

Benefits of Cardiac Rehabilitation on Cardiovascular Outcomes in Patients With Diabetes Mellitus After Percutaneous Coronary Intervention

Manuel F. Jiménez-Navarro, MD, PhD; Francisco Lopez-Jimenez, MD, MS; Luis M. Pérez-Belmonte, MD, PhD; Ryan J. Lennon, MS; Carlos Diaz-Meleán, MD; J. P. Rodríguez-Escudero, MD; Kashish Goel, MD; Daniel Crusan, BS; Abhiram Prasad, MD; Ray W. Squires, PhD; Randal J. Thomas, MD, MS

Background—Participation in cardiac rehabilitation (CR) is an essential component of care for patients with coronary artery disease. However, little is known about its benefit on cardiovascular outcomes in patients with diabetes mellitus (DM) who have undergone percutaneous coronary intervention. The aim of our study was to evaluate the impact of CR in this high-risk group of patients.

Methods and Results—We performed a retrospective analysis of all patients with DM who underwent percutaneous coronary intervention in Olmsted County (Minnesota) between 1994 and 2010, assessing the impact of CR participation on clinical outcomes. CR participation was significantly lower in patients with DM (38%, 263/700) compared with those who did not have DM (45%, 1071/2379; $P=0.004$). Using propensity score adjustment, we found that in patients with DM, CR participation was associated with significantly reduced all-cause mortality (hazard ratio, 0.56; 95% confidence interval, 0.39–0.80; $P=0.002$) and composite end point of mortality, myocardial infarction, or revascularization (hazard ratio, 0.77; 95% confidence interval, 0.60–0.98; $P=0.037$), during a median follow-up of 8.1 years. In patients without DM, CR participation was associated with a significant reduction in all-cause mortality (hazard ratio, 0.67; 95% confidence interval, 0.55–0.82; $P<0.001$) and cardiac mortality (hazard ratio, 0.67; 95% confidence interval, 0.47–0.95; $P=0.024$).

Conclusions—CR participation after percutaneous coronary intervention is associated with lower all-cause mortality rates in patients with DM, to a similar degree as for those without DM. However, CR participation was lower in patients with DM, suggesting the need to identify and correct the barriers to CR participation for this higher-risk group of patients. (*J Am Heart Assoc.* 2017;6:e006404. DOI: 10.1161/JAHA.117.006404.)

Key Words: cardiac rehabilitation • diabetes mellitus • percutaneous coronary intervention

Cardiac rehabilitation (CR) is a multidisciplinary program designed to optimize patients with cardiovascular diseases. It is an essential component of care for patients with coronary artery disease (CAD).¹ Several studies have shown that

participation in CR after myocardial infarction (MI), percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) surgery significantly reduces morbidity, mortality, and hospital readmission rates in a cost-effective manner.^{2–4}

Diabetes mellitus (DM) is a known cardiovascular risk factor for CAD that has increased in prevalence in epidemic proportions, affecting >340 million people globally⁵ and posing a major public health problem because of its associated morbidity and mortality.^{6,7} Among patients undergoing PCI, studies suggest that participation in CR is associated with improved cardiovascular health, medication adherence, and mortality.^{2,4} However, less is known about the association between CR and outcomes after PCI in patients with DM, a higher-risk subgroup that has a worse prognosis after PCI than does the subgroup of patients without DM.^{8,9}

The aim of our study was 2-fold: (1) to evaluate the impact of CR on cardiovascular events and mortality after PCI in patients with DM and (2) to compare the relative impact of CR on these outcomes in patients with and without DM.

From the UGC Corazón, Hospital Universitario Virgen de la Victoria, Instituto de Biomedicina de Málaga, CIBERCV Enfermedades Cardiovasculares, Universidad de Málaga, Spain (M.F.J.-N., L.M.P.-B.); and the Department of Cardiovascular Diseases and Department of Health Sciences Research, Mayo Clinic, Rochester, MN (F.L.-J., R.J.L., C.D.-M., J.P.R.-E., K.G., D.C., A.P., R.W.S., R.J.T.).

Correspondence to: Luis M. Pérez-Belmonte, MD, PhD, or Manuel F. Jiménez-Navarro, MD, PhD, Unidad de Gestión Clínica del Corazón, Hospital Clínico Universitario Virgen de la Victoria, Campus Universitario de Teatinos, s/n, 29010 Málaga, Spain. E-mails: luismiguelpb1984@gmail.com or mjimeneznavarro@gmail.com

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Clinical Perspective

What Is New?

