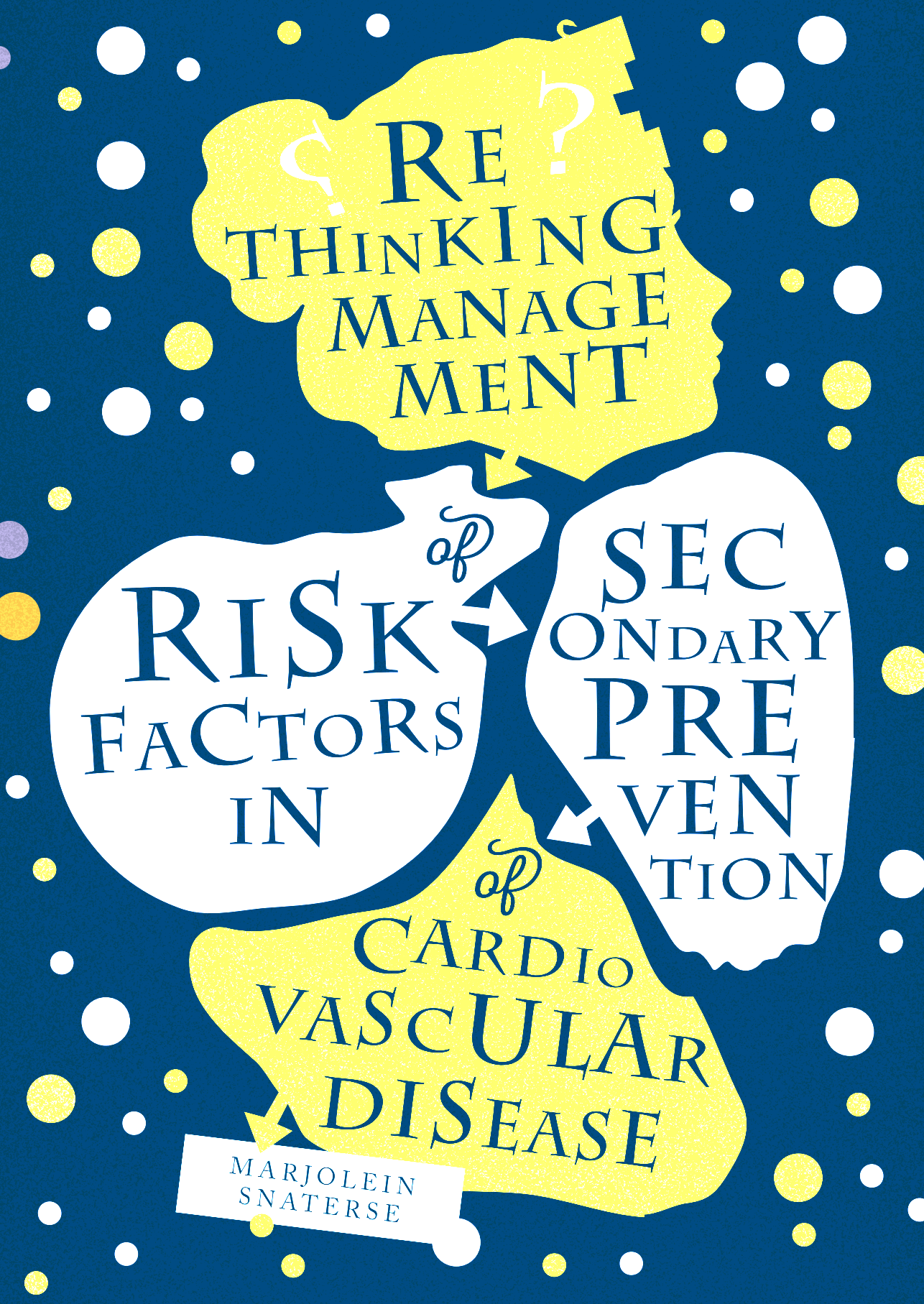
Re thinking management of risk factors in secondary prevention of cardio vascular disease
Marjolein Snaterse

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Rethinking Management of Risk Factors in Secondary Prevention of Cardiovascular Disease

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Chapter 1

Introduction and general outline

'The paramedics immediately could see on their screens what was going on: I was having a heart attack! Within almost no time, we arrived at the hospital, I was brought to the catheterization room, and the doctors opened one of the blood vessels in my heart, which was causing the heart attack. After I left the hospital, I have to admit that everything that had happened had given me a real fright. It was clear to me that I had to change my lifestyle to avoid another heart attack. Therefore, I immediately stopped smoking. Unfortunately, I have now gained a few kilos. What is the best thing to do now? Is the weight reduction programme of RESPONSE 2 something for me? Will it work for me? I have never attended a programme like that before in my life. Will I even like it? I do like the fact that it takes place close to home, in my own neighbourhood. I really am prepared to change my lifestyle, that will be necessary, to live healthier, to see my grandchildren grow up. I would like to be more physically active but I don't have much energy. I am also interested in the cardiac rehabilitation programme and talking with a nurse about everything that is going on. It would be nice if somebody could coach you in the choices which you have to make. It is not a minor thing; my life was turned upside down from one day to the next.' (Mr P. Sanders, 63 years old)

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for more than 17 million deaths every year, and 31% of all global deaths. Of these deaths, an estimated 7.4 million (42%) were due to coronary heart disease (CHD)[1], which refers to a narrowing or occlusion of the coronary arteries that provide oxygen and blood to the heart. Patients who have suffered an event due to CVD are at high risk of recurrent events. Secondary prevention aims to reduce this risk by stopping or slowing the progression of the underlying disease, i.e. atherosclerosis. The main objectives of CVD prevention are to reduce morbidity and mortality, to improve quality of life and add healthy life years.[2,3] CVD prevention guidelines have been formulated by the Joint European Societies on CVD Prevention, with clear targets for secondary prevention[2]. Management of risk factors of patients with CVD consists of a combination of medical treatment and lifestyle modification. Guideline-recommended treatment targets are shown in Table 1.

Table 1.
Joint European Societies guideline recommendations for secondary prevention of cardiovascular disease[2]

Guideline recommendations
Smoking cessation among smokers
Regular physical activity, ≥30 min. 5x/week
BMI <25 kg/m^2
Waist circumference:
<94 cm (men)
<80 cm (women)
Blood pressure <140/90 mmHg
Total cholesterol <4.5 mmol/L
LDL-cholesterol <1.8 mmol/L
Among patients with type 2 diabetes:
Fasting glycaemia <7.0 mmol/L
HbA1c <6.5%

BMI=Body mass index; HbA1c=glycated haemoglobin;
LDL=low-density lipoprotein

Secondary prevention is highly effective in reducing the risk of recurrent CVD events. The potential cumulative risk reduction by pharmacological treatment of blood pressure and LDL-cholesterol only has been estimated to be as high as 75%.[4] Adherence to recommendations regarding smoking, diet, and exercise after an acute coronary

syndrome is associated with a substantially lower risk of recurrent events rate.[5] However, in real life a large majority of patients fail to achieve the therapeutic targets indicated by the guidelines.[6]

The EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to reduce Events) surveys on lifestyle and risk factor management and on the use of drug therapies in patients with CHD aim to evaluate guideline implementation in clinical practice. These European surveys show that between 1996-2013, in patients who have suffered an acute coronary event, control of lifestyle risk factors has deteriorated, with increasing prevalences of obesity and central obesity, and unaltered rates of persistent smoking. Medication use has increased, with a concomitant improvement of blood pressure and LDL-cholesterol control.[6] In spite of this, the majority of patients still do not achieve the guideline recommended targets. Of these risk factors, smoking may be the strongest, and is highly prevalent in patients with CVD.

Chapter 2 serves as an introduction to the current clinical situation in the Netherlands. We provide an overview of the prevalence of cardiovascular risk factors in the Dutch study population of EUROASPIRE IV. In this introductory chapter, we report that the current level of risk factor management is far from optimal. Our results show that there is room for improvement of the current risk management in secondary prevention of cardiovascular disease.
Currently, the greatest challenge in preventive cardiology is not to develop more powerful drug interventions, but to implement highly effective treatments and strategies that are already available. Rethinking current concepts and strategies in risk factor management is warranted, and in this thesis, we address this issue. We present studies evaluating **the coordinating role of nurses in secondary prevention** (part 1), and studies on **smoking cessation** (interventions) in coronary patients (part 2).

PART 1 NURSE-COORDINATED CARE

Multidisciplinary approaches, including nurse-coordinated care, are recommended in the European prevention guidelines to improve secondary prevention of CVD.[2] This recommendation is based on a limited, yet increasing number of studies investigating the effects of various forms of nurse-coordinated care. Nurse-coordinated care in secondary prevention in general consists of cardiovascular risk assessment and supporting the patient to achieve the goals and target levels for risk factors. Nurses work as part of a multidisciplinary team, and are trained to support patients and their families in making lifestyle changes and adhering to (drug)therapy.[7] Next to these skills, care coordination is

part of a nurse's repertoire of skills and experiences and is increasingly being recognised as a pivotal part of secondary prevention.[8] According to Krumholz et al., coordinated care encompasses the development and implementation of a therapeutic plan designed to integrate the efforts of multiple health professionals.[9] Ideally, secondary prevention consists of a team-based patient-centred approach, benefitting from the expertise of multiple health professionals. Nurses have been shown to be effective coordinators of such preventive care.[7,10,11]

Studies investigating nurse-coordinated prevention programmes have shown promising results.[12-14] However, these initial landmark studies were conducted before clear definitions were developed of what nurse-coordinated care entails, and how to distinguish this care from other approaches, such as traditional disease and/or case management. Furthermore, these trials were carried out in widely varying healthcare settings, with a plethora of interventions, strategies, and outcomes. The effective components of nurse-coordinated care lack clear definitions, hampering the further investigation and implementation of these components. We therefore performed a comprehensive systematic review of the available evidence of nurse-coordinated care in secondary prevention of CHD aiming to clearly define intervention components and the effects thereof**.**

Lifestyle modification

A healthy lifestyle is the cornerstone of secondary prevention. Guidelines on secondary prevention of cardiovascular disease emphasise the importance of lifestyle interventions.[2] Lifestyle is based on long-standing behavioural patterns that are maintained in daily life. Many patients adopt healthier lifestyles directly after an event, or during the subsequent cardiac rehabilitation programme, but relapse into old habits when returning to everyday life.[15,16] Lasting improvement of lifestyle in patients with CVD has been shown to be challenging. A number of studies have demonstrated that health care professionals are often unable to help patients achieve a healthier lifestyle.[15] This may reflect a lack of skills, or a lack of time, with a limited number of brief clinic visits.

The Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists (RESPONSE-1) trial was designed to evaluate the effects of a nurse-coordinated prevention programme in patients after an acute coronary syndrome, focussing on both medication optimisation and lifestyle modification.[15] At 12 months, patients in the nurse-coordinated care group had better control of risk factors and a predicted relative risk of mortality (calculated using the SCORE algorithm) that was 17% lower than the usual care group. However, lifestyle-related risk factors were common and remained largely unchanged at follow-up in most patients.

Other studies evaluating health-care provider driven lifestyle programmes for patients with CHD have shown limited to no beneficial effects on lifestyle risk factors.[17,18] To achieve long-term improvements in lifestyle, a 'medical' approach may not be suitable. Rethinking the current approaches to secondary prevention programmes is therefore

warranted. This entails re-evaluating the role of medical professionals (doctors, nurses, other affiliated professionals), the components included in prevention programmes, and the setting. Potentially, secondary prevention programmes aimed at maximum reduction of cardiovascular risk factors, that are comprehensive and accessible (community-based), adapted to the medical and personal setting of patients, and involving patients' partners, can lead to improved risk factor control.[19] We therefore designed a nurse-coordinated prevention programme for coronary patients which included medical management but also coordinated referral of patients and their partners to a comprehensive set of lifestyle programmes, using up to three community-based interventions: the RESPONSE-2 trial.

RESPONSE-2

RESPONSE-2 was a multi-centre, randomised trial in 15 hospitals in the Netherlands. We hypothesized that a comprehensive intervention, involving patients' partners, would have a greater impact compared to a single risk factor approach.[12,17] We designed a strategy of nurse-coordinated referral based on patient preferences to a set of ≥ 1 community-based, existing interventions to achieve weight loss, improvement of physical activity, and smoking cessation, on top of usual care and including the patient's partner. These up to three community-based lifestyle programmes were offered uniformly, in their existing commercial formats.

The three existing community-based lifestyle programmes

Smoking cessation programme

Luchtsignaal® is an existing national smoking cessation programme in the Netherlands, offering up to seven telephone counselling sessions during a period of three months. The programme is based on the stages of change from the transtheoretical model and used strategies from motivational interviewing, action and coping planning, self-control training, and relapse prevention. Depending on patients' preferences, pharmacological therapy for smoking cessation could be prescribed.

Weight reduction programme

Weight Watchers® aims to reduce weight by emphasizing a healthy diet, change in behaviour, physical activity and group motivation and offers weekly group meetings for a weigh-in and group discussion, coordinated by a coach. Furthermore, dietary intake is based on a points system that addresses the total caloric energy in each product.

Physical activity programme

Philips DirectLife® is an internet-based coaching activity health programme that includes an accelerometer, comparable to a small USB memory device. The programme monitors daily physical activities, provides feedback via the accelerometer and offers personalized, internet-based coaching.

Nurses were trained in a systematic referral approach, consisting of risk status assessment, discussing the current risk status with patients, and assessing the level of motivation to change or sustain the current cardiovascular risk status. Depending on the level of motivation, participation in relevant lifestyle programme(s) was advised, followed by an official referral to the lifestyle programme after patient consent. This was the first trial to study referral of patients and their partners to existing community-based lifestyle programmes in secondary prevention, coordinated by hospital-based nurses.
To evaluate the effects of the comprehensive lifestyle modification programmes within the context of nurse-coordinated care, we defined a unique outcome parameter. To qualify for a successful outcome, a patient was only deemed successful if reaching the target (improvement) for at least one of the three lifestyle risk factors, without deterioration in any of the other two at 12 months follow-up. Success was defined as either 1) significant weight loss (≥5% weight reduction), 2) total smoking cessation (urine cotinine <200 ng/ml), or 3) at least 10% improvement on 6-minute walking distance test. Deterioration was defined as: 1) any weight gain in combination with a BMI >25 kg/m^2 ;2) any decrease in 6-minute walking distance compared with baseline; and 3) a positive cotinine test in non-smokers at baseline. Two exceptions were made: in patients who stopped smoking and/or improved their 6-minute walking distance, a BMI increase of ≤2.5% was classified as no deterioration.

PART 2 SMOKING CESSATION

The association between smoking and cardiovascular disease is one of the best-established relationships in modern medicine.[20] Consequently, smoking cessation after a coronary event is potentially the most effective of all preventive measures. A systematic review and meta-analysis showed a relative risk in myocardial infarction (MI) of 0.57 (95% 0.36-0.89) and in the composite endpoints of death/MI 0.74 (95% 0.53-1.02), compared with continued smoking in the short term of 6 months.[5]
Since smoking is the most important risk factor for CVD, we investigated smoking cessation rates in Europe and the Netherlands, the success of different smoking cessation interventions, and the dynamics of smoking cessation after an acute coronary event or revascularisation.

Smoking cessation intervention

According to the European guidelines on cardiovascular disease prevention, smoking cessation must be encouraged in **all** smoking patients.[2] It is recommended to identify (pre-event) smokers and to provide repeated advice on stopping, with offers to assist. Guidelines recommend that health care professionals and patients agree on a smoking cessation strategy which includes established cognitive-behavioural strategies (e.g.

motivational interviewing) and pharmacological support.[2,21,22] Professional support provided by a dedicated research nurse or trained smoking cessation counsellor can increase the odds of stopping [RR 1.66 (95% CI 1.42, 1.94)].[23] Both individual and group behavioural interventions are effective in helping smokers to quit.[24] The community-based smoking cessation intervention of our RESPONSE-2 trial was a protocol-driven intervention that included professional smoking cessation counsellors, behavioural therapy including motivational interviewing, intensive individual (telephone) follow-up support after discharge, and pharmacological treatment offered as adjunct to behavioural counselling.[23,25]

Hospitalisation for an acute coronary event provides an important opportunity to address smoking cessation. Several characteristics have been described that are associated with a lower likelihood of successful smoking cessation, such as exposure to environmental tobacco use, lower educational level, and higher scores on the Hospital Anxiety and Depression Scale (HADS).[26,27] However, considering the temporal trends and changing smoking legislation in Europe, a continuous re-evaluation of cessation rates and the characteristics of successful quitters is warranted. Better understanding of such characteristics may guide the development of more effective smoking cessation interventions. We investigated smoking cessation rates and quitter characteristics across different national and international settings, within two randomised clinical trials (RESPONSE 1 and 2) and three large European surveys (EUROASPIRE 2-4).

Aims of this thesis

To rethink the current management of risk factors in secondary prevention by:

1. Investigating the efficacy of nurse-coordinated care and its components in secondary prevention of coronary heart disease and evaluating the impact of nurse-coordinated referral to community-based lifestyle programmes.

2. Studying smoking behaviour in coronary heart disease patients and identifying characteristics of successful quitters after an acute coronary event or revascularisation.

Outline of the dissertation

Chapter 2 serves as an introduction, describing the prevalence of cardiovascular risk factors and their treatment in Dutch patients with coronary heart disease (the EUROASPIRE- project), and comparing these data with those from 6, 13, and 17 years previously.

Part 1 Nurse-coordinated care (chapters 3-6)

The first part of the thesis concerns nurse-coordinated care in the secondary prevention of coronary heart disease patients. In **chapter 3** we systematically review the available evidence on the efficacy of nurse-coordinated care. In **chapter 4** we present the objectives, design and expected results of our randomised controlled trial investigating a community-based comprehensive lifestyle programme on top of usual care, in patients who were recently hospitalised for coronary heart disease in the Netherlands (RESPONSE-2). In **chapter 5** we present the main findings of our RESPONSE-2 trial. In **chapter 6** we performed a subanalysis of the RESPONSE-1 trial presenting the effect of a nurse-coordinated prevention programme on the achievement of LDL-cholesterol targets in patients hospitalised for an acute coronary syndrome.

Part 2 Smoking cessation (chapters 7-9)

In the second part of this thesis we evaluate smoking behaviour in (European) coronary heart disease patients and to identify characteristics of successful quitters after an acute coronary event or revascularisation procedure. In **chapter 7** we present characteristics of successful quitters after an acute coronary syndrome in the population of the RESPONSE-1 trial. In **chapter 8** we investigate the characteristics of successful quitters, the use of cardiac rehabilitation programmes, including the smoking cessation programme, and the level of general risk factor management in persistent smokers versus in those who successfully quit smoking in Europe (EUROASPIRE IV). Finally, in **chapter 9** we investigate characteristics of successful quitters and their use of the smoking cessation programme and the other lifestyle interventions (RESPONSE-2), to improve lifestyle-related risk factors.

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'My father died of a heart attack, many years ago, but I survived. Are there many people that survive a heart attack, and how is this going to change my life?'
(Mr P. Sanders, 63 years, myocardial infarction)

Chapter 2

Secundaire preventie van coronaire hartziekte. Resultaten van Euroaspire IV.

(EuroASPIRE: European Action on Secondary Prevention by Intervention to Reduce Events)

Snaterse M, Khatibi S, Scholte op Reimer WJM, Peters RJG, Feng Y, Deckers JW.

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Samenvatting

Doel

Secundaire preventie is een belangrijk onderdeel van cardiovasculair risicomanagement. In het kader van European Action on Secondary Prevention by Intervention to Reduce Events (Euroaspire) worden sinds 1996 cardiovasculaire risicofactoren en hun behandeling periodiek geïnventariseerd bij patiënten met een coronaire hartziekte.

Opzet

Retrospectief onderzoek van achtereenvolgens opgenomen patiënten met een coronaire hartziekte.

Methode

In de regio's Rijnmond en Amsterdam zijn in 2012-2013 de belangrijkste cardiovasculaire risicofactoren en hun behandeling op gestandaardiseerde wijze onderzocht bij patiënten die waren opgenomen na een eerste hartinfarct of coronaire revascularisatie. Het onderzoek werd gemiddeld 18 maanden na de opname verricht. Bij patiënten zonder bekende diabetes mellitus werd een orale glucosetolerantietest uitgevoerd.

Resultaten

We onderzochten 498 patiënten. De gemiddelde BMI was 28 kg/m^2, bijna 75% had een BMI ≥25 kg/m^2 en 29% had een BMI ≥30 kg/m^2. Het gemiddelde van het totaal cholesterol was 4,4 mmol/L. Van de deelnemers rookte 16% en had 20% diabetes mellitus; de orale glucosetolerantietest leidde slechts bij 1% tot een nieuwe diagnose. Verreweg de meeste deelnemers (91%) gebruikten antihypertensiva, iets meer dan de helft gebruikte 2 of meer middelen. Desondanks had de helft van de patiënten hypertensie.

Conclusie

Van de cardiovasculaire risicofactoren bij hartpatiënten is het roken in de afgelopen 20 jaar gehalveerd. De secundair preventieve medicatie is in die periode gestegen tot een stabiel hoog niveau. Bloeddruk en overgewicht blijven echter serieuze aandachtspunten. Vooral de behandeling van hypertensie behoeft verbetering, bijvoorbeeld door dosisverhoging of combinatie van antihypertensiva. Routinematige orale glucosetolerantietests bij hartpatiënten zijn niet zinvol.

Introductie

Nationale en internationale richtlijnen onderstrepen het grote belang van cardiovasculair risicomanagement. Secundaire preventie, in de vorm van medicatie en betere leefgewoonten, is een belangrijk element in dit risicomanagement. Anno 2017 komen ongeveer 600.000 Nederlanders in aanmerking voor secundaire preventie vanwege een klinisch manifeste coronaire hartziekte.[1,2] In het kader van het onderzoeksproject 'European Action on Secondary Prevention by Intervention to Reduce Events' (Euroaspire) wordt de behandeling van risicofactoren bij patiënten met een coronaire hartziekte periodiek geëvalueerd.[3] In Nederland werden 3 eerdere metingen uitgevoerd, in 1995-1996, 1999 en 2006-2007.[4] In dit artikel geven we een samenvatting van de bevindingen van Euroaspire IV uit 2012-2013, en vergelijken we deze met de eerder gerapporteerde uitkomsten.

Methode

Euroaspire IV omvatte in totaal 7998 patiënten uit 24 landen; de internationale opzet is elders in detail beschreven.[3] Het doel was, kort gezegd, de aanwezigheid en niveaus van de belangrijkste cardiovasculaire risicofactoren op een gestandaardiseerde manier vast te stellen tenminste 6 maanden na de eerste opname wegens hartinfarct, instabiele angina pectoris, coronair chirurgie of percutane coronaire interventie. Een belangrijk verschil tussen Euroaspire IV en de 3 voorgaande inventarisaties was dat patiënten tot de leeftijd van 80 jaar werden geïncludeerd (eerder was dat 70 jaar) en dat bij patiënten zonder bekende diabetes mellitus een orale glucosetolerantietest werd gedaan.

Wij beperken ons hier tot het onderzoek in Nederland. De voorgaande metingen vonden plaats in de regio Rijnmond; aan Euroaspire IV namen voor het eerst ook Amsterdamse centra deel. De deelnemende centra waren het Sint Franciscus Gasthuis, het Maasstad ziekenhuis en het Erasmus MC in Rotterdam, en het AMC en Ziekenhuis Amstelland in Amsterdam. Patiënten die in de periode 1 januari -31 december 2011 achtereenvolgens waren opgenomen in deze ziekenhuizen en blijkens de gemeentelijke basisadministratie medio 2012 nog in leven waren, ontvingen een schriftelijke uitnodiging. Meer dan 70% van hen ging akkoord en werd onderzocht. Niet-deelnemers en deelnemers waren gemiddeld even oud en hadden een vergelijkbare klinische cardiale manifestatie doorgemaakt.

De onderzochte risicofactoren waren overgewicht, gedefinieerd als een BMI ≥25 kg/m^2, ernstig overgewicht gedefinieerd als BMI ≥30kg/m^2, en hypertensie, gedefinieerd als ≥140/90 mmHg. Voor de statistische analyse verwijzen we naar de internationale publicatie voor dit onderzoek.[3]

De medisch-ethische toetsingscommissies van de deelnemende ziekenhuizen gaven toestemming voor het onderzoek.

Resultaten

De risico-inventarisatie vond plaats bij 498 achtereenvolgens opgenomen patiënten, gemiddeld 18 maanden na hun opname.
Bijna 50% van de deelnemers had een percutane coronaire interventie gehad en 24% had coronairchirurgie ondergaan. De gemiddelde leeftijd bij opname bedroeg 62 jaar, 79% was man. De mediane tijd tussen opname en risico-inventarisatie bedroeg 18 maanden.

Bijna 75% van de patiënten was te zwaar (BMI ≥25 kg/m^2), 29% had ernstig overgewicht (BMI ≥30kg/m^2). Het gemiddelde gewicht van de vrouwen was 76 kg, dat van de mannen bijna 90 kg. Het aantal patiënten met diabetes mellitus bedroeg 20%. De orale glucosetolerantietest bij deelnemers zonder bekende diabetes mellitus leidde bij slechts 1% tot een nieuwe diagnose 'diabetes mellitus'. Het percentage deelnemers dat rookte, bedroeg bij opname nog 30%, maar was bij inventarisatie gedaald tot 16%. De gemiddelde cholesterolconcentratie was 4,4 mmol/L, het gemiddelde LDL was 2,4 mmol/L. Ruim de helft van de deelnemers had hypertensie (tabel).

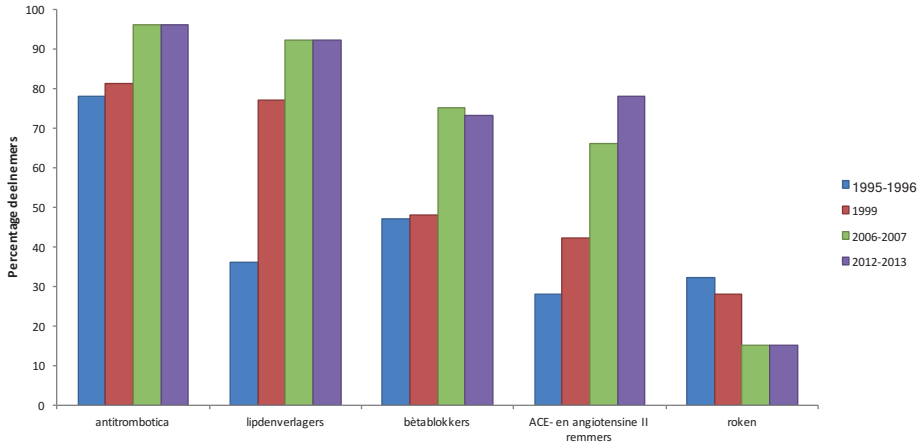
Tabel 1.
Risicomanagement bij patiënten met een coronaire hartziekte ≥ 6 maanden na een eerste gebeurtenis of ingreep, zoals geïnventariseerd in het kader van Euroaspire I (1995-1996), Euroaspire II (1999), Euroaspire III (2006-2007) en Euroaspire IV (2012-2013) *

	1995-1996		1999		2006-2007		2012-2013	
	NL	Eu	NL	Eu	NL	Eu	NL	Eu
risicofactor								
roken	123/387 (32)	646/3180 (20)	101/357 (28)	631/2971 (21)	28/185 (15)	434/2381 (18)	75/469 (16)	1280/7998 (16)
overgewicht	273/387 (71)	2439/3174 (77)	278/354 (79)	2368/2963 (80)	146/185 (79)	1965/2376 (83)	380/494 (77)	6558/7998 (82)
hypertensie	218/387 (56)	1847/3178 (58)	202/355 (57)	1730/2969 (58)	116/183 (63)	1452/2385 (61)	257/492 (52)	3439/7998 (43)
cholesterolwaarde ≥ 4.5 mmol/L	165/170 (97)	2268/2399 (95)	232/348 (82)	2122/2766 (77)	60/181 (33)	1049/2273 (46)	178/431 (42)	2959/7998 (37)
diabetes mellitus	40/387 (10)	552/3180 (17)	47/357 (13)	598/2970 (20)	38/184 (21)	664/2371 (28)	99/498 (20)	2159/7998 (27)
medicatie								
antitrombotica	300/387 (78)	2570/3180 (81)	289/357 (81)	2486/2973 (83)	177/185 (96)	2214/2376 (93)	478/498 (96)	7518/7998 (94)
antihypertensiva	275/387 (71)	2687/3180 (85)	278/357 (78)	2694/2973 (91)	174/185 (94)	2301/2376 (97)	451/494 (91)	6113/7823 (78)
lipidenverlagers	139/387 (36)	1025/3180 (32)	272/357 (76)	1864/2973 (63)	171/185 (92)	2110/2376 (89)	433/498 (87)	6878/7998 (86)

NL=Nederland; Eu=België, Bosnië-Herzegovina, Bulgarije, Cyprus, Duitsland, Finland, Frankrijk, Griekenland, Groot-Brittannië, Ierland, Kroatië, Letland,
Litouwen, Nederland, Oekraïne, Polen, Roemenië, Rusland, Servië, Slovenië, Spanje, Tsjechië, Turkije, Zweden.
*Alle getallen zijn n/N (%).

De grote meerderheid (91%) van de deelnemers gebruikte bloeddrukverlagers in de vorm van diuretica (24%), bètablokkers (76%), ACE of angiotensine II remmers (68%), dan wel calciumantagonisten (22%). Iets meer dan de helft van de patiënten gebruikte 2 of meer antihypertensiva. We vonden geen statistisch significante of klinisch relevante verschillen in medicatie tussen beide deelnemende regio's, behalve voor ACE- of angiotensine II remmers: deze werden in de regio Rijnmond gebruikt door 78% van de patiënten, in de regio Amsterdams door 67%. In de X^2- toets bleek dit verschil marginaal significant (p= 0.05).

Voor de deelnemers uit de regio Rijnmond zijn we de ontwikkeling nagegaan van het rookgedrag en het gebruik van preventieve medicatie in de afgelopen 20 jaar, zoals geregistreerd in Euroaspire I-IV (figuur). De figuur toont een grote toename van het preventieve medicatiegebruik en een bijna halvering van het aantal rokers ten opzichte van de eerste metingen.



Figuur 1.
Medicijngebruik en rookgedrag van patiënten met een coronaire hartziekte, 6 maanden na de eerste gebeurtenis of ingreep, zoals geïnventariseerd in de regio Rijnmond in het kader van Euroaspire I (1995-1996), Euroaspire II (1999), Euroaspire III (2006-2007) en Euroaspire IV (2012-2013).

Beschouwing

Onze recente registratie van het risicomanagement bij patiënten die werden opgenomen vanwege een coronaire hartziekte illustreert dat de medicamenteuze preventie steeds intensiever is geworden. Vrijwel alle patiënten werden behandeld met antitrombotica, lipidenverlagers of antihypertensiva. Sinds de eerste metingen uit 1995-1996 is het

medicatiegebruik ter secundaire preventie zeer sterk toegenomen; na de eeuwwisseling lijkt het nieuwe, hoge niveau zich gestabiliseerd te hebben.[4]

Levensstijl is een belangrijke oorzaak van coronaire hartziekten; naast roken zijn lichamelijke inactiviteit en een ongezonde voeding de bekendste factoren.[5] Overgewicht, diabetes en hypertensie zijn daarvan de meest in het oog springende gevolgen. In alle inventarisaties had driekwart van de patiënten overgewicht en was 29% obees. Het gemiddelde gewicht van Nederlandse hartpatiënten is voor mannen bijna 90 kg en voor vrouwen 76 kg, in beide gevallen ongeveer 5 kg hoger dan het algemene gemiddelde. De remedie tegen deze cardiovasculaire risicofactor is minder calorie-inname in combinatie met meer lichaamsbeweging, maar dat blijkt in de praktijk moeilijk haalbaar.[6]

Stoppen met roken lijkt voor veel patiënten echter wel te doen: bijna de helft van de betrokkenen is ertoe in staat gebleken. Daarbij moet worden opgemerkt dat bij de allereerste Euroaspire-metingen nog 30% van de deelnemers rookte en dat de sterke daling in het aantal rokende deelnemers ook kan samenhangen met de algemene afname van het aantal rokers in Nederland en de inmiddels ook wat hogere gemiddelde leeftijd van 'de hartpatiënt'. Vergeleken met de internationale Euroaspire-cijfers zijn de cijfers voor Nederland in elk geval niet ongunstig. De aantallen rokers zijn vergelijkbaar, het aantal patiënten met overgewicht is lager (zie de tabel)[3]. De Nederlandse patiënten blijken wat vaker lipidenverlagers te gebruiken.
De regio's in ons onderzoek zijn niet per definitie representatief voor heel Nederland, maar de bevindingen in beide onderzochte regio's waren goed vergelijkbaar, dus het is plausibel dat de bevindingen wel generaliseerbaar zijn. Ook de relatief kleine verschillen tussen de deelnemende landen wijzen in die richting.

Nieuw in de inventarisatie van 2012-2013 was de orale glucosetolerantietest bij deelnemers zonder bekende diabetes. Deze toevoeging leverde echter nauwelijks nieuwe diagnoses op; het routinematig uitvoeren van orale glucosetolerantietests bij patiënten met een coronaire hartziekte is dus waarschijnlijk niet zinvol.

Om de representativiteit van de uitkomsten te vergroten is de maximale leeftijd van de deelnemers aan Euroaspire IV verhoogd tot 80 jaar. Dat zou van invloed moeten zijn op bijvoorbeeld de gemiddelde bloeddruk, maar het aantal patiënten met een te hoge bloeddruk bleek toch iets lager dan in alle eerdere Euroaspire-metingen. Dat kan het gevolg zijn van het gestegen antihypertensivagebruik in de afgelopen twintig jaar. Dat nog steeds echter ongeveer de helft van de hartpatiënten een te hoge bloeddruk heeft, wijst erop dat goede bloeddrukcontrole ook met medicatie moeilijk haalbaar is. Bij dit alles moet wel bedacht worden dat de in dit onderzoek beschreven prevalentie van hypertensie berust op slechts een enkele bloeddrukmeting en dus ongetwijfeld een overschatting van de werkelijke prevalentie.

Conclusie

Onze recente inventarisatie van een relatief niet-geselecteerde groep patiënten met een coronaire hartziekte laat zien dat de preventieve medicatie bij de meeste patiënten uitgebreid en doorgaans adequaat is. Het niveau van de secundaire preventie is in medicamenteus opzicht min of meer gestabiliseerd ten opzichte van de eerdere metingen.

Het cardiovasculaire risicoprofiel van de patiënten is in de loop van de tijd gewijzigd, met minder rokers en meer mensen met diabetes. Het gegeven dat hartpatiënten tegenwoordig gemiddeld ouder zijn dan twintig jaar geleden speelt daarin zeker een rol. Dat de bloeddruk het bij zeer veel patiënten nog te hoog is, ondanks het inmiddels algemeen geworden gebruik van antihypertensiva, hangt daar ook mee samen. Voor de praktijk betekent dit dat veel patiënten met een coronaire hartziekte baat kunnen hebben bij het combineren van verschillende antihypertensiva.

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PART 1:

NURSE-COORDINATED CARE

Mr A. Vos: 'A nurse? What can nurses do that doctors can't?'
Nurse Emy: Let me tell you…It's nurses and doctors together!
(Mr A. Vos, 52 years, bypass operation)

Chapter 3

Effective components of nurse-coordinated care to prevent recurrent coronary events: a systematic review and meta-analysis.

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Heart 2016

Abstract

Background

Current guidelines on secondary prevention of cardiovascular disease recommend nurse-coordinated care (NCC) as an effective intervention. However, NCC programmes differ widely and the efficacy of NCC components has not been studied.

Purpose

To investigate the efficacy of NCC and its components in secondary prevention of coronary heart disease (CHD) by means of a systematic review and meta-analysis of randomised controlled trials.

Results

Eighteen randomised trials (11,195 patients in total) using 15 components of NCC met the predefined inclusion criteria. These components were placed into three main intervention strategies: 1) risk factor management (13 studies); 2) multidisciplinary consultation (11 studies), and 3) shared decision-making (10 studies). Six trials combined NCC components from all three strategies. In total, 30 outcomes were observed. We summarized observed outcomes in four outcome categories: 1) risk factor levels (16 studies); 2) clinical events (7 studies); 3) patient perceived health (7 studies), and 4) guideline adherence (3 studies). Compared to usual care, NCC lowered systolic blood pressure (weighted mean difference (WMD) 2.96 mmHg; 95% CI 1.53-4.40 mmHg) and LDL cholesterol (WMD 0.23 mmol/L; 95% CI 0.10-0.36 mmol/L). NCC also improved smoking cessation rates by 25% (Risk ratio 1.25; 95% CI 1.08-1.43).

Conclusions

NCC demonstrated to have effect on a small number of outcomes. NCC that incorporated blood pressure monitoring, cholesterol control and smoking cessation has 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.

Introduction

Coronary heart disease (CHD) remains a major cause of morbidity and mortality worldwide. Important determinants are the aging of populations and unhealthy lifestyles. [1 2] Patients with established CHD are at very high risk for recurrent cardiovascular events and mortality and are therefore considered the first priority in secondary prevention. [3] Although adequate risk factor control to guideline-recommended target levels is highly effective in the secondary prevention setting, recent surveys have shown that risk factor control in clinical practice is far from ideal, leaving substantial room for improvement.[4-6]

Secondary prevention provided and coordinated by nurses, i.e. nurse-coordinated care (NCC), has the potential to improve patient compliance and risk factor control in CHD patients, although previous reports on the effect of NCC have not shown clear and convincing results. [7 8] A previous review concluded that NCC in secondary prevention has a beneficial effect on quality of life. [9] However, no consistent relationships were observed between NCC interventions and other outcomes; in another review, almost half of the interventions had no significant effect on study outcomes. [10] Heterogeneity in intervention strategies and outcomes hinders comparison between the various studies. [10] The European guideline on cardiovascular disease prevention states that NCC prevention programmes are effective, based on two trials. [11 12] Available research is however more extensive and the overall findings appeared less conclusive. In the present study we therefore systematically reviewed the available evidence on the efficacy of NCC in secondary prevention of CHD.

Methods

Search strategy and selection

Using a comprehensive search strategy, we searched MEDLINE, the Cochrane Central Register of Controlled Trials and CINAHL from 1990 up to January 2015, with no language restriction. Since evidence for NCC has evolved after 1990s, the review was limited to studies published after 1990. The following search terms were entered as independent terms, text words, or MESH terms: (1) coronary heart disease or cardiovascular patient or cardiovascular diseases and (2) nurse led or case manage* or nurse practitioner or managed care programs/organization and administration. In addition, reference lists of existing reviews were manually searched to identify additional relevant studies. Our MEDLINE search strategy is described in detail in online supplement 1.

Two reviewers independently screened all titles and abstracts identified by the search. Studies that were classified as possibly relevant by at least one reviewer were retrieved

in full text and assessed for inclusion using a standardised inclusion form. Multiple publications reporting on the same study were included only when additional relevant outcomes were presented; they were counted as one study. Disagreements were solved by discussion between the two reviewing authors. We conducted our systematic review according to the PRISMA statement. [13]

Selection criteria

Studies were included only if: (a) they were designed as a randomised controlled trial (RCT); (b) patients were hospitalized or being treated by a GP for secondary prevention of CHD; (c) they included at least 70% of participants with established cardiovascular disease or reported data separately on a secondary prevention group; (d) a registered nurse was involved as a 'nurse-coordinator', using Krumholz's description of coordinated care: the development and implementation of a therapeutic plan to integrate the efforts of multiple health professionals [14]; and (e) the outcomes reported included risk factors, health behaviours, clinical events, patient perceived health or guideline adherence. For studies meeting these criteria, all other outcomes, except costs, were taken into account in our analysis.

Quality assessment

Two reviewers independently assessed the risk of bias in the included studies using the Cochrane Collaboration's risk of bias tool, which requires critical evaluation of the following domains: sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other source of bias. [15] After this evaluation, each domain of the studies was classified as having low, high or unclear risk of bias.

