European Heart Journal (2015) **36**, 1519–1528
doi:10.1093/eurheartj/ehv111

Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients†

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Received 20 January 2014; revised 25 February 2015; accepted 17 March 2015; online publish-ahead-of-print 17 April 2015

See page 1500 for the editorial comment on this article (doi:10.1093/eurheartj/ehv138)

Aims To assess the effects of multi-disciplinary cardiac rehabilitation (CR) on survival in the full population of patients with an acute coronary syndrome (ACS) and patients that underwent coronary revascularization and/or heart valve surgery.

Methods and results Population-based cohort study in the Netherlands using insurance claims database covering ~22% of the Dutch population (3.3 million persons). All patients with an ACS with or without ST elevation, and patients who underwent coronary revascularization and/or valve surgery in the period 2007–10 were included. Patients were categorized as having received CR when an insurance claim for CR was made within the first 180 days after the cardiac event or revascularization. The primary outcome was survival time from the inclusion date, limited to a total follow-up period of 4 years, with a minimum of 180 days. Propensity score weighting was used to control for confounding by indication. Among 35 919 patients with an ACS and/or coronary revascularization or valve surgery, 11 014 (30.7%) received CR. After propensity score weighting, the adjusted hazard ratio (HR) associated with receiving CR was 0.65 (95% CI 0.56–0.77). The largest benefit was observed for patients who underwent coronary artery bypass grafting (CABG) and/or valve surgery (HR = 0.55, 95% CI 0.42–0.74).

Conclusion In a large and representative community cohort of Dutch patients with an ACS and/or intervention, CR was associated with a substantial survival benefit up to 4 years. This survival benefit was present regardless of age, type of diagnosis, and type of intervention.

Keywords Cardiac rehabilitation • Coronary artery disease • Acute coronary syndrome • Survival • Outcomes research • Observational study

Introduction

Millions of deaths due to cardiovascular disease (CVD) can be prevented,[1] with cardiac rehabilitation being one of several recommended treatments. Specifically, international guidelines recommend cardiac rehabilitation (CR) for all patients with an acute coronary syndrome [ACS; acute myocardial infarction (MI) or unstable angina pectoris], and for those who have undergone coronary revascularization [coronary artery bypass graft surgery (CABG) or percutaneous coronary interventions (PCI)], or valvular surgery.[2,3] Nevertheless, CR uptake remains low.[4–9]

Recently, the American Heart Association suggested that a lack of knowledge about the benefits of outpatient CR among both patients and healthcare providers is a major contributor to its persistent

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underutilization and stressed the need for research initiatives to fill gaps in the CR literature.[10] Although the efficacy of CR has been studied in at least 47 separate randomized controlled trials (RCTs),[11,12] most of these studies were performed in the 1980s and 90s. After this period, treatment options for coronary artery disease have been improved substantially [e.g. by the introduction of primary PCI and the implantable cardioverter defibrillator (ICD)]. Therefore, it has been questioned whether CR has retained its efficacy in the modern era.[13,14] Moreover, these trials typically enrolled predominately low-risk, middle-aged males following MI or PCI.[12] Therefore, it is not clear if the results of these trials can be extrapolated to other subgroups (e.g. females, elderly, and high-risk CR patients).

To date, few studies have documented the effect of outpatient CR on survival in community-based cohorts in daily clinical practice, i.e. outside the tightly controlled setting of an RCT. Most of these studies were conducted in the USA,[15–20] and were limited to subgroups of the overall population, including only Medicare beneficiaries aged 65 and older,[15] dialysis patients,[16] patients receiving PCI,[17] patients receiving coronary artery bypass surgery (CABG),[18] patients receiving combined heart valve and CABG,[19] or post-MI patients.[20] Outside the USA, Alter *et al.*[21] and Martin *et al.*[22] reported the effect of CR on survival in Canada; Beauchamp *et al.*[23] reported the effect of attendance at CR on survival in Australia; and Lewinter *et al.*[24] reported the effect of referral for CR (irrespective of participation) on survival in the UK. These studies, however, were limited to a single CR program, city, hospital, or county, respectively.

The objective of this study was to estimate the effect of CR in the full population and across the entire spectrum of acute indications for CR, using a large health insurance claims database in the Netherlands. Responding to the call for incorporating the impact of patient characteristics,[10] we report the effect of CR stratified by age, gender, and cardiac diagnosis/intervention. We hypothesized that CR in the Netherlands is associated with a survival benefit in the full population across all strata.

Methods

Cohort selection

The cohort consisted of 3.7 million persons insured for any period between 1 January 2007 and 1 June 2010, with 'Achmea Zorg en Gezondheid', a Dutch health insurance firm covering ~22% of the Dutch population. The population insured with Achmea includes people from all age categories and from both urban and rural areas, and has shown to be representative of the full Dutch population with respect to the prevalence of cardiac surgery and PCI.[4]

We identified patients eligible for CR based on insurance claims for hospital admissions or consultations related to ACS or cardiac interventions (CABG, PCI, valve surgery). In the Netherlands, these claims are filed according to a national diagnosis-treatment classification (DTC) system based on a combination of the hospital registration of diagnoses [International Classification of Diseases, 9th revision, clinical modification (ICD-9- CM) codes] and applied therapeutic interventions. We considered only those events for which the patient was alive and insured with Achmea for a 365-day period prior to, and during a 180-day period following the starting date of the event. Each patient was included in the study only once, with the inclusion date determined by the occurrence of the diagnosis or intervention with the highest expected CR uptake rate according to a prioritization algorithm that was defined in previous research.[4] Specifically, we first selected all patients who underwent one of the following interventions during the study period (in this order): CABG, valvular surgery, PCI acute, and PCI elective. Each patient was retrieved only once. Secondly, for patients who underwent CABG, valvular surgery, or PCI, we linked one of the following diagnoses (established in the previous 12 months) to these interventions (in this order): ST-elevation MI (STEMI), non-STEMI, unstable angina pectoris (AP), stable AP, and chronic heart failure (CHF). If no diagnosis was found, patients were retained in the study data set without listed diagnosis. Finally, the database was searched again, selecting from the remaining patients those with the following diagnoses during the study period (in this order): STEMI, non-STEMI, or unstable AP. These groups include patients who did not undergo one of the aforementioned interventions during the study period.

