

Invited Review for *Current Treatment Options in Cardiovascular Medicine*

Cardiac Rehabilitation Following Acute Coronary Syndrome in Women

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OPINION STATEMENT

Acute coronary syndrome (ACS) is among the leading burdens of disease among women, and is a significant driver of morbidity and chronically undermines their quality of life. Cardiac rehabilitation (CR) is indicated for ACS patients in clinical practice guidelines, including those specifically for women. CR is a multi-component model of care, proven to reduce mortality and morbidity, including in women. However, women are significantly less likely to be referred to CR by providers, and if they are referred, to enroll and adhere to programs. Reasons include lack of physician encouragement, preference not to feel fatigue and pain, transportation barriers, comorbidities and caregiving obligations. Strategies to mitigate this under-use include systematic early inpatient referral, tailoring programs to meet women's needs and preferences (e.g., offering dance, opportunities for social interaction), and offering non-supervised delivery models. Unfortunately these strategies are not widely available to women. Given the greater longevity seen in women, CR is key to augmenting quality of life in this population and hence we must do more to ensure they access CR services that meet their care needs.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States (US) and globally, and is also the leading cause of death among women.¹ An estimated 1 in 4 deaths among women are attributable to CVD; however, female awareness of risk is disproportionately low.² Following successful treatment for the common ischemic form of CVD, namely acute coronary syndrome (ACS), patients remain at increased risk of developing heart failure (HF), as well as higher risk of mortality.³ Cardiac rehabilitation (CR) following ACS is instrumental in reducing this risk. Regardless of gender, CR is a Class I Level A recommendation for post-ACS.⁴ Despite the clear advantages associated with participation in CR, utilization among female ACS survivors remains low. Accordingly, this review will briefly characterize current knowledge regarding ACS in women, and what is known about the benefits of CR in women. Finally, this review will explore CR utilization among women and what can be done to optimize these rates.

ACS IN WOMEN

Sex Differences in Clinical Presentation

The average woman presenting with ACS is typically older and has more comorbidities than her male counterpart⁵ rendering these patients more complex to manage and confers a mortality detriment.⁶ Beyond these confounders, it is well known that women with ACS may not present with the classic substernal chest pain, but rather with a myriad of symptoms ranging from fatigue to nausea and lightheadedness. Women may also have more diffuse disease in their coronary vasculature, which may not be captured by traditional diagnostic tests. Moreover, women more often present with unstable angina than myocardial infarction (MI). These differences in presentation can lead to delays in care-seeking and assessment, resulting in greater myocardial death.

Gender Differences in Social Context at ACS Presentation

Depression, which is twice as common in women as men, is now also a recognized risk factor for ACS. Among elderly women with CVD, physical activity (PA) is frequently lower, and correspondingly functional capacity is typically lower at the time of presentation. Because women with MI typically present at an older age, they are correspondingly more likely to be socially-isolated due to widowhood. Given this and that women had less time in the workforce due to parenting roles in previous generations, women ACS patients often are of lower socioeconomic status than men. This is an impactful social determinant of health, associated with poorer outcomes.

CARDIAC REHABILITATION

CR is an outpatient chronic disease management program designed to optimize secondary prevention.⁷ Core components include patient assessment, risk factor modification, as well as stress management, and screening for psychological conditions such as anxiety and depression.⁸ CR is a Class

I, Level A indication in CVD guidelines for women.⁹⁻¹⁰ The benefits of CR are summarized in Figure 1.

