To thrive or just survive

Wieringa, T.H.

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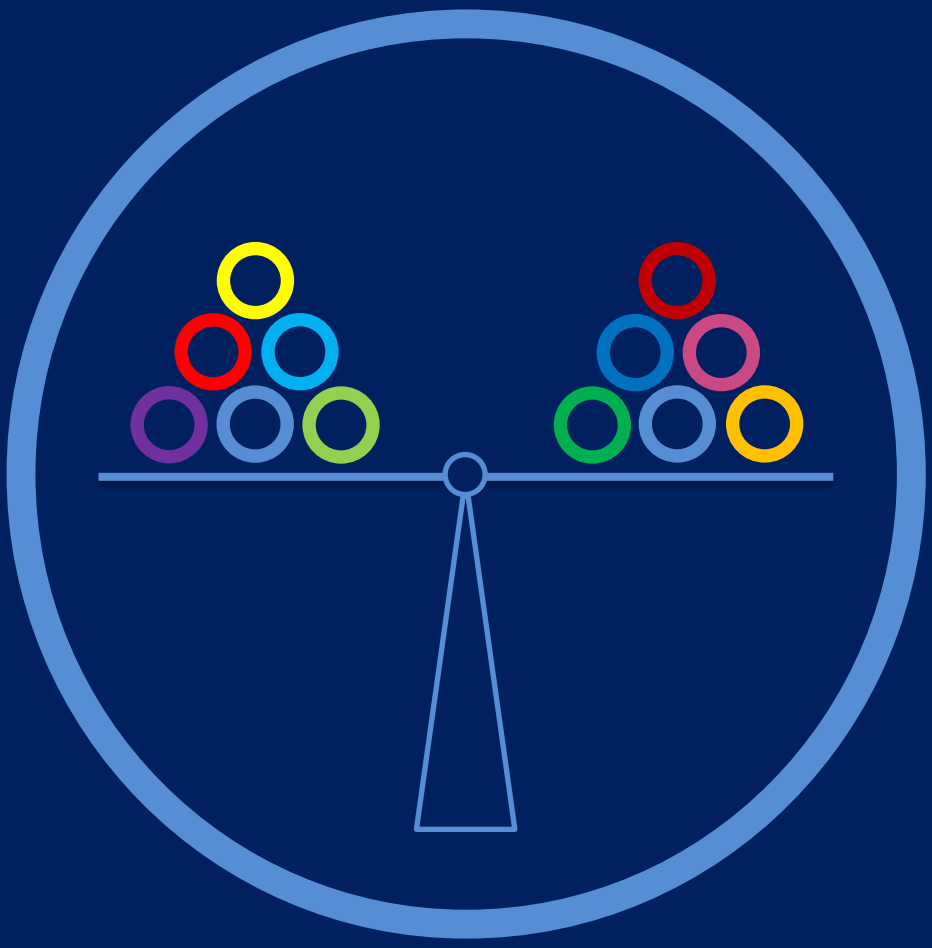

Towards personalized care for type 2 diabetes with the help of decision aids and patient-reported outcomes

Thomas Wieringa

To thrive or just survive – Towards personalized care for type 2 diabetes with the help of decision aids and patient-reported outcomes

PhD thesis, department of Medical Psychology, Amsterdam UMC (location VU University Medical Center), the Netherlands

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To thrive or just survive

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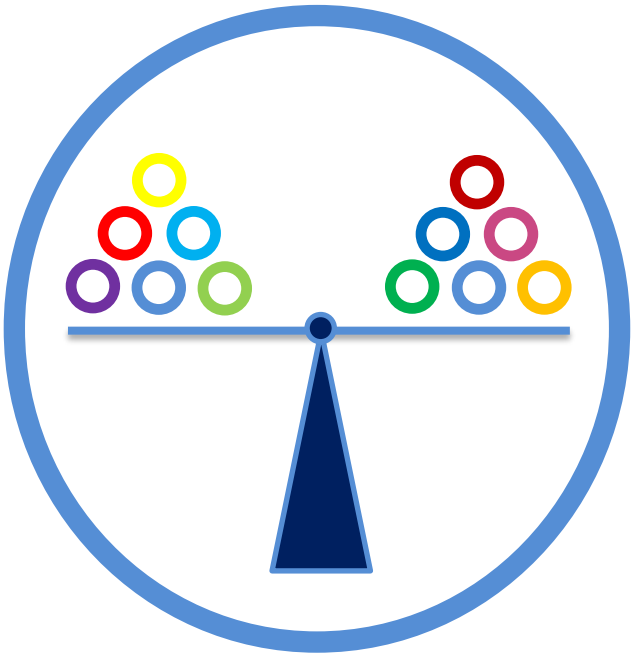
I learned that courage was not the absence of fear, but the triumph over it.
The brave man is not he who does not feel afraid, but he who conquers that fear.
(Nelson Mandela)

Table of Contents

Chapter 1

General introduction



Diabetes

Diabetes mellitus is a disease in which the blood sugar levels are too high as a result of an absolute or relative insulin deficiency.[1] 415 Million people are living with diabetes worldwide, and an estimated 193 million people have undiagnosed diabetes.[2] Diabetes was the sixth leading cause of disability in 2015[3] and places a considerable socioeconomic pressure on the individual suffering from diabetes, as well as global health economies.[4] Two main types of diabetes mellitus are type 1 and type 2 diabetes.[1]

Type 1 diabetes accounts for about 7% to 12% of all cases with diabetes in high income countries,[5] and has a strong genetic component.[6] Type 1 diabetes is generally thought to be precipitated by an immune-associated, or even directly immune-mediated, destruction of insulin-producing pancreatic β-cells.[7, 8] Environmental factors, such as inflammation and hygiene (deficits), may also play a role in the onset of type 1 diabetes.[6, 9, 10] The pancreatic β-cell destruction usually leads to absolute insulin deficiency.[6] Therefore, insulin treatment is needed for lifetime in this type of diabetes.[9] Type 1 diabetes usually begins earlier in life than type 2 diabetes[6] and a key distinguishing feature between both types is the presence of autoantibodies against β-cell autoantigens in type 1 diabetes.[9]

The current dissertation focuses on type 2 diabetes, a disease that is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs.[2] Type 2 diabetes accounts for more than 90% of people with diabetes and may lead to microvascular (e.g., retinopathy, nephropathy, neuropathy) and macro vascular (e.g., myocardial infarction, stroke, angina, need for coronary artery revascularization) complications.[2, 9] In turn, these complications may cause profound psychological and physical distress and put a huge burden on health-care systems. Intensive management of glucose, lipid concentrations, and blood pressure is needed in order to minimize the risk of complications and disease progression.[11] Hemoglobin A1c (HbA1c) is a measure of blood glucose control over the past 6-8 weeks and an established marker of

complication risk.[12] Despite increasing knowledge about risk factors for type 2 diabetes and evidence for successful prevention programs the incidence and prevalence of type 2 diabetes is rising globally.[2]

Older persons with type 2 diabetes commonly live with a variety of comorbidities which need to be considered when caring for this group of persons.[13] Research into the care for persons living with multiple chronic conditions has found it often to be fractured, where prescriptions and recommendations are poorly coordinated amongst different clinicians.[14, 15] Polypharmacy, increased treatment costs, side effects, and unintended drug interactions may be the result of fractured care,[14] which in turn may result in poor adherence, wasted resources, and poor outcomes.[14, 16-19] Therefore, coordination and integration of services for managing all individual diseases is needed in multi-morbid patients in order for care to be efficient, safe, and minimally burdensome.[20, 21]

Minimally disruptive medicine

Minimally disruptive medicine is a patient-centered approach to care that focuses on achieving patient goals for life and health by seeking care strategies to fit patient context.[14, 15] The quality of the Dutch diabetes care is internationally respected,[22] in particular for its multidisciplinary approach.[23] The Dutch Diabetes Federation recommends “customized care”,[24] fitting the contexts of individuals. Understanding the patient context is a prerequisite for care to fit the patient context, and important for adhering to treatment strategies.[25]

The cumulative complexity model practically orients minimally disruptive medicine.[26] In the cumulative complexity model, the patient imbalance between workload (“what patient have to do”) and capacity (“what patients can do”) is the central mechanism driving patient complexity and can lead to problems accessing and using care and enacting self-care, and ultimately to poor adherence and poor patient outcomes.[18, 19, 27] Paradoxically, health care professionals may respond to poor patient outcomes by intensifying treatment, resulting in more complex treatment regimens and thus higher workload.[14, 28] This creates a vicious cycle in which more burden of treatment (i.e., the impact of the work patients must do for their healthcare on their functioning and well-being[18]) results in a

higher workload. If patients do not have the capacity to cope with this burden, they may not adhere to treatment. This could result in an aggravated burden of illness (i.e., the impact of aspects of poor health on patients' functioning and quality of life), which in turn can deteriorate capacity.[26]

Shared-decision making and patient-reported outcome (PRO) monitoring are tools to identify the right care[15] and subject of the current dissertation. Shared-decision making can be "used to incorporate patient values and preferences into management decisions, legitimize partnership, and arrive at feasible care strategies" and PRO monitoring is the "systematic, ongoing recording of patient-reported health status, burdens of life and health, and changes in the quality or availability of support".[15]

Shared-decision making

The care for persons with type 2 diabetes heavily relies on self-management, and thus requires most decisions to occur in the patients' own "space".[12] Only a minority of decisions may occur in the health care facility, and these decisions need to be implemented in the patient space.[12] This implementation seems to be facilitated by enabling patients to play their preferred role in decision making, and thus by shared-decision making.[12] The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advocate for patient-centeredness, which is defined as an approach to "providing care that is respectful of and responsive to individual patient preferences, needs and values and ensuring that patient values guide all clinical decisions".[29] In this context, shared-decision making seems to be perfectly suitable as it is a useful strategy to arrive at the best treatment course for an individual.[30]

Although no widely supported or clear definition of shared-decision making exists, most do acknowledge that the clinician and patient should work together in making decisions, using the best available evidence.[31-35] Two distinct types for medical decisions exist, namely: 1) effective decisions, which have an optimal strategy available and 2) preference-sensitive decisions which have no "best strategy".[36, 37] Shared-decision making is often described as being most relevant for preference-

sensitive decisions, in which there is no best option from an evidence standpoint.[38] Some ethical and clinical arguments advocate for shared-decision making.[12, 39-47] Despite these argument is shared-decision making not yet routine in clinical practice.[33] Multiple reasons may be present for this suboptimal implementation of shared-decision making, among others a perception-reality gap in which clinician feel they are practicing shared-decision making[33] and time constraints.[48]

To facilitate implementation of shared-decision making, decision aids have been developed for use by clinicians and patients, either in preparation for or during the clinical encounter.[33, 49, 50] Decision aids are tools designed to help patients participate in decisions that involve weighing the harms and benefits of different treatment options.[49] They may help patients understand these options, as well as their harms and benefits[33] and consider them from a personal point of view.[51] Decision aids can help patients choose an option that is congruent with their values[49] and may be pamphlets, videos, or web based tools that describe the options available.[33] The use of decision aids in routine care is low[52], mainly due to poor design and lack of access to decision aids.[53] Decision aids are neither always attractive for use in clinical practice as they are often not based on current evidence or rapidly outdated, at least in part because of funding limitations after the tool is developed.[54]

Patient-reported outcomes

According to the ADA and EASD, there is a huge gap between knowledge gained from clinical trials and its application in clinical practice, and better application of “real-world evidence” is needed to complement randomized trials and for results to be more generalizable.[30] PROs may play an important role in filling this gap,[55, 56] and in turn inform shared-decision making practice.

Besides shared-decision making is PRO monitoring a way to identify the right care as well.[15] PROs are subjective reports that represent what is most important to patients about a condition and its treatment and can be defined as “reports coming directly from patients about how they feel and function in relation to a health condition and its therapy, without interpretation by healthcare

professionals or anyone else".[57] Two types of PROs exist, namely generic (considering general aspects, allowing comparison across conditions) and disease specific (tailored to symptoms and impact on function of a specific condition).[58]

PROs are most frequently measured in observational studies as they depict results of treatment in real life.[55] As a result, PROs complement data on efficacy and safety usually generated in clinical trials.[56] They are becoming increasingly important in weighing the pros and cons of a particular medication or treatment regimen incorporating the patient's perspective.[59] In this way, evidence generated from PROs may inform the harms and benefits of options discussed in shared-decision making conversations.

PROs were initially developed for use in research, but are increasingly used by clinicians.[58] This seems to be a positive development as health care aims to reduce symptoms, minimize disability, and improve quality of life, which only can be assessed by patients themselves.[58] Furthermore, PROs may bridge the gap between clinicians' and patients' understanding of disease and treatment effects as the direct self-reporting on health problems may facilitate discussion of important symptoms and quality of life aspects.[56] In this way, PROs may put patient-relevant problems on the encounter agenda and create a starting point for shared-decision making.

Aim and outline of this dissertation

The current dissertation aims to give more direction to the development and use of decision aids for implementing shared-decision making, as well as to clarify the (potential) roles of PROs in both research and clinical practice. This dissertation consists of two parts: the first part (Chapters 2 and 3) is about decision aids and the second part (Chapters 4 to 6) is about PROs.

Chapter 2 and **Chapter 3** describe the protocol and the results, respectively, of a systematic review about decision aids in chronic illnesses. The focus of this review is on persons suffering from

diabetes, as well as persons with cardiovascular and chronic respiratory diseases. This review aimed to assess shared-decision making elements handled in decision aids, as well as their effects.

Chapter 4 describes the observational Optimizing Patient-relevant outcomes with Toujeo (insulin glargine 300 U/mL) IN Routine Diabetes care (OPTIN-D) study about the development in PROs in type 2 diabetes when switching to a particular treatment option, namely insulin glargine 300 U/mL. Less risk of hypoglycemia is one of the observed benefits of insulin glargine 300 U/mL. The association between hypoglycemia and PROs in type 2 diabetes is assessed in **Chapter 5**. One of the most frequently used instruments as PRO in outcomes research is the Diabetes Symptom Checklist-Revised (DSC-R), for which a first attempt towards use in clinical practice is made in **Chapter 6**.

Finally, **Chapter 7** provides a general discussion, including a summary of the results and future directions.

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Part I: Decision aids for shared-decision making

Chapter 2

A systematic review of decision aids that facilitate elements of shared-decision making in chronic illnesses: A review protocol

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Abstract

Background: Shared-decision making (SDM) is a patient-centered approach in which clinicians and patients work side-by-side to decide together on the best course of action for each patient's particular situation. Six key elements of SDM can be distinguished: situation diagnosis, choice awareness, option clarification, discussion of harms and benefits, deliberation of patient preferences and making the decision. Decision aids (DAs) are tools that facilitate SDM. The impact of DAs for chronic illnesses on SDM, clinical and patient reported outcomes remains uncertain. **Methods:** We will perform a systematic review aiming to describe (a) which SDM elements are incorporated in DAs for adult patients with chronic conditions and (b) the effects of DA use on SDM, clinical and patient reported outcomes. This manuscript reports on the protocol for this systematic review. The following databases will be searched for relevant articles: PubMed, Embase, Web of Science, CINAHL and PsycINFO, from their inception to October 2016. We will ascertain ongoing research by querying experts and searching trial registries. To enhance feasibility, we will limit the review to randomized controlled trials (RCTs) including patients with chronic cardiovascular and/or respiratory diseases and/or diabetes. SDM elements incorporated in DAs, DA effects and DA itself will be described. **Discussion:** This study will characterize DAs for chronic illness and provide an overview of their effects on SDM, clinical and patient reported outcomes. We anticipate this review will bring to light knowledge gaps and inform further research into the design and use of DAs for patients with chronic conditions. **Systematic review registration:** PROSPERO registration number: CRD42016050320; http://www.crd.york.ac.uk/PROSPERO.

Background

Shared-decision making (SDM) is a patient-centered approach in which clinicians and patients work together to choose the best course of action for each patient's particular situation.[1] Although most SDM research has been conducted in the context of one-time decisions, SDM is also relevant in decisions that can be reconsidered over time, as is often the case in the self-management of chronic conditions.[2]

In general, a distinction can be made between six key elements of SDM: situation diagnosis, choice awareness, option clarification, discussion of harms and benefits, deliberation of patient preferences and making the decision.[1-4] The opening of an SDM interaction involves a diagnostic conversation (situation diagnosis).[1] This conversation focuses first on understanding the patient's situation and establishing what aspects require action.[1, 4] When more than one reasonable alternative option is available, the clinician should clearly indicate this and highlight that the preferences of the patient are important in deciding on the course of action (choice awareness).[3] Subsequently, the clinician and the patient discuss how each option fits and accommodates within each patient's situation (option clarification, discussion of harms and benefits and deliberation of patient preferences). Finally, the clinician and patient reach a decision.[2, 4] When fruitful, SDM results in a course of action that is needed, wanted and more likely to be implemented.[5, 6] SDM may also help facilitate a stronger clinician-patient relationship and shared understanding of treatment of patients health and life goals.[7, 8] To date, the effects of SDM on clinical outcomes have been found to vary across studies.[9-11]

To facilitate SDM, decision aids (DAs) have been developed for use by clinicians and patients, either in preparation for or during the clinical encounter[12, 13] and are designed to help them participate in decisions that involve weighing the harms and benefits of different treatment options.[12] DAs can increase patient knowledge, reduce decisional conflict, help patients choose an option that is congruent with their values, reduce the proportion of patients remaining undecided

and/or who play a passive role in the decision-making process and can have a positive effect on patient-clinician communication.[12, 14-17] These findings, however, mostly relate to one-time decisions. Whether the DAs designed for use in chronic conditions actually support the key elements of SDM and improve outcomes is unclear.

The aims of this review therefore are to 1) describe which SDM elements are present in DAs for patients with chronic conditions, including cardiovascular diseases, chronic respiratory diseases and/or diabetes, 2) determine the effects of these DAs compared to usual care or active controls (i.e., alternative interventions such as patient education) on frequently studied SDM outcomes (i.e., decisional conflict, knowledge, patient participation in decision making, treatment decision (preference), treatment satisfaction, decision satisfaction, conversation satisfaction, risk expectations and perceptions, consultation time) and 3) determine the effects of these DAs on clinical outcomes (i.e., lipid levels, blood pressure, smoking status, (maximal) oxygen uptake, glycemic control, Body Mass Index (BMI), adherence, achieving treatment goals) and patient reported outcomes (i.e., quality of life, perceived health status, emotional distress, self-efficacy) compared to usual care or active controls.

Since collecting data on DAs available for all chronic illnesses is unfeasible, we selected those chronic conditions the World Health Organization recognizes as most prevalent[18-20] and are most likely to require self-management. The selected SDM, clinical and patient reported outcomes are considered by the authors as most relevant for the selected chronic conditions. We hypothesize that DAs that cover multiple elements of SDM will be more likely to have positive effects on SDM (process) outcomes, as well as on patient reported outcomes. For clinical outcomes, we have no reason to hypothesize a consistent response.

Methods

Study design

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P).[21]

Eligibility criteria

Type of studies

Articles will be selected if they report on randomized controlled trials (RCTs) comparing the use of DAs for one or more of the selected chronic conditions to usual care and/or active controls. There will be no limit to the study setting and time frame.

Type of participants

Studies enrolling adult (18 years or older) patients with a diagnosis of a chronic condition defined by the World Health Organization as main types[18-20] and requiring self-management: cardiovascular diseases (e.g., coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, pulmonary embolism, myocardial infarction and stroke), chronic respiratory diseases (e.g., chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and pulmonary hypertension) and/or diabetes (type 1 and type 2) will be included.

Type of interventions

Any DA designed to help clinicians and/or adult patients in shared-decision making will be included.[12]

Type of outcome measures

SDM outcomes (i.e., decisional conflict, knowledge, patient participation in decision making, treatment decision (preference), treatment satisfaction, decision satisfaction, conversation satisfaction, risk expectations and perceptions, consultation time) will be assessed. Clinical outcomes (i.e., lipid levels (LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides), blood pressure, smoking status, (maximal) oxygen uptake, glycemic control, BMI, adherence, achieving treatment

goals) and patient reported outcomes (i.e., quality of life, perceived health status, emotional distress (anxiety, illness-related distress), self-efficacy) will also be extracted. There will be no restrictions based on measurement methods.

Information sources and search strategy

With the help of an expert librarian (LJS), we will design and conduct a search strategy to find eligible articles on RCTs in the following databases from inception to October 2016: PubMed, Embase, Web of Science, CINAHL (through EBSCO), PsycINFO (through EBSCO) and Cochrane Library (see Appendix 1 for the search strategy). The design and conduction of this search strategy will be finished around October 2016. There will be no restrictions based on language, year of publication or year of development of the DAs. Around September 2017, the initial electronic search strategy will be carried out a second time for articles published between October 2016 and September 2017. This second electronic search strategy will be supplemented by screening the reference lists from included studies to identify potentially eligible studies that may have been missed. In addition, ongoing research will be traced by contacting experts in the field and searches in databases for ongoing research (including: http://isrctn.com, http://narcis.nl, http://trialregister.nl, http://www.controlled-trials.com and http://www.clinicaltrials.gov). If published before the publication date of our systematic review (submission will take place around December 2017), ongoing studies will be included when data extraction for included studies is completed (September 2017). We will contact field experts to inquire about ongoing RCTs fulfilling our eligibility criteria. These contacts will be established through e-mail, Facebook, LinkedIn, other media or face-to-face contact in February 2017. Author contact will be documented by name of sender, date of contact and full content of e-mail, Facebook message, LinkedIn message or other way of contact. If multiple articles are available on one RCT, all will be included (articles on interim analyses as well). Search activities will be documented by filling in a table including search term(s), information source, date of coverage and total number of publications found.

Data management

All search results will be uploaded into Covidence for automatic deduplication (October 2016). Covidence will be used for both abstract (November and December 2016) and full-text screening (January 2017 until March 2017). The total number of results before and after de-duplication will be documented per database.

Selection process

Prior to abstract screening, eligibility criteria will be iterated for clarity to ensure comprehension by reviewers. Two reviewers will independently assess whether the abstracts of articles meet eligibility criteria. Since some outcomes may not be reported in the abstract (e.g., due to word restrictions) but are in the full-text article, outcomes will not be considered during the abstract screening phase. When reviewers disagree about including an abstract, the full text will be considered. Abstract screening will take place from November to December 2016.

Following the screening of titles and abstracts, corresponding full-text articles will again be assessed independently by two reviewers. After a pilot with 20 included full-texts, discrepancies will be discussed and instructions and/or criteria adapted if needed. Disagreements at this phase will be resolved by consensus or arbitration by a third reviewer. Reasons for non-eligibility will be documented by the reviewers. Furthermore, agreement between reviewers (yes/no) and decision following consensus agreement (including date of consensus) will be captured for every reference. Chance-adjusted inter-rater agreement for full-text screening will be estimated using the Kappa statistic.[22] Full-text screening will take place from January 2017 until March 2017.

During both title/abstract and full-text screening the total number of titles/abstracts or full-texts before and after screening will be documented, as well as the number of excluded titles/abstracts or full-texts (including reasons for exclusion of full-texts).

Data collection process

Two reviewers will independently collect data for all eligible full-text articles on RCTs. Data will not be collected for articles on interim analyses, if articles on the same RCT based on the total follow-up period are available (we will include those with the total follow-up). Results for all time spans (follow-up measurements/time intervals) will be captured. If one DA is tested in multiple trials, all will be included. A data extraction form, including information about publication, DA characteristics, SDM elements and effectiveness, will be designed and pilot tested before. After extracting data from five full text reports (or all articles when less than five full-text articles will be eligible), the noted differences between reviewers will be discussed in order to get optimal calibration for data-extraction. If necessary or desired, the extraction form will be adapted based on feedback from the reviewers to improve usability and ensure completeness. Similar to article selection, two or more reviewers will independently extract data. Disagreements will be resolved by consensus. If consensus on data extraction between the two parties cannot be reached, a third reviewer will arbitrate.

A recent study showed that health information tools developed and tested online hardly remain available and accessible.[23] Therefore, all corresponding authors of included studies will be contacted through e-mail to assess whether the DA is currently available and used in practice. Non-responders will be sent a reminder email after two weeks. If the second attempt is unsuccessful, other authors will be contacted. If none of the authors responds, we will contact the corresponding author (or other authors) by phone. Every author contact will be documented by name of the sender, date of contact and full content of e-mail contact or a summary of telephone contact. Data collection will take place around August 2017.

Missing data

If data presented in the studies is unclear, missing or presented in a form that is either un-extractable or difficult to reliably extract, we will request data from the authors following the same

author contact protocol described above. As above, author contact will be documented by date and full content of e-mail contact.

Risk of bias in individual studies

Risk of bias will be assessed in individual studies using the Cochrane Collaboration's tool for assessing RCTs risk of bias. This tool takes into consideration six domains: 1) sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective outcome reporting and 7) other bias. Two reviewers will independently assess the risk of bias at all domains for every RCT.[24] Criteria for judgement per domain are to be found in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.[25] Disagreement will again be resolved by consensus or if not possible, by arbitration of a third reviewer. Risk of bias in individual studies will enable a critical view on interpretation of DA effects found and will be assessed around September 2017.

Outcomes and data synthesis

We will describe the RCTs included in our review, as well as the DAs that are tested in these studies. This includes the SDM elements incorporated in DAs, the effects of DAs on SDM outcomes (i.e., decisional conflict, knowledge, patient participation in decision making, treatment decision (preference), treatment satisfaction, decision satisfaction, conversation satisfaction, risk expectations and perceptions, consultation time), clinical outcomes (i.e., lipid levels (LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides), blood pressure, smoking status, (maximal) oxygen uptake, glycemic control, BMI, adherence, achieving treatment goals) and patient reported outcomes (i.e., quality of life, perceived health status, emotional distress (anxiety, illness-related distress) self-efficacy). For continuous outcomes mean (change) differences between intervention and control group, together with p-values and 95%-confidence intervals (95%-CIs), will be extracted. Regarding dichotomous outcomes, both risk ratios (RRs) and odds ratios (ORs) with 95%-CIs will be extracted or calculated if needed and possible. Furthermore, elements of SDM incorporated in DAs, risk of bias

per RCT and DA itself will be described. Since heterogeneous populations and outcomes will be synthesized and much heterogeneity in time spans/intervals is expected, performing a meta-analysis will be difficult and perhaps not as useful. Therefore, in the likely event that conducting random-effects meta-analyses of the effects of these DAs on outcomes proves unwise, we will summarize the results narratively. Data will be synthesized around October 2017.

Discussion

This is an overview of chronic care DAs developed and tested in RCTs, SDM elements they support and their effects on SDM, clinical and patient reported outcomes. The insights produced in it will help inform further research aimed at developing, testing and successfully implementing future DAs in clinical practice for patients with chronic conditions.

Our proposed review also has potential limitations. Other than duplicate assessment and clear eligibility criteria, we do not have safeguards in place to prevent a biased set of studies to be included. Also, since we are interested in the efficacy of DAs, we will limit our search strategy to RCTs as these have the most valid experimental design of research.[26] This may exclude (well designed and developed) DAs that have not (yet) been tested in trials. Finally, we limit our search strategy to the most prevalent cardiovascular diseases, chronic respiratory diseases and diabetes,[18-20] an incomplete list of chronic diseases. Learnings from this review may help further study the utility of DAs in the SDM process in less prevalent chronic conditions.

This review will provide a broad overview of DAs available for patients with cardiovascular, chronic respiratory diseases and diabetes, as well as SDM elements they incorporate and their effects on a broad range of outcomes. It may bring to light useful information to a variety of stakeholders including funding agencies, policy-makers, researchers, clinicians and patients with chronic conditions with the objective of delivering kind and careful care to patients with chronic conditions.

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Chapter 3

Decision aids that facilitate elements of shared-decision making in chronic illnesses: A systematic review

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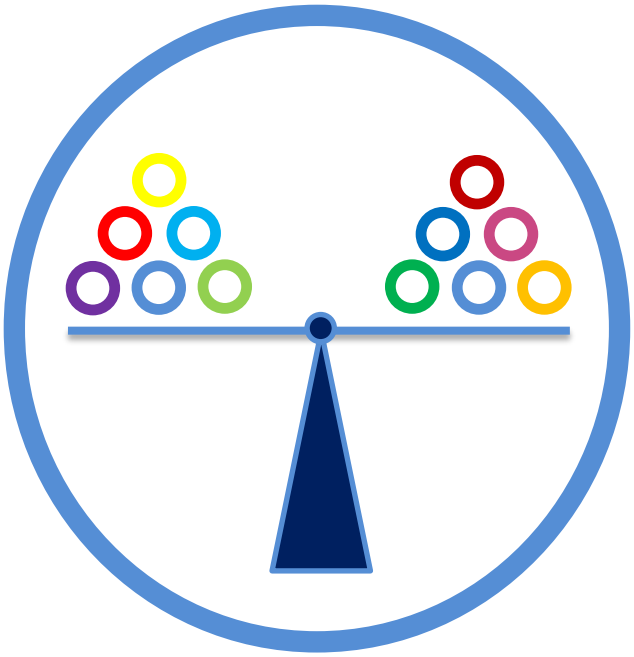

Abstract

Background: Shared-decision making (SDM) is a patient-centered approach in which clinicians and patients work together to find and choose the best course of action for each patient's particular situation. Six SDM key elements can be identified: situation diagnosis, choice awareness, option clarification, discussion of harms and benefits, deliberation of patient preferences, and making the decision. The International Patient Decision Aid Standards (IPDAS) require that a decision aid (DA) support these key elements. Yet, the extent to which DAs support these six key SDM elements and how this relates to their impact remain unknown. **Methods:** We searched bibliographic databases (from inception until November 2017), reference lists of included studies, trial registries, and experts for randomized controlled trials of DAs in patients with cardiovascular or chronic respiratory conditions or diabetes. Reviewers worked in duplicate and independently selected studies for inclusion, extracted trial and DA characteristics, and evaluated the quality of each trial. **Results:** DAs most commonly clarified options (20 of 20; 100%) and discussed their harms and benefits (18 of 20; 90%; unclear in two DAs); all six elements were clearly supported in 4 DAs (20%). We found no association between the presence of these elements and SDM outcomes. **Conclusions:** DAs for selected chronic conditions are mostly designed to transfer information about options and their harms and benefits. The extent to which their support of SDM key elements relate to their impact on SDM outcomes could not be ascertained. **Systematic review registration:** PROSPERO registration number: CRD42016050320; http://www.crd.york.ac.uk/PROSPERO.

Background

Shared-decision making (SDM) is a patient-centered approach in which clinicians and patients work together to find and choose (by taking into account the best available evidence, as well as the patients' problems, values, preferences, and contexts) the best course of action for each patient's particular situation,[1] an approach that is pertinent to the care of patients with chronic conditions.[2] Decisions in the context of self-management of chronic conditions differ from one-times decisions, as in the former decisions can often be reconsidered.[2] Six key elements of SDM can be identified from the literature: situation diagnosis, choice awareness, option clarification, discussion of harms and benefits, patient preferences deliberation and making the decision.[1-4] As noted by Stiggelbout and others,[5, 6] SDM promotes actions that are needed, wanted, and more likely to be implemented. A shared understanding and treatment focused on patients' health and life goals, as well as a stronger clinician-patient relationship, may also be facilitated by SDM.[7, 8]

A SDM interaction starts with a diagnostic conversation (situation diagnosis).[1] This opening first focuses on understanding the patient's situation and establishing the aspects that require action.[1, 4] When multiple reasonable options are available, then the clinician should indicate this and highlight the importance of the patient's preferences in deciding on the course of action (choice awareness).[3] Subsequently, the patient and clinician deliberate about the way each option fits and accommodates within each patient's situation (option clarification, discussion of harms and benefits, and patient preferences deliberation). Finally, a decision is made by the clinician and patient (making the decision).[2, 4]

SDM can be facilitated by decision aids (DAs) that have been developed for use by clinicians and patients, either during or in preparation for the clinical encounter.[9-11] DAs can help patients choose an option that is congruent with their values, reduce the proportion of patients remaining undecided and/or who play a passive role in the decision-making process, and improve patient knowledge, decisional conflict, and patient-clinician communication.[11-15] The International Patient

Decision Aid Standards (IPDAS) Collaboration aims to enhance the quality and effectiveness of DAs by establishing an evidence-informed framework for improving their content, development, implementation, and evaluation.[16] The IPDAS Collaboration defines a DA as "a tool designed to help people participate in decision making about health care options",[9] and developed a minimal set of standards for qualifying a tool as a DA.[17] According to this minimal set, all SDM key elements, except making the decision, should be handled by a tool in order to regard it as a DA.[17] Despite this minimal set of qualifying criteria, investigators have found that fostering choice awareness through the use of a DA was not a prerequisite for fostering choice awareness per se during the encounter.[18] Therefore, it is unclear whether tools should support all qualifying IPDAS criteria for these tools to support SDM. Therefore, we define a DA in the current review as "any tool designed to support SDM".