Data extraction

Data were extracted about the setting and study population, NCC intervention components, and both primary and secondary outcomes of included studies. Two reviewers independently extracted all relevant information using a data extraction form. Due to heterogeneity of the data, a descriptive approach was used to summarize components of NCC and their effect on outcomes. Based on consensus we distinguished three intervention strategies: 1) risk factor management, 2) multidisciplinary consultation and 3) shared decision-making. We rated the intensity of the intervention as high (> 4 visits plus more than one NCC strategy used), intermediate (3-4 visits), or low (1-2 visits). We defined a multidisciplinary team as a team with > 2 disciplines. Furthermore, we classified the observed outcomes into four categories: 1) risk factor levels, 2) clinical events, 3) patient perceived health and 4) guideline adherence. In our meta-analysis, we pooled the sufficiently homogeneous outcomes to determine the effectiveness of the NCC intervention.

Statistical analysis

We used forest plots to visualize the effects of NCC on systolic blood pressure, LDL cholesterol and smoking cessation compared to usual care, stratified for treatment intensity (high, intermediate, low, unknown). To indicate the differences between these methods, random and fixed effect models were used to pool treatment effects. Mantel-Haenszel fixed effect pooling assumes a single true treatment effect and ignores between-study heterogeneity. DerSimonian-Laird random effects pooling takes between-study heterogeneity into account and leads to wider confidence intervals. However, in random effects pooling, small studies receive more weight and this may affect the pooled treatment estimates. If no between-study heterogeneity exists, both methods yield identical results. Heterogeneity was expressed using the I-squared (I^2) statistic. (Pooled) risk ratios were calculated from 2×2 tables, which were derived from the publications, using the metan command (version 3.04, 21 September 2010) in Stata 13.1.

Results

Study selection

A total of 3524 publications were initially identified (Figure 1). Screening the references in these publications yielded another four potentially relevant studies. After two reviewers reviewed titles and abstracts, 44 publications were retrieved in full text. We excluded 25 of these publications after reading the full text (online supplement 2). To prevent double counting, only Voogdt-Pruis' primary care study (2010) was included, as it matched our review purpose best. [16] Campbell et al. reported different outcomes of the same study in two publications. We counted these as one study. [17 18] In total, we included 18 studies in our systematic review.

Trial characteristics

Total sample sizes ranged from 138 to 2142 participants in twelve countries of four continents (online supplement 3). Patients with CHD were recruited during hospital admission [11 19-26] or at outpatient clinics [27 28], a community health clinic [29], a secondary prevention unit [30] or general practices. [16 18 31 32] The study participants' mean age ranged from 54 to 75 years. [22 29] 'Usual care' generally consisted of routine aftercare by a GP or cardiologist (online supplement 3). In six of the trials routine care was more intensive, and included a cardiac rehabilitation programme. [23 25 26 28 30 33]

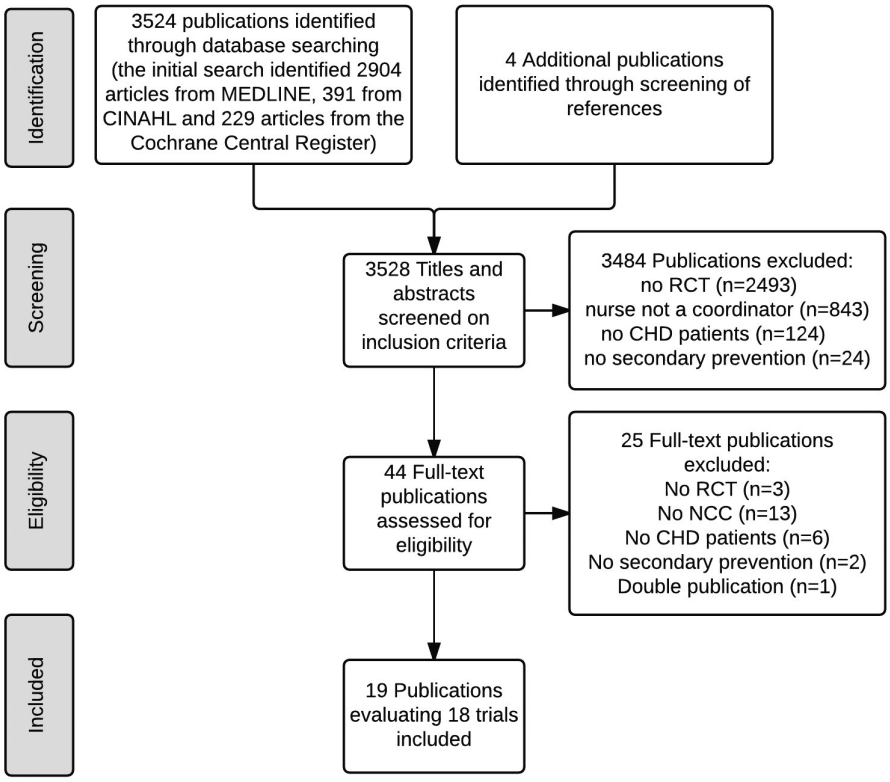

Figure 1.
Flow diagram of selection of trials

Risk of bias in included studies

Online supplement 4 presents the risk of bias across the included studies; 13 of 18 studies (72%) were considered to have a high risk of bias for one or more domains. In general, there was a low risk of selection bias; all studies, except two [30 33], used a valid method for random sequence generation; 4 of 18 trials (22%) used non-individual randomization methods. [11 24 31 32] Allocation concealment was unsatisfactory or not reported in five trials (28%). [11 18 24 30 33] In one trial 'the patients were randomized by the researchers' [18], which resulted in a high risk of bias. Blinding of intervention is not possible in this type of studies, which increases the possibility of performance bias. Four trials (22%) blinded the outcome assessors using an independent research assistant to carry out the clinical assessments, [21 24 28 32] and in three additional trials outcome data were independently retrieved from hospital records. [22 23 25] The risk of detection bias in the other trials was classified as either unclear or high. Six trials collected outcome data incompletely [11 16 21 24 27 30], had many missing values, [16] or unclear exclusions from the analysis. [11] Seven studies

(39%) did not report prespecified outcomes [19-21 26 27 30 33] in the primary publication or in a trial registry or design paper, if available. Of 18 trials in total, 5 recent trials (28%) were registered in a trial registry. [11 22 25 28 29] Eleven studies (61%) used one or more self-reported outcomes for lifestyle-related risk factors, which may have introduced bias. [34]

Description of the intervention by strategy

The NCC programmes varied in components and intensity (online supplement 3). We identified 15 components of the NCC intervention and grouped them into three strategies (Figure 2): (1) risk factor management, for example lifestyle counselling, blood pressure and lipid control; (2) multidisciplinary consultation, e.g. consultation and referral; and (3) shared decision-making, e.g. goal setting and family support.

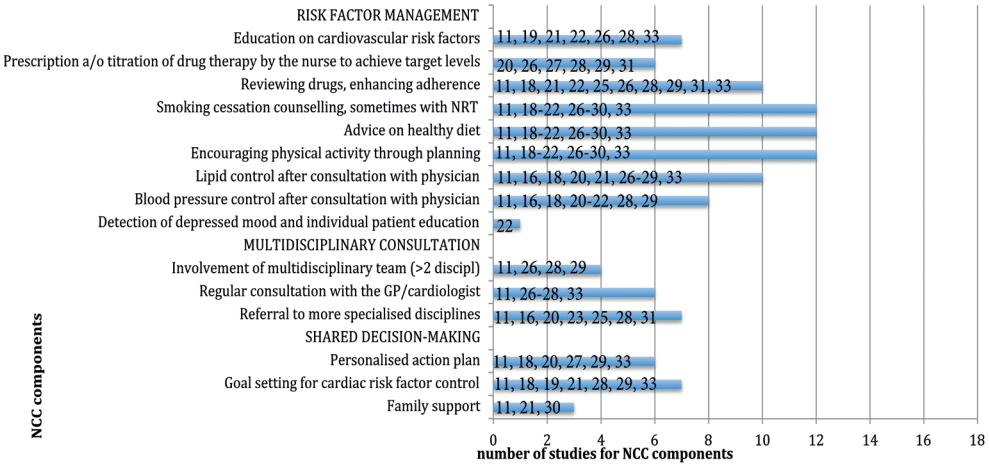

Figure 2.
Components of nurse-coordinated care by strategy in 18 studies
Presented numbers in figure are study references.
Abbreviations: a/o and/or; GP general practitioner; NCC nurse-coordinated care; NRT nicotine replacement therapy.

Risk factor management

Risk factor management was the most commonly used NCC strategy and was reported in 13 studies (72%). In six studies (33%) nurses were authorised to prescribe or titrate medication. [20 26-29 31] In two of these studies, this was done according to prespecified algorithms. [26 29] To encourage a more active lifestyle, NCC interventions consisted of 'instruction to participate in a home-based exercise programme' [29], 'Stepping Out' programmes to promote physical activity [18], starting a physical training programme in the first 3 months of the intervention [30], recommendation to walk briskly for 20 minutes daily [26], or referral to a physiotherapist. [11]

Multidisciplinary consultation

The second strategy, multidisciplinary consultation, was assessed in 11 studies (61%). 'Involvement of a multidisciplinary team' was part of this strategy in four trials (22%). [11 26 28 29] Seven trials [11 16 20 23 25 28 31] (39%) incorporated 'referral to more specialised disciplines' as needed.

Shared decision-making

The third strategy, 'shared decision-making', was incorporated in 10 studies (56%). This strategy refers to implementing family support [11 21 30], goal setting for cardiac risk factor control [11 18 19 21 28 29 33], and a personalised action plan. [11 18 20 27 29 33]

The included studies varied in terms of duration of the intervention (2 to 24 months), frequency of visits (3 to 14 contacts) and follow-up time (3 to 24 months). The majority used a 12-month follow-up period (online supplement 6). In eight studies (44%), telephone follow-up was used [19 21 22 25-27 29 33], and in six studies (33%) home visits were part of the intervention (online supplement 3) [19 21-23 25 27]. Six trials included four of more visits plus more than one NCC strategy (high intensity) [11 18 26-29]; six trials were rated as intermediate intensity [16 19-21 30 33], three trials were rated as low intensity [22 25 31], and three studies were rated as unclear intensity (online supplement 3). [23 24 32]

Description of outcomes by category

Outcomes of NCC varied considerably (online supplement 5a, 5b). In total, 30 NCC outcomes were measured. We grouped observed outcomes into four categories: 1) risk factor levels; 2) clinical events; 3) patient perceived health and 4) guideline adherence.

Risk factor levels

In 14 studies (78%), outcomes of NCC studies were measured as improvement of risk factor levels with heterogeneous treatment effects (online supplement 6). One study used SCORE, a comprehensive cardiovascular risk algorithm designed for the primary prevention setting, as the study outcome. [28] Figures 3, 4 and 5 present our meta-analyses of weighted mean differences (WMD) and relative risk (RR) calculations of trials reporting on systolic blood pressure (SBP), LDL cholesterol and smoking cessation, respectively.

Seven studies reported on SBP outcomes. The NCC intervention decreased systolic blood pressure by 2.96 mmHg (95% CI 1.53-4.40 mmHg) compared to usual care with low to moderate between-study heterogeneity (I^2 =37.1%). Eight trials reported on LDL-cholesterol outcomes. The effect of NCC compared to usual care on LDL cholesterol was -0.23 mmol/L (95% CI -0.36 to -0.10 mmol/L.), with substantial heterogeneity (I^2 =74.3%). Trials incorporating prescription and/or titration of drug therapy by nurses were associated with a significant reduction in LDL cholesterol and

systolic blood pressure, compared to usual care. Meta-analysis of eight trials comparing smoking cessation rates, generally self-reported (75%), between NCC and usual care yielded a pooled RR of 1.25 (95% CI 1.08-1.43). Random and fixed effect models showed no between-study heterogeneity in treatment effects (I^2 =0.0%). Six studies reported smoking cessation rates at 12 months [16 19 24 26 28 30], one study at 6 months [21] and one study at 12 weeks of follow-up. [33]

Clinical events

In total, seven studies reported on clinical events (online supplement 5b); five studies on recurrent events and duration of hospitalization [17 23 25] or readmission rates [17 20 25 28] at assessment time > 6 months. In four of these studies a reduction was shown for all-cause and cardiovascular readmission rates or duration of hospitalization and other CVD rates or recurrent coronary events. [17 18 20 23 28] A disease management programme [23] significantly reduced the secondary outcomes emergency department encounters (Incidence Density Ratio -2.08, p<0.001), claims for diagnostic or therapeutic services (830 versus 1208 claims, p=0.012), and use of laboratory services (1481 versus 2401, p=0.007) in favour of the NCC intervention. The trials that assessed the outcomes all-cause mortality [20 25], time to readmission or death [22] or event free survival [25] all showed no effect of NCC versus usual care on these outcomes.

Patient perceived health

Six publications reported patient perceived health outcomes with different instruments and showed small effects (online supplement 5b, 6). [18 20 24 25 29 31] Three studies showed a statistically significant improvement on the following questionnaires (or one of their subscales): the SF-36 [18], chest pain [18], perception of chronic illness care [29], and the Seattle Angina questionnaire. [31]

Guideline adherence

Three trials reported better results for the NCC intervention compared to the usual care group on the outcome category 'guideline adherence', which implies assessment of risk factors according to secondary prevention guidelines. [18 31 32]

Summary of effective interventions and their NCC components

We found that interventions that include independent prescription and/or titration of drug therapy by nurses and a high intensity strategy appeared to be effective in reducing systolic blood pressure and LDL-cholesterol (Figure 3,4). [20 26-29 31] Effective components regarding behavioural interventions were goal setting for cardiac risk factor control plus identification of barriers, an approach that positively affected the risk factor profile in several studies. [11 18 19 21 29]

Of 11 trials with prespecified primary outcomes, eight trials demonstrated positive outcomes for NCC compared to usual care: for the outcome category risk factor levels: total cholesterol [16 29 31], LDL cholesterol [29], triglyceride [29], pharmacological treatment [31], SCORE [28], blood pressure [28 29] and diet [11]; clinical events: all-cause and cardiovascular readmission (days) [23]; and guideline adherence. [18 32] Half of these studies were classified as high intensity, including > 4 face-to-face contacts [11 18 28 29] and frequent telephone follow-up in one of them. [29]

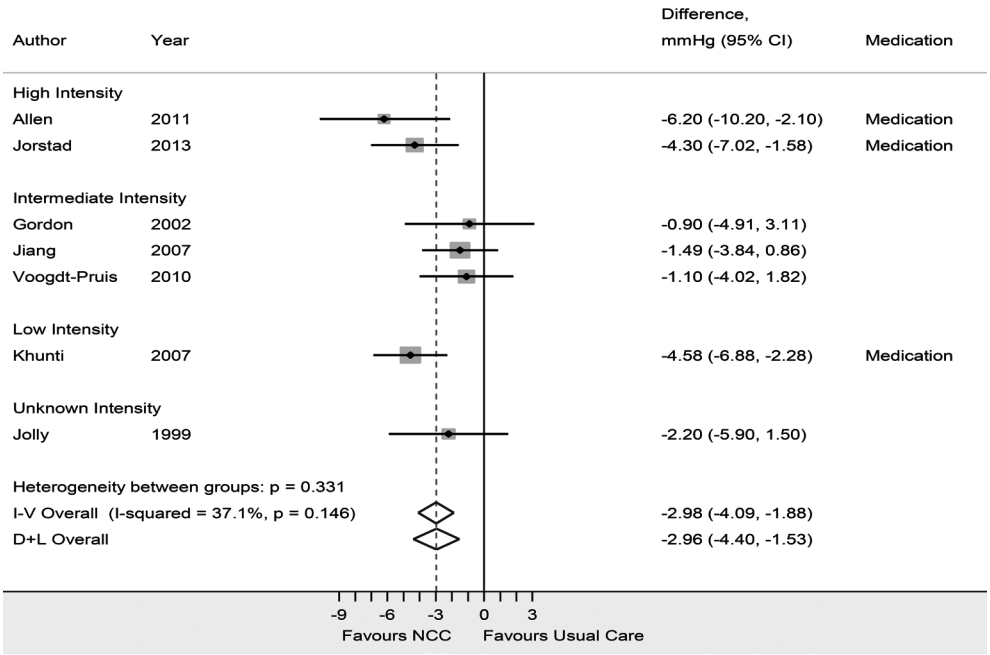

Figure 3.
Forest plot of seven randomized trials on the effect of nurse-coordinated care (NCC) on systolic blood pressure.
Trials are ordered by treatment intensity and year. Medication indicates trials using medication-titration; I-V, inverse -variance (fixed effect); D+L, DerSimonian-Laird (random effects). Random effects estimates in the subgroups are identical to the fixed effect estimates, no between trial heterogeneity. Except for two trials (Gorden et al., Jiang et al.), all trials used a 12-month follow-up period.

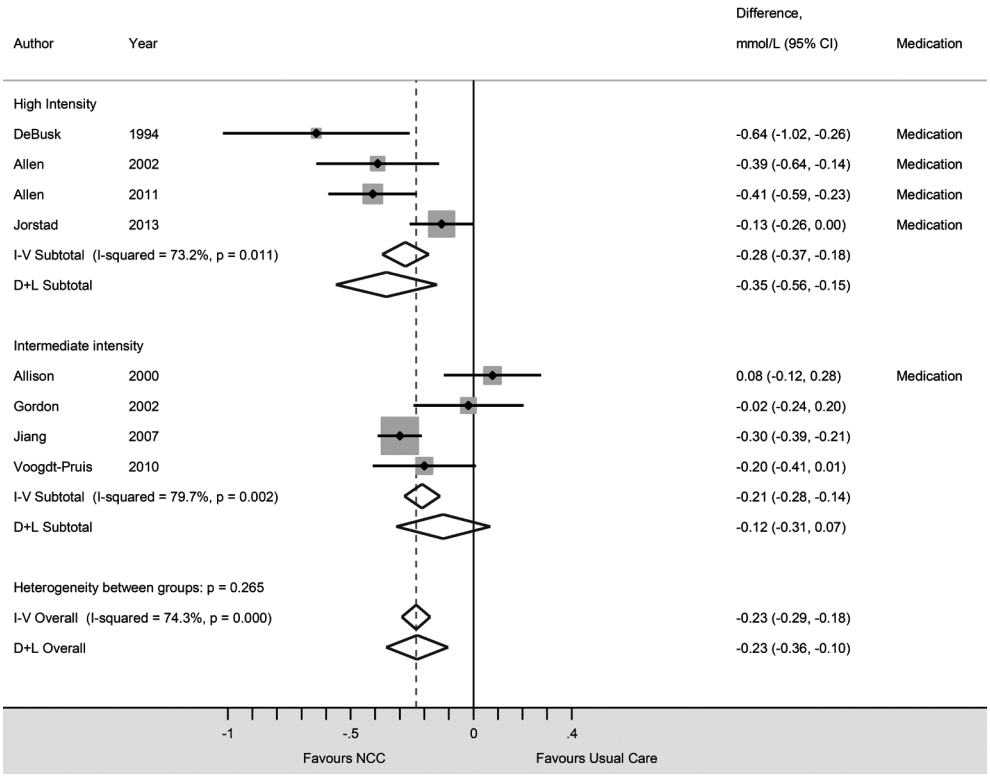

Figure 4.
Forest plot of eight randomized trials on the effect of nurse-coordinated care (NCC) on serum low-density cholesterol (LDL) concentrations.
Trials are ordered by treatment intensity and year. Medication indicates trials using medication-titration; I-V, inverse -variance (fixed effect); D+L, DerSimonian-Laird (random effects). Except for three trials (Allison et al., Gorden et al., Jiang et al.), all trials used a 12-month follow-up period.

Discussion

The evidence summarized in this review suggests that prescription and/or titration of drug therapy by nurses, in combination with a high intensive strategy, can decrease systolic blood pressure and LDL cholesterol. NCC also improved smoking cessation substantially by 25%, but, although nurses' attention for lifestyle-related risk factors was a common component in the reviewed studies, this did not result in weight loss.
Evidence from cardiac rehabilitation studies with exercise and multimodal interventions showed an effect on mortality[35]. This effect might have been achieved through improved adherence to lifestyle modification and medication, which may be a result of frequent follow-up visits by nurses.
The intervention components and outcome measures were very heterogeneous. This indicates that NCC is not yet a clearly defined concept, as well as a complex

intervention. Complex interventions, including several components, are made up of various interconnecting parts and it is therefore difficult to evaluate the contribution of individual components. Furthermore, breaking down these complex interventions into separate components does not take into account the synergistic effects of combining these components. In most studies, NCC interventions were multifaceted, broadly structured and therefore lacked focus. As there is a variation in the selection of outcomes in the included studies it is important to answer the question what should be appropriate goals for nurse-coordinated care. Consensus about NCC content and reporting of outcome measurements for RCTs would facilitate a better evidence base for the future. In 2006, the American Heart Association Disease Management Taxonomy Writing Group published a statement about defining and classifying different care models, in particular disease management. [14] The interdisciplinary writing group designed a conceptual model and its proposed components to allow comparisons across interventions of disease management trials. This statement forms an ideal starting point to compare diverse disease management programmes and to assess specific components associated with effectiveness. Such an initiative would also be valuable for the development of NCC programmes.

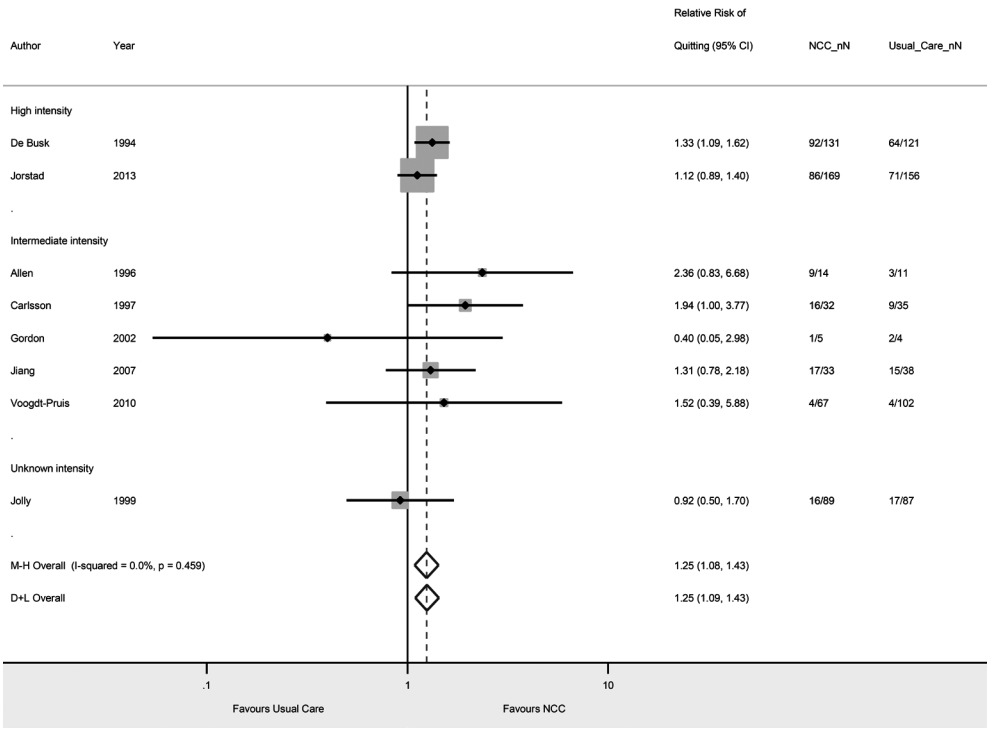

Figure 5.
Forest plot of eight randomized trials on the effect of nurse-coordinated care (NCC) on smoking cessation rates.
Trials are ordered by treatment intensity and year. M-H indicates Mantel-Haenszel (fixed effect), D+L

indicates DerSimonian-Laird (random effects). The trial by Wood et al. (2008) was excluded since only the absolute cessation risk difference (of 10.4% (-0.30 – 21.20) in favour of NCC) was reported and pooling of absolute risk differences caused much heterogeneity in the stratum with the intermediate intensity trials. NCC_nN and Usual_Care_nN denote the number of quitters (n) of the total number of smokers at baseline (N) in the NCC intervention groups and usual care groups, respectively. Except for one trial (Jiang et al.), all trials used a 12-month follow-up period.

Limitations

We encountered heterogeneity in our meta-analyses. We also observed between-study differences that we could not explain. Although the composition of NCC programmes was heterogeneous, this was not always the case for their relative effects on outcomes.

The overall quality of the RCTs in this review was moderate. At the same time it was encouraging that more recent studies had better methodological quality and clinical trial registration. One older study was deemed to be of low or unclear quality since it did not describe critical components for assessing the risk of bias. [30] We nevertheless included this study in the meta-analysis of smoking cessation.

Many studies were at risk of selective reporting. In several studies no pre-specified primary and secondary endpoints were stated. Self-reported outcomes were used as well, so the observed effects could be overestimated or underestimated. The results should therefore be interpreted with caution.

Overweight and smoking remained persistent and prevalent risk factors in many of the studies. A recent review on the efficacy of lifestyle modification programmes to support behaviour change in CHD patients found that comprehensive lifestyle modification programmes reduced mortality by 34% and cardiac readmissions by 35%. [36] Interventions incorporating four self-regulation techniques (i.e. goal setting, planning, self-monitoring, feedback) were associated with greater lifestyle benefits. This is in line with our finding that goal setting is a successful component for both behavioural counselling and medication-regulated risk factors. Community-based comprehensive lifestyle programmes take this approach and this might be a new opportunity to achieve weight reduction in CHD patients. [37-40]

Despite clinical heterogeneity, we conclude that effective NCC interventions consist of these components i) prescription and/or titration of drug therapy by nurses [26-29 31], particular with predefined algorithms [26 29] ii) tailored behavioural counselling with goal setting [11 18 19 21 29 33] and iii) frequent follow-up visits and telephone contacts.[26 27 29]

Our review shows that when NCC incorporates blood pressure monitoring, cholesterol control and smoking cessation, it may improve secondary prevention. Finding effective interventions to achieve weight reduction in CHD patients remains an important challenge for the future. Additionally, NCC has shown to be a heterogeneous concept. We recommend a shared definition of NCC to facilitate better comparisons of NCC content and outcomes.

Acknowledgements

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Competing interests: None to declare.

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Supplementary files for online publication

Online supplement 1.
Medline search strategy

(systematic[sb] OR (Therapy/Broad[filter])) AND ("Coronary Disease"[Majr] OR coronary disease*[tiab] OR coronary heart disease*[tiab] OR cardiovascular patient*[tiab] OR "Cardiovascular Diseases"[Majr] OR cardiovascular disease*[tiab] OR "Coronary Artery Disease"[Majr] OR "Heart Diseases"[Majr] OR cardiac disease*[tiab] OR "Coronary Disease"[Mesh:noexp] OR coronary risk[tiab] OR "Myocardial Infarction"[Majr] OR cardiovascular[ti] OR coronary[ti] OR cardiac[ti] OR Myocardial Infarction[ti]) AND ("Disease Management"[Mesh] OR Disease Management[tiab] OR Diseases Management[tiab] OR "Patient Education as Topic"[Mesh] OR nurse led[tiab] OR nursing management[tiab] OR nurse case management[tiab] OR case manage*[tiab] OR registered nurse*[tiab] OR "Nurse Practitioners"[Mesh] OR nurse practitioner*[tiab] OR nurse coordinat*[tiab] OR nurse delivered[tiab] OR "Nurse's Role"[MAJR] OR "Models, Nursing"[MAJR] OR "Nurse Clinicians"[Mesh] OR "Managed Care Programs/organization and administration"[Majr] OR "Case Management"[Majr] OR nurse counselor*[tiab] OR advanced practice nurse*[tiab] OR ((led) AND (nurse*)) OR ((clinic) AND (nurse*)))

Online supplement 2.
Excluded studies

Study	Reason/ selection criterion
Allison TG, Squires RW, Johnson BD, et al. Achieving national cholesterol education program goals for low-density lipoprotein cholesterol in cardiac patients: Importance of diet, exercise, weight control, and drug therapy. *Mayo Clin Proc* 1999;74:466-473.	No nurse-coordinated care
Broers CJM, Smulders J, van der Ploeg TJ, et al. Nurse practitioner equally as good as a resident in the treatment of stable patients after myocardial infarction, but with more patient satisfaction. *Ned Tijdschr Geneeskd*. 2006;150:2544-8.	No secondary prevention
Coburn KD, Marcantonio S, Lazansky R, et al. Effect of a community-based nursing intervention on mortality in chronically ill older adults: a randomized controlled trial. *PLoS Med*.2012;9(7).	No CHD patients
Giannuzzi P, Temporelli PL, Maggioni AP, et al. Global Secondary Prevention strategies to Limit event recurrence after myocardial infarction: the GOSPEL study. A trial rom the Italian Cardiac Rehabilitation Network. *Arch Intern Med*. 2008;168:2194-2204.	No nurse-coordinated care
Goessens BM. A Randomised, controlled trial for risk factor reduction in patients with symptomatic vascular disease: the multidisciplinary Vascular Prevention by Nurses Study (VENUS). *Eur J Cardiovasc Prev Rehabil*. 2006;13:996-1003.	No CHD patients
Goldie CL, Prodan-Bhalla N, Mackay M. Nurse practitioners in postoperative cardiac surgery: Are they effective? *Can J Cardiovasc Nurs*. 2012;22: 8-15.	No secondary prevention
Gould, KA. A Randomized controlled trial of a discharge nursing intervention to promote self-regulation of care for early discharge interventional cardiology patients. *Dimens Crit Care Nurs* 2011;30:117-25.	No nurse-coordinated care
Johnston M, Foullkes J, Johnston DW, et al. Impact on patients and partners of inpatient and extended cardiac counseling and rehabilitation: a controlled trial. *Psychosomatic medicine* 1999;61:225-233.	No nurse-coordinated care

Jun M. Case management to reduce risk of cardiovascular disease in a county health care system. *Arch Intern Med.* 2009;169:1988-1995.	No CHD patients
Lapointe F, Lepage S, Larrivee L, et al. Surveillance and treatment of dyslipidemia in the post-infarct patient: can a nurse-led management approach make a difference? *Can J Cardiol* 2006 Jul;22:761-767.	No nurse-coordinated care
Leemrijse CJ, vanDijk L, Jorstad HT, et al. The effects of Hartcoach, a life style intervention provided by telephone on the reduction of coronary risk factors: a randomised trial. *BMC Cardiovasc Disord*.2012;12:47.	No RCT
Mainie PM. To examine the effectiveness of a hospital-based nurse-led secondary prevention clinic. *Eur J Cardiovasc Nurs*. 2005;4:308-13.	No RCT
McHugh F. Nurse led share care for patients on the waiting list for coronary artery bypass surgery: a randomised controlled trial. *Heart* 2001;86:317-23.	No nurse-coordinated care
Miller P. Regimen compliance two years after myocardial infarction. *Nursing Research* 1990;39:33-6.	No nurse-coordinated care
Mills M, Loney P, Jamieson E, et al. A primary care cardiovascular risk reduction clinic in Canada was more effective and no expensive than usual on demand primary care - a randomised controlled trial. *Health and Soc Care in the Community* 2010;18:30-40.	No CHD patients
Patja K, Absetz P, Auvinen A, et al. Health coaching by telephony to support self-care in chronic diseases: clinical outcomes from The TERVA randomized controlled trial. *BMC Health Services Research*. 2012;12:147.	No nurse-coordinated care
Roderick P, Ruddock V, Hunt P, et al. A randomized trial to evaluate the effectiveness of dietary advice by practice nurses in lowering diet-related coronary heart disease risk. *Br J Gen Pract* 1997;47:7-12.	No nurse-coordinated care
Selvaraj FJ, Mohamed M, Omar K, et al. DISSEMINATE study group. The impact of a disease management program (COACH) on the attainment of better cardiovascular risk control in dyslipidaemic patients at primary care centers (The DISSEMINATE Study): a randomised controlled trial. *BMC Fam Pract*. 2012;13:97.	No nurse-coordinated care

Shah BR, Adams M, Peterson ED, et al. Secondary prevention risk interventions via telemedicine and tailored patient education (SPRITE): a randomized trial to improve post-myocardial infarction management. *Circ Cardiovasc Qual Outcomes* 2011;4:235-242.	No RCT
Taylor CB, Housten N, Smith PM, et al. The effect of a home-based, case managed, multifactorial risk-reduction program on reducing psychological distress in patients with cardiovascular disease. *J of Cardiopulm Rehab*. 1997;17:157-162.	No nurse-coordinated care
Vale MJ, Jelinek MV, Best JD, et al. For the COACH Study Group. Coaching patients On Achieving Cardiovascular Health (COACH). *Arch Intern Med. 2003*;163:2775-2783.	No nurse-coordinated care
Voogdt-Pruis HR, Van Ree JW, Gorgels AP, et al. Adherence to a guideline on cardiovascular prevention: a comparison between general practitioners and practice nurses. *Int J Nurs Stud* 2011;48:798-807.	Double publication
Woollard J. Effects of general practice-based nurse-counselling on ambulatory blood pressure and antihypertensive drug prescription in patients at increased risk of cardiovascular disease. *J Hum Hypertens* 2003;17:689-95	No CHD patients
Woollard J. Effects of a general practice-based intervention on diet, body mass index and blood lipids in patients at cardiovascular risk. *J Cardiovasc Risk* 2003;10:31-40	No CHD patients
Zhao Y, Wong FK. Effects of a post-discharge transitional care programme for patients with coronary heart disease in China: a randomised controlled trial. *J Clin Nurs* 2009;18:2444-2455.	No nurse-coordinated care

Chapter 3

Online supplement 3.
Characteristics of included studies

Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Allen et al. (1996)	138	Women after CABG. Hospital (start pre-discharge) and outpatient clinic, USA. Usual care by primary provider, standard discharge teaching and physical therapy instructions, pre-discharge group class.	64	0%	I: Nurse-directed behavioural interventions with elements of self-efficacy construct, starting the day before hospital discharge with a videotape and workbook. Hospital-based smoking cessation counselling. Feedback on food questionnaire, short-term goals for diet, exercise and smoking cessation.	**Consultation**: first visit before hospital discharge, 1 follow-up counselling after one month. **Home visits**: 1 visit, after 2 weeks. **Telephone follow-up**: 1 phone call, after 2 months. ***Intensity**: intermediate*
Allen et al. (2002)	228	Hypercholesterolemia and CHD patients. Outpatient clinic, USA. Usual care by primary provider/cardiologist enhanced with feedback on lipids.	60	72%	I: NP (case manager) + cardiologist/primary provider participated in managing patient's lipids. NP had permission to prescribe and monitor lipid-lowering drug therapy. One outpatient visit 4-6 weeks after discharge to initiate a lipid management plan. Lipid testing, medication and lifestyle modifications were an integral part of lipid management. Nutritional counselling, physical activity, smoking cessation counselling and relapse prevention.	**Consultation:** first visit 4-6 weeks after discharge. 7 contacts per patient within 12 months. **Home visits:** 1 visit. **Telephone follow-up:** yes. **Duration:** average of 4.5 hours per patient **Intensity**: high
Allen et al. (2011)	525	African American or Caucasians CVD patients. Community health clinics, USA. Usual care from primary provider with enhanced feedback regarding CVD risk factors.	54	29%	I: Behavioural interventions to effect lifestyle changes. Aggressive pharmacologic management, lifestyle modification, identification of barriers to attainment of goals by a NP functioning as a case coordinator. Pre-appointment reminders. Specific algorithms for drug treatment were developed; a low-literacy Wellness Guide was developed specially for the study as a behavioural tool to promote lifestyle changes. Instructions to participate in a home-based exercise program.	**Consultation:** 7 visits within 12 months. **Telephone follow-up:** 6 contacts between the consultations. ***Intensity**: high*

Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Allison et al. (2000)	326	Instable AP or elective PCI patients without myocardial infarction from chest pain unit. Cardiovascular health clinic, USA. Usual care from cardiologist, one follow-up appointment within 48 hours after discharge.	58	56%	I: Risk factor modification plan by a nurse interventionist, pharmacologic lipid management, referrals, and additional follow-up as indicated (check lipids).	**Consultation:** 3 one-hour visits or more if indicated within 6 months after discharge. **Duration:** 3 hours or more ***Intensity**: intermediate*
Campbell et al. (1998)	1343	CHD patients, 19 general practices. North Scotland. Usual care from general practitioner.	66	58%	I: Nurse clinic visits contains (1) symptoms reviewing to identify poor control and referral, (2) assessing drug treatment, (3) blood pressure and lipid control, (4) behavioural risk factors were assessed. Feedback, goal planning and an agreed action plan were outlined on a take home form. Leaflets to help with dietary modifications and Stepping Out programmes to promote physical activity were available. Health visitors, district nurses or practice nurses run the clinics. A clinic coordinator provided support by phone.	**Consultation:** 2 to 6 visits within 12 months. **Duration:** first visit around 45 min., follow-up visits around 20 minutes. ***Intensity**: high*
Carlsson et al. (1997)	168	Acute myocardial infarction patients. Secondary prevention unit, Sweden. Usual care from general practitioner, 2 or 3 visits in one year. *Before randomization:* The first five weeks all patients were scheduled for two visits: at a nurse and one visit at a cardiologist. They were informed about CAD risk factors and the effect of lifestyle changes on the prognosis. All patients were invited to join an exercise program, with extra information about the positive effects of physical activity.	62	75%	I: 3- month period education program, individually and in group sessions: counselling for smoking cessation, dietary education -information orally and in writing- and physical activity. Continued with 2-3 times weekly exercise training sessions for 10-12 weeks (40 min.)	**Consultation:** 4 visits within ten months. **Duration:** total of 9 hours per patient. ***Intensity**: intermediate*

Chapter 3

Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Carrington et al. (2013)	602	Elective and emergency patients with any cardiac diagnosis requiring ongoing management. Home visits, Australia. Usual care consists of ongoing care by their treating specialists physician and family physician. Access to follow-up health care services (including cardiac rehabilitation program).	70	72%	I: Home visit within 7-14 post index hospitalization according to GARDIAN system. Intensity of management by the cardiac nurse including repeat home visits, telephone coaching, and referral was adjusted accordingly. Detailed clinical report and recommendations were sent to the patient's specialist and family physician. Patients were able to contact the cardiac nurse for continued advice and support.	**Home visits:** 1 or more **Telephone follow-up:** average of 3.3 calls per patient (duration of 7.5 minutes) ***Intensity**: low*
DeBusk et al. (1994)	585	Acute myocardial infarction patients. Hospital (start pre-discharge) and outpatient clinic, USA. Usual care consists of follow-up care by internist, physician counselling on smoking cessation (50 dollar) and nutritionist counselling.	57	79%	I: (1) Nurse-initiated telephone contacts, (2) Computer-generated progress reports mailed to the patients, (3) visits for treadmill exercise testing, nutritional counselling, lipid lowering drug therapy (algorithms), or smoking relapse counselling by nurses. Nurses obtained permission to add a new drug; changes in dosage did not require permission.	**Consultations:** 4 visits to nurse case manager within 6 months. **Telephone follow-up:** max. 14 calls. **Duration:** 9 hours. ***Intensity**: high*

Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Gordon et al. (2002)	155	Diagnosed CAD patients. Cardiac rehabilitation clinic (I_1), outpatient clinic (I_2), and shopping mall kiosk/hospital outpatient complex (I_3), USA. No usual care, 3 interventions.	60	75%	All patients received a computer-generated cardiac risk factor report, goal level based on guidelines and an individualized action plan. Usual care by physicians. I_1: Cardiac rehabilitation program. 3 days/week, additionally education on CAD disease, risk factors and lifestyle modification. Included written materials, audiotapes, group education, one-on-one counselling. Referral for medication changes. I_2: Physician-supervised, nurse-care-managed program. Education on CAD disease, risk factors and lifestyle modification. Included written materials, audiotapes, one-on-one counselling. Home-based exercise plan, nutrition, weight, stress management, smoking cessation program. Supervising physician made medication changes or referral. I_3: Community-based program at a shopping mall kiosk or hospital outpatient complex. Administered by exercise physiologists. Counselling on site or via telephone, 1-2/week. Education on CAD disease, risk factors and lifestyle modification, ca. 15 min. Included written materials, audiotapes, one-on-one counselling. Home-based exercise plan, nutrition, weight, stress management, smoking cessation program. Referral for medication changes.	**Consultation:** 2 visits with the physician and nurse. **Telephone follow-up:** 4 calls ***Intensity**: intermediate*

