DIABETES CARE IN GENERAL PRACTICE

From monitoring to insulin therapy

A.N. Goudswaard

The author wishes to thank Novo Nordisk Pharma B.V. for the unrestricted grant through which the studies in this thesis were made possible.
This thesis was printed with support from the Dutch Diabetes Research Foundation and the Julius Center for Health Sciences and Primary Care

Cover Design: Gerard van der Krogt, Utrecht
Layout: Gerard van der Krogt, Utrecht
Printed by: PlantijnCasparie, Nieuwegein

CIP-gegevens Koninklijke Bibliotheek, Den Haag
A.N. Goudswaard
Diabetes care in general practice
Utrecht: Universiteit Utrecht, Faculteit Geneeskunde
Thesis Universiteit Utrecht. With a summary in Dutch.

Subject headings: type 2 diabetes, primary care, glycaemic control, self-management education, insulin therapy, general practice, systematic review

ISBN 90-393-3702-0

DIABETES CARE IN GENERAL PRACTICE

From monitoring to insulin therapy

with a summary in Dutch

Proefschrift

ter verkrijging van de graad tot doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus, prof. dr W.H. Gispen ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op dinsdag 25 mei 2004 des middags om 12.45 uur

door

Alexander Nicolaas Goudswaard

geboren op 6 september 1950 in Tinaarlo

Promotor

Prof. dr G.E.H.M. Rutten
Julius Center for Health Sciences and Primary Care

Co-promotores

Dr R.P. Stolk
Julius Center for Health Sciences and Primary Care

Dr H.W. de V alk
Department of Internal Medicine

University Medical Center Utrecht
The Netherlands

Contents

Chapter 1

General Introduction

Introduction

In 1978, in the days of my vocational training as a future general practitioner, a middle-aged man had made an appointment with complaints of fatigue, weight loss and thirst. It was not difficult to consider diabetes, and I performed diagnostic stick urinalysis. After the suspect colour showed up, I referred the patient to the local diabetologist who confirmed the diagnosis and hospitalized the patient the same afternoon. Subsequently, he sta yed under specialist care, and the general practice had no further influence on his diabetes management.

Nowada ys, some twenty-five years later, the involvement of primary care in the management of patients with type 2 diabetes has increased dramatically. For example, my own practice maintains a record of more than eighty type 2 patients (almost three per cent of the entire practice population), and a team consisting of general practitioners, practice assistants, and a diabetes nurse are involved in the daily care of this patient group. This includes: three-monthly reviews, periodic recall, laboratory tests, additional consultations for other complaints and therapy-adjustments, educational sessions for patients and partners, referrals for diet advice, foot care and eye examination, and last but not least, the initiation of insulin therapy. It is fascinating to recognize that these important changes in diabetes care took place fully within the period of one professional career. Additionally, in the Netherlands new tasks for the general practice, like diabetes care, greatly supported the development of practice guidelines. In 1989 the Diabetes Mellitus Type II guideline was the first in an extensive series of so called “Standards” from the Dutch College of General Practitioners (DCGP). [1] Over all, both my involvement as a GP in the daily care for patients with diabetes, and my work as guideline developer for the DCGP formed a main source of inspiration for writing this thesis.

Evolution in diabetes care

The personal observations described in the first paragraph illustrate the changes in the care of patients with type 2 diabetes during the last two decades. In the seventies and eighties in the Netherlands, and in other countries like the United Kingdom, general practitioners (GPs) acquired more responsibility for the surveillance of their patients, with a gradual transition from secondary to primary care, not necessarily driven by guidelines, nor by working agreements with local specialists. [2-6] This so called ‘substitution of care’ was greatly urged by policy makers, unmistakably for economic reasons. [7] In parallel to this, the general opinion became widely accepted that

patients should be treated at the lowest possible echelon of care, without compromising quality. Individual GPs and their professional organizations seized this new challenge with enthusiasm, resulting in the publication of a first treatment and control scheme for type 2 diabetes, [8] followed in 1983 by a formal integration of diabetes care in the complex of job responsibilities for GPs. [9]

Six years later this process continued with the publication of the first guideline of the Dutch College of General Practitioners (DCGP). [1] Perhaps not coincidentally , in the same year European health care authorities, patient organisations and diabetes experts convened a conference in Saint Vincent (Italy), which resulted in the well known "Saint Vincent Declaration". [10] The motivation for this meeting stemmed from the notion that the impact of diabetes was seriously underestimated. The Declaration established ambitious goals for diabetes care.

In the decade after the Declaration results from long-term trials became available, along with the introduction of more powerful treatment options for cardiovascular risk factors. [11-18] It proved that patients with diabetes were at considerably increased risk of cardiovascular complications compared to the general population, [6,19] and within the diabetic population, h yperglycaemia appeared to be correlated with increased morbidity and mortality. [19,20] One of the main findings of the United Kingdom Prospective Diabetes Study (UKPDS) was that 'intensive' glucose control compared with 'conventional' treatment, resulted in a significant reduction of microvascular end-points, though not a reduction of macrovascular complications or total mortality. [13] Conversely , tight control of blood pressure appeared more successful in preventing macrovascular complications than tight glucose control. [15,16] These parts of the UKPDS gave cause for considerable dispute concerning the interpretation of its results and the implications for daily practice. [21-25] By now it is accepted that within the realms of diabetes care, glycaemic control is just one of the key areas, and that reducing blood pressure, treating hyperlipidaemia and stopping smoking are also of importance. [26,27]
Due to these studies guidelines became more evidence-based. [28,29] Although this feature should favour the use of recommendations, [30] it appeared difficult to implement them in daily practice. [31-34] Research in primary care both in and outside the Netherlands revealed significant variability in the delivery of diabetes care, while a substantial percentage of patients did not reach the targets of glycaemic control, or other cardiovascular risk factors. [35,36] A variety of contextual, physician and patient factors are held responsible for this deficit. [31,33,36-39] Unstructured care by disinterested and unsupported GPs was

found to be ineffective and waste of resources. [40,41] Conversely , prompting systems that recalled patients for appointments, adherence to standard management protocols including well-defined targets, and outreach visits from trained facilitators appeared to be features of more successful care. [32,37,40] In the Netherlands, several long-term programmes were initiated by GPs, local GP Laboratory Corporations and hospitals, to improve adherence to the diabetes guideline from the DCGP. A number of these initiatives were scientifically evaluated. One of the first projects of this kind was the Utrecht Diabetes Programme (UDP), set up in 1990 in the region where the studies in this thesis were planned. [42] Ten years after the start of this shared-care project 110 GPs had included 1900 patients. An evaluation in 1997 showed better record keeping in UDP patients compared with non-UDP patients. In addition, glucose and lipid levels and diastolic blood pressure had improved significantly after inclusion in the UDP. [43] In other regions such programmes were also initiated and evaluated. In general, they showed increased ph ysical examination and laboratory testing in diabetic patients (so-called process measures), but the effects on glycaemic control and cardiovascular risk factors (i.e. outcome measures) were variable. Besides, a considerable number of patients did not meet the recommended goals of care. [44-46] These results were comparable with research in primary care outside the Netherlands. [34,36,41.]

Aims of the thesis

The studies and research questions in this thesis cover essential parts of management and treatments across the disease process of patients with type 2 diabetes in primary care. This includes the following themes: monitoring of clinical data, predictors of poor glycaemic control, treatment of hyperglycaemia with oral hypoglycaemic agents and patient education, and the initiation of insulin therapy. The central aim is to investigate the effectiveness of these themes in the current management of h yperglycaemia in patients with type 2 diabetes in primary care.

Monitoring of clinical data: from process to outcome

The shift of diabetes care towards the general practice (supported by a variety of shared-care projects), together with the dissemination of evidence-based practice guidelines, emphasised the necessity for GPs to comply with the guideline recommendations in order to reach the targets of care. These targets should include both process - (e.g. careful monitoring of results from blood tests) and outcome measures (e.g. level of blood glucose). However, it is unclear whether improved process measures are related to improved outcome measures. In other words: is it to be expected that efforts to monitor more

data from reviewed patients (as encouraged by guidelines and post-graduate education), will be followed by improved outcome, such as better glycaemic control? The recognition of such a possible discrepancy is of importance, since focusing on the process of diabetes care without simultaneously improving its outcomes might be considered waste of time and resources of both patients and doctors.

The first objective is to investigate the relationship between monitoring of data and the outcome of diabetes care.

Subsequently , we will focus on patients with inadequate glycaemic control, aiming at identifying characteristics of patients, practices and care that could predict poor glycaemic control. Such information might be helpful to improve the quality of diabetes care.

The second objective is to identify characteristics of patients, practices and care that could predict poor glycaemic control.

Improving glycaemic control without insulin

It is assumed that a considerable percentage of patients with type 2 diabetes ultimately requires insulin to maintain acceptable glycaemic control. Data from secondary care suggest that insulin therapy could be prevented or delayed through maximizing oral therapy, and education by a diabetes nurse.[47] However , to what extent these approaches are feasible and ef fective in primary care is unknown. Moreover, in contrast with countries like the UK, in Dutch primary care support of the GP by nurse facilitators and diabetes nurses has started only recently, so the influence on management and outcome of diabetes is not well established yet. Combining these facts, we decided to study the effect of optimising oral medication with help from a nurse facilitator. Subsequently we studied the effects of an educational programme provided by a diabetes nurse for patients with inadequate glycaemic control despite using maximal oral medication.

The third objective is to study the effects of optimising oral h ypoglycaemic therapy with help from a nurse facilitator in patients with inadequate glycaemic control.

The fourth objective is to study the effects of an educational programme by a diabetes nurse in patients with inadequate glycaemic control despite maximum dosages of hypoglycaemic agents.

Improving glycaemic control with insulin

In contrast with the first Dutch diabetes guideline (1989), the revised version in 1999 introduced insulin therapy as optional for the GP. Until that moment, in the Netherlands most patients needing insulin therapy were referred to secondary care. This new guideline made it possible for the GP to initiate insulin treatment, provided a number of conditions were met, amongst others cooperation with a diabetes nurse. However, the guideline leaves to the GP the choice for either the use of insulin in combination with oral agents or as monotherapy, since it is unclear which of both is most preferable.
To clarify this, firstly we carried out a study in general practice comparing insulin monotherapy versus insulin with oral hypoglycaemic agents. We included in particular outcome measures as treatment satisfaction, general well-being and fear of injections, since these issues were hardly studied in insulin using type 2 diabetes patients. Secondly, a systematic review of randomised controlled trials was performed in order to determine the ef fects of insulin monotherapy compared with combination therapy.

The fifth objective is to study the effects of insulin monotherapy compared with insulin in combination with oral hypoglycaemic agents.

Structure of the thesis

The ordering of the studies follows the structure of the diabetes guidelines of the DCGP. A brief overview of studies is shown in Figure 1.

Practices and patients

The studies were carried out in the Utrecht region (city of Utrecht and surrounding cities) between July 1999 and February 2003. Only patients with known type 2 diabetes registered in general practice, and treated by the GP were included. Initially, 110 practices were invited to take part, of which 52 agreed to participate in the first part of the study. In addition, for the two randomised controlled trials (Chapter 5 and 6) another ten practices were incorporated. In order to avoid a selection of practices with a special interest in diabetes, which could reduce the generalizability of the findings, both practices connected to the Utrecht Diabetes Programme (UDP), and non-UDP practices were invited. Of the participating practices 27 (52%) were connected to the UDP, and of the practices that refused to participate, 55% were involved in the UDP.

Process and outcome

According to the guidelines patients should be reviewed 3-monthly, while once a year a more thorough check-up is recommended. This ‘annual review’

includes history taking, physical examination, and laboratory tests. Data should be recorded carefully to provide an accurate overview of the course of the disease, and to justify continuing or changing treatment.

In Chapter 2 we assess the quality of data recording by GPs in 1641 medical records of patients treated in general practice. Subsequently we in vestigate the association between completeness of medical records and glycaemic control.
The research questions are:
- Which relevant data are missing most of ten?
- What proportion of data is found to exceed target values?
- Is the completeness of data recording associated with improved control of glycaemia?

Chapter 3 investigates in the same population whether characteristics of patients, practices and diabetes care could predict poor glycaemic control. The research question is:
- Which characteristics of patients, practices or diabetes care do predict poor glycaemic control?

Improving glycaemic control without insulin

In patients with type 2 diabetes oral blood glucose lowering medication should be initiated if dietary measures and increased physical activity were insufficient to reach the target blood glucose levels after 3 months. The Dutch guidelines recommend increasing the dosage of this medication in line with the clinical response every 2 to 4 weeks until target blood glucose levels have been achieved.

In Chapter 4 we investigate the effect of this policy, if it is followed rather strictly and supported by outreach visits from a nurse facilitator. The following research question is addressed:
- What are the effects on glycaemic control of encouraging GPs to adjust oral
  medication by a target-driven flow-chart and outreach-visits from trained facilitators in patients without satisfactory glycaemic control?

Patient education is an essential part of diabetes management. Educational programs should focus on general knowledge on diabetes, adherence to medication, lifestyle changes, and if possible self-monitoring of blood glucose. However, the long-term effects are unclear and not well investigated in primary care.

In Chapter 5 we describe the results of a randomised controlled trial comparing an educational programme by a diabetes nurse with usual care in 54 patients treated with maximal dosages of oral hypoglycaemic agents, needing to start with insulin therapy.
The research question of this study is:

- What are the short- and long-term effects on glycaemic control and the need for insulin therapy of a six month educational programme in patients without satisfactory glycaemic control despite treatment with maximal dosages of oral hypoglycaemic agents?

Improving glycaemic control with insulin

Insulin therapy is recommended as last step for patients who fail to achieve or maintain the target for glycaemic control with maximal dosages of oral hypoglycaemic agents. Whether insulin should be applied as monotherapy, or in addition to a present regimen of oral agents is still a subject for debate. The Dutch guidelines put forward: "There are two ways in which a patient may be treated with insulin. Insulin may be supplementary to existing oral treatment, or it may replace the tablets. There is no clear preference for either of these two methods".

Chapter 6 describes the results of a randomised controlled trial comparing insulin monotherapy (mixed insulin twice daily) with insulin combination therapy (bedtime insulin plus daytime oral hypoglycaemic agents) in 64 patients without satisfactory glycaemic control despite maximal dosages of oral hypoglycaemic agents.

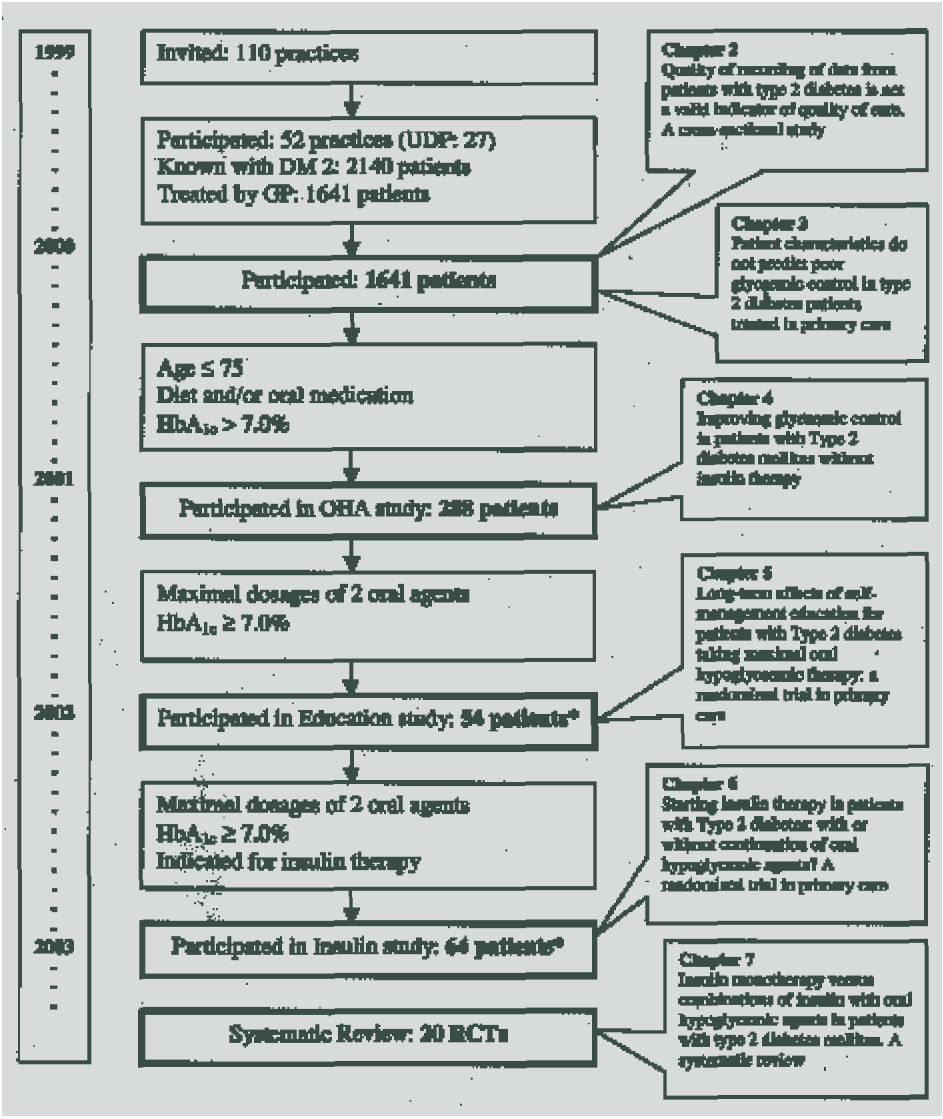
Chapter 7 draws upon the results of a systematic review carried out within the Metabolic and Endocrine Disorders Group of the Cochrane Collaboration. The objective of this review is to assess the effects of insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in insulin naïve patients with type 2 diabetes mellitus.
In both chapters we search for an answer on the following question:

- What are the effects on glycaemic control, side effects, and quality of life issues of insulin monotherapy compared with insulin combined with oral hypoglycaemic agents in patients without satisfactory glycaemic control despite treatment with oral hypoglycaemic agents?

Discussion

Chapter 8 presents and discusses the main conclusions of the studies in this thesis. Additionally, recommendations are made for the management of type 2 diabetes in primary care, together with implications for future diabetes

Figure 1 Overview of practices, patients and studies



UDP Utrecht Diabetes Programme; DM diabetes mellitus; OHA oral hypoglycaemic agents

* additional practices invited: 10

References

1 Cromme PVM, Mulder JD, Rutten GEHM, Zuidweg J, Thomas S. Diabetes Mellitus Type II. NHG-standaard. Huisarts Wet 1989; 32: 509-12.

2 Wilks JM. Diabetes-a disease for general practice. J R Coll Gen Pract 1973; 23: 46-54.

3 Wilkes E, Lawton EE. The diabetic, the hospital and primary care. J R Coll Gen Pract 1980; 30: 199-206.

4 van Weel C, van Zelst PAM. Diabetes mellitus in a general practice II (in Dutch). Huisarts Wet 1983; 214-7.

5 Rutten G, van Eijk J, de Nobel E, Beek M, van der Velden H. Feasibility and ef fects of a diabetes type II protocol with blood glucose self-monitoring in general practice. Fam Pract 1990; 7: 273-8.

6 Reenders K, de Nobel E, van den Hoogen HJ, Rutten GE, van Weel C. Diabetes and its long term complications in general practice: a survey in a well-defined population. Fam Pract 1993; 10: 169-72.

7 Staatssecretaris VOMIL. Structuurnota gezondheidszorg. 1974. Den Haag, Staatsuitgeverij.

8 Diabetes mellitus (special). Huisarts Wet 1979; 22 (supplement 3).

9 Springer MP. Basistakenpakket van de huisarts. 1983. Utrecht, LHV.

10 Diabetes care and research in Europe: the Saint Vincent declaration. Diabet Med 1990; 7: 360.

11 DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-86.

12 Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Sim vastatin Survival Study (4S). Diab Care 1997; 20: 614-20.

13 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphon ylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 83753.

14 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive bloodglucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65.

15 UK Prospective Diabetes Study (UKPDS) Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 39). BMJ 1998; 317: 713-20.

16 UK Prospective Diabetes Study (UKPDS) Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). BMJ 1998; 317: 703-13.

17 Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Ef fects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351: 1755-62.
18 Yusuf S, Lonn E, Bosch J, Gerstein H. Summary of randomized trials of angiotensin converting enzyme inhibitors. Clin Exp Hypertens 1999; 21: 835-45.
19 de Grauw WJC, van de Lisdonk EH, van den Hoogen HJ, van Weel C. Cardiovascular morbidity and mortality in type 2 diabetic patients: a 22 year historical cohort study in Dutch general practice. Diabet Med 1995; 12: 117-22.
20 Groeneveld Y, Petri H, Hermans J, Springer MP. Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. Diabet Med 1999; 16: 2-13.
21 Zaat J. Tight control of diabetes is nonsense [in Dutch]. Huisarts Wet 2000; 43: 374.
22 McCormack J, Greenhalgh T. Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data. United Kingdom prospective diabetes study. BMJ 2000; 320: 1720-3.
23 Ewart RM. The case against aggressive treatment of type 2 diabetes: critique of the UK prospective diabetes study. BMJ 2001; 323: 854-8.
24 Holman RR, Matthews DR, Meade T. Commentary: UKPDS is well designed and clinically important. BMJ 2001; 323: 857.
25 Rutten GEHM, de Grauw WJC, Reenders K. Tight control of diabetes is useful and necessary [in Dutch]. Huisarts Wet 2002; 45: 548-53.
26 Adler A. Does tight control of hyperglycaemia limit morbidity and mortality in type 2 diabetes? In: Williams R, Herman W, Kinmonth A-L, Wareham NJ, editors. The evidence base for diabetes care. Chichester,England: John Wiley & Sons, 2002.
27 Jarrett RJ. Does tight control of hyperglycaemia limit morbidity and mortality in type 2 diabetes?: a commentary. In: Williams R, Herman W, Kinmonth A-L, Wareham NJ, editors. The evidence base for diabetes care. Chichester, England: John Wiley & Sons, 2002.
28 Rutten GEHM, Verhoeven S, Heine RJ, de Grauw WJC, Cromme PVM, Reenders K, van Ballegooie E, Wiersma Tj. Diabetes Mellitus Type 2. NHG-standard (first revision) [in Dutch]. Huisarts Wet 1999; 42: 67-84.
29 European Diabetes Policy Group (EDPG). A desktop guide to Type 2 diabetes mellitus. European Diabetes Policy Group 1999. Diabet Med 1999; 16: 716-30.
30 Grol R, Dalhuijsen J, Thomas S, Veld C, Rutten G, Mokkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. BMJ 1998; 317: 858-61.
31 Konings GPJM, Rutten GEHM, Wijkel D. Why don't general practitioners comply with the NHG-Standard Diabetes Mellitus Type II? [in Dutch] Huisarts Wet 1995; 38: 602-7.
32 Jacobs ML, Akkerhuis KM, van Dijk MJ, Kuis FB, Veldkamp RT, Weber RF. Improved diabetes control through strict observance of the standard 'Type II Diabetes

Mellitus' from the Dutch College of Family Physicians [in Dutch]. Ned Tijdschr Geneeskd 1995; 139: 1241-5.
33 Helseth LD, Susman JL, Crabtree BF, O'Connor PJ. Primary care physicians' perceptions of diabetes management. A balancing act. J Fam Pract 1999; 48: 37-42.
34 Hetlevik I, Holmen J, Midthjell K. Treatment of diabetes mellitus - physicians' adherence to clinical guidelines in Norway. Scand J Prim Health Care 1997; 15: 193-7.
35 Konings GPJM, Wijkel D, Rutten GEHM. The Dutch standard for Diabetes Mellitus Type II, does it work? [in Dutch]. Huisarts Wet 1995; 38: 10-4.
36 Khunti K, Baker R, Rumsey M, Lakhani M. Quality of care of patients with diabetes: collation of data from multi-practice audits of diabetes in primary care. Fam Pract 1999; 16: 54-9.
37 Pringle M, Stewart-Evans C, Coupland C, Williams I, Allison S, Sterland J. Inf luences on control in diabetes mellitus: patient, doctor, practice, or delivery of care? BMJ 1993; 306: 630-4.
38 Dunn N, Pickering R. Does good practice organization improve the out come of care for diabetic patients? Br J Gen Pract 1998; 48: 1237-40.
39 Larme AC, Pugh JA. Attitudes of primary care providers toward diabetes: barriers to guideline implementation. Diabetes Care 1998; 21: 1391-6.
40 Greenhalgh PM. Shared care for diabetes. A systematic review. Occasional paper 67. The Royal Collage of General Practitioners, 1994.
41 Griffin S. Diabetes care in general practice: meta-analysis of randomised control trials. BMJ 1998; 317: 390-6.
42 de Valk HW. The Utrecht diabetes programme [in Dutch]. In: Bilo HJG, van Nunen F, editors. Shared care projects of diabetes mellitus: a review of the situation in 2000. Zwolle: Isala klinieken, 2000: 236-44.
43 Rutten GE, Maaijen J, Valkenburg AC, Blankestijn JG, de Valk HW. The Utrecht Diabetes Project: telemedicine support improves GP care in Type 2 diabetes. Diabet Med 2001; 18: 459-63.
44 Bouma M, Dekker JH, van Eijk JT, Schellevis FG, Kriegsman DM, Kostense PJ, Heine RJ. The effects of the introduction of a quality system in general practice on the glycaemic control of Type 2 diabetic patients. In: Bouma M. Improving diabetes care in general practice [Thesis]. Amsterdam: Vrije Universiteit, 1999.
45 Groeneveld Y, Petri H, Hermans J, Springer M. An assessment of structured care assistance in the management of patients with type 2 diabetes in general practice. Scand Prim Health Care 2001; 19: 25-30.
46 de Sonnaville JJ, Bouma M, Colly LP, Deville W, Wijkel D, Heine RJ. Sustained good glycaemic control in NIDDM patients by implementation of structured care in general practice: 2-year follow-up study. Diabetologia 1997; 40: 1334-40.
47 Goddijn PP, Meyboom-de Jong B, Feskens EJ, van Ballegooie E, Bilo HJ. Differences between diabetes mellitus type 2 patients switched and not switched over to insulin treatment after specialist consultation [in Dutch]. Ned Tijdschr Geneeskd 1998; 142: 1023-6.

Chapter 2

Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study

Published as:
Goudswaard AN, Lam K, Stolk RP and Rutten GEHM. Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study. Family Practice 2003; 20: 173–7.

Abstract

Background

The quality of recording of clinical data in diabetes care in general practices is very variable. It has been suggested that better recording leads to improved glycaemic control.

Objectives

The purpose of this study was to assess the completeness of recording by GPs of data from type 2 diabetes patients; to compare recorded and missing data; and to in vestigate the association between completeness and glycaemic control.

Methods

A cross-sectional survey was carried out in 52 general practices. Medical records were scrutinized for the presence of 11 variables. Examining patients through an active approach completed incomplete records. We compared recorded and unrecorded items. Completeness of recording was determined at both patient and practice levels.

Results

Fifty-two general practices with 1641 type 2 diabetes patients cared for by the GP participated. The frequency of absence of any particular item ranged from 12 to 70%. Weight, systolic blood pressure and HbA_{1c} were slightly lower in patients with those items missing on their files, and more such patients were non-smokers ($P< 0.05$). The percentage of patients with unrecorded variables that exceeded target values ranged from 39 to 75. Neither at practice level nor at patient level was any association between the completeness of the data recording and HbA_{1c} found.

Conclusion

Records often were incomplete, which hampers a systematic approach to care of diabetic patients. However, the lack of association between completeness of data recording and control of glycaemia indicates that improved recording is not a valid indicator of good quality of care.

Introduction

The management of diabetes mellitus type 2 in general practice should focus on both glycaemic control and cardiovascular risk factors. Reducing these factors decreases the risk of diabetic complications. [1–3] Following treatment protocols and guidelines for diabetes care is likely to improve the outcome of care.[4–6] Physician-related factors that are considered to contribute to the quality of diabetes care include special interest in diabetes, use of a recall

system and careful recording of clinical data. [7–10] Careful recording of clinical data as part of the diabetes care makes it possible to compare past and present status, to review the course of the disease and to justify continuing or changing treatment. [10] Previous studies in general practice, however, ha ve found that important clinical data may be poorly recorded, even when physicians have a special interest in management of diabetes. [6,11–13] While missing items may indicate that clinical examinations or tests have been omitted, with likely adverse effect on treatment, they may, on the other hand, merely represent failure to record normal values. Therefore, it is not clear if we can consider 'completeness of data recording' as a valid indicator of quality of diabetes care. In this study, at first we assessed the completeness of the medical records of patients with type 2 diabetes treated in general practice. Subsequently, in order to get a full overview, we completed the records as much as possible by questioning and examining the patients. We compared the values of initially recorded data with values ascertained later for initially missing data.
We sought answers to the following questions.

- Which relevant variables are missing most of ten?
- Do the values of unrecorded data differ from those of recorded data?
- What proportion of missing data is found to exceed target values?
- Is the completeness of data recording associated with improved control of glycaemia?

Methods

Setting and participants

The study was carried out between July 1999 and October 2000. One hundred and ten practices in the Utrecht region were invited, of which 52 were willing to participate. Of these, 27 (52%) were connected to the Utrecht Diabetes Project (UDP), a shared care project providing remote diabetologist support for GPs. [5] Of the practices that refused to participate, 55% were involved in the UDP. All practices were computerized and they were asked to generate a list of their known type 2 diabetes patients. Patients treated only by their GP were selected for the study. The medical-ethical committee of the University Medical Center of Utrecht approved the study.

Design

The sentinel items investigated in the patients' files are given in Table 1. These items were extracted from the first as well as the updated Guidelines on Diabetes Type 2 from the Dutch College of General Practitioners [14,15]

Table 1 List of measures that should be assessed once, 3-monthly or annually by the GP in diabetes mellitus type 2 patients [14,15]

Variable	Target value	Frequency
Family history of diabetes		Once
Smoking	No	Annually
Duration of diabetes		Once
Height		Once
Body weight	BMI < 27	Annually
Blood pressure	< 150/85 mmHg	Annually
HbA_{1c}	< 7.0 %	Annually
Total cholesterol	< 5.0 mmol/l	Annually
Serum creatinine		Annually
Fasting blood glucose	< 7.0 mmol/l	3-monthly
Annual review		Annually

BMI = body mass index

Two research assistants visited the practices and checked the patients' medical records for the presence or absence of these items. An item was considered as 'present' when it was recorded and, in the case of laboratory findings, blood pressure or body weight, had been measured within the last 14 months before the audit. For fasting blood glucose we chose a limit of 4 months. The item 'annual review' was considered to be 'present' when the patient had been reviewed within the previous 14 months and at least the following five items had been measured and recorded at the time of the review: body weight, blood pressure, total cholesterol, serum creatinine and fasting blood glucose.

Every practice later received a list of data that were missing or outdated in their patients' records, and the GPs were encouraged to complete the data sets by questioning and examining the patients. This was supported by sending invitations to the patients to report to their GPs. Data initially present in patients' records and data that were missing at the initial survey but obtained later were registered separately as dataset 1 and dataset 2, respectively , using the statistical software program SPSS.

All laboratory data were measured in the GP Lab Corporation of Utrecht. HbA_{1c} was measured with turbidimetric inhibition immunoassay Hitachi 917, Roche (range for normal subjects 4.0–6.0%).

Data analysis

The differences between 'present' and 'missing' data were calculated by chi-square test and t-test. Completeness of data recording was assessed at both patient and practice levels. Patient scores were calculated by counting the

number of items recorded in dataset 1. Practice scores were the mean of patient scores per practice. Both could range from 0 to 11 points. To assess glycaemic control, we used the most recent individual and mean practice HbA_{1c}, respectively. The association between the completeness of data recording and HbA_{1c} concentration was calculated by Pearson's correlation coefficient.

Results

Fifty-two practices with 67 GPs participated. Thirty-eight practices were single-handed (of which 24 worked independently in a group practice, sharing basic facilities) and 14 were two-doctor or three-doctor practices. A total of 131 000 people were registered with these practices (mean per practice: 2519). At the start of the study, 2140 patients with type 2 diabetes were known (average per practice: 41, crude prevalence 1.6%). Of this group, 77% (1641) were under general practice care. The mean age of these patients was 65.3 years, 25% were aged ≤ 75 years and 44% were male. Twenty-two per cent of patients under GP care were being treated with diet only, 66% with oral antihyperglycaemic agents and 12% with insulin.

Missing items

The items most frequently missing were family history of diabetes (70%) and the annual review (60%), while blood pressure and duration of the disease were the most consistently recorded: 80 and 88%, respectively (Table 2).

Comparison of recorded and unrecorded data

Table 3 shows the values of the recorded and initially unrecorded variables. Fewer of the patients whose smoking habits were not recorded were smokers. Patients whose body weight was not recorded were less overweight. Patients with missing glycaemic control data had lower HbA_{1c} values but higher fasting blood glucose levels.

Patients whose missing data exceeded target values

Table 4 shows that 18–72% of the patients had outcome measures that exceeded the current target values but nevertheless appeared to be unrecorded.

Table 2 Frequency of missing or outdated items in 1641 type 2 diabetic patients

Variable	Frequency of absence (%)
Family history of diabetes	70
Smoking habits	59
Duration of diabetes	12
Height	57
Body weight	40
Blood pressure	20
Serum creatinine	39
Total cholesterol	37
HbA_{1c}	37
Fasting blood glucose	33
Annual review [a]	60

[a]At least the following 5 items must be measured and recorded at the time of the review: body weight, blood pressure, total cholesterol, serum creatinine and fasting blood glucose.

