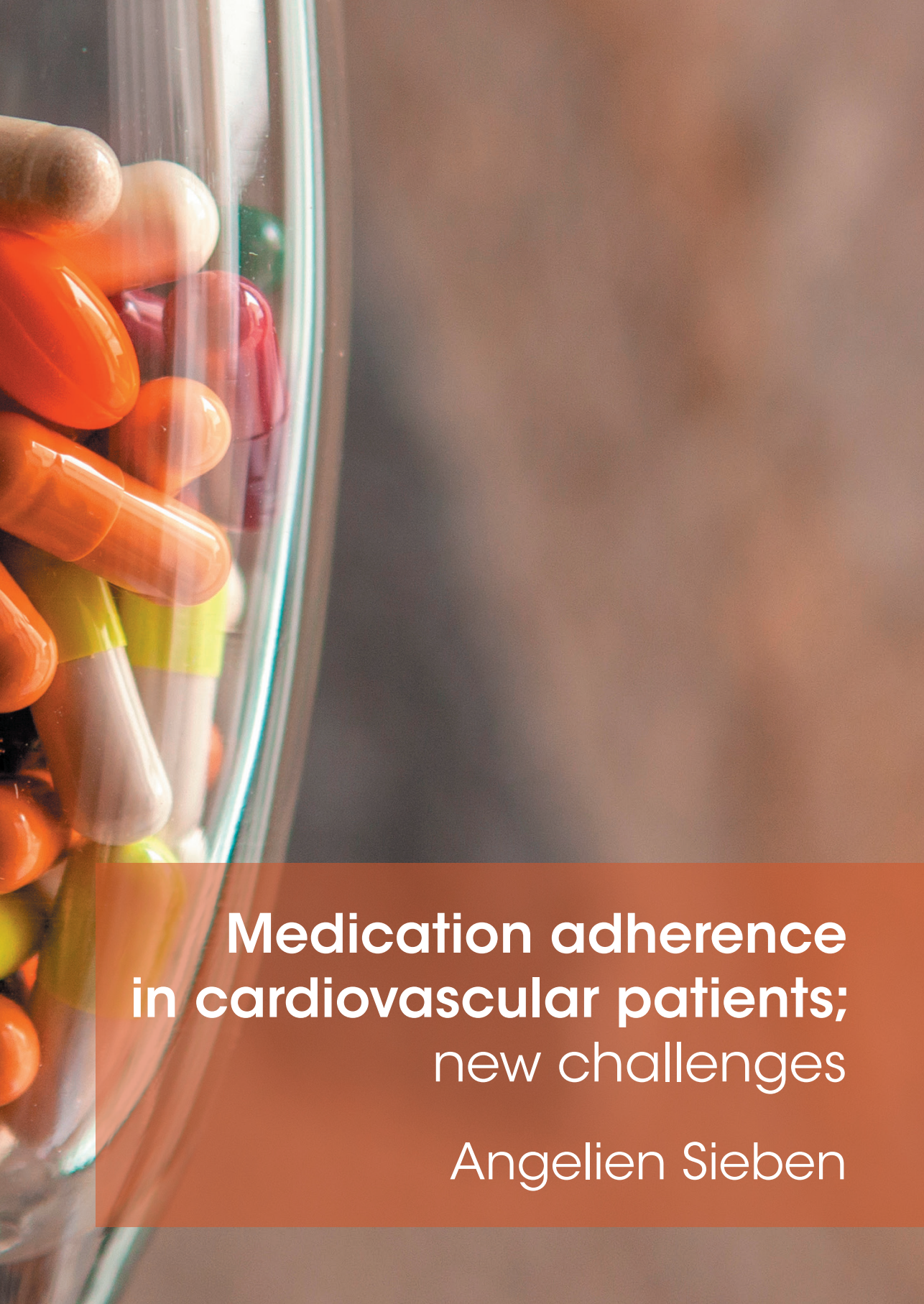

Medication adherence in cardiovascular patients; new challenges

Angelien Sieben

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Medication adherence in cardiovascular patients; new challenges

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"Let us never consider ourselves finished nurses….
we must be learning all of our lives."

– Florence Nightingale

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Chapter I

Introduction

Introduction

I Cardiovascular diseases

In this general introduction we provide information about the rationale of this PhD thesis followed by the general aim and main research questions and a description of the structure of the thesis.

I.1 Prevalence of cardiovascular diseases

Cardiovascular diseases (CVD), including ischemic heart disease, ischemic stroke, peripheral arterial disease and aortic aneurysm, remain a major cause of death worldwide. There are an estimated 422 million prevalent cases of CVD and 18 million people died from CVD (one-third of all deaths in 2015) globally, with projections showing an increase to 23.3 million in 2030.[1,2] In Europe alone, 4 million people died of CVD in 2015.[3] Twenty-five percent of these CVD events happen in individuals with a previously established CVD, and after initiation of cardiovascular risk management.[4] Factors associated with higher risk of recurrence include: older age, lower socio-economic status, presence of co-morbidities, and lack of adherence to secondary prevention medication.[2] Both acute interventions after an event and best medical treatment, including cardiovascular risk management, are important in improving the long-term outcome of hospitalized patients.[1]

I.2 Risk factors for cardiovascular diseases

Most CVD occur when an atherosclerotic plaque ruptures and a thrombus occludes the artery. Atherosclerosis is a process that develops slowly over many years [5], and is the result of multiple, interacting risk factors. These are the well-known risk factors as hypertension, dyslipidemia and diabetes, which in turn are influenced by behavioural factors such as smoking, sedentary lifestyle with low physical inactivity, and bad eating habits.[6] Although there has been continued research to other risk factors, the conventional risk factors still account for more than 90% of the attributable risk of CVD.[7] Reduced exposure to these risk factors has a significant impact on the occurrence and re-occurrence of a CVD.[8]

I.3 Management of cardiovascular risk reduction

According to the World Health Organization (WHO), effective reduction of cardiovascular morbidity and mortality should be based on three key points: surveillance (mapping and monitoring the epidemic of CVDs), prevention (reducing exposure to risk factors) and management (equitable health care for people with CVD).[9] This thesis focuses on the secondary prevention for patients with manifest CVD. Secondary prevention aims to reduce the impact of a disease that is already manifest and so prevent more severe problems. Cardiovascular secondary prevention aims to reduce the recurrence of cardiovascular disease and to improve long-term prognosis[10] Secondary

prevention in CVD is predominantly based on lipid and blood pressure lowering treatment, inhibition of platelet aggregation and lifestyle interventions on smoking behaviour and eating habits.[1] Applying the recommended guidelines for the secondary prevention of CVD has been estimated to be responsible for one-half of the overall 50% reduction in mortality in CVD over the past twenty years.[11] A prerequisite to achieve this reduction is that patients adhere to their prescribed medication. Medications do not work in patients who do not take them. This true statement highlights the importance of medication adherence.[12] Nevertheless, only 60% of people who use cardiovascular medication, are fully adherent to their cardiovascular medication.[13] About ten percent of all CVD events may even be attributed to poor adherence to medication alone.[13]

2 Medication adherence

2.1 Medication adherence

Medication adherence is defined by the WHO as 'the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider'.[9] Patients may be poor adherent during different stages of their treatment. They may decide not to collect their prescriptions at the pharmacy and/or not start their treatment at all. Patients may use the prescribed medication at the wrong time or in a wrong way. They may also discontinue treatment prematurely, especially when the underlying disease is asymptomatic.[14] Failure to comply with cardiovascular medication in the context of secondary preventive care in CVD results on average in worse outcomes after four years. [15] A large observational study in patients with established CVD showed that nonadherence with any of the cardiovascular medication is independently associated with an increased risk of adverse clinical outcomes including all-cause mortality and cardiovascular mortality.[15] Patients who were nonadherent to any evidence-based secondary prevention medication at 1-year follow-up demonstrated a 19% higher risk of cardiovascular death/myocardial infarction/stroke at 4 years compared to patients who were adherent. [15] High levels of adherence to statins (80% adherence levels or higher) are associated with reductions in all-cause mortality and fatal and nonfatal cardiovascular events.[16] To achieve full benefit of medication in cardiovascular patients, it is necessary to assure a lifelong adequate adherence to this treatment.

2.2 Determinants of medication adherence

Many studies have addressed the complexity of adequate adherence to treatment and tried to identify causal or related factors.[17] The WHO determined a conceptual framework containing five sets of determinants that influence nonadherence: social and economic-, health system-, condition-, therapy- and patient related determinants.[9] This thesis focuses mainly on the patient related determinants of nonadherence. These are potentially modifiable within the existing management of cardiovascular risk management (CVRM). Patient related determinants can be grouped into unintentional and intentional determinants. Regarding the intentional determinants,

there is an increasing recognition of patients' beliefs about their illness and treatment as determinants of adherence. Patients seek to balance perceived treatment necessity and concerns with a minimum use of prescribed medication. They then can make an active decision to be adherent or not.[17] This decision is evaluated by knowledge (or lack of) regarding prescribed medication and the effect on risk reduction, patients' beliefs, perception and management of their illness or medication. These beliefs are influenced by illness related factors as not accepting the illness or underestimating its severity.[18,19] Cardiovascular medication in particular may be perceived by patients as not providing benefit because they do not feel better by taking the drugs.[20] Also, past experiences, social and cultural norms, and received information from various sources can lead to doubts about the efficacy or necessity of the medication.[17,18,21,22]. Unintentional nonadherence can be determined by more practical barriers that prevent patients from following their decision to be adherent. These unintentional barriers can be related to cognitive problems (e.g. forgetting instructions or forgetting to the take medication) or more practical skills. These practical skills can relate to difficulties in opening medication containers or being unaware how to refill a prescription at the pharmacy (knowledge).[17] Of course, intentional and unintentional determinants can influence each other or be simultaneously present in an individual.[9]

2.3 Adherence enhancing interventions

There is substantial research in adherence-enhancing strategies. Most interventions have limited effect at best, are mostly complex and require significant investment due to the ongoing support of allied health professionals. They provide intensive training, counselling or daily treatment support (or both), sometimes with support from family or peers.[23,24] Consequently, implementation of these interventions into daily practice has not routinely taken place.[25] Evidence suggests that interventions should be based on patients' perspective, target patients' capacity and practical barriers, and address their beliefs and perceptions regarding illness and medication.[14,17] In CVD, life-long adherence is important, which implies that interventions should improve patients' intentions to take medication, as well as solve emergent practical barriers. To incorporate and address the different and complex determinants that lead to medication nonadherence, a theory that addresses behavioural change in general is often lacking.[26] However, to develop an intervention which can be effective in research and can be scaled into daily practice, there are some challenges to be met. These challenges for research in medication adherence are similar to those for the improvement of other health-related behaviours, such as smoking cessation, exercise and diet: how to influence and change behaviour of patients on a long-term basis. Interpreting research results on the effect of adherence-enhancing interventions is difficult because of the multi-faceted determinants which lead to nonadherent behaviour.[27,28] To interpret research results and scale them to daily practice interventions are likely to benefit from a taxonomy to categorize the used behaviour change techniques.[27] There is some specific guidance regarding research which evaluates (new) interventions to improve patient behaviour. A process evaluation is highly recommended because it helps to understand the relationship between how

well an intervention was delivered, the different elements of an intervention and the main outcomes of a trial.[29,30] It furthermore improves the validity and interpretation of these outcomes and gives information so the intervention can be replicated.[31]

2.4 Measurement of adherence

Another challenge in medication adherence is to make an accurate estimate of the degree of adherence of patients. There are many methods for measuring levels of medication adherence, but each method has its strengths and limitations. Currently none of the available methods can be considered as a gold standard and a combination of methods is recommended.[32] The methods used can roughly be divided into two groups: objective and subjective measurements. Pill counts, electronic monitoring, database analysis of pharmacy refill dates and biochemical measures are considered objective methods. Subjective measures involve those requiring provider's or patient's evaluation of their medication taking behaviour[33]. Self-reported questionnaires and assessments are two examples of subjective measurements. Patients' overestimation of their adherent behaviour to get approval from their healthcare provider is the main disadvantage of all tools. All methods are circumstantial and some are very expensive. Also, improved patient adherence around clinic visits is a well-known phenomenon when applying adherence measurements.[33] Ideally, patients should not be aware that their adherence is monitored which is impossible when using subjective measures.

3 Aim and outline of this thesis

3.1 Aim

The overall aim of this thesis was to develop and evaluate an intervention to enhance medication adherence in cardiovascular patients. The aim for the intervention was set for three levels; it should change patients' adherence behaviour, it should change patients' perceptions and beliefs and the intervention should successfully improve the clinical outcome by achieving target levels in cholesterol and blood pressure. An intervention to enhance medication adherence in CVD patients was developed.

3.2 Usual care and population

The existing cardiovascular risk management program was the starting point for our intervention. The Radboud university medical center applies a hospital-wide screening program on cardiovascular risk factors in patients with an established cardiovascular disease (acute coronary syndrome, peripheral arterial disease, an aneurysm of the aorta or stroke/TIA).[6] This screening program is situated at the cardiovascular outpatient clinics. Patients referred to the departments of Vascular Surgery, Neurology or Cardiology with a manifestation of CVD are included in the screening program. A cardiovascular risk profile is assessed including an automated lifestyle questionnaire[34], blood lipid levels, blood pressure, waist circumference, BMI, blood level of glucose and a family history for cardiovascular diseases. A multidisciplinary team proposes an integral individualized

plan of care based on this assessment. During follow-up, a nurse-led lifestyle intervention program, including a brief tailored behavioural feedback procedure is offered. This is in line with nurse coordinated programs which are recommended in the guideline on cardiovascular disease prevention. Also, the best medical treatment is offered.[6,35] This includes the prescription (or continuation) of plated aggregation inhibitors, antihypertension agents and lipid modifying agents.

3.3 Outline of the thesis

Chapter 2 describes the management of the cardiovascular risk screening at Radboud university medical center. In patients with established cardiovascular disease, a cardiovascular risk profile was assessed, and lifestyle was evaluated by using an automated questionnaire. A multidisciplinary team proposed an integral individualized plan of care based on these assessments. During follow-up, a nurse-led lifestyle intervention program and the best medical treatment were offered. The impact of this structured screening and nurse-based intervention on cardiovascular risk factors are evaluated in this chapter.

Chapter 3 provides an overview of available e-health interventions and the extent to which they can improve medication adherence. E-health interventions, health-related information and interventions that are supported by the internet, may have a positive effect on medication adherence. These interventions aim to bring about a positive change or to increase knowledge, awareness and understanding. This is done by offering health-related information and using internet-based interactive components.

Chapter 4 describes the rationale and design of the MIRROR-trial, a nurse- and web-based intervention to improve medication adherence. The theory used to develop the intervention is the Health Belief Model. Also, both intentional and non-intentional determinants of nonadherence are considered in the development of the intervention.

In chapter 5 the process and effect of a nurse-led, web-based intervention to improve medication adherence in patients with cardiovascular disease are evaluated. This intervention program aimed to improve patient's necessity beliefs about medication, which is expected to lead to better adherent behaviour in cardiovascular patients. A process evaluation of this intervention program was also included. A process evaluation helps to understand the relationship between how well an intervention was delivered, the different elements of an intervention and the main outcomes of the trial. It furthermore improves the validity and interpretation of these outcomes and gives information, so the intervention can be replicated.

Chapter 6 describes in a retrospective cohort study the existing levels of medication adherence of participants and non-participants prior to inclusion in a randomized controlled study. It is suggested that patient recruitment methods in randomized controlled trials (RCTs) to improve patient adherence to medication may influence outcome. An important observation is that patients participating in RCTs generally

have higher adherence rates at baseline than could be expected based on observational studies. In this study we evaluated this hypothesis.

In chapter 7 a cluster analysis was performed. By combining and clustering well-known risk factors of CVD (such as high blood pressure, high cholesterol levels and an unhealthy life style), patient groups who are at risk of non-adherent behaviour, might be better determined. Identifying these high risk groups could enable developing an intervention and target patients more appropriately

The thesis concludes with a summary and an overall discussion of the findings and its implications.

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2

Chapter 2

A Nurse-Led Multidisciplinary Intervention to Improve Cardiovascular Disease Profile of Patients

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Abstract

The aim of this study was to evaluate the impact of a structured screening and nurse-based intervention on cardiovascular risk factors. In patients with established cardiovascular disease, a cardiovascular risk profile was assessed, and lifestyle was evaluated by using an automated questionnaire. A multidisciplinary team proposed an integral individualized plan of care on the basis of these assessments. During follow-up, a nurse-led lifestyle intervention program and the best medical treatment were offered. A total of 328 outpatients were included. After screening, a follow-up term of at least 1 year was reached in 176 patients (59.9%). Low-density lipoprotein cholesterol and systolic blood pressure were significantly reduced. A reduction in the amount of smoking, alcohol consumption, and unhealthy eating habits was observed. However, the amount of physical activity was unaffected, and body mass was increased. A structural evaluation of cardiovascular risk factors and an integrated nurse-led approach can successfully reduce risk in cardiovascular patients.

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the Netherlands and other industrialized countries and is taking the lead in developing countries.[1] In 2013, 39,000 Dutch people died because of CVD, which is almost one third of the total mortality.[2] Most CVD occurs in the presence of well-known risk factors, including hypertension, dyslipidemia, and type 2 diabetes, which in turn are influenced by behavioral factors such as smoking, alcohol consumption, physical activity, and eating habits. [3] Early recognition and treatment of these risk factors reduce the morbidity and mortality of any cardiovascular event and improves the short- and long-term preventive effects of conservative and interventional treatment.[3] Thus, cardiovascular risk management, including interventions on lifestyle, can enhance the prognosis of CVD.[4] Health care professionals, such as nurses, are increasingly more involved in executing cardiovascular prevention protocols and advising patients to improve their lifestyle behavior. Although the role of nursing professionals in improving lifestyle is less-clearly defined, there is reasonable evidence that smoking cessation advice and/or counseling given by nurses to patients can be effective. Suggested success rates range from 5% to 29% in the general population.[5]

Lifestyle behavioral interventions are not routinely monitored as part of standard outpatient practices. Not all patients are asked about their tobacco and alcohol use, nutritional habits, and physical activity level, nor are patients given advice and counseling, combined with reinforcement and structured follow-up, to incorporate behavioral lifestyle changes. Recently, we introduced a structured lifestyle inventory with a brief individually tailored behavioral feedback procedure as part of usual care for patients with manifest CVD or elevated cardiovascular risk.[6] This is in line with nurse-coordinated programs which are also recommended in the latest European Society of Cardiology (ESC) guideline on cardiovascular prevention.[7] However, we focus on a broader patient population than only coronary patients, targeting multiple risk factors. Previous research has measured the combined impact of lifestyle factors on CVD and indicated that even modest differences in lifestyle can have a substantial impact on reducing mortality.[8,9] However, changing cardiovascular risk in the long term has been shown difficult.[10] In addition, it is necessary to understand the effect of an intervention on various risk factors, including lifestyle behavior, to prioritize clinical health efforts.

This study was performed to evaluate the magnitude of change in various modifiable cardiovascular risk factors, such as body mass index, waist, blood pressure, lipid levels, and lifestyle parameters, during short- and long-term follow-up, in an outpatient population presenting with CVD. This was accomplished by an implemented multidisciplinary approach of cardiovascular risk reduction based on the Dutch guidelines for cardiovascular risk management.[11]

Method

Patients

Patients above the age of 18, who were referred with a manifest atherosclerotic vascular diseases (cardiac, cerebral, or peripheral diseases) to one of the participating departments (i.e., Cardiology, General Internal Medicine, Neurology, or Vascular Surgery) of our hospital, routinely participated in an outpatient care program, if their physical and mental state allowed. This care program, in which cardiovascular risk factors and lifestyle factors were evaluated on a structural basis, was led by specialized nurses (nurse practitioners), and patients immediately followed this program after hospitalization due to a cardiovascular event.

The changes in observed risk factors (including lifestyle) of these patients were retrospectively evaluated. From January 2010, consecutive patients were enrolled in this evaluation until a predefined number of 110 patients per department was achieved. Patients presenting with only an elevated risk for CVD but without manifestation of CVD (primary prevention) did not participate in this study. Furthermore, patients with missing baseline values were excluded from further analysis. Informed, written consent was obtained from all patients who visited the university hospital outpatient clinic regarding the use of their data for retrospective analysis of regular care outcome.

Risk Profile Identification

At baseline (before the intervention), a complete vascular risk profile of each patient was conducted by a nurse practitioners, all of which have extensive experience (more than 3 years) with Cardiovascular risk management (CVRM). Data were collected using a structured overall questionnaire, which consisted of information on general sociodemographic factors, anthropometric variables, lifestyle habits, a problem-oriented medical his- tory, drugs therapy, and family history of CVD (first degree relatives). In addition, anthropometry (body mass index [BMI], waist circumference) and a standard physical exam were performed, in which systolic and diastolic blood pressure was recorded as a mean of three measurements with an automatic blood pressure monitor in sitting position after 5 min of rest.[12] Furthermore, fasting glucose and lipid profiles, creatinine level and urine analysis, as well as electrocardiography were routinely performed.

After collecting and storing all data in an electronic patient file, a dedicated Multidisciplinary Advice Group, consisting of an internist and a cardiologist, and four nurse practitioners from participating departments (Neurology, Cardiology, Vascular Surgery, and Internal Medicine), dis- cussed these data weekly to optimize secondary prevention. Finally, a team- wise integral recommendation was proposed to reduce the amendable risk factors and lifestyle factors corresponding to the Dutch guideline for cardio- vascular risk management.[11,12]

Results from the Multidisciplinary Advice Group were reported back to the patient, after which interventions were planned (Figure 1). Finally, an individually tailored treatment plan, combining both medical treatment and lifestyle interventions, was initiated.

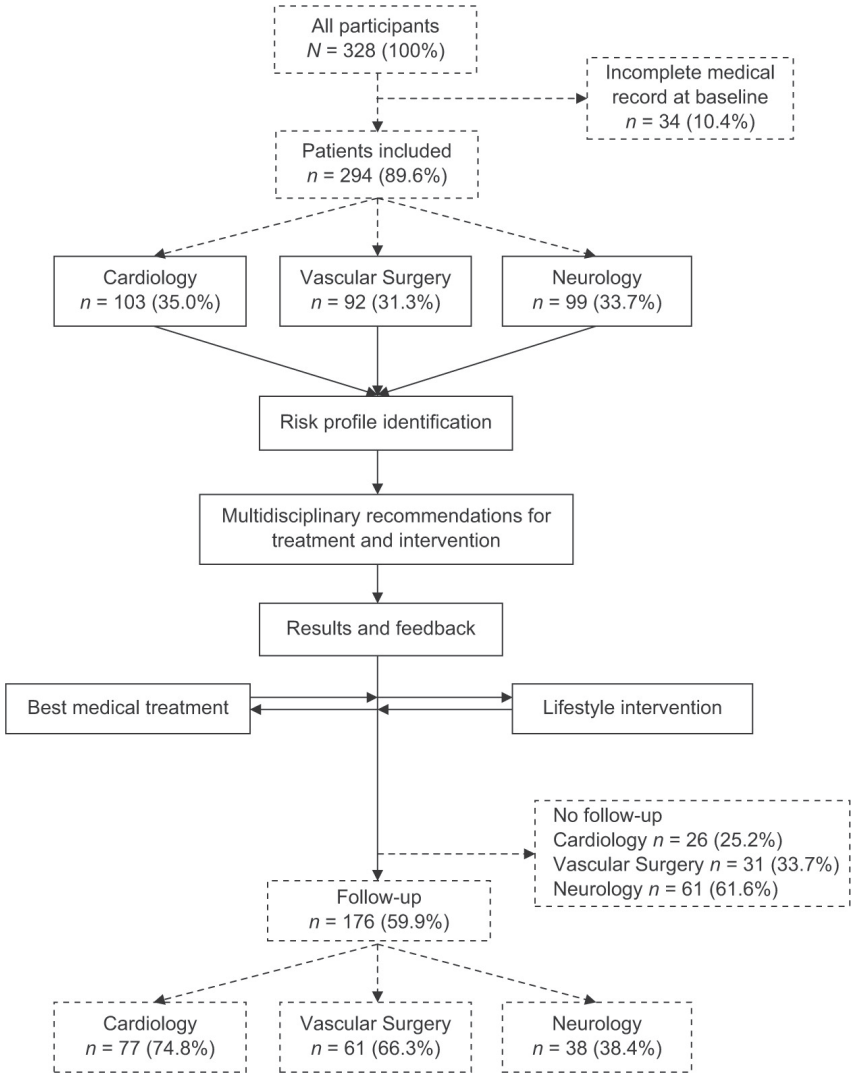

Figure 1. Organogram the Vascular Centre of the Radboud University Medical Centre (solid lines), in which the flow of included patients and numbers of follow- up are depicted (dotted lines).

Lifestyle Questionnaire

The lifestyle of each patient was evaluated using an online lifestyle questionnaire, which was also available for patients to use at the outpatient clinic, and comprised a compilation of existing validated questionnaires regarding smoking, physical activity, eating habits, and alcohol consumption.[13] The questionnaire consisted of the following sections:

A total of 11 questions were asked about smoking. Five general questions regarding pack per year, mean number of cigarettes, and type of tobacco smoked as well as six items of the Fragerström Test for Nicotine Dependence to evaluate the degree of nicotine dependency of each patient.[14]

Seven questions about habitual physical activity were asked, including intensity and frequency of physical activity per week. The questions were consistent with the short version of the International Physical Activity Questionnaire.[15]

A total of 28 questions about eating habits were asked, using three separate questionnaires, which were validated in a Dutch eating habit study concerning fat, fiber, vegetable, and fruit intake.[16] Fourteen questions evaluated total and saturated fat intake as a percentage of total energy intake, eight questions measured fiber intake in grams per kilocalorie, and six questions measured vegetables and fruit intake in grams per day.

Ten questions about alcohol drinking behavior were asked using the Alcohol Use Disorders Identification Tests (AUDIT).[17] The AUDIT measured the frequency, quantity, and psychosocial problems concerning alcohol consumption. Three questions were regarding frequency and amount of alcohol consumption, three regarding alcohol dependency, and four regarding possible psychosocial problems.

The automated questionnaire generated a summary of lifestyle issues, which were visualized in smileys. A green, orange, and red smiley referred to a healthy, a not really harmful but could be improved, and an unhealthy life- style, respectively.

Nurse-Led Intervention Program

After feedback of the screening results was provided to the patient, best medical treatment and a lifestyle intervention program to reduce smoking, alcohol use, body weight, or to increase healthy nutrition could be initiated and conducted by a nurse practitioner of each department using hospital proto- cols. An individual care plan including information of the intervention steps was available online for patients and nurses via an electronic interactive file, integrated in the hospital website.

Best medical treatment was tailored by the nurse practitioner to the patient clinical situation. In general, in all patients, not on oral anticoagulant therapy or platelet aggregation inhibitors, for example, acetylsalicylic acid 80 mg once daily (o.d.) was

initiated. Furthermore, a statin-based cholesterol lowering therapy was initiated (simvastatin 40 mg o.d. or atorvastatin 20 to 80 mg o.d.), or the statin dosage was adjusted in case of preexisting us. Also angiotensin converting enzym (ACE) inhibitor (lisinopril 5-10 mg o.d.), or thiazide diuretic–based (chlortalidone 12.5-25 mg o.d.) blood pressure lowering medication was started when systolic blood pressure was on average above 140 mmHg after the standardized measurement. Medication was adapted by the internist and cardiologist in case of side effects, in elderly age, or with preexisting hypertension, or existing vascular complication, for example, carotid stenosis, or renal artery stenosis. The treatment targets to be achieved during follow-up for low-density lipoprotein (LDL) cholesterol was 2.5 mmol/l and for blood pressure 140/90 mmHg.

In case of smoking, excessive alcohol consumption, lack of exercise, or an unhealthy diet or obesity, a nurse-led lifestyle intervention program was initiated based on motivational interviewing according to Prochaska and DiClemente's Transtheoretical Model [18], matched with the determined readiness for behavioral change. [19] All nurse practitioners have followed at least 10 training sessions in motivational interviewing and continued to increase their skills by discussing results together. Nurse practitioners could start their intervention by using the visualized screening results, including motivation to change scores. An intervention lasted 3 months and individual care plan and obtained results were structured recorded in the patient record. The intervention targets to be achieved during follow-up are "nonsmoking," "alcohol intake below 3 (for men) and 2 (for women) standardized units daily for 5 days or less a week," "at least 30 min of moderate exercise per day" and "a diet with less than 35% of the total caloric intake as fat; more than 3 g of fiber per day; more than 200 g of vegetables per day and at least 2 servings of fruit per day."

Feedback of the screening results was provided during a 1-hr visit, after which an intervention was performed during 3 to 4 follow-up visits of 30 to 45 min. In individual cases, additional visits of 30 min were scheduled for additional support. In case of extended follow-up due to complex care (e.g., follow-up of an growing abdominal aneurysm), CVRM was combined with regular care for these presenting CVDs. Cardiovascular risk management was transferred back to first line care (i.e., general practitioner) as soon as possible after treatment and lifestyle intervention were initiated, except for patients who needed a follow-up for their actual CVD or those with complex cardiovascular risk profiles, who did not reach the predefined target values.

Follow-Up

After the initial treatment of the presenting vascular disease, a patient's follow-up was determined by the severity of their clinical symptoms. Generally, a follow-up was terminated after 3 months, after which patients were referred to their general practitioner. Only in a situation of complex care it was continued for a longer period. In this study, only patients with follow-up period for at least 9 months were included. BMI, waist circumference, blood pressure, and LDL-cholesterol were monitored during each face-

to-face follow- up visit and evaluated at 3 to 6 months (short-term follow-up) and after 9 to 15 months (long-term follow-up). In contrast to the initial data collection, in which data were obtained using a lifestyle questionnaire, follow-up data were collected from each individual patient file using predefined parameters, namely, smoking habits, alcohol use, physical activity, eating habits, LDL- cholesterol, systolic blood pressure, BMI, and waist circumference. When lifestyle changes or risk factor reductions were not recorded, these data were defined as missing values.

Data Analysis

Statistical analyses were performed using SPSS (version 18.0). Differences in parameters between specialties were tested by univariate ANOVA test. The effect of interventions on risk factors (follow-up vs. baseline) was tested by a paired *t* test, or chi-square test in case of normal distribution, or non parametric tests (Wilcoxon signed rank test), in case of skewed distribution. For evaluation of the effects of the intervention on alcohol use, physical activity and eating habits, the number of patients in the healthy category were compared with the sum of patients in the "could be improved" category and "unhealthy" category. Alpha was set at the 0.05 level for all statistical comparisons , with data reported as means and standard errors of the means (±), unless stated otherwise as standard deviation (*SD*).

Outcomes

Patients. From January 2010 until July 2010, 328 patients who were referred to the Radboud University Medical Centre were included in this analysis (Figure 1). Out of these patients, 34 were excluded due to missing values at the start of the study (i.e., baseline). A follow-up of at least 3 months till a maximum of 15 months after inclusion into this study was performed for 59.9% of the total patient population (N = 294). Therefore, 176 follow-up data were available for analyses. At the department of cardiology, a total of 103 patients were included, of which 74.8% had a follow-up longer than 3 months. Similar results were observed at the department of vascular surgery and neurology, where, respectively, 92 and 99 patients were included, of which 66.3% and 38.4% had a follow-up longer than 3 months through the outpatient clinic (Figure 1). In 40.1% of the total study population, no follow- up was achieved, primarily due to patient referral back to either a general practitioner or primary hospital after the treatment of the cardiovascular event (~70%). In addition, 10.0% of the patients did not meet the predefined inclusion window for follow-up (3-15 months), predominantly caused by the course of their vascular disease. About 13% of the patients refused interventions and follow-up, and in about 7% of the patients, follow-up data were incomplete.

Baseline characteristics. Tables 1 and 2 represent the baseline characteristics for the total study population and for each department separately. It illustrates the large number of patients who did not meet the recommended level of risk factors according to the Dutch guideline at baseline, that is, before commencing their individual health program. In this patient population, 65.0% were male, with a mean age of 65.1 ± 11.9 years. Furthermore,

29.3% of the patients were regular smokers and 15.6% consumed unhealthy amounts of alcohol prior to the intervention. The average value of the Fragerström test score for nicotine dependence was 3.1 ± 2.6 for the total population and 2.0 ± 2.6, 4.0 ± 2.2 and 3.3 ± 2.5 for cardiology, vascular surgery, and neurology, respectively. In addition, 39.8% of the population performed less than aver- age amounts of physical activity and 19.5% had unhealthy eating habits. BMI ≥ 25 kg/m2 or a waist circumference ≥ 94 cm (males) or ≥ 88 cm (females) was observed in the 55.7% and 31.2% of patients, indicating that most patients were overweight. Furthermore, high systolic blood pressure (³140 mmHg) as well as a high LDL-cholesterol level (≥ 2.5 mmol/L) was observed in 41.8% and 41.8% of the patients (Table 1).

Table 1. Baseline Characteristics of the Study Population.

