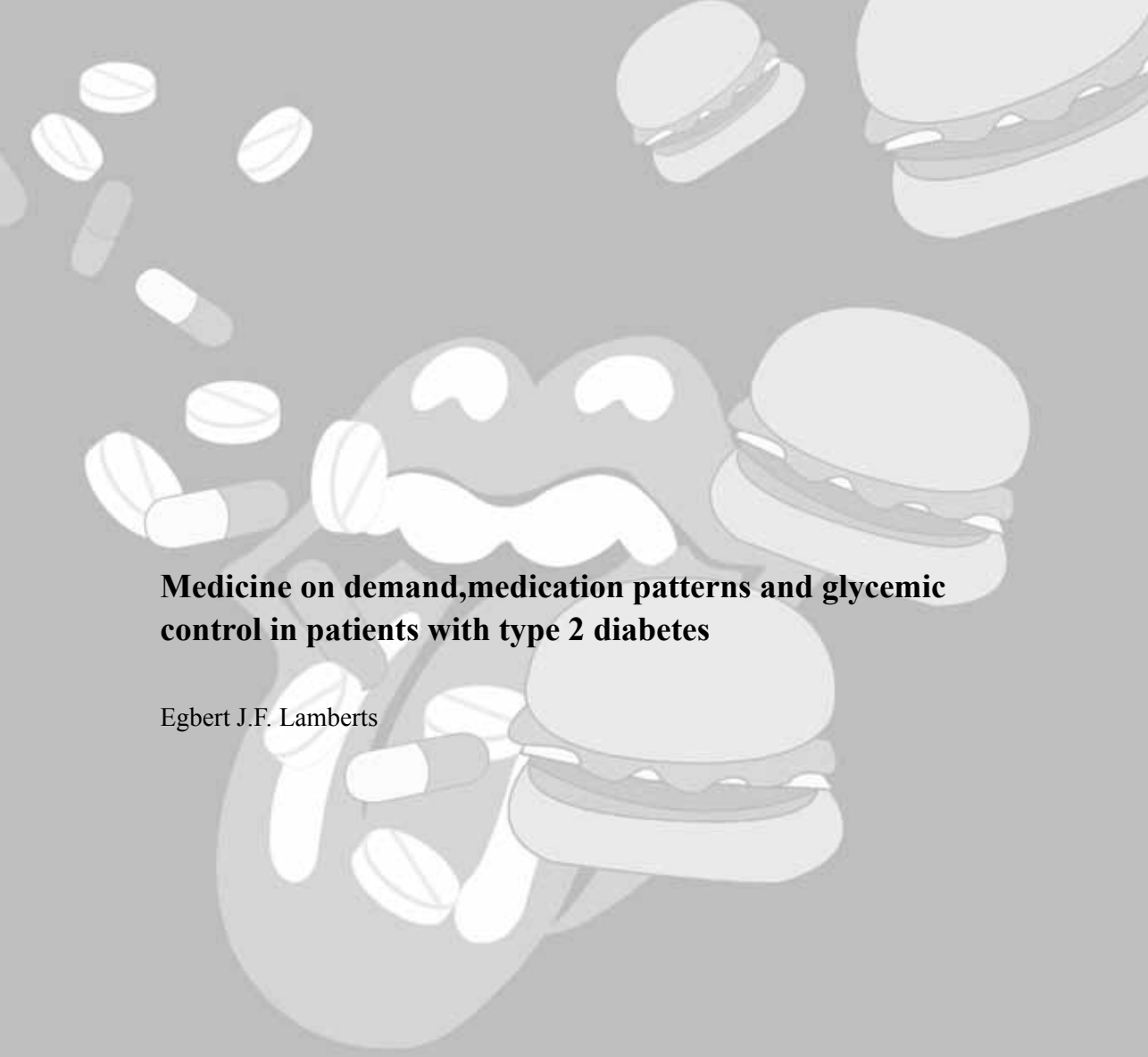

Medicine on demand,medication patterns and glycemic control in patients with type 2 diabetes

Egbert J.F. Lamberts

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Medicine on demand, medication patterns and glycemic control in patients with type 2 diabetes

Vraaggestuurde zorg, medicatiepatronen en glycemische controle bij patiënten met type 2 diabetes (met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 19 juni 2013 des middags te 2.30 uur

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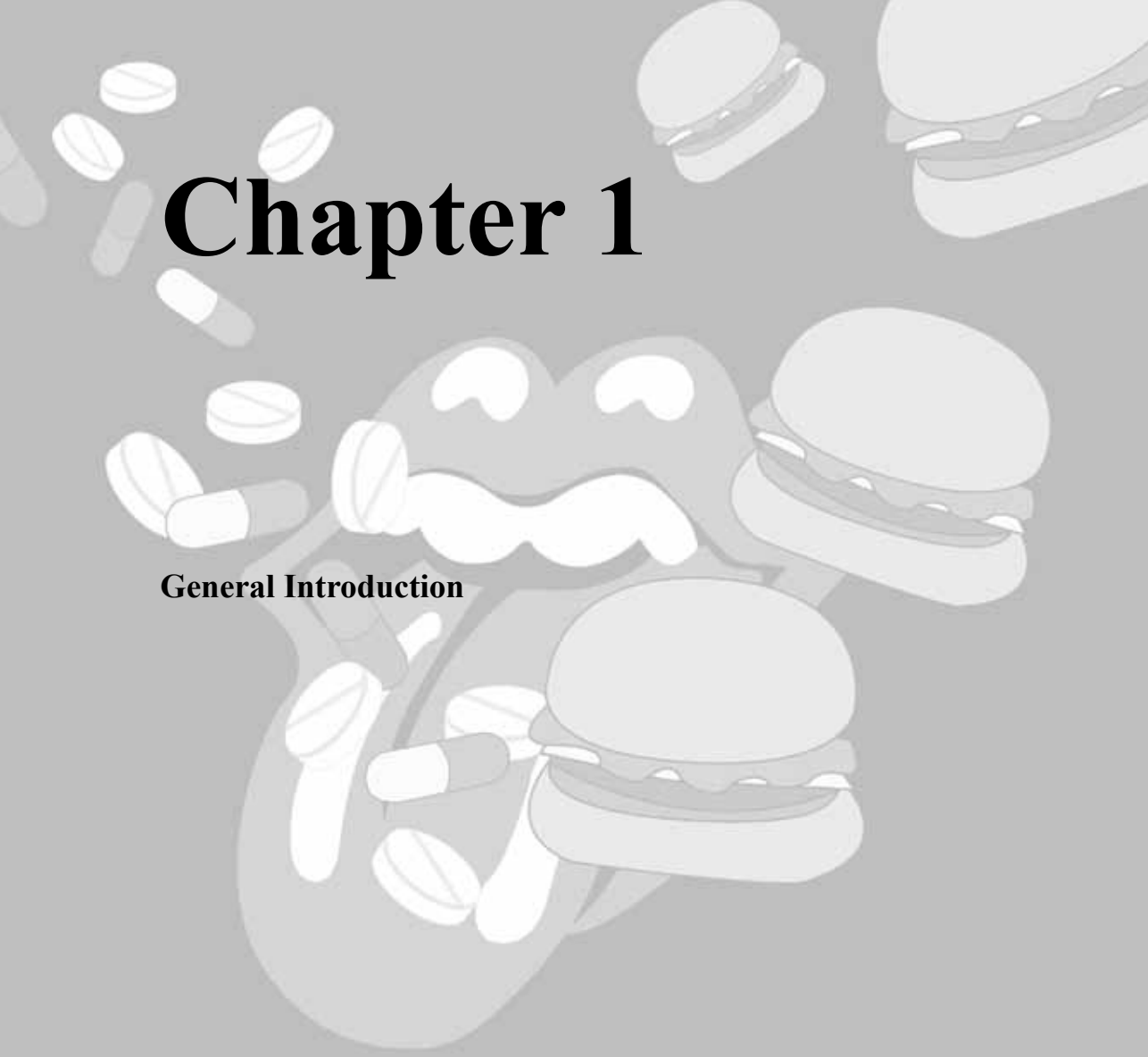
voor Stijn & Bart

"Cash your dreams before they slip away"

Mick Jagger, Keith Richards, 1967

Table of contents

Chapter 1



General Introduction

General introduction

Diabetes mellitus is a metabolic disease currently affecting approximately 5% of the general population. Type 2 diabetes mellitus (T2DM) accounts for 90-95% of all cases. In the last decades the prevalence of T2DM has increased steeply due to ageing, unhealthy diets, obesity and increasingly inactive lifestyles. Moreover, the widespread availability of point of care testing and specific screening programs have led to earlier identification of T2DM. [1-4] In The Netherlands an estimated 740,000 people were suffering from T2DM in 2007. This number is expected to increase to 1.3 million in 2025.[5, 6]

The risk of developing cardiovascular disease is 2 to 3 fold increased in patients with T2DM, making diabetes one of the most important risk factors for cardiovascular disease.[7, 8] Other cardiovascular risk factors such as smoking, hypertension and hyperlipidemia further increase the risk on T2DM associated cardiovascular disease.[9, 10]

T2DM and health care

The increasing number of patients with T2DM is leading to an exponential rise in health care and societal cost. In 2006, the total costs (health care and societal) of diabetes in The Netherlands were estimated at €6.2 billion.[9] Early identification and disease management of T2DM is expected to reduce morbidity and mortality, to save long term costs and to improve patients' overall health related quality of life.[10] The number of users of antidiabetics increased to 771,000 in 2011 from 672,500 in 2007. This is an average increase of 3.5% per year. Over the years the increase in the use of the oral agents was 4.4% per year, which is slightly higher than the yearly increase (3.2%) of the number of insulin users. The difference is due to an ageing population and consequential rise of incidence of T2DM. The 65 + age group is the largest user group followed by the group of 45-64 years. They are responsible for 55% and 37% of total use, respectively. In 2007 the total costs for diabetes supplies amounted to slightly

over €250,000,000. Insulins are responsible for 68% of the total cost. In 2011, a mean 12.4 prescriptions were dispensed per user resulting in a mean €329 pharmacy costs per user per year.[11]

An average community pharmacy in The Netherlands is responsible for the pharmaceutical care of 400 patients with diabetes. Since medication plays a pivotal role in the treatment of T2DM, patients regularly visit a community pharmacy for a prescription refill. This generates the opportunity for community pharmacists to support patients with their medication use and monitor the medication prescribed by GPs.[12-16] The community pharmacy guides patients in their medication when the first medication for diabetes is dispensed. Patients receive information about the use and the expected effects. When patients visit the pharmacy for their first prescription refill they are asked whether they are satisfied with their medicines and whether they have experienced side effects. In the case that any side effects have been experienced, patients are instructed how to cope with the discomfort. If necessary they are referred to their general practitioner.[17] Pharmacy services for T2DM also include the supply of tools like glucose monitoring devices, syringes and needles and regular checks on their functioning. Patients are instructed to properly use these tools.[18]

Long term patterns of diabetes pharmacotherapy in daily clinical practice

The benefits of antidiabetic drug therapy on glycemic control and reduction of cardiovascular risk factors are well established. Evidence based treatment guidelines are exclusively based on the results of randomized clinical trials. In the past ten to fifteen years T2DM treatment guidelines have recommended increasingly tighter glycemic control. Over the years this led to an intensification of treatment and increased use of medicines.[12]

In The Netherlands diabetes treatment is predominantly initiated by GPs who are expected to follow the national diabetes guideline.[12] These guidelines provide evidence based recommendations aimed at glycemic control and the prevention of both microvascular and macrovascular disease.[13] Since 2006 GP guidelines

recommend metformin as the first step in diabetes treatment.[12] If metformin treatment does not result in adequate glycemic control, it is usually combined with a sulfonylurea, thiazolidinedione or DPP4 inhibitors. When a combination of two oral antidiabetics does not give adequate control of diabetes, in most cases insulin must be added. [12, 14, 15]

However, in daily clinical practice guideline recommendations are not always fully implemented.[18] Clinical trials describe drug utilization patterns over restricted time periods and in selected groups of probably highly motivated patients.[19-21] Long term drug utilization studies in daily clinical practice will give more insight in the actual use of oral antidiabetics.

Glycemic control in daily clinical practice

A more intensive pharmacotherapeutic approach in daily clinical practice is not a goal in itself, but should lead to a better glycemic control. A recent review suggested that the benefits of drug treatment could be attenuated by erratic behavior in the process from prescribing to taking (Figure 1).[22, 23] In this process erratic drug taking by the patient is the most important cause of loss of therapeutic effect. Prescribing and dispensing mistakes play a smaller role. The actual beneficial effect of medication will be even lower because not all patients who actually take a properly prescribed drug respond to treatment.

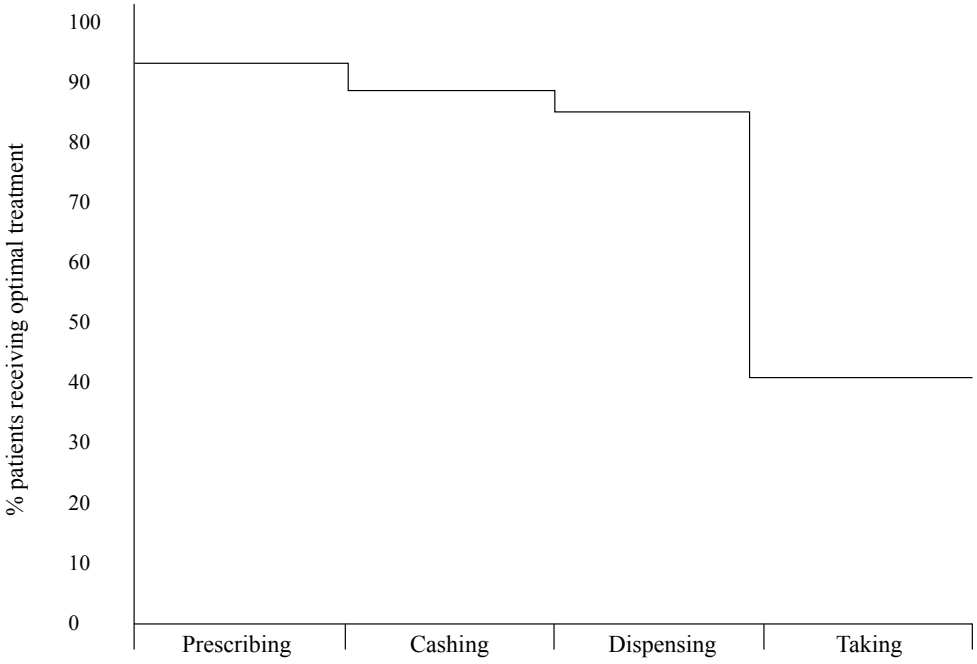


Figure 1. *Decrease of medication effectiveness after prescription.*[23]

In addition to describing drug utilization patterns, measuring the effect of guidelines on clinical outcomes in daily clinical practice may contribute to our knowledge of medication use and outcomes. Several observational studies have suggested that at least 30% of patients with T2DM do not reach their glycemic control targets.[24-26] Good glycemic control in combination with lowering of other cardiovascular risk factors (e.g. hypertension and dyslipidemia) has proven to decrease cardiovascular disease rates.[27] A reduction of 1% point in HbA1c has been associated with a 37% relative risk reduction of microvascular complications and 21% relative risk reduction for any T2DM related end point.[28] Maintaining appropriate HbA1c levels is therefore considered one of the key objectives in diabetes treatment.[29] Despite adequate diagnosis and medical care, patients may fail to derive the optimal clinical benefit of drug therapy.[30] Initiating drug therapy involves ensuring that the prescribed medication is

appropriate to improve the patient's personal medical condition, that it is the most effective and safest medication available, and that the patient is able and willing to use the medication as intended.[31] Poor medication adherence appears to be a major cause why patients do not achieve glycemic control. Therefore, it is highly relevant to explore how medication use can be improved.

Providing patients with adequate information about their medication may contribute to an appropriate use and understanding of the benefits and risks of the treatment. Currently, community pharmacy is shifting from compounding and logistics towards patient focused pharmaceutical care activities aimed at optimizing medication use.[32-34] It was proven that adequate information enables patients to make informed decisions on the use of their medication.[35, 36] Research into patients' information needs is necessary in order to optimize both the quality and quantity of diabetes information for patients.[37-40]

Setting

In The Netherlands several diabetes cohorts have been formed that longitudinally follow patients with T2DM such as the "Maastricht Studie" in the southern part of The Netherlands and the "Groningen initiative to analyze type 2 diabetes treatment", GIANTT, in the northern part of The Netherlands.[41, 42] The Diabetes Care System (DCS) in West Friesland was the first of such cohorts. The DCS started in 1996 with the aim to provide adequate diabetes care for patients with T2DM.[43] During the years more and more elements of the Chronic Care Model (CCM) were introduced. According to the CCM, improvement of care can be achieved by separating acute care from the planned management of chronic diseases, offering the patient education about the disease and supporting self management.[44] A computerized information system can be used as a reminder system to comply with evidence based guidelines, for planning individual patient care and for feedback to caregivers about their performance. The Diabetes Care System West-Friesland is a centrally guided diabetes care organization. Patients treated by the DCS receive an annual extended diabetes check-up at the

specialized Diabetes Care Centre, in addition to the diabetes care by patients' GP, according to the Dutch guidelines for type 2 diabetes. Patients have a central role in their care and self management is stimulated by providing education and information programs. Individual care plans are discussed with the patient and patients are stimulated to make their own choices with respect to treatment options and lifestyle behaviour. Also, patients are encouraged to participate in community programs. The DCS coordinates diabetes care between primary and secondary care. Using a centrally organized database, clinical information of patients is accessible to involved health care providers. Diabetes nurses visit participating GPs twice a year for feedback about their performance. Individual patients are evaluated and mean values of risk factors of the diabetes population of the GP are compared to the diabetes populations of other participating GPs.[43,45]

However, in spite of these efforts the information on the use of medication in the DCS before 2009 was rather limited. Strengths, dosage regimens and dispensing dates were not available. We therefore collected detailed data on the use of T2DM medication from pharmacy information systems in West Friesland and linked these to the clinical data for the studies conducted in this thesis.

Objectives and outline of the thesis

The present thesis deals with both the adherence of physicians to guidelines and the adherence of patients to their medication regimens. In the intersection of these topics is the counseling of patients. Physicians and pharmacist should properly advice patients in order to make an informed decision regarding their use of medication.

Chapter 2 of the thesis deals with the patients' information needs concerning oral antidiabetic medication at the initiation of T2DM treatment. Moreover, we aim to investigate the opportunities for pharmacists to help patients adequately use their medication.

Diabetes is a chronic disease that requires pharmacotherapy over a lifelong period. Relatively little is known about longterm utilization patterns of oral antidiabetic drugs. The aim of the study in Chapter 3 is to describe longitudinal patterns of antidiabetic drug modifications after initiation of oral antidiabetic therapy in a large cohort of T2DM patients.

In parallel glycemic control has to be maintained over years. Chapter 4 presents longitudinal patterns of HbA1c levels in daily clinical practice of patients with T2DM. In addition, the study aims to identify the characteristics of patients with seemingly poorly controlled diabetes.

Chapter 5 describes patterns of use of oral antidiabetic medication in relation to glycemic control as reflected by HbA1C levels. The study focuses on the influence of the initial oral antidiabetic medication and subsequent treatment modifications on the achievement of long term glycemic control in T2DM patients.

Chapter 6 describes discontinuation of treatment among T2DM patients prescribed statins prior to, and after initiation of therapy with oral antidiabetics. Discontinuation rates of statins and oral antidiabetic drugs are also compared.

As diabetes has been reported to lead to both cardiovascular and other comorbidity Chapter 7 describes longitudinal patterns of concomitant medication use in T2DM patients.

Chapter 8 discusses the main findings of the thesis. Implications for clinical and pharmacy practice are addressed and suggestions for future research are made.

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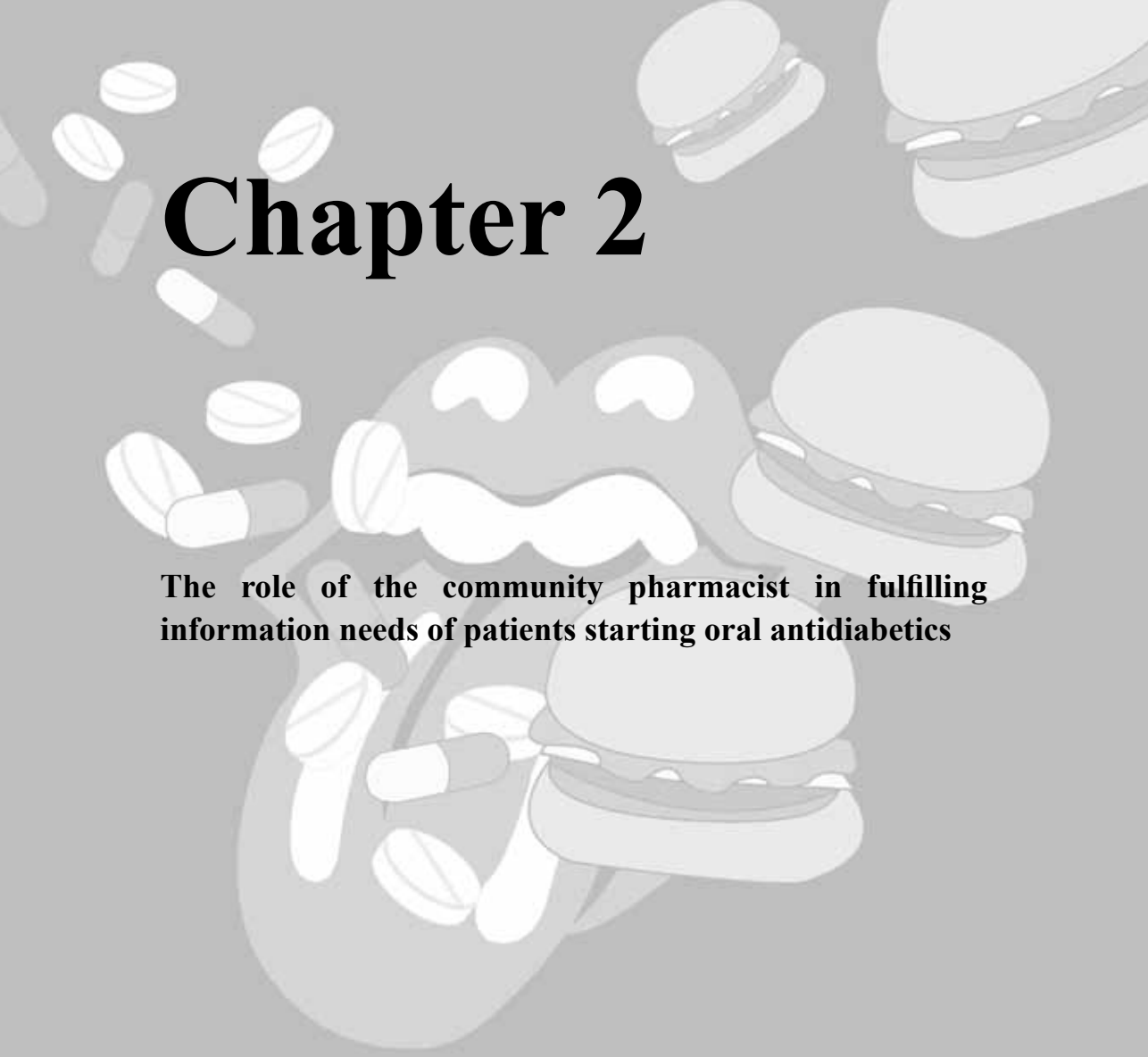

Chapter 2

The role of the community pharmacist in fulfilling information needs of patients starting oral antidiabetics

Res Social Adm Pharm 2010;6:354-64

E.J.F. Lamberts
M.L. Bouvy
R.P. van Hulten

Abstract

Background

Community pharmacy is in the middle of a paradigm shift from provider of medication to provider of care around medication. Much of this care involves giving information to patients in order to maximize pharmacotherapy outcomes. However, this is not necessarily recognized by patients. The initiation of chronic medication for diseases such as type 2 diabetes mellitus (T2DM) arouses much uncertainty in patients and it is not certain how information provision roles by pharmacists are viewed.

Objectives

To obtain insight in the information needs of patients who have recently started treatment with oral antidiabetics and to investigate the opportunities for pharmacy regarding the provision of information for patients with T2DM.

Methods

A qualitative study with both semi-structured telephone interviews and patient focus group discussions was conducted. Individual patients' comments were categorized and used in a, strengths, weaknesses, opportunities and threats (SWOT) analysis exploring the role for the community pharmacist in the field of providing information at the moment of initiation of T2DM oral medication.

Results

From interviews with 42 patients and 2 focus group discussions emerged that the GP does not fulfill all information needs. For the pharmacist there is an opportunity as patients feel a need for information and like to discuss drug related issues. SWOT analysis revealed as main strengths of the pharmacy "expertise" and "service and kindness". Together with more cooperation with GPs and nurse practitioners these strengths give the pharmacist the opportunity to further develop pharmaceutical care activities.

Conclusions

Pharmacists are challenged to increase their visibility as health care provider whilst keeping logistic service on a high level and improving cooperation with other health care providers.

Introduction

Pharmacy practice is gradually moving away from its original focus on compounding and dispensing towards a more patient focused role as a provider of services and information and forms of direct patient care. The latter role emphasizes a shared responsibility between the patient, prescriber and pharmacist for optimal drug therapy outcomes.[1,2]

Standards of practice for diabetes care have changed considerably in recent years. As a chronic disease in which medicines play a pivotal role, diabetes is a suitable area for research on the role of the pharmacist.[3] The incidence and prevalence of type 2 diabetes mellitus (T2DM) have risen steeply in the past years due to several factors such as lifestyle, obesity, ageing and better diagnosis.[4] The worldwide prevalence of diabetes is expected to increase further in the coming decades. Diabetes mellitus already affects approximately 5% of the population in the western world. T2DM accounts for 90% of all cases of diabetes.[4] In the Dutch population, existing of 16.2 million people in 2007 about 740,000 (4.6% of the total population) diabetes patients were known.[5,6]

Many patients with T2DM do not reach treatment targets. An important factor contributing to this suboptimal treatment is the lack of medication adherence. Several studies suggest that adherence with the use of antidiabetic drugs is poor.[7-9] Increasing adherence may have a greater impact on the health of the population than improvement in specific medical treatments.[10,11]

Interventions aimed at improving medication adherence have demonstrated mixed results. It has been shown, however, that merely providing patients with information is not enough to increase medication adherence, as individual's

illness and medication beliefs also play a role.[12] However, providing patients with information about their medicines is essential to facilitate their appropriate use and understanding of the likely benefits and risks. Appropriate drug information has been associated with improvements in medication adherence.[13,14]

Although ways to improve drug information and counselling have been studied widely, more research is needed in order to improve the knowledge about the needs, opportunities and attitudes of the individual patient.[15] The objectives of this study were to obtain insight in the information needs of patients who have recently started treatment with oral antidiabetics and to investigate the opportunities for pharmacy regarding the provision of information for patients with T2DM.

Method

Study Design

A qualitative research existing of semi-structured telephone interviews followed by patient focus group discussions. This combination of qualitative techniques is used to both obtain the opinions of more reserved individuals and to profit optimally from the interaction in the focus groups.[16-18]

Answers given by participants were labeled Strengths, Weaknesses, Opportunities and Threats. Subdivision into care oriented issues and logistic and organizational issues were made in each labeling group.

Setting

Six community pharmacies in two middle sized towns in the central part of The Netherlands.

Patients

Men and women between 18 and the 80 years old who were dispensed a first prescription of an oral antidiabetic (ATC, A10B) between 1 April and 1 October

2006.[19] First dispensing was defined as the absence of a prescription for any antidiabetic (ATC, A10B) in the previous 12 months.

Procedure

Patients fulfilling inclusion criteria were informed of the study by postal mail. Patients could refuse to participate. When patients were interviewed by telephone they were asked to cooperate in a focus group discussion. They were told about the procedure and that the meeting would be videotaped. When between five and eight people coming from one town were willing to participate they were grouped in a focus group. Focus group discussions were held in one of the pharmacies in both towns, where the participants were selected from.

Telephone interview

The telephone interview was semi-structured and based on the "Satisfaction about Information on Medicines questionnaire" (SIMS).[15] The interviews were carried out by one of the researchers (EL). Each interview took about thirty minutes. The results are presented in Table 2. The information provided by the GP versus the pharmacist was compared using a Chi-square test. In order to further elaborate the findings from the individual interviews, two focus group discussions were organized.

Focus group discussion

The results of the telephone interviews were used to prepare the focus group discussions. In the focus groups both content bound issues (e.g. concerns about medication) and context bound issues (e.g. waiting time in a pharmacy) were discussed.