To the best of our knowledge, there is no empirical data to tell us which of the six key elements are supported by DAs and whether there is an association between support for these key elements and SDM outcomes. We hypothesize that DAs that cover multiple elements of SDM are more likely to have positive effects on SDM outcomes, as well as on patient-reported outcomes (PROs). With regard to surrogate and clinical outcomes, there is no reason to expect a consistent response. A previous systematic review of the effects of DAs found that more detailed DAs better improve knowledge and reduce some aspects of decisional conflict compared to simple DAs, and concluded that more research is needed to evaluate the level of detail needed in DAs.[19] The current review aims to meet this need by studying the SDM elements incorporated in DAs and their effect on SDM outcomes.

This review aims to: 1) describe the SDM elements present in DAs for patients with common chronic conditions (cardiovascular, chronic respiratory diseases or diabetes) tested in randomized controlled trials (RCTs), and 2) determine an association between the key elements present and the effects of these DAs compared to usual care or active controls on SDM outcomes (e.g., conversation duration, patient participation, knowledge, and decisional conflict).

Methods

The protocol of this systematic review was previously published[20] and registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42016050320; http://www.crd.york.ac.uk/PROSPERO). The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Study eligibility

We searched RCTs comparing the use of DAs (any tool designed to support SDM) to usual care or active controls (except other DAs) in adults with cardiovascular disease, chronic respiratory disease, or diabetes and measuring their impact on SDM and health outcomes (patient-reported, surrogate, and clinical outcomes). As described in detail previously,[20] we selected chronic conditions that are most prevalent according to the World Health Organization,[22-24] most likely to require self-management, and for which decisions may be revisited. We included all pertinent publications of an eligible study. There were no exclusions based on language or year of publication.

Information sources and search strategy

To identify all relevant publications we performed systematic searches, in collaboration with a medical librarian (LJS) in the bibliographic databases PubMed, Embase.com, Web of Science, CINAHL (through EBSCO), PsycINFO (through EBSCO), and the Cochrane Library from inception to November 7th, 2017. Search terms included MesH in PubMed, EMtree in Embase.com, Cinahl headings in Cinahl, indexed terms from the Thesaurus in PsycINFO as well as free text terms. We used free text only in the Cochrane Library and Web of Science. Search terms compressing “shared decision making” were used in combination with “cardiovascular diseases” OR “chronic respiratory diseases” OR “diabetes”. Search results were limited to RCTs. Duplicate articles were excluded. All languages were accepted. The full search strategies for all databases can be found in Appendix 1. In early 2017, THW contacted by email and queried SDM experts participating in the Facebook group “Shared@ Shared Decision Making Network”, and in the LinkedIn groups “Platform SDM GB” and

"Shared Decision Making in Netherlands" for additional eligible studies. THW also reviewed trial registries including http://isrctn.com, http://narcis.nl, http://trialregister.nl, and http://www.clinicaltrials.gov. MFSH reviewed the reference lists from included studies.

Study selection process

After deduplication, pairs of reviewers (two hired persons, GSB, RRG, and THW) working independently and in duplicate, assessed each abstract for eligibility. Studies considered potentially eligible by at least one reviewer were included for the full text phase. THW and RRG reviewed selected full-text articles independently and in duplicate. Disagreements were resolved by a third reviewer (GSB or OJP).

Data collection process

Data about study and DA characteristics, study quality, and outcomes were extracted by pairs of reviewers working in duplicate (two hired persons, RRG, MFSH, YZI, and THW) with conflict resolved by a third reviewer (GSB, NRE, YZI, and RRG; YZI and RRG resolved conflicts of parts for which they did not collect data). We used the definitions in Box 1 to determine which key SDM components were present. Sets of three articles were used to train and calibrate reviewers through extraction and discussion of results among reviewers. Outcomes collected were those most proximate to the encounter of interest.

Box 1. Definitions for the key elements of SDM in decision aids

Key element of SDM	Definitions for this study[4, 18]
Situation diagnosis	The DA explicitly describes the patient's problem.
Choice awareness	The DA explicitly acknowledges that the patient's situation is mutable, that there is more than one sensible way to address or change this situation, and that patient input matters in deciding how to proceed.
Option clarification	The DA explicitly lists and describes the options available.
Harms and benefits discussion	The DA explicitly explains the harms and benefits of the available options.
Patient preferences deliberation	The DA explicitly elicits the patient's preferences or explicitly motivates the parties to discuss them.
Making the decision	The DA explicitly elicits the patient's wish to make or defer a decision, asks for the patient's choice, or describes the patient's choice.

Risk of bias in individual studies

OJP and THW independently assessed the risk of bias on outcome level at all domains of the Cochrane Collaboration's tool for RCTs,[25, 26] with disagreement resolved by consensus. Because blinding of patients and clinicians to the use of conversation aids is not possible, we ignored the two blinding factors. Otherwise, when one or more of the five other domains was regarded as being at high risk of bias, then the summary assessment of risk of bias was "high". If one or more domain was "unclear" and all others were "low risk", then we summarized the risk of bias as "unclear". If all domains were "low risk," then the summary assessment of risk of bias was "low".

Outcomes and data synthesis

Data on both SDM (e.g., conversation duration, patient participation, knowledge, and decisional conflict) and health outcomes (patient-reported, surrogate, and clinical outcomes) were collected. Standardized mean differences (SMDs) together with their 95% confidence intervals (95%-CIs) were calculated for continuous outcomes using Review Manager 5.3.[27] Odds ratios (ORs) together with their 95%-CIs were directly extracted from the reports. If the mean difference and/or its standard error (SE) and 95%-CI were not presented in the article, then the SMD together with its 95%-CI were calculated by entering the mean score/value per arm together with their standard deviations (SDs). If the 95%-CI for an OR was not presented, then numbers for every cell in the 2x2-table were inserted into Review Manager 5.3 to be calculated. The SMD could not be calculated when only interquartile ranges were reported. We also summarize the data narratively according to our protocol.[20]

Missing data and author contact

All corresponding authors (or other authors if no response after approximately six weeks) of included studies were contacted through e-mail and, if no response, again approximately four weeks later (although originally planned, we did not contact authors by phone) to request missing data or clarifications. If authors did not respond or could not provide a missing standard deviation needed to

calculate the SMD, then the SD of the most comparable study with the same outcome and measurement instrument was imputed.

Results

Figure 1 describes the flow of the study selection. Chance-adjusted inter-reviewer agreement (k) for eligibility was only fair (k=0.3-0.4).[28] We found 24 articles reporting on 23 RCTs of 20 DAs (10 DAs for cardiovascular disease, two DAs for respiratory diseases, and eight DAs for diabetes). The effectiveness of Statin Choice was studied in three RCTs described in four articles meeting our criteria and The Diabetes Medication Choice Decision Aid was studied in two RCTs described in two separate articles. Other DAs were studied in one RCT described in one article. Appendix 2 presents the risk of bias assessment on outcome level per study. Besides the study of Gagné et al. 2017,[29] all studies have an unclear or high risk of bias for all outcomes assessed in this review.

Figure 1. Flowchart of study selection

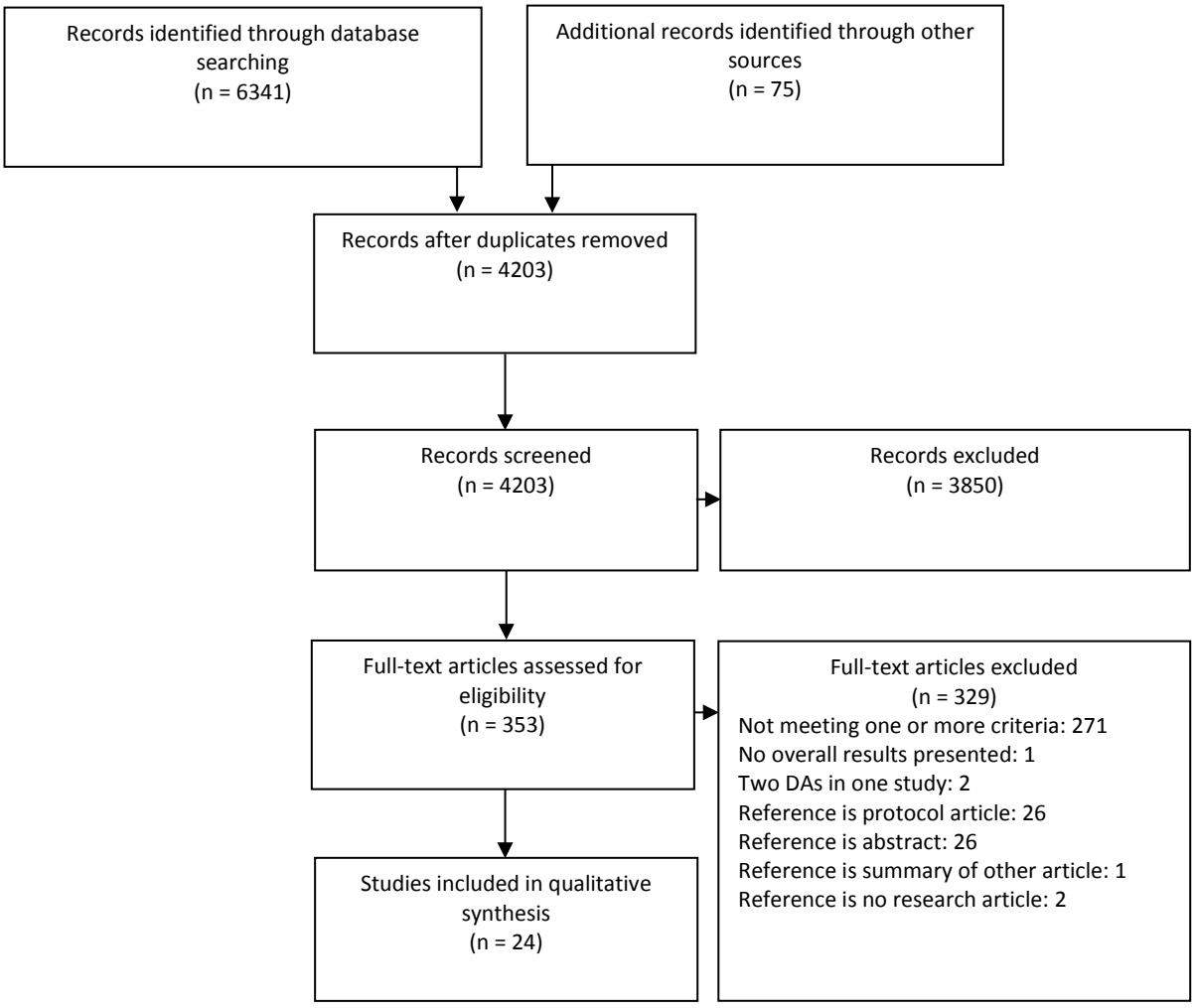

Table 1 shows the SDM elements supported per DA. The elements were described as "unclear" if the DAs were neither described clearly or available for our inspection, and/or if reviewers were uncertain whether the regarding element was included in the DA. The option clarification element (included in 20 of 20 DAs; 100%) and the harms and benefits discussion (included in 18 of 20 DAs; 90%; unclear in two DAs) are the elements most commonly clearly included in the DAs. The other elements are less common and more uncertainty is present whether these elements are included, especially with regard to choice awareness (uncertain in 14 out of 20 DAs; 70%). All elements were clearly supported in four DAs (20%). Table 1 also shows the DA effects on SDM outcomes. We could not glean any association between SDM elements present in the DAs and SDM outcomes. Appendix 3 reports details of the DAs included here and Appendix 4 their impact on SDM and health outcomes. We imputed the SD for the decisional conflict outcome for Mann et al. 2010[30] using the SD found by Weymiller et al. 2007[31] for the same outcome in the same context.

Table 1. SDM elements included in DAs and DA effects on SDM outcomes

DA Study, year	**SDM elements in DA**						**SDM outcomes**				
	Situation diagnosis	**Choice Awareness**	**Option clarification**	**Harms & Benefits**	**Patient preferences**	**Making decision**	**Knowledge**	**Patient participation**	**Decisional conflict**	**Satisfaction**	**Time**
Cardiovascular diseases											
Knops et al. 2014[32]	✔	✔	✔	✔	✔	✔	↔	•	↔	↔	•
Man-Son-Hing et al. 1999[33]	?	?	✔	✔	✔	✔	•	↔	↔	↔	•
Fraenkel et al. 2012[34]	✔	?	✔	✔	✔	•	•	•	•	•	•
Thomas et al. 2013[35]	✔	?	✔	✔	?	?	↔	•	↔	•	•
El-Jawahri et al. 2016[36]	✔	✔	✔	?	?	?	↑	•	•	•	•
Korteland et al. 2017[37]	✔	✔	✔	✔	✔	✔	•	•	↔	•	•
Thomson et al. 2007[38]	?	?	✔	✔	✔	✔	↔	•	↑	•	•
Morgan et al. 2000[39]	✔	?	✔	✔	?	?	↑	•	•	↔	•
Coylewright et al. 2016[40]	•	?	✔	✔	✔	✔	•	↔	↔	•	•

Table 1. Continued

McAlister et al. 2005[41]	✔	✔	✔	✔	✔	✔	•	•	↑	•	•
Respiratory diseases											
Gagné et al. 2017[29]	✔	?	✔	✔	✔	✔	↔	•	↔	•	•
Slok et al. 2016[42]	✔	?	✔	?	✔	✔	•	•	•	•	•
Diabetes											
Huang et al. 2017[43]	✔	✔	✔	✔	✔	•	•	•	↔	•	•
Statin Choice[44 30 31 45]	✔	?	✔	✔	•	✔	↑	↑	↑/↔	↑	↔
Mathers et al. 2012[46]	?	?	✔	✔	✔	?	•	•	↑	•	↔
Heisler et al. 2014[47]	✔	?	✔	✔	✔	✔	↔	•	↔	•	•
Bailey et al. 2016[48]	✔	?	✔	✔	✔	✔	↑	•	↑	•	•
Denig et al. 2014[49]	✔	✔	✔	✔	✔	✔	•	•	•	•	•
Diabetes Medication Choice[50 51]	•	?	✔	✔	✔	•	↔	↑	↔	•	•
den Ouden et al. 2017[52]	•	?	✔	✔	✔	✔	•	•	•	•	•

Elements: • = not present; ? = unclear; ✔ = present; Outcomes: • = not reported; ↔ = no statistically significant effect; ↑ = favored DA

Discussion

This review presents an overview of chronic care DAs developed and tested in RCTs, SDM elements they support, and their effects on SDM outcomes and health outcomes. Most DAs support the clarification of options and the discussion of their benefits and harms, while other elements are less prevalent. Almost all trials were at an unclear or high risk of bias, and no association between SDM elements supported in the DA on the one hand and SDM outcomes achieved versus control on the other hand could be determined.

SDM elements handled by DAs

Our analysis of SDM elements supported is consistent with previous literature stating that most DAs focus and are tested on providing information or discussing choices rather than on creating

empathic conversations.[53] We could not, however, estimate the relationship between the extent to which DAs support SDM elements and SDM outcomes.

Possibly, some SDM elements may have been left out of DAs by design. This choice may depend on what features were thought most important by the developers (e.g., patient education, risk communication, preference elicitation, or patient empowerment). The importance of incorporation of SDM elements in DAs may be situation-dependent, but the way this works is unclear. Future research should clarify this situation-dependence and eventually inform possible reconsideration of the IPDAS minimum standards for DA qualification.[17]

DA effects

The inability to find any empiric association between features present and SDM outcomes prevents us from using this evidence base to make recommendations about the content of DAs for use in patients with chronic conditions. Multiple factors potentially explain the varying effects, including: whether a *patient decision aid* or *conversation* aid is used,[10] chronicity of conditions,[2] design process,[54, 55] context, target population,[19] and degree of detail needed.[19] Future studies may assess the dependency of DA effects on these factors and their interactions with the SDM elements.

Difficulties faced

Some difficulties were faced when conducting this review. A major difficulty during the article selection was the suboptimal reporting of DA characteristics. The aim of DAs is not always explicitly described and if described, it still may be questionable whether implementing SDM is implicitly aimed for as the concept of SDM itself is highly debatable.[56] Namely, a review found 31 separate concepts to explicate SDM.[57] Our ability to categorize whether SDM elements were present was limited by the fact that some DAs were not available and/or the description of the DA's content was not clear and detailed. The latter is in line with literature.[58, 59] Even when DAs were available and/or content was clearly described, it may not always be clear-cut whether or not an element is handled. Therefore, data regarding the SDM elements is based on reviewers' judgements.

Furthermore, it may sometimes be unclear whether or not a condition is chronic (e.g., aneurysms). These conditions were included in this review in order to be as comprehensive as possible, but the decisions to be made may not be reversible over time or only to a limited extent. These aspects may have resulted in the fair inter-rater agreement. Another difficulty was found in the large methodological heterogeneity across studies (e.g., measurement instruments, timing of outcome measurements, and presentation of results).

More guidance is needed on the reporting of SDM elements and DA aims, the measurement instruments to use in RCTs studying DA effects, as well as the timing of outcome measurements and the way results are presented in articles. Furthermore, the quality of RCTs studying DA effects can be improved. The new Standards for UNiversal reporting of patient Decision Aid Evaluation studies (SUNDAE) checklist seems to meet this need as it helps to ensure the high-quality reporting of DA evaluation studies, as well as its intelligibility and transparency.[59]

Strengths and limitations

This review is the first to report on SDM elements included in DAs developed for chronic conditions, and its relations to a range of SDM outcomes. This review underscores the importance of methodological improvement of DA evaluation studies, which hopefully will be attained by the new SUNDAE checklist.[59]

Our review has some limitations. Since we were interested in the efficacy of DAs, we have limited our search strategy to RCTs,[60] which may have led to exclusion of (well designed and developed) DAs that have not been tested in trials. Finally, we limited our search strategy to the most prevalent cardiovascular diseases, chronic respiratory diseases, and diabetes,[22-24] an incomplete list of chronic diseases. This while a silver bullet of the literature, probably brings to light what is happening in other chronic illnesses.

Future research

Future research should focus on empirically testing which SDM elements should be included in DAs, and take situation-dependency into account. This warrants studies with a sound methodology and low risk of bias that are currently lacking.

Conclusions

Tools to promote SDM for patients with chronic conditions support only some key recommended SDM elements thought to be important for SDM. The literature has not examined the relationship between explicit support for these elements in DAs and SDM outcomes.

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Part II: Patient-reported outcomes

Chapter 4

Improved diabetes medication convenience and satisfaction in persons with type 2 diabetes after switching to insulin glargine 300 U/mL: Results of the observational OPTIN-D study

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Abstract

Objective: Insulin glargine-300 (Gla-300) provides less hypoglycemia risk and more flexibility in injection time. The extent to which these effects translate into improved patient-reported outcomes (PROs) is unknown, and is the subject of this observational study. **Research Design and Methods**: Adults with type 2 diabetes treated with basal insulin for at least 6 months initiating Gla-300 were included. Data were collected at baseline (start Gla-300) and at 3-month and 6-month follow-up. Patients and physicians gave reasons for switching to Gla-300 at baseline and the extent to which Gla-300 fulfilled their expectations at 6 months. Mixed model analyses examined PRO changes over time, with emotional well-being (WHO-5 Well-Being Index) as the primary outcome. The secondary outcomes were hypoglycemia incidence, hemoglobin A1c (HbA1c), hypoglycemia worries (worry subscale of the Hypoglycemia Fear Survey), diabetes distress (short form of the Dutch version of the Problem Areas In Diabetes Scale), diabetes medication convenience (Diabetes Medication System Rating Questionnaire (DMSRQ)), sleep quality and duration (Pittsburgh Sleep Quality Index), and adherence (Summary of Diabetes Self-Care Activities). **Results:** 162 patients participated: 53.70% were men, the mean age was 65.54 years (9.05), baseline mean HbA1c was 7.87% (1.15) (62.48 mmol/mol (12.61)), and mean diabetes duration was 15.14 years (6.65). Mean WHO-5 Well-Being Index scores improved non-significantly from 61.94 (19.52) at baseline (T0) to 63.83 (19.67) at 6 months (T2). Mean DMSRQ scores improved significantly from 32.96 (9.02) (T0) to 36.70 (8.85) (T2) ($p<.001$). Dose (less volume) was a switching-reason in 69.60% of patients and 63% of physicians, and flexibility in 33.30% and 24.70%, respectively. Gla-300 fulfilled the expectations or even better than expected in 92.30% of patients and 88.90% of physicians. **Conclusions**: In a relatively well-controlled sample of adults with type 2 diabetes, switching to Gla-300 improves diabetes medication convenience.

Introduction

Long-acting (basal) insulin analogs have contributed to improved management of diabetes over the last decade. The first and most commonly used analog is insulin glargine 100 U/mL (Gla-100),[1, 2] with a well-established mode of action and profile of efficacy and safety.[3-5] It has advantages compared with human neutral protamine Hagedorn (NPH) insulin, notably reduction of nocturnal and overall hypoglycemia.[1, 6] This benefit is clinically relevant because, in addition to concerns about medical risks associated with hypoglycemia, fear of hypoglycemia is a leading barrier to starting and continuing insulin therapy.[7-9] However, hypoglycemia continues to be observed during Gla-100 treatment,[1, 4, 6, 10] suggesting that a basal insulin with an even flatter and longer action profile might further improve safety and tolerability. Research to date shows that the new insulin glargine 300 U/mL (Gla-300) provides a flatter and more prolonged pharmacokinetic and pharmacodynamic profiles as compared with Gla-100,[11] thereby meeting this need. With regard to hemoglobin A1c (HbA1c), Gla-300 appears to perform as well as Gla-100 in patients with type 2 diabetes, but with less risk of hypoglycemia and more flexibility in injection time.[11] It is unknown if these benefits of Gla-300 relative to Gla-100 translate into improved patient-relevant outcomes. We could hypothesize that Gla-300 may improve patients' well-being due to a reduction in glycemic variability and hypoglycemia, and perhaps more convenience due to more flexibility in injection time. Patient-reported outcomes (PROs) are subjective reports and represent what is most important to patients about a condition and its treatment.[12] These reports come directly from patients about how they feel and function in relation to a health condition and its therapy, without interpretation by healthcare professionals or anyone else. PROs are becoming increasingly important in weighing the pros and cons of a particular medication or treatment regimen incorporating the patient's perspective. The American Diabetes Association and the European Association for the Study of Diabetes advocate for patient-centeredness, which is defined as an approach to "providing care that is respectful of and responsive to individual patient preferences, needs and values and ensuring that patient values guide all clinical decisions".[5] While the glycemic benefits of Gla-300 have been studied extensively before,

evidence from clinical practice whether these benefits translate into PROs is lacking and is the primary focus of the current OPTIN-D (Optimizing Patient-relevant outcomes with Toujeo (insulin glargine 300 U/mL) IN Routine Diabetes care) study. The following are the two research questions underpinning OPTIN-D: (1) Do PROs improve following switching to Gla-300? (2) What reasons do patients and physicians see for switching to Gla-300 and are these expectations met? Well-being may be expected to increase as a result of reduced hypoglycemia and/or more injection time flexibility. Hypoglycemia reduction may lead to less hypoglycemia worry,[13, 14] less diabetes distress,[15] and improved sleep quality and duration in case of nocturnal hypoglycemia reduction.[16] Flexibility may favor well-being indirectly through an increase of convenience and ease to be adherent. Patients and physicians may have different perspectives on why switching to Gla-300 might be relevant and what is expected. Weighting the harms and benefits of treatment options is critical in the process of shared-decision making when initiating a new medication. Therefore, insight into (differences between) patients' and physicians' reasons to switch to Gla-300, as well as the extent to which Gla-300 meets expectations, may inform future shared-decision making practices in which Gla-300 is one of the available options.[17-19]

Research Design and Methods

Design and setting

We carried out a prospective observational study with three repeated measurements and a follow-up period of 6 months.

Participants

Physicians involved in the management of type 2 diabetes in primary and secondary care were invited to participate. The prescription of therapies remained under the responsibility of the specialist or general practitioner. Only persons for whom the physician decided recently (0-1 week) to prescribe Gla-300 independently from study entry were enrolled in the study.

The following were the inclusion criteria: diagnosed with type 2 diabetes, started Gla-300 within 1 week before study entry, treated with basal insulin for at least 6 months prior to the start of Gla-300, 18 years or older, able to read and write in Dutch, and signed a written informed consent. Patients were excluded when pregnant at baseline and/or diagnosed with a psychiatric disorder.

Data collection

Data were collected at baseline (start Gla-300; T0) and at 3 months (T1) and 6 months (T2) after Gla-300 initiation at regular visits. Patients with type 2 diabetes signed written consent after the study was explained to them by their physician and before any study-related procedure. Checks at regular visits were performed in accordance with the Guideline of the Dutch College of General Practitioners[20] and the Clinical Guideline of the Dutch Diabetes Federation.[21]

Measures

Reason(s) for starting Gla-300 (at T0) and *evaluation of* experiences with Gla-300 (at T2) were asked from both patients and physicians, independently, using a self-developed topic list. A maximum of three reasons out of seven could be given by patients and physicians. Options were quality of life, (fear of) hypoglycemia, treatment satisfaction, dose (less volume), flexibility, adherence, and HbA1c. Evaluation of Gla-300 (extent to which Gla-300 met the expectations) was assessed by checking one of five categories, namely worse than expected, slightly worse than expected, as expected, slightly better than expected and better than expected.

At every visit *emotional well-being* (WHO-5 Well-Being Index (WHO-5), 5 items), *worries about hypoglycemia* (worry subscale of the Hypoglycemia Fear Survey (HFS-W), 18 items), *diabetes distress* (short form of the Dutch version of the Problem Areas In Diabetes Scale (PAID-SF), 5 items), *diabetes medication convenience* (Diabetes Medication System Rating Questionnaire (DMSRQ), 17 items), *sleep quality and duration* (Pittsburgh Sleep Quality Index (PSQI), 3 items) and *treatment adherence* (Summary of Diabetes Self-Care Activities (SDSCA), 1 item) were assessed by self-report. Below are a brief description of the measures and their psychometric properties.

Emotional well-being was assessed with the WHO-5, a well-validated instrument assessing emotional well-being pertaining to the past 2 weeks.[22] The WHO-5 consists of five positively stated items including positive mood, vitality and general interests. Scores are transformed to 0-100, with higher scores representing better emotional well-being. A score <50 is considered indicative of low mood and a score ≤28 indicative for clinical depression.[22, 23]

The number of *hypoglycemic episodes* (symptomatic, nocturnal, and severe) during the last 3 months was based on self-report using standardized questions asked by the physician. Symptomatic hypoglycemia is defined as symptoms due to low blood glucose levels during daytime, that the participant can correct independently from others. A nocturnal hypoglycemic episode was defined as a symptomatic episode taking place during the night. Severe hypoglycemia was defined as a low blood glucose level during which the participant is in need of another person (not necessarily medical professional) in order to recover. A severe hypoglycemic episode taking place during the night was defined as a severe episode, not as nocturnal.

Worries about hypoglycemia experienced in the 3 months prior to filling out was assessed using the validated HFS-W.[24] The HFS-W consists of 18 items and the scores range from 0 to 72, with higher scores indicating more worries about hypoglycemia. An elevated score (≥3) on more than one HFS-W item is suggested to be indicative of clinically relevant fear of hypoglycemia.[25]

Diabetes distress was measured using the well-validated five-item PAID-SF.[26] The PAID-SF measures diabetes-specific emotional distress on a 5-point Likert scale (not a problem – a serious problem). Total scores were transformed to a 0-100 range, with higher scores indicating more diabetes distress. PAID-scores of ≥40 are indicative of severe diabetes-specific emotional problems.[26-28]

Diabetes medication convenience was assessed with a selection of 17 items from four subscales (convenience, interference, efficacy, treatment satisfaction) of the DMSRQ. The original 55-

item DMSRQ was validated in persons with type 2 diabetes.[29] Since no Dutch DMSRQ version was available at the start of the study, the selected items were translated by us using the back-translation procedure. Total scores ranging from 0 to 58 were computed by summing all items, with higher score indicating more favorable diabetes medication convenience.

Sleep quality and duration over the past month was assessed by a selection of three items of the validated PSQI.[30]: (1) mean number of hours slept per night; (2) how many times the person experienced trouble sleeping; and (3) global assessment of the sleep quality. The latter two items are scored on a 4-point Likert scale.

Treatment adherence was measured by the one item of the SDSCA on insulin injection adherence.[31] This SDSCA item asks how many of the last 7 days the person took the recommended insulin injections as prescribed. Scores range from 0 to 7 days.

The physician collected the following data from the medical chart during the baseline visit: age, gender, education level, diabetes duration, height, previous and current diabetes medication, diabetes complications, and comorbidities. The data collected by the physician from the medical charts at all visits were the most recent HbA1c and weight/body mass index.

Data analyses

With the WHO-5 as primary outcome, a sample size of 119 would achieve 90% power to detect an effect size of 0.3, indicating a moderate effect over 6 months, with an estimated SD of differences of 1.0 and a significance level (alpha) of 0.05. Taking into account a 25% dropout, we aimed to include at least 160 patients.

Both *reasons for switching to Gla-300* and the *evaluation of Gla-300* were analyzed using descriptive statistics, namely frequencies and valid percentages per category. Mixed model analyses were used to analyze the change over time in the primary outcome, *emotional well-being* (WHO-5), and the secondary outcomes: *hypoglycemia* (symptomatic, nocturnal, severe), *HbA1c*, *hypoglycemia*

worries (HFS-W), *diabetes distress* (PAID-SF), *diabetes medication convenience* (DMSRQ), *sleep quality and duration* (PSQI), and *injection adherence* (SDSCA). Linear mixed model analyses were used for continuous outcomes and logistic mixed model analyses for dichotomous outcomes. Time was treated as categorical represented by dummy variables. For every model a random intercept for patient was added in order to adjust for the dependency of the observations within the patient. Significance was set at a p value threshold of 0.05 for the relationship between time and the primary outcome. For the secondary outcomes, significance was set to a p value of 0.01 to correct for multiple testing and reduce the risk of type 1 error. Since no other variables than the outcomes were expected to be related to the independent variable time, we did not adjust for potential confounding.

Multiple imputation on item level was used only for missing values where the total scores were to be calculated (WHO-5, HFS-W, PAID-SF, DMSRQ), because this gives the most accurate regression model estimates for total scores.[32] When all items of a questionnaire were missing on a certain visit, no imputation for this questionnaire was performed. For patients dropping out of the study, missing items were imputed until the moment of dropout.

Hypoglycemia (symptomatic, nocturnal, severe) was measured on a discrete scale, but as its distribution was skewed to the right analyzed as dichotomous ("0 episodes" versus "1 or more episodes"). All PSQI items were analyzed as continuous in the longitudinal analyses, but because PSQI items 2 and 3 were skewed to the right, they were log-transformed. The SDSCA score was dichotomized ("<7 days a week adherent" vs "7 days a week adherent").

Results

Participants

In total 162 patients from 10 primary and 13 secondary diabetes care clinics spread over the Netherlands participated in the study. Seventeen dropouts were registered: 12 participants 3 months after baseline and 5 participants 6 months after baseline. The main reasons for dropout were

changing healthcare professional, changing treatment regimen, difficulties completing the questionnaire, and adverse events.

Patient characteristics are described in table 1. Of the 162 patients included, 53.70% were men and the mean age was 65.54 years (9.05). The baseline (T0) mean HbA1c was 7.87% (1.15) (62.48 mmol/mol (12.61)), and the mean diabetes duration was 15.14 years (6.65).

Table 1. Demographic and medical characteristics of the study population[a]

Demographics	**Baseline**	**3 months**	**P value Change from baseline to 3 months**	**6 months**	**P value Change from baseline to 6 months**
N	162				
Gender					
Men	87 (53.70%)				
Women	75 (46.30%)				
Age (years)	65.54 (9.05)				
Level of education					
Low	81 (57.10%)				
Average	39 (27.50%)				
High	22 (15.50%)				
Diabetes duration (years)	15.14 (6.65)				
BMI	33.58 (6.09)	33.87 (6.17)		33.74 (6.11)	

Table 1. Continued

Total number of currently ongoing complications and/or co-morbidities					
0	53 (34.20%)				
1	44 (28.40%)				
2	37 (23.90%)				
3 or more	21 (13.50%)				
HbA1c (%)	7.87 (1.15)	7.70 (1.03)	.072	7.67 (1.11)	.020
HbA1c (mmol/mol)	62.48 (12.61)	60.63 (11.29)	.072	60.32 (12.09)	.020
Self-reported symptomatic hypoglycemia (N (%))					
0 episodes	111 (68.50%)	118 (79.20%)	.026	109 (75.20%)	.176
1 or more episodes	51 (31.50%)	31 (20.80%)		36 (24.80%)	
Self-reported nocturnal hypoglycemia (N (%))					
0 episodes	151 (93.20%)	144 (96.60%)	.351	139 (95.90%)	.472
1 or more episodes	11 (6.80%)	5 (3.40%)		6 (4.10%)	
Self-reported severe hypoglycemia (N (%))					
0 episodes	154 (95.10%)	149 (100%)	.198	145 (100%)	.202
1 or more episodes	8 (4.90%)	0 (0%)		0 (0%)	

[a]For dichotomous or categorical variables the absolute numbers by subgroups and the valid percentages relative to the study population without missing values for the regarding variables are displayed. For normally distributed variables the mean and standard deviation are shown. For skewed variables the median and the 25th and 75th percentile are shown.
BMI, body mass index; HbA1c, hemoglobin A1c.

