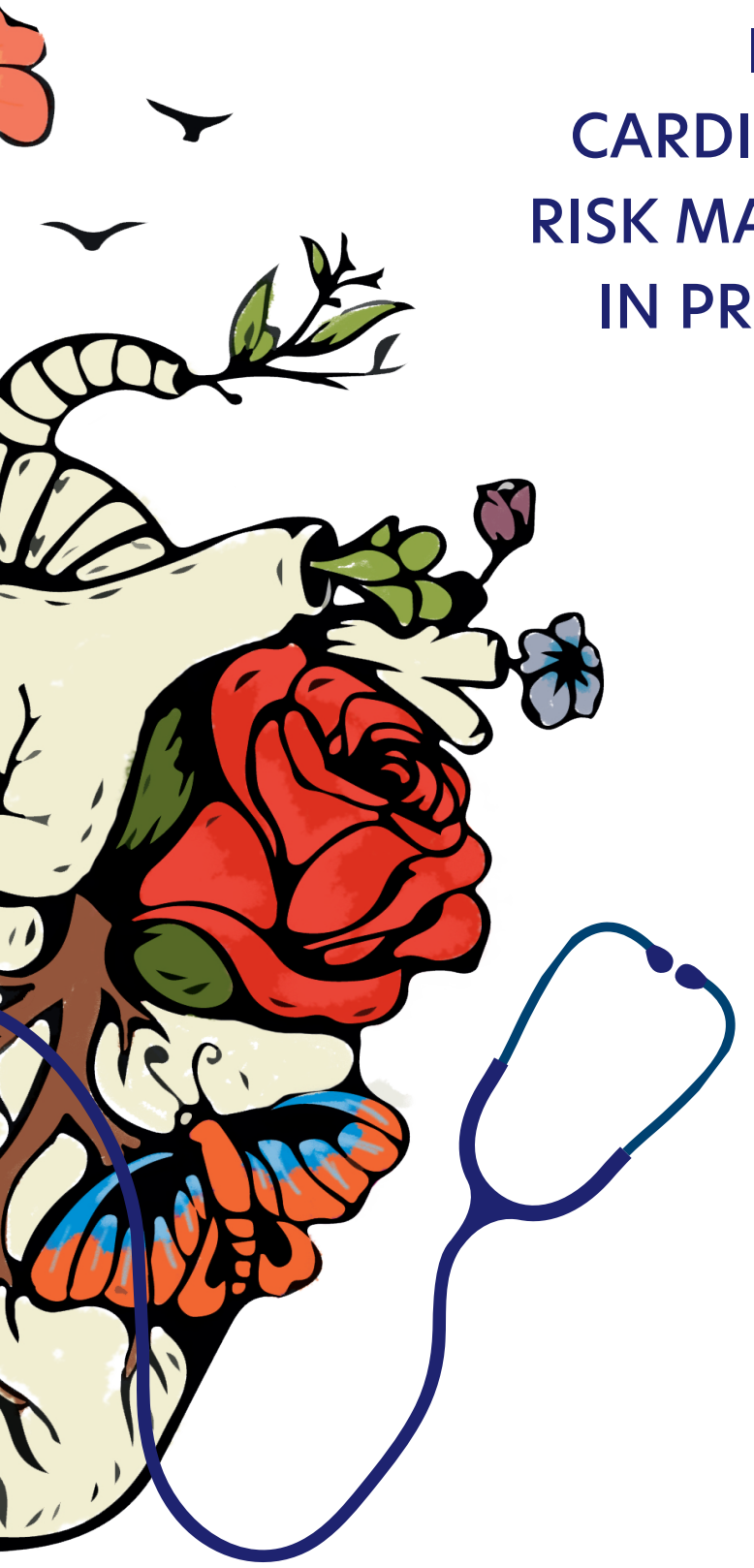

INTEGRATED CARDIOVASCULAR RISK MANAGEMENT IN PRIMARY CARE

SUZANNE MARCHAL

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Integrated cardiovascular risk management in primary care

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in de eerste lijn

(met een samenvatting in het Nederlands)

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Promotoren: Prof. dr. A. W. Hoes
Prof. dr. A. W. J. van ’t Hof

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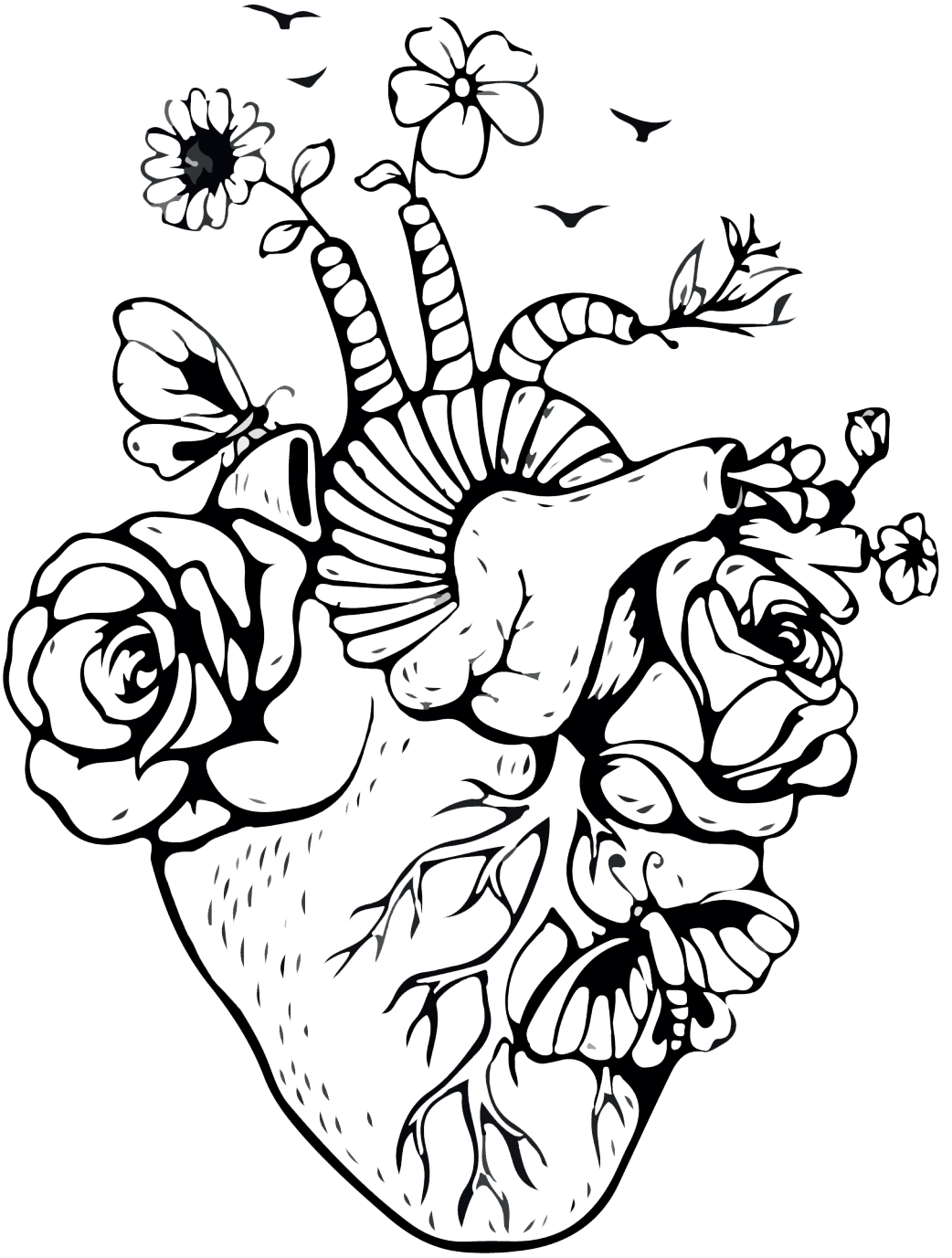

CHAPTER 1

Introduction

The burden of cardiovascular disease

Cardiovascular disease (CVD) has remained the leading cause of death worldwide as well as in the region of Europe, accounting for 47% and 39% of all deaths in respectively females and males in Europe.[1,2] Despite sustained declines in CVD mortality in many countries across Europe, it is unlikely that the World Health Organisation (WHO) target to achieve a 25% relative reduction in the overall mortality from CVD, cancer, diabetes, and chronic respiratory disease will be attained.[1] Besides, the decline in the age-standardized incidence and prevalence of CVD has been small during the last 27 years.[1] In the Netherlands, the prevalence of CVD increased with 150,000 to 1.55 million people between 2015 and 2019, possibly due to ageing, but at least also partly attributable to an increase in prevalence of obesity.[3] There is concern about achievement of the WHO and United Nations targets in cardiovascular risk factor reductions by 2025.[1,4] In Europe, the prevalence of obesity has more than doubled in the last 36 years, 1 in 3 adults is insufficiently physically active and the downward trend in prevalence of elevated blood pressure appears to be minimal.[1]

The burden of CVD also poses a financial challenge. In the Netherlands, CVD accounted for more than 10% of health expenditure and was at the top of the list of hospital spending in 2016.[5] Health-care expenditures in Western countries are already high and expected to increase further due to the ageing of the population and an increase in the prevalence of chronic disease. If health expenditure increases steadily in the near future, it will rise to 30% of the gross domestic product in 2040 in the Netherlands.

Cardiovascular risk factors

The concept of cardiovascular risk factors, including age, smoking and blood pressure, was already introduced over 50 years ago by the Framingham Heart study investigators.[6] Especially cardiovascular risk factors that are modifiable and when appropriately treated reduce cardiovascular risk are of major significance for public health. Major modifiable risk factors include high blood pressure, elevated blood lipids, smoking, physical inactivity, obesity and an unhealthy diet.

Blood pressure (BP) has a strong log-linear association with the occurrence of CVD.[7] A reduction of 10 mm Hg in systolic BP or 5 mm Hg in diastolic BP is associated with about 40% lower relative risk of stroke death and about 30% lower

relative risk of death from CVD in middle age,[8] with larger absolute risk reductions for patients with a higher baseline cardiovascular risk.[9]

There is convincing evidence that reducing plasma LDL-cholesterol levels reduces CVD risk. Meta-analyses have showed that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one fifth per mmol/L reduction in LDL cholesterol.[10] A more intensive lowering of LDL-cholesterol by statins further reduces major vascular events,[11] but it remains unclear whether below a certain level of LDL-cholesterol the benefit ends and/or harm occurs.

Besides the clear associations of blood pressure and LDL-cholesterol with CVD risk and the beneficial effects of lowering the levels of these risk factors, it is well known that cardiovascular disease and mortality risk can be reduced by a adopting a healthier lifestyle, including increasing physical activity, keeping a healthy diet, smoking cessation and weight reduction.[12-16] In 2017, smoking, high body mass index (i.e. weight / length^2), alcohol abuse and diets high in sodium were among the largest contributors to global disability-adjusted life-years (DALYs).[17] While contributing to the burden of chronic disease, including CVD, these risk factors also provide opportunities for intervention.

A strong dose–response relationship between the number of cigarettes smoked and CVD exists,[18] and smoking cessation is the most effective measure to prevent CVD.[14]

An increase in physical activity to levels recommended in cardiovascular prevention guidelines has a substantial positive impact on incident CVD and all-cause and cardiovascular mortality.[19] Benefits already start from any physical activity and can reduce mortality by about 31% in individuals who meet guidelines compared with individuals reporting no physical activity.[19,20] Guidelines recommend 150 to 300 minutes a week of moderate intensity physical activity in healthy adults and avoid sitting for more than eight hours a day.[21,22]

Further, a healthy diet, low in sodium intake, rich in vegetables, fruits, and low-fat dairy products, can lower blood pressure substantially.[23] Also, higher intakes of polyunsaturated fatty acids (PUFAs) and carbohydrates from whole grains are

significantly associated with a lower risk of CHD.[24] In addition, it is well known that smoking is associated with excess mortality.[25] Lastly, an increased BMI is associated with an adverse effect on all major CVD risk factors, including a higher LDL- and lower HDL-cholesterol levels and in increase in blood pressure.[26] Weight reduction in overweight and obese people will improve their CVD risk.[27]

The evidence to practice gap

A wide gap still exists between evidence-based cardiovascular risk factor management recommendations in CVD prevention guidelines and everyday clinical practice. Despite the clear relation between lifestyle, blood pressure, LDL-cholesterol and CVD risk, cardiovascular risk factors are generally insufficiently controlled. Also in primary care poor implementation of preventive measures are of major concern, as consistently shown by EUROASPIRE surveys.[28-30] The most recent EUROASPIRE V cross sectional primary care study among 16 European countries found that among patients at high risk, without a history of CVD in primary care, 18.1% was smoker, 43.5% obese (body mass index ≥30 kg/m2) and 63.8% centrally obese (waist circumference ≥88 cm for women, ≥102 cm for men).[30] Of patients on BP lowering medication 47.0% reached the target of <140/90 mm Hg and among treated dyslipidaemia patients only 46.9% attained the LDL-cholesterol target of <2.6 mmol/l. Besides, many patients in the primary care arm of EUROASPIRE V reported low rates of having received lifestyle advice. For example, one-fifth of obese patients were never told that they were overweight, and more than a third were unaware of their weight target. Also, less than half of patients on lipid-lowering medication were aware of their cholesterol levels and less than a third knew their cholesterol target.

These, and others, findings clearly show that to achieve adequate prevention of CVD an effective integrated strategy that can address multiple risk factors is needed.[31]

Cardiovascular risk management and the role of primary care

Healthcare providers face the challenge to identify, manage and monitor cardiovascular risk factors in large numbers of individuals at increased risk for developing CVD. Moreover, most patients have more than one risk factor. The total CVD risk is a consequence of the interaction of many risk factors and modest increases of several risk factors can be more harmful than a high level

of a single risk factor.[32] This underlines the importance of multifactorial and multidisciplinary cardiovascular risk factor management (CVRM) interventions, as also recommended by the European guidelines on cardiovascular disease prevention.[27] These interventions include promoting a healthy lifestyle through behavioural changes, including diet, physical activity and smoking cessation programmes for resistant smokers. Further, psychosocial risk factors (stress, social isolation, and negative emotions) should be taken into account as these may act as barriers against behavioural change.

General practitioners play a key role in multifactorial and multidisciplinary CVRM, as they have a longstanding relationship with their patients and, often, family members. The longitudinal nature of primary care provides multiple opportunities for clinicians to provide health behaviour advice and counselling over long periods of time. Therefore, an integrated multidisciplinary CVRM programme in primary care offers a potentially effective way to improve the implementation of CVD guideline recommendations and thereby the quality of CVD prevention.[33]

Integrated care to improve cardiovascular risk management

In some European countries, integrated and multidisciplinary CVRM programmes were introduced in primary care in recent years. Most of these programmes are based on the Chronic Care Model (CCM).[34] This model is a guide to improve care for patients with chronic conditions such as cardiovascular diseases.[35] The model predicts that improvement in its 6 interrelated components - self-management support, clinical information systems, delivery system redesign, decision support, health care organization, and community resources - can produce system reform in which informed, activated patients interact with prepared, proactive practice teams (figure 1).[35] Programmes based on the CCM have shown to improve process and outcome measures, particularly in patients with diabetes.[36] However, evidence on the effect of integrated care programmes for CVRM in primary care on outcomes such as blood pressure, cholesterol levels, smoking status and cardiovascular risk is scarce.[31,37-39] Furthermore, multidisciplinary integrated CVRM is a heterogeneous concept. Therefore, an overall assessment of the effectiveness of integrated programmes for CVRM is hindered by heterogeneity in intervention strategies, target populations and reported outcomes. A systematic review of 31 randomized controlled trials (RCTs) on the effects of multiple health behavioural changes in primary care to reduce cardiovascular risk in people

without established CVD found a modest, statistically significant effect on some CV risk factors, including blood pressure and cholesterol, but not on lifestyle (smoking, diet, physical activity) and overall CVD risk.[40] Also for patients with known CVD RCTs have shown positive effects of CVRM programmes on blood pressure and cholesterol[41], whereas other RCTs did not find an effect.[42] Moreover, effects are often not sustained on the long term.[43] A possible explanation might be that many interventions that prove to be efficacious in randomized trials are much less effective in the real world setting, which may be attributable to many factors, including differences in patient populations.[44] Importantly, most evidence on complex interventions is based on RCTs, presenting the effect of the intervention when carefully implemented according to the existing guidelines under optimal conditions.[45] However, such studies oversimplify reality and the results are not automatically applicable in daily practice. Therefore, more real-world evidence is needed.

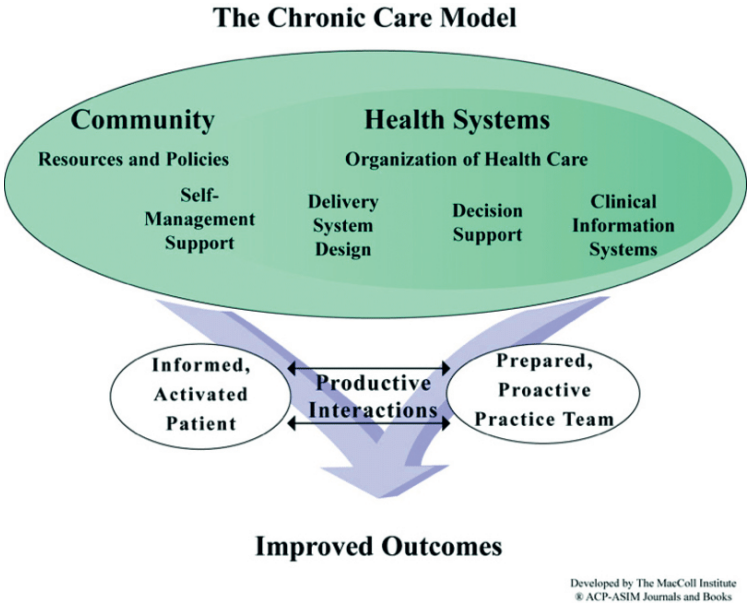

Figure 1. The different components of Wagner's Chronic Care Model and how they are used to facilitate productive interactions between the patient and healthcare team to improve outcomes.

Aim and outline of this thesis

The principle aim of this thesis is to provide insight in the effectiveness of an integrated and multidisciplinary programme for CVRM in a real-world primary care setting. Furthermore, this thesis describes the challenges of the implementation of CVRM in general practice in chapters about the process of implementation and therapeutic inertia.

In **Chapter 2** we comment on the *2016 European Guidelines on cardiovascular disease prevention in clinical practice* and address challenges and feasibility of the recommendations for everyday general practice. **Chapter 3** describes the design of the ZWOT-CASE study ((ZWOlle inTegrated care for CArdiovaScular risk managEment study), a prospective observational study among patients with a high CV risk, assessing the effects of an integrated care programme for cardiovascular risk management (CVRM) in general practice on systolic blood pressure and LDL-cholesterol compared to usual care. The results of the ZWOT-CASE study are presented in **Chapter 4.** In **Chapter 5** we evaluated the process of the implementation of the integrated care programme for CVRM within the framework of the ZWOT-CASE study, to gain a deeper understanding of the lack of effectiveness of the programme. In **Chapter 6** we compared hospital care and costs related to CVRM in the period before and after implementation of an integrated care programme for CVRM in primary care among patients with established CVD. **Chapter 7** describes therapeutic inertia in dyslipidaemia in primary care. This thesis ends with a general discussion **(Chapter 8)** including an overall interpretation of the main findings, recommendations for improvement in integrated CVRM in primary care and suggestions for further research. The RE-AIM model is used to discuss the potential impact of the integrated multidisciplinary CVRM programme in daily practice.

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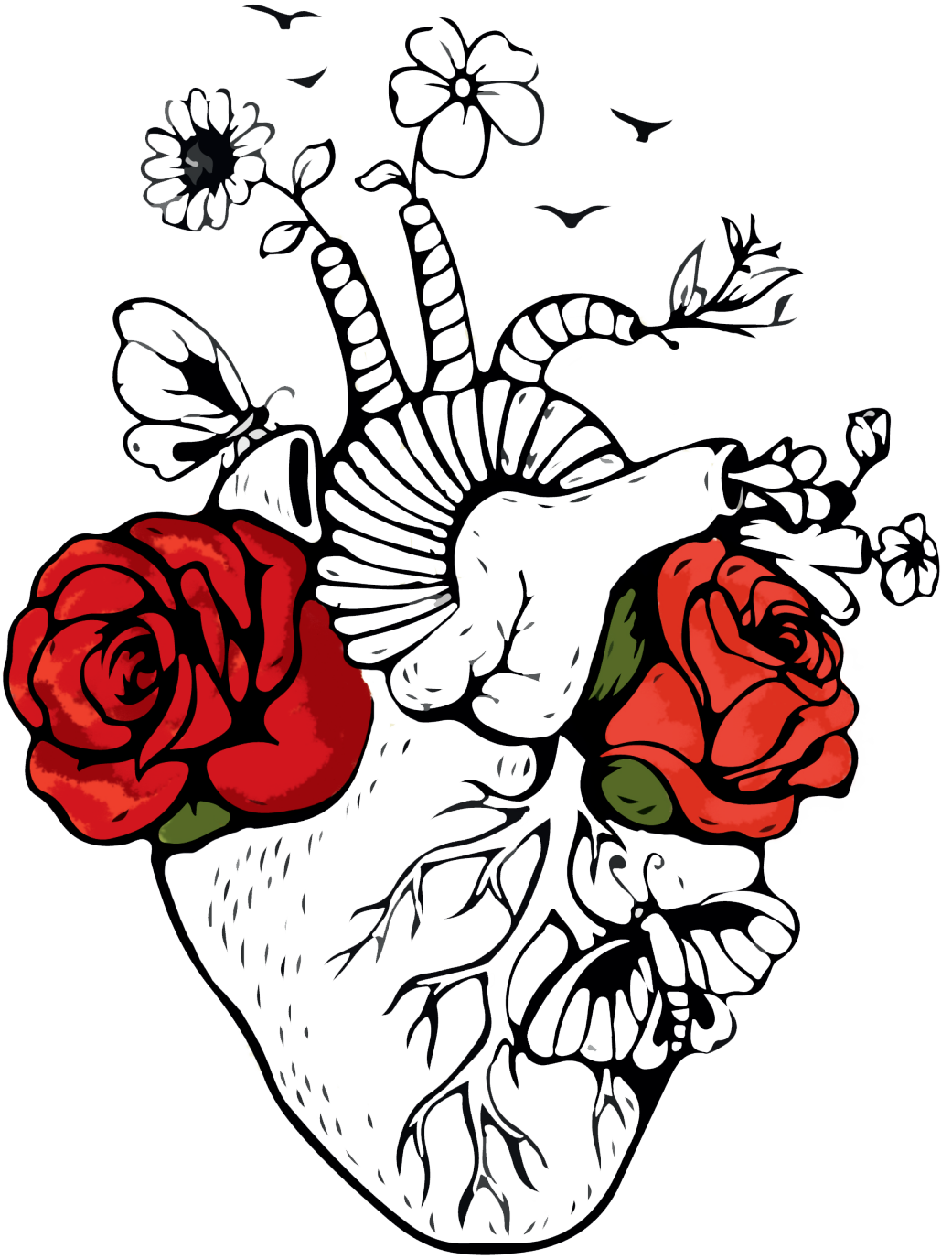

CHAPTER 2

The new European guideline on cardiovascular disease prevention; how to make progress in general practice?

Suzanne Marchal
Arnoud W. J. van't Hof
Monika Hollander

European Journal of General Practice, 2017

ABSTRACT

The new guideline on cardiovascular disease (CVD) prevention, issued by the European Society of Cardiology was endorsed by 10 other societies, including Wonca Europe. It advices on how to reduce the cardiovascular (CV) risk in the population and attributes an important role to the general practitioner (GP). The GP is involved in treatment of the high-risk population as well as in public health measures to encourage a healthy lifestyle and CV risk factor reduction in the whole population. The new guideline gives room for a personalized approach and emphasizes that CV risk estimation and counselling need regular follow-up. We highlight the recommendations that most caught our eye and comment on the challenges for general practice.

KEY MESSAGES

- CVD prevention asks for a personalized approach, taking into account biological age, ethnicity, vitality, comorbidity and personal preferences.
- Estimation of the CV risk and assessment of lifestyle factors, including psychosocial aspects, should regularly be repeated.
- Depending on the healthcare system, GPs can play an essential role both in individual risk assessment and implementation of the guideline in national and regional prevention frameworks.
- CVD prevention needs to get a prominent place in clinical practice, supported by a clear policy and adequate organization.

COMMENTARY

Risk estimation and personalized approach

In the new guideline[1], the accessible and simple to use risk chart to estimate the short-term (10 years) risk of cardiovascular death remains the basis for the total CV risk approach for prevention. Given that in this algorithm, age is the main driver of CV risk, young people may have many risk factors but almost never reach the treatment threshold, while most elderly have a high short-term risk based on age alone. A challenge is how to motivate young people for lifestyle change, even when the short-term risk is low. Fortunately, the new guideline provides practical tools that can help in the communication about CV risk and the urgency of lifestyle change, namely the relative risk score and 'risk age.' They can be used in all populations, irrespective of baseline risk. In the elderly, the new guideline recommends personalized care by taking into account quality of life, frailty or biological age. In general, more lenient treatment goals could be applied in elderly, for example, for systolic blood pressure or HbA1c. However, in vital elderly a more strict treatment regimen should be applied than in the frail. For the GP, guidance that is more practical is needed on how to assess and discuss vitality and personal preferences in the elderly.[2] Furthermore, attention is paid to the higher CVD risk in some ethnic minorities, survivors of cancer after treatment with chemotherapy or radiotherapy, women with a history of pre-eclampsia, pregnancy-induced hypertension, gestational DM, and/or a history of giving birth prematurely. Besides, estimation of the CV risk should be repeated every five years. For individuals with risks close to treatment thresholds, an even more frequent CV risk assessment is recommended and patients with adverse lifestyle factors should regularly be counselled. The new guideline continues to recognize the role of psychosocial stressors as CVD risk modifiers, barriers to treatment adherence and hampering factors for efforts to promote a healthy lifestyle. It provides a questionnaire to screen for psychosocial factors. However, implementation of this kind of tool in daily general practice has not been evaluated yet and will require sufficient consultation time and a plan to alleviate stress factors. Furthermore, referral options to social and psychological healthcare workers and support from local frameworks should be provided if indicated. Altogether, it is a challenge for general practice to organize the care aligned to these recommendations. For the implementation of broad CVD prevention, adequate ICT support, as well as a trained multidisciplinary team, is essential including, e.g. GPs, practice nurses, dieticians,

physiotherapists, psychologists and medical specialists. One of the challenges that lie ahead is how to exchange smoothly patient data and responsibilities in the healthcare chain.

Role of measures of subclinical vascular disease in persons with moderate CV risk

The new guideline acknowledges that especially in patients with moderate risk who are near the treatment threshold, additional information on the presence of subclinical vascular diseases such as carotid plaques, coronary calcium score and the ankle–brachial index could be of help to reclassify the patient's CV risk. However, systematically measuring these markers is not recommended since they have not yet been studied as screening tools. Further, clear thresholds above which a risk is substantially higher are also lacking. In clinical practice, GPs are increasingly confronted with information on measurements that could reclassify someone's risk. Weighing this information should be done with caution and should be done continuously at the discretion of the GP. It could be discussed in the shared decision-making process with the patient and/or the vascular specialist.

Role of the GP and public health

Organizing broad CVD prevention is still a huge challenge in which the general practice plays an important role in promoting a healthy lifestyle across the population. It is important to realize that the responsibility of the GP extends beyond the clinical practice. What do GPs need to make it feasible? In addition, what is the role of the GP in unifying different stakeholders? If a policy exists, GPs should have a role in integrating this policy into national and regional prevention frameworks. At the same time, the extra efforts of GPs in CVD prevention should be supported by concordant actions of surrounding organizations and (local) government and adequate finance. All involved organizations, including the government, local and regional authorities, and insurance companies need to take a stand on this issue. The guideline acknowledges that organizing CVD prevention is resource dependent. A fundamental question to be answered is who is the problem-owner and who is responsible for orchestrating the process? To take responsibility, but also to explore borders, GPs have to outline a clear vision of their role in CVD prevention.[3] This vision may be dependent on the organization of healthcare in different countries.

Evaluation of CVD prevention

Due to various causes, about half of the GPs use the European guidelines.[4] To improve the translation of the recommendations into clinical practice, the new guideline recommends monitoring and evaluating CVD prevention. Furthermore, there are still gaps in the evidence for CVD prevention.[5] For example, the combined effect of the high-risk and population approach should be studied. Since this concerns a combination of two complex interventions, several methodological challenges will be encountered.

Conclusion

The new European guideline on cardiovascular disease prevention provides room for improvement of CVD prevention in general practice. As we have to deal with an ageing population, an increasing prevalence of DM, a diverse target population for CVD prevention and the need for a more personalized approach and repeated CV risk-assessment of diverse target groups, GP's will have to develop a vision on how to organize the practice providing the adequate care as is recommended in this guideline. GPs need to be proactive and need to collect data on possible CV risk factors systematically and routinely. Adequate ICT support with a reminder system should be considered and collaboration with other healthcare providers needs to be established. GPs need to show leadership and to look over the walls of their practices to help build foundations for CVD prevention across the whole spectrum and to help promote a healthy lifestyle in the whole population. Finally, scientific evaluation of the effects of the combined high risk and population approach is needed for sustainable CVD prevention.

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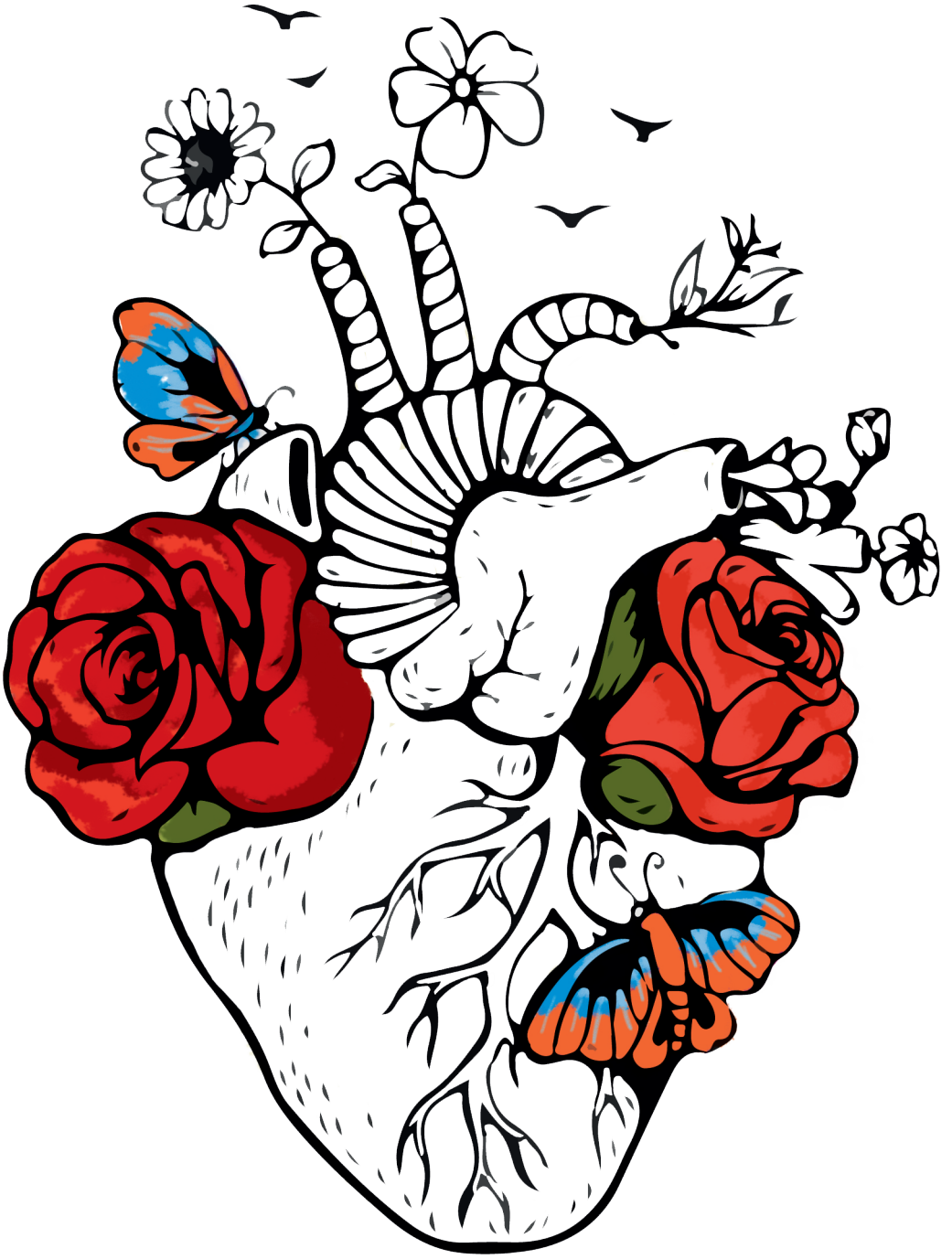

CHAPTER 3

Design of the ZWOT-CASE study: an observational study on the effectiveness of an integrated programme for cardiovascular risk management compared to usual care in general practice

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ABSTRACT

Background

Cardiovascular diseases (CVD) contribute considerably to mortality and morbidity. Prevention of CVD by lifestyle change and medication is important and needs full attention.

In the Netherlands an integrated programme for cardiovascular risk management (CVRM), based on the Chronic Care Model (CCM), has been introduced in primary care in many regions in recent years, but its effects are unknown.

In the ZWOT-CASE study, we will assess the effect of integrated care for CVRM in the region of Zwolle on two major cardiovascular risk factors: systolic blood pressure (SBP) and low-density lipoprotein cholesterol (LDL-cholesterol) in patients with or at high risk of CVD.

Methods

This study is a pragmatic observational study comparing integrated care for CVRM with usual care among patients aged 40-80 years with CVD (n= 370) or with a high CVD risk (n= 370) within 26 general practices. After one year follow-up, primary outcomes (SBP and LDL-cholesterol level) are measured. Secondary outcomes include lifestyle habits (smoking, dietary habits, alcohol use, physical activity), risk factor awareness, 10-year risk of cardiovascular morbidity or mortality, health care consumption, patient satisfaction and quality of life.

Conclusion

The ZWOT-CASE study will provide insight in the effects of integrated care for CVRM in general practice in patients with CVD or at high CVD risk.

INTRODUCTION

Cardiovascular disease (CVD) is still the leading cause of death in the world and the second cause of death in Western societies.[1,2] Because of the ageing population, the prevalence and associated costs of CVD are expected to increase considerably.[3] Moreover, due to adverse lifestyle factors an increase in the prevalence of obesity and diabetes mellitus has been observed in the past 25 years. In addition, we are dealing with high levels of persistent smoking. These trends partly negate the beneficial effect of improvements in blood pressure and lipid control achieved in the last decades.[4] Therefore, prevention of (re)occurrence of CVD remains crucial.

To prevent CVD, national and international guidelines for cardiovascular risk management (CVRM) provide clinical and organisational recommendations.[5-7] However, implementation of evidence-based guidelines is far from optimal and treatment goals are often not achieved.[8-10] Thus, despite the availability of accurate guidelines, CVRM needs improvement.

In the Netherlands, integrated care programmes were introduced to implement CVRM in general practices in recent years. The integrated CVRM care programme includes a patient-centred focus, use of clinical information systems, execution by practice nurses (PNs) and systematic invitation of patients for a CV risk assessment. The integrated CVRM care programme is based on the Chronic Care Model (CCM) that focuses on informed and activated patients who interact with trained, proactive practice teams.[11,12]

Integrated programmes compose a promising procedure to enhance chronic care and management of cardiovascular risk factors. However, solid evidence on the effect of integrated care programmes for CVRM in primary care on outcomes such as blood pressure, cholesterol levels, smoking status and cardiovascular risk is limited.[13-15]

A nurse-coordinated CVD prevention programme (Euro Action) has been shown to improve blood pressure targets.[16] Also, a disease management programme for patients with coronary heart disease (CHD) in primary care led to more adequate treatment of blood pressure and cholesterol compared to usual care and to a better-controlled hypertension in high-risk patients.[17] Additionally, a

tailored implementation of cardiovascular risk management in general practice increases physical activity in cardiovascular patients, but did not affect other cardiovascular risk factors.[18] More recently, a multicomponent cardiovascular prevention programme did not improve the overall risk profile in older adults free from CVD in primary care, compared to usual care.[19] However, the usefulness of these previous studies is restricted by the heterogeneity in study designs, variety in the interventions tested and in the target populations. Most of the previous studies evaluated only a limited number of elements of the disease management programme for CVRM, such as lifestyle treatment or educational interventions. Rarely, effects of an integrated approach programme has been evaluated by analysing clinical parameters before and after implementation of the intervention, but adequate comparisons with control groups are lacking.[20]

In the ZWOT-CASE study (ZWOlle inTegrated care for CArdiovaScular risk managEment study), we will investigate the effect of integrated care for CVRM compared to usual care within general practices in the region of Zwolle in the eastern part of the Netherlands. In this paper, we describe the design of the study.

METHODS/ DESIGN

Study aim

The primary aim of the ZWOT-CASE study is to investigate whether the execution of an integrated primary care programme for CVRM in general practice leads to a more favourable CV risk profile in patients with known CVD or at high CVD risk as compared to usual care.

Study design

The ZWOT-CASE study is a prospective pragmatic observational study, performed among 740 patients with known CVD or at high CVD risk in general practice, comparing integrated care for CVRM with usual care. Patients in the usual care group are matched with patients in the intervention group according to age, gender and risk group (high CV risk or CVD). After one year of follow-up outcomes are compared between the intervention group and the usual care group. Primary outcomes are levels of systolic blood pressure and LDL-cholesterol. The study was reviewed by the Isala hospital Review Board and exempted from full assessment under the Medical Research Involving Human Subjects Act on the 16th of June 2016.

Setting

The study is performed in the Zwolle region in the Netherlands. This region includes 56 general practices (solo, duo and group practices) with in total 157 general practitioners (GPs), which are all affiliated to a care group 'Medrie'. Integrated care for CVRM is implemented in this region and coordinated by this care group by providing a practical guideline for the implementation of integrated care for CVRM, offering training to the PNs and organizing yearly benchmark meetings. Furthermore, all general practices collaborate with the same regional hospital (Isala Hospital) with dedicated medical specialists involved in organizing integrated care for CVRM. The care group reached an agreement on integrated care for CVRM with the regionally largest health care insurance company for three years. Implementation of other disease management programmes e.g. for diabetes mellitus and COPD is also organized by the same care group.

From January 2016, all practices were given the opportunity to participate in the integrated care for CVRM. Every three months there was a possibility to start with the programme. Participation was not mandatory. Consequently, the intervention was not randomly allocated to the practices Prior to our study, approximately two third of the general practices (n=37) chose to implement integrated care for CVRM, while the remaining general practices (n=19) will continue usual care due to a variety of reasons. The practices in the usual care group will not have the opportunity to start with the integrated care for CVRM during the study. This allowed the opportunity to compare integrated care for CVRM (intervention group) with usual care.