Treatment

In the Netherlands, it is mandatory to have health insurance. Reimbursement for outpatient CR after an ACS or cardiac intervention is provided by all insurance companies on the condition that a patient is referred by a cardiologist. Patients entering outpatient CR in The Netherlands are offered a comprehensive multi-disciplinary rehabilitation programme with a typical duration of 6–12 weeks, consisting of one or more group-based therapies (education, exercise training, relaxation therapy, and lifestyle modification therapy) supplemented by individual counselling when indicated (e.g. by a psychologist, dietician, or social worker). Consistent with international guidelines the Dutch guidelines for CR state[25] that the individualized programme should be based on a needs assessment procedure where data items concerning the patient's physical and psychosocial condition are gathered. In general, 85% of the patients receive exercise training, 75% receive education, 39% receive relaxation therapy, and 17% receive lifestyle modification therapy.[26]

Concerning exercise training, there is no fixed volume of training hours in these programmes, as baseline aerobic exercise capacity and personal training goals vary from patient to patient. However, programmes typically last 8–12 weeks during which patients attend two training sessions per week and training intensity is generally based on maximal heart rate which is determined by symptom limited exercise testing. Dutch CR guidelines recommend that training intensity should commence on a moderate intensity level with a gradual increase until the final intensity level in 1–2 weeks. According to a recent survey study[27] among Dutch CR centres, exercise training consists of aerobic training and strength training in the vast majority of the centres with a mean frequency of 2.3 per week, a session duration of 30 min and a total training volume of 6.7 h in post-ACS patients. The mean intensity of aerobic training in this group was 65% of maximal heart rate. Education therapy in Dutch CR centres is usually organized in four group sessions provided by a cardiologist, a dietician, a psychologist or social worker, and a physical therapist. A relaxation therapy program is generally based on the principles outlined by van Dixhoorn *et al.*[28] and typically consists of 4–6 sessions lasting 60–90 min. A lifestyle modification therapy program comprises individual screening and four group sessions, focusing on cognitive aspects of lifestyle behaviour (e.g. stress management, dietary habits, exercise behaviour, and smoking cessation). In addition to these group therapies, patients may be referred for individual treatment when needed (e.g. to a psychologist, dietician, or smoking cessation program). Specialized rehabilitation centres in the Netherlands typically offer nutritional counselling by a clinical dietitian to patients with overweight, hypertension, diabetes, or hypercholesterolaemia. Patients are sometimes referred to these specialized rehabilitation centres when their own hospital does not offer this service.

In the present study, consistent with previous observational studies,[15,17,19,22] patients were classified as having received CR when a claim was filed for at least one of the group-based outpatient treatments. Treatment status (CR vs. no CR) was determined between study inclusion and a 180-day landmark (i.e. during a 180-day period following the ACS or the cardiac intervention). Patients were excluded if they started CR prior to the inclusion date, more than 180 days after the inclusion date, or both.

Outcome

Survival time (in days) from the inclusion date onward was our main outcome, limited to a total follow-up period of 4 years, with a minimum of 180 days (the landmark period). For all patients who switched to another insurer during the study period or were alive at the end of the study period, survival status was unobserved (right-censored).

Confounders

We included six categories of potential confounders, all measured during the 365-day period up to (and including) the study inclusion date. The first five categories comprise variables which we expected a priori to be a potential confounder: (a) age and gender; (b) cardiac diagnoses and interventions recorded during hospital visits and admissions; (c) outpatient cardiac medication prescriptions; (d) co-morbid conditions derived from hospital diagnoses (part of the DTC system) and outpatient prescriptions; (e) total healthcare expenditure; the sixth category (f), included any other characteristics associated with survival, observed from the data, without a specific a priori expectation on its status as a confounder.

For this latter category, we examined all available information in the data, comprising hospital diagnoses-treatment combinations (DTC), outpatient prescriptions based on the hierarchical Anatomical Therapeutic Chemical (ATC) classification, and medical devices, the occurrence of lab tests, GP visits, intensive care unit (ICU) days, and other services not covered by the DTC system, to construct a large set of (proxies for) potential confounders [Whereas these characteristics all applied to the year before the inclusion date, we also added diagnoses and treatments occurring at the inclusion date. All variables occurred twice in the data, coded as 'at least 1' (0/1 indicator) and as the actual amount/quantity]. Because many of these characteristics applied to small groups of patients, lacking statistical power at this most detailed level, we added indicator variables aggregated across various dimensions. Specifically, we added aggregated variables for diagnoses, grouped diagnoses, treatments, grouped treatments, physician specialty, and 3-digit ATC prescription groups. Physician specialty and (grouped) diagnoses were interacted with being hospitalized (vs. outpatient care) in separate variables.

From this large set, confounders with a prevalence <100 or perfect correlation with treatment, outcome, or both, were excluded from the analysis. When two confounders had perfect correlation, only one was included in the analysis.

Statistical method

To estimate the effect of CR on survival, while controlling for potential confounders, we used a three-step approach. First, we aimed to select, from the six categories of confounders described in the previous section, a parsimonious set of variables related to the outcome of interest (survival time), using an automated variable selection method known as the lasso. Secondly, we applied inverse propensity score weighting to obtain a treatment (CR) and control (no CR) group, aiming for each of these variables to be distributed equally across both groups. Thirdly, we compared survival between both groups and estimated the effect of CR on survival using a Cox proportional hazards model. We further clarify each of the previous three steps in Supplementary material online, Technical Appendix.

Besides estimating the effect of CR in the entire cohort, we estimated the effect of CR in subgroups stratified by age, gender, type of intervention, and diagnosis. We used the same (propensity score) weights for each individual as before, then restricted the cohort to the subgroup of interest, and, within this subgroup, estimated a Cox proportional hazards model.

In an additional analysis, we also added potential confounders related to the period between inclusion and the 180-day landmark, i.e. the timeframe we used to determine treatment status. Because these potential confounders relate to events that might occur before or after the start of CR treatment, they can be true confounders (e.g. onset of a terminal disease preventing the patient to enter CR) or a result of the treatment (e.g. prescription of antidepressant medication for a mental condition diagnosed within the CR program). As such, we expected this analysis to yield a most conservative estimate of the effect of CR on survival, adjusting for both confounders preceding or occurring concurrent in time with CR treatment and any immediate effects of CR on downstream utilization.