- Cardiac rehabilitation (CR) participation after percutaneous coronary intervention is associated with a lower all-cause mortality in patients with and without diabetes mellitus (DM).
- In patients with DM, CR participation was associated with a reduced composite end point of mortality, myocardial infarction, or revascularization. In patients without DM, CR participation was associated with a reduction in cardiac mortality.
- Despite the fact that CR was associated with a lower mortality risk after percutaneous coronary intervention in patients with and without DM, CR participation was lower in diabetic patients.

What Are the Clinical Implications?

- These findings highlight the benefits of CR, while supporting efforts, including the development and dissemination of clinical practice guidelines, performance measures, and policy initiatives, that are aimed at increasing CR participation after percutaneous coronary intervention.
- Methods to identify and correct barriers to CR after percutaneous coronary intervention, thereby improving patient participation, appear to be warranted for patients with DM.

Methods

Residents of Olmsted County (Minnesota) were included in our study if they had a diagnosis of DM and if they were discharged alive after undergoing PCI between 1994 and 2010. Data from the electronic medical record system, PCI registry,¹⁰ and CR database^{3,4} from the Mayo Clinic (Rochester, MN) were used for the study, similar to the methods used for a previously published study.²

The study sample is a community-based sample, in that all PCI and CR services performed in Olmsted County during the study period were exclusively performed at the Mayo Clinic and its affiliated hospitals. Of the patients with DM included in the current study (N=700), 517 (73.9%) were in a previous report published by Goel et al² about the impact of CR on mortality and cardiovascular events after PCI. For the patients without DM, 1878 of 2389 (78.6%) were included in the previous study.

Several patient characteristics were identified and analyzed from the Mayo Clinic databases listed above. DM was defined as having a history of DM diagnosed and/or treated with medication or diet. PCI was defined as nonelective if performed within 14 days of an acute coronary syndrome, whereas all others were defined as elective. Patients were

considered to have participated in CR if they attended at least 1 CR session within 3 months after the qualifying PCI procedure. CR participation status was validated in a random year-by-year sample of study patients. Methods used for CR at the Mayo Clinic have been previously published.²⁻⁴ In brief, patients in the Mayo Clinic CR program undergo a comprehensive, multidisciplinary program lasting ≈ 12 weeks (3-hour-long sessions per week, generally). This program aimed at optimizing lifestyle and medication therapy for guideline-based cardiovascular disease risk reduction and identifying and managing pertinent comorbid conditions (eg, depression or sleep apnea). All patients who complete the Mayo Clinic CR program are encouraged to follow up with quarterly clinic visits during the subsequent year through a nurse-case management system⁴ and are also encouraged to follow up long-term with their primary care provider. Only patients who had previously given consent to use their medical records for medical research were included in this study. This study was approved by the institutional review board from Mayo Clinic.

Methods used for obtaining clinical outcomes have been previously described.²⁻⁴ Study outcome data were obtained by telephone interview at 6 and 12 months after the qualifying PCI, and then once yearly. All-cause mortality was the primary outcome measure; the secondary outcome measures included a composite outcome of death, MI, and revascularization (PCI or CABG surgery). Deaths were validated, along with the cause of death, using patient death certificates. Nonfatal events were validated by medical record review.

Statistical Analysis

Continuous variables are summarized as mean \pm SD or median (quartile 1–quartile 3) with Student 2-sample *t* test or Mann-Whitney-Wilcoxon rank-sum test used to test the significance of between-group differences. Discrete variables are presented as frequencies and percentages, with between-group differences tested using the Pearson χ^2 test. Between-group differences for ordinal data were analyzed using the rank-sum test; and for time-to-event variables, using the log-rank test. Kaplan-Meier methods were used to estimate post-PCI event rates (ie, the time to the first event after hospital discharge after the qualifying PCI). Date of discharge after the index PCI was used as time 0 for follow-up analyses. SAS version 9.3 was used for analyses. All hypothesis tests were done as 2 sided, with $P=0.05$.

