PERSONALISED AND PATIENT-CENTRED DIABETES CARE

HENK DEN OUDEN

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Personalised and Patient-centred diabetes care

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht

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Author	Henk den Ouden
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PERSONALISED AND PATIENT-CENTRED DIABETES CARE

Gepersonaliseerde en patiëntgerichte diabeteszorg

(met een samenvatting in het Nederlands)

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Copromotor:	Dr. R.C. Vos
Beoordelingscommissie:	Dr. A.H. Pieterse
	Prof. dr. F.H. Rutten
	Prof. dr. G.D. Valk
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MANUSCRIPTS BASED ON THE STUDIES PRESENTED IN THIS THESIS.

Metabolomic biomarkers for personalised glucose lowering drugs treatment in type 2 diabetes.

Authors H. den Ouden, L. Pellis, G.E.H.M. Rutten, I.K. Geerars-van Vonderen, C.M. Rubingh, B. van Ommen, M.J. van Erk, J.W.J. Beulens.
Published in Metabolomics 2016;12:27. doi: 10.1007/s11306-015-0930-4.

Effect of six years intensified multifactorial treatment on levels of hs-CRP and adiponectin in patients with screen detected type 2 diabetes: the ADDITION-Netherlands randomized trial.

Authors H. den Ouden, J. Berends, R.K. Stellato, J.W. Beulens, G.E.H.M. Rutten.
Published in Diabetes Metab Res Rev 2015 Oct;31(7):758-66. doi: 10.1002/dmrr.2669.

Shared decision making in type 2 diabetes with a support decision tool that takes into account clinical factors, the intensity of treatment and patient preferences: design of a cluster randomised (OPTIMAL) trial.

Authors H. den Ouden, R.C. Vos, C. Reidsma, G.E.H.M. Rutten.
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Effectiveness of shared goal setting and decision making to achieve treatment targets in type 2 diabetes patients: A cluster-randomized trial (OPTIMAL).

Authors H. den Ouden, R.C. Vos, G.E.H.M. Rutten.
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Shared decision making in primary care: Process evaluation of the intervention in the OPTIMAL study, a cluster randomised trial.

Authors H. den Ouden, R.C. Vos, A.H. Pieterse, G.E.H.M. Rutten.
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CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

Type 2 diabetes

Diabetes mellitus is diagnosed by the presence of glucose levels exceeding a threshold blood glucose concentration which predisposes to microvascular end-organ complications.

About 90 to 95% of people with diabetes mellitus have type 2 diabetes mellitus (T2DM), a heterogeneous group of disorders caused by a combination of insulin resistance and impairment of insulin secretion. T2DM can develop at any age, but is mostly linked to middle and older age, whether or not in combination with excess weight, physical inactivity or a family history of diabetes (McCarthy et al., 2017); (Mühlbacher et al., 2021); (Williams et al., 2016).

Treatment of type 2 diabetes

The treatment of T2DM requires controlling blood glucose levels, cardiovascular risk factor management and regular follow-up/monitoring (Davies et al., 2018); (Raz et al., 2013). Non adherence to therapy (lifestyle and medication) and the loss of effectiveness of most antidiabetic drugs over time emphasise the need for individualised interventions to maintain control over the patients' blood glucose levels (Aquilante et al., 2010); (Raz et al., 2013); (Gorter et al., 2012). In clinical practice, drugs are prescribed in a trial-and-error manner for each patient to achieve therapeutic targets, like HbA1c, blood pressure and cholesterol (Raz et al., 2013). If physicians could predict the patients' response to treatment, a more individualised approach could be established. A patient-centred approach has been shown to enhance patient engagement in self-care activities (general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking) (Rutten et al., 2020); (Olesen et al., 2020).

Moreover, early diagnosis of T2DM and reaching treatment targets in the first year after diagnosis have been shown to improve both quality of life and life expectancy (Davies et al., 2018); (Varghese et al, 2021); (Faselis et al., 2020). Currently, the implementation of a personalised and patient-centred approach in T2DM treatment is far from optimal. Despite the continuous evolution of new therapies and technologies, many patients with T2DM are not able to achieve their diabetes management goals (Kalra et al., 2022); (Mühlbacher et al., 2021).

Personalised medicine

The concept of precision medicine or personalised medicine is defined by the Precision Medicine Initiative as 'an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person' (Chung et al., 2020). What has changed radically in the digital age is our ability to characterise and understand biological variation through; 1. the assessment of a patients' genetic and metabolic state, 2. using (digital) data to determine disease categories, and 3. science-guided treatment decisions and preventive measures tailored to specific pathological conditions (Chung et al., 2020); (Fleming et al., 2020). The current focus on personalised (or precision) medicine reflects the expectation that developments in genomics (Udler et al., 2019), imaging and other domains will extend our diagnostic and prognostic capabilities, and will enable more effective targeting of current and future preventative and therapeutic options. The clinical benefits of this approach are already being realised in rare diseases and cancer, but the impact on management of complex chronic diseases, such as T2DM, remains limited (Chung et al., 2020); (McCarthy, 2017).

Though promising, these -omics and big data approaches addressing both personal and environmental factors and their interaction are largely unrealised in T2DM care and will require large investments and coordination to have impact (Chung et al., 2020).

One of the tools in developing personalised medicine is the use of pharmacogenomics. Thus far, pharmacogenomics has been used to investigate the response to blood glucose reduction treatment with a focus on genetic variations in drug metabolising enzyme and drug target genes. A recent study reviewed all the studies in which genetic variants were assessed with respect to metabolic response to treatment with novel glucose-lowering drugs. However, the relevance of the included studies is limited due to small genetic effects, low sample sizes, limited statistical power, inadequate statistics (lack of gene–drug interactions), inadequate accounting for confounders and effects modifiers, and a lack of replication studies (Rathmann et al, 2021); (Pacanowski et al., 2008).

Another approach to identify metabolites and to investigate the treatment response is by using metabolomics. The advantages of metabolomics over genomics include its direct relation with metabolism and the analysis of relatively few metabolites compared with the unwieldy number of genes. Moreover, metabolomics is more sensitive to detect short-term and/or long-term changes (Lu et al., 2013).

Personalised medicine and cardiovascular disease risk management

Inflammation is a major risk factor for cardiovascular disease (CVD) (Ross, 1999). T2DM is associated with inflammation that promotes the development of CVD (Danesh et al., 2004). Little is known about the effects of intensive glucose control on inflammation, and data are inconsistent (Schulze et al., 2004).

Hs-CRP and adiponectin have been evaluated in cohort studies and are accepted cardiovascular biomarkers for the risk of CVD (Buckley et al., 2009). Hs-CRP has consistently been associated with CVD (Danesh et al., 2004). A meta-analysis suggested that hs-CRP improves risk prediction for CVD beyond traditional risk factors (Buckley et al., 2009). Effects of intensive blood glucose control on hs-CRP vary according to the strategy and agent(s) used for blood glucose control (Danesh et al., 2004); (Schulze et al., 2004); (Belalcazar et al., 2010); (De Jager et al., 2005);

(Pradhan et al., 2009); (Prasad, 2006). Determining the CVD risk on the basis of someone's hs-CRP could be a building block for personalised medicine. In that context, it would be important if it could be demonstrated that hs-CRP can actually be lowered by an early multifactorial treatment, aimed to get people on target during the first year after T2DM diagnosis.

Adiponectin is an adipokine with various functions, including energy-saving in triglyceride (TG) and anti-inflammatory activity, and anti-oxidative functions in several organs and cells (Karamian et al., 2021). Circulating adiponectin levels are lower than normal in subjects with high body mass index (BMI), large subcutaneous fat area (SFA) or large visceral fat area (VFA). In obese subjects, circulating adiponectin concentrations correlate inversely with VFA. Reduction of visceral fat increases circulating adiponectin levels in both males and females (Abdella & Mojiminiyi, 2018). Low circulating adiponectin concentrations (hypoadiponectinemia; < 4 μg/mL) are associated with a variety of diseases, including T2DM, coronary artery disease, stroke and peripheral artery disease (Abdella & Mojiminiyi, 2018).
On the other hand, blood levels of adiponectin are significantly increased in heart failure. Therefore, it is still controversial to consider adiponectin as a marker of cardiovascular disease (Woodward et al., 2017).

Patient-centred care: Shared Decision Making (SDM) in T2DM treatment
In addition to the concept of personalised medicine, the concept of patient-centred medicine is also important. Patient-centeredness is often described as a paradigm shift in which the role of the T2DM patient has evolved from a passive recipient of medical care to an active, empowered and informed coproducer of health. Providing patient-centred care that acknowledges multimorbidity and is respectful of and responsive to individual patient preferences and barriers, including the different costs of therapies, is essential to effective T2DM treatment (Davies et al., 2018); (Inzucchi

et al., 2012); (Charles et al., 1999). Treatment targets concerning blood glucose levels should be individualised based on patient preferences and goals, risks or adverse effects of therapy in addition to patient characteristics, including overall health/lifestyle and comorbidities. To achieve and maintain treatment targets, not only individual clinical characteristics should be considered, but also patients' preferences for treatment intensity. Generally speaking, the doctor is the expert on medicine, while the patient is the expert on his or her priorities.

Careful consideration of patient factors and preferences should form the basis for individualising treatment goals and strategies (Davies et al., 2018). Shared decision making (SDM) is an approach that respects the clinical evidence and the patients' preferences for treatment goals and is considered an essential part of patient-centred diabetes care. SDM is defined as 'an approach where clinicians and patients make decisions together, using the best available evidence' (Elwyn et al., 2010). Despite the weight of evidence and a growing consensus regarding its centrality in patient-centred care, SDM remains underutilised in diabetes care (Elwyn et al., 2012; Saheb Kashaf et al., 2017). As reviewed by Serrano *et al*, there is substantial evidence of an association between SDM and improved decision quality, patient knowledge and patient risk perception, but there is little evidence of an association between SDM and glycaemic control, patient satisfaction, quality of life, medication adherence or trust in physician (Serrano et al., 2016). Despite that, patients and clinicians must work together to create plans of action in response to the often troubling and confused situations of people living with diabetes (Elwyn et al., 2010).

SDM facilitated by decision aids that show the benefits and risks of available treatment options might be a useful strategy to discuss the best treatment course with the patient. Patient-centred approaches, professional skill training, personal goal setting, problem-solving skills in self-management and peer support have been suggested as effective ingredients to facilitate patient-centredness in T2DM self-management education and support programs (Davies et al., 2018). Physicians should be trained in a patient-centred attitude rather than a paternalistic attitude. It is

known that GPs perceive barriers to implement SDM consequently in daily practice (Alsulamy et al., 2020); (Driever et al., 2020); (Pel-Littel et al., 2021).
Against this background, it would be valuable to study the effect of SDM training on sustaining high levels of SDM.

This thesis relates to both personalised and patient-centred diabetes care.
Chapter 2 and 3 refer to **personalised medicine:**
In *chapter 2*, we report the outcomes of a metabolic study on the patients' responsiveness to metformin and/or sulphonylurea (SU). We aimed to identify metabolic biomarkers to predict patients' responsiveness to metformin and/or SU during the first five years after screen-detection of T2DM, so in treatment naïve patients with T2DM. Our study population consisted of participants in the ADDITION-Europe study. The ADDITION-Europe study included screen detected T2DM patients and compared an intensive multifactorial treatment of HbA1c, cholesterol, blood pressure and body weight with less intensive usual care according to national guidelines. People with screen-detected T2DM were followed up for five years (Griffin et al., 2011).
The long-term effects of multifactorial therapy in T2DM patients on inflammation (hs-CRP and adiponectin) are unknown. In *chapter 3* we analyse the effectiveness of the five years ADDITION intervention on hs-CRP and adiponectin levels, taking into account practice, baseline levels and different medications.

The chapters 4-6 report on studies on **patient-centred diabetes care**.
At the end of the ADDITION study, all participating Dutch patients were invited to attend a meeting for the presentation of the 5-years results. During that meeting with around 100 participants the idea arose to implement the intensive treatment in daily practice, but on the other hand patients stated that each individual should have the choice to choose the intensive or less intensive treatment option. The idea for the OPTIMAL study came up.

In usual care, no more than 10-20% of T2DM patients achieve all treatment goals regarding glycaemic control, lipids and blood pressure (Camara et al., 2014); (Stark Casagrande et al., 2013). Clinicians are sometimes hesitant to intensify treatment (Khunti et al., 2013); (Schmittdiel et al., 2008) and patients are not always adherent to medical treatment. and doctors do not acknowledge this. A collaborative approach by using SDM and goal setting could be helpful for both patient and clinician and might increase treatment adherence and the proportion of patients who successfully reach all their treatment targets (Coronado-Vazquez et al., 2020); (Meddings et al., 2012); (Voorham et al., 2011).

Because SDM is especially useful when there are two or more equally beneficial treatment options, the results of the ADDITION-Europe study, in which Dutch primary care practices participated, could be used in a SDM approach in patients with T2DM. In the OPTIMAL study we used a special decision aid, based on the ADDITION-Europe study and comparing two (almost) equally effective treatments but with slightly different intensities (Griffin et al., 2011).

In *chapter 4*, the design and methods of the OPTIMAL study are described.

In *chapter 5*, we report the two years difference between 'treatment as before' and our intervention with SDM, taking into account both the intensity of treatment, clinical factors and the patients' preferences.

Chapter 6 describes the implementation of the intervention during a two-years-period and the short training fidelity. The GPs' and patients' perceived levels of SDM were measured at baseline and at 24-months follow-up, as well as the perceived actual role in making the final decision.

Chapter 7 summarises and discusses the results of the different studies.

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CHAPTER 2

METABOLOMIC BIOMARKERS FOR PERSONALISED GLUCOSE LOWERING DRUGS TREATMENT IN TYPE 2 DIABETES.

H. den Ouden, L. Pellis, G.E.H.M. Rutten, I.K. Geerars-van Vonderen, C.M. Rubingh, B. van Ommen, M.J. van Erk, J.W.J. Beulens.

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ABSTRACT

Objective

We aimed to identify metabolites to predict patients' response to glucose lowering treatment during the first five years after detection of type 2 diabetes.

Research design and Methods

Metabolites were measured by GC-MS in baseline samples from 346 screen-detected type 2 diabetes patients in the ADDITION-NL study. The response to treatment with metformin and/or sulphonylurea (SU) was analysed to identify metabolites predictive of 5 year HbA1c change by multiple regression analysis.

Results

Baseline glucose and 1,5 anhydro-glucitol were associated with HbA_{1c} decrease in all medication groups. In patients on SU no other metabolite was associated with HbA1c decrease. A larger set of metabolites was associated with HbA1c change in the metformin and the combination therapy (metformin + SU) groups. These metabolites included metabolites related to liver metabolism, such as 2-hydroxybutanoic acid, 3-hydroxybutanoic acid, 2-hydroxypiperidine and 4-oxoproline). Metabolites involved in oxidative stress and insulin resistance were higher when the HbA1c decrease was larger in the metformin/sulphonylurea group.

Conclusions

The associations between baseline metabolites and responsiveness to medication are in line with its mode of action. If these results could be replicated in other populations, the most promising predictive candidates might be tested to assess whether they could enhance personalized treatment.

INTRODUCTION

The management of type 2 diabetes is complex and its complications remain a great burden to individual patients and the larger society (Raz et al., 2013). Incomplete response rates to therapy and the waning durability of response over time with most antidiabetic drugs emphasize the need for personalized interventions to maintain tight glycaemic control (Aquilante, 2010). Trial evidence is limited for the optimal use of agents, especially in dual and triple combinations (Raz et al., 2013); (Gorter et al., 2012). In clinical practice drugs are prescribed in a trial-and-error manner for each patient to achieve therapeutic targets (Raz et al., 2013). If physicians could predict the patients' response to treatment, a more individualised approach could be established.

The first line pharmaceutical treatment is metformin. Metformin acts as an insulin sensitizer, suppressing hepatic glucose production and ameliorating insulin resistance in peripheral tissues. In addition, metformin promotes glycogen synthesis and decreases intestinal glucose absorption (Kirpichnikov et al., 2002). Clinical trials showed that metformin has a wide therapeutic response range of HbA_{1c} (glycosylated haemoglobin) reductions from 0.8 to 3%. Moreover, less than two-thirds of patients achieve the fasting glucose target with metformin alone (Hermann et al., 1994).

Metformin may be moderately protective against mortality and cardiovascular morbidity (Gorter et al., 2012); (Setter et al., 2003). If needed, mostly sulphonylurea (SU) is added to metformin. Sulphonylureas stimulate insulin release in a glucose-independent manner and may reduce microvascular complications (Inzucchi et al., 2012); (Defronzo, 2009). Sulphonylureas lower HbA_{1c} by on average 1–2% (Gorter et al., 2012); (Inzucchi et al., 2012). However, approximately 50–60% of patients with an initially greater than 30 mg/dl reduction of fasting plasma glucose will fail to reach the desired glycaemic treatment target (Defronzo, 2009). To make patient-centred care and standardized algorithmic management of type 2 diabetes more compatible it is important to know a patients' responsiveness to treatment (Raz et

al., 2013). Thus far, pharmacogenetics have been used to investigate response to glucose lowering treatment with a focus on genetic variations in drug metabolizing enzyme and drug target genes (Pacanowski et al., 2008). Metabolomics is another approach to identify metabolites predicting response to treatment. The advantages of metabolomics over genomics include its direct relation with metabolism and the analysis of relatively few metabolites compared with the unwieldy number of genes. Moreover, metabolomics is more sensitive to detect short-term and/or long-term changes (Lu et al., 2013). During the last decade, metabolomics has provided valuable insights into the pathophysiology of type 2 diabetes (Lu et al., 2013); (Bao et al., 2009); (Li et al., 2009). Whether metabolomics can be used to investigate response to glucose lowering treatment in screen-detected diabetes patients has not been investigated to date. We aimed to identify metabolic biomarkers to predict patients' responsiveness to metformin and/or SU during the first five years after detection of type 2 diabetes mellitus in a unique population with screen-detected and thus treatment naïve patients with type 2 diabetes mellitus.

METHODS

Design

This study was performed in the Dutch part of the European ADDITION Study. This randomized, single-blind trial consisted of a screening study and a subsequent intervention study. The practices were randomly assigned to provide routine diabetes care or an intensive multifactorial treatment in a 1:1 ratio by statisticians in each centre according to computer-generated list, independent of measurement teams. The intervention study evaluated the effect of intensified multifactorial treatment on cardiovascular morbidity and mortality in about 3000 screen-detected type 2 diabetes patients aged 40 to 69 years. Details of the study have been reported previously (Griffin et al., 2011); (Van den Donk et al., 2013). For the study website see: http://www.addition.au.dk/. In the ADDITION-Netherlands study 56,978 people aged 50 to 69 years from 79 primary care practices were invited to participate. Individuals at risk were assessed in general practice and those diagnosed as having type 2 diabetes according to WHO criteria including the requirement for confirmatory testing on a separate occasion, were included in the study. Exclusion criteria were assessed by family physicians. They were illness with a life expectancy of less than 12 months or psychological or psychiatric disorders that might invalidate informed consent, or being housebound or pregnant, or lactation. Between 2002 and 2004 586 new type 2 diabetes patients were detected (Janssen et al., 2009). The study was approved by the medical-ethical committee of the University Medical Centre Utrecht. Participants gave written informed consent before study entry.

Randomisation and interventions

In ADDITION Netherlands 498 screen-detected type 2 diabetes patients were included in a single-blind trial with practice-level randomisation to intensified multifactorial treatment (n = 255) or routine care (n = 243). Allocation was concealed from patients throughout the trial. In total 54 patients were excluded from the

longitudinal analyses because they lacked follow-up data. Patients were blinded to which treatment arm their family physician had been randomised.

The patients in the intensive treatment group were treated to achieve an HbA_{1c} < 7.0% (53 mmol/mol). Alternations or additions to glucose-lowering therapy should be initiated when HbA_{1c} > 6.5% (48 mmol/mol). If HbA_{1c} remained above 7.0% (53 mmol/mol) with oral agents, insulin therapy should be initiated. A healthy diet was advised to all participants (low fat, 600g of fruit and vegetables/day) (Janssen et al., 2009).

Patients in the routine care group were treated following the guidelines from the Dutch College of General Practitioners. In the 1999 guidelines HbA_{1c} levels between 7.0% (53 mmol/mol) and 8.5% (69 mmol/mol) were described as acceptable (Wiersma et al., 1999). In 2006 the HbA1c target became stricter with ≤ 7.0% (53 mmol/mol) for all patients (Bouma et al., 2006). Blood pressure and lipid lowering treatments have been described previously (Griffin et al., 2011).

Measurements

Participants were invited for health assessments at inclusion between 2002-2004 and for the final measurement in 2009. If participants did not complete follow-up questionnaires or measurements the most recent values were obtained from the primary care practice records. Between the baseline and final measurement all patients had three-monthly and annual check-ups in the primary care practices. Baseline and subsequent HbA1c and lipid levels were all analysed in one regional laboratory, the SHL Centre for Diagnostic Support in Primary Care, Etten-Leur. HbA1c was analysed with high-performance liquid chromatography using a Menarini 8160 machine. Lipids were determined with standard enzymatic techniques using a Beckman LX-20 until November 2008 and thereafter a Roche Hitachi Modular P. An extra blood sample was taken at baseline and plasma was

kept frozen at -80°C. Participants gave an additional written informed consent for this procedure.

Standardized self-report questionnaires were used to collect information on prescribed medication. Height and weight were measured using a fixed rigid stadiometer and a Tanita scale respectively.

Metabolomics

Baseline blood samples with sufficient blood volume and without missing study data were defrosted (n = 346). From each sample 100 µl was extracted with methanol and after evaporation the metabolites were derivatized (oximation and silylation). The GC-MS method used for analysing a broad range of metabolites was identical to the method reported for microbial metabolic profiling, (van der Greef et al., 2007); (Wopereis et al., 2009) except for the sample type.

Performance of the metabolic profiling GC-MS platform.

The performance of the applied metabolic profiling platform was assessed through frequent analysis of the Quality Control (QC) sample (Bijlsma et al., 2006). QC samples, prepared from pooled study plasma samples, were analysed after every 10th study sample (in total 72 QC samples). This QC sample represents the full biochemical diversity of the study samples and allows the calculation of the analytical precision for all metabolites measured. The QC sample data is also used to adjust systematic errors (e.g. batch to batch response differences) by a single point calibration model. Typically, this procedure offers excellent precision for a large majority of metabolites (i.e. 77% of the metabolites have a relative standard deviation (RSD) of less than 10%). Metabolites with RSD > 50% (very high imprecision), were removed from the data. Furthermore, method performance was carefully monitored using multiple internal standards (5 to 10 depending on method, including analogues, ^{2}H and ^{13}C labelled metabolites) and duplicate analysis of

samples. Consequently the metabolite data used for statistical data analysis in this study met all of the quality requirements (e.q. RSD < 10%).

Pre-processing of metabolic profiling data

Data for each subject were corrected for the recovery of the internal standard for injection. Batch to batch differences in data were removed by synchronizing medians of QC-samples per batch. The GC-MS data set contained 174 metabolites of which 140 were annotated metabolites.

Statistical analysis

The primary outcome was the relative HbA1c change after five years. All values in our analyses were measured at baseline (including all analyses of metabolomics), with the exception of HbA1c after five years. Relative HbA1c change was defined as the absolute differences in HbA1c over time adjusted for baseline HbA1c ($(HbA_1c_{t5}\text{-}HbA_1c_{t0}/HbA_1c_{t0})$ x100%). So, relative HbA1c change is defined as the absolute differences in HbA1c over time adjusted for baseline HbA1c.

Baseline differences of patient characteristics and all measured metabolites between the medication groups were analysed with ANOVA. To check correlations between all 174 metabolites, Spearman correlations were calculated between all GC-parameters (= GC-MS metabolite) without stratifying for medication groups (n = 346). A mixed model was made per GC parameter with the relative change in HbA_{1c} as dependent factor in the model and the continuous GC parameter (measured at baseline) as an independent variable in the model. Medication group was included as an independent variable as well and included as a fixed factor. Finally, the interaction of GC parameter with medication group was included as an independent variable in the model. In this analysis, the no medication group was used as the reference group for the interaction between GC parameter and medication. The beta for the interaction of the GC parameter with that medication group is reported here

for each medication group. This beta represents the additional contribution of each metabolite in the specific medication group compared with the no medication group. The model was run with data from all subjects as well as with data from the subset of subjects with HbA_{1c} > 6.5% at start of the study (n = 219). This level was the threshold to start oral blood glucose lowering therapy and is nowadays used as threshold for the diagnosis of diabetes. In a secondary analysis, the results were adjusted for baseline BMI and baseline HbA1c, since these parameters were significantly different between the medication groups at baseline. Multiple testing correction was performed by submitting the data to Benjamini and Hochberg test (Benjamini & Cohen, 2017). Statistical analyses were done with SAS version 9.3.

RESULTS

Patients (n = 346) were divided into groups according to use of medication after five years of follow-up: no medication (n = 82), only metformin (n = 132), the combination metformin and sulphonylurea (n = 94), and only sulphonylurea (n = 38). The four groups were comparable at baseline with respect to age and blood pressure, but baseline HbA_{1c}, body weight, BMI, waist circumference, and cholesterol levels differed significantly between the groups **(Table 1)**.

Table 1 | Baseline characteristics of the different medication groups.

	No med (n = 82) Mean (SD)	**Metf** (n = 132) Mean (SD)	**SU** (n = 38) Mean (SD)	**Combi** (n = 94) Mean (SD)	**All** (n = 346) Mean (SD)
Age (yrs)	60.7 (5.1)	59.6 (5.2)	60.6 (6.0)	60.0 (5.2)	60.1 (5.3)
SBP (mmHg) **DBP** (mmHg)	169.7(20.7) 86.9 (7.3)	162.7 (20.2) 89.9 (9.9)	162.5 (27.6) 93.1 (11.1)	162.4 (26.3) 88.0 (11.9)	164.3 (23.1) 89.3 (10.7)
Cholesterol (mmol/l)*	5.6 (1.0)	5.6 (1.0)	5.8 (1.3)	5.7 (1.1)	5.6 (1.1)
LDL (mmol/l)	3.5 (0,9)	3.7 (0.9)	3.9 (1.2)	3.8 (0.9)	3.7 (1.0)
HbA_{1c} (%)*	6.3 (0.8)	7.3 (1.4)	7.0 (1.1)	8.2 (1.8)	7.3 (1.5)
BMI (kg/m^2)*	29.2 (4.3)	31.9 (4.7)	29.7 (4.3)	30.3 (4.4)	30.6 (4.6)
Weight (kg)*	85.9 (15.7)	93.8 (15.6)	86.1 (16.7)	88.2 (15.1)	89.5 (15.9)
Waist circumference* **Statin use** (n, (%)	104.2 (12.2) 7 (8.8)	110.0 (11.4) 17 (13.2)	104.6 (14.6) 5 (14.3)	106.6 (11.7) 14 (15.1)	 43 (13.1)

***groups differ significantly ($p < 0.05$)**

Abbreviations are No Med = no medication, Metf = metformin, SU = sulphonylurea, Combi = combination of metformin and sulphonylurea, SBP = systolic blood pressure, Cholesterol = total cholesterol, LDL = Low-density lipoprotein cholesterol, HbA1 = glycated haemoglobin, BMI = body mass index

In patients who were prescribed combination therapy HbA1c differed significantly from both other groups: 8.2% (66 mmol/mol) versus 7.3% (56 mmol/mol) (metformin) and 7.0% (53 mmol/mol) (sulphonylurea). Patients who were prescribed combination therapy differed significantly in weight from those on metformin alone (88.2 kg and 93.8 kg respectively). The baseline BMI of patients on metformin alone differed significantly from the BMI in the other groups. Of all metabolites, 22 (12.6%) of all measured metabolites were significantly different at baseline between medication groups. Of these metabolites, five showed a significant

interaction with medication group on relative HbA1c change (oxoproline, hydroxypiperidine, uric acid, glutamic acid internal amide (formed during derivatisation step, measure for glutamate), and pseudouridine).