	Total group	**Cardiology**	**Vascular Surgery**	**Neurology**	**Differences Between Specialism[a]**
	N = 294 (100%)	*n* = 103 (35.0%)	*n* = 92 (31.3%)	*n* = 99 (33.7%)	
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Male gender	191 (65.0)	76 (73.8)	63 (68.5)	53 (53.5)	<.001
Smoking habits					
Actual smoking	86 (29.3)	23 (22.3)	51 (55.4)	12 (12.1)	<.001
Nonsmoking	208 (70.7)	80 (77.7)	41 (44.6)	87 (87.9)	
Alcohol use					
Healthy	191 (65.0)	61 (59.2)	51 (57.3)	79 (79.8)	<.001
Could be improved	57 (19.4)	22 (21.4)	21 (22.8)	15 (15.2)	
Unhealthy	46 (15.6)	20 (19.4)	20 (21.7)	5 (5.1)	
Physical activity					
Healthy	145 (49.3)	62 (60.2)	42 (45.7)	41 (41.4)	.09
Could be improved	32 (10.9)	5 (4.9)	13 (14.1)	14 (14.1)	
Unhealthy	117 (39.8)	37 (35.9)	37 (40.2)	44 (44.4)	
Eating habits					
Healthy	13 (4.4)	4 (3.9)	5 (5.4)	4 (4.1)	n.s.
Could be improved	223 (76.1)	73 (70.9)	73 (79.3)	78 (78.6)	
Unhealthy	57 (19.5)	26 (25.2)	14 (15.2)	17 (17.3)	

Note. n.s. = not significant.
a. One way ANOVA.

Table 2. Baseline Characteristics of the Study Population.

	Total group		**Cardiology**		**Vascular Surgery**		**Neurology**		***p* Value for**
	N = 294 (100%)		*n* = 103 (35.0%)		*n* = 92 (31.3%)		*n* = 99 (33.7%)		Differences Between
	M ± *SD*	*n* (%)	*M* ± *SD*	*n* (%)	*M* ± *SD*	*n* (%)	*M* ± *SD*	*n* (%)	Specialism[a]
Age[b]	63.2 ± 11.9		59.4 ± 10.8		65.0 ± 10.6		65.3 ± 13.4		<.001
Male gender		191 (65.0)		76 (73.8)		63 (68.5)		53 (53.5)	<.001
LDL-cholesterol[c]	2.51 ± 0.84		2.26 ± 0.69		2.90 ± 0.97		2.41 ± 0.73		<.001
<2.5 mmol/L		171 (58.2)		68 (66.1)		33 (35.9)		69 (69.7)	
³2.5 mmol/L		123 (41.8)		35 (33.9)		59 (64.1)		30 (30.3)	
Systolic BPd	138.3 ± 20.7		131.6 ±21.3		146.6 ±19.3		137.3 ± 18.5		<.001
<140 mmHg		171 (58.2)		72 (70.0)		35 (38.0)		65 (65.7)	
³140 mmHg		123 (41.8)		31 (30.0)		57 (62.0)		34 (34.3)	
Body mass index[e]	26.6 ± 4.5		27.3 ± 4.8		25.8 ± 4.6		26.8 ± 4.1		n.s.
<25 kg/m²		130 (44.3)		42 (40.8)		24 (26.1)		41 (41.4)	
³25 kg/m²		164 (55.7)		61 (59.2)		68 (73.9)		58 (58.6)	
Waist circumference[f]	97.4 ± 13.3		100.7 ±13.2		97.1 ± 13.1		94.2 ± 12.8		.002
<80 cm/94 cm[g]		92 (31.2)		25 (24.3)		29 (31.5)		37 (37.4)	
≥80 cm/94 cm[g]		202 (68.8)		78 (75.7)		63 (68.5)		63 (62.6)	

Note. LDL = low-density lipoprotein; BP = blood pressure; n.s. = not significant.
a. One-way ANOVA.
b. In years.
c. In mmol/L.
d. In mmHg.
e. In kg/m².
f. In cm.
g. 80 cm for females/94 cm for males.

Table 3. Results of Cardiovascular Risk Management in Patients With Short- and Long-Term Follow-Up.

	Baseline	**After Short-Term Follow-Up**	**Absolute**		**After Long-Term Follow-Up**	**Absolute**	
	(*N* = 294)	(*n* = 176)	Change		(*n* = 176)	Change	
	n (%)	%	%	*p* Value	%	%	*p* Value
Smoking habits							
Nonsmoking	208 (70.7)	71.2	+0.5	n.s.	77.4	+6.7	<.0001
Smoking	86 (29.3)	28.8			22.6		
Alcohol use							
Healthy[a]	191 (65.0)	71.9	+6.9	.002	76.7	+11.7	<.0001
Could be improved	57 (19.4)	18.0			13.7		
Unhealthy	46 (15.6)	10.1			9.6		
Physical activity[b]							
Healthy[c]	145 (49.3)	53.6	+4.3	n.s.	45.2	–4.1	n.s.
Could be improved	32 (10.9)	33.0			44.0		
Unhealthy	117 (39.8)	13.4			10.7		
Eating habits[d]							
Healthy[e]	13 (4.4)	64.2	+59.8	<.0001	85.7	+81.3	<.0001
Could be improved	223 (76.1)	34.6			11.1		
Unhealthy	57 (19.5)	1.2			3.2		

Note. n.s. = not significant.

a. Alcohol intake below 3 (for men) and 2 (for women) standardized units daily for 5 days or less a week.

b. Results obtained in *n* = 175 patients.

c. At least 30 min of moderate exercise per day.

d. Results obtained in *n* = 159 patients.

e. Diet with less than 35% of the total caloric intake as fat; more than 3 g of fiber per day; more than 200 g of vegetables per day and at least 2 servings of fruit per day.

Follow-up. After receiving individually tailored recommendations and life- style interventions during follow-up, the amount of smokers was reduced from 51 to 40 of 176 patients with follow-up (–6.7%; p < .0001; Table 3). The number of patients who reduced their alcohol consumption to the recommended standards increased from 114 to 135 of 176 patients (–11.7%; p <.0001). Healthy physical activity, however, decreased from 86 to 79 of 175 patients on a recommended level (–4.1%; not significant). Most patients adjusted their eating habits to a healthy standard (from 7 to 129 of 159 patients (+81.3%; p < .0001). In addition, a significant reduction in systolic blood pressure (138.3 ± 20.7 mmHg to 128.7 ± 17.7 mmHg; p < .01) and LDL-cholesterol level (2.55 ± 0.87 mmol/L to 2.16 ± 0.73 mmol/L; p < .01) was observed after follow-up. However, toward the end of the follow-up, less patients were physically active, and consequently, waist circumference increased from 97.4 ± 13.3 to 98.5 ± 12.8 cm and BMI from 26.6 ± 4.5 to 27.5 ± 4.8 kg/m^2; p = .01, after the lifestyle intervention program (Table 4).

Discussion

This study demonstrated that CVD occurs in the presence of multiple risk factors, including behavioral risk factors, in almost all patients who were referred with a manifest CVD at the Radboud University Medical Centre. Structural multidisciplinary evaluation and initiation of the best medical treatment in combination with lifestyle interventions decreased cardiovascular risk as seen by a reduction in smoking, alcohol consumption, unhealthy eating, blood pressure, and LDL-cholesterol level. However, physical activity level decreased and BMI increased in this patient population.

The magnitude of present risk factors in this population is comparable with previous studies in patients as well as with the general Dutch population. [2] In 2010, approximately 27% of the Dutch population were tobacco smokers, 16% regularly consumed unhealthy amounts of alcohol, 44% performed inadequate amounts of physical activity, 42% was over- weight, and a majority did not meet the guidelines for healthy eating habits. However, less is known about more relevant accumulation of risk factors in individual vascular patients compared with the general population.

Health care strategies often fail to achieve optimal risk reduction and treatment goals are frequently not reached.[20] However, our results showed risk factor cessation or reduction after a strategy of structural screening for complete cardiovascular risk, receiving multidisciplinary recommendations for medication and lifestyle changes, and structural feedback on these results by a professional. The observed changes in lifestyle and cardiovascular risk pro- file were similar to those of a previously reported integral approach in vascular patients [21], with a moderately more pronounced effect on systolic blood pressure in the current study. Characteristics of both approaches were sufficient attention to lifestyle habits and unequivocal advice from health care professionals, in accordance to the patient's acceptance of responsibility for their own care. Furthermore, we applied a stepped care approach, which has been recently proved to have the ability to greater lifestyle behavioral outcomes compared with care as usual.[22] Encouragement and an accurate, systematic evaluation or follow-up of behavioral change by professionals has been indicated to reduce the risk for CVD and to enhance the quality of life.[23]

Table 4. Results of Cardiovascular Risk Management in Patients After Short- and Long-Term Follow-Up.

	Baseline (*N* = 294)		**After Short-Term Follow-Up (*n* = 176)**		**Absolute Change**		**After Long-Term Follow-Up (*n* = 176)**		**Absolute Change**	
	M ± *SD*	%	*M* ± *SD*	%	%	*p* Value	*M* ± *SD*	%	%	*p* Value
LDL-cholesterol[a]	2.51 ± 0.84		2.44 ± 0.82			<.0001	2.16 ± 0.73			.006
<2.5 mmol/L		58.3		64.9	+6.6			80.4	+22.1	
³2.5 mmol/L		41.7		35.1				19.6		
Systolic BP[b]	138.3 ± 20.7		129.5 ± 19.2			<.0001	128.7 ± 17.7			<.0001
<140 mmHg		58.2		77.6	+19.4			77.2	+19.0	
³140 mmHg		41.8		22.4				22.8		
Body mass index[c]	26.6 ± 4.5		28.3 ± 4.4			n.s.	27.5 ± 4.8			.01
<25 kg/m²		44.4		21.5	−22.9			31.0	−13.4	
³25 kg/m²		55.6		78.5				69.0		
Waist circumference[d]	97.4 ± 13.3		98.9 ± 12.3			.002	98.5 ± 12.8			.02
<80 cm/94 cm[e]		31.2		28.8	−2.9			30.6	−1.4	
≥80 cm/94 cm[e]		68.8		71.2				69.4		

Note. LDL = low-density lipoprotein; n.s. = not significant.
a. In mmol/L.
b. BP = blood pressure in mmHg.
c. In kg/m².
d. In cm.
e. 80 cm for females/94 cm for males.

Integral nurse-led risk reduction may be more successful than an approach of risk factors isolated from presenting CVD. Personalized treatment, such as individualized treatment plans, has shown that they can tailor the nurses' care to the patients sufficiently.[24] Furthermore, nurse- led interventions on lifestyle may be more efficient than interventions by physicians.[21] Although the role of nursing professionals in smoking cessation is less-clearly defined, there is reasonable evidence that smoking cessation advice and/or counseling given by nurses to patients can be effective. Suggested success rates range from 5% to 29% in the general population.[5,25] Previously, it was demonstrated that the feasibility and effectiveness of nurse-based motivational interviewing on top of routine patient-based lifestyle inventory with feedback was beneficial.[19] In this study, 16% of all included smokers refrained from smoking after 3 months follow-up. The absolute reduction in smoking appeared 6.7% after a longer follow-up period in the current study (relative risk reduction was 22.9%).

Besides effectiveness on smoking cessation, there is also evidence that nurse-based risk factor management leads to frequent achievement of treatment goals for different risk factors, for example, lifestyle factors other than smoking, such as blood pressure and LDL-cholesterol.[26] For example, in this study, alcohol consumption was reduced, and more patients met the criteria for healthy alcohol consumption. Compared with other studies, this result is more pronounced.[27] Next to this, a substantial enhancement in healthy eating habits was also observed in this study. This could be explained by a lack of knowledge about unhealthy habits. Moreover, the eating habits of majority of patients were easily improved by making small adjustments. Blood pressure and lipid level were also improved after the best medical treatment and lifestyle interventions in accordance with general expectations after initiating drug treatment.[28] Furthermore, interventions addressing diet, exercise, and smoking have additional effects on blood pressure and lipid level.[29] Matching the stage of behavioral change of patients with the planned intervention seems crucial to improve its success.[30]

Waist circumference and BMI did not improve after intensive follow-up. This result could be explained by the reduction in physical activity observed after follow-up, potentially caused by the inability of patients to exercise after manifestation of the CVD. For example, after a stroke, more than 80% of patients suffer one or more paralyses and more than 70% of patients are affected by chronic fatigue. Furthermore, it is well known that patients indicate different levels of performance they believe they can surmount and there is an underestimation of the difficulty of self-management of behavioral risk.[31] Therefore, physical activity needs to be mitigated by appropriate preparticipation screening, patient counseling, and a gradual, staged approach to an exercise program to gain the best result.[32]

An increase in waist circumference and BMI during follow-up was also observed by Goessens et al.[26], which was attributed to weight gain after smoking cessation and increased inactivity after cardiovascular event. Individuals who successfully quit smoking

typically gain between 3 and 10 kg within 8 years of quitting, whereas those who continue to smoke gain an average of 2 to 3 kg.[33,34] Furthermore, intervention based on motivational interviewing may be less sufficient to obtain weight reduction, and participation in specific behavioral therapy may be necessary to establish a reduction in weight. [33,35] Remarkable differences between participating departments were observed, with, in general, a more pronounced cardiovascular risk in patients from vascular surgery, compared with other vascular patients. Most likely patients with peripheral arterial diseases with an increased comorbidity burden often have a lower socioeconomic status.[36,37] Furthermore, patients with acute coronary syndrome were younger, whereas patients with Transient Ischemic Accident (TIA) or stroke were older than the mean age of the study population.

A potential limitation of this study was the lack of a control population without CVD undergoing the same intervention. In addition, this study was restricted in that changes from baseline could only be evaluated during follow-up in those patients who had their follow-up at the outpatient clinic. These were patients with, in general, more complex morbidity, predominantly in patients of cardiology and vascular surgery in which a longer follow-up was indicated. Patients from neurology could be more frequently referred back to their general practitioner within 3 months. It is currently unclear whether these patients also differed from cardiovascular risk or motivation to change behavior. Furthermore, no comparisons within patients could be made from results obtained by their general practitioner. However, cardiovascular risk management in primary care showed wide variation within and between countries and the effects of a 1-year intensive intervention for cardiovascular prevention could no longer be demonstrated after a long-term follow-up.[10,38]

Finally, the possibility exists that the observed results were less pronounced because a majority of the patients already used risk lowering medication after advice from their general practitioner. This study demonstrated that structural screening of risk factors in patients who were referred with a manifest CVD shows unfavorable cardiovascular risk profile and lifestyle in majority of the patients. A multidisciplinary integrated approach, with interventions by dedicated nurses, may be successful in improving cardiovascular risk profile, including lifestyle, in outpatients with different clinical presentations of vascular disease.

Declaration of Conflicting Interests

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3

Chapter 3

E-health interventions and improving therapy compliance

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Introduction

Reduced compliance with medication therapy is one of the most important determinants in the treatment of patients with chronic disorders and asymptomatic disorders in particular. According to the World Health Organization, 30-50% of patients do not take their medications or do not use them as prescribed.[1] This can lead to hospital admissions, disease progression, resistance to treatment, failure to achieve treatment goals and death.[2-4] Therefore, interventions that can improve patient therapy compliance are urgently needed.

In recent years, much research has been conducted into the effect of interventions with the aim of improving therapy compliance. These interventions include additional consultations with and information from pharmacists, group meetings with other patients focusing on information and education, and reward systems such as gift vouchers in response to verified therapy compliance. However, these interventions appear to be effective only in the short term. Moreover, the interventions are often complex, and that is one of the reasons why they are difficult to implement in daily practice.

Interventions that are supported by the internet, known as e-health interventions, may have a positive effect on therapy compliance. With internet applications, health-related information and support can be offered to large groups of patients in a relatively simple way. An e-health intervention is an internet-supported program in which patients look for health-related information. The intervention aims to bring about a positive change or to increase knowledge, awareness and understanding. This is done by offering health-related information and using internet-based interactive components.[5]

The generally accepted definition of e-health does not exclusively concern internet-supported interventions, but also includes e-health interventions based on technologies such as apps, web portals or text message services.[6] Previous research has shown that these types of interventions can positively influence healthy behavior,[7] which can also result in a positive effect on therapy compliance. In this article, we provide an overview of the role of e-health interventions in improving therapy compliance. We also describe the studies on interventions that have been published since 2010.

Search Strategy

As a basis for this article we used the systematic review 'Effects of e-health interventions on medication adherence: a systematic review of the literature', published in 2011.[8] The review described the effect of e-health interventions on therapy compliance based on the available literature up to 2010, was carried out in accordance with the guidelines for systematic reviews and carried out tests on internal and external validity. [9] The inclusion criteria were: (a) the study described a patient-centered internet intervention; (b) the study described an intervention for patients who used medication for a chronic condition; (c) one of the outcome measures was medication therapy compliance; (d) it was a quantitative study; and (e) the study was published in Dutch or English. Based on the search criteria in the present review, we repeated the search, this time searching for articles that were published after 2010. The search covered publications from 1 January 2010 to 1 June 2014. The studies described in the 2011 review were not assessed for the present review. We searched for relevant articles in the PubMed, Cinahl, PsycInfo and Embase databases. The inclusion and exclusion and retrieval of complete manuscripts was performed by one author (AS). In the event of a lack of clarity about the article, a second author (HvO) assessed whether the article in question should be included.

Search strategy (2010-2014)
PubMed: (medication therapy management OR medication adherence) AND (internet) AND (intervention study OR randomized controlled trial OR clinical controlled trial)

Cinahl: medication compliance AND internet PsycInfo: patient compliance AND internet

Embase: (medication therapy management OR medication adherence) AND (internet) AND (intervention study OR randomized controlled trial OR clinical controlled trial)

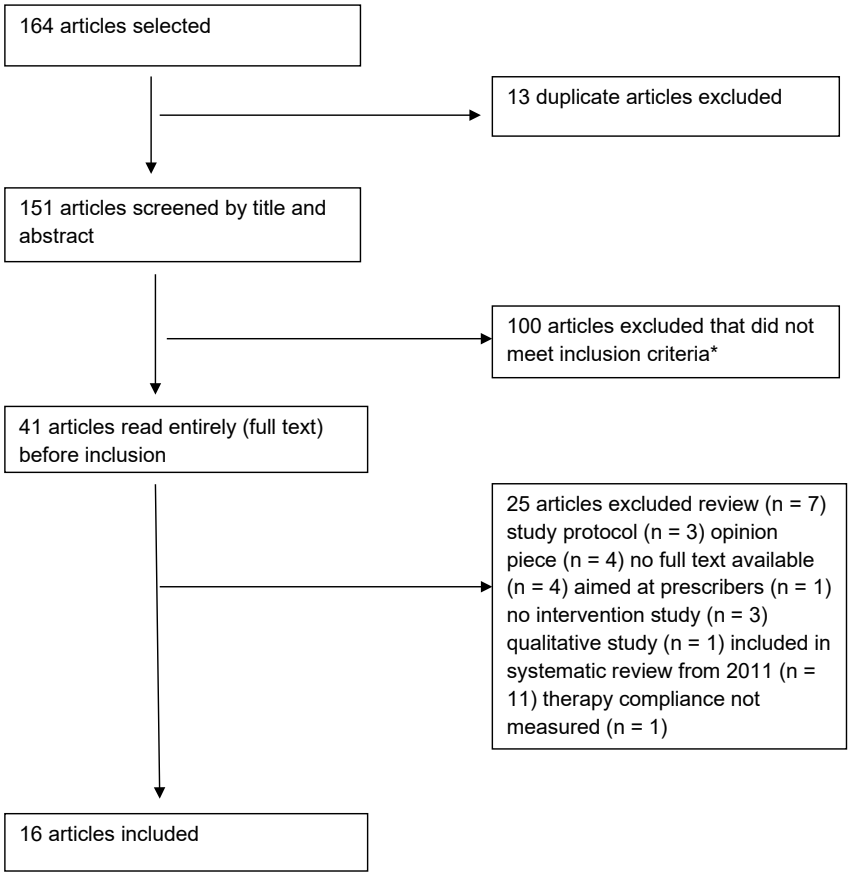

Figure 1. Flow chart of the search strategy for relevant articles on the effect of e-health interventions on medication therapy compliance. * The inclusion criteria are listed in the article under the heading 'Search strategy'.

Table Characteristics of the 16 included studies on medication therapy compliance

intervention; reference	condition	method for measuring therapy compliance	effect of intervention on therapy compliance
educational material via email and monitoring asthma management [10 11]	asthma	pharmacy sales data	improvement (p = 0.01)
website with feedback based on social cognitive theory [12]	asthma	non-validated questionnaire	no improvement
action plan and alerts based on online questionnaires about quality of life, therapy compliance, adverse effects, disease activity and body weight [13]	IBD	*'Morisky medication adherence scale'* – questionnaire	no improvement
patients were given access to their own GP file [14]	Various disorders	non-validated questionnaire	improvement
web-based program of 6 weeks with modules on sleep, medication or stress [15]	epilepsy	*'Medication adherence scale'* – questionnaire	improvement (p = 0.049)
daily personal text messages with feedback about taking medication[16]	HIV	VAS and *'AIDS clinical trials group adherence'* – questionnaire	improvement (p = 0.005)
website with feedback by web-doctor[17]	IBD	non-validated questionnaire and partial pharmacy sales data	improvement (p = 0.005)
website with video information and feedback; formulating improvement goals for therapy compliance, exercise and diet with or without social support and group meetings[18]	diabetes mellitus	*'Hill-Bone compliance scale'* – questionnaire	no improvement
intervention for parents (tools), children (game) and case managers via e-mail and website with discussion group with fellow patients [19]	asthma	*'Wisconsin Medicaid'* – program with insurance claims for picked-up medications; validated bi-weekly diary	no improvement
website with audio and interactive modules on therapy compliance with explanations, questionnaires for making a personal plan on therapy compliance, stress and HIV [20]	HIV	*'AIDS clinical trials group adherence'* – questionnaire; questionnaire; electronic monitoring	improvement (p <0.05)
interactive website with text message alert, filled with messages and reactions about therapy compliance, informative literature and videos; financial reward for logging in frequently [21]	HIV	non-validated questionnaire	no improvement
access to personal medical eye care records with graphical representation of glaucoma test results and medication[22]	glaucoma	pharmacy sales data	no improvement
automatically generated questionnaires on symptoms and side effects with reminder to take medication and feedback from clinicians to patients [23]	depression	non-validated questionnaire	no improvement

intervention; reference	condition	method for measuring therapy compliance	effect of intervention on therapy compliance
online questionnaires with specific feedback for parents about symptoms of their child and medication therapy compliance[24]	asthma	questionnaire	improvement (p = 0.04)
app with reminder function to take medication, including photos of the correct packaging; shows personal therapy compliance [25]	elderly people with multiple morbidity and polypharmacy	*'Morisky medication adherence scale'* – questionnaire; questionnaire	no improvement
website with animation, interactive activities with peer videos and expert videos; feedback on missed medication and blood values [26]	HIV	non-validated questionnaire	improvement (p = 0.008)

IBD = inflammatory bowel disease; VAS = visual-analogue scale.

Results of the literature study

The search resulted in a total of 164 titles and abstracts. After removing duplicate publications and applying the inclusion criteria, the full text of 41 articles was retrieved. After further assessment, 16 articles remained (see Figure). The characteristics of these studies are shown in the Table.

Publications until 2010

The authors of the systematic review from 2011 identified 13 articles. [8] The most commonly used intervention was a website in which the level of personalization ranged from 'none' (online access only) to 'complex'. In the latter case, a personal health program was made available that was based on measurement results, registration of symptoms, use of emergency medication and other parameters. In addition, diaries or information brochures were offered online to patients. Other programs focused on changing the attitudes or beliefs of patients with regard to the treatment and eliminating barriers; personal goals could be set and pursued. Of the 13 studies, 5 reported a significant positive effect on medication therapy compliance. In 6 studies the reported effects were not significant.

Publications from 2010 through 2014

Of the 16 included studies published after 2010, 15 studies used a website and 1 used an app. The studied interventions involved patients with the following conditions: 4 studies with HIV patients, 4 studies with asthma patients (both adults and children), 2 studies with inflammatory bowel disease patients and 2 studies in patients with various disorders, i.e. they were frequent visitors to their GP and used medication regardless of the condition. Furthermore, the intervention was investigated in some studies in patients with epilepsy, glaucoma, diabetes mellitus and depression.

The most commonly used methods to measure therapy compliance were patient-completed questionnaires (n = 14), both validated and not validated, and pharmacy

sales data (n = 4). Ten studies reported a significant improvement in therapy compliance after the intervention. This is an increase in the proportion of successful interventions relative to the results of the 2011 review: 5/13 (38%) versus 10/16 (63%).

Most studies investigated an intervention that consisted of a combination of information about the disease, which was specified based on the knowledge and symptoms that the patients reported themselves, and reminders in the form of e-mails or text messages. The interventions were often extensive and tried to match the various determinants for the individual patients. These determinants include training or education, perception and interpretation of the disorder and treatment, and belief in the efficacy of medication. The Table provides an overview of the studies with a description of the e-health interventions.

Seven studies tested interventions in which patients were asked to define personal goals based on information that they had entered online or that had been obtained from measurements.[12,13,17,18,20,24,26] Based on these personal goals, feedback was provided in follow-up consultations. Of these 7 studies, 4 reported a significant improvement in therapy compliance.[17,20,24,26] In 5 studies, patients were reminded when it was time to take their medication, in addition to other interventions. Three of these studies reported a significant improvement in therapy compliance.[13,23,25]

Four studies involved relatively simple interventions.[14,16,22,25] In 2 studies, the intervention involved making medical records available to the patient.[14,22] In an American study, patients could design their own text message that was sent as a reminder when it was time to take their medication,[16] In a Spanish study, an app was used in which details about the medication, including a picture of the packaging, could be saved. [25] It was also possible to send reminders to take the medication that included a photo of the packaging. All 4 of these interventions reported a significant positive effect on therapy compliance.

Interpretation of the results

Since the publication of the systematic review from 2011, a total of 16 new studies have been published on the effect of e-health interventions on therapy compliance. Of these studies, 10 reported an improvement in therapy compliance. Compared to the review from 2011, the proportion of successful interventions has increased. The interventions studied were usually complex and addressed multiple determinants for reduced therapy compliance. Various therapy compliance factors can be categorized as patient-related, care-related and environment-related factors. In addition, the causes of reduced therapy compliance can be roughly categorized as either intentional or unintentional. Do patients forget their medication or do they actively decide not to take the medication? All these factors interact in a unique way for each patient, making it difficult to predict the effect of a complex intervention on an individual. Of the 10

studies that reported improvements in therapy compliance,[4] involved a relatively simple intervention. This observation supports previous recommendations in which the use of complex interventions was not preferred.[1-4]

One factor that complicates the interpretation of therapy compliance data is the method used to measure therapy compliance. This makes it difficult to compare the effects of the interventions on therapy compliance with each other. In 14 of the 16 studies, therapy compliance was measured with questionnaires. Although questionnaires are simple to use in practice, it is known that questionnaires generally do not provide good insight into therapy compliance. This data should therefore always be seen in the light of the clinical outcome measures.

Even though the various interventions are difficult to compare because they are all designed differently, they have two common aspects: they used e-health and they aimed to increase the participation of patients. This was done by actively involving patients in their treatment by setting goals and providing feedback, or by giving patients more access to their medical records and informing them about the treatment. Patient participation in healthcare has an increasingly important role and, as shown in this overview, appears to improve therapy compliance. However, it is difficult to improve control over the other determinants. Despite these limitations, the development of e-health interventions is a logical step forward in research into therapy compliance. More and more patients have contact with mobile devices, and more and more online applications are available for these devices. In addition, the use of mobile devices is commonplace in daily life and enables patients to find information about their condition online quickly and easily. The interventions studied are therefore relatively easy to use in daily practice.

Conclusion

E-health interventions to promote therapy compliance appear to be becoming increasingly effective. Research on simple interventions and their implementation should therefore continue.

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4

Chapter 4

A Multifaceted Nurse- and Web-Based Intervention for Improving Adherence to Treatment in Patients With Cardiovascular Disease: Rationale and Design of the MIRROR Trial

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Abstract

Background: Poor adherence to medication is one of the limitations in the treatment of cardiovascular diseases, thereby increasing the risk of premature death, hospital admissions, and related costs. There is a need for simple and easy-to-implement interventions that are based on patients' perspectives, beliefs, and perceptions of their illness and medication.

Objective: The objective is to test the effectivity of this intervention to improve medication adherence in patients with established cardiovascular disease, that is, in secondary prevention.

Methods: In this study the effect of a personalized visualization of cardiovascular risk levels through a website aiming at supporting self management in combination with a group consultation and communication intervention by a nurse on adherence to treatment in 600 patients with manifest cardiovascular diseases will be assessed. The health belief model was chosen as main theoretical model for the intervention.

Results: Primary outcome is adherence to treatment calculated by refill data. Secondary outcomes include the Beliefs about Medication Questionnaire and the Modified Morisky Scale. Patients are followed for one year. Results are expected by 2015.

Conclusions: This study assesses adherence to treatment in a high-risk cardiovascular population by applying an intervention that addresses patients' capacity and practical barriers as well as patients' beliefs and perceptions of their illness and medication.

Introduction

Background and rationale

According to the World Health Organization almost 50% of all chronic patients do not adhere to their prescribed drug regimen.[1] This is also true for cardiovascular diseases (CVD) ; only 60% of all cardiovascular patients adhere to their cardiovascular medications (e.g. statins, antihypertensives, antithrombotic agents).[2] This prevalence is similar across all individual CVD medications and occurred in patient who take these medications for primary and secondary prevention of CVD.[2] These figures are startling given that poor adherence results in an increased risk of death in cardiovascular patients.[3-5]

Current methods for improving adherence are mostly complex and have limited effectiveness; simple interventions that are easy to implement in daily practice are preferred.[6] Evidence suggests that interventions should be based on the patients' perspective[7], target patients' capacity and practical barriers, and address their beliefs and perceptions regarding illness and medication.[8,9] In CVD, life-long adherence is important, and interventions should improve patients' intentions to take medication, as well as solve emergent practical barriers.

These principles were used in the development of the current trial. Specifically, the intervention is based on the health belief model (HBM)[10,11], tailored for the specific purpose of this trial. HBM provides a useful framework for designing behavior change strategies.[12] It is based on the understanding that a person will take health-related action (eg, being adherent to cardiovascular medication) given four main factors. The first two factors are perceived susceptibility and perceived severity; understanding of the high personal risk and seriousness of a condition (eg, because of the cardiovascular event in the past I am at greater risk for another cardiovascular event. The third factor is perceived benefits; belief that a negative health condition can be avoided (eg, being adherent to the cardiovascular medication can help to prevent another cardiovascular event. The last factor are the perceived barriers, cue to action and self-efficacy; belief in the ability to successfully undertake the recommended health action; (eg, I know *how* to take my medication on a daily base).[12,13]

Trial design and aim of the study

The study will use a single-center, prospective, randomized controlled clinical trial design. This study will examine the effectiveness of a new intervention that incorporates the HBM and behaviour change strategies to improve adherent behaviour in cardiovascular patients. The intervention consists of a patient-based screening method; a specific nurse-based intervention (structural informative consulting and motivational counseling) and personalized visualization of cardiovascular risk levels via a website. The objective is to test the effectivity of this intervention to improve medication adherence in patients with established CVD (i.e., in secondary prevention).

Methods

Study setting

Participants will be drawn from a hospital-wide screening program. This screening program is situated at the cardiovascular outpatient clinics in an academic medical center in Nijmegen, the Netherlands. All new patients diagnosed in the last 6 months with acute coronary syndrome, peripheral arterial disease, an aneurysm of the aorta or stroke/ transient ischemic attack (TIA) referred to the departments of Vascular Surgery, Neurology or Cardiology are automatically included in this program.

Eligibility criteria

From this population, participants aged 18 years and older will be selected based on the following inclusion criteria: presence of CVD (acute coronary syndrome, peripheral arterial disease, an aneurysm of the aorta, or stroke/TIA), diagnosed in the last 6 months by a medical specialist; willingness to remain in follow-up for a period of one year, and provision of signed, informed consent. Exclusion criteria are; pregnancy (reported by the patient); severe co-morbidity (eg, a mental health diagnosis considered by a physician to be a contraindication); problems with the Dutch language (reported by the nurse), or logistic problems such as lack of computer access.

Intervention

For the intervention, the group participants will be split in three groups. Participants in group I (control group) receive only usual care. Group II participants receive usual care plus access to a personalized website. For the group III participants, in addition to usual care and access to the personalized website, the intervention program will also include a single group consultation of 60 minutes led by a nurse and a pharmacist, followed by two individual consultations of 30 minutes with a nurse.

We want to test if treatment II (only the web portal) can give the same results as treatment III (the web portal and the single group consultation followed by two individual consultations). The need for low-cost effective interventions in our health care system lead to the motivation for this three-arm protocol.

Usual Care (Groups I, II and III)

All new CVD-patients receive the hospital-wide screening program according to the Dutch guidelines[14] (based on the European guidelines0.[15] The screening assesses cardiovascular risk factors in all patients with CVD. It screens for lifestyle risk factors, blood lipid levels, blood pressure, waist circumference, body mass index, blood glucose levels and a family history of CVD's. Lifestyle is evaluated through a questionnaire which is a compilation of existing validated questionnaires, regarding demographic data, smoking, alcohol use, physical activity and eating habits. For each of these lifestyle issues, the patient's motivation to change is evaluated.[16] Adherence is measured by the Modified Morisky Scale © (MMS)[17] and the Beliefs about Medication Questionnaire

(BMQ).[18] Medication use will be monitored. If necessary and if the patients agree they attend consultations with a nurse based on motivational interviewing to help them lose weight, stop using alcohol or stop smoking.

