Computerized Decision Support Task Delegation and Feedback on Performance in type 2 Diabetes Care

The Diabetes Care Protocol

Frits Cleveringa

Computerized Decision Support, Task Delegation and Feedback on Performance in type 2 Diabetes Care. The Diabetes Care Protocol

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Computerized Decision Support, Task Delegation and Feedback on Performance in type 2 Diabetes Care
The Diabetes Care Protocol

Beslissingsondersteunende Software, Taak Delegatie en Feedback op het Handelen in de Zorg voor Diabetes type 2
Het Diabetes Zorg Protocol

(met een samenvatting in het Nederlands)

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Chapter 1

General Introduction

Working as general practitioner I deliver care to many type 2 diabetes patients. When I had seen a type 2 diabetic patient for a diabetes control visit, I often wondered if I had paid enough attention to all the different care aspect of his or her chronic disease. In a ten or twenty minutes encounter it is almost impossible to pay attention to all relevant chronic care aspects, because there are so many, for example the levels of HbA1c, blood pressure, and lipids, the role of diet, regular eye and foot care, renal function control, erectile dysfunction, medication and compliance.

Another factor that makes organizing diabetes care difficult is the number of patients. In the Netherlands there were approximately 740,000 patients diagnosed with diabetes in 2007(1) and the number of diagnosed patients is likely to increase to 1.32 million patients in 2025.(2) About 90% of these patients have type 2 diabetes(2) and 95% of these patients contact a primary care physician.(3)

Compared with non-diabetic patients, type 2 diabetic patients have a two to three fold increased risk for a cardiovascular event and 70% of the mortality of type 2 diabetic patients is due to coronary heart disease.(4;5) Strict control of glucose, lipids and blood pressure leads to reduction of the risk of diabetes related coronary heart disease and other micro- and macrovascular complications.(6-11) These complications also cause a considerable burden on the health related quality of life.(12) It is also stated that improving the diabetes care process and delaying diabetes complications will save health care costs(13). This is why the current diabetes guidelines recommend ambitious treatment targets for HbA1c, blood pressure and cholesterol levels.(14) Unfortu-

nately, recent studies have shown that at least 30% of type 2 diabetic patients in general practice do not meet the strict targets for good glycemic and cardiovascular control.(15-20) Calculations showed that current practice guidelines for only 10 chronic illnesses require more time than primary care physicians have available for patient care overall.(21) Therefore, it is important to develop and evaluate diabetes management systems that provide high quality and cost-effective diabetes care.(22) Against this background the Diabetes Care Protocol has been developed for the care of type 2 diabetes patients in the primary care setting.

The Diabetes Care Protocol

Numerous interventions in diabetes care have been studied. It has been shown that structured and regular review of patients improve the process of care(23), computerized decision support systems improve practitioner‘s performance,(24) team changes and case managers who are allowed to make medication adjustment may improve glycemic control(25) and feedback on performance given to primary care physicians is likely to improve HbA1c levels and practitioner behavior.(26) The fact that good recording is not a valid indicator for good quality of care(27), emphasizes that it is not sufficient to improve the process of care but also to focus on patient outcome.

The Diabetes Care Protocol (DCP) is a multifaceted intervention in which all the above mentioned interventions are combined. It consists

of 1) a diabetes consultation hour run by a practice nurse/case manager, 2) a computerized decision support system (CDSS) that contains a diagnostic and treatment algorithm based on the Dutch type 2 diabetes guidelines(14) and provides patient-specific treatment advice, 3) a recall system, 4) feedback on performance every three months regarding the percentage of patients meeting the treatment targets (cessation of smoking, HbA1c<7%, systolic blood pressure <140 mmHg, total cholesterol <4.5mmol/L, LDL-cholesterol <2.5mmol/L and BMI <27kg/m²)(14) on both practice and patient level.

Information on patient's history, medication use and clinical parameters is brought together in the CDSS. Old information as well as newly added information can be used during the consultation. Patients are seen every three months and the CDSS guides the practice nurse through the consultation. The CDSS indicates what information should be asked from the patient and which examinations should be performed. After every consultation a new appointment is made. This very structured type of diabetes care reduces the chance that important items in diabetes care are neglected during the consultation.

Aims of the thesis

The studies and research questions in this thesis cover three parts of type 2 diabetes management in primary care. The themes are: effectiveness of the Diabetes Care Protocol, erectile dysfunction and car-

diovascular risk assessment, and which part of the Diabetes Care Protocol is likely to be the most successful.

Effectiveness of the Diabetes Care Protocol

Several aspects of the effectiveness of DCP were studied. The first research question was whether the DCP improves patient outcome in type 2 diabetic patients in primary care. This was evaluated by a randomized controlled trial with a follow-up of one year and looking at differences in HbA1c, cardiovascular risk and cardiovascular risk factors. Secondly the effects of DCP on health status and satisfaction with care were assessed. We hypothesized that DCP did not have a negative effect on health status, despite the intensification of care. Third we evaluated whether DCP was a cost effective health care intervention.

Erectile dysfunction and cardiovascular risk assessment

One of the questions in the DCP is whether men have erectile dysfunction (ED) or not. This single question might be just as good as making use of time consuming ED questionnaires.(28) We aimed to assess the "single question ED prevalence". ED is very common in men with diabetes(29-32) and both diabetes and cardiovascular disease are independently associated with ED.(33) However, it is less clear whether routinely asking patients with type 2 diabetes about ED will identify patients with elevated risk for cardiovascular disease. We therefore aimed to assess the cardiovascular risk of type 2 diabetic patients with ED.

Which part of DCP is likely to be the most successful

The Diabetes Care Protocol is a multifaceted intervention with a computerised decision support system (CDSS). Earlier review studies on the effectiveness of CDSS showed mainly improvements in the process of care.(24;34) Because most studies with CDSS were also multifaceted we aimed to investigate which combination of interventions was most successful in improving both the process of care and patient outcome.

Structure of the thesis

Because DCP was already used on a large scale throughout the Netherlands before we started our studies, we did not begin with a systematic review on the different parts of DCP. The structure of this thesis reveals the steps we went through in order to reveal the 'black-box' that covers DCP.

Chapter 2

In this chapter the results of a before-after study with DCP in a nation wide population are described. It could be considered as a preliminary study for the randomized controlled trial (RCT) and revealed possible effects of DCP on patient outcome in diabetes care.

Chapter 3

The results of the cluster randomized controlled trial with DCP in 55

practices across the Netherlands are described in chapter 3. The aim of this RCT was to investigate the effects of DCP on HbA1c% and cardiovascular risk in type 2 diabetic patients in primary care.

Chapter 4

In chapter 4 the effects of DCP on health status and satisfaction with care are reported. In the same RCT as described above, health status and satisfaction with care were also recorded. The aim of this study was to evaluate the effects of DCP on diabetes specific health status. Long term diabetes complications are strongly associated with reduced health.(12) It is therefore unlikely that DCP will have a large effect on health status after just one year. On the other hand, some primary care phycicians and practice nurses are reluctant to intensify diabetes care, because they assume that such an intensification would almost immediately result in a diminished quality of life and treatment satisfaction of their patients. We therefore hypothesized that DCP is not inferior to usual care with respect to health status in the short term.

Chapter 5

For this chapter, the one year follow-up patient RCT data were used in a modified Dutch micro-simulation diabetes model. This model extrapolated the study data and computed individual lifetime, health related costs and health effects. Although it is stated that information technology, like CDSS, in diabetes care may improve care processes, delay diabetes complications and save health care costs,(13) most studies in this field do not include a cost-effectiveness analysis.(35)

We therefore performed a cost-effectiveness analysis of the DCP versus usual care from a Dutch health care perspective.

Chapter 6

The baseline study data from the RCT were used in this chapter. The aim of this study was to assess the "single question ED prevalence". Further we aimed to investigate whether ED was associated with a history of cardiovascular disease and/or cardiovascular risk.

Chapter 7

In this chapter we performed a systematic review of interventions that are often combined with computerized decision support in primary diabetes care. We aimed to investigate whether a CDSS alone or a CDSS in combination with a reminder system and/or with feedback on performance and/or as part of a structured case management system has the ability to improve both patient outcome and practitioner performance.

Chapter 8

In the General discussion in chapter 8 the main conclusions of the studies are presented and implications for future research, policy makers and clinical practice are formulated.

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Chapter 2

Task Delegation and Computerized Decision Support Reduce Coronary Heart Disease Risk Factors in Type 2 Diabetes Patients in Primary Care

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Abstract

Objective: Reducing cardiovascular risk in type 2 diabetic patients is important in diabetes care. However, treating patients according to diabetes guidelines appears to be difficult. Delegating routine tasks to a practice nurse combined with computerized decision support systems (CDSS) may be helpful. We studied the effectiveness of a practice nurse-managed CDSS for diabetes care on improving cardiovascular risk factors in type 2 diabetic patients.

Research Design and Method: In 113 primary care practices (n = 7,893) across the Netherlands, the Diabetes Care Protocol (DCP) was assessed in a before-after study, lasting 1 year. All practices implemented DCP, which is characterized by delegating routine tasks in diabetes care to a practice nurse, software that supports diabetes management, medical decisions, and benchmarking (CDSS). All type 2 diabetic patients treated by their primary care physician were asked to attend the program. Primary outcome was the percentage of patients achieving treatment targets: HbA1c ≤7%, blood pressure ≤150/85 mmHg and total cholesterol ≤5 mmol/L.

Results: The percentage of type 2 diabetic patients who achieved targets increased significantly, from 60.6% to 66.5% for HbA1c, from 48.7% to 61.9% for blood pressure, and from 47.4% to 60.6% for total cholesterol. The percentage of patients achieving all three targets increased from 15.3% to 26.9% (all $p < 0.01$).

Conclusion: Delegating routine task in diabetes care to a practice nurse combined with CDSS and benchmarking helps achieve treatment goals for HbA1c, blood pressure and cholesterol and reduce the cardiovascular risk of type 2 diabetic patients in primary care.

Introduction

Seventy percent of type 2 diabetic patients die from coronary heart disease (CHD).(1) The lifetime risk of vascular death among type 2 diabetic patients has been reported to be as high as that for patients with CHD alone.(2) Therefore, it is important to treat cardiovascular risk factors adequately in patients with diabetes.

Strict control of glucose, lipids and blood pressure, as recommended in most clinical guidelines, can lead to a reduction in the risk for diabetes-related CHD and other vascular complications.(3-5) In type 2 diabetic patients this risk reduction can be expressed by calculating 10-year CHD risk estimates using the UK Prospective Diabetes Study (UKPDS) risk engine.(6) Calculating cardiovascular risks for clinical purposes is recommended by the British National Institute for Clinical Excellence.(7) Both UKPDS and Framingham CHD risk calculations identify about 65% of type 2 diabetic patients who require primary CHD prevention, under National Institute of Clinical Excellence recommendations.(8)

However, implementing guidelines appears to be difficult, resulting in an increased risk of cardiovascular disease. Most type 2 diabetic patients are treated in primary care, but recent studies show that at least 30% of type 2 diabetic patients in primary care do not meet the strict targets for good glycemic and cardiovascular control.(9;10) When all guidelines for chronic illnesses in primary care are followed as recommended, primary care physicians (PCPs) do not have sufficient time to care adequately for chronic disease patients.(11)

Possible solutions for this management problem may be delegating specified (routine) tasks in chronic care to practice nurse, a nurse specialized in care for chronically ill patients, as well as using computerised decision support systems (CDSS). CDSS are a rapidly evolving type of health care innovation. They aim to improve both process of care and the patient outcome. The process of care is improved by structured and regular review of patients.(12) Glycemic control can be improved with case management, especially for interventions in which case managers could adjust medications without awaiting the physician's approval.(13) A recent review of clinical trials evaluating the effects of CDSS in diabetes care showed that these systems can improve practitioners' performance; however, the results on patient outcome are less clear and remain understudied.(14) Another meta-analysis showed that the use of computer-based systems for DM patients improved metabolic control.(15) Individual studies mainly show beneficial effects on process indicators, such as frequency of blood sugar monitoring, but no improvement on patient outcomes, notably the actual levels of HbA1C, blood pressure and cholesterol.(14;16-18) Therefore, the aim of this study is to investigate the effects of a diabetes care program, which consists of task delegation to a practice nurse supported by CDSS and benchmarking, on the risk factors for CHD in type 2 diabetic patients in primary care.

Research design and Methods

Study Design

We conducted a pragmatic prospective study with a before-after design. Primary care practices throughout the Netherlands were asked whether they were interested in changing their usual diabetes care to a practice nurse led categorical diabetes office hour using a new CDSS for diabetes care. These practices were not participating in any other diabetes care improvement program. Practices were included in this study if they were willing to change their diabetes care, accepted the conditions of the Diabetes Care Protocol (DCP), worked with an electronic medical record, and were not involved in any other diabetes care improvement program.

113 primary care practices across the Netherlands participated. Of these practices, 53 were run by one single PCP working in his or her own office together with at least one practice assistant who acted as receptionist and performed easy medical tasks. In 33 practices two PCPs worked together in one office, a so-called duo-practice, and 27 were group practices, with three or more PCPs working together. In total, 445,891 patients were registered in these practices. Prior to the intervention, the majority of PCPs (n = 67) performed most diabetes care activities themselves, although they were sometimes assisted by a practice assistant who measured blood pressure and fasting glucose. In 33 practices, diabetes care was performed by a practice nurse. Ten of these practices also used a recall system for diabetes care. The remaining 13 practices worked with a so called ‘diabetes service’, in which

the majority of diabetes care was delivered by other personnel than the primary care practice staff.

Study population

In all participating practices, type 2 diabetic patients were selected from the electronic patients database through ICPC-code (T90.2, Type 2 diabetes), diabetes as a point of attention in the patient's record, or ATC-code (A10A, insulin and analogues; A10B: oral blood glucose lowering drugs). The list of type 2 diabetic patients was subsequently checked by the PCP for specific exclusion criteria, including having a terminal illness or complex multimorbidity, being unable to visit the primary care practice, or receiving diabetes treatment from a medical specialist. All other type 2 diabetic patients were invited to attend the diabetes consultation hour introduced by DCP.

Type 2 diabetic patients were enrolled between 1 January 2003 and 1 June 2004. Informed consent was obtained from all study participants. No formal approval of the medical ethical committee was necessary because the care given was based on the Dutch Primary Care Guidelines on type 2 diabetes. After informed consent was obtained, data from each participant were collected electronically at baseline and 1-year follow-up and pooled in a central database. Because there were no records on patient's hospitalization, migration, or death during the study period, we included only patients with data at baseline and 1-year follow-up. In total the database consisted of 7,893 type 2 diabetic patients.

Intervention

In all participating practices the DCP, developed by Diagnosis for Health (Baarn, the Netherlands), was introduced. (Diagnosis for Health develops and supplies software in combination with practice reorganisation and support for primary and secondary care to improve the management of patients with or at risk for chronic illnesses.) DCP is characterized by delegation of routine diabetes care tasks to a trained practice nurse, who uses the DCP software that supports management and medical decisions, during office hours exclusively scheduled for type 2 diabetic patients.

Before DCP was implemented, a systematic evaluation of prior diabetes care in each primary care practice was performed. Agreements on mutual consultation and responsibilities were made between practice nurse and PCP. The PCP also had to make arrangements with other primary care providers (podiatrists, dieticians, diabetes nurses, medical specialists) about indications for consultation.

The practice nurse was trained in performing diabetes care according to the Dutch Primary Care Guideline on type 2 Diabetes Mellitus(19) and in using the CDSS during diabetes consultation hours. The software indicated what type of information should be requested from the patient and what sort of examinations and tests should be performed. Patients were sent to a local laboratory 1 week before the office visit, to ensure that test results would be available to the practice nurse during the patient's visit. The CDSS structured and presented all relevant parameters, tests, and questions necessary for diabetes care according to the guidelines.(19) The practice nurse manually entered

the information in the CDSS and to enter every item before she could continue with the next patient. With this real-time database, it was possible to give each patient specifically tailored treatment advice at the end of his or her visit. Where relevant, and as indicated by the CDSS, this could include patient education. The treatment changes were performed by the practice nurse after they were approved by the PCP. At the end of every visit a new appointment was made. Patients were seen at least once every 3 months. The CDSS distinguished between yearly and three monthly visits. In this study we only used the information collected during the extensive investigation of he yearly visit.

As an integral part of DCP, the PCP and practice nurse received benchmark reports every 3 months. Patient outcome parameters for diabetes from the practice, such as HbA1c, blood pressure, cholesterol, body mass index and smoking, were compared with the other DCP practices in the database. The DCP software also generated a list of all type 2 diabetic patients with their cardiovascular risk factors and indicators of metabolic control. Patients with a high cardiovascular risk and / or poor metabolic control were highlighted, so the practice nurse could easily focus on patients who needed the most improvement on their results.

Outcome measures and data collection

The primary outcome was the percentage of patients who achieved the target values of HbA1c, blood pressure, and total cholesterol. The targets from the Dutch Primary Care Guidelines on type 2 Diabetes

Mellitus (1999) were used: HbA1c ≤7%, blood pressure ≤150/85 mmHg and cholesterol ≤5.0 mmol/L.(19) For patients with a recorded date of onset of diabetes, we calculated the 10-year CHD risk estimate using the UKPDS CHD risk algorithm.(6) The following risk factors are used: sex, ethnicity, current smoker, duration of diabetes, HbA1c, systolic blood pressure, and total cholesterol / HDL-cholesterol ratio.

The practice nurse registered gender, age, ethnicity, and duration of diabetes. Ethnicity was recorded as considering oneself Caucasian / Afro-Caribbean / Asian-Indian. Smoking habits were recorded at baseline and after 1-year follow-up, as smoker / non-smoker / ex-smoker. HbA1c levels, total cholesterol, and HDL-cholesterol were all measured in local laboratories. The practice nurses were trained to measure blood pressure according to standard operating procedures.

Statistical analysis

To calculate the 10-year UKPDS CHD risk, the date of onset of diabetes was needed. Unfortunately, this item was not included in former version of the CDSS. As a consequence, the duration of diabetes was recorded for only 20% of patients. For that reason, we did two separate analyses.

The differences between the two patient groups were compared with Student's t-test for continuous variables and chi-square test or Fisher's exact test for nominal variables. Baseline and 1-year follow-up diabetes parameters (HbA1c, blood pressure, and cholesterol) were compared with Student's paired t-test. McNemar's test was used to test before-after differences of proportions. The one sample t-test was

used for the difference in 10-year UKPDS CHD risk estimate. The difference in 1-year change between patients from practices that used a diabetes service prior to the intervention and patients from the other practices was compared with the independent-sample t-test. $P < 0.05$ was considered statistically significant.

Analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 12.0.1 (SPPS Inc., Chicago, IL).

Results

Of the 7,893 patients with available data at baseline and 1-year follow-up, 48.5% were men, and age at baseline was 67.3 ± 11.6 years. Of the patients, 99.5% were Caucasians. The percentage of patients with a family history of diabetes or cardiovascular disease was 56.3% and 29.7%, respectively. A total of 17.6% were current smokers.

In table 2.1 the main characteristics of the total group and of patients with and without a registered duration of diabetes are presented. At baseline these two groups differed significantly in age and percentage HbA1c. The other parameters were comparable. The mean duration of diabetes for patients with a recorded date of onset of diabetes was 4.4 ± 4.8 years.

Table 2.1 Baseline characteristics of 7,893 type 2 diabetic patients in primary care

	Total group N = 7,893	Patients by recorded duration of diabetes		P for difference between patient group 1 and 2
		without (group 1) N = 6,255	with (group 2) N = 1,638	
Mean age (years ± SD) (years)	67.3 ± 11.7	67.6 ± 11.5	66.0 ± 11.8	0.000
sex (% female)	51.5	52.9	49.5	0.07
Race (%)				
Caucasian	99.5	99.6	99.1	0.06
Afro-Caribbean	0.1	0.1	0.1	
Asian / Indian	0.4	0.3	0.7	
Smoking (%)	17.6	17.3	18.7	0.16
Family history of diabetes (%)	56.3	56.1	56.7	0.27
Family history of cardiovascular disease (%)	29.7	29.4	30.9	0.05
HbA1c (mean ± SD) (%)	7.0 ± 1.30	7.0 ± 1.26	7.2 ± 1.46	0.000
blood pressure (mean ± SD) (mmHg)				
Systolic	149 ± 21.1	149 ± 21.1	148 ± 21.1	0.34
Diastolic	83 ± 10.8	83 ± 10.8	83 ± 10.8	0.53
Total cholesterol (mean ± SD) (mmol/L)	5.2 ± 1.1	5.2 ± 1.1	5.1 ± 1.1	0.08

Student's t-test was used for continuous variables
Nominal variables were compared with Chi-square test, except for race (Fisher's exact test).

Change in CHD risk factors

The percentages of type 2 diabetic patients who achieved the treatment goals for HbA1c, blood pressure, and total cholesterol improved significantly: from 60.6% to 66.5%, from 48.7% to 61.9% and from 47.4% to 60.6%, respectively. The percentage of patients that reached all three target values improved from 15.3% to 26.9% (table 2.2).

Table 2.2 Quality indicators at baseline and 1-year follow-up, for 7,893 type 2 diabetic patients after the diabetes care intervention using task delegation and computerized decision support.

	Time		
Quality indicator	Baseline (%)	1-year follow-up (%)	McNemar test p-value
HbA1c ≤ 7.0%	60.6	66.5	0.000
Blood pressure ≤ 150/85 mmHg	48.7	61.9	0.000
Total cholesterol ≤ 5.0 mmol/L	47.4	63.2	0.000
All targets met	15.3	26.9	0.000

In table 2.3 baseline and 1-year follow-up levels are given for each of the cardiovascular risk factors. The HbA1c level, systolic and diastolic blood pressure, total cholesterol, HDL-cholesterol, and smoking all improved significantly 1 year after the intervention (all p <0.001).

Risk of coronary heart disease in a subgroup of type 2 diabetic patients

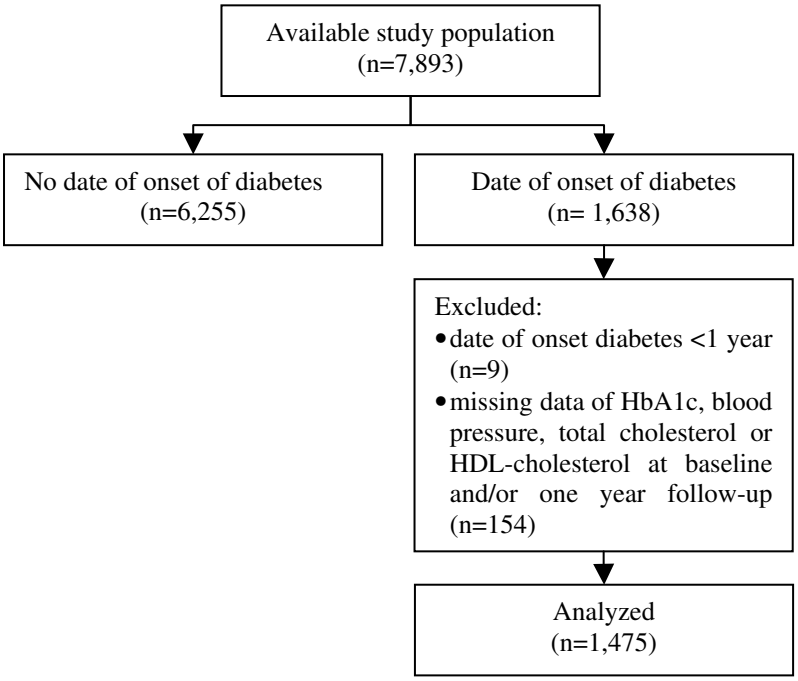
In a subgroup of 1,638 patients, the date of onset of diabetes was recorded. Nine patients were excluded because the date of onset was <1 year. Another 154 patients were excluded because of missing data in other variables (figure 2.1). So the 10-year UKPDS CHD risk estimate was calculated for 1,475 patients and decreased from 25.8% to 23.0%. For men and women the reduction was 3.5% (95% confidence interval 2.7% - 4.4%) and 2.1% (95% confidence interval 1.5% - 2.7%), respectively (table 2.3).

Table 2.3: Change of CHD risk factors and 10-year CHD risk in type 2 diabetic patients 1 year after the start of task delegation and computerized decision support

Risk factor (n = 7,893)	Time		1-year change	95% CI	p-value
	baseline	1-year follow-up			
HbA1c (%)	7.0 ± 0.01	6.8 ± 0.01	0.21 ± 0.01	0.19 – 0.24	<0.001
Blood pressure (mmHg)					
Systolic	149 ± 0.2	143 ± 0.2	5.2 ± 0.2	4.8 – 5.7	<0.001
Diastolic	83 ± 0.1	80 ± 0.1	3.1 ± 0.1	2.9 – 3.4	<0.001
Total cholesterol (mmol/L)	5.2 ± 0.01	4.8 ± 0.01	0.41 ± 0.01	0.38 – 0.43	<0.001
HDL-cholesterol (mmol/L)	1.25 ± 0.004	1.28 ± 0.004	-0.026 ± 0.004	- 0.031 to - 0.021	<0.001
Cholesterol/HDL-cholesterol ratio	4.39 ± 0.016	3.96 ± 0.014	0.43 ± 0.015	0.40 – 0.46	<0.001
Smoking (%)	17.6	16.8	0.8		<0.001*
CHD risk estimate (n=1475) UKPDS CHD rik (%)					
All	25.8 ± 0.5	23.0 ± 0.4	2.8 ± 0.3	2.3 - 3.3	<0.001
men	31.0 ± 0.6	27.7 ± 0.6	3.5 ± 0.4	2.7 - 4.4	<0.001
women	20.4 ± 0.5	18.3 ± 0.5	2.1 ± 0.3	1.5 - 2.7	<0.001

Data are mean ± standard error of the mean (SEM). 95% CI, 95% confidence interval.
* For smoking the McNemar test was used

Figure 2.1. Flow of patients with and without a date of onset of diabetes.