Gla-100 was the most frequently used basal insulin prior to switching to Gla-300 (128 patients); all other patients (2 missing) had used insulin detemir (32 patients). Of the patients, 80.20% used a short-acting insulin at baseline. Basal insulin dose increased from 54.85 (23.71)

units/day (0.55 (0.22) units/kg bodyweight) at baseline to 57.63 (25.94) units/day (0.57 (0.23) units/kg bodyweight) and 57.78 (26.73) units/day (0.57 (0.24) units/kg bodyweight) at 3 and 6 months, respectively.

Table 2 shows the scores for PROs. Symptomatic hypoglycemia incidence decreased non-significantly from 31.50% at baseline (T0) to 24.80% at 6 months (T2) (T0-T2, p=0.176), from 6.80% at T0 to 4.10% at T2 (T0-T2, p=0.472) for nocturnal episodes, and from 4.90% at T0 to 0% at T2 (T0-T2, p=0.202) for severe episodes (see table 1 and appendix 5). The mean HbA1c decreased non-significantly to 7.67% (1.11) (60.32 mmol/mol (12.09)) at T2 (T0-T2, p=0.020) (see table 1 and appendix 5).

Table 2. Changes in patient-reported outcomes over time[a]

	Baseline	**3 months**	**P value Change from baseline to 3 months**	**6 months**	**P value Change from baseline to 6 months**
WHO-5 Mean (SD)	61.94 (19.52)	62.59 (22.01)	.429	63.83 (19.67)	.135
HFS-W Median (IQR)	11 (3-20)	7 (2-16)	.086	8 (2-18)	.024
PAID-SF Median (IQR)	20 (10-35)	15 (5-30)	.286	15 (5-30)	.039
DMSRQ Mean (SD)	32.96 (9.02)	36.62 (7.89)	<.001	36.70 (8.85)	<.001
PSQI item 1 (hours sleep per night)	6.75 (1.49)	6.67 (1.39)	.318	6.66 (1.39)	.292

Table 2. Continued

PSQI item 2					
(trouble sleeping)					
Not at all	65 (41.90%)	46 (31.30%)	.139	59 (41.80%)	.382
Less than once a week	28 (18.10%)	39 (26.50%)		35 (24.80%)	
Once or twice a week	29 (18.70%)	32 (21.80%)		23 (16.30%)	
Three times or more a week	33 (21.30%)	30 (20.40%)		24 (17%)	
PSQI item 3					
(global sleep quality)					
Very good	35 (22.30%)	36 (24.50%%)	.202	39 (27.50%)	.091
Fairly good	90 (57.30%)	86 (58.50%)		78 (54.90%)	
Pretty bad	24 (15.30%)	20 (13.60%)		21 (14.80%)	
Very bad	8 (4.90%)	5 (3.40%)		4 (2.80%)	
SDSCA					
6 Days or less	28 (18.70%)	20 (13.50%)	.224	22 (15.60%)	.531
7 Days	122 (81.30%)	128 (86.50%)		119 (84.40%)	

[a]Scores based on the original (non-imputed) data. P values based on imputed data for WHO-5, HFS-W, PAID-SF, and DMSRQ. For dichotomous or categorical variables, the absolute numbers by subgroups and the valid percentages relative to the study population without missing values for the regarding variables are displayed. For normally distributed variables, the mean and SD are shown. For skewed variables (PAID-SF and HFS-W), the median and the 25th and 75th percentile are shown.
DMSRQ, Diabetes Medication System Rating Questionnaire; HFS-W, worry subscale of the Hypoglycemia Fear Survey; PAID-SF, short form of the Dutch version of the Problem Areas In Diabetes Scale; PSQI, Pittsburgh Sleep Quality Index; SDSCA, Summary of Diabetes Self-Care Activities; WHO-5, WHO-5 Well-Being Index.

Reasons for switching and evaluation of Gla-300

Table 3 shows *patients' top three reasons* for switching to Gla-300: (1) dose (less volume) (69.60%); (2) quality of life (48.60%); and (3) flexibility (33.30%). *Physicians' top three reasons* are (1) dose (less volume) (63%); (2) flexibility (24.70%); and (3) HbA1c (22.20%). According to 88.90% of physicians and 92.30% of patients, Gla-300 fulfilled their *expectations* (or better than expected) (see table 3).

Table 3. Reasons for and evaluation of switching to glargine 300 (Gla-300)

	Patients[a]	**Physicians**[b]
Reasons for switching to Gla-300		
Quality of life	67 (48.60%)	35 (21.60%)
(Fear of) hypoglycemia	14 (10.10%)	26 (16%)
Treatment satisfaction	15 (10.90%)	7 (4.30%)
Dose (less volume)	96 (69.60%)	102 (63%)
Flexibility	46 (33.30%)	40 (24.70%)
Adherence	3 (2.20%)	0 (0%)
HbA1c	19 (13.80%)	36 (22.20%)
Evaluation of switching to Gla-300		
Worse than expected	4 (2.80%)	3 (2.10%)
Slightly worse than expected	7 (4.90%)	13 (9%)
As expected	48 (33.60%)	58 (40%)
Slightly better than expected	28 (19.60%)	24 (16.50%)
Better than expected	56 (39.10%)	47 (32.40%)

[a]The n regarding reasons for switching to Gla-300 is 138; the n regarding evaluation of Gla-300 is 143.
[b]The n regarding reasons for switching to Gla-300 is 162; the n regarding evaluation of Gla-300 is 145.

Primary analyses

The mean WHO-5 scores improved non-significantly from 61.94 (19.52) at baseline (T0) to 62.59 (22.01) at 3 months (T1) and 63.83 (19.67) at 6 months (T2) (see table 2). The estimated change from T0 to T1 was 1.283 (p=0.429; 95% CI -1.895 to 4.462), for T1-T2 was 1.150 (p=0.485; 95% CI -2.079 to 4.379) and for T0-T2 was 2.433 (p=0.135; 95% CI -0.756 to 5.622) (see table 2 and appendix 5).

Based on imputed data, in total 41 patients (25.50%) reported suboptimal well-being at baseline: 27 patients (16.70%) scored between 29 and 50 at baseline (indicative for low mood), and 14 patients (8.60%) scored 28 or lower (indicative for clinical depression).

Secondary analyses

The mean DMSRQ scores improved from 32.96 (9.02) at baseline (T0) to 36.62 (7.89) at 3 months (T1) (estimated change T0-T1=3.280; p<0.001; 95% CI 1.670 to 4.890) and 36.70 (8.85) at 6 months (T2) (estimated change T0-T2=4.396; p<0.001; 95% CI 2.774 to 6.019) (see table 2 and appendix 5).

All other secondary longitudinal analyses showed non-significant changes at a p value threshold of 0.01, although a trend toward improvement in HbA1c (T0-T2), HFS-W (T0-T2), PAID-SF (T0-T2), and PSQI item 2 (trouble sleeping; T1-T2) was found using a significance level of 0.05 (see tables 1 and 2 and appendix 5).

Based on imputed data, 33 patients (20.40%) had more than one elevated HFS-W items (indicative of clinically relevant fear of hypoglycemia) at baseline and 36 patients (22.20%) had a PAID score of ≥40 (indicating severe diabetes-specific emotional problems) at baseline.

Post-hoc analyses

Based on imputed data, the mean WHO-5 and DMSRQ scores were calculated to assess differences between the original and imputed WHO-5 and DMSRQ scores. No remarkable differences were observed (see appendix 6).

We also performed linear mixed model analyses to check for changes over time *per DMSRQ item*. A p value threshold of 0.01 was used. The DMSRQ total score improved significantly between T0 and T1, as well as between T0 and T2 (p<0.01). This pattern is seen in all items of the *convenience* and *treatment satisfaction* subscale, as well as multiple, but not all, *efficacy* scale items. Only one *interference* subscale item improved significantly over 6 months (see appendix 7 and 8).

Conclusions

This is to the best of our knowledge the first observational study looking at PROs following switching to Gla-300 in patients with type 2 diabetes treated in primary and secondary care, and

adds to previous literature.[11] Patients with type 2 diabetes who changed to Gla-300 experienced more convenience with respect to their diabetes medication over 6 months. No changes were seen in emotional well-being and other PROs. This finding should not surprise given the relatively favorable profile of the patients in this study. Compared with other studies, the level of well-being at baseline was relatively high (mean WHO-5 score >60) and the proportion of patients reporting low well-being or depressed mood (about a quarter) was relatively low.[33-35] The same is true for fear of hypoglycemia and diabetes-related distress, suggesting little room for improvement. The EDITION 1 study in people with type 2 diabetes using mealtime insulin and basal insulin (Gla-100 or Gla-300)[36] found a higher symptomatic, nocturnal, and severe hypoglycemia incidence based on confirmation by plasma glucose compared with the current study in which 80% of patients at baseline used mealtime insulin in addition to basal insulin. Possibly, this difference in hypoglycemia incidence is due to the difference in measurement methods and/or case-mix. Future studies are warranted to explore the potential benefits of switching to Gla-300 in patients more frequently experiencing hypoglycemia and related (sleep) problems.

Post-hoc analyses regarding the changes *per DMSRQ item* showed that overall the improvements over time were seen in the *convenience*, *efficacy*, and *treatment satisfaction* domains, and barely in the *interference* domain. This may be explained by the fact that low interference was experienced already at the outset of the study, leaving again little room for improvement.

We asked both patients and physicians to indicate the most important reasons for switching (predominantly from Gla-100) to Gla-300. The two most common reasons for both patients and physicians were *dose (less volume)* and *flexibility*, which may underlie the observed improvement in *diabetes medication convenience*. As patients changed their basal insulin and their pen device as well, this may have played a role in the improved medication convenience. Therefore, future studies may capture additional information about the (change of) injection device.

Gla-300 does allow for more *flexibility* in injection timing and therefore an indication to consider. It is possible that the advantage of *flexibility* and greater *diabetes medication convenience* is less pronounced in patients with a basal-bolus insulin regimen. Nonetheless, our results regarding *diabetes medication convenience* are in line with previous studies[36, 37] that reported increased treatment satisfaction. However, these studies also observed improved treatment satisfaction in patients treated with Gla-100, and most patients in these randomized controlled trials were using Gla-100 as previous basal insulin.[36, 37] Although not likely, we cannot rule out the possibility that medication convenience would also have improved if patients had stayed on Gla-100 due to a study effect. A controlled study design is needed to draw firm conclusions regarding a causal relationship between initiating Gla-300 and improved patient-reported medication convenience.

In this observational study, we included patients from a mix of regions in the Netherlands and settings, adding to the external validity. The observational single-arm character of the study is a limitation, as we have no control group to compare with and therefore cannot ascertain a causal relationship between the observed changes and the switch to Gla-300. Attentional bias may be introduced by physicians expecting greater flexibility and reduction of the volume to be injected, and mentioning these expectations to their patients, but we have not documented this. It would seem interesting to record what physicians actually say to patients as a way of capturing a possible placebo-by-proxy effect.[38] In contrast to our expectations, we did not find a significant improvement in well-being scores (WHO-5) following Gla-300 initiation. This may be explained by larger SD than previously observed, indicating large heterogeneity. The study may have been underpowered to detect changes in the secondary outcomes as well, where changes in the expected direction were found but failed to reach statistical significance. Overall, our population sample was generally a well-functioning group of persons in terms of PROs, glycemic control, and hypoglycemia. This has likely limited the possibility to show significant improvements. Further research therefore is needed to examine the impact of Gla-300 in persons with type 2 diabetes with a less favorable psycho-medical profile.

After switching to Gla-300, the most prominent change observed was an improvement in medication convenience. This matches the finding that the vast majority of patients (and physicians) found Gla-300 to meet their expectations, with most patients wishing for a volume reduction. Insulin Gla-300 is experienced as a convenient glucose-lowering medicine by persons with type 2 diabetes wishing their current treatment to increase flexibility of injection time, as well as to decrease the volume to be injected and the risk of hypoglycemia. These data provide a basis for future research to identify which patients may benefit most from this new long-acting insulin analog.

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Chapter 5

Does hypoglycemia affect the improvement in QoL after the transition to insulin in people with type 2 diabetes?

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Abstract

Purpose: Quality of life (QoL) of insulin-naïve people with type 2 diabetes mellitus (T2DM) improves after transition to insulin. Little is known about the role of hypoglycemia in this context. Secondary analyses of the Study of the Psychological Impact in Real care of Initiating insulin glargine Treatment (SPIRIT) aimed to investigate the relationship between hypoglycemia and QoL when transitioning to insulin. **Methods:** Insulin-naïve Dutch people with T2DM in suboptimal glycemic control (HbA1c >53 mmol/mol; 7.0%) on maximum dose of oral glucose-lowering medications were included from 363 primary care practices (n=911). Participants started insulin glargine and completed QoL-questionnaires (WHO-5 Wellbeing Index (WHO-5; emotional wellbeing), Hypoglycemia Fear Survey worry scale (HFS-W; hypoglycemia fear) and Diabetes Symptom Checklist-Revised (DSC-R; diabetes symptom distress) at baseline, three and six months follow-up. Linear GEE analyses were used to investigate the association between symptomatic, nocturnal, severe hypoglycemia (number of episodes in three months prior visit) and QoL over time. **Results:** 52.5% Men participated, mean age 62.2 years (SD±10.92), median HbA1c 67 mmol/mol (range 61-77) (8.3%). More symptomatic hypoglycemic episodes were associated with higher HFS-W and DSC-R scores ($p<.01$). Experiencing multiple nocturnal or severe episodes was related to higher symptom distress as well, when compared to no episodes. These associations did not change significantly over time. **Conclusions:** Hypoglycemia is associated with lower QoL in terms of hypoglycemia fear and diabetes symptom distress. The transition to insulin does not affect this relationship, suggesting hypoglycemia in itself has a detrimental effect on diabetes-related QoL independent of treatment regimen.

Background

Hypoglycemia is a common, unpredictable and potentially dangerous side effect of insulin therapy for diabetes.[1] Hypoglycemia can be characterized as: symptomatic hypoglycemia (an episode of hypoglycemia which is self-treated), nocturnal hypoglycemia (a symptomatic episode which takes place at night) and severe hypoglycemia (an episode of hypoglycemia in which assistance from a third party is required).

Hypoglycemia is inversely related to quality of life (QoL) in people with type 2 diabetes mellitus (T2DM).[2-4] There is consensus that insulin therapy and insulin secretagogues (e.g., sulfonylureas, meglitinides) due to their mode of action are the main drivers of hypoglycemia in T2DM.[2] It is estimated that 51% of people with T2DM recently commenced on insulin therapy (less than 3 years) experience at least one episode of symptomatic hypoglycemia per year, while 7% experience at least one severe hypoglycemia.[1] Research on the impact of hypoglycemia on the QoL of people with T2DM suggests a greater depression burden.[5] Lifestyle and daily activities can be hampered by hypoglycemia as a result of the symptoms negatively affecting performance, and/or as a consequence of worrying about hypoglycemia leading to avoidant, precautionary or compensatory actions aimed to minimize the risk of hypoglycemic episodes.[6] Fear of hypoglycemia in people with T2DM is in itself burdensome and may translate into avoidance behaviors resulting in elevated blood glucose levels, and increased risk of long-term complications.[7] We previously demonstrated that QoL improves in people with T2DM six months after initiation of insulin therapy, and even after three months for emotional wellbeing.[8] However, it is unknown whether this holds for those experiencing episodes of hypoglycemia as well.

Using data from the Study of the Psychological Impact in Real care of Initiating insulin glargine Treatment (SPIRIT),[8] a prospective observational study in routine primary care, we analyzed the relationship between hypoglycemia and QoL in people with T2DM from the moment of transition to insulin glargine onwards. Insulin glargine is a long-acting insulin analogue with a more prolonged,

consistent duration of action and a lower risk of hypoglycemia compared to NPH (humane isophane) insulin.[9-11] The SPIRIT database was chosen, because patients transferred from oral treatment to insulin treatment which heightened the risk of hypoglycemia. We hypothesize that those who experience hypoglycemia will have a less increase in QoL after transition to insulin compared to those who do not experience hypoglycemia.

Methods

Participants and procedure

We used an observational longitudinal dataset for the analyses obtained from the SPIRIT.[8] Data collection took place between January 2006 and July 2008. This study examined the change in emotional wellbeing, diabetes symptom distress and fear of hypoglycemia in Dutch people with T2DM who previously used a maximum dose of oral anti-hyperglycemic medication and were in suboptimal glycemic control (Hemoglobin A_{1c}>53 mmol/mol; 7.0%).[12] People who used oral anti-hyperglycemic agents were recruited from 363 Dutch primary care practices, spread across the Netherlands. General practitioners invited eligible people to participate. Inclusion criteria were: in clinical need of initiating long-acting insulin in accordance with the directive of the Dutch College of General Practitioners (which states that insulin therapy should be initiated if, after treatment with a maximum dose of two oral agents, optimal glycemic control (HbA1c>53 mmol/mol; 7.0%) is not achieved), and the ability to complete questionnaires.

Measures

Measurements were conducted at baseline (moment of transition to insulin therapy, i.e. the day clinician and person with T2DM agreed on starting insulin therapy) and three and six months after initiation of insulin glargine.

<u>Quality of life</u>

Emotional wellbeing was assessed with the World Health Organization (WHO)-5 wellbeing index, a well validated instrument in people with diabetes assessing emotional wellbeing

experienced in the two preceding weeks.[13] The WHO-5 consists of 5 positively stated items including positive mood, vitality and general interests. Scores were transformed to 0-100, with higher scores representing better emotional wellbeing. A score <50 is considered indicative of low mood.

Fear of hypoglycemia was assessed using the worry subscale of the Hypoglycemia Fear Survey (HFS-W), which assesses hypoglycemia fear experienced in the three months prior filling out.[7] HFS-W scores were transformed into a 0-100 scale, with higher scores indicating more worries about hypoglycemia.

Diabetes symptom distress was measured using the revised version of the Diabetes Symptom Checklist (DSC-R), that has good psychometric properties and assesses diabetes symptom distress experienced in the month prior filling out.[14] The DSC-r consists of 34 items grouped into eight symptom subscales: hyperglycemia, hypoglycemia, cognitive burden, fatigue, cardiovascular burden, neuropathic pain, neuropathic sensitivity and ophthalmic function.[14] Each item asks about the presence of symptoms and, if any, to the burden of this complaint (to answer on a 5-point scale). Scores are transformed to a 0-100 score. A higher score indicates higher diabetes symptom burden.

Demographic and medical outcomes

Demographic and clinical data were obtained through self-report: age, sex, weight, height, diabetes duration (years), previous medication use, diabetes-related complications, comorbidity and level of education.

Hypoglycemia was self-reported as number of episodes in three months prior visit and divided in symptomatic hypoglycemia (defined as an episode of hypoglycemia which is self-treated by the affected individual), nocturnal (defined as a symptomatic episode which takes place at night) and severe hypoglycemia (defined as an episode of hypoglycemia in which assistance from a third party is required).

Glycosylated hemoglobin (HbA1c) was obtained from medical charts.

Statistical analyses

Generalized Estimating Equations (GEE) analyses were conducted to examine the association between hypoglycemic episodes and QoL outcomes over time. For every outcome a crude and an adjusted analysis was performed. Adjustments were made for age, gender, diabetes duration, HbA1c, body mass index (BMI), level of education, and the number of complications. Additionally, the interaction between time and hypoglycemic episodes was added to both the crude and the adjusted model. Outcome variables with a skewed distribution were log transformed. Hypoglycemic episodes were treated as categorical variables. The categories were defined according to the median of non-zero values. Categories for symptomatic hypoglycemia were “no hypoglycemia”, “1-3 hypoglycemic episodes” and “≥4 hypoglycemic episodes”. Categories for nocturnal hypoglycemia were “no hypoglycemia”, “1-2 hypoglycemic episodes” and “≥3 hypoglycemic episodes”. Categories for severe hypoglycemia were: “no hypoglycemia”, “1 hypoglycemic episode” and “2 hypoglycemic episodes”.

Multiple imputation was used for missing data.[8] All the analyses were performed on the imputed dataset. IBM SPSS 20 was used for all analyses. Because of multiple testing, a p-value threshold of .01 was used for statistical significance.

Results

A total of 1063 people with T2DM consented to participate in the study, of which 43 were found to already use insulin and 109 were not in suboptimal control (HbA1c ≤53 mmol/mol; 7.0%).[8] These subgroups were removed from the analyses, resulting in a sample of 911 people. In the original article of SPIRIT,[8] analyses were based on the intention-to-treat principle; persons who withdrew from glargine use (n = 99; 11%) were thus included in the analyses. In the same study, logistic regression analyses revealed that dropout was not selective. More information about this sensitivity analysis can be found in the original article.[8] For the WHO-5, missing data were 18.0% and 43.0%. For the HFS-w, missing data were noted for 28.0% of the participants at the start up to 50.0%

at six-months follow-up. For the DSC-R, these percentages were 28.0% and 50.0% respectively.[8] Characteristics of the study population are shown in Table 1. Changes in HbA1c, QoL-outcomes and hypoglycemia together with p-values are described in the original article of SPIRIT.[8] Since both HFS-W scores and DSC-R scores were distributed as skewed to the right, they were analyzed as log transformed in the GEE analyses.

Table 1. Demographics of the study population and changes in clinical outcomes and QoL during the period of study

Demographics		**Baseline**	**Three months**	**Six months**
N		911		
Gender				
Men		479 (52.5%)		
Women		432 (47.5%)		
Age (years)		62.15 ± 10.92		
Level of education				
Low		626 (68.7%)		
Average		188 (20.7%)		
High		97 (10.7%)		
Diabetes duration (years)		6.00 (3.00 - 9.00)		
HbA1c (mmol/mol)[a]	**Mean±SD**	72 ± 17	61 ± 11	57 ± 11
	Median (25^{th}–75^{th})	67 (61 - 77)	60 (53 - 67)	56 (50 - 63)
HbA1c (%)[a]	**Mean±SD**	8.7 ± 1.5	7.7 ± 1.0	7.4 ± 1.0
	Median (25^{th}–75^{th})	8.3 (7.7 - 9.2)	7.6 (7.0 - 8.3)	7.3 (6.7 - 7.9)

Table 1. Continued

Symptomatic hypoglycemia[b]			
0 episodes	572 (62.8%)	524 (57.6%)	514 (56.5%)
1,2 or 3 episodes	163 (17.9%)	211 (23.2%)	232 (25.4%)
4 or more episodes	176 (19.3%)	176 (19.3%)	165 (18.1%)
Nocturnal hypoglycemia[b]			
0 episodes	783 (86.0%)	781 (85.8%)	745 (81.8%)
1 or 2 episodes	62 (6.8%)	85 (9.4%)	110 (12.1%)
3 or more episodes	66 (7.2%)	45 (4.9%)	56 (6.1%)
Severe hypoglycemia[b]			
0 episodes	882 (96.8%)	872 (95.7%)	860 (94.3%)
1 episode	14 (1.5%)	28 (3.1%)	27 (3.0%)
2 episodes	15 (1.6%)	11 (1.2%)	24 (2.6%)
Previous treatment[c]			
SU-derivate	697		
Other	743		
Body Mass Index (BMI)	30.09 ± 5.85	30.17 ± 5.80	30.51 ± 5.76
Complications			
0	648 (71.1%)		
1 or more	263 (28.9%)		
Complications[d]			
Nephropathy	21 (2.3%)		
Neuropathy	86 (9.4%)		
Retinopathy	42 (4.6%)		
Macroalbuminuria	26 (2.9%)		
Macroangiopathy	64 (7.0%)		
Microalbuminuria	110 (12.1%)		

Table 1. Continued

WHO-5[e]	56.71 (25.52)	63.33 (21.22)	65.27 (20.52)
HFS-W[f]	7.69 (1.92 - 21.15)	5.77 (0.00 - 15.38)	3.85 (0.00 - 15.38)
DSC-R[g]	11.71 (4.71 - 22.14)	8.07 (3.13 - 17.14)	8.09 (2.88 - 16.04)

For dichotomous or categorical variables the absolute numbers by subgroups and the percentage compared to the overall study population are displayed. For normally distributed variables the mean and standard deviation are shown. For skewed variables the median and the 25th and 75th percentile are shown

[a]At baseline HbA1c was skewed distributed, but normally distributed at three and six months

[b]Number of episodes in three months prior visit

[c]One case may use multiple oral agents

[d]One case may have multiple complications

[e]Measured as emotional wellbeing experienced during two weeks prior visit

[f]Measured as hypoglycemia fear experienced during three months prior visit

[g]Measured as diabetes symptom distress experienced during month prior visit

Symptomatic hypoglycemia

Those who experienced one or more hypoglycemic episodes reported more worries about hypoglycemia compared to those not reporting any hypoglycemic episode. The symptom burden of patients who experienced four or more episodes was higher compared to patients reporting fewer to no episodes (Table 2). There were no differences in emotional well-being. Changes in hypoglycemia fear and symptom burden per symptomatic hypoglycemia category are graphically illustrated in Figure 1 and Figure 2, respectively.

Table 2. Association between symptomatic hypoglycemia and WHO-5, HFS-W and DSC-R[a,b]

	Unadjusted model			**Adjusted model**[c]		
	Beta	**P-value**	**95%-CI**	**Beta**	**P-value**	**95%-CI**
WHO-5						
0-1[d]	0.33	.565	-0.79 to 1.44	-0.27	.673	-1.53 to 0.99
1-2[e]	-0.75	.260	-2.05 to 0.55	-0.52	.499	-2.02 to 0.99
0-2[f]	-0.42	.523	-1.72 to 0.87	-0.79	.302	-2.29 to 0.71

Table 2. Continued

	Ratio of geometric averages[g]	P-value	95%-CI	Ratio of geometric averages[g]	P-value	95%-CI
HFS-W						
0-1[d]	1.16	<.001	1.08 to 1.24	1.24	<.001	1.15 to 1.35
1-2[e]	1.04	.321	0.96 to 1.13	1.07	.174	0.97 to 1.17
0-2[f]	1.21	<.001	1.11 to 1.31	1.33	<.001	1.20 to 1.47
DSC-R						
0-1[d]	1.01	.721	0.96 to 1.06	1.04	.240	0.98 to 1.10
1-2[e]	1.08	.004	1.03 to 1.14	1.10	.004	1.03 to 1.17
0-2[f]	1.09	.002	1.03 to 1.16	1.14	<.001	1.06 to 1.22

[a]Hypoglycemia was self-reported as number of episodes in three months prior visit
[b]WHO-5 was self-reported as emotional wellbeing experienced during two weeks prior visit; HFS-W as hypoglycemia fear experienced during three months prior visit; DSC-R as diabetes symptom distress experienced during month prior visit
[c]Adjusted for age, diabetes duration, HbA1c, body mass index, level of education, the number of complications and gender
[d]Comparison between group 0 (no hypoglycemia) and group 1 (1,2 or 3 hypoglycemic episodes) regarding symptomatic hypoglycemia
[e]Comparison between group 1 (1,2 or 3 hypoglycemic episodes) and group 2 (4 or more hypoglycemic episodes) regarding symptomatic hypoglycemia
[f]Comparison between group 0 (no hypoglycemia) and group 2 (4 or more hypoglycemic episodes) regarding symptomatic hypoglycemia
[g]HFS-W and DSC-R scores were analyzed as log transformed, and back transformed with a ratio of geometric averages as a result. This can be interpreted as follows: "the geometric average of the reference group … times greater compared to the geometric average of the compared group"

Figure 1. Changes in median HFS-W score per symptomatic hypoglycemia category

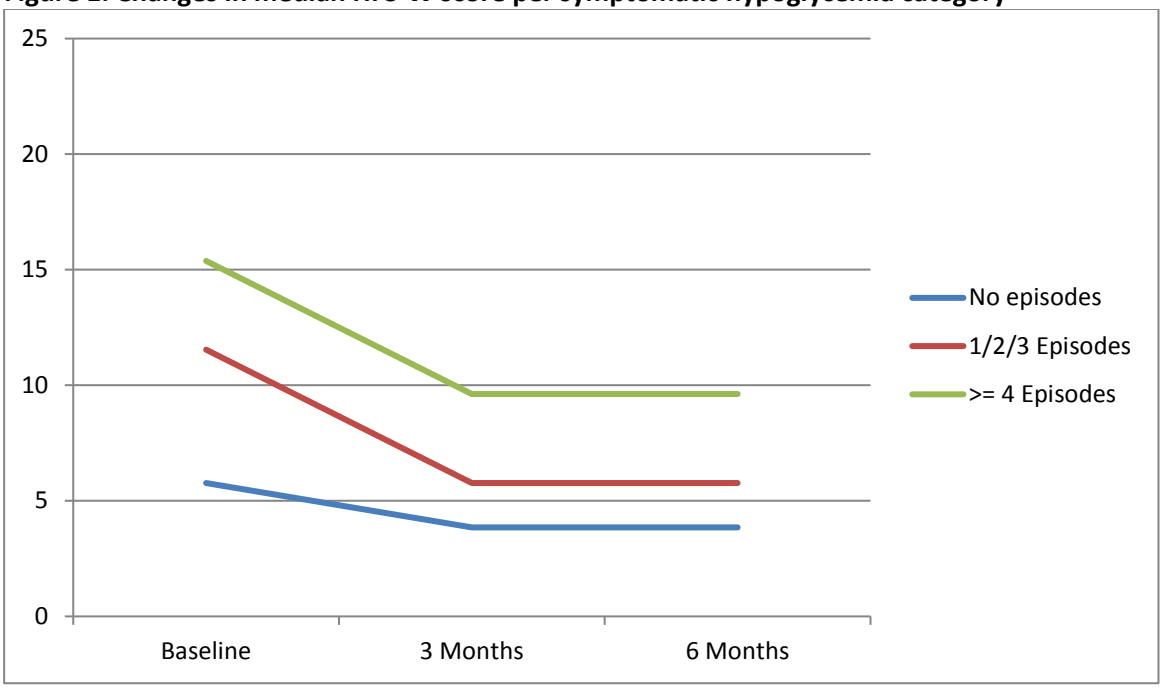
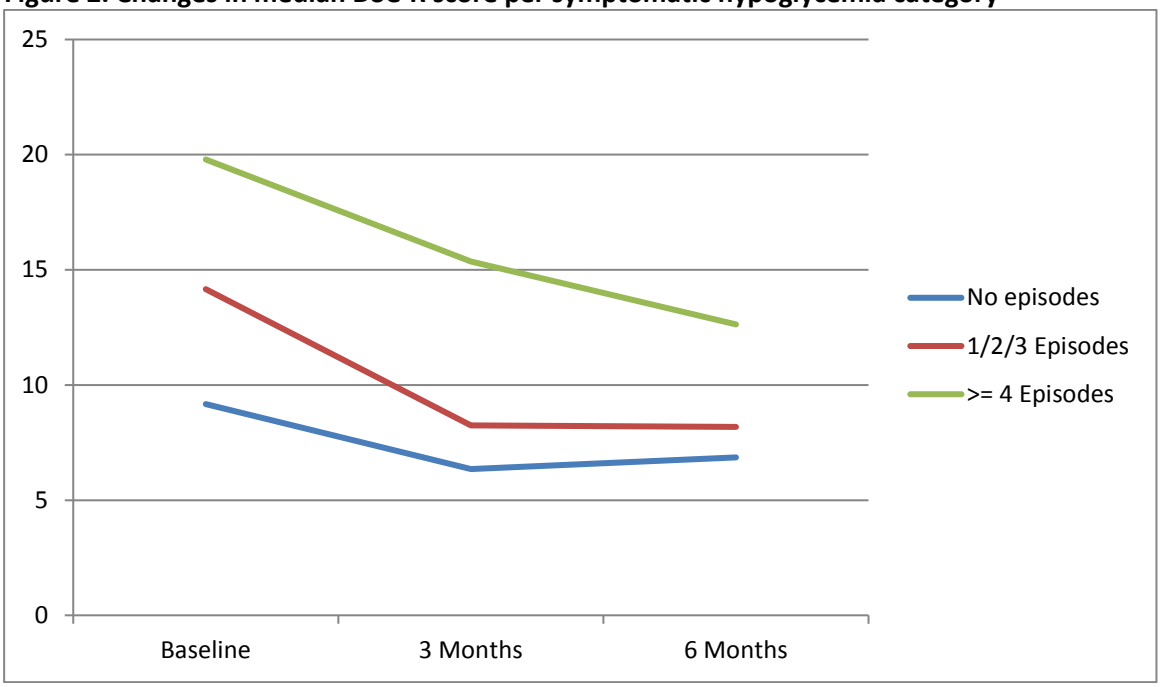


Figure 2. Changes in median DSC-R score per symptomatic hypoglycemia category



Nocturnal hypoglycemia

DSC-R scores were significantly higher for those experiencing three or more nocturnal hypoglycemic episodes compared to those not experiencing any nocturnal hypoglycemia (Table 3 and Figure 3). No significant changes were found for emotional well-being and hypoglycemia fear.

