Original research

Weight management and determinants of weight change in patients with coronary artery disease

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ABSTRACT

Objective To study the effects of a comprehensive secondary prevention programme on weight loss and to identify determinants of weight change in patients with coronary artery disease (CAD).

Methods We performed a secondary analysis focusing on the subgroup of overweight CAD patients (BMI ≥27 kg/m^2) in the Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists-2 (RESPONSE-2) multicentre randomised trial. We evaluated weight change from baseline to 12-month follow-up; multivariable logistic regression with backward elimination was used to identify determinants of weight change.

Results Intervention patients (n=280) lost significantly more weight than control patients (n=257) (−2.4±7.1 kg vs −0.2±4.6 kg; p<0.001). Individual weight change varied widely, with weight gain (≥1.0 kg) occurring in 36% of interventions versus 41% controls (p=0.21). In the intervention group, weight loss of ≥5% was associated with higher age (OR 2.94), lower educational level (OR 1.91), non-smoking status (OR 2.92), motivation to start with weight loss directly after the baseline visit (OR 2.31) and weight loss programme participation (OR 3.33), whereas weight gain (≥1 kg) was associated with smoking cessation ≤6 months before or during hospitalisation (OR 3.21), non-Caucasian ethnicity (OR 2.77), smoking at baseline (OR 2.70), lower age (<65 years) (OR 1.47) and weight loss programme participation (OR 0.59).

Conclusion The comprehensive secondary prevention programme was, on average, effective in achieving weight loss. However, wide variation was observed. As weight gain was observed in over one in three participants in both groups, prevention of weight gain may be as important as attempts to lose weight.

Trial registration number NTR3937.

INTRODUCTION

Overweight is a global health problem and highly prevalent (70%–80%) in patients with established cardiovascular disease (CVD).[1] Weight loss interventions have been shown to achieve meaningful weight loss of 5%–10%, which is associated with a clinically significant reduction of CVD risk.[2 3] Few such interventions, however, can be delivered on a large scale.[4]

In the setting of primary prevention, referral to a commercial weight loss programme (Weight Watchers) has been demonstrated to be effective in achieving meaningful weight loss.[5] An advantage of such a commercial intervention is that it is widely available in many countries at low cost. We recently investigated this weight loss programme as part of a comprehensive secondary prevention strategy in the Randomised Evaluation of Secondary Prevention by Outpatient Nurse-SpEcialists-2 (RESPONSE-2) trial. We found that in patients with coronary artery disease (CAD), a combination of nurse-coordinated care and referral to up to three widely available community-based lifestyle programmes, on top of usual care, is significantly more effective in improving at least one lifestyle-related risk factor (LRF) when compared with usual care alone.[6] The lifestyle programmes addressed weight reduction (Weight Watchers), promoting physical activity (Philips DirectLife) and smoking cessation (Luchtsignaal), and referral was dependent on the patients' risk profile and preferences. The difference in the primary outcome was mainly driven by improvements in weight reduction.

In this secondary analysis, we aimed to rigorously evaluate the effects of referral to the comprehensive intervention on weight change and to identify determinants associated with weight change.

METHODS

Study design

We used data on a subgroup of overweight CAD patients (body mass index (BMI) ≥27 kg/m^2) from the RESPONSE-2 trial, a multicentre randomised controlled trial conducted in the Netherlands. Study methods and main results have been published and are summarised further.[6 7]

Patient population

Eligible patients had been hospitalised for CAD and/or underwent revascularisation. For the main trial, we included patients with at least one of three LRFs: (1) smoking at baseline or stopped ≤6 months before hospitalisation, (2) overweight (BMI ≥27 kg/m^2) and (3) self-reported physical inactivity (≤150 min of moderate intensity physical activity per week) and were willing to attend any of the lifestyle programmes. The current analysis excluded patients with a BMI<27 kg/m^2, as the study protocol allowed only individuals with a BMI ≥27 kg/m^2 for participation in the weight loss programme.

Usual care

All patients received usual care. This included visits to the cardiologist and/or other specialists, cardiac

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rehabilitation and up to four visits to a nurse-led secondary prevention programme. Cardiac rehabilitation consisted of up to 12 weeks of outpatient physical rehabilitation and counselling on secondary prevention, work resumption and psychological support. The nurse-led secondary prevention programme addressed healthy lifestyles, drug-treated risk factors and medication adherence, according to national and international guidelines.[8–10] We encouraged patients to bring their partners to counselling sessions.

Intervention

In addition to usual care, patients and their partners in the intervention group were offered free participation in up to three community-based lifestyle programmes to achieve weight reduction (Weight Watchers), increase physical activity levels (Philips DirectLife) and smoking cessation (Luchtsignaal). Specifics of the lifestyle programmes have been described previously and are outlined in the online appendix.[7] Patient preferences were leading in the choice of programme(s), the number of programmes followed and the sequence and duration. Programmes were offered unmodified, as they were available in the community.

Patient and public involvement

RESPONSE-2 was developed based on experiences with RESPONSE-1 including an evaluation study involving patients and nurses.[11] Results from the main paper have been distributed among patients and nurses.

Data collection and measurements

Nurses collected demographic and medical data at baseline (first outpatient clinic visit ≤8 weeks after hospital discharge) and at 12-month follow-up. Patients' motivation towards lifestyle change ('motivated'/'not motivated') was assessed with motivational interviewing during each outpatient clinic visit. Subsequently, for interventions, motivation was ranked as 'motivated for short-term (<1 month) lifestyle improvement' or 'ambivalent'. Weight was measured in light clothes without shoes using bioimpedance scales. Physical activity level was assessed through self-report based on WHO recommendations and by completing a 6 min walking distance (6MWD) test.[12 13] Smoking status was assessed by self-report and by urinary-cotinine test (UltiMed one step; Dutch Diagnostic, Zutphen, The Netherlands; detection limit 200 ng/mL).[7] Weight change from baseline to 12-month follow-up was categorised in three groups: weight gain (≥1 kg), unchanged (weight change <1 kg) and weight loss (≥1 kg). Successful weight loss was defined according to the European Society of Cardiology (ESC) prevention guidelines as ≥5% reduction of weight compared with baseline.

Outcomes

The primary outcome was weight change from baseline to 12-month follow-up. Secondary outcomes were changes in body composition (body fat percentage and waist circumference), changes in associated CVD risk factors (blood pressure, lipids, glucose and glycated haemoglobin levels) and achievement of LRF targets (≥5% weight loss, ≥10% increase in 6MWD and smoking cessation).

Statistical methods

We analysed patients according to intention to treat, irrespective of attendance to the lifestyle interventions. Loss to follow-up was assessed following the methods proposed by Carpenter and Kenward.[14]

The primary analysis compared the mean weight change from baseline to 12-month follow-up in intervention and control patients. Comparisons between groups were made by linear or logistic regression analysis, independent samples t-tests and Fisher's exact tests, as appropriate. To assess the stability of weight change and change in CVD risk factors, we performed a sensitivity analysis adjusted for covariates that were used to stratify the randomisation, covariates that were part of the loss to follow-up mechanism and education level, which was unbalanced at baseline.[6]

We used stepwise regression with backward elimination ($p<0.157$) to identify determinants of successful weight loss and of weight gain.[15] Covariates included in the backward elimination procedures were selected a priori based on literature and expert knowledge. The models were estimated in 20 imputed datasets and regression coefficients, and p values were pooled using Rubin's rule. The models were validated in 250 bootstrap samples drawn from the original data with missing values and missing values filled in by multiple imputation ($m=20$) in each bootstrap sample.[16] A full description of the analyses is presented in the online appendix. Because several covariates were not available for control patients, we included only intervention group patients in the analyses.

Finally, all determinant–outcome associations were assessed for interaction with treatment allocation ($p<0.05$) to identify patients on whom the intervention impacted significantly. All statistical tests were two tailed, and a p value of <0.05 was used to indicate statistical significance. Analyses were performed using R-studio, V.3.6.1.