Chapter 3

Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Jiang et al. (2007)	167	First hospitalization with AP or myocardial infarction. Hospital (start pre-discharge) and home visits, China. Usual care unclear.	62	71%	I: Cardiac rehabilitation program: *Phase I: Hospital based patient/family education on seven topics:* (1) CHD and self-management principles, (2) medication management (3) angina prevention and management (4) physical exercise (5) dietary management (6) smoking cessation and (7) family support. *Phase II: Home-based rehabilitative care* (1) setting of daily behavioural goals (2) setting of goals for cardiac physiological risk control (3) goal directed self-management (4) log record (5) participated family members (6) follow-up care through home visits and telephone calls for monitoring, facilitating and reinforcing the self-management practice of the patients and supportive behaviours of family members.	**Consultation:** 3 months, intensity unclear **Home visits:** yes **Telephone follow-up:** yes ***Intensity**: intermediate*
Jolly et al. (1999)	597	Newly diagnosed patients with myocardial infarction and angina. General practices, United Kingdom. Usual care unclear.	64	71%	I: An undefined program to coordinate preventive care from hospital-home led by three specialist liaison nurses. Coaching of practice nurses to provide structured follow-up care and seek advice. Responsibility for coordinating follow-up care. Each patient received a record, which prompted and guided follow up at standard intervals.	**Consultations:** visit practice staff every 3-6 months. **Telephone follow-up:** yes, support of practice staff by phone. ***Intensity**: unclear*
Jorstad et al. (2013)	754	ACS patients. 11 outpatients clinic, The Netherlands. Usual care by cardiologist and cardiac rehabilitation programme.	58	80%	I: Nurse-coordinated prevention program in addition to UC based on guidelines. Focus on (1) healthy lifestyles (2) biometric risk factors (3) medication adherence. This included medication titration as needed. Referral to other health professions or treating physician for diabetes as needed.	**Consultations:** 4 visits in six months. ***Intensity**: high*
Khunti et al. (2007)	1316	CHD and CHF patients from 20 general practices, United Kingdom. Usual care from primary healthcare team, also open access to ECG and secondary care clinic.	70	62%	I: In addition to UC, two peripatetic nurse specialists trained in the management of CHD and CHF travelled between practices, where they held weekly clinics. Including assessment, conformation of diagnosis by investigations, medication management and titration and liaison between primary and secondary care.	**Consultations:** Weekly clinics, intensity unclear. **Home visits:** only for housebound patients with CHF. ***Intensity**: low*

Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Meisinger et al. (2013)	340	MI patients of ≥65 years. Hospital (start pre-discharge) and home visits, Germany. Usual care unclear.	75	62%	I: Intervention combining (1) case management and (2) disease management components: (1) identification of individual care problems, the facilitation of care coordination, (2) management of cardiac risk factors and the provision of information and individual education, including medication and medication adherence.	**Home visits:** Varying number of home visits (0-4), dependent on patients' needs and risk level. First consultation before discharge. **Telephone follow-up:** at least every 3 months, average of 19 minutes per phone call. **Duration:** Average of 117 minutes per home visit. ***Intensity**: low*
Moher et al. (2011)	2142	CHD patients from 21 general practices, United Kingdom. No usual care, 3 interventions.	66	68%	3 methods of promoting secondary prevention. I_1: Audit group. Audit of summary feedback by primary health care team at a practice meeting; amount of patients with CHD, proportion of patients with adequate assessment, data from other practices for comparison. I_2: GP group. Same information as audit group. Recall to general practitioner for patient assessment according to guidelines. Setting up a disease register and systematic recall of patients. I_3: Nurse group. Same information as GP group. Recall to nurse-clinic for patient assessment according to guidelines of secondary prevention. Nurses received education to implement it. Setting up a disease register and systematic recall of patients in a nurse led clinic.	**Consultations:** unclear ***Intensity**: unclear*
Voogdt-Pruis et al. (2010)	701	Patients with high risk for or documented CVD. Primary care, The Netherlands. Usual care from the general practitioner. Treatment protocol adhered to the Dutch guideline.	64	64%	I: Nurse consultation for cardiovascular risk management according to Dutch guideline with referral to other professions (dietician). Lifestyle and medical advice.	**Consultations:** 3 to 4 consultations within 12 months. ***Intensity**: intermediate*

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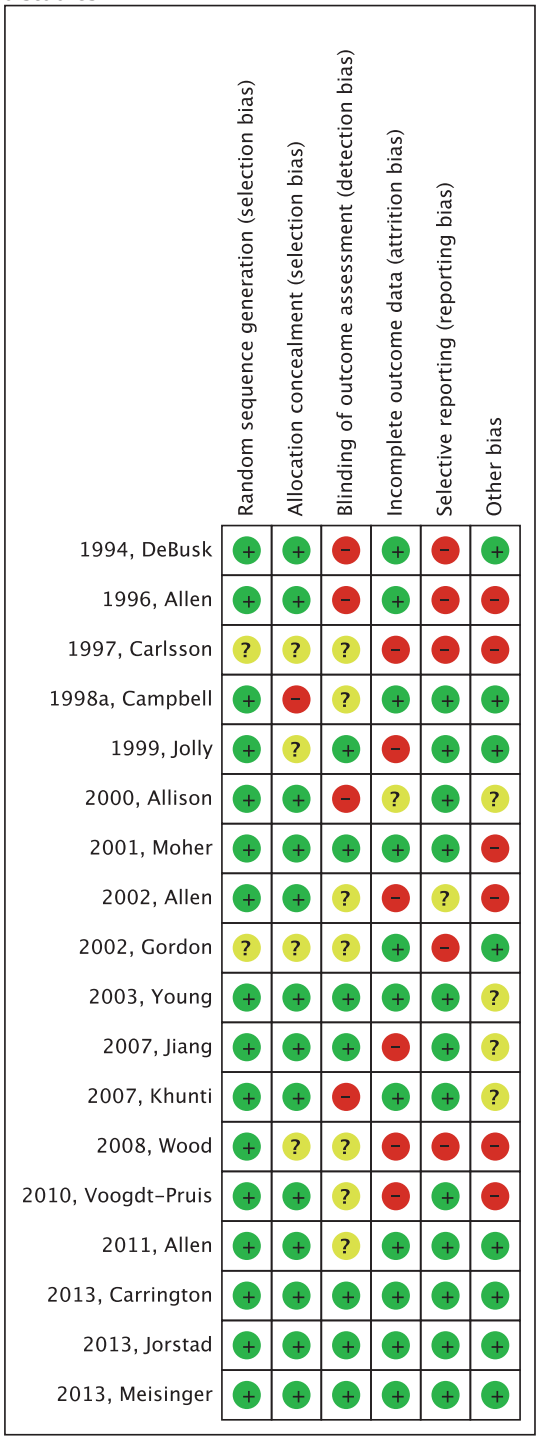
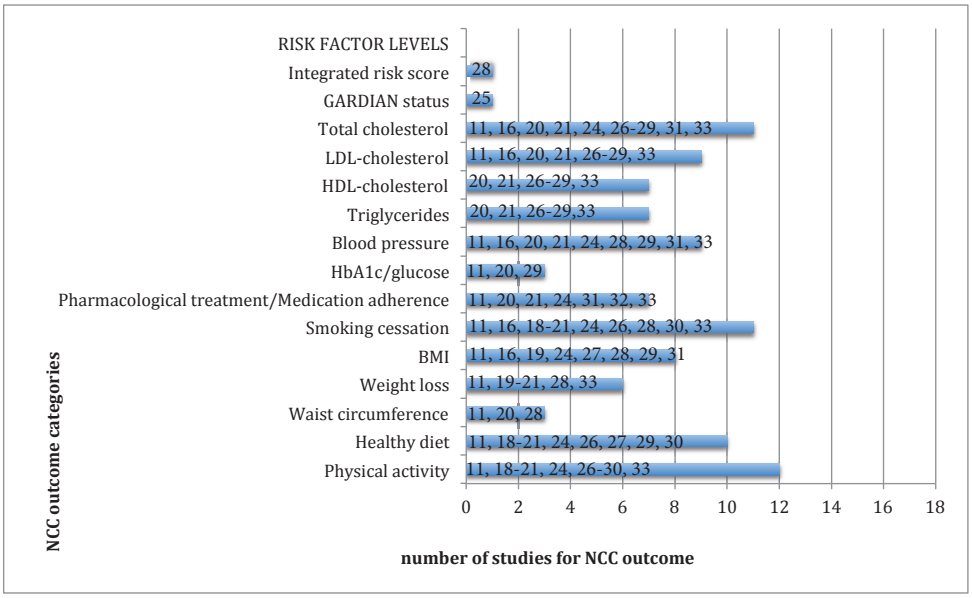
Study	Sample size (=n)	Study population, setting, usual care	Mean age in years	Men (%)	Intervention content and coordinating activities	Intensity
Wood et al. (2008)	946 (hospital)	ACS or high-risk patients and their partners. Only hospital arm taken, 12 hospitals in Europe. Usual care unclear.	63	70%	I: Initial assessment of risk factors, lifestyle, drug treatment of patients and partners. Reassessment of patient and partner at 16 weeks, reassessment at one year. Medication titration by *cardiologist*. D*ieticians* (hospital) gave advice in terms of food and patterns and set realistic goals for patient and families. *Nurse* smoking cessation, quit date+ plan. Blood pressure cholesterol and glucose monitoring, education to improve medication compliance. *Physiotherapist* patterns, capacity, plan+ goals, step counter, 7-day activity recall diary.	**Consultations:** at least 8 sessions, plus a group workshop and exercise class in 4 months. ***Intensity**: high*
Young et al. (2003)	162	MI patients at hospital discharge, home visits. Canada. Usual care consists of follow-up by own cardiologist, information in cardiac teaching class and cardiac rehabilitation programme.	69	60%	I: Disease management program. A standardized pathway 'the nursing checklist', referral criteria for specialty care, communication system with the family physician and patient education.	**Home visits:** minimum of 6 home visits within 8 weeks. ***Intensity**: unclear*

Abbreviations: ACS: Acute Coronary Syndrome, AP: Angina pectoris, C: Control, CABG: Coronary arterial bypass graft, CHD: Coronary heart disease, CHF: Coronary heart failure, CVD: Cardiovascular disease, ECG: Electrocardiogram, GP: General practitioner, I: Intervention, MI: myocardial infarct, NP: Nurse practitioner, PCI: Percutaneous coronary intervention.

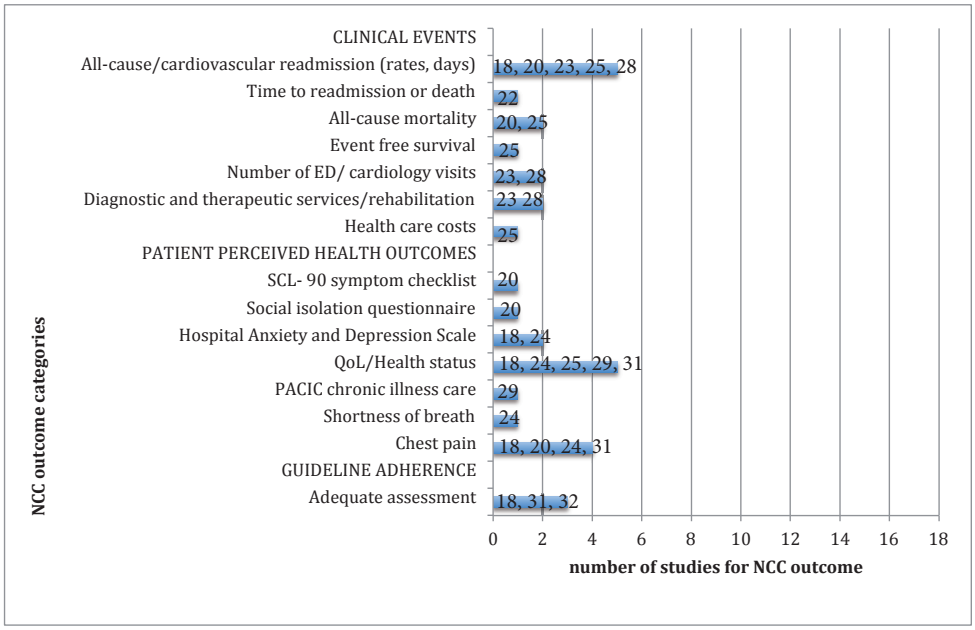
Online supplement 4.
Risk of bias in included studies



Online supplement 5a.
Assessed outcomes of nurse-coordinated care by category in 18 studies
Presented numbers in figure are study references.
Abbreviations: NCC nurse-coordinated care.



Online supplement 5b.
Assessed outcomes of nurse-coordinated care by category in 18 studies
Presented numbers in figure are study references.
Abbreviations: ED emergency department; NCC nurse-coordinated care; SCL-90 Symptom Check List; QoL quality of life; PACIC Patient Assessment of Chronic Illness Care



Online supplement 6.
Description of outcomes

Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
Allen et al. (1996)	Risk factor levels	Smoking	Self-reported	NS	12 months
		BMI	Kg/m^2	NS	
		Weight loss	Not reported	NS	
				NS	
		Dietary intake	Questionnaire: dietary intake of previous month	Fat(%) p=0.008, saturated fat (%) p=0.02	
		Physical activity	Questionnaire: 7-day activity recall	NS	
Allen et al. (2002)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	-0.4 mmol/L, p=0.008	12 months
			LDL-C (mmol/L)	-0.39 mmol/L, p=0.001	
			HDL-C (mmol/L)	NS	
			Triglycerides (mmol/L)	NS	
			LDL-C<2.59 mmol/L, n (%)	NR	
		Smoking	Exhaled carbon monoxide + self-reported	NR	
		Dietary intake	Questionnaire: fat intake (%)	-3.7%, p=0.004	
			Questionnaire: saturated fat intake (%)	-1.4%, p=0.004	
			Questionnaire: cholesterol intake (mg)	-62.5 mg, p=0.017	
			Questionnaire: fiber intake	NS	
		Physical activity	Questionnaire: physical activity	18 METS, p=0.05	
Allen et al. (2011)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	-0.51 mmol/L, p<0.001	12 months
			LDL-C (mmol/L)	-0.41 mmol/L, p<0.001	
			HDL-C (mmol/L)	NS	
			Triglycerides (mmol/L)	-0.18 mmol/L, p=0.003	
		Blood pressure	Systolic BP (mmHg)	-6.2 mmHg, p=0.013	
			Diastolic BP (mmHg)	-3.1 mmHg, p=0.013	
		HbA1c	Mean HbA1c	-0.5%, p=0.034	
		Smoking cessation	Not reported	NR	

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Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
		BMI	Kg/m^2	NS	
		Dietary intake	Questionnaire: Habits and History Food Frequency	NS	
		Physical activity	Questionnaire: Stanford 7-Day Physical Activity	NS	
	Perceived health outcomes	Quality of life	Questionnaire: EQ-5D	Reported elsewhere	
		Perception of chronic illness care	Questionnaire: PACIC	1.2 points, p<0.001	
Allison et al. (2000)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	NS	6 months
			LDL-C (mmol/L)	NS	
			HDL-C (mmol/L)	NS	
			Triglycerides (mmol/L)	-0.37 mmol/L, p<0.001	
		Blood pressure	Systolic BP (mmHg)	NS	
			Diastolic BP (mmHg)	NS	
		Glucose	Fasting blood glucose (mg/dL)	NS	
		Pharmacological treatment	Pharmacological treatment rates	NS	
		Smoking	Exhaled carbon monoxide + self-reported	NS data not applicable for meta-analysis	
		Weight loss	Kg	-1.0 kg, p=0.007	
		Low fat diet	Questionnaire: no data	p=0.012	
		Regular exercise	Questionnaire (in min.)	25 min, p=0.049	
	Clinical events	**Recurrent events**			
		Recurrent coronary event	Rate	-8%, p=0.002	
		Rehospitalization	Rate	NS	
		Death	All causes	NS	
	Perceived health outcomes	Psychosocial evaluation	Questionnaire: SCL-90-R	NS	
			Questionnaire: Social isolation questionnaire	NR	
		Chest pain	Reporting episodes (%)	NS	

Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
Campbell et al. (1998)	Risk factor levels	Aspirin management	On target (%)	NS	12 months
		Blood pressure management	On target (%): ≤ 160/90 mmHg	RR=1.09 (1.06-1.13)	
		Lipid management	On target (%): ≤ 5,2 mmol/L	RR=1.9 (1.59-2.29)	
		Smoking cessation	On target (self-reported) (%)	NS data not applicable for meta-analysis	
		Low fat diet	On target (DINE-score) (%)	RR=1.16 (1.03-1.31)	
		Physical activity	On target (%)	RR=1.35 (1.16-1.58)	
	Clinical events	Use of health service	Difference in length of stay (days)	NS	
			Hospital admissions (OR)	OR=0.64 (0.48-0.86), p=0.003	
	Perceived health outcomes	Anxiety and depression	Questionnaire: HADS	NS	
		Health status	Questionnaire: SF-36 score		
		Physical domain		4.33, p<0.001	
		Social domain		3.51, p=0.007	
		Role domain		8.52, p<0.001	
		Role emotional domain		4.66, p=0.045	
		Mental domain		NS	
		Energy domain		NS	
		Pain domain		2.50, p=0.035	
		General domain		2.34, p=0.013	
		Chest pain	Worsening	OR=0.59 (0.37-0.94), p=0.025	
			Reporting chest pain	NS	
Carlsson et al. (1997)	Risk factor levels	Smoking habits	Questionnaire, self-reported	NS	12 months
		Food habits	Questionnaire	Unclear, p=0.008	
		Physical activity	Questionnaire	NS	
Carrington et al. (2013)	Risk factor levels	Clinical status	**GARDIAN risk status (effect sizes unknown)**		24 months
			Low risk group	p<0.001	
			Medium risk group	p=0.004	
			High risk group	p=0.004	
	Clinical events	All-cause and cardiovascular hospitalization	Rate	NS	

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Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
		All cause hospital stay	Days/patient per month	NS	
		All-cause mortality	Rate	NS	
		Event free survival	Rate	NS	
		Health care costs	Associated costs/patient per month	NS	
	Perceived health outcomes	Quality of life	Questionnaire: SF-12 (physical domain)	NS	
			Questionnaire: SF-12 mental domain)	NS	
			Questionnaire: EQ-5D (health state)	NS	
			Potential depression	NS	
DeBusk et al. (1994)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	-0,63 mmol/L, p<0.001	
			LDL-C (mmol/L)	-0,64 mmol/L, p<0.001	
			HDL-C (mmol/L)	NS	12 months
			Triglycerides (mmol/L)	NS	
		Smoking cessation	Biochemically + self-reported (%)	17%, p=0.03	
		Nutritional management	Questionnaire: food frequency	Unclear	
		Functional capacity	Treadmill exercise test (METS)	0.9 METS, p=0.001	
Gordon et al. (2002)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	NS	12 weeks
			LDL-C (mmol/L)	NS	
			HDL-C (mmol/L)	NS	
			Triglycerides (mmol/L)	NS	
		Blood pressure	Systolic BP (mmHg)	NS	
			Diastolic BP (mmHg)	NS	
		Medication use	Change in %	NS	
		Smoking	Self-reported	NS	
		Weight loss	LBS	NS	
		VO2 max	VO2 max (ml/kg/min)	NS	
Jiang et al. (2007)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	-0.33 mmol/L, p=0.001	
			LDL-C (mmol/L)	-0.30 mmol/L, p=0.001	6 months

Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
			HDL-C (mmol/L)	NS	
			Triglycerides (mmol/L)	-0.10 mmol/L, p=0.011	
		Blood pressure	Systolic BP (mmHg)	NS	
			Diastolic BP (mmHg)	NS	
		Medication adherence	Self-reported	NS	
		Smoking	Self-reported	NS	
		Weight	Kg	NS	
		Diet	Mean no. of patients with step II diet adherence	-10.28, p=0.002 (netto change)	
		Walking	Activity total score: Jenkins Activity Checklist for Walking	1.91, p=0.002 (netto change)	
Jolly et al. (1999)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	NS	12 months
		Blood pressure	Systolic and diastolic differences (mmHg)	NS	
		Pharmacological treatment	Difference in prescribed drugs (%)	NS	
		Smoking cessation	Biochemically + self-reported (%)	NS	
		BMI	Kg/m2	NS	
		Diet	Mean difference in score for intake (self-reported)	NS	
		Exercise	Distance walked in 6 min. (test)	NS	
	Clinical events	Practice attendance	Difference in mean no. of visits	NS	
		Rehabilitation	Attendance at at least one session (%)	18%, p<0.001	
	Perceived health outcomes	Anxiety	Questionnaire: HADS subscale	NS	
		Depression	Questionnaire: HADS subscale	NS	
		Quality of life	Questionnaire: EuroQol	NS	
		Shortness of breath	Self-reported (%)	NS	
		Chest pain	Self-reported (%)	NS	
Jorstad et al. (2013)	Risk factor levels	10-year cardiovascular mortality (SCORE)	Estimation of SCORE risk reduction (%)	-17.4%, p=0.021	12 months
		Reduction of 10-year incidence of coronary mortality and morbidity	Framingham Coronary Risk Score (FCRS)	-12.5%, p=0.017	

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Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
		Lipids	Total Cholesterol (mmol/L)	NS	
			LDL-C (mmol/L)	NS	
			HDL-C (mmol/L)	NS	
			Triglycerides (mmol/L)	NS	
		Blood pressure	Systolic BP (mmHg)	-4.3 mmHg, p=0.002	
			Diastolic BP (mmHg)	NS	
		Smoking	Self-reported	NS	
		BMI	Kg/m2	NS	
		Weight	Kg	NS	
		Waist circumference	Cm	-2.1 cm , p=0.048	
	Clinical events	Total number of readmissions	N (%)	-22%, p=0.023	
		Readmissions for ACS	N (%)	NS	
		Other CVD readmissions	N (%)	-48%, p<0.001	
		Elective interventions	N (%)	NS	
Khunti et al. (2007)	Risk factor levels	Total cholesterol	Total Cholesterol (mmol/L)	- 0.18 mmol/L (-0.30, -0.05)	12 months
		Systolic BP	mmHg	-4.58 mmHg (-6.88, -2.28)	
		Diastolic BP	mmHg	-3.53 mmHg (-4.78, -2.29)	
		ACE inhibitor	Prescribed drugs (OR)	NS	
		Aspirin	Prescribed drugs (OR)	NS	
		Beta-blocker	Prescribed drugs (OR)	1.43 (1.19-1.99)	
		Lipid lowering medication	Prescribed drugs (OR)	1.99 (1.06-3.74)	
		BMI	Kg/m2	NS	
	Process of care	**Risk factor management**			
		Cholesterol measured	OR	NS	
		Cholesterol < 5mmol/L	OR	1.58 (1.05-2.37)	
		BP measured	OR	22.61 (6.47-70.13)	
		BP < 140/85 mmHg	OR	1.61 (1.22-2.37)	
		Smoking status recorded	OR	33.96 (14.49-79.62)	
		BMI/weight measured	OR	10.14 (4.99-20.55)	

Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
	Perceived health outcomes	**Quality of life**	Questionnaire: SF-36		
		Physical functioning		5.33, p=0.02	
		Role physical		NS	
		Body pain		NS	
		General health		2.56, p=0.0001	
		Vitality		5.53, p=0.0001	
		Social functioning		7.76, p=0.0002	
		Role emotional		NS	
		Mental health		4.49, p=0.001	
		Angina pectoris	Questionnaire: Seattle Angina Questionnaire		
		Exertional capacity		5.25, p=0.001	
		Angina stability		NS	
		Angina frequency		2.69, p=0.045	
		Treatment satisfaction		NS	
		Quality of life		NS	
Meisinger et al. (2013)	Clinical events	First unplanned readmission or death	Time-to-event from initial discharge (HR)	NS	12 months
		Intervention costs		Reported elsewhere	
	Perceived health outcomes	Functional ability	Questionnaires: the Barthel Index, HAQ-DI, IADL	Not yet been published	
		Social support	Questionnaire: F-sozU		
		Depressive symptoms	Questionnaire: GDS		
		Emotional well-being	Questionnaire: WHO-5		
		Cognitive function	MMSE		
Moher et al. (2001)	Risk factor levels	**Pharmacological treatment**			18 months
		Antiplatelets	Mean (range percentage)	Nurse-Audit: 10%, p=0.009	
		Hypotensive	Mean (range percentage)	NS	
		Lipid lowering	Mean (range percentage)	NS	
	Process of care	Overall adequate assessment	Mean (range percentage)	Nurse: 85%, GP:76%, Audit: 52%	
				Nurse vs. audit p<0.001	
				GP vs. Audit p=0.002	

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Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
		Adequate assessment of:			
		Blood pressure	Mean (range percentage)	GP:97%, Audit:86%, p<0.001	
		Cholesterol	Mean (range percentage)	Nurse:88%, Audit:67%, p=0.001	
		Smoking status	Mean (range percentage)	Nurse:95%, Audit:78%, p=0.001	
Voogdt-Pruis et al. (2010)	Risk factor levels	Lipids	Total Cholesterol (mmol/L)	-0.2 mmol/L, p=0.009	12 months
			LDL-C (mmol/L)	NS	
		Blood pressure	Systolic BP	NS	
		Smoking cessation	Self-reported	NS	
		BMI	BMI (kg/m2)	NS	
Wood et al. (2008)	Risk factor levels	Lipids	Total Cholesterol <5 mmol/L	NS	12 months
			LDL-C (<3mmol/L)	NS	
Hospital arm		Blood pressure	BP < 140/90 mmHg	10.4%, p=0.04	
		HbA1C	Difference (%)	NS	
		ACE inhibitor	Difference (%)	NS	
		Antiplatelet drug	Difference (%)	NS	
		Beta-blocker	Difference (%)	NS	
		Statin	Difference (%)	NS	
		Not smoking	Exhaled carbon monoxide + self-reported	NS data not incorporated in meta-analysis	
		BMI	BMI < 25 kg/m2	NS	
		Weight loss	Weight loss ≥5% in patients with BMI >25 kg/m2 at initial assessment (%)	NS	
		Waist circumference	Women <80cm, men <94cm	NS	
		Diet	**Questionnaire: food habits**		
			Saturated fat <10% of total energy (table 3) (%)	17.4%, p=0.009	
			Saturated fat <10% of total energy (p.2003) (%)	NS	
			Eating oily fish ≥ 3 times per week (%)	8.9%, p=0.04	
			Eating fruit/vegetables >400 gr per day (table 3) (%)	37.3%, p=0.004	
			Eating fruit/vegetables >400 gr per day (p.2003) (%)	15.8%, p=0.03	
		Physical activity	Physical activity ≥30 min. ≥ 4 times per week (%)	35.6%, p=0.002	

Study	Outcome category	Outcomes	Unit of measurement	Results: difference between I and C	Follow-up
Young et al. (2003)	Clinical events	All-cause readmission days	Days per 1000 follow-up days (IDR)	1.53, p<0.001	454 days
		Readmission days for angina, CHF and COPD	Days per 1000 follow-up days (IDR)	1.59, p<0.001	
		ED visits	Number of ED visits	2.08, p<0.001	
		Physician visits		NS	
		Diagnostic and therapeutic services	Absolute numbers (≤225 days of discharge)	-378, p=0.012	
		Laboratory services	Absolute numbers (≤225 days of discharge)	-920, p=0.007	

Abbreviations:

A: Audit group, ACE: Angiotensin converting enzyme, ACS: Acute Coronary Syndrome, BMI: Body mass index, BP: Blood pressure, C: Control, CHF: Chronic Heart Failure, Cm: Centimeters, ED: Emergency Department EQ-5D: 5 item EuroQoL questionnaire, GP: General practitioner, HDL-C: High density lipoprotein cholesterol, I: Intervention, kg: Kilograms, LDL: Low density lipoprotein, Mg: Milligram, MET(S): Metabolic Equivalent Task, NR: Not reported, NS: Non-significant, OR: Odds ratio, PACIC: Patient assessment of chronic illness care, QoL: Quality of life, RR: Relative Risk .

Chapter 3

'I think the RESPONSE-2 study has actually made me more aware of my lifestyle, like, types of foods to get those healthy food choices and daily exercise. I think it's just that, what do you call it, sort of like a recognition that you need to do something.'
(Mrs M. de Koning, 58 years, myocardial infarction)

Chapter 4

Community-based comprehensive lifestyle programmes in patients with coronary artery disease: Objectives, Design and Expected Results of Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists 2 trial (RESPONSE-2)

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Abstract

Patients with coronary artery disease (CAD) are at high risk of recurrent events. A healthy lifestyle can significantly reduce this risk. A previous trial, Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists (RESPONSE), demonstrated that nurse-coordinated outpatient clinics improve drug treatment for cardiovascular risk factors. However, lifestyle-related risk factors, including smoking, overweight and physical inactivity, were common and remained largely unchanged at follow-up in the majority of the patients (66%). The aim of the current study is to evaluate the impact of three community-based lifestyle programmes in patients after hospitalization for CAD. We are conducting a multicentre (n=15), randomized trial that will recruit 800 patients to test the efficacy of up to three widely available commercial lifestyle programmes, aimed at patients and their partners, on top of usual care. These programmes are aimed at smoking cessation (Luchtsignaal®), weight loss (Weight Watchers®) and improving physical activity (Philips DirectLife®).

Outcomes

The primary outcome at 12 months is the proportion of patients in whom at least one lifestyle risk factor is improved without deterioration in any of the other two, and a relative increase of at least 30% in this proportion is considered clinically relevant.

Introduction

Patients with coronary artery disease (CAD) are at high risk of recurrent events and mortality.[1] This risk can be reduced by effective secondary prevention, which consists of appropriate medical therapy and improvement of lifestyle-related risk factors including smoking, unhealthy diet, overweight or obesity and a sedentary lifestyle.[2-4]
Physician compliance with guidelines for drug treatment of hypertension, diabetes mellitus and dyslipidemia has improved substantially. This can be explained by accumulating evidence for the efficacy of these drugs, increased awareness among physicians, and implementation of dedicated outpatient support[5]. The health benefits from improving lifestyle-related risk factors are at least as great as the benefits of pharmacological secondary prevention.[2,5-8] Therefore, current guidelines promote lifestyle risk management in patients with CAD.
However, implementation of lifestyle risk management has been challenging. The Prospective Urban Rural Epidemiology study found that the prevalence of healthy lifestyle behaviours was low in a worldwide sample of patients with CAD or stroke.[9] Data from four consecutive EUROASPIRE registries in Europe in fact showed a trend of increasing overweight and obesity among patients with CAD.[5,10]
Nurse-coordinated outpatient clinics are now common and nurses are engaged in cardiovascular risk management. Yet, their impact on lifestyle risk factors is limited.[11,12] A medical approach may not be suitable to improve a patient's lifestyle long term.
Home-based, long-term support involving patients' partners may potentially be more effective.[12-14] Since lifestyle-related risk factors tend to cluster, a comprehensive intervention may be expected to have a greater impact than interventions on a single risk factor.[3,11]
We aim to evaluate three community-based comprehensive lifestyle programmes which have previously been validated[15-18]aimed at smoking cessation (Luchtsignaal®), weight reduction (Weight Watchers®) and promoting physical activity (Philips DirectLife®) with referral to these community-based programmes coordinated by nurses at outpatient clinics.

Methods

Study Design

A multicentre (n=15) randomized trial to assess the efficacy of three widely available community-based lifestyle programmes, on top of usual care, in patients who have recently been hospitalized for CAD in the Netherlands.

Timeline

Inclusion of patients has started in April 2013 and will be closed on June 30, 2015, with an expected overall number of 1000 patients.

Funding

The study was supported by unrestricted grants from Weight Watchers International, Inc., New York, NY USA, Philips Consumer Lifestyle, the Netherlands.
The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patient population, recruitment and randomisation

Patients aged ≥18 years are recruited at outpatient clinics by treating cardiologists or nurses, within 8 weeks after hospitalization, which is defined as unstable angina and ST-Elevation Myocardial Infarction and non ST-Elevation Myocardial Infarction, coronary artery bypass graft surgery or percutaneous coronary intervention (PCI) with at least one of the following 3 lifestyle risk factors: (1) current smoking, defined as smoking of any tobacco product in the 6 months preceding hospitalization, (2) body mass index (BMI) ≥27 kg/m², or and (3) physical inactivity. Physical inactivity is defined as <30 minutes of physical activity of moderate intensity 5 times per week according to the current recommendation of the World Health Organization (WHO). Whereas guidelines recommend a BMI of ≤25 kg/m^2, the criterion of BMI ≥27 kg/m^2 was selected to ensure that there is a clear indication for weight reduction. A weight loss of ≥5%, as recommended by the current guideline[2,3] is equivalent to a reduction from 27 to ≤25.65 kg/m^2.
Exclusion criteria include planned revascularization after hospital discharge, a limited life expectancy (≤2 years), heart failure classified as New York Heart Association (NYHA) class III or IV or inability to follow the programme.
Patients with a Hospital Anxiety and Depression screening score (HADS) >14 are excluded, as they may not be able to address their lifestyle-related CAD risk factors prior to treatment of the mood disorder.[19] Written informed consent is obtained from patients and cardiologists. The study protocol has been approved by the local Medical Ethics Committees (METC 2012_272) and is registered online (www.trialregister.nl, trial ID NTR3937). Randomisation is performed through an automated online protocol. Patients are randomized to either the lifestyle intervention programme on top of usual care, or to usual care alone in a 1:1 fashion. To ensure concealment of allocation, the automated online randomisation protocol uses block randomisation with randomly varying block sizes (4, 6 or 8 allocations). The flowchart of the trial is presented in figure 1.

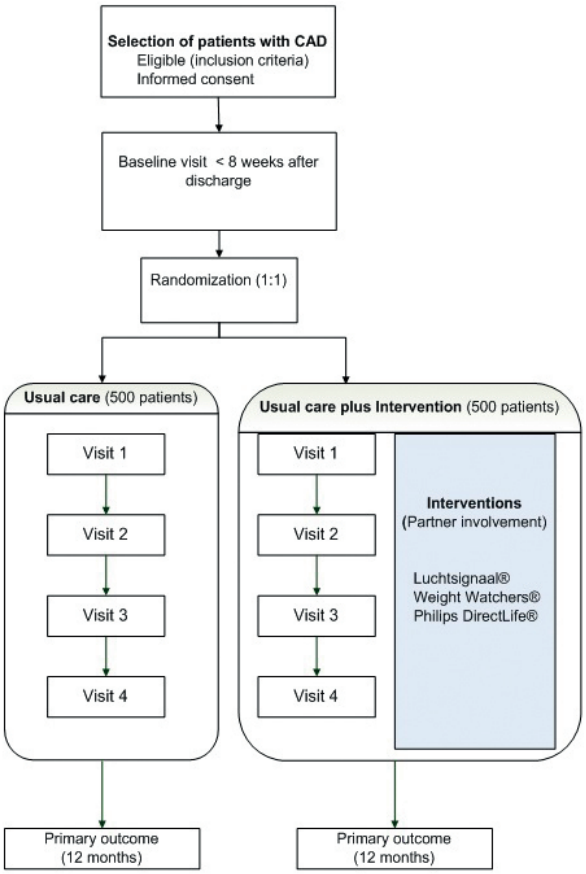

Figure 1.
Flowchart of the study design

Usual care, nurse-coordinated outpatient clinic

Usual care includes outpatient clinic visits to physicians and nurses and referral to cardiovascular rehabilitation according to national guidelines.[2,3] Cardiologists are expected to adhere to current national and international guidelines for secondary prevention of cardiovascular disease (**table 1**). Trial visits at the outpatient clinic in all participating hospitals are scheduled for all patients at baseline and at final follow-up at 12 months. During this year, between 2 and 4 visits to the outpatient clinics are planned and patients are encouraged to bring their partners. The trial nurse addresses the cardiovascular risk factors according to the European Society of Cardiology (ESC) 2012 guidelines. As per current guidelines[3,4], all patients are advised by their health professionals to improve their lifestyle where appropriate, and blood pressure, (fasting) blood glucose and lipids are monitored at outpatient clinics. Patients may be referred to existing prevention programmes as part of cardiac rehabilitation as per local practice.

Table 1.
Lifestyle and biometric targets according to 2012 ESC guidelines.[3]

Diet	**1.** Vegetable consumption ≥200 grams daily **2.** Fruit consumption ≥2 pieces daily **3.** Alcohol consumption: for ♀ ≤ 1 units per day, for ♂ ≤ 2 units per day
Smoking	non-smoking status
Physical activity	≥30 min of moderate intensity physical activity 5 days a week
Blood pressure	Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg
Cholesterol	LDL cholesterol concentration ≤1.8 mmol/L
HbA1c%	HbA1c of <7.0% (<53 mmol/mol)
Anthropometry	**1.** Body mass index ≤25 kg/m² **2.** Waist circumference: ♀ ≤ 88 cm, ♂ ≤102 cm

Table 2.
Definitions of successful outcomes at 12 months

Patient categories based on lifestyle risk factors at baseline	Definition of success
1. Smoking only	non-smoking status[b]
2. BMI ≥27 kg/m² only	≥5% weight reduction[a]
3. Physical inactivity only	increase of >10% in 6MWD[c]
4. Smoking and BMI ≥27 kg/m²	non-smoking status and/or ≥ 5% weight reduction[b]
5. BMI ≥27 kg/m² and Physical inactivity	≥5% weight reduction and/or increase of >10% in 6MWD[d]
6. Smoking and Physical inactivity	non-smoking status and/or increase of >10% in 6MWD[b]
7. BMI ≥27 kg/m², Smoking and Physical inactivity	≥5% weight reduction, non-smoking status and increase of >10% in 6MWD[b]

Legend
a: and no deterioration in other 2 factors: no smoking and no deterioration of 6MWD
b: Non-smoking status and an increase of ≤ 2.5% of BMI or BMI ≤ 25 kg/m² is defined as successful outcome
c: 6MWD > 10% and an increase of ≤ 2.5% of BMI or BMI ≤ 25 kg/m² is defined as successful outcome
d: and non-smoking status

Information facilities
All trial patients are offered access to a trial website (www.response2.nl) and are provided with general information about the trial design and existing healthcare infrastructure in the local hospital, similar to the informed consent form. This website includes existing links of the participating centres that were not created for trial purposes.
During the trial, meetings for all participating nurses are organized to provide education in motivational interviewing and the referral infrastructure.

Interventions
On top of usual care, patients in the intervention group are referred to one or more of the three community-based lifestyle programmes, depending on which of the three lifestyle risk factors are present.
If multiple lifestyle factors need to be addressed, the sequence of the interventions is discussed with the patient and decided by patient's preference. Interventions include community-based lifestyle programmes for smoking cessation (Luchtsignaal®), weight reduction (Weight Watchers®,) and physical activity (Philips DirectLife®). If appropriate, partners are encouraged to participate in all programmes. Participation is free of charge. The content of the lifestyle programmes is offered as they are available in the community. Each intervention programme takes at least 3 months.

Smoking cessation – Luchtsignaal® (www.luchtsignaal.nl)
Luchtsignaal® is an existing national smoking cessation programme that offers telephone counselling by professionals for the duration of 3 months. The programme is based on the stages of change from the trans- theoretical model and uses strategies from motivational interviewing, action and coping planning, self-control training and relapse prevention.[20] If appropriate and dependent on individual needs, nicotine replacement therapy or varenicline can be prescribed.

Weight reduction – Weight Watchers® (www.weightwatchers.com)
Weight Watchers® is aimed at reducing weight by emphasizing a healthy diet, change in behaviour, physical activity and group motivation and offers weekly group meetings for a weigh-in and group discussion, coordinated by a Weight Watchers' coach. Furthermore, the diet intake is based on the pro-points' system that addresses the total caloric energy in each product. Access to a supportive internet-based system is offered to monitor daily food intake, activity, and weight change.