Table 3. Association between nocturnal hypoglycemia and WHO-5, HFS-W and DSC-R[a,b]

	Unadjusted model			**Adjusted model[c]**		
	Beta	**P-value**	**95%-CI**	**Beta**	**P-value**	**95%-CI**
WHO-5						
0-1[d]	1.15	.093	-0.19 to 2.50	0.62	.423	-0.90 to 2.14
1-2[e]	-3.03	.002	-1.10 to -4.96	-1.97	.059	-4.02 to 0.08
0-2[f]	-1.88	.027	-3.53 to -0.22	-1.35	.154	-3.20 to 0.51
	Ratio of geometric averages[g]	**P-value**	**95%-CI**	**Ratio of geometric averages[g]**	**P-value**	**95%-CI**
HFS-w						
0-1[d]	1.03	.481	0.95 to 1.12	1.09	.101	0.98 to 1.20
1-2[e]	1.09	.145	0.97 to 1.22	1.04	.574	0.91 to 1.19
0-2[f]	1.12	.015	1.02 to 1.23	1.13	.029	1.01 to 1.26
DSC-r						
0-1[d]	1.00	.906	0.93 to 1.07	1.05	.255	0.97 to 1.14
1-2[e]	1.10	.059	1.00 to 1.21	1.10	.093	0.99 to 1.22
0-2[f]	1.09	.029	1.01 to 1.18	1.15	.004	1.05 to 1.26

[a]Hypoglycemia was self-reported as number of episodes in three months prior visit

[b]WHO-5 was self-reported as emotional wellbeing experienced during two weeks prior visit; HFS-W as hypoglycemia fear experienced during three months prior visit; DSC-R as diabetes symptom distress experienced during month prior visit

[c]Adjusted for age, diabetes duration, HbA1c, body mass index, level of education, the number of complications and gender

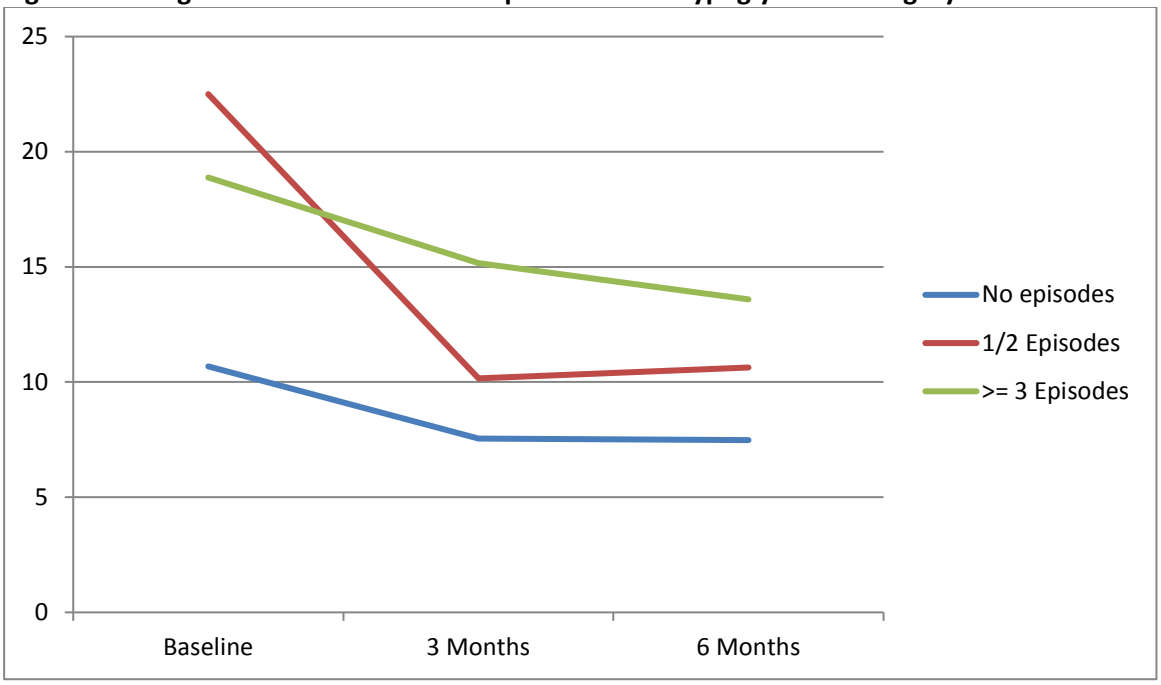
[d]Comparison between group 0 (no hypoglycemia) and group 1 (1 or 2 hypoglycemic episodes) regarding nocturnal hypoglycemia

[e]Comparison between group 1 (1 or 2 hypoglycemic episodes) and group 2 (3 or more hypoglycemic episodes) regarding nocturnal hypoglycemia

[f]Comparison between group 0 (no hypoglycemia) and group 2 (3 or more hypoglycemic episodes) regarding nocturnal hypoglycemia

[g]HFS-W and DSC-R scores were analyzed as log transformed, and back transformed with a ratio of geometric averages as a result. This can be interpreted as follows: "the geometric average of the reference group … times greater compared to the geometric average of the compared group"

Figure 3. Changes in median DSC-R score per nocturnal hypoglycemia category



Severe hypoglycemia

Significantly higher DSC-R scores were found for those experiencing two severe hypoglycemic episodes compared to those not experiencing any episode (Table 4 and Figure 4). No significant changes were found for emotional well-being and hypoglycemia fear.

Table 4. Association between severe hypoglycemia and WHO-5, HFS-W and DSC-R[a,b]

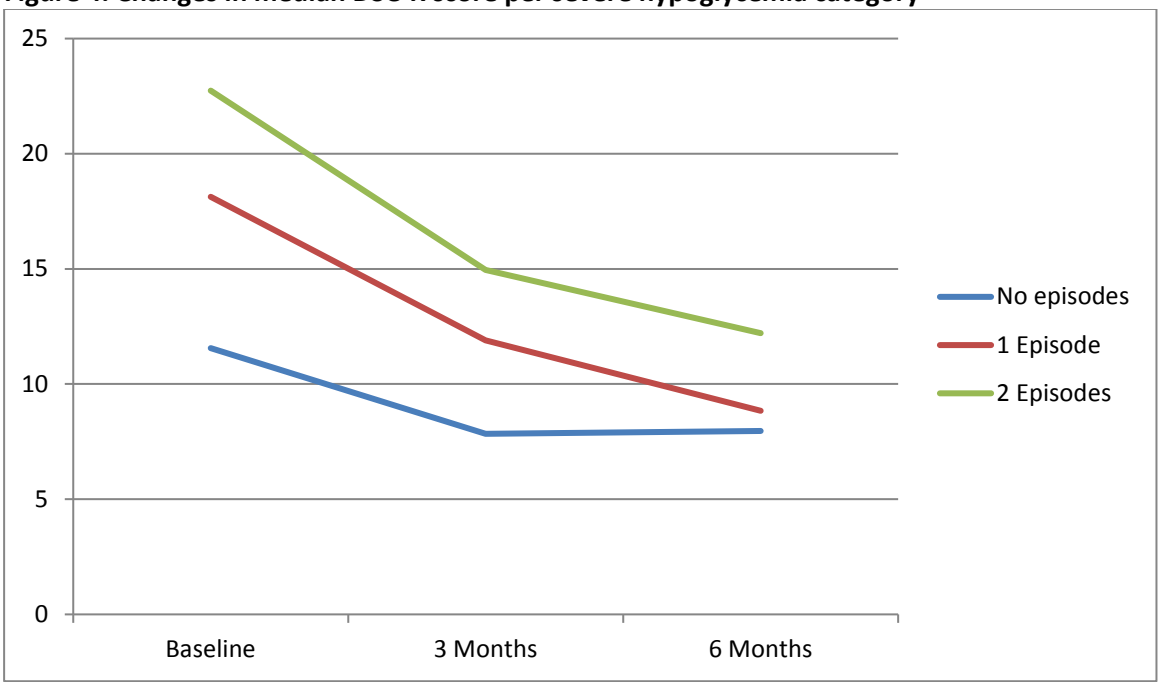
	Unadjusted model			**Adjusted model[c]**		
	Beta	**P-value**	**95%-CI**	**Beta**	**P-value**	**95%-CI**
WHO-5						
0-1[d]	1.45	.214	-0.84 to 3.73	0.96	.517	-1.94 to 3.86
1-2[e]	-1.77	.286	-5.03 to 1.48	-2.58	.224	-6.75 to 1.58
0-2[f]	-0.33	.801	-2.87 to 2.21	-1.63	.305	-4.73 to 1.48

Table 4. Continued

	Ratio of geometric averages[g]	P-value	95%-CI	Ratio of geometric averages[g]	P-value	95%-CI
HFS-W						
0-1[d]	1.01	.915	0.90 to 1.13	1.04	.573	0.91 to 1.19
1-2[e]	1.03	.753	0.85 to 1.26	1.09	.480	0.86 to 1.39
0-2[f]	1.04	.651	0.88 to 1.22	1.13	.229	0.92 to 1.39
DSC-R						
0-1d	0.99	.827	0.89 to 1.10	1.00	.996	0.87 to 1.15
1-2[e]	1.12	.101	0.98 to 1.27	1.16	.068	0.99 to 1.37
0-2[f]	1.10	.041	1.00 to 1.21	1.17	.004	1.05 to 1.29

[a]Hypoglycemia was self-reported as number of episodes in three months prior visit
[b]WHO-5 was self-reported as emotional wellbeing experienced during two weeks prior visit; HFS-W as hypoglycemia fear during three months prior visit; DSC-R as diabetes symptom distress during month prior visit
[c]Adjusted for age, diabetes duration, HbA1c, body mass index, level of education, the number of complications and gender
[d]Comparison between group 0 (no hypoglycemia) and group 1 (1 hypoglycemic episode) regarding severe hypoglycemia
[e]Comparison between group 1 (1 hypoglycemic episode) and group 2 (2 hypoglycemic episodes) regarding severe hypoglycemia
[f]Comparison between group 0 (no hypoglycemia) and group 2 (2 hypoglycemic episodes) regarding severe hypoglycemia
[g]HFS-W and DSC-R scores were analyzed as log transformed, and back transformed with a ratio of geometric averages as a result. This can be interpreted as follows: "the geometric average of the reference group … times greater compared to the geometric average of the compared group"

Figure 4. Changes in median DSC-R score per severe hypoglycemia category



In all analyses, the interaction between time and hypoglycemic episodes were not statistically significant. This implicates that the association between hypoglycemic events and QoL does not change over time.

Discussion

This study aimed to assess the association between hypoglycemia and QoL in people with T2DM on maximum dosage oral blood glucose lowering medication and examine whether this association changes over time, after transition to insulin glargine. Hypoglycemia was associated with lower QoL in terms of both hypoglycemia fear and diabetes symptom distress, the diabetes related aspects of QoL and not the overall, generic emotional well-being. The initiation of insulin therapy did not affect the relationship between hypoglycemia and QoL. This suggests that hypoglycemia in itself has a detrimental effect, independent of treatment regimen.

Previous studies reported severe hypoglycemia to have a greater impact on QoL compared to symptomatic hypoglycemia, and nocturnal hypoglycemia to influence QoL more than daytime episodes.[15] In our study we could not demonstrate these associations, probably due to the low

number of people experiencing nocturnal and severe episodes. We did find, in line with previous studies, that frequency of hypoglycemia is negatively associated with QoL.[3, 5, 15, 16] However, further research is warranted in people with T2DM with higher incidence of severe hypoglycemia.

The question arises whether the negative impact of hypoglycemia on diabetes-related QoL found in this study is to be regarded clinically relevant. For diabetes symptom distress we found statistically significant increases in patients experiencing multiple hypoglycemia episodes (both symptomatic, nocturnal and severe) and for hypoglycemia fear we found a statistically significant increase in patients experiencing one or more symptomatic episodes compared to those with no symptomatic hypo's, but very little is known about the clinical relevance of these measures. This stresses the importance of future research studying the clinical relevance of hypoglycemia fear and changes in diabetes symptom distress.

Remarkably, hypoglycemia rates when using oral agents are relatively high and insulin glargine is having a scarce effect on these rates. However, this is in line with previous studies.[1] The UK Hypoglycaemia Study Group (2007) found no difference in T2DM patients treated with sulfonylureas (SUs) or insulin for less than two years in both the proportion experiencing severe hypoglycemia and the proportion experiencing mild symptomatic hypoglycemia over a 9-12 month period.[1] A large proportion of patients in our study, (76,51% (697 patients)), used SU-derivates before changing to glargine. Furthermore, Marrett et al. (2011) estimated 63% of the T2DM patients on oral medication experiencing one or more self-reported hypoglycemic events per half a year.[3] As insulin glargine provides a more prolonged, consistent duration of action and a lower risk of hypoglycemia compared to NPH (humane isophane) insulin,[3, 4, 17] glycemic control improves while having a scarce effect on hypoglycemia rates.

This study has several limitations that are worth mentioning. First, hypoglycemic episodes were self-reported. This may have resulted in underreporting of hypoglycemia in our study population, as people with diabetes may not always recall or recognize symptoms of hypoglycemia[18,

[19] or may have limited knowledge about hypoglycemia itself.[20] However, comparable or even lower prevalence rates of severe hypoglycemia are found in previous research.[1, 21] Continuous glucose monitoring (CGM) could help establish the reliability of self-report, but is not feasible in a large observational study in primary care. In addition, the relatively large number of missing data is a potential weakness of observational studies, and confirmed in our study.[8] However, multiple imputation can be viewed as the most robust way of dealing with missing data.[22]

This study has strengths as well. We used well-validated measures of quality of life, supporting internal validity. The study was conducted in a large and heterogeneous sample of people with T2DM in primary care settings across different regions of the country,[8] which favors external validity i.e. generalizability of our findings. We set the p-value threshold at .01 in order to higher the probability of the findings, which can be regarded as a strength of this study as well.

Conclusions

In conclusion, we found that hypoglycemic episodes have a negative impact on QoL in terms of both hypoglycemia fear and diabetes symptom distress, therefore deserving clinical attention. We observed an impact on both hypoglycemia fear and diabetes symptom distress with more than one episode. The initiation of insulin glargine does, however, not affect this association. Those experiencing multiple hypoglycemic episodes report lower diabetes-related QoL compared to those not experiencing hypoglycemia, regardless of treatment regimen. Future studies should be focused on clinically relevant changes in hypoglycemia fear and diabetes symptom distress in order to interpret our findings for clinical practice. Prevention and adequate management of hypoglycemia remains valuable and should be adequately monitored as well as the QoL of people with T2DM, with as much attention for patients using oral agents as for patients initiating insulin therapy.

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Chapter 6

Improving interpretability of individual Diabetes Symptom Checklist-Revised (DSC-R) scores: The role of patient characteristics

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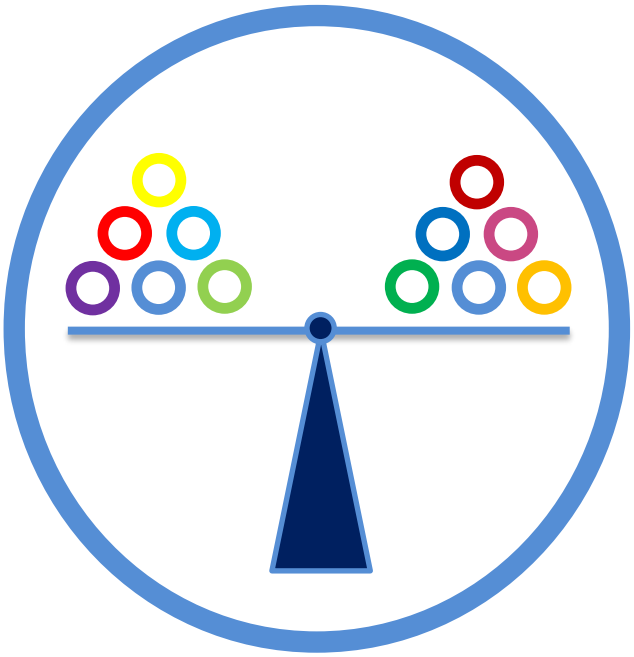

Abstract

Background: The Diabetes Symptoms Checklist-Revised (DSC-R) is a well-validated patient-reported outcome (PRO) designed to assess symptom burden in persons with type 2 diabetes mellitus (T2DM) across eight domains. The DSC-R has so far primarily been used in research settings. With the aim to make the DSC-R applicable in clinical practice, we took the first step to identify patient characteristics associated with DSC-R (domain) scores as a first step towards reference values. **Methods:** We used two existing databases to select patient characteristics significantly associated with DSC-R total and domain scores. Multivariate Tobit analyses with the backward procedure per (domain) score are performed. **Results:** Data from 1531 participants with T2DM were included. On a 0-100 scale, median DSC-R total score was 15.88 (7.06 – 29.41), with domain scores ranging from 5.00 (0.00 – 22.50) (pain) to 35.00 (10.00 – 60.00) (fatigue). Low well-being status was most profoundly associated with higher scores on all domains and total scale. Of the clinical characteristics, persons with one or more complication, as well as one or more symptomatic hypoglycemic event during the past three months, scored higher on (almost) all domains and the total scale. **Conclusions:** Complications, symptomatic hypoglycemia, and low well-being are important characteristics to take into account when using the DSC-R in individual patients. Further validation of our findings is warranted in diverse patient populations.

Background

The Diabetes Symptoms Checklist (DSC) was developed by Grootenhuis et al.[1] almost 25 years ago in the context of the Hoorn study, to reliably capture the experience of diabetes-related symptom distress of persons with type 2 diabetes mellitus (T2DM) and changes therein as a result of medical treatment.[1] Based on research data, the DSC was revised in two ways: 1) for the sake of simplicity and to avoid confusion, the frequency scale was replaced by a dichotomous yes/no response for the presence or absence of each symptom, and 2) the scaling was changed from a 4-point to a 5-point Likert scale to enhance the variability,[2] resulting in the DSC-Revised (DSC-R).[3] The DSC-R consists of 34 items grouped into eight symptom subscales: fatigue, cognitive symptoms, pain, sensitivity symptoms, cardiologic symptoms, ophthalmic symptoms, hypoglycemia, and hyperglycemia. It asks about the burden of diabetes symptoms experienced during the past month. The DSC-R has good psychometric properties[3] and has been validated in a multitude of languages and used primarily as patient-reported outcome (PRO) in clinical trials.

When aiming to use the DSC-R as PRO in clinical practice, reference values are an important feature to consider. Interpretability is a key issue for using the DSC-R in clinical practice, i.e. in individual patients, and can be defined as "the degree to which one can assign qualitative meaning – that is, clinical or commonly understood connotations – to an instrument's quantitative scores or change in scores".[2] Interpretability is not a measurement property, like validity and reliability, because it does not refer to the quality of an instrument. Rather, it refers to what the scores on an instrument mean and is a prerequisite for any instrument to be applicable in clinical practice. In this context it is essential to have reference values,[2] differentiated according to relevant patient characteristics. For example, previous research has shown that symptom report is partly explained by negative affect.[4-6] In the Hoorn Screening study, negative mood was found to significantly amplify diabetes symptom burden, as measured by the DSC-R.[5] In other words, when interpreting DSC-R scores on an individual basis, we need to be recognizant of patient-related factors that may influence symptom reporting, such as gender, age, and complication status and these associations may be

generic or domain specific. For this purpose we need to assess which patient characteristics are associated with DCS-R domain and total scores.

The current study aims to improve the clinical usefulness of the DSC-R through establishing which patient characteristics are associated with DSC-R (domain) scores.

Methods

Baseline data were used from the SPIRIT (Study of the Psychological Impact in Real care of Initiating insulin glargine Treatment)[7] and the ESPRIT (Effect Study on Patient-Reported outcomes in Insulin glargine Treatment)[8] studies and merged. The SPIRIT database includes data from 1021 persons with T2DM prior to switching from oral agents to a long-acting insulin (glargine-100). The ESPRIT database includes 510 persons with T2DM prior to switching from any long-acting insulin to insulin glargine-100. Details of the SPIRIT and the ESPRIT study are reported elsewhere.[7, 8]

In both SPIRIT and ESPRIT, HbA1c was retrieved from the medical chart and demographic and clinical data were self-reported.[7, 8] The DSC-R and the World Health Organization-Five (WHO-5) Well-being Index were completed, and used in the current study. The WHO-5 Well-being index consists of five positively worded items assessing emotional well-being pertaining to the past two weeks.[9] Scores are transformed to 0-100, with higher scores representing better emotional well-being.[9, 10] Scores were divided into categories: a score ≤28 is indicative for depression,[11] a score >28 and ≤50 is indicative for low mood,[10, 12] and scores higher than 50 indicative for normal well-being.

Analyses

Multiple imputation on item level was performed, in which imputation models were created per DSC-R domain score. These imputation models contained items of the regarding domain, as well as the original (non-dichotomized) patient characteristics potentially associated with DSC-R (domain) scores. Multiple imputation using five imputations was performed in SPSS version 22.

Both DSC-R total and subscale scores were standardized to 0-100 score. Because of the large numbers of zero-scores for the DSC-R domains and total scale, Tobit regression analyses are performed.[13] Stata version 15 was used for the Tobit analyses. All analyses were repeated in five different databases and existed of three parts: 1) a backward procedure to select the characteristics significantly associated with total DSC-R score and per domain;[14] 2) final models were created only for those variables significantly associated with the regarding outcome in at least three imputed datasets; 3) based on the final models, Rubin's rule was used to obtain pooled regression coefficients and 95% confidence intervals. A p-value of .05 was used as threshold for a statistically significant association.

Patient characteristics potentially associated with DSC-R (domain) scores were dichotomized in order to enhance interpretability and clinical applicability based on medians and guidelines.[15, 16] Variables found to be associated with symptom burden in previous studies and included as independent variables in the first model for the backward procedure were: socio-demographics: gender, age (<70 years versus ≥70 years), level of education (low, middle, high); clinical characteristics: diabetes duration (<10 years versus ≥10 years), complication status (0 versus ≥ 1), comorbidity (0 versus ≥ 1), glycemic control (HbA1c; ≤64.00 mmol/mol (≤8.00%) versus >64.00 (>8.00%)), BMI (non-obese (<30) versus obese (≥30)), treatment (using oral agents versus using insulin), self-reported symptomatic hypoglycemia (0 versus ≥1 episodes in the past three months), self-reported severe hypoglycemia (0 versus ≥1 episodes in the past three months); and psychological well-being status (normal well-being, low mood, likely depression).[3, 5, 6, 17-22]

Results

The total dataset included 1531 patients with T2DM, 49.20% female and with a mean diabetes duration of 7 years (Table 1).

Table 1. Baseline data of the study population (N = 1531)[a,b]

Gender	
female	750 (49.20%)
Age	61.37 (10.90)
Education level	
low	699 (53.60%)
middle	467 (35.80%)
high	138 (10.60%)
Diabetes duration (years)	7.00 (4.00 – 12.00)
Complications	
0	881 (62.70%)
≥1	523 (37.30%)
Comorbidities	
0	1367 (89.30%)
≥1	164 (10.70%)
HbA1c	
mmol/mol	69.32 (16.45)
%	8.49 (1.51)
Body Mass Index	30.53 (6.27)
Treatment	
oral agents	1021
insulin	510
Symptomatic hypoglycemia during past 3 months (self-report)	
0 episodes	584 (48.90%)
≥1 episodes	610 (51.10%)

Table 1. Continued

Severe hypoglycemia during the past 3 months (self-report)	
0 episodes	1191 (94.30%)
≥1 episodes	72 (5.70%)
WHO-5 score (well-being)	60.00 (40.00 – 76.00)

[a]Based on non-imputed data
[b]For categorical variables: frequencies (valid percentages); for normally distributed continuous variables: mean (SD); for skewed distributed continuous variables: median (25^{th} – 75^{th} percentile)

The median and interquartile ranges (IQRs; 25^{th} – 75^{th} percentile) for the DSC-R total and domain scores of the study population are presented in Table 2. The median DSC-R total score was 15.88 (7.06 – 29.41), median domain scores ranged from 5.00 (0.00 – 22.50) (pain) to 35.00 (10.00 – 60.00) (fatigue).

Table 2. Median and IQRs for DSC-R total scores and domain scores (N = 1531)[a]

Total	15.88 (7.06 – 29.41)
Fatigue	35.00 (10.00 – 60.00)
Cognitive symptoms	15.00 (0.00 – 40.00)
Pain	5.00 (0.00 – 22.50)
Sensitivity symptoms	6.67 (0.00 – 26.67)
Cardiologic symptoms	10.00 (0.00 – 25.00)
Ophthalmic symptoms	8.00 (0.00 – 24.00)
Hypoglycemia	6.67 (0.00 – 26.67)
Hyperglycemia	20.00 (5.00 – 40.00)

[a]Based on non-imputed (original) data

Tobit regression analyses

The patient characteristics that were significantly associated with DSC-R scores are presented in Table 3. Persons with a diabetes duration of 10 years or more report less burden of fatigue, cognitive symptoms, and hyperglycemia, as well as total burden, compared to those with a shorter

disease duration. Suffering from one or more complications was associated with a higher total score as well as higher scores on all DSC-R domains, except for the hypoglycemia domain. Reporting one or more symptomatic hypoglycemic event was found to be significantly associated not only with higher hypoglycemia symptom burden, but also with higher scores on all domains and total score. Lower well-being status (both low versus normal and likely depression versus normal) showed to be strongly associated with higher scores for all DSC-R domains, and total score.

Table 3. Effect estimates of patient characteristic significantly associated with DSC-R (domain) scores; results from multivariable Tobit analyses[a]

	Gender[b]	Age	Education	Diabetes duration	Complications
Total				-1.49 (0.02 to -3.00)	3.52 (1.91 to 5.13)
Fatigue	4.96 (1.94 to 7.98)			-4.10 (-6.96 to -1.24)	3.53 (0.75 to 6.31)
Cognitive symptoms				-2.95 (-6.09 to 0.19)	4.21 (0.00 to 8.42)
Pain		4.88 (0.53 to 9.23)			8.75 (5.01 to 12.49)
Sensitivity symptoms					9.22 (5.87 to 12.57)
Cardiologic symptoms	3.43 (0.45 to 6.41)				5.63 (2.32 to 8.94)
Ophthalmic symptoms					4.92 (1.24 to 8.60)
Hypoglycemia		-10.77 (-15.26 to -6.28)			
Hyperglycemia				-3.73 (-7.12 to -0.34)	4.66 (1.27 to 8.05)

Comorbidity	HbA1c	BMI	Treatment[c]	Symptomatic hypoglycemia	Severe hypoglycemia	Low mood[d]	Likely depression[e]
2.29 (0.09 to 4.49)		2.57 (1.18 to 3.96)		5.74 (4.25 to 7.23)	3.92 (0.76 to 7.08)	11.09 (9.44 to 12.74)	19.56 (17.54 to 21.58)
		5.47 (2.63 to 8.31)		11.42 (8.83 to 14.01)		33.03 (29.85 to 36.21)	46.44 (42.72 to 50.16)
				7.43 (4.22 to 10.64)		20.56 (16.93 to 24.19)	33.20 (29.12 to 37.28)
		5.65 (1.91 to 9.39)		9.36 (5.54 to 13.18)		8.38 (3.87 to 12.89)	14.46 (9.64 to 19.28)
5.11 (-0.06 to 10.28)		6.67 (3.48 to 9.86)	4.61 (0.63 to 8.59)	8.70 (5.52 to 11.88)		9.09 (5.39 to 12.79)	16.42 (11.87 to 20.97)
				6.32 (2.64 to 10.00)		10.67 (6.83 to 14.51)	17.81 (12.89 to 22.73)
				6.90 (3.51 to 10.29)	6.98 (0.20 to 13.76)	6.29 (2.25 to 10.33)	17.27 (12.68 to 21.86)
				12.98 (8.65 to 17.31)		20.28 (15.42 to 25.14)	33.67 (27.10 to 40.24)
5.66 (0.31 to 11.01)	5.74 (2.60 to 8.88)	6.46 (3.30 to 9.62)	5.56 (1.70 to 9.42)	7.94 (4.80 to 11.08)		16.34 (12.36 to 20.32)	25.79 (21.67 to 29.91)

[a]The group with the lowest value(s) is used as reference (see the method section for the categories per patient characteristic)

[b]Males are coded as zero, females as one

[c]Using oral agents is coded as zero, using insulin as one

[d]Normal well-being is coded as zero, low mood as one

[e]Normal well-being is coded as zero, likely depression as one

Discussion

Based on combined data from two large observational studies including insulin naïve and insulin treated T2DM patients, we investigated which patient characteristics are associated with patient reported diabetes symptom burden. Responses on the DSC-R showed a wide variation in occurrence and degree of troublesomeness, underscoring the need to better understand inter-individual differences, taking patient characteristics into account.

Fatigue is reported as most common and most burdensome symptom of diabetes. Indeed, fatigue is known to be prevalent in persons with type 1 and type 2 diabetes, although the etiology is not yet fully understood.[23-25] Fatigue was most pronounced in patients with lower well-being status. Persons with low mood score around 33 points (on a 0-100 scale) higher compared to persons with normal well-being. Likely depressed persons score approximately 46 points as high as compared to those with normal well-being. Low mood and likely depression do not only impact on fatigue, but also amplify scores on all domains of the DSC-R, and in particular cognitive symptoms, hypoglycemic and hyperglycemic symptoms. Our findings are consistent with previous studies that found psychological well-being to be associated with subjective symptom report.[4-6] Several plausible explanations for the association between depression and symptom burden have been suggested, but the causation is unclear. Painful symptoms may induce or further increase depressed mood,[26] while depression appears to amplify reported symptom burden, possibly due to a focus on symptoms[27] and selective recalling negative events.[28] Furthermore, negative affect may induce hyper-vigilance, which leads to an increase in scanning of the body, i.e. attention directed to the body, resulting in more somatic symptoms being detected. Negative affect may lead to arousal and stress related symptoms being detected.[29] This mechanism may drive the association between symptomatic hypoglycemia and DSC-R scores as well,[19] given the fact that symptomatic hypoglycemia is self-reported as well. Reporting one or more symptomatic event in the past three months showed to be associated with higher symptom burden. Future research should clarify this by using continuous glucose monitoring for administering hypoglycemic events.

It is unclear why patients with diabetes duration of 10 years or more report a lower fatigue, cognitive, hyperglycemia, and total symptom burden relative to those with shorter disease duration. Response shift may play a role in this.[2] Possibly, people suffering longer from diabetes may be less emotionally burdened compared to those recently diagnosed, resulting in lower negative affectivity in the latter group. Further research into the role of age and diabetes duration as a determinant of symptom distress is warranted.

Besides symptomatic hypoglycemia and diabetes duration, important clinical characteristics to take into account seem to be complication status and BMI. Interestingly, treatment regimen and glycemic control seem to differentiate less in terms of symptom burden. The strength of the association is probably dependent on the level of glycemic control, where one could expect a stronger impact on symptom burden in patients in poorer control versus those in better control.[22]

Future research should replicate our study in diverse patient populations to define and further validate reference values. Of special interest is the role of diabetes complications, that were found to be associated with all DSC-R domain scores, with the exception of hypoglycemic symptom burden. Future research should further explore the impact of specific diabetes complications and their severity as well as co-morbidities on DSC-R scores.

The significant associations and their effect estimates presented here need further testing, but should help clinicians to interpret DCS-R domain and total scores, taking relevant patient characteristic into account. As to the clinical application of our findings, it is advised to focus on (changes in) DSC-R scores on domain level.[2] The total DSC-R score is informative, but we should be aware that no difference in total DSC-R score over time does not exclude the possibility that there actually might have been changes within domains (e.g. one domain score worsened while another improved). Further research into the minimal clinically important difference (MCID) for the DSC-R is warranted for interpretation of changes in scores, building on a previous study providing preliminary

results.[3] The MCID is the smallest benefit of value to persons with T2DM capturing both the magnitude of the improvement and the value persons place on the change.[30]

Strengths and limitations

The study was conducted in a large sample of persons with T2DM in primary and secondary care settings, at different stages of (insulin) therapy across different regions of the Netherlands,[7, 8] which favors external validity i.e. generalizability of our findings.

