Zorgkwaliteit van diabetes mellitus type 2 patiënten: hoe kunnen we dat verbeteren?

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Abstract

Context: Diabetes mellitus type 2 (DM2) is een van de meest voorkomende niet-overdraagbare ziekten en er treedt een drastische toename op, samen met het verhogen van invaliditeit en sterfte. Chronische behandeling is nodig om acute en chronische complicaties te verminderen, en zo ook het risico op hart- en vaatziekten. De therapietrouw aan een langdurige behandeling is een grote uitdaging en is gekoppeld aan verschillende factoren.

Onderzoeksvraag: Het eerste doel van het onderzoek was om de literatuur te analyseren en te classificeren, afhankelijk van de verschillende interventies, gebruikt om de therapietrouw van de diabetes medicatie te verbeteren, met de nadruk op efficiënte en patiëntgerichte methoden en de beoordeling van de haalbaarheid ervan op een grote schaal. Ten tweede, analyseren van de huidige Belgische diabeteszorgstrategie en verkennen van de mogelijke toepasselijkheid van die methoden.

Methoden: Een scoping review werd uitgevoerd met behulp van de zoekmachines PubMed, Medline en Google Scholar, met behulp van 'diabetes mellitus type 2' en de begrippen, 'medicatie therapietrouw', 'Chronic Care Model (CCM)' en 'Diabetes Self Management Education (DSME)' . Zesendertig studies werden gevonden en ze werden verdeeld afhankelijk van de gebruikte strategieën.

Resultaten: De CCM is het theoretisch framework op basis van het ontwerp en de analyse van de gevonden studies. Patiëntgerichte zorg is een van de belangrijkste thema's van het CC model met onderwijs en self-management strategieën. Een enorme hoeveelheid literatuur over de correlatie tussen klinische resultaten en interventiestrategieën is beschikbaar, maar weinig specifiek gericht op medicatietherapietrouw als uitkomst. We konden enkel 36 studies vinden en verdeelden ze in vijf groepen, afhankelijk van die factoren, die invloed hebben op de therapietrouw: ziektegerelateerde, patiëntgebonden, socio-economische verwante, therapie-gerelateerde en gezondheidszorg-gerelateerde factoren. De interventies met behulp van educatieve strategieën, de patiënt-zorgverlener communicatie interventies, mobiele telefoon- en teksttechnologieën, Medication Event Monitoring System, apotheker-gebaseerde interventies, en de continuïteit van de zorg en zelf-management support strategieën lijken effectief in het verbeteren van de medicatietherapietrouw. De sociale ondersteuning, met name peer support, moet nog meer onderzocht worden op grote schaal, want er werd geen bewijs gevonden of het de therapietrouw verbetert. Zelfs als er goede resultaten werden gezien, heeft deze studie vele beperkingen en is verder onderzoek nodig.

Conclusies: Therapietrouw heeft een belangrijke invloed op de opvolging van diabetes, maar veel factoren beïnvloeden de therapietrouw van diabetes type 2 patiënten. Het verbeteren ervan bij

chronische ziekten is meestal complex en er zijn geen erg effectieve methoden. Uit dit review kunnen we besluiten dat de resultaten veelbelovend lijken, met name voor wat betreft het onderwijs, relationele en technologische strategieën, maar verder onderzoek is nog nodig om haalbare en kosteneffectieve strategieën te ontwikkelen.

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1 Introduction

Diabetes mellitus type 2 (DM2) is one of the most common non-communicable diseases and its burden is estimated to increase dramatically: from a global prevalence in the adult population of 8.3 % in 2013 to 10% in 2035. Eighty percent of DM2 patients live in low-middle income countries and about 175 million patients are estimated to be undiagnosed [1]. DM2 causes macrovascular (coronary heart diseases, ischemic stroke) and microvascular complications (retinopathy, nephropathy, neuropathy), acute glycemic complications and foot complications (diabetic foot), which increase the mortality and worsen the quality of life [2-4]. Other cardiovascular risk factors are commonly associated with diabetes, and cardiovascular disease (CVD) is the major cause of morbidity and mortality for individuals with diabetes. It also contributes to direct and indirect costs: controlling the risk factors is proven to prevent CVD in these patients [5]. The Belgian guidelines [6] call for a multiple approach based on three pillars: correction of hyperglycemia, correction of other cardiovascular risk factors and treatment of early stage complications. The treatment consists in life-style changes (diet, sport, weight control), medications (oral and injectable diabetes medications, cardio-aspirin, statins, and vaccinations as appropriate) and a systematic follow up (blood control, foot control, ophthalmologist, diet, etc..).

While guidelines are now widely available and used, poor adherence to long-term treatment for chronic diseases is a worldwide problem of striking magnitude: adherence in developed countries averages 50%, but in developing countries, it is assumed to be much lower given the scarcity of health resources and inequities in access to health care [7]. The burden of non-communicable diseases combined represents the 54% of all illness worldwide in 2001 and will exceed the 65% in 2020 [8]. The consequences of poor adherence to long-term therapies are thus poor health outcomes that lead to medical and psychosocial complications and reduced patients' quality of life [7]. Indeed, the absolute and relative risk assessments demonstrate that a considerable proportion of all CVD events (~9% in Europe) could be attributed to poor adherence to vascular medications alone [9]. The health care costs derived from poor adherence (in terms of hospitalization and use of emergency units) are very high and much higher than what we can expect from drug expenditure in case of full adherent patients [10]. Avoidance of further complications and postponement of death (productivity gains) have an important economical impact [11].

The aim of this paper is to explore the concept of adherence and apply the insights gained to the analysis of why and how adherence to diabetes medication can be improved. For the latter, we will apply the insights from the scoping review to the current policy of diabetes care in Belgium.

We first present a Background on adherence in general, adherence to diabetes medication and a general framework on adherence that can be used to analyze the root causes. We then proceed with the Methods section, explaining why and how we adopted the scoping review method of literature review. We then present the Results of the scoping review, and my review of the diabetes care approach currently used in Belgium. This is followed by a Discussion and a Conclusion.

2 Background

What is ‘adherence’?

Adherence is defined as the extent to which a person’s behavior corresponds with agreed recommendations from a health care provider about medication, diet, and/or lifestyle changes [7]. Three measurable components of adherence can be identified: initiation, implementation, and discontinuation. Considering for example the medication intake, initiation is defined as the moment when the patient takes the first dose of a prescribed medication. The implementation is the extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen from initiation until the last dose taken. Discontinuation is the end of therapy. Also important is the definition of persistence as the length of time between initiation and the last dose that immediately precedes discontinuation [12,13].

Non-adherence to medications can thus take the following forms [12]:

- late or non-initiation of the prescribed treatment
- sub-optimal implementation of the dosing regimen
- early discontinuation of the treatment

Vrijens [12] emphasizes the importance of the relationship between the patient and the health-care provider: this should be a partnership that draws on the abilities of each and on good communication between the different actors and that makes the patient to be an active partner in his own care. In this definition, there is a clear shift from the concept of ‘compliance’ to ‘adherence’ that reflects a fundamental change in understanding relationships between patients and practitioners, moving away from the negative connotation of a 'patient as subservient to prescribers to a patient who actively cooperates with them' [12].

Measuring adherence

According to Farmer KC [14], there is no "gold-standard" method to measure adherence. Several direct and indirect measure methods have been used in the literature. Direct measures of adherence include assessment of the drug's action on the body (i.e. drug assays of blood or urine), use of drug markers with the target medication and direct observation of the patient receiving the medication (directly observed therapy - DOT, wirelessly observed therapy - WOT). Indirect measures of adherence include various types of self-reporting by the patient or by the healthcare provider, medication measurement (pill count), use of electronic monitoring devices and review of prescription records and claims [14, 15].

All these methods have limits. Drug assays of biological markers are influenced by a variety of individual factors including diet, absorption and rate of excretion. Subjective ratings of adherence can be inaccurate as patients often tend not to admit poor adherence. Providers tend to overestimate the adherence when they have to rate it [7]. Standardized, patient-administered questionnaires and assessments of global patient characteristics or “personality” traits have proven to be poor predictors of adherence [14]. Remaining dosage units commonly overestimate the adherence behavior and miss important information [7]. The Medication Event Monitoring System (MEMS), recording the time and date of medication container opening, is used in many studies as referred standard [14], but it may influence adherence [16]. Since no single measurement strategy can combine reliable and validate psychometric standards with the available resources, the WHO

advocates for developing a multi-method approach that combines feasible self-reporting and reasonable objective measures of adherence [7].

