Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Developments in Exercise Capacity Assessment in Heart Failure Clinical Trials and the Rationale for the Design of METEORIC-HF

Gregory D. Lewis, MD; Kieran F. Docherty, BSc, MBChB; Adriaan A. Voors, MD, PhD; Alain Cohen-Solal, MD; Marco Metra, MD; David J. Whellan, MD, MHS; Justin A. Ezekowitz, MBBCh, MSc; Piotr Ponikowski, MD; Michael Böhm, MD; John R. Teerlink, MD; Stephen B. Heitner, MD; Stuart Kupfer, MD; Fady I. Malik, MD, PhD; Lisa Meng, PhD; G. Michael Felker, MD

ABSTRACT: Heart failure with reduced ejection fraction (HFrEF) is a highly morbid condition for which exercise intolerance is a major manifestation. However, methods to assess exercise capacity in HFrEF vary widely in clinical practice and in trials. We describe advances in exercise capacity assessment in HFrEF and a comparative analysis of how various therapies available for HFrEF impact exercise capacity. Current guideline-directed medical therapy has indirect effects on cardiac performance with minimal impact on measured functional capacity. Omecamtiv mecarbil is a novel selective cardiac myosin activator that directly increases cardiac contractility and in a phase 3 cardiovascular outcomes study significantly reduced the primary composite end point of time to first heart failure event or cardiovascular death in patients with HFrEF. The objective of the METEORIC-HF trial (Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure) is to assess the effect of omecamtiv mecarbil versus placebo on multiple components of functional capacity in HFrEF. The primary end point is to test the effect of omecamtiv mecarbil compared with placebo on peak oxygen uptake as measured by cardiopulmonary exercise testing after 20 weeks of treatment. METEORIC-HF will provide state-of-the-art assessment of functional capacity by measuring ventilatory efficiency, circulatory power, ventilatory anaerobic threshold, oxygen uptake recovery kinetics, daily activity, and quality-of-life assessment. Thus, the METEORIC-HF trial will evaluate the potential impact of increased myocardial contractility with omecamtiv mecarbil on multiple important measures of functional capacity in ambulatory patients with symptomatic HFrEF.

REGISTRATION: URL: https://clinicaltrials.gov; Unique identifier: NCT03759392.

Key Words: exercise tolerance ■ heart failure ■ oxygen consumption ■ quality of life

Heart failure (HF) affects over 64 million people worldwide,[1] half of whom have HF with reduced ejection fraction (HFrEF).[2,3] Although a growing array of therapies has led to improvements in overall mortality, HFrEF remains a highly morbid condition for which exercise intolerance is a cardinal manifestation.

It has been underrecognized that virtually all of the many pharmacological agents definitively shown to decrease clinical events in HFrEF have modest, if any, benefit for the important, clinically relevant outcome of objectively measured exercise capacity.[4] Oral pharmacotherapies that improve systolic function may augment functional capacity in individuals in whom left ventricular systolic dysfunction (LVSD) is a major mechanism by which cardiorespiratory performance is limited (Table S1). However, such therapies have previously led to increased adverse clinical event rates. Omecamtiv mecarbil is a selective cardiac myosin activator[5] that improves

Correspondence to: Gregory D. Lewis, MD, Division of Cardiology, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114. Email glewis@partners.org
This manuscript was sent to Barry A. Borlaug, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.121.008970.
For Sources of Funding and Disclosures, see page 520.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

Nonstandard Abbreviations and Acronyms

6MWT	6-minute walk test
ACE	angiotensin-converting enzyme
COSMIC-HF	Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure
CPET	cardiopulmonary exercise testing
CRT	cardiac resynchronization therapy
GALACTIC-HF	Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	left ventricular
LVSD	left ventricular systolic dysfunction
METEORIC-HF	Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure
NYHA	New York Heart Association
pVo_2	peak oxygen uptake
SGLT2i	sodium-glucose cotransporter 2 inhibitor

cardiac function in patients with chronic HFrEF[6,7] and was recently shown to improve the combined end point of cardiovascular death or HF events in the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) trial.[8] The double-blind, randomized, placebo-controlled trial METEORIC-HF (Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure; NCT03759392) will test the hypothesis that omecamtiv mecarbil can improve exercise capacity in patients with HFrEF. This review highlights the clinical relevance of exercise capacity as an objective outcome measure in trials while summarizing results of previous approaches to exercise capacity assessment in relation to both guideline-directed therapies and positive inotropic agents. Finally, we describe the design of METEORIC-HF trial in the context of conveying the importance of exercise capacity assessment in HF clinical trials, particularly for interventions that directly impact cardiac performance.

HFrEF AND EXERCISE INTOLERANCE

Exercise intolerance is a common initial presentation of HFrEF. Thereafter, exertional dyspnea, fatigue, increased need to rest, and difficulty ambulating are dominant symptoms in HF patients for the vast majority of time when they are not hospitalized for pulmonary edema or hemodynamic instability. While exercise intolerance is associated with reduced quality of life and correlates with higher mortality risk,[9,10] interventions that improve HF event rates have not translated to improved exercise capacity. Moreover, symptoms related to exercise intolerance often remain severe, even when patients with HFrEF are nonedematous on guideline-directed therapies. The extent to which specific activities elicit symptoms is often used to grade HF severity (ie, New York Heart Association [NYHA] class) and inform the use of certain HF therapies.[11] Additionally, measurement of exercise capacity is guideline directed and mandated by the Centers for Medicare and Medicaid Services for consideration of advanced HF interventions.[12] Given the inextricable link between exercise intolerance and HF, there is a need for standardized approaches for assessment of exercise tolerance in relation to HF therapeutics.

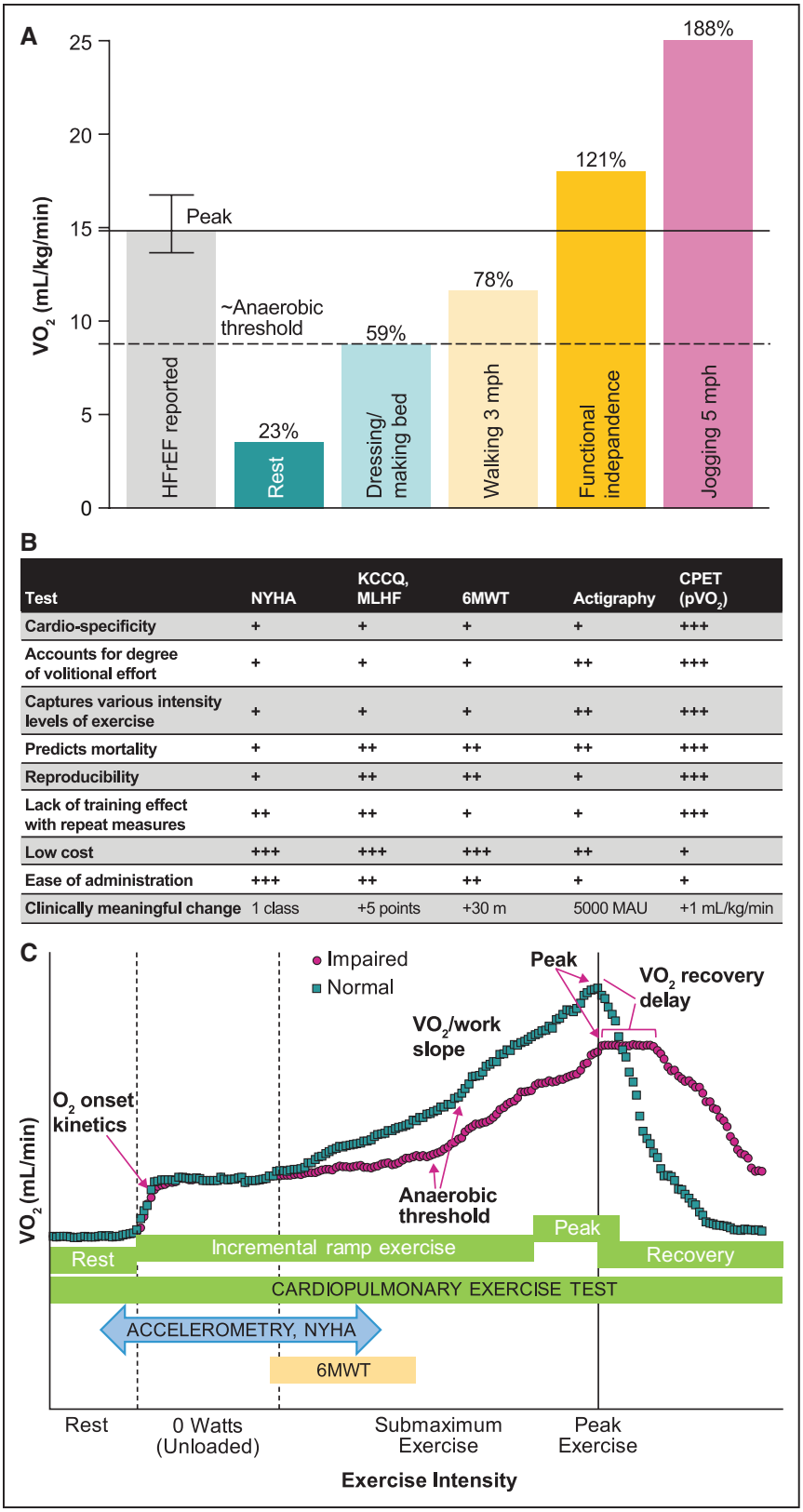
Clinical trials that have directly measured maximum exercise capacity (peak oxygen uptake [pVo_2]) in patients with symptomatic HFrEF have shown that the patients' average pVo_2 best approximates the metabolic costs of routine activities of daily living (Figure 1).[13] The degree of functional impairment in symptomatic patients with HFrEF frames the need to pursue therapies that even modestly improve exercise capacity (by 0.7–1.0 mL/kg per minute), which can significantly mitigate symptom burden and permit performance of routine activities of daily living.[14]

