Impact of Cardiac Rehabilitation on Mortality and Cardiovascular Events After Percutaneous Coronary Intervention in the Community

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Background—Although numerous studies have reported that cardiac rehabilitation (CR) is associated with reduced mortality after myocardial infarction, less is known about its association with mortality after percutaneous coronary intervention.

Methods and Results—We performed a retrospective analysis of data from a prospectively collected registry of 2395 consecutive patients who underwent percutaneous coronary intervention in Olmsted County, Minnesota, from 1994 to 2008. The association of CR with all-cause mortality, cardiac mortality, myocardial infarction, or revascularization was assessed with 3 statistical techniques: propensity score–matched analysis (n=1438), propensity score stratification (n=2351), and regression adjustment with propensity score in a 3-month landmark analysis (n=2009). During a median follow-up of 6.3 years, 503 deaths (199 cardiac), 394 myocardial infarctions, and 755 revascularization procedures occurred in the study subjects. Participation in CR, noted in 40% (964 of 2395) of the cohort, was associated with a significant decrease in all-cause mortality by all 3 statistical techniques (hazard ratio, 0.53 to 0.55; $P<0.001$). A trend toward decreased cardiac mortality was also observed in CR participants; however, no effect was observed for subsequent myocardial infarction or revascularization. The association between CR participation and reduced mortality rates was similar for men and women, for older and younger patients, and for patients undergoing elective or nonelective percutaneous coronary intervention.

Conclusion—We found that CR participation after percutaneous coronary intervention was associated with a significant reduction in mortality rates. These findings add support to published clinical practice guidelines, performance measures, and insurance coverage policies that recommend CR for patients after percutaneous coronary intervention. **(*Circulation*. 2011;123:2344-2352.)**

Key Words: angioplasty ■ cardiac rehabilitation ■ exercise ■ mortality ■ prevention ■ stents

Cardiac rehabilitation (CR) is associated with a 20% to 30% reduction in mortality in persons with coronary artery disease, particularly after myocardial infarction (MI).[1–3] This benefit is thought to be mediated by several factors, including the physiological benefits of exercise training,[4,5] psychological benefits of group support and counseling,[6] improved adherence to preventive therapies,[7] and improved control of cardiovascular risk factors.[4,8] Unfortunately, even with this strong evidence, only ≈25% of eligible patients in the United States participate in CR.[9]

Clinical Perspective on p 2352

More than 1 million percutaneous coronary intervention (PCI) procedures are performed in the United States annually.[10] However, very little direct evidence has been published regarding CR participation rates and the impact of CR on mortality after PCI. Even with the paucity of data, several national guidelines have recommended CR after PCI,[11] and in 2006, the Centers for Medicare and Medicaid Services included PCI as a covered indication for CR.[12]

The aim of our study was to add to the understanding of CR after PCI by assessing CR participation and its association with mortality after PCI in a community-based study.

Methods

The Mayo Clinic PCI registry contains data collected prospectively since 1979 on all patients undergoing PCI at the Mayo Clinic and its affiliated hospitals in Rochester, MN.[13] For the present study, we included only patients from the Rochester area (Olmsted County) who had undergone PCI between January 1, 1994, and June 30, 2008, and were discharged alive. If patients had >1 PCI, their CR

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and follow-up data were considered only for the earliest PCI. Because the Mayo Clinic is the only location in Olmsted County that performed PCI during the study period, the study sample very closely approximates a community-based sample of people undergoing PCI in Olmsted County.[14] To assess CR participation, we analyzed data from the same time period using the database of the Mayo Clinic Cardiac Rehabilitation Program, the only CR program available in Olmsted County during the study period. We did not include data before 1994 because the PCI registry data variables were incomplete for many patients before that time (ie, there was a significant upgrade in the PCI registry in 1994). This study was approved by the Mayo Clinic Institutional Review Board. In accordance with Minnesota State law, patients were excluded from the study if they had not given prior authorization to use their medical records for research purposes (n=153).

Demographic, clinical, angiographic, procedural, and medication data available in the data registry were assessed for all patients (see Table 1 and the Appendix in the online-only Data Supplement for a complete list of data variables). History of heart failure was defined as a clinical diagnosis of active heart failure at the time of PCI. A patient's predominant presenting symptom at the time of PCI was classified as chest pain, a positive exercise test, or other. Nonelective PCI was defined as one that was associated with an acute coronary syndrome (ACS) within the prior 14 days.[15] All other PCI procedures were classified as elective.

Cardiac Rehabilitation

Data from all patients who attended at least 1 outpatient CR session since 1990 were included in the Mayo Clinic CR database. Participation in CR was defined as attending at least 1 outpatient CR session within 3 months of the index PCI. The accuracy of the data for CR participation was validated in a blinded fashion (by K.G.) through the use of a random sampling technique for patients from each year of the study period. The Mayo Clinic electronic medical records of all the patients who were reported as nonparticipants in our CR database were checked until 3 months to verify that there was, indeed, no record of CR participation after the PCI date. Patients who did not attend CR within 3 months after the index PCI but attended CR after a subsequent qualifying event were considered nonparticipants.

Outcomes Data

An experienced data technician obtained follow-up data, including vital status and information on any hospitalization, by telephone interview 6 and 12 months after the index PCI, and annually thereafter. The primary end point was all-cause mortality after being discharged alive from PCI hospitalization. Secondary end points were cardiac death, MI, and coronary revascularization (PCI or coronary artery bypass graft surgery [CABG]), which were ascertained by a review of patient medical records at each subsequent hospitalization.[13,16] Death certificates were used to classify cardiac and noncardiac causes of death.

Statistical Methods

The Student 2-sample *t* test, Pearson χ^2 test, Mann–Whitney–Wilcoxon rank-sum test, and log-rank test were used to compare the differences between groups for continuous, categorical, ordinal, and time-to-event variables, respectively. Kaplan–Meier statistics were used to estimate event rates during the follow-up period. Time to an event was defined as the time to the first event after the discharge date for the index PCI.

Multiple logistic regression analysis was used to identify predictors of CR participation. Potential predictor variables that had a statistically significant univariate (unadjusted) association with CR participation ($\alpha<0.15$ with $<10\%$ missing data) were identified and included as covariates in a multivariate model. Missing values were imputed with sample medians. Splines with 3 *df* were used to allow nonlinear associations between age, body mass index, and procedure date with CR use. All 2-way interactions were tested for significance in a model containing only the main effects variables.

