EFFICIENT MONITORING OF TYPE 2 DIABETES IN PRIMARY CARE

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Efficient monitoring of type 2 diabetes in primary care

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Efficient monitoring of type 2 diabetes in primary care

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(met een samenvatting in het Nederlands)

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te Roosendaal en Nispen

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Submitted

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Accepted by Primary Care Diabetes

General introduction

Definition and prevalence of type 2 diabetes

Type 2 diabetes mellitus is a chronic, metabolic disease characterised by high blood glucose levels. The major risk factors for developing type 2 diabetes are: increasing age, gender, ethnicity, obesity, hypertension and family history of diabetes [1]. Usually diabetes remains unrecognised until the first symptoms (e.g. frequent urination, increased thirst and itching in the genital region) appear. However, due to the preceding persistent high blood glucose levels in the asymptomatic stage the body has already suffered damage before symptoms arise. On the long term, type 2 diabetes patients are at risk of developing retinopathy, foot problems, nerve damage, kidney disease and cardiovascular disease [2].

In 2007, 740,000 persons were diagnosed with diabetes in the Netherlands and this number is expected to increase to 1.3 million in 2025 [3]. Approximately 90% of these have type 2 diabetes. Worldwide there are 366 million people (8.3% of the adults) with type 2 diabetes and this number is expected to increase to 552 million (10% of the adults) by 2030 [2].

Because of the expected rise in the future, their healthcare facilities use will also increase. This will lead to an increased workload of healthcare professionals. It is therefore important to make diabetes care as efficient as possible, without compromising the quality of diabetes care.

Treatment of type 2 diabetes

To reduce the risk of complications and to maintain good health of diabetes patients, adequate and regular monitoring is important. From a biomedical point of view, this involves maintaining or achieving normal levels of blood glucose (glycated haemoglobin, HbA1c <53 mmol/mol), blood pressure (<140/80 mmHg) and cholesterol (total cholesterol <5.0 mmol/l) [4]. People who achieve all these three treatment targets are considered well-controlled.

According to the current Dutch guidelines, all type 2 diabetes patients should be monitored every three months. In 2010, approximately two out of three patients were monitored at least four times [5]. During each three-monthly visit blood pressure, blood glucose, body weight, smoking habits and lifestyle factors should be monitored. This is usually performed by the practice nurse. Once a year, HbA1c, lipid levels and kidney function should be measured in a laboratory; and feet and eyes checked for complications. The results are assessed by the general practitioner.

Monitoring frequency

Many of the recommendations within the guidelines are evidence-based, but this does not hold for the monitoring frequency. A randomised equivalence trial on the frequency of blood pressure monitoring among well-controlled hypertensive patients showed that the monitoring frequency could be halved without any negative outcomes for the patient [6]. This raised the question whether this could also be applied to well-controlled type 2 diabetes patients.

There is debate on the effect of the diabetes monitoring frequency on patient outcomes. To date, six studies have investigated this relationship. However, since two studied uncontrolled patients [7,8] and two others were set up to increase access to care [9,10], these results are not generalisable to well-controlled patients. Two observational studies showed that the number of visits was not related to glycaemic control, which suggests that less frequent monitoring could be possible [11,12]. However, a major limitation is that these studies were observational.

So far, there is no conclusive evidence about the optimal monitoring frequency per year to maintain sufficient cardiometabolic control in diabetes patients. With the EFFIcient MOnitoring of DIabetes (EFFIMODI) study we aim to provide conclusive evidence for the monitoring frequency in well-controlled type 2 diabetes patients. If the diabetes monitoring frequency in well-controlled type 2 diabetes patients could be reduced up to fifty percent without deteriorating the quality of care, this could reduce the patient burden and workload of healthcare providers and save direct medical costs.

Patients' preferences

In daily practice, the monitoring frequency is mostly determined by the physician [13-16], but the relevance of patients' preferences is increasingly acknowledged by healthcare professionals [17,18]. Especially in diabetes care this topic is highly relevant, since self-management of the patient is an important issue.

A study in type 2 diabetes patients showed that participatory decision-making resulted in a decreased HbA1c and LDL cholesterol by improved patient activation, which in turn resulted in a better medication adherence [19]. Because accounting for patient's preferences may positively influence patient outcomes, we propose that healthcare providers should involve patients' preferences more often in

diabetes care. Therefore, the EFFIMODI study was designed as a patient preference study to also include patients' preferences.

The EFFIMODI study

The *main objective* of the EFFIMODI study was to investigate whether six-monthly monitoring of well-controlled type 2 diabetes patients in primary care results in equivalent cardiometabolic control compared to three-monthly monitoring. Furthermore, the study aimed to provide a comprehensive overview of the effects of the monitoring frequency on many other aspects of diabetes care like costs, patients' preferences, patients' perceived health status and other biomedical outcomes. To facilitate implementation of six-monthly monitoring, if the results of the trial would justify to do so, we also considered patients' satisfaction and the experiences of the participating diabetes care providers.

The EFFIMODI study was *designed as a randomised controlled patient-preference equivalence trial.* Participants were asked if they strongly preferred three-monthly or six-monthly diabetes monitoring. Only if they did not have a strong preference, they were randomised to a three-monthly or six-monthly monitoring group. If patients preferred either three-monthly or six-monthly monitoring, they were treated according to their preference. This resulted into four study groups (see ***Figure 1***).

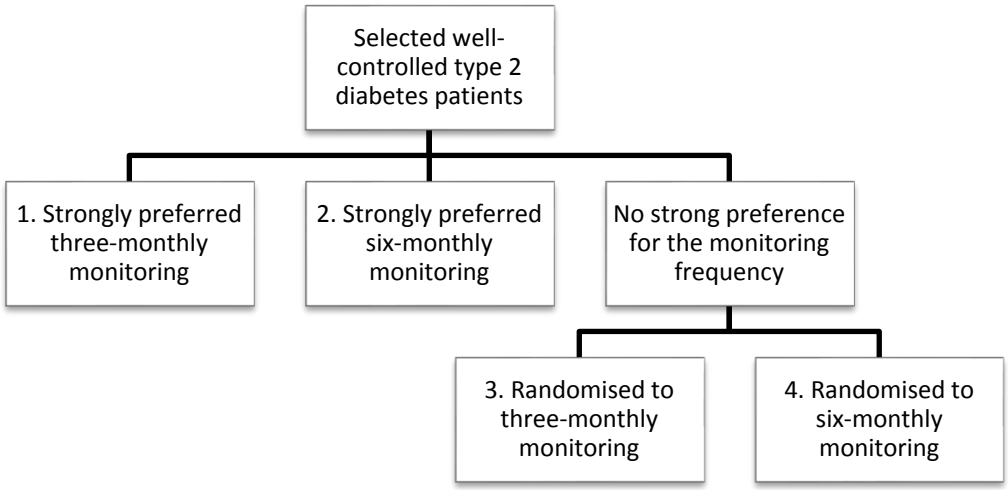

Figure 1 - Study flowchart of the patients, which resulted in four study groups

The *primary outcome* of the study was the percentage of people that remained under good cardiometabolic control, defined as: HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l after a period of eighteen months of either a three-monthly or a six-monthly monitoring frequency.

Outline of this thesis

In the **first chapter**, the design and methods of the EFFIMODI study have been described. Chapters two and three describe two analyses of the baseline data of the study. **Chapter 2** reports the preferences of well-controlled diabetes patients regarding their monitoring frequency. Furthermore, the patients' characteristics which were associated with their preference is described. The relation between the number and type (cardiovascular and non-cardiovascular) of comorbidities and health status is investigated in **chapter 3**.

Chapters four and five describe the main outcomes of the study. **Chapter 4** presents the results of the randomised equivalence trial. Here is described whether six-monthly monitoring resulted in equivalent cardiometabolic control compared to three-monthly monitoring and whether the monitoring frequency affected other outcomes such as smoking, physical activity, health status, diabetes-related distress, satisfaction with diabetes treatment and medication use. Furthermore, this chapter describes the economic evaluation of three-monthly versus six-monthly monitoring, accounting for both the outcomes and costs of the randomised equivalence trial. **Chapter 5** describes the relation between the monitoring frequency and cardiometabolic control and all other outcomes of the study among patients with a baseline preference for either three-monthly or six-monthly monitoring. In this chapter, we also describe whether having a specific preference for monitoring frequency affected the results in comparison to those in patients without such a preference and thus were randomised.

Chapters six and seven describe the opinions of the patients and the primary diabetes care providers regarding the monitoring frequency. **Chapter 6** studies how satisfied the patients were with their monitoring frequency and which patients were more satisfied. Furthermore, this chapter describes how often the patients want to be monitored in the future. In **chapter 7**, the participating healthcare providers indicate how they experienced six-monthly monitoring, whether they want to continue six-monthly monitoring and for which type of patients they think six-monthly monitoring is sufficient.

Finally, in the **general discussion**, we comment on all chapters of this thesis and present a comprehensive discussion on the monitoring frequency for type 2 diabetes patients.

Chapter 1

Design of the EFFIMODI study

PR Wermeling, M van den Donk, KJ Gorter, GA de Wit, Y van der Graaf, GEHM Rutten

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Abstract

Background: Scientific evidence for the frequency of monitoring type 2 diabetes patients is lacking. If three-monthly monitoring in general practice could be reduced to six-monthly monitoring in some patients, this would on the one hand reduce the use of medical services including involvement of practice nurses, and thus reduce costs, and on the other hand alleviate the burden of people with type 2 diabetes. The goal of this study is to make primary diabetes care as efficient as possible for patients and healthcare providers. Therefore, we want to determine whether six-monthly monitoring of well-controlled type 2 diabetes patients in primary care leads to equivalent cardiometabolic control compared to the generally recommended three-monthly monitoring.

Methods and design: The study is a randomised controlled patient-preference equivalence trial. Participants are asked if they prefer three-monthly (usual care) or six-monthly diabetes monitoring. If they do not have a preference, they are randomised to a three-monthly or six-monthly monitoring group. Patients are eligible for the study if they are between 40 and 80 years old, diagnosed with type 2 diabetes more than one year ago, treated by a general practitioner, not on insulin treatment, and with HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. The intervention group (six-monthly monitoring) will receive the same treatment with the same treatment targets as the control group (three-monthly monitoring). The intervention period will last one and a half year. After the intervention, the three-monthly and six-monthly monitoring groups are compared on equivalence of cardiometabolic control. Secondary outcome measures are HbA1c, blood pressure, cholesterol level, Body Mass Index, smoking behaviour, physical activity, loss of work due to illness, health status, diabetes-related distress, satisfaction with treatment and adherence to medications. We will use intention-to-treat analysis with repeated measures. For outcomes that have only baseline and final measurements, we will use ANCOVA. Depending on the results, a cost-minimisation analysis or an incremental cost-effectiveness analysis will be done.

Discussion: This study will provide valuable information on the most efficient monitoring frequency of well-controlled type 2 diabetes patients in primary care.

Background

At the end of 2007 more than 660.000 people were diagnosed with type 2 diabetes in the Netherlands [3]. The number of type 2 diabetes patients is still increasing [3], and also their use of healthcare facilities. Furthermore, the overall workload of general practitioners is increasing [20].

The current guideline on type 2 diabetes in primary care in the Netherlands advises to monitor type 2 diabetes patients four times a year [4], but this advice is not evidence-based. Three quarterly visits are done by the practice nurse and the general practitioner is advised to perform the annual check-up. Comparing 15 diabetes guidelines in 13 countries, the advised frequency of monitoring HbA1c ranged from one to four times a year and monitoring blood pressure ranged from one to six times a year [21]. It is obvious that the workload for healthcare professionals will differ significantly, depending on the guideline that is followed.

A retrospective, observational study in Spain demonstrated that the improvement in glycaemic control over time in patients with type 2 diabetes in general practice was not related to the number of visits to the general practitioner, but to changes in treatment [12]. More evidence on the desired frequency of type 2 diabetes monitoring in general practice is lacking.

A randomised equivalence trial in Canada compared blood pressure control, adherence to treatment and patient satisfaction in patients with treated hypertension followed up by their family physicians every three or six months. Patients with follow-up every six months achieved the same levels of blood pressure control, adherence to treatment and patient satisfaction compared to patients with follow-up every three months [6].

If, in accordance with the hypertension example, the contact time with the diabetes team in well-controlled type 2 diabetes patients could also be reduced up to 50% without deteriorating their quality of care, this could reduce the patient burden as well as induce savings on direct medical costs and relieve the workload of practice nurses.

Therefore we designed the EFFIcient MOnitoring of DIabetes (EFFIMODI) study, aiming to make primary diabetes care as efficient as possible for patients and healthcare providers. We hypothesise that six-monthly monitoring of well-controlled patients with type 2 diabetes in primary care results in equivalent cardiometabolic control as the currently recommended three-monthly monitoring, with less costs.

Methods and design

Study design

The study has been designed as a randomised controlled patient-preference equivalence trial. In practice this design means that participants are asked if they prefer three-monthly (usual care) or six-monthly diabetes monitoring. If they do not have a preference, they are randomised to a three-monthly or six-monthly monitoring group. This will result into four study groups (see ***Figure 1***).

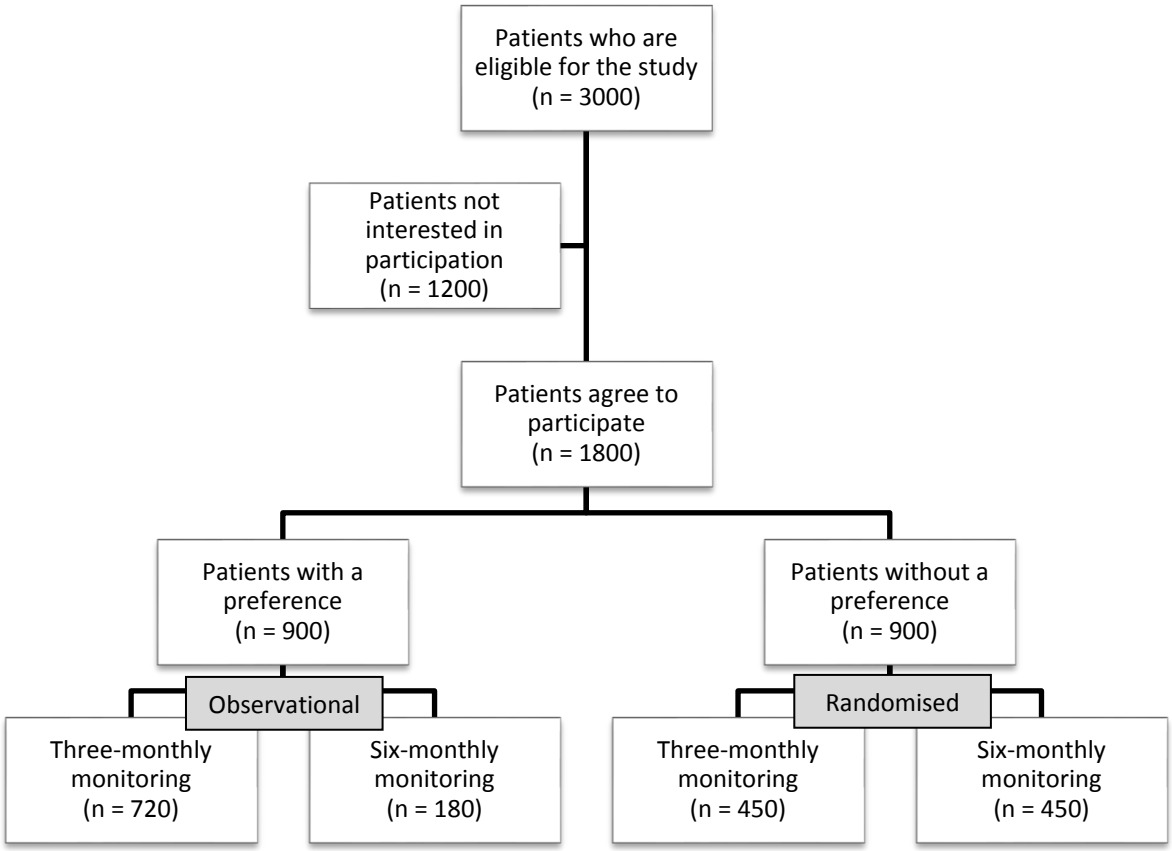

Figure 1 - Participant flowchart
The participant flowchart with the expected number of patients, based on a small survey.

We chose to conduct a patient-preference study because of two reasons [22]. First, it gives us the possibility to compare the relationship between patients' preference for a frequency of diabetes monitoring and the study outcomes. Second, more people will participate in the study, as people can choose not to be randomised; they can be included in the so-called 'observational' study arm of their choice. Doing so, we will have information about people who are not randomised and this will help in generalising the results. In conducting a patient-preference study we will avoid selection and probably also drop-out after randomisation.

We chose to conduct an equivalence trial, because we want to assess whether six-monthly monitoring results in equal cardiometabolic control compared to the current frequency of control [23]. Since we expect that six-monthly monitoring will not give better cardiometabolic control than three-monthly monitoring, we did not choose a non-inferiority trial. The intervention period will last one and a half year, so patients will be seen either seven or four times during the intervention period.

The Medical Research Ethics Committee of the University Medical Center Utrecht has approved the study protocol (Protocol number: 08-453).

Study population

Patients are eligible for the study if they are between 40 and 80 years old, diagnosed with type 2 diabetes for more than a year, treated by their general practitioner, not on insulin treatment and overall well-controlled, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. These HbA1c, systolic blood pressure and total cholesterol values are a little higher than the Dutch target values (HbA1c ≤53 mmol/mol, systolic blood pressure ≤140 mmHg and total cholesterol ≤4.5 mmol/l [4]). We decided to choose more liberal values to create a larger target population to be randomised. According to the stricter target values only 18.9% of all type 2 diabetes patients fulfilled these values [24]. Because of the minimal difference with the target values, we assume that 20% of the type 2 diabetes patients will fulfil the inclusion criteria.

Recruitment of practices and patients

We will approach the boards of several care groups to recruit general practitioners. These care groups have a central database in which all type 2 diabetes patients are recorded. In this database all determinants that are needed for the selection of study patients are included (see **study population** for the inclusion criteria). The care groups will ask all their affiliated general practitioners to participate in the study. If a general practitioner wants to participate he will obtain the selection of patients, according to the inclusion criteria, from the care group. The general practitioner sends an information letter as well as an informed consent form to the selected patients.

Patients who want to participate have to fill in the informed consent form. The participants are asked whether they strongly prefer three-monthly (current care) or six-monthly diabetes monitoring or whether they have no preference. Patients

with a preference will enter the 'observational arm'. If participants do not have a strong preference for the frequency of care, they will be randomised.

Randomisation and blinding

Participants without a preference for either three-monthly or six-monthly monitoring are randomised into one of the two randomised study arms in a 1:1 ratio: a control group that will receive current care, comprising diabetes monitoring once per three months, and an intervention group that will receive diabetes monitoring once per six months. In both randomised groups the extensive annual check-up will be done by the general practitioner. The treatment targets, therapeutic algorithms and lifestyle advices will remain unchanged and do not differ between the intervention and control groups.

Randomisation is generated at the patient level by a computerised random-number generator at the Julius Center. Participants are randomised before baseline data are collected. Since this is a pragmatic trial, it is not necessary to blind participants and general practitioners for the treatment allocation. However, the laboratory technicians who measure HbA1c and cholesterol are not aware of study participation of the patients.

Outcomes

The primary outcome measure is the percentage of people that remains under good cardiometabolic control, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. Secondary outcome measures are HbA1c, blood pressure, cholesterol, Body Mass Index, fasting blood glucose, smoking behaviour, physical activity, loss of work due to illness, health status, diabetes-related distress, satisfaction with treatment and adherence to medications. These outcomes are collected either from the medical records or from a patient questionnaire.

Medical records

Biomarkers (HbA1c, cholesterol, fasting blood glucose) and anthropometric variables (blood pressure, Body Mass Index) will be collected from the general practitioners' computerised information system. Information on the most recently measurements of the biomarkers and anthropometric variables before the study, medical history, medication use before the study and all measurements performed during the first EFFIMODI visit will be collected just after the start of the study. All

measurements during the follow-up period will be collected after the end of the follow-up period. The same applies to the number of diabetes and non-diabetes related visits to the general practitioner and (differences in) medication use during the study.

Questionnaires

The participants will be asked to complete an extensive questionnaire before (t=0) and after (t=18 months) the intervention period. This questionnaire comprises general background information on age, gender, ethnicity, education, smoking, physical activity, occupation and loss of work due to illness, health status, diabetes-related distress and satisfaction with diabetes treatment.

Current smoking is measured as the number of cigarettes per day or the number of cigars per week. Smoking in the past is measured the same way. Also the number of pack years is recorded. Physical activity is measured with the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [25]. The SQUASH is a reliable and valid questionnaire to measure the level of physical activity in an adult population. The questionnaire was designed to give an indication of the habitual activity level. Information on light (range: 2–4 Metabolic Equivalent of Task (MET)), moderate (range: 4–6.5 MET) and vigorous (>6.5 MET) intensity physical activities will be obtained. Physical activity will be expressed in minutes per week and in a total activity score. The total activity score will be calculated by multiplying the minutes per week by the actual MET score of the specific activity (MET/min/week).

Occupation and loss of work due to illness are measured with the Short Form Health and Labour Questionnaire (SF-HLQ) [26]. The SF-HLQ consists of three parts: absenteeism from paid work, production losses without absenteeism from paid work and hindrance in the performance of paid and unpaid work. Data derived with this questionnaire will be used to calculate costs of productivity losses, should incremental cost-effectiveness be merited at closure of the trial (see **economic evaluation**).

Two questionnaires are used to measure health status: Short-Form 36 (SF-36) [27] and EQ-5D [28]. The SF-36 generates a profile of scores on eight dimensions of health. These dimensions are: (1) physical functioning; (2) limitations due to physical difficulties (physical role functioning); (3) bodily pain; (4) social functioning; (5) mental health; (6) limitations due to emotional difficulties (emotional role functioning); (7) vitality; and (8) general health perception. For all

eight dimensions an average score for all items in the scale is calculated, with a range from 0 (least favourable health state) to 100 (most favourable health state). Two summary scales for mental and physical functioning can be calculated as well. The SF-36 is validated in the Dutch population [29].

The EQ-5D is a generic questionnaire, consisting of a Visual Analogue Scale (EQ-5D VAS) and a classification system (EQ-5D Profile) [28]. The EQ-5D Profile covers five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of functioning: level 1, no problems; level 2, some problems; level 3, severe problems. The EQ-5D VAS is a graded, vertical line, anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). The patient is asked to mark a point on the EQ-5D VAS that best reflects his/her actual health state.

To measure diabetes-related distress, the Problem Areas In Diabetes (PAID) questionnaire is used [30]. This is a widely recognised measure of diabetes distress, assessing the general emotional burden of diabetes and distress related to treatment, food choices and social support. The 20 items are scored on a 5-point scale yielding a sum score (0-80), with higher scores representing higher distress. The Dutch PAID scale has good convergent and discriminate validity and high internal consistency [31].

To measure satisfaction with diabetes treatment, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) is used [32]. The DTSQ measures satisfaction with treatment regimen (six items), perceived frequency of hyperglycaemia (one item) and perceived frequency of hypoglycaemia (one item) over the past few weeks. The treatment satisfaction score can range from 0 (very dissatisfied) to 36 (very satisfied).

Economic evaluation

To be able to calculate direct healthcare costs, data on healthcare use are needed. Data concerning consultations beyond the planned monitoring consultations, medication use and referral rates to other healthcare professionals will be collected from the general practitioners' computerised information system. Should this trial provide evidence that three-monthly monitoring results in better outcomes than six-monthly monitoring, an incremental cost-effectiveness analysis becomes warranted, that quantifies the additional cost related to the additional health effects. For such an economic evaluation we will use data on healthcare use as recorded in the information system of the general practitioners, and data

recorded with the SF-HLQ and the EQ-5D (see above). The EQ-5D is of special importance, as utilities, and consequently, quality adjusted life years (QALYs) can be elicited using this generic questionnaire.

Sample size calculation

The sample size is calculated on the assumption of equivalence of cardiometabolic control. Therefore, we used the formula from Jones et al. [23]: $n=(2p(100-p)*(Z_{(1-\alpha)}+Z_{(1-\beta)})^2)/\delta^2$, where p is the overall percentage of successes to be expected if the treatments are equivalent, δ indicates the range of equivalence for the difference in percentage success rates, α is the probability of type I error and β the probability of type II error.

We assume equivalence if the two-sided 95% confidence interval (α=0.05; $Z_{(1-\alpha)}$=1.96) for the difference in cardiometabolic control between the two intervention groups is completely in the range from -5 to 5% (δ=5). With a supposed overall percentage of success of 95% and a power of 90% (β=0.1; $Z_{(1-\beta)}$=1.28), we need a sample size of 399 people per randomised group. Based on a small survey that was performed by the Julius Center, we assume that ~50% of the people have no preference and thus will be randomised. About the other half of the people is assumed to have a strong preference for the frequency of monitoring. Therefore, we need to include 1596 patients: 798 in the randomised arms and 798 in the observational arms.

As said earlier in the **study population** section, we assume that 20% of the type 2 diabetes patients will fulfil the inclusion criteria. With an average of 80 type 2 diabetes patients per practice, we expect that sixteen patients in each general practice will meet the eligibility criteria. Taking into account a response rate of 60%, ten patients in each practice will be willing to participate in the study: five in the observational arm and five in the randomised arm, so at least 160 general practitioners will have to be recruited. As people may drop out during the study, we will recruit 1800 patients allowing an 11% drop-out; therefore we need 180 general practitioners. ***Figure 1*** shows the participant flowchart with the expected numbers.

Analysis

We will use repeated measures analysis for all recorded measurements of HbA1c, blood pressure, cholesterol and fasting blood glucose to optimally use all available data. Data from the questionnaires at the start and at the end of the intervention

period will be analysed using ANCOVA. Data will be analysed according to intention-to-treat. For handling missing data we will use multiple imputation [33]. After the intervention, the randomised three-monthly and six-monthly monitoring groups are compared on equivalence of cardiometabolic control.

Since this trial is a patient preference study, we will also compare the three-monthly preference group with the three-monthly randomised group. Depending on the number of patients opting for the six-monthly controls, we will compare this group with the six-monthly randomised group. In these analyses, we will examine determinants of preference, and we will determine risk profiles of patients. This will facilitate the applicability of the results and we can demonstrate if people who are more motivated will have better cardiometabolic control. ***Figure 2*** provides an overview of all comparisons that will be made between the groups.

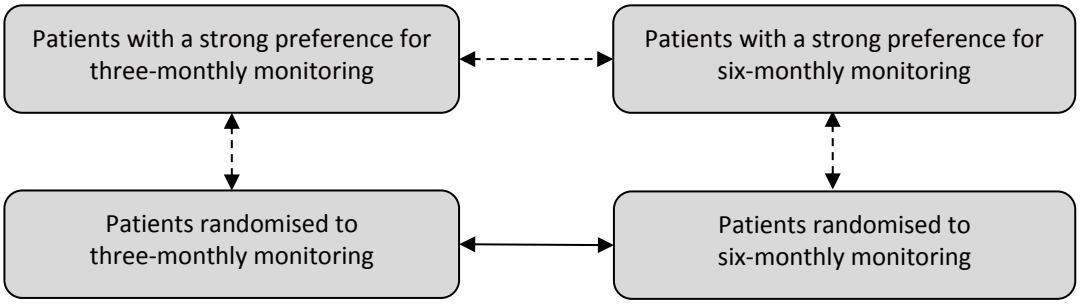

Figure 2 - Group comparisons
An overview of all comparisons that will be made between the four groups. The solid arrow is the comparison to answer the main research question. The dotted arrows are other comparisons that will be made.

Economic evaluation

Should this study demonstrate equivalent outcomes with different frequencies of diabetes monitoring, the evident cost-reduction of less monitoring visits merit the conclusion that six-monthly monitoring is the approach of first choice and a cost-minimisation analysis will be done. This is likely to provide sufficient evidence to change the frequency of monitoring in well-controlled type 2 diabetes patients in general practice.

However, should the three-monthly monitoring scheme result in a better cardiometabolic control, a cost-effectiveness analysis will be performed. If better outcomes can be realised with a higher monitoring frequency at an associated higher cost to society, or vice versa, (somewhat) worse patient outcomes at a lower cost, the balance between costs and outcomes is of interest. Differences in the number of QALYs between groups during the study period will be assessed.

The difference in treatment effect will be calculated as follows: for each group the difference between baseline and final measurements in percentage of patients with good cardiometabolic control will be determined. The absolute difference between measurements pre- and post-intervention will be taken as the intervention effect. Accordingly, differences in QALYs between groups will be calculated. The 'incremental cost-effectiveness ratio' (ICER) will be expressed as cost differences between groups divided by differences in treatment effects between groups. Confidence intervals will be determined using bootstrapping [34]. A 'cost-effectiveness acceptability curve' (CEAC) will also be drawn using the bootstrap sample. Cost-utility estimates will be derived accordingly, using QALY differences between groups as outcome measure.

Discussion

If the results of this study will show that equivalent cardiometabolic control is achieved following six-monthly diabetes monitoring in a sub-sample of generally well-controlled people with type 2 diabetes in general practice as compared to the usual three-monthly diabetes monitoring, their diabetes monitoring frequency can be reduced. This will reduce the use of medical services and direct healthcare costs, alleviate the burden of a substantial part of the people with type 2 diabetes and relieve the workload of diabetes nurses. If three-monthly monitoring turns out to result in a better regulation of diabetes, a cost-effectiveness analysis is necessary to estimate whether the higher costs of three-monthly monitoring balance the better patient outcomes.

The results of this study will provide valuable information for healthcare professionals and policy makers on cost-effectiveness of diabetes monitoring. In the case of proven cost-effectiveness, we will recommend implementing a lower monitoring frequency for well-controlled type 2 diabetes patients.

Chapter 2

Patients' preferences and frequency of diabetes monitoring

PR Wermeling, M van den Donk, KJ Gorter, JWJ Beulens, GEHM Rutten

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Abstract

Objective: To describe the preferences and the associated patients' characteristics of well-controlled type 2 diabetes patients for the diabetes monitoring frequency in primary care.

Methods: Cross-sectional study with 233 participating general practitioners across the Netherlands. Eligible patients were between 40 and 80 years, diagnosed with type 2 diabetes for more than one year, not on insulin, and with HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. Participants were asked whether they had a preference for three-monthly or six-monthly monitoring or no preference.

Results: From 2215 patients, 747 patients (33.7%) preferred three-monthly and 677 (30.6%) six-monthly monitoring by either the general practitioner or the practice nurse. The former group consisted of less smokers, felt less healthy, reported more diabetes-related distress, had the highest reported frequency of hyperglycaemic episodes and used more oral blood glucose lowering drugs compared to the other patients. Those preferring six-monthly monitoring were least satisfied with diabetes treatment, reported the lowest frequency of hyperglycaemic episodes and used less oral blood glucose lowering drugs compared to the other patients.

Conclusion: A preference for more frequent monitoring was associated with a worse disease status, whereas a preference for less frequent monitoring tended to be associated with the opposite. Patients seem to have logical preferences that need to be accounted for in diabetes care.

Introduction

One of the cornerstones of diabetes care is the regular monitoring of patients. Most guidelines on type 2 diabetes advise to monitor type 2 diabetes patients four times a year [4,35,36], but they are not consistent. Comparing diabetes guidelines in 17 countries, the advised frequency of monitoring HbA1c ranged from one to four times a year and the advised blood pressure monitoring frequency ranged from one to six times a year [21,37]. Moreover, this advice is not evidence-based and the preference of the patient is not taken into account. The current Canadian guidelines recommend that HbA1c should be measured every three months when glycaemic targets are not met or when medication is adjusted [36]. In adults with treatment and lifestyle stability measuring HbA1c may be considered every six months. Neither patient's preference nor the blood pressure or cholesterol are considered of interest with regard to the monitoring frequency.