Physiologic Benefits of CR

CR participation is associated with dramatic reductions in CVD mortality, morbidity, and hospitalizations, and increases in quality of life (QoL).¹¹ While there are few women included in randomized trials of CR, recent observational data suggests that women who fully participate in CR can achieve better mortality outcomes than their male counterparts.¹² Each of the core components of CR are designed to achieve measurable improvement in risk factors, as well as increased functional capacity and improvements in peak oxygen consumption (VO₂).¹³ The exercise component of CR typically yields increased physical strength, increased aerobic and functional capacity, as well as improved balance and flexibility, regardless of gender.¹⁴ The positive CVD effects of exercise are dose-dependent, and research has demonstrated that the effects are enhanced in women compared to men.¹⁵

Psychosocial Benefits of CR

Beyond the physical improvements noted through completion of CR, participants also experience psychosocial and behavioral benefits from these programs, which positively impacts their physical health.¹⁶ Patients receive intensive education that increases awareness and capacity to modify CVD risk factors. Such improvements result in improved heart-healthy behaviors and medication adherence. Improvements in patient perceptions of their own health as well as improved physician-patient relationships are often also achieved as a result. Chiefly, improvements in QoL, and reductions in anxiety, depression and stress are also realized among participants.

CR Benefits in Women

In addition to the above benefits observed in men and women, some additional benefits related to women warrant summarizing. First, microvascular cardiac disease and angina –both of which are the predominant forms of CVD among women—are particularly responsive to exercise in CR.¹⁷ Second, exercise participation has also been associated with improvements in menopausal symptoms. Finally, women with ACS are disproportionately impacted by depression and anxiety.¹⁸ This psychological distress is associated with two-times greater mortality in CVD patients.¹⁹ As outlined above, CR participation is associated with substantive reductions in depression and anxiety.

CR UTILIZATION

Despite the benefits and corresponding clinical practice recommendations for patient referral, utilization rates of CR are low in the US²⁰ and throughout the world.²¹ While rates vary significantly based on health system funding models, approximately 30% of eligible patients receive CR; with rates being significantly lower in women.²² CR utilization is comprised of three elements: referral, enrollment and adherence. Between each step, there is attrition. Meta-analyses demonstrate 49% of men, but only 39%

of women are referred.²³ Of those referred to CR, 45% of men, and 39% of women go on to subsequently enroll.²⁴ Patients must then adhere to sessions and complete the program to accrue all the benefits of CR participation; this is also lower in women.²⁵

CR referral requires paperwork completion and transmission by a physician. Hence, it is directly dependent on physician practice patterns, CR knowledge and beliefs.²⁶ Studies have shown that provider bias has limited Phase II referrals to female patients.²⁷ The highest utilization rates are found among post-surgical patients and in those centers with automatic referral policies.²⁸

Once referred, patients must present to enroll into a (hopefully local) program. Enrollment may be limited by availability of location or provider access depending on the maturity of the CR system in the patient's region. Currently, formal CR is conducted through center-based programs. Some regions have greater access to facilities and trained personnel than others. In these instances, travel may become a limiting component for patients.

Following enrollment, patients must adhere to the program (typically 36 sessions in the US). Subsequently, participation in CR may involve commitments of time or financial cost for additional medical therapies. Finally, patients are reassessed at program completion to ensure any outstanding uncontrolled risk factors are identified, and ongoing treatment is transitioned to the patient's primary or secondary care provider.

ISSUES AFFECTING CR UTILIZATION RATES IN WOMEN

Despite recent efforts to increase participation, utilization rates among eligible female patients remain lower than that of male candidates.²⁹ Reasons for under-utilization of CR are well-known, and occur at the level of the health system, provider, CR program and also relate to patients themselves. At each step of the utilization pathway, female patients experience far greater rates of underutilization and attrition than their male counterparts.³⁰ Factors that explain why women are less likely to utilize CR are considered below, and summarized in Figure 2.

Referral Bias

Despite awareness of sex differences in CR use for over 2 decades, women continue to be referred to CR at a lower rate than men.³¹ This may be explained by several factors. Women have a higher incidence of Takotsubo cardiomyopathy and microvascular disease compared to men,³² and these conditions are not as established as indications for CR.³³ Second, there may be unconscious physician bias in referral based on sex.³⁴ Finally, women do report different barriers to CR than men (considered below), and may report these to physicians, who subsequently do not refer their patient.

