RESPONSE study: Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists

Study design, objectives and expected results

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Background. Patients with coronary artery disease are at high risk of coronary events and death, but effective secondary prevention can reduce this risk. There is a gap between guidelines on secondary prevention and the implementation of these measures, which could potentially be reduced by nurse led prevention clinics (NLPC).

Objectives. The aim of the current study is to quantify the impact of NLPC on the risk of cardiovascular events in patients with established coronary artery disease.

Methods. A randomised, multicentre clinical trial of NLPC in addition to usual care or usual care alone in post-acute coronary syndrome patients. (*Neth Heart J* 2009;17:322-8.)

Keywords: cardiovascular diseases, aetiology, prevention & control, coronary disease, complications, drug therapy, health behaviour, lifestyle, nurse's role, risk factors

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Patients with established coronary artery disease (CAD) are at particularly high risk of subsequent coronary events and death. Effective secondary prevention can reduce this risk. Modification of cardiovascular risk factors can reduce the incidence of recurrent myocardial infarction, decrease the need for interventional procedures, improve quality of life, and effectively extend survival.¹

Comprehensive guidelines for the long-term management of patients with CAD have been issued by the American Heart Association/American College of Cardiology (AHA/ACC)² and the European Society of Cardiology (ESC).³ Effective secondary prevention includes interventions to change behaviour and modify lifestyle (smoking cessation, regular exercise, weight control and healthy food choices) and pharmaceutical interventions (antiplatelet agents, statins, β -blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers).²⁻⁵ In a systematic review of lifestyle interventions in patients with CAD, a marked reduction in mortality risk was associated with smoking cessation (35-50%), physical activity (20-30%), moderate alcohol consumption (15-20%) and healthy dietary choices (15-45%).⁶ Risk reductions were seen in both CAD patients and in general population cohorts.⁶ Different pharmacological interventions have also been shown to reduce mortality risk in CAD patients, demonstrating a risk reduction associated

with low-dose aspirin (18%),⁷ statins (21%),⁸ β -blockers (23%)⁹ and ACE inhibitors (26%).¹⁰ Combined, these interventions could potentially reduce the risk of recurrent events by more than two thirds.¹¹

At present, a considerable gap exists between guidelines on secondary prevention and the actual implementation of these measures.¹² The results of the EUROASPIRE III survey (European Action on Secondary Prevention by Intervention to Reduce Events)¹³ have shown that the implementation of secondary prevention is seriously lagging behind. Compared with the results of the earlier EUROASPIRE I and II data,^{12,14} EUROASPIRE III showed some improvement in lipid management, but no change in the prevalence of smoking and an inverse trend in the prevalence of obesity/central obesity and blood pressure control, despite increased use of antihypertensive medication. It also showed an increase in the prevalence of diabetes, both self-reported and undetected, and a deterioration in therapeutic glucose control. These findings led to the statement that professional comprehensive multidisciplinary ambulatory preventive cardiology programmes should be available for all coronary patients, and the call for prevention centres.¹³

One approach may be to create nurse led prevention clinics (NLPC). Such clinics have now been introduced in different locations globally, but their impact is largely unknown, as no study has quantified the effect of a comprehensive secondary care (hospital based) NLPC. In a meta-analysis of secondary prevention programmes, a wide variety of programmes were shown to have variable effects in improving health outcomes in patients with coronary disease, mainly in primary care based programmes or hospital based programmes focusing on a small number of risk factors.¹⁵ No studies included in the meta-analysis investigated comprehensive nurse led hospital based programmes targeting all modifiable risk factors. Overall, secondary prevention programmes were shown to positively affect (1) the processes of care (risk factor profiles and use of proven efficacious therapies), (2) functional status, and (3) quality of life for participants. In addition, such programmes reduced myocardial infarctions by 17% during a median follow-up of 12 months. The mortality reduction that was associated with participation in secondary prevention programmes (15% overall and 47% at two years) became apparent with longer follow-up and was of similar magnitude in recently published trials and in trials published more than two decades ago (before the widespread use of contemporary medical therapies).¹⁵