The integrated CVRM programme

The intervention under study is the integrated care programme for CVRM (see table 1), based on the Dutch CVRM guideline and the practical manual for CVRM provided by the Dutch Society of General Practitioners. [7,21] The intervention includes features of the Chronic Care Model (CCM), such as self-management support (help patients to set limited goals and identify barriers to reach their goals), regular follow-up, registration of patient data in clinical information systems, a structured, nurse-led health care organization and easy accessible consultation of a specialist.[22] The aim of the integrated care programme for CVRM is to decrease the risk of CVD for patients with a high CV risk or history of CVD by lifestyle treatment and medication if needed. Treatment goals are according to the

Dutch guideline for CVRM, including systolic blood pressure ≤140/90 mmHg, LDL-cholesterol <2,5 mmol/L, no smoking, BMI ≤ 25 kg/m2 (< 70 years) or ≤ 30 kg/m2 (≥ 70 years), ≥ 5 days a week moderate intense physical activity ≥ 30 minutes/day, and a healthy diet (daily 150 – 200 grams vegetables and 200 grams fruit; daily 30 – 40 grams dietary fibres; twice a week 100 – 150 gram fish, at least once fatty fish; maximum of 6 grams salt per day; maximum of 2 (men) or 1 (women) alcohol consumptions per day).

Table 1. Elements of the integrated care for CVRM

Element	Contents
Systematic selection of target population	Systematic screening of practice population based on ICPC-codes
	Systematic screening of practice population based on ATC-codes
	Check of medical records according to in- and exclusion criteria of the programme
Active invitation of patients for the programme	Active invitation for an intake consultation by letter
	Reminder in case of no response
Collaboration with different disciplines	Well trained practice nurses, supervised by GPs
	Optional involvement of physiotherapist or dietician
	Online consultation of medical specialist
Data registration in multidisciplinary information system for integrated care (KIS, Portavita®)	Including data on laboratory measurement, intake consultation and follow-up controls
Benchmark meetings	Comparison op patient data of general practice with national data
Laboratory measurement (prior to intake consultation)	Lipids (total cholesterol, HDL-cholesterol, TC/HDL-cholesterol ratio, LDL-cholesterol, triglycerides)
	Renal function (creatinine, GFR estimated by MDRD)
	Glucose
Intake consultation	
Interview	Cardiovascular complaints
	Family history of CVD
	Medication adherence
	Lifestyle
	Motivation to change behaviour
Physical examination	Length, weight, BMI and waist circumference

Table 1. (Continued)

Element	Contents
	Blood pressure
	Pulse rate
Estimation of 10-years cardiovascular risk	Based on the risk chart in the Dutch guideline
Individual treatment goals	By shared decision making
General lifestyle advice	According to physical activity and diet
Medication (initiated or adapted if necessary)	Blood pressure lowering drugs
	Lipid lowering drugs
	Anticoagulants
Referral (if necessary)	Smoking cessation programmes
	Dietician
	Exercise programmes
	Physiotherapist
	Medical specialist
Regular follow-up	Evaluation of personal goals
	Adjustment of treatment

Organisation strategies of the integrated CVRM programme

The organisation strategies of integrated CVRM programme include:

- Systematic identification of patients eligible for CVRM
- Active invitation of patients for the programme
- Regular follow-up of patients
- Collaboration with different disciplines in the health care chain
- Registration of data in an information system for integrated care

General practices need to systematically organize their practice and identify the eligible population prior to implementation of integrated care for CVRM, based on a regional protocol ('Organized Practice') provided by the care group. According to this protocol patients with a history of CVD, at high CV risk (>10%) or prescribed blood pressure or lipid lowering drugs are included in the programme. To identify the patients, the practice population is systematically screened based on International Classification of Primary Care (ICPC)-coded diagnoses and on Anatomical Therapeutic Chemical-codes (ATC-codes), a classification system for drugs (tables 2, 3 and 4). Since they already are included in a separate disease management programme, patients with diabetes mellitus (DM) with ICPC-codes

T90.01 (DM type I) and T90.02 (DM type II) are not included in the CVRM care programme. Subsequently, medical records of identified patients are manually checked to define whether they meet the in- and exclusion criteria.

Table 2. ICPC-coded diagnoses for patients with cardiovascular disease

Diagnosis	ICPC-code
Angina pectoris	K74/ K74.01/ K74.02
Acute myocardial infarction	K75
Other/chronical ischemic heart disease	K76
Coronary sclerosis	K76.01
Previous myocardial infarction (>4 weeks ago)	K76.02
Transient ischaemic attack (TIA)	K89.01
Cerebral infarction	K90.3
Intermittent claudication	K92.01
Aneurysm aortae	K99.01

Table 3. ICPC-coded diagnoses for patients with high (>10%) cardiovascular risk

Diagnosis	ICPC-code
Hypertension without organ damage	K86.00
Hypertension with organ damage	K87.00
Disorder of lipid metabolism	T93.00
Hypercholesterolemia	T93.01
Mixed hyperlipidaemia	T93.03
Familial hypercholesterolemia/-lipidaemia	T93.04
Rheumatoid arthritis	L88.01
M. Bechterew	L88.02
Psoriatic arthritis	S91.00

Table 4. ATC-codes

Medicine	ATC-code
Antithrombotic agents	B01
Cardiac therapy	C01
Blood pressure lowering drugs	C02
Diuretics	C03
Beta blocking agents	C07
Calcium channel blockers	C08
Agents acting on the renin-angiotensin system	C09
Lipid modifying agents	C10A

Once the eligible patients are identified, patients are actively invited by mail for an intake consultation. In this letter, patients are informed about the CVRM programme and invited to make an appointment for an intake consultation. If a patient does not respond to the invitation letter, a reminder is sent.

After the intake consultation, patients are monitored on a regular base in general practice. The frequency of follow-up visits depends on cardiovascular risk and treatment goals of individual patients, but a follow-up visit should be performed at least once a year.

Collaboration with several disciplines in the health care chain, such as GPs, medical specialists, practice nurses and -assistants, dieticians and physiotherapists, is an important focus of the CVRM programme. General practices implementing the integrated care intervention have well trained PNs, who identify the patients, review medical records and interview and examine the patients. All the PNs followed basic training including basic education in CVRM. In addition, some of the PNs followed a specialization course in CVRM, but this is not obligatory. The GP supervises the PNs. A dietician or physiotherapist may be involved if necessary. In addition, a hospital specialist can be consulted easily online if necessary. If other disciplines are involved, they are given access to the patient data collected in a multidisciplinary information system for integrated care (KIS, Portavita®). This KIS is also used as a communication platform between the disciplines.

All patient data collected during the intake visit and follow-up visits will be registered in the KIS. These data will be used for benchmark purposes, including comparison of mean systolic blood pressure and LDL-cholesterol levels and smoking rates per practice with national data. Practices receive a benchmark report once a year and benchmark meetings will be organized by the care group.

Integrated CVRM programme for individual patients
For individual patients, the integrated CVRM programme includes:

- An intake consultation
- Regular follow-up visits
- Options for referral to get support in changing lifestyle

All eligible patients are invited for an individual face-to-face intake consultation at the general practice. Prior to the consultation, lipids (total cholesterol, HDL-cholesterol, TC/HDL-cholesterol ratio, LDL-cholesterol, triglycerides), renal function (creatinine, glomular filtration rate (GFR) estimated by the formula based on the Modification of Diet in Renal Disease study (MDRD)) and glucose are measured. The consultation consists of several components, including an interview to assess cardiovascular complaints, family history of CVD and difficulties with taking medication. Further, smoking habits, diet, alcohol, physical activity and psychological stress are assessed, as well as the patient's motivation to change any factor if needed (table 5).

Table 5. Assessment of lifestyle during intake consultation

Assessment of lifestyle	
Smoking	Units per day Smoking history Attempts to quit Motivation to quit
Dietary habits	Knowledge of healthy dietary habits Insight into own dietary habits Necessity to change dietary habits Motivation to change dietary habits
Alcohol use	Units per week Knowledge of effects of alcohol use Insight into own alcohol use Necessity to change alcohol use Motivated to change alcohol use
Physical activity	Days a week Knowledge of importance of physical activity Insight into own physical activity Necessity to change physical activity Motivated to change physical activity
Stress	Stress symptoms > 3 months Insight into own stress

Physical examination includes measurement of length, weight, (calculation of) BMI, waist circumference, blood pressure (manual or electronic oscillometric measurement, at least 2 measurements with an interval of 1-2 minutes) and pulse rate.

For patients without CVD an up-to-date 10-years CV morbidity and mortality risk based on the risk chart in the Dutch guideline (based on the SCORE risk function) will be estimated.[5]

During the intake visit, individual treatment goals are determined, regarding smoking, physical activity, dietary habits, weight, BMI, blood pressure and LDL-cholesterol. These treatment goals are set by shared decision making between the caregiver and the patient based on the Dutch guideline for CVRM within the context of a patient's personal preferences. If indicated, treatment with medication, including blood pressure and lipid lowering drugs, and anticoagulants will be initiated. All patients will be given general lifestyle advice by the PN. Patients not achieving a healthy lifestyle according to the Dutch guideline can be referred to smoking cessation programmes, dieticians and exercise programmes or a physiotherapist to get support in changing their lifestyle.

After the intake consultation, patients will be monitored on a regular base in general practice to evaluate and when necessary adjust their personal goals. At least once yearly, all measurements including estimation of the 10-years CV risk will be repeated.

Usual care

Usual care is based on the Dutch CVRM guideline, describing how to calculate the CV risk and advice to lower this risk by lifestyle intervention and/or medication. However systematic identification of patients eligible for CVRM, actively inviting patients for a visit, regular follow-up and standardized collaboration with other disciplines in the health care chain are not routinely part of usual care. Usual care practices may work with a PN. Most PNs in the Netherlands have had a basic training in CVRM. Furthermore, data are not registered in an information system for integrated care and GPs do not participate in benchmark meetings.

ZWOT-CASE study population

The ZWOT-CASE study population will consist of a subgroup of 370 patients from the integrated CVRM care group (intervention) and 370 patients in the usual care group. Both groups consist of respectively i) 185 patients with known CVD and ii) 185 patients with a high (>10%) ten year risk of CVD morbidity and mortality based on the Dutch Guideline for CVRM.[7,23,24]

Inclusion criteria for patients with CVD:

- Patients with a history of atherosclerotic CVD defined as documented angina pectoris, myocardial infarction, chronic ischemic heart disease, coronary sclerosis, transient ischaemic attack (TIA), cerebral infarction, intermittent claudication or aneurysm of the abdominal aorta
- The CV risk of the patient is managed in primary care, not in the hospital or outpatient clinic by a medical specialist
- Age between 40 and 80 years

Inclusion criteria for high-risk patients:

- Use of blood pressure lowering or lipid lowering drugs
- A 10 -years CV risk > 10%, based on the Dutch guideline for CVRM and i) either 1 strongly cardiovascular risk enhancing factor or 2 mildly cardiovascular risk enhancing factors (see table 6) or ii) ≥ 1 CV risk factor (current smoking, SBP>140 mmHg, LDL>2.5 mmol/L, TC/HDL-ratio > 8, chronic renal impairment (age < 65 years: eGFR < 60 ml/min/1,73 m2; age ≥ 65 years: eGFR < 45 ml/min/1,73 m2, and/or (micro)albuminuria).
- A 10-year CV risk of >20% and ≥ 1 CV risk factor (current smoking, SBP>140 mmHg, LDL>2.5 mmol/L, TC/HDL-ratio > 8, chronic renal impairment (age < 65 years: eGFR < 60 ml/min/1,73 m2; age ≥ 65 years: eGFR < 45 ml/min/1,73 m2, and/or (micro-)albuminuria).
- The CV risk of the patient is managed in primary care, not in the hospital or outpatient clinic by a medical specialist
- Age between 40 and 80 years

Table 6. Risk enhancing factors[7]

	Not risk enhancing	Mildly risk enhancing	Strongly risk enhancing*
First-degree relative with CVD	No	1 family member < 65 years	≥ 2 family members with CVD < 65 years or 1 < 60 years
Physical activity	≥ 30 min/d, ≥ 5 d/wk	< 30 min/d, ≤ 5 d/wk	Sedentary
Body mass index	BMI < 30 kg/m2	BMI 30-35 kg/m2	BMI > 35 kg/m2
eGFR	< 65 years: > 60 ml/min/1,73 m2 ≥ 65 years: > 45 ml/min/1,73 m2	< 65 years: 30-60 ml/min/1,73 m2 ≥ 65 years: 30-45 ml/min/1,73 m2	All ages: < 30 ml/min/1,73 m2

CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; d = day or days; wk = week.
*In patients with rheumatoid arthritis a high disease activity is a strongly risk enhancing factor.

Exclusion criteria for all patients:

- Diabetes mellitus, as these patients are already included in a disease management programme for diabetes mellitus
- Limited life expectancy, as assessed by the GP
- Cognitive impairment, as assessed by the GP
- No Dutch language proficiency
- Staying abroad for longer than three months during the duration of the study.
- The CV risk of the patient is managed in the hospital or outpatient clinic by a medical specialist

Recruitment of patients for the ZWOT-CASE study

The source population consists of 56 general practices. All practices were invited to participate in the study. Eventually, 26 general practices agreed to participate (17 in the intervention group and 9 in the usual care group).

Intervention group

Between September and December 2016, general practices randomly invited eligible patients for an intake visit for the integrated CVRM programme. After one year of follow-up, these patients are invited for the study until enough patients are included. The invitation for the study will be sent just before the yearly follow-up visit in the CVRM programme. This visit will be used as the endpoint visit for the study. Just before this follow-up visit, the patients receive a letter from their GP to inform them about the study. If the patient agrees to participate, informed consent is obtained during the follow-up visit.

Patients will be selected in such way, that 50% will be below 65 years and 50% over 65 years, to achieve a reasonable distribution across age categories.

Usual care group

In order to create the same study population as in the intervention group, we identify patients in the usual care group according to the protocol ('Organized Practice') as described before, including systematically screening of the practice population based on ICPC-coded diagnoses and ATC-codes, and manually checking of medical records. As the general practices in the usual care group do not start with the integrated care programme for CVRM, patients in the usual care group

will not be invited for an intake consultation at baseline. Subsequently, a risk profile based on complete data on age, sex, smoking status, blood pressure and lipid spectrum may be missing. In that case, patients can be included if the 10-yeas risk is at least 10%, based on the data that are available. For example, a 55-year old male patient with a missing smoking status and missing total cholesterol/ HDL- cholesterol ratio can be classified as having a CV risk >10% based on a known systolic blood pressure of 160 mmHg.

Patients in the usual care group are matched to patients in the intervention group. Therefore, the patient in the usual care group will only be invited for the study after the patient in the intervention group agreed to participate. Patients in the usual care group will be invited by letter and subsequently by telephone. If this patient does not agree with participation in the study, the second matched patient from the usual care group will receive an invitation. If the second matched patient also does not agree with participation, we will randomly invite one of the remaining patients from the usual care group who were not invited for the study.

Matching
Patients in the usual care group are consecutively matched with the intervention group according to age (per 5 years age categories), gender and risk group (high CV risk or CVD) at the beginning of the study. Each patient in the intervention group is matched to two patients in the usual care group. These patients in the usual care group are randomly selected from the eligible population in practices delivering usual care.

Study procedures

Patients will be identified at the beginning of the study in order to be able to analyse factors such as mortality and comorbidity during follow-up. The study starts when patients in the intervention group visit the general practice for an intake consultation (t=0). After the intake visit, the one year follow-up period commences. After one year of follow-up, patients are invited for an endpoint visit. A questionnaire will be attached to the invitation letter.

Prior to the endpoint visit, all patients who agree with participation in the study will be asked to fill out the questionnaire at home. The timeline of the study procedures is represented in figure 1.

Figure 1. Schedule of enrolment, interventions, and assessments.

	Enrolment	Allocation	Post-allocation
TIMEPOINT	$-t_1$	0	t_1
ENROLMENT:			
Eligibility screen	X		
Informed consent			X
Matching	X		
Allocation		X	
INTERVENTIONS:			
Integrated care for CVRM		■	■
Usual care		■	■
ASSESSMENTS:			
Baseline variables: age, sex, risk category	X	X	
Baseline variables*: morbidity, comorbidity, medication use			X
Primary outcomes: systolic blood pressure and LDL-cholesterol			X
Secondary outcomes			X

*These baseline variables are collected retrospectively after one year of follow-up

Ethical aspects and informed consent

General practices in both groups will not be informed about which patients are identified at baseline to prevent any influence on their management. Consequently, it will not always be possible to take into account the life expectancy, cognitive function and language skills of the identified patients at baseline, as information on these exclusion criteria is not always adequately registered in the medical records. Just before the end of follow-up, GPs will be informed about the identified patients and asked to assess these exclusion criteria.

In addition, at baseline patients in both groups will not yet be informed about the study to prevent that they are aware of being observed and modify their behaviour (Hawthorne effect). Based on the Dutch law for data protection, obtaining informed consent for the identification of patients is not necessary. All obtained data (age, gender and risk category) during the identification will be processed pseudo anonymised and the key to the data will be kept within the general practices. The researchers do have access to this information. Baseline data will be collected

retrospectively for all patients, as patients are not invited for a baseline visit in the context of the study.

Written informed consent is obtained by the GP or PN during the end-point visit and includes an agreement stating that he or she i) is sufficiently informed, had the opportunity to ask additional questions and had enough time to make a decision; ii) agrees with voluntary participation and at any time can withdraw from participation; iii) agrees with use of medical data and data of questionnaires for the purposes described in the information form; iv) agrees with the storage of the study data for 15 years after this study.

The study was reviewed by the Isala hospital Review Board and exempted from full assessment under the Medical Research Involving Human Subjects Act on the 16th of June 2016 (reference number 16.06104).

Outcomes and data collection

An overview of the outcomes of the ZWOT-CASE study is shown in Table 7. The primary outcome is systolic blood pressure and LDL-cholesterol. Patients fill out a questionnaire prior to the endpoint-visit including physical activity (squash questionnaire), quality of life (EQ-5D and SF-12), employment (iPCQ), patient satisfaction regarding the provided care (Patient Reported Experience Measure (PREM)), self-management (Patient Activity Measure (PAM)), and anxiety and depression (Hospital Anxiety and Depression Scale (HADS)). Besides, social status, education (UCC-1 questionnaire) [25], food habits, and CV risk perception are measured by a questionnaire. Further, a blood sample is taken for measurement of lipids (total cholesterol, HDL-cholesterol, TC/HDL-cholesterol ratio, LDL-cholesterol, triglycerides), renal function (creatinine, MDRD), glucose and for patients with CVD hs-CRP.

The endpoint visit consists of the same components as the intake consultation in the integrated programme for CVRM as described before. Data collected during the endpoint visit will be registered in the electronic medical record.

Table 7. Primary and secondary endpoints

Primary endpoints	
1.	Systolic blood pressure
2.	LDL-cholesterol
Secondary endpoints	
1.	10-years cardiovascular morbidity or mortality risk (percentage) (Risk chart Dutch guideline or SMART)
2.	Smoking status
3.	Body mass index (BMI)
4.	Lifestyle (modification) (smoking cessation, healthy food habits, physical activity, motivation for modification and awareness of received advices with respect to weight, food habits and physical activity in the past year)
5.	Awareness of CVD and cardiovascular risk factors
6.	Use of adequate medication (blood pressure lowering drugs, anticoagulants and lipid lowering drugs)
7.	Morbidity (newly developed CVD)
8.	Developed comorbidity (CVD, diabetes mellitus, COPD, heart failure, atrial fibrillation)
9.	Mortality
10.	Primary treating practitioner (GP or medical specialist)
11.	Health care consumption in the past year
12.	Self-management in the past year (patient knowledge, skills, and confidence in managing one's health and healthcare) (Patient Activity Measure (PAM))
13.	Self-measurements of blood pressure in the past year
14.	Patient satisfaction regarding the provided care in the past year Patient Reported Experience Measure (PREM)
15.	Quality of life (EQ-5D and SF-12)
16.	Anxiety and depression (Hospital Anxiety and Depression Scale (HADS)
17.	Cost-efficiency (iPCQ)

* HIS = general practice information system

An up-to-date 10-years cardiovascular morbidity or mortality risk will be estimated according to the algorithm of the Dutch national guideline for CVRM. This algorithm is based on the SCORE-function, adapted to the Dutch population and converted from a mortality risk to morbidity and mortality risk (based on the MORGEN-cohort and the Rotterdam Study-cohort).[26-29] The risk chart takes into account age, sex, smoking status, systolic blood pressure and total cholesterol-HDL cholesterol ratio.[23,24] For patients taking blood pressure or lipid lowering drugs, the actual SBP and cholesterol levels during treatment are used. For patients with CVD the SMART-function will be used to calculate the CV risk.[30] This function is based on age, sex, smoking status, systolic blood pressure, history of diabetes mellitus, ischemic heart disease, cerebrovascular disease, aortic aneurysm, peripheral arterial disease, time since first diagnosis of CVD, HDL-cholesterol,

total cholesterol, renal function (eGFR), and high-sensitivity CRP. Furthermore, baseline data and data concerning health care use in the past year and in the period prior to the study will be collected by scrutinizing the electronic medical files. Finally, GPs will be asked to complete a survey about the CVRM care, including questions on the practice setting (rural/urban, solo/group), organization of their practice, availability of trained PNs, CVRM programme and possibilities to refer for lifestyle treatment (social map).

Sample size calculation

Calculation of the sample size is based on a reduction in SBP and LDL-cholesterol in the intervention group after 1 year of follow-up. We consider a 5 mmHg absolute reduction in SBP and a 0.3 mmol/L reduction in LDL-cholesterol in the intervention group as clinically relevant.[5,31] We assume that SBP and LDL-cholesterol levels in the usual care group remain stable. To detect these differences we need a sample size of 370 patients in the intervention group. This calculation is based on an alpha of 0.05, a power of 80%, and an intra-cluster correlation coefficient of 0.05 for the general practice cluster level. Furthermore, we take into account the response rate. We expect that the response rate in the intervention group will be 70%. This results in a sample size of 587 patients in the intervention group. The intervention patients are matched to patients from the usual care group. In the usual care group we estimated a lower response rate of 50%, as these patients might be less used to visit the general practice compared to the probably regularly controlled patients in the intervention group. Therefore, each intervention patient will be matched with two patients from the usual care group. This results in 587 × 2 = 1174 patients in the usual care group. The intervention group and usual care group are both divided into two groups (patients with CVD and patients with high CV risk) equal in size. The intervention group is selected from 17 general practices and the usual care group from 9 general practices.

Statistical analyses

The aim of the main analysis is to compare the SBP and LDL-cholesterol levels after one year of follow-up between patients in the intervention group receiving integrated care for CVRM and the patients in the usual care group receiving usual CVRM care. For the main analysis, we will use linear regression. For secondary outcomes, linear regression will be used for continuous outcomes, logistic regression for dichotomous outcomes and multinomial logistic regression for categorical outcomes. All analyses will be corrected for clustering.

Given that patients of clusters of patients are not randomly allocated to the intervention or usual care group, we anticipate that differences in baseline risk might be present between both groups. Hence, we will adjust the analyses for these confounders, including patient characteristics and practice characteristics. To do such adjusted analysis we a priori define the following baseline covariates which are well-known to be related to the outcomes: i) patient characteristics, including relevant medication use, such as blood pressure lowering drugs[32], anticoagulants[33] and lipid lowering drugs[34], relevant comorbidity, including COPD[35], heart failure[36,37], atrial fibrillation[38], renal failure[39], ii) practice characteristics, such as involved disciplines in CVRM care (including number of PNs)[31], number of patients, and number of GPs. Results will be reported both without (i.e. crude results) and after correction for confounders. Confounders are defined a priori and not selected based on statistical significance.

Furthermore, we will examine whether the effect of the integrated care for CVRM is modified by differences in the following practice characteristics: practice organization (solo/duo/group), availability of CVRM protocol and existence of other disease management programmes (COPD, DM). This will be done by adding interaction effects.

All analyses are applicable to patient data matched on age and gender.

DISCUSSION

Disease management programmes for CVRM are gradually implemented in Western countries. So far, it is unclear whether such integrated programmes have a positive effect on cardiovascular risk factors and this may lead to discussions between GPs, health insurers and policy makers. Previous studies are heterogeneous in studied interventions and study populations differ substantially in for example included risk categories and the way they are selected, e.g. by active screening or not. In addition, adequate comparisons with control groups are lacking.[20]

In the region of Zwolle, we have the opportunity to compare integrated care for CVRM with usual care. The aim of the ZWOT-CASE study is to evaluate the effectiveness of integrated care for CVRM compared to usual care in real practice. Since this is a pragmatic study, some choices in the study design were made

that may have some methodological drawbacks. Below the major strengths and limitations of our study will be discussed.

Strengths

First, the pragmatic design of the ZWOT-CASE study will give insight into whether integrated care for CVRM compared to usual care is effective in a real world environment. If integrated care for CVRM has a positive effect on our outcomes, it supports the idea that the intervention is beneficial in daily practice.

Furthermore, all the general practices are affiliated to the care group 'Medrie'. The regional implementation of integrated care for CVRM will lead to a more uniform intervention and to less differences between general practices in the intervention group and consequently to less between-cluster variability. In addition, the care group reached an agreement on integrated care for CVRM with the health care insurance for the coming three years, ensuring an adequately financed and stable health care environment during the follow-up of the ZWOT-CASE study. GPs in the usual care group are also members of the care group. This makes the usual care group probably more comparable with the intervention group with regard to socioeconomic characteristics and available opportunities for referrals.

Finally, a strength of the ZWOT-CASE study is the lenient inclusion criteria, i.e. patients with a CV risk of >10%. Since usually more strict inclusion criteria are used in other regions, subgroup analysis will enable us to translate our results to other regions.

LIMITATIONS

One limitation is the lack of random allocation to the two arms. This might lead to differences in practice characteristics between the intervention group and the usual group, and lead to either an over- or underestimation of the effect of integrated care for CVRM, when these differences are not adequately adjusted for. Besides, there may be differences in given care before implementation of integrated care for CVRM between different practices within the intervention group. This could also influence the effect of integrated care of CVRM. However, due to the complete registration of patient data in the Dutch general practice information system, we will be able to accurately collect patient data on years prior to the study and take into account the given care prior to the intervention. Furthermore, ample measures have been taken (notably matching of patients, multivariable analyses) to prevent confounding in our study.

Since patients will be selected from different general practices, we have to deal with a cluster effect. The intervention under study may be heterogeneous.[40] For example, differences in practice size, practice facilities and space, training of GP and staff, availability of supportive staff, time-management, attitude towards prevention and the GP-patient relationship might lead to cluster-level differences.

Another limitation of our study design is that it is not possible to blind GPs, PNs and participants for the intervention. Blinding is impossible due to the nature of the intervention. To minimize bias and maximize the validity of the results, participants are selected just before the end of the study. In addition, during follow-up the general practices are not informed about which patients are identified as eligible to participate in the study.

A disadvantage of the regional approach of our study is the risk of contamination between the usual care group and the intervention group. Usual care may change in the direction of the intervention and therefore the effect of the intervention may be underestimated. However, as GPs in the usual care group do not use the guideline for the implementation of integrated care for CVRM, do not register patient data in an information system for integrated care, and yearly benchmark meetings are not mandatory, we expect the effect of contamination to be minimal. We will collect data on provided CVRM care to assess contamination.

The regional approach of this study could reduce the generalizability of the findings to other regions in the Netherlands. However, we expect that most of the integrated care programmes for CVRM are based on the same Dutch guideline for CVRM and the same international guidelines for CVRM.

The follow-up of 1 year could be too short to analyse the full effect of integrated care for CVRM. However, we expect that the largest gained improvements in cardiovascular risk factors will occur within one year. Therefore, a follow-up of one year will be sufficient to assess the effectiveness of the intervention on these cardiovascular risk factors. But, if integrated care for CVRM is effective, it would be interesting to analyse whether the effect continues. In addition, improvements in cardiovascular risk factors will only translate in a lower cardiovascular morbidity and mortality in the longer term.[3] To observe the durability of an effect, and to assess the effect of integrated care for CVRM on absolute cardiovascular morbidity and mortality, studies with a longer follow-up period should be conducted.

Finally, a general limitation of studies in general practice is that due to a lot of variation in the organization of primary care across Europe and beyond[41,42], the results of a study in one country will probably only be generalizable to countries with similarly organised primary health care systems. However, to support the implementation as well as continuation of disease management programmes scientific evidence is needed. Integrated programmes for CVRM have been introduced in Western countries in recent years. Evidence on the effect of such integrated CVRM care is very limited. The ZWOT-CASE study will give insight into the effectiveness of integrated care for CVRM compared to usual care in general practice.

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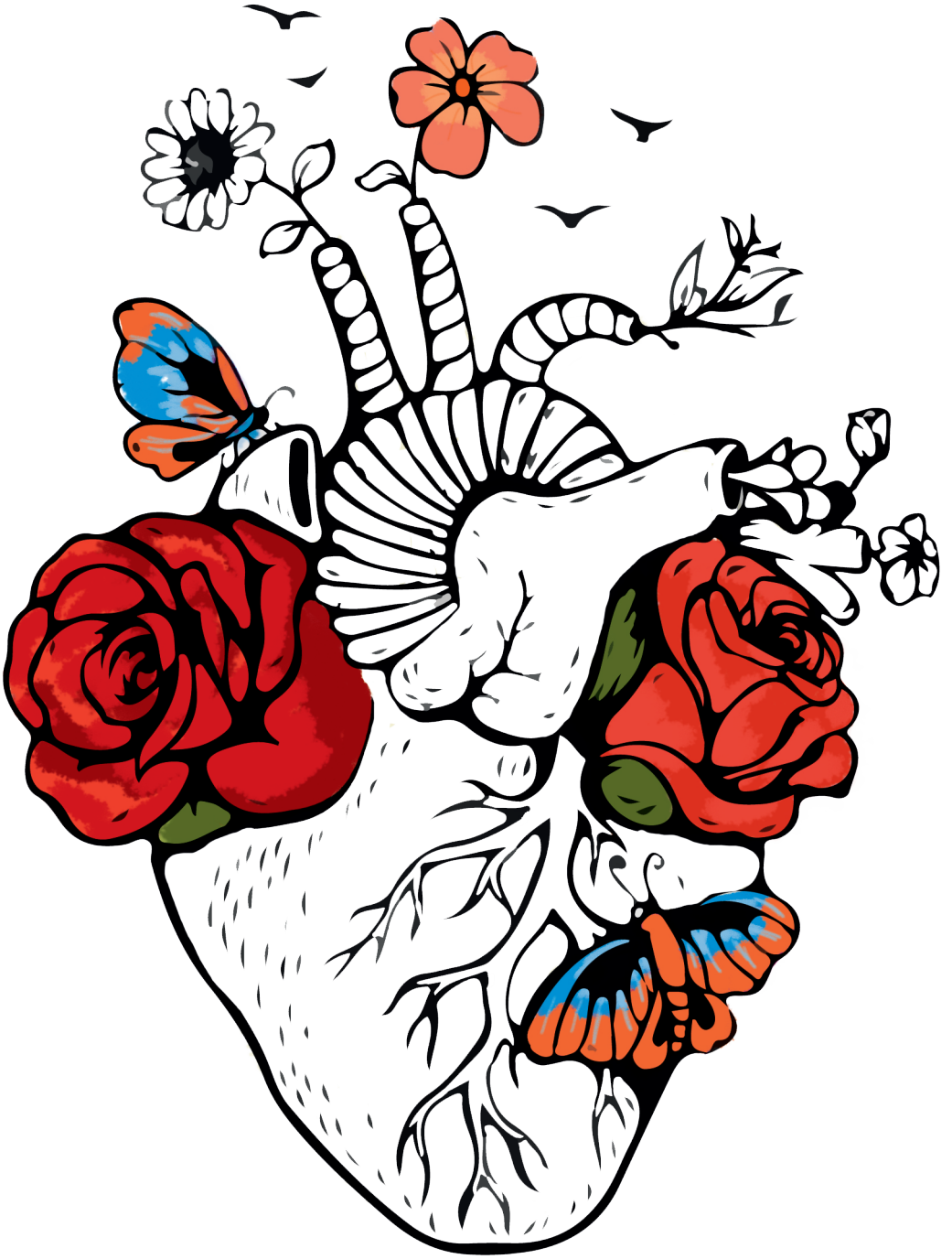

CHAPTER 4

Integrated cardiovascular risk management programme versus usual care in high CV risk patients: an observational study in general practice

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ABSTRACT

Background

Cardiovascular diseases (CVD) are the leading cause of death and cardiovascular (CV) risk factors are often insufficiently controlled in high risk patients. Recently, integrated multidisciplinary cardiovascular risk management (CVRM) programmes were introduced in primary care.

Aim

The present study investigates the effects of a CVRM programme on systolic blood pressure (SBP) and LDL-cholesterol.

Design and setting

A prospective observational study, in high CV risk patients aged 40-80 years in general practice, comparing integrated CVRM care with usual care.

Methods

Intervention and usual care patients were matched at baseline on age, gender and presence of CVD. During one year of follow-up patients received integrated or usual CVRM care in general practice. Primary outcomes were SBP and LDL-cholesterol. Secondary outcomes included calculated 10-year CV risk, BMI, lifestyle (smoking, physical activity, dietary habits), medication use, patient satisfaction, health care consumption, morbidity, comorbidity and mortality. We used mixed-model analyses to assess the outcomes.

Results

We included 372 and 317 patients in the intervention and usual care group, respectively. Mean age at baseline was 65.1 and 66.2 years respectively and 42% were women in both groups. After one year, we observed no difference in SBP (137.2 mmHg vs 139.0 mmHg in the intervention and usual care group, respectively) and LDL-cholesterol (2.6 mmol/L in both groups), nor in any of the secondary outcomes.

Conclusion

Integrated CVRM care in general practice did not lead to a lower SBP or LDL-cholesterol in patients at high CV risk. Further research is needed to improve CVRM.

INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of mortality worldwide.[1,2] The European Society of Cardiology recommends preventive, multidisciplinary programmes for cardiovascular risk management (CVRM), also in primary care.[3] However, survey studies have shown that CVRM in primary care is suboptimally implemented, as control rates of cardiovascular risk factors are disappointing.[4-6]

In some European countries, integrated and multidisciplinary CVRM programmes were introduced in primary care in recent years. Core elements of these programmes include systematic selection, invitation, cardiovascular risk assessment, shared decision in treatment and follow-up of eligible patients, stimulation of self-management, registration of patient data in clinical information systems and yearly feedback to general practitioners (GPs) on delivered CVRM care.[7] So far, studies on the effectiveness of CVRM programmes are scarce and the available evidence is inconsistent.[8-10] Some studies showed a trend towards improved lifestyle, but did not show an effect on cardiovascular risk factors and cardiovascular outcomes.[11-13] However, the studies were heterogeneous in design, target population and interventions tested and adequate comparison with usual care was often lacking.

The present ZWOT-CASE study (ZWOlle inTegrated care for CArdiovaScular risk managEment study) reports the effects of the implementation of an integrated CVRM care programme on systolic blood pressure (SBP) and LDL-cholesterol in general practice as compared to usual care.

METHODS

Design

A prospective observational study comparing integrated care for CVRM with usual care during 1 year of follow-up. The details of the study design have been described elsewhere.[14]

Setting

The study was performed in the Zwolle region in the Netherlands, including 56 general practices, affiliated to a care group 'Medrie'. All practices delivered usual

care prior to the implementation of integrated care for CVRM. From January 2016, 37 general practices implemented integrated CVRM care and 19 general practices continued usual care. All practices were invited to participate in the study; 17 intervention and 9 usual care practices participated.

Patients

In total, we aimed to include 370 patients in each group consisting of respectively i) 185 patients with CVD and ii) 185 patients with a high (>10%) ten year risk of CVD morbidity and mortality based on the Dutch Guideline for CVRM and a modifiable risk factor (SBP > 140 mmHg, LDL-cholesterol > 2.5 mmol/L, smoking or BMI > 30 kg/m2).[15] We ensured that 50% was aged below 65 years and 50% over 65 years. In- and exclusion criteria are shown in box 1.

Intervention

Implementation of the integrated CVRM programme was coordinated by the care group 'Medrie' in accordance with the regional hospital and the regionally largest health care insurance company, based on the Dutch CVRM guideline and the practical manual for CVRM provided by the Dutch Society of General Practitioners.[15,16] GPs screened their practice population for eligible patients and invited them for an intake consultation for the integrated CVRM programme, mostly done by PNs under supervision of the GP.[17] During this consultation the researchers identified patients for the study. To prevent a Hawthorne effect, GPs and patients were not informed about the identification. Patients received the integrated CVRM programme as previously described.[14] In short, prior to the intake, a blood sample was taken to measure lipids, renal function (MDRD), and glucose. The intake included assessment of cardiovascular complaints, lifestyle (smoking habits, diet, alcohol, physical activity), prescribed medication, measurement of blood pressure and BMI, estimation of the 10-year CV risk according to the Dutch CVRM guideline in patients without CVD[15], and defining individual treatment goals in shared decision. Patients were monitored at least once a year for control of cardiovascular risk factors. If necessary, other disciplines were involved, including dieticians, physiotherapists and medical specialists. All disciplines had access to the patient data in the multidisciplinary information system, facilitating care coordination across organizations and ensuring a consistent policy in individual patients. After one year the study patients were revealed to the GP and received a

letter from their GP to inform them about the study. After agreement to participate, written informed consent was obtained during the endpoint visit.

Box 1. In- and exclusion criteria

Inclusion criteria for patients with CVD:

- Patients with a history of atherosclerotic CVD, including angina pectoris, myocardial infarction, chronic ischemic heart disease, coronary sclerosis, transient ischaemic attack (TIA), cerebral infarction, intermittent claudication or aneurysm of the abdominal aorta and
- The patient is primarily managed by the general practitioner (GP) and
- Aged 40 to 80 years

Inclusion criteria for high CV risk patients:

- No previous CVD and
- Use of antihypertensive or lipid lowering drugs or
- A 10-year CV risk > 10%, based on the Dutch guideline for CVRM and i) either 1 strongly CV risk enhancing factor or 2 mildly CV risk enhancing factors (based on family history of CVD, physical activity, BMI and renal function) or ii) > 1 CV risk factor (current smoking, SBP>140 mmHg, LDL>2.5 mmol/L, TC/HDL-ratio > 8, chronic renal impairment (age < 65 years: eGFR < 60 ml/min/1,73 m2; age ≥ 65 years: eGFR < 45 ml/min/1,73 m2, and/or (micro)albuminuria) or
- A 10-year CV risk of >20% and > 1 CV risk factor, as mentioned above and
- At least one modifiable risk factor and
- The patient is primarily managed by the GP and
- Aged 40 to 80 years

Exclusion criteria for all patients:

- Diabetes mellitus (DM), as these patients receive CVRM in a DM programme
- Limited life expectancy
- Cognitive impairment
- No Dutch language proficiency
- Staying abroad > 3 months
- Patient receives CVRM in the hospital or outpatient clinic from a medical specialist

Usual care

Practices in the usual care group continued usual care. Patients were consecutively matched with intervention patients at baseline, on the basis of age (5 years categories), gender and presence of CVD. Similar to the intervention group, the patients and their GPs were not informed about the identification. After one year,

the matched patient was invited for a CVRM consultation if the corresponding intervention patient agreed to participate. Written informed consent was obtained and endpoints were measured during this consultation.