Focus group discussions provide a forum to discuss a broader range of issues than would arise from individual interviews.[16] Duration of both discussions was 2 hours. At the two discussions a chairman, a moderator and two observers were present. The role of the chairman was to monitor the discussion process

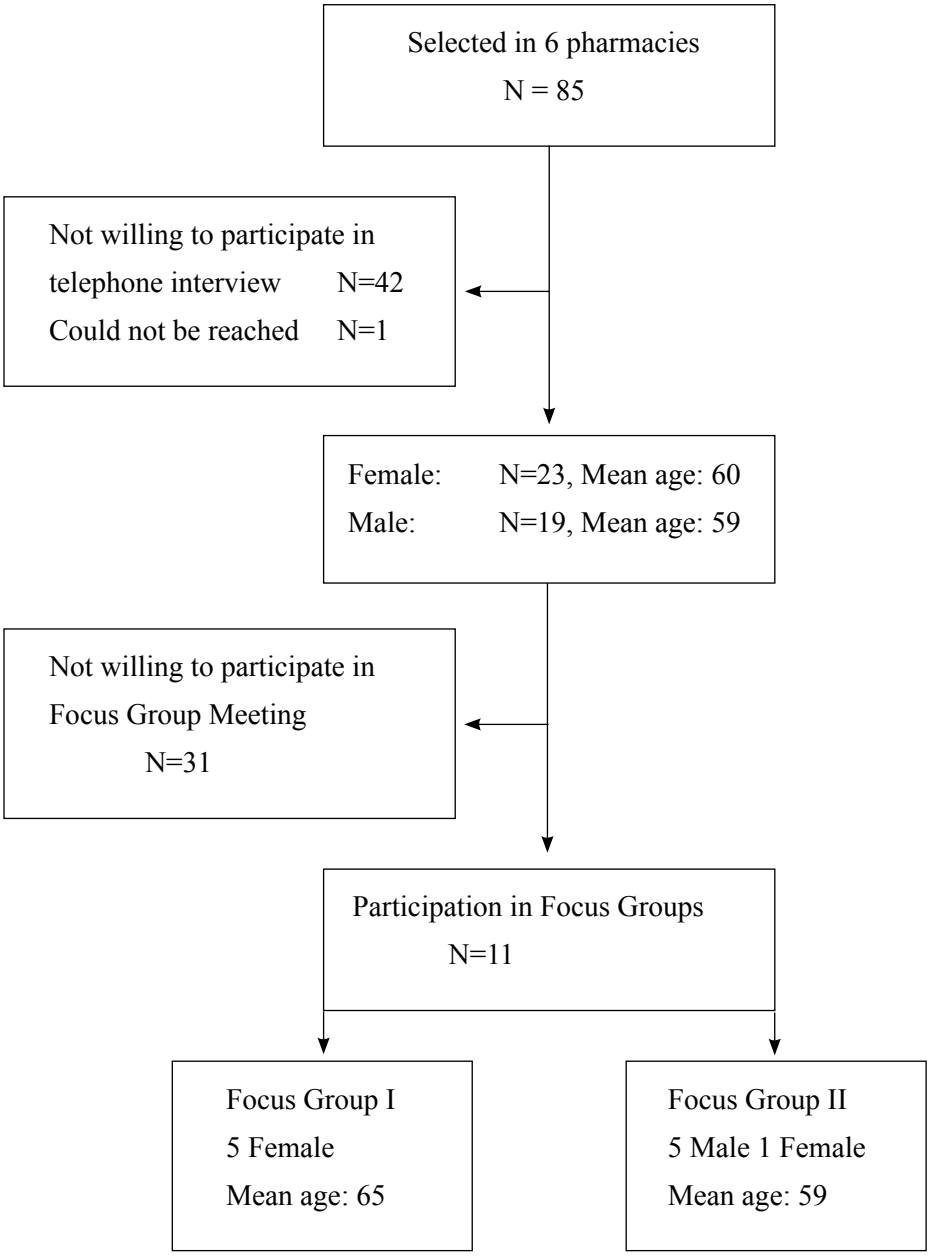

Figure 1. *Patient characteristics.*

from a technical standpoint. The moderator was responsible for encouraging active participation and interaction within the group. The two observers did not interfere in the discussion but were independently recording and capturing the proceedings and information of the discussion. The discussion was recorded on video. Using the reports of the observers of the focus groups, the three researchers (MB; RvH; EL) each coded and categorized all individual quotes of the participants. In case of ambiguity or lack of consensus the videos were viewed and coded live and categorized by the researchers. In total, three meetings took place to come to full consensus about coding, interpreting, and categorizing. The issues or quotations were categorized in the strengths, weaknesses, opportunities, and threats (SWOT) matrix. Consequently, ten community pharmacists belonging to the Utrecht pharmacy practice research network (UPPER), independently scored the 4 quadrants of the SWOT matrix resulting into the Confrontation matrix (see below).

Table 1. *Schematic view of confronted relationships between external and internal factors influencing each other.*

Internal	External	
	Opportunities	*Threats*
Strengths	1: Grow	2: Defend
Weaknesses	3: Improve	4: Solve problem

SWOT matrix

Statements made during the focus group discussions are presented in a SWOT matrix. The aim of a SWOT analysis is to combine the external and internal factors to gain insight into the organization in its current position and to discern new opportunities.[20] In this study we investigate the position and perspective of community pharmacists in their role as information provider. In the SWOT matrix, external factors are subdivided into opportunities and threats. Patient or

consumer needs can be seen as opportunities. An external threat is a challenge posed by an unfavorable trend or development that could hinder the professional development of the pharmacy (e.g. the information needed is already given elsewhere). The internal analysis focuses on the strengths and weaknesses within the organisation.[20] In the SWOT matrix the strengths, weaknesses, opportunities and threats are subdivided into care oriented issues and logistic oriented issues.

Confrontation matrix

By confronting the opportunities and threats with strengths and weaknesses a co-ordinated view of the organization and four possibilities of action can arise. This is called a confrontation matrix. 1. Confrontation of opportunities with strengths. Does it concern a strength with which an opportunity can be exploited? 2. Confrontation of threats with strengths. Is this a strength with which a threat can be turned away? 3. Confrontation of opportunities with weaknesses. Is this a weakness that obstructs exploiting an opportunity?
4. Confrontation of weakness with threat. Is this weakness as such that the threat becomes a serious risk for the organization? [21]

In the cells of the four quadrants of the confrontation matrix an expert team of ten independent community pharmacists belonging to the Utrecht pharmacy practice research network (UPPER), independently scored the specific confrontation with, – –, –, 0, +, ++. The scores were added up and presented in the matrix as follows:

-20 to -13 is scored as – –;
-12 to -5 is scored as –;
-4 to +4 is scored as 0;
+5 to +12 is scored as +; and
+13 to +20 is scored as ++.

Double "+" or double "–" indicates a higher relationship between the internal and external issues. Disagreement was defined as 10% or more scores/ratings with more than one step from the median score (e.g. when median is +, less than 10% of pharmacists should score – or – –).[22]

Results

In six community pharmacies 85 patients who recently started oral antidiabetics were selected. Forty-two patients were willing to give a telephone interview (23 females and 19 males). The interviews showed that pharmacists provide less information than GPs on six out of ten issues. Furthermore, most participants reported to be in need for more information (Table 2). Practical issues such as 'What you should do if you forget to take a dose' or 'Whether the medicine interferes with other medicines' are examples of issues on which more information is needed.

Only 11 people were willing to participate in a focus group discussion. The division of female and male participants in the two focus groups is not intentional. The female group had a mean age of 65, while the male group a mean age of 58. All patients initiated treatment with metformin, which is commensurate with current Dutch guidelines for the treatment of T2DM.[23]

In Table 3, both internal and external issues are presented with examples of literal quotes by the patients who participated in the focus groups. During analysis of proceedings and information from both focus groups, saturation of data was observed.

In the confrontation matrix (Table 4.) the consolidated statements considering the discussed issues are presented. In the confrontation matrix , "+" and "+ +" indicate that the strength can exploit the opportunities and the threats can be averted. The score "+ +" indicates that the experts give more weight to the confrontation than with a score of "+". The scores "–" and "– –" indicate that the confrontation of weaknesses with opportunities and threats can lead to the

opportunity being missed or the threat not being turned away. A score of "– –" indicates that the panelists weighted the weakness higher in confrontation with the opportunity or threat.

Agreement among the ten panelists about the scoring was very high. There was no disagreement on separate issues, thus resulting in an overall disagreement level less than 10% compared to the median score.

Table 2. *Summary of information provided and needed according to patients (n=42) who participated in a telephone interview starting oral type 2 diabetes mellitus medication.*

	"Did you receive information on the following aspects of your medicine?"						"Do you need information on the following aspects of your medicine?"		
	Information from GP			Information from pharmacist					
	Yes	No	Neutral	Yes	No	Neutral	Yes	No	Neutral
What your medicine is for	27	12	3	12	20	10	22	2	18
How it works	23	14	5	7	22	12	10	2	30
How long it will take to act	13	23	6	6	21	15	12	1	29
How long you will need to be on your medicine	16	21	5	5	23	14	13	1	28
How to use your medicine	17	19	6	23	17	2	15	1	26
Whether the medicine has any unwanted effects	10	26	6	8	25	10	11	4	27
What are the risks of you getting side effects	10	27	5	0	30	12	1	20	21
Whether the medicine interferes with other medicines	9	23	10	9	25	8	15	2	25
What you should do if you forget to take a dose	6	30	6	4	26	12	16	1	25
What are the risks of stopping the medicine	12	24	6	0	27	15	8	3	31
Total	143	219	58	74	236	110	123	37	260

Table 3. *Issues and quotes from two focus groups.*

		Internal issues
Strengths	Care oriented	**Expertise** "They provide me with good answers to my questions and practical information about the products; they are friendly and show expertise". "The pharmacist is the one with the right knowledge" **Service and Kindness** "The attendance and service is good". "I feel welcome in this pharmacy". **Meaningful Interventions** "A few times the pharmacists made a telephone call to the hospital to be sure if the prescription was correct". "I experienced myself that the pharmacist gave the advice not to use the prescribed medication".
	Logistic and organizational oriented	**Availability and accessibility of medicines** "Most of the prescribed medicines are in stock". "The pharmacy is not far from home".
Weaknesses	Care oriented	**Conflicting information with other care suppliers** "Information given by the pharmacist can contradict with information given by the doctor". "When I asked about the possibility of combining my medication, they told me that the doctor would otherwise not have prescribed it" **Pharmacist is not available** "You can't build a relationship with the pharmacist, while he is not around. He is not close enough to the patient". "More attention and privacy is needed if you want to occupy a position as a care provider". "We asked several times but never had a satisfying answer. This is an opportunity for a pharmacist". "At the start with new medication it should be standard procedure to be informed in a private consultation room. This is a missed chance for pharmacists"

Weaknesses	Logistic and organizational oriented	**Unclear activities behind the scenes** "It is annoying to see a lot of personnel busy in the pharmacy but you don't have any idea what they are doing". "Don't bother patients with what you are doing behind the scenes". **Crowdedness and long waiting times** "It is too busy to give information". "Long waiting times need to be addressed" **Too much change in personnel** "You never see the same assistant". "When there is too much change in personnel there is no possibility of getting to know each other better". **Shortage of personnel** "I have a feeling that market forces will lead to fewer staff and increased workload. This is unfavourable for the contact with the pharmacy staff." **Too busy with logistics** "Personnel seem to be too busy with other things to be able to take care of patients".
		External issues
Opportunities	Care oriented	**Most people have questions after visiting their GP** "A lot of people do have questions after visiting their GP". **Worried about side effects, unclear inserts or information** "The information given in the insert is unclear and without nuance". "You would like to know if it is a side effect". "It is confusing when you get another medicine which is the same but you don't know what it is". **Cooperation between healthcare providers** "It has to be teamwork between GP and pharmacists "To reduce the use of too much medication GP and pharmacist need to consult together", "If doctors and pharmacists would cooperate more they would drive back unnecessary medicines use", "I like the idea of regular discussion of my medication with a pharmacist but it has to be in line with the doctor".

Opportunities		**Adherence matters are not discussed with GP** "If you don't want to take it, it is your own business". **GP's shortage of time** "The doctor doesn't listen". "It is an opportunity to profile your pharmacy".
Threats	Care oriented	**Information is gathered on the internet** "I do not need to take medication anymore just to lose weight, I found this out myself by searching on the Internet", "I trust the Internet more than my doctor". **Sufficient information given by GP,** "My general practitioner gave me enough information". "Willingness to provide information is nice but the same information is provided by the GP". **Nurse practitioner is primary contact** "The nurse practitioner is well equipped to give relevant information". "I generally trust the nurse practitioner." **No need for personal contact with pharmacists** "A confidential relationship with your pharmacist is nonsense". "A pharmacist is not competent; he is not a discussion partner".
	Logistic and organizational oriented	**Pharmacy primarily seen as dispensing outlet** "A pharmacist is just somebody who pushes boxes over the counter" **Patients are often in hurry** "Just give it on request"

Table 4. *Confrontation Matrix.*

		Opportunities					**Threats**						
		Most people have questions after visiting GP	Worries about side effects; Unclear insert	Cooperation between healthcare providers	Adherence matters are not discussed with GP	GPs Shortage of time	**Care oriented issues**	Information is gathered from the internet	Decision concerning drugs made by GP	Nurse practitioner is primary contact	No need for personal contact with the pharmacist	**Logistic / Organizational issues**	Pharmacy primarily perceived as dispensing outlet	Patient is often in a hurry
Strengts	**Care oriented issues**													
	Expertise	++	++	++	++	++		+	+	+	+		0	0
	Service and Kindness	++	+	++	++	+		+	+	+	++		+	+
	Meaningful Intervention	+	++	++	++	+		+	+	+	+		+	+
Weaknesses	**Logistic / Organizational issues**													
	Availability of medicines	0	0	+	+	+		+	+	0	0		+	++
	Care oriented issues													
	Conflicting Information pharmacists and GP	--	-	--	-	-		-	-	--	-		-	0
	Pharmacist is not available	--	--	-	-	-		-	--	-	--		-	-
	Logistic / Organizational issues													
	Unclear activities behind the scenes	-	-	-	-	-		-	-	-	-		-	-
	Crowdedness / Long waiting times	--	--	-	-	-		-	-	-	--		-	--
	Change in personnel	-	--	-	-	-		0	0	-	-		--	-
	Shortage of personnel; high working pressure	--	--	--	--	--		-	-	-	-		--	--
	Too busy with logistics to give information	--	--	--	--	--		--	--	-	--		--	-

Discussion

This study revealed that in case of T2DM there is an opportunity to provide more information at the start of pharmacotherapy. Patients still receive much of their medication information from the GP, but the GP does not yet fulfill all patients' information needs.

The confrontation matrix shows a clear opportunity for pharmacists, as patients feel a need for information about medicines and like to discuss drug related issues such as adherence. Although patients primarily would like to receive this information from their GP and perceive the GP as the primary health care provider who decides about the drug regimen, they also realize that their GP does not have enough time to give attention to these needs. Expertise is the major strength of pharmacists that could be used to fill the information gap patients experience after consulting their GP. In a recent study in the US diabetic patients see pharmacists' role primarily in information on side effects and lowering costs of medication. Only 10% of the respondents expect their pharmacist to play a more active role in diabetes management.[24] The fact that patients gather information independently (e.g. on the internet) could be easily converted to an opportunity as patients do need help, from a dedicated health care provider, in interpreting the information they have gathered.

As patients build up personal relationship more easily with nurse practitioners, they might turn more naturally to nurse practitioners than to pharmacists. As pharmacists are still perceived mainly as distributors of medicine they have to invest in building up relationships with patients. Patients do trust the interventions by the pharmacy. Despite this trust most participants do not feel the need for personal contact with the pharmacists. This need for personal contact is also lowered by limited visibility of the (Dutch) pharmacist, according to the participants. Dutch pharmacies focus solely on prescription medicines. The average pharmacy has 1.6 pharmacists and 9.5 technicians. Patients' first contact

will generally be the pharmacy technician.[25] Moreover, participants stated that shortages and changes of personnel prevent building up closer relationships between patient and pharmacy personnel. Service and kindness could help pharmacists in building a relationship with the patient. This is a prerequisite for the development of a shared responsibility and eventually better therapeutic outcomes.[26, 27] It is recognized that lack of kindness is a barrier to effective patient communication.[28] As long as pharmacists are primarily perceived as medication providers and patients perceive their visit to the pharmacy as necessary but time-consuming, it remains important that medication is readily available for patients (logistic and organizational strength). As this is a strong incentive for patients to return to the pharmacy, it provides pharmacists the opportunity to demonstrate their expertise and initiate counseling activities.

A qualitative Portuguese study suggested that the public perceives long waiting times negatively and have a "commercial" image of pharmacy. A professional fee independent of the amount of drugs sold could stimulate the development of pharmaceutical care. [29] In Iceland, the public has been reportedly critical of pharmacists, including the quality of information they provide.[30] It is not easy for patients to understand what is happening behind the scenes, which leads to irritation and does not encourage patients to gather information in a pharmacy. Pharmacists have to invest in clearer communication to patients on their back-office activities.

With strengths like "expertise" and "service and kindness" and with more cooperation with GPs and nurse practitioners, pharmacists could further develop their pharmaceutical care activities. The importance of multidisciplinary cooperation is underlined by the fact that patients find it confusing and annoying that the information provided by different health care professionals is sometimes conflicting. More cooperation between the different professions could improve the whole care process. An integrated healthcare approach including the community pharmacists with focus on Drug Related Problems, monitoring and measurement of patient knowledge lead to better clinical outcomes.[12, 31]

Well organized pharmaceutical care programs can improve diabetes care and clinical outcomes.[32, 33] Multidisciplinary cooperation within these programs may improve outcomes. An organizational change in Dutch community pharmacy to reduce the workload of the staff would contribute to facilitate care programs.

Strengths and limitations of the research

The recruitment of participants, done by using pharmacy records, provided a wide range of patients. Moreover, 50% of the selected patients who recently started with oral antidiabetics were willing to participate in an interview. The collecting of data was performed by two different methods, telephone interview and two focus groups.

Bias could be expected due to the fact that the participants in the focus group discussions tended to be those who were most assertive in the telephone interviews. Furthermore, socially desirable answers could have been provided by interviewees and by panelists. Focus groups have to be continued in number until the moderator does not expect to hear new items.[34] Running at least a third focus group was not possible, as there were no more patients willing to participate and the results from the telephone interviews did not show additional issues. Participants in both groups did not vary much in opinion suggesting that the additional information that could be retrieved was saturated. In order to reduce subjectivity of the analysis, at each level of the study different experts were employed. In the scoring of the confrontation matrix by ten experts there was a high level of agreement.

Conclusion

Patients still perceive the pharmacy primarily as a dispensing outlet. Although the expertise of the pharmacists is recognized, this expertise is not sought frequently. Pharmacists are therefore challenged to increase their visibility

as health care provider whilst keeping logistic service on a high level and improving cooperation with other health care providers.

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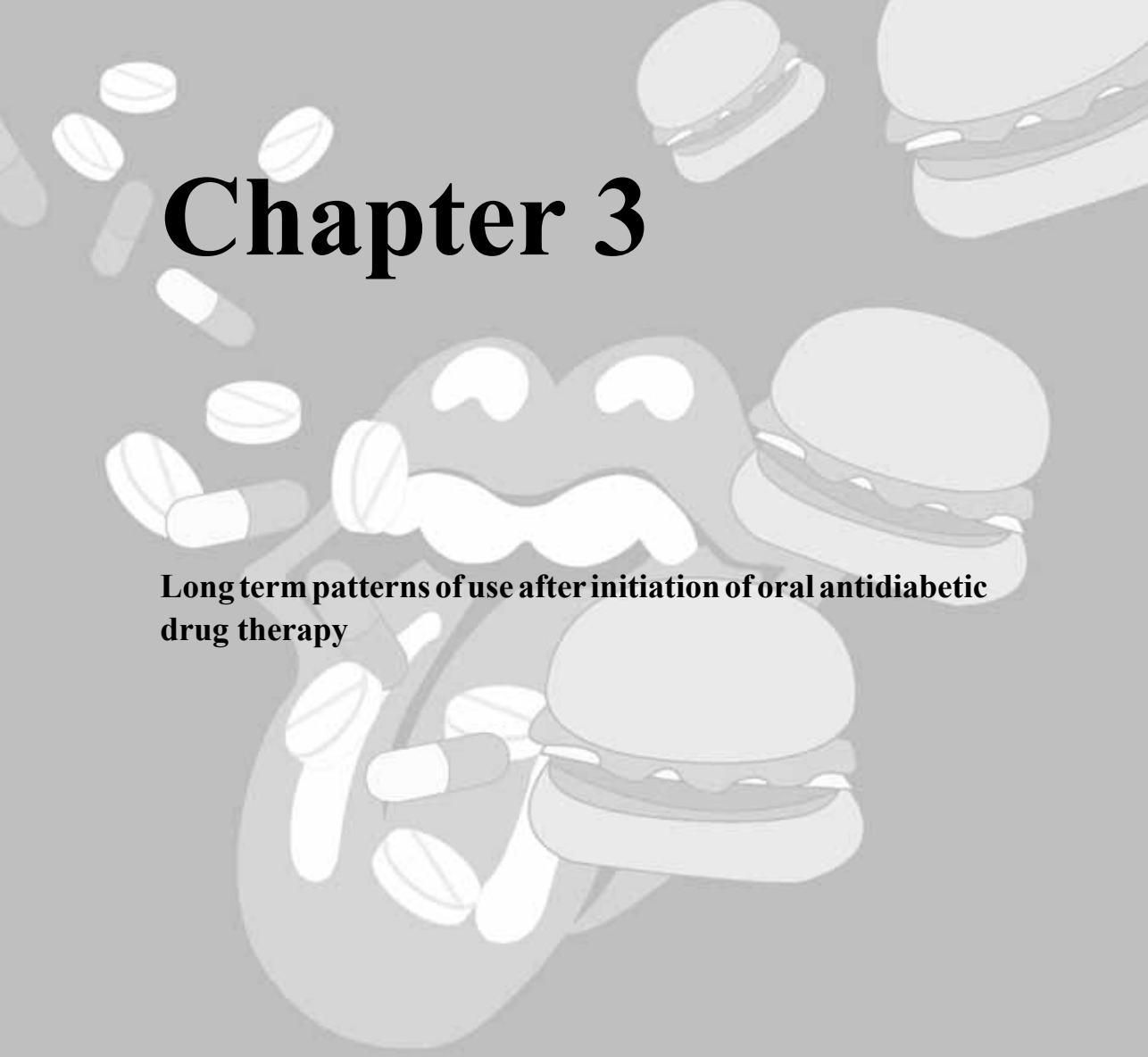

Chapter 3

Long term patterns of use after initiation of oral antidiabetic drug therapy

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Abstract

Background

The benefits of intensive and continuous antidiabetic drug therapy have been extensively described. Data on long term patterns and modifications of antidiabetic drug use are scarce however. Moreover, randomized controlled studies may not reflect actual drug use in daily clinical practice.

Objectives

The aim of this study is to describe the longitudinal patterns of antidiabetic drug modifications after initiation of oral antidiabetic therapy in a large cohort of type 2 diabetes patients. The study will focus specifically on differences between patients who initiate treatment with metformin compared to patients who initiate treatment with sulfonylureas.

Methods

An observational study of longitudinal patterns of use and modification of oral antidiabetic drug therapy in 3323 patients who started with oral antidiabetic treatment between 1999 and 2007. Drug dispensing data were extracted from pharmacy information systems.

Results

This study shows that changes in international guidelines recommending metformin as first choice initial drug therapy in all patients were rapidly followed by prescribers. Patients starting diabetes treatment with metformin showed fewer modifications to treatment compared to patients initiating treatment with sulfonylureas. After correction for duration of follow up, Cox regression analysis showed a hazard ratio of 0.84 for any modification in the metformin group compared to the sulfonylureas group.

Conclusions

This study shows that adherence to type 2 diabetes treatment guidelines for initial treatment is implemented on a large scale. Longitudinal patterns show that the majority of patients receive a small number of modifications to their drug regimen. Discontinuation rates were relatively low.

Introduction

The prevalence of type 2 diabetes has risen steeply in the past years due to lifestyle changes (increased energy intake and less physical exercise, both leading to increased Body Mass Index) and the ageing of the population.[1] Type 2 diabetes now affects approximately 5% of the general population in the Western world.[2]

Guidelines for the treatment of type 2 diabetes provide evidence based recommendations aimed at preventing both microvascular complications such as nefro-, retino-, and neuropathy and major cardiovascular outcomes.[3] Lifestyle recommendations such as smoking cessation, increased physical exercise, dietary advice and weight loss are the primary treatment strategies, advised by international guidelines.[4,5] In addition to lifestyle modifications, chronic drug therapy is often inevitable to achieve optimal glycemic and metabolic control.[4] Intensive glycemic control, (HbA1c <7% and Fasting Glucose between 4 and 7 mmol/l) has been proven to decrease the risk long term complications.[6 - 9]

However guideline recommendations are not always implemented in daily clinical practice.[10] At least 30% of patients with type 2 diabetes do not reach targets for glycemic control.[11 - 14] Clinical trials only describe drug utilization patterns over restricted periods and in a highly selected group of probably motivated patients. Treatment of type 2 diabetes in general practice is characterized by initiating, adding and switching of drugs with different mechanisms in order to maintain glycemic control.[15] Studies that describe the utilization of oral antidiabetic drugs either remain cross sectional or have relatively short

follow up.[15 - 17] Other studies collected additional data on patients included in randomized clinical trials that might not reflect daily clinical practice.[18]
The aim of this study is to describe the longitudinal patterns of antidiabetic drug modifications after initiation of oral antidiabetic therapy in a large cohort of type 2 diabetes patients.
The study will focus specifically on differences between patients who initiate treatment with metformin compared to patients who initiate treatment with sulfonylureas.

Patients and Methods

Study design
An observational study of patients initiating oral antidiabetic drug therapy.

Setting
Drug dispensing data for this study were obtained from fifteen community pharmacies and two dispensing general practices in a geographically well defined region in The Netherlands. This region (West-Friesland) has 200,000 inhabitants and a relatively stable composition of the population that is representative for a Dutch or Western European population.[19] In The Netherlands, the vast majority of the population obtains their medication from only one community pharmacy, enabling collection of complete medication histories of individual subjects over a long period of time. [20, 21]

Study population
Between 1999 and 2007, 6401 patients with at least one prescription for an oral antidiabetic were selected. The following patients were excluded: 1428 patients who were already using antidiabetic drugs in 1998, 1036 patients with less than 365 days of medication data before initiation of oral antidiabetics, 210 patients under the age of 40 at the moment of the first prescription of an oral antidiabetic

drug (potential sub variants of diabetes like MODY)[22], 332 patients with less than 365 days follow up after initiation of oral antidiabetics, 72 patients who initiated treatment with insulin. This resulted to the inclusion of 3323 patients in the analysis.

Data content

Of each patient the following data were extracted from the pharmacy information systems: gender, date of birth and complete coded dispensing records, including date of dispensing, drug name, dosing regimen and amount dispensed. All drugs were coded according to the Anatomic, Therapeutic and Chemical (ATC) classification system.[23]

Definition of drug utilization episodes

For each prescription a theoretical duration of use was calculated by dividing the number of tablets dispensed by the number of tablets used per day. When patients retrieved a new prescription before the end of the previous episode, the new episode was pasted after the previous one. In The Netherlands chronic medication is usually dispensed for a period of ninety days. Therefore a period of less than ninety days between two episodes was considered as continuous drug use. A period between ninety and hundred eighty days was considered as a drug use interruption. Longer periods (>180 days) were considered as (temporarily) discontinuation of drug use.

In The Netherlands, insulin can be dispensed for more than 90 days. Moreover, for insulin the number of international units used was not registered in the database. Therefore we could not calculate drug episodes. As it is unlikely that patients starting insulin will discontinue treatment preliminary it was estimated that patients were using insulin for up to one year (365 days) after each insulin prescription.

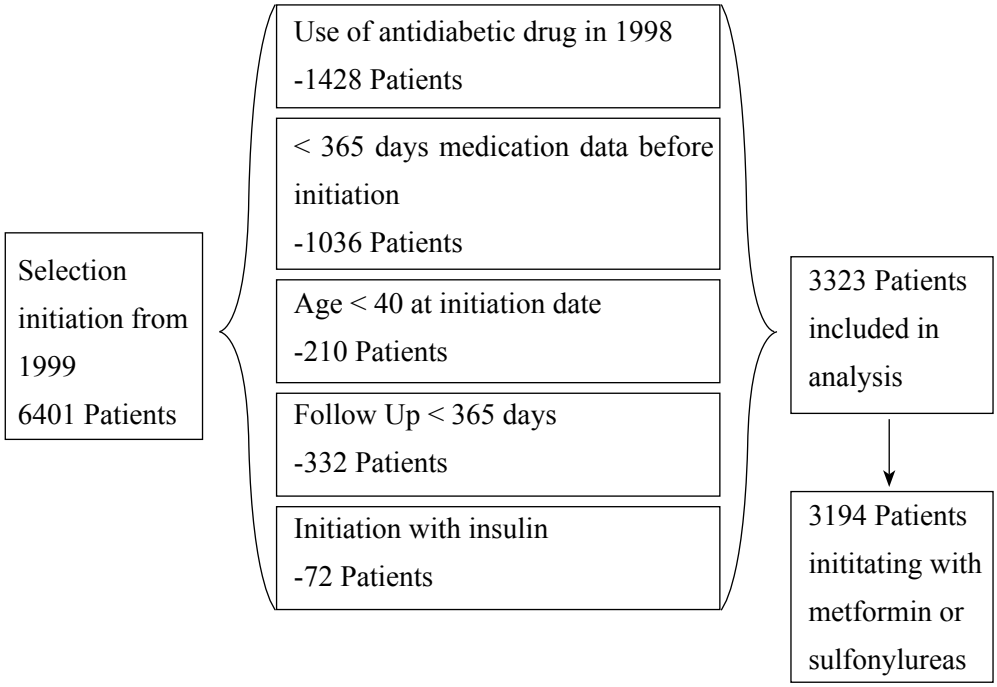

Figure 1. *Patients initiated antidiabetic drug treatment from 1999 up and until 2007; selection and exclusion criteria.*

Definition of modifications of the drug regimen

Patients who continued to use the initial antidiabetic drug until the end of follow up were defined as having no modification. Any changes to the initial drug regimen, except dose modification, were considered as modifications.

The prescription of a second antidiabetic drug class, including insulin, while the patient continued to receive prescriptions for the previous antidiabetic drug, was considered an addition. Periods of 90-180 days without drug exposure were defined as interruptions. Longer periods (>180 days) without drug exposure were considered as discontinuation. Reduction occurred when a patient uses more than one drug and one of the drugs was discontinued in the next episode of the drug regimen. When patients received a new antidiabetic, after more than

180 days without drug exposure, this was defined as a restart. Discontinuation with concomitant initiation of a new antidiabetic drug class was defined as switching of therapy. Patients who restarted the initial antidiabetic drug after switching, addition or discontinuation were defined as return to initial therapy.

Statistical analysis

Kaplan-Meier survival curves were used to describe the time until the first modification to medication and to test differences between metformin and sulfonylureas (Log-rank test). Cox-regression analysis was used to calculate hazard ratios and to correct for potential confounders like gender, age and year of initiation. We used Chi-square tests to compare the difference in proportion of patients with a first modification among metformin and sulfonylureas starters within the first year and after the first year of follow up.

Results

The basic characteristics of 3323 patients initiating treatment with oral antidiabetic treatment are given in table 1. Half of the population was male (50.5%) and mean age was 62.7 years. The mean follow up of patients after the initiation of an oral antidiabetic was 4.7 (± 2.3) years. In 2007 relatively many patients were excluded because of insufficient follow up (<365 days).

Table 1. *Patient characteristics of patients and initiation of treatment with oral antidiabetic drugs (OAD).*

Characteristics	**N=3323**	
Male	50.5%	
Age (mean, SD) in years	62.7	± 11.3
Follow up (mean, SD) in years	4.7	± 2.3
Year of initiation of OAD		
1999	267	(8.0%)
2000	338	(10.2%)
2001	365	(11.0%)
2002	378	(11.4%)
2003	431	(13.0%)
2004	489	(14.7%)
2005	425	(12.8%)
2006	441	(13.3%)
2007	189	(5.7%)
Primary treatment at start		
Metformin	2348	(70.6%)
Sulfonylureas	846	(25.4%)
Thiazolidinediones	53	(1.6%)
Combination of Metformin and Sulfonylureas	64	(1.9%)
α-Glucosidase inhibitors	6	(0.2%)
Combination of Metformin and Thiazolidinediones	4	(0.2%)
Repaglinide	2	(0.1%)

Over the years most patients initiated oral therapy with metformin (70.6%) or sulfonylureas (25.4%) The relative use of metformin increased from 32% in 1999 up to 88% in 2007 (figure 2). The mean follow up period for patients initiating treatment was 4.2 years (± 2.1) for metformin and 5.9 years (± 2.4) for sulfonylureas.

