International Journal of Cardiology 285 (2019) 108–114

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiac rehabilitation in people with peripheral arterial disease: A higher risk population that benefits from completion☆,☆☆,★,★★

Andrea N. Devrome [a], Sandeep Aggarwal [b,c], M. Sean McMurtry [d], Danielle Southern [e], Trina Hauer [b], Brea Lamb [b], Ross Arena [f], Randy D. Moore [a], Stephen B. Wilton [c,e], James Stone [b,c], Billie-Jean Martin [b,g,*]

[a] Department of Vascular Surgery, University of Calgary, Calgary, Canada
[b] TotalCardiology-Rehabilitation, Calgary, Canada
[c] Libin Cardiovascular Institute, University of Calgary, Calgary, Canada
[d] Division of Cardiology, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada
[e] Department of Community Health Sciences, University of Calgary, Calgary, Canada
[f] Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, Chicago, IL, USA
[g] Department of Cardiothoracic Surgery, Stanford University, Stanford, CA, USA

ARTICLE INFO

Article history:
Received 17 January 2019
Accepted 27 February 2019
Available online 5 March 2019

Keywords:
Cardiac rehabilitation
Peripheral arterial disease
Outcomes

ABSTRACT

Background: Peripheral arterial disease (PAD) is common in people referred for cardiac rehabilitation (CR). However, the associations between PAD diagnosis and CR attendance and mortality remain to be defined.
Methods: All patients referred to a 12-week exercise-based CR program were included. Associations between PAD diagnosis and starting CR as well as between PAD diagnosis and completing CR were measured using multivariable logistic regression. Associations between CR completion and mortality were measured using adjusted Cox proportional hazards models, and a propensity-based matching sensitivity analysis was performed.
Results: 23,215 patients (mean age 61.3 years; 21.6% female) were referred to CR; 1366 (5.9%) had PAD. Those with PAD were less likely to start CR (57.0% vs 68.2%, adjusted OR 0.81, 95%CI 0.72, 0.91) and complete CR if they started (70.6% vs 76.7%, adjusted OR 0.80, 95%CI 0.68, 0.94). Patients with PAD completing CR had lower exercise capacity at baseline (6.6 vs. 7.6 METs, $p < 0.0001$) and completion (7.5 vs 8.6 METs, $p < 0.0001$). There were 3510 deaths over follow-up; 10-year survival was lower in those with PAD (66.9 vs 84.5%; $p < 0.0001$). CR completion was associated with lower mortality for all (adjusted HR 0.62 (95%CI 0.57, 0.67)), and the magnitude of the association was independent of PAD status.
Conclusions: Patients with PAD referred to CR had a higher mortality than those without, and were less likely to start and complete CR. Completion of CR was associated with improved fitness and survival for PAD patients. These data support broader use of CR by those with PAD.

© 2019 Published by Elsevier B.V.

1. Introduction

Peripheral arterial disease (PAD) is an atherosclerotic disease causing stenosis and occlusion of non-coronary and non-cerebral vessels. Patients may be asymptomatic or have symptoms ranging from claudication to critical limb ischemia (CLI), where patients experience rest pain, digital gangrene, or lower extremity ulcers. Patients with PAD frequently have other cardiovascular diseases and risk factors, including hypertension, dyslipidemia, diabetes, genetic factors and smoking. Patients with PAD are vulnerable to a high rate of CVD events and cardiovascular mortality [1].

Patients with PAD require risk factor modification, appropriate pharmacological therapy and exercise training to optimize outcomes. There are extensive data showing the benefits of both supervised and home exercise programs in patients with PAD [2]. Studies have shown that exercise programs can be as effective as surgical interventions in increasing maximal walking distance as well as increasing quality of life among PAD patients [2]. Established cardiac rehabilitation (CR) program delivers these interventions in a comprehensive way.

The efficacy of CR programs is well established in subjects with coronary artery disease (CAD): completion of a CR program improves fitness, decreases risk of re-hospitalization, and reduces mortality [3,4]. Though there are randomized trial data supporting that CR improves symptoms and quality of life for patients with PAD, whether

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
☆☆ The authors report no relationships that could be construed as a conflict of interest.
★ The authors have no conflicts of interest related to this work.
★★ This work did not receive any grant support.

* Corresponding author at: 300 Pasteur Drive, Falk Building, Stanford, CA 94305-5407, USA.
E-mail address: billieje@stanford.edu (B.-J. Martin).

https://doi.org/10.1016/j.ijcard.2019.02.070
0167-5273/© 2019 Published by Elsevier B.V.

there is a mortality benefit is less well established. Additionally, starting a CR program may be less likely in subjects with PAD, given mobility limitations and comorbidities [5–7]. Further, given exercise limitations inherent with PAD, subjects with PAD may be less likely to complete CR or demonstrate improvements in exercise capacity [8,9].

The objectives of our study were to assess: (1) the association between PAD diagnosis and starting CR, (2) the association between PAD diagnosis and completing CR; (3) the association between CR completion and mortality, overall as well as for those with and without PAD; (4) the association between PAD diagnosis and change in exercise time and cardiorespiratory fitness.

2. Method

In Calgary, AB, Canada, CR has been provided by the Total Cardiology Rehabilitation (TCR), a single centralized program, since 1996. A comprehensive 12-week, exercise based CR program is offered to all patients referred. The reason for referral, provincial health number, and baseline demographics are recorded for all referrals received, regardless of attendance. Patients with a first referral for CR for coronary artery disease from the inception of the program who underwent coronary catheterization before March 31, 2016 made up the study population.

