It takes two: the synergistic role of patients and healthcare providers in reducing drug-related problems

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It takes two

The synergistic role of patients and healthcare providers in reducing drug-related problems

Victor Huiskes

Concept omslag

Op de omslag ziet u een patiëntreis van een patiënt die geneesmiddelen gebruikt. Tijdens de patiëntreis komt een patiënt allerlei geneesmiddel gerelateerde *problemen* tegen. De patiënt heeft tijdens deze patiëntreis interactie met zorgverleners, waarin zij beiden de verantwoordelijkheid hebben om deze problemen te *voorkomen*, of tijdig te identificeren en te adresseren, teneinde deze *problemen op te lossen*. De patiënt heeft hiervoor *kennis*, *vaardigheden* en *daadkracht* nodig. Zorgverleners *begeleiden* patiënten daar waar nodig en moeten daarbij zorgen voor adequate *communicatie*. Zorgverleners dienen oog te hebben voor de autonomie van patiënten, patiënten *vertrouwen* te geven en aan te moedigen om deel te nemen in interacties. Tijdens deze interacties dienen zorgverleners in te gaan op de geneesmiddel gerelateerde *problemen* die de patiënt noemt en op de behoeften, voorkeuren en doelen van de patiënten. Op deze manier kunnen patiënten en zorgverleners vanuit synergie een effectieve en veilige behandeling met geneesmiddelen bereiken. De patiëntreis is uitgebeeld aan de hand van de symbolische betekenis van bloemen. Daarin komen inhoudelijke thema's in dit proefschrift en mijn liefde voor de natuur bij elkaar. Voor de symbolische betekenis van de bloemen heb ik gebruik gemaakt van de volgende bronnen: Floriografie, Wat bloemen ons vertellen, S. Coulthard, 2021; Planten en hun naam, Botanisch lexicon voor de Lage Landen, H. Kleijn, 1980; Folklore and Symbolism of Flowers, Plants and Trees, J. Lehner & E. Lehner, 1960.

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Chapter 1

General introduction

This thesis explores the synergistic role that patients and healthcare providers (HCPs) can play in improving effective and safe drug treatment. Although it is without doubt that medication use often leads to better health outcomes, this general introduction will re-emphasize that medication use might also result in negative effects (drug-related problems (DRPs)), which can be reduced with pharmaceutical care. As the medication process encompasses (1) prescribing by the physician, (2) dispensing by the pharmacist and (3) medication use by the patient, pharmaceutical care should incorporate interventions on the level of the patient, the HCP and the interactions between them. These topics and how this results in the chapters of this thesis are elaborated in this general introduction.

Drug treatment

Prescribing medication is one of the most commonly applied medical interventions in healthcare aiming to prevent, treat or manage many illnesses or conditions[1]. Medications are involved in 80 percent of all medical treatments[2]. In the Netherlands over 11 million people (65% of the population) use at least one prescribed drug and 25% of these persons uses 6 or more prescribed drugs[3,4].

Although medications usually improve a patient's quality and/or duration of life, they also have the potential to cause negative health outcomes, such as increased morbidity and mortality and reduced quality of life[5-7].

Drug-related problems

All the problems that might lead to negative outcomes of medication are called drug-related problems (DRPs)[8,9]. DRPs are defined as all events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes and includes extrinsic DRPs, that are caused by a medication error (ME) as well as intrinsic DRPs that are not caused by an error, but caused by an adverse drug reaction (ADR)[8-10]. Examples of MEs are erratic prescriptions, mistakes made during dispensing of the drug or inadequate medication use by the patient, see table 1 [8,10].

When a DRP results in clinical consequences, it is called an adverse drug event (ADE). These ADEs represent a major source of morbidity (and sometimes mortality) globally[6,7]. This is also expressed by the fact that ADEs cause a substantial part of the unplanned hospital admissions[1,11-13]. In addition, ADEs are associated with higher healthcare costs[2,13,14].

DRPs occur frequently: several studies have demonstrated that the number of actual DRPs identified per patient ranges from one to six[15-18]. Noteworthy, a substantial part of the DRPs in ambulatory care are deemed to be preventable (up to 38%)[19]. Also hospital admissions due to drug-related problems are often considered to be preventable (median preventability rate of 76% (IQR 61-87%))[20]. Patients with polypharmacy (use of ≥5 drugs), comorbidity and the use of specific drugs have an increased risk of DRPs[11,12,19,21-24]. Consequently, the risk of DRPs is greater in settings where patients with these risk factors are treated, such as geriatric settings (elderly with comorbidity and polypharmacy) and for example outpatient cardiology departments (high risk medication, polypharmacy)[25-27].

In summary, DRPs are common, often preventable and can have significant impact on health outcomes. Consequently interventions are needed to reduce and prevent DRPs[6].

Table 1. Causes for drug-related problems as described by the Pharmaceutical Care Network Europe[10]

	Primary Domain	Code V8.01	Cause
Prescribing	**1. Drug selection** The cause of the (potential) DRP is related to the selection of the drug	C1.1	Inappropriate drug according to guidelines/formulary
		C1.2	Inappropriate drug (within guidelines but otherwise contra-indicated)
		C1.3	No indication for drug
		C1.4	Inappropriate combination of drugs or drugs and herbal medication
		C1.5	Inappropriate duplication of therapeutic group or active ingredient
		C1.6	No drug treatment in spite of existing indication
		C1.7	Too many drugs prescribed for indication
	2. Drug form The cause of the DRP is related to the selection of the drug form	C2.1	Inappropriate drug form (for this patient)
	3. Dose selection The cause of the DRP is related to the selection of the dose or dosage	C3.1	Drug dose too low
		C3.2	Drug dose too high
		C3.3	Dosage regimen not frequent enough
		C3.4	Dosage regimen too frequent
		C3.5	Dose timing instructions wrong, unclear or missing
	4. Treatment duration The cause of the DRP is related to the duration of treatment	C4.1	Duration of treatment too short
		C4.2	Duration of treatment too long
Disp	**5. Dispensing** The cause of the DRP is related to the logistics of prescribing and dispensing process	C5.1	Prescribed drug not available
		C5.2	Necessary information not provided
		C5.3	Wrong drug, strength or dosage advised (OTC)
		C5.4	Wrong drug or strength dispended
Use	**6. Drug use proces** The cause of the DRP is related to the way the patient gets the drug administered by a health professional or care despite proper dosage instructions (on the label)	C6.1	Inappropriate timing of administration and/or dosing intervals
		C6.2	Drug under-administered
		C6.3	Drug over-administered
		C6.4	Drug not administered at all
		C6.5	Wrong drug administered
		C6.6	Drug administered via wrong route
	7. Patient related The cause of the DRP is related to the patient and his behaviour (intentional or non intentional)	C7.1	Patient uses/takes less drug than prescribed or does not take the drug at all
		C7.2	Patient uses/takes more drug than prescribed
		C7.3	Patient abuses drug (unregulated overuse)
		C7.4	Patient uses unnecessary drug
		C7.5	Patient takes food that interacts
		C7.6	Patient stores drug inappropriately
		C7.7	Inappropriate timing or dosing intervals
		C7.8	Patient administers/uses the drug in a wrong way
		C7.9	Patient unable to use drug/form as directed
	8. Other	C8.1	No or inappropriate outcome monitoring (incl. TDM)
		C8.2	Other cause; specify
		C8.3	No obvious cause

Pharmaceutical care to solve and prevent DRPs

High quality pharmaceutical care can help to reduce preventable DRPs[1,2,6]. Pharmaceutical care is defined as the responsible provision of drug therapy for the purpose of achieving outcomes that improve a patient's quality of life, by ensuring that each medication is appropriate for the patient, effective for the medical condition, safe given the comorbidities and other medications being taken, and able to be taken by the patient as intended[2,28,29]. Furthermore, high quality pharmaceutical care will have a positive impact on the cost-effectiveness of health care systems and resources[30].

Pharmaceutical care targeting patients and HCPs

HCP(s) (e.g. physicians and pharmacy staff) and patients are important actors involved in the process of pharmaceutical care[8,10,12]. As such both HCPs and patients are, each in their own way, important targets for preventing and decreasing drug-related problems and maximizing the effectiveness of drug treatment (see figure 1)[1,2,6,22,28,31]. The importance of targeting both HCPs and patients is underlined by the chronic care model (CCM), an organizing framework for improving chronic illness care at a population level that can be used for improving care at an individual level too. The model describes that improvement in care requires an approach that incorporates patient, HCP and system level interventions. In the context of this thesis the part of the framework focusing on the patient and HCP as target for intervention is used, in which the CCM strives for more empowerment of the patient, who is held responsible for his/her own health and takes an active role in his/her care process[32]. In the chronic care model this is called the "*informed activated patient*". The CCM no longer sees the role of HCPs as limited to guiding the medical aspects, but also to include, for example, support in the changes that (the treatment of) chronic illness cause in the daily life of the patient[32]. In the chronic care model this is called a "*prepared, proactive practice team*". Finally, high quality interactions between HCPs and patients, in the chronic care model referred to as "*productive interactions*" are needed, as involvement of the patient and *productive patient-HCP interactions* are associated with better health outcomes, such as health status, self-management, adherence and satisfaction with care[33]. The importance of productive patient-HCP interactions are described in several guidelines about optimizing medication safety. These guidelines also recommend specific interventions, as, for example, systematic involvement of patients in interventions like medication review, making use of patient-held medication records and making use of patient resource materials to improve patients' understanding on medicines so they are able to make decisions on prevention of problems[1,22,34-36]. Productive patient-HCP interactions minimize drug-related problems and maximize the effectiveness of drug treatment, as incidents involving medication may also be caused by for example interruptions, poor instruction and poor communication[1,2,6,37]. Suboptimal communication between HCPs and patients increases the incidence of DRPs and negatively influences the management of DRPs[37,38]. Patients do not always report medication-related symptoms and/or adverse events to physicians, and physicians do not always respond when patients actually report them[39,40]. But also HCPs contribute to the "conspiracy of silence" between HCPs and patients[41]. Research has found that adverse events, patients' experiences with their drug use and adherence are often not explored by HCPs during clinical visits[41,42]. Thus, patient-HCP interactions about DRPs with patients should be improved[1,2,6,22,34].

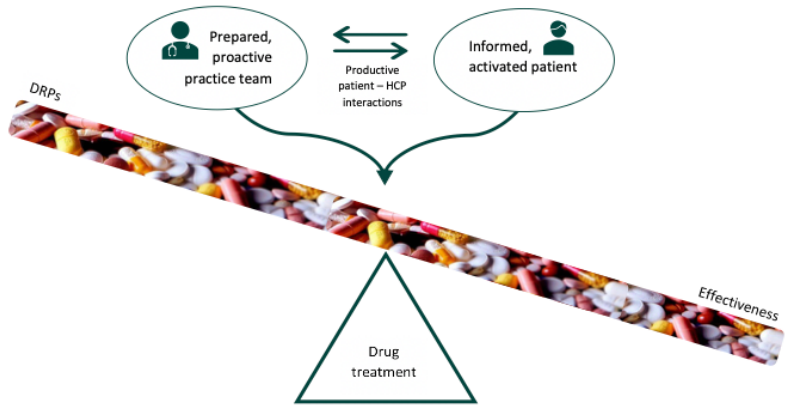

Figure 1. Pharmaceutical care to optimize the balance between effectiveness and DRPs when conditions are treated with medication.

In order to prevent and decrease drug-related problems and maximize the effectiveness of drug treatment, pharmaceutical care with 1) informed, activated patients 2) prepared, proactive practice teams, and 3) productive patient-HCP interactions is needed. Adapted from Wagner[43]

The role of HCPs and patients in medication review and in improving medication adherence as important pharmaceutical care activities

As described above both patients and HCPs are major actors (and the productive interaction between them plays an important role) in enabling pharmaceutical care. Therefore, their roles and their interaction in pharmaceutical care will be further elaborated in this thesis. In order to create focus, this thesis will mainly study two key pharmaceutical care activities: medication review and adherence support[1,2,6,22,34].
Therefore this thesis primarily concentrates on
1) medication review and adherence support as important pharmaceutical care activities
2) the role of informed activated patients; prepared, proactive practice teams and productive patient-HCP interactions in these pharmaceutical care activities.

Medication review

Medication review is defined as "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting DRPs and recommending interventions"[44]. In order to reduce the number of preventable DRPs and their consequences, medication review is often recommended, incorporated in several guidelines and also frequently reimbursed by health care insurers in various countries[1,34,45-47].

Although several systematic reviews and meta-analyses already examined the effectiveness of medication review, *the effectiveness on clinical, drug-related and economic outcomes have not been unambiguously proven*[48-57]. Most trials in these systematic reviews assessed the effect of medication review as part of long-term multi-faceted pharmaceutical care interventions, consisting of for instance transitional care, adherence counseling and education of patients and healthcare providers, besides medication review. Therefore, insight into the effectiveness of how medication review is operationalized in practice, as a single, short-term intervention is required.

Furthermore, in medication review studies *patients are not always involved in medication reviews, while research on medication review showed that DRPs that were identified during patient interviews were considered clinically more relevant than DRPs based on medical records only*[58]. The need of the involvement of patients during medication reviews is also endorsed by guidelines on medication review[1,34]. Therefore it's prudent to investigate whether medication reviews with *informed activated patients* and *productive patient-HCP interactions* are effective in reducing the number of DRPs.

Potential targets to improve medication adherence

Adherence to medication is defined as the extent to which the patient's behaviour in terms of actually taking medication corresponds with agreed recommendations from the healthcare practitioner[59,60]. Adherence has three phases, the initiation phase (in which the drug treatment is started by a patient taking the first dose), the implementation phase (the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken) and the discontinuation phase (the end of drug therapy, when the next dose to be taken is omitted and no more doses are taken thereafter)[61]. Non-adherence is a major drug-related problem, particularly in patients with multiple chronic conditions who are treated with a great number of medications (polypharmacy). Even though it is difficult to express non-adherence in numbers (e.g. because many different outcome measures are used), non-adherence rates to long-term therapy for chronic illnesses as reported by the WHO are around at least 50%[59]. Non-adherence may be the result of practical barriers (e.g. capacity, resources and opportunities), which leads to unintentional non-adherence (unplanned non-adherent behaviour)[62,63]. Non-adherence may also be the result of perceptual barriers, (e.g. beliefs and emotions)[62-65]. Patients with perceptual barriers seem to weigh their beliefs about the necessity of medication and concerns about the potential adverse effects of medication, leading to intentional non-adherence (a patient's active decision to not adhere to the prescribed treatment)[64-67]. These beliefs of patients have a direct association with adherence to medication for a wide range of medicines for chronic conditions[64]. Intentional and unintentional non-adherence may exist simultaneously within one patient.

Adherence supporting interventions such as (cognitive) education, behavioural counseling and electronically monitored adherence feedback have been proven to be partly effective[66,68]. These studies mainly focused on "patient-related factors". Although some studies examined interventions that target relevant factors related to the HCPs (prepared, proactive practice team) and productive patient-HCP interactions, more insight in these factors is necessary, as these can impact adherence as well[59]. Besides this, influencing pharmaceutical care on HCP level may affect the adherence of several patients, which makes interventions on this level potentially more impactful than interventions on patient level only.

Perceptual barriers (e.g. beliefs) of patients may result in non-adherence, but also the beliefs of HCPs may play a role[69-71]. Previous research has shown that the beliefs of the physician about a particular treatment may influence the patient's choice to undergo and the patient's adherence to that treatment, *so HCPs' beliefs about medication may be an interesting target to enhance productive patient-HCP interactions in order to improve the adherence of patients.*

Furthermore, patients who experience a higher quality of care and/or a higher degree of shared decision making have more knowledge of their illness, are more actively involved in

their own treatment, are more confident in their communication with healthcare providers and have higher adherence rates[72,73]. This implicates that *higher quality of care (e.g. the extent of adherence supporting activities) performed by a HCP (prepared proactive practice team), might positively influence medication adherence, and could be an interesting target for interventions to improve adherence of patients.*

Aim of this thesis

Overall this thesis aims to explore the role of *informed, activated patients; prepared, proactive practice teams* and *productive patient-HCP interactions* in reducing drug-related problems (DRPs), by (a) gaining insight into the existing role of patients and HCPs in pharmaceutical care (with a focus on adherence support and communication in usual care) and (b) assessing the effectiveness of a pharmaceutical care intervention (and more specific medication review) in which patients and HCPs have a role.

Because more than a quarter of the Dutch population uses 1 or more drugs for cardiovascular risk management (and the use of these type of drugs make up 40% of the total medication use in the Netherlands) and these medicines are often associated with DRPs, several studies in this thesis will be conducted in patients with cardiovascular diseases[3,25,26,74,75].

Outline of this thesis

Chapter 2 of this thesis systematically summarizes the evidence for the effectiveness of medication review as stand alone, short-term intervention on clinical outcomes, quality of life, drug-related and economical outcomes. Subsequently, in order to get insight into the effectiveness of medication review targeting *patients, HCPs* and *embedding productive patient-HCP interactions*, a randomized controlled trial (RCT) described in **Chapter 3** was conducted in a setting with a high risk of having DRPs. In this RCT the effectiveness of a pharmacist-led medication review with patient-involvement was studied, comprising a questionnaire for patients to report their drug utilization experience, a computer-assisted medication review based on both the input of patients and automated clinical decision support based on the actual medication use and a planned interaction between HCP and patient to discuss DRPs prior to a scheduled visit to the outpatient clinic.

The content of communication about medication during *patient-HCP interactions* is rarely assessed by direct observation[39,40,76,77]. Consequently, little information (based on direct observation) exists on the number and type of DRPs raised and not raised during patients' visits to the HCP, by both the patient and the HCP, and the extent to which the DRPs raised are actually discussed between patients and HCPs. Therefore, **Chapter 4** describes a quantitative study in which an inventory is made of the number and type of DRPs (1) raised and discussed, (2) raised but not discussed, or (3) not even raised during patients' visits to HCPs involved in the prescribing and dispensing of medication in a daily clinical practice situation.

Strategies to improve adherence that target relevant factors related to *prepared, proactive practice teams* and *patient-HCP interactions* are required, as these can impact adherence, whereas earlier studies about strategies to improve medication adherence mainly focused on "patient-related factors"[59]. **Chapters 5** and **6** explore the association between factors related

to *prepared, proactive practice teams* and *patient-HCP interactions* and patient's adherence to medication in the implementation phase. As the number of dispensed drugs for cardiovascular disorders (like cholesterol-lowering medication) make up three-quarter of the total number of dispensed drugs for the 6 most common chronic conditions and as non-adherence rates to statins, the most frequently prescribed type of cholesterol lowering medicines, are high, factors related to *prepared, proactive practice teams* and *patient-HCP interactions* are an interesting target for interventions to improve the adherence of patients to statins. Therefore, **Chapter 5** describes a cross-sectional study that assesses HCPs' (physicians, pharmacists and pharmacy technicians) and patients' beliefs about statins and whether the HCPs' beliefs are associated with the patients' medication beliefs and adherence to statins. **Chapter 6** reports on a cross-sectional study that documents the nature and extent of adherence supporting activities provided in a usual care setting by physicians, pharmacists and pharmacy technicians and that examines the association between the extent of adherence supporting activities of physicians, pharmacists and technicians and adherence to statins.

Finally, the results of this thesis are discussed from a broader perspective in **Chapter 7** and recommendations for clinical practice and future research are provided.

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Chapter 2

Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background
Medication review is often recommended to optimize medication use. In clinical practice it is mostly operationalized as an intervention without co-interventions during a short term intervention period. However, most systematic reviews also included co-interventions and prolonged medication optimization interventions. Furthermore, most systematic reviews focused on specific patient groups (e.g. polypharmacy, elderly, hospitalized) and/or on specific outcome measures (e.g. hospital admissions and mortality). Therefore, the objective of this study is to assess the effectiveness of medication review as an isolated short-term intervention, irrespective of the patient population and the outcome measures used.

Methods
A literature search was performed in MEDLINE, EMBASE and Web of Science from their inception through September 2015. Randomized controlled trials (RCTs) with medication review as isolated short term intervention (<3 months) were included. There were no restrictions with regard to patient characteristics and outcome measures. One reviewer extracted and a second checked data. The risk of bias of studies was evaluated independently by two reviewers. A best evidence synthesis was conducted for every outcome measure used in more than one trial. In case of binary variables a meta-analysis was performed in addition to the best evidence synthesis, to quantify the effect.

Results
Thirty-one RCTs were included in this systematic review (55% low risk of bias). A best evidence synthesis was conducted for 22 outcome measures. No effect of medication review was found on clinical outcomes (mortality, hospital admissions/healthcare use, the number of patients falling, physical and cognitive functioning), except a decrease in the number of falls per patient. However, in a sensitivity analysis using a more stringent threshold for risk of bias, the conclusion for the effect on the number of falls changed to inconclusive. Furthermore no effect was found on quality of life and evidence was inconclusive about the effect on economical outcome measures. However, an effect was found on most drug-related problems: medication review resulted in a decrease in the number of drug-related problems, more changes in medication, more drugs with dosage decrease and a greater decrease or smaller increase of the number of drugs.

Conclusions
An isolated medication review during a short term intervention period has an effect on most drug-related outcomes, minimal effect on clinical outcomes and no effect on quality of life. No conclusion can be drawn about the effect on economical outcome measures. Therefore, it should be considered to stop performing cross-sectional medication reviews as standard care.

Background

In order to reduce the number of preventable adverse drug events and hospital admissions, medication review is often recommended, incorporated in several guidelines and also frequently reimbursed by health care insurers in various countries[1-10]. Medication review is defined by the Pharmaceutical Care Network Europe (PCNE) as "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions"[11]. In clinical practice, for each individual patient, medication review is mostly operationalized as an isolated intervention during a short term intervention period[5,6,8,12,13].

Several systematic reviews and meta-analyses already examined the effectiveness of medication review and these did not unequivocally prove the effectiveness of medication review[14-23]. However, these systematic reviews did not only include trials assessing the effect of medication review in terms of how it is mostly operationalized in practice: an isolated cross-sectional assessment of total medication use during a short term intervention period less than 3 months. Most trials in the systematic reviews assessed the effect of medication review as part of multi-faceted pharmaceutical care interventions, consisting of for instance transitional care, adherence counseling and education of patients and healthcare professionals, besides medication review. Such interventions also often last longer than 3 months. Furthermore, most systematic reviews focus on specific patient groups (e.g. polypharmacy, elderly, hospitalized) and/or on specific outcome measures (e.g. hospital admissions and mortality). As a result, more insight is necessary in the effectiveness of medication review as an isolated short-term intervention on clinical outcomes, quality of life, drug-related and economical outcomes.

Therefore, this systematic review aims to summarize the evidence of medication reviews as performed in clinical practice, irrespective of patient characteristics, setting and outcome measures.

Methods

This systematic review, assessing the effectiveness of medication review, irrespective of the outcome measures used, follows the PRISMA-guidelines[24,25].

Data Sources and Searches

A literature search was performed in MEDLINE, EMBASE and Web of Science from their inception through September 2015. For the development of the search strategy and the full electronic search, see Additional file 1.

Study Selection

The inclusion criteria were operationalized based on the PICO model. No restrictions were set concerning the P (patients) and O (outcome measures): interventions could be conducted in any setting and there were no restrictions with regard to patient characteristics and outcome measures. The I (intervention) had to be medication review, which was defined as follows: a structured cross-sectional assessment of a patient's total medication use leading to recommendations that had to be discussed with the patient and/or clinician within 3

months, in order to improve safety, efficacy or cost-effectiveness. Medication review had to be the single intervention; co-interventions with potential impact on the outcome measures (e.g. discharge counseling, transitional care, non-pharmacological interventions) were not allowed. The C (comparison) was defined as usual care. In addition to PICO the following study selection criteria were formulated: trials had to be randomized controlled trials (RCTs) and only full-length articles were considered for inclusion in this review. Two reviewers independently selected titles/abstracts and the corresponding full text articles to be included in this systematic review. Discrepancies in judgment were discussed in order to reach consensus (VH-BvdB) about final inclusion.

Data Extraction and Risk of Bias Assessment

Relevant data on study characteristics and outcomes were extracted by one reviewer (VH) and checked by a second reviewer (NW). P-values ≤ 0.05 were considered as statistically significant. Two reviewers independently assessed the risk of bias of the studies eligible for inclusion by using the checklist with criteria for risk of bias from the Cochrane Back Review Group[26,27]. To determine whether a study had a low risk of bias (LRB) or a high risk of bias (HRB), a consensus (VH-BvdB) based scorings method was developed based on the risk of bias assessment.

The twelve Cochrane criteria[26,27] were designated essential (4) or non-essential (8) in relation to research on medication review by a consensus discussion (VH-BvdB). Essential criteria were: was the method of randomization adequate?; Was the drop-out rate described and acceptable?; Were the groups similar at baseline regarding the most important prognostic indicators?; Were co-interventions avoided or similar?. To be considered a study with a low risk of bias, all the essential Cochrane criteria had to be scored positive, whereas a total of at least 6 of the 12 criteria (50%) had to be scored positive. A cutoff of 50 percent was chosen, as it is not feasible for medication review trials to score positive on certain criteria, like: "was the patient blinded to the intervention"; "was the care provider blinded to the intervention"; "was the outcome assessor blinded to the intervention". Discrepancies in judgment were discussed in order to reach consensus (VH-BvdB) about the designation of low or high risk of bias for each criterion for each study. If for a specific study an "unclear risk of bias" was scored for the same criterion by both reviewers, the criterion was designated "high risk of bias. The inter-rater agreement of the assessment of risk of bias was assessed by calculating the Cohen's kappa.

A sensitivity analysis was performed regarding a more stringent cut-off point for risk of bias. The actually used cut-off point for risk of bias was compared with a threshold of ≥8 (2/3 of the attainable 12) of the criteria to be scored positive for a study to be considered a study with a low risk of bias.

Data Synthesis and Analysis

An adapted version from previously published best evidence syntheses[28,29] was conducted for every outcome measure used in more than one trial, combining a) the percentage of intervention patients included in studies showing effect on the outcome measure and b) the risk of bias of the set of trials using the outcome measure.

The following methodology was used for this purpose:

1) First, for each outcome measure, the percentage of intervention patients included in studies showing effect on the outcome measure was calculated

2) The risk of bias of a set of studies per outcome measure was subsequently determined as follows: if 50 percent or more of the intervention patients included in trials using the outcome measure had a low risk of bias, the set of studies was designated overall low risk of bias
3) Finally, both the percentage of intervention patients included in studies showing effect on the outcome measure and the risk of bias score for the set of trials per outcome measure were combined to conclude whether medication review has effect on the outcome measure by using the method depicted in Figure 1.

In case of binary variables a meta-analysis was performed in addition to the best evidence synthesis, to quantify the effect. In these meta-analyses, effect sizes of binary variables were pooled using their weighted average for the treatment effect (using a random-effect meta-analysis method). Forest plots were created with STATA version 13.1 to summarize the risk ratio (RR) and the 95% confidence interval (CI). Heterogeneity across studies was assessed using I^2 statistics (studies with an $I^2 > 50\%$ were considered heterogeneous). Outcome measures reported in only one trial were reported descriptively.

A sensitivity analysis was performed with regard to the impact of large trials with a high risk of bias, on every individual outcome measure. In this sensitivity analysis, large trials with a high risk of bias, with a number of intervention patients greater than the median number of intervention patients per outcome measure, were excluded from the best evidence synthesis.

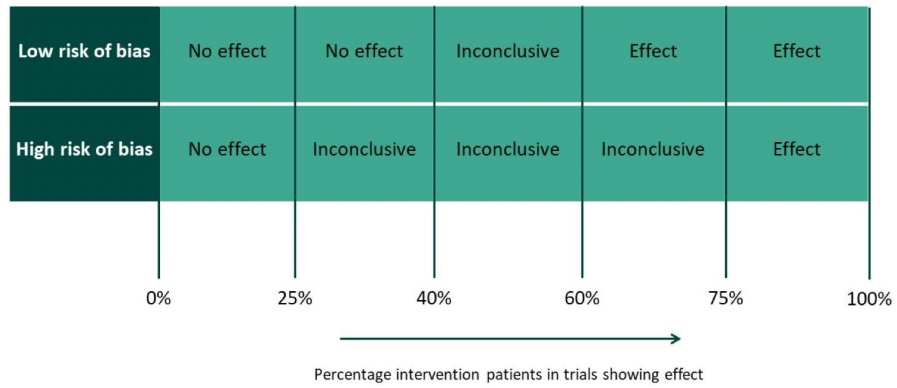

Figure 1. Schematic representation of the best evidence synthesis.

Schematic representation of the best evidence synthesis, combining a) the percentage of intervention patients included in studies showing effect on the outcome measure and b) the risk of bias of the set of trials using the outcome measure. For details: see Additional file 3.

Results

The literature search provided a total of 13,870 potentially relevant publications which were screened for eligibility. After screening titles and abstracts, 154 articles were left for full text screening. After this screening, 31 RCTs met the inclusion criteria and were included in this systematic review. A flow diagram of the literature search is represented in Figure 2.

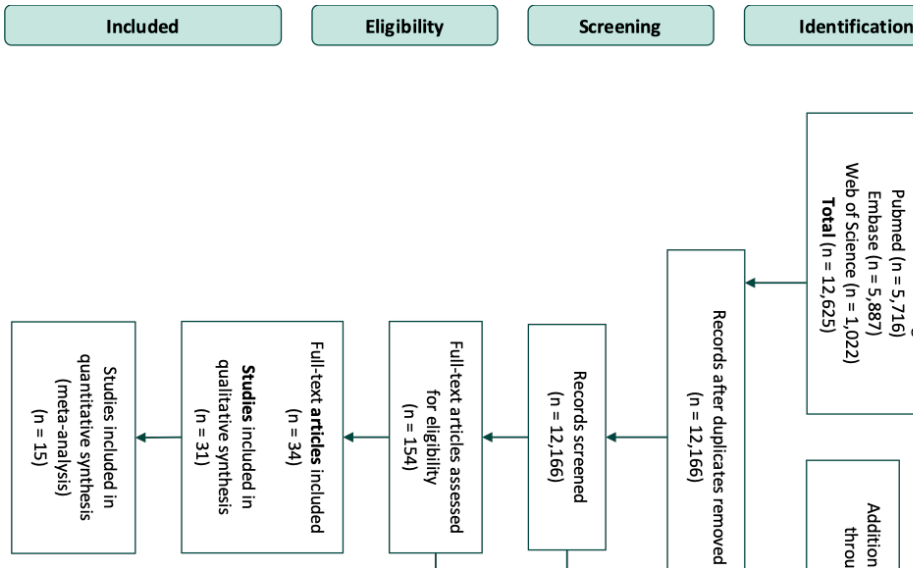

Figure 2. Flow diagram of the literature search and study selection process.

An overview of the study characteristics of the included studies is depicted in Table 1. Most studies were conducted in primary care (52%), sample size ranged from 64 to 2014 patients, the observation period ranged from 0 to 12 months and 17 (58%) of the trials were conducted in Europe and 7 (23%) in the United States. Patients were involved in the medication reviews in 21 of the 31 studies, the mean age (as reported in 24/31 trials) and the number of drugs (as reported in 18/31 studies) of the intervention patients in each trial ranged from 51.4 years to 87.0 years and from 4 to 14 drugs, respectively.

Seventeen studies (55%) met the criteria for low risk of bias. The inter-rater agreement between the two assessors of risk of bias was 0.74 (Cohen's Kappa). Most common reasons for designating studies high risk of bias were methodological shortcomings on "compliance", "treatment allocation concealment", "blindness of patient, care provider and outcome assessor", "randomization", "similarity of study groups at baseline" and "drop-out rate".

Table 1. Study characteristics of the included studies

Author (Year)	Risk of bias	Follow up (mos.)	Country and setting	Mean age (IG), years	No. Pts.	Description intervention				Patient selection criteria for medication review		
						HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Nr assessments/ Nr patient contacts	Additional education HCP	Age, years	Nr drugs	Other
Bond[30] (2007)	LRB	12	GB, general practices	Nr	2014	R: Pharmacist	No	1	Yes	< 65 *	No	Specific conditions*
Briggs[31] (2015)	HRB	4	AU, tertiary referral hospital	82.0	2015	R: Hospital pharmacist D: GP	Yes	1	Nr	>70*	>5*	Living at home*
Britton[32] (1991)	HRB	3	US, general medicine clinic	Nr	760	R: Clinical pharmacist D: physician (assistant)	No	1	Yes	No	> 5	No
Burns[33]/ Furniss[34] (2000)	HRB	4	GB, nursing homes	83.5	330	R: (study) pharmacist D: multidisciplinary team	No	2	Nr	No	No	Living in nursing home
Gallagher[35] (2011)	LRB	6	GB, tertiary medical centre	74.5	400	R: (research) physician, medical team D: physician	No	1	Nr	≥ 65*	No	Emergency admission*
Graffen[36] (2004)	HRB	6	AU, general practices	Nr	402	R: Pharmacist D: GP and patient	Yes	1	Nr	> 65*	≥ 5*	Living independently*; ≥ 1 of following*: use of predefined risk drugs; > 12 doses per day; > 6 diagnoses; BMI < 22
Heselmans[37] (2015)	HRB	0†	BE, general and specialized hospitals	66.6	600	R: Pharmacist D: Ward physician	No	1	Nr	>15*	No	ICU stay of at least three consecutive day*

Holland[38] (2005)/ Pacini[39] (2007)	LRB	6	GB, emergency wards	85.4	855	R: (study) pharmacist D: pharmacist or GP	Yes	2	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*
Jameson[40] (1995)	HRB	6	US, family health center	Nr	64	R: Clinical pharmacist D: Physician and pharmacist	Yes	2	Nr	No	≥ 5 (see other)	≥ 2 of following risk factors: ≥ 5 drugs; ≥ 12 daily doses; ≥ 4 medication changes last 12 mos.; >3 concurrent diseases; noncompliance; drugs requiring TDM
Jameson[41] (2001)	HRB	6	US, private physicians	51.4	340	R: Clinical pharmacist D: Physician and pharmacist	Yes	1	Nr	No	≥ 5	No
Krska[42] (2001)	HRB	3	GB, medical practices	74.8	381	R: Clinical pharmacist D: GP and pharmacist	Yes	1	Nr	≥ 65*	≥ 4*	≥ 2 chronic conditions*
Kwint[43] (2011)	LRB	6	NL, community pharmacies	78.7	118	R: 2 research pharmacists D: GP and community pharmacist	No	1	Nr	≥ 65*	≥ 5*	living at home*; at least one drug had to be dispensed via an automated system*
Lenaghan[44] (2007)	HRB	6	GB, general practices	84.5	136	R: study-pharmacist D: GP and study-pharmacist	Yes	2	Nr	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines
Lenander[45] (2014)	HRB	12	SE, primary care centre	79.0	209	R: Geriatrics pharmacist D: GP and patient	Yes	1	No	> 65*	≥ 5*	already scheduled for an appointment with a GP*

Lim[46] (2004)	LRB	2	SG, geriatric outpatient clinic	79.6	126	R: pharmacist (of a pharmacist consult clinic) D: primary physician	Yes	1	Nr	No	> 3 (see other)	≥ 1 of following criteria: TDM required; polypharmacy (>3 drugs or >9 doses per day); non-compliance; self-administered drugs that require psychomotor skill and co-ordination; nasogastric tube feeding; >1 doctor managing care; hospitalized within the last 6 months.
Lisby[47] (2010)	LRB	3	DK, acute ward	80.2	100	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	2	Nr	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*
Lisby[48] (2015)	LRB	3	DK, regional hospital	80.4	108	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	2	Nr	> 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours*
Mannheimer[49] (2006)	LRB	6	SE, clinical internal medicine	71.0	305	P: nurse and clinical pharmacologist D: physician in charge	Yes	1	Nr	No	≥ 2*	patients who had been in hospital for < 24 hr on Tue. to Fri. or for < 60 hr on Mon. before a nurse screened the computerized medical record*
Meredith[50] (2002)	LRB	1.5	US, home care	80.3	317	P: nurse and clinical pharmacist D: Physician	Yes	1	Yes	≥ 65*	No	had ≥ 1 of the four possible study medication problems*; projected duration of home health care of ≥ 4 wks*
Meyer[51] (1991)	HRB	12	US, VAMC	Nr	312	R: study-physician (Group III, intensive intervention) D: Physicians and nurse practitioners	No	1	Nr	No	≥ 10	being followed by providers at the medical center

Michalek[52] (2014)	LRB	0†	DE, tertiary medical center	84‡	114	R: Physicians D: Physicians	No	1	Nr	> 70*	≥ 3*	admitted to the acute geriatric unit*, stable health condition defined as no need for intermediate or intensive care unit treatment*, had at least three diseases in need for drug treatment*.
Milos[53] (2013)	LRB	2	SE, primary health care centres	87.0	374	R: Clinical pharmacist D: Physician	No	1	Yes	≥ 75*	No	users of the multi-dose drug dispensing system; living in nursing homes or their own homes with municipally provided home care
Olsson[54] (2012)	HRB	12	SE, primary care	83.4	150	R: study-physician D: Family physician	Yes	1	Nr	≥ 75*	≥ 5*	living in ordinary homes*
Pit[55] (2007)	HRB	12	AU, general practice	Nr	849	R: Doctors D: Doctors	Yes	1	Yes	≥ 65*	No	living in the community*
Pope[56] (2011)	LRB	6	GB, community hospitals	83.3	225	R: multidisciplinary panel D: General practitioner	No	1	Nr	No	No	permanent patients on the continuing-care wards
Sellors[57] (2001)	LRB	6	CA, family physician practice	76.4	132	R: study-pharmacist D: family physician	Yes	1	Yes	≥ 65*	≥ 4*	No
Sellors[58] (2003)	LRB	5	CAN, family physician practices	74.0	889	R: Pharmacist D: Physician	Yes	1	Nr	≥ 65*	≥ 5*	had been seen by their physician within; the past 12 months*; no evidence of cognitive impairment; could understand English.
Williams[59] (2004)	HRB	1.5	US, general medicine clinic	73.5	140	R: Interdisciplinary team (consultant pharmacist, physician and nurse) D: Primary physician	Yes	1	Nr	≥ 65*	≥ 5*	≥ 2 of the medications were potentially problematic drugs for common geriatric problems*; cognitively intact *
Zermansky[60] (2001/2002)	LRB	12	GB, general practices	74.0	1188	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	1	Nr	≥ 65*	≥ 1*	No
Zermansky[61] (2006)	LRB	6	GB, care homes	85.3	661	R: Study-clinical pharmacist D: GP	Yes	1	Nr	≥ 65*	≥ 1*	No
Zillich[62] (2014)	LRB	2	US, home health care centers	73.0	895	R: Pharmacist D: Patient, pharmacist, physician	Yes	03-apr	Nr	No	No	All new patients admitted into Medicare's defined 60-day home health care episode were eligible. Medicare eligibility for home health benefits requires ordering services by a physician who reviews the need for a patient's care and certifies that the patient is homebound

mos.= months; IG=intervention group; Pts. = patients; HCP= healthcare professional; LRB = low risk of bias; HRB = high risk of bias; * = combination of inclusion criteria (= "and"); Nr = not reported; †outcome measures determined directly after discharge from ICU and/or discharge from hospital; TDM = therapeutic drug monitoring; hr = hours; ‡median; VAMC= Veterans Affairs Medical Center

Clinical outcomes

As summarized in Figure 3, no effect of medication review was found on clinical outcomes, except for a decrease in the number of falls.

Mortality

Eleven trials (overall low risk of bias, including 2403 intervention patients) assessed the effect of medication review on mortality (for details, see Additional file 4 Table 1). Data were pooled in a meta-analysis (Additional file 4 Figure 1) and with a RR of 0.94 (CI, 0.76 - 1.17) no effect of medication review on mortality was found. Moderate heterogeneity was found between the trials (I^2 = 22.0%, P = 0.234).

Hospital admissions and healthcare use

Data of 11 trials (Additional file 4 Table 2), including 2041 intervention patients, showed evidence with a low risk of bias for no effect of medication review on the number of hospital admissions (including emergency admissions and visits). Meta-analysis of data from five trials with overall low risk of bias, including 2000 intervention patients, assessing the effect of medication review on the number of patients admitted to the hospital revealed no effect, with a RR of 0.94 (0.82, 1.08) and with moderate heterogeneity (I^2 = 42.3%, P = 0.139) (Additional file 4 Figure 2 and Additional file 4 Table 3). The same applies to the time to first (re)admission in three trials with low risk of bias, including 518 intervention patients, except for a subgroup with only emergency department visits or a low baseline risk for hospital admission (Additional file 4 Table 4)[48,62]. In addition, no effect of medication review was found on the length of hospital stay in seven trials with overall high risk of bias, including 1330 intervention patients and the number of emergency admissions/visits in seven trials with overall low risk of bias, including 1243 intervention patients (Additional file 4 Table 5 to Table 6). Furthermore, no effect of medication review was demonstrated on the number of General Practitioner (GP) visits in 6 trials with low risk of bias including 1582 intervention patients and on the number of outpatient visits in four trials with overall low risk of bias, including 1144 intervention patients (Additional file 4 Table 7 to 8). The meta-analysis of data of 2 trials with overall high risk of bias, including 825 intervention patients, found no effect on the number of patients admitted to residential homes with a RR of 1.17 (0.79, 1.74), with limited heterogeneity (I^2 = 0.0%, p = 0.997) (Additional file 4 Figure 3 and Table 9).