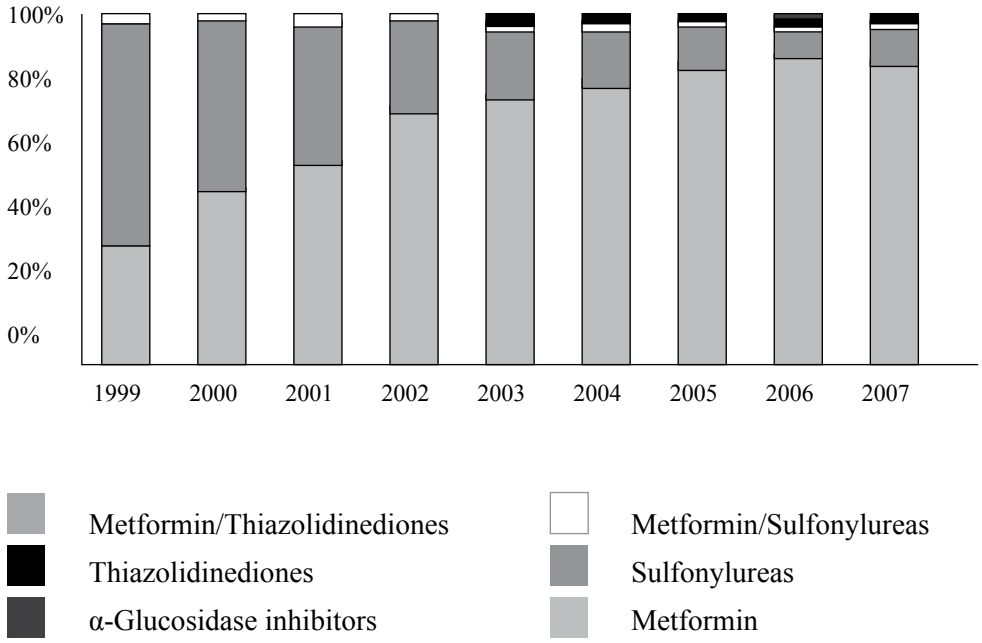

Figure 2. *Initial antidiabetic treatment between 1999 and 2007.*

Of all 3323 patients initiating oral antidiabetic drug treatment 2080 (62.6%) had at least two or more medication episodes, 1357 (40.8%) had at least three medication episodes (figure 3).

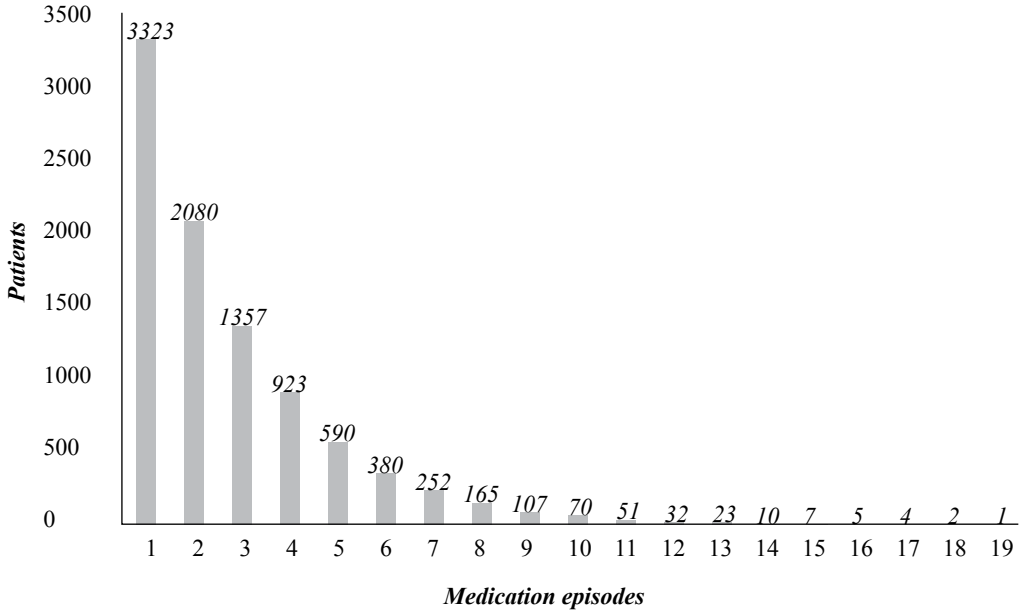

Figure 3. *The number of patients with at least N medication episodes.*

Because of the small proportion of patients who initiated with other drugs, further analysis was limited to patients who either started with metformin or sulfonylureas, n=3194 (96%) The drug dispensing records of these patients were used to describe the first and second modification of drug therapy (Table 2).

Of patients who initiated therapy with metformin, 830 (35.3%) patients had no modification (except dose changes) during the follow up period. Of the remaining patients 138 (5.9 %) interrupted their medication between 90 and 180 days (127 (92%) of them went back to the initial therapy with metformin), 239 (10.2%) discontinued medication for more than 180 days 114 (46.7%) restarted metformin later during follow up), 76 (3.2%) patients switched to another

drug class either directly or after interruption or discontinuation. In 1075 of metformin starters a second type of antidiabetic drug was added (45.8%). The most frequent first additions these patients received to there regimens were: sulfonylureas (829; 77.1%), thazolidinediones (154; 14.3%) and insulin (44; 4.1%). A third drug class was added to 200 (8.5%) of patients who initiated therapy with metformin during follow up. Of those patients 102 (4.3%) additionally received insulin, 43 (1.8 %) patients were added thiazolidinediones and 30 (1.3%) Patients were added sulfonylureas as second addition, after a first addition of thiazolidinediones.

Of patients who initiated therapy with sulfonylureas, 18.9% had no modification during the follow up period. 6.1 % interrupted their medication of which 88.5% went back to the initial therapy with sulfonylureas. 138 (16.3%) patients discontinued medication of which 43.5% restarted with initial therapy, 1.9% of the patients switched to another drug class. Of 56.7% of the cases a next drug class was added representing 480 patients. In 432 of sulfonylureas user's metformin was added while thiazolidinediones were added in 16 cases. 28 Patients (3.3%) were added insulin to therapy. The remaining 4 patients were added an α-glucosidase inhibitor or a fixed combination of metformin and thiazolidinediones. To 114 of patients (13.5%) who initiated therapy with sulfonylureas a third drug class was added. 71 (62.3%) of these patients received insulin as second addition.

Table 2. *Types and frequencies of the first two modifications after initiation with metformin or sulfonylureas.*

Start		First modification	No.	(%)	Second modification	No.	(%)
Metformin	2348 (100%)	No modifications	830	(35.3)			
		Addition	1075	(45.8)	Addition	200	(8.5)
					Reduction	412	(17.5)
					Switch	1	(0.04)
					Interruption	4	(0.2)
					No modifications	456	(19.4)
					Discontinuation	2	(0.1)
		Switch	66	(2.8)	Addition	21	(0.9)
					Switch	2	(0.1)
					Interruption	2	(0.1)
					Back to initial	2	(0.1)
					Discontinuation	10	(0.4)
					No modifications	29	(1.2)
		Interruption	138	(5.9)	Back to initial	127	(5.4)
					Addition	1	(0.04)
					Switch	10	(0.4)
Sulfonylureas	846 (100%)	No modifications	160	(18.9)			
		Addition	480	(56.7)	Addition	114	(13.5)
					Reduction	167	(19.7)
					Switch	2	(0.2)
					Interruption	1	(0.1)
					No modifications	196	(23.2)
		Switch	16	(1.9)	Addition	10	(1.2)
					Interruption	1	(0.1)
					No modifications	5	(0.6)
		Interruption	53	(6.3)	Back to initial	46	(5.4)
					Addition	2	(0.1)
					Switch	5	(0.6)
		Discontinuation	137	(16.2)	Restart	47	(5.5)

Figure 4 shows Kaplan Meier survival curves for the first modification of the regimen among patients initiating treatment with metformin or sulfonylureas. Over the first year 61.9% of patients initiating metformin and sulfonylureas showed no modifications (Chi-square test, p=0.748). After the first years of follow up, 27.1% of metformin starters showed no modifications compared to 20.5% of sulfonylurea starters (Chi-square test, $p< 0.01$). Cox regression analysis showed a crude hazard ratio of 0.84 [CI95%: 0.76-0.92] for any modification in the metformin group compared to the sulfonylureas group. Adjustment for gender, age and year of start had no effect on the crude hazard ratio: adjusted hazard ratio 0.85 [CI95%: 0.77-0.94].

To 428 patients (13.4%) who initiated therapy with metformin or sulfonylureas insulin was introduced in their drug regimen. The mean time to the introduction of insulin was 2.6 years (± 2.2) for metformin starters (n=246) and 3.4 years (± 2.4) for sulfonylureas starters (n=182). Adjusting for the year of initiation with Cox regression analysis showed no difference in the time to introduction of insulin between patients initiating with either metformine or sulfonylureas: adjusted hazard ratio 0.91 [CI95%: 0.74-1.12].

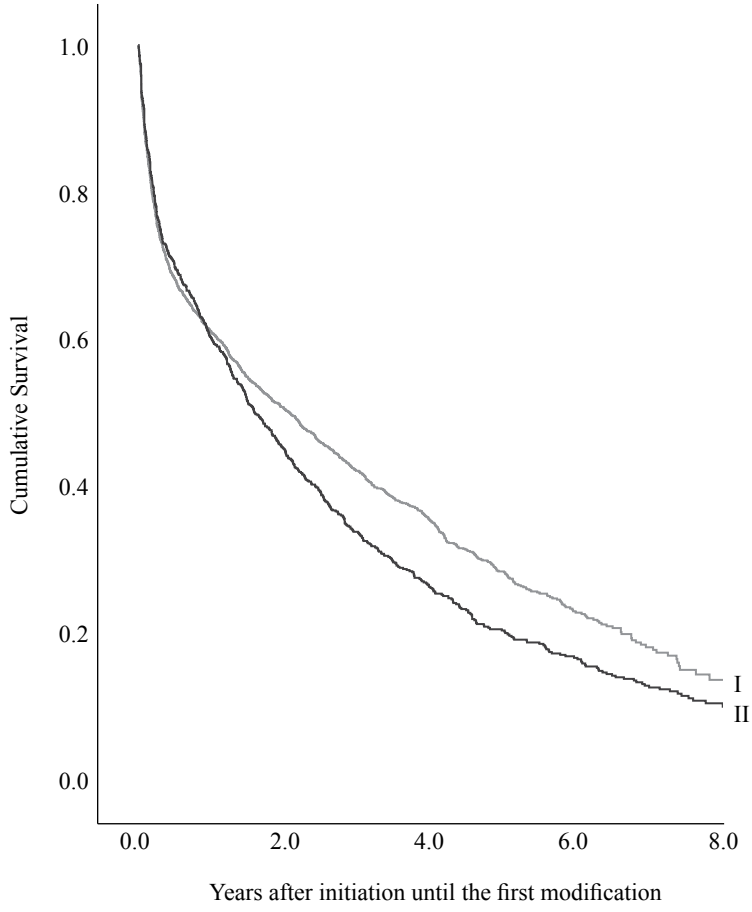

Figure 4. *Number of years after initiation with metformin (I) or sulfonylureas (II) until the first modification in medication appeared.*
(Log-rank rest, $p < 0.01$)

Discussion

This study shows that changes in international guidelines recommending metformin as first choice initial drug therapy in all patients were rapidly followed by prescribers.

Patients starting diabetes treatment with metformin showed fewer modifications to treatment compared to patients initiating treatment with sulfonylureas. After correction for duration of follow up, cox regression analysis showed a hazard ratio of 0.84 for any modification in the metformin group compared to the sulfonylureas group. As the difference between patients initiating treatment with metformin or sulfonylureas occurred after approximately 1 year this suggests that the difference is mostly related to better glucose regulation with metformine compared to sulfonylureas. However, statistically significant, absolute differences were small and of little clinical relevance.

This is endorsed by the fact that no significant differences in time to the addition of insulin were found for patients starting with either metformin or sulfonylureas. Difference in time to addition of insulin was probably related to the fact that over time physicians are striving for tighter glycemic control and therefore start insulin earlier in therapy. Sulfonylureas were predominantly started in the earlier years of the study at times physicians were more reluctant to initiate insulin.

Strengths of the present study include the large stable population, which is representative for a North European population and well documented data over a long period of time.[19] The study was performed in a region were a structured diabetes care system was implemented in 1997.[24, 26] The Diabetes Care System provides therapeutic protocols, coordination of the regional care, and benchmarking of main treatment outcomes with feedback to the general practitioners. Patients are offered annual medical examinations and extensive education given by diabetes nurses and dieticians in order to improve patient empowerment. Observational studies with focus on examining longitudinal

medication patterns in type 2 diabetes are scarce and have generally limited follow up or include small numbers of patients.[13, 16, 18] Moreover, studies often only provide cross sectional data on the use of medication.[27, 28] The high quality of the dispensing data enabled us to provide insight in actual patterns of treatment over longer periods.

There are some limitations too. The study showed a high variety of modification patterns that become more diverse over time. The study therefore had to focus on the first two modifications. This seems reasonable as 59% of patients had no more than two modifications to therapy (1966/3323 patients). Modifications of dosage regimens were not taken into account. Dosage modifications within the same drug group would be an interesting subject for a separate study but in this study inclusion of dosage modifications in the flowcharts would make those too fragmented.

The use of more than two different oral antidiabetics which is discouraged in most diabetes guidelines was only done in 4.2% of patients initiating treatment with metformin.[4] Over 13 % of the total study population initiating therapy with metformin or sulfonylureas received insulin sometime during follow up. Of 314 patients with a third addition 173 patients received insulin, which is in line with treatment guidelines.

Besides high adherence of general practitioners to guidelines, high adherence was seen in patients as well. Discontinuation and interruption are low compared to other studies.[17, 29, 30] This could be related to the high standard of diabetes management in the study region.

We did not have clinical data to link glycemic control to drug utilization patterns. Conclusive evidence on the quality of diabetes management can only be provided by combining drug utilization patterns with relevant clinical data.[31,32]

Results from this study suggest that physicians generally adhere to type 2 diabetes treatment guidelines for initial treatment. Discontinuation rates were relatively low and modification patterns suggest that approximately half of patients are adequately treated with mono therapy over longer periods. No

clinically relevant differences seem to exist between patients initiating treatment with metformine or sulfonylureas.

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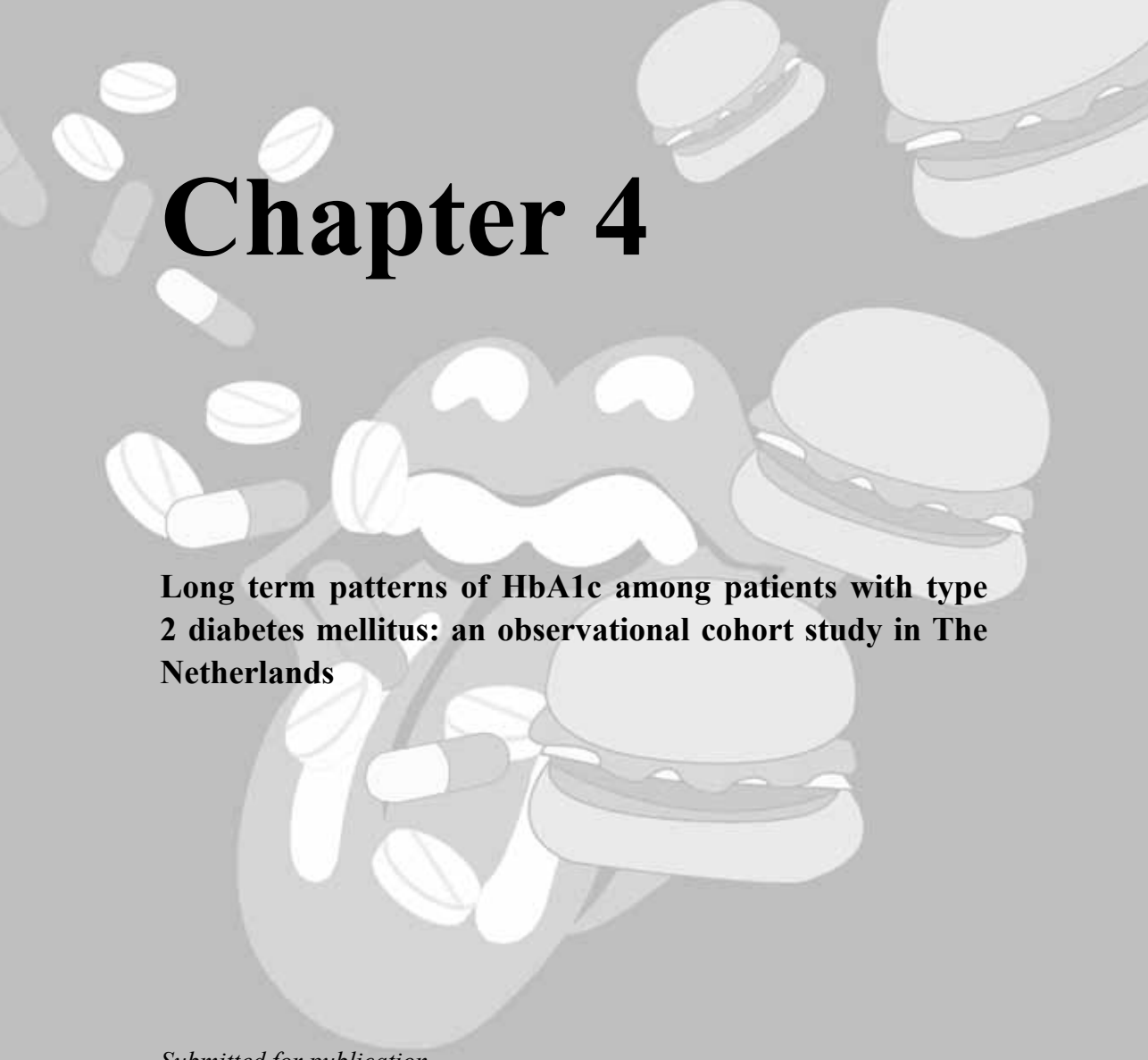
Chapter 4



Long term patterns of HbA1c among patients with type 2 diabetes mellitus: an observational cohort study in The Netherlands

Submitted for publication

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Abstract

Background

Diabetes treatment guidelines recommend strict glycemic control. HbA1c has been used as a marker for glycemic control. Maintaining appropriate HbA1c levels have proven to decrease micro vascular and macro vascular disease. Identifying long-term trends and predictors of glycemic control may enable clinicians to identify patients at risk of inadequate glycemic control.

Objectives

The objective of this study was to determine longitudinal HbA1c categories in daily clinical practice of patients with type 2 diabetes and to identify predictors of these categories.

Methods

A retrospective observational cohort study was conducted among patients with type 2 diabetes. Data were obtained from a protocolled Diabetes Care System (DCS), situated in West-Friesland, The Netherlands. All annually measured clinical data, including HbA1c, were registered in a central database. For each patient, linear regression analysis was conducted starting from the second HbA1C measurement to the end of follow up. The slope of the regression line (β-coefficient) was used as an indicator for the individual time trend of the HbA1c progress. Patients were classified as either deteriorating (β-coefficient > +0.1), improving (β-coefficient < -0.1) or stable (β-coefficient between -0.1 and +0.1). Logistic regression analysis was used to calculate the odds ratios of the potential predictors for HbA1c deterioration with combined improving and stable categories as reference category with 95% confidence intervals. Crude and adjusted odds ratios were calculated. Adjustment was done for all the predictors in the total model. We stratified for age category at baseline to assess HbA1c progress up to seven years of treatment. Linear mixed effects model

with random intercepts and random slopes was used to assess the association between demographic and clinical factors and HbA1c values.

Results

We included 4689 patients in the study cohort. HbA1c levels in the youngest group (35-45 years) increased more strongly compared to the older age groups who tended to stabilize at suboptimal levels of 7.5% (58 mmol/mol), while the 45-54 age category stabilizes at 7.2% (55 mmol/mol). Younger age was associated with an increased risk of deterioration compared to older age (adjusted odds ratio 1.44 [CI95%: 1.04-1.99]).

Conclusions

Patients with younger age at baseline were more likely to be in the deteriorating HbA1c category. Our findings recommend more intensive monitoring and treatment of younger patients. More research is needed for a better understanding of the relationship between younger age and long term increase in HbA1c.

Introduction

Type 2 diabetes mellitus is a progressive chronic metabolic disorder characterized by elevated blood glucose levels and is associated with micro- and macrovascular complications. Treatment guidelines recommend in general strict glycemic control.[1] In several large prospective randomized clinical trials (RCT) in which glycated haemoglobin (HbA1c) has been used as a marker for glycemic control.[2-6] HbA1c shows an association with cardiovascular risk factors and cardiovascular disease.[7] Good glycemic control has proven to decrease micro vascular and macro vascular disease.[8] Therefore, maintaining appropriate HbA1c levels is considered one of the key objectives in diabetes treatment.[9] Antidiabetic medication is aimed at attaining tight glycemic control, although it is not clear what level of glycemic control is needed for what age

group and at what diabetes duration.[10,11] From several recently published RCT it was clear that not every diabetes patient profits from a strict glycemic control.[2,5,6] Older diabetes patients and patients with a longer duration even had a higher mortality rate at stricter glycemic control.[2] A total of almost 25,000 T2DM patients were included in three large RCTs: ACCORD, ADVANCE and VADT.[2, 5, 6, 12-14] Although these large trials resulted in important information about glycemic control, these populations already had multiple risk factors, prior cardiovascular disease or longstanding poor glycemic control and therefore it is not to be expected for these particular populations to benefit from glycemic regulation in the short term.[15] Longitudinal observational studies of antidiabetic medication use and HbA1c outcomes will therefore increase our knowledge of medication use, representative for populations and treatment in real life situations, additional to insights obtained from RCT.[2, 5, 6, 14-17] Unfortunately, most observational studies have a relatively short follow up or have a limited number of HbA1c measurements over time. The objective of this study was to determine long term HbA1c development based on repeated measurements in a cohort of type 2 diabetes patients with a long follow up.

Methods

Design

A retrospective observational cohort study was conducted among type 2 diabetes (T2DM) patients.

Setting

Data were obtained from the Diabetes Care System (DCS). The DCS is situated in West-Friesland, The Netherlands, a region that has approximately 200,000 inhabitants and is representative for the Dutch and Western European population.[18] Diabetes care in this region is coordinated by the DCS. Each patient in the DCS is annually invited for a highly protocolled routine visit

with specialized diabetes nurses and dieticians.[19] All clinical patient data are registered in a central database. We identified all patients enrolled in the DCS between 1997-2010. Patients were eligible for inclusion in the study cohort if they were 35 years or older at cohort entry and had at least 4 consecutive yearly HbA1c measurements.

Definition of HbA1c categories

We considered the first year of treatment in the DCS as a more intensive treatment period to regulate glycemic control. The definition of patients' HbA1c categories was therefore based on the measurements after the first year of treatment in the DCS. For each patient, linear regression analysis was conducted starting from the second HbA1C measurement to the end of follow up. The slope of the regression line (β-coefficient) was used as an indicator for the individual time trend of the HbA1c progress. Patients were classified as either deteriorating (β-coefficient > + 0.1), improving (β-coefficient < -0.1), stable (β-coefficient between -0.1 and +0.1). Sensitivity analyses were conducted for different cut-off points of the β-coefficient of the regression lines. Figure I in the appendix shows illustrations of regression lines of individual patients. In case of missing HbA1c measurements linear regression was conducted including the next measurement.

Assessment of determinants

Clinical parameters measured at each yearly visit included fasting blood glucose, HbA1c, Body Mass Index, blood pressure, lipid profile (total cholesterol, triglycerides) and estimated renal function. Values were dichotomized based on the clinical target values as recommended by Dutch clinical practice guidelines.[11] Target values are shown in Table 2.

Data analysis

Numbers and percentages of patients at target clinical values were determined

at baseline. Baseline clinical values were compared between the deteriorating category and the combined stable and improving categories using Chi-square tests. In case of missing values we used the valid percentage of the number available. Logistic regression analysis was used to calculate the odds ratios of the potential predictors for HbA1c deterioration with combined improving and stable categories as reference category with 95% confidence intervals. Crude and adjusted odds ratios were calculated. Adjustment was done for all variables in the total model. We stratified for age category at baseline to assess HbA1c progress up to seven years of treatment. We tested for effect modification between HbA1c and age by introducing an interaction term (HbA1c*Age) to the model. To take into account the longitudinal nature of the collected data, a linear mixed effects model with random intercepts and random slopes was used to assess the association between demographic and clinical factors and HbA1c values. The mixed effects model included baseline age, sex, diabetes duration, baseline HbA1c value at cohort entry, body mass index and systolic blood pressure. We stratified for age categories: 35-44, 45-54 and 55 years and older.

Results

During the study period a total of 8237 patients entered the DCS, of whom 4753 had at least three subsequent yearly HbA1c measurements after the first year of treatment. Exclusion of 64 patients who were younger than 35 years at DCS entry left 4689 patients for the study cohort.

Table 1 shows the baseline characteristics of the study population. The mean age was 61.8 years and 74% was older than 55 years of age at DCS entry. Subjects were enrolled in the study cohort proportionally over time, except for the last period (2005-2008) because the shorter duration of follow up constrained the number of patients with sufficient measurements after one year of treatment. The mean duration of diabetes at the time before DCS entry was 3.2 years. The

average follow up available was 7 years. The mean decrease in HbA1c was 0.5% in the first year of treatment.

Table 2 shows the baseline characteristics of patients categorized according to the three different HbA1c categories: “Stable” (n=2117), “improving”(n=932) and “deteriorating” (n=1640). Sensitivity analysis with cut off points for β-coefficient of 0.05 and 0.15 showed different distributions in numbers of patients over these categories, but no significant differences in mean clinical values at baseline (data not shown). Baseline differences between the groups were small but statistically significant, except for BMI. Patients in the deteriorating HbA1c category were relatively younger and had a shorter duration of diabetes. Figure 1 shows the progress of mean HbA1c of the three HbA1c categories in time. Figure 2 shows decreasing mean HbA1c values in all age categories over the first year of treatment. Therefore, linear regression was done after the first year of treatment. After the first year of treatment, HbA1c levels in the youngest group (35-45 years) increased more strongly compared to the older age groups who tended to stabilize at sub clinical levels of 7.5%, while the 45-54 age category stabilizes at 7.2%.

Table 1. *Baseline characteristics of the study cohort (n=4689).*

Characteristics	N or mean (% or Standard Deviation)	
Male	2430	(51.8%)
Mean age in years	61.8	(± 10.8)
Age categories at T_0 (years)		
35-44	278	(5.9%)
45-54	939	(20.0%)
55-64	1568	(33.4%)
65-74	1262	(26.9%)
75 and older	642	(13.7%)
Duration of diabetes before DCS entry (years)	3.2	(± 5.2)
Follow up after DCS entry (years)	7.0	(± 2.9)
Number of measurements	7.4	(± 1.7)
HbA1c T_0	7.4	(± 1.7)
HbA1c T_1	6.9	(± 1.2)
HbA1c difference after first year of treatment	-0.5	(± 1.6)
Glucose (mmol/l)	8.6	(± 2.7)
Body Mass Index (kg/m^2)	29.8	(± 5.3)
Systolic blood pressure (mm Hg)	143.4	(± 21.2)
Diastolic blood pressure (mm Hg)	81.3	(± 10.9)
Total cholesterol (mmol/l)	5.3	(± 1.2)
Triglycerides (mmol/l)	2.0	(± 1.9)
Estimated creatinin clearance (ml/min)	89.3	(± 38.0)
Year of DCS entry		
1997-2000	1740	(37.1%)
2001-2004	1709	(36.5%)
2005-2008	1240	(26.4%)

Table 2. *Baseline characteristics of patients categorized according to HbA1c categories and clinical target values (n=4689).*

HbA1c Category		**Improving**	**Stable**	**Deteriorating**
		N=932	**N=2117**	**N=1640**
Gender*	Male	53.9%	48.9%	54.4%
Age*	35-44	6.0	5.0	7.1
	45-54	17.8	19.5	22.0
	55+	76.2	75.5	70.9
Diagnosis*	<5 years**	75.5	80.9	85.5
HbA1c at T_0*	<7	32.9	54.7	52.6
HbA1c at T_1*	<7	29.3	66.3	74.9
Glucose (mmol/l)*	<7	14.8	24.8	27.1
BMI (kg/m^2)	<25	13.7	16.1	15.3
SBP (mm Hg)*	<135	32.5	38.3	35.6
DBP (mm Hg)*	<85	59.2	60.4	64.5
Cholesterol (mmol/l)*	<4.5	23.3	20.2	27.5
Triglycerides (mmol/l)*	<1.7	44.1	50.0	50.6
Clearance*	≥60	70.1	81.8	81.0

T_0: Time of entering Diabetes Care System (DCS), T_1: after first year of treatment in DCS.

** Chi-square test $p < 0.05$*

*** Diagnosis less than 5 years before entering the DCS*

Table 2 shows the crude and adjusted odds ratios for potential determinants of HbA1c category 'deteriorating' with the combined "Improving" and "Stable" categories as reference. Younger age was associated with an increased risk of deterioration compared to older age, adjusted odds ratio 1.44 [CI95%: 1.04-1.99]. Patients with HbA1c values below target of 7% at baseline had lower risk to deteriorate, odds ratio 0.74 [CI95%: 0.62-0.89), whereas patients with HbA1c values below target of 7% after one year of treatment had increased risk to

deteriorate, odds ratio 2.98 [CI95%: 2.46-3.61]. Odds ratios were adjusted for: HbA1c at both baseline and after one year, baseline fasting blood glucose, Body Mass Index, blood pressure, total cholesterol, triglycerides and estimated renal function. Patients with lower baseline systolic blood pressure had lower risk to deteriorate, odds ratio 0.75 [CI95%: 0.62-0.89]. Patients with lower diastolic blood pressure, odds ratio 1.34 [CI95%: 1.13-1.61] and lower total cholesterol, odds ratio 1.37 [CI95%:1.34-1.64] were at increased risk to deteriorate.