Outcomes

The primary outcomes were SBP and LDL-cholesterol. Secondary outcomes included diastolic blood pressure, achievement of treatment goals (blood pressure < 140/90 mmHg, LDL-cholesterol ≤ 2.5 and ≤ 1.8 mmol/L for all patients and those with CVD, respectively), smoking status, BMI, 10-year cardiovascular morbidity or mortality risk (according to SMART and the Dutch guideline for patients with and without CVD, respectively)[15,18], healthy food habits (according to Dutch guideline for CVRM[15] and guideline Healthy Food of the Dutch Health Council[19]), alcohol consumption, physical activity (squash questionnaire)[20], medication use (antihypertensive drugs, lipid lowering drugs and anticoagulants), primary treating practitioner in CVRM (GP or medical specialist), total number of consultations in general practice, patient satisfaction regarding the provided care (Patient Reported Experience Measure (PREM)), quality of life (EQ-5D and SF-12), anxiety and depression (Hospital Anxiety and Depression Scale (HADS)), newly developed (co)morbidity and mortality.

Data collection

Prior to the endpoint visit, patients filled out a paper questionnaire (including the squash questionnaire, EQ-5D, SF-12, PREM, HADS and food habits) and a blood sample was taken for measurement of lipids, renal function, glucose and hs-CRP for CVD patients (to calculate SMART risk). During the endpoint visit practice nurses (PNs) assessed office blood pressure[16], BMI, smoking status, alcohol consumption and primary treating practitioner. After the endpoint visit we manually scrutinized electronic medical records to assess baseline data, medication use, health care consumption, (co)morbidity and mortality, and whether a patient received previous CVRM care, defined as at least yearly visiting the general practice for a CVRM consultation, including measurement of lipids, renal function and blood pressure.

We pseudonymised all data relating to patients. The Isala hospital Review Board reviewed the study and exempted it from full assessment under the Medical Research Involving Human Subjects Act (reference number 16.06104).

Sample size

The sample size was based on a 5 mmHg (SD 15.9) absolute reduction in SBP and a 0.3 mmol/L (SD 1.0) reduction in LDL-cholesterol in the intervention group as compared to usual care after 1 year of follow-up, with an alpha of 0.05, a power of 80% and an intra-cluster correlation coefficient of 0.05 for the general practice cluster level. This led to a need of 370 patients in both groups. Accounting for a response rate of 70% in the intervention group, we planned to invite 587 intervention patients. Anticipating a 50% response rate in the usual care group, each intervention patient was matched to 2 usual care patients, resulting in 587 × 2 = 1,174 patients in the usual care group.

Statistical analyses

We used generalized linear mixed-model analyses. For continuous, count and dichotomous outcomes we assumed a linear, poisson and logistic distribution, respectively. For skewely distributed continuous outcomes we conducted analyses with a logarithmic transformed variable if appropriate and calculated the reversed logarithm of the B values and confidence intervals resulting into a ratio (interpreted as a multiplication factor).

We used crude mixed model analyses with a random intercept to correct for clustering within practices and additionally corrected for a priori defined potential confounding baseline covariates (use of antihypertensive and lipid lowering drugs and anticoagulants, comorbidity (chronic obstructive pulmonary disease (COPD), heart failure, atrial fibrillation, renal failure) and practice characteristics (number of PNs, GPs, and patients)).

We examined potential effect modification of differences in practice characteristics (practice organization (solo/duo/group), availability of CVRM protocol and existence of other disease management programmes (COPD, DM) and CVRM usual care given prior to the intervention (yes or no), by adding them as interaction terms to the crude model. If an interaction term was statistically significant ($p < 0.05$), we conducted stratified analyses.

Statistical analyses were conducted in R studio (version 3.5.1, Copyright (C) 2018 The R Foundation for Statistical Computing).

RESULTS

In total, 689 patients were included; 372 intervention and 317 usual care patients (figure 1). In the intervention and control group, 439 (54%) and 384 (54%) of the invited patients did not participate, respectively (50% and 45% were women, mean age was 63.5 years and 39% had CVD in both groups).

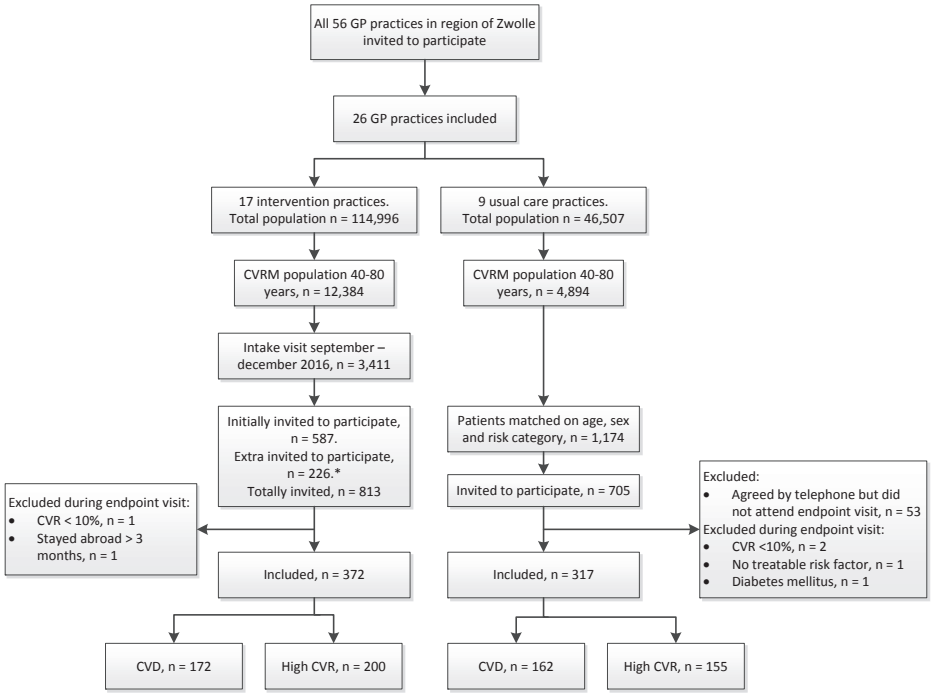

Figure 1. ZWOT-CASE study flow diagram
GP, general practitioner. CVRM, cardiovascular risk management. CVR, cardiovascular risk. CVD, cardiovascular disease. * As the response rate in the intervention group was lower than the expected 70%, we did not reach the required sample size after we invited 587 intervention patients. Therefore we had to invite 226 extra patients in the intervention group (totally invited n = 813) and matched them retrospectively to the usual care group.

Mean age in included patients was 65.1 vs. 66.2 years, respectively and in both groups 42% were women (table 1). At baseline, we observed no differences in cardiovascular risk factors, CVD, comorbidities and medication use across the groups. Prior to the study, the proportion receiving CVRM care was higher in the intervention than in the usual care group (67% vs 51%, $p < 0.001$).

Table 1. Baseline characteristics.

Characteristics	Intervention group (n = 372)	Usual care group (n = 317)
Mean age in years (SD)	65.1 (8.3)	66.2 (7.5)
Age < 65	175 (47)	132 (42)
Female	158 (42)	132 (42)
Western	358 (99)	295 (99)
Cardiovascular risk factors		
Hypertension [a]	280 (77)	234 (75)
Hypercholesterolemia [a]	91 (25)	91 (29)
Current smoking [b]	43 (12)	32 (11)
Chronic kidney disease [c]	40 (11)	51 (16)
Micro-albuminuria [c]	15 (4)	10 (3)
Rheumatoid arthritis [a]	4 (1)	10 (3)
Cardiovascular diseases [a, d]	172 (46)	162 (51)
Myocardial infarction	41 (11)	48 (15)
Coronary sclerosis	46 (13)	44 (14)
Angina pectoris	44 (12)	39 (12)
Transient ischaemic attack	33 (9)	31 (10)
Cerebral infarction	35 (10)	17 (5)
Aneurysm aortae	8 (2)	11 (4)
Intermittent claudication	12 (3)	13 (4)
Atherosclerosis	4 (1)	4 (1)
Comorbidities (including other CVD) [a]		
COPD	9 (2)	14 (4)
Atrial fibrillation	23 (6)	16 (5)
Heart failure	1 (0)	3 (1)
Medication use [b]		
Antihypertensive agents	299 (83)	251 (81)
Statins/lipid lowering agents	190 (52)	167 (54)
Anticoagulants	169 (47)	154 (50)
Measurements [e]		
Mean SBP in mmHg (SD)	136.7 (15.2)	
Mean DBP in mmHg (SD)	80.3 (9.5)	
Mean LDL-cholesterol in mmol/L (SD)	2.8 (0.9)	
Mean BMI (SD)	27.7 (4.0)	

SD, standard deviation. CVD, cardiovascular diseases. COPD, chronic obstructive pulmonary disease. SBP, systolic blood pressure. DBP, diastolic blood pressure. LDL, low-density lipoprotein. BMI, body mass index.
Absolute numbers (%) are presented unless stated otherwise.
[a] Based on International Classification of Primary Care (ICPC)-coded diagnoses.
[b] Based on medical records.
[c] Based on ICPC-coded diagnoses and/ or laboratory measurements. Micro-albuminuria: albumin-creatinine ratio > 3 mg/mmol. Chronic kidney disease: ≥ 3 months impaired renal function (eGFR < 60 ml/min/1.73m^2) and/ or micro-albuminuria.
[d] Cardiovascular diseases as inclusion criteria for integrated CVRM care and for the study.
[e] Baseline measurements of the control group at t=0 are not presented, as there was no routine intake consultation.

In the intervention and usual care group we were able to collect data on SBP in 96% and 94% of the patients and data on LDL-cholesterol in 93% and 98% of the patients, respectively. We did not observe differences in both mean SBP and LDL-cholesterol between the intervention and usual care group at the endpoint (137.2 mmHg vs. 139.0 mmHg, respectively and 2.6 mmol/L in both groups)) (table 2 and 3). None of the interaction terms for the primary outcomes were statistically significant (data not shown). Therefore, stratified analyses were not performed.

Table 2. Primary and secondary outcomes, descriptives

Outcomes	**Intervention group (n = 372)**		**Usual care group (n = 317)**	
Primary outcomes	*n*		*n*	
Mean systolic blood pressure in mmHg (SD)	358 [a]	137.2 (16.2)	298 [b]	139.0 (16.8)
Mean LDL-cholesterol in mmol/L (SD)	347 [c]	2.6 (0.8)	310 [d]	2.6 (1.0)
Secondary outcomes				
Mean diastolic blood pressure in mmHg (SD)	358	80.3 (10.2)	298	80.6 (10.1)
Blood pressure ≤ 140/90 mmHg (%)	358	214 (60)	298	175 (59)
LDL-cholesterol ≤ 2.5 mmol/L (%)	347	178 (51)	310	168 (54)
LDL-cholesterol ≤ 1.8 mmol/L (%) [e]	166	45 (27)	163	58 (36)
Smoking (%)	363	31 (9)	311	30 (10)
Mean BMI (SD)	349	27.3 (5.2)	300	27.7 (4.8)
10-year CVD morbidity or mortality risk in % [f]				
All patients, median (IQR)	317	22.0 (11.7 - 36.4)	267	24.0 (13.7 - 38.0)
Patients with CVD, median (IQR)	159	26.2 (17.9 - 38.5)	144	27.8 (18.7 - 39.5)
Patients without CVD, median (IQR)	158	15.5 (5.4 - 31.9)	123	18.7 (8.4 - 34.3)
Healthy food habits (%)				
Vegetables ≥ 150 - 200 grams/ day	360	142 (39)	294	99 (34)
Fruits ≥ 200 grams/ day	354	214 (60)	294	187 (64)
Red meat ≤ 300 grams/ week	356	207 (58)	286	155 (54)
Fatty fish ≥ 1/ week	358	244 (68)	296	187 (63)
Unhealthy fat products ≤ 3/ week & healthy fat products > 3/ week	352	121 (34)	289	75 (26)
Sweet & salty snacks ≤ 3/ week	357	196 (55)	295	157 (53)
Table salt ≤ 3/ week	360	335 (93)	294	265 (90)
Alcohol consumption, units/week, median (IQR)	311	3 (0 - 7)	292	2 (0 - 7)
Physically active (%) [g]	303	230 (76)	250	178 (71)
Medication use				
Patients with CVD				
Antihypertensive drugs (%)	174	137 (79)	160	121 (76)
Lipid lowering drugs (%)	174	139 (80)	160	127 (79)

Table 2. (Continued)

Outcomes	Intervention group (n = 372)		Usual care group (n = 317)	
Anticoagulants (%)	174	160 (92)	160	146 (91)
Patients without CVD				
Antihypertensive drugs (%)	187	167 (89)	149	126 (85)
Lipid lowering drugs (%)	188	52 (28)	149	46 (31)
GP as primary treating practitioner (%) [h]	368	366 (99)	314	307 (98)
Consultations in general practice, median (IQR) [i]	361	6 (3 - 10)	311	6 (3 - 10)
Patient satisfaction (PREM) (1-5) [j], mean (SD)	359	3.6 (0.7)	283	3.5 (0.8)
Recommendation score (0-10) [j], mean (SD)	352	8.3 (1.3)	275	8.2 (1.3)
EQ-5D-5L index score (-0.45-1) [j], mean (SD)	353	0.9 (0.1)	290	0.8 (0.1)
SF-12 Mental component (7.9-72.0) [j], mean (SD)	353	53.9 (7.5)	290	52.3 (9.3)
SF-12 Physical component (5.2-64.7) [j], mean (SD)	353	48.1 (9.2)	290	46.7 (10.0)
HADS Anxiety (0-7) [j], mean (SD)	342	4.1 (3.3)	286	4.5 (3.7)
HADS Depression (0-7) [j], mean (SD)	347	3.2 (3.0)	283	3.9 (3.3)
Newly developed CVD (%) [k]	364	10 (3)	311	10 (3)
Newly developed comorbidity (%) [l]	363	13 (4)	311	12 (4)
Mortality (%)	372	5 (1)	318	3 (1)

SD, standard deviation; LDL, low-density lipoprotein; BMI, body mass index; CV, cardiovascular; IQR, interquartile range; CVD, cardio vascular disease; GP, general practitioner; PREM, Patient Reported Experience Measure; EQ-5D, five-level EuroQoL-5 Dimensions; SF-12, Short Form–12 Health Survey; HADS, Hospital Anxiety and Depression Scale.

[a] Reasons for missing data: died before endpoint (n = 5), not measured (n = 7), data not available due to change of GP (n = 2)

[b] Reasons for missing data: died before endpoint (n = 3), not measured (n = 16)

[c] Reasons for missing data: died before endpoint (n = 5), not measured (n = 16), data not available due to change of GP (n = 4)

[d] Reasons for missing data: died before endpoint (n = 3), not measured (n = 3), data not available due to change of GP (n = 1)

[e] For patients with CVD, n = 175 in intervention group and n = 164 in usual care group.

[f] For patient with known CVD the SMART-function was used to calculate the risk; for patients without CVD the risk was based on the risk chart in the Dutch guideline (based on the SCORE risk function).

[g] ≥ 5 days a week moderate intense physical activity ≥ 30 minutes/day.

[h] Primary treating practitioner could be the GP or a medical specialist.

[i] Including all visits and telephone calls with the general practice for all reasons.

[j] Minimum and maximum possible values.

[k] Including cardiovascular diseases as inclusion criteria for integrated CVRM care and for the study.

[l] Including diabetes mellitus, chronic obstructive pulmonary disease, heart failure, atrial fibrillation and chronic renal impairment.

Table 3. Effect of integrated CVRM care on the primary and secondary outcomes compared to usual care, using generalized mixed model analyses.

		Crude model [a]				Adjusted model [b]		
Outcomes	*n*	Beta [c]	95%-CI	*p*	*n*	beta [c]	95%-CI	*p*
Primary outcomes								
Systolic blood pressure	656	-1.75	-5.78, 2.29	0.38	647	-1.78	-6.09, 2.53	0.40
LDL-cholesterol	657	0.05	-0.13, 0.23	0.58	653	0.01	-0.15, 0.18	0.86
Secondary outcomes, continuous								
Diastolic blood pressure	656	0.04	-3.05, 3.13	0.97	647	-0.37	-3.78, 3.04	0.82
BMI	649	-0.27	-1.28, 0.74	0.59	641	0.09	-0.83, 1.02	0.84
EQ-5D-5L index score	643	0.01	-0.02, 0.04	0.46	633	0.01	-0.02, 0.03	0.64
SF-12 Mental component	643	1.61	0.21, 3.02	0.03*	633	1.39	-0.17, 2.95	0.08
SF-12 Physical component	643	1.45	-0.38, 3.28	0.12	633	1.01	-0.74, 2.76	0.25
Patient satisfaction (PREM)	642	0.13	-0.03, 0.29	0.11	631	0.14	-0.03, 0.32	0.10
Recommendation score	627	0.13	-0.10, 0.36	0.24	616	0.11	-0.13, 0.36	0.35
HADS Anxiety	628	-0.39	-1.05, 0.27	0.23	618	-0.35	-1.06, 0.37	0.32
HADS Depression	630	-0.61	-1.27, 0.06	0.07	620	-0.45	-1.19, 4.41	0.22
	n	Ratio [d]	95%-CI	*p*	*n*	Ratio [d]	95%-CI	*p*
Secondary outcomes, log transformed								
10-year CV risk								
All patients	584	0.87	0.75, 1.02	0.08	583	0.90	0.76, 1.06	0.21
Patients with CVD	303	0.98	0.86, 1.12	0.76	303	1.04	0.90, 1.20	0.59
Patients without CVD	281	0.81	0.62, 1.06	0.11	280	0.80	0.60, 1.08	0.15

Table 3. (Continued)

		Crude model [a]				Adjusted model [b]		
Outcomes	*n*	Ratio [d]	95%-CI	*p*	*n*	Ratio [d]	95%-CI	*p*
Secondary outcomes, dichotomous								
Blood pressure ≤ 140/90 mmHg	656	0.96	0.54, 1.83	0.99	647	0.97	0.52, 1.83	0.93
LDL-cholesterol ≤ 2.5 mmol/L	657	0.89	0.64, 1.23	0.48	653	1.13	0.74, 1.72	0.57
LDL-cholesterol ≤ 1.8 mmol/L	329	0.64	0.37, 1.13	0.12	326	0.70	0.39, 1.26	0.24
Smoking	674	0.87	0.52, 1.48	0.62	671	1.00	0.54, 1.85	0.99
Healthy food habits [e]								
Vegetables	654	1.28	0.93, 1.77	0.13	643	1.26	0.87, 1.83	0.21
Fruits	648	0.88	0.64, 1.20	0.41	637	0.94	0.65, 1.35	0.72
Red meat	642	1.17	0.86, 1.61	0.32	632	1.21	0.85, 1.74	0.29
Fatty fish	654	1.30	0.89, 1.91	0.18	643	1.24	0.83, 1.85	0.30
Fatty products	641	1.49	1.06, 2.11	0.02*	631	1.41	0.95, 2.08	0.09
Snacks	652	1.07	0.79, 1.46	0.67	641	1.22	0.85, 1.73	0.28
Table salt	654	1.47	0.84, 2.58	0.18	643	1.68	0.84, 3.35	0.14
Physical activity	553	1.29	0.83, 1.99	0.25	543	1.31	0.84, 2.06	0.24
Medication use								
Patients with CVD								
Antihypertensive drugs	334	1.19	0.72, 1.99	0.50	334	5.09	0.56, 46.0	0.15
Lipid lowering drugs	334	1.03	0.61, 1.76	0.91	334	0.97	0.26, 3.57	0.96
Anticoagulants	334	1.10	0.51, 2.38	0.82	334	1.52	0.23, 9.90	0.66

Table 3. (Continued)

		Crude model [a]				Adjusted model [b]		
Outcomes	*n*	Ratio [d]	95%-CI	*p*	*n*	Ratio [d]	95%-CI	*p*
Patients without CVD								
Antihypertensive drugs	336	1.52	0.80, 2.90	0.20	336	1.23	0.12, 12.2	0.86
Lipid lowering drugs	337	0.86	0.53, 1.37	0.52	337	0.71	0.18, 2.79	0.62
GP as primary treating practitioner	682	3.93	0.74, 21.0	0.11	671	10.5	0.80, 138.3	0.07
Newly developed CVD	675	0.85	0.35, 2.07	0.72	671	0.99	0.37, 2.64	0.99
Newly developed comorbidity	674	0.91	0.34, 2.41	0.85	671	1.11	0.43, 2.91	0.83
Mortality	689	1.48	0.32, 6.89	0.62	672	0.37	0.00, 38.8	0.68
Secondary outcomes, count								
Alcohol consumption	601	0.88	0.65, 1.19	0.39	594	0.81	0.60, 1.09	0.17
Consultations in general practice	672	1.05	0.89, 1.25	0.54	670	1.04	0.89, 1.21	0.65

CI, confidence interval; LDL, low-density lipoprotein; BMI, body mass index; EQ-5D, five-level EuroQoL-5 Dimensions; SF-12, Short Form–12 Health Survey; PREM, Patient Reported Experience Measure; HADS, Hospital Anxiety and Depression Scale; CV, cardiovascular; CVD, cardio vascular disease; GP, general practitioner.

[a] Corrected for clustering within practices.

[b] Corrected for clustering within practices and predefined confounders.

[c] Difference between intervention and usual care group.

[d] Ratio, should be interpreted as a multiplication factor. For example, a ratio of 1.05 should be interpreted as a 5% higher outcome score in the intervention group compared with the usual care group.

[e] Healthy food habits: Vegetables ≥ 150 - 200 grams/ day; Fruits ≥ 200 grams/ day; Red meat ≤ 300 grams/ wk; Fatty fish ≥ 1/ wk; Unhealthy fatty products ≤ 3/ wk & healthy fatty products > 3/ wk; Sweet & salty snacks ≤ 3/ wk; Table salt ≤ 3/ wk.

Treatment goals for blood pressure and LDL-cholesterol were achieved in slightly more than half of the patients in both groups (table 2); 60% vs. 59% reached a blood pressure target of ≤140/90 mmHg and 51% vs. 54% achieved target of LDL-cholesterol ≤2.5 mmol/L. In CVD patients, 27% vs. 36% reached a LDL-cholesterol < 1.8 mmol/L. Smoking rates were 9% vs 10%, respectively. BMI, CV risk, physical activity, alcohol consumption and food habits did not differ between both groups. Approximately one-third of participants in both groups achieved healthy food habits regarding vegetables and fats and 50-60% reported a healthy dietary pattern concerning intake of fruit, red meat, fatty fish and snacks. We observed no difference between the groups in medication use, number of consultations during follow-up (median 6), satisfaction with the delivered care (median 3.7 on a scale of 1 to 5) and recommendation scores to their GP (median 8 on a scale of 0 to 10). We observed similar results for quality of life and anxiety and depression scores.

DISCUSSION

In this observational study one year of integrated primary care for CVRM following usual care did not lead to better outcomes for SBP and LDL-cholesterol or any of the secondary outcomes of the study, as compared to usual care.

Strengths and limitations

Strengths of the ZWOT-CASE study are its prospective design, the real-world setting, the matched groups from the same environment and the reliably measurable outcomes and reasoned statistical methods. However, the lack of random allocation to the two study arms may have led to confounding bias. Ample measures have been taken (notably matching of patients, multivariable analyses) to prevent and correct for confounding and baseline characteristics were comparable between both groups. Also, we found that given care before implementation of integrated CVRM care did not affect the effect of the intervention. Although residual confounding is possible, we believe that the observational design of our study is of large value, as randomisation of regionally implemented complex interventions is hardly possible.

All the general practices in this study were from the region of Zwolle and affiliated to the care group 'Medrie'. Therefore, usual care may have changed in the direction of the intervention and consequently the effect of the intervention may have been

underestimated. However, this setting reflects real practice as integrated CVRM care is always implemented regionally in the Netherlands.

Another limitation is the lower statistical power than calculated a priori due to the 14% lower participation rate in the usual care group. However, a post-hoc power analysis showed that we still would have been able to find a difference of 3.65 mmHg in SBP, which we consider as still clinically relevant.

In both groups, the response rates were lower than expected. We assume that reasons for (non) participation are similar in both groups but cannot rule out that this has led to some bias.

Finally, we had some missing outcome data in both groups. Since missing data were not extensively present in the primary outcomes and we did not observe important differences in missing endpoints between both groups, we expected that imputation would not change our results.

Comparison with existing literature

Our results are in line with previous studies, showing disappointing findings.[9] One Dutch study on the effect of disease management programmes (DMPs) for CVRM in general practice, showed a trend towards improved lifestyle (physical activity, smoking) after 2 years.[13] However, this study included a heterogeneous population (some DMPs targeted only CVD patients, some included high risk patients without CVD as well) and comparison with usual care and assessment of clinical outcomes (SBP, lipids) was lacking.

A cluster randomized controlled trial (RCT) compared a tailored implementation of CVRM in general practice to usual care and found a significant improvement in physical activity, but not in other outcomes (SBP, LDL-cholesterol, smoking status, BMI, and diet) after 6 months.[12] However, this intervention is not easily comparable to ours as it focused on motivational interviewing, online education for PNs and e-health options for patients.

The follow-up time of the current study was shorter than the follow-up in a Dutch cluster RCT (1 vs 5.4 years). In that study, a CVRM programme in primary care significantly reduced SBP with 2.39 mmHg in older adults (70 – 78 years) without

CVD. However, this reduction was largely obtained in the first year of follow-up.[21] This suggests that we would have been able to observe an effect after one year. However, it is known that it takes time to implement a new programme and to improve health care as practices have to adapt to new standards of quality and reorganize their practice.[22] Therefore, we can't rule out that a longer follow-up time would have resulted in better outcomes.

Comparison with other studies is difficult, given the heterogeneity in study design, interventions tested, outcomes measured and target populations. Overall, most studies point towards no robust effect on cardiovascular risk factors or outcomes.[9,23]

Several reasons could explain the lack of effectiveness. First, the intervention itself could be ineffective due to insufficient intensity, lack of personalized health promotion or multidisciplinary collaboration. Possibly, PNs are insufficiently prepared, as their workload increases and patients become more complex.[24]

Besides, intensifying medication according to the guidelines if needed may have failed.[25] Although GPs received yearly feedback on the state of cardiovascular risk factors of their CVRM population in the intervention group, not achieving treatment goals had no consequences. A reward system might enhance risk factor control and a continuous feedback system could improve CVRM in daily practice.[25] Further, patient-related factors, such as inadequate risk and lifestyle perception, nonadherence to lifestyle advice and medication could have played a role. More insight in the patient perspective of CVRM care could lead to better communication about CV risk, more patient empowerment and possibly, better adherence to the advised therapy.[26] Moreover, the efforts of primary care need support from government and society regarding lifestyle improvement.[9]

A second reason could be that usual care was already of high quality, diminishing the contrast between the intervention and usual care. As more than half of the patients in both groups received usual CVRM care previous to our study, the largest reduction in SBP and LDL-cholesterol may already have been gained, leaving little room for further improvement. Still, there is room for improvement, as less than 60% reached blood pressure and LDL-targets.

Implications for research and practice

Despite the lack of effect, we should not depreciate the potential of CVRM programmes to reduce CV risk, but look for potentials to improve their quality. To help reshaping CVRM in primary care, a process evaluation is needed to provide a deeper understanding of the lack of effectiveness of the intervention in the present study. For GPs participating in a programme for CVRM we would recommend to critically evaluate the process of care in their daily practice and to organize direct and adequate feedback regarding adherence to CVRM guidelines, if possible supported by information and communication technology.

Furthermore, the effect of CVRM programmes in countries with lower quality of CVRM in usual primary care should be evaluated, as they may be more effective there.[27] Also, out-of-the-box strategies to organise CVRM care should be considered, e.g. other settings than general practice or a more multidisciplinary approach. Finally, modernisation of prevention programmes, for example by a more continuous telemetric risk factor control, may be promising.[8]

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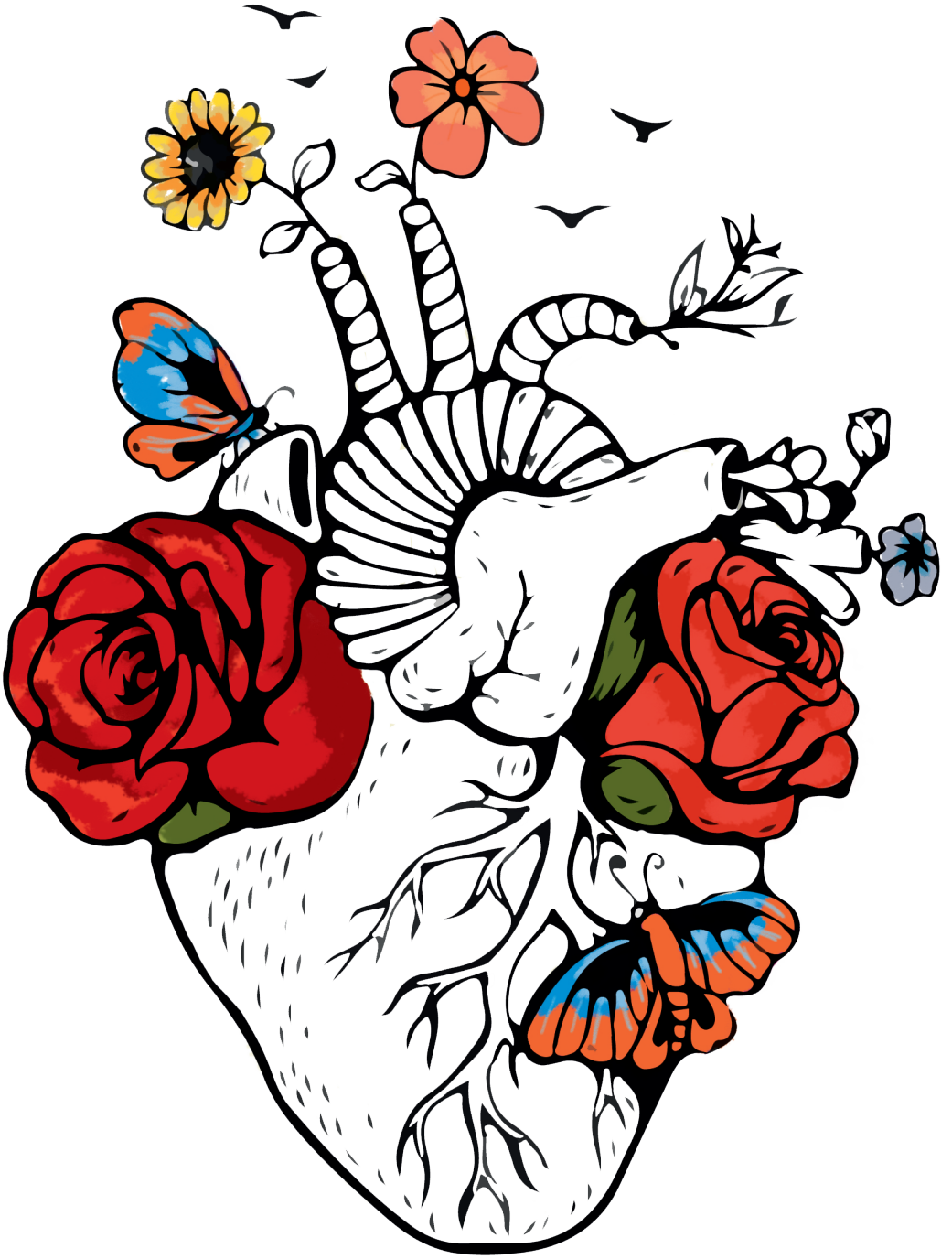

CHAPTER 5

Fidelity to a cardiovascular risk management programme in patients with a high cardiovascular risk in primary care; a process evaluation

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ABSTRACT

Background

Studies on the effectiveness of integrated cardiovascular risk management (CVRM) programmes show disappointing results. An underlying mechanism might be lack of fidelity to the programme. We aimed to assess the fidelity to such a programme.

Methods

We conducted a prospective observational study among high CV risk patients who received integrated CVRM (intervention) or usual care. Assessment of fidelity included adequacy of delivered CVRM care and patients' perception of CV risk (factors) and lifestyle (advice).

Results

In total, 85% and 32% intervention and usual care patients received at least one consultation, including measurements of blood pressure (BP), weight, LDL-cholesterol and renal function.

In intervention patients with hypertension or hypercholesterolemia but not on BP- or lipid lowering medication at baseline, medication was started in 57% vs 14% and 9% vs 3%, in patients with an off- vs near-target systolic BP or LDL-cholesterol, respectively. In patients using such medication at baseline, the prescription was changed in 33% vs 19% and 28% vs 8%, respectively.

In total, 12-14% of intervention and 13-22% of usual care patients correctly labelled their CV risk as intermediate to high. Adequacy of patient's perception of CV risk factors and lifestyle did not differ between the groups. Less than one-third of patients who received lifestyle advice reported having received the advice.

Conclusion

Integrated CVRM improved CV risk factor assessment. However, actions taken in patients with hypertension or hypercholesterolemia seem to be insufficient. Patients' perception of risk (factors) and lifestyle (advice) was poor. Further research is needed to improve risk awareness and therapeutic inertia.

INTRODUCTION

Cardiovascular disease (CVD) is still the leading cause of death globally.[1] Despite decreasing mortality rates in high-income countries, worrying trends in CVD risk factor prevalence have been observed.[2] This underlines the importance of guideline-recommended prevention to further reduce CVD morbidity and mortality.[3] However, studies, such as the EUROASPIRE surveys, have consistently shown that cardiovascular (CV) risk factors are insufficiently controlled, in primary care.[4,5] Therefore, effective cardiovascular risk management (CVRM) programmes are needed.[6] General practitioners (GPs) play an important role in CVRM, as they have a longstanding relationship with their patients. To promote and structure implementation of CVRM in general practice, integrated and multidisciplinary CVRM programmes were introduced in recent years.[7] However, studies investigating the effect of CVRM programmes on mortality, cardiovascular events, blood pressure (BP), cholesterol and life style show disappointing results.[8-12] The reasons underlying these findings remain unclear.[13] Inadequately addressing essential elements may play a role, including assessment of risk factors and lifestyle, therapeutic action, communication on risk factors and lifestyle, and patients' perception of risk (factors) and lifestyle.[14-16] Further, to achieve fidelity to CVRM prevention programmes, a well organised practice is of particular relevance, including involvement of nurses in CVRM, cooperation among clinicians and feedback mechanisms for reporting.[17-19] To guide future development of CVRM interventions, it is vital to gain a deeper understanding of to what extent the essential elements of integrated CVRM programmes are addressed. The aim of the present study was to assess the fidelity to the integrated care programme for CVRM.[20]

METHODS

Design

We performed a process evaluation within the framework of the ZWOT-CASE study, a prospective observational study on the effectiveness of an integrated CVRM programme in general practice on systolic blood pressure (SBP) and low-density lipoprotein (LDL)-cholesterol as compared to usual care. It was performed in 689 primary care patients at high CVD risk in the Zwolle region in the Netherlands. Prior to the study all practices delivered usual care for CVRM. The design of the ZWOT-CASE study has been extensively described elsewhere and will be briefly summarized below.[20] The Isala hospital Review Board reviewed the study and exempted it from full assessment under the Medical Research Involving Human Subjects Act (reference number 16.06104).

Participants

Patients at high CV risk (having CVD or a > 10% 10-years CVD risk according to the Dutch CVRM guideline)[21] were included. In total 372 patients were included in the intervention and 317 patients in the usual care group. Written informed consent was obtained from all participants.

Intervention

The intervention consisted of an integrated and multidisciplinary CVRM programme in general practice performed by practice nurses (PNs) and GPs.[20] PNs had at least 3-4 years of nursing education, including basic CVRM training, were supervised by the GP, and had access to the Dutch CVRM guideline and the practical manual for CVRM provided by the Dutch Society of General Practitioners.[21-23] Some of the PNs followed a specialization course in CVRM, but this was not obligatory. General practices systematically scrutinized their practice population to identify patients eligible for the CVRM programme, who were subsequently invited to a face-to-face intake consultation. Prior to the intake consultation a blood sample was taken to measure lipids and renal function (glomular filtration rate (GFR) estimated by the formula based on the Modification of Diet in Renal Disease study (MDRD)). The intake consultation included assessment of (cardiovascular) complaints (angina, dyspnoea, painful cramping in lower leg muscles, limited walking distance, sexual disorder), family history of CVD, lifestyle (smoking habits, diet, alcohol, physical activity), medication, measurement of BP and calculation of

the body mass index (BMI).[21] Besides, estimation of the 10-year CV risk according to the Dutch CVRM guideline in patients without CVD was an important part of the intake. In addition, individual treatment goals were defined applying shared decision making, taking into account the CV risk in communication with patients. All patients were given general lifestyle advice. Patients not achieving a healthy lifestyle according to the Dutch guideline could be referred to smoking cessation programmes, dieticians, exercise programmes or a physiotherapist to get support in changing their lifestyle. If treatment goals according to the Dutch guideline for CVRM (SBP < 140 mmHg, LDL-cholesterol < 2.6 mmol/L), were not reached through life style changes, treatment with medication was indicated, including antihypertensive and/or lipid lowering drugs.[21] After the intake consultation, patients were monitored on a regular base, depending on the control of cardiovascular risk factors and individual treatment goals, but at least once a year.

From the start of the intervention, all practices started to work with a multidisciplinary information system for integrated care (KIS, Portavita®), in which they registered all patient data collected during the visits. All involved disciplines, including dieticians, physiotherapists and medical specialists, had access to the patient data in the multidisciplinary information system, facilitating care coordination across organizations and ensuring a consistent policy in individual patients. Besides, these data were used for yearly feedback to the GP on delivered CVRM, including comparison of mean SBP and LDL-cholesterol levels and smoking rates per practice with national data. Once a year, practices received a benchmark report and regional benchmark meetings were organized.

Usual care

Usual care was based on the Dutch CVRM guideline, describing how to calculate the CV risk and advice to lower this risk by lifestyle intervention and/or medication.[21] However, scrutinizing the practice for and actively inviting eligible patients for a visit and regular follow-up was not formalized. Finally, data were not registered in a multidisciplinary information system, GPs did not receive feedback on delivered CVRM and care coordination across different disciplines was not facilitated.

