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Rethinking Rehabilitation: A REVIEW OF PATIENT POPULATIONS WHO CAN BENEFIT FROM CARDIAC REHABILITATION

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Rethinking Rehabilitation

A REVIEW OF PATIENT POPULATIONS WHO CAN BENEFIT FROM CARDIAC REHABILITATION

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Although cardiac rehabilitation (CR) is safe and highly effective for individuals with various cardiovascular health conditions, to date there are only seven diagnoses or procedures identified by the Centers for Medicare & Medicaid Services that qualify for referral. When considering the growing number of individuals with cardiovascular disease (CVD), or other health conditions that increase the risk for CVD, it is important to determine the extent for which CR could benefit these populations. Furthermore, there are some patients who may currently be eligible for CR (spontaneous coronary artery dissection, left ventricular assistant device) but make up a relatively small proportion of the populations that are regularly attending and participating. Thus, these patient populations and special considerations for exercise might be less familiar to professionals who are supervising their programs. The purpose of this review is to summarize the current literature surrounding exercise testing and programming among four specific patient populations that either do not currently qualify for (chronic and end-stage renal disease, breast cancer survivor) or who are eligible but less commonly seen in CR (sudden coronary artery dissection, left ventricular assist device). While current evidence suggests that individuals with these health conditions can safely participate in and may benefit from supervised exercise programming, there is an immediate need for high-quality, multisite clinical trials to develop more specific exercise recommendations and support the inclusion of these populations in future CR programs.

Key Words: cardiac rehabilitation • exercise • special populations

Cardiac rehabilitation (CR) is a class 1 guideline-based therapy that provides comprehensive secondary prevention strategies. Best practices for CR include exercise training, outcome assessments, risk factor management, and nutritional/behavioral education to individuals who qualify. Research indicates that CR participation provides many health benefits including reduced risk for morbidity and mortality, increased cardiorespiratory fitness (CRF), enhanced quality of life, and improved mood and symptoms.[1,2] Furthermore, CR is cost-effective by reducing the rate of recurrent myocardial infarctions (MIs) and hospital readmissions.[3] Several meta-analyses have demonstrated the benefits of CR programs, specifically examining the individual components of these programs and their impact on patient well-being.[4,5] Despite the large number of different cardiovascular diseases (CVD), only seven diagnoses or procedures qualify an individual for CR (Table 1).

While this list may seem robust to some, it is only a fraction of the chronic health conditions that physical activity and lifestyle interventions (ie, education, counseling, and social support) have been shown to benefit. Specifically, exercise is beneficial for individuals with conditions that are strongly associated with CVD including chronic kidney disease (CKD)[6-11] and breast cancer (BC).[12-15] Given the observed associations between these diseases and CVD, it seems appropriate to consider the inclusion of these individuals in CR as a strategy to help manage their CVD risk.

Additionally, some patients who attend CR present with cardiovascular comorbid conditions (eg, spontaneous coronary artery dissection, [SCAD]; left ventricular assist device, [LVAD]), not easily identified in Table 1. Often, these individuals will make up a relatively small proportion of the populations that traditionally participate in CR and thus professionals may be less familiar with the current guidelines for patient-centered care.

The purpose of this review is to present relevant information for the CR practitioner about patient populations that either do not currently qualify for (ie, chronic and end-stage CKD, BC survivor) or who are eligible but less commonly cared for in CR (ie, SCAD and LVAD). We also address special CR-related considerations and expected outcomes to better inform clinicians and researchers. Additionally, randomized control trials and clinical trials from the past decade, which support the benefits of exercise programming for CKD, SCAD and LVAD patient populations, have been summarized in Tables 2, 3, and 4. While not a systematic review, our tables provide important references for CR professionals to better understand the potential benefits of exercise for these populations. A summary for BC survivors was not provided, as a recent systematic review by Furmaniak et al[16] provides the information CR professionals would find beneficial regarding this population.

REVIEW OF RELEVANT LITERATURE

CHRONIC AND END-STAGE KIDNEY DISEASE

Chronic kidney diseases represent a major public health problem, affecting at least one in seven adults in the United States.[17] The disease progresses through five stages,

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Table 1

Medical Conditions Eligible for Cardiac Rehabilitation Approved by the Centers for Medicare & Medicaid Services

Eligibility Criteria	Class of Indication
Myocardial infarction within the last 12 mo	Class 1[a] indication
Coronary artery bypass graft surgery	Class 1 indication
Current stable angina	Class 1 indication
Heart valve repair or replacement	Class 1 indication
Percutaneous coronary angioplasty or coronary stent	Class 1 indication
Heart or heart-lung transplant	Class 1 indication
Stable chronic heart failure with New York Heart Association class II-IV and left ventricular ejection fraction ≤35%	Class 2a[b] indication

[a]Strong recommendation.
[b]Moderate recommendation.

classified according to the estimated glomerular filtration rate, with the fifth stage requiring some form of renal replacement therapy (eg, dialysis or a kidney transplant). Patients with CKD experience a substantial CVD burden, the etiology of which is not fully explained by traditional risk factors.[17] Despite advancements in the development of pharmaceutical agents targeting hypertension and diabetes, patients with CKD are more likely to die from CVD than progress to end-stage renal disease (ESRD).[17] Furthermore, statin therapies are ineffective at improving outcomes in the ESRD population.[18] As a result, there is a critical unmet clinical need to develop and implement strategies to improve cardiovascular health in this patient population. Targeted interventions, such as CR, that address the prevention and management of CVD progression, would be notably beneficial in the earlier stages of the disease. In this respect, clinical guidelines specify the management of CVD progression as a treatment for CKD as early as stages one and two.[19]

There is a wealth of evidence documenting a myriad of health benefits of exercise training across the spectrum of kidney diseases (Table 2).[9,20-28] Regular exercise on most, if not all days of the week, is currently recommended by the Kidney Disease Quality Initiative clinical guidelines.[19] Despite the current evidence and clinical guidelines, exercise is still not integrated as part of standard of care treatment in nephrology. One consistently cited barrier to implementing exercise in this patient population is a lack of time and information among nephrology health care providers to effectively counsel and prescribe exercise.[6] Therefore, referral to CR represents an attractive strategy to facilitate the integration of exercise for CVD prevention and management in these patients.

Exercise Testing

Exercise testing prior to enrollment in CR can provide clinicians valuable information regarding underlying disease, contraindications to starting exercise, and current CRF. Protocols including a 6-min walk test (6MWT), intermittent shuttle walk test, and timed get up and go assessment are commonly used to assess functional fitness in this population. These tests are typically easy to administer and relatively safe for higher risk populations. While these assessments provide information such as heart rate (HR) and blood pressure (BP) responses, which are very useful for exercise programming, cardiopulmonary exercise tests (CPX) can provide other values useful to the CR team. Prior studies involving CPX reveal lower CRF levels (peak oxygen uptake [$\dot{V}O_{2peak}$] = 17.4 vs 28 mL/kg/min), ventilatory-perfusion mismatch ($\dot{V}_E/\dot{V}CO_2$ slope 32 vs 28 and $PetCO_2$: 27 vs 31 mm Hg), as well as blunted maximal HR (134 vs 159 bpm) and 1-min HR recovery responses in patients with CKD compared with healthy controls (15 vs 20 bpm, respectively).[7] In this respect, CPX is a useful tool for identifying subclinical cardiovascular abnormalities in this population.