Table 3 Values in patients with items present, or missing and obtained later

Variable	Present	Absent and obtained later	p-Value
Positive family history	55%	60%	NS
Current smoker	23%	18%	0.011
Duration of diabetes (years)	5.3	7.7	0.000
Height (cm)	169	169	NS
Body weight (kg)	82	80	0.039
Body mass index (kg/m^2)	29.0	28.5	NS
Blood pressure (mmHg)	148/84	145/83	0.050/NS
Serum creatinine (μmol/l)	92	91	NS
Total cholesterol (mmol/l)	5.8	5.7	NS
HbA_{1c} (%)	7.2	6.9	0.001
Fasting blood glucose (mmol/l)	7.9	9.3	0.000

Table 4 Patients with variables that exceeded target values, but appeared to be unrecorded (%)

Variable	Target	Exceeding target (%)
Current smoker	No	18
Blood pressure	<150/85 mmHg	39
Body mass index	< 27 kg/m^2	48
Total cholesterol	< 5.0 mmol/l	72
Fasting blood glucose	< 7.0 mmol/l	71
HbA_{1c}	< 7.0 %	36

Association between completeness of the registration and glycaemic control

The mean completeness patient score was 6.35 (range 0–11), while the mean completeness practice score was 6.30 (range 1.6–10.3). The mean individual HbA_{1c} was 7.1 (SD 1.7) and the mean practice HbA_{1c} was 7.2 (SD 0.6). There was no association between completeness of data recording and glycaemic control: Pearson correlation coefficients were 0.017 (P = 0.51) at patient level and 0.183 (P = 0.20) at practice level (Fig. 1). One practice with both incomplete registration and a high HbA_{1c} proved to be an outlier, with an apparent correlation between diabetes regulation and registration (Fig. 1). Consequently , when the analyses were performed without this practice, no association was found (Pearson correlation coefficients: -0.004; P = 1.0).

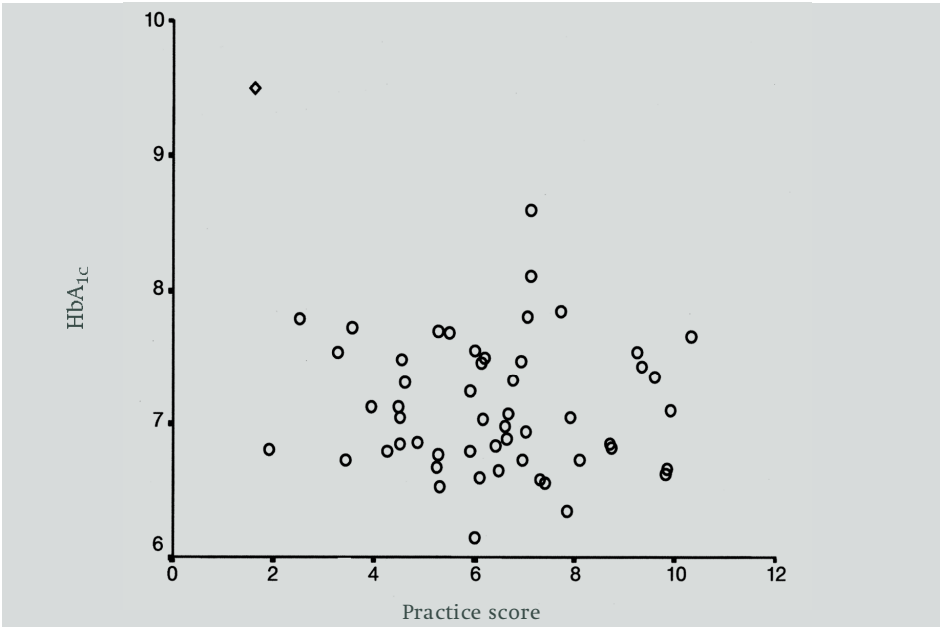


Figure 1 Scatterplot of practice completeness of recording score and HbA_{1c}

Discussion

Reliability of results

In this study, we collected the data first by extracting the items directly from the patients' records, and secondly by an active approach of patients in order to find out the values of variables that were missing or outdated. Except the 3-monthly checks of fasting blood glucose, which were done mostly at each practice, all laboratory tests were performed by the same GP laboratory. It is

likely that this procedure gave a reliable and fairly complete insight into both the data that should be collected by GPs and their data-recording habits in a large sample of known type 2 diabetes patients.

Generalizability of findings

The different practice forms in which the participating GPs were organized seemed to be rather typical for urbanized areas such as the Utrecht region. [16] Because connection to the UDP may reflect a special interest in diabetes, it is of importance that the percentage of UDP practices was virtually equal in both participating and non-participating practices. In addition, age, sex and treatment of the patients, and the known duration of the disease were comparable with those of other recent investigations in general practice. [4,9,17–19] Finally, the prevalence of diabetes in our study (1.6%) corresponded well to the prevalence of patients with known type 2 diabetes in Dutch general practices, which is estimated to be between 1.5 and 2.0%. [20] Thus, it is highly likely that our findings were representative of general practice.

Recording of data

Monitoring and careful recording of important clinical data are considered to be a vital part of diabetes care. [21] However, in our study, 12 - 70% of the variables were not recorded. This corresponds to findings in other studies in general practice in the last decade. Dunn et al. Found between 18 (fasting blood glucose, blood pressure) and 75% (total cholesterol) of items missing in a study of 37 practices, [11] and Hetlevik et al. had comparable results. [9] In a large survey in 495 practices with 38 288 patients with diabetes, Khunti et al. found between 12 (blood pressure) and 51% (serum creatinine) of measurements missing. [17] On the other hand, compared with a similar study at the end of the 1980s, [10] our study showed an improvement in data recording of nearly all items. Nevertheless, the results show that we are still far a way from what is considered desirable. Does that matter?

Quality of care

As far as we know, this is the first study in this area that revealed the values of important but unrecorded clinical parameters of diabetic patients. The values for smoking habits, body weight, blood pressure and HbA_{1c} proved to be better in patients in whose records they were not recorded initially. Although these differences were statistically significant, they seem to be too small to have any clinical importance. The discrepancy between the near normal HbA_{1c} value (6.9%) and the abnormal fasting blood glucose (9.3 mmol/l) is difficult to explain, although it is known that fasting blood glucose measures do not always correlate with HbA_{1c} values. [22]

From a clinical point of view, GPs are likely not to omit recording measures because the values were normal. This finding suggests that not recording measures in patient records could be associated with worse outcome of diabetes care. Indeed, in a substantial number of the patients, the unrecorded variables exceeded the target values advised in the guidelines. Abnormal but unrecorded values deprive the GP of possible indications for starting or adjusting treatment, and may therefore hamper the achievement of optimal diabetes care on an individual level. Poor levels of recording of risk factors for diabetes in itself constitutes suboptimal care. Nevertheless, the lack of association between the completeness of data and glycaemic control definitely means that more careful data recording does not automatically result in better control of patients' diabetes. This finding attenuates the suggested association between recording of data and outcome of diabetes care. Recording of data should be followed by rigorous efforts to attain recommended targets of care. In conclusion, the quality of data recording is not a valid indicator of the quality of diabetes care.

References

1 O'Connor PJ, Spann SJ, Woolf SH. Care of adults with type II diabetes mellitus. A review of the evidence. J Fam Pract 1998; 47(5 Suppl): S13–S22.

2 Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type II diabetes (UKPDS 35): prospective observational study. Br Med J 2000; 321: 405–412.

3 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macro-vascular and microvascular complications in type II diabetes: UKPDS 38. Br Med J 1998; 317: 703–713.

4 de Sonnaville JJ, Bouma M, Colly LP, Deville W, Wijkel D, Heine RJ. Sustained good glycaemic control in NIDDM patients by implementation of structure care in general practice: 2-year follow-up study. Diabetologia 1997; 40: 1334–1340.

5 Rutten GE, Maaijen J, Valkenburg AC, Blankestijn JG, de Valk HW. The Utrecht Diabetes Project: telemedicine support improves GP care in type II diabetes Diabetic Med 2001; 18: 459–463.

6 Chesover D, Tudor-Miles P, Hilton S. Survey and audit of diabetes care in general practice in south London. Br J Gen Pract 1991; 41: 282–285.

7 Griffin S. Diabetes care in general practice: meta-analysis of randomised controlled trials. Br Med J 1998; 317: 390–396.

8 Griffin S, Kinmonth AL. Diabetes care: the effectiveness of systems for routine surveillance for people with diabetes. Cochrane Database Syst Rev 2000; 2: CD000541.

9 Hetlevik I, Holmen J, Midthjell K. Treatment of diabetes mellitus— physicians' adherence to clinical guidelines in Norway. Scand J Primary Health Care 1997; 15: 193–197.

10 Rutten G, Van Eijk J, Beek M, van der Velden H. The quality of diabetes registration in eight general practices. Allgemeinmedizin 1990; 19: 68–72.

11 Dunn NR, Bough P. Standards of care of diabetic patients in a typical English community Br J Gen Pract 1996; 46: 401–405.

12 Williams DR, Munroe C, Hospedales CJ, Greenwood RH. A threeyear evaluation of the quality of diabetes care in the Norwich community care scheme. Diabetic Med 1990; 7: 74–79.

13 Pringle M, Ward P, Chilvers C. Assessment of the completeness and accuracy of computer medical records in four practices committed to recording data on computer . Br J Gen Pract 1995; 45: 537–541.

14 Cromme PVM, Mulder JD, Rutten GEHM, Zuidweg J. NHG-Standaard Diabetes Mellitus type II. Huisarts Wet 1989; 32: 15–18.

15 Rutten GEHM, Verhoeven S, Heine RJ, de Grauw WJC, Cromme PVM, Reenders K, et al. NHG-standaard diabetes mellitus type II (first revision). Huisarts Wet 1999; 42: 67–84.

16 Kenens R, Hingstman L. Cijfers uit de registratie van huisartsen. Peiling 2001. Nivel. Utrecht 2001 (www .nivel.nl).
17 Khunti K, Baker R, Rumsey M, Lakhani M. Quality of care of patients with diabetes: collation of data from multi-practice audits of diabetes in primary care. Fam Pract 1999; 16: 54–59.
18 Dunn N, Pickering R. Does good practice organization improve the outcome of care for diabetic patients? Br J Gen Pract 1998; 48: 1237–1240.
19 Bouma M, Dekker JH, Van Eijk JT, Schellevis FG, Kriegsman DM, Heine RJ. Metabolic control and morbidity of type II diabetic patients in a general practice network. Fam Pract 1999; 16: 402–406.
20 Ruwaard D, Feskens EJM. Suikerziekte. In Volksgezondheid Toekomst Verkenningen 1997. I De gezondheidstoestand: een Actualisering. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, 1997: 269–280.
21 O'Connor PJ. Organizing diabetes care: identify, monitor, prioritize, intensify. Diabetes Care 2001; 24: 1515–1516.
22 Bouma M, Dekker JH, de Sonnaville JJ et al. How valid is fasting plasma glucose as a parameter of glycemic control in noninsulin- using patients with type 2 diabetes? Diabetes Care 1999; 22: 904–907.

Chapter 3

Patient characteristics do not predict poor glycaemic control in type 2 diabetes patients treated in primary care

Published as:
Goudswaard AN, Stolk RP, Zuithoff NPA, Rutten GEHM. Patient characteristics do not predict poor glycaemic control in type 2 diabetes patients treated in primary care. Eur J Epidemiol 2004; in press

Abstract

Many diabetic patients in general practice do not achieve good glycaemic control. The aim of this study was to assess which characteristics of type 2 diabetes patients treated in primary care predict poor glycaemic control (HbA $_{1c}$ ≥ 7%). Data were collected from the medical records. 1641 patients were included who had mean HbA $_{1c}$ 7.1(SD 1.7)% , and 42% had HbA $_{1c}$ ≥ 7%. On univariate analysis younger age; longer duration of diabetes; higher levels of blood glucose at diagnosis; most recent fasting blood glucose (FBG), total cholesterol, and triglyceride; higher body mass index (BMI); treatment with oral hypoglycaemic agents (OHA); treatment with insulin; more GP-visits for diabetes in the last year; and lower educational level were associated with poor control. Both in multiple linear regression and in multiple logistic regression higher levels of FBG (odds ratio (OR): = 1.6, 95% confidence interval (CI): 1.49, 1.70), treatment with OHA (OR: 2.1, 95% CI: 1.41, 3.04), treatment with insulin (OR: 7.2, 95% CI: 4.18, 12.52), lower educational level (OR: 1.26, 95% CI: 1.01, 1.56) were independently associated with poor levels of HbA $_{1c}$. When FBG levels were excluded from the model, higher blood glucose at diagnosis, higher values for triglyceride and total cholesterol, and younger age predicted poor glycaemic control, but these variables explained only 15% of the variation in HbA $_{1c}$. In conclusion prediction of poor glycaemic control from patient characteristics in diabetic patients in general practice is hardly possible. FBG appeared to be a strong predictor of HbA $_{1c}$, which underlines the usefulness of this simple test in daily diabetes care. The worse metabolic control in those treated with either OHA or insulin suggests that current treatment regimes might be not sufficiently applied to reach the targets of care. Providers of diabetes care should be attentive to patients with lower educational level.

Introduction

Improved glycaemic control reduces the risk of diabetic complications and mortality , although in patients with type 2 diabetes the effect on macrovascular outcome is less clear. [1] In current guidelines HbA $_{1c}$ <7% is considered as treatment goal for most patients. [2, 3] However , many patients in general practice do not meet this target. [4,5] To improve quality of care, information might be helpful on patient and treatment characteristics that are possibly associated with poor levels of HbA $_{1c}$. In previous studies a variety of factors are identified that may influence the outcome of care, but results are conflicting and in most studies more than half of the variance of HbA $_{1c}$ remained unexplained. [6-9] Therefore we collected a large number of patient-, disease-, and treatment characteristics in a primary care population of patients with type 2 diabetes, including data of both compliant and non-compliant patients. The aim of the study was to assess which of these characteristics could predict poor glycaemic control in this population.

Materials and methods

Setting and participants

The study was carried out in the Utrecht region between July 1999 and October 2000. Of 110 general practices invited to take part, 52 (67 doctors) were willing to participate. Twenty-seven practices (52%) were connected to the Utrecht Diabetes Project (UDP), a shared-care project providing remote diabetologist support for GPs. [10] Of the practices that refused to participate, 55% were involved in the UDP.

The study was approved by the medical-ethical committee of the University Medical Centre Utrecht. All patients provided written informed consent.

Design and patients

The practices covered 131,000 people and included 2140 patients diagnosed with type 2 diabetes. The criterion to be included in the study was treatment for diabetes in primary care. Two research assistants retrieved relevant information from the patients' medical records. This included information on sociodemographic and disease factors (age, sex, educational level, marital status, duration of diabetes, blood glucose at diagnosis, number of diabetes-related disorders); clinical parameters (fasting blood glucose (FBG), HbA_{1c}, lipid status, body mass index (BMI), blood pressure, and actual smoking); and factors related to treatment processes (actual treatment for diabetes, shared care involvement, and number of visits for diabetes in the past 12 months). When data were missing or outdated (i.e. if data not had been measured within the past 14 months before the audit; for FBG we set a limit of 4 months), GPs were requested to update the medical records by reviewing the patients. This was supported by sending invitations to the patients to report to their GPs. [5] For data on diabetes-related morbidity the medical records were searched for 13 relevant micro- and macrovascular disorders, recorded by the GPs based on their own criteria. Except for FBG, which was mostly measured at the practices, all laboratory data were measured in the GP Lab Corporation of Utrecht, using standard biochemical essays. HbA_{1c} was measured with turbidimetric inhibition immunoassay Hitachi 917, Roche (normal range 4.0–6.0%).

Statistical analysis

Statistical analyses were performed by using SPSS release 11.0. Means are expressed with standard deviation (SD). The associations between glycaemic control and potential predicting factors were evaluated with univariate and

multiple linear regression analyses using HbA $_{1c}$ as dependent variable. In addition, logistic regression was performed considering glycaemic control as 'poor' when HbA $_{1c}$ was ≥ 7.0%. Variables were included in forward stepwise multiple regression analyses if there was a significant association in univariate analysis ($p < 0.05$), or if they were likely to be a confounder.

Results

Of 2140 patients with type 2 diabetes, 1641 (77%) were treated in primary care. The clinical characteristics of these patients are shown in Table 1. After reviewing patients with missing or outdated data, more than 90% of the patients records were complete, except for blood glucose at diagnosis, that could be assessed in 61% of the patients. With average HbA $_{1c}$ of 7.1% glycaemic control was moderate, but 42% of the patients had values over 7%. Table 2 shows that in univariate regression, most variables tested were associated with HbA $_{1c}$ levels. The variables significantly associated in univariate regression, and also sex, were entered in stepwise multiple regression analysis. Variables left in the model are shown in Table 3. These variables accounted for 46% of the variance in HbA $_{1c}$ (total R^2 0.462), and 43% of the variance was explained by FBG on its own. Therefore in additional analyses we omitted FBG from the models. The results of the new multivariate model are given in Table 4. The variables in this model explained 15% of the variance in HbA $_{1c}$. Besides treatment and lower educational level, higher blood glucose at diagnosis, higher levels of triglyceride and total cholesterol, and younger age, contributed to the model.

Subsequently, multiple logistic regression was performed to investigate which factors predict poor glycaemic control (HbA $_{1c}$ ≥ 7.0%). As in multiple linear regression higher levels of FBG (odds ratio (OR): 1.6, 95% confidence interval (CI): 1.49, 1.70), treatment with oral hypoglycaemic agents (OHA) (OR: 2.1, 95% CI: 1.41, 3.04), treatment with insulin (OR: 7.2, 95% CI: 4.18, 12.52), and lower educational level (OR: 1.26, 95% CI: 1.01, 1.56), were independently associated with poor levels of HbA $_{1c}$.

Discussion

In this general practice population of type 2 diabetes patients nearly half of the patients had levels of HbA $_{1c}$ over 7.0%, the current target for good control. We found that higher level of FBG, treatment with OHA or insulin, and lower educational level predicted a higher level of HbA $_{1c}$. After excluding FBG from the model, also blood glucose at diagnosis, triglyceride, total cholesterol, and age did contribute to the model. These variables could explain only 15% of the variance in HbA $_{1c}$, so we found little evidence that in this population the

Table 1. Characteristics of type 2 diabetes patients treated in general practice N=1641

Age (years)	65.3 (13.3)
Male (%)	44
Educational level (%)	
Low	59
Middle	31
High	10
Living with a partner (%)	68
Duration of diabetes (years)	5.5 (6.0)
BG at diagnosis (mmol/l)	12.5 (5.4)
Diabetes-related complications (% of patients)	
None	49
1 or 2	44
≥3	7
FBG (mmol/l)	9.0 (3.2)
HbA_{1c} (%)	7.1 (1.7)
Patients with HbA_{1c} ≥ 7,0% (%)	42
Total cholesterol (mmol/l)	5.8 (1.2)
Triglyceride (mmol/l)	2.2 (2.0)
BMI (kg/m^2)	28.7 (5.2)
Blood pressure (mmHg)	148 (21) / 84 (11)
Actual smoking (%)	18
Treatment (%)	
Diet only	22
OHA('s)	66
Insulin + OHA('s)	5
Insulin	7
Enrolled in shared care (%)	37
Number of GP-visits for diabetes in past 12 months	4.2 (2.7)

Results as means (SD) or percentages.

(F)BG = (fasting) blood glucose; BMI = body mass index; OHA = oral hypoglycaemic agent

characteristics studied provide sufficient explanation for the variation in HbA_{1c}. The data in this study were collected both directly from the patients' records, and by an active approach of patients in case of missing or outdated variables as well. With this procedure it seems plausible that underrepresentation of patients non-compliant to medical care was limited. The prevalence of diabetes, mean age, sex, glycaemic control, treatment of patients, and the known duration of the disease were comparable to other recent investigations in general practice. [10–12] Thus, it is highly likely that our findings were representative of general practice in the Netherlands.

Table 2. Associations between patient characteristics and HbA $_{1c}$ level in type 2 diabetes patients treated in general practice N = 1641

Independent variable	B[a]	95% CI for B	p-Value
Age (year)	- 0.01	- 0.02; -0.003	0.004 [b]
Female	0.11	- 0.06; 0.28	0.21 [b]
Duration of diabetes (year)	0.03	0.01; 0.04	< 0.0011 [b]
BG at diagnosis (mmol/l)	0.07	0.05; 0.09	< 0.001 [b]
FBG (most recent) (mmol/l)	0.34	0.33; 0.37	< 0.001 [b]
Total cholesterol) (mmol/l)	0.12	0.05; 0.19	< 0.00 [b]
Triglyceride) (mmol/l)	0.09	0.04; 0.14	< 0.001 [b]
BMI (kg/m ^{2})	0.02	0.004; 0.04	0.01 [b]
SBP (mm Hg)	- 0.003	- 0.007; 0.001	0.19
DBP (mm Hg)	0.002	- 0.006; 0.010	0.65
Smoking	- 0.003	- 0.22; 0.22	0.98
Number of diabetes related complications	- 0.055	- 0.14; 0.027	0.18
Enrolled in shared care program (UDP)	- 0.008	- 0.18; 0.17	0.92
Treatment with OHA('s)	0.37	0.19; 0.56	< 0.001 [b]
Treatment with insulin	0.83	0.57; 1.1	< 0.001 [b]
Number of GP-visits for diabetes past 12 months	0.08	0.051; 0.11	< 0.001 [b]
Educational level	- 0.3	- 0.4; -0.12	< 0.001 [b]
Marital state	- 0.07	0.2; 0.1	0.45

CI = confidence interval; (F)BG = (fasting) blood glucose; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; UDP = Utrecht Diabetes Program (see text); OHA = oral hypoglycaemic agent.

[a] The regression coefficient B reflects the estimated difference in HbA $_{1c}$ level as a result of one unit increase in the independent variable; [b] Variables used in multiple linear regression analysis.

Of the clinical parameters the most recently measured FBG appeared to be a strong predictor, with 0.34 point% increase of HbA $_{1c}$ per mmol/l FBG. Although this association underlines the usefulness of this simple and cheap test to assess glycaemic control in daily diabetes care, caution is necessary. A study of Bouma et al. in non-insulin-using patients revealed that the prediction of HbA $_{1c}$ from good fasting plasma glucose levels (<7.8 mmol/l) tended to be too optimistic, especially in patients using OHA, with therefore a risk for under-treatment. [13] Overweight was not significantly related to glycaemic control in this study, which confirms the findings from another cross-sectional study in primary care. [14] The well-known metabolic relationship between lipids and glycaemia is likely to explain in this study the association of an unfavourable lipid status with worse glycaemic control.

Table 3 Multiple linear regression analyses between patient characteristics and HbA $_{1c}$ in type 2 diabetes patients treated in general practice N = 1641

Independent variable	B[a]	95% CI for B	p-Value
FBG (mmol/l)	0.34	0.32; 0.36	< 0.001
Treatment with insulin b	0.98	0.72; 1.25	< 0.001
Treatment with OHA('s) [b]	0.44	0.26; 0.62	< 0.001
Educational level	- 0.13	- 0.24; -0.03	0.02

CI = confidence interval; FBG = fasting blood glucose; OHA = oral hypoglycaemic agent

Excluded variables were: age, sex, triglyceride, total cholesterol, duration of diabetes, frequency of visits for diabetes in past 12 months, blood glucose at diagnosis, and BMI. 46% of the variance of HbA $_{1c}$ was explained by the variables in the model (total $R^2 = 0.462$)

[a] The regression coefficient B reflects the estimated difference in HbA $_{1c}$ level as a result of one unit increase in the independent variable; [b] Compared to patients with diet alone.

Table 4 Multiple linear regression analyses between patient characteristics and HbA $_{1c}$ in type 2 diabetes patients treated in general practice N = 1641

Independent variable	B[a]	95% CI for B	p-Value
Blood glucose at diagnosis (mmol/l)	0.05	0.03; 0.08	< 0.001
Treatment with insulin [b]	1.7	1.2; 2.2	<0.001
Treatment with OHA('s) [b]	0.7	0.4; 1.0	<0.001
Educational level	- 0.3	- 0.5; -0.1	0.001
Age (year)	- 0.02	- 0.03; -0.006	0.001
Triglyceride (mmol/l)	0.11	0.03; 0.20	0.006
Total cholesterol (mmol/l)	0.13	0.03; 0.20	0.008

CI = confidence interval; OHA = oral hypoglycaemic agents

15% of the variance of HbA $_{1c}$ was explained by the variables in the model (total $R^2 = 0.154$). Analysis without fasting blood glucose.

[a] The regression coefficient B reflects the estimated difference in HbA $_{1c}$ level as a result of one unit increase in the independent variable; [b] Compared to patients with diet alone

The association of treatment with OHA or insulin with higher levels of HbA $_{1c}$ is consistent with results of other studies. [15, 16] This finding reflects both the deterioration of diabetes over the time, as well as that current treatment regimens might be not sufficiently applied to reach the targets of care. From the UKPDS it is known that even with intensive treatment only 50% of patients achieved the target HbA $_{1c}$ level of 7%, and this percentage decreased dramatically in the long term. [17] However, a recent study in primary care revealed a 17% reduction in HbA $_{1c}$ in 288 poorly controlled patients, af ter supporting GPs with flow-charts, treatment schemes for OHA and visits from facilitators, suggesting a certain degree under-performance. [18] No matter how, these findings force us to be realistic regarding the control of h yperglycaemia

that can be achieved with current treatment regimens, in particular insulin therapy .[19]

Other treatment factors as involvement in shared care, and more visits for diabetes, were not associated with better glycaemic control. This confirms the results of a study by Hansen et al. who found that none of a set of GP– and practice related characteristics could predict glycaemic control. [8] However , the finding that shared care was not associated with better glycaemic control must be interpreted with caution, because our study design might be less suitable to assess the effects of the UDP in this population. In the first place GPs are inclined to select for shared care only patients with a more problematic condition of their diabetes. [10] Secondly , it is not unlikely that within the UDP-practices also patients not included in shared care had profited by the support from the diabetologist. Finally, non-UDP GPs could have improved their performance by attending the three-monthly free accessible local UDP courses, resulting in a so-called contamination effect.

Younger age appeared to be associated with worse control, although the ef fect was small and clinical insignificant. [20] Finally , a moderate inverse relationship was observed between educational level and glycaemic control. Other authors have emphasised the significance of health literacy in diabetes care. [21, 22] In our population almost 60% of the patients had a low educational level. Since diabetes is a 'complex' disease, it seems of importance that providers of diabetes care are conscious of the potential influence of educational level on the outcomes of diabetes care.

In conclusion, we found that prediction of poor glycaemic control from patient characteristics in diabetic patients in general practice is hardly possible; that in daily diabetes care in addition to measurements of HbA_{1c}, measuring of FBG is useful to assess glycaemic control; that treatment with OHA or insulin were associated with inadequate glycaemic control; and that providers of diabetes care should be attentive to patients with lower educational level.

References

1 Implications of the United Kingdom Prospective Diabetes Study. American Diabetes Association, Diabetes Care 2002; 25: S28–S32.

2 Woolf SH, Davidson MB, Greenfield S, et al. Controlling blood glucose levels in patients with type 2 diabetes mellitus. An evidence-based policy statement by the American Academy of Family Physicians and American Diabetes Association, J Fam Pract 2000; 49: 453–460.

3 Wiersma TJ, Heine RJ, Rutten GE. [Summary of the practice guideline 'Diabetes mellitus type 2' (first revision) of the Dutch College of GeneralPractitioners], Ned Tijdschr Geneeskd 1999; 143: 1688–1691.

4 Khunti K, Baker R, Rumsey M, Lakhani M. Quality of care of patients with diabetes: Collation of data from multi-practice audits of diabetes in primary care, Fam Pract 1999; 16: 54–59.

5 Goudswaard AN, Lam K, Stolk RP, Rutten GE. Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study, Fam Pract 2003; 20: 173–177.

6 Pringle M, Stewart-Evans C, Coupland C, Williams I, Allison S, Sterland J. Influences on control in diabetes mellitus: Patient, doctor, practice, or delivery of care? Br Med J 1993; 306: 630–634.

7 Khunti K, Ganguli S, Baker R, Lowy A. Features of primary care associated with variations in process and outcome of care of people with diabetes, Br J Gen Pract 2001; 51: 356–360.

8 Hansen LJ, Olivarius N de F, Siersma V, Andersen JS. Doctors' characteristics do not predict long-term glycaemic control in type 2 diabetic patients, Br J Gen Pract 2003; 53: 47–49.

9 Brown JB, Harris SB, Webster-Bogaert S, Wetmore S, Faulds C, Stewart M. The role of patient, physician and systemic factors in the management of type 2 diabetes mellitus, Fam Pract 2002; 19: 344–349.

10 Rutten GE, Maaijen J, Valkenburg AC, Blankestijn JG, de Valk HW. The Utrecht Diabetes Project: Telemedicine support improves GP care in Type 2 diabetes, Diabet Med 2001; 18: 459–463.

11 Bouma M, Dekker JH, Van Eijk JT, Schellevis FG, Kriegsman DM, Heine RJ. Metabolic control and morbidity of type 2 diabetic patients in a general practice network, Fam Pract 1999; 16: 402–406.

12 De Grauw WJ, van Gerwen WH, van de Lisdonk EH, van Den Hoogen HJ, van den Bosch WJ, van Weel C. Outcomes of audit-enhanced monitoring of patients with type 2 diabetes, J Fam Pract 2002; 51: 459–464.

13 Bouma M, Dekker JH, de Sonnaville JJ, et al. How valid is fasting plasma glucose as a parameter of glycemic control in non-insulin-using patients with type 2 diabetes?

Diabetes Care 1999; 22: 904–907.
14 Blaum CS, Velez L, Hiss RG, Halter JB. Characteristics related to poor glycemic control in NIDDM patients in community practice, Diabetes Care1997; 20: 7–11.
15 Harmel AP, Ryan D, Thompson R. Glycohemoglobin assessment program: Glycated hemoglobin and epidemiologic variables in patients with type 2 diabetes, Endocr Pract 2002; 8: 184–190.
16 Shorr RI, Franse LV, Resnick HE, Di Bari M, Johnson KC, Pahor M. Glycemic control of older adults with type 2 diabetes: Findings from the Third National Health and Nutrition Examination Survey, 1988–1994, J Am Geriatr Soc 2000; 48: 264–267.
17 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (UKPDS 49), JAMA 1999; 281: 2005–2012.
18 Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. Improving glycaemic control in patients with type 2 diabetes mellitus without insulin therapy, Diabet Med 2003; 20: 540–544.
19 Winocour PH. Effective diabetes care: A need for realistic targets, Br Med J 2002; 324: 1577–1580.
20 Rothenbacher D, Rüter G, Saam S, Brenner H. Younger patients with type 2 diabetes need better glycaemic control: Results of a community-based study describing factors associated with a high HbA_{1c} value. Br J Gen Pract 2003; 53: 389–391.
21 Schillinger D, Grumbach K, Piette J, et al. Association of health literacy with diabetes outcomes, JAMA 2002; 288: 475–482.
22 Fisher E. Low literacy levels in adults: Implications for patient education, J Contin Educ Nurs 1999; 30: 56–61.

Chapter 4

Improving glycaemic control in patients with Type 2 diabetes mellitus without insulin therapy

Published as:
Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. Improving glycaemic control in patients with Type 2 diabetes mellitus without insulin. Diabet Med 2003; 20: 540–544

Abstract

Aims

In general practice at least 30% of those with Type 2 diabetes do not achieve good glycaemic control. We studied the effect of improving oral glucose-lowering medication in a primary care setting in patients treated with oral hypoglycaemic agents without satisfactory glycaemic control.

Methods

We provided flowcharts to general practitioners and outreach visits by trained facilitators, who checked adherence to the protocol. Fifty-two Dutch general practices with 2140 Type 2 diabetes mellitus (DM) patients recruited 288 patients ≤ 75 years old inadequately controlled (HbA $_{1c}$ > 7%) by diet or oral medication. Outcome measures were decrease of HbA $_{1c}$, number of patients with HbA $_{1c}$ ≤ 7%, and non-compliance rate.

Results

After a mean of 3.3 consultations over 14 weeks, 209 patients were following the protocol fully with a reduction in HbA $_{1c}$ from 8.7% to 6.7% (P< 0.001). One hundred and fifty-eight patients (55%) achieved HbA $_{1c}$ ≤ 7%, and 51 (18%) persisted with HbA $_{1c}$ > 7% unless fasting blood glucose ≤ 7 mmol/l (n = 18) or a maximum of medication (n = 33). Seventy-nine patients (27%) did not adhere to the protocol, mostly due to loss of motivation and non-attendance.

Conclusions

A simple flowchart and relatively little support by trained facilitators results in improved glycaemic control.

Introduction

In patients with Type 2 diabetes even a small improvement in glycaemic control reduces the risk of diabetic complications. [1–3] In general practice, however , at least 30% of patients do not achieve the targets for good glycaemic control. [4–8] Besides the unfavourable course of the disease, [9] patient-related factors such as non-attendance [10] and non-compliance with medication, [11] and on the part of general practitioners (GPs) inadequate management and treatment [10,12,13] contribute to these outcomes. GPs often do not adjust treatments to achieve glycaemic targets, even with regular follow-up and review. [14] For example, they may not prescribe adequate doses of oral hypoglycaemic agents. Insulin therapy is expensive and associated with lower health-related quality of life and treatment satisfaction, [15] and it may be worthwhile maintaining normal glycaemia using oral agents. Guidelines

for diabetes treatment in primary care are available, but doctors often find them complex and feel they have insufficient staff to follow the recommendations. [16,17]

We therefore investigated the effect on glycaemic control of encouraging GPs to adjust oral medication for Type 2 diabetes according to Dutch guidelines [18] in patients with HbA_{1c} > 7%, by flowcharts and help from trained facilitators.

Patients and methods

The study was carried out in the Utrecht region between July 1999 and June 2000. Of 110 practices invited to take part, 52 (67 doctors) agreed to participate. Thirty-eight practices were single handed, of which 24 worked independently but sharing basic facilities in groups. Fourteen were practices run by either two or three doctors. The practices covered 131 000 people, including 2140 Type 2 diabetes patients (average per practice 41, crude prevalence 1.6%), and 1641 of these were treated in primary care. The medical ethical committee of the University Medical Centre of Utrecht approved the study.

Before the treatment protocol was introduced, the following data were collected from the medical records: medical history, glycaemic control (HbA_{1c} and fasting blood glucose), cardiovascular risk factors, treated in primary or secondary care, and presence of complications. Any data missing or outdated for the patients being treated in primary care were reported to the practices concerned, and their doctors were asked to complete the data sets by questioning and examining the patients. [19]

Patient selection and characteristics

The inclusion criteria were: treatment in primary care only; under age 76 years; treated with diet or hypoglycaemic agents or both; HbA_{1c} > 7.0% (measured by turbidimetric inhibition immunoassay Hitachi 917 (Roche Diagnostics, Basel, Switzerland); normal range 4–6%). Patients were excluded if they were already on maximal oral medication, required insulin therapy in the short term, or had severe co-morbidity. Patient selection is shown in Fig. 1.