Data collection

After 1 year of follow-up, patients in both the intervention and usual care group visited the general practice for the endpoint visit of the ZWOT-CASE study, during

which an office BP, BMI, smoking status and alcohol consumption were assessed. Further, an up-to-date CV risk score was calculated (for patients without CVD the risk chart in the Dutch guideline was used, based on the SCORE risk function;[21] for patients with known CVD the SMART-risk score was used).[24] Prior to the endpoint visit, a blood sample was taken to measure lipids, renal function and hs-CRP for CVD patients (to calculate SMART risk) and patients were asked to fill out a questionnaire. The questionnaire included questions on perception of risk factors and lifestyle, such as "How high do you think your risk of cardiovascular disease is for the next ten years?" (answer options: low; medium; high) and "Is your physical activity sufficient?", "Do you have a healthy body weight?", "Do you have a high blood pressure?" (answer options: yes; no; I don't know) and questions on received lifestyle advice, such as "In the last year, did you receive advice to increase physical activity?", "… to lose weight?", "… to eat healthier?", "… to do something about your high blood pressure?" (answer options: yes; no; I don't know; not applicable). Further, physical activity was assessed by the questionnaire (the squash questionnaire).[25] Also, the questionnaire included the level of education. After the follow-up visit we scrutinized electronic medical records to assess the number of consultations in the last year in the context of CVRM, measurements of BP, weight and/ or BMI, LDL-cholesterol and renal function, lifestyle advice given, including dietary habits, physical activity and smoking, and medication use (including antihypertensive and lipid lowering medication) and changes in medication. We pseudonymised all data relating to patients. As data from the endpoint visit and questionnaires were not available in patients who died during follow-up, they were excluded from the current process evaluation.

Process evaluation measures

The assessment of fidelity was twofold: 1) adequacy of delivered CVRM care, including assessment of risk factors, lifestyle advice as given by the PN or GP and start or intensification of targeted medication in patients with increased BP or cholesterol levels; and 2) adequacy of patients' perception of CV risk (factors) and lifestyle (advice).

We operationalized the adequacy of the delivered care by assessing the proportion of patients that had a consultation in the context of CVRM, whose BP, weight and/ or BMI, LDL-cholesterol and renal function were measured and in whom lifestyle advice was given on dietary habits, physical activity and smoking if indicated.

Start or intensification of medication was only assessed in the intervention group as the usual care group did not have an intake consultation and no baseline measurements. Therefore, it was not possible to assess whether medication adjustment was needed in the usual care group. In the intervention group we assessed whether antihypertensive medication was changed during follow-up in patients who already used antihypertensive and in patients who did not use any antihypertensive at baseline and with a BP ≥ 140/90 mmHg and a near-target (≥ 140 and < 150 mmHg) or off-target SBP (≥ 150 mmHg) at baseline. This BP was based on a single office measurement. We did not have data on BP home measurements. Similarly we assessed whether lipid lowering medication was changed in patients who did or did not use lipid lowering drugs at baseline and with near-target (≥ 2.6 and < 3.5 mmol/L) or off-target (≥ 3.5 mmol/L) LDL-cholesterol at baseline. Lack of change in medication when indicated could suggest clinical inertia.[14]

To evaluate the extent to which the intervention and given advice reached the patient, we assessed the adequacy of the patient's perception regarding their cardiovascular risk (factors) and lifestyle at the endpoint in both groups. Perception was defined as adequate if: patients with CV risk ≥10% and <20% (according to risk chart in Dutch CVRM guideline) considered their CV risk as intermediate or high and patients with CVD or CV risk ≥ 20% considered it as high; patients with BP ≥ 140/90 mmHg or antihypertensive drug use considered themselves to have hypertension; patients with a LDL-cholesterol ≥ 2.6 or lipid lowering drug use considered themselves to have hypercholesterolemia; patients who were < 5 days a week moderate intense physically active for ≥ 30 minutes/ day considered physical activity as insufficient; patients with BMI ≥ 30 considered body weight as unhealthy; men consumed > 2 alcohol units/ day and women > 1 alcohol unit/ day considered their alcohol consumption as too much.

Further, lifestyle advice given by the GP or PN in the last year as reported by the patient was assessed and compared to reporting of lifestyle advice given by the GP/ PN in the patient's file during follow-up, including advice on diet, physical activity and smoking cessation.

Statistical analyses

To analyse the process data descriptive statistics were used. To test for statistical differences between the intervention group and the usual care group, Pearson $\chi 2$

test was used for dichotomous outcomes and Kruskal-Wallis test for categorical outcomes. To assess whether level of education influenced the adequacy of the patient's perception regarding their cardiovascular risk (factors) and lifestyle we did an exploratory analysis in subgroups of 3 different levels of education (low, intermediate, high). Statistical analyses were performed using R studio (version 3.5.1, Copyright (C) 2018 The R Foundation for Statistical Computing).

RESULTS

Patient and practice characteristics

In total, we obtained process measures of 367 (99%) from the intervention and 314 (99%) patients from the usual care group of the ZWOT-CASE study, as respectively 5 (1%) and 3 (1%) patients who died during follow-up were excluded. In both groups 42% were women and the mean age was 65.0 (SD 8.3) in the intervention and 66.2 (SD 7.5) in the usual care group (table 1).

The median number of GPs per practice was 3.5 vs 2.0 and 100% vs 78% worked with a PN in the intervention and usual care practices respectively (table 1). Most practices in both groups offered an integrated care programme for diabetes mellitus and Chronic Obstructive Pulmonary Disease (COPD).

Table 1. Baseline characteristics

Patient characteristics	**Intervention group (n = 367)**	**Usual care group (n = 314)**
Mean age in years (SD)	65.0 (8.3)	66.2 (7.5)
Age < 65	175 (48)	130 (41)
Female	155 (42)	131 (42)
Level of education [a]		
Low	171 (47)	167 (53)
Intermediate	100 (27)	69 (22)
High	84 (23)	54 (17)
Cardiovascular risk factors		
Hypertension [b]	280 (77)	234 (75)
Hypercholesterolemia [b]	91 (25)	91 (29)
Current smoking [c]	43 (12)	32 (11)
Chronic kidney disease [d]	40 (11)	51 (16)

Table 1. (Continued)

Patient characteristics	Intervention group (n = 367)	Usual care group (n = 314)
Micro-albuminuria [d]	15 (4)	10 (3)
Rheumatoid arthritis [b]	4 (1)	10 (3)
Cardiovascular diseases [b, e]	170 (46)	159 (51)
Myocardial infarction	40 (11)	48 (15)
Coronary sclerosis	46 (13)	44 (14)
Angina pectoris	44 (12)	39 (13)
Transient ischaemic attack	33 (9)	31 (10)
Cerebral infarction	35 (10)	16 (5)
Aneurysm aortae	8 (2)	11 (4)
Intermittent claudication	12 (3)	13 (4)
Atherosclerosis	4 (1)	4 (1)
Comorbidities (including other CVD) [b]		
COPD	9 (2)	14 (5)
Atrial fibrillation	23 (6)	15 (5)
Heart failure	1 (0)	3 (1)
Medication use [c]		
Antihypertensive agents	298 (83)	250 (81)
Statins/lipid lowering agents	189 (52)	166 (54)
Anticoagulants	168 (47)	153 (50)
Measurements [f]		
Mean SBP in mmHg (SD)	136.8 (15.2)	
Mean DBP in mmHg (SD)	80.3 (9.6)	
Mean LDL-cholesterol in mmol/L (SD)	2.8 (0.9)	
Mean BMI (SD)	27.7 (4.0)	
Uncontrolled RR (≥ 140/90)	166 (45)	
Uncontrolled LDL- cholesterol (≥ 2.6 mmol/L)	214 (59)	
Practice characteristics	**(n = 16)**	**(n = 9)**
Median number of GPs (IQR)	3.5 (2-4)	2 (2-3)
Solo	1 (6)	2 (22)
Duo	5 (31)	3 (33)
Group	10 (63)	4 (44)
Practice location		
Urban	8 (50)	5 (56)
Rural	8 (50)	4 (44)
Availability of practice nurse	16 (100)	7 (78)

Table 1. (Continued)

Practice characteristics	(n = 16)	(n = 9)
Practice nurse followed CVRM training	16 (100)	3 (33)
Median number of PNs (IQR)	2 (1.8-3)	2 (1-2)
Integrated care diabetes mellitus	16 (100)	8 (89)
Integrated care COPD	14 (88)	8 (89)

SD, standard deviation. CVD, cardiovascular diseases. COPD, chronic obstructive pulmonary disease. SBP, systolic blood pressure. DBP, diastolic blood pressure. LDL, low-density lipoprotein. BMI, body mass index.

Absolute numbers (%) are presented unless stated otherwise.

[a] Low level: no education, (pre-)primary education, pre-vocational secondary education, first 3 years of senior general secondary education, first 3 years of pre-university education. Intermediate level: senior general secondary education, pre-university education, senior secondary vocational education and training. High level: associate degree, bachelor's degree, master's degree, doctoral degree.

[b] Based on International Classification of Primary Care (ICPC)-coded diagnoses.

[c] Based on medical records.

[d] Based on ICPC-coded diagnoses and/ or laboratory measurements. Micro-albuminuria: albumin-creatinine ratio > 3 mg/mmol. Chronic kidney disease: ≥ 3 months impaired renal function (eGFR < 60 ml/min/1.73m^2) and/ or micro-albuminuria.

[e] Cardiovascular diseases as inclusion criteria for integrated CVRM care and for the ZWOT-CASE study.

[f] Baseline measurements of the usual care group at t=0 are not presented, as there was no routine intake consultation.

Adequacy of delivered CVRM care - assessment of risk factors and given lifestyle advice

In one year, all intervention patients compared to 79% of patients in the usual care group had at least one consultation and in 85% and 32% BP, body weight, LDL-cholesterol and renal function were all measured (table 2). The median number of consultations was 2 (IQR 1 – 3) in both groups. In a higher proportion of intervention patients BP (99% vs 74%), body weight (95% vs 46%), LDL-cholesterol (94% vs 57%) and renal function (93% vs 65%) was measured as compared to usual care patients during the 1-year follow-up period. Likewise, a higher proportion of intervention patients received advice on diet (59% vs 19%), physical activity (85% vs 22%) and smoking cessation in smokers (71% vs 20%). All these differences were statistically significant ($p < 0.001$).

Adequacy of delivered CVRM care - start or intensification of medication

In the intervention group, 63 (17%) patients did not use antihypertensive medication at baseline and among them 14 (23%) and 7 (12%) had an off- and near-target SBP, respectively. During follow-up, medication was started more often in patients with an off-target SBP as compared to near-target SBP (57% vs 14%, respectively) (figure S1). Among 298 (83%) patients who used antihypertensive medication at baseline 54 (19%) and 72 (25%) had an off- and near-target SBP, respectively. Antihypertensive medication was more often changed in patients with off-target SBP as compared to near-target SBP (33% vs 19%, respectively). This concerned starting additional medication in 12 (22%) vs 3 (4%), uptitration in 8 (15%) vs 4 (6%) and replacement in 1 (2%) vs 5 (7%).

In total 172 (48%) intervention patients did not use lipid-lowering drugs at baseline and among these, 70 (41%) and 76 (44%) had an off- and near-target LDL-cholesterol. Lipid-lowering medication was started in 9% and 3% (figure S2). Among 189 (52%) patients who used lipid-lowering drugs at baseline 18 (10%) and 50 (27%) had an off- and near-target LDL-cholesterol. Lipid-lowering medication was changed more often in patients with an off-target as compared to near-target LDL-cholesterol (28% vs 8%, respectively).

Adequacy of patients' perception of risk (factors) and lifestyle (advice)

Overall, adequacy of patients' perception of risk (factors) and lifestyle (advice) did not statistically differ between intervention and control patients (table 3). Among patients without CVD, 14% vs 22% correctly classified themselves as having an intermediate or high risk of CVD and among CVD patients 12% vs 13% correctly classified themselves as having a high CV risk. In hypertensive patients 51% correctly labelled themselves as having hypertension in both groups and in patients with hypercholesterolemia 25% vs 28% correctly classified themselves as having hypercholesterolemia.

Regarding lifestyle, 73% vs 65% correctly classified themselves as being physically active and 88% vs 86% as drinking not too much alcohol in respectively the intervention and usual care group and 70% as having a healthy weight in both groups.

Table 2. Adequacy of delivered care in the intervention compared to usual care

	Intervention group (n = 367)			Usual care group (n = 314)			P – value[a]
	n	Dichotomous Yes, n (%)	Count median (IQR)	n	Dichotomous Yes, n (%)	Count median (IQR)	
Consultations	365	365 (100)	2 (1 – 3)	311	245 (79)	2 (1 – 3)	< 0.001
Measurements							
Blood pressure	365	361 (99)	2 (1 – 3)	311	230 (74)	1 (0 – 2)	< 0.001
Body weight/ BMI	364	347 (95)	1 (1 – 2)	311	144 (46)	0 (0 – 1)	< 0.001
LDL-cholesterol	361	340 (94)	1 (1 – 1)	311	177 (57)	1 (0 – 1)	< 0.001
Renal function	360	334 (93)	1 (1 – 1)	311	201 (65)	1 (0 – 1)	< 0.001
Consultation including all measurements [b]	360	307 (85)		311	100 (32)		< 0.001
Lifestyle advice							
Healthy diet (all patients)	350	205 (59)	1 (0 – 1)	311	60 (19)	0 (0 – 0)	< 0.001
Physically activity (all patients)	351	299 (85)	1 (1 – 1)	310	67 (22)	0 (0 – 0)	< 0.001
Physical activity (inactive patients)	69	58 (84)	1 (1 – 2)	71	16 (23)	0 (0 – 0)	< 0.001
Stop smoking (in smokers)	31	22 (71)	1 (1 – 1)	30	6 (20)	0 (0 – 0)	< 0.001
CV risk discussed	350	25 (7)	0 (0 – 0)	311	13 (4)	0 (0 – 0)	0.14

[a] Differences in dichotomous variables between treatment groups tested with Pearson $\chi 2$ test.

[b] At least once yearly a consultation including measurement of blood pressure, weight and/ or BMI, LDL-cholesterol and renal function.

Overall, level of education did not influence the adequacy of patients' perception of risk (factors) and lifestyle, except for physical activity. Patients with a high level of education classified themselves more often correctly as being physically active (85% and 76%) than patients with an intermediate (66% and 68%) or low level of education (71% and 59%) in the intervention and control group respectively.

In both groups, the proportion of lifestyle advice given as reported by the GP or PN in medical records was much higher than "lifestyle advice received" reported by patients. In patients who filled out the questionnaire, in 299 (82%) intervention and 64 (22%) usual care patients advice by the GP or PN to stay physically active was given, but among them only 67 (22%) vs 19 (30%) patients reported having received such advice. Similarly, in 205 (56%) and 56 (19%) patients advice to maintain a healthy diet was given and 30 (16%) vs 10 (19%) reported having received the advice. The proportion of smokers that reported to have received a smoking cessation advice was higher, 13 of 22 (59%) intervention patients vs 5 of 6 (83%) usual care patients.

Table 3. Adequate patients' perception of risk (factors) and lifestyle (advice), intervention vs usual care

	Intervention group n = 367		Usual care group n = 314		P – value
Adequate patients' perception of:	n		n		
Cardiovascular risk [1, a]					
In patients without CVD	155	22 (14)	109	24 (22)	0.14
In patients with CVD	149	18 (12)	135	18 (13)	0.89
Cardiovascular risk factors [1, b, c]					
Hypertension (all patients)	353	195 (55)	290	158 (54)	0.91
Hypertension (hypertensive patients)	318	161 (51)	262	134 (51)	0.97
Hypercholesterolemia (all patients)	348	110 (32)	292	90 (31)	0.90
Hypercholesterolemia (hypercholesterolemia patients)	306	78 (25)	265	74 (28)	0.57
Lifestyle [1]					
Physical activity [d]	300	219 (73)	246	160 (65)	0.06
Body weight [e]	346	242 (70)	282	196 (70)	0.97
Alcohol consumption [f]	310	272 (88)	276	236 (86)	0.50
Patients' perception of:					
Received lifestyle advice to... [2, g]					
Stay physically active (all patients)	365	85 (23)	292	61 (21)	0.89
In case of reported advice in EMR	299	67 (22)	64	19 (30)	0.28
Increase physical activity (in inactive patients)	73	24 (33)	72	21 (29)	0.92
In case of reported advice in EMR	58	19 (33)	16	7 (44)	0.60
Maintain healthy weight (all patients)	365	107 (29)	293	68 (23)	0.29
Lose weight (in case of BMI > 30)	72	42 (59)	78	32 (44)	0.13
Drink not too much alcohol (all patients)	365	28 (8)	293	19 (6)	0.97
Decrease alcohol consumption (when too high)	27	7 (26)	27	6 (23)	0.84

Table 3. (Continued)

	Intervention group n = 367		Usual care group n = 314		P – value
Patients' perception of:					
Maintain a healthy diet (all patients)	366	45 (12)	293	31 (11)	0.85
In case of reported advice in EMR	205	30 (15)	56	10 (18)	0.70
Treat hypertension (all patients)	364	130 (36)	290	92 (32)	0.99
Treat hypertension (if RR ≥ 140/90 mm Hg)	168	75 (45)	132	47 (36)	0.46
Treat hypercholesterolemia (all patients)	362	98 (27)	289	77 (27)	0.98
Treat hypercholesterolemia (if LDL ≥ 2.6 mmol/L)	169	48 (29)	142	76 (26)	0.25
Decrease stress (all patients)	362	33 (9)	290	26 (9)	0.80
Quit smoking (in smokers)	31	22 (71)	26	23 (88)	0.19
In case of reported advice in EMR	22	13 (59)	6	5 (83)	0.54

Absolute numbers (%) are presented. CVD, cardiovascular disease. EMR, electronic medical record. BMI, body mass index. LDL, low-density lipoprotein.

[1] Differences between treatment groups tested with Pearson $\chi 2$ test.

[2] Differences between treatment groups tested with Kruskal-Wallis test.

[a] Adequate perception: if CV risk (according to risk chart in Dutch CVRM guideline) is ≥ 10% and < 20% considered as intermediate or high, or considered as high in case of CV risk ≥ 20% or history of CVD.

[b] Adequate perception of hypertension: if blood pressure ≥ 140/90 mm Hg or antihypertensive drug use patient considered to have hypertension, otherwise considered to have no hypertension.

[c] Adequate perception of hypercholesterolemia: if LDL-cholesterol ≥ 2.6 or lipid lowering drug use patient considered to have hypercholesterolemia, otherwise considered to have no hypercholesterolemia.

[d] Adequate perception of physical activity: if < 5 days a week moderate intense physical activity ≥ 30 minutes/day patient considered physical activity as insufficient, otherwise as sufficient.

[e] Adequate perception of body weight: if BMI ≥ 30 patient considered body weight as unhealthy, otherwise as healthy.

[f] Adequate perception of alcohol consumption: if men consumed > 2 alcohol units/ day and women > 1 alcohol unit/ day and considered their alcohol consumption as too much, otherwise as not too much.

[g] Answer options were "yes"; "no"; "I don't know"; "not applicable".

DISCUSSION

In patients receiving integrated care for CVRM in general practice, CV risk factors and lifestyle advice were more often assessed and discussed as compared to usual care. However, in patients receiving CVRM care, antihypertensive medication often remained unchanged and in particular lipid-lowering drugs were seldom started or uptitrated when indicated. The CV risk and risk factor awareness in patients was poor; only one out of eight intervention patients with a high risk or CVD correctly labelled themselves as having a high risk. No more than a half and a quarter of patients correctly indicated themselves as having hypertension or hypercholesterolemia, respectively. The adequacy of patient's perception of CV risk (factors) and lifestyle (advice) did not differ between the groups and there was a huge gap between lifestyle advice documented in the medical files and that what was reported by patients.

Strengths and limitations

This process evaluation is among the first to evaluate the fidelity to an integrated care programme for CVRM in general practice. It adds to a deeper understanding of what elements need to be addressed to improve the outcomes of such programmes. A strength is that this study was conducted in a clinical context that reflects reality, making the results applicable in daily practice. Another strength is the complete data on adequacy of the delivered care; we were able to collect data from more than 95% of patients.

Bias cannot be entirely eliminated. First, the usual care group included less group practices compared to the intervention group. However, as we did not observe differences in outcomes between practices in the ZWOT-CASE study, we expect that the difference in group practices would not have influenced the differences in fidelity. Second, data on lifestyle and perceived CV risk could suffer from 'social-desirability bias'. Third, the prevalence of received lifestyle advice in according to the patient could be subject to recall bias, leading to considerable underreporting.

Another limitation is the difference in registration of patient data between both groups. In intervention practices patient data were registered in a multidisciplinary information system for integrated care (KIS, Portavita®) with boxes to enter predefined data and prompts to give lifestyle advice. In usual care, a general

information system with free text fields was used without any encouragement to register data on lifestyle advice given to the patient. Therefore, the number of given lifestyle advice could be underreported in the usual care group. We were not able to analyse the quality of the lifestyle advices in depth.

Further, the lack of qualitative data in our study may have limited complete assessment of the organization of CVRM care, including interdisciplinary collaboration.

Finally, misclassification of hypertension may have occurred as the analyses were based on a single office blood pressure measurement and repeated office BP measurements, home or 24-hour BP measurements were not available. This could partly explain the low uptake of BP lowering drugs in those with 'increased BP levels'.

Interpretation of the results and comparison with existing literature

Integrated CVRM care improved the assessment of CV risk factors and lifestyle counselling compared to usual care, also when compared to the findings from the EPA-cardio study. That large European observational study on CVRM in high risk patients without CVD in primary care, reported lower assessment rates of BP (92.5%), cholesterol (83.9%) and weight/ BMI (66.4%) and lifestyle counselling on diet (42.9%), physical activity (38.8%) and smoking (65.6%) compared to the intervention group in our study.[26]

In our study, medication was added or up-titrated in less than one-third of patients using antihypertensive or lipid-lowering medication who had an off-target SBP or LDL-cholesterol. This is in line with previous studies, reporting clinical inertia rates between 37% and 88% in patients with an uncontrolled BP in general practice.[14,27-29] However, in more than half of patients with an off-target SBP who were not already on antihypertensive medication, antihypertensive medication was started. The corresponding percentage for lipid-lowering medication was much lower (9%). At one hand, clinical inertia could play a role.[14,30] On the other hand GPs and patients may have primarily tried to achieve targets by lifestyle change as specifically recommended in cardiovascular prevention guidelines.[21] Also, patient-related factors may have limited adequate therapeutic interventions, such as reluctance to take medication due to various reasons. Especially, reluctance

to taking lipid-lowering drugs is widespread.[31,32] Unfortunately we did not collect detailed information on why therapy was not initiated. Further, inadequate risk factor awareness that we observed in our study may have played a role; a finding in line with previous research.[15,33] Since risk factor awareness is related to medication adherence, this is of major concern.[34,35]

Consistent with our results, an earlier Dutch primary care study reported CV risk to be perceived inappropriately by nearly 4 out of 5 high-risk patients, suggesting incorrect optimism.[15] Suboptimal communication between the PN/ GP and patients may explain the gap between communicated and perceived risk factor levels and lifestyle advice by patients.[36] Possibly, the attention of PNs and GPs focused more on checking boxes than on providing tailored lifestyle counselling. Further, variation in health literacy and numeracy of patients could make risk communication challenging.[37] Adequate counselling takes time and effort and as their workload increases and patients become more complex PNs may have been insufficiently prepared.[38] PNs and GPs might need support and tools to communicate about CV risk and how to empower patients to change their lifestyle.[39-42] For example, a short e-learning course has shown to improve risk communication skills of health care providers.[43]

An observational study showed that local variations between primary care practices with regard to implementation of a CVRM programme (resources, programme compliance to the planned regional clinical process, internal coordination of the health team, and programme experience) had no positive effect on SBP and physical activity.[44] Another observational study concluded that a favourable perception by team members regarding interdisciplinary collaboration (nurse, nutritionist, kinesiologist, pharmacist, social worker and GP) was associated with better patient outcomes (SBP, diet, quality of life) and less patient withdrawal from the programme, whereas the frequency of clinical information sharing was similar.[45] This suggests that the qualitative aspect of the interaction between interdisciplinary teams and GPs is of great importance. It raises the question to what extent the CVRM programme in our study, while on paper describing interdisciplinary collaboration, involved genuine collaboration across interdisciplinary teams. Instead of integrated care, referring patients from one to the other discipline may have occurred, lacking high qualitative communication

and cohesive information sharing with patients. Such a fragmented approach may hinder a more holistic, patient-centred response and, hence, effective CVRM.

Future considerations

In summary, implementation of integrated CVRM care in general practice leads to a higher proportion of patients in whom CV risk, risk factors, and lifestyle advice are registered and discussed. However, clinical action by primary care workers and risk (factor) and lifestyle awareness in patients remain problematic. This is in line with other studies that consistently have shown that adherence to guidelines and adequate lifestyle counselling is a challenge.[4,5,33] Possibly, a learning healthcare system including reminders and targeted feedback on performance might enhance risk factor control.[14] Future studies should focus on improvement of the communication between GP/PN and the patient, including the use of modern risk reduction tools, such as lifetime risk and the absolute risk reduction tool, and CVD free survival (available at https://u-prevent.com).[46] Also, greater collaborative efforts from various relevant stakeholders and additional financial support may be required to adequately manage CV risk.[47] Further, qualitative data could give more insight into the real content of interdisciplinary collaboration in primary care and explore what is needed for a more holistic approach. Finally, studies with longer follow-up should be considered, to assess whether improvement in process measures leads to improvement in (intermediate) outcomes in the longer term.[48]

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SUPPLEMENTARY FIGURES

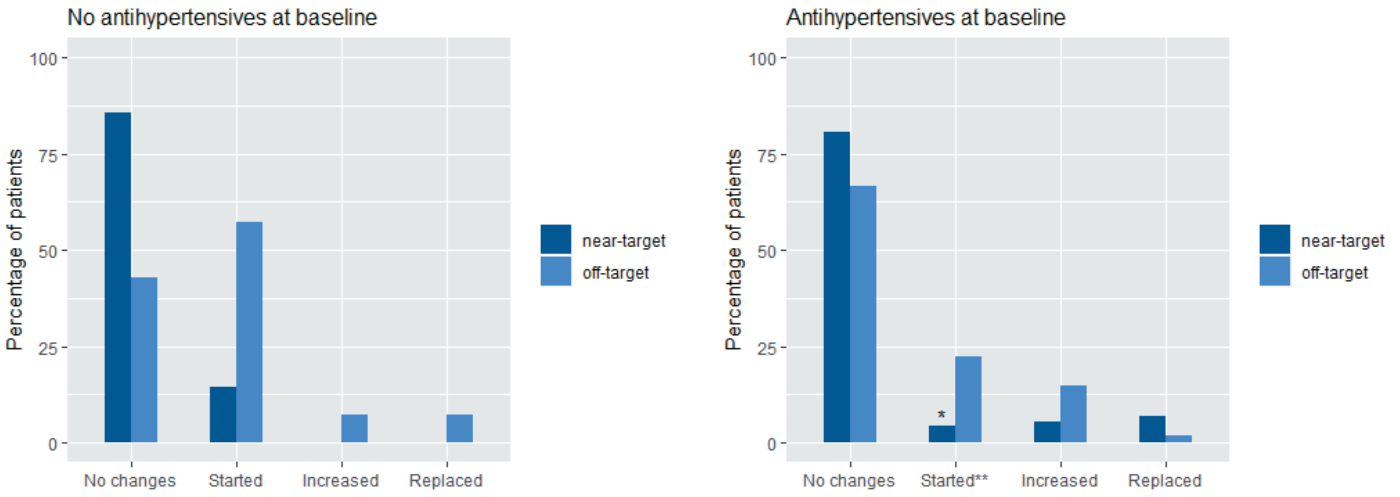


Figure S1. Changes in antihypertensive medication in intervention patients during 1 year of follow-up. Left: patients who did not use antihypertensive medication at baseline and had a near-target SBP (≥ 140 and < 150 mmHg) (n = 7) or off-target SBP (≥ 150 mmHg) (n = 14) at baseline. Right: patients who did use antihypertensive medication at baseline and had a near-target SBP (≥ 140 and < 150 mmHg) (n = 72) or off-target SBP (≥ 150 mmHg) (n = 54) at baseline. * Difference between near-target and off-target group statistically significant, $p < 0.05$. ** Another antihypertensive drug was added to the antihypertensive medication already in use.

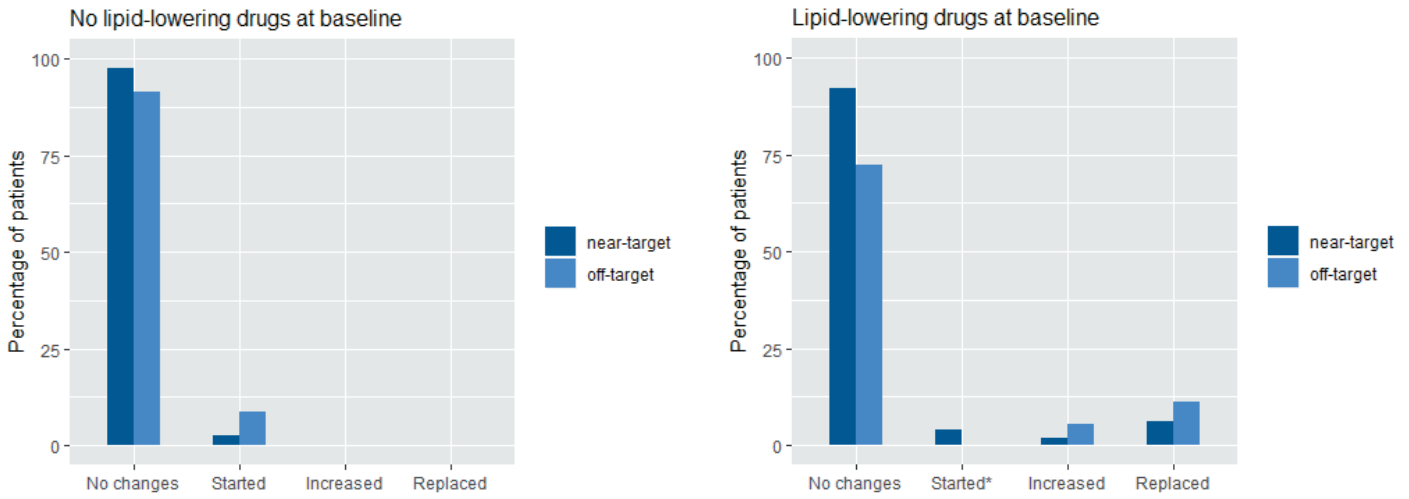
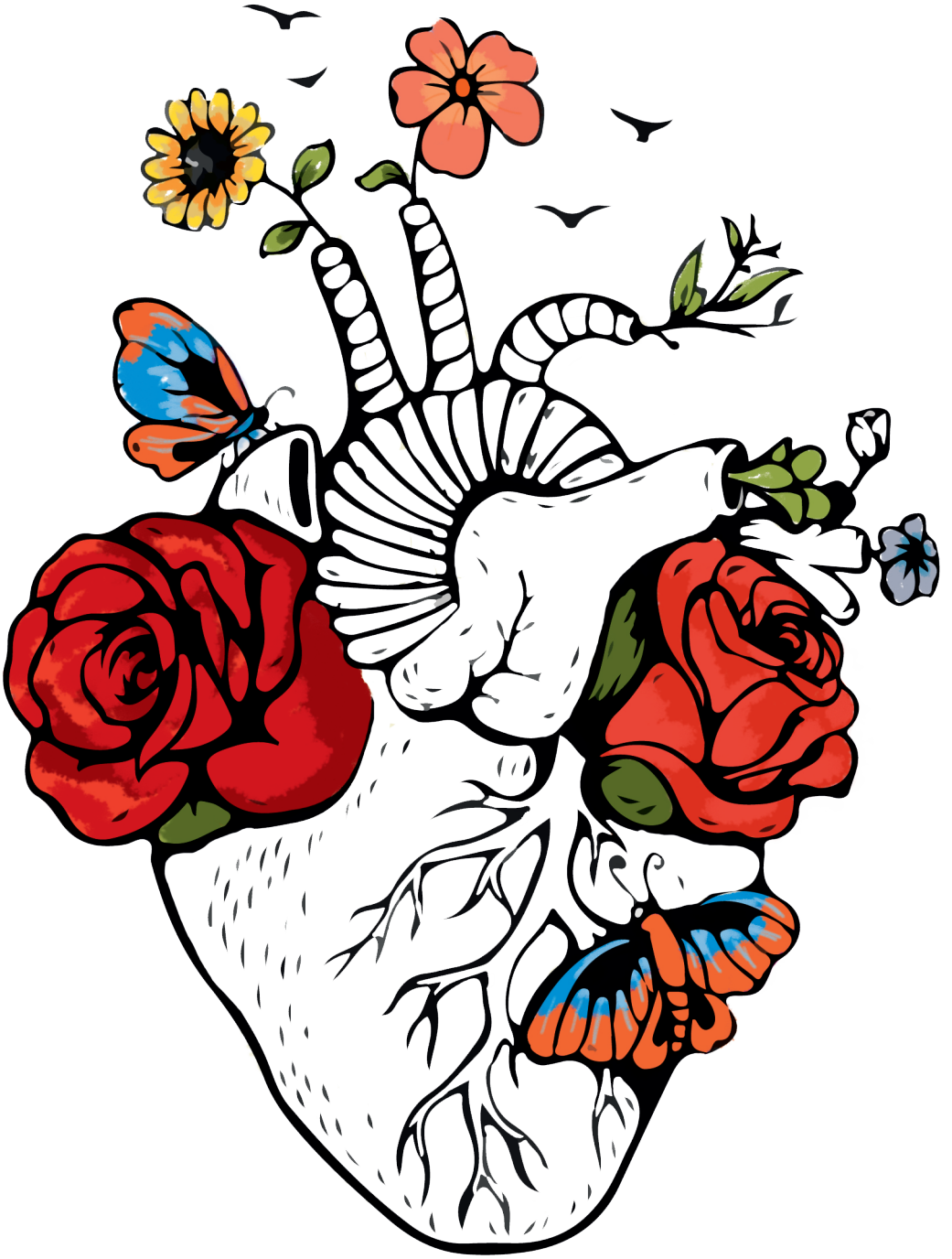


Figure S2. Changes in lipid-lowering drugs in intervention patients during 1 year of follow-up. Left: patients who did not use lipid-lowering drugs at baseline and had a near-target LDL-cholesterol (≥ 2.6 and < 3.5 mmol/L) (n = 76) or off-target LDL-cholesterol (≥ 3.5 mmol/L) (n = 70) at baseline. Right: patients who did use lipid-lowering drugs at baseline and had a near-target LDL-cholesterol (≥ 2.6 and < 3.5 mmol/L) (n = 50) or off-target LDL-cholesterol (≥ 3.5 mmol/L) (n = 18) at baseline. * Another lipid-lowering drug was added to the lipid-lowering medication already in use.



CHAPTER 6

Unravelling the impact of integrated care for cardiovascular risk management on hospital care and costs; a retrospective cohort study among patients with cardiovascular disease

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ABSTRACT

Background

Hospital and outpatient care for patients with cardiovascular disease (CVD) constitutes a large part of the health care budget. Integrated care for cardiovascular risk management (CVRM) could reduce costs by substitution of hospital care by care in primary care.

Aim

To assess costs for hospital care over time and to evaluate whether an integrated care programme for CVRM reduces hospital care and subsequent costs.

Methods

A retrospective cohort study among patients enlisted in the Isala hospital with atherosclerotic CVD. We assessed patient-level data on diagnoses and care activities from the Isala hospital between January 1st, 2014 and January 1st, 2018. From January 1st, 2016 onwards, an integrated primary care programme for CVRM was implemented in the adherent region. We compared duration of hospital care, number of care activities and corresponding costs prior and after starting integrated CVRM care and used descriptive statistics to assess differences between the two periods.

Results

We included respectively 5,215 and 5,449 CVD patients, (mean age 70 years, 35% female), in the period before and after 01-01-2016. The median length of treatment at the hospital decreased from 149 (IQR 12-389) to 128 (IQR 10-386) days and the total median costs of CVRM related hospital care per patient decreased by 13% from 583 euros (IQR 272 – 2586) the period before to 507 euros (IQR 262 – 2119) during the period after implementation of the programme.

Conclusion

Real-world hospital data can be an efficient method to evaluate the cost impact of healthcare interventions over time. After introduction of an integrated CVRM programme in primary care, length of treatment decreased slightly and the total costs of CVRM related hospital care decreased by more than 10%.

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death in Europe.[1] Between 2015 and 2019, the prevalence of CVD in the Netherlands increased by 150,000 patients to 1,55 million, due to ageing, smoking and increase in prevalence of obesity.[2] In 2016, CVD accounted for more than 10% of health expenditure and was at the top of hospital spending.[3] Due to ageing and an increase in the prevalence of chronic diseases, expenditures are expected to increase further in the near future.[4] Therefore, policymakers look for solutions to control health care costs, with programmes such as 'right care in the right place'.[4] This policy aims to reduce health care costs, by relocating care from hospitals closer to people's homes without reducing and preferably improving quality of care. This approach is based on the Triple Aim principle that pursuits the following aims: improving both the quality of care and the health of the population, while reducing the increase of health-care costs.[5] Integrated multidisciplinary care programmes, such as for cardiovascular risk management (CVRM) in primary care, correspond to this policy by aiming to improve health of patients and reduce costs by substitution of, expensive, hospital care by cheaper care in primary care.[6] General practitioners (GPs) are the key persons to deliver CVRM, as they have a longstanding relationship with their patients.[7] In addition, GPs in the Netherlands have a gatekeeping role, which means that hospital care is only accessible through GP referral.[8] However, it is unknown whether an integrated and multidisciplinary CVRM programme indeed leads to substitution of hospital care by care in the primary care and to reduction of costs.[9] In theory, improved CVRM in general practice could lead to less referrals to a medical specialist at the hospital.[10] It may also trigger medical specialists to refer patients back to the GP. Therefore, it composes a promising intervention to support substitution and to slow down the increase in expenditures.

The aim of the current study is to compare hospital care and costs related to CVRM in the period before and after implementation of an integrated care programme for CVRM in primary care among patients with established CVD.

METHODS

Design

We performed a retrospective cohort study among patients enlisted in the Isala hospital with an atherosclerotic CVD. An integrated and multidisciplinary CVRM programme in primary care was implemented in the region of Zwolle on January 1st, 2016. We assessed the effect of the programme on CVRM related care at the hospital, including length of hospital care, number of care activities and associated costs by comparing patient-level data from the Isala hospital on diagnoses and care activities, including associated costs, during 2 years before and 2 years after January 1st, 2016. The study was conducted following the privacy legislation of the Netherlands. A trusted third party anonymized the data.

Setting

The study was conducted in the region of Zwolle, including the Isala hospital, a large general hospital in the Netherlands, and 56 surrounding general practices affiliated to a care group 'Medrie' and who collaborated with the Isala hospital. From January 2016, integrated care for CVRM was implemented in 39 general practices (70%, including 115 general practitioners) in this region and coordinated by this care group. The medical specialists of the Isala hospital were involved in organizing integrated care for CVRM together with the GPs.