According to European guidelines[15] all patients with established CVD (this means all participants of this trial) should have antiplatelet therapy (eg, aspirin or clopidrogel) and a lipid lowering drug (eg, simvastatin or atorvastatin). The use of antihypertensive drugs is dependent on the systolic blood pressure. Except for the specific additions for the study, all participating and non-participating patients receive the same regular preventive cardiovascular care, including monitoring of medication use. All patients receive regular vascular care from their medical specialist.

Website (Groups II and III)

The website contains an individualized web portal called Interactive File Vascular Care', (Interactive Dossier Vaatzorg, or iVAZ). his is developed to support patient-based self-evaluation and management.[19,20] Patients can log on and see their own cholesterol levels, blood pressure, and lifestyle (smoking habit, exercise and eating habits) in a risk monitor. Patients can ask questions by e-mail to their nurses, and they can enter changes in their medication. iVAZ provides risk communication, the feedback of clinical outcome will be provided individually and patients are invited to be active in managing their illness and medication.

Group and Individual Consultations (Group III)

For group III, the intervention program will also include a single group consultation of 60 minutes led by a nurse and a pharmacist followed by two individual consultations of 30 minutes with a nurse.

During the group consultations patients receive information about their disease, cardiovascular medication (such as statins, antihypertensive, and antithrombotic agents) and the importance of treatment adherence. Patients will receive an information booklet with all information presented during the plenary session. At the end of this consultation patients are asked to keep a diary of their medication intake during a 2-week period and to set a personal goal for the upcoming individual consultation with a nurse. The group consultation is regarded as an efficient way to increase knowledge and understanding of the risks. It also provides a gathering with other patients (peers).

During individual consultations, the intervention is further tailored based on the goal previously set, patient's concerns, and necessities using the results of the screening questionnaire (see Data Collection). The following topics will be discussed during the individual consultation: patient's motivation and confidence (barriers, concerns, and positive self-motivational statements about their adherence behavior), options for increasing adherence to treatment, and a global summary of the counseling session.

Both the group and the individual consultations take place at the outpatient clinic. The involved nurses have had training in motivational interviewing[21] and were especially trained for this intervention by a psychologist.

For each of the constructs, we used the recommended behavior change strategies.[12,13] We tailored the intervention further by using the taxonomy of Abraham and Michie[22,23] and the coding manual by de Bruin[24] to categorize the behavior change techniques to be included in the intervention. For each of the components of the HBM, the determinants, techniques and application strategy were developed and are detailed in Figure 1 to 4.

Table 1. Techniques and applications influence perceived susceptibility in the current trial. The main determinant behind perceived susceptibility is a lack of knowledge, regarding prescribed medications and the influence on risk reduction.

Technique	**Practical applications/Strategy**
	Group consult:
Increase understanding	Providing general information about atherosclerosis
Provide general information	Providing written material with information about cardiovascular medication and how it should be taken
Risk communication	Providing general information about cholesterol and blood pressure and their influence on cardiovascular risk.
Persuasive communication	Providing general information about cardiovascular medication and how it works.
Group sessions with peers	Discussion within a group of cardiovascular patients about being adherent and non-adherent to medication

Table 2. Techniques and applications influence perceived severity in the current trial. The main determinant behind perceived severity is patients' beliefs, perception and management of their illness (awareness, outcome expectations).

Technique	Practical applications/Strategy
Risk communication Feedback of clinical outcome	Personalized website: Visualization of the personal cardiovascular risk through a risk monitor
Revaluation of outcomes, self-evaluation	Individual consult: Evaluating a medication taking diary
Goal setting	Group consultation and individual consult: Ask patients to describe a goal according to their medication adherence and evaluate this on their next appointment with their nurse

Table 3. Techniques and applications influence perceived benefits in the current trial**.** The main determinant behind perceived benefits is patients beliefs, perception and management of their illness (awareness)

Technique	Practical applications/Strategy
Persuasive communication	Individual consult: Consults are given based on motivational interviewing and goal setting
Revaluation of outcomes, self-evaluation	Evaluating target levels
Reinforcement on behavioural progress	Personalized website: Providing a risk monitor that will be green if outcome targets are achieved

Table 4. Techniques and applications influence perceived barriers, cue to action and self-efficacy in the current trial**.** The main determinant behind perceived barriers is skills and self-efficacy

Technique	Practical applications/Strategy
Self-report of behaviour	Let the patient keep a diary of his medication taking two weeks for each individual consultation
Verbal persuasion	Individual consult: Talk with the patients about the barriers and effect and side effects of the medication
Plan coping responses	If necessary, the nurse and patient make a plan together how to overcome the barriers.
Set graded tasks, goal setting	The patient and nurse formulate a goal at the end of each consultation reflecting the barriers they evaluated

Outcomes

Primary Outcome

The primary outcome of our study is adherence to the CVD –medication (classified by the Anatomic Therapeutic Chemical classification system), measured with a dedicated calculation of refill data of the used plated aggregation inhibitors and lipid modifying agents, obtained from patient's pharmacy.

Refill records of computerized pharmacy systems will be collected from 3 years prior to a patient's cardiovascular event through up to 3 years after the study follow-up period. Prescription records include the names of all of the dispensed drugs, prescribed daily dose, quantity dispensed at each pharmacy fill, and the dates of the prescription fills. Adherence will be calculated for the CVD- medications, as the theoretical duration divided by the period between the start date and the date of the last prescription filled. The theoretical duration will be calculated by dividing the number of units dispensed by the prescribed daily dose.[25]

Patients will be categorized into non-adherent and adherent patients. Patients with an adherence level of at least 80% will be classified as adherent, and patients with an adherence level less than 80% will be classified as non-adherent. Secondary prevention studies showed that patients with an adherence of less than 80% have an increased risk of death.[26]

Refill adherence rates have been used extensively for the assessment of drug acquisition and dispensing. Compared with electronic monitoring, refill data provide researchers with a relatively simple method for investigating exposure to medication in large populations.[27-29] Moreover, this method is suitable for investigating long-term persistence to treatment and gaps in medication supply.[30]

Secondary Outcomes

All secondary outcome measurements will be obtained just before inclusion (in the usual care screenings program) and one year after inclusion. The secondary outcome measurements include clinical responses to drug therapy (eg, cholesterol level), self-report questionnaires, and changes in systolic blood pressure.

Clinical responses to drug therapy will be recorded. A recorded low-density lipoprotein cholesterol level above 20% of pre estimated low-density lipoprotein cholesterol reduction during follow up will be considered as possible indication of poor adherence. If the patient also uses anti hypertension drugs, the blood pressure on baseline will be compared to blood pressure after one year and will need to be within target blood pressure for cardiovascular risk management (systolic <135 mmHg). These office blood pressure measurements are performed according to the recommendations of the European Society of Hypertension[31] with a validated automated device and is based on a mean of four office measurements.

Second, two validated self-report questionnaires will be used. The MMS © [17] will be used to measure adherence. Each of the 8 items measures a specific medication-taking behavior. MMS© scores can range from 0 to 8 and can be classified into three levels of adherence: low adherence (score off less than 6), medium adherence (score of 6 to less than 8) and high adherence (score of 8).[32] The Beliefs about Medication Questionnaire (BMQ)[18] will be used to provide information about the beliefs, perceived necessity, and

concerns patient have regarding their illness and prescribed medication. Respondents indicate their degree of agreement with each individual statement about medicines on a 5-point Likert scale. It is then possible to differentiate between patients on the basis of their beliefs about the necessity of their medication and their concerns about taking it. Patients can be classified into four different categories: accepting (high necessity and low concerns), ambivalent (high necessity and high concerns), skeptical (high concerns and low necessity), and indifferent (low concerns and low necessity).[33,34]

Participant Timeline

Baseline scores will be collected for all groups. Follow-up scores will vary depending on group and will be collected at 6 and 12 weeks (all groups), and 16 and 28 weeks (intervention groups II and III) (see Figure 1 for flow chart).

Sample Size

This study is mainly powered on the primary outcome, the detection of a significant difference between the three degrees of care (usual, additional website, additional counseling) on medication adherence as determined by refill records of computerized pharmacy systems. Based on previous research in our population and data from the literature [26], we estimate that the adherence at the start of the study will be 65% in each group with a standard deviation (SD) of 30%. We hypothesize that the intervention given in group II and the intervention given in group III, will result in an increase of 10% in adherence to treatment, resulting in mean adherence rates of 75% and 85% in groups II and III, respectively. To detect these differences in medication adherence the estimated group size with a power of 80% and an alpha of 0.05 (2-sided) would be 200 in each group, resulting in 600 participants in total.

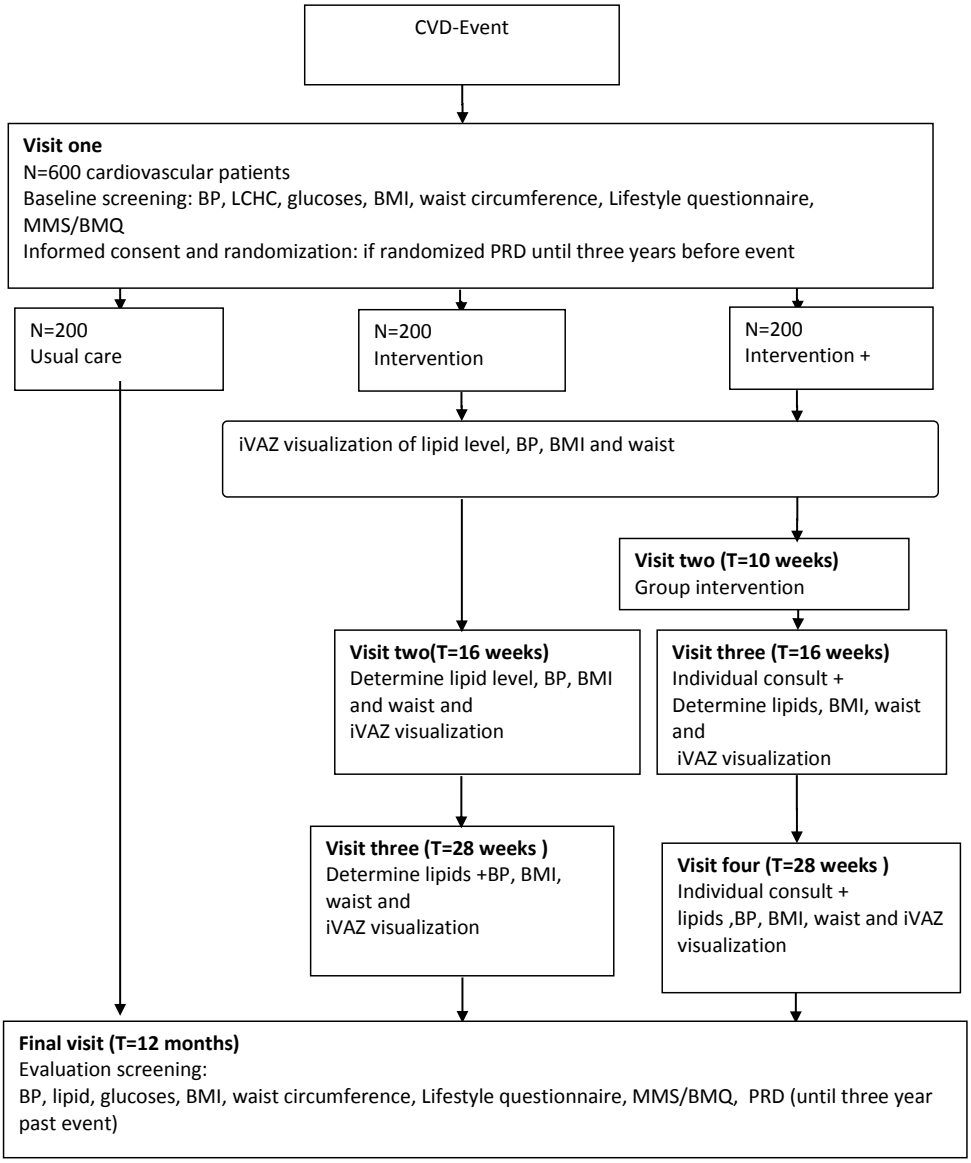

Figure 1. Flow Chart

Recruitment

All cardiovascular patients who receive the regular cardiovascular preventive care will be asked to participate by a nurse when they arrive at the outpatient clinic for their screening consult. Patients will receive a letter explaining the study, documenting their ability to withdraw at any time without explanation and confirming that their medical care will in no way be influenced by their decision regarding participation. At a minimum of 24 hours later written consent will be sought by a research assistant, prior to the patient entering the study.

We chose to include all cardiovascular patients in our study, rather than only non-adhering patients as done in many other studies.[6,9,35] We have a three-year follow-up planned and want to be able to see how adherence develops over time, for initial adherers and non-adherers alike.

Assignment of interventions

Patients who meet the criteria and consent to participate will then be randomized by the nurse, using blocked randomization, stratified by department (eg, neurology, vascular surgery, and cardiology) in a 1:1:1 ratio into one of the three groups using computer randomization.

Blinding

The principal investigator and the researcher will be blind to randomization. However, due to the need for active participation, the patient, nurse, and pharmacist delivering the individual consultations will not be blind to assignment of individuals in group III.

Data Collection and Management

The primary data collected will be provided by the initial screening. Obtained data from the screening are blood lipid levels, blood pressure, waist circumference, body mass index, blood glucose levels, and medication use. Lifestyle is evaluated through a questionnaire which is a compilation of existing validated questionnaires, regarding demographic data, smoking, alcohol use, physical activity and eating habits. For each of these lifestyle issues, patient's motivation to change is evaluated.[16] Adherence is measured by the MMS © [17] and beliefs about medication by the BMQ.[18]

To monitor whether the website intervention is used, log-in information per patient, expressed as the number of log-ins and times and dates of log-in, will be recorded.

To measure the nurses' performance skills required in the individual consultations, the behavior change counseling index will be used[36]. This validated checklist aims to measure the nurses' competence in behaviour change counseling and adaptation of motivational interviewing in healthcare settings. The group consultations are video recorded and evaluated in order to validate the quality of the motivational interviewing techniques applied.

Data will be entered by the nurses who perform the screening and the intervention consults in iVAZ. iVAZ is a secured website which can only be entered by the participants by using their social security codes and by selected nurses using security codes. In addition, all patients' pharmacists will receive a letter of information about the trial, consent of the ethical committee and the informed consents of the participants. They will be asked to send the data on refill records of their computerized pharmacy systems through a secured e-mail address. All the data will be anonymized according to the privacy protocols from the ethical committee and imported by the researcher into SPSS (IBM Corp).

Statistical Methods

The data will be analyzed based on the intention-to-treat principle and evaluated using SPSS, with descriptive statistics (mean, median, SD, and interquartile range) being determined for all variables. The data will be presented in quantitative format (eg, biometrics, laboratory results, blood pressure, lifestyle scores, adherence score on the basis of refill data and the MMS ©) and in descriptions of observed effects (eg, change in BMQ, determinants for adherence, evaluation of the use of iVAZ, and appreciation of nurse intervention).

To evaluate the difference between the groups, an analysis of variance test will be performed on the outcome measures for the three patient groups. Specifically, we will compare the difference between the first and last time point between groups for the primary and secondary outcomes measures. For the intervention groups II and III, we will also compare the outcomes of the clinical data at 16 and 28 weeks. To correct for multiple comparison, a Duncan's multiple range test will be performed. Furthermore, we will perform a receiver operating characteristic (ROC) curve analysis to compare the outcome of the screening instruments (MMS © and BMQ) with the pharmacy refill dates. In the ROC curve plot, -specificity of the questionnaire is on the x-axis and sensitivity of the question is on the y-axis.. Plausible relations between parameters of cardiovascular risk factors, motivation to change, and socio-economic class, and parameters of adherence (calculated refill score and, BMQ score and MMS scores) will be tested in a univariate manner. Individual parameters will be tested for normality using the Kolomogorov-Smirnov test, in order to select adequate univariate tests. Multiple logistic regression analysis will be performed to assess the relative importance of selected parameters for the likelihood of low adherence, as defined by the refill data algorithm. In all analyses, potential confounders will be included if they independently changed the beta -coefficient for dedicated calculation of refill data by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature.

Missing data is unfortunately very common in eHealth research. Therefore we follow the recommendation for eHealth research to use the multiple imputation technique in SPSS (SPSS MI) when analyzing our dataset with missing observations.[37]

Ethics and Dissemination

The study protocol has been approved by the local ethical committee before inclusion of patients into the study. The study has been registered (trial registration ID number NCT01449695, approved May 2011). Since the only intervention consists of a web tool support or communication with a nurse, serious adverse events and suspected unexpected serious adverse reaction related to the trial protocol are unlikely to occur. Subjects may leave the study protocol at any time for any reason, without any consequences for regular cardiovascular care. The investigator or patients 'specialists may also decide to withdraw a subject from the study for urgent medical reasons. There are no conflicts of interest to report (all authors). The authors are did not develop the intervention-website.

Discussion

Nonadherence to medication prescriptions in cardiovascular patients reduces the positive effects of medical treatment in chronic care. However, improvement of medication adherence in these patients is a serious challenge. Patient beliefs, perceptions and management of medication, their illness (intentional nonadherence), and skills to integrate medication taking in their daily life (unintentional nonadherence) need to be addressed to make an intervention successful.

There is no one-size-fits-all solution for nonadherence[35,9] nor does previous research provide evidence to choose a single intervention [38]. By reviewing the literature it becomes evident that determinants for non-adherent behavior are complex and underlying theory for a successful intervention is frequently lacking [35,39,40]. In a review of 193 health behavior change articles only 36% of the authors mentioned a theory and only 22% of them applied the theory [41].

We based our method on the HBM adopted the approach of Horne[42], and defined the main determinants of non adherent behavior in intentional and nonintentional determinants. Because we address both types of determinants, we expected to develop an intervention that will be more successful than most existing interventions, which only take into account one of these sets of determinants.

Specifically, by choosing a group consultation, information is provided in an efficient manner and the patient is given an opportunity to discuss the need for adherence (intentional nonadherence) as well as getting practical information (unintentional adherence) with peers. Further tailoring the intervention in individual contacts provides

the opportunity for the nurse to identify the need to change objectives of unintentional or intentional nonadherence (or a mix of both). These individual consultations are patient-centered, with emphasis on patient perspective and shared-decision making[43]. The individual website and visualization of personal cardiovascular risk furthermore addresses one of the difficulties in cardiovascular adherence: awareness of the influence of taking medication on personal cardiovascular risk.[41] Lastly, the combination of Web-based intervention with face-to-face contact is expected to give better results than either alone[44].

Based on this integration of factors, we hope that the resulting data of this trial will contribute important knowledge about adherence in this population.

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5

Chapter 5

A nurse-based intervention for improving medication adherence in cardiovascular patients: an evaluation of a randomized controlled trial

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Patient Preference Adherence, May 2019

Abstract

Background: Poor medication adherence is a limitation in the secondary prevention of cardiovascular diseases and leads to increased morbidity, mortality and costs.

Purpose: To examine the process and effect of a nurse-led, web-based intervention based on behavioral change strategies to improve medication adherence in patients with cardiovascular disease.

Patients and methods: In this single-center, prospective, controlled clinical trial, cardiovascular patients were assigned to usual care, usual care plus a personalized website or usual care plus a personalized website and personal consultations. Primary outcome was the level of adherence to cardiovascular medication. Data collection occurred between October 2011-January 2015.

Results: In total 419 patients were randomized. Just 77 patients logged on the website and half of the invited patients attended the group consultation. Due to the limited use of the website we combined the results of usual care and the usual care plus website group in one group (usual care) and compared these with the results of the group which received the nurse intervention (intervention group). No significant difference in adherence between the usual care group and the intervention group was observed. The adherence level in the usual care group was 93%, compared to 89% in the intervention group (p=0.08). 29% (usual care) and 31% (intervention group) of the patients showed a low adherence according to the Modified Morisky Scale® (p-value=0.94). The mean Necessity Concern Differential was 3.8 with no differences between the two studied groups (mean 3.8 vs. mean 3.9, p-value =0.86).

Conclusion: Our intervention program did not show any effect. This could indicate that structured usual care provided to all cardiovascular patients already results in high medication adherence or that shortly after a cardiovascular event adherence is high. It could also indicate that our intervention program did not have enough impact because there was not enough compliance with the intervention protocol.

Trial registration ID number NCT01449695, approved May 2011.

Keywords: medication adherence, nurses, e-health, Health Belief Model, cardiovascular, changing behaviour, process evaluation.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. Although lifestyle risk factors of patients with high cardiovascular risk are monitored regularly as part of the risk reducing programs, there is limited structural attention to medication adherence.[1] This is startling because it is known that poor medication adherence is a major limitation in the secondary prevention of cardiovascular diseases (CVD) that may lead to increased morbidity, mortality, and costs.[2-4] Approximately 50% of the patients using medication for a chronic disorder do not adhere to the prescribed drug regimen according to The World Health Organization (WHO).[5] In patients with CVD adherence rates remain low, ranging between 50-79%.[2,6] As a consequence, in Europe an estimated 9% of preventable CVD events can be attributed to poor adherence to vascular medications alone.[7]

Current methods for improving adherence are mostly complex and not very effective, and simple interventions that are feasible in usual practice settings are preferred.[8] There is however a need for more understanding in patient-related determinants of poor adherence to medication. These determinants can either be intentionally or unintentionally driven. Unintentional poor adherence occurs when patients are inclined to adhere but are not able to because of a lack of capacity or resources. Intentional poor adherence occurs when patients decide not to follow the agreed recommendations.[9] To be effective, interventions should address both unintentional and intentional determinants of poor adherence.[10] Central to patients' medication adherence is their judgment of their personal need for taking medication. Key beliefs that influence patients' judgment about their medication are perception of personal needs for treatment (necessity beliefs) and concerns about several potential negative consequences (concern beliefs).[9,11,12] Though life-long adherence is important in CVD, absence of symptoms in the years after an event may result in the perception that the illness is benign. This may lead to doubts about the necessity of continuous treatment.[13] A patient-centered approach with emphasis on patients' perspectives might encourage CVD patients to take their medication.[14,15] The principles of the patients' perspective were used in the development of the intervention under study. The intervention was therefore based on the Health Belief Model (HBM)[16,17] in which the Necessity-Concern Framework was applied[9] and adapted for the specific purpose of this trial.

Material and methods

Aim

This study aimed to evaluate the process and outcomes of an intervention program consisting of a single group consultation, two individual follow-up consultations with a nurse and access to an interactive personalized website, incorporating evidence-based determinants of poor adherent behaviour in high risk cardiovascular patients. The Health

Belief Model (HBM)[18] was chosen as central theoretical model for the interventions. The intervention program aims to improve patient's necessity and concern beliefs about medication, which is expected to lead to better adherent behaviour in cardiovascular patients.

Design / Methodology

The design of this study (with an acronym: the MIRROR-trial) has been described in detail earlier.[19] The MIRROR study is a single-center, prospective, three-arm randomized controlled clinical trial. Patients were randomly assigned to usual care (group I), usual care plus access to a personalized website (group II), or usual care, access to a personalized website plus a group consultation with a pharmacist and a nurse, followed by two individual nurse-led consultations at the outpatient clinic (group III).

Sample

All patients referred to the Radboud University Nijmegen Medical Center with a new diagnosis of acute coronary syndrome, myocardial infarction, peripheral arterial disease, an aneurysm of the aorta or transient ischemic attacks (TIA) or stroke over the last 6 months were included into the hospital CVD screening program. This screening program aims to identify cardiovascular risk factors and consists of screening of lifestyle (smoking, diet and exercise), blood lipid levels, blood pressure, waist circumference, body mass index (BMI), glucose blood levels and a family history of cardiovascular diseases. If indicated, preventive therapies (medication and lifestyle interventions) are structurally initiated and followed over time.[20] From this program, participants aged 18 years and older were eligible for the MIRROR-trial if they were willing to stay in a one year follow-up period, and provided signed informed consent for an intervention on medication adherence. Exclusion criteria were pregnancy reported by the patient, severe co-morbidity (e.g. lung cancer, end stage heart failure), difficulties with Dutch language or no access to a computer.

Randomization

Patients who consented to participate were randomized using block randomization stratified by department (i.e. neurology, vascular surgery, and cardiology) in a 1:1:1 ratio into one of the three groups. Randomization was blinded for the principal investigator and the primary researcher. Either the patient, the nurse or the pharmacist delivering the individual consultations could be blinded to the intervention assignment in group III.

Power calculation

The study was powered on adherence to medication expressed as MPR. We estimated that adherence levels at the start of the study would be 65% in each group with a standard deviation of 30%. We hypothesized that the intervention given in group II and the intervention given in group III would result in an increase of 10% and 20% in adherence to treatment, resulting in a mean adherence rate of 75% and 85% in group II and III, respectively. Consequently, the estimated group size with a power of 80% and

an alpha of 0.05 (two-sided) would be 200 in each group, resulting in 600 participants in total.

Timeline

The intervention period lasted 12 months. Within, on average, six weeks after the CVD-event, baseline characteristics were collected for all patients. Follow-up outcomes were collected at twelve months after inclusion for all patients.

Data collection

Process evaluation

As recommended by the Medical Research Council Guidance [21] we included a process evaluation of this intervention program. A process evaluation helps to understand the relationship between how well an intervention was delivered, the different elements of an intervention and the main outcomes of a trial.[22,23] It furthermore improves the validity and interpretation of these outcomes and gives information so the intervention can be replicated.[24] This intervention program was performed at an outpatient clinic for cardiovascular risk management in our academic hospital. Nurses, who deliver the individual consultations, already counsel cardiovascular patients in changing their lifestyle (e.g. stop smoking. losing weight) through motivational interviewing techniques. In addressing the problem of non-adherence as a behavioral problem, the intervention program could fit really well in the existing clinical setting. There is also a broad recognition that nurses have a key role in understanding and addressing patients 'beliefs during consultations about their medication.

Adherence

The primary outcome of our study was adherence to cardiovascular medication. Adherence was based on pharmacy refill dates (PRD) of participants' filled prescriptions obtained from computerized pharmacy systems. Data were collected for prescribed cardiovascular drugs (plated aggregation inhibitors, lipid modified agents and antihypertensive drugs) for the period of 3-years prior to a patient's cardiovascular event and at least one year after cessation of the intervention of this trial. All prescription records included the Anatomic Therapeutic Chemical code (ATC), the names of the dispensed drugs, prescribed daily dose, quantity dispensed at each pharmacy fill, and the dates of the prescription fills. Adherence was reported as the mean possession ratio (MPR) for all cardiovascular medication. The MPR was defined as the number of days of treatment dispensed divided by the number of days prescription refills[25]. We calculated adherence levels at baseline (T1), at the end of the intervention (T2) and at one year after ending the intervention (T3). Patients with an adherence level of at least 80% were considered adherent, whereas patients with an adherence level lower than 80% were considered as non-adherent.

Secondary outcomes

Clinical responses

According to the hospital screening program, blood was drawn from all patients to determine LDL cholesterol levels. A recorded LDL-cholesterol level of 20% above the baseline level during follow up was considered as an indication for of poor adherence. If patients used antihypertensive drugs, they were classified adherent if the systolic blood pressure was below 135 mmHg after the intervention. Target blood pressure levels were set according to the European Society of Hypertension (ESH) recommendations (i.e. a systolic blood pressure level of < 135 mmg Hg). These office blood pressure measurements were performed according to the recommendations of the ESH with a validated automated device and based on a mean of four office measurements.[26]

Patient outcomes

All patients filled out the MMS® and the BMQ at baseline and at the end of the follow-up period. The MMS® is a validated questionnaire consisting of eight items aimed at measuring adherence.[27-29] Each item accounts for 0 or 1 in the case questions are answered by No or Yes, respectively. Consequently, total MMS® scores range between 0 and 8. These scores were divided into three levels of adherence: low adherence (sum score < 6), medium adherence (sum score 6 to <8) and high adherence (sum score of 8). To evaluate patients' beliefs and perceptions about their medication, the BMQ was used.[30] Respondents stated their degree of agreement with each individual statement about medicines on a five-point Likert scale. The necessity–concerns differential (NCD) was calculated as the difference between necessity and concerns scores and had a possible range of -20 to 20. If the difference was positive, the patient perceived that the benefits of medication outweighed the concerns. Contrarily, if the differential was negative, the patient perceived more costs than benefits.[13,31] To separate patients on the basis of their beliefs about the necessity of their medication and their concerns about taking medication, the total necessity and concern scores (5-25) were split at midpoint (thus 5 - 12 was considered as low and 13 t/m 25 was considered as high). Patients were then classified into four different categories: accepting (high necessity and low concerns), ambivalent (high necessity and high concerns), skeptical (high concerns and low necessity) and indifferent (low concerns and low necessity).[32-34] From all patients the type of CVD (acute coronary syndrome, myocardial infarction, peripheral arterial disease, an aneurysm of the aorta or TIA) was recorded. Also, the following baseline and clinical characteristics were collected: age, sex, level of education, employment status and the country of origin. Whether patients were new or chronic users of cardiovascular medication was also registered. To classify patients as a chronic medication user, they had to use a plated aggregation inhibitor and/or a lipid modified agents more than two months before baseline according to PRD. All other patients were classified as new users. The log-on information expressed as the number of log-ins, times and dates on the personalized website of each patient were recorded.

Ethics

Written informed consent was collected from all patients prior to entering the study. The study protocol was approved by the local ethical committee. Approval for this study was obtained by the Local Ethical Committee, the human related research committee of the Arnhem-Nijmegen region (CMO no 2011/062), which applied criteria described in the Medical Scientific Research with People Act (WMO), the Helsinki Declaration, the Good Clinical Practice (GCP), EU Guideline Good Clinical Practice, Clinical trials guidelines on medicinal products and in CCMO guidelines.

Data analysis

Data were analyzed based on the intention-to-treat principle and evaluated by using SPSS, with descriptive statistics (mean, median, standard deviation [SD]) being determined for all variables. Differences between the patient groups were tested by performing an ANOVA test on the outcome measures. All socio-demographic and disease related factors so they could be taking into account as potential confounders.[14,35,36] To handle with missing data, we followed the recommendations for eHealth research and used multiple imputation techniques in SPSS.[37] Multiple imputation is considered as the standard procedure for dealing with missing data. It has the advantage of incorporating auxiliary information about missing data into the analysis, thereby reducing bias and improving accuracy.[38] Analysis of multiple imputated data shows greater power and efficiency than complete case analyses. Multiple imputations makes better use of available data and can generate different results from simpler techniques.[39] The datasets generated and analyzed during this study are not publicly available due to the Dutch privacy laws. But they are available from the corresponding author on reasonable request.

Validity and reliability

This study used instruments with their validity and reliability tested in previous studies.[40,27,30] Participants were randomized using block randomization. The intervention was delivered by well trained nurses who all had a training specific for delivering the intervention.

Results

Process evaluation

Development of the intervention program

The intervention program consisted of a nurse-based intervention providing structured information and motivational counseling, and a personalized visualization of cardiovascular risk levels on a website. The intervention was based on evidence-based behaviour change theory, the Health Belief Model (HBM)[16] and by applying the Necessity-Concern Framework.[9] This Necessity-Concern Framework is a useful model for understanding and addressing both unintentional and intentional nonadherence.[9] By using the Beliefs about Medicines Questionnaire (BMQ)[30], nurses could get insight into the necessity and concern beliefs of their patients and were able to tailor their consultation to the needs of

each individual patient. The HBM is based on the understanding that a person will take health related action (e.g. being adherent to cardiovascular medication) given four main factors. The first two factors are perceived susceptibility and perceived severity, reflecting the understanding of the high personal risk and seriousness of a condition (e.g. because of the cardiovascular event in the past I am at greater risk for another cardiovascular event). The third factor is perceived benefits, aimed at the belief a negative health condition can be avoided (e.g. being adherent to the cardiovascular medication can help to prevent another cardiovascular event). The last factor covers the perceived barriers, cue to action and self-efficacy, aimed at the belief to have the ability to successfully undertake the recommended health action (e.g. I know *how* to take my medication on a daily base). The group consultation with between ten to twelve patients was chosen for delivering knowledge and understanding of the risks. Moreover, it also provided a gathering with other patients (peers) in which patients were given the possibility to discuss adherence behaviour and learn from each other. In the individual consultations, the intervention was further tailored to each individual, so nurses were able to identify objectives for change of (un) intentional non-adherence (or a mix of both) and were able to address the determinants of patients' beliefs, perceptions and management of their illness and medication next to patients' skills and memory.[8] To support the individual and group consultations, an interactive and personalized website was developed. On this website, patients could see their own cholesterol levels, blood pressure and lifestyle (smoking, physical activity and eating habits) in a risk monitor. Patients had the opportunity to ask questions by e-mail to their nurse and enter changes in their medication. We choose a three-arm randomized controlled trial to determine if the website alone was effective or if group consultations and individual consultations had add-on effects. The participating nurses were trained in motivational interviewing and had applied this as part of the usual care program for several years.[41] They received an extra training for this intervention.[42,43]

The website was expected to be effective on itself by creating awareness (risk monitor), providing (written) information and tailoring of the information by the e-mail facility.[44,45] Risk communication and the feedback of clinical outcome can be provided personally and patients were encouraged to be active in handling their disease and medication. The website was connected to the hospital laboratory system to provide personal clinical results. Logging in was due to high privacy levels. Patients had to use a special personal code, and had to confirm their password with a code they received from a text message. For developing the intervention program, we used the recommended behaviour change strategies of the Health Belief Model (HBM). We tailored further by using the taxonomy of Abraham and Michie[46,47] and the coding manual by de Bruin to categorize the behaviour change techniques that required to be enclosed in the intervention.[46,48]

For each of the components of HBM, the determinants, techniques, and application strategy that were developed are described in Table 1, process evaluation: Method, corresponding determinants, techniques, practical applications and the materials of the developed intervention.