2.1. Data sources & patient selection

The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) database was used to obtain further information on all patients. The APPROACH database has captured information on all patients undergoing cardiac catheterization in Alberta since 1995 [10]. The TCR and APPROACH databases were linked through the use of provincial health numbers. 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 after catheterization [3].

2.2. Study variables

The TCR database was used to identify those who were referred for and completed CR. The APPROACH database linkage was used to obtain further clinical covariates. At the time of catheterization, data are prospectively collected in APPROACH on comorbidities, including age, sex, family history, hypertension, hyperlipidemia, diabetes mellitus, lung disease, cerebrovascular disease, congestive heart failure, peripheral vascular disease, renal disease, need for dialysis, gastrointestinal or liver disease and diagnosis of malignancy. In APPROACH, peripheral arterial disease is defined as either the presence of typical symptoms of claudication, or prior corrective surgery, angioplasty or amputation to the extremities. Also recorded are results of coronary catheterization (including coronary anatomy, as summarized by the Duke jeopardy score) and ejection fraction [10]. Because clinical covariates are captured only at the time of the initial catheterization, only those who were referred for CR within 1 year of their catheterization were included to ensure that the covariate data reasonably reflected the state of the patient as they appeared at CR.

2.3. Intervention

All the patients who started CR underwent a baseline assessment that included a graded exercise test (GXT) on a treadmill to determine peak metabolic equivalents (METs). The peak MET value was calculated from treadmill speed and grade during the final stage of the exercise protocol using an established equation [11]. Exercise testing was repeated at CR completion (12 weeks). Subjects were also asked to report their exercise frequency and exercise time per sessions at program start and completion. Subjects were categorized as doing no exercise (zero minutes/week), some exercise at baseline (0–150 min/week) or meeting exercise targets (≥150 min) at baseline and 12 weeks [12]. Beginning in 2004, subjects additionally had their depressive symptoms measured at CR start and completion using the Hospital Anxiety and Depression Scale Depression Index (HADS-D) [13,14]. Based on their scores, subjects were classified as having normal (0–7), mild (8–10), moderate (11–14), or severe (15–21) symptoms.

2.4. Outcomes

Outcomes of interest included starting CR, completing CR, and mortality. Additionally, exercise capacity at baseline and completion, exercise times and HADS depressive symptoms were considered at program start and completion for all subjects who completed CR. Mortality was considered only after the date on which subjects attended their first CR session. For subjects who did not attend at least 1 session of CR, their outcomes were considered after the median time from catheterization to CR attendance, 74 days. Follow-up was complete to March 31, 2017.

2.5. Statistical methods

Continuous variables were tested for the normality of their distribution and are presented as means with standard deviation or medians with interquartile range, and differences between those with and without PAD were assessed using t-Tests or Kruskal-Wallis tests as appropriate for normal or non-normally distributed variables. Categorical variables are presented as counts and percentages and were analyzed using the Chi-square test or ANOVA if there were three or greater outcome categories. Separate logistic regression models were used to determine the association between PAD and starting CR, the association between PAD and completing CR among those who start. Initial models were unadjusted, and then adjusted for all available co-variables as listed above. Cox proportional hazard models were then used to determine the association between CR status and survival. These models were adjusted for all available clinical risk factors (as noted above), severity of CAD (Duke jeopardy score), and ejection fraction. Multiple interaction terms were constructed to assess interactions between PAD and patient characteristics; in particular, to address issues around sex and PAD, interaction terms were created to assess the differential impact of PAD on CR attendance, completion and CR association reduction in mortality in women with PAD [15]. Potential interactions between PAD and CR completion in terms of survival were assessed in two ways: first, models looking at the association between CR completion and mortality were stratified by PAD status; second, a model including a CR*PAD interaction term was built. Finally, we also performed a propensity-matched analysis as a sensitivity test. We calculated the propensity to PAD using logistic regression, including all baseline variables as listed above. The propensity score was then used to match subjects with PAD to those without in a greedy 1-to-1 manner using psmatch2 within Stata (version 14; Stata Corp, College Station, TX) [16]. Balance in the matched groups was assessed by looking at the standardized differences between groups, with a difference of 10% deemed acceptable [17]. The associations between PAD and starting CR, PAD and completing CR, and completing CR and mortality were then assessed in the matched cohort.

Among those subjects who completed CR, difference in exercise capacity at baseline and 12 weeks, as well as differences in changes in exercise capacity over the course of CR, were compared between those with and without PAD using t-tests. Additionally, HADS scores and exercise times at start and finish were compared between groups.

A 2-tailed value of P 0.05 was defined as statistically significant. All statistical analyses were conducted with intercooled Stata version 14 (College Station, Texas). The study protocol was approved by the University of Calgary's Health Research Ethics Board, including the waiver of obtaining individual informed consent for data linkage.

3. Results

A total of 23,215 patients with CAD who were referred to CR in Calgary, Canada between 1996 and 2016 were included in this study. Of those, 1366 (5.9%) were identified as having PAD. Subjects with PAD were more likely to be female and were significantly older than those without PAD (Table 1). Patient with PAD were more likely to have cardiovascular risk factors including diabetes and chronic kidney disease; they were also more likely to be current or ex-smokers. Furthermore, PAD patients had more extensive cardiovascular disease: they were more likely to have a diagnosis of congestive heart failure, low ejection fraction, left main coronary disease, and to have previously undergone cardiopulmonary bypass grafting (Table 1).

3.1. Starting and completing cardiac rehabilitation

Subjects with PAD were more likely to not even start CR than those without (43.0% vs 31.8%, $p < 0.0001$; Table 1). Further, patients with PAD were also less likely to complete CR (of those referred, 40.3% vs. 52.3%; of those who started, 70.6% vs 76.7%; both $p < 0.0001$).