We assessed the relationship between CR participation and the study outcome variables by using 3 separate analytical techniques to provide a robust, conservative assessment of the relationship. First, propensity score (PS) analysis was applied in the following manner. The logistic regression model for CR participation outlined above was used to calculate a PS for each patient in the study group. The ability of the PS to balance the covariates between groups was tested as follows: For continuous covariates, a linear regression model was used to regress the covariate on CR participation and PS quintiles. For categorical variables, a Cochran–Mantel–Haenszel test was used for the same purpose. We estimated the impact of CR participation on outcomes within each PS quintile and combined those estimates with an inverse-variance–weighted average. Patients whose PS was outside the range of values common to both the CR and non-CR groups were excluded from the stratified analysis.

Second, we performed a matched-group analysis using PSs. A matched group of patients who did not participate in CR were selected for patients who participated in CR with the use of a greedy matching algorithm, restricting the matches to PSs within one quarter of the PS standard deviation, PCI dates within 1 year of each other, and similar classification of elective versus nonelective PCI. Furthermore, the matched non-CR group had to survive at least as many days as the time that lapsed between post-PCI discharge and the start of CR for patients who participated in CR. Conditional logistic regression was then used to compare variables between matched cases and controls. Time-to-event variables were compared between cases and controls with a Cox proportional hazards model with a random effect (frailty) term unique to each matched pair of CR and non-CR patients. The number needed to treat in CR was calculated.[17]

Finally, we performed a landmark analysis in which all patients who died (n=102) had a cardiac event (MI, n=107; revascularization, n=149) within 3 months after PCI and those with follow-up of <3 months (n=28) were excluded; the 3-month mark after PCI was considered day 0 for analysis. For risk adjustment, we used a 3-*df* spline with the PS in a Cox proportional hazards model.

We also used these analytical techniques to investigate the interaction between CR participation and sex, age (≥65 years of age versus younger), and elective PCI (non-ACS setting versus ACS setting). SAS version 9.1 (SAS Institute Inc, Cary, NC) was used for nearly all modeling analyses; the survival package of R version 2.11 was used to fit a frailty term to Cox models. A value of $P<0.05$ was considered statistically significant.

Results

Patient Population

Among the 2395 patients in our cohort, 40% (964) participated in at least 1 CR session during the 3 months after PCI. Table 1 lists comparative differences between individuals who participated in CR and those did not. After PS matching between the CR participants and nonparticipants, no significant difference was noted in the demographic, medication, angiographic, and clinical characteristics (Table 1).

Cardiac Rehabilitation Participation

Figure 1 shows the percentage of patients who enrolled in CR between 1994 and 2008. Overall, the percentage of patients participating in CR after PCI was 40%. Of note, in a non-ACS elective setting, CR participation increased significantly from 25% before 2006 to 42% after 2006 ($P=0.004$), the year when the Centers for Medicare and Medicaid Services regulations were changed to include PCI as a covered indication for CR. Participation rates did not change significantly over time in patients undergoing PCI in an ACS setting. The mean and median numbers of CR sessions attended per participant during the study period were 13.5 and 13, respectively. Variables associated with

Table 1. Descriptive Characteristics of the Entire Cohort and Matched-Pair Group Stratified by Participation in Cardiac Rehabilitation

	Entire Cohort			Matched-Pair Group		
Variables	No CR (n=1431)	CR (n=964)	*P*	No CR (n=719)	CR (n=719)	*P*
Clinical characteristics						
Age, y	66.8±13.5	62.5±11.7	<0.001	63.5±12.4	63.5±11.9	0.98
Male sex, n (%)	942 (66)	697 (72)	<0.001	491 (68)	498 (69)	0.69
Most recent MI, n (%)			<0.001			0.17
<24 h	364 (26)	415 (43)		259 (37)	242 (34)	
1–7 d	196 (14)	156 (16)		81 (11)	138 (19)	
>7 d	221 (16)	51 (5)		51 (7)	50 (7)	
Never	627 (45)	333 (35)		317 (45)	280 (39)	
Unstable angina, n (%)	836 (58)	509 (53)	0.007	400 (56)	399 (55)	0.95
Heart failure, n (%)			<0.001			0.92
Never	1150 (84)	858 (92)		631 (91)	633 (91)	
Previous	42 (3)	10 (1)		8 (1)	9 (1)	
Current	182 (13)	61 (7)		53 (8)	53 (8)	
Diabetes mellitus, n (%)	340 (24)	165 (17)	<0.001	134 (19)	141 (20)	0.60
Hypertension, n (%)	886 (64)	564 (62)	0.19	408 (60)	434 (63)	0.33
Preprocedural cardiac arrest, n (%)	2 (0)	9 (1)	0.005	0 (0)	5 (1)	0.008
Body mass index, kg/m^2	29.1±5.8	29.4±5.5	0.18	29.3±5.9	29.4±5.7	0.63
Hypercholesterolemia, n (%)	909 (70)	585 (68)	0.24	448 (70)	443 (69)	0.84
Family history of CAD, n (%)	289 (20)	223 (23)	0.11	169 (24)	161 (22)	0.90
Smoking status, n (%)			0.80			0.91
Never	495 (35)	323 (34)		245 (35)	235 (33)	
Former	578 (41)	406 (43)		288 (41)	309 (44)	
Current	333 (24)	220 (23)		177 (25)	165 (23)	
MI (>7 d), n (%)	300 (21)	92 (10)	<0.001	73 (10)	81 (11)	0.60
Prior PCI, n (%)	80 (6)	23 (2)	<0.001	22 (3)	20 (3)	0.75
Prior CABG, n (%)	215 (15)	71 (7)	<0.001	57 (8)	54 (8)	0.75
PVD, n (%)	158 (11)	39 (4)	<0.001	42 (6)	35 (5)	0.39
CVA, n (%)	163 (12)	79 (8)	0.010	64 (9)	65 (9)	1.00
Moderate/severe renal disease, n (%)	47 (3)	12 (1)	0.001	10 (1)	10 (1)	1.00
LV ejection fraction, n (%)			0.76			0.29
>40%	679 (47)	453 (47)		319 (44)	353 (49)	
N/A	622 (43)	443 (46)		354 (49)	310 (43)	
≤40%	130 (9)	68 (7)		46 (6)	56 (8)	
Angiographic characteristics, n (%)						
Multivessel disease	912 (65)	596 (63)	0.34	440 (62)	451 (64)	0.44
Thrombus (any lesion)	503 (37)	476 (52)	<0.001	328 (48)	312 (46)	0.49
Ulcer (any lesion)	121 (10)	122 (15)	<0.001	68 (11)	90 (14)	0.07
Calcium (any stenosis)	481 (39)	268 (32)	0.002	197 (31)	202 (33)	0.89
Minor branches	457 (34)	362 (40)	0.003	254 (38)	264 (39)	0.56
TIMI grade 0 before the procedure	229 (21)	245 (34)	<0.001	144 (27)	148 (28)	0.56
Procedural characteristics and outcomes, n (%)						
Urgency of PCI			<0.001			0.63
Elective	418 (29)	196 (20)		169 (24)	169 (24)	
Urgent	638 (45)	376 (39)		304 (42)	311 (43)	
Emergency	373 (26)	392 (41)		246 (34)	239 (33)	
Drug-eluting stents	477 (33)	285 (30)	0.05	243 (34)	246 (34)	0.76
Glycoprotein IIa/IIIb therapy	749 (52)	626 (65)	<0.001	449 (63)	453 (63)	0.69
In-hospital death/MI/CABG/PCI	73 (5)	72 (7)	0.017	39 (5)	42 (6)	0.72
Medications at discharge, n (%)						
Aspirin	1370 (96)	943 (98)	0.005	701 (98)	698 (97)	0.48
β-blockers	1124 (79)	819 (85)	<0.001	601 (84)	595 (83)	0.72
Calcium channel blocker	260 (18)	96 (10)	<0.001	85 (12)	81 (11)	0.73
Lipid-lowering drugs	754 (53)	555 (58)	0.016	414 (58)	416 (58)	0.78
ACE inhibitors	681 (48)	474 (49)	0.43	349 (49)	355 (50)	0.66
Diuretics	351 (25)	171 (18)	<0.001	135 (19)	141 (20)	0.72
Clopidogrel	1031 (72)	728 (76)	0.060	552 (77)	565 (79)	0.041