Exercise Prescription and Training

Regular exercise training improves CRF, muscular strength, and quality of life in patients with CKD.[8] In nondialysis CKD, moderate- to vigorous-intensity aerobic exercise improves endothelial and microvascular function, both of which are precursors to the development of atherosclerosis.[9] Additionally, in these patients regular aerobic exercise reduces chronic inflammation, a consistently cited nontraditional risk factor of CVD that is a hallmark of CKD.[10] Given the independent association between muscular strength and CVD,[29] improvements in muscular strength that accompany exercise training in these patients[8] may also be beneficial in mitigating cardiometabolic risk. As CKD progresses to require renal replacement therapy, exercise training is a powerful tool for improving CRF and counteracting muscle wasting and frailty while also improving prognosis once a patient initiates dialysis or receives a kidney transplant.[11]

For individuals who receive a kidney transplant, exercise training may be helpful to counteract the cardiometabolic risk factors associated with immunosuppression medication therapy.[30] Once a patient initiates dialysis, it may be more difficult to enroll them in CR on their dialysis day due to the time burden of their dialysis treatments. For these patients, exercising during hemodialysis (intradialytic exercise) may be an alternative strategy that has proven benefits for improving physical function, lessening hemodialysis-related myocardial stunning, sarcopenia, dialysis adequacy, and dialysis-related symptoms.[31-33] While it is understood that exercise training in these patients during hemodialysis would not be practical within the traditional CR class setting, CR staff do have the ideal clinical skill set to supervise such training and provide surveillance.

Current recommendations are to implement aerobic, resistance, balance, and flexibility exercises according to current guidelines for older adults and to take into account special considerations for any comorbidities that the patient may present with.[34,35] A summary of the current exercise recommendations from the American College of Sports Medicine[35] can be found in Table 5. Lastly, patients should avoid exercise if acute infection, hyperkalemia, excess intradialytic weight gain, or peripheral or pulmonary edema is present.[35]

BREAST CANCER SURVIVORS

Breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer mortality among female patients worldwide.[36] In the United States, female BC mortality has decreased by 41% since 1989 due to advances in prevention, early detection, and adjuvant therapy.[37] A consequence of improved survival and population aging is that BC survivors face an important new set of health challenges. Specifically, CVD is a leading cause of death in older BC survivors.[38] The increased CVD risk has been attributed to unfavorable lifestyle factors (eg, sedentary lifestyle and obesity) combined with the adverse effects of anticancer therapy.[39,40] Accordingly, an important goal is to improve overall health and CRF across the continuum of BC survivorship.[41] A recent scientific statement from the American

Table 2

Key Randomized Controlled Trials Investigating the Effects of Exercise on Cardiovascular Disease-Related Outcomes in CKD

Author	Groups	Exercise Intervention	CV Outcome Measures	Findings
Mustata et al (2011)[20]	Exercise (n = 10) Control (n = 10)	F: 5x/wk (60 min) I: 40-60% $\dot{V}O_{2peak}$ T: Aerobic T: 52 wk	Arterial compliance CRF	No change in pulse wave augmentation index Increase in $\dot{V}O_{2peak}$ with ExT
Headley et al (2012)[21]	Exercise (n = 10) Control (n = 11)	F: 3x/wk (45 min) I: 50-60% $\dot{V}O_{2peak}$ T: Aerobic and resistance T: 48 wk	Ambulatory BP Autonomic function Blood lipids Inflammatory biomarkers Vascular biomarkers CRF	No change in 24-hr BP Increase in 1-min exercise heart rate recovery with ExT Decrease in total cholesterol and LDL-C in control group No change in IL-6 or hs-CRP No change in ADMA Increase in $\dot{V}O_{2peak}$ with ExT
Howden et al (2013)[22]	Exercise (n = 36) Control (n = 36)	F: 2x/wk (75 min) I: 11-13 RPE T: Aerobic T: 18 wk	Central BP Blood lipids Ventricular-vascular interaction Arterial compliance Cardiac function CRF	No change in central BP No change in blood lipids Improvement in arterial elastance with ExT No change in pulse wave velocity or pulse wave augmentation index Improvement in left ventricular systolic and diastolic function Increase in $\dot{V}O_{2peak}$ with ExT
Headley et al (2014)[23]	Exercise (n = 25) Control (n = 21)	F: 3x/wk (55 min) I: 50-60% $\dot{V}O_{2peak}$ T: Aerobic T: 16 wk	BP Arterial compliance Inflammatory biomarkers Vascular biomarkers Body composition CRF	No change in BP No change in pulse wave velocity No change in hs-CRP Decrease in circulating Endothelin-1 with ExT No change in % fat mass Increase in $\dot{V}O_{2peak}$ with ExT
Greenwood et al (2015)[24]	Exercise (n = 8) Control (n = 10)	F: 3x/wk (40 min) I: 80% HRR T: Aerobic and resistance T: 52 wk	BP Blood lipids Arterial stiffness Inflammatory biomarkers Body composition CRF	No change in BP No change in blood lipids Decrease in pulse wave velocity with ExT No change in hs-CRP Decrease in waist circumference with ExT Increase in $\dot{V}O_{2peak}$ with ExT
Van Craenenbroeck et al (2015)[25]	Exercise (n = 19) Control (n = 21)	F: 4x/wk (10 min) I: 90% AT T: Aerobic T: 12 wk	BP Blood lipids Vascular endothelial function Arterial compliance Vascular biomarkers Inflammatory biomarkers CRF	No change in BP Decrease in total cholesterol in control group No change in flow-mediated dilation No change in pulse wave velocity or pulse wave augmentation index No change in endothelial progenitor cell proliferation or circulating cell migratory capacity No change in hs-CRP Increase in $\dot{V}O_{2peak}$ with ExT
Headley et al (2017)[26]	Exercise (n = 25) Control (n = 21)	F: 3x/wk (55 min) I: 50-60% $\dot{V}O_{2peak}$ T: Aerobic T: 16 wk	Ambulatory BP Post-exercise hypotension	No change in daytime or nighttime BP No change in post-exercise hypotension
Kirkman et al (2019)[9]	Exercise (n = 15) Control (n = 16)	F: 3x/wk (45 min) I: 60-85% HRR T: Aerobic T: 12 wk	Central BP Microvascular function Vascular endothelial function Arterial compliance Arterial hemodynamics Oxidative stress biomarkers CRF	No change in central BP Improvement in microvascular conductance with ExT Flow-mediated dilation preserved with ExT No change in pulse wave velocity or pulse wave augmentation index No change in forward or reflect traveling waveform amplitudes No change in urinary F_2-isoprostanes Increase in $\dot{V}O_{2peak}$ with ExT
Huppertz et al (2020)[28]	Exercise (n = 81) Control (n = 80)	F: 2x/wk (75 min) I: 11-13 RPE T: Aerobic T: 18 wk	Autonomic function CRF	No change in heart rate variability and 1-min exercise heart rate recovery Increase in $\dot{V}O_{2peak}$ with ExT
Kirkman et al (2020)[27]	Exercise (n = 14) Control (n = 12)	F: 3x/wk (45 min) I: 60-85% HRR T: Aerobic T: 12 wk	Autonomic function Cardiac function Ventilation-perfusion matching CRF	No change in autonomic function Improvement in indexed O_{2pulse} with ExT No change in $\dot{V}_E/\dot{V}CO_2$ and $\dot{V}_E/\dot{V}O_2$ slopes Increase in $\dot{V}O_{2peak}$ with ExT

Abbreviations: ADMA, asymmetric dimethylarginine; AT; BP, blood pressure; CKD, chronic kidney disease; CRF, cardiorespiratory fitness; ExT, exercise training; F, frequency of exercise; GSH, glutathione; HRR, heart rate reserve; hs-CRP, high-sensitivity C-reactive protein; I, intensity of exercise; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; LPO, lipid peroxidation product; RPE, rating of perceived exertion: T, type of exercise; T, time of exercise training intervention.

