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Cardiac rehabilitation referral, attendance and mortality in women

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Abstract

Background: Cardiac rehabilitation (CR) reduces mortality in women and men with coronary artery disease (CAD). The objective of this study was to examine sex differences in long-term mortality, based on CR referral rates and attendance patterns in a large CAD population.

Design: This is a retrospective cohort study.

Methods: The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) and Cardiac Wellness Institute of Calgary (CWIC) databases were used to obtain information on all patients. Rates of referral to and attendance at CR were compared by sex. Logistic regression models were constructed to assess whether sex predicted CR referral or completion. The association between referral, completion, and survival was assessed by sex using Cox proportional hazard models.

Results: 25,958 subjects (6374—24.6%—were women) with at least one vessel CAD were included. Females experienced reduced rates of CR referral (31.1% vs 42.2%, $p < 0.0001$) and completion (50.1 vs 60.4%, $p < 0.0001$). Adjusting for demographic and clinical characteristics, relative to men, CR referral was significantly lower in women (adjusted odds ratio (OR) 0.74, 95% CI 0.69, 0.79) as was CR completion (adjusted OR 0.73, 95% CI 0.66, 0.81). Women completing CR experienced the greatest reduction in mortality (HR 0.36, 95% CI 0.28, 0.45) with a relative benefit greater than men (HR 0.51, 95% CI 0.46, 0.56).

Conclusion: This is the first large cohort study to demonstrate that referral to and attendance at CR is associated with a significant mortality reduction in women, comparatively better than that in men.

Keywords

Coronary artery disease, women, cardiac rehabilitation

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Introduction

Cardiac rehabilitation (CR) is a proven, systematic intervention for the secondary prevention of subsequent myocardial infarction, hospitalization, and death in patients with coronary artery disease (CAD).[1–5] Although women have been included in CR studies to date, a recent large meta-analyses revealed they comprise only 20% of the populations studied.[4] Despite major efforts to encourage referral to and participation in CR for appropriate patients,[6–10] the majority of patients, both women and men, are not referred and therefore do not participate.[11–15]

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Despite the established benefits of CR, smaller studies have suggested that women are less likely to be referred to and attend than men.[14,16–19] The reasons for non-referral include physician perceptions of CR based on quality, perceived benefit, and past experience.[20,21] The reason why women are referred less than men to CR is poorly understood; however, women are also less likely to receive cardiac interventions and guideline-indicated pharmacotherapies.[22] One study has suggested that when compared to women, men with greater spousal support were more likely to be referred.[23] Explanations for decreased attendance include lack of interest, more musculoskeletal issues, multiple co-morbidities, and difficulties with logistical issues such as transportation and family obligations.[24] While the sex disparities in referral and attendance to CR are concerning, there have been no large, well-defined cohort studies to date confirming that lack of referral and attendance significantly impacts clinical outcomes.

The objective of our study was to assess whether or not sex is associated with referral to, and completion of, CR in a large, well-described cohort of patients who have undergone coronary angiography, and when clinically appropriate, coronary revascularization. Additionally, we assessed if referral to and completion of CR was associated with reduced mortality in women vs men.

Methods

Data sources

The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database was used to obtain demographic, clinical, and procedural information on all patients. The APPROACH database captures all patients admitted with an acute coronary syndrome diagnosis or who underwent a cardiac catheterization procedure in Calgary, Alberta, Canada.[25]

In Calgary, CR has been uniformly provided through the Cardiac Wellness Institute of Calgary (CWIC), a single centralized program since 1996.[1] A multidisciplinary 12-week CR program at CWIC is offered. The CWIC and APPROACH databases were linked through the use of provincial health numbers, which are unique identifiers.

Study population

Patients identified in the APPROACH database from the Calgary region with at least one vessel coronary artery disease were included and deemed appropriate for referral to CR at CWIC. Patients were excluded if they were under 18 years of age, did not have a valid Provincial health number, or if they did not survive for at least 6 months following catheterization as these patients may have died before referral and thus, potentially bias study findings in favor of CR.