Nowadays, the relevance of patients' preferences is increasingly acknowledged by diabetes healthcare professionals [17,18], although implementation of "shared decision-making" is proceeding slowly. A review on the effectiveness of shared decision-making showed that shared decision-making may lead to improvement in patient satisfaction, treatment adherence, quality of life and well-being, although the results are inconclusive and none of the included studies were performed in diabetes populations [38]. However, it seems that especially for chronic diseases shared decision-making seems effective [38], suggesting it would be highly relevant for diabetes patients. A study in type 2 diabetes patients indeed showed that participatory decision making resulted in a decreased HbA1c and LDL cholesterol by improved patient activation, which again resulted in a better medication adherence [19]. Therefore, we propose that healthcare providers should involve patients' preferences more often in diabetes care.

To our knowledge, no research has been performed on patient preferences in the frequency of diabetes monitoring. This study will investigate whether well-controlled patients have a preference for either three-monthly monitoring or six-monthly monitoring and which patients' characteristics are associated with this preference. This study was part of a so-called randomised controlled patient-preference equivalence trial which examines whether six-monthly monitoring of well-controlled type 2 diabetes patients leads to equivalent cardiometabolic control compared to the generally recommended three-monthly monitoring (**Chapter 1**). From this trial we used the baseline data to fulfil our research aim.

Methods

Patients were recruited in general practices across the Netherlands in the period from April 2009 to August 2010. Patients were eligible for the study if they were between 40 and 80 years old, diagnosed with type 2 diabetes for more than one year, treated by their general practitioner, not on insulin treatment and overall well-controlled. This was defined by having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. These cut-off values were a little higher than the Dutch target values, namely HbA1c ≤53 mmol/mol, systolic blood pressure ≤140 mmHg and total cholesterol ≤4.5 mmol/l [4]. We decided to use more liberal values to create a larger target population, because only 18.9% of the diabetes patients meet all three treatment targets [24,39]. Because of the minimal differences between our inclusion values and the Dutch target values, we assumed that approximately 20% of the type 2 diabetes patients would fulfil the inclusion criteria.

According to the current Dutch guidelines, patients with type 2 diabetes should be monitored three times per year by the practice nurse (including blood glucose, blood pressure, weight, lifestyle and medication) and once a year an extensive yearly visit should be performed by the general practitioner (including the same as mentioned and also complications, comorbidities and 'living with diabetes') [4]. Neither patient's preference nor cardiometabolic status has to be taken into account. From all diabetes patients treated in primary care (85% of all type 2 diabetes patients), about two thirds was monitored at least four times in 2010 [5].

The boards of several regional care groups were asked to recruit general practitioners. These groups hold a central database with data of all type 2 diabetes patients, thus enabling the selection of eligible patients. If a general practitioner was willing to participate, the patient selection of the practice was obtained according to the inclusion criteria from the care group. All selected patients were contacted by mail by their general practitioner with an information letter and an informed consent form. The study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht (protocol number 08-453).

Measures

To determine the patient's preference for the monitoring frequency, participants were asked to mark one of three boxes on the informed consent form. These boxes stated: (1) I have a strong preference for three-monthly monitoring, (2) I have a strong preference for six-monthly monitoring and (3) I have no strong

preference for the monitoring frequency. After returning the informed consent form, participants received a postal questionnaire to complete at their homes and return to the investigators. If patients failed to return the questionnaire, they received a reminder twice. The patient questionnaire consisted of information on age, gender, ethnicity, education, smoking, living status, physical activity, working status, health status, diabetes-related distress and satisfaction with diabetes treatment.

Ethnicity was classified according to the Statistics Netherlands definition [40] and divided into Dutch and non-Dutch. No distinction was made between western and non-western ethnicities, because of the low numbers of non-Dutch patients. Educational level was divided into three categories: low (primary school and lower vocational education), middle (intermediate general secondary education and intermediate vocational education) and high (higher general secondary education, higher vocational education and university education). Smoking was divided into never smoker, ex-smoker and current smoker. Living status was divided into living alone or living with other(s).

Physical activity was assessed using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [25], which calculates the minutes of physical activity per week per intensity level (light, moderate and vigorous). We defined physically active as meeting the recommended guideline of at least 30 minutes of moderately intensive physical activity on at least five days a week.

Working status was determined by a question of the Short Form Health and Labour Questionnaire (SF-HLQ), and defined as having a paid job, keeping house, being retired, being a student, having no paid job because of health problems and doing no paid work because of other reasons [26]. We recoded this question into: having a paid job, being retired or other.

The Short-Form 36 (SF-36) [27] and EuroQol (EQ) [28] were used to measure health status. The SF-36 generates two component scores for physical and mental functioning: the Physical Component Score (PCS) and the Mental Component Score (MCS). Both scores range from 0 (least favourable health state) to 100 (most favourable health state).

The EuroQol consists of two parts: the EQ-5D and the EQ VAS [28]. The EQ-5D covers five domains of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of functioning: level 1, no problems; level 2, some problems; level 3, severe problems. We used a Dutch

valuation study to recode these questions into a value between -0.329 and 1, where 0 means death [41]. The EQ VAS is a graded, vertical line, anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). The patient is asked to mark a point on the EQ VAS that best reflects his/her actual health state.

To measure diabetes-related distress, we used the Problem Areas In Diabetes (PAID) questionnaire [30]. The 20 items are scored on a 5-point scale (0-4) yielding a sum score (0-80), with higher scores representing higher distress.

To measure satisfaction with diabetes treatment, the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) was used [32]. The DTSQ measures satisfaction with the treatment regimen (six items), perceived frequency of hyperglycaemia (one item) and perceived frequency of hypoglycaemia (one item) over the past few weeks. The treatment satisfaction score ranges from 0 (very dissatisfied) to 36 (very satisfied) and the perceived frequency of hyper- and hypoglycaemia score from 0 (never) to 6 (very often).

Furthermore, anthropometric and biochemical measures were collected by a case report form filled in by the general practitioner or practice nurse. For weight (kg), HbA1c (mmol/mol), systolic and diastolic blood pressure (mmHg), HDL and LDL cholesterol (mmol/l) the last known measurement before informed consent was reported. Medication use (type and dosage of oral blood glucose lowering drugs, antihypertensive drugs and lipid lowering drugs) was assessed by current use. Height (cm), year of diabetes diagnosis and medical history (myocardial infarction, angina pectoris, heart surgery, heart failure, stroke, transient ischemic attack, peripheral arterial disease, COPD, rheumatoid arthritis and osteoarthritis of hip or knee) were also determined. Based on this information the BMI (kg/m^2) and duration of diabetes (years) could be calculated. Furthermore, patients were categorised into those with no, one and more than one comorbidities. Every specific condition was counted as one comorbidity, except stroke and transient ischemic attack.

Statistical analysis

Data from the patient questionnaires and the medical records were used to investigate which patient characteristics were associated with patients' preferences for the frequency of diabetes monitoring. Descriptive statistics were used to describe the characteristics of the total population and the three

'preference groups'. Categorical variables were expressed as percentages and continuous variables as means with standard deviations (SD).

For handling missing data we used multiple imputation [33]. We assumed that the missing data were missing at random and we generated 10 imputed datasets. Before multiple imputation, we tested if patients with either a missing patient questionnaire or missing medical data were comparable to patients with complete data for age and gender, for HbA1c and duration of diabetes if the questionnaire was missing and for education and ethnicity if medical data were missing. Continuous variables were compared with the independent samples t-test for normally distributed variables and the Mann-Whitney test if they were not normally distributed. The chi-square test was used for categorical variables. In case of significant differences ($p<0.05$) we did not impute data for the questionnaire and/or medical data, but only analysed patients with both a patient questionnaire and medical data.

After multiple imputation, univariable logistic regression was done in each imputed dataset to compare the different patient groups: three-monthly versus six-monthly, three-monthly versus no preference and six-monthly versus no preference. Rubin's rules were used to combine the estimates of the parameters [33]. Then we used three multivariable logistic models to determine which patients' characteristics were independently associated with their preference. We first put all variables that were mentioned in the measures section in to the model and then used the stepwise selection method using the Akaike's information criterion (AIC). At every step we selected the model with the lowest AIC and continued with this model. We considered a p-value of <0.05 as statistically significant. All variables are expressed as odds ratios (ORs) and their corresponding 95% confidence interval (CI). Data were analysed with SPSS version 17 and R version 2.10.

Results

From 107 different practices, 233 general practitioners participated in the study. Of these general practitioners 24 held a solo practice and the others were located within a duo or group practice. The average number of patients per general practice was 4860 (range: 1200-13,601) and the average number of diabetes patients was 222 (range: 27-548). On average 21 patients were included per practice with a range from 2 to 70. Of 4040 patients invited to participate, 2215 (54.8%) agreed.

The participants had a mean age of 64 years (SD=9), 59% were male and the mean duration of diabetes was 6 years (SD=4). 747 patients (33.7%) had a preference for three-monthly monitoring, 677 (30.6%) for six-monthly monitoring and 791 (35.7%) had no preference. 2114 patients (95.4%) filled in the questionnaire and of 2182 patients (98.5%) medical data were available (***Table 1***). Five patients missed both questionnaire and medical data and were therefore excluded.

The maximum number of missing values on an item was less than 15% (SF-36 PCS and SF-36 MCS). Furthermore, non-response analysis showed that patients without a questionnaire or medical data were comparable to patients with both a questionnaire and medical data and missing data were therefore imputed.

In univariable analyses, patients preferring three-monthly monitoring scored lower on three different health status measures and reported more diabetes-related distress compared to the other two groups. Patients preferring three-monthly monitoring also smoked less (14%) than those preferring six-monthly monitoring (21%) and those without preference (19%). Perceived frequency of hyperglycaemic episodes and use of oral blood glucose lowering drugs (70%) were lowest among patients preferring six-monthly monitoring and highest for those preferring three-monthly monitoring (83%).

Multivariable analyses showed that the three-monthly preference group compared with the six-monthly preference group consisted of less current smokers, had a lower EQ VAS score, reported more diabetes-related distress, were more satisfied with diabetes treatment, perceived more hyperglycaemias and used more oral blood glucose lowering drugs (***Table 2***). Also in comparison to the no preference group the three-monthly group consisted of less current smokers, had a lower EQ VAS score, reported more diabetes-related distress, perceived more hyperglycaemias and used more oral blood glucose lowering drugs. Compared to people with no preference, the six-monthly preference group was less satisfied with the diabetes treatment, perceived less hyperglycaemias and used less oral blood glucose lowering drugs.

Table 1 - Characteristics of participants for the total group and per preference group

	Total		Preferred three-monthly monitoring		Preferred six-monthly monitoring		No preference for monitoring frequency	
	N	mean ± SD or n (%)	n	mean ± SD or n (%)	n	mean ± SD or n (%)	n	mean ± SD or n (%)
Age (years)	2210	64.4 ± 8.8	745	64.6 ± 8.8	676	64.1 ± 8.7	789	64.5 ± 8.8
Gender (male)	2209	1311 (59.3%)	745	437 (58.7%)	676	404 (59.8%)	788	470 (59.6%)
Dutch ethnicity	2100	1877 (89.4%)	684	600 (87.7%)	655	591 (90.2%)	761	686 (90.1%)
Educational level	1938		629		608		701	
Low		798 (41.2%)		270 (42.9%)		233 (38.3%)		295 (42.1%)
Middle		709 (36.6%)		224 (35.6%)		239 (39.3%)		246 (35.1%)
High		431 (22.2%)		135 (21.5%)		136 (22.4%)		160 (22.8%)
Duration of diabetes in years	2127	5.8 ± 3.7	719	6.0 ± 3.8	648	5.8 ± 3.6	760	5.7 ± 3.7
Smoking	2103		689		652		762	
Never smoker		608 (28.9%)		218 (31.6%)		175 (26.8%)		215 (28.2%)
Ex-smoker		1118 (53.2%)		372 (54.0%)		340 (52.1%)		406 (53.3%)
Current smoker		377 (17.9%)		99 (14.4%)		137 (21.0%)		141 (18.5%)
Living alone	2080	408 (19.6%)	682	135 (19.8%)	646	116 (18.0%)	752	157 (20.9%)
Working status	2071		670		648		753	
Paid job		539 (26.0%)		172 (25.7%)		175 (27.0%)		192 (25.5%)
Retired		1138 (54.9%)		371 (55.4%)		350 (54.0%)		417 (55.4%)
Other		394 (19.0%)		127 (19.0%)		123 (19.0%)		144 (19.1%)
Physically active	2010	1427 (71.0%)	650	460 (70.8%)	632	453 (71.7%)	728	514 (70.6%)
SF-36 PCS	1893	46.6 ± 10.2	615	44.9 ± 10.3	598	47.6 ± 9.9	680	47.1 ± 10.2
SF-36 MCS	1893	54.0 ± 8.6	615	53.4 ± 9.2	598	54.5 ± 8.4	680	54.2 ± 8.3
EQ-5D	2049	0.86 ± 0.18	666	0.83 ± 0.19	641	0.87 ± 0.17	742	0.86 ± 0.17
EQ VAS	1984	76.3 ± 14.6	638	74.0 ± 14.4	628	77.6 ± 15.0	718	77.3 ± 14.2
PAID	2012	6.9 ± 9.1	653	9.1 ± 10.5	631	5.7 ± 7.8	728	5.8 ± 8.3
DTSQ status	2053	32.2 ± 4.3	673	31.8 ± 4.4	638	32.0 ± 4.4	742	32.6 ± 3.9
DTSQ hyper	2085	1.2 ± 1.6	676	1.7 ± 1.8	652	0.8 ± 1.4	757	1.1 ± 1.5
DTSQ hypo	2087	0.8 ± 1.3	681	1.0 ± 1.5	650	0.6 ± 1.2	756	0.8 ± 1.3

Table 1 - continued

	Total		Preferred three-monthly monitoring		Preferred six-monthly monitoring		No preference for monitoring frequency	
	N	mean ± SD or n (%)	n	mean ± SD or n (%)	n	mean ± SD or n (%)	n	mean ± SD or n (%)
Anthropometric and biochemical measurements								
BMI (kg/m^2)	2134	29.3 ± 4.8	725	29.2 ± 4.7	649	29.1 ± 4.6	760	29.6 ± 4.9
HbA1c (mmol/mol)	2142	46 ± 6	722	48 ± 6	657	46 ± 6	763	46 ± 6
Systolic blood pressure (mmHg)	2169	132 ± 14	734	132 ± 14	659	132 ± 14	776	132 ± 13
Diastolic blood pressure (mmHg)	2168	77 ± 9	733	77 ± 9	659	77 ± 9	776	77 ± 8
HDL cholesterol (mmol/l)	2134	1.2 ± 0.4	718	1.2 ± 0.4	650	1.2 ± 0.3	766	1.2 ± 0.3
LDL cholesterol (mmol/l)	2134	2.3 ± 0.6	718	2.3 ± 0.6	651	2.3 ± 0.7	765	2.3 ± 0.6
Co-morbidity	2182		736		665		781	
No comorbidity		1350 (61.9%)		439 (59.6%)		435 (65.4%)		476 (60.9%)
One comorbidity		539 (24.7%)		196 (26.6%)		147 (22.1%)		196 (25.1%)
More than one comorbidity		293 (13.5%)		101 (12.7%)		83 (12.5%)		109 (13.9%)
Medication use								
Oral blood glucose lowering drugs	2182	1659 (76.0%)	736	607 (82.5%)	665	462 (69.5%)	781	590 (75.5%)
Antihypertensive drugs	2182	1572 (72.0%)	736	544 (73.9%)	665	469 (70.5%)	781	559 (71.6%)
Lipid lowering drugs	2182	1765 (80.9%)	736	612 (83.2%)	665	516 (77.6%)	781	637 (81.6%)

SD, standard deviation; SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score; EQ, EuroQol; VAS, Visual Analogue Scale; PAID, Problem Areas In Diabetes; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

Table 2 - Univariable and multivariable model

	Three-monthly vs. six-monthly* N = 1421		Three-monthly vs. no preference* N = 1534		Six-monthly vs. no preference† N = 1465	
	Crude OR (95% CI)	Adj. OR (95% CI)	Crude OR (95% CI)	Adj. OR (95% CI)	Crude OR (95% CI)	Adj. OR (95% CI)
Smoking						
Never smoker	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)		
Ex-smoker	1.14 (0.89-1.46)	1.08 (0.83-1.40)	1.11 (0.88-1.40)	1.11 (0.87-1.41)		
Current smoker	1.73 (1.24-2.40)	1.70 (1.20-2.41)	1.43 (1.04-1.95)	1.46 (1.05-2.03)		
SF-36 PCS	1.02 (1.01-1.03)		1.02 (1.01-1.03)			
EQ-5D	2.79 (1.53-5.10)		2.36 (1.31-4.26)			
EQ VAS	1.02 (1.01-1.02)	1.01 (1.00-1.02)	1.02 (1.01-1.02)	1.01 (1.00-1.02)		
PAID	0.96 (0.95-0.97)	0.97 (0.96-0.99)	0.96 (0.95-0.98)	0.97 (0.96-0.99)		
DTSQ status		0.95 (0.92-0.98)	1.04 (1.02-1.07)		1.03 (1.01-1.06)	1.05 (1.02-1.08)
DTSQ hyper	0.71 (0.66-0.77)	0.75 (0.69-0.82)	0.80 (0.75-0.85)	0.86 (0.80-0.92)	1.11 (1.03-1.20)	1.14 (1.05-1.23)
DTSQ hypo	0.82 (0.75-0.89)		0.88 (0.82-0.95)			
HbA1c (mmol/mol)	0.96 (0.94-0.98)		0.98 (0.97-1.00)		1.02 (1.00-1.04)	
Oral blood glucose lowering drug use	0.49 (0.38-0.63)	0.53 (0.41-0.69)	0.66 (0.51-0.84)	0.74 (0.57-0.96)	1.35 (1.07-1.70)	1.33 (1.05-1.69)
Lipid lowering drug use	0.70 (0.54-0.91)					

The multivariable model started with all variables from table 1. If a variable was neither univariable nor multivariable significant, this variable is not shown in this table.

* Preference for three-monthly monitoring is the reference group.

† Preference for six-monthly monitoring is the reference group.

OR, Odds Ratio; 95% CI, 95% Confidence Interval; Adj. OR, Adjusted Odds Ratio; SF-36, Short-Form 36; PCS, Physical Component Score; EQ, EuroQol; VAS, Visual Analogue Scale; PAID, Problem Areas In Diabetes; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

Discussion

In this large sample of well-controlled Dutch type 2 diabetes patients, about one third reported a preference for three-monthly monitoring and about one third for six-monthly monitoring. Patients preferring three-monthly monitoring, felt less healthy, reported more diabetes-related distress, had the highest reported frequency of hyperglycaemic episodes and used more oral blood glucose lowering drugs. On the other hand, patients preferring six-monthly monitoring were least satisfied with diabetes treatment, had the lowest reported frequency of hyperglycaemic episodes and used less oral blood glucose lowering drugs.

The strength of this study is that the results can easily be generalised because we used a large study population in primary care with robust information on each patient and we included general practitioners and patients across the whole nation. However, there are certain limitations that need to be addressed. Firstly, there could be other (extrinsic) factors that could have influenced patients' choice as well, for example the access or distance to the general practice and the patient-doctor relationship, that were not included in this study. The gender or age of the general practitioner or the quality of care could be potential determinants of patients' preferences. However, to distinguish categories of patients with regard to the frequency of diabetes monitoring, we think we measured all relevant variables. Secondly, because of its cross-sectional design, we could only assess associations and not causality. Finally, because no research had been performed on this topic yet, this study was an explorative study and we therefore included as many potential predictors as possible. The inclusion of many predictors in our analyses may have led to false-positive results due to multiple testing. This needs to be kept in mind when interpreting our results.

In this study a preference for three-monthly monitoring was associated with feeling less healthy, more diabetes-related distress, the highest reported frequency of hyperglycaemic episodes and more oral blood glucose lowering drugs. This indicates that patients with a worse disease status generally preferred a higher monitoring frequency. Patients preferring six-monthly monitoring, on the other hand generally had a better disease status with less oral blood glucose lowering drugs and less hyperglycaemic episodes. This shows that patients appear to be able to make a good estimation for the most suitable monitoring frequency. This suggests that these patients made a rational choice in choosing their preferred monitoring frequency. This has not been demonstrated before in type 2 diabetes patients. However, in a preference study in older patients with chronic

knee pain they concluded that when giving patients a choice, they seem to make logical choices in choosing their treatment [42]. These findings underpin the recommendation to take patients' preferences into account when tailoring diabetes care [43], also with regard to monitoring frequency.

Despite differences in the patient's perceived healthiness between the three preference groups, outcomes on anthropometric measures and medical data were equal. The patients were selected based on their cardiometabolic status; meaning they were rather well-controlled regarding HbA1c, systolic blood pressure and total cholesterol. The group who preferred three-monthly monitoring did not seem to feel so well-controlled compared to the other two groups. Whether the former patients are less self-confident or have a lower self-efficacy with regard to diabetes management is unclear, but we feel it is of interest to further investigate the difference between the 'objective' diabetes control and the 'subjective' one by carrying out a qualitative study.

Furthermore, the three-monthly monitoring group used more medication than the two other groups. The current higher medication use could indicate worse control in the past. Perhaps patients in the three-monthly group based their choice on their experiences in the past. Another explanation of this difference could be that they currently have an underlying worse control, because they need more medication to stay at the same level.

Unexpectedly, age, gender and education were comparable between the three groups, also when combining the two preference groups and comparing them with the no preference group. This is surprising because a review showed that younger, better educated patients and women prefer a more active role in decision making [44]. This discrepancy may demonstrate that an active role in decision making does not necessarily correspond to having a preference for the monitoring frequency.

All participating patients were relatively well-controlled and did not use insulin therapy. Therefore the average scores for EQ VAS, EQ-5D, DTSQ, SF-36 and PAID are comparable or somewhat better than in other studies in type 2 diabetes patients from general practices in the Netherlands [43,45-48]. As a consequence, this could increase the generalisability of this study.

It is known that the time interval between monitoring visits is mainly predicted by the characteristics of the physician [14-16]. However, in this study we tried to exclude their influence by letting patients decide for themselves.

In conclusion, two-thirds of well-controlled type 2 diabetes patients have a preference for the monitoring frequency. Several patient characteristics were found to be associated with having a preference. A preference for more frequent monitoring is associated with a worse disease status, whereas a preference for less frequent monitoring tended to be associated with the opposite. This indicates that patients appear to make logical decisions in choosing the monitoring frequency. Therefore, also in well-controlled patients the preferences regarding monitoring frequency need to be accounted for in diabetes care, because this may encourage patient activation and medication adherence.

Chapter 3

Relation between comorbidity and health status

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Abstract

Background: Type 2 diabetes patients have a decreased health-related quality of life compared to healthy persons, especially regarding physical functioning and well-being. Health-related quality of life is even lower in type 2 diabetes patients when other diseases co-exist. In contrast to earlier studies, we assessed the associations between the number and type of comorbidities and health status in well-controlled type 2 diabetes patients, in whom treatment goals for HbA1c, blood pressure and cholesterol had been reached. Approximately one in five type 2 diabetes patients belongs to this group.

Methods: Cross-sectional analysis was performed in 2086 well-controlled (HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg, total cholesterol ≤5.2 mmol/l and not using insulin) type 2 diabetes patients in general practice. Both number and type (cardiovascular and non-cardiovascular) of comorbidities were determined for each patient. Health status was assessed with the questionnaires Short Form-36 (SF-36) and EuroQol (EQ). The SF-36 generates eight dimensions of health and a Physical and Mental Component Score (PCS and MCS), scale: 0-100. The EQ consists of two parts: EQ-5D and EQ Visual Analogue Scale. Multivariable linear regression analysis was used to assess if number and type of comorbidities were associated with health status.

Results: Well-controlled type 2 diabetes patients with comorbidities had a much lower health status, with a decrease ranging from -1.5 for the MCS to -26.3 for role limitations due to physical problems, compared to those without. Health status decreased when the number of comorbidities increased, except for mental health, role limitations due to emotional problems, MCS and both EQ measures. In patients with both cardiovascular and non-cardiovascular comorbidity, physical functioning, role limitations due to physical problems and PCS were significantly lower than in patients with only cardiovascular comorbidity. Physical functioning was also lower compared to patients with only non-cardiovascular comorbidity.

Conclusions: Even acceptable values of HbA1c, blood pressure and cholesterol in type 2 diabetes patients are not necessarily related with a good health status. We have shown that comorbidities have a large impact on health status. Physicians may take into account patient's health status and integrate the impact of comorbidities into diabetes care.

Background

Type 2 diabetes patients have a decreased health-related quality of life compared to healthy persons, especially regarding physical functioning and well-being [49,50]. Furthermore, diabetes patients with co-existing macrovascular or non-vascular diseases have an even lower health-related quality of life [50].

Cardiovascular diseases [51,52] are associated with a lower health-related quality of life but also more specific types, like: myocardial infarction [53], stroke [53-56], heart disease [55-57], heart failure [53,58] and peripheral vascular disease [55]. Non-vascular diseases which are associated with a lower health-related quality of life are: emphysema/COPD [51,52], (osteo)arthritis [51,56,57,59] and depression [53,54,56,58,60]. For most of these comorbidities mainly physical health was decreased, except for depression.

Not only the type of comorbidity but also the absolute number of diseases is associated with a decreased health-related quality of life in type 2 diabetes patients [55,56,59,61,62]. Type 2 diabetes patients with comorbidities visit their general practitioner and medical specialist more often and are more frequently admitted to the hospital than patients without [63]. Therefore, this group deserves special attention.

In contrast to the above mentioned research, we studied the health status of well-controlled type 2 diabetes patients, in whom treatment goals for HbA1c, blood pressure and cholesterol had been reached. About one in five type 2 diabetes patients belongs to this group [24,39]. Many physicians are likely to be satisfied if treatment goals are achieved, but also health status should be addressed according to the American Diabetes Association [64]. Therefore, we aimed to assess the association between the number and type of comorbidities and health status in a large sample of well-controlled type 2 diabetes patients in general practice.

Methods

Design

We present a cross-sectional analysis on baseline data from the EFFIMODI study. The design and rationale of EFFIMODI have been described elsewhere (**Chapter 1**). Patients were selected from the computerised medical records of 233 general practitioners across the Netherlands. Patients were eligible if between 40 and 80 years old, diagnosed with type 2 diabetes for more than a year, treated by their

general practitioner, not on insulin treatment and were well-controlled, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. These cut-off values were a little higher than the Dutch target values, namely HbA1c ≤53 mmol/mol, systolic blood pressure ≤140 mmHg and total cholesterol ≤4.5 mmol/l [4].

The general practitioner sent an information letter as well as an informed consent form to all eligible patients by mail. Patient who were willing to participate signed informed consent. After returning the informed consent form, they received a postal questionnaire to complete and return it to the investigators. In case of non-response they received two reminders.

The Medical Research Ethics Committee of the University Medical Center Utrecht has approved the study protocol (Protocol number: 08-453) and we conducted the study according to the 1964 Declaration of Helsinki.

Measurements

Both the patient questionnaire and medical data were used. Medical data of the patients were collected by a case report form that was filled in by the general practitioner or practice nurse. Data were collected about the following eleven conditions: myocardial infarction, angina pectoris, heart surgery, heart failure, stroke, transient ischemic attack, peripheral arterial disease, COPD, rheumatoid arthritis, osteoarthritis of hip or knee or any other diseases.

Despite the fact that the terms ‘health status’ and ‘health-related quality of life’ have different meanings, they are used interchangeably in literature. Impaired health status may lead to impaired quality of life, but this is not always the case [65]. We have chosen to measure health status, because this is relatively easy to measure in daily practice [27].

Health status was measured with the self-administered questionnaires Short Form-36 (SF-36) [27] and EuroQol (EQ) [28,66]. The Dutch translation of the SF-36 has been validated in both general and disease-specific samples [67]. The SF-36 consists of 36 questions and generates a profile of scores on eight dimensions of health, namely: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), social functioning (SF), mental health (MH), role limitations due to emotional problems (RE), vitality (VT) and general health (GH). For all eight dimensions a score is calculated, with a range from 0 (least favourable health state) to 100 (most favourable health state) [68]. Two summary scales with a

similar range for physical and mental functioning can be calculated as well: the Physical Component Score (PCS) and the Mental Component Score (MCS) [69].

The EuroQol is a generic questionnaire, consisting of a classification system (EQ-5D) and a Visual Analogue Scale (EQ VAS). The EQ-5D covers five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each with three levels of functioning: no problems, some problems and severe problems. These questions were used to compute an index value based on a Dutch valuation study [41]. The index value ranges between +1 and -0.329, where 0 means death. The EQ VAS is a graded, vertical line, anchored at 0 (worst imaginable health state) and 100 (best imaginable health state). The patient is asked to mark a point on the EQ VAS that best reflects his/her actual health state.

Age, gender, ethnicity (Dutch or non-Dutch), educational level (low, middle or high) and living alone (yes or no) were collected with the patient questionnaire and BMI (in kg/m^2) and duration of diabetes (in years) were collected with the case report form. We considered these variables as potential confounders based on literature [49,51,55,57,70]. HbA1c, blood pressure and lipid levels were not considered as potential confounders because the well-controlled study population was rather homogeneous in this respect. Also, because of the low levels of these variables, they were not likely to be associated with health status.

Statistical analysis

Descriptive statistics were used to describe the characteristics of the population. Categorical variables were expressed as percentages and continuous variables as a mean with standard deviation (SD). From the answers to the open question of 'any other diseases', we selected 'cancer of all causes' (except skin cancers other than melanoma) to be added to the comorbidities because of its frequently mentioned occurrence.

Patients were categorised into those with no, one, two and more than two comorbidities. Every specific condition was counted as one comorbidity, except having a stroke or transient ischemic attack. Having one or both of these conditions was counted as one comorbidity. Myocardial infarction, angina pectoris, heart surgery, heart failure, stroke, transient ischemic attack and peripheral arterial disease were aggregated as cardiovascular comorbidities; and all other conditions as non-cardiovascular.

To assess the relation between comorbidity and health status we used: the eight health status dimensions of the SF-36, the PCS and the MCS of the SF-36, the EQ-5D and the EQ VAS. Comorbidity was categorised in two different ways: 1) no, one, two and more than two comorbidities and 2) diabetes only, diabetes with cardiovascular comorbidity, diabetes with non-cardiovascular comorbidity and diabetes with both cardiovascular and non-cardiovascular comorbidities. For each health status measure a multiple linear regression model was used to assess the association between type and number of comorbidities and health status, adjusted for potential confounders. These linear regression models give Betas for each group of comorbidity. The Betas are the differences in health status compared to the reference group (no comorbidity or diabetes only), for example a Beta of -5 means that a group scored 5 points lower on a particular health status score than the reference group. A p-value of <0.05 was considered statistically significant. Although health status had a skewed distribution in our study population, we chose to perform a linear regression analysis, to control for confounders. The latter is not possible with Mann-Whitney or Kruskal-Wallis tests.

For handling missing data in the confounders and health status domains we used multiple imputation. We assumed that the missing data were missing at random. We generated 10 imputed datasets and used Rubin's rules to combine the estimates of the parameters [33].

To examine if significantly different health status scores between groups of comorbidities are clinically relevant, we used the commonly used effect size: the average difference between groups divided by the SD [71]. An effect size of >0.2 is called a small effect, >0.5 is a medium effect and >0.8 is a large effect [71]. Data were analysed using SPSS version 17 and R version 2.10.

