Rethinking management of risk factors in secondary prevention of cardiovascular disease

Snaterse, M.

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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. 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.

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. The health benefits from improving lifestyle-related risk factors are at least as great as the benefits of pharmacological secondary prevention. 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. Data from four consecutive EUROASPIRE registries in Europe in fact showed a trend of increasing overweight and obesity among patients with CAD.

Nurse-coordinated outpatient clinics are now common and nurses are engaged in cardiovascular risk management. Yet, their impact on lifestyle risk factors is limited. 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. 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.

We aim to evaluate three community-based comprehensive lifestyle programmes which have previously been validated 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/m², the criterion of BMI ≥27 kg/m² was selected to ensure that there is a clear indication for weight reduction. A weight loss of ≥5%, as recommended by the current guideline is equivalent to a reduction from 27 to ≤25.65 kg/m².

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. 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.
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. 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, 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

<table>
<thead>
<tr>
<th>Patient categories based on lifestyle risk factors at baseline</th>
<th>Definition of success</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Smoking only</td>
<td>non-smoking status³</td>
</tr>
<tr>
<td>2. BMI ≥27 kg/m² only</td>
<td>≥5% weight reduction³</td>
</tr>
<tr>
<td>3. Physical inactivity only</td>
<td>increase of &gt;10% in 6MWD³</td>
</tr>
<tr>
<td>4. Smoking and BMI ≥27 kg/m²</td>
<td>non-smoking status and/or ≥ 5% weight reduction³</td>
</tr>
<tr>
<td>5. BMI ≥27 kg/m² and Physical inactivity</td>
<td>≥5% weight reduction and/or increase of &gt;10% in 6MWD³</td>
</tr>
<tr>
<td>6. Smoking and Physical inactivity</td>
<td>non-smoking status and/or increase of &gt;10% in 6MWD³</td>
</tr>
<tr>
<td>7. BMI ≥27 kg/m², Smoking and Physical inactivity</td>
<td>≥5% weight reduction, non-smoking status and increase of &gt;10% in 6MWD³</td>
</tr>
</tbody>
</table>

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 (Luchtsinaal®), 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 – Luchtsinaal® (www.luchtsinaal.nl)
Luchtsinaal® 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 transtheoretical 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 MacNew21, HADS22 and the standards of physical activity based on the WHO23, 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/m² only
3. Physical inactivity only
4. Smoking and BMI ≥27 kg/m²
5. Smoking and physical inactivity
6. BMI ≥27 kg/m² and physical inactivity
7. Smoking, BMI ≥27 kg/m² 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 <25 kg/m² will be classified as no deterioration.

An increase of ≤2.5% in the BMI or remaining <25 kg/m² 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/m²), 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, 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: $\alpha=0.05$, $\delta=0.096$, 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.\textsuperscript{28,29} Jorstad et al. found significant improvement in LDL cholesterol and blood pressure levels, with nurse led risk factor management in outpatient clinics.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

\textit{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.\textsuperscript{30,31} The medical application of the Weight Watchers\textsuperscript{®} programme has been studied in primary prevention in general practices.\textsuperscript{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\textsuperscript{®} programme, have been found to be accurate tools in estimating energy expenditure and effective tools in improving physical activity.\textsuperscript{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 DirectLife® 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.

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