Adherence in diabetes

In DM2 control, adherence plays an important role in order to avoid acute and chronic complications and to reduce the risk of cardiovascular disease (CVD). Long-term complications in terms of major morbidity and mortality can be prevented with a good glycemic control in patients with insulin-dependent diabetes mellitus (IDDM), delaying the onset and slowing the progression of diabetic retinopathy, nephropathy, and neuropathy [17], in combination with lifestyle changes, blood pressure (BP) control and lipids management [18]. Besides the clinical complications, diabetes has also a huge and increasing economic burden: the total cost of treating more than 10 million patients with type 2 diabetes in the European countries studied was approximately US 29 billion dollars, which represents an average of 5% of the total health care expenditure in each country. The overall cost of treating patients with diabetes is on average over 1.5 times higher than per capita health care expenditure. Furthermore, this cost increases 2- to 3.5-fold once patients develop preventable microvascular and macrovascular complications. Hospitalization costs, which include the treatment of long-term complications, account for about 30-65% of the overall costs of the disease. The direct costs of complications attributable to poor control of diabetes are 3-4 times higher than the costs of a good control. The indirect costs (production losses due to sick leave, early retirement and premature death) are of approximately the same magnitude as these direct costs [19]. Good medication adherence leads to increased drug expenditure, but it reduces the expenses caused by hospitalization and emergency department visits for diabetes or related conditions. Cheng and colleagues [20] show that the difference in total healthcare expenses produced by good adherence began to decrease 5 years after the time of diabetes onset, while Roebuck [21] reports an average benefit-cost ratio 6.7:1 in case of adherence on diabetes therapy.

Despite the recommendations about lifestyle changes, BG and BP control and lipids management [18], a study [19] found that only 43%, 29%, and 52% of patients with DM2 achieved guideline targets for glycosylated hemoglobin (HbA_{1c}), BP and low-density lipoprotein cholesterol (LDL-C) levels, respectively. Furthermore, the CODE-2 study [22] found that, in Europe, only 28% of patients treated for diabetes achieved good glycemic control and in the United States less than 2% of adults with diabetes perform the full level of care that has been recommended by the American Diabetes Association [23]. Many patients to whom diabetes medications were prescribed are poor compliers with treatment, including both oral hypoglycemic agents (OHAs) and insulin. Cramer et al. report that the overall rate of adherence with OHAs was 36–93% with a persistence of 6–24 months, while in patients receiving insulin, only 63% of doses were taken as prescribed [24].

Such low adherence puts patients at an increased risk for intermediate and long-term complications and increased mortality, provoking an important economic burden to the health care system. In multivariable analyses, non-adherent patients had significantly increased risk for all-cause hospitalization and for all-cause mortality [19]. According to the recent guidelines, the patient has to have a central role in the self-management of DM2, including self-care behaviors such as home glucose monitoring (in blood or urine); adjustment of food intake to meet daily needs and match available insulin; administration of medications; regular physical activity; foot care; regular medical monitoring visits and other self practices [18]. The importance of the patient's role and of his collaboration with care-givers is also stressed by the World Health Organization (WHO) that

described adherence to self-care as an 'active, responsible and flexible process of self-management, in which the patient strives to achieve good health by working in close collaboration with health care staff, instead of simply following rigidly prescribed rules' [7]. Despite that, different studies report that self-monitoring of blood glucose as prescribed is performed only from the 33% of DM2 patients in the USA and only 23 % in India, while diet adjustment is regularly done by 52% of patients in the US and 37% in India. Physical activity has also poor adherence as well as the intake of medication (only the 15% of patients take the prescribed therapy after 1 year)[7].

Reasons for low adherence in diabetes

Many conceptual models have been used to help understanding the barriers to medication adherence (including the transtheoretical model of change, the theory of reasoned action, locus of control, the health belief model, social learning theory and theory of self-regulation). However, none of these fully explains the barriers to medication adherence [25].

The World Health Organization (WHO) suggested a five dimensions framework through which many different factors associated with a non-adherent behaviors can be identified and classified as follows [7]:

- socio-economical factors
- health care systems factors
- health condition-related factors
- therapy-related factors
- patient-related factors

Socio-economical factors

The socio-economical status of the patient influences adherence. Economic factors, such as unemployment, poverty, lack of or inadequate medical/prescription coverage, and high out-of-pocket cost of drugs play a role. In fact, diabetes patients are usually prescribed many drugs simultaneously, thus the resulting out-of-pocket costs put a significant burden on them and decrease the adherence [26]. Policies shifting the costs to patients through co-payments or coverage gaps reduce the use of both preventive services and recommended medications [27]. Not only the costs, but, in general, an unsure economic situation, as well as racial and social disparities and segregation have been found to be linked to lower access to care and poorer health outcomes [28]. Family and social support have been significantly associated with better self-care behaviors: it is crucial to get the family involved in the care [29,30]. Patients need to tailor their self-care behaviors to the environmental situation: the so-called "high-risk environmental situations" as described by Schlundt are linked with poor adherence in dietary therapy [31].

Health care team and health systems factors

Although non-adherence has often been perceived as the fault of patients, there is evidence that health care providers and health systems play an important role in determining how the patient will adhere to the prescribed self-care behaviors. Communication issues can be an important barrier in the doctor-patient relationship and patients' adherence, and need to be tackled [32]. Discordance in language between physician and patient is an independent predictor in glycemic control [33] and poor patient-provider communication in general is associated with poorer treatment adherence [34]. A patient-centered communication may stimulate patients to improve self-efficacy and adherence [35]. Poor access to healthcare, poor drug supply, unclear information about drug administration,

poor follow-up, and poor provider-patient communication and relationship may reduce the extent to which patients follow the treatment plan [7]. The TRIAD study group [27] focused on the association between health outcomes in DM2 patients and system-levels structures and strategies: it found that health systems implementing more intensive disease management strategies and using financial incentives related to quality, achieve higher levels of diabetes care processes. Programs such as the Alliance Programs [36] aims to reduce the health care disparities for the participants thanks a multicomponent, multilevel program focusing on patient's education, provider education about cultural and communication skills and health care system change; its application showed an increased quality of life and improvements in diabetes self-care behaviors.

Health conditions-related factors

The asymptomatic nature of the disease at the early stages, as well as its clinical development may reduce patient's motivation to take the drugs as prescribed, whereas disease severity has a positive effect on adherence [7]. The chronicity and the duration of the disease influence negatively the adherence: old diagnosed patients adhere less than recent diagnosed ones [37]. The number, the severity and the type of non-diabetes related co-morbidities influence diabetes self-management [38]. Major depression has a high incidence in DM2 patients and together with alcohol abuse [39], it is associated with low therapeutic adherence [40], while diabetes-related distress influences the glycemic control [41].

Therapy-related factors

The type and the intake frequency of the medication influences adherence: once-daily dose medication regimes are associated with better adherence and persistence than more complex ones [42]. Frequent dosing, high number of medications, longer duration of treatment, drug formulation or taste and presence of adverse effects make the adherence drop [7]. Patient's beliefs are linked with adherence: medications, especially insulin, are seen as more effective than life-style changes [43]. Despite the recognized importance of the life style changes, it appears from a patient survey [44] that only 52% of patients follow a meal plan and only 26% an exercise plan. Many factors were seen as barriers from both the patients and the care provider such as not eating at home.

Patient-related factors

Age, gender, self-esteem, self-efficacy and stress have an influence on adherence: in particular self-efficacy is a strong predictor of adherence and together with autonomy, it predicts life satisfaction [7].
Patients' formal beliefs are predictors of diabetes self-management for what concerns physiological and behavioral outcomes: multiple regression analysis conducted by Griva et al. [45] demonstrated that 30.8% of the variance in HbA1C assays was explained by patients' self-efficacy, consequences and identity. Perceptions about the gravity of the disease and the therapy have an influence on the adherence: lower perceived consequences of the disease, lower distress, higher personal control over diabetes, and fewer symptoms are related with worse adherence. Disease and medication beliefs not consistent with a chronic disease model are significant predictors of poor medication adherence [46]. A positive family history and pre-existing ideas about the DM2 can influence the understanding of the disease and consequently the adherence [47]. Comorbidities, especially psychiatric conditions, alcohol and drug dependence, have a negative effect on adherence [13].

How to tackle the problem of low adherence

'Current methods of improving adherence for chronic health problems are mostly complex and not very effective' [48]. The WHO advocates that a stronger commitment to a multidisciplinary approach is needed and states it requires coordinated action from health professionals, researchers, health planners and policy-makers [7].

The American Diabetes Association proposes to use the Chronic Care Model (CCM) as an effective framework for improving the quality of diabetes care and for coordinating the delivery system, useful to face the complexity of chronic care [49].

The CCM stipulates that six core elements are necessary for providing optimal care:

1. Delivery system design (proactive care with planned visits and a collaborative, multidisciplinary teams based approach)
2. Self-management support
3. Decision support (evidence-based guidelines)
4. Clinical information systems (in the form of registries)
5. Community resources and policies (to support healthy lifestyles)
6. Health systems (to create a quality oriented culture).