Table 3. *Odds ratios of HbA1c category 'deteriorating' compared to 'combined improving and stable' as reference category.*

		Crude odds ratio [CI95%]	Adjusted odds ratio # [CI95%]
Gender	Male	1.17 [1.04-1.32]	1.15 [0.98-1.35]
Age*	35-44	1.44 [1.13-1.85]	1.44 [1.04-1.99]
	45-54	1.23 [1.06-1.43]	1.28 [1.05-1.52]
	55+	1.00	1.00
HbA1c T0	<7	0.83 [0.74-0.94]	0.74 [0.62-0.89]
HbA1c T1	<7	2.44 [2.14-2.78]	2.98 [2.46-3.61]
Diagnosis**	<5	1.49 [1.23-1.80]	1.14 [0.92-1.42]
Glucose	<7	1.34 [1.16-1.54]	1.30 [1.07-1.57]
BMI	<25	0.99 [0.84-1.20]	1.01 [0.81-1.27]
SBP	<135	0.96 [0.80-1.11]	0.75 [0.62-0.89]
DBP	<85	1.21 [1.07-1.37]	1.34 [1.13-1.61]
Cholesterol	<4.5	1.41 [1.23-1.62]	1.37 [1.34-1.64]
Triglycerides	<1.7	1.10 [0.98-1.24]	0.99 [0.84-1.16]
Clearance	>60	1.18 [1.00-1.39]	1.11 [0.88-1.34]

\# *Adjusted for all determinants in the model*

* *Age category compared to category 55+*

** *Diagnosis less or more than 5 years before entering the DCS*

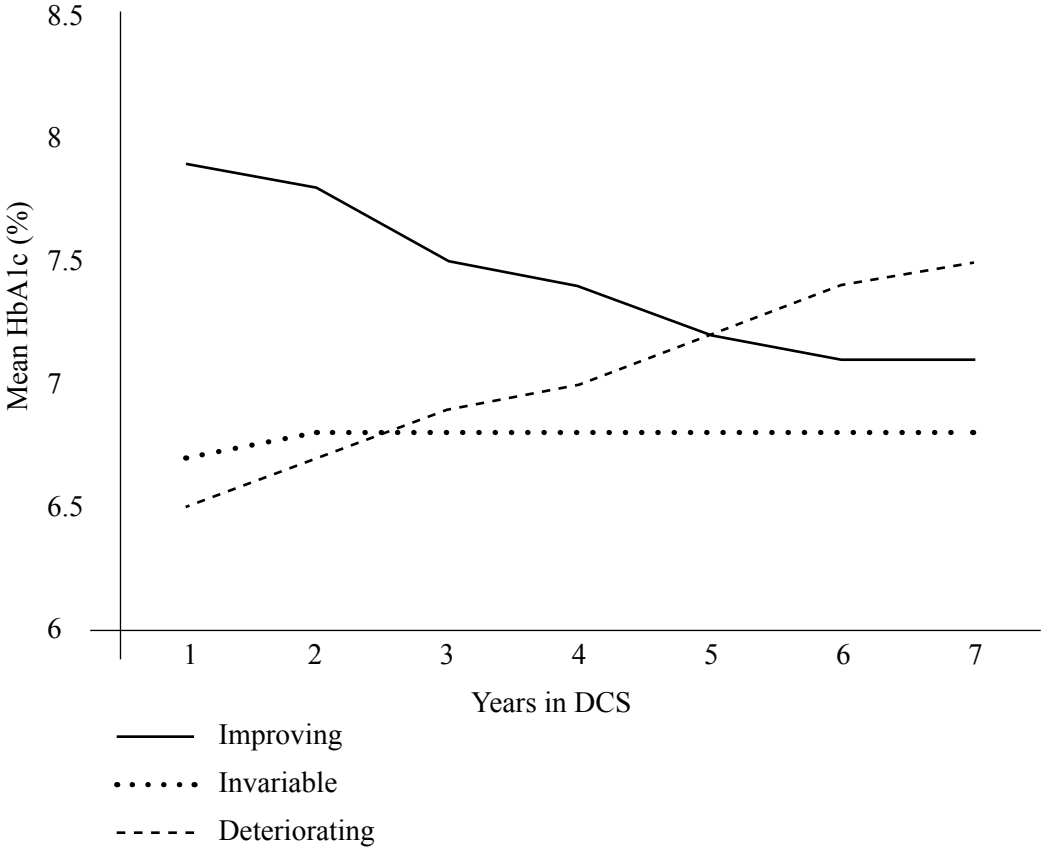

Figure 1. *Progression of mean HbA1c values of HbA1c categories after 1 year of treatment in Diabetes Care System (DCS).*

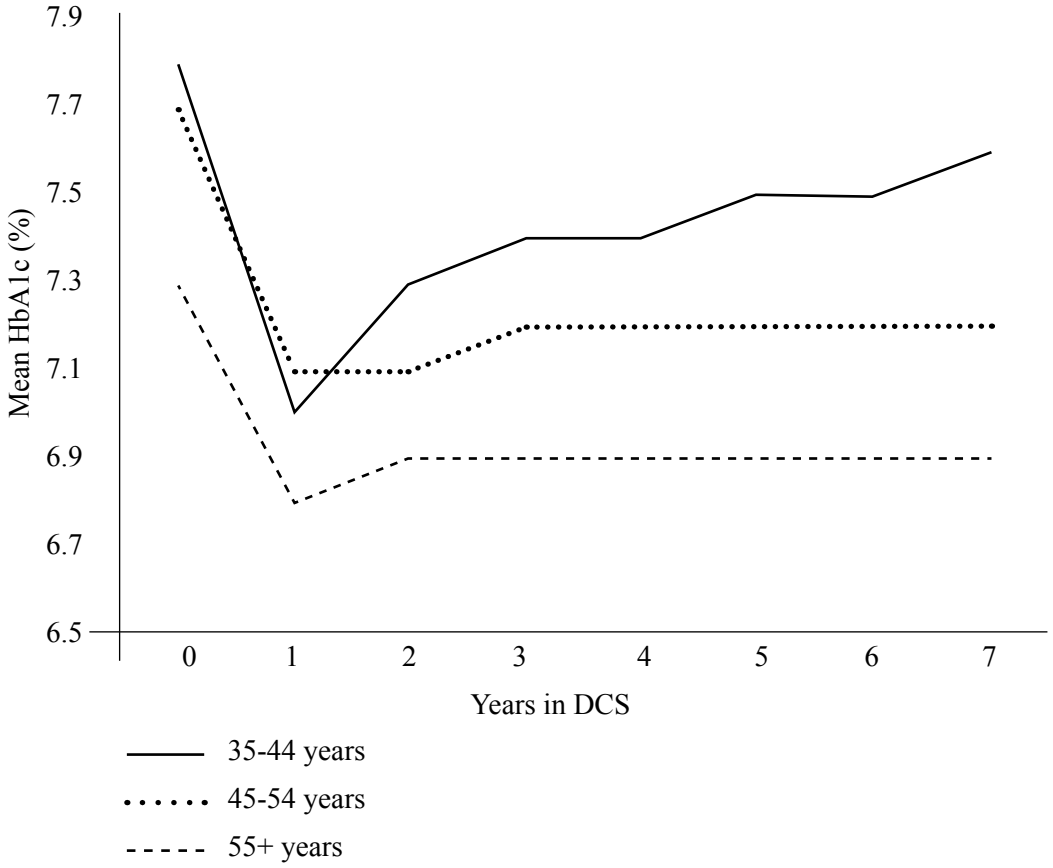

Figure 2. *Mean HbA1c by age category shown per year of treatment in the Diabetes Care System (DCS).*

Table 4 shows the results from the multivariate model testing the association of HbA1c as a continuous variable with the annual measurements. Age at t=0, was significant associated with deterioration in both the overall and stratified model. In the stratified model the highest association for annual measurement was found in the youngest age group. Highest associations were found for diabetes duration especially in the youngest age group.

Table 3. *Multivariate model with HbA1c as continuous variable*

	β-coefficient	95% Confidence Interval
Overall		
Annual measurement	0.024	[0.018 - 0.029]
Age at t=0	-0.011	[-0.013 - -0.0085]
Diabetes duration	0.44	[0.37 - 0.50]
Age category 35-44		
Annual measurement	0.059	[0.030 - 0.089]
Age at t=0	-0.025	[-0.076 - 0.0026]
Diabetes duration	0.79	[0.39 - 1.18]
Age category 45-54		
Annual measurement	0.029	[0.015 - 0.042]
Age at t=0	-0.015	[-0.038 - 0.0073]
Diabetes Duration	0.52	[0.33 - 0.71]
Age category 55+		
Annual measurement	0.019	[0.013 - 0.025]
Age at t=0	-0.0021	[-0.0058 - 0.0016]
Diabetes duration	0.40	[0.33 - 0.47]

β-coefficient indicate the HbA1c(%) change over time (annual meassurements). Positive β-coefficient indicates HbA1c detoriation and negative β-coefficient indicates HbA1c improvement.

Discussion

This study showed that the majority of patients could be categorized as having a “stable” or “improving” HbA1c over longer periods of time. Younger patients and patients with a relatively recent diagnosis were at increased risk of a

deteriorating HbA1c over time.

Other studies found similar relationships between age and worsening HbA1c.[20-23] It has been suggested that differences exist between early and late onset phenotype of T2DM. Patients with early onset type 2 diabetes seem less responsive to medical therapy.[23, 24] We also found that the HbA1c during the first year of inclusion in the DCS showed the most dramatic changes in HbA1c levels. The highly protocolled treatment appeared to improve glycemic control in the majority of patients with diabetes within one year.

Although there is debate about the level of glycemic control and the risk of macro and microvascular risk,[25, 26] low mean HbA1c levels in the stable HbA1c category as found in our study are in line with current clinical target values.[11,26]

The reasons for suboptimal glycemic control in the deteriorating category are unclear. Some explanations could be lack of treatment intensification, a lack of response on appropriate treatment or lower medication adherence at the younger age. A combination of these factors seems most likely.[27-30]

To our knowledge this is the first study to describe long term HbA1c progress based on repeated measurements in daily clinical practice. Most previous studies on glycemic control are restricted to baseline and last measured HbA1c values. Moreover, the ADVANCE, VADT and ACCORD studies were intervention studies, whereas longitudinal studies in daily practice on HbA1c to monitor development in daily clinical practice might be more informative.[2, 3, 5, 6, 22, 24, 26]

Some study limitations have to be discussed. We did not include information about treatment and patients' life style and drug taking behaviour, which could have influenced the outcomes. We did not include information about antiglycemic medication use. However, in an earlier study we showed that discontinuation rates in this particular population were low and that patients were treated according to treatment guidelines.[14, 17] More than 50% of the DCS population, was included in these previous studies.[14] Patients with fewer than 4 measurements were excluded and might have different progress of HbA1c. Due to the high protocolled care system our results may underestimate deterioration

of HbA1c in comparison with other diabetes care situations. However, all age groups were well represented in this study as well as diabetes patients with different diabetes durations.

In conclusion, our main finding is that patients with younger age at baseline are more likely to be in the deteriorating HbA1c category. Our findings recommend more intensive monitoring and treatment of younger patients. More research is needed for a better understanding of the relationship between younger age and long term increase in HbA1c.

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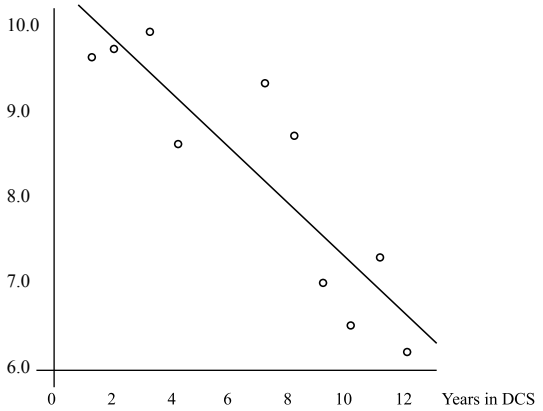
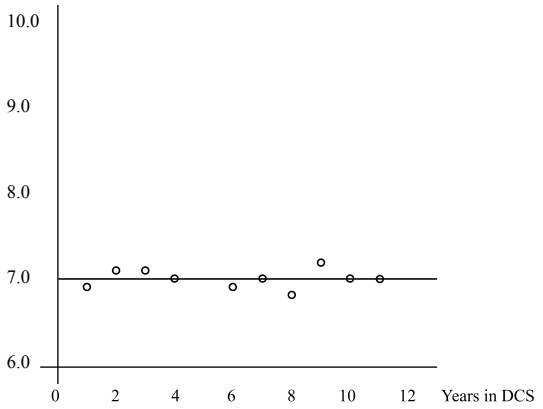


Improving

Observed

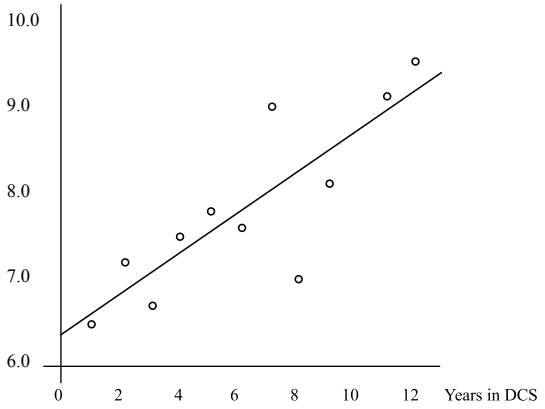
Fitted regression line



Stable

Observed

Fitted regression line



Deteriorating

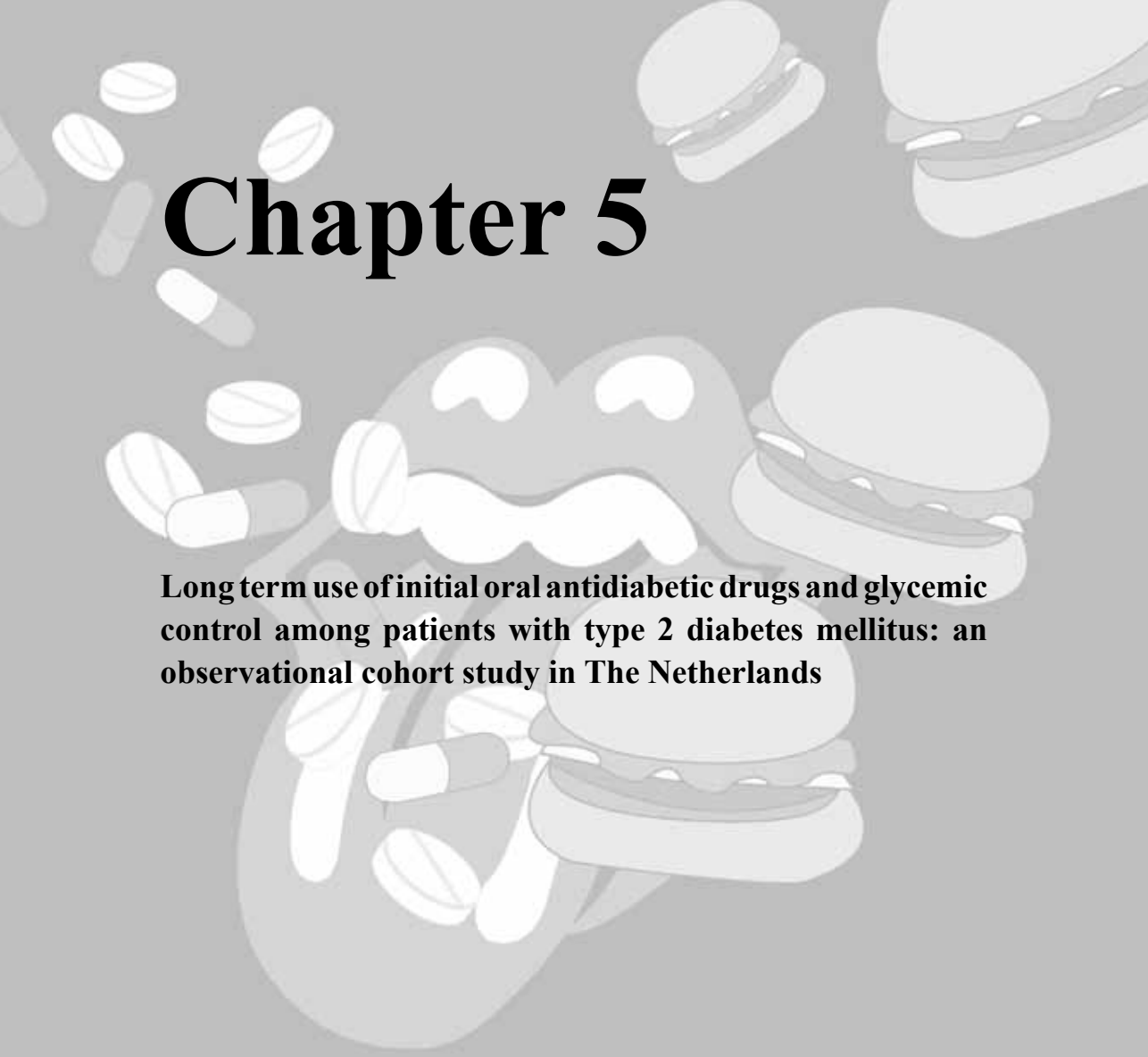
Observed

Fitted regression line

Appendix 1. *Examples of HbA1c measurements of individual patients in time showing HbA1c categories.*

(Improving: slope < -0.1; Stable -0.1 ≥ slope ≤ 0.1; Deteriorating: slope > 0.1)

Chapter 5



Long term use of initial oral antidiabetic drugs and glycemic control among patients with type 2 diabetes mellitus: an observational cohort study in The Netherlands

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M.L. Bouvy
P.C. Souverein
J.G. Hugtenburg
G. Nijpels

Abstract

Background

Type 2 diabetes imposes a large burden on patients' quality of life and number of healthy life years due to both microvascular complications and an increased risk of developing cardiovascular disease. The onset of these complications can be delayed and its progression reduced by sustaining a good glucose control. Dutch guidelines recommend drug treatment in the management of T2DM but patients do not always achieve treatment targets for glycemic control. The randomized clinical trial (RCT) is regarded as the gold standard for judging treatment effects, but may have limited generalizability. Observational longitudinal studies of antidiabetic medication use and glycemic control in daily clinical practice can increase our knowledge of adequate medication use and add other insights obtained from RCTs.

Objectives

The aim of this study was to describe the relationship between long-term medication use and changes in HbA1c level in various subgroups. Moreover, we studied the effects of medication use in the light of changing insights in treatment in the years of observation.

Methods

A retrospective observational cohort study was conducted, among patients with type 2 diabetes mellitus initiating oral antidiabetic drug (OAD) therapy with metformin or sulfonylureas. We classified patients according to baseline HbA1c-value $\geq$ 7% or <7% at the time of treatment initiation. Patients were followed for up to three years to assess whether they reached a Hba1c-value < 7% or $\geq$ 7%, respectively. Statistical analysis was done by Kaplan-Meier estimation and Cox regression.

Results

A total of 531 patients were included in the study cohort. It was observed that metformin favored sulfonylureas as initial OAD in patients who started with an HbA1c level of >7.0%, but not in patients with lower HbA1c levels in which there was no statistically significant difference. It also was found that 54.9% of the patients who started with sulfonylureas were added metformin during follow up and 40.6% of the metformin starters were added sulfonylureas. The proportion of metformin as initial treatment increased rapidly and according to treatment guidelines.

Conclusions

Our analysis supports the use of metformin as the first choice oral antidiabetic drug in T2DM patients.

Introduction

Type 2 diabetes (T2DM) imposes a significant burden on patients' quality of life and number of healthy life years due to both microvascular complications (e.g. retinopathy, nephropathy, neuropathy) and an increased risk of developing cardiovascular disease.[1-3] The onset of these complications can be delayed and its progression reduced by, among others, sustaining a good glucose control. In addition to advices on lifestyle changes, international and Dutch guidelines recommend drug treatment in the management of T2DM. Antidiabetic medication is aimed at attaining tight glycemic control, although it is not clear what level of glycemic control is needed for what age group and at what diabetes duration.[1-3] Metformin is nowadays recommended as the first line treatment option in patients with T2DM in most diabetes guidelines. In case of insufficient results, next steps are addition of sulfonylureas, in some cases other oral antidiabetic drugs or the addition of insulin.[4, 5] Due to the progressive nature of the disease, many patients are administered combinations of antidiabetic drugs.

Nevertheless, patients do not always achieve guideline recommended treatment targets for glycemic control.[5-8]

The randomized clinical trial (RCT) is regarded as the gold standard for judging treatment effects, but they do not necessarily provide the final answer to treatment effectiveness, due to limited generalizability.[9] In the field of T2DM care RCTs are often restricted to relatively small sample sizes consisting of patients younger than 70 or 75 years and without comorbidity, therapy regime is often highly protocolized while trial duration is limited to a relatively short time period. A recently published meta-analysis reported that only few studies included adults older than 65 years, while most T2DM patients are older.[10] When RCTs are not ethical or feasible, or when RCTs are available but severely lack generizability, observational nonrandomized studies have a role to quantify treatment effectiveness in patients encountered in daily clinical practice.[9] Observational studies typically include a larger and broader population than RCTs, place no restriction on treatments provided, follow patients over a longer time frame and are less costly.[11] Consequently, longitudinal studies of antidiabetic medication use and HbA1c outcomes in daily clinical practice can increase our knowledge of adequate medication use and add other insights obtained from RCTs, which may not represent populations and treatment in real life situations.[1, 2, 12, 13] However, currently available observational studies focusing on both drug treatment and glycemic control still had relatively small sample size, short follow up and did not adjust for confounders like diabetes duration or adjustments of treatment recommendations during the years of observation.[14-21] In this light, the aim of this study was describe the relationship between long-term medication use and changes in HbA1c level in various subgroups. Moreover, we studied the effects of medication use in the light of changing insights in treatment in the years of observation.

Methods

Setting

A retrospective observational cohort study was conducted, among patients with type 2 diabetes mellitus initiating oral antidiabetic drug (OAD) therapy with metformin or sulfonylureas. Data were obtained from the Diabetes Care System. In short, the DCS is situated in region of West-Friesland in The Netherlands that has about 200,000 inhabitants and is representative for the Dutch or a Western-European population.[22] Diabetes care in this region is coordinated by the DCS. The DCS collects clinical patient data in a central database. Each patient in the DCS is annually invited for a routine visit where specialized diabetes nurses and dieticians conduct a follow-up assessment and registration of clinical outcomes. The assessment includes glycemic control, lipid spectrum and cardiovascular risk profile.[23] Data from the DCS were available for the period 1997-2010. Drug dispensing data for this study were obtained from fifteen community pharmacies and two dispensing general practices in the same region. In The Netherlands, the vast majority of the population obtains their medication from only one community pharmacy, enabling collection of complete and detailed medication histories of individual subjects over a long period of time.[24, 25] Dispensing data including information on sex, date of birth, postal code, date of dispensing, drug name, dosing regimen and amount dispensed. All drugs were coded according to the Anatomic, Therapeutic and Chemical classification system.[26] Deterministic record linkage on gender, date of birth and postal code was used to combine dispensing data with clinical DCS data. If this approach did not generate any candidates, the postal code criterion was dropped and unique matches on sex and date of birth were used instead.

Cohort definition

All patients with a first prescription for an OAD between 1999 and 2007 were identified. To be eligible for inclusion, patients had to start with either metformin

or sulfonylureas, continue on the initially prescribed OAD for a minimum of three years, have at least 365 days of pharmacy information prior to treatment start and be 35 years or above to exclude diabetes variants like MODY.[27] Subsequently, we linked these patients to DCS data. Patients were excluded if they had no HbA1c measurement in around 90 days around treatment start and had less then three visits to the DCS during the study period.

We classified patients according to baseline HbA1c-value ≥ 7% or <7% at the time of treatment initiation. Patients were followed for up to three years to assess whether they reached a Hba1c-value < 7% or ≥ 7%, respectively. If patients had already had the event prior to the start of treatment they were excluded from the analysis.

Data analysis

Kaplan-Meier survival curves were used to show graphically the time to event in both sub-cohorts and the log rank test was used to test for differences between patients initiating with metformin or sulfonylurea. Subsequently, Cox-regression analysis was used to calculate crude and adjusted hazard ratios (HR) with 95% confidence intervals (95% CI). Adjustment was made for gender, age, duration of diabetes, body mass index (BMI) and time period (before/after 2003, when treatment guidelines were changed). Forest plots were used to display hazard ratios.[28]

Results

Figure 1 shows the flowchart of the selection of the study cohort. Out of a total of 2003 incident users of metformin or sulfonylureas between 1999 and 2007, there were 1604 patients that met the age and history criteria and could be linked to clinical information in the DCS. There were 432 metformin users and 171 sulfonylureas users for whom HbA1c measurement in a three-month period around treatment initiation was available to establish baseline glycemic

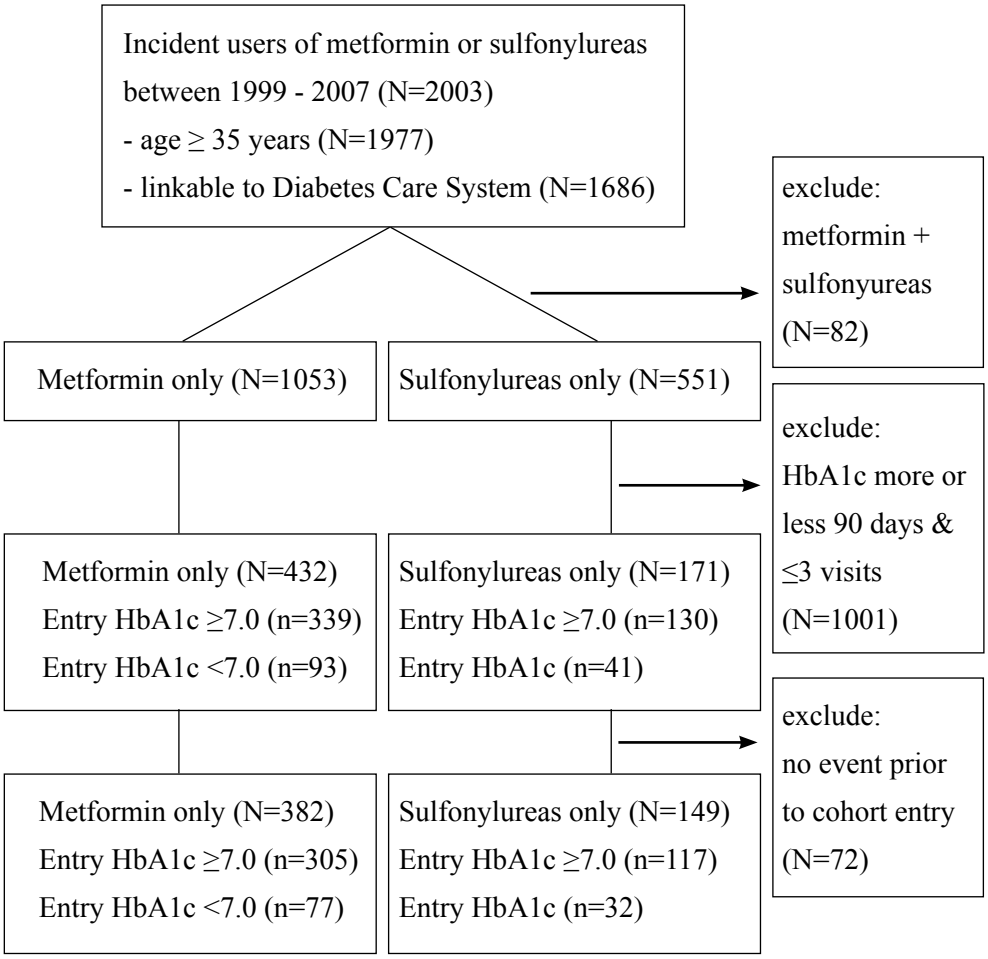

Figure 1. *Flowchart of patient selection.*

Table 1. *Baseline characteristics of total study cohort N=531.*

Characteristics	**Metformin (n=382)**		**Sulfonylureas (n=149)**	
Male	201	(52.6%)	93	(62.4%)
Age in years; mean (SD)	59.2	(± 10.1)	62.6	(± 10.7)
Mean HbA1c (SD)	8.7	(± 2.0)	8.6	(± 2.1)
Mean BMI (SD)	31.0	(± 5.3)	27.9	(± 4.4)
Number of patients entering cohort				
1999 - 2002	163	(42.7%)	113	(75.8%)
2003 - 2005	219	(57.3%)	36	(24.2%)
Duration of diabetes				
0-1 years	270	(70.7%)	92	(61.7%)
>1 years	36	(9.4%)	23	(15.4%)
Missing	76	(17.3%)	34	(22.8%)

Table 2. *Proportion (%) of additions to initial oral antidiabetic drug in study cohort in first three years of follow up.*

Addition to Initial Drug in subcohort HbA1c > 7.0% (N=422)					Total added drugs		
	Metformin	Sulfonylureas	Insulin	Other	1	2	3
Metformin	-	48.9	7.2	10.5	47.5	8.5	0.7
Sulfonylureas	63.2	-	8.9	8.9	49.2	15.0	10.0

Addition to Initial Drug in subcohort HbA1c ≤ 7.0% (N=109)					Total added drugs		
	Metformin	Sulfonylureas	Insulin	Other	1	2	3
Metformin	-	13.0	1.3	1.3	15.6	0.0	0.0
Sulfonylureas	31.3	-	3.1	6.3	25.0	3.1	3.1

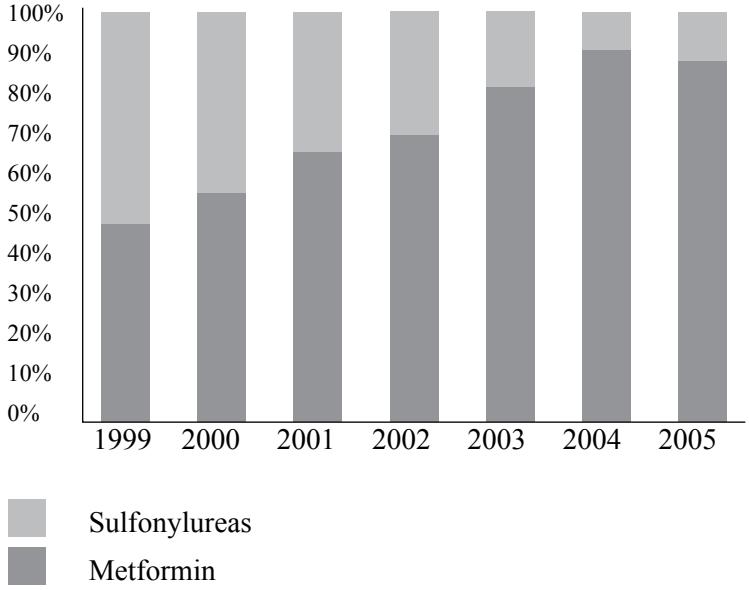

Figure 2. *Proportion of initiation with metformin and sulfonylureas during the years of follow up.*