Barriers to Women's CR Participation

When compared to males who have been referred, female patients are 36% less likely to enroll in CR.²⁴ Known factors associated with lower rates of enrollment in CR such as older age at time of referral,

unmarried status, and low socioeconomic status are all more prevalent in female CVD patients.³⁵ Female CR enrolment may also be influenced by patient perception of lack of encouragement to enroll by their provider. It has been shown that women perceive less encouragement to attend than their male counterparts, and that positive encouragement is associated with two-times greater utilization.³⁶ Factors such as lack of understanding of the disease severity and low perceived need to enroll, lack of transportation, as well as caregiving obligations (e.g., grandchildren, older spouse with illness) impact not only enrolment but also program adherence.³⁷⁻³⁸

Of those patients who successfully enroll, greater than two-thirds generally complete the full CR program in the US.²⁵ While completion rates vary widely, female completion rates are significantly lower than those of their male counterparts.³⁹ This could be due to the nature of the programs themselves. Female participants report a preference to avoid experiencing pain or fatigue during exercise; however, their more deconditioned status at program entry likely results in such experiences.⁴⁰ As outlined above, women more often have comorbidities, and these may hinder their participation. This includes urinary incontinence leading to concerns over leakage during exercise, osteoporosis leading to fear of falls during exercise, and diabetes leading to concerns over hypoglycemia and foot care during exercise. Finally, women report they prefer not to exercise on a treadmill or bike, but these are often the modalities available at CR.⁴⁰ Recent research has demonstrated that alternate models and expanded capability CR programs may be helpful in increasing female participation.⁴¹

WAYS TO OVERCOME LOW CR USE IN WOMEN

Increasing Referral to CR

Referral must be increased in men and women. This can be achieved through more intensive referral strategies such as bedside discussions with allied healthcare professionals and systematic inpatient referral.⁴² Indeed these strategies are shown to increase CR use in women.⁴³ The existence of referral targets⁴⁴, as well as performance measures/quality indicators for referral are also influential.⁴⁵⁻⁴⁶ Nursing-driven protocols implemented on a system-wide level have increased patient subsequent enrollment.⁴⁷ Creation of and training for specialty-based teams have helped to reduce gender and gender-related-diagnosis bias.⁴³

Decreasing Time to Enrollment

Numerous studies have demonstrated that an inverse correlation exists between the length of time to enrollment in CR and enrollment rate. Similarly, longer length of time to CR enrollment has a direct and negative effect on patient outcomes from CVD.⁴⁸ Delay of initiation of guideline-directed medical therapy and risk factor optimization places these patients at high risk of readmission and increased morbidity/mortality.⁴⁹ By providing patients with early access to CR evaluation and services capitalizes on the momentum created by Phase I interventions and CR completion rates are improved.⁵⁰ Decreasing

wait times requires early inpatient referral and increased CR program capacity.

CHANGES TO CR TO INCREASE ADHERENCE AMONG WOMEN

Several successful interventions in promoting patient uptake and adherence to CR have been identified. These include self-monitoring of activity, action planning, and individually tailored counseling.⁵¹ Strategies more pertinent to women are considered below.

Women-Only, Gender-Tailored CR

Early studies where women were interviewed to ask them about their preferences for CR demonstrated they appreciate the social interaction with other CVD patients and staff, and may prefer more focus on psychosocial well-being.⁵² These participants cited a dislike for public weighing and an appreciation for increased privacy. Studies also suggest that female participants of center-based CR may prefer programs which a wide variety of exercise options as well as additional forms of support.⁵³ More recent work provides further insights on their preferences for the types of activities conducted in the CR environment; consequently, alternative exercise modalities such as yoga and dance have become more-frequently integrated into CR in recent years.