A randomised study of nurse led secondary prevention clinics in primary care in the United Kingdom has been described by Murchie et al.¹⁶ A total of 1343 patients (673 with intervention and 670 controls) with stable coronary artery disease were seen every two to six months for the duration of one year at the nurse led clinics in general practice. The clinics promoted medical

and lifestyle components with the focus on risk assessment, medication, blood pressure, lipid profile, physical activity, smoking and diet. Data were collected after one year and after four years (mean follow-up 4.7 years). After 4.7 years the cumulative mortality in interventions vs. controls was 14.5 vs. 18.9% with a relative risk of 0.78; the cumulative coronary event rate was 14.2 vs. 18.2% with a relative risk of 0.80.¹⁶

For secondary (hospital based) care, no such studies exist. Because of the limited evidence of efficacy, funding for prevention clinics is not structural and is difficult to obtain. Insurance companies generally require solid evidence, preferably local, before structural funding is considered.

We have designed the RESPONSE study to quantify the impact of nurse led prevention clinics on cardiovascular risk in patients with established coronary artery disease.

Study design

Patient selection

Patients with documented evidence of coronary artery disease are selected during hospitalisation for an acute coronary syndrome.

Inclusion criteria are:

- Age 18-80 years;
- Hospitalisation less than 8 weeks before inclusion for a documented acute coronary syndrome (ACS), irrespective of ST-segment shift or cardiac marker elevation.

Exclusion criteria are:

- NLPC visits not feasible;
- Patient not available for follow-up;
- Surgery, percutaneous coronary intervention or other interventions expected within 8 weeks;
- Life expectancy considered limited (≤ 2 years);
- Previously enrolled in NLPC;
- NYHA class III or IV heart failure.

Informed consent and randomisation

Informed consent will be obtained during hospitalisation or shortly after for randomisation and for collection of baseline data and follow-up data at six and 12 months. Patients are informed about the subject of the study, i.e. secondary prevention of coronary disease, but the details about the comparison between the two study groups will not be disclosed. The informed consent information letter to the patients in the RESPONSE study contains information about the nature of the study (secondary prevention of coronary disease), randomisation and data collection at baseline, and at 6 and 12 months. It also states that some aspects of the study will not be disclosed before the completion of the study, but that these aspects convey no extra risk and include no experimental treatments:

'Participants in this scientific study are randomised to one of two groups. This concerns a second observation included in the study that would, if fully explained, influence the outcomes. There are no disadvantages or extra risks associated with this aspect of the study.'

This type of design has previously been applied in other studies in the Netherlands,¹⁷ and is done in order to prevent a 'Hawthorne effect',¹⁸ i.e. change in behaviour or compliance in patients and health professionals as a consequence of the awareness of being observed. At

the end of the study, all information about this aspect of the study will be provided.

After informed consent has been obtained, patients are randomised to either the NLPC in addition to usual care (intervention group) or usual care alone (control group). Randomisation is performed per patient by a stratified randomisation protocol on the study website (www.responsestudie.nl).

Treating specialists (i.e. cardiologist) are instructed that the study will take place in their medical centre and are informed about the study question. Individual

Table 1. Study parameters, definitions, targets, strategies and measurements.

Parameter	Definition ⁴	Target ⁴	Strategy	Measurement
Smoking	Current smoker yes/no	Smoking cessation	Counselling/support Educational material	Self-reported
Physical exercise	Minimal intensity equivalent to brisk walk	≥30 min 5x/week	Counselling/support Educational material	Self-reported
Weight/fat distribution	BMI Waist circumference	♂: BMI ≤25 kg/m ² or waist circumference <94 cm ♀: BMI ≤25 kg/m ² or waist circumference <80 cm	Counselling/support Educational material	Height/Weight Waist circumference
Hypertension	SBP >140 mmHg, DBP >90 mmHg measured twice with >24 hour interval	SBP<140 mmHg	Active screening Counselling/support Educational material Referral to treating specialist if outside target range	Blood pressure (right and left arm)
Dyslipidaemia	TC ≥5 mmol/l LDL ≥2.5 mmol/l HDL ≤1.0 mmol/l TG ≥2.0 mmol/l	LDL ≤2.5 mmol/l HDL ≥1.0 mmol/l TG ≤2.0 mmol/l	Active screening Counselling/support Educational material Referral to treating specialist if outside target range	Fasting venous blood sample: TC, LDL, HDL, TG
Antithrombotic therapy	All patients should be treated with adequate antithrombotic therapy	Maximum adherence to treatment	Interview about compliance	Self reported
Medication adherence	Maximum adherence to prescribed medication	Maximum adherence to medication	Interview about compliance Counselling/support Referral to treating specialist	Self reported
Quality of Life				Questionnaires: SF-36 MacNew