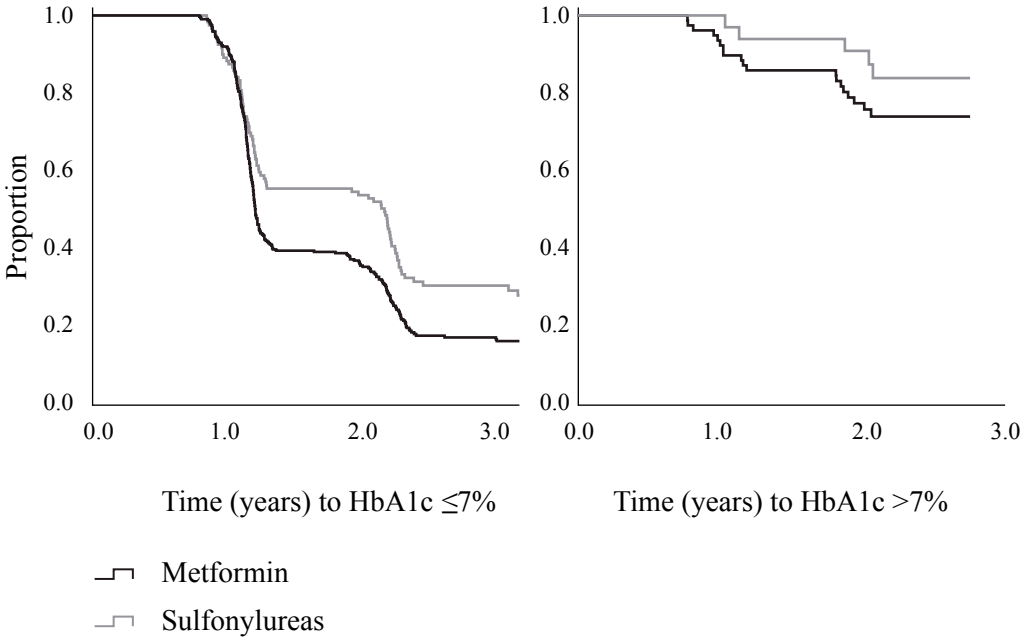

Figure 3. *Kaplan Meier estimation curves of patients starting with metformin or sulfonyureas and HbA1c > 7% and time till HbA1c ≤ 7%, Log-rank test <0.05 (left) and of patients starting with metformin or sulfonyureas and HbA1c ≤ 7% and time till HbA1c > 7%, Log-rank test = 0.54 (right).*

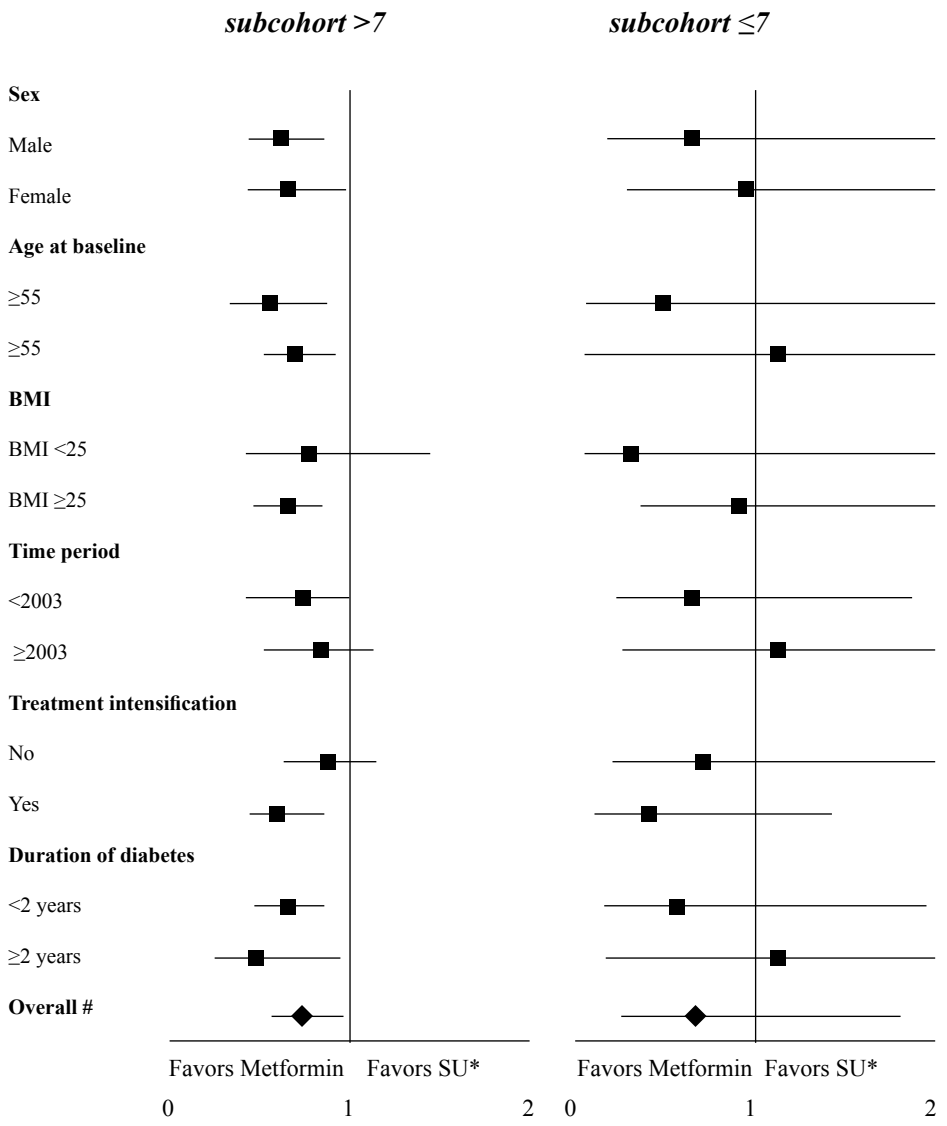

Figure 4. *Forest plots of crude stratum specific Hazard Ratios of determinants of patients starting with HbA1c > 7% and reach HbA1c ≤ 7% and patients starting with HbA1c ≤ 7% and reach HbA1c > 7%.*

**SU=Sulfonylureas*

 # adjusted for time period

control. After excluding patients who had already reached HbA1c target value prior to the start of treatment, a total of 531 patients were included in the final study cohort. Table 1 shows the characteristics of these patients. Compared to metformin starters, patients starting sulfonylureas were more often men (62.4% vs. 52.6%) and had a higher mean age (63 vs. 59 years). Metformin users had a higher BMI at baseline. The proportion of patients with a longer-existing diagnosis of diabetes was low in both groups. Figure 2 shows the proportion of patients starting on either drug during the study period. The proportion of metformin as initial treatment increased rapidly and according to treatment guidelines from 50% in 1999 to 90% in 2005

Table 2 shows the frequency of add-on of antidiabetic drugs to the initial medication. The proportion of patients with treatment intensification in the sub-group of patients with a baseline HbA1c >7% was high in both medication categories. Figures 3 shows the Kaplan Meier curves of the two sub-cohorts. Patients starting OAD treatment with metformin at an HbA1c > 7% (B) showed a statistically significant faster decrease to HbA1c ≤7% compared to patients starting sulfonylureas (Log-rank test $p<0.001$). Patients on sulfonylureas had a statistically significant lower probability of reaching HbA1c < 7% compared to metformin, crude HR 0.65 [95% CI: 0.51-0.83]. After adjustment for confounders this association was sustained: adjusted HR 0.75 [95% CI: 0.58-0.98]. We found no evidence for effect measure modification. Figure 4 shows forest plots of crude stratum specific HRs of determinants of patients starting with HbA1c > 7% and who reached HbA1c ≤ 7% and of patients starting with HbA1c ≤ 7% and who reached HbA1c > 7%. The overall HR was adjusted for the time period of OAD initiation.

Discussion

In this study metformin favored sulfonylureas as initial OAD in patients who initiated treatment with an HbA1c level of > 7.0%, but not in patients

with HbA1c levels < 7.0%. It also was found that 54.9% of the patients who started with sulfonylureas were added metformin during follow up, whereas 40.6% of the metformin starters additionally received a sulfonylurea. Finally, the proportion of patients that received any additional drug after the initial OAD was higher in patients initiating drug therapy with sulfonylureas. These combined findings suggest better glycemic control after initiation of metformin compared to initiation with sulfonylureas, which underlines current treatment guidelines for T2DM.

The proportion of patients with metformin as initial treatment increased rapidly and according to these treatment guidelines.[5] In another study in The Netherlands the proportion of metformin as initial antidiabetic drug increased from approximately 14% in 1998 to 50% in 2003, which is lower than our findings (approximately 50% in 1998 and 90% in 2003). This difference suggests that prescribers in this study adapted treatment guidelines earlier, which might be explained by the highly protocolled DCS.[25] Addition of sulfonylureas to metformin and vice versa is frequent in many observational studies due to the progressive nature of T2DM in order to meet glycemic goals.[25,29] Studies comparing metformin with sulfonylureas are scarce. Our results are not consistent with reviews that found that metformin and sulfonylureas had similar efficacy in achieving glycemic control.[30, 31]

The evidence for the clinical efficacy of metformin is largely based on the United Kingdom Prospective Study (UKPDS).[36] The UKPDS-study showed that metformin reduced total mortality with 36% in obese patients with T2DM compared to diet.

A retrospective observational cohort study concluded that metformin resulted in similar glycemic control compared to sulfonylureas but improved BMI compared to sulfonylureas.[32] Although individual studies suggest a beneficial effect of adding metformin to insulin on BMI, glycemic control and diabetes complications[35], two recent meta-analysis did not confirm all beneficial effects of metformin addition to insulin.[33, 34] These meta-analysis suggest that

combination of metformin and insulin does lower BMI and HbA1c and the need for insulin, but does not reduce macrovascular complications.[33, 34]

Our study has some limitations. Although the study did not include "hard" clinical endpoints, results nevertheless showed beneficial effects for metformin compared to initial therapy with sulfonylureas. We cannot exclude the possibility of selection bias because of the strict inclusion criteria applied. These criteria were chosen to ensure that selected patients were using their initial medication for at least three years, as this enabled us to study patients having at least four subsequent annual HbA1c measurements, including baseline HbA1c. Patients who started with other drugs than metformin or sulfonylureas were not included in out study, but such patients were limited to less than 2% of all incident OAD users. A concern is that we could adjust for prescriber bias caused by GPs having specific reasons to choose for a certain OAD at treatment initiation. Furthermore, the follow up period was limited to three years. Still, this is much longer than in most other studies, where follow up was usually not more than twelve months.[33, 34, 37]

A major strength of this study is that because of the routine in data collection there were limited missing values, often a common problem in data reflecting daily clinical practice.[33] Besides high-quality pharmacy data we had data of the highly protocolized DCS were clinical data are accurately recorded.[23, 24, 25]

The benefits and risks of metformin remain a research topic. Future research should especially focus on hard clinical endpoints such as cardiovascular events. Therefore larger scale observational studies or even longer follow up is needed in order to have sufficient statistical power. Notwithstanding ‘softer’ outcomes such as HbA1c and BMI should also be taken into account, especially to measure short term effects. For now, this study supports the use of metformin as the first choice oral antidiabetic drug in T2DM patients.

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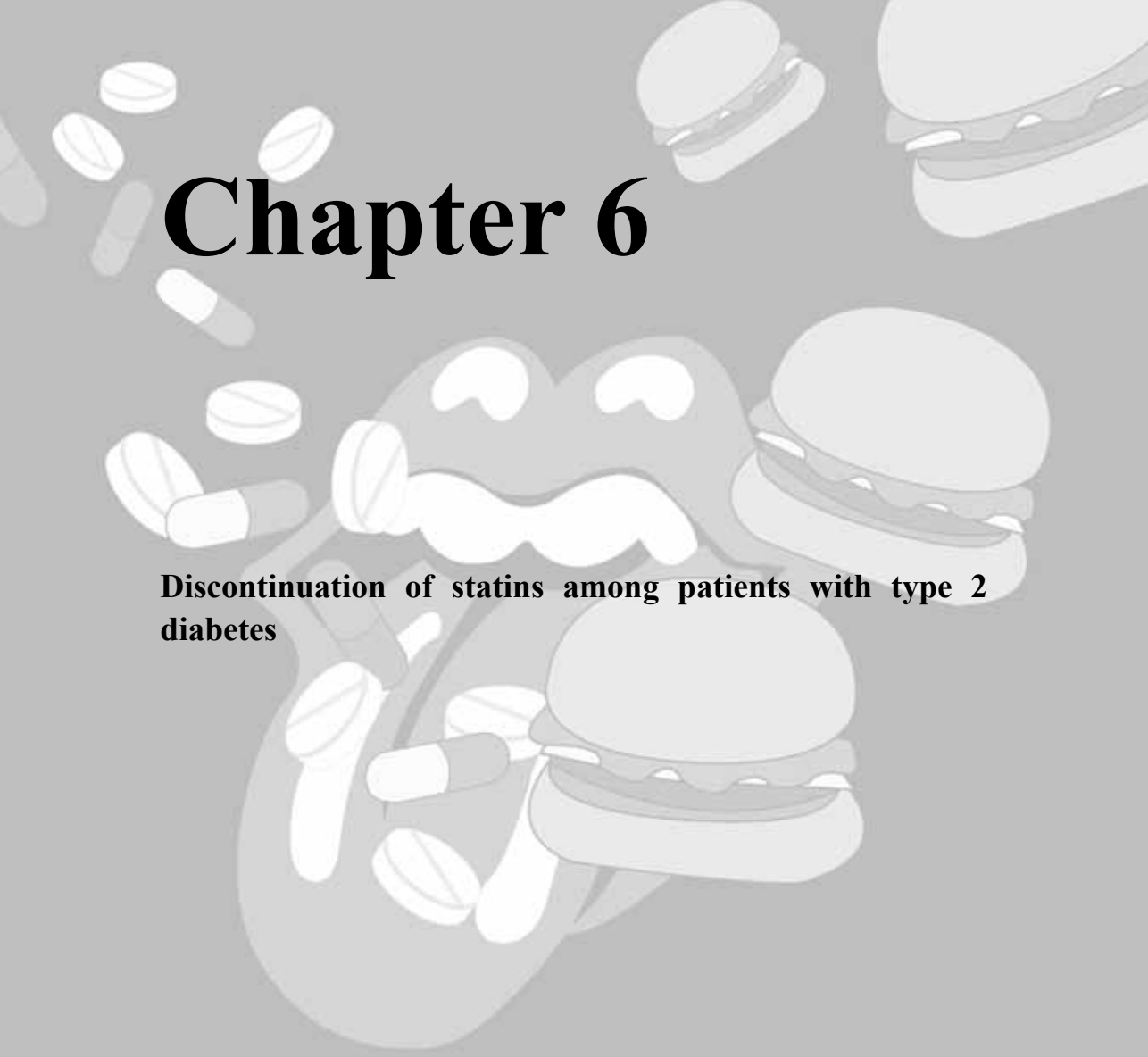
Chapter 6



Discontinuation of statins among patients with type 2 diabetes

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Abstract

Background

Statins play an important role in the prevention of cardiovascular disease in type 2 diabetes. Several studies have reported low adherence with statins among patients with type 2 diabetes. Studies comparing discontinuation of statins compared with discontinuation of oral antidiabetics within the same individuals before and after initiation of oral antidiabetic drugs are not available.

Objectives

The aim of this study was to describe discontinuation among patients with type 2 diabetes prescribed statins prior to and after initiation of oral antidiabetics and to compare statin discontinuation with discontinuation of oral antidiabetics.

Methods

We report an observational cohort study among patients initiating treatment with statins prior to or after initiation of oral antidiabetics between 1999 and 2007. Patients were classified as starting statins prior to initiation (Prior users) or after initiation (After users) of antidiabetics. Discontinuation was defined as an interval of 180 days or more between the theoretical end date of a statin/antidiabetic prescription and the dispensing date of the next statin/antidiabetic prescription.

Results

We included 3323 starters with oral antidiabetic drugs in our study; 2072 patients initiated statins in the period of observation. Discontinuation rates for statins were higher compared with oral antidiabetics (52.1 vs 15.0%). After users discontinued statin therapy more frequently compared to prior users (62.8 vs 48.2%).

Conclusions

Discontinuation of statins is higher compared with antidiabetic discontinuation. Patients starting statins after the initiation of oral antidiabetic treatment are more likely to discontinue treatment than patients who initiate statins before the start of oral antidiabetics.

Introduction

Cardiovascular disease is the leading cause of death in patients with type 2 diabetes (T2DM). This increased cardiovascular risk is predominantly caused by a higher prevalence of cardiovascular disease risk factors, such as hyperlipidemia and hypertension.[1,2] Strategies aimed at prevention of cardiovascular disease in T2DM therefore focus on management of these risk factors. Patients with T2DM seem to benefit even more from lipid lowering treatment than non diabetic patients.[3] Guidelines for the treatment of T2DM include clear targets for total and low density lipoprotein cholesterol based on epidemiological and clinical trial data.[4,5] Despite recommendations in treatment guidelines to initiate statin therapy in patients with T2DM, the proportion of T2DM patients receiving statins remains low, and treatment targets are not met.[6–8] In addition, when statins are prescribed, adherence to treatment is often low. Several studies reported low adherence to statin use within diabetes populations. However, most studies on adherence to statins within patients with diabetes have relatively short follow up, whereas statins have long term beneficial effects. Moreover, adherence to statins was not compared with adherence with oral antidiabetics within the same individuals.[7-10] The only study that did compare adherence with both statins and oral antidiabetics in the same population did only look into taking compliance and not into discontinuation.[11] None of these studies compared adherence in patients who already use statins before oral antidiabetics are initiated with adherence among patients who initiate statins after the start of oral antidiabetics.[7–9,11–14]

This study aims to describe discontinuation among T2DM patients prescribed statins prior to and after initiation of oral antidiabetics and to compare discontinuation rates of statins and oral antidiabetic drugs (OAD).

Methods

Design

An observational cohort study was conducted among patients who initiated statin treatment prior to or after the initiation of oral antidiabetic drugs.

Setting

Drug dispensing data for this study were obtained from fifteen community pharmacies and two dispensing general practices in a geographically well defined region in the Netherlands. The region (West-Friesland) has 200,000 inhabitants and a relatively stable composition of the population that is representative for a Dutch or Western European population.[15] Available data included gender, date of birth and complete drug dispensing information, including date of dispensing, drug name, coding according to international Anatomic, Therapeutic and Chemical classification (ATC), dosing regimen and amount dispensed.[16] In the Netherlands, the vast majority of the population obtain their medication from only one community pharmacy, enabling collection of complete medication histories of individual subjects over a long period of time.[17]

Study population

We identified all patients with at least one prescription for an OAD between 1999 and 2007. Patients were included in the study when they were 40 years or older and had at least 365 days of medication history prior to this first OAD prescription. Moreover, patients with less than 365 days of follow up were excluded, as well as patients who initiated treatment with insulin. Within this population of patients who initiated oral antidiabetics, we identified patients

who initiated statin treatment either before or after the start of oral antidiabetics. Similar criteria applied for the inclusion of patients who initiated therapy with statins.

Definition of drug utilization episodes and discontinuation

We identified all prescriptions for both oral antidiabetics and lipid lowering drugs. For each prescription, the theoretical duration of use was calculated by dividing thenumber of tablets dispensed by the number of tablets used per day. Treatment episodes were calculated as a series of subsequent prescription refills, independent of switching to another type of drug class or change of dose. Patients were considered to have discontinued therapy when an interval of 180 days or more occurred between the theoretical end date of a statin/ oral antidiabetic prescription and the dispensing date of the next statin/oral antidiabetic prescription for the same patient.

Data analysis

Patients were classified into two groups, the first group being patients already using statins more than 90 days before initiation of oral antidiabetics (prior users). The second group comprised patients who started statin use less than 90 days before or after the initiation of oral antidiabetics (after users). This 90-days grace period was used because we assumed that patients might have already been diagnosed with diabetes but have not yet started oral antidiabetic treatment, and the initiation with statins was related to T2DM. We used Chi-square tests to test differences in proportions and used Kaplan-Meier survival estimation to evaluate continuation of statin use between the subgroups and compare these with continuation of oral antidiabetics. Cox regression analysis was used to calculate hazard ratios and to correct for confounding. Potential confounders evaluated included gender, age, year of initiation of statin, type of oral antidiabetic used and use of cardiovascular medication, antidepressants and antipsychotics between 90 days before and after statin treatment start. We

stratified the analysis for the cohorts 1998–2004 and 2005–2007. All analyses were performed in SPSS, version 18.

Results

We identified 3323 patients starting with oral antidiabetic treatment. The proportion of patients using statins at OAD start increased steeply, both with regard to patients already using statins at OAD start and with regard to patients who initiated statins within 90 days of OAD start. In 2006 and 2007, more than 50% of patients starting oral antidiabetics received a statin prescription concurrently (Figure 1). Patients numbering 2449 (73.7%) used statins at some moment during the total observation period. We excluded 377 patients, with less than 365 days of medication history before the initiation of statin treatment and/or less than 365 days of follow up after the initiation of statin treatment. All further analyses refer to the remaining 2072 patients. Table 1 shows the characteristics of these patients. More than half of these new statin users were male patients with a mean age around 62 years at the time of treatment initiation. The mean follow up period after initiation of statin use was 7.4 years (SD±2.6) for the prior users and 3.4 years (SD±1.8) for the after users. The exposure of prior and after users on cardiovascular, and psychiatric comedication is shown in the lower part of Table 1.

Table 1. *Characteristics of patients who initiated statin treatment before (Prior users) or after initiation (After users) with oral antidiabetic drugs (n=2072).*

	Prior users		**After users**	
Characteristics	*N=551*		*N=1521*	
Male	302	(54.8%)	789	(51.9%)
Age (Mean, SD) in years	61	± 10	62	± 10
Follow up (Mean, DS) in years	7.4	± 2.6	3.4	± 1.8
Year of inititation of statin n=2072				
≤ 1998	194		0	
1999 – 2001	163		129	
2002 – 2004	148		564	
2005 - 2007	46		828	
Comedication use (%)				
Platelet aggregation inhibitors	233	(42.3)	299	(19.7)*
Coumarin derivatives	47	(8.5)	80	(5.3)*
Thiazide diuretics	104	(18.9)	373	(24.5)*
Loop diuretics	64	(11.6)	109	(7.2)*
RAAS inhibitors	180	(32.7)	621	(40.8)*
Beta blockers	258	(46.8)	555	(36.5)*
Calcium channel blocker	168	(30.5)	237	(15.6)*
Nitrates	138	(25.0)	109	(7.2)*
Antidepressants	47	(8.5)	128	(8.4)
Antipsychotics	9	(1.6)	31	(2.0)

**p<0.05*

(Comedication use was defined as at least 1 prescription 91 days before till 91 days after initiation of statin). Abbreviations: SD= standard deviation.

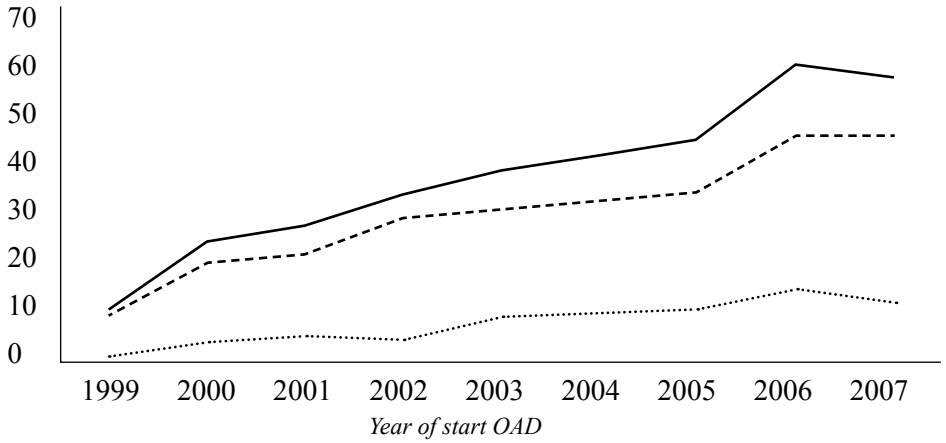

Figure 1. *Percentage of starters with oral antidiabetic drugs (OAD) per year and use of statine at the moment of OAD start.*

Total of OAD starters using statine at start OAD

Started statin prior to start with OAD and still using statin at start OAD

Start with statin within 90 days after start of OAD

There were no significant differences for antidepressants and antipsychotics. In the Prior user group, platelet aggregationinhibitors, coumarin derivates, loop diuretics, beta blockers, calcium channel blockers and nitrates were used significantly more often compared with the After user group at the initiation of statins. Thiazide diuretics and RAAS inhibitors were used statistically significantly more frequently in the After user group. About one third of patients (34%) initiated statin therapy more than 90 days before initiation of oral antidiabetic treatment (Prior users). The remaining patients initiated statin therapy less than 90 days before the start or after the start of oral antidiabetic treatment (After users) (Figure 2).

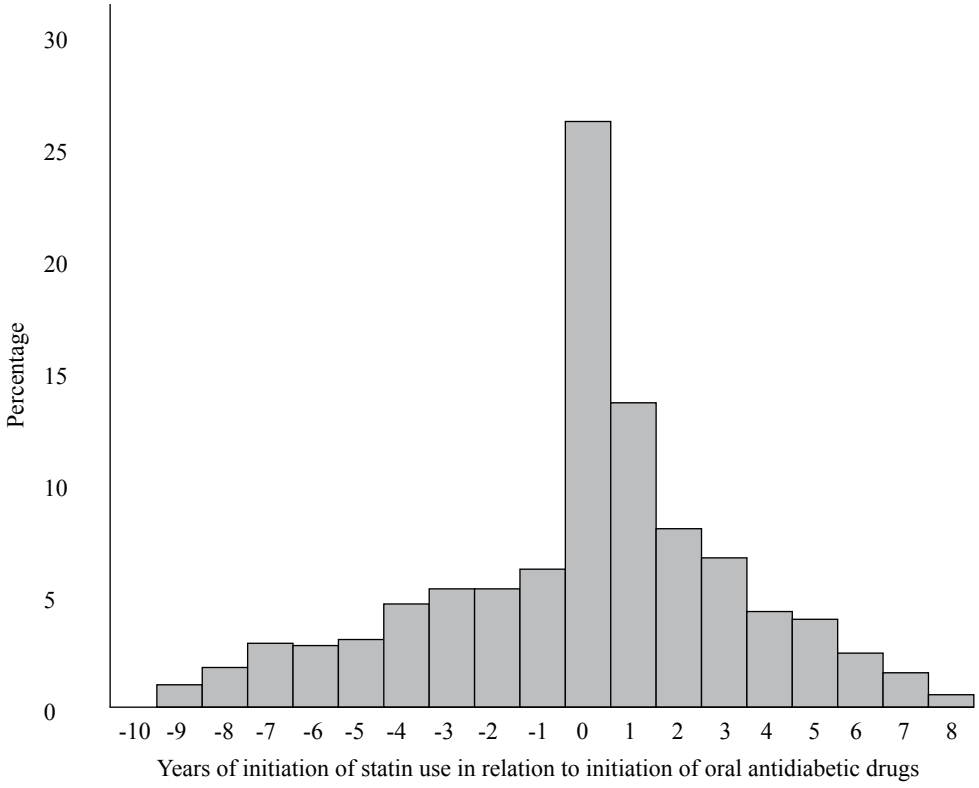

Figure 2. *Year of initiating statins in relation to the initiation of oral antidiabetic drugs (t=0).*

Kaplan-Meier survival estimates show that statin users discontinued statins more frequently after 5 years than those of oral antidiabetics (52.1 vs 15.0%, Log-rank test, $p<0.05$). Moreover, after statin users were more likely to discontinue statin therapy compared with prior statin users (62.8 vs 48.2%, log-rank test, $p<0.05$) (Figure 3).

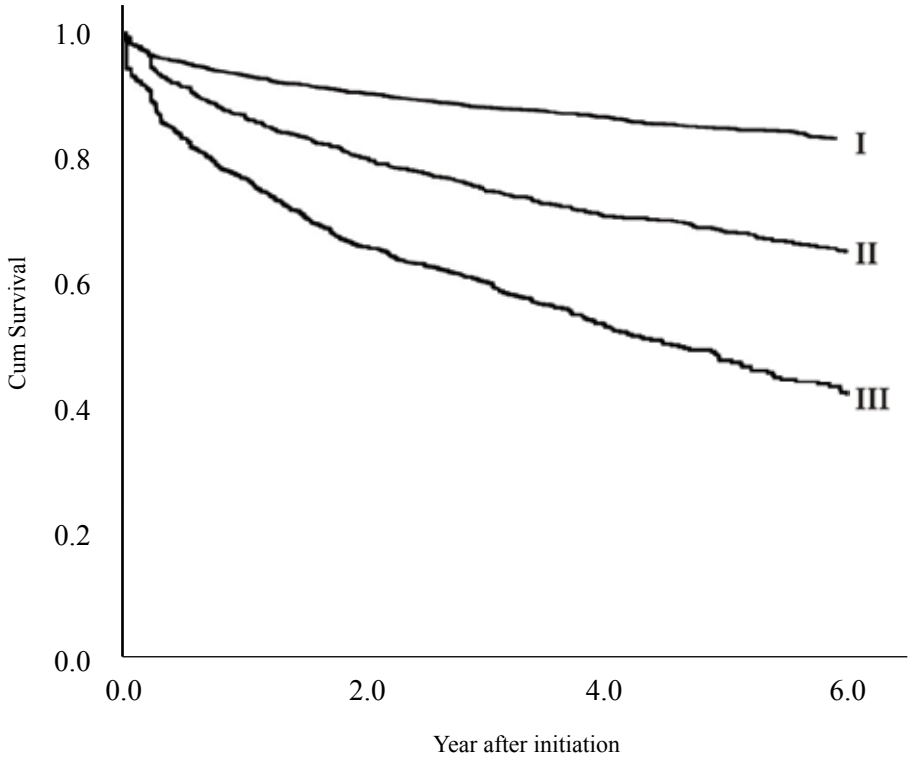

Figure 3. *Long term continuation of statins and oral antidiabetic drugs. Shown for oral antidiabetics (I), "Prior users", initiation of statins before oral antidiabetics (II) and "After users", initiation of statins after or simultaneously with initiation of oral antidiabetics (III). (Log-rank test, P<0.0001)*

Using Cox regression analysis, the magnitude of the latter association was estimated, showing a 70% increased risk of discontinuation among after statin users: crude hazard ratio 1.7 [CI95%: 1.4–1.9]. Given the skewed distribution of the year of statin initiation (almost all after users are in the 2005–2007 cohort; whereas almost all prior users are in the 1998–2004 cohort), we stratified the analysis for the cohorts 1998-2004 and 2005–2007. This resulted in the following hazard ratios: 1998–2004, 1.4 [CI95%: 1.1–1.6] and 2005–2007, 1.5 [CI95%: 0.9–2.4]. The Kaplan-Meier estimates for the 2005–2007 had a steeper slope compared with the 1998–2004 graph. Moreover, the 1998–2004

Kaplan-Meier shows separation only after 3 years. There were no differences in discontinuation between patients initiating therapy with metformin or sulfonylureas.