Outcomes of interest

Three outcomes were analyzed: referral to CR, completion of CR, and mortality. Subjects were considered to have been referred to CR if they had a referral recorded in the CWIC database. Subjects were considered to have completed CR if they completed both their baseline and 12-week post-rehabilitation assessment.[26] Patients must have attended at least 12 of 24 CR sessions to be invited for a 12-week cardio-metabolic fitness assessment (exercise test and clinically relevant blood work). Mortality was considered over the entire time period of follow-up, from the date of the initial cardiac catheterization. The first referral date was 19 January 1996. Follow-up was completed to 31 August 2012.

Statistics

Baseline characteristics were compared between men and women, using t-tests for measured variables and chi-squared statistics for categorical variables. Separate logistic regression models were constructed to assess whether sex predicted CR referral or completion. The association between CR referral, completion, and survival was assessed by sex using Cox proportional hazard models. In the survival models, CR was considered as a three level categorical variable: subjects were classified as: (1) never referred; (2) referred but not completing CR; or (3) referred and completed CR. For all survival models, those subjects who were never referred to CR were the reference group. Initial models were unadjusted. Subsequent models were adjusted for age, coronary disease severity (defined by Duke Coronary Index),[27] coronary interventions (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within one year of referral), ejection fraction (EF), hypertension, hyperlipidemia, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), congestive heart failure (CHF), peripheral vascular disease (PVD), renal disease (serum creatinine $>177\,\mu mol/l$), dialysis, smoking status, gastrointestinal disease, and presence of malignancy. Models were then stratified by sex. Survival was compared between sexes in each category of CR (non-referred, referred and did not complete, referred and did complete CR) using log rank tests. A two-tailed value of $p < 0.05$ was defined as statistically significant. All statistical analyses were conducted with intercooled Stata version 11 (College Station, TX). The study protocol was approved by the Conjoint Health Ethics Review Board of the University of Calgary.

Results

Baseline characteristics

There were 36,264 patients identified who underwent cardiac catheterization, of which 25,958 subjects with at least one vessel CAD were included; of those, 6374 (24.6%) were female (Table 1). Of the 36,264 patients, 11,120 were female and 6374 had significant CAD (57.3%). Of the 25,144 male patients, 19,587 (77.9%) had significant CAD ($p < 0.001$). Relative to male subjects in the baseline cohort, women were older, had a higher prevalence of cardiac risk factors including

Table 1. Baseline population characteristics by sex.

	Women (6374)	Men (19,584)	*p*-value
Referred to CR, n (%)	1979 (31.1)	8257 (42.2)	<0.01
Attended CR[a], n (%)	991 (50.1)	4984 (60.4)	<0.01
Mean age (years)	67.3 (SD, 11.3)	62.7 (SD, 11.3)	<0.01
Hypertension, n (%)	4468 (70.1)	11,633 (59.4)	<0.01
Hyperlipidemia, n (%)	3958 (62.1)	12,867 (65.7)	<0.01
Diabetes mellitus, n (%)	1695 (26.6)	4387 (22.4)	<0.01
Renal disease, n (%)	268 (4.2)	685 (3.5)	<0.01
On dialysis, n (%)	115 (1.8)	255 (1.3)	<0.01
CHF, n (%)	1115 (17.5)	2428 (12.4)	<0.01
PVD, n (%)	631 (9.9)	1625 (8.3)	<0.01
CVD, n (%)	606 (9.5)	1351 (6.9)	<0.01
COPD, n (%)	1160 (18.2)	2683 (13.7)	<0.01
Current smoker, n (%)	2014 (31.6)	4406 (22.5)	<0.01
Previous smoker, n (%)	1887 (29.6)	8245 (42.1)	<0.01
Known malignancy, n (%)	338 (5.3)	940 (4.8)	0.12
GI or liver disease, n (%)	510 (8.0)	1253 (6.4)	<0.01
Previous MI, n (%)	2601 (40.8)	8480 (43.3)	<0.01
Prior PCI, n (%)	504 (7.9)	1939 (9.9)	<0.01
Prior CABG, n (%)	261 (4.1)	1293 (6.6)	<0.01
Treatment within one year post-cardiac catheterization			
PCI, n (%)	3181 (49.9)	9929 (50.7)	0.24
CABG, n (%)	1128 (17.7)	4583 (23.4)	<0.01
Duke Coronary Index			<0.01
Low risk, n (%)	3812 (59.8)	10164 (51.9)	
High risk, n (%)	2103 (33.0)	7462 (38.1)	
Left main, n (%)	459 (7.2)	1958 (10.0)	
Indication for catheterization			<0.01
Stable angina, n (%)	1390 (21.8)	5581 (28.5)	
Myocardial infarction, n (%)	2632 (41.3)	8127 (41.5)	
Unstable angina, n (%)	1829 (28.7)	4543 (23.2)	
Other, n (%)	523 (8.2)	1332 (6.8)	
Ejection fraction, n (%)			<0.01
>50	4455 (69.9)	12,828 (65.5)	
35–49	1071 (16.8)	3976 (20.3)	
20–34	261 (4.1)	979 (5.0)	
<20	25 (0.4)	157 (0.8)	
Not available	554 (8.6)	1665 (8.5)	