Comparison of Methods to Measure Exercise Capacity in HF Trials

Unlike focused assessments of outcomes such as mortality in HF clinical trials, metrics to assess functional capacity vary widely. Relative strengths, limitations, and complementarity of functional capacity assessments are summarized in Figure 1.

Self-Assessed and Physician-Reported Categorization

This approach relies on what the patient perceives as the limits of his/her daily activities. While NYHA classification is widely rooted in guidelines, clinical trial entry criteria, Food and Drug Administration labeling, and clinical decision-making, it lacks objectivity and has poor reproducibility.[15] Across 4 National Institutes of Health trials with multimodality assessments of functional capacity, NYHA class did not reliably predict clinical outcomes and poorly differentiated patients across HF severity with substantial (>50%) overlap in the 2 most common classes (II and III) compared with the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, 6-minute walk test (6MWT) distances, pVo_2, and measured exercise duration.[16]



Test	NYHA	KCCQ, MLHF	6MWT	Actigraphy	CPET (pVO_2)
Cardio-specificity	+	+	+	+	+++
Accounts for degree of volitional effort	+	+	+	++	+++
Captures various intensity levels of exercise	+	+	+	++	+++
Predicts mortality	+	++	++	++	+++
Reproducibility	+	++	++	+	+++
Lack of training effect with repeat measures	++	++	+	+	+++
Low cost	+++	+++	+++	++	+
Ease of administration	+++	++	++	+	+
Clinically meaningful change	1 class	+5 points	+30 m	5000 MAU	+1 mL/kg/min

Figure 1. Functional capacity assessments.
A, Oxygen uptake (Vo_2) required for activities of daily living relative to average Vo_2 observed in 42 heart failure with reduced ejection fraction (HFrEF) trials in which peak Vo_2 (pVo_2) was measured. **B**, Comparison between commonly used assessments of functional capacity in heart failure (HF) clinical trials. **C**, Relative exercise intensity levels associated with measures of functional capacity in patients with HF. 6MWT indicates 6-minute walk test; CPET, cardiopulmonary exercise testing; KCCQ, Kansas City Cardiomyopathy Questionnaire; MAU, mean accelerometer unit; MLHF, Minnesota Living With Heart Failure Questionnaire; and NYHA, New York Heart Association.

Health-related quality of life is defined as the overall effect and outcome of an illness and its treatment on an individual's physical, psychological, and social well-being, as perceived and reported by the patient. Of the 7 health-related quality-of-life instruments used in evaluation of patients with HF, the KCCQ[17,18] emerged as the highest rated overall instrument according to a standardized tool for evaluating patient-reported outcomes.[19] The KCCQ led other instruments in validity and sensitivity to change, with the Minnesota Living With Heart Failure Questionnaire[20]

and Chronic Heart Failure Questionnaire also performing relatively well compared with other HF-specific health-related quality-of-life assessment tools.[19] The KCCQ has a specific physical limitation section that aims to capture physical activity intensity and perceived level of difficulty.

Accelerometry

Accelerometer-derived daily physical activity has been shown to correlate with established measures of HF severity and performance metrics[21,22] and may serve to bridge the gap between discrete measures of functional capacity[23,24] and high-density assessments of daily activity levels. Additionally, accelerometer-derived daily physical activity data are continuous and independent of patient or clinician perception, interpretation, or recollection. Increased daily activity, as measured by accelerometer-derived daily physical activity, has been associated with improved outcomes in patients with and without heart disease[25–27] and has been shown to correlate with the efficacy of therapeutic interventions.[22,28,29] However, standardized approaches to accelerometer-derived daily physical activity (including device type, body placement site, monitoring duration, handling of missing data) are lacking as highlighted by a recent review of actigraphy use in HF clinical trials.[30] Furthermore, accelerometry devices represent a significant burden to some patients, while compliance with devices and troubleshooting device malfunction pose additional challenges to their routine incorporation into trials as metrics to assess the impact of a given therapy on functional capacity.

Six-Minute Walk Test

The 6MWT offers convenience and low cost as a simple test that does not require specialized equipment or advanced training, though standardized methodology should be followed.[31] Limitations of the 6MWT include the lack of information provided about the proportion of maximum volitional effort expended and training effects of repeated 6MWT performance in HF.[32] Moreover, cardiospecific information is lacking without electrocardiography, blood pressure, or imaging during exercise to permit assessment of cardiac and other organ-specific responses that can limit walk distance. There is a mild-to-moderate inverse correlation between 6MWT distance and NYHA, with similar averages of 400 m for NYHA I and II, reflecting a ceiling effect, compared with 320 and 225 m for NYHA III and IV, respectively.[33] Correlation between 6MWT and pVo_2 assessed during incremental ramp exercise across 16 HF studies was only moderate (r=0.59±0.13 [mean±SD]).[34]

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) permits measurement of pVo_2, the gold standard indicator of cardiorespiratory fitness.[12] Less well appreciated is the simultaneous ability to ascertain breath-by-breath gas exchange patterns that reflect O_2 onset kinetics upon exercise initiation, during low-level exercise (oxygen uptake/work slope), during submaximal exercise (ie, ventilatory anaerobic threshold), and during peak exercise and recovery. Integration of ventilation measurements provides complementary prognostic information.[9] Moreover, independent of metabolic cart measurements and their potential variability, exercise time and workload are readily available within standardized CPET protocols. CPET is associated with a higher cost than 6MWT or health-related quality of life, requires site expertise, staff distinct from study coordinators/principal investigators to conduct studies, and core laboratory oversight to ensure uniformity. However, the multiple mechanisms that contribute to exercise intolerance in HF support the premise of capturing comprehensive physiological responses to graded-intensity exercise with CPET to reliably assess exercise capacity as an outcome in clinical trials.

Cardiac and Extracardiac Contributions to Exercise Intolerance in HFrEF

Despite the prominence of exercise intolerance in HFrEF, sole attribution of exercise intolerance to the degree of LVSD should be avoided in clinical practice and in trial design. Unlike discrete events that abruptly compromise cardiac function and exercise capacity, such as ventricular tachycardia or myocardial infarction, chronic LVSD influences exercise tolerance through multiple mechanisms.[35–38] Anemia, iron deficiency, and pulmonary vascular adverse remodeling, thought to be related to chronic elevations in left-heart filling pressures, are prevalent in HFrEF.[39,40] These abnormalities compromise convective delivery of O_2 to exercising skeletal muscle. Upon delivery of O_2 to the periphery, diffusive O_2 conductance and utilization is limited by impaired capillary and mitochondrial function within skeletal muscle.[41] Histochemical changes in skeletal muscle in chronic HFrEF include a shift to type II glycolytic fibers that fatigue rapidly and a reduction in oxidative enzymes.[42] An early transition from oxidative to glycolytic metabolism, combined with glycolytic end products, in turn stimulates exaggerated ventilatory responses to exercise through intramuscle afferents sensitive to products of skeletal muscle work (eg, ergoreflex signaling).[43] The question of whether cardiospecific interventions can overcome the impairments at multiple levels of the O_2 cascade that arise in chronic HFrEF, and how quickly they can do so, merits careful consideration when developing and evaluating interventions aimed at improving functional capacity in HF.

Impact of Interventions on Exercise Capacity in Patients With HFrEF

To understand whether cardiospecific interventions can impact global metabolic reserve reflected in pVo_2, both device-based and pharmacological interventions merit

consideration. Cardiac resynchronization therapy (CRT) and cardiac contractility modulation are both cardiospecific and result in immediate improvement in left ventricular (LV) systolic function. Both interventions have improved NYHA functional class as well as objective measures of pVo_2 in the majority of studies to date, typically by ≈1.0 mL/kg per minute, which represents an improvement of ≈7% in average baseline pVo_2.