BMI=body mass index, SPD=systolic blood pressure, DBP=diastolic blood pressure, TC=total cholesterol, LDL=low-density lipoproteins, HDL=high-density lipoproteins, TG=triglycerides.

cardiologists are informed if patients attending their outpatient clinic are included in the study, but are not informed about the result of the randomisation.

The general practitioners whose patients are included in the study will be informed that their patients are included in the study and about the data collection. They will not be informed about the comparison investigated in the study. When a patient is randomised to the NLPC, the general practitioner will be informed that the patient is attending the NLPC, but not that this is a part of the study.

The RESPONSE study has been approved by the Medical Ethics Board of the University of Amsterdam, the Netherlands.

Treatment of study patients

All patients, irrespective of randomisation, will receive usual care, including outpatient visits to a cardiologist after discharge. Cardiologists are encouraged to provide optimal care according to national (CBO)⁴ guidelines and are instructed to take all the necessary preventive measures, irrespective of visits to the NLPC. The care provided to patients randomised to the control group (thus receiving no study intervention and only attending data collection visits) is not influenced by the study.

Nurse led prevention clinic

Patients randomised to the intervention group are referred to the NLPC in addition to receiving usual care. That the reason for the referral is the result of randomisation is not communicated to the patients.

Referral to an NLPC includes up to four visits during the first six months after inclusion, at week 2, week 7, week 12, and week 17 after baseline with a time window of 10 days. At each visit, patients are seen by a trained nurse specialist. The NLPC follows a protocol based on national guidelines,⁴ focusing on (1) healthy lifestyles, (2) biometric risk factors and (3) medication adherence. Main targets for healthy lifestyles are smoking cessation, adequate physical exercise and healthy weight/fat distribution. In addition, general lifestyle advice will be given (including dietary advice and educational material concerning healthy food choices). Targets for biometric risk factors are blood pressure control, lipid control, screening for diabetes in non-diabetics, and glycaemic control in diabetics and insulin resistant individuals. If blood pressure control or lipid control is inadequate, medication is titrated in cooperation with the treating specialist or the patient is referred to the treating specialist. Medication adherence targets maximal adherence to prescribed medication. Adequate anti-thrombotic therapy and statin use is specifically checked during each NLPC visit. If use has been discontinued since the previous visit, reasons for discontinuation are documented and if possible the therapy is reinitiated. Tables 1 and 2 show the definitions, targets, strategies and measurements for the different NLPC parameters.

Table 2. Diabetes mellitus.

	Capillary (mmol/l)	Venous (mmol/l)
Definition²²		
Normal		
- Fasting glucose	<5.6	<6.1
- Non-fasting glucose	<7.8	<7.8
Impaired		
- Fasting glucose	>5.6 and <6.0	>6.1 and <6.9
Diabetes mellitus		
- Fasting glucose	>6.0	>6.9
- Non-fasting glucose	>11.0	>11.0
Treatment targets		
Fasting glucose	4.5-8	4-7
Glucose 2 hours postprandial	<9	<9
HbA1c (%)		<7
Strategy		
Active screening		
Counselling/support		
Educational material		
Referral to treating specialist if outside target range		

Training of nurses

Nurses contributing to the prevention clinic are trained specialist nurses or nurse practitioners with experience in the care of cardiac patients. They are selected by the local investigators and receive at least one day of central and one day local individual training in addition to investigators meetings. All nurses are given a three-day course in motivational interviewing at the Department of Medical Psychology, Academic Medical Center in Amsterdam, the Netherlands, and are given the opportunity to participate in national and international cardiovascular nursing trainings and congresses.