Logistic regression models were built to predict starting CR, and completing CR among those who start the program. In multivariable models including all variables outlined in Table 1, multiple predictors of not starting CR were identified, including female sex, diabetes diagnosis and age at referral (Table 2). Importantly, a PAD diagnosis was a significant predictor of not starting CR (Odds Ratio (OR) 0.80; 95% confidence interval (CI) 0.72, 0.90) even in the multivariable model. There were significant differences between predictors of starting CR and completing CR among those who started the program (15,691 subjects): while congestive heart failure diagnosis, coronary disease severity, and cerebrovascular disease all predicted not starting CR, subjects with those diagnoses were no less likely to complete CR if they started.

Table 1
Baseline population characteristics by Peripheral arterial disease status. CR: Cardiac Rehabilitation; BMI: Body Mass Index; LVEF: Left Ventricular Ejection Fraction; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Grafting.

	Overall (n = 23,215)	No PAD (n = 21,849)	PAD (n = 1366)	*p*-value
Rehab status				<0.001
Did not start	7524 (32.4%)	6937 (31.8%)	587 (43.0%)	
Started, did not complete	3710 (16.0%)	3481 (15.9%)	229 (16.8%)	
Completed	11,981 (51.6%)	11,431 (52.3%)	550 (40.3%)	
Female (%)	5008 (21.6%)	4683 (21.4%)	325 (23.8%)	0.040
Mean age (years)	61.3 (11.3)	61.1 (11.3)	64.3 (10.6)	<0.0001
Age by decade (n, %)				<0.0001
<40	642 (2.8%)	621 (2.8%)	21 (1.5%)	
40–49.9	3117 (13.4%)	3010 (13.8%)	107 (7.8%)	
50–59.9	7033 (30.3%)	6700 (30.7%)	333 (24.4%)	
60–69.9	6991 (30.1%)	6523 (29.9%)	468 (34.3%)	
70–79.9	4345 (18.7%)	3987 (18.3%)	358 (26.2%)	
>80	1087 (4.7%)	1008 (4.6%)	79 (5.8%)	
Hypertension (%)	14,534 (62.6%)	13,571 (62.1%)	963 (70.5%)	<0.0001
Hyperlipidemia (%)	15,743 (67.8%)	14,735 (67.4%)	1008 (73.8%)	<0.0001
Diabetes mellitus (%)	5178 (22.3%)	4814 (22.0%)	364 (26.7%)	<0.0001
Family history (n = 21,252)	6281 (29.6%)	5913 (29.6%)	368 (29.7%)	0.907
Renal disease (%)	521 (2.2%)	438 (2.0%)	83 (6.1%)	<0.0001
On dialysis (%)	103 (0.4%)	86 (0.4%)	17 (1.2%)	<0.0001
Previous MI	5255 (22.6%)	4871 (22.3%)	384 (28.1%)	<0.0001
Congestive heart failure (%)	2268 (9.8%)	2030 (9.3%)	238 (17.4%)	<0.0001
Cerebrovascular disease (%)	1120 (4.8%)	919 (4.2%)	201 (14.7%)	<0.0001
COPD (%)	3062 (13.2%)	2470 (12.5%)	322 (23.6%)	<0.0001
Current smoker (%)	6240 (26.9%)	5791 (26.5%)	449 (32.9%)	<0.0001
Previous smoker (%)	7426 (32.0%)			
Known malignancy (%)	956 (4.1%)	892 (4.1%)	64 (4.7%)	0.277
GI or Liver disease	1785 (7.7%)	1624 (7.4%)	161 (11.8%)	<0.0001
BMI (mean, SD) (n = 21,097)	28.6 (5.5)	28.6 (5.5)	28.3 (5.5)	0.0883
Prior PCI (%)	2031 (8.8%)	1854 (8.5%)	177 (13.0%)	<0.0001
Prior CABG (%)	2087 (9.0%)	1889 (8.7%)	198 (14.5%)	<0.0001
Duke Jeopardy Score				<0.0001
Normal	816 (3.5%)	739 (3.4%)	77 (5.6%)	
<50%	1279 (5.5%)	1162 (5.3%)	117 (8.6%)	
Low risk	11,500 (49.5%)	10,982 (50.3%)	518 (37.9%)	
High risk	7677 (33.1%)	7209 (33.0%)	468 (34.3%)	
Left main	1801 (7.8%)	1629 (7.5%)	172 (12.6%)	
Missing	142 (0.6%)	128 (0.6%)	14 (1.0%)	
Indication for catheterization				<0.0001
Stable angina	4990 (21.5%)	4717 (21.6%)	273 (20.0%)	
Myocardial infarction	11,883 (51.2%)	11,288 (51.7%)	595 (43.6%)	
Unstable angina	3566 (15.4%)	3342 (15.3%)	224 (16.4%)	
Other	2776 (12.0%)	2502 (11.5%)	274 (20.1%)	
Ejection fraction (%)				<0.0001
>50	15,283 (65.8%)	14,480 (66.3%)	803 (58.8%)	
35–50	4173 (18.0%)	3924 (18.0%)	249 (18.2%)	
20–34	775 (3.3%)	715 (3.3%)	60 (4.4%)	
<20	131 (0.6%)	112 (0.5%)	19 (1.4%)	
Missing	2853 (12.3%)	2618 (12.0%)	235 (17.2%)	

Table 2
Multivariable predictors of starting CR (among the whole population) and completing CR (among those who start).