The objectives of the CCM are to optimize provider and team behavior, support patient behavioral change and change the care system. Patient behavior change includes healthy lifestyle choices, prevention of diabetes complications and disease self-management, of which an important part is taking and managing medications. Self-management can be improved thanks to high-quality diabetes self-management education (DSME): its aim is to improve patient self-management, satisfaction, and glucose control providing clinical content and skills, behavioral strategies (as goal setting, problem solving), and engagement with psychosocial concerns. Diabetes self-management support (DSMS) is defined as any kind of support needed by the patient for implementing and sustaining the coping skills and behaviors needed to self-manage [50]. DSME and DSMS should be patient-centered, respectful, and responsive to individual patient preferences, needs, and values, and should guide clinical decisions [49]. Patient centeredness is one of the most important aspects of the CCM: patients need to receive high-quality DSME in order to improve self-management, satisfaction and clinical outcomes with an integrated approach. This approach includes clinical content and skills, behavioral strategies (goal setting, problem solving), and engagement with psychosocial concerns. A close working relationship between the patient and clinicians involved in care planning and delivery is required.

The CCM is also the theoretical framework used for writing the national guidelines for diabetes care in Belgium [51].

3 Methods

A scoping review to identify and analyze different interventions used to improve adherence to diabetes medication., used to improve adherence to diabetes medication, has been performed. Particular attention has been put in the identification of efficient and patient-centered methods and the assessment of their feasibility on a big scale.

A scoping review is defined as a literature review, aiming at the generation of a map of the key concepts in a specific area. This map should include the main sources and the type of the available evidence. This would allow to examine the extent and the range of the findings, to summarize and disseminate them and to identify the gaps in existing literature [52].

Secondly, we presented briefly the Belgian organization of care for DM2 and used the findings of the scoping review to analyze it.

The scoping review was performed in April 2016 using the PubMed, Medline and Google Scholar search engines, using the terms 'diabetes mellitus type 2', 'medication's adherence', 'Chronic Care Model', and 'DSME'. The inclusion criteria were: adherence to oral anti-diabetic medications as outcome, adherence to oral medication, study analyzing strategies to improve adherence, interventions based on the Chronic Care Model. The exclusion criteria were: studies focusing on diabetes other than type 2, DM2 associated with other pathologies, studies written before the year 2000, papers presenting interventions to improve exercise or diet or to improve adherence to the administration of insulin. Outcomes other than adherence, such as clinical outcomes and self-care outcomes, were also analyzed as secondary outcomes (see table 3).

Thirty-six studies were included in this study. Fifteen studies are randomized controlled trials (RCT), 5 prospective studies, 5 cross-sectional studies, 2 survey studies, 2 longitudinal analyses, 2 mixed methods studies, 2 interventional study, 1 systematic literature review, 1 pilot study and 1 cohort study, as shown in Table 1.

Table 1 - List of papers included in the scoping review

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For what concerns the Belgian model for diabetes care, we identified and analyzed the current guidelines and papers available about the organization of the diabetes care in Belgium (Domus medica diabetes richtlijnen [51], KCE report [88], website LMN Maas en Kempen [89]) and applied the lessons learnt from the scoping review to the policy.

4 Results

In this section, the key issues emerging from the scoping review are described. A detailed overview of interventions used to improved adherence to diabetes medication and their effectiveness is also presented.

Insights from the scoping review

There are three issues that are striking. First, the review identified only 36 studies that focused explicitly on medication adherence. In most studies, adherence is just one of the researched outcomes and not the primary outcome, thus it is researched less systematically than the other outcomes.

Second, the studies we found tackle different factors associated with the lack of adherence and in very different ways as barriers to medication adherence. Therefore, a comparison between them cannot be performed.

Third, the studies were not homogeneous in term of study design and the evaluation methodologies, thus hampering their comparison (see table 2). Different methodologies were used to measure medication adherence, some of them already validated (i.e. Medication Adherence Scale [90] or Summary of Diabetes Self-Care Activities questionnaire [91], while others were created for the study (i.e. Self-Appraisal Diabetes Self-Management Scale (SADSM)[58]). Most of the studies were randomized clinical trials, but also other kind of study's design was included.

Table 2 - Type of study and adherence's measurement method. (RCT = randomized control trial)

Reference	Type of factor tackled	Type of study	Adherence's measurement method
Al Hayek AA et al, 2013 [53]	patient-related factors	Prospective study	8-Item Medication Adherence Scale [90]
Arora S et al, 2012 [54]	health care system factors	Prospective trial	Morisky Medication Adherence Scale [90]
Ciechanowski PS et al., 2001 [55]	health care system factors	Survey study	Summary of Diabetes Self-Care Activities Questionnaire [92]
Chen CC et al, 2013 [56]	health care system factors	Longitudinal analysis	Random intercept models
Chung WW et al., 2014 [57]	health care system factors	RCT	Malaysian Medication Adherence Scale [93]
Collins-McNeil J et al, 2012 [58]	patient-related factors	Interventional study	○ The Diabetes Self-Care Practices Measurement Questionnaire (DSCPM) [94] ○ Self-Appraisal Diabetes Self-Management Scale (SADSM)
Dick JJ et al., 2011 [59]	health care system factors	Pilot study	Skaff and colleagues' diabetes self efficacy (DSE) scale [95]
Doucette WR et al, 2009 [60]	patient-related factors	RCT	Diabetes Selfcare Activity Measurement Scale [91]
Duru OK et al., 2010 [61]	health care system factors	Cross-sectional study	Continuous measure of medication gaps (CMG) [96]

Farmer A et al., 2012 [62]	health care system factors	RCT	○ Percentage of days of taken medication measured over 12weeks with an electronic medication-monitoring device (TrackCap, Aardex, Switzerland) [97] ○ Medication Adherence Report Scale (MARS) [98]
Heisler M et al., 2010 [63]	socio-economical factors	RCT	○ Self-report outcomes measured via survey at baseline and 6 months included validated measures of medication adherence [99] ○ Diabetes-related emotional distress [100] ○ Diabetes-specific social support [101]
Heisler M et al., 2014 [64]	health care system factors	RCT	Four-item Morisky Self-Reported Medication Taking Scale [102]
Hong JS et al, 2014 [65]	health care system factors	Longitudinal analysis	Medication possession ratios (MPRs) [103]
Jahangard-Rafsanjani Z et al., 2015 [66]	patient-related factors	RCT	○ Morisky Medication Adherence Scale [90] ○ Diabetes Selfcare Activity Measurement Scale [91]
Jarab AS et al., 2012[67]	therapy-related factors	RCT	4-item Morisky Scale [102]
Kaissi AA et al, 2009 [68]	health care system factors	Cross-sectional study	Patient exit surveys
Kocarnik BM et al, 2012 [69]	health care system factors	Retrospective cohort study	Medication possession ratios (MPRs) [104]
Krass I et al, 2005[70]	therapy-related factors	RCT	Brief Medication Questionnaire (BMQ) [105]
Ku GM et al., 2014 [71]	patient-related factors	Prospective study	One-on-one interviews using a structured questionnaire inquiring on knowledge, attitudes, perceptions and self-care practices.
Mayberry LS et al, 2012 [72]	socio-economical factors	Mixed-methods approach (focus groups, survey)	12-item Adherence to Refills and Medication Scale (ARMS) [106]
Mitchell B et al, 2011[73]	patient-related factors	RCT	Brief Medication Questionnaire (BMQ) [105]
Nundy S et al., 2014 [74]	health care system factors	Mixed methods observational cohort study, theory-driven mobile phone intervention	○ Summary of Diabetes Self-Care Activities questionnaire [91] ○ Morisky 4-Item Self-report Measure of Medication-Taking Scale [102]
Odegard PS et al, 2012 [75]	patient-related factors	RCT	Medication possession ratio (MPR) [103]
Piette JD et al, 2000 [76]	health care system factors	RCT	Reported self-care survey
Piette JD et al., 2003 [77]	health care system factors	Cross-sectional survey	○ Interpersonal Processes of Care (IPC) questionnaire [107] ○ Summary of Diabetes Self-Care Activities questionnaire [91]
Rosen MI et al., 2004 [78]	health care system factors	RCT	MEMS (Medication Event Monitoring System) [14]
Schmittdiel J et al, 2008 [79]	health care system factors	Cross-sectional survey	Adapted item from Chesney medication adherence assessment [108]
Schunk M et al., 2015[80]	health care system factors	Survey study	Self-reported information and questionnaires
Siminerio L et al., 2014 [81]	health care system factors	Survey study	Summary of Diabetes Self-care Activities Measure (SDSCA) [91]
Shah M el al, 2013 [82]	health care system factors	RCT	Prescription of days covered (PDC) method [109]