Table 1. Process evaluation: Method, corresponding determinants, techniques, practical applications and the materials of the developed intervention. (1=Determinants of the Health Belief Model. 2=Definitions according to the taxonomy of behaviour change techniques by Abraham and Michie and de Bruin).

Health Belief Model	Determinant [1]	Technique [2]	Practical applications/Strategy	Materials
Perceived susceptibility *Beliefs about the chances of getting another cardiovascular event*	Knowledge *Lack of knowledge regarding prescribed medications and the influence on risk reduction*	Increase understanding Provide general information Risk communication Persuasive communication Group sessions with peers	<u>Group consultation:</u> Providing general information about atherosclerosis Providing written material with information about cardiovascular medication and how it should be taken Providing general information about cholesterol and blood pressure and their influence on cardiovascular risk. Providing general information about cardiovascular medication and how it works. Discussion within a group of cardiovascular patients about being adherent and non adherent to medication	The group consultation was led by a pharmacist and a nurse. A PowerPoint was made containing information about the need for low cholesterol and low blood pressure and how to use the most common cardiovascular medication. All these information is also given to the patients in a brochure. Patients are invited to discuss their personal beliefs about their cardiovascular medication and the practical implications of taking medication on a daily base.
Perceived severity *Beliefs about the seriousness of that event and its consequences*	Patients beliefs, perception and management of their illness (awareness, outcome expectations) *Personal judgement of need for the medication influenced by perception and management of the disease:* *Not accepting their illness* *Thinking it is more benign than it is (because of absence of symptoms).*	Risk communication Feedback of clinical outcome Revaluation of outcomes, self-evaluation	<u>Personalized website:</u> Visualization of the personal cardiovascular risk through a risk monitor <u>Individual consultation:</u> Evaluating the filled out questionnaires BMQ[a] and MMS[b]. Evaluating a medication taking diary	A website where patients can log in to see their own cholesterol and blood pressure level was built. These levels are visualized as a speedometer. When at target level, an arrow is in the green part of the scale when not at target level an arrow is in the red part of the scale. An intervention chart was created. It contained different topics according to the determinants of poor adherence with subsequent questions the nurse can ask specified for each topic.

Health Belief Model	Determinant [1]	Technique [2]	Practical applications/Strategy	Materials
Perceived benefits *Beliefs about the effectiveness of taking action to reduce risk.*	Patients beliefs, perception and management of their medication(awareness) *Personal judgement of need for the medication influenced by perception of prescribed medication.* *Negative associations with medication (in general or specific) and/or health care providers*	Persuasive communication Verbal persuasion Revaluation of outcomes, self-evaluation Feedback on clinical outcome	<u>Individual consultation:</u> Consultations are given based on motivational interviewing and goal setting Evaluating the filled out questionnaires BMQ and MMS . Evaluating target levels <u>Personalized website:</u> Providing a risk monitor that will be green if outcome targets are achieved	Nurses participating in this intervention (already trained in motivational interviewing) were trained .The program contained general information of poor adherence and the most common cardiovascular medication. Information was provided on how to achieve behavioural change and what the specific change objectives were in this intervention. The nurses then performed these consultations in a role play and were given feedback by the medical psychologist. At the end of the training day documents which contained all the given information was provided.
Perceived barriers **Cue to action** **Self-efficacy**	Memory loss or forgetfulness Lack of knowledge or skills how to order new prescriptions or to set up memory cues	Self report of behaviour Goal setting Plan coping responses Set graded tasks Use of cues Cope with side effects	Let the patient keep a diary of his medication taking two week for each individual consultation <u>Individual consultation:</u> Talk with the patients about the barriers and effect and side effects of the medication If necessary the nurse and patient make a plan together how to overcome the barriers (e.g. alarm devices, doses of medication at visible location) or when side effects occur switch medication The patient and nurse formulate a goal at the end of each consultation reflecting the barriers they evaluated	In the brochure there is a section were patients can fill in when they took their medication. Patients are asked to do at least ten days before their individual consultation. In the individual consultation the intervention chart also contains topics according to memory and skills (e.g. ordering medication on time, forgetting medication) and possible solutions (e.g. help ordering a dosette box) are provided.

Uptake of the intervention Patient enrollment and inclusion

Of a total of 1201 patients with a cardiovascular event who enrolled the screening program, 900 were eligible to participate in this study. Of these, 481 declined to participate. In total 419 patients were randomized into group I (n=133), group II (n=138), and group III (n=148). Data collection occurred between October 2011-January 2015. After randomization, 148 patients were invited to attend the group and individual consultations of which 79 of these participated in the group consultation. One-hundred-and –thirty- four and 79 of these patients visited the first and second individual consultation, respectively. In total 286 patients got access to the website and were requested to visit the website. Seventy-seven patients actually logged- in on the website of which only 37 logged-in more than once. Since only a small proportion of the patients in group II en group III logged-in on their personalized website (34 and 43 patients for group II en III, respectively) it was questionable whether there could be an effect of the website when compared to usual care. Therefore, we decided to report the results based on two groups, in which group I and II combined were compared to group III, i.e. we examined the effects of the group consultation plus the extra individual consultations.

From the 419 randomized patients, refill data of 260 patients were available. We used multiple imputation techniques for all missing data. See figure 1: Patient enrollment and participation.

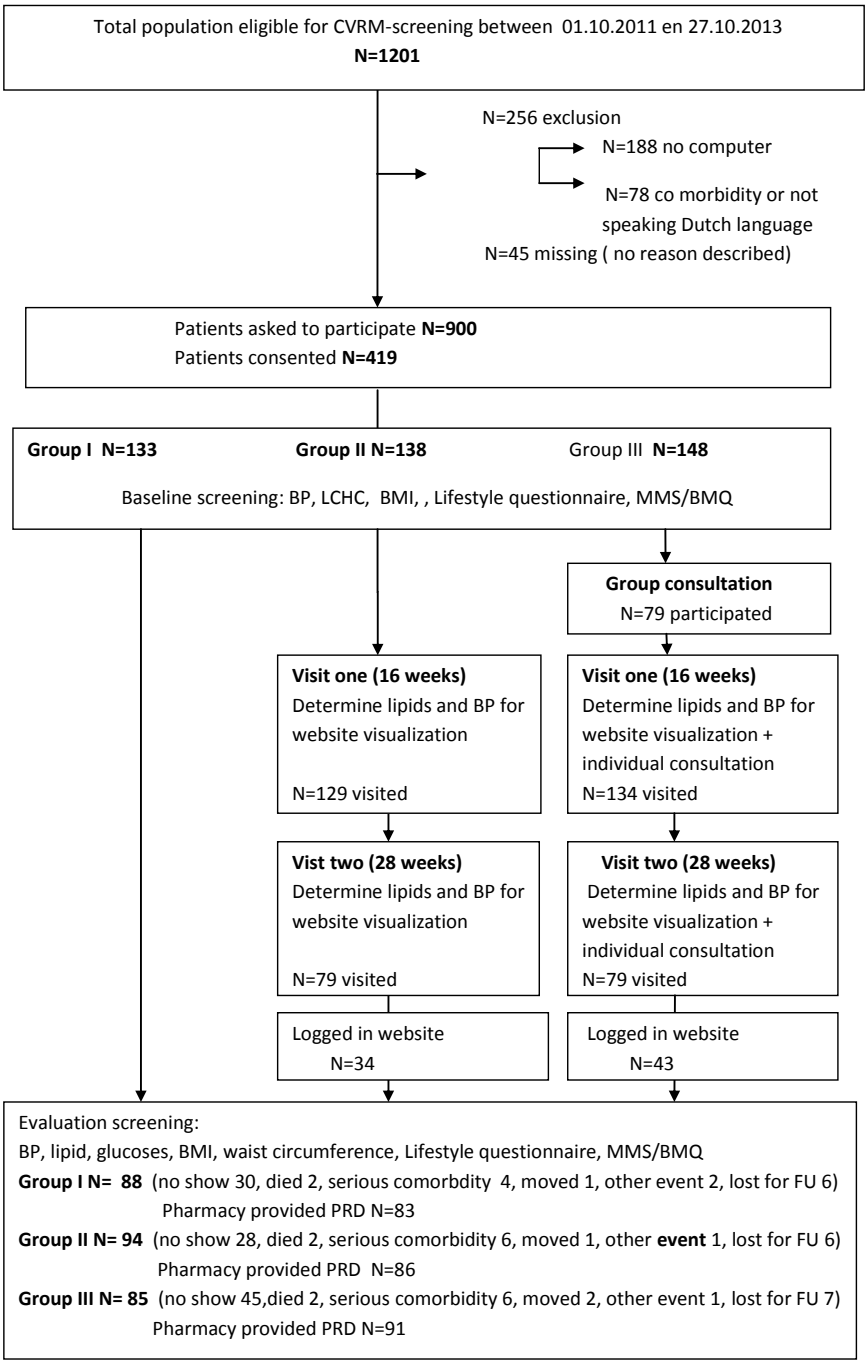

Figure 1 Patient enrollment and participation.
Note: LCHC depicts lipoprotein analysis with determination of high density lipoprotein-cholesterol and low density lipoprotein-cholesterol calculation.
Abbreviations: BMI, body mass index; PRD,pharmacy refill dates; FU, follow up; MMS, Modified Morisky Scale; BMQ, Beliefs about Medicines Questionnaire; CVRM, cardiovascular risk management; BP, blood pressure.

Results of the intervention

Baseline characteristics

At baseline the mean age of the participants was sixty one years and 67% were male. Forty-seven percent of the participants were diagnosed with a stroke or TIA, 36% with an acute coronary syndrome and 17 % with peripheral arterial disease. Ninety-eight percent received an antithrombotic agent and 94% received lipid-lowering medication after the event. At baseline, MPR for all cardiovascular medication was 72%. According to the MMS® 20% of all patients were low adherent, 46% and 35% were medium and high adherent, respectively. Mean NCD according to the BMQ was 3.6. Mean LDL was 2.5 mmol/L and mean systolic blood pressure was 137 mmHg. See table 2

Table 2: Patient characteristics at baseline

	Usual care (UC) N=133	UC + website N=138	UC + website + consultations N=148
Socio-demographic characteristics			
Age, in years [a]	60.4 (10.0)	60.2 (8.8)	60.9 (11.8)
Sex Female [b]	36 (27.1)	38 (27.5)	49 (33.1)
Education level [b]			
Primary	28 (21.9)	20 (16.4)	18 (14.4)
Secondary	65 (50.8)	65 (53.3)	55 (44)
University	35 (27.3)	37 (30.3)	52 (41.6)
Labour[b]			
Paid labour	45 (33.8)	61 (44.2)	47 (31.7)
Unemployed	7 (5.2)	4 (3)	2 (1.3)
Unfit for work	21 (16.0)	24 (17.4)	28 (19)
Retired	50 (37.5)	42 (30.4)	63 (24.3)
Housewife	10 (7.5)	7 (5.0)	8 (5.4)
Country of origin is the Netherlands [b]	110 (89.4)	108 (91.5)	109 (88.6)
Clinical Characteristics			
Reason referral [b]	46 (34.5)	51 (37.0)	53 (36.0)
Acute Coronary Syndrome	65 (49.0)	64 (46.4)	69 (46.5)
Stroke or Transient Ischemic Attack	22 (16.5)	23 (16.6)	26 (17.5)
Peripheral arterial Disease			
Blood pressure, mmHg [a]			
Systolic	137.3 (16.8)	135.5 (17.5)	136.7 (19.7)
Diastolic	78.1 (11.3)	78.2 (9.6)	76.5 (10.7)
Lipids mmol/L [a]			
Totaal cholesterol	4.6 (1.2)	4.5 (1.0)	4.5 (1)
Triglyceriden	1.9 (1.0)	1.7 (0.9)	1.8 (1.1)
High- Density Cholesterol	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
Low-Density Lipoprotein	2.6 (1.0)	2.6 (0.9)	2.5 (0.9)
Body Mass Index, kg/m^2 [a]	27.2 (4.0)	27.5 (4.0)	27.1 (4)
Medication use[b]			

	Usual care (UC) N=133	UC + website N=138	UC + website + consultations N=148
Medication (ATC) used			
Antithrombotic agents (B01)	128 (98.5)	132 (97.1)	144 (98.0)
Diuretics (C03)	36 (26.5)	36 (26.5)	37 (25.1)
Beta Blocking agents (C07)	72 (55.4)	85 (62.5)	82 (55.8)
Calcium channel blockers (C08)	20 (15.4)	21 (15.4)	24 (16.3)
Agents acting on the angiotensin system (C09)	76 (58.5)	83 (61.0)	85 (57.8)
Lipid modifying agents (C10)	120 (92.3)	129 (95.0)	138 (93.9)
Chronic users[b+c+d]	85 (64.4)	85 (62)	90 (61.2)
Questionnaires			
The Modified Morisky Scale © (MMS)			
Adherence [b]			
Low	23 (18.9)	21 (17.1)	26 (20.5)
Medium	63 (51.6)	54 (43.9)	53 (41.7)
High	36 (29.5)	48 (39)	48 (37.8)
Beliefs about Medication Questionnaire			
Necessity Concern differential [a]	3.9 (4.9)	3.9 (4.4)	3.6 (4.6)
Categories [b]			
Accepting	35 (28.7)	33 (26.6)	32 (25)
Ambivalent	81 (66.4)	87 (70.2)	87 (68)
Sceptical	4 (3.3)	2 (1.6)	3 (2.3)
Indifferent	2 (1.6)	2 (1.6)	6 (4.7)
Mean Possession Ratio [d+e]			
Cardiovascular medication total	0.74	0.73	0.72
Antithrombotic agents (B01)	0.79	0.75	0.73
Diuretics (C03)	0.77	0.81	0.73
Beta Blocking agents (C07)	0.86	0.87	0.83
Calcium channel blockers (C08)	0.96	0.95	0.94
Agents acting on the angiotensin system (C09)	0.80	0.80	0.79
Lipid modifying agents (C10)	0.82	0.79	0.76

(a) Data are presented as means and SD (+/-)
(b) Data are presented as numbers and percentages (N+%)
(c) Chronic use =starting medication > two months before baseline.
(d) Data from imputated data.
(e) Mean number of days dispended divided by the mean number of days between prescription refill.

Adherence

The intervention did not show an effect on adherence to treatment. Patients in the usual care group had an adherence level of 93%, compared to 89% in the intervention group (p-value=0.08) at T2. At T3 there also was no significant difference detected (adherence level was 81% and 76% respectively for groups I and II with a p-value of 0.23). Percentage of adherent patients was 86.3 % in the usual care group and 76.4 % in the intervention group (p-value= 0.17) at T2. This was 65% and 57.4% (p-value=0.38) at T3. Though we didn't see differences in adherence between the usual care and intervention group, we observed a difference in adherence in time for both groups combined. Therefore we performed a Repeated Measurement ANOVA in time

without differentiating in trial groups. At T1, at T2 and at T3 the overall adherence was 72%, 92% and 80%, respectively. During the study period medication adherence increased with 20% (95% CI 0.065 – 0.335). One year after this period it declined with 12% (95% CI 0.073-0.17).

Clinical outcomes

At T2, mean LDL level was 2.2 mmol/L (2.5 mmol/L at baseline) and mean systolic blood pressure was 155 mmHg (136 mmHg at baseline) for both groups. There were no differences in LDL and blood pressure alteration between both groups. Blood pressure was above target level in 76% of all patients and 12% showed a recorded LDL-cholesterol level of 20% above the baseline LDL-level (p-value between groups was 0.52 and 0.4 respectively).

Patient outcomes

No differences between the MMS® and the BMQ were detected at T2 between both groups. 29% (usual care) and 31% (intervention group) of the patients showed a low adherence according to the MMS®. There were no differences between the two groups studied (p-value=0.94). The mean NCD was 3.8 at T2. Again, no differences between the two studied groups were present (mean 3.8 vs. mean 3.9, p-value =0.86). We did observe a difference in the four BMQ categories. In the intervention group there was a shift from ambivalent (from 60% at T1 to 37% at T2) towards accepting (25% at baseline to 33% at T2). In the usual care group this shift was from ambivalent (63% to 43%) to skeptical (4% to 15%) and indifferent (6% to 15%).

See table 3: Differences in adherence, beliefs about medication and clinical outcomes is shown in table 3A. The observed adherence difference in time is shown in table 3B: Differences in mean medication adherence in time.

Table 3A: Differences in medication adherence, beliefs about medication and clinical outcome between usual care and intervention groups at baseline, after intervention and at follow up of 12 months (all after imputation).

	Group I +II UC N=271	**Group II UC +consultations N=148**	**p-value (a)**
Mean Possession ratio[(b)]			
Total of cardiovascular medication			
Baseline (T1)	0.74	0.73	
After intervention (T2)	0.93	0.89	0.08
Follow up of 12 months (T3)	0.81	0.76	0.23
Per ATC-code			
Baseline (T1)			
Antithrombotic agents (B01)	0.77	0.73	
Diuretics (C03)	0.79	0.73	
Beta Blocking agents (C07)	0.87	0.83	
Calcium channel blockers (C08)	0.95	0.94	
Agents acting (.) angiotensin..(C09)	0.80	0.79	
Lipid modifying agents (C10)	0.80	0.76	
After intervention (T2)			
Antithrombotic agents (B01)	0.92	0.91	0.65
Diuretics (C03)	0.88	0.82	0.40
Beta Blocking agents (C07)	0.91	0.91	0.89
Calcium channel blockers (C08)	0.89	0.87	0.57
Agents acting (..) angiotensin..(C09)	0.92	0.91	0.56
Lipid modifying agents (C10)	0.90	0.89	0.06
Follow up of 12 months (T3)			
Antithrombotic agents (B01)	0.86	0.82	0.27
Diuretics (C03)	0.83	0.76	0.12
Beta Blocking agents (C07)	0.80	0.80	0.87
Calcium channel blockers (C08)	0.93	0.91	0.34
Agents acting (.) angiotensin..(C09)	0.84	0.80	0.48
Lipid modifying agents (C10)	0.84	0.78	0.06
Adherent [(c)]			
Baseline (T1)	53.5	48	
After intervention (T2)	86.3	76.4	0.17
Follow up of 12 months (T3)	64.9	57.4	0.38
Modified Morisky Scale [(d)]			
Baseline (T1)			
low	19.6	21.6	
medium	46.5	41.2	
high	32.7	37.2	
After intervention (T2)			
low	28.7	31	0.94 [(e)]
medium	38	38.5	
high	33.3	30.5	
Beliefs about Medication Questionnaire			
Necessity Concern Differential [(f)]			
Baseline (T1)	3.7	3.4	
After intervention (T2)	3.8	3.9	0.86

	Group I +II UC N=271	Group II UC +consultations N=148	p-value (a)
Categories [g]			
Baseline (T1)			
Accepting	27.3	25	
Ambivalent	62.7	60.1	
Sceptical	4.4	5.4	
Indifferent	5.5	9.5	
After intervention (T2)			
Accepting	26.6	32.8	
Ambivalent	43.2	37.1	
Sceptical	14.8	17.6	
Indifferent	15.2	12.6	
Clinical outcomes			
Systolic Blood Pressure (mmHg)			
Baseline (T1)	136.4	136.7	
After intervention (T2)	155	155	0.71
Adherent (h)	25	20.9	0.52
Low- Density Cholesterol (mmol/L)			
Baseline (T1)	2.5	2.5	
After intervention (T2)	2.2	2.2	0.74
Adherent [i]	90.4	86.4	0.4

Legend:

a) Usual care and usual care + are combined and compared with usual care ++ group.
b) Mean number of days dispended divided by the mean number of days between prescription refill.
c) Percentage of patients (%) considered adherent according to PRD total of the cardiovascular medication (PRD was above or equal to 0.8).
d) Percentage of patients (%) who had low, medium or high adherent scores.
e) Low and medium adherence are combined and compared with high adherence group.
f) Differences between concern and necessity scores (means).
g) Percentage of patients (%) who are classified in the four different categories of the BMQ.
h) Percentage of patients (%) considered adherent according to systolic bloodpressure (<135 mmHg) and percentage (%) of patient using anti hypertension drugs.
i) Percentage of patients (%) considered adherent according to LDL-level (The recorded LDL- level after intervention was 20% lower of baseline LDL-cholesterol).

Table 3B: Differences in mean medication adherence in time.

All participants (N=419)	Baseline (T1)	After intervention(T2)	Follow up 12 months (T3)
Mean Possession Ratio			
Total of cardiovascular medication	0.72	0.92*	0.80**

* *p*-value <0.05 relative to T1
***p*-value<0.05 relative to T2

Discussion

This study evaluated a nurse-led web-based intervention based on the Health Belief Model [11,16,49] and the Necessity-Concern Framework[50] on medication adherence to treatment. Although we developed the intervention considering the recommendations of major reviews on medication adherence interventions[8,51-53] we did not see an effect of the developed intervention on our main adherence outcome. There are several explanations for the absence of an effect of this intervention. First, all patients in our study received the same structural cardiovascular care according to the European Guidelines of prevention of cardiovascular diseases.[20] A previous evaluation of our cardiovascular screening program showed that a structural multidisciplinary evaluation and initiation of the best medical treatment in combination with addressing unhealthy lifestyle reduces cardiovascular risk as indicated by a reduction in smoking, alcohol consumption, unhealthy eating, blood pressure, and LDL-cholesterol level.[54] Although medication adherence was not a structural approach in our usual care setting, the attention and screening on CVD-risk factors may have influenced adherence to medication adherence positively.

Second, in this study we used pharmacy refill data as adherence measure. Refill adherence rates have extensively been used for the evaluation of medication adherence. Compared to electronic monitoring, refill data provide researchers with a relatively simple method for investigating adherence to medication in large populations.[55] However, due to the increasing availability of automatic refills in the Netherlands, this measure may represent high adherence levels while patients do not necessarily take their medication.[10] By combining the refill data with a self reported questionnaire we therefore wanted to gain a fuller understanding of the adherence behaviour of the patients. The results of the used questionnaire also showed no differences in medication adherence between the groups. Last, although the use of eHealth interventions is recommended to improve healthy behaviour and for tailoring adherence interventions[44,56], the website was rarely used by our patients. Consequently, we were not able to study the perceived benefits of our eHealth intervention on adherence. Future studies should address this. There are several explanations why patients didn't use the website. Patients had to use a special personal code, and had to confirm their password with a code they received from a text message. These complicated steps may have influenced the use of the website negatively. High dropout rates may be a natural and typical feature of eHealth interventions[57], as was observed in our trial. There were fewer patients as expected who actually used the website and/or participated in the group consultation. This could be an indication that the intervention might be too intensive and experienced as a burden for patients. It could also mean that the intervention program was not enough exposed to enough patients to show a significant difference between the intervention group and usual care group. We developed the intervention program by using constructs of the HBM en the Necessity-Concern Framework but without involving patients. By personalizing the content of the individual consultations we believed we tailored the intervention to the personal need of the patients. On the other hand, the process in which the content of

the program was delivered was not tailored at all. Maybe only tailoring the content is not enough and should the process in which the intervention is delivered also be more tailored. For further research, we highly recommend involving patients in designing the intervention.

The study did show a difference in adherence in time for all groups. Adherence rates were higher during the study period and declined to levels comparable to baseline one year after the end of the study. Several explanations can be addressed for this phenomenon. First, participation in a study may have encouraged patients to be more adherent.[9] Second, all patients who participated in this study recently had a cardiovascular event. For these patients, the need for adherent behaviour is emerging.[35,58] Yet, as the event fades and there are no more symptoms, adherence can also decline.[2] This was also observed in our study. We looked even further to see if there was a difference in new users of CVRM medication and chronic users. We did observe a relatively high cohort of chronic users in our population but this did not have any effect on the outcome. Although we did not establish a difference between groups in the NCD, we observed a shift in the categories from ambivalent towards accepting in the intervention group, this shift was not observed in the usual care group. In the ambivalent group necessity beliefs are high but concern beliefs also. In the acceptance group necessity beliefs are high but the concern beliefs are low. In order to know if the change in necessity category for the intervention group will have a positive effect on the adherence rate over time, we need to measure the adherence rate further in time.

Although overall adherence was relatively high at 12 months follow-up, only 20 % of all patients had a systolic blood pressure within target. The mean blood pressure was even higher than it was at baseline. In contradiction, only 12% of all patients showed a LDL-cholesterol level of 20% above the baseline LDL-level. We can't really explain this difference. Several major studies have demonstrated nonadherence as a major determinant for not reaching target levels, as well for lipid lowering medication as for antihypertensive medication.[59,60] It can be suggested that not reaching target level of systolic blood pressure is not necessarily due to nonadherence of the medication.[61-63]

Limitations

The study had several shortcomings. There were challenges with recruitment and due to an organizational decision to no longer supporting the website, we had to stop inclusion early and the original recruitment target was not met. This may have underpowered our results. However, the confidence interval of the mean of the main outcome (the MPR), showed only a very small interval from -.005 to 0.082. Therefore we may assume that a larger population size would not have made a difference in MPR between groups. We also had to deal with missing data especially on the pharmacy refill data. The Dutch healthcare system doesn't provide a closed pharmacy system to a point of care

(like a hospital). Therefore, we were dependent on the willingness of the pharmacists to provide us with refill data. This led to missing data. We also had a relatively high percentage of patients who did not complete the intervention and/or did not show up at the evaluation screening. By using multiple imputations golden standard for dealing with missing data we believe we still provided a valid result of this study.[38,39] Last, the nurses who performed the individual usual care consultations if needed (e.g. to loose weight or to quit smoking) were the same nurses as the nurses who performed the consultations in our intervention group. This and the fact that all patients visited the same outpatient clinic while on chronic care support may led to contamination among the groups. In order to prevent from contamination among the groups, the nurses who give the usual care should be different from those in the intervention groups.

Conclusion

Our intervention to improve medication adherence in cardiovascular patients did not show an effect on improving poor medication adherence. The intervention program was developed using the existing evidence and by applying this evidence. The intervention was also developed so it could easily be applied to the already existing structured usual care for secondary preventive cardiovascular care. By performing a process evaluation we gained information that could help future researchers to include elements of this intervention. Elements of our intervention program could still lead to improving medication adherence, but we were not able to demonstrate it in this trial. This is maybe due to high adherence rates in both groups and/or the limited number of patients that complied with the intervention program. Adherence rates after the intervention were high in both the usual care and the intervention group. This could indicate that the structured provided care we already deliver to all cardiovascular patients has a positive effect on medication adherence. Or the effect of having a cardiovascular event was the key to better adherence.

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6

Chapter 6

Prior medication adherence of participants and non-participants of a randomized controlled trial to improve patient adherence in cardiovascular risk management

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Abstract

Background: Poor medication adherence is a major factor in the secondary prevention of cardiovascular diseases (CVD) and contributes to increased morbidity, mortality, and costs. Interventions for improving medication adherence may have limited effects as a consequence of self-selection of already highly adherent participants into clinical trials.

Methods: In this retrospective cohort study, existing levels of medication adherence were examined in self-decided participants and non-participants prior to inclusion in a randomized controlled study (RCT), evaluating the effect of an intervention to improve adherence. In addition, the non-participants were further divided into 'responders' and 'non responders'. All individuals had manifest cardiovascular disease and completed a questionnaire with baseline characteristics, the Beliefs about Medicines Questionnaire (BMQ) and the Modified Morisky Scale® (MMS®) as part of a regular screening program. A logistic regression was conducted to examine the relationship between study participation willingness, adherence level and the beliefs about medication.

Results: According to the MMS® the adherence level was comparable in all groups. In both (non)-participants groups, 36 % was classified as high adherent; 46% participants versus 44% non-participants were classified as medium adherent and 19% of the participants versus 20% of the non-participants were low adherent (p=0.91. The necessity concern differential (NCD) from the BMQ was 3.8 for participants and 3.4 for non-participants (p=0.32).

Conclusion: This study shows that adherence to medication and beliefs about medication do not differ between participants and non-participants before consenting to participate in an RCT. The study design seems not to have led to greater adherence in the study group.

Keywords: randomized controlled trials, informed consent, participation, selection bias, adherence.

I. Background

Cardiovascular risk reduction is predominantly based on lipid and blood pressure lowering treatment, inhibition of platelet aggregation, smoking cessation and control of obesity[1]. A limitation in lowering cardiovascular risk is poor adherence to prescribed medication[2] which may consequently can lead to increased morbidity, mortality and costs[3-6]. Nevertheless, a recent review with mostly cohort studies, showed that only 60% of people who use cardiovascular medication, were adherent to their cardiovascular medication[7]. In view of that there is a need for interventions to improve medication adherence in this population. Although there is a considerable amount of research in the field of interventions to improve medication adherence in cardiovascular patients, they often show only small effects[8]. It is suggested that patient recruitment methods in randomized controlled trials (RCT) to improve patient adherence to medication may influence outcome[8, 9]. An important observation is that patients participating in RCTs generally have higher adherence rates at baseline than could be expected based on observational studies[10-14]. It is conceivable that the informed consent procedure results in a selection of patients with higher adherence rates[12]. Willingness to participate is positively influenced by patients' engagement with their medical condition, high level of education and the influence of an important person[11, 15]. These characteristics are also considered as positive determinants for medication adherence[16]. Although a recent review showed that the inclusion of non-adherent patients was the single feature significantly associated with effective adherence interventions, most studies seem to include patients because they are willing to participate not because they are poor adherent[11]. It is suggested that patients participating in these RCTs already have a pre-existing high adherence level at baseline[10, 12-14]. Selection of participants with high levels of adherence at baseline, makes it difficult to show an improving intervention effect (ceiling effect)[8]. More understanding about the medication adherence of participants as well as non-participants before the start of these RCT's may contribute to a better understanding of why so many studies show no improvement in medication adherence. One possible explanatory determinant for (non) adherent behaviour is medication beliefs. Personal beliefs about need for treatment (necessity beliefs) and concerns about several potential adverse consequences (concern beliefs) could explain a large part of (non) adherent behaviour[16-18]. If patients perceive that the need for medication outweighs the concerns, they are more likely to be adherent to their medication(s)[19].

2. Methods

2.1 Aim

The aim of this study is to explore possible differences in adherence to existing prescribed medication in cardiovascular patients who did or did not consent to participate in an RCT which expressly explored the effects of an intervention to improve adherence. We hypothesized that patients who are willing to participate in a clinical trial are more likely to be medication adherent and have more 'necessity beliefs' about their medication compared to patients who are not willing to participate.

2.2 Study design and setting

In this retrospective cohort study we included patients who participated or declined participation in the (MIRROR) trial (a Multifaceted nurse -and web-based Intervention for impRoving adheRence to treatment in patients with cardiOvasculaR disease)[20]. In brief, the MIRROR trial was a prospective, randomized controlled trial in which patients aged ≥ 18 years and diagnosed with a manifest cardiovascular disease (i.e. acute coronary syndrome, peripheral arterial disease or stroke/Transient Ischemic Attack (TIA)) after providing written informed consent, were included. The MIRROR trial aimed to study the effect of different adherence enhancing strategies on cardiovascular medication adherence. Within this context, patients were randomized to usual care, an e-health intervention, and an e-health intervention combined with motivational technique consultations.

2.3 Participants

All patients referred to the Radboud University Medical Center with a new diagnosis of acute coronary syndrome, myocardial infarction, peripheral arterial disease, an aneurysm of the aorta or TIA or stroke over the prior 6 weeks were included into the hospital CVD screening program. This screening program aims to identify cardiovascular risk factors and consists of screening for lifestyle (smoking, diet and exercise), medication adherence by the self reported questionnaires Modified Morisky Scale ® (MMS®) and the Beliefs about Medication Questionnaire (BMQ), blood lipid levels, blood pressure, waist circumference, body mass index (BMI), glucose blood levels and a family history of cardiovascular diseases. If indicated, preventive therapies (medication and lifestyle interventions) are initiated and followed over time[1]. All patients referred to this screening program were asked to participate in the MIRROR- trial. 'Participants' were patients who were willing to participate in the intervention study and 'non-participants' were patients who declined informed consent for the MIRROR trial. Because adherence to medication may also differ between responders and non- responders to surveys, with responders having higher adherence levels[21] we divided the group of non-participants further. Retrospectively of the MIRROR trial, a letter was sent to all non-participants for a different study not subject to this paper. For this study, a signed informed consent was requested from the non-participants. Non-responders were patients who did not sign this letter. Responders were patients who signed the informed consent letter. We

aimed to explore if the non-responding subgroup of the non-participants differed from the responders with respect to their level of medication adherence on the basis of prior MMS® from the screening program.

2.4 Ethical Approval

The Ethical Committee waived the need for a formal informed consent for this study. The study was conducted according to the good clinical practice protocol and we used usual care data considering the research question of this study. Data was anonymized according to the research protocols of the Ethical Committee.