Results

The study population consisted of 2215 type 2 diabetes patients. We excluded patients that did not fill in a questionnaire (n=96), with missing medical data (n=28) or who missed both (n=5), leaving 2086 patients for further analyses. Their mean age was 65 years, 60% were males and the mean diabetes duration was 6 years. 62% of the type 2 diabetes patients had no comorbidity, 24% had one comorbidity, 9% had two comorbidities and 5% had more comorbidities. Of all patients, 26% had a cardiovascular comorbidity and 18% a non-cardiovascular comorbidity (***Table 1***).

Table 1 - Characteristics of the study population (N=2086)

	N	mean ± SD or n (%)
Age (years)	2086	64.4 ± 8.8
Gender (male)	2086	1240 (59.4%)
Dutch ethnicity	2073	1852 (89.3%)
Educational level	1912	
Low		789 (41.3%)
Middle		699 (36.6%)
High		424 (22.2%)
Living alone	2053	399 (19.4%)
BMI (kg/m^2)	2039	29.2 ± 4.7
Duration of diabetes in years	2034	5.8 ± 3.7
No comorbidity	2086	1290 (61.8%)
One comorbidity	2086	517 (24.8%)
Two comorbidities	2086	179 (8.6%)
More than two comorbidities	2086	100 (4.8%)
Cardiovascular comorbidity	2086	549 (26.3%)
Non-cardiovascular comorbidity	2086	383 (18.4%)

Table 2 - Mean health status scores for type 2 diabetes patients with and without different types of comorbidity

	Diabetes only	Myocardial infarction	Angina pectoris	Heart surgery	Heart failure	Stroke	Transient ischemic attack	Peripheral arterial disease	COPD	Rheumatoid arthritis	Osteoarthritis hip/knee	Cancer
	n=1290	n=180	n=200	n=118	n=57	n=120	n=54	n=96	n=147	n=40	n=176	n=69
PF	81.4	69.7	69.7	64.0	56.5	67.7	71.3	59.2	63.0	59.4	61.2	66.6
RP	82.1	70.7	70.4	56.9	61.6	73.0	74.8	67.1	65.5	53.4	66.3	74.6
BP	79.8	74.6	73.2	68.6	72.8	75.5	79.7	68.3	74.1	62.3	66.3	73.6
SF	87.2	80.2	83.3	78.0	74.1	77.7	80.5	80.4	81.5	78.2	78.7	77.6
MH	80.7	77.3	78.0	77.9	73.9	75.7	79.1	76.7	76.9	78.1	77.7	75.3
RE	90.1	84.3	83.9	83.8	73.8	84.0	82.3	84.2	84.1	82.9	84.0	83.9
VT	69.3	64.2	64.8	61.3	58.6	62.0	64.9	62.0	60.3	59.6	63.3	61.8
GH	66.3	58.4	57.6	52.9	52.0	59.1	63.0	58.0	52.8	52.4	58.7	59.7
PCS	48.3	44.3	43.8	40.1	41.2	44.6	45.6	41.3	41.9	38.0	41.2	45.3
MCS	54.4	53.2	53.8	53.5	51.5	52.2	52.8	54.3	53.7	54.8	54.6	52.7
EQ-5D	0.88	0.84	0.84	0.82	0.81	0.80	0.82	0.77	0.82	0.76	0.77	0.81
EQ VAS	78.7	74.0	72.8	71.4	69.4	73.1	75.1	70.1	69.7	69.6	72.5	71.1

COPD, Chronic Obstructive Pulmonary Disease; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; SF, social functioning; MH, mental health; RE, role limitations due to emotional problems; VT, vitality; GH, general health; PCS, Physical Component Score; MCS, Mental Component Score; EQ-5D, EuroQol 5 Dimensions; EQ VAS, EuroQol Visual Analogue Scale.

The N does not sum up to the total number of the study population. This is because when a patient has two or more comorbidities, it will be handled into two or more of the groups.

Type 2 diabetes patients with comorbidities had a much lower health status compared to those without any comorbidity. Especially type 2 diabetes patients with co-existing heart failure, peripheral arterial disease, COPD and rheumatoid arthritis had a lower health status (***Table 2***).

All health status domains were significantly lower in patients who had one or more comorbidities compared to type 2 diabetes patients with no comorbidities (***Table 3***). Almost all health status measures further decreased when the number of comorbidities increased, with the exception of mental health, role limitations due to emotional problems, mental component score, EQ-5D and EQ VAS. Physical functioning and general health showed a significant decrease (-5.5 and -5.2, respectively) between the groups with one and with two comorbidities. The health status domains physical functioning, role limitations due to physical problems, bodily pain, social functioning, vitality, general health and the physical component score differed significantly between the groups with one and with more than two comorbidities. Furthermore, the domains physical functioning, role limitations due to physical problems and the physical component score were significantly lower (-8.0, -14.8 and -3.8, respectively) in the group with more than two comorbidities compared to the group with two comorbidities.

Patients with only diabetes had a significantly higher health status on all domains (***Table 4***). Whether patients had a cardiovascular or non-cardiovascular comorbidity was not significantly associated with their health status. If patients had both cardiovascular and non-cardiovascular comorbidities, they had a significantly lower score (-6.8 compared to only non-cardiovascular and -9.0 compared to only cardiovascular) on physical functioning. Compared with patients with only cardiovascular comorbidity, patients with both cardiovascular and non-cardiovascular comorbidity scored worse on role limitations due to physical problems and physical component score (-11.9 and -4.0, respectively). Furthermore, all other health status domains were not significantly different between the three groups.

When comparing the differences between the groups on clinical importance, most domains showed a small effect (>0.2), some showed a medium effect (>0.5) (mainly physical domains) and three had a large effect (>0.8), namely zero versus more than two comorbidities on both physical functioning and the physical component score and diabetes only versus diabetes with both cardiovascular and non-cardiovascular comorbidity with respect to physical functioning.

Table 3 - Number of comorbidities and difference in health status domains compared to people with 0 comorbidities

	0 comorbidities n=1290	1 comorbidity n=517	2 comorbidities n=179	>2 comorbidities n=100
	Mean ± SD	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
PF	81.4 ± 20.3	-8.8 (-10.9 to -6.7)*	-14.3 (-17.6 to -11.0)†	-22.3 (-26.6 to -18.0)‡
RP	82.1 ± 33.1	-8.2 (-11.8 to -4.5)*	-11.5 (-17.1 to -5.9)*	-26.3 (-33.6 to -19.0)‡
BP	79.8 ± 22.0	-5.9 (-8.2 to -3.5)*	-8.0 (-11.6 to -4.4)*	-13.1 (-17.7 to -8.4)†
SF	87.2 ± 18.6	-5.0 (-7.1 to -3.0)*	-7.5 (-10.6 to -4.3)*	-12.0 (-16.1 to -7.9)†
MH	80.7 ± 15.0	-3.6 (-5.2 to -2.0)*	-4.5 (-6.9 to -2.1)*	-4.6 (-7.8 to -1.5)*
RE	90.1 ± 26.0	-6.0 (-9.1 to -2.9)*	-7.3 (-12.0 to -2.5)*	-10.6 (-16.7 to -4.4)*
VT	69.3 ± 17.7	-5.5 (-7.3 to -3.7)*	-8.6 (-11.4 to -5.8)*	-11.7 (-15.3 to -8.0)†
GH	66.3 ± 18.6	-6.1 (-8.1 to -4.2)*	-11.3 (-14.2 to -8.3)†	-13.3 (-17.2 to -9.5)†
PCS	48.3 ± 9.4	-3.3 (-4.3 to -2.3)*	-5.4 (-6.9 to -3.9)*	-9.2 (-11.2 to -7.3)‡
MCS	54.4 ± 8.2	-1.5 (-2.4 to -0.6)*	-1.8 (-3.1 to -0.4)*	-1.6(-3.3 to 0.2)
EQ-5D	0.88 ± 0.16	-0.06 (-0.08 to -0.05)*	-0.07 (-0.10 to -0.05)*	-0.11 (-0.15 to -0.08)*
EQ VAS	78.7 ± 13.8	-4.8 (-6.3 to -3.4)*	-7.8 (-10.0 to -5.5)*	-8.9 (-11.8 to -6.0)*

Linear regression analyses were adjusted for age, gender, ethnicity, education, living alone, BMI and duration of diabetes.
* significantly different from the group with 0 comorbidities.
† significantly different from the group with 0 and the group with 1 comorbidity.
‡ significantly different from the groups with 0, 1 and 2 comorbidities.
SD, standard deviation; 95% CI, 95% confidence interval; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; SF, social functioning; MH, mental health; RE, role limitations due to emotional problems; VT, vitality; GH, general health; PCS, Physical Component Score; MCS, Mental Component Score; EQ-5D, EuroQol 5 Dimensions; EQ VAS, EuroQol Visual Analogue Scale.

Table 4 - Type of comorbidity and difference in health status domains compared to people with only diabetes

	Only diabetes n=1290	Diabetes with only cardiovascular disease n=413	Diabetes with only non-cardiovascular disease n=247	Diabetes with both cardiovascular and non-cardiovascular diseases n=136
	Mean ± SD	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
PF	81.4 ± 20.3	-9.4 (-11.8 to -7.0)*	-11.6 (-14.5 to -8.8)*	-18.4 (-22.2 to -14.6)†
RP	82.1 ± 33.1	-7.9 (-11.9 to -3.9)*	-11.6 (-16.6 to -6.6)*	-19.8 (-26.2 to -13.4)‡
BP	79.8 ± 22.0	-6.0 (-8.6 to -3.4)*	-7.4 (-10.5 to -4.3)*	-10.4 (-14.5 to -6.3)*
SF	87.2 ± 18.6	-6.0 (-8.3 to -3.8)*	-5.1 (-7.8 to -2.4)*	-10.0 (-13.6 to -6.4)*
MH	80.7 ± 15.0	-4.4 (-6.1 to -2.6)*	-3.1 (-5.2 to -1.1)*	-4.0 (-6.8 to -1.2)*
RE	90.1 ± 26.0	-7.4 (-10.8 to -4.0)*	-4.0 (-8.1 to 0.1)	-10.6 (-16.0 to -5.2)*
VT	69.3 ± 17.7	-6.5 (-8.5 to -4.5)*	-6.2 (-8.6 to -3.8)*	-9.6 (-12.8 to -6.4)*
GH	66.3 ± 18.6	-6.8 (-9.0 to -4.7)*	-8.3 (-10.9 to -5.7)*	-11.7 (-15.0 to -8.3)*
PCS	48.3 ± 9.4	-3.3 (-4.4 to -2.2)*	-4.8 (-6.1 to -3.5)*	-7.3 (-9.0 to -5.6)‡
MCS	54.4 ± 8.2	-2.1 (-3.0 to -1.1)*	-0.7 (-1.9 to 0.4)	-1.7 (-3.2 to -0.1)*
EQ-5D	0.88 ± 0.16	-0.06 (-0.08 to -0.04)*	-0.07 (-0.10 to -0.05)*	-0.10 (-0.13 to -0.07)*
EQ VAS	78.7 ± 13.8	-5.4 (-7.0 to -3.7)*	-5.9 (-8.0 to -3.9)*	-7.8 (-10.4 to -5.3)*

Linear regression analyses were adjusted for age, gender, ethnicity, education, living alone, BMI and duration of diabetes.
* significantly different from the group with only diabetes.
† significantly different from the other three groups.
‡ significantly different from the groups with only diabetes and diabetes with only cardiovascular disease.
SD, standard deviation; 95% CI, 95% confidence interval; PF, physical functioning; RP, role limitations due to physical problems; BP, bodily pain; SF, social functioning; MH, mental health; RE, role limitations due to emotional problems; VT, vitality; GH, general health; PCS, Physical Component Score; MCS, Mental Component Score; EQ-5D, EuroQol 5 Dimensions; EQ VAS, EuroQol Visual Analogue Scale.

Discussion

This study showed that type 2 diabetes patients with a comorbidity had a lower health status than patients without. Furthermore, health status decreased with an increasing number of comorbidities, except for the mental health measures. Patients with both cardiovascular and non-cardiovascular comorbidities, had a significantly lower physical health than patients with only cardiovascular or non-cardiovascular comorbidity. The percentage of type 2 diabetes patients with one or more comorbidities in our study was 38%, while in another study in the Netherlands this was 44% [63]. This difference is probably due to our selection of well-controlled, no insulin using diabetes patients.

While the link between diabetes patients with comorbid diseases and poor health status is well established, our study is novel because it looked at a group of people with well-controlled type 2 diabetes. Our results are consistent with findings from general diabetes populations. We found that comorbidity in diabetes patients was mainly associated with diminished physical health, as was described for osteoarthritis, stroke, cardiovascular disease, respiratory disease and myocardial infarction [51-55,59]. Furthermore, we also found that a higher number of comorbidities is associated with a decreased health-related quality of life in type 2 diabetes patients [55,56,59,61,62].

In contrast to aforementioned types of comorbidities, comorbid depression is associated with both a lower physical and mental health status [53,54,56,58,60]. This means that the mental health status scores are likely to be associated with depression, however we did not measure depression. We found that a higher number of comorbidities did not further decrease mental health, role limitations due to emotional problems and mental component score. Furthermore, the Mental Component Scores in our population were rather high (mean: 54) indeed and patients with scores above 42 are not likely to have a depression [68]. These findings suggest that depression (and thus a decreased mental health) was not a major issue in our study population. This is in accordance with the fact that depression is associated with poor glycaemic control [72] and we studied a selection of well-controlled diabetes patients.

The decrease in health status with increasing number of comorbidities seen in most SF-36 domains was also seen in the EQ-5D and EQ VAS. However, these changes were not significant. This could be explained by the fact that these health status measures combine both physical and mental health in one score. Therefore,

the differences between one, two and more than two comorbidities might be diluted by the large differences for physical health on one side and almost no differences for mental health on the other. Furthermore, this could be due to the relatively small groups of people with two and more than two comorbidities. Also, we found rather high values for health status. This could be due to the fact that poor self-rated health is associated with increasing glucometabolic disturbances [73] and such patients were not included in the study.

Also patients with diabetes and microvascular complications [55,58,74,75] have a lower health-related quality of life compared to patients with diabetes alone; however we did not look at the association between microvascular complications and health status. Patients with end stage renal disease were not included, because they are not treated by their general practitioner. The same applies to patients with diabetic foot disease or neuropathy. Retinopathy is estimated to be present in about 7.4% of the type 2 diabetes patients in the Netherlands [76]. Because our population had a relatively short diabetes duration and people were well-controlled, our retinopathy prevalence would have been low. This was confirmed by the fact that retinopathy was only mentioned nine times among 'other diseases'. Therefore we think this will not have influenced our results.

Several studies studied the relation between comorbidity and glycaemic control and since we looked at comorbidity in a selection of well-controlled type 2 diabetes patients, their findings might be of interest to interpret our findings. The risk of cardiovascular diseases increases with a higher HbA1c [77], so our study population had a relatively low risk of getting 'new' complications. On the other hand, diabetes patients with coronary heart disease or congestive heart failure have a lower odds of having at least one cardiovascular risk factor (glycaemia, blood pressure and lipids) out of control [78]. Since our results are similar to studies in general (both well-controlled and not well-controlled patients) diabetes populations, we think that 'good cardiometabolic control' was not a confounder in the association between comorbidity and health status. In the relationship between diabetes control and comorbidities, general practitioners' treatment and patients' health behaviour are likely to play a role as well [79]. Because of the homogeneity of the study population (all were well-controlled) we were not in the position to elucidate whether the health status of patients is associated with patient's behaviour.

Although quality of care may increase with an increasing number of chronic conditions [80], our study demonstrated that acceptable or good cardiometabolic

control does not automatically reflect a good health status. So far, three types of interventions were designed to improve quality of life in diabetes patients: a disease management program [81], implementing several elements of the Chronic Care Model [82] and a structured group self-management educational intervention [83]. Diabetes patients in the German disease management program had higher health-related quality of life in the dimensions mobility, self-care and performing usual activities compared to routine care. The same was shown for patients with a high number of comorbidities [81]. The disease management program also improved processes of care and intermediate outcomes. However, there were no differences in intermediate outcomes between the disease management program and routine care [84]. The number of secondary diseases and the presence of a disabling secondary disease were related to drop-out of the disease management program [85]. This disease management program showed that it may improve health-related quality of life and therefore may be useful in clinical practice. However, one might question their usefulness for diabetes patients with comorbidities. Disease management programs focus on a single disease and as we could demonstrate health status does not depend on a single disease. In our opinion the above mentioned drop-out is not surprising; in disease management programs special attention should be paid to patients with both cardiovascular and non-cardiovascular comorbidity. The other two mentioned interventions are still ongoing.

Strengths of this study are that we have measured multiple health status domains and multiple comorbidities. On top of that, we have measured them all in one, large population. This allowed us to quantify the impact of comorbidity on several health status domains. This could be helpful in providing specific treatment options to type 2 diabetes patients, depending on the different comorbidities and the different aspects of their health status. Because the included patients were not only recruited for a randomised controlled equivalence trial but were also part of a patient preference study, we minimised selection bias [22]. Besides, we had a high response rate on the patient questionnaires, probably due to the fact that patients had already agreed to participate in a larger study and thus were more motivated to fill in the questionnaire.

There are also limitations that need to be addressed. Firstly, comorbidity in our study population might be underreported, and lack of disease coding in the electronic medical records might play a role. We cannot assess its role, but underreporting is not likely to influence the direction of our results. Secondly, we

selected only eleven conditions, seven of which were vascular diseases. Conceptually, multimorbidity includes all potential other conditions. However, other diseases were hardly reported as meaningful diseases, with the exception of cancer. Therefore we assume that this will not have biased our results. Thirdly, we have no information about the medication used for the comorbidity. So we do not know if it is the comorbidity itself that decreased health status or the medication patients are using for it. Fourthly, we wanted to assess the impact of comorbidity regardless of possible confounders such as age, gender, ethnicity and educational level of patients. However, adjusting for these possible confounders implies that the impact of these confounders on health status could not be assessed separately. Lastly, because of the cross-sectional design no causal relationship could be established. However, a cohort study with a follow-up of five years showed that in elderly diabetes patients the diabetes-related complications were predictive of reduced health-related quality of life, but the number of comorbid diseases did not [86]. We found that both diabetes-related complications (cardiovascular comorbidity) and the number of comorbidities were associated with a reduced health status, so the cohort study only partly confirms to our results. The fact that in the cohort study the number of comorbid diseases did not predict reduced health-related quality of life may be explained by the fact that at baseline health-related quality of life was already lower in diabetes patients with comorbid diseases, therefore during the study period no further reduction in health-related quality of life might be detectable.

Conclusions

Our study demonstrates that even acceptable values of HbA1c, blood pressure and cholesterol in type 2 diabetes patients are not enough for good clinical care. A higher number and both cardiovascular and non-cardiovascular comorbidities are associated with a decreased health status. Increasing the health status of type 2 diabetes patients is necessary, irrespective of comorbidity, and should be considered a physician's task. Our data suggest that physicians should not be satisfied if a patient with type 2 diabetes has achieved acceptable values of HbA1c, blood pressure and cholesterol, but may take into account patient's health status and integrate the impact of comorbidities into diabetes care.

Chapter 4

Randomised equivalence trial & economic evaluation

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Submitted

Abstract

Background: Most guidelines recommend monitoring type 2 diabetes patients four times a year, but this is not evidence-based. We aimed to investigate effectiveness and cost-effectiveness of six-monthly monitoring compared with three-monthly monitoring of well-controlled type 2 diabetes patients in primary care.

Methods: We randomly assigned 791 well-controlled type 2 diabetes patients without a strong preference for their monitoring frequency to either three-monthly (usual care) or six-monthly monitoring (intervention). The primary outcome was the percentage of patients remaining under good cardiometabolic control, meaning: HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. Follow-up was eighteen months. Equivalence was assumed if the two-sided 95% confidence interval for the difference in overall cardiometabolic control between the two groups was in the range from -5 to 5%. Healthcare use was recorded using the general practitioners' information system. Cost-effectiveness was determined using a cost-minimisation or cost-utility analysis.

Results: In the three-monthly group 69.5% remained under good cardiometabolic control, versus 69.8% in the six-monthly group (difference: 0.3%; 95% CI: -6.2% to 6.7%). None of the secondary outcomes differed significantly, except patient's perceived frequency of hyperglycaemia (difference: 0.26; 95% CI: 0.03 to 0.50) and hypoglycaemia (difference: 0.26; 95% CI: 0.07 to 0.44). Six-monthly monitoring was €387 cheaper per patient compared to three-monthly monitoring during the study period.

Conclusions: Cardiometabolic control of six-monthly monitoring was not different from three-monthly monitoring. Therefore patients with good cardiometabolic control and without preference for their monitoring frequency can visit the general practice less often.

Background

Currently, more than 300 million people live with diabetes and this number is still increasing [2]. This results in a heavy burden for healthcare providers and increasing costs. It is therefore important to make diabetes care as efficient as possible.

Most guidelines for treatment of type 2 diabetes recommend monitoring type 2 diabetes patients four times a year [4,37,87], but this recommendation is not evidence-based and differs per country [21,37].

Two observational studies showed that in type 2 diabetes patients the number of visits was not related to glycaemic control [11,12]. Similarly, a randomised equivalence trial showed that six-monthly monitoring of well-controlled hypertensive patients achieved the same levels of blood pressure control as three-monthly monitoring [6]. We therefore hypothesize that this could be similar for well-controlled diabetes patients.

We aimed to investigate whether six-monthly monitoring of well-controlled type 2 diabetes patients results in equivalent cardiometabolic control at reduced costs compared to three-monthly monitoring.

Methods

Design and patients

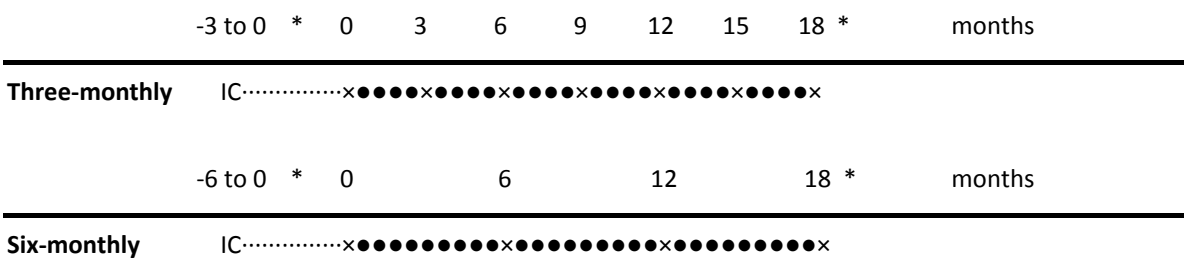
The EFFIMODI study was designed as a randomised controlled patient-preference equivalence trial in primary care (**Chapter 1**). With this design only patients without a strong preference for their monitoring frequency are randomised.

Patients were eligible if between 40 and 80 years old, diagnosed with type 2 diabetes for more than a year, treated by their general practitioner, not on insulin treatment and well-controlled during the last year. The latter was defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l.

From April 2009 to August 2010, 2215 patients from 233 general practitioners across the Netherlands were included. Of these, 747 preferred three-monthly monitoring, 677 preferred six-monthly monitoring and 791 had no preference for the monitoring frequency (**Chapter 2**). Only the latter group was randomised.

Randomisation, intervention and follow-up

Patients were randomised to three-monthly (control group) or six-monthly (intervention group) monitoring in a 1:1 ratio. Randomisation was generated at patient level by a computerised random-number generator at the research centre. The control group visited the practice every three months and the intervention group every six months. Patients were followed for eighteen months, and thus were on average seen either seven (control group) or four (intervention group) times during that period ***(Figure 1)***. Obviously, it was impossible to blind participants and general practitioners for the treatment allocation. However, laboratory technicians who measured HbA1c and cholesterol were blinded to randomisation.



IC	= Moment at which informed consent is signed
·····	= Time between signing of informed consent and start of the study period (variable)
×	= Interval visit
●●	= Time between interval visits
*	= Moment at which patient questionnaires were filled in by the patients

Figure 1 - Schematic overview of the planned diabetes visits and follow-up time of patients in the three-monthly and six-monthly group

At each interval visit blood pressure and weight should be measured. Usually once a year one of the interval visits is an extensive yearly visit. This visit is usually performed by the general practitioner and HbA1c and cholesterol are also measured then.

According to the Dutch guideline [4], blood pressure and weight should be measured at each diabetes visit. The frequency of measuring HbA1c and cholesterol differs between practices. Usually, and according to the guidelines, HbA1c and cholesterol are measured once a year during an extensive annual visit, usually done by the general practitioner. All other visits are performed by the practice nurse. The treatment targets, therapeutic algorithms and lifestyle advices given were according to the current guidelines [4] and did not differ between the intervention and control group. In the event of complications (diabetes-related or other) or poorly controlled HbA1c, blood pressure or cholesterol, patients from both groups could visit their practice more often or be referred to secondary care.

Since this was a pragmatic trial, additional study measurements on top of routine care were not performed. Therefore, the extensive yearly visit was included in the six-monthly visit cycle and we used the last known routine care HbA1c, systolic blood pressure and total cholesterol measurements for the primary outcome.

Outcomes

The primary outcome measure was the percentage of people who remained under good cardiometabolic control, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. The separate targets for HbA1c, systolic blood pressure and total cholesterol were used as secondary outcomes (percentage below target). Other secondary outcomes were: HbA1c, blood pressure and cholesterol (HDL, LDL and total) on a continuous scale; BMI; current smoking; physical activity (measured with SQUASH [25]); mean health status scores (measured with SF-36 [27] and EQ-5D [28]); diabetes-related distress (measured with PAID [30]); satisfaction with diabetes treatment and perceived frequency of hyper- and hypoglycaemias (measured with DTSQ status [32]); and medication use. The costs of both treatment arms were also compared.

Data collection

Medical data were collected with two case report forms (at baseline and at the end of the study period), filled in by the general practitioner or practice nurse. At baseline, height, year of diabetes diagnosis and medical history were determined. Type of medication use was assessed at the beginning and at the end of the study period. The last recorded measurement before the first study visit plus all measurements performed during the planned diabetes visits were reported for weight, HbA1c, blood pressure and HDL, LDL and total cholesterol. Furthermore, hospital stay and the number and type of practice visits were collected. In case of drop-out, medical data were collected until drop-out (if possible).

At baseline and after eighteen months, participants filled in a questionnaire. If patients failed to return the questionnaire, up to two reminders were sent. The patient questionnaires consisted of demographic information, physical activity, health status, diabetes-related distress, satisfaction with diabetes treatment and perceived frequency of hyper- and hypoglycaemias.

Sample size

The sample size was calculated on the assumption of equivalence of cardiometabolic control, using the formula of Jones et al. [23]. We assumed equivalence if the two-sided 95% confidence interval (α=0.05) for the difference in cardiometabolic control between the two intervention groups is completely in the range from -5 to 5% (δ=5). With an expected overall 95% of success (i.e. adequate cardiometabolic control) and a power of 90% (β=0.1), a sample size of 399 people per group was required.

Economic evaluation

For the economic evaluation we performed a piggyback study alongside the randomised equivalence trial. The type of economic evaluation was based on the outcome of the equivalence trial (**Chapter 1**). If three-monthly and six-monthly monitoring were equivalent, a cost-minimisation analysis was performed and if three-monthly and six-monthly monitoring were not equivalent, a cost-utility analysis was performed.

We extracted data on healthcare use (practice visits, hospitalizations and medication use) from the general practitioners' information system to calculate the direct healthcare costs during the study period. For every type of healthcare use, we determined the reference costs (see ***Table 1***).

Table 1 - Reference costs per unit

Direct medical costs	**Value in € per unit (in 2011)**	**Reference**
Visits to the general practice	29.02 per visit	[88]
Hospital stay	473.65 per day	[88]
Medication use	See ***Table 6***	[89]
Indirect costs		
Absenteeism from paid work		
Hourly wage	Age and gender specific	[26]
Friction period	115 days (2010*)	[26]
Production losses without absenteeism from paid work		
Hourly wage	Age and gender specific	[26]

*This was not yet available for 2011

The costs for practice visits and hospitalizations were calculated by multiplying the number of visits or days in the hospital with the corresponding reference costs. If patients had a shorter follow-up period, the costs were divided by the number of months of follow-up and then multiplied by 18.

Medication costs were determined using national data on the average annual cost of a user of a specific medication [89]. If a type of medication was only used at baseline or at the end of the study, we assumed usage for half of the follow-up period and the annual costs were multiplied by 0.75 (reflecting nine months). If a type of medication was used both at baseline and follow-up, we multiplied the annual costs by 1.5. If information about baseline or follow-up medication was missing (missing case report form), the costs of the medication at baseline or follow-up were multiplied by 1.5.

The indirect non-healthcare costs (absenteeism from paid work and production losses without absenteeism from paid work) were measured using the Short Form-Health and Labour Questionnaire (SF-HLQ) [26]. We used the follow-up questionnaire to extrapolate the indirect non-healthcare costs to the entire follow-up period. Costs of absenteeism from paid work were calculated according to the friction cost approach [90].

For the cost-utility analysis we also used the utilities derived from the patients' answers to the EQ-5D questionnaire [28]. We used a Dutch valuation study to recode the EQ-5D into an index value indicating the utility of the health status of the patient [41]. This value can be used to determine Quality Adjusted Life Years (QALYs). If a patient missed their baseline or final measurement of the EQ-5D, we used the available measurement to calculate the QALYs (last observation carried forward/backward). The calculation of the QALYs per person during the study period was as follows: $(EQ\text{-}5D_{baseline} + EQ\text{-}5D_{end}) / 2 * 1.5$ *years*.

If information on any of these variables was not available, we imputed data using the Expectation Maximization algorithm.

We performed the economic evaluation from a societal perspective (reference year 2011). We did not discount the costs, because the study period was rather short. If cost data were available from other years, prices were adjusted using consumer price indexes.

The 'incremental cost-utility ratio' (ICUR) was expressed as cost differences between groups divided by differences in QALYs between groups. A 'cost-utility plane' and a 'cost-utility acceptability curve' were drawn using bootstrapping.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics. We calculated the difference between the three-monthly and six-monthly groups in

percentage of good cardiometabolic control, with the corresponding confidence interval using method 10 of Newcombe [91]. This confidence interval was compared to the prespecified range of equivalence. The same was done for the separate targets.

These outcomes were analysed according to the intention-to-treat principle (with last observation values carried forward in case of missing values). We also performed per-protocol analyses according to the following criteria:

1. The patient did not drop out during the study.
2. In the three-monthly group at least six scheduled diabetes visits (but not more than seven) and in the six-monthly group at least three scheduled diabetes visits (but not more than four) were performed.

We also performed two sensitivity analyses to handle situations in which HbA1c, systolic blood pressure and total cholesterol were measured at different time points or with a relatively short follow-up. In the first analysis, we only included HbA1c, systolic blood pressure and total cholesterol measured on the same date. In the second analysis, we only included measurements of HbA1c, systolic blood pressure and total cholesterol with a minimum follow-up of twelve months.

To compare smoking behaviour, physical activity and medication use between both groups, we used generalized linear models. HbA1c and cholesterol were compared with an analysis of variance. Blood pressure, BMI, health status, diabetes-related distress and satisfaction with diabetes treatment were compared with an analysis of covariance adjusting for baseline values. For HbA1c and cholesterol it was not possible to correct for baseline measurement, since not every patient had a HbA1c or cholesterol measurement at every diabetes visit.

Linear mixed models were used to examine the course of blood pressure and BMI over time with random intercepts and random linear effect of time per patient. Fixed effects were BMI or blood pressure at baseline, time, intervention, and an intervention*time interaction. The effect of intervention was evaluated by testing the last two terms using a likelihood ratio test.