CR, cardiac rehabilitation; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.; [a]As a proportion of those referred.

hypertension and diabetes, and were more likely to be current smokers (however, cumulative results of current and previous smokers indicate any history of smoking is more common in men). Women were more likely than men to have significant comorbid disease, including CHF, renal disease, COPD, CVD, and PVD.

Referral

The percentage of the entire cohort of patients who are referred to and attended CR is depicted in Figure 1. The percentage of women referred to and attending CR was significantly lower than that for men. Female sex was associated with reduced rates of referral relative to the male CAD patients (Table 2). Statistically significant predictors of referral to CR in this model included hypertension, hyperlipidemia, prior PCI, prior CABG, and EF 35–50%. Statistically significant predictors of non-referral in addition to female sex, included age >75 years, diabetes mellitus, renal disease, dialysis, CHF, PVD, CVD, COPD, current smoker, previous smoker, and EF <20%.

Program completion

Female sex was associated with reduced rates of attendance to CR (Table 2). The only statistically significant predictor of CR attendance and completion was a history of CABG within one-year post cardiac catheterization. The statistically significant predictors of non-completion included age >75 years, hypertension, diabetes mellitus, renal disease, PVD, CVD, COPD, current smoker, and EF 35–50%.

Mortality benefit

For the survival analysis, median follow-up was 7.4 years (inter-quartile range, 4.3–10.9 years). In this study population, subjects who attended CR had greater survival than those who were referred and did not attend. (Figure 2 and Table 3). The women who were not referred to CR had the highest mortality of all subjects, and had higher mortality relative to men who were not referred (log rank, $p < 0.0001$). Compared to women not referred to CR, those who were referred to CR but did not attend had significantly improved survival; an even greater relative benefit was demonstrated for those women who were referred and completed the program. Men derived survival benefit from being referred to CR compared to men not referred. Men who completed CR had a greater survival benefit compared to men not referred to CR. The survival benefit observed in men completing CR was not as large as the relative survival benefit observed in women (Figure 2).

Discussion

This large cohort study of CR referral and completion demonstrated that while women have a significant mortality benefit from completing CR, they are significantly less likely than men to be referred or complete CR. These observations have substantive implications for those who treat and care for women with coronary artery disease, refer patients to CR, provide CR services, and pay for those services. These findings are likely to be generalizable beyond Canada, as previous work in European CR populations have identified gender bias as an issue in CR referral, in a similar patient population.[18]

Referral bias

The explanation for decreased CR referral and attendance, in both women and men, is complex and multifactorial. The excess cardiovascular morbidity and

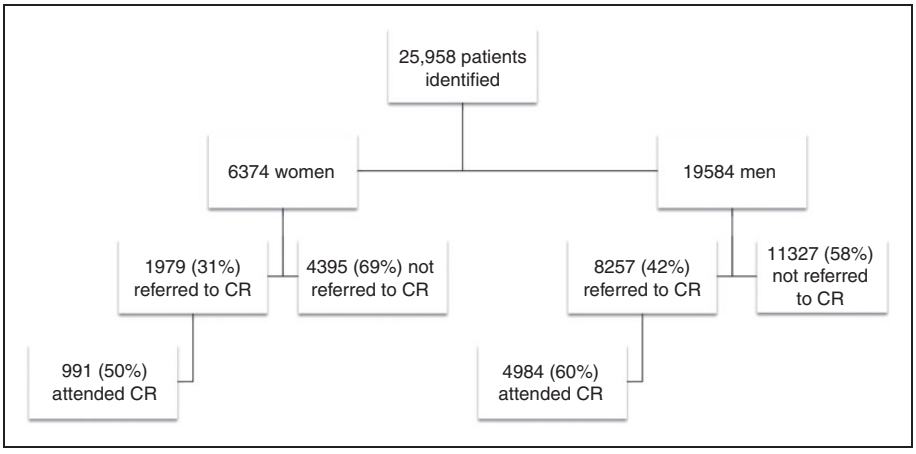

Figure 1. Study population flow diagram. Study patients identified by sex, referral, and attendance at cardiac rehabilitation.