The relevant associations were found in a sample of mainly Caucasian T2DM patients. Therefore, it is unclear whether these results are generalizable to non-Caucasian T2DM patients as well. In line with this, the association of culture and/or cultural background and symptom burden could not be taken into account. The relatively large number of missing data is a potential weakness of observational studies, and confirmed in the current study. However, multiple imputation can be viewed as the most robust way of dealing with missing data.[31]

Conclusions

The relevant associations presented and their directions can help improve interpretability of DCS-R domain and total scores. Especially mood status should be taken into account. Future research may focus on creating reference values or weights for different groups, as well as establishing clinically meaningful differences in diabetes symptom burden.

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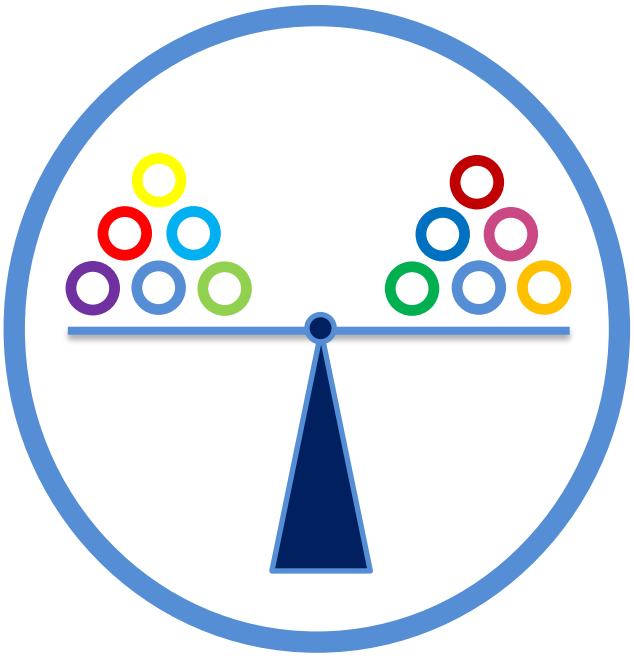
Chapter 7

General discussion



The most important findings deriving from this dissertation are:

1. Most decision aids developed for persons suffering from cardiovascular diseases, diabetes and/or chronic respiratory diseases are focused and tested on two particular elements of shared-decision making, namely the option clarification and harms and benefits discussion.
2. Insulin glargine 300 U/mL is found to be a convenient glucose lowering drug by persons with type 2 diabetes requiring insulin therapy who wish their current treatment to be more flexible, as well as to decrease the volume to be injected.
3. Hypoglycemia is found to be associated with higher hypoglycemia fear and diabetes symptom burden, independent of treatment regimen (oral vs. insulin).
4. Low mood and likely depression are two important patient characteristics to take into account, because they amplify scores on all domains of the Diabetes Symptom Checklist-Revised (DSC-R), particularly the fatigue, cognitive symptoms, hypoglycemic, and hyperglycemic domains.

Decision aids

The International Patient Decision Aid Standards (IPDAS) Collaboration aims to enhance the quality and effectiveness of decision aids by establishing an evidence-informed framework for improving their content, development, implementation, and evaluation.[1] According to the IPDAS collaboration, all shared-decision making elements, except making the decision, should be incorporated in tools in order to qualify them as decision aids.[2] However, as we found in our systematic review (Chapter 3), most decision aids developed for and tested in persons suffering from the selected chronic conditions are focused on providing information (option clarification) or discussing choices (harms and benefits discussion), rather than on creating empathic conversations.[3] Noteworthy, decision aids for chronic conditions other than the selected ones, as well as decision aids not tested in randomized controlled trials, may be missed in our review as they were excluded and limit the external validity of our findings. Future research should look at decision aids for other

(chronic) diseases and focus on the consequences of leaving out shared-decision making elements, as well as its situation-dependency, in terms of shared-decision making outcomes.

Multiple difficulties were faced during the conduction of this review, pointing towards the need for quality improvement of randomized controlled trials studying decision aid effects and their publications. The new Standards for UNiversal reporting of patient Decision Aid Evaluation studies (SUNDAE) checklist seems to meet this need to a large extent.[4] However, the measurement instruments to use in these randomized controlled trials, as well as the timing of outcome measurements, are not handled by the SUNDAE checklist and is needed to reduce the heterogeneity across studies in this field of research. Therefore, a "core outcome set" for research in the area of decision aids (for persons with chronic conditions) would be desirable to compare and contrast research findings.[5] A core outcome set is "an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population. It is a recommendation of what should be measured and reported in all clinical trials".[5] There are many initiatives on (involving patients in) the choice of core outcome sets or the development of patient-reported outcomes (PROs), among others COMET,[6] PCORI,[7] OMERACT,[8] COSMIN,[9] ISOQOL,[10] and ICHOM.[11] These initiatives may play an important role in developing core outcome sets for research in the field of decision aids. A recently published handbook on how to develop a core outcome set may be helpful in doing so.[12]

The use of a decision aids is not a prerequisite for shared-decision making, and the use of decision aids alone is not enough to implement shared-decision making.[13, 14] Implementation of shared-decision making needs multifaceted strategies coupled with culture change among professionals, their organizations, and patients.[14] Guidelines or protocols are useful starting points, but they need to be integrated into practice, among others through education, in order to be optimally effective.[15] Health professionals should be educated about the importance of creating and fostering a culture of shared-decision making and the skills needed to communicate evidence and its

limitation in an understandable way.[13] Patients may be educated as well, and decision aids may play an important role in doing so. According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), diabetes self-management education and support are key to enable patients to make informed decisions and to assume responsibility for diabetes management.[16] In this context, decision aids may be useful as tools to build health literacy and educate patients to play an active role in self-management.[17]

Besides educating patients and health professionals, other ways to shape an environment that facilitates shared-decision making are, among others, an adequate appointment duration, short (or at least flexible) periods between visits, continuity of care, and a system in which the medication choice is driven by personal contexts, values, and preferences of patients.[18] Importantly, shared-decision making should not be seen as a tedious added extra, but as the core of good clinical practice, with patients placed at the center of all decisions.[14]

Patient-reported outcomes

PROs may inform shared-decision making in two ways: 1) informing the situation diagnosis element by use in clinical practice and 2) informing the harms and benefits discussion by use in research. An example of the latter is the Optimizing Patient-relevant outcomes with Toujeo (insulin glargine 300 U/mL) IN Routine Diabetes care (OPTIN-D) study (Chapter 4), in which the changes in PROs are assessed after switching to insulin glargine 300 U/mL. Our study regarding improvement of the interpretability of individual DSC-R scores is an example of the way in which PROs may become more useful for clinical practice.

Patient-reported outcomes in research

When applying shared-decision making in persons suffering from type 2 diabetes, insulin glargine 300 U/mL may be one of the available options. The study described in Chapter 4 found insulin glargine 300 U/mL to be a convenient glucose lowering medicine by persons with type 2 diabetes who wish their current treatment to be more flexible, as well as to decrease the volume to

be injected. As we cannot rule out the possibility of the findings regarding medication convenience being due to a study effect, a controlled study design is needed to draw firm conclusions regarding a causal relationship between initiating insulin glargine 300 U/mL and improved patient-reported medication convenience. Our observational study in Chapter 4 did not find changes in hypoglycemia or other PROs than medication convenience, probably because of the relatively favorable psycho-medical profile of the study population. Therefore, future studies need to examine the impact of insulin glargine 300 U/mL in persons with type 2 diabetes with a less favorable psycho-medical profile.

Reducing the burden of hypoglycemia is important to persons with type 2 diabetes as we showed in Chapter 5, where hypoglycemia was found to be associated with higher hypoglycemia fear and diabetes symptom burden, independent of treatment regimen. Prevention and adequate management of hypoglycemia at least deserves full clinical attention. This is true for both persons using oral agents and persons initiating insulin therapy as, in line with previous studies,[19] hypoglycemia rates when using oral agents were found to be relatively high and insulin glargine cannot fully eradicate the burden of hypoglycemia.

A minimal clinically important difference for both hypoglycemia fear and diabetes symptom burden is needed to make scores interpretable.[20] The minimal clinically important difference is “the smallest benefit of value to persons with type 2 diabetes capturing both the magnitude of the improvement and the value persons place on the change”.[21] Previous studies proposed a minimal clinically important difference for the Worry subscale of the Hypoglycemia Fear Survey[22] and the DSC-R,[23] but these studies did not use an optimal anchor. As the anchor-based method is recommended to assess the minimal clinically important difference,[20] future studies may focus on clinically relevant differences in hypoglycemia fear and diabetes symptom burden using optimal anchors in order to enhance interpretation of results.

Patient-reported outcomes in clinical practice

In Chapter 6, we made a first attempt to improve the interpretability of (domain) scores on the DSC-R by assessing their association with patient characteristics. Our study found that low mood and likely depression amplify scores on all domains of the DSC-R. This is in particular the case for the fatigue, cognitive symptoms, hypoglycemic, and hyperglycemic domains, which can be regarded as measures of acute diabetes-associated symptoms resulting from fluctuating blood sugars.[24] Previous studies also found psychological well-being to be associated with subjective symptom report[25-27] and several plausible explanations have been suggested, but the causation is unclear. Nonetheless, the findings in Chapter 6 underscore the importance of attention for and accurate treatment of low mood and depression in clinical practice. The other way around may an excessive burden of fatigue, cognitive symptoms, hypoglycemia, and/or hyperglycemia direct to an underlying low mood or depression.

The relevant associations and their effect estimates presented in Chapter 6 may be useful in assessing to what extent a certain symptom burden can be regarded as excessive given certain patient characteristics. However, the associations and their effect estimates need further testing in more diverse patient populations as the current study merely included Caucasian persons and it is unclear whether these results are generalizable to non-Caucasian persons as well. Future research may focus on creating reference values or weights for different groups, as well as establishing clinically meaningful differences in diabetes symptom burden. This will enhance the score interpretation and in turn the clinical usefulness of the DSC-R. When using the DSC-R in clinical practice, then it is advised to focus on (changes in) DSC-R scores on domain level.[20]

Before using in clinical practice, future studies should further evaluate the content validity of the DSC-R in greater detail as it may lack relevant items, e.g. regarding itchy skin, increased hunger, sweating, and gender-specific sexual symptoms.[28] The DSC-R combines a reflective model, in which items reflect the domains, with a formative model, in which the domains form the total symptom

burden. As the most important items should all be represented in formative models,[20] it is concerning that domains are neglected. Therefore, future research may assess the content validity of the DSC-R by using the new criteria and rating system for evaluating the content validity of PRO measures as suggested by the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative.[29] Eventually, the content of the DSC-R may be adjusted based on this content validity evaluation.

Besides enhancing the content and interpretation of scores, new data collection technologies will facilitate PROs to become part of everyday care.[30] Computer adaptive testing seems to be promising as it demands to fill out a small number of items while keeping a high reliability,[20] and thus saving time collecting data in clinical practice. Training in the use and interpretation of PROs is needed when aiming for optimal use in routine practice.[31, 32] These investments may be worthwhile if they will be translated into an improved patient-clinician relationship and quality of care.[33]

Making the right care happen

Importantly, identifying the right care is not enough as it must actually be carried through.[34] Several tools are available to make the right care happen, which is important in preventing a workload-capacity imbalance.[34] When capacity cannot bear the workload, then patients with multiple chronic conditions will just “survive” rather than thrive.[34]

Future research may focus on …

- The consequences of leaving out shared-decision making elements from decision aids, as well as its situation-dependency in terms of shared-decision making outcomes.
- Developing a core outcome set for research in the field of decision aids (for persons with chronic conditions).
- A controlled study design to draw firm conclusions regarding a causal relationship between initiating glargine 300 U/mL and improved patient-reported medication convenience.
- The impact of glargine 300 U/mL in persons with type 2 diabetes with a less favorable psycho-medical profile compared with our observational study.
- Assessing the clinically relevant differences in hypoglycemia fear and diabetes symptom burden using optimal anchors.
- Re-evaluating the content validity of the Diabetes Symptom Checklist-Revised.
- Further testing of the relevant associations between patient characteristics and (domain) scores on the Diabetes Symptom Checklist-Revised, as well as their effect estimates, in diverse patient populations.
- Creating reference values or weights for different groups, besides establishing clinically meaningful differences, in diabetes symptom burden.

Clinical practice may improve by …

- Educating health professionals about the importance of creating and fostering a culture of shared-decision making and the skills needed to communicate evidence and its limitation in an understandable way.
- Offering diabetes self-management education and support to patients (decision aids may be useful as tools).
- Appreciation of shared-decision making as the core of good clinical practice, with patients placed at the center of all decisions.
- Shaping an environment that facilitates shared-decision making.
- Prevention and adequate management of hypoglycemia (both in persons using oral agents and persons initiating insulin therapy).
- Having attention for and accurate treatment of low mood and depression in clinical practice.
- Using the Diabetes Symptom Checklist-Revised on domain level, when used in clinical practice.
- Using new data collection technologies (e.g., computer adaptive testing).
- Training in the use and interpretation of patient-reported outcomes.

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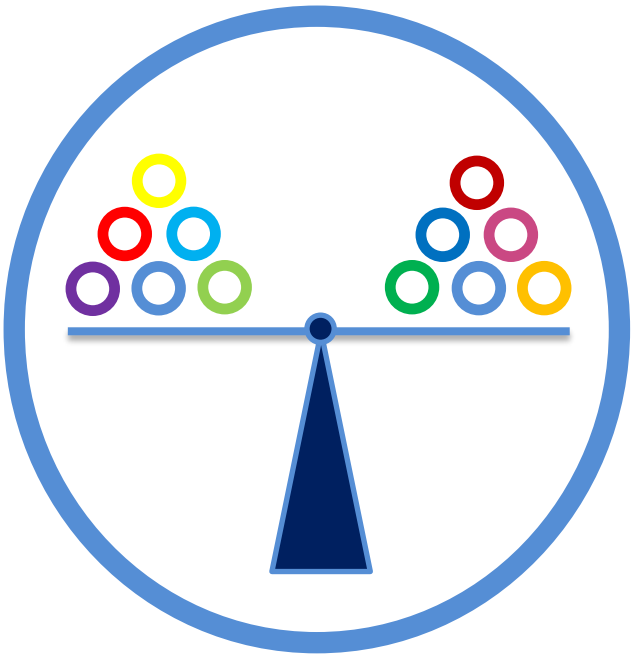
Appendix 1 – Search strategy (Chapter 2 and 3)



Pubmed

1. **Decision**

"Decision Making"[Mesh] OR "Clinical Decision-Making"[Mesh] OR Decision*[tiab]

2. **Shared**

"Patient-Centered Care"[Mesh] OR "Patient Participation"[Mesh] OR "Patient Preference"[Mesh] OR share*[tiab] OR sharing[tiab] OR engage*[tiab] OR patient centered*[tiab] OR patient centred[tiab] OR patient focused[tiab] OR sdm[tiab] OR prefer*[tiab]

3. **Aids**

"Decision Support Techniques"[Mesh] OR "Decision Making, Computer-Assisted"[Mesh] OR tool*[tiab] OR aid[tiab] OR aids[tiab] OR intervention*[tiab] OR support*[tiab] OR instrument*[tiab]

4. **Chronisch zieken**

"Asthma"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR asthma*[tiab] OR copd[tiab] OR chronic respiratory disease*[tiab] OR chronic obstructed pulmonary disease*[tiab] OR chronic obstructive airway disease*[tiab] OR chronic obstructive lung disease*[tiab] OR chronic bronchitis[tiab] OR emphysema[tiab] OR coad[tiab] OR chronic airflow obstruction*[tiab] OR "Diabetes Mellitus"[Mesh] OR diabetes[tiab] OR diabetic*[tiab] OR dm2[tiab] OR niddm[tiab] OR dm 2[tiab] OR t2d*[tiab] OR dm type 2[tiab] OR dm type II[tiab] OR dm1[tiab] OR iddm[tiab] OR dm 1[tiab] OR t1d*[tiab] OR dm type 1[tiab] OR dm type I[tiab] OR "Cardiovascular Diseases"[Mesh] OR cardiovascular disease*[tiab] OR cardiovascular disorder*[tiab] OR cardiovascular disturbance*[tiab] OR cardiovascular lesion*[tiab] OR cardiovascular syndrome*[tiab] OR cvd[tiab] OR myocardial ischem*[tiab] OR myocardial infarct*[tiab] OR heart disease*[tiab] OR coronary disease*[tiab] OR artery disease*[tiab] OR arterial disease*[tiab] OR heart attack*[tiab] OR heart failure*[tiab] OR cardiac failure*[tiab] OR high blood pressure*[tiab] OR hypertensi*[tiab] OR heart patient*[tiab] OR cerebrovascular disease*[tiab] OR cerebrovascular disorder*[tiab] OR vein thrombos*[tiab] OR embolism*[tiab] OR stroke*[tiab] OR cerebrovascular accident*[tiab] OR cva[tiab] OR cvas[tiab] OR vascular accident*[tiab] OR apoplexy[tiab] OR brain infarction*[tiab]

5. **Studiefilter**

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR clinical trial*[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR rct[tiab] OR intervention*[tiab] OR "latin square"[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control[tw] OR controll*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])

Embase

1. **Decision**

'decision making'/exp OR 'clinical decision making'/exp OR decision*:ab,ti

2. **Shared**

'patient participation'/exp OR 'patient preference'/exp OR share*:ab,ti OR sharing:ab,ti OR ‘patient centered*’:ab,ti OR ‘patient centred’:ab,ti OR ‘patient focused’:ab,ti OR sdm:ab,ti OR prefer*:ab,ti

3. **Aids**

'decision support system'/exp OR tool*:ab,ti OR aid:ab,ti ORaids:ab,ti OR intervention*:ab,ti OR support*:ab,ti OR instrument*:ab,ti

4. **Chronisch zieken**

'asthma'/exp OR 'chronic obstructive lung disease'/exp OR asthma*:ab,ti OR copd:ab,ti OR ‘chronic respiratory disease*’:ab,ti OR ‘chronic obstructed pulmonary disease*’:ab,ti OR ‘chronic obstructive airway disease*’:ab,ti OR ’chronic obstructive lung disease*’:ab,ti OR ‘chronic bronchitis’:ab,ti OR emphysema:ab,ti OR coad:ab,ti OR ‘chronic airflow obstruction*’:ab,ti OR 'diabetes mellitus'/exp OR diabetes:ab,ti OR diabetic*:ab,ti OR dm2:ab,ti OR niddm:ab,ti OR ‘dm 2’:ab,ti OR t2d*:ab,ti OR ‘dm type 2’:ab,ti OR ‘dm type II’:ab,ti OR dm1:ab,ti OR iddm:ab,ti OR ‘dm 1’:ab,ti OR t1d*:ab,ti OR ‘dm type 1’:ab,ti OR ‘dm type I’:ab,ti OR 'cardiovascular disease'/exp OR ‘cardiovascular disease*’:ab,ti OR ‘cardiovascular disorder*’:ab,ti OR ‘cardiovascular disturbance*’:ab,ti OR ‘cardiovascular lesion*’:ab,ti OR ‘cardiovascular syndrome*’:ab,ti OR cvd:ab,ti OR ‘myocardial ischem*’:ab,ti OR ‘myocardial infarct*’:ab,ti OR ‘heart disease*’:ab,ti OR ‘coronary disease*’:ab,ti OR ‘artery disease*’:ab,ti OR ‘arterial disease*’:ab,ti OR ‘heart attack*’:ab,ti OR ‘heart failure*’:ab,ti OR ‘cardiac failure*’:ab,ti OR ‘high blood pressure*’:ab,ti OR hypertensi*:ab,ti OR ‘heart patient*’:ab,ti OR ‘cerebrovascular disease*’:ab,ti OR ‘cerebrovascular disorder*’:ab,ti OR ‘vein thrombos*’:ab,ti OR embolism*:ab,ti OR stroke*:ab,ti OR ‘cerebrovascular accident*’:ab,ti OR cva:ab,ti OR cvas:ab,ti OR ‘vascular accident*’:ab,ti OR apoplexy:ab,ti OR ‘brain infarction*’:ab,ti

5. **Studiefilter**

'intervention study'/exp OR 'clinical trial'/exp OR 'study design'/exp OR 'Latin square design'/exp OR 'comparative study'/exp OR 'controlled study'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'prospective study'/exp OR 'comparative study'/exp OR 'evaluation study'/exp OR 'crossover procedure'/exp OR intervention*:ab,ti OR rct:ab,ti OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR ‘cross over*’:ab,ti OR placebo*:ab,ti OR comparative:ab,ti OR comparing:ab,ti OR ‘evaluation stud*’:ab,ti OR trial*:ab,ti OR control*:ab,ti OR prospective:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl*:ab,ti OR doubl*:ab,ti OR trebl*:ab,ti OR tripl*:ab,ti) AND (mask*:ab,ti OR blind*:ab,ti)) NOT ('animal'/exp NOT 'human'/exp)

Cinahl

1. **Decision**

MH ("Decision Making" OR "Decision Making, Clinical" OR "Decision Making, Patient") OR TI decision* OR AB decision*

2. **Shared**

MH ("Patient Centered Care" OR "Consumer Participation") OR TI (share* OR sharing OR patient centered* OR patient centred* OR patient focused OR sdm OR prefer*) OR AB (share* OR sharing OR patient centered* OR patient centred* OR patient focused OR sdm OR prefer*)

3. **Aids**

MH ("Decision Support Techniques+" OR "Decision Support Systems, Clinical" OR "Decision Making, Computer Assisted") OR TI (tool* OR aid OR aids OR intervention* OR support* OR instrument*) OR AB (tool* OR aid OR aids OR intervention* OR support* OR instrument*)

4. **Chronisch zieken**

MH (Asthma+ OR Pulmonary Disease, Chronic Obstructive+ OR Cardiovascular Diseases+ OR Diabetes Mellitus+ OR Diabetes Mellitus, Type 2 OR Diabetes Mellitus, Type 1+ OR Diabetes Mellitus, Gestational) OR TI (asthma* OR copd OR chronic respiratory disease* OR chronic obstructed pulmonary disease* OR chronic obstructive airway disease* OR chronic obstructive lung disease* OR chronic bronchitis OR emphysema OR coad OR chronic airflow obstruction* OR diabetes OR diabetic* OR dm2 OR niddm OR dm 2 OR t2d* OR dm type 2 OR dm type II OR dm1 OR iddm OR dm 1 OR t1d* OR dm type 1 OR dm type I OR cardiovascular disease* OR cardiovascular disorder* OR cardiovascular disturbance* OR cardiovascular lesion* OR cardiovascular syndrome* OR cvd OR myocardial ischem* OR myocardial infarct* OR heart disease* OR coronary disease* OR artery disease* OR arterial disease* OR heart attack* OR heart failure* OR cardiac failure* OR high blood pressure* OR hypertensi* OR heart patient* OR cerebrovascular disease* OR cerebrovascular disorder* OR vein thrombos* OR embolism* OR stroke* OR cerebrovascular accident* OR cva OR cvas OR vascular accident* OR apoplexy OR brain infarction*) OR AB (asthma* OR copd OR chronic respiratory disease* OR chronic obstructed pulmonary disease* OR chronic obstructive airway disease* OR chronic obstructive lung disease* OR chronic bronchitis OR emphysema OR coad OR chronic airflow obstruction* OR diabetes OR diabetic* OR dm2 OR niddm OR dm 2 OR t2d* OR dm type 2 OR dm type II OR dm1 OR iddm OR dm 1 OR t1d* OR dm type 1 OR dm type I OR cardiovascular disease* OR cardiovascular disorder* OR cardiovascular disturbance* OR cardiovascular lesion* OR cardiovascular syndrome* OR cvd OR myocardial ischem* OR myocardial infarct* OR heart disease* OR coronary disease* OR artery disease* OR arterial disease* OR heart attack* OR heart failure* OR cardiac failure* OR high blood pressure* OR hypertensi* OR heart patient* OR cerebrovascular disease* OR cerebrovascular disorder* OR vein thrombos* OR embolism* OR stroke* OR cerebrovascular accident* OR cva OR cvas OR vascular accident* OR apoplexy OR brain infarction*)

5. **Studietypes**

MH ("Clinical Trials+" OR "Quantitative Studies" OR "Study Design+" OR "Random Assignment" OR "Evaluation Research" OR "Comparative Studies") OR (PT Clinical trial) OR (TX clini* N1 trial*) OR (TX ((singl* N1 blind*) OR (singl* N1 mask*)) OR TX ((doubl* N1 blind*) OR (doubl* N1 mask*)) OR TX ((tripl* N1 blind*) OR (tripl* N1 mask*))) OR (TX randomi* control*) OR ((TX random* allocat*) OR (TX allocat* random*)) OR (TX placebo*) OR (TX (waitlist* OR (wait* AND list*)) AND (control* OR group))) OR ((TX "treatment as usual") OR (TX tau)) OR (TX (control* N3 (trial* OR study OR studies OR group*))) OR TX (rct OR intervention* OR “latin square” OR prospectiv* OR volunteer OR follow or factorial* OR crossover* OR “cross over” OR comparative OR comparing OR evaluation stud*)

PsycINFO

1. **Decision**

DE "Decision Making" OR TI decision* OR AB decision*

2. **Shared**

DE ("Client Participation") OR TI (share* OR sharing OR patient centered* OR patient centred* OR patient focused OR sdm OR prefer*) OR AB (share* OR sharing OR patient centered* OR patient centred* OR patient focused OR sdm OR prefer*)

3. **Aids**

DE "Decision Support Systems" OR TI (tool* OR aid OR aids OR intervention* OR support* OR instrument*) OR AB (tool* OR aid OR aids OR intervention* OR support* OR instrument*)

4. **Chronisch zieken**

DE ("Asthma" OR "Chronic Obstructive Pulmonary Disease" OR "Bronchial Disorders" OR "Pulmonary Emphysema" OR "Cardiovascular Disorders" OR "Aneurysms" OR "Arteriosclerosis" OR "Blood Pressure Disorders" OR "Cerebrovascular Disorders" OR "Embolisms" OR "Heart Disorders" OR "Hemorrhage" OR "Hypertension" OR "Ischemia" OR "Thromboses" OR "Diabetes" OR "Diabetes Insipidus" OR "Diabetes Mellitus" OR "Type 2 Diabetes" OR "Gestational Diabetes" OR DE "Blood Sugar") OR TI (asthma* OR copd OR chronic respiratory disease* OR chronic obstructed pulmonary disease* OR chronic obstructive airway disease* OR chronic obstructive lung disease* OR chronic bronchitis OR emphysema OR coad OR chronic airflow obstruction* OR diabetes OR diabetic* OR dm2 OR niddm OR dm 2 OR t2d* OR dm type 2 OR dm type II OR dm1 OR iddm OR dm 1 OR t1d* OR dm type 1 OR dm type I OR cardiovascular disease* OR cardiovascular disorder* OR cardiovascular disturbance* OR cardiovascular lesion* OR cardiovascular syndrome* OR cvd OR myocardial ischem* OR myocardial infarct* OR heart disease* OR coronary disease* OR artery disease* OR arterial disease* OR heart attack* OR heart failure* OR cardiac failure* OR high blood pressure* OR hypertensi* OR heart patient* OR cerebrovascular disease* OR cerebrovascular disorder* OR vein thrombos* OR embolism* OR stroke* OR cerebrovascular accident* OR cva OR cvas OR vascular accident* OR apoplexy* OR brain infarction*) OR AB (asthma* OR copd OR chronic respiratory disease* OR chronic obstructed pulmonary disease* OR chronic obstructive airway disease* OR chronic obstructive lung disease* OR chronic bronchitis OR emphysema OR coad OR chronic airflow obstruction* OR diabetes OR diabetic* OR dm2 OR niddm OR dm 2 OR t2d* OR dm type 2 OR dm type II OR dm1 OR iddm OR dm 1 OR t1d* OR dm type 1 OR dm type I OR cardiovascular disease* OR cardiovascular disorder* OR cardiovascular disturbance* OR cardiovascular lesion* OR cardiovascular syndrome* OR cvd OR myocardial ischem* OR myocardial infarct* OR heart disease* OR coronary disease* OR artery disease* OR arterial disease* OR heart attack* OR heart failure* OR cardiac failure* OR high blood pressure* OR hypertensi* OR heart patient* OR cerebrovascular disease* OR cerebrovascular disorder* OR vein thrombos* OR embolism* OR stroke* OR cerebrovascular accident* OR cva OR cvas OR vascular accident* OR apoplex* OR brain infarction*)

5. **Study type**

DE "Treatment Effectiveness Evaluation" OR DE "Clinical Trials" OR DE "Placebo" OR TI (placebo* OR randomly) OR AB (placebo* OR randomly) OR TX randomi* OR TI trial OR AB trial OR TX ((singl* OR doubl* OR trebl* OR tripl*) N3 (blind* OR mask* OR dummy)) OR TI (control* N3 (trial* OR study OR studies OR group*)) OR AB (control* N3 (trial* OR study OR studies OR group*)) OR TI factorial* OR AB factorial* OR TI allocat* OR AB allocat* OR TI assign* OR AB assign* OR TI volunteer* OR AB volunteer* OR TI (crossover* OR cross over*) OR AB (crossover* OR cross over*) OR TX (quasi N5 (experimental OR random*)) OR AB (intervention* OR rct OR comparative OR comparing OR evaluation stud* OR prospective) OR TI (intervention* OR rct OR comparative OR comparing OR evaluation stud* OR prospective)

Web of Science

1. **Decision**

TS = (Decision*)

2. **Shared**

TS=(share* OR sharing OR “patient centered*” OR “patient centred” OR “patient focused” OR sdm OR prefer*)

3. **Aids**

TS =(tool* OR aid OR aids OR intervention* OR support* OR instrument*)

4. **Chronisch zieken**

TS=(asthma OR "chronic obstructed pulmonary disease*" OR copd OR “chronic respiratory disease*” OR “chronic obstructive airway disease*” OR “chronic obstructive lung disease*” OR “chronic bronchitis” OR emphysema OR coad OR “chronic airflow obstruction*” OR diabetes OR diabetic* OR dm2 OR niddm OR “dm 2” OR t2d* OR “dm type 2” OR “dm type II” OR dm1 OR iddm OR “dm 1” OR “t1d*” OR “dm type 1” OR “dm type I” OR “cardiovascular disease*” OR “cardiovascular disorder*” OR “cardiovascular disturbance*” OR “cardiovascular lesion*” OR “cardiovascular syndrome*” OR cvd OR “myocardial ischem*” OR “myocardial infarct*” OR “heart disease*” OR “coronary disease*” OR “artery disease*” OR “arterial disease*” OR “heart attack*” OR “heart failure*” OR “cardiac failure*” OR “high blood pressure*” OR hypertensi* OR “heart patient*” OR “cerebrovascular disease*” OR “cerebrovascular disorder*” OR “vein thrombos*” OR embolism* OR stroke* OR “cerebrovascular accident*” OR cva OR cvas OR “vascular accident*” OR apoplexy OR “brain infarction*”)

5. **Studietypes**

TS = (rct OR random* OR control* OR trial OR placebo* OR compar* OR group OR groups OR therapy OR treatment OR intervention OR “research design” OR comparative OR “evaluation stud*” OR “follow-up stud*” OR prospective ” OR “single blind” OR “double blind” OR “trebl* blind” OR “triple blind” OR factorial OR allocat* OR assign* OR volunteer* OR crossover OR “cross over”)

Cochrane Library

1. **Decision**

decision*:ti,ab,kw (Word variations have been searched)

2. **Shared**

share* OR sharing OR “patient centered*” OR “patient centred” OR “patient focused” OR sdm OR prefer*:ti,ab,kw (Word variations have been searched)

3. **Aids**

tool* OR aid OR aids OR intervention* OR support* OR instrument*:ti,ab,kw (Word variations have been searched)

4. **Chronisch zieken**

asthma OR "chronic obstructed pulmonary disease*" OR copd OR “chronic respiratory disease*” OR “chronic obstructive airway disease*” OR “chronic obstructive lung disease*” OR “chronic bronchitis” OR emphysema OR coad OR “chronic airflow obstruction*” OR diabetes OR diabetic* OR dm2 OR niddm OR “dm 2” OR t2d* OR “dm type 2” OR “dm type II” OR dm1 OR iddm OR “dm 1” OR “t1d*” OR “dm type 1” OR “dm type I” OR “cardiovascular disease*” OR “cardiovascular disorder*” OR “cardiovascular disturbance*” OR “cardiovascular lesion*” OR “cardiovascular syndrome*” OR cvd OR “myocardial ischem*” OR “myocardial infarct*” OR “heart disease*” OR “coronary disease*” OR “artery disease*” OR “arterial disease*” OR “heart attack*” OR “heart failure*” OR “cardiac failure*” OR “high blood pressure*” OR hypertensi* OR “heart patient*” OR “cerebrovascular disease*” OR “cerebrovascular disorder*” OR “vein thrombos*” OR embolism* OR stroke* OR “cerebrovascular accident*” OR cva OR cvas OR “vascular accident*” OR apoplexy OR “brain infarction” :ti,ab,kw (Word variations have been searched)