Pharmacotherapies are often mechanistically more nonspecific, with cardiac and extracardiac influences that can impact exercise capacity. HF pharmacotherapies approved by the Food and Drug Administration, including β-blockers, renin-angiotensin-aldosterone system blockade, and SGLT2i (sodium-glucose cotransporter 2 inhibitors), lack cardiospecificity. Hence, it is not surprising that the ability to more than double cardiac output commensurate with physiological needs of acute exercise exposure are not significantly altered by neurohormonal blockade. Among the current pillars of HFrEF pharmacotherapy (β-blockade, ACE [angiotensin-converting enzyme]/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor antagonist, SGLT2i), composite weighted average effect sizes on exercise ability compared with placebo are minimal (Figure 2). Despite potent effects on reverse LV remodeling, β-blockers are known to limit chronotropic responses and do not benefit exercise capacity.[4] As shown in Table S1, results are mixed for SGLT2i, with the 2 largest studies of empagliflozin showing no improvement in the 6MWT[44,45] and 1 smaller study indicating a marked improvement.[46] Evidence of exercise capacity benefits with ACE inhibitors and angiotensin receptor blockers is mixed,[47,48] and improvements observed with spironolactone are modest (Figure 2).[49,50]

Milrinone has both positive inotropic and vasodilatory properties and has been shown to improve exercise duration and pVo_2 by >15%; other positive inotropic agents have shown mixed success in improving exercise capacity (Figure 2; Table S1). One of the major reasons for the failure of these so-called calcitropes[51] in intermediate to long-term studies is increased myocardial oxygen consumption and subsequent cell injury, adverse cardiac remodeling, proarrhythmia, and increased mortality.[51–53]

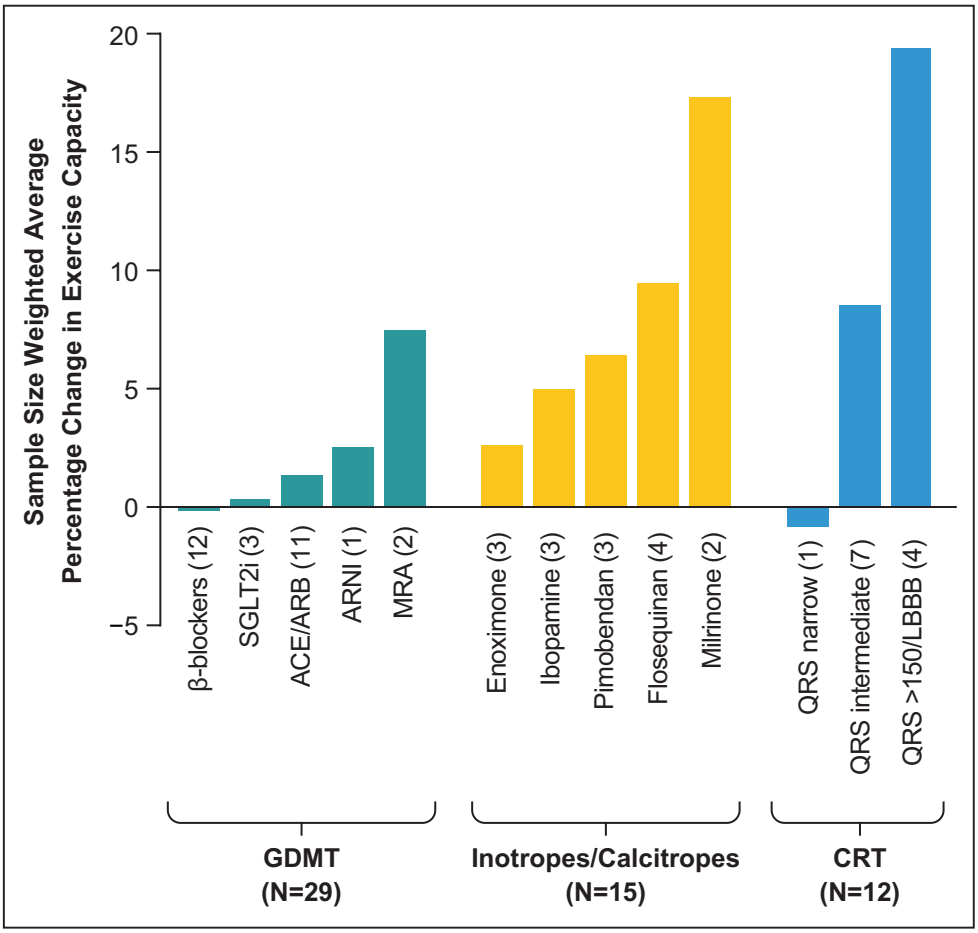


Figure 2. Sample size weighted average percentage change in exercise capacity relative to placebo in randomized placebo-controlled trials with exercise end points consisting of 6-minute walk test distance, exercise time, or peak oxygen uptake.
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; and SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Omecamtiv mecarbil is a selective cardiac myosin activator that increases cardiac contractility by specifically binding to myosin at an allosteric site that results in a greater number of cardiac myosin heads being primed for engagement with actin before onset of cardiac contraction.[5,7,54] The mechanism of action is unique, and preclinical studies have demonstrated that the increase in contractility is calcium-independent and not associated with alteration in oxygen demand.[7] Furthermore, in conjunction with increases in systolic ejection time and stroke volume, the COSMIC-HF study (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) in patients with chronic HFrEF demonstrated a reduction in LV chamber size and decreased plasma concentration of N-terminal pro-B-type natriuretic peptide.[7] In addition, omecamtiv mecarbil did not exacerbate exertional angina in patients with ischemic cardiomyopathy and angina despite reduction in diastolic time during exercise.[55] Recently, treatment with omecamtiv mecarbil has also been shown to lower the composite end point of HF events and cardiovascular mortality in the GALACTIC-HF study.[8]

METHODS

Study Design: METEORIC-HF

METEORIC-HF is a randomized, placebo-controlled, double-blind, multicenter study in participants with HFrEF. Patient selection criteria (Table 1) are intended to produce a cohort of patients with severe LVSD that serves as the predominant reason for exercise limitation (Figure 3). Patients must be symptomatic and functionally impaired despite receiving optimal guideline-directed medical therapy and have been clinically stable for at least 3 months before enrollment.

Approximately 270 eligible participants are to be randomized in a 2:1 ratio to receive either omecamtiv mecarbil or placebo, respectively. Each study site must be prequalified by the Massachusetts General Hospital CPET core laboratory; in addition, each patient must qualify for randomization based on evaluation of their CPET at the same core laboratory. Randomization is stratified based on the respiratory exchange ratio on the baseline CPET (1.05–1.15 and ≥1.15) and presence or absence of persistent atrial fibrillation at screening. The proportion of patients with persistent atrial fibrillation at screening is capped at 20%, and patients with paroxysmal atrial fibrillation are excluded. Investigational product is started at 25 mg orally twice a day, titrated based on predose plasma concentrations at week 2 and week 6 to doses of 25, 37.5, or 50 mg BID, and continued for a total of 20 weeks (Figure 4).

Investigational Product Dosage and Administration

As shown in Figure 4, omecamtiv mecarbil or placebo is administered orally twice a day (≈12±3 hours apart) in the morning and evening and can be taken under fasted or fed conditions. Participants randomized to omecamtiv mecarbil initiate administration at 25 mg twice a day. Blood samples from all participants are collected at study visits on weeks 2, 6, 14, and 20 to determine the predose omecamtiv mecarbil plasma concentration. The results are blinded to investigators, the study sponsor (Cytokinetics Inc), and study participants. In an identical fashion to that used in the GALACTIC-HF study, a pharmacokinetic-directed dose adjustment algorithm is implemented to target a plasma drug concentration of ≥300 to <1000 ng/mL based on week 2 and week 6 predose omecamtiv mecarbil plasma concentration, with participants continuing on the adjusted