Shane-McWhorter L et al., 2014 [83]	health care system factors	Non-randomized prospective observational study	Eight-items Medication Adherence Scale [90]
Strom JL et al, 2012 [84]	socio-economical factors	Systematic literature review	Review of 13 studies
Sutton S et al., 2014 [16]	health care system factors	RCT	MARS (Medication Adherence Report Scale) [98]
Vaccaro JA et al., 2014 [85]	socio-economical factors	Cross-sectional study	Michigan Diabetes Research and Training Center (MDRTC) Diabetes Care Profile questionnaire [110] consisting of: FSS (Family and friend social support) questionnaire DSM (diabetes self-management) composite score (including also medicine' adherence)
Walker EA et al., 2011 [86]	health care system factors	RCT	Four-item Morisky Self-Reported Medication Taking Scale [102] Medication possession ratio(MPR) [103] Summary of Diabetes Self-Care Activities questionnaire [91]
White AJ et al., 2012. [87]	health care system factors	Prospective study	MEMS (Medication Event Monitoring System) [14]

Effectiveness of the interventions

The research primary outcome was adherence to medication and the results for each study are shown in Table 3. As already mentioned, medication adherence was measured using different methods, creating issues in extrapolating a final conclusion. In most of the studies, clinical outcomes such as HbA1C and complications are the main researched outcomes together with self-care behaviors and follow up plans. These outcomes are presented in Table 4 in the appendix.

Table 3 - Adherence outcomes in the analyzed studies.

P probability, CI confidence interval, OR odds ratio, Medication possession ratio (MPR), interquartile range (IQR), PACIC (the Patient assessment Chronic Illness care), COC(I)Continuity of Care(Index), MARS (Medication Adherence Report Scale)

Reference	Primary outcome (medication adherence)
Al Hayek AA et al, 2013 [53]	Improvement of adherence to medication (P 0.007)
Arora S et al, 2012 [54]	Improvement of score from 3.5 to 4.75 on the Morisky Medication Adherence Scale.
Chen CC et al, 2013 [56]	High or intermediate COC scores associated with better adherence [odds ratio (OR), 3.37; 95%CI, 3.15–3.60] compared with those with low COC scores [OR, 1.84; 95%CI, 1.74–1.94].
Chung WW et al., 2014 [57]	Medication adherence significantly associated with pharmaceutical care, with 75.0% adherence in the intervention group and 58.7% in control group (P0.007).
Ciechanowski PS et al., 2001 [55]	The dismissing/poor provider communication group had a significantly greater number of interruptions in treatment with oral hypoglycemics: days in interruption mean 24.0 % (SD 19.0) in dismissing/poor provider communication group; mean 12.5 % (SD 19.0) in all the others.
Collins-McNeil J et al, 2012 [58]	Significant increases in medication adherence (P0.006)
Dick JJ et al., 2011 [59]	Number of reported missed medication doses decreased from a mean of 1.9 doses per week to 0.6 during the study period (P0.003) and 0.8 at 1-month follow-up (P<0.001).
Doucette WR et al, 2009 [60]	Increase of the mean number of days per week per activity for the set of 5 diabetes management activities (including medication adherence) in the intervention group by 0.73 days versus the control group.
Duru OK et al., 2010 [61]	Patients receiving medications by mail had a better adherence compared with those who used

	only local pharmacies (84.7% vs 76.9%, P <0.001)
Farmer A et al., 2012 [62]	Greater mean percentage of adherent days in the intervention group (mean 77.4%, SD 26.3) than in standard care (mean 69.0% SD30.8) (mean difference between groups 8.4%, 95%CI 0.2% to 16.7%, P0.044).
Heisler M et al., 2010 [63]	No differences in self-reported medication adherence in the target group.
Heisler M et al., 2014[64]	Significant improvement in medication adherence in iDecide (P0.036) and in printed material (P< 0.001) group but no difference between the two groups (P0.33).
Hong JS et al, 2014 [65]	Increasing of medication adherence with the increasing of COCI [0.2≤COCI<0.4, odds ratio (OR)=2.20; 0.4≤COCI<0.6, OR=3.46; 0.6≤COCI<0.8, OR=4.76; 0.8≤COCI<1.0, OR=4.43; COCI=1.0, OR=7.24].
Jahangard-Rafsanjani Z et al., 2015 [66]	Significant improvement in medication adherence
Jarab AS et al., 2012 [67]	Better adherence in the intervention group: nonadherent patients in the intervention group are 28.6% vs 64.6% of the usual care group (P0.003)
Kaissi AA et al, 2009 [68]	Self-management support positively associated with medication adherence, while community linkages were negatively associated with it
Kocarnik BM et al, 2012 [69]	No significant association between pharmacist presence and adherence
Krass I et al, 2005 [70]	Significantly improvement in self-reported nonadherence.
Ku GM et al., 2014 [71]	Significant increase in adherence to medications (P0.001)
Mayberry LS et al, 2012[72]	Non-supportive family behaviors is significantly associated to worse dose adherence (rho= 0.44,P,0.001) and marginally associated with worse refill adherence (rho=0.24, P 0.07)
Mitchell B et al, 2011 [73]	Reduced risk of non-adherence to medications.
Odegard PS et al, 2012 [75]	MPR significantly improved for the study group (P=0.004) compared with the control group (difference between groups, P0.01) with a greater effect for patients with baseline MPR less than 80% (difference between groups, P0.02). Higher likelihood of MPR above 80% for patients in the intervention group (OR 4.77 [95% CI 2.00–11.40]).
Piette JD et al, 2000 [76]	Fewer problems with medication adherence (P-0.03) in the intervention group.
Piette JD et al., 2003 [77]	General communication and diabetes-specific communication associated with patients' self-reported level of adherence: 77% of probability of taking medications in patients with poor general and diabetes-specific communication have, 95% in patients with the best scores on both. 11% absolute adherence improvement (from 77% to 85%) if improvement in diabetes-specific communication in the patients with the worst general communication. 13% absolute improvement (from 77% to 90%) if improvements in general communication in patients with the lowest diabetes-specific communication score.
Rosen MI et al., 2004 [78]	Cue-dose training associated with significantly better adherence to metformin (mean improvement of 15%) but not to other oral antihyperglycemic medication
Nundy S et al., 2014 [74]	The 4-item Morisky Medication Adherence score improved compared to baseline at 3 months (P<0.01) and 6 months (P0.02); no change in weekly medication adherence
Schmittdiel J et al, 2008 [79]	No significant association between the PACIC and adherence to medications (OR=1.06, 95%CI=0.98, 1.15).
Schunk M et al., 2015[80]	Patient-perceived positive quality of relationship with the physician strongly associated with adherence to medication (OR 1.92; CI: 1.39, 2.64)
Shah M el al, 2013[82]	Patients in the intervention group had greater diabetes medication adherence rate 150 days after discharge (55.2%) compared with control group (34.8%; P0.002).
Shane-McWhorter L et al., 2014 [83]	Medication adherence improved, but not significantly (mean score pre-intervention 6.2; post-intervention 6.5; P0.089)

Siminerio L et al., 2014 [81]	Adherence to medications measured in days/week did not change (before study 6.2 ± 1.4, end of Study 6.3 ± 1.4, P 0.44)
Strom JL et al, 2012 [84]	All the studies, except one show correlation between increased medication adherence and increased social support.
Sutton S et al., 2014 [16]	Non-significantly higher adherence in the electronic container group (MARS 0.4 [95 %CI−0.1to0.8, P=0.11])
Vaccaro JA et al., 2014 [85]	Higher family and friend social support was associated with higher diabetes self-management
Walker EA et al., 2011 [86]	Improvement in medication adherence (P0.005) with the telephonic intervention.
White AJ et al., 2012 [87]	Prescribed doses were taken in overall 99.1% (median, IQR: 96.8-100%), with inverse correlation with daily dose frequency (Spearman's rho=0.37, P=0.004).

Interventions used to improve adherence to diabetes medication

We analyzed the papers using the WHO framework [7], and we categorized them in groups according to the factors influencing adherence tackled from the intervention. We found 4 studies designed for tackling the socio-economical factors using social support-based approaches [63, 72, 84, 85], 7 studies focusing on patient-related factors, 3 of which using DSME/S strategies [53, 58, 71] and 4 using pharmacist-based programs [60, 66, 73, 75]. Only 2 tackled the therapy-related factors [67, 70] using pharmacist-based approaches and 23 articles focused on health care system factors in different ways (four focused on patient-provider communication strategies [55, 62, 77, 80], eleven focused on technology-based strategies for following up patients [16, 54, 59, 64, 74, 76, 78, 81, 83, 86, 87], four focused on health system organizational programs [56, 65, 68, 79] and 4 on pharmacist-based programs [57, 61, 69, 82]). No study focusing on the health condition-related factors was found.