2.5 Outcomes

Participation or declining to participate to the RCT was the independent variable in this study. Adherence to medication and the beliefs about medication the dependent variables. Adherence to cardiovascular medication was calculated by the MMS® [22-24]. It consists of eight items aimed at measuring adherence. Each item accounts for 0 or 1 in the case questions are answered by no or yes respectively. Consequently, total MMS® scores range between 0 and 8. These scores were divided into three levels of adherence: low adherence (sum score < 6), medium adherence (sum score 6 to <8) and high adherence (sum score of 8)[25] . To evaluate patients' beliefs and perceptions about their medication, BMQ [26] was used. This validated questionnaire provides information about the beliefs, perceived necessity and concerns the patient has regarding their illness and prescribed medication. There are five statements regarding "necessity beliefs" and five regarding "concern beliefs". Patients indicated their degree of agreement with each individual statement about the use of their medicines on a five-point Likert scale. Thus, total scores for the necessity and concerns scales could range from 5 to 25. The necessity–concerns differential (NCD) was then calculated as the difference between necessity and concerns scores and had a possible range of -20 to 20.[19, 27]. To differentiate between patients on the basis of their beliefs about the necessity of their medication and their concerns about taking medication, the total necessity and concern scores[5-25] were split at midpoint (thus 5 - 12 was considered as low and 13 t/m 25 was considered as high). Patients were then classified into four different categories: accepting (high necessity and low concerns), ambivalent (high necessity and high concerns), skeptical (high concerns and low necessity) and indifferent (low concerns and low necessity) [28-30].

From all patients the type of CVD (acute coronary syndrome, myocardial infarction, peripheral arterial disease, an aneurysm of the aorta or TIA) was recorded. Also, the following baseline and clinical characteristics were collected: age, sex, level of education, employment status, the country of origin and the type of cardiovascular medication used.

2.6 Data collection and timeline

Data were derived from the screening program. Data were registered in a secure website which could only be accessed by nurses involved in the screening program. Within, on average, six weeks after the CVD-event, baseline characteristics and the questionnaires were collected for all patients as part of the screening program.

2.7 Statistical analyses

Data were analyzed and evaluated using SPSS version 22. Descriptive statistics (mean, median, standard deviation) were used for all variables. A Mann-Whitney Test was used to compare groups (participants and non-participants) with the non parametric outcome, the MMS®. Confounders were explored by performing a logistic linear test of all the characteristics in the case the groups significantly differed (including the NCD). The same Mann-Whitney test was performed to compare the NCD between the groups. A logistic regression was used to explore differences between (non) participants and the four belief groups. The same statistical analyses were performed for the responders and non-responders. A Kruskal-Wallis test was performed to explore the relationship between the NCD and the MMS® for all groups.

3. Results

In total, 900 patients with a new cardiovascular event between October 2011 and October 2013 were eligible for participation into the MIRROR trial. Of these, 419 agreed and 481 refused participation. Of all the non-participants who received a letter for another study, 220 did not respond. Consequently, 261 non-participants were classified as responders (Figure 1).

3.1 Patient Characteristics

The total cohort (participants and non-participants) had a mean age of 62 years and was predominantly male (67%). Participants significantly differed from non-participants with respect to age (61 years versus 63 years, p=0.001), male sex (71% versus 58%, p=0.001), systolic blood pressure (136 mmHg versus 142 mmHg, p=0.001). Participants were more frequently diagnosed with an acute coronary syndrome (36% versus 16%, p<0.001]), were using more beta blocking agents or agents acting on the renin-angiotensin system (58 % versus 46 % p= 0.001 and 59% versus 44 % p=0.001, respectively), and were using more lipid lowering medication (94% versus 82%, p<0.001). Among the non-participants, responders were older (64 versus 60 years, p=0.002) and used more agents acting on the renin-angiotensin system (48% versus 37 %, p=0.02) than non-responders (Tables 1 and 2).

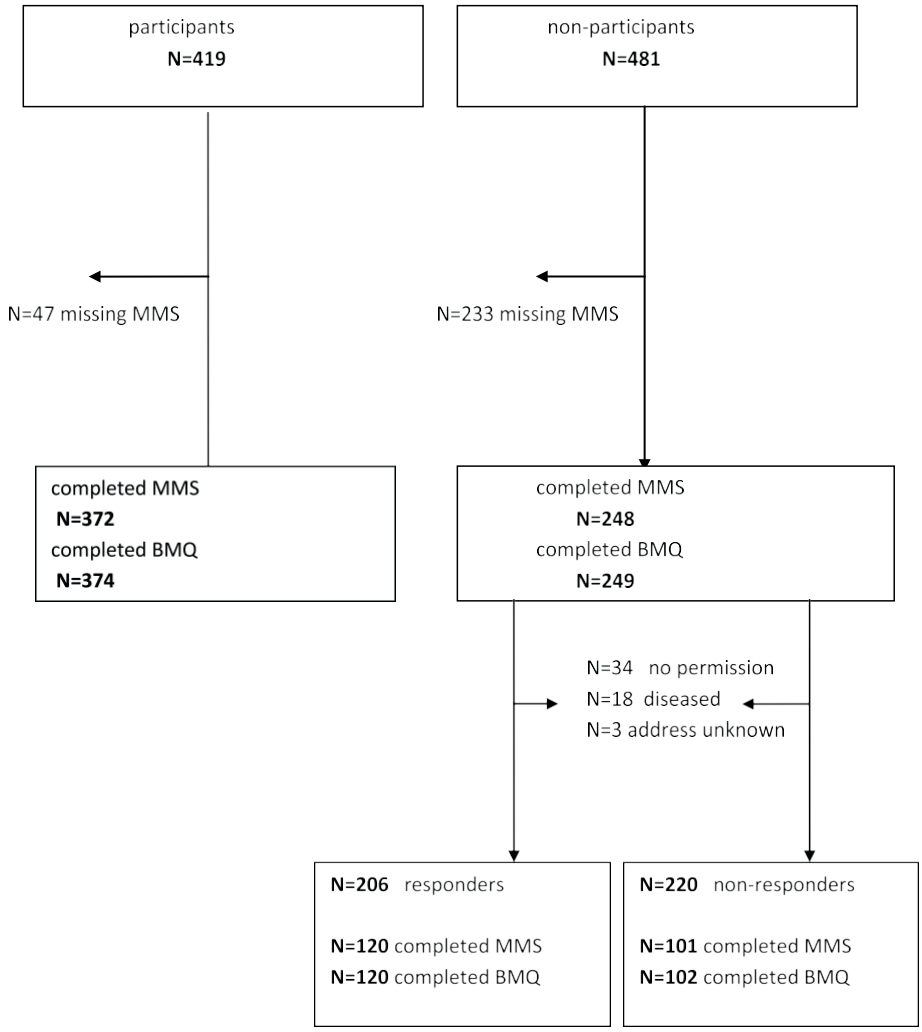

Figure 1 Participants, non-participants, responders and non responders and MMS and BMQ

Table 1 Differences in patient characteristics between participants and non participants in a RCT-trial on adherence

	Participants [*n* = 419]	**Non-participants [*n* = 481]**	***P*-value**
Age [mean, ±SD)	60.5 [±10]	63 [11]	0.001
Gender (N[%])			
Male	296 [7]	279 [58]	< 0.001
Female	123 [29	202 [42]	
Education level (N[%])			< 0.001
Primary	66 [18]	141 [31]	
Secondary	185 [49]	180 [39]	
University	124 [33]	140 [30]	
Labour (N[%])			0.08
Paid labour	137 [37]	123 [27]	
Unemployed	98 [26.3]	138 [30]	
Retired	138 [37]	199 [43.3]	
Country of origin is the Netherland (N[%])			0.66
Yes	327 [90]	398 [86]	
No	37 [10]	64 [14]	
Reason referral (N[%])			< 0.001
acute coronary syndrome	150 [36]	79 [16]	
peripheral arterial disease	71 [17]	101 [21]	
troke/TIA	198 [47]	301 [63]	
Blood pressure (mmHg; mean ± SD)			< 0.001
Systolic	136 [±18]	142 [±20]	0.23
Diastolic	77 [±11]	78 [±11]	
Body Mass Index (mean ± SD)	27 [±4]	26 [±4]	0.30
Waist (mean ± SD)			
Male	99.5 [±9]	98.4 [±12]	0.10
Female	92 [±14]	90 [±13]	0.07
Lipids (mmol/ltr, mean SD)			
Totaal cholesterol	4.5 [±1.1]	4.6 [±1]	0.7
Triglyceriden	1.8 [±1]	1.7 [±1]	0.01
HDL	1.2 [±0.3]	1.2 [±0.3]	0.002
LDL	2.5 [±0.9]	2.6 [±0.9]	0.66
Medication (N [%])			
Antithrombotic agents [ATC B01]	404 [98]	461 [98]	0.78
Diuretics [ATC C03]	109 [26]	135 [29]	0.44
Beta Blocking agents [ATC C07]	239 [58]	218 [46]	0.001
Calcium channel blockers [ATCC08]	65 [16]	72 [15]	0.86
Agents acting on [..] system [ATC C09]	244 [59]	206 [44]	0.001
Lipid modifying agents [ATC C10]	387 [94]	384 [82]	< 0.001

3.2 Medication Adherence

We did not observe differences in adherence measured by the MMS® between both groups (p= 0.99). According to the MMS® 19% of the participants was classified as low adherers compared to 20% in the non-participants group. Forty-six percent of the participants and 44% of the non-participants were classified as medium adherers, whereas 36% and 37% were classified as high adherers, respectively. There were no differences in adherence according to the MMS® between responders and non-responders (p=0.47). In both the responders and non-responders group, 36% scored high on adherence. Sixteen percent of the responders were low adherent compared to 24% in the non-responder group. Forty-eight percent of the responder group scored a medium adherence and 41% of the non-responders. Compared to study participation all characteristics that significantly differed between both groups were separately analyzed by a logistic regression analyses. None of the variables significantly influenced the association between study participation and adherence according to the MMS®. (Tables 3 and 4)

Table 2 Differences in patient characteristics between responders and non-responders

	responder [*n*=206]	**Non-responder [*n* = 220]**	***P*-value**
Age (mean ± SD)	64 [10]	60 [12]	0.002
Gender (N[%])			
Male	120 [58]	129 [59]	0.93
Female	86 [42]	91 [41]	
Education level (N[%])			
Primary	52 [26]	67 [32]	0.43
Secondary	80 [41]	81 [39]	
University	66 [33]	62 [29]	
Labour (N [%])			
Paid labour	49 [25]	68 [33]	0.08
Unemployed	55 [28]	64 [31]	
Retired	94 [47]	77 [36]	
Country of origin is the Netherlands (N[%])			
Yes	174 [88]	181 [86]	0.62
No	24 [12]	29 [14]	
Reason referral (N[%])			0.89
acute coronary syndrome	34 [16]	37 [17]	
peripheral arterial disease	47 [23]	46 [21]	
stroke/TIA	125 [61]	137 [62]	
Blood pressure (mmHg; mean ± SD)			
Systolic	140 [±19]	142 [±20]	0.30
Diastolic	78 [±11]	79 [±10]	0.23
Body Mass Index (mean ± SD)	26 [±4]	26 [±4]	0.22

	responder [*n*=206]	Non-responder [*n* = 220]	*P*-value
Waist (mean ± SD)			
Male	97 [±11]	99 [±12]	0.16
Female	91 [±13]	89 [±13]	0.36
Lipids (mmol/ltr; mean ± SD)			
Totaal cholesterol	4.6 [±1]	4.6 [±0.9]	0.73
Triglyceriden	1.7 [±1]	1.7 [±0.9]	0.01
HDL	1.3 [±0.3]	1.2 [±0.3]	0.06
LDL	2.5 [±0.9]	2.6 [±0.9]	0.78
Medication(N [%])			
Antithrombotic agents [ATC B01]	196 [97]	213 [98]	0.27
Diuretics [ATC C03]	62 [31]	56 [26]	0.28
Beta Blocking agents [ATC C07]	93 [46]	96 [44]	0.74
Calcium channel blockers [ATCC08]	30 [15]	34 [16]	0.80
Agents acting on [..] system [ATC C09]	98 [48]	80 [37]	0.02
Lipid modifying agents [ATC C10]	166 [82]	173 [80]	0.59

3.3 Beliefs about medication

Based on the BMQ the necessity concerns differential (NCD) was 3.8 among participants compared to 3.4 among non-participants (p= 0.13). Of all the participating and non-participating patients 26% were in the accepting group, 67% in the ambivalent group, 3% in the skeptical and 4% in the indifferent group. No differences were observed between the two groups (p=0.23). The mean score of the NCD in the responders and non-responders groups was 3.6 and 3.1 respectively (p=0.21). Among the non-responders 24% were in the accepting group, 61% in the ambivalent group, 6% in the skeptical group and 9% in the indifferent group. For the responders this was 27%, 72%, 2% and 0% respectively. Differences between both groups were statistically significant (p<0.01). Logistic regression analysis on NCD did not significantly influence the association between study participation and adherence according to the MMS®.

Table 3 Differences participants and non-participants in adherence and beliefs about medication

	Totaal	Non-participants	Participants	P-value
Adherence according to the MMS N [%]				0.99
Low adherence	119 [19]	49 [20]	70 [19]	
Medium adherence	279 [45]	109 [44]	170 [46]	
High adherence	222 [36]	90 [36]	132 [35]	
NCD mean [SD]	3.65[±4.8]	3.4 [±5]	3.8 [±4.9]	0.13
Belief Groups [N%]				0.23
Accepting	160 [26]	61 [24]	100 [27]	
Ambivalent	418 [67]	165 [67]	255 [68]	
Sceptical	19 [3]	10 [4]	9 [2]	
Indifferent	23 [4]	13 [10]	10 [3]	

Table 4 Differences responders and non-responders in adherence and beliefs about medication

	Totaal	Non-responders	Responders	P-value
Adherence according to the MMS N [%]				0.47
Low adherence	43 [20]	24 [24]	19 [16]	
Medium adherence	99 [45]	41 [40]	58 [48]	
High adherence	79 [36]	36 [36]	43 [36]	
NCD mean [SD]	3.6 [±4.9]	3.1 [±5]	4 [±4.9]	0.17
Belief Groups [N%]				0.001
Accepting	56 [25]	24 [24]	32 [27]	
Ambivalent	148 [67]	62 [61]	86 [72]	
Sceptical	8 [4]	6 [6]	2 [2]	
Indifferent	10 [4]	10 [9]	0 [0]	

4. Discussion

To our knowledge this is the first study exploring the differences in medication adherence in patients who did or did not consent to participate in an RCT evaluating the effect of an intervention to improve medication adherence. Our study showed that patients willing to participate in an RCT evaluating the effect of an intervention to improve medication adherence, have a comparable adherence level to patients who declined participation. Even by further exploring the non-participant group in responders and non-responders, we did not observe differences in adherence between the groups. Consequently, the results of this study suggest that a population representative in adherence level participated in an RCT evaluating the effect of an intervention to improve medication adherence.

Previous studies suggested that patients not participating in RCTs to improve medication adherence have a different pre-existing adherence level from patients who participate[10-14]. This was supported by the observed differences in adherence levels between these RCTs and observational studies[10-14]. Typically, adherence levels among patients in RCTs were higher than in observational studies. Although not different among participants and non-participants, adherence in this study was also high. An explanation for the high adherence rate in both groups could be that we started inclusion for the RCT within six weeks after the cardiovascular event. For cardiovascular patients who just had an event, the need for adherent behaviour is emerging[31, 32]. Yet, as the event fades and symptoms subside, adherence levels can also decline[33]. Research with a long follow up is needed to establish if there will be a difference in adherence between participants and non-participants over time.

In all groups, we observed significant differences in patient characteristics. Compared to non-participants, participants were younger and more were highly educated. This was also observed among responders and non-responders. These are known as prognostic characteristics for patients who are willing to participate in a clinical trial[15] and for a high adherence level[34, 35]. Although the relationship between socio-demographic variables and adherence is mainly weak and inconsistent[34, 36, 37] it was expected that these characteristics could have been an explanation for the assumed higher adherence rates in the participant groups. However, we could not support this hypothesis. Also, next to the high adherence rate, a high mean NCD score was present in all groups. This only confirmed the adherent behaviour in both groups[19]. It is also congruent with earlier studies showing that medication beliefs can be a more powerful predictor of medication adherence than clinical and socio-demographic factors[19, 38]. However, we did not observe a relationship between NCD and trial participation. We did observe a significant difference in the beliefs about medication groups in the (non) responder groups. More patients of the non-responder group were also in the indifferent and skeptical group. Non-responders of surveys are known for more negative evaluations of healthcare[39]. This could be associated with higher concern beliefs in medication as these are partly influenced by the prescriber-patient relationship in healthcare[40]. The number of patients

who differed in these groups was very small and the NCD did not differ. More research is needed to draw any conclusions on this point.

This study had some limitations. We had to deal with missing data especially in the self reported questionnaires BMQ and MMS®. There were fewer missing in the participants group compared to the non-participants group. The questionnaires were just implemented in the screening program. As the questionnaires were also part of the MIRROR trial, more attention could have been paid to participants for documenting these questionnaires. So there were more patients in the non-participant group who did not fill out the MMS®. These patients could very well be non-adherent[21]. There are different methods available to measure adherence. Each method has advantages and disadvantages. The MMS® [22, 24, 41] is a validated questionnaire that can be easily applied to large populations. As MMS® is a subjective measure, adherence levels may be higher than what is expected in real life. Refill data from the out-patient pharmacy on the other hand has been used extensively to provide insight into drug acquisition and dispensing[42]. However, to use the pharmacy refill data we need an informed consent from patients. This study however used data from patients collected only in standard care because we wanted to include patients who declined participation in a RCT. Other methods, such as MEMS or pill count, seem to influence patient's behavior through direct confrontation . Moreover, application of MEMS is relatively expensive, especially when applied in standard care[42]. The BMQ was used because, to our knowledge, is the only validated questionnaire that evaluates patients' beliefs, necessity and concerns the patient has according to his illness and prescribed medication. This in contrast to other validated adherence questionnaires that measure specific medication-taking behavior of patients[26, 43]. The high NCD score confirmed the prediction of adherent behaviour in both groups[19, 38].

4.1 Conclusion

This study showed no differences in medication adherence between participants and non-participants prior to the inclusion of the MIRROR trial. A representative group seems to have participated in this randomized controlled trial designed to improve medication adherence[20].

6. Abbreviations

CVD	cardiovascular diseases
RCT	randomized controlled study
BMQ	Beliefs about Medicines Questionnaire
MMS®	Modified Morisky Scale®
NCD	necessity concern differential
MIRROR trial	a Multifaceted nurse -and web-based Intervention for impRoving adheRence to treatment in patients with cardiOvasculaR disease
TIA	Transient Ischemic Attack
BMI	body mass index

6. Declarations

6.1 Ethics approval
The Ethical Committee (the human related research committee of the Arnhem-Nijmegen region) waived the need for a formal informed consent for this study. The study was conducted according to the good clinical practice protocol and we used usual care data considering the research question of this study. Data was anonymised according to the research protocols of the Ethical Committee.

6.2 Consent for publication
Not applicable

6.3 Availability of data and materials
The datasets generated and analyzed during this study are not publicly available due to the Dutch privacy laws. But are available from the corresponding author on reasonable request.

6.4 Competing interests
The authors declare that they have no competing interest.

6.5 Funding

There was no funding for this study.

6.6 Authors 'contributions

AS, SB, HvO have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AS and JL have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. AvD and KvL have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

6.7 Acknowledgement

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Chapter 7

Identification of Cardiovascular Patient Groups at Risk for Poor Medication Adherence: A Cluster Analysis

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Abstract

Background: Poor medication adherence limits the secondary prevention of cardiovascular diseases (CVDs) and leads to increased morbidity, mortality, and costs. Identifying groups of patients at risk of poor adherence behavior could enable an intervention to be developed and target patients appropriately.

Objective: The first aim of this study was to identify homogeneous subgroups of cardiovascular outpatients based on their cardiovascular risk factors. Subsequently, differences in medication adherence between these groups were examined.

Methods: In this retrospective, observational study, patients with an established CVD were included. Well-known cardiovascular risk factors such as smoking, diet, exercise, blood lipid levels, blood pressure, and body mass index were collected. To identify patient subgroups, a 2-step cluster analytic procedure was performed. Differences between the groups on medication adherence were determined on the outcome of the Modified Morisky Scale. Data collection took place between October 2011 and January 2013.

Results: Cardiovascular risk factors of 530 patients were included in the cluster analysis. Three groups were identified. Compared with other clusters (clusters 1 and 2), cluster 3 contained significantly fewer patients who could be classified as highly adherent and more patients classified as medium adherent (23% and 57%, respectively; P = .024). This group was characterized by a younger age (53% were <55 years old) and using a relatively low number of different medications (41% used <4 different medications). Besides, in this subgroup the most smokers (37%), unhealthy alcohol users (27%), and patients with unhealthy eating habits (14%) were present. Conclusion: This study showed that cardiovascular patients who are relatively young and have an unhealthy lifestyle are at risk for nonadherent behavior.

Key words: cardiovascular nursing, cluster analysis, lifestyle, medication adherence, secondary prevention

Introduction

Cardiovascular disease (CVD) remains a major cause of death worldwide. In 2015, 17.9 million people died of the disease.[1] Twenty-five percent of these CVD events occur in individuals with a previously established CVD.[2] The risk for CVDs can be reduced by improving the behavioral risk factors associated with CVD, such as smoking, an unhealthy diet, obesity, physical inactivity, and harmful use of alcohol.[3] In addition to these behavioral interventions, pharmaceutical

treatment with aspirin, statins, and blood pressure (BP)–lowering medication significantly reduces morbidity and mortality in patients with established CVD.[4,5] Unfortunately, a substantial proportion of people do not adhere adequately to cardiovascular medications. A recent review showed that only 60% of people who use cardiovascular medication were adherent to their cardiovascular medication.[6] About 10% of all CVD events may even be attributed to poor adherence to medications alone.[7] Barriers contributing to suboptimal medication adherence can be distinguished in objective factors, such as sociodemographic and clinical variables, and more subjective factors, such as patients' personal beliefs about medication.[8] Such determinants for nonadherent behavior are mostly difficult to change and influence each other.[9]

Even though there are numerous interventions to improve medication adherence in cardiovascular patients, they often show only small effects.[10] Besides, these interventions are often complex, which make adaptation, implementation, scalability, and sustainability difficult in cardiovascular risk management (CVRM).[2] To adequately target interventions to patients who are at risk of nonadherent behavior, we need to have a better understanding of who should be targeted through what interventions.

According to the European guidelines in CVRM, in all patients who have had a cardiovascular event, risk factors of CVD (high BP, high cholesterol levels, and unhealthy lifestyle behavior) should be identified and preventive therapies (medication and lifestyle interventions) should be taken.[11] It is known that multiple barriers can influence adherence.[12] Therefore, these risk factors, together with baseline characteristics (such as age and occupation),may also be used to identify patients with CVD who are at risk of nonadherent behavior. Other studies applying cluster analysis to medication adherence indicate that these homogeneous groups can be identified.[13-15] By combining and clustering the risk factors of CVD, patient groups who are at risk of nonadherent behavior might be better determined. Consequently, an intervention to improve medication adherence can be better targeted. The present study applies the well-known CVD risk factors of individual patients to a subgroup of patients with suboptimal adherence levels. The discriminative power of these subgroups might be enhanced by incorporating data about patients' beliefs about medication. Building on results of previous research,[16] the first aim of this study is to identify homogeneous subgroups of cardiovascular patients based on their potential cardiovascular risk factors and beliefs about their medication.

The second aim of this study is to examine whether these subgroups of patients differ in the level of medication adherence. Identifying these high-risk groups could enable an intervention to be developed and patients to be targeted more appropriately.[13]

METHODS

Setting and Sample

All patients referred to the Radboud University Medical Center with a new diagnosis of 1 of the following conditions are included in the hospital CVD screening program: acute coronary syndrome, myocardial infarction, peripheral arterial disease, an aneurysm of the aorta, or transient ischemic attacks or ischemic stroke. This regular screening program aims to identify cardiovascular risk factors and consists of a screening of lifestyle (smoking, diet, and exercise), blood lipid levels, BP, and body mass index(BMI). If indicated, preventive therapies (medication and lifestyle interventions) are structurally initiated and followed over time.[11] For the sample size, all the patients who participated in this hospital screening program between 2012 and 2013 (530) were included in the analysis. Seven percent of the patients did not fill out the Modified Morisky Scale (MMS) document and therefore were excluded.

Data Collection and Timeline

Data were derived from the screening program and captured in a secured website that could be accessed only by the nurses involved in the screening program by entering a security code.

Within, on average 6 weeks after the CVD event, baseline characteristics and the questionnaires were collected for all patients as part of the screening program. The data used to identify patients at risk for nonadherent behavior were organized using the World Health Organization (WHO) Multidimensional Adherence Model. This conceptual framework allows the construction of poor adherence profiles in patients with chronic diseases.[17] The WHO organizes adherence barriers into 5 dimensions; healthcare/health system–, therapy-, condition-, social/economic-, and patient-relatedbarriers.[18] Data from the regular screening program and from an additional questionnaire used in a previous study were classified according this framework.

Healthcare System–Related Factors

Major components of the healthcare system dimension are patients' perceptions about the healthcare system, satisfaction with pharmacy services, and availability of financial compensation for the medication.[12] In our population, all patients were drawn from the same hospital wide screening program and were already discharged from the hospital. The hospital care and drugs for all these patients are reimbursed according to the national healthcare insurance terms. As a result, healthcare-system characteristics do not

vary among eligible patients and were therefore not considered as a separate dimension in the present study.

Therapy-Related Factors

Examples of barriers identified in this dimension are occurrence of side effects, complexity of drug regimens, and interference of medication taking with daily routines.[12] Collected data from the regular screening program for this dimension were the number of doses of all medication and the type of cardiovascular drugs (platelet aggregation inhibitors, lipid-modifying agents, and antihypertensive drugs) prescribed. All data included the names of the medication arranged by the Anatomic Therapeutic Chemical code. The Anatomic Therapeutic Chemical classification system is a measuring unit for international drug utilization monitoring and research.[19] For the cluster analysis, the number of prescribed medications was categorized by the researchers into small (<4 different drugs), medium (4–8 different drugs), and large (using ≥9 different drugs).

Condition-Related Factors

Absence of symptoms in the years after an event may result in the perception that the illness is benign. This may lead to doubts about the necessity of continuous treatment.[20] All different CVDs were recorded in our sample. Although a high BMI and especially hypertension and hyperlipedemia are clinical outcomes, they can also be considered as an indicator for (non)adherent behavior.[21] In conformity with the hospital screening program, blood was drawn from all patients to determine low-density lipoprotein (LDL) cholesterol levels. Blood pressure was measured according to the recommendations of the European Society of Hypertension[22] with a validated automated device and based on a mean of 4 office measurements. The BMI was calculated for each patient. All variables were dichotomized for the cluster analysis (within target levels or not). Target BP levels were set according to the European Society of Hypertension recommendations (i.e., a systolic BP level of <140 mm Hg). Target LDL cholesterol level should be 1.8 mmol/L (70 mg/dL). Overweight (yes or no) was defined by a BMI ranging greater than 25 kg/m2.

Social/Economic Factors

Barriers identified from this dimension can be a lack of social support, financial burden of medications, and health literacy.[12,23] It is also generally assumed that older (≥65 years) patients with CVD usually have worse medication adherence compared with younger (<55 years) patients.[23,24] The following social economic characteristics were collected as part of the usual screening program: age, level of education, and employment status. Age was divided into 3 groups: young (<55 years), middle-aged (55–75 years), and aged (>75 years).

Patient-Related Factors

An unhealthy lifestyle (smoking, unhealthy diet, and a lack of physical exercise) is associated with an increased risk of cardiovascular events.[22] It is questionable whether

poor medication adherence directly causes worse health outcomes or whether there are concomitant factors. It has been speculated that medication adherence is a marker for other health choices, the so-called "healthy adherer effect." [25] Indeed, adherence to lifestyle modification was significantly associated with medication adherence in patients with post–acute myocardial infarction, suggesting that patients with low medication adherence may have an unhealthy lifestyle. [26] If this hypothesis is correct, an (un) healthy lifestyle could be a marker for (non)adherent behavior. [27] The hospital CVRM program includes a lifestyle risk assessment for smoking, alcohol use, physical activity, and eating habits. [28] Lifestyle is evaluated through self-report using a computerized lifestyle questionnaire and covers smoking, alcohol use, physical activity, and eating habits, based on validated questionnaires. They comprise the following sections ; Questions regarding smoking status using questions from the Fragerström questionnaire with11questionsaboutcurrent smoking status, smoking history, smoking patterns, and smoking addiction.[29] If a patient smoked at the time the questionnaire was completed, he/she was identified as having a risky smoking lifestyle.

Ten questions from the Alcohol Use Disorders Identification Tests were used to measure the quantity and frequency of alcohol consumption and problems associated with it. [30-32] Three questions ask about the frequency and amount of use,3 questions ask about alcohol dependency, and 4 questions ask about drinking-related problems. Risky alcohol consumption was defined by the Dutch College of General Practitioners as men drinking more than 3 (standard Dutch glass) units a day and women drinking more than 2 units a day [33] and concerned a score of 6 or more on the Alcohol Use Disorders Identification Tests.

Three questionnaires, with in total 28 questions, measured eating habits. These questionnaires have been validated in a Dutch eating-habits study about fat, fibre, fruit, and vegetable intake.[34,35 36,37] Fourteen questions measured total and saturated fat intake as a percentage of total caloric intake. Eight questions measured fibre intake in grams/ kilocalories, and 6 questions measured fruit and vegetable intake in grams per day. Having an unhealthy diet was based on 4 criteria: more than 35% of the total caloric intake as fat, less than 3 g of fibre per day, more than 200 g of vegetables per day, and less than 2 servings of fruit per day. These criteria fit the Dutch standards of healthy diet.

Finally, 7 questions assessed habitual physical activity. These questions were taken from the short version of the International Physical Activity Questionnaire.[38,39] The questions asked about the frequency and intensity of physical activity each week. Patients who had fewer than 30 minutes of moderate exercise per day were placed into the "risky lifestyle" category.

Central to patients' medication adherence is their judgment of their personal needs for taking medication. [9,40,41] One possible explanatory determinant for (non)adherence behavior comprises the beliefs about medication. Personal beliefs about needs for

treatment (necessity beliefs) and concerns about several potential adverse consequences (concern beliefs) could explain a large part of (non)adherent behavior.[9,40,41] If patients perceive that the need for medication outweighs the concerns, they are more likely to be adherent to their medication.[42] To evaluate these patients' beliefs and perceptions about their medication, the Beliefs About Medicine Questionnaire (BMQ) [43] was used. This questionnaire was completed as part of the parent study.[16] Respondents stated their degree of agreement with each individual statement about medicines on a 5-point Likert scale. To separate patients based on their beliefs about the necessity of their medication and their concerns about taking medication, the total necessity and concern scores (5–25) were split at midpoint (thus, 5–12 was considered as low and 13–25 was considered as high). Patients were then classified into 4 different categories according to the guideline : accepting(high necessity and low concerns), ambivalent (high necessity and high concerns), skeptical (high concerns and low necessity),and indifferent (low concerns and low necessity).[44-46] Adherence was measured using the MMS © [47-49] a validated questionnaire consisting of 8 items aimed at measuring adherence. Each item accounts for 0 or 1 when questions are answered by no or yes, respectively. Consequently, total MMS scores range between 0 and 8. These scores were divided into 3 levels of adherence: low adherence (sum score <6), medium adherence (sum score 6 or 7), and high adherence (sum score of 8).

Statistical Analysis

Cluster analysis was used to identify groups of patients at risk for nonadherence.

To identify patient subgroups with different adherence behavior, a 2-step cluster analytic procedure was performed. [13] First, a hierarchical cluster analysis (the Ward method) was performed to determine the number of clusters. The dendrogram obtained with the Ward procedure was inspected to identify the best cluster solution. Then, a K-means cluster analysis was undertaken to specify the cluster number derived from the Ward method. To establish the difference between the groups on medication adherence, the groups (clusters) were compared by a $\chi 2$ test (all variables were categorical) on the outcome of the MMS. SPSS version 25 was used to perform the analyses.

RESULTS

Study Sample

A total of 530 patients participated in this hospital screening program between 2012 and 2013. Thirty-eight (7%) patients did not fill out the MMS, so 492 patients were included in the analysis. For the demographics of the total sample, see Table 1. On average, most patients used a medium amount of medication (n = 325 [66%]) and almost all used a plated aggregation inhibitor (n = 485 [99%]). Lipid-modifying medication was also used by a large number of patients (n = 453 [92%]). The least frequently used medication was cardiac therapy (n = 65 [13%]). Blood pressure and LDL were within target level for

294 (60%) and 281 (57%) of the patients, respectively. Most patients were middle aged (n = 296 [60%]) and retired (n = 192 [39%]) and had completed secondary education (n = 223 [45%]). Based on the BMQ, we could differentiate between 4 belief groups. In total, 134 patients (27%) were in the accepting group and 324 (66%) in the ambivalent group. Concerning their lifestyle, 117 patients (24%) were smokers, 77 patients (15%) had unhealthy alcohol consumption, 175 patients (36%) had an unhealthy physical activity, and 54 patients (11%) had unhealthy eating habits. The sample characteristics regarding the variables as addressed in the Methods section are presented in Table 2.

Table 1: Demographics Total Sample

	n (%) or Mean ± SD
Gender Male	324 (66)
Age, y	61 ± 11
Young (<55)	150 (31)
Middle-age (56–75)	296 (60)
Aged (>75)	46 (9)
Education level Primary	109 (22)
Secondary	223 (45)
University	160 (33)
Employment status Employed	162 (33)
Unemployed	15 (3)
Incapacitate	82 (17)
Retired	192 (39)
Housewife/-men	41 (8)

Clusters of Patients

Cluster analysis using the Ward method led us to the selection of a 3-cluster solution. This was followed by a K-means cluster analyses where the number of clusters was defined in advance. Table 3 shows the validity of the cluster solutions. Some of the used medication, LDL, level of education, and the belief groups showed no significant difference between the clusters. According to the variables on which the clusters significantly differed, the cluster profiles are described as follows.