Table 1. Entry Criteria

Inclusion criteria
Male or female, ≥18 to ≤85 y of age at signing of the informed consent
History of chronic HF, defined as requiring continuous treatment with medications for HF for a minimum of 3 mo before screening
NYHA class II or III at screening
LVEF ≤35% per participant's most recent medical record or an echocardiogram at screening
The qualifying LVEF must be the most recent assessment of LVEF in the chronic, stable setting and must be within 12 mo before screening
On maximally tolerated SoC HF therapies consistent with regional clinical practice guidelines, if not contraindicated and according to investigator judgment of the participant's clinical status; β-blocker dose must be stable for 30 d before randomization
NT-proBNP level ≥200 pg/mL at screening assessment by the central laboratory
pVo_2 ≤75% of the predicted normal value with RER ≥1.05 on the screening (week −2) CPET, confirmed by CPET core laboratory
Exclusion criteria (designed to limit the impact of comorbidities on the primary end point)
Major medical event or procedure within 3 mo before randomization, including hospitalization, surgery, renal replacement therapy, or cardiac procedure
This includes episodes of decompensated HF that require IV HF treatment
Minor hospitalizations or procedures that are not expected to impact the safety of the participant or the integrity of the study results, per investigator, are allowed
Resting systolic BP >140 or <85 mm Hg or diastolic BP >90 mm Hg (mean of triplicate readings) at screening
Resting HR >90 or <50 bpm (mean of triplicate readings) at screening
Room air oxygen saturation <90% at screening
Hemoglobin <10.0 g/dL at screening
eGFR <30 mL/min per 1.73 m^2 (by the modified Modification of Diet in Renal Disease equation) at screening
Hepatic impairment defined by a total bilirubin ≥2×ULN or alanine aminotransferase or aspartate aminotransferase ≥3×ULN at screening
Severe uncorrected valvular heart disease
Paroxysmal atrial fibrillation or flutter requiring treatment documented within the 6 mo before randomization
Participants with persistent atrial fibrillation and no sinus rhythm documented in the previous 6 mo are permitted
Untreated severe ventricular arrhythmias
Symptomatic bradycardia, second-degree Mobitz type II, or third-degree heart block without a pacemaker
Recipient of a major organ transplant (eg, heart, lung, liver, bone marrow, renal) or ventricular assist device or anticipated transplantation or chronic mechanical circulatory support within 12 mo from randomization

BP indicates blood pressure; bpm, beats per minute; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; IV, intravenous; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVo_2, peak oxygen uptake; RER, respiratory exchange ratio; SoC, standard of care; and ULN, upper limit of normal.

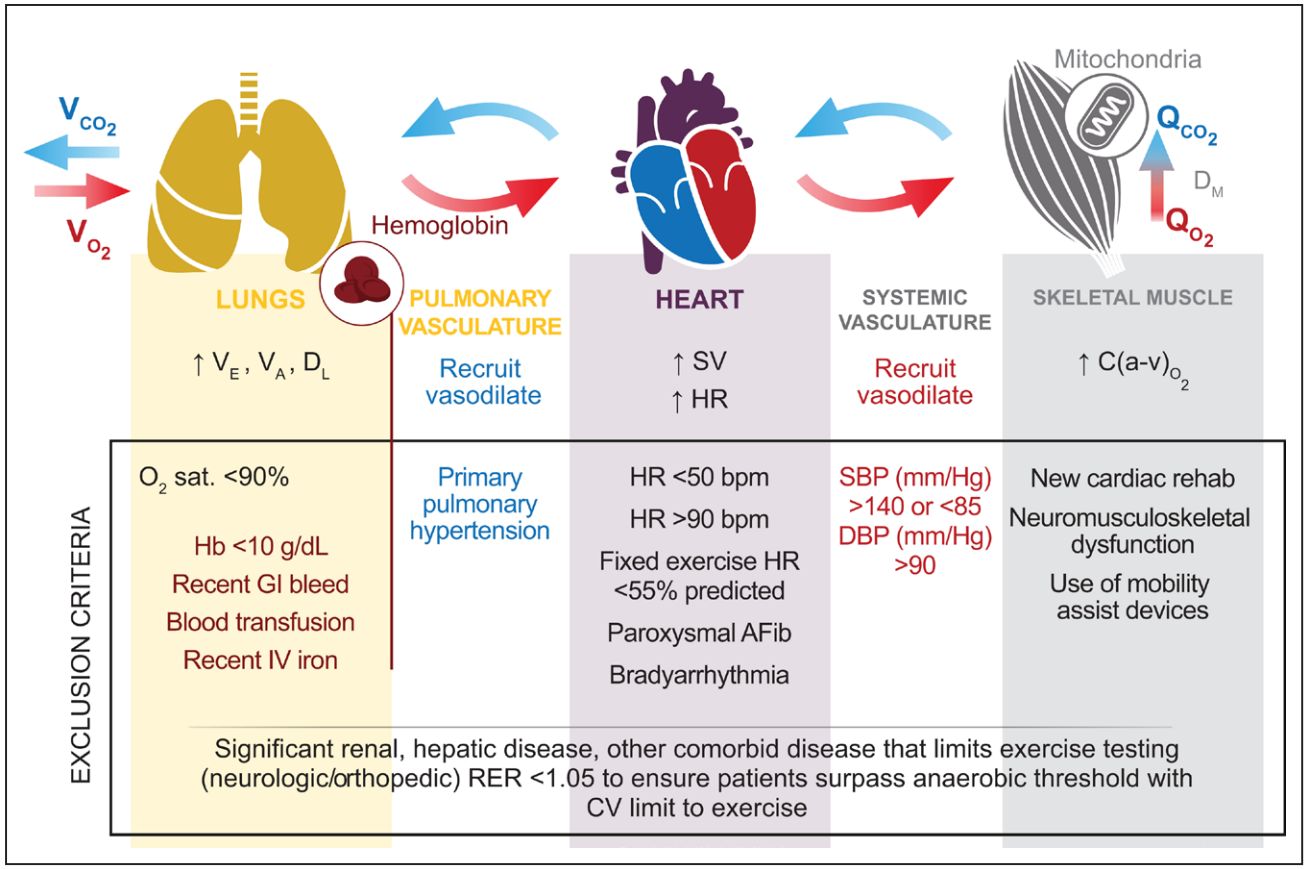


Figure 3. Oxygen uptake cascade that is activated by initiation of exercise.
METEORIC-HF trial (Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure) exclusion criteria were selected to minimize the influence of extracardiac comorbid conditions on exercise capacity and to isolate left ventricular systolic dysfunction that is being targeted by omecamtiv mecarbil. AFib indicates atrial fibrillation; bpm, beats per minute; $C(a\text{-}v)_{O2}$, arterial-venous O_2 content difference; CV, cardiovascular; DBP, diastolic blood pressure; D_L, lung diffusion; D_M, muscle diffusion; GI, gastrointestinal; hb, hemoglobin; HR, heart rate; IV, intravenous; Q_{CO2}, metabolic quotient; Q_{O2}, oxygen consumption rate; RER, respiratory exchange ratio; sat., saturation; SBP, systolic blood pressure; SV, stroke volume; V_A, alveolar volume; V_{CO2}, rate of elimination of CO_2; V_E, expiratory volume; and Vo_2, rate of elimination of O_2.

omecamtiv mecarbil dose for the remainder of the study. Participants with plasma concentration ≥1000 ng/mL at any point after the titration stage will have drug discontinued.[56]

Study Duration for Participants

After signing the informed consent, participants are randomized within 6 weeks for an on-study drug period of ≈20 (±4) weeks and safety follow-up of 4 weeks. The entire duration of the study is 26 to 30 weeks (Figure 4).

All participants are followed according to the Schedule of Assessments, from randomization through the date of their final visit, irrespective of whether the participant is continuing to receive study treatment, unless the participant has discontinued prematurely from the study or withdrawn consent.

Study End Points

The primary end point is change from baseline in pVo_2, measured by CPET, for omecamtiv mecarbil compared with placebo groups. CPET offers a wealth of information beyond pVo_2 that will be captured in secondary end points (Table 2); these include indicators of cardiac performance during exercise (ie, cardiac power, ventilatory efficiency), indicators of cardiorespiratory fitness that are independent of volitional effort (oxygen uptake efficiency slope, ventilatory anaerobic threshold), as well as recovery O_2 kinetic patterns post-exercise.[9] Actigraphy measurements, KCCQ scores, and workload achieved during exercise will complement CPET measures for assessment of functional capacity.

Statistical Considerations

Sample size was calculated assuming a difference in change from baseline in pVo_2 of 1.0 mL/kg per minute for omecamtiv mecarbil compared with placebo (which is clinically meaningful in the setting of depressed Vo_2 [Figure 1A]),[10] an SD of 2.5 mL/kg per minute in participants receiving omecamtiv mecarbil, and 2.0 mL/kg per minute in participants receiving placebo. Assuming 15% of participants missing change from baseline data for the primary end point, a sample size of 270 participants (≈180 randomized to omecamtiv mecarbil and 90 randomized to placebo) provides 90% power to detect the difference in pVo_2 change from baseline to week 20, with a 2-sided type I error of 0.05.