Figure 1 shows a large variation in response to glucose lowering drug treatment after 5 years. The metformin and sulphonylurea combination group showed both the largest decrease and variation in 5 year change of HbA_{1c} with a mean of -16.3 mmol/mol and a range of -28.7 to -6.0 mmol/mol, while the control group (no medication) had the smallest decrease and variation in 5 year HbA_{1c} change with a mean of -3.2 mmol/mol and range -8.1 to 3.1 mmol/mol.

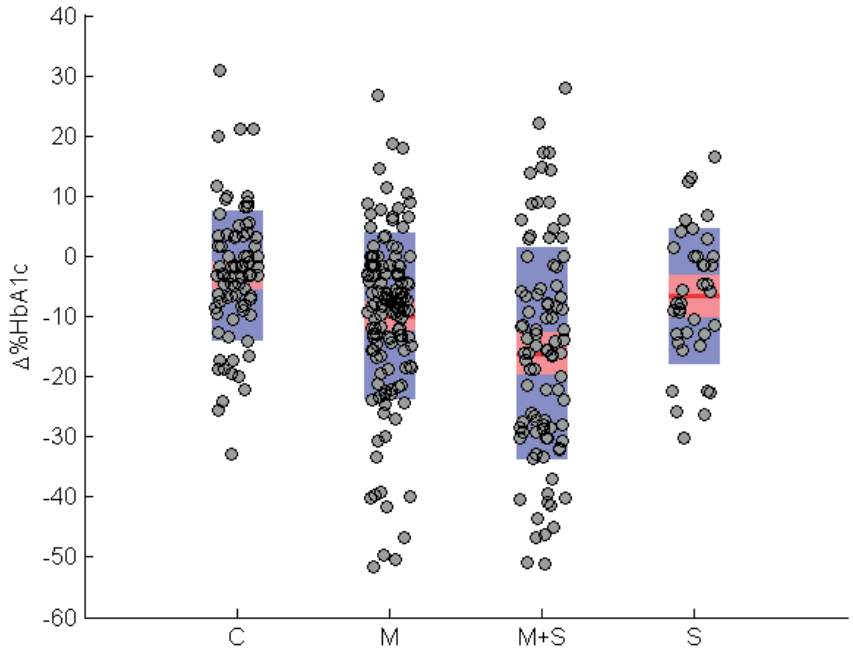

Figure 1 | Relative HbA_{1c} after 5 years for each medication group ($\Delta\%HbA_{1c}$ = ((t5-t0/t0)*100%)) (C = no medication, M = metformin, M+S = combination metformin and sulphonylurea, S = sulphonylurea, * = mean, * = 1 SD, * = 95% confidence interval and * = individual data), n = 264.

Spearman correlations between all 174 metabolites (30.102 in total) were generally low with only 5.8% of coefficients above 0.4, of which a majority ranked between 0.4 and 0.6.

Using spearman univariate analyses among all subjects, only 1.5 anhydro-glucitol (0.537) and glucose (-0.419) were significantly correlated with 5 year change in HbA_{1c}. Only these associations remained significant after adjusting for multiple testing (FDR corrected p-value < 0.05). No correlations were found between age, weight, BMI and waist circumference and relative HbA1c change in the entire study population (data not shown).
Table 2 shows the baseline metabolite values with an unadjusted significant interaction with medication group on relative HbA_{1c} change after five years in the three groups.

In the metformin group, high levels of 3-hydroxybutanoic acid and low levels of 2-hydroxypiperidine and 4-oxoproline were associated with the 5 year HbA_{1c} change. In the combined therapy group, similar associated metabolites were identified. All above mentioned correlations became stronger in the combination group. Other significant metabolites in the metformin group are glutamic acid internal amide, myo-inositol, pseudo uridine, LCB 18:1-17:0 SM, L-methionine, L-phenylalanine, 4-hydroxyglutamate hydroxyaldehyde and 2-hydroxybutanoic acid. Furthermore, lower concentrations of sphingomyelins (18:0-16:0, 18:1-18:0, 18:1-17:0), pseudo uridine, myo-inositol, glutamic acid internal amide and uric acid baseline were associated with a larger decrease in HbA_{1c} in the combination group.

Table 2 | Metabolites with a significant unadjusted interaction with medication group on relative HbA_{1c} change in the entire study population (n = 264)

	Metformin		**Sulphonylurea** (SU)		**Metformin and SU**	
	coefficient	p-value	coefficient	p-value	coefficient	p-value
1,5 anhydroglucitol (HMDB 02712, CAS 154-58-5)	14.2	0.001	10.8	0.043	29.8	< 0.0001
2-hydroxybutanoic acid (HMDB 00008, CAS 5094-24-6)	-60.7	0.011	14.6	0.716	-68.5	0.013
2-hydroxypiperidine (Pubchem 24847875, CAS 5382-16-1)	781.4	0.016	333.5	0.511	1164.2	0.002
3-hydroxybutanoic acid (HMDB 00357, CAS 300-85-6)	-18.2	0.029	-4.6	0.850	-54.3	0.015
4-oxoproline (KEGG C01877, CAS 4347-18-6)	517.9	0.002	409.5	0.096	682.0	0.001
Glucose (HMDB 00122, CAS 50-99-7)	-1.7	0.001	-1.3	0.043	-1.8	0.0003
glutamic acid internal amide [a] (HMDB 00267, CAS 98-79-3)	26.6	< 0.0001	9.8	0.296	15.6	0.026
myo-inositol (HMDB 00211, CAS 87-89-8)	51.3	0.050	6.7	0.818	106.0	0.038
pseudo uridine (HMDB 00767, CAS 1445-07-4)	109.3	0.012	35.1	0.519	140.1	0.007
LCB 18:1-17:0 SM	1079.0	0.044	409.7	0.586	1830.9	0.003
L-methionine (HMDB 00696, CAS 63-68-3)	191.1	0.018	101.8	0.363	25.1	0.768

L-phenylalanine (HMDB 00159, CAS 63-91-2)	24.3	0.034	17.0	0.317	2.5	0.843
4-hydroxyglutamate semialdehyde (HMDB 06556)	654.1	0.034	527.3	0.192	457.6	0.162
LCB18:0-16:0 SM (HMDB 10168)	30.2	0.334	33.3	0.500	93.5	0.010
LCB18:1-18:0 SM (HMDB 01348, CAS 58909-84-5)	-0.9	0.763	4.5	0.236	6.6	0.038
uric acid (HMDB 00289, CAS 69-93-2)	0.7	0.163	0.4	0.526	1.3	0.020

a: Formed during derivatisation step, measure for glutamate
This beta represents the additional contribution of each metabolite in the specific medication group compared with the no medication group.

In patients who were prescribed only sulphonylurea, no other metabolite was correlated with the decrease in HbA_{1c} after 5 years besides glucose and 1.5 anhydroglucitol.

Adjusting for baseline differences in BMI did not substantially alter our results in all groups (data not shown). However, after adjusting for baseline differences in HbA_{1c} and BMI in all groups, only 1,5 anhydroglucitol ($p < 0.033$), 2-hydroxybutanoic acid ($p < 0.003$), 2-hydroxypiperidine ($p < 0.012$), glucose ($p < 0.029$), sphingomyelin 18:1-17:0 ($p < 0.040$) and phenylalanine ($p < 0.048$) remained significant.

When restricting to 219 patients with an $HbA_{1c} > 6.5\%$ at start of the study **(table 3)**, we generally observed comparable results. Although the metabolites are different, the metabolites are involved in the same biological processes. Regardless of medication groups, 1.5 anhydro-glucitol and glucose, glutamic acid internal amide and 4-hydroxy hydroxyglutamate semialdehyde were associated with the 5 year

change in HbA_{1c}. In the metformin group, higher levels of 2-hydroxybutanoic acid, 3-hydroxybutanoic acid and 3-amino-2-piperidon and lower levels of 2-hydroxypiperidine and 4-oxoproline were associated with a larger decrease in HbA_{1c}. In the combined therapy group, similar metabolites were identified with mostly stronger associations. Furthermore, in the combined therapy group lower levels of two sphingomyelins (18:0-16:0 and 18:1-17:0) and myo-inositol were associated with a larger 5 year HbA1c decrease, as well as higher baseline levels of four fatty acids (C14:0, C17:0, C18:0, C20:1), mannose and xanthine. In the sulphonylurea group, high levels of fumaric acid were associated with a greater decrease in HbA_{1c} after 5 years.

Table 3 | Metabolites with a significant unadjusted interaction with medication group on relative HbA_{1c} change among patients with $HbA_{1c} > 6.5\%$.

	Metformin		**Sulphonylurea** (SU)		**Metformin and SU**	
	coefficient	p-value	coefficient	p-value	coefficient	p-value
Glucose (HMDB 00122, CAS 50-99-7)	-2.7	0.0003	-2.2	0.012	-2.8	0.0002
glutamic acid internal amide (HMDB 00267, CAS 98-79-3)	39.1	0.001	28.1	0.042	29.5	0.009
1,5anhydroglucitol (HMDB 02712, CAS 154-58-5)	23.7	0.003	21.2	0.018	42.4	< 0.0001
4- hydroxyglutamate semialdehyde (HMDB 06556)	1327.7	0.007	1219.7	0.030	1180.1	0.018
2- hydroxybutanoic acid (HMDB 00008, CAS 5094-24-6)	-85.8	0.009	-6,5	0.898	-110.6	0.002
3-amino 2 piperinidon (HMDB 00323, CAS 1892-22-4)	-23.2	0.013	-250.8	0.792	-1535.5	0.023
3 hydroxybutanoic acid (HMDB 00357, CAS 300-85-6)	-23.2	0.013	-39.4	0.297	-58.3	0.012
4-oxoproline (KEGG C01877, CAS 4347-18-6)	464.6	0.029	224.7	0.477	576.8	0.022
2-hydroxypiperidine (Pubchem 24847875, CAS 5382-16-1)	1126.4	0.045	696.3	0.319	1283.3	0.033
xanthine (HMDB 00292, CAS 69-89-6)	2086.6	0.501	-4215.6	0.261	-8405.6	0.004
C20:1 fatty acid (HMDB 02231, CAS 26764-41-0)	-1590.6	0.103	-1724.4	0.176	-2701.4	0.009
C14:0 fatty acid (HMDB 00806, CAS 544-63-8)	-267.3	0.243	-219.4	0.534	-527.4	0.026

C18:0 fatty acid (HMDB 00827, CAS 57-11-4)	-804	0.231	-27.1	0.771	-145.8	0.030
C17:0 fatty acid (HMDB 02259, CAS 506-12-7)	-1273.0	0.476	368.5	0.880	-3742.5	0.039
Mannose (HMDB 00169, CAS 3458-28-4)	-58.5	0.425	-13.2	0.898	-152.6	0.042
LCB 18:1-17:0 SM	1348.7	0.090	675.3	0.493	1702.6	0.043
myo-inositol (HMDB 00211, CAS 87-89-8)	53.1	0.083	-12.2	0.735	67.2	0.044
LCB 18:0-16:0 SM (HMDB 10168)	61.8	0.217	67.8	0.351	105.4	0.046
fumaric acid (HMDB 00134, CAS 110-17-8)	-979.8	0.266	-2234.0	0.044	-926.0	0.329

DISCUSSION

This study shows a large variation in response to glucose lowering drug treatments in screen detected type 2 diabetes patients. In the different treatment groups, different metabolites could be identified that were associated with the response to metformin and/or sulphonylureas. This indicates that metabolomics can be used as a tool to identify potential biomarkers for response to diabetes treatment.

Regardless of medication, high plasma levels of glucose and low plasma 1,5-anhydroglucitol at the time of screen-detection were associated with the HbA_{1c} decrease after 5 years. Only these markers remained significant after adjustment for multiple testing. The metabolite 1,5 anhydro-glucitol is a well-known short term biomarker of hyperglycaemia (48 hours-2 weeks). As a result of glucose's competitive inhibition of 1,5-anhydroglucitol reabsorption in the kidney tubule, these concentrations are low during hyperglycaemia (Lyons & Basu, 2012); (Pal et al., 2010); (McGill et al., 2004). As expected, our results show that subjects with a larger dysregulation in glucose metabolism were more prone to respond to glucose lowering treatment regardless of medication and BMI. In line with previous studies we found that the predictive values of other characteristics such as age, BMI and lipid levels at baseline are small in predicting the change in HbA_{1c} after follow-up (Prentki & Madiraju, 2012); (Goudswaard et al., 2004); (Janghorbani & Amini, 2012).

In patients on metformin, high levels of liver metabolites 2-hydroxybutanoic acid and 3-hydroxybutanoic acid at diagnosis were correlated with a larger decrease in HbA_{1c} after 5 years. Hydroxybutanoic acid is produced mainly in the liver, during detoxification or oxidative stress (Brosnan & Brosnan, 2009); (Wu et al., 2004). 3-Hydroxybutanoic acid is a ketone body that decreases after stimulation of the glucose metabolism (Shaham et al., 2008). Metformin usage increases serum 3-

hydroxybutanoic acid levels in type 2 diabetes (Huo et al., 2009). Likewise 2-hydroxybutanoic acid is an early biomarker of insulin resistance in non-diabetic subjects and increased in diabetes type 2 patients (Gall et al., 2010); (Li et al., 2009). One could hypothesize that subjects with high levels of these liver metabolites might have insulin resistance in the liver (Defronzo, 2009). Also 4-oxoproline was identified as a metabolite to predict response to metformin. Oxoproline is an intermediate in arginine and proline metabolism, which can be used for glutamate production and forms a link between the tricarboxylic acid and urea cycle (Bertolo & Burrin, 2008). Both 2-hydroxybutanoic acid and oxoproline indicate an increased liver metabolism, in line with the mode of action of metformin that specifically acts on the liver by blocking hepatic gluconeogenesis (Gallagher & LeRoith, 2011). One could postulate that type 2 diabetes patients with glucose dysregulation and increased liver metabolism will respond well to metformin treatment. This is in line with the results in the metformin and sulphonylurea combination group, where high plasma levels of liver metabolites 2-hydroxybutanoic acid, 3-hydroxybutanoic acid, and low levels of 2-hydroxypiperidine, 4-oxoproline were also correlated with a larger decrease in HbA_{1c} after 5 years.

In the metformin/sulphonylurea combination group, we could also identify mannose, xanthine and uric acid as metabolites associated with HbA_{1c} change. Oxidative stress is increased in type 2 diabetes compared to healthy subjects and corresponding metabolites like mannose and uric acid are increased with oxidative stress (Gall et al., 2010); (Suhre et al., 2010). Xanthine oxidase is also increased in oxidative stress and is an enzyme involved in uric acid synthesis (Dikalov, 2011). Low myo-inositol concentrations were also associated with a higher decrease in HbA_{1c} after 5 years. Indeed, myo-inositol concentrations are lower in insulin resistant subjects (Gall et al., 2010). Myo-inositol is involved in the activation of protein kinase C (PKC), which plays an important role in glucose metabolism (Lamb & Goldstein, 2008; Nishizuka, 1995).

In addition, four fatty acids were found to be higher at baseline in subjects that had the largest decrease in HbA_{1c}, receiving both metformin and sulphonylurea. Free fatty acids originate from adipose tissue (Prentki & Madiraju, 2012); (Capurso & Capurso, 2012) and may cause insulin resistance (Capurso & Capurso, 2012). It is known that insulin resistance and increased oxidative stress can be caused by multiple organs dysregulation.
Increased C18:0 is found in serum of type 2 diabetics (Kellow et al., 2011). Impaired glucose tolerant subjects have increased C14:0, C17:0 and C18:0 fatty acids levels (Gall et al., 2010) and C14:0, C17:0, C18:0 and C20:1 levels are increased in diabetics compared to insulin sensitive subjects (Suhre et al., 2010). Altogether, we have identified several metabolites involved in insulin resistance in adipose tissue. This could indicate that when subjects have adipose tissue insulin resistance in addition to liver insulin resistance, they should be placed on combination therapy.
Altogether, one could postulate that subjects with glucose dysregulation in multiple organs (liver and adipose tissue) would better respond to a combined metformin/ sulphonylurea treatment.

In the sulphonylurea group only high levels of fumaric acid were correlated to decrease in HbA_{1c} after 5 years, but only in subjects with HbA_{1c} over 6.5% at baseline. Fumarate is involved in the tricarboxylic acid cycle, necessary for the insulin secretion by the ß-cells of the pancreas (Bain et al., 2009). Sulphonylureas stimulate insulin release in a glucose-independent manner by acting on the ß-cells of the pancreas. One could postulate that subjects with glucose dysregulation and altered pancreatic metabolism would better respond when prescribed sulphonylurea treatment.

Specifically in subjects with an HbA_{1c} above 6.5% at baseline, low glutamic internal amide (as a marker of glutamate) and 4-hydroxy glutamate semialdehyde were associated with the decrease in HbA_{1c} after 5 years in all medication groups. Elevated

blood levels of the former may be associated with problems of glutamine or glutathione metabolism (Brosnan & Brosnan, 2009); (Brosnan, 2000). 4-Hydroxyglutamate semialdehyde is an intermediate in arginine and proline metabolism, which can be used for glutamate production (Brosnan, 2000). Glutamate plays a central role in hepatic amino acid metabolism, maintaining normal amino acids concentrations and energy usage (Brosnan & Brosnan, 2009); (Defronzo, 2009). Plasma glutamate levels are elevated in several diseases characterized by chronic oxidative stress and inflammation, like obesity and type 2 diabetes (Davalli et al., 2012). Since low levels of both these glutamate related metabolites were associated with HbA_{1c} decrease, one could hypothesize that our data indicate that drug treatment could still be effective since our subjects were newly diagnosed and therefore the glutamate-induced cytotoxicity (Davalli et al., 2012) had not yet taken place.

Strengths of this study include the quite large patient group of screen detected diabetes patients before use of any antidiabetic drug and the long follow-up time with a median of approximately 6 years. However, certain limitations need to be addressed. The number of patients per group differs from 38 to 132 which makes some analyses less robust. This difference was due to the ADDITION-treatment algorithm that suggested to start with metformin, to add a sulphonylurea if necessary and to treat a patient with sulphonylurea monotherapy in case of contra-indications for or side effects of metformin (Griffin et al., 2011). Although the metabolites identified in this study are all well-known metabolites associated with oxidative stress, insulin resistance or type 2 diabetes, our results should be seen as hypothesis generating and require further investigation. Because of multiple testing, our results are prone to false positive findings. Indeed, when we adjusted our p-values for multiple testing, only metabolites of dysregulation remained significant. This is probably due to the relatively small sample size of this study. This also makes it difficult to predict which of the other markers are least likely to be false positives.

Although we identified metabolites that are biologically plausible to predict response to the different hypoglycaemic treatments, these results need to be replicated in independent populations.
We observed that total cholesterol levels, but not LDL cholesterol levels, were different between the medication groups. Therefore we checked statin use between our defined medication groups. Importantly, it was not different, since the use of statins increases the risk of elevation of blood glucose (Chapman et al., 2011). The use of blood pressure lowering drugs could have been different between the three glucose lowering medication groups and influence the outcome.

Furthermore, we were certain of the use of medication in the population, but the dosage and duration of the sulphonylurea and metformin use during the follow up period of six years are uncertain. Of all participants to the ADDITION-study 96% was of Caucasian race. So race is of minimal influence on the results presented in our study. Finally, when the results were adjusted for baseline HbA_{1c} several metabolites lost significance. This indicates that certain metabolites were driven by baseline HbA_{1c} levels. However, our results show that not only baseline HbA1c determines 5 years HbA1c change. Moreover, perhaps the metabolites that were independent from baseline HbA1c could be regarded as the most promising ones for further investigation.

In conclusion, we aimed to identify metabolites to predict response to metformin and/or sulphonylurea treatment during five years after detection of type 2 diabetes. Apart from markers of glucose dysregulation, we identified metabolites associated with 5 year HbA_{1c} change that were in line with the mode of action of metformin, sulphonylureas or the combination therapy. If these results could be replicated in other populations, the most promising predictive candidates might be tested to assess whether they could enhance personalized treatment.

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CHAPTER 3

EFFECT OF SIX YEARS INTENSIFIED MULTIFACTORIAL TREATMENT ON LEVELS OF HS-CRP AND ADIPONECTIN IN PATIENTS WITH SCREEN DETECTED TYPE 2 DIABETES: THE ADDITION-NETHERLANDS RANDOMIZED TRIAL.

H. den Ouden, J. Berends, R.K. Stellato, J.W. Beulens, G.E.H.M. Rutten

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ABSTRACT

Background

Levels of hs-CRP and adiponectin, reflecting chronic inflammation, are associated with cardiovascular disease in type 2 diabetes. The long term effects of multifactorial therapy in type 2 diabetes patients on hs-CRP and adiponectin are unknown.

Methods

The ADDITION-NL study is a RCT among screen-detected type 2 diabetes patients, randomised to intensive treatment (IT; HbA_{1c} < 7.0% (53 mmol/mol), blood pressure ≤ 135/85 mmHg, total cholesterol ≤ 3.5 mmol/l) or routine care (RC). Hs-CRP and adiponectin were measured before and one, two and six years after inclusion. We analysed the effectiveness of the intervention on hs-CRP and adiponectin levels using a mixed effects model, taking into account practice, baseline levels and different medications.

Results

424 patients were included (IT n = 235; RC n = 189). Both groups were well matched. BMI, systolic blood pressure, total cholesterol and HbA_{1c} improved significantly more in the IT group compared to RC. Levels of hs-CRP decreased significantly in both treatment groups over time. Mean hs-CRP in the routine care group was 24% higher (p = 0.0027) than in the intensive treatment group during follow-up. After an initial increase the adiponectin values levelled off to nearly baseline values in both groups. The difference between the two groups after six years was 0.44 μg/ml (p = 0.27).

Conclusions

Intensified multifactorial treatment in type 2 diabetes results in an enhanced decrease in hs-CRP. Whether this is clinically meaningful remains uncertain. The role of adiponectin seems to be more complex.

INTRODUCTION

Inflammation is a major risk factor of cardiovascular disease (Ross, 1999). Diabetes is associated with inflammation that promotes the development of cardiovascular disease (CVD) (Danesh et al., 2004). Little is known about the effects of intensive glucose control on inflammation and data are inconsistent (Schulze et al., 2004). Adiponectin and hs-CRP have been evaluated in cohort studies and are accepted cardiovascular biomarkers in this respect (Buckley et al., 2009). Hs-CRP has consistently been associated with cardiovascular disease (Danesh et al., 2004); (Schulze et al., 2004). A meta-analysis suggested that hs-CRP improves risk prediction for cardiovascular disease beyond traditional risk factor (Buckley et al., 2009). Effects of intensive glucose control on hs-CRP vary according to the strategy and agent(s) used for glucose control (Danesh et al., 2004); (Schulze et al., 2004); (Belalcazar et al., 2010); (De Jager et al., 2005); (Pradhan et al., 2009); (Prasad, 2006).

Adiponectin, a protein secreted by adipocytes is a key regulator of insulin sensitivity and tissue inflammation (Kadowaki et al., 2006); (Whitehead et al., 2006); (Hajer et al., 2008). Levels of adiponectin differ between gender (Nishizawa et al., 2002). Meta-analyses and systematic reviews did not show a protective effect of adiponectin against CHD and all cause/CVD mortality (Hotta et al., 2000); (Nakashima et al., 2006). Effects of treatment on adiponectin concentrations are inconsistent. Body weight reduction, improved glycaemic control, improved lipid profile and blood pressure lowering drugs as RAAS/blocking agents increase levels of adiponectin (Yang et al., 2001). Statins, however, have differential metabolic effects (Koh et al., 2011); (Sandbaek et al., 2008).

Effects of treatment on hs-CRP and adiponectin, are mainly based on observational studies, and investigated separately for different treatments. Meanwhile, type 2 diabetes patients are treated multifactorially. The effect of intensive multifactorial

treatment on inflammation in type 2 diabetes patients has not been investigated to date.

We aimed to determine the effectiveness of an intensified treat-to-target treatment in screen-detected type 2 diabetes patients on levels of hs-CRP and adiponectin, compared to routine care. We hypothesize that the levels of hs-CRP will decrease and the levels of adiponectin will increase over time to a greater extent in the intensive treatment group.

METHODS

Design

This randomised, single-blind trial is part of the international ADDITION study that consists of a screening study and a subsequent intervention study. The intervention study evaluated the effect of intensified multifactorial treatment on cardiovascular morbidity and mortality in about 3000 screen-detected type 2 diabetes patients aged 40 to 69 years. Details of the study have been reported previously (Lauritzen et al., 2000); (Sandbaek et al., 2008); (Griffin et al., 2011). For the study website see: http://www.addition.au.dk/. In the ADDITION-Netherlands study 56,978 people aged 50 to 69 years from 79 primary care practices were invited to participate. Individuals at risk were assessed in general practice and those diagnosed as having type 2 diabetes according to WHO criteria including the requirement for confirmatory testing on a separate occasion, were included in the study. Exclusion criteria were assessed by family physicians. They were illness with a life expectancy of less than 12 months or psychological or psychiatric disorders that might invalidate informed consent, or being housebound or pregnant, or lactation (Griffin et al., 2011). Between 2002 and 2004 we detected 586 new type 2 diabetes patients (Janssen et al., 2007). The study was approved by the medical-ethical committee of the University Medical Centre Utrecht. Participants gave written informed consent before study entry.

Randomisation and interventions

In total 498 screen-detected type 2 diabetes patients were included in a single-blind trial with practice-level randomisation to intensified multifactorial treatment (n = 255) or routine care (n = 243). Allocation was concealed from patients throughout the trial. In total 54 were excluded from the longitudinal analyses because they lacked follow-up data. Patients in the intensive treatment group were treated to the following targets: HbA_{1c} < 7.0% (53 mmol/mol), blood pressure ≤ 135/85 mmHg and total cholesterol levels ≤ 3.5 mmol/liter. Alternatives or additions to glucose-lowering therapy were to be initiated when HbA_{1c} > 6.5% (48 mmol/mol). If HbA_{1c} remained above 7.0% with oral agents, insulin therapy should be initiated. An angiotensin-converting enzyme (ACE) inhibitor (or, in case of side-effects, an angiotensin-II receptor antagonist) were to be prescribed if blood pressure was >120/80 mmHg. If blood pressure was >135/85 mmHg, the dose had to be increased, and calcium channel blockers, thiazides, or beta-blockers were added in a stepwise approach. Treatment with a statin was indicated if cholesterol was > 5.0 mmol/liter and > 4.5 mmol/liter in patients with a known history of cardiovascular disease. The dose of statin was increased up to maximum if cholesterol remained above threshold. Acetylsalicylic acid (80 mg per day) was given to patients treated with antihypertensive agents. In 2003 the protocol changed after publication of the Heart Protection Study (Griffin et al., 2011): all participants with cholesterol > 3.5 mmol/liter were treated with lipid lowering drugs.

Patients in the routine care group were treated following the guidelines from the Dutch College of General Practitioners. In the 1999 guidelines HbA_{1c} levels between 7.0% (53 mmol/mol) and 8.5% (69 mmol/mol) were described as acceptable. Lipid-lowering drugs were recommended for people without a known history of cardiovascular disease and a ten-year cardiovascular risk above 25% and in all people with previous cardiovascular disease. The blood pressure treatment target was <150/85 mmHg (25). In 2006 the guideline was revised and the treatment targets

became stricter: $HbA_{1c} \leq 7.0\%$ (53 mmol/mol), systolic blood pressure < 140 mmHg and total cholesterol < 4.5 mmol/liter with a statin prescribed to almost all patients.