Patient-related approaches

This kind of approaches aim to improve the self-management and self-efficacy of the patient, thanks to DSME/S strategies and pharmacist-based programs.

DSME and DSMS, as defined before, are strategies used in three studies that focused on their implementation. In the first, a mixed approach, consisting of pamphlets/handouts, special videotapes and specific educational programs provided through diabetes educators and one-on-one counseling sessions with doctors was shown to be significantly effective in improving adherence after six months [53]. A program based on a context-adapted chronic disease care model-based DSME/S, containing a 32 hours training workshop on primary diabetes care and DSME/S for the staff, one-on-one DSME sessions done at least once every 3 months and DSMS continued by health providers through home visits [71] showed improved adherence over 2 year's time. Collins-McNeil J [58] implemented a program of church-based culturally targeted DSME modules and culturally targeted written materials, videotapes and presentations. In particular, 'the medication taking' module, a one-on-one education session, assessed the knowledge about medications and intake and led to a significant improvement in adherence to medication during the 12-week DSME intervention.

Pharmacists have a crucial role in the management of diabetes in primary care, holding a unique position for educating patients on the importance of medication adherence and facilitating communication with health care professionals. A personal relationship between patient and pharmacist can be harnessed to improve diabetes care and outcomes [111]. Addressing lifestyle and

self-care behaviors can be a beneficial component of a pharmacist-provided extended diabetes care service: because of their strategic position, pharmacists see patients more often than their physicians, are able to provide drug recommendations and are skilled to identify adherence's problems [60].

A community pharmacist–delivered diabetes support program, consisting of a qualified community pharmacist who educated patients about medications, clinical goals, self-care activities and of follow-up visits has shown an improvement of patients' adherence [66].

Trained community pharmacists in diabetes care and the authors [73] found that behavior change strategies could contribute to significant health benefits for patients, including a reduced risk of non-adherence to medication through self-management support interventions. Interventions including discussing medications, clinical goals, and self-care activities with patients and recommending appropriate medication changes to physicians, gave a significant increasing in the number of days per week that patients engaged in a set of diet and diabetes self-care activities [60].

A pharmacist telephone-initiated adherence support intervention was evaluated in the study of Odegard PS [75]. Pharmacist using a guided standardized script could determine whether patients had exhausted the medication supply, identify and address adherence challenges, provide customized diabetes adherence education and encouragement, and develop a self-management action plan. The medication possession ratio at 12 months was significantly improved for the study group: this study adds evidence suggesting that small, focused interventions can have a positive, measurable impact on diabetes self-management, with minimal interruption in pharmacy workflow.

Socio-economical approaches

Four studies focused on socio-economical factors and particularly on the importance of social support.

Social support is a multifaceted experience that involves the perception that one is accepted, cared for, and provided with assistance or the realization of actual support received from another. There is evidence that higher levels of social support are associated with increased knowledge and treatment adherence, better glycemic control, and improved quality of life. It provides also a better acceptance of the diagnosis and emotional adjustment. Social support can come from informal sources (family, friends, and peers) and formal sources such as healthcare professionals and organizations [84].

Peer support is the support provided from a person who has similar characteristics as the target population and experience of a specific behavior or stressor that can be shared with others helping them in their self-management issues [112]. Only one RCT [63] focused on the peer support as tool for improving adherence was found. The study's participants were divided in a nurse care management group (with information session, scheduled telephone calls and/or face-to-face visit follow ups, and diabetes self-management educational materials) and in a reciprocal peer support group (group sessions in basic peer communication skills and pairing of participants who are stimulated to call each other at least once a week using an interactive voice response-facilitated telephone platform, DVD demonstrating peer communication skills and a diabetes self management workbook). No statistically significant difference in medication's intake between the two groups was seen at 6 months, but in the peer support group, there was an evident decrease of HbA1C and increase in starting insulin and diabetes-specific social support.

Culturally targeted diabetes interventions that include family members produce successful results: growing evidence shows that implementation of a family model may be beneficial for both the patient and the family members [113]. Not only the family, but also the friends have a vital importance to support self-management strategies [85]. A qualitative study with focus groups [72] was conducted to explore the relationship between participants' diabetes medication adherence and glycemic control and the perceptions of family's diabetes-specific supportive and non-supportive behaviors and self-care knowledge. Low adherence to medication was associated with perceived family non-supportive behaviors, but whenever diabetes-specific supportive behaviors were performed there was no improvement in adherence. In their systematic review, Strom [84] showed that social support has an consistent impact on behavioral outcomes: evidence suggests that higher levels of social support are associated with increased diabetes self-management and self-care behaviors. Participants of this cross-sectional study [85] confirmed the hypothesis that perceived family and social support is positively associated with diabetes self-management, including medicines' adherence.

Health care systems approaches

We found different types of interventions focusing on health care system factors, some trying to improve patient-provider communication, some using technology-based strategies for following up patients (including mobiles, telemedicine, telemonitoring and automated monitoring systems and medication aids), others focusing on health system organizational programs and finally on pharmacist-based programs.

Patient-provider communication is essential for effective diabetes' care: if patients play a central role in their disease management, they adhere better to the treatment and engage self-management regimen [77]. A study demonstrated that patient-perceived positive quality of relationship with the provider was strongly associated with adherence to medication. The quality of the relationship between patient and provider should be addressed when developing an intervention for improving adherence [80].

Starting from the psychological evidence and theory that non-adherence can be related to weak motivation (intentional non-adherence) and to forgetting (non-intentional non-adherence), a nurse-led consultation-based intervention was designed. The intervention aimed to strengthen patient motivation to take tablets regularly and support medicine taking through action-plans, reinforcing positive beliefs and facilitating problem-solving around negative beliefs. The intervention group showed a significant increase of its percentage of days of medicine's intake compared to the standard care group [62].

General communication and diabetes-specific communication, as distinct facets of patients' communication experience, were analyzed by Piette and colleagues. They found these two different way of communication to be predictors and having independent impacts on diabetes self-care practices. The study suggests that improving both general and diabetes-specific communication could be ideal, but improvement of self-care activities can be obtained just by improving one of the two dimensions [77]. Ciechanowski PS and colleagues [55] explored whether attachment theory [114] can be applied to the health care relationship: people with a dismissing attachment style develop more often a need to dependence and not self-sufficiency regarding their care, rate their patient-provider communication as poor and have a significantly greater number of interruptions in treatment.

The role of pharmacist is very important as discussed before. We found one RCT [57] that focused on pharmaceutical care (PC) model for improving adherence. The PC model is a responsible medicine provision method based on collaboration between the patient and the clinical pharmacist, who tries to resolve any drug-related problems. The application of this model resulted in a significant improvement in medication adherence. Duru OK [61] compared the adherence between patients who obtained medication refills at local pharmacies and patients who received them by mail, a common method used in the US. In the study, patients using the email refill were more likely to have good adherence, but patients with low socioeconomic status showed particularly low rates of mail-order pharmacy use. According to the author, these findings suggest the intriguing potential of larger organization-level interventions by promoting increased mail-order use as a novel, low-cost, and sustainable approach to improve medication adherence, but they need to be confirmed in a randomized clinical trial. Good results are shown by diabetes transitional care in the form of inpatient pharmacist discharge counseling that geared to improve outpatient adherence rate with medications after hospital discharge [82]. Another study [69] examined whether the presence of pharmacists in primary care clinics was associated with improved adherence, analyzing also the relationship between the degree of bottleneck in pharmacy services and clinic-level medication adherence. The adherence scores were not significantly better within clinics that have a pharmacist present and the perception of pharmacy services as a bottleneck was associated with lower clinic level medication adherence.

Technology can help in improving the adherence: mobile phone technologies, especially text messages, can promote behavior changes and improve clinical outcomes [74].

We found 11 studies that focused on the use of mobile phones, texts, telemedicine and electronic records were found. A telephonic intervention, consisting of regular calls from health educators, tailored on the participant and reported needs, and focused on diabetes medication adherence and lifestyle changes, showed a significant improvement in medication adherence [86]. In another interventional study [76] where patients received the usual care plus bi-weekly automated assessment through a telephone messaging computer program there was a reduction of problems in medicine's adherence. The assessment consisted in structured messages composed of statements and queries used to check the patients' health status, followed by optional "health tips" and self-care education calls by a nurse educator. Automated text messages with information, education, reminders and self-assessments, together with a remote nursing telephone-based coaching and assistance with refills, led to behavioral change and improvement of self-care, including medication taking, and of self-efficacy, social support, and health beliefs [74]. Also the participants of a text messaging pilot study reported by Dick [59] with customized daily medication reminders, reported high satisfaction and feasibility in this method. It helped them to avoid missing their medications, to regularly perform foot checks, and to avoid missing their appointments. Arora S [54] conducted a pilot trial in order to examine text-based mHealth (mobile health): it showed a dramatic improvement in medication's adherence, using three text messages daily for 3 weeks containing educational/motivational messages, medication reminders, healthy living challenges, diabetes trivia, and links to free diabetes management tools.