Multiple logistic regression analysis was used to model the probability of CR participation separately within patients with and without DM for use as a propensity score, for propensity score adjustment. The covariates in these models were age, sex, recent MI, unstable angina, predominant symptom, chronic heart failure on presentation, smoking status, history

of MI, prior PCI, prior CABG, history of peripheral vascular disease, cerebrovascular accident/transient ischemic attack, renal disease, chronic obstructive pulmonary disease, cancer, severity of CAD (eg, presence of triple-vessel disease), lesion characteristics (eg, presence of thrombus complex lesion), use of drug-eluting stents, use of glycoprotein IIb/IIIa inhibitors, vein graft intervention, thrombosis in MI III flow after PCI, discharge medications, procedure data, post-PCI mortality risk score, and an interaction between procedure date and recent MI. Sample medians were used in the modeling analyses only, to impute missing values. We used splines with 3 *df* to adjust for nonlinear relationships between CR use and age, PCI date, and body mass index.

Two different applications of the propensity score were attempted for risk adjustment. First, patients were classified according to quintiles of the propensity score, and comparisons of the patients in the CR and non-CR groups were made within each quintile. The resulting estimated effects (log hazard ratios [HRs]) of CR participation were then combined across all 5 quintiles with a weighted average (inverse variance). When a patient's propensity score fell beyond the values that were common to the non-CR and CR subgroups, the patient was excluded from the stratified analysis. Second, we used propensity scores to match patients in the non-CR and CR groups in a 1:1 manner. A greedy matching algorithm was used to match patients in the non-CR and CR groups that used the following matching criteria: MI symptoms within 24 hours of PCI, PCI date within 1 year, and propensity score less than or equal to one fourth of the SD.

Results

Patient Characteristics and CR Participation

Among the 700 patients with DM in our study cohort, 38% (n=263) participated in at least 1 session of CR during the 3 months after PCI; however, we had available data about the number of sessions for only 168 patients. The median number of sessions attended by those patients was 9 (interquartile range, 13–19), with 18 patients (11%) participating in 25 sessions or more. Table 1 shows clinical, angiographic, and procedural characteristics of patients with DM, grouped by CR participation status.

Among patients with DM, those entering CR tended to be younger, were more likely to have had a recent MI, and were less likely to be seen with heart failure or have a history of CAD, cerebral vascular disease, chronic kidney disease, or peripheral artery disease. Drug-eluting stents and glycoprotein IIb/IIIa inhibitors were more often used in patients undergoing CR.

Clinical characteristics of patients with DM included in matched-pair analysis, grouped by CR participation status, are

Table 1. Clinical and Procedural Characteristics of Patients With Diabetes Mellitus, Grouped by Cardiac Rehabilitation Participation Status

Variable	No Rehabilitation (N=437)	Rehabilitation (N=263)	P Value
Age, mean±SD, y	68.2±12.1	63.5±11.2	<0.001
Male sex	278 (64)	168 (64)	0.94
History of smoking	253 (59)	162 (63)	0.21
Most recent MI			0.01
<24 h	84 (20)	83 (33)	
1–7 d	80 (19)	42 (16)	
>7 d	97 (23)	35 (14)	
Never	165 (39)	95 (37)	
Definite/probable angina	284 (65)	176 (67)	0.60
Unstable angina	258 (59)	156 (59)	0.94
CHC ≥III	238 (54)	136 (52)	0.48
Prior PCI	78 (18)	23 (9)	<0.001
Prior CABG	111 (25)	44 (17)	<0.01
Multivessel disease	311 (73)	175 (68)	0.15
Urgency of PCI			0.09
Elective	136 (31)	72 (27)	
Urgent	203 (46)	116 (44)	
Emergency	98 (22)	75 (29)	
Use of DE stents	148 (34)	113 (44)	0.009
GP IIb/IIIa use	240 (55)	177 (67)	<0.001
CHF	110 (27)	37 (15)	<0.001
LVEF ≤40%	52 (12)	28 (11)	0.52
Hypertension	343 (79)	214 (84)	0.18
BMI, mean±SD, kg/m ²	31.2±6.6	32.2±6.6	0.05
Hypercholesterolemia	331 (80)	213 (85)	0.09
PVD	83 (19)	18 (7)	<0.001
CVD	64 (16)	29 (11)	<0.01
CKD	33 (8)	5 (2)	<0.01
In-hospital MI/CABG/target re-PCI	20 (5)	17 (6)	0.28

Data are given as number (percentage) unless otherwise indicated. BMI indicates body mass index; CABG, coronary-artery bypass grafting; CHC, Canadian Heart Class; CHF, cardiac heart failure; CKD, chronic kidney disease; CVD, cerebral vascular disease; DE, drug-eluting; GP, glycoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.

listed in Table 2. There was a significantly higher incidence of MI, CABG, or re-PCI in target vessel before discharge from the hospital in patients who participated in CR.