In case of significant differences between the groups, we used the effect size (the average difference between groups divided by the standard deviation) to determine clinical relevance [71]. An effect size of >0.2 is called a small effect, >0.5 is a medium effect and >0.8 is a large effect [71]. Data were analysed using SPSS software, version 20.

Results

394 patients were randomised to three-monthly monitoring and 397 to six-monthly monitoring. In total, 774 patients (97.9%) were included in the intention-to-treat analysis and 68 (8.6%) were lost to follow-up or discontinued the intervention (***Figure 2***). The patients were aged 65 years and 60% were men. The groups were well matched (***Table 2***).

In the three-monthly group 69.5% remained under good cardiometabolic control versus 69.8% in the six-monthly group (***Figure 3***). Though the difference was not significant (p=0.94), the confidence interval was not within the prespecified range and therefore equivalence is uncertain. None of the separate treatment targets differed significantly between both groups, and HbA1c and total cholesterol were within the range of equivalence. The blood pressure target was outside the range of equivalence due to a low percentage reaching this target (±80%) and was further studied.

Of the 142 patients not reaching this target, 51 (35.9%) started a new/extra antihypertensive drug during follow-up (24 in the three-monthly group and 27 in the six-monthly group) and 11 (7.7%) patients had been prescribed an increased dosage of their antihypertensive drug (4 in the three-monthly group and 7 in the six-monthly group). We used a change in antihypertensive medication as a proxy for failing control of blood pressure by re-classifying patients without changes in blood pressure medication as 'systolic blood pressure target reached'. This resulted in a success rate of 93.1% in the three-monthly group and 92.3% in the six-monthly group. With these numbers 78.6% of the patients remained under good cardiometabolic control in the three-monthly group and 79.6% in the six-monthly group (difference: 1.0%; 95% CI: -4.7% to 6.8%).

The per-protocol and sensitivity analyses produced similar results (***Table 3***).

No significant differences were observed between three-monthly and six-monthly monitoring, except for the perceived frequency of hyperglycaemia (difference: 0.26; 95% CI: 0.03 to 0.50) and hypoglycaemia (difference: 0.26; 95% CI: 0.07 to 0.44) (***Table 4***). These differences had a very small effect size (both <0.2).

The linear mixed models for BMI, systolic and diastolic blood pressure showed no effect of group or interaction between time and group (p-values of 0.724, 0.399 and 0.220, respectively), indicating no significant difference in course of outcomes over time for the two groups (see ***Figure 4***).

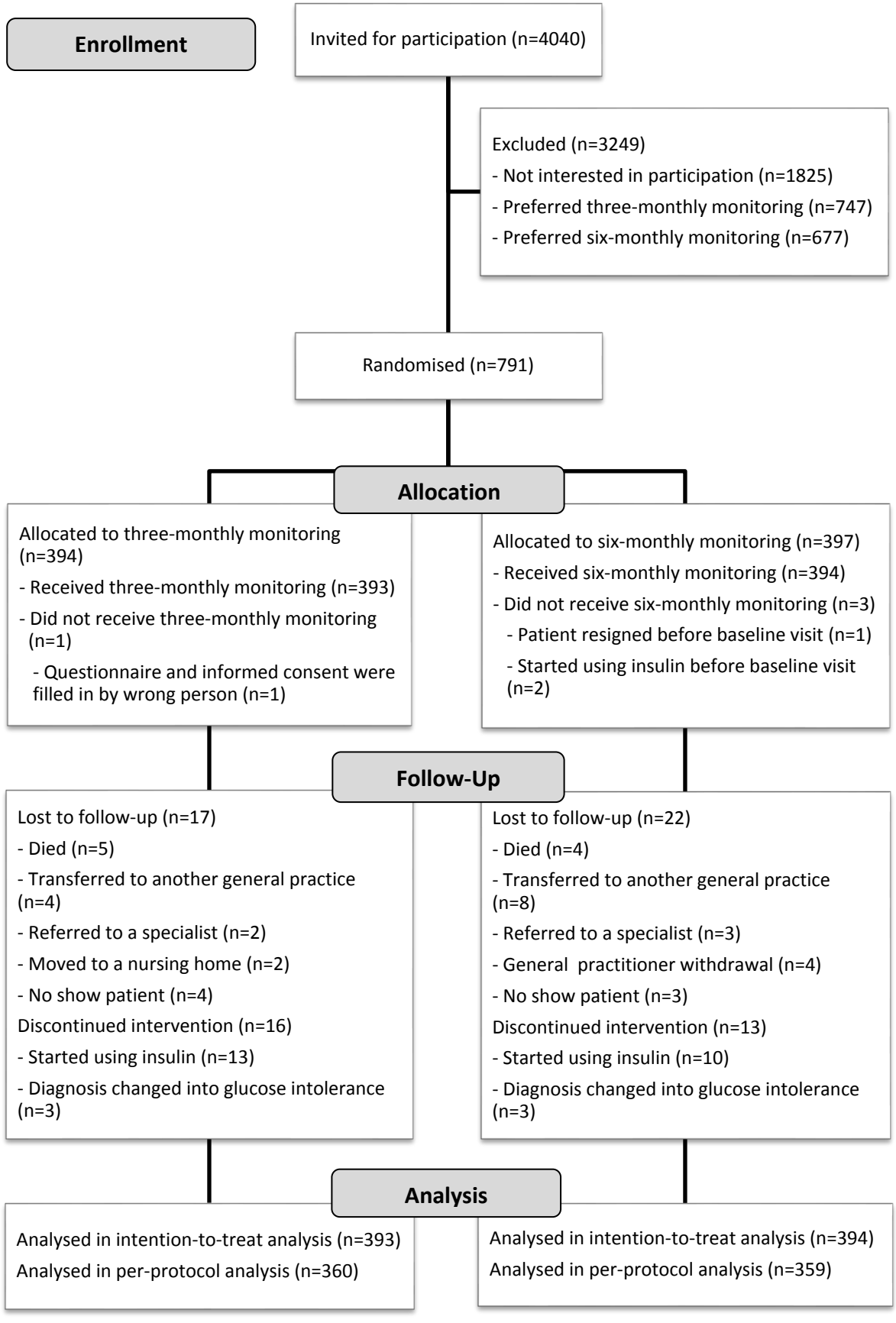


Figure 2 - Flowchart

Table 2 - Baseline characteristics of the study population who were allocated to three-monthly or six-monthly monitoring

	Randomised to three-monthly monitoring (n=394)		Randomised to six-monthly monitoring (n=397)	
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)
Age (years)	393	64.7 ± 8.8	396	64.4 ± 8.8
Gender (male)	393	239 (60.8%)	395	231 (58.5%)
Dutch ethnicity	380	348 (91.6%)	381	338 (88.7%)
Educational level	344		357	
Low		138 (40.1%)		157 (44.0%)
Middle		125 (36.3%)		121 (33.9%)
High		81 (23.5%)		79 (22.1%)
Living alone	377	83 (22.0%)	375	74 (19.7%)
Working status	373		380	
Paid job		92 (24.7%)		100 (26.3%)
Retired		209 (56.0%)		208 (54.7%)
Other		72 (19.3%)		72 (18.9%)
Duration of diabetes (years)	378	5.5 ± 3.5	382	5.9 ± 3.8
Medical history				
Myocardial infarction	391	33 (8.4%)	390	36 (9.2%)
Angina pectoris	391	40 (10.2%)	390	33 (8.5%)
Heart surgery	391	21 (5.4%)	390	28 (7.2%)
Heart failure	391	12 (3.1%)	390	12 (3.1%)
Stroke	391	29 (7.4%)	390	20 (5.1%)
Transient ischemic attack	391	13 (3.3%)	390	10 (2.6%)
Peripheral arterial disease	391	19 (4.9%)	390	19 (4.9%)
COPD	391	42 (10.7%)	390	23 (5.9%)
Rheumatoid arthritis	391	7 (1.8%)	390	10 (2.6%)
Osteoarthritis of the hip or knee	391	26 (6.6%)	390	33 (8.5%)

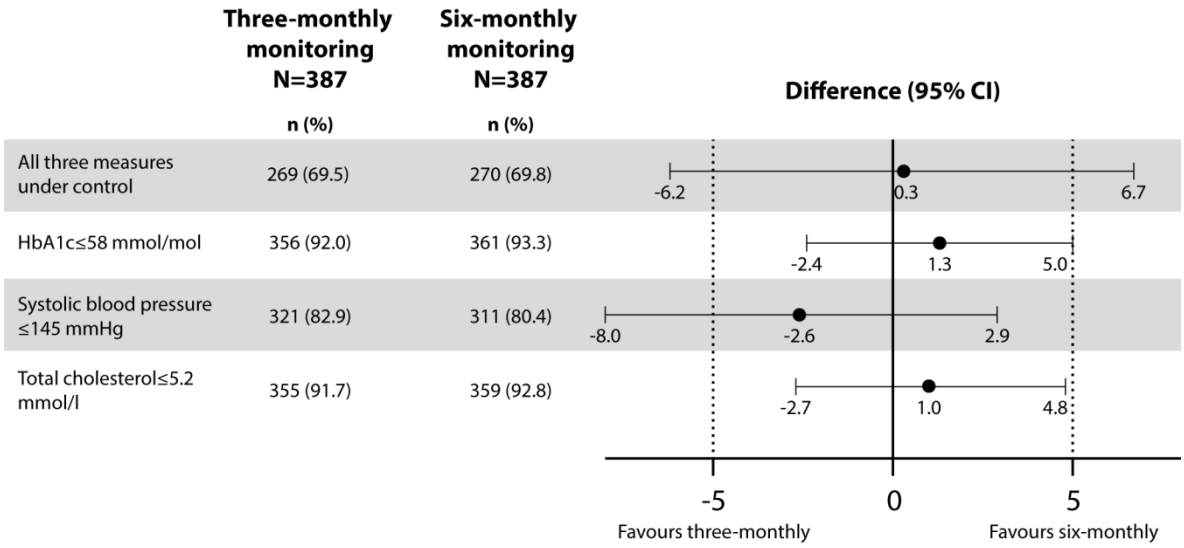


Figure 3 - Assessment of equivalence

Percentage of people who reached the target(s) at the last known measurement. The dots represent the differences between the three-monthly and six-monthly monitoring groups and the horizontal lines are the corresponding 95% confidence intervals (95% CI). If the entire confidence interval is between the range -5 and 5, three-monthly and six-monthly monitoring can be considered equivalent. If it is completely outside this range it is not equivalent and otherwise it is uncertain.

Table 3 - Per-protocol and sensitivity analyses

	Three-monthly monitoring			Six-monthly monitoring			Six-monthly – three-monthly
Per-protocol analysis	**N**	**n (%)**	**Follow-up time (months)**	**N**	**n (%)**	**Follow-up time (months)**	**Difference (95% CI)**
All three measures under control	330	238 (72.1%)	-	275	199 (72.4%)	-	0.2 (-6.9% to 7.4%)
HbA1c ≤58 mmol/mol	330	309 (93.6%)	15.8 ± 3.5	275	260 (94.5%)	15.7 ± 3.4	0.9 (-2.9% to 4.7%)
Systolic blood pressure ≤145 mmHg	330	276 (83.6%)	18.0 ± 1.3	275	227 (82.5%)	17.5 ± 2.2	-1.1 (-7.1% to 4.9%)
Total cholesterol ≤5.2 mmol/l	330	304 (92.1%)	14.1 ± 3.8	275	254 (92.4%)	14.3 ± 3.7	0.2 (-4.0% to 4.5%)
Sensitivity analysis 1							
All three measures under control	355	253 (71.3%)	13.6 ± 4.1	354	248 (70.1%)	13.9 ± 4.1	-1.2% (-7.9% to 5.5%)
HbA1c ≤58 mmol/mol	355	331 (93.2%)	13.6 ± 4.1	354	331 (93.5%)	13.9 ± 4.1	0.3% (-3.4% to 3.9%)
Systolic blood pressure ≤145 mmHg	355	296 (83.4%)	13.6 ± 4.1	354	288 (81.4%)	13.9 ± 4.1	-2.0% (-7.6% to 3.6%)
Total cholesterol ≤5.2 mmol/l	355	325 (91.5%)	13.6 ± 4.1	354	326 (92.1%)	13.9 ± 4.1	0.5% (-3.5% to 4.6%)
Sensitivity analysis 2							
All three measures under control	267	191 (71.5%)	-	283	196 (69.3%)	-	-2.3% (-9.9% to 5.4%)
HbA1c ≤58 mmol/mol	323	296 (91.6%)	16.8 ± 2.3	328	308 (93.9%)	16.5 ± 2.7	2.3% (-1.7% to 6.2%)
Systolic blood pressure ≤145 mmHg	370	309 (83.5%)	18.0 ± 1.5	354	282 (79.7%)	17.8 ± 1.6	-3.9% (-9.5% to 1.8%)
Total cholesterol ≤5.2 mmol/l	275	254 (92.4%)	15.7 ± 2.6	291	268 (92.1%)	15.5 ± 3.0	-0.3% (-4.7% to 4.1%)

The per-protocol analysis only included patients who: did not drop-out during the study and had at least six (three-monthly monitoring) or three (six-monthly monitoring) diabetes visits.
Sensitivity analysis 1 only included measurements which were measured at the same date.
Sensitivity analysis 2 only included measurements which were measured after at least twelve months.

Table 4 - Baseline and follow-up measurements for the three-monthly (n=393) and six-monthly (n=394) monitoring groups with the corresponding differences (95% confidence interval) between groups

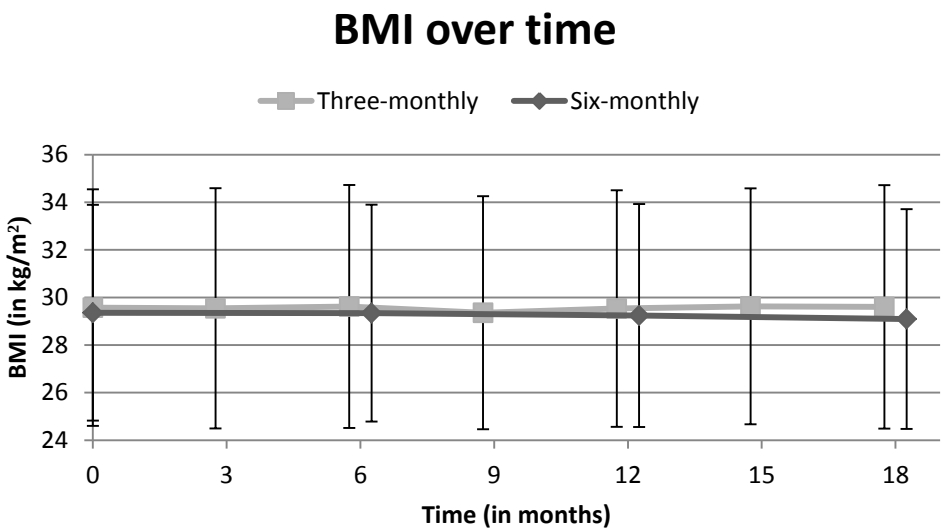
	Three-monthly monitoring				Six-monthly monitoring				Six-monthly – three-monthly
	Baseline		Follow-up		Baseline		Follow-up		
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	Difference (95% CI)*
HbA1c (mmol/mol)**	380	46.8 ± 6.0	391	48.4 ± 8.4	383	46.7 ± 6.0	391	48.2 ± 7.4	-0.25 (-1.36 to 0.86)
HDL cholesterol (mmol/l)**	386	1.2 ± 0.3	391	1.2 ± 0.3	380	1.2 ± 0.3	391	1.3 ± 0.4	0.04 (-0.02 to 0.09)
LDL cholesterol (mmol/l)**	386	2.3 ± 0.6	391	2.3 ± 0.6	379	2.3 ± 0.6	391	2.2 ± 0.6	-0.03 (-0.12 to 0.06)
Total cholesterol (mmol/l)**	367	4.2 ± 0.7	388	4.3 ± 0.8	378	4.2 ± 0.7	388	4.1 ± 0.8	-0.11 (-0.22 to 0.00)
Systolic blood pressure (mmHg)	385	132.4 ± 14.4	336	133.1 ± 14.6	384	134.5 ± 14.5	332	133.8 ± 15.2	0.02 (-2.07 to 2.11)
Diastolic blood pressure (mmHg)	385	76.8 ± 8.6	336	76.2 ± 9.1	384	77.4 ± 9.0	332	76.1 ± 9.1	-0.23 (-1.48 to 1.03)
BMI (kg/m^2)	371	29.6 ± 5.0	322	29.6 ± 5.1	364	29.4 ± 4.5	310	29.1 ± 4.6	-0.06 (-0.30 to 0.19)
Current smoker	379	76 (20.1%)	348	63 (18.1%)	381	65 (17.1%)	348	48 (13.8%)	-0.9% (-3.1% to 1.3%)
Physically active	367	252 (68.7%)	330	238 (72.1%)	359	260 (72.4%)	331	252 (76.1%)	1.0% (-5.0% to 7.0%)
SF-36 PCS [scale: 0-100]	343	47.1 ± 10.3	320	45.7 ± 10.6	335	47.2 ± 10.1	309	46.1 ± 10.4	0.45 (-0.78 to 1.68)
SF-36 MCS [scale: 0-100]	343	54.2 ± 8.0	320	54.3 ± 8.3	335	54.2 ± 8.4	309	54.6 ± 9.1	0.66 (-0.52 to 1.85)
EQ VAS [scale: 0-100]	361	77.6 ± 13.8	324	75.8 ± 14.6	355	77.1 ± 14.5	319	75.1 ± 15.1	-0.46 (-2.26 to 1.35)
PAID [scale: 0-80]	364	5.7 ± 8.1	337	6.3 ± 9.0	362	5.9 ± 8.6	328	6.0 ± 8.8	-0.42 (-1.49 to 0.66)
DTSQ [scale: 0-36]	371	32.5 ± 3.6	345	31.9 ± 5.0	369	32.7 ± 4.3	335	31.8 ± 4.9	-0.06 (-0.76 to 0.64)
DTSQ hyper [scale: 0-6]	377	1.1 ± 1.6	352	1.1 ± 1.7	378	1.0 ± 1.5	344	1.4 ± 1.7	**0.26 (0.03 to 0.50)**
DTSQ hypo [scale: 0-6]	376	0.7 ± 1.3	352	0.6 ± 1.2	378	0.8 ± 1.3	344	1.0 ± 1.5	**0.26 (0.07 to 0.44)**
Medication use									
Oral blood glucose lowering drugs	391	294 (75.2%)	383	306 (79.9%)	390	296 (75.9%)	377	296 (78.5%)	0.1% (-2.9% to 3.2%)
Antihypertensive drugs	391	289 (73.9%)	383	288 (75.2%)	390	271 (69.5%)	377	282 (74.8%)	2.6% (-0.3% to 5.4%)
Lipid lowering drugs	391	322 (82.4%)	383	320 (83.6%)	390	315 (80.8%)	377	319 (84.6%)	1.1% (-2.3% to 4.6%)

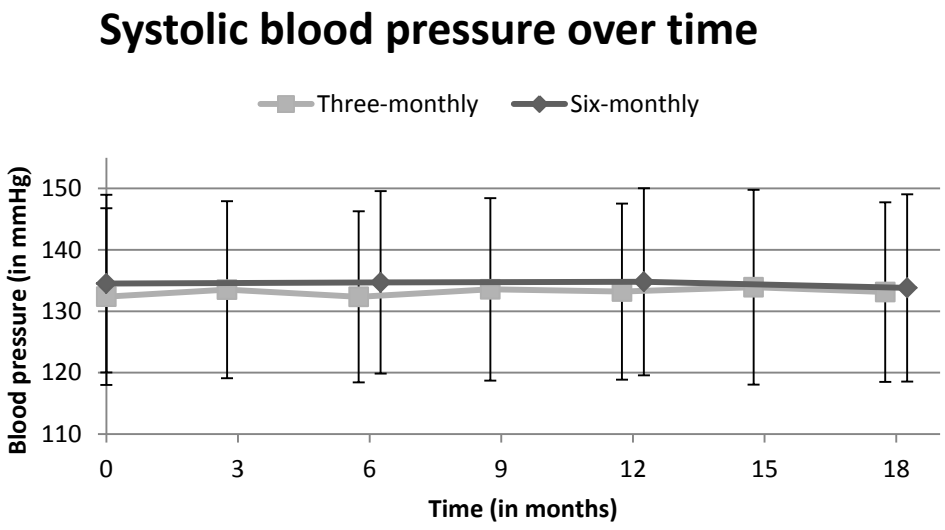
Differences displayed in bold were statistically significant ($p<0.05$).

* The differences in follow-up measurements were corrected for baseline measurement. If the difference is positive this indicates that the six-monthly group has a higher value for that specific variable than the three-monthly group.

** For these variables we displayed the last known measurement before informed consent in the baseline column and the last known measurement during the study period (with last observation values carried forward in case of missing values) in the follow-up column. Only for these variables the observed differences were not corrected for baseline measurement.

SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score; EQ VAS, EuroQol Visual Analogue Scale; PAID, Problem Areas In Diabetes; DTSQ, Diabetes Treatment Satisfaction Questionnaire.





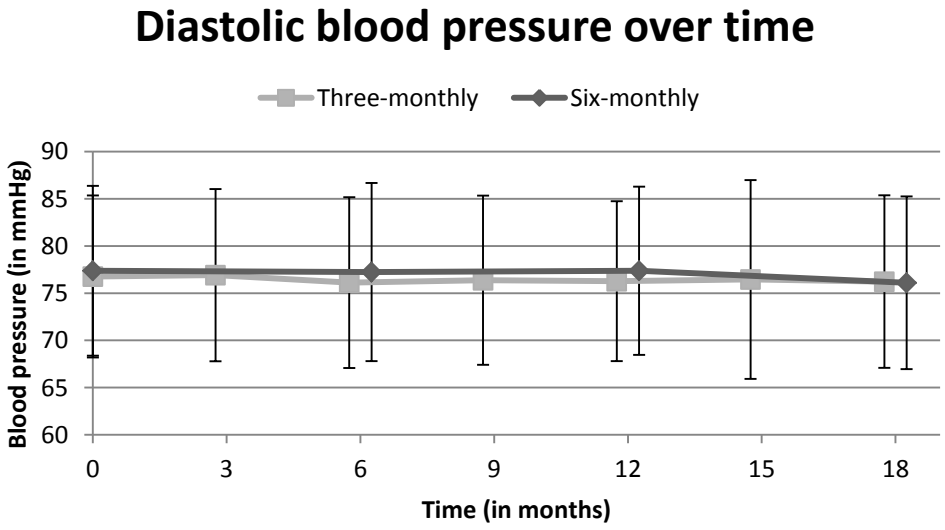


Figure 4 - Linear mixed models of BMI, systolic blood pressure and diastolic blood pressure
The error bars represent the standard deviations.

Table 5 - Units and total costs

Healthcare use and costs	Three-monthly monitoring			Six-monthly monitoring		
	n	Unit	Total costs ± SD	n	Unit	Total costs ± SD
Diabetes visits						
Scheduled	383	6.6 ± 0.9		377	3.9 ± 0.4	
Unscheduled	383	1.3 ± 2.3		377	2.0 ± 3.2	
Total	383	7.8 ± 2.5		377	5.9 ± 3.2	
Other visits	383	5.9 ± 5.6		377	5.5 ± 5.9	
Total number of visits	383	13.7 ± 6.3	**397.65 ± 182.96**	377	11.4 ± 7.0	**331.08 ± 203.30**
Hospitalized	383	78 (20.4%)		377	63 (16.7%)	
Total number of days in the hospital	373	0.94 ± 3.13	**445.72 ± 1480.55**	372	1.16 ± 5.08	**548.78 ± 2408.10**
Indirect non-healthcare costs						
Paid work	332	86 (25.9%)		324	84 (25.9%)	
Absenteeism of paid work	332	9 (2.7%)	**1595.36 ± 12,567.18**	324	7 (2.2%)	**1042.80 ± 9312.51**
Production losses without absenteeism from paid work	331	9 (2.7%)	**10.49 ± 85.62**	321	3 (0.9%)	**4.28 ± 45.38**

The mean number of diabetes visits during 1.5 years of follow-up was higher in the three-monthly group than in the six-monthly group (7.8 versus 5.9, p<0.001); the number of other visits was equal (p=0.28) (***Table 5***).

Economic evaluation

Since equivalence of cardiometabolic control was uncertain according to our formal criterion, we performed both the cost-minimisation analysis and the cost-utility analysis. ***Tables 5 and 6*** display the healthcare use and healthcare costs and indirect non-healthcare costs of both study groups.

The cost-minimisation analysis showed that six-monthly monitoring was €387 cheaper per patient than three-monthly monitoring during the study period (see ***Table 7***).

The ICUR was €33,041 per QALY. The cost-utility analysis showed that most patients were in the lower left part of the cost-utility plane, meaning that six-monthly monitoring resulted in a net loss of QALYs at lower costs (see ***Figure 5***). With a threshold of €20,000 per QALY, the probability that six-monthly monitoring is cost-effective is less than 60% (see ***Figure 6***).

Since the QALYs were slightly lower in the six-monthly group, we further examined this finding to explain this difference. At baseline the six-monthly group had a lower EQ-5D score (0.862) compared to the three-monthly group (0.867).

Table 6 - Medication use and costs

	Annual costs per user in 2011 (in €)	Three-monthly monitoring		Six-monthly monitoring	
		Baseline (n=391)	Follow-up (n=383)	Baseline (n=390)	Follow-up (n=377)
Blood glucose lowering drugs		**294**	**306**	**296**	**296**
Insulin		**-**	**13**	**-**	**10**
Rapid-acting insulin	388.60	-	2	-	0
Intermediate-acting insulin	235.40	-	3	-	5
Extended-release insulin	466.90	-	7	-	3
Biphasic insulin	545.10	-	3	-	2
Sulfonylureas		**127**	**125**	**120**	**119**
Glibenclamide	66.52	0	0	5	4
Gliclazide	67.61	19	24	25	20
Glimepiride	59.05	63	59	57	50
Tolbutamide	60.44	45	42	34	46
Thiazolidinediones		**8**	**6**	**7**	**7**
Pioglitazone	463.40	5	6	7	6
Rosiglitazone	53.48	3	0	0	1
Other blood glucose lowering drugs		**273**	**287**	**266**	**272**
Metformin	51.53	269	286	261	267
Combination of blood glucose lowering drugs					
Metformin/rosiglitazone	84.30	3	0	2	0
Pioglitazone/metformin	404.10	0	0	2	0
Sitagliptin/metformin	377.10	0	0	1	1
Vildagliptin/metformin	385.20	0	0	0	1
Other blood glucose lowering drugs					
Liraglutide	1124.00	0	0	0	1
Repaglinide	118.10	1	1	0	0
Saxagliptin	344.30	0	2	0	0
Sitagliptin	392.80	2	5	0	3
Vildagliptin	328.10	1	2	0	2
Antihypertensive drugs		**289**	**288**	**271**	**282**
Diuretics		**93**	**101**	**88**	**90**
Chlorothiazide	26.09	0	0	0	3
Chlortalidone	53.12	13	12	11	7
Furosemide	58.56	16	15	15	18
Hydrochlorothiazide	45.08	60	71	58	59
Indapamide	62.80	2	1	1	0
Triamterene	66.78	2	3	2	1
Other diuretics					
Bumetanide	74.30	0	0	2	3
Spironolactone	62.13	4	6	2	3
Beta blockers		**131**	**141**	**112**	**119**
Atenolol	45.30	11	11	4	2
Bisoprolol	50.31	18	18	19	21
Carvedilol	121.50	2	1	1	0
Labetalol	126.30	1	1	0	0
Metoprolol	52.60	84	93	76	81

Other beta blockers					
Acebutolol	111.10	0	0	1	2
Celiprolol	121.60	0	0	1	1
Nebivolol	70.24	3	5	0	1
Pindolol	116.40	1	1	3	2
Propranolol	41.78	5	4	1	2
Sotalol	58.81	7	7	6	7
ACE inhibitors		**122**	**128**	**111**	**115**
Captopril	51.95	5	7	2	1
Enalapril	44.63	60	60	55	53
Fosinopril	67.60	1	2	4	5
Lisinopril	45.60	28	29	21	19
Perindopril	60.52	19	20	19	23
Ramipril	52.33	5	7	4	8
Other ACE inhibitors					
Quinapril	78.84	4	3	5	5
Zofenopril	204.30	0	0	1	1
Angiotensin II receptor antagonists		**58**	**56**	**70**	**81**
Candesartan	225.20	8	6	2	5
Irbesartan	246.40	12	10	13	16
Losartan	59.33	19	19	32	31
Telmisartan	229.90	3	4	4	5
Valsartan	245.90	14	15	18	23
Other angiotensin II receptor antagonists					
Olmesartan	209.40	2	2	1	1
Calcium channel blockers		**58**	**72**	**44**	**47**
Amlodipine	43.99	28	37	20	24
Diltiazem	123.20	6	6	3	3
Felodipine	113.10	2	2	0	0
Nifedipine	95.48	17	16	16	12
Verapamil	78.89	2	4	1	1
Other calcium channel blockers					
Barnidipine	301.60	2	2	1	3
Isradipine	188.70	1	2	0	0
Lercanidipine	67.10	1	3	3	4
Nitrendipine	120.00	0	1	0	0
Other antihypertensive drugs		**55**	**45**	**49**	**48**
Combination of antihypertensive drugs					
Aliskiren/hydrochlorothiazide	226.00	0	0	0	1
Amiloride/hydrochlorothiazide	53.76	3	1	7	5
Amlodipine/valsartan	265.20	0	0	1	2
Atenolol/chlortalidone	73.83	1	0	3	4
Bisoprolol/hydrochlorothiazide	64.36	1	0	1	0
Candesartan/hydrochlorothiazide	249.90	0	1	0	0
Captopril/hydrochlorothiazide	46.65	3	1	1	2
Enalapril/hydrochlorothiazide	54.49	7	6	6	4
Fosinopril/hydrochlorothiazide	67.56	2	1	0	0
Irbesartan/hydrochlorothiazide	266.30	4	5	6	6

Lisinopril/hydrochlorothiazide	59.49	1	2	2	4
Losartan/hydrochlorothiazide	87.75	11	10	10	9
Metoprolol/hydrochlorothiazide	118.50	2	2	1	2
Perindopril/indapamide	149.30	1	0	1	0
Telmisartan/hydrochlorothiazide	256.10	3	2	1	1
Triamterene/epitizide	72.33	5	4	2	2
Triamterene/hydrochlorothiazide	53.76	2	0	3	2
Valsartan/hydrochlorothiazide	342.50	6	7	3	2
Other antihypertensive drugs					
Aliskiren	249.10	0	0	0	1
Doxazosin	115.10	3	4	2	2
Lipid lowering drugs		**322**	**320**	**315**	**319**
Statins		**311**	**309**	**307**	**306**
Atorvastatin	397.20	60	65	66	63
Pravastatin	50.71	38	38	32	31
Rosuvastatin	287.60	19	19	20	24
Simvastatin	40.63	191	185	187	184
Other statins					
Fluvastatin	104.40	3	2	3	4
Fibrates		**3**	**4**	**2**	**3**
Bezafibrate	88.40	0	0	1	1
Ciprofibrate	237.70	0	0	0	1
Gemfibrozil	150.80	3	4	1	1
Other lipid lowering drugs		**19**	**18**	**14**	**20**
Ezetimibe	401.20	9	9	12	17
Combination of lipid lowering drugs					
Ezetimibe/simvastatin	540.50	10	9	2	3
Total costs medication		**463.36 ± 314.15**		**446.69 ± 341.89**	

The numbers presented in bold are the number of people who used at least one type of medication from that specific group. The medications below the groups in italics were obtained from an open answer.
If a patient used a medication only at baseline or follow-up, the costs of the medication were multiplied by 0.75 years. If a patient used a medication both at baseline and follow-up, the costs of the medication were multiplied by 1.5 years. Annual costs reflect the cost of purchase of the medication and a three-monthly fee for the dispensing pharmacists, according to Dutch guidelines for cost research in healthcare [88].