Outcomes and measurements

Participants were invited for health assessments at inclusion between 2002-2004 and for the final measurement in 2009. Between the first and final measurement all patients had three-monthly and annual check-ups in the primary care practices. Laboratory results from the first two annual diabetes check-up visits were extracted from the regional laboratory where all patients' samples were analysed, independent of the treatment arm. Extra blood samples were taken during this yearly diabetes control and plasma was kept frozen at -80°C. Blood samples taken between 6 and 18 months after the start of the study were identified as T_{12} measurement, and blood samples taken between 18 and 30 months after inclusion were designated as T_{24} measurement. Centrally trained staff assessed patients' health at baseline and after 5 years by collection of data on biochemical and anthropometric features and use of questionnaires to assess activities, including use of medication, according to standard operating procedures and unaware of study group allocation.

Initial and final health assessments were undertaken by centrally trained staff following standard operating procedures and unaware of study group allocation. Standardized self-report questionnaires were used to collect information on lifestyle habits and prescribed medication. Blood pressure was calculated as the mean of three measurements using an Omron device. Height and weight were measured using a fixed rigid stadiometer and a Tanita scale respectively. Additional anthropometric data from the routine care group were derived from patients' files at the practices by research assistants only after one year and in the intervention group from Case Report Forms that had been completed by primary care physicians or diabetes nurses during the first two annual diabetes control visits. HbA_{1c} levels were measured with high-performance liquid chromatography using a Menarini 8160 machine. Lipids

were determined with standard enzymatic techniques using a Beckman LX-20 until November 2008 and thereafter a Roche Hitachi Modular P. All biochemical tests were performed in the SHL Centre for Diagnostic Support in Primary Care, Etten-Leur, the Netherlands. Hs-CRP and adiponectin concentrations were determined in stored plasma at the University Medical Centre Utrecht: in 2006 for the baseline and first two annual measurements, and in 2010 for the final measurement. Serum hs-CRP was determined by chemiluminescent enzyme immunoassay on the Konelab analyser in 2006 and on the Immulite 1000 analyser in 2010. The lower limit of quantitation was 0.3 mg/liter. Interassay variation of the Konelab analyser was 1.12-4.5% at 0.97-4.85 mg/liter (n = 24), and of the Immulite 1000 analyser was 3.5-3.9% at 1.2-65 mg/liter (n = 9). Hs-CRP values generated from these two different assay methods are highly correlated(Kimberly et al., 2003). Levels of adiponectin were determined in a sandwich ELISA (Quantikine, R&D Systems) in 2006 as well as 2010. The lower limit of detection was 0.25 ng/ml for undiluted samples. Plasma samples were diluted 100-fold. In 2006 interassay variation was 2.5-4.7% at 2.0-14.3 µg/ml (n = 20). In 2010 interassay variation was 3.9-2.6% at 3.0-12.0 µg/ml (n = 18). Hs-CRP and adiponectin were not pre-specified outcome-measures of the ADDITION-study.

Statistical analysis

We assessed the effect of an intensified multifactorial treatment versus routine care on the levels of hs-CRP and adiponectin with a mixed effects model, modelling the outcome over time from one year, two years and final measurement. Since the models adjusted for baseline value of the markers, this model covers the entire study period from baseline to final measurement. To this model we added a random intercept for primary care practice and for patient to take into account correlation of patients within practices and measurements within patients. Fixed effects were time and treatment, and the interaction between time and treatment effect was tested to examine whether the trend over time after the first year differed between the

treatment groups. The models were adjusted for baseline hs-CRP or adiponectin levels and the adiponectin model was further adjusted for gender. Hs-CRP values were log-transformed to correct for a right-skewed distribution. Similar models were also estimated for BMI, systolic blood pressure, total cholesterol and HbA1c. For all outcomes, the effect of intervention was estimated as the difference between treatment groups when the time*treatment effect was not statistically significant. In the presence of significant interaction, the effect of intervention was estimated by a contrast between treatment groups at the final measurement. These mixed models account for missing data in a longitudinal study.

To examine whether the hs-CRP and adiponectin results could be explained by changes in BMI, lipids, or statin use, an additional model for each outcome was estimated including BMI, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and statin use as potential intermediaries.

Differences in prescribed medication use between the two groups were examined using a mixed effects logistic regression model with medication use at final follow-up as the outcome, treatment and medication use at baseline (where possible) as the fixed effects, and a random effect for primary care practice to account for correlation of patients within practices. Effect of intervention was expressed as the odds ratio for medication use for the intensive treatment group as compared to the routine care group.
A p-value < 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

RESULTS

In total 498 patients were included. The trial profile is shown in **Figure 1**. The two groups were well matched with respect to all relevant baseline characteristics (**Table 1**).

Figure 1 | Flowchart

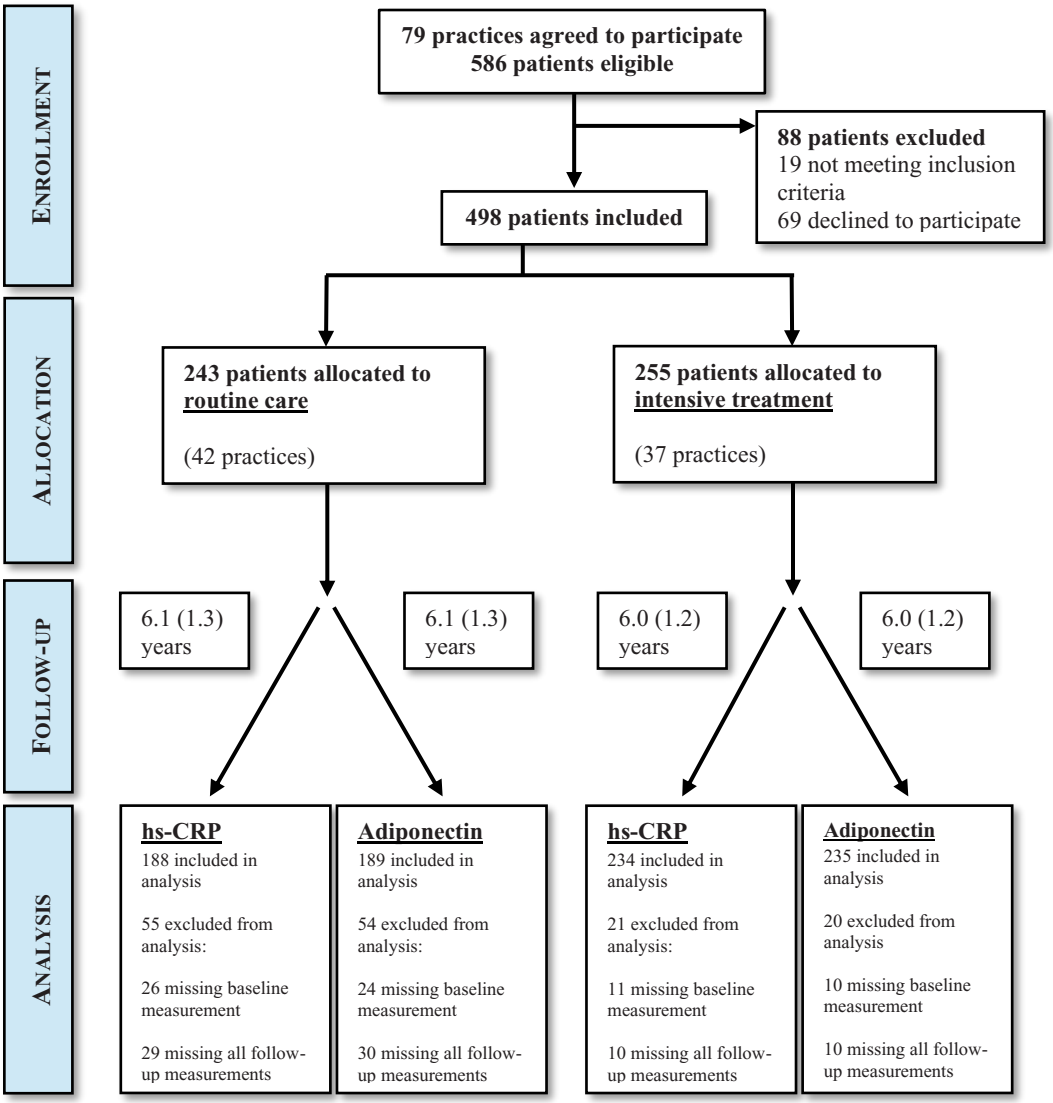

Table 1 | Baseline characteristics and results of the follow-up measurements

	Routine care (n = 189)		**Intensive treatment** (n = 235)	
	Baseline	Final	Baseline	Final
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Demographic variables				
Male gender (%)	57.7		53.2	
Age at diagnosis (years)	60.3 (5.2)		60.4 (5.4)	
Behavioural variables				
Current smoking (%)	22.1	17.7	26.1	21.1
Clinical variables				
History of myocardial infarction (%)	6.4		3.8	
History of stroke (%)	1.2		1.4	
Anthropometric variables				
BMI (kg/m²)	30.3 (4.4)	30.3 (5.2)	31.4 (5.6)	30.9 (5.2)
Waist circumference (cm)	106.8 (11.8)		108.0 (12.6)	
Systolic blood pressure (mm Hg)	161 (23)	146 (19)	167 (23)	139 (16)
Biochemical variables				
Total cholesterol (mmol/liter)	5.6 (1.1)	4.5 (1.0)	5.6 (1.1)	4.0 (0.8)
HbA1c (%)	7.3 (1.5)	6.4 (0.6)	7.4 (1.6)	6.4 (0.7)
Log hs-CRP (mg/liter)	1.4 (1.0)	0.4 (1.1)	1.4 (1.0)	0.2 (1.1)
Hs-CRP (mg/liter)[1]	4.1 (1.8; 8.9)	1.2 (0.7; 3.4)	4.5 (2.4; 8.6)	1.1 (0.6; 2.6)
Adiponectin (µg/ml)	6.6 (3.7)	7.1 (4.4)	5.8 (3.2)	6.2 (4.4)

Changes in prescribed medication in the two groups during follow-up are shown in **Table 2.**

Table 2 | Self-reported medication use at baseline and follow-up and the effect of intensive treatment compared to routine care based on the mixed model analyses.

Medication (%)	**Routine care** (n = 189)		**Intensive treatment** (n = 235)		**Effect of intervention**	
	Baseline (*n* = 178)	**Final** (*n* = 176)	**Baseline** (*n* = 217)	**Final** (*n* = 229)	**Odds Ratio**	**95% CI**
Any glucose lowering drugs	0	72.7	0	82.1	**1.81**	1.01 to 3.24
Metformin	0	60.8	0	70.3	1.55	0.99 to 2.42
Sulphonylurea	0	35.2	0	39.3	1.22	0.75 to 1.97
Thiazolidinedione	0	8.0	0	8.7	1.18	0.32 to 4.34
Insulin	0	2.3	0	5.2	2.34	0.68 to 8.12
Other	0	1.1	0	0.87	0.77	0.07 to 8.32
Any hypertensive drugs	30.3	72.7	29.0	88.2	**3.17**	1.64 to 6.14
ACE inhibitor or ARB	13.5	56.3	9.2	77.7	**2.93**	1.72 to 5.01
β-blocker	15.7	33.5	15.2	46.3	**1.98**	1.21 to 3.21
Calcium-channel blocker	4.5	17.1	4.6	19.2	1.17	0.66 to 2.06
Diuretic	11.8	42.6	11.1	58.5	**1.79**	1.17 to 2.75
Other	1.7	1.7	1.8	3.5	1.86	0.10 to 35.9
Any lipid lowering drugs	11.2	73.9	13.4	87.3	**2.68**	1.32 to 5.43
Statins	11.2	72.2	12.0	86.0	**2.44**	1.31 to 4.53
Simvastatin	NA	39.8	NA	45.0		
Pravastatin	NA	9.7	NA	13.5		
Fluvastatin	NA	0.6	NA	2.2		
Atorvastatin	NA	13.1	NA	18.3		
Rosuvastatin	NA	9.1	NA	7.0		
Acetylsalicylic acid	6.2	20.5	4.6	69.4	**15.0**	7.17 to 31.3

NA = not applicable **Bold** = significant

Significantly more patients in the intensive treatment group were prescribed glucose-lowering drugs, ACE- inhibitors or ARBs and β-blockers, lipid lowering drugs and acetylsalicylic acid at follow-up than in the routine care group.

Figure 2 shows the course of the mean values of the different variables over time. BMI decreased in the first year and increased in the years following. The levels of BMI, systolic blood pressure, total cholesterol and HbA_{1c} improved significantly more in the intensive treatment group compared to the routine care group during the first year. After the steep decrease of systolic blood pressure in the first year of the intervention, the levels in both groups gradually increased. Total cholesterol levels steadily decreased in both groups between the first and the final measurements.

Levels of hs-CRP decreased significantly in both treatment groups over time. In the first year hs-CRP levels decreased remarkably in the intensive treatment group, whereas in the routine care group the decrease was more gradual. In the mixed effects model **(Table 3)** the difference between routine care and intensive treatment was 0.22 mg/liter on the natural log scale; after translation back to the original scale this means that at any point during follow-up, the mean hs-CRP in the routine care group is 24% higher than in the intensive treatment group ($p = 0.0027$).

Figure 2 | Course of mean values over time by treatment group

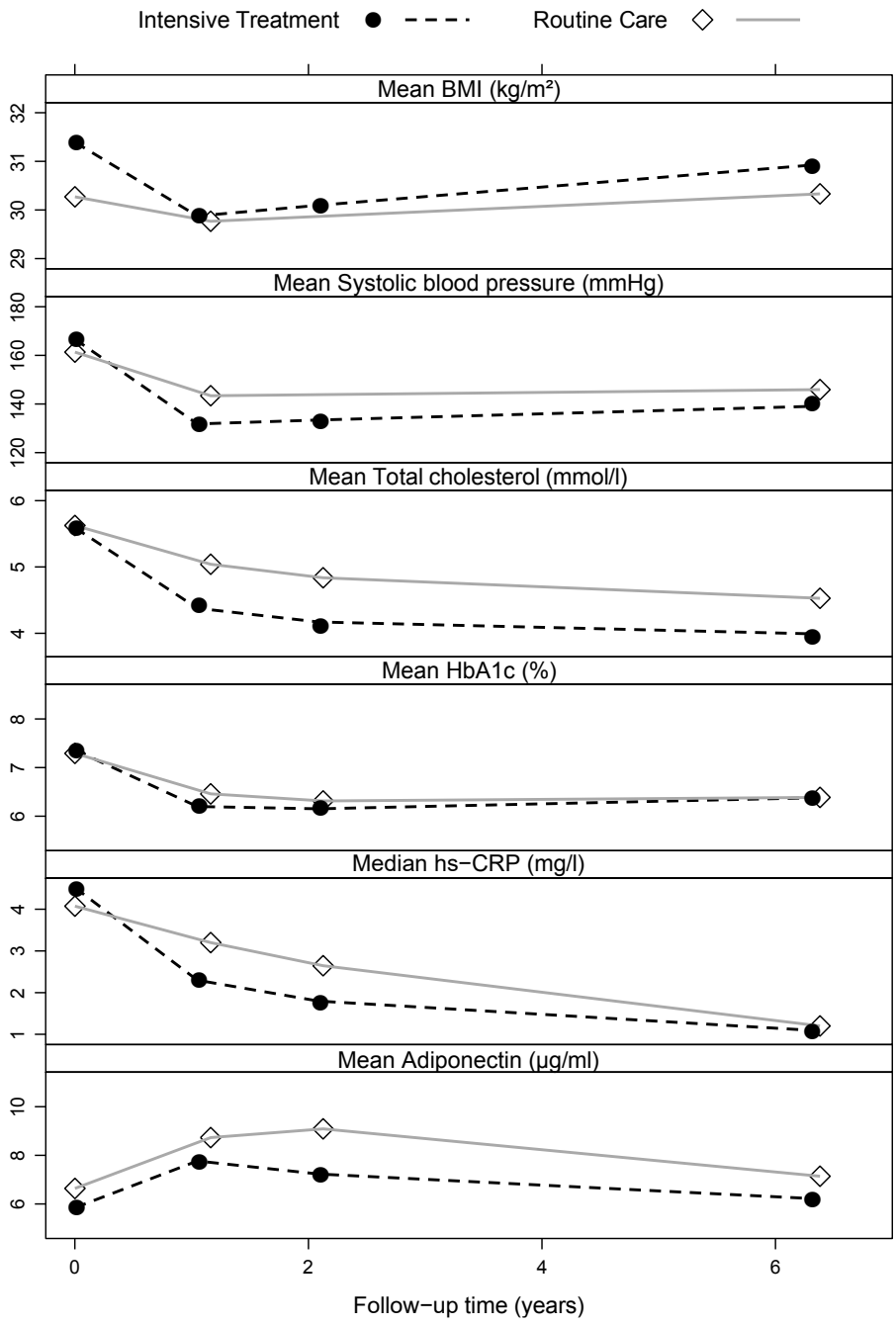

Table 3 | Results mixed model analysis of anthropometric and biochemical variables over time for intensive treatment compared to routine care

Variable	**BMI** (kg/m^2)	**Systolic blood pressure** (mm Hg)	**Total cholesterol** (mmol/liter)	**HbA1c** (%)	**Log hs-CRP** (mg/liter)		**Adiponectin** (µg/ml)	
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate *(95% CI)	Estimate (95% CI)	Estimate *(95% CI)
Intercept	5.65	101.26	3.68	5.22	0.29	0.24	3.56	3.53
Time	0.06 (-0.03 to 0.14)	0.53 (0.0007 to 1.06)	-0.08 (-0.09 to 0.06)	0.01 (-0.03 to 0.01)	-0.11 (-0.13 to -0.09)	-0.11 (-0.13 to -0.09)	-0.28 (-0.37 to -0.20)	-0.28 (-0.37 to -0.20)
Intensive treatment	-1.30 (-1.93 to -0.68)	-13.77 (-17.29 to -10.26)	-0.62 (-0.76 to -0.48)	-0.38 (-0.52 to -0.25)	-0.22 (-0.36 to -0.08)	-0.20 (-0.34 to -0.05)	-0.44 (-1.22 to 0.34)	-0.42 (-1.21 to 0.37)
Routine care	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Intensive treatment x Time	0.17 (0.07 to 0.28)	0.84 (0.14 to 1.53)	NS	0.05 (0.03 to 0.07)	NS	NS	NS	NS
Routine care x Time	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Effect of inter-vention	**-0.26** ‡ (-0.79 to -0.27)	**-8.76** ‡ (-11.77 to -5.75)	**-0.62** † (-0.76 to -0.48)	**-0.09** ‡ (-0.21 to -0.04)	**-0.22** † (-0.36 to -0.08)	**-0.20** † (-0.34 to -0.05)	-0.44 † (-1.22 to 0.34)	-0.42 † (-1.21 to 0.37)

NS = not significant and was therefore not included in the model
Bold = significant between the groups
* Corrected for statin use
† Difference between treatment groups during follow-up (no interaction between treatment group and time)
‡ Difference between treatment groups at six years follow-up (interaction between treatment group and time)

Mean changes in adiponectin levels were similar for both treatment groups. However, after an initial increase the values levelled off to nearly baseline values. The difference between the two groups after six years was 0.44 µg/ml (p = 0.27). Women had significantly higher adiponectin levels with a mean difference of 0.93

µg/ml (p = 0.0064). The additional adiponectin and hs-CRP analyses, controlling for BMI, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides, had little effect on the findings presented in **Table 3**. For adiponectin, the effect of intervention remained non-significant, although the difference between the intensive treatment group and the routine care group became positive (0.16 µg/ml, 95% CI: -0.66 to 0.98); the reduction of adiponectin over time was nearly identical (-0.30 µg/ml per year, 95% CI: -0.40 to -0.19). For hs-CRP, the effect of intervention was nearly identical (-0.21 ln(mg/liter), 95% CI: -0.36 to -0.06), and the effect of time remained statistically significant, though slightly reduced in magnitude (-0.08 ln(mg/liter) per year, 95% CI: -0.10 to -0.05). **Table 2** also shows the estimates of the biomarkers when corrected for statin use, which had little effect on the results. Also controlling for use of acetylsalicylic acid did not substantially change the effect of intervention on hs-CRP.

There was no difference in baseline adiponectin between included and excluded patients in the intensive care group, but patients lost to follow-up in the routine care group had significantly higher (1.50 µg/ml, 95% CI: 0.16 to 2.82) baseline adiponectin levels than those included in the analyses. This implies that the effect of intervention may have been underestimated by the longitudinal model. The opposite pattern was seen for baseline hs-CRP levels: there was no difference between included and excluded patients in the routine care group, but patients lost to follow-up in the intensive care group had significantly higher (0.88 ln(mg/liter), 95% CI: 0.25 to 1.55) baseline hs-CRP levels than those included in the analyses. This implies that the effect of intervention may have been overestimated by the longitudinal model.

Discussion

We could demonstrate a continuing and significant improvement of hs-CRP in screen-detected type 2 diabetes patients during six years of multifactorial treatment.

Changes in the intensive treatment group were significantly greater than those in the routine care group. The increase in adiponectin did not differ between the treatment groups. Both hs-CRP levels and adiponectin levels decreased in the period after the first year until the final measurement. This finding is in contrast with the inverse relationship between both biomarkers known from other studies. (Ouchi et al., 2003). In the same period both systolic blood pressure and BMI increased in the intensive treatment group, HbA_{1c} remained stable, whereas total cholesterol further decreased. Previous studies showed that intensive glycaemic control, blood pressure and blood lipid lowering treatment reduce inflammation (Danesh et al., 2004); (Schulze et al., 2004); (Belalcazar et al., 2010); (Whitehead et al., 2006); (Koh et al., 2011); (Koh et al., 2009); (Lauritzen et al., 2000). The marginal differences between groups with respect to HbA1c level might suggest that there was more attention to non-glycaemic targets. However, the treatment in the intervention group was equally directed to glycaemic and non-glycaemic risk factors. We should take into account that all participants were screen-detected T2DM patients, without high levels of HbA1c at baseline. Moreover, the trial was undertaken against a background of improvements in the delivery of diabetes care in general practice and evidence-based guidelines, which might also have lowered the achievable difference in HbA1c levels between groups (Griffin et al., 2011). We now show that multifactorial treatment decreases the inflammatory process as measured by hs-CRP. Statins may lower hs-CRP-levels (Prasad, 2006). However, adjustment for lipids or statin use did not change our results, suggesting that the decrease of hs-CRP levels is not only an effect of statin use. In other studies short-term treatment with metformin or insulin did not reduce hs-CRP levels despite improving glucose control (De Jager et al., 2005); (Pradhan et al., 2009); (De Jager et al., 2005) and adjustment for other potential intermediates such as acetylsalicylic acid use or HbA1c did not alter our findings as well. Therefore, a multifactorial treatment seems to have an independent effect on hs-CRP-levels. Hs-CRP levels increase due to weight increase (Belalcazar et al., 2010). This mechanism is likely to diminish the effectiveness of multifactorial therapy on

inflammation. Taking weight increase into account in a treatment strategy, for example in the choice of blood glucose lowering agents, might therefore decrease inflammation. In this respect it is beneficial that the vast majority of ADDITION patients started oral blood glucose lowering treatment with metformin, which does not cause weight gain (Griffin et al., 2011). However analysis with adjustment for BMI did also not change our results. Since abdominal fat accumulation may be an important determinant of adiponectin levels, it would have been better to include waist circumference in our analysis. Unfortunately, a waist measurement was not performed at follow-up, but only measured at baseline. Levels of adiponectin decreased after an initial increase in both treatment groups. This result might be explained by the change in body weight during the second part of the study. Because only a small number of patients used TZDs, thiazolidinedione use is unlikely to contribute to a differential change in adiponectin levels (Combs et al., 2002); (Yang et al., 2002). The decrease of adiponectin levels may have been caused by simvastatin (Koh et al., 2009); (Koh et al., 2011). On the other hand RAAS-blockers will have increased adiponectin levels (Chang et al., 2009); (Delles et al., 2008). We are unable to explain the change of adiponectin in two opposite directions over time with our results. The role of adiponectin seems to be more complex (Cook & Semple, 2010). The median follow-up time of approximately 6.1 years in the routine care group and 6.0 years in the intensive treatment group, is a major strength of this study. Furthermore, we used several measurements of a biomarker for each person over time. The population-based approach ensures the generalizability of our results. A different hs-CRP assay was used at study initiation than at study completion. However, both methods were highly correlated and since similar methods were used in all individuals, this does not systematically influence the differences between treatment arms. Nevertheless, we cannot exclude that this may have influenced the results. To our knowledge, this is the first study to investigate long-term changes in hs-CRP and adiponectin in a randomized controlled trial in screen-detected type 2 diabetes patients. The decreased hs-CRP levels over time are an important finding.

An intensive treatment appears to result in an enhanced decrease in the inflammation process reflected by hs-CRP. This study expands our understanding of a process that is apparently impaired in the first stage of diabetes and seems reversible. In the current article we used HbA1c, lipids, BMI and blood pressure as indirect endpoints and could demonstrate that the first year of the ADDITION study showed the most remarkable differences with respect to these endpoints. However after six years the Dutch patients within the ADDITION study did not demonstrate a reduction in 'hard' endpoints, (Griffin et al., 2011). Whether the difference in hs-CRP in the first four years is clinically meaningful remains uncertain. The findings related to adiponectin demonstrated that the role of adiponectin and adipose tissue is more complicated than possibly thought.

Conclusion

The long term change in hs-CRP reflects the overall intermediate results of a multifactorial intervention. Adjustment for lipids, statin use and BMI did not change our results, so a multifactorial treatment seems to have an independent effect on hs-CRP-levels. Whether the difference in hs-CRP in the first four years is clinically meaningful remains uncertain. The role of adiponectin seems to be more complex.

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CHAPTER 4

SHARED DECISION MAKING IN TYPE 2 DIABETES WITH A SUPPORT DECISION TOOL THAT TAKES INTO ACCOUNT CLINICAL FACTORS, THE INTENSITY OF TREATMENT AND PATIENT PREFERENCES: DESIGN OF A CLUSTER RANDOMISED (OPTIMAL) TRIAL.

H. den Ouden, R.C. Vos, C. Reidsma, G.E.H.M. Rutten,

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ABSTRACT

Background

No more than 10-20% of type 2 diabetes mellitus (T2DM) patients achieve all treatment goals regarding glycaemic control, lipids and blood pressure. Shared decision making (SDM) should increase that percentage; however, not all support decision tools are appropriate. Because the ADDITION-Europe study demonstrated two (almost) equally effective treatments but with slightly different intensities, it may be a good starting point to discuss with the patients their diabetes treatment, taking into account both the intensity of treatment, clinical factors and patients' preferences. We aim to evaluate whether such an approach increases the proportion of patients that achieve all three treatment goals.