RESULTS

In total, 824 patients provided informed consent and were randomised, of whom 609 patients had a BMI ≥27 kg/m^2. After 12 months, 537 (88%) patients attended the follow-up visit and were included in the current analysis (figure 1). Patients attending the 12-month follow-up had a mean age of 59.1 (±9.1) years, 23% were women and 83% were living with a partner (table 1). The majority of patients (64%) had no previous history of CVD. In total, 42% of patients smoked during the 6 months preceding hospitalisation, mean body mass index (BMI) was 31 kg/m^2 and 61% of patients did not meet the criterion for adequate physical activity. At baseline, the use of preventive medication was high, and most patients (90%) attended cardiac rehabilitation.

Compared with those who completed the 12-month follow-up visit, patients lost to follow-up were more often controls, of lower age, smoking at baseline and had at baseline a slightly higher systolic blood pressure (area under curve (AUC) 0.68). We found no evidence of differential loss to follow-up between treatment arms (online appendix, table 1a and 1b).

In the intervention group, a total of 182 patients (65%) participated in the weight loss programme. Patients attended a median of 12 (range 0–50) meetings, and 81 patients (43%) were joined by their partners. The number of meetings was positively associated with the mean change in weight ($p<0.001$) (online appendix, figure 1). Patient motivation, programme attendance and partner participation in patients with and without successful weight loss are shown in the online appendix table 2.

At 12-month follow-up, patients in the intervention group had lost significantly more weight than those in the control group (average −2.4±7.1 kg vs −0.2±4.6 kg, $p<0.001$) (table 2). Similar results were seen for decreases in waist circumference (−3.7±6.8 cm in interventions vs −1.9±5.4 cm in controls; $p<0.001$) and body fat percentage (−1.2% ±7.3 in interventions

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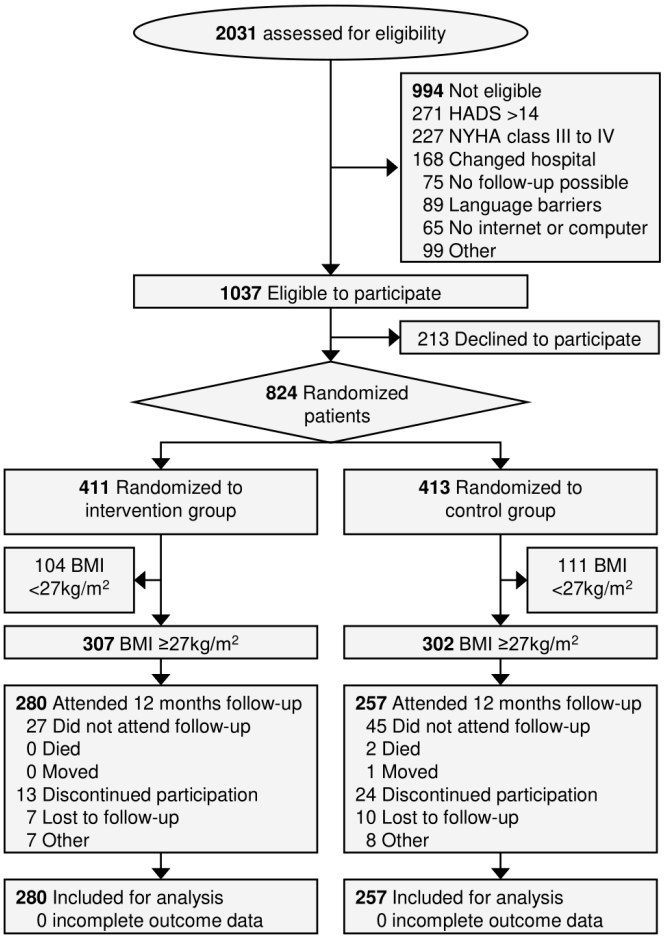

Figure 1 Study flow chart.

vs. +0.3% ±6.5 in controls; p=0.02). Improvements in body weight and waist circumference were greater in patients who had attended the weight loss programme. These findings were stable for adjustments as described in the sensitivity analysis (online appendix table 3).

Successful weight loss was observed more frequently in the intervention group than in controls (32% vs 16%; p<0.001) (online appendix, table 4). Four per cent of patients in the intervention group achieved a BMI of ≤25 kg/m^2 compared with none in the control group (p=0.002). Moreover, patients in the intervention group who smoked at baseline quit more frequently than controls (30% vs 11%; p<0.05). Mean weight gain among patients who had quit smoking at 12-month follow-up was 0.9 kg (±7.4) in the intervention group and 1.8 kg (±5.2) in the control group (p=0.45).

Observed weight change varied widely between individual patients, as shown in the waterfall plots (figure 2). Weight change in the intervention group ranged from +23 kg to −25 kg and from +13 kg to −15 kg in the control group. A considerable number of patients gained weight (≥1.0 kg): 36% and 41% (p=0.21) in the intervention and control group, respectively (mean +4.4±3.3 kg vs +4.0±2.5 kg; p=0.33). Evaluation of weight change per baseline LRF group demonstrated that in the intervention group, patients with overweight only and patients with overweight and inadequate physical activity lost substantially more weight compared with controls (−4.7 kg vs −1.0 kg; p<0.001 and −4.4 kg vs −0.1 kg; p<0.001) (table 3).

Stepwise regression with backward elimination identified five determinants associated with successful weight loss in the intervention group (n=280): higher age (≥65 years) (OR 2.94), lower educational level (OR 1.91), non-smoking status (defined as never smoking or quit ≤6 months before hospitalisation; OR 2.92), being motivated to start the weight loss

Table 1 Baseline characteristics

	Intervention group (n=280)	Control group (n=257)
Demographics (%)		
Age (years)	58.6±9.0	59.7±9.2
Sex (female)	65 (23.2)	57 (22.2)
Ethnicity (Caucasian)	264 (94.3)	238 (92.6)
Education (higher)*	105 (37.5)	68 (26.5)
Partner	234 (83.6)	211 (82.1)
Index event (%)		
STEMI	114 (40.7)	98 (38.1)
NSTEMI	103 (36.8)	88 (34.2)
Unstable AP	26 (9.3)	26 (10.1)
Stable angina revascularisation	37 (13.2)	45 (17.5)
Treatment index event (%)		
PCI	214 (76.4)	202 (78.6)
CABG	29 (10.4)	30 (11.7)
Medication only	37 (13.2)	25 (9.7)
Previous CVD (%)		
Myocardial infarction	58 (20.7)	65 (25.3)
Percutaneous coronary intervention	45 (16.1)	44 (17.1)
Coronary artery bypass surgery	15 (5.4)	10 (3.9)
Stroke	5 (1.8)	9 (3.5)
Peripheral artery disease	18 (6.4)	11 (4.3)
No known previous CVD	184 (65.7)	157 (61.1)
CVD risk factors (%)		
Diabetes mellitus	48 (17.1)	47 (18.3)
History of hypertension	108 (38.6)	115 (44.7)
History of dyslipidaemia	73 (26.1)	67 (26.1)
Smoking		
Pre-event smoking†	122 (43.6)	104 (40.5)
Smoking at baseline‡	39 (13.9)	45 (17.5)
Inadequate physical activity§	108 (38.6)	101 (39.3)
BMI category		
≥27–<30 kg/m^2	109 (38.9)	118 (45.9)
≥30–<35 kg/m^2	126 (45.0)	100 (38.9)
≥35–<40 kg/m^2	37 (13.2)	31 (12.1)
≥40 kg/m^2	8 (2.9)	8 (3.1)
Lifestyle-related risk factor groups (%)		
BMI≥27 kg/m^2 only	65 (23.2)	63 (24.5)
BMI≥27 kg/m^2 and inadequate physical activity	93 (33.2)	90 (35.0)
BMI≥27 kg/m^2 and smoking	43 (15.4)	38 (14.8)
BMI≥27 kg/m^2, inadequate physical activity and smoking	66 (25.7)	79 (28.2)
Medication (%)		
Antiplatelet	278 (99.3)	250 (97.3)
β-blockers	234 (83.6)	227 (88.3)
ACE inhibiter/ARB	220 (78.6)	185 (72.0)
Lipid-lowering drugs	271 (96.8)	250 (97.3)