Table 2. Estimated odds ratios predicting cardiac rehabilitation referral and attendance.

	Referral	95% CI	Attendance	95% CI
Female sex	0.75	0.70, 0.80	0.73	0.66, 081
Age (per year)	0.96	0.96, 0.96	1.00	0.99, 1.00
Age over 75 years	0.80	0.73, 0.89	0.50	0.42, 0.59
Hypertension	1.07	1.01, 1.13	0.89	0.81, 0.96
Hyperlipidemia	1.31	1.23, 1.39	1.06	0.97,1.16
Diabetes mellitus	0.86	0.81, 0.92	0.65	0.59, 0.72
Renal disease	0.72	0.59, 0.88	0.53	0.37, 0.74
On dialysis	0.21	0.14, 0.32	0.92	0.42, 1.99
Congestive heart failure	0.84	0.76, 0.93	0.88	0.75, 1.03
Peripheral vascular disease	0.70	0.62, 0.78	0.71	0.59, 0.86
Cerebrovascular disease	0.82	0.73, 0.92	0.76	0.62, 0.92
COPD	0.88	0.81, 0.96	0.87	0.76, 0.99
Current smoker	0.84	0.78, 0.90	0.50	0.45, 0.55
Previous smoker	0.92	0.86, 0.97	1.04	0.95, 1.14
Known malignancy	0.89	0.78, 1.02	0.87	0.70, 1.09
GI or liver disease	1.05	0.94, 1.18	0.92	0.77, 1.09
Treatment within one year post-cardiac catheterization				
PCI	3.23	3.01, 3.45	0.96	0.86, 1.07
CABG	3.33	3.05, 3.63	1.25	1.09, 1.43
Duke Coronary Index				
Low risk	1.00		1.00	
High risk	0.97	0.91, 1.04	1.01	0.92, 1.11
Left main	1.06	0.94, 1.19	0.91	0.76, 1.09
Ejection fraction				
>50%	1.00		1.00	
35–50	1.17	1.09, 1.26	0.83	0.75, 0.92
20–34	0.88	0.76, 1.01	0.83	0.66, 1.04
<20	0.63	0.34, 0.94	1.24	0.63, 2.43

COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

mortality experienced by women with CAD, in general, is under-appreciated by health-care practitioners.[22,28] Our results confirm previous studies that women referred to but not completing CR were more likely to be significantly older and experience more clinically important comorbidities such as CHF and diabetes mellitus.[29] Although this observation suggests that referring physicians adjust their referral patterns to CR depending on patient comorbidities, non-referral of these potentially sicker patients deprives those with arguably the most to gain from CR.[30] Use of a systematic referral system could decrease this bias towards non-referral in women.[7,8]

Attendance bias

It has been suggested that baseline factors more commonly seen in women, such as musculoskeletal complaints, multiple medical issues, transportation, and family obligations predict CR attendance.[24] The results from our study suggest that other clinically relevant medical comorbidities may also result in a referral and attendance bias among those patients referred for CR. These issues could be successfully addressed in a clinically sensitive CR environment that recognizes these limitations and specifically addresses them.[31] In addition, a recent systematic review examining the