CR participation was significantly lower in patients with DM (38%, 263/700) compared with those who did not have DM

Table 2. Clinical Characteristics of Patients With Diabetes Mellitus Included in Matched-Pair Analysis, Grouped by Cardiac Rehabilitation Participation Status

Variable	No Rehabilitation (N=161)	Rehabilitation (N=161)	P Value
Age, mean±SD, y	64.5±11.1	64.9±11.3	0.73
Male sex	103 (64)	100 (62)	0.71
History of smoking	93 (58)	91 (65)	0.21
Most recent MI			0.37
<24 h	35 (23)	35 (23)	
1–7 d	26 (17)	32 (21)	
>7 d	25 (16)	26 (17)	
Never	67 (44)	60 (39)	
Definite/probable angina	105 (65)	118 (73)	0.08
Unstable angina	93 (58)	102 (63)	0.27
CHC ≥III	86 (53)	90 (56)	0.65
Prior PCI	19 (12)	16 (10)	0.56
Prior CABG	32 (20)	34 (21)	0.77
Multivessel disease	110 (70)	103 (66)	0.32
Urgency of PCI			0.29
Elective	48 (30)	53 (33)	
Urgent	75 (47)	75 (47)	
Emergency	38 (24)	33 (20)	
Use of DE stents	66 (41)	71 (44)	0.87
GP IIb/IIIa use	100 (62)	103 (64)	0.70
CHF	25 (16)	28 (17)	0.65
LVEF ≤40%	16 (10)	21 (13)	0.82
Hypertension	120 (75)	123 (79)	0.49
BMI, mean±SD, kg/m ²	32.5±7.3	31.9±6.8	0.39
Hypercholesterolemia	126 (83)	129 (85)	0.37
PVD	12 (7)	14 (9)	0.68
CVD	20 (12)	21 (13)	0.85
CKD	2 (1)	2 (1)	0.97
In-hospital MI/CABG/target re-PCI	3 (2)	11 (7)	0.027

Data are given as number (percentage) unless otherwise indicated. BMI indicates body mass index; CABG, coronary-artery bypass grafting; CHC, Canadian Heart Class; CHF, cardiac heart failure; CKD, chronic kidney disease; CVD, cerebral vascular disease; DE, drug-eluting; GP, glycoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.

(45%, 1071/2379; $P=0.004$ for the difference between the 2 groups). In 2006, Medicare and Medicaid Services regulations started to cover CR after PCI, increasing significantly CR participation after that time (14% of eligible patients undergoing PCI participated in CR before and 40% after 2006; $P<0.001$), although the difference in CR participation among patients with and without DM persisted. Participation rates

also increased from before to after 2006 for patients undergoing nonelective PCI (16%–38%; $P<0.001$).

Impact of CR on Mortality and Composite End Points

During a median follow-up of 8.1 (4.1–11.4) years, there were 109 cardiovascular and 149 noncardiovascular deaths in the 700 individuals with DM in our cohort. In addition, 232 patients had a repeated revascularization (PCI or CABG) and 130 had a subsequent MI during the follow-up.

In our primary adjusted analysis, we stratified patients with DM into homogeneous strata, according to quintiles of the propensity score, and found a significantly lower all-cause mortality rate among patients undergoing CR compared with those not undergoing CR (HR, 0.56; 95% confidence interval [CI], 0.39–0.80; $P=0.002$). Largely attributable to a lower mortality, individuals with DM who participated in CR were also significantly less likely than nonparticipants to experience the composite end point of mortality, MI, or revascularization (HR, 0.77; 95% CI, 0.60–0.98; $P=0.037$). However, the difference in cardiac mortality between the groups was nonsignificant (HR, 0.71; 95% CI, 0.40–1.25; $P=0.24$); the difference in MI alone (HR, 1.20; 95% CI, 0.78–1.83; $P=0.41$) and the difference in revascularization alone (HR, 0.95; 95% CI, 0.70–1.29; $P=0.75$) were also nonsignificant. In individuals without DM, CR participation was associated with a significant reduction in all-cause mortality (HR, 0.67; 95% CI, 0.55–0.82; $P<0.001$) and cardiac mortality (HR, 0.67; 95% CI, 0.47–0.95; $P=0.024$), but not MI (HR, 0.97; 95% CI, 0.75–1.26; $P=0.84$) or revascularization (HR, 1.00; 95% CI, 0.84–1.18; $P=0.97$).