Cluster 1

This cluster comprised 212 patients (43% of the total population).Compared with other clusters, patients were of higher age (n = 36[17%] were>75 years), used more medication (n = 38 [18%] used >9 different medications), and reached target BP the least (n = 95 [55%] did not reach target BP). On the other hand, patients were more likely to have a healthy lifestyle, as reflected by healthy eating habits (n = 64 [31%]) and healthy alcohol use (n = 153 [72%]).

Table 2: Medication Details, Clinical Outcomes, Lifestyle Characteristics, and the Belief Groups;

Total Sample (N = 402)	**n (%) or Mean ± SD**
Number of used medication Small (<4)	99 (20)
Medium (4–8)	325 (66)
Large (>9)	68 (14)
Used medication Platelet aggregation	485 (99)
Lipid modifying	453 (92)
Antihypertensive Cardiac therapy	65 (13)
Diuretics	120 (24)
β-Blockers	269 (55)
Calcium channel blockers	70 (14)
RAAS inhibitors	268 (55)
Blood pressure, mm Hg	138.3 ± 19.4
Blood pressure at target level	294 (60)
LDL, mmol/L	2.5 ± 0.9
LDL at target level	281 (57)
BMI, mean ± SD	26.9 ± 4.3
BMI at target level	181 (37)
Currently smoking	117 (24)
Alcohol use Healthy	318 (65)
Could be improved	97 (20)
Unhealthy	77 (15)
Physical activity Healthy	265 (54)
Could be improved	52 (11)
Unhealthy	175 (36)
Eating habits Healthy	118 (24)
Could be improved	320 (65)
Unhealthy	54 (11)
Belief group Accepting	134 (27)
Ambivalent	324 (66)
Skeptical	15 (3)
Indifferent	19 (4)

Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; RAAS, Renin-angiotensin-aldosterone system inhibitors.

Cluster 2

This cluster comprised 174 patients (35% of the total population). Compared with the other clusters, the highest number of patients reached target BP (n = 133 [76%]) and were mostly overweight (n = 134 [77%]). In this cluster, patients used the lowest number of medications (n = 4 [2%] used<4 medications). Most used a medium number of drugs, of which β-blockers (n = 164 [94%]), Renin-angiotensin-aldosterone system inhibitors (n = 147 [85%]), cardiac therapy (n = 45 [26%]), and lipid modifying medication (n = 168 [97%]) were highest when compared with those in the other groups. According to their lifestyles, most patients were unhealthy with respect to physical activity (n = 86 [49%]) and healthy eating habits (n = 32 [18%]). On the other hand, non-smokers were highly present in this group(n=151[87%]).

Table 3: Cross tabulation of the 3-cluster solutions using Ward and K-Means Methods Cohen K= 0.42)

K-Means				**Total**
Ward	Cluster 1	Cluster 2	Cluster 3	
Cluster 1	200	11	1	212
Cluster 2	108	1	65	174
Cluster 3	0	0	106	106

Cluster 3

This cluster comprised 106 patients (22% of the total population). Compared with other clusters, patients were relatively young (n = 56 [53%] were younger than 55 years) and were employed (n = 100 [94%]). This group contained the highest number of patients who used a small amount of medication (n = 44 [41%]) and represented a low use of β-blockers (n = 23 [22%]), RAAS inhibitors (n = 35 [33%]), and cardiac therapy (n = 1 [1%]). On the other hand, compared with other clusters, most of these patients used more than 3 units of alcohol a day (n = 29 [27%]), smoked (n = 39 [37%]), and had unhealthy eating habits (n = 15 [14%]).

Table 4 presents the demographics, medication details, clinical outcomes, lifestyle characteristics, and the belief groups for all clusters.

Medication Adherence

Eighteen percent (n = 90) of all patients had a suboptimal level of adherence. Forty-six percent (n = 225) were medium adherent and 36% (n = 177) were highly adherent. Among the 3 clusters, patients in cluster 3 were significantly less highly adherent (n = 38 [23%]). In addition, 57% (n = 60) of the patients in cluster 3 were classified as medium adherent. Differences among the 3 clusters were significantly different (P = .024).

Table 4: Demographics, Medication Details, Clinical Outcomes, Lifestyle Characteristics, and the Belief Groups for All Clusters

	Cluster 1 (n = 212)	**Cluster 2 (n = 174)**	**Cluster 3 (n = 106)**	**P**
Number of used medication				<.001
Small (<4)	51 (24)	4 (2)	44 (41)	
Medium (4–8)	123 (58)	145 (84)	57 (54)	
Large (>9)	38 (18)	25 (14)	5 (5)	
Used medication Platelet aggregation	209 (99)	171 (98)	105 (99)	.87
Lipid modifying	189 (89)	168 (97)	96 (91)	.02
Antihypertensive Cardiac therapy	19 (9)	45 (26)	1 (1)	<.001
Diuretics	58 (27)	33 (19)	29 (27)	.12
β-Blockers	82 (39)	164 (94)	23 (22)	<.001
Calcium channel blockers	34 (16)	28 (16)	8 (8)	.08
RAAS inhibitors	86 (40)	147 (85)	35 (33)	<.001
Blood pressure at target level	95 (45)	133 (76)	66 (62)	<.001
LDL at target level	111 (52)	112 (64)	58 (55)	.051

	Cluster 1 (n = 212)	Cluster 2 (n = 174)	Cluster 3 (n = 106)	P
BMI at target level	95 (45)	40 (23)	46 (43)	<.001
Age				<.001
Young (<55)	33 (16)	61 (35)	56 (53)	
Middle-age (56–75)	143 (67)	103 (59)	50 (47)	
Aged (>75)	36 (17)	10 (6)	0 (0)	
Level of education				.09
Primary	55 (26)	40 (23)	14 (13)	
Secondary	96 (45)	77 (44)	50 (47)	
University	61 (29)	57 (33)	42 (40)	
Employment status				<.001
Employed	0 (0)	62 (36)	100 (94)	
Unemployed	3 (1)	6 (3)	6 (6)	
Incapacitate	51 (24)	31 (18)	0 (0)	
Retired	122 (58)	70 (40)	0 (0)	
Housewife/-men	36 (17)	5 (3)	0 (0)	
Belief group				.18
Accepting	62 (29)	40 (23)	32 (30)	
Ambivalent	136 (64)	125 (72)	63 (59)	
Skeptical	4 (2)	6 (3)	5 (5)	
Indifferent	10 (5)	3 (2)	6 (6)	
Currently smoking	55 (26)	23 (13)	39 (37)	<.001
Alcohol use				<.001
Healthy	153 (72)	109 (63)	56 (53)	
Could be improved	38 (18)	38 (22)	21 (20)	
Unhealthy	21 (10)	27 (15)	29 (27)	
Physical activity				<.001
Healthy	116 (63)	71 (41)	78 (74)	
Could be improved	26 (12)	17 (10)	9 (9)	
Unhealthy	70 (33)	86 (49)	19 (18)	
Eating habits				.05
Healthy	64 (31)	32 (18)	22 (21)	
Could be improved	130 (61)	121 (70)	69 (65)	
Unhealthy	18 (8)	21 (12)	15 (14)	
Belief group				.18
Accepting	62 (29)	40 (23)	32 (30)	
Ambivalent	136 (64)	125 (72)	63 (59)	
Skeptical	4 (2)	6 (3)	5 (5)	
Indifferent	10 (5)	3 (2)	6 (6)	

Data are presented as n (%) of patients.
Abbreviations: BMI, body mass index; LDL, low-density lipoprotein; RAAS, Renin-angiotensin-aldosterone system inhibitors.

Table 5 presents the differences in level of adherence based on the MMS, by cluster.

Table 5: Differences in Level of Adherence Based on the Modified Morisky Scale by Cluster

	Cluster 1	Cluster 2	Cluster 3	P
Low adherence	43 (20)	26 (32)	21 (20)	.024
Medium adherence	88 (42)	77 (44)	60 (57)	a
High adherence	81 (38)	71 (63)	38 (23)	b

DISCUSSION

In this study, we identified homogeneous subgroups of cardiovascular patients based on their cardiovascular risk factors and beliefs about medication. We determined 3 different clusters, in which we were able to identify patients' profiles associated with adherence levels. The WHO model in which the 5 dimensions of adherence are classified[18] was used to organize the classical cardiovascular risk factors that might influence adherence behavior. Three different groups of patients with CVD could be distinguished in level of medication adherence. Consistent with the conclusions found in other research, isolated established predictors of adherence are often insufficient to identify individual patients who are likely to be nonadherent.[27]

Compared with clusters 1 and 2, patients in cluster 3 had a significantly poorer medication adherence. This patient group was characterized by those of a relatively young age, using a limited number of medication, and an unhealthy lifestyle. As older age has previously been identified as a major determinant for nonadherence.[23,24]

We looked for explanations for these findings. We found that a younger age at the time of a stroke or acute coronary syndrome could possibly be associated with reduced medication adherence.[50] Although this was an inconclusive finding, it suggests that younger patients may be more likely to be nonadherent to preventive medications because of lower perceived risk of another CVD, misconceptions about the duration of treatment, or concerns about potential harm fromstatins.[51] By analysing the single variable age in relation to adherence in this population, there was no significant difference in adherence among the 3 age groups observed. Only when clustering the variables was there a significant difference between the groups on adherence. This also suggests that nonadherence manifests itself in interaction with underlying vulnerabilities.[27] Considering an unhealthy lifestyle as a marker for nonadherent behavior[27] seems to be confirmed in this study. Although clinical outcomes are well-known indicators for nonadherence,[52,53] our cluster analyses did not show such association. Patients who did not reach target BP and LDL levels were not more likely to be nonadherent. There may be several explanations for this finding. In our population, LDL and BP were measured just at cardiovascular follow-up. Consequently, residual confounding may have limited our analyses. Another explanation could be the relatively young age of this group. With aging, the prevalence of metabolic syndrome (including hypertension and dyslipidaemia) increases.[54] Thus, younger patients may already have a (sub)optimal level of LDL and BP before the cardiovascular event. Also, a suboptimal adherence

level might still achieve clinical benefits with respect to BP and cholesterol levels.[55] Another remarkable finding was that, although a complex drug treatment plan is often associated with lower medication adherence,[56] only a small number of medications were used in the cluster that showed the poorest adherence. This could be explained by the clinical outcomes that already were at target. Indication for prescribing medication was simply less present. We expected there would be a difference between the clusters in the outcome of the BMQ. The clusters, however, showed no significant differences in the outcome categories of the BMQ. In our previous studies, the continuous outcome of the BMQ, that is, the necessity-concern differential (NCD), was used.[57,58] In these studies, the NCD corresponded with the outcome of the MMS; next to the high adherence rate, a high mean NCD score was present. In the present study, we applied the categorical outcomes of the BMQ, the 4 different belief groups, because categorical outcomes are the preferred measure for a cluster analysis. The difference between the continuous and categorical outcome may explain the absence of an association between the BMQ and the MMS.

This study had some limitations. First, we had to deal with non responders of the self-reported questionnaires BMQ and MMS. It is suggested that non responders have poorer adherence levels and beliefs about medication.[59] This may limit the extra polarity of the results obtained. Second, there are different methods available to measure adherence. Each method has advantages and disadvantages.[60] The MMS is a validated questionnaire that can be applied easily to large populations. However, as MMS is a subjective measure, adherence levels may be higher than what is expected in real life.[60] Other methods, such as the Medication Event Monitoring System or pill count, seem to influence patient's behavior through direct confrontation. Moreover, application of Medication Event Monitoring System is relatively expensive, especially when applied in standard care.[61] Second, although comorbidities can play an important role in medication adherence, we did not have access to valid data for this study.[8]

Hence, determinants for nonadherent behavior are mostly complex and influence each other.[9] Identifying nonadherent behavior in cardiovascular patients by clustering these determinants based on their structural cardiovascular screening outcomes can lead to a more effective CVRM. The group of patients that showed the poorest medication adherence was characterized by a relatively young age, using a limited number of medications. This might explain why interventions to improve medication adherence in cardiovascular patients were not very successful if they were targeting the elderly, polypharmaceutical patients. By developing a new intervention to improve medication adherence in cardiovascular patients, there should be a different approach, targeting a different patient group. Further research in interventions to improve medication adherence in this subgroup of cardiovascular patients is needed to confirm this presumption.

CONCLUSION

Cardiovascular patients who are relatively young and have an unhealthy lifestyle should be identified as patients who are at risk for nonadherent behavior. When identified these patients should be offered more guidance on medication adherence. Specifically, adherence improving interventions targeting this population may be successful and should be subject for future research.

What's New and Important

- Identifying nonadherent behavior in cardiovascular patients by clustering determinants based on the structural cardiovascular screening outcomes can lead to a more effective approach to improve medication adherence.
- The group of patients that showed the poorest medication adherence was characterized by a relatively young age, using a limited number of medications. This is in contrast to the more traditionally known determinants of poor adherence (elderly age and polypharmaceutical use of medications).
- Further studies could lead to a different approach to improve medication adherence in patients with CVD, targeting a different patient group.

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Chapter 8

Summary & General Discussion

Aim & summary of the chapters

In this chapter we provide information about the aim of the thesis and a summary of the chapters.

1.1 Aim of thesis

Cardiovascular diseases (CVD's) remain a major cause of death worldwide. In 2019 there were an estimated 523 million prevalent cases of CVD and 18 million people died from CVD (one-third of all deaths in 2019) globally, with projections showing an increase to 23.3 million in 2030.[1,2] Twenty-five percent of these CVD events are relapses in individuals with a previously established CVD. Many studies have proven that the risk for a new event can be reduced by improving the behavioural risk factors associated with CVD such as smoking, an unhealthy diet, obesity, physical inactivity and harmful use of alcohol.[3] In addition to these behavioural interventions, pharmaceutical treatment with aspirins, statins and blood pressure lowering medication significantly reduces morbidity and mortality also in patients with established CVD.[4,5] This knowledge has been incorporated into the World Health Organization guidelines for the prevention of CVD.[3] Unfortunately, a substantial proportion of people does not adhere adequately to prescribed cardiovascular medications. It was shown that only 60% of the people who use cardiovascular medication, was adherent to their cardiovascular medication as it was prescribed.[6] Poor medication adherence may be responsible for ten percent of the relapse CVD events.[7] Therefore, improving medication adherence may have significant impact on reducing the number of CVD relapses.

The overall aim of this thesis was to develop and evaluate an intervention to enhance medication adherence in cardiovascular patients. The intervention should improve patients' adherence behaviour, change patients' treatment perceptions and beliefs, and it should increase the number of patients reaching their target cholesterol and blood pressure level. In developing the intervention, the subsequent recommendations for adherence intervention were followed: simple interventions that are easy to implement in daily practice[8], based on patients' perspectives[9], target patients' capacities and practical barriers as well as patients' beliefs and perceptions of their illness and medication.[10,11] In the following paragraphs the context and the targeted population (chapter 2), the effectiveness of an eHealth intervention (chapter 3) and the development of the intervention (chapter 4) are described. The subsequent paragraph deals with the effect of the intervention on improving adherent behaviour (chapter 5). The studies on the pre-existing adherence levels of participants and non-participants in a randomized controlled study (chapter 6) and the identification of cardiovascular patient groups who are at risk for non-adherent behaviour (chapter 7) conclude this chapter.

1.2 Context and population (chapter 2)

The existing cardiovascular risk management program for new patients diagnosed with acute coronary syndrome, peripheral arterial disease, an aneurysm of the aorta, or stroke/

transient ischemic attack (TIA) was the starting point for our intervention. The routines of structured cardiovascular risk management (CVRM) program and performing nurse led lifestyle-focused consultations to reduce other cardiovascular risks such as smoking, already exist in the outpatient clinic of the Radboud university medical center.[12,13] Nurses are running this program very successfully. Therefore, it was likely that nurses were also very well capable in running an intervention program for medication adherence. They are close to the patient and often his family, so there can be a therapeutic partnership that is respectful of the beliefs and choices of the patient in determining when and how treatment is followed.[14] There is also a broad recognition that nurses have a key role in understanding and addressing patients' beliefs during consultations about their medication. [15,16]

1.3. eHealth interventions (chapter 3)

Interventions to improve adherent behaviour which are easy to implement in daily practice led us to the opportunities of adherence enhancing eHealth interventions. With internet applications health-related information support can be offered to large groups of patients in a relatively simple way. The definition of eHealth concerns internet-supported interventions and eHealth interventions based on technologies such as apps, web portals or text message services.[17] A review of the literature on this topic was executed (chapter 3).[17,18] The various interventions appeared to have two common aspects: they used eHealth and aimed to increase the participation of patients. This was done by actively involving patients in their treatment by setting goals and providing feedback, or by giving patients access to their medical records and informing them about the treatment. Patient participation in healthcare is playing an increasingly important role and can positively influence healthy behaviour, which can result in a positive effect on adherence.[19] It aims to bring about a positive change or to increase knowledge, awareness and understanding. This is done by offering health-related information and using internet-based interactive components.[20] Based on this knowledge we designed an interactive website to provide individual risk communication, feedback of clinical outcomes and also an invitation for the patient to become active in managing his/her illness and medication.

1.4 Development of the intervention (chapter 4).

Medication adherence enhancing interventions should improve patients' intentions to take medication and take away emergent practical barriers as well. Such interventions should be based on patients' perspectives[9], target patients' capacities and practical barriers, and address their beliefs and perceptions regarding illness and medication [10,11] All these principles have led us to adopt the Health Belief Model (HBM) as the theoretical framework which we used to design the intervention.[21, 22] The HBM provides a useful framework for designing behaviour change strategies.

The intervention included 1) the existing care from the cardiovascular risk management program (CVRM) [12] ; 2) access to a personalized website. This website provided risk

communication, feedback on whether or not target levels of cholesterol and blood pressure have been reached, and patients were invited to be active in managing their illness and medication; 3) a single group consultation led by a nurse and a pharmacist followed by two individual consultations with a nurse. During the group consultations patients received information about their disease, cardiovascular medication (such as statins, antihypertensive, and antithrombotic agents) and the importance of medication adherence. The group consultation was regarded as an efficient way to increase knowledge and understanding of the risks. It also provided a social gathering with other patients (companions). During the individual consultations, the intervention was further tailored on patient's concerns using the results of the screening questionnaires. The involved nurses were especially trained in the importance of medication adherence and in motivational interviewing [22]. In order to tailor the individual consultations to individual patients' beliefs and perceptions about their medication, the Beliefs about Medication Questionnaire (BMQ)[23,24] and the Modified Morisky Scale (MMS®)[25] were part of the intervention. These questionnaires provide a structured evaluation of possible adherence problems and enable nurses to emphasize patient centeredness in their consultation.

1.5 Results of the intervention (chapter 5)

To study the effectiveness of the intervention, a single-center, prospective, controlled clinical trial was performed**.** The outcomes for the RCT were set for three levels; how much did the intervention change patients' adherence behaviour, how much did it change patients' perceptions and beliefs and did the intervention successfully improve the clinical outcome by achieving target levels in cholesterol and blood pressure? The primary outcome was adherence to CVD medication measured with a dedicated calculation of refill data (pharmacy refill dates). The secondary outcomes were the outcomes of the BMQ, the MMS and clinical outcomes. As recommended by the Medical Research Council Guidance [26] a process evaluation of this intervention program was also included.[27,28]

The process evaluation showed that in total 419 patients were randomized to the different groups. After randomization, 148 patients were invited to attend the group and individual consultations of which 79 of these participated in the group consultation. One-hundred-and–thirty-four and 79 of these patients visited the first and second individual consultation, respectively. In total 286 patients got access to the website and were requested to visit the website. Seventy-seven patients of both groups actually logged-in on the website of which only 37 logged-in more than once.

The intervention did not show an effect on adherence to medication. The percentage of adherent patients was 86% in the usual care group and 76% in the intervention group at the end of the intervention. One year after the intervention, there also was no significant difference detected (percentage of adherent patients was 65% in the usual care group and 57% in the intervention group). According to the MMS, 71% (usual care) and 68%

(intervention group) was medium or high adherent at the end of the intervention. There were no significant differences between the two groups

No differences between the groups in the results of the BMQ were observed either. At the end of the intervention, mean LDL level was reduced from 2.5 mmol/L at baseline to 2.2 mmol/l and mean systolic blood pressure was increased from 136 mmHg to 155 mmHg at baseline. There were no differences in LDL and blood pressure alterations between both groups.

I.6 Adherence in (non) participants in a randomized controlled trial (chapter 6)

Because of the unexpected high adherence rates in the group of patients that only received usual care, we wanted to explore if this could be related to patient characteristics. It has been suggested that patients participating in these RCT's already have a pre-existing high adherence level at baseline [29-32]. Selection of participants with high levels of adherence at baseline makes it difficult to show an improving intervention effect (ceiling effect)[33]. The aim of this analysis was to explore possible differences in adherence to existing prescribed medication in cardiovascular patients who did or did not consent to participate in an RCT which explored the effects of an intervention to improve adherence. We hypothesized that patients who are willing to participate in a clinical trial are more likely to be medication adherent and score higher on the necessity concerns differential (NCD) of the BMQ compared to patients who are not willing to participate. In this retrospective cohort study, we included patients who participated or declined participation in the (MIRROR) trial (chapter 5).

Participation or declining to participate to the RCT was the independent variable in this study. Adherence to medication and the beliefs about medication were the dependent variables. Adherence to cardiovascular medication was calculated by the MMS. To evaluate patients' beliefs and perceptions about their medication, the BMQ was used. In total, 900 patients with a new cardiovascular event were eligible for participation in the MIRROR trial. Of these, 419 agreed and 481 refused participation. The total cohort (participants and non-participants) had a mean age of 62 years and was predominantly male (67%). Participants significantly differed from non-participants with respect to age (61 versus 63 years), male sex (71% versus 58%) and systolic blood pressure (136 versus 142 mmHg). We did not observe differences in adherence measured by the MMS between both groups. According to the MMS 19% of the participants were classified as low adherers compared to 20% in the non-participants group. Forty-six percent of the participants and 44% of the non-participants were classified as medium adherers, whereas 36% and 37% were classified as high adherers, respectively. Based on the BMQ, the necessity concerns differential (NCD) was 3.8 among participants compared to 3.4 among non-participants.

For the MIRROR trial all patients who had a CVD event were included. However, considering the results of our previous studies we came to new insights. We were not able to show a significant difference in medication adherence behaviour before or after the intervention because there was already a high level of adherent behaviour at start. We could not attribute this to participation in a randomized control trial. So we needed to have a better understanding of who is at risk for non-adherent behaviour in this specific population. This led to the next study.

1.7 Identification of cardiovascular patient groups at risk for poor medication adherence (chapter 7)

According to the European guidelines in cardiovascular risk management, in all patients who have had a cardiovascular event, risk factors of CVD (high BP, high cholesterol levels, and unhealthy lifestyle behaviours) should be identified and preventive therapies (medication and lifestyle interventions) should be taken.[34] These risk factors, together with baseline characteristics (such as age and occupation), may also be used to identify CVD patients who are at risk of non-adherent behaviour. By combining and clustering the risk factors of CVD, patient groups who are at risk of non-adherent behaviour might be better determined. Consequently, an intervention to improve medication adherence may be better targeted. The study described in this chapter, applied the well-known CVD risk factors of individual patients to a subgroup of patients with suboptimal adherence levels. In this retrospective, observational study, patients with an established CVD were included. The discriminative power of these subgroups might be enhanced by incorporating data about patients' beliefs about medication. The first step of this study was to identify homogeneous subgroups of cardiovascular outpatients based on their cardiovascular risk factors. Subsequently, differences in medication adherence between these groups were examined. To identify patient subgroups, a 2-step cluster analytic procedure was performed. Differences between the groups on medication adherence were determined on the outcome of the Modified Morisky Scale. During one year, 530 patients participated in this hospital screening program. Cluster analysis using the Ward method led to the selection of a 3-cluster solution. Eighteen percent of all patients had a suboptimal level of adherence. Forty-six percent were medium adherent and 36% were highly adherent. Differences in adherence between the three clusters were significantly different.

Compared to clusters 1 and 2, patients in cluster 3 had a significantly poorer medication adherence. This patient group was characterized by a relatively young age, the use of a limited number of medicines and an unhealthy lifestyle.

2. Discussion

The blended intervention we developed and implemented on the basis of currently existing knowledge did not result in higher medication adherence rates. In this chapter we discuss the results and place them in perspective of the findings in similar studies by others.

2.1 Process evaluation

There were fewer patients than expected who actually used the website and/or participated in the (group) consultations. Although the use of eHealth interventions is recommended to improve healthy behaviour and for tailoring adherence interventions[17,35], the majority of the participants in the study visited the website only once. Only a small proportion visited the website regularly. Consequently, we were not able to study the perceived benefits of our eHealth intervention on adherence. There are several explanations why patients did not use the website much. High dropout rates are a well-known feature of eHealth interventions[36], as was confirmed in our trial. Our patients had to use a special personal code with an SMS-text authentication. These steps may have complicated the use of the website. The website gave access to patients' LDL and blood pressure results. However, these results could also be obtained by making a telephone appointment. Or, as one patient put it: "If there would be something wrong with my outcomes you would have called me anyway." We assumed patients would prefer to see their outcomes in their own time and not depend on the availability of a nurse in the outpatient clinic. This assumption may not be correct. Also, the uptake of the group- and individual consultations was less than expected. All patients signed an informed consent form before participation in our study in which the information about the possibility of the high frequency of extra visits was explained. We made extra phone calls if they did not show up to ask them if they still wanted to participate. Most of them answered with yes but still did not show up the next time. Again, perhaps the effort they had to put in did not outweigh the potential benefits. We learned that despite a thorough literature search, the use of evidence and the use of a theoretical framework, we ignored a crucial element; we did not ask patients themselves for their wishes in terms of e-support. When we started the development of this intervention, patient participation was not as common as it is now. The process evaluation gave us much insight in the patient perspective. This evaluation showed that the patients did not use the intervention enough to be effective as planned. By tailoring the intervention for the individual consults we made the content of the intervention as individualized as possible. But maybe only tailoring the content is not enough. The format and the way in which the intervention is delivered may also be tailored to patient's information and support preferences.

We developed the intervention considering the recommendations of major reviews on medication adherence interventions[8,37-39]. However, we did not see an effect of the developed intervention on our main adherence outcome. There are some explanations for the absence of an effect of this intervention.

2.2 Methodology

First, patients may not have been exposed enough to the intervention (see paragraph 3.1). Second, in this study we used pharmacy refill data (PRD) as adherence measure. Refill adherence rates have extensively been used for the evaluation of medication adherence. Compared to electronic monitoring, refill data provide researchers with a relatively simple method for investigating adherence to medication in large populations.[40] However, due to the increasing availability of automatic refills in the Netherlands, this measure may represent high adherence levels while patients do not necessarily take their medication.[41] Since there is no ideal medication adherence measure, it is appropriate to use more than one measure. This recommended multi-measure approach was applied in this study and both showed medium to high adherence rates. The results of the MMS also showed no differences in medication adherence between the groups. One can consider to perform adherence research with more direct measurements as measurement of the medication in body fluids, such as blood or urine or the presence of a biological marker given with the drug or a direct observation of patient's medication-taking behavior.[42] Even though these measures are considered to be the very accurate and can be used as physical evidence to prove that the patient has taken the medication, there are also concerns regarding their use. They simply generate a yes or no result without revealing any pattern of nonadherence. Also drug metabolism should be taken into account while considering using these methods. Furthermore, direct measures are very expensive and difficult to perform. It will also make the patient aware of the observation of his medication adherence which can be seen as an intervention in itself.[42] However, much more research in adequate and objectively measuring medication adherence is needed because even after decades of research, it is difficult for healthcare professionals and researchers to choose the most suitable adherence measures. Third, all patients in our study received the same structural cardiovascular risk assessment, lifestyle intervention and best medical treatment and supportive care according to the European Guidelines of prevention of cardiovascular diseases.[34] All patients in our study received the same usual cardiovascular care from the nurses. Although medication adherence was not a structural approach in our usual care setting, the attention and screening on CVD-risk factors may have influenced adherence to medication positively. A previous evaluation of our nurse-led cardiovascular vascular risk program showed that a structural multidisciplinary evaluation and initiation of the best medical treatment in combination with addressing unhealthy lifestyle reduces cardiovascular risk as indicated by a reduction in smoking, alcohol consumption, unhealthy eating, blood pressure, and LDL-cholesterol level.[12] A reduction in mortality and morbidity by these nurse-led programs is shown more often.[43] Moreover, nurses are achieving results, equal or even better than GPs, for the management of cardiovascular risk factors.[44] Nurses do have a key role in understanding and addressing patients' beliefs during consultations about their medication. Nurses are close to the patient and often his family, so there can be a therapeutic partnership that is respectful of the beliefs and choices of the patient in determining when and how treatment is followed.[14] The CVRM at our hospital is performed by specifically trained nurses. They are trained in knowledge about cardiovascular diseases and their

risk factors. They are also trained in motivational interviewing to support patients to a healthy life style. And they are successful in it.[12] Nonetheless, the present study did not evaluate the actual performance of the nurses in this matter, and quality and individual differences in nurses' communication are likely to exist.

2.3 High adherence in all groups

Because of the high adherence rates in all groups, it was difficult to demonstrate a difference between the groups. A power calculation was executed to establish the number of patients needed to demonstrate a difference in adherence. But contrary to the level of poor adherence we found in our literature search, the overall adherence rate in our total population was much higher (50-60% in the literature to 80% in our population). So, patients who participate in an adherence study may be patients who already are more adherent. This will be discussed further in paragraph 3.5.

2.4 Pharmacy Refill Dates (PRD)

Trying to get the data needed to calculate the PRD turned out to be a major challenge. There was no central database we could use. There was no information about refill dates of our patients available for the prescribing clinicians. We had to ask every single pharmacist (more than a hundred) if they would be willing to provide us with the refill dates of the patients participating in this study. Some pharmacy databases were easy to use for the calculation of the PRD. Other databases needed to be cleaned up first because all kinds of supplements were documented like non-prescription medication and medical aids. Eventually we were able to calculate the PRD for over 80% of the patients. It made us aware that in the circle around the patient nobody knows exactly if and how often a patient's medication is supplemented. A prescribing clinician or a pharmacist can only rely on the information a patient reports and has no other tools at his disposal. Personalized feedback using data obtained from electronic devices who monitor the patient's adherence also tends to have a positive effect on medication adherence.[45]

2.5 Patient's perceptions and beliefs

In order to enhance adherent behaviour, the perceptions and beliefs of the patient need to be taken into account.[46] Using the answers of the BMQ enabled the nurses to individualize their consultations. A shift in the categories showed from ambivalent towards accepting in the intervention group was shown. This was not observed in the usual care group. was observed in this study. In the ambivalent group, necessity beliefs were high but concern beliefs too. In the acceptance group necessity beliefs were high but the concern beliefs were low. In order to know if the change in the necessity category for the intervention group would have a more positive effect on the adherence rate over time, we need to measure the adherence rate more than one year after the intervention, because one year after the intervention, adherence rates were still high in both groups.

2.6 Effect on cholesterol and blood pressure levels

Although overall adherence was relatively high at 12 months follow-up, only 20% of all patients had a systolic blood pressure within target. The mean blood pressure (BP) was even higher than it was at baseline. We did not expect this result at all. Several major studies did, however, demonstrate that nonadherence is a major determinant for not reaching target levels, for lipid lowering medication as well as for antihypertensive medication.[47,48] There are several ways to elaborate on this finding. The PRD and the MMS, even if in combination, may not have been sensitive enough to detect nonadherence in our population. We discussed this in paragraph 3.1. Another explanation could be that failure to achieve the target systolic blood pressure level is not due to nonadherence.[30,31] It sometimes seems to be difficult to establish the relationship between adherence and BP.[49] Also, all BP-measurements were done at the outpatient clinic. A 24- hour ambulatory home BP monitoring would have been more accurate.[50]

2.7 Adherence in (non) participants of a randomized controlled trial

Because of the unexpected and surprisingly high adherence rates at baseline of our study population we wanted to explore the suggestion that patient recruitment methods in randomized controlled trials could have resulted in inviting a population with high adherence to medication.[29,51] Our study of the differences in medication adherence among patients who did or did not consent to participate in an RCT showed that patients who were willing to participate in the RCT to evaluate the effect of an intervention to improve medication adherence had a comparable adherence levels to patients who declined to participate. However, the participants were younger and were more educated. Because these characteristics are known as prognostic characteristics for patients who are willing to participate in a clinical trial [52] and for a high adherence level as well,[53,54] it was expected that these characteristics could explain the assumed higher adherence rates in the participant groups. We could not confirm this hypothesis.

Also, next to the high adherence rate, a high mean NCD score was present in all groups. This is congruent with earlier studies showing that medication beliefs can be a more powerful predictor of medication adherence than clinical and socio-demographic factors.[23,46] However, we did not observe a relationship between NCD and trial participation. This suggests that a population representative in adherence levels was included in our RCT evaluating the effect of an intervention to improve medication adherence. An alternative explanation for the high adherence rates in both groups could be that we started inclusion shortly after the initial cardiovascular event, a period in which the importance of being adherent is emerging in most patients. Yet, as the impact of the event fades and symptoms subside, adherence levels may decline.[55,56] Studies with a long follow up are needed to establish a difference in adherence between participants and non-participants over time.