Values presented as mean±SD and counts (%)
*Higher education: universities of applied sciences and research universities.
†Smoking ≤6 months before hospital admission.
‡Baseline urine-cotinine level >200 ng/mL.
§Self-reported based on WHO recommendations.
AP, angina pectoris; ARB, angiotensin II-receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CVD, cardiovascular disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

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Table 2 Outcome data at 12-month follow-up in patients with baseline BMI ≥27 kg/m^2

	Baseline		Change at 12 months				
	Intervention (n=280)	Control (n=257)	Intervention (n=280)	Control (n=257)	Between group difference, mean (95% CI)	P value	WW participants (n=182)
Primary outcomes							
Body weight, kg	97.8±13.7	96.6±14.2	−2.4±7.1	−0.2±4.6	−2.2 (−3.2 to −1.2)	<0.001	−3.6±7.6
BMI, kg/m^2	31.7±3.6	31.2±3.5	−0.8±2.3	−0.1±1.5	−0.7 (−1.1 to −0.4)	<0.001	−1.2±2.5
Secondary outcomes							
Body fat percentage, %	33.5±8.5	32.3±8.7	−1.2±7.3	0.3±6.5	−1.6 (−2.9 to −0.3)	<0.05	−1.3±7.5
Waist circumference, cm	111.6±10.1	110±10.2	−3.7±6.8	−1.9±5.4	−2.0 (−3.1 to −1.0)	<0.001	−4.9±7.3
Blood pressure, mm Hg							
Systolic	134±18.4	135±17.5	−2.1±19.0	1.9±18.6	−4.1 (−7.3 to −0.9)	<0.05	−2.5±18.6
Diastolic	79±9.6	79±10.3	−0.3±10.9	1.9±11.6	−2.1 (−4.0 to −0.2)	<0.05	−0.3±11.3
Cholesterol, mmol/L							
Total cholesterol	4.1±0.9	4.1±1.2	−0.03±0.94	−0.07±1.24	0.04 (−0.15 to−0.23)	0.67	−0.03±0.87
LDL-C	2.2±0.8	2.2±0.8	0.01±0.85	−0.01±0.90	0.03 (−0.12 to 0.18)	0.68	−0.02±0.78
HDL-C	1.1±0.4	1.2±0.4	0.06±0.34	0.04±0.33	0.02 (−0.04 to 0.08)	0.45	0.10±0.25
Triglycerides	1.5 (1.1–2.1)	1.5 (1.1–2.0)	−0.14±0.90	−0.05±1.14	−0.09 (−0.27 to 0.09)	0.34	−0.20±0.89
Fasting glucose, mmol/L	5.9 (5.4–6.7)	5.9 (5.4–6.6)	−0.15±1.64	−0.17±1.43	0.01 (− 0.29 to 0.30)	0.95	−0.19±1.63
HbA1c, mmol/mol	40.9±12.3	40.5±12.5	0.41±10.10	1.66±11.31	−1.78 (−3.77 to 0.20)	0.08	0.77±9.86

Values presented as mean±SD or median (IQR).
BMI, body mass index; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WW, weight loss programme.

programme directly after the baseline visit (OR 2.30) and weight loss programme participation (OR 3.33) (table 4) (model performance after internal validation: AUC 0.76, R^2 0.24, slope: 0.79). Allocation to the intervention group significantly increased the likelihood of successful weight loss for patients with a higher age (≥65 years; p value interaction <0.01), non-smoking status (p value interaction=0.01) and/or motivated to lose weight (p value interaction <0.001). Stratum specific effect sizes are presented in the online appendix table 5.

Weight gain was found to be associated with five determinants in the intervention group (n=280): smoking cessation ≤6 months before or during hospitalisation (OR 3.21), non-Caucasian ethnicity (OR 2.77), smoking at baseline (OR 2.70), lower age (<65 years) (OR 1.47) and weight loss programme participation (OR 0.59) (table 5) (model performance after internal validation: AUC 0.77, R^2 0.26, slope 0.79). For patients smoking at baseline, and thus eligible for the smoking cessation programme, allocation to the intervention group increased the likelihood of weight gain (p value interaction <0.01) (online supplemental appendix, table 5).

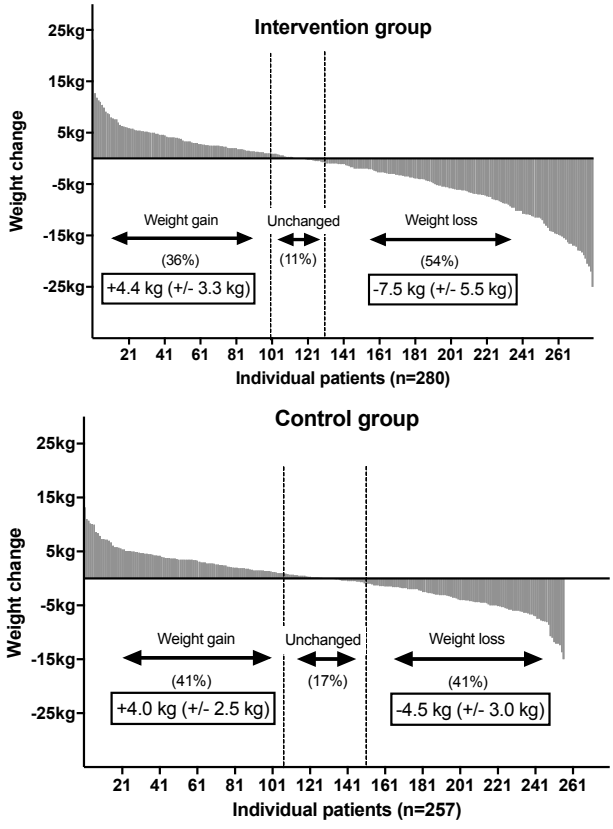

Figure 2 Waterfall plots; weight change from baseline to 12-month follow-up stratified by randomised treatment allocation.

DISCUSSION

The main finding of our study is that in patients with CAD and overweight, referral to a community-based commercial weight loss programme as part of a comprehensive lifestyle intervention results in significantly more weight loss (mean 2.4±7.1 kg vs 0.2±4.6 kg, p<0.001) as compared with usual care alone. Patients in the intervention group more often achieved clinically meaningful weight loss and attained meaningful improvements in several other CVD risk factors such as body fat percentage, waist circumference and blood pressure. In the intervention group, weight loss was associated with age over 65 years, lower educational level, non-smoking status, motivation to start with weight loss directly after the baseline visit and weight loss programme participation. A significant proportion of patients in both groups gained weight: 36% and 41% in the intervention and control group, respectively. For intervention patients, weight gain was associated with smoking cessation ≤6 months before or during hospitalisation, non-Caucasian ethnicity, smoking at baseline, age under 65 years and not participating in the weight loss programme.

In line with our findings Jebb *et al*[5] showed that in participants with at least one risk factor for obesity-related disease, referral by a healthcare professional to the same weight loss programme as used in our trial resulted in a mean weight loss of

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Table 3 Weight change in patients with baseline BMI ≥27 kg/m^2 from baseline to 12-month follow-up stratified per baseline lifestyle-related risk factor group

	Intervention group (n=280)	Control group (n=257)	Between group mean difference (95% CI)	p-value
Lifestyle-related risk factor groups				
BMI≥27 kg/m^2 only	−4.7±6.8	−1.0±4.1	−3.7 (−5.6 to −1.7)	<0.001
BMI≥27 kg/m^2 and smoking*	1.4±6.5	−0.1±4.9	1.5 (−1.1 to 4.1)	0.25
BMI≥27 kg/m^2 and inadequate physical activity†	−4.4±6.8	−0.1±4.1	−4.3 (−5.9 to −2.7)	<0.001
BMI≥27 kg/m^2, smoking and inadequate physical activity*†	−0.3±6.7	0.4±5.5	−0.7 (−2.7 to 1.4)	0.52

Weight change in kg presented as mean±SD.
*Smoking at baseline or smoking ≤6 months before hospitalisation.
†Self-reported based on WHO recommendations.
BMI, body mass index.