Study population

Inclusion criteria for patients were:

- History of atherosclerotic CVD defined as angina pectoris, myocardial infarction, chronic ischemic heart disease, coronary sclerosis, transient ischaemic attack (TIA), cerebral infarction, intermittent claudication or aneurysm of the aorta
- Treatment for atherosclerotic CVD by a medical specialist in the Isala hospital
- At least one care activity at the hospital in the context of CVRM during the period 2014-2018
- Registered with a GP who participated in the integrated CVRM programme

History of atherosclerotic CVD of patients was based on diagnosis codes used in the hospital (table S1). "Treatment by a medical specialist" was defined as having

at least one care activity at the hospital related to CVRM during the period 2014-2018. To be able to select patients of GPs participating in the integrated CVRM programme, we used the personal code of the GPs registered at the hospital file for each patient. We asked the GPs for permission to use this personal code.

We compared two periods: the 2 years before January 1st, 2016 (control period) and 2 years after January 1st, 2016 (intervention period). Information on hospital care and associated costs for CVD patients treated in the Isala hospital during this period was included in the analysis. Patients treated at the hospital in both periods contributed information to both periods.

Intervention

The intervention under study was an integrated and multidisciplinary programme for CVRM in primary care.[11] Core elements of this programme include systematic selection and invitation, cardiovascular risk assessment, shared decision in treatment and follow-up of eligible patients, stimulation of self-management, registration of patient data in a multidisciplinary information system and yearly feedback to GPs on delivered CVRM care. GPs collaborated with several health care professionals in the health care chain, including dieticians, physiotherapists and medical specialists. All involved health care professionals had access to the patient data in the multidisciplinary information system. This system also facilitated online consultation between health care professionals.

The aim of the integrated care programme for CVRM was to enhance chronic care and management of cardiovascular risk factors in primary care. Besides, the programme aimed to substitute hospital care by CVRM care in primary care. This substitution can be achieved by several mechanisms. First, improving CVRM in primary care may result in prevention of new cardiovascular events and reduce the need for referral to the hospital. Second, the possibility of an online consultation of a medical specialist can make hospital referral unnecessary. Third, referral from the hospital back to the GP is encouraged by adhering to regional agreements pertaining to some specific patient groups[12], including patients:

- 6 months after myocardial infarction (MI)
- 1 month after percutaneous coronary intervention (PCI) (no MI)
- 6 months after uncomplicated coronary artery bypass grafting (CABG)
- 12 months after established stable coronary artery disease

According to the regional agreements, substitution of hospital care by CVRM care in primary care was only possible in case of stable complaints and adequate medication use. In case of residual ischemia after an intervention, clinically manifest heart failure or an ejection fraction of less than 30% patients remained under control of a medical specialist.

In patients with other CVDs, it was decided on a case-by-case basis whether substitution of hospital care by CVRM care in primary care was possible. At the start of the integrated care programme for CVRM, GPs invited all patients with CVD for an intake visit. If a patient was under control for a CVD at the hospital, the GP considered ending this hospital care after agreeing on this with the medical specialist and the patient.

Data collection

We used patient-level data on diagnoses and care activities at the Isala hospital. In the Netherlands, diagnoses and care activities are currently coded using a national system adopted by all hospitals and are primarily for financial reimbursement.[13] Each diagnosis code consists of a specialism code and a more specific diagnosis code. For the current study, we extracted all coded diagnoses of included patients from the electronic medical hospital file. We selected 50 coded diagnoses concerning atherosclerotic CVD of five medical specialties (cardiology, neurology, internal medicine, surgery and cardiothoracic surgery) (table S1).

Besides, we extracted all care activities belonging to the diagnoses, including the date of the activity. We divided activities related to CVRM in 3 main groups: diagnostic activities, paramedical care and consultation activities (table S2). Besides, we extracted outpatient visits, day-care admissions and hospital admissions (number of admission days) related to CVD.

Further, the dataset encompasses information on patient characteristics, including gender and age.

Data were extracted from 2 years before (January 1st, 2014) until 2 years after (January 1st, 2018) implementation of the integrated CVRM programme on January 1st, 2016. The dataset was anonymised by a third party.

Outcome measures

The outcomes of the study included:

- Duration of CVD care at the hospital in days
- Number of CVRM related care activities during treatment at the hospital
- Costs of CVRM related care at the hospital

First, duration of CVD care at the hospital was based on dates of all care activities related to the 50 CVD diagnoses. The date of the first care activity was defined as the start of treatment at the hospital; the date of the last care activity was defined as the end of treatment at the hospital. To calculate the length of duration of care at the hospital, we calculated the number of days between these two dates.

Second, we counted the number of CVRM related activities during the treatment at the hospital within the 50 CVD diagnoses, including outpatient visits, day-care admissions, hospital admissions, diagnostics, paramedical care activities and consultations (table S2).

Lastly, we assessed the costs of CVRM related care at the hospital, both for the total group and per patient within the 50 CVD diagnoses. Costs were based on CVRM related care activities (table S2). We calculated the costs of each activity by multiplying the actual number of care activities delivered during treatment at the hospital with standardized national prices for the specific activities.[14] To avoid price difference over time, we used 2018 unit prices and did not apply a discount rate. In case a standardized national unit price was not available, we estimated the price of an activity. If possible, we estimated the price by taking the price of a very similar activity. Otherwise, we estimated the price by estimating and multiplying the duration of the activity in hours by the salary per hour of the health care worker who delivered the activity.[14]

To check whether other factors may have influenced the outcome measures, such as an ageing population or changed hospital policy, we assessed the number of outpatient visits and hospital admissions and corresponding costs of all other diagnoses excluding the 50 atherosclerotic CVD diagnoses (non-CVD care) between January 1st, 2014 and January 1st, 2018 within the same study population.

Statistical analyses

To describe the prevalence of different atherosclerotic CVD in the study population, we used the 50 coded diagnoses of atherosclerotic CVD. The aim of the main analysis was to compare the duration of CVD care at the hospital, number of CVRM related care activities at the hospital and corresponding costs between the 2 years before and the 2 years after implementation of the integrated programme for CVRM on January 1st, 2016. For this analysis, we used descriptive statistics. To assess the impact of uncertainties in estimated prices on the robustness of the results concerning total costs a sensitivity analysis was done, using a standard error of 10% for the estimated prices. Analyses were performed using R studio (version 3.5.1, Copyright (C) 2018 The R Foundation for Statistical Computing).

RESULTS

In total, 82 of 115 general practitioners agreed to participate in the study. From these participating general practices, we included 5,215 and 5,449 patients in, respectively, the 2 years before and after implementation of the integrated care for CVRM on January 1st, 2016 (figure 1).

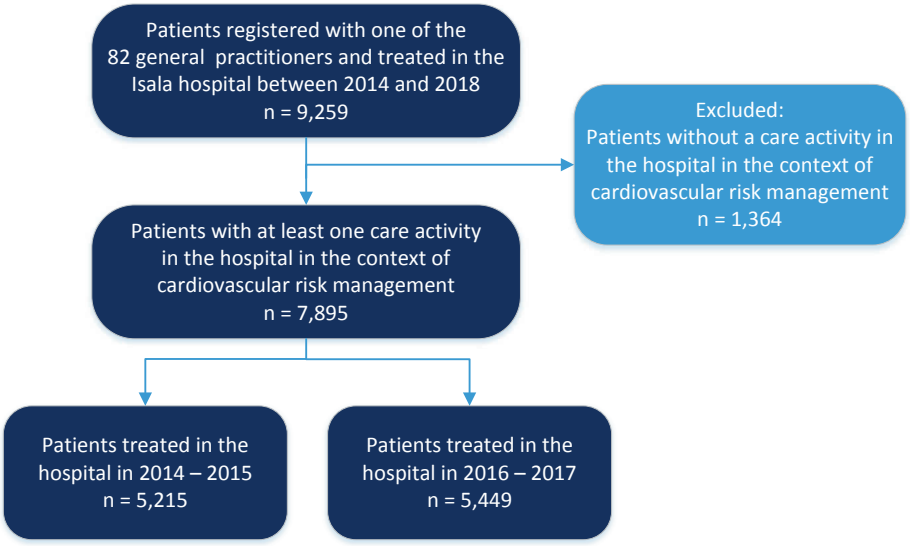

Figure 1. Flowchart selection of study population

Mean age in included patients was 70.2 (SD 11.5) and 70.6 (SD 11.5) years, on July 1st, 2016 and on July 1st, 2018 respectively (table 1). In both periods, 35% were female. The most common CVD diagnosis codes were 'follow-up after percutaneous coronary angioplasty and/or coronary artery bypass graft' (35% and 33%), 'angina pectoris' (31% and 30%), 'cerebrovascular accident/stroke or transient ischemic attack' (21% and 20%) and 'peripheral atherosclerotic disease' (12% during both periods), in respectively the period before and after January 1st, 2016. We observed no clear differences in CVD diagnosis codes between both periods.

Table 1. Patient characteristics

Characteristics	**Before (2014 – 2015) n = 5,215**	**After (2016 – 2017) n = 5,449**
Mean age in years (SD)	70.2 (11.5)	70.6 (11.5)
Female (%)	1,827 (35)	1,893 (35)
*Diagnoses**		
Angina pectoris	1,634 (31)	1,622 (30)
Myocardial infarction	482 (9)	473 (9)
Other ischemic heart disease	4 (0)	4 (0)
CABG	311 (6)	321 (6)
Aortic aneurysm	341 (7)	403 (7)
Cerebrovascular accident /TIA	1,088 (21)	1,105 (20)
Peripheral atherosclerotic disease	643 (12)	659 (12)
Other atherosclerotic CVD	152 (3)	205 (4)
Follow-up after acute coronary syndrome	36 (1)	40 (1)
Follow-up after PTCA and/or CABG	1,819 (35)	1,790 (33)
Follow-up after vascular operation	23 (0)	23 (0)
Cardiac rehabilitation	919 (18)	865 (16)

* Diagnoses were based on 50 coded diagnoses of atherosclerotic cardiovascular diseases.
CABG, coronary artery bypass graft. PTCA, percutaneous coronary angioplasty. SD, standard deviation. TIA, transient ischemic attack.
Absolute numbers (%) are presented unless stated otherwise.

The median length of CVD care at the hospital decreased from 149 days (IQR 12 – 389) to 128 days (IQR 10 – 386) per patient in the period before versus after implementation of integrated CVRM care, respectively (table 2).

Table 2. Outcome measures per patient

	Before (2014 – 2015) n = 5,215	After (2016 – 2017) n = 5,449	
Outcomes			**Change in costs**
Length of hospital care in days, mean (SD)	216 (211)	212 (210)	
Length of hospital care in days, median (IQR)	149 (12-389)	128 (10-386)	
Median number of activities (IQR)			
Outpatient visits	2 (1 – 4)	2 (1 – 3)	
Hospital admissions	0 (0 – 4)	0 (0 – 3)	
Day care	0 (0 – 0)	0 (0 – 0)	
Diagnostic activities	6 (2 – 12)	6 (2 – 12)	
Paramedical care	0 (0 – 1)	0 (0 – 1)	
Consultations	0 (0 – 0)	0 (0 – 0)	
Sum of all activities	9 (4 – 23)	9 (4 – 21)	
Median costs (IQR)			
Outpatient visits	167 (83 – 260)	167 (83 – 250)	0%
Hospital admissions	0 (0 – 1,844)	0 (0 – 1,383)	0%
Day care	0 (0 – 0)	0 (0 – 0)	0%
Diagnostic activities	188 (61 – 385)	187 (61 – 348)	-0.5%
Paramedical care	0 (0 – 66)	0 (0 – 34)	0%
Consultations	0 (0 – 0)	0 (0 – 0)	0%
Sum of all activities	583 (272 – 2,586)	507 (262 – 2,119)	-13.0%

SD, standard deviation. IQR, interquartile range.

The median number of the sum of all CVRM related activities per patient was 9 (IQR 4 – 23) and 9 (IQR 4 – 21) in respectively the period before and after implementation of integrated CVRM (table 2). At the group level, the sum of all CVRM related care activities during the treatment in the hospital decreased from 98,924 to 95,439, whereas the total number of patients with at least one CVRM related care activity increased from 5,199 to 5,413 (table 3).

Table 3. Total costs per group

	Before (2014 – 2015) n = 5,215			After (2016 – 2017) n = 5,449			
Outcomes	**Patients n**	**Activities n**		**Patients n**	**Activities n**		**Change in costs**
Total costs of hospital care							
Outpatient visits	4,980	14,364	1,112,595	4,850	13,695	1,064,286	-4.3%
Hospital admissions	1,818	16,462	7,589,068	1,773	14,738	6,794,295	-10.5%
Day care	1,224	1,596	245,254	1,142	14,68	225,585	-8.0%
Diagnostic activities	4,987	58,262	1,468,803	5,235	57,652	1,441,669	-1.8%
Paramedical care	1,589	7,206	278,228	1,407	6,808	248,496	-10.7%
Consultations	457	1,034	36,414	235	1,078	32,813	-9.9%
Sum of all activities	5,199	98,924	10,730,365	5,413	95,439	9,807,146	-8.6%

The median costs per patient of the sum of all CVRM related care activities decreased by 13.0% from 583 euros (IQR 272 – 2,586) to 507 euros (IQR 262 – 2,119) (table 2). At the group level, the total costs of CVRM related care at the hospital decreased by 8.6%, from 10,730,365 euros in the period before to 9,807,146 euros in the period after implementation of the programme (table 3). This included a decrease in the costs of outpatient visits by 4.3% (from 1,112,595 to 1,064,286 euros), hospital admissions by 10.5% (from 7,589.068 to 6,794,295 euros), day care admissions by 8.0% (from 245,254 to 225,585 euros), diagnostics activities by 1.8% (from 1,468.803 to 1,441,669 euros), paramedical care by 10.7% (from 278,228 to 248,496 euros) and consultations by 9.9% (from 36,414 to 32,813) (table 3 and figure S1).

The sensitivity analysis showed that uncertainties in estimated prices did not influence the results concerning total costs.

The hospital costs related to other diagnoses than CVD for the CVD patients also decreased, but to a much lower extent from 2014-2015 to the 2016-2017 period; the costs of non-CVD related outpatient visits even slightly increased (table S3).

DISCUSSION

In this study, we analysed costs of CVRM related care in the hospital over time and evaluated the effect of an integrated and multidisciplinary CVRM programme in primary care on CVRM related care in the hospital. The median length of treatment in the hospital decreased slightly from 149 days (IQR 12 – 389) to 128 days (IQR 10 – 386). Further, the median costs per patient of CVRM related care at the hospital decreased by 13.0%, from 583 euros (IQR 272 – 2,586) to 507 euros (IQR 262 – 2,119), mainly due to a decrease in the costs of hospital admissions.

Strengths and limitations

This study is among the first to evaluate the effect of an integrated care programme for CVRM on hospital care, including costs. A strength is that we had access to a large and complete dataset of delivered healthcare in one hospital. Further, the Isala hospital is the only hospital in the region, minimizing the chance that patients were referred to another hospital. Another strength is that we were able to compare relative long periods (2 years each) before and after the introduction of the integrated CVRM care programme. Substitution initiatives require enough time for professionals to adapt to the new policy.[15] We believe that a follow-up of 2 years after implementation was long enough to demonstrate an effect on hospital care.

Unfortunately, we had no access to data from the general practices, but only to hospital data. Therefore, we were not able to estimate the effects on care activities or costs in primary care and thus to describe the "true substitution" for this patient cohort, but only assessed the effects on hospital care. We also cannot be sure whether CVRM care was started in primary care when care at the hospital ended. However, it is known that a decreased use of hospital care is associated with increased use of primary care.[16]

As this study had a before-after design without a parallel group, we cannot rule out that the observed effects on costs and length of hospital care are due to time dependent trends or other interventions. However, the trend analysis of non-CVD care showed a much smaller decrease in the costs of hospital admissions and even a small increase in the total costs of outpatient visits suggesting that any effect of such time dependent trends is likely to be small.

The before-after study design is, by design, a non-randomised comparison. Hence, the samples may not have been completely comparable in their characteristics. However, we did not observe any relevant differences in age, gender and type of CVD diagnoses between the two periods.

Lastly, generalisability of the results to countries with other healthcare and referral systems may be limited.

Interpretation of the results and comparison with existing literature

The mechanism behind the reduction in the number of care activities and corresponding costs in the current study is uncertain. We assume that our findings may be explained by a decrease in referrals from primary care to the hospital due to both intensifying of CVRM care in primary care as improved accessibility of consultation of a medical specialist in primary care as part of the integrated CVRM programme. Further, medical specialists were probably more compliant with regional agreements on substitution for some specific patient groups, leading to an increase in referral from the hospital back to the GP.

Comparison with existing literature is limited, as previous studies on the effect of integrated care for CVRM on hospital care and substitution are very scarce and differ considerably in study aim and design. In line with our results, an Australian study showed that a chronic disease management programme for patients with CVD or diabetes successfully reduced the frequency and duration of hospital admissions.[17] The magnitude of the effect increased over time and persisted after 4 years, demonstrating the importance of a sustained programme to maximise its impact.[17,18]

Several reviews evaluating other integrated care programmes or substitution initiatives also showed beneficial effects on hospital care. A meta-review of 27 reviews comparing integrated care interventions with usual care, found effects in favour of integrated care on hospital admissions and re-admissions, but no reduction in costs.[19] Further, a scoping review concluded that transfer of services from secondary to primary care and strategies aimed at changing referral behaviour of primary care clinicians can be effective in reducing outpatient referrals.[20] Also, a systematic review of Faulkner et al. suggested that a diverse range of interventions to improve health care at the primary–secondary interface

could suppress referral rates from primary to secondary care.[21] However, there was little evidence available on cost consequences.[20]

Future considerations

Substitution of hospital care by primary care for selected patients should be encouraged, as general practitioners are able to deliver care of equal quality against lower costs for several patient groups.[22,23] However, more evidence is needed on the effect of such interventions to stimulate such substitution. For example, longitudinal research comparing a regional intervention with national trends on a population level should be conducted to assess the effect of a regional substitution initiative.[15] Further research is also needed to clarify whether such interventions are cost-effective, taking into account the health of the population, quality of care and costs across the whole health system.[20,24] Such evidence is also needed to ensure that the enthusiasm surrounding substitution intervention does not lead to overly optimistic, essentially uncontrolled, experiments, without first evaluating whether these interventions negatively affect quality of care, health care outcomes or costs.

Ideally, reductions in healthcare expenditure are based on a decrease in the claims burden for health insurers.[15] However, our research shows that financial hospital data, despite their inherent limitations, can be an efficient method to evaluate the cost impact of healthcare implementations over time. If performed properly, cost analysis on big cohorts can support decision makers in evaluating healthcare patterns. We propose that such analyses could be used more often to evaluate the impact of healthcare interventions.

Besides further research on substitution, the continuity of care between the hospital and general practice should receive more attention, as a collaborative and multidisciplinary approach is crucial to ensure high quality cardiovascular care after substitution.[25,26]

In conclusion, real world hospital data can be an efficient method to evaluate the cost impact of healthcare interventions over time. After introduction of an integrated CVRM programme in primary care, length of treatment decreased slightly and the total costs of CVRM related hospital care decreased by more than 10%.

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SUPPLEMENTARY TABLES AND FIGURES

Table S1. 50 coded diagnoses used for selection of study population

Specialism	Diagnosis code	Diagnosis
Surgery	0303|402	Carotid pathology
Surgery	0303|403	Thoracic aortic aneurysm
Surgery	0303|405	Iliac artery aneurysm
Surgery	0303|406	Abdominal aortic aneurysm
Surgery	0303|408	Renal artery stenosis
Surgery	0303|418	P.A.O.D.[a] 2, intermittent claudication
Surgery	0303|419	P.A.O.D.[a] 3, rest pain
Surgery	0303|420	P.A.O.D.[a] 4, gangrene
Internal medicine	0313|101	Symptomatic ischemic heart disease, not diagnosis 0313|102
Internal medicine	0313|102	Unstable angina pectoris, myocardial infarction
Internal medicine	0313|121	Cerebrovascular accident /TIA[b]
Internal medicine	0313|124	Atherosclerosis of the extremities /peripheral vascular disease
Internal medicine	0313|129	Aneurysm and other arterial vascular disorders
Cardiology	0320|202	Angina pectoris, stable
Cardiology	0320|203	Angina pectoris, unstable
Cardiology	0320|204	ST-elevation myocardial infarction
Cardiology	0320|205	Non ST-elevation myocardial infarction
Cardiology	0320|601	Arterial vascular defect / stenosis
Cardiology	0320|801	Follow-up after acute coronary syndrome
Cardiology	0320|802	Follow-up after PTCA[c] and/or CABG[d]
Cardiology	0320|808	Follow-up after vascular operation (arterial/ venous)
Cardiology	0320|821	Cardiac rehabilitation
Cardiothoracic surgery	0328|2320	CABG[d], venous grafts and max. 1 arterial graft
Cardiothoracic surgery	0328|2400	CABG[d] (>=2 arterial grafts)
Cardiothoracic surgery	0328|2415	CABG[d] (1 arterial graft) + MVR[e]
Cardiothoracic surgery	0328|2425	CABG[d] (1 arterial graft) + AVR[f]
Cardiothoracic surgery	0328|2470	Left ventricular plasty + CABG[d]
Cardiothoracic surgery	0328|2550	CABG[d] + MPL[g] +/- TPL[h]
Cardiothoracic surgery	0328|2555	CABG[d] (2 arterial grafts) + MVR[e]
Cardiothoracic surgery	0328|2560	CABG[d] (1arterial graft) + AVR[f] + MVR[e]
Cardiothoracic surgery	0328|2570	CABG[d] (2 arterial grafts) + AVR[f]
Cardiothoracic surgery	0328|2585	CABG[d] + HOCM[i]
Cardiothoracic surgery	0328|2630	VT[i] + CABG[d]
Cardiothoracic surgery	0328|2635	Maze + CABG[d]

Table S1. (Continued)

Specialism	Diagnosis code	Diagnosis
Cardiothoracic surgery	0328|2640	VSR[k] + CABG[d]
Cardiothoracic surgery	0328|2645	MPL[g] + AVR[f] + CABG[d]
Cardiothoracic surgery	0328|2650	MPL[g] + CABG[d] (2 arterial grafts)
Cardiothoracic surgery	0328|2655	AVR[f] + CABG[d] + HOCM[i]
Cardiothoracic surgery	0328|2665	Aortic root + CABG[d]
Cardiothoracic surgery	0328|2720	Aortic dissection +/- CABG[d]
Cardiothoracic surgery	0328|2740	Ascending aorta + CABG[d]
Cardiothoracic surgery	0328|2770	Aortic root + CABG[d] + MPL[g]/MVR[e]
Cardiothoracic surgery	0328|2785	Maze + CABG[d] or AVR[f] + MPL[g] +/- TPL[h]
Cardiothoracic surgery	0328|2810	Thoracic-abdominal aneurysm
Cardiothoracic surgery	0328|3210	Carotid endarterectomy
Cardiothoracic surgery	0328|3310	Carotid endarterectomy, both sides
Cardiothoracic surgery	0328|3320	Abdominal aortic aneurysms
Cardiothoracic surgery	0328|3340	Endoprosthesis
Neurology	0330|1111	Ischeamic stroke
Neurology	0330|1112	TIA[b] (including amaurosis fugax)

[a] P.A.O.D.: Peripheral Arterial Occlusive Disease. [b] TIA: Transient Ischaemic Attack. [c] PTCA: Percutaneous Transluminal Coronary Angioplasty. [d] CABG: Coronary Artery Bypass Graft. [e] MVR: Mitral Valve Replacement. [f] AVR: Aortic Valve Replacement. [g] MPL: Mitral valve Plasty. [h] TPL: Thoracoplasty. [i] HOCM: Hypertrophic Obstructive Cardiomyopathy. [j] VT: Ventricular Tachycardia. [k] VSR: Ventricular Septal Rupture.

Table S2. CVRM related activities

Group	Short description	Details	Price in euros
Outpatient visits	Outpatient visit		83
Outpatient visits	Consultation by telephone		83
Outpatient visits	Short teleconsultation		10
Day-care admissions	Day-care admission		154
Hospital admissions	Hospitalization day		461
Diagnostics	Ultrasound of the heart	Ultrasound of the heart	139
Diagnostics	Ultrasound of the heart	Ultrasound of the heart and/ or thorax	123
Diagnostics	Ultrasound of the heart	Ejection fraction left and / or right ventricle with wall motion analysis	287
Diagnostics	Cardiac stress test	Simple	145
Diagnostics	Cardiac stress test	Comprehensive	185

Table S2. (Continued)

Group	Short description	Details	Price in euros
Diagnostics	24-hour blood pressure measurement		125
Diagnostics	Duplex blood vessels in extremities		108
Diagnostics	Examination of arterial obstructions of extremities	Including blood pressure measurement of arms and / or legs or penis with continuous wave doppler or plethysmography	93
Diagnostics	Electrocardiogram		48
Diagnostics	Laboratory measurement	Creatinine clearance	5
Diagnostics	Laboratory measurement	Microalbumin in urine	3
Diagnostics	Laboratory measurement	Triglycerides	2
Diagnostics	Laboratory measurement	High-density lipoprotein cholesterol	2
Diagnostics	Laboratory measurement	Total cholesterol	2
Diagnostics	Laboratory measurement	Glucose Galactose tolerance test	2
Diagnostics	Laboratory measurement	Creatinine	2
Diagnostics	Telemonitoring		30
Paramedical care	Dietician, consultation		17
Paramedical care	Physiotherapist, consultation		34
Paramedical care	Psychologist, consultation		67
Paramedical care	Psychologist, peer consultation		17
Paramedical care	Nurse practitioner, consultation		30
Consultations	Multidisciplinary consultation		30
Consultations	Multidisciplinary consultation	Heart team	40

Table S3. Costs of outpatient visits and hospital admissions for non-CVD care

	Before (2014 – 2015) n = 5,215			After (2016 – 2017) n = 5,449			
Outcomes	**Patients**	**Activities**		**Patients**	**Activities**		**Change**
	n	**n**		**n**	**n**		**in costs**
Median costs per patient (IQR)			500 (88 – 2,177)			500 (83 – 2,069)	0%
Outpatient visits			343 (83 – 759)			343 (83 – 759)	0%
Hospital admissions			0 (0 – 1,383)			0 (0 – 1,383)	0%
Total costs	4,265	58,550	11,469,584	4,426	58,718	11,393,398	-1%
Outpatient visits	4,243	40,012	2,923,469	4,401	40,422	2,958,846	+1%
Hospital admissions	1,703	18,538	8,546,115	1,710	18,296	8,434,551	-1%

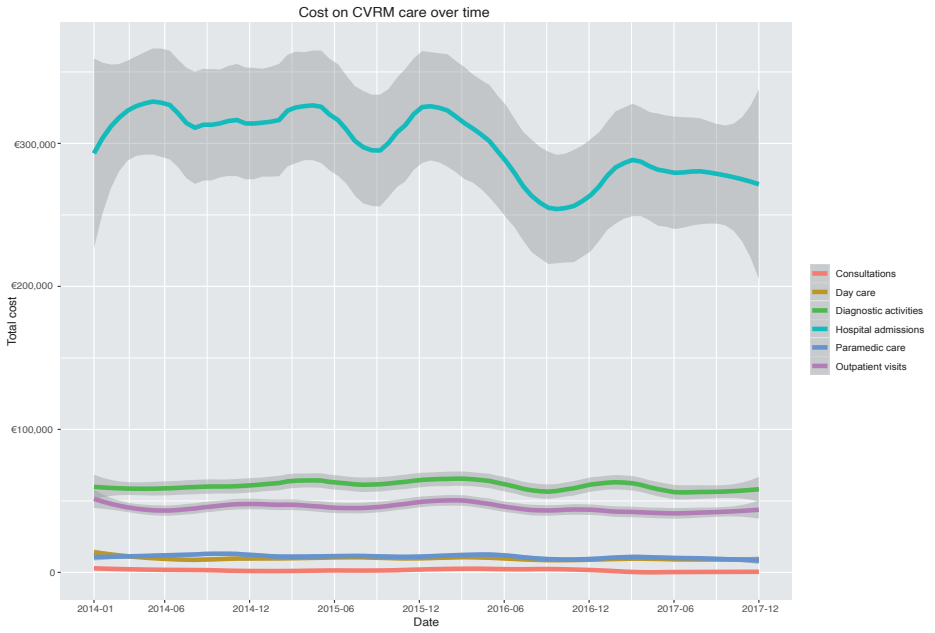

Figure S1. Costs of care activities

CHAPTER 7

Inadequate management of dyslipidaemia in primary care

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ABSTRACT

Background

The management of dyslipidaemia in primary care remains suboptimal. Therapeutic inertia may be a possible explanation.

Aim

To assess characteristics associated with therapeutic inertia in general practitioner's lipid-management.

Design and setting

An observational study in patients labelled (ICPC coded) for dyslipidaemia, atherosclerotic cardiovascular disease (CVD) or diabetes mellitus (DM) in general practice.

Methods

Electronic health record data of patients registered in the Julius General Practitioners' Network (n=530,564) were used. We selected patients with dyslipidaemia, CVD or DM, and with a recently measured uncontrolled LDL-cholesterol level (> 2.5 mmol/L). Therapeutic inertia was defined as absence of lipid-lowering drug adjustment within three months after the LDL-cholesterol measurement. We used logistic-regression analyses to identify characteristics associated with therapeutic inertia.

Results

Out of 21,310 patients with dyslipidaemia, atherosclerotic CVD and/or DM with a recently measured LDL-cholesterol we identified 6,854 (32%) patients with a LDL-cholesterol > 2.5 mmol/L. Mean age was 68 (SD 12.2) years and 57% were women. The median LDL-cholesterol was 3.1 mmol/L (IQR 2.8 – 3.7) and 45% used a lipid-lowering drug in the 6 months prior to the measurement. Therapeutic inertia was present in 93% and did not differ between patients with a CVD, DM or dyslipidaemia. Age (OR per year 1.01, 95%-CI 1.01 to 1.02) was positively, while LDL-cholesterol level (OR per mmol/L 0.63, 95%-CI 0.56 to 0.70) and being a current or past smoker (OR 0.66, 95%-CI 0.54 to 0.80) were inversely associated with therapeutic inertia.

Conclusion
Therapeutic inertia was seen in nearly all patients in whom lipid-lowering treatment was indicated. This huge gap between guidelines and daily practice warrants further attention and action.

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide.[1,2] There is convincing evidence for a log-linear relationship between plasma LDL-cholesterol levels and the risk of CVD.[3,4] Lowering LDL-cholesterol with statins reduces the risk of vascular events by about 20% per one mmol/L reduction.[5] More intensive lowering of LDL-cholesterol further reduces major vascular events.[6] The Dutch College of General Practitioners guidelines 'Cardiovascular Risk Management' (CVRM) for the management of dyslipidaemia valid from 2012 to May 2019 recommends to achieve a LDL-cholesterol of ≤ 2.5 mmol/L for patients at moderate or high risk of CVD.[7] The guideline of the European Society of Cardiology for the management of dyslipidaemias and the new CVRM guidelines for the Netherlands (based on this European guideline) from May 2019, recommend stricter target values, and the latter is currently being implemented.[8,9]

To achieve LDL-cholesterol goals, uptitration of existing therapy, switching to another more effective statin or combining another lipid-lowering agent with a statin has been proven to be effective.[10-13] However, studies such as the EUROASPIRE surveys, have consistently shown that management of dyslipidaemia remains suboptimal, especially in primary care.[14-16] In the most recent survey, among treated patients with dyslipidaemia less than 50% attained the LDL-cholesterol target of < 2.6 mmol/L.[16] Furthermore, only 38% of patients with diabetes mellitus (DM) type 2 irrespective of the presence of CVD were on statins at all.[16] This marks the considerable gap between evidence and daily practice.

A possible explanation for the disappointing findings on lipid management in everyday practice is therapeutic inertia, as has been reported in several high-risk groups.[17-20] Inertia is defined as failure to initiate or intensify therapy in patients who have not yet reached their target.[17] Limited knowledge exists on determinants of therapeutic inertia in dyslipidaemia, especially in primary care. One primary care study has shown that higher LDL-cholesterol levels were inversely associated

with therapeutic inertia and older age and diabetes were positively associated with therapeutic inertia.[21]

More insight in modifiable characteristics associated with therapeutic inertia is crucial to improve the treatment and prognosis of patients with dyslipidaemia. The current study aims to assess characteristics associated with therapeutic inertia in lipid-management in primary care.

METHODS

Study design and data source

We conducted a cohort study with data from the Julius General Practitioner Network (JGPN). The JGPN database consists of routine care data extracted from electronic health records (EHR) of 72 general practices in the vicinity of Utrecht, the Netherlands. JGPN covers approximately 530,000 registered community people and is considered an adequate representation of the population in the Netherlands.[22] Data available include diagnostic measurements, laboratory test results, diagnoses recorded with the International Classification of Primary Care (ICPC) codes and prescriptions based on the Anatomical Therapeutic Chemical (ATC) codes. The last date of data extraction differed per practice, ranging from December 2017 up to August 2019.

Research in JGPN is conducted following the privacy legislation of the Netherlands. All JGPN practices informed their patients on the JGPN database and provided information on the opt-out procedure.[22]

Population selection

Information was extracted from patients ≥18 years with a clinical indication for lipid-lowering treatment (based on ICPC codes), i.e.; dyslipidaemia, atherosclerotic CVD (angina pectoris, coronary heart disease, ischemic stroke, transient ischemic attack (TIA), aortic aneurysm, peripheral artery disease), or DM (type I or II) (table S1). We selected patients with a measured LDL-cholesterol level > 2.5 mmol/L, within the 12 months before the date of data extraction. LDL-cholesterol measurements within three months before the last date of extraction were excluded, as we considered at least three months necessary for GPs to adjust lipid-lowering medication after the index high LDL-cholesterol measurement. We

excluded patients without a LDL-cholesterol measurement in the study period. Poorly controlled dyslipidaemia, defined as LDL-cholesterol > 2.5 mmol/L in patients with established atherosclerotic CVD or a high CVD risk, including DM, was based on the Dutch College of General Practitioners guidelines 'Cardiovascular Risk Management' (CVRM) for the management of dyslipidaemia valid from 2012 to May 2019.[7]

We excluded patients registered with a new diagnosis of dyslipidaemia, CVD or DM less than six months before the index LDL-cholesterol measurement to allow a period of 6 months to achieve the treatment goal after initiating lipid-lowering therapy.

In order to focus on patients in whom uptitration or change of medication was evidently needed, we only included patients with dyslipidaemia, but without CVD or DM, in case they used lipid-lowering drug(s) in the year before the measurement. We excluded these patients if they were not on lipid-lowering drugs since they might have not completed the steps prior to initiating pharmacological therapy. Patients were also excluded when the GP prescribed new drugs or intensified the dose of prescribed drugs less than six weeks before the LDL-cholesterol measurement because their effect may not yet be set.

Definition of therapeutic inertia

Therapeutic inertia was defined as no drug change or adjustment within three months after the LDL-cholesterol measurement with the aim to decrease LDL-cholesterol. Therapeutic inertia was deemed absent in case of: (i) start of lipid-lowering drugs, (ii) addition of a different class of lipid-lowering drug, (iii) change to a same class lipid-lowering drug and (iv) uptitration within three months after the measurement.

Classes of lipid-lowering drugs were categorized according to ATC codes into statins, fibrates, bile acid sequestrants, nicotinic acid and derivatives and other lipid-lowering drugs (including ezetimibe). PCSK9 inhibitors were not considered, as these drugs are not prescribed by GPs in the Netherlands.

To assess medication adjustments, we compared prescription records up to three months after the LDL-cholesterol measurement to prescription records of up to

one year before cholesterol measurements. If the drug had already been prescribed previously, this was not registered as a new drug.

Variables

We explored which characteristics were associated with therapeutic inertia in univariable logistic regression models. Characteristics included age, sex, LDL-cholesterol level, near-target LDL (defined as LDL-cholesterol > 2.5 and < 3.5 mmol/L), atherosclerotic CVD, DM, dyslipidaemia, hypertension, smoking, obesity, renal insufficiency, heart failure, atrial fibrillation, family history of dyslipidaemia or CVD, muscle pain and use of a lipid-lowering drug in the previous six months. All characteristics were considered present when the date of registration was prior to the LDL-cholesterol measurement. Definitions are given in Supplementary Table 1.

In a multivariable model, we considered a priori defined characteristics potentially associated with therapeutic inertia, based on theory and literature.[20,21,23-25] For this model, we selected age, sex, LDL-cholesterol level, CVD, DM, hypertension, smoking, obesity and renal insufficiency. We did not select 'family history of CVD' for this model as the prevalence in our database was very low and it is known to be poorly reported in EHR.

Data analyses

To assess therapeutic inertia we used descriptive statistics for the total group and for different subgroups, as the indication for lipid-lowering drugs may vary among these groups, including patients with CVD, DM, dyslipidaemia and aged ≤ 70 years old. We used univariable and multivariable logistic regression models to study characteristics potentially associated with therapeutic inertia in the total group. The results were reported as odds ratios (OR) and corresponding 95% confidence intervals (CI). Two-sided P-values <0.05 indicated statistical significance. Statistical analyses were performed using R studio (version 3.5.1, Copyright (C) 2018 The R Foundation for Statistical Computing).

RESULTS

Patient characteristics

In the JGPN database, 78,952 patients with a history of CVD, DM or dyslipidaemia were identified (figure 1). In 21,310 (27%) of these patients LDL-cholesterol was measured in the past 12 months. Among these 6,854 (32%) patients had uncontrolled LDL-cholesterol (> 2.5 mmol/L) and were included in our study.

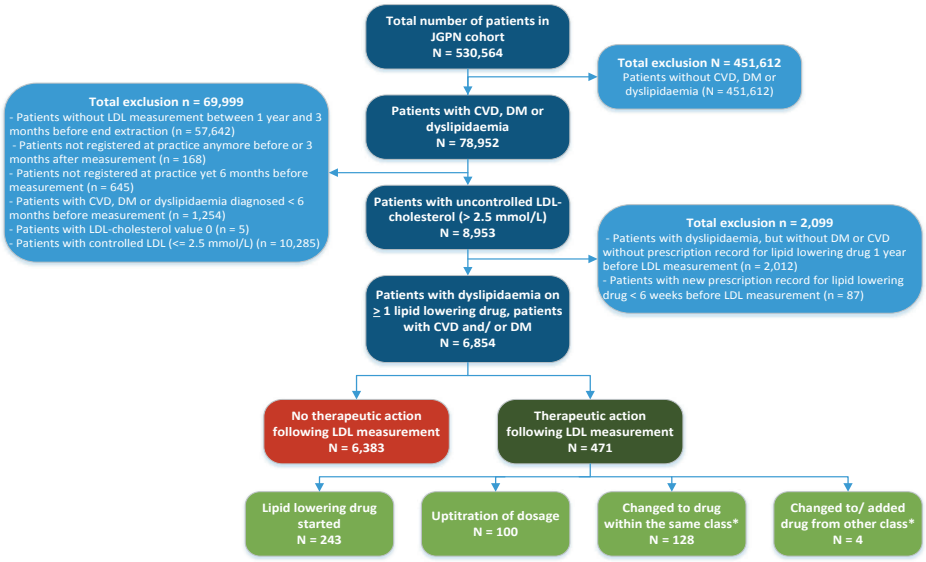

Figure 1. Flowchart of the selection of patients with dyslipidaemia, cardiovascular disease and/or diabetes mellitus within the Julius General Practitioners' Network cohort, divided in those with or without therapeutic inertia.