5. **Studietypes**

rct OR random* OR control* OR trial OR placebo* OR compar* OR therapy OR treatment OR intervention* OR “research design” OR comparative OR (evaluation NEAR/3 stud*) OR “follow-up stud*” OR prospective OR “single blind” OR “double blind” OR “trebl* blind” OR “triple blind” OR factorial OR allocat* OR assign* OR volunteer* OR crossover OR “cross over”

Appendix 2 – Risk of bias assessment (Chapter 3)

Study	Outcome	Risk of bias assessment[a,b]							
		RSG	AC	BPP[c]	BOA[c]	IOD	SR	OB	Summary assessment of risk of bias
Knops et al. 2014[1]									
	Decisional conflict	+	?	-	?	-	+	?	High risk of bias
	Knowledge	+	?	-	?	+	+	?	Unclear risk of bias
	Anxiety	+	?	-	?	+	+	?	Unclear risk of bias
	Conversation satisfaction	+	?	-	?	-	+	?	High risk of bias
	Quality of life	+	?	-	?	+	+	?	Unclear risk of bias
	Treatment decision (preference)	+	?	-	?	+	+	?	Unclear risk of bias
Man-Son-Hing et al. 1999[2]									
	Decisional conflict	+	+	-	?	?	?	?	Unclear risk of bias
	Satisfaction with the decision making process	+	+	-	?	?	?	?	Unclear risk of bias
	Patient participation in decision making	+	+	-	?	?	?	?	Unclear risk of bias
	Proportion undecided	+	+	-	?	?	?	?	Unclear risk of bias
	Treatment decision (preference)	+	+	-	?	?	?	?	Unclear risk of bias
	Adherence	+	+	-	?	?	?	?	Unclear risk of bias
Thomson et al. 2007[3]									
	Decisional conflict	+	?	-	?	-	+	-	High risk of bias
	Knowledge	+	?	-	?	-	+	-	High risk of bias
	Anxiety	+	?	-	?	-	+	-	High risk of bias
	Treatment decision (preference)	+	?	-	?	-	+	-	High risk of bias
Fraenkel et al. 2012[4]									
	Anxiety	?	?	-	+	?	?	+	Unclear risk of bias

Nannenga et al. 2009[5]									
	Decisional conflict	+	+	-	?	?	-	+	**High risk of bias**
	Knowledge	+	+	-	?	?	-	+	**High risk of bias**
	Conversation duration	+	+	-	-	?	-	+	**High risk of bias**
	Patient participation in decision making	+	+	-	-	?	-	+	**High risk of bias**
	Trust in physician	+	+	-	?	?	-	+	**High risk of bias**
Mathers et al. 2012[6]									
	Decisional conflict	+	-	-	-	?	+	+	**High risk of bias**
	Conversation duration	+	-	-	-	?	+	+	**High risk of bias**
	Proportion undecided	+	-	-	-	?	+	+	**High risk of bias**
	Glycemic control	+	-	-	-	?	+	+	**High risk of bias**
Heisler et al. 2014[7]									
	Decisional conflict	+	+	-	+	?	+	+	**Unclear risk of bias**
	Knowledge	+	+	-	+	?	+	+	**Unclear risk of bias**
	Illness distress	+	+	-	+	?	+	+	**Unclear risk of bias**
	Adherence	+	+	-	+	?	+	+	**Unclear risk of bias**
	Glycemic control	+	+	-	+	?	+	+	**Unclear risk of bias**
	Diabetes care self-efficacy	+	+	-	+	?	+	+	**Unclear risk of bias**
Thomas et al. 2013[8]									
	Decisional conflict	+	+	-	?	?	+	+	**Unclear risk of bias**
	Knowledge	+	+	-	?	?	+	+	**Unclear risk of bias**
	Treatment decision (preference)	+	+	-	?	?	+	+	**Unclear risk of bias**
Bailey et al. 2016[9]									
	Decisional conflict	?	+	-	+	+	+	+	**Unclear risk of bias**
	Knowledge	?	+	-	+	+	+	+	**Unclear risk of bias**
	Decision self-efficacy	?	+	-	+	+	+	+	**Unclear risk of bias**

Perestelo-Perez et al. 2016[10]									
	Decisional conflict	+	-	-	?	?	+	+	High risk of bias
	Anxiety	+	-	-	?	?	+	+	High risk of bias
	Satisfaction with the decision making process	+	-	-	?	?	+	+	High risk of bias
	Conversation duration	+	-	-	-	-	+	+	High risk of bias
	Illness distress	+	-	-	?	-	+	+	High risk of bias
Slok et al. 2016[11]									
	Quality of life	+	-	-	+	-	-	+	High risk of bias
	Treatment satisfaction	+	-	-	+	-	-	+	High risk of bias
	Health status	+	-	-	+	-	-	+	High risk of bias
Denig et al. 2014[12]									
	Quality of life	+	?	-	?	+	+	-	High risk of bias
	Illness distress	+	?	-	?	+	+	-	High risk of bias
	Smoking status	+	?	-	?	+	+	-	High risk of bias
	Treatment satisfaction	+	?	-	?	+	+	-	High risk of bias
	Diabetes care self-efficacy	+	?	-	?	+	+	-	High risk of bias
Huang et al. 2017[13]									
	Decisional conflict	?	-	-	?	?	+	+	High risk of bias
	Treatment decision (preference)	?	-	-	?	?	+	+	High risk of bias
El-Jawahri et al. 2016[14]									
	Knowledge	+	+	-	-	?	-	+	High risk of bias
	Proportion undecided	+	+	-	-	?	-	+	High risk of bias

Morgan et al. 2000[15]									
	Knowledge	+	-	-	?	-	?	+	**High risk of bias**
	Satisfaction with the decision making process	+	-	-	?	-	?	+	**High risk of bias**
	Treatment decision (preference)	+	-	-	?	-	?	+	**High risk of bias**
Mullan et al. 2009[16]									
	Decisional conflict	+	-	-	?	?	+	+	**High risk of bias**
	Patient participation in decision making	+	-	-	?	?	+	+	**High risk of bias**
	Trust in physician	+	-	-	?	?	+	+	**High risk of bias**
	Treatment decision (preference)	+	-	-	?	?	+	+	**High risk of bias**
	Glycemic control	+	-	-	?	?	+	+	**High risk of bias**
	Health status	+	-	-	?	?	+	+	**High risk of bias**
Mann et al. 2010[17]									
	Decisional conflict	?	?	-	?	?	?	?	**Unclear risk of bias**
Karagiannis et al. 2016[18]									
	Decisional conflict	+	-	-	-	?	+	+	**High risk of bias**
	Knowledge	+	-	-	-	?	+	+	**High risk of bias**
	Glycemic control	+	-	-	-	-	+	+	**High risk of bias**
	BMI	+	-	-	-	-	+	+	**High risk of bias**
Coylewright et al. 2016[19]									
	Decisional conflict	+	+	-	-	?	-	+	**High risk of bias**
	Patient participation in decision making	+	+	-	-	-	-	+	**High risk of bias**

den Ouden et al. 2017[20]									
	Glycemic control	+	-	-	?	?	-	+	**High risk of bias**
	Blood pressure	+	-	-	?	?	-	+	**High risk of bias**
	Total cholesterol	+	-	-	?	?	-	+	**High risk of bias**
	BMI	+	-	-	?	-	-	+	**High risk of bias**
Gagné et al. 2017[21]									
	Decisional conflict	+	+	-	+	+	+	+	**Low risk of bias**
	Knowledge	+	+	-	+	+	+	+	**Low risk of bias**
	Achieving treatment goals (asthma control)	+	+	-	+	+	+	+	**Low risk of bias**
	Adherence	+	+	-	+	+	+	+	**Low risk of bias**
Korteland et al. 2017[22]									
	Decisional conflict	+	+	-	?	+	+	?	**Unclear risk of bias**
	Anxiety	+	+	-	?	+	+	?	**Unclear risk of bias**
McAlister et al. 2005[23]									
	Decisional conflict	+	+	-	+	?	-	+	**High risk of bias**
Weymiller et al. 2007[24]									
	Decisional conflict	+	+	-	?	?	-	+	**High risk of bias**
	Treatment decision (preference)	+	+	-	?	?	-	+	**High risk of bias**
	Adherence	+	+	-	?	?	-	+	**High risk of bias**

[a]RSG = random sequence generation; AC = allocation concealment; BPP = blinding of participants and personnel; BOA = blinding of outcome assessment; IOD = incomplete outcome data; SR = selective reporting; OB = other bias

[b]+ = Low risk of bias; - = high risk of bias; ? = unclear risk of bias

[c]This element is not taken into account in the summary assessment of risk of bias

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Appendix 3 – Decision aid information (Chapter 3)

Information regarding decision aids for cardiovascular diseases

DA without a name (described in Knops et al. 2014)

DA characteristics					
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**	
Patients with asymptomatic abdominal aortic aneurysms	Elective surgery or watchful waiting	Patient decision aid	Computer-based	Not available anymore, but the content can be viewed through: https://sdmstaging.medify.eu/surgery/index_keuzehulp-aneurysma_nl.html	
SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**+**	**+**	**+**	**+**	**+**
Study information					
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Knops et al. 2014[1]	The Netherlands	Asymptomatic abdominal aortic aneurysm	Secondary/tertiary care	Secondary/tertiary care	Only DA	Usual care

Effects on decisional conflict	
Measurement moment	1 To 4 weeks post-encounter
Measurement instrument	Decisional Conflict Scale
Effect[b]	NS
Risk of bias	High risk

Effects on conversation satisfaction	
Measurement moment	1 To 4 weeks post-encounter
Measurement instrument	Patient Satisfaction Questionnaire
Effect[b]	NS
Risk of bias	High risk

Effects on treatment decision (preference)	
Measurement moment	9 To 10 months post-encounter
Measurement instrument	Extracted from the medical record
Effect[b]	NS[c]
Risk of bias	Unclear risk

Effects on knowledge	
Measurement moment	1 To 4 weeks post-encounter
Measurement instrument	13 Items of the Dutch multiple-choice Aneurysm Knowledge Questionnaire
Effect[b]	NS
Risk of bias	Unclear risk
Effects on (health-related) quality of life	
Measurement moment	1 To 4 weeks post-encounter
Measurement instrument	12-Item Short Form Health Survey (SF-12)
Effect[b]	NS
Risk of bias	Unclear risk
Effects on anxiety	
Measurement moment	1 To 4 weeks post-encounter
Measurement instrument	Hospital Anxiety and Depression Scale (HADS)
Effect[b]	NS
Risk of bias	Unclear risk

[a]+ = The DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as not choosing elective aneurysm impair

DA without a name (described in Man-Son-Hing et al. 1999)

DA characteristics					
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**	
Patients with atrial fibrillation	Taking aspirin or taking warfarin	Patient decision aid	Both paper-based and audio-based	Not available anymore	
SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
?	**?**	**+**	**+**	**+**	**+**
Study information					
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Man-Son-Hing et al. 1999[2]	Canada and the United States of America	Atrial fibrillation	Unclear	Secondary/tertiary care	Only DA	Usual care

Effects on decisional conflict	
Measurement moment	1 To 4 days post-encounter
Measurement instrument	Decisional Conflict Scale and two additional items to elicit patients' perceptions about the extent they were informed about 1) the benefits and risks of warfarin and 2) about benefits and risks of aspirin
Effect[b]	NS
Risk of bias	Unclear risk

Effects on patient participation in decision making	
Measurement moment	1 To 4 days post-encounter
Measurement instrument	5-Point Likert scale to judge the relative strength of the patient's personal input into the choice versus their physician
Effect[b]	NS[c]
Risk of bias	Unclear risk

Effects on satisfaction with the decision making process	
Measurement moment	1 To 4 days post-encounter
Measurement instrument	6 Items using a 5-point Likert scale
Effect[b]	NS
Risk of bias	Unclear risk

Effects on treatment decision (preference)	
Measurement moment	1 To 4 days post-encounter
Measurement instrument	Questionnaire in which participants were, among others, asked what decision regarding antithrombotic therapy was made
Effect[b]	NS[d]
Risk of bias	Unclear risk
Effects on proportion undecided	
Measurement moment	1 To 4 days post-encounter
Measurement instrument	Participants were asked to indicate whether a decision regarding the choice of antithrombotic therapy had been made in conjunction with their physician
Effect[b]	+[e]
Risk of bias	Unclear risk
Effects on adherence	
Measurement moment	6 Months post-encounter
Measurement instrument	Participants were asked by telephone which therapy they were currently taking
Effect[b]	NS[f]
Risk of bias	Unclear risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as patient reported that he/she made the decision, rather than his/her physician

[d]For this dichotomous outcome is an event regarded as deciding to take warfarin

[e]Odds on not being able to make a definite choice was smaller for the decision aid group compared to the control group

[f]For this dichotomous outcome is an event regarded continuing to take the therapy that was initially chosen

DA without a name (described in Fraenkel et al. 2012)

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with non-valvular atrial fibrillation (NVAF)	Taking aspirin or taking warfarin	Both patient decision aid and conversation aid	Both paper-based and computer-based	Unclear

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**?**	**+**	**+**	**+**	**-**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Fraenkel et al. 2012[3]	The United States of America	Non-valvular atrial fibrillation	Primary care	Primary care	Only DA	Unclear

Effects on anxiety	
Measurement moment	Immediately post-encounter
Measurement instrument	Spielberger State Anxiety Index
Effect[b]	NS
Risk of bias	Unclear risk

[a] + = The DA handles the regarding element; - = the DA does not handle the regarding element

[b] + = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

DA without a name (described in Thomas et al. 2013)

DA characteristics						
DA target group		**Decision to be made**		**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Individuals eligible for an implantable cardioventer/defibrilator (ICD)		Whether or not to have an implantable cardioventer/defibrilator (ICD)		Conversation aid	Computer-based	Not available
SDM elements[a]						
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**		**Making or deferring a decision**
+	**?**	**+**	**+**	**?**		**?**
Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Thomas et al. 2013[4]	The United States of America	Heart failure (class II to III of the New York Heart Association and ejection fraction ≤35%)	Secondary/tertiary care	Secondary/tertiary care	DA + an information sheet	Usual care
Effects on decisional conflict						
Measurement moment	1 Week post-encounter					
Measurement instrument	A modified version of the Decisional Conflict Scale					
Effect[b]	NS					
Risk of bias	Unclear risk					
Effects on treatment decision (preference)						
Measurement moment	3 Months post-encounter					
Measurement instrument	Unclear					
Effect[b]	NS[c]					
Risk of bias	Unclear risk					

Effects on knowledge	
Measurement moment	Immediately post-encounter
Measurement instrument	A developed 13-item questionnaire to assess participant's knowledge of SCA, associated risk factors, and ICD therapy
Effect[b]	NS
Risk of bias	Unclear risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as ICD implantation within 3 months

DA without a name (described in El-Jawahri et al. 2016)

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with advanced heart failure with a limited prognosis	Choosing between three kinds of goals-of-care: life-prolonging care, limited medical care, and comfort care	Patient decision aid	Video-based	https://www.acpdecisions.org/

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**+**	**+**	**?**	**?**	**?**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
El-Jawahri et al. 2016[5]	The United States of America	Advanced heart failure	Secondary/tertiary care	Secondary/tertiary care	DA + listening to a description of the 3 goals of care read out loud by the research assistant	Listening to the same description of the 3 goals of care used in the video (DA) arm read out loud by the research assistant.

Effects on knowledge	
Measurement moment	Immediately post-encounter
Measurement instrument	5 True/false items and 1 multiple choice item
Effect[b]	+
Risk of bias	High risk

[a] + = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b] + = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

DA without a name (described in Korteland et al. 2017)

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients accepted for elective isolated or combined aortic valve replacement and mitral valve replacement	Mechanical valve replacement or biological valve replacement	Patient decision aid	Computer-based	www.hartklepkeuze.nl

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	+	+	+	+	+

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Korteland et al. 2017[6]	The Netherlands	Accepted for elective isolated or combined aortic valve replacement and mitral valve replacement	Secondary/tertiary care	Secondary/tertiary care	Only DA	Usual care

Effects on decisional conflict	
Measurement moment	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale[c,d]
Effect[b]	SMD could not be calculated, but there was a non-significant difference in DCS score (median intervention group = 24 (0-69); median control group = 24 (0-72))
Risk of bias	Unclear risk

Effects on anxiety	
Measurement moment	Immediately post-encounter
Measurement instrument	The Hospital Anxiety and Depression Scale (HADS)[e,f]
Effect[b]	SMD could not be calculated, but there was a significant difference in HADS score (median intervention group = 6 (0-33); median control group = 9 (0-41))
Risk of bias	Unclear risk

[a]+ = The DA handles the regarding element
[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect
[c]Higher scores indicate less favorable decisional conflict
[d]Scores range from 0 to 100
[e]Higher scores indicate more anxiety
[f]Scores range from 0 to 42

The Decision Analysis in Routine Treatment Study (DARTS) tool

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with atrial fibrillation	Taking aspirin or taking warfarin	Both patient decision aid and conversation aid	Computer –based	The DA is not available in the public domain and is now outdated

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
?	**?**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Thomson et al. 2007[7]	England	Atrial fibrillation	Primary care	Primary care	DA + physician training (in use of the DA)	Decision analysis derived guidelines + physician training (in use of the guideline)

Effects on decisional conflict	
Measurement moment	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale
Effect[b]	+
Risk of bias	High risk

Effects on treatment decision (preference)	
Measurement moment	3 Months post-encounter
Measurement instrument	Extracted from the primary care record
Effect[b]	The DA group's odds on starting or continuing warfarin is significantly lower compared to the control group's odds
Risk of bias	High risk

Effects on knowledge	
Measurement moment	Immediately post-encounter
Measurement instrument	23 True/false items about atrial fibrillation and stroke
Effect[b]	NS
Risk of bias	High risk
Effects on anxiety	
Measurement moment	Immediately post-encounter
Measurement instrument	State Trait Anxiety Inventory (STAI)
Effect[b]	NS
Risk of bias	High risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

Ischemic Heart Disease Shared Decision-Making Program (IHD SDP)

DA characteristics					
DA target group	**Decision to be made**		**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with ischemic heart disease	Choosing between treatment alternatives for ischemic heart disease: medical therapy, bypass surgery, and angioplasty		Unclear	Both computer-based and video-based	Unclear
SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**?**	**+**	**+**	**?**	**?**
Study information					
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Morgan et al. 2000[8]	Canada	Ischemic heart disease	Secondary/tertiary care	Secondary/tertiary care	DA + brochure	Usual care
Effects on satisfaction with the decision making process					
Measurement moment	At time of treatment decision				
Measurement instrument	A modified version of the 12-item decision making process questionnaire developed by Barry et al. (1997)[9]				
Effect[b]	NS				
Risk of bias	High risk				
Effects on treatment decision (preference)					
Measurement moment	Unclear				
Measurement instrument	Recorded				
Effect[b]	The DA group's odds on deciding upon revascularization as initial decision is significantly lower compared to the control group's odds				
Risk of bias	High risk				

Effects on knowledge	
Measurement moment	Time of treatment decision
Measurement instrument	20 True/false items to assess knowledge deemed necessary for an informed treatment decision. This item set was reduced to 15 for patients who were not eligible for angioplasty
Effect[b]	+
Risk of bias	High risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

PCI choice

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with stable coronary artery disease (SCAD)	Optimal medical therapy (OMT) or percutaneous coronary intervention (PCI)	Conversation aid	Paper-based	https://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/pci-choice/

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
-	**?**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Coylewright et al. 2016[10]	The United States of America	Stable coronary artery disease	Secondary/tertiary care	Secondary/tertiary care	DA + physician training (in use of the DA)	Usual care

Effects on decisional conflict	
Measurement moment	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale
Effect[b]	NS
Risk of bias	High risk

Effects on patient participation in decision making	
Measurement moment	During the encounter (analyzes based on recorded encounters)
Measurement instrument	Observing Patient Involvement in Decision Making Scale (OPTION12)
Effect[b]	NS
Risk of bias	High risk

[a] + = The DA handles the regarding element; - = the DA does not handle the regarding element

[b] + = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

Decision Aid in Atrial Fibrillation (DAAFI)

DA characteristics					
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**	
Patients with non-valvular atrial fibrillation (NVAF)	Warfarin, aspirin or no therapy	Patient decision aid	Both paper-based and audio-based	Not available anymore	
SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**+**	**+**	**+**	**+**	**+**
Study information					
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
McAlister et al. 2005[11]	Canada	Non-valvular atrial fibrillation	Primary care	Primary care	Only DA	Usual care
Effects on decisional conflict					
Measurement moment	2 Weeks post-intervention				
Measurement instrument	Decisional Conflict Scale				
Effect[b]	+				
Risk of bias	High risk				

[a] + = The DA handles the regarding element

[b] + = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

Information regarding decision aids for chronic respiratory diseases

What are my options regarding inhaled corticosteroids use to improve asthma control? A four-step decision aid / What are my options regarding the combination of inhaled corticosteroids and a long-term action bronchodilator use to improve asthma control? A four-step decision aid

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with mild to severe asthma	There are two versions of the decision aid, with both a different decision. In one DA, patients are asked whether or not they will take their prescribed inhaled corticosteroids to optimize asthma control. In the other DA, patients are asked whether or not they will take their prescribed inhaled corticosteroids in combination with long-acting β2-agonists to optimize asthma control.	Both patient decision aid and conversation aid	Paper-based	https://www.coeurpoumons.ca/

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**?**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Gagné et al. 2017[12]	Canada	Asthma	Secondary/tertiary care	Secondary/tertiary care	DA + patient education	Patient education

Effects on decisional conflict	
Measurement moment	2 Months post-intervention
Measurement instrument	French version of the Decisional Conflict Scale
Effect[b]	NS
Risk of bias	Low risk

Effects on knowledge	
Measurement moment	2 Months post-intervention
Measurement instrument	Questionnaire de connaissances sur l'asthme de langue francaise (QCALF)
Effect[b]	NS
Risk of bias	Low risk

Effects on adherence	
Measurement moment	2 Months post-intervention
Measurement instrument	A 4-item face-to-face interviewer-administered questionnaire
Effect[b]	NS[c]
Risk of bias	Low risk
Effects on achieving treatment goals	
Measurement moment	2 Months post-intervention
Measurement instrument	The clinical and physiological subscales of the Asthma Control Scoring System (ACSS)
Effect[b]	NS
Risk of bias	Low risk

[a]+ = The DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as appropriate use of pharmacotherapy (asthma drugs). For participants to be considered as appropriate users of asthma drugs, they needed to meet eleven hierarchical criteria, which included using their controller medications for the same number of times every day and at an adequate frequency

The Assessment of Burden of COPD (ABC) tool

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with chronic obstructive pulmonary disease (COPD)	No specific decision: provides the opportunity to support personalized care planning including a personal treatment goal, and to decide on a treatment plan together through shared-decision making	Conversation aid	Computer-based	The DA is available through multiple providers, which can be found through www.ziektelastmeter.nl

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**?**	**+**	**?**	**+**	**+**

Study						
Author	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Slok et al. 2016[13]	The Netherlands	Chronic obstructive pulmonary disease (COPD)	Both primary and secondary/tertiary care	Both primary and secondary/tertiary care	Only DA	Usual care

Effects on treatment satisfaction	
Measurement moment	12 Months post-encounter
Measurement instrument	Patient Assessment of Chronic Illness Care (PACIC)
Effect[b]	+
Risk of bias	High risk

Effects on (health-related) quality of life	
Measurement moment	18 Months post-encounter
Measurement instrument	COPD Assessment Test (CAT)
Effect[b]	NS
Risk of bias	High risk

Effects on health status	
Measurement moment	6 Months post-encounter
Measurement instrument	St. George's Respiratory Questionnaire (SGRQ)
Effect[b]	NS
Risk of bias	High risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

Information regarding decision aids for diabetes

DA without a name (described in Huang et al. 2017)

DA characteristics					
DA target group	**Decision to be made**		**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus (T2DM)	No specific decision: aims to individualize the HbA1c goal		Both patient decision aid and conversation aid	Both paper-based and computer-based	Not available anymore
SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**+**	**+**	**+**	**+**	**-**
Study information					
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Huang et al. 2017[14]	The United States of America	Type 2 diabetes mellitus	Secondary/tertiary care	Secondary/tertiary care	DA + physician training (in use of the DA)	Educational brochure

Effects on decisional conflict	
Measurement moment	Immediately post-encounter
Measurement instrument	The low literacy version of the Decisional Conflict Scale
Effect[b]	NS
Risk of bias	High risk
Effects on treatment decision (preference)	
Measurement moment	Immediately post-encounter
Measurement instrument	Physician survey (a change in goal was defined as a 0,5% increase or decrease in HbA1c goal from pre-survey to post-survey responses)
Effect[b]	NS[c]
Risk of bias	High risk

[a]+ = The DA handles the regarding element; - = the DA does not handle the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as goal stayed the same

Statin Choice

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus (T2DM)	Whether or not to use statins	Conversation aid	Paper-based	https://statindecisionaid.mayoclinic.org/

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	?	+	+	-	+

Study information						
Studies	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Weymiller et al. 2007[15]; Nannenga et al. 2009[16] (both publications are based on the same RCT)	The United States of America	Type 2 diabetes mellitus	Secondary/tertiary care	Secondary/tertiary care	Only DA	Educational pamphlet
Mann et al. 2010[17]	The United States of America	Diabetes mellitus (any type)	Primary care	Primary care	Only DA	Printed material
Perestelo-Perez et al. 2016[18]	Spain (Spanish version of Statin Choice)	Type 2 diabetes mellitus	Primary care	Primary care	DA + physician training (in use of the DA)	Usual care

Effects on decisional conflict			
Study	**Nannenga et al. 2009 / Weymiller et al. 2007**	**Mann et al. 2010**	**Perestelo Perez et al. 2016**
Measurement moment	Immediately post-encounter	Immediately post-encounter	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale	Decisional Conflict Scale	Decisional Conflict Scale
Effect[b]	+	NS	NS
Risk of bias	High risk	Unclear risk	High risk

Effects on trust in physician		
Study	**Nannenga et al. 2009**	
Measurement moment	Immediately post-encounter	
Measurement instrument	Trust in Physician Scale	
Effect[b]	NS	
Risk of bias	High risk	
Effects on patient participation in decision making		
Study	**Nannenga et al. 2009**	
Measurement moment	During the encounter (analyzes based on recorded encounters)	
Measurement instrument	Observing Patient Involvement in Decision Making Scale (OPTION12)	
Effect[b]	NS	
Risk of bias	High risk	
Effects on conversation duration		
Study	**Nannenga et al. 2009**	**Perestelo Perez et al. 2016**
Measurement moment	During the encounter	During the encounter
Measurement instrument	Videotapes of the encounters	Documented by the physician
Effect[b]	NS	NS
Risk of bias	High risk	High risk
Effects on knowledge		
Study	**Nannenga et al. 2009**	
Measurement moment	Immediately post-encounter	
Measurement instrument	16 Knowledge items	
Effect[b]	NS	
Risk of bias	High risk	
Effects on treatment decision (preference)		
Study	**Weymiller et al. 2007**	
Measurement moment	Immediately post-encounter	
Measurement instrument	Percentage of participants not receiving statin therapy at baseline deciding to start statin therapy (unclear whether this is measured based on recordings or by questionnaires)	
Effect[b]	NS[c]	
Risk of bias	High risk	

Effects on satisfaction with the decision making process	
Study	**Perestelo Perez et al. 2016**
Measurement moment	Immediately post-encounter
Measurement instrument	A modified version of the 12-item decision making process questionnaire developed by Barry et al. (1995)[19]
Effect[b]	+
Risk of bias	High risk
Effects on illness distress	
Study	**Perestelo Perez et al. 2016**
Measurement moment	3 Months post-encounter
Measurement instrument	Problem Areas In Diabetes (PAID)
Effect[b]	NS
Risk of bias	High risk
Effects on anxiety	
Study	**Perestelo Perez et al. 2016**
Measurement moment	Immediately post-encounter
Measurement instrument	Spanish version of the State Trait Anxiety Inventory (STAI)
Effect[b]	NS
Risk of bias	High risk
Effects on adherence	
Study	**Weymiller et al. 2007**
Measurement moment	3 Months post-encounter
Measurement instrument	Mailed survey (and telephone calls for non-responders) to determine whether participants had missed any doses in the last week
Effect[b]	NS[d]
Risk of bias	High risk

[a]+ = The DA handles the regarding element; - = the DA does not handle the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as deciding not to take statin therapy

[d]For this dichotomous outcome is an event regarded as not missing any dose in the last week

PANDAs

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus	Make no change, lifestyle modification, or insulin therapy	Both patient decision aid and conversation aid	Paper-based	Academic Unit of Primary Medical Care, Faculty of Medicine, University of Sheffield: https://www.sheffield.ac.uk/medicine/research/aupmc

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
?	**?**	**+**	**+**	**+**	**?**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Mathers et al. 2012[20]	United Kingdom	Type 2 diabetes mellitus	Primary care	Primary care	DA + physician training (in use of the DA)	Usual care

Effects on decisional conflict	
Measurement moment	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale
Effect[b]	+
Risk of bias	High risk

Effects on proportion undecided	
Measurement moment	Immediately post-encounter
Measurement instrument	Unclear
Effect[b]	NS[c]
Risk of bias	High risk

Effects on conversation duration	
Measurement moment	During the encounter
Measurement instrument	Timed by the researcher from the point the patient entered the consultation room to the time patient left
Effect[b]	NS
Risk of bias	High risk

Effects on glycemic control	
Measurement moment	6 Months post-encounter
Measurement instrument	Reported by the healthcare provider based on latest HbA1c on the medical records
Effect[b]	NS
Risk of bias	High risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as being undecided

iDecide (Spanish: iDecido)

DA characteristics					
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**	
Patients with type 2 diabetes mellitus (T2DM)	No specific decision: enables navigation by the community health worker and the patient to selectively explore diabetes treatment issues most important to the patient	Patient decision aid	Computer-based	Unclear	

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**?**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Heisler et al. 2014[21]	The United States of America	Diabetes mellitus (any type)	Unclear	Location agreed upon with community health worker	DA + community health worker training (in motivational interviewing-based communication approaches and diabetes self-management support)	Booklets (guides) + community health worker training (in motivational interviewing-based communication approaches and diabetes self-management support)

Effects on decisional conflict	
Measurement moment	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale
Effect[b]	NS
Risk of bias	Unclear risk

Effects on knowledge	
Measurement moment	Immediately post-encounter
Measurement instrument	Items regarding knowledge about anti-hyperglycemic medications
Effect[b]	NS
Risk of bias	Unclear risk
Effects on diabetes care self-efficacy	
Measurement moment	Immediately post-encounter
Measurement instrument	Unclear
Effect[b]	NS
Risk of bias	Unclear risk
Effects on illness distress	
Measurement moment	3 Months post-encounter
Measurement instrument	Diabetes Distress Scale
Effect[b]	+
Risk of bias	Unclear risk
Effects on glycemic control	
Measurement moment	3 Months post-encounter
Measurement instrument	HbA1c in % (measured by the Bayer DCA 2000+ point-of-care analyzer)
Effect[b]	NS
Risk of bias	Unclear risk
Effects on adherence	
Measurement moment	3 Months post-encounter
Measurement instrument	A self-reported measure of medication adherence developed by Morisky et al (1986)[22]
Effect[b]	NS
Risk of bias	Unclear risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

Diabetes Decision Aid for T2DM

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus (T2DM)	Decisions about anti-hyperglycemic medication intensification for patients for whom first-line treatment with metformin is no longer effective	Patient decision aid	Computer-based	To preview the DA, or to learn how to use it within individual practices, clinicians must register through http://www.diabetesdecisionaid.com/. The DA is being used in integrated delivery networks (IDNs) in the USA. Clinicians in the IDNs have access through their institutions.