4.1 kg (±6.0) compared with 1.8 kg (±3.8) in the control group. Our study adds that such a weight loss programme can also be successfully offered in patients with CAD. Though average weight lost was modest, twice as many patients in the intervention group achieved a clinically relevant weight reduction of ≥5% as compared with controls (32% vs 16%; p<0.001).

While the relatively large number of patients who managed to lose weight in the first year after hospitalisation is encouraging, the considerable number of patients who gained weight despite being offered participation in a dedicated weight loss intervention is alarming. A weight gain in over one of three patients was seen against a background of a high level of usual care, with almost all patients (99.6%) attending a nurse-coordinated secondary prevention programme and the majority of patients (90%) attending cardiac rehabilitation. Prevention of weight gain may be as important as attempts to lose weight and should be an interest of future research.[17 18]

Weight gain in patients with CAD has been reported to be associated with factors such as age, smoking status, obesity and depression.[19–21] A central factor in weight gain among CAD patients is smoking cessation. Our findings support that patients who quit smoking immediately after hospitalisation for CAD are more likely to gain weight. Surprisingly, our study found that in the intervention group, smoking at baseline was also associated with weight gain at 12-month follow-up. Referral to the smoking cessation programme and subsequent increased smoking cessation at 12-month follow-up among intervention patients smoking at baseline compared with their control counterparts may have contributed to this finding. On average, patients who stop smoking after a myocardial infarction gain 4.8 kg (±8.6) in

Table 4 Determinants of successful weight loss in the intervention group; candidate variables stratified by successful weight reduction (≥5% of baseline weight)

	Univariable analysis				Multivariable model*	
	Successful patients (%) (n=90)	Unsuccessful patients (%) (n=190)	OR (95% CI)	P value	OR (95% CI)	P value
Demographics						
Age (≥65 years)	39 (43.3)	36 (19.0)	3.27 (1.88 to 5.67)	<0.001	2.94 (1.57 to 5.48)	<0.001
Sex (female)	26 (28.9)	39 (20.5)	1.57 (0.88 to 2.79)	0.12		
Level of education (lower)†	62 (68.9)	113 (59.5)	1.51 (0.87 to 2.57)	0.13	1.91 (1.05 to 3.50)	0.04
Having a partner	77 (85.6)	157 (82.6)	1.24 (0.63 to 2.58)	0.54		
Baseline lifestyle-related risk factors						
Non-smoking status‡	69 (76.7)	89 (46.8)	3.73 (2.12 to 6.56)	<0.001	2.92 (1.56 to 5.46)	<0.001
BMI, kg/m^2	32.0±3.4	31.5±3.6	1.04 (0.97 to 1.12)	0.23		
Inadequate physical activity§	33 (36.7)	75 (39.5)	0.89 (0.53 to 1.49)	0.65		
Overweight as only lifestyle-related risk factor	27 (30.0)	38 (20.0)	1.71 (0.96 to 3.04)	0.07		
Participation in lifestyle programmes						
Smoking cessation programme	4 (4.4)	26 (13.7)	0.29 (0.08 to 0.78)	0.03		
Physical activity programme	52 (57.8)	107 (56.3)	1.06 (0.64 to 1.77)	0.82		
Weight loss programme (WW)	76 (84.4)	106 (55.8)	4.30 (2.33 to 8.42)	<0.001	3.33 (1.60 to 6.99)	0.002
Partner participating in WW	42 (65.6)	39 (42.9)	2.55 (1.32 to 4.99)	<0.01		
Motivation variables						
Motivated for WW	77 (92.8)	139 (78.1)	3.60 (1.56 to 9.81)	<0.01		
Motivated to start WW directly after the baseline visit	77 (92.8)	131 (71.2)	5.19 (2.29 to 14.00)	<0.001	2.31 (0.88 to 6.02)	0.09
Referred to WW in first outpatient clinic visit	69 (89.6)	109 (83.2)	1.74 (0.76 to 4.37)	0.21		

Values presented as mean±SD or counts (%).
*Variables selected with backward elimination (p<0.157) in 20 imputed datasets and estimates pooled using Rubins' rule.
†Lower education: all except universities of applied sciences and research universities.
‡Never smoking or quit >6 months before hospitalisation.
§Self-reported based on WHO recommendations.
BMI, body mass index.

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Table 5 Determinants of weight gain in the intervention group; candidate variables stratified by weight gain (≥1 kg of baseline weight)

	Univariable analysis				Multivariable model*	
	Weight gain (≥1 kg) (n=100)	No weight gain (n=180)	OR (95% CI)	P value	OR (95% CI)	P value
Demographics						
Age (<65 years)	81 (81.0)	124 (68.9)	1.93 (1.08 to 3.54)	0.03	1.47 (0.78 to 2.78)	0.23
Sex (female)	20 (20.0)	45 (25.0)	0.75 (0.41 to 1.34)	0.34		
Ethnicity (non-Caucasian)	10 (10.0)	6 (3.3)	3.22 (1.16 to 9.74)	0.03	2.77 (0.90 to 8.55)	0.08
Level of education (lower)†	62 (62.0)	113 (62.8)	0.97 (0.59 to 1.61)	0.90		
Having a partner	83 (83.0)	151 (83.9)	0.94 (0.49 to 1.84)	0.85		
Baseline lifestyle-related risk factors						
Smoking						
Smoking at baseline‡	29 (29.0)	28 (15.6)	2.22 (1.23 to 4.02)	0.01	2.70 (1.38 to 5.27)	0.004
Quit smoking before or during hospitalisation§	34 (34.0)	31 (17.2)	2.48 (1.41 to 4.38)	<0.01	3.21 (1.70 to 6.08)	<0.001
BMI, kg/m^2	31.5±4.0	31.7±3.3	0.98 (0.91 to 1.05)	0.62		
Inadequate physical activity¶	63 (63.0)	109 (60.6)	1.11 (0.67 to 1.85)	0.69		
Established diabetes mellitus type 2	16 (16.0)	32 (17.8)	0.88 (0.45 to 1.68)	0.71		
Participation in lifestyle programmes						
Smoking cessation	16 (16.0)	14 (7.8)	2.26 (1.05 to 4.91)	0.04		
Physical activity	49 (49.0)	110 (61.1)	0.61 (0.37 to 1.00)	0.05		
Weight loss	54 (54.0)	128 (71.1)	0.48 (0.29 to 0.79)	<0.01	0.59 (0.34 to 1.02)	0.06
Partner participating in WW	21 (44.7)	60 (55.6)	0.65 (0.32 to 1.28)	0.21		
Motivated for WW	75 (78.9)	141 (84.9)	0.66 (0.35 to 1.29)	0.22		

Values presented as mean±SD or counts (%).
*Variables selected with backward elimination (pp<0157) in 20 imputed datasets and estimates pooled using Rubins' rule.
†Lower education: all except universities of applied sciences and research universities.
‡Baseline urine–cotinine level >200 ng/mL.
§Smoking cessation ≤6 months before or during hospitalisation.
¶Self-reported based on WHO recommendations.
BMI, body mass index; WW, weight loss programme.

the first year.[22] Our analysis in patients with a BMI≥27 kg/m^2 found less pronounced weight gain in patients who successfully quit smoking at 12-month follow-up (+0.9±7.4 kg in interventions vs +1.8±5.2 kg in controls, p=0.16). Participation in a weight loss or physical activity programme may have attenuated weight gain associated with smoking cessation.

Five determinants were found to be associated with achieving successful weight loss in the intervention group. Although older age is generally associated with weight gain, our findings are in line with previous reports that observed higher age as an important determinant for dietary adherence and weight loss in lifestyle interventions.[23 24] Intended weight loss through dieting and exercise can greatly improve health-related quality of life in elderly CAD patients.[25] Unintended weight loss, however, can be a sign of underlying pathology or deconditioning and should prompt appropriate investigations. A lower educational level was, after adjustment for smoking status, significantly associated with a higher chance of successful weight loss. Consistent with previous reports that identified autonomous motivation as an important factor in sustaining lifestyle improvements, motivation to start with weight loss directly after the baseline visit was strongly associated with successful weight loss.[26] Finally, a non-smoking status and attending the weight loss intervention were the strongest determinants of successful weight loss.