We carried out sensitivity analyses to evaluate the robustness of our main result. First, we changed the landmark period from 180 to 90 days, and repeated the analyses. Secondly, we used conditioning rather than propensity score weighting to control for potential confounders in the Cox proportional hazards regression. All analyses were performed using SAS Version 9.1 (SAS, Cary, NC, USA) and R version 2.15.2[29] using the R packages glmnet,[30,31] twang,[32] and survival.[33]

Results

We identified 38 369 patients eligible for CR during the period 1 January 2007–3 June 2010 [24 014 with at least one of the interventions CABG, valve surgery, or PCI; and 14 355 with an acute coronary syndrome (MI or unstable AP)], continuously insured with Achmea during a period starting 365 days before the event and ending 180 days thereafter (see *Figure 1* for patient flow). We excluded 2450 patients because of the following reasons: initiation of CR during the year before the inclusion date (1312 patients); initiation of CR more than 180 days after the inclusion date (556); unknown gender (6); initiation of inpatient cardiac rehabilitation within 1 year after the inclusion date (635); or censored within 10 days of follow-up (23).

The final study population included 35 919 patients. The mean age of the population was 66.7 years and the majority was male (63.5 percent). Medication use and comorbid conditions in the treatment and control groups are listed in *Table 1*.

Out of a total of 919 potential confounders, 99 remained after applying automated variable selection (details on these results and methodology are provided in Supplementary material online, Technical Appendix). Of these 99 variables, we show a subset of 26 in *Table 1* (a table including all 99 variables is added as a Supplementary material online, Appendix). *Table 1* shows substantial and statistically significant differences between both groups (CR vs. no CR). For example, patients not receiving CR were on average 4.8 years older, more likely to be female, had 1220 euro higher medical cost in the prior year, were more likely to have specific comorbid conditions and were more likely to have received specific cardiac medications, including statins and antiplatelets (clopidogrel and aspirin). Patients receiving CR were more likely to have received CABG or

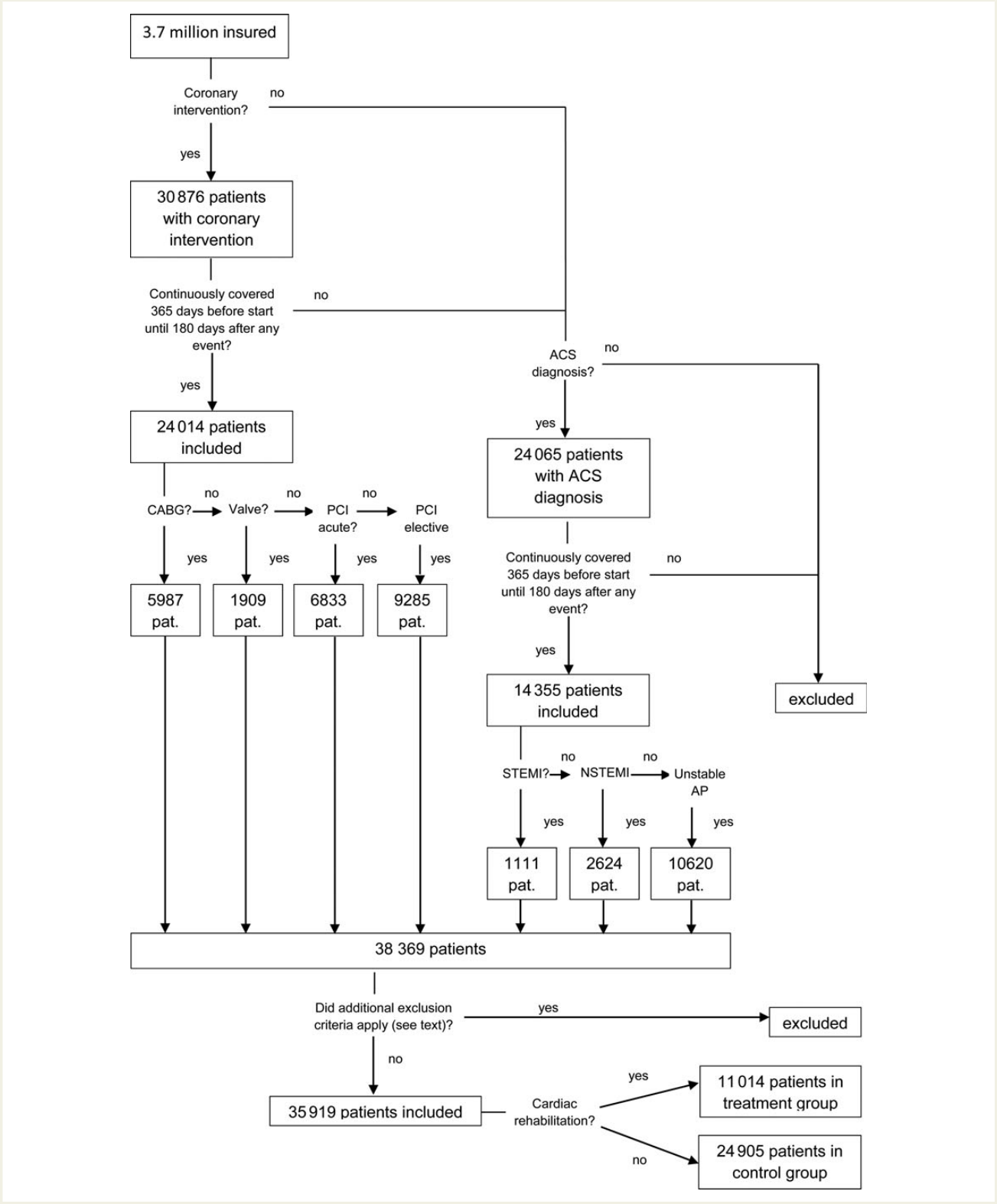

Figure 1 Flow of participants through study.

acute PCI; and were more likely to have been diagnosed with MI in the year prior to inclusion. The full set of 99 variables included indicators of underlying co-morbidities, for example hospital visits/admissions related to a heart failure diagnosis; and physical limitations, such as hospital visits/admissions to the orthopaedic, pulmonology, or neurology department, and visits of the GP to the patient's home.