Influence of prior type of diabetes care

At baseline, patients from the 13 practices using a diabetes service had significantly better values regarding HbA1c, blood pressure, total cholesterol, HDL-cholesterol and 10-year UKPDS CHD risk. As with patients from other practices, this "diabetes service group" also achieved significant improvement in some cardiovascular risk factors, including blood pressure, total cholesterol, HDL-cholesterol, cholesterol ratio and 10-year CHD risk estimate but not HbA1c. However, changes in HbA1c, blood pressure and HDL-cholesterol were signifi-

Table 2.4: 1-year change, difference between diabetes service, and other forms of diabetes care prior to the intervention (PCP, practice nurse or recall system)

	Group 1 (from practice with diabetes service) (n = 690)		Group 2 (from other practices) (n = 7,203)		95% CI of difference between groups 1 + 2	p-value of difference between groups 1 + 2
Risk factor	Baseline*	1-year Change*	Baseline	1-year Change		
HbA1c (%)	6.9 ± 0.04	-0.06 ± 0.04†	7.1 ± 0.02	-0.23 ± 0.0‡	-0.25 to -0.08	<0.001
Blood pressure						
Systolic (mmHg)	142 ± 0.8	-3.7 ± 0.7‡	149 ± 0.2	-5.4 ± 0.2‡	-3.2 to –0.05	0.04
Diastolic (mmHg)	80 ± 0.4	-2.3 ± 0.4‡	84 ± 0.1	-3.2 ± 0.1‡	-1.7 to -0.03	0.04
Total cholesterol (mmol/L)	5.1 ± 0.04	-0.36 ± 0.03‡	5.2 ± 0.01	-0.42 ± 0.01‡	-0.03 to 0.15	0.2
HDL cholesterol (mmol/L)	1.30 ± 0.013	0.02 ± 0.006‡	1.24 ± 0.004	0.03 ± 0.002‡	- 0.03 to 0.001	0.07
Cholesterol/HDL ratio	4.1 ± 0.05	-0.34 ± 0.03‡	4.4 ± 0.02	-0.45 ± 0.02‡	-0.05 to 0.15	0.3
UKPDS CHD risk (%)	20.7 ± 1.0	-1.7 ± 0.6‡	26.6 ± 0.5	-3.1 ± 0.3‡	-2.9 to 0.2	0.1

Data are mean ± SEM values. 95% CI, 95% confidence interval. * Difference between groups at baseline significant for all risk factors ($P < 0.05$). † 1-year change within patient group not significant ($P = 0.09$). ‡ 1-year change within patient group significant ($p< 0.05$

cantly lower compared to practices that had not collaborated with a diabetes service. For total cholesterol and 10-year UKPDS CHD risk there was no significant difference between both groups (table 2.4).

Discussion

Summary of the main findings

The implementation of the Diabetes Care Protocol engendered significant improvements in the three main treatment goals of diabetes (HbA1c ≤7%, blood pressure ≤150/80 mmHg, and total cholesterol ≤5mmol/L, all p <0.001), as recommended by the Dutch Primary Care Guidelines on type 2 Diabetes Mellitus.(19) The percentage of patients who reached all three treatment goals increased from 15.3% to 26.9% between baseline and 1-year. For a subset of 1,475 patients, with known duration of diabetes, we found a significant absolute risk reduction in the 10-year UKPDS CHD risk score of 2.8%. The DCP was effective in all practices, but had less impact among patients from practices already using a diabetes service.

Strengths and limitations

The study was performed in several regions in the Netherlands. The distribution of the different types of practices (solo 46.9%, duo 29.2%, and group 23.9%) is more or less comparable to the distribution of primary care practices across the Netherlands (solo 51.1%, duo 30.5% and group 18.5%).(20)

In the 113 practices 445,891 patients were registered. Of these patients, 7,893 type 2 diabetic patients under PCP treatment were included. This is 1.77% of the total registered practice patient population and was comparable to diabetes studies in the Netherlands, using similar selection criteria.(9;21) On the other hand, about half of the primary care diabetes population was excluded in this study because of, among other reasons, terminal illness, inability to visit the primary care office and complex multimorbidity. From a clinical point of view, however, it is likely that the quality of life will not be improved by treating these patients strictly according to the treatment targets in the guidelines.(22)

Some limitations have to be recognized when considering these data. With no control group, the effectiveness of the DCP may be influenced by other factors than just the intervention, such as regression to the mean. Further, we performed a complete case analyses, because there were no records available of patients who moved, died, or who were hospitalized. This may lead to an overestimation of the measured effect. Because the baseline HbA1c, blood pressure and cholesterol levels of our study population were lower than in most studies(9;17;21;23), there was less room for improvement, but nevertheless we found relevant and significant changes in HbA1c, blood pressure, and cholesterol levels, so the effect of this overestimation is probably small.

Furthermore, the practices in this study were self-selected, reflecting a special interest of the PCPs in improving diabetes care. This may also lead to an overestimation of the effect. Finally, since the follow-

up period is only 1 year, we do not know if the effectiveness of DCP will be sustained over a longer period of time.

Comparison with other studies

Winocour pleaded for realistic targets in the treatment of type 2 diabetic patients, because the current treatment targets could only be met in research settings and are impractical in daily practice with patients taking too many drugs, to which they often will not comply.(24) Some recently performed trials on improving diabetes care in the Netherlands showed that about 40% of the patients reached HbA1c $\leq$ 7.0%, 55% reached a blood pressure $\leq$ 150/85 mmHg, and 40% reached a total cholesterol $\leq$ 5.0 mmol/L. (9;21) In our study, the targets for HbA1c, blood pressure, and total cholesterol were reached by > 60% of the patients and 26.9% of the patients reached all three treatment goals in one year. This suggests that the DCP may make it possible to achieve research based targets in daily clinical practice.

The 10-year UKPDS CHD risk estimate was calculated to have one outcome measure in which all cardiovascular risk factors were combined and weighted by their importance.(23) Because the date of onset of diabetes was added in the software at a later time, these calculations could only be made for about 20% of the patients. In these patients the 10-year UKPDS risk estimate improved 2.8%. From the Steno 2 study we learned that intensive treatment in a group of relatively young type 2 diabetic patients with albuminuria significantly lowered the risk of cardiovascular disease.(5) The multi factorial intervention mainly reduced HbA1c, blood pressure, and cholesterol levels. In our study, we

achieved smaller reductions in HbA1c, blood pressure, and total cholesterol, but reductions in the 10-year UKPDS CHD risk estimates were still significant. Because there were no clinically relevant differences between both groups we estimate that the improvements in 10-year UKPDS CHD risk estimate could be extrapolated to the whole group of patients.

In diabetes care many computer applications have been introduced. Database systems are accepted, but for decision support systems this is more complex.(25) Because good recording is not a valid indicator of good quality of care,(26) just recording is not enough. Recording has to be followed by treatment changes where necessary and better adherence to guidelines. In DCP the practice nurse, operating as the diabetes care case manager, received patient-specific treatment advice by the CDSS, immediately after completing the office hour visit. Second, both PCP and nurse received benchmark information every 3 months. Most of the multifaceted interventions in DCP – task delegation, structured care, and feedback – are also used in a diabetes service. Because there were still significant improvements in this group for all parameters except HbA1c, which was below treatment target at baseline, we conclude that it is likely that the CDSS in DCP contributed to the positive effects of the total intervention.

Implications for clinical practice and future research

The DCP seems a promising way for improving patient outcome in diabetes care. Diabetes care performed by practice nurses using DCP appears to be at least as good as and may even be better than the dia-

betes care given before the introduction of DCP. Further randomized research is necessary to explore the possibilities for task delegation and the introduction of CDSS in primary care.

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Chapter 3

Combined Task Delegation, Computerized Decision Support, and Feedback Improve Cardiovascular Risk for Type 2 Diabetic Patients

A Cluster Randomized Trial in Primary Care

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Abstract

Objective: The Diabetes Care Protocol combines task delegation (a practice nurse), computerized decision support, and feedback every 3 months. We studied the effect of the Diabetes Care Protocol on HbA1c and cardiovascular risk factors in type 2 diabetic patients in primary care.

Research Design and Methods: In a cluster randomized trial, mean changes in cardiovascular risk factors between intervention and control groups after 1 year were calculated by generalized linear models.

Results: Throughout the Netherlands, 26 intervention practices included 1,699 patients and 29 control practices 1,692 patients. The difference in HbA1c change was not significant, whereas total cholesterol, LDL-cholesterol, and blood pressure improved significantly more in the intervention group. The 10-year coronary heart disease risk estimate of the UK Prospective Diabetes Study improved 1.4% more in the intervention group.

Conclusions: Delegation of routine diabetes care to a practice nurse combined with computerized decision support and feedback did not improve HbA1c but reduced cardiovascular risk in type 2 diabetic patients.

Introduction

Improving patients' outcomes, in order to reduce cardiovascular risk, remains one of the most important goals in diabetes care. Structured and regular review of patients improve the process of care(1), and team changes and case management showed improvements in glycemic control.(2) Computerized Decision Support Systems (CDSSs) have been shown to improve practitioners' performance(3), and feedback on performance given to Primary Care Physicians (PCPs) has been demonstrated by Ziemer et al. to lower patients' HbA1c and improved practitioners' behavior.(4)

Against this background, the Diabetes Care Protocol (DCP) was developed, which reduced patients' cardiovascular risk in a before after study.(5)The current randomized clinical trial aims to investigate the effects of DCP on HbA1c and cardiovascular risk in type 2 diabetic patients in primary care.

Research Design and Methods

Primary care practices throughout the Netherlands that were not involved in other diabetes care improvement programs, were block randomized to intervention (26 practices) or the control group (29 practices). The number of PCPs working in each practice and the presence of a practice nurse before intervention were taken into account before

randomization. The intervention, also described elsewhere(5), consisted of 1) a diabetes consultation hour run by a practice nurse, 2) a CDSS that contained a diagnostic and treatment algorithm based on the Dutch type 2 diabetes guidelines (6) and provided patient-specific treatment advice, 3) a recall system, and 4) feedback every 3 months regarding the percentage of patients meeting the treatment targets (cessation of smoking, HbA1c <7%, systolic blood pressure <140 mmHg, total cholesterol <4.5 mmol/L, LDL-cholesterol <2.5 mmol/L and BMI <27 kg/m²)(6) on both practice and the patient levels. The PCPs were advised that they should prescribe new medication and refer patients if necessary. The control group continued with the same diabetes care that they had received before entering the study, which means that diabetes care was provided by the PCP or by a practice nurse under PCP responsibility. The University Medical Center Utrecht ethics committee approved the study, and patients provided written consent. (ISRCTN21523044)

From the 171,821 registered patients, all type 2 diabetic patients were identified. Patients who had a short life expectancy, were unable to visit the primary care practice, or were receiving diabetes treatment from a medical specialist were excluded. Initially, 3,979 patients were eligible (2,136 in the control group and 1,843 in the intervention group), but 548 subjects refused to participate (409 control and 139 intervention subjects), and an additional 40 (35 control and intervention subjects) failed to participate for unknown reasons. (for both groups, $p < 0.05$) The final, mainly Caucasian, study population consisted of 3,391 patients (1,692 control and 1,699 intervention). After 1

year, 2,841 patients (1,389 control and 1,452 intervention) completed follow-up examination: 187 patients (115 control and 72 intervention) refused to participate in final measurements, and 13 others (12 control and 1 intervention) failed to show for unknown reasons (for both groups $p < 0.05$). The groups did not differ with regard to the number of patients who died, moved, became terminally ill, or were referred to a specialist.

Between March 2005 and August 2007, patients were each seen twice for annual diabetes checkups. Patients who did not show received one reminder. In the CDSS, age, sex, ethnicity, duration of diabetes, and smoking habits were registered. HbA1c%, total cholesterol, and HDL-cholesterol were measured in local laboratories. LDL-cholesterol was calculated. Blood pressure was measured according to a standard operating procedure.

The 10-year coronary heart disease (CHD) risk estimate, as established by the UK Prospective Diabetes Study (UKPDS) (7), was calculated using the abovementioned variables, excluding LDL-cholesterol.

The primary outcome was the 1-year difference in HbA1c%. Secondary outcomes were the 1-year difference in 10-year UKPDS CHD risk estimate and the percentage of patients that reached HbA1c $\leq$7%, systolic blood pressure $\leq$140 mmHg, total cholesterol $\leq$4.5 mmol/L, LDL-cholesterol $\leq$2.5 mmol/L.(6)

We performed intention-to-treat analyses with baseline values carried forward in case of missing values. To correct for clustering at practice level, generalized linear models were used and after cluster-

ing had been taken into account, a 0.3% difference in HbA1c and a 2% UKPDS CHD risk could be detected with 90% power ($\alpha = 0.05$), with at least 1,080 patients in each treatment arm.

Results

There were more solo practices (58 vs. 50%) and fewer duo practices (24 vs 30%) compared with national data.(8) The mean ± SD age (46.8 ± 7.4 years) of the participating PCPs was comparable to the mean Dutch PCP age.(8)

Baseline characteristics of the intervention and control group were comparable, except for smoking status, history of cardiovascular disease and HDL-cholesterol levels (table 3.1).

The difference in HbA1c change between the two groups was not significant. Systolic and diastolic blood pressure, total and LDL-cholesterol improved significantly more in the intervention group. As a result the calculated 10-year UKPDS CHD risk decreased 1.4% more in the intervention group. After one year, significantly more patients in the intervention group reached the treatment targets, with 18.9% of the patients meeting all treatment targets (table 3.1).

Table 3.1: Baseline parameters, 1-year differences of clinical outcome parameters and process parameters within and between groups

	Intervention group n = 1,699		Control group n = 1,692		Difference in change between groups*	95% CI difference between groups
	Baseline	After 1-year	Baseline	After 1 year		
Baseline characteristics						
Age (years)	65.2 ± 11.3		65.0 ± 11.0			
Sex (male %)	48.2		49.8			
Caucasian (%)	97.7		97.6			
Duration of diabetes	5.8 ± 5.7		5.4 ± 5.8			
History of cardiovascular disease (%)	47.1		63.3			
Current smoking (%)	22.6	20.7	16.6	15.5	1.1†	0.7 – 1.7
Clinical outcome						
HbA1c (%)	7.1 ± 1.3	6.9 ± 1.	7.0 ± 1.1	6.9 ± 1.0	0.07	-0.02 – 0.16
Systolic blood pressure (mmHg)	149 ± 22	143 ± 20	149 ± 21	147 ± 20.8	3.3‡	0.5 - 6.0
Diastolic blood pressure (mmHg)	83 ± 11	80 ± 11	82 ± 11	82 ± 10.6	2.2‡	1.0 – 3.5
Total cholesterol (mmol/L)	5.0 ± 1.0	4.6 ± 0.9	4.9 ± 1.1	4.8 ± 1.1	0.2‡	0.1 – 0.3
HDL cholesterol (mmol/L)	1.36 ± 0.36	1.37 ± 0.37	1.32 ± 0.35	1.33 ± 0.36	-0.007	-0.038 – 0.023
LDL cholesterol (mmol/L)	2.8 ± 0.92	2.5 ± 0.88	2.8 ± 0.95	2.6 ± 0.97	0.15‡	0.07 – 0.23
10 year UKPDS CHD risk (%)§	22.5 ± 16.5	20.6 ± 15.0	21.7 ± 15.8	21.6 ± 15.6	1.4‡	0.3 – 2.6
Process of care						
HbA1c ≤ 7 % (%)	60.8	68.0	61.6	64.2	1.4†‡	0.3 – 2.6
Systolic blood pressure ≤ 140 mmHg	41.0	53.9	39.5	42.2	1.7†‡	1.2 – 2.2
Total cholesterol ≤ 4.5 mmol/L	36.2	49.0	38.5	45.3	1.3†‡	1.0 – 1.6
LDL cholesterol ≤ 2.5 mmol/L	41.1	53.5	43.8	49.8	1.3†‡	1.0 – 2.8
All treatment targets	10.3	18.9	10.9	13.4	1.6†‡2*	1.3 – 2.1

Data are means ± SD or percent unless otherwise indicated. 1*generalized linear model. †2OR. ‡*p <0.05 for between-group comparison. §The 10-year UKPDS CHD risk (%) was calculated using date of onset of diabetes (age – duration of diabetes), sex, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL-cholesterol

Conclusions

The Diabetes Care Protocol is the first pragmatic diabetes care intervention using a CDSS that improves patient outcome. As recommended by National Institute of Clinical Excellence we calculated the 10-year UKPDS CHD risk for all subjects and used this measurement as a determinant of clinical care. Recently, the Action in Diabetes and Vascular Disease (ADVANCE) study showed that HbA1c reduction does not prevent CHD.(9) This result indicates that we should focus on the patients' total cardiovascular risk profile. Our study showed no difference in HbA1c change between the two treatment arms, but the DCP led to improved diabetes care, which is shown by a 1.4% higher reduction in 10-year UKPDS CHD risk in the intervention group.

The DCP combines several interventions. The CDSS structures diabetes care, which may lead to improvements in the process of care.(1) Besides, the DCP added a practice nurse who acted as a case manager and periodic feedback. Both interventions can improve blood glucose control.(2;4)

Practices were self-selected, which may suggest a special interest of the PCP in improving diabetes care. This could be the reason why baseline values of HbA1c, blood pressure and cholesterol were lower than those of most other Dutch primary care diabetes studies.(10) Because mean HbA1c% at baseline was almost at treatment target, there was little room for improvement. Changes in blood pressure and cholesterol, however, were significant.

The percentage of patients that reached all treatment targets re-

mained strikingly low: 18.9%. This could be explained by overly strict targets (11), physicians inert in prescribing more medications (4), or noncompliant patients.(12)

Whether the effects of the DCP will sustain has to be determined by longer-term follow-up data.

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Chapter 4

Diabetes Care Protocol: Effects on Patient-Important Outcomes

A Cluster Randomized Non-inferiority Trial in Primary Care

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Abstract

Objective: The Diabetes Care Protocol (DCP) combines task delegation, intensification of diabetes treatment and feedback. It reduces cardiovascular risk in type 2 diabetic patients. This study determines the effects of DCP on patient-important outcomes.

Research design and method: A cluster randomized, non-inferiority trial, by self-administered questionnaires in 55 Dutch primary care practices: 26 practices DCP (1,699 patients), 26 usual care (1,692 patients). Type 2 diabetic patients treated by their primary care physician were included. Main outcome was the 1-year between group difference in Diabetes Health Profile (DHP-18) total score. Secondary outcomes: DHP-18 subscales, general perceived health (SF-36, EQ-5D/EQ-VAS), treatment satisfaction (DTSQ) and psychosocial self-efficacy (DES-SF). Per protocol (PP) and intention-to-treat (ITT) analyses were performed: non-inferiority margin Δ=-2%. At baseline 2,333 questionnaires were returned and 1,437 1-year thereafter.

Results: Comparing DCP to usual care, DHP-18 total score was non inferior: PP -0.88 (95%-CI: -1.94 to 0.12), ITT -0.439 (95%-CI: -1.01 to 0.08), SF-36 "Health change" improved: PP 3.51 (95%-CI: 1.23 to 5.82), ITT 1.91 (95%-CI: 0.62 to 3.23), SF-36 "Social functioning" was inconclusive: PP -1.57 (95%-CI: -4.3 to 0.72), ITT -1.031 (95%-CI: -2.52 to -0.25). Other DHP and SF-36 scores were inconsistent or non-inferior. DHP-18 "disinhibited eating" was significantly worse in PP analyses. For EQ-5D/EQ-VAS, DTSQ and DES-SF no significant between group differences were found.

Conclusion: DCP does not seem to influence health status negatively, therefore diabetes care providers should not shrink from intensified treatment. However, they should take possible detrimental effects on "social functioning" and "disinhibited eating" into account.

Introduction

Primary care physicians (PCPs) confronted with an increasing prevalence of type 2 Diabetes Mellitus(1) and limited time(2), are in need of new strategies to improve the quality and efficiency of diabetes management in primary care. Improving cardiovascular risk factors, in order to reduce diabetes-related morbidity and mortality, remains an important treatment goal. However, lower HbA1c%, blood pressure and lipid levels do not necessarily reflect how patients feel.(3) Micro- and macro-vascular complications are common in type 2 diabetes and cause a considerable burden on health related quality of life.(4) Preventing complications might improve health status. However, pursuing strict treatment targets might increase the disease burden. The effects of diabetes care interventions on patient-important outcomes, such as health status should therefore be assessed. The term 'health status' is often used synonymously with the term 'health related quality of life'.(5;6) Impaired health status may lead to impaired quality of life, but this is not inevitably the case.(7) Other important patient outcomes are treatment satisfaction and perceived self-efficacy. They may improve health status(8;9) and treatment adherence(10;11). Remarkably however, of the registered ongoing trials in diabetes, only 18% include such patient-important outcomes as their primary outcome.(12)

The Diabetes Care Protocol (DCP) was developed to improve the quality of diabetes management in primary care. In DCP, routine diabetes care is delegated to a practice nurse, who uses a computerized

decision support system (CDSS) that structures diabetes care and sets strict therapeutic targets.(13) It enables patient-specific treatment advice, feedback information on both practice and patient level and a recall system facilitating the follow-up of non-adherent patients. We demonstrated that DCP reduces cardiovascular risks in type 2 diabetic patients.(14) This could prevent complications, which might improve patients' health status.

Ten years ago health-related quality of life was not affected by an intensive policy to improve blood glucose and blood pressure control, although diabetes related complications significantly reduced health status.(15) Currently, diabetes targets are much stricter and patients will have to take more medication, which might negatively affect health status. A recent trial corroborated that an intensive therapy of cardiovascular risk factors did not affect health related quality of life; the most negative impact of diabetes on health related quality of life was related to diet.(16) Continuity of care may improve quality of life.(17)

Because of the short follow-up with probably no effect on complications and the possible negative effects of treatment intensification, we hypothesize that DCP is not inferior to usual care with respect to health status in the short term. Our primary aim is to determine the effects of DCP on diabetes specific health status. Secondly, we will investigate the effects of DCP on other (general) health status scales, satisfaction with diabetes care and psychosocial self-efficacy.

Research Design and Methods

Design

This study was part of our previous cluster randomized trial(14), carried out from March 2005 until August 2007 in 55 primary care practices throughout the Netherlands. A non-inferiority design was chosen to investigate whether the DCP is not worse than usual care with regard to patient-important outcomes. A strict non-inferiority margin of Δ=-2%(18) was selected on the assumption that from a 0-100 scale, differences of less than 2 are of no clinical relevance. Self-administered questionnaires were used to measure health status, satisfaction with care and psychosocial self-efficacy.

Only practices not involved in any other diabetes care improvement program and working with an electronic medical record were included in the study. Randomization was at practice level with stratification by the number of PCPs working in the practice and the presence of a practice nurse prior to the intervention. 26 practices were randomized to the intervention group and 29 practices to the control group (figure 1). During a period of 1-year, DCP was implemented in the intervention group. The control group continued with usual care as before entering the study. The study protocol (ISRCTN21523044) was approved by the medical ethics committee of the University Medical Center Utrecht. Written informed consent was obtained from all participants.

Population

Type 2 diabetic patients were identified from the electronic medical record through ICPC-code (T90.2: type 2 diabetes), ATC-code (A10A: insulin and analogues, A10B: oral blood glucose lowering drugs) or diabetes as a point of attention in the patient's medical records. Type 2 diabetic patients were excluded if they were unable to visit the primary care practice, received diabetes care from a medical specialist or had a short life expectancy.

Intervention

The intervention, also described elsewhere(14;19), consisted of: 1. A diabetes consultation hour run by a practice nurse. 2. A CDSS that contains a diagnostic and treatment algorithm based on the Dutch type 2 diabetes guidelines(13;14), which provides patient specific treatment advice regarding diet, lifestyle habits, medication and when necessary referral to a specialist. 3. A recall system. 4. Feedback every three months regarding the percentage of patients meeting the treatment targets (no smoking, HbA1c <7%, systolic blood pressure <140 mmHg, total cholesterol <4.5 mmol/l, LDL-cholesterol <2.5 mmol/l and BMI <27 kg/m²)(13) on both practice and patient levels. The PCPs were advised that they should prescribe new medication and refer patients if necessary. The control group continued usual care as before entering the study, which means that diabetes care was either provided by the PCP or by a practice nurse under the responsibility of the PCP.

Table 4.1: Description of questionnaires

Questionnaire	Description	Score range	Validity and reliability
DHP-18	18-item diabetes specific health questionnaire. Developed for use in patients with type 2 diabetes. Three subscale scores: 1. Psychological Distress 2. Barriers to activity 3. Disinhibited eating	Range: 0-100 100 = no dysfunction	Satisfactory internal reliability and validity and measurement equivalence across language groups (31).
Short Form-36 (SF-36)	36-item questionnaire measures perceived general health. Eight subscales: 1. Physical functioning 2. Social functioning, 3. Role limitations due to physical problems 4. Role limitations due to emotional problems 5. Mental heath 6. Vitality 7. Bodily pain 8. General heath perception. One item was later added: 9. Health change	Range: 0-100 0 = worst health 100 = best health	The Dutch version has proven to be a practical, reliable and valid instrument to measure health in chronic disease populations in the Netherlands.(27)
Euroqol 5D: EQ5D/EQVAS	The EQ5D measures general health status. Five dimensions: 1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression. The EQ Visual Analogue Scale (EQ-VAS): measures the overall health state	Scores were valued by the general public in the UK. Range: -0,549 – 1 -0,549= health state worse than death 0= death 1= perfect health Range: 0-100 0 = worst health state 100 = perfect health	Well- validated, reliable and responsive instrument for health measurement in patients with a wide range of medical conditions. (32;33) Values found in the UK have been validated for the Netherlands.(34)
DTSQ status	8-item questionnaire. Designed to make the initial assessment of satisfaction with diabetes treatment regimes and perceived frequencies of hyper- and hypoglycaemia. Six of the eight items measure treatment satisfaction and were used in this trial.	Range: 0-36. Higher scores = greater satisfaction	It has been shown to be reliable, valid and sensitive to change in diabetes patients.(23;35)
DES-SF	Diabetes Empowerment Scale Short Form: 8-item questionnaire measuring psychosocial self-efficacy like: able to turn diabetes goals in workable plans; try out different ways to overcome barriers to diabetes goals.	Range: 1-5 5 = high sense of psychosocial self-efficacy	Found to be a valid and reliable measure of overall diabetes related psychosocial self-efficacy in type 1 and 2 diabetes patients.(36)

Outcome measures

The aim of this study was to determine whether DCP has a non-inferior effect on patient-important outcomes in comparison with usual care. The primary outcome was the 1-year between group difference of change in diabetes specific health status, measured by the total score of the Diabetes Health Profile (DHP-18).