As a secondary analysis, we matched participants in the non-CR group to participants in the CR group using propensity scoring, in both patients with and without DM. In this matched comparison, CR participation in patients with DM was significantly associated with lower all-cause mortality but not with a significant reduction in cardiac mortality, MI, or revascularization. However, in the matched-pair analyses for people without DM, CR participation was significantly associated with reduced all-cause mortality and cardiac mortality, but not MI or revascularization. These results are summarized in Figure 1. Figure 2 shows curves of these end points according to CR participation in patients with DM. Within those patients who participated in CR, we did not find any evidence of a dose-effect ($P=0.62$) for reducing risk of mortality and cardiovascular events.

Discussion

Our study found that CR participation after PCI is associated with a lower all-cause mortality in patients with and without

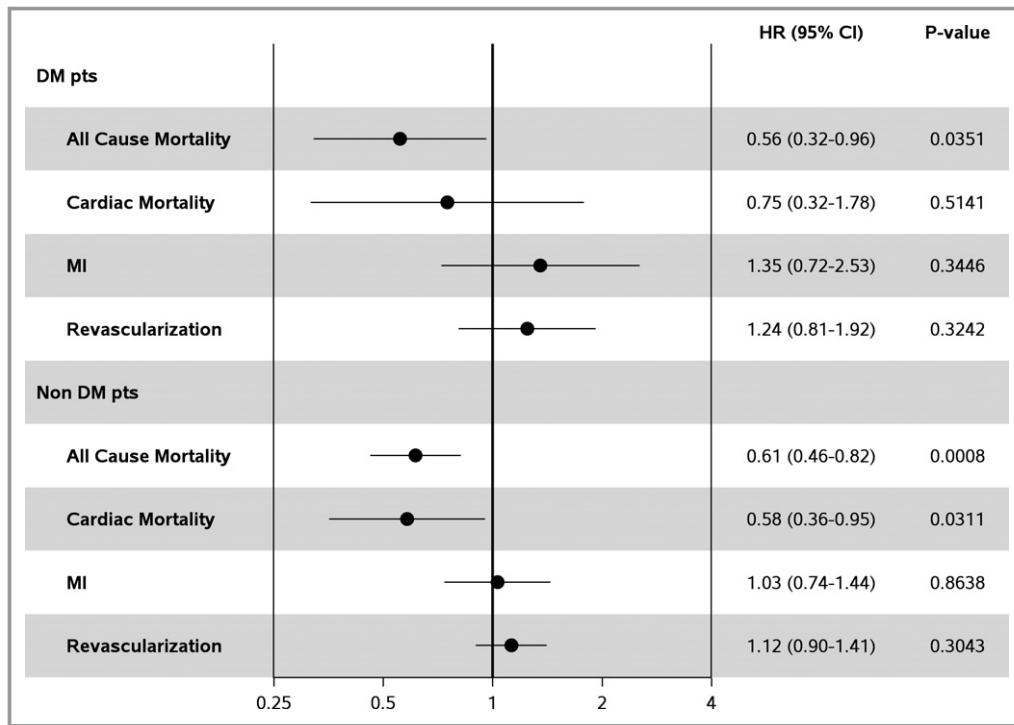


Figure 1. Impact of cardiac rehabilitation on mortality and composite end points. Propensity score adjustment matching participants without cardiac rehabilitation to participants with cardiac rehabilitation in both patients with and without diabetes mellitus (DM). CI indicates confidence interval; HR, hazard ratio; and MI, myocardial infarction.

DM who have undergone PCI. Also, in patients with DM, CR participation was associated with a reduced composite end point of mortality, MI, or revascularization. In patients without DM, CR participation was associated with a reduction in cardiac mortality. Despite the fact that CR was associated with a lower mortality risk after PCI in patients with and without DM, CR participation was lower in diabetic patients.

These findings are important because they support, with community-based data, the hypothesis that CR participation is associated with lower mortality in patients with DM, and that this benefit is similar to the benefit noted in patients without DM. This is one of few studies that have explored the association between CR participation and all-cause mortality in people with CAD who have DM. In addition, this study is unique in that it assessed the association between CR participation and cardiovascular outcomes after PCI in people with and without DM, using extensive procedural, hospital, and posthospitalization data that are available through the Mayo Clinic database systems.