Table 1 Comparison of treatment and controls in original cohort and propensity score weighted cohort ($N_{Treatment}$ = 11 014; $N_{Control}$ = 24 905)

Variable	Treatment	Control (original)	*P*-value	Control (weighted)	*P*-value
Age, years [standard deviation (SD)]	63.38 (10.82)	68.13 (13.21)	<0.01	63.53 (10.82)	0.35
Female (%)	2801 (25)	10 391 (42)	<0.01	2603 (25)	0.40
Prior year medical expenditures[a], × 1000 euro (SD)	6.30 (8.29)	7.52 (12.26)	<0.01	6.30 (8.49)	0.98
Cardiac medications, any prescription during 365-day period preceding study inclusion (%)					
Beta blockers	5335 (48)	13 689 (55)	<0.01	5066 (49)	0.98
Statins	4915 (45)	12 508 (50)	<0.01	4634 (44)	0.70
ACE inhibitors	2613 (24)	7295 (29)	<0.01	2426 (23)	0.41
Angiotensin II receptor antagonists	1874 (17)	4985 (20)	<0.01	1806 (17)	0.66
Clopidogrel	931 (9)	2418 (10)	<0.01	930 (9)	0.28
Aspirin	4894 (44)	13 006 (52)	<0.01	4641 (44)	0.96
Intervention (%)					
CABG	3358 (31)	2008 (8)	<0.01	3136 (30)	0.53
Valve surgery	910 (8)	807 (3)	<0.01	855 (8)	0.86
PCI acute	3460 (31)	2956 (12)	<0.01	3329 (32)	0.58
PCI elective	2186 (20)	6368 (26)	<0.01	2112 (20)	0.51
None of the above	1100 (10)	12 766 (51)	<0.01	1022 (10)	0.55
Diagnosis (%)					
STEMI	3487 (32)	2940 (12)	<0.01	3339 (32)	0.72
NSTEMI	1745 (16)	3499 (14)	<0.01	1742 (17)	0.15
Unstable AP	2722 (25)	13 802 (55)	<0.01	2514 (24)	0.29
Stable AP	1633 (15)	3481 (14)	0.04	1518 (15)	0.56
CHF	125 (1)	144 (1)	<0.01	109 (1)	0.55
None of the above	1302 (12)	1039 (4)	<0.01	1234 (12)	0.97
Comorbid conditions, any during 365-day period preceding study inclusion (%)					
Diabetes medication use	1630 (15)	4934 (20)	<0.01	1504 (14)	0.42
Stroke/TIA hospital diagnosis	218 (2)	660 (3)	<0.01	201 (2)	0.79
Cancer hospital diagnosis	648 (6)	1986 (8)	<0.01	590 (6)	0.48
COPD/Asthma medication use	1566 (14)	4932 (20)	<0.01	1488 (14)	0.98
Antigout medication use	293 (3)	889 (4)	<0.01	293 (3)	0.58
Sulfonamide medication use	903 (8)	4337 (17)	<0.01	840 (8)	0.65

AP, angina pectoris; CABG, coronary artery bypass graft; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary interventions; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; TIA, transient ischaemic attack.
Diabetes medication use refers to ATC class A10 (including, e.g. insulin and oral glucose lowering medications), COPD/Asthma medication use refers to ATC class R03 (including, e.g. beta-2-adrenoreceptor agonists, anticholinergics, and glucocorticoids), Antigout medication use refers to ATC class M04 (including, e.g. allopurinol and colchicine), Sulfonamide medication use refers to ATC class C03CA (including, e.g. loop diuretics).
[a]Sum of all reimbursements for medical treatments by health insurer during 365-day period preceding study inclusion

In total, 11 014 patients (30.7%) started CR within 180 days after the inclusion date. Median follow-up (counting from the study inclusion date) was 25.2 months (min. 6 months, max. 48 months). *Table 2* compares crude mortality rates between patients who received CR and those who did not receive CR. In the full cohort, the mortality rate (deaths per 1000 person-years) for the former was 12.2, more than three times lower than the mortality rate (39.6) for patients who did not receive CR. Across the eight subgroups shown in *Table 2*, crude mortality rates were consistently lower for patients receiving CR compared with those not receiving CR.

After applying propensity score weighting, the characteristics shown in *Table 1* are distributed evenly between both groups, with no differences being statistically significant for any variable. In the full set of 99 variables, 92 differed significantly ($P < 0.05$) without propensity score adjustment. After propensity score adjustment, two differences remained statistically significant ($P < 0.05$), less than half of the expected number to occur by chance alone, suggesting excellent balance between both groups. In the subgroup analyses, the number of statistically significant differences varied between zero (age ≤70) and six (females, no ACS). *Figure 2* shows, for all 99 variables, the absolute standardized difference before and after propensity score weighting. After propensity score weighting, these standardized differences are well below 10%, a threshold commonly considered to indicate sufficient balance.

Table 3 shows the effect of cardiac rehabilitation on survival, estimated through the Cox proportional hazards model, after propensity score weighting to adjust for observable confounders. In the full cohort, patients receiving CR had a large and statistically

Table 2 Crude death rates in full cohort and subgroups

		Cardiac rehabilitation			No cardiac rehabilitation		
	n	Deaths	*n*	Deaths/1000 person-years	Deaths	*n*	Deaths/1000 person-years
Full cohort	35 919	287	11 014	12.2	2160	24 905	39.6
Age ≤70	20 357	117	7728	7.1	394	12 629	13.9
Age >70	15 562	170	3286	24.9	1766	12 276	67.7
Male	22 727	208	8213	11.9	1275	14 514	40.0
Female	13 192	79	2801	13.3	885	10 391	39.0
CABG/valve surgery	7083	108	4268	11.6	192	2815	30.1
No CABG/valve surgery	28 836	179	6746	12.7	1968	22 090	40.9
ACS	28 195	206	7954	12.3	1905	20 241	43.2
No ACS	7724	81	3060	12.1	255	4664	24.5

ACS, acute coronary syndrome; CABG, coronary artery bypass graft.