These determinants of weight change represent statistical associations and could potentially assist clinicians and researchers in further developing weight loss programmes in patients with CAD. Hypothetically, when tailoring such programmes, selecting patients based on one or more of these determinants could lead to a more cost-effective approach with higher success rates (figure 3). While both the American College of Cardiology and ESC guidelines recommend personalised secondary prevention,[8 9] recommendations on how to implement this are lacking. Our findings show determinants that could be of use to personalise weight loss interventions.

Strengths and limitations

There are several strengths to our study. First, our study investigated a highly practical approach, using widely available lifestyle interventions, without modifications, which facilitates implementation of these programmes into daily practice. Second, compared with other weight loss trials, our study had little loss to follow-up,[5 27] which we thoroughly evaluated. Finally, the multivariable regression analysis provides insights in achieving meaningful weight loss in overweight CAD patients and can potentially assist in further personalisation of weight loss programmes.

Some aspects of our study merit consideration. First, we used a subgroup of patients from the original randomised trial, because of which comparability between treatment arms cannot be fully guaranteed. Second, we excluded patients with depressive symptoms, congestive heart failure, a language barrier or without internet access. Potentially, these individuals represent patients with a lower socioeconomic status, who are in particular need of optimal secondary prevention.[28] Third, to evaluate long-term impact on prognosis, a longer follow-up period is necessary. Most studies evaluating weight loss programmes report positive results for short term (≤12 months) but limited or conflicting results for intermediate or long-term follow-up (≥24 months).[29 30] We are currently collecting long-term follow-up data of the RESPONSE-2 trial. Finally, our analyses of determinants of weight change should

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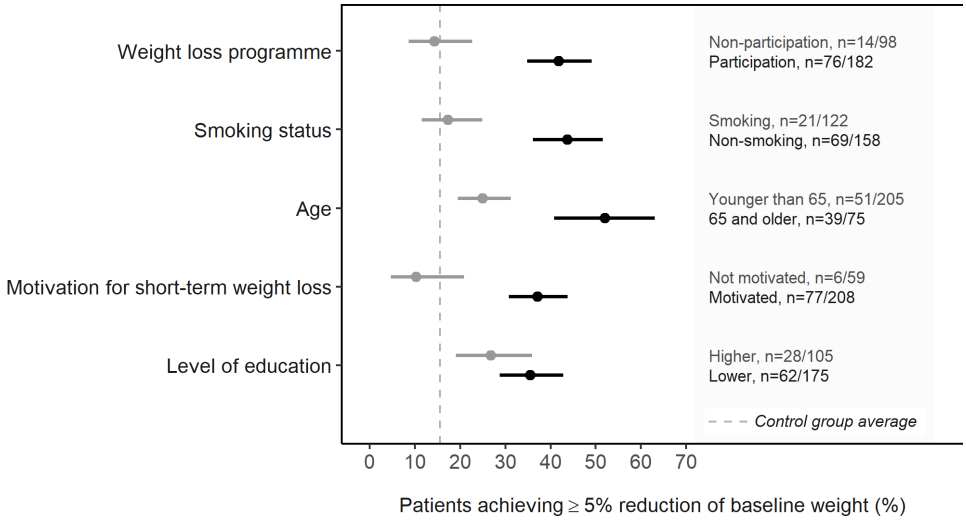

Figure 3 Percentage of intervention group patients achieving successful weight loss at the 12-month follow-up, stratified per determinants of successful weight loss.

be interpreted with caution. Though we used extensive resampling methods, data-driven variable selection is susceptible to overfitting. In new populations, these models may perform less well and external validation is advised.

CONCLUSION

Our highly practical approach of nurse-coordinated referral to a community-based weight loss intervention, as part of a comprehensive secondary prevention strategy, leads to significantly increased rates of weight loss in CAD patients with overweight. Alarmingly, weight gain was highly prevalent, and prevention of weight gain may be as important as attempts at weight loss. The identified determinants of weight change may contribute to further development of effective weight management strategies.

Key messages

What is already known on this subject?

- In patients with obesity and cardiovascular disease, weight loss of 5%–10% can significantly reduce lifetime risk of recurrent events. As cardiac rehabilitation alone is insufficient to achieve meaningful weight loss, there is a need for effective, targeted weight loss strategies.

What might this study add?

- Referral to a commercial weight loss intervention, as part of a secondary prevention programme, leads to significantly more weight loss on average at 12-month follow-up than usual care alone in patients with cardiovascular disease (−2.4 kg vs −0.2 kg). In the intervention group, determinants of ≥5% reduction of baseline weight were higher age, lower level of education, non-smoking status, motivation to start with weight loss directly after the baseline visit and attending the weight loss intervention. On average, patients who successfully quit smoking in the intervention group gained less weight through the combined lifestyle intervention than patients who quit smoking in the control group.

How might this impact on clinical practice?

- Referral to a commercial weight loss programme as part of a comprehensive strategy increases the likelihood of achieving meaningful weight loss in patients with coronary artery disease and overweight. Potentially, tailoring weight management strategies to patient characteristics associated with meaningful weight loss can lead to a more cost-effective approach and higher success rates.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The institutional committees on human research of all recruiting hospitals approved the protocol (METC 2012_272; Netherlands Trial Registry: NTR3937), and written informed consent was obtained from all patients.

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Data availability statement Data are available on reasonable request. Requests for analyses of deidentified data from this trial should be directed to: M Snaterse (m.snaterse@hva.nl).

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ONLINE APPENDIX

Community-based commercial lifestyle programmes

Weight loss programme

The weight reduction programme offered by Weight Watchers™ (www.weightwatchers.com) promotes a healthy diet using the ProPoints system, which addresses the total energy value in each product, healthy behaviour and regular physical activity, and utilizes group motivation. Patients were encouraged to attend weekly workshops and could use digital tools to monitor food intake, physical activity and weight change. A free subscription was provided for one year.

Physical activity programme

Philips DirectLife™ (www.philips.nl/c-m-pe/actieve-levensstijl/directlife/nieuwste#availability=all) is an internet-based health programme that encourages stepwise increases in levels of physical activity by promoting awareness of all daily exercise, independent of its intensity or type of activity. The programme uses a personal accelerometer to monitor daily physical activities, provide feedback and offer personalised internet-based coaching. After three months of active coaching, participants could continue to use the accelerometer and online portal to monitor their physical activity.

Smoking cessation counselling

Luchtsignaal™ (www.luchtsignaal.nl) is an existing national smoking cessation programme in The Netherlands, offering up to seven personalised telephone-based counselling sessions by professionals during a period of three months. The programme is based on the stages of change concept from the trans-theoretical model and uses strategies from motivational interviewing, action and coping planning, self-control training and relapse prevention. If necessary, nicotine replacement therapy or varenicline could be prescribed.

Statistical methods to identify determinants of successful weight loss and weight gain

Determinants of successful weight loss (≥5%) or weight gain (≥ 1 kg) compared with baseline were identified using individual patient data from intervention group patients with a BMI ≥27 kg/m^2 form the RESPONSE-2 trial. For both weight loss and weight gain, a set of candidate predictors assumed to influence weight change based on current literature and expert knowledge was selected a priori and are listed below. Because several candidate predictors were not available for control patients, we included only patients from the intervention group in the analyses.

We used stepwise multivariable logistic regression analysis with backward elimination and with successful weight loss (≥5%) or weight gain (≥ 1kg) as dependent variables. In the backward elimination procedure, variables with the largest p-value were removed sequentially and the logistic regression analysis was repeated until all p-values were smaller than <0.157, corresponding with an all-subset approach with selection based on Aikaike's information criterion (15).

We estimated the models in 20 imputed datasets and regression coefficients and p-values were pooled using Rubin's rule. Non-normal distributed continuous variables were log-transformed before imputation. In the final models, continuous variables were assed for linearity by visual plots and model performance based on the R^2, C-statistic and Aikaike Information Criterion and were categorised or transformed with restricted cubic splines if indicated.