Discussion

Although this study showed that the number of T2DM patients receiving statins increased considerably between 1999 and 2007, 52.1% of these patients discontinued statin treatment in the subsequent years. Moreover, patients discontinued statin treatment more frequently than their oral antidiabetic treatment. Patients using statins before the initiation of oral antidiabetics (prior users) discontinued treatment less frequently (48.2% vs 62.8%) compared with patients starting statins concomitantly or after the initiation of oral antidiabetics (after users). The finding that discontinuation with statin treatment was higher than discontinuation to oral antidiabetics is intriguing. Oral antidiabetics are expected to have at least comparable risks of bothersome side effects as statins, and could therefore be expected to have similar adherence.[18] In addition, the beneficial effects of statins on major cardiovascular outcomes in T2DM patients are better established than those of oral antidiabetics.[1,19] The incentive to continue statin treatment is therefore expected to be at least as high as to continue oral antidiabetics.[18] On the contrary, studies in the general population did show better adherence to oral antidiabetics compared with statins.[10] Our findings are in line with other observational studies that suggest that the beneficial effects of statins shown in clinical studies are not achieved in daily practice.[12,20,21] Although our results suggest an improved abidance of diabetes guidelines related to the prescription of statins, more attention is needed to improve long term adherence to statin use.[22,23] Improving knowledge and motivation of both patient and health care providers may improve treatment quality.[8] Studies have suggested that screening on diabetes in order to intensify multifactorial treatment and interventions developed for subgroups might improve medication

adherence so that patients can achieve higher benefits of statin therapy.[24, 25] Continuation of statin therapy was higher among prior users compared with after users. However, we are not able to conclude on the reason for this, given the skewed distribution of Prior and After users over the observation period. On the one hand, this could have been influenced by the fact that from 2004 on, general practitioners started to prescribe statins on a routine basis to almost all patients with diabetes. These patients might be less motivated to use statins, as a higher proportion

of these patients will have relatively low starting cholesterol levels. Moreover, on 5 March 2007, a broadcast of a popular Dutch consumer television program was very critical on the widespread use of statins. This might have especially influenced those patients that recently started statins, which at that time were mostly after users.

It is plausible that patients who already used statins before starting oral antidiabetics more often have additional indications for initiating statins, such as familial hypercholesterolemia or secondary prevention in relation to cardiovascular morbidity. Other studies report higher adherence to statins among patients with secondary prevention. These patients might therefore be more motivated to adhere to statin treatment compared with patients with newly diagnosed diabetes who are predominantly prescribed statins as primary prevention.[26] Medication in the Prior user group implicates a higher rate of cardiovascular disease, which can be expected to result in higher awareness of severity.[12, 27, 28] A limitation of this study is that we have no information on the underlying reasons for discontinuation of statin therapy. We could not assess whether non adherence was driven by physicians or by patients themselves. Further research is therefore needed into reasons for non adherence of patients. Moreover, this study might have missed those statin users with concomitant diabetes that were not yet prescribed oral antidiabetics. Studying adherence by using medication gaps requires well defined cut of points, and some patients do restart their medication.[28, 29] In this specific study, we defined discontinuation

as a gap of at least 180 days after the theoretical end date of a prescription, which makes reinitiating less likely compared with studies that use shorter gaps. Finally, we were unable to link clinical data (e.g. LDL levels) to drug utilization patterns. Combining drug utilization patterns with relevant clinical data could provide conclusive evidence on the quality of hyperlipidemia treatment among patients with T2DM.

In conclusion, prescribing of statins increased steeply within the past years among patients with T2DM. However, non adherence is a major problem in the use of statins. Statin use therefore needs special attention as comedication in T2DM in order to prevent cardiovascular disease. Because discontinuation rates were higher in the After users group, active intervention, screening and sustained follow up is especially recommended in these patients.

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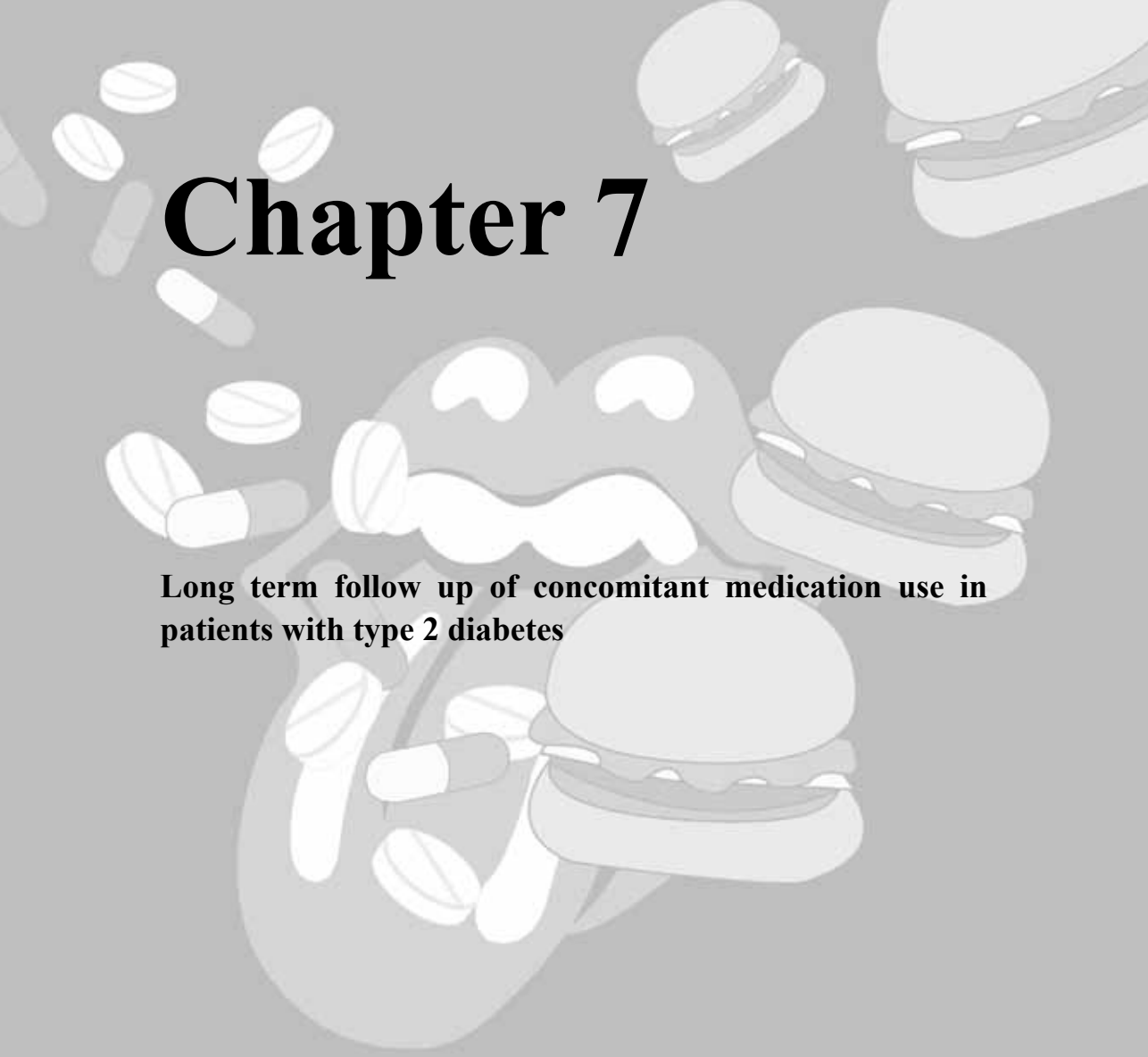
Chapter 7



Long term follow up of concomitant medication use in patients with type 2 diabetes

Submitted for publication

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Abstract

Background

Patients with type 2 diabetes frequently have comorbidity and use concomitant medications.

Objectives

The aim of the study was to determine longitudinal patterns of concomitant medication use in type 2 diabetes patients in a type 2 diabetes patient cohort.

Research design and methods

We conducted an observational cohort study among new users of oral antidiabetic drugs. Descriptive statistics were used to describe the annual proportions of patients who were prescribed different types of medication both before and after the start of oral antidiabetics.

Results

We identified 2933 new users of oral antidiabetic drugs. In the year prior to start of oral antidiabetics, 58.7% of the patients used cardiovascular drugs. In the first year after initiation this increased to 73.9%. In the tenth year after initiation, the proportion of patients using cardiovascular medication was over ninety percent. RAAS inhibitors and statins attributed most to the increase of the overall cardiovascular medication use. The proportion of patients using more than one cardiovascular drug rose steadily. The use of non cardiovascular medication increased from 56.4% ten years before t=0 to 77.0% after t=0.

Conclusions

The increase in concomitant medication use among patients with type 2 diabetes is mostly attributable to an increase of cardiovascular medication according to

guidelines aimed at prevention of cardiovascular disease among patients with type2 diabetes.

Introduction

In addition to adequate glycemic control, international diabetes guidelines also recommend treatment of hypertension and hyperlipidemia. It is therefore expected that treatment according to these guidelines will result in an increase in cardiovascular medication after initiation of oral antidiabetic medication.[1] Besides to cardiovascular disease, it has been established that diabetes is associated with a wide range of other health problems such as musculoskeletal disorders, depression, increased risk of infections and gastrointestinal disease.[2,3] Moreover, patients with type 2 diabetes (T2DM) are generally older and therefore at an increased risk of acquiring comorbid diseases with consequential increase in the number of medications.[4,5] However, as far as we know studies on such use of comedication in persons with T2DM are scarce and those available had a cross sectional design or focused on a short period of time or had small study populations. Most studies dealt with diabetes related comorbidities such as cardiovascular disease.[4, 6-10] To document long term patterns of medication use in persons with T2DM, will add important facts to our knowledge of the course of T2DM over time and may have implications for diabetes care programs.[5, 7, 11] Therefore, the aim of the study was to determine longitudinal patterns of concomitant medication use, prior and after start with oral antidiabetic drugs, distinguishing between cardiovascular and other non cardiovascular comedication, in a well defined population of T2DM patients.

Methods

Design

An observational cohort study among incident users of oral antidiabetic drugs.

Setting

The study was performed in the Diabetes Care System (DCS) which was implemented in 1997.[12] The DCS is situated in West-Friesland, a Dutch region with approximately 200,000 inhabitants and a relatively stable composition of the population that is representative for a Western European population.[13] We linked patients receiving care from the DCS with drug dispensing data obtained from fifteen community pharmacies and two dispensing general practices in this region.

In The Netherlands, the vast majority of the population obtains their medication from only one community pharmacy, enabling collection of complete medication histories of individual subjects over a long period of time.[14, 15] Data on medication extracted from the pharmacy information systems included information of: sex, date of birth and complete coded dispensing records, including date of dispensing, drug name, dosing regimen and amount dispensed. All drugs were coded according to the Anatomic, Therapeutic and Chemical classification system.[8, 16]

Study population

We identified all patients, 35 years or older to exclude potential subvariants like MODY, who were referred by their general practitioner to the DCS in the period 1998 to 2007 and were an incident user of an oral antidiabetic drug.[17] Incident use of oral antidiabetics was defined as having a first prescription for an oral antidiabetic drug while having at least 365 days of exposure history available in the community pharmacy database. To be sure all subjects received care from the DCS we included patients who were known in the DCS and could be linked

with the data from pharmacy information systems.

Definition of medication use

The date of the first prescription was defined as t=0. Medication use was assessed up to ten years before and after t=0, where use was defined as having at least one prescription in the corresponding year of observation. We examined both cardiovascular and non cardiovascular medication. Cardiovascular drugs assessed included anticoagulants (platelet aggregation inhibitors and antithrombotic agents), diuretics, beta blockers, Renin Angiotensin Aldosteron System inhibitors, calcium channel blocker and statins. Furthermore, we assessed use of non cardiovascular drugs, which included NSAIDs, antidepressants, antipsychotics, antiepileptics, benzodiazepines, antibacterial and antifungal drugs, respiratory medication, opthalmic medication, H2 receptor antagonists and proton pump inhibitors.

Data Analysis

Descriptive statistics were used to describe the annual proportions of patients who were prescribed different types of medication. Use of cardiovascular medication was stratified according to gender and age. Chi-square test was used to compare the difference in proportions among gender and age.

All analyses were performed using SPSS for Mac, (version 18.01.3, IMB Inc., Armonk, NY).

Results

We identified 3323 patients over 35 years of age who initiated OAD in the period between 1998 and 2007. We linked the data from the DCS and the pharmacy information systems of 2933 patients, 88.3%. Table 1 shows the characteristics of the study cohort. About half of the subjects (51.9%) were men and the mean age was 60.6 years (SD 11.5).

Table 1. *Characteristics of the study cohort (n=2933), in the year of initiation of oral antidiabetic drugs (OAD).*

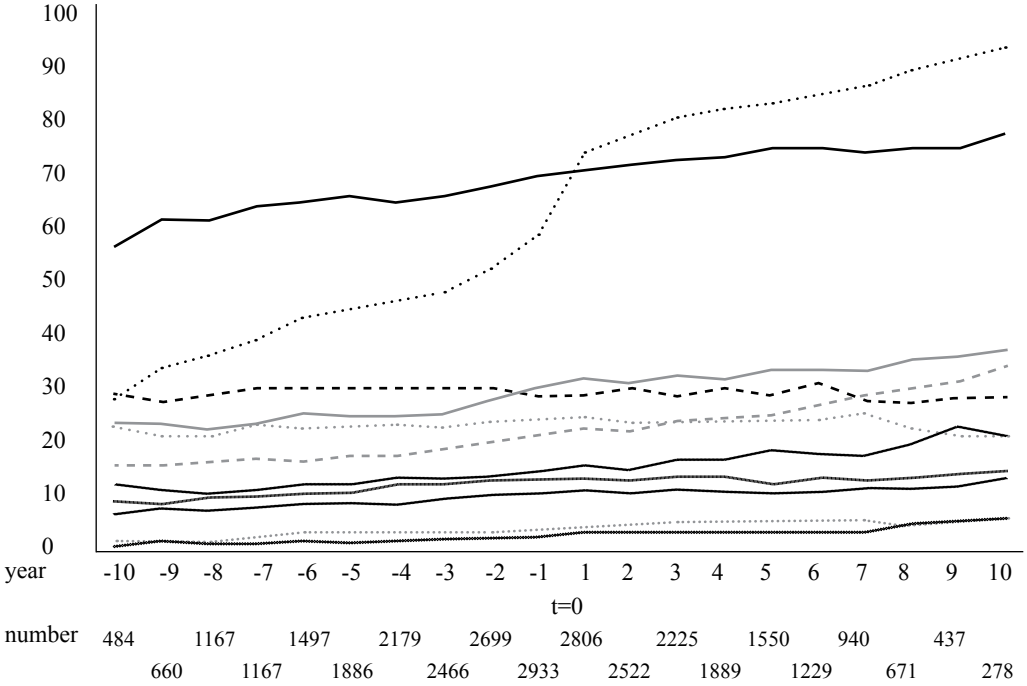
	N (%)	
Male (%)	1523	(51.9%)
Mean Age OAD (SD)	60.6	(± 11.5)
Age groups:		
35-44	249	(8.5%)
45-54	622	(21.2%)
55+	2062	(70.3%)
Mean Time OAD to DCS (SD)	0.4	(± 2.1)
Mean Follow Up (SD)	11.4	(± 3.4)
Year of OAD initiation:		
1998/1999	617	(21.1%)
2000/2001	546	(18.6%)
2002/2003	601	(20.4%)
2004/2005	640	(21.8%)
2006/2007	529	(18.1%)

SD: Standard Deviation

DCS: Diabetes Care System

Figure 1 shows the prevalence of medication use ten years before and after OAD start (t=0). The prevalence of non cardiovascular medication use increased from 56.4% ten years before t=0 to 77.0% after t=0. The increase was mostly due to antibiotics, heartburn medication and opthalmic medication. The prevalence of NSAID use was stable at around 30% during the period of observation. In the same period the increase for cardiovascular medication was from 27.7% to 93.5%. In the year prior to OAD initiation, 58.7% of the patients used

cardiovascular drugs, while in the first year after OAD initiation this increased to 73.9%. Subsequently, we stratified according to the type of cardiovascular drug. Figure 2 shows the proportion of various types of cardiovascular drugs. The use of all cardiovascular medications increased over time. The increase was highest during the years before and after OAD initiation. RAAS inhibitors and especially statins attributed most to the increase of the overall cardiovascular medication use. Twenty four percent of the study cohort used statins in the year before OAD initiation, which nearly doubled (43.3%) in the first year after OAD start and further increased to 58.6% in the fifth year after OAD initiation. The use of RAAS inhibitors increased from 24.1% to 35.2% from the year before, to the first year after OAD initiation.



Any cardiovascular drug
Any non-cardiovascular drug
Antibiotics
NSAID
Benzodiazepines
H2 receptor antagonists and proton pump inhibitors
Opthalmic medication
Respiratory medication
Antidepressants
Thyroid hormones
Antiepileptics

Figure 1. *Proportion of patients using comedication, 10 years before initiating oral antidiabetic drugs (t=0) and 10 years after initiating oral antidiabetic drugs.*

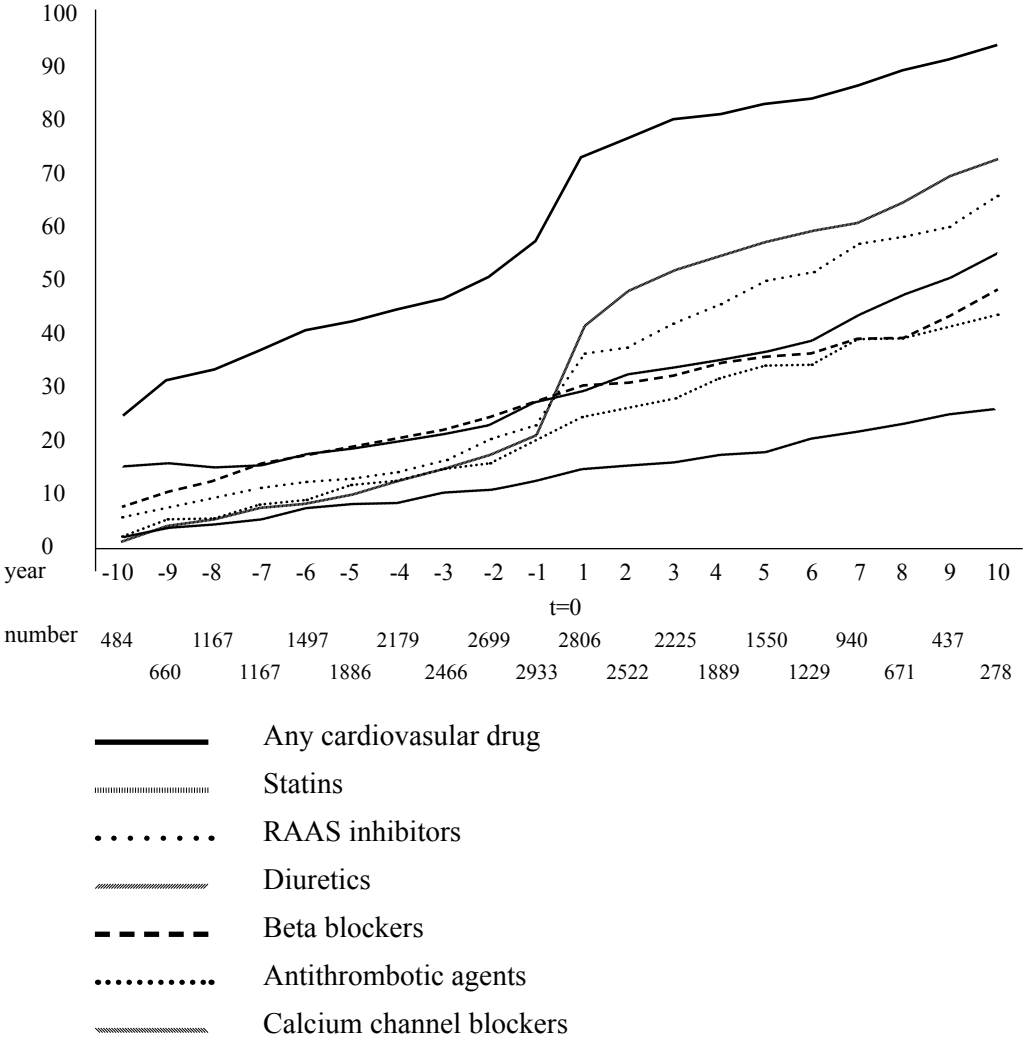


Figure 2. *Proportion of patients using cardiovascular medication, 10 years before initiating oral antidiabetic drugs (t=0) and 10 years after initiating oral antidiabetic drugs.*

Figure 3 shows the proportion of patients and the number of different types of cardiovascular medication used in the year of observation. The proportion of patients using no cardiovascular medication decreased over time and the proportion of patients using multiple cardiovascular medication rose steadily.

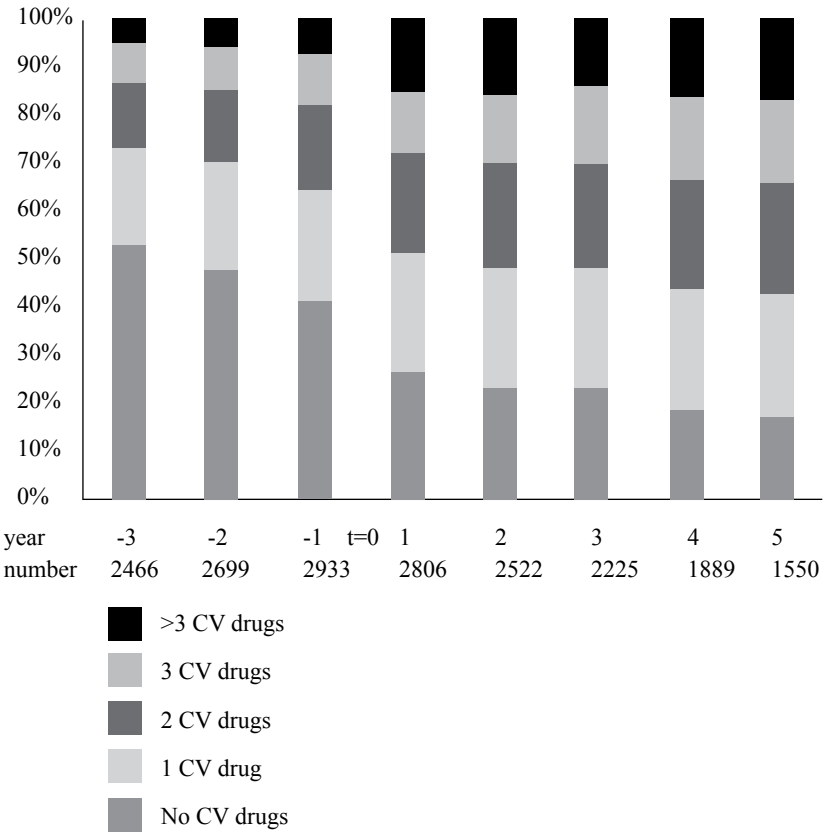


Figure 3. *Proportion of patients using several types of cardiovascular (CV) medication, 3 years before initiating OAD and 5 years after initiating OAD.*

Figure 4 shows the proportion of patients using cardiovascular medication stratified according to gender. In all years female subjects used more cardiovascular medication compared to male subjects. These differences were statistically significant from ten years before up to eight years after OAD

initiation (Chi-square test, $p<0.05$).

Figure 5 shows the proportion of cardiovascular medication use, stratified according to age groups. The proportion of cardiovascular medication use was highest in the group of subjects who were over 55 years of age at OAD initiation. Chi-square test showed significant difference between age groups from ten years before up to ten years after OAD initiation, $p<0.05$.

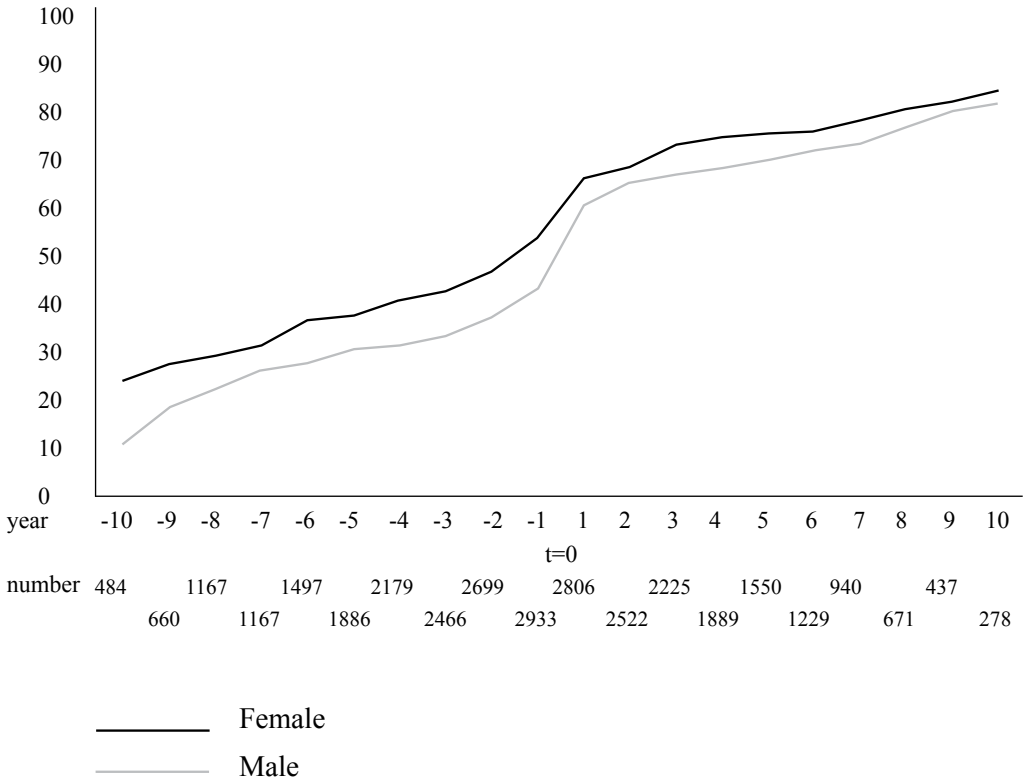


Figure 4. *Proportion of patients with cardiovascular medications stratified according to gender 10 years before and after start with oral antidiabetic drugs. (t=0) (p<0.05; years minus 10 up to 10 years after t=0).*

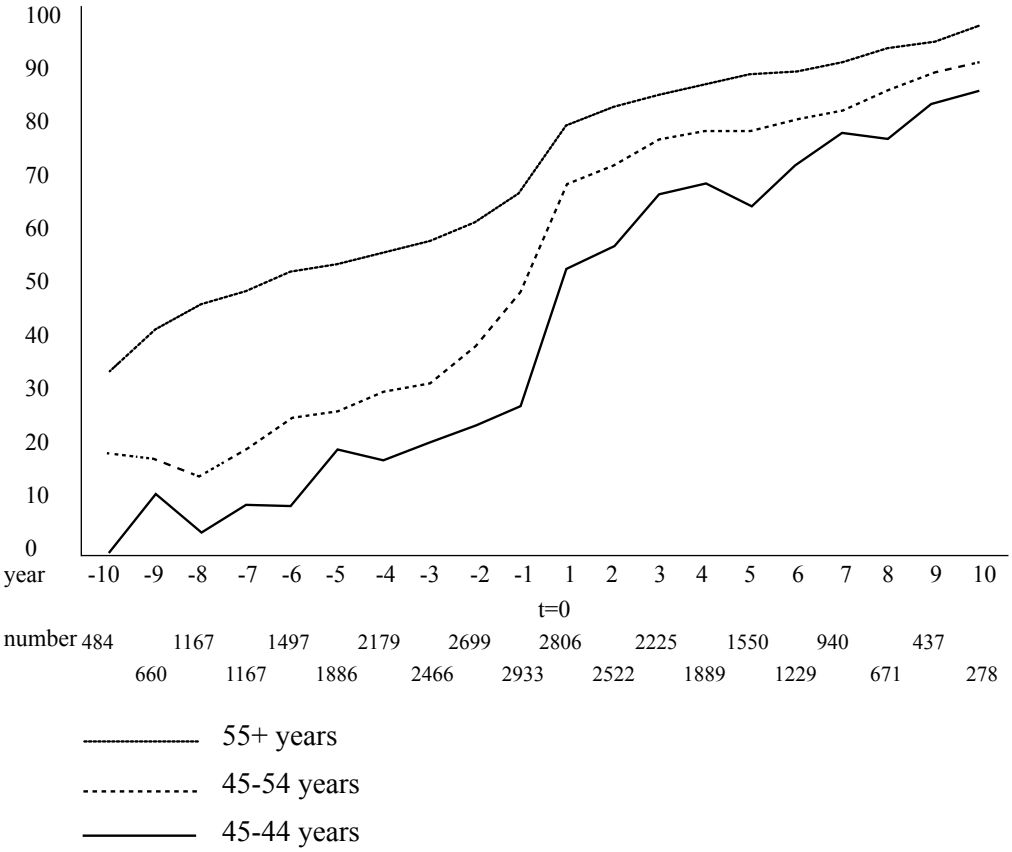


Figure 5. *Proportion of patients with cardiovascular medications stratified according to age 10 years before and after start with oral antidiabetic drugs. (t=0) (p<0.05).*

Discussion

This study showed an increase in the prevalence of all medication use over the years in patients initiating oral antidiabetic drug treatment. The use of non cardiovascular medication increased little over time mainly due to antibiotics, heartburn medication and opthalmic medication. However, the use of cardiovascular medication increased much more strongly than non cardiovascular medication in the year following the initiation of oral antidiabetic medication,

in comparison with the year prior to OAD start. T2DM has been associated with increased rates of common infections.[2] Our results showed an increase of the use of antibiotic drugs, this could be the reason of the progressive nature of T2DM and the increased risk for infections of T2DM patients.[2] Although it was expected that non cardiovascular medication use increased because of T2DM, ageing in the twenty years of observation also seems an important factor.[5]

More than half of the proportion of cardiovascular medication could be attributed to statins. Besides statins, especially RAAS inhibitors contributed to the increase in the proportion of cardiovascular medication. This is in accordance with international treatment guidelines in which statin treatment is recommended in almost all T2DM patients and ACE inhibitors are the preferred treatment of hypertension among patients with diabetes.[1] It may be necessary to use more than one antihypertensive drug in case of patients with T2DM, which is also recommended by the international guidelines.[1, 18] In this population the proportion of patients using three or more cardiovascular drugs increased but the majority used two cardiovascular drugs. Higher age showed an overall higher use of cardiovascular drugs compared to younger subjects. Whereas older patients might have more concomitant cardiovascular disease, relatively young patients might have more sustained long term effects of cardiovascular medication.[19-21] A previous study showed a higher increase in cardiovascular medication use before OAD initiation than in non diabetic subjects suggesting a common underlying mechanism of these two disorders.[6] We found similar results in our study.