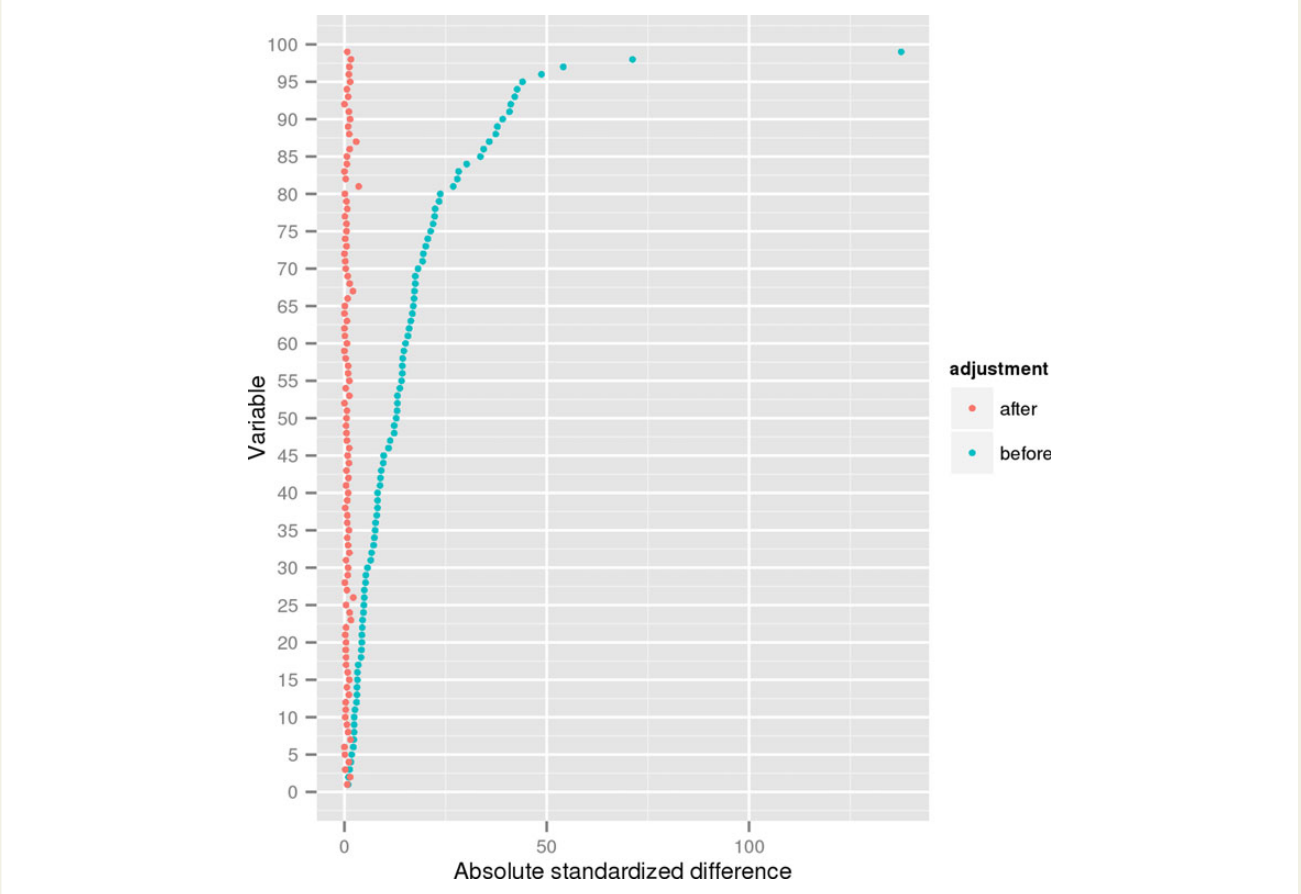

Figure 2 Absolute standardized differences (%) for all 99 variables, before and after propensity score weighting.

significant survival benefit [hazard ratio (HR) = 0.65, 95% CI 0.56–0.77] compared with patients not receiving CR, over the full (48 months) follow-up period. For shorter follow-up periods the effect was larger (HR = 0.5, 95% CI 0.37–0.67), which is an indication that the assumption of proportional hazards did not hold. Specifically, when testing for constant proportionality of hazards over time, we observed a statistically significant association between the scaled Schoenfeld residuals and time. We therefore report, in *Table 3*, the

Table 3 Effect of CR vs. no CR (adjusted hazard ratio) over time in full cohort and subgroups

	Month 6–12 Adjusted hazard ratio (95% CI)	Month 6–24 Adjusted hazard ratio (95% CI)	Month 6–48 Adjusted hazard ratio (95% CI)
Full cohort	0.50** (0.37–0.67)	0.58** (0.48–0.71)	0.65** (0.56–0.77)
Age ≤70	0.48** (0.29–0.78)	0.52** (0.38–0.72)	0.60** (0.45–0.78)
Age >70	0.50** (0.34–0.73)	0.63** (0.50–0.79)	0.68** (0.56–0.83)
Male	0.45** (0.31–0.64)	0.55** (0.44–0.70)	0.62** (0.51–0.74)
Female	0.71 (0.41–1.24)	0.67* (0.45–0.98)	0.79 (0.58–1.08)
CABG/valve surgery	0.43** (0.26–0.71)	0.54** (0.38–0.75)	0.55** (0.42–0.74)
No CABG/valve surgery	0.58** (0.40–0.84)	0.62** (0.49–0.79)	0.71** (0.58–0.86)
ACS	0.55** (0.39–0.77)	0.61** (0.48–0.76)	0.68** (0.57–0.82)
No ACS	0.42** (0.23–0.74)	0.52** (0.36–0.76)	0.57** (0.41–0.79)

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CR, cardiac rehabilitation.
All (adjusted) hazard ratios correspond to the Average Treatment effect on the Treated (ATT) of CR vs. no CR, after adjusting for confounders using doubly robust propensity score weighting.
*$P < 0.05$ (CR vs. no CR).
**$P < 0.01$ (CR vs. no CR).

effect of CR separately for three different follow-up periods (12, 24, and 48 months from the study inclusion date). Our study was not designed to estimate the duration of the effect of CR. The results presented in *Table 3* should not be interpreted with respect to the duration of the effect of CR.

The effect of CR was present, regardless of age category, type of intervention, type of diagnosis, or follow-up period. However, for females, the effect of CR was statistically significant only for the 24-month follow-up period (HR = 0.67, 95% CI 0.45–0.98). The largest benefit, over the full follow-up period, was observed for patients who had CABG/valve surgery (HR = 0.55, 95% CI 0.42–0.74). Kaplan–Meier survival curves for both groups, after propensity score weighting, are shown in *Figure 3*.

When extending the initial set of covariates related to the year prior to inclusion, with a similar set related to the landmark period, the set of variables selected by the automated variable selection method increased from 99 to 246. Re-estimating the effect of CR on survival using this larger set, yielded a (most conservative and still statistically significant) HR of 0.79 (95% CI 0.66–0.95).

To evaluate the robustness of our main result, we re-estimated the effect of CR in the full cohort, using a 90-day instead of a 180-day landmark period and found the difference to be negligible ($HR_{90\text{-day}} = 0.63$, 95% CI 0.54–0.73 vs. $HR_{180\text{-day}} = 0.65$, 95% CI 0.56–0.77). In an additional sensitivity analysis, we re-estimated the effect in a single Cox proportional hazards model including the treatment and all 99 covariates directly, i.e. without using the propensity score approach, observing a hazard ratio of 0.68 (95% CI 0.59–0.78).