CR indicates cardiac rehabilitation; MI, myocardial infarction; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; PVD, peripheral vascular disease; CVA, cerebrovascular accident or transient ischemic attack; LV, left ventricular; TIMI, Thrombolysis in Myocardial Infarction; and ACE, angiotensin-converting enzyme. Hypercholesterolemia is defined as total cholesterol ≥240 mg/dL. Other variables that were considered are presented in the Appendix in the online-only Data Supplement. Values are mean±SD when appropriate.

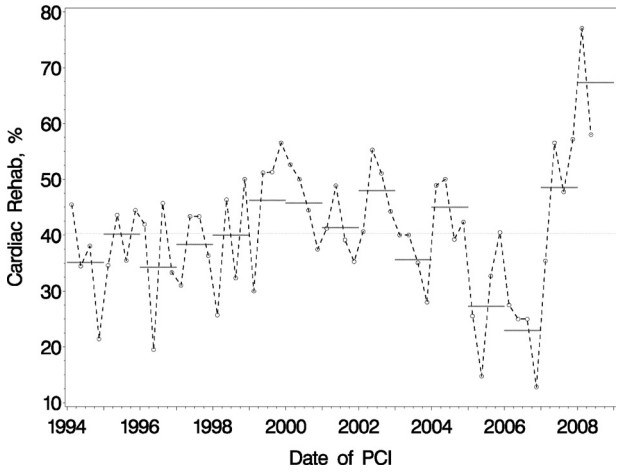

Figure 1. Percent participation in cardiac rehabilitation (CR) after percutaneous coronary intervention (PCI) from 1994 to 2008. Individual points indicate quarterly percentages; horizontal bars, yearly percentages.

CR participation after PCI are noted in Table 2. Independent factors that were positively associated with CR participation in the multiple logistic regression model include age (Figure 2), year of PCI (Figure 2), history of acute MI, involvement of minor branches of the coronary artery, antiplatelet therapy during PCI, and occurrence of in-hospital MI/CABG/PCI. On the other hand, smoking, history of diabetes mellitus, previous PCI, and use of drug-eluting stents were independently associated with decreased participation in CR after PCI (Table 2).

Impact of Cardiac Rehabilitation on Mortality and Composite End Points

During a median follow-up of 6.3 years (interquartile range, 3.2 to 10.0 years), there were 503 deaths, of which 199 were due to cardiovascular causes. Revascularization (PCI or CABG) was noted in 755 individuals and subsequent MI in 394 individuals during the follow-up period. The overall rate of mortality, recurrent MIs, and revascularization in our study was similar to those in previously published observational studies and randomized controlled trials in post-PCI patients (Table 3).

Figure 3 shows Kaplan–Meier graphs for the matched groups (n=1438) and landmark analysis groups (n=2009). In the landmark group, the unadjusted rates of all-cause and cardiac mortality were significantly lower in CR participants compared with nonparticipants ($P<0.001$). The difference between the mortality rates in the 2 groups was observed as early as 1 year after PCI and remained significant for the 15 years of follow-up.

With the 3 different analytical techniques, CR participation was associated with decreased all-cause mortality in the patients undergoing PCI after adjustment for demographic, clinical, angiographic, procedural, and treatment variables (see Table 1 and the Appendix in the online-only Data Supplement for a complete list of data variables). First, using PS analysis in matched pairs of CR participants and nonparticipants (719 pairs; see Figure 4), we noted a 46% relative reduction in all-cause mortality in CR participants (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.41 to 0.71; $P<0.001$). The number of PCI patients needed to treat with CR to prevent 1 death was 34 at 1 year after PCI and 22 at 5 years after PCI. Of note, we found a significant difference in clinical and angiographic characteristics between the patients who were included in the PS matched-pair analysis (n=1438) and those left out of it (n=957). The patients included were younger and healthier (data not shown).