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**?**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Bailey et al. 2016[23]	The United States of America	Type 2 diabetes mellitus	Both primary and secondary/tertiary care	Both primary and secondary/tertiary care	DA + physician training (in use of the DA)	Usual care

Effects on decisional conflict	
Measurement moment	4 To 6 weeks post-intervention
Measurement instrument	Decisional Conflict Scale
Effect[b]	+
Risk of bias	Unclear risk

Effects on decision self-efficacy	
Measurement moment	4 To 6 weeks post-intervention
Measurement instrument	Decision Self Efficacy Scale (DSES)
Effect[b]	+
Risk of bias	Unclear risk

Effects on knowledge	
Measurement moment	4 To 6 weeks post-intervention
Measurement instrument	A developed questionnaire to assess understanding of how different treatments differ in terms of their impact on glycemic control (amount and durability), impact on weight, risk of hypoglycemia and other adverse events, route of administration, frequency of dose administration and blood glucose monitoring, and financial costs
Effect[b]	+
Risk of bias	Unclear risk

[a]+ = The DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

Patient-oriented treatment decision aid for diabetes (PORTDA-diab)

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus (T2DM)	No specific decision: stimulates and supports effective interactions between patients and healthcare providers	Both patient decision aid and conversation aid	Both paper-based and computer-based	The computer-based version is not available anymore. The paper-based version is available by contact the first author of the article (p.denig@umcg.nl)

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
+	**+**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Denig et al. 2014[24]	The Netherlands	Type 2 diabetes mellitus	Primary care	Primary care	Only DA	Usual care

Effects on treatment satisfaction	
Measurement moment	3 To 4 months post-encounter
Measurement instrument	Patients' Evaluation of Quality of Diabetes care (PEQD) questionnaire
Effect[b]	NS
Risk of bias	High risk

Effects on (health-related) quality of life	
Measurement moment	3 To 4 months post-encounter
Measurement instrument	Dutch version of the EuroQol (EQ-5D)
Effect[b]	NS
Risk of bias	High risk

Effects on illness distress	
Measurement moment	3 To 4 months post-encounter
Measurement instrument	Problem Areas In Diabetes (PAID)
Effect[b]	NS
Risk of bias	High risk

Effects on smoking status	
Measurement moment	6 Months post-encounter
Measurement instrument	Extracted from the medical record
Effect[b]	NS[c]
Risk of bias	High risk

[a]+ = The DA handles the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as smoking

Diabetes Medication Choice Decision Aid

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus (T2DM)	Whether or not adding an anti-hyperglycemic agent, and if choosing to add which option to choose	Conversation aid	Paper-based	https://shareddecisions.mayoclinic.org/decision-aid-information/decision-aids-for-chronic-disease/diabetes-medication-management/

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
-	**?**	**+**	**+**	**+**	**-**

Study information						
Studies	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
Mullan et al. 2009[25]	The United States of America	Type 2 diabetes mellitus	Primary care	Primary care	DA + physician training (in use of the DA)	Pamphlet
Karagiannis et al. 2016[26]	Greece	Type 2 diabetes mellitus	Both primary and secondary/tertiary care	Both primary and secondary/tertiary care	DA + physician training (in use of the DA)	Usual care

Effects on decisional conflict		
Study	**Mullan et al. 2009**	**Karagiannis et al. 2016**
Measurement moment	Immediately post-encounter	Immediately post-encounter
Measurement instrument	Decisional Conflict Scale	13-Item modified version of the Decisional Conflict Scale
Effect[b]	NS	NS
Risk of bias	High risk	High risk

Effects on trust in physician	
Study	**Mullan et al. 2009**
Measurement moment	Immediately post-encounter
Measurement instrument	9-Item version of the Trust in Physician Scale
Effect[b]	NS
Risk of bias	High risk

Effects on patient participation in decision making	
Study	**Mullan et al. 2009**
Measurement moment	During the encounter
Measurement instrument	Observing Patient Involvement in Decision Making Scale (OPTION12)
Effect[b]	+
Risk of bias	High risk
Effects on treatment decision preference	
Study	**Mullan et al. 2009**
Measurement moment	Immediately post-encounter
Measurement instrument	Physician survey
Effect[b]	NS[c]
Risk of bias	High risk
Effects on knowledge	
Study	**Karagiannis et al. 2016**
Measurement moment	Immediately post-encounter
Measurement instrument	6-Item questionnaire addressing general knowledge about T2DM management and medications
Effect[b]	NS
Risk of bias	High risk
Effects on health status	
Study	**Mullan et al. 2009**
Measurement moment	6 Months post-encounter
Measurement instrument	Asking patients by telephone to rate their health as excellent, very good, good, fair, or poor
Effect[b]	NS
Risk of bias	High risk

Effects on glycemic control		
Study	**Mullan et al. 2009**	**Karagiannis et al. 2016**
Measurement moment	6 Months post-encounter	3 Months post-encounter
Measurement instrument	HbA1c in % (extracted from the medical record)	HbA1c in % (measured at a local lab or lab of patient's choice)
Effect[b]	NS	NS
Risk of bias	High risk	High risk

Effects on BMI	
Study	**Karagiannis et al. 2016**
Measurement moment	6 Months post-encounter
Measurement instrument	BMI (measured by physician)
Effect[b]	NS
Risk of bias	High risk

[a]+ = The DA handles the regarding element; ? = it is doubtful or unclear whether the DA handles the regarding element; - = the DA does not handle the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

[c]For this dichotomous outcome is an event regarded as continue taking current medications

OPTIMAL

DA characteristics				
DA target group	**Decision to be made**	**Patient decision aid or conversation aid**	**DA format**	**Availability (besides screenshots in articles and/or appendices)**
Patients with type 2 diabetes mellitus (T2DM)	Two decisions: 1) regular treatment or intensive treatment and 2) prioritizing treatment targets (HbA1c, cholesterol, blood pressure, body weight, smoking habits)	Conversation aid	Paper-based	Not available

SDM elements[a]					
Situation diagnosis	**Choice awareness**	**Option clarification**	**Discussion of harms and benefits**	**Deliberation of patient preferences**	**Making or deferring a decision**
-	**?**	**+**	**+**	**+**	**+**

Study information						
Study	**Country**	**Participants' condition**	**Setting in which patients are treated (beyond the study)**	**Setting DA use within the study**	**Entire intervention of interest**	**Comparison**
den Ouden et al. 2017[27]	The Netherlands	Type 2 diabetes mellitus	Primary care	Primary care	Only DA	Usual care

Effects on glycemic control	
Measurement moment	24 Months post-encounter
Measurement instrument	HbA1c in mmol/mol (measured by a high-performance liquid chromatography (Tosoh G8 machine))
Effect[b]	NS
Risk of bias	High risk

Effects on total cholesterol	
Measurement moment	24 Months post-encounter
Measurement instrument	Total cholesterol in mmol/L (measured by standard enzymatic techniques (Cobas 8000 machine))
Effect[b]	NS
Risk of bias	High risk

Effects on blood pressure	
Measurement moment	24 Months post-encounter
Measurement instrument	Systolic blood pressure in mm Hg (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)
Effect[b]	NS
Risk of bias	High risk

Effects on BMI	
Measurement moment	24 Months post-encounter
Measurement instrument	BMI (measured by general practitioner)
Effect[b]	NS
Risk of bias	High risk

[a]+ = The DA handles the regarding element; - = the DA does not handle the regarding element

[b]+ = Statistical significant effect favoring the DA group; - = statistical significant effect favoring the control group; NS = no statistical significant effect

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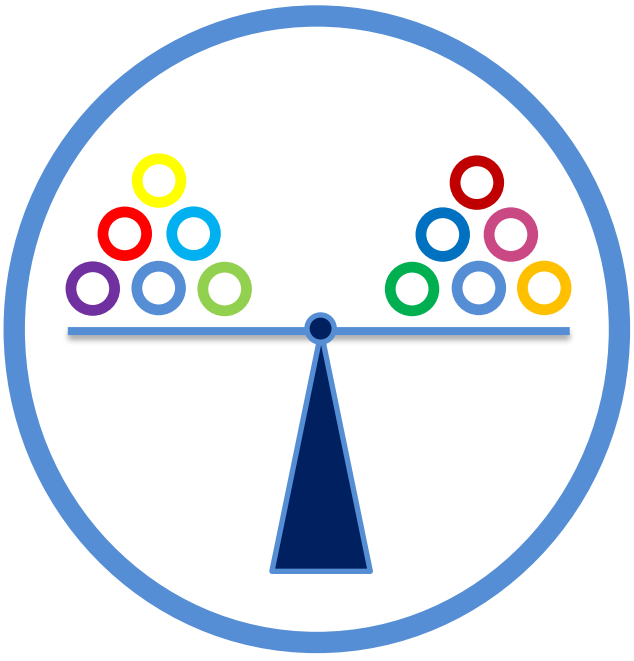
Appendix 4 – Decision aid effects (Chapter 3)



Decision aid effects on SDM outcomes

Decision aid effects on decisional conflict

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Knops et al. 2014[1]	1 To 4 weeks post-encounter	73	81	Decisional Conflict Scale[b]	-0.12 (-0.43 to 0.20)	High risk
Man-Son-Hing et al. 1999[2]	1 To 4 days post-encounter	139	148	Decisional Conflict Scale and two additional items to elicit patients' perceptions about the extent they were informed about 1) the benefits and risks of warfarin and 2) about benefits and risks of aspirin[b]	-0.18 (-0.41 to 0.05)	Unclear risk
Thomas et al. 2013[3]	1 Week post-encounter	39	17	A modified version of the Decisional Conflict Scale[b]	0.29 (-0.29 to 0.86)	Unclear risk
Korteland et al. 2017[4]	Immediately post-encounter	66	70	Decisional Conflict Scale (score range: 0-100)[b,c]	SMD could not be calculated, but there was a non-significant difference in DCS score (median intervention group = 24 (0-69); median control group = 24 (0-72))	Unclear risk
Thomson et al. 2007[5]	Immediately post-encounter	53	55	Decisional Conflict Scale[b]	-0.40 (-0.78 to -0.02)	High risk
Coylewright et al. 2016[6]	Immediately post-encounter	58	48	Decisional Conflict Scale[b]	-0.20 (-0.59 to 0.18)	High risk
McAlister et al. 2005[7]	2 Weeks post-intervention	219	215	Decisional Conflict Scale[b]	-0.20 (-0.39 to -0.01)	High risk
Huang et al. 2017[8]	Immediately post-encounter	75	25	The low literacy version of the Decisional Conflict Scale[b]	-0.42 (-0.88 to 0.04)	High risk
Nannenga et al. 2009[9d]	Immediately post-encounter	51	46	Decisional Conflict Scale[b]	-0.88 (-1.30 to -0.46)	High risk
Mann et al. 2010[10]	Immediately post-encounter	80	70	Decisional Conflict Scale[b]	-0.25 (-0.58 to 0.07)[e]	Unclear risk
Weymiller et al. 2007[11d]	Immediately post-encounter	51	46	Decisional Conflict Scale[b]	-0.89 (-1.31 to -0.47)	High risk

Perestelo-Perez et al. 2016[12]	Immediately post-encounter	78	77	Decisional Conflict Scale[b]	0.00 (-0.31 to 0.32)	High risk
Mathers et al. 2012[13]	Immediately post-encounter	89	78	Decisional Conflict Scale[b]	-0.49 (-0.80 to -0.18)	High risk
Heisler et al. 2014[14]	Immediately post-encounter	91	95	Decisional Conflict Scale[b]	-0.01 (-0.29 to 0.28)	Unclear risk
Bailey et al. 2016[15]	4 To 6 weeks post-intervention	114	111	Decisional Conflict Scale[b]	-0.78 (-1.05 to -0.51)	Unclear risk
Mullan et al. 2009[16]	Immediately post-encounter	48	37	Decisional Conflict Scale[b]	-0.08 (-0.51 to 0.34)	High risk
Karagiannis et al. 2016[17]	Immediately post-encounter	101	103	13-Item modified version of the Decisional Conflict Scale[b]	-0.13 (-0.40 to 0.15)	High risk
Gagné et al. 2017[18]	2 Months post-intervention	26	25	French version of the Decisional Conflict Scale[b]	-0.15 (-0.70 to 0.40)	Low risk

[a]Control group is reference group
[b]Higher scores indicate less favorable decisional conflict
[c]Scores range from 0 to 100
[d]Weymiller et al. 2007 and Nannenga et al. 2009 are based on the same RCT
[e]SD of Weymiller et al. 2007 is imputed to calculate the SMD and its 95%-CI

Decision aid effects on treatment satisfaction

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Denig et al. 2014[19]	3 To 4 months post-encounter	205	108	Patients' Evaluation of Quality of Diabetes care (PEQD) questionnaire[b]	-0.05 (-0.28 to 0.19)	High risk
Slok et al. 2016[20]	12 Months post-encounter	141	152	Patient Assessment of Chronic Illness Care (PACIC)[b]	0.26 (0.03 to 0.49)	High risk

[a]Control group is reference group

[b]Higher scores indicate more favorable perceived quality of care

Decision aid effects on decision self-efficacy

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Bailey et al. 2016[15]	4 To 6 weeks post-intervention	114	111	Decision Self Efficacy Scale (DSES)[b]	0.38 (0.12 to 0.65)	Unclear risk

[a]Control group is reference group

[b]Higher scores indicate more favorable decision self-efficacy

Decision aid effects on trust in physician

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Nannenga et al. 2009[9]	Immediately post-encounter	51	46	Trust in Physician Scale[b]	0.29 (-0.11 to 0.69)	High risk
Mullan et al. 2009[16]	Immediately post-encounter	48	37	9-Item version of the Trust in Physician Scale[b]	0.23 (-0.20 to 0.66)	High risk

[a]Control group is reference group

[b]Higher scores indicate more favorable trust in physician

Decision aid effects on patient participation in decision making

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Odds ratio (95%-CI)	Risk of bias
Man-Son-Hing et al. 1999[2]	1 To 4 days post-encounter	139	148	5-Point Likert scale to judge the relative strength of the patient's personal input into the choice versus their physician	Not applicable	1.23 (0.77 to 1.97)[b]	Unclear risk
Coylewright et al. 2016[6]	During the encounter (analyzes based on recorded encounters)	34	20	Observing Patient Involvement in Decision Making Scale (OPTION12)[c]	0.50 (-0.06 to 1.06)	Not applicable	High risk
Nannenga et al. 2009[9]	During the encounter (analyzes based on recorded encounters)	52	46	Observing Patient Involvement in Decision Making Scale (OPTION12)[c]	1.08 (0.66 to 1.51)	Not applicable	High risk
Mullan et al. 2009[16]	During the encounter	30	21	Observing Patient Involvement in Decision Making Scale (OPTION12)[c]	1.36 (0.74 to 1.98)	Not applicable	High risk

[a]Control group is reference group

[b]Event is regarded as patient reported that he/she made the decision, rather than his/her physician; control group is reference group

[c]Higher scores indicate more patient involvement in decision making

Decision aid effects on conversation satisfaction

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Knops et al. 2014[1]	1 To 4 weeks post-encounter	74	80	Patient Satisfaction Questionnaire[b]	0.06 (-0.26 to 0.37)	High risk

[a]Control group is reference group

[b]Higher scores indicate more favorable conversation satisfaction

Decision aid effects on satisfaction with the decision making process

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Man-Son-Hing et al. 1999[2]	1 To 4 days post-encounter	146	138	6 Items using a 5-point Likert scale	-0.07 (-0.30 to 0.16)	Unclear risk
Morgan et al. 2000[21]	At time of treatment decision	90	97	A modified version of the 12-item decision making process questionnaire developed by Barry et al. (1997)[22b]	0.07 (-0.22 to 0.36)	High risk
Perestelo-Perez et al. 2016[12]	Immediately post-encounter	80	73	A modified version of the 12-item decision making process questionnaire developed by Barry et al. (1995)[23b]	0.42 (0.10 to 0.74)	High risk

[a]Control group is reference group

[b]Higher scores indicate more favorable satisfaction with the decision-making process

Decision aid effects on treatment decision (preference)

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Odds ratio (95%-CI)	Risk of bias
Knops et al. 2014[1]	9 To 10 months post-encounter	91	87	Extracted from the medical record	0.94 (0.52 to 1.71)[a]	Unclear risk
Man-Son-Hing et al. 1999[2]	1 To 4 days post-encounter	139	148	Questionnaire in which participants were, among others, asked what decision regarding antithrombotic therapy was made	0.73 (0.33 to 1.59)[b]	Unclear risk
Thomas et al. 2013[3]	3 Months post-encounter	39	20	Unclear	0.59 (0.14 to 2.47)[c]	Unclear risk
Thomson et al. 2007[5]	3 Months post-encounter	53	56	Extracted from the primary care record	0.33 (0.12 to 0.95)[d]	High risk
Morgan et al. 2000[21]	Unclear	90	97	Recorded	0.45 (0.24 to 0.84)[e]	High risk
Huang et al. 2017[8]	Immediately post-encounter	75	25	Physician survey (a change in goal was defined as a 0,5% increase or decrease in HbA1c goal from pre-survey to post-survey responses)	0.40 (0.15 to 1.07)[f]	High risk
Weymiller et al. 2007[11]	Immediately post-encounter	23	19	Percentage of participants not receiving statin therapy at baseline deciding to start statin therapy (unclear whether this is measured based on recordings or by questionnaires)	0.61 (0.15 to 2.51)[g]	High risk
Mullan et al. 2009[16]	Immediately post-encounter	48	37	Physician survey	0.55 (0.21 to 1.48)[h]	High risk

[a]Event is regarded as not choosing elective aneurysm impair; control group is reference group
[b]Event is regarded as deciding to take warfarin; control group is reference group
[c]Event is regarded as ICD implantation within 3 months; control group is reference group
[d]Event is regarded as starting or continuing warfarin; control group is reference group
[e]Event is regarded as revascularization as initial decision; control group is reference group
[f]Event is regarded as goal stayed the same; control group is reference group
[g]Event is regarded as deciding not to take statin therapy; control group is reference group
[h]Event is regarded as continue taking current medications; control group is reference group

Decision aid effects on proportion undecided

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Odds ratio (95%-CI)	Risk of bias
Man-Son-Hing et al. 1999[2]	1 To 4 days post-encounter	139	148	Participants were asked to indicate whether a decision regarding the choice of antithrombotic therapy had been made in conjunction with their physician	0.11 (0.01 to 0.90)[a]	Unclear risk
Mathers et al. 2012[13]	Immediately post-encounter	89	78	Participants were asked a question on readiness for decision making	0.76 (0.28 to 2.07)[b]	High risk

[a]Event was regarded as not being able to make a definite choice; control group is reference group
[b]Event is regarded as being undecided; control group is reference group

Decision aid effects on conversation duration

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Nannenga et al. 2009[9]	During the encounter	52	46	Videotapes of the encounters	0.22 (-0.17 to 0.62)	High risk
Perestelo-Perez et al. 2016[12]	During the encounter	61	63	Documented by the physician	-0.18 (-0.53 to 0.17)	High risk
Mathers et al. 2012[13]	During the encounter	89	78	Timed by the researcher from the point the patient entered the consultation room to the time patient left	-0.19 (-0.50 to 0.11)	High risk

[a]Control group is reference group

Decision aid effects on knowledge

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Knops et al. 2014[1]	1 To 4 weeks post-encounter	80	84	13 Items of the Dutch multiple-choice Aneurysm Knowledge Questionnaire[b]	0.28 (-0.03 to 0.59)	Unclear risk
Thomas et al. 2013[3]	Immediately post-encounter	39	20	A developed 13-item questionnaire to assess participant's knowledge of SCA, associated risk factors, and ICD therapy[b]	0.45 (-0.09 to 1.00)	Unclear risk
El-Jawahri et al. 2016[24]	Immediately post-encounter	123	123	5 True/false items and 1 multiple choice item[b]	0.76 (0.50 to 1.01)	High risk
Thomson et al. 2007[5]	Immediately post-encounter	53	55	23 True/false items about atrial fibrillation and stroke[b]	0.04 (-0.34 to 0.42)	High risk
Morgan et al. 2000[21]	Time of treatment decision	90	97	20 True/false items to assess knowledge deemed necessary for an informed treatment decision. This item set was reduced to 15 for patients who were not eligible for angioplasty[b]	0.74 (0.45 to 1.04)	High risk
Nannenga et al. 2009[9]	Immediately post-encounter	51	46	16 Knowledge items[b]	0.70 (0.29 to 1.11)	High risk
Heisler et al. 2014[14]	Immediately post-encounter	92	95	Items regarding knowledge about anti-hyperglycemic medications	-0.06 (-0.35 to 0.23)	Unclear risk
Bailey et al. 2016[15]	4 To 6 weeks post-intervention	114	111	A developed questionnaire to assess understanding of how different treatments differ in terms of their impact on glycemic control (amount and durability), impact on weight, risk of hypoglycemia and other adverse events, route of administration, frequency of dose administration and blood glucose monitoring, and financial costs[b]	1.09 (0.81 to 1.37)	Unclear risk

Karagiannis et al. 2016[17]	Immediately post-encounter	101	103	6-Item questionnaire addressing general knowledge about T2DM management and medications[b]	-0.03 (-0.31 to 0.24)	High risk
Gagné et al. 2017[18]	2 Months post-intervention	26	25	Questionnaire de connaissances sur l'asthme de langue francaise (QCALF)[b]	0.32 (-0.23 to 0.87)	Low risk

[a]Control group is reference group

[b]Higher scores indicate greater knowledge

Decision aid effects on patient-reported outcomes

Decision aid effects on diabetes care self-efficacy

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Heisler et al. 2014[14]	Immediately post-encounter	92	94	Unclear	0.27 (-0.02 to 0.56)	Unclear risk

[a]Control group is reference group

Decision aid effects on (health-related) quality of life

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Knops et al. 2014[1]	1 To 4 weeks post-encounter	80	84	12-Item Short Form Health Survey (SF-12)[b]	0.10 (-0.21 to 0.41)	Unclear risk
Denig et al. 2014[19]	3 To 4 months post-encounter	203	105	Dutch version of the EuroQol (EQ-5D)[b]	-0.05 (-0.28 to 0.19)	High risk
Slok et al. 2016[20]	18 Months post-encounter	144	152	COPD Assessment Test (CAT)[b]	0.05 (-0.18 to 0.27)	High risk

[a]Control group is reference group

[b]Higher scores indicate more favorable (health-related) quality of life

Decision aid effects on health status

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Mullan et al. 2009[16]	6 Months post-encounter	47	37	Asking patients by telephone to rate their health as excellent, very good, good, fair, or poor[b]	-0.03 (-0.46 to 0.40)	High risk
Slok et al. 2016[20]	6 Months post-encounter	160	161	St. George's Respiratory Questionnaire (SGRQ)[c]	-0.10 (-0.32 to 0.12)	High risk

[a]Control group is reference group

[b]Higher scores indicate more favorable self-reported health

[c]Higher scores indicate more favorable disease-specific health status

Decision aid effects on illness distress

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Perestelo-Perez et al. 2016[12]	3 Months post-encounter	67	64	Problem Areas In Diabetes (PAID)[b]	0.17 (-0.17 to 0.51)	High risk
Heisler et al. 2014[14]	3 Months post-encounter	87	89	Diabetes Distress Scale[b]	-0.39 (-0.68 to -0.09)	Unclear risk
Denig et al. 2014[19]	3 To 4 months post-encounter	204	107	Problem Areas In Diabetes (PAID)[b]	0.23 (0.00 to 0.47)	High risk

[a]Control group is reference group

[b]Higher scores indicate less favorable diabetes distress

Decision aid effects on anxiety

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Knops et al. 2014[1]	1 To 4 weeks post-encounter	81	85	Hospital Anxiety and Depression Scale (HADS)[b]	-0.16 (-0.46 to 0.15)	Unclear risk
Fraenkel et al. 2012[25]	Immediately post-encounter	69	66	Spielberger State Anxiety Index[b]	-0.12 (-0.46 to 0.22)	Unclear risk
Korteland et al. 2017[4]	Immediately post-encounter	67	71	The Hospital Anxiety and Depression Scale (HADS)[b,c]	SMD could not be calculated, but there was a significant difference in HADS score (median intervention group = 6 (0-33); median control group = 9 (0-41))	Unclear risk
Thomson et al. 2007[5]	Immediately post-encounter	53	55	State Trait Anxiety Inventory (STAI)[b]	-0.11 (-0.49 to 0.28)	High risk
Perestelo-Perez et al. 2016[12]	Immediately post-encounter	80	77	Spanish version of the State Trait Anxiety Inventory (STAI)[b]	-0.09 (-0.40 to 0.23)	High risk

[a]Control group is reference group
[b]Higher scores indicate more anxiety
[c]Scores range from 0 to 42

Decision aid effects on surrogate outcomes

Decision aid effects on total cholesterol

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
den Ouden et al. 2017[26]	24 Months post-encounter	66	75	Total cholesterol in mmol/L (measured by standard enzymatic techniques (Cobas 8000 machine))	0.15 (-0.18 to 0.49)	High risk

[a]Control group is reference group

Decision aid effects on blood pressure

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
den Ouden et al. 2017[26]	24 Months post-encounter	66	73	Systolic blood pressure in mm Hg (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)	-0.27 (-0.60 to 0.07)	High risk

[a]Control group is reference group

Decision aid effects on glycemic control

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Mathers et al. 2012[13]	6 Months post-encounter	89	78	Reported by the healthcare provider based on latest HbA1c on the medical records	0.24 (-0.06 to 0.55)	High risk
Heisler et al. 2014[14]	3 Months post-encounter	86	89	HbA1c in % (measured by the Bayer DCA 2000+ point-of-care analyzer)	-0.06 (-0.35 to 0.24)	Unclear risk
Mullan et al. 2009[16]	6 Months post-encounter	48	37	HbA1c in % (extracted from the medical record)	-0.01 (-0.44 to 0.42)	High risk
Karagiannis et al. 2016[17]	3 Months post-encounter	91	96	HbA1c in % (measured at a local lab or lab of patient's choice)	0.28 (0.00 to 0.57)	High risk
den Ouden et al. 2017[26]	24 Months post-encounter	65	72	HbA1c in mmol/mol (measured by a high-performance liquid chromatography (Tosoh G8 machine))	0.22 (-0.12 to 0.55)	High risk

[a]Control group is reference group

Decision aid effects on clinical outcomes

Decision aid effects on Body Mass Index

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Karagiannis et al. 2016[17]	6 Months post-encounter	84	83	BMI (measured by physician)	-0.20 (-0.50 to 0.11)	High risk
den Ouden et al. 2017[26]	24 Months post-encounter	62	60	BMI (measured by general practitioner)	-0.14 (-0.50 to 0.21)	High risk

[a]Control group is reference group

Decision aid effects on smoking status

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Odds ratio (95%-CI)	Risk of bias
Denig et al. 2014[19]	6 Months post-encounter	184	98	Extracted from the medical record	0.40 (0.04 to 3.77)[a]	High risk

[a]Event is regarded as smoking; control group is reference group

Decision aid effects on adherence

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Odds ratio (95%-CI)	Risk of bias
Man-Son-Hing et al. 1999[2]	6 Months post-encounter	129	134	Participants were asked by telephone which therapy they were currently taking	Not applicable	1.48 (0.51 to 4.27)[b]	Unclear risk
Weymiller et al. 2007[11]	3 Months post-encounter	33	29	Mailed survey (and telephone calls for non-responders) to determine whether participants had missed any doses in the last week	Not applicable	1.9 (0.40 to 9.80)[c]	High risk
Heisler et al. 2014[14]	3 Months post-encounter	87	89	A self-reported measure of medication adherence developed by Morisky et al (1986)[27d]	0.07 (-0.23 to 0.37)	Not applicable	Unclear risk
Gagné et al. 2017[18]	2 Months post-intervention	26	25	A 4-item face-to-face interviewer-administered questionnaire	Not applicable	2.05 (0.67 to 6.24)[e]	Low risk

[a]Control group is reference group

[b]Event is regarded as continuing to take the therapy that was initially chosen; control group is reference group

[c]Event is regarded as not missing any dose in the last week; control group is reference group

[d]Higher scores indicate more favorable medication adherence

[e]Event is regarded as appropriate use of pharmacotherapy (asthma drugs). For participants to be considered as appropriate users of asthma drugs, they needed to meet eleven hierarchical criteria, which included using their controller medications for the same number of times every day and at an adequate frequency; control group is reference group

Decision aid effects on achieving treatment goals

Study	Measurement moment	N intervention group included in analyses	N control group included in analyses	Measurement instrument	Standardized mean difference (95%-CI)[a]	Risk of bias
Gagné et al. 2017[18]	2 Months post-intervention	26	25	The clinical and physiological subscales of the Asthma Control Scoring System (ACSS)[b]	-0.05 (-0.60 to 0.50)	Low risk

[a]Control group is reference group
[b]Higher scores indicate better asthma control

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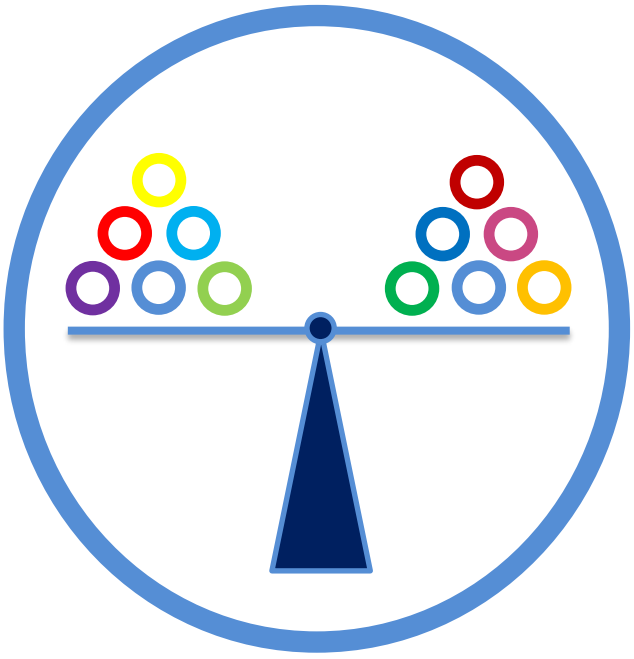
Appendix 5 – The association between time and outcomes (Chapter 4)



	Estimated change	P-value	95%-CI
WHO-5			
T0-T1	1.283	.429	-1.895 to 4.462
T1-T2	1.150	.485	-2.079 to 4.379
T0-T2	2.433	.135	-0.756 to 5.622
	OR[a]	**P-value**	**95%-CI**
Symptomatic hypoglycemia incidence			
T0-T1	0.542	.026	0.316 to 0.929
T1-T2	1.285	.386	0.728 to 2.270
T0-T2	0.696	.176	0.411 to 1.177
Nocturnal hypoglycemia incidence			
T0-T1	0.636	.351	0.245 to 1.650
T1-T2	1.117	.834	0.395 to 3.168
T0-T2	0.711	.472	0.280 to 1.806
Severe hypoglycemia incidence			
T0-T1	0.466	.198	0.146 to 1.493
T1-T2	1.000	1.000	0.254 to 3.943
T0-T2	0.466	.202	0.144 to 1.508
	Estimated change	**P-value**	**95%-CI**
HbA1c (%)			
T0-T1	-0.128	.072	-0.267 to 0.011
T1-T2	-0.039	.588	-0.181 to 0.103
T0-T2	-0.167	.020	-0.307 to -0.027
HbA1c (mmol/mol)			
T0-T1	-1.395	.072	-2.916 to 0.126
T1-T2	-0.426	.588	-1.974 to 1.122
T0-T2	-1.821	.020	-3.353 to -0.290

	Ratio of geometric averages[b]	**P-value**	**95%-CI**
HFS-W			
T0-T1	0.862	.086	0.729 to 1.021
T1-T2	0.952	.576	0.802 to 1.131
T0-T2	0.821	.024	0.693 to 0.974
PAID-SF			
T0-T1	0.895	.286	0.731 to 1.096
T1-T2	0.899	.315	0.732 to 1.106
T0-T2	0.806	.039	0.656 to 0.989
	Estimated change	**P-value**	**95%-CI**
DMSRQ			
T0-T1	3.280	<.001	1.670 to 4.890
T1-T2	1.116	.182	-0.522 to 2.754
T0-T2	4.396	<.001	2.774 to 6.019
PSQI item 1			
T0-T1	-0.101	.318	-0.299 to 0.097
T1-T2	-0.006	.950	-0.208 to 0.195
T0-T2	-0.107	.292	-0.307 to 0.093
	Ratio of geometric averages[b]	**P-value**	**95%-CI**
PSQI item 2			
T0-T1	1.077	.139	0.976 to 1.189
T1-T2	0.888	.021	0.803 to 0.982
T0-T2	0.957	.382	0.866 to 1.057
PSQI item 3			
T0-T1	0.960	.202	0.901 to 1.022
T1-T2	0.986	.671	0.925 to 1.051
T0-T2	0.946	.091	0.889 to 1.009

	OR[c]	P-value	95%-CI
SDSCA			
T0-T1	1.495	.224	0.781 to 2.863
T1-T2	0.820	.565	0.416 to 1.616
T0-T2	1.226	.531	0.647 to 2.321

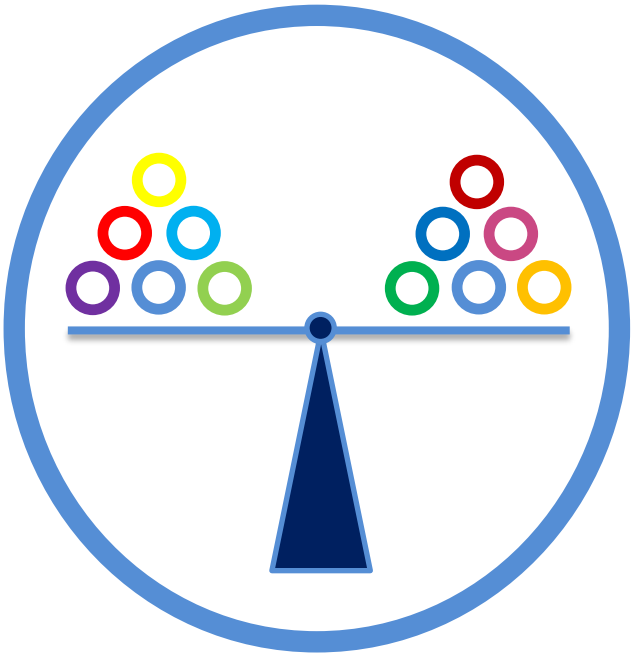
[a]Odds Ratio for the groups "zero hypoglycemic events" (reference category) and "one or more hypoglycemic events"
[b]HFS-w, PAID-SF, PSQI item 2 and PSQI item 3 were analyzed as log transformed and back transformed afterwards, resulting in a ratio of geometric averages
[c]Odds Ratio for the groups "less than 7 days a week adherent" (reference category) and "7 days a week adherent"