Unless specified otherwise, efficacy analyses will be performed on the full analysis set, which includes all randomized participants who receive at least 1 dose of randomized study medication, by randomized treatment group. The primary analysis is to test the null hypothesis that there is no treatment

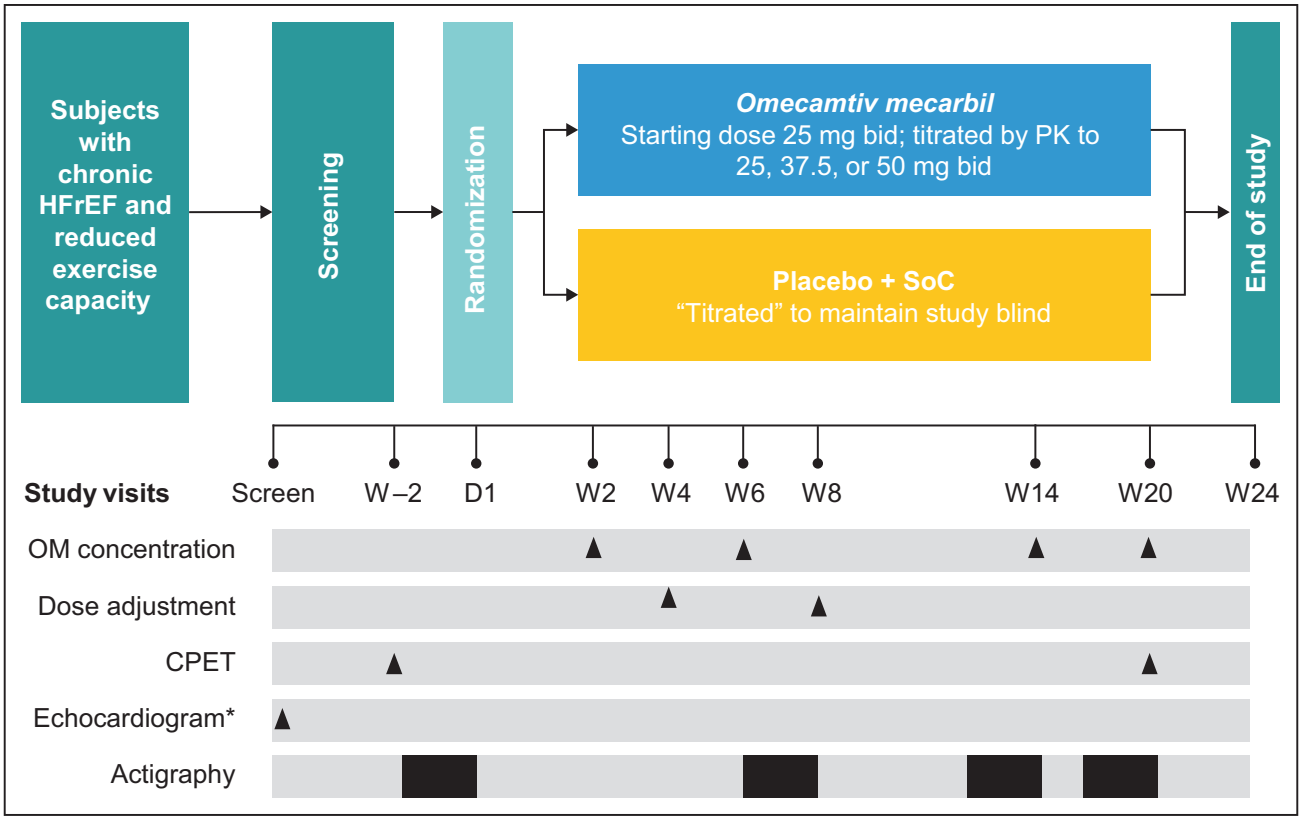


Figure 4. METEORIC-HF study (Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure) overview.
After an initial screening period of up to 2 weeks, eligible participants are randomized to omecamtiv mecarbil (OM) with pharmacokinetic (PK)-guided levels or placebo titrated to maintain the study blinding. Cardiopulmonary exercise test (CPET) occurs before randomization and then at week 20. D indicates day; HFrEF, heart failure with reduced ejection fraction; SoC, standard of care; and W, week. *The echocardiogram refers to the most recent assessment in the chronic, stable setting and was required to be within 12 months before screening.

difference in the change in pVo_2 from baseline at week 20 between participants randomized to placebo and those randomized to omecamtiv mecarbil in the full analysis set during the placebo-controlled double-blind treatment. The analysis will be performed using an ANCOVA model that will include terms of treatment, baseline pVo_2, respiratory exchange ratio randomization stratum (<1.15 and ≥1.15), persistent atrial fibrillation (Y/N), age, sex, and baseline hemoglobin level. Missing pVo_2 at week 20 regardless of the type of intercurrent event will be imputed using multiple imputation methodology under the missing at random assumption for the primary analysis. Sensitivity analyses of the primary analysis will be performed by excluding week 20 CPET scores for participants who are infected with COVID-19 or have a major protocol deviation due

Table 2. End Points

End point	Description
Primary	Change in pVo_2 on CPET from baseline to week 20
Secondary	Change in total workload during CPET from baseline to week 20
	Change in V_E/V_{CO2} slope during CPET from baseline to week 20
	Change in the average daily activity units measured over a 2-week period from baseline (week −2 to day 1) to weeks 18–20
Exploratory	Change from baseline to week 20 in Vo_2/logVE slope, ventilatory threshold (by the V-slope method), Vo_2 recovery kinetics, pVo_2 predicted percentage, circulatory power (Vo_2×systolic BP), and exercise duration
	Change from baseline in the average daily activity units at weeks 6–8 and at weeks 12–14
	Change from baseline in the KCCQ Total Symptom Score and its subdomains from baseline to week 20
Safety	Incidence of reported adverse events and serious adverse events
	Major adverse CV events will be adjudicated by a CEC, including all-cause death, CV death, major cardiac ischemic events (myocardial infarction, hospitalization for unstable angina, percutaneous coronary intervention, and coronary artery bypass graft), HF events, and stroke

BP indicates blood pressure; CEC, Clinical End Points Committee; CPET, cardiopulmonary exercise testing; CV, cardiovascular; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; pVo_2, peak oxygen uptake; V_{CO2}, rate of elimination of CO_2; VE, ventilatory efficiency; and Vo_2, oxygen uptake.

to COVID-19 per the mitigation strategy described in the next section. The safety analyses will be performed on the safety analysis set, which includes all dosed participants. Additional sensitivity analyses will be performed to take into account the potential impact of COVID-19 and prolonged exposure to the investigational product.

Impact of COVID-19 Pandemic and Mitigation Strategy

Like almost all contemporary cardiovascular clinical trials, the ongoing conduct of the METEORIC-HF study was significantly impacted by the COVID-19 pandemic. The challenges of cardiovascular clinical trials during COVID-19 have been discussed in detail elsewhere.[57,58] The nature of the METEORIC-HF trial, in particular, the primary end point of change in pVo_2 from baseline to 20 weeks using CPET, created unique challenges requiring specific mitigation strategies. First, the CPET requires specialized equipment and expertise, and data cannot be collected remotely without direct face-to-face interaction with the research participant. These challenges are in contrast to event-driven trials, for which procedures to collect primary event data (such as deaths or hospitalizations) could be done remotely by investigators or through centralized call centers. Second, the requirement for follow-up CPET at 20 weeks (±7 days) from baseline created an imperative not only for testing at a specific location but also within a specific time window. Given that research sites in some locations were temporarily unable to conduct in-person research activities during the COVID-19 pandemic, this created significant issues with potential protocol deviations for out-of-window evaluations. Furthermore, the nature of conducting CPET with requisite high-volume unobstructed air expulsion into indoor testing facilities led to further challenges in CPET-based research protocols due to concerns for airborne spread of COVID-19. These challenges required specific mitigation strategies and adaptions to maintain study integrity, which are described in the following sections.

Specific Mitigation Strategies for COVID in METEORIC-HF

Protocol Adjustments

The METEORIC-HF protocol specified 9 in-person visits (including a screening visit) over the 24 weeks of study follow-up. Given the challenges with in-person follow-up at many sites during the pandemic, a number of these were allowed to be done virtually as remote televisits (at weeks 4, 8, and 24) or removed from the protocol altogether (week 14), and direct shipment of investigational product to patients was implemented. Temporary suspension of enrollment was implemented at sites unable to conduct any in-person research activities due to COVID-19 restrictions.

Steps Taken to Maximize CPET-Based Primary End Point Data Acquisition

Regular communication with participating CPET laboratories was implemented to understand operational modifications during COVID-19 and share information about phone-based screening for symptoms of active COVID-19, sanitation practices, extended time between tests, and use of air filters.[59] Due to the obvious importance of minimizing missing data for the primary CPET end point, we implemented an extended window for the week 20 follow-up CPET, from ±7 days to up to 90 days beyond the week 20 time point. While recognizing that this prolonged time window between baseline and follow-up could introduce other sources of variability (eg, participants could develop noncardiovascular issues that could interfere with or limit CPET), we opted for maximizing timing flexibility to minimize missing data. Study participants who needed an extended time window for follow-up CPET continued on blinded investigational product until follow-up testing was completed.