Of 350 patients with HbA_{1c} > 7.0%, 62 were excluded because they were already on maximal oral medication (n = 27), insulin therapy was required (n = 12), serious co-morbidity in the opinion of the GP was present (n = 13), or for other reasons (moved, deceased, abroad, change of GP; n = 10). Examples of co-morbidity were: lung cancer, leukaemia, mental disorders, dementia, recent cerebral infarction, and pregnancy. The characteristics of the 288 patients eligible for the study are shown in Table 1. When compared with the

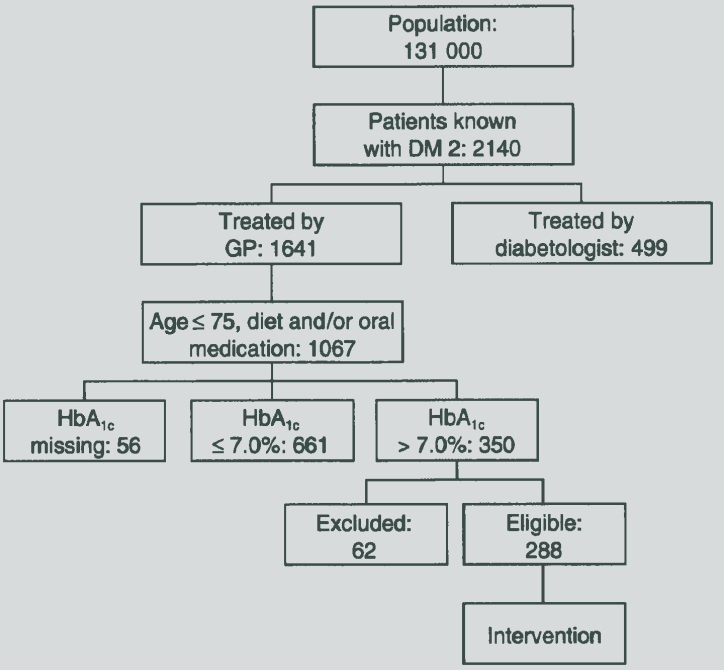


Figure 1 Patient selection. Absolute numbers.

Table 1 Characteristics of patients at baseline (n = 288)

Age (years)	59.9 (10.6)
Sex (male %)	45
Mean duration of diabetes (years)	4.6 (4.3)
Body mass index (kg/m ^{2})	29.2 (5.3)
HbA_{1c} (%)	8.8 (1.7)
Mode of treatment (%)	
Diet only	11
Sulfonylurea	40
Metformin	8
Sulfonylurea and metformin	39
Other	2

Results as means (SD) or percentages.

661 patients with good glycaemic control ($HbA_{1c} \leq 7.0\%$) (Fig. 1), the study group patients were of similar age and body mass index, had a longer duration of diabetes (4.6 vs. 3.1 years, $P < 0.001$), were less often on diet alone (11% vs. 34%, $P < 0.001$), and were more often treated with a combination of a sulphonylurea and metformin (39% vs. 18%, $P < 0.001$).

Visit number ☐☐

1. date: ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)
2. fasting blood glucose (fbg): ☐☐ ☐ mmol/l
3. plan (mark box):
   - ☐ fbg ≤ 7.0 → measure HbA_{1c} after 6 weeks and send chart with result* to researcher
   - ☐ fbg > 7.0 ánd medication is not maximal → increase dosage or ad new medication (see scheme below) and measure fbg after 2 weeks
   - ☐ fbg > 7.0 ánd medication is maximal → measure HbA_{1c} after 6 weeks and send chart with result* to researcher
4. medication ☐ mg ☐ time(s) a day ☐ tablet(s)
   ☐ mg ☐ time(s) a day ☐ tablet(s)

*result HbA_{1c} %: ☐☐.☐ date: ☐☐ ☐☐ ☐☐☐☐

Scheme for treatment with oral medication

Adjust dosage till fasting blood glucose is ≤ 7.0 mmol/l

Step 1: Body mass index ≤ 27: sulfonylurea
> 27: metformin

Step 2: add metformin or sulfonylurea respectively

In case of side effects or contraindications, switch to acarbose

Maximum daily dosage (in so far as feasible)

tolbutamide	2000 mg
tolazamide	1000 mg
glibenclamide	15 mg
gliclazide	240 mg
glipizide	30 mg
glimepiride	6 mg
metformin	2550-3000 mg
acarbose	600 mg

Figure 2 Flow chart (partly shown). Above the line a box for consultation data (there are five boxes on one chart), including a scheme of 'next steps' dependent on the level of the fasting blood glucose. Below the line a two-steps scheme for the adjustment of oral medication, as well as the maximum daily dosages. [18]

Intervention

For every eligible patient the doctor had to complete a study flowchart (Fig. 2). This displayed both control and treatment algorithms, and showed the maximum daily dosages of the different oral hypoglycaemic agents. The doctors were asked to measure fasting blood glucose every 2 weeks and to

adjust oral medication according to the algorithm until either a fasting blood glucose concentration of ≤ 7.0 mmol/ l was achieved or the maximum feasible dosages of the hypoglycaemic preparations in use were reached (depending on side-ef fects or contraindications). HbA $_{1c}$ was measured 6 weeks after either of these targets had been reached, and oral medication had not been further adjusted. Two trained facilitators visited the practices every 3 weeks to check both patient and doctor compliance. Based on the previous audit by research assistants, the facilitators were informed about the eligible patients in every practice. During their visit they checked the progress of the consultations, and discussed the adherence to the flowchart's treatment and control schemes, as well as the correct adoption of the (maximum) daily dosages of oral hypoglycaemic agents (Fig. 2). They also supervised conscientious completion of the forms. Finally, in case patients did not show up, or exceeded the control interval of 2 weeks, practice assistants were asked to try to get defaulting patients to report in. When a patient did not adhere to the protocol treatment, doctors were asked to note the reasons on the form.

Statistical analysis

Data analyses were performed with SPSS release 10.0 (SPSS Inc., Chicago, IL, USA). Baseline and follow-up results were compared by paired t-tests. Patient related outcomes (HbA $_{1c}$) were calculated both in a per-protocol as well in an 'intent-to-treat' manner, assuming that patients lost to follow-up had no change in HbA$_{1c}$ percentage. $P < 0.05$ was considered statistically significant.

Results

The protocol was followed fully and HbA $_{1c}$ measured in 209 patients, of whom 158 (55%) achieved good glycaemic control (HbA $_{1c}$ ≤ 7.0%). Overall, mean HbA $_{1c}$ decreased from 8.7% to 6.7% ($P < 0.001$). Including all eligible 288 patients, assuming that the 79 non-compliant patients had no change in HbA $_{1c}$, a 17% reduction in HbA $_{1c}$ (8.8 to 7.3%; $P < 0.001$) was still achieved, while the number of patients with poor control (HbA $_{1c}$ > 8.5%) decreased from 126 to 51. The average number of consultations was 3.3 (range 1–10), while the a verage intervention period was 14.3 weeks per patient (1–49). Fewer patients at the end of the study than at baseline were being treated by diet alone (6%) or a single hypoglycaemic agent (36%), and more patients were being treated with two (56%) or three (2%) agents.

Of 51 patients (18%) with HbA $_{1c}$ persistently over 7.0%, drug dosages had not been further adjusted in 18 because their fasting blood glucose concentrations were ≤ 7.0 mmol/l. In the remaining 33 patients the HbA $_{1c}$ concentration was still > 7.0% in spite of a maximum dosage of oral hypoglycaemic treatment.

A total of 79 patients (27%) did not adhere to the protocol for the following reasons: loss of motivation or non-attendance (n = 50), referral to secondary care (n = 4), insulin therapy required (n = 8), language barrier (n = 6), or other reasons (moved, abroad, mental disorders, deceased, unknown; n=11). Compared with the 209 patients who completed the intervention, the 79 non-compliant patients were younger (56.5 vs. 60.4 years, $P < 0.01$), but other characteristics, such as HbA_{1c} at baseline, body mass index, duration of diabetes, and treatment, were similar (data not shown).

Discussion

The results of this study indicate that in general practice a simple f lowchart supported by a limited number of outreach visits was successful in improving glycaemic control. The treatment and control schemes in this study were extracted from the Guideline on Type 2 diabetes from the Dutch College of General Practitioners, [18] so they may be considered as 'recommended care'. In 209 patients in whom the intervention was fully applied we found a 23% reduction in mean HbA_{1c}. According to intention to treat, 55% of the patients reached good glycaemic control ($HbA_{1c} \leq 7.0\%$). As a result, in the initial population of 1067 patients under 76 years treated with diet and/or oral hypoglycaemic agents, the percentage with good glycaemic control increased from 62% to 77%. In 18 patients the HbA_{1c} remained above 7.0% in spite of fasting blood glucose ≤ 7.0 mmol/l. In clinical practice this is not uncommon in patients on diet or on oral hypoglycaemic drugs. [20] In such patients better control might have been achieved if the therapeutic algorithm had been based solely on regular HbA_{1c} measurements.

The mean number of consultations per patient was 3.3, during an a verage period of 14.3 weeks, so the instruction to measure glucose every 2 weeks in those with high values was not attained. A 2 weeks control scheme might be too tight, but compliance might improve in time as GPs and patients become more familiar with the approach.

Despite the combined efforts of facilitator, practice assistant and GP, the drop-out rate was quite high (27%, 79 patients), mostly due to lack of motivation of the patient. Patients who did not receive the maximum dose of oral agents (mostly metformin) because of side-effects were considered as having a maximum feasible dosage, and were not classified as dropouts. Our drop-out rates were comparable to other studies. [10]

It is probable that the outreach visits were important in improving glycaemic control. Based on the schedules from the facilitators, the 3-weekly visits took on average 1 h per practice, suggesting a rather modest time investment. It is noteworth y that an average general practice in the Netherlands (2500 patients)

is staffed by one GP and one practice assistant, which is probably insuf ficient to provide an adequate degree of diabetes care. [21] In addition to following guidelines, additional support will be needed to improve diabetes care in general practice.

Important limitations need to be recognized when considering these data. With no control group, the net study effect might be influenced by other factors than just the intervention, such as 'regression to the mean' of HbA_{1c} values. [22] Furthermore, the practices in this study were self-selected, reflecting a special interest in diabetes. Finally, the short duration of follow-up must be taken into account. In most patients, diabetes worsens over time, [9] and most patients need multiple therapies to achieve good glycaemic control. [23] It is likely that the effect of our intervention will diminish. However, if both patients and practice staff can continue this approach, glycaemic control may be maintained.

The improvement in glycaemic control in our study is comparable to that found in several controlled studies aimed at improving glycaemic control with oral hypoglycaemic agents. DeFronzo and colleagues found in a randomized double-blind study that HbA_{1c} values improved an average of 1.5% after addition of metformin in patients whose diabetes was poorly controlled with diet or sulphon ylurea therapy alone. [24] This was confirmed in the UKPDS, which studied the addition of metformin in suboptimally controlled overweight patients receiving maximum dosages of a sulphon ylurea. [25] Gregorio and colleagues randomly assigned elderly Type 2 diabetes patients to a sulphon ylurea up to maximum dosage or to addition of metformin, and found that HbA_{1c} declined 1.6% in both groups. [26] Notably , as in our study, this ef fect was achieved within 3 months, and was still present at 18 months. These studies as well as ours demonstrate that patients with poor control and inadequate therapy benefit from optimisation of oral medication irrespective of age, body mass index, or duration of diabetes. Both increasing the dosage in case of monotherapy and adding a second agent resulted in 1–2% lower HbA_{1c} concentrations, which should lead to fewer complications. In diabetic populations with worse control this approach might prove more successful. On the other hand, our results are in contrast to those of Frijling and colleagues, [27] in which a multifaceted and more elaborate intervention did not af fect metabolic control. However, a systematic review of the effects of educational outreach visits showed positive results, especially on modifying prescribing. [28] Our experience may be useful in implementing current evidence-based treatment guidelines in daily practice and might be broadened towards the approach of other risk factors in patients with diabetes. This attitude can be promoted if support and interventions from health professionals such as facilitators or nurses are focused on both process and patient outcomes. [29]

References

1 O'Connor PJ, Spann SJ, Woolf SH. Care of adults with type 2 diabetes mellitus. A review of the evidence. J Fam Pract 1998; 47: S13–S22.

2 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000; 321: 405–412.

3 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281: 2005–2012.

4 Bradsha w C, Steen IN, Eccles M. Glycated haemoglobin levels in patients with diabetes in one general practice over a 10-year period. Diabet Med 1995; 12: 628–631.

5 Hanninen J, Keinanen KS, Takala J. Population-based audit of noninsulin-dependent diabetic patients aged under 65 years in primary health care. Scand J Prim Health Care 1998; 16: 227–232.

6 Bouma M, Dekker JH, Van Eijk JT, Schellevis FG, Kriegsman DM, Heine RJ. Metabolic control and morbidity of type 2 diabetic patients in a general practice network. Fam Pract 1999; 16: 402–406.

7 Dunn NR, Bough P. Standards of care of diabetic patients in a typical English community . Br J General Pract 1996; 46: 401–405.

8 De Grauw WJC, Van Gerwen WHEM, Van de Lisdonk EH, Van den Hoogen HJM, V an den Bosch WJHM, Van Weel C. Outcome of care for type 2 dia betes mellitus with audit-enhanced monitoring in a practice based research network. J Fam Pract 2002; 51: 459–464.

9 Anon ymous. UKPDS 16: Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995; 44: 1249–1258.

10 Peters AL, Legorreta AP, Ossorio RC, Davidson MB. Quality of out patient care provided to diabetic patients. A health maintenance organization experience. Diabetes Care 1996; 19: 601–606.

11 Skaer TL, Sclar DA, Markowski DJ, Won JK. Effect of value-added utilities on prescription refill compliance and Medicaid health care expenditures. A study of patients with non-insulin-dependent diabetes mellitus. J ClinPharm Ther 1993; 18: 295–299.

12 Pringle M, Stewart-Evans C, Coupland C, Williams I, Allison S, Sterland J. Influences on control in diabetes mellitus: patient, doctor, practice, or delivery of care? Br Med J 1993; 306: 630–634.

13 Renders CM, Valk GD, Franse LV, Schellevis FG, Van Eijk JT, van der Wal G. Long-term effectiveness of a quality improvement program for patients with type 2 diabetes in general practice. Diabetes Care 2001; 24: 1365–1370.

14 van den Arend I, Stolk RP, Krans HM, Grobbee DE, Schrijvers AJ. Management of type 2 diabetes: a challenge for patient and physician. Pat Educ Couns 2000; 40: 187–194.
15 Redekop WK, Koopmanschap MA, Stolk RP, Rutten GE, W olffenbuttel BH, Niessen LW. Health-related quality of life and treatment satisfaction in Dutch patients with type 2 diabetes. Diabetes Care 2002; 25: 458–463.
16 Chesover D, Tudor-Miles P, Hilton S. Survey and audit of diabetes care in general practice in south London. Br J General Pract 1991; 41: 282–285.
17 Helseth LD, Susman JL, Crabtree BF, O'Connor PJ. Primary care ph ysicians' perceptions of diabetes management. A balancing act.J Fam Pract 1999; 48: 37–42.
18 Rutten GEHM, Verhoeven S, Heine RJ, de Grauw WJC, Cromme PVM, Reenders K. NHG-standard diabetes mellitus type 2 (first revision). Huisarts Wet 1999; 42: 67–84 (in Dutch).
19 Goudswaard AN, Lam PK, Stolk RP, Rutten GEHM. Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study. Fam Practice 2002; 20: 173–177.
20 Bouma M, Dekker JH, de Sonnaville JJ, van der Does FE, de Vries H, Kriegsman DM et al. How valid is fasting plasma glucose as a parameter of glycaemic control in non-insulin-using patients with type 2 diabetes? Diabetes Care 1999; 22: 904–907.
21 Valk GD, Blankenstein AH. Hoeveel tijd kost toepassing van de herziene NHG-standaard diabetes mellitus type 2? Huisarts Wet 2000; 43: 151–154 (in Dutch).
22 Yudkin PL, Stratton IM. How to deal with regression to the mean in intervention studies. Lancet 1996; 347: 241–243.
23 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfon ylurea, metformin, or insulin in patients with type 2 diabetes mellitus. Progressive requirement formultiple therapies (UKPDS 49). JAMA 1999; 281: 2005–2012
24 DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995; 333: 541–549.
25 Anonymous. UKPDS 28: A randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. U.K. Prospective Diabetes Study Group. Diabetes Care 1998; 21: 87–92.
26 Gregorio F, Ambrosi F, Manfrini S, Velussi M, Carle F, Testa R et al. Poorly controlled elderly Type 2 diabetic patients: the effects of increasing sulphon ylurea dosages or adding metformin. Diabet Med 1999; 16: 1016–1024.
27 Frijling BD, Lobo CM, Hulscher MEJL, Akkermans RP, Braspenning JCC, Prins A et al. Multifaceted support to improve clinical decision making in diabetes care: a randomised controlled trial in general practice. Diabet Med 2002; 19: 836–842.
28 Thomson O'Brien MA, Oxman AD, Davis DA, Haynes RB, Freemantle N, Harvey EL. Educational outreach visits: effects on professional practice and health care outcomes. (Cochrane Review). In: The Cochrane Library. Issue 1. Oxford: Update Software, 2002.

29 Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JT, Assendelft WJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings (Cochrane Review). In: TheCochrane Library, Issue 1. Oxford: Update Software, 2002.

Chapter 5

Long-term effects of self-management education for patients with Type 2 diabetes taking maximal oral hypoglycaemic therapy: a randomized trial in primary care

Published as:
Goudswaard AN, Stolk RP, Zuithoff NPA, de Valk HW, Rutten GEHM. Long-term effects of self-management education for patients with Type 2 diabetes taking maximal oral hypoglycaemic therapy: a randomized trial in primary care. Diabet Med 2004; 21: 491–496

Abstract

Aims

Education is an essential part of the management of patients with Type 2 diabetes, but the long-term effects are unclear and not well investigated in primary care.

Methods

Fifty-four patients (39 - 75 years) treated with maximal dosages of oral h ypoglycaemic agents, needing to start insulin ($HbA_{1c} \geq 7.0\%$), were randomly allocated to a 6-month educational programme by a diabetes nurse (DN group) or usual care (UC group). Main outcome measures were HbA_{1c}, number of patients with $HbA_{1c} < 7.0\%$, and number of patients treated with insulin 18 months after baseline.

Results

Six weeks after the intervention HbA_{1c} levels had improved from 8.2 (1.1) to 7.2 (1.3) in the DN group, and from 8.8 (1.5) to 8.4 (1.7) in the UC group. Adjusted for baseline values, at 6 weeks HbA_{1c} improved 0.7% (95% confidence interval 0.1, 1.4) more in DN than in UC. Of the patients in DN, 60% reached $HbA_{1c} < 7.0\%$ compared with 17% in UC ($P < 0.01$). However, at 18 months there were no significant differences for HbA_{1c}, number of patients with $HbA_{1c} < 7.0\%$, or number treated with insulin.

Conclusions

Education was effective in improving glycaemic control and in delaying the need for insulin therapy in patients treated with maximal oral hypoglycaemic therapy. The reduced effect after one year was probably due to the discontinuation of the educational programme. Short-term education should not be offered without regular reinforcements integrated into standard diabetes care.

Introduction

In current guidelines self-management education is considered an essential part of the approach of patients with Type 2 diabetes. [1] Educational programmes should focus on general knowledge of diabetes, adherence to medication, lifestyle changes, and if possible self-monitoring of blood glucose. [2] One of the fundamental goals is to optimize glycaemic control, in order to prevent acute and chronic complications and to improve quality of life. [3] However , while there is unanimity about the importance of education, its effectiveness is still debated. [4] Recently , two systematic reviews of randomized controlled trials of the efficacy of self-management education in adults with Type 2 diabetes reported significant effects on glycaemic control shortly after the last patient-educator contact, but this effect tended to

diminish with longer follow-up. [5,6] These reviews, however, included only a few studies with a follow-up of more than 6 months. So the effects of education in the medium and long-term seem to be poor, and in any case not well established. Finally, most of the studies reviewed were conducted in secondary care, which hampers the generalizability of the results to patients treated in primary care.
Therefore we studied the efficacy in the short and long-term of a 6-month educational programme in Type 2 diabetes patients treated in primary care. We included those treated with maximal dosages of oral hypoglycaemic agents but still inadequately controlled ($HbA_{1c} \geq 7.0\%$), to assess the net effect of education.

Methods

Design

Patients were randomly assigned to an individual educational programme by a diabetes nurse (DN group), or to usual care by their general practitioner (GP) (UC group). Randomization was done by a telephone call to an independent trial centre, which used a computer-generated random assignment with blocks of eight at a time. The intervention period lasted 6 months. The medical ethics committee of the University Medical Centre of Utrecht approved the study. All patients gave written informed consent.

Patients and practices

Patients were recruited from 57 general practices (78 GPs) in and around the city of Utrecht, the Netherlands. The CONSORT flow chart (Fig. 1) shows the recruitment process. An assessment of 1810 patients' medical records by two research assistants was followed by a completion of the database. [7] Subsequently, in patients under age 76 years and with $HbA_{1c} \geq 7.0\%$, oral medication was optimized. [8] After this optimization, 76 patients had $HbA_{1c} \geq 7.0\%$ while taking the maximum feasible dosages of two different oral hypoglycaemic agents, mostly sulphonylurea and metformin. These patients were eligible for the present study. Exclusion criteria were: severe comorbidity (defined as having an illness that surpasses the impact of diabetes); insufficient understanding of spoken Dutch to follow instructions; or requirement for insulin therapy in the short term on account of severe hyperglycaemic symptoms. After 18 exclusions, and four withdrawals after randomization, the final study population included 54 patients.

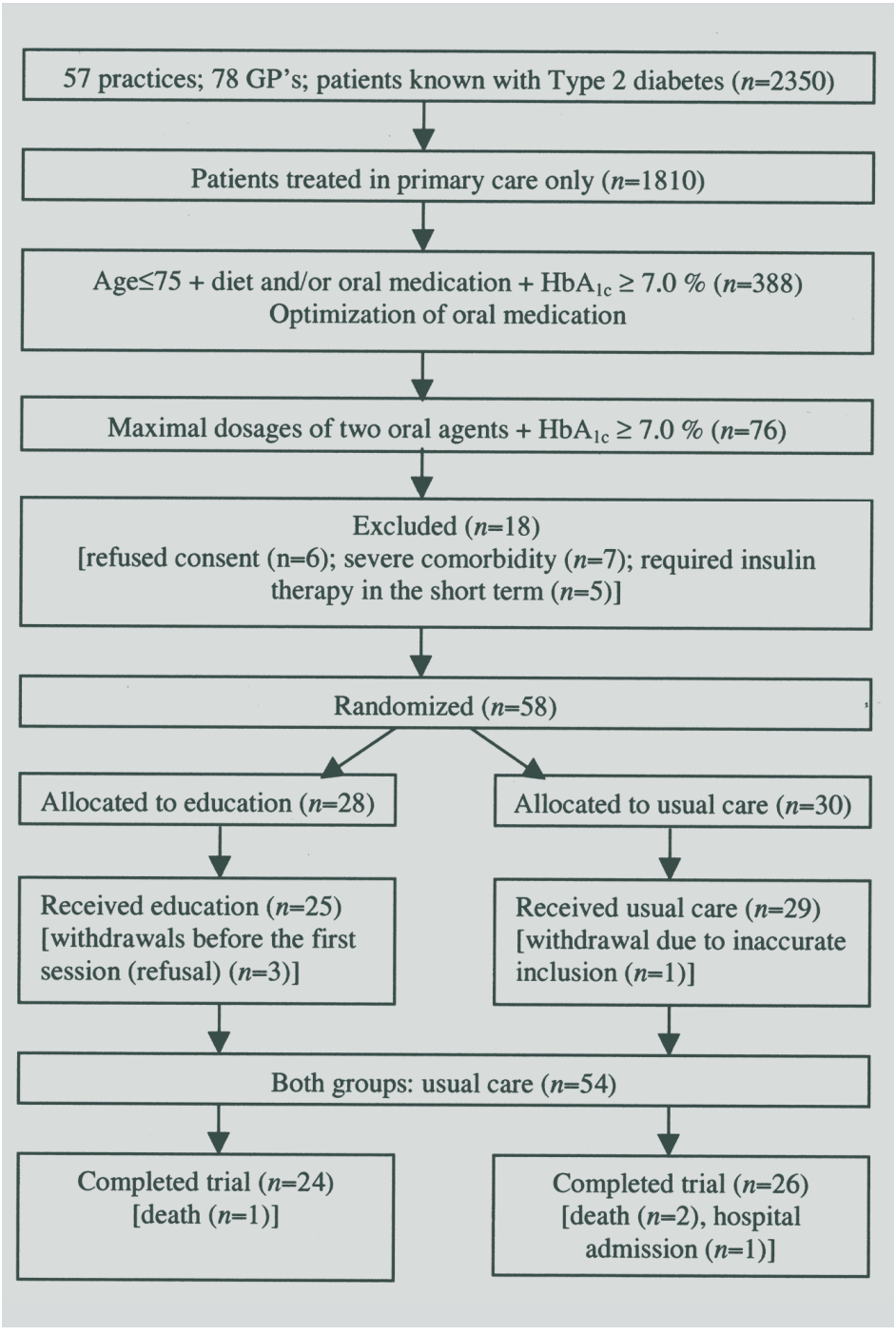


Figure 1 Trial profile

Table 1. Brief summary of the educational programme.

Session	Week	Duration (min)	Backgrounds	Medication	Physical exercise	Nutritional advice	Self-monitoring of blood glucose
1	0	45	Outline of diabetes Rationale of treatment	Compliance Time of taking drugs Adverse effects	Actual status Why of importance Measurement of body weight Tailored advice and goal setting		How to perform a self-test How to record results in a diary
2	3	30	Normal values for blood glucose and HbA_{1c} goal setting	Compliance	Evaluation and questions		Evaluation How to perform and interpret self-tests throughout the day
3	8	15	Questions	Compliance	Progress Evaluation of potential barriers	Review of actual calorie intake Ever visited a dietician? (if no: initiate referral)	Evaluation of self-tests How to code the meter Referral for HbA_{1c} test
4	14	15	Signs and symptoms of hypo- and hyperglycaemia?	Questions	Evaluation	Evaluation of potential barriers	Evaluation of HbA_{1c} test Evaluation of self-tests
5	20	15	Questions	Questions	Evaluation	Repetition	Evaluation of self-tests
6	26	15	Questions	Questions	Evaluation Measurement of body weight	Repetition, evaluation and questions	Evaluation of self-tests

Educational programme

The educational programme was developed in collaboration with the Dutch Foundation of Diabetes Nurses. It could be classified as a collaborative, 'mixed' educational intervention, [5] and was provided by two skilled diabetes nurses in one-to-one sessions. It focused on: general information on diabetes; reinforcing compliance with actual medication; importance of ph ysical exercise and losing body weight; and nutritional advice. All patients were also taught how to control their blood glucose at home on a regular basis, for which they were given a blood glucose meter (Glucotouch; Lifescan Benelux, Beerse, Belgium) and necessary materials (reagent strips, lancets). During the 6-month period, six sessions were given, at intervals of 3-6 weeks. The sessions were intended to take between 15 and 45 min, resulting in a total contact time of approximately 2.5 h. A brief outline of the programme is shown in Table 1. After the last session patients returned to usual care.

Usual care

Patients in the UC group remained under the care of their GP, and were managed according the current Dutch guideline on Type 2 diabetes. [9] This guideline recommends 3-monthly reviews, focusing on diabetic symptoms and measurement of fasting blood glucose, with education being given during normal medical appointments. During the 6-month intervention period the GP was asked not to refer the patient to a diabetes nurse. Furthermore, the GP was instructed not to alter the medication, unless a patient developed severe hyperglycaemic symptoms.

Outcome measures

HbA_{1c}% was measured at randomization, 7.5 months after randomization (6 weeks after the last session of the programme), and again 18 months af ter randomization, by turbidimetric inhibition immunoassay (Hitachi 917; Roche Diagnostics, Basel, Switzerland; normal range 4-6%). As part of the educational programme, in the DN group HbA_{1c} was also measured after the third session. Body weight was measured at randomization, and 6 months after randomization. One year after the last session the GPs were asked if patients had started with insulin treatment.

Statistical analysis

The primary outcome measure was the difference in HbA_{1c} between the two intervention groups. To detect a difference of at least 0.8%, which we assessed as clinically useful for this category of patients, 26 patients were needed in each group (SD 1.0, α 0.05, power 80%). Data are expressed as means and SD unless indicated otherwise. Analyses were based on intention to treat, with

the last value carried forward for missing data. Ineligible patients mistakenly randomized, and patients who withdrew before the start of the intervention, were excluded from analysis. [10]

Comparison between the two groups for HbA_{1c} and body weight was performed by analysis of covariance (ANCOVA), adjusting for baseline values. [11]

In addition, logistic regression was applied to assess the difference in proportion of patients who reached $HbA_{1c} < 7.0\%$, and who were treated with insulin.

Additionally , stepwise multiple linear regression analysis was used to assess the potential confounding effect on HbA_{1c} level reached at 6 weeks after the intervention by age, sex, body mass index, duration of diabetes, and educational level.

Results

The baseline characteristics of the participants, and of the original population from which they were drawn, are shown in Table 2.

Table 2 Characteristics at baseline of the original population, the final study group, and both intervention groups

	Original population	Final study group	Diabetes nurse group	Usual care group
Number of patients	1810	54	25	29
Age (years)	65.3 (10.4)	60.5 (13.3)	62.6 (9.0)	58.7 (11.4)
Sex (male %)	44	48	52	44
Educational level (%)				
Low	59	65	66	64
Middle	31	26	28	24
High	10	9	8	10
Duration diab (years)	4.6 (5.6)	7.5 (4.4)	7.3 (5.0)	7.6 (3.8)
Body mass index (kg/m^2)	28.7 (5.2)	30.0 (5.0)	30.2 (4.4)	29.8 (5.5)
HbA_{1c} (%)	7.1 (1.7)	8.5 (1.4)	8.2 (1.1)	8.8 (1.5)

Results are means (SD) or percentages.

In the original population 22% of the patients was treated with diet only, 66% with oral hypoglycaemic agents, and 12% with insulin. Characteristics of excluded patients were comparable to those of the study group (data not shown).

In the DN group all 25 patients completed the six sessions with the diabetes nurse, and during the programme there were no changes of medication for diabetes, nor any referrals for insulin therapy. In the UC group, however, two

patients (one man, age 42; one woman, age 50) were referred to secondary care before the end of the intervention period, because of symptomatic hyperglycaemia and comorbidity. The other 27 patients in the UC group had no change in antidiabetic medication.
The HbA_{1c} levels in both groups are shown in Fig. 2.

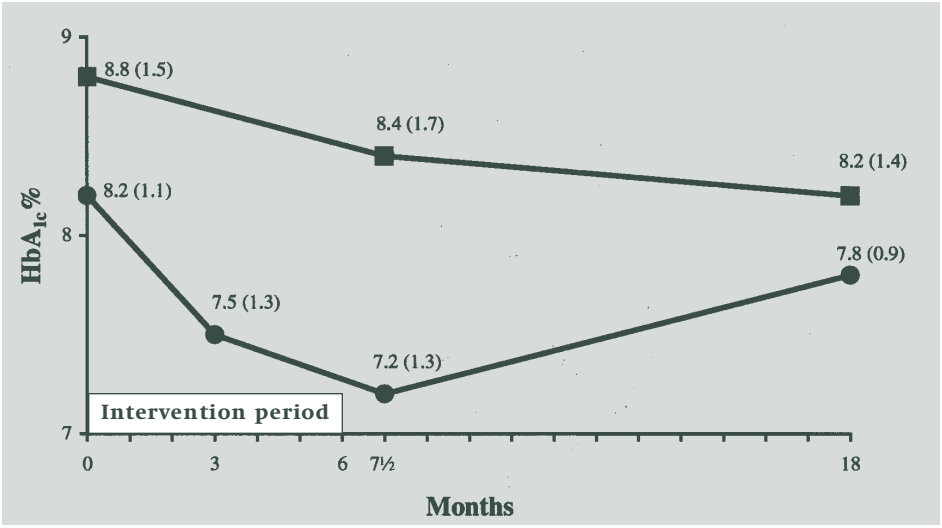


Figure 2. Mean HbA_{1c} values (SD) at baseline (0), and 3 (DN only) 7 and 18 months af ter randomization. Black squares: usual care group (UC), black circles: education group (DN) White bar: 6-month intervention period.

HbA_{1c} changed from 8.2 (1.1) to 7.2 (1.3) in the DN group, and from 8.8 (1.5) to 8.4 (1.7) in the UC group. Adjusted for baseline values, mean HbA_{1c} % in the DN group fell by 0.7 more than in the UC group (95% confidence interval (CI) 0.1, 1.4; P = 0.025). After adjustment for sex and duration of diabetes, the mean difference in HbA_{1c} % was 0.6 (95% CI 0.03, 1.2; P = 0.039). Further adjustment for other variables did not change the result. In the DN group 60% of the patients achieved HbA_{1c} levels < 7.0%, compared with 17% in the UC group (odds ratio 6.6; 95% CI 1.8, 24.5; P = 0.004). Finally, adjusted for baseline values, mean body weight in the DN group fell by 2.0 kg more than in the UC group (95% CI 0.4, 3.6; P = 0.013).
One year after the last session of the programme, data were available for 50 patients, three (one in the DN group and two in the UC group) having died, and one in the UC group having been hospitalized (Fig. 1). Adjusted for baseline, the difference between the mean change in HbA_{1c} in the two groups was 0.2% in favour of the DN group, not statistically significant (95% CI -0.7, +0.4; P = NS). Of the patients in the original DN group, 17% still had HbA_{1c}

levels < 7.0%, vs. 15% in the UC group (NS). Six patients (25%) of the DN group were receiving insulin therapy, vs. 10 patients (38%) of the UC group (NS).

Discussion

This randomized study involved patients in general practice, needing insulin therapy . Follow-up data were obtained 18 months after baseline, greater than most diabetes education studies. [6] Moreover , in addition, the net effect of education was studied since medication was not changed in both groups during 6 months.

The characteristics of the original population of diabetes patients were comparable to other recent investigations in general practices in the Netherlands, although glycaemic control seemed slightly better. [12,13] However , we assessed glycaemic control in a selection of the entire DM population of these practices, since patients treated by a diabetologist were excluded. The study group clearly differed from the original population: they were younger (age 60.5 vs. 65.3), had poorer glycaemic control (HbA $_{1c}$ % 8.5 vs. 7.1), and all had maximum oral medication.