Table 7 - Outcomes CUA

	Three-monthly monitoring	**Six-monthly monitoring**
Costs visits	€ 403.87 ± 183.84	€ 339.42 ± 218.54
Costs hospital stay	€ 473.82 ± 1505.43	€ 613.93 ± 2646.35
Costs medication	€ 469.30 ± 313.17	€ 459.83 ± 347.82
Direct costs	**€ 1346.99 ± 1605.25**	**€ 1413.19 ± 2714.46**
Costs production losses due to absence	€ 1560.42 ± 11654.90	€ 1111.69 ± 8560.50
Costs production losses due to reduced productivity	€ 10.10 ± 79.39	€ 5.41 ± 41.71
Indirect costs	**€ 1570.52 ± 11658.09**	**€ 1117.11 ± 8562.05**
Total costs	**€ 2917.51 ± 11797.13**	**€ 2530.29 ± 8975.01**
Utilities	**1.3008 QALY ± 0.2315**	**1.2890 QALY ± 0.2485**

The displayed costs represent the mean costs ± standard deviation for each patient during eighteen months. The costs were based on the values after imputation. Negative costs were set to zero.

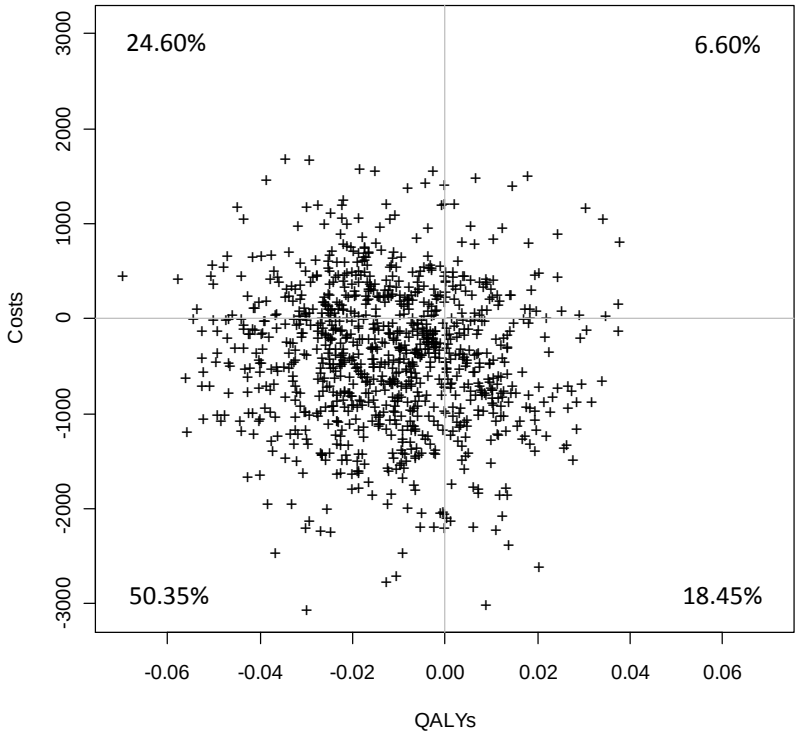


Figure 5 - Cost-utility plane
The numbers in the corners represent the percentage of crosses in each quadrant.

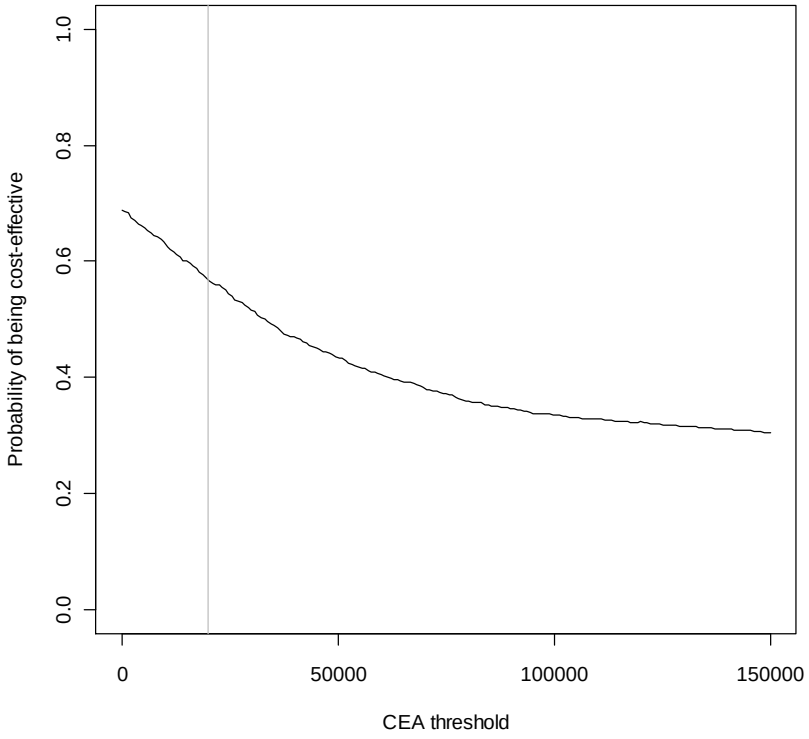


Figure 6 - Cost-utility acceptability curve
The grey line represents the commonly used cut-off of €20,000 per QALY.

The percentage of patients who decreased their EQ-5D score between baseline and end was lower in the six-monthly group (26.3% vs. 27.5%). However, the patients who declined showed a steeper decrease in the six-monthly group (-0.157) compared to the three-monthly group (-0.123). From the patients who decreased six were (very) dissatisfied with the monitoring frequency at the end of study and had the lowest EQ-5D score at the end of the study (0.529). These six patients were all from the six-monthly group.

Discussion

To our knowledge this is the first study to investigate monitoring frequency in well-controlled type 2 diabetes patients. Equivalence on cardiometabolic control between three-monthly and six-monthly monitoring was uncertain. However, the difference in cardiometabolic control between three-monthly and six-monthly monitoring was small and only slightly crossed the boundaries of equivalence. No secondary outcomes indicated relevant differences between the two groups. The economic evaluation showed that six-monthly monitoring was cheaper, but with lower QALYs.

Six previous studies have investigated the relationship between number of visits and patient outcomes in diabetes patients [7-12]. Since two studied uncontrolled patients [7,8] and two others were set up to increase access to care [9,10], the results of these four studies are not comparable with our results. Two observational studies showed that the number of visits was not related to glycaemic control, which is in line with our results [11,12]. However, a major limitation is that these studies were observational. Randomised trials in well-controlled asthma and hypertensive patients also showed that six-monthly monitoring was sufficient [6,92].

These studies and our results suggest that monitoring frequency could be reduced without compromising patient outcomes in well-controlled diabetes patients. Nevertheless, equivalence could not be formally ascertained in our trial. This can be explained by the lower success rate of reaching all three targets than expected (±70%, instead of an expected 95%). With a 70% success rate, a sample size of 1764 patients per group would have been necessary to demonstrate equivalence.

The lower than expected success rate is mainly related to not reaching the systolic blood pressure target. Blood pressure is known to be highly variable (between readings and visits), particularly in diabetes patients [93]. Most physicians will be

likely not to change antihypertensive medication after a first reading above target. They consider such measurements as 'false positives'. Therefore, we investigated whether patients who did not reach the systolic blood pressure target were potential 'false positive' cases by checking whether the prescription of antihypertensive drugs had changed during follow-up. This was the case in 40.1%, suggesting that a substantial proportion of the patients with blood pressure above target could be 'false positive'. If classifying these people as 'systolic blood pressure under control' the difference in cardiometabolic control would be closer to equivalence. However, clinical inertia cannot be excluded [94].

Another explanation for the lower success rate is the fact that some of the patients were no longer well-controlled at 'baseline' (first study visit). Patients were selected for the study based on measurements during the year preceding the start of the study, so their HbA1c or total cholesterol values may have worsened at the start of the study.

The only significant difference observed was a higher perceived frequency of hyper- or hypoglycaemia in the six-monthly monitoring group. This finding might indicate more insecurity in the six-monthly group, which could lead to a higher visit frequency. Patients with a higher perceived frequency of hyper- or hypoglycaemia had a higher number of visits compared to those with a lower score. These results suggest that some patients on six-monthly monitoring were more uncertain about their treatment. Indeed, the difference in mean number of visits between three-monthly and six-monthly monitoring was only 1.9, while it was expected to be 3 during follow-up. As we randomised at patient, not practice, level another explanation for this difference might be related to contamination of the monitoring frequency within general practices. However, the per-protocol analysis showed comparable results as the intention-to-treat analysis and therefore it is unlikely that either contamination or the increased consulting frequency of a small number of patients changed our conclusions.

Since equivalence was uncertain, we performed both a cost-minimisation analysis and a cost-utility analysis. Both analyses indicated that six-monthly monitoring is cheaper. We demonstrated that decreasing the monitoring frequency was associated with a reduction in costs of visits to the general practice and in reduced societal costs overall. The latter reduction was mainly related to differences in hospitalisation costs and in non-medical costs. However, only a small part of the patients experienced these costs and costs were highly skewed, hampering generalisability of total cost differences.

The ICUR was relatively high (above €20,000) and the probability of cost-effectiveness was quite low (<60%). These results were not unexpected, since we assumed little or no QALY difference between three-monthly and six-monthly monitoring at somewhat lower costs (3 visits*€29.02). With a small denominator, the ICUR becomes large. In the economic evaluation we did not include the costs of patients who had to take time off from their work to visit their general practice. Including these costs would be in favour of six-monthly monitoring. The decreased burden on the general practice staff was also not included.

The large ICUR was in particular driven by slightly lower QALYs in the six-monthly than in the three-monthly group. Further analysis showed that the QALY decrease was steeper in the six-monthly than three-monthly group, which was driven by a few participants with a steep decrease. This decrease was associated with dissatisfaction with the monitoring frequency, suggesting that a small number of patients on six-monthly monitoring would rather be monitored three-monthly.

Strength of this study was its randomised design. Since the study was part of a patient preference study, the generalisability of the results is higher than it would have been after performing a classic randomised controlled trial. Certain limitations need to be addressed. Firstly, the study was designed as a pragmatic study, which had consequences for the blinding and the timing of measurements. Because the trial was conducted as part of usual care, measurements of blood pressure and weight were not blinded. Furthermore, it was not possible to measure HbA1c and cholesterol for all patients exactly at baseline and after eighteen months, resulting in different follow-up periods for patients. However, excluding patients with less than twelve months of follow-up produced comparable results. We therefore think that the difference in length of follow-up between patients did not affect the direction of our results. Secondly, the follow-up period of eighteen months might be too short to detect deterioration of control. However, if on the longer run deterioration would indeed occur, the monitoring frequency could be adjusted. Six-monthly monitoring is not meant as a rigid schedule, patients can be advised to return to three-monthly monitoring at any time. Thirdly, the percentage of patients reaching the three targets was lower than expected, which indicates a high rate of overall failure. We presume that the relatively low percentage of people who maintained good cardiometabolic control is mainly caused by not reaching the systolic blood pressure target, but could also be a result of dichotomising the outcome data. Therefore, we also analysed HbA1c, blood pressure and cholesterol on a continuous scale, which revealed little or no

deterioration after eighteen months and also no difference between three-monthly and six-monthly monitoring. Finally, our definition of “well-controlled” is arbitrary. We have chosen values a little higher than the currently used targets in the Netherlands [4] in order to create a larger target population. Of course, in clinical practice both the targets for cardiometabolic control and the monitoring frequency should be individualised. The aim of this study was not to investigate the most ‘optimal’ frequency, but we advocate a tailored monitoring frequency. Based on our results it is possible that different risk factors need different intensity of follow-up to maintain optimal control: cholesterol the least, then HbA1c, then blood pressure needing relatively more frequent follow-up. In addition, patients who lose control or who frequently perceive hyper- and hypoglycaemias should be monitored more often.

Although equivalence of cardiometabolic control between three-monthly and six-monthly monitoring was uncertain, differences between three-monthly and six-monthly monitoring were not clinically relevant. We therefore conclude that patients with good cardiometabolic control can visit the general practice less often than the current three-monthly monitoring. Of course we should keep in mind that this conclusion only relates to well-controlled type 2 diabetes patients without a preference for the monitoring frequency. In the Netherlands approximately 20% of the diabetes patients achieve good cardiometabolic control [24].

Implementing six-monthly monitoring will save costs in these patients and both patient burden and practice workload could be reduced. Diabetes guidelines should include six-monthly monitoring as an option for patients with good cardiometabolic control and no strong preference for their monitoring frequency.

Chapter 5

Patient preference study

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Submitted

Abstract

Objective: To investigate whether three-monthly or six-monthly monitoring of well-controlled type 2 diabetes patients was associated with sustained good cardiometabolic control and to assess the influence of the patient's preference for monitoring frequency.

Research Design and Methods: A patient preference study in 2215 well-controlled (HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l) type 2 diabetes patients. Participants were asked whether they had a strong preference for three-monthly or six-monthly monitoring. If not, they were randomised to either three-monthly or six-monthly monitoring; if yes, they were monitored according to their preference. First, the preference groups were compared to determine whether they remained under good cardiometabolic control. Second, the preference groups were compared with the randomised groups. Patients were followed for eighteen months.

Results: Good cardiometabolic control in the three-monthly preference group (69.9%) did not differ from the six-monthly preference group (67.3%) (difference: -2.6%; 95% CI: -7.5% to 2.3%). After adjusting for confounders, the six-monthly preference group had a higher total cholesterol (difference: 0.10 mmol/l; 95% CI: 0.01 to 0.19), lower perceived frequency of hyper- (-0.28; 95% CI: -0.47 to -0.10) and hypoglycaemias (-0.15; 95% CI: -0.30 to -0.00) and less frequent use of oral blood glucose lowering drug (OR: 0.58; 95% CI: 0.37-0.92) compared with the three-monthly preference group. Randomised and preference patients, from both the three-monthly and six-monthly group, did not differ on cardiometabolic control.

Conclusions: Good cardiometabolic control was equally sustained in well-controlled type 2 diabetes patients, whether they were monitored three-monthly or six-monthly and whether they had a preference for the monitoring frequency or not. This indicates that six-monthly monitoring could be offered to well-controlled type 2 diabetes patients.

Introduction

International diabetes guidelines recommend different monitoring frequencies ranging from one to four times a year [21,37]. However, these recommendations are not evidence-based.

Two observational studies demonstrated that in type 2 diabetes patients the number of visits was not related to glycaemic control [11,12]. Similarly, in a randomised equivalence trial six-monthly monitoring of well-controlled hypertensive patients achieved the same levels of blood pressure control, adherence to treatment and patient satisfaction as patients on three-monthly monitoring [6]. We therefore hypothesised that lowering the monitoring frequency in well-controlled diabetes patients will not lead to poorer patient outcomes and could reduce costs.

Because patient's preferences might influence treatment adherence [19] and thus cardiometabolic control, we conducted a patient preference study [22], accounting for the preferences of the patients regarding the monitoring frequency. Part of the study was a randomised controlled patient-preference equivalence trial, which demonstrated that well-controlled type 2 diabetes patients without a preference for the monitoring frequency who were randomised to six-monthly monitoring achieved similar cardiometabolic control compared to those randomised to three-monthly monitoring (**Chapter 4**). However, the external validity (generalisability) of randomised trials has been criticised [22,95,96]. Participants in a trial are thought to be unrepresentative of the wider population, because patients with a strong treatment preference might refuse randomisation or simply not comply with treatment if it is not the preferred treatment. Clear baseline differences were present between patients with and without a preference for three-monthly or six-monthly monitoring (**Chapter 2**). The patient preference design allows us to study the influence of patients' preferences and the generalisability of the trial results.

First, we assessed whether well-controlled type 2 diabetes patients with a strong preference for six-monthly monitoring achieved equal cardiometabolic control after eighteen months compared to patients with a strong preference for three-monthly monitoring. Secondly, we compared the outcomes of the patients who had a strong preference for the monitoring frequency with the patients randomised to three-monthly or six-monthly monitoring (see ***Figure 1***).

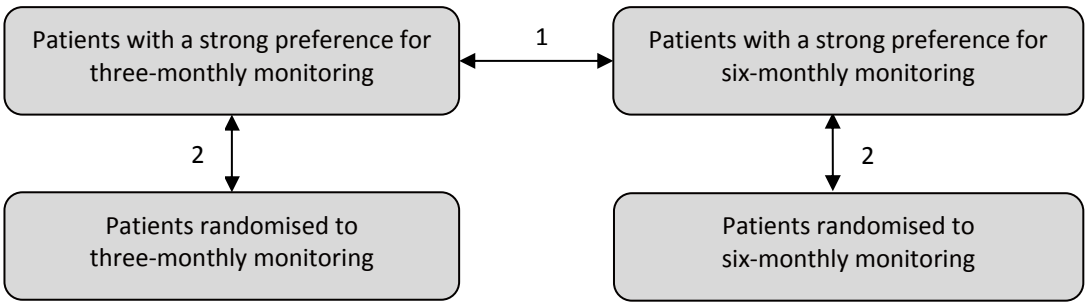


Figure 1 - Comparisons that were made between the groups
Comparison 1 determined if six-monthly monitoring is equivalent to three-monthly monitoring. Comparisons 2 showed if the three-monthly and six-monthly groups were comparable with each other.

Research design and methods

Study design

This study was part of the EFFIMODI study, a randomised controlled equivalence trial with a patient preference study (**Chapter 1**). At inclusion, all patients were asked whether they had a strong preference for three-monthly or six-monthly monitoring. Those with a strong preference for either three-monthly or six-monthly monitoring were treated according to their preference, while those without a strong preference were randomised to either three-monthly or six-monthly monitoring. This procedure resulted in four study groups: randomised to three-monthly monitoring, randomised to six-monthly monitoring, preferring three-monthly monitoring and preferring six-monthly monitoring. The Medical Research Ethics Committee of the University Medical Center Utrecht approved the study protocol (Protocol number: 08-453).

Participants

Patients were recruited from general practices across the Netherlands within the period April 2009 to August 2010. They were eligible if between 40 and 80 years old, diagnosed with type 2 diabetes for more than one year, treated by their general practitioner, not on insulin treatment and overall well-controlled, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l.

The boards of several regional care groups [97] were asked to recruit general practitioners. These groups care have a central database in which data of all type 2 diabetes patients are recorded, thus enabling the selection of eligible patients. When a general practitioner wanted to participate, the selection of patients according to the inclusion criteria was obtained from the care group. The general

practitioner sent an information letter as well as an informed consent form to all selected patients by mail.

To determine the patient's preference for the monitoring frequency, participants were asked to mark one of three boxes on the informed consent form. These boxes stated: (1) I have a strong preference for three-monthly monitoring, (2) I have a strong preference for six-monthly monitoring and (3) I have no strong preference for the monitoring frequency.

Outcomes

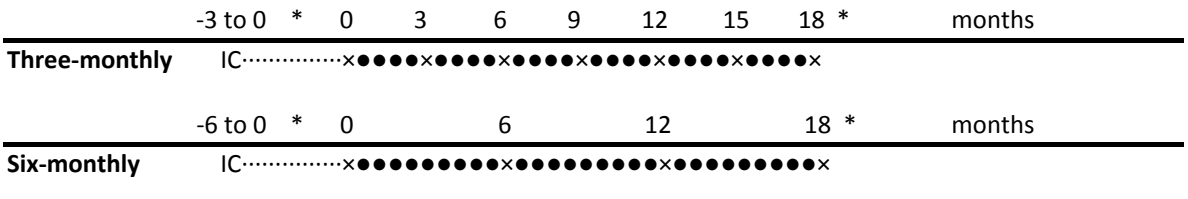
The primary outcome measure was the percentage of people who remained under good cardiometabolic control, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. The separate targets for HbA1c, systolic blood pressure and total cholesterol were used as secondary outcomes (percentage below target). Other secondary outcomes were: HbA1c, blood pressure (systolic and diastolic) and cholesterol (HDL, LDL and total) on a continuous scale; BMI; the percentage of current smokers; the percentage of physically active people (measured with the SQUASH questionnaire [25]); mean health status scores (measured with the SF-36 [27] and EQ VAS questionnaires [28]); diabetes-related distress (measured with the PAID questionnaire [30]); satisfaction with diabetes treatment and perceived frequency of hyper- and hypoglycaemias (measured with DTSQ status [32]); and medication use.

Intervention and follow-up

According to the Dutch guidelines on type 2 diabetes [4], blood pressure and weight should be measured at each diabetes visit. The frequency of measuring HbA1c and cholesterol differs between practices. Usually, and according to the guidelines, HbA1c and cholesterol are measured once a year during an extensive yearly visit. An extensive yearly visit is usually done by the general practitioner; all other visits are performed by the practice nurse. The treatment targets, therapeutic algorithms and lifestyle advice were according to the current guidelines [4] and did not differ between the groups. In the event of complications (diabetes-related or other), or poorly controlled HbA1c, blood pressure or lipids, patients from both groups could visit their practice more often or be referred to secondary care.

Patients were followed for eighteen months, and thus were seen either seven (three-monthly group) or four (six-monthly group) times during that period (see

Figure 2). Since this was a pragmatic study we did not want to perform additional study measurements beyond routine care. Therefore, the extensive yearly visit was also included in the six-monthly visit cycle and we used the last known routine care HbA1c, systolic blood pressure and total cholesterol measurements for the primary outcome.



IC	= Moment at which informed consent is signed
·····	= Time between signing of informed consent and start of the study period (variable)
×	= Interval visit
●●	= Time between interval visits
*	= Moment at which patient questionnaires were filled in by the patients

Figure 2 - Schematic overview of the planned diabetes visits and follow-up time of patients in the three-monthly and six-monthly group

At each interval visit blood pressure and weight should be measured. Usually once a year one of the interval visits is an extensive yearly visit. This visit is usually performed by the general practitioner and HbA1c and cholesterol are also measured then.

Data collection

Medical data were collected with two case report forms (at baseline and at the end of the study period) filled in by the general practitioner or practice nurse. At baseline, height (cm), year of diabetes diagnosis and medical history were determined. Type and dosage of oral blood glucose lowering drugs, antihypertensive drugs and lipid lowering drugs were assessed at the beginning and at the end of the study period. The last recorded measurement before the first study visit plus all measurements performed during the planned diabetes visits were reported for weight (kg), HbA1c (mmol/mol), systolic and diastolic blood pressure (mmHg), HDL, LDL and total cholesterol (mmol/l). Furthermore, the number of days in the hospital and the number of scheduled and unscheduled diabetes visits and other visits during the study period were collected. In case of drop-out, medical data were collected until drop-out (if possible).

At baseline and after eighteen months, participants filled in a questionnaire. If necessary, participants received up to two reminders. The patient questionnaires consisted of demographic information, physical activity, health status, diabetes-related distress, satisfaction with diabetes treatment and perceived frequency of

hyper- and hypoglycaemias. The content of the patient questionnaires has been described in detail elsewhere (**Chapter 1**).

Statistical analysis

First, we compared the three-monthly preference group with the six-monthly preference group on all outcomes. Next, we compared patients with a preference for monitoring frequency with randomised patients without a preference, separately for three-monthly and six-monthly monitoring (***Figure 1***).

The primary outcome was analysed according to the intention-to-treat principle (with last observation values carried forward in case of missing values). In addition, we performed a sensitivity analysis for HbA1c, systolic blood pressure and total cholesterol measurements on patients with a minimum of twelve months of follow-up. This was to reduce the influence of patients with a relatively short follow-up on the primary outcome.

To calculate the crude difference in outcomes between two groups we used generalized linear models with a binomial distribution and the identity link function for dichotomous outcomes and linear regression for continuous outcomes, correcting for baseline measurement if applicable.

To measure the independent influence of preference on cardiometabolic control and all other outcomes, we adjusted for potential confounding factors associated with preferences for monitoring frequency at baseline. These were smoking, health status, diabetes-related distress, satisfaction with diabetes treatment, perceived frequency of hyperglycaemias and oral blood glucose lowering drug use (adopted from **Chapter 2**).

For the continuous outcomes we modelled differences by adding the confounders in the linear regression models. Because of convergence problems of the models for the dichotomous outcomes we adjusted for confounders by calculating a propensity score based on the probability of being in a study group given the potential confounders. This propensity score summarises all confounding factors in one score [98]. Then we modelled risk differences by including the propensity score to the generalized models. When convergence problems were encountered for the generalized linear models we used logistic regression.

To handle missing data in the confounders and baseline measurements we used multiple imputation, assuming that the missings were at random. We generated

10 imputed datasets and used Rubin's rules to combine the estimates of the parameters [33]. Data were analysed using the SPSS software, version 20.

Results

In ***Table 1*** the baseline characteristics of the four study groups are shown. At baseline, 747 patients (33.7%) had a preference for three-monthly monitoring, 677 (30.6%) had a preference for six-monthly monitoring and 791 (35.7%) had no preference. The latter were randomised to three-monthly (n=394) or six-monthly monitoring (n=397).

After eighteen months the percentage of people who remained under good cardiometabolic control was 69.9% in the three-monthly preference group and 67.3% in the six-monthly preference group (unadjusted difference: -2.6%; 95% CI: -7.5% to 2.3%). In the three-monthly and six-monthly group the HbA1c target was reached by 92.7% and 94.0%, respectively; the systolic blood pressure target by 82.7% and 79.8%, respectively; and the total cholesterol target by 91.6% and 90.3%, respectively. None of these differences were significant. Results did not change after adjusting for confounders. The sensitivity analysis showed comparable results (data not shown).

Table 2 describes the secondary outcomes in the preference groups. After eighteen months the six-monthly group had a lower HbA1c (-1.36 mmol/mol; 95% CI: -2.23 to -0.49), a higher HDL cholesterol (0.04 mmol/l; 95% CI: 0.00 to 0.07), a better physical health (0.93; 95% CI: 0.10 to 1.76), and a lower perceived frequency of hyper- (-0.36; 95% CI: -0.55 to -0.18) and hypoglycaemias (-0.24; 95% CI: -0.38 to -0.09). After adjusting for confounders the differences in HbA1c, HDL cholesterol and physical health became non-significant, while total cholesterol became significantly higher in the six-monthly group (difference: 0.10 mmol/l; 95% CI: 0.01 to 0.19).

Table 3 describes the differences between the randomised trial and the preference study. Both the perceived frequency of hyper- and hypoglycaemias were significantly lower in the randomised three-monthly group compared to the preference three-monthly group (difference: -0.33; 95% CI: -0.55 to -0.12 and -0.33; 95% CI: -0.49 to -0.16, respectively). After adjusting for confounders, the differences attenuated but remained significant (difference: -0.25; 95% CI: -0.47 to -0.04 and -0.25; 95% CI: -0.42 to -0.09, respectively). In addition, total cholesterol rose significantly in the randomised three-monthly group compared to the

preference three-monthly group (difference: 0.11 mmol/l; 95% CI: 0.01 to 0.21) after adjustment.

The randomised six-monthly group perceived hyperglycaemias more frequently than the preference six-monthly group (difference: 0.27; 95% CI: 0.07 to 0.47) and was less satisfied with diabetes treatment (difference: -0.57; 95% CI: -1.13 to -0.01). After adjusting for confounders only the perceived frequency of hyperglycaemias remained significant (difference: 0.25; 95% CI: 0.06 to 0.44).

The number of scheduled diabetes visits was comparable in the three-monthly and in the six-monthly groups. The number of unscheduled diabetes visits was equal between the preference groups, however between the randomised groups there was a difference of 0.7 visits. The total number of diabetes visits and the total number of visits were highest in the three-monthly preference group and lowest in the six-monthly preference group (***Table 4***).

Table 1 - Baseline characteristics of the different patient groups

	Preference study				Randomised trial			
	Three-monthly monitoring (n=747)		Six-monthly monitoring (n=677)		Three-monthly monitoring (n=394)		Six-monthly monitoring (n=397)	
	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)	n	Mean ± SD or n (%)
Age (years)	745	64.6 ± 8.8	676	64.1 ± 8.7	393	64.7 ± 8.8	396	64.4 ± 8.8
Gender (male)	745	437 (58.7%)	676	404 (59.8%)	393	239 (60.8%)	395	231 (58.5%)
Dutch ethnicity	684	600 (87.7%)	655	591 (90.2%)	380	348 (91.6%)	381	338 (88.7%)
Educational level	629		608		344		357	
Low		270 (42.9%)		233 (38.3%)		138 (40.1%)		157 (44.0%)
Middle		224 (35.6%)		239 (39.3%)		125 (36.3%)		121 (33.9%)
High		135 (21.5%)		136 (22.4%)		81 (23.5%)		79 (22.1%)
Living alone	682	135 (19.8%)	646	116 (18.0%)	377	83 (22.0%)	375	74 (19.7%)
Working status	670		648		373		380	
Paid job		172 (25.7%)		175 (27.0%)		92 (24.7%)		100 (26.3%)
Retired		371 (55.4%)		350 (54.0%)		209 (56.0%)		208 (54.7%)
Other		127 (19.0%)		123 (19.0%)		72 (19.3%)		72 (18.9%)
Duration of diabetes (years)	719	6.0 ± 3.8	648	5.8 ± 3.6	378	5.5 ± 3.5	382	5.9 ± 3.8
Medical history								
Myocardial infarction	736	63 (8.6%)	665	53 (8.0%)	391	33 (8.4%)	390	36 (9.2%)
Angina pectoris	736	75 (10.2%)	665	63 (9.5%)	391	40 (10.2%)	390	33 (8.5%)
Heart surgery	736	39 (5.3%)	665	34 (5.1%)	391	21 (5.4%)	390	28 (7.2%)
Heart failure	736	20 (2.7%)	665	15 (2.3%)	391	12 (3.1%)	390	12 (3.1%)
Stroke	736	42 (5.7%)	665	33 (5.0%)	391	29 (7.4%)	390	20 (5.1%)
Transient ischemic attack	736	21 (2.9%)	665	13 (2.0%)	391	13 (3.3%)	390	10 (2.6%)
Peripheral arterial disease	736	35 (4.8%)	665	28 (4.2%)	391	19 (4.9%)	390	19 (4.9%)
COPD	736	52 (7.1%)	665	41 (6.2%)	391	42 (10.7%)	390	23 (5.9%)
Rheumatoid arthritis	736	9 (1.2%)	665	16 (2.4%)	391	7 (1.8%)	390	10 (2.6%)
Osteoarthritis of the hip or knee	736	76 (10.3%)	665	49 (7.4%)	391	26 (6.6%)	390	33 (8.5%)

Table 2 - Baseline and follow-up measures for the three-monthly and six-monthly preference groups (means or percentages) with the corresponding differences between these groups

	Preferred three-monthly monitoring				Preferred six-monthly monitoring					
	Baseline		Follow-up		Baseline		Follow-up		Six-monthly – three-monthly monitoring	
	n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	n	Mean ± SD or %	Crude difference (95% CI)	Adjusted difference (95% CI)
HbA1c (mmol/mol)*	722	47.4 ± 5.7	735	48.9 ± 8.8	657	45.9 ± 5.9	665	47.8 ± 7.6	**-1.36 (-2.23 to -0.49)**	-0.47 (-1.37 to 0.44)
HDL cholesterol (mmol/l)*	718	1.2 ± 0.4	735	1.2 ± 0.3	650	1.2 ± 0.3	664	1.2 ± 0.3	**0.04 (0.00 to 0.07)**	0.03 (-0.01 to 0.06
LDL cholesterol (mmol/l)*	718	2.3 ± 0.6	735	2.2 ± 0.7	651	2.3 ± 0.7	664	2.3 ± 0.7	0.05 (-0.02 to 0.13)	0.05 (-0.03 to 0.13)
Total cholesterol (mmol/l)*	677	4.2 ± 0.7	726	4.2 ± 0.8	637	4.2 ± 0.8	657	4.2 ± 0.9	0.08 (-0.01 to 0.17)	**0.10 (0.01 to 0.19)**
Systolic blood pressure	722	133 ± 13	643	134 ± 14	640	134 ± 15	543	135 ± 15	1.06 (-0.52 to 2.63)	0.93 (-0.75 to 2.61)
Diastolic blood pressure	721	77 ± 9	642	77 ± 9	640	78 ± 9	542	77 ± 10	-0.20 (-1.12 to 0.72)	-0.50 (-1.48 to 0.49)
BMI (kg/m^2)	693	29.0 ± 4.8	615	29.1 ± 4.9	614	29.3 ± 5.1	511	29.1 ± 4.6	-0.15 (-0.43 to 0.13)	-0.14 (-0.44 to 0.15)
Current smoker	689	14.4%	627	12.1%	652	21.0%	583	19.2%	0.0% (-1.5% to 1.5%)	*OR: 1.13 (0.80-1.59)***
Physically active	650	70.8%	592	72.6%	632	71.7%	556	72.5%	-0.4% (-5.0% to 4.3%)	-1.8% (-6.7% to 3.2%)
SF-36 PCS [scale: 0-100]	615	44.9 ± 10.3	573	44.0 ± 10.6	598	47.6 ± 9.9	526	47.2 ± 10.2	**0.93 (0.10 to 1.76)**	0.82 (-0.05 to 1.69)
SF-36 MCS [scale: 0-100]	615	53.4 ± 9.2	573	53.1 ± 9.1	598	54.5 ± 8.4	526	54.0 ± 8.9	0.24 (-0.65 to 1.13)	-0.48 (-1.39 to 0.44)
EQ VAS [scale: 0-100]	638	74.0 ± 14.4	582	73.8 ± 13.7	628	77.6 ± 15.0	552	75.7 ± 15.4	-0.36 (-1.67 to 0.96)	-0.59 (-1.96 to 0.78)
PAID [scale: 0-80]	653	9.1 ± 10.5	594	8.8 ± 10.5	631	5.7 ± 7.8	551	5.7 ± 8.3	-0.78 (-1.63 to 0.06)	-0.56 (-1.45 to 0.32)
DTSQ [scale: 0-36]	673	31.8 ± 4.4	612	31.8 ± 4.5	638	32.0 ± 4.4	567	32.2 ± 4.5	0.33 (-0.12 to 0.79)	-0.03 (-0.51 to 0.44)
DTSQ hyper [scale: 0-6]	676	1.7 ± 1.8	620	1.8 ± 1.8	652	0.8 ± 1.4	574	1.0 ± 1.5	**-0.36 (-0.55 to -0.18)**	**-0.28 (-0.47 to -0.10)**
DTSQ hypo [scale: 0-6]	681	1.0 ± 1.5	616	1.1 ± 1.5	650	0.6 ± 1.2	577	0.7 ± 1.3	**-0.24 (-0.38 to -0.09)**	**-0.15 (-0.30 to -0.00)**
Oral blood glucose lowering drugs	736	82.3%	720	86.3%	665	69.5%	642	72.7%	-0.1% (-2.1% to 1.9%)	*OR: 0.78 (0.58-1.06)***
Antihypertensive drugs	736	73.8%	720	77.4%	665	70.4%	642	72.0%	-1.2% (-3.5% to 1.0%)	-1.4% (-3.9% to 1.1%)
Lipid lowering drugs	736	83.2%	720	83.5%	665	77.6%	642	81.2%	0.1% (-2.5% to 2.7%)	0.3% (-2.5% to 3.1%)

The crude differences were only corrected for baseline measurement. The adjusted differences were corrected for baseline measurement, smoking, health status, diabetes-related distress, satisfaction with diabetes treatment, perceived frequency of hyperglycaemias and oral blood glucose lowering drug use. If the difference is positive this indicates that the six-monthly preference group has a higher percentage or mean for that specific variable than the preference group.