Methods

In a cluster-randomised trial including 40 general practices, that participated until 2009 in the ADDITION Study, 150 T2DM patients 60–80 years, known with T2DM for 8-15 years, will be included. Practices are randomised a second time, i.e. intervention practices in the ADDITION study could be control practices in the current study and vice versa. For the GPs from the intervention group a 2-hour training in SDM was developed as well as a decision support tool to be used during the consultation. GPs plan the first visit with the patients to decide on the intensity of the treatment, personalised targets and the priorities of treatment. The control group will continue with the treatment they were allocated to in the ADDITION study. Follow-up: 24 months. The primary outcome is the proportion of patients who achieve all three treatment goals. Secondary outcomes are the proportion of patients who achieve five treatment goals (HbA1c, blood pressure, total cholesterol, body weight, not smoking), evaluation of the SDM process (SDM-Q9 and CPS), satisfaction with the treatment (DTSQ), wellbeing and quality of life (W-BQ12, ADD QoL-19), health status (SF-36, EQ-5D) and coping (DCMQ). The proportions

of achieved treatment goals will be compared between both groups. For the secondary outcomes mixed models will be used.

Discussion

This trial will provide evidence whether an intervention with a multi-faceted decision support tool increases the proportion of achieved personalised goals in type 2 diabetes patients.

Introduction

Successful prevention of complications in the increasing number of patients with type 2 diabetes (T2DM) appears to be difficult. In primary care no more than 10-20% of the patients with T2DM achieve all three treatment targets (glycaemic control, lipids, blood pressure) (Berkowitz et al., 2013; Camara et al., 2014; Cleveringa et al., 2008; Gaede et al., 2003; Griffin et al., 2011; van Hateren et al., 2012). For separate targets much higher percentages of about 30-70% are reported (Berkowitz et al., 2013; Camara et al., 2014; Cleveringa et al., 2008; Gaede et al., 2003; van Hateren et al., 2012). Therefore, it has been suggested that a more personalised and patient-centred approach might increase the proportion of patients who successfully reach all their treatment targets (Inzucchi et al., 2012; White, 2012). To personalise treatment targets for HbA1c, lipids, blood pressure, weight loss and smoking cessation, several factors have to be considered in order to encourage active participation of patients in evidence based clinical decision making.

Physicians are advised to consider the patients' age, motivation, risk of hypoglycaemia, diabetes duration, comorbidity and established vascular complications in setting the glucose control target (Inzucchi et al., 2012; Ismail-Beigi et al., 2011). For statin therapy, physicians should consider the patients' individual cholesterol level, his/her risk for cardiovascular mortality, age and T2DM duration (Robinson, 2014). The blood pressure target for patients with T2DM is below 140/80 (American Diabetes, 2014; Esposito et al., 2014), but for older patients a less strict treatment target may result in a higher survival rate (de Ruijter et al., 2009). With regard to weight control, physicians have to consider the side effects of weight gain of medication. Intensive lifestyle modification remains an elusive gold standard for weight reduction (Niswender, 2010). Although smoking cessation has been associated with weight gain, it is recommended as a routine component of the treatment of diabetes; however, evidence to guide best practice is limited (Nagrebetsky et al., 2014).

To achieve and maintain treatment targets, not only individual clinical characteristics should be considered, but also patients' preferences for treatment intensity. Generally speaking, the doctor is the expert on medicine, while the patient is the expert on his or her priorities (Mulley et al., 2012). Shared decision making (SDM) is an approach that takes into account both the clinical evidence for treatment goals as well as the patients' preferences. SDM is defined as 'an approach where clinicians and patients make decisions together, using the best available evidence'(Stiggelbout et al., 2012). It promotes patient autonomy and patient engagement in the treatment decision making by giving the patient an active role in weighting the benefits and harms of more than one evidence based treatment option (Stiggelbout et al., 2012). Although SDM is promising for patients with chronic diseases by setting realistic treatment targets, such an extensive approach had not been broadly studied in T2DM patients before 2008 (Joosten et al., 2008). Recently the effects a patient oriented decision aid for SDM and goal setting in T2DM patients on patient empowerment and treatment decisions have been published (Denig et al., 2014). No effect was found on empowerment, the decision aid was not used to measure the effect on clinical outcomes and achievement of goals.

Because SDM is especially useful when there are two or more equally beneficial treatment options, the results of the ADDITION-Europe study, in which the Netherlands participated, could be used in a SDM approach in patients with T2DM. The ADDITION study included screen detected T2DM patients and compared an intensive multifactorial treatment of HbA1c, cholesterol, blood pressure and body weight with less intensive usual care according to national guidelines. The intensive treatment was associated with a significant increase in prescribed medications and a non-significant 17% reduction of cardiovascular events and death after 5 years. However, the rate of cardiovascular events seemed to diverge after 4 years of follow-up. It was concluded that intensified treatment and treatment according to national guidelines can theoretically be equally effective (Griffin et al., 2011). Based on the

results of the ADDITION study, it is questionable which evidence based treatment advice the diabetes care provider should give to the T2DM patient. There is no decisive evidence for either option. This situation is very appropriate for treatment decisions that incorporate the patients' preferences.

In a recent statement of both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) personalised and patient-centred care is mentioned as the cornerstone of the treatment of patients with T2DM. The use of a decision support tool is strongly advocated (Inzucchi et al., 2012). A decision support tool can encourage active patient participation in many evidence-based healthcare decisions (Barry & Edgman-Levitan, 2012); (Coulter & Collins 2011); (International Patient 2005). In the last decade decision support tools have been developed to support the achievement of cardiometabolic goals and to select patient-centred treatment options for lifestyle modifications or medication use (Inzucchi et al., 2012); (Corser et al., 2007; Holbrook et al., 2009; Mann et al., 2010; Mullan et al., 2009; Rodbard & Vigersky, 2011; Wilkinson et al., 2013). However, most of them focus on a single risk factor (Mann et al., 2010), on only the patients' preferences (Corser et al., 2007; Mullan et al., 2009) or on some individual clinical characteristics (Holbrook et al., 2009). We hypothesise that a decision support tool that takes into account both treatment intensity, patients' clinical characteristics and patients' preferences can facilitate a SDM process and will be effective in achieving treatment targets. We aim to evaluate whether such an approach increases the proportion of treatment targets that T2DM patients achieve.

The following research questions are addressed:

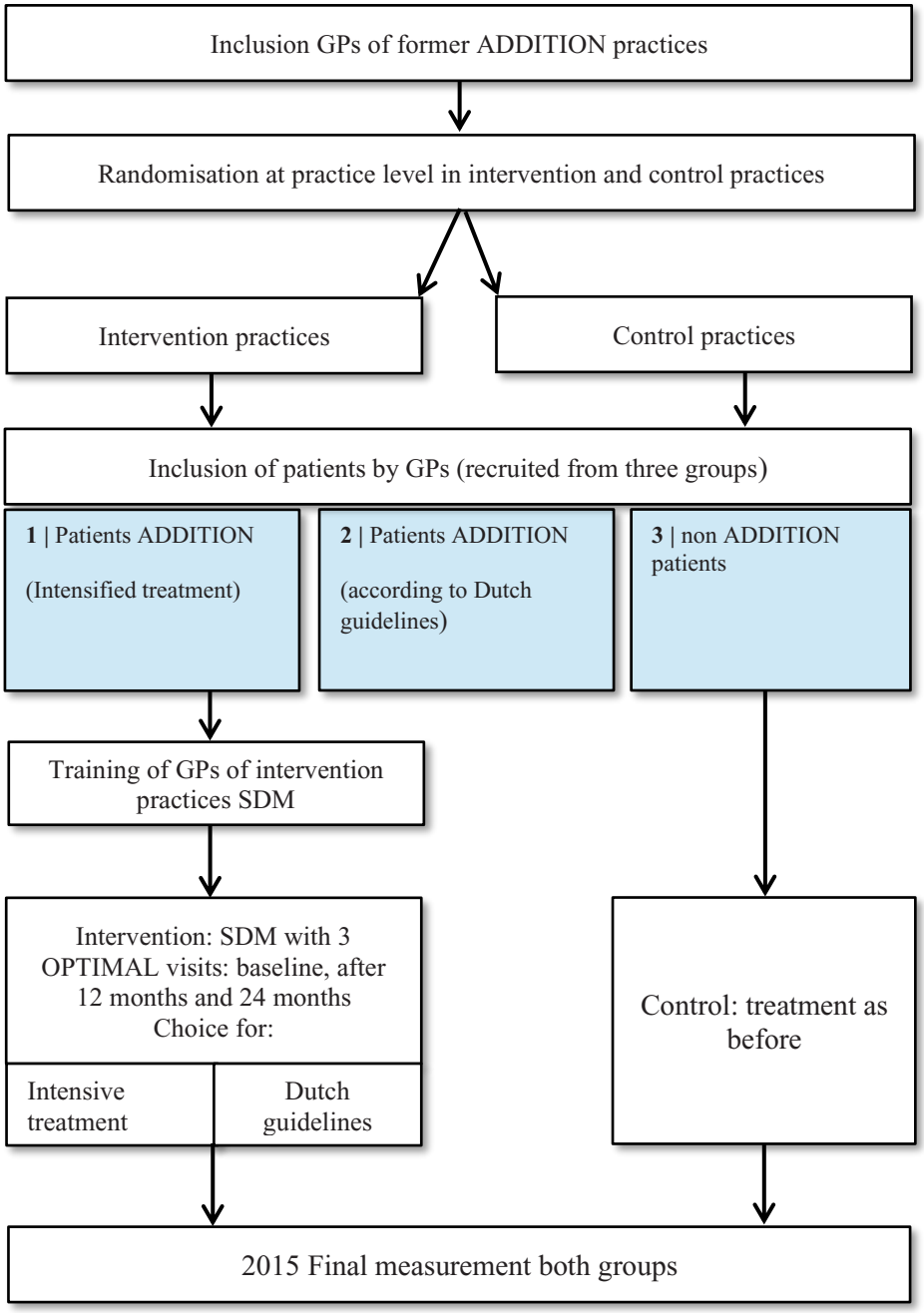
1. What is the effect of shared decision making with a multi-faceted decision support tool on the percentage of patients with T2DM that achieve all individualised treatment targets for HbA1c, blood pressure and LDL-cholesterol; and to identify determinants for achieving all individualised treatment targets.
2. What is the effect of shared decision making with a multi-faceted decision support tool on treatment satisfaction, quality of life, health status, well-being and on coping styles?
3. What is the level of SDM-knowledge/attitude of the GPs from both treatment groups after 24 months?

Methods

Study design and setting

The OPTIMAL study is a cluster-randomised trial with randomisation at practice-level and two years follow-up. We developed an intervention to promote SDM with a decision support tool based on the results of the above mentioned ADDITION-Europe study. Since for an optimal SDM approach physicians should have some experience with all treatment options, patients are recruited from the 79 general practices that participated in the ADDITION study (Janssen et al., 2009). For the OPTIMAL study practices are randomised again **(Figure 1)**. GPs in the intervention group were trained in SDM (see further).

Figure 1 | flow chart design OPTIMAL



Practices and patients

Eligible GPs are those who included at least included one patient in the ADDITION-study. For the OPTIMAL study each GP should include at least two more or less comparable patients: 1) former 'ADDITION' patients diagnosed with T2DM in 2002-2004 by screening, aged between 50-70 years at that time and having participated in the ADDITION study that ended in 2009; 2) Patients between 60 and 80 years in 2012-2014, known with type 2 diabetes for 8-12 years but not diagnosed in the ADDITION study. Patients will be excluded if they have a history of alcoholism, drug abuse, psychosis, personality disorder or another emotional, psychological or intellectual problem that is likely to invalidate informed consent, or limit the ability of the individual to comply with the protocol requirements. Also, patients with a limited life expectancy will not be approached.

Randomisation

Randomisation is executed at the research center at practice-level, without any stratification. It is not possible to blind participants and GPs for the treatment allocation. Practices are randomised a second time, i.e. intervention practices in the ADDITION study could be control practices in the current study and vice versa.

Intervention

1.The decision support tool

The OPTIMAL decision support tool is a simple paper-based tool, aimed to be easy to use for both the GP and the patients. It should be used to discuss the treatment options and the prioritising of treatment targets during the first visit and the 12- and 24-months follow-up visits. The tool consists of three steps: 1) considering the pros and cons of two almost equally effective evidence based multifactorial treatments, namely the intensified ADDITION protocol and the protocol derived from the 2006 Dutch guidelines for GPs (Griffin et al., 2011) (for details see **Figure 2**, step 1b), and the shared decision on which option will be chosen; 2) prioritising of treatment

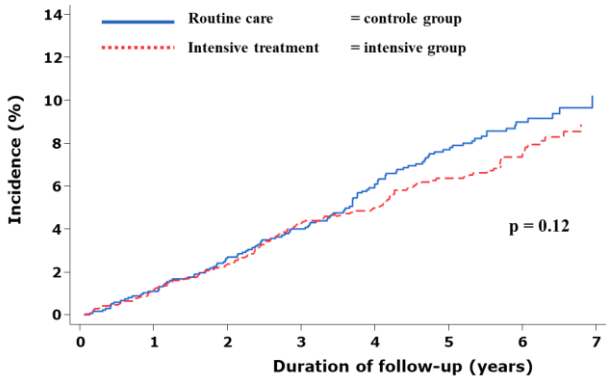
targets according to the chosen option, and 3) treatment selection (medication or lifestyle) to achieve the treatment targets. For detailed information about the two treatment options and the different targets see **figure 2**.

Figure 2 | decision support tool

OPTIMAAL- Support decision tool in the treatment of T2DM, Shared decision in primary care

Step 1a

There are two options to consider as a treatment for your diabetes	***Regular treatment*** *according Dutch guidelines of General Practitioners*	*Both options improve health status. It seems that the intensive (ADDITION) treatment will give a better long-term health status.*	*There is no difference between both groups with regard to check-ups or venapunctions. Intensive treatment-> targets are stricter.*
	Intensive treatment *According ADDITION-study*		



Step 1b

Treatment targets →	**Blood pressure**	**Total Cholesterol**	**HbA1C**	**Smoking**	**Weight**
Regular treatment	< 140 mmHg	< 4.5 mmol/L cardiovascular disease < 3.5 mmoL/l	<53 mmol/mol (< 7%)	Stop	Loss weight Shared decision on your weight loss, write down the target in kg.
Intensive treatment	< 135/85 mmHg Start treatment if > 120/80 mmHg	< 3.5 mmol/L	48 - 53 mmol/mol (< 6.5% - 7%)	Stop	Loss weight BMI > 27 Than ≥ 5% weight loss.

Step 1c

Regular treatment	**Pro:** We will not ask more effort of you. Your treatment targets are not changed.	**Con:** Perhaps this treatment does give less improvement in health status on the long-term compared to the more intensive treatment.
Intensive treatment	**Pro:** It seems that the treatment will give you a better health status at the long-term compared to regular guidelines.	**Con:** Perhaps you have to start earlier with medication and also have to use more medication.

Step 1:

Patients' preferences, choice of treatment

What is according to you positive in both treatments?

What is according to you negative about both treatments?

What is important for you in your treatment of T2DM?

The best choice depends on what matters most to the patient.

Step 2 A

Treatment goals→	**Blood pressure**	**Total cholesterol**	**HbA1C**	**Smoking**	**Weight**
Most recent individual values	...../..... mmHg Date:	.....mmol/L Date:	.....% of ..... mmol/mol Date:	Yes/no Number of cigarettes per day Date:	.....kg BMI: Date:
Treatment goals as chosen in step 1	...../..... mmHg	.....mmol/L	.....% or mmol/mol	Yes/no	.....kg Weight loss BMI:

Step 2B

and

Step 3

Which goal gets highest priority?

Prioritise five treatment goals

Select treatment *how* to achieve the goals

Treatment goals	By medication changes or extra lifestyle changes? Which?
1	
2	
3	
4	
5	

2. Visits during the OPTIMAL study

During the first visit, and guided by the decision tool, the GP and the patient discuss the two evidence based T2DM treatments. The GP will explain the pros and cons of each option, and the treatment targets that should be achieved, depending on the option that is chosen. The GP should explain that both treatments are equally suitable for treating T2DM. Next, the patients' preferences and lifestyle habits are discussed against the background of the patients' most recent values of HbA1c, lipids, blood pressure, body weight and smoking habits. Then the GP and the patient will together decide on the preferred treatment option and the accompanying treatment targets. For a patient who underwent the intensified treatment in the ADDITION study and did not change it after the end of ADDITION, this visit provides him/her the opportunity to choose a less intensive treatment. Also the other way around is possible. The patient will prioritise the five treatment targets (HbA1c, cholesterol, blood pressure, body weight, smoking habits) for the first 12 months. The target with the highest priority will get the most attention and require the most effort of both the patient and GP. There will be no pre-defined way in how the patients should reach their targets; the patient and the GP need to determine this way together in a final step in the decision process. The patient and GP decide whether medication changes and/or lifestyle changes should be made in order to reach the prioritised targets. During the second and third OPTIMAL visit (12 and 24 months later) the patient and GP evaluate the decisions they made during the first visit using the decision support tool. The priority of the treatment targets can be changed during these visits, but not the choice between the two treatment options (ADDITION protocol or the less intensive protocol). During the third and final visit the patient and the GP will decide whether or not to keep to the chosen treatment option. Between the first and third visit, three monthly T2DM visits will take place either with the GP or the practice nurse.

Training

The GPs from the practices randomised to the SDM-treatment arm are trained in the SDM approach during a two hours training session. During this session the study protocol is discussed as well as the SDM principle (see further) and the OPTIMAL decision support tool. By use of role-plays the SDM process will be practiced by the GPs.

Control group

Patients in the control practices will receive treatment-as-before. Also, the GPs will not be asked to engage in a SDM process, nor be trained to do this and they will not be offered the decision support tool. The GP will treat the patients as they were used to since the ending of the ADDITION study (2009), either following the national guidelines or the ADDITION intensive treatment algorithm, each with their respective targets (Griffin et al., 2011).

Outcome measures

Primary outcome will be the proportion of patients that achieve all the three treatment goals for HbA1c, blood pressure and total cholesterol. In addition to identify determinants of better performing patients for the primary outcome will be performed taken into account the interaction of SDM with age, gender, education level, duration of diabetes and comorbidities.

Secondary outcomes:

- The proportion of patients that achieve the all five treatment goals for HbA1c, blood pressure, total and LDL-cholesterol, body weight, and smoking.
- The following patient reported outcomes: diabetes treatment satisfaction, perceived quality of life, health status, well-being, and coping style.

- A process evaluation of the shared decision making ability of the general practitioners during the complete study. Outcome on GP level: the level of SDM-knowledge/attitude.

Measurements, data collection

Data about the patients' socio-demographic background, the level of education, smoking status and whether the patient lives alone or together will be collected by patients' self-report at baseline. HbA1c, blood pressure, body weight, total cholesterol and LDL-cholesterol, and smoking habits as well as patient characteristics (age, gender, duration of diabetes and comorbidities) will be reported every year by the GPs on a specific Case Report Form in both groups.

Blood pressure is measured by two measurements after at least 10 minutes rest, while participants are seated with the cuff on the predominant arm at the level of the heart, using an automatic sphygmomanometer. Height and body weight are measured in light indoor clothing and without shoes using a fixed rigid stadiometer and a scale respectively. Laboratory results (HbA1c, LDL-cholesterol) were obtained with case report from the GPs electronic records.

Participants in both groups will be asked to complete and return the following questionnaires baseline and after 24 months at home.

a) the Diabetes Treatment Satisfaction Questionnaire (DTSQ) (Bradley et al., 1994) which includes 8 items; scores range from 0 (very dissatisfied) to 6 (very satisfied), totally from 0 to 48. The DTSQ is reliable, valid and sensitive to change in diabetes patients (Bradley et al., 1994);

b) the Audit of Diabetes Dependent Quality of Life (ADD QoL-19), which measures the perceived impact of diabetes on the quality of life; it includes 19 items, ranging from -3 to 3 on different questions, with 0 as the neutral score. Scores below 0 reflect a negative influence of the item on quality of life, and all above 0 reflect positive influences. The impact scores are weighted (impact rating x importance rating), so the actual scores per item can range from -9 to 9. The ADDQoL-19 has good

psychometric properties and provides clinicians and researchers with a useful tool for comprehensively assessing quality of life in adults with T2DM (Bradley et al., 1999);

c) the Well-Being Questionnaire (W-BQ12) that consists of 12-items in three 4-item subscales: negative well-being (item 1-4, higher score reflects a greater sense of negative well-being), energy (items 6 and 7 are reversed, and then together with 5 and 8 form the total amount of energy) and positive well-being (items 9-12, the higher the score the greater the sense of positive well-being). The total score ranges from 0 to 36 and is called the general well-being score. Higher scores indicate a higher overall sense of well-being (Pouwer et al., 1999);

d) the European Quality of Life (EQ-5D) questionnaire, that covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a Visual Analogue Scale (VAS) where respondents can rate their health. Item scores range from 1-3, and a 5-digit health profile is formed, placing the 5 numbers behind each other. It is a well-validated, reliable and responsive instrument for health measurement in patients with a wide range of medical conditions. Values found in the UK have been validated for the Netherlands (Gaede et al., 2003; Janssen et al., 2011; Lamers et al., 2006).

the Short Form-36, a validated 36-item instrument for the self-evaluation of health status with eight subscales: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role-Emotional (3 items) and Mental Health (5 items). These scales can be summarised in Physical Health and Mental Health. The 36 items differ in the scoring ranges. The Dutch version has proved to be a practical, reliable and valid instrument (Aaronson et al., 1998; Ware & Sherbourne, 1992)

f) the Diabetes Coping Measurement Questionnaire (DCMQ), consisting of 21 items in 4 subscales: spirit coping, avoidance coping, passive resignation coping and diabetes integration coping. Overall scores range from 7 to 35. The items are measures on a 5-point Likert scale, ranging from 1 (‘disagree’) to 5 (‘agree strongly’)

or the other way around from 1 ('I strongly agree') to 5 (I 'disagree'). Higher scores on tackling spirit and diabetes integration indicate more adaptive coping. Higher scores on passive resignation and avoidance indicate poor coping.

A process evaluation of the shared decision making ability of the general practitioners will be measured in the intervention group at baseline and after 12 months, and in both treatment groups at 24 months. Both the patients and GPs will be asked to complete The Shared Decision Making Questionnaire, both the patient (SDM-Q9-patient) and GP (SDM-Q9-doc) version will be used to evaluate this process.

The Shared Decision Making Questionnaire (both SDM-Q9 versions) (Kriston et al., 2010; Rodenburg-Vandenbussche et al., 2015; Scholl et al., 2012) includes 9 items with ratings from 0 (completely disagree) to 6 (completely agree); the total score ranges from 0 to 54. It is a continuous scale, and the questionnaire developers did not describe any thresholds for 'bad' or 'good' SDM. Over the last years the SDM-Q9 has become a frequently used instrument in clinical practice. It has been translated into several languages. Internal consistency has been assessed for the Spanish and Dutch version (Rodenburg-Vandenbussche et al., 2015). Item discrimination parameters were above 0.4 for all but one item. An analysis of internal consistency yielded a Cronbach's α of 0.88. (Kriston et al., 2010). The Dutch version is currently being validated (Rodenburg-Vandenbussche et al., 2015). A modified version of the Control Preferences Scale (CPS) is used to determine the experienced role of decision making of the GP and patient. The CPS measures at a 5-point Likert scale, and has shown good reliability and validity (Degner et al., 1997; Kasper et al., 2011). The original Control Preference Scale by Degner (Degner et al., 1997), was developed to measure preference for involvement and is one of the most commonly used instruments to assess preferred decisional role (Degner et al., 1997; Kasper et al., 2011).

Subsequently, the GPs of both groups (the intervention group trained, the control group not) will audio- or videotape one of their yearly consultations with a T2DM

patient. They can choose the consultation to be taped themselves. These tapes will be evaluated by two independent observers, making use of the SDM-Q9, to assess the extent to which the GP is likely to involve his/her patients in the diabetes treatment.

Sample size

As stated in the Introduction, only 10-20% of T2DM patients achieve all three treatment targets for both HbA1c, lipids and blood pressure. We estimate the percentage of patients that already has reached three targets at the start of the study will be approximately 10%. We hypothesise that in the OPTIMAL study, after two years of follow-up, the intervention group will show an increase of this percentage until 30% (about 10% increase per year), whereas in the treatment-as-before-group this percentage will stay at 10%. Assuming a two-sided significance level of 5%, with alpha 0.05 and power of 80% and with a drop-out of 10%, 65 patients will be needed in each treatment group (Department of Statistics Sample Size Calculator, University of British Columbia). Because the OPTIMAL study is a cluster randomized study the sample size will require an correction for the cluster effect. The used correction factor is equal to [1 + (m - 1) r], where 'm' is the total amount of eligible patient per practice (approximatly 6), and 'r' the within-cluster correlation coefficient. For 'r' we use a within-cluster correlation coefficient of 0.025, based on the cluster correlation found in the ADDITION-Europe study. When taken the cluster effect (1.125) into account, 73 patients per group are needed.

Statistical Analyses

Intention-to-treat analyses (ITT) will be performed to examine between-group differences. Generalized linear models will be used to correct for clustering at practice level. The proportions of achieved treatment goals of HbA1c, blood pressure, LDL-cholesterol within each study group will be estimated by calculating relative risk. The same applies to the difference between groups in the proportion of

patients which achieved all the five above mentioned treatment goals. A p-value of < 0.05 is considered statistically significant. To identify patients who show better results after the SDM process, the analysis for the primary outcome will be repeated with taken into account interaction of SDM with age, gender, education level, duration of diabetes and comorbidities. Within and between group differences in treatment satisfaction, perceived quality of life, health status, well-being, and coping style between baseline and 24 months follow-up will be analysed by using paired t-tests and mixed models respectively. We will add random effects for patient and practice.

The SDM-Q9 will be analysed in the intervention group by using paired t-tests. Mixed models will be used to study the between groups differences after 24 months. We will add random effects for patient and practice.

To evaluate the SDM proces, the tapes will be evaluated by two independent observers by making use of the SDM-Q9.

Discussion

The treatment of T2DM is mostly target driven. However, only a low percentage of all patients with T2DM achieve all goals. SDM and goal setting can be useful to increase the percentage of patients' that achieve all targets. However, the decision support tool to be used in SDM should likely not only focus on the clinical factors of the patients but also on the patients' preferences, because each of these variables may affect the optimal treatment targets. Besides, the decision support tool should be used in a SDM process during more than one consultation (Inzucchi et al., 2012). The results of the ADDITION trial, in which half of the participants of the current study also participated, offers a unique opportunity to discuss with the patient two almost equally effective treatment strategies.

In the current cluster-randomised controlled trial we will evaluate the effectiveness of such a repeated use of a decision support tool, taking into account both the

intensity of treatment, individual clinical factors and the patients' experiences and preferences. We hypothesise that the SDM process with such a well-balanced decision support tool will improve the percentage of patients that achieve all three individual goals compared to the control group, making SDM really beneficial.

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CHAPTER 5

EFFECTIVENESS OF SHARED GOAL SETTING AND DECISION-MAKING TO ACHIEVE TREATMENT TARGETS IN PATIENTS WITH TYPE 2 DIABETES. A CLUSTER RANDOMISED TRIAL (OPTIMAL).

H. den Ouden, R.C. Vos, G.E.H.M. Rutten.

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ABSTRACT

Objective

About 20% of patients with type 2 diabetes achieve all their treatment targets. Shared decision making (SDM) using a support aid based on the 5-years results of ADDITION study on multifactorial treatment, could increase this proportion.

Research Design and Methods

Cluster-randomised trial in 35 former ADDITION primary care practices. Practices were randomised to SDM or care as usual (1:1). Both ADDITION and non-ADDITION type 2 diabetes patients, 60–80 years, known with diabetes for 8-12 years, were included. In the intervention group patients were presented evidence about the relationship between treatment intensity and cardiovascular events. They chose intensive or less intensive treatment and prioritised their targets. After one year priorities could be rearranged. Follow-up: 24 months. Intention-to-treat analysis. Main outcome measure: proportion of patients that achieved all three treatment targets.