The study demonstrates that in the short term structured individual education by a diabetes nurse led to a significant, and clinically relevant improvement in HbA $_{1c}$ level, with an average change of 0.7% at 6 weeks af ter intervention. In addition, 60% of the patients in the DN group, vs. only 17% in the UC group, reached HbA $_{1c}$ levels < 7.0%, an important indicator of the need for insulin.[3,9]

One year after the last session of the educational programme, however, most of the effects were lost. Thus, the long-term results of an educational programme without structured follow-up were disappointing.

The decline in HbA $_{1c}$ was accompanied by a considerable decrease of body weight in the DN group. This finding underlines the importance of weight management in patients with Type 2 diabetes, and it seems to rebut the widespread belief that people with diabetes cannot lose weight. [14]

It is noteworthy that glycaemic control in the control group gradually improved during the study (Fig. 2). This might be a regression-to-the-mean effect. [15] Moreover , since this was an unblinded study and randomization was done on a patient level, in the control group patients as well as doctors ha ve become increasingly aware of the issue of tighter control and started acting upon it. This may have diminished the effect of the intervention. Further improvement of HbA $_{1c}$ in the control group after the intervention could be the result of the switch to insulin therapy in 38% of the patients.

In this study the intervention was delivered by two skilled nurses with long experience in the field of diabetes, while in routine daily practice, educators

are likely to be less experienced and thus probably less effective. This aspect of the study might limit its generalizability.

If we compare our results with the outcomes of a systematic review by Norris et al,[6] which assessed the efficacy of 31 randomized controlled trials of self-management education on glycaemic control, some differences and some similarities stand out. Compared with the review' average decrease of HbA_{1c} of 0.3% at 1-3 months of follow-up, our result is encouraging. This does demonstrate that an educational intervention focused on blood glucose control using 2.5 h contact time was able to facilitate a relevant improvement in the short term.[6,16] However , probably a more comprehensive programme is needed to judge the effectiveness on other important issues, such as other cardiovascular risk factors, psychosocial well-being, and quality of life. The deterioration after 18 months was comparable to that found by Norris, who included only two studies with follow-up longer than 6 months.[17,18] It was probably due to the discontinuation of the educational programme, rather than worsening of diabetes over time.[19] The question remains whether the educational materials or the method of working of the diabetes nurses was (most) responsible. Nevertheless, the course was short and the educational materials were simple and cheap. Indeed, the nurses were experienced and for that reason we did not train them. One might argue that less experienced nurses should be trained before this intervention, and this might limit the generalizability of our results. This type of educational intervention is widely promoted in diabetes guidelines, without specifying possible subgroups of patients who might have the greatest benefit. Our results are encouraging for patients taking maximal oral medication who should start with insulin therapy . We expect that around two or three patients per practice (of 2500 patients) would need such an intervention each year. Our results stress the limited value of short-term educational programmes in diabetes care, and we are doubtful if education in this form should be offered without regular reinforcements integrated in standard diabetes care. Further research is needed to show whether such reinforcements can achieve sustained improvements in glycaemic control, and what time intervals are most cost-effective.[4,5]

References

1 Burgers JS, Bailey JV, Klazinga NS, Van der Bij AK, Grol R, Feder G. Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. Diabetes Care 2002; 25: 1933-9.

2 Piette JD, Glasgow RE. Education and home glucose monitoring. In: Gerstein HC, Haynes RB eds. Evidenced-Based Diabetes Care, Vol. 1. Hamilton/London: BC Decker , 2001; 207-51.

3 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002; 25: S33-49.

4 Wheeler ML, Wyle-Rosett J, Pichert JW. Diabetes education research. Care 2001; 24: 421-2.

5 Norris SL, Engelgau MM, Venkat Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001; 24: 561-87.

6 Norris SL, Lau 1 Smith SJ, Schmid CH, Engelgau MM. Selfmanagement education for adults with type 2 diabetes. A meta-analysis of the effect on glycemic control. Diabetes Care 2002; 25: 1159-71.

7 Goudswaard AN, Lam K, Stolk RP, Rutten GE. Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study. Fam Pract 2003; 20: 173-7.

8 Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. Improving glycaemic control in patients with type 2 diabetes mellitus without insulin therapy. Diabet Med 2003; 20: 540-4.

9 Rutten GEHM, Verhoeven S, Heine RJ, de Grauw WJC, Cromme PVM, Reenders K. NHG-Standaard diabetes mellitus type 2 (first revision). Huisarts Wet 1999; 42: 67-84 (in Dutch).

10 Fergusson D, Aaron SD, Guyatt G, H.bert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. Br Med J 2002; 325: 652-4.

11 Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. Br Med J 2001; 323: 1123-4.

12 Bouma M, Dekker JH, Van Eijk JT, Schellevis FG, Kriegsman DM, Heine RJ. Metabolic control and morbidity of type 2 diabetic patients in a general practice network. Fam Pract 1999; 16: 402- 6.

13 De Grauw WJ, van Gerwen WH, Van de Lisdonk EH, Van den Hoogen HJ, Van den Bosch WJ, van Weel C. Outcomes of auditenhanced monitoring of patients with type 2 diabetes. J Fam Pract 2002; 51: 459-64.

14 Pinkney J. Prevention and cure of type 2 diabetes. Br Med J 2002; 325: 232-3.

15 Yudkin PL, Stratton IM. How to deal with regression to the mean in intervention studies. Lancet 1996; 347: 241-3.

16 Raji A, Gomes H, Beard JO, MacDonald P, Conlin PR. A randomized trial comparing intensive and passive education in patients with diabetes mellitus. Arch Intern Med 2002; 162: 1301-4.
17 Kaplan R, Wilson D, Hartwell S, Merino K, Wallace J. Prospective evaluation of HDL cholesterol changes after diet and physical conditioning programs for patients with type II diabetes mellitus. Diabetes Care 1985; 8:343-8.
18 Mazzuca SA, Moorman NH, Wheeler ML, Norton JA, Fineberg NS, Vinicor F et al. The diabetes education study: a controlled trial of the effects of diabetes patient education. Diabetes Care 1986; 9: 1-10.
19 Anonymous. UKPDS 16: Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995; 44: 1249-58.

Chapter 6

Starting insulin therapy in patients with type 2 diabetes: with or without continuation of oral hypoglycemic agents? A randomized trial in primary care

Published as:
Goudswaard AN, Stolk RP, Zuithoff NPA, de Valk HW, Rutten GEHM. Starting insulin therapy in patients with type 2 diabetes: with or without continuation of oral hypoglycemic agents? A randomized trial in primary care. J Fam Pract 2004: in press.

Abstract

Objective

To evaluate the effects of insulin 30/70 twice daily or bedtime isophane (NPH) insulin plus continued sulfonylurea and metformin in patients with type 2 diabetes in primary care.

Study design

Open-label, randomized trial.

Population

Persons younger than 76 years with type 2 diabetes whose disease had not been controlled with oral hypoglycemic agents alone. A total of 64 insulin-naïve patients treated with maximal feasible dosages of sulfonylurea and metformin (baseline glycosylated hemoglobin [HbA_{1c}] 8.5%) were randomly assigned to insulin monotherapy (IM group; n=31) or insulin in addition to unchanged oral hypoglycemic medication (IC group; n=33) for 12 months. Insulin doses were adjusted to obtain fasting glucose <7.0 mmol/L and postprandial glucose <10.0 mmol/L.

Outcomes measured

Outcome measures included HbA_{1c}, treatment failure, weight, hypoglycemic events and symptoms, satisfaction with treatment, general well-being, and fear of injecting insulin and testing.

Results

HbA_{1c} improved from 8.3% to 7.6% in the IC group, and from 8.8% to 7.6% in the IM group (P=NS). The IC group had 24% treatment failures, compared with 2% in the IM group (P=.09). Patients in the IC group had less weight gain than those in the IM group (1.3 vs 4.2 kg; P=.01), and they reported fewer hypoglycemic events (2.7 vs 4.3; P=.02). Increased satisfaction with treatment was equal in the two groups, and general well-being improved by 3.0 points more in the IC group (P=.05). Fear of self-injecting and self-testing did not dif fer.

Conclusions

Bedtime NPH insulin in addition to an existing maximal therapy with sulfonylurea and metformin is an effective, simple, and well tolerated first choice approach for patients with uncontrolled type 2 diabetes.

Introduction

The goal for glycemic control in current guidelines on type 2 diabetes is a glycosylated hemoglobin (HbA_{1c}) value of <7.0%. [1] If this target is not achieved or maintained with sulfonylurea and metformin at maximally tolerated

dosages, insulin therapy is recommended as the next step for patients without advanced diabetes complications and with a reasonably long life expectancy .[2] There is little doubt that exogenous insulin aids in glycemic control at this stage of disease. It is still debated, though, whether insulin should be used as monotherapy or be added to a regimen of 1 or 2 oral agents (combination therapy). [3,4]

Guidelines on type 2 diabetes conflict with one another about indications for treatment and preferred regimens, and most recommendations are based on less-than-sufficient evidence. [1] For example, it is unclear in the case of combination therapy whether sulfonylurea or metformin or both should be continued. Moreover, the Dutch guideline on type 2 diabetes recommends that in combination therapy, the dose of isophane (neutral protamine Hagedorn or NPH) insulin be taken to a maximum of 40 IU, after which one should switch to a regimen of twice-daily insulin only. This recommendation is not based on published evidence. [5]

A number of randomized controlled trials have investigated the efficacy of different insulin regimens in patients whose diabetes was not controlled with oral agents. Few studies, though, have included patients using both sulfonylurea and metformin.[6] In addition, studies that have measured treatment satisfaction, general well-being, fear of injections, and hypoglycemic complaints are sparse. Although we know from observational studies that insulin therapy is usually well accepted, [7,8] little is known as to what extent patient satisfaction and quality of life are influenced by either treatment schemes.

The purpose of this study was to compare insulin monotherapy with insulin combination therapy in patients whose diabetes was inadequately controlled (HbA_{1c} ≥7.0%) despite maximally tolerated dosages of sulfonylurea and metformin. Endpoints included glycemic control, insulin dosage, body weight, number of treatment failures, number of hypoglycemic events and symptoms, treatment satisfaction, general well-being, and fear of injections and self testing.

Methods

Design

This was an open-label, parallel group trial of 12 months duration. Patients were randomly assigned to receive NPH insulin at bedtime (Insulatard; Novo Nordisk, Copenhagen, Denmark) in addition to current treatment with sulfonylurea and metformin (insulin combination [IC] group) or to receive a mixture of 30% soluble and 70% NPH insulin (Mixtard 30/70; Novo Nordisk, Copenhagen, Denmark), twice daily before breakfast and dinner

(insulin monotherapy [IM] group). Randomization was performed by a telephone call to an independent trial center that used a computer-generated random assignment. The medical ethics committee of the University Medical Centre of Utrecht approved the study. All patients ga ve written informed consent.

Patients

Patients were recruited from family practices in and around the city of Utrecht, the Netherlands. Patients were asked to participate if they were under age 76 years, had HbA_{1c} ≥7.0% despite treatment with both sulfonylurea and metformin in maximally tolerated dosages, were willing to start insulin therapy, and were deemed by their family physician to be candidates for more tight glycemic control.

Exclusion criteria were severe comorbidity (ie, an illness that surpasses the impact of diabetes or was associated with a short life expectancy) and insufficient understanding of spoken Dutch to follow instructions. The final study population was 64 patients (Figure 1).

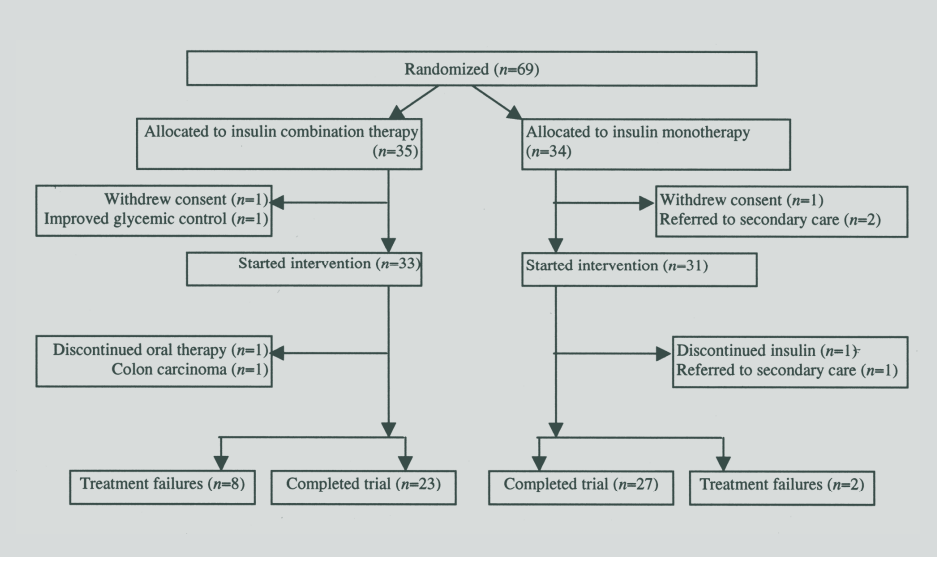


Figure 1 Trial profile

Study protocol

After randomization, patients were referred to the diabetes nurse of the family practice concerned to receive usual education for patients who should start with insulin therapy. This included information on diabetes (eg, symptoms of hypoglycemia), dietary counseling, and instructions on

how to inject insulin, how to monitor blood glucose levels before breakfast, after meals, and before bedtime twice weekly. Also, patients were instructed to register any symptomatic hypoglycemic event, with accompan ying measurement of the blood glucose value if possible, and to report whether assistance from a third party was required. Blood glucose values and hypoglycemic events were to be recorded in a personal diabetes diary.
Insulin therapy was initiated with 8 IU before bedtime in the IC group, and with 12 and 6 IU before breakfast and dinner in the IM group, respectively. Insulin dosages were adjusted twice weekly by telephone contact with the diabetes nurse (adjusting phase), aiming for a target fasting blood glucose of 4.0–7.0 mmol/L, and a target postprandial glucose of 4.0–10.0 mmol/L. When these targets were achieved and had proved stable, the insulin dose was fixed and telephone contacts were decreased to once monthly (stable phase).
Treatment failure was declared for patients in the IC group if glucose targets were not reached with a maximum daily dose of 40 IU NPH insulin. In the IM group, no ceiling was set for the insulin dose, but treatment was declared a failure when patients were switched to other treatment regimens due to unsatisfactory diurnal blood glucose profiles. Practice visits with the diabetes nurse or the family physician (according to local policy) were scheduled for 3, 6, 9, and 12 months after start of treatment.

Outcome measures

HbA_{1c}—measured by turbidimetric inhibition immunoassay (Hitachi 917; Roche Diagnostics, Basel, Switzerland; normal range 4%–6%)—and body weight were documented at randomization and at 3, 6, 9, and 12 months.
Frequency and severity of hypoglycemic events were monitored during telephone contacts and by checking patients' diaries. At 3 and 12 months, patients completed a hypoglycemic symptoms checklist including 18 autonomic, neuroglycopenic, and malaise symptoms, severity of which was scored on a 7-point scale, ranging from 0 (not at all) to 6 (very intense), providing a potential range of 0 to 108.
Treatment satisfaction was measured at baseline and at 3 and 12 months with the Dutch version of the Diabetes Treatment Satisfaction Questionnaire (DTSQ). [9] The DTSQ is a validated self-report questionnaire and consists of 8 questions, 6 of which refer to satisfaction with treatment. The answers were scored on a 0 to 6 Likert scale and summed to produce a measure of satisfaction with diabetes treatment, providing a potential range of 0 (very dissatisfied) to 36 (very satisfied).
Well-being was measured at baseline and at 3 and 12 months with the Dutch version of the 12-item Well-Being Questionnaire (WBQ-12). [10] The WBQ-12 consists of 12 assertions about the patients' feelings, and is divided into 3

subscales from which a General Well-Being score is calculated, providing a potential range of 0 (low) to 36 (high).
Fear of self-injecting with insulin (FSI) and fear of self-testing for blood glucose levels (FST) was assessed at 3 and 12 months by the short version of the Diabetes Fear of Injecting and Self-Testing Questionnaire (D-FISQ), which has proved useful for research in insulin-treated diabetes patients. [11] This self-report questionnaire consists of a 6-item subscale for FSI, and a 9-item subscale for FST. The items were scored on a 4-point Likert scale, ranging from 0 (almost never) to 3 (almost always), referring to the past month.

Statistical methods

The primary outcome of the study was the difference in HbA_{1c} between the interventions. To detect a difference of at least 0.8%, 32 patients were needed in each group (standard deviation [SD]=1.1, α=0.05, power=80%). Data were expressed as means ± SD unless indicated otherwise. Analyses were based on intention to treat, and missing data were fitted by the last-observation-carried-forward principle. Last available measurements were used for patients reaching a study end point before 12 months of follow-up. Outcome measurements were compared between the 2 intervention groups by either analyses of covariance (ANCOVA) adjusting for baseline values, [12] unpaired t tests, or Mann-Whitney U test. The probability of treatment success was analyzed using Kaplan-Meier plots with the log-rank test. $P<.05$ was considered statistically significant. Data analyses were performed with SPSS release 11 (SPSS Inc, Chicago, Ill, USA).

Results

In total, 69 patients were randomized, 5 of whom did not initiate the intervention. The flow through the trial of the remaining 64 patients is shown in Figure 1. Baseline characteristics of included patients are summarized in Table 1. Except for weight and body mass index, no significant differences were found between the groups.

Glycemic control and insulin dosage

In both groups, HbA_{1c} improved, mainly during the first months (Figure 2). In the IC group, mean decrease was 0.8 ± 1.3%, vs 1.2 ± 1.2 in the IM group. Adjusted for baseline values, HbA_{1c} for IM fell by 0.14% more than for IC (95% confidential interval [CI], −0.72 to 0.44; P=NS). In the IC group, 36% of the patients reached HbA_{1c} levels <7.0%, compared with 42% in the IM group (P = NS). When treatment failures (see below) were omitted, mean decrease of HbA_{1c} for IC was 1.0 ± 1.2% (Figure 3). Mean daily insulin dosages at endpoint

Table 1. Characteristics at baseline N=64

	IC	IM
Number of patients	33	31
Age (years)	58,6 (8,6)	58.3 (11.3)
Sex (male/female) (%)	54 / 46	42 / 58
Duration of diabetes (years)	7.2 (3.9)	7.7 (4.8)
Body weight (kg)	96.3 (19.4)	81.0 (14.3)*
Body mass index (kg/m ^{2})	33.2 (6.4)	28.5 (3.8)*
HbA_{1c} (%)	8.3 (0.9)	8.8 (1.5)
Satisfaction with treatment	28.0 (8.2)	26.1 (8.1)
General well-being	21.7 (8.1)	22.7 (6.9)

Results are means (SD), numbers, or percentages; * $P < 0.01$

IC insulin combination therapy; IM insulin monotherapy

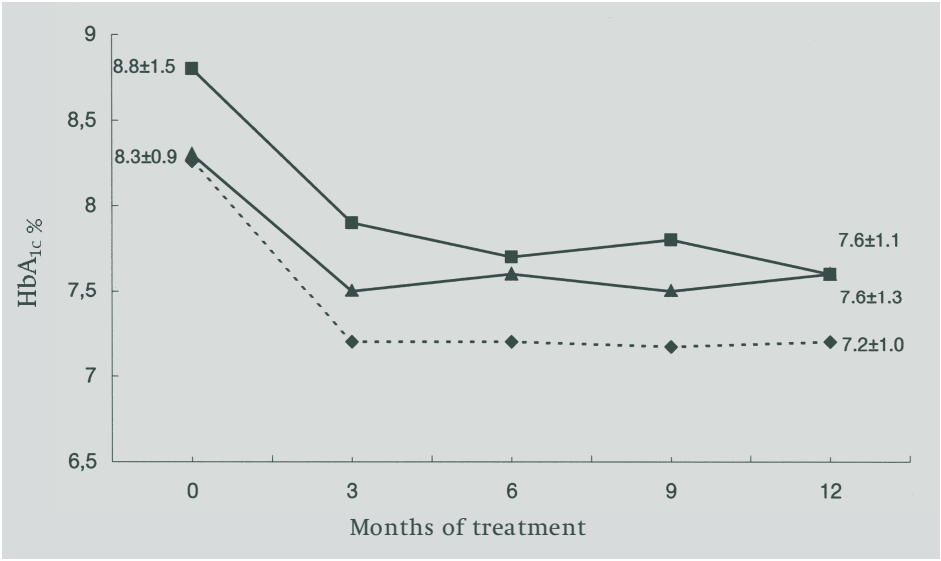


Figure 2 Course of HbA_{1c} values (SD) during the study.

Black squares: IM group; Black triangles: IC group; Black diamonds: IC group without treatment failures

were 25.8 ± 12.2 IU for IC vs 68.3 ± 27.5 for IM. Mean daily dosages adjusted for body weight were 0.27 ± 0.13 IU/kg for IC vs 0.86 ± 0.37 for IM.

Treatment failures

In the IC group, 8 patients (24%) experienced a treatment failure because glucose targets were not reached with a daily dose of 40 IU NPH insulin. The mean time for reaching this study end point was 4.6 months (range, 1–10).

HbA_{1c} deteriorated in this period from 8.5 ± 1.3 % to 8.6 ± 1.5%. Age, sex, duration of diabetes, and baseline values for HbA_{1c}, body mass index, treatment satisfaction, and general well-being of these patients did not significantly differ from those who completed the study on IC therapy (data not shown). Mean daily insulin dosages at end point, adjusted for body

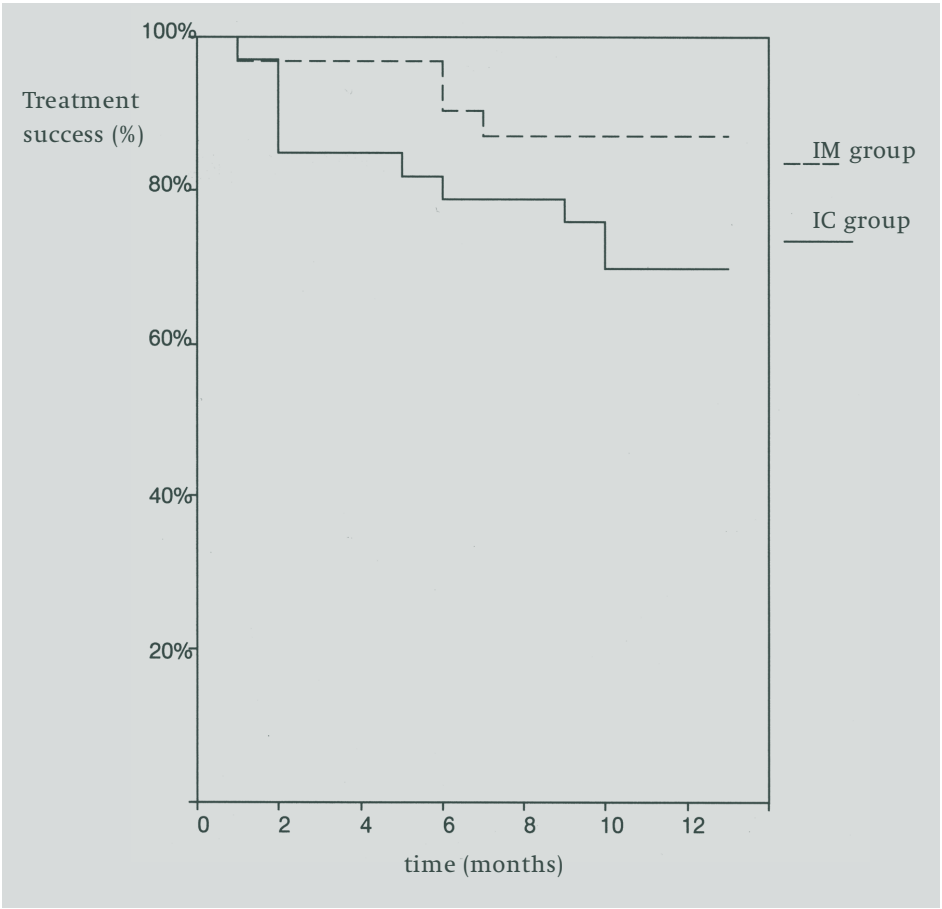


Figure 3 Kaplan-Meier curves showing treatment success of insulin combination therapy (IC) and insulin monotherapy (IM)

weight, were 0.41 ± 0.13 IU/kg for treatment failures vs 0.23 ± 0.11 for non-treatment failures (95 % CI, 0.10 to 0.28; P<.001). In the IM group, 2 patients (6%) were switched to another insulin regimen due to unsatisfactory diurnal glucose profiles. Figure 3 shows the Kaplan-Meier curves of probability of treatment success. Log-rank test showed a borderline significant dif ference between the groups (P=.09).

Weight gain

In the IC group, body weight increased with 1.3 ± 3.9 kg, compared with 4.2 ± 4.3 kg in the IM group. Adjusted for baseline values, body weight in the IM group increased by 3.0 kg more than in the IC group (95% CI, 0.68 to 5.25; P=.01).

Hypoglycemic events and symptoms

The average number of hypoglycemic events per patient was 2.7 ± 5.2 in the IC group, and 4.3 ± 4.3 for the IM group (P=.02). For events accompanied by documented blood glucose values <4.0 mmol/L, the results were 2.4 ± 5.2 and 2.7 ± 3.5, respectively (P=.1). All events were mild, expect for 1 patient in the IM group who experienced 2 severe events (unconsciousness and support needed from a third party). At 3 and 12 months, hypoglycemic symptoms scores were 17.2 ± 13.3 and 16.3 ± 16.0 for IC, vs 19.1 ± 15.6 and 22.4 ± 15.7 for IM (P=NS).

Diabetes treatment satisfaction and general well-being

Satisfaction with treatment improved in the IC group from 28.0 ± 8.2 to 30.9 ± 5.1, and in the IM group from 26.1 ± 8.1 to 28.4 ± 7.4. Adjusted for baseline values, the difference between the mean change scores was not significant (95% CI, −5.0 to 1.0; P=NS). Well-being scores increased from 21.7 ± 8.1 to 25.1 ± 6.8 in the IC group, vs 22.7 ± 6.9 to 22.8 ± 7.6 in the IM group. Adjusted for baseline scores, well-being for IC improved by 3.0 points more than for IM (95 % CI, 0.02 to 5.8; P=.05).

Fear of self-injecting and self-testing

At 3 and 12 months, FSI scores were 0.6 ± 1.3 and 0.5 ± 1.1 in the IC group, vs 2.1 ± 4.1 and 1.0 ± 2.1 in the IM group. For FST, these scores were 0.6 ± 1.9 and 2.3 ± 4.8 in the IC group, and 2.5 ± 4.4 and 1.7 ± 3.6 in the IM group. At neither 3 nor 12 months were statistical differences found between the groups. Approximately 70% of the patients in both groups had scores of 0 (no fear at all) on both subscales.

Discussion

In this practice-based study of insulin-naïve patients, HbA_{1c} improved ~1 percentage point with both insulin combination therapy and insulin monotherapy . However, with both strategies, around 40% of patients reached HbA_{1c} levels <7%, which forces us to be realistic regarding the glycemic target that can be achieved in the current family practice setting. Despite systematic titration of the insulin dosage, 24% of the patients in the IC group did not

reach the titration targets. In addition, HbA $_{1c}$ levels for those patients did not change from baseline, in contrast with patients in the IC group who did reach the targets (Figure 2). So it is doubtful if lower HbA $_{1c}$ levels could have been achieved if the study design had allowed for increasing the daily insulin dose over 40 IU.

Treatment failure rate in this study was considerably lower compared with 66% failures reported in another trial in which insulin NPH or glargine was added to oral therapy. [13] However , this difference could probably be explained by a difference in target for fasting blood glucose: ≤5.6 mmol/L vs ≤7.0 in our study. So it might be relevant in future research to seek factors that could predict failure on oral agent/insulin combinations. [14]

With insulin monotherapy, body weight increased significantly more, and patients experienced more hypoglycemic events. Treatment satisfaction did not differ, whereas general well-being improved more with combination therapy. For most patients, the injection- and test-activities appeared to be well tolerated, with no differences between treatment groups.

Though several trials have been conducted to compare insulin combination therapies with insulin monotherapy in insulin-naïve patients, [6,15–17] studies with follow-up >6 months, and including patients taking maximum dosages of two oral agents, are sparse. Moreover, no studies have been conducted in a primary care setting. Chow et al compared a regimen of bedtime NPH insulin and 1 or 2 oral agents with a regimen of premixed insulin 30/70 in 53 mostly lean patients during 6 months. [18] The effects on HbA $_{1c}$, body weight, and number of hypoglycemic events were comparable to our results, and a similar treatment failure rate in the combination group was found.

Yki-Järvinen et al studied the effects of 4 insulin regimens including the addition of bedtime NPH insulin to either morning NPH, glyburide, metformin, or glyburide plus metformin in patients previously treated with maximal dosage sulfonylurea. [19] The greatest decrease in HbA $_{1c}$ accompanied by the lowest number of hypoglycemic events was observed in the insulin/metformin group. However, the impact of these results might be limited, since current guidelines recommend treatment with maximum doses of both sulfonylurea and metformin before introducing insulin therapy. [2,8] Nevertheless, the results underline the favorable influence on relevant outcomes of insulin combination therapy compared with insulin monotherapy , provided that at least metformin is used.

Patients in our study were recruited during regular appointments with their own care provider, and insulin treatment was established under “usual care” conditions. So it is likely that this study group represents the type 2 diabetes patients in primary care that, sooner or later, should start insulin therapy, and that the results of this study are highly applicable to them. Our results

suggest that an evening injection with NPH insulin in addition to an existing maximal therapy with sulfonylurea and metformin can be recommended as an effective, simple, and well-tolerated first-choice approach with patients who are willing to continue oral medication. Since both family physicians and patients are inclined to delay starting insulin, [20] such a strategy might encourage the timely use of insulin. [14]

References

1 Burgers JS, Bailey JV, Klazinga NS, Van der Bij AK, Grol R, Feder G Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. Diabetes Care 2002; 25:1933–1939.

2 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002; 25:S33–S49.

3 Garber AJ. Benefits of combination therapy of insulin and oral h ypoglycemic agents. Arch Intern Med 2003; 163:1781–1782.

4 Westphal SA, Palumbo PJ. Insulin and oral hypoglycemic agents should not be used in combination in the treatment of type 2 diabetes. Arch Intern Med 2003; 163:1783–1785.

5 Rutten GEHM, Verhoeven S, Heine RJ, et al. Diabetes mellitus type 2. NHG standaard (eerste herziening) (in Dutch). Huisarts Wet 1999; 42:67–84.

6 Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care 2001; 24:758–767.

7 De Sonnaville JJ, Snoek FJ, Colly LP, Deville W, Wijkel D, Heine RJ. Well-being and symptoms in relation to insulin therapy in type 2 diabetes. Diabetes Care 1998; 21:919–924.

8 De Grauw WJ, Van de Lisdonk EH, Van Gerwen WH, Van Den Hoogen HJ, Van W eel C. Insulin therapy in poorly controlled type 2 diabetic patients: does it af fect quality of life? Br J Gen Pract 2001; 51:527–532.

9 Bradley C. Handbook of Psychology and Diabetes. A Guide to Psychological Measurement in Diabetes Research and Practice. Amsterdam: Harwood Academic Publishers; 1994.

10 Pouwer F, Snoek FJ, Van der Ploeg HM, Ader HJ, Heine RJ. The well-being questionnaire: evidence for a three-factor structure with 12 items (W-BQ12). Psychol Med 2000; 30:455–462.

11 Mollema ED, Snoek FJ, Pouwer F, Heine RJ, Van der Ploeg HM. Diabetes Fear of Injecting and Self-Testing Questionnaire: a psychometric evaluation. Diabetes Care 2000; 23:765–769.

12 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. BMJ 2001; 323:1123–1124.

13 Riddle MC, Rosenstock J, Gerich JL. The treat-to-target trial. Diabetes Care 2003; 26:3080–3086.

14 Riddle MC. Timely addition of insulin to oral therapy for type 2 diabetes. Diabetes Care 2002; 25:395–396.

15 Peters AL, Davidson MB. Insulin plus a sulfonylurea agent for treating type 2 diabetes. Ann Intern Med 1991; 115:45–53.

16 Pugh JA, Wagner ML, Sawyer J, Ramirez G, Tuley M, Friedberg SJ. Is combination sulfonylurea and insulin therapy useful in NIDDM patients? A meta-analysis.

Diabetes Care 1992; 15:953–959.
17 Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. Arch Intern Med 1996; 156:259–264.
18 Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. Diabetes Care 1995; 18:307–314.
19 Yki-Järvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999; 130:389–396.
20 Veltmaat LJ, Miedema K, Reenders K. Overschakeling op insuline bij NIADM-patiënten. Een literatuurstudie naar criteria, voorkomen en belemmerende factoren (in Dutch). Huisarts Wet 1995; 38:608–613.

Chapter 7

Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. A systematic review

An extended version of this review is accepted with minor revisions by the Metabolic and Endocrine Disorders group of the Cochrane Collaboration as:
Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus.

Abstract

Objectives

It is unclear, whether patients with type 2 diabetes who have insufficient glycaemic control despite maximal oral hypoglycaemic agents should be switched to insulin as monotherapy or in combination with oral agents (combination therapy). The objective of this systematic review was to assess the effects of monotherapy versus combination therapy on glycaemic control, patient satisfaction, quality of life, diabetes related morbidity and mortality, and adverse effects (e.g. h ypoglycaemia, weight gain) in patients with insulin-requiring type 2 diabetes mellitus.

Methods

Eligible studies were identified by searching MEDLINE, EMBASE, and the Cochrane Controlled Trials Register (CCTR) up to May 2002. Included were randomised controlled trials (RCTs) of minimum treatment duration 2 months, comparing insulin monotherapy (all schemes) with combinations of insulin with single or multiple oral hypoglycaemic agents. There was no restriction on language of the publications. Data extraction and assessment of study quality were undertaken by three reviewers in pairs.

Results

Mean methodological quality score (range 0 - 7) of the 20 included RCTs was 2.6 (95% CI 1.5 to 3.7). Twenty-eight comparisons in 20 RCTs were ordered according to clinical considerations. Sufficient data could be extracted from 12 studies to calculate pooled effects on glycaemic control. No significant differences with respect to glycaemic control were detected between oral hypoglycaemic agents with bedtime NPH insulin compared with insulin monotherapy given as twice daily, or multiple daily injections. Combination therapy was associated with a relative reduction in total daily insulin requirement of 46% compared to monotherapy (all schemes). Of 14 studies that reported hypoglycaemia, all but one demonstrated no significant difference in the frequency of hypoglycaemic events (symptomatic or biochemical) between monotherapy and combination therapy. Combination therapy including bedtime NPH insulin and metformin, resulted in statistically significant less weight gain compared to monotherapy. Quality of life related issues were investigated in only four studies.