Physical activity – DirectLife® (www.directlife.com)
Philips DirectLife® is an internet-based coaching activity health programme that includes an accelerometer, comparable to a small USB device. The programme monitors daily physical activities, provides feedback via the accelerometer and offers personalized,

internet-based coaching. Directlife® encourages stepwise increases in the level of physical activities by promoting awareness of all daily exercise, independent of its intensity or type of activity. Patients are able to adjust their targets during the programme.

Data collection and measurements

At baseline and at 12 months we collect data on cardiovascular risk factors, medication, quality of life and depression and anxiety, participation to lifestyle programmes, laboratory measurements, urinary tests, anthropometrical measurements, laboratory measurements and 6-minute walking distance (6MWD).

Clinical events are documented by the trial nurse during the one year follow-up. Questionnaires are completed for assessing heart disease related quality of life, signs of depression and the level of physical activity by MacNew[21], HADS[22] and the standards of physical activity based on the WHO[23], respectively. The questionnaire on physical activity is a national questionnaire based on WHO criteria and was selected on the basis of its widespread use in cardiac rehabilitation in the Netherlands.

Laboratory measurements include total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, fasting glucose and HbA1c. Spot urine is collected for assessment of smoking status using a quantitative test of urine cotinine (UltiMed one step, Dutch Diagnostic, Zutphen, the Netherlands. Detection limit 200 ng/ml).

Body weight, height and waist circumference are measured and BMI is calculated. Body composition is analysed using commercially available bio impedance scales (Tanita scale SC-240-MA). Blood pressure is measured twice by an automated sphygmomanometer. Physical activity is measured by a 6-minute walking distance (6MWD) as per protocol.

Six-minute walking test (6MWT)

The 6MWD represents a daily activity performed in a moderate intensity. The 6MWT is conducted according to a protocol and includes measurement of distance in meters (m). The results of the 6MWD test depend on several variables, including age, sex, weight and left ventricular ejection fraction. Assuming a selection of patients with relatively well-preserved ejection fraction and an average age of 60-65 years in the study population, the expected 6MWD at baseline will be in the range of 400 - 600 meters.[24,25] At follow-up, improvement may be expected in both groups through recovery from CAD, cardiac rehabilitation and through training effects on the test. An improvement of at least 10% in 6MWD is accepted as a clinically meaningful improvement.[26]

Primary outcomes

The primary outcome of the trial is the proportion of patients who achieve a successful outcome, defined as reaching their target for at least one of the three lifestyle-related risk factors, without deterioration in any of the other two. Targets are defined as follows:

1. Non-smoking status defined as urine cotinine concentration <200 ng/ml
2. Reduction of at least 5% in body mass index (BMI)
3. Improvement of 6MWD of at least 10%

Secondary outcomes

Secondary outcomes include self-reported smoking status and the smoking status assessed by cotinine concentration, BMI, self-reported physical activity and 6MWD, self-reported quality of life, blood pressure, cholesterol, LDL, HDL, triglycerides, glucose levels and HbA1c% and creatinine levels, waist circumference, blood pressure, and additional measurements of heart frequency and recovery after one minute, duration, frequency and intensity of attendance to lifestyle programmes and predictors of success and failure in completing the lifestyle programme. Finally, hospitalization (including emergency department visits), adverse events and newly diagnosed diabetes mellitus will be assessed after one year follow-up.

Definition of successful outcomes at patient level

The following LRRFs combinations are possible at the individual level at baseline:
1. Smoking only
2. BMI ≥27 kg/m^2 only
3. Physical inactivity only
4. Smoking and BMI ≥27 kg/m^2
5. Smoking and physical inactivity
6. BMI ≥27 kg/m^2 and physical inactivity
7. Smoking, BMI ≥27 kg/m^2 and physical inactivity

For each of these subgroups, definitions of successful outcomes at 12 months are presented in **table 2**. Treatment success is defined as achieving the target for at least one of the three lifestyle-related risk factors, without deterioration in any of the others. If smoking cessation is accomplished, an increase of ≤2.5% in the BMI or BMI remaining <25kg/m^2 will be classified as no deterioration.
An increase of ≤2.5% in the BMI or remaining <25 kg/m^2 in case of significantly improved level for physical activity is also classified as no deterioration, because of the possibility that exercise may increase muscle mass.

Statistical analysis

The main analysis will compare the proportions of patients between the treatment groups who have achieved a successful outcome at 12 months (**table 2**). The treatment effect will be expressed as a difference with its corresponding 95% confidence interval. Multivariable logistic regression analysis will be used with the following variables in the

model: experimental treatment (main variable of interest), six dummy variables for the seven subgroups of possible risk factor combinations. Random effects models or robust variance estimation will be used if significant clustering by institute is found (likelihood ratio test). The intention-to-treat principle will be used for the main analysis, using multiple imputation where appropriate.
The following analyses will be performed:

1. Effect by lifestyle programme (smoking cessation, weight loss, physical activity) using relevant co-variables since these comparisons are not protected by the randomisation and the choice of a specific programme is made after randomisation;
2. Effect by centre (to link effects of exceptional size to our process data on compliance and skills;
3. Probability of success of treatment on more than one outcome (ordered logistic regression with 0, 1, 2 or 3 successful outcomes as the dependent variable);
4. Subgroup analysis by profile at baseline (seven in total, see section on 'outcome definitions').

Secondary outcomes are also compared between the intervention and the control group at baseline and 12 months. Comparison for smoking status (urinary cotinine <200 ng/ml), BMI (kg/m^2), waist circumference (cm) and 6MWD (m) are analysed. Linear regression analyses similar to the logistic models described above will be used for fasting serum LDL level (mmol/l), systolic blood pressure (mmHg), control of existing diabetes mellitus (fasting blood glucose and plasma HbA1c) and body composition (fat mass). Logistic regression analysis is used for the occurrence of newly diagnosed diabetes mellitus and hospital readmission rates after 12 months.

Sample size calculation
In RESPONSE,[27] the overall success of improvement of lifestyle related risks factors was 32% across all outcome groups. In RESPONSE-2, we defined a 30% relative increase in the overall success rate in the intervention group as clinically meaningful. Such an increase would correspond to a success rate of 41.6% in the intervention group. In order to detect a statistically significant difference with 80% power and a significance level of 5 % in a two-sided test, a sample size of 395 patients in each trial arm is required. We will include 425 patients in each group to accommodate an expected withdrawal rate of up to 7%. The target sample size was reduced during the trial from 1000 to 800, due to limited resources and time constraints. Nevertheless, a sample size of 800 patients has over 80% power at the hypothesized inter-group difference of 9.6% (**figure 2**).

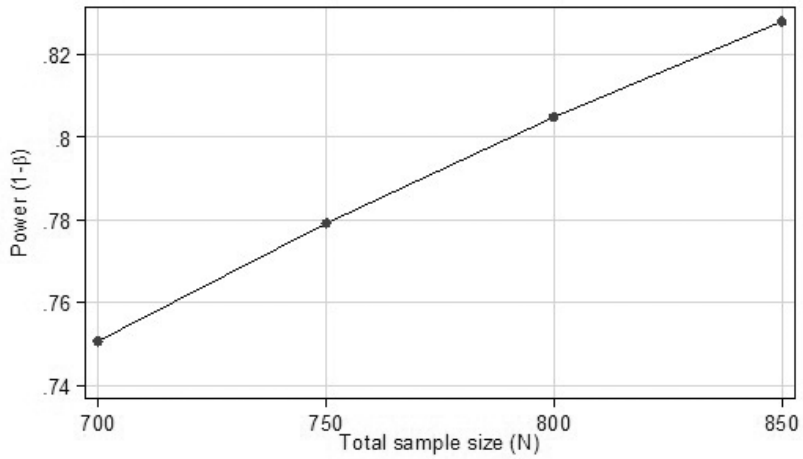

Figure 2.
Parameters: α=0.05, δ=0.096, proportion 1 (overall success in RESPONSE1) = 0.32 and proportion 2 (estimated overall success in RESPONSE2) = 0.42
Estimated power for a two-sample proportions test, Pearson's chi squared test
H_0: $p_2=p_1$ versus H_1: $p_2 \neq p_1$

Discussion

The RESPONSE-2 trial evaluates the efficacy of a comprehensive lifestyle intervention in secondary prevention, consisting of up to three widely available community-based lifestyle programmes, aimed at patients and their partners on top of usual care.
We believe this is the first trial to study referral of patients and their partners to community-based lifestyle programmes in secondary prevention, coordinated by in-hospital nurses. We hypothesize that participation in one or more of the community-based lifestyle programmes leads to an improvement in cardiovascular risk profiles, compared to usual care alone.
The EUROASPIRE, cross-sectional cohort studies in Europe in CAD patients (1995 to 2013) found increasing trends in overweight and obesity, from 25% to 38%, in most participating countries.[5,6,10] The proportion of persistent smokers remained largely unchanged (20% to 16%) and low physical activity was reported by approximately 60% in the latest registry. These results emphasize the difficulties of implementing the guidelines for lifestyle related risk factors (LRRFs) into practice.
EUROACTION, a randomized trial in CAD patients and asymptomatic participants in European countries studied a preventive lifestyle programme using nurse coordination and family involvement. Higher rates of healthy food choices and physical activities were achieved. However, no significant changes in overweight and smoking were observed.[12]
Results from In-hospital programmes aimed at lifestyle in patients with CAD vary from modest

beneficial effects on BMI and waist circumference to no significant differences regarding smoking, overweight or physical inactivity[28,29]. Jorstad et al. found significant improvement in LDL cholesterol and blood pressure levels, with nurse led risk factor management in outpatient clinics[27]. However, smoking cessation and obesity were not improved. Physical activity tended to improve, yet it was not objectively measured. Thus, whereas preventive interventions are generally effective regarding drug treatment, improvement of LRRFs remains challenging. This may be related to a number of factors.

First, lifestyle related habits are developed during decades and may be resistant to change. Second, they are related to the patient's physical, social and financial environment. Durable change may require addressing these environmental factors. The influence of the patient's partner may be decisive and durable improvement may require the involvement of the partner.[12-14] Third, whereas drug therapy leads to measurable improvements in risk factors, such as blood pressure and LDL cholesterol, the benefits of changing lifestyles are much less apparent. For a patient to understand the benefits of smoking cessation requires a basic understanding of the concepts of risk and risk reduction, as a long-term reward for the immediate loss of quality of life.

Finally, sedentary lifestyles, unhealthy food choices and smoking tend to cluster. Therefore, interventions may be more effective if they target these clusters of risk factors in a comprehensive way, instead of targeting risk factors separately.[3] On the other hand, patients may not be expected to change all risk factors at the same time. Therefore, tailored approaches may be preferable, in which patients and physicians may also decide on the sequence by which the individual LRRFs will be addressed.

Selection of the community-based lifestyle programmes

The three lifestyle programmes in the trial were selected on the basis of being established, community based, widely available professional programmes. Thus, findings in the trial may be translated into practice internationally. Smoking cessation can be achieved by combining pharmacotherapy and educational strategies including individual or telephone counselling, and may be more effective in achieving smoking cessation compared to solely pharmacotherapy.[30,31]

The medical application of the Weight Watchers® programme has been studied in primary prevention in general practices.[17,32] Overweight participants were able to lose twice as much weight compared with usual primary care. Given the impact of overweight on a very broad range of diseases, medical application of a successful programme may potentially have a great impact.

Accelerometers, such as used in the Philips DirectLife® programme, have been found to be accurate tools in estimating energy expenditure and effective tools in improving physical activity.[33,34] Again, medical application needs to be explored and may provide important benefits.

Limitations

This trial design carries several limitations. First, it is not feasible to completely conceal treatment allocation to both healthcare providers and patients. This may result in increased awareness of behavioural habits in all patients and in the physicians (Hawthorne effect).[35]

Second, the DirectLife® and Weight Watchers® lifestyle programme include web-based support and this could be challenging for elderly patients. However, the use of DirectLlife® was studied in elderly participants, aged >65 years, and the programme appeared to be feasible.[16]

Third, the interventions will likely be less effective in unmotivated patients. Finally, study effects may in part be dependent on the communicative skills of the nurses in the outpatients' clinics. Motivational interviewing skills are trained in RESPONSE2 trial during periodical trial meeting, to reduce differences among nurses.

Conclusions

In patients with established coronary disease, there is a clear need for effective interventions aimed at improvement of LRRFs. The RESPONSE-2 trial tests the hypothesis that referral to comprehensive community-based widely available programmes of CAD patients and their partners is more effective than current usual care in improving LRRFs.

Funding sources

Weight Watchers International, Inc., New York, NY USA, Philips Consumer Lifestyle, the Netherlands.

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'I would like to change my lifestyle, especially lose weight. Doing it as a couple, like, making sure that my partner is involved, I'm not doing this on my own.'
(Mr J. Wolters, 68 years, myocardial infarction)

Chapter 5

Community-based lifestyle intervention in patients with coronary artery disease. The RESPONSE-2 trial

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Abstract

Background:
Among patients with coronary artery disease (CAD), improvement of lifestyle-related risk factors (LRFs) reduces cardiovascular morbidity and mortality. However, modification of LRFs is highly challenging.

Objectives:
To evaluate the impact of combining community-based lifestyle programmes with regular hospital based secondary prevention.

Methods:
We performed a randomized controlled trial of nurse-coordinated referral of patients and their partners to 3 widely available community-based lifestyle programmes, in 15 hospitals in the Netherlands. Patients admitted for acute coronary syndrome and/or revascularization, with at least one LRF (BMI >27 kg/m^2, self-reported physical inactivity and/or smoking) were included. All patients received guideline-based usual care. The intervention was based on 3 lifestyle programmes for: weight reduction, increasing physical activity, and smoking cessation. The primary outcome was the proportion of success at 12 months, defined as improvement in at least one qualifying LRF (using weight (≥5% reduction), 6-minute walking distance (≥10% improvement) and urinary cotinine (200 ng/ml detection limit) without deterioration in the other two.

Results:
We randomized 824 patients. Complete data on the primary outcome were available in 711 patients. The proportion of successful patients in the intervention group was 37% (133/360) compared with 26% (91/351) in the control group (p=0.002), (RR 1.43 95% CI 1.14-1.78). In the intervention group, partner participation was associated with a significantly greater success rate (46% vs. 34%, p=0.03).

Conclusie:
Among CAD patients, nurse-coordinated referral to a comprehensive set of community-based, widely available lifestyle interventions, with optional partner participation, leads to significant improvements in LRFs.

Introduction

Patients with coronary artery disease (CAD) are at high risk of recurrent events and mortality. Improvement of lifestyle-related risk factors (LRFs), including overweight, physical inactivity, and smoking, is associated with a significantly lower risk of recurrent events.[1, 2] Therefore, guidelines on secondary prevention of CAD recommend medical treatment plus lifestyle interventions for all patients.[3-5] However, a significant gap exists between guideline recommendations and daily practice. In particular, attempts at improving LRFs have been disappointing.[6-8]

Most studies have focused on a single LRF – including counselling, support systems, or easy access.[9-11] Nurse-coordinated referral to a comprehensive set of easily accessible, existing community-based programmes has not been studied. In addition, most studies have not included patients' partners, which may be essential to change a patient's daily routines.[12, 13]

The Randomized Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists (RESPONSE 1) trial showed that nurse-led care was effective in reducing drug-treated cardiovascular risk factors and improving quality of life in CAD patients.[14, 15] Guidelines now recommend the integration of nursing care into secondary prevention.[16] However, the impact of nurse-led care on LRFs has been shown to be limited.[11, 15, 17]

We hypothesized that a strategy of nurse-coordinated referral to a comprehensive set of up to three community-based, existing interventions to achieve weight loss, improvement of physical activity, and smoking cessation, on top of usual care, and including the patient's partner, improves LRFs in CAD patients.

Methods

Study Design

The RESPONSE-2 trial was a randomized trial conducted in 15 hospitals in the Netherlands. Study methods have been published and are summarized below.[18] The institutional review boards of all recruiting hospitals approved the protocol, and written informed consent was obtained from all patients. The protocol was registered at the Dutch trials register on April 8th 2013 (www.trialregister.nl, trial ID NTR3937).

Patient Population

Adult patients were eligible <8 weeks after hospitalization for acute coronary syndrome, and/or coronary revascularization, if they had at least one of the following LRF: (1) body mass index (BMI) ≥27 kg/m^2 (as a BMI only slightly above 25 may not provide sufficient motivation, and minor improvement could be classified as success), (2) self-reported physical inactivity (<30 minutes of physical activity of moderate intensity five

times per week, guideline based), (3) self-reported smoking <6 months before hospital admission, and if motivated to attend at least one lifestyle programme.
Exclusion criteria were: planned revascularization after discharge, life expectancy ≤2 years, congestive heart failure New York Heart Association class III or IV, visits to outpatient clinic and/or lifestyle programme not feasible, no internet access, and anxiety or depressive symptoms (Hospital Anxiety and Depression Scale (HADS) >14), as this was expected to hinder lifestyle changes.[19]

Randomisation

After the baseline interview, patients were randomised by an automated online protocol to the intervention group or the control group, using randomly varying block sizes (4, 6, or 8 allocations), stratified by hospital.[18]

Usual Care

All patients received usual care, including visits to the cardiologist and cardiac rehabilitation, according to national and international guidelines[4, 5], and up to four visits to a nurse-led secondary prevention programme. The nurse programme addressed (counselling on) healthy lifestyles, drug treated risk factors and medication adherence.[4, 5, 20]
As per current guidelines, cardiac rehabilitation included up to 12 weeks of outpatient physical rehabilitation plus counselling on secondary prevention, psychological support, and work resumption.
Patients were seen by registered nurses, with experience in cardiovascular care and training in motivational interviewing.

Intervention

Patients in the intervention group were referred by the nurse to up to three community-based lifestyle programmes.[18] The number and sequence of the lifestyle programmes was determined by the patient's risk profile and preference. Partners were offered free participation in the programmes.
Three lifestyle programmes were used in their existing format, uniformly in all participants:

1. Weight Watchers® offers a programme that emphasizes a healthy diet, changing unhealthy behaviour and regular physical activity, and utilizes group motivation, coordinated by a Weight Watchers' coach. Access to this programme was for the duration of 1 year.
2. Philips DirectLife® offers an internet-based programme aimed at improving physical activity. An accelerometer measures physical activity and an online coach provides personalized feedback. Access to this programme was for the duration of 1 year.

3 Luchtsignaal® is a smoking cessation programme in the Netherlands that uses telephone counselling based on motivational interviewing by trained professionals, for the duration of 3 months. Nicotine replacement or varenicline therapy was prescribed, as appropriate.

Data collection and measurements

Data were collected at baseline (first visit after discharge) and 12 months, including cardiovascular risk factors, cardiovascular history, physical activity, smoking status, and medication use. Blood pressure was measured twice by an automated sphygmomanometer and the average of the two was used. Body weight, height and waist circumference were measured, and BMI was calculated. Body composition, including fat percentage, was analysed using bio-impedance scales (Tanita scale SC-240-MA, Tokyo, Japan). Fasting blood samples were analysed for lipid profiles and glucose. Urinary cotinine was measured (UltiMed one step, Dutch Diagnostic, Zutphen, the Netherlands; detection limit 200 ng/ml). The six-minute walking distance (6MWD) was performed according to validated protocols.[21, 22] Partner participation was defined as a partner attending at least one visit to a lifestyle programme.

Outcomes

The primary outcome was the proportion of successful patients at 12 months follow-up, defined as improvement of at least one qualifying LRF, without deterioration in the other two.

Improvement per LRF was defined:

1 weight loss of ≥5%
2 ≥10% increase in 6MWD.
3 a urine cotinine level <200ng/ml.

Deterioration was defined as:

1 Any weight gain in combination with a BMI >25kg/m^2.
2 Any decrease in 6MWD compared with baseline.
3 A positive cotinine test (>200ng/ml) in non-smokers at baseline.

Two exceptions were made: in patients who stopped smoking and/or improved their 6MWD, an increase of ≤2.5% in BMI was classified as no deterioration.

Secondary outcomes included differences in isolated LRFs (weight, 6MWD, and smoking), attendance rates of lifestyle programmes, blood pressure, lipid profiles and hospital readmissions.

Statistical methods

Sample size calculation

We estimated that a sample size of 790 patients, with a withdrawal rate of 7%, had 80% power at a 5% significance level in a two-sided test to detect at least a 30% relative increase in the proportion of successful patients.[18] All participants were analysed by initial group assignment, irrespective of attending a lifestyle programme. The primary analysis compared the proportion of successful patients at 12 months between the two groups. The treatment effect was expressed as risk ratio (RR) and the corresponding 95% confidence intervals based on chi-squared test. Where appropriate, logistic regression analysis was used. Continuous variables are presented as means with standard deviation for normally distributed data, and as median with quartiles (Q1 and Q3) for non-normally distributed data. Categorical variables are presented as frequencies and percentages.

Sensitivity analysis

A predefined multiple imputation analysis was performed to analyse the impact of selective drop-out[18] using iterative chained equations, separately for the intervention and control group (detailed information is provided in the appendix: Online Table 2). RR was calculated for each of the 50 imputed sets and pooled using Rubin's rule to derive the correct confidence intervals. Adjustment was made for the 7 possible subgroups of LRFs combinations (smoking only, BMI ≥27 kg/m^{2}only, physical inactivity only, smoking and BMI ≥27 kg/m^2, smoking and physical inactivity, BMI ≥27 kg/m^2 and physical inactivity and smoking, BMI ≥27 kg/m^2 and physical inactivity).

All statistical tests were two-tailed and a p-value of <0.05 was considered significant. We used IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA) and Stata (Stata Corp. 2013. Stata Statistical Software: Release 13.1, College Station, TX: StataCorp LP).

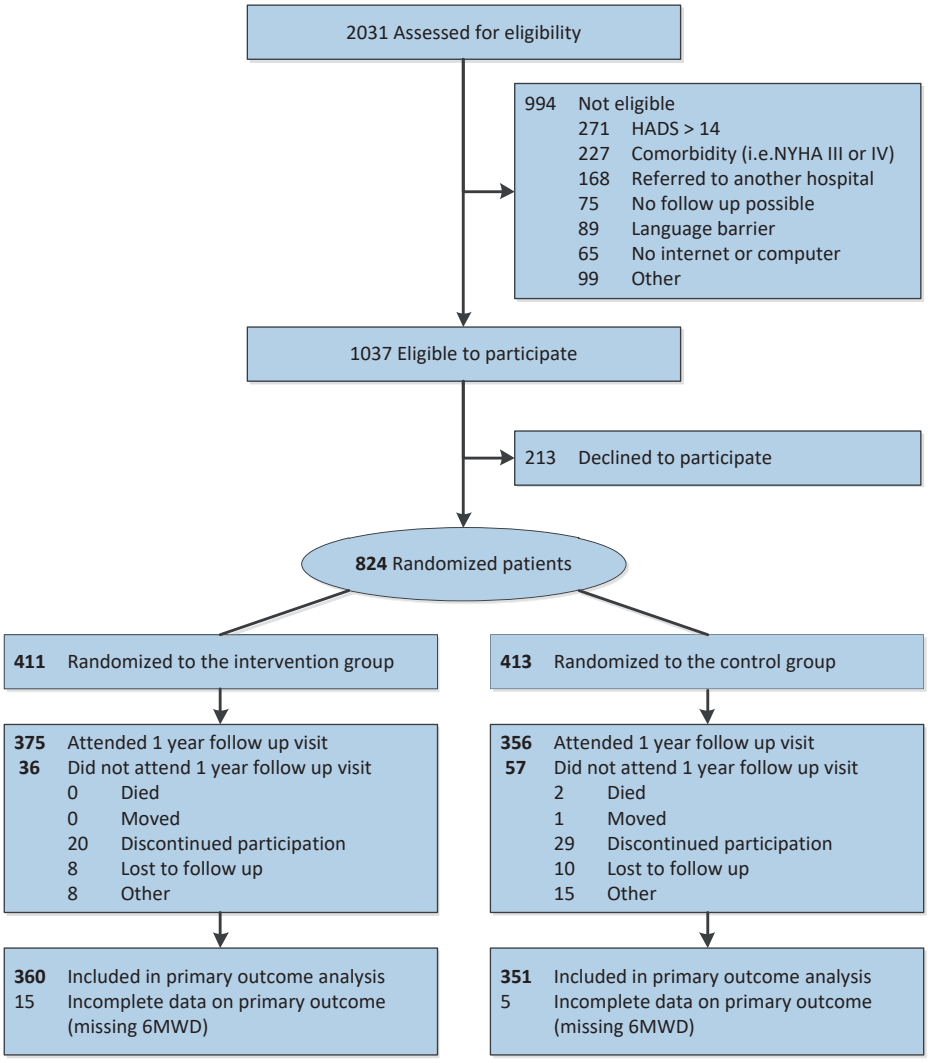

Figure 1.
Flowchart RESPONSE-2 trial
HADS: Hospital Anxiety and Depression Scale, 6MWD: six-minute walk distance

Results

From April 2013 to July 2015, 2031 CAD patients were screened for enrolment. Based on exclusion criteria, 994 were ineligible (Figure 1). In total, 824 patients provided informed consent and were randomized, of whom 731 patients attended the 12 months follow-up visit. In 20 patients, outcome data for the primary analysis were incomplete, and 711 patients were included in the primary analysis (360 intervention, 351 control) (Figure 1).

Patients who did not attend the one year follow-up visit (36 intervention, 57 control, p=0.02) were more frequently younger, had a higher education profile, and were more often smokers, as compared with those who completed the 1 year follow-up visit [55.0 vs. 58.7 years (p<0.001), higher education profile 50% vs. 39% (p=0.05), smokers 33% vs. 21% (p=0.01)].

Patients (overall) had a mean age of 58.7 (SD ± 9.2) years, 21% were female (Table 1). The majority of patients (66%) had no history of cardiovascular disease prior to the index hospitalization. At the baseline visit, 21% of the patients were smoking, and 27% had quit at (or <6 months before) hospital admission. Overweight (BMI >25kg/m^2) was present in 87%, and 63% did not meet the target for adequate physical activity. A total of 36% patients had one LRF, 45% had two LRFs and 19% had three LRFs. At baseline (i.e. after discharge), the use of preventive medication was high (98% antiplatelet therapy, 85% beta-blockers, 74% ACE inhibitors or angiotensin receptor blockers (ARB), and 97% lipid-lowering drugs). A cardiac rehabilitation programme was followed by 91% of the patients in both groups. Overall, 82% (582/711) of patients were living with a partner.

Table 1.
Baseline Characteristics

	Intervention (n= 360)	Control (n= 351)
Demographics		
Age, years	58.2 ± 9.0	59.2 ± 9.4
Female	77 (21)	72 (21)
Caucasian	339 (94)	322 (92)
Higher education (>13 years)	157 (44)	124 (35)
Relationship (married or cohabiting)	298 (83)	284 (81)
Index event		
ST elevation myocardial infarction	153 (42)	135 (39)
Non-ST elevation myocardial infarction	133 (37)	122 (35)
Unstable angina	25 (7)	31 (9)
Stable angina requiring revascularization	50 (14)	63 (18)

Treatment		
Percutaneous coronary intervention	274 (76)	280 (80)
Coronary artery bypass surgery	38 (11)	39 (11)
Medication only	48 (13)	32 (9)
Previous cardiovascular disease		
Myocardial infarction	73 (20)	88 (25)
Percutaneous coronary intervention	52 (14)	56 (16)
Coronary artery bypass surgery	16 (4)	11 (3)
Stroke	7 (2)	15 (4)
Peripheral artery disease	19 (5)	14 (4)
No known previous cardiovascular disease	246 (68)	220 (63)
Risk profiles		
BMI, mean (SD), kg/m^2	29.8 ± 4.3	29.3 ± 4.3
Overweight (BMI ≥25 kg/m^2)	316 (88)	301 (86)
Overweight (BMI ≥27 kg/m^2)	269 (75)	253 (72)
Physically inactive	227 (63)	216 (62)
Smoking at baseline	72 (20)	76 (22)
Recent quitters (≤ 6 months prior to baseline)	100 (28)	90 (25)
Systolic blood pressure ≥140 mmHg	100 (28)	116 (33)
History of dyslipidemia	78 (22)	76 (22)
LDL-cholesterol ≥70 mg/dl	251 (70)	238 (68)
Waist circumference, cm	107 ± 12	106 ± 11
6MWD, meters	492 ± 112	481 ± 107
No. of lifestyle-related risk factors		
1. Smoking only	28/360 (8)	36/351 (10)
BMI ≥27 only	64/360 (18)	63/351 (18)
Physical inactivity only	33/360 (9)	32/351 (9)
2. Smoking & BMI ≥27	41/360 (11)	36/351 (10)
Smoking & physical inactivity	30/360 (8)	30/351 (9)
BMI ≥27 & physical inactivity	91/360 (25)	90/351 (26)
3. Smoking & BMI ≥27 & physical inactivity	73/360 (20)	64/351 (18)
Medication		
Antiplatelet agents	356 (99)	342 (97)
Beta-blockers	300 (83)	305 (87)
ACE inhibiter/ARB	275 (76)	251 (72)
Lipid-lowering drugs	350 (97)	339 (97)

Values are presented as mean ± standard deviation or number (percentage). 6MWD: 6-minute walking distance. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; BMI: body mass index; LDL: low-density lipoprotein.

Attendance to the lifestyle programmes

In the intervention group, 85% (305/360) patients followed at least one lifestyle programme: 48% (174/360) followed one, 34% (121/360) followed two, and 3% (10/360) followed three lifestyle programmes. The frequency and duration of attendance varied per lifestyle programme and per patient (appendix: Online Table 1).

Primary outcome

The proportion of successful patients, who improved at least one of the nonoptimal LRFs without deterioration in the other LRFs at 12 months, was 37% (133/360) in the intervention group compared with 26% (91/351) in the control group, a RR of 1.43 (95% C.I. 1.14-1.78, p=0.002) (Table 2 and Figure 2). Drop-out was 8.8% and 13.8% in the intervention and control group, respectively. After multiple imputation and reanalysis of the primary outcome, the RR remained significant: 1.48 (95% CI 1.18-1.86, p=0.001). The RR remained significant after adjusting for LRF groups: 1.46 (95% CI 1.17-1.82, p=0.001).

Secondary outcomes

Improvement in 2 or more LRFs (without deterioration in the third LRF) was seen in 47 (13%) in the intervention group compared with 20 (6%) in the control group (p=0.001) (Table 2).

We observed a significantly higher rate of ≥5% weight reduction in the intervention group as compared with the control group (27% vs. 14%, p<0.001), respectively. Weight reduction to a BMI≤25kg/m^2 was achieved in 15% of patients in the intervention group compared with 11% in the control group (p=0.10) (Table 2). Overall improvement in the 6MWD was seen in 45% and 40% (p=0.13). Negative cotinine tests were found in 76% and 74%, respectively (p=0.55) (Table 2).

The subgroup of patients eligible to receive each individual intervention programme, and the effects on the relevant LRFs are shown in the supplemental material, online table 3. The proportion of patients with 3 LRFs at baseline who attained the risk factor goal for each risk factor is shown in the supplemental material, online table 4.

In both groups, living with a partner (irrespective of participation) was associated with a greater proportion of success (Figure 3). Among patients in the intervention group who had a partner (298/360 (82.8%)), partner participation in a lifestyle programme (137/298 (46%)) was associated with a significantly greater success rate: (46% vs. 34%, p=0.03).

Self-reported adherence to medication at 12 months was high in both groups: 92% and 93% were on antiplatelet therapy, 66% and 73% on beta-blockers, 69% and 67% used ACE inhibitors or ARBs, and 93% and 93% were on lipid lowering drugs, in the intervention

Table 2.
Outcomes at 12 months

	No./Total (%)		Mean Difference % points	Relative Risk	p value
	Intervention	Control	(95% C.I.)	(95% C.I.)	
Primary outcome					
Success[a]	**133/360 (37)**	**91/351 (26)**	**0.11 (0.04 -0.18)**	**1.43 (1.14-1.78)**	**0.002**
Secondary outcomes					
Improvement in at least 1 isolated LRF	215/360 (60)	175/351 (50)	0.10 (0.03-0.17)	1.20 (1.05-1.37)	0.008
Improvement of ≥ 2 LRFs*	47/360 (13)	20/351 (6)	0.07 (0.03-0.12)	2.29 (1.39-3.79)	0.001
Weight reduction					
≥5% weight reduction	97/360 (27)	48/351 (14)	0.13 (0.07-0.19)	2.0 (1.44-2.70)	<0.001
≥5% Weight reduction in patients with baseline BMI ≥ 27 kg/m^2	88/269 (33)	39/253 (15)	0.17 (0.10-0.24)	2.12 (1.52-2.97)	<0.001
BMI ≤ 25kg/m^2	55/360 (15)	37/351 (11)	0.05 (-0.00-0.09)	1.41 (0.96-2.08)	0.10
Physical activity					
Self-reported physically active	280/360 (77)	254/351 (72)	0.05 (-0.10-0.12)	1.08 (0.99-1.17)	0.10
≥10% Improvement on 6MWT	163/360 (45)	139/351 (40)	0.06 (-0.01-0.13)	1.15 (0.97-1.36)	0.13
≥10% Improvement on 6MWT in baseline physically inactive	106/227 (47)	90/216 (42)	0.05 (-0.04-0.14)	1.12 (0.91-1.38)	0.29
Smoking status					
Self-reported non-smoking	285/360 (79)	270/351 (77)	0.02 (-0.04-0.08)	0.90 (0.68-1.19)	0.53
Urine cotinine <200 ng/ml	272/360 (76)	258/351 (74)	0.02 (-0.04-0.08)	1.03 (0.94-1.12)	0.55
Urine cotinine <200 ng/ml in smokers <6 months before admission	86/172 (50)	76/166 (46)	0.04 (-0.06-0.15)	1.09 (0.87-1.37)	0.45
Systolic blood pressure <140 mmHg	252/360 (70)	219/351 (62)	0.07 (0.00-0.14)	1.12 (1.00-1.24)	0.04
LDL-cholesterol ≤ 70 mg/dL	117/349 (34)	130/341 (38)	–0.05 (-0.12-0.03)	0.88 (0.72-1.07)	0.23

Values are n/N (%). [a] Success is defined as improvement of at least one LRF without deterioration of the other two. *Without deterioration in the third LRF. LRF: lifestyle-related risk factor, 6MWD: 6-minute walking distance; other abbreviations as in Table 1.

and control group, respectively. A systolic blood pressure < 140 mmHg was observed in 70% in the intervention group compared with 62% in the control group (p=0.04). In the intervention group, LDL-cholesterol <70 mg/dL was 34% compared with 38% in the control group (p=0.23). There were no significant differences in hospital readmission rates between intervention and control group (94/360 (26%) and 102/351 (29%) patients, p = 0.63).

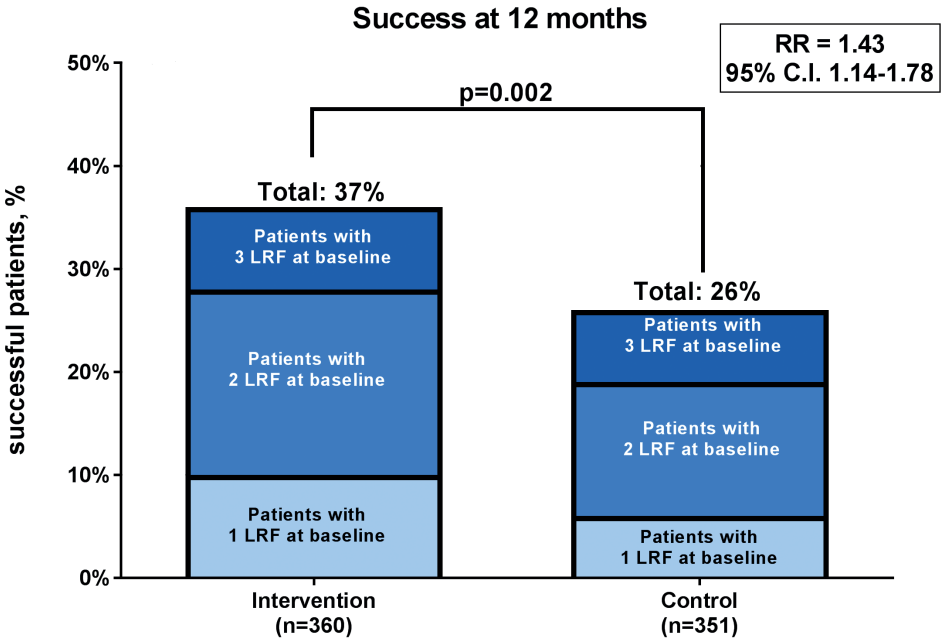

Figure 2.
Primary outcome: Proportion of patients with success at 12 months by randomization group, and numbers of lifestyle-related risk factors (LRFs).
Success is defined as improvement of at least one qualifying LRF without deterioration in the other two. CI: confidence interval; LRF: lifestyle-related risk factor; RR: risk ratio.

Discussion

The main finding of the RESPONSE-2 trial is that among CAD patients, nurse coordinated referral to a comprehensive set of up to three widely available community-based lifestyle programmes, with encouragement of partner participation, on top of usual care, is more effective in improving lifestyle related risk factors than usual care alone. One in three patients in the intervention group successfully improved their LRFs without deterioration in the others; an absolute increase of 11%, and a relative increase of 42% compared with the control group. The number needed to treat was 10. This

improvement in LRFs was seen in spite of a rigorous definition of success and against the background of a high standard of usual care based on contemporary guidelines, with all patients receiving care from cardiologists and specialized nurses, in addition to cardiac rehabilitation.[4,5] The approach was highly practical, which suggests that wide application is feasible. Although the overall rates of success are modest, our findings do provide clinicians with evidence-based options in patients who may be suitable candidates.

Key to our intervention is the comprehensive approach in targeting LRFs. Nurses explained the interactions between the interventions and the importance of reducing in overall risk. Patients were offered a choice of three different lifestyle programmes, depending on their risk profiles and motivation. According to individual preferences, patients were able to follow one or more programmes, sequentially or simultaneously. Partners were encouraged to participate in the lifestyle programmes. Consistent with previous observations, patients with partner participation had the highest proportion of success.[23, 24] This tailored, comprehensive approach may have enabled more patients to change their daily routines.

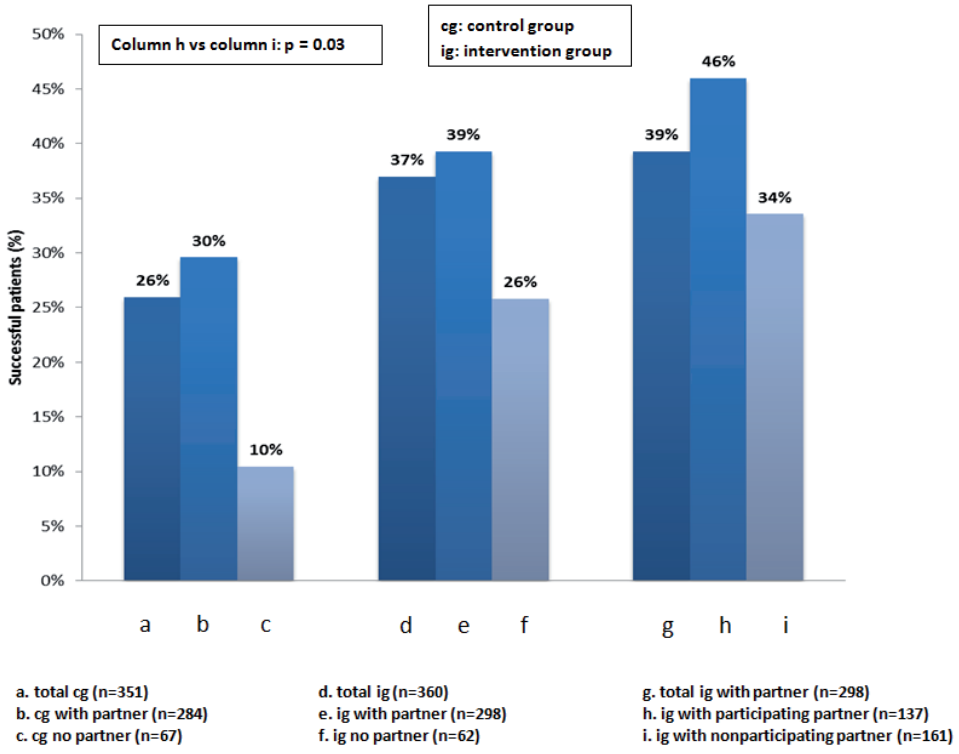

Figure 3.
Impact of having a partner and of partner participation on the proportion of success at 12 months.
Living with a partner was associated with greater proportion of success in both groups: intervention group and control group. Partner participation in a lifestyle programme in the intervention group was associated with a significantly greater success rate of 46% versus 34% (p=0.03). cg=control group; ig=intervention group.