BP, blood pressure; DBP, diastolic blood pressure; GP, general practitioner; JGPN, Julius General Practitioners' Network; LDL, low density lipoprotein.
* Classes of lipid-lowering drugs included statins, fibrates, bile acid sequestrants and nicotinic acid and derivatives.

Mean age of these patients with uncontrolled LDL was 68 (SD 12.2) years and 57% were women (table 1). The median LDL-cholesterol level was 3.1 mmol/L (IQR 2.8 – 3.7). A history of CVD was present in 44%, DM in 45% and dyslipidaemia in 74%. Thirty percent were either a past or current smoker, 38% were obese and 62% had hypertension. Less than half of the patients (45%) used a lipid-lowering drug in the 6 months prior to the uncontrolled LDL-cholesterol measurement. Muscle pain was recorded in 9% of the patients.

Table 1. Patient characteristics

Characteristics	Total group n = 6,854	CVD n = 3,040	DM n = 3,087	Dyslipidaemia n = 5,098
Age in years, mean (SD)	68 (12.2)	71 (11.4)	67 (12.9)	68 (11.4)
Women (%)	3,900 (57)	1,685 (55)	1,720 (56)	2,920 (57)
LDL-cholesterol in mmol/L, median (IQR)	3.1 (2.8 – 3.7)	3.2 (2.8 – 3.8)	3.1 (2.8 – 3.6)	3.1 (2.8 – 3.7)
Near-target LDL-cholesterol* (%)	4,566 (67)	1,916 (63)	2,132 (69)	3,456 (68)
Cardiovascular disease (%)	3,040 (44)	3,040 (100)	816 (26)	2,142 (42)
Diabetes mellitus (%)	3,087 (45)	816 (27)	3,087 (100)	2,091 (41)
Dyslipidaemia (%)	5,098 (74)	2,142 (70)	2,091 (68)	5,098 (100)
Current or past smoker (%)	2,053 (30)	1,014 (33)	831 (27)	1,637 (32)
Obesity, BMI>30 kg/m^2 (%)	2,615 (38)	944 (31)	1,687 (55)	1,960 (38)
Hypertension (%)	4,221 (62)	1,998 (66)	1,826 (59)	3,257 (64)
Muscle pain (%)	647 (9)	290 (10)	304 (10)	514 (10)
Use of lipid lowering drug (%)	3,072 (45)	1,044 (34)	1,040 (34)	3,028 (59)

* Near-target LDL-cholesterol was defined as LDL-cholesterol > 2.5 and < 3.5 mmol/L.
BMI, body mass index. CVD, cardiovascular disease. LDL, low-density lipoprotein.

Therapeutic inertia

In 471 (7%) patients with uncontrolled LDL-cholesterol medication was adjusted within three months after the LDL-cholesterol measurement; (i) in 243 (52%) of these patients a lipid-lowering drug was started, (ii) 4 (1%) patients received a lipid-lowering drug from another class, (iii) 128 (27%) patients were prescribed a lipid-lowering drug within the same class and (iv) in 100 (21%) patients lipid-lowering drugs were uptitrated (figure 1). In 6,383 patients (93%), medication was not adjusted (table 2). Therapeutic inertia increased with age (figure 2). In patients at younger age (≤ 70 years) therapeutic inertia was slightly less prevalent compared to older patients (>70 years); 92% vs 95% respectively. Therapeutic inertia was more commonly observed in patients with a near-target LDL-cholesterol (>2.5 and < 3.5 mmol/L) than in patients with an off-target LDL-cholesterol (≥ 3.5 mmol/L); 95% vs 90% respectively. Therapeutic inertia did not differ between patients with a history of CVD, DM and dyslipidaemia (93%) and in younger patients (≤ 70 years) in these subgroups, therapeutic inertia was common as well (92%, 91% and 91% respectively). In patients with hypertension, in smokers (past or current) and patients with obesity, therapeutic inertia was present in 94%, 91% and 92%, respectively.

Table 2. Presence of therapeutic inertia in different subgroups

Group	N	Therapeutic inertia	No therapeutic inertia
Total	6,854	6,383 (93)	471 (7)
Age ≤ 70 years	3,961	3,634 (92)	327 (8)
Age > 70 years	2,893	2,749 (95)	152 (5)
Women	3,900	3,651 (94)	249 (6)
Men	2,954	2,732 (92)	222 (8)
LDL-cholesterol near-target*	4,566	4,317 (95)	249 (5)
LDL-cholesterol off-target**	2,288	2,066 (90)	222 (10)
Cardiovascular disease	3,040	2,838 (93)	202 (7)
Age ≤ 70 years	1,456	1,344 (92)	112 (8)
Diabetes mellitus	3,087	2,868 (93)	219 (7)
Age ≤ 70 years	1,819	1,662 (91)	157 (9)
Dyslipidaemia	5,098	4,734 (93)	364 (7)
Age ≤ 70 years	2,933	2,682 (91)	251 (9)
Hypertension	4,221	3,957 (94)	264 (6)
Current or past smokers	2,053	1,868 (91)	185 (9)
Obesity (BMI>30 kg/m^2)	2,615	2,414 (92)	201 (8)
Renal insufficiency	659	628 (95)	31 (5)
Heart failure	286	278 (97)	8 (3)
Atrial fibrillation	496	471 (95)	5 (25)
Family history of dyslipidaemia	28	26 (93)	2 (7)
Family history of CVD	178	164 (92)	14 (8)
Muscle pain	647	595 (92)	52 (8)
Use of lipid-lowering drug	3,072	2,873 (96)	199 (4)
No use of lipid-lowering drug	3,782	3,510 (93)	272 (7)

Values are presented as numbers (%).
* Near-target LDL-cholesterol was defined as LDL-cholesterol > 2.5 and < 3.5 mmol/L.
** Off-target LDL-cholesterol was defined as LDL-cholesterol ≥ 3.5 mmol/L
BMI, body mass index. CVD, cardiovascular disease. LDL, low-density lipoprotein.

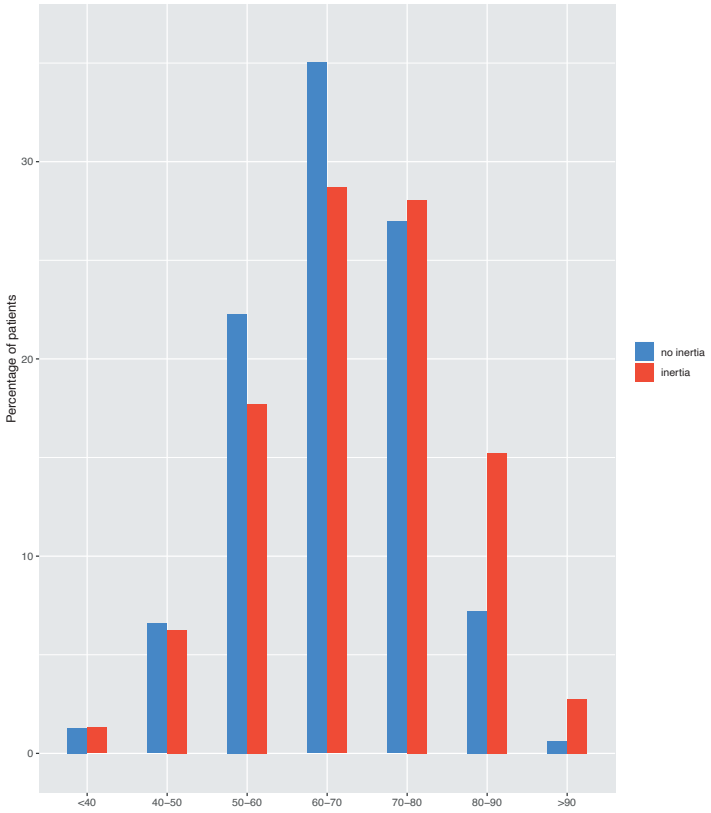

Figure 2. Distribution of age groups in patients with poorly controlled LDL-cholesterol, with and without inertia in the Julius General Practitioners' Network cohort.

Characteristics associated with therapeutic inertia

Univariable regression analyses showed that older age (OR per year 1.02, 95%-CI 1.01 to 1.03), near-target LDL-cholesterol (OR 1.86, 95%-CI 1.54 to 2.25), a history of hypertension (OR 1.28, 95%-CI 1.06 to 1.54), renal insufficiency (OR 1.55, 95%-CI 1.08 to 2.29) and heart failure (OR 2.64, 95%-CI 1.39 to 5.84) were positively associated with therapeutic inertia (table 3). The LDL-cholesterol level (OR per mmol/L 0.63, 95% CI 0.56 to 0.70), being a current or past smoker (OR 0.64, 95%-CI 0.53 to 0.78), and having obesity (OR 0.82, 95%-CI 0.68 to 0.99) showed an inverse association.

Multivariable regression showed that older age (OR per year 1.01, 95%-CI 1.01 to 1.02) was positively and independently associated with therapeutic inertia.

The LDL-cholesterol level (OR per mmol/L 0.63, 95%-CI 0.56 to 0.70) and being a current or past smoker (OR 0.66, 95%-CI 0.54 to 0.80) were inversely and independently associated with therapeutic inertia.

Table 3. Univariable and multivariable logistic regression of variables and their association with therapeutic inertia

	Univariable		**Multivariable**	
Factor	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Age per year	1.02 (1.01, 1.03)	< 0.001	1.01 (1.01, 1.02)	0.002
Women	1.19 (0.99, 1.44)	0.067	1.16 (0.95, 1.40)	0.14
LDL cholesterol per mmol/L	0.63 (0.56, 0.70)	< 0.001	0.63 (0.56, 0.70)	< 0.001
Near-target LDL*	1.86 (1.54, 2.25)	< 0.001		
Cardiovascular disease	1.07 (0.88, 1.29)	0.51	0.99 (0.80, 1.22)	0.92
Angina pectoris	1.15 (0.89, 1.50)	0.31		
Coronary heart disease	1.05 (0.78, 1.44)	0.76		
Ischemic stroke and/or TIA	0.97 (0.76, 1.27)	0.84		
Aortic aneurysm	1.18 (0.61, 2.65)	0.65		
Peripheral artery disease	0.94 (0.69, 1.30)	0.70		
Diabetes mellitus	0.94 (0.78, 1.13)	0.51	0.95 (0.77, 1.18)	0.66
Dyslipidaemia	0.84 (0.67, 1.05)	0.14		
Hypertension	1.28 (1.06, 1.54)	0.012	1.12 (0.91, 1.37)	0.27
Smoker (current or past)	0.64 (0.53, 0.78)	< 0.001	0.66 (0.54, 0.80)	< 0.001
Obesity (BMI>30 kg/m^2)	0.82 (0.68, 0.99)	0.037	0.83 (0.68, 1.02)	0.078
Renal insufficiency	1.55 (1.08, 2.29)	0.022	1.31 (0.90, 1.98)	0.17
Heart failure	2.64 (1.39, 5.84)	0.007		
Atrial fibrillation	1.42 (0.96, 2.20)	0.096		
Family history of dyslipidaemia	0.96 (0.29, 5.96)	0.96		
Family history of CVD	0.86 (0.51, 1.57)	0.60		
Muscle pain	0.83 (0.62, 1.13)	0.22		
Use of lipid-lowering drug	1.12 (0.93, 1.35)	0.25		

* Near-target LDL was defined as LDL-cholesterol > 2.5 and < 3.5 mmol/L.
BMI, body mass index. CVD, cardiovascular disease. LDL, low-density lipoprotein. TIA, transient ischemic attack.

DISCUSSION

In this cohort study, we showed that there is a gap between recommended lipid-lowering prescription and what is seen in daily primary care practice. In patients with a CVD, DM or dyslipidaemia in whom LDL-cholesterol was measured in the

last year, 32% had uncontrolled LDL-cholesterol levels (> 2.5 mmol/L) and less than half of these patients had a prescription for lipid-lowering drugs in the 6 months prior to an elevated LDL-cholesterol measurement, also in patients with a CVD. In 93% there was therapeutic inertia, i.e. LDL-lowering medication was not started or uptitrated. In different subgroups, rates of therapeutic inertia were high as well. Younger age, a higher LDL-cholesterol level and current/past smokers were independent determinants of intensified lipid-lowering medication.

Strengths and limitations

A strength is that we had access to a large dataset resembling real-world general practice in the Netherlands. However, as is common with routine care data, we had to depend on the information registered in the EHRs. Diagnoses were therefore considered present if recorded by GPs, and absent if not. This may have led to an underestimation of the prevalence of comorbidities.

Another strength is that we defined therapeutic inertia in 'favour of the GP', i.e. defined such that the number of false-positives was low. First, we selected a wide time window to enable adjustments of medication. Second, we excluded patients with a new, recent diagnosis of dyslipidaemia, CVD or DM, to allow enough time to achieve the treatment goals with lipid-lowering therapy. Third, we used a rather lenient LDL-cholesterol target of ≤ 2.5 mmol/L for all patients, following the Dutch guidelines on CVRM valid at that time,[7] while more recent guidelines apply stricter target levels.[9] All these choices reduced the risk of overestimation of therapeutic inertia.

A limitation of the study was the lack of data on the CV risk score, for patients without established CVD, making it less certain whether lipid-lowering drugs were definitely indicated in patients labelled as dyslipidaemia or DM. However, in patients with dyslipidaemia their CV risk was elevated and considered large enough by the GP to have initiated lipid-lowering medication, given their LDL-level >2.5 mmol/L while on lipid-lowering treatment (our inclusion criterion). In the majority of patients with DM, it was very likely that their CV risk was large enough as the mean age of this group was 67 years and according to the guideline fifteen years should be added to their age to calculate their CV risk.

We could not further classify patients above the age of 70 years into frailty categories, and thus were unable to assess whether a more lenient LDL-cholesterol target should indeed be considered.[7,26] However, we assumed that the GP would not measure a LDL-cholesterol in frail patients.

Comparison with existing literature

Our study expands the scarcely available evidence on therapeutic inertia in lipid-management in primary care. We showed that the management of dyslipidaemia could be improved, as we found low levels of lipid-lowering drug use (45%) and high levels of therapeutic inertia (93%) in patients with an uncontrolled LDL-cholesterol. The high level of therapeutic inertia was in line with some previous studies in primary care (80% to 86%)[27,28], whereas others reported lower rates, ranging from 44% to 70%.[20,29,30] The evidence on use of lipid-lowering drugs is more consistent across studies; most studies report rates between 31% and 69% in patients with elevated cholesterol levels, CVD or DM. [16,31-34] One study focusing on patients with established CVD in primary care reported higher rates (80%).[35]

It is speculative why we found such high levels of inertia compared to other studies. One explanation may be that rates of therapeutic inertia vary among studies because of different treatment goals and time windows.[36] Further, therapeutic inertia may partly be explained by certain patient characteristics. We assessed the association between a large number of patient characteristics and therapeutic inertia and found that patients at older age and with lower LDL-cholesterol levels had higher risk of therapeutic inertia, consistent with other studies.[21,25] Likely, reduced life expectancy, frailty and comorbidity may affect the clinical decision between GPs and patients not to increase or start treatment in older patients.[37,38] However, as this is allowed according to the Dutch CVRM guideline it should not be assigned as therapeutic inertia and this may have artificially increased our therapeutic inertia estimastes.[7] In contrast, the tendency for GPs to consider higher LDL-cholesterol values as adequately controlled is worrisome.[17] Probably, GPs are not convinced of the importance of attaining the LDL-cholesterol treatment goal. However, a qualitative study reported that most GPs (89%) agreed with the content of lipid treatment guidelines and reported to apply these in daily practice (81%).[39] Barriers to the implementation of guidelines seem to be of more importance, including lack of time and the complexity of guidelines.[39]

The patient characteristics that we assessed do not sufficiently explain the high rate of therapeutic inertia. Other reasons should be considered, including physician factors, patient factors and office system factors.

First, physician factors that contribute substantially to inertia include (i) physicians overestimating their adherence to guidelines, (ii) 'soft' reasons to avoid intensifying treatment, such as the perception that control was improving over time and (iii) physicians' lack of training on how to achieve goals (e.g. optimal dosages, how to deal with polypharmacy and statin intolerance).[17,36] It is unknown to what extent practice nurses contribute to inertia. However, studies have shown that in chronic care practice nurses probably provide equal or possibly even better quality of care compared to primary care doctors.[40]

Second, patient factors such as reluctance to taking lipid-lowering drugs, for example due to scepticism about statins or fear for side effects such as muscle pain, may have hindered adequate LDL-cholesterol control.[18,41,42] In some cases GPs may be incorrectly considered as reacting inadequately whereas it may be an appropriate shared decision with the patient to set an individual target, try lifestyle interventions first or to use no medication if patients are well informed about the benefits and risks.

Third, office system factors that may influence prescription include the "style of practice" (reactive or more proactive concerning prevention) and the primary care setting with variation in health care professionals involved in delivering chronic disease care, including practice nurses.[36,43]

Lastly, suboptimal communication between GPs and patients may be an important key to therapeutic inertia.[44]

Implications for research and practice

Guidelines become more complex and their complexity hinders adequate implementation.[45,46] The gap between evidence and practice is expected to increase further with the even stricter LDL-cholesterol target values for high-risk patients in the new guidelines.[9,47] Therefore, there is an urgent need for interventions to overcome inertia, including training of health care providers. Interventions that simultaneously target various factors contributing to clinical inertia (physician

factors, patient factors, and office system factors) seem promising.[36,48] Future studies should focus on improvement of the communication between GP and the patient, including the use of modern risk reduction tools, such as lifetime risk and the absolute risk reduction tool, and CVD free survival (available at https://u-prevent.com).[44,49-51] In such a patient-centred and lifetime benefit-based approach shared decision-making is crucial.[52] Importantly, a low awareness of CV risk in patients should be taken into account in the physician-patient discussion.[53] Enhancement of patients' involvement in their goal setting and achievement may be beneficial.[46] For example, feedback on care directly to patients may work synergistically by activating both the patient and the patient's physician to intensify treatment.[36] However, we have to consider that shared decision-making may also result in deliberate deviation from the guidelines if patients have their reasons not to adhere. At least, in order to further study therapeutic inertia, the efforts taken by the GP to discuss the treatment goals and reasons not to adhere should be recorded. Lastly, a decision support program in the EHR, including reminders and targeted feedback on performance, might facilitate lipid-management.[17,36]

Conclusion

The management of dyslipidaemia in primary care was suboptimal. In patients with dyslipidaemia, CVD or DM and an uncontrolled LDL-cholesterol only 45% used a lipid-lowering drug and in 93% therapeutic inertia was observed. There is an urgent need for effective interventions to overcome therapeutic inertia in primary care.

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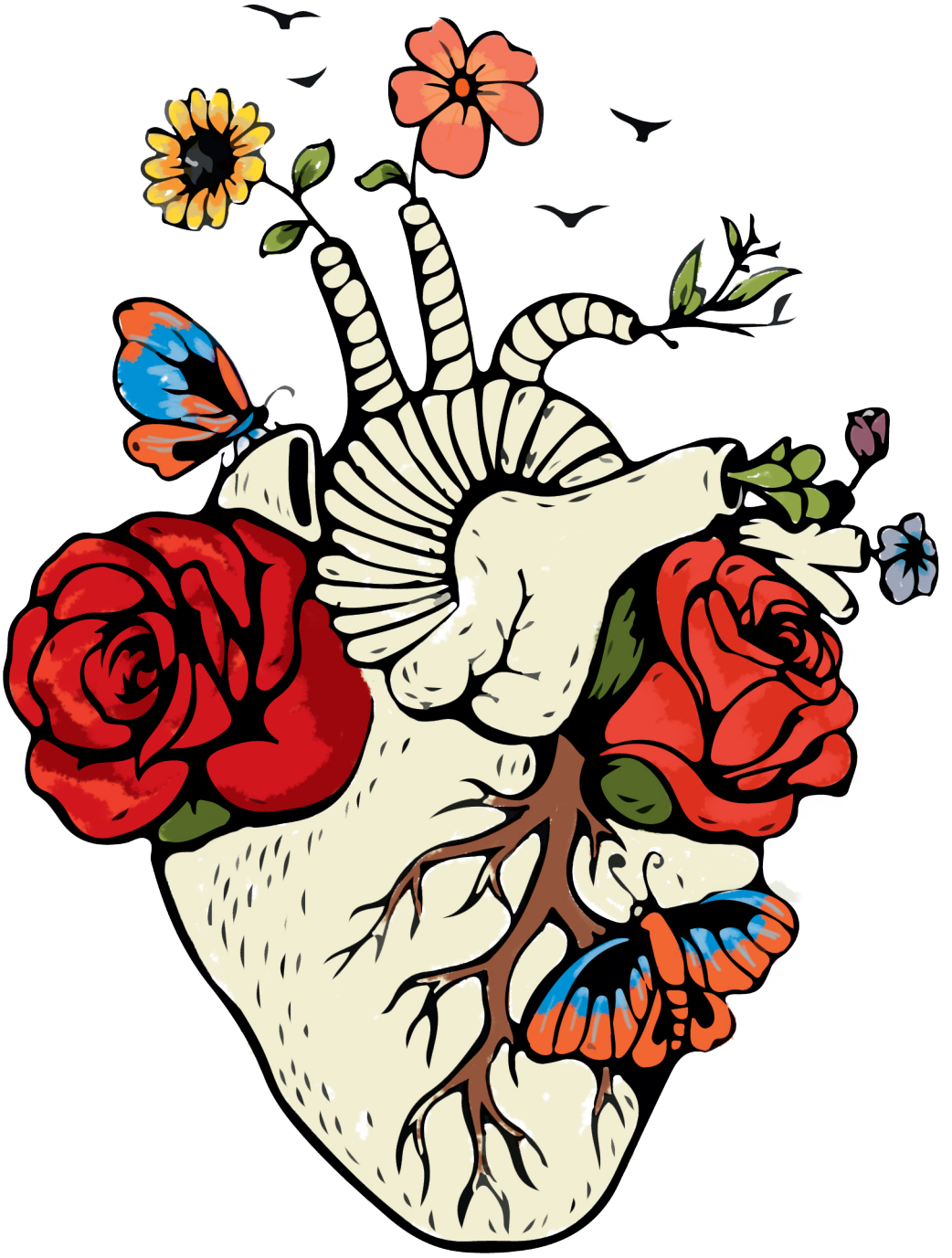
SUPPLEMENTARY TABLES AND FIGURES

Table S1. ICPC codes of medical diagnoses used in our study.

Variable	ICPC codes*	Used for selection of population
Dyslipidaemia	T93, T93.01, T93.02, T93.03, T93.04 or use of lipid-lowering drug	X
Diabetes mellitus	T90, T90.01, T90.02	X
Angina pectoris	K74, K74.01, K74.02	X
Coronary heart disease	K75, K76, K76.01, K76.02	X
Ischemic stroke and/or TIA	K89, K90, K90.03	X
Peripheral artery disease	K91, K92, K92.01	X
Aortic aneurysm	K99.01	X
Hypertension	K86, K87	
Smoker (current or past)	P17 or pack years mentioned in EHR	
Obesity	T82 or BMI >30 kg/m^2	
Renal insufficiency	U99.01	
Heart failure	K77	
Atrial fibrillation	K78	
Family history of CVD	A29.01	
Family history of hyperlipidaemia	A29.06	

BMI, body mass index; CVD, cardiovascular diseases; EHR, electronic health record; TIA, transient ischaemic attack, *All medical diagnoses are based on International Classification of Primary Care (ICPC) codes. As described, additional information was used for obesity, smoking and dyslipidaemia.



CHAPTER 8

General Discussion

MAIN FINDINGS OF THIS THESIS

This thesis aims to provide insight in the effectiveness of an integrated and multidisciplinary programme for cardiovascular risk management (CVRM) in primary care in a real-world setting and to describe the challenges of the implementation of CVRM in daily practice.

The main findings of the studies included in this thesis are as follows:

- In patients receiving integrated care for CVRM in general practice, blood pressure, body weight, low-density lipoprotein (LDL)-cholesterol and renal function were more often measured compared to usual care. In addition, in a higher proportion of patients in the CVRM programme dietary habits, physical activity and smoking cessation were discussed.
- One year of integrated primary care for CVRM following usual care did not result in better outcomes for systolic blood pressure (SBP) and LDL-cholesterol compared to usual care. Moreover, no differences were observed in cardiovascular (CV) risk, smoking rates, body mass index (BMI), physical activity, alcohol consumption, dietary habits, medication use, number of consultations during follow-up, satisfaction with delivered care, quality of life, anxiety and depression scores, morbidity and mortality.
- In patients with hypertension or hypercholesterolemia, receiving integrated CVRM in general practice, actions to optimize drug treatment seemed to be insufficient; antihypertensive medication often remained unchanged and in particular lipid-lowering drugs were seldom initiated or uptitrated when indicated.
- The CV risk and risk factor awareness in patients was poor, both in patients participating in the integrated CVRM programme and in patients receiving usual care. The adequacy of patient's perception of CV risk (factors) and lifestyle (advice) did not differ between the groups and there was a huge gap between lifestyle advice documented in the medical files and what was reported by patients.
- In patients with dyslipidaemia, known cardiovascular disease (CVD), or diabetes mellitus (DM) and uncontrolled LDL-cholesterol therapeutic inertia was very common (>90%).

- The integrated and multidisciplinary CVRM programme in primary care may have some effect on cardiovascular disease (CVD) related hospital care. After introduction of the programme, length of treatment at the hospital slightly decreased and the costs of hospital care decreased considerably, mainly caused by a decrease in the costs of hospital admissions. Importantly, non-CVD hospital care showed a much smaller decrease in the total costs of hospital admissions and even a small increase in the total costs of outpatient visits.

These findings indicate that the current integrated CVRM programme in the Netherlands is not effective in a real-world setting, during the first year after the start of the programme and that implementation of CVRM in daily practice according to the guidelines is insufficient.

It raises the question whether this integrated CVRM programme should be implemented and advocated further. Before these future considerations are discussed, the RE-AIM model, developed to evaluate preventive intervention, will be applied to assess the potential impact of integrated multidisciplinary CVRM programmes in daily practice, in the light of the results of studies included in this thesis and available evidence from earlier studies.

THE RE-AIM MODEL

A structural method to evaluate preventive interventions is the RE-AIM model, developed in 1999 by Glasgow et al.[1] It conceptualizes how well a programme works in the complex setting of the real world by addressing five dimensions: Reach, Efficacy/Effectiveness, Adoption, Implementation, and Maintenance. The RE-AIM model is summarized in Box 1. The idea behind RE-AIM is that efficacy-based research (typically randomised controlled trials within a selected patient population) oversimplifies reality by testing an intervention under controlled conditions; the results are not automatically applicable to daily practice. Many interventions that prove efficacious in randomized trials are much less effective in the real-world setting. The effectiveness of an intervention in daily practice is influenced by the interaction of the five dimensions of the RE-AIM model. Therefore, this model is a useful method to evaluate the impact of an intervention

and therefore provides a framework to determine whether an intervention should be continued in daily practice or not.

The first character of the acronym RE-AIM stands for **Reach** and concerns the extent to which the target population participates in the intervention and whether participants are representative. It gives an idea of the degree to which the intervention reaches the intended patients/ those who need it.

The second character stands for **Efficacy/Effectiveness**. Efficacy refers to the success of an intervention when it is implemented according to the guidelines under optimal conditions. Effectiveness reflects the success of an intervention when implemented in daily practice.

The third character stands for **Adoption**, the degree of acceptance of the intervention within the intended settings, including the health care staff. Assessment of adoption should include barriers for settings or staff to participate and adopt the intervention.

The fourth character stands for **Implementation** and concerns the extent to which a programme is delivered as intended and relates to adherence to guidelines within the intervention/ the intervention protocol.

The last character stands for **Maintenance** and describes whether an intervention becomes part of regular daily practice (institutionalized), reflecting long-term effects of the intervention.

Box 1. The RE-AIM model

Reach	Proportion of the target population that participated in the intervention
Efficacy/ Effectiveness	Success rate if implemented as in guidelines/ if implemented in daily practice
Adoption	Proportion of settings, practices, and plans that will adopt this intervention
Implementation	Extent to which the intervention is implemented as intended in the real world
Maintenance	Extent to which a programme is sustained over time

Reach

Ideally, when a programme is implemented, all indicated patients should be reached. Broad implementation is crucial for a programme to be successful. In the Netherlands, implementation of integrated CVRM is organized regionally. General practitioners (GPs) are member of one of the 115 regional care groups that coordinate the implementation of the programme. In the region of our study, the Zwolle region, approximately two third of the general practices chose to participate, the others continued usual care. For us, this provided the opportunity to compare integrated care for CVRM with usual care. However, apart from the research potential, it limited the degree to which the programme reached the intended patients. National participation rates are even lower; just 55% of the GPs participate in a CVRM programme coordinated by a regional care group.[2] Among GPs in Europe, 49% to 74% participate in a disease management programme for patients with risk factors for cardio metabolic disease.[3] It is not known why practices decide to participate or not. In the literature, limited time and access to appropriate resources in primary care, the lack of evidence of effectiveness/efficacy of interventions and the difficulty to achieve sustained behavioural change in patients are mentioned as barriers for healthcare professionals to deliver interventions aimed at changing patient behaviour in primary care.[4,5] It may be more attractive for GPs to participate in a more lean CVRM programme in primary care.

If a general practice participates in integrated care for CVRM this does not guarantee patient participation in the programme. In the ZWOT-CASE study, we did not assess the participation rate of patients in the CVRM programme. A report on CVRM programmes in the Netherlands in 2019 reported that almost 10% of the patients with CVD and 25% of the patients with a high CVD risk did not participate, despite implementation of an integrated CVRM programme by their GPs.[6] Reasons for patients at high CVD risk not to participate in the programme (anymore) included: significantly improved lifestyle habits, presence of dominant co-morbidity and insufficient motivation. In addition, limitations on inclusion rates installed by the health care insurer can be a reason not to include patients in the programme.[6] The same report disclosed that only 68% of CVD patients received CVRM by their GP while 23% was treated in the hospital, suggesting enough room for (additional) substitution from secondary to primary care.[6] CVRM requires

a lifelong, holistic and multidisciplinary approach. As GPs have a longstanding relationship with their patients, they are well suited to deliver this care.

Evidence for non-participation of patients and room for further substitution of secondary by primary CVRM care raises the question how patients are invited and motivated to participate in the programme. In Europe, 71% of GPs invite their patients to attend cardio metabolic disease risk assessments; less than half of these GPs use an active approach to invite their patients, while the others used an opportunistic approach.[3] Encouragement of patients to attend preventive programmes can feel as a waste of time when patients lack motivation and GPs might feel unable to deliver adequate preventive care to their patients.[7] Lack of time and resources make this task even more challenging and GPs increasingly question their role and obligation in preventive care.[7]

Efficacy/Effectiveness

Multidisciplinary integrated CVRM is a heterogeneous concept. An overall assessment of studies on the efficacy and effectiveness of integrated programmes for CVRM is hindered by heterogeneity in intervention strategies, target populations and outcomes. Unsurprisingly, the overall findings of studies on the effects of disease management programmes for CVRM are inconclusive.[8,9]

In the ZWOT-CASE study (chapter 4), one year of an integrated programme for CVRM did not improve blood pressure, cholesterol levels, lifestyle, quality of life and morbidity and mortality in a real-world setting. Some other studies showed similar disappointing results of CVRM programmes, while others found beneficial effects. Evidence published during the preceding 10 years, on the effect of multifactorial interventions to prevent CVD in primary care is summarized in supplementary table 1. We focused on systematic reviews and an individual study was only included if it was not already included in one of the systematic reviews. It is important to note that this overview itself is not a systematic review. We should be cautious to draw conclusions as most of the reviews reported extensive heterogeneity in results. Outcomes evaluated in the studies included lifestyle, intermediate outcomes such as CV risk factors, clinical outcomes (CVD events and mortality) and quality of life. Unfortunately, improvements in lifestyle, including smoking cessation, physical activity and dietary habits, were only reported in

a minority of the studies.[9-11] This is disappointing as especially smoking and insufficient physical activity are clearly associated with CVD events and mortality.

Some studies found beneficial effects on weight/BMI.[12] The effect on weight/BMI is less important, as it is not sure whether (small) reductions in weight/BMI translate into decreased CVD events and/or mortality from CVD.[13] Clinical significance of changes in weight/BMI should primarily be based on accompanying changes in lipid, blood pressure, and glucose metabolism.

Studies reporting positive findings of integrated CVRM care mainly found an effect on intermediate outcomes. Several reviews showed a small effect on blood pressure (figure 1).[10,12,14-17] These small effects on blood pressure are of value, as it is known that small reductions may result in longer-term reduction in CVD morbidity and mortality. Even a 2 mm Hg lower 'usual' SBP would confer a 10% lower risk of stroke mortality and 7% lower mortality from ischemic heart disease or other vascular causes.[18] LDL-cholesterol was less often reported as an outcome and the effects were less clear. The review of Snaterse et al. reported a small reduction in LDL-cholesterol of 0.23 mmol/L (95%-CI 0.10-0.36) in patients with coronary heart disease[9], whereas Lin et al. found no effect on LDL-cholesterol (-0.09 mmol/L (95% CI -0.14 to -0.04)) in CVD-free patients with at least one CV risk factor.[10]

The changes in intermediate outcomes were not reflected in reductions in CVD events and mortality in the findings of most studies that reported on these outcomes.[9,10,14,15] Possibly, the lack of an effect on clinical outcomes is due to (heterogeneity in) study designs, including selected study populations, a short follow-up period and small sample sizes, resulting in limited power to detect effects on these outcomes. Thus, the possibility of beneficial effect on these clinical outcomes cannot be ruled out.

As integrated care for CVRM is a multicomponent intervention, it would be interesting to define which components are associated with effectiveness. The benefits of drug treatments for lowering blood pressure and cholesterol are well known. It may explain the lack of positive findings in the ZWOT-CASE study, as therapeutic inertia was common. Alageel et al. argued that reductions in blood pressure and total cholesterol might be mediated by pharmacological treatment instead of the multiple health behavioural change (MHBC) interventions.[12] In

contrast, Álvarez-Bueno et al. reported that advice on nutrition and physical activity was the most effective intervention in producing risk factor modifications.[14] Glynn et al. assessed different interventions to reduce blood pressure and concluded that an organized system of regular follow-up had the greatest impact.[17] These heterogeneous conclusions indicate that it is very difficult to assign the most effective components of complex interventions. Moreover, we should be cautious to evaluate the contribution of individual components, as it does not take into account the synergistic effects of combining these components of complex interventions. Lin et al. showed that benefits on intermediate health outcomes are most robust for combined lifestyle counselling compared to interventions focused on diet or physical activity alone.[10]

Besides the different components, effectiveness may depend on the intensity of the intervention. Probably, the intensity of the integrated CVRM programme in the ZWOT-CASE study was too low with a median number of consultations of 2 (IQR 1 – 3) during 12 months. One study in the review of Álvarez-Bueno et al. associated the decrease in blood pressure and total cholesterol with high-intensity interventions.[14] In contrast, in the review of Alageel et al. no association was observed between intervention intensity (number of sessions and intervention duration) and intervention outcomes.[12] Lin et al. found that both medium- and high-intensity interventions were effective.[10] However, the intensity of the ZWOT-CASE study could still be too low, as it is not comparable with medium- (median of 5 contacts) and high-intensity (median of 16 contacts) interventions.[10] Regardless of whether interventions that are more intensive produce better effects, the question is whether such interventions are feasible in routine practice. In addition, adherence rates might decrease in case of higher intensity. Adherence, and therefore effectiveness, in trials may be higher than in real-world practice, especially for higher-intensity interventions. There is no evidence available on a minimum threshold of time/intensity of integrated CVRM care that is effective.

Lastly, only certain populations might benefit from integrated care for CVRM. Interventions in high-risk individuals have shown to be more effective than in lower-risk populations.[15] Patients are much more motivated to change their behaviours following a CVD event. Another explanation might be a “ceiling effect”, whereby it becomes more difficult to show benefits once a certain baseline level of care has been reached.[19] Strong associations have been observed between baseline

levels of risk factors and effectiveness, suggesting that interventions may be more effective in populations with particularly adverse risk-factor profiles.[15] Therefore, resources and time in primary care might be better spent on patients at higher risk of CVD.[20]

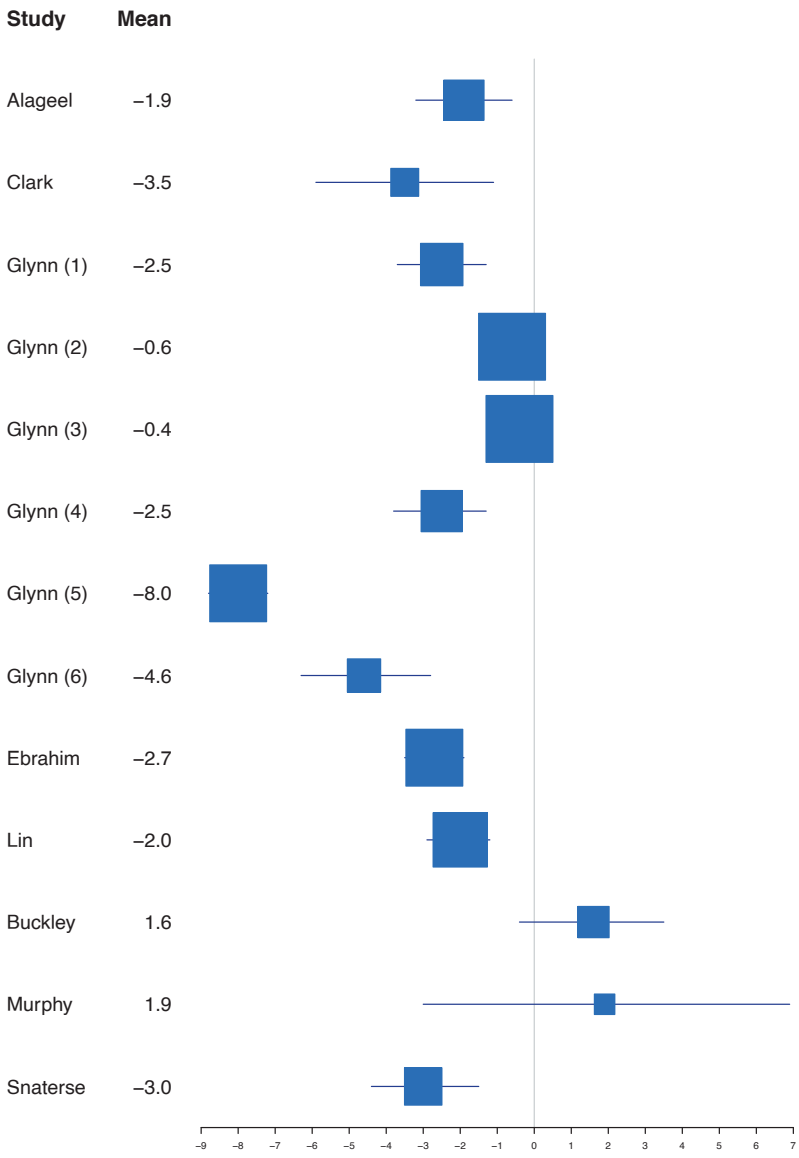


Figure 1. Overview of study findings. Mean difference in systolic blood pressure, including 95% CI

Adoption

The studies in this thesis did not focus on the degree of uptake of the integrated programme for CVRM. During the recruitment of general practices for the ZWOT-CASE study, I discussed arguments of GPs in favour and against participation in the programme during some informal conversations, reflecting the degree of acceptance of the programme by the GP. Interestingly, financial profit was often mentioned as argument to participate. Furthermore, some GPs participated because they expected no efforts were required to implement the programme as their CVRM care was already well organized. Others decided to participate based on the motivation to structure and improve CVRM in their practice. Some GPs who continued usual care argued that they expected no benefit from the intervention beyond usual care, as they already considered their CVRM care as very good. Other reasons not to participate in the programme included the increase in workload, requirements for reorganization of the practice, registration of data in an extra information system, and lack of evidence.