Finally, we internally validated the models in 250 bootstrap samples drawn from the original data with missing values and missing values filled in by multiple imputation (m=20) in each bootstrap sample (Heymans M. Psfmi package. Available at: https://mwheymans.github.io/ psfmi/index.html.). We report pooled regression coefficients without shrinkage and AUCs and R^2 after shrinkage. We used the mice and psfmi packages in R-studio (version 3.6.1.) for these analyses.

Determinants of successful weight loss

Determinant	Data type	Missing data
1. Age	Continuous	-
2. Sex	Binary	-
3. Level of education	Binary	-
4. Having a partner at baseline	Binary	-
5. Never smoking or quit >6 months before hospitalisation	Binary	-
6. Baseline BMI	Continuous	-
7. Physical inactivity at baseline	Binary	-
8. Only overweight as risk factor at baseline	Binary	-
9. Participation in the weight loss programme	Binary	-
10. Participation in the smoking cessation programme	Binary	-
11. Participation in the physical activity programme	Binary	-
12. Partner participation in the weight loss programme *	Binary	125
13. Being motivated to lose weight	Binary	19
14. Being motivated to start weight loss directly after the baseline visit *	Binary	13
15. Referral to the weight loss programme directly after the baseline visit *	Binary	72

* Covariate not available in control patients

Determinants of weight gain

Determinant	Data type	Missing data
1. Age	Continuous	-
2. Sex	Binary	-
3. Ethnicity	Binary	-
4. Level of education	Binary	-
5. Having a partner	Binary	-
6. Smoking at baseline	Binary	-
7. Smoking cessation ≤6 months before or during hospitalization	Binary	-
8. Established type-2 Diabetes	Binary	-
9. Baseline BMI	Continuous	-
10. Baseline physical inactivity	Binary	-
11. Participation in the weight loss programme	Binary	-
12. Participation in the smoking cessation programme	Binary	-
13. Participation in the physical activity programme	Binary	-
14. Partner participation in the weight loss programme *	Binary	125
15. Not motivated to lose weight	Binary	19

* Covariate not available in control patients

Analysis of loss to follow-up

We used univariable logistic regression analysis to evaluate associations between patients' baseline characteristics and the probability of being lost to follow-up at the 12 months follow-up (online appendix, table 1a, 'Overall LTFU') and whether or not the probability of being lost to follow-up was significantly interacted on by treatment allocation (online appendix, table 1a, 'Between-group LTFU'). Variables with a standardized mean difference (SMD) of ≥0.20 and/or a p-value <0.05 were evaluated for their ability to identify patients lost to follow-up at the 12 months follow-up using the Receiver Operating Characteristic Area Under the Curve (AUC) and the Aikaike's Information Criterion (AIC) (online appendix, table 1b). The loss to follow-up mechanism was defined as the model with the highest AUC and the lowest AIC.

Online appendix, table 1a: Analysis of patients lost to follow-up

	Intervention group		Control group		Overall LTFU *		Between-group LTFU *
	Attendees	**Patients LTFU**	**Attendees**	**Patients LTFU**	**SMD**	**p-value**	**p-value**
Randomization							
Treatment allocation	280 (91.2)	27 (8.8)	257 (85.1)	45 (14.9)	0.30	0.03	
Demographics							
Age (y)	58.6 ±9.0	57.3 ±9.0	59.7 ±9	55.6 ±9	0.33	0.01	0.53
Sex (Female)	65 (23)	6 (2.2)	57 (22)	14 (31)	0.12	0.42	0.29
Ethnicity (Caucasian)	264 (94)	25 (92.6)	238 (93)	41 (91)	0.07	0.74	0.30
Education (Higher) †	105 (38)	9 (33.3)	68 (27)	16 (36)	0.05	0.77	0.07
Partner	234 (84)	20 (74.1)	211 (82)	36 (80)	0.13	0.37	0.81
Index event					0.26	0.23	0.31
STEMI	114 (41)	15 (55.6)	98 (38)	22 (49)			
NSTEMI	103 (37)	7 (25.9)	88 (34)	14 (31)			
Unstable AP	26 (9)	1 (3.7)	26 (10)	6 (13)			
Stable angina revascularization	37 (13)	4 (14.8)	45 (18)	3 (7)			
Treatment					0.05	0.94	0.41
PCI	214 (76)	23 (85)	202 (79)	34 (76)			
CABG	29 (10)	1 (4)	30 (12)	6 (13)			
Medication only	37 (13)	3 (11)	25 (10)	5 (11)			
Previous CVD							
MI	58 (21)	9 (33)	65 (25)	6 (14)	0.04	0.85	0.27
PCI	45 (16)	8 (30)	44 (17)	7 (16)	0.12	0.43	1.00
CABG	15 (5)	0 (0)	10 (4)	4 (9)	0.04	0.95	0.99
Stroke	5 (2)	1 (4)	9 (4)	3 (7)	0.15	0.30	0.99
Peripheral artery disease	18 (6)	2 (7)	11 (4)	3 (7)	0.07	0.77	0.24
No known previous CVD	184 (66)	11 (41)	157 (61)	29 (66)	0.15	0.30	0.37
CVD risk factors							
Diabetes Mellitus	48 (17)	6 (22)	47 (18)	10 (22)	0.11	0.44	0.65
History of hypertension	108 (39)	8 (30)	115 (45)	23 (52)	0.04	0.83	0.68
History of dyslipidaemia	73 (26)	8 (30)	67 (26)	12 (27)	0.05	0.82	0.23
Smoking							
Smoking at baseline ‡	39 (14)	9 (33)	45 (18)	10 (22)	0.31	0.01	0.07
Pre-event smoking §	122 (44)	13 (48)	104 (41)	24 (53)	0.11	0.48	0.73
WHO physical activity norm **	108 (39)	7 (26)	101 (39)	14 (31)	0.21	0.14	0.94
Clinical data							

BMI, kg/m^2	31.7 ±3.6	32.3 ±4.5	31.2 ±3.5	31.6 ±3.6	0.12	0.33	0.34
Blood pressure, mmHg							
Systolic	134 ±18	137 ±19	135 ±18	140 ±16	0.23	0.08	0.57
Diastolic	79 ±10	83 ±11	79 ±10	83 ±12	0.36	<0.01	0.65
Cholesterol, mmol/L							
Total cholesterol	4.1 ±0.9	4.1 ±1.0	4.1 ±1.2	4.2 ±1.0	0.11	0.39	0.8
LDL-cholesterol	2.2 ±0.8	2.2 ±0.8	2.2 ±0.8	2.3 ±0.7	0.07	0.59	0.46
HDL-cholesterol	1.1 ±0.4	1.1 ±0.3	1.2 ±0.4	1.1 ±0.3	0.12	0.39	0.73
Triglycerides	1.5 [1.1–2.1]	1.6 [1.4–2.1]	1.5 [1.1–2.0]	1.5 [1.2–2.4]	0.19	0.12	0.79
Fasting plasma glucose, mmol/L	5.9 [5.4–6.7]	6.4 [5.3–8.0]	5.9 [5.4–6.6]	5.8 [5.4–6.5]	0.18	0.59	0.65
HbA1c, mmol/L	40.9 ±12.3	44.3 ±16.6	40.5 ±12.6	39.2 ±15.8	0.04	0.76	0.39
Medication							
Antiplatelet	278 (99)	27 (100)	250 (97)	43 (96)	0.08	0.85	1.00
β-Blockers	234 (84)	23 (85)	227 (88)	37 (82)	0.07	0.70	0.08
ACE inhibiter/ARB	220 (79)	16 (59)	185 (72)	37 (82)	0.04	0.85	0.07
Lipid lowering drugs	271 (97)	25 (93)	250 (97)	44 (99)	0.06	0.86	1.00