Previous trials have reported modest rates of success in modifying single LRFs in CAD patients.[11, 15, 17, 25-27] However, none of these trials have taken deterioration of other LRFs into account when analysing success rates. While it may be possible to achieve significant improvement in one LRF, this should not come at the cost of deterioration of other LRFs. Our primary outcome therefore had a stricter definition of success, which incorporates deterioration in other LRFs. Minimal weight gain was accepted with smoking cessation (because of a net benefit in overall risk) or with improvement of physical activity (allowing for a small increase in lean body mass). Even with this strict definition of success, a significantly larger success rate was seen in the intervention group as compared with the control group. For isolated LRFs, success rates were considerably higher: 50% vs. 46% for smoking cessation, 33% vs. 15% for weight reduction, and 45% vs. 40% for improvement in the 6MWD (intervention vs. control).

The community-based lifestyle programmes were offered uniformly, in their existing commercial format. A large majority of patients followed at least one programme (84%), and a 42% of those followed 2 or more programmes. The effect of the weight reduction component was the most pronounced in our study. Almost twice as many patients achieved significant weight loss in the intervention group as in the control group. The effects of the intervention programme on smoking cessation and on physical activity were modest. While this suggests differences in effectiveness among the programmes, we believe that a comprehensive approach is key. Nurses explained the concept of overall risk and the impact of multiple interventions. Moreover, the repeated and consistent attention to risk and lifestyle in the separate interventions may reinforce the information and support patients in their efforts to change their daily routines.

Against a background of very high levels of preventive drug therapy, we found no statistically significant improvement of blood pressure control in favour of the intervention group. The proportion of patients who reached the LDL-cholesterol target was disappointing in both groups, in spite of the high level of care offered by multiple caregivers, and a high prescription rate of lipid lowering medication. Lifestyle interventions may not be expected to improve these risk factors, and possibly more potent statin therapy was required. However, this was not analysed.

Limitations

Patients were eligible based on ESC guideline criteria for LRFs, including self-reported smoking and physical activity. However, for outcome assessment we used objective measurements. Thus, although part of the primary outcome, urinary cotinine and 6MWD were not used as inclusion criterion.

Physical activity is preferably measured using an accelerometer. However, this instrument was part of the physical activity programme and using it for outcome assessment in both groups would have reduced contrast, in addition to introducing a Hawthorne effect.[28] Physical fitness is ideally assessed using maximal exercise performance (VO_2max),

however this was not feasible. As self-report is unreliable[29], we selected the 6MWD as a practical and objective tool. Participation in the lifestyle programmes was free of charge. In clinical practice, the costs of the interventions may limit the generalizability of our findings.
We collected outcome measurements at 12 months only. Therefore, we cannot analyse the dynamics of change during the first year. However, by design patients varied in the selection and the sequence of lifestyle programmes and observations before 12 months would therefore be less meaningful. Using a 12 months outcome, we included some time for potential loss of effect after initial success. Clearly, in order to reduce the risk of adverse events, longer persistence of improvements is required. This will be addressed in a follow-up investigation.

Conclusions

The RESPONSE-2 trial demonstrates that nurse-coordinated referral of CAD patients and their partners to a comprehensive set of lifestyle programmes, using up to three community-based interventions, improves lifestyle related risk factors significantly more than usual care alone. Partner participation was associated with a higher rate of success. Referral to these widely available programmes requires minimal effort, and this strategy can be easily implemented into daily practice to improve secondary prevention of CAD.

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Authors' contributions

MM, SL, MS, HTJ, SMB, WJMSR and RJG participated in the design of the trial. MM, SL and MS were responsible for the coordination and acquisition of the data. MM, SL, MS and GR performed the statistical analysis. All authors contributed to the preparation, critical review and approved the final manuscript. RJG obtained funding for the trial.

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Online Table 1.
Attendance to lifestyle programmes during the study.

	Intervention, n=360	Control, n= 351
Weight loss /Weight Watchers™		
Participation total	185/360 (51)	4/351 (1)
Participation if indicated	179/269 (67)	4/249 (2)
Meetings, median total	12 (3-30)	8 (1-22)
Meetings range 0-1	34/185 (18)	1/4 (25)
Partner involvement	83/185 (45)	0
Physical activity/ Directlife™		
Participation total	211/360 (59)	0
Participation if indicated	159/227 (70)	0
Assessment week only	7/211 (3)	0
Participation <6 weeks	14/211 (7)	0
Participation 7-12 weeks	14/211 (7)	0
>12 weeks	176/211 (83)	0
Partner involvement	87/211 (41)	0
Smoking cessation/ Luchtsignaal™		
Participation total	50/360 (14)	1/351 (0.3)
Participation if indicated	50/172 (29)	1/165 (0.6)
Program completed	34/50 (68)	0
Followed ≥50% of program	9/50 (18)	1/1 (100)
Followed <50% of program	7/50 (14)	0
Partner involvement	8/50 (16)	0

Values are presented as mean ± standard deviation or number (percentage), median (interquartile range) for continuous variables with a non-normal distribution.
Note: participation in programs was allowed occasionally in patients without indication for that program, in order to increase motivation for participation in the indicated programs.
Lifestyle programs: Weight Watchers™ is the weight reduction program, Directlife™ is the physical activity program and Luchtsignaal™ is the smoking cessation program.

Imputation

To repair any impact of potentially selective drop-out (12.4% and 15% in the intervention and control group, respectively) on the primary outcome, we performed a multiple imputation (mi) analysis. We used iterative chained equations in Stata version 13.1 (MI version 1.3.0), separately for the intervention and control group. Imputing separately by treatment group prevents any treatment effect from influencing the imputations across the treatment groups. Using subject matter knowledge, we selected 27 predictors to impute missing values, creating 50 complete datasets. The distributions of total cholesterol at baseline, body weight and total cholesterol at 12 months were right-skewed and were log-transformed prior to imputation in order not to violate the assumption of normality of the dependent variable underlying linear regression. The primary outcome ('success') was imputed passively from the four re-estimated variables constituting the primary outcome variable as defined in the methods section: 6-minute walking distance at baseline (4 and 5 missing values in the intervention and control group, respectively), 6-minute walking distance at 12 months (51 and 62 missing values), body mass index at 12 months (56 and 36) and cotinine test (57 and 36). Body mass index at baseline was complete and required no imputations. Continuous variables were imputed using predictive mean matching using the nearest three neighbours option (knn(3)) to avoid imputations in an implausible range. We used augmented multinomial and logistic regressions to avoid implausible values if zero cell counts occurred[1].

The structure of the command we used was:

mi impute chained (pmm, knn(3)) {set of 17 continuous variables} (logit, augment) {set of 6 binary variables} (mlogit, augment) {set of 3 nominal variables} (ologit) {one 1 ordinal variable}, add(50) by(group) rseed(1960) replace dots

Using the binary regression command *binreg* (version 7.5.4, 26 January 2012) in mi estimate, we calculated risk differences (rd) and risk ratios (rr) for each of the 50 imputed sets and pooled these using Rubin's rule to find the average and derive the correct corresponding confidence intervals. Adjustment was made for the 7 possible subgroups of LRF combinations (smoking only, BMI ≥ 27 kg/m^{2}only, physical inactivity only, smoking and BMI ≥ 27 kg/m^2, smoking and physical inactivity, BMI ≥ 27 kg/m^2 and physical inactivity and smoking, BMI ≥ 27 kg/m^2 and physical inactivity):mi estimate: binreg group success, rd mi estimate, eform: binreg group success, rr

In table 2 below shows the variables used for imputation, the numbers missing and the model used to impute them.

Online Table 2.
Variables used for imputation

Variable	Functional form	Number missing	Imputed using
BMI at 12 months	continuous	92	pmm, knn(3)
6MWD at baseline	continuous	9	pmm, knn(3)
6MWD at 12 months	continuous	113	pmm, knn(3)
Natural logarithm of body weight at 12 months	continuous	92	pmm, knn(3)
Fat percentage at baseline	continuous	104	pmm, knn(3)
Fat percentage at 12 months	continuous	164	pmm, knn(3)
Abdominal circumference at baseline	continuous	9	pmm, knn(3)
Abdominal circumference at 12 months	continuous	99	pmm, knn(3)
Natural logarithm total cholesterol at baseline	continuous	14	pmm, knn(3)
Natural logarithm total cholesterol at 12 months	continuous	110	pmm, knn(3)
LDL-cholesterol at baseline	continuous	23	pmm, knn(3)
LDL-cholesterol at 12 months	continuous	114	pmm, knn(3)
Systolic blood pressure at 12 months	continuous	94	pmm, knn(3)
Serum glucose at baseline	continuous	28	pmm, knn(3)
Serum glucose at 12 months	continuous	125	pmm, knn(3)
Age at baseline	continuous	0	*
Sex	binary	0	*
Smoking at baseline	binary	0	*
Cotinine at baseline	binary	1	(augmented) logistic
Cotinine at 12 months	binary	93	(augmented) logistic
Smoking of partner at baseline	binary	164	(augmented) logistic
Patient exercises at least 30 min/day, 5 times/week	binary	0	*
Education (number of categories)	nominal (7)	0	*
Living with a partner (number of categories)	nominal (3)	0	*
Discharge diagnosis (number of categories)	nominal (4)	0	*
Opinion about own fitness (scale: 1 – 10)	continuous	93	pmm, knn(3)
Opinion on amount of healthy exercise	ordinal	84	ordinal logistic

Legend: BMI = body mass index; 6 WMD = 6 minute walking distance; pmm knn(3) indicates predictive mean matching using nearest of three neighboring values; asterisks indicate that these variables were not imputed, but were used to improve the imputations of those variables needing imputation. 1. Greenland S, Mansournia MA and Altman DG. Sparse data bias: a problem hiding in plain sight. *Bmj*. 2016; 352: i1981.

Online Table 3.
Change in BMI, 6MWD and smoking at 12-months follow-up

	Intervention, n=360	Control, n= 351	p-value
Overweight (BMI ≥27m^2)	269 (75)	253 (72)	ns
Attendance to WRP (%) total	185/360 (51)	4/351 (1)	na
Proportion of attendance with BMI≥27m^2	179/185 (97%)	4/4	na
Mean change in kg in subgroup BMI≥27m^2	-2.5 ± 7.2	-0.2 ± 4.6	<0.001
Mean weight change (kg) overall	-1.5 ± 6.8	0.35 ± 4.7	<0.001
Physically inactive (PI)	227 (63)	216 (62)	ns
Attendance to PAP (%) total	211/360 (59)	0	na
Proportion of attendance with physical inactivity	159/211 (75%)	0	na
Mean change in 6MWD, meters in PI subgroup PI	39.0 ± 98.0	34.3 ± 105.2	0.6
Mean change of 6MWD, meters overall	42.6 ± 96.4	33.1 ± 98.7	0.2
Smoking at baseline	72 (20)	76 (22)	ns
Attendance to SCP (%) total	50/360 (14)	1/351 (0.2)	na
Smoking cessation in pre-event smokers	86/172 (50)	76/166 (46)	0.5
Smoking cessation (smoking at baseline)	16/72 (22)	9/76 (12)	0.1

Values are presented as mean ± standard deviation or number (percentage), median (interquartile range) for continuous variables with a non-normal distribution. BMI= body mass index, WRP=weight reduction program, kg=kilogram, 6MWD= 6 minutes walking distance, PAP=physical activity program, PI=physical inactive and SCP=smoking cessation program, na =not applicable, ns=non-significant.

Online Table 4.
Risk factor on goal at 12 months for each risk factor in patients with 3 LRFs at baseline

	Intervention (n=73)	Control (n=64)	p-value
primary outcome, n (%)	31 (64)	24 (38)	0.55
non-smoking	43 (59)	32 (50)	0.30
reduction of ≥5% in BMI	13 (18)	10 (16)	0.73
improvement on 6MWD	37 (51)	25 (39)	0.17

BMI= body mass index, 6MWD= 6 minutes walking distance, LRF: Lifestyle Related Risk factor.

'I had several visits at the nurse outpatient clinic. Just to make sure everything was hunky-dory, and we discussed my cholesterol and medication. The nurse really takes time to check everything!'
(Mr S. van Beek, 55 years)

Chapter 6

Nurse-coordinated care improves the achievement of LDL cholesterol targets through more intensive medication titration

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Abstract

Background

Nurse-coordinated care (NCC) improves the achievement of LDL-cholesterol targets after an acute coronary syndrome (ACS). We hypothesised that NCC improves achievement of LDL-C targets through more intensive medication titration.

Methods

We used data from RESPONSE, a multicentre randomised trial on the efficacy of NCC in 754 ACS patients. Follow-up data were collected at 6 and 12 months. To enable comparison between the various types and dosages of statins, we used the average lipid-lowering potency (ALLP, % LDL-C lowering) as an indicator of lipid-lowering medication intensity.

Results

Most patients in NCC intervention and usual care groups (96%) had started lipid-lowering therapy during the index hospitalisation. At 6 months, titration activities (up or down) were applied in 45% of NCC patients compared with 24% of patients receiving usual care ($p<0.001$), and a difference was also seen at 12 months follow-up (52% vs 34%, $p<0.001$). In patients not on LDL-C target at baseline, titration activities at 6 months were recorded in 63% and 30% of NCC and usual care patients respectively ($p<0.001$), with increased titration activities in both groups at 12 months (69% vs 43%, $p<0.001$).

Conclusion

Nurse-coordinated care is associated with more frequent and intense lipid-lowering medication titration to reach LDL-C targets as compared with usual care alone. Further, merely starting the guideline-recommended dose is insufficient to reach the guideline-recommended LDL-C target level.

Introduction

Among patients with coronary heart disease (CHD), treatment of risk factors is the cornerstone of secondary prevention.[1] In the last decade, a substantial increase in antihypertensive and lipid-lowering medication prescriptions has been observed.[2] Despite a substantial increase in the number of patients receiving guideline-recommended medication, the the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) survey showed that up to three years after hospitalisation, two thirds of patients have uncontrolled hypertension, and only half of the patients achieve the guideline-recommended target level for LDL-cholesterol (LDL-C).[3,4] It has been hypothesised that factors contributing to this suboptimal risk factor control include prescriptions with inadequate dosage, inadequate up-titration of medication, poor adherence of patients to recommended lifestyle changes, poor medication compliance, and low standards of follow-up care.[5]

Nurse-coordinated care (NCC) has shown to be a promising strategy to improve secondary prevention, and is currently recommended in the 2016 European prevention guidelines.[1] In line with this recommendation, we found in a recent systematic review that NCC programmes successfully reduce systolic blood pressure and LDL-C.[6] However, a clear understanding of how NCC improves achievement of LDL-C targets is still needed. More specifically, no studies have investigated the effect of medication titration in NCC, but it has been hypothesised that medication titration could cause this effect.[7]

To address this gap in knowledge, we investigated the process of medication titration in the treatment of LDL-C in NCC. We used data from the andomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists (RESPONSE) trial (see below). As the lifestyle risk factors were comparable in both groups in the study, the previously reported improvement of the proportion of patients on target for LDL-C in the NCC intervention group could not be explained by lifestyle changes. Additionally, participating nurses in this trial reported that the NCC intervention allowed them more frequent contact with patients and the opportunity to monitor targets more carefully.[8] We therefore hypothesised that lipid-lowering medication titration activities occurred more often in the NCC than usual care group, and that this led to better achievement of LDL-C targets.

Methods

Study design and population

We used data from the RESPONSE trial, a multicentre randomised clinical trial including 754 patients from 11 centres in the Netherlands.[9] The study was designed to quantify the impact of a practical, hospital-based nurse-coordinated prevention programme on

cardiovascular risk in patients discharged after an acute coronary syndrome (ACS), as compared with usual care alone. Patients aged 18-80 years were eligible if they had been diagnosed with ACS within 8 weeks prior to entry into the trial. Patients were excluded if they (1) were unable to visit the nurse-coordinated prevention programme, (2) were not available for follow-up, (3) had a limited life expectancy (≤2 years), and (4) were diagnosed with heart failure New York Heart Association class III or class IV.

Nurse-coordinated care

Nurses participating in the NCC programme were registered nurses with at least a four years bachelor's degree in nursing. They had experience in cardiovascular care and were trained in motivational interviewing. Patients in the NCC group visited the outpatient clinic up to 4 times during the first 6 months after inclusion, in addition to outpatient clinic visits to their cardiologist (usual care). During each nurse visit, cardiovascular risk factors were assessed, lipid profiles (including LDL-C) were reviewed, medication therapy evaluated, and patient compliance with medical treatment and lifestyle recommendations was encouraged. To achieve the target lipid levels, the nurses were also encouraged to titrate medication in collaboration with the treating cardiologist.

Data collection

Data on clinical and demographic characteristics and CHD risk factors were collected at baseline and at 6 and 12 months after randomisation. Baseline measurements were performed within eight weeks after ACS. Patients were enrolled at an average of four weeks (SD 2.7) after the ACS. Data on medication use was collected at baseline, 6 months, and 12 months follow-up. The data on lipid-lowering medication included number of lipid-lowering medications and for each medication the generic name, dosage and frequency. When LDL-C was not on target during the four NCC visits, nurses documented when medication was changed during the NCC visit, and if the treating specialists were consulted and/or patients were referred to treating specialists. All venous blood measurements were taken after a minimum of 8 hours of fasting. The target for LDL-C level was ≤2.5 mmol/L, as recommended by the national CVD prevention guideline at that time.[10] Dyslipidaemia was defined by the following criteria: a history of deviated serum cholesterol values (LDL-C >4 mmol/L, HDL-cholesterol <1.0 mmol/L, triglycerides >2 mmol/L, or total cholesterol >5 mmol/L), or treatment for dyslipidaemia. Further details on the trial have been published previously.[9,11]

Lipid-lowering medication intensity and titration

Our main outcome of interest was the proportion of patients with up- or down-titration activities in the NCC compared with usual care, assessed by changes in lipid-lowering medication intensity at 6 months and 12 months, relative to baseline medication intensity. The 6 months follow-up visit was performed directly after completion of the

NCC intervention (i.e. after up to four NCC visits), while between 6 and 12 months follow-up, no specific interventions took place in either group. To account for the use of different lipid-lowering agents and dosages, the intensity of each prescription was expressed as a potential average lipid-lowering potency (ALLP, % LDL-C lowering) ranging from 13 to 70.[12] ALLP and up- or down-titration was measured at 6 and 12 months follow-up. Up-titration was defined as an increase in ALLP as compared with baseline ALLP, whereas down-titration was defined as a decrease in ALLP.
As the Dutch guideline for cardiovascular risk management recommends starting with simvastatin 40 mg daily when patients are diagnosed with ACS[13], we defined simvastatin 40 mg as the lowest recommended dose approved for the management of ACS.

Statistical analysis

Comparisons between groups were performed using chi-square test for categorical variables. Differences between characteristics of up- and down-titrated patients were analysed by the Chi-square test. The P-values presented in Figure 1 were up-titration vs. no titration (none), and down-titration versus no titration (none). A two-sided p-value of <0.05 was considered statistically significant. As ALLP is not a continuous variable, we expressed ALLP as a sum of the prescribed potencies per group. SPSS Statistics for Macintosh, version 22.0. (Armonk, NY, USA) was used for descriptive statistical analyses.
In order to include the NCC intervention effect at 6 months, we plotted ALLP changes between baseline and 6 months. We assessed if patients in the NCC group who were (not) on target at baseline received greater intensity changes than those in the usual care group by estimating the interaction between treatment arm and (not) being on target at baseline in a linear regression analysis. These analyses were performed using Stata, version 13.1 (College Station, TX, USA).
To check for selective drop-out, we used a logistic regression model and regressed a binary variable indicating missingness (1=yes, 0=no) on the following variables as predictors of missingness under the hypothesis that if all odds ratios were close to one, selective drop out due to these predictors is unlikely: age, gender, education level, index event, history of cardiovascular disease (CVD), alcohol, smoking at baseline, diabetes mellitus and their interaction with randomisation group.

Results

Our population consisted of 754 patients with a mean age of 58 years (SD 10.1), 80% were men. The majority (73%) had no history of CVD prior to the index hospitalisation. As previously described, baseline patient characteristics did not differ between the NCC and usual care groups.[9] In the NCC group, 92% of 365 patients attended all four

Table 1.
LDL-cholesterol and the Average Lipid-Lowering Potency (ALLP) in NCC versus usual care patients at baseline, 6 and 12 months follow-up

	Baseline[1]		F6			F12		
Parameter	NCC	Usual care	NCC	Usual care	P-value[2]	NCC	Usual care	P-value[2]
	(n=365)	(n=367)	(n=356)	(n=346)		(n=357)	(n=352)	
On lipid-lowering medication, n (%)	350 (96%)	352 (96%)	345 (96%)	335 (96%)	0.70	331 (93%)	328 (94%)	0.64
LDL-cholesterol OT (≤2.5 mmol/L)	247 (68%)	249 (68%)	284 (80%)	241 (69%)	<0.001	263 (74%)	223 (64%)	<0.01
Total ALLP[3] (% LDL-C lowering)	14.366	13.943	15.003	14.030	NA	14.564	13.964	NA

NA: not applicable; NCC: nurse-coordinated care; OT: on target.
[1]At baseline differences not statistically significant at the 5% level; [2]calculated between NCC and usual care (between-groups); [3]ALLP: the Average Lipid-Lowering Potency (ALLP) as an indicator of lipid-lowering medication intensity using the method by Besseling et al.[12] (ref); Total ALLP is the sum of the prescribed lipid-lowering potencies (%) per group.

NCC consultations as scheduled during the first 6 months. In total, 46 patients in the intervention and 33 patients in the usual care group had one or more missing values for our analyses (11%). Logistic regression did not reveal an indication for selective dropout between the NCC and usual care group.

Titration activity outcome

The proportion of patients with up- or down-titration of lipid-lowering medication from baseline to 6 and 12 months follow-up was higher in the NCC group as compared with the usual care group (Figure 1). Reflective of the NCC titration intervention, markedly more lipid-lowering titration was seen at 6 months follow-up in the NCC group compared with the usual care group (any titration in all patients 45% vs 24%, $p<0.001$) (Figure 1). At 12 months, a slight increase of titration activities was seen in both groups, yet a statistical significant difference between the two groups remained (52% vs 34%, $p<0.001$). While both up- and down titrations in ALLP was seen in both groups, more patients in the NCC than in the usual care group were up-titrated (6 months 30% vs 13% of, $p<0.001$; 12 months 33% vs 19% $p<0.001$).

In patients not on LDL-C targets at baseline (Figure 1), most titration activities (up or down) and the largest difference between NCC and usual care groups were observed in the first 6 months (6 months: 63% vs 30%, $p<0.001$; 12 months: 69% vs 43%, $p<0.001$). Similarly, in patients not on target at baseline, also up-titration activities were more often observed in the NCC than in the usual care group, particularly in the first 6 months (6 months: 51% vs 24%, $p<0.001$; 12 months: 58% vs 33%, $p<0.001$).

Figure 2 shows all ALLP changes between baseline and 6 months as a function of LDL-C at baseline for NCC and usual care patients (not) on target at baseline. On average, NCC had an (absolute) effect on ALLP compared to usual care alone, especially if patients were not on target at baseline (slope 2.3, (95% -0.11 – 4.72)). The differences in standard deviation between NCC and usual care reaffirm the spread of ALLP between these two groups.

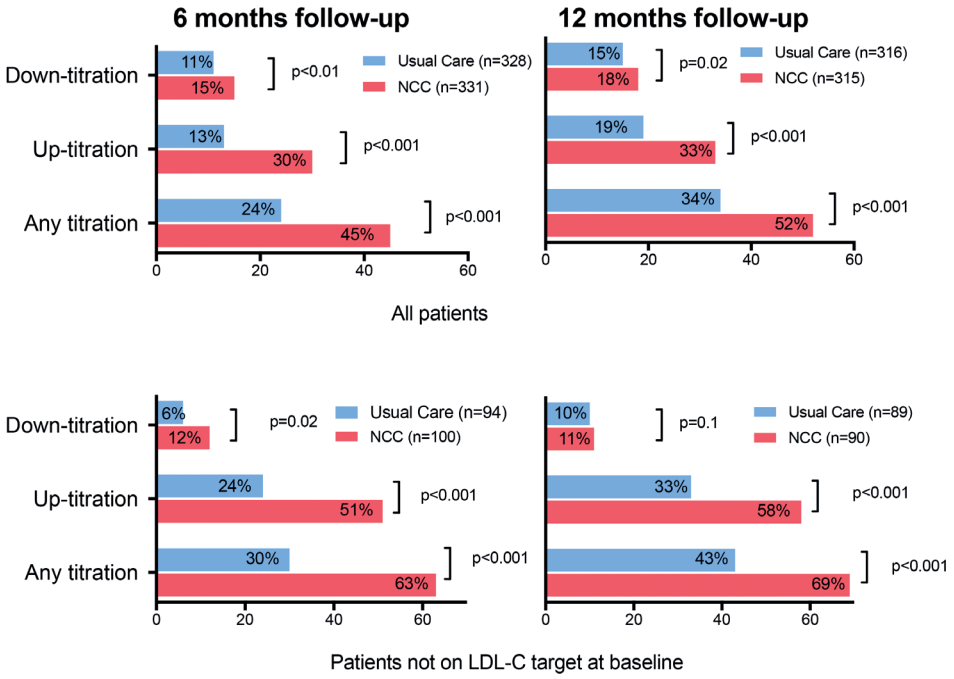

Figure 1.
Titration activities from baseline up to 6 and 12 months follow-up in NCC versus usual care patients.

Legend: X-as: patients (percentage), Y-as: titration activities. Up- and down titrations are relative to baseline. Percentages are % of total population (upper panel) and % of population not on target (lower panel). All p-values are calculated with the relevant parameter (down-titration, up-titration, or any titration) vs. no titration (none).

Upper panel: percentage of patients with titrations of total population.
All patients: Usual care at 6 months n=328, NCC at 6 months n=331; Usual care at 12 months n=316, NCC at 12 months n=315.

Lower panel: percentage of patients with titrations of patient population not on LDL-C target at baseline: Usual care at 6 months n=94, NCC at 6 months n=100; usual care at 12 months n=89, NCC at 12 months n=90.

Not on target is defined as LDL-cholesterol >2.5 mmol/L; NCC: nurse-coordinated care. Analysis applied for patients on lipid-lowering medication and patients with complete medication data.

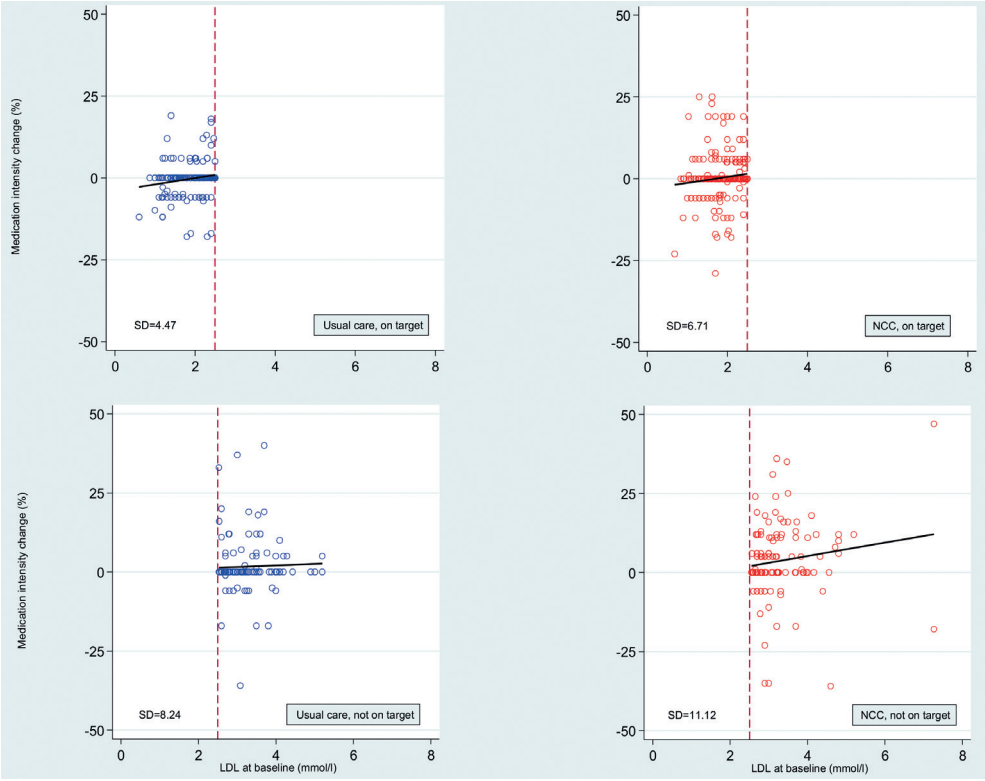

Figure 2.
Medication intensity (ALLP) changes between baseline and 6 months, by (not) being LDL-C target at baseline for NCC (red dots) and usual care (blue dots) patients.

Legend: Dots represent individual patients. The right lower graph shows, on average, more medication intensity changes in NCC patients not on target at baseline compared with usual care patients (left). The red dashed vertical lines indicate the cut-off LDL-C serum concentration of 2.5 mmol/l. The black lines are the slopes based on a linear regression analysis of the medication intensity changes against LDL-C levels at baseline.

ALLP: the Average Lipid-Lowering Potency (ALLP, % LDL-C lowering) as an indicator of lipid-lowering medication intensity; LDL: low-density lipoprotein; mg: milligram; mmol/l: millimol per liter.

Lipid-lowering medication data

At baseline, the proportion of patients on lipid-lowering medication was high in both the NCC (96%) and the usual care group (96%), and 68% of all patients were on LDL-C target at baseline (Table 1). Simvastatin (43%), followed by atorvastatin (41%) were the most commonly used lipid-lowering medications prescribed at baseline. During follow-up, a higher proportion of patients in the NCC group were on target compared with the usual care group (6 months: 80% vs 69%, p<0.001; 12 months: 74% vs 64%, p<0.01). Total ALLP was slightly higher in the NCC as compared with usual care at both 6 months (15.003 vs 14.030) and 12 months (14.564 vs 13.964) (Table).

Characteristics of up- and down-titrated patients compared to patients with no titration

There were no differences in demographic or clinical characteristics as age, gender, level of education, index event or cardiovascular risk factors of up- and down titrated patients (data not shown). However, up-titrated patients had dyslipidaemia more frequently as compared with patients with no titration (79% vs 70% respectively, p=0.04), and up-titrations were associated with allocation to the NCC group (62% vs 43%, p<0.001). Down-titrated patients had dyslipidaemia less frequently as compared with patients with no titration (56% vs 70% respectively (p=0.02). Down-titration was also more frequently seen in patients allocated to the NCC group as compared with patients with no titration (55% vs 43% respectively (p=0.02).

Discussion

Our study demonstrates that nurse-coordinated care in patients with ACS is associated with more frequent lipid-lowering medication titration and with higher ALLP values to reach LDL-C targets as compared with usual care alone. These titrations took place in a relatively short amount of time (four visits in 6 months after an ACS), but changes made in the first 6 months in lipid-lowering medication were also observed 6 months after completion of the NCC programme, and were reflected in a higher proportion of patients reaching targets for LDL-C.

Our study took place in a context of high prescription rates of lipid-lowering medication (96% in both groups at baseline). Despite these high prescription rates, the target for LDL-C (2.5 mmol/L) was not reached in a considerable number of patients in both groups (NCC 26% vs usual care 36%). Our study shows that there is considerable room for individual tailoring of lipid-lowering medication therapy, with more both up- and down titrations in medication intensity in the NCC group. While lifestyle modification could account for some changes in LDL-C levels, it is unlikely that this can explain the differences in the higher proportion of patients on target in the NCC group, as lifestyle risk factors were comparable through the study up until 12 months follow-up.[9] Despite

a small difference in the total sum of ALLP in both groups at 6 and 12 months, the proportion of patients on target for LDL-C was markedly higher in the NCC group as compared with the usual care group, reflecting the efficacy of adequate individual medication titration.

Large proportions of high-risk cardiovascular patients have been shown to discontinue their statin therapy, emphasising the need for healthcare providers to discuss medication use with their patients.[14] An integral part of the NCC intervention in our study was interviewing patients about their compliance, asking about barriers concerning adherence, and titrating medication (i.e. lipid lowering medication) to optimise adherence. Our data showed that down-titrations were made in NCC patients. A possible reason for these down-titrations could be maintaining compliance in case of side effects, as patients on high-intensity statin therapy who experience side effects (such as myopathy) are likely to be less compliant than patients down-titrated to a better tolerated statin intensity.

According to the ESC guideline, reducing dosage is an effective approach for enhancing medication adherence.[1,15] Nurse-coordinated programmes are associated with modest but positive effects on reducing cholesterol levels according to recent meta-analyses.[6,16] However, studies assessing patients' medication adherence found improved patient adherence in one study[17] and no differences between NCC and usual care in two other studies.[18,19] Reasons for poor patient adherence are multifactorial. According to the WHO, reasons for medication non-adherence are categorised in five groups: health system, condition, patient, therapy and socio-economic factors.[15] In particular, education and frequent follow-up visits have been shown to be associated with improved adherence, [20] and NCC potentially positively influences several of these categories. While we found that targets for LDL-C were more frequently achieved in NCC, more research on the role of NCC to improve medication adherence in general would be valuable.

Patients allocated to the NCC group reached the target level of LDL-C in a short period of time after discharge. This is likely to be beneficial, as several trials have demonstrated important reductions in major cardiovascular events from lowering cholesterol, especially LDL-C.[21] The total sum of ALLP for NCC patients was only slightly higher compared with patients in usual care. This should be seen as clinically relevant as this difference probably led to a larger proportion of patients achieving target level for LDL-C, and the clinical benefits of LDL-C lowering in general are well known.[22,23]

Secondary prevention based on nurses' collaboration has the potential to improve patient care. While health care organisations differ widely across Europe, the ESC prevention guidelines recommend a multidisciplinary team for secondary prevention including physicians and nurses. In some countries, secondary prevention is mainly the task of physicians, while in others, specially educated and trained nurses play a more prominent role.[1] Physicians and nurses are recommended to work together as a team to provide the most effective multidisciplinary care. Nurse-coordinated care has proven to be effective

in reducing risk factors[9,6] anxiety and depression[24], and nurses reported to appreciate participating in such multidisciplinary teams.[8] Therefore, depending on local practice, integrating NCC should be considered in secondary prevention in ACS patients.

New developments and limitations

The ESC guideline target for LDL-C changed from 2.5 mmol/L to 1.8 mmol/L after the completion of inclusion of patients in the RESPONSE trial.[15] This change increases the need for new initiatives to reach LDL-C targets in patients with CHD, as it is shown that only a minority of patients reach these stricter targets.[4] The specific role of NCC in this process needs further evaluation, especially with the upcoming availability of new pharmacological strategies, such as PCSK9-inhibitors.

Moreover, it should be noted that our data on medication use was based on self-report by professionals, and not corroborated with additional questionnaires regarding adherence or pill counts. While side effects were discussed with patients during NCC consultation, we did not specifically collect data on such side effects. This might be a valuable part of follow-up research.

Furthermore, we did not correct for possible confounders such as lifestyle factors in our analysis. The development of a model with the hypothesised pathways between LDL-C on target and NCC interventions, including all potential confounders of this relation, could potentially help to more fully investigate the association between NCC titration and LDL-C on target. Such causal mediation analysis may be used to investigate the causal role of titration activities relative to other factors associated with NCC in future trials.[25,26]

Conclusion

In conclusion, among patients hospitalised for ACS, NCC resulted in more intensive medication titration compared with usual care alone. The greater proportion of patients on LDL-C target at 6 and 12 months follow-up is likely explained by the more intensive titration of lipid-lowering medication in NCC patients compared with usual care alone. Merely starting the guideline-recommended dose is insufficient to reach the guideline-recommended LDL-C target level. Nurse-coordinated care, combined with guideline-based titration recommendations, can improve ACS patient outcomes and should become part of routine daily practice.

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PART 2:

SMOKING CESSATION

'I experienced having a heart attack as a 'warning shot' and I don't want to smoke anymore. 'I think I can manage that. It is already going well for five weeks'.
(Mr M. Bosman, 70 years, myocardial infarction)

Chapter 7

Smoking cessation after an acute coronary syndrome: immediate quitters are successful quitters

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ABSTRACT

Background

Cardiovascular disease (CVD) prevention guidelines stress the importance of smoking cessation and recommend intensive follow-up. To guide the development of such cessation support strategies, we analysed the characteristics that are associated with successful smoking cessation after an acute coronary syndrome (ACS).

Methods

We used data from the Randomised Evaluation of Secondary Prevention for ACS patients coordinated by Outpatient Nurse SpEcialists (RESPONSE) trial (n=754). This was designed to quantify the impact of a nurse-coordinated prevention program, focusing on healthy lifestyles, traditional CVD risk factors and medication adherence. For the current analysis, we included all smokers (324/754, 43%). Successful quitters were defined as those who reported abstinence at one year of follow-up.

Results

The majority of successful quitters quit immediately after the ACS event and remained abstinent through one year of follow-up, without extra support (128/156, 82%). Higher education level (33% vs. 15%, $p<0.01$), no history of CVD (87% vs. 74%, $p<0.01$) and being on target for LDL-cholesterol level at one year (78% vs. 63%, $p<0.01$) were associated with successful quitting.

Conclusion

The majority of successful quitters at one year stopped immediately after their ACS. Patients in this group showed that it was within their own ability to quit, and they did not relapse through one year of follow-up. Our study indicates that in a large group of patients who quit immediately after a life-threatening event, no relapse prevention programme is needed.

Introduction

Coronary heart disease (CHD) patients are at high risk of recurrent coronary events and mortality. Risk reduction strategies are therefore offered to patients with established CHD or other atherosclerotic cardiovascular disease (CVD). Smoking is known to be a major health risk factor.[1,2] Smoking cessation after CHD is diagnosed is potentially the most effective preventive measure. It is associated with a 33%-50% reduction in risk of recurrent myocardial infarctions or cardiovascular death[3-5] and a life expectancy gain of three years after coronary artery bypass surgery.[6] Nevertheless, although smoking cessation is potentially the most effective CVD prevention strategy, quitting smoking is difficult and secondary prevention is suboptimal. Studies from Europe and the USA have shown that half of the patients continue to smoke despite a life-threatening event.[7,8] Although the majority received personal advice to stop or were offered counselling, many were not able to quit.[7,9] In general, surveys revealed a disappointing situation with regard to secondary prevention actions. A substantial potential to reduce the risk of recurrent cardiovascular disease or death still remains.

Successful strategies for smoking cessation include pharmacological therapy (nicotine replacement therapy, bupropion and varenicline) and behavioural counselling for smokers willing to quit.[10-12] Successful behavioural support in smoking cessation has been reported for group therapy, individual counselling[11] and telephone counselling[13] and to a lesser extent for individually tailored self-help materials.[11] In addition, guidelines on CVD prevention recommend frequent follow-up visits for all smokers who have quit to increase long-term success.[14] However, as shown in a recent review[15], the effectiveness of behavioural relapse prevention methods for any initially successful subgroup of former smokers has not been demonstrated.