Results

At baseline 26.4% in the SDM group (n = 72) had already achieved all three treatment goals (CG: 23.5%, n = 81). In the SDM group 44 patients chose intensive treatment, 25 continued their former less intensive treatment and three people switched from the more to the less intensive protocol. After 24 months 31.8% of the patients in the SDM group achieved all three treatment targets (CG: 25.3%), RR 1.26 (95% CI 0.81-1.95). Mean systolic blood pressure decreased in the SDM group (-5.4 mmHg, $p < 0.01$). Mean HbA1c and total cholesterol did not change.

Conclusions

Despite an already high baseline level of diabetes care we found strong indications that SDM on both intensity of treatment and prioritising treatment goals further improved outcomes.

Introduction

The control of type 2 diabetes mellitus (T2DM) involves a complex series of medical decisions with respect to treatment goals, self-care behaviours, and medical treatments (Inzucchi et al., 2012*)*; (Wilkinson et al., 2013). It requires frequent follow-up visits with reconsidering treatment priorities and patients' preferences (Wilkinson et al., 2013). The quality of these decisions could influence the appropriate treatment of T2DM (Coulter et al., 2015; Gionfriddo et al., 2013; Montori et al., 2006; Wilkinson et al., 2013). Adequate treatment of multiple risk factors can prevent or postpone diabetes related complications (Inzucchi et al., 2012); (Gaede et al., 2008); (Griffin et al., 2011); (Buse et al., 2007).

In practice about 10-20% of T2DM patients achieve all treatment targets for glycaemic control, lipids and blood pressure (Camara et al., 2014); (Stark Casagrande et al., 2013*)*, whereas reported percentages for separate targets are much higher (30-70%) (Schmittdiel et al., 2008); (Cleveringa et al., 2008); (Braga et al., 2012); (Voorham et al., 2008). Clinicians are sometimes hesitant to intensify treatment (Schmittdiel et al., 2008); (Khunti et al., 2014) and patients are not always adherent to medical treatment (Meddings et al., 2012); (Voorham et al., 2011) and doctors do not acknowledge this (Schmittdiel et al., 2008); (Meddings et al., 2012; Voorham et al., 2008). A collaborative approach with shared decision making (SDM) and goal setting could be helpful for both patient and clinician and might increase treatment adherence and the proportion of patients who successfully reach all their treatment targets (Inzucchi et al., 2012); (Mulley et al., 2012); (Bodenheimer & Handley, 2009); (Lenzen et al., 2015); (De Sutter et al., 2013).

SDM is an approach that respects the clinical evidence and patients' preferences for treatment goals. SDM is defined as 'an approach where clinicians and patients make decisions together, using the best available evidence'. It promotes patients' involvement in weighting benefits and harms of evidence based treatment options (Mulley et al., 2012). Shared goal setting is defined as the agreement between healthcare professionals and patients on health-related goals (Bodenheimer & Handley, 2009); (Lenzen et al., 2015); (De Sutter et al., 2013).

The quality of diabetes care with integration of SDM and goal setting could be enhanced by a personalised decision aid, that takes into account both the patients' clinical characteristics as well as treatment preferences (Agoritsas et al., 2015); (Stacey et al., 2017); (Rodbard & Vigersky, 2011). Decision aids are proven effective in involving the patient in the shared decision making process (Montori et al., 2007). During the last decade such aids were developed to support the achievement of patient-centred treatment goals and options for lifestyle modifications and medication use (Montori et al., 2007); (Rodbard & Vigersky, 2011); (Mann et al., 2010); (Mullan et al., 2009); (Corser et al., 2007); (Denig et al., 2014); (Holbrook et al., 2009). More than ever diabetes guidelines are encouraging active personalising of diabetes goals for glucose, blood pressure and cholesterol levels (Inzucchi et al., 2012).

We hypothesized that SDM with a decision aid tool that takes into account both treatment intensity, patients' clinical characteristics and patients' preferences could be effective in increasing the proportion of patients' with T2DM who achieve all their personalised targets (Den Ouden et al., 2015). We compared the results of multifactorial diabetes treatment after shared goal setting and prioritising targets with a physician driven multifactorial diabetes treatment.

Research design and Methods

Study setting, practices and patients

The OPTIMAL study is an open cluster-randomised controlled trial with a follow-up of 24 months. It was not possible to blind participants and physicians for the treatment allocation. The full details of the rationale and design of this trial have been described previously (Den Ouden et al., 2015). In short, the intervention included SDM with personalised goal setting and the use of a decision aid. Because SDM and goal setting are especially useful when there are at least two equally beneficial treatment options, the study was performed in primary care practices that participated in the ADDITION study between 2002 and 2009. The ADDITION study included screen detected patients with T2DM and compared an intensive multifactorial treatment with less intensive usual care according to national guidelines. The intensive treatment was associated with a significant increase in prescribed medications and a non-significant 17% reduction of cardiovascular events and death after five years (Griffin et al., 2011). The rate of cardiovascular events seemed to diverge after four years of follow-up. It was concluded that intensified treatment and treatment according to national guidelines can theoretically be equally effective (Griffin et al., 2011). In 2011/2012, all primary care practices that participated in the ADDITION study were invited to participate in the OPTIMAL study. Eligible practices were those familiar with the ADDITION-protocol and which had included at least one patient in the ADDITION-study (Den Ouden et al., 2015). Randomisation was executed at practice-level at the research centre according to computer generated list independent of the study team, without any stratification. Practices were randomised a second time (1:1), i.e. intervention practices in the ADDITION study could be control practices in the current study and vice versa. The general practitioners (GPs) from the intervention group were trained in the SDM approach during a two hours training session, in which the study protocol, the SDM principles and the OPTIMAL decision aid were discussed (Den Ouden et al., 2015).

GPs were trained with role-plays in the SDM process. All participating GPs included at least two more or less comparable patients: 1. Patients diagnosed with T2DM in 2002-2004 by screening, aged between 50-70 years at that time and having participated in the ADDITION study; 2. Patients with T2DM not diagnosed in the ADDITION study, between 60 and 80 years in 2012-2014 and with a T2DM duration between 8 to 12 years. Patients with a history of alcoholism, drug abuse, psychosis, personality disorder or another emotional, psychological or intellectual problem that is likely to invalidate informed consent, or limit the ability of the individual to comply with the protocol requirements were excluded. Also, patients with a limited life expectancy were not approached (Den Ouden et al., 2015).
After informed consent, patients were invited for the first visit.
The study protocol was registered at the International trial registration (NCT02285881) and approved by the Medical Ethical Committee of the University Medical Centre Utrecht (Protocol number: 11-153).

Patient involvement

At the end of the ADDITION study, all participating Dutch patients were invited to attend a meeting for the presentation of the 5-years results. During that meeting with around 100 participants the idea arose to get the intensive treatment implemented in daily practice, but on the other hand patients stated that each individual should have the choice to choose the intensive or less intensive treatment option. During that meeting the idea for the OPTIMAL study came up. Later on, some patients were involved in the design of the decision aid. Patients were not involved by the recruitment and design of participants for the OPTIMAL study.

Intervention

Theoretical framework

A theoretical framework for SDM in clinical practice was provided by Charles *et al* (Charles et al., 1997).

They highlighted the need for bidirectional information exchange and agreement about the treatment. Originally this framework was developed for the acute setting; it was modified for chronic conditions in 2006 (Montori et al., 2006). In chronic conditions a long-term relationship between clinicians and patients is essential, and the opportunity to revise decisions should be possible. The other components of the framework (partnership, information, deliberation, decision) remained similar to the original one.

Decision support aid

The OPTIMAL decision support aid is a simple paper-based tool, easy to use for both GP and the patient (Den Ouden et al., 2015). It was used during the first visit to discuss 1) two treatment protocols; 'usual care' versus 'intensified' care, and 2) to prioritise five treatment targets (see below). Against that background, the decision aid consists of three steps: 1) considering the pros and cons of two almost equally effective evidence based multifactorial treatments, namely the intensified ADDITION protocol and the protocol derived from the Dutch guidelines for GPs (Rutten et al 2006) followed by a shared decision on which protocol will be used; 2) prioritising of treatment targets according to the chosen treatment protocol, and 3) treatment selection (medication and/or lifestyle change); the way how to achieve the treatment targets (Den Ouden et al., 2015). The same tool was used during the 12 months follow-up visit to reconsider the treatment priorities, not the intensity of treatment. Patients who were treated before the start of the study according to the Dutch guidelines could change their therapy to the intensified treatment and patients who were treated intensively in the ADDITION study could alter their treatment to

the less intensive option at baseline. So at the start of the OPTIMAL study all patients in the intervention group could change the intensity of their treatment or not.

Control group

The GPs from the control practices were not asked to engage in SDM, nor trained to do so and they were not offered the decision support aid. They were requested to treat the patients as they were used to since the ending of the ADDITION study (2009), either following the national guidelines or the ADDITION intensive treatment protocol, each with their respective targets. So patients in the control practices received treatment-as-before with their respective targets (Den Ouden et al., 2015).

Treatment targets

Thresholds to start lowering the HbA1c-level for the intensive treatment (derived from the ADDITION-protocol) and according to the less intensive treatment (based on the Dutch guidelines) were 48 mmol/mol and 53 mmol/mol, respectively. With regard to the systolic blood pressure these thresholds were 120 mmHg versus 140 mmHg and for cholesterol levels 3.5 mmol/l versus 4.5 mmol/l respectively.

Treatment *targets* for HbA1c were < 53 mmol in both treatment options, for systolic blood pressure ≤ 135 mmHg (intensive) versus < 140 mmHg (less intensive) and – surprisingly - for cholesterol < 5.0 mmol/l versus < 4.5 mmol/l. Besides the above mentioned thresholds and targets participants were recommended in both treatment options to stop smoking and in case of a BMI > 25 to lose at least 5% of their body weight. Therefore also weight and smoking status were considered treatment targets.

Outcome measures and data collection

Primary outcome was the proportion of patients that achieve all three treatment goals for HbA1c, blood pressure, and total cholesterol after 24 months.

Data on patient characteristics were collected at baseline by patients self-report on a case report form and included age, gender, education level, diabetes duration, living situation (alone or together), and smoking status. Data about medication, comorbidity, the shared choice for intensive or less intensive treatment, the prioritising of the targets; and how to achieve the treatment targets (by medication and/or lifestyle changes) were reported on a separate case report form by the GP during visit 1 (baseline) and after 12 and 24 months.

HbA1c and total cholesterol, both at baseline and after 12 and 24 months, were analysed at the SHL Centre for Diagnostic Support in Primary Care, Etten-Leur. HbA1c levels were analysed with high-performance liquid chromatography (Tosoh G8 machine) and total cholesterol levels with standard enzymatic techniques (Cobas 8000 machine).

Height and body weight were measured in light indoor clothing and without shoes using a fixed rigid stadiometer and a scale respectively. Blood pressure was measured by two measurements after at least 10 minutes rest, while participants were seated with the cuff on the predominant arm at the level of the heart (Den Ouden et al., 2015).

Statistical analyses

In order to detect a difference of 20% between groups in the proportion of patients achieving all treatment targets (Griffin et al., 2011), assuming a two-sided significance level of 5%, with alpha 0.05 and power of 80% and with a drop-out of 10% and a cluster effect of 1.125 (Den Ouden et al., 2015), a minimum number of 73 patients in each treatment group is required (Department of Statistics Sample Size Calculator, University of British Columbia).

Data were compared by group allocation, using either means (standard deviation, SD) or medians (inter quartile range, IQR) for continuous variables, and counts and percentages for nominal variables. The number of targets achieved at baseline was based on the source of recruitment (ADDITION Intensive, ADDITION Dutch

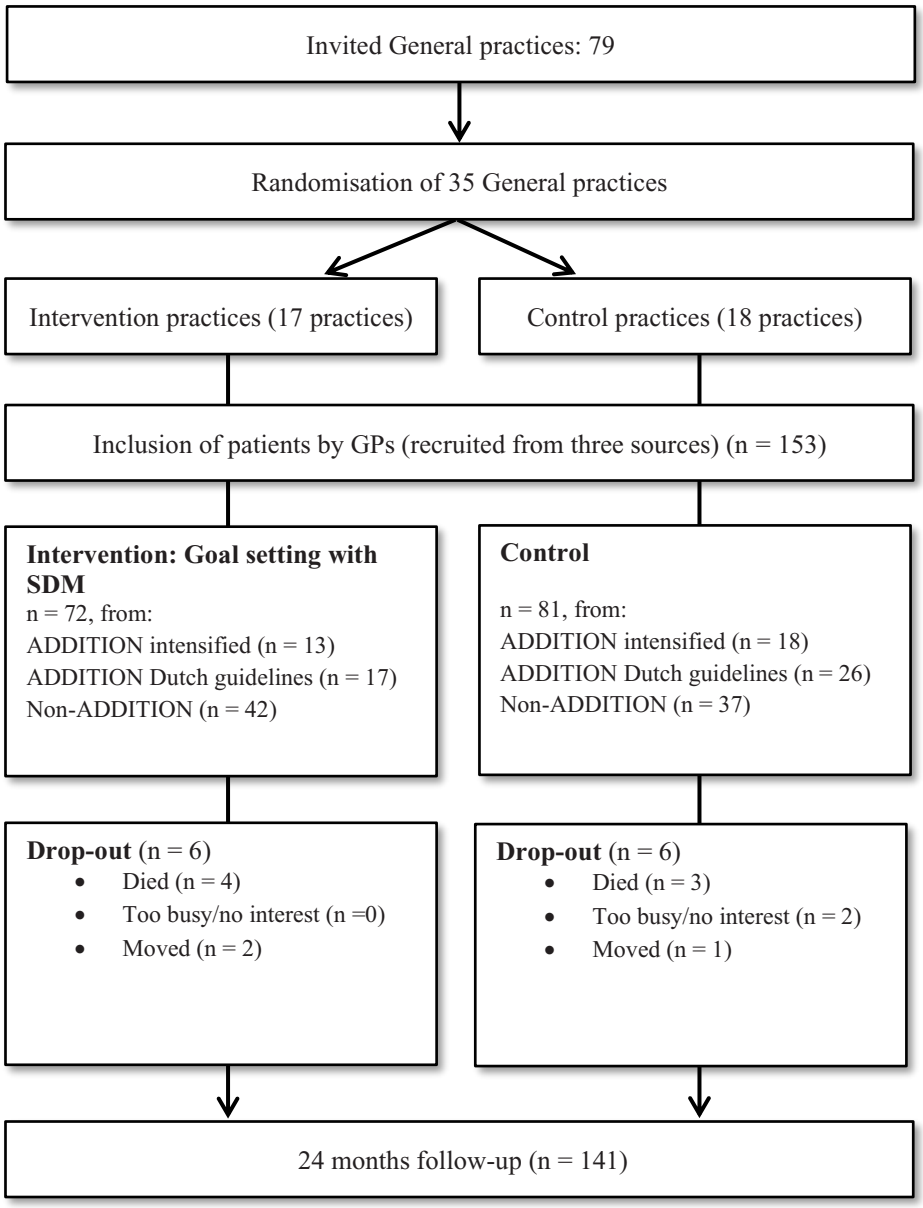
Guidelines and non- ADDITION). The treatment targets for the control group were assumed to be unchanged during the whole study period. Because it became clear that almost 90% of the participants did not smoke (anymore) and because in the control group there was no specific treatment target formulated for weight loss, we decided to analyse the proportion of patients that achieved treatment goals with respect to HbA1c, SBP and cholesterol levels.

Intention-to-treat analyses (ITT) were performed to examine between-group differences. To analyse the proportion of achieved treatment goals for all three treatment goals (blood pressure, lipids and HbA1c) relative risks and the number needed to treat (NNT) were calculated. Relative risks were assessed at 24 months follow-up for the complete cases (scenario 1), with the last observation carried forward (scenario 2), and as 'targets not achieved' if the last measurement was missing (scenario 3). Generalized linear models were used to correct for clustering at practice level. A p-value of < 0.05 is considered statistically significant. Two years differences between groups for Hba1c, total cholesterol, BMI and blood pressure were analysed using ANCOVA with change scores. In the model, treatment allocation (intervention or control group) was included as factor and the baseline score as covariate. Differences within groups with respect to HbA1c, systolic blood pressure and total cholesterol were tested with paired t-tests.

Results

All 79 former ADDITION practices were invited, of which 35 practices agreed to participate (n = 17 intervention and n = 18 control group). From the original 435 ADDITION patients in these 35 practices, 74 patients could be included. Besides 79 more or less comparable non-ADDITION patients were included. As a result, 153 patients were allocated to either the intervention or the control group **(Figure 1)**.

Figure 1 | Flow diagram of patient enrollment, allocation and analysis



Overall, both groups were well matched, but fewer patients in the intervention group were treated with insulin or prescribed a statin **(Table 1)**.

Table 1 | Baseline characteristics of participants in intervention and control group. Values are counts (percentages) unless stated otherwise.

	Intervention (n = 72)	**Control** (n = 81)
Male gender	39 (54.2)	50 (58.8)
Age (years) mean (SD)	70.0 (5.7)	68.5 (5.7)
Duration of type 2 diabetes (years) mean (SD)	10.2 (2.3)	10.8 (3.5)
Education *High* *Middle* *Low*	 12 (16.7) 23 (31.9) 37 (51.4)	 14 (17.3) 25 (30.9) 42 (51.9)
Living alone	17 (24.2)	13 (15.6)
Current smoking	8 (11.1)	11 (12.9)
Body weight (kg) Mean (SD)	83.8 (14.8)	87.9 (13.4)
HbA1c (mmol/mol) Median (IQR)	49.0 (10)	50.5 (9)
Systolic blood pressure (mmHg) Mean (SD)	138.1 (14.3)	137.2 (12.1)
Diastolic blood pressure (mmHg) Median (IQR)	78 (10)	77 (10)
Total cholesterol (mmol/l) Median (IQR)	4.0 (1.2)	4.1 (1.0)
LDL- cholesterol (mmol/l) Median (IQR)	2.2 (1.2)	2.2 (0.8)
Medication		
Oral diabetes medication	61 (84.7)	70 (82.3)
Insulin	8 (11.1)	16 (18.8)
Statin	54 (75.9)	68 (80.0)
Other lipid regulating drugs	5 (6.9)	6 (7.0)
Use of blood pressure lowering drugs	60 (83.3)	72 (84.7)
Comorbidities		
Cardiac	15 (20.8)	15 (17.6)
Stroke	3 (4.2)	3 (3.5)
Chronic lung disease	5 (6.9)	5 (5.9)
Peripheral arterial disease	5 (6.9)	5 (5.9)

During the study, seven participants deceased and four did not complete the final measurement. Dropout rates were similar in both groups **(Figure 1)**.

At baseline 26.4% of the 72 patients in the intervention group had achieved all treatment goals (control group: 23.5% of 81) **(Table 2)**.

Table 2 | Numbers and percentages of participants at target for HbA1c, SBP and total cholesterol at baseline and at 24 months.

	Intervention		**Control**	
	Baseline (n = 72)	Follow up (n = 66)*	Baseline (n = 81)	Follow up (n = 75)*
HbA1c	49 (68.1)	38 (57.6) 39 (54.2) 38 (52.8)	46 (56.8)	38 (50.7) 40(49.4) 38(46.9)
Systolic Blood pressure	37 (51.4)	43 (65.2) 46 (63.9) 43 (59.7)	35(43.2)	46 (61.3) 50 (61.7) 46 (56.8)
Total cholesterol	50 (69.4)	53 (80.3) 55 (76.4) 53 (69.4)	54 (66.7)	51 (68.0) 54 (66.7) 51 (63.0)
All three treatment targets	19 (26.4)	21 (31.8) 22 (30.6) 21 (29.2)	19 (23.5)	19 (25.3) 20 (24.7) 19 (23.5)

*Numbers and percentages after 24 months in case of complete cases (scenario 1), as last observation carried forward (scenario 2), and as 'not achieved' if the last measurement was missing (scenario 3).

After SDM 44 patients chose the intensive therapy: 10 of 13 patients continued their former intensive ADDITION therapy and 34 switched from less intensive to intensive. Twenty-eight patients chose the less intensive protocol: 25 continued their former treatment and three people switched from the more intensive to the less intensive protocol. During the first visit 45.8% of participants prioritised weight loss, while blood pressure and glycaemic control were prioritised by 25.0% and 20.8%, respectively. These percentages hardly changed during the 12 and 24 months follow-up visits. After 24 months follow-up the proportion of patients that achieved all three

targets had increased in the intervention group from 26.4% to 31.8% (n = 66); it remained stable in the control group (25.3% (n = 75), with a NNT of 13 and a non-significant relative risk of 1.26 (95% CI:0.81-1.95). If last value was carried forward the relative risk was 1.24 (95% CI 0.80-1.90). Assuming that dropouts did not achieve all three treatment targets, percentages were 29.2% (n = 72) and 23.5% (n = 81) respectively. After adjustment for practice level, patients in the intervention group still reached more often all three treatment goals, although the intervention effect was not significant (regression coefficients 0.277, p = 0.71). The proportion of participants that achieved two treatment goals (all combinations) was similar in both groups (39.4% in the intervention and 38.2% in the control group) **(Table 3)**.

Table 3 | Number of people (%) achieving 0 - 3 targets after 24 months, specified for specific targets and study group.

Number of targets	HbA1c	SBP	Total Cholesterol	Number (%) of patients	All patients
Intervention group (n = 66)				**Intervention group**	
n = 3				21 (31.8)	21 (31.8)
n = 2				3 (4.5)	
n = 2				12 (18.2)	26 (39.4)
n = 2				11 (16.7)	
n = 1				3 (4.5)	
n = 1				3 (4.5)	15 (22.7)
n = 1				9 (13.6)	
n = 0				4 (6.0)	4 (6.0)
	38 (57.6)	43 (65.2)	53 (80.3)		
Control group (n = 76)				**Control group**	
n = 3				18 (24.0)	19 (25.0)
n = 2				8 (10.7)	
n = 2				9 (12.0)	28 (37.3)
n = 2				11 (14.7)	
n = 1				5 (6.7)	
n = 1				9 (12.0)	26 (34.7)
n = 1				12 (16.0)	
n = 0				2 (2.7)	2 (2.7)
	38 (50.0)	46 (60.5)	51 (67.1)		

Seven participants in the intervention group and eight participants in the control group achieved all treatment goals both at baseline and after 24 months. No participant achieved all three treatment goals after 24 months if at baseline none targets had been achieved and vice versa. Four patients in the intervention group had achieved one goal at baseline and achieved all three treatment goals after 24 months, and one participant achieved the opposite. In the control group these numbers were three and two participants respectively. Four participants in the intervention group (control group: two) did not achieve any goal during the study period. From all the treatment goals, the target for total cholesterol was most often met in both groups (80.3% versus 67.1% respectively, ($p = 0.076$). Blood pressure decreased significant only in the intervention group (-5.4 mmHg, $p < 0.01$). Mean HbA1c, total cholesterol and BMI did not change during follow-up in either group. Between group differences were not significant **(Table 4)**.

	Intervention			**Control**					
	Baseline	2 years	p-value	Baseline	2 years	p-value	F	Mean difference	p-value
HbA1c (mmol/mol)	50.7 (9.6)	52.9 (11.1)	0.07	51.6 (9.0)	51.8 (7.0)	0.69	2.3	2.15	0.14
SBP (mmHg)	138.1 (14.3)	132.7 (15.3)	<0.01	137.2 (12.1)	135.7 (12.2)	0.11	2.1	-3.3	0.15
Total cholesterol (mmol/l)	4.2 (1.0)	4.2 (1.0)	0.98	4.3 (1.0)	4.2 (0.9)	0.09	0.84	0.13	0.36
BMI	29.6 (3.8)	29.4 (4.0)	0.48	30.1 (4.5)	30.0 (4.4)	0.53	1.71	-0.07	0.82

Table 4 | HbA1c, SBP, total cholesterol and BMI both at baseline and after 24 months. Means (SD) and p-values within and between groups.

* ANCOVA, adjusted for baseline value

Conclusions

This study shows that taking into account both patients' preferences with regard to the intensity of treatment, their priorities for the targets that should be achieved and making shared decisions in this respect resulted in a higher proportion of people who achieved all their treatment goals for both blood pressure, lipids and HbA1c. After 24 months, that proportion was around 30%, whereas it did not change in the control group. However, the difference between groups did not reach significance, which is possibly the result of a higher (24.8%) than expected (10%) proportion of participants that already had achieved all three treatment goals at baseline. The relative improvement was about 20% in the intervention group. Our primary outcome measure was based on intermediate biochemical endpoints, which is necessary to convince physicians to implement the SDM-goal setting approach within chronic care (Coulter et al., 2015). However, it is not only biochemical outcome that matter. From a Cochrane review it became clear that the use of a decision aid resulted in a significant improvement in many aspects of the decision making process with more accurate perceptions of health outcome probabilities, and more congruence between the chosen options and the persons' values (Stacey et al., 2017); (van Puffelen et al., 2015). We think it is important that in the OPTIMAL study the treating physician presented comparative evidence to the patient of two multifactorial treatment protocols and could demonstrate the possible impact of treatment-intensity on cardiovascular morbidity and mortality. Weight loss was the highest priority of most patients, both at baseline and after 12 and 24 months. However, body weight did not change over time. The direct effectiveness of weight loss on both intermediate and cardiovascular outcome could also have been presented to the patient, which might have been helpful in achieving the targets in this respect. To further increase the proportion of patients who achieve their treatment targets it is suggested to write the shared goals on a specific form both for the patient to take home and the physician to register in the medical records and also to discuss the agreed targets during 3-monthly check-ups with the practice nurse

(Coulter et al., 2015)*;* (Bodenheimer & Handley, 2009); (Lenzen et al., 2015). One might argue that the decision aid we used, based upon a study with treatment options that do not differ largely, will have limited effects on biomedical and clinical outcomes (Stacey et al., 2017). In a meta-analysis the pooled effect of personalised care planning with SDM-goal setting showed a small decrease of HbA1c of -0.24% (-0.35 to -0.14) and a -2.64 mmHg (-4.47 to -0.82) decrease in systolic blood pressure (Coulter et al., 2015). Compared to these results a larger decrease in SBP was found in the current study, but less in HbA1c. This result is not surprising considering the already low baseline levels of HbA1c.

Strength of the current study is that in the SDM process the treating physician could present evidence with a direct relation between intensity of treatment and so-called 'hard outcome'. Furthermore, the patients' usual diabetes care provider performed the SDM goal setting approach, which is an essential element in the context of chronic conditions. The follow-up time of 24 months with yearly recalibration of chosen goals reflects changes in conditions and side effects of interventions within chronic care. With a follow-up time of 24 months in 35 general practices with 208 intervention consultations we had a real pragmatic trial. In contrast to most RCTs, in the current study the percentage of participants with a high education was relatively low (17% high vs. 40% low educated) and therefore more representative for the average population with T2DM. However, several limitations should also be considered. For an optimal connection between Evidence Based Medicine and SDM in our intervention, the physician should have presented all available evidence with regard to the effectiveness of multifactorial diabetes treatment on cardiovascular outcomes. Given the diabetes duration in our study population of more than 10 years on average, the results of the STENO-2 study could have been included in the decision aid. (Gaede et al., 2008). Our decision aid did not mention explicitly how individual characteristics like age, diabetes duration or comorbidity had to be taken into account during the SDM process with regard to the intensity of the multifactorial

treatment. However, the way to achieve treatment targets was part of the SDM process acknowledging the clinicians' medical knowledge, the social context of the patient and the patients' preferences. Finally, we should realise that in SDM it is also important to set emotional and social management goals (Lenzen et al., 2015). In our intervention we did not measure this type of goals, which could be considered as a drawback.