Follow-up and data collection

All patients (regardless of study group) are seen at baseline, and at six- and 12-month follow-up for data collection. At baseline, gender, educational status, work status, civil status, the occurrence of life events in the previous 12 months, ethnicity, stress status, cardiovascular history, smoking status, dietary status, levels of physical exercise, weight, height, waist circumference, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, HbA1c, and medication are recorded. At 6- and 12-month follow-up, all adverse and serious adverse events since the last visit are recorded, in addition to the occurrence of life events in the previous 6 months, stress status, smoking status, dietary status, level of physical exercise, weight, waist circumference, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, HbA1c and medication. All blood measure-

ments are taken after a minimum of 8 hours of fasting. Data collection at baseline and at 6- and 12-month follow-up is performed independently of the NLPC by research personnel not involved in the treatment of the patient, and no interventions take place during these data collection sessions.

Patients randomised to the NLPC have additional data collected during the four intervention visits in the first six months. Adverse events, smoking status, dietary status, level of physical exercise, weight, waist circumference, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose and HbA1c are recorded. The current medication is also recorded, in addition to any changes in medication carried out at the NLPC and any referrals initiated during the NLPC in patients with inadequate blood pressure, lipid and/or glycaemic control.

Between six months and 12 months follow-up, there are no visits to the NLPC.

Outcomes and statistical analysis

The primary outcome of the study is the difference in the Copenhagen Risk Score¹⁹ between the two groups at 12-month follow-up. The Copenhagen Risk Score includes nine factors: gender, diabetic status, previous MI, familial predisposition for MI, total cholesterol, HDL cholesterol, systolic blood pressure, BMI and smoking status, and predicts the risk of acute myocardial infarction during the following ten years.

Secondary outcomes are changes in individual risk factors, changes in alternative risk scores at 12-month follow-up relative to baseline, six-month follow-up relative to baseline, 12-month follow-up relative to six-month follow-up, and changes in quality of life. Risk factors consist of smoking status, exercise status, BMI, waist circumference, blood pressure, lipid profile, glucose parameters and diabetic status. Details of individual risk factors are described in table 3. Risk scores consist of the Copenhagen Risk Score (at six months), Europa Score, PROCAM Score and Euroscore. Changes in quality of life at 6- and 12-month follow-up relative to baseline and between groups are measured with questionnaires SF-36 and MacNew.

Sample size considerations

A sample size of at least 533 patients is needed in both groups for detecting differences of at least 25% at conventional levels of type 1 and type 2 errors (two-sided $\alpha = 0.05$, $\beta = 0.2$) in the Copenhagen Risk Score, in addition to prevalence of lifestyle, other risk factors and use of prophylactic drug therapies.

Data analysis

Data are recorded and stored on dedicated case report forms, and are duplicated in a central electronic database. Continuous variables will be analysed using the two-sample t-test, categorical data using Fisher's exact test.

Table 3. Secondary endpoints.

Smoking status
Exercise status
Body mass index
Waist circumference
Blood pressure
- Systolic
- Diastolic
Glucose parameters
- HbA1c
- Fasting glucose
Lipid profile
- Total cholesterol
- HDL
- LDL
- Triglycerides
- ApoB/apoA1 ratio

Change in diabetes status

The following diabetic secondary endpoints will be considered:

- Incidence of diabetes among patients without diabetes at baseline
- Incidence of diabetes and glucose intolerance among patients with normal glucose tolerance at baseline
- Incidence of diabetes among patients with glucose intolerance at baseline
- Resolution of glucose intolerance among patients with glucose intolerance at baseline

HDL=high-density lipoproteins, LDL=low-density lipoproteins.

Timelines

The inclusion of patients into the study is estimated at 100 per centre (calculated with ten participating centres). Follow-up is one year for each individual patient. Per centre, the study duration includes three to six months of preparation, 18 months of inclusion and 12 months of follow-up, to a total of at least 33 months. The total duration of the study will be four years, including analysis of the results.