DISCUSSION

The METEORIC-HF trial is an international, multicenter, randomized, double-blind, placebo-controlled trial designed to test the hypothesis that omecamtiv mecarbil can improve exercise capacity and quality of life in patients with HFrEF. The study rationale is based on preclinical and clinical trial data demonstrating the ability of omecamtiv mecarbil to safely enhance cardiac contractility.

Omecamtiv mecarbil serves as an ideal physiological probe to test the effects of an intervention that safely improves cardiac function on exercise capacity. Device therapies that are cardiospecific and deployed in appropriate patient populations (Figure 2) provide proof of principle that exercise capacity can be augmented commensurate with improvement in other metrics of cardiovascular performance.[60,61]

As shown in Figure 2, the heterogeneity in pVo_2 responsiveness to CRT is partially due to the fact that appropriate patient selection for CRT was still being defined when these studies were conducted. For example, there was no change in pVo_2 (−0.1 mL/kg per minute, −1%) in patients with normal QRS duration studied in the RethinQ trial, intermediate changes in the sample size weighted average effect size in studies that selected patients on the basis of QRS prolongation >120 ms (+9%) independent of bundle branch block type, and the greatest average increment in pVo_2 (+19%) in studies that only included patients with left bundle branch block and QRS >150 ms, directly mirroring what is now known about optimal CRT responsiveness and patient selection for CRT.

For cardiac contractility modulation, immediate improvements in +dP/dt and stroke volume are evident with variable influence on LV ejection fraction (up to 17% with a fall in systolic volume by 12% in 1 trial[62]), with a meta-analysis of studies of pVo_2 showing average improvement in pVo_2 of 0.71 mL/kg per minute (≈5%).[63] Correction of cardiac output deficit during exercise may only translate to partial improvement in Vo_2 deficits when other components of the O_2 cascade are impaired and there is less transit time for O_2 uptake and extraction.[64] Although it stands to reason that correction of abnormal cardiac function would eventually lead to reversal of

abnormalities arising secondary to LVSD (which has been the case with a 24-month CRT study in which pVo_2 percentage change was similar to the percentage change in LV ejection fraction[60]), the plasticity of physiological and anatomic changes is variable. These considerations do not reduce the merit of targeting improvement in impaired overall functional capacity in HF with novel therapies but do provide a context in which to interpret trial results.

In contrast to device therapies for HF, current Food and Drug Administration–approved drug therapies for HF have more wide-ranging physiological effects that are not cardiospecific, and their impact on functional capacity tends to be minimal (Figure 2). For a pharmacotherapy to augment exercise capacity, it must augment stroke volume, heart rate, or peripheral O_2 utilization during exercise. Importantly, the magnitude of Vo_2 augmentation during moderate-to-vigorous exercise is typically more than 4-fold, reflecting acute adaptation to a distinct physiological state. Hence, it should not be assumed that a drug that confers chronic cardioprotection or favorably influences HF prognosis will necessarily permit greater exercise capacity. Use of ACE inhibitors and angiotensin receptor blockers is associated with lower hemoglobin levels[65] and lower LV end-diastolic volume, which can negatively impact convective O_2 delivery during exercise. Heart rate lowering at rest and during exercise with β-blockade is a clear example in which chronic cardioprotective effects do not align with promoting higher aerobic capacity. Furthermore, if a drug helps to prevent sudden cardiac death, in part, via counteracting potassium losses from loop diuretic use (ie, spironolactone), it would be expected to improve clinical event rates without necessarily improving cardiac performance during physical activity.

The effect on exercise capacity following correction of iron deficiency with ferric carboxymaltose was compared with standard of care in EFFECT-HF (Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Iron Deficiency and Chronic Heart Failure)—a prospective, randomized controlled trial enrolling 172 patients with HF.[66] Although correction of iron deficiency had a favorable effect on pVo_2, this effect was highly sensitive to the imputation strategy for pVo_2 among patients who died, further showing the challenges of demonstrating a favorable effect on exercise capacity in patients with HF. When considering further polypharmacy among symptomatic HF patients with exercise intolerance, there is an unmet need not only to understand safety and effects on clinical event rates but also to determine whether novel therapies will improve exercise tolerance. This will become increasingly important as more drugs are shown to improve hospitalization and mortality outcomes, particularly if their use comes at a high cost and a shared price for limited blood pressure, for example.

Finally, whether improved cardiac performance promotes mitigation of, or permits compensation for, other abnormalities that may arise secondarily due to HF highlights the importance of accounting for each component of the O_2 cascade in designing HF trials with functional capacity end points (Figure 3).

Clinical Trial Design to Detect Benefits in Exercise Performance

Technical variance in repeated measures is important to consider in trials investigating the impact of therapeutic interventions on exercise capacity. An HF trial that measured both 6MWT and pVo_2 in the same individuals showed SDs for repeated measures in the placebo arm for 6MWT versus pVo_2 of 2.6-fold versus 1.6-fold the minimal clinically important difference of 10%,[67] respectively, which translates to higher requisite sample sizes for trials assessing 6MWT versus pVo_2. However, unlike trials powered to detect differences in mortality or cardiovascular hospitalizations, HF trials assessing functional end points to date vary widely in sample size (n=14–950; Table S1). Notably, <30% of placebo-controlled trials of interventions summarized in Table S1 had adequate sample size. Such studies are predisposed to type II error in attempting to draw conclusions about how interventions impact functional capacity.

Accounting for extracardiac contributions to functional capacity will also influence the degree to which improving cardiac performance during exercise translates to improved functional capacity, as will accounting for physical activity level, which is critically important for generating improvements in exercise capacity. Therefore, the METEORIC-HF trial is designed to minimize the influence of predominant extracardiac limitations and to permit assessment of exercise capacity dictated by cardiac performance. To this end, METEORIC-HF excludes fixed low HR that is anticipated to remain adynamic and also excludes patients with marked anemia, severe lung disease, and primary orthopedic limitations (Figure 3). In addition, the trial accounts for other conditions, such as iron deficiency and activity exposure, and objectively measures exercise intolerance at different intensity levels through high-density home-based measures (actigraphy) and gold standard assessments of cardiorespiratory fitness (CPET; Figure 1).

GALACTIC-HF: Results and Implications for METEORIC-HF

During the conduct of the METEORIC-HF trial, the results of the GALACTIC-HF trial were published.[8] Briefly, GALACTIC-HF compared omecamtiv mecarbil to placebo in a broad population of 8256 patients with symptomatic HF (NYHA classes II–IV) and ejection fraction ≤35%. The primary outcome event of time to first HF event or cardiovascular death was less common in the omecamtiv mecarbil group compared with the placebo

group (hazard ratio, 0.92 [95% CI, 0.86–0.99]; *P*=0.03). Subgroup analyses demonstrated significant heterogeneity by ejection fraction (lower ejection fraction having greater benefit)[68] and atrial fibrillation (patients without atrial fibrillation having greater benefit than those with atrial fibrillation who were treated with digoxin). The entry criteria for GALACTIC-HF were less stringent than those for METEORIC-HF with regard to ensuring cardiospecific limitations to functional capacity (Figure 3) such that symptoms and hospitalizations may have been influenced by other comorbidities. The results from GALACTIC-HF only increase the importance of the METEORIC-HF trial to further define the net clinical benefits of omecamtiv mecarbil in the population of patients with symptomatic HFrEF in whom improving functional capacity represents an unmet clinical need despite optimal guideline-directed medical therapy.

Additional Limitations/Challenges

Anticipated findings will be limited to participants with HFrEF who meet entry criteria and will not be generalizable to those with comorbidities that compete with predominantly cardiac limitations to exercise. Ensuring comorbidities do not predominate in limiting functional capacity and insisting on minimal peak respiratory exchange ratio levels at baseline does not preclude comorbidities becoming predominant at week 20 or submaximal effort with week 20 testing. Despite mitigation efforts, unforeseen impacts of COVID-19 are possible.

Conclusions

In conclusion, HFrEF is associated with marked limitations in functional capacity that are not substantially improved by current guideline-directed medical therapy. The design, implementation, and analysis of METEORIC-HF will determine the impact of augmenting cardiac contractility with omecamtiv mecarbil on multiple measures of functional capacity in HFrEF.