Table 3

Exercise Intervention in Those With Spontaneous Coronary Artery Dissection

Study	Patients	Exercise Assessment	Exercise Intervention	Sessions Attended	Outcomes	Notes
de Carvalho Pinto et al (2014)[56]	1 female (age 36 yr)	6MWT	3x/wk, 1 hr (20-min WU, 15-min TM, 15-min bike, 4-min supine recovery)	21	445-m pre-, 540-m post-exercise intervention (21% improvement)	Time to enrollment not reported
Silber et al (2015)[54]	9 women, 0 men (average age 47 yr)	Pre and post-CPX or 6MWT	1-3x/wk (5-min WU, 30- to 45-min CV exercise, 5-min CD). RT/core 10-20 min. THRR 60-70% HRR and/or RPE 12-14. HIIT performed once able to complete 20-min MICT (1-2 min at RPE 15-17 interspersed with moderate-intensity intervals of RPE 12-14).	28 (5-39) visits	CPX: peak oxygen uptake increased by 18% (4.4 mL/kg/min, average). 6MWT increased 22%.	CR initiated 1-2 wk post-MI. Education and counseling regarding nutrition, weight control and stress management
Chou et al (2016)[61]	70 women, 0 men (average age 52 yr)	Pre and post-ETT	1 hr, 1x/wk (15-min WU, 30 min-CV exercise, 15-min CD). RT with 2-12 lb. THRR 50-70% of HRR. SBP $<$130 mm Hg. Advised not to lift $>$20 lb.	12.4 $\pm$ 10.5 wk	10 METs at program initiation $\pm$ 3 METs; at exit 11.5 $\pm$3.5 At entry, 63% had recurrent CP, at exit 37%	Enrollment median 0.6 yr after event. Supervised exercise in open gym available in addition to 1x/wk session. 20-min education/wk on nutrition, risk factors, stress management; counseling and peer support available.
Patterson et al (2016)[53]	1 female (age 39 yr)	Submax CPX 1 mo post-event. Submax ETT (no CPX) at 3 and 6 mo post-event	Initial 2 mo: CV exercise $\leq$30 min, longer WU than usual, RPE 3-5 (on 1-10), HR $<$140 bpm, avoided jogging. RT: 3-7 d, light effort. At mo 3: HR $<$150 bpm up to 1 hr, added interval jogging. RT moderate effort. At mo 6: no limit to duration, HR $<$165 bpm, 6-7 on RPE 1-10, avoided training for marathon distances. RT: up to moderate/vigorous effort, avoiding Valsalva.	NA	Max ETT at 6 mo post-event: 13 METs	ET initiated 1 mo post-event. At 8 mo post-event, patient was running 3-5 mi 3x/wk, elliptical 30-45 min and/or spin cycle for 45 min 1x/wk.
Weber et al (2018)[55]	1 male (age 22 yr)	CPX post-exercise intervention only	WU and CD. Initial 23 sessions: low-/moderate-intensity TM, bike and RT; then 32 sessions over 11 mo with simulated competitive cycling.	55 over 3 yr	Achieved 14 METs	Time to enrollment not reported. Training was symptom limited (no limits on HR, BP, RPP, RPE).
Brown et al (2019)[60]	1 female (age 53 yr)	Final CR session: peak transient change in BP over time (dP/dt) was continuously recorded during RT and core exercise as well as during cough, forced Valsalva, and provoked sneeze	5-min WU before 20-30 min jogging or stepper. Two sets of 10 (moderate intensity) of 1 RT activity and 2 sets of 1 core activity for 30 sec.	18	Cough, Valsalva and sneeze were shown to have the greatest dP/dt over RT and core exercise.	Enrolled 1 yr post-event to specifically perform RT and core activities

Abbreviations: BP, blood pressure; CD, cool down; CP, chest pain; CPX, cardiopulmonary exercise test; CR, cardiac rehabilitation; CV, cardiovascular; dP/dt, derivative of pressure over time; ET, exercise training; ETT, exercise treadmill test; HIIT, high-intensity interval training; HR, heart rate; HRR, heart rate reserve; MET, metabolic equivalent of task; MI, myocardial infarction; MICT, moderate-intensity continuous training; NA, not applicable; RPE, rating of perceived exertion; RPP, rate pressure product; RT, resistance training; SBP, systolic blood pressure; THRR, target heart rate range; TM, treadmill; WU, warm up; 6MWT, 6-min walk test.

Table 4

Exercise Intervention in Those With Left Ventricular Assist Devices

Study	Patients (Female, Male), n	Age, yr	Device Type	Exercise Testing and QOL Metrics	Exercise Intervention	Outcomes	Average Sessions Attended	Signs, Symptoms and/or Adverse Events	Notes
Laoutaris et al (2011)[70]	1, 14	38 ± 16	First-generation pulsatile and second-generation continuous flow	$\dot{V}O_{2peak}$, 6MWT, PFT, MLWHFQ	10-wk training period. 45 min, on a bike or treadmill at an RPE of 12-14 on the Borg scale.	Within group improvements in $\dot{V}O_{2peak}$, $\dot{V}_E/\dot{V}CO_2$ slope, 6MWD, inspiratory muscle endurance, and MLWHFQ for the training group	Not reported	None reported	Randomized control design. Combined home and supervised exercise.
Hayes et al (2012)[71]	2, 10	47 ± 15	VentrAssist	$\dot{V}O_{2peak}$, 6MWT, SF-36	8-wk training period. 60 min, 3 d/wk using combined stationary cycling, treadmill, and 6 strength training exercises. Cycling intensity was 50% of heart rate reserve or an RPE of >13 on the Borg scale.	Both groups showed improvements in $\dot{V}O_2$, and 6MWD. No significant difference between groups. Some domains of the SF-36 improved in the training group	21.3 ± 1.5 out of 24 sessions	None reported	Randomized control design. First randomized exercise trial in patients with LVADs
Karapolat et al (2013)[68]	2, 9	46 ± 14	EXCOR HeartWare	$\dot{V}O_{2peak}$, Beck Depression Scale, SF-36	8-wk training period. 90 min, 3 d/wk using various aerobic modalities and 8 upper and lower body resistance exercises. Aerobic exercise was at 60-70% $\dot{V}O_{2peak}$	Within group improvements in $\dot{V}O_{2peak}$, symptoms of depression, and some domains of the SF-36	Not reported	None reported	Retrospective study comparing patients with heart failure, to transplant, to LVAD who participated in CR.
Kerrigan et al (2014)[69]	7, 19	55 ± 13	HeartMate II HeartWare	$\dot{V}O_{2peak}$, 6MWT, isokinetic leg strength, KCCQ	6-wk training period 30 min, 3 d/wk of combined stationary cycling, treadmill, or recumbent stepper. Intensity was set at 60% or heart rate reserve or an RPE of 11-14 on the Borg scale.	Within group improvements in $\dot{V}O_{2peak}$, $\dot{V}O_2$ at VT, and 6MWD for the training group. Within and between group improvements for treadmill time, KCCQ, and isokinetic leg strength	17.8 ± 3.2 out of 18 sessions	One patient had a syncopal event associated with nonsustained ventricular tachycardia immediately after exercise	Randomized control design. Training was conducted within CR classes
Marko et al (2015)[72]	8, 33	55 ± 12	HeartMate II HeartWare	$\dot{V}O_{2peak}$, resistance training workloads	~32 CR sessions using a combination of stationary cycling and free walking at an RPE of 13 on the Borg scale. Lower extremity strength training 2 sets, 12 reps	Within group improvements in $\dot{V}O_{2peak}$ and leg strength based upon increased training workload	32 ± 6 sessions. No predetermined total expected	One patient experienced an episode of nonsustained ventricular tachycardia	Retrospective analysis. Training was conducted within CR classes
Villela et al (2021)[73]	5, 10	51 (29-71)	HeartMate II HeartMate III	$\dot{V}O_{2peak}$, KCCQ, and LV echocardiogram measures	5-wk training period, 3 d/wk^{-1} of high-intensity exercise training on a cycle ergometer. HIIT protocol: 30-sec warm-ups. Six 30-sec high-intensity intervals followed by 4-min active recovery.	Within group improvements in $\dot{V}O_2$ at VT and LV end-diastolic volume	Median 13 out of 15 sessions	One subject had recurrent asymptomatic supraventricular tachycardia that occurred after the planned increase in workloads during the fourth training session	Prospective, observational study. Supervised training was conducted individually with a physician. Median time of LVAD support prior to training was 18 mo (range 3-64 mo).