Electronic monitoring such as a container caps that record the date and time of each opening, is a widely recommended research method as it can provide detailed and precise data on the daily adherence on an extended period [115]. Despite that, its applicability in research can have limitations because it may influence adherence, reducing it if it disrupts patients' established routine

or increasing it because patients know that they are checked by researchers or because the container acts as a novel visual prompt [16]. Rosen MI and colleagues [78] conducted a randomized clinical trial, where a Medication Event Monitoring System (MEMS) was used to determine the proportion of prescribed doses taken within a predetermined 4-hours window. Patients who had less than 80% baseline adherence received a cue-dose training and improved significantly their adherence to metformin. Another study, using MEMS as dispensing method, showed high rates of adherence to hypoglycemic medication with an overall 99.1% of prescribed doses taken during the study period [87]. A 8-weeks RCT analyzed the utility of electronic containers that records the date and time of each opening: no significant improvement in adherence was shown in the intervention group [16].

Telemonitoring is also a possibility that seems to improve clinical outcomes and may be a useful tool to help enhance disease management and care of patients with diabetes [83]. In a prospective observational study where patients received 8-week education messages curriculum focusing on knowledge about the disease and reminders about target values, medications, and life style changes, many clinical outcomes improved significantly, but not the medication adherence. It is though interesting to note that the 78.5% of participants believe that telemonitoring improved their medication adherence and that 97.2% reported a great satisfaction in this experience. Telemedicine is for definition the application of telecommunications technology to connect providers and patients who are geographically separated, offering potential solutions to poor access to care [81]. The 'Telemedicine for Reach, Education, Access, and Treatment (TREAT)' model, a team care–based approach that uses telemedicine to provide a metropolitan-based endocrinologist's consultation and a diabetes educator in a rural setting, looks very promising showing a significant improvement in empowerment, self-care, reduction in diabetes distress and reported high levels of satisfaction, but not for medicine's adherence [81]. A RCT [64] evaluated iDecide, a personally tailored, interactive diabetes medication decision aid that provides information about risk factors, diabetes, medications combined with a session about setting goals and developing action plans. The participants reported bigger improvements in satisfaction with medication information, but no improvement in other outcomes, in particular in medicine's adherence.

The organization of the health system is one of the six core elements of the Chronic Care Model [49]. It aims at facilitating a move from a reactive to a proactive care delivery system design where planned visits are coordinated through a team-based approach. Redesigning the care process and expanding the role of teams to implement more intensive disease management strategies are the objectives. The Chronic Care Model survey [68] analyzed how the organizational characteristics of the clinic influence self-management behaviors of patients, including the medication's adherence. Six structural dimensions (organization support, community linkages, self-management support, decision support system, delivery system design, and clinical information systems) were linked with 4 self-management behaviors: self-management support was positively linked with adherence. An assessment tool for patients, the PACIC (the Patient assessment Chronic Illness care) was developed to test the implementation of CCM for what concerns the patient's centeredness and the self-care behaviors, but no improvement in adherence was seen [79]. A study by Hong JS and colleagues [65] demonstrated that an improvement in medication adherence could be achieved through an institution-level continuity of ambulatory care and a high frequency of ambulatory visits. Chen CC and colleagues [56] argue that improving the continuity of care for patients with type 2 diabetes results in higher medication adherence and better health care outcomes, in general.

Therapy-related approaches

Only two studies deepen the problems related with therapy and they do it with pharmacist-based interventions. In the first, a small but statistically significant improvement in self-reported medication adherence was found [67]. This was a clinical pharmacist intervention that consisted of optimizing pharmacotherapy with an individualized face-to-face objective-directed self-management education that emphasizes the importance of adherence to treatment recommendations,. In the second, a significant improvement in the self-reported non-adherence with an 9 months intervention was found when pharmacists contacted patients approximately monthly and where each patient received adherence support and a medication review as part of the intervention [70].

5 The diabetes care policy in Belgium

The current policy

The National plan: “Priority to chronic patients!” published in 2008 [116] aimed to improve chronic care and focused on the following domains:

- Information to the patient;
- Measures to improve the accessibility to care for chronic patients with improvement of the economical accessibility (right to higher reimbursement with statute OMNIO, reimbursement of specific medications transport, physiotherapy, etc..), of online application (MyCareNet), of administration accessibility;
- Integration of chronic patients in the society: financial support for the informal caregivers, help to go back to work, etc.
- Setting up an observatory for chronic diseases in which patient organizations and mutual health organisations (ziektefondsen) play a major role.

For type 2 diabetic patients, KCE (Federaal Kenniscentrum voor de Gezondheidszorg) gave recommendations for the organization of care [88]:

- chronic care to be provided by a multidisciplinary team at the primary care level (in collaboration with circles, local discussion platforms or diabetes networks)
- central role for GP’s (general practitioner) in care coordination
- the new crucial role of diabetes educators (for activities like healthy life style advice and education to use of insulin injections) and hospital-based educators
- clear role description for specialized physicians (i.e. coaching of other health care providers and treating complex clinical situations)
- proactive, patient-focused and integrated care with patient education, follow-up and secondary/tertiary prevention of complications

Three possibilities are given for helping in the follow up [51]:

1. "Diabetes Conventions”: agreements for functional rehabilitation in order to finance the holistic care of chronic patients thanks a multidisciplinary team. They cover the costs of non medical professionals (e.g. social workers)
2. Diabetes passport: multidisciplinary consultations with the aim of promoting the coordination and care centered on the patient, with specific care plan

3. Care trajectory (zorgtraject/trajet de soins): special trajectories for the treatment and following up, developed to enhance the collaboration in care between the patient, the GP, the specialist and other caregivers. It has the form of a contract of 4 years, based on evidence-based clinical practice, between the GP, playing the coordination role, the patient, having an active role in the management of disease, and the specialist. It provides financial incentives to the physicians and to the patient (complete reimbursement of consultations, access to self management material, education sessions e.g. on dietetics, etc.).

Recently, the Health Ministry launched a new 'Care model' (zorgmodel) for uniforming the diabetes care at primary level [117]: it is a protocol for GPs for following up the patient and for stimulating them to get in contact with the LMN. It will take the place of the "diabetes passport" in 2 years time.

Another resource to enhance the collaboration between all caregivers (especially between the GP and the specialists) and to optimize the quality of care are the local multidisciplinary networks (LMN). They implement operational plans to gather information about the caregivers and the local organizations, to support local initiatives, to inform caregivers and patients, to facilitate the communication between caregivers and to evaluate the local network.

The guidelines [51] describe very well the tasks of the GP: screening of the patient, periodic follow ups, coordination of care with the other care providers, evidence based therapy, adequate referral to the specialists, management of acute complications, prevention plans, compilation of electronic medical dossier, implementation of personalized care plans based on 'shared decision making'. The GP has indeed a central role in coordinating care for type 2 diabetic patients, while specialists are mainly involved in case of complications.

Applying insights from the scoping review to the Belgian policy

The Belgian model for diabetes care takes inspiration from the CCM: it calls for a proactive approach with a high quality interaction between care providers, organized in teams with different specialists, and patients who have a central role in their care and with whom the decisions have to be shared, accordingly with the local care context and possibilities [51].

We analyzed the current policy for care for diabetes patients in Belgium using the 5 groups of factors influencing the adherence.

- socio-economical factors
  - Interventions to improve financial accessibility: OMIO statuut (reduced care costs depending on incomes), derdebetalersregeling (partial cover of the out-of-pocket costs from patients) [118], full cover of care costs for patients having a care traject or a "diabetes convention"
  - presence of peer organizations (Diabetes Liga, etc..)
- health care systems factors approaches
  - Diabetes passport, care trajectory, diabetes convention
  - Team-based care with multisciplinary teams with the aim of improving communication between the different care actors: LMN
  - continuity between primary and secondary care
  - implementation of electronic medical dossier
  - quality checks
- therapy-related factors approaches

- Open accessibility to EBM guidelines (Domus Medica, CEBAM, LMN)
- patient-related factors approaches
  - Patient education with educator:
  - 'Shared decision making' : empowerment
- health condition-related factors
  - EBM care
  - prevention of complications through dedicated follow ups with GP, specialists and other care provider (nephrologist, oculist, neurologist, dietist, physiotherapist, etc..)
  - appropriate referral to secondary care.

While its seems that the policy takes into account key features of good practice in diabetes care policies, at this moment, it is not clear in how far these guidelines are effectively implemented. Case-finding of diabetes is in the hands of the GP who is to propose the screening (basing also on complaints and a risk factor evaluation). Even if the LMN and diabetes educators are available (LMN), the diffusion and the use of them is very different in the different parts of Belgium. Furthermore, there are currently no structured quality checks to assess the rationality of prescription and the regularity of the follow ups. More systematic monitoring of policy implementation and of its quality and effectiveness are needed.