*Continuous variables presented as mean ± standard deviation or median [inter quartile range] and dichotomous variables as counts (%); * P-values based on univariable logistic regression analysis (overall LTFU) and with treatment allocation as interaction (between group LTFU), † Higher education: universities of applied sciences and research universities, ‡ Baseline urine-cotinine level >200 ng/ml, § Patients who quit smoking ≤6 months before hospitalisation, ** Self-reported based on WHO recommendations; ACE: Angiotensin-converting enzyme, AP: Angina pectoris, ARB:* Angiotensin II-receptor blocker, *BMI: Body mass index, CABG: Coronary artery bypass grafting, CVD: cardiovascular disease, HDL-C: High density lipoprotein cholesterol, HbA1c: Glycated haemoglobin, LDL-C: Low density lipoprotein cholesterol, LTFU: loss/lost to follow-up, NSTEMI: Non ST-elevation myocardial infarction, PCI: Percutaneous coronary intervention, SMD: Standardized mean difference, STEMI: ST-elevation myocardial infarction.*

Online appendix, table 1b: Coefficients and model performance from logistic regression models for the probability of patients being lost to follow-up at the 12 months assessment

Baseline variable	Models							
	1	2	3	4	5	6	7	8
Treatment allocation (Intervention group)	1.82 *							*0.54 **
Age (y)		1.4 *						*0.97 **
Index event								
STEMI			0.62					
NSTEMI			1.34					
Unstable AP			1.00					
Stable angina revascularization			1.67					
Smoking at baseline †				0.50 *				*1.80 **
Inadequate physical activity ‡					1.55			
Systolic blood pressure, mmHg						0.99		
Diastolic blood pressure, mmHg							0.96 **	*1.04 **
ROC-AUC	**0.57**	**0.60**	**0.57**	**0.43**	**0.45**	**0.57**	**0.60**	***0.68***
AIC	**441**	**440**	**446**	**440**	**444**	**444**	**438**	***427***

*Regression coefficients presented as odds ratios; Significance codes: '**' <0.01, '*' <0.5, '•' <0.1; ROC-AUC: Receiver Operating Characteristic Area Under the Curve, AIC: Aikaike's Information Criterion; † Baseline urine-cotinine level >200 ng/ml, ‡ Self-reported based on WHO recommendations.*

Online appendix, table 2: Lifestyle programme participation in the intervention group stratified by successful weight loss (≥5% reduction of baseline weight in patients with baseline BMI ≥27 kg/m^2)

	Total	Successful (n=90)	Unsuccessful (n=190)	p-value
Participation in lifestyle programs				
WW	182 / 280 (0.65)	76 / 90 (0.84)	106 / 190 (0.56)	≤0.001
Smoking cessation programme	30 / 280 (0.11)	4 / 90 (0.04)	26 / 190 (0.14)	≤0.05
Physical activity programme	159 / 280 (0.57)	52 / 90 (0.58)	107 / 190 (0.56)	0.82
WW and smoking cessation programmes	15 / 280 (0.05)	3 / 90 (0.03)	12 / 190 (0.06)	0.31
WW and physical activity programmes	110 / 280 (0.39)	44 / 90 (0.49)	66 / 190 (0.35)	≤0.05
None	40 / 280 (0.14)	5 / 90 (0.06)	35 / 190 (0.18)	≤0.01
Partner participation	120 / 227 (0.53)	49 / 81 (0.60)	71 / 146 (0.49)	0.09
Partner participation in WW	81 / 190 (0.43)	42 / 71 (0.59)	39 / 119 (0.33)	≤0.001
Attendance to lifestyle programmes *				
Weight loss programme				
Median meetings (range)	12 (0–50)	30 (0–50)	7 (0–50)	
0 meetings	5 / 181 (0.03)	2 / 76 (0.03)	3 / 105 (0.03)	
1-9 meetings	70 / 181 (0.39)	16 / 76 (0.21)	54 / 105 (0.51)	
10-19 meetings	29 / 181 (0.16)	7 / 76 (0.09)	22 / 105 (0.21)	
20-29 meetings	27 / 181 (0.15)	12 / 76 (0.16)	15 / 105 (0.14)	
30-39 meetings	18 / 181 (0.10)	13 / 76 (0.17)	5 / 105 (0.05)	
>40 meetings	32 / 181 (0.18)	26 / 76 (0.34)	6 / 105 (0.06)	
Physical activity programme				
12 weeks completed	133 / 159 (0.84)	47 / 52 (0.90)	86 / 107 (0.80)	0.12
Smoking cessation programme				
Full programme completed	26 / 30 (0.87)	3 / 4 (0.75)	23 / 26 (0.88)	0.47
Motivation characteristics				
Previous weight loss attempts	186 / 280 (0.66)	67 / 90 (0.74)	119 / 190 (0.63)	0.06
Motivated for WW	216 / 261 (0.83)	77 / 83 (0.93)	139 / 178 (0.78)	≤0.01
Motivated to start WW within 1 month	208 / 267 (0.78)	77 / 83 (0.93)	131 / 184 (0.71)	≤0.001
Referred to WW in 1st outpatient clinic visit	178 / 208 (0.86)	69 / 77 (0.90)	109 / 131 (0.83)	0.21
Started with WW after first outpatient clinic visit	132 / 174 (0.76)	61 / 65 (0.94)	71 / 109 (0.65)	≤0.001

*Data on intervention group only; Values presented as counts (%); * Data on patients who agreed to participate in and were referred to a lifestyle programme: WW: weight loss programme.*

Online appendix, table 3: Results from the sensitivity analysis; Adjusted outcome data at 12 months follow-up in patients with baseline BMI ≥27 kg/m^2

	Baseline		Change at 12 months					
	Intervention (n=280)	Control (n=257)	Intervention (n=280)	Control (n=257)	Between group difference, mean (95% CI)	p-value	WW participants (n=182)	Missing data (interventions/ controls)
Primary outcomes								
Body weight, kg	97.8 ±13.7	96.6 ±14.2	-2.4 ±7.1	-0.2 ±4.6	-2.4 (-3.4 – -1.4)	<0.001	-3.5 ±7.3	-
BMI, kg/m2	31.65 ±3.6	31.18 ±3.5	-0.8 ±2.3	-0.1 ±1.5	-0.8 (-1.1 – -0.5)	<0.001	-1.1 ±2.4	-
Secondary outcomes								
Body fat percentage, %	33.5 ±8.5	32.3 ±8.7	-1.2 ±7.3	0.3 ±6.5	-1.6 (-2.9 – -0.3)	<0.05	-0.9 ±7.9	29/26
Waist circumference, cm	111.6 ±10.1	110 ±10.2	-3.7 ±6.8	-1.9 ±5.4	-2.2 (-3.3 – -1.2)	<0.001	-3.3 ±7.5	0 4
Blood pressure, mm Hg								
Systolic	134.2 ±18.4	134.9 ±17.5	-2.1 ±19.0	1.9 ±18.6	-4.2 (-7.2 – -1.3)	<0.01	4.2 ±21.6	0/1
Diastolic	79.2 ±9.6	79 ±10.3	-0.3 ±10.9	1.9 ±11.6	-2.2 (-3.8 – -0.6)	<0.01	-2.4 ±11.6	0/1
Cholesterol, mmol/L								
Total cholesterol	4.1 ±0.9	4.1 ±1.2	-0.03 ±0.94	-0.07 ±1.24	0.03 (-0.16 – 0.22)	0.73	0.06 ±1.32	9/7
LDL-C	2.2 ±0.8	2.2 ±0.8	0.01 ±0.85	-0.01 ±0.90	0.03 (-0.13 – 0.18)	0.74	0.04 ±1.07	11/7
HDL-C	1.1 ±0.4	1.2 ±0.4	0.06 ±0.34	0.04 ±0.33	0.01 (-0.04 – 0.07)	0.65	0.05 ±0.41	9/7
Triglycerides	1.5 [1.1–2.1]	1.5 [1.1–2.0]	-0.14 ±0.90	-0.05 ±1.14	-0.07 (-0.33 – 0.26)	0.45	-0.17 ±1.24	12/10
Glucose, mmol/L	5.9 [5.4–6.7]	5.9 [5.4–6.6]	-0.15 ±1.64	-0.17 ±1.43	-0.03 (-0.33 – 0.26)	0.82	-0.04 ±2.02	17/11
HbA1c, mmol/mol	40.9 ±12.3	40.5 ±12.5	0.41 ±10.10	1.66 ±11.31	-1.70 (-3.72 – 0.24)	0.08	-0.93 ±12.24	24/25

Values presented as mean ±SD or median [inter quartile range]; BMI: body mass index, CI: Confidence interval, HDL-C: High density lipoprotein cholesterol, HbA1c: Glycated haemoglobin, LDL-C: Low density lipoprotein cholesterol, WW: Weight loss programme; Results are adjusted for covariates used to stratify the randomisation, covariates that were part of the loss to follow-up mechanism and level of education.