Second, when the entire study population (n=2351) except those with extreme PS values were included, PS stratification analysis showed a 47% relative reduction in all-cause mortality in CR participants (HR, 0.53; 95% CI, 0.42 to 0.67).

Table 2. Factors Associated With Cardiac Rehabilitation Participation After Percutaneous Coronary Intervention

Variables	Estimate	OR	95% CI	*P*
Age, y*				<0.001
65 (vs 55)	0.0896	1.09	0.90–1.33	
75 (vs 55)	−0.2956	0.74	0.60–0.92	
85 (vs 55)	−1.3560	0.26	0.19–0.36	
History of acute MI*	0.6274	1.87	1.13–3.09	0.014
History of MI (>7 d)	−0.4189	0.66	0.49–0.88	0.006
Current smoker	−0.3840	0.68	0.52–0.89	0.005
Diabetes mellitus	−0.2606	0.77	0.61–0.98	0.032
Prior PCI	−0.6147	0.54	0.32–0.92	0.024
Prior CABG	−0.3893	0.68	0.43–1.06	0.090
COPD	−0.3088	0.73	0.53–1.02	0.062
PCI date*				<0.001
January 1, 2000 (vs January 1, 1994)	0.2945	1.34	1.06–1.71	
January 1, 2005 (vs January 1, 1994)	−0.0548	0.95	0.75–1.19	
January 1, 2008 (vs January 1, 1994)	0.7564	2.13	1.50–3.02	
Minor branches (any lesion)	0.2470	1.28	1.06–1.55	0.012
Drug-eluting stents	−0.3670	0.69	0.49–0.98	0.041
Glycoprotein IIa/IIIb therapy	0.3782	1.46	1.14–1.87	0.003
In-hospital MI/CABG/PCI	0.5558	1.74	1.18–2.58	0.006
Calcium channel blockers	−0.3107	0.73	0.55–0.98	0.039
Lipid-lowering drugs	0.3496	1.42	1.13–1.78	0.003
Cardiac glycoside	−0.4934	0.61	0.38–0.98	0.043

OR indicates odds ratio; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and COPD, chronic obstructive pulmonary disease. Acute MI is defined as a history of MI within 24 hours of the procedure The following variables had a significant univariate association with cardiac rehabilitation participation ($\alpha<0.15$) but were not associated with it after adjustment in the multiple logistic regression model: definite/probable angina on presentation; New York Heart Association class; heart failure; family history of CAD; peripheral vascular disease, cerebrovascular accident, moderate/severe renal disease, and cancer; predominant symptom of chest pain or positive exercise test; presence of thrombus; PCI in the right coronary artery, PCI in a severe bend, or Thrombolysis in Myocardial Infarction grade 3 flow after the procedure; vein graft intervention; and use of aspirin, β-blockers, diuretics, oral nitrates, anticoagulants, and antihypertensives at discharge.

*Age and procedure date were modeled as 3-*df* splines. See Figure 2 for more details. The hazard ratios here represent the fit of those splines at specific points within the variable range with other variables set to the sample mean.

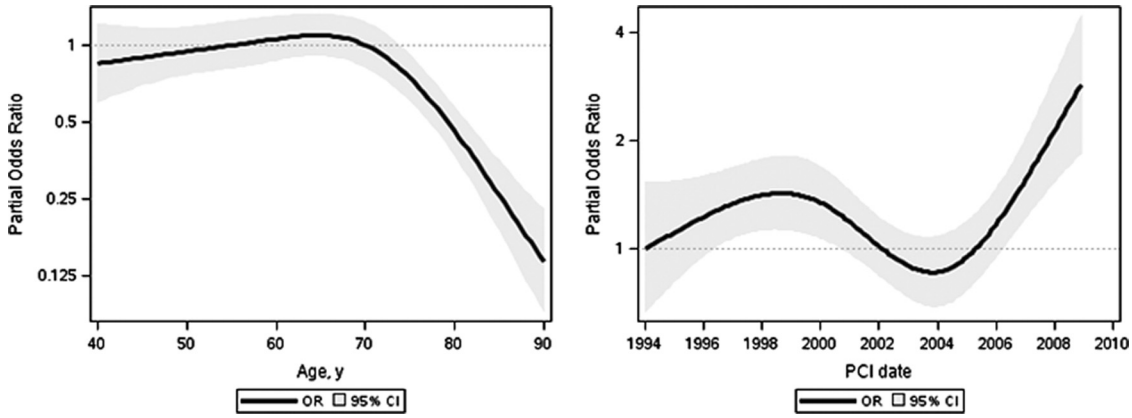

Figure 2. Plots of the relationship between age and percutaneous coronary intervention date with cardiac rehabilitation participation. The multiple logistic regression model presented in Table 2 was used to estimate these relationships; the partial odds ratio (OR) estimates are plotted over the continuous variables. CI indicates confidence interval.

The HRs were generally consistent across all the PS quartiles (0.49 to 0.63). Finally, a 3-month landmark analysis also showed a significant reduction in all-cause mortality in CR participants compared with nonparticipants (HR, 0.55; 95% CI, 0.42 to 0.72; Table 4).

Cardiac mortality was significantly lower in CR participants than in nonparticipants in the PS stratification analysis (HR, 0,61; 95% CI, 0.41 to 0.91), but it was not significantly different using matched-pair PS analysis (HR, 0.69; 95% CI, 0.44 to 1.07) or landmark analysis (HR, 0.67; 95% CI, 0.44 to 1.04). There was no difference in MI or revascularization (PCI or CABG) rates among the CR participants and nonparticipants using all the analytical techniques. Hazard ratios of 0.89 to 0.93 were noted for the first 3 PS quartiles, with a trend showing an increase in MI rates for the fourth and fifth PS quartiles (HR, 1.19 and 1.38, respectively).

The composite end point of death/MI/PCI/CABG was significantly reduced in CR participants in PS stratification and landmark analyses (Table 4). Hazard ratios were 0.60, 0.65, 1.05, 0.89, and 1.02 from the first through fifth PS quartiles. Findings for all analyses were similar for men and women, for older and younger patients, and for patients undergoing either elective or nonelective PCI procedures.