	Predictors of starting cardiac rehab		Predictors of completing rehab, among starters	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Peripheral vascular disease	0.81 (0.72, 0.91)	<0.0001	0.80 (0.68, 0.94)	0.007
Male sex	1.36 (1.19, 1.56)	<0.0001	1.28 (1.16, 1.42)	<0.0001
COPD	0.82 (0.75, 0.89)	<0.0001	0.80 (0.71, 0.89)	<0.0001
Renal failure	0.73 (0.60, 0.89)	0.001	0.68 (0.52, 0.91)	0.008
Dialysis	0.54 (0.35, 0.83)	0.005	0.50 (0.26, 0.95)	0.034
Current smoker	0.58 (0.54, 0.62)	<0.0001	0.54 (0.49, 0.59)	<0.0001
Prior MI			1.35 (1.22, 1.49)	<0.0001
Diabetes	0.68 (0.59, 0.78)	<0.0001	0.69 (0.62, 0.76)	<0.0001
Prior PCI	0.67 (0.61, 0.74)	<0.0001	0.57 (0.50, 0.66)	<0.0001
Prior CABG	0.89 (0.80, 0.98)	0.019		
Age				
<40	0.92 (0.77, 1.11)	0.395	0.65 (0.52, 0.80)	<0.0001
40–49.9	1.11 (1.00, 1.22)	0.041	0.94 (0.83, 1.06)	0.264
50–59.9	Referent		Referent	
60–69.9	0.85 (0.79, 0.91)	<0.0001	0.97 (0.88, 1.07)	0.576
70–79.9	0.51 (0.47, 0.56)	<0.0001	0.98 (0.87, 1.11)	0.774
>80	0.25 (0.22, 0.28)	<0.0001	0.49 (0.40, 0.61)	<0.0001
Cerebrovascular disease	0.78 (0.69, 0.89)	<0.0001		
Congestive heart failure	0.84 (0.76, 0.92)	<0.0001		
Hypertension	0.86 (0.80, 0.91)	<0.0001		
Hyperlipidemia	0.91 (0.85, 0.97)	0.002		
Duke Jeopardy Score				
Normal	Referent			
<50%	1.13 (0.94, 1.36)	0.189		
Low risk	2.15 (1.84, 2.50)	<0.0001		
High risk	2.12 (1.81, 2.49)	<0.0001		
Left main	1.73 (1.44, 2.07)	<0.0001		
Missing	2.05 (1.39, 3.03)	<0.0001		
Women with diabetes	0.85 (0.72, 0.99)	0.037	0.74 (0.60, 0.91)	0.005

However, a PAD diagnosis remained a barrier to CR completion even among those who started (OR 0.80; 95% CI, 0.68, 0.94).

3.2. Exercise metrics for those who attended cardiac rehabilitation

Supplementary Table 2 outlines the exercise metrics for the patients who attended CR. Patients with PAD had lower levels of fitness both before and after CR ($p < 0.0001$), however both groups showed a similar relative increase in fitness after completing the rehabilitation program, improving by nearly 1 MET over the course of 12 weeks. Both subjects with and without PAD maintained their CR-completion exercise capacity at one and two years post CR completion, though patients without PAD had consistently higher exercise capacity. At CR start there was no difference in the amount of exercise done by the PAD versus the non-PAD patients ($p = 0.420$). However, by CR completion PAD patients were significantly more likely to not be exercising at all and less likely to reach weekly exercise time targets (≥150 min) than the non-PAD patients ($p < 0.05$). Subjects with PAD were also more likely to have systolic blood pressures above target goals (140 mmHg), both at program start and completion. Notably, while there were no differences in baseline prevalence of depressive symptoms between those with and without PAD, subjects with PAD were less likely to not have depressive symptoms at CR completion.

3.3. Survival

Median follow-up time for the cohort was 7.2 years (IQR 3.9, 11.4 years) and there were 3510 deaths (328 in those with PAD; 338 within first year of CR referral). Overall 10-year survival was significantly higher in those without PAD (84.5% vs 66.9%; $p < 0.0001$). At 10 years survival among PAD patients who completed CR was similar to non-PAD patients who did not complete CR (76.4% and 78.7%, respectively) (Fig. 1). In cox proportional hazards models, PAD diagnosis was associated with increased mortality (unadjusted hazard ratio (HR) 2.34, 95% CI 2.08, 2.64; adjusted HR 1.39, 95% CI 1.23, 1.56). CR completion was associated with significantly reduced mortality (unadjusted HR 0.49 (95% CI 0.46, 0.53); adjusted HR 0.62 (95% CI 0.57, 0.67)). In multivariable models stratified by PAD diagnosis, CR completion was associated with similar reductions in risk of mortality for both those with (HR 0.64, 95% CI 0.51, 0.80) and without PAD (HR 0.62, 95% CI 0.57, 0.67). Likewise, in a model with a PAD-CR interaction term, the