No best evidence synthesis could be conducted for a variety of other healthcare use related outcome measures used in only one trial. In 6 trials no effect was found on these outcome measures[33,37,38,45,47,48,58], whereas in 2 trials an effect was found only in a subdomain of healthcare use related outcome measures or a subgroup of patients[30,33] and in one trial a positive effect was found in favor of patients receiving usual care[48].

Falls

It was observed in two trials with overall low risk of bias, including 467 intervention patients, that medication review decreases the number of falls per patient (Additional file 4 Table 10). Data of four trials with overall low risk of bias, including 929 intervention patients, were pooled in a meta-analysis (Additional file 4 Figure 4). This meta-analysis suggested that medication review decreases the number of patients falling (RR 0.68 (0.52, 0.90); I^2 = 41.0%, p = 0.166). However, the best evidence synthesis was inconclusive about the effect on the number of patients falling (Additional file 4 Table 11). Furthermore, a significant lower fall rate

per 1000 patient days (only assessed by Michalek et al) due to medication review was found[52].

Health status, physical and cognitive outcome measures

Three trials with low risk of bias, including 499 intervention patients, showed no effect of medication review on physical functioning using the Barthel index (Additional file 4 Table 12). This was confirmed in one study, using three different outcome measures for physical functioning[59].

Medication review neither improved clinical status[46], health status[59] and patient's perception of severity of illness[46]. In one study, however, a smaller decrease in self-rated health due to medication review was found[45].

Two trials, with overall low risk of bias, including 449 intervention patients, found no effect of medication review on cognitive functioning, using the Standard Mini Mental State Examination (Additional file 4 Table 13). Medication review also did not affect cognitive functioning, expressed with other outcome measures[34,56,59], except for the Chrichton-Royal Behaviour Rating Scale[34].

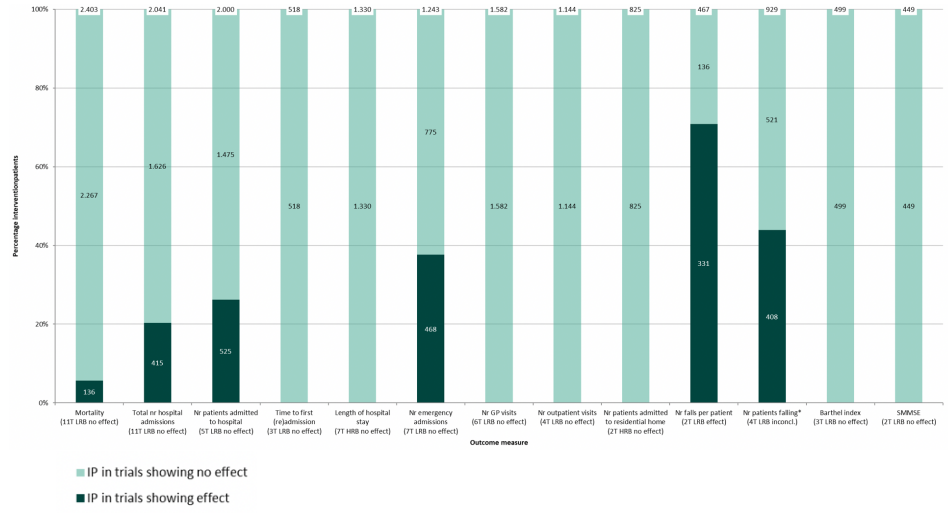

Figure 3. Effect of medication review on clinical outcome measures as assessed in more than 1 trial.

The percentage of intervention patients is shown on the y-axis. The black part of the bar represents the percentage of intervention patients included in a trial with a positive effect on a specific outcome measure. The outcome measures, the number of trials using the specific outcome measure, the overall risk of bias of the set of evidence per outcome measure and the conclusion of the best evidence synthesis are shown on the x –axis. T= trials; LRB = low risk of bias; HRB = High risk of bias; inconcl. = inconclusive

Quality of life

The effect of medication review on quality of life is outlined in Figure 4. There is evidence with overall low risk of bias that medication review has no effect on quality of life, as measured with the EQ-5D score (based on 6 trials, including 1583 intervention patients) or the SF-36 score (based on two trials, including 547 intervention patients), whereas evidence with overall high risk of bias was inconclusive about the effect of medication review on the EQ5D-VAS (used in five trials, including 798 intervention patients) (Additional file 4 Table 14). Pit et al also found no effect of medication review on quality of life measured with the SF-12 score[55].

Drug-related outcome measures

The effect of medication review on drug-related outcome measures is represented in Figure 4. An effect of medication review was found on most drug-related outcome measures (the number of drugs, the number of drug changes, the number of drug-related problems and the number of drugs with a dosage decrease), but not on the number of drugs with dosage increase.

Drug-related problems

In four trials with overall high risk of bias, including 599 intervention patients, medication review decreases the number of drug-related problems (Additional file 4 Table 15). The results of two trials assessing the effect of medication review on the number of patients with drug-related problems (with different pre-defined drug-related problems per trial) were conflicting[50,54].

Number of drug changes and number of drugs with a dosage decrease or increase

Data of three trials with low risk of bias, including 965 intervention patients, showed an increase of the number of drug changes as a result of medication review (Additional file 4 Table 16). Two other trials with overall high risk of bias, including 486 intervention patients, found an increase of the number of drugs with a dosage decrease, whereas no difference was found with regard to the number of drugs with dosage increase (Additional file 4 Table 17 to 18).

Number of drugs and doses

Twelve studies with overall low risk of bias, including 1972 intervention patients, found that medication review leads to a greater decrease or smaller increase of the number of drugs used (Additional file 4 Table 19). Sellors et al, however, found no difference in the absolute number of drugs used after 5 months due to medication review[58]. Furthermore, no effect of medication review was found on the number of individual doses per day 40 and the dosing frequency per day[60].

Other drug-related outcome measures

Various outcome measures, only used in one trial, but covering the same outcome domains, could not be incorporated in a best evidence synthesis. Two studies assessing the effect of medication review on adherence and knowledge found conflicting results[40,46]. Results with regard to appropriate prescribing and medication use were also conflicting. In two trials, medication review did not improve a set of predefined indicators of prescription quality[54,55], whereas other trials showed improvement of (part of) the indicators[30,35,52]. Trials reporting the effect of medication review on scores for appropriateness of prescribing and medication use also found conflicting results. Although medication review improved

prescribing appropriateness as measured with the Medication Appropriateness Index (MAI) and the Assessment of Underutilization of Medication Index (AOU)[35], no effect was found on a composite score reflecting appropriate prescribing of benzodiazepines, NSAIDs and thiazide diuretics[55]. Finally, the effect of medication review on adverse effects was inconclusive, as one trial demonstrated that medication review decreases adverse effects[41] and a second trial did not show a significant effect[40].

Economical outcomes

Figure 4 shows the effect of medication review on drug costs. Based on the data of 9 trials with overall low risk of bias, including 2511 intervention patients, no conclusion could be drawn about the effect of medication review on drug costs (Additional file 4 Table 20). Trials using various other outcome measures for drug and supply costs did generally not observe effect of medication review on costs[32,57,58], except for one study demonstrating that medication review might decrease drug and supply costs due to discontinuation[32]. Inconclusive results were also observed with respect to total healthcare costs, as 2 studies found a positive effect of medication review on total healthcare costs[33,39], one study found a temporary positive effect[30] and two studies did not find any effect[56,58]. Besides this, Burns et al found no decrease or increase of costs related to non-drug GP visits, in patient days, outpatient visits, domiciliary visits and primary care visits due to medication review[33].

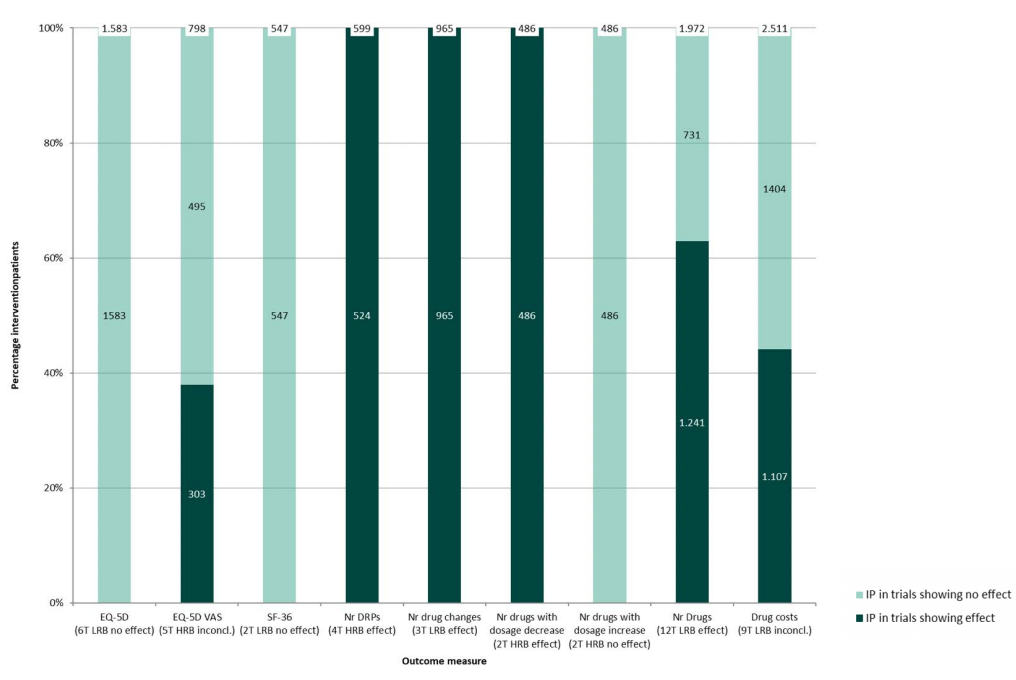

Figure 4. Effect of medication review on quality of life, drug-related outcome measures and economical outcome measures as assessed in more than 1 trial.

The percentage of intervention patients is shown on the y-axis. The black part of the bar represents the percentage of intervention patients included in a trial with a positive effect on a specific outcome measure. The outcome measures, the number of trials using the specific outcome measure, the overall risk of bias of the set of evidence per outcome measure and the conclusion of the best evidence synthesis are shown on the x-axis. T= trials; LRB = low risk of bias; HRB = High risk of bias; inconcl. = inconclusive

Sensitivity analyses

The sensitivity analysis with a more stringent threshold for risk of bias (≥8; 2/3 of the attainable 12) yielded similar results except for the number of falls per patient, which changed from effective to inconclusive, see Additional file 2. Based on the sensitivity analysis excluding large trials with high risk of bias from the best evidence synthesis, twice the conclusion changed from effective to inconclusive (number of drug-related problems (DRPs) and number of drugs), twice from inconclusive to not effective (number of patients falling and drug costs), once from not effective to inconclusive (number of emergency admissions) and once from inconclusive to a decreased quality of life (EQ-5D VAS), see Additional file 3.

Discussion

This is the first systematic review exploring the effect of medication review as an isolated intervention without co-interventions during a short term (≤3 months) intervention period (as advocated in most medication review guidelines[4-10] and operationalized in practice). Furthermore this systematic review provides an overview of all outcome measures and selection criteria without exclusion criteria based on patient characteristics. In this study, a beneficial effect of medication review was found on most drug-related outcome measures. However, minimal effect was observed on clinical outcomes, no effect was found on quality of life and evidence was inconclusive concerning the effect on economical outcome measures. Only seventeen trials (55%) were designated low risk of bias.

The findings of this systematic review are in line with the findings of other systematic reviews assessing the effect of medication review, although these systematic reviews used other inclusion criteria. Previously published systematic reviews often focused on specific patients (e.g. elderly or hospitalized patients etc.) and/or included trials with multifaceted interventions and/or limited the scope to specific outcome measures.

First of all, the lack of effect of medication review on clinical outcomes (e.g. mortality, number of hospital admissions) observed in this systematic review is in line with the findings of other systematic reviews[16-22], although Patterson found conflicting results concerning hospital admissions[14]. In other systematic reviews a positive effect of medication review on some clinical outcomes was suggested only when non RCTs[21], unpublished data [18], co-interventions[15,18] and/or lengthier interventions (> 3 months)[21] were included. Secondly, no effect of medication review on quality of life was found by this systematic review, which is also confirmed by other systematic reviews[14,16,21,22,38]. Thirdly, the effect of medication review on drug-related outcomes (e.g. a decrease in the number of drug-related problems and the number of drugs) found in this systematic review was confirmed by other systematic reviews[17,19], although Patterson found no consistent intervention effect on medication-related problems across studies[14]. In addition, in these systematic reviews an effect of medication review on some other drug-related outcome measures (e.g. adherence, adverse drug events, medication appropriateness) was reported[14-17,19,21,23]. Finally, based on this systematic review, no conclusion could be drawn about the effect of medication review on economical outcome measures, including drug costs. These results were confirmed by the majority of other systematic reviews, since only one out of six other systematic reviews[23] reported effect of medication review on certain subdomains of economical outcome measures[15-17,19,21,23].

Thus, when the effect of medication review is assessed in terms of how it is operationalized in practice (with medication review as isolated intervention) and even when this effect is assessed irrespective of the patient population and on all available outcome measures, the impact found on clinical outcomes and quality of life is minimal, the observed effect on drug-related outcomes is limited and the evidence about the effect on economical outcome measures is inconclusive. This requires further elaboration of the possible explanations of these findings. Several aspects seem to contribute to these findings, including the 1) selection of patients, the 2) interventions (how medication reviews are being operationalized in practice) and the 3) outcome measures and follow-up time used in trials assessing the effect of medication review. Besides these explanations it might also be the case that the hypothesis that medication review significantly improves clinical outcomes, economical outcomes and quality of life should be rejected.

A possible explanation for the lack of evidence about the effect of medication review is that the 1) selection of patients does not fit the aim of the intervention. If the aim of medication review is, for example, decreasing mortality or preventing patients from being admitted to the hospital, one should select a population with high risk for any of these events. Inclusion criteria often mentioned in medication review trials are age 65-plus and a minimum number of drugs used. Although age and polypharmacy are predominantly positively associated with the risk of having drug-related problems[63-68], several other risk factors (e.g. co-morbidity, renal impairment, high risk medication) contributing to the occurrence of DRPs and/or hospital admissions are found in literature[63,69-78]. This suggests that a more sensitive selection of patients for medication review in order to reduce the risk of hospital admission and or death may increase the chance of demonstrating an effect of medication review on these outcomes. Consequently, another aim of the intervention (e.g. increasing adherence) will require a different selection of patients (e.g. lack of therapeutic effect, adherence scores). A second explanation for the lack of evidence about the effect of medication review might be the heterogeneity of 2) the interventions. No golden standard exists for how medication review should be operationalized in practice. Several implicit as well as explicit medication review methods are used[79]. Furthermore, different levels of medication review are applied in daily practice[10]. This limits the ability to compare the results of trials assessing the effect of medication review. In addition, the multidisciplinary character of medication reviews is possibly a complicating factor. Often problems are difficult to solve 1) as many care-practitioners are involved and 2) as it is not always clear which healthcare practitioner should be addressed and/or 3) as the responsible physician may not agree with implementation of a recommendation made by another healthcare practitioner. Once the aims of medication review are known, one or more consistent (international) definitions and accompanying operationalizations of medication review should be put into practice. Uniform medication reviews are easier to compare in systematic reviews, this will contribute to the ability to demonstrate effect of these interventions. Finally, the lack of evidence about the effect of medication review might be explained by 3) the outcome measures and follow-up time used in trials assessing the effect of medication review. The outcome measures used in published RCTs examining the effect of medication review are often broad outcome measures, as for instance hospital admissions and all-cause mortality, which are affected by multiple (also not drug-related) factors. Although in RCTs these outcome measures may be the ideal outcome measures, since these reflect the overall benefit/risk ratio of drug treatment, no effect of medication review on these outcome measures is found, possibly because the intervention

medication review is not powerful enough to have impact on hospitalizations and mortality. Therefore (clinical) outcome measures should be chosen which fit 1) the aim of the medication review (improve safety and (cost-)effectiveness of a patient's medication use) and 2) are more disease/medication specific (e.g. blood pressure, HbA1c)[12,80]. However, these more disease/medication specific outcome measures should not only reflect the negative effects, but also the positive effects of drug treatment. Although it is often seen in medication review trials, only reporting drug-related outcome measures (e.g. DRPs, number of drugs, adverse events) is suboptimal, as these outcome measures only focus on the disadvantages of drug treatment. Furthermore the outcome measures used are often heterogeneous, as for each outcome a different set of outcome measures is used per trial. This limits the ability to draw robust conclusions. Standardization of outcome measures and time of follow-up should be applied in order to increase the ability to compare the results of trials assessing the effect of medication review. For instance, as one of the aims of the intervention is to improve the quality of life of patients, a standard set of quality of life scores (e.g. EQ-5D and SF-36) should be defined and subsequently used in future research to measure the effect of medication review on quality of life.

In the meantime, it is also conceivable that even when medication review is operationalized and/or investigated as described above, it is not effective on clinical outcomes, economical outcomes and quality of life. A possible explanation is that medication review is a cross-sectional intervention at an arbitrary moment during patient's drug therapy. However, it might be assumed that at specific moments of drug therapy (e.g. when drugs are started, adapted or stopped) the risk for preventable drug-related problems causing negative clinical outcomes is higher. These specific high-risk moments seem to be the best occasion to apply medication optimization in order to prevent clinically relevant drug-related problems. It can therefore be suggested to redesign the cross-sectional medication review to longitudinal medication therapy management, directly from the start of a drug, targeting at specific risk moments[81]. Furthermore a more integral approach of pharmaceutical care will give room for medication improvement strategies to shift from a system repairing overdue maintenance to a more individualized approach. Problems related to prescribing according to general guidelines should be solved by means of population based interventions like for instance clinical rules. Other interventions should be developed to address issues related to a patient's use of medication in the context of his medical condition. For instance individualized medication coaching consults with non-adherent patients or patients experiencing drug-related problems or adverse events.

A couple of limitations are associated with this systematic review. In order to provide a broad overview on the literature about the effect of medication review, no inclusion criteria were applied with regard to outcome measures. Consequently, in the best evidence syntheses, both trials using a specific outcome measure as primary outcome measure and trials using the outcome measure as secondary outcome measure were included. This possibly leads to underpowered trials being part of the best evidence synthesis (BES). However, large trials (with more power) have more impact in the BES. Furthermore, in the best evidence synthesis, it is theoretically possible that a large trial with a high risk of bias has decisive impact on both the overall risk of bias of a set studies and the conclusion about the effect of medication review on a specific outcome measure. However, only in 1/22 best evidence syntheses would the conclusion change to effect (EQ-5D VAS), when studies with a high risk of bias with a number of intervention patients greater than the median number of intervention patients of the trials would be excluded from the best evidence synthesis. Finally a limitation might be the fact that only RCTs were included in this systematic review, although it was a deliberate choice not to include observational studies, as a randomized controlled trial is the most appropriate study design to demonstrate effect of an intervention.

Besides these limitations, some remarks can be made with regard to the robustness of the conclusions. Firstly, only 55% of the included studies were designated a low risk of bias, which results in a smaller body of evidence. In a sensitivity analysis, increasing the threshold for the risk of bias assessment to an arbitrary 2/3 of the attainable maximum score, the percentage of trials with low risk of bias decreased to 39%. For medication review trials, however, on the one hand it is reasonable to relax the threshold to some extent when it comes to blindness of the patient, care provider and outcome assessor. On the other hand this may lead to an overestimation of positive findings of assessor dependent outcome measures, for instance when a non-blinded assessor has to assess whether an outcome is drug-dependent or not. Secondly, the variety of the included patients and settings in this systematic review should be considered. Although no exclusion criteria based on patient characteristics may have resulted in more power, this also may have led to false negative results in subgroups. In other systematic reviews, however, often no effect was found in these subgroups.

Conclusions

Although an isolated medication review during a short term intervention period (how it is mostly operationalized in practice) has an effect on most drug-related outcomes, medication review has minimal effect on clinical outcomes, no effect on quality of life and no conclusion could be drawn about the effect on economical outcome measures. Therefore, it should be considered to stop performing cross-sectional medication reviews as standard care. It may also be considered to shift the focus of research from cross-sectional medication review to other strategies to improve the safety and (cost-)effectiveness of drug treatment. If, despite this, research on the effect of cross sectional medication review is still continued, high quality studies including high-risk patients and using relevant outcome measures should be conducted to assess if/when medication reviews can contribute to better medication use and subsequent better clinical outcomes. However, more effort should be put in the development and evaluation of other medication improvement strategies, like more individualized and longitudinal medication therapy management, targeting at specific risk moments of drug treatment and targeting at problems that patients experience themselves.

List of abbreviations

RCT= randomized controlled trial; PCNE = Pharmaceutical Care Network Europe; RR = risk ratio; CI = confidence interval; AOU = Assessment of Underutilization of Medication Index; DRP = drug-related problem; MAI = Medication Appropriateness Index; GP = General Practitioner; LRB = low risk of bias; HRB = High risk of bias

Competing interests

The author(s) declare that they have no financial and non-financial competing interests.

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Additional file 1. Development of the search strategy and full electronic search

Development of the search strategy

As various terms are used for medication review in published articles (like medication review, medication management, drug review, pharmacist intervention etc.), terms used to describe a medication review were identified as much as possible by first selecting references based on mesh-terms and published systematic reviews. The descriptions of medication review in these references were subsequently used as text words in a text-based search strategy. Therefore, the MEDLINE selection of eligible references consisted of a three-step approach: 1) MeSH-based selection 2) Selection of references included in published systematic reviews, 3) Text-based selection (based on text words of included references from step 1 and 2).

1) MeSH-based selection of references

First, studies were identified in MEDLINE by using the MeSH headings "Drug Utilization Review" or "Pharmaceutical Services" to search for interventions. These were combined with both a MeSH heading and text words to search for randomized controlled trials ("Randomized Controlled Trial" [Publication Type] OR randomized controlled trial[tw] OR randomised controlled trial[tw]).

2) Selection of references based on published systematic reviews

The same MeSH headings to search for interventions ("Drug Utilization Review" or "Pharmaceutical Services") were combined in a second search with the MeSH headings "Review" or "Meta-Analysis" as publication type to identify systematic reviews and meta-analyses on this subject (from January 2007 through September 2015). References from these systematic reviews were independently screened by two reviewers for studies to be included in this review.

3) Text-based selection of references

Finally, the abstracts of the included references from step 1 and 2 of the literature search were independently screened by two reviewers for text words to develop a third search consisting of a broad range of text words to search for "interventions" and "drug use". These text words were also combined with the MeSH heading and text words for the publication type randomized controlled trial.

In order to perform the same search in EMBASE, the MeSH headings used for the MEDLINE search were converted to subject headings and the text words were converted to the category "multi-purpose". Subsequently, the references of all articles included were screened for eligible references. Finally, in Web of Science, the citations of all included trials were checked to identify eligible references.

Full electronic search (MEDLINE)

(((((((("Drug Utilization Review"[Mesh]) OR "Pharmaceutical Services"[Mesh])) AND (((((("Randomized Controlled Trial"[Publication Type]) OR "randomized controlled trial"[tw]) OR "randomised controlled trial"[tw]) OR "randomised controlled study"[tw]) OR "randomized controlled study"[tw])))) OR ((("pharmacist review"[TW] OR "pharmacist intervention"[TW] OR "pharmacist program"[TW] OR "pharmacist assessment"[TW] OR "pharmacist management"[TW] OR "pharmacist care"[TW] OR "pharmacist consult"[TW] OR "pharmacist counselling"[TW] OR "pharmacist evaluation"[TW] OR "pharmacist reviews"[TW] OR "pharmacist interventions"[TW] OR "pharmacist programs"[TW] OR "pharmacist assessments"[TW] OR "pharmacist consults"[TW] OR "pharmacist evaluations"[TW] OR "pharmacologist review"[TW] OR "pharmacologist intervention"[TW] OR "pharmacologist program"[TW] OR "pharmacologist assessment"[TW] OR "pharmacologist management"[TW] OR "pharmacologist care"[TW] OR "pharmacologist consult"[TW] OR "pharmacologist counselling"[TW] OR "pharmacologist evaluation"[TW] OR "pharmacologist reviews"[TW] OR "pharmacologist interventions"[TW] OR "pharmacologist programs"[TW] OR "pharmacologist assessments"[TW] OR "pharmacologist consults"[TW] OR "pharmacologist evaluations"[TW] OR "drug review"[TW] OR "drug intervention"[TW] OR "drug program"[TW] OR "drug assessment"[TW] OR "drug management"[TW] OR "drug care"[TW] OR "drug consult"[TW] OR "drug counselling"[TW] OR "drug evaluation"[TW] OR "drug reviews"[TW] OR "drug interventions"[TW] OR "drug programs"[TW] OR "drug assessments"[TW] OR "drug consults"[TW] OR "drug evaluations"[TW] OR "medication review"[TW] OR "medication intervention"[TW] OR "medication program"[TW] OR "medication assessment"[TW] OR "medication management"[TW] OR "medication care"[TW] OR "medication consult"[TW] OR "medication counselling"[TW] OR "medication evaluation"[TW] OR "medication reviews"[TW] OR "medication interventions"[TW] OR "medication programs"[TW] OR "medication assessments"[TW] OR "medication consults"[TW] OR "medication evaluations"[TW] OR "medicine review"[TW] OR "medicine intervention"[TW] OR "medicine program"[TW] OR "medicine assessment"[TW] OR "medicine management"[TW] OR "medicine care"[TW] OR "medicine consult"[TW] OR "medicine counselling"[TW] OR "medicine evaluation"[TW] OR "medicine reviews"[TW] OR "medicine interventions"[TW] OR "medicine programs"[TW] OR "medicine assessments"[TW] OR "medicine consults"[TW] OR "medicine evaluations"[TW] OR "pharmaceutical review"[TW] OR "pharmaceutical intervention"[TW] OR "pharmaceutical program"[TW] OR "pharmaceutical assessment"[TW] OR "pharmaceutical management"[TW] OR "pharmaceutical care"[TW] OR "pharmaceutical consult"[TW] OR "pharmaceutical counselling"[TW] OR "pharmaceutical evaluation"[TW] OR "pharmaceutical reviews"[TW] OR "pharmaceutical interventions"[TW] OR "pharmaceutical programs"[TW] OR "pharmaceutical assessments"[TW] OR "pharmaceutical consults"[TW] OR "pharmaceutical evaluations"[TW] OR "pharmaceutic review"[TW] OR "pharmaceutic intervention"[TW] OR "pharmaceutic program"[TW] OR "pharmaceutic assessment"[TW] OR "pharmaceutic management"[TW] OR "pharmaceutic care"[TW] OR "pharmaceutic consult"[TW] OR "pharmaceutic counselling"[TW] OR "pharmaceutic evaluation"[TW] OR "pharmaceutic reviews"[TW] OR "pharmaceutic interventions"[TW] OR "pharmaceutic programs"[TW] OR "pharmaceutic assessments"[TW] OR "pharmaceutic consults"[TW] OR "pharmaceutic evaluations"[TW] OR "pharmacology review"[TW] OR "pharmacology intervention"[TW] OR "pharmacology program"[TW] OR "pharmacology assessment"[TW] OR "pharmacology management"[TW] OR "pharmacology care"[TW] OR "pharmacology consult"[TW] OR "pharmacology counselling"[TW] OR "pharmacology evaluation"[TW] OR "pharmacology reviews"[TW] OR "pharmacology interventions"[TW] OR "pharmacology programs"[TW] OR "pharmacology assessments"[TW] OR "pharmacology consults"[TW] OR "pharmacology evaluations"[TW] OR "pharmacotherapeutic review"[TW] OR "pharmacotherapeutic intervention"[TW] OR "pharmacotherapeutic program"[TW] OR "pharmacotherapeutic assessment"[TW] OR "pharmacotherapeutic management"[TW] OR "pharmacotherapeutic care"[TW] OR "pharmacotherapeutic consult"[TW] OR "pharmacotherapeutic counselling"[TW] OR "pharmacotherapeutic evaluation"[TW] OR "pharmacotherapeutic

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Additional file 2. Risk of bias assessment: sensitivity analysis

Table 1. Sensitivity analysis regarding a more stringent cut-off point for risk of bias

	Trials changed from low risk of bias to high risk of bias					Percentage of intervention patients in trials showing effect	Risk of bias with actually used threshold for risk of bias (% studies with LRB*)	Risk of bias with more stringent threshold for risk of bias (% studies with LRB*)	Conclusion with actually used threshold for risk of bias	Conclusion with more stringent threshold for risk of bias
Outcome measure	**Kwint**	**Lisby (2010)**	**Pope**	**Zermanksy (2001/2002)**	**Zermansky (2006)**					
Mortality		x	x	x	x	6%	low (79%)	high (34%)	no effect	no effect
Total nr hospital admissions		x	x		x	20%	low (75%)	low (51%)	no effect	no effect
Nr patients admitted to hospital				x	x	26%	low (74%)	high (28%)	no effect	no effect
Time to first (re) admission		x				0%	low (100%)	low (90%)	no effect	no effect
Length of hospital stay		x				0%	high (22%)	high (18%)	no effect	no effect
Nr emergency admissions		x	x			38%	low (81%)	low (68%)	no effect	no effect
Nr GP visits		x		x	x	0%	low (100%)	high (39%)	no effect	no effect
Nr outpatient visits		x		x		0%	low (88%)	high (33%)	no effect	no effect
Nr patients admitted to residential home						0%	high (36%)	high (36%)	no effect	no effect
Nr falls per patient					x	71%	low (71%)	high (0%)	effect	**inconclusive**
Nr patients falling					x	44%	low (62%)	high (27%)	inconclusive	inconclusive
Barthel index			x		x	0%	low (100%)	high (12%)	no effect	no effect
SMMSE					x	0%	low (74%)	high (0%)	no effect	no effect
EQ-5D		x				0%	low (70%)	low (67%)	no effect	no effect
EQ-5D VAS		x				38%	high (42%)	high (36%)	inconclusive	inconclusive
SF-36						0%	low (69%)	low (69%)	no effect	no effect
Nr DRPs	x					87%	high (9%)	high (0%)	effect	effect
Nr drug changes	x			x	x	100%	low (100%)	high (0%)	effect	effect
Nr Drugs				x	x	63%	low (52%)	high (6%)	inconclusive	inconclusive
Nr drugs with dosage decrease						100%	high (35%)	high (35%)	effect	effect
Nr drugs with dosage increase						0%	high (35%)	high (35%)	no effect	no effect
Drug costs				x	x	44%	low (66%)	high (30%)	inconclusive	inconclusive

Additional file 3. Best evidence synthesis: sensitivity analysis

Table 1. Sensitivity analysis with regard to the impact of large trials with high risk of bias on every individual outcome measure in the best evidence synthesis.

Outcome measure	Median number of intervention patients of trials using this outcome measure	Trials with a high risk of bias and number of intervention patients > median number of intervention patients of trials using this outcome measure	Percentage intervention patients in trials showing effect based on all included trials	Percentage intervention patients in trials showing effect after exclusion of large trials with high risk of bias	Risk of bias based on all included trials	Risk of bias after exclusion of large trials with high risk of bias	Conclusion based on all included trials	Conclusion after exclusion of large trials with high risk of bias
Mortality	150	Heselmans (301)	6%	7%	low (79%)	low (90%)	No effect	No effect
Total nr hospital admissions	168	Gallagher (190)	20%	23%	low (75%)	low (83%)	No effect	No effect
		Holland (415)						
Nr patients admitted to hospital	415	Briggs (525)	26%	0%	low (74%)	low (100%)	No effect	No effect
Time to first (re)admission	518	N/A	0%	0%	low (100%)	low (100%)	No effect	No effect
Length of hospital stay	136	Briggs (525)	0%	0%	high (22%)	low (58%)	No effect	No effect
		Heselmans (301)						
Nr emergency admissions	110	Krska (168)	38%	44%	low (81%)	low (94%)	No effect	**Inconclusive**
Nr GP visits	261	N/A	0%	0%	low (100%)	low (100%)	No effect	No effect
Nr outpatient visits	258	N/A	0%	0%	low (88%)	low (88%)	No effect	No effect
Nr patients admitted to residential home	413	Briggs (525)	0%	0%	high (36%)	low (100%)	No effect	No effect
Nr falls per patient	234	N/A	71%	71%	low (71%)	low (71%)	Effect	Effect
Nr patients falling	261	Pit (350)	44%	10%	low (62%)	low (100%)	Inconclusive	**No effect**
Barthel index	110	N/A	0%	0%	low (100%)	low (100%)	No effect	No effect
SMMSE	225	N/A	0%	0%	low (74%)	low (74%)	No effect	No effect
EQ-5D	192	Pit (350)	0%	0%	low (70%)	low (90%)	No effect	No effect
EQ-5D VAS	72	Pit (346)	38%	67%	high (42%)	low (74%)	Inconclusive	**Effect**
SF-36	274	N/A	0%	0%	low (69%)	low (69%)	No effect	No effect
Nr DRPs	122	Heselmans (301)	87%	42%	high (9%)	high (42%)	Effect	**Inconclusive**
		Krska (168)						
Nr drug changes	331	N/A	100%	100%	low (100%)	low (100%)	Effect	Effect
Nr Drugs	74		63%	58%	low (52%)	low (83%)	Effect	**Inconclusive**
Nr drugs with dosage decrease	243	Britton (315)	100%	100%	high (35%)	low (100%)	Effect	Effect
Nr drugs with dosage increase	243	Britton (315)	0%	0%	high (35%)	low (100%)	No effect	No effect
Drug costs	168	Britton (315)	44%	36%	low (66%)	low (95%)	Inconclusive	**No effect**

LRB = Low risk of bias; x = outcome measure used in trial

Additional file 4. Data not shown in the results section of the main text of the manuscript

Table 1. Effect of medication review on mortality

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N) (%)	Control (n/N) (%)	RR (95% CI) (I^2, p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	4/136 (3)	14/158 (9)	0.33 (0.11, 0.98)	HRB
Gallagher[35] (2011)	6	R: (research) physician, medical team D: physician	No	≥ 65*	No	Emergency admission*	10/190 (5)	14/192 (7)	0.72 (0.33, 1.58)	LRB
Heselmans[37] (2015)	0†	R: Pharmacist D: Ward physician	No	>15*	No	ICU stay of at least three consecutive day*	22/301	22/299	0.99 (0.56, 1.75)	HRB
Holland[38] (2005)	6	R: (study) pharmacist D: pharmacist or GP	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*	49/415 (12)	63/414 (15)	0.78 (0.55, 1.10)	LRB
Lenaghan[44] (2007)	6	R: study-pharmacist D: GP and study-pharmacist	Yes	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines	7/69 (10)	6/67 (9)	1.13 (0.40, 3.19)	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	8/50 (16)	5/49 (10)	1.57 (0.55, 4.46)	LRB
Lisby[48] (2015)	3	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	≥ 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours	3/53 (6%)	3/55 (5%)		LRB

Mann-heimer[49] (2006)	6	P: nurse and clinical pharmacologist D: physician in charge	Yes	No	≥ 2*	patients who had been in hospital for < 24 hr on Tue. to Fri. or for < 60 hr on Mon. before a nurse screened the computerised medical record*	29/150 (19)	22/150 (15)	1.32 (0.79, 2.19)	LRB
Pope[56] (2011)	6	R: multidisciplinary panel D: General practitioner	No	No	No	permanent patients on the continuing-care wards	17/110 (15)	11/115 (10)	1.62 (0.79, 3.29)	LRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	15/598 (3)	25/579 (4)	0.58 (0.31, 1.09)	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	51/331 (15)	48/330 (15)	1.06 (0.74, 1.52)	LRB
Best evidence synthesis		136/2403 (6%) of intervention patients in a trial showing effect on mortality 1844/2403 (79%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on mortality							**Overall RR** 0.94 (0.76, 1.17) (I^2 = 22.0%, p = 0.172)	

mos.= months; HCP= healthcare professional; RR = risk ratio; *combination of inclusion criteria (= "and"); †outcome measures determined directly after discharge from hospital; ICU = intensive care unit; GP = general practitioner; hr = hours; LRB = low risk of bias; HRB = high risk of bias

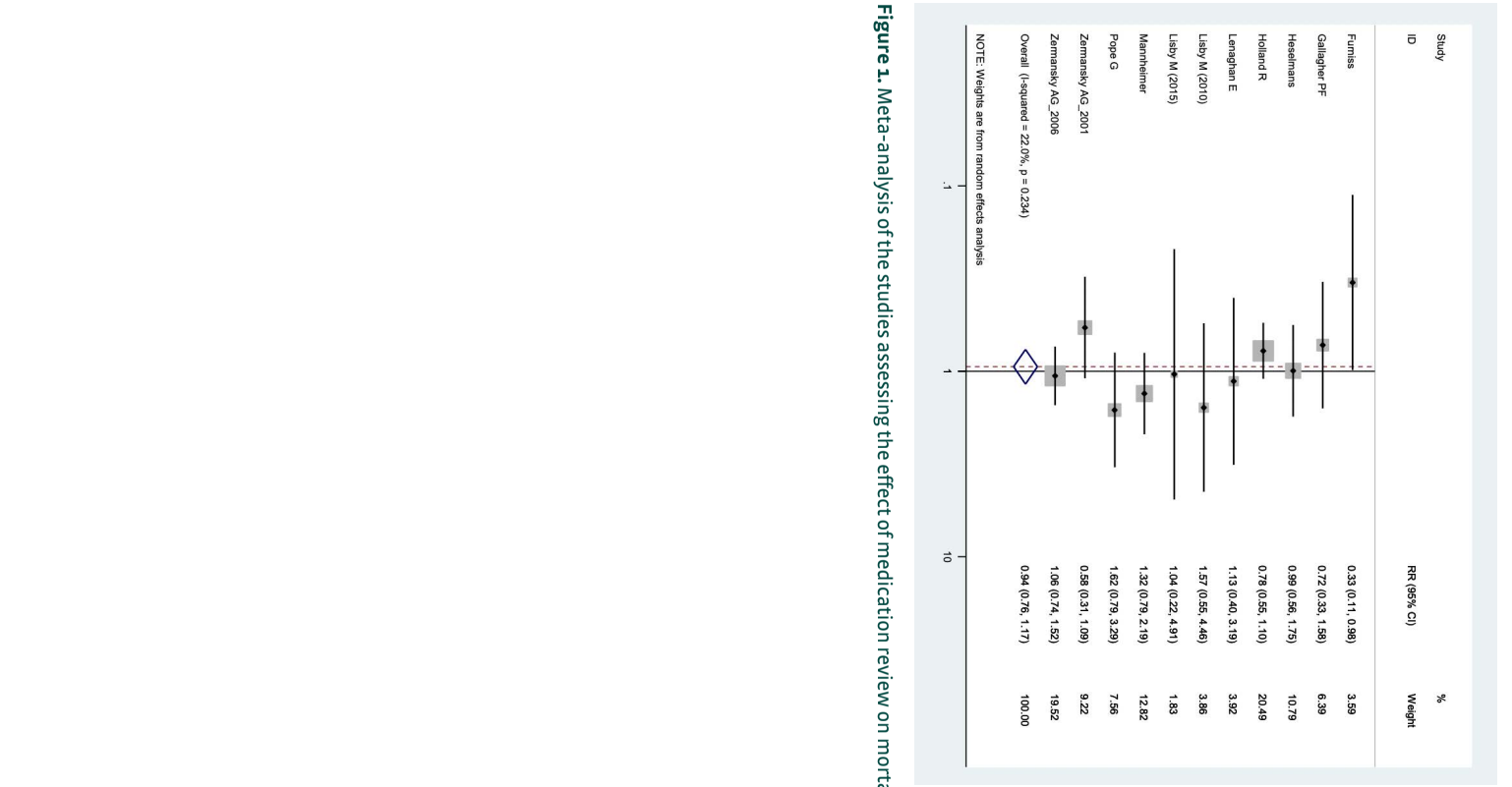

Figure 1. Meta-analysis of the studies assessing the effect of medication review on mortality