Table 3. Comparison of Mortality, Recurrent Myocardial Infarction, and Revascularization Rates Among Different Studies in Percutaneous Coronary Intervention Patients

Studies (n, Follow-Up y)	All-Cause Mortality, %	Recurrent MI, %	Revascularization, %
Observational studies			
Present study (2395, 5 y)			
CR	7*	9*	22*
Non-CR	21	13	25
Suaya et al[1] (14 679, 5 y)†			
CR	14.7	NR	NR
Non-CR	20.8		
Northern New England Cardiovascular Disease Study Group[18] (n=4295, 5 y)	16.1	NR	NR
New York cardiac registries[19] (22 102, 3 y)	7.6–8.8 (2-Vessel disease) 15.1 (3-Vessel disease)	NR	27.3 PCI 7.8 CABG
Randomized controlled trials			
COURAGE trial[20] (1149, 4.6 y)	7.6	13.2	21.1
BARI 2D trial[21] (1605, 5 y)	10.2 (Insulin sensitization) 11.4 (Insulin provision)	NR	21.1–24.9 of major cardiovascular events in the PCI group
MASS-II study[22] (205, 5 y)	15.5	11.2	32.2

MI indicates myocardial infarction; CR, cardiac rehabilitation; NR, Not reported; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; and MASS-II, Medicine, Angioplasty, or Surgery Study.

*Unadjusted Kaplan–Meier rates.

†This study reporting data in CR patients; others reported the outcomes data in the whole study group.

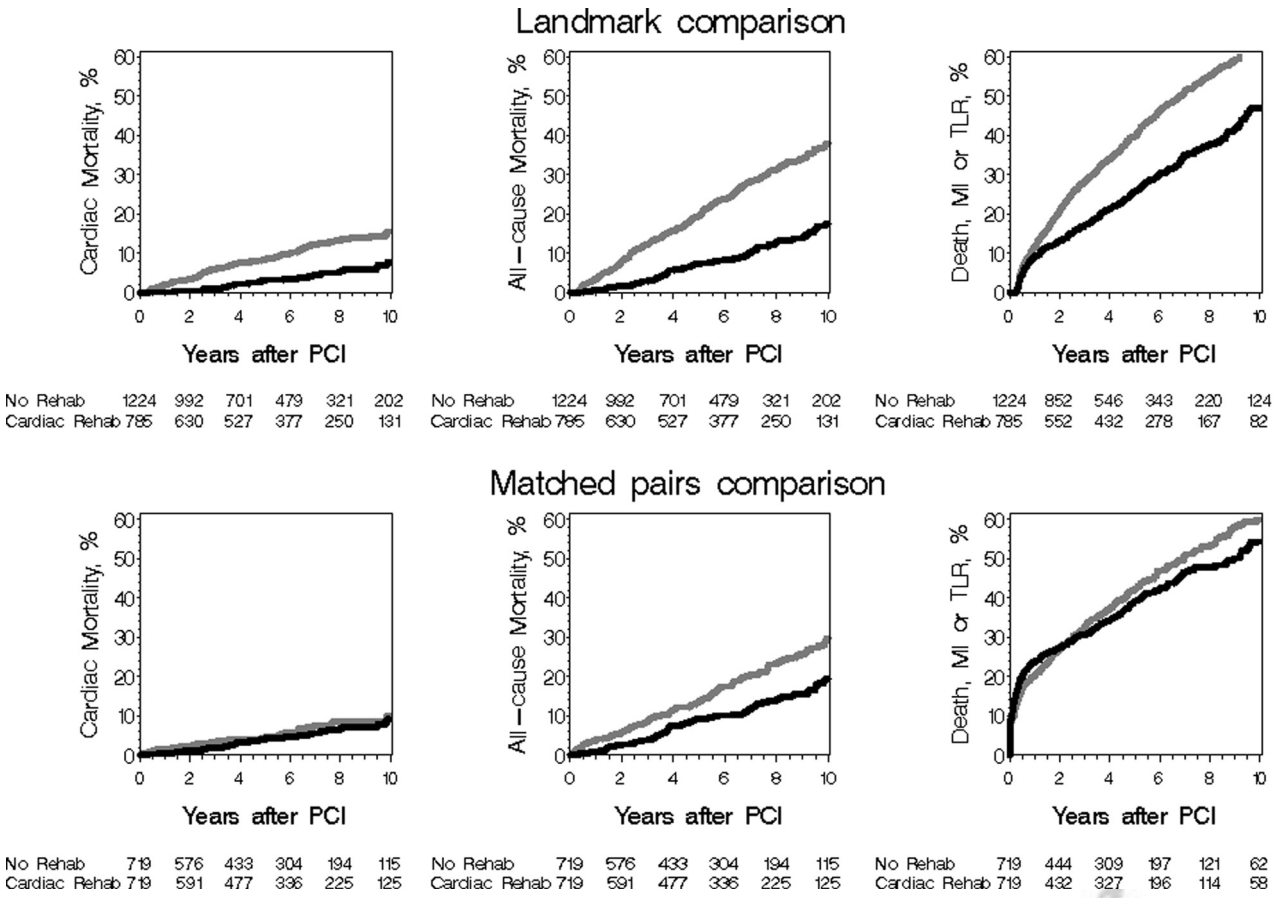

Figure 3. Kaplan–Meier curves showing the association between cardiac rehabilitation (CR) participation and outcomes. Outcomes include cardiac mortality, all-cause mortality, and the composite end point (death/myocardial infarction/percutaneous coronary intervention [PCI]/coronary artery bypass graft surgery [CABG]). **Top**, Curves for the landmark study analysis group (excluding patients who had major adverse cardiac events within 3 months after PCI, n=2009). $P<0.001$ for each of the 3 graphs. **Bottom**, Curves for the propensity score–matched analysis groups (n=1438). $P=<0.001$ for all-cause mortality; $P=0.14$ for cardiac mortality; and $P=0.71$ for composite end point. Black line represents CR participants; gray line, nonparticipants. TLR indicates target lesion revascularization (PCI/CABG).