2.8 Identification of patient groups at risk for nonadherent behaviour

In this study, cardiovascular patients who were relatively young, used a limited number of medicines and had an unhealthy lifestyle were identified as patients who are at risk for non-adherent behaviour. It has been speculated that medication adherence is a marker for other health choices, the so-called "healthy adherer effect".[57] Patients with low medication adherence may have an unhealthy lifestyle.[32] It is suggested that factors associated with an unhealthy lifestyle such as poor health knowledge and low self-efficacy to change behaviour, also lead to poor adherence. [58 59] But one can also easily turn this around. 'By living as a very healthy person, I don't need my medication anymore'. This would mean that if someone is living really healthy, one would be worse medication adherence (trade-off). Both groups are described in the literature.[57,60]

Although older age and complexity of drug regimens have previously been identified as a major determinant for non-adherence,[61,62] we unexpectedly found that a younger age at the time of a TIA/stroke or acute coronary syndrome was associated with a reduced medication adherence.[63] Although this was an inconclusive finding, it suggests that younger patients may be more likely to be nonadherent to preventive medications due to lower perceived risk of another CVD, misconceptions about the duration of the treatment, or concerns about potential harm from statins.[64] The other remarkable finding was that although a complex drug treatment plan is often associated with lower medication adherence [65] in the cluster with the poorest adherence only a small number of medicines were used. This could be explained by the clinical outcomes which already were at target at baseline. The indication for prescribing medication was simply less present. Although cluster three (i.e., patients who are relatively young) showed the poorest adherence, our cluster analysis did not show an association between nonadherence and clinical outcomes at target level. An explanation could be the relatively young age of this group. With aging, the prevalence of metabolic syndrome (including hypertension and dyslipidemia) increases.[66] Younger patients may already have a (sub)optimal level of LDL and BP before the cardiovascular event. By analyzing the single variable age in relation to adherence in this population, no significant difference in adherence was observed between the three age groups. Only when clustering the variables a significant difference between the groups on adherence could be reported.[41]

We expected there would also be a difference between the clusters in the outcome of the BMQ. The clusters, however, showed no significant differences in the outcome categories of the BMQ. In this study, we only used the categorical outcomes of the BMQ (the four different belief groups) because categorical outcomes are the preferred measure for a cluster analysis. The difference between the continuous and categorical outcome may explain the absence of an association between the BMQ and the MMS. Identifying non-adherent behaviour in cardiovascular patients by clustering determinants based on the structural cardiovascular screening outcomes can lead to a more effective approach to improve medication adherence. The study showed that isolated established predictors of adherence are often insufficient to identify individual patients who are likely to be non-

adherent.[41] Identifying patients who are at risk for nonadherent behaviour should not be simply identified with single measures for assessing medication adherence. Different risk factors should be taken into account to identify a patient at risk.

3. Conclusion

Complex problems and partly unexpected interactions between patient characteristics, beliefs and behaviour underly poor adherence in cardiovascular patients. Because these patients should take their medication for the rest of their lives, the impact of poor adherence is huge. Measuring medication adherence is challenging and labour intensive. Although the prevalence of non-adherence over a longer period after the initial CVD event seems far less than previously thought, there is still a need for interventions to tackle this problem. In developing such an intervention, we were convinced that we took the right design steps, taking existing knowledge into account. By evaluating this study, new insights emerged:

Pharmacy Refill Dates
Improve the way in which data from refill prescriptions are available for the prescribers and pharmacists. In order to improve communication about medication adherence between prescribers, pharmacists and patients, PRD should be easy to access for clinicians. There is a world to win concerning the use of information about medication, even in daily practice.

Development of interventions
To improve behavioural change interventions and tailor them to patient's needs, involve patients in the development of these interventions. However, recent studies which involved patients in developing interventions did not show a better uptake of the interventions. They considered that patient's needs can differ from each other so even if you include patients in intervention development, patients who will be offered this intervention can have another, specific need.[67,68] A recent review of adherence to eHealth technology confirms there still is much to learn about how to adhere patients to eHealth.[69,70,71] More research should be done on what is effective in getting patients to use behaviour change programs in general and eHealth in particular .[68,72,71]

Cardiovascular risk management (CVRM) by nurses
The key role nurses have in cardiovascular risk programs and improving outcomes should be recognized and stimulated. Recognition of the role of nurses in general in improving health is increasing. However, nurses have a shared concern about staffing problems and inadequate education, training and support. This can result in poor quality care.[73] Moreover, nurses report that they are frequently not permitted to practice their competence to the full and are unable to share their learning, have too few opportunities to develop leadership and fulfill leadership roles.[74] The world needs 9 million more

nurses and midwives to achieve universal health coverage by 2030.[75] That is why the World Health Organization (WHO) has designated 2020 as the universal year of the nurse and the midwife. By investing in and developing nursing worldwide, a triple aim should be achieved; greater gender equality, stronger economies and better health.[73]

Risk profile of patients
The group of patients that showed the poorest medication adherence was relatively young and used a limited number of medicines. This is in contrast to the more traditionally known determinants of poor adherence (elderly age and polypharmaceutical use of medications). Further studies could lead to a different approach to improve medication adherence in CVD patients, targeting a different patient group.

4. Recommendations

4.1 Recommendations for further research

In developing an intervention to influence patients' behaviour, especially e-Health programs, we need more insight in patients' needs and in how to meet these needs. In defining the use of a technology and selecting valid adherence measures , the goal or the assumed working mechanisms should be leading. Adherence measures can then be standardized, which will improve the comparison of adherence rates to different technologies with the same goal and will provide insight into how adherence to different elements contribute to the outcomes.

In order to confirm that the time to initiate an intervention is important, and perhaps should occur much later after a CV event, adherence rates must be measured further in time, up to two years after an event. If the adherent rates are lower, a retrospective study should be done with the same determinants we used in our study to identify even better who are at risk for non adherent behaviour.

The cluster analysis which can help identify CVD patients who are at risk for non adherence should be done in a much larger cohort to confirm the findings of this study.

To confirm that our regular nurse led CVRM program is also helpful in improving non adherence, we should compare the medication adherence of patients who followed such a program with patients who did not.

4.2 Recommendations for clinical practice

Improve the feedback for prescribing clinicians on the refill data on medications of their patients. This could be very helpful in the communication between clinician and patient about adherent behaviour.

Continue with the CVRM program led by nurses. This program is well implemented in the Netherlands and could also be very helpful in reducing medication adherence.

Be critical in the kind of patient you think is at risk for nonadherence on the basis of their higher age or large number of prescribed medicines. Although these patients are often described as at-risk patients, in CVD the relatively young patient with an unhealthy lifestyle could be more at risk. Nurses who lead the CVRM programs can help their patients and use their skills to help these group of patients especially about their adherent behaviour.

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Chapter 9

Nederlandse samenvatting
Dankwoord
Curriculum Vitae
PhD Portfolio

Nederlandse samenvatting

Introductie

Hart- en vaatziekten (HVZ) blijven wereldwijd een belangrijke doodsoorzaak. In 2019 waren er wereldwijd naar schatting 523 miljoen mensen met een hart- of vaatziekte en stierven er 18 miljoen mensen aan een hart- of vaatziekte (een derde van alle sterfgevallen in 2019) Er wordt verwacht dat er in 2030 23,3 miljoen mensen aan een HVZ lijden. [1,2] Vijfentwintig procent van deze HVZ zijn recidieven bij personen met een eerder vastgesteld HVZ. Het risico op een nieuwe HVZ kan worden verminderd door gedragsinterventies om de risicofactoren die in verband worden gebracht met HVZ, zoals roken, een ongezond dieet, obesitas, lichamelijke inactiviteit en schadelijk alcoholgebruik, te verbeteren.[3] Naast bovenstaande interventies vermindert farmaceutische behandeling met antitrombotica, statines en bloeddrukverlagende medicatie de morbiditeit en mortaliteit ook aanzienlijk bij patiënten met een HVZ. [4,5] Deze kennis is opgenomen in de richtlijnen van de Wereldgezondheidsorganisatie voor de preventie van HVZ. [3] Helaas houdt een aanzienlijk deel van de mensen zich niet voldoende aan de voorgeschreven cardiovasculaire medicatie. Gebleken is dat slechts 60% van de mensen die cardiovasculaire medicatie gebruiken, zich houdt aan de medicatie voorschriften. [6] Een slechte medicatie therapietrouw kan verantwoordelijk zijn voor tien procent van de recidief HVZ-gebeurtenissen. [7] Het verbeteren van de medicatie therapietrouw kan een belangrijke invloed hebben op het verminderen van het aantal terugvallen van HVZ.

Doel proefschrift

Het algemene doel van dit proefschrift was het ontwikkelen en evalueren van een interventie om medicatie therapietrouw bij hart- en vaatpatiënten te verbeteren. De interventie heeft als doel het gedrag dat leidt tot medicatie therapietrouw te verbeteren, de behandelpercepties en -overtuigingen te veranderen en het aantal patiënten dat hun streefwaarden voor cholesterol en bloeddruk bereikt, te verhogen. Bij het ontwikkelen van de interventie zijn de volgende aanbevelingen voor interventies ten behoeve van verbetering van de medicatie therapietrouw gevolgd: Het moeten eenvoudige interventies zijn die gemakkelijk in de dagelijkse praktijk te implementeren zijn [8], gebaseerd op de perspectieven van de patient [9], gericht op de capaciteiten en op de praktische barrières van patiënten en op de overtuigingen en percepties van patiënten over hun ziekte en medicatie. [10,11]

Samenvatting van de hoofdstukken

Context (hoofdstuk 2)

Het bestaande cardiovasculaire risicomanagement (CVRM) programma voor nieuwe patiënten met de diagnose acuut coronair syndroom, perifeer arterieel vaatlijden, een aneurysma van de aorta, of een beroerte/transient ischemisch attack (TIA) was het uitgangspunt voor onze interventie. Het gestructureerde CVRM programma en de uitvoering van door verpleegkundigen geleide leefstijlgerichte consulten om cardiovasculaire risico's, zoals roken, te verminderen, bestaat al in het Radboudumc. [12,13] Verpleegkundigen voeren dit programma met succes uit. Het was aannemelijk dat deze verpleegkundigen ook heel goed in staat waren om een interventieprogramma voor verbetering van de medicatie therapietrouw te leiden. Zij staan dicht bij de patiënt en vaak ook diens familie, zodat er een therapeutisch partnerschap kan ontstaan met respect voor de overtuigingen en keuzes van de patiënt bij het bepalen wanneer en hoe de behandeling wordt gevolgd. [14] Ook wordt algemeen erkend dat verpleegkundigen een sleutelrol hebben in het begrijpen en aanspreken van de overtuigingen van patiënten tijdens consulten over hun medicatie. [15,16]

eHealth interventies (hoofdstuk 3)

De aanbeveling voor interventies die eenvoudig in de dagelijkse praktijk te implementeren zijn, leidden ons naar de mogelijkheden van eHealth interventies. Via internet kan aan grote groepen patiënten op een relatief eenvoudige manier informatie worden aangeboden. De Nederlandse definitie van eHealth is als volgt: het gebruik van informatie- en communicatietechnologie ter ondersteuning of verbetering van de gezondheid en de gezondheidszorg betreft internet ondersteunde interventies en eHealth interventies gebaseerd op technologieën zoals apps, web portals of sms-diensten. Een review van de literatuur over dit onderwerp werd uitgevoerd. [17,18] De succesvolle interventies bleken twee gemeenschappelijke aspecten te hebben: ze maakten gebruik van eHealth en hadden tot doel de participatie van patiënten te vergroten. Dit werd gedaan door patiënten actief te betrekken bij hun behandeling door doelen te stellen en feedback te geven, of door patiënten toegang te geven tot hun medisch dossier en hen te informeren over de behandeling. Patiëntenparticipatie in de gezondheidszorg speelt een steeds belangrijkere rol en kan een positieve invloed hebben op gezond gedrag, wat kan resulteren in een positief effect op medicatie therapietrouw. [19] Het is de bedoeling een positieve verandering teweeg te brengen of kennis, bewustzijn en begrip te vergroten. Dit gebeurt door het aanbieden van gezondheids gerelateerde informatie en door het gebruik van interactieve componenten. [20]

Op basis van deze kennis is er een interactieve website ontworpen voor individuele risicocommunicatie, terugkoppeling van klinische resultaten met een uitnodiging aan de patiënt om zijn/haar ziekte en medicatie actief te managen.

Ontwikkeling van de interventie (hoofdstuk 4).

Therapietrouw bevorderende interventies dienen de intentie van patiënten om medicatie in te nemen te verbeteren en tevens praktische barrières weg te nemen. Dergelijke interventies dienen gebaseerd te zijn op het perspectief van de patiënt [9], gericht te zijn op de capaciteiten en praktische belemmeringen van de patiënt, en op de overtuigingen en percepties ten aanzien van ziekte en medicatie [10,11] Al deze uitgangspunten hebben ons ertoe gebracht het Health Belief Model (HBM) te gebruiken als het theoretische kader om de interventie te ontwerpen. [21], [22] Het HBM biedt een nuttig kader voor het ontwerpen van gedragsveranderingsstrategieën. De interventie omvatte 1) de bestaande zorg van het cardiovasculair risico management programma (CVRM) [12]; 2) toegang tot een gepersonaliseerde website. Deze website bood risicocommunicatie, feedback over het al dan niet bereiken van streefwaarden voor cholesterol en bloeddruk, en patiënten werden uitgenodigd actief te zijn in het managen van hun ziekte en medicatie; 3) één groepsconsult onder leiding van een verpleegkundige en een apotheker, gevolgd door twee individuele consulten met een verpleegkundige. Tijdens de groepsconsulten kregen de patiënten informatie over hun ziekte, cardiovasculaire medicatie (zoals statines, antihypertensiva en antitrombotica) en het belang van medicatie therapietrouw. Het groepsconsult werd beschouwd als een efficiënte manier om de kennis en het begrip van de risico's te vergroten. Het voorzag ook in een sociaal samenzijn met andere patiënten ("peers"). Tijdens de individuele consulten werd de interventie verder afgestemd op de behoeften van de patiënt. De betrokken verpleegkundigen zijn speciaal getraind in het belang van medicatie therapietrouw en in motivational interviewing. [22] Om de individuele consulten af te kunnen stemmen op de overtuigingen en percepties van individuele patiënten over hun medicatie, maakten de Beliefs about Medication Questionnaire (BMQ) [23,24] en de Modified Morisky Scale (MMS®) [25] deel uit van de interventie. Deze vragenlijsten bieden een gestructureerde evaluatie van mogelijke problemen met medicatie therapietrouw en stellen verpleegkundigen in staat om in hun consultatie de nadruk te leggen op patiëntgerichtheid.

Resultaten van de interventie (hoofdstuk 5)

Om de effectiviteit van de interventie te onderzoeken, werd een single-center, prospectieve, gecontroleerde klinische trial uitgevoerd**.** De uitkomsten van de RCT werden op drie niveaus vastgesteld; in hoeverre veranderde de interventie het medicatie therapietrouw gedrag van patiënten, in hoeverre veranderde de interventie de percepties en overtuigingen van patiënten en verbeterde de interventie met succes de klinische uitkomst door het bereiken van streefwaarden voor cholesterol en bloeddruk? De primaire uitkomst was de medicatie therapietrouw van HVZ-medicatie gemeten met een specifieke berekening van apotheek refill data. De secundaire uitkomsten waren de uitkomsten van de BMQ, de MMS® en de klinische uitkomsten. Zoals aanbevolen door de Medical Research Council Guidance [26] is ook een procesevaluatie van dit interventieprogramma opgenomen. [27,28]

In totaal zijn 419 patiënten gerandomiseerd naar de verschillende groepen. Na randomisatie zijn 148 patiënten uitgenodigd voor de groeps- en individuele consulten, waarvan er 79 deelnamen aan het groepsconsult. Honderdvierendertig en 79 van deze patiënten bezochten respectievelijk het eerste en tweede individuele consult. In totaal kregen 286 patiënten toegang tot de website en werd hen gevraagd de website te bezoeken. Zevenenzeventig patiënten van beide groepen logden daadwerkelijk in op de website, waarvan slechts 37 patiënten meer dan één keer inlogden.

De interventie bleek geen effect te hebben op de medicatie therapietrouw. Het percentage medicatie therapietrouwe patiënten was 86% in de controlegroep en 76% in de interventiegroep, aan het einde van de interventie. Een jaar na de interventie is er ook geen significant verschil vastgesteld (het percentage therapietrouwe patiënten was 65% in de controle groep en 57% in de interventiegroep). Volgens de MMS® was 71% (controle groep) en 68% (interventiegroep) gemiddeld of zeer adherent aan het einde van de interventie. Er waren ook geen significante verschillen tussen de twee groepen in de resultaten van de BMQ. Aan het einde van de interventie was bij alle patienten de gemiddelde LDL-spiegel verlaagd van 2,5 mmol/L naar 2,2 mmol/l en was de gemiddelde systolische bloeddruk verhoogd van 136 mmHg naar 155 mmHg. Er waren geen verschillen in LDL- en bloeddruk veranderingen tussen beide groepen.

Medicatie therapietrouw bij (niet) deelnemers aan een gerandomiseerde gecontroleerde trial (hoofdstuk 6)

Vanwege de onverwacht hoge medicatie therapietrouw in de totale groep patiënten, wilden we onderzoeken of dit gerelateerd kon worden aan patiëntkenmerken. Er is gesuggereerd dat patiënten die deelnemen aan deze RCT's bij de start al een hoge medicatie therapietrouw hebben. [29-32] Selectie van deelnemers met een hoge medicatie therapietrouw op baseline maakt het moeilijk om een verbeterd interventie-effect aan te tonen (plafondeffect). [33] Het doel van deze analyse was het onderzoeken van mogelijke verschillen in medicatie therapietrouw aan bestaande voorgeschreven medicatie bij hart- en vaatpatiënten die wel of niet instemden met deelname aan een RCT waarin de effecten van een interventie ter verbetering van de therapietrouw werden onderzocht. Wij stelden de hypothese dat patiënten die bereid zijn deel te nemen aan een klinische trial vaker medicatie therapietrouw zijn en hoger scoren op de necessity concerns differential (NCD) van de BMQ in vergelijking met patiënten die niet bereid zijn deel te nemen. In deze retrospectieve cohort studie hebben we patiënten geïncludeerd die wel of niet hebben deelgenomen aan de (MIRROR) trial (hoofdstuk 5).

Deelname of afwijzing van deelname aan de RCT was de onafhankelijke variabele in deze studie. Medicatie therapietrouw en de overtuigingen over medicatie waren de afhankelijke variabelen. De medicatie therapietrouw aan cardiovasculaire medicatie werd berekend aan de hand van de MMS® . Om de overtuigingen en percepties van patiënten over hun medicatie te evalueren, werd de BMQ gebruikt. In totaal kwamen 900 patiënten met een nieuwe cardiovasculaire gebeurtenis in aanmerking voor deelname

aan de MIRROR trial. Hiervan gingen er 419 akkoord en weigerden er 481 deelname. Het totale cohort (de 900 deelnemers en niet-deelnemers) had een gemiddelde leeftijd van 62 jaar en was overwegend mannelijk (67%). Deelnemers verschilden significant van niet-deelnemers met betrekking tot leeftijd (61 versus 63 jaar), mannelijk geslacht (71% versus 58%) en systolische bloeddruk (136 versus 142 mmHg). We hebben geen verschillen waargenomen in de medicatie therapietrouw gemeten door de MMS® tussen beide groepen. Volgens de MMS® werd 19% van de deelnemers geclassificeerd als laag medicatie therapietrouw vergeleken met 20% in de niet-deelnemersgroep. Zesenveertig procent van de deelnemers en 44% van de niet-deelnemers werden geclassificeerd als gemiddeld medicatie therapietrouw terwijl respectievelijk 36% en 37% werden geclassificeerd als hoog therapietrouw. Op basis van de BMQ was de "necessity concerns differential" (NCD) 3,8 bij de deelnemers vergeleken met 3,4 bij de niet-deelnemers.

Gezien de resultaten van onze eerdere studies kwamen wij tot nieuwe inzichten. We konden geen significant verschil aantonen in medicatie therapietrouw voor of na de interventie mede omdat er al een hoog niveau van medicatie therapietrouw was bij aanvang. We konden dit hoge niveau niet toeschrijven aan deelname aan een gerandomiseerde controlestudie. We moesten dus een beter inzicht krijgen in wie in deze specifieke populatie dan wel het risico loopt op niet medicatie therapietrouw gedrag. Dit leidde tot de volgende studie.

Identificatie van cardiovasculaire patiëntengroepen met een risico op slechte medicatie therapietrouw (hoofdstuk 7)

Volgens de Europese richtlijnen voor cardiovasculair risicomanagement moeten bij alle patiënten die een HVZ hebben gehad, risicofactoren van HVZ (hoge bloeddruk, hoog cholesterolgehalte en een ongezond leefstijlgedrag) worden geïdentificeerd en preventieve therapieën (medicatie en leefstijlinterventies) worden gevolgd. [34] Deze risicofactoren kunnen, samen met basiskenmerken (zoals leeftijd en beroep), ook worden gebruikt om HVZ-patiënten te identificeren die het risico lopen op niet-adherent gedrag. Door de risicofactoren van HVZ te combineren en te clusteren, kunnen patiëntengroepen die risico lopen op een lage medicatie therapietrouw wellicht beter worden geïdentificeerd. Vervolgens kan een interventie om de medicatie therapietrouw te verbeteren gerichter ingezet worden. In de studie die in dit hoofdstuk wordt beschreven, zijn de bekende HVZ-risicofactoren van individuele patiënten toegepast op een subgroep van patiënten met een lage medicatie therapietrouw. In deze retrospectieve, observationele studie werden patiënten met een vastgesteld HVZ geïncludeerd. Het discriminerend vermogen van deze subgroepen werd vergroot door gegevens op te nemen over de overtuigingen van patiënten over medicatie (BMQ). De eerste stap van deze studie was het identificeren van homogene subgroepen van cardiovasculaire poliklinische patiënten op basis van hun cardiovasculaire risicofactoren. Vervolgens werden verschillen in medicatietrouw tussen deze groepen onderzocht. Om subgroepen van patiënten te identificeren werd een 2-staps clusteranalyseprocedure uitgevoerd. Verschillen tussen de groepen in medicatie therapietrouw werden bepaald aan de hand van de uitkomst van de MMS® .

Gedurende een jaar namen 530 patiënten deel aan het CVRM screeningsprogramma van het ziekenhuis. Clusteranalyse volgens de Ward methode leidde tot de selectie van een 3-cluster oplossing. Achttien procent van alle patiënten had een lage medicatie therapietrouw niveau. Zesenveertig procent was gemiddeld medicatie therapietrouw en 36% was zeer therapietrouw. De verschillen in medicatie therapietrouw tussen de drie clusters waren significant verschillend.

Vergeleken met de clusters 1 en 2 hadden de patiënten in cluster 3 een significant slechtere medicatie therapietrouw. Deze patiëntengroep werd gekenmerkt door een relatief jonge leeftijd, het gebruik van een beperkt aantal geneesmiddelen en een ongezonde leefstijl.

Conclusie

Complexe problemen en deels onverwachte interacties tussen patiëntkenmerken, overtuigingen en gedrag liggen ten grondslag aan de matige medicatie therapietrouw bij hart- en vaatpatiënten. Omdat deze patiënten hun medicatie voor de rest van hun leven moeten innemen, is de impact van een suboptimale therapietrouw groot. Het meten van medicatie therapietrouw is een uitdaging en bleek arbeidsintensief. Hoewel de prevalentie van een lage medicatie therapietrouw over een langere periode na de eerste HVZ-gebeurtenis lager lijkt dan eerder gedacht, is er nog steeds behoefte aan interventies om dit probleem aan te pakken. Bij het ontwikkelen van de interventie voor deze studie, waren we ervan overtuigd dat we de juiste ontwerpstappen hadden genomen, rekening houdend met bestaande kennis.

Onze studie heeft geleid tot de volgende nieuwe inzichten:

Er is een verbetering nodig van de wijze waarop gegevens van herhaal recepten beschikbaar zijn voor de voorschrijvers en apothekers. Om de communicatie over medicatie therapietrouw tussen voorschrijvers, apothekers en patiënten te verbeteren, moet deze informatie gemakkelijk toegankelijk zijn voor zorgverleners. Er is nog een wereld te winnen wat betreft het gebruik van informatie over medicatie, zelfs in de dagelijkse praktijk.

Zoals de proces evaluatie liet zien, hebben maar weinig patienten gebruik gemaakt van de (website) interventie. Om interventies voor gedragsverandering te verbeteren en op de behoeften van de patiënt af te stemmen, moeten patiënten bij de ontwikkeling van deze interventies worden betrokken. Recente studies waarin patiënten bij de ontwikkeling van interventies werden betrokken, wezen echter niet op een betere acceptatie van de interventies. Een verklaring hiervoor is dat de behoeften van patiënten van elkaar kunnen verschillen, dus zelfs als je patiënten betrekt bij de ontwikkeling van interventies, kunnen patiënten die deze interventie aangeboden krijgen een andere, specifieke behoefte hebben. [35,36] Een recent onderzoek naar de acceptatie en het gebruik

van eHealth-technologie door patienten, bevestigt dat er nog veel te leren valt over hoe patiënten aan eHealth zullen gebruiken. [37-39] Er moet meer onderzoek worden gedaan naar welke interventies effectief zijn om patiënten aan te zetten tot het gebruiken van gedrag veranderingsprogramma's in het algemeen en eHealth in het bijzonder . [36,39,40]

De groep patiënten die de slechtste medicatie therapietrouw vertoonde, was relatief jong en gebruikte een beperkt aantal geneesmiddelen. Dit staat in contrast met de meer traditioneel bekende determinanten van slechte therapietrouw (oudere leeftijd en polyfarmaceutisch gebruik van geneesmiddelen). Verdere studies zouden kunnen leiden tot een andere aanpak om de medicatietrouw bij HVZ-patiënten te verbeteren, gericht op een andere patiëntengroep.

De sleutelrol die verpleegkundigen spelen bij cardiovasculaire risicoprogramma's en het verbeteren van de uitkomsten moet worden erkend en gestimuleerd. De erkenning van de rol van verpleegkundigen in het algemeen bij het verbeteren van de algemene gezondheid neemt toe. Verpleegkundigen uiten echter hun zorg over een tekort aan personeel en inadequate opleiding, training en ondersteuning. [41] Ook melden verpleegkundigen dat zij vaak niet in staat worden gesteld hun bekwaamheid ten volle uit te oefenen en dat zij daardoor niet in staat zijn hun kennis te delen, te weinig mogelijkheden hebben om leiderschap te ontwikkelen en leiderschapsrollen te vervullen. [42] De wereld heeft 9 miljoen meer verpleegkundigen en verloskundigen nodig om in 2030 universele dekking van de gezondheidszorg te bereiken.[43] Daarom heeft de Wereldgezondheidsorganisatie (WHO) 2020 uitgeroepen tot het universele jaar van de verpleegkundige en de verloskundige. Door wereldwijd te investeren in verpleging en deze te ontwikkelen, moet een drievoudig doel worden bereikt: meer gendergelijkheid, sterkere economieën en een betere gezondheid. [41]

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Dankwoord

De titel van dit proefschrift had ook kunnen zijn “nooit gedacht…”. Toen ik begon met mijn verpleegkundige carrière was het geen normale stap voor een verpleegkundige om te promoveren. Gestimuleerd door mijn professionele ontwikkeling van de afgelopen jaren denk ik daar inmiddels anders over. Verpleegkundigen zijn continue in contact met de patiënt op een kwetsbaar moment in hun leven. De betekenis die wij daaraan kunnen geven maakt een wezenlijk verschil. Dat moeten we erkennen, laten zien en daar moeten we toe in staat gesteld worden. In de afgelopen jaren heb ik veel betrokken en excellente collega’s leren kennen die het verschil maken. Toch blijven we vaak op de achtergrond. We kunnen onze expertise veel meer delen en laten zien. En dat kan alleen als we onze expertise op peil houden en kenbaar maken aan collega’s, management en bestuurders. Dan dragen we bij aan de persoonsgerichte, veilige en onderscheidende patiëntenzorg die wij uiteindelijk allemaal ambiëren.

Het onderwerp van dit proefschrift sprak me heel erg aan. Medicatie therapietrouw is een samenspel van behandeling en een goede integratie van die behandeling in het persoonlijk leven van de patient. Alleen de noodzakelijke medicatie voorschrijven is niet voldoende om ook het daadwerkelijke behandeleffect te bereiken. De drie eenheid tussen patient, arts en verpleegkundige die hiervoor nodig, is vraagt om goede afstemming en teamwork. Laat ik daar nu veel energie van krijgen.

Speciaal woord van dank gaat uit naar mijn promotieteam: prof. dr. Kees van Laarhoven, prof. dr. Sandra van Dulmen, dr. Bas Bredie en dr. Hein van Onzenoort.

Kees, dank voor het vertrouwen en het creëren van de randvoorwaarden die nodig waren om te kunnen promoveren. Zoals eerder gezegd; het is niet gewoon dat een verpleegkundige deze kans krijgt. Dat jij je daarvoor hebt ingezet waardeer ik zeer. Bijzonder is ook je interesse als chirurg in het onderwerp gedragsbeïnvloeding om de patient te ondersteunen te komen tot een gezonde leefstijl. Daardoor past het onderwerp van dit proefschrift heel goed bij je. Ik hoop dat we op dit gebied nog vaker met elkaar kunnen samenwerken.

Sandra, niets ten nadele van de heren maar wat vond ik het fijn dat er ook een vrouw toegevoegd werd aan het team. Dat gaf toch een andere dynamiek. Je hebt ontzettend veel expertise op dit onderwerp, ik heb veel van je geleerd. Daarnaast was je ook heel benaderbaar en snel met je (altijd opbouwende) feedback. Het vertrouwen wat je steeds weer in mij uitsprak heeft me in staat gesteld elke keer opnieuw de schouders eronder te zetten. Ik ben erg blij en dankbaar dat je deel uit hebt willen maken van mijn proces om tot dit proefschrift te komen.

Hein, wat heb ik veel van je geleerd. Elke vrijdagmiddag opnieuw kwam je langs om te polsen hoe het ging. En elke keer had je het geduld om samen te kijken naar de vragen

die ik had. Ik heb wat geworsteld met statistiek en SPSS. Het was bijzonder dat dit jou makkelijk afgaat maar dat je tegelijk het vermogen had om mij elke keer opnieuw te helpen, onvermoeibaar en zonder mij het gevoel te geven dat ik vreemde vragen stelde. Ik heb genoten van de groepsconsulten die wij samen hebben gegeven. Het was mooi om samen met patienten in gesprek te gaan over medicatie en belang daarvan. Ook toen je tijdelijk het Radboudumc verliet ben je me blijven bellen en stimuleren dit proefschrift af te ronden. Ik waardeer je erg als expert op dit onderwerp maar nog meer als mens die het vermogen heeft anderen mee te nemen in zijn eigen bijzondere kwaliteiten.

Bas, toen ik te horen kreeg van de manuscript commissie dat mijn proefschrift was goedgekeurd appte ik je “nooit gedacht”. Jij appte daarop heel rustig terug “ik wel”. Dat geeft in een notendop weer hoe wij twee dit traject zijn gestart. Jij was de eerste die uitsprak dat ik op dit onderwerp kon promoveren. Je had er eerder vertrouwen in dan ik. Ook jij hebt mij onvermoeibaar steeds opnieuw gestimuleerd om verder te gaan. Je hebt altijd de keuze bij mij gelaten maar wist elke keer wel de juiste woorden te vinden zodat ik zelf verder wilde. Jij bent een van die mensen die je in je leven op je pad moet krijgen zodat je boven jezelf kunt uitstijgen. Ik ben je daar zo dankbaar voor.

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Bij de start van het onderzoek was ik werkzaam als verpleegkundig specialist bij de vaatchirurgie binnen de heelkunde. Er waren een aantal mensen die mogelijk hebben gemaakt dat ik dit kon doen. Dank daarvoor; Nan Pluymackers, Robert Opsteeg, Daan van der Vliet en Luc Knap. Ik kan niet voldoende benadrukken dat het bijzonder is dat er op deze wijze in de verpleegkunde is geïnvesteerd. Op de polikliniek is er ook altijd een oprechte interesse geweest in de vorderingen van het onderzoek door de staf

van de vaatchirurgie, de altijd enthousiaste polikliniek assistenten en de verpleegkundig specialisten. Dank daarvoor, dat gaf elke keer weer opnieuw de goede energie!

Door de ontwikkeling van de website voor dit onderzoek begon ook mijn interesse in eHealth. Ik ben ervan overtuigd geraakt dat de (technologische) innovaties ons verpleegkundig vak nog persoonlijker kunnen maken en kunnen zorgen voor een hernieuwde energie in deze krappe arbeidsmarkt. Ik heb het geluk gehad deze visie verder te ontwikkelen binnen de energieke innovatie afdeling REshape. In het bijzonder de samenwerking met mensen als Concha Celeste en Lucien Engelen en de REshape reizen naar Exponential Medicine hebben me veel inspiratie gegeven. Op het podium staan samen met Lucien op verpleegkundige congressen om ons gedachtengoed verder te brengen binnen het verpleegkundig domein, was geweldig.