Nurse-coordinated prevention programs also aim to increase the proportion of patients achieving CVD prevention targets, but these initiatives have not resulted in higher smoking cessation rates.[16-19] With the RESPONSE trial we evaluated whether a nurse-coordinated prevention program leads to better achievement of guideline-recommended CVD prevention targets.[20] We found this program improved blood pressure and lipid management, but did not have a significant impact on lifestyle factors, including smoking cessation.[20]

It is currently unknown which patients benefit from intensive smoking cessation counselling after hospital admission for acute coronary syndrome (ACS). Better understanding of the characteristics of patients who are likely to quit successfully after ACS may provide useful information to guide development of more effective smoking cessation interventions. We therefore addressed the following research question: what are the characteristics of successful quitters after a recent ACS?

Methods

Design and study population

The RESPONSE trial (n=754) was a multicentre, randomised controlled trial conducted in 11 centres in the Netherlands with one year of follow-up. Patients aged 18-80 years were eligible if they had been diagnosed and hospitalised with ACS within 8 weeks prior to enrolment in the trial. Patients were excluded if they (1) were unable to visit the nurse-coordinated prevention program, (2) were not available for follow-up, (3) had a limited life expectancy (≤2 years), and (4) were diagnosed with a New York Heart Association class III or class IV heart failure. Patients were randomised to either the nurse-coordinated prevention program or usual care alone. Detailed information about the study methods has been reported elsewhere.[20,21] For the current analyses, we selected 324 patients who smoked before the index ACS event (43%) and reported a smoking and quitting status at one year of follow-up.

We defined successful quitters as patients who reported abstinence accompanied by a quit date at one year of follow-up. We defined relapsers as those patients who had attempted to quit smoking but reported that they began smoking again within one year, and were therefore classified as 'smoker' in the main analysis at one year of follow-up. Patients who reported that they continued smoking in the year of follow-up were also classified as smokers.

Data collection and follow-up

Baseline measurements were performed within 8 weeks after ACS. Patients were enrolled at an average of 4 weeks (SD 2.7). Patients in the intervention group visited the outpatient clinic four times during the first 6 months after inclusion, in addition to visits to their treating cardiologist (usual care). During each nurse visit cardiovascular risk factors were evaluated. Data on clinical and demographic characteristics, CHD risk factors and smoking quit dates were collected at baseline and follow-up. Smoking behaviour was measured by means of interview questions. Health-related quality of life was assessed with the MacNew questionnaire.[22,23] Scores on each quality of life domain were calculated as the average of the responses in that domain. We used the Systematic Coronary Risk Evaluation (SCORE) as an integrated measure to estimate the overall impact of smoking cessation on cardiovascular risk.

Statistical analysis

The results of our statistical analysis are presented as absolute numbers and percentages. Differences between successful quitters and smokers were analysed by using unpaired t-tests for continuous variables and chi-square statistics for categorical variables. We used SPSS (version 20.0) for all data analysis.

Results

Of 324 smokers admitted to hospital with ACS, 186 (57%) reported a cessation attempt in the year after the event. Of those, 156 (86%) were successful quitters in up to one year of follow-up. The majority of this group quit immediately after the event (128/156, 82%; Fig. 1) and received no smoking cessation counselling after discharge. Patients making a later cessation attempt were less successful in quitting smoking (28/44, 64%). As shown in Table 1, successful quitting up to one year after ACS was associated with a higher education level (33% vs. 15%, p<0.01), no history of CVD (87% vs. 74%, p<0.01), being on target for LDL-cholesterol level at one year (78% vs. 63%, p<0.01) and adequate physical activity at one year (65% vs. 52%, p=0.01).

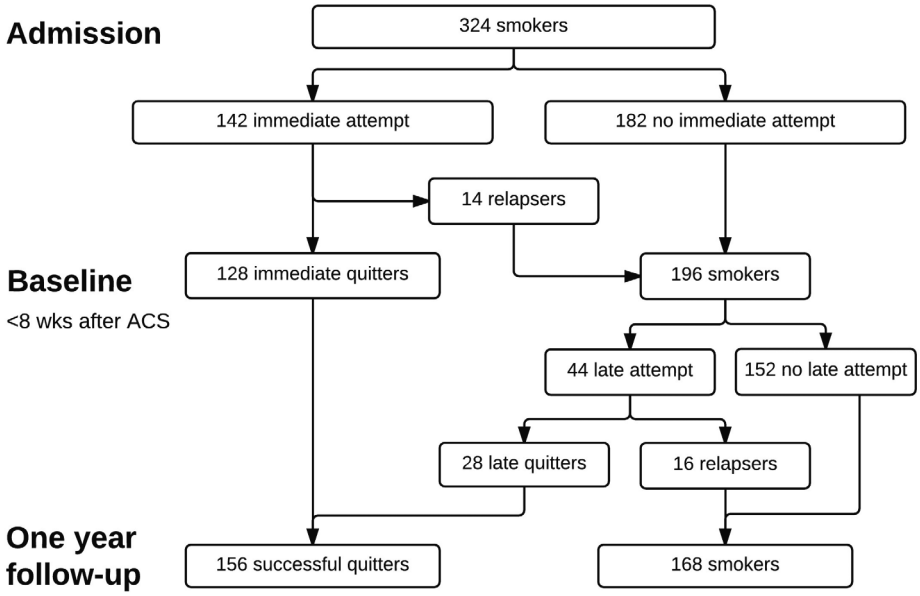

Figure 1.
Flowchart of 324 smokers after an acute coronary syndrome (ACS) from hospital admission up to one-year follow-up.
Immediate: immediately after hospital discharge; late: during one year of follow-up.

At 12 months, the estimated SCORE cardiovascular 10-year mortality risk was 2.9% (SD 0.03) for successful quitters and 5.7% (SD 0.07) for smokers (p<0.01). Successful quitters and smokers were comparable in other lifestyle risk factors than smoking at baseline, while after one year successful quitters more frequently had a body mass index (BMI) >25 kg/m^2 compared with smokers (81% vs. 67%, p<0.01) Mean BMI at one year was 29.0 kg/m^2 (SD 4.93) in successful quitters and 27.5 kg/m^2 (SD 5.04) in smokers. Smoking cessation after ACS was associated with an average weight gain of 3.36 kg (SD 5.48) at one year. In our study we observed a maximal weight gain in successful quitters of 21 kg, whereas 9% of successful quitters gained >10 kg after smoking cessation.

Within the group of smokers, 63% reduced smoking cigarettes at one year of follow-up compared with baseline level. These patients had a higher level of education and smoked a higher number of cigarettes per day compared with smokers not reducing cigarette smoking. We observed a median reduction of 5 (IQR 0-15) cigarettes for smokers at one year of follow-up. In smokers who reduced cigarette smoking, we found that after one year they smoked a median of 13 cigarettes (IQR 6-20) less than at baseline.

In total, 30 relapsers were presented (Table 1). The majority (90%) of these were younger than 60 years of age, relatively more were female (33%) than both successful quitters and smokers and diagnosed with ST-segment-elevation myocardial infarction (60%). We found that a group of 14 relapsers before baseline measurements were predominantly male coronary artery bypass graft (CABG) patients (86%).

Of 44 patients making later cessation attempts, 73% were in the nurse-coordinated prevention program group. This group was encouraged to quit smoking and was given information about a healthy lifestyle. However, participation in the nurse-coordinated prevention program group did not significantly increase smoking cessation rates in patients making a late attempt (p=0.8).

Table 1.
Characteristics of successful quitters versus smokers in ACS patients (n=324)

	Successful quitters[1] n=156	Smokers n=168	P-value[2]	Relapsers[3] n=30
Age				
<50 years	53 (34%)	61 (36%)	0.89	14 (47%)
50-59 years	67 (43%)	71 (42%)		13 (43%)
≥60 years	36 (23%)	36 (21%)		3 (10%)
Male, n (%)	127 (81%)	125 (74%)	0.13	20 (67%)
Highest level of education, n (%)				
Fewer than 8 years	41 (28%)	63 (38%)	0.02	13 (43%)
College or university	49 (33%)	25 (15%)	<0.001	5 (17%)
No history of CVD, n (%)	136 (87%)	124 (74%)	<0.01	19 (63%)
Index event, n (%)				
STEMI	89 (57%)	89 (53%)	0.89	18 (60%)
NSTEMI	50 (32%)	51 (30%)		7 (23%)
Unstable angina pectoris	17 (11%)	26 (16%)		4 (13%)
Nurse Coordinated Prevention Programme	89 (57%)	83 (49%)	0.17	16 (53%)
No. cigarettes/day				
≤10	62 (40%)	59 (35%)	0.36	10 (33%)
>10	93 (60%)	109 (65%)		20 (67%)
Quality of life at baseline[4] (mean, SD)	5.13 (1.06)	5.02 (1.14)	0.47	5.0 (0.9)
Quality of life at one-year follow-up	5.66 (1.01)	5.46 (0.99)	0.66	5.6 (0.7)
Risk factors at baseline				
Systolic blood pressure >140 mmHg	36 (24%)	33 (20%)	0.12	4 (13%)
LDL-cholesterol >2.5 mmol/L	46 (31%)	66 (39%)	0.15	13 (43%)
Body mass index >25 kg/m^2	116 (74%)	115 (68%)	0.12	22 (73%)
Inadequate physical activity[5]	89 (57%)	98 (58%)	0.81	16 (53%)
Risk factors at one-year follow-up				
Systolic blood pressure >140 mmHg	41 (28%)	43 (26%)	0.79	9 (30%)
LDL-cholesterol >2.5 mmol/L	32 (22%)	62 (37%)	<0.01	16 (57%)
Body mass index >25 kg/m^2	127 (81%)	112 (67%)	<0.01	23 (78%)
Inadequate physical activity	54 (35%)	81 (48%)	0.01	15 (50%)
Systematic Coronary Risk Evaluation (SCORE)	2.9%	5.7%	<0.01	4.2%

[1] Defined as non-smoking at outcome assessment date; [2] Between successful quitters and smokers; [3] note that these 30 relapsers are a subgroup of the 168 smokers; [4]*assessed with the MacNew questionnaire;* [5] *<30 min/5 times a week.*

Discussion

Our study demonstrates that immediate cessation after hospitalisation for ACS is the most important characteristic of successful quitters. A higher level of education, no history of CVD, LDL-cholesterol level on target and adequate physical activity at one year characterised successful quitters at one year after ACS as well. At one year, however, successful quitters more often had a BMI >25 kg/m^2 compared with smokers.

The REPONSE trial showed that a nurse-coordinated prevention program improved systolic blood pressure and blood levels of LDL-cholesterol. However, this program was less successful in achieving smoking cessation.[20] In the current paper we explored characteristics that may increase successful smoking cessation, for smoking is a major risk factor of mortality and recurrent events in CHD patients.

Our study confirms that quitting smoking is extremely difficult for many patients, even after being hospitalised for a life-threatening event, especially for those with a lower education level. Only half of the patients succeeded in quitting smoking after ACS, which is consistent with success rates in previous studies.[7,9]

On the positive side, however, our study also shows that almost half of all smokers succeeded in quitting up to one year after ACS. Moreover, of those who quit immediately after the acute event, the majority are successful through one year. Our study confirms earlier findings indicating that a clinical event acts as an important motivator and may induce behavioural change[24], particularly if this event is perceived as life-threatening as is the case with patients' first ACS.[9,25] In accordance with European Society of Cardiology (ESC) guidelines, clinicians may make greater use of this opportunity by addressing the issue before discharge.[14] These guidelines also recommend that support for cessation of smoking is initiated for all smokers during hospital admission and is continued for a prolonged period after discharge.[10,14] Our study shows, however, that the majority of successful quitters stop immediately after discharge, triggered by the ACS event, and that it is within their own ability to quit and remain abstinent.

This continued change of behaviour may be explained by the theory of self-perception, which describes how people use their own behaviour to learn what they believe.[24] In our study, during admission almost half of the smokers showed that they were willing to change and felt able to change. The feeling of being able to change is strengthened when these patients indeed quit smoking after discharge. These patients soon perceive themselves as 'successful quitters'[24], which subsequently strengthens them in their resolve to remain abstinent. Moreover, for these patients - who are in a 'ready for action' stage, according to the stages of change theory of Prochaska and Diclemente[26] -counselling seems unnecessary and may be even counterproductive.[24,27] The results of our study therefore suggest that the WHO smoking cessation algorithm, which is included in the ESC guideline and recommends intensive follow-up for all smokers, may not be appropriate for smokers who quit immediately after ACS. In the decision-

making process about smoking cessation interventions, a distinction could be made between types of smokers, such as quitters triggered by an acute life-threatening event or other triggers and immediate or late quitters. In patients hospitalised for acute events who immediately quit after discharge, and do not relapse up to their first outpatient clinic visit, relapse prevention by counselling or pharmacological therapy may not be necessary. In our study, none of the immediate quitters who remained abstinent up to their first outpatient visit reported a relapse up to one year after ACS, and evidence for the effectiveness of relapse prevention for patients who immediately quit smoking after an acute hospitalisation is lacking.[15]

Our results are, however, less clear about the effectiveness of smoking cessation interventions at hospital discharge, as we observed a number of relapsers between hospital discharge and the first visit to the outpatient clinic. This occurred particularly in CABG patients, who may feel the external pressure not to smoke, but may not be intrinsically motivated to quit or not feeling able to quit. Smoking reduction to support smoking cessation could be considered for smokers who are willing but unable to quit[28]. Reduced smoking can be advised until these patients are ready for a new attempt.[28,29]

More research is needed on characteristics of ACS patients who intend to quit smoking during hospitalisation, in order to focus on those who are willing to quit but are at risk for relapse after discharge. Our study confirms earlier research showing that successful quitting is strongly associated with a higher education level and no history of CVD[9,25]. Deferral of smoking cessation interventions after hospital discharge should be considered in patients with these characteristics. In our study, pharmacological support was not part of the smoking cessation counselling, although guidelines recommend offering aids to assist cessation. Nicotine replacement therapy, bupropion and varenicline have been shown to improve the chances of successful quitting, although patients with a recent history of cardiac disease were excluded in these studies.[12,30] Therefore, the results of pharmacological studies may not be applied to immediate quitters after an acute event. Regarding relapse prevention, the only medical therapy for which there is compelling evidence is varenicline.[15] More research is needed on the effectiveness of pharmacological aids in immediate quitters after an acute life-threatening event.

Furthermore, since nurses obtained information on smoking quitting dates retrospectively, recall bias may play a role. Successful quitters may remember quitting dates better than smokers who attempted to quit but relapsed. In addition, we may have underestimated the problem of unsuccessful quit attempts, as self-report information is less reliable than measurements of nicotine concentration.[31]

Lastly, we observed that successful quitters have an unfavourable risk factor profile after one year. Consistent with previous reports, quitters were more often overweight.[32,33] We also observed that quitters did not improve on systolic blood pressure targets at one year of follow-up compared with their baseline values, despite the fact that they reported being physically more active. It is well known that quitting smoking decreases

the metabolic rate, which results in a mean increase of 4-5 kg in body weight after 12 months.[14,32,33] Moreover, some patients exchange one addiction for another, and gain weight after quitting smoking.[34] In fact, the addiction may not be interrupted, but simply replaced by another.[34] Future research is needed to investigate the mechanisms involved and to improve weight loss interventions for this subgroup.

We conclude that the majority of successful quitters stop immediately after their ACS. Patients in this group showed that it was within their own ability to quit, and they did not relapse in one year of follow-up. We found no evidence to support the use of relapse prevention in ACS patients who stop smoking immediately after the event, and our study indicates that there is no need for this during follow-up visits in a large group of patients. The momentum for smoking cessation is particularly strong immediately after ACS and our study reinforces the importance of clinicians' explicit advice to stop smoking during hospitalisation of ACS patients. New strategies are needed in patients with a late attempt. Smoking cessation strategies in secondary prevention could differentiate between acute and non-acute patients, since an acute event acts as an important motivator for behavioural change. Furthermore, smoking cessation support should differentiate between immediate and late attempts, since relapse prevention seems unnecessary for immediate quitters. However, patients with a late attempt may benefit from more intensive therapy. Future research is needed to assess the cost-effectiveness of differentiating between acute or non-acute admissions and immediate or late quit attempts.

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Conflicts of interests
None.

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'I tried to stop smoking, but I just couldn't. But, there can't be that many people that stop after a heart attack, can there?
(Mr A. de Jong, 52 years, bypass operation)

Chapter 8

Smoking cessation in European patients with coronary heart disease. Results from the EUROASPIRE IV survey: a registry from the European Society of Cardiology.

Snaterse M, Deckers JW, Lenzen M, Jorstad HT, De Bacquer D, Peters RJG, Jennings C, Kotseva K, Scholte op Reimer WJM. for the EUROASPIRE investigators.

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Abstract

Objective

We investigated smoking cessation rates in coronary heart disease (CHD) patients throughout Europe; current and as compared to earlier EUROASPIRE surveys, and we studied characteristics of successful quitters.

Methods

Analyses were done on 7998 patients from the EUROASPIRE-IV survey admitted for myocardial infarction, unstable angina and coronary revascularisation. Self-reported smoking status was validated by measuring carbon monoxide in exhaled air.

Results

Thirty-one percent of the patients reported being a smoker in the month preceding hospital admission for the recruiting event, varying from 15% in centres from Finland to 57% from centres in Cyprus. Smoking rates at the interview were also highly variable, ranging from 7% to 28%. The proportion of successful quitters was relatively low in centres with a low number of pre- event smokers. Overall, successful smoking cessation was associated with increasing age (OR 1.50; 95% CI 1.09-2.06) and higher levels of education (OR 1.38; 95% CI 1.08-1.75). Successful quitters more frequently reported that they had been advised (56% vs. 47%, $p<0.001$) and to attend (81% vs. 75%, $p<0.01$) a cardiac rehabilitation programme.

Conclusion

Our study shows wide variation in cessation rates in a large contemporary European survey of CHD patients. Therefore, smoking cessation rates in patients with a CHD event should be interpreted in the light of pre-event smoking prevalence, and caution is needed when comparing cessation rates across Europe. Furthermore, we found that successful quitters reported more actions to make healthy lifestyle changes, including participating in a cardiac rehabilitation programme, as compared with persistent smokers.

Background

Smoking is the most important modifiable risk factor for coronary heart disease (CHD) and a leading cause of death.[1] In patients with CHD, smoking cessation reduces the risk of recurrent events by 50%.[2] However, only half of smokers with CHD in Europe were able to successfully quit smoking.[3,4]
The European guidelines on cardiovascular prevention in clinical practice recommend a comprehensive approach to risk factor management in secondary prevention of CHD.[5] Optimal secondary prevention includes lifestyle modification, treatment to target for biometric risk factors, such as blood pressure and low-density lipoprotein cholesterol (LDL) and no exposure to tobacco in any form.[5] To evaluate the implementation of these guidelines in clinical practice, the EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) repeated cross-sectional, surveys have been conducted, EUROASPIRE IV performed in 2012-1013. In the current analysis, we focussed on smoking cessation rates throughout Europe; drawing on data from EUROASPIRE IV and the earlier surveys. Furthermore, we aimed to investigate the characteristics of successful quitters, the use of cardiac rehabilitation programmes, and the level of general risk factor management in persistent smokers versus in those who successfully quit smoking.

Methods

Design and study population
The four EUROASPIRE surveys are cross-sectional studies which took place between 1999-2013 and have been described in detail elsewhere.[3] Briefly, the EUROASPIRE IV survey (2012-2013) was carried out in selected geographical areas in 24 European countries (78 hospitals). Consecutive patients (≥18 years and ≤80 years of age at the time of their recruiting event or procedure) were retrospectively identified with one of the following diagnoses: elective or emergency coronary artery bypass graft (CABG), elective or emergency percutaneous coronary intervention (PCI), acute myocardial infarction, and acute myocardial ischaemia. The local research ethics committee of all recruiting hospitals gave permission for the study. The medical records of 16,426 CHD patients were reviewed and 7998 (48.7%) of them accepted the invitation for the interview and were examined in the period of 6 months to 3 years following hospital discharge for the recruiting event. On average, EUROASPIRE IV patients were interviewed after 1.4 (0.95-1.95) years. Thirty-five patients reported not to smoke in the month prior to the recruiting event, but presented an expired carbon monoxide concentration >10 p.p.m. at the time of interview. These smokers were not included in our pre-event smokers analyses. Appendix Figure 1 shows the study flowchart.

Assessment of smoking behaviour

Information on smoking behaviour was collected using an interview questionnaire. Patients were asked if they had ever smoked, if they were smoking in the month prior to hospital admission for the recruiting event, or if they were current smokers. Smoking status was verified by the concentration of breath carbon monoxide using a smoker analyser (Bedfont Scientific, Model Micro+). Interview questions contained items concerning lifestyle risk factor targets and awareness and steps taken since the recruiting event or procedure. EUROASPIRE II-IV data were used for the evaluation of smoking cessation over time. Therapeutic targets for secondary prevention were defined according to the ESC guidelines on secondary prevention (2007 and 2012).[6,7]

We defined successful quitters as pre-event smokers who reported a non-smoking status at the time of interview and an expired carbon monoxide concentration ≤10 p.p.m. We defined persistent smokers as pre- event smokers who at the time of interview reported that they were currently smoking *or* had an expired carbon monoxide concentration >10 p.p.m. Relapsers were defined as patients who had a quit attempt in the last year for at least 24 hours but were smoking at the time of interview.

Statistical methods

Data on smoking behaviour prior to the recruiting event and at the time of the interview are presented as absolute numbers and percentages and stratified by country. We calculated cessation rates of the number of pre- event smokers versus successful quitters, overall and per country. Countries were stratified as above (high) or below (low) mean European pre- event smoking rate (>30%) and above (high) or below (low) mean European cessation rate (>50%). Hospital readmissions were reported between recruiting event and date of interview. Further data are presented as number (percentage) or mean (± standard deviation), or median (interquartile range (IQR), 25^{th}-75^{th}) as appropriate. Dichotomous variables were analysed using $\chi 2$ or Fisher's exact tests, continuous normally distributed variables using independent samples t-tests. We analysed a broad range of clinical and demographic characteristics to evaluate the relation with smoking cessation based on the model used in the analysis of Scholte op Reimer et al.[8] (EUROASPIRE II), using multivariable logistic regression analyses adjusted for age, gender, and country of enrolment where appropriate. Adjusted odds ratios and corresponding 95% confidence intervals (95% CI) are reported. Most data items that entered the regression models were determined at the interview, simultaneously with the patient's smoking behaviour. Statistical significance was concluded when p-values were not reaching the α=0.05 probability level. Statistical analyses were performed using SPSS version 23.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

Results

Information on smoking status was available in all interviewed patients (n=7998). A total of 2458 (31%) patients were smoking in the month prior to the recruiting event or procedure. Of n=2458 pre-event smokers, 1263 (51%) were successful quitters at the time of the interview (median 1.2 years [range 0.5 to 3 years]) (Appendix Figure 1). Of 1195 (49%) persistent smokers, 593 reported at least one quit attempt in the last year (relapsers).

Table 1.
Smoking prevalence in EUROASPIRE IV according to country of enrolment in 7998 patients at the time of interview

Country	Number of interviewed patients	Number of patients who ever smoked (%)	Number of pre-event smokers (%)	Number of current smokers (%)	Quit rate
Belgium	343	238 (69%)	67 (20%)	26 (8%)	0.61
Bosnia Herzegovina	316	190 (60%)	133 (42%)	45 (14%)	0.66
Bulgaria	120	84 (70%)	35 (29%)	21 (18%)	0.40
Croatia	467	306 (66%)	140 (30%)	77 (16%)	0.45
Cyprus	90	73 (81%)	51 (57%)	24 (27%)	0.53
Czech Republic	490	342 (70%)	162 (33%)	84 (17%)	0.48
Finland	464	242 (49%)	58 (15%)	31 (7%)	0.47
France	377	288 (76%)	133 (35%)	94 (25%)	0.29
Germany	536	354 (66%)	100 (19%)	52 (10%)	0.47
Greece	51	36 (71%)	19 (37%)	10 (20%)	0.47
Ireland	201	158 (79%)	66 (33%)	33 (16%)	0.50
Latvia	294	143 (49%)	75 (26%)	36 (12%)	0.52
Lithuania	499	290 (58%)	164 (33%)	86 (17%)	0.48
Netherlands	498	378 (76%)	146 (29%)	73 (15%)	0.50
Poland	377	273 (72%)	137 (36%)	71 (19%)	0.48
Romania	522	340 (65%)	195 (37%)	58 (11%)	0.70
Russian Federation	424	266 (58%)	138 (33%)	89 (21%)	0.36
Serbia	391	296 (76%)	181 (46%)	68 (17%)	0.62
Slovenia	245	158 (64%)	54 (22%)	24 (10%)	0.55
Spain	173	139 (80%)	71 (41%)	19 (11%)	0.73
Sweden	359	265 (74%)	98 (28%)	49 (14%)	0.50
Turkey	239	170 (71%)	100 (42%)	53 (22%)	0.47
Ukraine	274	149 (54%)	76 (28%)	36 (13%)	0.53
United Kingdom	248	146 (59%)	59 (24%)	36 (15%)	0.39
All patients	7998	5324 (67%)	2458 (31%)	1195 (16%)	0.51

Smoking rates differed markedly among the participating countries (Table 1). The pre-event smoking rates varied from 15% (Finland) to 57% (Cyprus). Smoking rates at the interview were also highly variable, ranging from 7% (Finland and Belgium) to 28% (Cyprus).

When stratifying individual countries as above (high) or below (low) mean European pre- event smoking rates and above (high) or below (low) mean European cessation rates, we observed considerable variation between countries. We observed four country groups: 1) high pre-event smoking prevalence, low quit rate (mean 0.45); 2) high pre-event smoking prevalence, high quit rate (mean 0.68); 3) low pre-event smoking prevalence, low quit rate (mean 0.45); 4) low pre-event smoking prevalence, high quit rate (mean 0.55). The two groups of countries with high pre-event smoking prevalences differed in mean quit rates (high-low 0.45 vs. high-high 0.68, p<0.001). The two groups of countries with low pre-event smoking prevalences similarly differed in quit rates (low-low 0.45 vs. low-high 0.55, p<0.01). (Appendix Figure 2).

Across the nine countries that participated in all EUROASPIRE II-IV survey cohorts, the smoking cessation percentage remained unchanged (48% vs. 45% vs. 47%, p=0.67) (Appendix Figure 3).

Determinants of successful smoking cessation are presented in Table 2. Overall, successful smoking cessation was associated with higher age, higher levels of education (OR 1.38; 95% CI 1.08-1.75), and BMI ≥ 30 kg/m2 (OR 1.45; 95% CI 1.22-1.72). Smokers were less likely to quit if they had a history of CHD (OR 0.68; 95% CI 0.58-0.79) or if they suffered from symptoms of anxiety (HADS anxiety scale >8) or depression (HADS depression scale >8).

Table 2.
Relation between selected characteristics and smoking cessation in the 2458 pre-event smokers who attended the interview.

Characteristics	Number of pre-event smokers n=2458	Number of successful quitters (%)	Odds ratio (95% CI)	P-value
Age (at index event)				
<50 years	520	238 (46)	1	
50-59 years	963	497 (52)	1.26 (1.02-1.56)	0.04
60-69 years	760	408 (54)	1.37 (1.10-1.72)	< 0.01
≥70 years	215	120 (56)	1.50 (1.09-2.06)	0.01
Gender				
Men	2020	1024 (51)	1	
Women	438	239 (55)	0.86 (0.70-1.05)	0.14

Educational level				
University, college, or equivalent	493	259 (53)	1.33 (1.01-1.73)	0.04
Intermediate school	954	510 (53)	1.38 (1.08-1.75)	<0.01
Secondary school	616	315 (51)	1.25 (0.97-1.62)	0.07
Primary school or less	378	172 (46)	1	
History of CHD				
No	1331	743 (56)	1	
Yes	1108	510 (46)	0.68 (0.58-0.79)	<0.001
History of hypertension				
No	765	367 (48)	1	
Yes	1469	772 (53)	1.14 (0.95-1.37)	0.15
History of hyperlipidaemia				
No	821	393 (48)	1	
Yes	1211	630 (52)	1.18 (0.99-1.41)	0.09
History of diabetes mellitus				
No	1760	906 (51)	1	
Yes	451	226 (50)	0.95 (0.77-1.16)	0.36
Obesity				
No	1313	622 (47)	1	
Yes	922	522 (57)	1.45 (1.22-1.72)	<0.001
HADS anxiety				
<8	1671	902 (54)	1	
8-10	343	187 (55)	0.72 (0.57-0.91)	<0.01
≥11	299	75 (25)	0.78 (0.61-1.00)	0.05
HADS depression				
<8	1740	940 (54)	1	
8-10	381	187 (49)	0.82 (0.66-1.02)	0.07
≥11	193	75 (39)	0.54 (0.40-0.73)	<0.001
ETS Home				
No	1959	1038 (53)	1	
Yes	652	206 (32)	0.32 (0.27-0.39)	<0.001
ETS Work				
No	1959	1070 (55)	1	
Yes	413	160 (39)	0.53 (0.42-0.65)	<0.001

Results of multivariable regression analyses with adjustment for age, gender, index event and country where appropriate. CHD coronary heart disease; CI confidence interval; ETS environmental tobacco smoke; HADS (at interview) Hospital Anxiety and Depression Scale; Intermediate school: intermediate between secondary level and university. Obesity (at interview): BMI ≥30 kg/m^2.

Exposure to environmental tobacco smoke (ETS) was associated with markedly lower rates of successful smoking cessation, both with ETS at home (OR 0.32; 95% CI 0.27-0.39) and at work (OR 0.53; 95% CI 0.42-0.65).
Across all domains, successful quitters reported more actions to make healthy lifestyle changes as compared with persistent smokers (p<0.001 in all comparisons), such as reducing calorie intake, increasing vegetable consumption, physical activity and participating in a cardiac rehabilitation programme (Figure 1). Furthermore, successful quitters more frequently reported that they had been advised (56% vs. 47%, p<0.001) and to attend (81% vs. 75%, p<0.01) a cardiac rehabilitation programme. Attendance at a smoking cessation programme was less prevalent in successful quitters as compared with persistent smokers (44% to 50%, p=0.04). Moreover, successful quitters less often reported the use of NRT, bupropion or varenicline (8% vs. 16%, p<0.001) (Appendix Table 1).

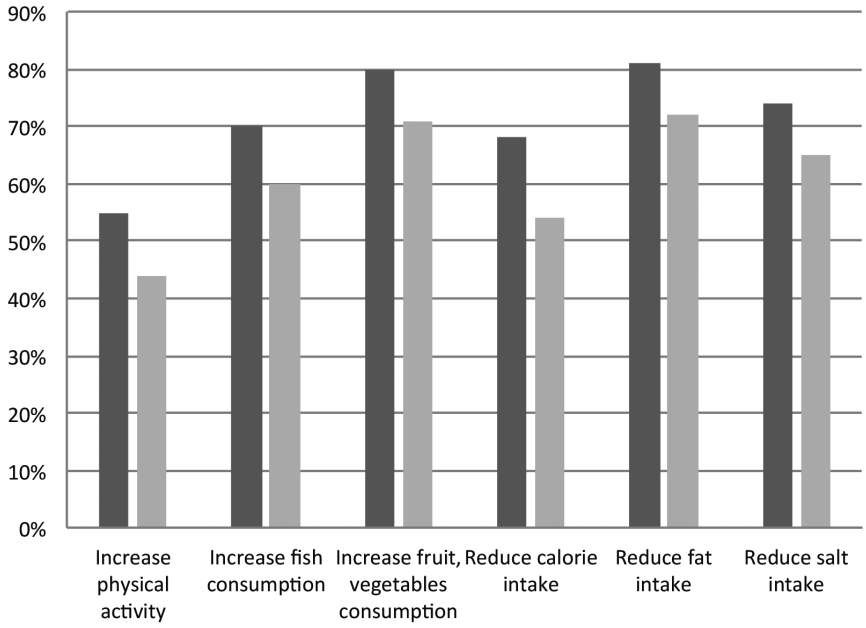

Figure 1.
Actions taken to make healthy lifestyle changes in successful quitters (dark grey) versus persistent smokers (light grey).

Both successful quitters and persistent smokers showed weight gain following hospital discharge, successful quitters in a larger proportion than persistent smokers (62% versus 55%, p<0.01). While the difference in mean weight gain was statistically different between the groups (successful quitters +2.8 kg (± 8.0) versus persistent smokers +1.3 kg (± 6.6) p<0.001), mean weight (BMI) was only slightly different (Table 3). There were no differences between successful quitters and smokers in the distribution of remaining risk factors on target (0-4) (Appendix Table 2). Out of a maximum number of 4, the mean number of risk factors on target was 2.5 (± 0.9) in the total study population, 2.4 (± 0.9) in successful quitters and 2.5 (± 0.9) in persistent smokers (p= 0.9). Compared with persistent smokers, successful quitters more frequently reached the ESC targets for physical activity (21% versus 17%, p<0.01), and LDL-C (55% vs. 47%, p<0.001), while successful quitters more frequently had a BMI≥25 kg/m^2 (89% vs. 81%, p<0.001). There were no significant differences in hospital readmission rates (recruiting event to time of interview) between successful quitters and persistent smokers (31% vs. 29%, p=0.46).

Discussion

Our study demonstrates substantial geographical variation in contemporary smoking cessation behaviour in patients with coronary artery disease in the large, cross-sectional EUROASPIRE IV survey. While the overall smoking cessation rate in the EUROASPIRE IV study was comparable to the cessation rates from earlier surveys (II-III), we observed large differences between participating countries. The proportion of patients who were successful quitters increased with increasing age and higher level of education, and smoking cessation was associated with weight gain.

Table 3.
Weight changes in successful quitters and persistent smokers between hospital admission and follow-up.

Weight variables	Successful quitters (n=1263)	Persistent smokers (n=1195)	P-value
BMI (mean, SD)	29.3 ± 4.5	28.3 ±4.8	<0.001
Weight change* (kg, mean, SD)	2.8 ± 8.0	1.3 ±6.6	<0.001
Weight gain ≥5%* (proportion, %)	337/831 (41)	224/807 (28)	<0.001
BMI ≥25kg/m2	1064/1192 (89)	888/1099 (81)	<0.001

*Missing variables in medical records, baseline weight only available in 831 successful quitters and 807 persistent smokers.

When stratifying individual countries as above (high) or below (low) mean European pre- event smoking prevalence and above (high) or below (low) mean European cessation rates, we observed considerable variation between countries (Appendix Figure 2). It should however be kept in mind that the EUROASPIRE surveys are based on national samples and not on comprehensive national rates of smoking in patients with CHD. Our study shows variability in both pre-event smoking prevalence as well as cessation rates. Therefore, national smoking cessation rates in patients with a CHD event should be interpreted in the light of pre-event smoking prevalences, and caution is advised when comparing cessation rates across different European countries. Potentially, high-low countries (i.e. high pre-event smoking prevalence, low cessation rate) can benefit from both population-based strategies to decrease the overall prevalence of smoking, and smoking cessation interventions after a CHD event. Countries where tobacco control has been effective in reducing prevalence and reducing it even more is a big challenge. The remaining smokers are more likely to be 'hard core smokers', although the literature is inconsistent in this respect.[9,10]

It is a cause for concern that the smoking cessation rates in our patient population have remained virtually unchanged over the past 14 years (since the EUROASPIRE II survey of 1999-2000). However, this should be viewed in the context that the proportion of pre-event smokers in the EUROASPIRE II-IV surveys has shown a slight decrease (II 37%, III, 32%, IV 33%). In spite of an increase in available smoking cessation strategies, national and international educational campaigns, laws that restrict smoking in public spaces in an increasing number of European countries, and a decline in average smoking prevalence in many European countries,[11] the post-event cessation rates in patients with CHD remain approximately 50%. Comparisons between the EUROASPIRE II-IV surveys were already made.[12] The distribution of sex and age have been shown to be similar, but lifestyle habits have been shown to deteriorate over time, with increases in obesity and diabetes, and stagnating rates of persistent smoking. While it is encouraging that 50% of smokers with CHD are successful in quitting their habit, the fact that no progress has been made in increasing this percentage is of concern. Consistent with previous reports, increasing age, a higher level of education, and obesity (at time of interview) were shown to be associated with successful smoking cessation in our population.[8,13-15] These patient characteristics have previously been shown to be associated with a greater intention to quit.[14-16] Smokers were less likely to quit if they had a history of CHD, suffered from symptoms of anxiety or depression, were exposed to environmental tobacco smoke (ETS), both ETS at home and at work. The associations of our current study are comparable to those found in the EUROASPIRE II and III survey.[8,16] Previous studies in coronary heart disease patients showed that having no previous coronary heart disease, low level of nicotine addiction and self-confidence in smoking cessation were positive predictors of abstinence.[17,18]

Compared to persistent smokers, successful quitters more frequently reported undertaking other favourable healthy lifestyle changes such as reducing calorie intake, increasing vegetable consumption, physical activity and participating in a cardiac rehabilitation programme. This suggests that a comprehensive lifestyle modification approach is achievable, if tailored to patient preferences and abilities. Successful quitters after a cardiac event may be more compliant with preventive behaviours than persistent smokers, possibly related to greater self-discipline. Potentially, future prevention programs should be tailored to better utilize this motivation for behavioural change in spontaneous, successful quitters.

Smoking cessation was associated with some weight gain at the follow-up interview. Additionally, overweight was the most prevalent risk factor in successful quitters. Weight gain after smoking cessation is a well-documented phenomenon, and in a recent review and meta-analysis, mean weight gain was estimated at 4.7 kg at 12 months after cessation in smokers treated for tobacco dependence.[19] Weight and appetite is regulated by a complex mechanism after smoking cessation. Previous studies have examined the role of changes in plasma leptin and ghrelin levels after cessation, which may lead to weight gain.[20-22] However, the results of these studies did not consistently support this hypothesis. Nicotine has furthermore been shown to change appetite and body composition.[23] Therefore, we recommend supporting successful quitters to control overweight as a main risk factor after sustained cessation. Referral of patients to an intensive weight reduction programme should be considered as an additional strategy.[24]

In the current study, we observed that successful quitters less frequently took part in a smoking cessation programme as compared with persistent smokers, although successful quitters more often attended a cardiac rehabilitation programme. In line with this, previous research has shown that the majority of successful quitters stopped immediately after the event, and that it was within their own ability to quit.[13] Our study indicates that in a large group of patients who quit immediately after a life-threatening event, no smoking cessation programme was needed.

Strengths and limitations

There are several strengths to our study. First, our study population consisted of a large number of CHD patients from 24 European countries, in a contemporary clinical setting. Second, due to the repeated surveys and standardised data collection, we were able to compare cessation rates for successful quitting across several decades. Third, all data were based on interviews and objectively measured outcomes, such as expired carbon monoxide for smoking. Therefore, our analysis was based on high quality comparative information on secondary prevention in clinical practice.

Some aspects of our study warrant consideration. First, selected hospitals in particular European countries participated in the EUROASPIRE IV survey, and the observed results may not be representative for individual countries or for Europe as a whole.

Second, we did not correct for possible confounders in the comparisons between countries in our smoking cessation analysis. The development of a model, including all potential confounders of the relation between smoking cessation, such as the availability of cardiac rehabilitation and level of addiction, could further expand the analysis of the association between smoking cessation and country of origin. Multilevel analysis with a 3-level structure (patients-centres-country) would have been preferable to investigate the difference between countries/centres and smoking cessation. However, due to the relatively low number of pre-event smokers per country/centre, we were unable to perform a robust multilevel analysis. Third, the low overall participation rate (48.7%) introduces a potential bias as non-participants could be more likely to have unhealthy lifestyles and poorer risk factor control.[3] Our data could therefore underestimate the true status of secondary prevention through Europe. However, possible selection bias does not invalidate our main conclusion: we observed large differences in smoking cessation behaviour between participating countries. Finally, while we were able to calculate weight in nearly all participants of EUROASPIRE IV, baseline weight of pre-event smokers at discharge was available in only 67% of patients. As overweight and obesity are both associated with an increased risk of risk of CVD death and all-cause mortality[25], we recommend communicating information of all important risk factors, including obesity, in the discharge letter.