Discussion

Data from our cohort provide evidence for a significant association between CR participation and lower mortality rates for patients undergoing PCI. Using 3 different analytical techniques, we found a 45% to 47% decrease in all-cause mortality in patients who participated in CR after PCI compared with those who did not participate in CR. This decrease is consistent with a previous study from Olmsted County that reported a 56% decrease in all-cause mortality associated with CR after MI,[23] but is even larger than the 20% to 30% decrease in all-cause mortality previously reported in other observational studies and meta-analyses of CR participation after MI.[1–3]

This report adds to the limited number of studies that have examined the association between CR participation and mortality after PCI.[1,24,25] An important observational study by Suaya and coworkers[1] reported, in a subgroup analysis of Medicare patients who had undergone PCI from 1997 to 2002, that CR participation was associated with a 30% relative reduction in all-cause mortality. Although the investigators used PS analyses to help adjust for potential confounding factors, they did not adjust for a number of factors that were included in our analysis (eg, smoking status, obesity, hypercholesterolemia, family history of coronary artery disease, ejection fraction, medication use, and variables from angiography and PCI), owing to limitations in the Medicare database. In addition, their study was limited to patients >65 years of age and did not include data on cardiac mortality and recurrent cardiovascular events.

In our study, cardiac mortality was reduced by 39% in CR participants when PS stratification analysis was applied to the whole study population. However, no significant effect on cardiac mortality was noted in the matched-pair analysis, which is the most robust of all the statistical methods used in this study. This finding is likely affected by ascertainment errors regarding cause of death, one reason why the use of cardiac death as an end point can be problematic. Because autopsy evidence is not available in all patients, confirmatory evidence in this regard cannot be presented. Given that all patients in our cohort had coronary artery disease, a cardiac cause should be responsible for majority of the deaths. However, only 39.5% of all deaths were attributed to cardiac causes in the present study. This percentage is consistent with a prospective registry of PCIs at 50 US centers[26] and a pooled analysis of 4 prospective, randomized, double-blind clinical trials[27] that attributed ≈40% of the total deaths to cardiac causes. Furthermore, cardiac death was responsible for only 27% of all the deaths in PCI patients enrolled in the Clinical

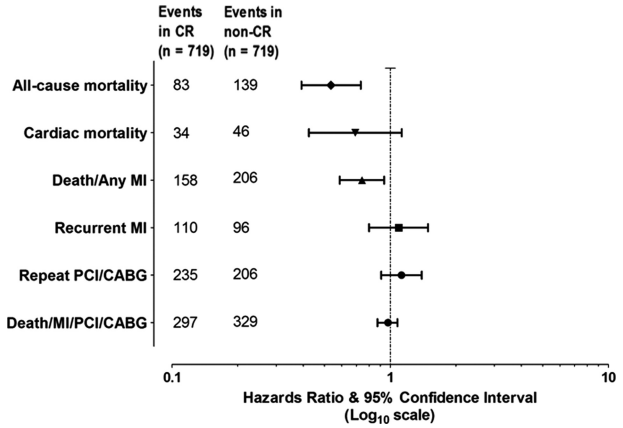

Figure 4. Association between cardiac rehabilitation (CR) participation and mortality in the propensity score–matched groups. Hazards ratio (boxes) and 95% confidence intervals (bars) for CR participation after percutaneous coronary intervention (PCI) in the propensity score–matched analysis (n=1438). The *x* axis is log transformed. The dotted line along the *y* axis is a hazard ratio of 1. MI indicates myocardial infarction; CABG, coronary artery bypass graft.

Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial.[20]

Another observational study by Dendale et al[24] in a relatively small group of patients (n=223) who had undergone PCI found that CR participation was not associated with a reduction in rate of recurrent MIs. However, a significant reduction was noted in revascularization rates and 15-month incidence of major adverse cardiovascular events, including MI, revascularization, recurrent stenosis, recurrent angina, and death, in CR participants compared with patients who did not participate in CR (24% versus 42%; $P<0.005$).[24] Results were adjusted for cardiovascular risk factors, but apparently not for medications, various comorbid conditions, and angiographic characteristics. Another relatively small randomized study (n=131), the Exercise Training Intervention After Coronary Angioplasty (ETICA) trial, found that exercise training was associated with a decreased 3-year incidence of major adverse cardiovascular events, including MI, PCI, CABG, or death and hospital admissions after PCI.[25] However, no difference was noted in the individual analyses for recurrent MI, CABG, PCI, or angiographic restenosis, respectively. Unlike our study, patients in both the Dendale et al[24] and ETICA[25] studies were excluded from analysis if they had an unsuccessful PCI, complications after PCI, or significant comorbid conditions.

Our results differed from those of Dendale et al[24] in that we did not find a significant reduction in revascularization rates. The reason for this difference in findings between our study and the Dendale et al study may be related to patient selection criteria, intervention duration, or differences in statistical adjustment techniques in the 2 studies. Dendale et al studied only patients free of important comorbidities and those who had a successful, uncomplicated PCI and adjusted their results by demographic and cardiovascular risk factors only.[24] On the other hand, we analyzed detailed sociodemographic, clinical, angiographic, procedural, and treatment data in a community-based, prospective, unselected cohort of patients undergoing PCI. In addition, we found evidence that CR was associated with a reduction in the composite end point of death, MI, PCI, or CABG.

The fact that we found a reduction in mortality rates without a reduction in recurrent MI or revascularization rates in CR participants is consistent with the findings of other studies of CR in PCI patients[24,25,28] and those involving CR after MI.[2,3,29] The explanation for these findings is unclear, but may involve 2 main factors. First, it is possible that the findings may be related to the effects of differential monitoring and follow-up of CR participants. This could increase the likelihood of identifying and treating recurrent cardiac symptoms in CR participants compared with nonparticipants. A second possible explanation could be that the effects of CR result in a shift from fatal to nonfatal events (ie, a reduced case fatality rate). Indeed, our data showed that the overall composite event rates (mortality plus nonfatal MI) were lower in CR participants compared with participants.