Abbreviations: CR, cardiac rehabilitation; HIIT, high-intensity interval training; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVAD, left ventricular assist device; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; PFT, pulmonary function test; QOL, quality of life; RPE, rating of perceived exertion; SF-36, Short-form 36-item Health Survey Questionnaire; THRR, target heart rate range; TM, treadmill; VT, ventilatory threshold; $\dot{V}O_{2peak}$, peak oxygen uptake; WU, warm up; 6MWT, 6-min walk test.

Table 5

American College of Sports Medicine's Exercise Recommendations for Chronic Kidney Disease and Cancer Survivors[a]

	Aerobic Exercise	Resistance Exercise	Flexibility Exercise
CKD			
Frequency	3-5 d·wk^{-1}	2-3 d·wk^{-1}	2-3 d·wk^{-1}
Intensity	Moderate intensity (40-59% $\dot{V}O_2R$, RPE 12-13 on a scale of 6-20)	65-75% estimated 1-RM. Performance 1-RM is not recommended unless medically cleared for such effort; instead, estimate 1-RM from a ≥3-RM test.	Static: Stretch to the point of tightness or slight discomfort. PNF: 20-75% maximum voluntary contraction.
Duration	20-60 min·d^{-1} of continuous activity; however, if this cannot be tolerated, use 3- to 5-min bouts of intermittent exercise aiming to accumulate 20-60 min·d^{-1}.	A minimum of 1 set of 10-15 repetitions, with a goal in most individuals to achieve multiple sets. Choose 8-10 different exercises targeting the major muscle groups.	60 sec/joint for static (10- to 30-sec hold/stretch); 3- to 6-sec contraction followed by 10- to 30-sec assisted stretch for PNF.
Modality	Prolonged, rhythmic activities using large muscle groups (eg, walking, cycling, and swimming)	Machines, free weights, bands, body weight	Static or PNF
Cancer survivors			
Frequency	3-5 d·wk^{-1}	2-3 d·wk^{-1} with a minimum of 48 h/ sessions	2-3 d·wk^{-1} up to daily
Intensity	40 to <60% $\dot{V}O_2R$ or HRR. Survivors may find RPE useful to gauge exercise intensity.	60-80% 1-RM or allow for 6-15 repetitions. Increase weight as tolerated and when repetitions >15. RPE is correlated with % 1-RM in cancer survivors.	Stretch within limits of pain to the point of tightness or slight discomfort.
Duration	≥30 min·d^{-1}. No lower limit on bout length. During treatment, exercise length may need to be modified due to chemotherapy or radiation-related toxicities.	≥1 set, ≥8 repetitions/set; ≥60-sec rest between sets	Static: 10-30 sec/stretch
Modality	Walking, cycling, swimming. Swimming should not be prescribed for survivors with central lines, those with ostomies, those in an immunocompromised state or who are currently receiving radiation therapy.	8-10 exercises of major muscle groups, machines, or free weights	Static stretches (passive and/or active), for all major tendon groups. Tai chi and yoga may be preferred.

Abbreviations: BC, breast cancer; CKD, chronic kidney disease; HRR, heart rate reserve; PNF, proprioceptive neuromuscular facilitation; RPE, rating of perceived exertion; $\dot{V}O_2R$, oxygen uptake reserve; 1-RM, 1-repetition maximum, 3-RM, 3-repetition maximum.

[a]These tables have been re-created, with permission, from the 11th edition of the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription.[35]

Heart Association by Gilchrist et al[42] provides an excellent example of a multimodal model like CR for cancer patients and survivors (ie, cardio-oncology rehabilitation) and emphasizes the need for research to determine the full impact that such services could have on the overall health of BC survivors. Furthermore, Dolan et al[43] observed improvements to physical (CRF, functional assessments) and mental (depression, quality of life) outcomes when implementing personalized exercise programs based on the CR model in BC survivors. Below is a summary of the current literature that supports the benefits of exercise testing and programming for this patient population.

Exercise Testing

While exercise testing is not required for BC survivors to begin an exercise program, reduced oxygen uptake at peak exercise is commonly observed in this population. Jones et al[44] reported that BC survivors (n = 248, mean age: 55 yr, mean left ventricular ejection fraction: 62%) have a $\dot{V}O_{2peak}$ that is 27% lower than age-matched healthy sedentary female populations. Also, 32% of BC survivors had a $\dot{V}O_{2peak}$ below the threshold level required for functional independence.[44] Exercise testing may be beneficial in identifying initial CRF levels as well as the mechanisms underpinning their reduced CRF. In accordance with the Fick principle, the reduced $\dot{V}O_{2peak}$ may be the result of cardiac and "noncardiac" peripheral factors that result in decreased convective and diffusive oxygen transport and reduced oxygen utilization by the exercising muscles.[12,41] Specifically, evidence to date suggests that the lower $\dot{V}O_{2peak}$ is due to a lower peak exercise cardiac output[39,45] secondary to a lower peak exercise stroke volume[39,45] and end-diastolic volume index,[45] as peak exercise HR[39,45] and arterial-venous oxygen difference[39] are not significantly different between BC survivors and controls. The finding of normal oxygen extraction despite a lower cardiac output suggests that peripheral vascular and/or skeletal muscle abnormalities that result in decreased muscle oxygen diffusive conductance may also limit $\dot{V}O_{2peak}$ in BC survivors.[12] Indeed, Beaudry et al[46] found that BC survivors had a significantly higher thigh and lower leg intermuscular fat to skeletal muscle ratio compared with controls, and this was inversely related to whole body $\dot{V}O_{2peak}$. Accordingly, therapies targeted to reduce intermuscular fat may be an important therapy to improve $\dot{V}O_{2peak}$ following BC therapy.[46]