Table 2. Effect of medication review on the total number of hospital admissions

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N)	Control (n/N)	Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Gallagher[35] (2011)	6	R: (research) physician, medical team D: physician	No	≥ 65*	No	Emergency admission*	67/190	64/192	0.691	LRB
Graffen[36] (2004)	6	R: Pharmacist D: GP and patient	Yes	> 65*	≥ 5*	Living independently*; ≥ 1 of following*: use of predefined risk drugs; > 12 doses per day; > 6 diagnoses; BMI < 22	Nr (no. IP:202)	Nr	ns	HRB
Holland[38] (2005)	6	R: (study) pharmacist D: pharmacist or GP	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*	234/415	178/414	0.009	LRB
Krska[42] (2001)	3	R: Clinical pharmacist D: GP and pharmacist	Yes	≥ 65*	≥ 4*	≥ 2 chronic conditions*	12/168	13/164	ns	HRB
Lenaghan[44] (2007)	6	R: study-pharmacist D: GP and study-pharmacist	Yes	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines	21/68	20/66	0.8	HRB
Lenander[45] (2014)	12	R: Geriatrics pharmacist D: GP and patient	Yes	> 65*	≥ 5*	already scheduled for an appointment with a GP*	128/75	178/66	ns	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	25/50	29/49	ns	LRB
Lisby[48] (2015)	3	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	≥ 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours	27/53	17/55	0.37	LRB
Pope[56] (2011)	6	R: multidisciplinary panel D: General practitioner	No	No	No	permanent patients on the continuing-care wards	11/110	6/115	0.213	LRB
Sellors[58] (2003)	5	R: Pharmacist D: Physician	Yes	≥ 65*	≥ 5*	had been seen by their physician within; the past 12 months*; no evidence of cognitive impairment; could understand English.	129/379	139/409	0.28 (ed); 0.77 (all)	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	66/331	86/330	0.11	LRB
Best evidence synthesis		415/2041 (20%) of intervention patients in a trial showing effect on the number of hospital admissions 1528/2041 (75%) of intervention patients in a trial with a low risk of bias								
		Conclusion: **evidence with low risk of bias for no effect** of medication review on the number of hospital admissions								

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); IP = intervention patients; GP = general practitioner; ns = nonsignificant BMI = body mass index; hr = hours; ed = emergency department; LRB = low risk of bias; HRB = high risk of bias

Table 3. Effect of medication review on the number of patients with hospital admissions

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N) (%)	Control (n/N) (%)	RR (95% CI) (I^2, p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Briggs[31] (2015)	4	R: Hospital pharmacist D: GP	Yes	> 70*	> 5*	Living at home*	277/525	308/496	0.85 (0.76, 0.94)	HRB
Mann-heimer[49] (2006)	6	P: nurse and clinical pharmacologist D: physician in charge	Yes	No	≥ 2*	patients who had been in hospital for < 24 hr on Tue. To Fri. or for < 60 hr on Mon. before a nurse screened the computerized medical record*	60/150	53/150	1.13 (0.85, 1.52)	LRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	110/579	92/550	1.14 (0.88, 1.46)	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	47/331	52/330	0.90 (0.63, 1.30)	LRB
Zilich[62] (2014)	2	R: Pharmacist D: Patient, pharmacist, physician	Yes	No	No	All new patients admitted into Medicare's defined 60-day home health care episode were eligible. Medicare eligibility for home health benefits requires ordering services by a physician who reviews the need for a patient's care and certifies that the patient is homebound	83/415	112/480	0.86 (0.67, 1.10)	LRB
Best evidence synthesis		525/2000 (26%) of intervention patients in a trial showing effect on the number of patients admitted to the hospital 1475/2000 (74%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the number of patients admitted to the hospital							**Overall RR** 0.94 (0.82, 1.08) (I^2 = 42.3%, p = 0.139)	

mos.= months; HCP= healthcare professional; *combination of inclusion criteria (= "and"); GP = general practitioner; hr = hours; LRB = low risk of bias; HRB = high risk of bias

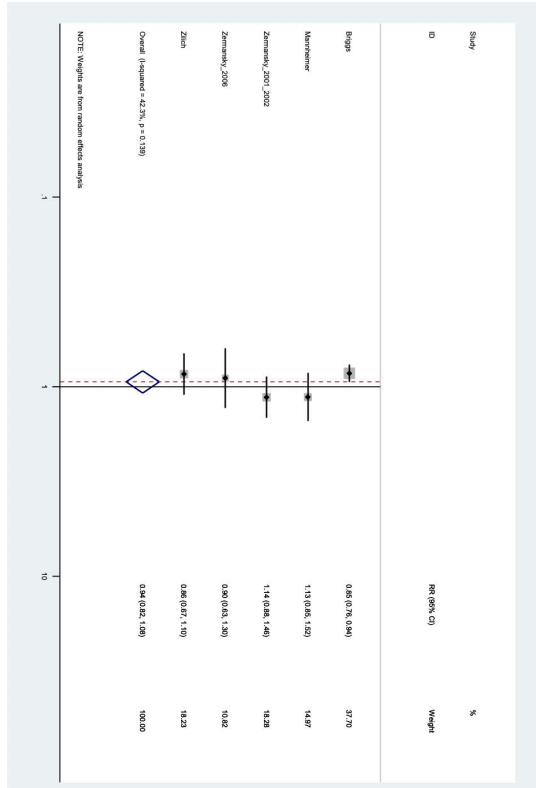

Figure 2. Meta-analysis of the studies assessing the effect of medication review on the number of patients with hospital admissions

Table 4. Effect of medication review on time to first hospital (re)admission

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	Time (days)	No. pts.	Time (days)		
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	50	Nr	49	Nr	0.92	LRB
Lisby[48] (2015)	3	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	≥ 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours	53	76	55	78	0.46	LRB
Zillich[62] (2014)	2	R: Pharmacist D: Patient, pharmacist, physician	Yes	No	No	All new patients admitted into Medicare's defined 60-day home health care episode were eligible. Medicare eligibility for home health benefits requires ordering services by a physician who reviews the need for a patient's care and certifies that the patient is homebound	415	Nr	480	Nr	0.12	LRB
Best evidence synthesis		0/518 (0%) of intervention patients in a trial showing effect on the time to first (re)admission 518/518 (100%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the time to first (re)admission										

mos.= months; HCP= healthcare professional; *combination of inclusion criteria (= "and"); Nr = not reported; hr = hours; LRB = low risk of bias

Table 5. Effect of medication review on the length of hospital stay (days)

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	Stay (days)	No. pts.	Stay (days)		
Briggs[31] (2015)	4	R: Hospital pharmacist D: GP	Yes	> 70*	> 5*	Living at home*	525	6	496	6	0.87	HRB
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	136	0.55	158	1.26	ns	HRB
Gallagher[35] (2011)	6	R: (research) physician, medical team D: physician	No	≥ 65*	No	Emergency admission*	190	8	192	8.5	0.471	LRB
Heselmans[37] (2015)	0†	R: Pharmacist D: Ward physician	No	>15*	No	ICU stay of at least three consecutive day*	301	34.2	299	34.5	ns	HRB
Lenander[45] (2014)	12	R: Geriatrics pharmacist D: GP and patient	Yes	> 65*	≥ 5*	already scheduled for an appointment with a GP*	75	12	66	18	ns	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	50	10	49	9.9	ns	LRB
Lisby[48] (2015)	3	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	≥ 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours	53	7.5	55	7	0.65	LRB
Best evidence synthesis		0/11330 (0%) of intervention patients in a trial showing effect on the length of hospital stay 293/1330 (22%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with a high risk of bias for no effect** of medication review on the length of hospital stay										

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); GP = general practitioner; ns = nonsignificant; †determined directly after hospital discharge; hr = hours; LRB = low risk of bias; HRB = high risk of bias

Table 6. Effect of medication review on the number of emergency admissions/visits

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N)	Control (n/N)	Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Holland[38] (2005)	6	R: (study) pharmacist D: pharmacist or GP	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*	234/415	178/414	0.009	LRB
Krska[42] (2001)	3	R: Clinical pharmacist D: GP and pharmacist	Yes	≥ 65*	≥ 4*	≥ 2 chronic conditions*	6/168	8/164	ns	HRB
Lenaghan[44] (2007)	6	R: study-pharmacist D: GP and study-pharmacist	Yes	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines	21/68	20/66	0.8	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	mei-50	mei-49	ns	LRB
Lisby[48] (2015)	3	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	≥ 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours	nov-53	22/55	.01	LRB
Pope[56] (2011)	6	R: multidisciplinary panel D: General practitioner	No	No	No	permanent patients on the continuing-care wards	11/110	6/115	0.213	LRB
Sellors[58] (2003)	5	R: Pharmacist D: Physician	Yes	≥ 65*	≥ 5*	had been seen by their physician within; the past 12 months*; no evidence of cognitive impairment; could understand English.	76/379	94/409	0.28	LRB
Best evidence synthesis		468/1243 (38%) of intervention patients in a trial showing effect on the number of emergency admissions 1007/1243 (81%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the number of emergency admissions								

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); GP = general practitioner; hr = hours; ns = nonsignificant; LRB = low risk of bias; HRB = high risk of bias

Table 7. Effect of medication review on the number of GP visits

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N)	Control (n/N)	Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Gallagher[35] (2011)	6	R: (research) physician, medical team D: physician	No	≥ 65*	No	Emergency admission*	Nr (IP:190)	Nr	0.063	LRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	440/50	515/49	ns	LRB
Lisby[48] (2015)	3	R: Clinical pharmacist and a clinical pharmacologist D: Orthopedic ward physicians	Yes	≥ 65*	≥ 4*	nonelective admission at orthopedic ward*; expected in-hospital length of stay (LOS) of a minimum of 24 hours	aug-53	aug-55	0.97	LRB
Sellors[58] (2003)	5	R: Pharmacist D: Physician	Yes	≥ 65*	≥ 5*	had been seen by their physician within; the past 12 months*; no evidence of cognitive impairment; could understand English.	1956/379	2033/409	0.65	LRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	Nr (IP: 579)	Nr (IP:550)	0.69	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	960/331	924/330	0.5	LRB
Best evidence synthesis		0/1582 (0%) of intervention patients in a trial showing effect on the number of GP visits 1529/1582 (100%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the number of GP visits								

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); GP = general practitioner; Nr= not reported; hr = hours; ns = nonsignificant; LRB = low risk of bias;

Table 8. Effect of medication review on the number of outpatient visits

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N)	Control (n/N)	Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	41/136	84/158	ns	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	60/50	54/49	ns	LRB
Sellors[58] (2003)	5	R: Pharmacist D: Physician	Yes	≥ 65*	≥ 5*	had been seen by their physician within; the past 12 months*; no evidence of cognitive impairment; could understand English.	110/379	127/409	0.4	LRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	Nr (IP: 579)	Nr (IP:550)	0.41	LRB
Best evidence synthesis		0/1144 (0%) of intervention patients in a trial showing effect on the number of outpatient visits 1008/1144 (88%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the number of outpatient visits								

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and); GP = general practitioner; Nr= not reported; hr = hours; ns = nonsignificant; LRB = low risk of bias; HRB = high risk of bias

Table 9. Effect of medication review on the number of patients admitted to residential homes

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention (n/N) (%)	Control (n/N) (%)	RR (95% CI) (I^2, p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other				
Briggs[31] (2015)	4	R: Hospital pharmacist D: GP	Yes	> 70*	> 5*	Living at home*	31/525	25/496	1.17 (0.70, 1.96)	HRB
Holland[38] (2005)	6	R: (study) pharmacist D: pharmacist or GP	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*	21/300	17/285	1.17 (0.63, 2.18)	LRB
Best evidence synthesis		0/825 (0%) of intervention patients in a trial showing effect on the number of patients admitted to residential homes 300/825 (36%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with a high risk of bias for no effect** of medication review on the number of patients admitted to residential homes							**Overall RR** 1.17 (0.79, 1.74) (I^2 = 0.0%, p = 0.997)	

mos.= months; HCP = healthcare professional; RR= risk ratio; *combination of inclusion criteria (= "and"); GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias

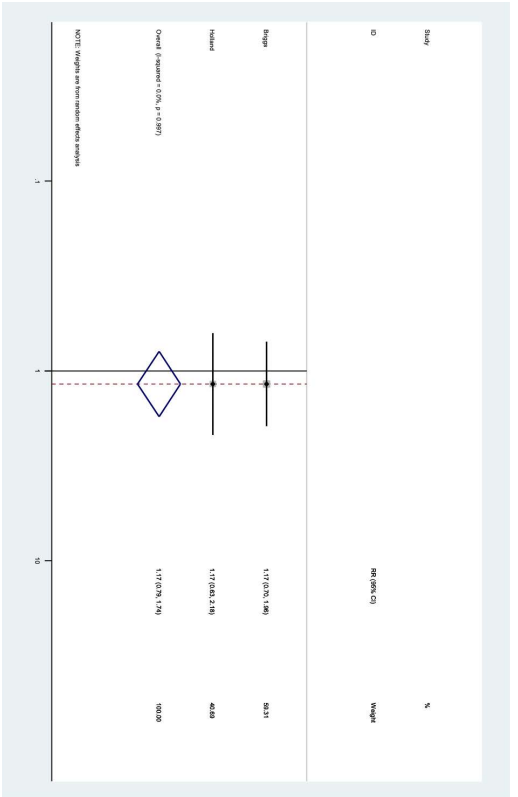

Figure 3. Meta-analysis of the studies assessing the effect of medication review on the number of patients admitted to residential homes

Table 10. Effect of medication review on the number of falls per patient

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention			Control			Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	t=0	t=1	No. pts.	t=0	t=1		
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	136	Nr	Nr	158	Nr	Nr	ns	HRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	331	1	0.8	330	0.9	1.3	<0.0001	LRB
Best evidence synthesis		331/467 (71%) of intervention patients in a trial showing effect on the number of falls 331/467 (71%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for effect** of medication review on the number of falls: medication review decreases the number of falls												

mos.= months; HCP = healthcare professional; Nr= not reported; ns = nonsignificant; *combination of inclusion criteria (= "and"); GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias

Table 11. Effect of medication review on the number of patients falling

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention			Control			RR (95% CI) (I^2, p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	t=0	t=1	No. pts.	t=0	t=1		
Gallagher[35] (2011)	6	R: (research) physician, medical team D: physician	No	≥ 65*	No	Emergency admission*	190	32	11	192	44	16	0.69 (0.33, 1.46)	LRB
Michalek[52] (2014)	0†	R: Physicians D: Physicians	No	> 70*	≥ 3*	admitted to the acute geriatric unit*, stable health condition defined as no need for intermediate or intensive care unit treatment*, had at least three diseases in need for drug treatment*.	58	Nr	2	56	Nr	12	0.16 (0.04, 0.69)	LRB
Pit[55] (2007)	12	R: Doctors D: Doctors	Yes	≥ 65*	No	living in the community*	350	86	70	309	100	94	0.66 (0.50, 0.86)	HRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	331	145	84	330	128	106	0.79 (0.62, 1.01)	LRB
Best evidence synthesis		408/929 (44%) of intervention patients in a trial showing effect on the number of patients falling 579/929 (62%) of intervention patients in a trial with a low risk of bias Conclusion: based on meta-analysis: **evidence with low risk of bias for effect** of medication review on the number of patients falling (see figure 4): medication review decreases the number of patients falling based on best evidence synthesis: **evidence (with a low risk of bias) is inconclusive** about the effect of medication review on the number of patients falling											**Overall RR** 0.68 (0.52, 0.90) (I^2 = 41.0%, p = 0.166)	

mos.= months; HCP = healthcare professional; RR= risk ratio; Nr= not reported; *combination of inclusion criteria (= "and"); †determined directly after hospital discharge
GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias

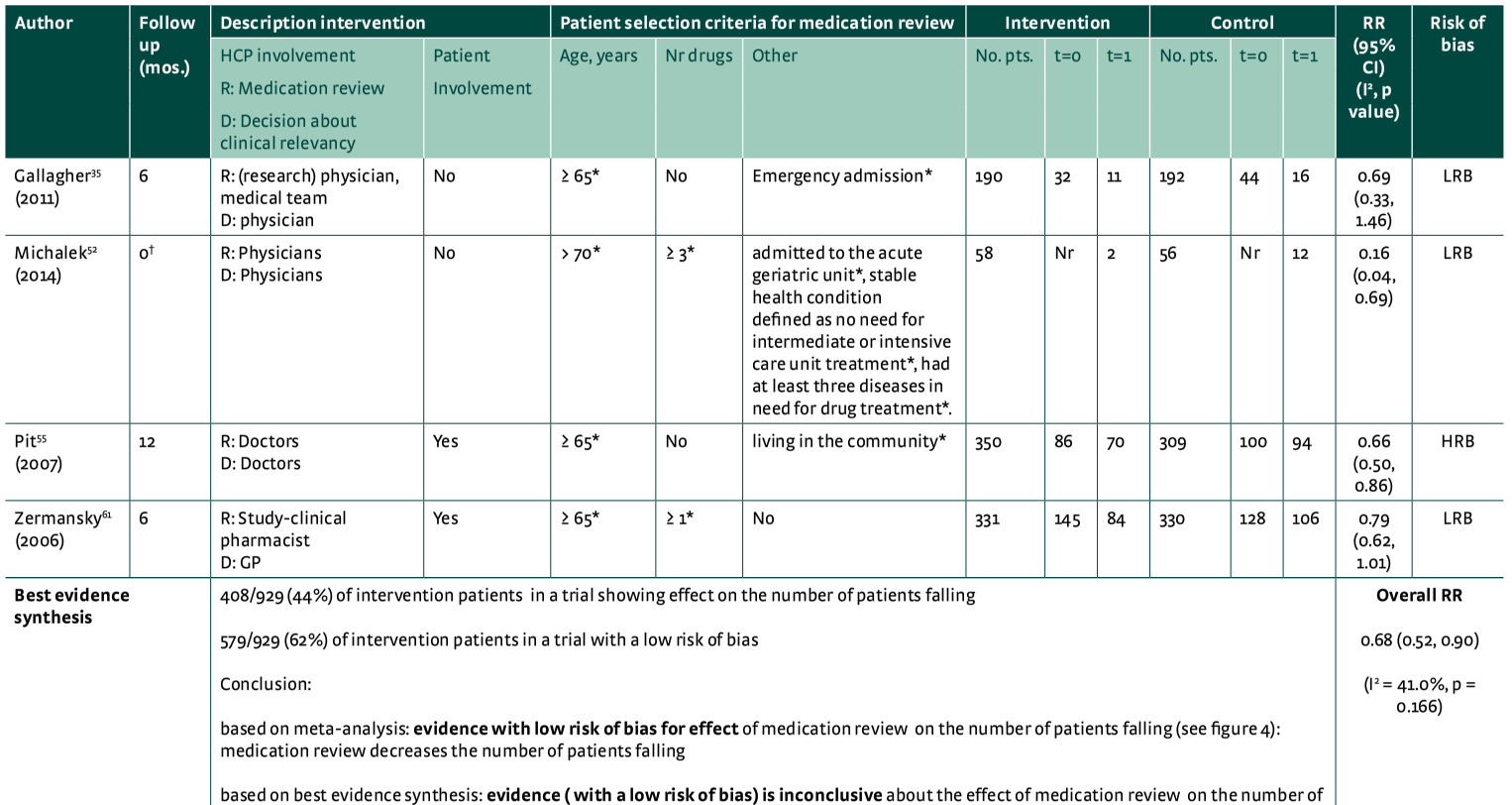

Figure 4. Meta-analysis of the studies assessing the effect of medication review on the number of patients falling

Table 12. Effect of medication review on the Barthel index

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Outcome measure	Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other		t=0 (n)	t=1 (n)	t=0 (n)	t=1 (n)		
Pope[56] (2011)	6	R: multidisciplinary panel D: General practitioner	No	No	No	permanent patients on the continuing-care wards	Barthel index	5.95 (n=110)	5.94 (n=110)	6.75 (n=115)	6.62 (n=115)	ns	LRB
Michalek[52] (2014)	0†	R: Physicians D: Physicians	No	> 70*	≥ 3*	admitted to the acute geriatric unit*, stable health condition defined as no need for intermediate or intensive care unit treatment*, had at least three diseases in need for drug treatment*.	Barthel index	Nr (n=58)	Nr (n=58)	Nr (n=56)	Nr (n=56)	0.226	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	Barthel index	10.00 (n=331)	9.80 (n=331)	10.10 (n=330)	9.30 (n=330)	0.06	LRB
Best evidence synthesis		0/499 (0%) of intervention patients in a trial showing effect on the Barthel index 499/499 (100%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the Barthel index											

mos.= months; HCP = healthcare professional; RR= risk ratio; ns = nonsignificant; Nr= not reported; *combination of inclusion criteria (= "and"); †determined directly after hospital discharge; GP = general practitioner; LRB = low risk of bias

Table 13. Effect of medication review on the Standard Mini Mental State Examination

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Outcome measure	Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other		t=0 (n)	t=1 (n)	t=0 (n)	t=1 (n)		
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	SMMSE	13.50 (n=132)	12.50 (n=118)	15.50 (n=149)	17.10 (n=116)	0.07	HRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	SMMSE	13.8 (n=331)	13.9 (n=331)	13.1 (n=330)	13.8 (n=330)	0.62	LRB
Best evidence synthesis		0/449 (0%) of intervention patients in a trial showing effect on the MMSE 331/449 (74%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the MMSE											

mos.= months; HCP = healthcare professional; SMMSE = Standard Mini Mental State Examination; *combination of inclusion criteria (= "and"); GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias

Table 14. Effect of medication review on the quality of life

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Outcome measure	Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other		t=0 (n)	t=1 (n)	t=0 (n)	t=1 (n)		
Bond[30] (2007)	12	R: Pharmacist D: GP	No	< 65 *	No	Specific conditions*	EQ-5D	Nr (n=899)	Nr (n=761)	Nr (n=914)	Nr (n=769)	ns	LRB
Holland[38] (2005)	6	R: (study) pharmacist D: pharmacist or GP	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*	EQ-5D	0.59 (n=422)	0.46 (n=311)	0.63 (n=417)	0.50 (n=288)	0.84	LRB
Lenaghan[44] (2007)	6	R: study-pharmacist D: GP and study-pharmacist	Yes	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines	EQ-5D	0.62 (n=68)	0.57 (n=56)	0.57 (n=66)	0.56 (n=49)	0.10	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	EQ-5D	Nr (n=50)	Nr (n=33)	Nr (n=49)	Nr (n=36)	ns	LRB
Olsson[54] (2012)	12	R: study-physician D: Family physician	Yes	≥ 75*	≥ 5*	living in ordinary homes*	EQ-5D	Arm B 0.65 (n=49) Arm C 0.61 (n=48)	Arm B 0.61 (n=39) Arm C 0.40 (n=33)	Arm B 0.61 (n=47) Arm C 0.61 (n=47)	Arm B 0.73 (n=34) Arm C 0.73 (n=34)	ns	HRB
Pit[55] (2007)	12	R: Doctors D: Doctors	Yes	≥ 65*	No	living in the community*	EQ-5D	0.83 (n=395)	0.89 (n=350)	0.78 (n=348)	0.87 (n=309)	0.7	HRB
Krska[42] (2001)	3	R: Clinical pharmacist D: GP and pharmacist	Yes	≥ 65*	≥ 4*	≥ 2 chronic conditions*	SF-36	Nr (n=168)	Nr (n=168)	Nr (n=164)	Nr (n=164)	ns	HRB
Sellors[58] (2003)	5	R: Pharmacist D: Physician	Yes	≥ 65*	≥ 5*	had been seen by their physician within; the past 12 months*; no evidence of cognitive impairment; could understand English.	SF-36	nr (n=431)	nr (n=379)	nr (n=458)	nr (n=409)	ns	LRB
Holland[38] (2005)	6	R: (study) pharmacist D: pharmacist or GP	Yes	> 80*	≥ 2*	Discharged after emergency admission to own home or warden controlled accommodation*	EQ-5D VAS for health	62.2 (n=404)	54.9 (n=303)	62.3 (n=406)	58.8 (n=275)	0.042	LRB
Lenaghan[44] (2007)	6	R: study-pharmacist D: GP and study-pharmacist	Yes	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines	EQ-5D VAS for health	63.7 (n=67)	63.8 (n=44)	65.2 (n=64)	68.3 (n=48)	0.21	HRB
Lisby[47] (2010)	3	R: Clinical pharmacist and a clinical pharmacologist D: ward physicians	Yes	≥ 70*	≥ 1*	expected to be admitted for more than 24 hr*	EQ-5D VAS for health	Nr (n=50)	60.9 (n=33)	Nr (n=49)	54.7 (n=36)	0.31	LRB

Olsson[54] (2012)	12	R: study-physician D: Family physician	Yes	≥ 75*	≥ 5*	living in ordinary homes*	EQ-5D VAS for health	Arm B 51 (n=49) Arm C 51 (n=48)	Arm B 54 (n=39) Arm C 56 (n=33)	Arm B 50 (n=47) Arm C 50 (n=47)	Arm B 56 (n=34) Arm C 56 (n=34)	ns	HRB
Pit[55] (2007)	12	R: Doctors D: Doctors	Yes	≥ 65*	No	living in the community*	EQ-5D VAS for health	77.0 (n=389)	80.4 (n=346)	73.5 (n=348)	77.9 (n=302)	0.54	HRB
Best evidence synthesis		0/1583 (0%) of intervention patients in a trial showing effect on quality of life, measured with the **EQ-5D questionnaire** 1105/1583 (70%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the quality of life measured with the **EQ-5D questionnaire** 0/547 (0%) of intervention patients in a trial showing effect on quality of life, measured with the **SF-36 questionnaire** 379/547 (69%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for no effect** of medication review on the quality of life measured with the **SF-36 questionnaire** 303/798 (38%) of intervention patients in a trial showing effect on quality of life, measured with the **EQ-5D VAS for health** 336/798 (42%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence (with a high risk of bias) is inconclusive about the effect** of medication review on the quality of life measured with the **EQ-5D VAS for health**										

mos.= months; HCP = healthcare professional; Nr = not reported; ns = nonsignificant; *combination of inclusion criteria (= "and"); GP = general practitioner; hr =hours; LRB = low risk of bias; HRB = high risk of bias

Table 15. Effect of medication review on the number of drug-related problems

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention			Control			Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	t=0	t=1	No. pts.	t=0	t=1		
Heselmans[37] -2015	0†	R: Pharmacist D: Ward physician	No	>15*	No	ICU stay of at least three consecutive day*	301	375	172	299	368	321	<0.001	HRB
Krska[42] -2001	3	R: Clinical pharmacist D: GP and pharmacist	Yes	≥ 65*	≥ 4*	≥ 2 chronic conditions*	168	1206	256	164	1380	838	significant‡	HRB
Kwint[43] -2011	6	R: 2 research pharmacists D: GP and community pharmacist	No	≥ 65*	≥ 5*	living at home*; at least one drug had to be dispensed via an automated system*	55	249	175	53	231	221	<0.01	LRB
Lenander[45] -2014	12	R: Geriatrics pharmacist D: GP and patient	Yes	> 65*	≥ 5*	already scheduled for an appointment with a GP*	75	130	98	66	90	73	0.72	HRB
Best evidence synthesis		524/599 (87%) of intervention patients in a trial showing effect on the number of drug-related problems 55/599 (9%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with a high risk of bias for effect** of medication review on the number of drug-related problems: medication review decreases the number of drug-related problems												

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); ICU= intensive care unit; GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias; †determined directly after hospital discharge; ‡no p value reported

Table 16. Effect of medication review on the number of drug changes

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	Mean no. drug changes	No. pts.	Mean no. drug changes		
Kwint[43] (2011)	6	R: 2 research pharmacists D: GP and community pharmacist	No	≥ 65*	≥ 5*	living at home*; at least one drug had to be dispensed via an automated system*	55	2.2	53	1	0.02	LRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	579	2.2	550	1.9	0.02	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	331	3.1	330	2.4	<0.0001	LRB
Best evidence synthesis		965/965 (100%) of intervention patients in a trial showing effect on the number of drug changes 965/965 (100%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for effect** of medication review on the number of drug changes: medication review increases the number of drug changes										

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias

Table 17. Effect of medication review on the number of drugs with a dosage decrease

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	Mean no. drugs with dosage decrease	No. pts.	Mean no. drugs with dosage decrease		
Britton[32] -1991	3	R: Clinical pharmacist D: physician (assistant)	No	No	> 5	No	315	0.09	257	0.03	0.006	HRB
Milos[53] -2013	2	R: Clinical pharmacist D: Physician	No	≥ 75*	No	users of the multi-dose drug dispensing system; living in nursing homes or their own homes with municipally provided home care	171	0.06	174	0	0.03	LRB
Best evidence synthesis		486/486 (100%) of intervention patients in a trial showing effect on the number of drugs with a dosage decrease 171/486 (35%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with a high risk of bias for effect** of medication review on the number of drugs with a dosage decrease: medication review increases the number of drugs with a dosage decrease										

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); LRB = low risk of bias; HRB = high risk of bias

Table 18. Effect of medication review on the number of drugs with a dosage increase

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other	No. pts.	Mean no. drugs with dosage decrease	No. pts.	Mean no. drugs with dosage decrease		
Britton[32] (1991)	3	R: Clinical pharmacist D: physician (assistant)	No	No	> 5	No	315	0.12	257	0.1	ns	HRB
Milos[53] (2013)	2	R: Clinical pharmacist D: Physician	No	≥ 75*	No	users of the multi-dose drug dispensing system; living in nursing homes or their own homes with municipally provided home care	171	0.006	174	0.006	0.995	LRB
Best evidence synthesis		0/486(0%) of intervention patients in a trial showing effect on the number of drugs with a dosage increase 171/486 (35%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with a high risk of bias for no effect** of medication review on the number of drugs with a dosage increase										

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); ns = nonsignificant; LRB = low risk of bias; HRB = high risk of bias

Table 19. Effect of medication review on the number of drugs

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Outcome measure	Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other		t=0	t=1	t=0	t=1		
Britton[32] (1991)	0*	R: Clinical pharmacist D: physician (assistant)	No	No	> 5	No	Nr drugs/ patient	8.72 (n=315)	-0.21 (n=315)	8.52 (n=257)	0.48 (n=257)	<0.001	HRB
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	Mean nr of prescribed drugs	5.1 (n=136)	4.2 (n=132)	4.5 (n=158)	4.4 (n=144)	<0.05	HRB
Jameson[40] (1995)	6	R: Clinical pharmacist D: Physician and pharmacist	Yes	No	≥ 5 (see other)	≥ 2 of following risk factors: ≥ 5 drugs; ≥ 12 daily doses; ≥ 4 medication changes last 12 mos.; >3 concurrent diseases; noncompliance; drugs requiring TDM	number of chronic prescription medications	5.6 (n=27)	5 (n=27)	5.7 (n=29)	6.2 (n=29)	0.004	HRB
Lenaghan[44] (2007)	6	R: study-pharmacist D: GP and study-pharmacist	Yes	> 80*	≥ 4*	living in own homes*; ≥ 1 of following criteria*: living alone; confused mental state, vision or hearing impairment; prescribed medicines associated with medication-related morbidity; prescribed >7 regular oral medicines	number of drug items prescribed	9.01 (n=68)	8.68 (n=59)	9.85 (n=66)	10.33 (n=55)	0.03	HRB

Lenander[45] (2014)	12	R: Geriatrics pharmacist D: GP and patient	Yes	> 65*	≥ 5*	already scheduled for an appointment with a GP*	number of drugs	8.6 (n=75)	7.9 (n=75)	7.4 (n=66)	7.5 (n=66)	0.046	HRB
Lim[46] (2004)	2	R: pharmacist (of a pharmacist consult clinic) D: primary physician	Yes	No	> 3 (see other)	≥ 1 of following criteria: TDM required; polypharmacy (>3 drugs or >9 doses per day); non-compliance; self-administered drugs that require psychomotor skill and co-ordination; nasogastric tube feeding; >1 doctor managing care; hospitalized within the last 6 months.	Mean number of medications	nr (n=64)	nr (n=64)	nr (n=62)	nr (n=62)	0.11	LRB
Michalek[52] (2014)	0†	R: Physicians D: Physicians	No	> 70*	≥ 3*	admitted to the acute geriatric unit*, stable health condition defined as no need for intermediate or intensive care unit treatment*, had at least three diseases in need for drug treatment*.	Median number of drugs	6 (n=58)	8 (n=58)	6 (n=56)	7 (n=56)	0.915	LRB
Meyer[51] (1991)	12	R: study-physician (Group III, intensive intervention) D: Physicians and nurse practitioners	No	No	≥ 10	being followed by providers at the medical center	Number of drugs	11.6 (n=206)	8.6 (n=206)	11.8 (n=88)	8.9 (n=88)	0.230	HRB

Olsson[54] (2012)	12	R: study-physician D: Family physician	Yes	≥ 75*	≥ 5*	living in ordinary homes*	Nr drugs/ patient	Arm B 10 (n=49) Arm C 10 (n=50)	Arm B 11 (n=39) Arm C 10 (n=33)	Arm B 8 (n=48) Arm C 8 (n=48)	Arm B 9 (n=33) Arm C 9 (n=33)	ns	HRB
Williams[59] (2004)	1.5	R: Interdisciplinary team (consultant pharmacist, physician and nurse) D: Primary physician	Yes	≥ 65*	≥ 5*	≥ 2 of the medications were potentially problematic drugs for common geriatric problems*; cognitively intact *	number prescription medication	11.7 (n=57)	10.2 (n=57)	12.3 (n=76)	12.2 (n=76)	0.001	HRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	Mean nr of repeat prescriptions over a 12 month period	4.8 (n=596)	5 (n=576)	4.6 (n=577)	5 (n=549)	0.01	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	number of repeat medicines per participant	6.9 (n=331)	6.7 (n=331)	6.9 (n=330)	6.9 (n=330)	0.5	LRB
Best evidence synthesis		1241/1972 (63%) of intervention patients in a trial showing effect on the number of drugs 1029/1972 (52%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence with low risk of bias for effect** of medication review on the number of drugs: medication review leads to a greater decrease or smaller increase of the number of drug											

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); Nr = not reported; GP = general practitioner; ns = nonsignificant; †determined directly after hospital discharge; LRB = low risk of bias; HRB = high risk of bias

Table 20. Effect of medication review on drug costs

Author	Follow up (mos.)	Description intervention		Patient selection criteria for medication review			Outcome measure	Intervention		Control		Significance (p value)	Risk of bias
		HCP involvement R: Medication review D: Decision about clinical relevancy	Patient Involvement	Age, years	Nr drugs	Other		t=0	t=1	t=0	t=1		
Bond[30] (2007)	12	R: Pharmacist D: GP	No	< 65 *	No	Specific conditions*	£/6mos.	Nr (n=899)	nr (n=761)	nr (n=914)	nr (n=769)	ns	LRB
Britton[32] (1991)	0†	R: Clinical pharmacist D: physician (assistant)	No	No	> 5	No	$	43.7 (n=315)	-0.6 (n=315)	40.84 (n=257)	3.31 (n=257)	<0.001	HRB
Burns[33]/ Furniss[34] (2000)	4	R: (study) pharmacist D: multidisciplinary team	No	No	No	Living in nursing home	$/4mos.	254.42 (n=136)	210.46 (n=132)	228.04 (n=158)	225.98 (n=144)	Significant‡	HRB
Jameson[40] -1995	6	R: Clinical pharmacist D: Physician and pharmacist	Yes	No	≥ 5 (see other)	≥ 2 of following risk factors: ≥ 5 drugs; ≥ 12 daily doses; ≥ 4 medication changes last 12 mos.; >3 concurrent diseases; noncompliance; drugs requiring TDM	$/6 mos.	929 (n=27)	799 (n=27)	889 (n=29)	1052 (n=29)	0.008	HRB
Jameson[41] (2001)	6	R: Clinical pharmacist D: GP and pharmacist	Yes	No	≥ 5	No	$/6 mos.	1593 (n=144)	1657 (n=144)	1582 (n=124)	1602 (n=124)	ns	HRB
Krska[42] (2001)	3	R: Clinical pharmacist D: GP and pharmacist	Yes	≥ 65*	≥ 4*	≥ 2 chronic conditions*	£/month	39.29 (n=168)	38.83 (n=168)	42.80 (n=164)	42.61 (n=164)	ns	HRB
Williams[59] (2004)	1.5	R: Interdisciplinary team (consultant pharmacist, physician and nurse) D: Primary physician	Yes	≥ 65*	≥ 5*	≥ 2 of the medications were potentially problematic drugs for common geriatric problems*; cognitively intact *	$/month	162.63 (n=57)	135.72 (n=57)	180.88 (n=76)	174.12 (n=76)	0.006	HRB
Zermansky[60] (2001/2002)	12	R: Study-clinical pharmacist D: Pharmacist or GP	Yes	≥ 65*	≥ 1*	No	£/28 days	29.27 (n=596)	31.07 (n=576)	28.23 (n=577)	34.85 (n=549)	0.0001	LRB
Zermansky[61] (2006)	6	R: Study-clinical pharmacist D: GP	Yes	≥ 65*	≥ 1*	No	£/28 days	42.91 (n=331)	42.24 (n=331)	41.67 (n=330)	42.95 (n=330)	0.41	LRB
Best evidence synthesis		1107/2511 (44%) of intervention patients in a trial showing effect on drug costs 1668/2511 (66%) of intervention patients in a trial with a low risk of bias Conclusion: **evidence (low risk of bias) is inconclusive** about the effect of medication review on drug costs											

mos.= months; HCP = healthcare professional; *combination of inclusion criteria (= "and"); †determined directly after visit; ‡no p value reported; TDM= therapeutic drug monitoring; GP = general practitioner; LRB = low risk of bias; HRB = high risk of bias

Chapter 3

Effectiveness of medication review on the number of drug-related problems in patients visiting the outpatient cardiology clinic: a randomized controlled trial

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Abstract

Aim
To assess the effectiveness of medication review on the number of drug-related problems (DRPs) in outpatient cardiology patients.

Methods
In this randomized controlled trial, a computer-assisted and pharmacist-led medication review with patient involvement (questionnaire and telephone call with pharmacist) was conducted in intervention patients prior to their visit to the cardiologist. The control group received usual care. Adult outpatient cardiology patients without support concerning the administration of medication, without a medication review in the past six months and who gave permission to access their electronic medication record were included. The primary outcome measure was the number of DRPs one month after the visit. Secondary outcome measures concerned the type of DRPs and the type of medication involved in the DRPs.

Results
175 patients (mean (SD) age 66.0 (12.5) years, 41% female) were included. Intervention (n=90) and control group (n=85) were comparable at baseline . The mean (SD) number of drugs used per patient was 7.9 (3.9). After one month the mean (SD) number of DRPs was 0.3 (0.7) and 0.8 (1.0) and the median (range) number of DRPs was 0 (0-4) and 0 (0-4) in the intervention group and control group respectively ($p<0.001$); In the intervention group, 75% of the DRPs identified at T0 were solved at T1 versus 14% in the control group.

Conclusions
This randomized controlled trial suggests that a pharmacist-led medication review in patients with a scheduled visit to the outpatient cardiology clinic decreases the number of DRPs.

Introduction

Although drug therapy has beneficial effects, such as reducing symptoms and improving quality of life, drugs can also be an important cause of drug-related problems. Drug-related problems are events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes[1]. DRPs are associated with increased morbidity and mortality[2]. Several studies have shown that 6-7% of all hospital admissions are related to drug use[3-6]. Most of these studies also demonstrate that at least half of these admissions were preventable, suggesting that interventions designed to reduce the number of drug-related problems could be a valuable option with an aim to decrease drug-related hospital admissions and probably drug-related mortality[4,7].

Medication review has frequently been proposed as a solution to improve the effectiveness and safety of pharmacotherapy. Indeed, several randomized controlled trials, all conducted in primary care or during hospital stay, confirm that medication review as the single intervention can reduce the number of drug-related problems to some extent[7-11]. However, DRPs identified during medication reviews have not been proven to be associated with reduced rates of re-hospitalization and/or death[12]. Furthermore most published randomized controlled trials on medication review as the single intervention showed no or little effect on clinical outcomes, such as hospital (re-) admissions and mortality[13-18].

One possible explanation for the limited effect of medication review on clinical outcomes like hospital (re-)admissions and mortality is that these studies were not always targeted at a patient population using medication with a high risk of drug-related problems. Most of the studies that examined the effect of medication review on drug-related problems were not conducted in an outpatient setting, whereas in this setting medical specialists often prescribe medications with a high risk of drug-related problems[19]. Another explanation might be the fact that medication review interventions are insufficiently standardized. Tools used to perform a medication review can be based on implicit or explicit criteria (or a combination). Explicit criteria are evidence based and/or guideline based criteria to identify inappropriate medication, whereas implicit criteria are criteria to identify DRPs based on knowledge of the healthcare practitioner that performs the medication review[20]. Examples of explicit criteria are the Beers and START (screening tool to alert doctors to the right treatment) and STOPP (Screening Tool of Older Persons potentially inappropriate Prescriptions) criteria[21,22]. One way in which standardization of medication review interventions can be increased is the application of explicit criteria[23]. These explicit criteria are also applicable in (partial) computer supported medication reviews. Also the fact that the patient is not always involved in the medication review might be an explanation for the limited effect of medication review, while research on medication review showed that DRPs that were identified during patient interviews were more clinically relevant than DRPs based on medical records only[24].