Secondary outcomes included 1-year between-group differences in: diabetes-specific health status measured by the subscales of the DHP-18, and general health status measured by Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). Other questionnaires used were Euroqol 5 Dimensions (EQ-5D/EQ-VAS), the Diabetes Treatment Satisfaction status Questionnaire (DTSQ-status), and the Diabetes Empowerment Scale Short Form (DES-SF) measuring self-efficacy. As these last 3 questionnaires do not have a 0-100 scale the non-inferiority margin was set a 2% difference on the scales used for these questionnaires: EQ-5D 0.03, DTSQ-status 0.72, DES-SF 0.08. The description, validity and reliability of these questionnaires are reported in table 1.

Data collection

Primary and secondary outcomes were measured by the self-administered questionnaires which were distributed during diabetes consultation hours at baseline and after 1-year of follow-up. Patients were asked to send the questionnaires by post to the administration office of the research center. When the original questionnaires were

not returned within three months, patients received a reminder letter and a copy of the questionnaires.

Socio-demographic and clinical parameters were electronically collected in the DCP software. Patients were seen twice for their annual diabetes check-up (baseline and final measurements). Patients who did not attend for their appointment received one reminder(14).

Power

1155 patients with completed DHP-18 questionnaires in each group, 25 clusters per group, would provide 90% power (z_β= 1.28), α=0.05 (z_α = 1.96), using a standard intra-class correlation of 0.05 to test the primary hypothesis. With 50 participating practices and a response rate of 60%(20) a total of 3840 type 2 diabetic patients were needed.

Analyses

The analyses were performed with SPSS version 14.0 and SAS version 9.0. Differences in baseline variables were analyzed with independent samples t-test for continuous variables, Chi-square test for nominal variables and Mann-Whitney U-test for ordinal and not normally distributed variables. Within-group change between baseline and after 1-year of follow-up was analyzed with paired t-test. Both per protocol (PP) analyses and intention-to-treat (ITT) analyses (with baseline values carried forward in case of missing values) were performed to examine between-group differences. Generalized Estimated Equations were used to correct for clustering at practice level. We

calculated 95% confidence intervals (CI) and used a two-sided α of 0.05 to test significance.

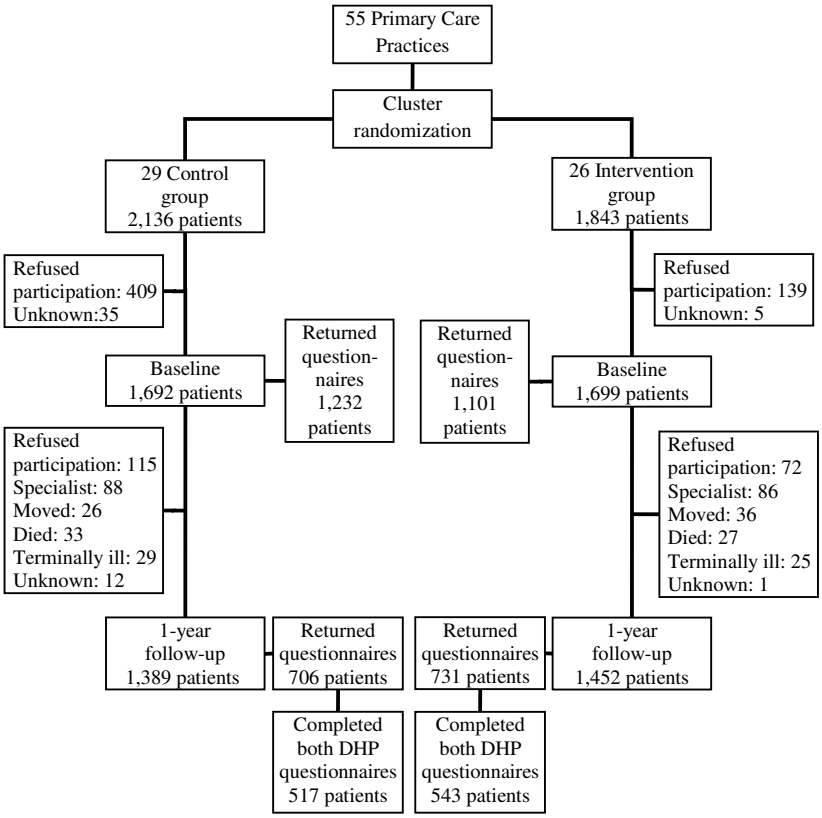
To demonstrate non-inferiority on the DHP-18 and SF-36 the two-sided 95% CI had to be entirely above the predefined non-inferiority margin of Δ=-2%. If the margin of Δ=-2% was included in the 95% CI, the result was inconclusive(21). If the results from the PP and ITT analyses were different, this result was defined as inconsistent.(21)

Results

Study participants

Of the 171,821 registered patients in the 55 primary care practices, 3,979 type 2 diabetic patients were eligible. Of these 2,136 patients were assigned to the control group (CG) and 1,843 patients to the intervention group (IG). Of the eligible subjects, 548 refused participation and an additional 40 failed to participate for unknown reasons. The final study population consisted of 3,391 patients (1,692 CG; 1,699 IG). All these patients received the questionnaires. At baseline 2,333 patients returned the questionnaires (1,232 CG; 1,101 IG). The 1-year of follow-up was completed by 2,841 diabetes patients (1,389 CG; 1,452 IG). Of these 1,437 (706 CG; 731 IG) returned the questionnaires. Eventually, a total of 1,060 patients (517 CG; 543 IG) fully completed the DHP-18 questionnaire both at baseline and after 1-year (figure 4.1).

Figure 1. Study flow chart



Compared to the non response group, patients who fully completed both DHP questionnaires were significantly younger, more often Caucasian, had a lower HbA1c and diastolic blood pressure, fewer smoked and more had a history of cardiovascular disease (data not shown).

Table 4.2: Baseline characteristics of patients who fully completed both DHP-18 questionnaires: Intervention group versus control group

	Intervention group *Value ± SD* *N=543*	*Control group* *Value ± SD* *N=517*	P-value (sig. 2-tailed)
Age (years)	64.9 ± 10.1	64.1 ± 9.7	0.17
Duration of diabetes (years)	5.7 ± 5.6	6.0 ± 5.1	0.53
Sex (% male)	50.3	51.6	0.66
Ethnicity (%)			
- Caucasian	100	99.8	0.30
Education (%)			0.45
- Low	62.4	66.5	
- Middle	26.4	24.7	
- High	11.2	8.8	
Current smoking (%)	17.7	14.5	0.16
History of cardiovascular disease (%)	48.1	69.4	<0.001
Biochemical variables:			
- HbA1c (%)	6.85 ± 1.0	6.94± 0.99	0.14
- Systolic blood pressure (mmHg)	150 ± 21	149 ± 20	0.57
- Diastolic blood pressure (mmHg)	83 ± 11	84 ± 10	0.36
- Total cholesterol (mmol/l)	4.99 ± 1.0	4.91 ± 1.0	0.18
- HDL cholesterol (mmol/L)	1.36 ± 0.34	1.30 ± 0.34	0.002
- LDL cholesterol (mmol/L)	2.82 ± 0.91	2.79 ± 0.89	0.54
10 year UKPDS CHD risk (%)	21.5 ± 16.0	21.3 ± 14.7	0.74
Health status Questionnaires(scale 0-100):			
- DHP total score	83.1 ± 11.9	83.6 ± 11.4	0.47
- DHP Barriers to activity	85.6 ± 13.4	86.1 ± 13.2	0.54
- DHP Psychological distress	89.5 ± 11.3	90.2 ± 10.9	0.27
- DHP Disinhibited eating	71.9 ± 20.9	72.2 ± 20.9	0.82
- SF-36 Physical functioning	73.2 ± 25.1	74.1 ± 23.2	0.52
- SF-36 Social functioning	85.2 ± 20.0	85.7 ± 19.2	0.65
- SF-36 Role physical	72.4 ± 39.9	75.7 ± 36.5	0.18
- SF-36 Role emotional	80.7 ± 36.6	84.2 ± 33.2	0.11
- SF-36 Mental health	77.1 ± 17.0	77.5 ± 16.4	0.74
- SF-36 Vitality	63.4 ± 20.5	64.8 ± 19.8	0.25
- SF-36 Bodily pain	79.3 ± 23.6	81.8 ± 21.5	0.08
- SF-36 General health	60.3 ± 18.4	62.5 ± 18.3	0.06
- SF-36 Health change	51.0 ± 18.6	52.2 ± 18.3	0.31
Other health status questionnaires			
- EQ-VAS	76.9 ± 15.1	78.7 ± 13.5	0.07
- EQ-5D	0.82 ± 0.22	0.84 ± 0.19	0.041
Diabetes Treatment Satisfaction			
- DTSQ	32.4 ± 4.5	32.2 ± 4.9	0.44
Diabetes Empowerment			
-DES-SF	3.78 ± 0.63	3.73 ± 0.67	0.22

For continuous variables: independent sample t-test. For nominal variables: chi-square test. For ordinal and not normally distributed variables (10-year UKPDS CHD risk): Mann-Whitney U-test.

Baseline characteristics for patients of the intervention and the control group who fully completed both DHP questionnaires, were comparable, except for history of cardiovascular disease, HDL-cholesterol and general health status (EQ-5D) (table 4.2). Compared with national data(22), more solo practices (58% versus 50%) and less duo practices (24% versus 30%) were included in this study. The mean age (46.8± 7.4 year (SD)) of the participating PCPs was comparable to the mean Dutch PCP age.

Within group analysis

Within group analyses showed that after 1-year of follow-up the intervention group worsened significantly on the dimensions: DHP barriers to activity, SF-36 social functioning and SF-36 bodily pain. Satisfaction with diabetes treatment improved significantly (table 4.3). The control group improved significantly on the total score of DHP-18 and the subscale DHP-18 disinhibited eating, but worsened significantly on five scales measuring general health (SF-36: Physical functioning, Role physical, Bodily pain, Health change and EQ-VAS) (table 4.3).

Primary outcome

Both PP and ITT analyses showed that the 95% CI of DHP total (PP: -1.94 to 0.12; ITT: -1.01 to 0.08) was above the predefined non-inferiority margin of Δ=-2%. Therefore, the hypothesis was confirmed: DCP is non-inferior to usual care with respect to change in diabetes related health status.

Secondary outcome measures

Although the results of DCP are worse concerning some of the measures, in both PP and ITT analyses inferiority could not be demonstrated. The results with regard to the SF-36 social functioning scale exceeded the non-inferiority margin and were inconclusive. Non-inferiority was unambiguous regarding DHP-psychological distress, SF-36: physical functioning, role physical, mental health, bodily pain, general health. A superior effect was found on the SF-36 health change item: in both PP and ITT analyses the 95% CI (PP: 1.23 – 5.82; ITT: 0.62 – 3.23) was entirely above 0.

Inconsistent results were found regarding the scales: DHP barriers to activity, DHP disinhibited eating, SF-36 role emotional and SF-36 vitality. The 95% CI of these scales exceeded the non-inferiority margin of Δ= -2% in the PP analyses but not in the ITT analyses. Of these scales, the DHP disinhibited eating was entirely under zero (-3.64 to -0.07). Although not consistently non-inferior, a null treatment difference for this scale is unlikely.

No significant differences between intervention and control group were found for the EQ-VAS and EQ-5D. Although the within group treatment satisfaction improved significantly after the introduction of the DCP, the improvement between the groups did not reach significance (DTSQ-status). Self efficacy remained totally unchanged in the DCP group and was not significantly reduced in the usual care group (DES-SF).

Table 4.3: One-year differences between groups in health status, satisfaction with diabetes care and psychosocial self-efficacy

	Intervention group			Control group		
	N	*Baseline*	*After 1- year*	*N*	*Baseline*	*After 1- year*
Health status Questionnaires						
- DHP total score	543	83.1 ± 11.9	82.9 ± 12.0	517	83.6 ± 11.4	84.3 ± 11.5*
- DHP Barriers to activity	602	85.7 ± 13.7	84.7 ± 13.7*	554	86.1 ± 13.2	86.3 ± 13.3
- DHP Psychological distress	610	89.6 ± 11.1	89.0 ± 12.4	574	90.7 ± 10.6	90.8 ± 11.1
- DHP Disinhibited eating	649	71.7 ± 20.7	71.9 ± 21.1	605	72.4 ± 20.9	74.4 ± 19.6*
- SF-36 Physical functioning	653	72.5 ± 25.4	71.5 ± 25.7	603	73.6 ± 23.3	72.0 ± 24.0*
- SF-36 Social functioning	591	85.4 ± 19.9	82.6 ± 22.4*	552	85.8 ± 19.2	84.6 ± 19.6
- SF-36 Role physical	627	71.8 ± 39.8	70.5 ± 39.4	582	75.3 ± 37.0	71.8 ± 39.6*
- SF-36 Role emotional	613	80.4 ± 36.4	81.0 ± 35.4	572	83.4 ± 33.9	83.8 ± 33.9
- SF-36 Mental health	662	76.7 ± 17.4	76.4 ± 18.4	611	77.7 ± 16.5	77.6 ± 16.6
- SF-36 Vitality	654	63.3 ± 20.2	62.9 ± 20.4	605	64.8 ± 19.7	64.8 ± 19.8
- SF-36 Bodily pain	669	79.7 ± 23.4	77.8 ± 23.8*	619	81.2 ± 21.8	77.7 ± 24.1*
- SF-36 General health	654	60.4 ± 17.9	59.8 ± 18.5	601	62.3 ± 18.4	61.8 ± 19.0
- SF-36 Health change	653	50.6 ± 18.8	52.0 ± 19.2	596	51.9 ± 18.2	49.8 ± 17.5*
- EQ-VAS	559	76.5 ± 15.7	76.1 ± 15.3	519	78.2 ± 14.0	76.5 ± 15.1*
- EQ-5D	657	0.817 ± 0.22	0.813 ± 0.23	598	0.838 ± 0.20	0.827±0.21
Diabetes Treatment Satisfaction						
- DTSQ	610	32.4 ± 4.7	32.8 ± 4.1º	562	32.2 ± 5.1	32.6 ± 4.8
Diabetes Empowerment						
- DES-SF	500	3.78 ± 0.64	3.78 ± 0.69	463	3.73 ± 0.65	3.69 ± 0.67

Data are mean ± SD. * $p<0.05$ compared with baseline.

Table 4.3: One-year differences between groups in health status, satisfaction with diabetes care and psychosocial self-efficacy (continued)

	Per protocol †		*Intention to Treat †*	
	Mean difference in change between Groups	95% CI difference between groups	*Mean difference in change between groups*	95% CI difference between groups
Health status Questionnaires				
- DHP total score	-0.880	-1.94 to 0.12	-0.439	-1.01 to 0.08
- DHP Barriers to activity	-1.163	-2.34 to 0.03‡	-0.676	-1.30 to -0.03
- DHP Psychological distress	-0.634	-1.72 to 0.43	-0.366	-0.97 to 0.22
- DHP Disinhibited eating	-1.832	-3.64 to -0.07‡	-0.920	-1.99 to 0.07
- SF-36 Physical functioning	0.530	-1.07 to 2.16	0.154	-0.73 to 1.05
- SF-36 Social functioning	-1.569	-4.30 to 0.72‡	-1.031	-2.52 to 0.25‡
- SF-36 Role physical	2.258	-1.61 to 6.31	0.983	-1.21 to 3.27
- SF-36 Role emotional	0.107	-3.25 to 4.10‡	0.112	-1.79 to 2.35
- SF-36 Mental health	-0.240	-1.52 to 1.15	-0.152	-0.86 to 0.61
- SF-36 Vitality	-0.344	-2.48 to 1.66‡	-0.211	-1.43 to 0.95
- SF-36 Bodily pain	1.629	-0.48 to 3.78	0.636	-0.57 to 1.85
- SF-36 General health	-0.136	-1.71 to 1.46	-0.137	-0.98 to 0.74
- SF-36 Health change	3.514	1.23 to 5.82	1.913	0.62 to 3.23
- EQ-VAS	1.235	-0.62 to 2.85	0.573	-0.48 to 1.48
- EQ-5D	0.007	-0.01 to 0.03	0.003	-0.008 to 0.01
Diabetes Treatment Satisfaction				
-DTSQ	0.116	-0.51 to 0.75	0.106	-0.25 to 0.47
Diabetes Empowerment				
-DES-SF	0.042	-0.06 to 0.14	0.019	-0.03 to 0.07

† generalized estimated equations. ‡ non-inferiority threshold above Δ=-2%

Conclusions

Principal findings

In this study the effects of the Diabetes Care Protocol on patient-important outcomes were examined. The DCP proved to be non-inferior to usual care with respect to changes in diabetes-related health

status. Although some results were worse, the secondary measures of health status as a result of the DCP compared to usual care were either inconsistent, inconclusive, or unambiguous with regard to non-inferiority. Superiority could be demonstrated on the SF-36 general health change item. No differences were found for the Euroqol 5D, diabetes treatment satisfaction and psychosocial self-efficacy.

Comparison with previous studies

Our results are in concordance with previous studies on health status(15;16), which also reported that intensive treatment of cardiovascular risk factors or blood glucose and blood pressure did not affect health status(15;16). Compared to usual care, the DCP group had an inconclusive but significant detrimental effect on the DHP disinhibited eating scale. Apparently the DCP group perceived more dysfunction on the eating scale (eating extra when feeling bored, difficult to say no to desirable food, wished not so many nice things to eat, not easy to stop eating and eat to cheer yourself up). As part of good diabetes care, DCP may more frequently address dietary habits than usual care. This awareness about dietary constraints may have resulted in a sense of illness burden in the DCP group. In the above mentioned study, diet had the most negative impact on health status(16). Another finding in this study was the negative effect of DCP on people's social functioning. Such a negative effect might be due to more frequently addressing type 2 diabetes health rules. Patients in the DCP group perceived more interference with social activities (visiting friends, normal activities with the family) as a result of physical and

emotional problems than the control group. We do not know whether such a possible negative effect of the DCP might counterbalance the perceived change in overall health status, an effect that may have been caused by better continuity and more structured care in the DCP group.(17)

Treatment satisfaction significantly improved in the DCP group, but there was no significant between-group difference. As patients were not informed about good diabetes care, this result is difficult to be interpreted. However, high levels of treatment satisfaction have been observed despite the negative impact of diabetes on quality of life.(23)

In this study there were no differences in self-efficacy between DCP and usual care. The same result was found by Thoolen at al. in a population of screen detected type 2 diabetic patients who were intensively treated for 2-3 years.(24)

However, comparison with previous studies in diabetes remains difficult because of differences in study design, study population, questionnaires that were used (the DTSQ-status can be limited by a ceiling effect), the implemented interventions and the lack of consistency in patient-important outcome measurements.(15;16;25)

Strengths and limitations

An active control group was used as a reference in order to evaluate non-inferiority of DCP. The enrolled PCPs and type 2 diabetes population resembled the Dutch PCP(22) and type 2 diabetes population treated in primary care.(26) The response rate was in accordance with

Dutch data of health survey response.(20) However, the response rate was lower then expected and thus we did not recruit sufficient patients. We therefore calculated the intra-class correlation coefficient in this study: 0.0013. This means 535 patients per treatment group were needed to detect a non-inferiority margin of Δ= -2% on the DHP-18 with a power of 90%. In our study 1060 patients (543 IG; 517 CG) completed both DHP-18 questionnaires, so the study sample was therefore sufficient with regard to our primary hypothesis. Because of large standard deviations of the SF-36 dimensions, the study sample was too small to detect a margin of Δ=-2% on these scales. However, compared to other studies this threshold is probably too strict. A Dutch study generating normative data on the SF-36 health survey reported a difference of 7 on a scale of 100 (7%) as a moderate effect.(27) None of the SF-36 confidence intervals exceeded the latter margin. Given that the study had sufficient power to detect inferiority using this Δ=-7% margin, DCP is non-inferior to usual care with respect to the SF-36 health survey outcomes. However, we have to keep in mind that the results of non-inferiority trails are not as credible as those from superiority trials.(28)

Different response rates were found on the used questionnaires, with DES-SF having the lowest response rate, followed by the DHP-18 total score. These differences may have been caused by the order of the questionnaires (DES-SF was the last), the difficulty of the DES-SF questions (>60% of the type 2 diabetic patients had a low educational level) and possible irrelevant DHP questions. DHP was measured by a 32-item questionnaire suitable for insulin treated diabetes

patients; the 18-item questionnaire, which is more relevant for non-insulin requiring type 2 diabetic patients, was later extracted.

A response bias was found between patients returning the questionnaires and those who did not. Although we do not know how this affected health status, we expect the response bias did not interfere with the main study outcome. The intervention and control group were comparable at baseline, except for history of cardiovascular disease, this did however not affect health status. At baseline the values of diabetes treatment satisfaction and health status were high, which might be explained by the relatively well controlled type 2 diabetes population.(29)

Finally, as is recommended in non-inferiority trials(21), both PP and ITT analysis were performed to assess non-inferiority. Well validated diabetes specific and generic questionnaires were administered to measure health status, as recommended because of their differences in strengths.(30) Specific validated questionnaires were administered to measure diabetes treatment satisfaction and psychosocial self-efficacy. All these features make generalizing our study results feasible.

In conclusion, the DCP seems a promising way for improving the quality and efficiency of diabetes management in primary care, by reducing cardiovascular risks.(14) Taking into account limitations of non-inferiority trials(28), intensified multi-factorial treatment of type 2 diabetic patients in DCP does not seem to influence health status negatively compared to usual care, although some detrimental effects on social functioning and disinhibited eating cannot be ruled out. Dia-

betes care providers should not shrink from intensified multi-factorial treatment in type 2 diabetes, but they should take into account possible negative effects on social functioning of the patients involved. Further research is necessary to investigate the long-term effects of DCP on patient-important outcomes.

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Chapter 5

Cost-effectiveness of the Diabetes Care Protocol, a Multi-faceted Computerized Decision Support Diabetes Management Intervention that Reduces Cardiovascular Risk

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Abstract

Objective: The Diabetes Care Protocol (DCP), a multifaceted computerized decision support diabetes management intervention, reduces cardiovascular risk of type 2 diabetic patients. We performed a cost-effectiveness analysis of DCP from a Dutch health care perspective.

Research Design and Methods: A cluster randomized trial provided data of DCP versus usual care. The 1-year follow-up patient data were extrapolated using a modified Dutch micro-simulation diabetes model, computing individual lifetime, health related costs and health effects. Incremental costs and effectiveness (quality-adjusted life-years [QALY]) were estimated using multivariate generalized estimating equations to correct for practice-level clustering and confounding. Incremental cost-effectiveness ratios (ICER) were calculated and cost-effectiveness acceptability curves were created. Stroke costs were calculated separately. Subgroup analyses examined patients with and without cardiovascular disease (CVD+ or CVD- patients).

Results: Excluding stroke, DCP patients lived longer (0.14 life-years, P = ns), experienced more QALYs (0.037, P = ns) and incurred higher total costs (€1,415, P = ns), resulting in an ICER of €38,243 per QALY gained. The likelihood of cost-effectiveness given a willingness-to-pay threshold of €20,000 per QALY gained is 30%. DCP had a more favorable effect on CVD+ patients (ICER = €14,814) than for CVD- patients (ICER = €121,285). Coronary heart disease costs were reduced (€-587, $p < 0.05$).

Conclusions: DCP reduces cardiovascular risk, resulting in only a slight improvement in QALYs, lower CVD costs, but higher total costs, with a high cost-effectiveness ratio. Cost-effective care can be achieved by focusing on cardiovascular risk factors in type 2 diabetic patients with a history of cardiovascular disease.

Introduction

Every year a large percentage of the total health care budget is spent on diabetes-related care. In European countries percentages of 2.5–6.5% have been reported and in the United States diabetes-related costs are even higher at 10% of the total health care budget.(1;2) Long-term clinical follow-up studies have shown that improvements in glycemic control, blood pressure and cholesterol levels lead to fewer micro- and macrovascular complications and improve health outcomes.(3-5) Intensive treatment, based on current guidelines, might lead to lower health care costs. However it seems difficult to follow guidelines, and many type 2 diabetic patients do not meet the strict targets for good glycemic and cardiovascular control.

New strategies like the Diabetes Care Protocol (DCP) have been developed to improve the quality and management of diabetes care.(6) The DCP comprises several interventions, including a diabetes consultation hour run by a practice nurse, a computerized decision support system (CDSS), a recall system, and feedback on performance. A cluster randomized trial proved that the DCP reduces the cardiovascular risk of type 2 diabetic patients in primary care.(6)

Although it is stated that information technology, like CDSS, in diabetes care may improve care processes, delay diabetes complications and save health care costs,(7) most studies in this field do not include a cost-effectiveness analysis.(8) We therefore performed a cost-effectiveness analysis of the DCP versus usual care from a Dutch health care perspective.

Research Design and Methods

Clinical Trial

Between March 2005 and August 2007, we performed a cluster randomized trial in 55 primary care practices throughout the Netherlands. The practices were not involved in any other diabetes care improvement program and worked with an electronic medical record. Randomization was performed at practice level with stratification for the number of primary care physicians (PCPs) working in the practice and the presence of a practice nurse prior to the intervention. Twenty-six practices were randomized to the intervention group and 29 to the control group.

Patients in the intervention group were treated according to the DCP, which is described elsewhere.(6) In brief, DCP consists of 1) a diabetes consultation hour run by a practice nurse, 2) a CDSS containing a diagnostic and treatment algorithm based on the Dutch primary care type 2 diabetes guidelines(9) and providing patient-specific treatment advice, 3) a recall system, and 4) feedback at both practice and patient level every three months regarding the percentage of patients meeting the treatment targets (smoking cessation, HbA1c <7%, systolic blood pressure <140mmHg, total cholesterol <4.5mmol/L, LDL-cholesterol <2.5mmol/L and BMI <27 kg/m²).(9) The PCP remained responsible for new prescriptions and referrals. The control group continued receiving usual diabetes care, meaning that diabetes care was either provided by a PCP or by a practice nurse under PCP responsibility.