Exercise Prescription and Training

A systematic review and meta-analysis by Scott et al[13] found that exercise training is an effective therapy to increase $\dot{V}O_{2peak}$ in cancer survivors. The mechanisms responsible for the exercise training-mediated increase in $\dot{V}O_{2peak}$ in BC survivors are not well known, however appear to be due to favorable peripheral (vascular and/or skeletal muscle) adaptations.[12] Howden et al,[14] using a nonrandomized controlled trial in female patients with early-stage BC, found that exercise training during anthracycline chemotherapy attenuated the decline in both $\dot{V}O_{2peak}$ and estimated arterial venous oxygen difference when compared to usual care, with no significant difference observed between groups for change in peak HR, stroke volume, or cardiac output. Finally, Mijwel et al[15] compared the effects of 16 wk of moderate-intensity aerobic training combined with high-intensity interval training (aerobic training-HIIT) and resistance training combined with HIIT (resistance training-HIIT) versus usual care on skeletal muscle morphology and function in female patients with BC undergoing chemotherapy. A main finding was that both aerobic training-HIIT and resistance training-HIIT counteracted the decline in citrate synthase activity, type I muscle fiber cross-sectional area, and capillaries/fiber found in the usual care group after 16 wk. Also, the change in cancer-related fatigue was inversely related to the change in citrate synthase activity. In addition to the improvements in overall $\dot{V}O_{2peak}$ and the central and peripheral factors, which influence CRF, exercise has been shown to reduce risk of cancer-specific mortality, improve lean body mass, reduce fatigue and depression, improve sleep, and improve overall quality of life for BC survivors. A summary of the current aerobic, resistance, and flexibility exercise recommendations,[35] which elicit these benefits for cancer survivors, can be found in Table 5.

SPONTANEOUS CORONARY ARTERY DISSECTION

Spontaneous coronary artery dissection is an infrequent, but increasingly recognized, event that can lead to acute coronary syndrome (ACS) including MI or sudden death.[47] Dissection of a coronary artery is characterized by the spontaneous formation of an intramural hematoma. When an intimal tear is present, it can result in the creation of a false lumen where blood can enter but not exit, leading to the creation of the hematoma. Pressure-driven expansion of the false lumen and enlargement of the hematoma can lead to worsening myocardial ischemia due to compression and narrowing of the true lumen, causing a reduction of blood flow in the affected artery.

Physical and emotional stressors are considered triggers of SCAD. In a cohort of 327 patients who suffered SCAD, 62% had a precipitating stressor within 1 wk prior to the event. Of these 48% were related to an emotional event, 28% to a physical event, and 12% triggered due to heavy isometric exertion.[48]

The diagnosis of SCAD is made with coronary angiography and current recommended treatment is conservative, including the use of β-blockers to reduce intracoronary shear stress and risk of reoccurrence.[47-50] Saw et al[48] reported that 83% of those suffering SCAD were initially treated conservatively, without stent or coronary artery bypass. Despite two different scientific statements suggesting optimal management,[47,49] there are currently no clinical practice guidelines.

Spontaneous coronary artery dissection occurs most often in young to middle-aged female populations, frequently at a time of high emotional stress, during intense exercise, or during childbirth.[47,49] It is responsible for up to 35% of ACS in female patients age ≤50 yr.[47] Additionally, there is a high probability of reoccurrence, leading to related anxiety and depression.[47,51,52] Frequently and paradoxical to most individuals with ACS and MI, those who suffer SCAD are in good health, physically fit, and often present with few risk factors for coronary artery disease.[50] Despite this, exercise training is recommended. However, little information exists about exercise training in patients with SCAD (Table 3).

Exercise Testing

Published data regarding exercise testing in this population are sparse. Although not required, testing prior to enrollment in CR may be useful for guiding the exercise prescription, especially in those highly active prior to their SCAD event. Several studies include completion of a CPX before and/or after an exercise regimen,[47,53-55] but there is no consensus as to protocol; 6MWTs have also been used.[54,56] Regardless of the testing method, improvements in functional capacity in the range of 1.5 metabolic equivalents (METs) of task have been observed. No adverse events were reported. Standard testing methods are likely appropriate, and the exercise testing protocol selected will likely be similar to that used in other patients who experienced ACS or a MI, including a pre-test assessment of functional capacity.

Exercise Prescription and Training

The American Heart Association recommends that all patients with MI caused by SCAD be referred to CR, and health care providers overwhelmingly support this,[57] yet referral rates remain low. This is possibly due to provider fear of reoccurrence (range for rate of recurrence: 0-37%) or the belief that young, fit patients without coronary artery disease may not benefit from CR.[47] Unfortunately, because of low referral rates and lack of specific exercise guidelines, CR staff frequently adopt the methods used with other CR patients. However, this can be frustrating for those patients with SCAD because they are often younger and engaged in higher levels of physical activity prior to their event. Not feeling challenged and/or being treated as if they have coronary artery disease may lead to low CR participation rates among patients with SCAD.[58,59] A few case reports address an individualized (1:1) or sports-specific approach for SCAD survivors,[53,55,60] but currently many CR programs may not have sufficient staffing or resources to allow for this level of care.

A multidisciplinary CR program in Vancouver, British Columbia, has published the largest experience of exercise in patients with SCAD. Exercise was performed 1 d/wk in a dedicated session that included peer support and consisted of 15 min of warm-up, 30 min of aerobic exercise, and 15 min of cool-down. Resistance training was performed with two 12-lb free weights and high repetitions. Target HR was set at 50-70% of HR reserve based on an entrance exercise treadmill test. Systolic BP during exercise was limited to <130 mm Hg. Exercise, HR, and BP thresholds were chosen with the intention of decreasing arterial wall stress and providing a conservative return to activity.[61] Outside of formal classes, participants were encouraged to exercise in a supervised gym setting.

In the Vancouver experience, patients were recommended to lift ≤20 lb during daily activities, as some in the cohort suffered their SCAD event after lifting more than 20 lb.[61] Other published reports have recommended that, after SCAD, females lift ≤20-30 lb and male patients ≤30-50 lb.[50,62,63] Because acute, high levels of exercise are associated with SCAD, some have recommended patients avoid activities performed to exhaustion, any highly competitive or contact sports, exercise performed in extremes of terrain or temperature, or activities that involve a Valsalva maneuver such as intense isometric activities.[47,53,63,64]

There are very limited data on high-intensity exercise in these patients. Silber et al[54] report on nine female patients who had an MI as the result of SCAD and subsequently participated in their CR program. Supervised exercise began within 1-2 wk post-event and was prescribed at 60-70% HR reserve from an entrance CPX and/or 12-14 on the 6-20 Borg rating of perceived exertion (RPE) scale. High-intensity interval training was performed after patients were able to exercise 20 continuous min at their prescribed intensity. One to two-min intervals at RPE 15-17 were interspersed with moderate-intensity intervals of RPE 12-14. Functional capacity increased by 18% (4.4 mL/kg/min) after completion of five 39 CR visits and no adverse events were reported.[54]

LEFT VENTRICULAR ASSIST DEVICES

Left ventricular assist devices (LVADs) continue to be used increasingly as a therapeutic option for patients with end-stage heart failure (HF). Improvements in LVAD technology have led to better survival. For example, the 2-yr survival rate for the HeartMate III LVAD (Abbott Cardiovascular), a fully magnetically levitated centrifugal continuous-flow pump, is 82.8%, compared with 76.2% for the older HeartMate II (Abbott Cardiovascular), a mechanical-bearing axial continuous-flow pump.[65] These advancements have resulted in a nearly six-fold increase in the number of LVAD recipients over the past decade.[66,67] However, despite improvements in both LVAD technology and outcomes, many patients on LVAD support have poor exercise capacity, especially compared with similar patients who received a heart transplant.[68]