To conclude, taking into account both patients' preferences with regard to the intensity of treatment and his/her priorities resulted in a higher proportion of people who achieve all treatment goals after two years. In this pragmatic trial in a substantial number of general practices with an already existing high baseline level of diabetes care we found strong indications that SDM on both intensity of treatment and prioritising treatment goals led to a further improvement of diabetes care.

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CHAPTER 6

SHARED DECISION MAKING IN PRIMARY CARE: PROCESS EVALUATION OF THE INTERVENTION IN THE OPTIMAL STUDY, A CLUSTER RANDOMISED TRIAL.

H. den Ouden, R.C. Vos, A.H. Pieterse, G.E.H.M. Rutten.

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ABSTRACT

Aims

To analyse the performance of a Shared Decision Making (SDM) intervention, we assessed perceived and experienced SDM in General Practitioners (GPs) and patients with type 2 diabetes (T2DM).

Methods

Cluster-Randomised Controlled Trial (cRCT) testing the effect of a decision aid. Opinions and experienced role regarding SDM were assessed in 72 patients and 18 GPs with the SDM-Q-9 (range 0-45) and Control Preferences Scale (CPS, 0-5), and observed SDM with the OPTION5 (0-20). SDM at baseline was compared to 24 months' follow-up using paired t-tests.

Results

At baseline, perceived levels of SDM did not significantly differ between GPs and patients with T2DM (difference of 2.3, $p = 0.24$). At follow-up, mean patients' perceived level of SDM was 7.9 lower compared to baseline ($p < 0.01$), whereas GPs' opinions had not changed significantly. After both visits, mean CPS scores differed significantly between patients and GPs. OPTION5 scores ranged between 6 and 20.

Conclusion

Patients and GPs perceived similar baseline levels of SDM. Two years later, patients perceived less SDM, while GPs did not change their opinion. SDM was appropriate immediately after training, but perhaps GPs fell back in old habits over time. We recommend repeated SDM training.

Introduction

The management of type 2 diabetes mellitus (T2DM) requires a multitude of decisions, each one entailing different combinations of possible therapeutic or adverse effects (Inzucchi et al., 2012); (Wilkinson et al., 2013). Therefore, T2DM patients need to be involved in determining the management strategy most consistent with their preferences and values (Davies et al., 2018). Shared Decision Making (SDM) is a healthcare decision making model that promotes patient involvement, and has been identified as the crux of patient-centred care (Bae, 2017). In SDM, both parties share information and expertise: the physician shares medical information about options and their benefits and risks, and T2DM patients share their preferences and values (Bomhof-Roordink et al., 2019). But how to implement SDM in daily practice? It has been demonstrated that general practitioners (GPs) can learn to deliver patient-centred care (Legare et al., 2013); (Coronado-Vazquez et al., 2020), and that options can be made clearer to patients using decision aids (Stacey et al., 2017). With regard to SDM, there is broad consensus about two core physician competencies that should be acquired during training. The first is *relational competence*, involving the creation of a favourable environment for communication, and an appropriate interaction during the clinical encounter. The second is *risk communication competence*, including discussion of uncertainty in treatment outcomes, and effective communication about benefits and risks of different treatment options (Legare et al., 2013); (Agoritsas et al., 2015); (Stacey et al., 2017); (Charles et al., 1997) highlighted the need for bidirectional information exchange, participation of both parties in deliberation and agreement about the resulting treatment plan. They developed their framework in the acute setting in which typically one-time decisions are made. Their framework is one of the most-often cited basis for later frameworks (Bomhof-Roordink et al., 2019). In 2006, Montori et al. modified it to make it applicable to the care of people with chronic conditions (Montori et al., 2006). This modification stressed the need for an ongoing partnership

between GP and patients with T2DM and the recognition that decisions in chronic care can be revised.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a decision cycle to manage hyperglycaemia in T2DM patients, to be used during consultations. It integrates current lifestyle, comorbidities, clinical characteristics, and issues such as patient preferences, motivation, diabetes-related distress, depression, and financial resources. SDM is explicitly integrated in the cycle and the cycle requests smart goals to be set (Davies et al., 2018).

We conducted a cluster-randomised controlled trial (cRCT, the OPTIMAL study) with a follow-up of 24 months to assess to what extent the implementation of SDM, based on the framework by Montori et al., would affect the proportion of T2DM patients who achieve all their treatment targets (glucose, systolic blood pressure, and LDL-cholesterol) (Den Ouden et al., 2015). Furthermore, we were interested in the experienced SDM 24 months after training, to evaluate the sustainability of the effect of SDM training. SDM was introduced using two elements: a decision aid for T2DM patients, combined with a training of GPs. Here we evaluate the SDM-process during the trial, aiming to answer the following research questions:

1. Did GPs and patients differ in their opinions regarding the extent to which SDM occurred during consultations at baseline and at 24 months follow-up?

2. Which decisional role did GPs and patients experience in making the final decision at baseline and at 24 months follow-up?

3. To what extent did the GPs adhere to the study protocol regarding the SDM elements?

Methods

Study design

The full details on the rationale and design of the study are described elsewhere (Den Ouden et al., 2015); (Den Ouden et al., 2017). In short, the OPTIMAL study was a Cluster-Randomised Controlled Trial (cRCT) with three annual reviews by the GP (at baseline and at 12- and 24-months follow-up). The intervention aimed at fostering SDM about diabetes treatment targets by means of a decision aid and SDM training for the GPs. The decision aid was designed according to the International Patient Decision Aids Standards (International Patient et al., 2005**)**, and based on the results of the ADDITION study, which ran between 2002 and 2009 (Griffin et al., 2011) (see below).

The study protocol was registered at ClicialTrials.gov (NCT02285881) and was approved by the Medical Ethical Committee of the University Medical Centre Utrecht (Protocol number: 11-153). All patients provided informed consent before entering the study.

Practices and patients

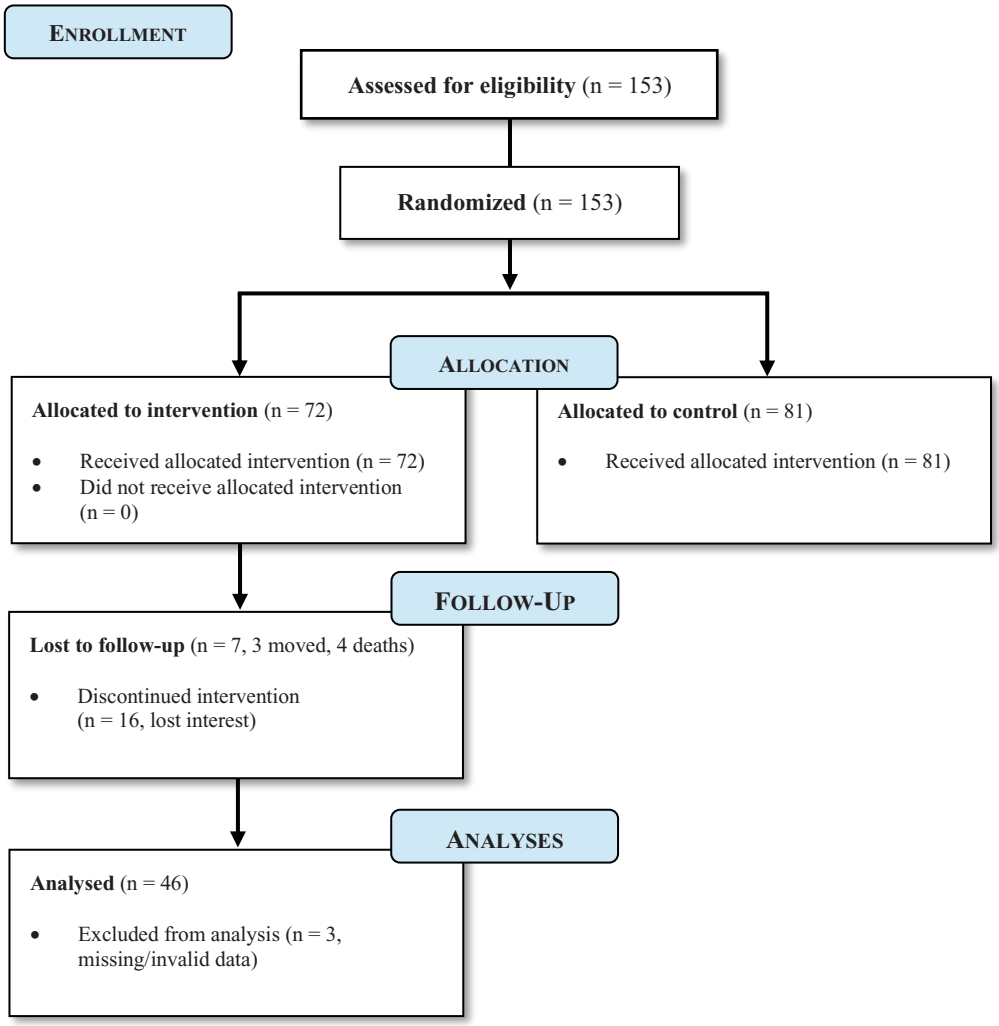
All 79 practices that had participated in the ADDITION study were invited to participate in the OPTIMAL study. Of these, 35 practices responded, and in each practice one GP participated in the study. Practices were randomised, resulting in an intervention (n = 18) and a control (n = 17) group. Randomisation was executed at the research centre at practice-level, without stratification. All participating GPs included at least one person with T2DM with either of the following sets of characteristics: 1. Screen-detected with T2DM between 2002 and 2004, aged between 50-70 years at time of diagnosis, and participated in the ADDITION study; 2. Diagnosed with T2DM for eight to 12 years, aged between 60 and 80 years at study entry, and did not participate in the ADDITION study. Patients from outside the ADDITION study were allowed to participate, as long as they were comparable in terms of age and time since diagnosis (summarised in **Table 1**).

Table 1 |. Characteristics of patients in the intervention group at the first visit (n = 72). Values are means (SD) or percentages unless stated otherwise.

Physical Characteristics	
Male sex - n (%)	39 (54.2)
Age (years)	70.0 (5.7)
Duration of type 2 diabetes (years)	10.2 (2.3)
Education High / Middle / Low	16.7%/ 31.9%/ 51.4%
Living alone - n (%)	17 (24.2)
Current smoking - n (%)	8 (11.1)
Body weight (kg)	83.8 (14.8)
HbA1c (mmol/mol) Median (IQR)	49.0 (10)
Systolic blood pressure (mmHg)	138.1 (14.3)
Diastolic blood pressure (mmHg)	78.0 (10)
Total cholesterol (mmol/l) Median (IQR)	4.0 (1.2)
LDL- cholesterol (mmol/l) Median (IQR)	2.2 (1.2)
Medication	
Oral diabetes medication - n (%)	61 (84.7)
Insulin - n (%)	8 (11.1)
Statin - n (%)	55 (75.9)
Other lipid regulating drugs - n (%)	5 (6.9)
Blood pressure lowering drugs - n (%)	60 (83.3)
Comorbidities	
Cardiac - n (%)	15 (20.8)
Stroke - n (%)	3 (4.2)
Chronic lung disease - n (%)	5 (6.9)
Peripheral arterial disease - n (%)	5 (6.9)

Patients with a history of alcoholism, drug abuse, psychosis, personality disorder or another emotional, psychological or intellectual problem that was likely to invalidate informed consent, were excluded **(Figure 1)**.

Figure 1 | CONSORT flow diagram of patient enrollment, allocation and analysis



In order to assess the sustainability of the intervention, only participants from the intervention group are described and analysed here.

SDM intervention: Development and content

The SDM intervention consisted of making a shared decision using a decision aid and training the GPs in SDM. Consequently, this decision aid first needed to be

developed. Therefore, all GPs in the intervention group were approached twice. First, to develop the decision aid; under the guidance of an OPTIMAL study researcher, 15 GPs working in OPTIMAL intervention practices had a discussion about SDM in five groups of three GPs. The purpose was to review the decision aid that the researchers had drafted. Several propositions about SDM were discussed. We checked whether the GPs thought more treatment targets would be achieved through SDM. Besides, the ADDITION study was once again explained and discussed with the GPs, to determine to what extent they agreed with the conclusions of the study and to know the background of the decision aid. Specifically, the ADDITION study included screen detected T2DM patients and compared an intensive multifactorial treatment with less intensive usual care according to national guidelines. The intensive treatment was associated with a significant increase in prescribed medications and a non-significant 17% reduction of cardiovascular events and death after five years. The rate of cardiovascular events seemed to diverge after four years of follow-up. It was concluded that intensified treatment and treatment according to national guidelines can theoretically be equally effective. Following this session, the decision aid was finalised. Secondly, all participating GPs from the intervention group received a one-hour training, during which the definitive decision aid was presented and explained. The study protocol was discussed and SDM principles were reviewed to foster a common understanding of SDM processes.

The final decision aid described both treatment options, indicating their possible beneficial and adverse effects. The more intensive regime aimed for stricter treatment targets, and the less intensive regime aimed for less strict targets, meaning less medication. The different thresholds and treatment targets were as follows. Less intensive therapy: blood pressure < 140 mmHg; total cholesterol < 4.5 mmol/L; in case of cardiovascular disease < 3.5 mmol/L; HbA1c < 53 mmol/mol; stop smoking and a shared decision about weight loss. Intensive treatment: blood pressure < 135/85

mmHg; total cholesterol < 3.5 mmol/L; HbA1c < 48-53 mmol/mol; stop smoking and if BMI > 27 five percent weight loss (Den Ouden et al., 2015).

In the first step of the decision aid T2DM patients could choose between usual or intensified diabetes care and secondly to prioritise which treatment targets they would like to achieve first; it provided a systematic ranking of the five treatment targets. Patients made a treatment decision based on their preference and prioritised treatment goals during the first consultation. Patients who had been treated according to the Dutch guidelines, i.e., the less intensive regimen, in or outside the ADDITION trial, could change their therapy to the intensified treatment, and vice versa. Following that choice, the patients were not allowed to switch between the intensive and less intensive treatment during the study period. The decision aid was used again during the 12 months follow-up visit, providing the patient the possibility to change treatment priorities. After the last visit at 24 months follow-up, patients could change treatment intensity and re-evaluate their priorities.

Patients in the control group received treatment-as-before, as they were used to in or outside the ADDITION study.

Outcome measures

The GPs' and patients' perceived levels of SDM were measured at baseline and at 24-months follow-up, using the validated Dutch translations of the SDM-Q-9-Doc (physician version) and SDM-Q-9 (patient version) questionnaires (Rodenburg-Vandenbussche et al., 2015) (Kriston et al., 2010) (Scholl et al., 2012). Both questionnaires include nine items to be answered on a six-point Likert-type scale, ranging from 0 (completely disagree) to 5 (completely agree) **(Table 1)**.

The total scores range from 0 to 45, with higher scores representing more perceived SDM; the questionnaire developers did not describe thresholds for poor SDM.

The perceived actual role in making the final decision at baseline and at 24-months follow-up was assessed using the modified Control Preferences Scale (CPS) (Degner et al., 1997). The CPS consists of five role descriptions, which for the patients are

the following: 1: 'I made my decision alone', 2: 'I made my decision alone, considering what my doctor said', 3: 'I shared the decision with my doctor', 4: 'My doctor decided, considering my preferences', 5: 'My doctor made the decision'. The role descriptions are mirrored for the GP. A score of 3 may be considered as describing a shared decision-making process. The modified patient-version of the CPS has shown good reliability and validity (Kasper et al., 2011). Participants (GPs and patients) were asked to complete a paper-based questionnaire after their first and last visit, and were given a return envelope. Participants in both groups will be asked to complete and return the following questionnaires at baseline and after 24 months at home.

Observed SDM was assessed using the OPTION5. The OPTION 5-item observation measure is a coding scheme of how much SDM occurred from an observer's perspective. Independent observers rate recordings of actual consultations using the 5 items, scored on a zero (no effort made by clinician to involve the patient) to four (exemplary effort) scale. Item scores are added and higher total scores imply higher degrees of SDM. Total scores range from 0 to 20 (Driever et al., 2020). Two independent observers (one psychologist and one GP, both experienced in assessing audiotapes of GP consultations on SDM) applied the scheme directly to the audiotapes. For that purpose, GPs were asked to audiotape one first consultation with a self-selected participant.

Statistical analyses

Descriptive statistics (means, standard deviations) were used to report patient characteristics, GP and patient scores on the questionnaires, and OPTION5 scores, per practice. The median with interquartile range was reported for HbA1c, total cholesterol and LDL-cholesterol, as a normal distribution could not be confirmed. We defined low, medium and high education levels as having completed only elementary school, secondary education, and university (of applied sciences), respectively. We evaluated the differences in levels and correlation of perceived

SDM (SDM-Q-9) and decisional roles (CPS) between GPs and patients who completed the intervention, both at baseline and at 24 months follow-up, using paired t-tests. This same approach was used to evaluate the differences in levels and correlation of perceived levels of SDM (SDM-Q-9) and decisional roles (CPS) between baseline and follow-up for GPs and patients. The differences between the drop-outs and completers were evaluated with the independent samples t-test.

Results

At 24 months follow-up, 23 out of 72 patients had dropped out of the study and three patients had incomplete data **(Figure 1)**. At baseline, the average age of the intervention participants with T2DM was 71 (SD 5.6) years. At baseline, the 23 drop-outs did not significantly differ in age (72 (SD 5.5) vs 70 (SD 5.5) years, p = 0.10) or self-reported SDM score (31.7 (SD 12.5) versus 36.6 (SD 9.8), (p = 0.08) compared to completers. Significantly more women (65%) than men dropped out of the study (p = 0.02).

The mean item scores on the SDM-Q-9 and SDM-Q-Doc questionnaires are summarised in **Table 2**.

Table 2 | Mean (SD) item scores on the SDM-Q-9 (patients*) and SDM-Q-Doc (GPs) at baseline and 24-months follow-up.

	Item	***Baseline*** *(n = 46)*	***Follow-up*** *(n = 46)*
1.	***My doctor made clear that a decision needs to be made.***	3.2 (1.9)	2.6 (2.0)
	I made clear to my patient that a decision needs to be made.	3.8 (1.2)	3.7 (1.1)
2.	***My doctor wanted to know exactly how I want to be involved in making the decision.***	3.6 (1.6)	3.0 (2.0)
	I wanted to know exactly from my patient how he/she wants to be involved in making the decision.	3.7 (0.9)	3.5 (1.1)

3.	***My doctor told me that there are different options for treating my medical condition.***	3.8 (1.6)	2.8 (1.9)
	I told my patient that there are different options for treating his/her medical condition.	3.7 (1.0)	3.7 (1.1)
4.	***My doctor precisely explained the advantages and disadvantages of the treatment options.***	4.3 (1.2)	2.7 (2.0)
	I precisely explained the advantages and disadvantages of the treatment options to my patient.	3.6 (1.1)	3.6 (1.1)
5.	***My doctor helped me understand all the information.***	4.3 (1.2)	3.4 (1.9)
	I helped my patient understand all the information.	4.0 (0.8)	4.0 (1.0)
6.	***My doctor asked me which option I prefer.***	4.4 (1.2)	3.3 (2.3)
	I asked my patient which treatment option he/she prefers.	4.1 (1.0)	4.0 (1.0)
7.	***My doctor and I thoroughly weighted the different treatment options.***	4.3 (1.2)	2.9 (2.0)
	My patient and I thoroughly weighed the different treatment options.	3.7 (0.9)	3.4 (1.1)
8.	***My doctor and I selected a treatment option together.***	4.2 (1.3)	3.3 (2.2)
	My patient and I selected a treatment option together.	4.0 (1.0)	3.6 (1.1)
9.	***My doctor and I reached an agreement in how to proceed.***	4.4 (1.2)	3.2 (2.0)
	My patient and I reached an agreement on how to proceed.	4.1 (0.8)	3.9 (1.1)
Total		**36.6 (9.9)**	**28.6 (14.2)**
		34.3 (7.0)	**32.8 (8.3)**

** Patient items and scores are shown in grey shading*

The differences between baseline and follow-up scores appear to be more substantial in patients compared to GPs, with a maximum reduction of 1.6 in patients (item 4) and a maximum reduction of 0.4 in GPs (item 8).

The mean scores on the SDM-Q-9, SDM-Q-Doc and CPS questionnaires are summarised in **Table 3**.

Table 3. | Mean scores (SD) of SDM-Q-9, OPTION-5 and CPS of patients (completers) and GPs per practice in the intervention group. Patient scores are on the upper line, physician scores on the lower line.

	First visit			**Follow-up**	
GP (number of patients)	SDM-Q-9 (t = 0)	CPS (t = 0)	OPTION-5*	SDM-Q-9 (t = 24)	CPS (t = 24)
1 (n = 4)	35.8 (5.6) 39.0 (2.2)	n.d. n.d.	n.d.	20.0 (11.9) 32.5 (4.5)	2.3 (1.0) 3.3 (1.0)
2 (n = 1)	43.0 (n = 1) 25.0 (n = 1)	1.0 (n = 1) 5.0 (n = 1)	n.d.	18.0 (n = 1) 24.0 (n = 1)	3.0 (n = 1) 4.0 (n = 1)
3 (n = 1)	27.0 (n = 1) 33.0 (n = 1)	4.0 (n = 1) 5.0 (n = 1)	n.d.	32.0 (n = 1) 35.0 (n = 1)	4.0 (n = 1) 2.0 (n = 1)
4 (n = 5)	38.8 (6.1) 33.4 (3.9)	2.2 (0.8) 4.2 (0.4)	15 16 (16)	22.6 (13.5) 32.3 (2.0)	3.0 (0.7) 1.0 (n = 1)
5 (n = 4)	29.0 (25.1) 33.5 (13.3)	3.0 (1.6) 3.0 (0.0)	6 9 (9)	22.3 (17.9) 26.3 (6.2)	3.0 (0.8) 3.0 (1.4)
6 (n = 3)	40.0 (3.5) 39.3 (6.4)	1.7 (1.2) 5.0 (0.0)	20 20 (20)	39.7 (4.6) 43.0 (1.0)	2.7 (0.6) 3.0 (0.0)
7 (n = 1)	35.0 (n = 1) 36.0 (n = 1)	2.0 (n = 1) 4.0 (n = 1)	n.d.	26.0 (n = 1) 33.0 (n = 1)	4.0 (n = 1) 4.0 (n = 1)
8 (n = 3)	38.7 (7.6) 34.7 (6.1)	2.0 (1.0) 3.7 (1.5)	n.d.	22.0 (16.6) 26.7 (1.5)	3.7 (1.2) 3.0 (1.4)
9 (n = 2)	41.5 (0.7) 35.0 (1.4)	n.d. n.d.	18 19 (19)	40.0 (2.8) 18.0 (25.5)	3.0 (0.0) 4.0(1.4)
10 (n = 4)	25.8 (19.0) 31.5 (1.3)	1.0 (0.0) 3.0 (0.0)	18 18 (18)	35.8 (14.6) 41.3 (0.5)	2.5 (1.0) 3.0 (0.0)
11 (n = 1)	40.0 (n = 1) 36.0 (n = 1)	n.d. n.d.	n.d.	38.0 (n = 1) 36.0 (n = 1)	2.0 (n = 1) 4.0 (n = 1)

12 (n = 1)	40.0 (n = 1) 34.0 (n = 1)	n.d. n.d.	n.d.	29.0 (n = 1) 41.0 (n = 1)	2.0 (n = 1) 5.0 (n = 1)
13 (n = 3)	41.0 (6.1) 35.7 (0.6)	3.0 (n = 1) 3.0 (n = 1)	n.d.	22.3 (22.5) 28.0 (1.7)	2.7 (0.6) 3.0 (0.0)
14 (n = 2)	36.5 (3.5) 26.5 (2.1)	2.0 (1.4) 2.5 (2.1)	15 16 (16)	36.0 (4.2) 30.5 (4.9)	2.0 (n = 1) 2.0 (n = 1)
15 (n = 1)	44.0 (n = 1) 37.0 (n = 1)	n.d. n.d.	20 20 (20)	41.0 (n = 1) n.d.	3.0 (n = 1) n.d.
16 (n = 1)	31.0 (n = 1) 9.0 (n = 1)	n.d. n.d.	20 20 (20)	45.0 (n = 1) 23.0 (n = 1)	2.0 (n = 1) 3.0 (n = 1)
17 (n = 4)	43.0 (2.4) 31.8 (1.5)	2.8 (1.3) 2.5 (0.6)	n.d.	37.3 (8.1) 31.5 (2.1)	3.0 (n = 1) 3.3 (0.6)
18 (n = 5)	34.2 (7.3) 41.0 (5.6)	n.d. n.d.	10 9 (11)	21.8 (19.1) 41.4 (3.0)	2.3 (1.2) 3.3 (0.6)
Total	36.6 (9.9) 34.3 (7.0)	2.3 (1.2) 3.6 (1.1)	16.6 (1.4)	28.6 (14.2) 32.8 (8.3)	2.8 (0.8) 3.2 (1.0)
Missing/invalid	n = 3** n = 0	n = 19 n = 19	n.a.	n = 4** n = 3	n = 6 n = 14

n.d. = not determined, n.a. = not applicable

* Values of two independent observers, the value after consensus between both observers is indicated between brackets. Mean of the total was calculated from the consensus values.

** Three patients did not respond at the first visit and another four people did not respond after follow-up.

At baseline, GPs' and patients' perceptions of SDM levels did not significantly differ: the mean difference was 2.3 (p = 0.24, **Table 4**).

Table 4. | Paired t-test means (SD) of SDM-Q-9 and CPS in the intervention group, patient scores are on the upper line, physician scores on the lower line.

	SDM-Q-9			**CPS**		
Pair	**First visit**	**24 months follow-up**	**Mean difference** (95%CI, p-value)	**First visit**	**24 months follow-up**	**Mean difference** (95%CI, p-value)
Patient t = 0 **vs** **Patient** t = 24	**36.6** (9.9, n = 45)	**28.6** (14.3, n = 45)	**-7.9** (-3.8 - 12.0, p < 0.01)	**2.3** (1.1, n = 23)	**3.0** (0.9, n = 23)	**0.7** (0.1 - 1.4, p = 0.04)
Doctor t = 0 **vs** **Doctor** t = 24	**34.1** (7.2, n = 44)	**32.8** (8.3, n = 44)	**-1.3** (-4.1 - 1.4, p =0.34)	**3.6** (1.1, n = 18)	**2.9** (1.0, n = 18)	**-0.6** (-1.4 - 0.2, p =0.11)
Patient t = 0 **vs** **Doctor** t = 0	**36.6** (9.9, n = 45) **34.2** (7.1, n = 45)		**2.3** (-1.6 - 6.2, p = 0.24)	**2.3** (1.2, n = 27) **3.6** (1.1, n = 27)		**1.3** (2.1 - 0.6, p < 0.01)
Patient t = 24 **vs** **Doctor** t = 24		**28.2** (14.4, n = 44) **32.8** (8.3, n = 44)	**-4.6** (-9.6 - 0.4, p = 0.07)		**2.7** (0.9, n = 28) **3.3** (1.0, n = 28)	**0.6** (1.1 - 0.0, p = 0.05)

At 24-months follow-up, the perceived SDM level was lower in patients compared to GPs (-4.6; p = 0.07). In patients, it had decreased significantly and was -7.9 lower (p < 0.01) than at baseline, whereas the GPs' perceived level of SDM remained more or less unchanged (difference of -1.3 (p = 0.34) at 24-months follow-up. There was no significant correlation between initial and follow-up scores.

After both visits, the mean CPS score differed significantly between patients and GPs, with -1.3 (p < 0.01) at baseline and -0.6 (p = 0.05) at 24 months follow-up **(Table 4)**. At 24-months follow-up, the patients' CPS score had increased with 0.7 (p = 0.04), whereas GPs' CPS scores decreased with on average -0.6 (p = 0.11). There was no significant correlation between initial and follow-up scores.