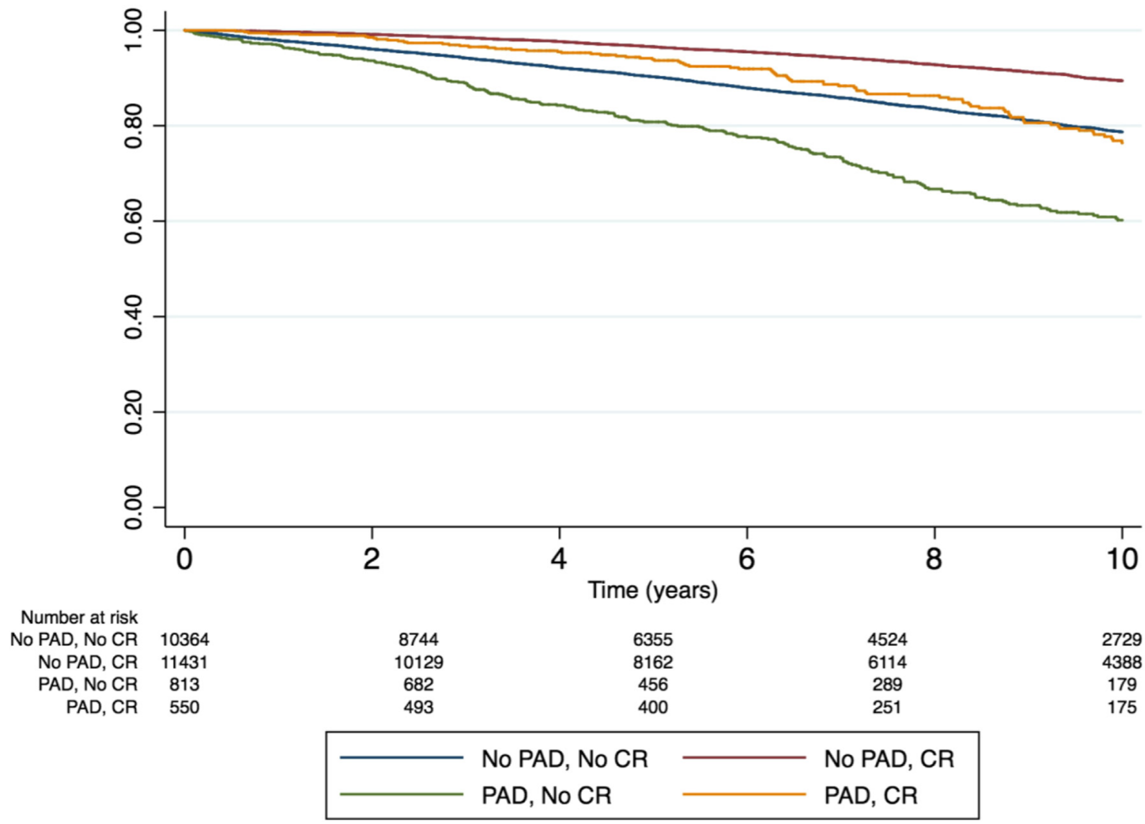

Fig. 1. Kaplan-Meier Survival (unadjusted), stratified by PAD diagnosis and CR completion. PAD – peripheral arterial disease; CR – cardiac rehabilitation.

interaction term was not significant, implying no differential effect of CR on subjects with PAD versus those without.

3.4. Sex interactions

PAD patients were more likely to be female than non-PAD patients (23.8% vs 21.4%, $p = 0.040$). However, there was no interaction between sex and PAD in terms of starting CR, completing CR, or the benefit of CR on mortality (p-values for all interactions >0.100). Furthermore, women and men who completed CR achieved equivalent improvements in exercise capacity over the 12-week program (0.80 (SD 1.1) vs 0.85 (SD 0.9) METs, $p = 0.689$).

3.5. Propensity-matched model

Of the 1366 subjects with PAD, 1365 were matched to non-PAD patients using the propensity score as described above (supplementary Table 2). Propensity matching resulted in a significant reduction in standardized differences and good balance between the matched PAD and non-PAD groups. Even within the propensity-matched cohort, PAD diagnosis was associated with decreased likelihood of starting CR (OR 0.62, 95%CI 0.53, 0.72) and completing CR if the program was started (0.72, 95%CI 0.58, 0.89). PAD diagnosis was associated with increased mortality (HR 2.26, 95%CI 1.90, 2.69) and in adjusted models CR was associated with improved survival (HR 0.60, 95%CI 0.50, 0.72) (Fig. 2). Exercise capacity was lower in patients with PAD than without at both baseline (6.6 (SD 2.1) vs 7.7 (SD 2.1) METs, $p < 0.0001$) and CR completion (7.5 (SD 2.1) vs 8.6 (SD 2.1) METs, $p < 0.0001$).

4. Discussion

We found that patients with PAD referred to CR have more co-morbidities than their non-PAD counterparts and have lower survival. Patients with PAD are less likely to start and complete CR, but completion of CR is associated with better fitness and survival and the relative magnitude of these associations are comparable to those for patients without PAD. These findings support previous research demonstrating the advanced disease severity and clinical complexity of patients diagnosed with PAD who attend CR [18]. Our findings significantly add to the literature by demonstrating that patients with PAD who participate in CR gain a significant improvement in clinical outcome (e.g., reduced mortality risk).

Previous authors have identified PAD as a predictor of non-attendance at CR in subjects post myocardial infarction [19]. In the study by Parashar et al. CR participation was ascertained by self-report, and patients with PAD were less than half as likely to report attending CR both at one and 6 months post-MI. Notably, program completion or changes in exercise capacity or times were not assessed. We have built upon Parashar's findings using hard data points to confirm CR enrollment and *completion* – and we have confirmed that PAD patients were less likely to not only attend a CR program, but to complete the program. A short term study from Switzerland also found that PAD patients were less likely to complete CR [20]. Completion of CR is an important end point, as we have previously demonstrated that simply starting a program is not associated with improved survival [3]. The finding of lower likelihood of CR completion is important as it highlights that barriers to CR are not limited to getting PAD patients through the door – further work must be done to help them complete the program.