Type 2 diabetic patients were selected from the electronic medical records. Patients under primary care treatment were eligible. We excluded patients if they were unable to visit the primary care practice, were under specialist treatment, or had a short life expectancy. The final, mainly Caucasian, study population consisted of 3,391 patients (1,699 intervention group, 1,692 control group). All patients were seen for their annual diabetes check-up at baseline and after one year follow-up.(6)

Lifetime extrapolation of trial results to costs and effects

Lifetime costs and health effects were estimated using a modified probabilistic diabetes model for The Netherlands. This validated model has been used before and is described in more detail elsewhere.(10-12) In brief, the model simulates the natural history of type 2 diabetes and calculates costs and quality-adjusted life years (QALYs) for Dutch type 2 diabetic patients(12). It accounts for aging, temporal increases in HbA1c and the age-related increase in complication risks.

The model includes a health state for cardiovascular disease (CVD) (angina pectoris and myocardial infarction), major type 2 diabetes-related complications (blindness, end-stage renal disease [ESRD], or lower-extremity amputation), minor type 2 diabetes complications (retinopathy or diabetic ulcers), uncomplicated type 2 diabetes and death. The model computes the occurrence of the above-mentioned diabetes-related complications and the excess mortality due to diabetes. Based on the estimated events and prevalence of complications, it

computes diabetes-related lifetime medical costs and QALYs.

To calculate lifetime costs and outcomes, each health state is assigned a value in terms of medical costs and utility (health-related quality of life), and this value is multiplied by the prevalence of the health states over time.

Absolute Dutch excess mortality risk estimates for type 2 diabetes were calculated by multiplying gender and age-specific national mortality rates by the observed excess mortality hazard ratio for diabetic patients.(10) The computed life-years were adjusted by quality-of-life results for major complications (blindness/poor vision, ESRD, lower-extremity amputation), as observed in earlier Dutch studies, to derive the QALYs.(10;12-14) The HbA1c levels for individual patients are used to adjust the baseline risks (transition probabilities) of blindness, renal failure, and lower-extremity amputation.(10;15)

For this study, three adaptations were made to the original Dutch model. First, the distribution of the difference in 10-year UK Prospective Diabetes Study (UKPDS) coronary heart disease (CHD) risk estimate between intervention and control group was used to account for the difference in the probability of first events and death from CHD.(16) Second, because patients with a history of CVD have an even higher increased risk of another cardiovascular event than diabetic patients without such a history, a separate extra risk for this subpopulation was added to the model. This correction was based on (unpublished) subgroup analyses of the original in-file Dutch data from the EUROPA trial in secondary cardiovascular prevention. In that population, men with diabetes and a history of CVD showed a risk of

a cardiovascular death that was 3.27 times that seen in the general population; in women, this relative risk was 4.63.(17) Finally, the costs of CHD complications were included in the model, based on resource use observed amongst Dutch diabetic patients with the mix of CHD complications observed in the EUROPA study.(17)

In addition to the model input data described above, medication costs of glucose-lowering drugs (oral drugs and insulin), ACE-inhibitors, Angiotensin-renin blockers and cholesterol-lowering drugs (ATC codes A10, C09, and C10) used during the one-year follow-up period were included in the cost calculation. The mean 1-year follow-up medication costs were €326.30 in the DCP group and €325.10 in the control group. These costs were extrapolated to estimate lifetime medication costs, assuming the cost difference between DCP and usual care remained constant over time. (Dutch Farmacotherapeutisch Kompas 2008) Because differences in use and costs of diuretics, β-blocking agents, and calcium channel blockers (ATC codes C03, C07, and C08) between both groups were negligible, they were left out of the medication cost calculations.

Costs regarding development and implementation of DCP were based on costs actually invoiced to Pfizer B.V.; maintenance costs of DCP were based on costs invoiced to PCPs. DCP costs were calculated per patient per year for a period of 10 years based on the CHOICE method.(18) The total DCP costs included practice nurse instructions working with DCP, reorganizing primary care practice type 2 diabetes care, CDSS with recall system and three-monthly feedback. The costs of developing DCP and a pilot study were divided

by the total Dutch type 2 diabetic population, resulting in costs of €1 per patient. Implementation costs (first three years) and the yearly maintenance costs thereafter were divided by the number of patients in the participating type 2 diabetic population. Annual implementation costs were €90 per patient for the first 3 years and annual maintenance costs were €12 per patient for years 4-10. Because time spent on diabetes care was not registered adequately, we performed a survey among the participating practices to study if there were extra costs for personnel, education, and medical equipment (response rate: 50% intervention vs. 65% control). Since no differences were found these costs were left out of the model.

Stroke was left out of the model calculations because there are no accurate Dutch data on survival rates of type 2 diabetic patients with stroke. In the appendix the estimated stroke costs are calculated.

Analyses

The one-year follow-up data from the trial were used, based on intention to treat with baseline values carried forward in case of missing values. The model used the following parameters from the 1-year follow-up results to calculate lifetime disease outcomes: age, sex, duration of diabetes, HbA1c, systolic blood pressure, total cholesterol, HDL cholesterol, BMI, smoking, diabetes complications at one-year follow-up (myocardial infarction, angina pectoris, stroke, lower extremity amputation, retinopathy [no, background or proliferate], neuropathy, and nephropathy [no, micro-albuminuria or macroalbuminuria]).

The model calculated six lifetime health outcomes (life years, QALYs) and costs for each patient (discounted and undiscounted). The averages of the six individual model outcomes were then analyzed using Generalized Estimating Equations (GEEs) to correct for clustering at practice level. To correct for confounding and to improve model estimates of the difference in outcomes between DCP and control, the following baseline covariates were used: age, sex, duration of diabetes, history of cardiovascular disease, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL cholesterol.

The primary outcome in our analysis was the cost-effectiveness of DCP versus current usual care, expressed as the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs by the incremental QALYs or incremental life years.

As recommended by the Dutch pharmacoeconomic guidelines, costs were discounted at 4%, QALYs at 1.5%, and life-years were undiscounted.(19;20) We also examined differences in diabetes-related costs, cardiovascular event costs, and number of cardiovascular events.

Uncertainty surrounding the cost-effectiveness ratios as calculated from the model was expressed using a cost-effectiveness plane. A cost-effectiveness acceptability curve was created to determine whether implementation of DCP was cost-effective given different thresholds of willingness to pay for a QALY (e.g., a threshold of € 20,000 per QALY).

After calculating the mean individual costs for each patient, we examined the cost-effectiveness of DCP for all patients in the study

population, patients with a history of CVD (CVD+) and patients without a history of CVD (CVD-).

Results

Trial

The mainly Caucasian study population had a mean age of 65 years and a mean diabetes duration of 5.5 years (table 5.1). Baseline characteristics of the two groups were comparable, except for smoking status, history of CVD, and HDL cholesterol level. At 1-year follow-up, patients in the intervention group showed significantly greater reductions in blood pressure, total cholesterol, and 10-year UKPDS CHD risk than patients in the control group. No significant difference in HbA1c% was found.(6)

Cost-effectiveness

Patients in the DCP group showed slightly more QALYs (0.037), slightly more life-years (0.14), and higher costs (€1,415) than patients in the control group (table 2). However, none of these differences were statistically significant. In the total population, patients receiving DCP care had significantly fewer cardiovascular events than patients receiving usual care (i.e., 0.11 fewer events). This was also true for patients without a history of CVD (CVD-) (i.e. 0.14 fewer events) (table 5.2). The costs of CHD in the DCP group were significantly lower than those in the control group (total population €-517; CVD+

Table 5.1: Baseline characteristics and clinical trial outcome (N = 3,391) between groups

	Intervention group n = 1,699		Control group n = 1,692		Difference in change between groups*	95% CI difference between groups
	Baseline	After 1-year	Baseline	After 1 year		
Baseline characteristics						
Age (years)	65.2 ± 11.3		65.0 ± 11.0			
Sex (male %)	48.2		49.8			
Caucasian (%)	97.7		97.6			
Duration of diabetes	5.8 ± 5.7		5.4 ± 5.8			
History of cardiovascular disease (%)	47.1		63.3			
Current smoking (%)	22.6	20.7	16.6	15.5	1.1[†]	0.7 – 1.7
Clinical outcome						
HbA1c (%)	7.1 ± 1.3	6.9 ± 1.	7.0 ± 1.1	6.9 ± 1.0	0.07	-0.02 – 0.16
Systolic blood pressure (mmHg)	149 ± 22	143 ± 20	149 ± 21	147 ± 20.8	3.3[‡]	0.5 - 6.0
Diastolic blood pressure (mmHg)	83 ± 11	80 ± 11	82 ± 11	82 ± 10.6	2.2[‡]	1.0 – 3.5
Total cholesterol (mmol/L)	5.0 ± 1.0	4.6 ± 0.9	4.9 ± 1.1	4.8 ± 1.1	0.2[‡]	0.1 – 0.3
HDL cholesterol (mmol/L)	1.36 ± 0.36	1.37 ± 0.37	1.32 ± 0.35	1.33 ± 0.36	-0.007	-0.038 – 0.023
LDL cholesterol (mmol/L)	2.8 ± 0.92	2.5 ± 0.88	2.8 ± 0.95	2.6 ± 0.97	0.15[‡]	0.07 – 0.23
10 year UKPDS CHD risk (%)[§]	22.5 ± 16.5	20.6 ± 15.0	21.7 ± 15.8	21.6 ± 15.6	1.4[‡]	0.3 – 2.6

Data are means ± SD or percent unless otherwise indicated. [1]*generalized linear model. [†][2]OR. [‡]*p <0.05 for between-group comparison. [§]The 10-year UKPDS CHD risk (%) was calculated using date of onset of diabetes (age – duration of diabetes), sex, ethnicity, smoking, HbA1c, systolic blood pressure, total cholesterol and HDL-cholesterol

Table 5.2 Costs and effects of DCP compared to usual care

	Total population (n = 3,391)		Patients *with* history of cardiovascular disease (n = 1,743)		Patients *without* history of cardiovascular disease (n = 1,648)	
	Mean difference*	95% CI	Mean difference*	95% CI	Mean difference*	95% CI
Differences in Health, model calculations						
Healthy years (QALYs, discounted)	0.037	-0.066 to 0.14	0.07	-0.051 to 0.19	0.014	-0.141 to 0.169
Life-years	0.14	-0.12 to 0.40	0.19	-0.07 to 0.45	0.10	-0.26 to 0.46
Number of cardiovascular	-0.11	-0.18 to –0.04	-0.08	-0.17 to 0.007	-0.14	-0.25 to -0.036
Differences in Costs, model calculations (€, discounted)						
Diabetes-related (excluding coronary heart disease)	1,698	187 to 3,209	1,167	-620 to 2,954	2,146	-189 to 4,482
Coronary heart disease	-587	-880 to –294	-433	-847 to –18	-721	-1,177 to –265
DCP	316	315 to 318	314	3,112 to 316	319	318 to 320
Total costs	1,415	-130 to 2,961	1,037	-891 to 2,967	1,698	-692 to 4,089
Cost- Effectiveness, model calculations						
Total costs per QALY gained	38,243		14,814		121,285	
Total costs per life-year gained	10,107		5,457		16,980	

Results are corrected for clustering, and baseline differences in age, duration of diabetes, sex, smoking, HbA1c, systolic blood pressure, total cholesterol, HDL cholesterol and history of cardiovascular disease (only total population).
*Mean difference between intervention and control group

patients €-433; CVD- patients €-721).

The ICER for the total population was €38,243 per QALY gained (i.e., €1,415/0.037), for the CVD+ patients €14,814 per QALY gained, and for CVD- patients €121,285 per QALY gained.

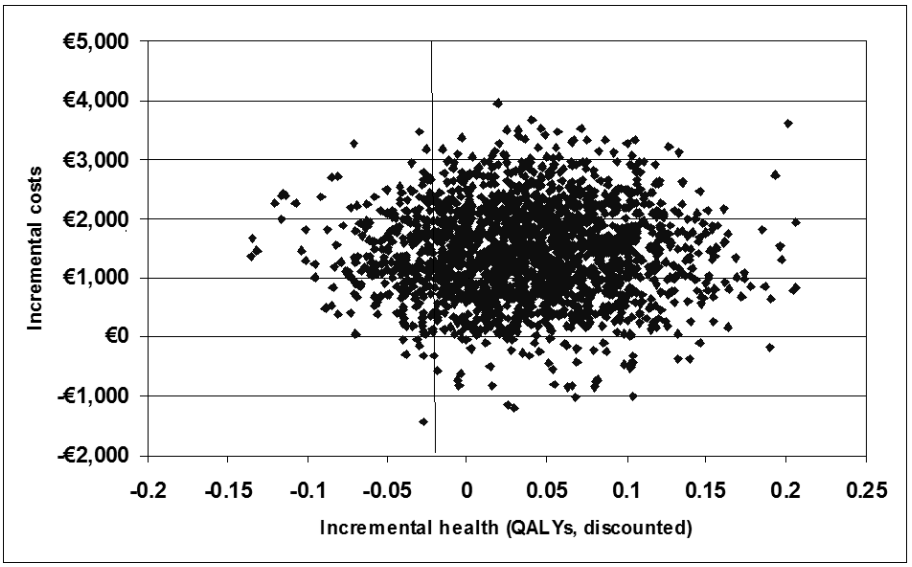

Figure 5.1: Scatter-plot showing incremental costs and health (QALYs discounted). The dots represent different patient populations and are the result of a second-order uncertainty analysis.

Figure 5.1 shows the degree of uncertainty around the differences in costs and QALYs between the DCP and control groups for the total population. The percentage of dots in the southeast quadrant (meaning lower costs and improved health) for these patients is 3%. Conversely, the percentage of dots in the northwest quadrant (where DCP increases costs and reduces health) is 26%.

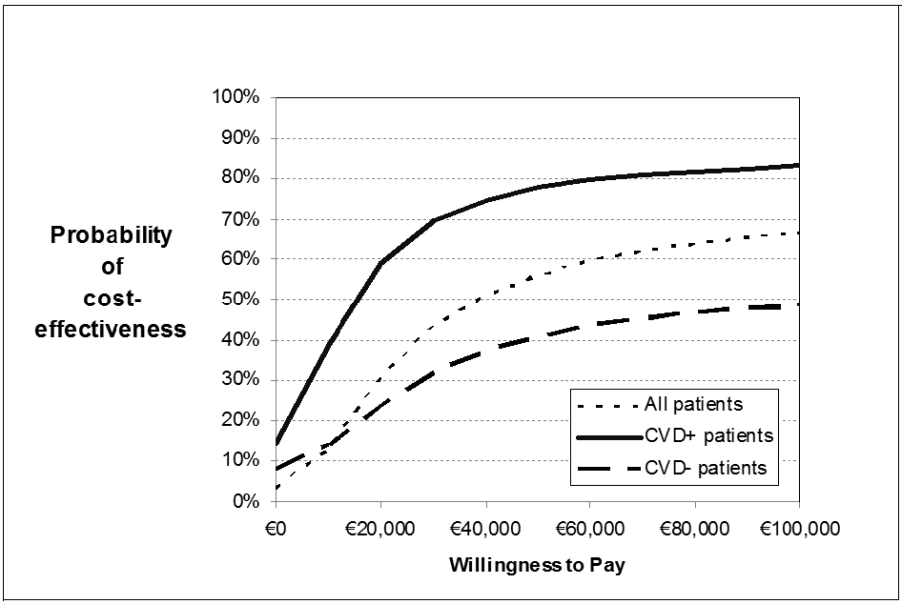

Figure 5.2: Cost-effectiveness acceptability curve, for patients with and without history of CVD (CVD+ patients, CVD- patients).

The cost-effectiveness acceptability curves (figure 5.2) show that the DCP for CVD+ patients is more likely to be cost-effective at any willingness-to-pay threshold than DCP for all patients or DCP for CVD- patients. If a threshold of €20,000 is applied(21), there is a probability of cost-effectiveness of 59% for CVD+ patients versus 30% for all patients and 24% for CV- patients.(figure 5.2)

Conclusion

After one year DCP results in reduced blood pressure, total cholesterol and estimated 10-year UKPDS CHD risk in comparison with usual

care. This resulted in a cost-effectiveness ratio of €38,243, which is higher than the often mentioned willingness-to-pay threshold of €20,000/QALY(21). In the long run, DCP is more costly and leads to only slightly more health than current care, although it does result in significantly lower CHD costs. The cost-effectiveness ratio for CVD+ patients is €14,814 and for CVD- patients €121,285. DCP for CVD+ patients has the highest probability of cost effectiveness (59% at a willingness-to-pay threshold of €20,000/QALY)(21).

When considering the one-year follow-up 10-year UKPDS CHD risk, 20.6% in the DCP group versus 21.6% in the control group, we see a significant though small relative risk reduction of 5%. Since DCP was compared with good usual care, this may explain why the size of improvements in QALYs (0.037) and life-years (0.14 years) was small. The costs per life-year gained were much smaller than the costs per QALY gained (total population €10,107; CVD+ €5,457; CVD- €16,980).

Although there were no significant differences in HbA1c between the intervention and control group after 1-year follow-up, the increase in diabetes costs was mainly caused by an age-related cumulative increase in renal failure and amputation.

Strengths and limitations

The existing type 2 diabetic model used in this study was improved by including medication and CHD costs. The increase in diabetes medication costs after one year was, however, assumed to be constant over lifetime. This might however be a conservative assumption, because it

is likely that diabetes-related costs and medication costs will also increase in the control group when more type 2 diabetic patients are treated according to current guidelines and treatment targets, independent of the intervention used.

Although we included a large unselected primary care type 2 diabetic population, it is difficult to generalize the results to other countries and settings. If DCP were to be applied in populations with higher mean HbA1c levels, larger HbA1c reductions would probably be obtained and more costly HbA1c-related complications would be prevented; this would improve the cost-effectiveness of DCP. However, in countries where the diabetic population is fairly adequately treated, the small improvement in QALYs will make cost-effectiveness less likely, even with less costly interventions. The results are limited by uncertainties in disease outcome. Although we calculated the average of 6 model outcomes per patient, this will probably not have led to a better cost-effectiveness estimation. Further, it is unlikely that the absence of many baseline values regarding history of CVD had any substantial effect on the results, since relatively few patients developed CVD in one year. Although stroke costs were not included in the model, the estimation of stroke costs did not have a significant effect on the study outcomes. (appendix)

Comparison with other studies

We observed that DCP is more cost-effective for use amongst patients with a history of CVD. These patients can be considered as high-risk patients, just like type 2 diabetic patients with microalbuminuria or

high CVD risk estimates, because they have an increased risk for a cardiovascular event. In fact, this was also shown by the intensive multifactorial intervention in the young high-risk type 2 diabetic population in the Steno-2 Study. They found a 53% reduction in cardiovascular events, which proved to be cost-effective.(22)

The baseline values in our trial are in accordance with a world wide positive trend in the general therapeutic approach of type 2 diabetes with increasing percentages of patients achieving their targets for HbA1c, blood pressure and lipids.(23) Under these conditions, a potential cost-effective outcome will be more difficult to achieve. Unlike blood glucose level, there is strong evidence that controlling high blood pressure and high cholesterol levels significantly reduces both macro and microvascular complications in type 2 diabetic patients. Recent trials suggest that early strict glycemic control is likely to be beneficial for many patients(24), but that setting a glycemic target is definitely more difficult in people with existing diabetes related complications.(25) This implies that PCPs will have to provide a more personalized kind of diabetes care for different kinds of patients (i.e., those with a short duration of diabetes and those at high risk). Based on the results of our study we think that DCP or comparable interventions are only useful instruments if they can identify these different categories of patients to facilitate structured personalized patient review.

In this study we showed that DCP, consisting of CDSS, a recall system, feedback and case management, improves clinical outcome in an

unselected primary care type 2 diabetic population, and results in lower CVD-related costs but much higher diabetes-related costs and a high cost-effectiveness ratio. In the effort to improve health in a cost-effective manner, PCPs should not simply focus on HbA1c percentage but rather on personalized need-differentiated type 2 diabetes care.

Appendix: Stroke Cost Estimation

The absolute stroke risk difference between the two groups was estimated separately by calculating 10-year UK Prospective Diabetes Study (UKPDS) stroke risk estimates(26) using generalized estimated equations (GEE) to correct for clustering and confounders (see average model outcome analyses). This difference in stroke risk was then multiplied by the mean costs of stroke and added to the total costs per patient.(27) Since the incidence of stroke is highest around 80 years, only the costs of stroke in the first year were taken into account.(28)

The difference in 10-year UKPDS stroke risk estimates between intervention and control group for the total population was -0.74% (95% CI: -1.29 to –0.19), for CVD+ patients -1.11% (95% CI: -1.83 to – 0.39) and for CVD- patients –0.51% (95% CI: -1.01 to – 0.02). Stroke risks were multiplied by the first year stroke costs (€20,500, not discounted)(27), resulting in stroke costs: total population €-151, CVD+ patients €-228 and CVD- patients €-105. When the differences in stroke costs are added to the model, the incremental cost-effectiveness ratio (ICER) for the total population is €34,162 per QALY gained

(i.e., €1,264/0.037), for CVD+ patients €11,557 per QALY gained, and for CVD- patients €113,785 per QALY gained.

These calculations show that the influence of stroke costs on the model is probably small and that these costs do not change the conclusions about the effectiveness and cost-effectiveness of DCP. This conclusion is also supported by the finding that stroke occurs late in life(28) and that type 2 diabetic patients have a higher mortality risk after stroke than other patients.(29)

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Chapter 6

The Association between Erectile Dysfunction and Cardiovascular Risk in Men with Type 2 Diabetes in Primary Care: It is a Matter of Age

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Abstract

Objective: Erectile dysfunction (ED) prevalence is usually based on questionnaires, too elaborate for daily practice. The single question for ED prevalence is unknown. Literature reports an independent association between ED and both cardiovascular disease (CVD) and diabetes. Whether routinely asking type 2 diabetic men about ED identifies those at elevated risk for CVD is unknown. We assessed cardiovascular risk of type 2 diabetic men with ED.

Research Design and Methods: This was a cross-sectional study in primary care. During annual check-up, the practice nurse asked 1823 type 2 diabetic men: "do you have erection problems? Yes/no." ED prevalence rate was calculated. Age, medication and other known factors associated with ED and/or CVD were used in univariate analysis (odds ratio [OR], Student's t-test and Mann-Whitney test). This revealed confounding variables used in the multivariable analysis. The association between ED and History of Cardiovascular Disease (HCVD) was assessed by logistic regression analysis. In patients with no HCVD we assessed the association between ED and 10-year UK Prospective Diabetes Study (UKPDS) coronary heart disease risk by linear regression analysis.

Results: The prevalence of ED in type 2 diabetic patients was 41.3%. There was no independent association between ED and HCVD [adjusted OR 1.2 (95% CI: 0.9 – 1.5)] 10-year UKPDS CHD risk difference between men with and without ED was 5.9% (95% CI: 3.2 – 8.7), but after adjustment for age this association disappeared. [adjusted risk difference 0.6% (95% CI: -1.5 – 2.7)].

Conclusion: The ED prevalence rate assessed by single question was comparable to that assessed by questionnaires. ED neither did independently relate to patients' cardiovascular history nor to cardiovascular risk.

Introduction

The prevalence of erectile dysfunction (ED) in the general population ranges from 2% in men younger than 40 years to 86% in men 80 years and older.(1) This wide prevalence range is caused by the use of various questionnaires and different definitions of ED.(1) The National Institutes of Health (NIH) defined ED as: 'a continuous or repetitive inability to achieve or maintain an erection sufficient for satisfying sexual activity'.(2) In patients with diabetes ED is even more common(3;4) with prevalence ranges from 34 to 89%.(5;6)

ED questionnaires are time consuming and not feasible in daily diabetes care. A single question for ED can accurately identify patients with clinically diagnosed ED.(7) However, the ED prevalence rate using a single question is unknown.

Cardiovascular disease (CVD) and diabetes are independently associated with ED.(8) Some authors even state that patients presenting with ED should be screened for cardiovascular risk factors, including diabetes, even if they have no symptoms.(9) However, it is less clear whether routinely asking patients with type 2 diabetes about ED will identify patients with elevated risk for cardiovascular disease.

Another important cause of ED is medication: 25% of all ED cases is medication related.(2) Type 2 diabetic patients often use several drugs that have ED as side effect. Medications that are mostly associated with ED are β-blocking agents, thiazide diuretics, ACE-inhibitors, digoxin, cimetidin, benzodiazepines, antidepressants, other psychiatric medications and occasionally lipid lowering drugs.(10)

The present study aims to assess the prevalence of ED measured by a single question asked by a practice nurse, and to assess the cardiovascular risk of type 2 diabetic patients with ED.

Research Design and Methods

Patients and practices

For this cross-sectional study we used the baseline data of the Diabetes Care Implementation Study (DIS) (ISRCTN21523044). DIS is an intervention study to evaluate the effectiveness of the Diabetes Care Protocol (DCP). DCP was described elsewhere (11) and is in short characterized by delegation of routine diabetes care tasks to a trained practice nurse, who uses software that supports diabetes management and medical decisions (Computerized Decision Support System [CDSS]), during office hours exclusively scheduled for type 2 diabetic patients. DCP is based on the Dutch primary care guideline on type 2 diabetes mellitus.(12) Fifty-five general practices (33 single handed [60%], 16 duos [29%] and 6 group practices [11%]) throughout the Netherlands participated. All practices were interested in changing their usual diabetes care into a practice nurse-led categorical diabetes consultation hour by using the DCP. The DCP software was used to collect all data from each participant.

In all practices, type 2 diabetic patients were selected from the Electronic Medical Record by ICPC-code (T90.2: type 2 diabetes), diabetes as a point of attention in the patient's record, or ATC-code

(A10A: insulin and analogues, A10B: oral blood glucose-lowering drugs). The list of type 2 diabetic patients was subsequently checked by the Primary Care Physician (PCP), for specific exclusion criteria, including receiving diabetes treatment from a medical specialist, having a terminal illness or complex multi-morbidity, or being unable to visit the general practice. These exclusion criteria were used because the PCP had to be responsible for optimal diabetes treatment, and because the CDSS could only be used in the physician's office. The remaining type 2 diabetic patients were invited to participate in the intervention study. The study was approved by the medical ethical committee of the University Medical Center in Utrecht. All participants gave informed consent.