De periode als voorzitter van de VAR heeft me gedwongen om mijn visie op het verpleegkundig domein verder te onderzoeken en te verwoorden. Ik ben daar erg goed in ondersteund door de verschillende bestuursleden van de VAR en in het bijzonder Chel Coenen. Hij heeft me ook gestimuleerd dit proefschrift af te ronden door elke keer weer een proefschrift op mijn bureau neer te leggen met de woorden "tja…die is al wel klaar…". Maar meer nog deelde hij zijn enorme kennis over het verpleegkundig vak en in het bijzonder de ontwikkeling hiervan binnen het Radboudumc, met me. Het is best uniek dat iemand zijn kennis deelt en anderen coacht en motiveert, zodat die ander het podium kan pakken. Daar is Chel een ster in. Ik ben dan ook erg blij en trots dat hij vandaag als mijn paranimf naast me staat.

Dankbaar ben ik ook voor alle prachtige, mooie, inspirerende verpleegkundigen die ik sinds de start van mijn opleiding heb mogen leren kennen. Rolmodellen zoals ik nu ook hoop iemand anders rolmodel te kunnen zijn. Verpleegkundigen die vol passie en overtuiging in de directe patiëntenzorg staan, verpleegkundigen die zich hebben ontwikkeld als verpleegkundig specialist, verpleegkundig docent, verpleegkundig onderzoeker, verpleegkundig manager en nog zoveel rollen en functies meer. Het is en blijft een prachtig vak. Ik hoop er recht aan te doen.

De afgelopen jaren heb ik mijn horizon ook buiten het verpleegkundig domein verbreed. Binnen de transmurale zorg heb ik veel geleerd van Sietske Grol en het was mooi dat ook zij net haar promotie heeft afgerond. Met Yvonne Schoon en Ilse de Walvaart hoop ik dat we in de toekomst een prachtig centrum gaan neer zetten wat recht gaat doen aan onze visie op zorg. Ik kijk met respect naar de medewerkers van CSKV en ik ben ervan overtuigd dat we gezamenlijk en met ieders eigen inbreng en kwaliteiten het Radboudumc nog een beetje mooier kunnen maken. In het bijzonder heb ik veel geleerd van de duale samenwerking met Joost Hopman. Je kunt pas goed met elkaar samen werken als je je bewust bent van je eigen professionele identiteit en waar je elkaar kunt versterken. We hebben een unieke samenwerking gevonden die me erg dierbaar is.

In mijn persoonlijke leven heb ik het geluk omringd te worden door prachtige en krachtige vrouwen. Zo inspirerend en energie gevend. Dank voor jullie vriendschap, ieder uniek; Debby Drost, Saskia Mink, Nanette Haze, Floor Felet, Suzanne Klep, Liesbeth Rota, Heleen Vermeulen, Eefke Zekhuis , Mariken Lohman. En mijn wijze vrouwen clubje; Nicoline Hoogerbrugge, Maroeska Rovers en Hanna Eilbracht.

Mijn broer is vandaag mijn andere paranimf. Zoals altijd als steun aan mijn zijde. Hij altijd beduidend de slimste, ik nu de enige gepromoveerde 😊. En wat een steun heeft hij mij gegeven. Toen onze vader bij de start van dit proces overleed was hij de eerste die zag dat ik wilde opgegeven. Dat vond hij onbespreekbaar en hij is sindsdien een enorme stimulerende factor gebleven.

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In dankbare herinnering aan mijn ouders:

Wim Sieben	* 1948 +2012
Mien Sieben- van Lier	* 1942 +1981

Curriculum Vitae

Angelien Sieben is geboren op 3 augustus 1973 in Boxmeer als dochter van Mien Sieben-van Lier en Wim Sieben. Ze groeide samen met haar oudere broer op in Vierlingsbeek en behaalde in 1990 haar havo diploma op het Elzendaalcollege in Boxmeer. Ze heeft altijd geweten dat ze verpleegkundige wilde worden en is gelijk na haar diplomering gestart met de inservice opleiding tot A-verpleegkundige in het Radboudumc. Na het behalen van dat diploma is zij gestart met de HBO-Vv op de hogeschool Inholland in Diemen. Tijdens deze opleiding heeft zij als verpleegkundige gewerkt bij diverse ziekenhuizen en VVT-instellingen in en rond Amsterdam. Na het behalen van het HBOV diploma is ze nog even blijven hangen in het westen en heeft ze gewerkt in de psychiatrie van het Kennemer gasthuis en de afdeling hematologie van het LUMC.

Uiteindelijk is ze weer terug gegaan naar haar thuishaven; Nijmegen en het Radboudumc. Daar heeft ze gewerkt als (senior)verpleegkundige op de afdeling algemene interne geneeskunde. Angelien heeft toen ook de opleiding tot docent verpleegkunde gevolgd en heeft een tijd les gegeven als docent verpleegkunde op het ROC Nijmegen. Na de afronding van de Master Advanced Nurse Practitioner (M ANP) is ze ook nog een aantal jaar verbonden geweest aan de HAN als intervisie docent van deze opleiding. De M ANP heeft ze gevolgd binnen de vaatchirurgie van de afdeling heelkunde. Samen met collega verpleegkundigen van de vaatchirurgie, cardiologie, neurologie en interne geneeskunde heeft ze daar vorm gegeven aan de inrichting en uitvoering van het cardiovasculaire risicoprogramma van het Radboudumc. Daar is ook de basis gelegd voor dit proefschrift.

In 2013 is Angelien voorzitter geworden van de verpleegkundige en paramedische adviesraad van het Radboudumc. In 2015 is Angelien daarnaast gestart als Reshape Fellow om de verbinding tussen verpleegkunde en technologische innovaties, te verstevigen. Dit heeft ze gecombineerd met het werk als verpleegkundig specialist binnen de vaatchirurgie en haar promotietraject. Twee jaar geleden heeft ze uiteindelijk de keuze gemaakt om niet meer als verpleegkundige in de directe patiëntenzorg te werken. Sindsdien richt ze zich op de transmurale zorg om deze verder te versterken, onder andere door het project ziekenhuis verplaatste zorg. Ook werkt ze sinds september 2019 als verpleegkundig directeur van de concernstaf kwaliteit en veiligheid, een duaal

functie met de medisch directeur. Er wacht nu weer een nieuwe uitdaging, namelijk als verpleegkundig directeur van het centrum voor geïntegreerde zorg.

Sinds de kennismaking met haar inmiddels echtgenoot, werkt Angelien ook graag ernaast in de horeca en probeert dit af en toe nog te blijven doen. Angelien is sinds 2003 getrouwd met Maurice van Osch en samen zijn ze de ouders van Lieve (2005) en Jan (2010).

PhD Portfolio

Name PhD candidate:	A Sieben	**PhD period:**	11-03-2011-22-10-2021
		Promotor(s):	prof. dr. C.J.H.M. van Laarhoven prof. dr. A.M. van Dulmen
Graduate school:	Radboud Institute for Health Sciences	**Co-promotor(s):**	dr. S.J.H. Bredie dr. H.A.W. van Onzenoort

Courses	**Year completed**	**ECTS**
RIHS PhD introduction course	2011	0.75
Scientific Writing for PhD candidates	2012	3
Presentation Skills	2011	1.5
Biometrics course (statistiek) PAOG Radboudumc, Nijmegen.	2012	5

Teaching	**Year completed**	**ECTS**
Gastdocent wondverpleegkundige opleiding . Radboud Health Academy, Nijmegen.	2018	2
Opdrachtgever en begeleider bachelor studenten HBO-V kwaliteitsproject	2019	3
Workshop beoordeling wetenschappelijk artikel. NVHVV CNE Vasculair, Utrecht.	2011	1
Opdrachtgever en supervisor innovatieproject bachelor geneeskunde studenten	2019	2
Gast docent Master Advanced Nursing Practice. HAN, Nijmegen.	2018	7

Conferences, seminars and lectures	**Year completed**	**ECTS**
CarVasz, oral presentation. NVHVV, Utrecht.	2011	0.5
ESPACOMP Meeting 2011, poster presentation. European Society for Patient Adherence and Compliance, Utrecht.	2011	1
European Wound Management Association Congress. EWMA, Copenhagen, Denmark.	2013	1
Jaarcongres CaludicatioNet, oral presentation. Claudiocationet, Utrecht)	2016	0.5
European Society for Vascular Surgery Congress, oral presentation. ESVS, Athens, Greece.	2011	1
Rho Chi Lecture “Zorgtechnologie, focus op werkproces en kwaliteit voor de patiënt”. Sigma Theta Tau International, Honor Society of Nursing, Utrecht.	2018	0.5
ICN NP/APN Conference, oral presentation. International Council of Nurses, Rotterdam.	2018	0.5
HIMS & Health 2.0 European , oral presentation. The Healthcare Information and Management Systems Society , Sitges, Spain.	2018	2
Exponential Medicine. Singularity University, San Diego, USA.	2018	2
ESVS annual meeting. European Society for Vascular Surgery, Porto, Portugal.	2015	2

Total EC points: 36.3 of which 36.3 completed

Data management

Data collection and management

The data of the was obtained in accordance with the findable Accessible, Interoperable and Reusable (FAIR) principles.

Data was entered by the nurses who performed the screening and the intervention consults in the developed website (iVAZ). iVAZ is a secured website which can only be entered by the participants by using their social security codes and by selected nurses using security codes. In addition, all patient pharmacists received a letter of information about the trial, consent of the ethical committee, and the informed consents of the participants. They were asked to send the data on refill records of their computerized pharmacy systems through a secured email address.

All the data were anonymized according to the privacy protocols from the ethical committee and imported by the researcher into SPSS (IBM Corp). These data will be stored for at least 15 years and will then be removed.

Informed consent

All cardiovascular patients who receive the regular cardiovascular preventive care were asked to participate by a nurse when they arrived at the outpatient clinic for their screening consult. Patients received a letter explaining the study, documenting their ability to withdraw at any time without explanation, and confirming that their medical care will in no way be influenced by their decision regarding participation. At a minimum of 24 hours later, written informed consent was sought by a research assistant prior to the patient entering the study. These informed consent paper forms are storage in a closed archive from the department of surgery.

Ethical Approval

The MIRROR trial (chapter 5)

The study protocol was approved by the local ethical committee. Approval for this study was obtained by the Local Ethical Committee, the human related research committee of the Arnhem-Nijmegen region (CMO no 2011/062), which applied criteria described in the Medical Scientific Research with People Act (WMO), the Helsinki Declaration, the Good Clinical Practice (GCP), EU Guideline Good Clinical Practice, Clinical trials guidelines on medicinal products and in CCMO guidelines.

Chapters 6 and 7

The Ethical Committee waived the need for a formal informed consent for this study. The study was conducted according to the good clinical practice protocol and we used usual care data considering the research question of this study. Data was anonymised according to the research protocols of the Ethical Committee.

Availability of data

The datasets of the studies described in this thesis are available from the corresponding author on reasonable request : angelien.sieben@radboudumc.nl


IO

Chapter 10

Appendices

Beliefs about medicines questionnaire (BMQ)

Original

Your views about medicines prescribed for you

We would like to ask you about your personal views about medicines prescribed for you. These are statements other people have made about their medicines. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
There are no right or wrong answers. We are interested in your personal views.

Rated: strongly agree, agree, uncertain, disagree, strongly disagree.

1. My health, at present, depends on my medicines.
2. Having to take medicines worries me.
3. My life would be impossible without my medicines.
4. Without my medicines I would be very ill.
5. I sometimes worry about long-term effect of my medicines.
6. My medicines are a mystery to me.
7. My health in the future will depend on my medicines.
8. My medicines disrupt my life.
9. I sometimes worry about becoming too dependent on my medicines.
10. My medicines protect me from becoming worse.

Your views about medicines in general

We would like to ask you about your personal views about medicines in general.
These are statements other people have made about medicines in general.
Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
There are no right or wrong answers. We are interested in your personal views.

Rated: strongly agree, agree, uncertain, disagree, strongly disagree.

1. Doctors use too many medicines
2. People who take medicines should stop their treatment for a while every now and again.
3. Most medicines are addictive
4. Natural remedies are safer than medicines.
5. Medicines do more harm than good.
6. All medicines are poison.
7. Doctors place too much trust on medicines.
8. If doctors had more time with patients they would prescribes fewer medicines.

Patient version

Uw mening over de medicijnen die u zijn voorgeschreven

We willen u graag vragen naar uw persoonlijke mening over *aan u voorgeschreven medicijnen.*
Hieronder staan uitspraken die andere mensen hebben gedaan over hun medicijnen. Geef aan in welke mate u het eens of oneens bent met de uitspraken door het passende vakje aan te kruisen.
Er zijn geen goede of foute antwoorden; het gaat om uw mening.

Mogelijke antwoorden: helemaal mee eens, mee eens, neutraal, mee oneens, helemaal mee oneens. Kruis het bolletje aan wat op u van toepassing is.

1. Mijn gezondheid is momenteel afhankelijk van mijn medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

2. Het baart mij zorgen dat ik medicijnen moet gebruiken.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

3. Ik kan absoluut niet zonder mijn medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

4. Zonder mijn medicijnen zou ik me erg ziek voelen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

5. Ik maak me soms zorgen over de effecten van mijn medicijnen op de lange termijn.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

6. Ik weet niets over mijn medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

7. Mijn toekomstige gezondheid hangt af van mijn medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

8. Mijn medicijnen ontregelen mijn leven.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

9. Ik ben soms bang dat ik te afhankelijk word van mijn medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

10. Mijn medicijnen zorgen ervoor dat mijn gezondheid niet achteruit gaat.
    Helemaal mee eens
    Mee eens
    Neutraal
    Mee oneens
    Helemaal mee oneens

Uw mening over medicijnen in het algemeen

We willen u graag vragen naar uw persoonlijke mening over *medicijnen in het algemeen*. Hieronder staan uitspraken die andere mensen hebben gedaan over medicijnen in het algemeen.
Geef aan in welke mate u het eens of oneens bent met de uitspraken door het passende vakje aan te kruisen.
Er zijn geen goede of foute antwoorden; het gaat om uw mening.

Mogelijke antwoorden: helemaal mee eens, mee eens, neutraal, mee oneens, helemaal mee oneens.

1. Artsen schrijven teveel medicijnen voor.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

2. Mensen die medicijnen gebruiken, zouden af en toe hun medicatie een tijdje moeten stoppen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

3. De meeste medicijnen zijn verslavend.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

4. Natuurlijke geneeswijzen zijn veiliger dan medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

5. Medicijnen schaden meer dan dat ze baten.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

6. Alle medicijnen zijn vergif.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

7. Artsen stellen te veel vertrouwen in medicijnen.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

8. Als artsen meer tijd voor patiënten zouden hebben, zouden ze minder medicijnen voorschrijven.
   Helemaal mee eens
   Mee eens
   Neutraal
   Mee oneens
   Helemaal mee oneens

Modified Morisky Scale (MMAS-8)

Original :

The first seven questions you can answer by a "yes" or a "no". The 8th question you can answer by : never, rarely, once in a while, sometimes, usually, all the time

1. Do you sometimes forget to take your medication?

2. Over the past two weeks, where there any days when you did not take your medicines?

3. Have you ever cut back or stopped taking your medicines without telling the doctor because you felt worse when you took it?

4. When you travel or leave home, do you sometimes forget to take along your medicines?

5. Did you take your medicines yesterday?

6. When you feel like your blood pressure is under control, do you sometimes stop taking your medicines?

7. Taking medicines every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment-plan?

8. How often do you have difficulty remembering to take all your blood pressure medication?

Patient version :

Vragenlijst naar het gebruik van uw medicijnen

De eerste zeven vragen kunt u met "ja" of "nee" beantwoorden. De achtste vraag kunt u beantwoorden met: nooit, zelden, soms, regelmatig, vaak, altijd.

1. Vergeet u wel eens uw medicijnen in te nemen?
   Ja
   Nee

2. Waren er gedurende de afgelopen twee weken dagen dat u uw medicijnen niet innam?
   Ja
   Nee

3. Hebt u ooit uw medicatie verminderd of gestopt zonder het de arts te melden, omdat u zich slechter voelde na het innemen van de medicijnen?
   Ja
   Nee

4. Vergeet u wel eens uw medicijnen mee te nemen wanneer u op reis gaat of de deur uitgaat?
   Ja
   Nee

5. Hebt u gisteren uw medicijnen ingenomen?
   Ja
   Nee

6. Stopt u wel eens met het innemen van uw medicijnen wanneer u het gevoel heeft dat uw ziekte onder controle is?
   Ja
   Nee

7. Voor sommige mensen veroorzaakt het dagelijks innemen van medicijnen veel ongemak. Voelt u zich wel eens gestrest omdat u zich aan het behandelingsplan voor uw ziekte moet houden?
   Ja
   Nee

8. Hoe vaak komt het voor dat u er niet aan denkt om al uw medicijnen in te nemen?
   - Nooit
   - Zelden
   - Soms
   - Regelmatig
   - Vaak
   - Altijd

DE LEEFSTIJLVRAGENLIJST

Universitair Medisch Centrum St. Radboud

INSTRUCTIE

Veel klachten en ziekten hangen samen met leefstijl. Met leefstijl bedoelen we de dagelijkse gewoonten: wat we eten en drinken, of we roken en hoeveel we bewegen.

Aan de hand van deze vragenlijst willen we uw leefstijl in kaart brengen. Het doel daarvan is om methoden te ontwikkelen om mensen beter te kunnen adviseren over hun leefstijl. De vragenlijst bestaat uit circa 90 eenvoudige vragen en uitspraken. Het invullen kost u ongeveer 25 minuten.
De meeste vragen kunt u beantwoorden door het hokje voor het antwoord van uw keuze in te kleuren. *U kunt steeds maar <u>één</u> antwoord geven.*

Bij een aantal vragen kunt u de antwoorden invullen op de stippellijntjes.

Deze vragen gaan over het <u>roken van tabak</u>.

1. Rookt u?
   Ja (u kunt doorgaan met **vraag 3**)
   Nee

2. Heeft u wel eens gerookt?
   Ja, maar ik ben het afgelopen jaar gestopt (u kunt doorgaan met de vragen over **beweging** op bladzijde 8)
   Ja, maar ik ben langer dan een jaar geleden gestopt (u kunt doorgaan met de vragen over **beweging** op bladzijde 8)
   Nee (u kunt doorgaan met de vragen over **beweging** op bladzijde 8)

3. Hoe lang rookt u al? (als u tussen door één jaar of langer gestopt bent, deze tijd niet meetellen)

   ……jaar

4. Wat rookt u? (hier zijn meerdere antwoorden mogelijk)
   Sigaretten
   Shag
   Sigaren
   Pijpen

5. Rookt u elke dag?
   Ja
   Nee (ga verder met vraag 12)

6. Hoe snel na het ontwaken ('s ochtends) rookt u voor het eerst?
   Binnen 5 minuten na ontwaken
   6-30 minuten na ontwaken
   31-60 minuten na ontwaken
   meer dan 60 minuten na ontwaken

7. Vindt u het moeilijk niet te roken op plaatsen waar het verboden is zoals bijvoorbeeld in de kerk, bibliotheek, bioscoop of andere openbare gelegenheden?
   Ja
   Nee

8. Op welk tijdstip van de dag kunt u het roken het moeilijkst missen?
   In de ochtend (eerste sigaret, shagje, sigaar of pijp van de dag)
   Op alle andere tijdstippen

9. Hoeveel sigaretten (of lees hier: shagjes, sigaren, pijpen) rookt u per dag?
   10 per dag of minder
   11-20 per dag
   21-30 per dag
   31 per dag of meer

10. Rookt u vaker gedurende de eerste uren van het ontwaken, dan gedurende de rest van de dag?
    Ja
    Nee

11. Rookt u wanneer u zo ziek bent dat u het grootste gedeelte van de dag in bed ligt?
    Ja
    Nee

12. Vindt u het een probleem dat u rookt?
    Ja
    Nee

13. Denkt u er wel eens over om te stoppen met roken?
    Ja
    Nee

14. Denkt u dat het u lukt om te stoppen met roken, als u dat zou willen?
    Ja
    Nee

15. Bent u van plan de komende maand te stoppen met roken?
    Ja
    Nee

16. Is het u in het afgelopen jaar wel eens gelukt om langer dan één dag bewust niet te roken?
    Ja
    Nee (ga verder met **vraag 18**)

17. Hoe vaak is het u in het afgelopen jaar gelukt om langer dan één dag bewust niet te roken?

    ……. keer

18. Rookt u wel eens marihuana of hasjies?
    nooit
    minder dan maandelijks
    maandelijks
    wekelijks
    dagelijks of bijna dagelijks

Deze vragen gaan over beweging.

De volgende vragen gaan over uw lichamelijke activiteit **gedurende de afgelopen 7 dagen**. Beantwoordt u alstublieft alle vragen, ook al beschouwt u uzelf als niet lichamelijk actief. Denkt u aan activiteiten die u doet op het werk, in en rond het huis, om van de ene naar de andere plaats te komen en activiteiten in uw vrije tijd voor recreatie, training of sport.

Denkt u aan alle zware lichamelijke activiteiten die u deed in **de afgelopen 7 dagen**. **Zware** lichamelijke activiteiten zijn activiteiten die veel lichamelijke inspanning kosten en voor een **veel snellere** ademhaling zorgen. Denk *alleen* aan de activiteiten die u **ten minste 10 minuten** per keer heeft verricht.

1. Als u denkt aan **de afgelopen 7 dagen**, op hoeveel van deze dagen heeft u zware lichamelijke activiteiten verricht zoals zware lasten tillen, spitten, aerobics of wielrennen?

   …….dagen per week
   geen zware lichamelijke activiteiten (ga naar **vraag 3**)

2. Op de dagen dat u **zwaar** lichamelijk actief was, hoeveel tijd heeft u daar dan gewoonlijk (ongeveer) aan besteed?

   …….uren per dag

   …….minuten per dag
   weet ik niet, ook niet bij benadering

Denkt u aan activiteiten die **matige** lichamelijke inspanning kosten en die u in **de afgelopen 7 dagen** heeft verricht. **Matig** intensieve lichamelijke activiteit laat u **iets sneller** ademen dan normaal. Denkt u weer alleen aan activiteiten die u **ten minste 10 minuten** per keer heeft verricht.

3. Als u denkt aan **de afgelopen 7 dagen**, op hoeveel van deze dagen heeft u **matig** intensieve lichamelijke activiteit verricht, zoals het dragen van lichte lasten, fietsen in een normaal tempo of dubbeltennis?

   Laat wandelen hier buiten beschouwing.

   …….dagen per week
   geen matig intensieve lichamelijke activiteiten (ga naar **vraag 5)**

4. Op de dagen dat u matig intensief lichamelijk actief was, hoeveel tijd heeft u daar dan gewoonlijk (ongeveer) aan besteed?

   …….uren per dag

   …….minuten per dag
   weet ik niet, ook niet bij benadering

5. Als u denkt aan de afgelopen 7 dagen, op hoeveel dagen heeft u tenminste 10 minuten per keer gewandeld? Denk hierbij aan wandelen op het werk en thuis, wandelen om van de ene naar de andere plaats te komen, en al het andere wandelen dat u deed tijdens recreatie, sport of vrijetijdsbesteding.

   …….dagen per week
   geen wandelen (ga naar **vraag 7**)

6. Op de dagen dat u ten minste 10 minuten per keer wandelde, hoeveel tijd heeft u daar dan gewoonlijk (ongeveer) aan besteed?

   …….uren per dag

   …….minuten per dag
   weet ik niet, ook niet bij benadering

7. Hoeveel tijd bracht u gewoonlijk zittend door gedurende een doordeweekse dag in de afgelopen 7 dagen? Bij deze tijd mag zitten achter een bureau, tijd die zittend wordt doorgebracht met vrienden, zittend lezen, studeren of tv kijken worden gerekend.

   …….uren per dag

   …….minuten per dag
   weet ik niet, ook niet bij benadering

8. Vindt u dat u te weinig beweegt?
   Ja
   Nee

9. Denkt u er wel eens over om meer beweging te nemen?
   Ja
   Nee

10. Denkt u dat het u lukt om meer beweging te nemen, als u dat zou willen?
    Ja
    Nee

11. Bent u van plan de komende maand meer beweging te gaan nemen?
    Ja
    Nee

12. Is het u in het afgelopen jaar wel eens gelukt om meer beweging te nemen?
    Ja
    Nee

Deze uitspraken gaan over eten.

1. Ik gebruik halfvolle of magere melkproducten (zoals halfvolle melk en koffiemelk, karnemelk en magere yoghurt) in plaats van volle producten.
   Ja
   Nee
   Soms

2. Als ik kaas eet, neem ik minder vette kaas, dus 20+ of 30+.
   Ja
   Nee
   Soms

3. Als ik mijn brood met vleeswaren beleg, dan kies ik uit de volgende soorten: achterham, casselerrib, fricandeau, kipfilet, rookvlees, rosbief, rollade of schouderham.
   Ja
   Nee
   Soms
   Ik eet nooit vleeswaren op brood.

4. Als ik mijn brood smeer, dan doe ik daar (dieet) halvarine op of een zogenaamd 'laagvet smeersel' in plaats van margarine of boter.
   Ja
   Nee
   Soms
   Ik smeer mijn brood nooit met boter, margarine, halvarine of iets dergelijks.

5. Als ik jus of saus gebruik bij mijn maaltijd, dan neem ik een met water aangelengde jus of een rode saus (bijvoorbeeld barbecuesaus of tomatenketchup).
   Ja
   Nee
   Soms
   Ik gebruik nooit jus of saus.

6. Het bakken of braden van vlees, vis of aardappelen doe ik in roomboter of margarine uit een pakje.
   Ja
   Nee
   Soms

7. Voor het roerbakken (in bijvoorbeeld een wok) van kleingesneden groenten, vlees, tahoe en dergelijke gebruik ik olie of vloeibaar braadvet.
   Ja
   Nee
   Soms

8. Ik vervang vlees wel eens door vis. Bij elkaar eet ik één keer vis per week of vaker (alle soorten vis tellen mee, ook vissticks).
   Ja
   Nee
   Soms

9. Ik eet per week twee keer of vaker de volgende vleessoorten: rookworst, slavink of speklappen.
   Ja
   Nee
   Soms

10. Ik eet meer dan twee keer per maand snacks zoals patat, een frikandel of een saucijzenbroodje.
    Ja
    Nee
    Soms

11. Ik eet gemiddeld meer dan twee koekjes of chocolaatjes per dag.
    Ja
    Nee
    Soms

12. Ik eet vaker dan twee keer per week een punt taart, een gebakje of een grote koek.
    Ja
    Nee
    Soms

13. Ik eet meer dan zeven handjes zoutjes (chips, pinda's enz.) per week.
    Ja
    Nee
    Soms

14. Ik eet meer dan één keer per week een candybar of een groot stuk chocolade.
    Ja
    Nee
    Soms

15. Mijn ontbijt of lunch bestaat voor het grootste deel uit brood of andere graanproducten zoals roggebrood, krentenbrood, muesli, tarwevlokken (in pap of ontbijtdranken), havermout, ontbijtkoek of crackers.
    Ja
    Nee

16. Ik kies vooral volkorenproducten (volkoren/bruinbrood, donker roggebrood) als ik brood of graanproducten eet.
    Ja
    Nee

17. Ik eet minstens zes dagen in de week aardappelen, rijst of pasta.
    Ja
    Nee

18. Bij de warme maaltijd eet ik minstens drie kleine aardappelen of drie opscheplepels (= 150 gram) gekookte rijst of pasta.
    Ja
    Nee

19. Als ik pasta of rijst eet, neem ik meestal de volkorenpasta en zilvervliesrijst
    Ja
    Nee
    Ik eet nooit pasta of rijst.

20. Ter vervanging of ter aanvulling op de aardappelen, rijst of pasta eet ik ook wel eens peulvruchten, zoals kapucijners, witte en bruine bonen, linzen of spliterwten.
    Ja
    Nee

21. Groenten eet ik
    elke dag
    vijf of zes dagen per week
    hooguit vier dagen per week of minder vaak

22. Tussendoor of bij mijn broodmaaltijd eet ik groenten, zoals rauwkost
    ja, bijna altijd
    soms
    nee, (bijna) nooit

23. Als ik op een dag groenten eet, dan is dat bij elkaar (rauwkost en groenten op brood of tussendoor tellen ook mee en een schaaltje rauwkost is ongeveer 50 gram groenten)
    ongeveer 2 opscheplepels (= 100 gram of minder)
    ongeveer 3 opscheplepels (= 150 gram)
    ongeveer 4 opscheplepels of meer (= 200 gram of meer)

24. Fruit eet ik
    elke dag
    vijf of zes dagen per week
    hooguit vier dagen per week of minder vaak

25. Als ik fruit eet, dan is dat (één keer fruit is bijvoorbeeld een middelgrote appel of twee mandarijntjes, maar ook een dessertschaaltje aardbeien of bessen. Ook een glas ongezoet vruchtensap of een dessertschaaltje appelmoes telt als één keer fruit)
    twee of meer keer fruit per dag
    één keer fruit per dag
    ik eet (bijna) nooit fruit

26. Ik drink ongezoete vruchtensappen- vers of uit een pak of fles- en dan meestal
    citrussappen zoals sinaasappelsap en grapefruitsap
    overige sappen zoals appelsap en druivensap
    ik drink (vrijwel) nooit vruchtensappen

27. Vindt u dat u over het algemeen gezond eet?
    Ja
    Nee

28. Denkt u er wel eens over uw eetgewoonten te veranderen?
    Ja
    Nee

29. Denkt u dat het u lukt uw eetgewoonten te veranderen, als u dat zou willen?
    Ja
    Nee

30. Bent u van plan de komende maand uw eetgewoonten te veranderen?
    Ja
    Nee

31. Is het u in het afgelopen jaar wel eens gelukt om uw eetgewoonten te veranderen?
    Ja
    Nee

Deze vragen gaan over het gebruik van alcohol.

Nu volgen enkele vragen over uw alcoholgebruik gedurende het **afgelopen jaar**. Met alcoholgebruik wordt bedoeld: het drinken van bier, wijn, likeur en andere gedestilleerde dranken.

1. Hoe vaak drinkt u alcoholhoudende drank?
   nooit (u bent klaar met de vragen over alcoholgebruik en hoeft alleen de **laatste vraag** nog te beantwoorden)
   maandelijks of minder
   2 à 4 keer per maand
   2 of 3 keer per week
   4 of meer keer per week

2. Hoeveel glazen drinkt u op een typische dag dat u drinkt?
   1
   2
   3
   4
   5 of 6
   7, 8 of 9
   10 of meer

3. Hoe vaak drinkt u 6 of meer glazen per gelegenheid?
   nooit
   minder dan maandelijks
   maandelijks
   wekelijks
   dagelijks of bijna dagelijks

4. Hoe vaak heeft u in het afgelopen jaar opgemerkt dat u niet in staat was het drinken te stoppen nadat u was begonnen met drinken?
   nooit
   minder dan maandelijks
   maandelijks
   wekelijks
   dagelijks of bijna dagelijks

5. Hoe vaak heeft u vanwege uw drankgebruik in het afgelopen jaar nagelaten om te doen wat normaal van u verwacht werd?
   nooit
   minder dan maandelijks
   maandelijks
   wekelijks
   dagelijks of bijna dagelijks

6. Hoe vaak heeft u gedurende het afgelopen jaar de behoefte gehad om 's ochtends uw eerste alcoholhoudende drank te gebruiken om weer op gang te kunnen komen na een sessie met overmatig drankgebruik?
   nooit
   minder dan maandelijks
   maandelijks
   wekelijks
   dagelijks of bijna dagelijks

7. Hoe vaak heeft u zich gedurende het afgelopen jaar schuldig gevoeld of zelfverwijt gehad over uw drankgebruik?
   nooit
   minder dan maandelijks
   maandelijks
   wekelijks
   dagelijks of bijna dagelijks

8. Hoe vaak kon u zich in het afgelopen jaar gebeurtenissen van de dag daarvoor niet meer herinneren vanwege uw drankgebruik?
   nooit
   minder dan maandelijks
   maandelijks
   wekelijks
   dagelijks of bijna dagelijks

9. Heeft u uzelf of iemand anders wel eens verwond als gevolg van uw drankgebruik?
   nee, nog nooit
   ja, maar niet in het afgelopen jaar
   ja, in het afgelopen jaar

10. Heeft een familielid, vriend of een dokter of een hulpverlener in de gezondheidszorg zijn bezorgdheid geuit over uw drankgebruik en u gesuggereerd uw drankgebruik te minderen?
    nee, nog nooit
    ja, maar niet in het afgelopen jaar
    ja, in het afgelopen jaar

11. Vindt u dat u teveel drinkt?
    Ja
    Nee

12. Denkt u er wel eens over om te stoppen met drinken?
    Ja
    Nee

Denkt u dat het u lukt om te stoppen met drinken, als u dat zou willen?
    Ja
    Nee

13. Bent u van plan de komende maand te stoppen met drinken?
    Ja
    Nee

14. Is het u in het afgelopen jaar wel eens gelukt om te stoppen met drinken?
    Ja
    Nee

Tot slot nog één laatste vraag

Graag willen we u over een aantal maanden nogmaals een aantal vragen over leefstijl stellen. U zal dan een kort vragenlijstje thuisgestuurd krijgen. Bent u bereid hieraan mee te werken?

Ja
Nee

Dit is het einde van de vragenlijst.

Hartelijk dank voor uw medewerking!

Institute for Health Sciences

Radboudumc