This information has been used to develop women-only program models to better meet their needs.⁵⁴ Beckie's seminal trial demonstrated that women-only, motivational stage-matched CR programs result in much greater adherence, with comparable outcomes.⁵⁵ The more recent CR4HER trial demonstrated significantly reduced anxiety and depressive symptoms among women-only CR participants.⁵³ Additional studies have demonstrated that gender-tailored, stage-matched, CR programs increase attendance rates among women.⁵⁵⁻⁵⁶

Alternative CR Delivery Models to Overcome Barriers Specific to Women

Other approaches to improving female enrollment and adherence to CR have focused on ways to overcome the physical barriers that are often cited by patients who are unable to complete CR. Low-income, distance required to travel and familial obligations are key factors explaining women's failure to enroll or complete CR. These can be mitigated through delivery of CR outside a center-based setting, given there is no need for transport and the associated out-of-pocket costs, and patients can exercise when it is convenient for them. Indeed, home-based CR has been an established model of care outside of the US for many years; however, recent data suggests many women prefer to be supervised during CR.⁵⁵ The most recent Cochrane review of home-based CR found that home-based CR may modestly increase retention and adherence rates with equivalent outcomes.⁵⁷

Telehealth CR (eCR) may also provide an alternate means of accessing CR. When compared with center-based CR programs, eCR was more effective in engagement of participants and increasing overall level of PA, exercise adherence, diastolic BP and lipids. eCR is shown to be equivalent in benefit (although mortality data is not available at this stage), and may result in longer-term exercise

adherence.⁵⁸⁻⁵⁹ As with women-only CR, currently eCR is not widely available.

CONCLUSIONS

The benefits of CR for women are clear, but women continue to be under-represented in CR and CR trials and hence there is room for more evidence. Regardless of sex, all post-ACS patients should be referred to CR. Early and equitable referral to CR increases the likelihood of CR utilization and hence optimization of outcomes for patients. However, a significant gender disparity exists in CR use. Advancements in our understanding of the nature of CVD in women, as well as the unique physical and psychosocial needs of this large group should be used to inform the nature of CR delivered to women. By achieving greater participation in CR, we can have a substantial impact on morbidity and mortality in women.

Table 1. Benefits of Cardiac Rehabilitation in Women. This table includes both the physical and psychological benefits reported and observed in female participants of cardiac rehabilitation.

Figure 1. Cardiac Utilization: Women-Specific Barriers. The progression from qualifying event through adherence and maintenance phases, this figure highlights the many personal and health system hurdles that women face in utilization of cardiac rehabilitation.

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This meta-analysis demonstrates that even in the current era, women are significantly less likely to enroll in CR than men. Across the 26 included studies reported on close to 300,000 patients, the average enrolment rates were 45% in men and 39% in women; this represented 36% lower enrolment.

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In this exploration into program model preferences in the CR4HER trial, it is revealed that while women may report preferring women-only CR, because it is offered infrequently due to low volume, women would prefer to attend a co-ed program offered at the most convenient time for their schedule. They did perceive some advantages to women-only CR, and some women disliked unsupervised CR. Overall, women were highly satisfied with the model they attended.

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Table 1. Benefits of Cardiac Rehabilitation in Women. This table includes both the physical and psychological benefits reported and observed in female participants of cardiac rehabilitation.

Benefits of Cardiac Rehabilitation in Women	
Physical	Psychological
Decreased	
• Hospitalizations • Mortality • Morbidity • Frailty	• Anxiety • Depression symptoms • Stress
Improved	
• Microvascular disease • Anginal symptoms	• Patient-physician relationship • Quality of life
Increased	
• Control of menopause symptoms • Peak VO₂ • Functional capacity • Strength • Balance	• Personal medical advocacy • Medication adherence • Heart-healthy behaviors • Social support