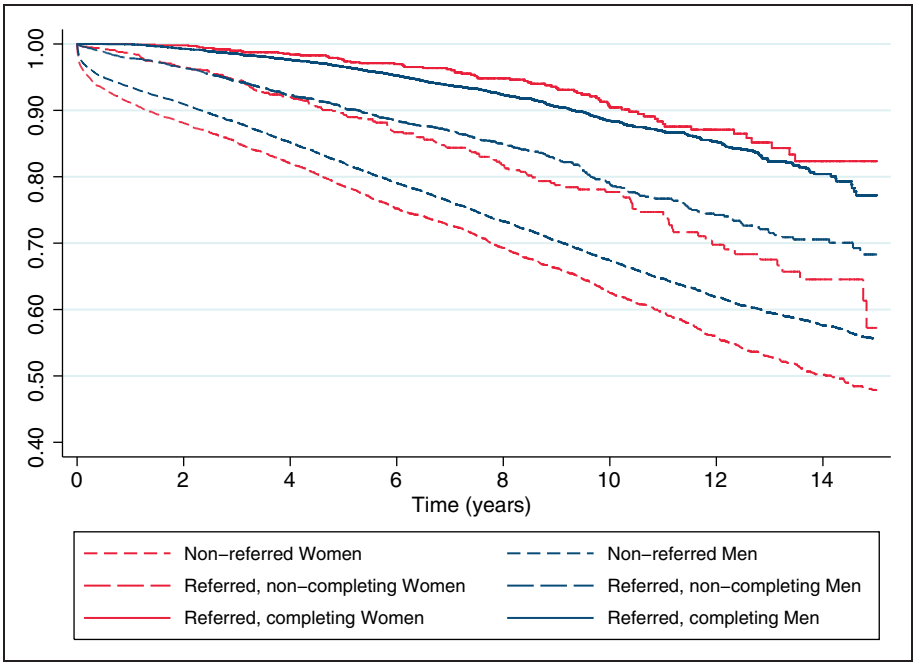

Figure 2. Survival stratified by referral, attendance and sex. Subjects classified as having never been referred, been referred but not completing CR, or having been referred and completed CR. For all survival models, subjects who were never referred to CR were the referent group.

Table 3. Hazard ratios for survival associated with cardiac rehabilitation referral and completion. Non-referred subjects are the reference group.

	Women	Men
	Adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
CR status		
Referred, did not complete	0.82 (0.70, 0.97)	0.86 (0.78, 0.94)
Completed	0.36 (0.28, 0.45)	0.51 (0.46, 0.56)

factors that influence attendance at CR demonstrated that patients' knowledge of services, their perceptions of heart disease, and their personal financial or occupational constraints all significantly affected CR program attendance.[32]

Mortality benefit

In a previous study, we reported a 41% relative risk reduction (RRR) in mortality in a large population of CR completers vs non-completers.[1] In this analysis, we noted similar benefits between men (49% RRR) and women (64% RRR) in terms of mortality reduction when comparing those subjects referred to CR who did not complete the program to those not referred to CR. The women in the present cohort were substantially older than their male counterparts, with a significantly higher burden of comorbid disease. These findings highlight the fact that CAD in women may be a more complex process compared to men.[33] This clinical complexity, in combination with the potential improvements in cardio-metabolic fitness achieved within comprehensive CR programs, may explain, at least in part, the mortality reductions we saw in our study population.

Limitations

Despite this important mortality benefit, a limitation to our data interpretation is that this was a non-randomized, retrospective analysis. While we adjusted for major clinical variables, without randomization, unmeasured or unappreciated variables may have affected the outcomes. It is important to note that CR is a well-established clinical standard of care and denial of this lifestyle intervention to eligible patients due to randomization would be unethical. Thus, while non-randomized trials such as this one come with limitations, it is currently the only feasible design to assess CR outcomes. The large sample size and multiple comparisons in the current study create the potential for some significant differences related to the male vs female baseline characteristics reported in Table 1, particularly those comparisons with closely approximating

values between groups, and thus, may lack clinical significance. However, the large sample size in the current study offsets the limitations associated with non-randomization as well as creating the opportunity for highly robust predictive and prognostic analyses (Tables 2 and 3).

Conclusion

Our study demonstrates the substantial survival benefit observed in patients with CAD who attend CR. The survival benefit in women is greater than that shown in previous studies with relatively few female participants. Despite the fact that the women with CAD in our study derived a greater mortality benefit from attending CR compared to men, women were both less likely to be referred and less likely to attend. As CAD is a leading cause of death in women, greater emphasis needs to be placed on improving referral to and attendance at CR for women, thereby positively impacting their quality of care and further decreasing mortality in women with CAD.

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Conflicts of interest

None declared by authors.

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