6 Discussion

We found only 36 studies that could be included in our review: a large amount of literature has been produced about the correlation between clinical outcomes and interventional strategies, but only few focused specifically on medication adherence as outcome. Further, we found that no study focused explicitly on the relationship between patient centered care and medication's adherence, but some insight are given in almost all the papers. Despite the limitations that preclude generalization, we found a number of interesting elements that should be further researched and good results in most of the studies.

Almost none of the studies tackled the problem of patient centeredness directly, but they developed strategies for improving self-care behaviors [53, 58, 60, 66, 71, 73, 75, 111], for improving the patient-care provider communication with intervention dedicated to this [55, 62, 77, 80] or with the help of the pharmacist [57,60, 82] and for tackling the organizational problems [56, 65, 68]. In two studies [79, 83], even if there was no improving in the outcomes, patients reported a high level of satisfaction for what concerns patient centeredness.

Most of the studies, especially the ones focusing on interventions for improving patient-related factors [53, 58, 60, 66, 71, 73, 75] and socio-economical factors [63, 72, 84, 85] as influencers of the adherence, tried to improve the self-care behaviours and health care organization, using clinical information systems to track the patients and the medication use.

We found that all the studies tackled a different group of factors influencing adherence as presented in the WHO framework [7] and we analyzed the papers accordingly as presented in the"Results". Most studies focused on health care system-related factors, while no studies was found tackling health condition-related factors.

The studies focusing on socio-economical factors presented approaches for improving the social support to the patient. The only study on peer support [63] did not show any statistically significant difference in the peer support group, even if the WHO underlines its centrality [112]. The studies about family and friends support [72, 84, 85, 113] showed a beneficial influence on adherence. While the results are not conclusive, it seems that social/family support affects adults' performance of diabetes self-care behaviors and developing effective family-based interventions needs to be further explored [72].

Patient-related approaches aim to improve the self-management and self-efficacy of the patient, thanks DSME/S strategies and pharmacist-based programs. We found that educational programs based on DSME/S are effective in improving self-management, clinical outcomes, health status, and quality of life [53, 58, 71] independently from the study design, as also indicated from the American Diabetes Association [49].

Interventions based on the relationship between pharmacists and patients, particularly community pharmacist–delivered diabetes support approaches [60, 66, 73] and pharmacist telephone-initiated adherence support intervention [75] confirmed the good potentiality of an approach based on pharmacist.

The role of the pharmacist is central also in the two studies tackling therapy related factors [67, 70] where he is the one deepening the problems related with therapy, but only Krass [70] showed a significant improvement in the self-reported non-adherence as the pharmacist pro-actively contacts the patients.

Interventions focusing on health care system factors were the majority and they tackled the problem of lack of adherence in different ways. Few of them [55, 62, 77, 80] focused on patient-provider communication as essential for effective diabetes' care and showed that a good relationship with care provider strengthens patient motivation to take tablets and has independent impacts on diabetes self-care practices. Also here, the pharmacist holds a strategic position, addressing lifestyle and self-care behaviors and being able to provide drug recommendations and to identify adherence's problems [60]. Pharmaceutical care (PC) [57] and diabetes transitional care [82] seem to improve adherence while the presence of pharmacists in primary care clinics [69] didn't make any difference. Mail-order pharmacy strategy was also studied and the author [61] suggests the intriguing potential of larger organization-level interventions.

Technology-based strategies including mobiles, telemedicine, telemonitoring and automated monitoring systems and medication aids are also broadly studied. The use of mobile phone technologies can promote behavior changes and improve clinical outcomes [74], as also seen in some of the studies we found [76, 86] and text messages strategies [54, 59 74].

Telemedicine strategy [81], electronic monitoring [16], interactive diabetes medication decision aid [64] and telemonitoring [83] strategies seem not really interesting while Medication Event Monitoring System (MEMS) strategies looks more promising [78, 87], but it has to be studied more.

Strategies focusing on improving the organization of the health system seem very promising in improving adherence, especially when tackling the continuity of care (65; 56) and self-management support [68].

Study limitations

This study has a number of limitations. First, our scoping review demonstrated that there is little literature available on adherence to treatment in patients with DM2 and that the majority of available studies focus on improving clinical outcomes through an improved treatment adherence [32]. Second, for some interventions, for example for peer support interventions, very few studies were conducted, and as a result, we cannot draw conclusions. Third, different evaluation methods have being used and this does not permit a comparison of adherence rates across studies [119]. A major issue is, indeed, the absence of a gold standard for measuring medication adherence in patients with diabetes (14). Fourth, the quality of some of the studies we found was not very good: some of them had a small and non randomized sample, some were conducted on minorities with particular believes and facing disparities, and as a consequence, the results cannot be extrapolated to a wider population. Fifth, most of the studies were short-term studies and none of them analyzed the strategy's feasibility from a health systems perspective. Finally, patient centered care was not explicitly analyzed, even if some insight were given as described before.

7 Conclusion

Adherence to medication affects the clinical outcomes of diabetes, but many factors influence medication adherence of diabetes type 2 patients.

We found that interventions using educational strategies, patient-provider communication interventions, mobile phone and text technologies, Medication Event Monitoring System, continuity of care and self-management support strategies and some of pharmacist-provided interventions gave good results concerning improving medication adherence.

However, much of the evidence is too weak to allow generalization of findings or scaling up interventions. It seems particularly important to carry out more research on the role of social support, especially for what concerns peer support. Further, the definition of a gold standard for measuring adherence is needed for allowing comparison between the different approaches. Many methods are widely used and validated, but a systemic review is needed. In short, educational, relational and technological strategies for improving adherence seem promising, however, further studies are needed in order to find feasible and cost-effective strategies for improving adherence. Most likely, interventions using mixed methods may be needed as the adherence to treatment in influenced by a number of factors and further research is needed in this field.

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Appendix

Table 3. Secondary outcomes. (BG blood glucose, WHR waisthip ratio, HbA1c glycosylated haemoglobin, BP blood pressure, RPS reciprocal diabetes peer support program, NCM nurse care management, FSS family/friend social support , F F-test, df degrees of freedom, SF-12 study health survey questionnaire (SF-12),PACIC the Patient assessment Chronic Illness care, COC Continuity of Care, OR odds ratio, CI confidence interval)

Reference	Secondary outcomes	
	Improvements	No changes
Al Hayek AA et al, 2013 [53]	Significant improvements in: patients' dietary plan (P0.0001), physical exercise (P0.0001), BG self-monitoring (P0.0001), HbA1c (P0.04), depression (P0.03).	/
Arora S et al, 2012 [54]	Reported improvement in eating fruits/vegetables daily (56.5% of the week before the intervention versus 83% after), in exercising (43.5% vs 74%) and performing foot checks (74% vs 85%). Self-efficacy, measured by the Diabetes Empowerment Scale-Short Form, improved from 3.9 to 4.2.	/
Ciechanowski PS et al., 2001 [55]	Significant effect on Hb1C level of attachment style (F=3.02, df=3, 292, P0.03) and interaction between attachment category and patient-rated quality of provider communication(F=2.74, df=3, 292, P<0.05). Communication quality in the dismissing attachment perceived poor communication is correlated with higher HbA1C (mean=8.50%, SD=1.55%) compared with good one (mean=7.49%, SD=1.33%) (F=4.32, df=1, 76, p<0.05)	Communication quality alone did not show a significant main effect (F=2.69, df=1, 294, p<0.11) on HbA1C
Chen CC et al, 2013 [56]	Association between COC and health care outcomes	/
Chung WW et al., 2014 [57]	Statistically significant differences between the control and intervention groups after the provision of PC in fasting blood sugar (9.0 versus 7.2 mmol/L [P<0.001]) and HbA1C (9.1% versus 8.0% [P<0.001])	/
Collins-McNeil J et al, 2012 [58]	Increase in healthy eating (P0.009), foot care adherence (P0.003). Clinically significant effect on systolic blood pressure, blood lipids, physical activity, and waist circumference.	Not significant improvements in depressive symptom scores and HbA1c
Dick JJ et al., 2011 [59]	Significant improvement in patient confidence in diabetes self-management during and 1 month follow up (P0.002, P0.008) and in reported being more able to meet the challenge of controlling their diabetes during (P0.001) and at 1-month follow-up (P0.006).	/
Doucette WR et al, 2009 [60]	In the intervention group, significantly increasing of number of days per week of engagement in diet and diabetes self-care activities (1.25 and 0.73 more days/wk, respectively). Some improvements in A1C (P0.27) and LDL-C (P0.32). Mean decrease in LDL-C was 12.0 mg/dL for the control group (P0.013) and 19.6 mg/dL for the intervention group (P0.003). Significantly increased reported engagement in healthy self-care activities in the intervention group.	The mean 12-month changes for A1C, LDL-C, and blood pressure were not significantly different between the 2 study groups. The mean 12-month changes for HbA1C, LDL-C and blood pressure were not significantly different between the study groups. Mean increase in systolic blood pressure of 4.5 mmHg for the control group (P0.254) and 7.1 mmHg for the treatment group (P 0.002).
Duru OK et al., 2010 [61]	/	/
Farmer A et al., 2012 [62]	/	No significant differences between groups for SF-12, diabetes treatment satisfaction, HbA1c, satisfaction with