* These differences were not corrected for baseline measurement.

** For these variables we displayed the Odds Ratio (OR) with the corresponding 95% confidence interval. This was because the generalized models could not converge when adjusting for the potential confounders, due to low numbers.

SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score; EQ VAS, EuroQol Visual Analogue Scale; PAID, Problem Areas In Diabetes; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

Table 3 - Follow-up measurements and the difference between the randomised trial and the preference study

	Randomised to three-monthly monitoring – preferred three-monthly monitoring		Randomised to six-monthly monitoring – preferred six-monthly monitoring	
	Crude difference (95% CI)	**Adjusted difference (95% CI)**	**Crude difference (95% CI)**	**Adjusted difference (95% CI)**
All three measures under control*	-0.4% (-6.1% to 5.3%)	-1.4% (-7.3% to 4.5%)	2.5% (-3.3% to 8.3%)	3.2% (-2.7% to 9.0%)
HbA1c ≤58 mmol/mol*	-0.8% (-4.1% to 2.5%)	*OR: 0.73 (0.46-1.18)***	-0.6% (-3.7% to 2.4%)	-0.3% (-3.4% to 2.7%)
Systolic blood pressure ≤145 mmHg*	0.4% (-4.2% to 5.0%)	0.8% (-3.9% to 5.6%)	0.7% (-4.3% to 5.7%)	0.9% (-4.1% to 5.9%)
Total cholesterol ≤5.2 mmol/l*	-0.1% (-3.5% to 3.3%)	-0.4% (-4.1% to 3.3%)	2.5% (-0.9% to 6.0%)	3.0 (-0.5% to 6.5%)
HbA1c (mmol/mol)*	-0.49 (-1.55 to 0.57)	0.18 (-0.89 to 1.25)	0.62 (-0.33 to 1.56)	0.42 (-0.51 to 1.34)
HDL cholesterol (mmol/l)*	0.01 (-0.03 to 0.05)	0.00 (-0.04 to 0.04)	0.01 (-0.04 to 0.06)	0.01 (-0.04 to 0.06)
LDL cholesterol (mmol/l)*	0.03 (-0.05 to 0.11)	0.03 (-0.05 to 0.12)	-0.05 (-0.14 to 0.03)	-0.05 (-0.14 to 0.04)
Total cholesterol (mmol/l)*	0.10 (-0.00 to 0.20)	**0.11 (0.01 to 0.21)**	-0.09 (-0.19 to 0.02)	-0.10 (-0.20 to 0.01)
Systolic blood pressure (mmHg)	-0.69 (-2.46 to 1.08)	-1.04 (-2.86 to 0.78)	-1.84 (-3.77 to 0.09)	-1.85 (-3.80 to 0.10)
Diastolic blood pressure (mmHg)	-0.54 (-1.57 to 0.50)	-0.71 (-1.78 to 0.36)	-0.70 (-1.85 to 0.44)	-0.58 (-1.73 to 0.58)
BMI (kg/m^2)	0.07 (-0.20 to 0.34)	0.08 (-0.20 to 0.36)	0.15 (-0.17 to 0.47)	0.19 (-0.14 to 0.51)
Current smoker	0.7% (-1.3% to 2.7%)	*OR: 1.04 (0.70-1.54)***	-0.3% (-2.0% to 1.4%)	*OR: 0.82 (0.56-1.21)***
Physically active	1.3% (-4.1% to 6.8%)	0.3% (-5.3% to 5.8%)	3.4% (-1.9% to 8.6%)	3.9% (-1.4% to 92.%)
SF-36 PCS [scale: 0-100]	-0.29 (-1.29 to 0.70)	-0.45 (-1.47 to 0.57)	-0.76 (-1.77 to 0.26)	-0.74 (-1.75 to 0.28)
SF-36 MCS [scale: 0-100]	0.54 (-0.45 to 1.54)	0.22 (-0.79 to 1.23)	0.70 (-0.37 to 1.77)	0.78 (-0.28 to 1.83)
EQ VAS [scale: 0-100]	-0.35 (-1.81 to 1.11)	-0.57 (-2.05 to 0.92)	-0.32 (-1.99 to 1.36)	-0.41 (-2.09 to 1.27)
PAID [scale: 0-80]	-0.25 (-1.30 to 0.79)	-0.07 (-1.12 to 0.98)	0.17 (-0.69 to 1.03)	0.13 (-0.73 to 1.00)
DTSQ [scale: 0-36]	-0.21 (-0.77 to 0.34)	-0.43 (-0.99 to 0.14)	**-0.57 (-1.13 to -0.01)**	-0.44 (-1.01 to 0.12)
DTSQ hyper [scale: 0-6]	**-0.33 (-0.55 to -0.12)**	**-0.25 (-0.47 to -0.04)**	**0.27 (0.07 to 0.47)**	**0.25 (0.06 to 0.44)**
DTSQ hypo [scale: 0-6]	**-0.33 (-0.49 to -0.16)**	**-0.25 (-0.42 to -0.09)**	0.16 (-0.00 to 0.32)	0.13 (-0.03 to 0.29)
Oral blood glucose lowering drugs	-1.3% (-4.0% to 1.4%)	*OR: 1.00 (0.70-1.43)***	-0.8% (-3.1% to 1.6%)	*OR: 1.10 (0.79-1.52)***
Antihypertensive drugs	-1.6% (-4.3% to 1.1%)	-1.6% (-4.6% to 1.4%)	2.2% (-0.1% to 4.5%)	*OR: 1.10 (0.82-1.48)***
Lipid lowering drugs	0.0% (-3.0% to 2.9%)	0.0% (-3.2% to 3.2%)	0.9% (-2.2% to 4.0%)	0.8% (-2.3% to 3.9%)

The crude differences were only corrected for baseline measurement. The adjusted differences were corrected for baseline measurement, smoking, health status, diabetes-related distress, satisfaction with diabetes treatment, perceived frequency of hyperglycaemias and oral blood glucose lowering drug use. If the difference is positive this indicates that the randomised group has a higher percentage or mean for that specific variable than the preference group.

* These differences were not corrected for baseline measurement.

** For these variables we displayed the Odds Ratio (OR) with the corresponding 95% confidence interval. This was because the generalized models could not converge when adjusting for the potential confounders, due to low numbers.

SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score; EQ VAS, EuroQol Visual Analogue Scale; PAID, Problem Areas In Diabetes; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

Table 4 - Number of visits during the study period

	Preference study				Randomised trial			
	Three-monthly monitoring		Six-monthly monitoring		Three-monthly monitoring		Six-monthly monitoring	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Scheduled diabetes visits	720	6.7 ± 0.8	642	3.9 ± 0.4	383	6.6 ± 0.9	377	3.9 ± 0.4
Unscheduled diabetes visits	720	1.6 ± 2.8	642	1.6 ± 2.1	383	1.3 ± 2.3	377	2.0 ± 3.2
Total number of diabetes visits	720	8.3 ± 3.0	642	5.5 ± 2.2	383	7.8 ± 2.5	377	5.9 ± 3.2
Other visits	720	6.3 ± 6.5	642	5.2 ± 6.2	383	5.9 ± 5.6	377	5.5 ± 5.9
Total number of visits	720	14.6 ± 7.5	642	10.7 ± 7.0	383	13.7 ± 6.3	377	11.4 ± 7.0

Conclusions

This study found that well-controlled diabetes patients with a strong preference for either three-monthly or six-monthly monitoring achieved the same level of cardiometabolic control. Comparing the 'preference' patients with the randomised patients, no difference in cardiometabolic control was observed for either three-monthly or six-monthly monitoring. The significant differences between the four study groups with regard to the secondary outcomes were relatively small and not clinically relevant.

Only six previous studies have investigated the relationship between number of diabetes visits and patient outcomes [7-12]. Two were performed in uncontrolled patients [7,8] with inconsistent results, while two were designed to increase access to care [9,10]. Therefore, their results are difficult to compare with ours. The two most similar studies both concluded that the number of visits was not related to glycaemic control [11,12], but these studies were observational. In the present study we found no difference in cardiometabolic control between patients preferring three-monthly monitoring and those preferring six-monthly monitoring. Small differences were found for some secondary outcomes, a few of which, possibly due to the large sample size, were statistically significant.

The randomised trial demonstrated that cardiometabolic control was comparable after three-monthly and six-monthly monitoring. Comparing the results in patients with a strong preference with those of the randomised patients provides an estimate of the additional influence of motivational factors [99]. Patients who receive their preferred treatment may have better compliance and be more motivated to follow treatment regimens [22,99]. In our study the two three-

monthly groups and the two six-monthly groups maintained comparable cardiometabolic control. Therefore, if well-controlled type 2 diabetes patients are not monitored against their preference, they could be monitored two times per year without compromising the cardiometabolic control. This conclusion is in line with the statement that taking into account patients' preferences might influence treatment adherence and thus clinical outcomes [19]. We cannot say what the effect would be if physicians would decrease monitoring frequency for patients with a strong preference for three-monthly monitoring (about one in three patients).

The design of this study as a patient preference study, which may lead to less selection bias and drop-out, is its greatest strength. In addition, this design helps in interpreting and generalising the results from the randomised trial. There are also limitations that need to be addressed. Firstly, although this was a patient preference study, we still encountered patients who did not want to participate (±45%). Secondly, the study was designed as a pragmatic study which had consequences for the blinding and the timing of measurements. Because the trial was conducted as part of usual care, measurements of blood pressure and weight were not blinded. Furthermore, it was not possible to measure HbA1c and cholesterol for all patients at baseline and exactly after eighteen months. However, the sensitivity analysis indicated that the difference in follow-up between patients did not affect our results to a large extent. Finally, our definition of "well-controlled" is arbitrary. We have chosen values a little higher than the currently used targets in the Netherlands [4] in order to create a larger target population. We estimate that approximately 20% of the type 2 diabetes patients is "well-controlled" according to our definition [24]. In clinical practice, of course, both the targets for cardiometabolic control and the monitoring frequency should be individualised.

In conclusion, cardiometabolic control remained quite similar whether patients were monitored three-monthly or six-monthly and whether they had a strong preference for their monitoring frequency or not. Since the preference patients and the randomised patients both maintained equal cardiometabolic control, the results of the preference study support the results of the randomised trial. This indicates that six-monthly monitoring could be sufficient for at least two-thirds of the well-controlled type 2 diabetes patients.

Chapter 6

Satisfaction of the patients

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Submitted

Abstract

Background: Patient's satisfaction with monitoring frequency is of interest when implementing six-monthly monitoring for well-controlled type 2 diabetes patients.

Aim: To determine the satisfaction of well-controlled type 2 diabetes patients with either three-monthly or six-monthly diabetes monitoring and their future preference.

Design and setting: Survey among 2215 well-controlled type 2 diabetes patients who participated in the EFFIMODI study, a randomised controlled patient-preference equivalence trial.

Method: At baseline, participants were asked whether they had a strong preference for three-monthly or six-monthly monitoring or not. If not, they were randomised to either three-monthly or six-monthly monitoring, while the others were monitored according to their preference. After eighteen months, all participants were asked whether they were satisfied with the monitoring frequency and about their future preference. Patient characteristics associated with satisfaction were also examined.

Results: Most patients (70.8%) would like to continue their monitoring frequency. Patients from the preference groups were more often satisfied than randomised patients (92.7% and 88.1%, respectively) and patients monitored three-monthly were more often satisfied than patients monitored six-monthly (93.5% and 88.5%, respectively). Higher age, better physical health, less diabetes-related distress, higher diabetes treatment satisfaction and less perceived hyper- and hypoglycaemias were associated with a higher monitoring satisfaction.

Conclusion: Most well-controlled type 2 diabetes patients were satisfied with their monitoring frequency and would like to continue it. Although the satisfaction for three-monthly monitoring was slightly higher, the satisfaction with six-monthly monitoring was still rather high (88.5%).

Introduction

Worldwide, the number of people with type 2 diabetes was 366 million in 2011 and this number is likely to increase with 50% by 2030 [100]. International diabetes guidelines recommend different monitoring frequencies ranging from one to four times a year, but these guidelines are not evidence-based [21,37].

If part of the patients with diabetes would visit their general practice less frequently, this could lessen the patients' and healthcare providers' diabetes-related burden and provide savings in healthcare costs. We could demonstrate that six-monthly monitoring of well-controlled diabetes patients who had no strong preference with regard to their diabetes monitoring frequency in primary care achieved comparable cardiometabolic control compared to three-monthly monitoring (**Chapter 4**). However, two out of three patients had a strong preference with regard to the monitoring frequency (**Chapter 2**). These preferences might hamper the implementation of six-monthly monitoring.

Besides costs savings, the satisfaction of the patients with their monitoring frequency is of interest when implementing six-monthly monitoring, since patient satisfaction is associated with treatment adherence [101,102]. To our knowledge, no research has been performed on satisfaction with monitoring frequency and which factors are associated with it.

Therefore, we aimed to assess patient's satisfaction with either three-monthly or six-monthly diabetes monitoring after eighteen months of experience in both patients with and without a strong preference at the start of that period. We also determined which patient characteristics and health-related factors are associated with this satisfaction and what patients prefer for the future with regard to their diabetes monitoring.

Methods

Study design and patients

This study is part of a randomised controlled patient-preference equivalence trial in primary care. Type 2 diabetes patients were recruited in general practices across the Netherlands from April 2009 to August 2010. Patients were eligible if between 40 and 80 years old, diagnosed with type 2 diabetes for more than a year, treated by their general practitioner, not on insulin treatment and overall well-controlled, defined as having HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l.

Eligible patients were contacted by mail by their general practitioner with an information letter and an informed consent form. At baseline, patients were asked whether they had a strong preference for three-monthly or six-monthly monitoring. Those with a strong preference for either three-monthly or six-monthly monitoring were treated according to their preference, while those without a strong preference were randomised to either three-monthly or six-monthly monitoring. After returning the informed consent form, all participants received a postal questionnaire to be completed at home and after eighteen months they received the end-of-study questionnaire.

The study was approved by the Medical Research Ethics Committee of the University Medical Center Utrecht (protocol number 08-453). A detailed protocol of the EFFIMODI study has been published elsewhere (**Chapter 1**). In this paper we describe the satisfaction of well-controlled type 2 diabetes patients with three-monthly and six-monthly monitoring.

Measurement of patient's satisfaction and preference for the monitoring frequency in the future

In the end-of-study questionnaire, the following two questions were included:

1) How satisfied were you with either three-monthly or six-monthly monitoring? (not at all, not, neutral, moderate, very much)

2) How often would you like to be monitored in the future? (every three months, every six months, no preference/I do not care, every (filled in by the patient) months)

Measurement of determinants of patient's satisfaction

Several possible determinants of patient's satisfaction were assessed. These were derived from the patient questionnaires or from the medical data collected by a case report form filled in by the general practitioner or practice nurse.

Both the baseline and end-of-study questionnaire included information on age, gender, smoking, health status (measured with the SF-36 [27] and EQ VAS [28]), diabetes-related distress (measured with the PAID [30]) and satisfaction with diabetes treatment and experienced hyper- or hypoglycaemias (measured with the DTSQ status [32]).

The case report form consisted of information on the year of diabetes diagnosis and comorbidities at baseline (myocardial infarction, angina pectoris, heart surgery, heart failure, stroke, transient ischemic attack, peripheral arterial disease,

COPD, rheumatoid arthritis, osteoarthritis of hip or knee or any other diseases). Furthermore, we used the last known measurement of HbA1c, HDL, LDL and total cholesterol levels as well as baseline and final measurements of blood pressure and weight.

Statistical analysis

Descriptive statistics were used to describe the satisfaction with the monitoring frequency and preference for future monitoring frequency for each study group. For the future monitoring frequency the answers of the second question were categorised into: frequent (every 1-4 months), infrequent (every ≥ 5 months) and does not care.

Then the answers to the first question were categorised into: (very) satisfied, neutral and not (at all) satisfied. The chi square test was used to examine if satisfaction differed between the three-monthly and six-monthly groups (both with and without a preference) and between the preference and randomised groups (both three-monthly and six-monthly monitoring).

Since the group who chose 'not (at all) satisfied' was small, this was combined with 'neutral' to compare the differences in patient characteristics and health-related factors between patients who were satisfied and those who were not. We used logistic regression for categorical variables and linear regression for continuous variables to demonstrate the association between satisfaction and patient characteristics and health-related factors. In addition, we added the four study groups as interaction terms to the regression models. If not significant, study group was added to the regression model as confounder. Data were analysed with SPSS version 20.

Results

Of the 4040 patients who were invited to participate, 2215 (54.8%) agreed. Participants had a mean age of 64 years (SD=9) at the start of the study period, 1311 (59%) were male and the mean duration of diabetes was 6 years (SD=4). Of all participants, 747 patients (33.7%) preferred three-monthly monitoring, 677 (30.6%) preferred six-monthly monitoring, 394 (17.8%) were randomised to three-monthly and 397 (17.9%) to six-monthly monitoring at baseline (***Table 1***).

Satisfaction with the monitoring frequency

In ***Table 1*** the satisfaction with the monitoring frequency per study group is shown. Patients from the preference groups were more often (very) satisfied compared to those who were randomised (92.7% and 88.1%, respectively; p=0.001) and patients from the three-monthly groups were more often (very) satisfied with their monitoring frequency compared to those in the six-monthly groups (93.5% and 88.5%, respectively; p<0.001).

Satisfaction with diabetes treatment (DTSQ) did not differ between the four study groups (ANOVA, p=0.454). The three-monthly preference group had a score of 31.8, the six-monthly preference group of 32.2, the randomised three-monthly group of 31.9 and the six-monthly group of 31.8.

Table 1 - Number (%) of patients who are satisfied with the monitoring frequency and how often they want to be monitored in the future, divided per study group

	Preferred three-monthly n=747	Preferred six-monthly n=677	Randomised to three-monthly n=394	Randomised to six-monthly n=397
Satisfaction with the monitoring frequency	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Very satisfied	291 (46.3%)	206 (35.6%)	106 (30.3%)	98 (28.1%)
Satisfied	303 (48.2%)	318 (55.0%)	214 (61.1%)	198 (56.7%)
Neutral	29 (4.6%)	39 (6.7%)	25 (7.1%)	38 (10.9%)
Not satisfied	3 (0.5%)	12 (2.1%)	4 (1.1%)	10 (2.9%)
Not at all satisfied	2 (0.3%)	3 (0.5%)	1 (0.3%)	5 (1.4%)
Preference for future monitoring	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Frequent (every 1-4 months)	545 (86.6%)	87 (15.0%)	203 (57.8%)	120 (34.4%)
Infrequent (every ≥5 months)	54 (8.6%)	445 (76.6%)	84 (23.9%)	159 (45.6%)
Does not care	30 (4.8%)	49 (8.4%)	64 (18.2%)	70 (20.1%)

Preference for the monitoring frequency in the future

Most patients (70.8%) would like to continue their monitoring frequency. 11.1% did not care about their future monitoring frequency and the remainder preferred either a more (10.8%) or less (7.2%) frequent monitoring in the future.

Patients who received their preferred monitoring frequency were more likely to insist on continuing their preferred monitoring frequency in the future, both in the three-monthly group (86.6%) and in the six-monthly group (76.6%) (***Table 1***). Only 19.1% of the patients who did not have a preference at baseline still did not care about the monitoring frequency in the future after their eighteen months of experience in the trial. The patients who were randomised to either three-monthly

or six-monthly monitoring were more likely to prefer the monitoring frequency they were assigned to, although this effect was slightly stronger in the three-monthly monitoring group.

Patient characteristics associated with satisfaction with the monitoring frequency

Satisfaction with the monitoring frequency was associated with: higher age, a better physical health, less diabetes-related distress, higher diabetes treatment satisfaction, less experienced hyper- and hypoglycaemias and a lower LDL and diastolic blood pressure (***Table 2***). No interaction by study group was observed in the association between satisfaction and patient characteristics and health-related factors. Besides, adding study group as a confounder to the models did not alter the results. Therefore, we only reported the crude p-values.

Table 2 - Satisfaction with the monitoring frequency (n=1905)

	Not satisfied n=171		Satisfied n=1734		
	n	mean ± SD or n (%)	n	mean ± SD or n (%)	p-value
Age at baseline	171	62.5 ± 8.9	1734	64.6 ± 8.6	**0.003**
Gender, male	171	111 (64.9%)	1734	1029 (59.3%)	0.156
One or more comorbidities at baseline	171	69 (40.4%)	1734	646 (37.3%)	0.425
Duration of diabetes (in years)	167	5.6 ± 3.3	1695	5.9 ± 3.7	0.283
Current smoker*	165	35 (21.2%)	1672	251 (15.0%)	0.137
SF-36 PCS [scale: 0-100]*	137	44.7 ± 10.4	1414	45.7 ± 10.5	**0.027**
SF-36 MCS [scale: 0-100]*	137	51.5 ± 10.5	1414	54.1 ± 8.7	0.407
EQ VAS [scale: 0-100]*	155	71.7 ± 13.8	1510	75.2 ± 14.7	0.100
PAID [scale: 0-80]*	152	10.3 ± 11.8	1539	6.5 ± 9.0	**<0.001**
DTSQ [scale: 0-36]*	158	26.8 ± 6.4	1607	32.4 ± 4.1	**<0.001**
DTSQ hyper [scale: 0-6]*	166	2.2 ± 1.9	1650	1.3 ± 1.7	**<0.001**
DTSQ hypo [scale: 0-6]*	166	1.3 ± 1.6	1652	0.8 ± 1.4	**0.001**
HbA1c (mmol/mol)**	160	49.3 ± 6.8	1656	48.2 ± 7.5	0.077
HDL cholesterol (mmol/l)**	159	1.2 ± 0.3	1637	1.2 ± 0.3	0.089
LDL cholesterol (mmol/l)**	159	2.4 ± 0.8	1634	2.3 ± 0.7	**0.044**
Total cholesterol (mmol/l)**	159	4.3 ± 0.9	1633	4.2 ± 0.8	0.069
Systolic blood pressure (mmHg)*	130	132.9 ± 15.1	1477	134.0 ± 14.7	0.680
Diastolic blood pressure (mmHg)*	130	78.1 ± 9.9	1474	76.3 ± 9.2	**0.025**
BMI (kg/m^2)*	120	29.1 ± 4.2	1373	29.1 ± 4.8	0.609

* Final measurement, corrected for baseline measurement.

** Last known measurement during follow-up.

SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score; EQ VAS, EuroQol Visual Analogue Scale; PAID, Problem Areas In Diabetes; DTSQ, Diabetes Treatment Satisfaction Questionnaire status.

Discussion

Summary

This study showed that most well-controlled type 2 diabetes patients were satisfied with their monitoring frequency whether self-chosen or allocated by randomisation. Besides, the majority would like to continue this frequency in the future. Patients being monitored three-monthly or according to their preference tended to be more satisfied. On the other hand, most patients assigned to their study group by randomisation wished to continue the assigned monitoring frequency in the future.

Strengths and limitations

One of the strengths of this study is that we included a large number of type 2 diabetes patients. Furthermore, extensive patient data were available providing the opportunity to explore both patient characteristics and health-related factors in relation to patient satisfaction. However, it is unknown whether additional patient factors may influence the satisfaction with the monitoring frequency. Unfortunately, we were unable to take unknown variables (such as travel time to the general practice, mean time in the waiting room, mean duration of the visits, compliance to therapy, knowledge of type 2 diabetes and patients' coping strategies) into account. Another limitation is that some patients might have misunderstood the question on the monitoring frequency. Some patients may have indicated how satisfied they were with the content of the visits instead of with the number of visits. This would also explain some 'implausible' answers. For example, 261 patients (13.7%) who liked their monitoring frequency preferred another frequency in the future and 17 patients (0.9%) who disliked their monitoring frequency chose the same frequency in the future (data not shown). However, we believe that because of the low percentage of these inconsistencies, this will not have influenced the direction of our results.

Comparison with existing literature

Overall, patients were satisfied with their monitoring frequency in our study. Despite this, patients who determined their own monitoring frequency were more satisfied. Therefore, in order to increase patient's satisfaction, patient's preferences should be taken into account. However, currently the monitoring frequency is mostly determined by the physician in patients with chronic diseases [13-16]. Patients usually prefer a slightly less frequent monitoring compared to

physicians [103] or as determined by guidelines [104]. This leads to the question: to whom should we listen?

A study in haemodialysis care showed that patients with less frequent patient-physician contact were less satisfied with their monitoring frequency, although no difference in satisfaction with overall quality of care was found [105]. A randomised equivalence trial comparing three-monthly and six-monthly monitoring in patients with hypertension in primary care showed no significant differences on satisfaction with care [6], although more patients in the six-monthly group thought that their general practitioner did not take their blood pressure problem seriously enough. In accordance with these studies, we also observed that the prevalence of satisfied patients was slightly higher among those randomised to three-monthly monitoring than those randomised to six-monthly monitoring. However, we have also measured satisfaction with the diabetes treatment, which is more comparable to the score used by Birtwhistle et al. Using this score, we could not detect any significant differences between the four study groups. So based on this, the patients who are monitored six-monthly are satisfied with the overall care, although they indicated to be slightly less satisfied with the monitoring frequency than those randomised to three-monthly monitoring.

Patients who had a lower physical health, a higher diabetes-related distress and perceived more hyper- and hypoglycaemias were less satisfied with the monitoring frequency. We also found significant differences for LDL cholesterol and diastolic blood pressure, but the absolute differences were very small. So it seems that well-controlled type 2 diabetes patients based their dissatisfaction with the monitoring frequency on logical reasons. This is in concordance with the preferences of the patients at baseline, where we showed that patients seem to make logical choices regarding the monitoring frequency (**Chapter 2**). These results confirm that patients themselves should also be involved in determining the monitoring frequency. One out of three had a strong preference for three-monthly monitoring and therefore, this should be taken into account.

Implications for research or practice

Based on the results we conclude that it is feasible to implement six-monthly monitoring in well-controlled type 2 diabetes patients. We have shown that patient's preferences should be taken into account to increase patient's satisfaction. Although the satisfaction for three-monthly monitoring was higher than in six-monthly monitoring, the satisfaction with six-monthly monitoring was

still rather high (88.5%). We expect that at least two out of three well-controlled type 2 diabetes patients can be eligible for six-monthly monitoring.

Chapter 7

Experiences of the primary care providers

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Accepted by Primary Care Diabetes

Abstract

Aims: To examine experiences of primary care providers with six-monthly diabetes monitoring of well-controlled patients.

Methods: This study was part of the EFFIMODI study, examining whether six-monthly monitoring of well-controlled (HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l) type 2 diabetes patients results in equivalent cardiometabolic control compared to three-monthly monitoring. Primary care providers completed a questionnaire about their experiences with six-monthly diabetes monitoring, whether they want to continue six-monthly monitoring and for which type of patients six-monthly monitoring is sufficient.

Results: Of 163 questionnaires, 157 (96.3%) were completed and returned. Only 14 (8.9%) primary care providers were negative about the six-monthly monitoring and 102 (65.0%) would like to continue six-monthly monitoring. Primary care providers disagreed about patients' ability to determine their own monitoring frequency and whether six-monthly monitoring was suitable for all well-controlled type 2 diabetes patients. Practical concerns emerged such as the inability to declare healthcare costs and the unsuitability of electronic health record systems.

Conclusions: Almost two out of three primary care providers would like to continue six-monthly monitoring of well-controlled type 2 diabetes patients. However, some diabetes care providers should be convinced and some practical concerns should be solved.

Introduction

Worldwide, the number of people with type 2 diabetes was approximately 366 million in 2011 [100]. As a result of ageing and population growth along with lifestyle changes, this number is expected to increase with over 50% by 2030 [100]. This may result in a heavy burden for healthcare workers and increasing costs.

For patients with type 2 diabetes regular monitoring is necessary to keep the disease under control. International diabetes guidelines recommend different monitoring frequencies ranging from one to four times a year [21,37], but these recommendations are not evidence-based.