ARTICLE INFORMATION

Affiliations

Division of Cardiology, Massachusetts General Hospital, Boston (G.D.L.). BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland (K.F.D.). Department of Cardiology, University Medical Center Groningen, the Netherlands (A.A.V.). Paris University, UMR-S 942, Department of Cardiology, Lariboisiere Hospital, Assistance Publique Hopitaux de Paris, France (A.C.-S.). Cardiology, ASST Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Italy (M.M.). Department of Medicine, Sidney Kimmel Medical College, Thomas Jefferson University Hospital, Philadelphia, PA (D.J.W.). Department of Medicine, University of Alberta, Canada (J.A.E.). Department of Heart Diseases, Wrocław Medical University, Poland (P.P.). Departments of Internal Medicine (M.B.) and Cardiology (M.B.), Saarland University, Homburg, Germany. Section of Cardiology, San Francisco Veterans Affairs Medical Center and University of California San Francisco (J.R.T.). Cytokinetics Inc, South San Francisco, CA (S.B.H., S.K., F.I.M., L.M.). Division of Cardiology, School of Medicine, Duke University Medical Center, Durham, NC (G.M.F.).

Acknowledgments

The authors thank patients participating in METEORIC-HF (Multicenter Exercise Tolerance Evaluation of Omecamtiv Mecarbil Related to Increased Contractility in Heart Failure), as well as the study staff at enrolling sites.

Sources of Funding

This study was funded by Amgen and Cytokinetics Inc.

Disclosures

Dr Lewis reports research funding from the National Institutes of Health (NIH) R01-HL 151841, R01-HL131029, and R01-HL159514, American Heart Association (AHA) 15GPSGC-24800006, and Amgen, Cytokinetics, Applied Therapeutics, AstraZeneca, and SoniVie. He has received honoraria for advisory boards outside of the current study from Pfizer, Merck, Boehringer Ingelheim, Novartis, American Regent, Cyclerion, Cytokinetics, and Amgen and receives royalties from UpToDate for scientific content authorship related to exercise physiology. Dr Docherty reports receiving honoraria from AstraZeneca and a research grant to his institution from Boehringer Ingelheim. Dr Voors reports receiving research support or has been a consultant for Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Cytokinetics, Merck, MyoKardia, Novo Nordisk, Novartis, and Roche Diagnostics. Dr Cohen-Solal reports receiving fees or honoraria from Amgen, Vifor Pharma, Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Impulse Dynamics, Novartis, CVRx, Leo, Sanofi, We-Heath, and Merck. Dr Metra reports receiving honoraria from AstraZeneca, Abbott Vascular, Amgen, and Edwards Therapeutics and personal fees for presentations or participation on a Data Safety Monitoring Board or Advisory Board for Actelion, Amgen, Servier, Livanova, Vifor Pharma, and Windtree Therapeutics. Dr Whellan reports receiving research grants to his institution from Novo Nordisk and consulting fees or honoraria from CVRx, Cytokinetics, and Novo Nordisk. Dr Ezekowitz reports receiving research grants or honoraria from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Cytokinetics, Merck, Novartis, Sanofi, and Servier and has equity in US2.ai. Dr Ponikowski reports receiving research grants to his institution from Amgen and Vifor Pharma and consulting fees or honoraria from Abbott Vascular, AstraZeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Cibiem, Coridea, Impulse Dynamics, Novartis, Pfizer, Renal Guard Solutions, Servier, and Vifor Pharma. Dr Böhm reports receiving funds from the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, ReCor, Servier, and Vifor Pharma. Dr Teerlink reports receiving research contract and consulting fees from Amgen and Cytokinetics; grants or contracts from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Medtronic, Novartis, and Windtree Therapeutics; consulting fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Medtronic, Novartis, Verily, and Windtree Therapeutics; and leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid for the Heart Failure Society of America as a Secretary, Treasurer, and President-Elect. Drs Heitner, Kupfer, Malik, and Meng report employment and stock options from Cytokinetics. Dr Felker reports receiving consulting or research grants from Amgen and Cytokinetics; grants or contracts from NIH, AHA, Novartis, Bayer, Bristol Myers Squibb, and Merck; consulting fees from Novartis, Bristol Myers Squibb, Medtronic, AstraZeneca, Abbott, Reprieve, and Sequana; and participated on a Data Safety Monitoring Board or Advisory Board for Amgen, Merck, Medtronic, EBR Systems, V-Wave, LivaNova, Siemens, and Rocket Pharma.

Supplemental Material

Table S1
References 69–111

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1789–1858. doi: 10.1016/S0140-6736(18)32279-7.
2. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J*. 2013;34:1424–1431. doi: 10.1093/eurheartj/eht066
3. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; Get With the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction:

prevalence, therapies, and outcomes. *Circulation*. 2012;126:65–75. doi: 10.1161/CIRCULATIONAHA.111.080770
4. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94:2807–2816. doi: 10.1161/01.cir.94.11.2807
5. Malik FI, Hartman JJ, Elias KA, Morgan BP, Rodriguez H, Brejc K, Anderson RL, Sueoka SH, Lee KH, Finer JT, et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science*. 2011;331:1439–1443. doi: 10.1126/science.1200113
6. Cleland JG, Teerlink JR, Senior R, Nifontov EM, Mc Murray JJ, Lang CC, Tsyrlin VA, Greenberg BH, Mayet J, Francis DP, et al. The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. *Lancet*. 2011;378:676–683. doi: 10.1016/S0140-6736(11)61126-4
7. Teerlink JR, Felker GM, McMurray JJ, Solomon SD, Adams KF Jr, Cleland JG, Ezekowitz JA, Goudev A, Macdonald P, Metra M, et al; COSMIC-HF Investigators. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. *Lancet*. 2016;388:2895–2903. doi: 10.1016/S0140-6736(16)32049-9
8. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Adams KF, Anand I, Arias-Mendoza A, Biering-Sørensen T, et al; GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med*. 2021;384:105–116. doi: 10.1056/NEJMoa2025797
9. Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. *JACC Heart Fail*. 2016;4:607–616. doi: 10.1016/j.jchf.2016.03.022
10. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, Wolfel G, Handberg EM, Bensimhon D, Illiou MC, et al; HF-ACTION Investigators. Modest increase in peak VO_2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail*. 2012;5:579–585. doi: 10.1161/CIRCHEARTFAILURE.111.965186
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136:e137–e161. doi: 10.1161/CIR.0000000000000509
12. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, et al; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:191–225. doi: 10.1161/CIR.0b013e3181e52e69
13. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39:1423–1434. doi: 10.1249/mss.0b013e3180616b27
14. Haykowsky MJ, Daniel KM, Bhella PS, Sarma S, Kitzman DW. Heart failure: exercise-based cardiac rehabilitation: who, when, and how intense? *Can J Cardiol*. 2016;32(10 Suppl 2):S382–S387. doi: 10.1016/j.cjca.2016.06.001
15. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, Mayet J, Francis DP. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. *Heart*. 2007;93:476–482. doi: 10.1136/hrt.2006.089656
16. Caraballo C, Desai NR, Mulder H, Alhanti B, Wilson FP, Fiuzat M, Felker GM, Piña IL, O'Connor CM, Lindenfeld J, et al. Clinical Implications of the New York Heart Association Classification. *J Am Heart Assoc*. 2019;8:e014240. doi: 10.1161/JAHA.119.014240
17. Kosiborod M, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, Spertus JA. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation*. 2007;115:1975–1981. doi: 10.1161/CIRCULATIONAHA.106.670901
18. Soto GE, Jones P, Weintraub WS, Krumholz HM, Spertus JA. Prognostic value of health status in patients with heart failure after acute myocardial infarction. *Circulation*. 2004;110:546–551. doi: 10.1161/01.CIR.0000136991.85540.A9
19. Garin O, Herdman M, Vilagut G, Ferrer M, Ribera A, Rajmil L, Valderas JM, Guillemin F, Revicki D, Alonso J. Assessing health-related quality of life in patients with heart failure: a systematic, standardized comparison of available measures. *Heart Fail Rev*. 2014;19:359–367. doi: 10.1007/s10741-013-9394-7
20. Kato N, Kinugawa K, Seki S, Shiga T, Hatano M, Yao A, Hirata Y, Kazuma K, Nagai R. Quality of life as an independent predictor for cardiac events and death in patients with heart failure. *Circ J*. 2011;75:1661–1669. doi: 10.1253/circj.cj-10-1308
21. Jehn M, Schmidt-Trucksäess A, Schuster T, Hanssen H, Weis M, Halle M, Koehler F. Accelerometer-based quantification of 6-minute walk test performance in patients with chronic heart failure: applicability in telemedicine. *J Card Fail*. 2009;15:334–340. doi: 10.1016/j.cardfail.2008.11.011
22. Snipelisky D, Kelly J, Levine JA, Koepp GA, Anstrom KJ, McNulty SE, Zakeri R, Felker GM, Hernandez AF, Braunwald E, et al. Accelerometer-Measured Daily Activity in Heart Failure With Preserved Ejection Fraction: Clinical Correlates and Association With Standard Heart Failure Severity Indices. *Circ Heart Fail*. 2017;10:e003878. doi: 10.1161/CIRCHEARTFAILURE.117.003878
23. Jehn M, Schmidt-Trucksäss A, Hanssen H, Schuster T, Halle M, Koehler F. Association of physical activity and prognostic parameters in elderly patients with heart failure. *J Aging Phys Act*. 2011;19:1–15. doi: 10.1123/japa.19.1.1
24. Kadhiresan VA, Pastore J, Auricchio A, Sack S, Doelger A, Girouard S, Spinelli JC; PATH-CHF Study Group. Pacing therapies in congestive heart failure. A novel method–the activity log index–for monitoring physical activity of patients with heart failure. *Am J Cardiol*. 2002;89:1435–1437. doi: 10.1016/s0002-9149(02)02364-0
25. Conraads VM, Spruit MA, Braunschweig F, Cowie MR, Tavazzi L, Borggrefe M, Hill MR, Jacobs S, Gerritse B, van Veldhuisen DJ. Physical activity measured with implanted devices predicts patient outcome in chronic heart failure. *Circ Heart Fail*. 2014;7:279–287. doi: 10.1161/CIRCHEARTFAILURE.113.000883
26. Fishman EI, Steeves JA, Zipunnikov V, Koster A, Berrigan D, Harris TA, Murphy R. Association between objectively measured physical activity and mortality in NHANES. *Med Sci Sports Exerc*. 2016;48:1303–1311. doi: 10.1249/MSS.0000000000000885
27. Tyagi S, Curley M, Berger M, Fox J, Strath SJ, Rubenstein J, Roth J, Widlansky ME. Pacemaker quantified physical activity predicts all-cause mortality. *J Am Coll Cardiol*. 2015;66:754–755. doi: 10.1016/j.jacc.2015.06.005
28. Gilliam FR 3rd, Kaplan AJ, Black J, Chase KJ, Mullin CM. Changes in heart rate variability, quality of life, and activity in cardiac resynchronization therapy patients: results of the HF-HRV registry. *Pacing Clin Electrophysiol*. 2007;30:56–64. doi: 10.1111/j.1540-8159.2007.00582.x
29. Kawabata M, Fantoni C, Regoli F, Raffa S, Pastori F, Fratini S, Prentice J, Klein HU, Auricchio A. Activity monitoring in heart failure patients with cardiac resynchronization therapy. *Circ J*. 2007;71:1885–1892. doi: 10.1253/circj.71.1885
30. Anchouche K, Elharram M, Oulousian E, Razaghizad A, Avram R, Marquis-Gravel G, Randhawa VK, Nkulikiyinka R, Ni W, Fiuzat M, et al. Use of actigraphy (wearable digital sensors to monitor activity) in heart failure randomized clinical trials: a scoping review. *Can J Cardiol*. 2021;37:1438–1449. doi: 10.1016/j.cjca.2021.07.001
31. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1428–1446. doi: 10.1183/09031936.00150314
32. Keteyian SJ, Brawner CA, Ehrman JK, Ivanhoe R, Boehmer JP, Abraham WT; PEERLESS-HF Trial Investigators. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise parameters: implications for clinical trials and clinical practice. *Chest*. 2010;138:950–955. doi: 10.1378/chest.09-2624
33. Yap J, Lim FY, Gao F, Teo LL, Lam CS, Yeo KK. Correlation of the New York Heart Association Classification and the 6-minute walk distance: a systematic review. *Clin Cardiol*. 2015;38:621–628. doi: 10.1002/clc.22468
34. Giannitsi S, Bougiakli M, Bechlioulis A, Kotsia A, Michalis LK, Naka KK. 6-minute walking test: a useful tool in the management of heart failure patients. *Ther Adv Cardiovasc Dis*. 2019;13:1753944719870084. doi: 10.1177/1753944719870084
35. Malhotra R, Dhakal BP, Eisman AS, Pappagianopoulos PP, Dress A, Weiner RB, Baggish AL, Semigran MJ, Lewis GD. Pulmonary vascular distensibility predicts pulmonary hypertension severity, exercise capacity, and