Females showed a higher overall proportional use of cardiovascular medication in comparison with male subjects. As previously shown by Framingham study, diabetic women have an increased cardiovascular risk.[22] Our results showed a similar outcomes. Before the initiation of OAD the proportion of use of cardiovascular medication is higher in the female stratum. Use of antibiotics increases gradually over time. To our knowledge this was the first study to assess concomitant medication use both before and after the initiation of oral

antidiabetics. In the region of our study, diabetes care is centrally organized, and protocolized. Regular benchmarks and centrally agreed protocols must assure the treatment of diabetes according to diabetes treatment guidelines.[12] This seems to have its effect on prescription behavior of the general practitioners indicating adaptation of the protocols.

There are some strengths and limitations to discuss. Although our observational study had a strong design, we were not able to compare our results with other populations. All T2DM patients were treated by the DCS; as a result we were aware that this population received protocolized care in a continuous setting. It is therefore unlikely that we missed chronic medications. We were not able to link all identities of the DCS and the data from the pharmacy information system. Still the numbers of analyzable patients were high. We have a long mean follow up period of more than ten years. In this study, we focused on all comedication use and not on OAD use.

In conclusion, this study demonstrated only a slightly increase in the use of concomitant medication apart from a strong increase in the use of cardiovascular medications after the initiation of oral antidiabetic drug therapy.

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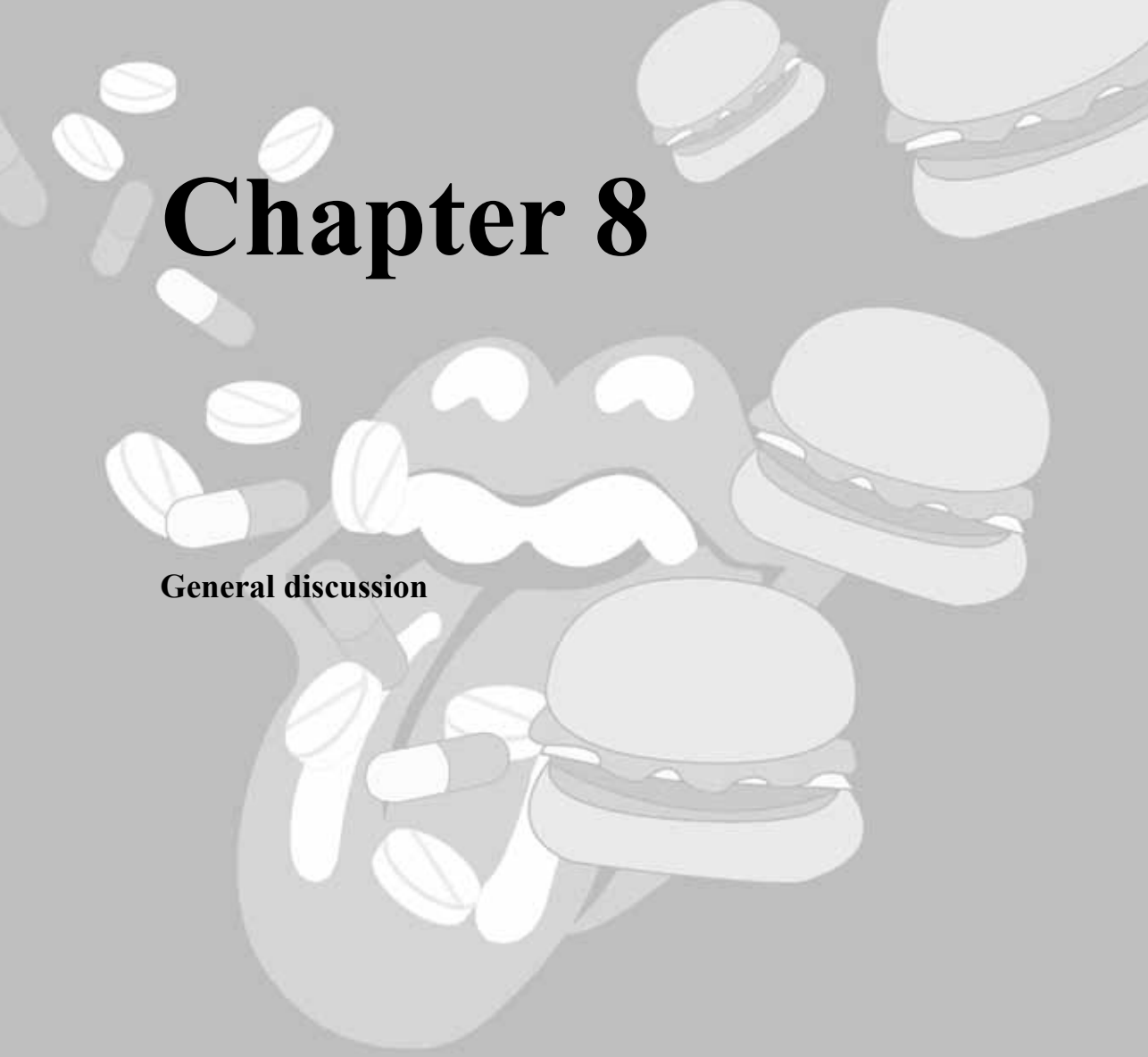
Chapter 8



General discussion

General discussion

In the introduction of this thesis, two major research topics were introduced. The first topic concerned the information needs of patients starting with oral antidiabetic medication and the role of the community pharmacist as an information provider. The second topic, related to the longitudinal patterns of medication use, glycemic control and the relationship between medication use and glycemic control in daily clinical practice. In this final chapter the results of the various studies conducted in this thesis will be discussed, the two major research topics will be linked and the findings will be placed in a broader perspective. Following a overview of the main findings, the study methods and their limitations will be evaluated. Finally, the relevance and implications of the study results for diabetes care will be discussed and recommendations to further improvement will be made.

Information needs concerning oral antidiabetic medication

Although the effects of unsolicited general information on disease and medicines often have limited effects on adherence and clinical outcomes, patients do have information needs. Providing patients with tailored information about medication has been associated with improved adherence resulting in improved treatment outcomes. In contrast, information not addressing patients' needs may produce opposite effects.[1, 2]

Since medicines play a pivotal role in the treatment of type 2 diabetes mellitus (T2DM), patients frequently visit a pharmacy to (re)fill their prescriptions.[1-3] Community pharmacists therefore have the opportunity to provide patients with adequate information, both at the start and during follow up of T2DM related pharmacotherapy. Although the expertise of the pharmacist is well recognized, it is not sought frequently.[4] In the past decade an increasing number of community pharmacists have made a transition from primarily logistics to counseling patients about medicines and helping patients with resolving their problems with

medicines. Although well documented guidance is available, many pharmacists still struggle with making this transition.[4-6] Moreover, the quality of existing pharmaceutical care programs are highly variable and must compete with treatment management programs of general practitioners generally involving nurse practitioners, which have proven to (effectively) improve clinical outcomes.[6-9] Pharmacists are therefore challenged to increase their visibility as a healthcare provider. As patients still perceive the pharmacy primarily as a dispensing outlet, concurrently logistic services must be kept on a high level to meet patients' expectations. In addition, from the patients' perspective the collaboration with other healthcare providers needs to be improved. Pharmacists must therefore expand their professional care services with a sense of urgency and implement sustainable business models around pharmaceutical patient care.[4, 10-13] In order to know where areas for improvement are it is necessary to know how (well) patients with diabetes are currently treated and controlled.

Long term patterns of medication use and clinical outcomes in daily practice

Oral therapies include several drug classes, which are commonly used before initiation of insulin therapy. In the period under study diabetes treatment guidelines positioned metformin as the drug of first choice in T2DM.[14-15] The studies presented in this thesis show that the proportion of patients starting T2DM treatment with metformin increased rapidly over time, indicating that recommendations concerning initial drug choices were indeed adhered to. Furthermore, both metformin and sulfonylurea discontinuation rates were relatively low with less than 20% and comparable with randomized clinical trials. Approximately half of the patients seemed to be adequately treated with monotherapy over longer periods of time. Moreover, the majority of patients had relatively good glycemic control. However, a minority of patients showed frequent medication changes, periods without medication and had inadequate glycemic control. Chapter 3 and 6 in this thesis did not investigate the relationship between non adherence and inadequate glycemic control, but it is

likely that non adherence is at least one of the contributing factors to inadequate control of T2DM.[16-17] It has been shown that in general between a third and half of chronically prescribed medication is not taken as prescribed.[18-24] Early discontinuation of treatment is responsible for the major part of overall non adherence.[25] Up to 37% of patients discontinued OADs within one year of initiating treatment.[18, 26, 27] Regardless of the treatment chosen, adherence is critical to achieving treatment goals.

A relationship between adherence to antidiabetic medication and HbA1c has been shown: when adherence increases, HbA1c decreases.[28] To effectively manage T2DM a multifaceted effort is needed, involving lifestyle interventions (diet and exercise) and, for most patients, drug therapy. Patients are in need of support to take responsibility for the day-to-day management of T2DM, including adherence to both lifestyle changes and medication.[29] Unintentional adherence may be the result of forgetfulness and not knowing exactly how to use medicines. Intentional non adherence refers to an active decision of the patient not to follow treatment recommendations. This can reflect a rational decisionmaking process in which the patient weighs the advantages and disadvantages of the treatment, but can also involve less rational elements such as fear of treatment side effects, in particular weight gain and hypoglycemia, needle anxiety (for parenteral administration) distrust in health care interventions in general or distrust in specific health care providers. Poor knowledge about the importance of therapies and the use of drugs play a role in the rational part of this process. The most common reason for unintentional non adherence is forgetfulness. Inconvenience or complexity of a prescribed treatment regimen can make it more difficult for the patient to adhere to the regimen.[30, 31]

Strategies directed at helping patients who are unintentional non adherent are of a more practical nature and include the simplification of dosing regimens and the use of reminder-methods. To address intentional non adherence more in depth communication between patient and health care providers is often required. This

includes motivational interviewing and other behavioral interventions. Often multi-faceted interventions are necessary with cooperation between different health care providers. Addressing patients' needs and concerns on medications is often required.[32-34] Increasing knowledge about the disease and its treatment is relevant, but is less likely to improve adherence, without a concomitant strategy aimed at patients' intrinsic motivation.[14, 35] The study in chapter 2 did indicate that there is ample room for improving the information provision to patients with T2DM.[4]

The potential benefits of achieving higher rates of treatment adherence in T2DM include improved clinical outcomes and cost savings.[29, 36-38] It should be noted that the need to balance therapeutic efficacy with tolerability (e.g. prevention of hypoglycemia) is challenging. The dual goal of achieving HbA1c target and avoiding or minimizing side effects that may impact tolerability and promote poor adherence need to be taken into consideration when formulating a treatment plan for patients with T2DM.

A plausible explanation for the relatively low discontinuation rates in the study population could be that studies were performed in a setting with a highly protocolized and stringent treatment policy. Although large differences exist in The Netherlands for several diabetes indicators regarding efficiency and quality, indicators reflecting recommendations in guidelines score well. In the case of the use of metformin as first choice medication adaptation ranges from 80 to over 90 %.[16, 39]

Adherence to guidelines for the choice of treatment however is not the ultimate goal of diabetes treatment. As HbA1c is considered a reliable marker for glycemic control and has become a "gold standard" for diabetes management. Lower HbA1c values had been linked to reduce risk of microvascular and macrovascular complications in T2DM.[40,41] Long term studies into patterns of HbA1c are, however, sparse. As indicated the studies in chapter 4 showed the majority of patients had relatively good glycemic control. In addition the

studies in chapter 5 suggested that patients initiating T2DM treatment on metformin may show better glycemic control compared to patients initiating treatment with sulfonylureas. This underlines guideline choices for a prominent role of metformin, which were based on the UK Prospective Diabetes Study that suggested a cardioprotective and therefore primary role for metformin.[42] Furthermore, it has been shown that metformin added to insulin in T2DM improves glycemic control and decreases body weight. Although the study does not give conclusive evidence for superiority of metformin compared to other OAD in daily clinical practice, the findings in chapter 5 of this thesis support the guiding principle to maintain treatment with metformin as first choice OAD and maintaining metformin treatment after initiation of insulin.[42-44]

Risk factors for suboptimal glycemic control

In chapter 4, it was suggested that the large majority of patients maintain glycemic control over the first years of treatment. However, certainly on a population basis, a non-negligible proportion of patients do not maintain glycemic control. For daily clinical practice it is relevant to characterize those patients. Chapter 4 presented in this thesis suggest that younger patients (35-44 years) at onset of diabetes are more likely to have increased HbA1c levels during follow up compared to patients in older age groups. This is especially worrying as these younger patients might therefore be at increased risk of long term negative micro- and macrovascular outcomes of T2DM.

The incidence of T2DM increases with age and older patients will experience an increased burden of diabetes on top of normal age-related physiological changes.[45] T2DM is a major risk factor for cardiovascular disease. Modifiable risk factors like obesity and low physical activity are important to address in patients with T2DM.[46] The association between these factors is especially relevant in patients with T2DM onset at younger age.[47] Heterogeneity in the clinical phenotype of T2DM has been shown and is influenced by gender and age.[48-50]

A limitation of the studies performed in this thesis was the absence of data on lifestyle such as diet and physical activity. Nevertheless the results are in line with the current concept that T2DM diagnosed at younger age may be a more aggressive (pheno-) type than T2DM, which becomes manifest at older age.[47] By linking HbA1c data with data of antidiabetic medicine use over a long period of time, we were able to study the effects of medication on HbA1c in a longer time frame. Again younger age was associated with worse prognosis marked by HbA1c measurements.

Treatment of concomitant risk factors

Cardiovascular disease is the leading cause of mortality and major contributor to comorbidity in patients with T2DM. This is predominantly caused by a higher prevalence of cardiovascular disease risk factors, such as hypertension and hyperlipidemia. With the aim to prevent T2DM associated cardiovascular disease, it is generally recommended to treat hypertension and hyperlipidemia alongside oral antidiabetic treatment.[14, 51-54] Adequate blood pressure control in patients with T2DM may even even exceed the benefits of adequate glycemic control in the prevention of major cardiovascular disease.[55, 56] Hypertension is common in patients with T2DM, but few reach target blood pressures, although guidelines for the treatment of T2DM include clear targets for blood pressure control.[14, 15, 57-61] A study on this subject was beyond the scope of this thesis. The large variation of drugs used to treat hypertension and the wide array of other indications for these drugs requires a complex study on long term patterns of hypertension treatment in T2DM to be reliable.[58, 60, 61] However, the outcomes of chapter 7 enabled us to design a reliable study in the near future. It remains a future challenge to study antihypertensives among patients with T2DM. Furthermore, such a study could compare adherence to antihypertensive treatment with adherence to OADs.

Chapter 6 does contain a study on lipid lowering treatment in patients with T2DM. Lowering of LDL cholesterol by using statins is considered highly

effective to decrease cardiovascular risk.[62, 63] Accordingly, within the past years initiation of statin use increased steeply among patients in our study population with T2DM[17] However, (early) discontinuation of statin treatment is not uncommon. Statin discontinuation rates were higher among patients starting with statins after having started OAD as compared to patients who started statins before OAD initiation. The finding that patients with a history of cardiovascular disease (secondary prevention) show better adherence than patients without such history (primary prevention) has also been shown in other patients without diabetes.[24, 63-67] Although there is limited evidence that well informed patients are more adherent to statin therapy, it is recommended to provide statin users with comprehensive information, especially when patients are using these drugs in primary prevention were treatment is already initiated in patients with moderate hyperlipidemia.[68]

Comorbidity in diabetes

In addition to cardiovascular comorbidity and treatment of cardiovascular risk factors, patients with T2DM frequently have other non-cardiovascular comorbidity and are likely to use more concomitant medications.[69-72] In a study, presented in chapter 7 of this thesis, aimed at describing longitudinal patterns of concomitant medication use in patients with T2DM, the increase in concomitant medication use was mostly attributable to a guideline induced increase of cardiovascular medication. Although there was an increase in concomitant medication for other indications that might be influenced by inadequate control of diabetes (e.g. antibiotics, psychiatric drugs and ulcer drugs), this increase remained modest over a prolonged follow up. This suggests that a majority of patients with T2DM do not develop diabetes related comorbidity during the first 10 years after diagnosis. Studies with even longer follow up may be required to assess the impact of T2DM on comorbidities. Moreover, there is a small subgroup of patients with T2DM who have several comorbid conditions and are receiving different classes of medication. In these patients the risks of polypharmacy and

the potential for inappropriate therapy must be considered and balanced against the possible benefits of multiple drug therapies. In order to reduce the risks and maximize the benefits of drug therapy some patients should regularly be subject of medication review.[63, 64] Probably a full medication review is not indicated in all patients with T2DM. More research is needed to identify those patients that can benefit from medication review. Beyond appropriate drug selection, medication review can also identify adherence issues.[69, 75] Pharmacists could address adherence issues by both practical (e.g. reminder calls or devices, pillboxes, educational materials) and behavioral (counseling) interventions.[75,76]

Representativeness of the study results

In the discussion paragraphs in the preceding chapters the strengths and limitations of the individual studies carried out in this thesis were discussed. Below these considerations will be addressed in a broader perspective.

Telephone interviews and patient focus group discussions

The qualitative study described in chapter 2 was conducted in another region than the other five studies. As the majority of studies in this thesis were performed in a region with a long established diabetes management system, it would have been interesting to investigate whether patient's information needs are different in this setting, compared to settings who lack this protocolled care.

Long term patterns in daily clinical practice

T2DM clinical guidelines are based on RCTs and provide evidence based recommendations aimed at glycemic control and the prevention of cardiovascular disease.[14, 15, 77] Although RCTs with concealed randomization are the gold standard to establish the efficacy of treatments, they do not reflect actual drug use in daily clinical practice and may therefore also not reflect clinical effectiveness in daily clinical practice.[61, 78-80] In chapters 3-7 observational

cohort studies were used to describe the use of medicines and outcomes of treatment in daily clinical practice. We obtained clinical data from the Diabetes Care System (DCS). Each patient in the DCS is annually invited for a highly protocolled routine visit with specialized diabetes nurses and dieticians. All clinical patient data are registered in a central database.[78, 80] The DCS does, however, not contain detailed information on medication, which prohibited earlier researchers to describe medication use in this cohort in depth. Therefore detailed medication data from pharmacy information systems in the same area as the DCS were collected. Pharmacy data contain details such as dispensing date, exact amount dispensed and prescribed dosage regimen. This offers major advantages for drug utilization studies.[80] In The Netherlands, the vast majority of patients always obtain their medicines from the same community pharmacy. This allows to collect virtually complete medication histories of individual subjects over a long period of time, and to reliably assess discontinuation and taking non compliance.[82, 83] Although dispensing data are a reliable instrument to assess whether patients have medication at their disposal, it remains possible that patients do not take their medicines. Ultimately treatment outcomes will depend on the individual patients' behavior both regarding to lifestyle adaptations and adherence to medication.[61, 81, 84] Therefore, as stated before, health care providers must address individual patients' needs in order to motivate them for long term adherence to therapeutic interventions.[4, 85]

The majority of general practitioners (GPs) in the region under study refer patients with T2DM to the DCS. The patients' own GP remains responsible for the provision of primary medical care, whereas the DCS coordinates diabetes treatment in a highly protocolled way.[86-88] Patients annually visit specialized diabetes nurses and dieticians. All physical examinations and laboratory blood measurements are registered in a central database. This routine method of data collection has the advantage of not only collecting data from patients where a clinical test is specifically requested but that we had access to all clinical

data of all patients in the study population.[79] These data are collected in a protocolled way and therefore have a relatively low proportion of missing values. However, a limitation of this method is that we do not have access to the data of individual GPs between the yearly visits to the DCS. The results of the annual visits are provided as feedback to the GPs who are supposed to treat T2DM patients according to the Dutch treatment guidelines.[15, 89] Moreover, efforts are made to train GPs to treat T2DM patients according to national treatment recommendations.[15] Results from our studies suggest that in this particular region GPs generally adhered to T2DM treatment guidelines. This is illustrated by the high uptake of metformin as initial treatment for diabetes and the steep increase of statin prescriptions over the study period. Nevertheless we did not have information of patients who were lost to follow up. It is possible that these patients are less likely to adhere to treatment. Thereby the studies could have given a more positive view on treatment in daily clinical practice. Furthermore, the question remains to what extent the results in this region with protocolled care apply to The Netherlands in general or even of Western Europe. Some support for this assumption can be drawn from another Dutch study performed in a different setting that showed a similar uptake of T2DM guidelines. The proportion of metformin as initial treatment increased rapidly in this study while the proportion of sulfonylureas decreased. Newer drugs, such as thiazolidinediones and meglitinides, were rarely used as initial treatment.[83]

Implications for further research

The results of our studies imply that the vast majority of T2DM patients enrolled in the DCS is treated according to T2DM guidelines and that new insights in diabetes treatment are adapted early. This results in improvement of glycemic control in, again the vast majority of patients. However, because no control group was included in the analysis, it is not possible to conclude that the type of protocolled care provide by DCS results in higher adherence to treatment guidelines and in a higher proportion of patients attaining glycemic control

than in regions that do not provide this type of T2DM care. Moreover, the lack of hard clinical endpoints (e.g. micro- or macrovascular complications) in the various studies refrains us from linking good glycemic control to decreased morbidity and mortality. In addition, it is unclear if the DCS is cost effective, especially in comparison with "usual" diabetes care in daily clinical practice. In potential primary care is more cost effective than secondary care.[90] It has been reported that nurses specialized in diabetes care using treatment protocols are able to provide the same quality of care as provided in a hospital setting.[9] The DCS could be considered intermediate care between primary and secondary care. The hypothesis that the DCS is more (cost) effective than usual care either in primary or secondary care must be demonstrated in future research. Besides effectiveness it remains of interest how patients perceive the care provided by the DCS compared to diabetes care in other settings. A qualitative study designed like the focus group study in this thesis could provide further information on how patients perceive the care provided by the DCS and if and how they would like to see pharmaceutical care integrated in the highly protocolled system.[4]

Implications for pharmaceutical care

Drugs can only be efficacious when they are appropriately prescribed, dispensed and taken. RCTs are designed to determine the effect of drugs under the most favorable conditions, but even in RCTs not all people will experience the optimal effects of drugs (e.g. because not everybody will actually take them). It is widely acknowledged that this gap between the potential efficacy of drug therapy and effectiveness is even wider in daily clinical practice. This is partly caused by so called Drug Related Problems (DRPs). These DRPs are diverse and include physician related factors such as suboptimal prescribing, drug related factors such as adverse drug reaction and drug interactions and patient related factors such as non adherence.[5, 6] According to Strand et al. the increased gap between efficacy and effectiveness is caused by a cascade of DRPs including both effectiveness and safety issues (Figure 2.).

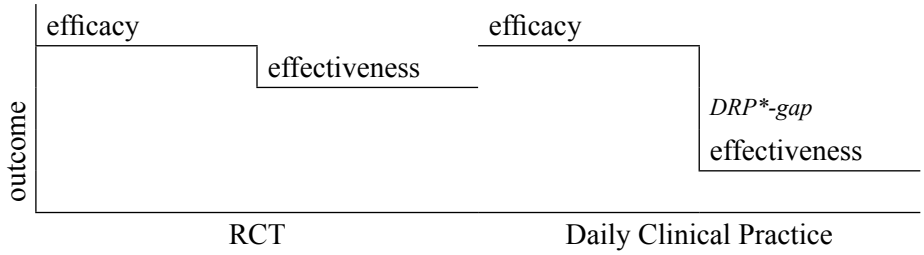


Figure 1. *Gap between efficacy and effectiveness of medication in a Randomized Clinical Trials (RCT) and in daily clinical practice.*
* DRP = Drug Related Problems

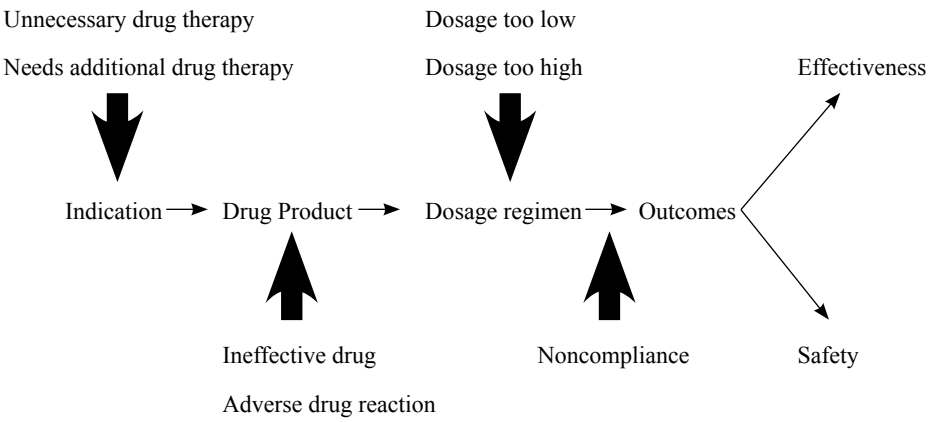


Figure 2. *Identification of Drug Related Problems.*

The challenge for community pharmacy is to deliver pharmaceutical care that minimizes the gap between efficacy and effectiveness. In the pharmaceutical care process identification of DRP is considered to be a major activity of pharmacists as making the correct diagnosis is for clinicians.[91]
Improved adherence to the medication regimen and reduction of adverse drug reactions is likely to contribute to the cost effectiveness of treatments.[92] Studies

have shown that increased adherence improves cost effectiveness of a variety of drugs such as antithrombotics and lipid lowering drugs.[93-97] Although the studies in this thesis suggested that adherence to oral antidiabetics is reasonable, there is still ample room for improvement. Especially adherence to lipid lowering drugs, which play a major role in reducing macrovascular morbidity in patients with T2DM, was reduced.[17, 18, 98] Any increase in adherence of drugs with proven (cost) effectiveness will further increase (cost) effectiveness of these drugs. With the current low cost of effective generic drugs in The Netherlands (and many other countries), pharmacotherapy will often be a very cost effective intervention. Improving the value of medication by diminishing the DRP gap, is therefore in line with modern ideas of added value in healthcare.[92]

Since value is defined as outcomes related to costs, it includes (medication) efficiency. Cost reduction however without regard to the outcomes may lead to false savings and potentially limiting effective care.[13] In other fields than healthcare performance and accountability is assumed to have the same goal leading to complementary activities and interests of all stakeholders. In healthcare, however stakeholders often seem to have conflicting goals including profitability, quality, safety, convenience and in particular costs. The current organizational structure of the healthcare system makes it challenging to measure and deliver value.[12, 99] Some estimates suggest that as much as 30% of healthcare spending is wasted, including failures in execution of care processes and treatment.[100, 101] DRPs, like undertreatment and non adherence contribute to inadequate drug treatment, in particular in chronic diseases like T2DM. Moreover, for some chronic conditions, like T2DM, increased drug utilization can provide a net economic return when it is driven by improved adherence with treatment guidelines.[92, 102]

How to establish a new business model for community pharmacy and T2DM?

Interventions aimed at improving disease management in diabetes with either specialized nurses or pharmacists have been shown to be effective.[9, 28, 94, 95]

Now, results from these studies have to be translated to daily clinical practice. The wide spread implementation of pharmaceutical care is still reluctant.

Current efforts for the implementation of pharmaceutical care did only partly consider the factors that are needed to facilitate the paradigm shift from traditional pharmacy compounding and logistics, to care and service providing pharmacy practice.[105-107] Opinion leaders in community pharmacy agree that the profession should transit from product to service orientation but in daily practice initiatives are hampered by various factors.[105, 108] Organizational change, especially in healthcare and community pharmacy, is a process of complex external dynamics that are influenced by political, economical, technological and legal aspects.[109] Moreover, healthcare workers are frustrated by continuously changing reimbursement issues, such as preferential prescribing and exclusion of several drug classes from reimbursement leading to unnecessary administrative load and costs. Concurrently there is no real responsibility of consumers for the costs of their drug treatment. Finally, costs are controlled in different compartments (e.g. primary and secondary care or pharmaceutical care and GP care), thereby making it impossible to see savings on hospital admissions by adequate preventive medicine or vice versa saving on medicine by more efficient operation techniques.[12, 13]

The implementation of pharmaceutical care is impaired by a complex interaction of several internal and external factors. Amongst these factors are cooperation with physicians, remuneration issues, pharmacy layout, patient expectations, amount and quality of pharmacy staff and external support.[110, 111]

Most pharmacies are still reimbursed on the basis of their logistic activities. Whereas the profits of these logistics used to be sufficient to deliver unpaid pharmaceutical care, community pharmacy is now confronted with decreasing margins and concurrently lack of direct reimbursement for pharmaceutical care. This lack of funding hampers investments in the quality and amount of pharmacy staff.

There is ample opportunity for community pharmacists to cooperate with

other health care providers as there is a general shortage of trained healthcare professionals like GPs and (T2DM specialized) nurses. Collaboration with other care providers seems therefore to be the best strategy for pharmacists to be integrated in the diabetes care process, which is also stated by the American standards for medical care of diabetes: "People with diabetes should receive medical care from a physician coordinated team. Such teams may include, but are not limited to, physicians, nurse practitioners, physicians assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. It is essential in this collaborative and integrated team approach that individuals with diabetes assume an active role in their care."[14] The studies in this thesis show that pharmacists do have opportunities to add to the quality of diabetes care. Dispensing data for example may give more insight in actual drug use of patients with T2DM and patients clearly have a need of more in depth information on their medication.