Therefore, this multicenter randomized controlled trial (RCT) aims to assess the effect of a computer-assisted and pharmacist-led medication review with patient involvement on drug-related problems in adult patients with a scheduled visit to the outpatient clinic. As cardiology patients are often polypharmacy patients and frequently use medicines associated with a higher risk of drug-related hospital admissions, this study is conducted in outpatient cardiology clinics[25].

Methods

Study design and setting

This multicenter open randomized controlled trial was conducted between November 2010 and October 2011 in three outpatient pharmacies of one university hospital and two general hospitals in the Netherlands. One pharmacist per pharmacy performed the medication reviews for patients visiting the cardiology outpatient clinic of the hospitals in which the participating outpatient pharmacies were located. Prior to the start of the study, the participating pharmacists practiced performing a medication review as described in the study protocol. The results of these medication reviews were discussed between the participating pharmacists and coordinating research pharmacists. The participating pharmacists did not need to have additional qualifications or knowledge with respect to performing medication reviews and/or drug treatment for cardiovascular diseases. The ethical Review Board of the CMO Region Arnhem/Nijmegen concluded that the Medical Research Involving Human Subjects Act did not apply to this study (protocol number: NL34438.091.10). All patients provided written informed consent. This study was reported according to the CONSORT guidelines[26].

Participants and recruitment

Patients visiting the cardiology outpatient clinic of the hospitals in which the participating outpatient pharmacies were located were eligible if they were ≥18 years, able to speak and understand the Dutch language, gave permission to access their electronic medical records, had no medication review in the past 6 months and did not have any kind of support (e.g. by homecare or informal caretakers) in administering their medication. There were no exclusion criteria. On a daily basis, 5 patients were randomly selected from the cardiology outpatient visit agenda of each participating hospital five weeks before a planned visit to the cardiologist. Random selection was based on the last digit of the patient number by selecting those 5 patients with the lowest last digits of their patient identification number. Selected patients aged ≥18 years received a telephone call from the pharmacist to explain the aim and design of the study and to assess the other eligibility criteria. If eligible, the patients were invited to participate in the study. Patients willing to participate were randomized after the telephone call and received written comprehensive study information, including a form to obtain written informed consent.

Trial randomization

Patients were randomly allocated in a 1:1 ratio to the intervention and control group. Randomization was performed using a computer-generated randomization list (VH) for subjects in permuted blocks of 6. Stratification on hospital level was used to ensure equal distribution of intervention and control patients between the hospitals[27]. Patients were allocated to the intervention group or control group by the pharmacist based on the randomization list, in the order of inclusion.

Intervention

A schematic representation of the study design is depicted in Figure 1. A multidisciplinary (cardiologist, patient, pharmacist) pharmacist-led and computer-assisted medication review was performed in order to identify potential drug-related problems (DRPs) in the patients who were randomly allocated to the intervention group.

The medication review consisted of the following elements:

1) Intervention patients received a questionnaire four weeks before their planned visit to the outpatient cardiology ward. In this questionnaire, which can be found in Appendix 1, patients were asked to report their drug utilization experience.
2) After the questionnaire was returned, the outpatient pharmacist performed a computer-assisted structured medication review of the patient's total medication use based on the information in the patient's medical record and the questionnaire. The items assessed during medication review were based on the structure of implicit criteria described by Leendertse et al. as derived from the classification by Strand et al. combined with the domains of the Medication Appropriateness Index (MAI)[28-30]. The pharmacist also used computer-generated explicit review criteria in addition to the implicit criteria to assess some of these items. These explicit criteria were based on the patients' actual medication use and were automatically displayed on the printed medication review form to support the pharmacist. These criteria came from different national and international recommendations regarding safe use of medication and on national treatment guidelines for cardiovascular-related disorders[25,31-42]. The items that were to be assessed during the medication review were shown on the medication review form, see Appendix 2.
3) One week prior to the patient's visit to the outpatient cardiology ward, the patient received a telephone call from the pharmacist to discuss the potential drug-related problems (DRPs) identified during the assessment of the patient's medication use. During this discussion, that could last as long as needed, the pharmacist also asked the patient which potential DRPs were actual/real DRPs according to the patient. All the potential DRPs with accompanying pharmacist's recommendations on how to solve the DRPs were written on a communication form for the cardiologist and attached to the patient's medical record prior to the live visit between the patient and the cardiologist. The cardiologist assessed whether the potential DRPs were actual and relevant DRPs and discussed the implementation of the solution to the drug-related problems in person with the patient during the visit. If a potential DRP was not an actual DRP according to the cardiologist, it was not counted as a DRP at baseline. The cardiologist noted his findings on the communication form and returned the form to the pharmacist. All DRPs concerning drugs not prescribed by the cardiologist were brought to the attention of the prescribing physicians by the pharmacist in a telephone call. In case of drugs prescribed by the general practitioner, the patient's community pharmacy was asked to provide more information about the DRP. Patients who were randomly allocated to the control group received usual care.

Outcome measures

The primary outcome measure was the difference between the intervention and control group in the number of DRPs 1 month after the visit to the cardiologist, based on the assumption that the number of drug-related problems at baseline (T0) in the intervention and the control group are comparable. Secondary outcome measures were the type of DRPs and the type of medication involved in the DRPs.

Assessment of outcome measures

In the intervention group, the number of actual DRPs on T0 were determined during the telephone call with the patient one week prior to the visit to the cardiologist and by means of the communication form between the pharmacist and the cardiologist. One month after the patient's visit to the cardiologist (T1), the pharmacist evaluated whether the actual DRPs from

T0 were solved or not (based on the recommendations that the pharmacist made). The first step concerned screening the medical record for information about the DRPs and the second step concerned an evaluation by telephone with the patient. If it was still unclear whether certain DRPs were solved, the pharmacist approached the cardiologist or another prescribing physician by telephone.

Patients in the control group were asked to visit the outpatient pharmacy after their visit to the cardiologist in order to fill out the same questionnaire about their drug utilization experience (appendix 1) as the intervention patients. They were instructed by the pharmacy staff to take in mind the situation before the visit to the cardiologist (with regard to medication use, adverse events etc.). The outpatient pharmacist subsequently performed a computer-assisted structured medication review of the patient's total medication use based on the information in the patient's medical record and the questionnaire to identify potential DRPs. Although this medication review was performed by the pharmacist right after the consult with the cardiologist, no recommendations were made on how to solve the potential DRPs identified. One month after the visit to the cardiologist, a telephone call took place between the pharmacist and the patient. The goals of this telephone call were a) to evaluate whether potential DRPs, identified by the pharmacist during the medication review, were actual DRPs at T0 according to the patient and b) to assess which DRPs were already solved by usual care during that month (T1) after the visit to the cardiologist. The cardiologist was also asked one month after the visit to confirm a) which potential DRPs were actual DRPs at T0 and b) which DRPs were already solved by usual care during that month (T1). The same communication form as in the intervention group was used for this purpose.

DRPs were coded independently by two researchers (VH-BvdB), using the types of drug-related problems that were assessed during the medication review[28-30]. Discrepancies in coding were discussed in order to reach consensus (VH-BvdB) about the final classification. The types of DRPs are displayed in appendix 3.

Sample size and data analyses

To detect a difference of 0.4 (± 1) in the number of DRPs after one month follow-up between the intervention and control group, we aimed to include 290 participants, based on an alpha of 0.05, a beta of 0.9, a SD of 1 and an attrition rate of 10%.

Data were analysed using STATA version 13. Descriptive statistics were provided using mean (± SD) or median (range) values depending on the (non-) parametric distribution of measured variables. Variables with a parametric distribution were tested by means of T-tests and variables with a non-parametric distribution were tested by means of Mann-Whitney U tests. Differences in proportions were tested by means of Chi-square tests.

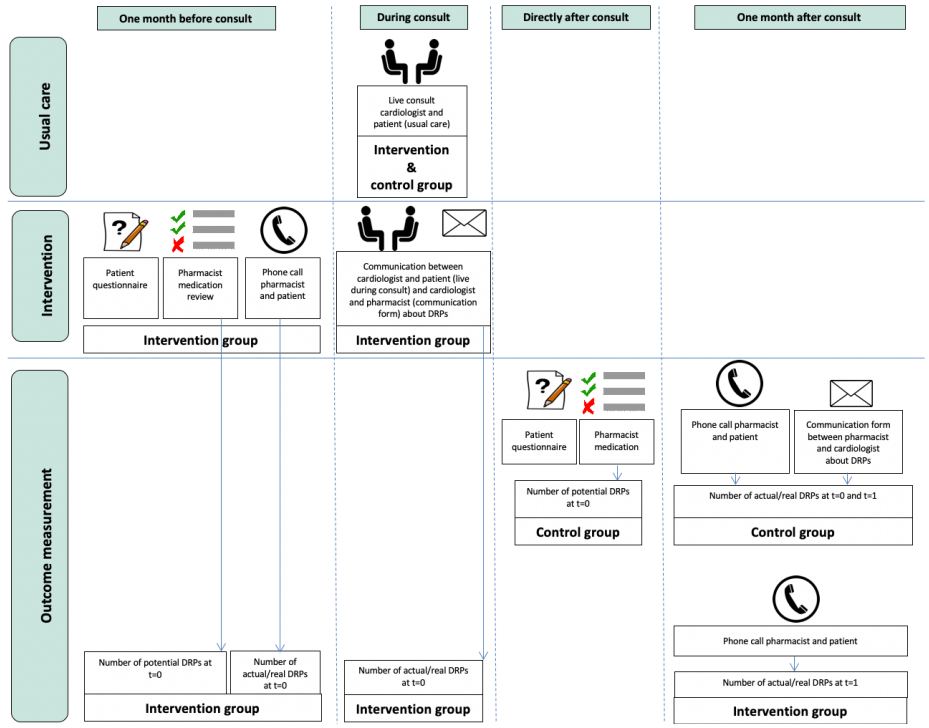

Figure 1. Schematic representation of the study design. DRPs = drug-related problems; "t=0" = baseline; "t=1" = one month after consult.

= live consult between cardiologist and patient (usual care). Furthermore, only in the intervention group, in addition to the usual care, communication between the cardiologist and the patient (live during consult) about the implementation of solutions to DRPs

= patient questionnaire to make an inventory of the patient's experiences with the use of his/her medicines

= medication review form, which is used by the pharmacist to perform the medication review. The items that were to be assessed during the medication review were shown on the medication review form. Assessment of all these items results in potential drug-related problems.

= telephone call between pharmacist and patient to assess which potential drug-related problems that were found during the medication review at t=0 (baseline) are actual/real DRPs according to the patient. And to assess which actual/real DRPs were solved at t=1 (1 month after the consult).

= communication form between the pharmacist and cardiologist about DRPs. The pharmacist reported to the cardiologist which potential drug-related problems were found during the medication review at t=0 (baseline). The cardiologist judged whether these potential drug-related problems were actual/real drug-related problems.

Results

Participants and attrition

A total of 224 patients orally consented to participate in the study after being contacted per telephone by the pharmacist and were randomized (before baseline assessments on T0) to either the intervention or the control group. Forty-nine patients declined to participate before their visit to the cardiologist and/or before they filled out the questionnaire on T0 and were therefore excluded from the study. The excluded patients were significantly older

than the included patients (mean age 71.2 (SD±11.4) versus 66.0 (SD±12.5) years (p<0.05)) and comparable with respect to gender at baseline. A total of 175 patients were included in this RCT, the flow of participants is depicted in Figure 2.

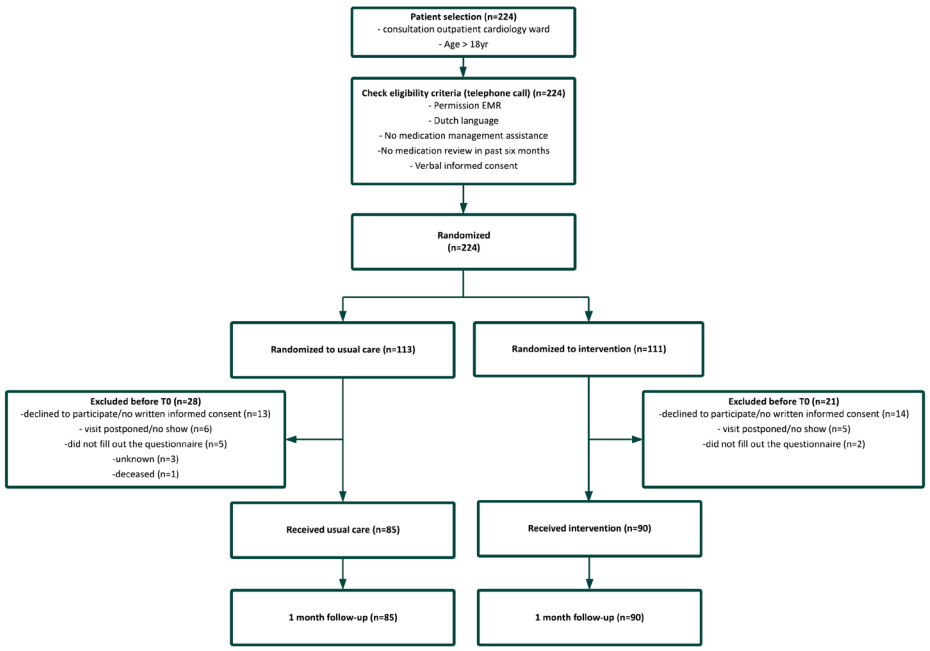

Figure 2. Flow diagram of the study. EMR = electronic medical record.

Baseline sample characteristics

175 patients (mean age 66.0 (SD±12.5) years, 41% female) were included in this RCT. Intervention (n=90) and control group (n=85) were comparable at baseline with respect to age, gender, number of drugs, number of co-morbidities and number of drug-related problems (Table 1). The mean number of drugs used by each patient was 7.9 (SD±3.9) of which 60% concerned cardiovascular related medication. The patients included per hospital were comparable with respect to age, gender, number of drugs, number of cardiovascular drugs, number of co-morbidities, number of years under care of the cardiologist.

Drug-related problems at baseline

The mean number of actual/real DRPs at baseline was 1.0 (SD±1.2) and the median number of DRPs at baseline was 1 (range 0-5). The most frequent DRPs could be categorized as "incorrect use" (16%), followed by undertreatment (15%) and insufficient drug monitoring (15%) (Table 2). Sixty-six % of the DRPs was related to cardiovascular drug treatment. DRPs were most often attributed to antihypertensive, antithrombotic and antilipaemic agents (Table 3).

Table 1. Baseline characteristics

Parameter	Control group (n = 85)	Intervention group (n= 90)	P value	Total (n= 175)
Gender (female) [n (%)]	32 (38)	40 (44)	0.361	72 (41)
Age (years) [mean (SD)]	66.2 (12.7)	65.8 (12.4)	0.8327	66.0 (12.5)
Number of drugs [mean (SD)]	7.8 (3.9)	8.0 (3.9)	0.7469	7.9 (3.9)
Number of cardiovascular drugs [mean (SD)]	4.8 (2.1)	4.7 (2.0)	0.7504	
Number of co-morbidities[a] [mean (SD)]	2.3 (1.2)	2.4 (1.4)	0.8004	2.3 (1.3)
Number of potential drug-related problems [median (range)]	3 (0-10)	4 (0-12)	0.0538	3 (0-12)
[mean (SD)]	3.6 (2.6)	4.4 (2.9)	0.0522	4.0 (2.8)
Number of drug-related problems [median (range)]	1 (0-4)	1 (0-5)	0.3366	1 (0-5)
[mean (SD)]	0.9 (1.0)	1.1 (1.3)	0.1320	1.0 (1.2)
Years under care cardiologist [mean (SD)]	11.0 (10.6)	9.3 (9.8)	0.2781	10.1 (10.2)

[a]Source: electronic medical record at T0

Table 2. Number of drug-related problems (DRPs) per type of DRP

Type of DRP	Number of DRPs (%)
Incorrect use	29 (16%)
Undertreatment	27 (15%)
Insufficient drug monitoring	26 (15%)
Inappropriate formulation	21 (12%)
Adverse events	17 (10%)
Overtreatment	15 (9%)
Package problem	9 (5%)
Dose too low	7 (4%)
No effect	7 (4%)
Non-adherence	7 (4%)
Interaction	5 (3%)
Dose too high	3 (2%)
Contra-indication	2 (1%)
Education	1 (1%)
Total	**176[a] (100%)**

[a] In the intervention group (n=90) 102 DRPs were identified, in the control group (n=85) 74 DRPs were identified

Table 3. Number of drug-related problems per type of drug of 175 patients included in this study

Type of drug	Number of DRPs (%)
Antihypertensive agents	43 (24%)
Antithrombotic agents	21 (12%)
Antilipaemic agents	20 (11%)
Other[a]	15 (9%)
Anti-ulcer agents	10 (6%)
Antidiabetic agents	9 (5%)
Nitrates	7 (4%)
Anti-asthmatic agents	6 (3%)
Anti-osteoporotic agents	5 (3%)
Antiarrhytmic agents	5 (3%)
Opioids	4 (2%)
NSAIDs	2 (1%)
DRP could not be attributed to 1 drug	29 (17%)
Total	**176 (100%)**

[a]Mineral supplements, antimuscarinics, corticosteroids, thyroid hormones, nicotine agonists, antihormones, antigout agents, alpha 1 blockers, ophthalmic agents

Effects of the intervention

One month after the visit to the cardiologist, the median number of DRPs was 0 (range 0-4) in the intervention group versus 0 (range 0-4) in the control group ($p<0.001$). The mean number of DRPs was 0.3 (SD±0.7) in the intervention group versus 0.8 (SD±1.0) in the control group ($p<0.001$); 95% CI between groups was: 0.21-0.72. In the intervention group 75% of the DRPs identified at T0 were solved at T1 versus 13.5 % in the control group. For 47% of the patients in the intervention group, at least 1 DRP was solved at T1 versus 12% of the patients in the control group. The distribution of patients by number of DRPs on T0 and T1 in control group versus the intervention group is outlined in Figure 3. Solved DRPs in the intervention group were most often of the type incorrect use (20%), inappropriate drug formulation (20%) and undertreatment (17%) (Table 4). DRPs of the type package problems (problems concerning the opening of the packaging), dose too high and education (questions the patient had about the drug treatment prior to the visit to the cardiologist) were always solved, DRPs of the type no effect (based on a visual analogue score from 1 (no effect) -10 (maximum effect) and insufficient drug monitoring (e.g. renal function and electrolytes) were least often solved (Table 4).

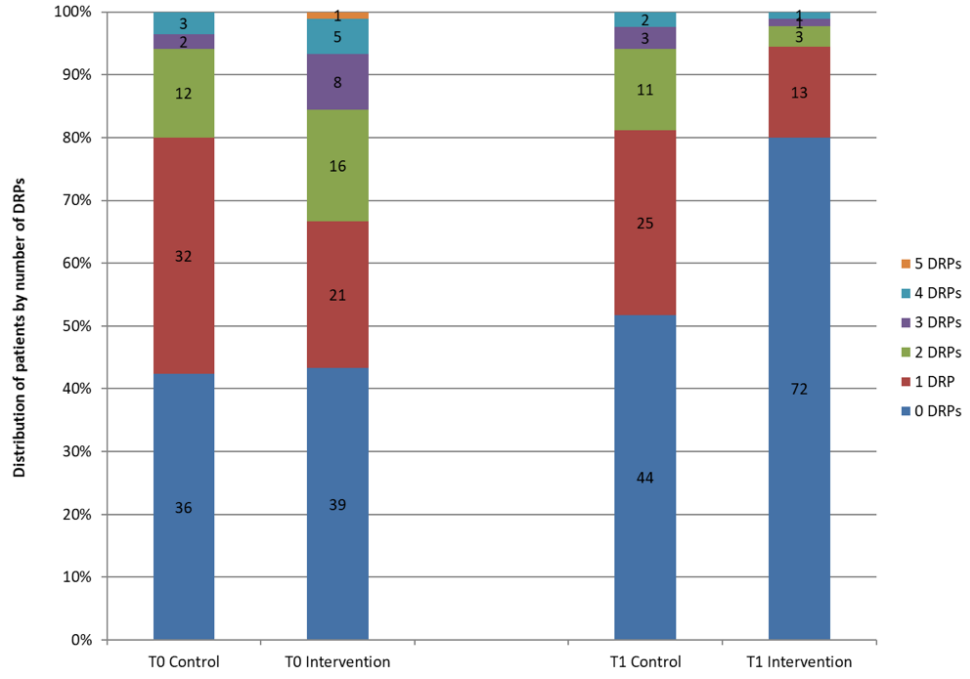

Figure 3. Distribution of patients by number of DRPs on T0 and T1 in the control versus the intervention group.

Table 4. Number and type of solved and unsolved drug-related problems (DRPs) in the intervention group

Type of DRP	Number	Solved n (%)
Incorrect use	17	15 (88%)
Undertreatment	17	13 (77%)
Inappropriate formulation	16	15 (94%)
Insufficient drug monitoring	13	5 (39%)
Adverse events	10	8 (80%)
Overtreatment	8	6 (75%)
Package problem	5	3 (60%)
Non-adherence	3	3 (100%)
Dose too low	3	2 (67%)
No effect	3	1 (33%)
Dose too high	2	2 (100%)
Contra-indication	2	1 (50%)
Interaction	2	1 (50%)
Education	1	1 (100%)
Total	**102**	**76 (75%)**

Discussion

This multicenter randomized controlled trial (RCT) demonstrates the effect of a medication review, as the single intervention, on drug-related problems in an outpatient cardiology clinic. To our knowledge this is the first pharmacist-led medication review with patient involvement in an outpatient cardiology clinic in which the pharmacist is supported with computer-generated explicit review criteria. In the intervention group 75% of the actual DRPs (0.8/patient) were solved, compared to 14% percent of the DRPs (0.1/patient) in the group receiving usual care.

In a previous RCT in patients with a cardiovascular disorder, conducted in a primary care setting, a similar number of DRPs was solved by medication review as the single intervention (1 DRP/patient in the experimental group, one year after the intervention) in the intervention group[43]. Although the mean number of drugs in the intervention group in both studies was comparable (7.8 vs 8.3), the mean number of potential DRPs in our study was twice as high (4.4 versus 2.2 DRPs/patient). A possible explanation might be that more potential DRPs were identified by adding the computer-assisted evidence based explicit criteria to the assessment by the pharmacist. Another explanation might be the use of a standardized patient questionnaire to inventory the drug utilization experience of patients instead of a patient interview by pharmacists with relatively little experience with performing patient-interviews in the context of a medication review in the study of Geurts et al[43]. The comparable rate of resolved DRPs in our study despite the higher number of potential DRPs per patient, might be explained 1) by a shorter follow-up time in our study and 2) by the fact that DRPs identified by clinical decision support are considered to be less relevant by physicians and patients[20].

Also, in non-cardiovascular patients most RCTs with an overall medication review as the single intervention showed a positive effect on the number of drug-related problems[9-11,44]. Although the mean number of drugs used by the intervention patients in these studies is comparable to our study (range 6-10 drugs/patient), the mean number of potential DRPs (range 4.4 – 8.6 potential DRPs/patient) and the mean number of actual DRPs/proposals for intervention per patient (range 1-6 per patient) reported in these studies with non-cardiovascular patients were generally higher[9-11,44,45]. There are several possible explanations for this difference in findings. Although the intervention in this study was an overall medication review there might have been a relative focus on cardiology medication, illustrated by the fact that 66% of the DRPs was related to cardiovascular drug treatment. Furthermore, the different settings and inclusion criteria of the other studies might explain differences in the number of drug-related problems; none of these studies were conducted in an outpatient setting (four in primary care and one in secondary care). Patients visiting the outpatient cardiology clinic might be relatively well monitored by their cardiologist. In addition, in contrast to the other studies, no selection criteria were set for age and number of drugs in this study. However, mean age and number of drugs in our study were similar to that in these medication review studies in primary care. In the only other study that also examined the effect of medication review on the number of DRPs in an outpatient setting, it was reported that medication review in patients with heart failure reduced the number of drug-related problems[46]. In this study by Yates et al., the mean number of DRPs per patient was reduced from 2.8 to 2.0 in the intervention group. So, in addition to the body of evidence regarding the effect of medication review in a community and hospital setting, the added value of medication review in reducing drug-related problems is now being demonstrated in an outpatient setting. One should therefore consider implementing interventions of this kind in outpatient settings as well.

A limitation of the design of our study is that the timing of the assessment of the number of drug-related problems at baseline was different between the intervention and the control group. On the one hand, this may have resulted in an overestimation of the effect of medication review because of a lower number of reported drug-related problems at baseline in the control group due to recall bias. On the other hand, this may have led to an underestimation of the effect of medication review due to greater awareness among patients in the intervention group about their drug use, as a consequence of the questionnaire about their drug utilization experience. This may have resulted in the patient taking action towards for instance the general practitioner to solve drug-related problems. However, this design was the optimal option to ensure that drug-related problems were detected in the control group in the same way as in the intervention group without affecting the usual care in the control group. Another limitation is the fact that a lower number of patients were included in the study than intended in the power calculation, which may have led to a less precise estimation. Despite this, a significant difference was found in the number of drug-related problems at T1 between the control and the intervention group. Initially, six centers were to participate in the study, but three centers withdrew right before the start of the study. The main reason for withdrawal was that they were unable to combine the medication reviews with regular care and business. Theoretically, this could have led to selection bias, however, these three centers were all general hospitals, comparable with the two general hospitals that participated in this study. The practices that actually participated in the study also had difficulties completing the intended number of medication reviews. Medication review is a time-consuming pharmaceutical care intervention. Given the modest effect on drug-related problems in patients with cardiovascular problems and elderly with polypharmacy, it should be reconsidered which patients benefit most from a medication review and which outcome measures are relevant in this context[47]. Furthermore, the clinical impact (improvement of the patients' well-being) of the effect on these drug-related outcome measures should be further explored. A recent study in the Netherlands from Verdoorn et al shows that medication review improved self-reported quality of life (EQ-5D VAS) and reduced the number of health problems with moderate to severe impact on daily life[48]. In addition, the use of a core outcome set for drug-related outcome measures is recommended, to enable comparison of outcomes across trials in future research[49,50]. Finally, an intention to treat analysis was not feasible as all excluded patients in both the intervention and the control group declined to participate after randomization but before baseline assessments on T0. Despite this, excluded patients were significantly older than included patients, which may have possibly led to an underestimation of the effect of medication review, as elderly patients often experience more DRPs.

Conclusion

Our findings suggest that a pharmacist-led medication review in patients with a scheduled visit to the outpatient cardiology clinic decreases the number of DRPs. One should therefore consider implementing interventions of this kind in outpatient settings as well. The clinical relevance of (the decrease of) drug-related problems, both from the point of view of the patient and the health care practitioners, should also be explored.

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Appendix 1

Patient questionnaire

Aim

The aim of the patient questionnaire was to make an inventory of the patient's experiences with the use of his/her medicines. Patients did not need knowledge about medication, they were only asked questions like: "do you experience side effects", "do you experience effect of the medication", etc.

Questionnaire about your medication use

1A. **Illnesses.** Some medicines should not be used by people who suffer from one of the conditions below. To be sure that the medicines you use can be combined with the disorders that you have, we would like to ask you to indicate in the list below which conditions you suffer from.

	Asthma		Gout
	Bipolar disorder		Long QT syndrome
	Crohn's disease / Ulcerative colitis		Peptic ulcer
	COPD		Esophagus stenosis
	Depression		Parkinson
	Myasthenia		Porphyria
	Epilepsy		Micturition with urinary retention
	Raynaud's Phenomenon		Psoriasis
	Liver cirrhosis		Diabetes
	Angina		Impaired renal function
	Phenylketonuria		Heart failure

1B. **Pregnancy, lactation and desire to have children.** Please indicate below if you are pregnant, if you are breastfeeding or if you have the desire to have children.

2. **Drug allergies or intolerances.** Please indicate below for which medicines you are allergic and what the complaints were with the allergic / hypersensitivity reaction.

3. **Your actual medication use.**
a. Below you find a list of medication that you use according to our electronic medical record. Please indicate below if this is still correct.
b. Do you use more medicines that are not listed in the overview above? Please note below the name and strength of the medicine, the dosage of the medicine and the times of administration.

4. **Feasibility instructions for use** [prefilled with standard instructions for use, based on the patient's list of medication available in the electronic medical record]. The following instructions for use apply to proper use of these medicines. Do you want to tick below which advice is feasible in daily practice?

5. **Effectiveness of your drug treatment.** Please indicate below how much effect you notice of the medicines you use? [prefilled with the patient's list of medication available in the electronic medical record and a 10 cm line for the patient to indicate the level of effect [based on a visual analogue score from 1 (no effect) -10 (maximum effect). The patient was asked to indicate the effect experienced per drug on a scale of 0 to 10. Only the medicines that can have an evident effect on the patient (noticeable by the patient) were shown. For example, statins were not shown, since a patient cannot experience himself/herself whether these kind of medication work]

6. **Side effects.** Do you suffer from side effects? Please complete the following questions:

Side effect	**Start date side effect**	**Name of the medicine that you believe causes the side effect**	**Start date medicine**	**Did you use a treatment to reduce or remedy the side effects? If so, which treatment?**
Example: headache	First week of January 2010	Acetaminophen 500mg	Last week of December 2010	no

[The patient was asked whether he/she experienced side effects of medicines. If that was the case, then the patient was subsequently asked how long he/she has suffered from side effects (to enable the pharmacist to assess the causality during the medication review). Furthermore, the patient was asked which drug(s) he/she thought could cause the side effect(s) he/she was experiencing]

7a. **Problems concerning the administration of drugs.** Do you have any problems with administering certain medicines (for example, problems swallowing or injecting)? If so, please indicate below

7b. **Problems concerning the opening of the packaging.** Do you have any problems with opening the package of certain medicines? If so, please indicate below

8. **Questions.** Do you have any other questions about your medication?

Appendix 2

Medication review form

Aim

During the medication review (assessment of the total medication use of the patient) the pharmacist used a medication review form. The items that were to be assessed during the medication review were shown on the medication review form. Where possible, explicit information (from literature and guidelines) was shown on the form based on the patient's medication use that was available in the electronic medical record. The pharmacist could use this information during the medication review.

1. **Indications.** Check whether there is a clear indication for each medicine. Use the patient's answer to question 1A of the patient questionnaire.

2. **Actual medication use.** [an overview of the patient's actual medication use was automatically displayed on the review form, after the electronic medication record was updated based on response of the patient to question 3 on the patient questionnaire]

3. **Dosage.** Check per medicine whether the dosage the patient is using is correct. [theoretical minimum and maximum dosage per drug, based on the patient's actual medication use, was automatically displayed on the review form]

4. **Instructions for use.** Check, based on the patient's answer to question 4 of the patient questionnaire, which instructions are not feasible for the patient. [standard instructions for use per drug, based on the patient's actual medication use, were automatically displayed on the review form]

5. **Contra-indications.** Use question 1 of the patient's questionnaire and the electronic medical record to check which contraindications the patient has. [potential contra-indications per drug, based on the patient's actual medication use, were automatically displayed on the review form]

6. **Pregnancy, lactation and desire to have children.** Check, based on the patient's answer to question 1B whether the patient is pregnant, is breastfeeding or has the desire to have a children. Assess whether an adjustment is needed. [advices with respect to pregnancy, lactation and the desire to have children (national guideline) per drug, based on the patient's actual medication use, were automatically displayed on the review form]

7a. **Interactions.** Assess which clinical relevant drug-drug interactions are actual for this patient. [potential drug-drug interactions per drug, based on the patient's actual medication use, were automatically displayed on the review form]

7b. **Adverse events.** Check, based on the answer of the patient to question 6 of the patient questionnaire, if side effects that the patient experiences, might be caused by the medicines the patient is using. [potential side effects per drug, based on the patient's actual medication use, were automatically displayed on the review form]

7c. **Monitoring.** Assess whether laboratory values (e.g. renal function and electrolytes) and clinical outcome measures (e.g. blood pressure) are within normal range. [relevant drug monitoring values and or clinical outcomes per drug, based on the patient's actual medication use, were automatically displayed on the review form]

7D. **Warnings and precautions.** Assess whether sufficient consideration has been given to the warnings that apply to the medication used by this patient. [warnings and precautions per drug (according (inter)national guidelines), based on the patient's actual medication use, were automatically displayed on the review form]

8. **Effectiveness.** Use the patient's answer to question 5 of the patient questionnaire to assess the effectiveness the patient experiences of the medicines he or she takes. Always formulate an advice if the patient reports a VAS score for effect less than 5 for a medicine.

9. **Inappropriate drug formulation/problems concerning administration of the drug/ problems opening the packaging of a drug.** Check, based on the answer of the patient to question 7 of the patient questionnaire, whether the patient experiences any problems with the administration of his/her medicines and/or opening the packaging. Also assess whether slow release formulations and or combination tablets should be useful for the patient.

10. **Overtreatment.** Assess whether medication should be stopped, based on indications; contra-indications; allergies; interactions; effectiveness; adverse events; unwanted combination of medication with a similar effect and pharmacotherapeutic rationality per drug.

11. **Undertreatment.** Assess whether medication should be added, based on untreated indications (use also "nr. 1. Indications" from this medication review form) and/or based on monitoring (e.g. laboratory value is too low and supplementation is necessary) and/or based on protective medication that is missing (e.g. gastroprotective agents in combination with NSAID use in patients with risk of gastro-intestinal bleeding).

Appendix 3

Types of drug-related problems

Aim:

DRPs were coded independently by two researchers (VH-BvdB), using the types of drug-related problems that were assessed during the medication review[28-30]. Discrepancies in coding were discussed in order to reach consensus (VH-BvdB) about the final classification.

Types of drug-related problems:

1. **Incorrect use** *(e.g. following standard instructions for use that apply to proper use of the medicine are not feasible for the patient).*
2. **Undertreatment** *(e.g. patient suffers from conditions not being treated, or patient does not use protective medication that is needed for safe use of other medication (e.g. gastroprotective agents in combination with NSAIDs, laxative agents in combination with opioids)*
3. **Inappropriate formulation** *(e.g. patient has problems administering the drug or for instance a slow release tablet is indicated)*
4. **Insufficient drug monitoring** *(monitoring of laboratory values (e.g. electrolytes, renal function) are insufficiently performed or not within range)*
5. **Adverse events** *(patient experience adverse events from medication)*
6. **Overtreatment** *(patient uses medicines without a clear indication)*
7. **Package problem** *(patient experiences problems concerning the opening of the packaging)*
8. **Non-adherence** *(patient does not take medication as prescribed by the physician (e.g. patient takes less or more medication than prescribed)*
9. **Dose too low** *(the dosage prescribed and/or taken is too low according to the prescribing guidelines)*
10. **No effect** *(the patient experiences no or insufficient effect from a medicine)*
11. **Dose too high** *(the dosage prescribed and/or taken is too high according to the prescribing guidelines)*
12. **Contra-indication** *(patient suffers from a condition that is a contra-indication for one or more drugs he or she is taking)*
13. **Interaction** *(the patient uses a drug that negatively affects the efficacy or toxicity of another drug he or she is using).*
14. **Education** *(questions from patients about their medication)*
15. **Allergies/intolerance**
16. **Irrational pharmacotherapy**
17. **Administrative problem**

Chapter 4

Communication about Drug-Related Problems (DRPs) during patients' visits to Dutch physicians and pharmacies

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Abstract

Objective
The objective of this study is to assess the frequency and type of drug-related problems (1) raised and discussed (2) raised but not discussed or (3) not raised during patients' visits to healthcare practitioners (HCPs).

Methods
In this cross-sectional study in Dutch outpatient clinics, GP practices and pharmacies, verbal cues from patients and HCPs indicating drug-related problems (DRPs) were inventoried by an observer during visits. It was also observed whether raised DRPs were discussed between patient and HCP. Post-encounter interviews (HCPs) were conducted and post-encounter questionnaires (patient) were distributed to identify DRPs not raised.

Results
In total 431 patients were observed during a single visit. In 42.2% of these visits, 311 DRPs were raised (weighted mean (SD) 0.7 (±1.1) DRP/patient). Of these 311 DRPs, 82.0% were discussed between HCP and patient. HCPs did not raise existing DRPs in 3.9% of the 431 visits; in 6.3% of the 176 questionnaires the patient reported an existing DRP that had not been raised.

Conclusion
In conclusion, almost one in six of the DRPs raised during visits are not discussed between HCP and patient. Furthermore, existing DRPs are not even raised in 4-6% of the visits. HCPs and patients should be aware that, although patients often have DRPs, these are not always discussed or not even raised during patients' visits.

Introduction

Medications are involved in 80 percent of all medical treatments[1]. Although medications usually improve a patient's quality and/or duration of life, they can also cause considerable harm. During medication reviews an average of 4 drug-related problems (DRPs) are identified per patient with polypharmacy. A drug-related problem is defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes[2]. DRPs can lead to serious consequences. The HARM-study (Hospital Admissions Related to Medication), for example, illustrated that 5.6% of the unplanned hospital admissions are directly drug-related. Almost half of these drug-related admissions (46.5%) could have been avoided[3].

Suboptimal communication between HCPs and patients increases the incidence and negatively influences the management of DRPs[4,5]. Patients do not always report medication-related symptoms and/or adverse events to physicians, and physicians do not always respond when patients actually report them[6,7]. Not only do patients not always mention drug-related issues, research has found that adverse events, patients' experiences with their drug use and adherence are often not explored by HCPs during clinical visits[8,9].

The need for better communication is also emphasized in several recommendations aiming to optimize the communication with patients about drugs[10,11]. Adequate communication between patients and healthcare practitioners is a process involving the building of a relationship, gathering information, understanding the patient's viewpoint, supplying information and decision-making[12]. These different aspects of the interaction between the healthcare provider and the patient are grounded in various theoretical frameworks[13,14].

Thus, communication about drug-related problems with patients should be improved. In order to find strategies to improve this communication, more information is necessary. Although communication about medication has been the subject of many published studies, these studies often only used indirect measures to evaluate the communication between patient and HCP. In several studies, the information was reported by the patient (barriers to participation in medical consultations) and was not gathered by means of a direct observation of the patient-HCP communication during visits[6,7]. Studies that actually examined communication about medication by direct observation of the HCP-patient communication often focussed on communication skills and style rather than on content[15,16]. Communication about DRPs during clinical consults is rarely assessed. Consequently, little information (based on direct observation) exists on the number and type of DRPs raised and not raised during patients' visits to the HCP, by both the patient and the HCP, and the extent to which the DRPs raised are actually discussed between patients and HCPs.

Therefore, this quantitative study aims to make an inventory of the number and type of drug-related problems (1) raised and discussed, (2) raised but not discussed or (3) not even raised during patients' visits to HCPs. The results of this study can be used to develop strategies to optimize communication about DRPs.

Methods

Design and setting

This quantitative cross-sectional study was conducted between September 27 and December 19, 2013 in four clinics (three surgical, one non-surgical; both academic and teaching hospitals), two general practices, and five pharmacies (three community, two outpatient) in the Nijmegen area, the Netherlands.

Selection of health practitioners

In order to obtain a diverse sample of HCPs that communicate with patients about drug-related problems (DRPs), we identified core characteristics of a variety of healthcare practitioners (e.g. surgical/non-surgical, primary care/secondary care, academic/teaching, physicians/pharmacists etc.). Based on these characteristics, we created a sampling frame of practitioners in one region in the Netherlands (Nijmegen) and at least two HCPs per profession were approached to participate in the study.

Patient inclusion and measurements

Inclusion

All consecutive patients visiting the healthcare practitioner (physician/pharmacist or pharmacy technician) during a regular visit on an observation day were eligible. Patients were included after obtaining verbal consent. There were no exclusion criteria, consequently patients without medication use were also included.

Observation during the visits

Each visit was observed by one and the same student. The student was trained to observe and report all communication about DRPs on the basis of a standardized observation scheme and data collection form (see supplementary file 1). One of the researchers (CC) audited the first observations by the student and provided the student with feedback. Verbal cues from patients and HCPs indicating drug-related problems (DRPs) were inventoried by the observer during patients' visits to the HCPs, irrespective of the type of DRP or the relation of the DRP to the type of visit. Everything that a patient or a doctor said about problems or lack of clarity regarding the medication (use) counted as a cue about (a) drug related problem(s). All these cues about DRPs were defined as DRPs raised during the visits and were reported descriptively. Subsequently it was observed whether these raised DRPs were discussed between the patient and the HCP or not. If the HCP and/or patient responded to the cue, then this was defined as a discussed DRP.

Measurements after the visits

We conducted post-encounter interviews (HCPs) and distributed post-encounter questionnaires (patient) to identify DRPs not raised by HCPs and/or patients. In the 11-item questionnaire (in Dutch), patients were also asked to report their actual prescription and over-the-counter medication use and socio-demographic data (age and gender). Patients were asked to fill out the questionnaire and to send it back to the researcher by post. Both the observations and the questionnaires were coded with the same number to match them afterwards.