Conclusions

No difference was found with respect to glycaemic control between insulin monotherapy versus a single bedtime injection of NPH insulin in addition to a common oral agent regimen. Therefore combination therapy should be recommended as an easy applicable starting point for insulin requiring type 2 diabetes patients.

Introduction

Diabetes mellitus is a chronic metabolic disorder resulting from a fundamental defect in insulin secretion, insulin action, or both. Insulin deficiency (relative or absolute) leads to chronic hyperglycaemia (i.e. elevated levels of plasma glucose) with associated disturbances of carbohydrate, fat and protein metabolism. Long-term (microvascular) complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease also increases. In the United Kingdom Prospective Diabetes Study (UKPDS) of newly diagnosed type 2 diabetes patients, compared with conventional therapy, intensive glucose control (mean HbA_{1c} 7.0% versus 7.9%) resulted in a statistically significant 25% risk reduction of microvascular complications, and in a non-significant 16% risk reduction of myocardial infarction.[1] Consequently , most guidelines on glycaemic management of type 2 diabetes recommend a target HbA_{1c} < 7%. Initial treatment of patients with type 2 diabetes should include dietary advice and education. Weight reduction in obese patients and exercise improve insulin sensitivity .[2,3] If non-pharmacological measures are insufficient, oral hypoglycaemic therapy is indicated. Later, as oral agents become less efficacious, exogeneous insulin, given either as monotherapy, or in combination with (an) oral hypoglycaemic agent(s), may be required to reach the target of HbA_{1c} < 7% .

The UKPDS also demonstrated that despite treatment with oral hypoglycaemic agents, a substantial proportion of patients need insulin therapy to maintain strict glycaemic control. [4]

Previously , the effects of insulin have been controversial. [5,6] The side effects of weight gain and hypoglycaemia are well known. Besides, exogenous insulin was considered to be a risk factor for cardiovascular complications for a long time. The UKPDS and other studies have found no evidence for this. [7] It is also uncertain if, and how, insulin therapy may influence 'quality of life' and patient treatment satisfaction. Improving glycaemia per se can improve general well-being. However, daily injections with insulin, home monitoring of blood glucose, episodes of hypoglycaemia and referral from primary to secondary care can interfere with daily functioning of patients. [8-10]

The UKPDS did not determine the optimum strategy for insulin therapy in type 2 diabetes i.e. insulin monotherapy or insulin combined with oral hypoglycaemic agents, because the latter regimen was not used. Three previous reviews comparing insulin monotherapy to insulin/oral hypoglycaemic agent combination therapy have focused on insulin combined with sulphonylureas or placebo, excluding other groups of oral agents. [11-13] The reviews included studies where either insulin-treated patients were

randomised to the addition of a sulphonylurea or placebo, or where insulin-requiring patients with insufficient glycaemic control with oral hypoglycaemic agents alone were randomised to insulin combined with sulphon ylurea therapy or insulin alone. These reviews were limited in design and did not explicitly address the aim of the present study; namely to determine the optimum insulin strategy for patients with unsatisfactory glycaemic control despite oral hypoglycaemic therapy. Despite the apparent similarities of the above mentioned reviews, the authors' conclusions differed. Peters et al. concluded that combination therapy should not be used in insulin treated patients with type 2 diabetes since improvement was only slight, and blood glucose values were not normalised with this therapy. [13] The later reviews of Pugh et al. and Johnson et al. however, recommended insulin/sulphon ylurea combination therapy, finding it to be more ef ficacious than insulin alone. [11,12] More recently, Yki-Järvinen published a qualitative overview of ten studies, [14] and concluded that insulin monotherapy was not superior to combination therapies with respect to glycaemic control. However , this review had a limited search strategy and does not meet the criteria of the Cochrane Collaboration. Therefore, an up-to-date systematic review conforming to the methods of the Cochrane Collaboration has been undertaken to clarify the potential benefits of combination therapy compared to insulin monotherapy.

The objective was to assess the effects of insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents on diabetes related morbidity and mortality, glycaemic control, patient satisfaction, quality of life, and adverse effects (e.g. hypoglycaemia, weight gain) in patients with type 2 diabetes mellitus with inadequate glycaemic control despite treatment with oral hypoglycaemic agents.

.

Methods of the review

Criteria for considering studies for this review

Included were RCTs comparing insulin monotherapy to combinations of insulin with single or multiple oral hypoglycaemic agents in patients with type 2 diabetes mellitus, with inadequate glycaemic control despite oral hypoglycaemic therapy. All trial designs including cross-over studies and cluster randomisation were not excluded.

Specific inclusion criteria were:

- Follow-up time: minimum of two months
- Types of participants: patients with type 2 diabetes (according to appropriate diagnostic criteria of the time) in any health care setting with inadequate glycaemic control with oral hypoglycaemic agents

- Types of interventions: insulin monotherapy compared to combinations of insulin with single or multiple oral hypoglycaemic agents
- Outcome measures: diabetes-related morbidity and mortality; glycaemic control (fasting blood glucose (FBG), HbA_{1c}, HbA_1); quality of life (ideally using validated scales); patient satisfaction (ideally using validated scales); amount of insulin required for good glycaemic control; adverse effects (frequency of hypoglycaemia, weight gain, gastrointestinal symptoms).

Search strategy for identification of studies

This review was conducted within the Metabolic and Endocrine Disorders Group (MEDG) of the Cochrane Collaboration and submitted to this group. Adaptations of the Cochrane Collaboration search strategy were used to identify randomized controlled trials (RCTs) with the following key words: randomised-controlled-trial, controlled-clinical-trial, random-allocation, double-blind, single-blind, clinical-trial and related free text words. The subject heading for the disease was Diabetes-Mellitus-Non-Insulin-Dependent. Subject headings and free-text words used to identify the intervention were insulin and hypoglycaemic agents. The reference lists of relevant studies identified were also scrutinised to identify other potentially relevant studies. The following databases were searched: Medline (1966 - 2002), Embase (1974 - 2002), and the Cochrane Controlled Trials Register (2002). Relevant published studies of any language were included. The full search strategy for each database can be obtained from the Editorial Base of the MEDG.

Trial selection

References identified from searches were entered into Reference Manager 10. To determine the studies to be assessed further, one reviewer (ANG) scanned titles, abstract and keywords of every record retrieved. Abstracts of potentially relevant studies were assessed by two reviewers independently (ANG, GDV). Full articles were retrieved for further assessment if the information given suggests that the study:

- Included patients with type 2 diabetes mellitus;
- Compared insulin with a combination of insulin with (an) oral hypoglycaemic agent(s);
- Assessed one or more relevant clinical outcome measure;
- Used random allocation to compare groups.

Where details regarding these criteria were inadequate from the information given in the title and abstract, the full article was retrieved for clarification. Interrater agreement for study selection was measured using the kappa statistic. [15] Differences in opinion were discussed with a third party (NJF).

Data extraction and quality assessment of trials

A template data extraction form was developed, piloted and approved by the MEDG Editorial Base before final data extraction commenced. Data extraction and data entry was performed independently in pairs (ANG+GDV and ANG+NJF). Differences in data extraction was resolved by consensus with the fourth reviewer (RPS), with referral to the original article. Where the published report contained incomplete (or absent) data, the reviewers contacted the first author. Interrater agreement was calculated and in cases of disagreement, the MEDG was consulted and a judgement made was based on consensus. The quality of the trials was assessed using standard criteria from the MEDG, which includes the criteria of Jadad and Schulz [16,17] and is subdivided in internal validity -, descriptive - and statistical criteria. In particular , the following factors were assessed:

Minimisation of selection bias

1 Was the randomisation procedure adequate?
2 Was the allocation concealment adequate?

Minimisation of performance bias

3 Were the patients blind to the intervention?
4 Were people administering the treatment blind to the intervention?

Minimisation of attrition bias

5 Were withdrawals and dropouts completely described?
6 Was analysis done by intention-to-treat?

Minimisation of detection bias

7 Were outcome assessors blind to the intervention?

Based on these criteria, studies were allocated a score that ranged from 0 to 7. Studies were not excluded on the basis of methodological criteria alone.

The same reviewers extracted and summarized the data including:

1 General information: title, authors, reference/source, contact address, country, urban/rural etc., language of publication, year of publication, duplicate publications, sponsoring, setting.
2 Trial characteristics: design, duration, randomisation (and method), allocation concealment (and method), blinding (patients, people administering treatment, outcome assessors), assessment of blinding.
3 Intervention(s): placebo included, interventions(s) (dose, route, timing), comparison intervention(s) (dose, route, timing).
4 Patients: sampling (random/convenience), exclusion criteria, total number and number in comparison groups, sex, age, duration of diabetes, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals/losses to follow-up (reasons/description), subgroups.
5 Outcomes: outcomes specified above (also: what was the main outcome

assessed in the study?), any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes.

6 Results: for outcomes and times of assessment (including a measure of variation), if necessary converted to measures of effect specified below; intention-to-treat analysis.

Data analysis

Due to the availability of data only the outcomes glycated haemoglobin (HbA_{1c} or HbA_1) and weight gain were (partially) pooled in a meta-analysis. If change-from-baseline values for $HbA_{1[c]}$ were not provided, these were computed using baseline and post-treatment values (eventually distracted from graphs). When standard deviations of mean differences for the main outcome $HbA_{1[c]}$ were not present in the publications, these data were computed assuming a general correlation coefficient that was derived from baseline and post-treatment outcomes for $HbA_{1[c]}$ in studies that presented accompan ying standard deviations (see Appendix for details). Glycated haemoglobin values determined with different methodologies were standardized to a reference range of 4.0 - 6.0 %. Insulin requirement in combination therapy regimens was expressed as a relative reduction in insulin dose compared to monotherapy, expressed a percentage (weighted mean). Differences underlying the results of studies (statistical heterogeneity) was assessed using both the Q-test (with a P-value < 0.1 considered as significant) and by I^2, which is a quantity that describes the degree of inconsistency across studies. [18] I^2 can range from 0% (no heterogeneity) to 100%. Clinical heterogeneity was determined by comparing the studies with regard to different clinical parameters: patient characteristics, disease duration, interventions, and outcome. Where significant clinical or statistical heterogeneity was found, it was considered unreasonable to assume one 'true' effect underlying the data constant across different populations, necessitating a random-effects model to pool data. [19]

Subgroup analyses were performed for the following variables: different oral hypoglycaemic agent(s) and different types of insulin, timing and frequency of insulin injections.

Sensitivity analyses were planned (when appropriate) in relation to study quality (as specified above), duration and sample size to determine how these factors influenced results.

Results

The search strategy provided 1709 citations. After exclusion of duplicate publications, and studies clearly not related to the objective of the review,

two reviewers independently assessed the remaining 192 abstracts. Full text was obtained of 127 potentially relevant studies, of which 22 fulfilled the inclusion criteria of the review. [20-41] After elimination of two duplicate publications, [26,29] 20 relevant studies remained. The observed agreement in trial selection was 94% (kappa=0.7; 95% CI 0.6 to 0.9). For unclear cases, agreement was reached by reading the article jointly, followed by discussion. The observed overall agreement in the extraction of the data was 95%. Af ter discussion all disagreements were resolved. We contacted Chow, Fövén yi, Holman, and Pontiroli for further details regarding their studies; all provided further information. Reasons for exclusion of studies were: patients were previous treated with insulin (n=47), absence of a treatment arm with either monotherapy with insulin or with a combination of insulin with oral hypoglycaemic agents (n=32), non-appropriate study design (n=12), and 'other reasons' (n=14). Fifteen articles (75%) were published in English, three in German, [20,27,28] one in Dutch, [37] one in Hungarian, [23] and two in Chinese. [36,39] No eligible trials were found before the year 1987. At least 50% of the studies were sponsored by the pharmaceutical industry.

Studies and participants

All included studies were randomised controlled studies (RCTs), of which 16 had a parallel design, and four a crossover design. [25,30,31,32] Weighted mean trial duration was 10.0 months (range 2 - 36 months). A total of 1811 participants (mean per study 91; range 10 - 432) were included, with 46% male (range 29 - 64%). Gender was not reported in 5 trials. [24,27,31,33,35] Participants had mean age 59.8 years (95% CI 57.6 to 62.1), and mean known duration of diabetes was 9.6 years (95% CI 8.3 to 10.9). All studies provided information on the treatment with oral hypoglycaemic agents at baseline. Further details and criteria for entry into the individual studies are listed in Table 1.

Study setting

In one study patients were recruited in primary care, [25] all others were conducted in secondary care. In 3 studies, patients were admitted to the hospital for baseline measurements and the initiation of insulin therapy. [24,31,40]

Characteristics of interventions

Twenty studies providing 28 relevant comparisons between insulin monotherapy and insulin-oral hypoglycaemic agent combination regimens were evaluated. In five studies more than one comparison were assessed. [21,25,38,41,41] In both mono- and combination therapy groups, insulin was applied as a once daily (morning or bedtime), a twice daily, or a multiple injection regimen. Sulphonylurea (SU) was the most frequently used class of

oral agent in combination therapy regimens (75%). Sulphonylurea plus metformin, and metformin alone accounted for 21 % and 4%, respectively. Comparisons were initially categorised according to mode of insulin monotherapy , and subsequently sub-categorised according to combination therapy regimen used, to provide clinically relevant comparisons:

1 Insulin monotherapy once daily versus combination regimens; [25,28,30,32-36,39]
2 Insulin monotherapy twice daily versus combination regimens; [20,22-24,27,31,37,38,40,41]
3 Insulin monotherapy multiple injections versus combination regimens. [21,25,40]

Outcome measures of included studies

None of the studies assessed diabetic complications, diabetes-related mortality or total mortality. All except three studies [20,28,31] reported glycaemic control as mean values of HbA_1 [25,27,32,33] or HbA_{1c}. Five studies provided change-from-baseline values for glycated haemoglobin with standard deviations. [21,33,34,40,41] Fasting blood glucose values were not reported in two studies. [23, 41] Three studies did not state the method of analysis for glycated haemoglobin. [21,36,39] Fourteen studies provided values for change from baseline of body weight, or body mass index. [21-25,27,32-35,37,38,40,41] Insulin requirement was reported in all but three studies. [31,36,39] Patient satisfaction, general well-being or quality of life was assessed in four studies. [22,37,38,40]

All but seven studies [23,28,30-32,37,39] provided some information regarding hypoglycaemia, though only three [33,40,41] provided quantitative data for hypoglycaemic events with standard deviations. Other kinds of adverse effects were reported in two studies. [21,34]

Methodological quality of included studies

Mean methodological quality was 2.6 (range 0 - 7; 95% CI 1.5 to 3.7). The methodological quality scores of the studies (scale range 0 - 7) were assigned using the criteria described above, and are listed in Table 1. Only published trial information was used to determine the quality score. Inter-observer calculation of the items of study quality revealed a substantial observed agreement of 82% (kappa = 0.6; 95% CI 0.5 to 0.8).

Of 20 RCTs, only five had adequate concealment of allocation. [32-34,40,41] Eight studies detailed the method of randomisation, [21,22,27,32,33,35,40,41] although in two trials the method could not be considered adequate. [22,27]

Stated method of blinding was open in eleven studies, single-blinding in two, double-blinding in three, and triple-blinding in four. None of the studies reported checking of blinding conditions in patients and health care providers.

Seventy per cent of studies reported drop-outs in some detail. Mean patients'

drop-out rate was 5.5%. Disregarding one study with a drop-out rate of 51%, [20] mean drop-out rate was 1.4%. Intention-to-treat analysis was described in six studies. None of the studies included a power calculation. Of the four cross-over studies none had a wash-out period, and two analysed data for carry over and period effects. Inclusion criteria were not described in four studies. [25,28,33,39] In most studies patients with co-morbidity and diabetes complications were excluded.

Glycaemic control (glycated haemoglobin)

Comparisons were initially categorised according to mode of insulin monotherapy , and subsequently subcategorised according to combination therapy regimen used, to provide clinically relevant comparisons.

- **Once daily insulin monotherapy versus insulin combination therapy**

In nine comparisons insulin monotherapy, applied as either a single morning [30] or evening injection [25,32-36,39] was compared with a matching insulin injection combined with a sulphonylurea (SU). One study provided no information on timing of insulin injections. [28] Data from five comparisons comparing a single evening insulin injection to evening insulin combined with daytime sulphonylurea were pooled in a meta-analysis. [33-36,39] Insulin combination therapy was associated with a significant mean (pooled weighted mean difference) lowering of HbA_{1c} of 0.3% (95% CI 0.03 to 0.6; P=0.03) compared to insulin monotherapy (Figure 1). Heterogeneity of study effects was low (I^2 =16%; Chi^2 = 4.8; P=0.3). Four comparisons were not included in the meta-analysis due to inappropriate outcome data, [28] or heterogeneous design with potential carry-over effect for glycated haemoglobin. Of these studies, two reported better glycaemic control with combination therapy, [30,32] whereas two studies found no difference between regimens. [25,28]

- **Twice-daily insulin monotherapy versus insulin combination therapy**

This category was subdivided in three subgroups according to differences in timing and frequencies of insulin injections in combination therapy: bedtime - (A), morning - (B), or twice daily insulin injection (C).

A. Twice daily insulin monotherapy versus bedtime insulin plus OHAs

Three studies combined bedtime NPH insulin with SU. [23,38,41] Monotherapy did not differ significantly from combination therapy (pooled weighted mean lowering of HbA_{1c} of 0.1%; 95% CI -0.9 to 1.1; P=0.9) (Figure 2). Heterogeneity

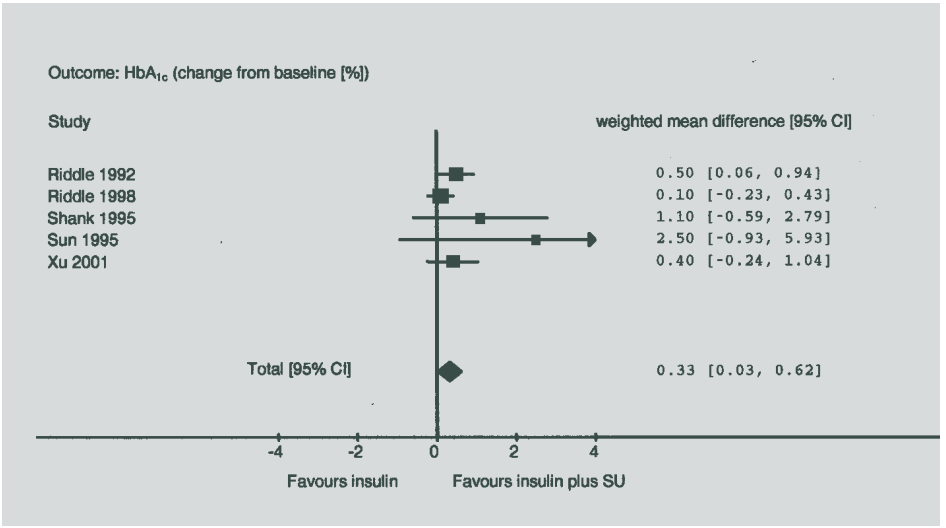


Figure 1. Once daily insulin monotherapy versus once daily insulin plus SU (sulphonylurea)

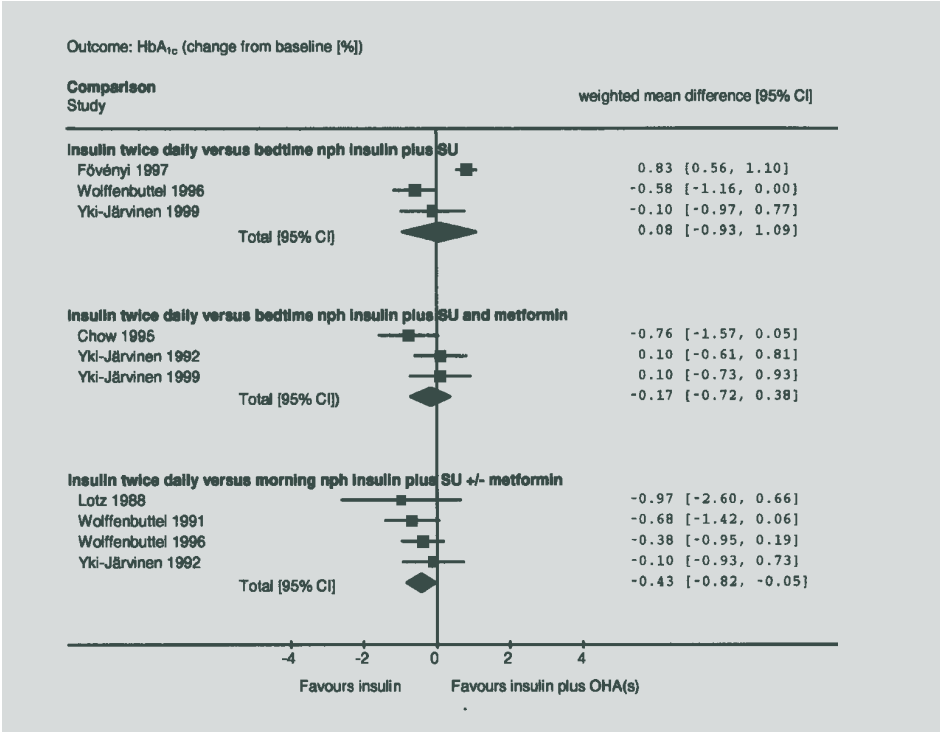


Figure 2. Twice daily insulin monotherapy versus insulin combination therapy

was high (I^2=90%; Chi^2=20.9; P<0.0001). Elimination of one large study of poor quality [23] did not significantly alter the result.
In three studies bedtime NPH insulin was combined with both SU and metformin together. [22,40,41] Monotherapy did not differ significantly from combination therapy (pooled weighted mean lowering of HbA_{1c} of 0.2%; 95% CI -0.7 to 0.4; P=0.5) (Figure 2). Heterogeneity was moderate (I^2=33%; Chi^2= 3.0; P=0.2). Elimination of one study of poor quality [22] did not significantly alter this result.
One study with multiple comparisons [41] combined bedtime NPH insulin with metformin alone. This combination provided significantly better glycaemic control than insulin monotherapy (mean lowering of HbA_{1c} of 0.6%; P<0.05). When this result was entered in the pooled analysis from the previous paragraph instead of the result from the same study [41] of the combination NPH insulin with both SU and metformin, the result did not change significantly (Figure not shown).

B. Twice daily insulin monotherapy versus morning insulin plus OHAs
In four studies twice daily insulin monotherapy was compared with morning NPH insulin combined with SU [27,37,38] or SU plus metformin. [40] Monotherapy was associated with a significant mean (pooled weighted mean dif ference) lowering of HbA_{1c} of 0.4% (95% CI 0.1 to 0.8; P=0.03) compared to combination therapy (Figure 2). There was no statistically significant heterogeneity (I^2=0%; Chi^2=1.5; P=0.7).

C. Twice daily insulin monotherapy versus twice daily insulin plus OHAs
In three studies twice daily insulin monotherapy was compared with twice daily (morning plus bedtime) premixed insulin 30/70 combined with SU. [20,24,31] These studies found no statistically significant difference between monotherapy and combination therapy.

- **Multiple daily insulin monotherapy versus insulin combination therapy**

In two studies a multiple insulin injection regimen (pre-meal soluble insulin with bedtime NPH) was compared to bedtime NPH insulin combined with SU [21] or SU plus metformin. [41] Monotherapy did not differ significantly from combination therapy (pooled weighted mean lowering of HbA_{1c} of 0.2%; 95% CI -0.4 to 0.1; P=0.3) (Figure 3). No statistically significant heterogeneity was detected (I^2=0%; Chi^2=0.4; P=0.5).
In two studies, similar multiple injection regimens were compared with morning ultralente [25] or NPH insulin [40] combined with SU. In both studies glycaemic control did not significantly differ between regimens. One study

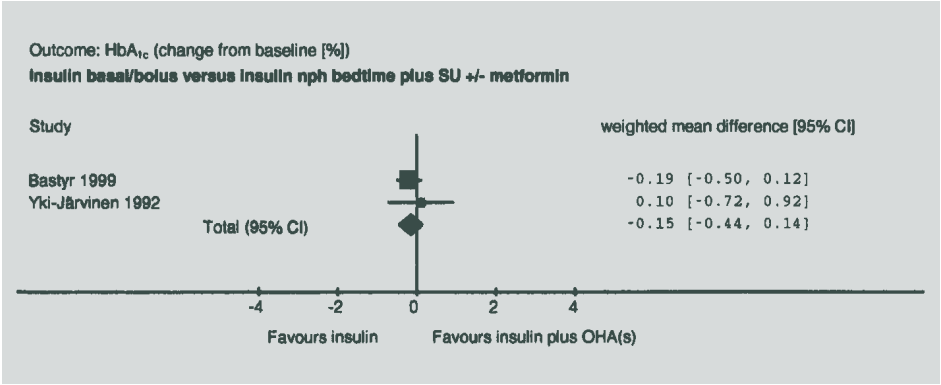


Figure 3. Multiple daily insulin monotherapy versus insulin combination therapy

compared a multiple insulin injection regimen with a matching multiple injection regimen combined with SU. [21] Similarly , mean decrease of HbA_{1c} did not significantly differ between regimens.

Insulin dose and treatment targets

Six studies did not formally report glucose targets to which insulin doses were titrated. [21,27,30-32,36] In the other fourteen studies insulin doses were titrated to predetermined glycaemic targets based on fasting, or diurnal mean glucose values. The median fasting glucose target was <7.0 mmol/l (range: <5.6 to <10.1 mmol/l). Three studies utilized structured insulin titration algorithms based on self-measured fasting capillary glucose levels. [33,34,41] In three studies the maximum dose of insulin in combination regimens using once daily NPH insulin was restricted to 40 units [23] (above this limit, patients were con verted to twice daily insulin monotherapy), 26 units, [22] or 28 units [27] respectively . Overall, insulin combination therapy was associated with a weighted mean relative reduction in total daily insulin requirement of 46% (range: -5 to 74%) compared to insulin monotherapy. Compared with once daily insulin monotherapy , regimens combining SU with a matched daily insulin injection were associated with a 29% relative reduction in total daily insulin dose. Compared with twice daily insulin monotherapy, combination regimens with bedtime NPH insulin were associated with relative reductions of 57%, 29% and 64%, for SU, metformin, or both oral agents, respectively. Similarly, regimens combining morning NPH insulin with SU, or SU plus metformin, and regimens utilizing twice daily insulin with SU, were associated with relative reductions in total daily insulin dose of 43%, and 42% respectively, compared to twice daily insulin monotherapy. In comparisons with multiple daily insulin injections, combination regimens were also associated with a relative reduction in daily insulin requirement of 48%.

Well-being, quality of life and treatment satisfaction

Two studies objectively assessed well-being, quality of life or treatment satisfaction. [22,40] One study [22] used a visual analogue score (VAS) based, structured well-being questionnaire to assess subjective well-being and acceptability of insulin injections. Similar significant improvements in subjective well-being following the initiation of insulin therapy were noted with both insulin monotherapy and insulin combination therapy groups. However , significantly more patients in the combination therapy group wanted to continue insulin therapy at the end of the study. Another study [40] assessed well-being using questionnaires. All treatment regimens were associated with improvement in the subjective sense of well-being, although no significant differences between insulin monotherapy and combination therapy regimens groups were found.

Two other studies [37,38] qualitatively reported "improved well-being in nearly all patients" , though methods for measuring well-being were not stated and no between-group comparisons were made.

Adverse effects

Weight gain

Fifteen studies [21-25,27,28,32-35,37,38,40,41] provided information on body weight outcomes (body weight or body mass index). Due to the heterogeneity of reported data only the results of three studies [22,40,41] in one subgroup (twice daily monotherapy versus combination therapy) were statistically pooled

- **Once daily insulin monotherapy versus insulin combination therapy**

One crossover study [32] reported significantly greater weight gain for patients when treated with combination therapy compared to insulin alone, though a significant confounding carry-over effect was observed, suggesting that the weight gain associated with each therapeutic intervention was affected by the order of treatment. All other studies showed no significant differences in results.

- **Twice daily insulin monotherapy versus insulin combination therapy**

One study [41] compared twice daily insulin monotherapy with bedtime NPH plus metformin and reported a significant 3.7 kg less weight gain for combination therapy.

In three studies [22,40,41] twice daily insulin monotherapy was compared with bedtime NPH insulin plus SU and metformin. Combination therapy was

associated with a non-significant (pooled weighted mean difference) 1.5 kg less weight gain (95% CI -0.1 to 3.2; P=0.07). Heterogeneity of these studies was notably (I^2=57%; Chi^2=4.7; P=0.1) (Figure 4). Elimination of one study of poor quality [22] did not significantly change this result. Of the other studies, none reported significant differences between either insulin therapies.

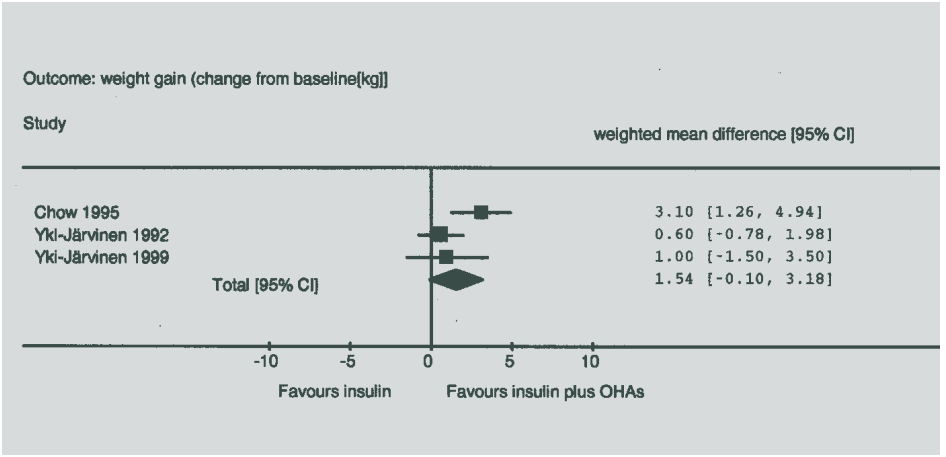


Figure 4. Insulin monotherapy versus insulin plus metformine +/- SU

- **Multiple daily insulin monotherapy versus insulin combination therapy**

Two studies reported significant less weight gain for combination therapy with SU [21] or SU plus metformin [40] compared to monotherapy with multiple insulin injections. In the other comparison in this category no significant differences between groups were found.

Hypoglycaemia

Hypoglycaemia was reported quantitatively or qualitatively in all but six studies. [23,28,30-32,39] Heterogeneity in the definitions used between studies, and the quality of reporting of hypoglycaemia precluded the pooling of data. Overall, only one episode of severe hypoglycaemia (requiring third party assistance) was reported. [38] One study [41] reported significantly less symptomatic hypoglycaemic episodes with bedtime NPH insulin plus metformin compared to insulin alone: mean (SD) episodes per patient: 1.8 (1.7) versus 3.9 (7.8) (P<0.05), though in this study confirmed fasting hypoglycaemic episodes (<3.5 mmol/l) were similar: (1.1% versus 1.2 %). In all other studies no significant difference in the frequencies of h ypoglycaemic events (symptomatic or confirmed) between insulin monotherapy and insulin combination therapy were demonstrated.

Other adverse effects

Gastrointestinal symptoms were not systematically reported as an outcome measure in any study, though in one study [41] side effects of metformin (diarrhoea, metallic taste, abdominal discomfort) necessitated study discontinuation for four (17%) patients.

Discussion

This review was performed to assess the effects of insulin monotherapy compared with combinations of insulin with oral hypoglycaemic agents in patients with inadequate glycaemic control despite treatment with oral hypoglycaemic agents. Twenty RCTs met the inclusion criteria, and 28 comparisons were evaluated and categorized according to clinically relevant treatment schemes. The methodological quality of many studies was poor (mean score 2.6 of maximal 7 points), and only five studies had adequate concealment of allocation. Most studies (85%) had a follow-op time of less than one year, so the long-term effects on glycaemic control, diabetes-related complications, and other relevant outcomes are unclear. The results of this review should therefore be interpreted against the background of these limitations.

Compared with insulin monotherapy, treatment with oral h ypoglycaemic agents combined with a single bedtime injection of NPH insulin provided comparable glycaemic control. Insulin combination therapy conferred better glycaemic control than insulin monotherapy when the latter was applied as a once daily injection of NPH insulin. Con versely , twice daily monotherapy (NPH or mixed insulin) provided superior glycaemic control to combination therapy in regimens where insulin was given as a single morning injection. Currently , both monotherapy with a single daily injection, and the combination therapy utilizing a morning injection of NPH insulin are infrequently used in type 2 diabetes, so conclusions drawn from the latter results are of minor interest.

Insulin combination therapy was associated with a relative reduction in mean daily insulin requirement of 46% compared to insulin monotherapy. This reflects the insulin saving influence of oral hypoglycaemic agents when combined with insulin. Compared with twice daily or multiple injection monotherapy regimens, the insulin saving effect of a sulphonylurea whether or not combined with metformin appeared superior to that of metformin alone (~50% versus 29%), though the latter figure was based on data from one study only.[41] In addition, no long term effects were measured.