Monitoring frequencies vary widely between physicians [106-108] and the frequency of visits is mainly determined by the physician, and to a lesser extent by patient factors and disease severity [13-16]. At this moment, it is not known how frequently monitoring is required and who should determine this.

Reducing the monitoring frequency of well-controlled type 2 diabetes patients may generate considerable savings of workload and healthcare costs. We could demonstrate that after eighteen months six-monthly monitoring results in comparable cardiometabolic control as three-monthly monitoring in well-controlled diabetes patients in primary care who had no strong preference with regard to their diabetes monitoring frequency (**Chapter 4**).

This finding could lead to a worldwide adjustment of the current guidelines on the frequency of diabetes monitoring, but before such an adjustment will have a chance to get implemented, experiences of healthcare providers and patients with six-monthly monitoring should be examined to identify potential bottlenecks for implementation in clinical practice. These considerations can also contribute to the discussion about who should make the decision about the monitoring frequency in clinical practice: the care provider, the patient or both? Here we describe the experiences of general practitioners and practice nurses with six-monthly monitoring of well-controlled type 2 diabetes patients.

Materials and methods

Setting

This study is part of a randomised controlled patient-preference equivalence trial (EFFIMODI study, **Chapter 1**) in primary care. Between April 2009 and August 2010 patients with type 2 diabetes were included in the EFFIMODI study if they were known with type 2 diabetes for more than one year, between 40 and 80 years old,

treated by the general practitioner, not using insulin and with HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l.

At baseline, patients were asked whether they had a strong preference for three-monthly or six-monthly monitoring. Those with a strong preference for either three-monthly or six-monthly monitoring were treated according to their preference, while those without a strong preference were randomised to either three-monthly or six-monthly monitoring.

Here the experiences of the primary care providers with the six-monthly monitoring of well-controlled type 2 diabetes patients are described. 233 general practitioners from 107 different practices across the Netherlands participated in the EFFIMODI study. Twenty-four held a solo practice and the others were working within a duo or group practice.

Measurements

When all patients within the practice had completed the study period of eighteen months (and before study outcomes were known), the practices received a questionnaire on their experiences with six-monthly monitoring. So the questionnaire concerned only patients who were monitored six-monthly during the EFFIMODI study, which were 1074 out of the 2215 participating patients. Of these, 677 (63.0%) preferred themselves to be monitored six-monthly and 397 (37.0%) had been randomised to six-monthly monitoring (**Chapter 2**). A questionnaire was sent to each practice; if two separate patient lists were used within a practice, two questionnaires were sent resulting in 163 questionnaires. The questionnaire consisted of five questions:

1) Who completed the questionnaire: the general practitioner or the practice nurse?

2) How did you experience the six-monthly monitoring: very good, good, neutral, bad or very bad?

3) Would you like to continue the six-monthly monitoring in the future: yes, no or ‘I do not care’?

4) Do you agree or disagree with the following six statements about six-monthly monitoring (multiple answers possible)?

- Six-monthly monitoring saves time compared to usual care
- Patients are able to determine their own monitoring frequency
- The health insurance company requests that I monitor all patients quarterly

- In the future, I will leave the decision about the monitoring frequency to the patient
- Patients are not able to determine their own monitoring frequency
- Six-monthly monitoring takes more time compared to usual care

Or they could fill in their own statement.

5) Which type of type 2 diabetes patients are eligible for six-monthly monitoring: no patients whatsoever, young patients with type 2 diabetes, patients who are well-controlled for a long time or otherwise (multiple answers possible)?

The answers to the open questions were assigned to a matching statement or if frequently mentioned a new category was created. Answers that were mentioned only once or twice were assigned to the category 'other'. All answers were independently classified by two different researchers (JJ and PW) and then compared. When the researchers disagreed a discussion followed to achieve consensus. The statements of question four were also divided into positive, neutral and negative statements.

Statistical analysis

Descriptive statistics were used to describe the experiences with six-monthly monitoring and whether participants want to continue six-monthly monitoring. Since multiple answers were possible with regard to questions four and five, we counted the number of primary care providers who agreed with a statement and divided this by the total number of agreed statements. Analyses were performed with SPSS software version 20.

Results

Of the 163 questionnaires sent to the participating general practices, 157 (96.3%) were completed and returned. The questionnaires were filled in by 19 (12.1%) general practitioners, 90 (57.3%) practice nurses, 3 (1.9%) by both and of 45 (28.7%) questionnaires it was unclear who completed it.

Experiences with six-monthly monitoring

Of the primary care providers, 15 (9.6%) had very good experiences with six-monthly monitoring, 60 (38.5%) had good experiences, 67 (42.9%) were neutral, 14 (9.0%) had bad experiences, none had very bad experiences and one answer was missing. Of the responders, 102 (65.0%) would like to continue six-monthly

monitoring, 35 (22.3%) did not want to continue, 19 (12.1%) were ambiguous in this respect and one answer was missing.

In ***Table 1***, the experiences of primary care providers with six-monthly monitoring are summarised. The most frequently mentioned statement was that six-monthly monitoring saves time (23.4%). The most frequently mentioned negatively worded statement was that patients are not able to determine their own monitoring frequency (11.3%). In the category 'other positive aspects' the following statements were made: "six-monthly monitoring improved self-management and motivation of patients" and "it will make healthcare more efficient". The category 'other neutral' and 'other negative' contained the following statements: "the electronic patient records system could not handle six-monthly monitoring", "less frequent monitoring caused patient's non-compliance" and "patient-physician contact was limited".

Table 1 - Primary care providers' experiences with six-monthly monitoring (n=157)

Statements	**N* (%)**
Positive	**197 (50.6%)**
Six-monthly monitoring saves time compared to usual care	91 (23.4%)
Patients are able to determine their own monitoring frequency	47 (12.1%)
For well-controlled type 2 diabetes patients, monitoring every six months is enough	20 (5.1%)
Six-monthly monitoring meets the desire of the patients	19 (4.9%)
Six-monthly monitoring makes it possible to offer customised care	14 (3.6%)
Other positive aspects	6 (1.5%)
Neutral	**76 (19.5%)**
The health insurance company requests that I monitor all patients quarterly	43 (11.1%)
I prefer to determine the monitoring frequency myself, in agreement with the patient	15 (3.9%)
In the future, I will leave the decision about the monitoring frequency to the patient	14 (3.6%)
Other neutral aspects	4 (1.0%)
Negative	**116 (29.8%)**
Patients are not able to determine their own monitoring frequency	44 (11.3%)
Six-monthly monitoring is not suitable for all well-controlled type 2 diabetes patients	20 (5.1%)
Six-monthly monitoring takes more time compared to usual care	18 (4.6%)
Because patients were not regularly seen, the diabetes deregulated or patients no longer showed up at appointments	16 (4.1%)
Patients visited the general practice more frequently in between scheduled appointments	10 (2.6%)
Difference in monitoring frequency led to confusion among patients and/or primary care providers	6 (1.5%)
Other negative aspects	2 (0.5%)
Total	**389 (100%)**

* The numbers indicate how many times a statement is mentioned. Because multiple answers were possible, the total number of statements exceeds the total number of questionnaires.

Opinion about patients' eligibility for six-monthly monitoring

In ***Table 2***, the view of primary care providers on which patients were eligible for six-monthly monitoring is shown. Most frequently, patients who are well-controlled for a long time were considered eligible (70.3%). Besides the eligibility criteria in ***Table 2*** additional selection criteria for six-monthly monitoring were mentioned by the primary care providers, such as: older age, higher education, no history of cardiovascular disease and a normal Body Mass Index.

Table 2 - Primary care providers' opinion about which patients are eligible for six-monthly monitoring (n=157)

Which patients should receive six-monthly diabetes monitoring in the future?	N* (%)
Patients who are well-controlled for a long time	147 (70.3%)
Patients who are well-controlled for a long time and have a good understanding of disease	14 (6.7%)
Patients who are well-controlled for a long time and who prefer less frequent monitoring	9 (4.3%)
Young patients with type 2 diabetes	9 (4.3%)
Patients who are well-controlled for a long time and who are good at self-management	7 (3.3%)
No patients whatsoever	3 (1.4%)
Other patients	20 (9.6%)
Total	**209 (100%)**

* The numbers indicate how many times a statement is mentioned. Because multiple answers were possible, the total number of statements exceeds the total number of questionnaires.

Discussion

This study demonstrated that more than ninety percent of the primary care providers had neutral or positive experiences with six-monthly monitoring of well-controlled type 2 diabetes patients and almost two out of three would like to continue six-monthly monitoring. These judgements were based on varying grounds. Time savings was the most important reason to continue with six-monthly monitoring. Besides, the primary care providers believe that patients who are well-controlled for a long time are the most eligible patients for six-monthly monitoring.

The results of our study did not show considerable objections by primary care providers to implement six-monthly monitoring. However, physicians commonly prefer a shorter visit interval than recommended in guidelines [109] or preferred by their patients [103]. This could be explained by the fact that more frequent monitoring in chronic diseases is thought to lead to better patient outcomes. Several studies have investigated the relation between the monitoring frequency and patient outcomes in patients with type 2 diabetes [7-12], but the results were inconclusive. The EFFIMODI trial showed that in well-controlled type 2 diabetes

patients cardiometabolic control was equal for three-monthly and six-monthly monitoring and fear of worsening of diabetes control should thus not be a major objection to implement six-monthly monitoring (**Chapter 4**).

A practical problem which some general practices faced was the inability to get their diabetes care reimbursed, since the health insurance companies that pay a lump sum to cover all the various components of diabetes care for a fixed period of time request to check all patients with diabetes every three months. Another practical concern was the inability of some electronic health record systems to deal with six-monthly monitoring. This caused problems with keeping an overview and scheduling appointments, resulting in confusion among patients, practice nurses and general practitioners. However, this practical problem can be solved by adapting the computer system and good communication between primary care providers and patients.

According to the general practitioners and practice nurses in our study only patients who are well-controlled for a long time should be eligible for six-monthly monitoring. Besides, they should also fulfil additional criteria, both subjective (understanding of disease and self-management) and objective (older age, higher education, no history of cardiovascular disease and a normal body mass index). Whether these additional criteria actually affect cardiometabolic control of the patients is unknown, since we only selected well-controlled patients based on HbA1c, systolic blood pressure and total cholesterol.

Currently, monitoring frequency of chronic disease patients is mainly determined by physician-related factors [13-16]. Other factors, such as the disease severity, account for only a small part. As a result, the monitoring frequency for patients with chronic diseases varies widely between physicians [106-108], even if the severity of disease is similar.

Our study aimed to contribute to the discussion about who should decide about the monitoring frequency in primary care: the care provider, the patient or both? The participating primary care providers differed in opinion whether patients are able to determine the monitoring frequency themselves. However, almost two-thirds of the well-controlled type 2 diabetes patients would like to choose their own monitoring frequency, with the choice for more frequent monitoring being associated with worse disease status compared to patients who prefer less frequent monitoring (**Chapter 2**). Patients therefore seem to make logical decisions in this aspect. So it seems justified to take their opinion into account when deciding about the monitoring frequency.

One of the strengths of this study is its high generalisability because a large number of general practices across the Netherlands participated. The answers of the diabetes care providers were based on an eighteen months experience in daily care in patients who were selected independently and based on solely objective measures, namely HbA1c, blood pressure and total cholesterol.

There are also some limitations that should be mentioned. Firstly, when processing the questionnaires it became apparent that fifteen questionnaires were identical to others. This was recognised by identical answering and handwriting in questionnaires that came from the same practice. We decided to include these questionnaires in the analysis assuming that these were completed double (or triple) because the primary care providers shared the same opinion. However, in this way it is possible that a single person completed two questionnaires without consulting anyone else. Secondly, the opinions of the primary care providers in this study were based on six-monthly monitoring of patients with and without a strong preference for this frequency. If the monitoring experiences of these groups could have been analysed separately, the results might have been different because patients who chose the monitoring frequency themselves may be more satisfied and motivated. Finally, from a substantial number of questionnaires it was unknown if general practitioner, practice nurse or both completed it. Therefore it was impossible to stratify the experiences for general practitioners and practice nurses.

We would suggest that primary care physicians and diabetes nurses propose a six-monthly monitoring scheme to all type 2 diabetes patients who are overall well-controlled for about a year and that only in case of explicit patient's objections to such a scheme the three-monthly scheme will be maintained. Of course, primary care providers and the patient should evaluate their experiences after a certain period. Because the majority of primary care providers had positive experiences with six-monthly monitoring of well-controlled diabetes patients and would like to continue with it, implementation on a large scale seems possible. However, some diabetes care providers should be convinced and some practical concerns should be solved.

General discussion

This thesis provides an overview of the EFFIMODI study which was conducted to investigate whether well-controlled type 2 diabetes patients in primary care who were monitored six-monthly remained under equivalent cardiometabolic control as those monitored three-monthly. Here we elaborate on the 'ideal' monitoring frequency and on how preferences of the patients should be taken into account. In addition, we describe costs and the experiences of patients and primary care providers with a change of monitoring frequency. The content of diabetes visits may be changed too, as we conclude from our study about the relation between comorbidity and health status. Furthermore, we propose how to implement six-monthly monitoring in primary care and what the clinical implications are.

EFFIMODI study

The main conclusions of the EFFIMODI study after eighteen months of follow-up are:

1. Patients without a strong preference and randomised to six-monthly monitoring had equal patient outcomes compared to patients randomised to three-monthly monitoring (**Chapter 4**).
2. Patients with a strong preference for six-monthly monitoring had equal patient outcomes compared to patients with a strong preference for three-monthly monitoring when monitored according to their preference (**Chapter 5**).
3. Patients from the randomised trial and the preference study had comparable patient outcomes, suggesting that the results of the trial can be generalised to a wider population (**Chapter 5**).
4. Nine out of ten patients who were monitored six-monthly were (very) satisfied with the monitoring frequency (**Chapter 6**).
5. Two-thirds of the healthcare providers would like to continue with six-monthly monitoring (**Chapter 7**).

Monitoring frequency

Several studies have investigated the relationship between diabetes monitoring frequency and patient outcomes. These studies were conducted in various populations. Two studies investigated not well-controlled diabetes patients [7,8]. One studied diabetes patients in primary care with an elevated HbA1c, blood pressure or LDL cholesterol (HbA1c >53 mmol/mol or blood pressure >130/85 mmHg or LDL cholesterol >2.6 mmol/l) [7]. Patients who visited their physician

every one to two weeks achieved their HbA1c target with a median of 4.4 months and patients who visited their physician every three to six months with a median of 24.9 months. So the HbA1c target was achieved faster when monitored more frequently. The same was shown for blood pressure and LDL cholesterol. The other study randomised diabetes patients whose blood glucose was not satisfactorily controlled after diet and exercise (fasting blood glucose ≥7.0 mmol/l) to either three-monthly (conventional therapy) and one-monthly monitoring (intensive therapy) [8]. Patients with an intensive therapy had improved quality of life and clinical indicators after one year. However, results for not well-controlled diabetes patients cannot be generalised to well-controlled diabetes patients.

Two randomised trials in the United States investigated an intervention to increase access to care for diabetes patients [9,10]. One study showed that the intervention (mailings and telephone calls) could increase office visits, but did not reduce nonelective hospital admissions in diabetes patients [9]. The other was in hospitalised veterans and showed that increased access to primary care was associated with an increased rate of rehospitalisation and comparable quality of life [10]. These two studies suggest that patients with an increased monitoring frequency did not perform better on patient outcomes.

Two observational studies were most comparable to the EFFIMODI study [11,12]. One was conducted in veterans (mean age: 64 years) and evaluated whether an education program for primary care providers could lengthen the return interval of their patients without compromising on quality indicators [11]. The mean return visit interval increased from 4.1 to 5.2 months and the percentage of patients having an HbA1c <64 mmol/mol increased from 53 to 70. The other study assessed the relation between the number of appointments in primary care and the degree of control in diabetes patients (mean age: 65 years, 57% women, mean HbA1c: 53 mmol/mol) [12]. The number of visits was not associated with HbA1c. Both studies were performed in non-selected diabetes patients and both concluded that the number of visits was not related to glycaemic control. Since these studies were observational, evidence from a randomised trial was lacking before the start of the EFFIMODI study.

In patients with well-controlled hypertension it had already been confirmed that six-monthly monitoring by a family practitioner is sufficient [6]. In patients with well-controlled hypertension (blood pressure <140/90 mmHg) blood pressure control, patient satisfaction and treatment adherence were comparable for three-monthly and six-monthly monitoring.

Based on these studies it seems that intensive monitoring is necessary in “not well-controlled patients” and less frequent monitoring could be implemented for “well-controlled patients” without compromising health outcomes. Whatever the definitions for these two terms exactly are, the conclusion is that an individualised monitoring frequency is necessary.

With the EFFIMODI study we were indeed able to show that patients who had no strong preference for their monitoring frequency and were monitored six-monthly remained under comparable cardiometabolic control as patients who were monitored three-monthly (**Chapter 4**). However, the results of the randomised trial might have a lower generalisability since two-thirds of the patients had a preference for their monitoring frequency (**Chapter 2**) and were not randomised.

Patients’ preferences

Taking into account patients’ preferences is an important issue nowadays [17,18]. A major advantage is that treating patients according their preference might improve treatment adherence and thus clinical outcomes [19]. Especially in diabetes care this is of utmost importance, since patients have to deal with treatment adherence and self-management to keep their diabetes under control. However, until now every diabetes patient is offered the same care and treated according to the same guidelines and therefore the preferences of the patient seem to be of less importance.

The EFFIMODI study showed that of the participating patients approximately one-third had a strong preference for three-monthly monitoring, one-third had a strong preference for six-monthly monitoring and the remainder had no strong preference for the monitoring frequency (**Chapter 2**). So the patients were almost equally distributed over the preference groups, which could suggest that their choice was almost randomly made. However, the choices patients made at baseline were rather logical since patients who wanted to visit the practice every three months appeared to feel less healthy. These patients indeed need to be seen more often by their healthcare provider. Therefore, taking into account patient’s preference when choosing a monitoring frequency is likely to be important.

After eighteen months of being monitored according to their preference, the EFFIMODI study showed that three-monthly and six-monthly monitoring did not result in different cardiometabolic control (**Chapter 5**). In addition, the patients monitored according their preference remained under the same level of

cardiometabolic control as the randomised patients. This suggests that well-controlled patients with a preference for six-monthly monitoring or without a preference could be monitored six-monthly in the future, since they do not perform worse compared to patients who are monitored three-monthly. This means that six-monthly monitoring could be sufficient for at least two-thirds of the well-controlled patients.

After the EFFIMODI study, it is still unknown what would happen if patients with a preference for three-monthly monitoring would be monitored six-monthly. We assume that part of the patients with a strong preference for three-monthly monitoring will get convinced that less frequent monitoring is an option for them, now it is evidence-based that six-monthly monitoring is sufficient. They could be monitored half-yearly; however these patients should be followed more closely to see if it is really sufficient for them. This could be done by paying extra attention to their medical outcomes during the six-monthly visits and asking them whether they are satisfied with the less frequent monitoring and if not, why they prefer three-monthly monitoring.

Patients who were monitored according to their preference were more satisfied with the monitoring frequency (**Chapter 6**). Patients' satisfaction with the monitoring frequency is of importance since patient satisfaction is associated with treatment adherence [101,102] and thus clinical outcomes. Therefore, we assume that patients who are monitored according their preference will be more satisfied with their diabetes care which may result in better clinical outcomes. Of the patients who were (very) dissatisfied with the monitoring frequency 51.3% and of the patients who were neutral or (very) satisfied with the monitoring frequency 69.7% maintained cardiometabolic control. This demonstrates that healthcare providers should ask patients about their satisfaction with the monitoring frequency to maintain good cardiometabolic control.

Recent literature stated that healthcare providers should take into account patients' preferences when making treatment decisions [110,111]. In addition, we would suggest that also the preference and satisfaction of type 2 diabetes patients for the monitoring frequency should be taken into account.

Comorbidity and health status

Type 2 diabetes patients have a decreased health-related quality of life compared to healthy persons and this is even lower when comorbidities are present [49,50].

Approximately 44% of the diabetes patients in the Netherlands has any comorbidity [63]; in our well-controlled study population in primary care this percentage was 38% (**Chapter 3**). Although the percentage of comorbidities in well-controlled type 2 diabetes patients was somewhat lower, we were still able to demonstrate that well-controlled type 2 diabetes patients with any comorbidity had a lower health status compared to patients without comorbidity.

Currently, the clinical guideline of type 2 diabetes only focuses on the treatment of diabetes and not on diabetes patients with comorbidities. Therefore, there is a need to adapt the clinical guidelines when there is multimorbidity [112]. Guthrie et al. suggest to cross reference between guidelines and to provide guidance in the harms and benefits of treatments. In the EFFIMODI study, patients with comorbidities achieved the same level of cardiometabolic control as patients without comorbidities (p=0.690). In addition, the relation between the monitoring frequency and cardiometabolic control was not modified by comorbidity (p=0.455).

Based on these findings, we do not think that the number of visits for patients with comorbidities is important in increasing their health status, but maybe the content of the visits should be adjusted. Therefore, we would suggest going from 'single disease management' to 'personalised care'. Also in patients with a good cardiometabolic control their comorbidity and their health status should be discussed during the annual extensive check-up. The general practitioner and the patient should balance the targets of diabetes care, patient's preferences and side-effects from medication, for example due to polypharmacy.

Costs

Besides cardiometabolic control, we investigated the costs of three-monthly versus six-monthly monitoring. The type of economic evaluation would be based on the outcome of the equivalence trial. If three-monthly and six-monthly monitoring were equivalent, a cost-minimisation analysis would be performed and if three-monthly and six-monthly monitoring were not equivalent, a cost-utility analysis would be performed. However, since the randomised equivalence trial was not able to either prove or reject equivalence (**Chapter 4**), both types of economic evaluation could be suitable. Therefore, in this thesis both options were described.

Both the cost-minimisation and cost-utility analysis showed that six-monthly monitoring could save costs compared to three-monthly monitoring. The cost-utility analysis resulted in an incremental cost-utility ratio of €33,041 per QALY. This is above the commonly used cut-off of €20,000 per QALY, which suggests that six-monthly monitoring is not cost-effective. We however are more inclining towards the cost-minimisation analysis. This is because the differences in effects and QALYs were negligible between three-monthly and six-monthly monitoring and therefore these outcomes could be left out in the economic evaluation. Then only the costs between three-monthly and six-monthly monitoring have to be compared, which is a cost-minimisation analysis. From the cost-minimisation analysis we concluded that six-monthly monitoring is cheaper and therefore the preferred monitoring frequency.

The EFFIMODI study showed that six-monthly monitoring could be applied to patients with a preference for six-monthly monitoring and to patients with no preference, which are in total approximately two-thirds of the well-controlled diabetes patients. Around 20% of the type 2 diabetes patients could be considered well-controlled [24] and with a prevalence of approximately 900,000 type 2 diabetes patients, about 120,000 patients could be monitored six-monthly in the Netherlands. This reduced monitoring frequency would have an immediate effect on the direct consultation costs of €29 per consultation [88]. Taking into account the difference in visits between the six-monthly and three-monthly monitoring groups (2.5 diabetes visits in one and a half year), it would save €48 euro per patient per year, which is nation-wide almost 6 million Euros per year.

Besides these direct costs, also indirect costs will decrease as well as patient's burden and general practice staff's burden. In the economic evaluation we did not include the costs of patients who had to take time off from their work to visit their general practice. The reduced burden on general practice staff is of major importance, since a huge labour shortage is expected in the future [113]. Introducing a 50% reduction in two out of three well-controlled type 2 diabetes patients could save 66,666 working hours per year (120,000 patients x 20 minutes x 1.67 visits per year), corresponding with 39 FTE.

Taking into account patient's preference in all type 2 diabetes patients might not only reduce the absolute number of visits to a large extent, but might also decrease other healthcare costs, because more patients than expected might prefer another follow-up visit interval than their healthcare providers think or because patients who are more involved in treatment decisions consume less

healthcare [103,110]. Both theories were confirmed in our study. Firstly, some general practitioners said to be surprised that some patients preferred to come every six months instead of every three months. Secondly, patients who were monitored six-monthly because they preferred it had less unscheduled and other visits than the patients who were randomised to six-monthly monitoring. Further (qualitative) research is needed to explore this phenomenon.

Experiences with a reduced monitoring frequency

Patients who were monitored three-monthly were more satisfied than patients who were monitored six-monthly (**Chapter 6**). However, satisfaction with six-monthly monitoring was still rather high (88.5%). This shows that the majority of well-controlled type 2 diabetes patients is likely not to have problems with being monitored six-monthly. Patients who were monitored six-monthly because they preferred this, were slightly more satisfied than patients who were monitored six-monthly after randomisation. This shows that patients who were treated according their preference were more satisfied.

Patients who had no strong preference and were randomised to six-monthly monitoring were somewhat less satisfied; had more unscheduled diabetes visits and perceived more frequently hyper- and hypoglycaemias. We hypothesise that a few patients who were randomised to six-monthly monitoring would rather have been monitored three-monthly. So when it is noticed that patients who are monitored six-monthly visit the practice more often in between, the healthcare provider might suggest returning to three-monthly monitoring. As stated above, general practitioners should discuss with the patient their satisfaction with the monitoring frequency and whether they perceive frequently hyper- and hypoglycaemias.

Our sample of participating healthcare providers was widely spread over the Netherlands. The percentage of general practitioners working in solo practices and participating in EFFIMODI (10%) was somewhat lower than on average (18% in 2011 [114]) in the Netherlands. This could be due to the fact that some solo practices have no practice nurse or less time available for study participation. Although our study included less solo practices than on average, we do not think this influenced our results.

Most healthcare providers indicated to have no major problems with implementation of six-monthly monitoring (**Chapter 7**). However, when six-

monthly monitoring will be implemented as a routine, some healthcare providers might object because some of them will think that patients are not able to determine the monitoring frequency themselves or are afraid that some patients may get out of their sight. The practical implementation issues that were mentioned by the healthcare providers are considered below.

Implementation of six-monthly monitoring

Since six-monthly monitoring results in equal cardiometabolic control in well-controlled type 2 diabetes patients compared to three-monthly monitoring, we propose to implement this finding into daily practice. When implementing six-monthly monitoring, healthcare providers should be informed about the EFFIMODI study since their current practice procedures must be changed. Training healthcare providers has been proven to be a good method to lengthen the interval between visits without compromising on quality indicators and performance [11]. This could be a method to implement six-monthly monitoring of well-controlled type 2 diabetes patients in primary care.

Our recommendation regarding the monitoring frequency in well-controlled type 2 diabetes patients would be to monitor ALL of them six-monthly, unless a patient specifically has an objection against six-monthly monitoring. Firstly, all well-controlled type 2 diabetes should be informed by their healthcare provider that six-monthly monitoring results in equal cardiometabolic control as three-monthly monitoring. If a patient objects, this patient could be monitored three-monthly since we have shown that patients who are monitored according their preference are more satisfied. In addition, we have shown that patients who were insecure about their health came more frequently in between six-monthly visits. Therefore, when a patient feels insecure they may also visit the general practice three-monthly. And finally, the extensive annual check-up should be used to discuss patient's satisfaction with the monitoring frequency, their feelings of hyper- and hypoglycaemias and their health status.

This type of recommendation is comparable to an opt-out approach. This has the advantage that fewer patients are 'unnecessarily' treated three-monthly, which saves costs and time. However, the disadvantage is that only patients who actively indicate that they have an objection to six-monthly monitoring are being monitored three-monthly. Doing so, the preferences of patients with a 'less strong' preference for three-monthly monitoring are being neglected. Because the general

practitioner can discuss the patient's preference repeatedly, we think this disadvantage is of less importance.

Implications for clinical practice

Currently almost every type 2 diabetes patient is being treated according to the same guideline with little individualised approach. We however propose to customise diabetes care. To realise this, the diabetes guidelines should be adapted. An extra paragraph should be included describing that six-monthly monitoring is sufficient in patients who are well-controlled.

Adjustments should be made to the general practice's information system. For example, during the planning of a new visit, the primary care provider should get a message that the next visit should be planned after six months. With the help of ICT these changes should be made possible.

In the Netherlands diabetes care in primary care is incorporated in care groups [97]. These care groups make agreements with healthcare insurers so that primary care providers receive a fixed price for every diabetes patient per year ('bundled payment approach'). When six-monthly monitoring is implemented for well-controlled type 2 diabetes patients, healthcare insurers might negotiate to lower the fixed price. This could save direct healthcare costs.

In the EFFIMODI study the content of the extensive yearly visit was not changed, therefore process indicators for diabetes in primary could remain equal when implementing six-monthly monitoring since they demand HbA1c, blood pressure and cholesterol measurements at least once a year [115]. We want the extensive yearly visit to remain so that the cardiometabolic variables can be measured at least once a year.

Methodological considerations

Performing a randomised trial has the advantage that there is no confounding. However, the external validity (generalisability) of randomised trials has been criticised [22,95,96]. Participants of a trial are thought to be unrepresentative of the wider population, because patients with a strong treatment preference might refuse randomisation (because they do not want to run the risk to be randomised to a treatment they strongly disagree with) or patients with a strong preference may not comply with treatment when not receiving their preferred treatment

(which leads to drop-out). Therefore, we decided to conduct a patient preference study.

This type of study has the advantage that more people will participate in the study, as people can choose not to be randomised. Patients with a preference can be included in the study arm of their choice, which leads to less selection bias and drop-out. So a patient preference design could be supportive in interpreting and generalising the results from the randomised trial. If in EFFIMODI the results of the patients with a preference regarding the monitoring frequency would have been different from the results of the randomised patients, our randomised patients would not have been representative of the target population. Besides, with the patient preference design we were also able to determine which patient characteristics were associated with patient preferences.

For the total study we had a response rate of approximately 55%, which is reasonably good and comparable to another patient preference study [42]. 20% of the invited patients were included in the randomised trial. We think that since we gave patients a choice, fewer patients chose to be randomised. If the invited patients were only invited for the randomised trial we assume that the response rate for the trial would be higher than 20%. This could have resulted in a higher power of the trial and thus a smaller confidence interval and possibly equivalence of six-monthly and three-monthly monitoring. However, we do not think the response rate would have been as high as 55% when patients were offered only a randomised trial. So the preference design is likely to result in less selection bias.

We expected that 95% of the well-controlled type 2 diabetes patients would stay well-controlled; but in reality we found that only 70% of the patients maintained the three targets. Due to this difference we would have needed a larger sample size, which would have been possible when only performing a randomised trial. The much lower percentage for reaching all three treatment targets in all four treatment groups may be the result of the design without a formal baseline measurement. We deliberately chose to do so because we did not want to perform additional measurements on top of routine care.

Based on our experiences we would recommend a patient preference study design if it is thought that (1) a large group of patients will refuse randomisation because they strongly prefer one of the two treatment options and (2) the number of patients preferring one of the two treatment options is higher than for the other treatment option. The EFFIMODI study fulfilled the first condition, because two-thirds of the eligible patients indicated to have a strong preference for the

monitoring frequency. Based on a small pilot study we thought this would be 50%. Beforehand, we assumed that we would also fulfil the second condition because we thought only a small group would prefer six-monthly monitoring. Afterwards, we found that the number of patients preferring six-monthly monitoring was comparable to patients preferring three-monthly monitoring. However, since the preferred six-monthly monitoring group was bigger than expected, we were also able to compare this group with the preferred three-monthly monitoring group. In short, a patient preference study design would not have been necessary to answer our research question, but it gave us more information and possibilities than only performing a randomised trial.

Conclusion

Based on this thesis we can conclude that six-monthly monitoring in well-controlled type 2 diabetes patients can safely be implemented in primary care. We suggest that primary care providers propose a six-monthly monitoring scheme to all type 2 diabetes patients who are overall well-controlled for about a year and that only in case of explicit patient's objections to such a scheme the three-monthly scheme will be maintained. This will result in a decreased patient burden, decreased work pressure for diabetes care providers and less costs.