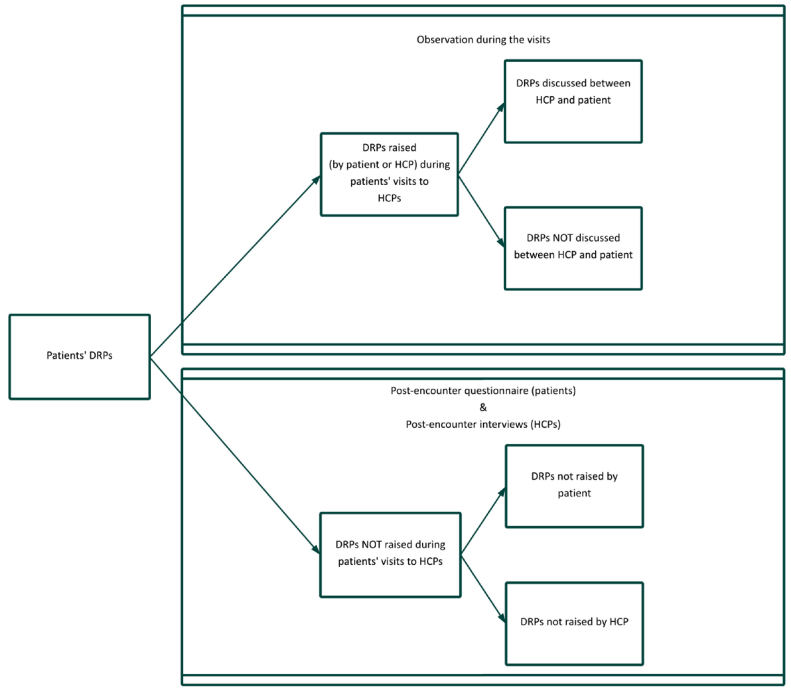

Figure 1. Schematic representation of data collection and outcome measures

DRP= drug-related problem; HCP = health care practitioner

Outcome measures

Main outcome measures were the number and type of DRPs raised during the visits, the number and type of raised DRPs that were subsequently discussed and the number and type of DRPs not raised during the visits by HCPs and patients.

All the DRPs were classified using the DOCUMENT classification system[17], with modifications as described by Kwint et al[18]. The DOCUMENT classification system encompasses eight main types of DRPs (*Drug selection, Over-/underdose prescribed, Compliance, Untreated indications, Monitoring, Education or information, Non-clinical and Toxicity or adverse reaction*) with corresponding subtypes to further classify the DRPs[19]. DRPs were coded (using the subtypes of the DOCUMENT classification system) independently by two researchers (CC-BvdB). Discrepancies in coding were discussed in order to reach consensus (CC-BvdB) about the final classification. A third investigator (CK) verified the coding.

Data analysis

Data were analysed using STATA version 13. Descriptive statistics were provided using (weighted) mean (± SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. The weights used to calculate the weighted mean (SD) were defined as 1 divided by the number of patients per type of healthcare practitioner.

Results

Sample characteristics

In total, 431 patients were included in this study during a single visit to the HCP (Table 1). These patients were observed while visiting 8 GPs (18.3%), 5 surgical specialists (17.4%), 7 non-surgical specialists (18.3%), 3 community pharmacy staff members (22.7%) and 2 outpatient pharmacy staff members (23.2%). Of all included patients, 385 (89.3%) received a questionnaire, the remaining 46 (10.7%) did not receive the questionnaire or refused to accept the questionnaire after the visit for various reasons. Finally, 176 (40.8%) of the observed patients (mean age 55.8 (SD: 15.8) years; 59.7% female) returned a completed questionnaire (table 1).

Table 1. Number of observed patients and returned questionnaires per type of HCP

	Total number of patients included n	Number of returned patient questionnaires n (%)
Medical specialist	**154**	**79 (51.3%)**
Surgical[1] Non-surgical[2]	75 79	39 (52.0%) 40 (50.6%)
General practitioner	**79**	**29 (36.7%)**
Pharmacy	**198**	**68 (34.3%)**
Community	98	39 (39.8%)
Outpatient	100	29 (29%)
Total	**431**	**176 (40.8%)**

[1]35% orthopaedic surgeon, 65% other surgeon
[2]54% internist, 46% rheumatologist

Drug-related problems raised during patients' visits to the HCP

In the study population 182 (42.2%) patients had at least one DRP raised during their visit, resulting in a weighted mean number of 0.7 (SD ± 1.1) DRPs raised per observed patient. In patients with at least one DRP raised during their visit, the weighted mean number of DRPs raised per patient was 1.7 (SD ± 1.5) (Table 2). DRPs were most frequently raised during patients' visits to non-surgical medical specialists followed by the outpatient pharmacy, the community pharmacy, the general practitioner and the surgical medical specialist.

Table 2. Number of DRPs raised and number of DRPs raised and discussed with the patient during patients' visits to the HCP

	Number of patients n	Number of patients' visits with at least one DRP during visit n (%)	Number of DRPs during visits n	Mean number of DRPs per observed patient M (SD)	Mean Number of DRPs per observed patient with DRPs raised M (SD)	Number of visits with DRPs raised and discussed between HCPs and patients n (%)	Number of DRPs discussed between HCPs and patients n (%)
Medical specialist	**154**	**72 (46.8%)**	**139**	**0.9 (1.3)**	**1.9 (1.3)**	**59 (81.9%)**	**105 (75.5%)**
Surgical	75	16 (21.3%)	22	0.3 (0.7)	1.4 (0.8)	12 (75.0%)	16 (72.7%)
Non-surgical	79	56 (70.9%)	117	1.5 (1.5)	2.1 (1.4)	47 (83.9%)	89 (76.1%)
General practitioner	**79**	**24 (30.4%)**	**42**	**0.5 (0.9)**	**1.8 (0.8)**	**23 (95.8%)**	**37 (88.1%)**
Pharmacy	**198**	**86 (43.4%)**	**130**	**0.7 (1.0)**	**1.5 (1.0)**	**79 (91.9%)**	**113 (86.9%)**
Community	98	38 (38.8%)	61	0.6 (0.9)	1.6 (0.9)	35 (92.1%)	54 (88.5%)
Outpatient	100	48 (48.0%)	69	0.7 (1.1)	1.4 (1.2)	44 (91.7%)	59 (85.5%)
Total	**431**	**182 (42.2%)**	**311**	**0.7 (1.1)[1]**	**1.7 (1.5)[1]**	**161 (88.5%)**	**255 (82.0%)**

[1]Weighted mean (±SD)

Figure 2 provides the number and type of the DRPs raised during patient's visits to the medical specialist, GP or pharmacy, coded according to the DOCUMENT classification system. Overall, the most common type of DRP was non-clinical (34.1%), which covers problems related to administrative aspects of the prescription. Other DRPs commonly raised were related to education or information (26.7%, mainly patient information requests) and toxicity and adverse reactions (13.5%).

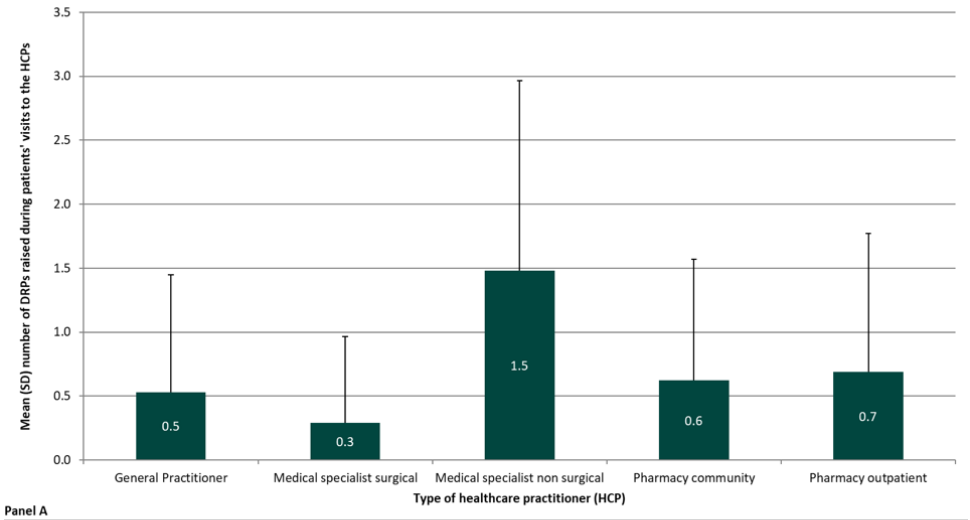

Figure 2. Distribution of DRPs raised during patients' visits to HCPs

Panel A depicts the mean (SD) number of DRPs raised per type of HCP
Panel B depicts the number DRPs raised in 100 visits per type of DRP and per type of HCP

Patients visiting non-surgical medical specialists were particularly found to experience DRPs about *education or information* (32.5%) and *toxicity and adverse reactions* (21.4%). These are also the types of DRPs most frequently raised during visits to general practitioners (35.7% and 23.8% respectively) and surgical medical specialists (27.3% and 22.7% respectively), whereas DRPs about *toxicity and adverse reactions* are rarely raised during the pharmacy visits (1.5%). The DRPs most frequently raised during visits to the pharmacy were *non-clinical* DRPs (60.0%) followed by DRPs about *education or information* (18.5%) and *drug selection* (11.5%).

Discussion between the patients and the HCPs about the DRPs raised during the visits

A total of 311 DRPs were raised by 182 (42.2%) of the observed patients. In total, 255 (82%) of these DRPs were subsequently discussed between the patient and the HCP. This occurred in 88.5% of the 182 visits in which one or more of these DRPs were raised. Details on the distribution by healthcare practitioner are depicted in table 2.

DRPs raised during the visits and actually discussed between the patient and the HCP

The 255 raised DRPs that were actually discussed between HCPs and patients were most frequently of the type non clinical (32.2%) and education or information (30.6%). Details on the proportions of DRPs discussed between patient and HCP per type of DRP are outlined in Figure 3.

DRPs raised during the visits and not discussed between the patient and the HCP

The 50 raised DRPs that were not discussed between HCPs and patients mostly concerned *non-clinical issues* (46.0%) and *toxicity or adverse reactions* (18.0%).

The types of DRPs that were raised during visits and that were relatively most often not discussed (in more than 20% of the cases of that type of DRP) concerned *compliance* (not discussed in 14 (27.3%) of the cases), *untreated indications* (15 (28.6%)), *non-clinical issues* (82 (22.6%)) and *toxicity or adverse reactions* (33 (21.4%)).

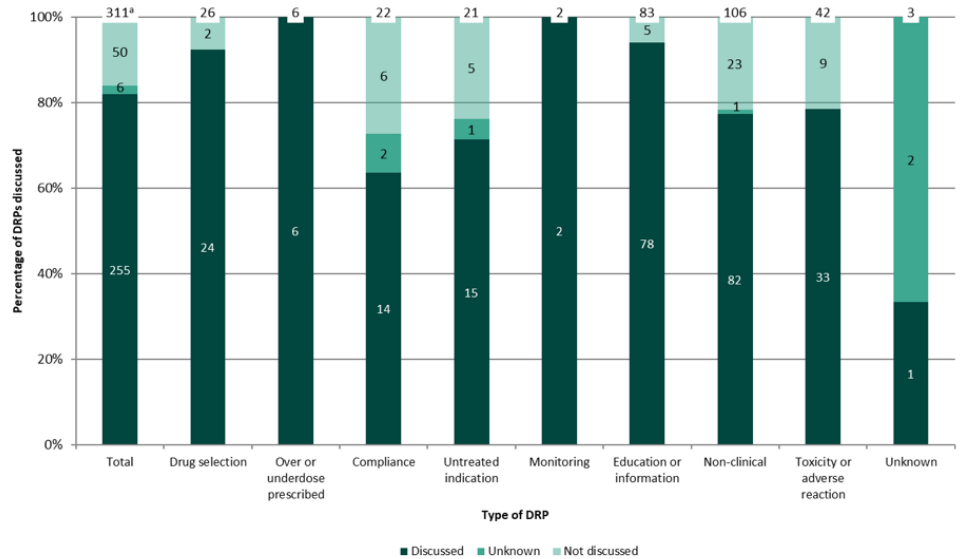

Figure 3. Proportion of DRPs discussed with the patient per type of DRP

[a]Total number of DRPs per type of DRP are represented on top of the bars

DRPs not raised during patients' visits by both HCPs and patients

DRPs not raised by patients

Eleven patients reported drug-related problems that had not been raised during their visits. These were reported in questionnaires after a visit to the medical specialist (n=4), the GP (n=4) and the pharmacy (n=3), respectively. These DRPs that had not been raised during the visits were problems concerning *education or information* (36.4%), *compliance* (27.3%), *drug selection* (18.2%) and *toxicity or adverse reactions* (18.2%). No DRPs at all were raised during 72% of the visits of these patients. Reasons for not raising DRPs from the patients' point of view were: "forgot to mention the DRP during the visit" (54.5%), "no idea why not discussed" (18.2%), "HCP did not take problems seriously" (9.1%), "HCP is not really listening to their problems due to lack of time" (9.1%) and no reason (9.1%).

DRPs not raised by HCPs

HCPs reported 17 visits during which drug-related problems had not been raised. These were reported in interviews with medical specialists (n=11) and GPs (n=6), respectively. HCPs stated that DRPs that had not been raised concerned *compliance* (23.5%), *non-clinical* issues (17.6%), mainly incomplete medication records), *toxicity or adverse reactions* (17.6%), *untreated indications* (11.8%), *drug selection* (11.8%), and *education or information* (11.8%) and 5.8% was not classifiable. No DRPs at all were raised during 47.1% of the visits of these patients.

HCPs reported "lack of time" (23.5%), "too much information/changes at once" (23.5%) and "not necessary/useful" (17.6%) as main reasons for not raising DRPs. In the other 35.3% of the cases, various reasons for not raising the DRP were reported.

There was hardly any overlap between the visits for which patients and HCPs reported DRPs that had not been raised during the visits. There was only one visit after which both the patient and the HCP reported a DRP that had not been raised. However, the DRP that had not been raised by the patient was different from the DRP that had not been raised by the HCP.

Discussion and conclusion

Discussion

To our knowledge, this is the first study examining the extent of communication about drug-related problems by directly observing the communication during patients' visits to the physician and the pharmacy. DRPs were often (in 42% of the visits) raised during patient-healthcare practitioner (HCP) interactions. The most DRPs per visit were raised during encounters with a non-surgical specialist (mostly with respect to *education or information* and *toxicity or adverse reactions*) and pharmacy staff members (predominantly about *non-clinical questions* and *education or information*). That DRPs are more often raised during consults with non-surgical specialists and pharmacy staff members might be caused by 1) the difference in the degree of focus on pharmacotherapy between the various healthcare practitioners and 2) the selection of patients. Both non-surgical specialists and pharmacy staff members are professionals who are mainly focused on medication and the interventions that they apply usually relate to drug therapy. Furthermore, non-surgical specialists probably see more patients that use high-risk and/or larger number of medications than surgical specialists and general practitioners.

However, these raised drug-related problems (DRPs) are not always discussed between patients and HCPs. In almost 12% of the patient visits in which DRPs were raised, at least one DRP was not discussed with the patient. A total of 16% of the DRPs raised were not discussed. The types of DRPs raised during visits that were discussed relatively less often were about *compliance*, *untreated indications*, *non-clinical issues* and *toxicity or adverse reactions*. Possibly because these types of DRPs are judged to be 1) more sensitive and time-consuming to discuss, 2) less urgent to intervene on immediately, 3) less important and/or 4) difficult to solve. Despite aforementioned reasons, not discussing DRPs (particularly in the category *toxicity or adverse reactions*, *compliance* and *undertreatment*) may possibly result in negative treatment outcomes.

Furthermore, both HCPs and patients reported existing DRPs that had not been raised at all during 4-6% of the visits. There was hardly any overlap between the visits for which patients and healthcare practitioners reported DRPs that had not been raised during the visits. This might be explained by the different priorities and expectations that HCPs and patients have during medical consultations[20]. Furthermore, the reasons for not mentioning drug-related problems differed among patients and HCPs. HCPs reported "lack of time" and "too much information/changes at once" and patients "forgot to mention" as reasons for not raising the drug-related problems during the visit. Possible solutions for these barriers might be to have both HCPs and patients be better prepared for the visit, prioritization of the issues to be discussed and alignment of the visit agendas at the start of the visit[21,22].

It is conceivable that better communication between HCP and patient improves the patient's understanding of drug treatment, shared decision making and patient's medication adherence. The clinical impact of enhanced patient-HCP communication about drug-related problems is, for example, illustrated by studies that show improved blood pressure control due to additional adherence communication between HCP and patient[23,24]. Furthermore, research on medication review showed that DRPs that were identified during patient interviews were more clinically relevant than DRPs based on medical records only[25]. Studies on non drug-related patient-HCP communication also indicated that effective HCP-patient communication may directly impact patient health outcomes[26,27]. Based on these studies, one might assume that more effective patient-HCP communication about drug-related problems will lead to increased patient knowledge, patient involvement and possibly better pharmacotherapy and health outcomes as well.

In this study, only existing drug-related problems spontaneously raised during the visits or reported in questionnaires/interviews after the visit were assessed. Physicians and pharmacy staff members did not actively ask or screen for DRPs. Consequently, the weighted mean number of DRPs per patient reported in this study (0.7 SD ± 1.1) is lower than the average number of 4 DRPs per patient reported in medication review trials, as the main goal during medication review trials (often including patients with polypharmacy) is to identify drug-related problems. Other explanations for the relatively low number of DRPs might be that a) patients without medication were not excluded and that b) issues other than drug-related problems were more important for patients to discuss with the healthcare practitioner. Furthermore, there may have been an information bias due to the presence of the observer in the consulting room.

Concerning the existing DRPs not even raised during the consults on the one hand, the reported number of DRPs not raised by both patients and HCPs might be an underestimation, as these were collected in response to a single question, instead of by an in-depth exploration using a list with different DRP categories, for example. This may implicate that the need for communication between HCPs and patients about DRPs is even greater. On the other hand, the reported number of existing DRPs not raised by patients might be an overestimation due to selection bias, as patients that actually encounter DRPs were possibly more willing to fill out the questionnaire.

Existing drug-related problems (noticed by the HCP or encountered by the patient) were not raised by HCPs in 3.9% and by patients in 6.3% of the consultations. Although these percentages seem to be relatively low, these percentages represent large absolute numbers. In the Netherlands, for example, 30 million patients visit the outpatient clinic yearly[28]. Taking these data into account, HCPs and patients do not raise and consequently do not communicate about at least one existing DRP during 7200 and 8400 visits every day, respectively.

The objective of this study was to assess the communication between a diverse sample of HCPs and patients about drug-related problems. Therefore, the communication between HCP and patients about DRPs was assessed in several primary- and secondary care settings with a large variety in HCPs. Although this variety yields a greater spread, it improves the generalizability to different HCPs with respect to the communication between HCP-patient about DRPs.

Conclusion

Healthcare practitioners (HCPs) and patients should be aware that, although DRPs are often raised during clinical consultations, almost one in six DRPs raised are not discussed between HCP and patient. Furthermore, HCPs and patients should realize that during 4-6% of the visits at least one DRP is not raised at all by HCPs and/or patients. As this might hamper patients' safety, further research is necessary 1) to find strategies/tools to enhance communication about DRPs and 2) to examine the impact of better communication about DRPs. Examples of these strategies encompass to have HCPs and patients be better prepared for the visit, prioritization of the issues and alignment of the visit agendas[21,22] and careful listening, explorative communication and tailoring the communication to the individual needs and situation of the patient[29].

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Chapter 5

Association between healthcare practitioners' beliefs about statins and patients' beliefs and adherence

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Abstract

Aims

Adherence to statins ranges from 32-79%. Patients' beliefs about medication are associated with adherence. There is lack of insight into the possible association between beliefs of healthcare practitioners (HCPs) about statins and patients' beliefs and adherence. This study aims to examine whether HCPs' beliefs about statins are associated with patients' beliefs and adherence about/to statins.

Methods

Cross-sectional study in 48 pharmacies and affiliated physicians' practices, between September 3, 2014 and March 20, 2015. HCPs' (prescribers and pharmacy staff) and patients' beliefs about statins were assessed with the Beliefs about Medicine Questionnaire (BMQ) specific. Adherence to statins was assessed with the MARS-5 questionnaire. Multilevel regression analysis was performed to assess the association between HCPs' beliefs and patients' beliefs and adherence.

Results

1504 patients (mean age 66.8 (SD±9.9) years, 46.5% female) and 734 HCPs (209 physicians, 118 pharmacists and 366 pharmacy technicians) participated in this study. Patients have higher BMQ necessity (16.9 (SD±4.3)) and BMQ concern (12.3 (SD±3.9)) scores than HCPs (15.0 (SD±3.0) and 11.5 (SD±2.9), $p<0.001$). No associations were found between any of the HCPs' BMQ and patients' BMQ scores and adherence to statins. Patients' BMQ necessity, concern and NC-differential scores were associated with patients' adherence (MARS-5) scores. B (95% CI) coefficients were .057 (.035 - .079), -.040 (-.064 - -.016) and .061 (.043 - .079).

Conclusions

Patients have stronger beliefs about medication compared to HCPs. No associations were found between HCPs' BMQ scores on the one hand and patients' BMQ scores and adherence to statins on the other hand.

Introduction

Statins are a proven therapy to lower serum concentrations of low density lipoprotein cholesterol, reducing the risk of ischaemic heart disease events by about 60% and stroke by 17%[1]. Despite this, the medication adherence, which is defined as the extent to which the patient's behavior in terms of actually taking medication corresponds with agreed recommendations from the healthcare practitioner[2], varies between 32-79% for statins[3-9].

Non-adherence to statins has a negative impact on treatment outcomes. Patients with poor adherence to statins are more likely to be admitted to the hospital due to cardiovascular heart disease, have a greater potential of having cardiovascular events and cause avoidable high health care costs[7,10-13].

Consequently, interventions to increase medication adherence to statin therapy are warranted to improve health outcomes. Adherence is, according to the WHO, a multidimensional phenomenon in which five dimensions are interrelated "Health-system/HCT factors", "Social/economic factors", "Condition-related factors", "Therapy-related factors" and "Patient-related factors"[14]. Research into the effectiveness of interventions to improve adherence to statins often focuses on the dimension "patient-related factors". So far, these studies show conflicting results (effect on adherence ranging from -3% up to 25%)[15-19]. Furthermore, most published studies focus on practical barriers like simplifying the dosing schedules and providing reminders. However, besides practical barriers, non-adherence can also be the result of perceptual barriers entailing that patients decide not to follow the prescribed dosing regimen based on their beliefs about medication. Patients with perceptual barriers seem to weigh their beliefs about the necessity of medication and concerns about the potential adverse effects of medication[13,20]. These beliefs of patients have a direct association with adherence for a wide range of medicines for chronic conditions[13] and are also modifiable, as demonstrated by Clifford et al.[21].

As previously mentioned, research on interventions to improve adherence to statins mainly focus on the dimension "patient-related factors" and interventions that target the relevant factors in the healthcare environment are urgently required[14]. Not only patients, but also HCPs have beliefs about the necessity and concerns of medication[22-25]. We hypothesize that HCPs' beliefs influence patients' beliefs. Previous research has shown that the beliefs of the physician about a particular treatment may influence the patient's choice to undergo and the patient's adherence to that treatment[24-27]. HCPs' beliefs about statins are therefore an interesting target for interventions to improve adherence of patients. Furthermore, influencing the beliefs of one healthcare provider may affect the beliefs and adherence of several patients. Currently no evidence is available about HCPs' necessity beliefs and concerns about cholesterol lowering medication. Furthermore, it is unknown whether these beliefs might affect patients' beliefs about medication and their adherence to cholesterol lowering medication.

This study therefore aims to assess HCPs' (physicians, pharmacists and pharmacy technicians) and patients' beliefs about statins and whether these HCPs' beliefs are associated with the patients' medication beliefs and adherence to statins. In addition, the possible association between patients' beliefs about cholesterol lowering medication and patients' adherence to statins will be assessed.

Methods

Study design and setting

This cross-sectional study was conducted between September 3, 2014 and March 20, 2015. The participating pharmacists from 48 Dutch pharmacies (44 community and 4 outpatient) were all enrolled in the post-graduate education program for becoming a specialized community pharmacist and participated in the study as part of their curriculum[28]. All pharmacists approached ten pharmacy technicians from their pharmacy (if available), all other pharmacists employed in their pharmacy and the top-5 of most frequently prescribers of statins (physicians and/or nurse practitioners) of patients visiting their pharmacy, to participate in this study.

Patient inclusion and measurements

Inclusion

From the start of data collection, all patients who visited the pharmacy with a statin prescription from one of the included prescribers were invited to participate in the study, up to a maximum of 50 patients per participating pharmacy. Patients were included after obtaining verbal informed consent. There were no exclusion criteria.

Variables and data collection

Patient variables were collected with a questionnaire assessing socio-demographic characteristics, medication related information (duration statin use, prescriber) and a patient's beliefs about medication. Beliefs about statins were assessed with the Beliefs about Medicine Questionnaire (BMQ) specific[29] and patients' adherence to statins was assessed with the Medication Adherence Rating Scale-5 (MARS-5)[30]. Patients were asked by the dispensing pharmacy technician to fill out the questionnaire in the pharmacy or to return the questionnaire by post. HCPs' socio-demographic characteristics and HCPs' beliefs about statins were assessed using the BMQ specific adapted for HCPs using a hardcopy questionnaire[26].

Measurement instruments

Beliefs about Medicines Questionnaire specific

The BMQ consists of 10 items, with 5 items for beliefs about necessity and 5 items about concerns. Items are rated on a five-point Likert Scale (from 1 (strongly disagree) to 5 (strongly agree)), resulting in sum scale scores of 5 to 25 for the necessity and concern beliefs subscales.

Self-reported adherence

The MARS-5 consists of five items, mainly addressing intentional non-adherence behaviour (4 out of 5 items). The items are rated on a five-point Likert scale (from 1 (always) to 5 (never)), resulting in a summated score of 5-25[30].

Sample size and data analyses

Data were analysed using STATA version 13. Descriptive statistics were provided using mean (± SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. P-values ≤0.05 were considered statistically significant.

In order to calculate the sample size, the common rule of thumb was used in which the sample size requirements are based on events per variable, with a minimum of 10-20 events per variable. Assuming a sample size requirement of 20 non-adherent patients per variable and a prevalence of 20% of non-adherence, a sample of 1000 patients is sufficient to build a reliable model including a maximum of 10 independent variables. Taking into account a 15% loss to follow-up, a sample size of 1150 patients was required. Because of the explorative (rather than hypothesis-testing) character of this study, no multiple testing corrections were performed over the separate correlational analyses.

To assess if hierarchical data structure (patients clustered within physician and physicians within pharmacy) influenced our outcomes, multilevel regression analysis was conducted with the levels pharmacy and prescriber (physician or nurse practitioner). As pharmacists and pharmacy technicians jointly provide pharmacotherapeutic care for patients, these HCPs have been combined in the pharmacy level. Multilevel regression analyses were performed on the association between beliefs of HCPs and beliefs of patients, the association between the beliefs of HCPs and the adherence of patients and the association between beliefs of patients and adherence of patients, respectively. If one or more items within a domain (necessity, concerns or adherence) were not answered by a patient or a healthcare practitioner, the respondent was treated as missing for that specific domain.

Results

Response rate

In total, 2229 patients visited the HCPs and were asked to participate in the study of whom 1504 (67.5%) agreed to participate and were included in this study (Table 1). The most common reasons for patients not to participate in the study were: "not in the mood", "lack of time", "already having responded previously to other questionnaires".

Further, a total 734 HCPs were asked to participate in the study of whom 693 (94.4%) agreed to participate and were included in this study. Response rates of the various HCPs were: 209 out of 225 (92.8%) physicians, 118 out of 119 (99.1%) pharmacists and 366 out of 390 (94.1%) pharmacy technicians.

Table 1. Baseline characteristics patients and HCPs

Parameter	Patient characteristics (n=1504)
Age (years) [mean (SD)]	66.8 (9.9)
Gender* (female) [n (%)]	675 (46.5)
Years of statin use [median (p25 p75)]	6 (3-10)
	Physician characteristics** (n=209)
Gender (female) [n (%)]	94 (45)
Age (years) [mean (SD)]	49.5 (10.0)
Years employed [median (p25 p75)]	19 (10-26)
	Pharmacist characteristics (n=118)
Gender* (female) [n (%)]	71 (60.2)
Age (years) [mean (SD)]	36.9 (11.0)
Years employed [median (SD)]	10.3 (10.0)
	Pharmacy technician characteristics (n=366)
Gender* (female) [n (%)]	353 (98.1)
Age (years) [mean (SD)]	39.7 (11.4)
Years employed [median (SD)]	16.2 (11.0)

* In this study, participants could score gender as 'male' or 'female'
** General practitioner 89.5%, general practitioner in training 1.0, cardiologist 2.9%, internist 1.9%, neurologist 0.5%, nurse practitioner 1.0%, practice assistant 2.9%, other 0.5%

Patients' and HCPs' beliefs about statins

The scores concerning both patients' and HCPs' beliefs about statins are depicted in table 2. The number of missings was less than 5%. Patients have higher BMQ necessity and BMQ concern scores compared to HCPs ($p < 0.0001$ for necessity and $p < 0.01$ for concerns). Among the HCPs, pharmacists have the highest BMQ necessity scores, followed by pharmacy technicians and physicians. Pharmacy technicians have the highest BMQ concern scores, followed by physicians and pharmacists. Pharmacists have a higher differential score than patients and other HCPs.

Table 2. Mean (SD) BMQ scores of patients and HCPs

	Patients (n = 1504) Mean (SD)	HCPs (n=693) Mean (SD)	Physicians (n=209) Mean (SD)	Pharmacists (n=118) Mean (SD)	Pharm.tech. (n=366) Mean (SD)
Necessity beliefs about medication	16.9 (4.3)	15.0 (3.0)	13.9 (2.7)	15.6 (2.9)	15.4 (3.0)
Concern beliefs about medication	12.3 (3.9)	11.5 (2.9)	11.5 (2.8)	9.3 (2.6)	12.3 (2.5)
Necessity-concerns differential	4.6 (5.2)	3.5 (4.1)	2.5 (4.3)	6.4 (3.8)	3.1 (3.6)

Association between HCPs' and patients' beliefs about statins

No associations were found between HCPs' (neither necessity scores, nor concerns and NC-differential) beliefs about statins and patients' beliefs about statins (table 3).

Table 3. Multilevel regression analysis for the association of HCPs' beliefs and patients' beliefs about medication, controlling for the pharmacy level and physician level

	Patients' BMQ_N B (95% CI) coefficient	Patients' BMQ_C B (95% CI) coefficient	Patients' BMQ_D B (95% CI) coefficient
Beliefs physicians			
BMQ_N	-.075 (.181 - .031)		
BMQ_C		-.007 (-.100 - .086)	
BMQ_D			-.022 (-.111 - .067)
Beliefs pharmacists			
BMQ_N	.133 (-.016 - .281)		
BMQ_C		-.042 (-.191 - .108)	
BMQ_D			.037 (-.123 - .199)
Beliefs pharmacy technicians			
BMQ_N	-.009 (-.032 - .014)		
BMQ_C		.005 (-.014 - .024)	
BMQ_D			-.011 (-.036 - .014)

* $p < 0.0001$; ** $p < 0.001$; *** $p < 0.01$ BMQ_N = BMQ necessity score; BMQ_C = BMQ concern score; BMQ_D = BMQ differential score

Patients' adherence to statins

The score (median (p25-p75)) concerning patients' adherence to statins as measured with the MARS-5 score was 25 (24-25). The proportion of patients with a MARS-5 score of ≥23 and ≥24 was 1349/1483 (91%) and 1215/1483 (82%), respectively.

Association between patients' beliefs about and adherence to statins

All domains of the patients' BMQ (necessity, concerns, and NC-diff) were associated with patients' adherence to statins based on the Mars-5 (table 4).

Association between HCPs' beliefs about and patients' adherence to statins

No associations were found between the HCPs' beliefs about statins and patients' adherence to statins (table 4).

Table 4. Multilevel regression analysis for the association of patients' or healthcare practitioners' beliefs about medication and patients' adherence to medication, with controlling for the pharmacy level and physician level

	Patients' MARS-5 adherence scores B (95% CI) coefficient
Beliefs patients	
BMQ_N	**.058 (.036 - .080) ***
BMQ_C	**-.041 (-.065 – -.017) *****
BMQ_D	**.062 (.043 - .080) ***
Beliefs physicians	
BMQ_N	-.004 (-.048 - .040)
BMQ_C	.028 (-.014 - .070)
BMQ_D	-.013 (-.043 - .017)
Beliefs pharmacists	
BMQ_N	-.019 (-.110 - .073)
BMQ_C	-.003 (-.108 - .103)
BMQ_D	-.011 (-.086 - .064)
Beliefs pharmacy technicians	
BMQ_N	-.011 (-.023 - .001)
BMQ_C	-.010 (-.022 - .001)
BMQ_D	-.009 (-.020 - .001)

* p < 0.0001; ** p < 0.001; *** p < 0.01; BMQ_N = BMQ necessity score; BMQ_C = BMQ concern score; BMQ_D = BMQ differential score

Discussion

To our knowledge, this is the first study examining the association between the beliefs about statins on the part of HCPs and the patients' beliefs about statins and their adherence to statins. Patients have higher scores on necessity and concerns than health care practitioners. Among the HCPs, pharmacists have the highest scores on necessity, followed by pharmacy technicians and physicians, whereas pharmacy technicians have the highest scores on concerns, followed by physicians and pharmacists. Although patients have higher scores on necessity than pharmacists, pharmacists have a higher differential score due to very low concern scores compared to the patients' other HCPs. Patients' BMQ necessity, concern and NC-differential scores were associated with patients' adherence (MARS-5) scores. However, no association between the beliefs of HCPs and beliefs of patients and adherence of patients was found.

Adherence (MARS-5) scores, of patients using statins in this study were similar to those in another study[31]. The results of this study furthermore show that patients have higher scores on necessity and concerns than health care practitioners. Although Driesenaar et al. also found higher concern scores in patients compared to HCPs, they found a lower score on necessity in patients than in HCPs[32]. This may be explained by the fact that our study was conducted among patients using statins and Driesenaar's study concerned patients using inhaled

corticosteroids. Although the effect of statins and inhaled corticosteroids is not directly noticeable by the patient, the negative effect of non-adherence to inhaled corticosteroids is more directly noticeable for the patient compared to non-adherence to statins.

There are several possible explanations for the fact that no association was found between HCPs' beliefs about medication and patients' beliefs about medication and the patients' adherence. Firstly, it could be that HCPs know how to empathize with a patient and thereby eliminate their own beliefs about medication, resulting in not discussing their own beliefs with patients[32,33]. A second explanation may be that ceiling effects occur when using the MARS-questionnaire, due to the lack of sensitivity to detect a difference in adherence, as described in the strengths and limitations section. A third explanation is that HCPs do not eliminate their own beliefs about medication, but that they insufficiently or ineffectively communicate with patients about their beliefs. Effective communication about beliefs about medication and adherence consists of various elements. Effective communication about beliefs about medication and adherence starts with facilitating and being aware of the patient's knowledge about medication. Several studies describe the importance of this knowledge for medication adherence[34,35]. To improve adherence, misconceptions about illness and treatment should be avoided by exploring, understanding and engaging with a patient's knowledge and ideas about causality, experiences of symptoms and concerns about treatment[36-38].

Another part of effective communication is creating a setting in which patients feel safe to raise their beliefs about medication and to speak out about medication non-adherence, so that non-adherence will not remain a hidden problem[34,39]. Finally, patients should be encouraged to raise issues concerning beliefs about medication and non-adherence in patient-HCP interactions. This can be achieved by communication tailored to the patient's illness- and treatment related needs, experiences and circumstances[14,40]. During this patient-HCP communication, patients can be elicited to share their concerns and adherence behavior, for instance by asking specific questions during or in preparation of their visit to the HCP[39].

One of the strengths of this study was the large sample of patients and HCPs, as well as the high response, increasing the accuracy of the results. This study was furthermore conducted in a large number of practices across the Netherlands, which increases generalizability. Nevertheless, there are some limitations to this study. First, adherence was only measured by self-report questionnaires in this study. Self-report questionnaires are subjective and therefore sensitive to social desirability bias. Therefore, preferably a combination of methods to measure adherence (e.g. self-report questionnaires, pill count, refill adherence, medication event monitoring systems and/or biochemical testing) should be used[14]. Furthermore, by examining an association between beliefs about medication and adherence, both measured by self-report questionnaires, it must be taken into account that the MARS questionnaire contains questions about cognitions like beliefs as well. This may result in a false-positive association between beliefs and adherence. However, no association between HCPs' beliefs about medication and patient's adherence was found, so it is not likely that this affects the outcome of this study at this point. Also, inclusion bias may have played a role in this study, as it is likely that adherent patients are more motivated to participate in this kind of study, which is confirmed by the fact that adherence rates were even higher in this study than in other studies with patients using statins[8,9]. If, as a result, there is not enough contrast in the included population (due to a small number of non-adherent patients), the MARS-5 may not

be sensitive enough to detect a difference. Despite this, an association between the patients' BMQ scores and MARS-5 scores was found. This may still explain the fact that no association was found between HCPs' beliefs and patients' adherence, because the correlation with HCPs' beliefs is more difficult to prove. The total number of participating patients was large, over 1400, so this reduces the chance that inclusion bias affected the results.

Conclusion

This study shows that patients' beliefs about statins are associated with patients' adherence to statins, so also for statins patients' beliefs are a potential target to improve adherence. Besides, patients using statins have higher scores on necessity and concerns than HCPs prescribing or dispensing statins. No association was found between the BMQ scores of healthcare practitioners and the BMQ scores of patients and adherence of patients based on MARS-5. As only questionnaires were used in this study to examine these associations, further research on this association in which questionnaires on beliefs and adherence are combined with other methods to measure adherence (e.g. MEMS devices, pill count, refill adherence etc.) is recommended. The further research could furthermore be supplemented with examining to which extent communication about beliefs about medication and adherence behavior during patient-HCP interactions takes place, by observing or audiotaping these interactions.

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Chapter 6

Impact of physician' and pharmacy staff supporting activities in usual care on patients' statin adherence

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Abstract

Purpose
Little is known about usual care by physicians and pharmacy teams to support adherence to statins and whether the extent of this care is associated with adherence to statins. Objective of the study was to examine the relationship between the extent of adherence supporting activities of HCPs and patients' adherence to statins.

Methods
Cross-sectional study in 48 pharmacies and affiliated physicians' practices, between September 3, 2014 and March 20, 2015. Patients visiting the pharmacy with a statin prescription from participating prescribers were invited to participate. Usual care to support adherence was assessed among HCPs with the Quality of Standard Care questionnaire about usual care activities to support adherence. Adherence to statins was assessed among patients with the MARS-5 questionnaire. The association between the extent of HCPs' adherence supporting activities and patients' adherence was examined by means of multilevel regression analysis.

Results
1,504 patients and 692 HCPs (209 physicians, 118 pharmacists and 365 pharmacy technicians) participated. No association was found between the extent of physicians' adherence supporting activities and patients' adherence to statins. The extent of adherence supporting activities by pharmacy teams in usual care was negatively associated with patients' adherence to statins (B coefficient -0.057 (95%CI: 0.112-0.002).

Conclusion
This study suggests that there is no positive relationship between the extent of HCPs' adherence supporting activities in usual care and patients' adherence to statins. Other methods than questionnaires (e.g. electronic monitors (to assess adherence) and observations (to assess usual care) should be applied to confirm the results of this study.

Introduction

Statins are a proven therapy to lower serum cholesterol concentrations, reducing the long-term risk of ischaemic heart disease events by about 60% and stroke by 17%[1]. Despite these therapeutic advantages, medication adherence to statins (defined as the extent to which the patient's medication taking behavior corresponds with the agreed recommendations from the healthcare provider) is suboptimal and varies between 32-77%[2-8].

Non-adherence to statin therapy has a negative impact on treatment outcomes. Patients with poor adherence to statins are at greater risk of cardiovascular events and hospitalization due to cardiovascular disease and cause avoidable high health care costs[9-15]. This makes improving medication adherence to statin therapy a key component of the treatment of hypercholesteremia[9,16].