Quality of life related issues were studied in only four studies, so this review remains inconclusive with respect to these outcomes. In general, studies

reported no significant differences between combination - and monotherapy regimens.
Occurrence of severe hypoglycaemia in all regimens appeared rare. Only one study reported significant less hypoglycaemic events with insulin combination therapy compared with monotherapy. [41] Heterogeneity in the definitions used between studies, and the quality of reporting of hypoglycaemic events precluded the pooling of data. Conclusions should therefore be drawn cautiously. Nevertheless, hypoglycaemia seems to be not a major problem in the management of type 2 diabetes, irrespective of the treatment scheme used.
In most studies no significant differences with respect to weight gain were detected between monotherapy and combination therapy regimens. However, combination therapies that included metformin showed a trend to less weight gain compared with insulin monotherapy, in particular when metformin was applied as a single agent. [41]

Implications for practice and research

This review found no difference with respect to glycaemic control and side effects between insulin monotherapy versus a single bedtime injection of NPH insulin in addition to a common oral agent regimen. Even multiple daily insulin injections were not more successful than combination therapy. Up to now, practice guidelines on type 2 diabetes are conflicting concerning the question whether insulin in patients with type 2 diabetes should be applied as monotherapy, or combined with oral agents. [42] This is relevant in particular for primary care, since the simple application of insulin once daily in addition to oral agents may allow family physicians and their patients to overcome a possible resistance to the use of insulin. Moreover, from a clinical standpoint the beneficial and insulin sparing effects of oral agents (most notably metformin) could be maintained. [43] Opponents to combination therapy suggested that glycaemic control remains sub-optimal with this approach.44
The results of this review however demonstrate that insulin monotherapy fares no better with respect to glycaemic control. Therefore, combination therapy should be considered a suitable starting point for most insulin requiring type 2 patients on maximal oral therapy.
Metformin reduces insulin requirement and may also prevent weight gain, even in combination with a sulfonylurea or intensive insulin treatment. [14,45] In this review only one trial included treatment with insulin in combination with metformin alone. [41] Whether metformin should be used as a single agent, or used in conjunction with other oral agents in insulin combination regimens is uncertain. More studies are required to determine the most favourable combination of antidiabetic agents for this category of patients.

These studies should also include newer oral agents (e.g. meglitinides, thiazolidinediones). Further research on this issue should assess also the possible long-term benefits over NPH insulin of recently introduced long-acting insulin analogues.[46] Future studies should also evaluate such regimens with respect to treatment satisfaction, quality of life, and general well-being. To conclude: insulin therapy in type 2 diabetes needs much more evaluation.

Acknowledgements
We thank the authors Francis Chow, József Fövényi, Rury Holman, and Antonio Pontiroli who kindly provided unpublished information.

Appendix

Methods of analysis

For each study the mean changes from baseline and standard deviations of the outcome $HbA_{1[c]}$ were extracted, if available. If not available, mean change scores of $HbA_{1[c]}$ were calculated by subtracting baseline from post-treatment values. Matching standard deviations were computed in SPSS 11.0 with formula 1, which included a general correlation coefficient between baseline and post-treatment values of $HbA_{1[c]}$ of 0.5. This figure was set 0.1 point lower than the correlation coefficient that was calculated from studies that provided information on change scores inclusive standard deviations, and which appeared to be 0.6 in most studies (Formula 2).[47]

Formula 1. Syntax for computing standard deviations of changes from baseline values of $HbA_{1[c]}$

SD = sqrt(sd_tr_b**2 + sd_tr_p**2 - 2 * corr * sd_tr_b * sd_tr_p).

Abbreviations

sd = standard deviation; sqrt = square root; sd_tr_b = standard deviation of mean baseline $HbA_{1[c]}$; sd_tr_p = standard deviation of mean post treatment $HbA_{1[c]}$; corr = correlation coefficient between baseline and post-treatment values of $HbA_{1[c]}$

Formula 2. Syntax for computing correlation coefficient between baseline and post-treatment values of $HbA_{1[c]}$

corr_tr = (sd_tr_b**2 + sd_tr_p**2 - sddiff_tr**2) / (2*sd_tr_b*sd_tr_p).

Abbreviations

corr_tr = correlation coefficient between baseline and post-treatment values of $HbA_{1[c]}$; sd_tr_b = standard deviation of mean baseline $HbA_{1[c]}$; sd_tr_p = standard deviation of mean post treatment $HbA_{1[c]}$; sddiff_tr = standard deviation of change from baseline $HbA_{1[c]}$

References

1 UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837-53.

2 Agurs Collins TD, Kumanyika SK, Ten Have TR, Adams Campbell LL. A randomized controlled trial of weight reduction and exercise for diabetes management in older African- American subjects. Diabetes Care 1997; 20:1503-11.

3 Bosello O, Armellini F, Zamboni M, Fitchet M. The benefits of modest weight loss in type II diabetes. Int J Obes Relat Metab Disord 1997; 21 Suppl 1:S10-3.

4 Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfon ylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999; 281:2005-12.

5 Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G et al. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 1989; 320:702-6.

6 Stout RW. Insulin and atheroma. 20-yr perspective. Diabetes Care 1990; 13: 631-54.

7 Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation 1998; 97: 996-1001.

8 de Sonnaville JJ, Snoek FJ, Colly LP, Deville W, Wijkel D, Heine RJ. Well-being and symptoms in relation to insulin therapy in type 2 diabetes. Diabetes Care 1998; 21: 919-24.

9 Goddijn PP, Bilo HJ, Feskens EJ, Groeniert KH, van der Zee KI, Meyboom-de Jong B. Longitudinal study on glycaemic control and quality of life in patients with Type 2 diabetes mellitus referred for intensified control. Diabet Med 1999; 16: 23-30.

10 van der Does FE, De Neeling JN, Snoek FJ, Kostense PJ, Grootenhuis PA, Bouter LM et al. Symptoms and well-being in relation to glycemic control in type II diabetes. Diabetes Care 1996; 19: 204-10.

11 Pugh JA, Wagner ML, Sawyer J, Ramirez G, Tuley M, Friedberg SJ. Is combination sulfon ylurea and insulin therapy useful in NIDDM patients? A meta-analysis. Diabetes Care 1992; 15: 953-9.

12 Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. Arch Intern Med 1996; 156: 259-64.

13 Peters AL, Davidson MB. Insulin plus a sulfonylurea agent for treating type 2 diabetes. Ann Intern Med 1991; 115: 45-53.

14 Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care 2001; 24: 758-67.

15 Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas 1960; 20: 37-46.

16 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.
17 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273: 408-12.
18 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-60.
19 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.
20 Bachmann W, Lotz N, Mehnert H, Rosak C, Schoffling K. [Effectiveness of combined treatment with glibenclamide and insulin in secondary sulfonylurea failure. A controlled multicenter double-blind clinical trial] (in German). Dtsch Med Wochenschr 1988; 113: 631-6.
21 Bastyr EJ, III, Johnson ME, Trautmann ME, Anderson JH, Jr., Vignati L. Insulin lispro in the treatment of patients with type 2 diabetes mellitus after oral agent failure. Clin Ther 1999; 21: 1703-14.
22 Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. Diabetes Care 1995; 18: 307-14.
23 Fövén yi J, Grosz A, Thaisz E, Lehotkai L, Sallai T, Kocsis G. [Daytime sulfonylurea - bedtime insulin combination therapy in Type II diabetes] (in Hungarian). Magy Belorv Arch (Hungarian Archive of Internal Medicine) 1997; 50: 607-13.
24 Gutniak M, Karlander SG, Efendic S. Glyburide decreases insulin requirement, increases beta-cell response to mixed meal, and does not affect insulin sensitivity: effects of short- and long-term combined treatment in secondary failure to sulfonylurea. Diabetes Care 1987; 10: 545-54.
25 Holman RR, Steemson J, Turner RC. Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement. Diabet Med 1987; 4: 457-62.
26 Karlander SG, Gutniak MK, Efendic S. Effects of combination therapy with glyburide and insulin on serum lipid levels in NIDDM patients with secondary sulfonylurea failure. Diabetes Care 1991; 14:963-967.
27 Lotz N, Bachmann W, Ladik T, Mehnert H. [Combination therapy with insulin/sulfonylurea in the long-term therapy of type II diabetes following "secondary failure"] (in German). Klin Wochenschr 1988; 66: 1079-84.
28 Lundershausen R, Orban S, Pissarek D, Panzram G. [Long-term effect of combination glibenclamide-insulin treatment in the secondary failure of sulfonylurea therapy–results of a one-year double blind study] (in German). Wien Klin Wochenschr 1987; 99: 603-8.
29 Makimattila S, Nikkila K, Yki-Järvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus.

Diabetologia 1999; 42: 406-12.
30 Pontiroli AE, Dino G, Capra F, Pozza G. Combined therapy with glibenclamide and ultralente insulin in lean patients with NIDDM with secondary failure of sulfonylureas. Follow up at two years. Diabetes Metab 1990; 16: 323-7.
31 Ravnik-Oblak M, Mrevlje F. Insulin versus a combination of insulin and sulfonylurea in the treatment of NIDDM patients with secondary oral failure. Diabetes Res Clin Pract 1995; 30: 27-35.
32 Riddle MC, Hart JS, Bouma DJ, Phillipson BE, Youker G. Efficacy of bedtime NPH insulin with daytime sulfonylurea for subpopulation of type II diabetic subjects. Diabetes Care 1989; 12: 623-9.
33 Riddle M, Hart J, Bingham P, Garrison C, McDaniel P. Combined therapy for obese type 2 diabetes: suppertime mixed insulin with daytime sulfonylurea. Am J Med Sci 1992; 303: 151-6.
34 Riddle MC, Schneider J. Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. Glimepiride Combination Group. Diabetes Care 1998; 21: 1052-7.
35 Shank ML, Del Prato S, DeFronzo RA. Bedtime insulin/daytime glipizide. Ef fective therapy for sulfonylurea failures in NIDDM. Diabetes 1995; 44: 165-72.
36 Sun Y, Xiong Y, Yang J. [The effectiveness of combined insulin and sulfonylurea in treating non-insulin dependent diabetic patients] (in Chinese). Zhonghua Nei Ke Za Zhi 1995; 34: 246-9.
37 Wolffenbuttel BH, Rondas-Colbers GJ, Menheere PP, Sels JP, Nieuwenhuijzen-Kruseman AC. [The effects of insulin combined with glibenclamide on glucose and lipid metabolism in patients with Type II diabetes mellitus] (in Dutch). Ned Tijdschr Geneeskd 1991; 135: 1080-4.
38 Wolffenbuttel BH, Sels JP, Rondas Colbers GJ, Menheere PP, Nieuwenhuijzen Kruseman AC. Comparison of different insulin regimens in elderly patients with NIDDM. Diabetes Care 1996; 19: 1326-32.
39 Xu WC, Chen CR, Chen YS. [Combination therapy with bedtime insulin and daytime oral hypoglycaemic agents in type 2 diabetic patients] (in Chinese). Hebei Medicine 2001; 23: 23-24.
40 Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1992; 327: 1426-33.
41 Yki-Järvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999; 130: 389-96.
42 Burgers JS, Bailey JV, Klazinga NS, van der Bij AK, Grol R, Feder G. Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. Diabetes Care 2002; 25: 1933-9.
43 Garber AJ. Benefits of combination therapy of insulin and oral h ypoglycemic

agents. Arch Intern Med 2003; 163: 1781-2.
44 Westphal SA, Palumbo PJ. Insulin and oral hypoglycemic agents should not be used in combination in the treatment of type 2 diabetes. Arch Intern Med 2003; 163: 1783-5.
45 Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger vdB et al. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care 2002; 25: 2133-40.
46 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-6.
47 Armitage P, Berry G, Matthews JNS. Statistical methods in medical research. 4th edition ed. Blackwell Science, 2002.

Table 1. Characteristics of included studies

Author Year (reference)	Design, quality score, sponsoring, notes	Country, setting, inclusion criteria, exclusion criteria, patients randomised, age, sex, diabetes duration	Interventions Insulin titration targets	Outcomes
Bachmann 1988 (21)	Design: randomised placebo controlled trial Duration: 6 months Quality score: 2 (Blinding: patients yes; care provider yes) Sponsoring: not specified	Country: Germany Setting: secondary care outpatient Inclusion criteria: > 40 years; > 3 year SU therapy; > 3 months max. SU therapy; FBG > 12.2 mmol/l or postprandial BG > 15.5 mmol/l; bodyweight < 150% of 'ideal bodyweight' Exclusion criteria: unclear Patients randomised: 140 Age (years, median): 66 / 69 Sex (% male): 38 / 19 Diabetes duration (years, median): 10 / 12	Group 1: mixed insulin (25% regular / 75% protamine insulin) + glibenclamide 15 mg Group 2: mixed insulin (25% regular / 75% protamine insulin) + placebo FBG <= 10 mmol/l and postprandial BG <= 12.2 mmol/l	Glycaemia: HbA1, FBG, postprandial BG Weight: Weight Insulin amount (E): mean daily insulin dose at final visit Hypoglycaemia: hypoglycaemic episodes Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Bastyr 1999 (22)	Design: randomised controlled trial Duration: 2 months Quality score: 3 (Randomisation procedure: computer generated, intention to treat: yes Sponsoring: pharmaceutical	Country: USA, Europe Setting: secondary care outpatient (11 countries) Inclusion criteria: 40-85 year; type 2 diabetes according WHO; secondary failure on SU; FBG > 7.8 mmol/l or AMBG > 10.0 mmol/l or HbA1c > 150% of the upper limit of the non-diabetic range at the local laboratory Exclusion criteria: unclear Patients randomised: 423 Age (years, median): 60.1 / 59.6 / 60.7 Sex (% male): 44 / 58 / 54 Diabetes duration (years): 10 / 9 / 9	Group 1: preprandial insulin Lispro + glibenclamide 15 mg (Europe) or glyburide 20 mg (USA) Group 2: preprandial insulin Lispro + bedtime NPH insulin Group 3: bedtime NPH insulin + glibenclamide 15 mg (Europe) or 20 mg (USA) Not available	Glycaemia: HbA1c, FBG, post prandial BG Weight: body weight, BMI Insulin amount (E): mean daily insulin dose at final visit Hypoglycaemia: hypoglycaemic episodes, Well-being: not reported Treatment Satisfaction: not reported Adverse events: reported
Chow 1995 (23)	Design: randomised controlled trial Duration: 8 months Quality score: 1 (drop-outs described) Sponsoring: pharmaceutical	Country: Hong Kong Setting: secondary care outpatients Inclusion criteria: age > 20 year and maximum dose of SU and/or metformine and FPG > 7.8 mmol/l Exclusion criteria: described Patients randomised: 55 Age (years): 57 / 51 Sex (% male): 33 / 35 Diabetes duration (years): 9.9 / 8.0	Group 1: OHA continued + bedtime NPH insulin Group 2: NPH before breakfast and dinner; one patient received mixed 30/70 insulin* FPG < 7.8 mmol/l (both groups) and postprandial PG < 11.1 mmol/l (group 2)	Glycaemia: HbA1c, FPG Weight: body weight, BMI Insulin amount (E): insulin doses at 6 months Hypoglycaemia: hypoglycaemia Well-being: well-being questionnaire Treatment Satisfaction: injection pain and problems questionnaire Adverse events: not reported
Fövényi 1997 (24)	Design: Randomised controlled trial Duration: 3 years Quality score: 1 (drop-outs	Country: Hungary Setting: Secondary care outpatient, single centre Inclusion criteria: HbA1c > 7.5% maximal oral therapy	Group 1: SU + bedtime NPH insulin Group 2: Twice daily mixed insulin 30/70 FBG < 7.0mmol/l; Pre-prandial /	Glycaemia: HbA1c Weight: Weight gain Insulin amount (E): Mean daily insulin dose at final visit

Author Year (reference)	Design, quality score, notes, sponsoring	Country, setting, inclusion criteria, exclusion criteria, patients randomised, age, sex, diabetes duration	Interventions Insulin titration targets	Outcomes
	described) Sponsoring: not stated	Exclusion criteria: unclear Patients randomised: 286 Age (years, mean): 59.8 yrs / 60.5 yrs Sex (% male): 41.8% / 40.7% Diabetes duration (years): 10.2 / 10.5	bedtime BG <10.0 mmol/l	Hypoglycaemia: not reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Gutniak 1987 (25)	Design: double-blind placebo controlled trial Duration: 10½ months Quality score: 2 (Blinding: patients yes; care provider yes) Sponsoring: pharmaceutical Data in text don't correspond with graphs	Country: Sweden Setting: secondary care outpatient Inclusion criteria: preprandial blood glucose > 11 mmol/l in 50% of the samples during 1 months unless diet, exercise, and 28 mg glyburide Exclusion criteria: unclear Patients randomised: 20 Age (years): 57 Sex (% male): unclear Diabetes duration (years): 14.1	Group 1: mixed insulin (NPH plus regular insulin) twice daily + glyburide 10.5 mg Group 2: mixed insulin (NPH plus regular insulin) twice daily + placebo tablets FBG < 8 mmol/l and postprandial BG < 10 mmol/l	Glucose profile: FBG, HbA1c Other: body weight, insulin amount Adverse effects: hypoglycaemia
Holman 1987 (26)	Design: randomised cross-over study Duration: 5 x 8 weeks Quality score: 1 (drop-outs described) Sponsoring: unclear	Country: United Kingdom Setting: primary care Inclusion criteria: maximal SU therapy Exclusion criteria: described Patients randomised: 17 Age (years): 57 Sex (% male): 50) Diabetes duration (years): 8	Group 1: maximal SU Group 2: maximal SU + metformin Group 3: maximal SU + long-acting insulin once daily Group 4: long-acting insulin once daily Group 5: long-acting insulin once daily + short-acting insulin twice daily FPG < 6 mmol/l	Glycaemia: HbA1, ; basal PG Weight: body weight Insulin amount (E): insulin amount Hypoglycaemia: hypoglycaemia reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Lotz 1988 (28)	Design: randomised controlled trial Duration: 2 year Quality score: 1 (Intention to treat: yes) Sponsoring: not reported	Country: Germany Setting: secondary care outpatient Inclusion criteria: age 45-80; maximal OHAs > 2 year; FBG > 11.1 mmol/l; postprandial BG > 13.9 mmol/l; HbA1 > 11.0%; weight < 130% BROCA (length (cm) – weight (kg)) Exclusion criteria: unclear Patients randomised: 16 Age (years): 65 / 59 Sex (% male): unclear Diabetes duration (years): 15 / 11	Group 1: insulin (not specified), twice daily Group 2: intermediate-insulin once a day + glibenclamid 7 mg Unclear	Glycaemia: HbA1, FBG Weight: weight (% BROCA) Insulin amount (E): daily insulin dose at final visit Hypoglycaemia: qualitatively reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Lundershausen 1987 (29)	Design: randomised controlled trial Duration: 6 months	Country: Germany Setting: unclear Inclusion criteria: maximal SU (glibenclamide 15 mg)	Group 1: insulin + glibenclamid 10 mg Group 2: insulin + placebo	Glycaemia: "glucose value (GV) according to Michaelis" Weight: weight change; BMI

Author Year (reference)	Design, quality score, notes, sponsoring	Country, setting, inclusion criteria, exclusion criteria, patients randomised, age, sex, diabetes duration	Interventions Insulin titration targets	Outcomes
	Quality score: 3 (Blinding: patients yes; care provider yes; intention to treat: yes) Sponsoring: not reported Type of insulin not specified	and FBG > 10 mmol/l, Exclusion criteria: described Patients randomised: 79 Age (years): 62 / 62 Sex (% male): 38 / 33 Diabetes duration (years): 11 / 11	"Glykämiewert" < 12.0 mmol/l	change (only reported for all patients) Insulin amount: daily insulin dose Hypoglycaemia: qualitatively reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Pontiroli 1990 (31)	Design: Randomised cross-over trial Duration: 2x 3 month Quality score: 1 (drop-outs described) Sponsoring: not stated	Country: Italy Setting: not stated Inclusion criteria: "Poor metabolic control" despite glibenclamide 15mg/day, normal bodyweight Exclusion criteria: described Patients randomised: 10 Age (years, mean): 61 yrs (all subjects) Sex (% male): 60% male (all subjects) Diabetes duration (years): 12.8 yrs	Group 1: Glibenclamide 5mg + ultralente insulin Group 2: ultralente insulin alone Cross-over after 3 months, no washout period, carry-over effect not described Not stated	Glycaemia: HbA1c Weight: Weight gain (comment only, no data) Hypoglycaemia: not reported Insulin amount (E): Mean daily insulin dose at final visit Well-being: not reported Treatment Satisfaction: not reported Adverse effects: not reported
Ravnik-Oblak 1995 (32)	Design: Randomised crossover trial Duration: 2x 3 month Quality score: 2 (drop-outs described; intention to treat: yes) Sponsoring: not stated Outcome data extracted from figures. Data expressed as median values	Country: Slovenia Setting: Secondary care outpatient Inclusion criteria: HbA1c > 9.0%, FBG > 10 mmol/l (for 3 months), Age >35 years, Diabetes duration > 3 years, BMI < 30 kg/m2, Fasting C-peptide > 0.3 mmol/l Exclusion criteria: described Patients randomised: 27 Age (years, median): 58 yrs (all subjects) Sex (% male): 56% (all subjects) Diabetes duration (years, median): 10.5 / 8	Group 1: Glibenclamide 10 mg twice daily + mixed insulin (short and intermediate acting insulin) once or twice daily Group 2: Insulin alone Cross-over after 3 months, no wash-out period, carry-over effect not described. Not stated	Glycaemia: HbA1c Weight: BMI Insulin amount (E): Median daily insulin dose at final visit Hypoglycaemia: not reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Riddle 1989 (33)	Design: Randomised crossover trial Duration: 2x 4 month Quality score: 6 (Randomisation; allocation concealment: yes; blinding: patients yes; care provider yes; outcome assessor yes) Sponsoring: pharmaceutical	Country: Oregon, USA Setting: Secondary care outpatient Inclusion criteria: Age 40-75 yrs, diabetes onset > 35 yrs, diabetes duration >1 and <15 yrs, weight < 160% ideal bodyweight, FPG >7.8 mmol/L Exclusion criteria: described Patients randomised: 21 Age (years, mean): 61 yrs (all subjects) Sex (% male): 40% male (all subjects)	Group 1: Glibenclamide 10mg + evening NPH insulin Group 2: Placebo + evening NPH insulin Crossover after 4 months, no washout period, treatment effect described Insulin increased at the physicians' discretion aiming for "excellent	Glycaemia: HbA1, FPG Weight: Weight gain Insulin amount (E): Mean daily insulin dose at final visit Hypoglycaemia: Mentioned in text, no data Well-being: not reported Treatment Satisfaction: not reported

Author Year (reference)	Design, quality score, notes, sponsoring	Country, setting, inclusion criteria, exclusion criteria, patients randomised, age, sex, diabetes duration	Interventions Insulin titration targets	Outcomes
		Diabetes duration (years, mean): 6 years	glycaemic control":	Adverse events: Reported
Riddle 1992 (34)	Design: Double-blind randomised placebo-controlled trial Duration: 16 weeks Quality score: 7 (all criteria) Sponsoring: pharmaceutical	Country: Oregon, USA Setting: Secondary care outpatient Inclusion criteria: Diabetes of gradual onset > 40 yrs of age, diabetes duration >1 yr, fasting plasma glucose >7.8 mmol/l despite glibenclamide 10mg bd. Exclusion criteria: described Patients randomised: 21 Age (years, mean): 55 / 52 yrs Sex (% male): not stated Diabetes duration (years): 6 / 4	Group 1: Glibenclamide 10mg twice daily + dinner mixed 30/70 insulin Group 2: Placebo + suppertime 30/70 insulin Structured insulin titration scheme based on home monitoring of blood glucose	Glycaemia: HbA1, FPG Weight: Weight gain Insulin amount (E): Mean daily insulin dose at final visit Hypoglycaemia: Symptomatic hypoglycaemic episodes Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Riddle 1998 (35)	Design: Double-blind randomised placebo-controlled trial Duration: 24 weeks Quality score: 6 (Randomisation procedure: not stated, other criteria yes) Sponsoring: pharmaceutical	Country: Oregon, USA Setting: Secondary care outpatient Inclusion criteria: Age 45-70 yrs, weight 130-170% IBW, FPG 10.0-16.7 mmol/l Exclusion criteria: described Patients randomised: 145 Age (years, mean): 58 / 58 yrs Sex (% male): 63% / 55% Diabetes duration (years): 7 / 7yrs	Group 1: Glimepiride 8mg twice daily + dinner mixed 30/70 insulin Group 2: Placebo + dinner 30/70 insulin FBG 5.5-6.7 mmol/l	Glycaemia: HbA1c Weight: Weight gain Insulin amount (E): Mean daily insulin dose at final visit Hypoglycaemia: Symptomatic hypoglycaemic episodes Well-being: not reported Treatment Satisfaction: not reported Adverse events: Reported
Shank 1995 (36)	Design: Double-blind randomised placebo-controlled trial Duration: 6 months Quality score: 6 (intention to treat: no; all other criteria: yes) Sponsoring: pharmaceutical	Country: Texas, USA Setting: Secondary care outpatient Inclusion criteria: FPG >7.77 mmol/l with max. Dose of sulphonylurea, FPG< 15.54 mmol/l without sulphonylurea. Exclusion criteria: described Age (years, mean): 53 yrs (all subjects) Sex (% male): not given Diabetes duration (years): not stated	Group 1: Glipizide 20 mg twice daily + bedtime NPH insulin Group 2: Placebo + bedtime NPH insulin Group 3: Glipizide 20 mg bd FPG 3.89-6.66 mmol/l	Glycaemia: HbA1c, FPG Weight: Weight gain Insulin amount (E): Mean daily insulin dose at final visit Hypoglycaemia: Symptomatic (and asymptomatic <3.89 mmol/l) hypoglycaemic episodes Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Sun 1995 (37)	Design: Randomised placebo controlled trial Duration: 4 months Quality score: 3 (blinding: patients yes; drop-outs described; intention to treat: yes)	Country: China Setting: Secondary care outpatient Inclusion criteria: Age >40 yrs, type 2 diabetes >5 yrs duration, treatment with max. Sulphonylurea > 3 weeks, FBG > 7.8mol/l, 2hr post-prandial > 11.1 mmol/l. Exclusion criteria: not stated	Group 1: Gliquidone 60mg + bedtime NPH insulin Group 2: Placebo + bedtime NPH insulin Group 3: Gliquidone 60mg Not stated	Glycaemia: HbA1c, FBG Weight: not reported Insulin amount (E): not given Hypoglycaemia: Symptomatic hypoglycaemic episodes Well-being: not reported Treatment Satisfaction: not

Author Year (reference)	Design, quality score, notes, sponsoring	Country, setting, inclusion criteria, exclusion criteria, patients randomised, age, sex, diabetes duration	Interventions Insulin titration targets	Outcomes
	Sponsoring: pharmaceutical	Patients randomised: 33 Age (years, mean): 53.6 / 54.4 /54.5 yrs Sex (% male): 50% / 45% / 60% male Diabetes duration (years): not stated		reported Adverse events: not reported
Wolffenbuttel 1991 (38)	Design: randomised controlled trial Duration: 6 months Quality score: 0 Sponsoring: pharmaceutical	Country: Netherlands Setting: secondary care outpatient Inclusion criteria: FBG > 8.0 mmol/l; maximal dosage SU (glibenclamide) and/or metformin Exclusion criteria: unclear Patients randomised: 47 Age (years): 70 / 68 Sex (% male): 83 / 47 Diabetes duration (median; years): 9 / 10	Group 1: NPH insulin before breakfast and dinner; eventually replaced by mixed 30/70 insulin in case of postprandial BG > 10.0 mmol/l Group 2: NPH insulin before breakfast or bedtime + glibenclamide 15 mg; eventually a second injection was added in case of postprandial BG > 10.0 mmol/l FBG < 7.0 mmol/l; postprandial BG < 10.0 mmol/l; HbA1c < 8.0%	Glycaemia: FBG; HbA1c Weight: weight Insulin amount (E): daily dose Hypoglycaemia: reported qualitatively Well-being: reported qualitatively Treatment Satisfaction: not reported Adverse events: not reported
Wolffenbuttel 1996 (39)	Design: Randomised controlled trial Duration: 6 months Quality score: 1 (drop-outs described) Sponsoring: pharmaceutical	Country: Netherlands Setting: Secondary care outpatient Inclusion criteria: Fasting blood glucose (mean of 3 measurements) >8.0 mmol/l, HbA1c > 8.9% despite diet & max. oral hypoglycaemic agents (glibenclamide 15mg / day ±metformin). Exclusion criteria: described Patients randomised: 102 Age (years, mean): 68 yrs (comleters) Sex (% male): 39% male (completers) Diabetes duration (years): median 9 yrs (completers)	Group 1: mixed 30/70 insulin Group 2: Glibenclamide 15mg + bedtime NPH insulin Group 3: Glibenclamide 15mg + NPH insulin before breakfast Fasting blood glucose < 7.0 mmol/l, pre-prandial glucose < 10 mmol/l, HbA1c <8.0%	Glycaemia: HbA1c, FBG Weight: Weight gain Insulin amount (E): Mean daily insulin dose at final visit Hypoglycaemia: Severe hypoglycaemic episodes reported Well-being: not formally reported Treatment Satisfaction: not formally reported Adverse events: Reported
Xu 2001 (40)	Design: Randomised controlled trial Duration: 6 months Quality score: 0 Sponsoring: unclear	Country: China Setting: Secondary care out – and inpatient Inclusion criteria: data missing Exclusion criteria: data missing Patients randomised: 90 Age (years, mean): 51.4 / 52.1 Sex (% male): 47 / 51 Diabetes duration (years): 7.3 / 7.4	Group 1: insulin once daily 24 IU/day Group 2: oral agents 1500 daily + insulin once daily 24U/day FBG: 3.5 - 7.0 mmol/l	Glycaemia: HbA1c, FBG Weight: data missing Insulin amount (IU): fixed insulin dose in both groups Hypoglycaemia: not reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: not reported
Yki-Järvinen 1992 (41)	Design: Randomised controlled trial Duration: 3 months	Country: Finland Setting: Secondary care outpatient Inclusion criteria: Age 40-70 yrs, type 2 diabetes > 3	Group 1: OHAs (SU +/- metformin) + NPH insulin before breakfast Group 2: OHAs (unchanged) +	Glycaemia: HbA1c, FBG Weight: Weight gain Insulin amount (E): Mean daily

Author Year (reference)	Design, quality score, notes, sponsoring	Country, setting, inclusion criteria, exclusion criteria, patients randomised, age, sex, diabetes duration	Interventions Insulin titration targets	Outcomes
	Quality score: 3 (Randomisation: yes; allocation concealment: yes; drop-outs described) Sponsoring: non-pharmaceutical	yrs, BMI <35 kg/m2, FPG > 8.0 mmol/l despite max. sulphonylurea +metformin. Fasting C-peptide > 0.33 nmol/l. Exclusion criteria: described Patients randomised: 153 Age (years, mean): 59 / 60 / 59 / 60 / 59 yrs Sex (% male): 38 / 54 / 41 / 60 / 37% Diabetes duration (years): 11 / 10 / 10 / 11 / 10	evening NPH insulin Group 3: mixed 30/70 insulin before breakfast and dinner Group 4: Basal-bolus regimen (soluble insulin before meals and evening NPH insulin) Group 5: OHAs (unchanged) (control group) FBG < 7.0mmol/l, post prandial <10 mmol/l	insulin dose at final visit Hypoglycaemia: Symptomatic and biochemical (<4.0 mmol/l) hyperglycaemia Well-being: Reported though method not stated Treatment Satisfaction: not reported Adverse events: Those resulting in withdrawal reported
Yki-Jarvinen (1999 (42)	Design: Randomised placebo controlled trial Duration: 1 year Quality score: 4 (Randomisation: yes; allocation concealment: yes; blinding: patients yes; drop-outs described)	Country: Finland Setting: Secondary care outpatient Inclusion criteria: Age 40-70 yrs, BMI <35 kg/m2, FBG >8.0mmol/l, diabetes duration >3 yrs, previous oral therapy with max. SU (glipizide >15mg / day, glibenclamide >10mg / day. Fasting C-peptide >0.33nmol/l. Exclusion criteria: described Patients randomised: 96 Age (years, mean): 61 / 57 / 55 / 58 yrs (completers) Sex (% male): 59 / 58 / 61 / 67 % (completers) Diabetes duration (years): not stated	Group 1: Glibenclamide 3.5mg + 7mg + bedtime NPH insulin (+ metformin placebo) Group 2: Metformin 1g + bedtime NPH insulin (+ glibenclamide placebo) Group 3: Glibenclamide (10.5mg) + metformin (1g) + bedtime NPH insulin Group 4: NPH insulin twice daily FPG <6.0mmol/l	Glycaemia: HbA1c, FPG Weight: Weight gain, BMI Insulin amount (E): mean daily insulin dose at final visit Hypoglycaemia: not reported Well-being: not reported Treatment Satisfaction: not reported Adverse events: Reported

Abbreviations: BMI =body mass index, (F)BG = (fasting) blood glucose, FPG = fasting plasma glucose, OHA = oral hypoglycaemic agents, SU = sulphonylurea
* Mixed 30/70 insulin includes 30 % regular insulin and 70% NPH insulin

Chapter 8

General Discussion

General Discussion

This chapter discusses the main conclusions of the studies in this thesis. Besides, recommendations are made for the management of type 2 diabetes in primary care, together with implications for future diabetes guidelines.

At present, a large majority of patients with type 2 diabetes is managed in primary care, in particular those treated with diet and oral h ypoglycaemic agents. An increased awareness on the impact of the disease, [1] along with the results of large and long standing studies, [2-4] did justify a more intensive ef fort to achieve near normal glucose levels in patients with diabetes. As a result, evidence-based clinical practice guidelines were developed [5-7] and used in vocational training and postgraduate education of GPs. However, in daily care adherence to the guidelines was found to be variable, and previous studies showed less optimal outcomes of care.
Diabetes type 2 patients in general practice with HbA_{1c} > 7% are the subjects of study in this thesis. The studies deal with the relationship between the quality of recording of clinical data and the level of glycaemic control, characteristics of patients that could predict poor glycaemic control, and three different kinds of interventions recommended by the guideline on type 2 diabetes from the Dutch College of General Practitioners. The main objective is to study the effectiveness of these issues in the current management of hyperglycaemia in patients with type 2 diabetes in primary care.

Quality of recording of data and quality of care
Guidelines and management schemes for type 2 diabetes strongly focus on recurrent review of patients, including 3-monthly follow-up visits and a more thorough check-up yearly. [5] Data from history taking, physical examination and laboratory tests should be recorded carefully (preferably using an electronic medical record system), to provide an accurate overview of the course of the disease, and to justify continuing or changing treatment.
However , in this cross-sectional study we found no association between the completeness of data and glycaemic control (Chapter 2). This suggests that in 'real life' diabetes care more careful data recording does not automatically result in better control of patients' hyperglycaemia. This finding, together with the absence of a straightforward 'annual review' in sixty percent of the files, indicates suboptimal care on an individual patient level. A few lessons could be drawn from these results.
Firstly , general practitioners should use their computers much more extensively for registration and recall of their patients, since these activities have proved to be positively associated with improvements in patient

outcomes. [8-11] Although most EMR systems do have such facilities, most doctors do not use them.