More formal research into the cost effectiveness of pharmaceutical care remains necessary. Pharmacists will have to accomplish an effective business plan, underpinned with the right drivers, motivators and facilitators, which add value based pharmaceutical care to patients with T2DM (but this also applies to any other disease area).[10, 12, 13, 105] Such a plan can, obviously, only be appropriate if it is based on the needs of patients, other health care providers, payers and policy makers. In order to spend more time for patient care internal systems and processes have to be optimized (e.g. by implementing central filling). Individual pharmacists will need to join forces in order to create critical mass. Pharmacists that hold on to pharmacy practice from the 19th century are unlikely to survive in the current health care environment. Like the change management guru Peter Drucker once said: "The greatest danger in times of turbulence is not the turbulence; it is to act with yesterday's logic".[103]

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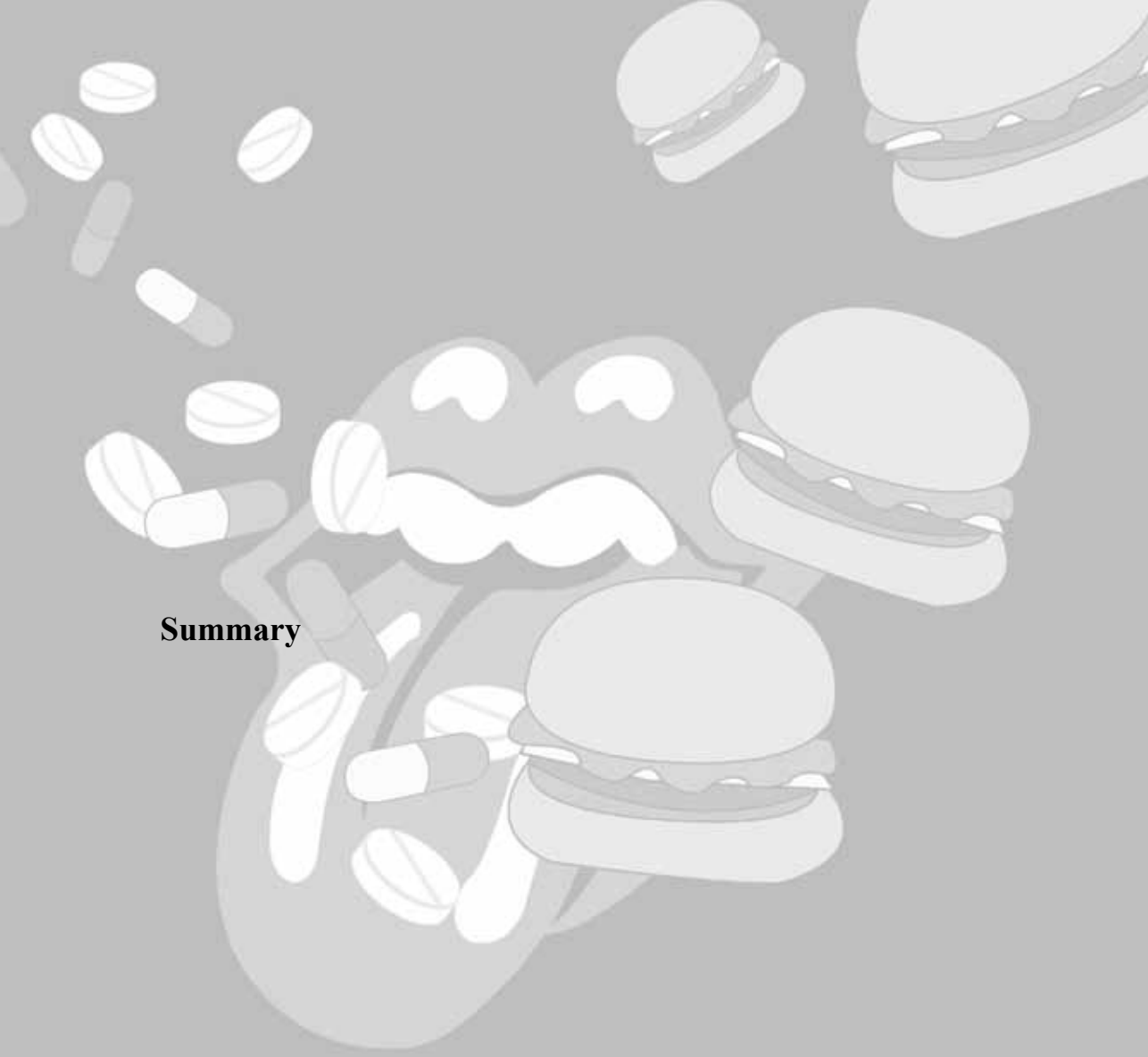

Summary

Summary

Diabetes mellitus is a metabolic disease that currently affects approximately 5% of the general population in Western countries. Type 2 diabetes mellitus (T2DM) accounts for 90-95% of all diabetes cases. In the last decades, the prevalence of T2DM has increased steeply due to a combination of ageing, unhealthy diets, obesity and increasingly inactive lifestyles, as well as an earlier identification of patients with diabetes. It was estimated that in 2007, 740,000 people were suffering from T2DM, a number that is expected to increase to 1.3 million by the year 2025. The risk of developing cardiovascular disease is 2 to 3 fold increased in patients with T2DM, making diabetes one of its most important risk factors. This thesis focuses on T2DM and deals with both the adherence of physicians to guidelines and the adherence of patients to their medication regimens. Patient counseling is the intersection of these topics. Physicians and pharmacists should properly advice patients in order to make an informed decision regarding their use of medication.

Chapter 2 of this thesis dealt with the patients' information needs concerning oral antidiabetic medication at the initiation of T2DM treatment and aimed aim to study opportunities for pharmacists to help patients use their medication adequately. A qualitative study with both semi-structured telephone interviews and patient focus group discussions was performed. Individual patients' comments were categorized and used in a strengths, weaknesses, opportunities and threats (SWOT) analysis exploring the role for the community pharmacist in the field of providing information at the moment of initiation of T2DM oral medication. From interviews with 42 patients and 2 focus group discussions emerged that the GP does not fulfill all information needs. There is an opportunity for pharmacists to contribute to patients' need for information on and discussions about drug related issues. SWOT analysis revealed as main strengths of the pharmacy "expertise" and "service and kindness". Together with more collaboration with GPs and nurse practitioners these strengths give

the pharmacist the opportunity to further develop pharmaceutical care activities. Pharmacists are challenged to increase their visibility as health care provider, whilst keeping logistic service on a high level and improving cooperation with other health care providers.

Diabetes is a chronic disease that requires pharmacotherapy over a lifelong period. Relatively little is known about long-term utilization patterns of oral antidiabetic drugs in daily clinical practice. The aim of the study in Chapter 3 was to describe longitudinal patterns of antidiabetic drug modifications after initiation of oral antidiabetic therapy in a large cohort of patients with T2DM. An observational study on patterns of use and modifications of oral antidiabetic drug therapy was conducted in 3323 patients, who started oral antidiabetic treatment between 1999 and 2007. Drug dispensing data were extracted from pharmacy information systems. Results indicated that changes in international diabetes treatment guidelines recommending metformin as first choice initial drug therapy in all patients were rapidly adhered to by prescribers. Patients starting diabetes treatment with metformin showed fewer modifications to treatment compared to patients initiating treatment with sulfonylureas; hazard ratio 0.84 [CI95%:0.76-0.92] This study shows that adherence to type 2 diabetes treatment guidelines for initial treatment was implemented on a large scale. Longitudinal patterns show that the majority of patients receive a small number of modifications to their drug regimen. Discontinuation rates were relatively low, 10% for metformin and 16% for sulfonylureas. In both cases about half restarted medication therapy.

In parallel, glycemic control has to be maintained over years. Chapter 4 presents a study on longitudinal patterns of HbA1c levels in daily clinical practice of patients with T2DM. In addition, this study aimed to identify characteristics of patients with seemingly poorly controlled diabetes. A retrospective observational cohort study was conducted among patients with T2DM. Data were obtained from a protocolled Diabetes Care System (DCS), situated in West-Friesland,

The Netherlands. All annually measured clinical data, including HbA1c, are registered in a central database. For each patient, linear regression analysis was conducted starting from the second HbA1C measurement to the end of follow up. The slope of the regression line (β-coefficient) was used as an indicator for the individual time trend of the HbA1c progress. Patients were classified as either deteriorating (β-coefficient > +0.1), improving (β-coefficient < -0.1) or stable (β-coefficient between -0.1 and +0.1). Logistic regression analysis was used to calculate the odds ratios of the potential predictors for HbA1c deterioration with combined improving and stable categories as s reference category with 95% confidence intervals. Linear mixed effects model with random intercepts and random slopes was used to assess the association between demographic and clinical factors and HbA1c values. We included 4689 patients in the study cohort. Younger age was associated with an increased risk of deterioration compared to older age adjusted odds ratio 1.44 [CI95%: 1.04-1.99]. Our findings recommend more intensive monitoring and treatment of younger patients. More research is needed for a better understanding of the relationship between younger age and long term increase in HbA1c.

Chapter 5 describes patterns of use of oral antidiabetic medication in relation to glycemic control as reflected by HbA1C levels. The study in this chapter focused on the influence of the initial oral antidiabetic medication and subsequent treatment modifications on the achievement of long term glycemic control in patients with T2DM. A retrospective observational cohort study was conducted among patients with T2DM initiating oral antidiabetic drug (OAD) therapy with metformin or sulfonylureas. We classified patients according to baseline HbA1c-value ≥ 7% or < 7% at the time of treatment initiation. Patients were followed for up to three years to assess whether they reached a Hba1c-value < 7% or ≥ 7%, respectively. Statistical analysis was done by Kaplan-Meier estimation and Cox regression analysis. A total of 531 patients were included in the study cohort. It was found that metformin favored sulfonylureas in patients who started treatment having a baseline HbA1c level ≥ 7.0%, but not in

patients with lower HbA1c levels in which there was no statistically significant difference. Furthermore, 54.9% of the patients who started with sulfonylureas were added metformin during follow up and 40.6% of the metformin starters were added sulfonylureas. The proportion patients starting on metformin as initial treatment increased rapidly and according to treatment guidelines. Our analysis supports the use of metformin as the first choice oral antidiabetic drug in T2DM patients with an HbA1c $\geq$ 7.0%.

Chapter 6 describes discontinuation of treatment among T2DM patients prescribed statins prior to, and after initiation of therapy with oral antidiabetics. Discontinuation rates of statins and oral antidiabetic drugs were also compared. An observational cohort study was conducted among patients initiating treatment with statins prior to or after initiation of oral antidiabetics between 1999 and 2007. Patients were classified as starting statins prior to initiation (Prior users) or after initiation (After users) of antidiabetics. Discontinuation was defined as an interval of 180 days or more between the theoretical end date of a statin/antidiabetic prescription and the dispensing date of the next statin/antidiabetic prescription. We included 3323 starters with oral antidiabetic drugs in our study; 2072 patients initiated statins in the period of observation. Discontinuation rates for statins were higher compared with oral antidiabetics (52.1 vs 15.0%). After users discontinued statin therapy more frequently compared to prior users (62.8 vs 48.2%). Discontinuation of statins was higher compared to that of oral antidiabetic drugs. Patients starting statins after the initiation of oral antidiabetic treatment were more likely to discontinue treatment than patients who initiate statins before the start of oral antidiabetics.

Chapter 7 describes longitudinal patterns of concomitant medication use in patients with T2DM. An observational cohort study was conducted among 2933 new users of oral antidiabetic drugs. Descriptive statistics were used to describe the annual proportions of patients who were prescribed different types of medication both before and after the start of oral antidiabetics. In the year prior to start of oral antidiabetics, 58.7% of the patients used cardiovascular

drugs. In the first year after initiation this increased to 73.9%. In the tenth year after initiation, the proportion of patients using cardiovascular medication was over ninety percent. RAAS inhibitors and statins attributed most to the increase of the overall cardiovascular medication use. The proportion of patients using more than one cardiovascular drug rose steadily. The use of non cardiovascular medication increased from 56.4% ten years before initiation of oral antidiabetics to 77.0% after. The increase in concomitant medication use among patients with T2DM was mostly attributable to an increase of cardiovascular medication according to guidelines aimed at prevention of cardiovascular disease among patients with T2DM.

In the general discussion the relevancy of observational studies with data collected from daily clinical practice in relation with Randomized Clinical Trials (RCTs) is discussed in more depth. RCTs are considered as the gold standard to establish the efficacy of treatments. However, they may not reflect actual drug use in daily clinical practice and may therefore not reflect real life clinical effectiveness.

Samenvatting voor niet-ingewijden

Samenvatting voor niet-ingewijden

Diabetes mellitus is een stofwisselingsaandoening die wordt gekenmerkt door een tekort aan en/of een verminderde gevoeligheid voor insuline, een hormoon dat wordt gemaakt in de alvleesklier en essentieel is bij een goede glucosehuishouding. Diabetes heeft meerdere verschijningsvormen waarvan type 1 en type 2 de belangrijkste zijn. Diabetes komt bij ongeveer 5% van de bevolking voor. Bij beide typen is de hoeveelheid glucose in bloed verhoogd. Bij type 1 diabetes maakt de alvleesklier geen insuline aan, bij type 2 in onvoldoende mate. Daarnaast is de insuline-gevoeligheid van de cellen bij type 2 diabetes verminderd.

Dit proefschrift gaat alleen over type 2 diabetes mellitus (T2DM). Deze vorm van diabetes treft ongeveer 90 à 95% van het totale aantal diabeten. In Nederland werd in 2007 het aantal mensen met T2DM geschat op 740.000. Per jaar worden ruim 60.000 nieuwe gevallen ontdekt. Het aantal patiënten met T2DM zal waarschijnlijk toenemen tot 1,3 miljoen in 2025. Deze toename komt behalve door vergrijzing ook door een toename van overgewicht en een steeds minder actieve leefstijl.

Patiënten met T2DM hebben een 2 tot 3 keer verhoogde kans op het ontwikkelen van hart- en vaatziekten. Roken, hoge bloeddruk, verhoogd cholesterol, overgewicht en te weinig beweging verhogen het risico op hart- en vaatproblemen nog eens extra.

De behandeling

De behandeling van T2DM is gericht op het goed reguleren van de hoeveelheid glucose in het bloed. Dit gebeurt allereerst door mensen te laten afvallen en meer te laten bewegen. Naast deze leefstijl adviezen is gebruik van geneesmiddelen vaak onontkoombaar. In eerst instantie wordt daarbij gekozen voor orale geneesmiddelen (orale antidiabetica of OAD). Bij een deel van de patiënten met T2DM hebben deze orale middelen onvoldoende effect. Zij zullen uiteindelijk

ook insuline moeten gaan spuiten, waarbij de OAD vaak worden gecontinueerd. De meeste patiënten met T2DM worden door de huisarts, ondersteund door een praktijkverpleegkundige behandeld. Hoe een patiënt het beste te behandelen is vastgelegd in de standaard van het Nederlands Huisartsen Genootschap, de NHG standaard. Deze standaard wordt op basis van wetenschappelijke literatuur bijgehouden en beoordeeld. In 1999 en in 2006 zijn de standaarden voor T2DM herzien. In 2013 wordt een nieuwe herziening verwacht.

Wetenschap

De wetenschappelijke basis voor de NHG standaard is gebaseerd op de uitkomsten van "Randomized Clinical Trials", RCTs. Dit type onderzoek is een gecontroleerd wetenschappelijk experiment en wordt gebruikt om de werkzaamheid en veiligheid van medische interventies te testen. RCTs worden beschouwd als de gouden standaard om de werkzaamheid van geneesmiddelen te onderzoeken. In de dagelijkse praktijk kan de behandeling echter soms anders uitpakken. Zo kan een arts niet het juiste middel voorschrijven of de patiënt het heel anders gebruiken dan de bedoeld door de voorschrijver. In dit proefschrift worden alleen zogenaamde observationele onderzoeken behandeld. Dit soort onderzoek kijkt naar patiënten in de dagelijkse klinische praktijk. We onderzoeken of artsen conform de NHG standaard voorschrijven, hoe patiënten de medicatie in de dagelijkse praktijk gebruiken en in hoeverre het gebruik van medicatie invloed heeft op de instelling van T2DM. Tevens onderzochten we de informatiebehoeften van de groeiende groep patiënten met T2DM.

De onderzoeken

In hoofdstuk 2 wordt het onderzoek gepresenteerd naar de informatiebehoefte van patiënten die starten met een OAD. Het idee hierbij was ondermeer dat apothekers hierin een belangrijker rol kunnen spelen. Dit is gedaan door patiënten die starten met medicatie telefonisch interviewen. Deze mensen werden uitgenodigd voor bijeenkomsten (focusgroepen) om nog dieper op de

informatie behoefte in te kunnen gaan. De conclusie van het onderzoek was dat patiënten veel behoefte hebben aan informatie over hun geneesmiddelen. Patiënten verwachten die informatie nog altijd vooral van de arts te krijgen. Tegelijkertijd realiseren patiënten zich dat de arts onvoldoende tijd heeft om deze informatie te geven. De apotheek wordt vooral als een distributiepunt gezien, hoewel patiënten wel overtuigd zijn van de inhoudelijke kennis van apothekers over geneesmiddelen. Apothekers kunnen inspelen op de informatiebehoefte van de patiënt. Daartoe moet de apotheker beter zichtbaar zijn in de apotheek. Tegelijkertijd moet de logistiek van geneesmiddelen op een hoog niveau worden gehouden. Verder werd de samenwerking met andere zorgverleners als verbeterpunt aangegeven. Apothekers en artsen moeten afspreken wie welke informatie geeft en zonodig herhaalt.

In hoofdstuk 3 worden medicatiepatronen beschreven na het starten van OAD.. Van 3323 patiënten uit 17 apotheken die voor het eerst een OAD kregen zijn de geneesmiddelgegevens geanalyseerd. Het middel "metformine" werd in de periode 1999 t/m 2008 steeds vaker als eerste keus voorgeschreven tot in ongeveer 80% van de gevallen vanaf 2005. Metformine werd in de NHG richtlijn pas als eerste keus middel voor alle patiënten aangewezen in 2006 (Sulfonylureum derivaten worden vaak toegevoegd als metformine niet werkzaam genoeg blijkt). Dit laat zien dat voorschrijvers in de onderzoekspopulatie al voorafgaand aan de herziening van de NHG standaard hun voorschrijfbeleid aanpasten. Andere belangrijke bevindingen in dit onderzoek waren dat de meeste patiënten over een langere periode slechts een middel gebruikte of een wijziging in hun medicatie kregen. Het aantal patiënten dat helemaal stopte met OAD was gering. In de groep patiënten die met metformine startte was dat ongeveer 10% tijdens de volgperiode. De helft van deze 10% vervolgde de therapie weer na een half jaar. Voor de groep die startte met sulfonylureum derivaten was dit 16%, waarvan ongeveer de helft ook weer de therapie hervatte.

In hoofdstuk 4 word na de instelling van T2DM op de lange termijn gekeken. Om de instelling van T2DM te controleren wordt gebruik gemaakt van de meting

van het geglycosyleerd ('versuikerd') hemoglobine (HbA1c). De waarde van het HbA1c geeft aan hoe de glucose huishouding was in de 2 tot 3 maanden voor de meting. Van 4686 patiënten die worden gevolgd door het Diabetes Zorgsysteem in West-Friesland is bekeken of de HbA1c waarden door de jaren heen verbeterde, gelijk bleef of verslechterde. Dit was respectievelijk het geval bij 20, 45, 35% van de patiënten. Jongere patiënten (35-45 jaar) hadden 1,4 keer zoveel kans om te verslechteren vergeleken met de oudste groep (55+). Bij de middengroep (45-55 jaar) was dit 1,3 keer zo groot. De achtergrond van deze bevinding is niet geheel duidelijk. Mogelijk hebben patiënten die al op jongere leeftijd T2DM ontwikkelen een moeilijker te behandelen aandoening of hebben zijn een ongezonder levensstijl. Meer onderzoek hiernaar is nodig maar op basis van deze bevindingen is het aan te raden jongere patiënten intensiever te volgen en te behandelen.

In hoofdstuk 5 worden de patronen van het gebruik van orale antidiabetica gecombineerd met de instelling van T2DM op basis van de HbA1c waarden. Er werd in het bijzonder gekeken naar verschillen in de bereikte HbA1c instelling tussen patiënten die de behandeling starten met metformine of met een zogenaamde sulfonylureum (SU) derivaat. Uit dit onderzoek bleek dat patiënten die met metformine begonnen minder vaak een tweede middel nodig hadden bovendien daalden hoge HbA1c waarden vaker bij de metformine starters en verslechterden HbA1C waarden minder vaak bij metformine starters. Hoewel er nog enige onzekerheid is over deze resultaten doordat er geen sprake is van een formele onderzoeksopzet, onderbouwen deze resultaten de keus voor metformine als eerste stap in de behandeling van T2DM. Dit onderzoek voegt daarmee iets toe aan RCTs die hebben laten zien dat metformine ook gunstiger is op cardiovasculaire eindpunten.

De behandeling van T2DM bestaat uit meer dan alleen controle van he bloedsuiker. Naast een goede glucosehuishouding is het van belang de bloeddruk en het cholesterolgehalte in het bloed te reguleren. Een verhoogd cholesterol verhoogt de kans op hart- en vaatziekten, dit geldt in hogere mate bij diabeten. Voor

regulering van het cholesterolgehalte worden statines gebruikt. In hoofdstuk 6 is bestudeerd in welke mate patiënten met T2DM over de jaren behandeld zijn met statines en hoe lang patiënten deze middelen blijven gebruiken. Van 3323 patiënten startten 2972 patiënten met een statine in de periode van 1999 t/m 2007. In deze periode nam het aantal patiënten met T2DM dat op jaarbasis een statine gebruikte toe van 10% in 1999 tot 60% in 2007. Het bleek dat patiënten statines vaker staakten dan de OAD, ongeveer 1,7 keer. Verder bleken patiënten die het statine later gestart waren dan het middel tegen T2DM vaker het statine staakten dan patiënten die al een statine gebruikten op het moment dat zij voor het eerst een OAD kregen. Mogelijk speelt hierbij een rol dat patiënten die al een statine gebruiken voorafgaand aan de start van een OAD daar een bepaalde reden voor hebben, zoals een doorgemaakt hartinfarct of CVA of een erfelijk verhoogd cholesterolgehalte. Deze onderliggende redenen zijn mogelijk een betere motivatie om de cholesterolverlager te blijven gebruiken. De conclusie van dit onderzoek is dan ook dat het van belang is de therapietrouw met statine te bewaken in het bijzonder bij patiënten die een statine toegevoegd krijgen aan de medicatie tegen T2DM, zonder aanvullende redenen zoals een hartinfarct of CVA.

Wanneer patiënten langere tijd T2DM hebben, zeker wanneer deze niet goed gereguleerd is, kan dit tot complicaties leiden zoals hart of herseninfarcten, een verhoogde kans op infecties, maagledigingsstoornissen en een verlies van gevoel in vingers en tenen. Deze complicaties kunnen op hun beurt leiden tot een toename in het geneesmiddelgebruik. In hoofdstuk 7 is bestudeerd wat voor middelen patiënten gebruiken voor en na het starten van middelen tegen T2DM. Het gebruik van middelen tegen hart- en vaatziekte nam spectaculair toe rond de eerste uitgifte van een oraal middel tegen T2DM terwijl het gebruik van andere middelen, zoals bijvoorbeeld pijnstillers, antibiotica en antidepressiva nauwelijks stijging vertoonde. De toename in het gebruik van hart- en vaatziekte middelen is vooral terug te voeren op het profylactisch gebruik van bloeddruk en cholesterolverlagende middelen zoals dat onder andere wordt aangeraden in

de NHG standaard.

In het laatste hoofdstuk worden de resultaten uit de onderzoeken samengevat en in een bredere context bediscussieerd. Samengevat kan worden gesteld dat voorschrijvers in een gebied waar sprake is van een sterk geprotocolleerd diabetes zorgsysteem zich in sterk mate houden aan richtlijnen voor de behandeling van T2DM. De meerderheid van de patiënten met T2DM blijkt gedurende langere tijd met beperkte wisselingen in de medicatie stabiel ingesteld. Voor een klein deel van de patiënten geldt dit niet. Zorgwekkend is dat dit vooral jongere patiënten zijn waarbij de gevolgen van langdurige slechte instelling van de diabetes op de lange termijn ernstig kunnen zijn. Aandachtspunten zijn verder de therapietrouw met name met bijkomende medicatie met cholesterolverlagende medicatie. Patiënten hebben behoefte aan veel informatie over T2DM. Apothekers kunnen mogelijk de instelling van patiënten met T2DM verder bevorderen door goede begeleiding van deze patiënten.

Dankwoord

Dankwoord

“It’s the singer not the song” zong Mick Jagger in de jaren 60 toen ik een jaar of twee was.[1] Wat hij daar mee wilde zeggen was dat tekst niet zonder goede presentatie en begeleiding kan. Nu zou ik mijzelf natuurlijk niet willen vergelijken met een grootheid als Mick Jagger. Maar de teksten in dit boekwerk had ik nooit kunnen maken zonder bijgestaan te worden door een bijzondere groep mensen. Hetzelfde geldt voor Jagger die natuurlijk nooit zo groot was geworden zonder een uitzonderlijke band, die samen met hem “The Rolling Stones” vormen. Het was een pittig traject en soms een zware last. Maar we zijn er samen doorheen gegaan, met de mensen van de Universiteit van Utrecht en de Vrije Universiteit.[1-4] Ik wil in dit dankwoord dan ook de vergelijking maken met de mensen die betrokken zijn geweest bij de totstandkoming van dit proefschrift en de bandleden van de Rolling Stones. Velen weten dat de Stones voor mij meer zijn dan alleen muziek.[5]

Marcel Bouvy. Beste Marcel, ik zou jou graag de functie van drummer willen geven en een vergelijking willen maken met Charlie Watts. De basis van een band is de drummer, die gedreven voor de voortgang van de muziek zorgt. Zonder de creatieve inbreng van Watts hadden de Stones nooit geweest wat ze nu nog steeds zijn. Ik heb veel geleerd van je scherpte, je gevoel voor detail, je gedrevenheid, je begrip en vooral ook je geduld.[6] Regelmatig floot je mij terug omdat het nog niet goed genoeg was, waarbij ik mijzelf soms bijna dom voelde.[7] Door toch aan je hoge eisen vast te houden heb je mij geholpen om op een hoger plan te acteren.[8]

Giel Nijpels. Beste Giel, je bent nog een stuk jonger en je ziet er ook veel gezonder uit, maar ik zou jou graag met Keith Richards willen vergelijken. Richards is de man die door zijn specifieke gitaarspel verantwoordelijk is voor het rauwe oergeluid van de Stones. Jij hebt dit natuurlijk mogelijk gemaakt door de data die je ingebracht hebt uit het Diabetes Zorg Centrum. Richards is

een hele belangrijke factor geweest in het doorzettingsvermogen van de band, dat heb je ook op mij weten over te brengen. Ik heb enorm genoten van ons wekelijkse telefonisch overleg waar je mij elke keer weer de moed gaf door te zetten.[9, 10] Naast je kennis werkte ook je opgewektheid aanstekelijk. Ik kon daar ook erg van genieten tijdens de EASD congressen in Stockholm en Berlijn.[11]

Patrick Souverein. Beste Patrick samen met Marcel vormde jij, net als Bill Wyman met Charlie Watts, de basis van dit boekwerk. Net als Wyman veel invloed op de Stones had, had jij dat op dit boekwerk. Stiekem was hij het meest "Rock 'n Roll".[12] Met fijnmazige database structuren legde jij de basis voor de analyses die we deden, net zoals Wyman dat met zijn basgitaar bij de Stones deed.[13] Ik heb respect voor je kunde en heb erg veel van je geleerd.[14]

Jacqueline Hugtenburg. Beste Jacqueline, "last but zeker niet least" van het vaste team. Ik zou je graag willen vergelijken met Ron Wood. De tweede gitarist van de Stones. Wood heeft aan de Stones bijgedragen zoals jij aan dit proefschrift hebt bijgedragen. Hij is de meester van de juiste toon op het juiste moment.[15] Je opgewektheid, opbouwendheid en opbeurendheid hebben me gesteund om dit te volbrengen.[16]

Als laatste vergelijking zou ik Lisa Fischer willen inbrengen. En wel in de persoon van Jacqueline Dekker. Als zeer gewaardeerd achtergrondzangeres heeft Fischer veel aan de Stones bijgedragen. Legendarisch is haar vocale solo die zij geeft tijdens "Gimme Shelter".[17] Zo ook jou vlijmscherpe bijdragen aan een aantal onderzoeken en onderzoeksoverleg.

Ik wil Laura Welschen en Esther van 't Riet heel hartelijk bedanken voor de bijdragen die zij geleverd hebben aan verschillenden onderzoeken in dit proefschrift.[18] Verder wil ik Rolf van Hulten heel hartelijk danken voor zijn bijdrage aan het onderzoek in hoofdstuk 2 van dit proefschrift. Dit was ook de eerste publicatie.[19] Het was altijd gezellig om samen, onder het genot van een kop koffie, de hedendaagse farmacie door te nemen.

Ik zal ongetwijfeld mensen vergeten persoonlijk te bedanken. Niettemin dank voor de steun en het vertrouwen dat mij steeds weer geholpen heeft om door te

gaan.[20] En natuurlijk de groep “fans” die eindeloos gewacht hebben tot het dan toch eindelijk zover was.[21] Gesmar en Gijsje heel veel dank voor het geduld bij de opmaak!![22]

Ageeth, ik bewonder je doorzettingsvermogen. Zeker ook in hetgeen je in de afgelopen jaren opgebouwd hebt.[3]

Als laatste wil ik mijn zoons Stijn en Bart bedanken, domweg omdat jullie er zijn, ik ben apentrots en ik houd onbeschrijfelijk veel jullie en dat wordt alleen maar meer!! Jullie zijn echt heel stoer en dapper.[23-24] Jaag vooral je dromen achterna en grijp de kansen om ze waar te maken.[25]

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“Please allow me to introduce myself”

Egbert Lamberts was born in Almelo, Twente, The Netherlands on September the 7th 1965. He finished secondary school in 1986. From the age of eleven he started playing the guitar and plays it ever since. He started his study “Pharmaceutical sciences” in 1986 and became a pharmacist in 1994.
He owned “Apotheek Lamberts” in IJsselstein from 1994 till 2005 and worked as a community pharmacist.
From 1997 till 2000 he studied business administration at the Sheffield University Management School and graduated as MBA.
In 2007 he started as a part time PhD student and as lecturer Pharmaceutical and Healthcare Business at the Utrecht University at the division of Pharmacoepidemiology and Pharmacotherapy.
Egbert Lamberts has two children: Stijn and Bart.

Notes

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