PAD and CAD share common risk factors that have been well outlined in the literature [20]. Common primary risk factors include smoking, dyslipidemia, hypertension, diabetes and inactivity; with common causative pathways, CAD and PAD frequently present in the same patient and portend worse survival and non-survival outcomes when they occur simultaneously [21–24]. The PAD patients identified in this cohort had a significantly higher number of co-morbidities as well as lower exercise capacity compared to those patients without

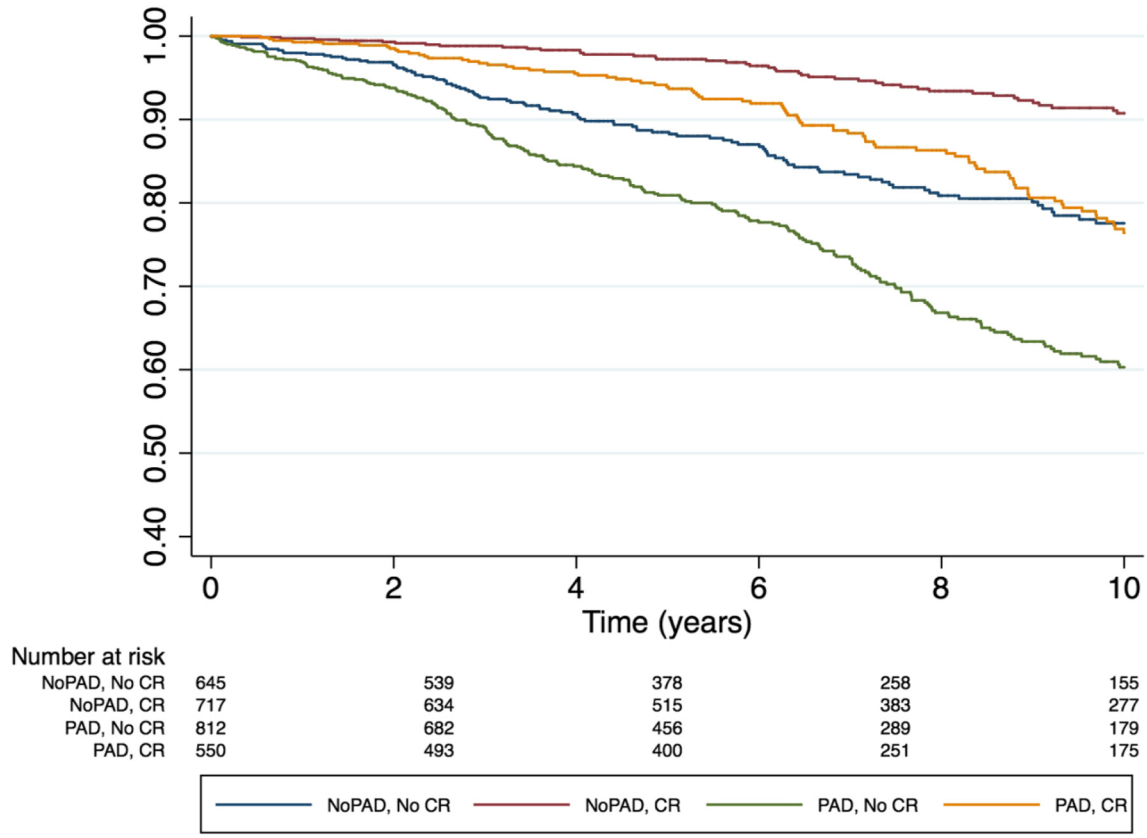

Fig. 2. Kaplan-Meier Survival in propensity matched cohort, stratified by PAD diagnosis and CR completion. PAD – peripheral arterial disease; CR – cardiac rehabilitation.

PAD. Previous work from our region has shown that subjects referred for coronary angiography who had PAD diagnosed by ankle brachial index (ABI) had higher SYNTAX scores, more myocardium at risk, and less complete coronary revascularization than patients with normal ABIs [25]. The high risk nature of this cohort further reinforces their need for secondary risk reduction and exercise therapy; the prevalence of modifiable risk factors are clear targets for specific intervention. However, even with adjustment for all available risk factors and in the propensity matched cohort, PAD patients were less likely to start or complete CR and had worse exercise capacity – the excess burden of comorbidities in PAD patients is insufficient to explain the differences seen, there are likely innate differences in the PAD patients.

Persistent exercise and activity in subjects with CAD is an important predictor of long-term survival. Subjects with PAD are known to be at particular risk of loss of mobility over time [26], which has implications both in terms of quality and longevity of life [27] – survival outcomes are perhaps even more impacted by loss of mobility in subjects with CAD in addition to PAD. We have demonstrated improvements in exercise time, exercise capacity and survival in patients with PAD completing CR. However, PAD patients were both less likely to start CR and complete CR than those without PAD. Specific barriers to completing CR in PAD patients have not been investigated, however several authors have looked at failure to complete rehabilitation specific to PAD. Brief psychological interventions to assess and improve motivation have been found to improve compliance with exercise therapy [28], and programs utilizing activity monitors have demonstrated good adherence [29]. Numerous barriers to participating in physical activity have been identified in patients with PAD, related to burden of co- morbidities, physical limitations, and practical concerns [30]. Older patients and women are less likely to participate in physical activity, yet are an increased risk of events related to PAD – and mortality if diagnosed with PAD [15]. Notably, we found in our study that women were more likely to have PAD, representing a particularly high risk cohort: however, there was no interaction between sex and PAD in terms of any CR metrics or mortality outcomes, implying women with PAD are as likely to start and finish CR as men with PAD, and achieve equivalent benefit.

Loss of mobility and function in subjects with even mild PAD is well established [8], as is the improvement in walking related disability with appropriate exercise training [31]. However, participation in exercise training programs for PAD is poor, at least in part due to lack of insurance coverage for such training [32,33]. Patients with PAD who have claudication report difficulty exercise due to pain, fatigue and discomfort. However, compliance with exercise therapy remains poor for PAD patients, especially relative to non-PAD CR referees. While our focus was on mortality, we see clear and persistent benefits in terms of METs achieved as well as average weekly exercise times. It is likely that CAD patients with

PAD who complete CR achieve additional benefit in terms of claudication symptoms. Highlighting these benefits to PAD patients may help encourage attendance and CR completion.