Secondly, abnormal values collected with recurrent reviews should be followed more rigorously by efforts to initiate or adjust glucose lowering treatment. The discrepancy between increased testing frequency and better outcomes in patients with chronic illness has been noticed by several researchers. [10,12-14] An explanation for this finding could be that general practitioners are not used to increase the frequency of follow-up visits and thus insufficiently treat to target values, even when all the data are available. [10,11,13,15-17]

Thirdly, future EMR systems might be more adapted to the specific needs associated with the complex care for patients with chronic conditions like diabetes. [18] Besides the already mentioned recall facility, these systems should at least provide screen displays of actual and earlier laboratory data with 'automatic' prompting in case of exceeding target values, combined with integrated clinical decision support linked to evidence-based treatment recommendations. Together with an indispensable "treat to target" attitude of professionals, this could lead to a more successful diabetes management. [19]

Finally, postgraduate education for providers of diabetes care should be focussed on improvement of patient outcomes, rather than increasing the number of measurements of blood glucose levels.

Treat to target with a flowchart and tight follow-up intervals

Based on the results from the first study we suggested that abnormal values may not be sufficiently followed by efforts to adjust treatment. Indeed, in daily practice a number of excuses could be available to escape from this responsibility. Nevertheless, in case of a patient with unsatisfactory glycaemic control the Dutch guideline recommends "to increase the dosage in line with the clinical response every 2 to 4 weeks until the target blood glucose level has been reached." In Chapter 4 we investigated the impact of this recommendation using a before-after design in 288 patients with unsatisfactory glycaemic control despite treatment with diet or oral hypoglycaemic agents. After a mean of three consultations per patient over 14 weeks a clinically significant reduction in HbA_{1c} was achieved, while the number of patients with poor control (HbA_{1c} > 8.5%) decreased with sixty percent. This result was attained simply by adjusting oral medication according to the level of the fasting blood glucose, together with a rigorous appointment policy. Despite a few limitations of this study (e.g. before-after design, short follow-up) these results undeniably reflect the potential strength of a well-ordered multifaceted intervention. Such interventions should focus on compliance with the guideline of both patients and doctors, and should be

targeted especially on patient outcome. Besides the influence of the facilitators, the target-driven instructions on just one issue and the short review intervals may have contributed to the effect. These findings are in accordance with the results of a systematic review of interventions targeted at achieving better glycaemic control. [10] This review found singlefaceted interventions to be less effective than multifaceted ones, while the involvement of trained nurses combined with arrangements for follow-up were associated with improvements in both patient outcomes and process measures.

Although it is not likely that one specific approach will be effective in all settings, we feel that diabetes care improvement programmes should comply with at least the following conditions:

- choose one single issue at the time;
- introduce orderly management schemes, derived from evidence based guidelines;
- focus in particular on patient outcomes, rather than process measures;
- apply tight review intervals for patients till the predefined targets are reached;
- bring in personal support to check compliance at both patient and practice level.

Of course, in the ideal situation such programmes should be incorporated in everyda y practice. However, in the Netherlands most general practices, like those in our study, are relatively understaffed. In fact, in the past decade personal support of primary care did fall out of step with the increased demands as laid down in a large number of clinical practice guidelines. [20,21] From this point of view, the relief of Dutch general practices by bringing in extra staff such as practice nurses should be continued unconditionally. [22]

Self-management education: a never ending story?

In most diabetes guidelines self-management education is considered an essential part of diabetes care, which is based on the idea that increased patient participation will contribute to better compliance and better clinical outcomes. [23] Although education studies are difficult to compare due to a considerable diversity of interventions, participants and settings, significant positive effects on glycaemic control in the short term are well documented, but the few studies with longer follow-up showed disappointing results. [24,25] So far, studies conducted in general practice are scarce. Besides, it is unclear which category of patients in primary care could benefit from such an intervention.

Our programme has proven to be a powerful instrument in this relatively young patient group (mean age 60 years) with poor glycaemic control despite

maximal treatment with oral agents. The decline of HbA_{1c} was greater than we had expected from literature (0.7 versus 0.3), [24] and for a majority of patients the urgency of a transfer to insulin therapy had disappeared. Therefore, this type of education should be delivered at least to all patients in this stage of diabetes, all the more since insulin therapy may be burdensome and expensive, and both GPs and patients are inclined to postpone that. [26] Moreover , the investment in time and materials of the programme were limited, and we expect that only about two or three patients per practice (2500 patients) would need such an intervention each year. Ideally, such programmes should be implemented by the 'local' practice nurse and supervised by the patients' own GP, in order that an integration in standard diabetes care is guaranteed.

The extent to which self-monitoring of blood glucose (SMBG) contributed to the result could be questioned, since it is hard to consider SMBG apart from the other aspects of the programme. This might be of importance, because the use of SMBG in all diabetic patients is widely promoted, [27,28] although its value is still a matter of debate. [29] A meta-analysis of randomised trials failed to show any benefit from SMBG in patients with type 2 diabetes. [30] Moreover , it is suggested that a daily use of SMBG in type 2 diabetes is associated with higher levels of distress, worries and depressive symptoms, because most patients, even those treated with insulin, may not be capable to translate all the information into clear adjustments of their treatments. [31] For the time being, we agree with the statement of Franciosi, which implies: "SMBG should be an integral part of a wider educational strategy devoted to the promotion of patient autonomy".[31] For daily practice this means that SMBG may be used by patients on insulin therapy, and patients who need feedback as part of a structured educational programme such as we studied.

The diminishing effects of our programme after one year underlines once again that changes in lifestyle are hard to sustain, [32] in particular in the absence of ongoing structured follow-up. [33] However , long-term studies providing clear evidence that lifestyle modification programmes could resist the habitual relapse of human behaviour (given the progressive worsening of diabetes over time) are not available. Therefore, future research on the issue of self-management education should be targeted on the long-term effects of prolonged educational programmes in daily diabetes care.

Insulin therapy in general practice

In daily practice yearly about 5 – 10 % percent of patients with type 2 diabetes will be eligible for treatment with insulin, if oral hypoglycaemic agents (OHAs) in maximal doses fail to maintain acceptable glycaemic control. [34-37] In general, the physician may count on an average 1%-point fall of HbA_{1c} level within

three months, though a recent and apparently rigorously conducted trial suggests that even a greater decrease could be obtained. [38] Insulin can be administrated as monotherapy or in combination with oral h ypoglycaemic agents (combination therapy), in which case as a rule a sulphon ylurea, metformin, or both are used. However, which of those treatment schemes is preferable is still an actual question. [39,40] The answer seems to be relevant in particular for primary care physicians, since the simple application of combination therapy would allow general practitioners and patients to overcome a possible resistance against the use of insulin. Moreover, from a clinical point of view in combination therapy the beneficial effects of oral agents (probably first of all metformin) could be maintained. [39] On the other hand, several objections were made against this approach: combination therapy may provide less-than-optimal glycaemic control, while conversely the use of insulin monotherapy early in the management of type 2 diabetes may improve ß-cell function, through which the progression of diabetes could be reversed. [40]

The results of both the randomised controlled trial (Chapter 6) and the systematic review (Chapter 7) showed that no evidence was found for insulin monotherapy regimens to provide superior glycaemic control compared with a common oral agent regimen combined with a single bedtime injection of intermediate-acting insulin. In contrast with our study, hypoglycaemia and weight gain appeared to be similar in the review, although combination therapies that included metformin showed a trend to less weight gain compared with insulin monotherapy, in particular when metformin was applied as a single agent. [46] In the systematic review only two out of twenty studies [41,42] assessed quantitatively well-being, quality of life or treatment satisfaction, so this review could not be conclusive with respect to these type of outcomes. These studies as well as ours showed significant better well-being with combination therapy. [41,42]

We conclude that insulin combination therapy may be considered a simple and safe starting point for insulin requiring type 2 diabetes patients. However, a number of questions with respect to combination regimens were not addressed by the findings of both studies. This regards in the first place the assumed ceiling for insulin dose. In our trial almost one quarter of patients receiving combination therapy did fail to reach satisfactory glycaemic control, maybe since the study protocol had not allowed for increasing the bedtime insulin dose over 40 IU. A higher dosage is expected to have no further positive influence on glycaemic control. [5] However , this supposition is not based on clear evidence. Treatment failure rate in combination therapy could probably

be reduced by a more aggressive titration policy without using a ceiling for insulin dose. More research is needed to clarify this.
Secondly , attempts to predict poor response from baseline parameters did fail, as was the case in a comparable study. [42] In another study, poor response on insulin was predicted from obesity and longer duration of diabetes, but no distinction was made between the different regimens used. [43] Further research is needed to identify predictors of poor response on insulin, irrespective of the chosen regimen.
Finally , it remains unclear whether metformin should be applied as a single agent or combined with other OHAs. Metformin prevents weight gain, even in combination with a sulfonylurea or intensive insulin treatment, and reduces the required insulin dose for adequate glucose control. [44,45] However , as was shown in the systematic review, only one trial included insulin in combination with metformin alone. [46] So, more long-term studies are needed to determine the most favourable combination of antidiabetic agents.

Implications for type 2 diabetes management

The results of this thesis provide considerable chances to improve the quality of diabetes care. Shortcomings in all stages of treatment of h yperglycaemia could be easily tackled with limited additional efforts. Although the research was targeted on glycaemic control, we feel that some of our management strategies might be applicable also on risk factors as blood pressure and hyperlipidaemia. To achieve that, general practitioners and their supporting staff should adopt in particular a more “outcome oriented” attitude. Figure 1 summarizes the key steps in the management of hyperglycaemia in type 2 diabetes, derived from the results of this thesis. The consecutive treatment recommendations are closely linked, and constitute in fact the bottom-line of modern diabetes care. This starts with careful recording of clinical data from all patients on the diabetes practice list. However, monitoring is useless if it is not followed by systematic attempts to meet the treatment goals. The use of target-driven flowcharts derived from evidence- based guidelines (ideally integrated in electronic medical record systems!) has proven to be effective.

Furthermore, the use of structured education (including blood-glucose self-monitoring) before starting insulin appears to be promising, although the long-term results should be a reason for concern. Finally, we consider insulin combination therapy a simple, safe and effective first choice for less well controlled patients on maximal oral medication.
We will conclude this thesis with handing over some suggestions for the next revision of the Dutch guideline on type 2 diabetes, which is likely to be published in the course of 2005. These proposals are summarized in Table 1. In

fact the current "Standard" laid (and still lays) an important underpinning for present diabetes care in the Netherlands, and much of the research questions in this thesis were derived from it. Of course, guideline development is just the first half of the game, and a vigorous and continuous application is needed to finish the job in daily practice. [47,48] The present study offers some tools to facilitate this process.

Although diabetes care is complex and time-consuming, and numerous other problems in general practice compete for attention, we believe that the general practitioner should retain a central position in the care for these patients. However, it is obvious that this task can only be fulfilled in the presence of sufficient specialised support, and - last but not least - in cooperation with the patients themselves.

Table 1 Suggestions for revision of the Dutch guideline on type 2 diabetes

Issue	Current version	Suggestions for revision
Management of diabetes in general practice	• Integrated registration and appointments system • 3-monthly - and annual reviews • careful data recording	• More attention for organizational aspects (staff, computers) • Emphasize significance of a diabetes register and regular recall of patients • Focus on patient outcomes rather than on process • Promote a 'treat to target' attitude
Treatment of hyperglycaemia with oral hypoglycaemic agents	• Treatment algorithm for oral agents • Follow-up intervals of 2 to 4 weeks until target or maximum dosage is achieved	• May be maintained • Focus on targets and compliance • Apply same approach to other risk factors (blood pressure, lipids)
Self-management education	• Patient education is an essential part of diabetes management.	• Provide content and aims of successful self-management educational programmes • Advice self-management education (including SMBG) for patients on maximal therapy with OHAs • Integrate recurrent educational sessions in daily care
Insulin therapy	• Insulin therapy is optional for the GP • No preference for either insulin in combination with OHAs or insulin monotherapy	• Insulin therapy is feasible in general practice • Insulin combination therapy is preferable over insulin monotherapy for most patients needing insulin

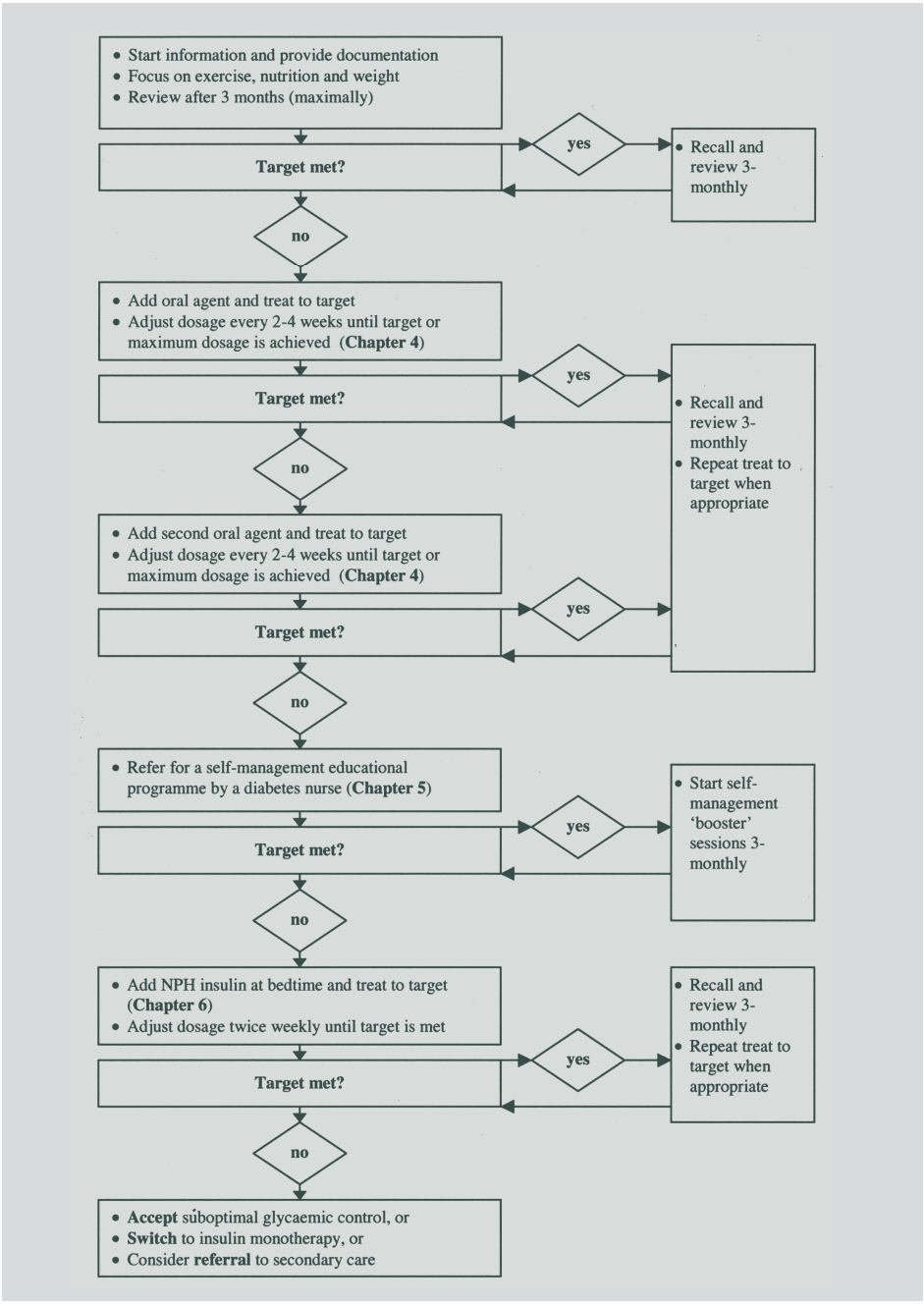


Figure 1. Key steps in management of hyperglycaemia after diagnosis of type 2 diabetes

References

1 de Grauw WJC, van de Lisdonk EH, van den Hoogen HJ, van Weel C. Cardiovascular morbidity and mortality in type 2 diabetic patients: a 22-year historical cohort study in Dutch general practice. Diabet Med 1995; 12: 117-2.

2 DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulindependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329: 977-86.

3 UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

4 UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65.

5 Rutten GEHM, Verhoeven S, Heine RJ, de Grauw WJC, Cromme PVM, Reenders K, van Ballegooie E, Wiersma Tj. Diabetes Mellitus Type 2. NHG-standard (first revision) [in Dutch]. Huisarts Wet 1999; 42: 67-84.

6 EDPG. A desktop guide to Type 2 diabetes mellitus. European Diabetes Policy Group 1999. Diabet Med 1999; 16: 716-30.

7 ADA. Standards of medical care for patients with diabetes mellitus.Diabetes Care 2002; 25(Supplement 1): S33-S49.

8 Pringle M, Ward P, Chilvers C. Assessment of the completeness and accuracy of computer medical records in four practices committed to recording data on computer . Br J Gen Pract 1995; 45: 537-41.

9 Greenhalgh PM. Shared care for diabetes. A systematic review. Occas Pap R Coll Gen Pract 1994; (67): i-35.

10 Renders CM, Valk GD, Griffin SJ, Wagner EH, Eijk VJ, Assendelft WJ. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. Diabetes Care 2001; 24: 1821-33.

11 Griffin S. Diabetes care in general practice: meta-analysis of randomised control trials. BMJ 1998; 317: 390-6.

12 Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. Milbank Q 1996; 74: 511-44.

13 Khunti K, Ganguli S, Baker R, Lowy A. Features of primary care associated with variations in process and outcome of care of people with diabetes. Br J Gen Pract 2001; 51: 356-60.

14 Schaars CF, Denig P, Kasje WN, Stewart RE, W olffenbuttel BH, Haaijer--Ruskamp FM. Physician, organizational, and patient factors associated with suboptimal blood pressure management in type 2 diabetic patients in primary care. Diabetes Care 2004; 27: 123-8.

15 Aubert RE, Herman WH, Waters J, Moore W, Sutton D, Peterson BL et al. Nurse case management to improve glycemic control in diabetic patients in a health maintenance organization. A randomized, controlled trial. Ann Intern Med 1998; 129: 605-12.
16 van den Arend I, Stolk RP, Krans HM, Grobbee DE, Schrijvers AJ. Management of type 2 diabetes: a challenge for patient and physician. Patient Educ Couns 2000; 40: 187-94.
17 O'Connor PJ. Organizing diabetes care: identify, monitor, prioritize, intensify. Diabetes Care 2001; 24: 1515-6.
18 O'Connor PJ. Electronic medical records and diabetes care improvement: are we waiting for Godot? Diabetes Care 2003; 26: 942-3.
19 Meigs JB, Cagliero E, Dubey A, Murph y-Sheeh y P, Gildesgame C, Chueh H et al. A controlled trial of web-based diabetes disease management: the MGH diabetes primary care im provement project. Diabetes Care 2003; 26: 750-7.
20 Burgers JS, Bailey JV, Klazinga NS, van der Bij AK, Grol R, Feder G. Inside guidelines: comparative analysis of recommendations and evidence in diabetes guidelines from 13 countries. Diabetes Care 2002; 25: 1933-9.
21 Valk GD, Blankenstein AH. Time-expenditure of protocolized care for patients with type 2 diabetes mellitus in general practice [in Dutch]. Huisarts Wet 2000; 43: 151-4.
22 Groeneveld Y, Petri H, Hermans J, Springer M. An assessment of structured care assistance in the management of patients with type 2 diabetes in general practice. Scand J Prim Health Care 2001; 19: 25-30.
23 Roter D, Kinmonth A-L. What is the evidence that increasing participation of individuals in self-management improves the processes of outcomes of care? In: Williams R, Herman W, Kinmonth A-L, Wareham NJ, editors. The evidence base for diabetes care. Chichester, England: John Wiley & Sons, 2002: 681-700.
24 Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. Diabetes Care 2002; 25: 1159-71.
25 Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care 2001; 24: 561-87.
26 Miedema K, Veltmaat LJ, Reenders K. Barriers for switching over to insulin treatment in patients with type 2 diabetes in general practice [in Dutch]. Huisarts Wet 1995; 38: 614-7.
27 Nederlandse Diabetes Federatie. Richtlijnen en Adviezen voor goede diabeteszorg. Leusden: Nederlandse Diabetes Federatie, 2000.
28 ADA. Tests of Glycemia in Diabetes. Diabetes Care 2002; 25: S97-9.
29 Kennedy L. Self-monitoring of blood glucose in type 2 diabetes: time for evidence of efficacy . Diabetes Care 2001; 24: 977-8.
30 Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R. Self-monitoring in T ype

2 diabetes mellitus: a meta-analysis. Diabet Med 2000; 17: 755-61.
31 Franciosi M, Pellegrini F, De Berardis G, Belfiglio M, Cavaliere D, Di Nardo B et al. The impact of blood glucose self-monitoring on metabolic control and quality of life in type 2 diabetic patients: an urgent need for better educational strategies. Diabetes Care 2001; 24: 1870-7.
32 Page RC, Harnden KE, Cook JT, Turner RC. Can life-styles of subjects with impaired glucose tolerance be changed? A feasibility study. Diabet Med 1992; 9: 562-6.
33 Fox C, Kilvert A. Intensive education for lifestyle change in diabetes. BMJ 2003; 327: 1120-1.
34 Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S. Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. JAMA 1997; 278: 1663-9.
35 de Sonnaville JJ, Bouma M, Colly LP, Deville W, Wijkel D, Heine RJ. Sustained good glycaemic control in NIDDM patients by implementation of structured care in general practice: 2-year follow-up study. Diabetologia 1997; 40: 1334-0.
36 Goddijn PP, Meyboom de Jong B, Feskens EJ, van Ballegooie E, Bilo HJ. Dif ferences between diabetes mellitus type 2 patients switched and not switched over to insulin treatment after specialist consultation [in Dutch]. Ned Tijdschr Geneeskd 1998; 142: 1023-6.
37 Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002; 25: 330-6.
38 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-6.
39 Garber AJ. Benefits of combination therapy of insulin and oral h ypoglycemic agents. Arch Intern Med 2003; 163: 1781-2.
40 Westphal SA, Palumbo PJ. Insulin and oral hypoglycemic agents should not be used in combination in the treatment of type 2 diabetes. Arch Intern Med 2003; 163: 1783-5.
41 Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L et al. Comparison of insulin regimens in patients with non-insulindependent diabetes mellitus. N Engl J Med 1992; 327: 1426-33.
42 Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. Diabetes Care 1995; 18: 307-14.
43 Wolffenbuttel BH, Sels JP, Rondas-Colbers GJ, Menheere PP. Prognostic factors for successful insulin therapy in subjects with type 2 diabetes. Neth J Med 1999; 54: 63-9.
44 DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999; 131: 281-303.
45 Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Berg B, Donker

AJ, Stehouwer CD. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care 2002; 25: 2133-40.

46 Yki-Järvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999; 130: 389-96.

47 Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. BMJ 1999; 318: 527-30.

48 Feder G, Eccles M, Grol R, Griffiths C, Grimshaw J. Clinical guidelines: using clinical guidelines. BMJ 1999; 318: 728-30.

Summary

Summary

The main objective of this thesis is to investigate essential components of hyperglycaemic management of patients with type 2 diabetes. We focus on patients with unsatisfactory glycaemic control (HbA_{1c} > 7 %) despite general advice and treatment with oral hypoglycaemic agents. In Chapter 1 we outline the present role of primary care in type 2 diabetes against the background of three important historical developments in diabetes care: the shift of care from the hospital to the general practice, advances in diabetes research, and the role of guidelines. Currently in the Netherlands general practice takes care of the large majority of patients with type 2 diabetes. During the past decade evidence-based guidelines and shared-care projects (like the Utrecht Diabetes Programme) did facilitate a more structural approach of diabetes care. Nevertheless, evaluations showed considerable numbers of patients being insufficiently reviewed or treated, resulting in less optimal outcomes of care. The studies in this thesis were conducted in a group of patients with known type 2 diabetes registered in over fifty general practices, and covered the following themes: monitoring of clinical data and outcome of care (chapter 2); predictors of poor glycaemic control (chapter 3); nurse facilitators and oral hypoglycaemic agent therapy (chapter 4); patient self-management education by a diabetes nurse (chapter 5); and insulin treatment (chapter 6 and 7).

Chapter 2

Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study

Objectives

The quality of recording of clinical data in diabetes care in general practices is very variable. It has been suggested that better recording leads to improved glycaemic control. The purpose of this study was to assess the completeness of recording by GPs of data from type 2 diabetes patients; to compare recorded and missing data; and to investigate the association between completeness and glycaemic control.

Methods

A cross-sectional survey was carried out in 52 general practices. Medical records were scrutinized for the presence of 11 variables. Examining patients through an active approach completed incomplete records. We compared recorded and unrecorded items. Completeness of recording was determined at both patient and practice levels.

Results

Fifty-two general practices with 1641 type 2 diabetes patients cared for by the GP participated. The frequency of absence of any particular item ranged from 12 to 70%. Weight, systolic blood pressure and HbA_{1c} were slightly lower in patients with those items missing on their files, and more such patients were non-smokers ($P < 0.05$). The percentage of patients with unrecorded variables that exceeded target values ranged from 39 to 75. Neither at practice level nor at patient level was any association between the completeness of the data recording and HbA_{1c} found.

Conclusion

Records often were incomplete, which hampers a systematic approach to care of diabetic patients. However, the lack of association between completeness of data recording and control of glycaemia indicates that improved recording is not a valid indicator of good quality of care.

Chapter 3

Patient characteristics do not predict poor glycaemic control in type 2 diabetes patients treated in primary care

Objectives

Many diabetic patients in general practice do not achieve good glycaemic control. The aim of this study was to assess which characteristics of type 2 diabetes patients treated in primary care predict poor glycaemic control ($HbA_{1c} \geq 7\%$).

Method

A cross-sectional survey was carried out in 52 general practices. Data were collected from the medical records. Examining patients through an active approach completed incomplete records. 1641 patients were included.

Results

Mean HbA_{1c} was 7.1 % (SD 1.7), and 42% had $HbA_{1c} \geq 7\%$. On univariate analysis younger age; longer duration of diabetes; higher levels of blood glucose at diagnosis; most recent fasting blood glucose (FBG), total cholesterol, and triglyceride; higher body mass index (BMI); treatment with oral hypoglycaemic agents (OHA); treatment with insulin; more GP-visits for diabetes in the last year; and lower educational level were associated with poor control. Both in multiple linear regression and in multiple logistic regression higher levels of FBG (odds ratio (OR): = 1.6, 95% confidence interval

(CI): 1.49, 1.70), treatment with OHA (OR: 2.1, 95% CI: 1.41, 3.04), treatment with insulin (OR: 7.2, 95% CI: 4.18, 12.52), lower educational level (OR: 1.26, 95% CI: 1.01, 1.56) were independently associated with poor levels of HbA_{1c}. When FBG levels were excluded from the model, higher blood glucose at diagnosis, higher values for triglyceride and total cholesterol, and younger age predicted poor glycaemic control, but these variables explained only 15% of the variation in HbA_{1c}.

Conclusions

Prediction of poor glycaemic control from patient characteristics in diabetic patients in general practice is hardly possible. FBG appeared to be a strong predictor of HbA_{1c}, which underlines the usefulness of this simple test in daily diabetes care. The worse metabolic control in those treated with either OHA or insulin suggests that current treatment regimes might be not sufficiently applied to reach the targets of care. Providers of diabetes care should be attentive to patients with lower educational level.

Chapter 4

Improving glycaemic control in patients with Type 2 diabetes mellitus without insulin therapy

Objectives

In general practice at least 30% of those with Type 2 diabetes do not achieve good glycaemic control. We studied the effect of improving oral glucose-lowering medication in a primary care setting in patients treated with oral h ypoglycaemic agents without satisfactory glycaemic control.

Methods

We provided flowcharts to general practitioners and outreach visits by trained facilitators, who checked adherence to the protocol. Fifty-two Dutch general practices with 2140 Type 2 diabetes mellitus (DM) patients recruited 288 patients ≤ 75 years old inadequately controlled (HbA_{1c} > 7%) by diet or oral medication. Outcome measures were decrease of HbA_{1c}, number of patients with HbA_{1c} ≤ 7%, and non-compliance rate.

Results

After a mean of 3.3 consultations over 14 weeks, 209 patients were following the protocol fully with a reduction in HbA_{1c} from 8.7% to 6.7% (P< 0.001). One hundred and fifty-eight patients (55%) achieved HbA_{1c} ≤ 7%, and 51 (18%) persisted with HbA_{1c} > 7% unless fasting blood glucose ≤ 7 mmol/l (n = 18) or a maximum of medication (n = 33). Seventy-nine patients (27%) did not adhere to the protocol, mostly due to loss of motivation and non-attendance.

Conclusions
A simple flowchart and relatively little support by trained facilitators results in improved glycaemic control.

Chapter 5

Long-term effects of self-management education for patients with Type 2 diabetes taking maximal oral hypoglycaemic therapy: a randomized trial in primary care

Objectives
Education is an essential part of the management of patients with Type 2 diabetes, but the long-term effects are unclear and not well investigated in primary care.

Methods
Fifty-four patients (39 - 75 years) treated with maximal dosages of oral hypoglycaemic agents, needing to start insulin ($HbA_{1c} \geq 7.0\%$), were randomly allocated to a 6-month educational programme by a diabetes nurse (DN group) or usual care (UC group). Main outcome measures were HbA_{1c}, number of patients with $HbA_{1c} < 7.0\%$, and number of patients treated with insulin 18 months after baseline.

Results
Six weeks after the intervention HbA_{1c} levels had improved from 8.2 (1.1) to 7.2 (1.3) in the DN group, and from 8.8 (1.5) to 8.4 (1.7) in the UC group. Adjusted for baseline values, at 6 weeks HbA_{1c} improved 0.7% (95% confidence interval 0.1, 1.4) more in DN than in UC. Of the patients in DN, 60% reached $HbA_{1c} < 7.0\%$ compared with 17% in UC ($P < 0.01$). However, at 18 months there were no significant differences for HbA_{1c}, number of patients with $HbA_{1c} < 7.0\%$, or number treated with insulin.

Conclusions
Education was effective in improving glycaemic control and in delaying the need for insulin therapy in patients treated with maximal oral hypoglycaemic therapy. The reduced effect after one year was probably due to the discontinuation of the educational programme. Short-term education should not be offered without regular reinforcements integrated into standard diabetes care.

Chapter 6

Starting insulin therapy in patients with type 2 diabetes: with or without continuation of oral hypoglycemic agents? A randomized trial in primary care

Objective

To evaluate the effects of insulin 30/70 twice daily or bedtime isophane (NPH) insulin plus continued sulfonylurea and metformin in patients with type 2 diabetes in primary care.

Study design

Open-label, randomized trial.

Population

Persons younger than 76 years with type 2 diabetes whose disease had not been controlled with oral hypoglycemic agents alone. A total of 64 insulin-naïve patients treated with maximal feasible dosages of sulfonylurea and metformin (baseline glycosylated hemoglobin [HbA_{1c}] 8.5%) were randomly assigned to insulin monotherapy (IM group; n=31) or insulin in addition to unchanged oral hypoglycemic medication (IC group; n=33) for 12 months. Insulin doses were adjusted to obtain fasting glucose <7.0 mmol/L and postprandial glucose <10.0 mmol/L.

Outcomes measured

Outcome measures included HbA_{1c}, treatment failure, weight, h ypoglycemic events and symptoms, satisfaction with treatment, general well-being, and fear of injecting insulin and testing.

Results

HbA_{1c} improved from 8.3% to 7.6% in the IC group, and from 8.8% to 7.6% in the IM group (P=NS). The IC group had 24% treatment failures, compared with 2% in the IM group (P=.09). Patients in the IC group had less weight gain than those in the IM group (1.3 vs 4.2 kg; P=.01), and they reported fewer hypoglycemic events (2.7 vs 4.3; P=.02). Increased satisfaction with treatment was equal in the two groups, and general well-being improved by 3.0 points more in the IC group (P=.05). Fear of self-injecting and self-testing did not dif fer.

Conclusions

Bedtime NPH insulin in addition to an existing maximal therapy with sulfon ylurea and metformin is an effective, simple, and well tolerated first choice approach for patients with uncontrolled type 2 diabetes.

Chapter 7

Insulin monotherapy versus combinations of insulin with oral hypoglycemic agents in patients with type 2 diabetes mellitus. A systematic review

Objectives

It is unclear, whether patients with type 2 diabetes who have insuf ficient glycaemic control despite maximal oral hypoglycaemic agents should be switched to insulin as monotherapy or in combination with oral agents (combination therapy). The objective of this systematic review was to assess the effects of monotherapy versus combination therapy on glycaemic control, patient satisfaction, quality of life, diabetes related morbidity and mortality, and adverse effects (e.g. hypoglycaemia, weight gain) in patients with insulin-requiring type 2 diabetes mellitus.

Methods

Eligible studies were identified by searching MEDLINE, EMBASE, and the Cochrane Controlled Trials Register (CCTR) up to May 2002. Included were randomised controlled trials (RCTs) of minimum treatment duration 2 months, comparing insulin monotherapy (all schemes) with combinations of insulin with single or multiple oral hypoglycaemic agents. There was no restriction on language of the publications. Data extraction and assessment of study quality were undertaken by three reviewers in pairs.

Results

Mean methodological quality score (range 0 - 7) of the 20 included RCTs was 2.6 (95% CI 1.5 to 3.7). Twenty-eight comparisons in 20 RCTs were ordered according to clinical considerations. Sufficient data could be extracted from 12 studies to calculate pooled effects on glycaemic control. No significant differences with respect to glycaemic control were detected between oral hypoglycaemic agents with bedtime NPH insulin compared with insulin monotherapy given as twice daily, or multiple daily injections. Combination therapy was associated with a relative reduction in total daily insulin requirement of 46% compared to monotherapy (all schemes). Of 14 studies that reported hypoglycaemia, all but one demonstrated no significant difference in the frequency of hypoglycaemic events (symptomatic or biochemical) between monotherapy and combination therapy . Combination therapy including bedtime NPH insulin and metformin, resulted in statistically significant less weight gain compared to monotherapy. Quality of life related issues were investigated in only four studies.

Conclusions

No difference was found with respect to glycaemic control between insulin monotherapy versus a single bedtime injection of NPH insulin in addition to a common oral agent regimen. Therefore combination therapy should be recommended as an easy applicable starting point for insulin requiring type 2 diabetes patients.