Online appendix, table 4: Achievement of lifestyle-related risk factor targets at 12 months follow-up in patients with baseline BMI ≥27 kg/m^2

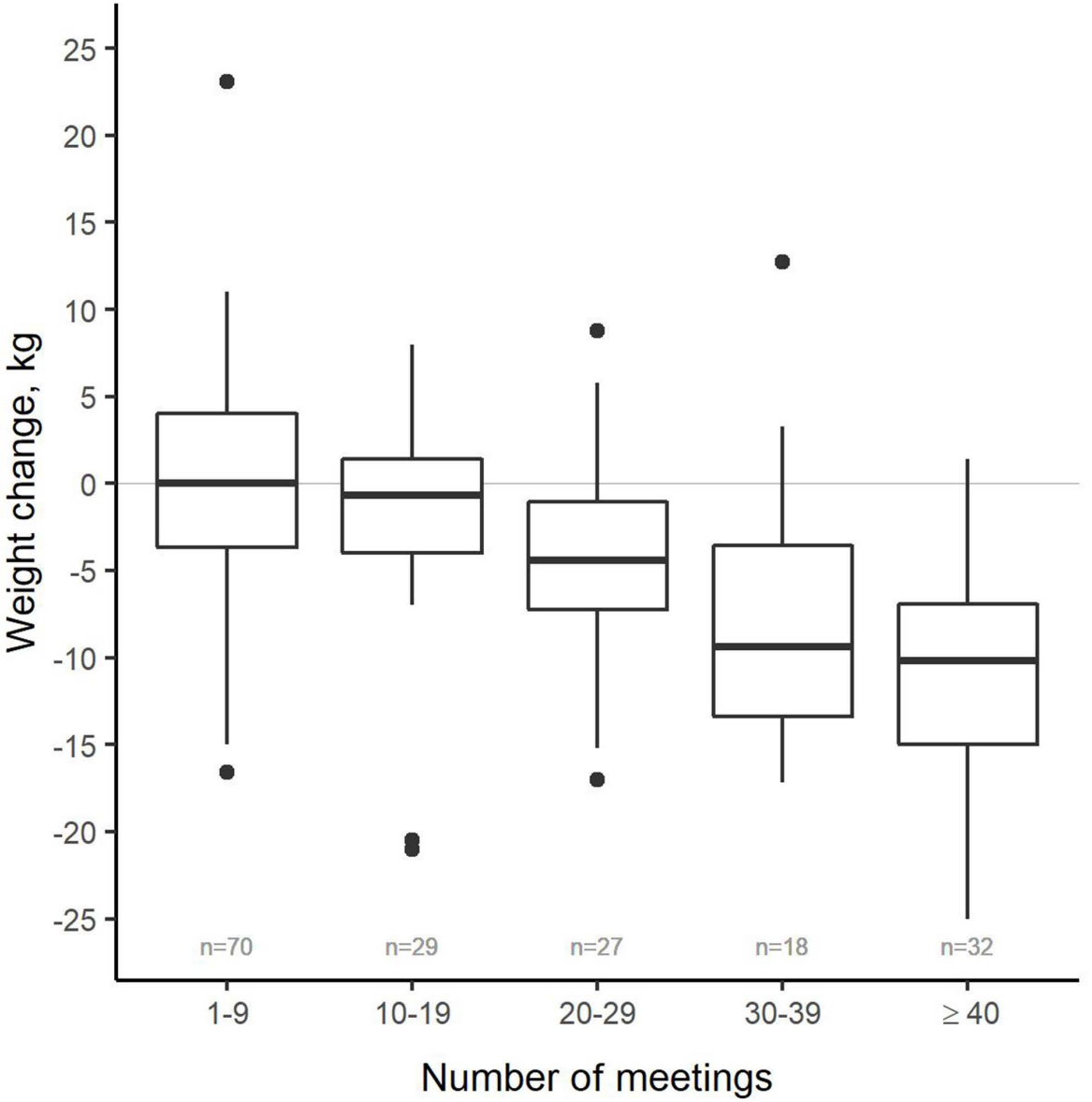
	Intervention group, No (%)	Control group, No (%)	Proportional difference, mean (95%CI)	Relative risk reduction (95%CI)	p-value
Lifestyle-related risk factor targets					
≥5% weight loss compared with baseline	90 / 280 (0.32)	40 / 257 (0.16)	0.17 (0.09 – 0.23)	2.07 (1.48 – 2.88)	<0.001
BMI ≤25 kg/m^2	10 / 280 (0.04)	0 / 257 (0.00)	0.04 (0.01 – 0.06)	Inf	<0.01
Non-smoking status					
Baseline smokers *	17 / 57 (0.30)	6 / 56 (0.11)	0.19 (0.04 – 0.33)	2.78 (1.18 – 6.54)	<0.05
Pre-event smokers †	48 / 65 (0.74)	42 / 48 (0.88)	-0.14 (-0.27 – 0.02)	0.84 (0.71 – 1.01)	0.10
≥10% increase in 6MWD compared with baseline ‡	79 / 164 (0.48)	64 / 154 (0.42)	0.07 (-0.04 – 0.17)	1.16 (0.91 – 1.48)	0.24
Absence of metabolic syndrome §	68 / 258 (0.26)	57 / 239 (0.24)	0.03 (-0.05 – 0.10)	1.11 (0.81 – 1.50)	0.54

*6MWD: 6-minute walking distance; All patients had a baseline BMI ≥27 kg/m^2; * In patients with a baseline urine-cotinine level >200 ng/ml, † In patients who quit smoking ≤6 months before hospitalisation, ‡ In patients with self-reported inadequate physical activity at baseline according to WHO recommendations, § According to American Heart Association guidelines.*

Online appendix, table 5: Significant effect modification of determinant-outcome associations for successful weight loss and weight gain by treatment allocation

	Intervention group, No (%)	Control group, No (%)	Risk ratio (95%CI)	p-value	p-value interaction
≥5% weight loss compared with baseline					
Age					<0.01
≥65 years	39 / 75 (0.52)	13 / 88 (0.15)	3.52 (2.04 – 6.08)	<0.001	
<65 years	51 / 205 (0.25)	27 / 169 (0.16)	1.56 (1.02 – 2.37)	0.04	
Smoking history					0.01
Non-smoking status	69 / 158 (0.44)	25 / 153 (0.16)	2.67 (1.79 – 3.99)	<0.001	
Smoking *	21 / 122 (0.17)	15 / 104 (0.14)	1.19 (0.65 – 2.19)	0.59	
Motivated for weight loss †					<0.001
Motivated	77 / 216 (0.36)	25 / 189 (0.13)	2.70 (1.79 – 4.05)	<0.001	
Not motivated	6 / 45 (0.13)	12 / 49 (0.25)	0.54 (0.22 – 1.33)	0.20	
≥1.0 kg weight gain compared with baseline					
Smoking at baseline					<0.01
Smoking at baseline ‡	28 / 57 (0.49)	18 / 56 (0.32)	1.53 (0.96 – 2.43)	0.07	
Not smoking	68 / 223 (0.31)	85 / 201 (0.42)	0.72 (0.56 – 0.93)	0.01	

*Values presented as counts, group size and percentage, * Patients with a baseline urine-cotinine level >200ng/ml or patients who quit smoking <6 months before hospitalization, † Patients who reported to be motivated for weight loss at the baseline visit, ‡ Patients with a baseline urine-cotinine level >200ng/ml.*


Weight change, kg
25
20
15
10
5
0
-5
-10
-15
-20
-25
n=70
n=29
n=27
n=18
n=32
1-9
10-19
20-29
30-39
≥ 40
Number of meetings