Data collection

During the diabetes consultation hours, all data were collected in the CDSS. Every practice nurse was trained in performing diabetes care according to the Dutch primary care guideline on type 2 Diabetes Mellitus (12) and in using the CDSS during diabetes consultation hours. According to a standard operating procedure, which followed the NIH definition of ED(2), all male subjects were asked about ED. First, the practice nurse explained that ED is the inability to achieve or maintain an erection sufficient for satisfying sexual activity, then she explained that ED is a common symptom in type 2 diabetic patients. After this she asked: "Do you have erection problems? (Yes/ No)."

The practice nurse registered age, gender, ethnicity ('Caucasian', 'Afro-Caribbean' or 'Asian / Indian'), duration of diabetes, history of

cardiovascular disease (HCVD), family history of diabetes, family history of CVD, smoking habits, alcohol consumption and present medication use. All medication were registered by generic or commercial name in the CDSS and then automatically translated to the corresponding ATC classification code.

HbA1c, total cholesterol and HDL-cholesterol were measured in local laboratories. Height and weight were measured with people wearing clothes, but without shoes. After patients had been seated for 5 minutes, the blood pressure was measured in seated patients at both left and right arm, the arm with highest pressure was then measured again. The mean blood pressure of the two measurements from the arm with the highest blood pressure was registered.

We calculated the 10-year CHD risk estimate for every patient without a history of cardiovascular disease using the UK Prospective Diabetes Study CHD risk algorithm (10-year UKPDS CHD risk).(13) The following risk factors are used: sex, ethnicity, current smoker, age at onset of diabetes, HbA1c, systolic blood pressure, and total cholesterol/ HDL-cholesterol ratio. For this calculation we used the values that were gathered during the office hour visit.

Statistical Analysis

Prevalence of ED was calculated for the whole population and in 10-year age categories.

The association between ED and a history of CVD was assessed with logistic regression analysis. To explore the confounding effect of different variables on this association, we first performed univariate

analyses. For dichotomous variables we used odds ratios (ORs); for continuous variables we used Student's t-test.

In the literature, we looked for variables that were both associated with ED and HCVD, for example medication with ED as possible side effect and prescribed in diabetes and/or cardiovascular disease.

All variables with a significant relationship ($P < 0.1$) with both ED and a HCVD were considered as potential confounders and were used in multiple logistic regression analysis to assess the adjusted association between ED (independent variable) and an HCVD (dependent variable). Potential confounders that did not influence the model were not included in the final model.

For patients without an HCVD, we explored the relationship between ED and the 10-year UKPDS CHD risk score by linear regression analysis. We used univariate analyses to assess possible confounding by the same set of variables, with the exception of HbA1c, systolic blood pressure, and total cholesterol / HDL-cholesterol ratio, because these variables were already used to calculate the 10-year UKPDS CHD risk score. We examined if the potential confounders, that is, all variables having a significant relation with both ED and 10-year UKPDS risk estimate ($P < 0.1$), did influence the difference in 10-year UKPDS CHD risk estimate between patients with ED and without ED. If so, variables were added to the final model.

We then calculated 10-year UKPDS CHD risks estimates in 3-year age categories for patients with and without ED.

All statistical analyses were performed using SPSS version 12.0. A P-value < 0.05 was considered as statistically significant.

Results

At baseline, 3,729 type 2 diabetic patients were included in DIS. The mean age was 65.0 ± 11.4 year with a mean duration of diabetes of 5.5 ± 5.8 year. 1,823 (48.9%) patients were male. In 1,611 (88.4%) male patients the answer on the single question for ED was registered. Patients with a missing ED answer were older and had a longer duration of diabetes. (table 6.1)

Table 6.1: Baseline characteristics

characteristic	ED registered n = 1,611	ED missing n = 212	P- value
Age (year)	63.3 ± 10.2	69.2 ± 12.5	<0.001*
Duration of diabetes (year)	5.8 ± 5.5	7.2 ± 7.6	0.01*
HbA1c (%)	7.1 ± 1.3	7.2 ± 1.2	0.1*
Systolic blood pressure (mmHg)	148 ± 21	145 ± 20	0.1*
Diastolic blood pressure (mmHg)	83 ± 11	81 ± 11	0.02*
Total cholesterol (mmol/L)	4.8 ± 1.1	4.8 ± 1.0	0.8*
HDL-cholesterol (mmol/L)	1.24 ± 0.34	1.27 ± 0.48	0.2*
Quetelet index (kg/m²)	29.6 ± 4.5	29.5 ± 5.0	0.8*
Ethnicity (%)			
Caucasian	98.4	97.6	0.5†
Afro-Caribbean	0.4	1.0	
Asian/Indian	1.2	1.4	
History of CVD (%)	45.7	43.5	0.6‡
Family history of diabetes (%)	59.2	60.5	0.7‡
Family history of CVD (%)	35.9	33.3	0.5‡
Smoking (%)	19.3	21.5	0.5‡
Alcohol (%)			
No alcohol use	43.7	52.7	0.07‡
≤2 units a day	42.3	35.2	
>2 units a day	14	12.1	
ED (%)	41.3	?	

Data are mean ± SD, unless otherwise indicated. * Student's t-test was used for continuous variables. †For ethnicity, Fisher's exact test was used. ‡ Nominal variables were compared with χ^2 test

The recorded ED prevalence was 41.3% in the group who answered the single question on ED. When categorizing by age, we found the following prevalences: <40 years 3.0%, 40-49 years 19.2%, 50-59 years 34.1%, 60-69 years 45.7%, 70-79 years 51.5%, and >80 years 49.4% (figure 6.1).

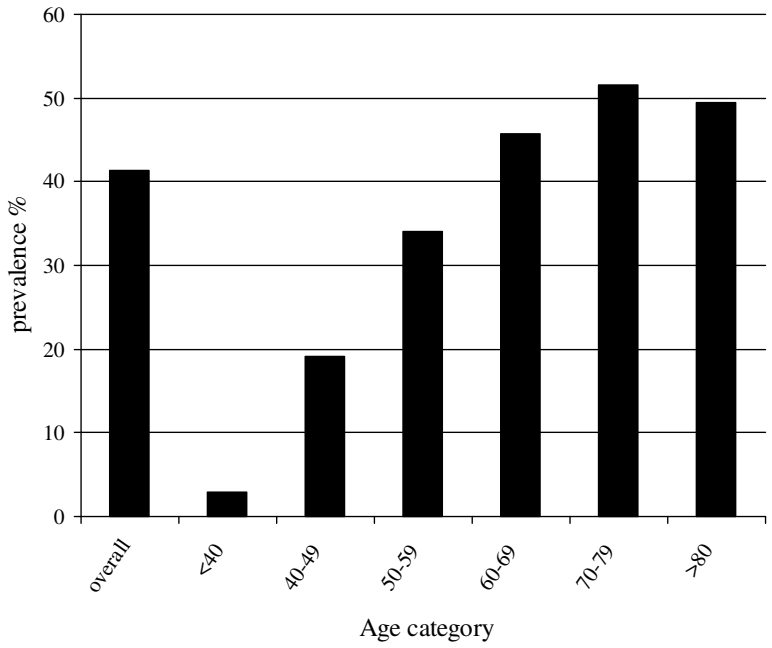

Figure 6.1: Prevalence of ED in men with type 2 diabetes by 10-year age category

Patients with ED had an unadjusted odds ratio (OR) of 1.6 (95% CI: 1.3 to 2.0) for having a HCVD. In table 6.2, the results of univariate analyses of all relevant variables with ED and a HCVD are shown. Possible confounders were ACE-inhibitors, lipid-lowering drugs, ß-blocking agents, benzodiazepines, systolic blood pressure, total cholesterol and age. (table 6.2)

Table 6.2: Associations between variables and ED and HCVD, univariate analysis

	ORs or difference between yes/no ED or yes/no HCVD (CI 95%)			
	ED	P-value	HCVD	P-value
HCVD*	1.6 (1.3 to 2.0)	<0.001	-	
Family history of CVD (yes/no)*	1.0 (0.8 to 1.2)	0.8	1.9 (1.5 to 2.4)	<0.001
Ethnicity				
Caucasian (yes/other) *	0.7 (0.1 to 1.4)	0.7	0.6 (0.1 to 3.2)	0.5
Smoking				
smoker/nonsmoker*	0.9 (0.7 to 1.1)	0.3	0.7 (0.5 to 0.9)	0.003
Alcohol consumption				
>2 units a day/no alcohol*	1.0 (0.7 to 1.3)	0.8	1.0 (0.8 to 1.4)	0.8
Current medication use				
Glucose-lowering drugs*	1.6 (1.2 to 2.1)	<0.001	1.1 (0.9 to 1.4)	0.4
ACE inhibitors*	1.6 (1.3 to 2.0)	<0.001	3.8 (3.0 to 4.9)	<0.001
Lipid-lowering drugs*	1.5 (1.2 to 1.8)	<0.001	2.1 (1.8 to 2.6)	<0.001
ß-blocking agents*	1.3 (1.1 to 1.6)	0.01	6.0 (4.6 to 7.9)	<0.001
Thiazide diuretics*	1.3 (0.9 to 1.9)	0.14	2.8 (1.9 to 4.3)	<0.001
Digoxin*	1.3 (0.8 to 2.3)	0.3	6.4 (2.7 to 15.2)	<0.001
Benzodiazepines*	2.1 (1.4 to 3.1)	<0.001	1.5 (1.0 to 2.2)	0.05
Antidepressants*	2.1 (1.2 to 3.6)	<0.001	1.0 (0.6 to 1.8)	0.95
Age (years)†	4.5 (3.4 to 5.5)	<0.001	4.8 (3.7 to 5.8)	<0.001
Duration of diabetes (years)†	0.9 (0.3 to 1.5)	0.003	0.16 (-0.76 to 0.44)	0.6
HbA1c (%)†	0.11 (-0.001 to 0.25)	0.07	-0.1 (-0.21 to 0.04	0.2
Blood pressure (mmHg)				
Systolic†	4 (1.6 to 5.8)	0.001	6 (4.3 to 8.5)	<0.001
diastolic†	1 (-1.5 to 0.7)	0.5	0 (-1.1 to 1.1)	0.95
Total cholesterol (mmol/L)†	-0.11 (-0.2 to 0.003)	0.06	-0.3 (-0.4 to –0.2)	<0.001
HDL-cholesterol (mmol/L)†	-0.01 (-0.04 to 0.03)	0.7	-0.04 (-0.07 to 0.002)	0.04
BMI (kg/m²)†	0.1 (-0.41 to 0.55)	0.8	-0.32 (-0.8 to 0.2)	0.2

* For all dichotomous variables, ORS (95% CI) for ED and history of CVD are presented. † For all continous variables, the difference (95% CI) for ED and history of CVD is presented

From a clinical point of view these possible confounders, besides age and benzodiazepines, usually cluster in patients with diabetes and/ or a HCVD. We therefore corrected for this cluster of variables in a multiple logistic regression analysis with ED as determinant of

HCVD. When the relation between ED and an HCVD was corrected for these confounders (ACE-inhibitors, Lipid-lowering drugs, ß-blocking agents, systolic blood pressure and total cholesterol), the adjusted OR was 1.3 (95% CI: 1.0 to1.6). As benzodiazepines did not materially change the OR, this was considered not to be a confounding factor and, thus, was not included in the model. When we also corrected this relation for age, there was no significant relation between ED and HCVD anymore (adjusted OR 1.2 [95% CI: 0.9 to 1.5]).

Table 6.3: Associations between variables and ED and 10-year UKPDS coronary heart disease risk estimate (UKPDS risk) in patients without an HCVD, univariate analysis

	ORs or difference between yes/no ED		UKPDS risk*
	ED (95% CI)	P-value	P-value
Age (years)†	5.3 (3.7 to 6.9)	<0.001	<0.001
Family history of CVD (yes/no)‡	1.0 (0.7 to 1.5)	0.9	0.03
Ethnicity			
Caucasian (yes/other)‡	1.9 (0.1 to 29.8)	0.9	0.3
Smoking (smoker/nonsmoker)‡	0.9 (0.7 to 1.3)	0.7	0.007
Alcohol consumption			
>2 units a day/ no alcohol‡	0.9 (0.6 to 1.4)	0.6	0.3
Current medication use			
Glucose-lowering drugs‡	1.8 (1.2 to 2.7	0.003	0.01
ACE inhibitors‡	1.5 (1.0 to 2.2)	0.07	0.6
Lipid-lowering drugs‡	1.4 (1.0 to 1.9)	0.05	<0.001
ß-blocking agents‡	1.3 (0.8 to 2.1)	0.2	0.01
Thiazide diuretics‡	1.9 (0.9 to 4.0)	0.08	0.2
Digoxin‡	9.4 (1.1 to 81.1)	0.01	0.02
Benzodiazepines‡	1.7 (0.9 to 3.1)	0.12	0.1
antidepressants‡	2.7 (1.2 to 6.1)	0.02	0.76

* For UKPDS risk (10-year UKPDS CHD risk estimate), we used Mann-Whitney's test for all variables; the P value is given. † For age, the difference (95% CI) between ED and no ED is given; we used Students t-test. ‡ For all dichotomous variables, OR (95% CI) between ED and no ED is given.

In 736 patients without a HCVD, we analyzed the relation between ED and 10-year UKPDS CHD risk score. Patients with ED had a 10-

year UKPDS risk estimate of 28.0% and patients without ED had a 10-year UKPDS risk estimate of 22.1%, so without correction patients with ED had an absolute 5.9% (95% CI: 3.2 to 8.7) higher 10-year UKPDS CHD risk estimate. Age, use of glucose-lowering drugs, lipid-lowering drugs and digoxin had a significant relation (P <0.1) with both ED and 10-year UKPDS risk estimate (table 6.3). However, after correction for the use of glucose-lowering drugs, lipid lowering drugs and digoxin, the difference in 10-year UKPDS CHD risk estimate between patients with ED and patients without ED did not change, so these medications were not considered to be confounding factors. After correcting for age, patients with ED had a 0.6% (95% CI: -1.5 to 2.7) higher 10-year UKPDS CHD risk estimate, which was not significant.

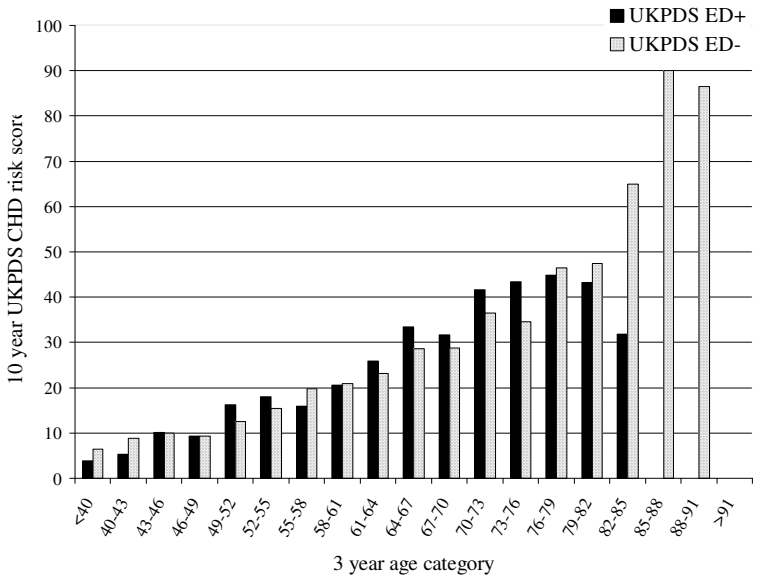

Figure 6.2: Relation between 10-year UKPDS CHD risk estimate for patients without an HCVD in 3-year age categories for patients with and without ED.

In figure 6.2, the relation between 3-year age categories and 10-year UKPDS CHD risk estimate is given for patients with and without ED. With increasing age category the 10-year UKPDS CHD risk estimate increases. This does not differ between patients with or without ED.

Discussion

The prevalence of ED in type 2 diabetic men in Dutch primary care, based on a single question asked by a practice nurse, is 41.3% and increases with age. When type 2 diabetic men, who were able to visit a diabetes consultation hour, are routinely asked about ED, there is no independent relation between ED and HCVD. Age and medication are the most important confounders. For patients without an HCVD the difference in 10-year UKPDS CHD risk estimate between men with ED and men without ED was 5.9% (95% CI: 3.2 to 8.7). However, when adjusted for age, this difference decreased to a non significant level.

Prevalence

Comparing prevalence data of ED is difficult because of differences in study population, questionnaires and definition.(1;14) We based our single question on the working definition of ED by the NIH (2), but there is no “gold standard” for ED assessment. The International Index of Erectile Function (IIEF) has become the most accepted and

best validated questionnaire for ED research (15). However, in daily clinical practice it may be difficult to use. Indeed, it has been shown that a single question can estimate the ED prevalence just as good as the IIEF.(16) Because the number of questions affects response rates, a uniform questionnaire with one or two questions is recommended.(14) A single question for ED accurately identifies patients with clinically diagnosed ED, with the best balance between sensitivity and specificity when every grade of ED (mild, moderate, complete) is compared to no ED.(7) Solstad found that interviewed patients had more often ED, but the percentage of patients that would seek help for their ED was comparable to that found by questionnaire.(17;18) In this study, we used a simple question, that followed the NIH definition of ED, with two answering categories (yes/no), which might be easily applicable in daily primary diabetes care.

The study population was comparable for age and duration of diabetes with other Dutch studies using similar selection criteria.(19;20) In this study, patients with terminal illness, patients unable to visit the primary care office, and patients with complex multi-morbidity were excluded. Because these patients usually suffer more from the burden of illness, the ED prevalence might have been underestimated.

Due to the aim of the study, we selected a primary care diabetes population, with only type 2 diabetic men. Patients under specialist treatment were not included, which would probably lead to an underestimation of the ED prevalence under diabetic men. It could be interesting to perform a similar study in patients under specialist treatment to see if there is a difference in ED prevalence.

Discussing sexual functioning during a medical encounter is difficult because of reluctance on the part of older patients to discuss sexual activities and lack of training in diagnosing and managing sexual disorders in primary care practitioners.(21) In our study, 212 patients from 42 different primary care practices did not answer the ED question, maybe because of embarrassment of both practice nurse and patient. These patients were older and had a longer duration of diabetes. Because ED prevalence increases with age, it is likely that this may have caused an underestimation of the ED prevalence rate, especially in the older age categories.

Nevertheless, our ED prevalence rate (41.3%), is comparable to the ED prevalence rate in Dutch type 2 diabetic men (44.4%) found by using a mail-sent standardized questionnaire. The mean age in the latter population was 61.4 year, and the mean duration of diabetes was 2.7 year.(22) Our study population was comparable with respect to age, but had a longer duration of diabetes, which may lead to a higher ED prevalence rate. Other studies examining ED prevalence rates in men with diabetes showed similar mean age groups and prevalence rates of 34 to 67%.(23-25)

In this study the actual ED prevalence is probably underestimated because data of older and more severely ill patients are missing. On the other hand, the prevalence is comparable with most other studies, so although the question was not validated, we think it might be likely that the single question used in the present study gives a reliable estimate of the clinically relevant ED prevalence in an unselected primary care diabetes population.

Cardiovascular disease and ED

Grover et al found that ED is independently associated with cardiovascular disease, diabetes, future coronary risk, and increasing fasting glucose levels in primary care (8). In the present study, however, we did not find a significant association between ED and a HCVD in type 2 diabetic men, after correction for confounders. Moreover, in the group of patients without a history of cardiovascular disease, type 2 diabetic men with ED did not have a higher 10-year UKPDS CHD risk after correction for age.

Figure 6.2 also illustrates that the 10-year UKPDS CHD risk estimate increases with age for both type 2 diabetic men with and without ED. There is no obvious difference in 10-year UKPDS CHD risks estimate between type 2 diabetic men with or without ED. There seems to be a difference only in patients over 82 years of age, but due to the small number of patients in these age categories, it is not possible to draw conclusions.

Studies performed in the general population suggest a strong association between ED and cardiovascular disease.(8;26-29) These studies assessed ED by questionnaires, and corrected for age, only 2 studies also corrected for medication.(26;28) One study found a strong relation between ED and silent myocardial ischemia in type 2 diabetic men but did not correct for age or medication use.(30) In the longitudinal general population study of Thompson (27), 8,063 patients aged 55 years or older were analyzed, but only 412 patients had a history of diabetes. A questionnaire was used to determine ED. In the analysis, the authors corrected for age, antihypertensive medication and history

of diabetes. ED was a harbinger of cardiovascular clinical events in some men even after adjustment for potential confounders, but history of diabetes was a more important risk factor for developing cardiovascular events.

The relation between ED and cardiovascular disease is less clear in type 2 diabetic men, probably because both ED and cardiovascular disease are more common in type 2 diabetic men.(3;4;31)

In the general population, ED is also related to smoking habits (26), but for the diabetes population this is under debate.(22) In our study, smoking was not related to ED.

According to Blumentals et al and Kirby et al, patients presenting with ED should be investigated for risk factors of cardiovascular disease and diabetes.(9;27;28) It has been suggested that asking whether ED is present, may be a useful tool for stratifying risk in individuals with suspected CHD.(32) In our opinion, routinely asking for ED should only be recommended in order to treat ED, for example by adjusting medication. Indeed, if ED is present, the cardiovascular risk is elevated, but the physician should realize that this is mainly a matter of age.

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Chapter 7

Computerized Decision Support Systems in Primary Type 2 Diabetes Care Can only Improve Patient Outcome when Combined with Feedback on Performance and Case Management: A systematic Review

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Submitted

Abstract

Context: Computerized decision support systems (CDSS) are often part of a multifaceted intervention to improve type 2 diabetes (DM2) care. They may be an important tool in successful type 2 diabetes management.

Objective: To review the effects of CDSS alone or in combination with other supportive tools and to identify successful interventions improving the process of care or patient outcome in primary type 2 diabetes care.

Data Sources: A systematic literature search, from January 1990 to March 2009, in Pubmed, Embase, the Cochrane database and consulting reference lists.

Study selection: RCTs in primary type 2 diabetes care were selected if the interventions consisted of a CDSS alone or combined with reminder system and/or feedback on performance and/or case management. The intervention had to be compared with usual care.

Data extraction: Two reviewers independently abstracted data on methods, setting, CDSS intervention and patient characteristics, and outcomes.

Results: 16 RCTs met our inclusion criteria. In 10 studies a CDSS was combined with another intervention. Two studies scored less then five (range 0-10) quality points and were left out of the analysis. Four studies with a CDSS alone showed improvements of the process of care. CDSS with reminders improved the process of care (two studies). CDSS with feedback on performance and/or reminders, improved the process of care (one study) and patient outcome (two studies). In one study a multivariable analysis showed that feedback on performance improved both the process of care and patient outcome. CDSS with case management improved patient outcome, (two studies). CDSS with reminders, feedback on performance and case management improved both patient outcome and the process of care (two studies).

Conclusion: Computerized decision support systems used by health care providers in primary type 2 diabetes care are only effective in improving the process of care; adding feedback on performance and/or case management may also improve patient outcome.

Introduction

Many patients with type 2 diabetes do not meet the targets for good glycemic and cardiovascular control.(1-3) Facing the management problems with chronic illnesses in primary care, structured and regular review of patients(4) as well as feedback on performance given to primary care physicians (PCPs)(5;6) are effective in improving diabetes care. Both interventions can easily be integrated in Computerized Decision Support Systems (CDSS). Therefore these information technology systems may be an important tool in successful diabetes management.

In most diabetes management systems physicians, practice nurses, or patients manually enter diabetes outcome parameters into the CDSS, or the electronic medical record (EMR) is electronically searched for patients' medical diabetes outcome parameters. These individual outcome parameters are then used in software algorithms and/or matched to a computerized knowledge base, to generate treatment recommendations.

Garg et al. performed a review on CDSS in clinical care, showing mainly improvements in practitioner performance.(7) However, diabetes care disease management systems were only a small part of the study. Another review by Jackson et al. evaluating the effects of interactive computer assisted technology in type 2 diabetes care concluded that there is growing evidence that information technology improves diabetes care.(8) However, this study evaluated a broad range of interventions, such as education, disease management, telephone auto-

mated calls and telemedicine, aimed at both health care provider and patient and performed in both primary and secondary care. Both randomized controlled trials and observational studies were included. Because of this heterogeneity in both studies and study outcomes (process of care and/or patient outcome), general inferences were impaired.

Therefore we aim to study whether a CDSS alone or a CDSS in combination with a reminder system or with feedback on performance or as part of a structured case management system has the ability to improve both patient outcome and practitioner performance.

Materials and Methods

Eligibility criteria

Eligible studies were randomized clinical trials published peer-reviewed journals in English, that compared the effectiveness of type 2 diabetes care with a CDSS to type 2 diabetes care without a CDSS on clinical performance (measure of process of care) and/or patient outcome. We searched for management interventions that were developed for use by a diabetes care provider in primary type 2 diabetes care and contained at least a computer system that generated decision support, and/or functioned as recall system, and/or made it possible to give feedback on performance on patient level and/or health care professional level and/or was integrated in a so called case management system.

Computerized glucose monitoring systems, diabetes self management programs, digital eye fundus screening programs, or patient education systems were excluded. The studies should include only type 2 diabetic patients and have a follow-up of at least six months.

Search strategy

Published studies were identified by searching the electronic databases of Pubmed, Embase and the Cochrane Library. The following search terms were used for each database: diabetes AND (decision support, OR computer-assisted decision making, OR computer, OR artificial intelligence, OR electronic intervention, OR internet, OR reminder systems, OR recall system, OR feedback, OR benchmark), AND (randomized OR randomised OR RCT OR trial OR evaluation studies). Since the development of CDSS started at the end of the 20th century, we included articles published between January 1990 and March 2009. Finally manual searches were performed by screening the reference sections of the relevant review articles and of the selected randomized controlled trials.