Chapter 8

In Chapter 8 we end in well-defined proposals for the treatment of hyperglycaemia in all stages of type 2 diabetes together with recommendations for revision of diabetes guidelines, based on the main findings of our studies. This thesis supplies considerable evidence that actual shortcomings in care could be tackled if providers of diabetes care adopt a more "outcome oriented" approach. Although the objective was targeted on glycaemic control, this attitude might also be effective in other risk factors for cardiovascular complications. Careful recording of data followed by systematic attempts to meet the treatment goals should be considered 'usual care' for all diabetic patients in the general practice. Flowcharts, nurse facilitators, structured educational programmes targeted on lifestyle and compliance, and finally insulin therapy have proven to be effective and feasible in primary care. However, the central position of general practice in the care for type 2 diabetes patients can only be sustained in the presence of sufficient specialised support.

Samenvatting

Samenvatting

Het centrale thema van dit proefschrift is de aanpak van een verhoogde bloedglucosespiegel (hyperglykemie) bij patiënten met type 2 diabetes die in de huisartspraktijk worden behandeld met dieet of bloedglucoseverlagende tabletten. Onder hyperglykemie wordt in dit proefschrift verstaan een HbA_{1c} % boven 7, waarbij een waarde tussen vier en zes procent als 'normaal' geldt. Uit eerder onderzoek is gebleken dat in de dagelijkse praktijk minstens dertig procent van de patiënten de streefwaarde voor het HbA_{1c} niet haalt, ondanks de in de laatste jaren toegenomen kennis over diabetes, de beschikbaarheid van richtlijnen en protocollen, en de invloed van transmurale diabetesprogramma's.

Het doel van dit onderzoek is meer inzicht te krijgen in de effectiviteit van verschillende behandelingen van patiënten met een verhoogd HbA_{1c}, waardoor een aanscherping zou kunnen plaatsvinden van de huidige richtlijnen voor het beleid bij hyperglykemie. De onderzoeken zijn uitgevoerd tussen 1999 en 2003 in een groep patiënten die met de diagnose type 2 diabetes zijn geregistreerd in ruim zestig huisartspraktijken in de Utrechtse regio. Eerst is onderzocht of er een samenhang bestaat tussen de kwaliteit van de gegevensregistratie in het medisch dossier en de glykemische controle (Hoofdstuk 2) en welke factoren een verhoogd HbA_{1c} kunnen voorspellen (Hoofdstuk 3). Vervolgens is onderzoek verricht naar de effectiviteit van drie soorten interventies: een geprotocolleerde behandeling met bloedglucoseverlagende tabletten (Hoofdstuk 4), een educatieprogramma door een diabetesverpleegkundige (Hoofdstuk 5), en behandeling met insuline al of niet gecombineerd met bloedglucoseverlagende tabletten (Hoofdstuk 6). Tenslotte is een systematisch literatuuronderzoek verricht naar studies die het effect onderzochten van de behandeling met alleen insuline in vergelijking met de behandeling met insuline gecombineerd met bloedglucoseverlagende tabletten (Hoofdstuk 7).

Hoofdstuk 1

In Hoofdstuk 1 gaan we in op de rol van de huisartspraktijk bij de behandeling van patiënten met type 2 diabetes in het licht van drie belangrijke ontwikkelingen in de laatste decennia: de verschuiving van de zorg van de tweede naar de eerste lijn, de toegenomen inzichten in beloop en behandeling van diabetes, en de rol van richtlijnen. Aan de hand van aanbevelingen in de Standaard Diabetes type 2 van het Nederlands Huisartsen Genootschap (NHG) worden voorts de onderzoeksvragen geïntroduceerd en nader uitgewerkt. Deze luiden als volgt:

Wat is de samenhang tussen de kwaliteit van de gegevensregistratie (het zorgproces) en de glykemische controle (de zorguitkomst) van patiënten met type 2 diabetes?
Welke kenmerken van patiënten, praktijken, en geleverde zorg voorspellen hyperglykemie?
Wat is het effect van de inzet van een praktijkconsulent gecombineerd met een geprotocolleerde behandeling met bloedglucoseverlagende tabletten bij patiënten met hyperglykemie?
Wat is het effect van een gestructureerd educatie programma door een diabetesverpleegkundige bij patiënten die ondanks behandeling met een maximale dosering van bloedglucoseverlagende tabletten nog steeds een HbA_{1c} > 7% hebben?
Wat is het effect van behandeling met insuline in vergelijking met de behandeling met insuline gecombineerd met bloedglucoseverlagende tabletten bij patiënten die met een maximale dosering van bloedglucoseverlagende tabletten toch onvoldoende glucosecontrole hebben?

Hoofdstuk 2

Hoofdstuk 2 beschrijft een onderzoek bij 1641 door de huisarts behandelde patiënten. De medische dossiers werden doorzocht op de aanwezigheid van elf klinische gegevens, waaronder de zogenaamde 'jaarcontrole'. Een gegeven werd als 'aanwezig' beschouwd als het in het dossier werd aangetroffen en niet was verouderd. Ontbrekende of verouderde gegevens werden vervolgens aangevuld door de patiënt op te roepen voor controle. Op deze manier ontstond een vrijwel compleet beeld van deze populatie en was het mogelijk de aanwezige en later aangevulde items met elkaar te vergelijken. Per praktijk werd de compleetheid van de registratie uitgedrukt in een 'praktijkscore' , die bestond uit het gemiddeld aantal aanwezige items per patiënt per praktijk (minimum te behalen score 0, maximum 11).
De afwezigheid van de afzonderlijke items varieerde van 12 tot 70 procent. Van de metingen die periodiek dienen te worden herhaald ontbrak de 'jaarcontrole' het meest (60 procent) en de bloeddrukmeting het minst frequent (20 procent). De gemiddelde praktijkscore kwam uit op 6.3, en het gemiddelde praktijk HbA_{1c} op 7.2%. Er bleek geen verband aantoonbaar tussen de hoogte van de praktijkscore enerzijds, en het HbA_{1c} percentage anderzijds (Pearson correlatiecoëfficiënt -0.18; p=0.2)
Deze resultaten laten zien dat in de huisartspraktijk de registratie van voor de diabeteszorg relevante variabelen van wisselende kwaliteit was. Dit belemmert een goede diabeteszorg. Immers, als gegevens ontbreken of zijn verouderd kunnen eventueel noodzakelijke aanpassingen van de behandeling niet plaatsvinden. Het ontbrekende verband tussen de kwaliteit van de

gegevensregistratie en glykemische controle duidt er echter op dat het controleren en onderzoeken van patiënten alléén niet genoeg is. Nog meer dan nu het geval is zal het vinden van afwijkende waarden moeten worden gevolgd door een intensivering van de behandeling, waardoor de kans op het halen van de streefwaarden wordt vergroot.

Hoofdstuk 3

Hoofdstuk 3 had als vraagstelling welke kenmerken van patiënten, praktijken, en diabeteszorg een verhoogd HbA_{1c} kunnen voorspellen. Het onderzoek werd uitgevoerd bij 1641 door de huisarts behandelde patiënten, bij wie een groot aantal gegevens werden verzameld. Met behulp van multiple lineaire regressie werd vastgesteld dat een hogere waarde van de nuchter bepaalde bloedglucose, behandeling met bloedglucoseverlagende tabletten, behandeling met insuline, en een lager opleidingsniveau onaf hankelijk waren geassocieerd met hyperglykemie. Indien de nuchtere bloedglucose uit het model werd verwijderd waren tevens een hogere waarde van de nuchtere bloedglucose bij diagnose, jongere leeftijd, en hogere waarden voor triglyceriden en totaal cholesterol geassocieerd met hyperglykemie, maar deze variabelen verklaarden slechts 15% van de variatie in het HbA_{1c}. We concluderen dat het voorspellen van een te hoog HbA_{1c} met behulp van patiëntkenmerken niet goed mogelijk is. De nuchter bepaalde bloedglucose is wel een goede voorspeller. Dit onderstreept de bruikbaarheid van deze goedkope test in de dagelijkse praktijk.

Hoofdstuk 4

In Hoofdstuk 4 onderzochten wij het effect op de glykemische controle van een geprotocolleerde behandeling met orale medicatie bij patiënten < 76 jaar en met een HbA_{1c} > 7%, ondanks behandeling met dieet of bloedglucoseverlagende tabletten. De praktijken werden hierbij geholpen door een periodiek bezoek van een praktijkconsulent. Tevens werd een patiëntenkaart ontwikkeld met daarop een op de NHG-Standaard gebaseerd stroomdiagram voor controle en behandeling, en een overzicht van de tot dat moment in Nederland beschikbare orale bloedglucoseverlagende medicijnen. De studiegroep bestond uit 288 patiënten. De huisartsen kregen de instructie bij de patiënten om de twee weken de nuchtere bloedglucose te (laten) bepalen en de dosering van de medicatie aan te passen (overeenkomstig het advies op de patiëntenkaart) tot een nuchtere bloedglucose van ≤ 7 mmol/l, dan wel de maximaal haalbare dosering van de medicatie was bereikt. In beide gevallen diende zes weken ná de laatste aanpassing van de medicatie het HbA_{1c} te worden bepaald. Twee goed geïnstrueerde praktijkconsulenten bezochten de praktijken iedere 3 weken en zagen erop toe dat de patiënten

daadwerkelijk werden gecontroleerd en de patiëntenkaarten correct werden ingevuld. Bovendien werden de praktijkassistentes aangemoedigd patiënten die 'niet kwamen opdagen' actief te benaderen. Indien bij een patiënt het protocol niet kon worden gestart of voltooid diende de reden hiervan op de kaart te worden vermeld.
Negenenzeventig patiënten vielen voortijdig af, zodat bij 209 patiënten het protocol volledig werd toegepast. 158 van hen bereikten een goede glykemische controle (HbA $_{1c}$ ≤ 7%). In deze groep daalde het HbA $_{1c}$ % van 8.7 naar 6.7 ($p<0.001$). Indien werd aangenomen dat de 79 afgevallen patiënten niet waren verbeterd, daalde het HbA $_{1c}$ % in de totale studiegroep van 8.8 naar 7.3 ($p<0.001$) Het aantal patiënten met een slechte controle (HbA $_{1c}$ > 8.5%) daalde van 126 tot 51. Dit resultaat werd bereikt in gemiddeld ruim drie consulten gedurende gemiddeld drie maanden.
Dit onderzoek toonde aan dat met een geprotocolleerde aanpak op basis van de NHG-Standaard, gecombineerd met praktijkondersteuning, in relatief korte tijd bij een goed herkenbare groep patiënten een significante verbetering van de glykemische controle mogelijk is. Een deel van het succes is waarschijnlijk toe te schrijven aan de 'aanjagende' rol van de praktijkconsulent. Het lijkt mogelijk deze aanpak tevens toe te passen op de andere risicofactoren bij diabetes, zoals verhoogde bloeddruk, te hoog cholesterol en roken.

Hoofdstuk 5

In Hoofdstuk 5 worden de resultaten beschreven van een onderzoek naar de effectiviteit van een educatieprogramma bij patiënten met h yperglykemie ondanks behandeling met een maximale dosering van bloedglucoseverlagende tabletten. Vieren vijftig patiënten (gemiddelde leeftijd 61 jaar, gemiddeld HbA $_{1c}$ 8.5%) kregen gestructureerde educatie door een diabetesverpleegkundige of 'gewone zorg' door de huisarts. Gestreefd werd naar een verbetering van de glykemische controle (HbA $_{1c}$ < 7%) waardoor een overstap naar behandeling met insuline kon worden voorkomen of uitgesteld. Het programma (zes bijeenkomsten van gemiddeld een half uur gedurende zes maanden) was gericht op het bevorderen van de therapietrouw van de bestaande medicatie, lichaamsbeweging, afvallen, en gezonde voeding. Daarnaast werd de patiënten geleerd thuis de bloedglucose te meten, met als doel een grotere betrokkenheid bij de behandeling.
Bij patiënten die educatie ontvingen was kort na afloop van het programma het HbA $_{1c}$ 0.7% méér gedaald dan bij de patiënten die gewone zorg ontvingen ($p<0.05$). Bovendien bleek dat 60 procent van de patiënten in de educatiegroep een goede glykemische controle had (HbA $_{1c}$ < 7%), tegen 17 procent in de gewone zorg groep ($p<0.01$). Tot slot kon worden vastgesteld dat

de patiënten in de educatiegroep gemiddeld 2 kg méér waren afgevallen dan de patiënten in de gewone zorg groep ($p<0.05$). Een jaar na afloop van de interventie, dus na een periode van twaalf maanden 'gebruikelijke zorg' voor alle 54 patiënten, bleken de verschillen tussen de twee groepen nagenoeg verdwenen. Dit werd vooral veroorzaakt door een terugval van de patiënten uit de educatiegroep. Inmiddels werden 16 patiënten met insuline behandeld, 6 uit de educatiegroep en 10 uit de gewone zorg groep. Dit verschil was niet statistisch significant.
Op grond van deze resultaten concluderen we dat het zinvol is om patiënten met maximale orale medicatie die in aanmerking komen voor behandeling met insuline eerst naar een diabetesverpleegkundige of een gespecialiseerde praktijkverpleegkundige te verwijzen voor gestructureerde educatie zoals in dit onderzoek beschreven. Na beëindiging van het programma moet echter wel rekening worden gehouden met een uitdoving van het positieve effect op langere termijn. Het lijkt aannemelijk dat 'opfriscursussen' deze terugval zouden kunnen voorkomen, maar verder onderzoek is nodig om deze hypothese te bevestigen.

Hoofdstuk 6

Hoofdstuk 6 beschrijft de resultaten van een gerandomiseerd onderzoek in de huisartspraktijk naar de effecten van behandeling met insuline in vergelijking met een combinatie van insuline met bloedglucoseverlagende tabletten bij patiënten met hyperglykemie ($HbA_{1c} > 7\%$) ondanks een maximale dosering bloedglucoseverlagende tabletten. Tot op heden zijn de aanbevelingen in diabetesrichtlijnen niet eensluidend ten aanzien van deze behandelingsmogelijkheden, en ook de NHG-Standaard spreekt geen voorkeur uit voor één van deze beide insulinetherapieën.

Vierenzestig patiënten (gemiddelde leeftijd 58 jaar, gemiddeld HbA_{1c} 8.5%) werden gedurende 12 maanden behandeld met tweemaal daags gemengde insuline 30/70 (monotherapie), of eenmaal daags insuline voor de nacht (tot een maximum van 40 eenheden), als toevoeging aan de bestaande orale medicatie (combinatietherapie). Onderzocht werd het effect op de glykemische controle, lichaamsgewicht, hypoglykemieën, tevredenheid met de behandeling, algemeen welbevinden en angst voor het spuiten van insuline en het prikken van bloedsuikers. De patiënten kregen instructies van een diabetes- of praktijkverpleegkundige over voeding, injecteren van insuline, en bloedglucose zelfcontrole. Alle patiënten noteerden de glucose dagcurves en het aantal hypoglykemieën in een dagboek. De insulinedosering werd tweewekelijks aangepast waarbij gestreefd werd naar een nuchtere glucosewaarde < 7 mmol/l, en een postprandiale waarde < 10 mmol/l.
Met combinatietherapie daalde het HbA_{1c}% van 8.3 naar 7.6, en met

monotherapie van 8.8 naar 7.6. Dit verschil in daling was niet statistisch significant. Acht patiënten (24%) in de combinatietherapiegroep vielen uit omdat met 40 eenheden insuline geen goede glykemische controle werd bereikt. Combinatietherapie gaf minder gewichtstoename vergeleken met monotherapie (1.3 tegen 4.2 kg, p=0.01), en het gemiddeld aantal hypoglykemieën per patiënt per jaar was met combinatietherapie geringer (2.7 tegen 4.3, p=0.02). Er was geen verschil tussen beide groepen in tevredenheid over de behandeling en ten aanzien van spuit- en prikangst, terwijl het algemeen welbevinden meer verbeterde met combinatietherapie (p=0.05).
Op grond van deze resultaten concluderen we dat combinatietherapie kan worden aanbevolen als een effectieve en simpel toepasbare eerste keus behandeling voor patiënten met maximale orale medicatie die moeten overstappen op insulinetherapie.

Hoofdstuk 7

In Hoofdstuk 7 worden de resultaten gepresenteerd van een systematische review die is uitgevoerd volgens de criteria van de Metabolic and Endocrine Disorders Group van de Cochrane Collaboration. Het doel van deze review was de effecten te beoordelen van behandeling met insuline als monotherapie vergeleken met insuline in combinatie met orale bloedglucose verlagende tabletten (combinatietherapie) bij patiënten met onvoldoende glykemische controle ondanks orale medicatie. Na een uitgebreide literatuursearch selecteerden twee reviewers onafhankelijk van elkaar aan de hand van expliciete criteria in totaal 20 studies. De gegevensverzameling en kwaliteitsbeoordeling werd eveneens onafhankelijk van elkaar uitgevoerd door drie reviewers.

De studies bevatten in totaal 28 vergelijkingen tussen verschillen vormen van mono- en combinatietherapie. V anwege de heterogeniteit van de interventies werd een onderverdeling gemaakt op basis van insulinesoort, tijdstip en frequentie van insuline injecties, en het soort orale middel.
De studies hadden gemiddeld een lage methodologische kwaliteit (2.6 van maximaal 7 punten). De gemiddelde duur van de follow-up was 10 maanden. Ten aanzien van het effect op de glykemische controle kon geen significant verschil worden vastgesteld tussen de op dit moment meest gangbare toepassingen van monotherapie (twee of meer insuline injecties per dag) en combinatietherapie (insuline voor de nacht als toevoeging aan de bestaande orale medicatie). Vergeleken met monotherapie leidde combinatietherapie tot minder dagelijks insulinegebruik. Eén studie rapporteerde significant meer hypoglykemieën met monotherapie, maar in de overige studies was er geen verschil. Ten aanzien van gewichtstoename was er geen verschil tussen beide

therapieën, tenzij insuline gecombineerd werd met uitsluitend het orale middel metformine. In dat geval was er significant minder gewichtstoename vergeleken met monotherapie. Omdat deze combinatie in slechts één studie werd toegepast is een definitieve conclusie hierover niet te trekken. Effecten op de kwaliteit van leven en op patiënttevredenheid werden slechts bestudeerd in vier studies, waarbij geen significante verschillen werden gerapporteerd.
Voor de dagelijkse praktijk betekenen de resultaten dat voor patiënten die in aanmerking komen voor insuline, een avondinjectie middellangwerkend insuline als toevoeging aan de bestaande orale medicatie kan worden beschouwd als een simpel toepasbare, veilige en effectieve behandeling.

Hoofdstuk 8
In Hoofdstuk 8 worden de belangrijkste conclusies van dit proefschrift nog eens tegen het licht gehouden. Daarna formuleren we aanbevelingen voor het beleid bij hyperglykemie in de dagelijkse praktijk en komen we met suggesties voor herziening van de NHG-Standaard type 2 diabetes. De resultaten laten zien dat er aanzienlijke mogelijkheden zijn om de kwaliteit van de diabeteszorg verder te beteren. Hoewel dit onderzoek zich beperkt tot uitsluitend beïnvloeding van de glykemische controle, lijkt het aannemelijk dat identieke strategieën met succes bij de andere risicofactoren kunnen worden toegepast. Daarvoor is een benadering nodig die meer gericht is op het daadwerkelijk halen van behandeldoelen dan op het regelmatig controleren van patiënten. Meten is weliswaar weten, maar na weten komt – indien nodig - behandelen. Goede diabeteszorg begint met het zorgvuldig registreren en monitoren van alle diabetespatiënten in de praktijk, gevolgd door een doelgerichte aanpak van afwijkende gegevens. In dit proces speelt idealiter het elektronisch medisch dossier (met daarin geïntegreerd de richtlijnen uit de NHG-Standaard) een faciliterende rol. Gestructureerde educatie door een diabetesverpleegkundige (inclusief bloedglucose zelfcontrole) is effectief bij patiënten met maximale orale medicatie. Een integratie van deze vorm van educatie in de dagelijkse diabeteszorg is echter noodzakelijk om het effect op de langere termijn vast te houden. Behandeling en begeleiding van patiënten die insuline spuiten is in de huisartspraktijk onder voorwaarden goed mogelijk. Een avondinjectie met een middellangwerkend insuline, toegevoegd aan de bestaande orale medicatie, is voor de meeste patiënten die moeten starten met insuline een effectieve, simpel toepasbare, en veilige behandeling.
Diabeteszorg is complex en tijdrovend, en hoewel veel andere problemen in de praktijk van alledag om de voorrang strijden, denken we dat de huisarts een centrale positie dient te hebben in de zorg voor deze patiënten. Dit is

echter alleen haalbaar als de huisarts zich hierbij voldoende laat ondersteunen door goed geschoolde professionals zoals praktijkondersteuners en diabetesverpleegkundigen.

Dankwoord

Vraag het een wielrenner: ligt de kern van de voldoening in de beklimming zelf of vooral in het aankomen op de top? Moe maar voldaan schrijf ik dit dankwoord en kijk terug op de afgelopen vijf jaar. Het dal ligt inmiddels diep onder mij en ik besef dat deze bult meer weg heeft van de Mont Ventoux dan van de Amerongse Berg. Ook realiseer ik mij dat ik de streep nooit zou hebben gehaald zonder de hulp van zeer velen. Daarom wil ik – alvorens aan de afdaling te beginnen – alle mensen bedanken die mij onderweg hebben geholpen. Een aantal van hen wil ik met name noemen.

Doorslaggevend was zonder enige twijfel het kopwerk van het gouden viertal Henny Otten, Joyce Hanschen, Marjolein van der Leeden en Yvonne de la Bye. Ik heb genoten van jullie eendrachtige samenwerking. Later nog versterkt met Simone Witziers gingen jullie als onderzoeksassistent, praktijkconsulent en diabetesverpleegkundige kop over kop en hielden mij op een geweldige manier uit de wind. Heel veel dank voor jullie energie en gedrevenheid. En met Marjolein als paranimf voel ik mij tot op de dag van de promotie door jullie gesteund.

Het begeleidingsteam bestond uit Guy Rutten, Ronald Stolk en Harold de Valk. Guy, jij was ploegleider, supporter, duwer en masseur tegelijk. Zelden zal een promovendus zich door zijn promotor meer gesteund hebben gevoeld dan ik door jou tijdens deze tocht. Onze visie op de diabeteszorg konden wij in dit proefschrift onderzoeken en met resultaten zichtbaar maken. Je was permanent aanspreekbaar, ook bij nacht en ontij, en zelfs op een terras in Zuid-Frankrijk. Ik verheug mij op een voortzetting van de discussie bij de herziening van de NHG-Standaard. Heel veel dank voor de geweldige samenwerking. En ik beloof je: ik zal zondagmiddag niet meer bellen en ook van de fax zul je niet meer wakker schrikken.

Ronald, hoewel ogenschijnlijk wat meer op afstand, was ook jij mede dankzij internet steeds bereikbaar. Je had oog voor zowel de grote lijnen als de details. Je daagde mij steeds uit hoofd- van bijzaken te scheiden en je commentaren op mijn teksten waren bondig en concreet.

Harold, jouw rol bij mijn onderzoek was een logisch gevolg van je betrokkenheid bij het Utrechts Diabetes Programma. Met plezier denk ik terug aan de nascholingen die we samen gaven en waarin steeds meer van dit onderzoek verwerkt kon worden. Jij las al mijn stukken (waar ook ter wereld) en zag dat het goed was.

Een bijzonder woord van dank is op zijn plaats voor Peter Zuithoff, statisticus op het Julius Centrum, en medeauteur van drie artikelen. Peter, ik heb heel veel van je geleerd en de snelheid waarmee je als een on vermoeibare

superknecht alle gaten dichtreed was ongeëvenaard. Bij het concert van Jackson Brown zullen we nog eens napraten.
Furthermore I would gratefully thank Gerlof Valk and Niall Furlong for their excellent contribution to the Cochrane review. This part of the thesis was definitely the steepest stage of the tour, but thanks to the cooperation we were able to finish in time. Many thanks!
Bovenal wil ik het peloton huisartsen, praktijkassistentes en patiënten bedanken dat bereid was aan het onderzoek mee te doen. In het bijzonder wil ik hier noemen de groep diabetesverpleegkundigen en huisartsen die het insuline onderzoek tot een succes maakte: Roelien Andeweg, Dineke Bisschop, Yvonne de la Bye, Marieke van Dreven, Marcel Ebbing, Elizabeth Fetter, Erna de Goede, Marjolein van der Leeden, Jannie Kleinjan, Ine de Klijne, Fia Koopman, Martin te Lintel Hekkert, Fief de Mol, Carel Moojen, Anneke Potharts en Dick Ta venier.
Bij het tot stand komen van dit proefschrift was de Commissie Wetenschappelijk Onderzoek (CWO) van het NHG voor mij het perfecte wetenschappelijke krachthonk. Ik wil daarom alle leden en ex-leden bedanken die mij al die jaren inspireerden, stimuleerden en al mijn concepten van kritisch commentaar voorzagen.
De hoogleraren Siep Thomas, Joost Hoekstra, Chris van Weel, Hein Koomans en Arno Hoes dank ik voor de snelheid waarmee zij als leden van de leescommissie het manuscript aan een stevige dopingcontrole onderwierpen.
Vanuit de afdeling datamanagement van het Julius Centrum waren Hanneke den Breejen en Frank Leus onmisbare schakels bij het invoeren en beschikbaar krijgen van alle gegevens. Edwin Martens en Ingeborg van den Tweel van het Centrum voor Biostatistiek hielpen mij weer op gang toen ik bij het analyseren in een sur place terecht kwam. Rianne Maillé zette mij op het spoor van de juiste vragenlijsten voor de insuline trial en Dorien Michels zorgde voor het prachtige logo. Khanh Lam dank ik voor zijn bijdrage als (toen nog) medisch student aan het eerste artikel.
Zonder financiële ondersteuning was deze tocht nooit mogelijk geweest. Daarom wil ik de sponsor Novo Nordisk bedanken voor het vertrouwen waarin ik dit onderzoek in alle onafhankelijkheid kon uitvoeren. De firma Lifescan dank ik voor het beschikbaar stellen van het testmateriaal voor de educatiestudie.

Tenslotte wil ik iedereen bij de vakgroep huisartsgeneeskunde bedanken voor de collegiale en hulpvaardige sfeer. Het was een voorrecht in dit wetenschappelijke milieu onderzoek te mogen doen. En tegen al mijn maten op kamer 101 zou ik willen zeggen: zet gerust nog een tandje bij, maar ik begin alvast aan de afdaling!

List of publications

Practice Guidelines of the Dutch College of General Practitioners (NHG-Standaarden)

Goudswaard AN, Luttik A, Van de Vijver FJM, Bakx HCA, Polderman JA. NHG-Standaard Randvoorwaarden verloskunde (NHG Practice Guideline Boundary conditions for obstetrics). Huisarts Wet 1993;36:102-5

Boeke AJP, Van Griethuysen JJI, Versteeg JW, Westerveld MC, Eizenga WH, Goudswaard AN, Van der Laan JR. NHG-Standaard Herpes Genitalis (NHG Practice Guideline Herpes Genitalis). Huisarts Wet 1995;38:576-80.

Versteeg JW, Westerveld MC, Boeke AJP, Van Griethuysen JJI, Eizenga WH, Goudswaard AN, Van der Laan JR. NHG-Standaard Condylomata Acuminata (NHG Practice Guideline Condylomata Acuminata). Huisarts Wet 1995;38:581-4

Cirkel JW, Klaassen WRC, Kunst JA, Aarns TEM, Plag ECM, Goudswaard AN, Burgers JS. NHG-Standaard Niet-traumatische knieproblemen bij kinderen en adolescenten (NHG Practice Guideline Nontraumatic kneeproblems in children and adolescents). Huisarts Wet 1998;41:246-51

Van de Plas CG, Dingjan RA, Hamel A, Jonker JC, Postema PhJ, Smorenburg HAAJ, Bijl D, Scholten RJPM, Kolnaar BGM, Eizenga WH, Goudswaard AN. NHG-Standaard Traumatische knieproblemen (NHG Practice Guideline Traumatic kneeproblems). Huisarts Wet 1998;41:296-300

Bijl D, Dirven-Meijer PC, Opstelten W, Raaijmakers AJ, Scholten RJPM, Eizenga WH, Goudswaard AN. NHG-Standaard Niet-traumatische knieproblemen bij volwassenen (NHG Practice Guideline Nontraumatic keeproblems in adults). Huisarts W et 1998;41:344-50

Winters JC, De Jongh AC, Van der Windt DAWM, Jonquière M, De Winter AF, Van der Heijden GJMG, Sobel JS, Goudswaard AN. NHG-Standaard Schouderklachten [eerste herziening] (NHG Practice Guideline Shoulder complaints [first revision]). Huisarts W et 1998;41:222-31

Goudswaard AN, Thomas S, Van den Bosch WJHM, Van Weert HCPM, Geijer RMM. NHG-Standaard Enkeldistorsie [eerste herziening] (NHG Practice Guideline Ankle sprains [first revision]. Huisarts Wet 2000;43:33-7

Other full papers and manuscripts

Meulenberg F, Goudswaard AN. Richtlijnen in de huisartsgeneeskunde: een gevolg van professionalisering en kwaliteitsdenken (Guidelines in general practice: a result of professionalizing and quality thinking). Issue 1997;4:32-4

Goudswaard AN. Huisarts en vasectomie; een vruchtbare combinatie? Een haalbaarheidsstudie (General practioner and vasectomy: a fertile combination? A feasibility study). Huisarts Wet 1999;42:350-3

Goudswaard AN, Van Dijk CN. De verzwikte enkel: diagnostiek en behandeling (Ankle sprains: diagnostics and treatment). Huisarts Wet 1999;42:391-4

Goudswaard AN, Lam K, Stolk RP, Rutten GEHM. Quality of recording of data from patients with type 2 diabetes is not a valid indicator of quality of care. A cross-sectional study. Fam Pract 2003;20:173-7

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. Improving glycaemic control in patients with Type 2 diabetes mellitus without insulin therapy. Diabet Med 2003;20:540-4

Goudswaard AN, Stolk RP, Zuithoff NPA, Rutten GEHM. Patient characteristics do not predict poor glycaemic control in Type 2 diabetes patients treated in primary care. Eur J Epidemiol 2004 [in press]

Goudswaard AN, Stolk RP, Zuithoff NPA, de Valk HW, Rutten GEHM. Long term effects of self-management education for patients with type 2 diabetes taking maximal oral hypoglycaemic therapy. A randomized trial in primary care. Diabet Med 2004;21:491-496

Goudswaard AN, Stolk RP, Zuif hoff NPA, de Valk HW, Rutten GEHM. Starting insulin therapy in patients with type 2 diabetes: with or without continuation of oral hypoglycemic agents? A randomized trial in primary care. J Fam Pract 2004 [in press]

Goudswaard AN. Verbetering van de glykemische instelling (Improvement of glycaemic control). In: Serie Diabetes deel 3: Diabetes en HbA1c. Leusden: Mark T wo Communications, 2004

Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combinations of insulin with oral antihyperglycaemic agents in patients with Type 2 diabetes mellitus. A Cochrane review [submitted]

Goudswaard AN, Quartel M, Zuithoff NPA, Rutten GEHM. Welke onderdelen van een

educatie programma voor patiënten met diabetes mellitus type 2 zijn haalbaar en effectief ? [in voorbereiding]

Abstracts and presentations

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. Is an HbA1c < 7% attainable with oral blood glucose lowering agents in general practice DM-patients? [abstract]. Diabetologia 2000;43 Suppl A:703. EASD, Jeruzalem 2000

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. Optimizing diabetes control in general practice [abstract]. WONCA, Durban 2001

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. A randomised trial of efficacy of an educational program by a diabetes nurse in poorly controlled type 2 diabetic patients [abstract]. WONCA, Durban 2001

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. De zuster als medicijn? Een RCT naar de effecten van een educatieprogramma bij patiënten met diabetes type 2 (The nurse as a drug? A RCT of efficacy of an educational program by a diabetes nurse in type 2 diabetic patients [abstract]. NHG Wetenschapsdag, Amsterdam 2001

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. A randomised controlled trial of an educational program by a diabetes nurse in poorly controlled type 2 diabetic patients [abstract]. Primary Care Diabetes Europe, Stockholm 2002

Goudswaard AN, Stolk RP, de Valk HW, Rutten GEHM. A randomised controlled trial of an educational program by a diabetes nurse in poorly controlled Type 2 diabetic patients [abstract]. Diabetologia 2002;45 Suppl A:316. EASD, Budapest 2002 (rewarded with the 'best poster' price on the EASD highlights symposium, The Hague 2002)

Goudswaard AN, Stolk RP, Zuithoff NPA, Rutten GEHM. Predictors of poor glycaemic control in patients with type 2 diabetes in primary care [abstract]. Diabetologia 2003;46 Suppl 2914. IDF, Paris 2003

Goudswaard AN, Stolk RP, Zuithoff NPA, de Valk HW, Rutten GEHM. Starting insulin therapy in patients with type 2 diabetes in primary care: with or without continuation of oral hypoglycemic agents? [abstract]. WONCA Europe, Amsterdam 2004

Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combinations of insulin with oral antihyperglycaemic agents in patients with Type 2 diabetes mellitus. A systematic review [abstract]. WONCA Europe, Amsterdam 2004

Curriculum vitae

Lex Goudswaard was born on September 6th 1950 in Tynaarlo. In 1952 he moved to Maarsbergen, a small town in the middle of the Netherlands. He attended secondary school at the Revius Lyceum in Doorn. He graduated in 1967 and chose for medical school at the University of Utrecht. After finishing his training in general practice medicine in 1979, he worked in nursing homes in Zeist and Woerden. In 1983 he set up a practice in Houten, in which he still works as GP, since 1995 in cooperation with Marjon Lamers.
As a member of the CME Committee Southwest Utrecht (WDH) he has been involved in postgraduate education for GPs between 1987 and 1998. He was also involved in the vocational training for GPs as trainer for trainee-physicians from 1991 to 1995. His membership since 1995 of the Research Committee (CWO) of the Dutch College of General Practitioners contributed to his scientific learning.
In 1994 he became staff member at the department of Guideline Development of the Dutch College of General Practitioners (NHG) in Utrecht. Additionally, from 1999 to 2003 he worked on his thesis at the Julius Center for Health Science and Primary Care of the University Medical Center Utrecht. He has defended this thesis in 2004.
Since January 1st 2004 he is the head of the department of Guideline Development and Research Policy of the NHG.

Correspondence to: lex@goudswaard.cx


STIP
STichts Insuline Project