Adherence is multifactorial; "Health-system/Health-care team factors", "Social/economic factors", "Condition-related factors", "Therapy-related factors" and "Patient-related factors" have been associated with/implicated in non-adherence[9]. Previous research on interventions to improve adherence to statins mainly focused on "patient-related factors", however these studies yielded small inconsistent results, with a range of effect of these interventions from -3% up to 25% improvement of adherence[17-20]. Therefore, interventions that target other factors that can have impact on adherence might also be required, like relevant factors in the health-system/health-care[9]. Yet, evidence on the impact of health-system/health-care team factors on implementation adherence to statins is scarce. Insight into the association between relevant factors in the health system/health-care team and adherence is warranted. Earlier studies demonstrated health system factors like continuity of care and complete treatment information are factors that are positively associated with adherence to drug treatment in chronic conditions as well as in statin use[16,21,22]. Furthermore, patients who experienced a higher quality of care and/or a higher degree of shared decision making had more knowledge of their illness, were more actively involved in their own treatment, were more confident in their communication with healthcare providers and had higher adherence rates[23,24]. The aforementioned examples in literature are about the impact of the overall quality of care on adherence, whereas literature about the impact of the quality of care activities employed by individual HCPs is scarce. Based on the findings about the positive impact of the overall quality of care on adherence, it is also conceivable that quality of care activities, including usual care adherence support activities) of a single HCP, might positively influence patients' medication adherence. Noteworthy, influencing the usual care of one single healthcare provider may affect the adherence of several patients, which makes interventions on HCP level potentially more impactful than interventions on patient level. Currently, no evidence is available about physicians' and pharmacy staff's' usual care to support adherence to statins and how this care affects patients' adherence.

The aim of this study is 1) to describe the nature and extent of adherence supporting activities provided in a usual care setting by physicians, pharmacists and pharmacy technicians; and 2) to examine the relation between the extent of adherence supporting activities of physicians, pharmacists and pharmacy technicians and adherence to statins. We hypothesized that increased HCPs' usual care activities to support statin adherence have a positive impact on patients' implementation adherence to statins.

Methods

Study design and setting

This cross-sectional study was conducted between September 3, 2014 and March 20, 2015 in 48 Dutch pharmacies (44 community and 4 outpatient). The EMERGE (ESPACOMP Medication Adherence Reporting Guideline) was used as guidance in reporting this study[25]. The Medical Research Ethics Committee (MREC) of Arnhem- Nijmegen waived official ethical approval (file number: 2021-13158) and assessed the trial as not being subject to the Medical Research Involving Human Subjects Act (WMO).

Eligibility criteria and selection procedures

All of the patients who came to the pharmacy with a prescription for a statin from one of the prescribers included were asked to participate in the study. For inclusion criteria, we refer to Huiskes et al.[26]. Patients were included only after verbal informed consent was obtained.

Measurements

Variables and data collection

Patient data were collected with a hardcopy questionnaire assessing socio-demographic characteristics, medication related information (duration statin use, prescriber) and patient's adherence to statins (see measurement instruments). In this study implementation adherence (defined in the ABC taxonomy of medication adherence) was studied, as current statin users were included[27]. Patients were asked by the dispensing pharmacy technician to fill out the questionnaire in the pharmacy or to return the questionnaire by mail. HCPs' socio-demographic characteristics and HCPs' usual care to support adherence (see measurement instruments) to statins were assessed using a hardcopy questionnaire.

Outcomes

An inventory of the nature and extent of adherence supporting activities provided in a usual care setting by physicians, pharmacists and pharmacy technicians and the association between the extent of these HCPs' adherence supporting activities and patients' adherence to statins.

Measurement instruments

Usual care Questionnaire

Usual care to support adherence to statins was assessed with a 47-item questionnaire about usual care activities to support adherence based on the Quality of Standard Care questionnaire as used by the Bruin et al[28,29]. The list was adapted to statin therapy by one of the researchers (BvdB) with permission from the original authors. HCPs were asked to score the extent of their care activities they performed to support adherence in the majority of their patients the past six months a) when initiating statin therapy, b) during follow-up visits with patients that already used statins for a longer period and c) for their patients regardless of whether they used a statin. Four out of the 47 items were qualitative questions and 43 items could be answered with yes or no. Due to the quantitative character of this study the four qualitative

questions were not included in the analysis. When the response to a quantitative question was answered with yes, the answer was awarded one point. The questions as presented to the HCPs are shown in table 2. A sum score was calculated by summing the scores of each question, resulting in a sum score from 0 to 43. Furthermore, in order to create a better understanding of the nature and extent of the usual care activities, usual care activities were grouped to sub scales. Also for these sub scales sum scores were calculated. The sub scales were based on the coding taxonomy provided by the original author: knowledge, awareness, attitude, social influence, self-efficacy, intention formation, action control, facilitation, metascore[29]. A higher sum score indicates a higher quality of the level of usual care.

Self-reported adherence to statins

The MARS-5 consists of five items, mainly addressing intentional non-adherence behaviour (4 out of 5 items). The items are rated on a five-point Likert scale (from 1 (always) to 5 (never)), resulting in a summated score of 5-25[30]. No standard cut-off point to define adherent versus nonadherent medication has been provided by the scale developers and it varies across studies[31]. In this study the MARS-5 cut-off scores of ≥ 23 and ≥ 24 to identify adherent and non-adherent patients are both reported, as these are cut-off points that are more often used and because adherence distributions found with the MARS-5 are often highly skewed[32-35].

Sample size and data analyses

Data analyses

Data were analyzed using STATA version 13. Descriptive statistics were provided using mean (± SD) or median (p25-p75) values depending on the (non-) parametric distribution of measured variables. P-values ≤0.05 were considered statistically significant.

The association between the extent of HCPs' usual care activities (sum score of the Quality of Standard Care questionnaire) and the adherence (MARS-5 total score) of patients was subjected to multilevel linear regression analyses (see Huiskes et al.[26]). If a healthcare practitioner did not answer one or more items of the usual care questionnaire within the total of usual care activities or within a sub scale, then the respondent was considered as lacking for the calculation of the total sum score or the sum score of that sub scale.

Sample size

In this study a convenient sample of 1504 patients was included as described by Huiskes et al.[26] in the methods section (eligibility criteria and selection procedures). Based on a conservative estimation of one-third non adherent patients in this population, 501 non-adherent patients were expected. As eight independent variables were planned to be included in these multilevel regression analyses, 62 cases per independent variable were available, which means enough power is achieved, even taking into account the variance attributable to the group level (based on an alpha of 0.05, a beta of 0.8).

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Results

Response rate

A total of 2229 patients visited the HCPs and were asked to participate in the study. Of these patients, 1504 (67.5%) agreed to participate and were included in this study (Table 1).

A total of 734 HCPs were asked to participate in the study, 692 (94.3%) of whom agreed to participate and were included. The response rates to the questionnaires per type of HCP were: 209 out of 225 (92.8%) physicians, 118 out of 119 (99.1%) pharmacists and 365 out of 390 (93.6%) pharmacy technicians. The following prescribers were included: general practitioner (89.5%), general practitioner in training (1.0%), cardiologist (2.9%), internist (1.9%), neurologist (0.5%), nurse practitioner (1.0%), nurse specialist in primary care (2.9%), others (0.5%). The mean (SD) number of patients per physician and pharmacy were 6,6 (SD± 5.0) and 31.1 (SD±15.0), respectively.

Table 1. Baseline characteristics patients and HCPs

Parameter	Patient characteristics (n=1504)
Age (years) [mean (SD)]	66.8 (9.9)
Gender* (female) [n (%)]	675 (46.5)
Years of statin use [median (p25 p75)]	6 (3-10)
	Physician characteristics (n=209)
Gender (female) [n (%)]	94 (45)
Age (years) [mean (SD)]	49.5 (10.0)
Years employed [median (p25 p75)]	19 (10-26)
	Pharmacist characteristics (n=118)
Gender* (female) [n (%)]	71 (60.2)
Age (years) [mean (SD)]	36.9 (11.0)
Years employed [median (SD)]	10.3 (10.0)
	Pharmacy technician characteristics (n=366)
Gender* (female) [n (%)]	353 (98.1)
Age (years) [mean (SD)]	39.7 (11.4)
Years employed [median (SD)]	16.2 (11.0)

* In this study, participants could score gender as 'male' or 'female'
** General practitioner 89.5%, general practitioner in training 1.0, cardiologist 2.9%, internist 1.9%, neurologist 0.5%, nurse practitioner 1.0%, practice assistant 2.9%, other 0.5%

Patients' adherence to statins

The median (p25-p75) MARS-5 score was 25 (24-25). A total of 1349/1483 (91%) and 1215/1483 (82%) of the patients were adherent to their statins using MARS-5 cut-off scores of ≥ 23 and ≥ 24 respectively.

HCPs' usual care activities to support adherence to statins

HCPs' (physicians, pharmacists and pharmacy technicians) usual care activities to support medication adherence to statins are reported in table 2. The median usual care activities total scores ranged from 21-23 between the three subgroups (table 3). The highest median sum scores (as percentage of the maximum sum score) were found on sub scales for attitude and facilitation (for all types of HCPs) and awareness (for physicians). The lowest median sum scores were found on sub scales for action control and social influence (for all HCPs) (table 3).

The top three most frequently reported usual care activities by physicians were: "Explain what cholesterol is and why raised cholesterol is undesirable", "Explain how often and how long the medication should be used", "Giving feedback about the effect of the statin using laboratory findings". For pharmacy teams this consisted of: "Monitor and/or discuss possible interactions with other drugs", "Discuss the common side effects of the drug", "Verbal explanation about statins" (table 2).

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Table 2. Usual care to support adherence to statins as reported by physicians, pharmacists, pharmacy technicians & pharmacy team

		Cat.	% yes phys. (n=209)	% yes pharm (n=118)	% yes pharm tech (n=366)	%yes pharm team (n=484)
Knowledge						
1.	Explain what cholesterol is and why raised cholesterol is undesirable	S	96	54	50	51
2.	Discuss what a statin is and the mechanism of action	S	77	92	80	83
3.	Hand out brochure or written information about statins	S	12	92	95	94
4.	Discuss drug storage recommendations	S	3	35	41	39
5.	Explain what to do if a dose is missed	S	22	34	44	42
6.	Do you ask patients to repeat the received information in their own words regularly, to check whether the information is understood properly? (Refers to items:1;2;3;4;5;12;15;16;26;31;32;33)	S	18	19	21	21
7.	Verbal explanation to the patient	S	94	99	98	98
8.	Use of illustrative materials (pictures/charts/video)	S	14	4	3	3
9.	Hand out written information	S	20	94	97	96
10.	Refer patients to websites	S	38	8	7	7
11.	Do you ask patients to repeat the received information in their own words regularly, to check whether the information is understood properly? (Refers to items:13;17;20;21;22;28;29;30)	S	19	17	19	18
Awareness						
12.	Discuss the consequences of non-adherence	S	49	50	48	49
13.	Encourage patients to use a 7-day pillbox	S	47	36	37	37
14.	Giving feedback about the effect of the statin using laboratory findings	F	95	18	10	12
Attitude						
15.	Explain that the patient doesn't notice the effect of the statin but that the effect is evaluated by blood tests to check cholesterol levels	S	87	82	79	80
16.	Discuss the importance of adherence	S	77	84	80	81
17.	Encourage patients to be adherent	S	81	77	78	78
18.	Ask the patient about non-practical problems with taking the medication as prescribed (unwilling to take medication, for example because of misunderstandings about taking medication)	F	56	36	35	35
19.	In case of non-practical problems, propose solutions to solve these problems (for example discussing the necessity or concerns, referral to nurse practitioner)	F	67	70	61	63
Social influence						
20.	Involve partner and/or relatives in the treatment	S	30	21	15	16
Self efficacy						
21.	Encourage patients to plan ahead (for example for holidays or social activities)	S	19	16	26	23
22.	Discuss potential barriers regarding adherence and possible ways to overcome them	S	41	42	26	30
23.	Ask the patient if he/she is taking the medication as prescribed	F	79	67	69	68
24.	Ask about practical problems with taking medication as prescribed (for example forgetting it or being unable to open the packaging)	F	29	41	34	36
25.	In case of practical problems, discuss solutions with the patient to reduce these practical problems	F	56	84	81	82
Intention formation						
26.	Explain how often and how long the medication should be used	S	95	93	96	95
27.	Develop and discuss a written individual dosing schedule	S	21	25	17	19
28.	Write down patients' dosing schedule (time, name of meds, number of doses)	S	22	41	39	39
Action control						
29.	Identify daily routines (like brushing teeth) and encourage patients to align the taking of medicines with their routines	S	36	35	39	38
30.	Encourage patients to use alarm devices as a reminder for taking the medication	S	9	16	10	11
Facilitation						
31.	Discuss the common side effects of the drug	S	86	97	99	98
32.	Discuss with the patient how to deal with side-effects	S	75	84	93	90
33.	Monitor and/or discuss possible interactions with other drugs	S	63	98	99	99
34.	Discuss the experienced positive effects of the treatment	F	47	38	38	38

35.	Asking about (perceived) side-effects of the treatment	F	91	82	88	87
36.	If patients experience side-effects, there is an active contribution to reduce these side-effects (sometimes by providing knowledge or adjusting the treatment)	F	93	92	81	84
37.	Suggesting a new medication regimen in case patients feel their present regimen is too complex	F	72	84	59	65
38.	Call the patient after the initiation of the drugs to ask about experiences	G	9	10	14	13
39.	Give the patient a telephone number and tell who to contact in case of side-effects	G	23	25	25	25
40.	Give the patient a telephone number and tell who to contact in case of problems with intake/medication adherence	G	19	15	21	20
41.	Explain patients who to contact in case they would run out of medication	G	74	69	84	80
Metascore						
42.	Intensify the number of follow-up visits in case of (possible) treatment non-adherence	G	38	19	12	14
43.	Refer patients to another health care provider for (co-)treatment (e.g., in case of side-effects)	G	35	60	47	50

S= when starting statin therapy; F= during follow-up visits; G= in general for their patients regardless of whether they used a statin.

Table 3. Median scores, interquartile ranges and median scores as percentage of the maximum score

		Physicians		Pharmacists		Pharmacy technicians		Pharmacy team**	
Sub scales*	Min - max	Median (p25 - p75)	Median score as % of max score	Median (p25 - p75)	Median score as % of max score	Median (p25 - p75)	Median score as % of max score	Median (p25 - p75)	Median score as % of max score
Knowledge	**(0-11)**	4 (3-5)	36	5 (4-7)	45	5 (4-7)	45	5 (4-7)	45
Awareness	**(0-3)**	2 (1-3)	67	1 (0-2)	33	1 (0-2)	33	1 (0-2)	33
Attitude	**(0-5)**	4 (3-5)	80	4 (3-5)	80	4 (3-4)	80	4 (3-4)	80
Social influence	**(0-1)**	0 (0-1)	0	0 (0-0)	0	0 (0-0)	0	0 (0-0)	0
Self efficacy	**(0-5)**	2 (1-3)	40	2 (1-4)	40	2 (1-3)	40	2 (1-3)	40
Intention formation	**(0-3)**	1 (1-2)	33	1 (1-2)	33	1 (1-2)	33	1 (1-2)	33
Action control	**(0-2)**	0 (0-1)	0	0 (0-1)	0	0 (0-1)	0	0 (0-1)	0
Facilitation	**(0-11)**	7 (5-8)	64	7 (6-8)	64	7 (6-8)	64	7 (6-8)	64
Meta-score	**(0-2)**	1 (0-1)	50	1 (0-1)	50	0 (0-1)	0	1 (0-1)	50
Sum score*	**(0-43)**	21 (16-26)	49	23 (18-27)	53	21 (17-26)	49	21.5 (18-26)	49

* Respondents were treated as a missing for calculation of the sum score if one or more items were missing. The number of missings was 21%.
** Pharmacy team is the combination of pharmacy technicians and pharmacists

Association between the extent of HCPs' adherence supporting activities and patients' adherence to statins

The extent of adherence supporting activities by pharmacy teams in a usual care setting was negatively associated with patients' adherence to statins (B coefficient -0.057 (95%CI: 0.112-0.002) (table 4). No association was found between the extent of physicians' adherence supporting activities and patients' adherence to statins (table 4).

Table 4. Multilevel regression analysis for the association between the extent of HCPs' adherence supporting activities and patients' adherence to statins, with controlling for the pharmacy level and physician level

	Patients' MARS-5 adherence scores B (95% CI) coefficient
Adherence supporting activities by physicians	0.085 (-0.010-0.027)
Adherence supporting activities by pharmacy teams	**-0.057 (0.112-0.002) ***

* $p \leq 0.05$

Discussion

To our knowledge, this is the first study examining the level of usual care by HCPs to support adherence to statins and the impact of the level of usual care on patients' adherence to statins. The results of this study did not confirm the hypothesis that there is a positive relationship between the extent of HCPs' adherence supporting activities in usual care and patients' implementation adherence to statins. The extent of usual care activities hardly differed between physicians, pharmacists and pharmacy technicians. The median sum scores on all sub scales of the Quality of Standard Care questionnaire were comparable for all HCPs, only on awareness physicians scored higher than pharmacy staff.

In this study the level of usual care to support adherence delivered by physicians is comparable and by pharmacists exceeded that reported by Timmers et al. (in patients using oral anti-cancer drugs)[36]. The latter might be explained by the fact that other HCPs than pharmacists (e.g. nurses) perform these activities (because of differences in setting and type of medication).

In our study, both pharmacists and physicians reported that half of the adherence supporting activities were performed and half were not. When HCPs coordinate their adherence supporting activities, this does not necessarily have to be a problem. This seems to be the case with respect to patient education to improve medication adherence: whereas doctors educate patients about the disease, the effect of the drug and treatment duration, pharmacy staff member tend to focus on adverse events, drug-drug interactions and storage conditions. Although doctors and pharmacy staff members seem to be synergistic with respect to education (sending information), neither doctors nor pharmacy staff members ask the patient about perceived barriers to take the medication as prescribed: patients' knowledge about medication and non-practical barriers and practical barriers taking medication as prescribed are hardly inventoried by both physicians and pharmacy staff.

The extent of usual care of HCPs to support adherence to statins was not positively associated with patients' adherence to statins. This in contrast with two meta-analyses on the quality of usual adherence care and medication adherence in patients infected with Human Immunodeficiency Virus (HIV) showing that a higher quality of self-reported usual care led to more patients being adherent to their medication[28,29]. This might be explained by differences in type of medication, and design and setting (cross-sectional inventory of usual care in our study in one country versus retrospective inventory of usual care in usual care arms of trials in several countries). Furthermore, in HIV care often nurses are involved, which requires another role of pharmacists with respect to adherence support. Finally, adherence was measured differently, as in our study the MARS questionnaire was used and in the studies included in the meta-analyses by de Bruijn et al. (2009 and 2010) both self-reported adherence measures and MEMS devices were used.

The lack of positive impact of usual care of both physicians and pharmacists to support adherence to statins on patients' adherence to statins may be explained by conceptual differences (the extent of unintentional and intentional non-adherence aspects that are incorporated in the questionnaire) between the usual care activity questionnaire and the patient adherence measure (MARS-5). The Quality of Standard Care questionnaire is balanced with respect to the proportion of aspects related to unintentional and intentional non-adherence, whereas the MARS-5 questionnaire used in this study is predominantly focused on intentional non-adherence. Another explanation may be that the overall high MARS-scores might lead to ceiling effects, which may account for not finding a difference in adherence scores, as described in the strengths and limitations section.

Furthermore, HCPs with a patient population with low adherence rates to statins possibly feel a greater need to perform activities to support adherence to statins and consequently have higher scores on the usual care questionnaire. Alternatively, social desirability bias may have led to an overestimation of the level of usual care reported by pharmacy staff. In that case HCPs provide less activities to support adherence than they say they deliver, tentatively resulting in lower adherence rates and no (or a weakly negative) association between the extent of adherence supporting activities and patients' adherence. Participatory observations to assess the actually delivered extent of usual care activities to support adherence could be applied to overcome this.

The current findings should be interpreted in light of the strengths and limitations of our study. One of the strengths of this study concerns the large sample of patients and HCPs, as well as the high response rate, which increases the accuracy of the results. This study was furthermore carried out in a large number of practices across the Netherlands. This last aspect increases the generalizability (with respect to adherence supporting activities of HCPs to stimulate patients' adherence to statins). The fact that the MARS-5 scores of patients using statins in this study were similar to those in another study and that 18% of patients are non-adherent to therapy (similar to the degree of non-adherence in other studies among Dutch patients taking statins), is a prove that a valid sample was included in the study and highlights generalizability[37-39].

However, this study does have its limitations. First of all, self-report questionnaires were the only means used in this study to measure adherence and the level of usual care.

Questionnaires of this kind are subjective and therefore sensitive to social desirability bias. It is preferable for that reason to use a combination of methods when measuring adherence (e.g. self-report questionnaires, pill count, refill adherence, medication event monitoring systems and/or biochemical testing) and to observe the HCPs to inventory the level of usual care. If the extent of usual care delivered by a HCP is assessed by observation, it can be decided to observe each HCP once, or to observe all individual patient-provider interactions. Preferably all the individual patient-provider interactions are observed, as the usual care actually provided may depend on a specific patient and/or moment. Seeing that it is likely that adherent patients are more motivated to participate in a study of this kind (confirmed by slightly higher adherence rates in this study than in other studies), inclusion bias may have played a role[3,8]. The chance that inclusion bias has affected the results, however, is reduced by that fact that the response rate of patients was high (67.5% of the selected patients agreed to participate in the study). Furthermore, due to a ceiling effect when using the MARS-5 and therefore little explained variance, no difference in adherence scores may be found.

This study provides an overview of usual care activities to support adherence to statins as reported by a large number of physicians, pharmacists and pharmacy technicians employed in a large number of practices in the Netherlands. Furthermore, the results of this study suggest that there is no positive relationship between the extent of HCPs' adherence supporting activities in usual care and patients' adherence to statins. Before trials are performed to improve adherence by intervening on HCPs, first more research with better techniques to objectify the level of usual care to support adherence and the impact on patients' adherence is warranted. As only questionnaires were used in this study to examine the impact of usual care on adherence, further research in which other methods to measure adherence are used are recommended. Further research could furthermore be supplemented with observing the patient-provider interactions to inventory the level of usual care delivered by HCPs.

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Conflict of interest statement

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6

Chapter 7

General discussion

Introduction

Drug therapy plays a key role in health care and usually contributes to improvements in patients' health outcomes and quality of life[1,2]. However, patients also often experience drug-related problems (DRPs) that may result in patient morbidity[3,4]. Drug-related problems find their origin in the entire process of prescribing (physician), dispensing (pharmacist) and using the medication (patient). High quality pharmaceutical care can reduce these DRPs, especially when patients and HCPs (e.g. physicians and pharmacists) both take the responsibility for their part and when they cooperate to ensure productive patient-provider interactions[5-7]. As such, both HCPs and patients are, each in their own way, important in preventing and decreasing DRPs and maximizing the effectiveness of drug treatment.

This thesis focused on the role of patients and HCPs in pharmaceutical care to reduce DRPs. Therefore, we studied three pharmaceutical care activities:

1. examining the effectiveness of medication reviews with patient involvement
2. inventorying the extent of patient-provider communication about DRPs
3. exploring the association between HCPs' medication adherence activities/beliefs and patients' beliefs and adherence

In this general discussion we will illustrate that the studies presented in this thesis, suggest that the extent to which patients and HCPs take their role and the extent to which they ensure productive patient-provider interactions might be insufficient, even though this is necessary to reduce DRPs[8]. More productive patient-provider interactions may better anticipate the patient's personal needs and problems. Improving patient-provider interactions combines the best of two worlds: the patient who knows himself best (e.g. goals, preferences, needs, concerns and problems) and the HCP as expert of the disease and the treatment options. With high quality patient-provider interactions, pharmaceutical care will shift from generic to more personalized pharmaceutical care.

In this final chapter, first the need to shift towards personalized pharmaceutical care in order to reduce DRPs will be further substantiated by discussing the insights from this thesis and the existing literature. Subsequently, these insights give room to further elaborate how pharmaceutical care can be made more personalized. This will be done by discussing the themes that have emerged during the conducting and reporting of the studies in this thesis and that go beyond the discussion of the individual studies. The following four topics will be addressed:

- Why personalization of pharmaceutical care results in better patient outcomes;
- How to create room for personalized pharmaceutical care;
- How to target the right patients benefiting from personalized pharmaceutical care;
- How to target the right moments with personalized pharmaceutical care.

Furthermore, methodological considerations of the studies presented in this thesis will be discussed from a broader perspective and recommendations for clinical practice and directions for further research will be provided.

Why personalization of pharmaceutical care results in better patient outcomes

When conditions are treated with medication, pharmaceutical care plays a major role in (cost-) effective and safe pharmacotherapy, in order to optimize the balance between the positive (effectiveness) and the negative potential of drug treatment (DRPs)[2,6,9-11]. Pharmaceutical care may be conducted on a generic, population based way, for instance proactive monitoring of medication safety by means of clinical rules (based on generic characteristics such as drug properties and objective patient characteristics (e.g. age, gender))[12]. However, both existing literature and the findings of the different studies in this thesis (as described below) increasingly indicate that personalized/patient-centred pharmaceutical care tailored to the patient's experiences (e.g. DRPs), needs and preferences is more effective[13-18]. In this paragraph the need for and benefits of personalized pharmaceutical care will be illustrated by means of the three pharmaceutical care activities studied in this thesis; medication review, patient-provider communication and adherence support.

Personalized medication reviews are more effective

Medication reviews are personalized when productive patient provider interaction takes place during medication reviews[19]. Productive patient-provider interactions during personalized medication reviews encompass, for example, discussing patients' medication experience (including burdens), medication beliefs, concerns and knowledge and ensuring that patients are active participant in their healthcare plans and goals[20]. Multiple systematic reviews have shown that by personalized medication reviews more clinically relevant DRPs are identified and/or solved[21,22]. This is in line with the findings in **Chapter 2**, that describes a systematic review into the effectiveness of medication reviews as how these are mostly performed in practice. In a sensitivity analysis of the findings in **Chapter 2** on the degree of patient involvement in studies with a positive effect on one or more outcomes, it was also found that more DRPs were identified and solved in studies with patient involvement. Noteworthy, effects on one or more clinical outcome measures (e.g. the number of hospital admissions, the number of falls) or quality of life (EQ5D-VAS) were also predominantly seen in studies with patient involvement in this systematic review.

Furthermore, several studies have demonstrated that patient-reported DRPs that were reported by patients during patient interviews were classified most relevant and/or were more often solved than DRPs based on medical records only and/or DRPs identified by clinical decision support systems[23-26]. These findings are confirmed in **Chapter 3**: In this multicentre randomised clinical trial on the effectiveness of medication review with patient involvement in outpatient cardiology clinics it was also found that patient-reported DRPs were more often solved. About the same proportion of DRPs was identified through patient interviews as through the combination of the assessment by the pharmacist and the computer-generated recommendations, whereas the resolution rate of DRPs reported by patients was 20% higher (84% versus 64%). So, DRPs reported by patients are considered clinically more relevant by physicians and patients[23-25].

Thus, in summary, a personalized medication review is more effective in identifying and reducing (clinically relevant) DRPs.

Patient-reported DRPs deserve more attention by the HCP in usual care

As described above, patient-reported DRPs are considered more clinically relevant and are more often solved during medication reviews. However, literature shows that patients do not always report medication-related symptoms and/or adverse events to physicians, and physicians do not always respond when patients actually report them[27,28]. This is confirmed by the findings in **Chapter 4**. In this cross-sectional study with participatory observations during regular visits from patients to physicians and pharmacies it was shown that although DRPs are often raised during clinical consultations, almost one in six DRPs raised were not discussed between HCP and patient. Furthermore, during 4–6% of the visits at least one DRP was not raised at all by HCPs and/or patients.

This implies that better communication about patient-reported DRPs is warranted. The challenge is to sufficiently address and prioritize patient-reported DRPs during patient-provider interactions, because once patient-reported DRPs are identified, HCPs are generally in the position to change therapy or to offer support to reduce DRPs and improve health outcomes[16-18,29].

Improving adherence requires a personalized approach

In patient-provider interactions aiming to improve medication adherence it is also important to personalize the conversation and to identify what DRPs the patient experiences (e.g. practical barriers to take the medication as intended), what the patient knows (knowledge about medication, symptoms and outcomes), what the patient does (medication taking behaviour) and feels (beliefs about medication, needs and preferences), so that nonadherence will not remain a hidden problem[30-33]. However, communication about these adherence related patient-reported DRPs during patient-provider interaction is suboptimal[33-37]. In our study described in **Chapter 6**, conducted among a large number of physician and pharmacy practices across the Netherlands, the association between the extent of adherence supporting activities of HCPs in *usual care* and patients' adherence to statins was examined. No positive relationship between the extent of HCPs' adherence supporting activities and patients' adherence to statins was found, which may be explained by high adherence rates at baseline in the included population. Nevertheless, it is recommended that HCPs – irrespective of adherence rates – discuss adherence related issues regularly with the patient[38]. However, our study shows that both physicians and pharmacy staff often do not ask the patient about their adherence related issues/DRPs. Although 79% of the 209 physicians and 68% of the 483 pharmacy staff members ask the patient whether they actually take their medication as prescribed, patients' knowledge about medication and (non-)practical barriers to medication adherence are hardly inventoried by HCPs. In the same study population, no association between HCPs beliefs about statins and beliefs and adherence of patients using a statin was found (**Chapter 5**). This may also have been caused by insufficient communication with patients, in this case about their beliefs (e.g. concerns) about medication.

So, HCPs do not pay enough attention to patient-reported DRPs during patient-provider interactions in current usual care. Meanwhile, personalized pharmaceutical care – in which productive patient-provider interactions and assessing patient-reported DRPs are embedded – appears to be more effective in identifying and solving clinically relevant DRPs that affect a patient's daily life. In order to successfully develop and implement personalized pharmaceutical care it is prudent to consider how room for personalized pharmaceutical care can be created and how the right patient can be targeted at the right moment.

7

How to create room for personalized pharmaceutical care

Time-constraints are often mentioned as a barrier for the implementation of personalized care[39]. This is confirmed in **Chapter 4**, in which both patients and HCPs report a lack of time – in addition to barriers related to attitude and competencies – as a barrier for adequate communication about DRPs. To overcome this time-related barrier it is prudent to think about ways how to efficiently organize pharmaceutical care in order to create room (dedicated time) for personalized pharmaceutical care. A potential strategy is to efficiently manage time for pharmaceutical care by integrating pharmaceutical care activities in population level pharmaceutical care, leaving more time for pharmaceutical care on a personal level[40].

Currently, pharmacists are involved in multiple, seldom coherent, pharmaceutical care activities such as the development of medication formularies, medication therapy guidelines, clinical rules and patient education, medication review and adherence counseling. A possible way to bring more coherence to these different activities is integration by means of the medication therapy management pyramid in which the base of the medication therapy management pyramid consists of *population pharmaceutical care* whereas the top of the pyramid consists of *personalized (patient centred) pharmaceutical care* (see figure 1)[40].

Population pharmaceutical care is often established in medication policy and medication therapy guidelines based on parameters that are unambiguous and often available in medical records, such as medication properties and single objective patient characteristics (e.g. one single condition/illness, a single laboratory value, gender, age etc.). Population pharmaceutical care is the most efficient care, as one single guideline (e.g. monitored with a clinical rule) might manage the total population pro-actively and executing population pharmaceutical care can be performed without patient involvement. An example of population pharmaceutical care is the application of clinical decision support systems to monitor clinical rules at population level, of which the added value has been extensively studied[12,41,42].

Personalized pharmaceutical care is tailored to the individual patient, based on a combination of the complete set of patient characteristics (age, gender, co-morbidity and co-medication, laboratory values and patient-reported outcomes, such as adverse drug events, adherence, concerns and experienced effect etc.) and productive interaction between the patient and the HCP. This productive patient-provider interaction often consists of shared decision making before starting medication therapy, followed by (continuous) support of the patient using medication (adherence counseling about the patient's beliefs about medication, discussing the patient's medication experience (e.g. patient-reported DRPs), medication review with patient involvement and education of the patient/provide information to the patient (e.g. after an information request by the patient)[6,18,43,44].

In order to create room for personalized pharmaceutical care (in which HCPs can respond to patient-specific DRPs and questions), interventions to prevent frequently observed DRPs in individual care should be implemented in population care as much as possible (see figure 1)[40]. Standardized (population) pharmaceutical care and personalized pharmaceutical care are sometimes seen as conflicting. However, also applying guidelines may include patients' preferences (e.g. if there is no absolute best treatment option or if non-drug therapy is an option)[45]. When interventions to prevent frequently observed DRPs in individual care are implemented in population care as much as possible, HCPs will be able to ensure productive patient-provider interactions in which they can focus on patient-reported DRPs. The challenge is how to target the right patients and moments with personalized pharmaceutical care.

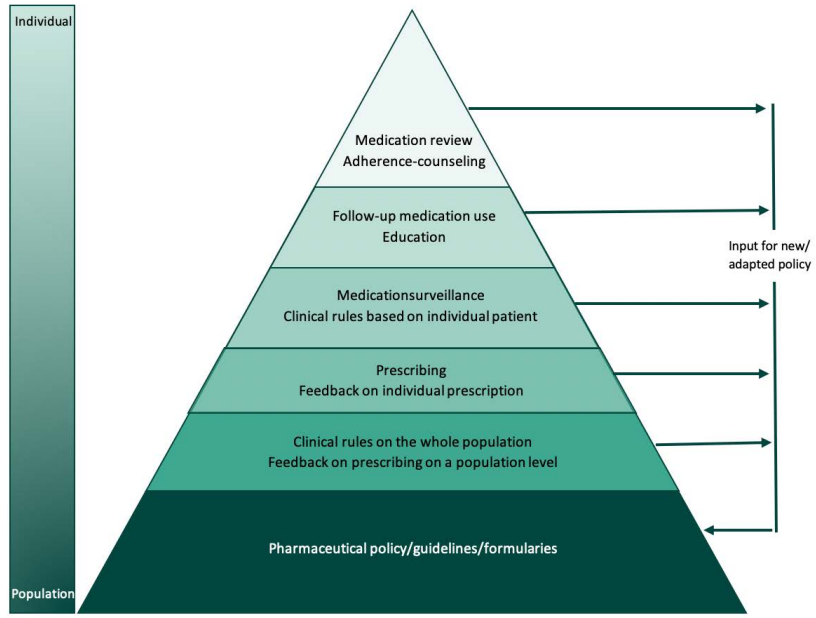

Figure 1. The Medication Therapy Management Pyramid: an integral approach of pharmaceutical care with population based pharmaceutical care (pharmaceutical care guidelines/-policy) as base of the pyramid. The more pharmaceutical care interventions are integrated in population based pharmaceutical care (base of the pyramid), the more time will be available for more personalized pharmaceutical care (top of the pyramid)[40].

How to target the right patients with personalized pharmaceutical care

Almost 40% of the DRPs in ambulatory care and at least half of the hospital admissions due to DRPs are preventable, so determining (patient, setting and drug-related) risk factors for developing DRPs may help to identify patients at risk for DRPs to target preventive measures[46-48]. Besides that, it is of course also important to identify and help patients that actually experience DRPs.

How to target the right patients *to prevent* DRPs

In literature numerous risk factors for preventable DRPs have been reported. Many studies report that patients with polypharmacy (use of ≥5 drugs), multiple comorbidities and the use of specific drugs (e.g. anticoagulants, NSAIDs, opioids) have an increased risk of developing DRPs[48-54]. Other risk-factors that are often found in literature are age over 65 years, dependent living situation, impaired cognition, impaired renal function, non-adherence to medication regimen, communication failures and knowledge gaps (e.g. missing information, half-knowledge of the patient, the patient does not understand the goal of the therapy), self-medication with non-prescribed medicines, impaired manual skills (causing handling difficulties) and visual impairment[46,48,49]. Patients for whom one or more of these risk factors

apply should be selected from the patient files and preventive measures have to be developed and implemented in order to prevent them from developing DRPs[46]. Both population based preventive measures and personalized preventive measures may contribute to avoiding DRPs. Population based preventive measures may be, for example, clinical decision support systems that target objective characteristics of a patient in order to identify potential DRPs followed by for instance deprescribing, changing prescriptions or adding preventive medication in order to prevent the patient from developing these DRPs[12,55-57]. Besides these population based preventive measures, patients with a high risk for developing DRPs may also benefit from (more extensive) personalized pharmaceutical care to prevent DRPs (possibly even more than patients without risk factors)[58]. This personalized preventive pharmaceutical care may prevent DRPs that originate from the way patients use medication and from other subjective patient-related factors, such as patients' concerns, knowledge and health goals[58]. Personalized pharmaceutical care activities (e.g. counseling, medication review, education) in which these type of factors are acknowledged may also prevent patients from developing DRPs[40,58].

How to target the right patients *to solve* DRPs

In order to target the right patients to adequately solve patient-reported DRPs that could not be prevented, it is necessary to identify patients that actually experience DRPs.
As described in **Chapter 4**, patients do not always mention (all) DRPs that they are actually experiencing during patient-provider interactions. Strategies that help to target patients that actually experience DRPs may encompass improvements in 1) the role of patients and HCPs 2) process and 3) technology.

1) The role of patients and HCPs: both patients and HCPs have responsibility to identify and timely address DRPs that affect a patient's daily life.
   Patients *need knowledge, skills and power* to become informed and activated patients in order to be responsible for their own treatment and to be able to self-manage DRPs and/or raise DRPs in contact with HCPs[28,43,59]. *Knowledge* encompasses knowledge about disease, symptoms and treatment options and (positive and negative) outcomes of the treatment[43]. Knowledge about medication will help patients to identify DRPs (e.g. adverse events, lack of effect) and take appropriate action (e.g. report DRPs to HCPs)[16,60-63]. Furthermore, knowledge about for instance adverse drug reactions (ADRs) and how to mitigate symptoms due to adverse drug reactions may enable patients to prevent DRPs or to take appropriate action when DRPs occur[64,65]. *Skills* needed to self-manage DRPs and to participate in patient-provider interactions about DRPs are skills related to health literacy. These skills comprise being visually literate (able to understand graphs or other visual information), computer literate (able to operate a computer and to search the internet and evaluate websites), information literate (able to obtain and apply relevant information), numerically or computationally literate (able to calculate or reason numerically), oral language skills (to articulate health concerns and describe symptoms accurately, to ask pertinent questions, to understand spoken medical advice or treatment directions, decision-making skills (the capacity to think critically and make autonomous, informed decisions)[66,67]. Health literacy is not only related to years of education or general reading ability. A person who functions adequately at home or work may have marginal or inadequate literacy in a health care environment[66]. Therefore, there is a growing recognition of education in health literacy as an essential daily resource for the life-course that starts at an early age (e.g. at school) and teachers and HCPs play a key role in this education[68]. *Power* is about that patients are able to take a self-determining role, to exercise their rights by believing in their capacities to self-manage their disease, requiring – in addition to knowledge and skills mentioned above – psychosocial skills, like self-efficacy[43,67]. Empowered patients can contribute to their own positive health outcomes and medication safety, including identifying DRPs and taking early action (report to HCPs or self-management) to minimize DRPs[16,63,69-72]. If patients are unable to take their role, it is desirable that they are assisted by an informal carer during patient-provider interactions. If they are deliberately not willing to take their role, then it is recommended that they inform their HCP about their desired role in the care process[43].

   HCPs have to 1) ensure adequate communication, 2) preserve patients autonomy, 3) encourage patients to participate and 4) focus on the patient's needs, preferences and goals[43,73]. First, for adequate communication a trusting relationship and creating a setting in which patients feel safe to raise their DRPs and questions is required[16,74]. Second, preserving patients autonomy encompasses that HCPs acknowledge the patient as an equal partner in the development and assessment of their care[39,75,76]. Third, encouraging patients to participate in identifying and solving DRPs means that HCPs should invite patients to actively participate as few patients are active participants by nature[39,70,75,76]. And fourth, for a patient to make a deliberate decision on how to solve a DRP, the HCP should facilitate that this choice best fits with the patient's personal values and lifestyle. So, the HCP should help the patient to find out his personal preferences, needs and goals and to stimulate the patient to make a decision in line with these.

2) Process: implementing instruments to identify patients that actually experience DRPs may also contribute to target the right patients. For example, a set of questions has been developed that can be used to reveal patient-reported DRPs during regular patient-care provider interactions[77]. Also the use of prompt cards to trigger patients to report adherence-related DRPs (like if they are able to take the medication as intended (to identify non-adherence behaviour) may be useful[78]. This can improve for instance effective communication about non-adherence and patients' beliefs about medication (Chapter 5), as such prompt cards facilitate asking the right questions and creating a safe setting in which patients feel safe to raise their beliefs about medication and to speak out about medication nonadherence[78]. If these type of instruments are not used during the visit, but if these are already provided to the patient in preparation for the visit, then it is important to ensure in the healthcare process that the visit agendas of patient and HCP are aligned and prioritized at the start of the visit, as mentioned in **Chapter 4**[79,80]. Inventorying the (health) goals of a patient by using goal attainment scales may help the patient and physicians to identify and solve clinically relevant DRPs and may also decrease the risk of developing DRPs[81].

3) Technology: patient-reported DRPs can be identified, by organizing pharmaceutical care on demand, by making it easy for patients to raise their DRPs at any time, at any place. This can be operationalized by making use of health technology and digital health. This will be described in more detail in the paragraph about targeting the right moments with pharmaceutical care.

How to target the right moments with personalized pharmaceutical care

Besides targeting the right patients in order to prevent or solve DRPs, also the right moments to perform personalized pharmaceutical care should be identified. If the aim is to prevent

DRPs, it is important to identify risk moments for the development of DRPs. If the aim is to solve existing DRPs it is necessary to adequately target the moments that patient's actually experience DRPs.