Prior studies have suggested, in contrast to our finding, that the benefit of CR after MI was significantly lower in DM, with less improvement in exercise capacity. Exercise capacity was measured by peak oxygen uptake, peak workload, maximum heart rate, percentage of the maximal predicted heart rate, exercise duration, and anaerobic threshold, potentially diminishing the benefit of CR on cardiovascular

morbidity and mortality.^{11,12} Underlying metabolic and myopathic limitations in people with DM in relationship with hyperglycemia were suggested as possible mechanisms for a lower improvement of exercise capacity after CR.^{12,13}

However, several studies have reported that completion of CR in patients with DM is associated with significant benefits on activities of daily living, quality of life, weight control, exercise tolerance, cardiac risk factor control, and risk of mortality. However, mortality has not been widely evaluated.^{14–16} In a recent and large cohort of 13 000 patients with CAD (2956 with DM), reported by Armstrong et al,¹⁷ CR was associated with significant reductions in mortality and cardiac hospitalizations in patients with DM, similar to outcomes in patients without DM. Although these studies are consistent with our findings, they differ from our study in that they have not been specifically focused on patients who have undergone PCI. Another large observational study by Mourot et al⁹ found CR benefits in patients with CAD who had undergone PCI, for both patients with and without DM, but the study did not report on mortality impact. A large study of Medicare patients who had undergone PCI from 1997 to 2002 found that CR participation was associated with reduction in all-cause mortality in individuals with DM.¹⁸ These results were similar to ours, but that study was limited to older patients (65 years and older) and did not include detailed procedural PCI/angiography data nor did it include data on