Cardiac Utilization: Women-Specific Barriers

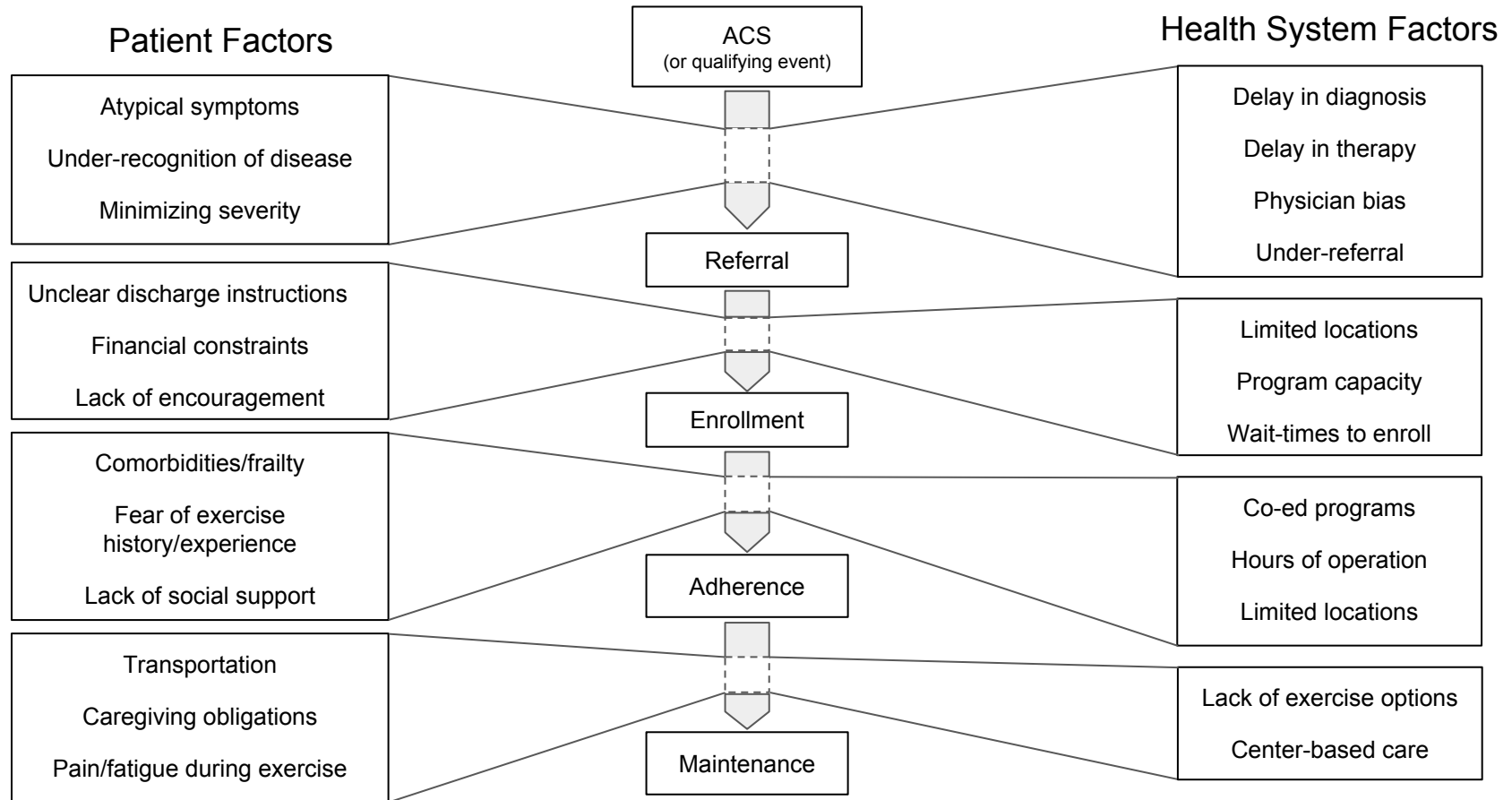


Figure 1. Cardiac Utilization: Women-Specific Barriers. The progression from qualifying event through adherence and maintenance phases, this figure highlights the many personal and health system hurdles that women face in utilization of cardiac rehabilitation.