Discussion

Methodological considerations and the Hawthorne Effect

A methodological problem in this type of randomised clinical trial is that when patients and physicians are aware of the fact that their actions are being observed and recorded, this can induce behavioural changes in both groups; this is known as the Hawthorne effect. In this study, complete knowledge as to receiving or not receiving the nurse's support could exercise a marked influence on the outcome parameters in both the intervention group and the control group.

From a methodological point of view it is therefore preferable *not* to give complete information of the nature of the comparison to the patients and treating physicians. However, due to the design of the study and regulations applying to scientific research, it is required to inform patients about randomisation, about data collections and about the fact that parts of the information about the study will become available to them only at the completion of the study.

Patients in both the control and the intervention group are therefore not informed about the nature of the intervention, and the NLPC is offered as a part of usual care. Treating specialists and general physicians are also not explicitly informed about the comparison between NLPC in addition to usual care and usual care alone. Treating specialists are informed about the study, the objective of the study and the comparison, but will not be informed about the result of the individual randomisations in their own outpatients. General physicians are informed that their patients are participating in the study, but are not informed about the comparison between the two groups or that the NLPC is part of the study.

The study design chosen to minimise the Hawthorne effect may be compromised if patients communicate their individual experiences to other patients included in the study. We did not incorporate any specific measures to prevent this. However, this potential confounder is examined with a questionnaire after completion of the study.

Choice of primary outcome parameter

The RESPONSE study does not include long-term follow-up. Ideally, total and cardiovascular mortality and morbidity rates should be assessed after follow-up of several years. An alternative to a prolonged follow-up is to assess risk of cardiovascular events using a validated risk model. However, there are currently no validated risk prediction models available for patients with established CAD in the secondary prevention setting.

The population from which the Copenhagen Risk Score was developed mainly consisted of individuals without established atherosclerotic disease, but did include 234 individuals with a previous myocardial infarction (2% of 11,765 individuals).¹⁹ This score may therefore be the most suitable for use in the RESPONSE study and has been used previously for quantification of preventive interventions in a non-randomised observation.²⁰ It must be noted that the true prognosis in ACS patients is determined by a number of additional factors (not included in the Copenhagen Risk Score) that are related to the extent of coronary disease and its complications.²¹

The immediate and potentially maximal impact of the NLPC in the RESPONSE study is seen at six-month follow-up (figure 1). Attrition is expected on this impact; thus, by selecting the main endpoint of the RESPONSE study at follow-up at 12 months, at

Figure 1. Graph depicting expected changes in risk levels, both of individual parameters and of the comprehensive Copenhagen Risk Score that is used as the primary endpoint in the study. R6c=risk level at six months in control group, R6i=risk level at six months in intervention group, R12c=risk level at 12 months in control group, R12i=risk level at 12 months in intervention group, L1=loss in control group, L2=loss in intervention group, A=result in control group, B=result in intervention group.

least an important part of the late loss-of-effect can be observed. The use of follow-up at 12 months as endpoint may underestimate the effect of the intervention on lifetime risk, but further attrition of the effect of the intervention may conversely also lead to an overestimation of NLPC-induced effects on prognosis. Our outcome results at 12 months follow-up are therefore suited to quantify the impact of an NLPC on modifiable risk factors for atherosclerosis.

Patient reporting bias

Smoking parameters and medication compliance will not be objectively documented. However, since data collection at baseline and at six- and 12-month follow-up is conducted by research personnel not involved in the NLPC visits of the individual patients, interviewer bias is minimised in both the control and the intervention group.

Limitations

This study only includes patients who have suffered an ACS. Other groups of cardiovascular disease could possibly also benefit from NLPC. The potential role of NLPC in other patient groups will have to be explored in future trials.

Expected results

We hypothesise that at six-month follow-up, patients randomised to the NLPC will have a significantly lower cardiovascular risk score than controls. This risk reduction is hypothesised to be achieved through a composite of lifestyle changes and pharmacological interventions. After 12 months, attrition of this effect

is expected, but the risk score of the patients randomised to the NLPC is still expected to be significantly lower than that of the control group (figure 1).