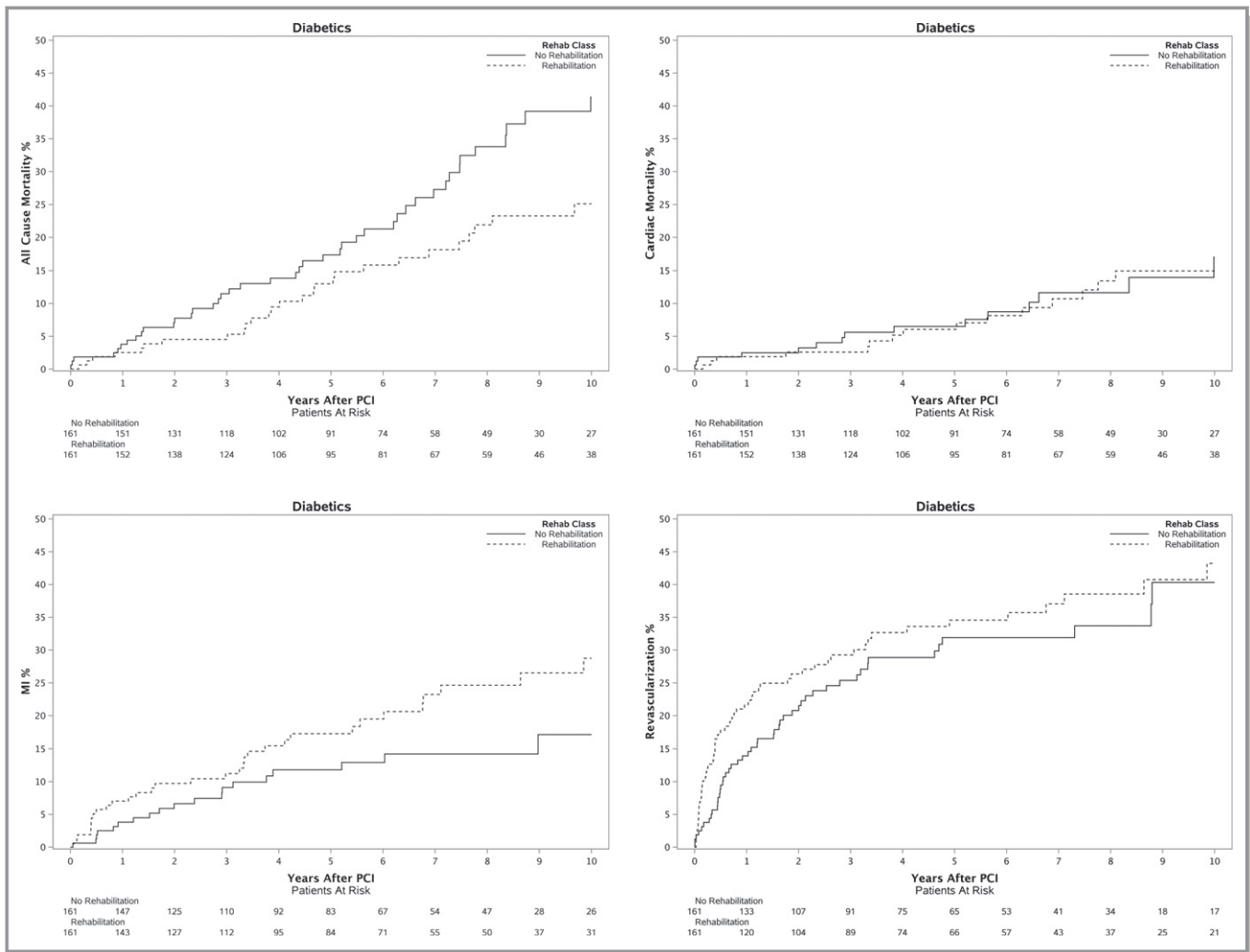


Figure 2. Curves of primary and secondary end points according to cardiac rehabilitation participation in patients with diabetes mellitus. MI indicates myocardial infarction; PCI, percutaneous coronary intervention.

cardiac mortality or recurrent cardiovascular events. Others reports have studied the effect of CR after PCI, although not separated by DM status. In these studies, CR participation was associated with a significant decrease in the incidence of death, major adverse cardiac events, and hospital admissions after PCI.^{19,20}

The current study, by focusing on outcomes in patients with and without DM, adds to our previously published study, in which we found a reduction in all-cause mortality and a trend toward decreased cardiac mortality associated with CR participation in all individuals who underwent PCI between 1994 and 2008 in Olmsted County (Minnesota).² We are unaware of other community-based reports that include detailed procedural, hospital, and posthospitalization data to compare cardiovascular outcomes after PCI, according to DM status and CR participation.

Although there is a significant and growing evidence base of the benefits of CR after PCI, evidenced by the fact that CR

participation is listed as a class I recommendation^{1,21} in the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI guidelines, there has been less clarity in the published literature about the benefits of post-PCI CR in patients with DM. This study sheds additional light on this important topic. The underlying mechanisms for CR benefits in patients with DM are not completely clear. It is likely that the underlying mechanisms are similar to those in patients undergoing CR generally, including the beneficial cardiovascular effects and reduction in cardiovascular end points from physical activity, healthy dietary habits, smoking cessation counseling, stress management, and medication adherence on improvements in glucose control, blood pressure control, lipid control, smoking cessation, and early symptom assessment.^{2,22,23}

Despite the significant benefits of CR, low rates of referral to CR have been noted after PCI in the United States between

2009 and 2012, with only $\approx 60\%$ of patients after PCI being referred to CR at hospital discharge.²⁴ Results obtained herein also reflect a need for greater CR participation by patients after PCI. Hospital-level factors (ie, hospital size, procedure volume, geographic location, and presence of systematic CR programs) may be even more important barriers to CR participation than patient-level factors (ie, age or comorbid conditions) and other factors, such as insurance status or clinical presentation.^{24,25}

This study is limited by the retrospective nature of our data. In addition, our data are from 1 center with a cohort of primarily white, non-Hispanic individuals, and, therefore, may not be representative of other populations. However, data from Olmsted County have been previously identified as being a representative community-based sample of data, with characteristics that are similar to those of other primarily white populations within the United States.^{26,27} Unfortunately, we did not have data available to us to allow us to assess socioeconomic status, an important influence on several health outcomes.²⁸ We also lacked data on changes in risk factor control, lifestyle habits, and adherence to preventive medications, which could have potentially had an impact on our results. Finally, because of the few events, we had limited statistical power to detect an impact of CR on cardiac mortality, MI, and revascularization in the matched-pair analysis of patients with DM.

Conclusions

Participation in CR after PCI is associated with similar lower all-cause mortality in individuals with and without DM, but CR participation after PCI in people with DM is lower than in people without DM. These findings highlight the benefits of CR, while supporting efforts, including the development and dissemination of clinical practice guidelines, performance measures, and policy initiatives, that are aimed at increasing CR participation after PCI. Methods to improve delivery of CR after PCI to patients with DM appear to be warranted.

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Disclosures

None.

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