A previous study by Hammill et al[30] reported a 47% reduction in all-cause mortality among Medicare beneficiaries attending 36 CR sessions compared with those who

Table 4. Association of Cardiac Rehabilitation Participation With Primary and Secondary Outcomes With 3 Types of Statistical Analysis

	Matched-Groups Analysis*		Propensity Score Stratification Analysis†		Landmark Analysis‡	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause mortality	0.54 (0.41–0.71)	<0.001	0.53 (0.42–0.67)	<0.001	0.55 (0.42–0.72)	<0.001
Cardiac mortality	0.69 (0.44–1.07)	0.095	0.61 (0.41–0.91)	0.016	0.67 (0.44–1.04)	0.07
Death/any MI	0.73 (0.59–0.90)	0.003	0.73 (0.61–0.88)	<0.001	0.68 (0.55–0.84)	<0.001
MI	1.11 (0.84–1.45)	0.47	1.07 (0.85–1.36)	0.56	1.01 (0.75–1.38)	0.92
Repeat PCI/CABG	1.16 (0.96–1.39)	0.13	1.06 (0.90–1.25)	0.47	1.01 (0.83–1.23)	0.94
Death/MI/PCI/CABG	0.92 (0.78–1.07)	0.28	0.85 (0.74–0.98)	0.022	0.77 (0.65–0.91)	0.0018

HR indicates hazards ratio; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft. Cardiac rehabilitation (CR) participation was used as a time-dependent variable.

*Only matched pairs were included (n=1438).

†Impact of CR participation on outcomes within each propensity score quintile (excluding patients outside the propensity score range common to both groups) was calculated, and these estimates were combined with an inverse-variance–weighted average (n=2351).

‡All patients who died or who had a cardiac event within 3 months after PCI were excluded (n=2009).

attended only 1 CR session. Although this reduction supports our findings of the mortality benefits associated with CR, their study differed from ours in that they studied the potential dose response of CR among CR attendees only. On the other hand, we studied the potential impact of CR on mortality rates in patients who attended CR compared with those who did not. Furthermore, the major indication for CR in the Hammill et al study was CABG (61%) compared with PCI in our study. Because the number of sessions prescribed to the patients in our cohort was individualized (eg, lower-risk CR patients are prescribed fewer sessions than higher-risk patients), we did not find a dose-response effect of CR on mortality rates in our cohort. The median number of CR sessions in our study was 13, nearly half the median of 25 sessions reported by Hammill et al.[30]

The overall rate of CR participation after PCI in our study was 40%, which was lower than the participation rate in post-MI patients (55%) in Olmsted County.[23] Our study is also the first to report data after 2006, the year when Medicare approved CR coverage for PCI patients.[12] Participation in CR after PCI in a non-ACS elective setting increased significantly after this change; however, no change was observed in those undergoing PCI in an ACS setting. Additional analysis, using the difference in differences approach, was done to assess the interaction between time period of care (before 2006 versus after 2006) and type of PCI (elective versus nonelective). Although we noticed a reduction in the relative hazard of elective PCI compared with PCI in the ACS setting after 2006, these results were not statistically significant. The lack of sufficient statistical power resulting from the small number of patients and events after 2006 could be the likely explanation for this.

Potential Explanations for Results

Several factors may be responsible for our findings. Cardiac rehabilitation increases physical activity and exercise capacity,[5] which in turn produce important physiological adaptations that improve cardiovascular health.[4] In addition, CR participation may improve medication adherence,[7] a factor likely to be very important for PCI patients who are prescribed antiplatelet therapy after PCI. Furthermore, cardiovascular risk factor control,[4,8] reduced inflammation,[31] depression identification and treatment,[32] and psychosocial support have been reported to be superior in CR participants than in nonparticipants.[6] Close follow-up of patients by CR program staff members as they interact with patients several times a month helps to identify new symptoms, side effects, and comorbid conditions that may require additional evaluations and/or adjustments in treatment.[8] Finally, it is possible that treatments received during CR may stimulate additional beneficial physiological adaptations, including an increase in the number of circulating endothelial progenitor cells.[33]

Limitations

This study is limited by several factors, including the observational nature of our data. To overcome the potential selection bias that can limit the accuracy of observational data, we used 3 different statistical analytical techniques, including PS techniques, an approach that has been used to help reduce the potential impact of bias.[1] However, it is still possible that selection bias might explain at least part of our results.

In addition, our data are somewhat limited by the fact that they originate from only 1 center and a patient population of primarily white, non-Hispanic individuals. The characteristics of our patient population are similar to those of whites in the United States overall, except that a higher proportion of the residents are employed in the healthcare sector.[34] However, the use of Olmsted County data has previously been shown to represent a community-based sampling of data.[23,35] The unavailability of socioeconomic data of our study subjects may have affected the results because insurance status, income, and education level can influence a number of different health determinants and outcomes.[36] We also lacked data on the functional capacity and quality of life of the study subjects.

Conclusions

Our data from Olmsted County, Minnesota, show that participation in CR after PCI is associated with a significant reduction in all-cause and cardiovascular mortality. Although only 40% of PCI patients in our overall cohort participated in CR, there was a significant improvement in CR participation after 2006, when the Centers for Medicare and Medicaid Services began covering CR after PCI. Our results provide supportive evidence for the decision by Centers for Medicare and Medicaid Services to cover CR in PCI patients and for the recommendations in clinical practice guidelines and performance measures that support CR for all PCI patients.

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CLINICAL PERSPECTIVE

Although participation in cardiac rehabilitation (CR) has been associated with reduced mortality after myocardial infarction, less is known about its impact after percutaneous coronary intervention (PCI). We studied the association between CR participation and outcomes in 2395 consecutive patients who underwent PCI in Olmsted County, Minnesota, from 1994 to 2008. Overall participation in CR was 40% after PCI over the length of our study. Using 3 different analytical techniques aimed at reducing potential sources of bias, we found that CR participation was associated with a 45% to 47% reduction in 5-year all-cause mortality rate compared with nonparticipation. These findings provide support for national guidelines that recommend CR for patients after PCI, and for the decision in 2006 by the Centers for Medicare and Medicaid Services to include PCI as a covered indication for CR services. Cardiac rehabilitation participation should be encouraged as part of an evidence-based secondary prevention plan for patients who have undergone PCI.