Nine GPs audiotaped a consultation. The mean OPTION5 score was 16.6. Three practices had a score of 20 after consensus and one practice scored below 10 after consensus. The practice with the lowest OPTION5 score did not have the lowest score on the questionnaires among the tested practices **(Table 3)**.

Discussion

This study shows that GPs and patients did not significantly differ in how much SDM they perceived during the first visit, when they first used the decision aid. However, patients experienced their role in making the final decision to be significantly more shared, while GPs experienced their own role to be more important. Regardless, we can conclude that both GPs and patients perceived to have shared the decision about treatment intensity, at the time they first used the decision aid. In contrast, patients perceived significantly less SDM during the follow-up visit 24 months later, while the GPs perceived the same level of SDM as during the first visit.

At first sight, perceived decisional roles and perceived levels of SDM seem contradictory: both patients' and GPs' experienced roles in making the final decision about treatment intensity during the 24 months' follow-up visit were almost identical and had both shifted significantly towards a shared decision (Kasper et al., 2011). However, decisional roles were not recorded for all the patients and GPs: the decisional roles were self-reported after the consultation, while perceived levels of SDM were assessed during the consultation. This may have led to self-report bias in the reported decisional roles.

Looking at the specific aspects of the decision-making process, differences between the consultation in which the decision aid was first used and the 24 months' months follow-up visit became apparent. In particular, GPs reported the largest reduction with regard to selecting the treatment option together. Possibly, the GPs' role became more important in the decision-making process during the intervention, which contradicts the reported decisional role. Patients reported to have been less informed by their GP during the follow-up visit. Taken together, these results suggest that GPs made less effort to explain the options well and to decide on the best treatment option together with the patient during follow-up. On the other hand it might be speculated that because a high degree of SDM took place at baseline, there was less need for a

SDM discussion at follow-up. It is known that GPs perceive barriers to implement SDM consequently in daily practice (Driever et al., 2020); (Alsulamy et al., 2020); (Pel-Littel et al., 2021). Against this background, it would be valuable to study the effect of repeated SDM training on sustaining high levels of SDM.

Similar to a previous study, the participating GPs in the current study experienced their own role in the SDM process to be quite important (Driever et al., 2020); they tended to limit SDM to only discussing treatment options and paid considerably less attention to other key elements of the SDM process. It appears that GPs should be more specifically trained to pay attention to other elements of the SDM process, in order to achieve a truly shared decisions with their patients. Patients' experiences at follow-up indicate the relevance of increasing GPs'awareness about what a shared decision making process entails, and how to involve patients actively in it.

A number of limitations of the study should be noted. Overall, the number of participants was low. This decreases the changes of finding subtle differences between baseline and follow-up. Additionally, there was a high number of drop-outs, but they did not significantly differ in perceived levels of SDM at baseline compared to the completers. Perhaps the drop-outs lost their interest in the study because they already felt well-involved in making the treatment decision (Doherr et al., 2017), did not believe their decision making could be improved, or did not have the time/motivation to fill in the questionnaires. Furthermore, the OPTION5 scores are based on recordings of a self-selected consultation. Since this is susceptible to reporting bias, the OPTION5 scores are only reported and not discussed.

In conclusion, patients with T2DM and GPs perceived similar and high levels of SDM at the time they first went through the decision aid and made a decision about treatment intensity, which also was shortly after the GPs had received SDM training. Twenty-four months later, GPs perceived similarly high levels of SDM while

patients perceived significantly less SDM. These results suggest that if the intervention was effective in helping achieve SDM shortly after GPs had been trained, boost sessions seem necessary to consolidate and understand key SDM elements and truly incorporate them into routine clinical practice.

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CHAPTER 7

SUMMARY AND GENERAL DISCUSSION

SUMMARY AND GENERAL DISCUSSION

In this thesis, different aspects of modern type 2 diabetes mellitus (T2DM) care are investigated, namely personalised medicine and patient-centred T2DM care with Shared Decision Making (SDM). The hypothesis is that a personalised and patient-centred approach improves care and leads to better clinical outcomes.

The dissertation consists of two parts. Part 1 focuses on personalised medicine, including metabolomics and inflammation among patients in the ADDITION cohort. The second part presents results of the patient-centred OPTIMAL study with shared decision making in former ADDITION practices. The results are successively discussed in the different parts.

Part 1: metabolomics

In the United States the top 10 highest grossing drugs help only up to 25% of the people who take them. Non-adherence to prescribed medication, related to adverse effects, is part of the reason for this disappointing percentage. Besides, the number needed to treat (NNT), derived from randomised clinical trials, is often quite high. Therefore a more personalised diabetes treatment is warranted. Precision medicine or personalised medicine is medical care designed to optimise therapeutic benefit for particular groups of patients, by using genetic or molecular profiling (Pintus et al., 2017). It combines data conventionally used for diagnosis and treatment like signs, symptoms, personal/family history and complementary exams, with the genetic or metabolomic profile of an individual. Its success highly depends on the patients' classification, the characterisation of the disease, its follow-up (the course of the disease over a longer period) and the way the treatment could be optimised (Beger et al., 2016); (Lepine et al., 2022); (Letertre et al., 2021). Medication changes the patients metabolic profile. In the pharmaceutical science field, pharmacometabolomics has arisen from the metabolomics research field to achieve

enhanced and systemic understanding of mechanisms for drug effects. They try to improve the prediction of individual variations in drug response phenotypes, based on both baseline metabolic profiles prior to treatment and on the effects of drug treatment over time. Clinically, pharmacometabolomics are anticipated to find novel response pathways or biomarkers, and to be combined with pharmacogenomics for understanding drug effects.

The globally most widely used medications in T2DM are metformin and sulphonylureas (SUs). Metformin acts as an insulin sensitizer, suppressing hepatic glucose production and ameliorating insulin resistance in peripheral tissues. In addition, metformin promotes glycogen synthesis and decreases intestinal glucose absorption (Kim, 2021). Compared with placebo, it lowers HbA_{1c} with on average 11mmol/mol. Compared with sulphonylureas, it is unclear whether metformin and sulphonylureas differ in effectiveness at reducing HbA_{1c} (low-quality evidence) (Gorter et al., 2012).

Good glycaemic control with metformin may reduce overall mortality in obese patients with type 2 diabetes, with an NNT of 14 for 10 years in the United Kingdom Prospective Diabetes Study (O'Connor et al., 1998). In a smaller Dutch study the NNT to prevent one macrovascular end point was 16.1 for 4.3 years, with a wide 95% confidence interval (95% CI, 9.2-66.6) for metformin (Kooy et al., 2009).

SUs stimulate insulin release in a glucose-independent manner and may reduce microvascular complications. SUs lower HbA_{1c} by on average 10-20 mmol/mol (Inzucchi et al., 2012) (DeFronzo, 1999). Yudkin et al. calculated the NNT for 10 years to prevent one myocardial infarction or stroke to be 29.4 (Yudkin et al., 2010).

Newer medication as SGLT2i and GLP-1RA have on average higher NNT for cardiovascular outcomes. In the EMPA-REG OUTCOME study for SGLT2i the NNT was 63 (34-882) for 3.1 years. (Zinman et al., 2015) and in the DECLARE-TIMI58 study it was 104 (66-355) for 4.2 years (Wiviott et al., 2019). With respect to GLP-1 RA different studies show NNT of 56 (33-243) for 3.8 years (LEADER

study), 45 (28-235) for 2.1 years (SUSTAIN-6 study) and 67 (38-80 3) for 5.1 years (REWIND study) (Marso et al., 2016); (Hernandez et al., 2018); (Ludwig et al., 2020). Because of these relatively high NNT and because of higher costs, type 2 diabetes treatment usually starts with metformin and / or a sulphonylurea.

A research goal for this thesis is to predict, based on the patients' metabolic profile, which of these two medications best fits the individual patient and may further lower the NNT for cardiovascular outcomes.

In the Dutch part of the ADDITION study 498 screen-detected T2DM patients were randomised to intensified multifactorial treatment (n = 255) or routine care (n = 243). In 346 of these patients metabolites were measured by GC-MS in baseline samples. The response to treatment with metformin and/or SU was analysed to identify metabolites predictive of five-year HbA_{1c} change by multiple regression analysis. The primary outcome was the relative HbA1c change after five years. Spearman correlations were calculated on all GC-parameters (= GC-MS metabolite) and relative HbA1c change ((HbA_1c_{t5}-HbA_1c_{t0}/HbA_1c_{t0}) x100%) without stratifying for medication groups (n = 346) and among all subjects with HbA_{1c} > 6.5% at start of the study (n = 219).

Only baseline glucose and 1,5 anhydro-glucitol were associated with HbA_{1c} decrease in all medication groups, which means that these metabolites do not differentiate between metformin, SU or metformin plus SU. As a result, they are likely not helpful to ameliorate the choice of starting diabetes treatment with, for example, metformin alone or a combination of metformin and SU. In patients on SU no other metabolite was associated with HbA_{1c} decrease. A larger set of metabolites was associated with HbA_{1c} change in the metformin and in the combination therapy (metformin + SU) groups. These sets included metabolites related to several mechanisms. First to liver metabolism, namely 2-hydroxybutanoic acid, 3-hydroxybutanoic acid, 2-hydroxypiperidine and 4-oxoproline. Metabolites involved in oxidative stress (mannose, xanthine and uric acid) were higher at baseline when the HbA_{1c} decrease was larger in the metformin and SU group. The associations between baseline

metabolites and responsiveness to medication are in line with their mode of action. In conclusion, the identified metabolites are biologically plausible to predict response to the different blood glucose lowering treatments.

However, when the results were adjusted for baseline HbA_{1c} values, several baseline metabolite concentrations lost statistical significance, which indicates that certain baseline metabolite concentrations were driven by baseline HbA_{1c} levels.

No comparable research is available in which patients were not yet taking glucose lowering medication for their diabetes. On the website https://clinicaltrials.gov, there appear to be two additional studies with diabetes medication and metabolomics, but both studies lack metabolite measurements of people with T2DM before starting any glucose lowering medication. Nor are there any studies that look specifically at metabolomics in combination with metformin or SU treatment. Therefore, our study provides valuable information on the metabolites associated with the start of glucose lowering medicines.

If the results could be replicated in other populations of newly diagnosed T2DM patients, the most promising predictive candidates in the metformin group are 4-oxoproline (p 0.002) and glutamic acid internal amide ($p < 0.0001$). In the metformin + SU group 2-hydroxypiperidine (p 0.002) and pseudouridine (p 0.007) and in the SU group fumaric acid ($HbA_{1c} > 6,5\%$) (p 0.044). These candidates might be tested to assess whether they could indeed differentiate between the three starting options, namely metformin monotherapy, SU monotherapy or combination therapy, If so, they could enhance personalised treatment. The results are not very promising in this respect. Because of multiple testing, they are prone to false positive findings. Indeed, after adjusting the p-values for multiple testing, only changes in metabolite concentrations of glucose dysregulation remained significant, namely glucose and 1,5 anhydro-glucitol. Exactly these two metabolites did not differentiate between metformin and SU.

A second methodological remark has to be made. Although there is certainty of the prescription of metformin and/or SU in the study population, the dosage and duration

of the SU and metformin use during the follow-up period of six years are uncertain. The impact of this lack of information cannot be assessed here.

Applicability of results

Although a great deal of effort has been made in the area of metabolomics to date, there are still multifaceted challenges. Technically, when compared with other –omics, especially genomics and transcriptomics, that have achieved great standardisation, the application of clinical metabolomics is hindered by its interlaboratory variations among different experiments. Studies in clinical pharmacology involve large sample sizes, which require highly reproducible and reliable metabolomics analyses. Further advancements in global metabolite profiling are needed, especially in methodological standardisation, to enable more consistent and reproducible data across various metabolomics laboratories and centres. Determining metabolites with improved accuracy and precision will allow investigators to detect subtle differences in metabolic phenotypes.

Metabolomics studies of large populations and patient cohorts may help to achieve more unbiased clinical data for better understanding of the drug response and offer better predictive power for outcome evaluation (Pang et al., 2019). Randomised controlled trials are needed to uncover potential biomarkers for treatment effect, response and toxicity. Besides, analyses are required that are capable of generating a far more comprehensive metabolic signature (Beger et al., 2016). A large study was recently published on genomics and GLP1RA and the authors also emphasize that large studies are needed to develop personalised medicine. In this genome-wide analysis they included 4571 adults with T2DM treated with GLP-1 RA with baseline HbA1c of 7% or more (53 mmol/mol). The primary endpoint was HbA1c reduction at 6 months after starting GLP-1 receptor agonists. They evaluated variants in GLP1RA, then did a genome-wide association study and gene-based burden tests. Clinically, when genotype is routinely available at the point of prescribing,

individuals with ARRB1variants might benefit from earlier initiation of GLP-1 receptor agonists (Dawed et al., 2023).

To conclude, this study in screen-detected diabetes patients identified multiple metabolites that may be predictive of whether metformin or SU is the best first choice to start blood glucose lowering medication. Further research with metformin, SUs, SGLT2i and GLP-1RA is needed. A personalised choice of blood glucose lowering treatment in T2DM, is still far away.

Part 1: hs-CRP and adiponectin

One of the options to make T2DM care more tailored to the patient, to personalise it, is the use of relevant biomarkers. Several biomarkers have already been highlighted as 'risk-enhancing factors' in the 2019 ACC/AHA prevention guideline. These include elevated low-density lipoprotein cholesterol (LDL-C), persistently elevated triglycerides (TG), elevated lipoprotein (a), apolipoprotein B, and high-sensitivity C-reactive protein (hs-CRP) (Sweeney et al., 2021).

In primary prevention, evaluation of the inflammatory biomarker hs-CRP adds prognostic information to conventional measurements of cardiovascular risk with a magnitude of effect comparable to that of LDL or high-density lipoprotein cholesterol (Elimam et al., 2019); (Ridker, 2018). Hs-CRP is the most well studied biomarker for assessing inflammation and the most used in research and clinical practice (Denegri & Boriani, 2021); (Sethwala et al., 2021); (Berk et al., 1990; Ridker, 2016). A proposed strategy for targeting residual cardiovascular risk incorporates measurement of hs-CRP, so that an individualised treatment plan to lower cardiovascular risk in patients can be made (Ridker, 2018).

We could demonstrate a continuing and significant decrease of hs-CRP in screen-detected T2DM patients during six years of multifactorial treatment. Changes in the intensive treatment group were significantly greater than those in the routine care group.

Adjustment for lipids or statin use did not change the results, suggesting that the decrease of hs-CRP levels is not only an effect of statin use. In other studies short-term treatment with metformin or insulin did not reduce hs-CRP levels despite improving glucose control (De Jager et al., 2005); (Pradhan et al., 2009). Adjustment for other potential intermediates such as acetylsalicylic acid use or HbA_{1c} did not alter these findings either. Therefore, a multifactorial treatment seems to have an independent effect on hs-CRP-levels. Besides the effect of statin and blood pressure lowering medication and maybe the effect of glucose-lowering on hs-CRP, one plus one makes three, resulting in an independent beneficial effect on hs-CRP, so on the infection parameter, on residual risk (Ridker, 2018).

No other studies were found that look at the course of inflammation over time in screen-detected diabetes patients, which increases the importance of our study.

So far, in a multifactorial therapy of T2DM, not only glucose lowering, blood pressure management and dyslipidaemia treatment should be combined, but fighting inflammation might be an additional purpose. Recently, studies have been published in which inflammation was counteracted with target therapy. The CANTOS study (canakinumab anti-inflammatory thrombosis outcome study) in more than 10.000 patients with a history of myocardial infarction and hs-CRP ≥ 2 mg/l showed a large and significant reduction in cardiovascular and all-cause mortality in patients who achieved the largest reductions in hs-CRP. Approximately 40% of them had a history of diabetes. At a median follow-up of 3.7 years, the incidence rate for the primary end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) was 4.50 events per 100 person-years in the placebo group, and 3.90 events per 100 person-years in the 300-mg canakinumab group (Davies et al., 2022); (Ridker et al., 2017).

The JUPITER study enrolled 17 802 apparently healthy middle-aged men and women with hs-CRP levels over 2.0 mg/l, and LDL less than 130 mg/dl. They were randomised to receive rosuvastatin 20 mg daily or placebo, and followed for a

primary endpoint of nonfatal myocardial infarction, non-fatal stroke, arterial revascularisation, hospitalisation for unstable angina, or cardiovascular death for 1.9 years. Rosuvastatin lowered both hs-CRP (37%) and LDL-cholesterol (50%) as well as nonfatal myocardial infarction (55%), nonfatal stroke (48%), hospitalisation and revascularisation (47%) and all-cause mortality (20%) (Kones, 2009). JUPITER and CANTOS represent a break from the concept that all patents need all therapies; yet, just as there is 'residual cholesterol risk' and 'residual inflammatory risk,' so too is there 'residual thrombotic risk,' 'residual triglyceride risk,' and 'residual lipoprotein(a) risk,' as well as fully unexplained disease. Each of these conditions has either a proven therapy or major trials are underway or planned to assess the effect of further lowering the size of this residual risk. (Ridker et al., 2017); (Ridker, 2018); (Ridker, 2019). Based on this research and the literature, diabetes care providers are advised to determine a patients' hs-CRP annually. Although medication cannot yet be prescribed, a strict multifactorial approach also helps and success of therapy can be measured more comprehensively. An updated patient decision aid (see further) should include data on the measurement and targeting of hs-CRP.

Adiponectin, a protein secreted by adipocytes is a key regulator of insulin sensitivity and tissue inflammation. Adiponectin circulates in blood in multiple isoforms. High molecular weight (HMW) adiponectin is thought to be most biologically active and promotes glucose uptake, insulin sensitivity, and fatty acid oxidation. In obesity, adiponectin isoform formation is disrupted, leading to an inverse association between metabolic disease on the one hand and HMW and total adiponectin levels on the other. Adiponectin isoforms also function as acute-phase reactants influencing inflammation in acute and chronic disease. Unfortunately, data concerning adiponectin and its pathophysiologic function conflict. This is predominantly due to difficulties in adequate measurement of adiponectin isoforms and lack of a gold standard (van Andel et al., 2018).

In our study, mean changes in adiponectin levels were similar for both treatment groups. After an initial increase the values levelled off to nearly baseline values, with a difference between the two groups after six years of 0.44 µg/ml (p = 0.27). Additional analyses, controlling for BMI, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides, had little effect on these findings.

There was no difference in baseline adiponectin between included and excluded patients in the intensive care group, but patients lost to follow-up in the routine care group had significantly higher (1.50 µg/ml, 95% CI: 0.16 to 2.82) baseline adiponectin levels than those included in the analyses. This implies that the effect of intervention may have been underestimated by the longitudinal model.

Since abdominal fat accumulation may be an important determinant of adiponectin levels, it would have been better to include waist circumference in the analysis. Unfortunately, a waist measurement was not performed at follow-up, but only measured at baseline.

Certain groups of drugs could have affected the adipocytes` physiology. Thiazolidinediones (TZDs), have been shown to increase levels of adiponectin in humans (Combs et al., 2002); (Koh et al., 2009). Because only a small number of patients used TZDs, TZD use is unlikely to contribute to a differential change in adiponectin levels. The decrease of adiponectin levels may have been caused by the lipophilic statin simvastatin (Koh et al., 2009); (Koh et al., 2011). On the other hand RAAS-blockers will have increased adiponectin levels (Chang et al., 2009); (Delles et al., 2008). It is not possible to explain the change of adiponectin in two opposite directions over time with the obtained data. The role of adiponectin seems to be more complex.

To conclude: the logical advice is not to measure a patients' adiponectin level as a risk marker in future diabetes care.

Part 2: OPTIMAL-study

A cluster-randomised study was set up to determine the effect of SDM on the achievement of treatment goals, along with an evaluation of whether SDM was continued at follow-up in the OPTIMAL study. (In short, between 2011 and 2012 a total of 35 general practices who participated in the ADDITION study were recruited in the south west of the Netherlands. Between 2012 and 2013 patients with T2DM were recruited for a shared goal setting and decision making intervention. In this region, the ADDITION-study was conducted between 2002 and 2009).

At least two factors complicate determining what is best for an individual: 1) a lack of reliable evidence with regard to issues that matter to individuals living with diabetes, i.e. uncertainty about the best treatment and 2) preferences and context, i.e. what the person values in living with and treating his or her T2DM (Serrano et al., 2016). The evidence that one medication is better in terms of patient-important outcomes is limited by the small number of head-to-head randomised trials; thus, by considering solely the evidence of randomised controlled clinical trials, it is quite often not possible to conclude that a patient will be better off with one option compared with another. However, in the Steno-2 Study, that compared the effect of almost eight years of intensified, multifactorial treatment with that of conventional treatment, people with established T2DM and micro-albuminuria, after 21.2 years of follow-up intensified treatment, demonstrated a median of 7.9 years of gain of life (Gaede et al., 2016). An intensified multifactorial approach in people with established T2DM seems desirable.

The ADDITION study included screen-detected patients with T2DM and compared an intensive multifactorial treatment with less intensive usual care according to national guidelines. The intensive treatment was associated with a significant increase in prescribed medications and a non-significant 17% (hazard ratio [HR] 0.83, 95% CI 0·65–1.05) reduction of cardiovascular events and death after five years. Five years after the end of the intervention there was also no significant difference between groups in the incidence of the primary composite outcome (16·1

per 1000 person-years in the former routine care group, 14·3 per 1000 person-years in the former intensive treatment group; HR 0·87, 95% CI 0·73–1·04; p = 0·14) or its components, nor in all-cause mortality (15·6 vs 14·3 per 1000 person-years; HR 0·90, 0·76–1·07) or predefined categories of cause-specific mortality.

Based on the results of the ADDITION study the question, whether an intensified multifactorial approach is also desirable in screen-detected people with T2DM has not definitely been answered (Simmons et al., 2016); (Griffin et al., 2019).

In cases of no proven beneficial effect in favour of one treatment option, but with differences in treatment intensity, SDM is strongly recommended. Besides, nearly 80% of patients with T2DM are estimated to suffer from at least one comorbid condition. Therefore, treatment plans will need to account for individual patient co-morbidities. Although SDM seems highly warranted, its implementation is impeded by numerous barriers, both on the GP side and the patient side. The largest barriers cited by GPs are (in order of frequency): time pressure, lack of applicability due to patient characteristics, lack of applicability due to the clinical situation, a perception that patients do not want to participate in decision-making, and unwillingness to ask patients about their preferred level of participation (Ankolekar et al., 2021).

Patient-reported barriers centre on logistical factors, such as a perception that clinicians have busy schedules; and a perceived lack of continuity between different clinicians and on consultation factors, for example a perceived power imbalance (Joseph-Williams et al., 2014). Many patients face difficulty in forecasting their future and often lack the skills to interpret risk figures and probabilities. Patients and clinicians will need new ways of collaborating to evaluate all relevant pieces of evidence and personal preferences to make optimal choices (Ankolekar et al., 2018); (Coulter et al., 2015); (Davies et al., 2018). One of these new ways is the use of a Patient Decision Aid (PDA). A typical PDA contains the following: information

about treatment options; risks, benefits, and uncertainties associated with each option; and a form of value clarification exercise in which patients are asked to make choices that build the basis of the trade-offs between the treatment options and risks. The purpose of value clarification is to allow patients to reflect on what aspects of the treatment options matter most to them so that it is easier for clinicians to engage with patients and guide the decision-making process toward the most ideal outcome (Ankolekar et al., 2018).

A review that has been published after the start of our study found substantial evidence of an association between SDM and improved decision quality, patient knowledge and patient risk perception. There was little evidence of an association between SDM and glycaemic control, patient satisfaction, quality of life, medication adherence or trust in physician (Saheb Kashaf et al., 2017); (Wang et al., 2019). These results should all be interpreted with caution, because the measurement of SDM is challenging (Kriston et al., 2010). It can be categorised into the decision process (e.g., observed or perceived behaviour of the clinician), or decision outcomes (e.g. decisional conflict, decisional regret, satisfaction) (Joosten et al., 2008).

The SDM process can be assessed by an external observer, the patient, or the physician. The OPTION ('observing patient involvement') scale is the most prominent instrument for assessing the extent to which clinicians actively involve patients in SDM (Nicolai et al., 2012).

With regard to the SDM outcome, although SDM is conceptualised as a process involving both the health care provider and the patient, only a few scales are available that assess SDM from both the patients' and the physician's points of view: the OPTION scale, the 9-item Shared Decision Making Questionnaire (SDM-Q-9), published in 2010 and the CPS. Of these measures, the SDM-Q-9 is used increasingly often to assess interventions aiming to improve SDM.

The intervention

We designed a Patient Decision Aid (PDA) using the framework designed by Wilkinson (see Introduction). Together with the patient, clinical factors and patient preferences are taken into account, goals are prioritised, and choices are made for treatment with medication or lifestyle advice or both. In our study, the intensity of the treatment was also discussed, using the cardiometabolic cut-off points of the ADDITION study.

Our PDA integrates both: clinical factors and patient preferences (Coates & Clerke, 2020); (Wilkinson et al., 2013). The participants of the study should choose between 'usual care' or 'intensified' care. Furthermore, they should prioritise five treatment targets. Against that background, the decision aid consisted of three steps. It proved to be suitable for patients and doctors, although it has not been made according to the official International Patient Decision Aid Standards (IPDAS) criteria, established in 2003. IPDAS guidelines recommend initial alpha tests among patients and clinicians in a laboratory setting, then broader beta testing in a real clinical practice setting. Finally, implementation must be evaluated using appropriate performance metrics—for example, the extent of use of the PDA (i.e., the number of patients who used the PDA as a proportion of those who were eligible to use it) or improvements in the quality of decision support provided by the clinician as measured by the Decision Support Analysis Tool (Butow et al., 2010).

IPDAS guidelines represent a standardised development process; however, questions have been raised about its validity in practice. For instance, little is known about which specific components of the IPDAS guidelines best facilitate the decision-making process (Bekker, 2010).

Furthermore, a well-designed PDA may not improve clinical outcomes unless it is properly implemented in clinical practice. With the designed multifactorial PDA, people's first choice was between intensive or less intensive multifactorial therapy against the background of the one randomised controlled trial performed in this respect, namely ADDITION. The PDA was a simple paper-based tool. Although

PDAs are increasingly being offered in a digital format, preliminary evidence suggests that, given a choice, patients tend to use paper PDAs more frequently than digital PDAs and rate them higher in terms of overall satisfaction (Stacey et al., 2019); (Tomko et al., 2015).

As mentioned, we used the Wilkinson framework. Because this framework is ideal for taking a holistic approach, turning it into a conversation aid, it seems the ideal one in such a complex disease as diabetes, with all its comorbidity. The PDA is to a large extent similar to the decision cycle of the ADA/EASD, which supports our approach (Davies et al., 2022)**.** In my opinion, it is important to follow the ADA and EASD, advising SMART (specific, measurable, achievable, realistic, time-bound) treatment goals instead of strict 'general' cut-off values for cholesterol, blood pressure, HbA_{1c}, weight and smoking.

Including the results of the STENO study in the development of a new PDA, the PDA might be interesting for implementation in regular diabetes care. It seems advisable to involve patients in the development of a new PDA through co-creation, because doctors cannot fully understand how information is processed by patients.

Should they design a multifactorial PDA? In daily practice separate decisions have to be made about all separate targets, even if you use a multifactorial PDA. No data was found about what is preferable, a single factorial or multifactorial PDA. Ultimately recommended here is a multifactorial approach in line with the ADA/EASD guidelines (Davies et al., 2022).