Study selection

The titles and abstracts were independently reviewed by 2 investigators (FC and MD or KG) for eligibility. The first 200 titles were reviewed by the three reviewers. The results were compared and discussed in order to reduce the variation in interpretation of in- and exclusion criteria between the reviewers. Full text articles were retrieved if any reviewer considered a citation potentially relevant. Two review-

ers then independently judged the full text of potentially eligible articles. Disagreements were resolved by discussion. In case no consensus could be achieved, the third reviewer was asked. When comparable outcome data of a study were published twice, we cited the publication providing most data and with the longest follow-up.

Data abstraction

Two reviewers independently abstracted the following data from all included studies meeting eligibility criteria: study setting, study methods, study intervention characteristics, and study outcomes. The same pairs of reviewers worked together, as with study selection. Disagreements were resolved by consensus and where no consensus could be achieved, the third reviewer decided. All studies were scored for methodological validity on a two point scale, yes (1 point), no or unclear (0 points). The nine methodological validity indicators from the Dutch Cochrane Centre were used: 1. intervention randomized, 2. randomization order not known by person who included patients/practices, 3. patients blinded, 4. therapist blinded, 5. outcome assessor blinded, 6.groups comparable, 7. proportion of follow-up of all included patients high enough, 8. included patients analyzed in group of inclusion, 9. groups equally treated, except for the intervention.(9) Studies could be cluster randomized or patient randomized. Whenever studies were cluster randomized, we identified whether appropriate analysis methods, e.g. Generalized Estimated Equations (GEE), were used in order to correct for clustering. Only studies that randomized patients or studies that were cluster randomized and ap-

plied appropriate methods to take cluster effects into account scored one point for the first item of the Cochrane Centre list. A tenth indicator was added: the use of power calculations. Adding all validity indicators the studies could score a maximum of ten points. Only the results of the studies scoring five or more points were used. Furthermore we reported country, commercial funding of studies, and the number of patients.

Studies were then grouped together depending on the type of intervention or combination of interventions. In each table we described the study intervention(s) and summarized outcome measures qualitatively.

Statistical analysis

Reviewer agreement on study eligibility was quantified using the Cohen's kappa.

Study methodological validity was expressed as mean with the standard deviation and the range, using the 10 validity indicators.

Results

Selection of studies

The electronic database search revealed 1,672 citations, when duplicate citations between databases were removed. The titles of these citations were reviewed and revealed 450 abstracts. After abstract selection 104 articles remained for full text review. Eventually 19 arti-

cles met our inclusion criteria. There were 2 duplicate publications (Glasgow et al, 6 months follow-up(10) and 12 months follow-up(11); Lobach et al, baseline compliance levels(12) and 6 months follow-up(13)), leaving 17 articles for review. The study from Philips et al(14) and Ziemer et al(6) regarded the same study population, with different outcome measures; thus 16 RCTs were included. Eighty five articles were excluded because of different reasons, for example: review article (n=12), no RCT (n=20), no CDSS used in the intervention (n=20), glucose monitoring system (n=10), diabetes self management program (n=11). (Figure 7.1)

There was substantial agreement between the reviewers for article inclusion, with a change-corrected agreement between 2 independent reviewers of $\kappa_{(FC \text{ and } KG)} = 0.62$ and $\kappa_{(FC \text{ and } MD)} = 0.73$.

Categories of studies

The 16 included studies were published between 1993 and 2009. The number of trials increased with time: one in 1990-1994, one in 1995-1999, five in 2000-2004, and nine in 2005-2009. 12 studies were conducted in the United States of America, one in the United Kingdom, one in Norway, one in Korea and one in the Netherlands. The number of patients included varied between 62(15) and 7101(16). 11 of the studies described funding from the public sector and 4% from the private sector. In six studies the only intervention was a CDSS (table 7.2), the other studies regarded a multifaceted intervention in which the CDSS was combined with a reminder system (table 7.3), CDSS with feedback on performance (table 7.4), CDSS with case manage-

ment or CDSS with case management and reminders (table 7.5), CDSS with a reminder system and feedback on performance (table 7.6) and CDSS with a reminder system, feedback on performance and case management (table 7.7).

Figure 7.1: Summary of the literature search

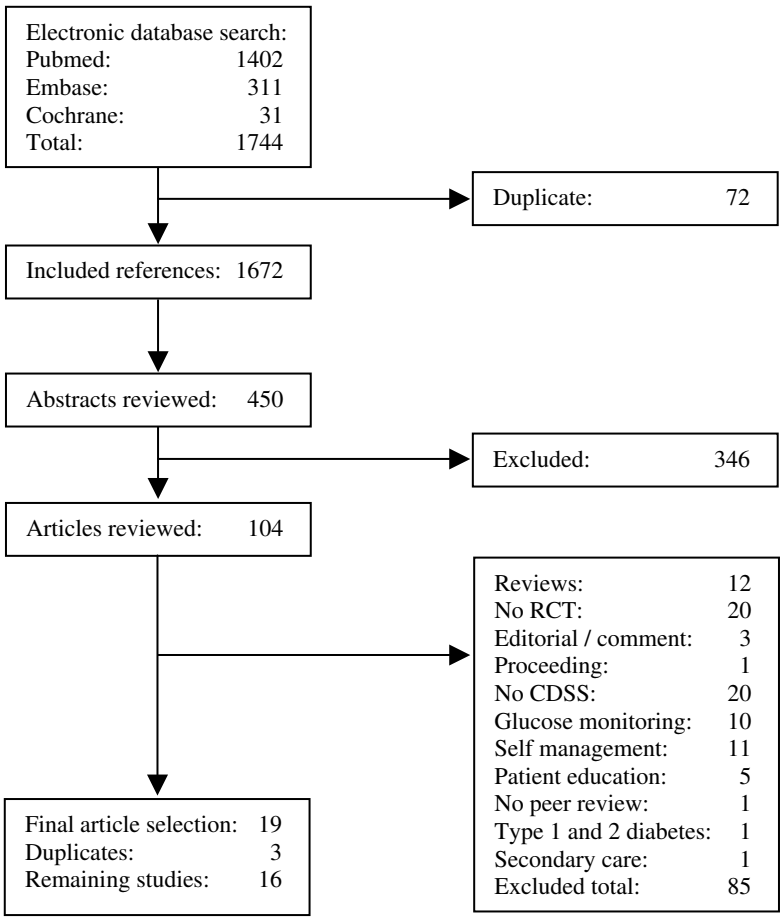

Table 7.1: Methodological validity

1. study	2. Total patients (n)	3. country	4. funding	5. Randomization level	6. Generalized Estimating Equation	7. randomized*	8. Randomization order blinded	9. Patient blinded	10. Physician blinded	11. Outcome assessor blinded	12. Groups comparable	13. follow-up of >70%	14. Patients analyzed in group of inclusion	15. Groups equally treated	16.Power calculation	17. Total†
Hurwitz 1993(18)	209	UK	public	patient	na	1	1	0	0	?	1	1	1	1	0	6
Lobach 1997(13)	359	USA	public	cluster	0	0	1	1	1	?	1	?	?	?	0	4‡
Hetlevic 2000(23)	1034	Norway	public	cluster	0	0	?	0	0	?	1	0	?	1	1	3‡
Lafata 2002(19)	3309	USA	none	patient	1	1	1	1	0	1	1	1	1	1	0	8
Hirsch 2002(24)	109	USA	private	cluster	1	1	1	?	0	0	1	1	1	1	0	6
Meigs 2003(26)	598	USA	private	cluster	1	1	1	?	0	1	1	?	1	1	1	7
Ilag 2003(25)	284	USA	public	cluster	1	1	1	0	0	?	1	0	1	1	1	6
Glasgow 2005(11)	886	USA	public	cluster	1	1	1	0	0	0	1	1	1	1	1	7
Sequist 2005(27)	4549	USA	public	cluster	1	1	1	?	0	?	1	?	?	1	1	5
Phillips 2005(14)	4138	USA	public	cluster	1	1	1	1	0	?	1	?	1	1	1	7
Ziemer 2006(6)	4138	USA	public	cluster	1	1	1	1	0	?	1	?	1	1	1	7
Cho 2006(17)	80	Korea	public	patient	na	1	1	0	0	1	1	1	1	1	0	7
Bond 2007(15)	62	USA	public	patient	na	1	1	0	0	?	1	1	1	1	1	7
Grant 2008(22)	244	USA	public	cluster	0	0	1	0	0	?	1	1	1	1	0	5
Peterson 2008(16)	7101	USA	public	cluster	1	1	1	0	0	1	1	1	1	1	1	8
Cleveringa2008(21)	3391	Netherlands	private	cluster	1	1	1	0	0	1	1	1	1	1	1	8
Ralston 2009(20)	83	USA	private	patient	0	1	1	0	?	?	1	1	1	1	1	7

na: not applicable. *Randomized column 7 is 1 if patients were randomized, or when cluster randomization with Generalized Estimating Equation was used. †Total validity score column 17 is the sum of column 7 to 16. ‡Not meeting minimal validity score. Phillips(14) and Ziemer(6) same study with different outcome parameters.

Because Philips et al(14) and Ziemer et al(6) compared four groups: usual care, CDSS with reminders, CDSS with feedback on perform-

ance and CDSS with feedback on performance and reminders, these studies appear in three tables. Every time one intervention group is compared to the usual care control group.

Methodological Validity Assessment

In five trials patients were randomized(15;17-20), one of them also corrected for clustering(19). The other 11 trials had a cluster randomized design(6;11;13;14;16;21-27), and eight trials adjusted for clustering in the analysis(6;11;14;16;21;24-27). Ten trials reported a power calculation for a specified difference between groups and a specific outcome(6;11;14-16;20;21;23;25-27).

Positive scores on the methodological validity indicators blinding of patient, therapist and outcome assessor were poor, 24%, 6% and 29% respectively. On the two point methodological validity scale the mean score was 6.4 (SD: 1.4) with a range from three to eight. Two studies scored less than five points(13;23) and were excluded from the result analysis.(table 7.1)

CDSS alone (Table 7.2)

The studies either used a computerized decision support system or a web based diabetes management support system. Most CDSSs generate patient specific recommendations regarding lab tests or physical examinations that are due. Patient specific treatment and/or follow-up recommendations are given based on the information entered in the CDSS, according to treatment algorithms.

Table 7.2 Computerized Decision Support Systems

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes: Measures	Study outcomes: Results control vs. intervention	Study outcomes: P-value
Meigs, 2003(26)	598	12	Usual diabetes care	Web based decision support tool. The diabetes management application displays interactive patient-specific clinical data, treatment advice, and links to web-based care sources.	HbA1c (%)	0.14 vs –0.23	n.s.
					LDL-cholesterol (mg/dl)	-9.4 vs –14.7	n.s.
					Blood pressure		
					Systolic (mmHg)	-2.2 vs 0.8	0.03
					Diastolic (mmHg)	-0.8 vs –1.8	n.s.
					Process:		
					1 HbA1c test/year	-1.0 vs 1.6	n.s.
					1 LDL test/year	3.4 vs 7.2	n.s.
					1 blood pressure measurement/ year	-1.4 vs 1.0	n.s.
					Eye exam	1.7 vs 5.5	n.s.
					Foot exam	0.7 vs 9.8	0.003
Ilag, 2003(25)	174	12	Usual diabetes care	Annual diabetes assessment program. Results reviewed with patients, mailed to providers and incorporated into EMR with guideline – generated suggestions for treatment and follow-up.	HbA1c:		
					<7% (%)	30 vs 28	n.s.
					7.1% – 8.0% (%)	32 vs 32	n.s.
					8.1% – 10.0% (%)	30 vs 28	n.s.
					>10.1% (%)	8 vs 12	n.s.
					Blood pressure:		
					Systolic<135mmHg	58 vs 60	n.s.
					Diastolic <80mmHg	75 vs 77	n.s.
					LDL-cholesterol:		
					<2.5mmol/L	35 vs 48	n.s.
					2.5 – 3.3 mmol/L	34 vs 23	n.s.
					>3.3 mmol/L	31 vs 29	n.s.
					Process:		
					Increase mean sum of measures	0 vs 1.5	0.014

Table 7.2 Computerized Decision Support Systems (continued)

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes		
					Measures	Results control vs. intervention	P-value
Glasgow, 2005(11)	886	12	Computer Touch screen with print out focusing on general health risks	Computer touch screen assessment and action plan including a summary of assays/checks the patient might be due for and a copy of the patients self management plan	Process:		
					Lab procedures completed (n)	3.97 vs 4.29	0.001
					Blood pressure measurements (%)	99.7% vs 100%	n.s.
					Eye exam (%)	72.4% vs 77.2%	n.s.
					Foot exam (%)	83.7% vs 93.6%	n.s.
					Microalbumin measurements (%)	81.4% vs 91.3%	n.s.
					HbA1c≤9.5% (%)	97.4% vs 93.9%	n.s.
					Patient centered activities completed	3.32 vs 3.73	0.001
					HbA1c (%)	-0.13 vs –0.22	n.s.
					Total cholesterol/ HDL-cholesterol ratio	-0.23 vs –0.21	n.s.
Grant, 2008(22)	244	12	Usual diabetes care	Diabetes specific web based personal health record, providing patient-tailored decision support and enabling the patient to author a “diabetes care plan” for electronic submission to their physician prior to up-coming appointments.	HbA1c (%)	0.26 vs 0.16	n.s.
					HbA1c<7% (%)	25 vs 45	n.s.
					Medication adjustments (%)		
					DM-related	15 vs 53	<0.001
					Hyperglycemia	15 vs 29	n.s.
					Hypertension	0 vs 13	0.02
					hyperlipidemia	0 vs 11	0.03

Table 7.3 Computerized Decision Support Systems with Reminders

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes		
					Measures	Results control vs. intervention	P-value
Lafata, 2002(19)	3,309	12	Web based diabetes care management support system	Web based diabetes management support system and mailed patient reminder with tailored recommendations for actions to be taken by the patient, a self care handbook and a preventive care checklist	Process:		
					1 HbA1c test	OR 1.21	0.05
					2 HbA1c tests	OR 1.04	ns
					Retinal exam	OR 1.23	0.01
					Fasting lipid profile	OR 1.14	ns
					All 3 tests	OR 1.25	0.01
					HbA1c<8%	OR 1.14	ns
					HbA1c>9.5%	OR 0.83	0.01
					LDL<130mg/dl	OR 1.11	ns
Sequist, 2005(27)	4,549	6	Usual diabetes care	Evidence based electronic reminders within patients' EMR.	Process:		
					LDL testing	OR 1.41	<0.001
					ACE in hypertension	OR 1.42	ns
					Biennial HbA1c	OR 1.14	ns
					Eye exam	OR 1.38	ns
					Statin if LDL-cholesterol >130 mg/dl	OR 1.10	ns
					Composite	OR 1.3(1.01-1.67)	<0.05

Table 7.3 Computerized Decision Support Systems with Reminders (continued)

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes: Measures	Study outcomes: Results control vs. intervention	Study outcomes: P-value
Phillips 2005 IP-CAAD (14)*	4,138	36 average 15	Usual care	Hard copy computerized reminders that provided patient specific recommendations for management	HbA1c (%)	-0.16 vs –0.3	ns
					Systolic blood pressure (mmHg)	-2.4 vs 1.2	ns
					LDL-cholesterol (mg/dl)	-15 vs -15	ns
Ziemer, 2006 IP-CAAD (6)*	See Phillips 2005 (14)	See Phillips 2005 (14)	See Phillips 2005 (14)	See Phillips 2005 (14)	Process: treatment intensification when glucose level >8.3 mmol/L	41 vs 39	ns
					Any intensification of therapy (%)	24 vs 26	<0.02
					Intensification of therapy met recommendations (%)	10 vs 11.5	<0.02

*Same study population, same intervention, different outcome. The study compared four interventions. In this table the results of CDSS with reminders is compared to usual care.

Table 7.4: CDSS and Feedback on Performance

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes: Measures	Study outcomes: Results control vs. intervention	Study outcomes: P-value
Phillips 2005 IPCAAD (14)*	4,138	36 average 15	Usual care	Computerized patient specific recommendations for management and individual face-to-face feedback on performance on providers actions and patient specific outcome, for 5 minutes every 2 weeks	HbA1c (%)	-0.16 vs 0.4	ns
					Systolic blood pressure	-2.4 vs –3.2	ns
					LDL-cholesterol (mg/dl)	-15 vs -14	ns
Ziemer 2006 IPCAAD (6)*	See Phillips 2005 (14)	See Phillips 2005 (14)	See Phillips 2005 (14)	See Phillips 2005 (14)	Process: treatment intensification when glucose level > 8.3 mmol/L	42 vs 50	<0.001
					Any intensification of therapy (%)	28 vs 40	<0.005
					Intensification of therapy met re-commendations (%)	11 vs 17	<0.005

* Same study population, same intervention, different outcome. The study compared four interventions. In this table the results of CDSS with Feedback on Performance is compared to usual care.

Table 7.4: CDSS and Feedback on Performance (continued)

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes		
					Measures	Results control vs. intervention	P-value
Cho, 2006(17)	80	30	Conventional office visits	Internet based individual electronic chart system. Patients entered self monitored blood glucose levels, current medication, blood pressure, and weight. PCP, nurse or dietician sent treatment recommendations, education and patient feedback every 2 weeks. 3 monthly face-to-face visits.	HbA1c (%)	-0.1 vs –1.0	0.009
					Total-cholesterol (mmol/L)	-0.31 vs -0.14	ns
					HDL-cholesterol (mmol/L)	0.01 vs 0.08	ns

In web based diabetes management support systems, patients are able to upload their glucose measurements and they have access to their health record. This enables patients to participate in designing a patient specific diabetes care plan and patient self management is encouraged.

Improvements were found in the number of completed foot exams(26), an increase in the mean sum of measures(25), the number of completed lab tests and completed patient centered activities(11). The most recent study showed more medication adjustments(22). Improvements in patient outcome were not significant. In one study the systolic blood pressure increased significantly more in the intervention group.(26)

CDSS with reminders (table 7.3)

In one study improvements were found in yearly HbA1c testing, retinal exams, the composite of three tests and less patients having HbA1c>9.5%.(19) In another study LDL-testing and the composite of all process measures significantly improved.(27) CDSS with reminders compared to usual care showed no improvement in patient outcome, but in significantly more patients treatment had been adjusted when glucose levels exceeded 8.3 mmol/L.(6;14)

CDSS and feedback on performance (table 7.4)

Compared to conventional visits, CDSS and feedback on performance led to a significant improvement in HbA1c% in one study(17), but not in the other study(14). However, intensification of therapy signifi-

Table 7.5: CDSS with Case management or CDSS with Case management and Reminders

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes		
					Measures	Results control vs. intervention	P-value
Bond, 2007(15)	62	6	Usual diabetes care	Web based diabetes management intervention by nurse. Patients entered blood sugar readings, exercise programs, weight changes, blood pressure, and medication data. PCP retained full responsibility and control.	HbA1c (%)	-0.05% vs -0.62%	<0.01
					HDL-cholesterol (mg/dl)	-0.16 vs 6.4	<0.05
					Total-cholesterol (mg/dl)	-5.1 vs –11.4	<0.05
					Weight (pounds)	2.5 vs –4.5	<0.001
					Blood pressure:		
					Systolic (mmHg)	-1.0 vs –6.8	<0.01
					Diastolic (mmHg)	-2.5 vs –5.2	ns
Ralston, 2009(20)	83	12	Usual diabetes care	Case manager, computerized decision support, clinical reminders, ability to upload glucose data by web and viewing patients own health record. Active follow-up by health care provider	HbA1c (%)	0.2 vs -0.9	<0.01
					HbA1c<7% (%)	11 vs 33	0.03
					Outpatient visits	-2.1 vs 0.6	ns
					Primary care provider visits	-0.2 vs 0.0	ns
					Specialty physician visits	-1.9 vs 0.6	ns
					Inpatient days	-0.3 vs 0.2	ns

Table 7.6: CDSS, Reminders and Feedback on Performance

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes		
					Measures	Results control vs. intervention	P-value
Hurwitz, 1993(18)	209	24	Hospital diabetes clinic	Computerized prompting system. Reminders for lab testing and doctors visits. Clinical review feedback form	Mean HbA1c (%)	10.6 vs 10.0	ns
					Process:		
					Patients without doctors review (%)	15.2 vs 3.4	0.013
					Mean number HbA1c tests	0.9 vs 2.4	<0.001
Hirsch, 2002(24)	109	14	Usual diabetes care	Reminder system, staged diabetes management protocol, computerized feedback, didactic teaching	HbA1c (%)	0.64 vs-0.07	0.02
					Blood pressure:		
					Systolic (mmHg)	3.1 vs –1.2	ns
					Diastolic (mmHg)	-0.8 vs –3.7	ns

Table 7.6: CDSS, Reminders and Feedback on Performance (continued)

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes: Measures	Results control vs. intervention	P-value
Phillips 2005 IPCAAD (14)*	4,138	36 average 15	Usual care	Hard copy computerized reminders providing patient specific recommendations for diabetes management . Individual face-to-face feedback on performance on providers actions and patient specific outcome, for 5 minutes every 2 weeks	HbA1c (%)	-0.16 vs –0.56	0.01
					Systolic blood pressure (mmHg)	-2.4 vs –3.4	ns
					LDL-cholesterol (mg/dl)	-15 vs -18	ns
Ziemer 2006 IPCAAD (6)*	See Phillips 2005 (14)	See Phillips 2005 (14)	See Phillips 2005 (14)	See Phillips 2005 (14)	Process:		
					treatment intensification when glucose level > 8.3 mmol/L	42 vs 51	<0.001
					Any intensification of therapy (%)	28 vs 40	<0.005
					Intensification of therapy met re-commendations (%)	11 vs 17	<0.005

* Same study population, same intervention, different outcome. The study compared four interventions. In this table the results of CDSS with Feedback on Performance is compared to usual care.

Table 7.7: CDSS, Reminders, Feedback on Performance and Case Management

Author, year	Sample (n)	Duration (months)	Control	Intervention	Study outcomes		
					Measures	Results control vs. intervention	P-value
Peterson, 2008(16)	7,101	12	Usual diabetes care	Electronic diabetes patient registry providing patient specific decision support, visit reminders, audit and feedback monthly, site coordinator.	Process:		
					HbA1c tests	-5.3 vs 2.8	<0.001
					Blood pressure monitoring	2.1 vs 1.3	0.05
					LDL-cholesterol testing	0.3 vs 8.9	<0.001
					Eye exam	1.2 vs 27	<0.001
					Foot exam	-5.6 vs 29.4	<0.001
					Renal testing	-5.3 vs 23.2	<0.001
					Composite of above	0.22 vs 1.29	<0.001
					Composite of HbA1c <7.0%, Systolic blood pressure <130mmHg, LDL-cholesterol <100mg/dl	0.02 vs 0.17	0.002
Cleveringa 2008(21)	3,391	12	Usual diabetes care	Diabetes consultation hour run by a practice nurse, computerized decision support providing patient specific feedback, recall system and feedback on performance 3 monthly	HbA1c (%)	-0.1 vs –0.2	ns
					Blood pressure:		
					Systolic (SBP) (mmHg)	-2 vs –6	<0.05
					Diastolic (DBP) (mmHg)	0 vs –3	<0.05
					Total cholesterol (mmol/L)	-0.1 vs -0.4	<0.05
					LDL-cholesterol (mmol/L)	-0.2 vs –0.3	<0.05
					10 year UKPDS risk (%)*	-0.1 vs –1.9	<0.05
					Composite of: HbA1c<7%, SBP<140mmHg, LDL<2.5mmoml/L	2.5 vs 8.6	<0.05

*10 year UKPDS risk is the estimated risk on death from coronary heart disease calculated by using the UK prospective diabetes study risk engine

cantly improved.(6) In a multivariable analysis CDSS with feedback on performance independently facilitated attainment of American Diabetes Association goals for HbA1c (<7%) and systolic blood pressure (<130 mmHg) and also independently contributed to therapy intensification; therapy intensification contributed independently to a fall in HbA1c%.(6)

CDSS with Case management or Case management and Reminders (table 7.5)

In one study case management was added to a web based diabetes management intervention. The CDSS had the ability to upload blood glucose measurements, exercise programs, weight changes, blood pressure and medication data and was compared to usual care. Although only 62 patients were randomized this intervention led to significant improvements in HbA1c%, total cholesterol, HDL-cholesterol, weight and systolic blood pressure.(15)

In another study a CDSS was combined with reminders and case management as well. Blood glucose measurements could be uploaded and patients were able to view their own health record in this web-based CDSS. Both HbA1c% and the percentage of patients reaching HbA1c <7% improved significantly. No differences were found in PCP visits, specialist visits or inpatient days.(20)

CDSS with reminders and feedback on performance (table 7.6)

In three studies (four publications) CDSS was combined with reminders and feedback on performance. In two of them HbA1c% im-

proved(14;24), one showed improved treatment intensification.(6) The third did not result in improvements in HbA1c%, but both the percentage of patients who had no doctors review and the percentage of patients without HbA1c testing decreased significantly.(18)

CDSS with reminders, feedback on performance, and case management (table 7.7)

In two large cluster randomized trials all four interventions were combined. In both studies, the composite endpoint of HbA1c <7%, systolic blood pressure <130 mmHg and LDL-cholesterol <100 mg/dl(16) or the composite of HbA1c <7%, blood pressure <140 mmHg and LDL-cholesterol <2.5 mmol/L significantly improved.(21) One study showed improvements in 10-year UK Prospective Diabetes Study (UKPDS) coronary heart disease risk estimate.(21) The process of care significantly improved in the other study.(16)

Discussion

In this review we evaluated RCTs that studied the effectiveness of a CDSS alone or in combination with other supportive tools to improve the quality of primary type 2 diabetes care. In almost two out of three studies the CDSS was combined with reminder systems, feedback on performance or case management. CDSSs, with or without reminders are effective in improving the process of care. However improving patient outcome is only reported when feedback on performance and

case management are added to the CDSS. One multivariable analysis showed that CDSS combined with feedback on performance independently attributed to both the improvement in patient outcome and process of care. This multivariable analysis was performed in a large cluster randomized trial of good quality.(6;14) Adding reminders to feedback on performance does not have a meaningful effect on patient outcome or the process of care.(6;14;18;24) In two small patient randomized studies of good quality, web-based CDSS with case management improved patient outcome.(15;17) Although baseline HbA1c%, systolic blood pressure and LDL-cholesterol were already near to the treatment targets in two recent studies, suggesting that primary care physicians were already performing good diabetes care, it was nevertheless possible to show significant improvements in both process of care and patient outcome after one year.(16;21)

Comparison with other studies

Most of the results of this review are in accordance with earlier reviews. Information technology alone mainly improves the process of diabetes care.(7;8) Adding reminder systems to the CDSS may also only improve the process of care(6;14;19;27). Both interventions mainly facilitate structured diabetes care and regular patient review. However, improving the process of care is not equal to improving patient outcome.(28) In order to reduce diabetes related complications patient outcome will also have to be improved.(29-31)

Case managers can improve glycemic control, especially when they are allowed to make medication adjustments.(32) In the reviewed stu-

studies adding a case manager also improved patient outcome. Nurses, under PCP supervision, can provide routine chronic diabetes care just as good as PCPs can.(33) However, to overcome clinical inertia health care providers need to be focused on patients' problem areas to make treatment adjustments.(6) Nurses are trained in working according to protocols, and they have more time for patients.