4.1. Applicability to general PAD population

These data are highly relevant to patients in the general population who have PAD. The incidence of PAD has increased over 10% in the past decade. It affects over 200 million people globally, with 8.5 million in the US [34]. It can be a debilitating condition causing limitations in mobility and quality of life, and patients suffering from PAD are unlikely to receive appropriate lifestyle and prevention counselling [26,35,36]. The patients in the present study have an advantage of being enrolled in the CR program based on the basis of CAD. There are many people suffering from PAD who do not have access to appropriate rehabilitation or exercise training programs, either due to lack of recognition of their PAD, lack of referral, or lack of funding to attend [36] [37]. The findings from this study help to provide education about the crucial importance of exercise training in the PAD patient population.

4.2. Limitations

Our study has limitations. Because this was not a randomized controlled trial, it is impossible to draw conclusions about causation, though the concordance of results found with the overall analysis and the propensity-matched analysis are reassuring. There may also be unmeasured functional differences between subjects who completed CR and those who did not, and this may be particularly applicable to the PAD group. Part of the impact of CR may be secondary to the healthy user effect or attendance bias; i.e., those who attended are possibly healthier than those who did not [38]. The PAD diagnosis was ascertained from a clinical database and is defined based on patient history rather than by ABI; it is known that occult PAD occurs in some patients attending CR [39]. However, previous work from our region with ABIs measured at cardiac catheterization demonstrated rates of PAD that were slightly higher but within the range found in the main APPROACH database [25]. We were also unable to ascertain the reasons PAD patients were less like to start and finish CR. Balancing these limitations are significant strengths, including a large sample size, ascertainments of both starting and completing CR, ascertainments of improvements in exercise capacity and mortality, and long follow-up time with minimal loss of follow-up.

5. Conclusions

We found that PAD patients are less likely to both start and finish an exercise–based CR program than non-PAD patients. Completion of a CR program is associated with improved fitness as well as improved mortality in PAD patients, and the relative magnitude of these associations is similar to those for patients without PAD. These data support broader use of CR by those with PAD.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.070.

References

[1] G. Agnelli, C. Cimminiello, G. Meneghetti, S. Urbinati, Low ankle–brachial index predicts an adverse 1-year outcome after acute coronary and cerebrovascular events, Journal of Thrombosis & Haemostasis. 4 (2006) 2599–2606.

[2] S. Aggarwal, R.D. Moore, R. Arena, B. Marra, A. McBride, B. Lamb, et al., Rehabilitation therapy in peripheral arterial disease, Can. J. Cardiol. 32 (2016) S374–S381.

[3] B.-J. Martin, T. Hauer, R. Arena, L.D. Austford, P.D. Galbraith, A.M. Lewin, et al., Cardiac rehabilitation attendance and outcomes in coronary artery disease patients, Circulation 126 (2012) 677–687.

[4] B.-J. Martin, R. Arena, M. Haykowsky, T. Hauer, L.D. Austford, M. Knudtson, et al., Cardiovascular fitness and mortality after contemporary cardiac rehabilitation, Mayo Clin. Proc. 88 (2013) 455–463.

[5] J.D. Colbert, B.-J. Martin, M.J. Haykowsky, T.L. Hauer, L.D. Austford, R.A. Arena, et al., Cardiac rehabilitation referral, attendance and mortality in women, Eur. J. Prev. Cardiol. 22 (2015) 979–986.

[6] S.L. Grace, C. Racco, C. Chessex, T. Rivera, P. Oh, A narrative review on women and cardiac rehabilitation: program adherence and preferences for alternative models of care, Maturitas 67 (2010) 203–208.

[7] M.J. Armstrong, R.J. Sigal, R. Arena, T.L. Hauer, L.D. Austford, S. Aggarwal, et al., Cardiac rehabilitation completion is associated with reduced mortality in patients with diabetes and coronary artery disease, Diabetologia 58 (2015) 691–698.

[8] M.M. McDermott, J.M. Guralnik, L. Tian, K. Liu, L. Ferrucci, Y. Liao, et al., Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study), J. Am. Coll. Cardiol. 53 (2009) 1056–1062.

[9] Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J. Am. Coll. Cardiol. 2017; 69:e71-e126.

[10] W.A. Ghali, M.L. Knudtson, Overview of the Alberta provincial project for outcome assessment in coronary heart disease. On behalf of the APPROACH investigators, CanJCardiol. 16 (2000) 1225–1230.

[11] T.R. McConnell, B.A. Clark, Prediction of maximal oxygen consumption during handrail-supported treadmill exercise, J. Cardpulm. Rehabil. 7 (1987) 324–331.

[12] K.L. Piercy, R.P. Troiano, R.M. Ballard, S.A. Carlson, J.E. Fulton, D.A. Galuska, S.M. George, R.D. Olson, The physical activity guidelines for Americans, JAMA 320 (2018) 2020–2028.

[13] A.S. Zigmond, R.P. Snaith, The Hospital Anxiety and Depression Scale, Acta Psychiatr. Scand. 67 (1983) 361–370.

[14] C. Hermann, International experiences with the Hospital Anxiety and Depression Scale: a review of validation data and clinical trials, J. Psychosom. Res. 42 (1997) 17–41.

[15] A.T. Hirsch, M.A. Allison, A.S. Gomes, M.A. Corriere, S. Duval, A.G. Ershow, et al., A call to action: women and peripheral artery disease. A scientific statement from the American Heart Association, Circulation 125 (2012) 1449–1472.