Impact of Cardiac Rehabilitation on Mortality and Cardiovascular Events After Percutaneous Coronary Intervention in the Community

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SUPPLEMENTAL MATERIAL

Appendix 1: Descriptive characteristics of the entire cohort and matched pair group stratified by participation in cardiac rehabilitation (variables not presented in table 1)

	Whole study group			Matched study group		
Variables	**No CR (n = 1431)**	**CR (n = 964)**	**p value**	**No CR (n = 719)**	**CR (n = 719)**	**p value**
Clinical Characteristics						
Pre-procedural shock	59 (4%)	46 (5%)	0.44	33 (5%)	31 (4%)	0.79
Definite/Probable Angina	933 (65%)	563 (58%)	<.001	445 (62%)	449 (62%)	0.81
NYHA class>=III	100 (8%)	31 (3%)	<.001	29 (4%)	28 (4%)	0.67
COPD	187 (13%)	74 (8%)	<.001	52 (7%)	64 (9%)	0.31
Peptic Ulcer Disease	81 (6%)	45 (5%)	0.29	42 (6%)	33 (5%)	0.22
Tumor	177 (12%)	80 (8%)	0.001	68 (10%)	66 (9%)	0.79
Metastatic Cancer	9 (1%)	3 (0%)	0.28	3 (0%)	3 (0%)	1.00
Prophylactic IABP	27 (2%)	18 (2%)	0.97	12 (2%)	16 (2%)	0.45
Predominant symptom			0.005			0.79
Chest pain	1231 (86%)	872 (90%)		649 (90%)	642 (89%)	
Positive Exercise test	110 (8%)	52 (5%)		42 (6%)	45 (6%)	
Others	90 (6%)	40 (4%)		28 (4%)	32 (4%)	
Angiographic Characteristics						
Number of diseased vessels			0.47			0.33

0	24	(2%)	9	(1%)		8	(1%)	9	(1%)	
1	460	(33%)	335	(36%)		257	(37%)	240	(35%)	
2	493	(36%)	329	(35%)		250	(36%)	245	(35%)	
3	401	(29%)	261	(28%)		181	(26%)	200	(29%)	
Worst Lesion Type					0.38					0.45
A	33	(3%)	26	(3%)		21	(3%)	19	(3%)	
B1	230	(18%)	124	(16%)		108	(18%)	110	(18%)	
B2	452	(35%)	270	(35%)		224	(37%)	209	(34%)	
C	560	(44%)	357	(46%)		258	(42%)	269	(44%)	
Major branches	253	(19%)	158	(17%)	0.42	130	(19%)	117	(17%)	0.47
Eccentric in any lesion	961	(81%)	604	(79%)	0.38	445	(78%)	474	(80%)	0.19
Bifurcation in any lesion	193	(14%)	140	(15%)	0.47	93	(14%)	102	(15%)	0.42
Any lesion ostial	218	(19%)	121	(16%)	0.06	101	(18%)	92	(16%)	0.37
Worst angulation in any lesion					0.049					0.44
None	275	(20%)	200	(22%)		133	(20%)	144	(21%)	
Mild	667	(49%)	475	(51%)		376	(55%)	347	(50%)	
Moderate	348	(26%)	225	(24%)		156	(23%)	180	(26%)	
Severe	68	(5%)	24	(3%)		16	(2%)	19	(3%)	
Maximum balloon length (mm)	16.9 ± 6.1		17.1 ± 5.3		0.48	16.4 ± 5.0		16.9 ± 5.1		0.31
Maximum device size (mm)	3.3 ± 0.7		3.3 ± 0.5		0.36	3.3 ± 0.6		3.3 ± 0.5		0.84
Procedural Characteristics and Outcomes										
No. of segments treated	1.4	± 0.7	1.4	± 0.7	0.94	1.4 ± 0.7		1.5 ± 0.7		0.47

Total no. of vessels treated					0.55					0.10
1	1241	(87%)	844	(88%)		633	(88%)	619	(86%)	
2	178	(12%)	105	(11%)		82	(11%)	85	(12%)	
3	12	(1%)	14	(1%)		4	(1%)	14	(2%)	
Total no. of stents placed	1.2	± 1.0	1.3	± 1.0	0.72	1.3	± 0.9	1.3	± 1.0	0.73
Procedural success	1309	(91%)	865	(90%)	0.15	664	(92%)	661	(92%)	0.75
PCI in native LAD	662	(46%)	448	(47%)	0.90	351	(49%)	348	(48%)	0.91
PCI in native LM	20	(1%)	9	(1%)	0.31	5	(1%)	8	(1%)	0.40
PCI in native RCA	496	(35%)	389	(40%)	0.004	262	(36%)	274	(38%)	0.48
PCI in native LCX	370	(26%)	225	(23%)	0.17	170	(24%)	183	(25%)	0.41
Vein graft intervention	87	(6%)	24	(2%)	<.001	18	(3%)	16	(2%)	0.73
TIMI=3 Post-procedure in all lesions	1301	(95%)	863	(93%)	0.07	646	(95%)	654	(95%)	0.53
In-Hospital Any MI	56	(4%)	49	(5%)	0.17	27	(4%)	30	(4%)	0.68
In-Hospital CABG	15	(1%)	16	(2%)	0.19	12	(2%)	8	(1%)	0.37
Medications at discharge										
Heparin	23	(2%)	21	(2%)	0.31	11	(2%)	18	(3%)	0.18
Anticoagulants	115	(8%)	61	(6%)	0.12	46	(6%)	43	(6%)	0.66
Nitroglycerin paste	22	(2%)	4	(0%)	0.009	5	(1%)	4	(1%)	0.74
Oral Nitrates	367	(26%)	181	(19%)	<.001	137	(19%)	143	(20%)	0.73
Nitroglycerin sub-lingual	808	(57%)	604	(63%)	0.002	442	(62%)	441	(62%)	0.95
Cardiac glycoside	107	(7%)	32	(3%)	<.001	31	(4%)	31	(4%)	1.00
Other anti-hypertensives	52	(4%)	23	(2%)	0.09	18	(3%)	21	(3%)	0.62

Values are presented as Number (%) or mean ± standard deviation;

NYHA, New York Hear Association; COPD, Chronic Obstructive Pulmonary Disease; Tumor, Any tumor including lymphoma and leukemia; IABP, Intra-aortic balloon pump; LAD, Left anterior descending artery; LM, Left marginal artery; LCX, Left Circumflex artery; RCA, Right Coronary artery; TIMI, Thrombolysis In Myocardial Infarction Other anti-hypertensives, does not include diuretics