These various arguments suggest that the degree of uptake is influenced by a wide variety of factors such as team composition and engagement and organizational structures.[21] Accordingly, barriers and facilitators to adopt complex interventions in primary care are diverse as summarized by Lau et al. in a comprehensive review.[22] These barriers and facilitators concern (1) the external context in which implementation was taking place, (2) organizational features, (3) characteristics of health professionals involved and (4) characteristics of the intervention (figure 2).

Ad (1). At the level of external context, especially the 'fit' between the intervention and the context seems to be of great importance for successful implementation. For example, access to appropriate resources, including well-integrated clinical software, enough time and adequate funding are necessary.[4,23]

Ad (2). At the organizational level, a bottom-up interdisciplinary collaboration approach across the health care system seems to be essential for integration of health care.[24] Diverse health care professionals must be strongly connected to disease management programmes to provide effective, holistic care that embraces all facets of the Chronic Care Model, including high quality of communication and task integration.[25] A high degree of perceived integration by all stakeholders is associated with effectiveness.[24] In an observational study, a favourable perception

by team members regarding interdisciplinary collaboration (nurse, nutritionist, kinesiologist, pharmacist, social worker and GP) was associated with better patient outcomes (SBP, diet, quality of life) and less patient withdrawal from the CVRM programme.[26] At the same time, the multidisciplinary character of CVRM programmes make a successful implementation more complex and challenging, as all involved disciplines together are responsible for its success.[27] In the process evaluation of the ZWOT-CASE study we had no data to analyse multidisciplinary collaboration. However, the lack of effectiveness of integrated CVRM in our study raises the question whether the programme involved genuine collaboration across interdisciplinary teams. Instead of integrated care, referring patients from one to the other discipline may have occurred. Such a fragmented approach may hinder a more holistic, patient-centred response and, hence, effective CVRM.

Ad (3). At the level of the health care professional, the knowledge of and attitude towards integrated CVRM care of involved health care providers plays an important role. Although health care professionals generally believe that prevention of CVD is important, they do not always feel competent to deliver CVRM.[7,28,29] Furthermore, the engagement of health care professionals in CVRM varies according to the level of interest in CVD prevention.[23] A strong interest in CVD prevention by one particular staff member can lead to a high level of engagement with the intervention.[23]

The process evaluation of the ZWOT-CASE study (chapter 5) showed that CV risk factors and lifestyle were more often assessed and discussed. At the same time, therapeutic inertia was very common and CV risk and risk factor awareness in patients was very poor. It is known that CVD prevention is experienced as a difficult task.[23] It might be that PNs and GPs were able to adopt 'the easiest part' of the programme, checking boxes of CV risk factors and lifestyle. Following the guidelines and a real conversation with patients about their CV risk requires training, experience and enough time. Therefore, continuous professional development, using training tailored to the different needs of individual health care professionals and practices, is necessary to build the competence of the team. In addition, effective interdisciplinary collaboration between health care professionals should be supported by training relational competence.[25] This may increase their ability to visualize the larger process and recognize their

interconnectedness in accomplishing their shared goal: prevention of CVD in patients at high risk.

Ad (4). Characteristics of the intervention that affect adoption include the complexity of the intervention, evidence of benefit, applicability and relevance, clarity, practicality and utility of intervention, customisation of intervention and compatibility with the currently used information system.[22] Interventions with a complex nature are associated with lower adoption rates.[22] This may also apply to CVRM programmes. Guidelines for CVRM are experienced as complex and their complexity hinders adequate implementation.[30,31] It may be one of the explanations why we found high levels of therapeutic inertia in our studies. Furthermore, lack of evidence on effectiveness can impede adoption of an intervention, as was mentioned by GPs in the ZWOT-CASE study. Implementation of an intervention can be facilitated by a good fit between intervention characteristics and the practice organization and provider needs.[22]

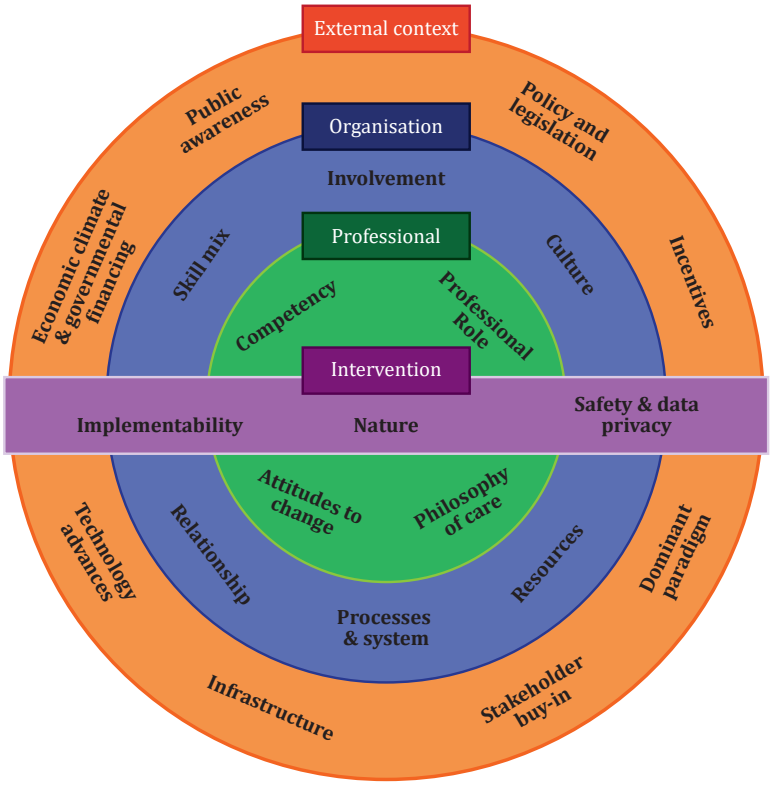


Figure 2. Barriers and facilitators to adopt complex interventions in primary care.[22]

Implementation

The success of CVRM programmes largely depends on the degree of implementation of the programme in the real world. In chapter 5 of this thesis, we found that some aspects of care improved in the integrated care programme for CVRM (CV risk factors were more often measured and lifestyle advice was more often discussed), which may suggest that the programme was well implemented. However, despite these improvements in process measures, a clinical benefit or an increased CV risk and risk factor awareness in patients was not achieved. Moreover, therapeutic inertia was a common phenomenon, both in the ZWOT-CASE study as well as in patients registered in the Julius General Practitioners' Network (chapter 7). It makes clear that guidelines are insufficiently implemented in daily practice, also when integrated care programmes for CVRM are initiated.

Although most GPs are aware of current guidelines, only 54% to 81% of GPs report frequent use of one of the CVD prevention guidelines.[32,33] Besides, only 18% of GPs across five European countries believe that guidelines are implemented to a major extent.[33] In chapter 2 of this thesis, we commented on the new European guideline on CVD prevention. Key messages in the guideline included that CVD prevention asks for a personalized approach and that estimation of the CV risk and assessment of lifestyle factors should regularly be repeated.[34] We stated that implementation of all recommendations in this new guideline would be challenging and requires more guidance for GPs as well as enough consultation time, ICT support, adequate reimbursement, a trained multidisciplinary team and support by concordant actions of surrounding organizations, insurance companies and government. Many of these requirements are mentioned in the literature as barriers to the implementation of guidelines.[27,32,33,35-37] One may wonder whether barriers to implementation of the integrated CVRM programme in the region of Zwolle were considered and whether measures to overcome these were taken. Prior to the implementation of the programme, GPs had to declare that they act in accordance with the most recent relevant national care standards. Furthermore, the care group provided a multidisciplinary information system for integrated care (KIS, Portavita®) and participating GPs agreed to register patient data in the KIS. Based on the data in this KIS GPs received yearly feedback on the state of cardiovascular risk factors of their CVRM population, but not achieving treatment goals had no consequences. It is very likely that barriers were still present during implementation of the integrated care programme. It may be that the programme

was implemented too much top-down, not taking into account the needs of individual practices. Alternatively, the programme could be still in the starting-phase of implementation and its evaluation (the ZWOT-CASE study) was timed too early. The process of developing an implementation strategy may take up to several years to complete and should consist of certain basic steps.[27] One may doubt whether these steps were taken prior to and during the implementation of the integrated CVRM programme. These steps pertain to several important questions; were GPs and PNs sufficiently trained or did they lack adequate knowledge and skills?; were guidelines clear enough or were they too comprehensive and should they be simplified for use in daily practice?; was there enough consultation time or were patients too complex, requiring more time and effort to be adequately counsel?; was the KIS supportive in daily practice or was it too time consuming to register all the data, without providing decision support and reminders in return? It would be useful to evaluate these steps in depth to improve the implementation of the CVRM programme.

Maintenance

Evidence of the long-term effects of an integrated programme for CVRM are crucial to decide whether the programme should be continued or not. The follow-up times of the studies in this thesis were relatively short. However, other studies in primary care had a longer follow-up and many of these showed that CVRM programmes were not successful in the long term either[38-40], whereas in a simulation study a primary care lifestyle intervention appeared to be (cost-)effective up to lifelong.[41]

Interestingly, some large Swedish studies, comparing regions with and without CVD prevention programmes in primary care, have shown positive results with regard to their ability to reduce CVD risk. In the 1980s, a regional prevention programme in the community and primary care led to significantly decreased CVD mortality compared to the whole of Sweden after 8 years.[42] Another CVD prevention programme (the Vasterbotten Intervention Programme) in Sweden between 1990 and 2006 was able to reduce all cause and CVD mortality for people aged 40-70 years.[43] More recently, another Swedish study showed that a CVD prevention programme (The Sollentuna Prevention Program) in primary care for patients with at least one CV risk factor but no established CVD, focusing on promotion of physical activity and healthy lifestyle, was associated with lower risk of CV events (12%), CV deaths (21%) and all-cause deaths (17%) after two

decades.[44] Importantly, the interventions in these studies combined an individual approach in primary care with community prevention strategies. This might be a successful combination, as the increased awareness of the need for CVD prevention in the entire population may very well facilitate CVRM care in general practice.[43]

To achieve effects over a longer period, sustained interventions seem important, preferably by using an integrated approach across the community and primary care. Behavioural changes are difficult to persist without continuation or intermittent exposure to interventions. A short (one-time) intervention is not likely to be effective on the longer-term,[45] and several studies have shown an increasing programme effect over time.[46] It may take time to improve quality of care and outcomes of CVRM. Intensive targeted feedback to general practices participating in an integrated care programme for CVRM has been shown to improve this process.[47] Possibly, a learning healthcare system, including a continuous cycle of targeted feedback based on real-time clinical data, taking into account patient preferences, and followed by implementation of potential improvements, might enhance and sustain cardiovascular risk factor control.[48] Further, a stable government policy and long-term agreements with health care insurers are important to improve CVRM programmes and let these become part of daily practice.

The RE-AIM model and integrated CVRM care programmes: conclusions

Although CVRM programmes have been implemented in many regions in the Netherlands, the evidence for their effectiveness in the real world shows disappointing short-term results. Some randomized controlled trials indicate a small positive effect on blood pressure and cholesterol levels. However, these findings are usually not accompanied by evidence of reductions in CVD events and mortality in the short- and long-term. Possible explanations for the lack of clear effectiveness may be poor guideline adherence, as shown by the prevalence of therapeutic inertia in high-risk populations. Further, lack of time and resources, insufficient training of involved health care professionals and inadequate multidisciplinary collaboration across the health care chain may have hindered effective CVRM.

Interventions that are more intensive are expected to improve the effectiveness of CVRM programmes. However, given the existing barriers to adequate implementation of the programme, increasing the intensity of the CVRM programme does not seem feasible in daily practice. Rather, a more lean CVRM programme in primary care with a focus on motivated and high-risk patients could be more promising.

Currently, by participating in a CVRM programme, GPs take responsibility for CVD prevention in a large group of patients at risk. The question is whether GPs are faced with an unfeasible task. Is primary care the right place for screening for patients at increased CV risk and implementing a comprehensive CVRM programme for all patients with increased risk of CVD?

POSSIBLE SOLUTIONS

'Right care in the right place'

Given the lack of effect, further implementation of the current CVRM programme in its current form is questionable. However, we should not depreciate the potential of CVRM programmes to reduce CV risk, but look for possible solutions to improve their impact. Currently, primary care plays a central role in CVRM programmes. The question is which tasks of CVRM, including screening, belong within the scope of primary care. Last year, Dutch GP discussed their core values during the "Woudschoten conference". Only 15% of GPs consider prevention in patients without established disease as one of their core tasks. A survey amongst patients showed that they agree that prevention should not be the primary task of the GP. Certain parts of CVRM may be better conducted in settings other than primary care. Therefore, collaborative efforts from various organisations beyond general practice are needed, including public health services and governmental organisations, to optimise CVRM.

I will discuss several options to reshape CVRM, considering both interventions beyond the limits of general practice as well as interventions to increase the quality of CVRM care in primary care.

Public health services and general practice

The efforts of general practices could be supported by involvement of Municipal Health Services in the prevention of CVD. General practices and Municipal Health Services have different qualities and competencies. Therefore, an integrated CVRM programme across these settings might be promising.

In the Netherlands, Municipal Health Services perform a number of public health tasks, including youth health care, infectious disease control and, most, vaccinations. Public health nurses and physicians in social medicine provide this care. Each Municipal Health Service is responsible for on average 600,000 residents. Besides, the network of Municipal Health Services includes many organizations in the municipality, creating opportunities for widely implemented interventions. In this way, the reach of citizens is optimal, in contrast to primary care CVRM programmes where reach of patients is dependent on participation of the general practice. Thus, Municipal Health Services are the designated organizations to apply prevention strategies at the population level. Further, Municipal Health Services are very well aware of problems in their different regions and districts and trained to reach people who live on the fringes of society, a population with a high prevalence of CV risk factors. Moreover, they have ample experience in the assessment of social problems, an important barrier to lifestyle changes. Physicians in social medicine are obviously less experienced in curative care, but CVRM interventions, including preventive medications, in individual men and women, might be considered an additional task.

General practitioners have a longstanding relationship with their patients, which gives them insight in their medical history, family structure and living circumstances. Thereby, guiding patients in the light of all above-mentioned factors is the key quality of general practice. In addition, medical specialists are easily accessible by GPs.

Given the different qualities of general practices and Municipal Health Services, some aspects of CVRM may be better performed by one and other parts by the other. I will give some currently non-evidence-based, suggestions for such a division of tasks pertaining to cardiovascular risk assessment, lifestyle modification and treatment of high-risk patients.

Outsourcing cardiovascular risk assessment

Systematic cardiovascular risk assessment in primary care in patients not yet known with risk factors is not cost-effective in the short- and long-term.[49] Therefore, primary care seems not to be the best setting for cardiovascular risk assessment. However, the European Guideline on cardiovascular disease prevention states that systematic CV risk assessment may be considered in men >40 years of age and in women >50 years of age or post-menopausal with no known CV risk factors.[34] It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment. Besides, the Dutch CVRM guideline recommends a mixture of opportunistic and systematic screening.[50] This poses the question who should be responsible for such screening activities.

Given their broad experience in public health, Municipal Health Services could play an important role in systematic screening. Similar to the health checks in children, Municipal Health Services could offer health checks to the population of an age of 40 years and older. These health checks should include an assessment of CV risk factors and lifestyle, but also assessment of social welfare and someone's financial situation, known as important barriers to a healthy lifestyle. Public health nurses could play a crucial role in these health checks. For healthy individuals this screening should be repeated every 5 years. Further research needs to be carried out to establish the value of repeated screening and the optimal time frame.

The GP can continue with opportunistic screening during consultations for some other reason in the primary care practice. Therefore, the GP is the key person to identify patients who will not be identified by systematic screening, for example younger patients or patients who avoid screening. Sufficient time and financial resources are needed to stimulate GPs to provide this opportunistic screening.

Lifestyle modification and treatment of high-risk patients: capacity issues

If GPs adhere to the guidelines, they would identify too many patients at risk of CVD who need further lifestyle advice or pharmacotherapy. Surprisingly, in many regions in the Netherlands, GPs are confronted with the limitation of, unjustified, inclusion rates for patients in the CVRM programme imposed by health care insurers. Consequently, not all patients who are eligible and may benefit from it

can be included in reimbursed CVRM programme. Further, lifestyle modification is a difficult and time-consuming task for GPs.[23] This poses the question whether general practice is the optimal place to treat all patients who need lifestyle modification or pharmacotherapy. With regard to lifestyle modification, Dutch general practices already have the opportunity to refer patients at high risk of CVD to a combined lifestyle intervention with coaches who can advise patients about healthy dietary habits, physical activity and other lifestyle factors such as stress. However, not all practices have access to or are aware of such combined lifestyle interventions, as is reflected by a Dutch monitor that reported that just over 7,000 people participated in this lifestyle intervention between October 2019 and April 2020, despite the intervention being reimbursed by health care insurance companies.[51] GP's access to and awareness of this combined lifestyle intervention option could be improved.

Alternatively, Municipal Health Services could be involved in lifestyle modification, after they identified patients who need further lifestyle advice during the systematic screening. This lifestyle counselling could be part of the screening visit. If more intense lifestyle modification is needed, Municipal Health Services could refer patients to lifestyle interventions, such as the combined lifestyle intervention. This could increase participation in such interventions.

Besides, Municipal Health Services could play a role in pharmacological therapy in individual patients. For example, patients without established CVD but at increased risk of CVD could be managed by physicians in social medicine, including prescription of preventive medication such a blood pressure and lipid lowering drugs and smoking cessation therapies. Physicians in social medicine could spend more time on high quality communication on risk factors and lifestyle. This may increase patients' awareness of their CV risk, adherence to medication and improve outcomes of CVRM.

Treatment of patients with established CVD and complex patients should continue in primary care, including patients with comorbidities and polypharmacy and young patients with a high absolute CV risk. In this way, the CVRM programme in primary care will be a lean variant of the current programme.

Quality improvement

A few measures may lead to a better quality of CVRM in primary care.

First, a lean CVRM programme in primary care, focused on patients with the highest CVD risk will give more room for improvement in quality of care. Fewer patients will be included in such a programme, making it manageable for the general practice to keep an overview. An important condition is that CVRM patients with lower CVD risk are managed adequately elsewhere.

Second, according to a learning healthcare system, continuous data collection and analyses could guide primary care in optimizing performance at the practice level. To support this, a continuous targeted feedback on performance regarding adherence to CVRM guidelines should be implemented. For example, a built-in feedback program in the electronic health system could send reminders or warnings when targets are not achieved and offer suggestions for adjustment of treatment. Such programs already exist, but could be more sophisticated and better suited to a patients' individual situation. In addition, continuous professional development in the context of CVRM for primary care health care providers, tailored to their personal needs, should get more attention.

Third, general practices could offer optimal versus regular CVRM care dependent on the motivation of a patient. A discount on health insurance costs could be used to motivate patients to participate in the optimal programme. In case of a lack of motivation in patients, targets will not be achieved. However, the responsibility of GPs for the health of their patients has its limits. If a patient is motivated, a contract could be signed that both GP/PN and patient will put optimal effort in optimizing CVRM care. Monitoring the adherence to lifestyle advices and medication could be considered to check whether patients' motivation actually translates into action, but is notoriously difficult and poses huge privacy and ethical issues. Continuous telemetric risk factor control, for example by devices such as step counters or activity trackers, could be provided to patients, including data transmission to their electronic health record.[52] However, adherence to a healthy diet or medication are more difficult to monitor. We should find a balance between trusting and monitoring patients.

Lastly, the process of the CVRM programme in primary care should be critically evaluated on a regular base, including actions taken by health care providers. This may increase the sense of ownership of the programme.[53] To stimulate this further, financial rewards could be made dependent on the performance of a general practice. The quality of performance should not be based on outcomes such as blood pressure or LDL-cholesterol targets, as these measures are not only dependent on actions taken by health care providers, but also on patients' motivation and compliance. However, process measures, such as delivered care and therapeutic inertia, could be good indicators of the quality of performance. For example, health care providers could report the given lifestyle advice and treatment recommendations to patients in the electronic health record, including the efforts that are taken to motivate patients. By reporting these actions, it could be assessed whether general practices have taken all steps as recommended in the guidelines. If so, the quality of performance should be considered as an indicator of success, independent of achieved treatment targets. This quality of performance could be used to assign a quality mark to well-performing practices.

Promotion of CVD prevention by governmental organisations

The efforts of primary care to prevent CVD require support from governments and society. Recently, the government has shown to be able to promote, install and finance preventive interventions during the urgent coronavirus pandemic. It has become clear that unhealthy lifestyle factors are related to worse COVID outcomes.[54] However, in the pandemic of lifestyle-associated diseases such as CVD the government has lacked a sense of urgency in the past decades. This is of major concern, as the burden of lifestyle diseases is huge, especially in the long-term. The coronavirus and its economic consequences have worsened the problem, as people became less physically active and experienced more stress.[55] At the same time, lifestyle diseases are risk factors for covid-19 and a healthy lifestyle protects against the coronavirus disease.[56,57] Therefore, the covid-19 pandemic emphasizes the importance of a healthy lifestyle and the need to tackle the pandemic of lifestyle diseases, including CVD.

As for most people it is very difficult to change their behaviour, the government could implement policies that nudge people into a healthy lifestyle.[58] Health protection through national fiscal and legislative changes that aim to reduce smoking, encourage a healthy diet, and increase facilities and opportunities for

physical activity, should have high priority to deal with the increasing burden of CVD. Basic health insurance should include reimbursement for lifestyle interventions. Lastly, the government must take back control of CVD prevention. Policies on prevention of CVD should aim at integrated care across the entire health care chain.

Future research

Although randomized trials to assess the long-term effects of CVRM integrated care programmes are needed, it is unlikely that such, logistically challenging and very expensive trials, will be performed in the near future. Non-experimental comparisons using before-after designs or external control groups are more feasible, but do have, other, inherent limitations, as was shown in the ZWOT-CASE study. Qualitative studies could provide additional information, by giving more insight into the 'black box' of complex interventions for CVD prevention. For example, it would be interesting to examine how health care providers communicate treatment advice and how patients perceive and respond to the advice. Further, better understanding the multidisciplinary cooperation could be very helpful in improving integration of future interventions. Finally, the consequences of strategies such as pay-for-performance should be evaluated.

CONCLUDING REMARKS

General practitioners should reconsider what role they want to play in CVD prevention, as the CVRM programme in its current form is not effective enough. My vision regarding future CVRM programmes is that general practices will continue to play a key role, but with an increased focus on high-risk, complex and motivated patients and more attention being payed to the quality of performance in primary care. To make this possible, Municipal Health Services could be involved more closely in cardiovascular risk assessment, lifestyle modification and treatment of individual, typically, low-risk patients. Moreover, it is time that the government recognises the urgency of the pandemic of lifestyle-associated diseases and much more actively stimulates a healthy lifestyle across the population. All these concordant actions could work synergistically and increase the success of CVRM.

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Supplementary table 1. Evidence on the effect of multifactorial interventions to prevent cardiovascular disease in primary care

First author (year of publication)	Design	Target population	Intervention	Mode of intervention delivery	Density of the intervention
Álvarez-Bueno (2014)	Systematic review of 8 reviews including 219 studies (mainly RCTs)	CVD-free adults, aged 18 – 75 years	Multifactorial interventions, targeting ≥ 1 CV risk factor, and implementing ≥ 1 type of intervention (education, behavioural strategies, psychological interventions) and may be combined with drug therapy	Individual sessions; Group sessions; Use of written or audio-visual educational materials; Follow-up e-mail and telephone contact; Use of mass media	NA
Alageel (2017)	Systematic review of 31 RCTs	CVD-free adults, aged >18 years old	Multiple health behaviour change (MHBC) interventions, aimed at reducing CVD risk by intervening on two or more risk behaviours (physical activity, diet, alcohol consumption, use of stress management and smoking). Comparators were usual care or less intensive interventions.	Individual sessions; Group sessions; Telephone sessions; Written materials	Number of sessions: 3 - 56 (median 6) Time: 45 min to 2.5 hours (median=300 min)
Clark (2010)	Systematic review of 14 RCTs	Adults aged > 18 years with hypertension with or without antihyperten-sive drugs	Nurse led interventions designed to improve blood pressure	Face to face visits	NA

Professionals	Setting	Follow-up	Outcomes	Effect size	Authors' conclusion
Nurses; Doctors; Dieticians; Behavioural scientists; Exercise instructors; Physiotherapists; Psychologists; Cooks	Primary care or community settings	≥ 6 months	Total mortality	OR close to 1 or no clear effect	Multifactorial community interventions improve cardiovascular risk factors and have a small but potentially important effect on mortality. These interventions seem to be more effective in the at-risk population and when they are carried out at a high level of intensity.
			CVD mortality	OR close 1 or no clear effect	
			CVD morbidity	Small or no effect	
			SBP	−0.7 to −4.2 mm Hg	
			DBP	−1.5 to −4.2 mm Hg	
			Total cholesterol	−0.01 to −0.24 mmol/L	
			Smoking	No clear effect	
			BMI	No clear effect	
General practitioners; Nurses; Dieticians; Others	Primary care	≥ 12 months	SBP	−1.86 mm Hg (95% CI −3.17 to −0.55; p=0.01)	MHBC interventions delivered to CVD-free participants in primary care did not appear to have quantitatively important effects on CVD risk factors. Better reporting of interventions' rationale, content and delivery is essential to understanding their effectiveness.
			DBP	−1.53 mm Hg (95% CI −2.43 to −0.62; p=0.001)	
			BMI	−0.13 kg/ m^2 (95% CI −0.26 to −0.01; p=0.04)	
			Total cholesterol	−0.13 mmol/L (95% CI −0.19 to −0.07; p<0.001)	
			Smoking	0% (95% CI −0.02 to 0.01; p=0.66)	
			CVD risk (SCORE)	0.12% (95% CI −0.37 to 0.61; p=0.61	
			Diet	No clear effect	
			Physical activity	No clear effect	
			Alcohol consumption	No clear effect	
Nurses; Nurse prescribers; Nurse practitioners	Primary care	NA	SBP change from baseline	−3.5 mmHg (95% CI −5.9 to −1.1; p = 0.16)	Nurse led clinics in primary care achieved greater reductions in systolic and diastolic blood pressure compared with usual care.
			DBP change from baseline	−1.9 mmHg (95% CI −3.4 to −0.5; p = 0.12)	

Supplementary table 1. (Continued)

First author (year of publication)	Design	Target population	Intervention	Mode of intervention delivery	Density of the intervention
Glynn (2010)	Cochrane review of 72 RCTS	Patients with hypertension	Interventions aimed to improve the control of high blood pressure:	NA	NA
			(1) self-monitoring		
			(2) educational interventions directed to the patient		
			(3) educational interventions directed to the health professional		
			(4) health professional (nurse or pharmacist) led care		
			(5) organisational interventions that aimed to improve the delivery of care		
			(6) appointment reminder systems		
Ebrahim (2011)	Cochrane review of 55 RCTs	CVD-free adults with or without a high risk of CVD	A health promotion activity to achieve behaviour change; more specifically counselling or educational interventions, with or without pharmacological treatments, which aim to alter more than one cardiovascular risk factor (i.e. diet, reduce blood pressure, smoking, total blood cholesterol or increase physical activity).	Workshops; Lectures; Individual sessions; Personal counselling; Provision of written material; Assignments; Shopping tours and cooking sessions	4 to 54 sessions over periods of two weeks to three years

Professionals	Setting	Follow-up	Outcomes	Effect size	Authors' conclusion
NA	Primary care, outpatient or community setting	NA			Family practices and community-based clinics need to have an organized system of regular follow-up and review of their hypertensive patients. Antihypertensive drug therapy should be implemented by means of a vigorous stepped care approach when patients do not reach target blood pressure levels. Self-monitoring and appointment reminders may be useful adjuncts to the above strategies to improve blood pressure control but require further evaluation.
			SBP	-2.5 mmHg (95% CI -3.7 to -1.3)	
			DBP	-1.8 mmHg (95% CI -2.4 to -1.2)	
			BP control	OR 0.97 (95% CI 0.81 to 1.16)	
			SBP	-0.57 mmHg (95% CI -1.22 to 0.08)	
			DBP	0.46 mmHg (95% CI 0.07 to 0.86)	
			BP control	OR 0.83 (95% CI 0.75 to 0.91)	
			SBP	-0.4 mmHg (95% CI -1.1 to +0.2)	
			DBP	-0.4 mmHg (95% CI -1.1 to +0.3)	
			BP control	0.85 (95% CI 0.80 to 0.90)	
			SBP	-2.52 mmHg (95% CI -3.77 to -1.27)	
			DBP	-1.49 mmHg (95% CI -2.02 to -0.96)	
			BP control	OR 0.30 (95% CI 0.24 to 0.38)	
			SBP	-8.00 mmHg (95% CI -8.81 to -7.18)	
			DBP	-4.27 mmHg (95% CI -4.65 to -3.89)	
			BP control	0.45 (0.41, 0.48)	
			Lost to follow-up	OR 0.4 (95% CI 0.3 to 0.5)	
			SBP	-4.56 mmHg (95% CI -6.31 to -2.81)	
			DBP	-0.53 mmHg (95% CI -2.01 to 0.95)	
			BP control	OR 0.54 (95% CI 0.41 to 0.73)	
Physicians; Nurses; Nutritionists: Dieticians; Exercise trainers; Cooks Psychotherapists; Physiotherapists	General practice or occupational health practices	≥ 6 months	Total mortality	RR 1.00 (95% CI 0.96 to 1.05)	Interventions using counselling and education aimed at behaviour change do not reduce total or CHD mortality or clinical events in general populations but may be effective in reducing mortality in high-risk hypertensive and diabetic populations. Risk factor declines were modest but owing to marked unexplained heterogeneity between trials, the pooled estimates are of dubious validity. Evidence suggests that health promotion interventions have limited use in general populations.
			CHD mortality	OR 0.99 (95% CI 0.92 to 1.07)	
			Stroke mortality	RR 0.75 (95% CI 0.60 to 0.95)	
			Fatal and non-fatal clinical events	RR 0.84 (95% CI 0.73 to 0.98)	
			SBP	-2.71 mm Hg (95% CI -3.49 to -1.93)	
			DBP	-2.13 mm Hg (95% CI -2.67 to -1.58	
			Total cholesterol	-0.07 mmol/L (95% CI -0.08 to -0.06)	
			Smoking	RR 0.87; 95% CI 0.75 to 1.00	

Supplementary table 1. (Continued)

First author (year of publication)	Design	Target population	Intervention	Mode of intervention delivery	Density of the intervention
Lin (2014)	Systematic review of 74 controlled trials	CVD-free adults with known CV risk factors (e.g., hypertension, dyslipidaemia, impaired fasting glucose or glucose tolerance, metabolic syndrome)	Behaviourally-based counselling interventions to improve diet and physical activity - alone or as part of a multicomponent intervention.	Face-to-face sessions, either in individual or group sessions; Telephone and mail contacts	Medium-intensity: median of 5 contacts, median duration of 9 months High-intensity: median of 16 contacts, median duration of 12 months
Buckley (2010)	Cochrane review of 11 RCTs	Patients with established IHD	Service organisation interventions whose main elements are specific planned changes in existing care provision in primary care and community settings and which are aimed at improved patient and clinician adherence with recommendations on secondary prevention of IHD.	Individual consultations; Leaflets posted to patients; Reminders/ distribution of guidelines to GP; Learning seminars/ training for staff; Feedback to GPs	NA

Professionals	Setting	Follow-up	Outcomes	Effect size	Authors' conclusion
Dieticians; Physiotherapists or exercise professionals; Trained interventionists (e.g., health educators, psychologists, nurses, case managers, life coaches)	Primary care	≥ 6 months	CVD events	No effect	Medium- and high-intensity diet and physical activity behavioural counselling in overweight or obese persons with CVD risk factors resulted in consistent improvements across a variety of important cardiovascular intermediate health outcomes up to 2 years. High-intensity combined lifestyle counselling reduced diabetes incidence in the longer term. The applicability of these findings depends largely on the availability of intensive counselling in practice and real-world fidelity and adherence to these interventions.
			Mortality	No effect	
			QoL	Increased or no effect	
			Depression	No effect	
			Total cholesterol	- 0.12 mmol/L (95% CI -0.16 to -0.07)	
			LDL-cholesterol	-0.09 mmol/L (95% CI -0.14 to -0.04)	
			SBP	-2.03 mmHg (95% CI -2.91 to -1.15)	
			DBP	-1.38 mmHg (95% CI -1.92 to -0.84)	
			Fasting glucose	-0.05 mmol/L (95% CI -0.09 to -0.02)	
			Diabetes incidence	RR of 0.58 (95% CI, 0.37 to 0.89)	
			Physical activity	Increased	
			Dietary habits	Improved	
Primary care clinicians; Nurses; Dieticians; Occupational therapists; Physiotherapists;	Primary care or community setting	≥ 12 months	BP control	OR 1.50 (95% CI 0.96 to 2.35)	There is weak evidence that regular planned recall of patients for appointments, structured monitoring of risk factors and prescribing, and education for patients can be effective in increasing the proportions of patients within target levels for cholesterol control and blood pressure. Further research in this area would benefit from greater standardisation of the outcomes measured.
			SBP	1.55 mmHg (95% CI -0.35 to 3.46)	
			DBP	0.70 mmHg (95% CI -0.35 to 1.76)	
			Total cholesterol control	OR 1.37 (95% CI 0.63 to 3.01)	
			Total cholesterol	0.06 mmol/L (95%CI -0.05 to 0.17)	
			Prescribed lipid lowering drugs	OR 0.97 (95% CI 0.79 to 1.19)	
			Prescribed *B*-blockers	OR 0.86 (95% CI 0.67 to 1.10)	
			Prescribed ACE-i	OR 0.86 (95% CI 0.63 to 1.18)	
			Prescribed antiplatelets	OR 1.16 (95% CI 0.86 to 1.57)	
			Exercise at target level	OR 1.11 (95% CI 0.95 to 1.29)	
			Smoking cessation	OR 1.06 (95% CI 0.89 to 1.25)	

Supplementary table 1. (Continued)

First author (year of publication)	Design	Target population	Intervention	Mode of intervention delivery	Density of the intervention
Cole (2010)	Systematic review of 21 RCTs	Adults aged > 18 years with a diagnosis of CHD	Interventions with a lifestyle and/or behaviour change focus, incorporating one or a combination of exercise and diet. Interventions may be categorized as follows: (1) Dietary. (2) Exercise. (3) Psychological. (4) Educational. (5) Multifactorial. (6) Organisational.	Individual sessions; Group sessions; Follow-up by telephone or e-mail; Educational material	Varying from intensive (for example 16 lectures + 8 group meetings + 6 exercise sessions + 3 social events within 16 months) to less intensive (3 education sessions in 1 year)
Murphy (2015)	Systematic review of 5 RCTs	Patients with established IHD	Interventions targeted at organizational change, aimed at improved clinician and patient adherence with recommendations on secondary prevention of IHD.	Individual consultations; Patient education; Clinician education	Length of intervention: 1-3 years
Snaterse (2016)	Systematic review of 18 RCTs	Patients with CHD	Nurse-coordinated care (NCC) including : (1) risk factor management (for example, lifestyle counselling, blood pressure and lipid control), (2) multidisciplinary consultation (for example, consultation and referral) and/ or (3) shared decision making (for example, goal setting and family support)	Visits; Home visits; Telephone follow-up	High: >4 visits plus more than one NCC strategy used. Intermediate: 3–4 visits. Low: 1–2 visits.