[16] P.C. Austin, Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score, Am. J. Epidemiol. 172 (2010) 1092–1097.

[17] P.C. Austin, Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples, Stat. Med. 28 (2009) 3083–3107.

[18] M. Ambrosetti, P.L. Temporelli, P. Faggiano, O. Febo, T. Diaco, G. Favretto, P. Calisi, M. Gabriele, C. Greco, L. Tavazzi, Lower extremities peripheral arterial disease among patients admitted to cardiac rehabilitation: the THINKPAD registry, Int. J. Cardiol. 171 (2014) 192–198.

[19] S. Parashar, J.A. Spertus, F. Tang, K.L. Bishop, V. Vaccarino, C.F. Jackson, et al., Predictors of early and late enrollment in cardiac rehabilitation, among those referred, after acute myocardial infarction, Circulation 126 (2012) 1587–1595.

[20] R.V. Jeger, P. Rickenbacher, M.E. Pfisterer, A. Hoffmann, Outpatient rehabilitation in patients with coronary artery and peripheral arterial occlusive disease, Arch. Phys. Med. Rehabil. 89 (2008) 618–621.

[21] R.S. Dieter, J. Tomasson, T. Gudjonsson, R.L. Brown, M. Vitcenda, J. Einerson, et al., Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease, Vasc. Med. 8 (2003) 233–236.

[22] J.M. Murabito, R.B. D'Agostino, H. Silbershatz, P.W.F. Wilson, Intermittent Claudication. A Risk Profile from the Framingham Heart Study, vol. 96, 1997 44–49.

[23] S.M. Conte, P.R. Vale, Peripheral arterial disease, Heart, Lung & Circulation 27 (2018) 427–432.

[24] J.A. Bittl, A.T. Hirsch, Concomitant peripheral arterial disease and coronary artery disease. Therapeutic opportunities, Circulation 109 (2004) 3136–3144.

[25] M. Sebastianski, S. Narasimhan, M.M. Graham, O. Toleva, J. Shavadia, S. Abualnaja, et al., Usefulness of the ankle-brachial index to predict high coronary SYNTAX scores, myocardium at risk, and incomplete coronary revascularization, Am. J. Cardiol. 114 (2014) 1745–1749.

[26] M.M. McDermott, J.M. Guralnik, L. Tian, L. Ferrucci, K. Liu, Y. Liao, et al., Baseline functional performance predicts the rate of mobility loss in persons with peripheral arterial disease, J. Am. Coll. Cardiol. 50 (2007) 974–982.

[27] M.M. McDermott, L. Tian, K. Liu, J.M. Guralnik, L. Ferrucci, J. Tan, et al., Prognostic value of functional performance for mortality in patients with peripheral artery disease, J. Am. Coll. Cardiol. 51 (2008) 1482–1489.

[28] M.A. Cunningham, V. Swanson, R.E. O'Caroll, R.J. Holdsworth, Randomized clinical trial of a brief psychological intervention to increase walking in patients with intermittent claudication, Br. J. Surg. 99 (2012) 49–56.

[29] A.W. Gardner, D.E. Parker, P.S. Montgomery, K.J. Scott, S.M. Blevins, Efficacy of quantified home-based exercise and supervised exercise in patients with intermittent claudication. A randomized controlled trial, Circulation 123 (2011) 491–498.

[30] D.P. Brostow, A.T. Hirsch, M.S. Kurzer, Recruiting older patients with peripheral arterial disease: evaluating challenges and strategies, Patient Preference and Adherence. 9 (2015) 1121–1128.

[31] F. Fakhry, K.M. van de Luijtgaarden, L. Bax, P.T. den Hoed, M.G.M. Hunink, E.V. Rouwet, et al., Supervised walking therapy in patients with intermittent claudication, J. Vasc. Surg. 56 (2012) 1132–1142.

[32] A.-E. Harwood, G.E. Smith, T. Cayton, E. Broadbent, I.C. Chetter, A systematic review of the uptake and adherence rates to supervised exercise programs in patients with intermittent claudication, Ann. Vasc. Surg. 34 (2016) 280–289.

[33] M. McDermott, M.R. Kibbe, Improving lower extremity functioning in peripheral artery disease: exercise, endovascular revascularization, or both? JAMA 317 (2017) 689–690.

[34] F.G.R. Fowkes, D. Rudan, I. Rudan, V. Aboyans, J.O. Denenberg, M.M. McDermott, et al., Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis, Lancet 382 (2013) 1329–1340.

[35] K. Matsushita, S.H. Ballew, Y. Sang, C. Kalbaugh, L.R. Loehr, A.T. Hirsch, et al., Ankle-brachial index and physical function in older individuals: the atherosclerosis risk in communities (ARIC) study, Atherosclerosis 257 (2017) 208–215.

[36] J.S. Berger, J.A. Ladapo, Underuse of prevention and lifestyle counseling in patients with peripheral artery disease, J. Am. Coll. Cardiol. 69 (2017) 2293–2300.

[37] W.R. Hiatt, R.K. Rogers, The treatment gap in peripheral artery disease, J. Am. Coll. Cardiol. 69 (2017) 2301–2303.
[38] D. Eurich, T. Marrie, J. Johnstone, S. Majumdar, Mortality reduction with influenza vaccine in patients with pneumonia outside "flu" season: pleiotropic benefits or residual confounding? Am. J. Respir. Crit. Care Med. 178 (2008) 527–533.
[39] M.C. Tam, C.T. Longenecker, C. Chow, M. Vest, R. Sukeena, S.K.M. Mohan, et al., Occult peripheral artery disease is common and limits the benefit achieved in cardiac rehabilitation, Vasc. Med. 21 (2016) 130–136.