Conclusions

Our study shows that smoking cessation rates in CHD patients throughout Europe have remained unchanged at around 50% since 1999 despite the availability of effective medications to support cessation. However, there is great variation between individual countries. Smoking cessation rates should therefore be interpreted in the light of pre-event smoking prevalences, and caution is advised when comparing individual European countries. Our findings may assist in developing strategies to assist smoking cessation, particularly in countries with a high prevalence and low cessation rate. In the large group of persistent smokers, novel strategies for optimal secondary prevention are needed.
Furthermore, we found that successful quitters reported more actions to make healthy lifestyle changes, including participating in a cardiac rehabilitation programme, as compared with persistent smokers.

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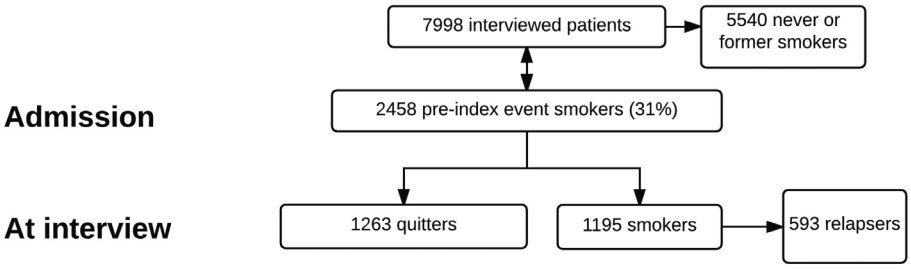
Conflict of interest

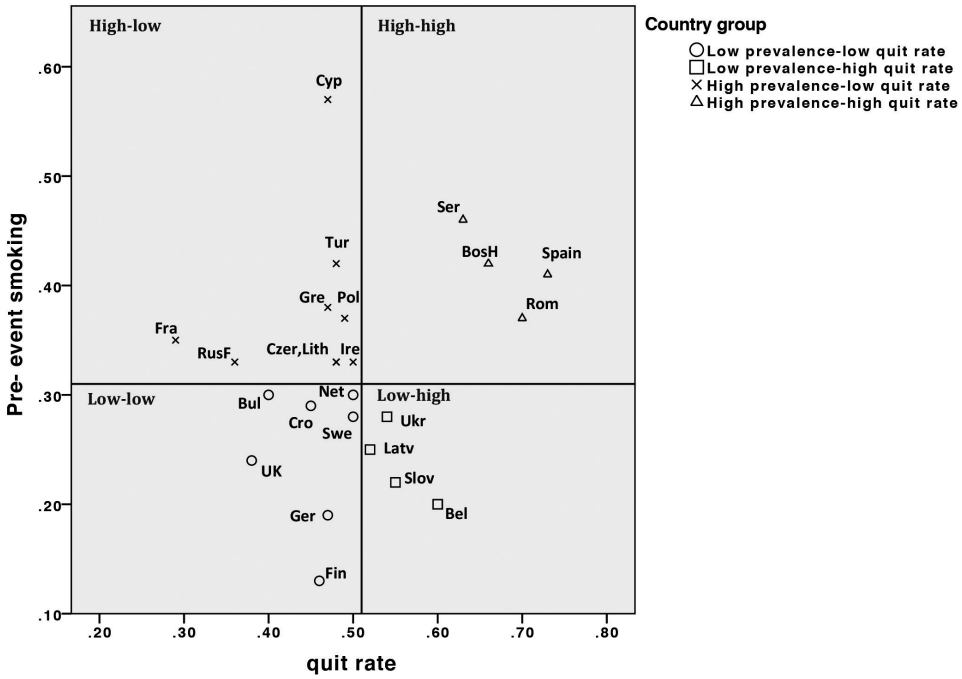
no conflict of interest exists with respect to this manuscript.

Supplementary files

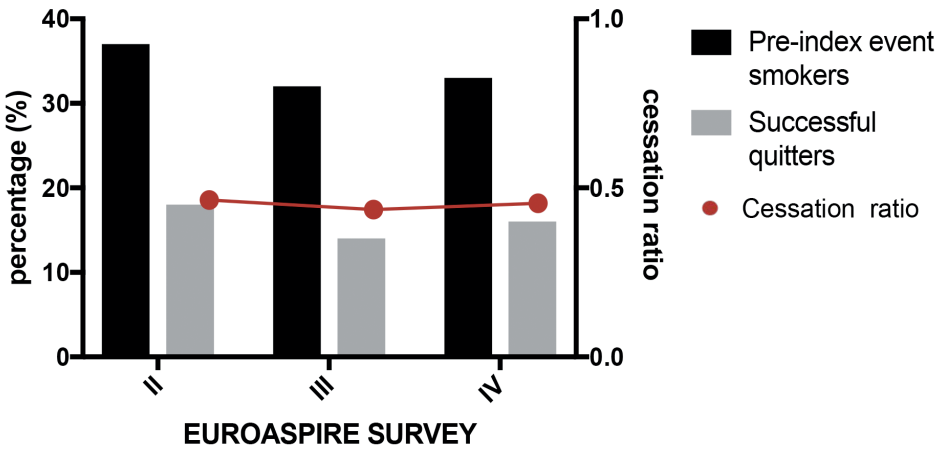


Flowchart of 2458 pre-index event smokers from hospital admission up to time of interview.
Relapsers: patients who had a quit attempt in the last year for at least 24 hours, but were smoking at the time of interview.

Appendix Figure 1.
Flowchart of 2458 pre- event smokers from hospital admission up to time of interview.



Appendix Figure 2.
Pre- event smoking prevalence and quit rate in European countries stratified by group.



Appendix Figure 3.
Pre-event smokers and successful quitters across the EUROASPIRE II-IV surveys.

Appendix Table 1
CVD prevention and cardiac rehabilitation in successful quitters and persistent smokers.

Cardiac rehabilitation programme	Successful quitters n (%)	Persistent smokers, n (%)	P-value
Advice to follow CR	698/1251 (56)	559/1179 (47)	<0.001
Attended CR	563/698 (81)	417/559 (75)	0.01
Use of NRT/Bupropion/Varenicline	103/1257 (8)	189/1195 (16)	<0.001
Received part of the CR programme			
Teaching sessions	388/611 (64)	260/455 (57)	0.37
Smoking cessation programme	268/611 (44)	228/452 (50)	0.04
Weight management/ Diet modification	434/611 (71)	321/451 (71)	0.89
Exercise programme	510/613 (83)	382/455 (84)	0.78
Stress modification & relaxation	341/610 (56)	277/453 (61)	0.09

Appendix Table 2.
Cumulative number of risk factors on target in successful quitters versus persistent smokers at the time of interview.

Lifestyle risk factors[1]	Successful quitters n (%)	Persistent smokers n (%)	P-value
BMI <25kg/m2	128/1192 (11)	211/1099 (19)	<0.001
Physical activity	270/1263 (21)	203/1195 (17)	<0.01
BP <140/90 mmHg	490/1165 (42)	495/1105 (45)	0.15
LDL-C <2.5 mmol/L	605/1099 (55)	500/1070 (47)	<0.001
LDL-C <1.8 mmol/L	209/1099 (19)	139/1070 (13)	<0.001
0 risk factors on target	109/958 (11)	110/914 (12)	0.66
1 risk factor on target	334/958 (35)	334/914 (36)	0.45
2 risk factors on target	378/958 (39)	348/914 (38)	0.54
3 risk factors on target	125/958 (13)	110/914 (12)	0.51
4 risk factors on target	12/958 (1)	12/914 (1)	0.91

[1]With the exclusion of smoking; Physical activity >5 times/ week 30 min.

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It is possible. I quit smoking myself and I want to be able to walk as long as I can. So that means I have to eat healthy and my other behaviours, you know... I am supported by the programmes. I always feel better when I come back from walking, exercising, I feel I've got more energy.'
(Mrs R. Bakker, 72 years, myocardial infarction)

Chapter 9

Nurse-coordinated referral to a community-based smoking cessation programme in patients with coronary artery disease: results from the RESPONSE-2 study.

Snaterse M, Jorstad HT, Minneboo M, Lachman S, Boekholdt SM,
ter Riet G, Scholte op Reimer WJM, Peters RJG.

Submitted

Abstract

Objective:
To investigate characteristics of successful quitters, their use of a smoking cessation programme, use of other lifestyle interventions to improve lifestyle related risk factors, within a nurse-coordinated care programme.

Methods
We used data from the multicentre randomised controlled RESPONSE-2 trial (n=824, the Netherlands). The trial was designed to assess the efficacy of nurse-coordinated referral to a comprehensive set of up to three community-based interventions, based on smoking cessation, healthy food choices, and physical activity to improve lifestyle related risk factors in CAD patients, compared to usual care. Smoking status was assessed using a urinary cotinine test at baseline and 12 months follow-up.

Results
At 12 months follow-up, cessation rates were comparable in both groups (50% intervention group vs. 46% usual care group, p=0.45). The majority of successful quitters in both groups quit immediately after hospitalisation (72% intervention group vs. 86% usual care group, p=0.29). Only 19% percent of successful quitters in the intervention group participated in the smoking cessation programme. However, successful quitters participated more frequently in other lifestyle programmes compared with persistent smokers (65% vs. 37%, p<0.01).

Conclusion
The majority of patients who successfully quit smoking are those who quit immediately after hospitalisation, without a need to participate in a smoking cessation programme. Moreover, this programme was attended by only a minority of successful quitters. Successful quitters were motivated to attend other lifestyle programmes addressing healthy food choices and physical activity. Our findings support a tailored, comprehensive approach to lifestyle interventions in secondary prevention of coronary artery disease.

Introduction

Improvement of lifestyle-related risk factors reduces cardiovascular morbidity and mortality in patients with coronary artery disease (CAD).[1,2] Accordingly, national and international guidelines on secondary prevention of cardiovascular disease emphasise the importance of healthy lifestyle changes in order to reduce the risk of recurrent events.[3,4] Of all traditional risk factors, smoking cessation has been shown to have the greatest impact on risk, with an average relative risk reduction of 33% in coronary heart disease patients.[2,5] However, modification of lifestyle-related risk factors, including smoking cessation, is difficult to achieve. The EUROASPIRE surveys have consistently shown that lifestyle modification is suboptimal after a coronary event or revascularisation, with especially high prevalences of persistent smoking and obesity.[6,7] There remains a need for further development of lifestyle modification strategies, in particular smoking cessation, in secondary prevention.

Previous studies have shown promising results of team-based, nurse-coordinated prevention programmes, focussing on risk factor management in a multidisciplinary setting.[8,9,10] However, such approaches are more successful in drug-based risk factor optimisation (i.e. blood pressure, cholesterol), as compared with lifestyle modification (i.e. weight reduction, physical activity and smoking cessation).[9,11] To address this issue, we designed the Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists-2 (RESPONSE-2) trial to investigate the effect of nurse-coordinated referral of patients and their partners to a comprehensive set of community-based lifestyle programmes in secondary prevention.[12,13] In short, the community-based intervention programmes focussed on a nurse-coordinated referral to weight reduction, improvement of physical activity, and/or smoking cessation programmes, based on patients' preferences. The RESPONSE-2 trial main analysis demonstrated that referral to the community-based lifestyle programmes was more effective in improving lifestyle related risk factors than usual care alone.[12,13] A pre-defined secondary outcome of the RESPONSE-2 trial was the analysis of smoking cessation and patient characteristics. In the current analysis, we investigate characteristics of successful quitters and their use of the smoking cessation programme and the other lifestyle interventions to improve lifestyle related risk factors.

Methods

Study design

We used data from the RESPONSE-2 trial (n=824), a multicentre randomised controlled trial conducted in 15 hospitals in the Netherlands.[12] The trial was designed to assess the efficacy of a nurse-coordinated referral to a comprehensive set of up to three community-

based interventions to improve lifestyle related risk factors in CAD patients.
All patients received usual care, according to (inter)national guidelines, including visits to a cardiologist, cardiac rehabilitation[3,4] and up to four visits to a nurse-coordinated secondary prevention programme, addressing healthy lifestyles, drug-related risk factors and medication adherence. The RESPONSE-2 trial is described in detail elsewhere[12,13] and is briefly summarised below. The current analysis focusses on the subgroup of patients who smoked before the index hospitalisation to identify characteristics of successful quitters and their use of interventions to improve their lifestyle related risk factors. This analysis was pre-specified as a secondary outcome in the original study protocol.[13] The local research ethics committees of all recruiting hospitals approved the study, and written informed consent was obtained from all patients.

Patient population

In the RESPONSE-2 trial, patients aged 18 years or older were eligible <8 weeks after hospitalization for acute coronary syndrome, and/or coronary revascularization, if they had at least one of the following lifestyle risk factors: (1) body mass index [BMI] ≥27 kg/m^2, (2) self-reported physical inactivity (<30 minutes of physical activity of moderate intensity five times per week), (3) self-reported current smoking or stopped ≤6 months before hospital admission, and motivated to attend at least one lifestyle programme.
Exclusion criteria were: planned revascularization after discharge, life expectancy ≤2 years, congestive heart failure New York Heart Association class III or IV, visits to outpatient clinic and/or lifestyle programme not feasible, no internet access, and anxiety or depressive symptoms (Hospital Anxiety and Depression Scale (HADS) >14), since this was expected to hinder lifestyle changes. For this analysis, we included all patients who reported to be current smokers or smoking ≤6 months before hospital admission.

Nurse-coordinated care

Patients in the intervention group were referred by the nurse to up to three lifestyle programmes. The number and sequence of the lifestyle programmes was determined by the patient's risk profile and preference. Patients were seen by registered nurses (n=24, first level nurse or higher degree n=20), with experience in cardiovascular care.
Nurses were trained in a systematic referral approach, consisting of risk status assessment, discussing the current risk status with patients, and assessing the level of motivation to change or sustain the current cardiovascular risk status. Depending on the level of motivation, participation in relevant lifestyle programme(s) was advised, followed by an official referral to the lifestyle programme after patient consent. During and after completion of lifestyle programme(s), patients and nurses re-evaluated further opportunities for lifestyle improvement or maintaining lifestyle changes (up to four visits). Nurses were trained in Motivational Interviewing (MI) by an accredited professional in four sessions. Selected patient visits were audiotaped and evaluated by

MI trainers, who provided personalised feedback to nurses to improve their MI skills. The three lifestyle programmes (Weight Watchers®, Philips DirectLife® and Luchtsignaal® smoking cessation) were used in their existing format. If multiple lifestyle factors needed to be addressed, the sequence and choice of the intervention(s) was discussed with the patient and decided by patient's preference.

Lifestyle programmes

Smoking cessation programme

Luchtsignaal® is an existing national smoking cessation programme in the Netherlands, offering up to seven telephone counselling sessions by professionals during a period of three months. The programme is based on the stages of change from the transtheoretical model and used strategies from motivational interviewing, action and coping planning, self-control training, and relapse prevention. Depending on patients' preferences, pharmacological therapy for smoking cessation could be prescribed.[14]

Weight reduction programme

Weight Watchers® is aimed at reducing weight by emphasizing a healthy diet, change in behaviour, physical activity and group motivation and offers weekly group meetings for a weigh-in and group discussion, coordinated by a coach. Furthermore, the diet intake is based on a points system that addresses the total caloric energy in each product.

Physical activity programme

Philips DirectLife® is an internet-based coaching activity health programme that includes an accelerometer, comparable to a small USB device. The programme monitors daily physical activities, provides feedback via the accelerometer and offers personalized, internet-based coaching.

Data collection and measurements

Data were collected at baseline (first visit <8 weeks after hospital discharge for the index event) and at 12 months, including cardiovascular risk factors, cardiovascular history, physical activity, smoking status, partner smoking status, and medication use. At each visit, the nurse documented patients' motivation and preferences for referral to a lifestyle programme, and participation in the cardiac rehabilitation programme. Physical activity was measured by the six-minute walking distance (6MWD) as per protocol.[13]

Smoking status was assessed by self-report and urinary cotinine test at baseline and at 12 months follow-up (UltiMed one step, Dutch Diagnostic, Zutphen, the Netherlands; detection limit 200 ng/ml). *Pre-event smoking* was defined as self-reported smoking ≤6 months before hospital admission (box 1). At baseline, we described *immediate quitters*: patients who quit smoking during or shortly before hospitalisation with a urine cotinine level <200ng/ml at baseline (i.e. after discharge), and *current smokers*, defined as pre-

event smoking with a baseline urine cotinine level >200ng/ml. At 12 months, we described *successful quitters*: patients who were classified as a pre-event smoker and had a urinary cotinine level <200ng/ml at 12 months follow-up, and *persistent smokers* defined as pre-event smoking and a urine cotinine level >200ng/ml at 12 months follow-up. *Relapse* was defined as baseline urine cotinine <200ng/ml and >200ng/ml at 12 months follow-up. Patients who quit after baseline and had a urine cotinine level <200ng/ml at 12 months follow-up were defined as *late quitters*.

Box 1.
Definitions of smoking behaviour

Pre-event smoking	Self-reported smoking ≤6 months before hospital admission.
Immediate quitters	Quit smoking ≤6 months before or during hospital admission and a negative cotinine test at baseline
Current smokers	Pre-event smoking and a positive cotinine test at baseline
Successful quitters	Pre-event smoker and a negative cotinine test at 12 months follow-up
Persistent smokers	Pre-event smoking and a positive cotinine test at 12 months follow-up.
Relapse	Negative cotinine test at baseline and a positive cotinine test at 12 months follow-up. (subgroup of the persistent smokers)
Late quitter	Positive cotinine test at baseline, and a negative cotinine test at 12 months follow-up (subgroup of the successful quitters)

Smoking status was assessed with urine cotinine, detection limit 200 ng/ml.

Statistical methods

Descriptive statistics included frequencies and percentages for categorical variables. Continuous variables were presented as means with standard deviation for normally distributed data, and as median with quartiles (Q1 and Q3) for non-normally distributed data. Comparisons were performed using unpaired t-tests (equal variances assumed) for continuous variables and Chi-square or Fishers Exact tests for categorical variables. We compared successful quitters in the intervention and control group to assess the effect of the smoking cessation programme. To analyse quitter characteristics, we compared successful quitters with persistent smokers in both the intervention and control group. In the intervention group, we compared patients' preferences for the lifestyle programmes in successful quitters versus persistent smokers. To analyse changes in lifestyle risk factors and the influence of the lifestyle programmes, we compared successful quitters in the intervention group with successful quitters in the usual care group.

Statistical significance was concluded when p-values did not reach the α=0.05 probability level. Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

In total 824 patients were randomised in the RESPONSE-2 trial (Table 1). Overall, mean age was 58.7 (SD ±9.2) years; 22% were female. The majority of patients (65%) had no history of cardiovascular disease prior to the index event or procedure. At baseline visit, 22% were current smokers, and an additional 19% had quit at (or ≤6 months before) hospital admission. Overweight (BMI ≥25kg/m^2) was present in 87%, and 63% did not meet the target for adequate physical activity (>5 times per week 30 minutes per day moderate physical activity). A cardiac rehabilitation programme was followed by 91% of the patients in both groups. Overall, 81% of patients were living with a partner.

Table 1.
Baseline characteristics of trial participants

		Intervention (n= 411)	Usual care (n= 413)
Demographics and medical history			
	Age, years	58.0 ± 9.0	58.6 ± 9.5
	Female	92 (22)	86 (21)
	Higher education (>13 years)	176 (43)	155 (38)
	Relationship (married or cohabiting)	336 (82)	333 (81)
	No known previous cardiovascular disease	275 (67)	262 (63)
Index event and treatment			
	ST elevation myocardial infarction	176 (43)	167 (40)
	Non-ST elevation myocardial infarction	152 (37)	139 (34)
	Unstable angina	28 (7)	40 (10)
	Stable angina requiring revascularization	55 (13)	67 (16)
	PCI	314 (76)	325 (79)
	CABG	39 (10)	48 (12)
	Medication only	58 (14)	40 (10)
Smoking behaviour			
	Pre-event smokers	172 (42)	166 (40)
	Smoking at baseline[1]	91 (22)	88 (21)
	No previous quit attempt	28 (30)	19 (20)
	Smoking partner	103 (31)	91 (28)
Risk profiles			
	Diabetes mellitus	57 (14)	70 (17)
	History of hypertension	149 (36)	177 (43)
	History of dyslipidemia	91 (22)	93 (23)
	Body mass index, kg/m^2	29.9 ± 4.5	29.5 ± 4.3
	Physically inactive	263 (64)	259 (63)

[1] Positive cotinine test at baseline.
Data are presented as mean ± standard deviation or number (percentage), where appropriate.
CABG = Coronary Artery Bypass Graft, PCI=Percutaneous Coronary Intervention

Smoking cessation

Figure 1 shows the flow chart of all (pre-event) smokers from hospital admission to 12 months follow-up. At baseline, there were 338 pre-event smokers across the two groups 42% (172/411) intervention group vs. 40% (166/413) usual care group. At the baseline study visit, 47% in both groups had a urine cotinine <200ng/ml and were thus classified as 'immediate quitters' (81/172 intervention group vs. 78/166 versus usual care group, p=0.99). At 12 months follow-up, the proportions of 'successful quitters' were comparable in both groups, 50% (86/172) in the intervention group vs. 46% (76/166) in the control group (p=0.45). Of the successful quitters at 12 months, the majority in both groups were immediate quitters, with cotinine levels <200ng/ml at baseline and 12 months follow-up (72% (62/86) intervention group vs. 86% (65/76) usual care group (p=0.29)). Relapse rates were comparable across both groups, with 23% (19/81) in the intervention group vs. 17% (13/78) in the usual care group (p=0.27). Of the 91 current smokers at baseline in the intervention group, 24 smokers (26%) quit during follow-up, as compared with 11 of the 88 smokers (13%) in the usual care group (p=0.02).

Characteristics of successful quitters

There were negligible differences between successful quitters and persistent smokers in the treatment groups (Table 2). Successful quitters in the intervention group more frequently underwent coronary artery bypass grafting (CABG) compared to persistent smokers (9 (11%) vs.1 (1%), p=0.02). Successful quitters in the usual care group less frequently had a smoking partner compared with persistent smokers; 31% vs. 51%, p=0.02.

Table 2.
Characteristics of successful quitters and persistent smokers (pre-event smokers=338)

At baseline	**Intervention**		**Usual care**	
	Successful quitter at 12 months n= 86	**Persistent smoker at 12 months n=86**	**Successful quitter at 12 months n=76**	**Persistent smoker at 12 months n=90**
Demographics				
Age, years	55.3 ± 8.8	55.0 ± 8.6	56.0 ± 7.6	56.1 ± 9.9
Female	19 (22)	20 (23)	16 (21)	15 (17)
Higher education (>13 years)	32 (37)	31 (36)	22 (29)	25 (28)
Relationship (married or cohabiting)	65 (76)	71 (83)	60 (79)	62 (69)
Smoking partner	25 (39)	36 (51)	18 (31) †	31 (51) †
No known previous cardiovascular disease	65 (76)	62 (72)	55 (73)	54 (60)

Index event and treatment				
ST elevation myocardial infarction	38 (50)	45 (52)	40 (47)	41 (46)
Non-ST elevation myocardial infarction	29 (34)	33 (38)	25 (33)	28 (31)
Unstable angina	5 (6)	4 (8)	5 (7)	9 (10)
Stable angina requiring revascularization	12 (14)	4 (8)	8 (11)	12 (13)
PCI	70 (81)	71 (83)	68 (90)	76 (84
CABG	9 (11) ∓	1 (1) ∓	5 (7)	4 (4)
Medication only	7 (8)	14 (16)	3 (4)	10 (11)
Risk profiles at baseline				
Diabetes mellitus	6 (7)	10 (12)	6 (8)	13 (14)
Systolic blood pressure ≥140 mmHg	26 (30)	26 (30)	18 (24)	24 (27)
LDL-cholesterol ≥1.8 mmol/L	65 (76)	61 (70)	59 (78)	72 (80)
Body mass index, kg/m^2	29.4 (± 4.4)	28.7 (4.6)	28.2 (± 4.0)	28.0 (4.5)
Waist circumference, cm	105.4 (± 12.1)	105.2 (13.1)	104.0 (± 11.6)	102.8 (11.8)
Overweight (BMI ≥25 kg/m^2)	75 (87)	67 (87)	61 (80)	67 (74)
Physically inactive	53 (62)	50 (58)	47 (62)	47 (52)

Coronary Intervention. Physically inactive= <30 minutes of physical activity of moderate intensity five times per week.
Data are presented as mean ± standard deviation or number (percentage), where appropriate.
CABG = Coronary Artery Bypass Graft, PCI=Percutaneous Coronary Intervention. Physically inactive= <30 minutes of physical activity of moderate intensity five times per week.
No statistically significant differences between successful quitters versus persistent smokers in intervention and control group, except for: † smoking partner in control group p=0.02; ∓ CABG intervention group p=0.02;

Participation in lifestyle intervention programmes

Fifty patients participated in the smoking cessation programme, of which 11 were baseline quitters and 39 current smokers. Of these, at 12-months follow up 16 (19%) were successful quitters (negative cotinine test) and 34 (40%) were persistent smokers (positive cotinine test) (p<0.01) (Table 3, 4). All successful quitters participating in the smoking cessation programme completed the programme as compared with approximately half of persistent smokers (100% vs. 53%, p<0.01) (Table 4). Furthermore, successful quitters participated more frequently in at least one of the other lifestyle programmes (i.e. the weight reduction and physical activity) compared with persistent smokers (65% vs. 37%, p<0.01), (Figure 1, Table 3). Overall, both successful quitters and persistent smokers participated most frequently in the physical activity programme (56% vs. 42%, p=0.62). Of patients who quit after baseline (late quitter), (intervention group n=24 vs. control group n=11; p=0.02), nine of 24 (38%) patients participated in the intervention smoking cessation programme. More detailed information on the attendance to the lifestyle programmes of successful quitters and persistent smokers is shown in Figure 1 and Table 4.

Table 3.
Smokers' preferences for lifestyle intervention programmes (intervention group, n=172)

	Successful quitters (n=86)	Persistent smokers (n=86)	p-value
Participation in a smoking cessation programme (total)	16 (19%)	34 (40%)	<0.01
Participation in smoking cessation and weight reduction programme	5 (6%)	11 (13%)	0.17
Participation in a smoking cessation and an improvement of physical activity programme	7 (8%)	14 (16%)	0.17
No smoking cessation programme, participation in one other lifestyle programme	56 (65%)	32 (37%)	<0.01
Three lifestyle programmes	3 (3%)	7 (8%)	0.25

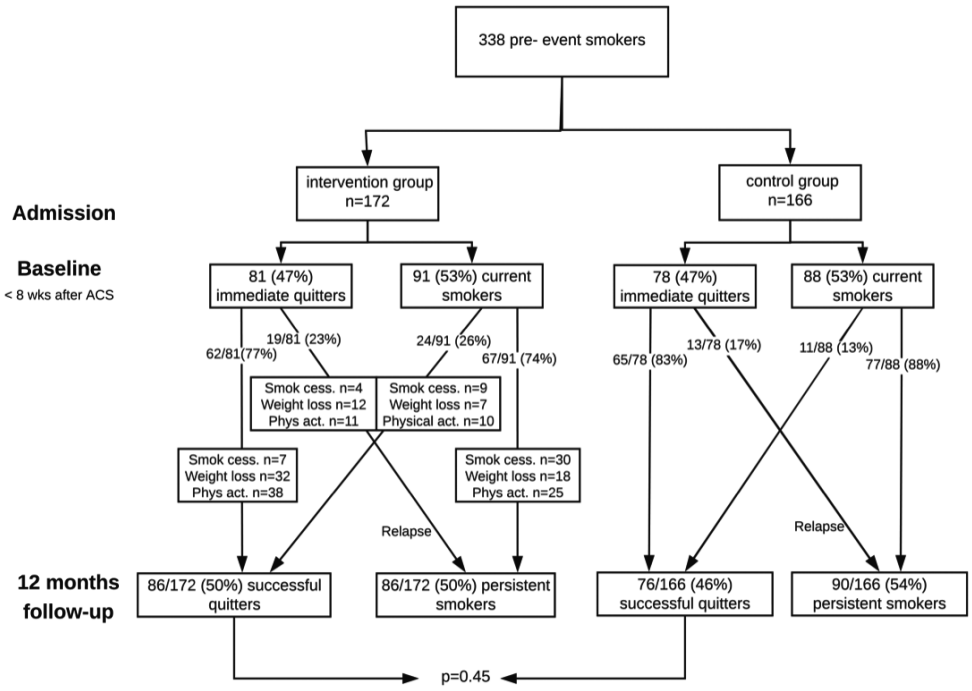

Figure 1.
Flow chart of 338 pre-event smokers after an acute coronary event or procedure from hospital admission to one year follow-up.

Lifestyle risk factors

Changes in achieved lifestyle risk factor targets in successful quitters are shown in Table 5. While not statistically significant, among smokers who quit successfully in the intervention group mean weight increase was 2.0 kg, as compared with 3.0 kg in successful quitters in the usual care group (2.0 ± 6.8 kg vs. 3.0 ± 5.1 kg, p=0.29). This difference was more pronounced in the 48 patients who attended the weight reduction programme (1.2 kg ± 8.3 kg vs. 3.0 ± 5.1 kg, p=0.17), albeit not statistically significant. We also observed a small non-significant difference in favour of successful quitters in the intervention group in achieving ≥ 10% improvement in 6-minute walking distance test (48% vs. 36%, p=0.12).

Table 4.
Attendance to lifestyle programmes of successful quitters versus persistent smokers (intervention group, n=172)

	Successful quitters (n=86)	Persistent smokers (n=86)	p-value
Smoking cessation counselling/ Luchtsignaal™ (n=50)			
Participation in programme	16 (19%)	34 (40%)	<0.01
Programme completed	16 (100%)	18 (53%)	<0.01
Weight reduction programme/Weight Watchers™ (n=69)			
Participation in programme	39 (45%)	30 (35%)	0.21
Meetings, mean total	15 (13.2)	13 (13.7)	0.53
Physical activity programme/ DirectLife™ (n=84)			
Participation in programme	48 (56%)	36 (42%)	0.07
≥12 weeks (completed)	39 (45%)	29 (34%)	1.0

Discussion

We found that in a large randomised controlled trial of multifactor lifestyle modification in secondary CAD prevention, the majority of patients who successfully quit smoking are those who quit immediately after their hospitalisation for an acute coronary syndrome or coronary revascularisation. We observed considerable cessation rates in both groups (50% vs. 46%), but referral to a community-based smoking cessation programme did not lead to a higher smoking cessation rate in the first year after hospitalisation.
Although we found no significant differences in cessation rates between the intervention and usual care groups, we found participation in the smoking cessation programme to be low in successful quitters as compared with persistent smokers (19% vs. 40%, p<0.01). However, of patients referred to the smoking cessation programme, all successful quitters completed the programme. While the overall effect of the smoking cessation programme is less than expected, we cannot exclude that it had beneficial effect in selected individuals. In line with these findings, in a previous trial we found that the majority of successful quitters stop immediately after an acute event, without referral to a dedicated cessation programme.[15] In contrast to the current recommendations in the ESC CVD prevention guideline,[4] which recommends smoking cessation counselling in all pre-event smokers, our findings suggest that in a large group of patients who quit immediately after hospitalisation for CAD, a smoking cessation or relapse prevention programme is not needed.

Table 5.
Changes of lifestyle risk factors in successful quitters at 12 months follow-up

	Successful quitters		
	intervention group (n=86)	**usual care group (n=76)**	**p value**
Smoking behaviour			
Pre-event smokers	86/172 (50)	76/166 (46)	0.45
Immediate quitters (baseline)	62/86 (72)	65/76 (86)	0.29
Quit smoking in LS participants (n=50)	16/50	n.a.	n.a.
Weight status			
BMI increase ≤ 2.5%	37/86 (43)	28/76 (37)	0.42
Mean weight change (kg), (mean, ± SD)	2.0 (± 6.8)	3.0 (± 5.1)	0.29
Mean BMI change (kg/m2)	0.6 (± 2.3)	1.0 (± 1.7)	0.27
Mean weight change in WW participants (kg) (n=39)	1.2 (± 8.3)	3.0 (± 5.1)	0.17
Physical activity level			
Improved physical activity	41/86 (48)	27/76 (36)	0.12
Mean change of 6MWD (m)	47.8 (-0.3- 86.3)	26.0 (-9.3- 76.3)	0.23
Mean change of 6MWD in DL participants (m) (n=48)	53.0 (-3.0- 95.0)	26.0 (-9.3- 76.3)	0.27

Data are presented as mean ± standard deviation, number (percentage), or median (IQR) where appropriate.
BMI=Body Mass Index, DL= participants of physical activity programme DirectLife, LS = participants of smoking cessation programme Luchtsignaal, WW= participants of weight loss programme Weight Watchers, 6MWD=6-Minute Walking Distance.

In patients who did not quit smoking during hospitalisation, the effect of the smoking cessation programme was limited. Of the 67 patients in the intervention group who were smokers at baseline and at 12 months follow-up, 30 (45%) participated in the smoking cessation programme. More patients in the intervention group quit after baseline as compared with the control group (n=24/91 (26%) vs. n=11/88 (13%), with moderate participation rates in all three lifestyle programmes (smoking cessation n=9, weight loss n=7, physical activity n=10). While an effect of the lifestyle programmes on late cessation rates cannot be excluded, it is unsatisfactory that a large number of smokers do not succeed in quitting smoking, in spite of smoking cessation programme attendance. This group of patients may benefit from a more intensive cessation therapy, for example based on the principles of addiction withdrawal instead of lifestyle modification. Additionally, other lifestyle programmes than smoking cessation may support patients in (maintaining) freedom from tobacco. Engaging in regular exercise may assist smoking cessation by increasing health consciousness, moderate nicotine withdrawal and cravings, and by supporting weight gain management.[16]

Participation rates in the other two lifestyle intervention programmes were markedly higher in successful quitters as compared with persistent smokers (45% vs. 35% weight loss programme, 56% vs. 42% physical activity programme). This may reflect increased motivation in successful quitters to further improve their lifestyle risk factors. This is in line with the findings of Scholte op Reimer et al., (2006) who found that successful quitters more frequently adopt healthier lifestyles after hospitalisation for CAD.[17] Explanations of this observed behavioural change may be found within the theory of self-perception and dissonance phenomena.[18] According to the self-perception theory, an individual's attitude may be viewed as conclusions from observations of their own behaviour. As such, a patient who quits smoking after hospitalisation perceives himself as a 'successful' quitter, and will behave accordingly. Moreover, in cognitive dissonance theory, individuals seek consistency among their beliefs and attitude statements. Thus, if a patient stops smoking or makes other favourable lifestyle changes, this can lead to further motivation to eliminate other unhealthy lifestyles (i.e. removal of dissonance). Alternatively, the findings may reflect greater discipline or self-control as a common explanation.

Weight gain after smoking cessation is common, with an average weight increase around 5 kg in the first 12 months.[19] In our study, the weight increase in successful quitters was less pronounced in both groups (intervention 2.0 kg vs. usual care 3.0 kg, p=0.29). In patients attending the weight reduction programme, the weight increase was lower than in the overall group of successful quitters, albeit not statistically significant (attending 1.2 kg vs. control 3.0 kg, p=0.17). Limiting weight gain after smoking cessation might positively influence the motivation to quit in patients concerned about weight gain. While our findings of a modest improvement in weight among successful quitters were not statistically significant, our study was not powered for this subgroup analysis. Considering the potential impact of smoking cessation and limiting weight gain in a high-risk population (i.e. coronary artery disease), investigation of specific strategies of concomitant interventions targeting both lifestyle risk factors seems warranted, especially as these risk factors frequently cluster. [9,20,21]

Nurse-coordinated referral

Our study included two distinctive roles for nurses. In all patients (interventions and controls), lifestyle counselling and risk factor modification by nurses was offered during the consultations. In the intervention group, nurses were additionally instructed to not only refer patients to one or more of the lifestyle programmes, but also to discuss patients' participation and progress of behavioural change within this context.

Multidisciplinary approaches, including nurse-coordinated care (NCC), are recommended in the ESC prevention guidelines as a part of primary and secondary prevention of CVD. Care coordination is a part of a nurse's skills and experiences.[10,22] Core components of NCC in secondary prevention include 1) risk factor management, 2)

multidisciplinary consultation, including referral, and 3) shared decision making.[8] Successful risk modification has been shown to be dependent on nurse/patient relationships, trustworthiness, goal setting and frequency of follow-up.[8,23] Nurses have intensive contact with patients and may therefore be in a favourable position to discuss lifestyle changes and patients' preferences. Importantly, the lifestyle programmes were not offered as independent interventions, but within the context of NCC. Furthermore, NCC offers a flexible platform to incorporate or evaluate different and new lifestyle intervention programmes.

Strengths and limitations

There are several strengths to our study. First, we assessed smoking in a large, contemporary randomised multicentre trial, with detailed information on lifestyle behaviour and a clear referral protocol. Second, in the RESPONSE-2 trial we used objectively measured lifestyle behaviour outcomes, including urinary cotinine measurements, rather than self-reported behaviour changes which are prone to misreporting. Finally, the community-based lifestyle programmes were offered uniformly, in their existing format, allowing for easy implementation into daily clinical practice.

Several limitations need to be considered. While our analysis was pre-specified in the original study protocol, the overall study was not powered for comparisons between different subgroups of smokers, nor between intervention and usual care group. However, our finding that successful quitters are motivated for additional lifestyle changes indicates opportunities for additional risk factor management. Second, the main analysis evaluating the effect of nurse referral to a smoking cessation programme was conducted in a randomised population. However, within group comparisons were non-randomised with the limitation inherent in this subgroup analysis. Third, our study included three different lifestyle programmes, with varying degrees of participation and duration. While a study evaluating a single intervention, such as a smoking cessation programme, might be superior in evaluating the isolated effects of such a programme, secondary prevention should consist of a multi-faceted approach targeting all relevant risk factors, consistent with daily practice. Fourth, overall participation rate in the smoking cessation programme was low. Of 172 patients eligible for the smoking cessation programme in the intervention group, only 50 patients participated in the programme. This might be a reflection of the referral process (selection of patients for referral), competing lifestyle programmes, or the attractiveness of the smoking cessation programme. Moreover, the majority of patients who successfully quit smoking showed that it was within their own ability to quit, with no need for the smoking cessation programme. Finally, the follow-up of our study was limited to 12 months. This duration of follow-up allows for some potential loss of effect after initial behavioural changes, but a longer follow-up is required to determine whether lifestyle improvements are longer-lasting. We are currently collecting longer term follow-up data in the RESPONSE-2 trial.

Conclusion

We found that the majority of patients who successfully quit smoking after an acute coronary syndrome and/or coronary revascularisation are those who quit immediately after hospitalisation without a need to participate in a smoking cessation programme. We were not able to demonstrate an effect of the telephone-based smoking cessation programme; moreover, this programme was attended by only a minority of successful quitters. However, successful quitters were motivated to attend other lifestyle programmes, addressing healthy food choices, weight maintenance and physical activity.
Our findings support a tailored, comprehensive approach to lifestyle interventions in secondary prevention of coronary artery disease.

Competing Interests
All authors reported that they have no relationship relevant to the content of this paper to disclose.