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Summary

Currently, three-monthly monitoring is recommended for all type 2 diabetes patients. However, scientific evidence for the monitoring frequency is lacking. If three-monthly monitoring in general practice could be reduced to six-monthly monitoring in well-controlled patients, this would reduce the use of medical services, decrease the workload for healthcare providers, alleviate the burden of type 2 diabetes patients and reduce costs. The goal of the EFFIMODI study was to make primary diabetes care as efficient as possible for both patients and healthcare providers. Therefore, we determined whether six-monthly monitoring of well-controlled type 2 diabetes patients in primary care led to equivalent cardiometabolic control compared to the generally recommended three-monthly monitoring. In addition, the effects of the monitoring frequency on many other aspects of diabetes care like costs, patients' preferences, patients' perceived health status and other biomedical outcomes were studied. Besides, we investigated patients' satisfaction and the experiences of the participating diabetes care providers at the end of the trial.

In **Chapter 1** the design of the EFFIMODI study is reported. It is a randomised controlled patient-preference equivalence trial. Participants were asked if they strongly preferred three-monthly (usual care) or six-monthly diabetes monitoring (intervention). If they did not have a strong preference, they were randomised to a three-monthly or six-monthly monitoring group. Patients were eligible for the study if they were between 40 and 80 years old, diagnosed with type 2 diabetes more than one year ago, treated by a general practitioner, not on insulin treatment, and with HbA1c ≤58 mmol/mol, systolic blood pressure ≤145 mmHg and total cholesterol ≤5.2 mmol/l. After the intervention period of one and a half year, the three-monthly and six-monthly monitoring groups were compared on equivalence of cardiometabolic control. Equivalence was assumed if the two-sided 95% confidence interval for the difference in overall good cardiometabolic control between the two groups was in the range from -5 to 5%. Secondary outcome measures were HbA1c, blood pressure, cholesterol level, BMI, smoking behaviour, physical activity, health status, diabetes-related distress, satisfaction with diabetes treatment and medication use. If both monitoring frequencies were equivalent, a cost-minimisation analysis was planned to compare the costs between three-monthly and six-monthly monitoring. If not equivalent, a cost-effectiveness analysis was planned.

The EFFIMODI study included 233 general practitioners from 107 different practices. Of the 4040 well-controlled type 2 diabetes patients invited to

participate, 2215 (54.8%) agreed. In **Chapter 2** we describe the preferences for the diabetes monitoring frequency in well-controlled type 2 diabetes patients and the associated patients' characteristics. 33.7% of the participants strongly preferred three-monthly monitoring, 30.6% strongly preferred six-monthly monitoring and the others had no preference and were randomised. The group who preferred three-monthly monitoring consisted of less smokers, felt less healthy, reported more diabetes-related distress, had the highest reported frequency of hyperglycaemic episodes and used more oral blood glucose lowering drugs compared to the other patients. Those preferring six-monthly monitoring were least satisfied with diabetes treatment, reported the lowest frequency of hyperglycaemic episodes and used less oral blood glucose lowering drugs compared to the other patients. It seemed that a preference for more frequent monitoring was associated with a worse disease status, whereas a preference for less frequent monitoring tended to be associated with the opposite. Therefore, patients seem to have logical preferences that need to be accounted for in diabetes care.

In **Chapter 3** the relation between comorbidity and health status in well-controlled type 2 diabetes patients is introduced. This was a cross-sectional analysis on the baseline data from the EFFIMODI study. Both number and type (cardiovascular and non-cardiovascular) of comorbidities were determined for each patient. We distinguished the following comorbidities: myocardial infarction, angina pectoris, heart surgery, heart failure, stroke, transient ischemic attack, peripheral arterial disease, COPD, rheumatoid arthritis, osteoarthritis of hip or knee or any other diseases. Health status was assessed with the questionnaires Short Form-36 (SF-36) and EuroQol (EQ). The SF-36 generates eight dimensions of health and a Physical and Mental Component Score (PCS and MCS). The EQ consists of two parts: EQ-5D and EQ Visual Analogue Scale. Of the 2215 well-controlled type 2 diabetes patients, 2086 were analysed. Their mean age was 65 years, 60% were males and the mean diabetes duration was 6 years. 62% of the type 2 diabetes patients had no comorbidity, 24% had one comorbidity, 9% had two comorbidities and 5% had more comorbidities. Of all patients, 26% had a cardiovascular comorbidity and 18% a non-cardiovascular comorbidity. Health status decreased when the number of comorbidities increased, except for mental health, role limitations due to emotional problems, the Mental Component Score and both EuroQol measures. In patients with both cardiovascular and non-cardiovascular comorbidity, physical functioning, role limitations due to physical problems and

the Physical Component Score were significantly lower than in patients with only cardiovascular comorbidity. Their physical functioning was also lower compared to patients with only non-cardiovascular comorbidity. So, even acceptable values of HbA1c, blood pressure and cholesterol in type 2 diabetes patients are not necessarily related with a good patient-reported health status. Physicians should take into account patient's health status and integrate the impact of comorbidities into diabetes care.

In **Chapter 4** the effectiveness and cost-effectiveness of six-monthly monitoring compared with three-monthly monitoring of well-controlled type 2 diabetes patients in primary care is described. 394 patients were randomised to three-monthly monitoring and 397 to six-monthly monitoring. In total, 774 patients (97.9%) were included in the primary analysis and 68 (8.6%) were lost to follow-up or discontinued the intervention. In the three-monthly group 69.5% remained under good cardiometabolic control, versus 69.8% in the six-monthly group. Although cardiometabolic control with six-monthly monitoring did not significantly differ from three-monthly monitoring, the 95% confidence interval of the difference between the groups (-6.2% to 6.7%) was not within the prespecified range of equivalence (-5% to 5%) and therefore equivalence is uncertain. However, the differences in secondary outcomes between three-monthly and six-monthly monitoring were not significant or clinically relevant. Besides, the cost-minimisation analysis showed that six-monthly monitoring was €387 cheaper per patient than three-monthly monitoring during the study period. The cost-utility analysis showed that six-monthly monitoring was cheaper, but with slightly lower quality adjusted life years (QALYs). The mean number of diabetes visits during follow-up was 7.8 in the three-monthly group and 5.9 in the six-monthly group. Therefore we conclude that patients with good cardiometabolic control and without preference for their monitoring frequency can visit the general practice six-monthly.

In **Chapter 5** we examine whether patient's preference for the monitoring frequency influences the relation between this monitoring frequency and cardiometabolic control. First, patients with a strong preference for three-monthly monitoring and six-monthly monitoring were compared on cardiometabolic control. Second, the preference groups were compared with the non-preference (randomised) groups. The percentage of people with good cardiometabolic control in the three-monthly preference group (69.9%) did not significantly differ from the six-monthly preference group (67.3%). Besides, randomised and preference

patients from both the three-monthly and six-monthly group, did not differ on cardiometabolic control. This indicates that six-monthly monitoring could be applied to well-controlled type 2 diabetes patients with a strong preference for six-monthly monitoring or without any preference.

In **Chapter 6** we determine the satisfaction of well-controlled type 2 diabetes patients with either three-monthly or six-monthly diabetes monitoring and their future preference regarding the monitoring frequency. After eighteen months, all participants were asked whether they were satisfied with the monitoring frequency (not at all, not, neutral, moderate, very much) and how often they would like to be monitored in the future (every three months, every six months, no preference/I do not care). Most patients (70.8%) would like to continue their received monitoring frequency. Patients from the preference groups were more often (very) satisfied than randomised patients (92.7% versus 88.1%) and patients monitored three-monthly were more often (very) satisfied than patients monitored six-monthly (93.5% versus 88.5%). Higher age, better physical health, less diabetes-related distress, higher diabetes treatment satisfaction and less perceived hyper- and hypoglycaemias were associated with a higher monitoring satisfaction. Although the satisfaction for three-monthly monitoring was slightly higher, the satisfaction with six-monthly monitoring was still rather high (88.5%). We therefore conclude that it is feasible to offer six-monthly monitoring to well-controlled type 2 diabetes patients.

In **Chapter 7** the experiences of primary care providers with six-monthly diabetes monitoring of well-controlled patients are described. At the end of the study, primary care providers completed a questionnaire about their experiences with six-monthly diabetes monitoring (very good, good, neutral, bad or very bad), whether they want to continue six-monthly monitoring (yes, no or 'I do not care') and for which type of patients six-monthly monitoring is sufficient. Only 8.9% of the primary care providers were negative about six-monthly monitoring and 65.0% would like to continue six-monthly monitoring. They disagreed about patients' ability to determine their own monitoring frequency and whether six-monthly monitoring was suitable for all well-controlled type 2 diabetes patients. Practical concerns emerged such as the inability to declare healthcare costs and the unsuitability of electronic health record systems. Since almost two out of three primary care providers would like to continue six-monthly monitoring of well-controlled type 2 diabetes patients, implementation of six-monthly monitoring on

a large scale seems possible. However, some diabetes care providers should be convinced and some practical concerns should be solved.

In the **General Discussion** we describe the generalisability of the results, the implications for clinical practice, the total costs that could be saved, the limitations of the study and the methodological considerations. Based on the results from the randomised trial and the patient preference study we concluded that six-monthly monitoring is sufficient for both patients with a strong preference for six-monthly monitoring and patients without a preference. However, after the EFFIMODI study it is still unknown what would happen if patients with a strong preference for three-monthly monitoring would be monitored six-monthly. In addition, patients who had no strong preference and were randomised to six-monthly monitoring were somewhat less satisfied; had more unscheduled diabetes visits and perceived more frequently hyper- and hypoglycaemias. We therefore hypothesise that a few patients who were randomised to six-monthly monitoring would rather have been monitored three-monthly.

Based on these results our recommendation is to propose a six-monthly monitoring scheme to all type 2 diabetes patients who are overall well-controlled for about a year. However, general practitioners should yearly discuss a few issues with the patient: (1) their satisfaction with the monitoring frequency; (2) whether the patient perceives frequently hyper- and hypoglycaemias; (3) whether the medical outcomes are getting worse in the meantime and (4) whether they frequently had unscheduled diabetes visits. In these cases, the healthcare provider might suggest returning to three-monthly monitoring. To successfully implement six-monthly monitoring the diabetes guidelines should be adapted, adjustments should be made to the general practice's information system and healthcare insurers might negotiate to lower the fixed price for every diabetes patient per year.

In addition, the EFFIMODI study shows that about 120,000 patients (patients with a strong preference for six-monthly monitoring and patients with no preference) could be monitored six-monthly in the Netherlands. Taking into account the difference in visits between the six-monthly and three-monthly monitoring groups (2.5 diabetes visits in one and a half year), it could save €48 euro per patient per year, which is nation-wide almost 6 million Euros per year.

The study also had some limitations. Firstly, it was designed as a pragmatic study, which had consequences for the blinding and the timing of measurements. Secondly, the follow-up period of eighteen months might be too short to detect

deterioration of control. However, if on the longer run deterioration would indeed occur, the monitoring frequency could be adjusted. Six-monthly monitoring is not meant as a rigid schedule, patients can be advised to return to three-monthly monitoring at any time. Thirdly, the percentage of patients reaching the three targets was lower than expected (±70%, instead of an expected 95%). With a 70% success rate, a sample size of 1764 patients per group would have been necessary to demonstrate equivalence. We presume that the relatively low percentage of people who maintained good cardiometabolic control is mainly caused by not reaching the systolic blood pressure target, but could also be a result of dichotomizing the outcome data. Therefore we also analysed HbA1c, blood pressure and cholesterol on a continuous scale, which revealed little or no deterioration after eighteen months and also no difference between three-monthly and six-monthly monitoring.

We have chosen to conduct a patient preference study instead of a classic randomised trial. This type of study has the advantage that more people will participate in the study, as people can choose not to be randomised. Patients with a preference can be included in the study arm of their choice, which leads to less selection bias and drop-out. However, we assume that if the invited patients were only invited for the randomised trial the response rate for the trial would be higher than the 20% we realised eventually. This would have resulted in a higher power of the trial and thus a smaller confidence interval; and possibly equivalence of six-monthly and three-monthly monitoring.

To conclude, six-monthly monitoring in well-controlled type 2 diabetes patients can safely be implemented in primary care. We suggest that primary care providers propose a six-monthly monitoring scheme to all type 2 diabetes patients who are overall well-controlled for about a year. Only in case of explicit patient's objections to such a scheme a three-monthly scheme will be maintained. This will result in a decreased patient burden, decreased work pressure for diabetes care providers and reduce costs.

Samenvatting

Momenteel wordt driemaandelijkse controle aanbevolen voor alle diabetes type 2 patiënten. Echter, wetenschappelijk bewijs voor de controlefrequentie ontbreekt. Als driemaandelijkse controle in de huisartspraktijk kan worden teruggebracht tot zesmaandelijkse controle bij goed ingestelde patiënten, dan zal dit leiden tot vermindering van zorggebruik, verlaging van de werkbelasting voor zorgverleners, verlichting van de last van diabetes type 2 patiënten en besparing van kosten. Het doel van de EFFIMODI studie was om de diabeteszorg in de eerstelijn zo efficiënt mogelijk te maken voor zowel patiënten als zorgverleners. Daarom hebben we onderzocht of zesmaandelijkse controle bij goed ingestelde diabetes type 2 patiënten in de eerste lijn leidt tot gelijkwaardige cardiometabole controle in vergelijking met de algemeen aanbevolen driemaandelijkse controle. Daarnaast is de studie gericht op de effecten van de controlefrequentie op vele andere aspecten van de diabeteszorg, zoals kosten, de voorkeuren van patiënten, de ervaren gezondheidstoestand van patiënten en andere biomedische resultaten. Tevens hebben we na afloop van de trial de tevredenheid van patiënten en de ervaringen van de deelnemende diabetes zorgverleners onderzocht.

In **Hoofdstuk 1** is de opzet van de studie EFFIMODI beschreven. Het is een gerandomiseerde gecontroleerde patiënten-voorkeur equivalentie trial. De deelnemers werden gevraagd of zij een sterke voorkeur hebben voor driemaandelijkse (gebruikelijke zorg) of zesmaandelijkse controle (interventie). Als ze geen voorkeur hadden, werd door het lot bepaald (randomisatie) of ze driemaandelijkse of zesmaandelijkse controle kregen. Patiënten kwamen in aanmerking voor het onderzoek als ze tussen de 40 en 80 jaar oud waren, minstens een jaar bekend waren met diabetes type 2, behandeld werden door hun huisarts, geen insuline kregen voorgeschreven, en met HbA1c ≤58 mmol/mol, systolische bloeddruk ≤145 mmHg en totaal cholesterol ≤5,2 mmol/l. Na de studieperiode van anderhalf jaar werden de driemaandelijkse en zesmaandelijkse controle groepen vergeleken op gelijkwaardigheid van cardiometabole controle. Gelijkwaardigheid werd aangenomen als het tweezijdige 95% betrouwbaarheidsinterval voor het verschil in cardiometabole controle tussen de twee groepen tussen de -5 en 5% lag. Secundaire uitkomstmaten waren HbA1c, bloeddruk, cholesterol, BMI, roken, lichamelijke activiteit, gezondheidstoestand, diabetes-gerelateerde zorgen, tevredenheid met de diabetesbehandeling en medicatiegebruik. Wanneer beide controlefrequenties gelijkwaardig waren, werd een kosten-minimisatie analyse gepland om de kosten te vergelijken tussen

driemaandelijkse en zesmaandelijkse controle. Als ze niet gelijkwaardig waren, werd een kosten-effectiviteitsanalyse gepland.

Aan de EFFIMODI studie deden 233 huisartsen uit 107 verschillende praktijken mee. Van de 4040 goed ingestelde diabetes type 2 patiënten die werden uitgenodigd om deel te nemen, deden 2215 (54,8%) patiënten mee. In **Hoofdstuk 2** beschrijven we de voorkeuren voor de controlefrequentie van goed ingestelde diabetes type 2 patiënten en de bijbehorende patiënten kenmerken. Van de deelnemers had 33,7% een sterke voorkeur voor driemaandelijkse controle, 30,6% voor zesmaandelijkse controle en de anderen hadden geen voorkeur en werden gerandomiseerd. De groep met een sterke voorkeur voor driemaandelijkse controle bestond uit minder rokers, voelde zich minder gezond, rapporteerde meer diabetes-gerelateerde zorgen, had de hoogste gerapporteerde frequentie van hyperglykemische perioden en gebruikte meer orale bloedglucoseverlagende geneesmiddelen in vergelijking met de andere patiënten. Degenen die de voorkeur gaven aan zesmaandelijkse controle waren het minst tevreden met de diabetesbehandeling, hadden de laagste frequentie van hyperglykemische perioden en gebruikten minder orale bloedglucoseverlagende geneesmiddelen in vergelijking met de andere patiënten. Het bleek dus dat een voorkeur voor meer frequente controle samenhing met een slechtere gezondheidstoestand, terwijl een voorkeur voor minder frequente controle geassocieerd was met het tegenovergestelde. Patiënten lijken dus logische voorkeuren te hebben en met die voorkeur moet rekening worden gehouden in de diabeteszorg.

In **Hoofdstuk 3** wordt het verband tussen comorbiditeit en de gezondheidstoestand van goed ingestelde diabetes type 2 patiënten behandeld. Dit was een cross-sectionele analyse op de baseline gegevens van de EFFIMODI studie. Zowel het aantal als het type (cardiovasculair en niet-cardiovasculair) comorbiditeiten werd bepaald voor iedere patiënt. We maakten daarbij een onderscheid in de volgende comorbiditeiten: myocardinfarct, angina pectoris, hartoperatie, hartfalen, beroerte, TIA, perifeer arterieel vaatlijden, COPD, reumatoïde artritis, artrose van de heup of knie of andere aandoeningen. De gezondheidstoestand werd gemeten met de vragenlijsten Short Form-36 (SF-36) en EuroQol (EQ). De SF-36 produceert acht gezondheidsdimensies en een Fysieke en Mentale Component Score. De EQ bestaat uit twee delen: EQ-5D en EQ VAS. Van de 2215 goed ingestelde diabetes type 2 patiënten, werden er 2086 geanalyseerd. Hun gemiddelde leeftijd was 65 jaar, 60% was man en de gemiddelde diabetesduur was 6 jaar. 62% van de diabetes type 2 patiënten had

geen comorbiditeit, 24% had één comorbiditeit, 9% had twee comorbiditeiten en 5% had meerdere comorbiditeiten. Van alle patiënten had 26% een cardiovasculaire comorbiditeit en 18% een niet-cardiovasculaire comorbiditeit. De gezondheidstoestand neemt af wanneer het aantal comorbiditeiten toeneemt, behalve voor wat betreft de onderdelen geestelijke gezondheid, rolbeperkingen als gevolg van emotionele problemen, de Mentale Component Score en beide EuroQol maten. Patiënten met zowel cardiovasculaire als niet-cardiovasculaire comorbiditeit hadden significant lagere scores voor de onderdelen fysiek functioneren, rolbeperkingen als gevolg van fysieke problemen en de Fysieke Component Score in vergelijking met patiënten met alleen cardiovasculaire comorbiditeit. Hun lichamelijk functioneren was ook minder in vergelijking met patiënten met alleen niet-cardiovasculaire comorbiditeit. Kortom, zelfs acceptabele waarden voor HbA1c, bloeddruk en cholesterol bij diabetes type 2 patiënten zijn niet noodzakelijkerwijs gerelateerd met een goede patiënt-gerapporteerde gezondheidstoestand. Artsen dienen rekening te houden met de gezondheidstoestand van de patiënt en moeten de impact van comorbiditeit integreren in de diabeteszorg.

In **Hoofdstuk 4** wordt de effectiviteit en kosten-effectiviteit van zesmaandelijkse controle in vergelijking met driemaandelijkse controle bij goed ingestelde diabetes type 2 patiënten in de eerstelijnszorg beschreven. 394 patiënten werden gerandomiseerd naar driemaandelijkse controle en 397 naar zesmaandelijkse controle. In totaal werden 774 patiënten (97,9%) geïncludeerd in de primaire analyse en 68 (8,6%) werden teruggetrokken uit de studie of stopten met de interventie. In de driemaandelijkse groep bleef 69,5% onder goede cardiometabole controle, tegenover 69,8% in de zesmaandelijkse groep. Hoewel de cardiometabole controle met zesmaandelijkse controle niet significant verschilde van driemaandelijkse controle, lag het 95% betrouwbaarheidsinterval van het verschil tussen de groepen (-6,2% tot 6,7%) niet binnen het vooraf gespecificeerde gelijkwaardigheidsinterval (-5% tot 5%) en daarom is de gelijkwaardigheid onzeker. De verschillen in secundaire uitkomsten tussen de driemaandelijkse en zesmaandelijkse controle waren echter niet significant of klinisch relevant. Daarnaast liet de kosten-minimisatie analyse zien dat zesmaandelijkse controle €387 goedkoper was per patiënt dan driemaandelijkse controle gedurende de studieperiode. De kosten-utiliteiten analyse liet zien dat zesmaandelijkse controle goedkoper was, maar met iets lagere ‘quality adjusted life years’ (QALYs). Het gemiddeld aantal diabetesconsulten tijdens de studie was 7,8 in de

driemaandelijkse groep en 5,9 in de zesmaandelijkse groep. Daarom concluderen we dat patiënten met een goede cardiometabole controle en zonder voorkeur voor de controlefrequentie voortaan minder vaak naar hun huisartsenpraktijk kunnen gaan.

In **Hoofdstuk 5** hebben we onderzocht of de voorkeur van patiënten voor de controlefrequentie van invloed is op het verband tussen deze controlefrequentie en de cardiometabole controle. Eerst werd de cardiometabole controle vergeleken van de patiënten met een sterke voorkeur voor driemaandelijkse controle met die van de patiënten die zesmaandelijkse controle prefereerden. Ten tweede werd de cardiometabole controle van de 'voorkeursgroepen' vergeleken met de 'niet-voorkeurs' (gerandomiseerde) groepen. Het percentage mensen met een blijvend goede cardiometabole controle in de driemaandelijkse voorkeursgroep (69,9%) verschilde niet significant van dat in de zesmaandelijkse voorkeursgroep (67,3%). Bovendien verschilde op het eind van de studie de cardiometabole controle niet tussen patiënten met en zonder voorkeur, van zowel de driemaandelijkse als zesmaandelijkse groep. Dit wijst erop dat zesmaandelijkse controle tenminste kan worden toegepast bij goed ingestelde diabetes type 2 patiënten met een sterke voorkeur voor zesmaandelijkse controle of zonder enige voorkeur.

In **Hoofdstuk 6** is de tevredenheid van goed ingestelde diabetes type 2 patiënten met een driemaandelijkse of zesmaandelijkse controle en hun toekomstige voorkeur voor de controlefrequentie beschreven. Na achttien maanden werd aan alle deelnemers gevraagd of zij tevreden zijn met de controlefrequentie (helemaal niet, niet, neutraal, redelijk, heel erg) en hoe vaak zij in de toekomst gecontroleerd willen worden (elke drie maanden, elke zes maanden, geen voorkeur/maakt me niet uit). De meeste patiënten (70,8%) zouden graag de in de EFFIMODI studie ontvangen controlefrequentie voortzetten. Patiënten uit de 'voorkeursgroepen' waren vaker tevreden (92,7%) dan gerandomiseerde patiënten (88,1%) en patiënten die driemaandelijkse werden gecontroleerd waren vaker (93,5%) tevreden dan patiënten die zesmaandelijks werden gecontroleerd (88,5%). Hogere leeftijd, een betere lichamelijke gezondheid, minder diabetes-gerelateerde zorgen, grotere tevredenheid met de diabetesbehandeling en minder ervaren hyper- en hypoglykemieën werden geassocieerd met een hogere tevredenheid met de controlefrequentie. Hoewel de tevredenheid voor driemaandelijkse controle iets groter was, was ook de tevredenheid met de zesmaandelijkse controle hoog (88,5%). We concluderen daarom dat het haalbaar is om zesmaandelijkse controle voor te stellen aan goed ingestelde diabetes type 2 patiënten.

In **Hoofdstuk 7** worden de ervaringen van de eerstelijns zorgverleners met zesmaandelijkse controle van goed ingestelde patiënten beschreven. Eerstelijns zorgverleners gaven in een korte vragenlijst na afloop van de EFFIMODI studie aan hoe zij de zesmaandelijkse controle hebben ervaren (zeer goed, goed, neutraal, slecht, zeer slecht), of ze willen doorgaan met de zesmaandelijkse controle (ja, nee, maakt me niet uit) en voor welk type patiënten zesmaandelijkse controle voldoende is. Slechts 8,9% van de eerstelijns zorgverleners was negatief over de zesmaandelijkse controle en 65,0% wil graag doorgaan met de zesmaandelijkse controle. De zorgverleners waren het oneens over het vermogen van patiënten om hun eigen controlefrequentie te bepalen en of zesmaandelijkse controle geschikt is voor alle goed ingestelde diabetes type 2 patiënten. Enkele praktische bezwaren kwamen naar voren, zoals het declareren van kosten en de ongeschiktheid van het huidige huisartsen informatie systeem. Omdat bijna twee van de drie zorgverleners wil doorgaan met de zesmaandelijkse controle van goed ingestelde diabetes type 2 patiënten, lijkt implementatie van zesmaandelijkse controle op grote schaal mogelijk. Toch zal een aantal diabetes zorgverleners nog overtuigd moeten worden en een aantal praktische bezwaren moeten worden opgelost.

In de **Algemene Discussie** beschrijven we de generaliseerbaarheid van de resultaten, de implicaties voor de klinische praktijk, de totale kosten die bespaard kunnen worden, de beperkingen van het onderzoek en de methodologische overwegingen. Op basis van de resultaten van de gerandomiseerde trial en de patiënten-voorkeur studie concluderen we dat zesmaandelijkse controle voldoende is voor patiënten met een sterke voorkeur voor zesmaandelijkse controle en ook voor patiënten zonder een voorkeur. Echter, na de EFFIMODI studie is nog niet bekend wat er zal gebeuren als patiënten met een sterke voorkeur voor driemaandelijkse controle zesmaandelijks worden gecontroleerd. Bovendien, patiënten die geen sterke voorkeur hadden en werden gerandomiseerd naar zesmaandelijkse controle waren iets minder tevreden, hadden meer ongeplande diabetesconsulten en ervaarden vaker hyper- en hypoglykemieën. Onze hypothese is daarom dat een aantal patiënten, die werden gerandomiseerd voor zesmaandelijkse controle, liever driemaandelijks gecontroleerd hadden willen worden.

Op basis van deze resultaten is onze aanbeveling om een zesmaandelijkse controle schema aan te bieden aan alle type 2 diabetes patiënten met ongeveer een jaar goede cardiometabole controle. Echter, huisartsen zullen een aantal zaken met de patiënt jaarlijks moeten bespreken: (1) hun tevredenheid met de

controlefrequentie; (2) of de patiënt vaak hyper- en hypoglykemieën ervaart; (3) of de medische resultaten in de tussentijd verslechteren en (4) of ze, achteraf gezien, vaak ongeplande diabetesconsulten hebben. In deze gevallen kan de zorgverlener voorstellen terug te keren naar driemaandelijkse controle. Om met succes zesmaandelijkse controle te implementeren moeten de diabetesrichtlijnen worden aangepast, moeten aanpassingen worden aangebracht aan het huisartsen informatie systeem en de zorgverzekeraars zouden kunnen onderhandelen om de vaste prijs voor iedere diabetespatiënt per jaar te verlagen.

Daarnaast toont de EFFIMODI studie aan dat ongeveer 120.000 patiënten (patiënten met een sterke voorkeur voor zesmaandelijkse controle en patiënten zonder voorkeur) zesmaandelijks kunnen worden gecontroleerd in Nederland. Rekening houdend met het verschil in bezoeken tussen de zesmaandelijkse en driemaandelijkse controle groepen (2,5 diabetesconsulten gedurende anderhalf jaar), zou dit €48 euro per patiënt per jaar kunnen besparen. Dat is over het hele land gezien bijna 6 miljoen euro per jaar.

De studie heeft ook een aantal beperkingen. Ten eerste, het onderzoek is opgezet als een pragmatische studie, wat gevolgen had voor de blindering en de timing van de metingen. Ten tweede, de follow-up periode van achttien maanden kan te kort zijn geweest om verslechtering van controle op te sporen. Echter, als op de langere termijn verslechtering inderdaad zou optreden, kan de controlefrequentie worden aangepast. Zesmaandelijkse controle is niet bedoeld als een strak schema, maar patiënten kunnen op elk gewenst moment worden geadviseerd om naar driemaandelijkse controle terug te keren. Ten derde, het percentage patiënten dat alle de drie doelen haalde was lager dan verwacht (±70%, tegen een verwachte 95%). Met een 70% kans op succes, zou een steekproef van 1764 patiënten per groep nodig zijn geweest om gelijkwaardigheid aan te tonen. We gaan ervan uit dat het relatief lage percentage van mensen die onder goede cardiometabole controle waren gebleven vooral veroorzaakt wordt door het niet bereiken van de streefwaarde voor de systolische bloeddruk, maar kan ook het gevolg zijn geweest van het dichotomiseren van de uitkomst. Daarom hebben we HbA1c, bloeddruk en cholesterol ook op een continue schaal geanalyseerd. Dit liet weinig of geen verslechtering na achttien maanden zien en ook geen verschil tussen de driemaandelijkse en zesmaandelijkse controle.

We hebben ervoor gekozen om een patiënten-voorkeur studie uit te voeren in plaats van een klassieke gerandomiseerde studie. Dit type onderzoek heeft als voordeel dat meer mensen zullen deelnemen aan de studie, omdat mensen ervoor

kunnen kiezen om niet gerandomiseerd te worden. Patiënten met een voorkeur komen in de studie-arm naar keuze, wat leidt tot minder selectiebias en drop-out. Echter, we denken dat als de uitgenodigde patiënten alleen werden uitgenodigd voor de gerandomiseerde studie dat de respons voor het onderzoek hoger zou zijn dan de 20% die we nu uiteindelijk gerealiseerd hebben. Dit zou hebben geleid tot een hogere power van de gerandomiseerde trial en dus een kleiner betrouwbaarheidsinterval en mogelijk gelijkwaardigheid van zesmaandelijkse en driemaandelijkse controle.

Tot slot, zesmaandelijkse controle in goed ingestelde diabetes type 2 patiënten kan veilig worden uitgevoerd in de eerstelijnszorg. Wij adviseren dat zesmaandelijkse controle door de zorgverleners wordt voorgesteld aan alle diabetes type 2 patiënten die ongeveer een jaar goed zijn ingesteld. Alleen in geval van uitdrukkelijke bezwaren van de patiënt zal een driemaandelijkse controle worden gehandhaafd. Dit zal resulteren in een verminderde patiëntenlast, verminderde werkdruk voor diabetes zorgverleners en de kosten verlagen.

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Curriculum Vitae

Paulien Renske Wermeling was born on July 1st, 1985 in Roosendaal en Nispen. She did Atheneum at the Markland College, Oudenbosch and in 2003 she obtained her degree. After high school, she started with the study Life Sciences and Technology at the Leiden University and the Delft University of Technology. At the beginning of 2004 she quit with this study. In September 2004, she started with the Bachelor of Health Sciences at the VU University, Amsterdam. After three years, she obtained her Bachelor degree and continued with the Master Infectious Diseases and Public Health at the VU University, Amsterdam. As part of her Master research project she did an internship at the GGD Amsterdam with the research department. After obtaining her Master degree, she started as a PhD student at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. During her PhD she also obtained her degree of the Master Epidemiology postgraduate, with a specialisation in Clinical Epidemiology.