Having that said, two questions arise: 1) what about the outcomes of the SDM consultations? 2) what about the implementation of the SDM process?

The preferred outcome was one in which significantly more goals would be achieved in the intervention group. That assumption was too optimistic, given the literature in which little significant improvement can be seen in the clinical outcomes with SDM and a decision tool. At baseline 26.4% of the participants in the SDM group (n = 72) had already achieved all three treatment goals. Of them, 44 chose intensive

treatment, 25 continued their former less intensive treatment and three people switched from the more to the less intensive protocol.

This study contains relatively few patients per practice and selection-bias could be an issue. Possibly the most motivated patients have participated, which would have favoured the results.

After 24 months 31.8% achieved all three treatment targets, RR 1.26 (95% CI 0.81-1.95). Mean systolic blood pressure decreased in the SDM group (-5.4 mmHg, $p < 0.01$). Mean HbA_{1c} and total cholesterol did not change. Overall the 31.8% of patients in the intervention group that achieved all three goals, is a much higher percentage than the 10-20% reported in the literature (see Introduction). Although the overall results of Dutch diabetes care are already quite good, this SDM approach seems to fill part of the room for improvement when it comes to just lowering blood pressure.

There are not many studies that measured SDM two years after the start of the study. At baseline, perceived levels of SDM did not significantly differ between GPs and patients with T2DM (mean difference of 2.3 in SDM-Q9 score, p 0.24). At follow-up, mean patients' perceived level of SDM was 7.9 (in SDM-Q9) lower compared to baseline ($p < 0.01$), whereas GPs' opinions had not changed significantly (-1.3 in SDM-Q9 p 0.34). GPs might have been too positive about their SDM during the second consultation. It is also possible that patients experienced less SDM after two years, while SDM was present. After both visits, the mean CPS score differed significantly between patients and GPs, with -1.3 ($p < 0.01$) at baseline and -0.6 (p 0.05) at 24 months follow-up. At 24-months follow-up, the patients' CPS score had increased with 0.7 (p 0.04), whereas GPs' CPS scores decreased with on average -0.6 (p 0.11). There was no significant correlation between initial and follow-up scores. The results of the CPS are not in agreement with the results of the SDM-Q9, but the CPS might have been better completed before the consultation, because it is originally intended to measure the preferred role of patient and physician in relation to SDM.

Nine GPs audiotaped a consultation. OPTION5 scores ranged between 6 and 20, which means that GPs differed substantially in SDM. The mean OPTION5 score was 16.6, which is quite high. Decisional roles were not recorded for all the patients and GPs: the decisional roles were self-reported after the consultation, while perceived levels of SDM were assessed during the consultation. This may have led to self-report bias in the reported decisional roles. By recording the conversations after 2 years and using OPTION5, we could have recognised this. Unfortunately, no records and audiotapes were made of the 24-months conversations. Looking at SDM over a longer period, one must also realise that obviously there are patients who don't want SDM, but a doctor to decide. In a nationwide study in 994 Dutch type 2 diabetes patients 41% of the respondents preferred their treating physician or nurse to determine personal treatment targets; 48% of the people preferred shared decision making (Gorter et al.,2011). No assessment can be made of the impact of the patients' preferences on the results of the process-evaluation.

Alltogether, SDM in the OPTIMAL study seems appropriate shortly after the one-hour training, in which the decision aid was systematically followed but without role-play to train SDM. Besides, it is the way SDM training is organised that matters. Reviews of SDM training are limited to programmes that were evaluated analytically and provided little detail in terms of programme design and content. A review identified 49 studies that met inclusion criteria, evaluating 36 unique training programs. Training in primary care was most likely delivered in the form of a single one- or half-day session. Most of the programme facilitators were also study investigators, with little or no detail provided on their skills and experience in delivering SDM programmes. Overall few programmes provided training to enhance the capacity of clinicians to develop their ability to reflect on their communication, for example, through methods informed by psychotherapy. This is important because there is evidence that shows that despite best intentions to adopt SDM, clinicians unconsciously steer patients toward the option they think is in their patients' best interest (Engelhardt et al., 2016); (Epstein & Gramling, 2013).

How SDM is best performed in a context of medical uncertainty or ambiguity remains not well understood, and our findings support previous calls for SDM training programmes to include a component on how to manage and communicate medical uncertainty.

To successfully implement SDM into routine care, interventions targeting both clinicians and patients are required. The recommendation here is repeated training for SDM and the use of a paper-based PDA by explaining SDM principles and by practicing role plays with actors. Although many studies used actors to play the role of patients in the role plays, there may be value in participants playing both the clinicians' role as well as the patients' role (Luttenberger et al., 2014).

The training duration will obviously be longer than one hour; however it should be limited due to the workload of both physicians and practice nurses. No literature was found that recommends how often a training in SDM with decision aid should be repeated. Looking at this study, the advice would be once every two years. Booster sessions seem necessary to consolidate and understand key SDM elements and truly incorporate them into routine clinical practice.

Overall conclusion

This thesis investigated aspects of both personalised and person-centred diabetes care. Incorporating the hs-CRP into daily care can make it a little more personalised. By applying shared decision-making in the treatment of patients with T2DM, care becomes more patient-centred, but there is still a lot to be done before shared decision-making can take place in diabetes care. It is easier said than done. The same applies to personalised diabetes care.

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NEDERLANDSE SAMENVATTING

Dit proefschrift betreft een onderzoek naar twee verschillende aspecten van de moderne behandeling van diabetes mellitus type 2 (DM2), namelijk de op de biologische eigenschappen van de patiënt afgestemde zorg, de zogenaamde gepersonaliseerde zorg ('personalised medicine') en een zogenaamde persoons- of patiëntgerichte ('patient-centred') diabeteszorg met gedeelde besluitvorming, shared decision making (SDM). De hypothese luidt dat een gepersonaliseerde en patiëntgerichte benadering tot betere zorg leidt en tot betere klinische resultaten.

De dissertatie bestaat uit twee delen. Deel 1 is gericht op 'personalised medicine', waaronder het gebruik van metabolomics en van inflammatie-parameters. Deel 2 bevat de opzet en de resultaten van het patiëntgerichte OPTIMAAL onderzoek met SDM. Beide onderzoeken vonden plaats bij patiënten die ofwel hadden deelgenomen aan de ADDITION-studie ofwel afkomstig waren uit voormalige ADDITION-praktijken (zie verderop).

Deel 1: metabolomics

In de Verenigde Staten zijn de tien medicijnen met de hoogste omzet effectief bij slechts 25% van de gebruikers. Dit teleurstellende percentage is deels te verklaren door het niet naleven van medicatievoorschriften, daarnaast speelt een hoog number needed to treat (NNT) een rol. Hierom is er behoefte aan een meer gepersonaliseerde behandeling van diabetes. 'Personalised medicine' is ontworpen om het therapeutisch voordeel te optimaliseren voor specifieke patiëntgroepen door middel van genetische of moleculaire profilering van het individu. Pharmaco-metabolomics tracht betere voorspellingen te maken van variatie tussen de reacties van mensen op medicijnen op basis van een meting van hun metabole profiel voorafgaand aan de behandeling en in de loop van de medicinale behandeling.

De wereldwijd meest gebruikte medicijnen voor DM2 zijn metformine en sulfonylureumderivaten (SU). Meestal starten nieuwe diabetespatiënten met metformine, soms met een SU. Vaak gebruiken zij in een later stadium beide soorten medicatie. Het is niet bekend welke start voor welke patiënt het beste werkt. Metformine verlaagt de glucoseproductie in de lever en verbetert de insulineresistentie in perifere weefsels. Daarnaast verhoogt metformine de glycogeensynthese en verlaagt het de intestinale glucoseabsorptie. Vergeleken met een placebo verlaagt metformine het HbA1c met gemiddeld 11 mmol/mol. Goede glykemische controle met behulp van metformine kan de sterfte onder mensen met diabetes type 2 en overgewicht verlagen, met een NNT van 14 gedurende 10 jaar. SU's stimuleren de insuline-afgifte en kunnen microvasculaire complicaties verminderen; zij verlagen het HbA_{1c} met gemiddeld 10-20 mmol/mol met een NNT van 29.4 gedurende 10 jaar. Nieuwe medicatie zoals SGLT2-remmers en GLP-1RA hebben gemiddeld een hogere NNT voor cardiovasculaire uitkomsten.

Wij hebben in ***hoofdstuk 2*** geprobeerd metabolieten vast te stellen die samenhangen met de daling van het HbA1c en die het mogelijk zouden kunnen maken op basis van het metabole profiel van een patiënt vast te stellen welke medicatie het beste past bij de individuele patiënt, om idealiter ook de NNT te verlagen. In het Nederlandse deel van de ADDITION studie zijn 498 patiënten met bij screening gedetecteerde DM2 aselect verdeeld over een intensieve multifactoriële behandeling (n = 255) of routinezorg (n = 243). Bij 346 van hen zijn metabolieten gemeten in basismonsters. Vervolgens is het effect op het HbA1c na vijf jaar van metformine en/of SU-derivaten (drie verschillende groepen) geanalyseerd, door middel van een meervoudige regressieanalyse, om zo metabolieten te identificeren die een verandering voorspellen in HbA1c-waarden over een periode van vijf jaar.
Alleen de basiswaarden van glucose en 1,5 anhydro-glucitol hadden verband met een verlaging in het HbA_{1c} in alle medicatiegroepen. Deze metabolieten onderscheiden dus niet tussen metformine, SU-derivaten, of metformine + SU-

derivaten en helpen niet om een betere keuze te kunnen maken tussen het starten van een diabetesbehandeling met bijvoorbeeld enkel metformine, of met een combinatie van metformine en SU-derivaten. Onder patiënten met SU-derivaten konden geen andere metabolieten in verband worden gebracht met HbA_{1c}-verlaging. Een grotere set van metabolieten had verband met HbA_{1c}-verandering in de groepen metformine en metformine plus SU. Hieronder bevonden zich metabolieten die gerelateerd zijn aan het levermetabolisme en metabolieten die betrokken zijn in oxidatieve stress.

Na correctie voor de HbA_{1c}-basiswaarden verloren meerdere metabolieten hun statistische significantie. Voor zover bekend is onze studie de eerste bij mensen met type 2 diabetes van wie metabolieten werden gemeten toen zij nog geen glucoseverlagende medicatie namen voor hun diabetes. Daarom biedt onze studie waardevolle informatie over de metabolieten die verband houden met de effectiviteit van glucoseverlagende medicijnen. Voortbordurend op de resultaten van dit onderzoek zou men in andere populaties van nieuw gediagnostiseerde DM2 patiënten de meest belovende voorspellers kunnen testen. Dat zijn in de metforminegroep 4-oxoproline (p 0.002) en glutaminezuur. ($p < 0.0001$). In de groep metformine + SU-derivaten zijn dit 2-hydroxypiperidine (p 0.002) en pseudouridine (p 0.007). In de groep SU-derivaten is dit fumaarzuur (althans bij mensen met HbA1c > 6,5%,) (p 0.044). De vooruitzichten zijn niet veelbelovend. Zodra de p-waarden werden aangepast voor meervoudige toetsing, bleven enkel de veranderingen glucose en 1,5 anhydroglucitol significant. Juist deze twee metabolieten vertoonden geen onderscheid voor wat betreft het effect op het HbA1c tussen de drie behandelgroepen.

Een tweede methodologische kanttekening betreft de onzekerheid over de dosering en de duur van het gebruik van zowel metformine als SU. Wat de impact is van dit gebrek aan informatie, valt moeilijk in te schatten.

De klinische toepassing van pharmacometabolomics wordt belemmerd door de variatie in bepalingen tussen de laboratoria. Metabolomics-onderzoek in grote populaties en patiëntcohorten kan mogelijk bijdragen aan het verkrijgen van

objectieve klinische data om de medicijnrespons beter te begrijpen en meer voorspelbaarheid bieden bij uitkomstevaluaties. In een in 2023 gepubliceerde studie onder 4571 patiënten met T2DM en een HbA1c > 53 mmol/mol bij wie genetische kenmerken in verband werden gebracht met het effect van GLP1-RA op het HbA1c na zes maanden bleek dat mensen van wie het genotype beschikbaar is profijt zouden kunnen hebben van een vroege start met een GLP1-RA als zij een ARRB1 variant bezitten. Ook hier concluderen de auteurs dat studies in grote populaties nodig zijn.

Conclusie: in deze studie onder patiënten bij wie bij screening diabetes type 2 was vastgesteld zijn geen metabolieten gevonden die voor iedere patiënt afzonderlijk zouden kunnen voorspellen dat ofwel metformine ofwel SU-derivaten de beste keuze is om de behandeling met bloedglucoseverlagende medicatie te starten. Verder onderzoek met metformine, SUs en SGLT2-remmers en GLP-1RA is gewenst, aangezien het onderzoeksdoel − het verlagen van de NNT op basis van een gepersonaliseerde keuze voor bloedglucoseverlagende medicatie bij DM2 − nog ver buiten bereik ligt.

Deel 1: hs-CRP en adiponectine

Een van de opties om de DM2-behandeling beter af te stemmen op de individuele patiënt, is het gebruik van de relevante biomarkers.

In de primaire preventie voegt het evalueren van de inflammatie-biomarker hs-CRP prognostische informatie toe aan de conventionele metingen van het cardiovasculaire risico, met een effectgrootte vergelijkbaar met die van LDL- of HDL cholesterol, Een mogelijke strategie die is gericht op residueel cardiovasculair risico omvat ook het meten van hs-CRP, wat het mogelijk maakt om een geïndividualiseerd behandelingsplan op te stellen dat cardiovasculair risico verlaagt

In ***hoofdstuk 3*** konden wij een blijvende en significante hs-CRP-verlaging aantonen in patiënten met bij screening vastgestelde DM2 gedurende zes jaar van multifactoriële behandeling. Veranderingen binnen de intensief behandelde groep

waren significant groter dan bij de routinebehandelingsgroep. Voor zover bekend zijn er geen andere studies naar het verloop van inflammatie bij patiënten met bij screening vastgestelde diabetes, wat het belang van deze resultaten vergroot.
Correctie voor het gebruik van of statine of acetylsalicylzuur, of van cholesterol- of HbA1c-waarden leidde niet tot andere resultaten
Dit wijst erop dat een multifactoriële behandeling een onafhankelijk effect heeft op de hs-CRP-waarden. Naast het effect van statine en bloeddrukverlagende medicatie en wellicht het effect van glucoseverlagende medicatie op hs-CRP, geldt hier één plus één is drie, wat resulteert in een onafhankelijk gunstig effect op hs-CRP, en dus op de infectieparameter, op residueel risico.
Onderzoeken waarin inflammatie werd tegengegaan met doelgerichte therapie, zoals de CANTOS studie (canakinumab anti-inflammatory thrombosis outcome study) lieten een grote en significante reductie in cardiovasculaire eindpunten en mortaliteit zien onder patiënten bij wie de hoogste reductie in hs-CRP werd behaald. Ongeveer 40% van de deelnemers had diabetes.
In de JUPITER studie onder ogenschijnlijk gezonde mannen en vrouwen van middelbare leeftijd met hs-CRP-waarden hoger dan 2.0 mg/l, en een LDL lager dan 130 mg/dl. verlaagde rosuvastatine behalve het LDL-cholesterol (50%), niet-fatale myocardinfarcten (55%) en fatale beroerte (48%), en sterfte (20%) ook het hs-CRP met 37%. Beide studies staan voor een breuk met de opvatting dat alle patenten alle therapieën nodig hebben. Maar zoals er ‘residueel cholesterolrisico’ en ‘residueel inflammatoir risico’ bestaat, zo is er ook ‘residueel trombotisch risico’, ‘residueel triglyceriderisico’ en ‘residueel lipoproteïne (a) risico’, evenals geheel onverklaarbare ziekte.

Op basis van ons onderzoek adviseren wij diabeteszorgverleners om het hs-CRP van een patiënt jaarlijks te meten. Om het succes van behandeling uitgebreider te meten. Een geactualiseerde patiënten keuzehulp (zie hieronder) zou ook data moeten bevatten over het meten en focussen op hs-CRP.

Adiponectine, is een belangrijke regulator van insulinegevoeligheid en weefselinflammatie. Helaas zijn de gegevens over adiponectine en de pathofysiologische functie ervan tegenstrijdig. Dit komt voornamelijk doordat het moeilijk is om adiponectine isovormen adequaat te meten en er een gouden standaard ontbreekt.

Wij vonden in ***hoofdstuk 3*** bij mensen in de ADDITION-studie vergelijkbare veranderingen in adiponectinewaarden tussen de intensief en de minder intensief behandelde groep. Na een aanvankelijke toename vlakten de waarden af tot bijna de basiswaarden, met een verschil tussen beide groepen van 0.44 μg/ml ($p = 0.27$) na zes jaar.Aanvullende analyses die corrigeerden voor BMI, totaal cholesterol, HDL-cholesterol, LDL-cholesterol en triglyceriden hadden nauwelijks effect op de resultaten.

Aangezien abdominale vetophoping mogelijk een belangrijke bepalende factor is voor adiponectinewaarden, zou het gunstiger zijn geweest als ook taille-omvang was meegenomen in de analyse. Helaas zijn taillemetingen niet verricht in de follow-up, maar enkel als nulmeting.

Met de data in deze studie is er geen verklaring te geven voor de verandering in adiponectine in de loop van de tijd. De rol van adiponectine blijkt complexer dan verwacht. Adiponectine lijkt niet geschikt als risico-indicator in de reguliere diabeteszorg.

Deel 2: OPTIMAAL-studie

Minstens twee factoren bemoeilijken het vaststellen van wat het beste is voor een individu, namelijk gebrek aan bewijs met betrekking tot wat voor een individueel persoon de beste medicatie is en de voorkeuren en context van de persoon in kwestie. De oorspronkelijke ADDITION studie omvatte patiënten met bij screening vastgestelde diabetes en vergeleek een intensieve multifactoriële behandeling met minder intensieve gewoonlijke zorg op basis van nationale richtlijnen. De intensieve behandeling ging gepaard met een significante toename in voorgeschreven medicatie

en een niet-significante reductie van 17% (hazard ratio [HR] 0.83, 95% CI 0·65–1.05) van cardiovasculaire aandoeningen en overlijden na vijf jaar.
Uit de resultaten van de ADDITION studie volgt geen definitief antwoord op de vraag of een intensieve multifactoriële behandeling ook wenselijk is bij patiënten met via screening vastgestelde DM2.
Zeker in gevallen waarin niet vaststaat dat een intensievere behandeling beter is dan een minder intensieve is het van groot belang met de patient daarover samen te beslissen. In de praktijk wordt gedeelde besluitvorming (SDM) echter bemoeilijkt door meerdere barrieres, zowel aan de zijde van de arts als de patiënt, bijvoorbeeld door tijdsdruk, de indruk dat patienten niet willen deelnemen aan de besluitvorming of de perceptie dat clinici drukke werkschema's hebben of een veronderstele machtsongelijkheid tussen arts en patiënt. Een van de hulpmiddelen bij de beoogde besluitvorming is een keuzehulp. Een keuzehulp bevat informatie over behandelingsopties: risico's, voordelen, en onzekerheden die met elke optie verband houden, en aandacht voor persoonlijke voorkeuren van de patiënt.

In ***hoofdstuk 4*** beschrijven we de opzet was een cluster-gerandomiseerd onderzoek om het effect te meten van SDM op het behalen van de behandeldoelen. In de OPTIMAAL studie werden 35 praktijken geïncludeerd die ook betrokken waren geweest bij de ADDITION studie. Er werden 74 voormalige ADDITION patiënten geïncludeerd en 79 min of meer vergelijkbare niet-ADDITION patiënten, met een leeftijd tussen de 60 en 80 jaar en 8-15 jaar DMT2. Praktijken werden tweemaal gerandomiseerd, interventiepraktijken in de ADDITION studie werden nu mogelijk controlepraktijken en vice versa. Huisartsen in de interventiepraktijken kregen een 1 uur durende training in SDM en gebruik van de keuzehulp (zie verderop). Na het eerste consult en na 2 jaar werd het SDM proces en of de behandeldoelen gehaald waren geëvalueerd.

Volgens de literatuur leidt gedeelde besluitvorming tot een hogere besluitvormingskwaliteit en meer kennis en risicoperceptie van patiënten, maar niet tot betere glykemische controle, patiënttevredenheid, levenskwaliteit, naleving van medicatie of vertrouwen in artsen. Al deze resultaten moeten echter met de nodige voorzichtigheid worden geinterpreteerd, omdat SDM zich moeilijk laat meten.
Er zijn slechts enkele meetinstrumenten beschikbaar die SDM toetsen vanuit het perspectief van zowel de patient als van de arts, te weten de OPTION schaal en de 9-item Shared Decision Making Questionnaire (SDM-Q-9) en de CPS.
Wij ontwierpen een keuzehulp op basis van het framework van Wilkinson. Samen met de patiënt worden de klinische factoren en patiëntvoorkeuren meegenomen, doelstellingen geprioriteerd en behandelkeuzes gemaakt. Patiënten kozen voor de intensiteit van de behandeling, gebruikmakend van de cardiometabole afkappunten uit de ADDITION-studie.
Verder dienden zij prioriteit aan te geven tussen vijf behandelingsdoelen. Zo bestond de keuzehulp uit drie stappen.
De keuzehulp was van papier. Vooralsnog blijkt uit onderzoek dat patiënten, wanneer zij de keuze hebben, de papieren keuzehulpen vaker gebruiken dan de digitale, en deze hoger beoordelen op algemene tevredenheid.
De keuzehulp is vergelijkbaar met de besluitvormingscyclus van de ADA/EASD. Het is van belang om de ADA en EASD na te volgen, met het advies om in overleg met de patiënt de behandelingsdoelen SMART (specific, measurable, achievable, realistic, time-bound) te formuleren.

Het zou goed zijn patiënten te betrekken bij het ontwikkelen van een nieuwe, up-to-date diabeteskeuzehulp. Er is geen antwoord op de vraag of die zich moet richten op een multifactoriële behandeling of op één risicofactor. In de dagelijkse praktijk moeten afzonderlijke beslissingen worden gemaakt over alle afzonderlijke doelen, zelfs indien een multifactoriële keuzehulp wordt ingezet.

Hoofdstuk 5 betreft de resultaten van de OPTIMAAL-studie. De hoop was dat patiënten door de interventie met SDM significant meer doelen zouden behalen. Bij de start van de studie had 26,4% van de deelnemers in de SDM-groep (n = 72) reeds alle drie de behandelingsdoelen op het gebied van glucoseregulering, bloeddrukcontrole en cholesterolcontrole behaald. Daarbij kozen 44 van hen de intensieve behandeling, 25 gingen door met hun eerdere minder intensieve behandeling en 3 personen stapten over van de meer intensieve behandeling naar een minder intensief protocol. De studie bevatte relatief weinig patiënten per praktijk. Het is mogelijk dat de meest gemotiveerde patiënten hebben deelgenomen en dat dit de uitkomsten in gunstige zin beïnvloedt.

Na 24 maanden had 31,8% alle drie de behandelingsdoelen behaald, RR 1.26 (95% CI 0.81-1.95). De SDM-groep vertoonde een verlaging van de gemiddelde systolische bloeddruk (-5.4 mmHg, $p < 0.01$), terwijl het gemiddelde HbA_{1c} en totale cholesterol gelijk gebleven. Deze 31,8% is aanzienlijk hoger is dan de 10 tot 20 procent die in de literatuur wordt gerapporteerd. Hoewel de algemene resultaten van de Nederlandse diabeteszorg al behoorlijk goed zijn, lijkt deze SDM-benadering dus een deel van de ruimte voor verbetering te benutten.

In ***hoofdstuk 6*** bestuderen we de continuïteit in de gedeelde besluitvorming na twee jaar. Bij de start van de studie verschilden de waargenomen niveaus van SDM niet significant tussen huisartsen en DM2-patiënten (gemiddeld verschil van 2,3 op een schaal van 0-45 in SDM-Q9 score, p 0.24). Bij de follow-up was de waargenomen mate van SDM door patiënten gemiddeld 7,9 (in SDM-Q9) lager ten opzichte van de nulmeting ($p < 0.01$), terwijl dit onder huisartsen geen significante verandering vertoonde (-1.3 in SDM-Q9 p 0.34). Het is mogelijk dat huisartsen te positief oordeelden over hun SDM tijdens het tweede consult. Een andere mogelijkheid is dat patiënten minder SDM ervaarden na twee jaar, hoewel van SDM wel sprake was.

Slechts negen huisartsen hebben een consult in audio opgenomen. OPTION5-scores (schaal 0-20) varieerden tussen 6 en 20, wat betekent dat de SDM tussen huisartsen

substantieel verschilde. De gemiddelde OPTION5-score was 16,6 wat hoog is. Helaas zijn er geen verslagen of audio-opnames gemaakt van de 24-maanden consulten. Uiteraard zijn er ook patienten zijn die geen SDM willen, maar willen dat de dokter beslist. In een landelijke studie naar 994 Nederlandse DM2-patiënten, had 41% van de respondenten liever dat hun behandelend arts of verpleegkundige hun persoonlijke behandelingsdoelen bepaalde. Het is niet mogelijk om de impact te beoordelen van de patiëntvoorkeuren op de resultaten van de procesevaluatie.

Al met al lijkt SDM in de OPTIMAAL-studie goed toepasbaar kort na de éénuurs training, waarin de de keuzehulp besproken werd, maar zonder rollenspel om SDM te oefenen. Uit de literatuur blijkt dat de manier waarop de SDM-training wordt georganiseerd van belang is. In het algemeen bieden weinig programma's een training die clinici in staat stelt hun vermogen tot reflectie op hun communicatie te ontwikkelen. Dit is echter belangrijk, aangezien er bewijs is dat clinici vaak onbewust hun patiënten sturen richting de optie waarvan zij denken dat die in het belang van hun patiënt is.
De resultaten van ons onderzoek bevestigen de eerdere oproepen om SDM-trainingsprogramma's aan te vullen met een onderdeel over hoe medische onzekerheid te managen en te communiceren is naar de patiënt.
Een training voor SDM, met gebruik van papieren keuzehulpen, waarbij SDM-principes worden uitgelegd en rollenspellen worden geoefend met acteurs lijkt de beste optie voor de toekomst. Booster-sessies lijken nodig voor het consolideren en begrijpen van de kernaspecten van SDM en om deze werkelijk onderdeel te maken van de praktische klinische routine.

Algemene conclusie

In het ***afsluitende hoofdstuk*** hebben wij de resultaten van het proefschrift samengevat en besproken op een wijze die in de hier beschreven samenvatting ook is weergegeven. Incorporatie van hs-CRP in de dagelijkse zorg kan deze enigszins

meer gepersonaliseerd maken. Door gedeelde besluitvorming toe te passen in de behandeling van patiënten met DM2, wordt de behandeling meer patiëntgericht. Zowel voor gepersonaliseerde als voor patiëntgerichte diabeteszorg geldt: het is gemakkelijker gezegd dan gedaan.

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CURRICULUM VITAE

Hendrik den Ouden was born on 31 October, 1976 in Gouda, the Netherlands. After graduating secondary school in Gouda, he started Medicine in Utrecht in 1996.
After his internships he started as MD internal medicine in St. Antonius hospital Nieuwegein in 2004, where he was trained in Gastroenterology. After four years he switched to General Medicine studies in 2008 in Utrecht. Since 2011, he started as General Practitioner in Rotterdam. In 2019 he continued as General Practioner in Brielle. In 2013 he started his PhD research at the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht. His research was supervised by Prof. Dr. G.E.H.M. Rutten and Dr. R.C. Vos, and resulted in the study presented in this thesis.