		communication with the nurse, or hypoglycaemia.
Heisler M et al., 2010 [63]	HbA_{1c} level decreased from 8.02% to 7.73% (change, P−0.29%) in the RPS group and increased from 7.93% to 8.22% (change, 0.29%) in the NCM group. More insulin starts among RPS than NCM participants (8 vs. 1, P0.02), and more intensification events on average among patients on oral anti-hyperglycemic medications (1.41 vs. 1.00, P0.01). RPS participants reported greater increases in diabetes-specific social support at six-months (+11.4 vs. +4.5, p=0.01)	No differences between groups at follow-up in number of other medication intensification events, self-reported medication adherence, or diabetes-specific quality of life
Heisler M et al., 2014 [64]	Significant improvements in decisional conflict about medications, medicines' knowledge, satisfaction with clarity and helpfulness of the information about medications(between-group p=0.028, p=0.007, respectively), diabetes care self-efficacy, HbA1c, diabetes distress, (14.1, within-group P<.001).	/
Hong JS et al, 2014[65]	/	/
Jahangard-Rafsanjani Z et al., 2015 [66]	Higher HbA1C reduction in the intervention group (1.0% ± 1.5% vs 0.5% ± 1.5%). Self-care activity (general diet, BG monitoring and foot care) improved in the intervention group and significant improvement in BMI.	No significant difference in HbA1C between study groups at the end of the trial
Jarab AS et al., 2012[67]	Patients in the intervention group had a mean reduction of 0.8% in HA1c (versus a mean increase of 0.1% from baseline in the usual care group [P0.019]), significant improvements in fasting blood glucose (-2.3 mmol/L [-5.7 to 1.1] vs. +0.9 [-0.8 to 2.8]); systolic BP (-5.8 mmHg [-8.2 to -3.2] vs. +1.1 [0.1 to 2.4]); diastolic BP (-7.1 mmHg [-9.8 to -4.2] vs. +1.8 [-1.1 to 4.8]); total cholesterol (-0.7 mmol/L [-1.7 to 0.3] vs +0.1 [-3.1 to 3.8]); LDL-C (-0.6 mmol/L [-1.7 to 0.6] vs. 0.0 [-0.4 to 0.4]); serum triglycerides (-0.5 mmol/L [-2.8 to 2.1] vs. +0.2 [-0.7 to 1.1]) and self-care activities.	No significant changes in HDL-C and BMI.
Kaissi AA et al, 2009 [68]	Decision support system was positively associated with all 4 self-management behaviors. All the dimensions were positively associated with only exercise.	clinical information system was negatively associated with all 4 self-management behaviors.
Kocarnik BM et al, 2012 [69]	/	/
Krass I et al, 2005 [70]	Mean significant decrease of prescribed medications (from 8.2+/-3.0 to 7.7+/-2.7) in the intervention group while no reduction among the control one (7.6+/-2.4 and 7.3+/-2.4). The overall prevalence of changes to the regimen significantly higher in the intervention group (51%) compared with controls (40%).	/
Ku GM et al., 2014 [71]	Significant increase in knowledge (P<0.001), positive attitude (P0.013), perceived ability to control BG (P0.004), 'perceived ability to adhere to diet and exercise'(P0.022), the 'fear of diabetes' (P<0.001). Significant decrease in the HbA1c (P<0.001), waist circumference (P0.007), WHR (P<0.001) and the 'perceived support received from family and friends'(p<0.001). Significant improvement in adherence in exercise (p<0.001), but a significant decrease in those adherent to diet (p<0.001).	/
Mayberry LS et al, 2012[72]	More knowledgeable family about diabetes was associated with more diabetes-specific supportive behaviors, but was not associated less nonsupportive behaviors. Perceiving one's family members with more supportive behaviors was also associated with perceiving perform of more non-	Nonsupportive family behaviors lead to higher A1C values (rho=0.29,P0.03).

	supportive behaviors.	
Mitchell B et al, 2011 [73]	Improved glycaemic control and patients reported improvements in their knowledge about diabetes self-management (over 90%).	/
Nundy S et al., 2014 [74]	Improvements in 5 of 6 domains of self-care in 1 or more measures of self-efficacy, social support, and health beliefs. Qualitatively improvement in knowledge, attitudes, and ownership thanks the program.	
Odegard PS et al, 2012 [75]	/	/
Piette JD et al, 2000 [76]	Intervention patients reported more frequent glucose monitoring (P -0.03), foot inspection (P -0.03), weight monitoring (P -0.03), better glycemic control (P = 0.005) and fewer diabetic symptoms (P <0.0001). HbA1C 0.3% lower in the intervention group (P 0.1) and 0.6% within the normal range (P0.04); BG 41 mg/dL lower (P0.002).	/
Piette JD et al., 2003 [77]	Strong association between general and diabetes-specific communication and patients' probability of daily exercise (12% lowest possible to 45% highest possible), dietary behavior (from 3% to 28%) and daily foot checks (from 63% to 91%)	/
Rosen MI et al., 2004 [78]	/	No differences in HbA1C
Schmittdiel J et al, 2008 [79]	The PACIC significantly associated with the use of at least one of the self-management services (OR = 1.40, 95%CI = 1.30, 1.53), greater engagement in all self-management behaviors (ORs ranged from 1.21 to 1.41), higher rating of health care (OR=2.36, 95%CI = 2.18, 2.56), and higher quality of life (OR=1.20, 1.13, 1.27)	/
Schunk M et al., 2015 [80]	Higher number of medical examinations and advice associated with: self-monitoring of BP (OR 1.18; CI: 1.03, 1.35), feet (OR 1.24; CI: 1.09, 1.42), and BG (OR 1.23; CI: 1.07, 1.42), difficulty in diet (OR0.82;CI0.70;0.95). Participation in diabetes education associated with selfmonitoring feet (OR 1.30; CI 1.06, 1.60) and BG (OR 1.50; CI 1.18, 1.90). Patient-perceived positive quality of relationship with the physician strongly associated with the mental component score (mean score difference 2.04 CI: 0.95, 3.13), with adherence to diet (OR 1.33; CI: 1.04, 1.71) and feet care (OR 1.33; CI: 1.02; 1.73), to self-monitoring of weight (OR1.26,CI:1.00;1.58). Multiprofessional care: positively associated with self-monitoring of BG (OR 1.63, CI: 1.02, 2.62).	/
Siminerio L et al., 2014 [81]	Significant improvement in empowerment (Diabetes Empowerment score 3.8 vs 4.5, P< .01), self-care (adherence to diet and monitoring up to 94.3%), and reduction in diabetes emotional distress (34.8 vs 20.9%, P< 0.01). Reported high levels of satisfaction (median score of 5.8 on a 6-point scale)	/
Shah M el al, 2013 [82]	Better rate of follow-up visits in the intervention group (60.5% vs 43.9%; P0.01) and reduction in HbA1C (-1.97% vs +0.114%; P0.003).	/
Shane-McWhorter L et al., 2014 [83]	Mean HbA1C decreased from 9.73% at baseline to 7.81% at the end of the program (P<0.0001). Knowledge of diabetes increased significantly (P<0.001). Patient engagement	/

	improved, but not significantly (P0.07).	
Strom JL et al, 2012 [84]	Improved clinical outcomes, decreased mortality, and increased mental stability. All the studies, except one show correlation between increased diabetes self-management and adoption of nutritional and active lifestyles and increased social support.	/
Sutton S et al., 2014 [16]	/	Non-significantly lower HbA1c (HbA1c (mmol/mol), −1.02 [−2.73 to 0.71,p=0.25])
Vaccaro JA et al., 2014 [85]	/	FSS not directly associated improvement in HbA1C
Walker EA et al., 2011 [86]	The telephone group had mean decline in HbA1C (0.23+/-0.11%) over 1 year compared with a rise for the print group (0.13+/-0.13%; P0.04), with a difference of A1C of 0.40% (95% CI 0.10 – 0.70,P0.009). Significant improvement in number of days per week following a healthy eating plan and doing 30 min of exercise in the telephone intervention group.	/
White AJ et al., 2012 [87]	/	/