How to target the right moments *to prevent* DRPs

DRPs should be preferably prevented. Therefore, ways have to be found to predict at which moments patients are at increased risk for developing DRPs. It might be assumed that at specific moments of drug therapy (e.g. when drugs are started, adapted or stopped) or during specific moments of the patient-journey of a patient using medication (e.g. transitions in care or during travelling) there is an increased risk for preventable drug-related problems[63,82]. These specific high-risk moments seem to be critical to apply personalized pharmaceutical care (e.g. medication optimization) in order to prevent clinically relevant DRPs. Examples of pharmaceutical care interventions targeting high risk moments in order to prevent DRPs are medication reconciliation prior to hospital admission, (post-)discharge counseling and providing information to the patient at first prescription encounters and discussing the patient's medication use experiences two weeks after the initial prescription[34,83]. However, in current practice pharmaceutical care interventions during patient's chronic drug therapy also often take place at an arbitrary moment and not necessarily at these high-risk moments for developing DRPs. This may be one of the reasons that, for example, the value of medication review has not been convincingly demonstrated, as these are performed at arbitrary moments during drug therapy and not at high-risk moments. That is why it is recommended in **Chapter 2** to stop performing cross-sectional medication reviews. Instead, it may be suggested to redesign the cross-sectional medication review to continuous medication therapy management, directly from the start of a drug, targeting all the risk moments the patient may encounter during his patient journey[40]. Examples of these risk moments are acute or chronic changes in health status, the occurrence of DRPs, non-adherence to therapy or a request for pharmaceutical care by the patient or physician. At all these moments (personalized) pharmaceutical care activities, such as a targeted medication consultation or a targeted short screening/analysis of the total medication list and/or deprescribing should be performed, if appropriate[84].

How to target the right moments *to solve* DRPs

Continuous pharmaceutical care instead of cross-sectional pharmaceutical care might also be appropriate to target the right moments to solve preventable DRPs that were not prevented, or to support patients to mitigate the symptoms or to cope with the symptoms of DRPs that are not preventable (e.g. ADRs). This is because problems with medication may arise every day in the life of patients who chronically use (multiple) medications. For example, in a longitudinally observational study in adult patients with rheumatoid arthritis using at least one disease modifying anti-rheumatic drug it was demonstrated that these patients frequently experience DRPs (like practical problems, side-effects and questions or concerns about medication) over time[85]. In the ideal situation these DRPs are promptly solved or a patient is promptly supported to deal with these DRPs. However, chronic patients have just a few (2-6) regular visits with their HCP per year and so they have only a few hours per year the possibility to interact personally with their HCPs (and then DRPs are frequently not raised and/or discussed). Consequently, the chance that the problems and questions of the patient arise at another moment than when the HCP is available (and in another place than where the HCP is present), is considerable. Therefore, ways have to be found to offer patients continuous support with their medication use, so that DRPs can be solved shortly after the moment they occur. This makes pharmaceutical care independent from time and place.

Continuous, time and place independent pharmaceutical care

Important components of continuous, time and place independent pharmaceutical care include 1) easily accessible and location-independent ways of contacting HCPs and 2) self-management by the patient.

1) Easily accessible and location-independent ways of contacting HCPs. Herewith pharmaceutical care shifts from supply driven to "on demand", by enabling patients to easily raise problems at any moment they actually experience DRPs, in case they need a HCP to solve their DRP. This can be realized by introducing (digital) communication channels to contact a HCP about DRPs if necessary (for example text messaging/chatting or video calling). Application of this easy accessible communication channels (also called telepharmacy) will contribute to decrease underreporting of DRPs by patients to their HCPs and to timely solving these DRPs[86–90].

2) Self-management by the patient. Additional to identifying and solving DRPs by making pharmaceutical care more accessible for patients, the facilitation of self-management by the patient may result in the patient being able to solve his DRPs himself[86,87]. In the COMPAR-EU project (Comparing effectiveness of self-management interventions in 4 high priority chronic diseases in Europe) self-management is defined as "actions that individuals, families, and communities engage in to promote, maintain, or restore health and cope with illness and disability, with or without the support of health professionals, and including but not limited to self-prevention, self-diagnosis, self-medication, and coping with illness and disability"[91]. Self-management of a chronic condition requires knowledge, skills and power (as described above) to cope with the consequences of the disease, including monitoring symptoms, understanding consequences and to take appropriate action. Supportive interventions by HCPs may consist of equipping patients with the necessary skills and to actively engage patients in the management of their disease[91]. Furthermore, self-management by patients may be facilitated by implementing information and communication technology (ICT). This comprises reliable and understandable digital content about medication (e.g. frequently asked questions, instruction materials, medication information) and ICT applications that facilitate the patient in finding and applying the content in order to solve DRPs. With regard to the content it is recommended to combine written, oral and visual health information, as the prevalence of low health literacy is high (e.g. more than a quarter of the adolescents in the Netherlands is insufficient or moderately health literate)[92–94]. So preferably, digital medication information about medication consists of pictures, symbols, (animated) videos and even spoken information by a digital human[95–97]. Conversational agents (like digital humans and chatbots) enable customers with access to large amounts of information quickly and might facilitate patients to apply that information[98,99]. Although the application of artificial intelligence based conversational agents for chronic conditions is promising, literature into the quality and impact is scarce, so further exploration of the acceptability, safety, and effectiveness of this kind of technologies to enhance self-management is needed[99–101]. Another digital facility that enables patients to self-manage their medication use is an online personal health record (PHR)[102]. In an online PHR the patient has access to an overview of his own medication, based on data from multiple HCPs

that are involved in the medical treatment of the patient. In the Netherlands, a PHR can be automatically provided with the patient's dispensed medication by multiple pharmacies by the Nationwide Medication Record System (NMRS)[103]. This overview in a PHR is a good basis for self-management and correct use of the medication by the patient. Several studies show that the use of a PHR results may result in more knowledge about medication, higher adherence rates and safer use of medication (e.g. awareness about side effects)[102,104]. An online PHR may also support patients to detect discrepancies in their drug list. A recent study in the Netherlands showed that patients were able to identify clinically relevant drug discrepancies in their drug list by using an online PHR to a similar degree compared to medication reconciliation by a pharmacy technician prior to elective admissions[105]. This might also help patients to prepare themselves well prior to their visit to a HCP and enhance effective communication about DRPs during patient-provider interactions (**Chapter 4**)[79,80].

Methodological considerations

As described in the systematic review in **Chapter 2**, methodological heterogeneity among studies examining the effectiveness of medication review may be one of the explanations for the fact that the found impact of medication review on clinical outcomes and quality of life is minimal, the observed effect on drug-related outcomes is limited and the evidence about the effect on economical outcome measures is inconclusive[21,22,106]. This is also the case in studies assessing the effectiveness of medication adherence interventions, the studies are heterogeneous and effects found are inconsistent[107,108]. The heterogeneity concerns the 1) the *target population* that is included 2) the *interventions* that are performed 3) the *outcome measures* (and follow-up time) that are used. As these methodological issues may hamper the building of body of evidence on the effectiveness and clinical impact of other personalized pharmaceutical care interventions these issues are further elaborated in this paragraph.

First, the *selection of patients* should fit the aim of the personalized pharmaceutical care intervention, in order to maximize the chance of demonstrating an effect. If the aim is, for example, preventing and decreasing DRPs and clinical consequences due to DRPs (e.g. admission to the hospital, morbidity, mortality) one should select a population with high risk for developing DRPs and/or a population actually experiencing DRPs. Consequently, another aim of the intervention (e.g. increasing adherence) will require a different selection of patients, for example, patients experiencing specific types of DRPs (e.g. lack of therapeutic effect, difficulties taking the medication as intended (low adherence scores)). Although several risk factors for developing DRPs are described in literature, the development and validation of screening tools to identify patients at risk for DRPs will enhance the selection of patients that will benefit the most from personalized pharmaceutical care. In the RCT into the effectiveness of medication review on the number of DRPs in **Chapter 3** no selection criteria (based on risk factors as described in literature) were set, which is one of the possible explanations for the fact that fewer DRPs were found than in other studies actually applying this type of inclusion criteria. Selecting patients with a high risk of developing DRPs by a standardized and validated tool, enhances both the chance of proving effectiveness of pharmaceutical care interventions and the comparability of study results of studies examining the effectiveness of pharmaceutical care interventions[46,109].

Secondly, interventions in personalized pharmaceutical care should be standardized (and compliance to the standards during studies should be reported) in order to enlarge the ability

to prove the effectiveness of personalized pharmaceutical care interventions. Standardized (interventions) and personalized (pharmaceutical care) seem to contradict each other, but if pharmaceutical care interventions consist of standardized (clearly described) elements, these elements may or may not be applied depending on the needs of the patient. In medication review studies – as described in **Chapter 2** – and adherence studies, for example, substantial heterogeneity of the interventions is reported, as no golden standard exists for how the interventions should be operationalized[21,110]. Interventions are often poorly described and/or disclosed. Initiatives such as a website in the Netherlands (www.interventienet.nl) that provides an overview of interventions developed to improve adherence to (chronic) medication will contribute to tackle this problem if this is widely rolled out for pharmaceutical care interventions. This website lists the content of the intervention, its implementability in daily practice, and the research used to evaluate its effectiveness for each intervention[111]. In **Chapter 3**, a medication review intervention was developed by our research team, consisting of various elements described in literature, because a uniform medication review intervention was lacking. Uniform personalized pharmaceutical care interventions will contribute to the ability to demonstrate effect of these interventions and these are easier to compare in systematic reviews. The Patient-Centered Outcomes Research Institute (PCORI) encourages researchers to fully and specifically describe complex personalized interventions in order to facilitate transparency and replicability of research findings. Furthermore they suggest that investigators should also report the fidelity of the delivery of the intervention (i.e., planned and unplanned adaptations) and the quantity or dose of the intervention actually delivered[112]. Therefore, it might be considered to standard report a detailed description of the intervention and an evaluation about the degree that the intervention has been delivered in the appendix of trials assessing the effectiveness of personalized pharmaceutical care interventions.

Thirdly, the outcome measures and follow-up time used in trials assessing the effect of personalized pharmaceutical care interventions should fit the aim of the intervention to increase the chance of proving (a clinically relevant) effect of the intervention. In addition, standardized sets of outcome measures will improve the ability to compare studies examining the effectiveness of personalized pharmaceutical care.

The aim of personalized pharmaceutical care interventions (e.g. medication review, patient counseling) is to improve safety and (cost-)effectiveness of a patient's medication use in order to have a positive impact on health outcomes that affects a patient's (daily) life. The outcome measures used in personalized pharmaceutical care should therefore be consistent with a clinical relevant outcome from the point of view of the patient[112,113]. In personalized pharmaceutical care often patient-relevant outcome measures like hospital admission- or mortality rates are used. However, it is challenging to prove effectiveness of pharmaceutical care interventions (like medication review and post-discharge counseling) on these outcome measures, as also confirmed in the systematic review in **Chapter 2**[21,22,106,114]. Therefore, also frequently intermediate outcomes are used (e.g. DRPs, number of drugs and adverse events). However, the clinical relevance of these intermediate outcomes (e.g. (the decrease of) potential DRPs) for the patient is not always evident. Improvements on these intermediate outcome measures do not necessarily imply that it has a noticeable positive impact for the patient. In literature it is demonstrated that when these type of intermediate outcomes are used, especially patient-reported outcomes are considered to be of clinical relevance (e.g. patient-reported DRPs are more often solved than DRPs identified by a computer or

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HCP)[23-26]. Also in **Chapter 3** was found that DRPs reported by patients were more often solved during medication reviews. The use of patient-reported outcome (PRO) measures and/or standardized questionnaires with appropriate measurement characteristics for the population being studied are recommended[112]. The PCORI states that researchers, in collaboration with patient and other stakeholder partners, should consider (1) the concept(s) underlying each PRO measure (e.g., symptom, impairment) and how it is meaningful to, and noticed by, patients in the population of interest; (2) how the concept relates to the health decisions the study is designed to inform; (3) how the PRO measure was developed, including how patients were involved in its development; and (4) evidence of measurement properties, including content validity; construct validity; reliability; responsiveness to change over time; and score interpretability, including meaningfulness of score changes in the population of interest with consideration of important subgroups[112].

PRO measures may be more often used in several outcome domains of safe and effective medication use. Outcome domains for safe and effective drug therapy in personalized pharmaceutical care may for instance be clinical outcomes (e.g. effectiveness experienced by the patient, number of falls), drug-related outcomes (e.g. patient-reported DRPs like (the burden of) adverse events, practical problems, adherence, beliefs about medication) and quality of life (e.g. EQ-5D and SF 36). In addition, goal-attainment scaling (GAS) may be a suitable outcome measure for pharmaceutical care interventions that potentially covers all the outcome domains (clinical outcomes, drug-related outcomes and quality of life)[81,115]. When using GAS it is prudent to be aware of several methodological challenges, such as reducing bias in assessment of the GAS scores (e.g. by using research assistants instead of HCPs and GAS assessment training to reduce variation in administration of the GAS) and the validation of the mathematical process of GAS (in order to be able to compare clinical relevant changes in GAS scores across studies)[115,116]. Appraisal criteria for the quality of GAS methodology may be used to minimize bias in studies utilizing GAS[117,118]. In **Chapter 3** and **Chapter 4**, the number of DRPs was the only outcome measure used, while the use of, for example, GAS or other PRO measures could have provided more insight into the clinical impact of the pharmaceutical care activities.

Finally, patient-reported experience measures (PREMs) and/or patient-reported activation measures (PAMs) may also be more often used in personalized pharmaceutical care, as better patient experiences seem to be related to better clinical outcomes[113]. Examples of PREMs and PAMs that may be appropriate to use in personalized pharmaceutical care are satisfaction about medication information, the experienced degree of shared decision making (respecting patient values and preferences) and patient knowledge, skill, and confidence for self-management[113,119].

Furthermore, the outcome measures used are often heterogeneous, as for each outcome a different set of outcome measures is used per trial. Standardization of (a set of) outcome measures and time of follow-up should be applied in order to increase the ability to compare the results of trials assessing the effect of personalized pharmaceutical care interventions. Then, outcome measures from a standardized set of outcome measures can be selected that fit the research question/hypothesis of the study being carried out. Sets of outcome measures may compiled for various outcome domains, in analogy to the OMERACT approach in rheumatology[120]. Several sets of standardized (and validated) outcome measures may be

developed within the domains of safe and effective medication use (clinical outcomes, drug-related outcomes and quality of life). For all these domains (if possible) a combination of objective outcome measures and subjective PRO measures with appropriate measurement characteristics for the population being studied may be developed. In **Chapter 5** and **Chapter 6**, for example, only self-report questionnaires to measure adherence were used. As self-report questionnaires are subjective and therefore sensitive to social desirability bias, also in this study it would have been better to use a combination with other methods to measure adherence (e.g. MEMS devices, pill count, refill adherence etc.).

Finally, when the impact of or associations between HCP and patient-provider related factors in personalized pharmaceutical care and the impact on health outcomes is studied, also for these independent variables (e.g. HCPs' beliefs about medication or the extent of personalized pharmaceutical care activities in usual care) standardized and validated questionnaires, if available, should be used. Questionnaires and cut-off points for this type of determinants are often not standardized and or validated[121-123]. If a questionnaire is not available for a specific domain, a new questionnaire should preferably be developed and validated. Furthermore, to assess certain HCP and patient-provider interaction related factors (e.g. extent of activities to support adherence or the quality of communication) participatory observations may be considered, as self-report questionnaires are subjective and therefore sensitive to social desirability bias.

Future perspectives

Recommendations for future research

Based on previous studies, the studies in this thesis and considering the methodological aspects described above, we suggest the following themes to be addressed in future research:

- More research into productive patient-HCP interactions about DRPs. In this research (potential) roles and responsibilities of the patient and the HCP should be explored and ways to improve competencies (knowledge, skills and power), attitude and synergy needed for productive patient-HCP interactions should be explored
- Exploration of enabling contextual factors to improve patient-HCP interactions, such as organization of care processes and the use of information technology
- Development of sets of standardized (and validated) outcome measures with appropriate measurement characteristics within the domains of safe and effective medication use, comprising a combination of objective outcome measures and subjective PROMs (e.g. GAS, adverse events) and PREMs
- Studying how the right patients can be targeted with personalized pharmaceutical care by making use of instruments and prompt systems to trigger patients to report DRPs
- Assessing the clinical impact of continuous personalized pharmaceutical care, including place- and time independent contact between patient and HCP and self-management by the patient
- Making a detailed description of the pharmaceutical care intervention studied and an evaluation about the degree that the intervention has been delivered a mandatory part of a publication (e.g. in the (open source) appendix)

Recommendations for clinical practice

The findings of this thesis have the following clinical implications:

- It should be considered to stop performing cross-sectional medication reviews without patient involvement as these have minimal clinical impact
- It might be considered to shift the focus from incidental cross-sectional pharmaceutical care to continuous pharmaceutical care at all the risk moments the patient may encounter during his patient journey, as this enlarges the chance of timely solving DRPs
- Implementing e-health solutions to facilitate place and time independent contact with an HCP and self-management by the patient is recommended in order to realize continuous pharmaceutical care
- Patients should be involved in pharmaceutical care interventions as patient-reported DRPs are more often considered clinically relevant by patients and HCPs
- More attention of HCPs for patient-reported DRPs during regular patient-provider interactions is needed
- Patients should become informed and activated and should take their role to ensure productive patient provider interactions about DRPs in order to decrease underreporting of DRPs
- HCPs should ask patients more frequently about adherence related DRPs and medication taking behaviour, like practical and non-practical barriers taking medication as prescribed and if they are taking medication as prescribed

In conclusion, both patients and HCPs should take their role to ensure personalized pharmaceutical care embedding productive patient-provider interactions with a focus on patient-reported DRPs. Furthermore, pharmaceutical care should shift from cross-sectional to continuous, place and time independent medication support following the patient's journey in order to prevent DRPs and to solve DRPs (that could not be prevented) shortly after they occur.

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Chapter 8

Summary

Summary

This thesis aims to explore the role of patients and healthcare providers (HCPs) in reducing drug-related problems (DRPs), by (a) gaining insight into the existing role of patients and HCPs in pharmaceutical care (with a focus on adherence support and communication in usual care) and (b) assessing the effectiveness of pharmaceutical care interventions (and more specific medication review) in which patients and HCPs have a role. This was operationalized by summarizing the evidence on the effectiveness of medication reviews in **Chapter 2** and examining the effectiveness of a medication review intervention with patient involvement in **Chapter 3**. Additionally, in **Chapter 4** an inventory of the extent of patient-HCP communication about DRPs was made. In **Chapters 5** and **6** the association between HCP and patient-provider interaction related factors and patients' beliefs about medication and/or adherence to medication were explored. Finally, in **Chapter 7** the overall results of this thesis were discussed from a broader perspective.

A medication review is defined as a structured evaluation of a patient's medicines with the aim of optimising medication use and, ultimately, improving health outcomes. This entails detecting DRPs and recommending interventions to solve these DRPs. In **Chapter 2**, we systematically summarized the effectiveness of medication review as how it is mostly operationalized in practice (as an isolated, short-term intervention), irrespective of the patient population and the outcome measures used. A literature search was performed in MEDLINE, EMBASE and Web of Science to identify randomized controlled trials (RCTs) comparing medication review with usual care. The risk of bias of studies was evaluated independently by two reviewers. A best evidence synthesis was conducted for every outcome measure used in more than one trial and in case of binary variables a meta-analysis was performed in addition to the best evidence synthesis, to quantify the effect. Of the 13,870 studies initially identified, thirty-one (55% low risk of bias) were included and a best evidence synthesis was conducted for 22 outcome measures. No effect of medication review was found on clinical outcomes (mortality, hospital admissions/healthcare use, the number of patients falling, physical and cognitive functioning), except a decrease in the number of falls per patient (which changed to inconclusive in a sensitivity analysis using a more stringent threshold for risk of bias). Furthermore no effect was found on quality of life and evidence was inconclusive about the effect on economical outcome measures. However, medication review showed to impact most drug-related outcomes: medication review resulted in a decrease in the number of DRPs, more changes in medication, more drugs with dosage decrease and a greater decrease or smaller increase of the number of drugs. Noteworthy, in a sensitivity analysis of the findings on the degree of patient involvement in studies with a positive effect on one or more outcomes, it was found that more DRPs were identified and solved in studies with patient involvement and that effect on clinical outcome measures or quality of life was also predominantly seen in studies with patient involvement. Considering the fact that the impact of medication review on clinical outcomes and quality of life is minimal, the observed effect on drug-related outcomes is limited and the evidence about the effect on economical outcome measures is inconclusive, it should be considered to stop performing cross-sectional medication reviews as standard care.

To assess the effectiveness of a (pharmacist-led) medication review with patient involvement on the number of drug-related problems (DRPs), a RCT comparing (a computer-assisted)

medication review with usual care in outpatient cardiology patients was conducted in **Chapter 3**. Adult patients without support concerning the administration of medication, without a medication review in the past 6 months and who gave permission to access their electronic medication record were included. The primary outcome measure was the number of DRPs 1 month after the visit. After 1 month, the mean number of DRPs in the intervention group was significantly lower than in the control group. Furthermore, in the intervention group 75% of the DRPs identified at baseline were solved after 1 month, versus 14% in the control group. Although the same proportion of DRPs was identified through patient interviews as through the combination of the assessment by the pharmacist and the computer-generated recommendations, DRPs reported by patients were more frequently solved compared to DRPs detected by the pharmacist/computer-system (84% versus 64%). So, medication review with patient involvement in an outpatient cardiology clinic decreases the number of DRPs and DRPs reported by patients are considered clinically more relevant by physicians and patients.

The extent of communication about DRPs during regular patient-provider interactions in Dutch outpatient clinics, GP practices and pharmacies was studied in a cross-sectional observation study in **Chapter 4**. An inventory was made of the frequency and type of drug-related problems (DRPs) (1) raised and discussed (2) raised but not discussed or (3) not raised during patients' visits to healthcare practitioners (HCPs). Verbal cues from patients and HCPs indicating DRPs were documented by an observer during visits and it was also observed whether the raised DRPs were discussed between patient and HCP. Post-encounter interviews (HCPs) were conducted and post-encounter questionnaires (patient) were distributed to identify DRPs that were not raised during the visits. Almost one in six of the DRPs raised during visits are not discussed between HCP and patient. Furthermore, existing DRPs (assessed by interviews/questionnaires afterwards) were not even raised in 4–6% of the visits. These outcomes emphasize that HCPs and patients should be aware that, although patients often have DRPs, these are not always discussed or not even raised during patients' visits.

Non-adherence is a major DRP, particularly in patients with chronic conditions who are treated with a great number of medications. Medication non-adherence is associated with negative treatment outcomes. Therefore adherence improving interventions are considered to be one of the key pharmaceutical care interventions. We studied adherence in patients with cardiovascular disease. These patients often use multiple drugs, including cholesterol-lowering drugs such as statins. Adherence to statins ranges from 32% to 79%. Although adherence has multifactorial causes, previous research on interventions to improve adherence to statins mainly focused on patient-related factors, however these studies yielded small inconsistent results. Therefore, research into other factors, such as health-care system/team factors may help to find other – probably more effective –targets to improve adherence. Insight into the association between relevant factors in the health system/healthcare team and adherence is warranted.

Therefore, in **Chapter 5** the possible association between beliefs of healthcare practitioners (HCPs) about statins and patients' statin beliefs and adherence was explored. This study was conducted in a large number of physician and pharmacy practices across the Netherlands (including large numbers of patients and HCPs). Beliefs about statins of HCPs (prescribers and pharmacy staff) and patients were assessed with the Beliefs about Medicine Questionnaire (BMQ) specific and adherence to statins was assessed with the MARS-5 questionnaire. Patients

had higher BMQ necessity and concern scores than HCPs. No associations were found between HCPs' BMQ scores and patients' BMQ scores and adherence to statins. As only questionnaires were used in this study to examine these associations, further research on this association in which questionnaires on beliefs and adherence are combined with other methods to measure adherence (eg. MEMS devices, pill count, refill adherence etc) is recommended. Further research could also be supplemented with examining to which extent communication about beliefs about medication and adherence behaviour during patient-HCP interactions takes place, by observing or audiotaping these interactions.

In the same study population, the association between the extent of adherence supporting activities of HCPs in usual care and patients' adherence to statins was examined, as described in **Chapter 6**. Usual care to support adherence to statins was assessed among HCPs with a questionnaire about usual care activities to support adherence. Both physicians and pharmacists reported that half of the adherence supporting activities were performed and half were not. Although 79% and 68% of the 209 physicians and 483 pharmacy staff members, respectively, inventory whether patients are actually taking their medication as prescribed, patients' knowledge about medication and (non-)practical barriers for taking medication as prescribed are hardly inventoried by both physicians and pharmacy staff. No positive relationship between the extent of HCPs' adherence supporting activities in usual care and patients' adherence to statins was found. Also in this case confirmation of the results is warranted, by making use of other methods than self-report questionnaires, like electronic monitors (to assess adherence) and (participatory) observations (to assess usual care).

In **Chapter 7** the findings in this thesis were put in a broader perspective. The studies presented in this thesis show that the extent to which patients and HCPs take their role in reducing DRPs is insufficient. More productive patient-provider interactions may better anticipate the patient's personal needs and problems, as the patient knows himself best (e.g. goals, preferences, needs, concerns and problems) and the HCPs is expert of the disease and the treatment options. With high quality patient-provider interactions, pharmaceutical care will shift from generic to more personalized pharmaceutical care. In this thesis it was argued that personalized pharmaceutical care is more effective in identifying and reducing DRPs. Furthermore, it was elaborated how to create room for personalized pharmaceutical care and how to target the right patients and moments with personalized pharmaceutical care.

The main conclusions of this thesis are:

1) if both patients and HCPs ensure productive patient-HCP interactions about DRPs, this results in better identification and resolution of clinically relevant DRPs.
2) a shift from incidental cross-sectional pharmaceutical care to continuous pharmaceutical care at all the risk moments the patient may encounter during his patient journey enlarges the chance of timely preventing and solving DRPs

8

Nederlandse samenvatting

Nederlandse samenvatting

Het voorschrijven van medicatie is één van de meest toegepaste interventies in de gezondheidszorg en heeft tot doel om verschillende ziekten en aandoeningen te voorkomen, te behandelen of de klachten ervan te verzachten. Hoewel geneesmiddelen meestal de kwaliteit van leven van patiënten verbeteren en de duur van hun leven verlengen, kunnen geneesmiddelen ook negatieve gevolgen voor de gezondheid hebben. Alle problemen met medicatie die potentieel tot negatieve gezondheidsuitkomsten leiden, worden geneesmiddel-gerelateerde problemen genoemd. Geneesmiddel-gerelateerde problemen kunnen worden veroorzaakt door medicatiefouten of bijvoorbeeld het gevolg zijn van bijwerkingen. Voorbeelden van medicatiefouten zijn foutieve medicatievoorschriften door voorschrijvers, fouten tijdens het afleveren door de apotheek of fouten tijdens het gebruik van de medicatie door de patiënt. Geneesmiddel-gerelateerde problemen die daadwerkelijk tot negatieve klinische consequenties leiden, zijn vaak de oorzaak van een verergering van ziekte, een verminderde kwaliteit van leven en kunnen ziekenhuisopnames of dood tot gevolg hebben. Geneesmiddel-gerelateerde problemen komen vaak voor, in verschillende studies is aangetoond dat het aantal geneesmiddel-gerelateerde problemen per patiënt varieert van één tot zes. Geneesmiddel-gerelateerde problemen zijn vaak te voorkomen en ook ziekenhuisopnames ten gevolge van geneesmiddel-gerelateerde problemen blijken vaak te kunnen worden voorkomen. Geneesmiddel-gerelateerde problemen hebben dus een significante impact op gezondheidsuitkomsten, komen vaak voor en zijn vaak te voorkomen. Daarom zijn er interventies nodig om geneesmiddel-gerelateerde problemen te verminderen en te voorkomen.

Het doel van dit proefschrift is het verkrijgen van inzicht in de rol van patiënten en zorgverleners bij het verminderen van geneesmiddel-gerelateerde problemen: enerzijds door inzicht te verkrijgen in de huidige rol van patiënten en zorgverleners in de farmaceutische zorg (met een focus op ondersteuning van therapietrouw en communicatie in de standaardzorg) en anderzijds door het onderzoeken van de effectiviteit van farmaceutische zorg interventies (en specifiek medicatiebeoordeling) waarin patiënten en zorgverleners beiden een rol hebben. Dit is geoperationaliseerd door het wetenschappelijk bewijs over de effectiviteit van medicatiebeoordelingen samen te vatten in **Hoofdstuk 2** en door de effectiviteit van een medicatiebeoordeling interventie met patiëntbetrokkenheid te onderzoeken in **Hoofdstuk 3**. Verder wordt er in **Hoofdstuk 4** een inventarisatie gemaakt van de mate van communicatie tussen patiënten en zorgverleners over geneesmiddel-gerelateerde problemen. In de **Hoofdstukken 5** en **6** wordt het verband tussen enerzijds zorgverlener gerelateerde factoren en patiënt-zorgverlener interactie gerelateerde factoren en anderzijds de opvattingen van patiënten over hun geneesmiddelen en hun therapietrouw onderzocht. Tot slot worden in **Hoofdstuk 7** de bevindingen van dit proefschrift in een breder perspectief geplaatst en worden aanbevelingen gedaan voor meer gepersonaliseerde farmaceutische zorg en toekomstig onderzoek op dit gebied.

De definitie van een medicatiebeoordeling is een gestructureerde evaluatie van het geneesmiddelgebruik van een patiënt met het doel het geneesmiddelgebruik te optimaliseren, teneinde gezondheidsuitkomsten te verbeteren. Dit omvat voornamelijk het identificeren van geneesmiddel-gerelateerde problemen en het doen van voorstellen om deze geneesmiddel-gerelateerde problemen op te lossen. In **Hoofdstuk 2** hebben we het bewijs voor de effectiviteit

van medicatiebeoordelingen zoals deze in de klinische praktijk worden uitgevoerd (als een geïsoleerde, kortdurende interventie) op een systematische manier samengevat, waarbij er geen restricties waren ten aanzien van de geïncludeerde patiënt populatie en de gebruikte uitkomstmaten. Hierbij is op een systematische manier in verschillende online databases (MEDLINE, EMBASE en Web of Science) gezocht naar literatuur over gerandomiseerde gecontroleerde onderzoeken waarin het uitvoeren van medicatiebeoordelingen vergeleken wordt met standaardzorg. Er werden 13.870 studies gescreend, waarvan er 31 werden geselecteerd. Van deze studies werd door twee onderzoekers onafhankelijk van elkaar de kwaliteit van de studies beoordeeld (55% van de studies hadden een laag risico op systematische fouten in de studieopzet) en kon het effect van medicatiebeoordeling op 22 uitkomstmaten worden bekeken (door middel van een best-evidence synthese en, in het geval van binaire variabelen, door middel van een meta-analyse). Er werd geen effect gevonden van medicatiebeoordelingen op klinische uitkomsten (overlijden, ziekenhuisopnames/ zorgconsumptie, het aantal patiënten dat valt, fysiek en cognitief functioneren), behalve een vermindering van het aantal keren dat patiënten vallen. Bovendien werd geen effect gevonden op de kwaliteit van leven en was het bewijs niet eenduidig ten aanzien van het effect van medicatiebeoordelingen op economische uitkomstmaten. Echter werd wel een effect gezien van medicatiebeoordelingen op de meeste geneesmiddel-gerelateerde uitkomsten: medicatiebeoordeling resulteerde in een afname van het aantal geneesmiddel-gerelateerde problemen, meer wijzigingen in medicatie, een groter aantal geneesmiddelen waarvan de dosering werd verlaagd en een grotere afname of kleinere toename van het aantal gebruikte geneesmiddelen. Vermeldenswaardig is dat in een sensitiviteitsanalyse van de bevindingen met betrekking tot de mate van betrokkenheid van de patiënt in studies waarin een positief effect werd gevonden, gevonden werd dat geneesmiddel-gerelateerde problemen vaker worden geïdentificeerd en opgelost in studies waarin de patiënt betrokken was. Tevens werd een effect op klinische uitkomstmaten of kwaliteit van leven ook voornamelijk gezien in studies waarin de patiënt betrokken was. Gezien het feit dat de impact van medicatiebeoordeling op klinische uitkomsten en kwaliteit van leven minimaal is, het geobserveerde effect op geneesmiddel-gerelateerde uitkomsten beperkt is en dat het bewijs ten aanzien van het effect op economische uitkomsten niet eenduidig is, zou moeten worden overwogen om te stoppen met het uitvoeren van medicatiebeoordelingen als standaardzorg.

Om het effect van een door een apotheker uitgevoerde medicatiebeoordeling waarbij de patiënt betrokken is op het aantal geneesmiddel-gerelateerde problemen te onderzoeken, is in **Hoofdstuk 3** een gerandomiseerd gecontroleerd onderzoek uitgevoerd waarin een (computerondersteunde) medicatiebeoordeling vergeleken werd met standaardzorg voor poliklinische cardiologie patiënten. Dit betrof volwassen patiënten zonder ondersteuning bij hun medicatiegebruik, die geen medicatiebeoordeling hadden gehad in de afgelopen zes maanden en die toestemming hadden gegeven om hun elektronisch patiëntendossier in te mogen zien. De primaire uitkomstmaat was het aantal geneesmiddel-gerelateerde problemen 1 maand na het consult bij de cardioloog. Na 1 maand was het gemiddeld aantal geneesmiddel-gerelateerde problemen in de interventiegroep significant lager dan in de controlegroep. Bovendien was in de interventiegroep 75% van de geneesmiddel-gerelateerde problemen die bij de start van de studie werden geïdentificeerd na 1 maand opgelost, daar waar in de controlegroep 14% was opgelost. Hoewel een even groot deel van de geneesmiddel-gerelateerde problemen geïdentificeerd werd door middel van gesprekken met patiënten als door de combinatie van de beoordeling door een apotheker en computer

gestuurde aanbevelingen, werden problemen die door patiënten werden gerapporteerd vaker opgelost in vergelijking met de problemen die gevonden werden door de apotheker en het computersysteem (84% versus 64%). Medicatiebeoordelingen waarbij de patiënt betrokken is op de polikliniek cardiologie verminderen dus het aantal geneesmiddel-gerelateerde problemen, bovendien worden geneesmiddel-gerelateerde problemen die gerapporteerd worden door patiënten klinisch relevanter gevonden door artsen en patiënten.

De mate van communicatie over geneesmiddel-gerelateerde problemen tijdens reguliere interacties tussen patiënten en zorgverleners in Nederlandse poliklinieken, huisartspraktijken en apotheken is onderzocht in een dwarsdoorsnede observationele studie in **Hoofdstuk 4**. Er werd een inventarisatie gemaakt van het aantal en het type geneesmiddel-gerelateerde problemen die (1) opgeworpen en bediscussieerd werden, (2) opgeworpen maar niet bediscussieerd werden of (3) niet opgeworpen werden tijdens bezoeken van patiënten aan zorgverleners. Verbale signalen van patiënten die op geneesmiddel-gerelateerde problemen duidden werden gedocumenteerd door een observant tijdens de bezoeken en ook werd gedocumenteerd of de opgeworpen geneesmiddel-gerelateerde problemen vervolgens bediscussieerd werden door de patiënt en de zorgverlener of niet. Na de bezoeken werden interviews gehouden met zorgverleners en vragenlijsten verstrekt aan patiënten met als doel om geneesmiddel-gerelateerde problemen te identificeren die niet opgeworpen werden tijdens de bezoeken. Bijna 1 op de zes geneesmiddel-gerelateerde problemen die werden opgeworpen tijdens de bezoeken werden niet verder besproken door zorgverlener en patiënt. Bovendien werden in 4-6% van de bezoeken actuele geneesmiddel-gerelateerde problemen (geïdentificeerd door middel van de interviews en vragenlijsten na de bezoeken) niet eens opgeworpen.

Therapieontrouw is een belangrijk geneesmiddel-gerelateerd probleem, in het bijzonder bij patiënten met chronische aandoeningen die worden behandeld met een groot aantal geneesmiddelen. Therapieontrouw is geassocieerd met negatieve behandeluitkomsten. Daarom worden interventies om therapietrouw te verbeteren gezien als één van de essentiële farmaceutische zorginterventies. Wij bestudeerden therapietrouw bij patiënten met cardiovasculaire aandoeningen. Deze patiënten gebruiken vaak meerdere geneesmiddelen, inclusief cholesterolverlagende geneesmiddelen, zoals statines. Therapietrouw aan statines varieert van 32% tot 79%. Hoewel therapietrouw meerdere oorzaken kent, richtte eerder onderzoek zich voornamelijk op patiënt-gerelateerde factoren, echter leverden deze studies inconsistente resultaten op. Daarom zou onderzoek naar andere factoren, zoals factoren gerelateerd aan het behandelteam en de organisatie van de gezondheidszorg kunnen helpen om andere – mogelijke effectievere – aangrijpingspunten te vinden om therapietrouw te verbeteren. Het is nodig om inzicht te verkrijgen in het verband tussen relevante factoren gerelateerd aan het behandelteam en het gezondheidszorgsysteem en therapietrouw.

Daarom is in **Hoofdstuk 5** het potentiële verband tussen de opvattingen van zorgverleners over statines en de opvattingen en therapietrouw van patiënten die statines gebruiken onderzocht. Deze studie werd uitgevoerd in een groot aantal arts-praktijken en apotheken verspreid over Nederland (waarbij grote aantallen patiënten en zorgverleners deelnamen aan de studie). Opvattingen over statines van zorgverleners en patiënten werden uitgevraagd met de Beliefs about Medicine Questionnaire (BMQ) specific en therapietrouw werd gemeten door middel van de MARS-5 vragenlijst. Patiënten hadden hogere BMQ noodzaak- en

zorgscores dan zorgverleners. Er werden geen verbanden gevonden tussen de BMQ scores van zorgverleners en de BMQ scores en therapietrouw aan statines van patiënten. Aangezien alleen vragenlijsten werden gebruikt in deze studie om deze verbanden te onderzoeken wordt er vervolgonderzoek aangeraden om dit verband te onderzoeken waarbij naast vragenlijsten over opvattingen en therapietrouw ook andere methoden worden gebruikt om therapietrouw te meten (bv. slimme geneesmiddelverpakkingen die registreren wanneer de verpakking wordt geopend, het tellen van tabletten, "refill therapietrouw" aan de hand van aflevergegevens van de apotheek etc.). Verder onderzoek kan ook worden aangevuld met het onderzoeken van de mate van communicatie over opvattingen tijdens interacties tussen patiënt en zorgverlener, door deze interacties te observeren of op te nemen.

In dezelfde studiepopulatie werd de associatie tussen de mate van therapietrouw ondersteunende activiteiten in de standaardzorg van zorgverleners en de therapietrouw van patiënten onderzocht, zoals beschreven in **Hoofdstuk 6**. Standaardzorg om therapietrouw te ondersteunen werd onderzocht door middel van een vragenlijst over standaardzorg activiteiten om therapietrouw te ondersteunen. Zowel artsen als apothekers rapporteerden dat de helft van de therapietrouw ondersteunde activiteiten werden uitgevoerd en dat helft niet werd uitgevoerd. Hoewel respectievelijk 79% en 68% van de 209 artsen en 483 apotheekmedewerkers inventariseerden of patiënten daadwerkelijk hun medicatie innemen zoals voorgeschreven, werd de kennis van patiënten over medicatie en praktische en niet praktische barrières om medicatie in te nemen zoals voorgeschreven nauwelijks geïnventariseerd door zowel artsen als apotheekmedewerkers. Er werd geen positieve relatie gevonden tussen de mate van therapietrouw ondersteunende activiteiten door zorgverleners en de therapietrouw van patiënten die statines gebruiken. Ook in dit geval is bevestiging nodig van de resultaten, door gebruik te maken van andere methode dan zelfrapportage vragenlijsten, zoals slimme geneesmiddelverpakkingen om therapietrouw te meten en (participerende) observaties om standaardzorg te inventariseren.

In het laatste hoofdstuk van dit proefschrift, **Hoofdstuk 7**, hebben we de belangrijkste bevindingen in een breder perspectief geplaatst en zijn de methodologische aspecten bediscussieerd. De studies die worden gepresenteerd in dit proefschrift laten zien dat de mate waarin patiënten en zorgverleners hun rol pakken in het verminderen van geneesmiddel-gerelateerde problemen onvoldoende is. Met productievere interacties tussen patiënt en zorgverleners kan mogelijk beter worden geanticipeerd op de persoonlijke behoeften en problemen van de patiënt, aangezien de patiënt zichzelf het beste kent (bv. doelen, voorkeuren, behoeften, zorgen en problemen) en de zorgverlener expert is van de ziekte en de behandelmogelijkheden. Met kwalitatief hoogstaande interacties tussen patiënt en zorgverlener zal farmaceutische zorg verschuiven van generiek naar meer gepersonaliseerde farmaceutische zorg. In dit proefschrift werd betoogd dat gepersonaliseerde farmaceutische zorg effectiever is in het identificeren en verminderen van geneesmiddel-gerelateerde problemen. Bovendien werd uiteengezet hoe ruimte gecreëerd kan worden voor gepersonaliseerde farmaceutische zorg en hoe de juiste patiënten en momenten kunnen worden geselecteerd voor gepersonaliseerde farmaceutische zorg.