Exercise training in this population has shown to be beneficial for both improvements in exercise capacity and patient-reported health outcomes (Table 4).[68-75] However, despite this, and despite the fact that the Centers for Medicare & Medicaid Services now covers CR in patients on LVAD support under HF, only 42% of eligible patients in this population utilize CR.[76]

Exercise Testing

While not widely utilized, performing a CPX on patients with LVAD support can be useful for guiding exercise prescription, risk stratification, and evaluation of native left ventricle recovery.[77,78] Imamura et al[77] reported that patients on LVAD support with a $\dot{V}O_{2peak}$ >14 mL·kg^{-1}·min^{-1} had significantly lower 2-yr hospital readmission rate. More recently, the use of CPX testing has shown potential to help decide whether selected patients on LVAD support have recovered substantial native function.[78] Specifically, the preservation of $\dot{V}O_{2peak}$ following serial CPX testing with full and minimal LVAD support (ie, LVAD speed is reduced) can show whether a patient might be a candidate for LVAD explanation (the so-called bridge to recovery).[78]

Two unique challenges to performing a CPX on these individuals are obtaining an accurate exercise BP and managing the LVAD equipment. Due to the nature of current second-generation LVAD models (eg, HeartMate II, HeartWare), which operate as continuous flow pumps, there is no detectable pulse, which makes both manual and automatic BP unreliable.[79] Therefore, it is recommended that BP be obtained using a Doppler and a sphygmomanometer.[79] While the third-generation HeartMate III does have a built-in artificial pulse, the use of a Doppler remains recommended at this time.[80]

The technique of measuring a Doppler BP is an acquired skill that takes practice. Therefore, performing periodic competencies for Doppler measurement is recommended. In addition, using a stationary cycle for testing is preferred to help reduce motion artifact when attempting a Doppler BP during exercise. Another consideration when choosing an exercise modality is the additional weight of the LVAD batteries and controllers, which may affect the patient balance with treadmill walking. Assessment of gait and balance should be done before determining an exercise modality. It is also important to be aware of the external driveline and battery lines, which supply power to the LVAD. Unnecessary exposure of these external lines may increase the risk of the power being disconnected. To avoid this, covering external lines with a driveline stabilization belt should be considered before beginning the test.[81]

Finally, the 6MWT is an additional exercise test to consider. Due to the low functional capacity in this population, the 6MWT can be used to show a training response from CR. Importantly, it has also been shown to be an independent prognostic predictor of survival with patients who achieved <300 m having an increased risk for mortality.[82]

Exercise Prescription and Training

The LVAD device itself is set at a fixed therapeutic speed (eg, typical speed of the HeartMate III is 5400 RPM, although this differs between devices) and thus does not adjust regardless if a person is at rest or exercise. Despite this, cardiac output can increase from 3-5 to ~10 L/min.[79] Factors, which contribute to this, are increased preload through the skeletal muscle pump, a reduction in afterload, which decreases the differential pressure between the LVAD device and the aorta, thus allowing greater pump flow and increased contribution by the native left ventricle to move blood through the aorta (independent of the LVAD).

Despite the presence of a foreign device augmenting cardiac output, the relationship between HR and $\dot{V}O_2$ remains intact.[83] An exception to this would be in patients who display chronotropic incompetence or are paced with inadequate HR responsiveness.[83] For these patients prescribing exercise at a RPE level of 11-14 on the Borg 6-20 scale would be appropriate. For patients on LVAD support who do have an intact HR response, a target HR range set at 40-80% HR reserve can be used.[35]

In this population, HIIT has shown promise with some preliminary data.[73,84] However, more research is needed on the safety of HIIT in this population and should only be considered in select patients, based upon factors such as age, balance, and overall functional abilities.

Muscular strength is an important fitness component related to patient-reported quality of life as well as length of hospital stay following LVAD implantation.[85,86] The few training studies that incorporated strength training showed favorable improvements in strength, and as a result, strength training should be incorporated as part of a comprehensive exercise program. As with other patients with a procedure requiring a sternotomy, precautions should be taken to limit upper-body strength training until 8-12 wk post-surgery. In addition, avoiding excessive trunk flexion (eg, sit-ups) or contact sports is necessary.

SUMMARY

The four patient populations discussed in this review have important clinical considerations that should be supervised by trained exercise professionals. Despite the uniqueness of the patient populations, compared with individuals without these health conditions, exercise testing and training appear to be safe and well tolerated, suggesting these individuals can greatly benefit from services commonly offered in CR. However, high-quality randomized controlled trials, multisite clinical trials, and additional in-clinic experience working with these patients are needed to develop more specific recommendations and ensure patient safety while maximizing the effectiveness of individualized exercise programming. Such research may also lead to the support necessary for insurance reimbursement for exercise training programs for patients with CKD or BC, similar to what has been approved by Medicare for individuals with symptomatic peripheral artery disease. It is worth noting that other clinical populations, such as individuals who have suffered a stroke, may also benefit from CR services. Recent studies have addressed the need for inclusion of this population in CR as well as benefits and barriers to participation.[87,88] To conclude, understanding these comorbid conditions that are seen in CR is important to be able to provide safe and effective therapy for these patients. As summarized in Tables 2, 3, and 4, current evidence suggests that each of these populations could experience physical and mental benefits from regular exercise participation including but not limited to increased CRF, maximal MET level during a graded treadmill test, 6MWT duration, muscular strength as well as improvements to depression symptoms, left ventricular end-diastolic volume, and oxygen uptake at ventilatory threshold. Thus, it is important to consider the inclusion of new populations to CR programs as well as better understand those who are less commonly seen in CR to help all patient populations maximize health outcomes and better manage their chronic disease(s).