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Trial register
NTR 3937
www.trialregister.nl

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Chapter 10

GENERAL DISCUSSION:
Rethinking current concepts and strategies

I got back on my feet again, and when I came home, I wasn't really frightened anymore. After my heart attack, I took steps to improve my lifestyle. I managed to stop smoking all by myself and wanted to exercise more. Together with my dog or with my wife I go for a walk or a bicycle ride every day. That is enjoyable and keeps me fit. Exercise has become second nature to me. Since I lost quite a lot of kilos with the weight reduction programme in RESPONSE 2 (Weight Watchers) I notice that I have more energy. Of course, I have to take pills now, that is also part of it. I benefited a lot from the consultations with the nurse during the cardiac rehabilitation. She encouraged me to participate in the lifestyle programmes, on my own I would not have done it. I know what's good for me now, much better than before all this happened.' (Mr P. Sanders, 63 years old)

Rethinking nurse-coordinated care

Based on this thesis, a number of concepts, definitions and strategies in secondary prevention merit rethinking. First, nurse-coordinated care as described in the current scientific literature covers concepts that are broad and heterogeneous. One of the central findings of our meta-analysis is that trials investigating nurse-coordinated care rarely adhere to or report on the definition of such care coordination. Our meta-analysis therefore provides a number of recommendations to assist researchers and clinicians when designing future nurse-coordinated care studies. These recommendations include consistently applying a (generally accepted) definition of nurse-coordinated care and selectively including proven effective components of the nurse-coordinated interventions, as opposed to letting included components be based on usual care and local expertise and preferences. Additionally, nurse-coordinated care should not refer to the coordination of the nurse's own work, but the nurse's role in facilitating multidisciplinary teamwork.

The success of the RESPONSE-2 trial also highlights an important pitfall. While demonstrating that care coordination with selected lifestyle programmes leads to a clinically important improvement in lifestyle risk factors, the control of two central biometric risk factors, LDL-cholesterol and blood pressure, was disappointing. The RESPONSE-1 trial successfully focussed on pre-defined targets for these risk factors, with clearly defined actions and/or interventions (medication assessment and titration, and referral). The use of these components was reflected in more patients achieving risk factor target levels at follow-up. In RESPONSE-2, we aimed to evaluate referral to lifestyle programmes on top of the already investigated effective components found in RESPONSE-1. However, the study protocol of RESPONSE-2 did not emphasize treatment to target for blood pressure and LDL-cholesterol to the same degree as RESPONSE-1. This might explain the modest rates of targets being met in the patients attending the nurse visits. Our experiences after conducting two large RCTs and one comprehensive meta-analysis highlight the importance of not only clearly defining intervention components, but also implementing detailed protocols next to training and monitoring to ensure adherence to the pre-defined interventions.

Rethinking secondary prevention

To reduce the impact of cardiovascular disease and to improve secondary prevention, the European Society of Cardiology (ESC) takes responsibility for education and training of health care professionals.[1] Guideline implementation is a part of the ESC education programmes to support health care professionals in clinical practice. The Euro Heart Survey Programme, of which the EUROASPIRE surveys are part of, monitors to what

extent clinical practice adheres to guideline recommendations.[2] The registries are part of a so-called '*quality loop*': research is the cornerstone, leading to the development of (European) guidelines, followed by education as part of guideline implementation, and finally, the adherence to guideline recommendations are evaluated in international surveys. For secondary prevention, the EUROASPIRE surveys have been conducted to evaluate adherence to the guidelines since 1995.[3,4]
The results of the EUROASPIRE surveys show that despite dissemination of evidence-based guidelines, the integration into routine clinical practice is disappointing.[5,6] The rate of adherence is likely to be influenced by several factors.[7] Health care systems in European countries differ, and subsequently the interpretation of the guideline will not always be uniform. As an example, the physician to nurse ratio is an important factor, with wide variation across countries, as well as the extent to which relevant treatments are reimbursed. It should be taken into account that health care professionals may not be familiar with or might not agree with the new guidelines. For this reason, it is of importance that national professional associations critically appraise the European guidelines. Furthermore, the guideline may not sufficiently take into account that life style recommendations should not ignore the complexity of lifestyle modification. To what extent and in which circumstances will lifestyle related risk factor targets be sufficiently realistic?

When interpreting the EUROASPIRE survey findings and using these to evaluate secondary prevention and the contribution of these surveys to the so-called 'quality loop', a number of points should be kept in mind. Participants were identified retrospectively from diagnostic registers and encouraged to participate in the survey. Such (motivated) patients may therefore not be a representative sample of all patients with coronary heart disease. Non-participants are more likely to have unhealthy lifestyles and poorer health status.[8] Hence, the selection of participants may lead to overestimation of the quality of current clinical practice in secondary prevention of coronary heart disease, and even in these patients the quality of secondary prevention leaves much to be desired.
Furthermore, the target population consisted of consecutive patients less than 70 years of age (EUROASPIRE I, II) and less than 80 years of age (EUROASPIRE III, IV). Given the ageing population of post-industrial nations and consequently, the growing number of elderly people with cardiovascular diseases, age limits in cardiovascular disease study populations are outdated.

Lifestyle modification, future directions

Unexpectedly, based on our findings, in a subset of patients (i.e. immediate quitters) smoking cessation support may be less urgent than currently assumed. Current prevention guidelines advise smoking cessation counselling in all (pre-event) smokers, regardless of characteristics of quitting. However, after evaluating smoking cessation in two large randomised trials in secondary prevention, this recommendation needs to be reconsidered. Our findings support a strategy in which clinicians can differentiate between immediate and late quitters. In the RESPONSE-1 and RESPONSE-2 trials, an unequivocal finding was that additional relapse prevention, through nurse counselling or a community based, comprehensive smoking cessation programme seems unnecessary - or even counterproductive - in immediate quitters.[9] Based on the RESPONSE-2 trial, with the benefit of hindsight, our findings suggest that in a large group of patients who quit immediately after hospitalisation for coronary heart disease, a smoking cessation or relapse prevention programme was not needed. Especially patients who have a higher level of education, who suffered from a first event, and 'immediate quitters' after hospitalisation have low recurrence rates in the absence of support programmes.
Patients who quit smoking are more frequently motivated to participate in other lifestyle programmes, such as a physical activity programme. Motivations for this may be the wish to reduce withdrawal symptoms through exercise or to manage weight gain secondary to smoking cessation. While there is insufficient evidence to recommend exercise as a smoking cessation strategy[10], our findings suggest that participation in a smoking cessation programme in immediate quitters should not have a higher priority than an exercise programme in terms of overall risk factor management. Furthermore, there is strong evidence to recommend exercise as an aid for reducing tobacco withdrawal and cravings.[10] Our results support a comprehensive approach to lifestyle risk modification and suggest that we should rethink the currently prevalent 'single risk factor approach'. Future research should investigate how to optimally select patients for dedicated prevention programmes directed at smoking cessation and/or physical activity.

To date, all modern secondary prevention trials have focused on success rates in reaching (pre-defined) target risk factor levels. However, improvement of one lifestyle-related risk factor often results in deterioration of another lifestyle-related risk factor - a finding that is consistently underreported in most major prevention trials. Therefore, outcome measures in future trials should apply a more rigorous standard to define successful outcomes. We recommend that such outcomes should incorporate pre-defined thresholds for 'no deterioration' in other risk factors (not targeted by the evaluated intervention) as a new standard in outcome measures. Alternatively, the outcome measure should reflect a quantitative estimation of overall risk.
Other investigators have evaluated a 'medical' approach to improve healthy lifestyles in

secondary prevention of coronary heart disease. The OPTImal CArdiac REhabilitation (OPTICARE) trial assessed the effects of two advanced and extended cardiac rehabilitation programmes compared with current standard cardiac rehabilitation in coronary patients. At 18 months, patients in the two intervention arms had higher health-related quality of life and were less anxious as compared with usual care.[11] However, there were no differences between the groups in mortality risk reduction as measured by SCORE (intention-to-treat analysis). These findings highlight the importance of investigating non-medical interventions for lifestyle modification in coronary patients.

While nurse-coordinated referral to lifestyle programmes has been shown to successfully modify risk in the short term, longer follow-up data are needed to evaluate whether the positive effects persist after discontinuation of the programme. To address this issue, we are currently collecting follow-up data in RESPONSE-2.
In conclusion, nurse-coordinated care, including community-based lifestyle programmes, improves lifestyle risk factors, and is a valuable addition to the current usual care. Such programmes can easily be implemented on a large scale, due to extensive availability. When implementing nurse-coordinated care, clear definitions and targets are needed in such programmes, and both improvement and deterioration of risk factors should be included in the evaluation. Based on our data, the current preventive guidelines should be revised to reflect this.

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Summary

SUMMARY

Cardiovascular disease is a growing health problem worldwide. As outlined in the introduction, a large majority of patients fail to achieve the therapeutic targets as set by the guidelines, and secondary prevention is far from optimal. In this thesis, we evaluated a number of strategies and concepts in secondary prevention. With the aim of rethinking the current management of risk factors for cardiovascular disease, we presented analyses of previously conducted trials, we identified effective components of existing (nurse-coordinated) prevention programmes, and based on our findings, we designed and conducted a randomised clinical trial to evaluate the effect of existing community-based lifestyle programmes coordinated by nurses.

In **chapter 2** we describe the context in which this thesis was written, demonstrating that in patients with coronary heart disease a number of cardiovascular risk factors are highly prevalent, and that their treatment is far from optimal. The observations were consistent throughout the EUROASPIRE-IV registry, which comprised hospitals in a range of European countries including the Netherlands. While almost all patients (n=498) received preventive medication (antiplatelet agents, statins and antihypertensive medication), lifestyle-related risk factors such as hypertension, obesity, and diabetes were highly prevalent. We conclude that in contemporary patients with coronary heart disease, secondary prevention falls short of achieving the targets specified in national and international guidelines. Current approaches are insufficient and lifestyle changes are rarely achieved in the majority of patients.

This thesis consists of two parts addressing these issues. In part 1, nurse-coordinated care is thoroughly evaluated, while part 2 deals with smoking cessation in particular.

PART 1 NURSE-COORDINATED CARE

In **chapter 3**, we investigate effective components of nurse-coordinated care by means of a systematic review and meta-analysis of randomised trials. In this comprehensive literature search we found that traditional risk factor management was the most commonly used nurse-coordinated strategy, followed by multidisciplinary consultation. However, the nurse-coordinated intervention had variable effects on the different risk factors – from none to important improvements. Based on our systematic review, we identified effective components in nurse-coordinated care of secondary prevention. First, prescription and/or titration of medication, in combination with a high-intensity strategy, can decrease systolic blood pressure and LDL-cholesterol, thus improving risk profiles. Second, when data are pooled across a large number of studies, nurse-coordinated care is associated

with higher positive effect on smoking cessation rates. However, interventions and outcomes of nurse-coordinated care vary considerably, hampering comparisons between studies. Finally, and potentially most important, we found a lack of clear definitions of nurse-coordinated care. Therefore, we recommend developing a universal definition of nurse-coordinated care and its individual components, to facilitate comparisons of content and outcomes.

In **chapter 4**, we describe the rationale and study design of the Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists (RESPONSE)-2 study. The RESPONSE-2 trial was designed to evaluate three community-based comprehensive lifestyle programmes that have previously been validated, aimed at smoking cessation (Luchtsignaal®), weight reduction (Weight Watchers®) and physical activity (Philips DirectLife®). The inclusion of patients started in April 2013 and continued until July 2015. We randomised 824 patients who had recently been hospitalized for coronary heart disease in 15 hospitals in the Netherlands. On top of usual care, patients in the intervention group were referred by the nurse to up to three lifestyle programmes. If multiple lifestyle factors needed to be addressed, the choice and the sequence of the interventions were based on patient preference. This was the first trial to study referral of patients and their partners to community-based lifestyle programmes in secondary prevention, coordinated by hospital-based nurses.

In **chapter 5**, we present the main outcomes of the RESPONSE-2 trial. The results showed that among patients with coronary heart disease, nurse-coordinated referral to a comprehensive set of up to three widely available community-based lifestyle programmes, with encouragement of partner participation, on top of usual care, was more effective in improving lifestyle-related risk factors than usual care alone at 12 months follow-up. The effect of the weight reduction component was the most prominent one in our study. Almost twice as many patients achieved significant weight loss in the intervention group, compared with control. We also found that in both groups, living with a partner (irrespective of participation) was associated with a greater proportion of success. Among patients in the intervention group who had a partner, partner participation in a lifestyle programme was associated with a significantly greater success rate. After multiple imputation and reanalysis of the primary outcome, the relative risk reduction remained significant. Attendance to the programme was high, with 85% of patients in the intervention group following at least one lifestyle programme.

In **chapter 6**, we present the outcomes of nurse-coordinated lipid-lowering medication titration based on an analysis of the RESPONSE-1 trial data. RESPONSE-1 found an improvement of the proportion of patients on target for LDL-cholesterol in the nurse-coordinated intervention group, while lifestyle-related risk factors were comparable

in both groups. Our systematic review previously showed that nurse-coordinated prevention programmes successfully reduce blood pressure and LDL-cholesterol. We therefore hypothesised that more intensive medication titration by nurses was associated with better LDL-cholesterol control. To account for the use of different lipid-lowering agents and dosages, the intensity of each prescription was expressed as an average lipid-lowering potency (ALLP, % potential LDL-cholesterol lowering). We found that nurse-coordinated care in patients after an acute coronary syndrome was associated with more intensive lipid-lowering medication titration and with higher achieved ALLP values as compared with usual care alone. Therefore, the greater proportion of patients on LDL-cholesterol target at 6 and 12 months follow-up was likely explained by the more intensive titration of lipid-lowering medication in the nurse-coordinated intervention group compared with usual care alone.

PART 2 SMOKING CESSATION

In **chapter 7**, we present the characteristics of patients who successfully quit smoking in a multicentre, randomised controlled trial (RESPONSE-1). We selected the 324 pre-event smokers (43%) and analysed the smoking and quit status during baseline and at one-year follow-up after an acute coronary syndrome. We found that the most important characteristic of successful quitters was immediate cessation after hospitalisation. In addition, a higher level of education, no previous history of coronary heart disease, LDL-cholesterol level on target and adequate physical activity at one-year characterised successful quitters.

In **chapter 8**, we present a detailed analysis on smoking cessation in European patients with coronary heart disease. This report from the EUROASPIRE IV survey was carried out in selected geographical areas in 24 European countries (78 hospitals) in 2012-2013 and compared with earlier surveys (EUROASPIRE II and III). In total, 7998 patients with coronary interventions (acute or elective) or events were interviewed and examined between 6 months and 3 years following hospital discharge. Information on smoking behaviour was collected using an interview questionnaire and smoking status was verified by the concentration of breath carbon monoxide using a smoker analyser (Bedfont Scientifc, Model Micro+). In EUROASPIRE IV, the proportion of patients who were successful quitters increased with an increasing age and higher levels of education, and smoking cessation was associated with weight gain. However, across the 3 different surveys (1999, 2006 and 2013), smoking cessation rates remained unchanged at approximately 50%, despite tobacco control measures and the availability of effective medications to support cessation. However, we found considerable variation between individual countries in pre-event smoking prevalences and cessation proportions.

Smoking cessation rates should therefore be interpreted in the light of pre-event smoking prevalences, and caution is advised when comparing individual European countries.
In the large group of persistent smokers, novel strategies for optimal secondary prevention are needed. Within this context, it should be taken into account that successful quitters report more actions to make healthy lifestyle changes, including participating in a cardiac rehabilitation programmes, as compared with persistent smokers. This motivation can potentially help the development of new strategies in secondary prevention, especially in patients with more than one lifestyle-related risk factor.

In **chapter 9**, we investigate the characteristics and preferences of patients who successfully quit smoking in the RESPONSE-2 trial as a pre-defined secondary outcome, embedded in the main RESPONSE-2 trial. We found that among the successful quitters at 12 months follow-up, the majority in both intervention and usual care group were immediate quitters (confirmed using urinary cotinine at baseline and 12-months follow-up). The study also shows that in the intervention group, successful quitters participated less frequently in the smoking cessation programme compared with persistent smokers. Furthermore, successful quitters participated more frequently in one of the other two lifestyle programme compared with persistent smokers. This suggests that successful quitters are also motivated for additional lifestyle improvements.

Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

'De ambulancebroeders zagen direct wat er aan de hand was: ik had een hartinfarct! Onmiddellijk werd ik naar het ziekenhuis gebracht, lag ik op de katheterisatiekamer en openden de artsen een van de bloedvaten die het infarct veroorzaakten. Ik moet toegeven dat ik, nadat ik uit het ziekenhuis kwam, enorm geschrokken was. Het was me duidelijk dat ik iets aan mijn leefstijl moest doen om een nieuw infarct te voorkomen. Ik ben daarom direct gestopt met roken. Helaas ben ik intussen wel wat kilo's aangekomen. Wat kan ik nu het beste doen? Is het gewichtsverlies programma uit RESPONSE-2 wat voor mij? Kan ik dit wel? Ik heb namelijk nog niet eerder zoiets ondernomen. Goed dat het gewoon bij mij in de buurt te volgen is. Ik ben bereid mijn leefstijl te veranderen. Dat zal echt nodig zijn, gezonder leven, om mijn kleinkinderen te zien opgroeien. Ik zou meer willen bewegen, maar ik heb er weinig energie voor. Ik ben ook geïnteresseerd in het hartrevalidatieprogramma en gesprekken met de verpleegkundige. Het lijkt me prettig dat iemand me begeleidt in de keuzes die je moet maken. Het was niet niks. M'n leven stond echt van de ene op de andere dag op z'n kop.'
(Dhr P. Sanders, 63 jaar)

Ondanks steeds betere behandelingen zijn hart- en vaatziekten wereldwijd nog steeds een belangrijke oorzaak van overlijden. Het gaat daarbij heel vaak om een coronaire aandoening. Coronairen, ook wel kransslagaderen genoemd, voorzien het hart van bloed en zuurstof. Door een vernauwing of afsluiting van een of meerdere coronairen kan een hartinfarct ontstaan. Hierna blijft er een verhoogd risico op een nieuw hartinfarct of een andere hart- en vaatziekte. Daarom is secundaire preventie, of anders gezegd, het inperken van risicofactoren, belangrijk om de ziekte te stoppen of te vertragen.

De behandeling van de risicofactoren voor patiënten met hart- en vaatziekten bestaat uit een combinatie van medicatie en aanpassing van leefgewoonten. Daarvoor zijn er zowel nationaal als internationaal uitgebreide richtlijnen opgesteld met duidelijke aanbevelingen voor behandelstreefwaarden. Het gaat dan om bloeddruk, gewicht, bewegen, roken, cholesterol- en bloedsuiker. De aanbevelingen uit de Europese richtlijn zijn weergegeven in Tabel 1.

Tabel 1.
Richtlijn aanbevelingen voor de secundaire preventie van hart- en vaatziekten

Aanbevelingen richtlijn
Stoppen met roken (voor rokers)
Regelmatige fysieke activiteit, ≥30 min. 5x/week
BMI <25 kg/m^2
Buikomvang:
<94 cm (mannen)
<80 cm (vrouwen)
Bloeddruk <140/90 mmHg
Totaalcholesterol <4.5 mmol/L
LDL-cholesterol <1.8 mmol/L
Voor patiënten met type-2 diabetes:
Nuchter glucose <7.0 mmol/L
HbA1c <6.5%

BMI=Body mass index; HbA1c=glycated hemoglobine;
LDL=low-density lipoproteïne

Secundaire preventieve interventies zijn effectief. Het naleven van de aanbevelingen gericht op leefgewoonten en de behandeling van bloeddruk en cholesterol met medicatie zorgt voor een aanzienlijke risicoverlaging. Uit de EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to reduce Events) surveys blijkt echter dat het de meerderheid van de patiënten niet lukt de streefwaarden te halen. Secundaire preventie is daarmee verre van optimaal.

In dit proefschrift evalueren we een aantal strategieën en concepten om risicofactoren in te perken. We analyseerden eerder uitgevoerde onderzoeken en identificeerden effectieve componenten van bestaande (door verpleegkundigen gecoördineerde) preventieprogramma's. Op basis van onze bevindingen ontwierpen en voerden we een nieuwe, op onze bevindingen gebaseerde, gerandomiseerde studie uit. Dit alles met als doel *het heroverwegen van de huidige aanpak van risicofactoren in de secundaire preventie van hart- en vaatziekten.*

Hoofdstuk 2 dient ter introductie en geeft inzicht over de huidige klinische praktijk in Nederland. De prevalentie van risicofactoren voor hart- en vaatziekten onder de Nederlandse deelnemers aan EUROASPIRE IV (n=498) wordt in kaart gebracht. Bijna alle patiënten ontvangen preventieve medicijnen (antistollingsmedicijnen, cholesterolverlagers en bloeddrukverlagers), terwijl leefstijl-gerelateerde risicofactoren, zoals verhoogde bloeddruk (hypertensie), overgewicht en diabetes veel voorkomend blijven. Wij concluderen dat in de onderzochte groep patiënten met een coronaire

hartziekte secundaire preventie te kort schiet. De aanpak blijkt onvoldoende en verbetering van ongezonde leefgewoonten wordt te weinig bereikt.
In de volgende twee delen wordt verslag gedaan van de resultaten van onze studies:

DEEL 1: DOOR VERPLEEGKUNDIGEN GECOORDINEERDE (NA)ZORG

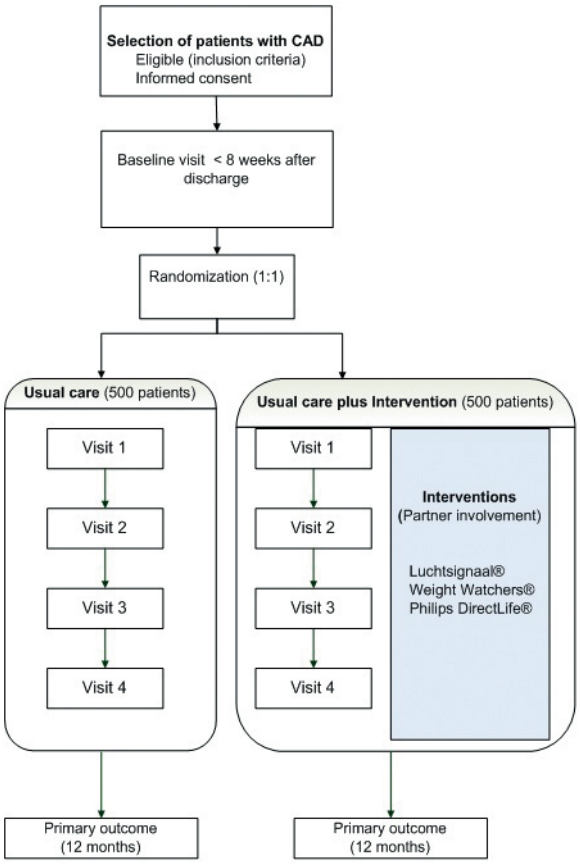
Een *multidisciplinaire* aanpak van risicofactoren, zoals bijvoorbeeld met 'door verpleegkundigen gecoördineerde (na)zorg', wordt aanbevolen in de Europese richtlijn om secundaire preventie te verbeteren. Deze aanbeveling is gebaseerd op een beperkt aantal studies waarin de effecten van door verpleegkundigen gecoördineerde zorg onderzocht werden. Deze zorg bestaat uit vaststelling van het cardiovasculair risicoprofiel en ondersteuning van de patiënt bij het behalen van behandelstreefwaarden en leefstijlaanpassing. Verpleegkundigen begeleiden patiënten en hun familie met betrekking tot verandering van leefgewoonten en het opvolgen van medicijnvoorschriften. Daarnaast is coördinatie van zorg een essentieel deel van het verpleegkundig taakgebied en relevant bij secundaire preventie.

In **hoofdstuk 3** onderzoeken we effectieve componenten van door verpleegkundigen gecoördineerde zorg door middel van een systematische review en meta-analyse van gerandomiseerde onderzoeken. Uit dit uitgebreide literatuuronderzoek blijkt dat risicofactor management de meest voorkomende strategie is, op de tweede plek gevolgd door multidisciplinaire consultatie. Door verpleegkundigen gecoördineerde zorg laat wisselende effecten zien op de verschillende risicofactoren. Gebaseerd op onze systematische review benoemen we effectieve componenten van door verpleegkundigen gecoördineerde zorg. Allereerst zorgt het (gedelegeerd) voorschrijven en indien nodig verhogen van de dosering van medicijnen door verpleegkundigen voor een verlaging van bloeddruk en cholesterol. Wanneer de effecten van een groot aantal studies wordt samengevoegd, blijkt bovendien dat door verpleegkundigen gecoördineerde zorg een positief effect heeft op het aantal gestopte rokers. Overige vergelijkingen worden belemmerd door onderlinge verschillen in interventies en uitkomsten in de studies. Daarom bevelen we aan dat een algemene, universele definitie van door verpleegkundigen gecoördineerde zorg wordt ontwikkeld waarin de verschillende onderdelen benoemd worden. Hiermee wordt het vergelijken van studies vereenvoudigd en kennisontwikkeling beter mogelijk gemaakt.

In **Hoofdstuk 4** beschrijven we het doel en het studieontwerp van de RESPONSE-2 (Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists) studie. De RESPONSE-2 studie is opgezet om het effect vast te stellen van een samengestelde interventie waarbij drie leefstijl programma's werden aangeboden aan

patiënten met een coronaire hartziekte. De programma's werden in de eigen plaatselijke omgeving van de patiënten georganiseerd en waren gericht op stoppen met roken, gewichtsverlaging en verbeteren van lichaamsbeweging.

Patiënten in de interventie groep kregen naast de gebruikelijke zorg (hartrevalidatie, consult bij de cardioloog, vier consulten bij de verpleegkundige) ook een verwijzing naar tenminste één bewezen effectief leefstijlprogramma (Figuur 1). De verpleegkundige besprak met de patiënt diens voorkeur voor het programma en de volgorde van deelname. Door loting werd bepaald of patiënten het interventieprogramma mochten volgen.



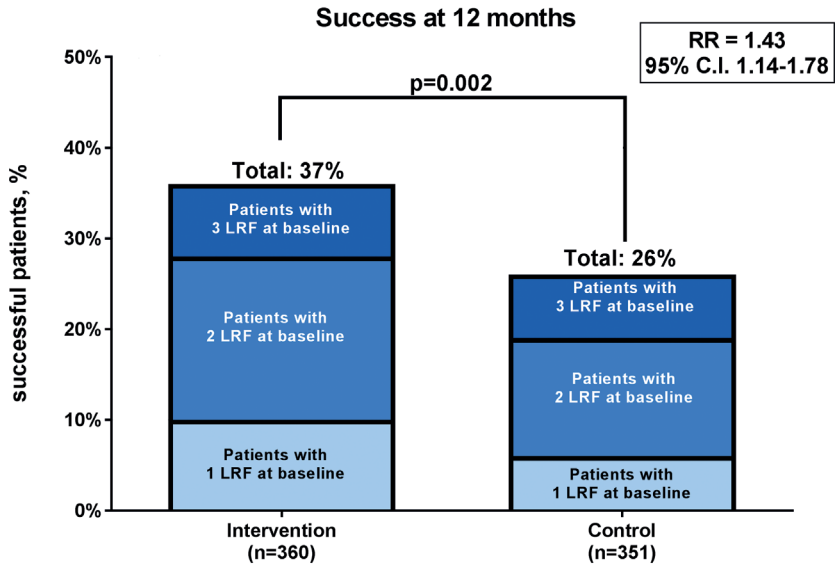
Figuur 1.
Stroomschema RESPONSE-2 studie

Het leefstijl interventie programma bestond uit drie onderdelen. In het stoppen met roken programma werd telefonische begeleiding geboden. Het gewichtsverlies programma bood de patiënt groepsbijeenkomsten inclusief toegang tot online faciliteiten. In het

beweegprogramma werd gebruik gemaakt van een accelerometer en bood een online coach ondersteuning. De inclusie van de 824 patiënten vond plaats tussen april 2013 en juli 2015 in 15 Nederlandse ziekenhuizen.

In **hoofdstuk 5** presenteren we de belangrijkste uitkomsten van de RESPONSE-2 studie.
Een jaar na ziekenhuisontslag bleek door verpleegkundigen gecoördineerde verwijzing naar tenminste één leefstijlprogramma effectiever om leefstijl risicofactoren te verbeteren dan wanneer alleen gebruikelijke zorg werd gegeven (Figuur 2). Het effect van het gewichtsverlies programma was het sterkst. We ontdekten daarnaast ook dat samenwonen met een partner in beide groepen geassocieerd was met een succesvolle uitkomst.

Het aantal patiënten in de interventiegroep dat gebruik maakte van het programma aanbod was hoog. Vijfentachtig procent van hen volgden een of meer leefstijlprogramma's.
Bij het vaststellen van het percentage patiënten met succes was een extra criterium dat bij een patiënt tenminste ten aanzien van één leefstijl risicofactor verbetering objectief kon worden vastgesteld en dat de overige twee leefstijl risicofactoren niet verslechterd mochten zijn.



Figuur 2.
Percentage patiënten met een succesvolle uitkomst en het aantal leefstijl gerelateerde risicofactoren (LRF), een jaar na ziekenhuisontslag.

In **Hoofdstuk 6** onderzochten we de gedelegeerde bevoegdheid aan verpleegkundigen om de dosering van medicatie aan te passen (titratie) op basis van de RESPONSE-1 data. De RESPONSE-1 studie liet een toename zien van het aantal patiënten dat de

streefwaarde voor LDL-cholesterol behaald had in de interventie groep in vergelijking met gebruikelijke zorg. Verondersteld werd dat titratie activiteiten van verpleegkundigen hieraan bijgedragen hadden. In onze analyse werd bevestigd dat door verpleegkundigen gecoördineerde (na)zorg voor patiënten met een hartinfarct geassocieerd kon worden met het vaker bijstellen van de dosering van medicatie en het bereiken van een gemiddeld hogere dosering.

DEEL 2: STOPPEN MET ROKEN

Het verband tussen roken en hart- en vaatziekten staat onomstotelijk vast. Daarom is stoppen met roken na een coronaire hartziekte een van de meest effectieve preventieve maatregelen die een patiënt kan nemen. Het zorgt voor een geschatte risicoverlaging van 33-50% op respectievelijk een herhaald infarct of overlijden, gemeten in studies met een follow-up tijd van minimaal twee jaar. Stoppen met roken is bijzonder moeilijk voor veel patiënten. Ongeveer de helft van de patiënten blijft roken na een ziekenhuisopname in verband met een coronaire hartziekte, zoals bij een hartinfarct. Daarom onderzochten wij kenmerken van succesvol gestopte rokers.

In **Hoofdstuk 7** presenteren we kenmerken van succesvol gestopte rokers in een gerandomiseerde studie (RESPONSE-1) in 11 Nederlandse ziekenhuizen. We selecteerden de rokers voor ziekenhuisopname bij een hartinfarct en analyseerden de rook- en stopstatus na ontslag en een jaar daarna. Deze studie laat vooral zien dat het meest belangrijke kenmerk van succesvol gestopte rokers is dat zij direct na ziekenhuisopname stoppen. Daarnaast waren zij vaker hoger opgeleid, was het voor hen vaker de eerste ziekenhuisopname voor een coronaire hartziekte, en behaalden zij een jaar na ziekenhuisontslag vaker de streefwaarden voor cholesterol en 'fysieke activiteit' volgens de richtlijn.

Hoofdstuk 8 richt zich op Europese patiënten met een coronaire hartziekte (EUROASPIRE IV). Aan deze grote Europese studie deden 78 ziekenhuizen uit 24 landen mee en werden in totaal 7998 patiënten geïnterviewd en onderzocht. De evaluatie van de cardiovasculaire risicofactoren en de behandeling vond plaats tussen zes maanden en drie jaar na ziekenhuisopname. Informatie over het rookgedrag werd verzameld door middel van een vragenlijst en objectief gemeten via de uitademingslucht met een smoking analyser. Tussen 1999 en 2013 (EUROASPIRE II-IV) blijft het percentage gestopte rokers rond de 50%. Dit ondanks strenger wordende tabaksontmoedigende maatregelen en betere beschikbaarheid van effectieve medicijnen ter ondersteuning van het stoppen met roken. Er zijn echter tussen de verschillende landen grote verschillen, zowel ten aanzien van de stoppercentages als de percentages patiënten die voorafgaand aan de

ziekenhuisopname rookte. Het percentage gestopte rokers per individueel land moet daarom gezien worden in het licht van de hoeveelheid rokers vóór de ziekenhuisopname en voorzichtigheid is geboden bij het vergelijken van de percentages gestopte rokers tussen landen. In vergelijking met patiënten met een coronaire hartziekte die bleven roken, gaven succesvol gestopte rokers vaker aan tevens de keuze voor gezonde leefgewoonten te maken, inclusief deelname aan het hartrevalidatie programma.

In **hoofdstuk 9** wordt dieper ingegaan op de kenmerken en voorkeuren van patiënten die succesvol stopten met roken in de RESPONSE-2 onderzoekspopulatie. We namen waar dat de meerderheid van de succesvol gestopte rokers één jaar na ziekenhuisontslag, in zowel de interventie als de controlegroep, tot de 'directe stoppers' behoorde. Deze patiënten stopten al tijdens de ziekenhuisopname en hadden zowel direct na ontslag, als 12 maanden daarna een negatief urine cotinine testresultaat. De studie laat ook zien dat succesvol gestopte rokers in vergelijking met patiënten die bleven roken minder vaak meededen aan het stoppen met roken programma en vaker aan een van de andere twee leefstijl programma's. Dit suggereert dat succesvol gestopte rokers gemotiveerd zijn om naast het stoppen met roken ook andere leefgewoonten te veranderen.

'Ik heb mijn leven weer opgepakt en toen ik thuiskwam was ik ook niet meer bang ofzo. Na mijn infarct heb ik stappen gezet richting een betere leefstijl. Ik was zelfstandig succesvol gestopt met roken en wilde meer gaan bewegen. Samen met mijn hond of mijn vrouw ga ik tegenwoordig elke dag een stuk wandelen of fietsen. Dat is gezellig en houdt me fit. Bewegen is nu een tweede natuur geworden. Sinds ik flink wat kilo's ben afgevallen met het gewichtsverlies programma uit RESPONSE-2 (Weight Watchers) merk ik dat ik meer energie krijg. Natuurlijk slik ik nu medicijnen, dat hoort er ook bij. Ik heb veel gehad aan de paar gesprekken met de verpleegkundige tijdens de hartrevalidatieperiode. Zij stimuleerde me van de leefstijlprogramma's gebruik te maken. Alleen was ik niet zover gekomen. Mijn risicofactoren kan ik nu zelf beter onder controle houden. Ik heb geen hartklachten meer, al ben ik wel wat sneller vermoeid.' (Dhr P. Sanders, 63 jaar)

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PhD Portfolio

PhD PORTFOLIO

Name PhD student: Marjolein Snaterse- Zuidam
PhD period: 2012-2018
Name PhD supervisor:
Prof. dr. RJG Peters,
Prof. dr. WJM Scholte op Reimer

	Year(s)	Workload ECTS
1.PhD Training		
Courses, seminars, workshops and master classes		
Scientific Writing in English for Publication	2013	1.5
Practical Biostatistics	2013	1.1
Basic Course in Legislation and Organisation for Clinical Researchers (BROK)	2012/2016	1.0
Clinical data management	2014	0.7
Advanced Topics in Biostatistics	2014	2.1
Qualitative Research	2016	1.9
Presentation at conference (oral or poster)		
CarVasZ, Ede, the Netherlands, Oral presentation	2013-2017	2.5
NVVC, Noordwijkerhout, the Netherlands, Poster Presentation	2014	0.5
EUROPREVENT, Lissabon, Portugal, Poster presentation	2015	1.0
EUROHEARTCARE, Dubrovnic, Croatia, Poster presentation	2015	1.0
ESC, Barcelona, Spain, Poster presentation	2016	0.5
ESC, Rome, Italy, Poster presentation	2016	1.0
EUROPREVENT, Malaga, Spain, Poster presentation	2017	1.0
Hartrevalidatie congres, the Netherlands, Oral presentation	2018	0.5
Visiting scientific conference		
EUROPREVENT, Dublin, Ireland	2012	0.5
Cardiac Rehabilitation congress, Amersfoort, the Netherlands	2012	0.25
ESC/EUROPREVENT, RAI, Amsterdam, the Netherlands	2013	0.5
American Heart Association, New Orleans, USA	2016	0,5
EUROHEARTCARE, Jonkoping, Sweden	2017	0,5
2.Teaching		
Lecturing		
Lecturer, School of Nursing, Faculty of Health, Amsterdam University of Applied Sciences (0.4 fte)	2012-present	12.0
Continuing Nursing Education, Dutch Society of Cardiovascular Nurses (NVHVV)	2014-2018	4.0
Teaching study nurses RESPONSE-2 trial Utrecht	2013-2016	3.0
Tutor Working group, Master Evidence Based Practice, University of Amsterdam	2012-2013	4.0
Journal Club School of Nursing, Faculty of Health, Amsterdam University of Applied Sciences	2012-present	2.0
Student coaching		
Master thesis, Marloes Klein Hesseling, Clinical Information and Health Technology, University of Amsterdam	2015	2.0

	Year(s)	Workload ECTS
3.Parameters of Esteem		
Grands, Awards and Prices		
Dutch Organisation for Scientific Research NWO, PhD. Grant	2014-2018	
Faculty of Health, Amsterdam University of Applied Sciences, Winner research award	2015	
EuroHeartCare, Dubrovnik, Croatia, Best poster category, moderated poster session	2015	
ESC, Barcelona, Spain, Best e-poster category	2016	
Other		
Chair Scientific committee Dutch Society of Cardiovascular Nurses (NVHVV)	2014-present	4.0
Member Education Committee Council on Cardiovascular Nursing and Allied Professions (CCNAP)	2017-present	1.0
Member Alliantieraad Nederland Rookvrij/Dutch Alliance for a Smoke Free Society (on behalf of NVHVV)	2015-present	1.0

Dankwoord

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De overige leden van de promotiecommissie, Prof. dr. R.J. de Winter, Prof. dr. K. Stronks, Prof. dr. R.J. de Haan, Prof. dr. F.L.J. Visseren, Prof. dr. J.W. Deckers, dr. M.J. Lenzen en dr. E.P. Moll van Charante wil ik bedanken voor het beoordelen van mijn proefschrift en jullie bereidheid zitting te nemen in de promotiecommissie.

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Alle cardiologen en verpleegkundigen van de RESPONSE-2 studiecentra. Zonder jullie was er geen RESPONSE-2 studie en was dit boekje er niet. In totaal 824 patiënten includeren en een heel jaar opvolgen is een heel prestatie. Ik kijk terug op een allerbeste samenwerking en op vruchtbare RESPONSE-2 bijeenkomsten met alle studieverpleegkundigen in Utrecht.

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Alle medeauteurs, Mattie Lenzen, Jaap Deckers, Gerben ter Riet, Patricia Jepma, Jos Dobber, Madelon Minneboo en Bianca Buurman wil ik bedanken voor het delen van hun kennis en waardevolle bijdrage aan de manuscripten. In addition I would like to thank Kornelia Kotseva, Dirk de Bacquer and Catriona Jennings for the enjoyable collaboration which resulted in a EUROASPIRE publication.

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Het leven is mooi, samen verder!

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Curriculum Vitae

Marjolein Zuidam was born in Soest on July 4, 1973. After having finished her secondary education in 1990, she started her nursing education in Leiderdorp (St. Elisabeth hospital), Leiden area. She worked as a nurse at the Vrije Universiteit Medical Centre (VUmc), Amsterdam, and after being trained in Intensive Care Nursing, she worked at the VUmc IC- unit from 1999-2006. She developed a real enthusiasm for tutoring students and teaching. Consequently, she took part in a two-year Higher Education for Health Care Professionals Programme (HGZO, Vrije Universiteit, Amsterdam) from 2002-2004.

From 2004 she worked as a lecturer at the Amsterdam University of Applied Sciences (Nursing Studies). Between 2006-2008 she studied Evidence Based Practice at the University of Amsterdam. Her master thesis, in collaboration with the Dutch Working Group on Infection Prevention (WIP), resulted in her first international research publication.

In 2012 she started her doctorate course at the Amsterdam University of Applied Sciences and University of Amsterdam under supervision of prof. dr. R.J.G. Peters and prof. dr. W.J.M. Scholte op Reimer. Marjolein combined her doctorate course with lecturing at the Amsterdam University of Applied Sciences (Hogeschool van Amsterdam). She is thesis coordinator of the bachelor programme and coordinates the Critical Care master programme.

Marjolein represents the scientific committee of the Dutch Society of Cardiovascular Nurses (NVHVV) and she is currently a member of the International Education Committee (Council on Cardiovascular Nursing and Allied Professions, CCNAP (ESC)).