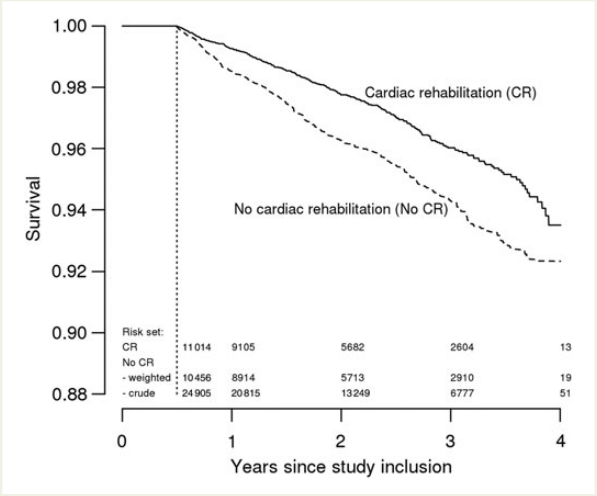

Figure 3 Kaplan–Meier survival curves for patients receiving CR (solid line) and patients not receiving CR (dotted line), after propensity score weighting to adjust for age, gender, clinical cardiac diagnosis, and intervention, prescribed medication, co-morbidities, total healthcare expenditure, and other confounding factors derived from the data.

Discussion

Our findings show that receiving multi-disciplinary cardiac rehabilitation in the Netherlands is associated with a substantial survival benefit in the first 4 years following an ACS or cardiac intervention. The survival benefit associated with CR was present regardless of age, type of diagnosis, type of intervention, and follow-up duration. For females, CR uptake was associated with a statistically significant survival benefit at 2 years of follow-up only.

To study the effect of medical treatments, there is a trade-off involved between internal and external validity. Randomized controlled trials typically have high internal validity because confounding is controlled for by randomization, but often lack external validity due to selection bias (e.g. when specific patient groups were underrepresented or not included) and an artificial setting. Observational designs (as used in this study) have high external validity because the study population and setting are highly representative of the real world, but confounding due to unobserved covariates cannot be controlled

for. We think both designs can complement each other to inform health policy decisions.

The main strength of our study is that it documents the effect of modern multi-disciplinary CR in its real-world implementation, as opposed to in an idealized, tightly controlled trial setting. Secondly, while previous studies documented this effect for the USA, Canada, and Australia, this is the first study to provide such estimates for a European country. Thirdly, our cohort is representative of the full Dutch population, and includes all patients with an ACS, eligible for CR based on current guidelines. Fourthly, the size of our cohort allowed direct comparisons between subgroups, some of which are often underrepresented in clinical trials, such as women, patients with a relatively poor survival prognosis (e.g. the elderly), and those at lower risk (e.g. patients without ACS). Finally, our study stands out in methodological rigour by adjusting both for known confounders such as clinical cardiac diagnosis and intervention, prescribed medication, and co-morbidities but also for all other confounding factors that could be derived from the data.

Our estimates on the effect of CR in the community are remarkably close to the 1-year 58.5% and 5-year 33% survival benefits reported by Suaya *et al.*[15] for a large cohort of Medicare beneficiaries aged 65 and older, even though the inclusion year (1997) for this study predates ours by more than 10 years. They are also close to the 33% survival benefit reported by Martin *et al.*[22] for Canadian CR participants who completed the program (compared with those who did not participate or complete). Our estimates are smaller compared with the 46% survival benefit of CR following PCI or CABG found by Goel *et al.*[17] and Pack *et al.*,[18] the 52% survival benefit of CR following combined heart valve and CABG surgery found by Goel *et al.*,[19] the 56% survival benefit found by Witt *et al.*[20] for US patients receiving PCI and post-MI, respectively, and the 53% survival benefit reported by Alter *et al.*[21] for Canadian patients following cardiac hospitalization. These differences are even more striking, because the magnitude of the effect in our study diminishes with longer follow-up times, and the average follow-up time in these three studies is approximately three times longer than in our study. A possible, although speculative, explanation for these differences is that CR has not yet reached its full potential in the Netherlands in terms of quality and comprehensiveness, compared with the USA and Canada. In fact, The Dutch Health Care Inspectorate recently released a report stating that both the participation rates and the quality of Dutch cardiac rehabilitation programs are insufficient[34] Another explanation is that our approach was able to remove more bias resulting from confounders, compared with these other studies, because we systematically searched and adjusted for all variables on prior utilization independently associated with survival, instead of only adjusting for a limited set of a priori chosen variables.

Compared with estimates on the effect of CR from clinical trials, our estimates are larger. A systematic review by Heran *et al.*[12] found a relative risk of exercise-based CR on total mortality up to 12 months of 0.82 (95% CI 0.67–1.01), and a relative risk of 0.87 (95% CI 0.75–0.99) for follow-up longer than 12 months, across a total of 33 studies. A possible explanation for the difference with our results is that these trials enrolled lower-risk patients, who might benefit less from CR, compared with the full population eligible for CR. Furthermore, this discrepancy with our study may be explained by differences in interventions that were used. As outlined, CR programs in The Netherlands generally consist of a combination of interventions (e.g. education, exercise training, relaxation therapy, lifestyle modification therapy and individual counselling by a psychologist, dietician or social worker) rather than exercise training only. Combining these different types of interventions may result in higher motivation, better self-management skills and, as a consequence, in more sustained lifestyle changes and a reduction of the risk for future cardiovascular events. In fact, a recent meta-analysis[35] showed a greater survival benefits of multimodal interventions (OR 0.48) when compared with exercise-based interventions only (OR 0.62). Finally, an explanation would be the presence of unobserved confounders for which our observational design could not control.

In contrast with previous large cohort studies,[15,17] we found smaller survival benefits in women, which were not longer significant at 4 years. A possible explanation for this finding may be a higher amount of non-completers/dropouts among females. This would be in line with the findings by Martin *et al.*,[22] indicating a relatively high percent of non-completers among females (approximately two-thirds) and a direct relation between CR attendance and survival. Proposed explanations for low CR attendance in women include lower referral by physicians, and less support/encouragement from healthcare personnel and spouses to participate in these programs.[36]