A Cochrane review regarding audit and feedback reported positive effects in the process of care but not in patient outcome, but this review was hampered by inadequate reporting of study methods for almost all studies(34). In our review two studies combined feedback on performance with CDSS(6;14;17), three studies combined feedback on performance with CDSS and reminders(6;14;18;24) and two combined feedback on performance with CDSS, reminders and case management(16;21). All these studies showed improvements in both the process of care and patient outcome except the oldest one.(18) When also taking into account the above mentioned multivariable analysis of the Improving Primary Care of African Americans with Diabetes (IPCAAD) study(6), we conclude that the combination of CDSS and feedback on performance is probably an important tool to improve patient outcome in diabetes care.

Strengths and weaknesses

This is the first review on CDSS that focused on primary care type 2 diabetes management programs for health care providers. Because most CDSSs use multifaceted interventions, we separated the different combinations of interventions in order to find the combination of in-

terventions that is most likely to improve both process and outcome of diabetes care. This has never been done before.

The methodological quality of the studies was scored and only two studies scored less then five points. Of these two studies, one showed improvements in the process of care(13), while the other showed no improvements in the process of care nor in patient outcome (23). The scores for blinding of patients, therapists and outcome assessors were low, which may be caused by the complexity of these interventions which makes it very difficult to blind patients and therapists for the intervention.

Several sources for funding of these studies were found, including: national institutes of health, national library of medicine, professional organizations and private foundations. Most studies were however publicly funded, so competing interests will probably be low.

We only included published articles, all with some significant results. Because studies not showing a statistically significant superior effect of a CDSS may be less easily accepted for publication, a publication bias cannot be ruled out.

Because of the heterogeneity in interventions, the difference in combination of interventions and the differences in outcome measures, a meta analysis was not possible.

Since the follow-up period of most studies was only 1-year, it is not possible to asses the long term outcome of a CDSS with or without additional support. No effects were reported on mortality, micro- or macro-vascular complications. Future research will have to reveal the

long term effectiveness on diabetes outcome of these multifaceted computerized decision support interventions.

Our search strategy did not reveal any cost effectiveness studies regarding these information technology based primary diabetes care management systems. Although it is not a weakness of our study as such, this is an important shortcoming for policy makers, because they have to decide about implementing cost effective health care improvement programs.

Conclusion

Computerized decision support systems in managing primary type 2 diabetes care are effective in improving the process of care. Only combining CDSS with feedback on performance and/or case management may also improve patient outcome.

CDSS is just a tool to combine all relevant patient information in order to give adequate treatment recommendations based on the protocols and to provide feedback on performance. When this information is used by case managers or practice nurses both process of care and patient outcome may improve.(35) Future research on CDSS in diabetes care has to focus on long term disease outcome and cost effectiveness.

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Chapter 8

General Discussion

The studies and research questions in this thesis are all related to the Diabetes Care Protocol (DCP). Two studies evaluated the effectiveness of DCP on clinical patient outcome and process of care measures. Patient important outcomes like health status and satisfaction with care were also assessed and a cost effectiveness analysis was performed. Furthermore, we studied the relationship between erectile dysfunction and cardiovascular disease in type 2 diabetes. And finally, because Computerized Decision Support Systems (CDSS) are often combined with other interventions, we answered the remaining question whether CDSS alone or in combination with other interventions is more successful in improving both the process of care and patient outcome in diabetes care. In the following paragraphs the main study findings, implications for future diabetes care and suggestions for further research are presented.

DCP and clinical patient outcome

The quality of diabetes care can be measured by both the process of care and patient outcome. For type 2 diabetic patients, improving patient outcome is probably most important.

In two studies we performed on this matter (chapters 2 and 3) the process of care was quite good in all intervention and control groups, because the CDSS was used to get a complete dataset at baseline and after 12 months follow-up. The CDSS forced the practice nurse to enter all clinical information available. Only the more complex vari-

ables, such as history of cardiovascular disease, were poorly registered in the control group, because for completing this variable a thorough patient history was necessary. This might be caused by the fact that the trained practice nurses of Diagnosis for Health (manufacturer of DCP) performed the baseline annual diabetes check-up in the control practices. They were not familiar with the registered type 2 diabetes population and because they were not responsible for the follow-up, they might have been less motivated to enter these complex variables.

In the before-after study (chapter 2) we found significant improvements in all clinical variables and also in the percentage of patients meeting the treatment targets. The randomized controlled trial (chapter 3) confirmed these findings. However there was no significant reduction in HbA1c%, the primary endpoint of the trial. This was probably due to the HbA1c level at baseline, which was already near treatment target. In European countries, including the Netherlands, the mean HbA1c% in many populations with type 2 diabetes is near the 7% treatment target.(1;2) HbA1c% is mainly related to microvascular complications (neuropathy, nephropathy and retinopathy) while coronary heart disease is the main cause of death in diabetes.(3) Further reduction in HbA1c% does not have a significant effect on cardiovascular disease, but may cause more periods of hypoglycaemia.(4;5) Therefore interventions that aim to reduce HbA1c below 7% will probably not improve cardiovascular outcomes, unless on the very long run. They may even be harmful on the short term.

As recommended by the National Institute of Clinical Excellence(6), we calculated the 10 year United Kingdom Prospective Dia-

betes Study (UKPDS) coronary heart disease (CHD) risk estimate(7) and used this measurement as a measure of clinical care.(8) Because improvements in blood pressure and lipids levels are likely to improve microvascular as well as macrovascular complications, primary care physicians should not only focus on blood glucose, but on the total cardiovascular risk profile. By using cardiovascular risk calculations, the different clinical outcomes are combined in one outcome measure. The improvements in diabetes care as a result of the introduction of the Diabetes Care Protocol are clearly illustrated by the absolute 1.4% reduction in the 10year UKPDS CHD risk estimate.

Systems like DCP that delegate diabetes care to practice nurses and facilitate structured diabetes care, focusing on the total cardiovascular risk profile and provide feedback on performance are necessary in primary diabetes care, because primary care physicians are mainly glucose focused, and not on blood pressure and lipid levels.(9) In order to overcome clinical inertia and improve the quality of diabetes care, health care providers need feedback to focus them on patient's problem areas.

Using cardiovascular risk calculations also facilitates recognizing patients that have an increased risk for a cardiovascular event. Such a differentiation between patients at 'normal' risk and 'increased' risk might be important for diabetes health care providers, as we could demonstrate in our cost-effectiveness analysis (see below).

It is furthermore important to differentiate treatment between newly diagnosed type 2 diabetic patients and those who are already known with type 2 diabetes for more than about five years, because recent

trials suggest that early strict glycemic control is likely to be beneficial for many patients (10) but that setting a strict glycemic target is less relevant in people known with diabetes for more than five years, many of whom are suffering from diabetes related complications.(4;5)

For high risk patients and newly diagnosed type 2 diabetic patients a personalized diabetes treatment plan has to be made. Electronic patient management systems that routinely calculate cardiovascular risk and identify high risk patients or patients with less than 5 years diabetes help general practitioners to focus on patients in need for more strict diabetes treatment.

DCP and health status

When evaluating any intervention, one should consider both beneficial effects and negative side effects. The same applies to the evaluation of a multifaceted intervention like DCP which aims to improve guideline adherence and therefore intensifies treatment. Diabetes complications cause a considerable burden on health related quality of life(11) and preventing complications might improve health status. However, pursuing strict treatment targets might increase the disease burden. Thus, in the short term the disease burden might increase, while the effect on the disease burden by the prevention of complications can only be measured in the long term. It is therefore important to evaluate the effects of diabetes care interventions on patient-important outcomes, like health status, treatment satisfaction and perceived self-efficacy.

The latter may improve health status(12;13) and treatment adherence.(14;15)

For this study (chapter 4) we chose a non-inferiority design, because it is unlikely that the intervention would have a positive effect on the occurrence of diabetes complications after one year. For that reason we hypothesized that the DCP despite its more intensive diabetes care according to the Dutch guideline(16) compared to 'usual care' would not have a negative effect on patient-important outcomes. Indeed, intensified treatment in DCP did not have an overall negative effect on health status, although there might be some detrimental effects on disinhibited eating and social functioning. Disinhibited eating is reflected by the following questions: 'eating when feeling bored', 'difficult to say no to desirable food', 'wished not so many nice things to eat', 'not easy to stop eating' and 'eat to cheer yourself up'. Social functioning means interference with social activities like visiting friends or normal activities with the family. This negative effect on social functioning was also found after one year in screen detected type 2 diabetic patients in the Netherlands.(17) The negative effect on disinhibited eating and social functioning might have been caused by more frequently addressing diabetes health rules in people from the DCP group. Having diabetes has impact on everyday life and might give a sense of illness burden. On the other hand, DCP had a positive effect on the perceived change in overall health status, an effect that might have been caused by better continuity and more structured care in the DCP group.(18)

Intensified treatment in type 2 diabetic patients is necessary to prevent long-term diabetes complications. In a screen detected primary care type 2 diabetes population intensified treatment showed more distress and less self efficacy after one year. After three years there was no difference in psychological outcomes between intensively treated patients and patients treated according to usual care.(17;19) So health related quality of life is likely to be improved by intensive diabetes treatment in the long-term, because diabetes complications will be prevented. In the short term intensive treatment has no negative effects on health status and therefore primary care physicians should not be reluctant to reach the strict current guideline treatment targets for type 2 diabetic patients to whom these strict targets are relevant.

DCP and costs

We performed a cost effectiveness analysis with the 1-year follow-up data from the DCP trial. A modified Dutch micro-simulation diabetes model extrapolated the 1-year follow-up data and computed individual life-time, health related costs and health effects. (chapter 5)

In the long run DCP is more costly and leads to only slightly more quality adjusted life years (QALY) than usual care, but it does result in significantly lower coronary heart disease costs. Although there were no significant differences in HbA1c levels between the intervention and the control group after one year of follow-up, the increase in diabetes costs in the intervention group was mainly caused by an age-

related exponential increase in renal failure and amputation. The costs of DCP were low compared with the diabetes related costs. Even when DCP costs were not taken into account the program would still not be cost effective. In our opinion these findings are of utmost importance, as they may indicate that we have reached the limits in cost-effective type 2 diabetes care.

Just like the world wide positive trend in general therapeutic approach of type 2 diabetes, with more patients reaching the guideline treatment targets of HbA1c%, blood pressure and lipids(2), our trial also showed an average HbA1c% near treatment target at baseline. This means that a potential cost-effective outcome as a result of further blood glucose lowering will be more difficult to demonstrate. Earlier research already showed that reductions in HbA1c and cholesterol levels do in fact increase health care costs, while a reduction in blood pressure decreases costs.(20) DCP was however cost effective for patients with a history of cardiovascular disease. These patients have a three to four times increased risk for a second cardiovascular event(21) and can be considered high-risk patients, just like patients with micro-albuminuria or patients with high UKPDS CHD risk estimates. Intensive multifactorial treatment in high-risk patients, like facilitated by the DCP, has been proven to be cost-effective.(22)

We found that DCP improves UKPDS CHD risk estimates.(23) Because intensified diabetes treatment is not cost-effective for all patients, calculating cardiovascular risk in diabetes care management may help primary care physicians to focus on the high-risk patients. In these patients all cardiovascular risk factors have to be treated and not

just blood glucose levels. In future primary diabetes care calculating cardiovascular risk might become an important tool for primary care physicians to personalize and optimize care for different types of type 2 diabetic patients. DCP or other systems that can identify these patients and facilitate structured diabetes care may therefore become important tools in future diabetes care.

Erectile dysfunction and cardiovascular disease

Cardiovascular disease and diabetes are independently associated with erectile dysfunction (ED).(24) Some authors even state that patients presenting with ED should be screened for cardiovascular risk factors, including diabetes, even if they have no symptoms.(25) However, it is less clear whether routinely asking patients with type 2 diabetes about ED will identify patients with elevated risk for cardiovascular disease.

In most research the ED prevalence is based on questionnaires.(26) Their use is too elaborate for daily practice. However the routinely asked ‘single question ED prevalence’ is unknown. The simple single question “Do you have erectile problems?” embedded in the diabetes care protocol was used in the study described in chapter 6. The study showed an ED prevalence rate that was comparable to other studies.(27-30) Although discussing sexual functioning during a medical encounter appears to be difficult(31), 88% of the male patients answered the ED question asked by the female practice nurse. This high

percentage is caused by the binding structure of DCP, which forces the practices nurses to ask about ED.

In the literature an independent association between ED and both cardiovascular disease and diabetes has been reported.(32) In our study we found no independent association between ED and history of cardiovascular disease. In contrast to a lot of other studies, we were in the position to adjust for many relevant confounders. The most important confounders we found were age and medication. When ED is present, the cardiovascular risk is elevated, but this association disappears after correcting for age and medication. In type 2 diabetic men with ED, but without a history of cardiovascular disease, the 10-year UKPDS CHD risk estimate was elevated, but this effect was also confounded by age.

In general routinely asking for ED is important, because ED is a common complication of diabetes in men and ED has a negative effect on the quality of life(33), although ED is no indicator of elevated cardiovascular risk. Indeed just a single question on ED should routinely be asked by the primary care physician or the practice nurse. The main reason to ask for ED is to search for treatment options, for example by adjusting medication.

Successful CDSS interventions in diabetes management

Computerized decision support in primary type 2 diabetes care has often been combined with other interventions. The systematic review

(chapter 7) showed that CDSS alone only improves the process of care, while adding feedback on performance and/or case management also improves patient outcome. Improving patient outcome is however the most relevant quality measure for type 2 diabetes care.

Nurses, under physicians' supervision, can provide routine chronic diabetes care just as good as primary care physicians.(34) While physicians are trained in making the right diagnosis, nurses are trained in signalizing symptoms that do not fit in the normal disease pattern. Further nurses or case-managers are trained in working according to protocols and they have more time for patients. This may explain why case managers can perform diabetes care just as good as or even better than physicians.(35)

As shown in the review, feedback on performance is a very important tool to improve patient outcome. In order to overcome clinical inertia health care providers need to be focused on patients' targets to make treatment adjustments.(36) The quality frameworks with modest financial incentives in the UK also led to improvements in both the process of care and patient outcome.(37) In fact the primary care physicians were provided with feedback on performance and they focused on patients' treatment targets, in order to make treatment adjustments for which they were rewarded. One of the most important features in DCP is probably feedback on performance both at practice and patient level which was given every three months. This made both practice nurse and primary care physician aware of treatment targets and poorly controlled patients.

Feedback on performance might be the strongest incentive to change, because every physician wants to be a good doctor. The effectiveness of the financial reward is still under discussion, but it is certainly not the only motivation for physicians to change their behavior.(38)

With the introduction of diabetes care treatment groups and health care insurers demands for objective measures of good quality of care we do need intelligent information systems that can easily generate these quality of care measures. However we have to keep in mind that reaching treatment targets is just a small part of high quality diabetes care. Clinical inertia, patient-important outcomes, patient adherence and patient experience measures, that reflect the interaction between health care providers and patients, are also very important factors in measuring the quality of diabetes care. The holistic patient view is one of the most important features of primary care/general practice. Intelligent software protocols for chronic diseases are preferably incorporated in the electronic health records to preserve this holistic patient view and to prevent fragmentation of care for people with type 2 diabetes and co morbidities.

Unanswered questions

Both the diabetes care implementation study and the review could not answer the question whether a multifaceted intervention like the Diabetes Care Protocol will be effective on the long term. Long term fol-

low-up of an intensive multifactorial intervention showed improvements in mortality and morbidity of cardiovascular disease in high risk type 2 diabetic patients.(39;40) This intervention also proved to be cost-effective.(22) It is however doubtful whether this is also true for an unselected primary care type 2 diabetes population instead of an high risk diabetes population. Because the HbA1c level is near treatment target in the Netherlands(1), all multifaceted interventions including CDSS should emphasize the necessity of lowering blood pressure levels. This is illustrated by the mean systolic blood pressure in the Netherlands, which is about 143mmHg(1), while the average systolic blood pressure in VADT, ACCORD, and ADVANCE trials was 126mmHg, 127mmHg and 135mmHg respectively.(4;5;41)

The intensified multifactorial treatment in DCP did not have any substantial effect on health status after one year. Reductions in diabetes complications are likely to improve quality of life(42), but at this moment the effects of intensified multifactorial treatment on long-term quality of life are unclear.

Well designed long term follow-up studies in populations of unselected (for example the ADDITION-study(43)) as well as selected type 2 diabetes patients (for example the UMCU Smart cohort(44)) are urgently needed to answer the question about the limits of diabetes care. Whether we have reached the limits of cost-effective diabetes care, should be confirmed in more cost-effectiveness analyses in this field.

Conclusion

The Diabetes Care Protocol (DCP), a multifactorial intensified treatment with the help of a CDSS, recall and feedback on performance by a case manager improves the cardiovascular risk in type 2 diabetes patients in primary care. DCP has no substantial negative effects on health status, and it is cost effective in high risk diabetes patients. The main reason for this positive result is the combination of the CDSS with feedback on performance and case-management. In future diabetes care, and preferably also in a newer version of the DCP, high-risk patients should be identified simply by calculating their cardiovascular risk. The possibility offered by the DCP to ask men for erectile dysfunction proved to be feasible and very relevant.

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Summary

Summary

In the Netherlands approximately 740,000 patients are diagnosed with diabetes. By 2025 this number is likely to increase to 1.3 million. 90% of these patients have type 2 diabetes and 95% frequently contact a primary care physician.

A good practice organisation and task delegation are necessary to manage the care for all these patients. Calculations showed that current practice guidelines for only 10 chronic illnesses require more time than primary care physicians have available for patient care overall.

Cardiovascular disease is the most important complication in patients with diabetes. Strict control of glucose, lipids and blood pressure leads to reduction of micro- and macrovascular complications. These complications also cause a considerable burden on the health related quality of life. Unfortunately at least 30% of type diabetes patients do not meet the target for glycemic and cardiovascular control.

Evaluating interventions that aim to solve these diabetes care management problems is therefore important.

Against this background the Diabetes Care Protocol (DCP) has been developed for the care of type 2 diabetes patients in the primary care setting. DCP is a multifaceted diabetes care management intervention. It consists of a diabetes consultation hour run by a practice nurse, a computerized decision support system (CDSS) that contains a diagnostic and treatment algorithm based on the Dutch type 2 diabetes guidelines and provided patient-specific treatment advice, a recall

system and feedback on performance on both patient and practice level.

In this thesis the effectiveness of the DCP is evaluated. We looked for 1. the reduction of cardiovascular complications, 2. the effects on quality of life, and 3. the cost effectiveness. Further we investigated if ED could be found by using a simple question that was incorporated in the DCP, and if there was a relation between ED en elevated cardiovascular risk. The last question was which parts of multifaceted DCP intervention contribute to its effectiveness.

In chapter 2 the question about lowering the cardiovascular risk is answered in of a before-after study in 113 primary care practices (n = 7,893) across the Netherlands. The percentage of type 2 diabetes patients who achieved the treatment targets increased significantly, for HbA1c from 60,6% to 66,5%, For blood pressure from 48,7% to 61,9% and for total cholesterol from 47,4% to 60,6%.

Because several external factors could have influenced this result, a cluster randomised trial with 1-year follow-up was performed (chapter 3). In 55 primary care practices across the Netherlands, DCP was compared to usual diabetes care. The practices were not involved in other diabetes care improvement programs. In 26 practices DCP was implemented, the 29 control practices continued the same diabetes care that they had received before entering the study. All type 2 diabetic patients were identified , patients who had a short life expec-

tancy, were unable to visit the primary care practice, or were receiving diabetes treatment from a medical specialist were excluded. In total 3,391 patients were included, 1,692 intervention group and 1,699 control group.

Between March 2005 and August 2007, patients were each seen twice for annual diabetes checkups. Patients who did not show received one reminder. In the CDSS, age, sex, ethnicity, duration of diabetes, and smoking habits were registered.

At baseline mean HbA1c was 7.1% in the intervention group and 7.0% in the control group, meaning The type 2 diabetes guideline treatment target was almost met. This means there was little room for improvement. After 1-year the for clustering corrected between group difference (intervention – control) in HbA1c was 0.07% (n.s.). For systolic blood pressure this was 3.3 mmHg, for diastolic blood pressure 2.2 mmHg, for total cholesterol 0.2 mmol/L and for LDL-cholesterol 0.15mmol/L, all significant. The 1-year follow-up results were combined by calculating the 10-year UK prospective diabetes study coronary heart disease risk, this improved 1.4%. Significantly more patients reached the guideline treatment targets, but strikingly few patients reached all three treatment targets: 18.9%. We conclude that DCP did not improve HbA1c but reduced cardiovascular risk in type 2 diabetic patients.

Besides clinical outcome, quality of life and quality of care are also important outcomes. (chapter 4) Unfortunately lower HbA1c levels do not necessarily reflect how patients feel. Diabetes complications cause

a considerable burden on health related quality of life and preventing complications might improve health status. However, pursuing strict treatment targets might increase the disease burden. Because of the short follow-up of the cluster randomized trial, with probably no effect on complications and the possible negative effects of treatment intensification, we hypothesized that DCP is not inferior to usual care with respect to health status in the short term. A non-inferiority trial with questionnaires was performed to test this hypothesis.

Main outcome was the 1-year between group difference in Diabetes Health Profile (DHP-18) total score. Secondary outcomes: DHP-18 subscales, general perceived health (SF-36, Euroqol 5D/ EQ-VAS), treatment satisfaction (DTSQ-status) and psychosocial self-efficacy (DES-SF). Per protocol (PP) and intention-to-treat (ITT) analyses were performed: non-inferiority margin Δ=-2%. At baseline 2,333 questionnaires were returned and 1,437 one year thereafter. Comparing DCP to usual care, DHP-18 total score was non inferior: PP -0.88 (95%-CI: -1.94 to 0.12), ITT -0.439 (95%-CI: -1.01 to 0.08), SF-36 “Health change” improved: PP 3.51 (95%-CI: 1.23 to 5.82), ITT 1.91 (95%-CI: 0.62 to 3.23), SF-36 “Social functioning” was inconclusive: PP -1.57 (95%-CI: -4.3 to 0.72), ITT -1.031 (95%-CI: -2.52 to -0.25). Other DHP and SF-36 scores were inconsistent or non-inferior. DHP-18 “disinhibited eating” was significantly worse in PP analyses. For Euroqol-5D/ EQ-VAS, DTSQ and DES-SF no significant between group differences were found.

The intensified treatment in DCP did not have a negative effect on health status, although there might be detrimental effect on disinhi-

bited eating and social functioning. Both these effects may have been caused by more frequently addressing diabetes health rules in de the DCP group. This might have given a sense of illness burden. DCP had a positive effect on the perceived change in overall health status, an effect that may have been caused by better continuity and more structured care in the DCP group. The treatment satisfaction improved significantly in the intervention group, but there were no significant between group differences.

Information technology enabled diabetes management systems, like DCP, have the potential to save health care costs. Unfortunately most studies in this field do not include a cost effectiveness analysis. We therefore performed a cost effectiveness analysis with the one-year follow-up data from the DCP trial. (chapter 6) A modified Dutch micro-simulation diabetes model extrapolated the one-year follow-up data and computed individual life-time, health related costs and health effects. Incremental costs and effectiveness (quality-adjusted life-years [QALY]) were estimated using multivariate generalized estimating equations to correct for practice-level clustering and confounding. Incremental cost-effectiveness ratios (ICER) were calculated and cost-effectiveness acceptability curves were created. These calculations were performed for the total population, patients with a history of cardiovascular disease and patients without a history of cardiovascular disease.

DCP patients lived longer (0.14 life-years, P = ns), experienced more QALYs (0.037, P = ns) and incurred higher total costs (€1,415,

P = ns), resulting in an ICER of €38,243 per QALY gained. The likelihood of cost-effectiveness given a willingness-to-pay threshold of €20,000 per QALY gained is 30%. DCP had a more favourable effect on CVD+ patients (ICER = €14,814) than for CVD- patients (ICER = €121,285). Coronary heart disease costs were reduced (€-587, $p < 0.05$). DCP costs for 10-year were €316.

In a normal type 2 diabetes primary care population with an average HbA1c of about 7%, like in our study, the changes that diabetes care interventions are cost-effective are small, even with less costly interventions. In order to provide more cost-effective diabetes care primary care physicians should focus on high risk patients, for example by calculating 10-year UK Prospective Diabetes Study cardiovascular risks. CDSS, like the DCP, can easily identify high risk patients. This may help primary care physicians and practice nurses to provide need-differentiated personalized type 2 diabetes care.

Cardiovascular disease and diabetes are independently associated with erectile dysfunction (ED). Some authors even state that patients presenting with ED should be screened for cardiovascular risk factors including diabetes, even if they have no symptoms. Because discussing sexual functioning is often difficult, this question was embedded in the DCP and routinely asked. In chapter 6 we investigate the ED prevalence when this question was used. Further we assessed the cardiovascular risk of type 2 diabetic men with ED compared to type 2 diabetic men without ED.

For this cross-sectional study the baseline trial data were used. After a short introduction the nurse practitioner asked 1823 men: ‘do you have erection problems?’.