Appendix 6 – Imputed WHO-5 and DMSRQ total scores (Chapter 4)

	Baseline	Three months	Six months
WHO-5			
Mean[a]	61.65	62.66	63.87
DMSRQ			
Mean[a]	32.66	35.94	37.07

[a]Scores based on imputed items. Items for drop-outs were not imputed from the moment of drop-out on. When all items of a questionnaire were missing on a certain visit, no imputation on this questionnaire for the regarding visit would take place. Pooled results do not provide a standard deviation

Appendix 7 – Changes in DMSRQ items over time (Chapter 4)

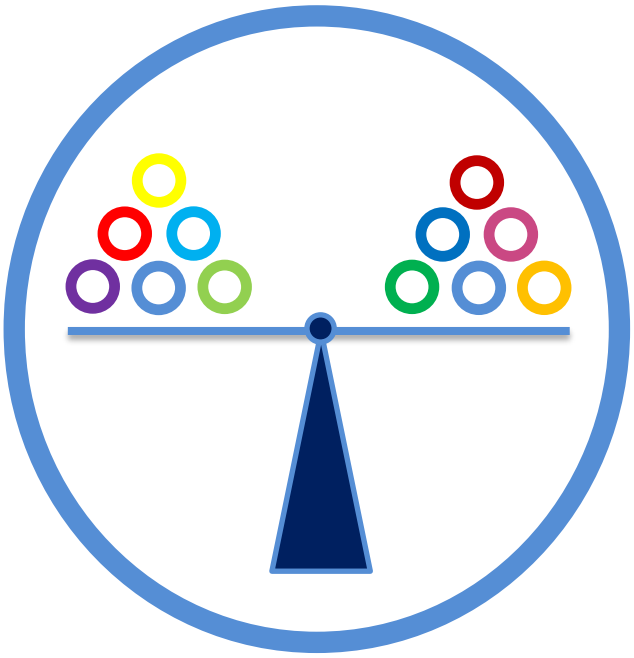


DMSRQ	Baseline	Three months	Six months
Item 1[a,b]			
satisfaction with…			
A. appropriateness of diabetes	1.97 (0.76)	2.24 (0.74)	2.28 (0.62)
medication	2.00 (1.25 – 2.75)	2.00 (2.00 – 3.00)	2.00 (2.00 – 3.00)
B. painfulness of diabetes medication	1.90 (0.82)	2.23 (0.83)	2.16 (0.82)
	2.00 (1.00 – 3.00)	2.00 (2.00 – 3.00)	2.00 (2.00 – 3.00)
C. user friendliness of diabetes	2.10 (0.78)	2.38 (0.67)	2.36 (0.68)
medication	2.00 (2.00 – 3.00)	2.00 (2.00 – 3.00)	2.00 (2.00 – 3.00)
Item 2[a,b]			
extent to which the diabetes medication			
hinders…			
A. having a good night sleep	2.30 (0.97)	2.39 (0.92)	2.51 (0.87)
	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)
B. sleeping late when you want	2.35 (0.98)	2.26 (1.10)	2.57 (0.83)
	3.00 (2.00 – 3.00)	3.00 (1.00 – 3.00)	3.00 (1.75 – 3.00)
C. eating when and what you want	1.96 (1.01)	1.99 (1.03)	2.15 (0.89)
	2.00 (1.00 – 3.00)	2.00 (1.00 – 3.00)	2.00 (2.00 – 3.00)
D. to do sports when you want	2.45 (0.92)	2.50 (0.89)	2.42 (0.87)
	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)
E. doing as much sports as you want	2.41 (0.92)	2.53 (0.77)	2.41 (0.85)
	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)

F. doing the kind of sports you want	2.42 (0.93)	2.54 (0.84)	2.50 (0.85)
	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)	3.00 (2.00 – 3.00)
Item 3[c]			
how well the diabetes medication			
helps with…			
A. getting good blood glucose control	2.10 (1.02)	2.26 (0.98)	2.39 (0.94)
B. avoiding low blood sugar levels without snacks	1.89 (1.08)	2.24 (0.86)	2.31 (0.98)
C. avoiding low blood sugar levels during the night	2.03 (1.10)	2.43 (0.90)	2.43 (0.97)
D. avoiding high blood sugar levels	1.74 (1.03)	1.98 (0.95)	2.04 (1.00)
E. avoiding weight gaining[b]	1.21 (1.14)	1.41 (1.07)	1.53 (1.18)
	1.00 (0.00 – 2.00)	1.00 (1.00 – 2.00)	1.00 (1.00 – 2.00)
F. losing weight[b]	0.83 (1.09)	0.78 (1.03)	0.93 (1.18)
	0.00 (0.00 – 1.00)	0.00 (0.00 – 1.00)	0.00 (0.00 – 2.00)
G. controlling appetite[b]	1.45 (1.12)	1.71 (1.10)	1.77 (1.15)
	1.00 (1.00 – 2.00)	2.00 (1.00 – 2.00)	2.00 (1.00 – 2.00)
Item 4[a,b]			
general satisfaction with the diabetes	1.71 (0.75)	2.05 (0.70)	2.20 (0.64)
medication	2.00 (1.00 – 2.00)	2.00 (2.00 – 2.75)	2.00 (2.00 – 3.00)

Scores based on the original (non-imputed) data
[a]Item contains four categories ranging from 0 to 3
[b]Since this item is (on some visits) skewed distributed, both the mean (SD) and median (25^{th} percentile – 75^{th} percentile) are given
[c]Item contains five categories ranging from 0 to 4

Appendix 8 – The association between time and DMSRQ items (Chapter 4)



	Estimated change	P-value	95%-CI
Item 1a			
T0-T1	0.264	.001	0.114 to 0.413
T1-T2	0.036	.640	-0.116 to 0.189
T0-T2	0.299	<.001	-2.390 to -2.154
Item 1b			
T0-T1	0.332	<.001	0.161 to 0.503
T1-T2	-0.071	.423	-0.246 to 0.104
T0-T2	0.261	.003	0.088 to 0.434
Item 1c			
T0-T1	0.280	<.001	0.149 to 0.410
T1-T2	-0.021	.757	-0.154 to 0.112
T0-T2	0.259	<.001	0.127 to 0.391
Item 2a			
T0-T1	0.090	.364	-0.105 to 0.286
T1-T2	0.120	.242	0.081 to 0.321
T0-T2	0.210	.038	0.011 to 0.409
Item 2b			
T0-T1	-0.074	.458	-0.269 to 0.122
T1-T2	0.309	.002	0.110 to 0.508
T0-T2	0.235	.020	0.037 to 0.433
Item 2c			
T0-T1	0.039	.701	-0.162 to 0.240
T1-T2	0.156	.138	0.050 to 0.362
T0-T2	0.195	.061	-0.009 to 0.399

Item 2d			
T0-T1	0.061	.497	-0.115 to 0.237
T1-T2	-0.111	.229	-0.292 to 0.070
T0-T2	-0.050	.583	-0.228 to 0.128
Item 2e			
T0-T1	0.119	.178	-0.055 to 0.293
T1-T2	-0.130	.152	-0.307 to 0.048
T0-T2	-0.011	.905	-0.186 to 0.165
Item 2f			
T0-T1	0.125	.160	-0.050 to 0.300
T1-T2	-0.065	.477	-0.244 to 0.114
T0-T2	0.061	.501	-0.116 to 0.237
Item 3a			
T0-T1	0.161	.073	-0.015 to 0.338
T1-T2	0.134	.144	-0.046 to 0.315
T0-T2	0.296	.001	0.118 to 0.474
Item 3b			
T0-T1	0.365	<.001	0.183 to 0.546
T1-T2	0.072	.445	-0.113 to 0.257
T0-T2	0.437	<.001	0.254 to 0.619
Item 3c			
T0-T1	0.401	<.001	0.206 to 0.597
T1-T2	-0.012	.917	-0.211 to 0.189
T0-T2	0.391	<.001	0.193 to 0.588

Item 3d			
T0-T1	0.254	.005	0.077 to 0.432
T1-T2	0.050	.584	-0.130 to 0.231
T0-T2	0.305	.001	0.127 to 0.483
Item 3e			
T0-T1	0.299	.036	0.015 to 0.442
T1-T2	0.120	.278	-0.098 to 0.338
T0-T2	0.349	.002	0.134 to 0.564
Item 3f			
T0-T1	-0.033	.764	-0.250 to 0.184
T1-T2	0.149	.186	-0.072 to 0.371
T0-T2	0.116	.297	-0.102 to 0.335
Item 3g			
T0-T1	0.289	.008	0.076 to 0.503
T1-T2	0.065	.556	-0.153 to 0.284
T0-T2	0.355	.001	0.140 to 0.570
Item 4			
T0-T1	0.342	<.001	0.196 to 0.489
T1-T2	0.145	.057	-0.004 to 0.295
T0-T2	0.488	<.001	0.341 to 0.634

Analyses based on non-imputed item scores
See appendix 7 for the content of items

Summary

Older persons with type 2 diabetes commonly live with a variety of comorbidities, which need to be considered when caring for this group of persons. Coordination and integration of services for managing all individual diseases is needed in multi-morbid patients in order for care to be efficient, safe, and minimally burdensome.

Minimally disruptive medicine is an approach in which the patient is central. The patient imbalance between workload ("what patient have to do") and capacity ("what patients can do") is the central mechanism driving patient complexity. The quality of the Dutch diabetes care is internationally respected, in particular for its multidisciplinary approach. The Dutch Diabetes Federation recommends "customized care", fitting the contexts of individuals. Understanding the patient context is a prerequisite for care to fit the patient context, and important for adhering to treatment strategies. Shared-decision making and patient-reported outcome (PRO) monitoring are tools to identify the right care.

Part 1: Decision aids for shared-decision making

Shared-decision making is often described as being most relevant for decisions in which there is no best option from an evidence standpoint. Despite some ethical and clinical arguments is shared-decision making not yet routine in clinical practice. To facilitate implementation of shared-decision making, decision aids have been developed.

Chapter 2 and 3 describe the protocol and the results, respectively, of a systematic review about decision aids. Most decision aids developed for persons suffering from cardiovascular diseases, chronic respiratory diseases, and/or diabetes are focused on providing information (option clarification) or discussing choices (harms and benefits discussion), rather than on creating empathic conversations. The consequences of leaving out shared-decision making elements, as well as its situation-dependency, in terms of shared-decision making outcomes is unknown and should be studied in future research.

Multiple difficulties were faced during the conduction of this review. These difficulties point towards the need for quality improvement of randomized controlled trials studying decision aid effects, as well as their publications. The new SUNDAE checklist seems to meet this need to a large extent. However, the choice for measurement instruments to use in these randomized controlled trials, as well as the timing of measurements, are not handled by the SUNDAE checklist and needed to reduce the heterogeneity across studies in this field of research. Therefore, a core outcome set for research in the field of decision aids (for persons with chronic illnesses) is warranted in order to compare research findings across studies.

The use of decision aids is not a prerequisite for shared-decision making. Implementation of shared-decision making needs multifaceted strategies coupled with culture change among caregivers, their organizations, and patients. Caregivers should be educated about the importance of creating and fostering a culture of shared-decision making and the skills needed to communicate evidence and its limitation in an understandable way. Patients may be educated as well, and decision aids may play an important role in this.

Besides educating patients and health professionals, other ways to shape an environment that facilitates shared-decision making are among others: 1) an adequate appointment duration, 2) short (or at least flexible) periods between visits, 3) continuity of care, and 4) a system in which the medication choice is driven by personal contexts, values, and preferences of patients. Importantly, shared-decision making should not be seen as a tedious added extra, but as the core of good clinical practice.

Part 2: Patient-reported outcomes

PROs are subjective reports and represent what is most important to patients about a condition and its treatment. They are becoming increasingly important in weighing the pros and cons of a particular medication or treatment regimen. In this way, patient perspectives can be taken into account. Evidence generated from PROs may inform the harms and benefits of options discussed

during shared-decision making conversations. PROs are originally developed for use in research, but are increasingly used by care providers. By use in clinical practice may patient-reported problems putted on the encounter agenda, and thus may PROs create a starting point for shared-decision making.

Patient-reported outcomes in research

When practicing shared-decision making in type 2 diabetes care, then insulin glargine 300 U/mL may be one of the available options. **Chapter 4** describes the observational OPTIN-D study. The OPTIN-D study found that insulin glargine 300 U/mL is a convenient glucose lowering medicine in persons with type 2 diabetes wishing their current treatment to increase flexibility of injection time and to decrease the volume to be injected. Future studies need to examine the impact of glargine 300 U/mL in persons with type 2 diabetes with a less favorable psychological and medical profile. Furthermore, a controlled study design is needed to draw firm conclusions regarding a causal relationship between initiating glargine 300 U/mL and improved patient-reported medication convenience.

Reducing the burden of hypoglycemia is important to persons with type 2 diabetes as in **Chapter 5** hypoglycemia was found to be associated with higher hypoglycemia fear and diabetes symptom burden, independent of treatment regimen. Prevention and adequate management of hypoglycemia at least deserve full clinical attention. This is true for both persons using oral agents and persons initiating insulin therapy. A minimal clinically important difference for both hypoglycemia fear and diabetes symptom burden is needed to make scores interpretable.

Patient-reported outcomes in clinical practice

In **Chapter 6**, a first attempt is made to improve the interpretability of (domain) scores on the Diabetes Symptom Checklist-Revised (DSC-R). We did so by assessing the associations between (domain) scores on the DSC-R and patient characteristics. Our study found that low mood and likely depression amplify scores on all domains of the DSC-R. This is in particular the case for the fatigue,

cognitive symptoms, hypoglycemic, and hyperglycemic domains. These domains can be regarded as measures of acute diabetes symptoms resulting from fluctuating blood sugars. These findings underscore the importance of attention for and accurate treatment of low mood and depression in clinical practice. The other way around may an excessive burden of fatigue, cognitive symptoms, hypoglycemia, and/or hyperglycemia direct to an underlying low mood or depression.

The relevant associations and their effect estimates may be useful in assessing to what extent a certain symptom burden can be regarded as excessive given certain patient characteristics. However, the associations and their effect estimates need further testing in more diverse patient populations. When using the DSC-R in clinical practice, then it is advised to focus on (changes in) DSC-R scores on domain level.

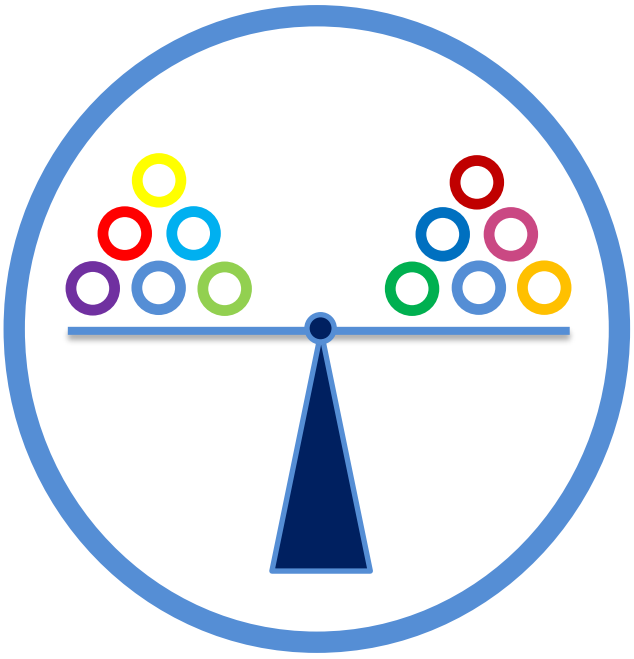
Before using in clinical practice, future studies should evaluate the content validity of the DSC-R in greater detail. Namely, it may lack relevant items, e.g. regarding itchy skin, increased hunger, sweating, and gender-specific sexual symptoms. Future research may focus on creating reference values or weights for different groups, as well as establishing clinically meaningful differences in diabetes symptom burden.

Besides enhancing the content and interpretation of scores, new data collection technologies (e.g., computer adaptive testing) will facilitate PROs to become part of everyday care. Furthermore, training in the use and interpretation of PROs is needed when aiming for optimal use in routine practice.

Making the right care happen

Importantly, identifying the right care is not enough as it must actually be carried out. Several tools are available to make the right care happen, which is important in preventing a workload-capacity imbalance. When capacity cannot bear the workload, then patients with multiple chronic conditions will just “survive” rather than thrive.

Samenvatting (summary in Dutch)



Oudere personen met diabetes type 2 leven vaak met verschillende comorbiditeiten, die meegenomen dienen te worden in de zorg voor deze groep mensen. Coördinatie en integratie van de zorgverlening omtrent alle individuele ziekten is noodzakelijk bij multimorbide patiënten om de zorg efficiënt, veilig en minimaal belastend te laten zijn.

Minimaal disruptieve geneeskunde (in het Engels: minimally disruptive medicine) is een benadering waarbij de patiënt centraal staat. De disbalans tussen werkdruk ("wat de patiënt moet doen") en mogelijkheden ("wat de patiënt kan doen") is het centrale mechanisme dat de complexiteit van de patiënt bepaald. De kwaliteit van de Nederlandse diabeteszorg wordt internationaal gerespecteerd, vooral vanwege haar multidisciplinaire aanpak. De Nederlandse Diabetes Federatie pleit voor "zorg op maat", passend bij de context van het individu. Het begrijpen van het leven van de patiënt is een voorwaarde voor het aansluiten van zorg bij dit leven, en belangrijk voor de therapietrouw van de patiënt. Gedeelde besluitvorming en het monitoren van patiënt-gerapporteerde uitkomsten zijn hulpmiddelen om de juiste zorg te identificeren.

Deel 1: Keuzehulpen voor gedeelde besluitvorming

Gedeelde besluitvorming wordt vaak beschreven als meest relevant voor beslissingen waarbij er geen beste optie is, op basis van wetenschappelijk bewijs. Ondanks sommige ethische en klinische argumenten is gedeelde besluitvorming nog geen routine in de klinische praktijk. Om de implementatie van gedeelde besluitvorming te faciliteren zijn er keuzehulpen ontwikkeld.

Hoofdstuk 2 en 3 beschrijven respectievelijk het protocol en de resultaten van een systematische review over keuzehulpen. De meeste keuzehulpen die zijn ontwikkeld voor personen die lijden aan cardiovasculaire ziekten, diabetes en/of chronisch respiratoire ziekten zijn gefocust op het geven van informatie (verduidelijking van de opties) of het bespreken van keuzes (bespreking van de nadelen en voordelen), in plaats van het creëren van empathische gesprekken. De consequenties van het weglaten van elementen van gedeelde besluitvorming, evenals de situatie-afhankelijkheid

ervan, voor gedeelde besluitvormingsuitkomsten is onbekend en dient te worden bestudeerd in toekomstig onderzoek.

Tijdens de uitvoering van deze systematische review kwamen meerdere moeilijkheden aan het licht. Deze moeilijkheden wijzen op de behoefte aan kwaliteitsverbetering van gerandomiseerde studies met een controlegroep (in het Engels: randomized controlled trials) naar de effecten van keuzehulpen, evenals hun publicaties. De nieuwe SUNDAE checklist lijkt grotendeels te voorzien in deze behoefte. Echter wordt de keuze voor te gebruiken meetinstrumenten in deze gerandomiseerde studies met een controlegroep, alsmede de timing van metingen, niet behandeld door de SUNDAE checklist en is nodig om de heterogeniteit tussen studies in dit onderzoeksveld te verminderen. Daarom is de ontwikkeling van een basisset van uitkomsten (in het Engels: core outcome set) voor onderzoek in het veld van keuzehulpen (voor mensen met een chronische aandoening) wenselijk om onderzoeksresultaten tussen studies te kunnen vergelijken.

Het gebruik van keuzehulpen is geen voorwaarde voor gedeelde besluitvorming. Implementatie van gedeelde besluitvorming vraagt om meerdere verschillende strategieën, gekoppeld aan cultuurverandering onder zorgverleners, hun organisaties en patiënten. Zorgverleners dienen te worden geschoold in het creëren en bevorderen van een cultuur van gedeelde besluitvorming, evenals in de vaardigheden die nodig zijn om op een begrijpelijke manier te communiceren over wetenschappelijk bewijs en de beperkingen ervan. Patiënten kunnen ook geschoold worden, en keuzehulpen kunnen hierbij een rol spelen.

Naast het scholen van patiënten en gezondheidsprofessionals zijn er andere manieren om een omgeving te creëren die gedeelde besluitvorming stimuleert: 1) een adequate afspraakduur, 2) korte (of ten minste flexibele) perioden tussen visites, 3) continuïteit van zorg, en 4) een systeem waarin de medicatiekeuze is gebaseerd op persoonlijke contexten, waarden en voorkeuren van de patiënt. Belangrijk om te noemen is dat gedeelde besluitvorming niet gezien moet worden als een vervelend toegevoegde extra, maar als de kern van gedegen klinisch handelen.

Deel 2: Patiënt-gerapporteerde uitkomsten

Patiënt-gerapporteerde uitkomsten zijn subjectieve rapportages en representeren datgene wat het meest belangrijk is voor patiënten met betrekking tot hun aandoeningen en de behandeling ervan. Patiënt-gerapporteerde uitkomsten worden steeds belangrijker in het afwegen van de voor- en nadelen van een bepaald medicijn of behandelingsregime. Hierbij kunnen de perspectieven van de patiënt worden meegenomen. Zo kan het bespreken van de voor- en nadelen van opties binnen gedeelde besluitvormingsgesprekken geïnformeerd worden door wetenschappelijk bewijs dat gegenereerd is vanuit patiënt-gerapporteerde uitkomsten. Patiënt-gerapporteerde uitkomsten zijn oorspronkelijk ontwikkeld voor gebruik in onderzoek, maar worden ook steeds vaker door zorgverleners gebruikt. Door gebruik in de klinische praktijk kunnen door de patiënt gerapporteerde problemen op de gespreksagenda gezet worden, en kunnen patiënt-gerapporteerde uitkomsten dus een startpunt voor gedeelde besluitvorming zijn.

Patiënt-gerapporteerde uitkomsten in onderzoek

Wanneer gedeelde besluitvorming in de zorg voor mensen met diabetes type 2 wordt toegepast, dan is insuline glargine 300 E/mL wellicht één van de beschikbare opties. **Hoofdstuk 4** beschrijft de observationele OPTIN-D studie. De resultaten van de OPTIN-D studie laten zien dat insuline glargine 300 E/mL een geschikt glucose-verlagend medicament is voor personen met diabetes type 2 die behoefte hebben aan meer flexibiliteit in injectietijd en een vermindering in het te injecteren volume. Toekomstige studies dienen de impact van glargine 300 U/mL te onderzoeken bij patiënten met diabetes 2 met een minder gunstig psychologische en medische profiel. Tevens is een gecontroleerd studie design nodig om stevige conclusies te kunnen trekken met betrekking tot een causale relatie tussen glargine 300 U/mL en verbeterde patiënt-gerapporteerde geschiktheid van medicatie.

Reductie van hypoglykemie is belangrijk voor personen met diabetes type 2, aangezien de resultaten van de studie beschreven in **Hoofdstuk 5** laten zien dat hypoglykemie is geassocieerd met

een hogere angst voor hypoglykemie en diabetes symptoomlast, onafhankelijk van het behandelregime. Het is twijfelachtig of deze bevindingen klinisch relevant zijn, maar preventie en adequaat management van hypoglykemie verdient op zijn minst klinische aandacht. Dit geldt zowel voor personen die orale medicatie gebruiken als voor personen die insulinetherapie initiëren. Toekomstige studies kunnen zich richten op het bepalen van klinisch relevante veranderingen in angst voor hypoglykemie en diabetes symptoomlast, om zodoende de scores interpretabel te maken.

Patiënt-gerapporteerde uitkomsten in de klinische praktijk

In **Hoofdstuk 6** is een eerste poging gedaan tot het verbeteren van de interpretatie van (domein)scores op de Diabetes Symptom Checklist-Revised (DSC-R). Hierbij zijn de associaties tussen DSC-R (domein)scores met verschillende patiëntkarakteristieken vastgesteld. Een verslechterde stemming en waarschijnlijke depressie versterken scores op alle domeinen van de DSC-R. Dit geldt in het bijzonder voor de vermoeidheid, cognitieve symptomen, hypoglykemische, and hyperglykemische domeinen, welke gezien kunnen worden als de acute symptomen voortkomend uit fluctuerende bloedsuikerwaarden. Deze bevindingen benadrukken het belang van aandacht voor en accurate behandeling van een verslechterde stemming en depressie in de klinische praktijk. Andersom wijst een overmatige last van vermoeidheid, cognitieve symptomen, hypoglykemie en/of hyperglykemie wellicht op een onderliggende verslechterde stemming of depressie.

De relevante associaties met bijbehorende effectschattingen kunnen bruikbaar zijn in het beoordelen van de mate waarin een bepaalde symptoomlast als overmatig beschouwd kan worden gegeven bepaalde patiëntkarakteristieken. Echter dienen de associaties en hun effectschattingen verder getest te worden in meer diverse patiëntpopulaties. Wanneer de DSC-R in de klinische praktijk gebruikt wordt, dan is te adviseren om te focussen op (veranderingen in) DSC-R scores op domeinniveau.

Vóór gebruik in de klinische praktijk dienen toekomstige studies de inhoudsvaliditeit van de DSC-R in meer detail te evalueren. Dit aangezien relevante items wellicht ontbreken, bijvoorbeeld

met betrekking tot een jeukende huid, toegenomen honger, zweten en geslacht-specifieke seksuele symptomen. Toekomstig onderzoek kan zich richten op het creëren van referentiewaarden of gewichten voor verschillende groepen, alsmede op het vaststellen van klinisch relevante verschillen in diabetes symptoomlast.

Naast het verbeteren van de inhoudsvaliditeit en interpretatie van scores helpen nieuwe dataverzamelingstechnologieën (b.v. computer adaptief testen; in het Engels: computer adaptive testing) om patiënt-gerapporteerde uitkomsten deel uit te laten maken van alledaagse zorg. Tevens is training in het gebruik en de interpretatie van patiënt-gerapporteerde uitkomsten noodzakelijk voor optimaal gebruik in de dagelijkse zorg.

Realiseren van de juiste zorg

Belangrijk om te benoemen is dat het identificeren van de juiste zorg niet genoeg is, omdat het daadwerkelijk gerealiseerd dient te worden. Meerdere hulpmiddelen zijn beschikbaar om de juiste zorg te realiseren, wat belangrijk is om een werkdruk-mogelijkheden disbalans te voorkomen. Wanneer de mogelijkheden de werkdruk niet kunnen dragen, dan zullen patiënten met meerdere chronische aandoeningen slechts “overleven” (in het Engels: survive) en niet gedijen (in het Engels: thrive).

Publications and presentations

Scientific publications

Peer-reviewed publications

Wieringa TH, Kunneman M, Rodriguez-Gutierrez R, Montori VM, de Wit M, Smets EMA, Schoonmade LJ, Spencer-Bonilla G, and Snoek FJ. A systematic review of decision aids that facilitate elements of shared decision-making in chronic illnesses: A review protocol. Systematic Reviews. 2017;6: 155.

Wieringa TH, de Wit M, Twisk JWR, and Snoek FJ. Does hypoglycaemia affect the improvement in QoL after the transition to insulin in people with type 2 diabetes? Journal of Endocrinological Investigation. 2018;41(2): 249-258.

Wieringa TH, de Wit M, Twisk JWR, and Snoek FJ. Improved diabetes medication convenience and satisfaction in persons with type 2 diabetes after switching to insulin glargine 300 U/mL: Results of the observational OPTIN-D study. BMJ Open Diabetes Research & Care. 2018;6: e000548.

Wieringa TH, Rodriguez-Gutierrez R, Spencer-Bonilla GS, de Wit M, Ponce-Ponte OJ, Sanchez-Herrera MF, Espinoza-Suarez NR, Zisman-Ilani Y, Kunneman M, Montori VM, and Snoek FJ. Decision aids that facilitate elements of shared-decision making in chronic illnesses: A systematic review. (Submitted 2018)

Wieringa TH, de Wit M, Twisk JWR, and Snoek FJ. Improving interpretability of individual Diabetes Symptom Checklist-Revised (DSC-R) scores: The role of patient characteristics. (Submitted 2018)

Moeijes J, van Busschbach T, **Wieringa TH**, Kone J, Bosscher RJ, and Twisk JWR. Sports participation and health-related quality of life in children: Results of a cross-sectional study. (Submitted 2018)

Wieringa TH, Sanchez-Herrera MF, Espinoza NR, Tran V-T, and Boehmer K. Viewpoint: Toward the care of each patient: Untangling the interactions between treatment burden, illness burden, and health through shared decision making. (Submitted 2019)

Other publications

Wieringa TH, de Wit M, Twisk JWR, and Snoek FJ. Improved diabetes medication convenience in persons with type 2 diabetes after switching to insulin glargine 300 U/mL (U-300)—The observational OPTIN-D study. Diabetes. 2018;67(Supplement 1)

Conference presentations

Oral presentations

Wieringa TH*, de Wit M, Smets EMA, Kunneman HJAM, Snoek FJ, Shared decision making in type 2 diabetes care: What is the research agenda? 21st PSAD Spring Scientific Meeting, Würzburg (Germany), 2016.

Wieringa TH*, de Wit M, de Grooth R, Snoek FJ. Does the transition to insulin in persons with type 2 diabetes alter the relationship between hypoglycaemia and quality of life? Secondary analyses of the SPIRIT study. NVDO jonge onderzoekers bijeenkomst, Soesterberg (the Netherlands), 2016.

Wieringa TH*, de Wit M, Twisk JWR, Snoek FJ. Improved diabetes medication convenience in persons with type 2 diabetes after switching to insulin glargine 300 U/mL: Results of the observational OPTIN-D study. NVDO jonge onderzoekers bijeenkomst, Soesterberg (the Netherlands), 2018.

Wieringa TH*, de Wit M, de Grooth R, Snoek FJ. Does the transition to insulin glargine in Dutch persons with type 2 diabetes alter the relationship between hypoglycaemia and quality of life? A prospective observational study. Annual Dutch Diabetes Research Meeting, Oosterbeek (the Netherlands), 2015.

Poster presentations

Wieringa TH*, de Wit M, Twisk J, Snoek FJ. Improved diabetes medication convenience in persons with type 2 diabetes after switching to insulin glargine 300 U/mL (U-300)—The observational OPTIN-D study. American Diabetes Association's 78th Scientific Sessions, Orlando (Florida, USA), 2018.

Wieringa TH*, OPTIN-D: An observational study documenting Patient Reported Outcomes (PROs) of people with type 2 diabetes treated with insulin glargine-300 U/mL. VUmc Science Exchange Day, Amsterdam (the Netherlands), 2017.

* presenting author

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Thomas Wieringa was born on 26 January 1988 in Emmeloord (Noordoostpolder), the Netherlands. He has been a youth player at the professional football clubs PEC Zwolle (2001-2004) and SC Heerenveen (2005-2006). He was selected twice for the Dutch national Under-15 team (2002-2003).

In 2005 he completed his senior general secondary education (in Dutch: HAVO) at the Thomas á Kempis College in Zwolle. In the same city, he studied Speech Therapy at Windesheim University of Applied Sciences, for which he obtained his degree in 2010.

After working as a speech therapist for almost a year, he started with the one-year premaster Health Sciences in 2011. He started the master, with Prevention and Public Health as chosen specialization, in 2012. Under supervision of **J. Moeijes**, he learned to collect and analyze data, as well as to report the results in a scientific article. In 2013, he obtained his master's degree.

Subsequently, he performed a study in the field of sex workers' health, with a focus on hepatitis B vaccination behavior. This research was commissioned by **Soa Aids Netherlands** and the **National Institute for Public Health and the Environment**.

The current dissertation is the result of a three-and-a-half year PhD-trajectory. During this PhD-period, he also worked as a Junior Quality Officer for the **EMGO+-research institute**, passed the exams for becoming registered as epidemiologist, and performed multiple education activities in order to obtain the University Teaching Qualification (in Dutch: Basiskwalificatie Onderwijs; BKO). In the context of his PhD, he won a Travel Grant, with which he visited the **Mayo Clinic** in Rochester (Minnesota, USA) for six weeks in October and November 2017.