A limitation of our observational study design, using inverse propensity score weighting, is that we could not control for confounders not observable in our data, including cardiovascular risk factors, fitness status, general activity, left-ventricular function, and patient motivation. Therefore, there may be residual confounding in the association between CR and outcomes in this study. Collecting these data was not feasible, due to our retrospective design and use of administrative data. Most of the recent observational studies on the effect of CR on survival, however, did not identify cardiovascular risk factors as major confounders. Specifically, three recent observational studies on the effect of CR on survival,[17–19] found no statistically significant differences between CR participants and non-participants with respect to smoking status, body-mass index (BMI), hypertension, and hypercholesterolaemia. In a fourth study,[22] differences for hyperlipidaemia, and hypertension were, although statistically significant, small from a clinical perspective (<5 percentage-points on baseline rates from 60 to 70%). We suspect that this is also true for fitness status and general activity levels, as these are likely correlated with smoking and BMI. This may, however, not be true for the presence of heart failure. Whereas Goel *et al.*[17] and Goel *et al.*[19] reported no difference in left-ventricular ejection fraction between CR participants and non-participants, Witt *et al.*[20] observed lower ejection fractions among CR participants. Pack *et al.*[18] observed a higher ejection fraction among CR participants compared with non-participants and Martin *et al.*[22] observed a higher ejection fraction among CR participants who completed the program when compared with non-completers. In our own analysis, we had no indication that left-ventricular function differed between CR participants and non-participants, for two reasons. First, we did not observe a significant difference ($P = 0.7$) in the number of ICD's in the weighted control and treatment groups (12 vs. 11). As current Dutch guidelines recommend ICD implantation in all patients with symptomatic heart failure (NYHA III)

and a left-ventricular ejection fraction $<30\%$,[37] this finding suggests that there is no substantial difference in heart failure patients in both groups. Secondly, after propensity score weighting, there was no significant difference in the use of aldosterone antagonists and sulphonamides (comprising the most commonly used loop diuretics) between patients receiving CR (2.6 and 8.2%, respectively) and not receiving CR (2.4 and 8.0%, respectively). Finally, if patient motivation (to adopt a healthy lifestyle) would have had a positive effect on CR participation, our estimates reflect a combined effect of cardiac rehabilitation and motivation, rather than the isolated effect of CR alone. However, due to the nature of the definition of CR in our study (i.e. a billing code for at least one of the therapies applied in CR), patients with insufficient motivation to complete the CR program and even early dropouts were still included in the treatment group. Therefore, we believe that motivational issues did not have a substantial influence on the results of this study.

A second potential limitation is that the data we used were collected for administrative (reimbursement) purposes, rather than scientific research, and lack detail in terms of secondary diagnoses, general practice diagnoses, and laboratory test results. The definition of diseases included as covariates were based on hospital admissions that may cause some misclassification. However, registration of the data is complete, accurate, subject to extensive control and comprehensive auditing because of the economic function of the data.[38] Thirdly, due to limitations in the data, we were not able to measure the composition of individual CR programs, to assess adherence or dropout, or to study actual reasons for patients not to participate in a CR program. Hence, our estimates might mask underlying heterogeneity and should be considered an average effect of CR as it was offered in the Netherlands between 2007 and 2010. However, patients who were referred to a CR program, but did not start the program (i.e. not even the intake) are most likely included in the control group in our study, because hospitals are not allowed to charge for services they did not provide.

A final limitation is that changes in cardiovascular medication might have occurred after the study inclusion date, and before, during or after the CR program, possibly confounding the effect estimate of CR. However, our most conservative estimate (HR 0.79), provides an estimate of the effect of CR, while controlling for such changes in medication and utilization of healthcare services occurring during the landmark period.

The substantial survival benefits documented in our study, together with the low uptake of CR in the Netherlands and elsewhere, suggest that many patients die unnecessarily due to undertreatment following a cardiac diagnosis or intervention. Strategies to improve uptake of CR include automatic referral systems, introduction of performance measures and education of both patients and health care professionals.[39] In addition, computerized decision support has been shown to improve CR quality by increasing professional concordance to clinical practice guidelines.[26] Future research should investigate whether these strategies indeed improve quality and uptake of CR, and whether improvements in uptake will indeed materialize into fewer deaths.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This project was funded by ZonMW, the Netherlands Organisation for Health Research and Development, Health Care Efficiency Research Program 2008, subprogram Implementation, under project no. 80-82315-98-08305.

Conflict of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: The study group had financial support from the Netherlands Organisation for Health research and Development (ZonMW) for the submitted work; R.A.K. is founder and director of the CardioVitaal cardiac rehabilitation program, chairman of the Committee Cardiovascular Prevention and Rehabilitation of the Dutch Cardiology Society (NVVC-CCPH) and chairman of the Dutch National Multidisciplinary Council for Cardiac Rehabilitation (LMDOH); no other financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. H.d.V. received consulting fees from AstraZeneca and Johnson & Johnson, unrelated to this study. H.d.V. was supported by Achmea as a salaried employee.

References

1. World Health Organization. Cardiovascular diseases. **http://www.who.int/cardiovascular_diseases/en/** (10 December 2013) 2011.
2. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler AD, Schmid JP. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:1–17.
3. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, Thompson PD, Williams MA, Lauer MS. Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease: An American Heart Association Scientific Statement From the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in Collaboration With the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2005;**111**:369–376.
4. van Engen-Verheul M, de Vries H, Kemps H, Kraaijenhagen R, de Keizer N, Peek N. Cardiac rehabilitation uptake and its determinants in the Netherlands. *Eur J Prev Cardiol* 2013;**20**:349–356.
5. Arthur HM, Suskin N, Bayley M, Fortin M, Howlett J, Heckman G, Lewanczuk R. The Canadian Heart Health Strategy and Action Plan: Cardiac rehabilitation as an exemplar of chronic disease management. *Can J Cardiol* 2010;**26**:37–41.
6. Cortes O, Arthur HM. Determinants of referral to cardiac rehabilitation programs in patients with coronary artery disease: a systematic review. *Am Heart J* 2006;**151**:249–256.
7. Bethell H, Lewin R, Evans J, Turner S, Allender S, Petersen S. Outpatient cardiac rehabilitation attendance in England: variability by region and clinical characteristics. *J Cardiopulm Rehabil Prev* 2008;**28**:386–391.
8. Márquez-Calderón S, Villegas Portero R, Briones Pérez de la Blanca E, Sarmiento González-Nieto V, Reina Sánchez M, Sáinz Hidalgo I, Velasco Rami JA, Ridocci Soriano F. Incorporation of cardiac rehabilitation programs and their characteristics in the Spanish National Health Service. *Rev Esp Cardiol* 2003;**56**:775–782.
9. Mendes M. National survey of cardiac rehabilitation programs in Portugal--situation in 1999. *Rev Port Cardiol* 2001;**20**:7–19.
10. Arena R, Williams M, Forman DE, Cahalin LP, Coke L, Myers J, Hamm L, Kris-Etherton P, Humphrey R, Bittner V, Lavie CJ. Increasing referral and participation rates to outpatient cardiac rehabilitation: the valuable role of healthcare professionals in the inpatient and home health settings: a science advisory from the American Heart Association. *Circulation* 2012;**125**:1321–1329.
11. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Am Heart J* 2011;**162**:571–584.
12. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2011;CD001800.