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REFERENCES

1. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol*. 2016;67(1):1-12.
2. Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. *Circulation*. 2010;121(1):63-70.
3. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart*. 2018;104(17):1403-1410.
4. Huang R, Palmer SC, Cao Y, et al. Cardiac rehabilitation programs for chronic heart disease: a Bayesian network meta-analysis. *Can J Cardiol*. 2021;37(1):162-171.
5. Lavie CJ, Ozemek C, Grace SL. More evidence of comprehensive cardiac rehabilitation benefits, even for all-cause mortality: need to increase use worldwide. *Can J Cardiol*. 2021;37(1):19-21.
6. Delgado C, Johansen KL. Barriers to exercise participation among dialysis patients. *Nephrol Dial Transplant*. 2012;27(3):1152-1157.
7. Kirkman DL, Muth BJ, Stock JM, Townsend RR, Edwards DG. Cardiopulmonary exercise testing reveals subclinical abnormalities in chronic kidney disease. *Eur J Prev Cardiol*. 2018;25(16):1717-1724.
8. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev*. 2011(10):CD003236. doi:10.1002/14651858.CD003236.pub2.
9. Kirkman DL, Ramick MG, Muth BJ, et al. Effects of aerobic exercise on vascular function in nondialysis chronic kidney disease: a randomized controlled trial. *Am J Physiol Renal Physiol*. 2019;316(5):F898-F905.
10. Kosmadakis GC, John SG, Clapp EL, et al. Benefits of regular walking exercise in advanced pre-dialysis chronic kidney disease. *Nephrol Dial Transplant*. 2012;27(3):997-1004.
11. Johansen KL, Kaysen GA, Dalrymple LS, et al. Association of physical activity with survival among ambulatory patients on dialysis: the comprehensive dialysis study. *Clin J Am Soc Nephrol*. 2013;8(2):248-253.
12. Haykowsky MJ, Beaudry R, Brothers RM, Nelson MD, Sarma S, La Gerche A. Pathophysiology of exercise intolerance in breast cancer survivors with preserved left ventricular ejection fraction. *Clin Sci (Lond)*. 2016;130(24):2239-2244.
13. Scott JM, Zabor EC, Schwitzer E, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2018;36(22):2297-2305.
14. Howden EJ, Bigaran A, Beaudry R, et al. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients. *Eur J Prev Cardiol*. 2019;26(3):305-315.
15. Mijwel S, Cardinale DA, Norrbom J, et al. Exercise training during chemotherapy preserves skeletal muscle fiber area, capillarization, and mitochondrial content in patients with breast cancer. *FASEB J*. 2018;32(10):5495-5505.
16. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev*. 2016;9:CD005001.
17. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2019 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2020;75(1, suppl 1):A6-A7.
18. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360(14):1395-1407.
19. Inker LA, Astor BC, Fox CH, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for the Evaluation and management of CKD. *Am J Kidney Dis*. 2014;63(5):713-735.
20. Mustata S, Groeneveld S, Davidson W, Ford G, Kiland K, Manns B. Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study. *Int Urol Nephrol*. 2011;43(4):1133-1141.
21. Headley S, Germain M, Milch C, et al. Exercise training Improves HR responses and $\dot{V}O_{2peak}$ in predialysis kidney patients. *Med Sci Sports Exerc*. 2012;44(12):2392-2399.
22. Howden EJ, Leano R, Petchey W, Coombes JS, Isbel NM, Marwick TH. Effects of exercise and lifestyle intervention on cardiovascular function in CKD. *Clin J Am Soc Nephrol*. 2013;8(9):1494-1501.
23. Headley S, Germain M, Wood R, et al. Short-term aerobic exercise and vascular function in CKD stage 3: a randomized controlled trial. *Am J Kidney Dis*. 2014;64(2):222-229.
24. Greenwood SA, Koufaki P, Mercer TH, et al. Effect of exercise training on estimated GFR, vascular health, and cardiorespiratory fitness in patients with CKD: A pilot randomized controlled trial. *Am J Kidney Dis*. 2015;65(3):425-434.
25. Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, et al. Effect of moderate aerobic exercise training on endothelial function and arterial stiffness in CKD stages 3-4: a randomized controlled trial. *Am J Kidney Dis*. 2015;66(2):285-296.
26. Headley S, Germain M, Wood R, et al. Blood pressure response to acute and chronic exercise in chronic kidney disease. *Nephrology*. 2017;22(1):72-78.
27. Kirkman DL, Ramick MG, Muth BJ, Stock JM, Townsend RR, Edwards DG. A randomized trial of aerobic exercise in chronic kidney disease: evidence for blunted cardiopulmonary adaptations [published online ahead of print December 11, 2020]. *Ann Phys Rehabil Med*. doi:10.1016/j.rehab.2020.101469.

28. Huppertz N, Beetham KS, Howden EJ, Leicht AS, Isbel NM, Coombes JS. A 12-month lifestyle intervention does not improve cardiac autonomic function in patients with chronic kidney disease. *Auton Neurosci*. 2020;224:102642.
29. Carbone S, Kirkman DL, Garten RS, et al. Muscular strength and cardiovascular disease: an updated state-of-the-art narrative review. *J Cardiopulm Rehabil Prev*. 2020;40(5):302-309.
30. Macdonald JH, Kirkman D, Jibani M. Kidney transplantation: a systematic review of interventional and observational studies of physical activity on intermediate outcomes. *Adv Chronic Kidney Dis*. 2009;16(6):482-500.
31. Hargrove N, El Tobgy N, Zhou O, et al. Effect of aerobic exercise on dialysis-related symptoms in individuals undergoing maintenance hemodialysis: a systematic review and meta-analysis of clinical trials. *Clin J Am Soc Nephrol*. 2021; 16(4):560-574.
32. Penny JD, Salerno FR, Brar R, et al. Intradialytic exercise preconditioning: an exploratory study on the effect on myocardial stunning. *Nephrol Dial Transplant*. 2019;34(11):1917-1923.
33. Kirkman DL, Scott M, Kidd J, Macdonald JH. The effects of intradialytic exercise on hemodialysis adequacy: a systematic review. *Semin Dial*. 2019;32(4):368-378.
34. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39(8):1435-1445.
35. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2022.
36. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
37. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.
38. Kirkham AA, Beaudry RI, Paterson DI, Mackey JR, Haykowsky MJ. Curing breast cancer and killing the heart: a novel model to explain elevated cardiovascular disease and mortality risk among women with early stage breast cancer. *Prog Cardiovasc Dis*. 2019;62(2):116-126.
39. Jones LW, Haykowsky M, Pituskin EN, et al. Cardiovascular reserve and risk profile of postmenopausal women after chemoendocrine therapy for hormone receptor–positive operable breast cancer. *Oncologist*. 2007;12(10):1156-1164.
40. Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol*. 2007;50(15):1435-1441.
41. Haykowsky MJ, Scott JM, Hudson K, Denduluri N. Lifestyle interventions to improve cardiorespiratory fitness and reduce breast cancer recurrence. *Am Soc Clin Oncol Educ Book*. 2017;37:57-64.
42. Gilchrist SC, Barac A, Ades PA, et al. Cardio-Oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. *Circulation*. 2019;139(21):e997-e1012.
43. Dolan LB, Barry D, Petrella T, et al. The cardiac rehabilitation model improves fitness, quality of life, and depression in breast cancer survivors. *J Cardiopulm Rehabil Prev*. 2018;38(4):246-252.
44. Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol*. 2012;30(20):2530-2537.
45. Beaudry RI, Howden EJ, Foulkes S, et al. Determinants of exercise intolerance in breast cancer patients prior to anthracycline chemotherapy. *Physiol Rep*. 2019;7(1):e13971.
46. Beaudry RI, Kirkham AA, Thompson RB, Grenier JG, Mackey JR, Haykowsky MJ. Exercise intolerance in anthracycline-treated breast cancer survivors: the role of skeletal muscle bioenergetics, oxygenation, and composition. *Oncologist*. 2020;25(5):e852-e860.
47. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the american Heart Association. *Circulation*. 2018;137(19):e523-e557.
48. Saw J, Humphries K, Aymong E, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol*. 2017;70(9):1148-1158.
49. Adlam D, Alfonso F, Maas A, Vrints C, Committee W. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD Study Group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. 2018;39(36):3353-3368.
50. Yang C, Alfadhel M, Saw J. Spontaneous Coronary artery dissection: latest developments and new frontiers. *Curr Atheroscler Rep*. 2020;22(9):49.
51. Liang JJ, Tweet MS, Hayes SE, Gulati R, Hayes SN. Prevalence and predictors of depression and anxiety among survivors of myocardial infarction due to spontaneous coronary artery dissection. *J Cardiopulm Rehabil Prev*. 2014;34(2):138-142.
52. Edwards KS, Vaca KC, Naderi S, Tremmel JA. Patient-reported psychological distress after spontaneous coronary artery dissection: evidence for post-traumatic stress. *J Cardiopulm Rehabil Prev*. 2019;39(5):E20-E23.
53. Patterson M, Hayes S, Squires R, Tweet M. Home-based cardiac rehabilitation in a young athletic woman following spontaneous coronary artery dissection. *J Clin Exerc Physiol*. 2016;5(1):6-11.
54. Silber TC, Tweet MS, Bowman MJ, Hayes SN, Squires RW. Cardiac rehabilitation after spontaneous coronary artery dissection. *J Cardiopulm Rehabil Prev*. 2015;35(5):328-333.
55. Weber N, Weber A, Carbone P, et al. High-intensity, sport-specific cardiac rehabilitation training of a 22-year-old competitive cyclist after spontaneous coronary artery dissection. *Proc (Bayl Univ Med Cent)*. 2018;31(2):207-209.
56. de Carvalho Pinto M, Camargo RC, Filho JC, et al. Influence of cardiac rehabilitation in primigravida with spontaneous coronary artery dissection during postpartum. *Int Arch Med*. 2014;7:20.
57. Bouchard K, Tarannum CN, Coutinho T, So D, Tulloch H. Secondary preventative care for patients after spontaneous coronary artery dissection: a qualitative analysis of health care providers' perspectives. *Can J Cardiol*. 2020;36(7):1156-1160.
58. Krittanawong C, Tweet MS, Hayes SE, et al. Usefulness of cardiac rehabilitation after spontaneous coronary artery dissection. *Am J Cardiol*. 2016;117(10):1604-1609.
59. Wagers TP, Stevens CJ, Ross KV, Leon KK, Masters KS. Spontaneous coronary artery dissection (SCAD): female survivors' experiences of stress and support. *J Cardiopulm Rehabil Prev*. 2018;38(6):374-379.
60. Brown K, Adams J, McCullough PA. Comparison of reflex, resistance training, and core activities using change in blood pressure over time after spontaneous coronary artery dissection. *Proc (Bayl Univ Med Cent)*. 2019;32(1):113-115.
61. Chou AY, Prakash R, Rajala J, et al. The first dedicated cardiac rehabilitation program for patients with spontaneous coronary artery dissection: description and initial results. *Can J Cardiol*. 2016;32(4):554-560.
62. Gilhofer TS, Saw J. Spontaneous coronary artery dissection: update 2019. *Curr Opin Cardiol*. 2019;34(6):594-602.
63. Saw J, Humphries K, Mancini GBJ. Reply: should we recommend cardiac rehabilitation in patients with spontaneous coronary artery dissection? *J Am Coll Cardiol*. 2018;71(4):473.
64. Borjesson M, Dellborg M, Niebauer J, et al. Brief recommendations for participation in leisure time or competitive sports in athletes-patients with coronary artery disease: summary of a position statement from the Sports Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol*. 2020;27(7):770-776.
65. Mehra MR, Goldstein DJ, Uriel N, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med*. 2018;378(15):1386-1395.
66. Kormos RL, Cowger J, Pagani FD, et al. The Society of Thoracic Surgeons Intermacs Database Annual Report: evolving indications, outcomes, and scientific partnerships. *J Heart Lung Transplant*. 2019;38(2):114-126.
67. Mehra MR, Uriel N, Naka Y, et al. A fully magnetically levitated left ventricular assist device—final report. *N Engl J Med*. 2019;380(17):1618-1627.
68. Karapolat H, Engin C, Eroglu M, et al. Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. *Transplant Proc*. 2013;45(9):3381-3385.
69. Kerrigan DJ, Williams CT, Ehrman JK, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD Randomized Controlled Trial. *JACC Heart Fail*. 2014;2(6):653-659.
70. Laoutaris ID, Dritsas A, Adamopoulos S, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term