With this single question the ED prevalence was 41.3%. This prevalence was comparable to other studies using validated questionnaires (prevalence rates between 34% – 67%).

Age, medication and other known factors associated with ED and/or CVD were used in univariate analysis (odds ratio [OR], Student’s t-test and Mann-Whitney test). This revealed confounding variables used in the multivariable analysis. The association between ED and History of Cardiovascular Disease (HCVD) was assessed by logistic regression analysis. In patients with no HCVD we assessed the association between ED and 10-year UK Prospective Diabetes Study (UKPDS) coronary heart disease risk by linear regression analysis. There was no independent association between ED and HCVD [adjusted OR 1.2 (95% CI: 0.9 – 1.5)]. The 10-year UKPDS CHD risk difference between men with and without ED was 5.9% (95% CI: 3.2 – 8.7), but after adjustment for age this association disappeared. [adjusted risk difference 0.6% (95% CI:-1.5 – 2.7)]

ED is common in men with type 2 diabetes. The routinely asked question, do you have erection problems?, embedded in DCP can be used for identifying ED patients. There seems to be no relation between ED and history of cardiovascular disease nor between ED and 10-year UKPDS coronary heart disease risk. Most important confounders are age and medication. The main reason to ask for ED is to search for treatment options, for example by adjusting medication.

The remaining question is which intervention or combination of interventions is responsible for the success of the Diabetes Care Protocol? In chapter 7 this question was answered with a review of the literature. Primary care diabetes management interventions using a CDSS combined with or without other interventions, aiming to improve the process of care and/or patient outcome were included.

A systematic literature search, from January 1990 to March 2009, in Pubmed, Embase, the Cochrane database and consulting reference lists. RCTs in primary type 2 diabetes care were selected if the interventions consisted of a CDSS alone or combined with reminder system and/or feedback on performance and/or case management. The intervention had to be compared with usual care. Two reviewers independently abstracted data on methods, setting, CDSS intervention and patient characteristics, and outcomes.

16 RCTs met our inclusion criteria. In 10 studies the CDSS was combined with another intervention. Two studies scored less then five (range 0-10) quality points and were left out of the analysis. Four studies with a CDSS alone showed improvements of the process of care. CDSS with reminders improved the process of care (two studies). CDSS with feedback on performance and/or reminders, improved the process of care (one study) and patient outcome (two studies). In one study a multivariable analysis showed that feedback on performance improved both the process of care and patient outcome. CDSS with case management improved patient outcome, (two studies). CDSS with reminders, feedback on performance and case manage-

ment improved both patient outcome and the process of care (two studies).

Computerized decision support systems used by health care providers in primary type 2 diabetes care are only effective in improving the process of care; adding feedback on performance and/or case management may also improve patient outcome.

The main findings and conclusions of the studies in this thesis are discussed in chapter 8. The Diabetes Care Protocol (DCP), a multifactorial intensified treatment with the help of a CDSS, recall and feedback on performance by a case manager improves the cardiovascular risk in type 2 diabetes patients in primary care. DCP has no substantial negative effects on health status, and it is cost effective in high risk diabetes patients. The main reason for this positive result is the combination of the CDSS with feedback on performance and case-management. In order to improve diabetes care in a cost-effective way, high-risk patients should be identified simply by calculating their cardiovascular risk. Further reductions in HbA1c% below 7% are not cost-effective. The possibility offered by the DCP to ask men for erectile dysfunction proved to be feasible and very relevant.

With current demands for objective measures of good quality of care we do need intelligent information systems that can easily generate these quality of care measures. This thesis proves the value of DCP and gives opportunities for improving both the information system as well as primary diabetes care in a cost-effective manner.

Samenvatting

Samenvatting

In Nederland zijn naar schatting 740.000 patiënten met diabetes gediagnosticeerd. In 2025 is dit aantal vermoedelijk toegenomen tot 1,3 miljoen. Van de patiënten met diabetes heeft 90% type 2 diabetes en 95% heeft vanwege de diabetes regelmatig contact met de huisarts.

Dit grote aantal patiënten vraagt om een goede organisatie van de praktijk en het delegeren van routinetaken. Berekeningen hebben namelijk laten zien dat huisartsen die volledig conform alle richtlijnen voor chronische aandoeningen behandelen onvoldoende tijd overhouden voor andere noodzakelijke patiëntenzorg.

Hart- en vaatziekten zijn de belangrijkste complicatie voor patiënten met diabetes. Een goede controle van het glucosegehalte, de bloeddruk en de lipiden verlaagt de kans micro- en macrovasculaire complicaties. Deze complicaties hebben een grote invloed op de kwaliteit van leven. Helaas blijkt dat in alle Westerse landen en ook in Nederland zeker 30% van de patiënten met diabetes type 2 niet de in de richtlijnen behaalde streefwaarde voor het HbA1c% bereikt.

Onderzoek naar interventies die een mogelijke oplossing kunnen bieden voor deze diabetes management problemen is dus noodzakelijk.

Tegen deze achtergrond werd het Diabetes Zorg Protocol (DZP) ontwikkeld. In het DZP worden de volgende interventies met elkaar gecombineerd: 1. Routinematige aspecten van de diabeteszorg wordt gedelegeerd aan de praktijkondersteuner, die case-manager wordt; 2.

Beslissingsondersteunende software (computerised decision support system (CDSS)), gebaseerd op de NHG-standaard diabetes mellitus type 2, structureert de zorg en geeft adviezen waar mogelijk; 3. Een oproepsysteem ondersteunt de controlefrequentie van de mensen die onder controle van de huisarts en praktijkondersteuner staan; 4. Elke drie maanden krijgt de praktijk feedback op de mate waarin de doelstellingen van de cardiovasculaire risicofactoren (roken gestaakt, HbA1c ≤7%, bloeddruk ≤140mmHg, totaal cholesterol ≤4.5mmol/L, LDL-cholesterol ≤2.5mmol/L, BMI ≤27kg/m²) worden behaald op praktijk- en op patiëntniveau.

Dit proefschrift onderzoekt de effectiviteit van het DZP. Hierbij is gekeken naar: 1. verlaging van het risico op cardiovasculaire complicaties; 2. de invloed op de kwaliteit van leven; 3. de kosteneffectiviteit. Daarnaast hebben wij onderzocht of erectiele disfunctie (ED) met een eenvoudige vraag in het DZP opgespoord kan worden en of er een relatie is tussen ED en een verhoogd cardiovasculair risico. Als laatste hebben we een antwoord proberen te vinden op de vraag welke onderdelen van het DZP bijdragen aan de effectiviteit ervan.

In hoofdstuk 2 wordt de vraag naar het verlagen van het cardiovasculaire risico beantwoord door middel van een voor- na studie in 113 huisartspraktijken verspreid over Nederland die met het DZP zijn gaan werken. De gegevens van 7.893 patiënten met type 2 diabetes werden geanalyseerd. Het aantal patiënten dat de streefwaardes behaalde steeg significant; voor het HbA1c van 60,6% naar 66,5%, voor de bloed-

druk van 48,7% naar 61,9% en voor het totaal cholesterol van 47,4% naar 60,6%.

Omdat allerlei externe factoren de uitkomsten van deze studie beïnvloed zouden kunnen hebben werd dit resultaat getoetst door middel van een clustergerandomiseerd onderzoek (hoofdstuk 3). In 55 huisartspraktijken, verspreid over heel Nederland, hebben we het DZP vergeleken met gewone diabeteszorg. De praktijken mochten niet deelnemen aan andere programma's om diabeteszorg te verbeteren. In 26 praktijken werd het DZP geïmplementeerd en gedurende een jaar uitgevoerd. De overige 29 praktijken gingen verder met het geven van gewone diabeteszorg, zoals ze dat op dat moment gewend waren. Er werd een lijst opgesteld van alle patiënten met type 2 diabetes in een praktijk. Patiënten met een korte levensverwachting, patiënten die niet in staat waren om de praktijk te bezoeken en patiënten die onder behandeling van de specialist waren, werden van deelname uitgesloten. In totaal werden er 3391 patiënten in het onderzoek geïncludeerd, 1699 in de interventiegroep en 1692 in de controlegroep.

Tussen maart 2005 en augustus 2007 ondergingen alle patiënten zowel op baseline als na één jaar het jaarlijkse diabetesonderzoek door de praktijkondersteuner. Patiënten die niet verschenen kregen één herinneringsoproep. De patiëntengegevens, zoals leeftijd, geslacht, etnische achtergrond, voorgeschiedenis, roken, klinische diabetesparameters werden verzameld in het CDSS.

Bij aanvang van het onderzoek was het HbA1c 7.1% in de interventiegroep en 7.0% in de controlegroep, waarmee de in de NHG-

standaard opgenomen streefwaarde reeds benaderd werd. Er was dus weinig ruimte voor verbetering. Na één jaar was het voor clustering gecorrigeerde delta van de verschillen in HbA1c percentage tussen de interventie- en controlegroep 0.07%(niet significant). De bloeddruk, het totaal cholesterol en het LDL-cholesterol verbeterenden significant meer in de interventiegroep. De voor clustering gecorrigeerde delta van de verschillen bedroegen: systolische bloeddruk 3.3 mmHg, diastolische bloeddruk 2.2 mmHg, totaal cholesterol 0.2 mmol/L en LDL-cholesterol 0.15 mmol/L. Het 10-jaars cardiovasculaire risico van de patiënten, berekend met de United Kingdom Prospective Diabetes Study (UKPDS) risico formule, daalde in de interventiegroep van 22.5% naar 20.6% en in de controlegroep van 21.7% naar 21.6%. Na correctie voor clustering bedroeg het verschil tussen beide groepen 1,4%. Het gaat daarbij om een absoluut risicoverschil. Significant méér patiënten in de interventie groep behaalden alle behandeldoelen, het percentage steeg van 10.3% naar 18.9%, terwijl dit percentage in de controle groep van 10.9% naar 13.4% ging. Wij concludeerden dat invoering van het DZP geen verbetering gaf van het HbA1%, maar wel leidde tot een verbetering van het cardiovasculaire risico.

Naast de klinische uitkomsten zijn kwaliteit van leven en kwaliteit van zorg belangrijke uitkomstmaten (hoofdstuk 4). Een lager HbA1c, bloeddruk of totaal cholesterol betekent namelijk nog niet dat mensen zich ook daadwerkelijk beter gaan voelen. Micro- en macrovasculaire complicaties hebben daarentegen een negatieve invloed op de kwaliteit van leven. Dit betekent dat het voorkomen van deze complicaties

de kwaliteit van leven op de lange termijn positief zou kunnen beïnvloeden, maar het nastreven van behandeldoelen zou mogelijk de ziektelast kunnen vergroten en daarmee de kwaliteit van leven in negatieve zin kunnen beïnvloeden.

Omdat het clustergerandomiseerde onderzoek slechts één jaar duurde is het niet waarschijnlijk dat dit een aantoonbaar effect zal hebben op het voorkomen van diabetes complicaties. Het intensiveren van de behandeling kan echter na één jaar wel negatieve gevolgen hebben. De hypothese in dit onderzoek is daarom dat het DZP niet inferieur maar ook niet superieur is aan 'gewone diabeteszorg' met betrekking tot kwaliteit van leven na één jaar. Door middel van een 'non-inferiority' onderzoek met vragenlijsten is deze hypothese getoetst. We gebruikten de volgende vragenlijsten: Diabetes Health Profile (DHP-18), Short-From-36 (SF-36), Euroqol 5 Dimensions (EQ-5D/EQ-VAS), de Diabetes Treatment Satisfaction Questionnaire (DTSQ) en de Diabetes Empowerment Scale Short Form (DES-SF). Non-inferiority werd aangetoond als het tweezijdige 95% betrouwbaarheidsinterval (95%BI) volledig boven het tevoren bepaalde non-inferiority marge van Δ=-2% lag. Als de Δ=-2% marge in het 95%BI lag was het resultaat niet-conclusief. Indien de resultaten tussen de per-protocol analyse (PP) en de intention-to-treat analyse (ITT) verschilden, dan was het resultaat inconsistent.

In de interventiegroep werden geen substantieel slechtere uitkomsten gevonden met betrekking tot kwaliteit van leven. Het primaire eindpunt 'DHP-18 total score' was niet inferieur, PP -0.88 (95%BI: -1.94 naar 0.12) en ITT –0.44 (95%BI: -1.01 naar 0.08). De SF-36

'Health Change" verbeterde: PP 3.51 (95%BI: 1.23 tot 5.82), ITT 1.91 (95%BI: 0.62 tot 3.23). SF-36 "Social functioning" was niet conclusief: PP -1.57 (95%BI: -4.3 tot 0.72), ITT -1.031 (95%BI: -2.52 tot -0.25). Andere DHP en SF-36 scores waren inconsistent of non-inferieur. DHP-18 "disinhibited eating" (eetpatronen/eetgedrag) was significant slechter in de PP analyse. Voor de EQ-5D/EQ-VAS, DTSQ en DES-SF werden geen significante verschillen gevonden tussen de groepen.

De negatieve effecten op het sociaal functioneren en op de eetpatronen / het eetgedrag worden mogelijk verklaard doordat huisartsen en praktijkondersteuners dieetadviezen en leefstijlinterventies meer benadrukken in de interventiegroep. Het lijkt dan ook zinvol om bij het benadrukken van leefstijladviezen rekening te houden met deze negatieve effecten. De tevredenheid met de behandeling (DTSQ) was na een jaar significant verbeterd in de interventiegroep, maar er was geen significant verschil tussen beide groepen. Het DZP heeft dus geen negatieve invloed op de kwaliteit van leven.

Omdat het verbeteren van de zorg extra kosten met zich meebrengt beschrijven we in hoofdstuk 5 of het DZP een kosteneffectieve interventie is. In Nederland wordt een interventie als kosteneffectief beschouwd als de kosten per gewonnen levensjaar in goede gezondheid (Quality Adjusted Life Year (QALY)) de €20.000 niet overschrijden.

De 1-jaar follow-up patiëntgegevens van de beide 'armen' uit de clustergerandomiseerde trial werden geëxtrapoleerd, gebruik makend van een gemodificeerd Nederlands microsimulatie diabetes model. Dit

gevalideerde model simuleert het natuurlijke beloop van type 2 diabetes. Voor elke patiënt worden de levensverwachting en de daarmee samenhangende kosten en QALYs berekend. Het model houdt rekening met veroudering, toename van het HbA1c% en de toename van met de leeftijd samenhangende complicaties en risico's. De kosten van het DZP werden berekend over een periode van 10 jaar. Incrementele kosteneffectiviteit ratios (ICER) werden berekend en kosteneffectiviteit aanvaardbaarheidscurves werden gemaakt. In de analyse onderscheidden wij respectievelijk de totale populatie, patiënten met hart- en vaatziekten in de voorgeschiedenis en patiënten zonder hart- en vaatziekten in de voorgeschiedenis.

In de totale populatie leefden DZP patiënten 0.14 jaar (p = n.s.) langer, was er een toename van 0.037 QALYs (p = n.s.) en waren de kosten €1.415 (p = n.s.) hoger, resulterend in een ICER van €38.243. De kans op kosteneffectiviteit van het DZP was 30%. Het effect van het DZP was veel gunstiger in de groep patiënten met hart- en vaatziekten in de voorgeschiedenis, ICER € 14.814, dan in de groep patienten zonder hart- en vaatziekten in de voorgeschiedenis, ICER €121.285. De kosten voor coronaire ziekten worden weliswaar met €587 verlaagd, maar de aan diabetes gerelateerde kosten (met name nierfalen en amputaties) nemen met €1.698 toe. De kosten voor het DZP gedurende 10 jaar zijn €316.

In een gemiddelde diabetespopulatie in de huisartsenpraktijk, zoals in dit onderzoek met als uitgangspunt een HbA1c van 7%, is de kans dat diabeteszorg interventies kosteneffectief zijn klein, zelfs bij minder kostbare interventies. Om de kosteneffectiviteit te vergroten zullen

huisartsen zich moeten richten op patiënten met een verhoogd cardiovasculair risico, bijvoorbeeld door UK Prospective Diabetes Study risico's uit te rekenen. Software programma's, zoals het DZP, kunnen de hoogrisico patiënten eenvoudig identificeren, zodat huisartsen / praktijkondersteuners zorg op maat kunnen geven, waarbij niet alleen op het HbA1c gefocust wordt.

Cardiovasculaire ziekte en diabetes hangen onafhankelijk van elkaar samen met erectiele disfunctie (ED). Sommige auteurs beweren zelfs dat mensen die zich bij de huisarts presenteren met ED gescreend zouden moeten worden op cardiovasculaire risicofactoren inclusief diabetes, ook al hebben ze geen klachten. Aangezien het bespreken van seksuele problemen vaak moeilijk is, werd deze vraag als vast onderdeel in de software van het DZP opgenomen. In hoofdstuk 6 onderzoeken we wat de prevalentie van ED is wanneer deze vraag gesteld wordt. Daarnaast hebben we onderzocht wat het cardiovasculaire risico is van mannen met type 2 diabetes en ED in vergelijking met mannen met type 2 diabetes zonder ED.

Voor dit cross-sectionele onderzoek hebben we gebruik gemaakt van de baseline gegevens van de trial naar de effectiviteit van het DZP. De praktijkondersteuner vroeg na een korte inleiding aan 1823 mannen met type 2 diabetes; "Heeft u erectie-problemen? ".

Met bovengenoemde vraag blijkt het heel goed mogelijk om een goede voorspelling te geven van de prevalentie van ED. De één-vraag prevalentie van ED in de mannelijke eerstelijns type 2 diabetespopulatie is 41,3%. Dit komt overeen met andere studies die gebruik maak-

ten van gevalideerde ED vragenlijsten; de ED prevalentie ligt hierbij tussen de 34% en 67%.

Leeftijd, medicatie en andere bekende factoren (etniciteit, roken, alcoholgebruik, de duur van de diabetes, HbA1c, bloeddruk, cholesterol) die geassocieerd zijn met zowel diabetes als cardiovasculaire ziekten werden gebruikt in een univariate analyse. De aldus gevonden verstorende variabelen werden gebruikt in een multivariabele analyse. Er bestond geen onafhankelijke relatie tussen ED en een voorgeschiedenis met hart- en vaatziekten (OR 1.2; 95%BI: 0.9 tot 1.5). Het verschil in 10-jaars UKPDS coronaire ziekten risico tussen patiënten met en zonder ED was 5.9% (95%BI: 3.2 tot 8.7). Na correctie voor leeftijd was dit risico verschil 0.6% (95%BI: -1.5 tot 2.7). Leeftijd en medicatie (o.a. ACE-remmers, cholesterolverlagers en ß-blokkers) zijn de belangrijkste verstorende variabelen.

ED komt veel voor bij mannen met type 2 diabetes. De in het DZP opgenomen routinevraag: heeft u erectie problemen?, kan goed gebruikt worden om ED op te sporen. Er lijkt echter geen relatie te zijn tussen ED en een voorgeschiedenis met hart en vaatziekten en ook niet tussen ED en het 10-jaars UKPDS coronaire ziekten risico. De belangrijkste verstorende variabelen zijn leeftijd en medicatie. Routinematig vragen naar ED is belangrijk omdat bij ED de aandacht gericht kan worden op eventuele bijwerkingen van medicatie.

De resterende vraag is welke interventie of combinatie van interventies het succes van het DZP kan verklaren. Deze vraag wordt beantwoord in hoofdstuk 7 met een review van de literatuur met betrekking

tot de toepassing van CDSS alleen, of gecombineerd met andere interventies die het zorgproces (de wijze waarop de zorg geleverd wordt) of de klinische uitkomsten voor patiënten met type 2 diabetes in de eerste lijn verbeteren.

Het systematisch literatuuronderzoek besloeg de periode van januari 1990 tot maart 2009. De volgende databases werden doorzocht: Pubmed, Embase, Cochrane en de in de bestudeerde artikelen opgenomen referentielijsten. RCTs in eerstelijns type 2 diabeteszorg werden geselecteerd wanneer de interventie bestond uit een CDSS alleen, of gecombineerd met een oproepsysteem en/of feedback op het handelen en/of case management. De interventie moest vergeleken worden met de tot dan toe gebruikelijke diabeteszorg. Twee onderzoekers abstraheerden onafhankelijk van elkaar gegevens over de methode, onderzoekssetting, de CDSS interventie, patiëntkarakteristieken en resultaten. De methodologische validiteit werd gescoord, gebruik makend van de validiteit indicatoren van het Nederlandse Cochrane centrum.

Van de 16 geïncludeerde RCT's bleken 10 een gecombineerde interventie te hebben. Twee studies scoorden minder dan vijf kwaliteitspunten en werden buiten de analyse gelaten. CDSS met of zonder een oproep systeem kan het proces van de zorg verbeteren (zes studies). CDSS met feedback op het handelen en/of een oproep systeem verbeterde het zorgproces in één studie en in twee studies verbeterden de klinische uitkomsten voor patiënten. Een multivariate analyse in een onderzoek, waarin vier interventies met elkaar werden vergeleken (gewone zorg, CDSS en oproepsysteem, CDSS en feedback op het handelen, en CDSS met oproepsysteem en feedback op het handelen)

liet zien dat feedback op het handelen zowel het proces van de zorg als het HbA1c% verbeterde. Ook een CDSS in combinatie met case management verbeterde klinische uitkomsten (twee studies) en een CDSS met zowel een oproepsysteem, feedback op het handelen als case management verbeterde zowel het proces als de klinische uitkomsten voor patiënten (twee studies).

Wij concludeerden dat alleen het gebruik van een CDSS in de eerstelijns diabeteszorg uitsluitend het proces van de zorg verbetert. Door feedback op het handelen en/of case management toe te voegen aan een CDSS verbetert ook de klinische uitkomst van de zorg voor patiënten.

In hoofdstuk 8 houden we de belangrijkste conclusies van dit proefschrift nog eens tegen het licht. De multifactoriële geïntensiveerde behandeling (volgens de NHG-standaard) in het DZP, welke tot stand komt door het CDSS, het oproepsysteem, de feedback op het handelen en het inschakelen van een praktijkondersteuner als case-manager, verbetert het cardiovasculaire risico van patiënten met type 2 diabetes. Het DZP heeft op korte termijn geen substantiële negatieve effecten op de kwaliteit van het leven en door het verlagen van het risico op hart- en vaatziekten op langere termijn mogelijk een positieve invloed op de kwaliteit van leven. Het DZP is kosteneffectief voor patiënten met een voorgeschiedenis met hart- en vaatziekten. De belangrijkste reden voor dit positieve resultaat is de combinatie van het CDSS met case management en feedback op het handelen van de huisartsenpraktijk.

Om diabeteszorg in de toekomst op een kosteneffectieve manier verder te verbeteren, lijkt het identificeren van hoogrisico patiënten door het berekenen van het 10-jaars cardiovasculaire risico de meest eenvoudige methode. Het verder verlagen van het HbA1c% onder de zeven procent is niet kosteneffectief. De routinevraag, “heeft u erectie problemen?”, in het DZP, levert voor zover wij konden nagaan een betrouwbaar antwoord op en is relevant, bijvoorbeeld doordat de aandacht wordt gericht op erectiele disfunctie als bijwerking van medicatie die veel bij de behandeling van type 2 diabetes wordt gebruikt.

Met de toenemende roep om objectieve maten voor goede kwaliteit van zorg lijken intelligentie informatiesystemen haast onmisbaar. Dit onderzoek bewijst de waarde van het DZP en biedt handvatten om zowel het informatiesysteem als de eerstelijns diabeteszorg in Nederland nog verder te verbeteren op een kosteneffectieve manier.

List of Publications

List of Publications

(1) Cleveringa FG, Gorter KJ, Van den Donk M, Pijman PL, Rutten GE. Task delegation and computerized decision support reduce coronary heart disease risk factors in type 2 diabetes patients in primary care. Diabetes Technol Ther 2007 Oct;9(5):473-81.

(2) Cleveringa FG, Gorter KJ, Van den Donk M, Rutten GE. Combined task delegation, computerized decision support, and feedback improve cardiovascular risk for type 2 diabetic patients: a cluster randomized trial in primary care. Diabetes Care 2008 Dec;31(12):2273-5.

(3) Cleveringa FG, Meulenberg MG, Gorter KJ, Van den Donk M, Rutten GE. The association between erectile dysfunction and cardiovascular risk in men with Type 2 diabetes in primary care: it is a matter of age. J Diabetes Complications 2009 May; 23(3):153-159.

(4) Cleveringa FG, Welsing PM, van den Donk M, Gorter KJ, Niessen LW, Rutten GE, W.K. Redekop. Cost-effectiveness of the diabetes care protocol, a multifaceted computerized decision support diabetes management intervention that reduces cardiovascular risk. Diabetes Care 2010 Feb;33(2):258-63.

(5) Cleveringa FG, Minkman MH, Gorter KJ, Van den Donk M, Rutten GE. Diabetes care protocol: effects on patient-important outcomes. A cluster randomized non-inferiority trial in primary care. Accepted Diabetic Medicine 2010;27:DME-2009-00562.R1

Dankwoord

Dankwoord

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Curriculum Vitae

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Frits Cleveringa was born on February 9, 1970, in Groningen, the Netherlands. During his youth he lived in Bedum. He attended secondary school at the RSG Kamerlingh Onnes (Atheneum) in Groningen. He graduated in 1988 and went to medical school at the University of Groningen. He obtained is medical degree in 1995 and had to fulfil his military service as first lieutenant medical officer in Garderen. After this he worked as an intern at the department of cardiology in Hospital Centre Apeldoorn, internal medicine in the Deventer Hospital and psychiatry in Psychiatric Hospital st. Franciscushof in Raalte.

In 2000 he started vocational training at the University of Groningen, including training periods in the practices of Otto Westra (Bathmen) and Herman Suichies (Eefde). Thereafter he worked as locum tenens for several general practitioners. In 2003 he started as part-time general practitioner in The Hof van Blom in Hattem. In this year he also started to work part-time for the Julius Center for Health Sciences and Primary Care, University of Utrecht, were he completed this thesis.

Since 2007 he works as general practitioner in health centre Gezondheidshuis Stadshagen in Zwolle. He now has a fulltime practice and is discipline coordinator for the general practitioners.