13. Lewin R, Doherty P. Cardiac rehabilitation and mortality reduction after myocardial infarction: the emperor's new clothes? Evidence in favour of cardiac rehabilitation. *Heart* 2013;**99**:909–911.
14. West R, Jones D. Cardiac rehabilitation and mortality reduction after myocardial infarction: the emperor's new clothes? Evidence against cardiac rehabilitation. *Heart* 2013;**99**:911–913.
15. Suaya JA, Stason WB, Ades PA, Normand SL, Shepard DS. Cardiac rehabilitation and survival in older coronary patients. *J Am Coll Cardiol* 2009;**54**:25–33.
16. Kutner NG, Zhang R, Huang Y, Herzog CA. Cardiac rehabilitation and survival of dialysis patients after coronary bypass. *J Am Soc Nephrol* 2006;**17**:1175–1180.
17. Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation* 2011;**123**:2344–2352.
18. Pack QR, Goel K, Lahr BD, Greason KL, Squires RW, Lopez-Jimenez F, Zhang Z, Thomas RJ. Participation in cardiac rehabilitation and survival after coronary artery bypass graft surgery: a community-based study. *Circulation* 2013;**128**:590–597.
19. Goel K, Pack QR, Lahr B, Greason KL, Lopez-Jimenez F, Squires RW, Zhang Z, Thomas RJ. Cardiac rehabilitation is associated with reduced long-term mortality in patients undergoing combined heart valve and CABG surgery. *Eur J Prev Cardiol* 2015;**22**:159–68.
20. Witt BJ, Jacobsen SJ, Weston SA, Killian JM, Meverden RA, Allison TG, Reeder GS, Roger VL. Cardiac rehabilitation after myocardial infarction in the community. *J Am Coll Cardiol* 2004;**44**:988–996.
21. Alter DA, Oh PI, Chong A. Relationship between cardiac rehabilitation and survival after acute cardiac hospitalization within a universal health care system. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:102–113.
22. Martin BJ, Hauer T, Arena R, Austford LD, Galbraith PD, Lewin AM, Knudtson ML, Ghali WA, Stone JA, Aggarwal SG. Cardiac rehabilitation attendance and outcomes in coronary artery disease patients. *Circulation* 2012;**126**:677–687.
23. Beauchamp A, Worcester M, Ng A, Murphy B, Tatoulis J, Grigg L, Newman R, Goble A. Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart* 2013;**99**:620–625.
24. Lewinter C, Bland JM, Crouch S, Doherty P, Lewin RJ, Køber L, Hall AS, Gale CP. The effect of referral for cardiac rehabilitation on survival following acute myocardial infarction: a comparison survival in two cohorts collected in 1995 and 2003. *Eur J Prev Cardiol* 2014;**21**:163–71.
25. Rehabilitation Committee: Netherlands Society for Cardiology (NVVC) and Netherlands Heart Foundation (NHS) (both Guidelines on Cardiac Rehabilitation 2004) and Working Group PAAHR (partial revision 2011). *Multidisciplinary Guidelines for Cardiac Rehabilitation (in Dutch)*. Utrecht: Netherlands Society for Cardiology (NVVC) **http://www.nvvc.nl/hr**, 26 March 2015, date last accessed; 2011.
26. Goud R, de Keizer NF, ter Riet G, Wyatt JC, Hasman A, Hellemans IM, Peek N. Effect of guideline based computerised decision support on decision making of multidisciplinary teams: cluster randomised trial in cardiac rehabilitation. *BMJ* 2009;**338**:b1440.
27. Vromen T, Spee RF, Kraal JJ, Peek N, van Engen-Verheul MM, Kraaijenhagen RA, Gijsbers HJ, Kemps HM. Exercise training programs in Dutch cardiac rehabilitation centres. *Neth Heart J* 2013;**21**:138–143.
28. Van Dixhoorn JJ, Duivenvoorden HJ. Effect of relaxation therapy on cardiac events after myocardial infarction: a 5-year follow-up study. *J Cardiopulm Rehabil* 1999;**19**:178–185.
29. R Core Team. *R: A language and environment for statistical computing*. **http://www.R-project.org/**, 26 March 2015, date last accessed. Vienna, Austria: R Foundation for Statistical Computing; 2012.
30. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010;**33**:1–22.
31. Simon N, Friedman J, Hastie T, Tibshirani R. Regularization paths for Cox's proportional hazards model via coordinate descent. *J Stat Softw* 2011;**39**:1–13.
32. Ridgeway G, McCaffrey D, Morral A, Griffin BA, Burgette L. Twang: Toolkit for Weighting and Analysis of Nonequivalent Groups. R package version 1.3–20. **http://cran.r-project.org/package=twang**, 26 March 2015, date last accessed.
33. Therneau T. A Package for Survival Analysis in S. R package version 2.37–4. 2013. **http://cran.r-project.org/package=survival**, 26 March 2015, date last accessed.
34. Reulings PG, van der Lans S. Cardiac rehabilitation with lifestyle counselling after myocardial infarction: it helps, but not everyone undergoes it. *Ned Tijdschr Geneeskd* 2012;**156**:A5758 [Article in Dutch].
35. Müller-Riemenschneider F, Meinhard C, Damm K, Vauth C, Bockelbrink A, Greiner W, Willich SN. Effectiveness of nonpharmacological secondary prevention of coronary heart disease. *Eur J Cardiovasc Prev Rehabil.* 2010;**17**:688–700.
36. Caulin-Glaser T, Blum M, Schmeizl R, Prigerson HG, Zaret B, Mazure CM. Gender differences in referral to cardiac rehabilitation programs after revascularization. *J Cardiopulm Rehabil* 2001;**21**:24–30.
37. van Erven L, van Dessel PFHM, Simmers TA, van Gelder IC, Hauer RNW, Wever EFD, Dijkman B, Jordaens L, Ramdat Misier A, Meijer A, Bosker HA, Schalij MJ. Guidelines ICD implantation 2005—an update. **https://www.nvvc.nl/media/richtlijn/25/Guidelines%20ICD%20implantation%202005%20-%20an%20update.pdf**, 26 March 2015, date last accessed. 2006.
38. Smeets HM, de Wit NJ, Hoes AW. Routine health insurance data for scientific research: potential and limitations of the Agis Health Database. *J Clin Epidemiol* 2011;**64**:424–430.
39. Reeves GR, Whellan DJ. Recent advances in cardiac rehabilitation. *Curr Opin Cardiol* 2010;**25**:589–596.