postimplantation. *Eur J Cardiovasc Prev Rehabil*. 2011;18(1):33-40.
71. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. *J Heart Lung Transplant*. 2012;31(7):729-734.
72. Marko C, Danzinger G, Käferbäck M, et al. Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. *Eur J Prev Cardiol*. 2015;22(11):1378-1384.
73. Villela M, Chinnadurai T, Salkey K, et al. Feasibility of high-intensity interval training in patients with left ventricular assist devices: a pilot study. *ESC Heart Fail*. 2021;8(1):498-507.
74. Alsara O, Perez-Terzic C, Squires RW, et al. Is exercise training safe and beneficial in patients receiving left ventricular assist device therapy? *J Cardiopulm Rehabil Prev*. 2014;34(4):233-240.
75. Mahfood Haddad T, Saurav A, Smer A, et al. Cardiac rehabilitation in patients with left ventricular assist device: a systematic review and meta-analysis. *J Cardiopulm Rehabil Prev*. 2017;37(6):390-396.
76. Ritchey MD, Maresh S, McNeely J, et al. Tracking cardiac rehabilitation participation and completion among Medicare beneficiaries to inform the efforts of a national initiative. *Circ Cardiovasc Qual Outcomes*. 2020;13(1):e005902.
77. Imamura T, Kinugawa K, Nitta D, et al. Perioperative hypoalbuminemia affects improvement in exercise tolerance after left ventricular assist device implantation. *Circ J*. 2015;79(9):1970-1975.
78. Christle JW, Moneghetti KJ, Duclos S, et al. Cardiopulmonary exercise testing with echocardiography to assess recovery in patients with ventricular assist devices. *ASAIO J*. 2021;Online First.
79. Slaughter MS, Pagani FD, Rogers JG, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant*. 2010;29(4 suppl):S1-S39.
80. Li S, Beckman JA, Welch NG, et al. Accuracy of Doppler Blood pressure measurement in HeartMate 3 Ventricular assist device patients. *ESC Heart Fail*. 2020;7(6):4241-4246.
81. Adamopoulos S, Corrà U, Laoutaris ID, et al. Exercise training in patients with ventricular assist devices: a review of the evidence and practical advice. A position paper from the Committee on Exercise Physiology and Training and the Committee of Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21(1):3-13.
82. Hasin T, Topilsky Y, Kremers WK, et al. Usefulness of the six-minute walk test after continuous axial flow left ventricular device implantation to predict survival. *Am J Cardiol*. 2012;110(9):1322-1328.
83. Kerrigan DJ, Williams CT, Brawner CA, et al. Heart rate and $\dot{V}O_2$ concordance in continuous-flow left ventricular assist devices. *Med Sci Sports Exerc*. 2016;48(3):363-367.
84. Christle JW, Boscheri A, Pressler A, et al. Interval exercise training increases maximal and submaximal exercise performance in heart failure with biventricular assist device therapy. *Int J Cardiol*. 2015;187:104-105.
85. Yost G, Bhat G. Relationship between handgrip strength and length of stay for left ventricular assist device implantation. *Nutr Clin Pract*. 2017;32(1):98-102.
86. Kerrigan DJ, Williams CT, Ehrman JK, et al. muscular strength and cardiorespiratory fitness are associated with health status in patients with recently implanted continuous-flow LVADs. *J Cardiopulm Rehabil Prev*. 2013;33(6):396-400.
87. Prior PL, Hachinski V, Chan R, et al. Comprehensive cardiac rehabilitation for secondary prevention after transient ischemic attack or mild stroke: physciological profile and outcomes. *J Cardiopulm Rehabil Prev*. 2017;37(6):428-436.
88. Marzolini S. Including patients with stroke in cardiac rehabilitation: barriers and facilitators. *J Cardiopulm Rehabil Prev*. 2020;40(5):294-301.