In June 2009, 733 patients had been included in the study.

Consequences for current practice

The targets in secondary prevention after an ACS are not being systematically addressed in the clinical centres in the Netherlands. If shown to be effective, NLPCs may play an important part in preventive cardiology programmes and should probably be made available to all coronary patients. In addition, other groups of patients with atherosclerotic disease could potentially benefit from a tailored NLPC.

If a relevant risk reduction by an NLPC can be demonstrated, this will furthermore provide a basis for the implementation and funding of such clinics in all hospitals where ACS patients are treated. In addition, the outcome of the RESPONSE study may stimulate the use of nurse practitioners in other areas of clinical medicine.

Trial registration number

NTR TC=1290.

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References

- Allen JK. Cholesterol management: an opportunity for nurse case managers. *J Cardiovasc Nurs* 2000;14:50-8.
- Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update: Endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363-72.
- De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *EurHeart J*. 2003;24:1601-10.
- Burgers JS, Simoons ML, Hoes AW, Stehouwer CD, Stalman WA. Guideline 'Cardiovascular Risk Management. *Ned Tijdschr Geneesk*. 2007;151:1068-74.
- Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358:1547-59.
- Iestra JA, Kromhout D, van der Schouw YT, Grobbee DE, Boshuizen HC, van Staveren WA. Effect Size Estimates of Lifestyle and Dietary Changes on All-Cause Mortality in Coronary Artery Disease Patients: A Systematic Review. *Circulation*. 2005;112:924-34.
- Weisman SM, Graham DY. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. *Arch Intern Med*. 2002;162:2197-202.
- LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-6.
- Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318:1730-7.
- Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. *Am J Med*. 2003;115:473-9.
- Yusuf S. Two decades of progress in preventing vascular disease. *Lancet*. 2002;360:2-3.
- EuroAspire II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J*. 2001;22:554-72.
- Wood D. EuroAspire III, Euro Heart Survey on Preventive Cardiology study. *Eur Soc Cardiol, Oral Presentation* 2007.
- Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. EUROASPIRE I and II Group. European Action on Secondary Prevention by Intervention to Reduce Events. *Lancet*. 2001;357:995-1001.
- Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta-analysis: secondary prevention programmes for patients with coronary artery disease. *Ann Intern Med*. 2005;143:659-72.
- Murchie P, Campbell NC, Ritchie LD, Simpson JA, Thain J. Secondary prevention clinics for coronary heart disease: four year follow up of a randomised controlled trial in primary care. *BMJ*. 2003;326:84.
- Wiggers LC, Smets EM, Oort FJ, Storm-Versloot MN, Vermeulen H, van Loenen LB, et al. Adherence to nicotine replacement patch therapy in cardiovascular patients. *Int J Behav Med*. 2006;13:79-88.
- Braunholtz DA, Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol*. 2001;54:217-24.
- Thomsen TF, Davidsen M, Ibsen H, Jorgensen T, Jensen G, Borch-Johnsen K. A new method for CHD prediction and prevention based on regional risk scores and randomized clinical trials; PRECARD and the Copenhagen Risk Score. *J Cardiovasc Risk*. 2001;8:291-7.
- Sprangers RLH, Stam F, Smid HEC, Stehouwer CDA, Hellemans IM. Multidisciplinary structured lifestyle intervention reduces the estimated risk of cardiovascular morbidity and mortality. *Neth Heart J*. 2004;12:443-9.
- Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A Validated Prediction Model for All Forms of Acute Coronary Syndrome: Estimating the Risk of 6-Month Post-discharge Death in an International Registry. *JAMA*. 2004;291:2727-33.
- Rutten G, De Grauw WJC, Nijpels G, Goudswaards AN, Uitewaal PJM, Van der Does FEE, et al. NHG-Standaard Diabetes Mellitus type 2. *HuisartsWet*. 2006;49:137-52.

Appendix 1. Members of the RESPONSE study group.

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