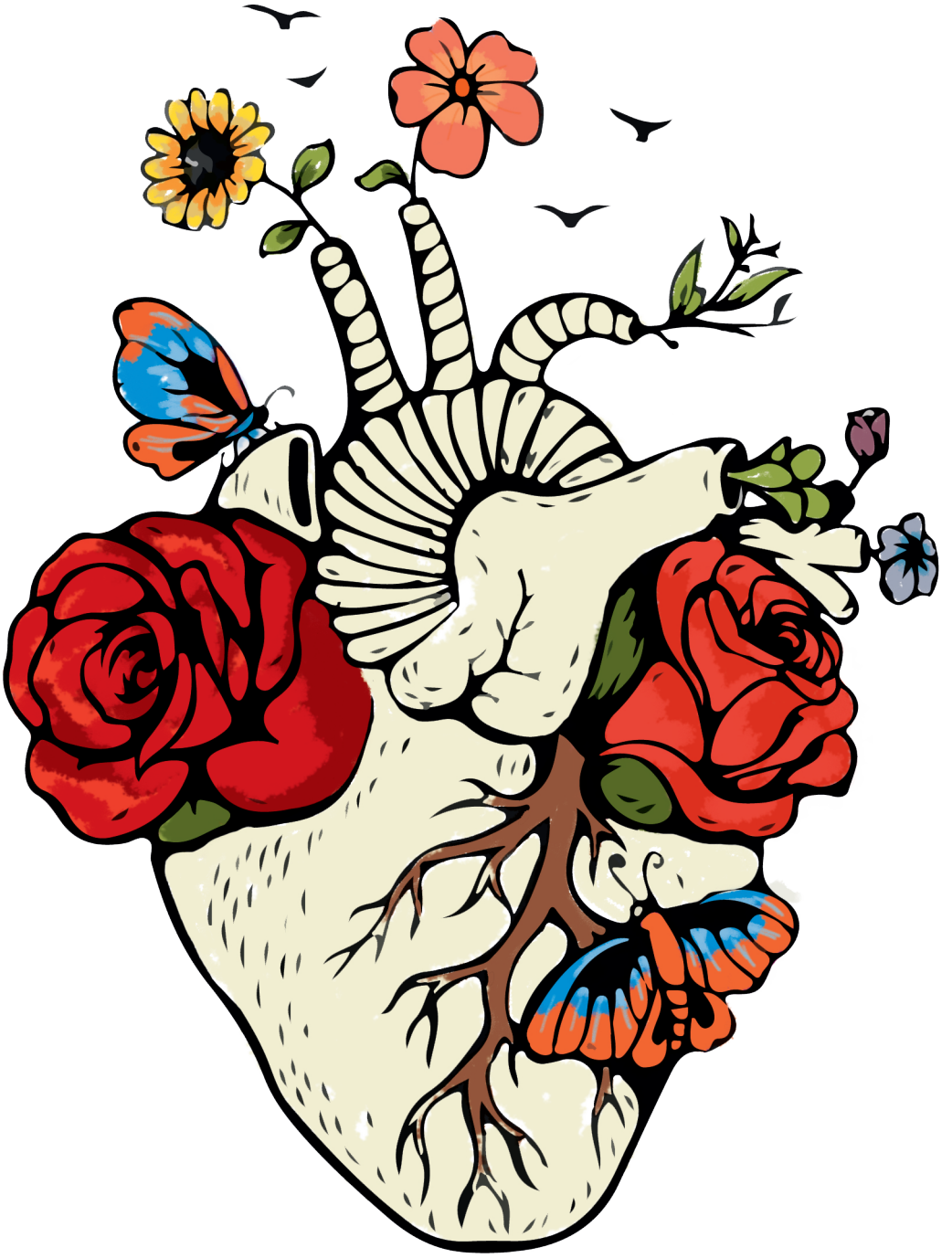
Professionals	Setting	Follow-up	Outcomes	Effect size	Authors' conclusion
General practitioners; Practice nurses; Community Pharmacists; Community and public health nurses; Dieticians; Occupational therapists; Physiotherapists; Psychologists; Social workers	Primary care or community settings	≥ 3 months	All-cause mortality	RR 0.75 (95% CI 0.65 to 0.87)	The review indicates that lifestyle interventions have mixed effects with some benefits in relation to total mortality, CV mortality, and nonfatal CV events as well as PA, diet, blood pressure, cholesterol, QOL, and medication adherence. The heterogeneity between trials and generally poor quality of trials make any concrete conclusions difficult. However, the beneficial effects observed in this review are encouraging and should stimulate further research.
			CV mortality	RR 0.63 (95% CI 0.47 to 0.84)	
			Nonfatal cardiac events	RR 0.68 (0.55, 0.84)	
			Hospital admissions	Trend to reduction, not significant	
			Diet	No clear effect	
			Physical activity	No clear effect	
			Smoking	No effect	
			BP	No effect	
			Total cholesterol	No clear effect	
			LDL-cholesterol	Significant effect	
			QoL	No effect	
			Medication	No clear effect	
NA	Primary or community care settings	≥ 24 months	All-cause mortality	RR 0.79 (95% CI 0.66 to 0.93)	Cardiac secondary prevention programmes targeting organisational change are associated with a reduced risk of death for at least 4–6 years. There is insufficient evidence to conclude whether this beneficial effect is maintained indefinitely
			Cardiac-related mortality	RR 0.74 (95% CI = 0.58 to 0.94)	
			Hospital admissions	No effect	
			BP control	RR 0.95 (95% CI 0.83 to 1.09)	
			Total cholesterol control	RR 0.98 (95% CI 0.89 to 1.07)	
			SBP	1.94 mmHg (–3.02 to 6.91)	
			Total cholesterol	0.03 mmHg (–0.12 to 0.18)	
			Smoking	No effect	
			Aspirin prescribed	RR 1.06 (95% CI 1.00 to 1.12)	
			Statins prescribed	RR 1.09 (95% CI 0.77 to 1.53)	
Nurses; General practitioners; Cardiologists; Dieticians; Physiotherapists	Primary care and hospital	3-24 months	SBP	- 2.96 mm Hg (95% CI - 4.40 mm Hg to - 1.53)	NCC demonstrated to have an effect on a small number of outcomes. NCC that incorporated blood pressure monitoring, cholesterol control and smoking cessation has an impact on the improvement of secondary prevention. Additionally, NCC is a heterogeneous concept. A shared definition of NCC may facilitate better comparisons of NCC content and outcomes.
			LDL-cholesterol	- 0.23 mmol/L (95% CI - 0.36 to - 0.10)	
			Smoking cessation rates	risk ratio 1.25 (95% CI 1.08 to 1.43)	
			Weight	No effect	
			Event free survival	No effect	
			All-cause mortality	No effect	

Supplementary table 1. (Continued)

First author (year of publication)	Design	Target population	Intervention	Mode of intervention delivery	Density of the intervention
Van Lieshout (2016)	Cluster RCT	Adults aged > 18 years with recorded CVD or high CV risk (estimated 10-year risk score of 20 % or higher for morbidity and mortality due to CVD)	A tailored implementation program, including communication skills training to practice nurses, online patient information, and a clinical protocol for managing depressive symptoms.	Visits	NA

BMI, body mass index. BP, blood pressure. CHD, coronary heart disease.
CV, cardiovascular. CVD, cardiovascular disease. DBP, diastolic blood pressure.
GP, general practitioner. IHD, intracoronary heart disease. QoL, quality of life.
RCT, randomized controlled trial. SBP, systolic blood pressure.

Professionals	Setting	Follow-up	Outcomes	Effect size	Authors' conclusion
Practice nurses; General practitioner	Primary care	6 months	Adequate performance practice nurse	No effect	The tailored improvement program showed no effect on the primary outcome. This challenges the methodology of tailoring. More involvement of the targeted health care professionals might offer ways to develop more effective implementation programs. Physical activity might be the lifestyle issue that can be more easily changed than smoking or dietary habits.
			SBP < 140 mmHg	OR 1.03 (95% CI 0.72–1.48)	
			LDL < 2.5 mmol/L	OR 0.85 (95% CI 0.53–1.38)	
			BMI < 25 kg/ m^2	OR 0.84 (95% CI 0.48–1.46)	
			Smoking	OR 1.11 (95% CI 0.68–1.82)	
			Physical exercise	*B* 0.18 (95%CI 0.02–0.35; $p < 0.05$)	
			Diet	*B* 0.03 (0.00–0.07)	



SUMMARY

Cardiovascular disease (CVD) has remained the leading cause of death worldwide and also in Europe.[1,2] There is concern about the prevalence of cardiovascular risk factors. In Europe, the prevalence of obesity has more than doubled in the last 36 years, 1 in 3 adults is insufficiently physically active and the downward trend in prevalence of elevated blood pressure appears to be minimal.[1] The occurrence of CVD can be reduced by adequate treatment of cardiovascular risk factors, including high blood pressure, elevated blood lipids, smoking, physical inactivity, obesity and an unhealthy diet. However, primary care survey studies have shown that control rates of cardiovascular risk factors are disappointing.[3,4] It underlines the need for effective multifactorial and multidisciplinary cardiovascular risk factor management (CVRM) interventions, as also recommended by the European guidelines on cardiovascular disease prevention.[5] Integrated multidisciplinary CVRM programmes in primary care offer a potentially effective way to improve the implementation of CVD guideline recommendations and thereby the quality of CVD prevention. Most of these programmes are based on the chronic care model (CCM) and include systematic selection, invitation, cardiovascular risk assessment, shared decision in treatment and follow-up of eligible patients, stimulation of self-management, registration of patient data in clinical information systems and yearly feedback to general practitioners (GPs) on delivered CVRM care.[6] So far, studies on the effectiveness of CVRM programmes are scarce and the available evidence is inconsistent, partly due to the heterogeneity in study designs.[7-11] Importantly, most evidence on integrated CVRM programmes is based on randomized controlled trials (RCTs), presenting the effect of the intervention when carefully implemented according to the existing guidelines under optimal conditions.[12] However, RCTs oversimplify reality and the results are not automatically applicable in daily practice. Therefore, more real-world evidence is needed.

This thesis aims to provide insight in the effectiveness of an integrated and multidisciplinary programme for cardiovascular risk management (CVRM) in primary care in a real-world setting and to describe the challenges of the implementation of CVRM in daily practice.

In **Chapter 2** of this thesis, we comment on the new European guideline on cardiovascular disease prevention. Key messages in the guideline include that CVD prevention asks for a personalized approach and that estimation of the CV risk and assessment of lifestyle factors should be repeated regularly.[5] We stated

that implementation of all recommendations in this new guideline would be challenging and requires more guidance for GPs as well as enough consultation time, ICT support, adequate reimbursement, a trained multidisciplinary team and support by concordant actions of surrounding organizations, insurance companies and government.

In the Netherlands an integrated programme for cardiovascular risk management (CVRM), based on the Chronic Care Model (CCM), has been introduced in primary care in many regions in recent years. In the ZWOT-CASE study (ZWOlle inTegrated care for CArdiovaScular risk managEment study), we investigated the effect of integrated care for CVRM compared to usual care within general practices in the region of Zwolle in the eastern part of the Netherlands. The design of the study is described in **Chapter 3**. We designed a prospective pragmatic observational study, performed among patients with known CVD or at high CVD risk in general practice. After one year of follow-up, integrated care for CVRM was compared with usual care. Patients in the usual care group were matched with patients in the intervention group according to age, gender and risk group (high CV risk or CVD). Primary outcomes included levels of systolic blood pressure and LDL-cholesterol. Secondary outcomes included calculated 10-year CV risk, BMI, lifestyle (smoking, physical activity, dietary habits), medication use, patient satisfaction, health care consumption, morbidity, comorbidity and mortality. We used mixed-model analyses to assess the outcomes.

In **Chapter 4** we describe the results of the ZWOT-CASE study. We included 372 patients in the intervention group and 317 patients in the usual care group. Mean age at baseline was 65.1 and 66.2 years respectively and 42% were women in both groups. After one year, we observed no difference in systolic blood pressure (137.2 mmHg vs 139.0 mmHg in the intervention and usual care group, respectively) and LDL-cholesterol (2.6 mmol/L in both groups), nor in any of the secondary outcomes.

In **Chapter 5** we describe a process evaluation of the ZWOT-CASE study. We aimed to gain a deeper understanding of the disappointing results of the study by assessing fidelity to the CVRM programme. Assessment of fidelity includes adequacy of delivered CVRM care and patients' perception of CV risk, risk factors, lifestyle and lifestyle advice. The results of this study show that in total, 85%

intervention and and 32% usual care patients received at least one consultation, including measurements of blood pressure (BP), weight, LDL-cholesterol and renal function. In intervention patients with hypertension that are not on blood pressure lowering medication at baseline, medication was started in 57% of patients with an off-target BP and in 14% of patients with an near-target BP. In intervention patients with hypercholesterolemia that are not on lipid lowering medication at baseline, medication was started in 9% of patients with an off-target LDL-cholesterol and in 3% of patients with a near-target LDL-cholesterol. In patients using blood pressure lowering medication at baseline, the prescription was changed in 33% of patients with an off-target BP and in 19% of patients with an near-target BP. In patients using lipid lowering medication at baseline, the prescription was changed in 28% of patients with an off-target LDL-cholesterol and in 8% of patients with an near-target LDL-cholesterol. Among patients without CVD, 14% of intervention patients vs 22% of the usual care group correctly classified themselves as having an intermediate or high risk of CVD. Among CVD patients 12% of the intervention group vs 13% of the usual care group correctly classified themselves as having a high CV risk. Adequacy of patient's perception of CV risk factors and lifestyle did not differ between the groups. Less than one-third of patients who received lifestyle advice reported having received the advice.

Chapter 6 describes a retrospective cohort study in which we evaluated whether an integrated care programme for CVRM reduced hospital care and subsequent costs. We included patients enlisted in the Isala hospital with atherosclerotic CVD and assessed patient-level data on diagnoses and care activities from the Isala hospital between January 1st, 2014 and January 1st, 2018. From January 1st, 2016 onwards, an integrated primary care programme for CVRM was implemented in the adherent region. We compared duration of hospital care, number of care activities and corresponding costs prior and after starting integrated CVRM care, and used descriptive statistics to assess differences between the two periods. We included respectively 5,215 and 5,449 CVD patients, (mean age 70 years, 35% female) in the period before and after 01-01-2016. The median length of treatment at the hospital decreased from 149 (IQR 12-389) to 128 (IQR 10-386) days and the total median costs of CVRM related hospital care per patient decreased by 13% from 583 euros (IQR 272 – 2586) the period before to 507 euros (IQR 262 – 2119) during the period after implementation of the programme.

In **Chapter 7** we describe an observational study in which we assessed therapeutic inertia and characteristics associated with therapeutic inertia in patients with dyslipidaemia, CVD or diabetes mellitus in primary care. Electronic health record data of patients registered in the Julius General Practitioners' Network (n=530,564) were used. We selected patients with dyslipidaemia, CVD or DM, and with a recently measured uncontrolled LDL-cholesterol level (> 2.5 mmol/L). Therapeutic inertia was defined as absence of lipid-lowering drug adjustment within three months after the LDL-cholesterol measurement. We used logistic-regression analyses to identify patient characteristics associated with therapeutic inertia. The results of this study showed that out of 21,310 patients with dyslipidaemia, atherosclerotic CVD and/or DM with a recently measured LDL-cholesterol we identified 6,854 (32%) patients with a LDL-cholesterol > 2.5 mmol/L. Mean age was 68 (SD 12.2) years and 57% were women. The median LDL-cholesterol was 3.1 mmol/L (IQR 2.8 – 3.7) and 45% used a lipid-lowering drug in the 6 months prior to the measurement. Therapeutic inertia was present in 93% and did not differ between patients with a CVD, DM or dyslipidaemia. Age (OR per year 1.01, 95%-CI 1.01 to 1.02) was positively associated with therapeutic inertia, while both LDL-cholesterol level (OR per mmol/L 0.63, 95%-CI 0.56 to 0.70) and being a current or past smoker (OR 0.66, 95%-CI 0.54 to 0.80) were inversely associated with therapeutic inertia.

In **Chapter 8** the main results of this thesis are summarized and interpreted. Furthermore, the potential impact of the integrated multidisciplinary CVRM programme in daily practice is discussed by using the RE-AIM model. Last, considerations are provided about the future of CVRM programmes in primary care.

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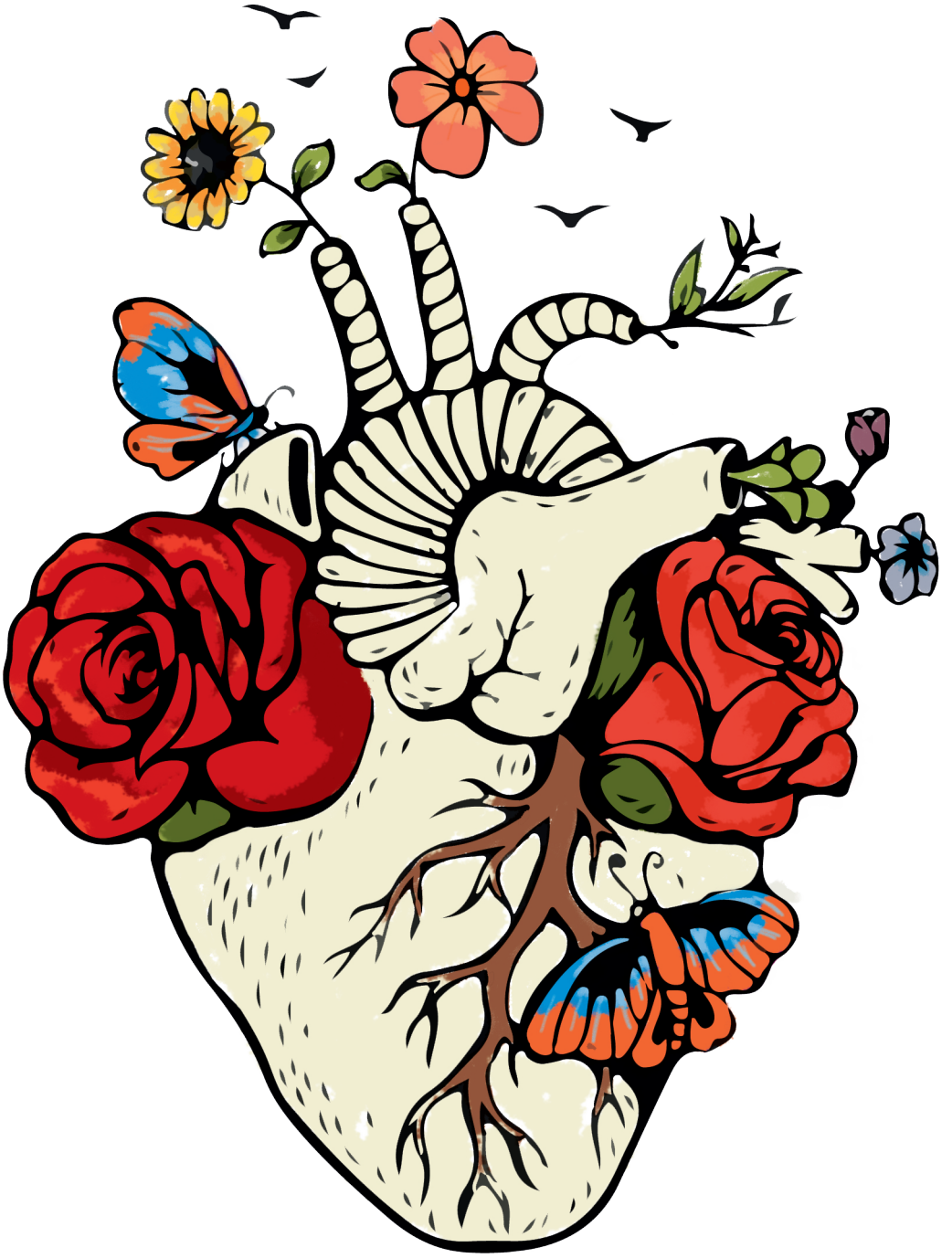


SAMENVATTING

Hart- en vaatziekten (HVZ) is zowel wereldwijd als in Europa de belangrijkste doodsoorzaak. Daarom zijn er zorgen over de prevalentie van risicofactoren voor HVZ. Zo is in Europa het aantal mensen met obesitas in de afgelopen 36 jaar meer dan verdubbeld, beweegt 1 op de 3 volwassenen beweegt te weinig en neemt het aantal mensen met een verhoogde bloeddruk niet verder af. HVZ kunnen worden voorkomen door behandeling van risicofactoren voor HVZ, zoals hoge bloeddruk, verhoogd cholesterol, roken, te weinig bewegen, obesitas en een ongezond voedingspatroon. Onderzoeken in de eerstelijnszorg hebben echter aangetoond dat risicofactoren voor HVZ onvoldoende onder controle zijn. Dit benadrukt dat effectieve multifactoriële en multidisciplinaire interventies voor cardiovasculair risicomanagement (CVRM) nodig zijn, zoals ook wordt aanbevolen door de Europese richtlijnen voor de preventie van HVZ. In de gehele zorgketen geïntegreerde, multidisciplinaire CVRM-programma's in de eerste lijn zouden de implementatie van de richtlijnen en daarmee de kwaliteit van HVZ-preventie mogelijk kunnen verbeteren. Deze programma's zijn meestal gebaseerd op het chronische zorgmodel en omvatten het systematisch selecteren en uitnodigen van patiënten, het maken van een cardiovasculaire risicoschatting, een gedeelde beslissing in behandeling en follow-up van in aanmerking komende patiënten en stimulering van zelfmanagement. Daarnaast worden patiëntgegevens geregistreerd in klinische informatiesystemen en wordt jaarlijks feedback gegeven aan huisartsen over de door hun geleverde CVRM-zorg. Tot dusver zijn studies naar de effectiviteit van CVRM-programma's schaars en is het beschikbare bewijs niet eenduidig, onder andere vanwege de verscheidenheid in de onderzoeksopzet. De meeste studies zijn gerandomiseerde gecontroleerde studies (randomized controlled trials; RCT's). In een RCT wordt het effect van het CVRM-programma onderzocht onder optimale omstandigheden, waarbij het programma wordt geïmplementeerd volgens de richtlijnen. Echter, de omstandigheden in RCT's komen niet overeen met de complexiteit van de werkelijkheid. Daarom zijn de resultaten van deze studies niet automatisch toepasbaar in de dagelijkse praktijk. Daarom zijn er meer studies nodig onder realistischere omstandigheden.

Dit proefschrift heeft als doel om inzicht te verschaffen in de effectiviteit van een geïntegreerd en multidisciplinair programma voor CVRM in de eerstelijnszorg in de dagelijkse praktijk. Daarnaast worden in dit proefschrift de uitdagingen van de implementatie van CVRM in de dagelijkse praktijk beschreven.

In **Hoofdstuk 2** van dit proefschrift geven we commentaar op de nieuwe Europese richtlijn voor het voorkomen van HVZ. Kernboodschappen in de richtlijn zijn onder meer dat HVZ-preventie een gepersonaliseerde aanpak vereist en dat het inschatten van het risico op HVZ en de beoordeling van leefstijlfactoren regelmatig herhaald moeten worden. De implementatie van alle aanbevelingen in deze nieuwe richtlijn is een uitdaging en vereist meer begeleiding voor huisartsen evenals voldoende consulttijd, ICT-ondersteuning, adequate financiële vergoeding, een opgeleid multidisciplinair team en overeenstemming met beleid van omliggende organisaties, verzekeraars en de overheid.

In de afgelopen jaren is in veel regio's in Nederland een geïntegreerd programma voor CVRM geïntroduceerd in de eerste lijn, gebaseerd op het chronisch zorgmodel. In de ZWOT-CASE studie (ZWOlse Transmurale CArdiovaSculaire risicomanagEment ketenzorg studie) onderzochten wij het effect van zo'n geïntegreerd programma voor CVRM (interventie) in vergelijking met gebruikelijke zorg in huisartspraktijken in de regio Zwolle. De opzet van de studie wordt beschreven in **Hoofdstuk 3**. De ZWOT-CASE studie is een prospectieve pragmatische observationele studie in de huisartspraktijk, uitgevoerd onder patiënten met bekende HVZ of met een hoog risico op HVZ. Na een jaar follow-up werd de geïntegreerde zorg voor CVRM vergeleken met een groep die gebruikelijke zorg ontving. Patiënten in de interventiegroep werden gekoppeld aan patiënten in de gebruikelijke zorggroep op basis van leeftijd, geslacht en risicogroep (HVZ of hoog risico op HVZ). Primaire uitkomsten waren systolische bloeddruk en LDL-cholesterol. Secundaire uitkomsten waren onder meer berekend 10-jaarsrisico op ziekte of sterfte door HVZ, BMI, leefstijl (roken, lichamelijke activiteit, voedingsgewoonten), medicatiegebruik, patiënttevredenheid, zorggebruik, nieuw ontwikkelde HVZ en sterfte door HVZ of een andere oorzaak. We gebruikten mixed-model analyses om de uitkomsten te beoordelen.

In **Hoofdstuk 4** beschrijven we de resultaten van de ZWOT-CASE studie. In de interventiegroep deden 372 patiënten mee en in de groep die gebruikelijke zorg ontving deden 317 patiënten mee. De gemiddelde leeftijd aan het begin van het onderzoek was respectievelijk 65,1 en 66,2 jaar en in beide groepen was 42% vrouw. Na een jaar zagen we geen verschil in systolische bloeddruk (137,2 mmHg versus 139,0 mmHg in respectievelijk de interventie- en gebruikelijke zorggroep)

en LDL-cholesterol (2,6 mmol / L in beide groepen), noch in een van de secundaire uitkomsten.

Om beter inzicht te krijgen in de tegenvallende resultaten van het CVRM-programma, onderzochten wij of het CVRM-programma zorgvuldig was uitgevoerd door middel van een procesevaluatie. Dit wordt beschreven in **Hoofdstuk 5**. Hiervoor gingen wij na welke CVRM-zorg precies was geleverd. Daarnaast onderzochten wij of de patiënt zijn of haar risico op HVZ, de eigen risicofactoren en leefstijl juist beoordeelt en of leefstijladviezen bij de patiënt zijn aangekomen.

De resultaten van deze evaluatie laten zien dat in totaal 85% van de patiënten in het CVRM-programma minimaal één keer op het spreekuur kwam voor CVRM, inclusief een bloeddrukmeting en bepaling van gewicht, LDL-cholesterol en nierfunctie, tegenover 32% van de patiënten die gebruikelijke zorg ontvingen.

Bij interventiepatiënten met een bekende hoge bloeddruk die bij aanvang van de studie geen bloeddrukverlagende medicatie gebruikten, werd medicatie gestart bij 57% van de patiënten met een bloeddruk boven de streefwaarde en bij 14% van de patiënten met een bloeddruk nabij de streefwaarde. Bij interventiepatiënten met een te hoog cholesterol die bij aanvang van de studie geen cholesterolverlagende medicatie gebruikten, werd medicatie gestart bij 9% van de patiënten met een LDL-cholesterol boven de streefwaarde en bij 3% van de patiënten met een LDL-cholesterol nabij de streefwaarde. Bij patiënten die bij aanvang al bloeddrukverlagende medicatie gebruikten, werd de medicatie gewijzigd bij 33% van de patiënten met bloeddruk boven de streefwaarde en bij 19% van de patiënten met bloeddruk nabij de streefwaarde. Bij patiënten die bij aanvang al cholesterolverlagende medicatie gebruikten, werd het recept gewijzigd bij 28% van de patiënten met een LDL-cholesterol boven de streefwaarde en bij 8% van de patiënten met een LDL-cholesterol nabij de streefwaarde.

Van de patiënten zonder HVZ beoordeelde 14% van de interventiepatiënten versus 22% van de gebruikelijke zorggroep het eigen risico op HVZ correct. Van de patiënten met een HVZ beoordeelde 12% van de interventiegroep versus 13% van de gebruikelijke zorggroep het eigen risico op HVZ correct. Er was geen verschil tussen de groepen in het aantal patiënten dat de eigen risicofactoren en

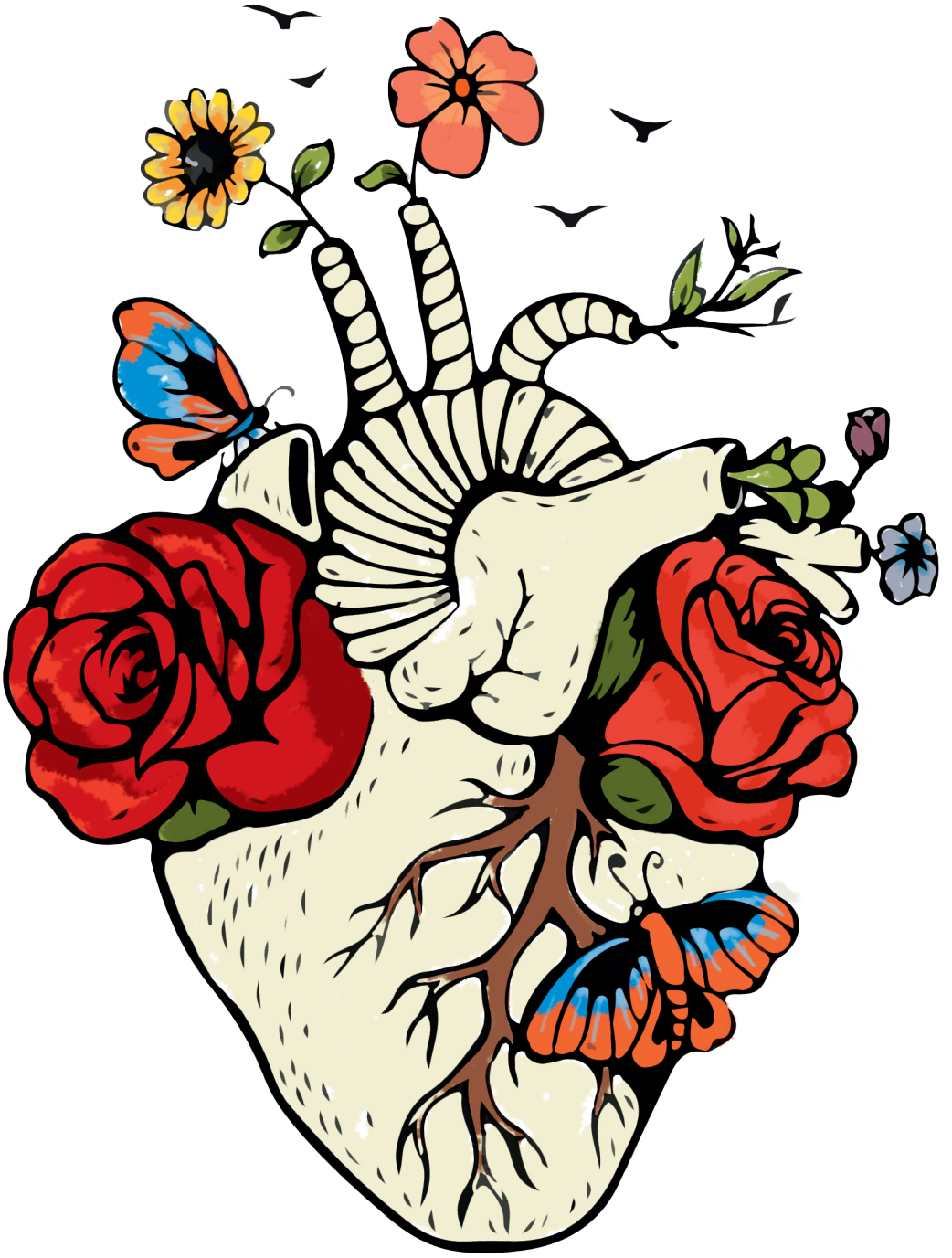
leefstijl juist inschatte. Tot slot gaf minder dan een derde van de patiënten die leefstijladvies kregen aan het advies te hebben ontvangen.

Hoofdstuk 6 beschrijft een retrospectieve cohortstudie waarin we evalueerden of het geïntegreerde zorgprogramma voor CVRM leidt tot minder ziekenhuiszorg en een daling van de daaruit voortvloeiende kosten. Het geïntegreerde eerstelijnszorgprogramma voor CVRM werd vanaf 1 januari 2016 geïmplementeerd in de regio Zwolle. We includeerden patiënten die tussen 1 januari 2014 en 1 januari 2018 in het Isala ziekenhuis waren opgenomen met atherosclerotische HVZ en beoordeelden gegevens op patiëntniveau over diagnoses en zorgactiviteiten van het Isala-ziekenhuis. We vergeleken de perioden voor en na het starten van geïntegreerde CVRM-zorg, en keken hierbij naar de duur van de ziekenhuiszorg, het aantal zorgactiviteiten en de bijbehorende kosten. Beschrijvende statistieken werden gebruikt om de verschillen tussen de twee perioden te beoordelen. In de periode voor en na 01-01-2016 includeerden we respectievelijk 5.215 en 5.449 patiënten met HVZ (gemiddelde leeftijd 70 jaar, 35% vrouw). De mediane duur van de behandeling in het ziekenhuis daalde van 149 dagen (IQR 12-389) naar 128 dagen (IQR 10-386). De totale mediane kosten van CVRM-gerelateerde ziekenhuiszorg per patiënt daalden met 13%, namelijk van 583 euro (IQR 272-2586) in de periode voor tot 507 euro (IQR 262 - 2119) gedurende de periode na invoer van het programma.

Om de uitdagingen van CVRM-zorg in de dagelijkse praktijk verder te onderzoeken deden wij een studie naar therapeutische inertie. In **Hoofdstuk 7** wordt deze studie beschreven. Het betreft een observationele studie in de eerste lijn waarin we therapeutische inertie en patiëntkenmerken geassocieerd met therapeutische inertie onderzochten. Hiervoor gebruikten we elektronische patiëntendossiers van patiënten geregistreerd in het Julius Huisartsennetwerk (n = 530.564). We selecteerden patiënten met hypercholesterolemie, HVZ of diabetes mellitus (DM), en met een recent gemeten ongecontroleerd LDL-cholesterolgehalte (> 2,5 mmol / L). Therapeutische inertie werd gedefinieerd als de afwezigheid van een aanpassing in cholesterolverlagende medicatie door de huisarts binnen drie maanden na de LDL-cholesterolmeting. We gebruikten logistische regressieanalyses om patiëntkenmerken op te sporen die samenhangen met therapeutische inertie. Van de 21.310 patiënten met hypercholesterolemie, atherosclerotische HVZ en / of DM met een recent gemeten LDL-cholesterol, hadden 6.854 (32%) patiënten

een LDL-cholesterol> 2,5 mmol / L. De gemiddelde leeftijd van deze patiënten was 68 (SD 12,2) jaar en 57% was vrouw. Het mediane LDL-cholesterol was 3,1 mmol / l (IQR 2,8 - 3,7) en 45% gebruikte een cholesterolverlagend medicijn in de 6 maanden voorafgaand aan de meting. In 93% van de patiënten was er sprake van therapeutische inertie en dit verschilde niet tussen patiënten met HVZ, DM of hypercholesterolemie. De leeftijd van de patiënt hing positief samen met therapeutische inertie (OR per jaar 1,01, 95% -CI 1,01 tot 1,02). Tussen zowel de hoogte van het LDL-cholesterol (OR per mmol / L 0,63, 95% -CI 0,56 tot 0,70) als roken (OR 0,66, 95% -CI 0,54 tot 0,80) en therapeutisch inertie was er een negatief verband.

In **Hoofdstuk 8** worden de belangrijkste resultaten van dit proefschrift samengevat en geduid. Verder wordt de mogelijke impact van het geïntegreerde multidisciplinaire CVRM-programma in de dagelijkse praktijk besproken aan de hand van het RE-AIM-model. We eindigen met ideeën voor de toekomst van CVRM-programma's in de eerste lijn.



DANKWOORD

In vijf jaar tijd Groningen verlaten, dan nog eens vier keer verhuizen, studeren om een goede huisarts te worden, de liefde ontmoeten en als kroon op alles moeder worden op de dag nadat ik mijn proefschrift indiende ter beoordeling. Daar tussendoor werd dit proefschrift in drie jaar tijd geschreven. Het behoeft denk ik geen verdere uitleg dat ik dit niet alleen heb kunnen doen. Mijn dank gaat uit naar vele collega's, vrienden en familie die betrokken waren. Een aantal mensen wil ik in het bijzonder noemen.

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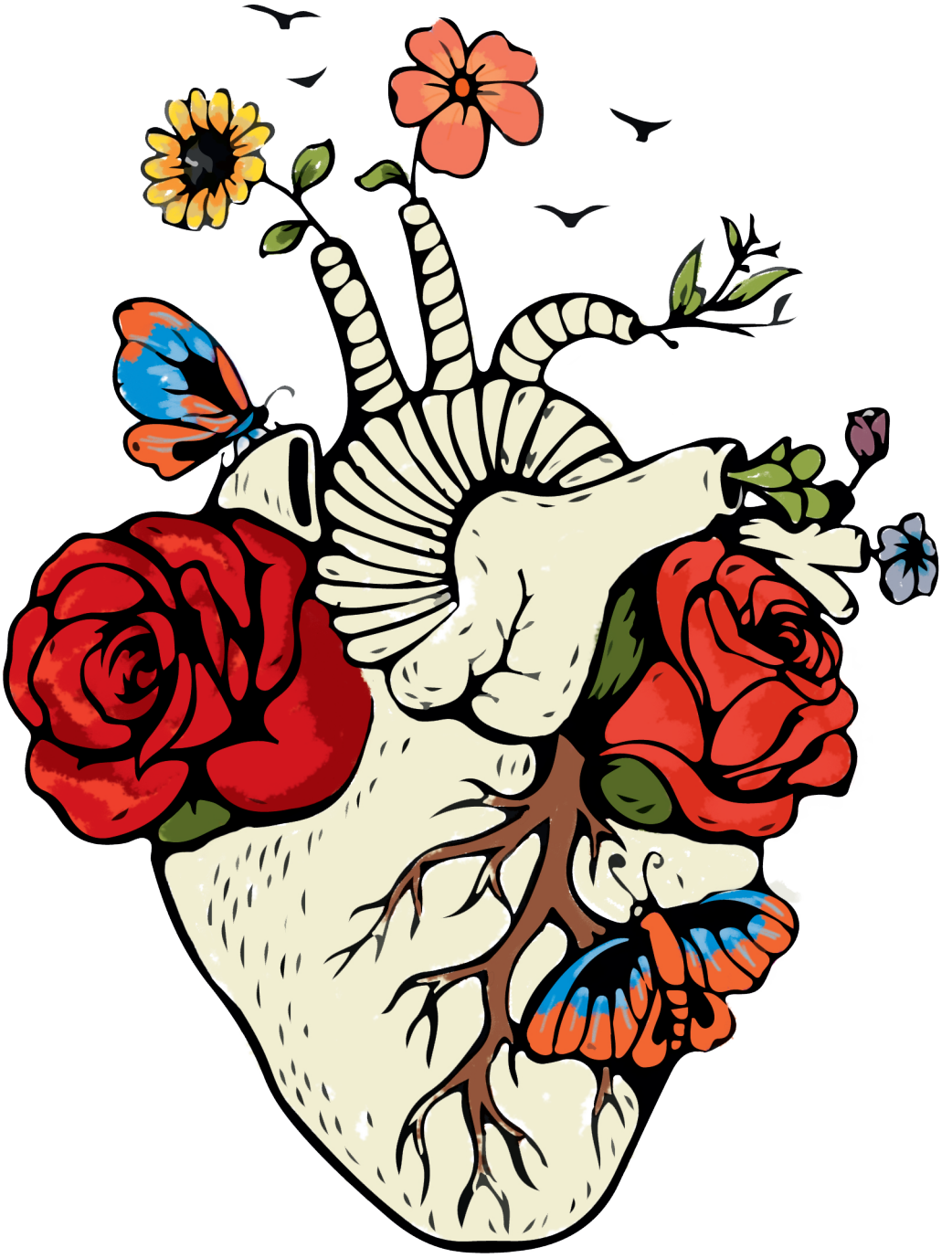

CURRICULUM VITAE

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Suzanne Marchal was born in Wijk bij Duurstede, the Netherlands, on 26th of June 1987. After graduation from secondary school in 2005 (Revius Lyceum, Doorn), she studied Medicine at the University of Groningen and graduated in 2012. Between 2012 and 2015 Suzanne worked as a resident at the intensive care of the University Medical Centre in Groningen, the emergency room of the Tjongerschans hospital in Heerenveen and the neurology department of Martini hospital in Groningen, respectively. In 2016 she started working on the research described in this thesis, at the Julius centre for Health Sciences and Primary Care of the University Medical Centre Utrecht, under supervision of prof. dr. A.W. Hoes, prof. dr. A.W.J. van 't Hof and dr. M. Hollander. She has combined her PhD project with the general practitioner vocational training at the Department of General Practice, Julius Centre Utrecht, of which she is currently at the beginning of the third year. In 2020 she received a master's degree in Clinical Epidemiology at Utrecht University. Results of her PhD research are presented in the current thesis entitled 'Integrated cardiovascular risk management in primary care'.