De belangrijkste conclusies van dit proefschrift zijn:

(1) Als zowel patiënten als zorgverleners zorgen voor productieve interacties tussen patiënt en zorgverlener over geneesmiddel-gerelateerde problemen dan leidt dit tot betere identificatie en oplossing van klinisch relevante geneesmiddel-gerelateerde problemen
(2) Een verschuiving van incidentele dwarsdoorsnede farmaceutische zorg naar continue farmaceutische zorg op alle risicomomenten die een patiënt ervaart tijdens zijn (chronische) medicamenteuze behandeling vergroot de kans op het voorkomen of tijdig oplossen van geneesmiddel-gerelateerde problemen

Dankwoord

Dankwoord

Laat ik er niet omheen draaien, dit was best een lang promotietraject. En dat vind ik fantástisch! Waarom? Omdat het geen doel op zich is geweest om te promoveren. En mensen die me goed kennen die weten dat. Allereerst veel dank aan iedereen die me niet al die tijd gevraagd heeft wanneer het af zou zijn!

Mijn werk als apotheker voer ik elke dag met veel passie uit. Wetenschappelijk onderzoek, om onder andere te bewijzen dat dingen die we in farmaceutische zorg doen wel of niet van toegevoegde waarde zijn voor patiënten en om aangrijpingspunten te vinden om deze zorg te verbeteren, vind ik een belangrijk onderdeel daarvan. Fantastisch dat ik de ruimte heb gekregen om op die manier promotieonderzoek te doen. Dat past namelijk heel erg goed bij mij. In vrijheid de dingen doen vanuit mijn intrinsieke motivatie.

Allereerst veel dank aan Bart Benraad dat je dit vanaf de start mogelijk hebt gemaakt. Jij vroeg mij regelmatig, terwijl ik al een tijd bezig was met onderzoeken uitvoeren: “wil je promotieonderzoek doen”? Mij op die manier met zachte hand wijzend op het feit dat er toch wel iets van kaders waren waarbinnen ik mij aan het bewegen was. En ook dank aan alle (ex-) collega apothekers die ruimte hiervoor hebben gegeven door bijvoorbeeld een dienst over te nemen, wanneer ik opeens bedacht dat ik toch eens even moest knallen voor een artikel of een bijdrage op een congres. Bart Benraad, Marjolein Deurvorst, Bart van den Bemt, Mieke Gijzels, Dayenne van Bergeijk, Karin Lancee, Kasper Meijerink, Ala Keyany, Karin Spijkers (ook als aanvoerder van topteam ksvh), Anne Houterman, Milou van Heuckelum (dank ook voor de onderzoektips!), Bart Pouls (zowel in de apotheek als bij research), Eward Melis en Janneke Lassche: dank jullie wel daarvoor! En graag wil ik daar ook Anouk Heinen, Julian Vlietstra en Saskia Buijs aan toevoegen, wat een prettige groep om mee samen te werken met alle goede ideeën en ruimte voor eenieders inzichten en kwaliteiten. In dit rijtje mag zeker niet ontbreken: het hele apotheekteam! Dank voor het tonen van interesse in de onderzoeken, luisteren naar enthousiaste verhalen over onderzoeken en congressen en vooral ook het bevlogen samenwerken in de directe farmaceutische patiëntenzorg, dat waar we het allemaal voor doen! En last but not least: de ondersteunende staf met in het bijzonder het secretariaat Farmacie. Jullie hebben me vaak enorm geholpen met het uitprinten van protocollen en vragenlijsten, het versturen en het ontvangen van onderzoeksdocumenten, het organiseren van bijeenkomsten. Echt onmisbare hulp. Door de jaren heen, Sonja, Estella, Joany, Jeanette, Lisette, Natasja en Marloes: enórm bedankt voor dit alles en ook voor de getoonde interesse.

Nog even een stapje terug in de tijd. Tijdens mijn studie farmacie aan de Rijksuniversiteit Groningen heb ik zoals iedereen een afstudeeronderzoek gedaan. Daarbij was het geijkte eindproduct een scriptie. Voor veel studenten een moetje. Het idee dat dat móest kon ik ook niet zoveel mee. En ook toen was er iemand die mij de vrijheid durfde te geven om het op mijn eigen manier aan te pakken. En mij daardoor júist enthousiast heeft gemaakt voor het doen van onderzoek, vanuit eigen motivatie om een bijdrage te leveren aan betere zorg. Daardoor kon ik naar Tanzania, om te onderzoeken of er een verschil is in de vetzuursamenstelling van de vaatwand van aderen in navelstrengen bij baby’s van vrouwen mét of zonder zwangerschapsvergiftiging. Mogelijk zou het een aangrijpingspunt opleveren voor het voorkomen van zwangerschapsvergiftiging door aanpassingen van het dieet of door medicamenteus ingrijpen. Ik heb géén scriptie geschreven, maar gevraagd of ik een artikel

mocht schrijven voor internationale publicatie. Het artikel had ik niet af toen ik afstudeerde, want ik wilde graag tegelijk met mijn studievrienden afstuderen. Vandaar de passende laatste zin van mijn laudatio, uitgesproken door Professor Frits Muskiet: “Gefeliciteerd, en voor vandaag een prettige dag met je familie en vrienden. En morgen gewoon om 9:00 uur weer verder werken aan je publicatie”. Beste Frits, hartelijk dank voor jouw vertrouwen in mij, de steun bij die prachtige onvoorspelbare ervaring in Afrika en het bijbrengen van de liefde voor wetenschap!

Zo fijn om mensen te kunnen bedanken voor het bieden van ruimte om mijn werk te doen op een manier die bij mij past. Een ander belangrijk aspect is natuurlijk het samenwerken aan wetenschappelijk onderzoek, de inhoudelijk discussies voeren met elkaar en het leren van je begeleidend promotieteam.

Bart (van den Bemt, wat ken ik toch veel Barten, maar ik zeg niks geks als ik zeg dat er maar 1 is zoals jij). Zeer veel dank voor... teveel om op te noemen. Ik doe een poging: jouw inspiratie, energie, kennis, denkkracht, flexibiliteit en humor. Je hebt veel voor me betekend in de afgelopen jaren. We begonnen als collega apothekers in de Maartensapotheek. Vervolgens begeleidde je mij bij mijn eerste onderzoek, dat begon vanuit een behoefte in de praktijk. Onze stelling was: als een computer adviezen kan geven ten aanzien van het expliciete deel van de medicamenteuze behandeling (bv. onjuiste doseringen en toevoegen van beschermende medicatie) dan kunnen zorgverleners zich richten op het impliciete deel van de medicamenteuze behandeling: de geneesmiddel gerelateerde problemen die de patiënt ervaart uitvragen en oplossen. Avonden lang hebben we samen als twee nerds in Crystal Reports deze computerondersteuning gemaakt. Om vervolgens te toetsen in een multicenter randomized clinical trial. We hebben door de jaren heen uren en uren gepraat over onze visie op farmaceutische patiëntenzorg en hoe daaraan onderzoek te doen. Dat stopte nooit. Als we samen op congres waren bijvoorbeeld. En ik moet toegeven: je bent 1 van de weinigen die ik ken die nog eindelozer doorgaat dan ik. Zo kan ik me herinneren dat we in het vliegtuig zaten naar San Francisco en dat ik na 8 uur praten dacht, nu even niks. Dat jij, toen ik dat zei, jouw laptop openklapte om een stuk te gaan schrijven. Dat we in Chicago elke avond met een groep artsen tot laat de kroeg ingingen (Aatke ook bedankt voor het hilarische moment waarbij jij in beschonken toestand de hotelsleutel kwijt was). Dat we in Chicago elke ochtend vroeg lopend een paar kilometer langs lake Michigan naar het congrescentrum gingen (ik had na het congres zo’n Goofy-gat in de zool van mijn schoen). Dat we ook kilometers liepen om het perfecte restaurant te vinden en dat ik alleen maar dacht ik wil nú eten en dat ik een keer zo gaar was dat ik na het eten in zo’n typisch amerikaans halfrond bankje aan tafel in slaap viel. Eindeloos praten. Eén van de vele memorabele momenten: zitten we samen (ik zoals vaak in een wit overhemd) in een onbtijtzaal met van die nisjes, wederom amerikaanse bankjes, tegenover elkaar te ontbijten. Bart, jij gaat naar het buffet, komt al pratend teruggelopen en schuift 1 nisje te vroeg tegenover een Amerikaan in wit overhemd aan. En maar doorpraten. Totdat je opkeek en in het gezicht van de volledig verbouwereerde Amerikaan staarde. Teveel om op te noemen dus. Maar je hebt me vooral ook veel geleerd als het gaat om onderzoek doen, schrijven, presenteren, de laatste tijd in de rol van eerste promotor. Jouw uitspraak ik wil nooit meer zo’n promotietraject, komt niet uit de lucht vallen. Je kan veel hebben en gaat tot het uiterste. Je stuurde alleen even bij toen in mijn planning voor de general discussion de reactietermijn voor jou herhaaldelijk bestond uit 1 enkele avond.

En dan de rest van mijn promotieteam, David, Els en Liset. David, je keek er als oorspronkelijk eerste promotor (leuk dat je de verschuiving daarin toestond) niet van op of ik wel of geen agenda had voor onze overleggen. Je wees me altijd op de uitdaging van het doen van promotieonderzoek naast het reguliere apothekerswerk. Je hield me bij de les met voorbeelden uit jouw brede ervaring met andere promovendi. En je sloot de gesprekken steevast af met het uitspreken van het vertrouwen in een succesvolle afloop. Ook zorgde je ervoor dat ik bij het opschrijven van de artikelen niet teveel redeneerde vanuit visie maar (ook) vanuit de verrichte onderzoeken en de bijbehorende resultaten. De discussies met jou hebben regelmatig geleid tot een essentiële extra invalshoek die ik kon gebruiken in de presentatie van de resultaten (bv bij de RCT) en het beschouwen van de resultaten in de discussie (bv de systematic review). En jouw positieve reacties op mijn stukken, waaronder in de eindfase waren een hele welkome stimulans! Els, wat fijn dat je onderdeel bent van mijn promotieteam. Jouw kennis en karakter was een zeer welkome aanvulling in mijn promotieteam. We hebben samengezeten om analyses door te nemen, deze vanaf het begin op te bouwen. En je hebt regelmatig kritisch doorgevraagd om zeker te weten dat de resultaten kloppen. Verder ga je enerzijds nauwgezet door de manuscripten heen waardoor je bijvoorbeeld met aanpassingen in tabellen komt, anderzijds stel je regelmatig voor om de opbouw van een stuk om te gooien. Ik hield om die reden wel af en toe mijn adem in als ik jouw reacties opende. Verder heb je ook vaak voorgesteld om stukken tekst weg te laten, niet zelden heb ik hele alinea’s geschrapt op jouw aangeven, waarna ik telkens weer verbaasd was dat de boodschap er daarna inderdaad nog stond. En tot slot, als jij dan zegt dat het goed is, dan durfde ik ook met een gerust hart in te dienen! Liset, jij hebt als laatste mijn promotieteam versterkt. Tijdens een congres in Belfast hebben we samen met Bart en Marcia (dank voor de vele mooie (dans)avonden op congressen!) zitten dineren in Robinsons bar, waarna het restaurant ook succesvol dienst deed als kroeg, zoals de naam al deed vermoeden. Toen we, op het moment dat het licht aanging, nog niet waren uitgepraat en gediscussieerd was dat natuurlijk het perfecte moment om eens te informeren of je bereid was onderdeel te worden van het promotieteam. Nogmaals dank dat je dat toen hebt toegezegd, jouw input is enorm waardevol geweest keer op keer. Onder andere jouw kennis op het gebied van communicatie over geneesmiddelen en beliefs en therapietrouw was zeer welkom. En daarbij bijvoorbeeld ook jouw kennis over farmaceutische zorg in de apotheek praktijk, iets dat de discussies enorm heeft verrijkt, onder andere met jouw concrete aanvullende suggesties met bijbehorende literatuur! Dank ook voor de vele gezellige momenten tijdens congressen, van tijdens borrels tot tafevoetbalspellen en op dansvloeren!

Beste leden van de manuscriptcommissie, prof. dr. A.M. van Dulmen, prof. dr. M.L. Bouvy en prof. dr. H. Schers, beste Sandra, Marcel en Henk, hartelijk dank voor het beoordelen van mijn manuscript en de bereidheid om zitting te nemen in de oppositie.

Verder veel dank aan iedereen waarmee ik samen heb mogen werken tijdens het uitdenken van verschillende onderzoeken, het verzamelen van de data en het opschrijven van de artikelen. Hartelijk dank Kees Kramers, Jacqueline Bos en Christine Kramer. Veel dank Joke Vriezekolk, voor je goede én concrete input tot en met de laatste versie van een artikel! En Rik Ensing, Marieke Meijs, Veronique Meijs enorm bedankt voor jullie doorzettingsvermogen tijdens het uitvoeren van de medicatiebeoordelingen en het verzamelen van de data, en natuurlijk ook het uitdenken van de studie tijdens de SIR Masterclass. Marcel Bouvy, Martine Kruijtbosch en andere medewerkers van SIR, hartelijk dank voor deze fijne samenwerking. Ook wil ik graag Mariëlle Bijlstra-Cramer, Naomi Wartenberg, Thien Pham en de apothekers in

opleiding tot openbaar apotheker specialist heel hartelijk danken voor hun belangrijke rol bij de dataverzameling en/of het ondersteunen van verschillende onderzoeken. Veel dank gaat uit naar alle patiënten en zorgverleners die hebben meegewerkt aan de onderzoeken. En dank aan collega onderzoekers bij de afdeling research van de Sint Maartenskliniek. Ondanks het feit dat ik door de vele andere werkzaamheden mijn neus niet veel kon laten zien, kan ik altijd terecht met vragen bij jullie en hebben we een gezellige tijd gehad bij schrijfdagen! Hartelijk dank daarvoor! ESPACOMP clan, dank voor jullie inhoudelijke bevlogenheid in combinatie met de gekte en energie tijdens de avonduren, fantastisch dat ik me regelmatig bij jullie mag aansluiten tijdens congressen. Henk Frans Kwint, Sanne Verdoorn en natuurlijk ook Marcel Bouvy, dank voor de leuke discussies tijdens ESCP congressen! Peter Brummelhuis en Simon Latumalea, veel dank voor de mooie ervaringen op de ESCP congressen, van uren aan de bar hangen tot het ons letterlijk naar buiten knokken tussen opvliegerige discotheek gangers en voor jullie keiharde applaus in combinatie met op vingers fluiten na presentaties van mij op congressen.

Lieve vrienden, mannen van de jaarclub, farmacievrienden van Aanwezig, hartelijk dank voor jullie interesse (ook) in dit deel van mijn werk en ook vooral de ouderwetse gezelligheid als we elkaar zien. Bart (van Det, weer een Bart en weer niet zomaar één), dank voor de vakanties en weekenden waarin we elkaar precies genoeg vragen, maar vooral bezig zijn met (in willekeurige volgorde) bier drinken en racefietsen. Dank dat je mijn paranimf bent! Emma (de Feijter), em, emsel, heerlijk om met jou te filosoferen over waar het met de farmacie naartoe zouden moeten, over het nut en de lol van het doen van (promotie)onderzoek en het vrij associëren over van alles en nog wat tot aan wereldproblematiek en klimaatverandering aan toe. Ik kijk uit naar meer! Dank ook dat je mijn paranimf wil zijn! Anneloes, bijzonder veel dank voor natuurlijk het schetsen van alle bloemen voor de omslag en het binnenwerk van dit proefschrift (wát een werk). En minstens zoveel dank voor het kritische meelezen en doorvragen, je hulp en adviezen bijvoorbeeld op het gebied van planning, anders was ik nog bezig!

Wouter en Quirijn, dank voor jullie niet al te intensieve informeren naar de stand van zaken door de jaren heen (zie begin van dit dankwoord, dat hadden jullie niet beter kunnen doen) en het, zoals het ons als broers typeert, op een licht cynische manier stimuleren om op te schieten in de afrondende fase: “is het nou een keer af”? Zwagers en schoonzussen en zeker ook Els en Eri dank voor de geïnteresseerde vragen over de inhoud vanuit het perspectief van jullie verschillende (in bepaalde gevallen ook medische) achtergrond. Els en Eri, naast de interesse ook enorm bedankt voor het faciliteren van momenten om even rustig door te kunnen werken aan onderzoek. En oma Salomé (en in gedachten ook opa Salomé), heel bijzonder dat ik het ook met jullie hierover heb gesproken zo nu en dan. Oma Salomé, de opmerking: “ga ik het meemaken denk je”, heb ik regelmatig aan moeten denken wanneer ik mijn best deed om stappen te zetten! Tot slot dank aan mijn tantes en ooms, voor jullie interesse in mijn bezigheden!

Lieve papa en mama, jullie hebben dit in de basis allemaal mogelijk gemaakt. Ik wilde graag geneeskunde studeren, maar werd herhaaldelijk uitgeloot. Jullie zochten voor me uit dat ik dan in Duitsland, Engeland of België aan de slag kon. Dat was voor mij een brug te ver. Dus steunden jullie mij op alle manieren bij het doen van mijn farmacie studie en zeker ook bij het léven van een fijn (studenten)leven. Mam, laatst zei je dat ik altijd heb gezegd dat ik graag met

mensen werk. Dat klopt! We hadden het erover of het dan logisch is om (ook) wetenschappelijk onderzoek te doen. Ik heb dat even laten bezinken en ik denk dat ik het antwoord heb. Onderzoek doen, doe je vóór mensen: patiënten. En onderzoek doen doe je mét mensen: in de samenwerking op de inhoud en tijdens het verenigen van het nuttige en het aangename (zoals op congressen).

Lieve Lize, Vera en Pieter (alle drie geboren tijdens mijn promotietraject), wat ben ik vréselijk trots op jullie en wat geniet ik elke dag van jullie!!! Jullie zijn altijd zó lief en (nu al!) zó geïnteresseerd!! Ongelofelijk blij dat jullie mijn kinderen zijn. Lieve His, wat een bijzondere jaren, waarin je mij altijd hebt gesteund in mijn ambitie. En ontzettend bedankt voor jouw geduld, het luisteren, het meedenken. En dat terwijl je zelf ook ambitieus bent, met meerdere opleidingen en banen in verschillende takken van de GZ psychologie. Ik ben je oneindig dankbaar voor hoe je dit hebt weten te combineren met onze gezamenlijke intensieve en liefdevolle zorg voor onze jonge kinderen.

About the author

Victor Huiskes was born on December 22nd 1980 in Almelo, the Netherlands. After graduating from the secondary school in 1999 at Het Noordik in Almelo, he started studying pharmacy at the Rijksuniversiteit Groningen. During his master, he conducted a research project in Mwanza, Tanzania in 2004-2005, which resulted in his first peer-reviewed scientific publication entitled "Higher de novo synthesized fatty acids and lower omega3- and omega6-long-chain polyunsaturated fatty acids in umbilical vessels of women with preeclampsia and high fish intakes".

In 2006, he obtained his Master of Science in Pharmacy, with distinction. After his graduation, he made the deliberate choice to get employed in the first outpatient pharmacy in the Netherlands, in the St. Maartenskliniek in Nijmegen, the only Dutch hospital specialized in posture and movement. In this setting he uses his specialized pharmacotherapeutic knowledge to assist patients with rheumatic diseases in fitting their medication use into their daily lives. His primary focus is medication safety and personalized medication therapy management, which includes the following activities: (1) designing and implementing (in person and digital) pharmaceutical care concepts, (2) scientifically evaluating of these concepts and (3) collaborating multidisciplinary to realize these concepts.

Within the Sint Maartenskliniek, one of Victor's main tasks (besides daily patient care) is the *design and implementation* of pharmaceutical care concepts, such as continuous pharmaceutical care. Continuous pharmaceutical care at all the risk moments the patient may encounter during his patient journey enlarges the chance of preventing and timely identifying and solving drug-related problems. Furthermore, he creates optimal conditions for continuous pharmaceutical care by implementing e-health solutions to facilitate place and time independent contact between patients and healthcare providers and self-management by the patient. He also participates in several (guideline) committees nationwide, concerning medication safety, pharmaceutical care and healthcare information technology (since 2006).

As these pharmaceutical care activities should be *scientifically evaluated*, Victor started his parttime PhD trajectory in 2010 – during 1 day a week alongside his work in the pharmacy – at the department of Pharmacy of the Sint Maartenskliniek in collaboration with the department of Pharmacy of the Radboud University Medical Center in Nijmegen, the Netherlands. His PhD was supervised by Prof. Dr. Bart JF van den Bemt, Prof. Dr. David M Burger, Dr. Cornelia HM van den Ende and Prof. Dr. Ir. Liset van Dijk. His PhD focused on the role of patients and HCPs in pharmaceutical care to reduce drug-related problems. The results of his PhD, described in this thesis, are published in peer-reviewed publications and presented at several (inter)national conferences.

Finally, pharmaceutical care is multidisciplinary care. In order to facilitate *multidisciplinary collaboration* and increase medication safety by uniform working methods, Victor is member

of the board of the regional pharmacists association since 2014 and member of several committees of the Dutch Association of Hospital Pharmacists and The Royal Dutch Pharmacists Association since 2006. Furthermore, he is chairman of the Maartensfacts committee since 2018, a group of medical specialists in the Sint Maartenskliniek, committed to using treatment outcomes – both clinical and patient-reported outcomes – to improve patient care.

Since January 2020, Victor is engaged in research projects from several PhD candidates employed at or collaborating with the department of Pharmacy of the Sint Maartenskliniek and the department of Pharmacy of the Radboud University Medical Center in Nijmegen, the Netherlands. These (personalized) pharmaceutical care research projects aim to improve effective and safe drug treatment.

List of publications

List of publications

This thesis

Huiskes VJ, Burger DM, van den Ende CH, van den Bemt BJ. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam Pract. 2017 Jan 17;18(1):5.

Huiskes VJB, Cramer-van der Welle CM, van den Ende CHM, van Dijk L, Bos JM, Kramers C, van den Bemt BJF. Communication about Drug-Related Problems (DRPs) during Patients' Visits to Dutch Physicians and Pharmacies. Health Commun. 2020 Feb;35(2):201-208.

Huiskes VJB, van den Ende CHM, Kruijtbosch M, Ensing HT, Meijs M, Meijs VMM, Burger DM, van den Bemt BJF. Effectiveness of medication review on the number of drug-related problems in patients visiting the outpatient cardiology clinic: A randomized controlled trial. Br J Clin Pharmacol. 2020 Jan;86(1):50-61.

Huiskes VJB, van den Ende CHM, van Dijk L, Burger DM, van den Bemt BJF. Association between healthcare practitioners' beliefs about statins and patients' beliefs and adherence. Br J Clin Pharmacol. 2021 Mar;87(3):1082-1088.

Huiskes VJB, Vriezekolk JE, van den Ende CHM, van Dijk L, van den Bemt BJF. Impact of physician' and pharmacy staff supporting activities in usual care on patients' statin adherence. Manuscript submitted

Other publications

Huiskes VJB, Kuipers RS, Velzing-Aarts FV, Dijck-Brouwer DA, van der Meulen J, Muskiet FA. Higher de novo synthesized fatty acids and lower omega3- and omega6-long-chain polyunsaturated fatty acids in umbilical vessels of women with preeclampsia and high fish intakes. Prostaglandins Leukot Essent Fatty Acids. 2009 Feb-Mar;80(2-3):101-6.

Van den Bemt BJF, **Huiskes VJB**. Therapietrouw komt vanuit de patiënt. Nodig: Overwegingen van patiënt in kaart brengen. Pharmaceutisch Weekblad 2010 may 7; 18:22-25

Huiskes VJB, van den Bemt BJF. Integrale farmazorg nodig. Medicatie Management Piramide klasseert zorg op individueel en populatieniveau. Pharmaceutisch Weekblad 2014 mrt 07; 10: 23

Wilmer CM, **Huiskes VJB**, Natsch S, et al. Drug-related problems in a clinical setting: a literature review and cross-sectional study evaluating factors to identify patients at risk. European Journal of Hospital Pharmacy 2015;22:229-235.

van den Bemt BJF, **Huiskes VJB**. The medication therapy management pyramid shifting medication review to an integrated medication therapy management process. European Journal of Hospital Pharmacy 2015;22:219-221.

Tweehuysen L, **Huiskes VJB**, van den Bemt BJF, Vriezekolk JE, Teerenstra S, van den Hoogen FHJ, van den Ende CH, den Broeder AA. Open-Label, Non-Mandatory Transitioning From Originator

Etanercept to Biosimilar SB4: Six-Month Results From a Controlled Cohort Study. Arthritis Rheumatol. 2018 Sep;70(9):1408-1418.

Kosse LJ, Jessurun NT, Hebing RCF, **Huiskes VJB**, Spijkers KM, van den Bemt BJF, Nurmohamed MT. Patients with inflammatory rheumatic diseases: quality of self-reported medical information in a prospective cohort event monitoring system. Rheumatology (Oxford). 2020 Jun 1;59(6):1253-1261.

Huiskes VJB, Rijcken, CAW, van den Bemt BJF. Van een persoonlijk gesprek tot een digital human apotheker. Farmaceutische begeleiding bij chronisch gebruik van reumageneesmiddelen. Pharmaceutisch Weekblad 2020 dec 04; 49:22-23

van der Nat DJ, Taks M, **Huiskes VJB**, van den Bemt BJF, van Onzenoort HAW. A comparison between medication reconciliation by a pharmacy technician and the use of an online personal health record by patients for identifying medication discrepancies in patients' drug lists prior to elective admissions. Int J Med Inform. 2021 Mar;147:104370.

Conference abstracts

Huiskes VJ, Burger DM, van den Ende CH, van den Bemt BJ. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. NVKFB announcements day, 2013 (oral presentation); ESCP, Copenhagen, 2014 (oral presentation); Dutch hospital pharmacy days, 2014 (mini oral presentation)

Huiskes VJB, van den Ende CHM, Kruijtbosch M, Ensing HT, Meijs M, Meijs VMM, Burger DM, van den Bemt BJF. Effectiveness of medication review on the number of drug-related problems in patients visiting the outpatient cardiology clinic: A randomized controlled trial. ESCP, Barcelona, 2012 (poster presentation); Regional meeting Dutch association for hospital pharmacists, 2013 (oral presentation); PRISMA symposium, Amersfoort, 2013 (oral presentation)

Huiskes VJB, Cramer-van der Welle CM, van den Ende CHM, van Dijk L, Bos JM, Kramers C, van den Bemt BJF. Communication about Drug-Related Problems (DRPs) during Patients' Visits to Dutch Physicians and Pharmacies. Dutch hospital pharmacy days, 2015 (mini oral presentation); ESCP, Lisbon, 2015 (poster presentation)

Huiskes VJB, Belliot S, Brummelhuis PR, Lamers T, van Lanen H, van Ree L, Spijkers K, van den Bemt BJF. Het effect van transmurale informatie- en kennisuitwisseling tussen apothekers op de bevindingen van medicatiereviews. Dutch hospital pharmacy days, 2015 (mini oral presentation); PRISMA symposium, Amersfoort, 2015 (oral presentation)

Huiskes VJB, van den Ende CHM, van Dijk L, Burger DM, van den Bemt BJF. Association between healthcare practitioners' beliefs about statins and patients' beliefs and adherence. ESPACOMP, Lisbon, 2016 (oral presentation); ESCP, Oslo, 2016 (oral presentation)

Huiskes VJB. Online medication reconciliation. ESCP, Ljubljana, 2019 (oral presentation); Dutch hospital pharmacy days, 2019 (mini oral presentation)

Research data management

Research data management

General information about the data collection

This research followed the applicable laws and ethical guidelines. Research Data Management was conducted according to the FAIR principles. The paragraphs below specify in detail how this was achieved.

Ethics

Chapter 3, Chapter 4, Chapter 5 and Chapter 6 of this thesis are based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The study protocol of Chapter 3 was submitted to the Medical and Ethical Review board Committee (MREC) on Research Involving Human Subjects Region Arnhem Nijmegen, Nijmegen, The Netherlands. The MREC region Arnhem Nijmegen provided a waiver for ethical approval. All patients provided written informed consent. The other studies in this thesis did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act. In these studies, verbal consent was obtained from all study participants prior to data collection and study procedures. The studies described in this thesis did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

FAIR principles

Findable: Data were stored on the server of the research department at the Sint Maartenskliniek. The paper CRF files were stored at the research department and will be transferred to the department's archive after publication of the study. Data sets and documentation to describe the data sets can be found on the department's server at V:\research_reuma_studies.

Accessible: All data will be available on reasonable request by contacting the staff secretary of the research department at the Sint Maartenskliniek (secretariaat.research@maartenskliniek.nl) or the corresponding author.

Interoperable: Documentation was added to the data sets to make the data interpretable. The documentation contains links to publications, references to the location of data sets and description of the data sets. The data were stored in the following formats: .xlsx (Microsoft Office Excel), .dta and .do (STATA). Data from Chapter 2, 3, 4, 5 and 6 were converged to Microsoft Excel and STATA for analyses.

Reusable: The data will be saved for 15 years after termination of the study concerned. Using these patient data in future research is only possible after a renewed permission by the patients as recorded in their informed consents (if applicable).

Privacy

The privacy of the participants in this thesis has been warranted using encrypted and unique individual subject codes. The encryption key was stored separately from the research data and was only accessible to members of the project who needed access to it because of their role within the project.

PhD portfolio

Sint Maartenskliniek

Institute for Health Sciences
Radboudumc

Name PhD candidate: V.J.B.Huiskes	PhD-period:	2010 - 2021
Department: Pharmacy, Sint Maartenskliniek	Promotor(s):	Prof. dr. B.J.F. van den Bemt Prof. dr. D.M.Burger Prof. dr. Ir. C.E.M.J. van Dijk
Graduate school: Radboud Institute for Health Sciences	Co-promotor(s):	Dr. C.H.M. van den Ende

		Year(s)	ECTS
TRAINING ACTIVITIES			
a)	**Courses & Workshops**		
	Basic training epidemiology	2010	1.5
	Course clinimetrics – department of epidemiology & biostatistics VU medical centre	2011	0.75
	SIR masterclass pharmaceutical practical research	2010-2011	2.0
	SIR masterclass pharmaceutical practical research	2014-2015	1.25
	Course Introduction to data analysis	2015	0.75
	eBROK course	2020	1.5
	Scientific Integrity course	2021	1.0
b)	**Seminars & lectures^**		
c)	**Symposia & congresses^**		
	Prisma symposium, Amersfoort	2011	0.5
	ACR congress	2011	1.0
	40th European Symposium on Clinical Pharmacy, Dublin	2011	1.0
	41th European Symposium on Clinical Pharmacy, Barcelona (poster presentation)	2012	1.25
	Prisma symposium, Amersfoort	2013	0.5
	42nd European Symposium on Clinical Pharmacy, Prague	2013	1.0
	Regional meeting Dutch association for hospital pharmacists (oral presentation)	2013	0.5
	Dutch hospital pharmacy days (mini oral presentation)	2014	0.75
	43rd European Symposium on Clinical Pharmacy, Copenhagen	2014	1.0
	Annual European Congress of Rheumatology – EULAR (Rome)	2015	1.0
	PRISMA-symposium (oral presentation)	2015	0.75
	Dutch hospital pharmacy days (3x mini oral presentation)	2015	0.75
	45th European Symposium on Clinical Pharmacy, Oslo (poster presentation)	2016	1.25
	20th Annual meeting of the European Society for Patient Adherence, Compliance and Persistence, Lisbon	2016	0.5
	47th European Symposium on Clinical Pharmacy, Belfast (oral presentation)	2018	1.25
	Annual European Congress of Rheumatology – EULAR (Amsterdam)	2018	1.0
	48th European Symposium on Clinical Pharmacy, Ljubljana	2019	1.0
	23th Conference of European Society for Patient Adherence, Compliance and Persistence, Porto (oral presentation)	2019	1.25
	Dutch hospital pharmacy days (mini oral presentation)	2019	0.75
d)	**Other**		
	Co-author Drug-related problems in a clinical setting: a literature review and cross-sectional study evaluating factors to identify patients at risk; European Journal of Hospital Pharmacy	2015	0.25

	Co-author The medication therapy management pyramid shifting medication review to an integrated medication therapy management process; European Journal of Hospital Pharmacy	2015	0.25
	Co-author Open-label non-mandatory transitioning from originator etanercept to biosimilar SB4: 6-month results from a controlled cohort study; Arthritis & Rheumatology	2018	0.25
	Co-author Richtlijn polyfarmacie bij ouderen in de tweede lijn – federatie medisch specialisten	2018	0.75
	Co-author Patients with inflammatory rheumatic diseases: quality of self-reported medical information in a prospective cohort event monitoring system; Rheumatology	2019	0.25
	Co-author A comparison between medication reconciliation by a pharmacy technician and the use of an online personal health record by patients for identifying medication discrepancies in patients' drug lists	2020	0.25
TEACHING ACTIVITIES			
e)	**Lecturing**		
	Medication review – Dutch association for outpatient pharmacy	2009	0.5
	External assessor case reports medication evaluation Periodieke Individuele Analyse Farmacotherapie (PIAF)	2012-2014	2.5
	Base day medication evaluation – Dutch association for outpatient pharmacy	2015	0.25
	Medication verification & medication evaluation AIOS hospital pharmacy	2018	0.5
	Refresher courses for specialized nurses, nursing specialists and physician assistants: the medication overview and the role of the patient	2019	0.25
f)	**Supervision of internships / other**		
	Supervision of 7 master students Pharmacy (6 months)	2011-2019	12.25
	Supervision of 3 pharmacists enrolled in the post-graduate education program for becoming a specialized community pharmacist		6.0
TOTAL			**50.0**

^Indicate oral or poster presentation

Theses Sint Maartenskliniek

Alingh, J. (2021). *Effect of robotic gait training on the post-stroke gait pattern. Evaluation of LOPES II.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Dijsseldonk, R. (2021). *Step into the future: mobility after spinal cord injury*. Radboud University Nijmegen, Nijmegen, The Netherlands.

Pelle, T. (2021). *Beating osteoarthritis by e-self management in knee or hip osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Heuckelum, M (2020). *Novel approaches to improve medication adherence in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Mathijssen, E. (2020). *The voice of patients with rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bakker, S. (2019). *Regional anesthesia and total knee arthroplasty. Anesthetic and pharmacological considerations.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Claassen, A. (2019). *Strategies for patient education in rheumatic diseases.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Fenten, M. (2019). *Optimizing locoregional anesthesia in fast track orthopaedic surgery.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Minten, M. (2019). *On the role of inflammation and the value of low dose radiation therapy in osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Verhoef, L. (2019). *Effective and efficient use of bDMARDs in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bekker, C. (2018). *Sustainable use of medication. Medication waste and feasibility of redispensing.* Utrecht University, Utrecht. The Netherlands.

Bikker, I.(2018). *Organizing timely treatment in multi-disciplinary care.* University of Twente, The Netherlands.

Bouman, C. (2018). *Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors.* Radboud University Nijmegen, The Netherlands.

Mahler, E. (2018). *Contributors to the management of osteoarthritis.* Utrecht University, The Netherlands.

Tweehuysen, L. (2018). *Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning.* Radboud University Nijmegen, Nijmegen, The Netherlands.

Geerdink, Y. (2017). *Getting a grip on hand use in unilateral cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Remijn, L. (2017). *Mastication in children with cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

Selten, E. (2017). *Beliefs underlying treatment choices in osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

Van Hooff, M. (2017). *Towards a paradigm shift in chronic low back pain? Identification of patient profiles to guide treatment.* VU University Amsterdam, Amsterdam, The Netherlands.

Lesuis, N. (2016). *Quality of care in rheumatology. Translating evidence into practice.* Radboud University, Nijmegen, The Netherlands.

Luites, J. (2016). *Innovations in femoral tunnel positioning for anatomical ACL reconstruction.* Radboud University, Nijmegen, The Netherlands.

Pakvis, D. (2016). *Survival, primary stability and bone remodeling assessment of cementless sockets. An appraisal of Wolff's law in the acetabulum*. Radboud University, Nijmegen, The Netherlands.

Schoenmakers, K. (2016). *Prolongation of regional anesthesia. Determinants of peripheral nerve block duration.* Radboud University, Nijmegen, The Netherlands.

Altmann, V. (2015). *Impact of trunk impairment on activity limitation with a focus on wheelchair rugby.* Leuven University, Leuven, Belgium.

Bevers, K. (2015). *Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis.* Utrecht University, Utrecht, The Netherlands.

Cuperus, N. (2015). *Strategies to improve non-pharmacological care in generalized osteoarthritis.* Radboud University, Nijmegen, The Netherlands.

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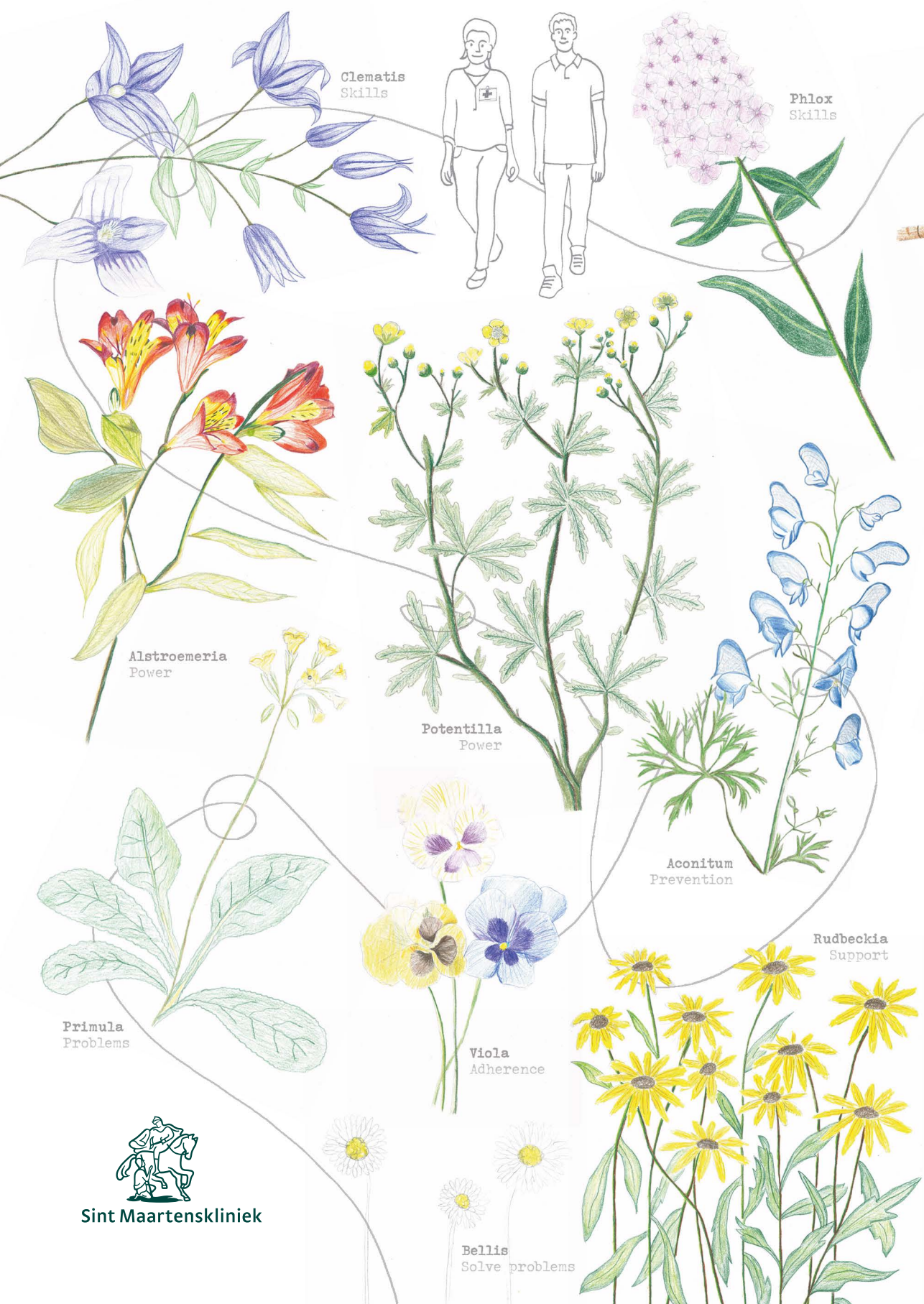

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