survival in heart failure. *Circ Heart Fail*. 2016;9:e003011. doi: 10.1161/CIRCHEARTFAILURE.115.003011
36. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA*. 2002;288:2144–2150. doi: 10.1001/jama.288.17.2144
37. Clark AL, Poole-Wilson PA, Coats AJ. Exercise limitation in chronic heart failure: central role of the periphery. *J Am Coll Cardiol*. 1996;28:1092–1102. doi: 10.1016/S0735-1097(96)00323-3
38. Massie BM, Conway M, Rajagopalan B, Yonge R, Frostick S, Ledingham J, Sleight P, Radda G. Skeletal muscle metabolism during exercise under ischemic conditions in congestive heart failure. Evidence for abnormalities unrelated to blood flow. *Circulation*. 1988;78:320–326. doi: 10.1161/01.cir.78.2.320
39. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J*. 2013;165:575–582.e3. doi: 10.1016/j.ahj.2013.01.017
40. Fang JC, DeMarco T, Givertz MM, Borlaug BA, Lewis GD, Rame JE, Gomberg-Maitland M, Murali S, Frantz RP, McGlothlin D, et al. World Health Organization pulmonary hypertension group 2: pulmonary hypertension due to left heart disease in the adult–a summary statement from the pulmonary Hypertension Council of the International Society for heart and lung transplantation. *J Heart Lung Transplant*. 2012;31:913–933. doi: 10.1016/j.healun.2012.06.002
41. Drexler H, Faude F, Höing S, Just H. Blood flow distribution within skeletal muscle during exercise in the presence of chronic heart failure: effect of milrinone. *Circulation*. 1987;76:1344–1352. doi: 10.1161/01.cir.76.6.1344
42. Sullivan MJ, Green HJ, Cobb FR. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation*. 1990;81:518–527. doi: 10.1161/01.cir.81.2.518
43. Bennett FM. A role for neural pathways in exercise hyperpnea. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56:1559–1564. doi: 10.1152/jappl.1984.56.6.1559
44. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation*. 2021;143:516–525. doi: 10.1161/CIRCULATIONAHA.120.052186
45. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, Filippatos G, Gniot J, Fu M, Gullestad L, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur Heart J*. 2021;42:700–710. doi: 10.1093/eurheartj/ehaa943
46. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, Macaluso F, Sartori S, Roque M, Sabatel-Perez F, et al; EMPA-TROPISM (ATRU-4) Investigators. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;77:243–255. doi: 10.1016/j.jacc.2020.11.008
47. Erhardt L, MacLean A, Ilgenfritz J, Gelperin K, Blumenthal M. Fosinopril attenuates clinical deterioration and improves exercise tolerance in patients with heart failure. Fosinopril Efficacy/Safety Trial (FEST) study group. *Eur Heart J*. 1995;16:1892–1899. doi: 10.1093/oxfordjournals.eurheartj.a060844
48. Granger CB, Ertl G, Kuch J, Maggioni AP, McMurray J, Rouleau JL, Stevenson LW, Swedberg K, Young J, Yusuf S, et al; Study of Patients Intolerant of Converting Enzyme Inhibitors (SPICE) Investigators. Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. *Am Heart J*. 2000;139:609–617. doi: 10.1016/s0002-8703(00)90037-1
49. Agostoni P, Magini A, Andreini D, Contini M, Apostolo A, Bussotti M, Cattadori G, Palermo P. Spironolactone improves lung diffusion in chronic heart failure. *Eur Heart J*. 2005;26:159–164. doi: 10.1093/eurheartj/ehi023
50. Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, Marino P, Zardini P. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol*. 2002;40:304–310. doi: 10.1016/s0735-1097(02)01965-4
51. Psotka MA, Gottlieb SS, Francis GS, Allen LA, Teerlink JR, Adams KF Jr, Rosano GMC, Lancellotti P. Cardiac calcitropes, myotropes, and mitotropes: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73:2345–2353. doi: 10.1016/j.jacc.2019.02.051
52. Elkayam U, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, Young JB, Rayburn BK, Rogers JG, DeMarco T, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J*. 2007;153:98–104. doi: 10.1016/j.ahj.2006.09.005
53. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, et al; Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547. doi: 10.1001/jama.287.12.1541
54. Planelles-Herrero VJ, Hartman JJ, Robert-Paganin J, Malik FI, Houdusse A. Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil. *Nat Commun*. 2017;8:190. doi: 10.1038/s41467-017-00176-5
55. Greenberg BH, Chou W, Saikali KG, Escandón R, Lee JH, Chen MM, Treshkur T, Megreladze I, Wasserman SM, Eisenberg P, et al. Safety and tolerability of omecamtiv mecarbil during exercise in patients with ischemic cardiomyopathy and angina. *JACC Heart Fail*. 2015;3:22–29. doi: 10.1016/j.jchf.2014.07.009
56. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Legg JC, Büchele G, Varin C, Kurtz CE, et al. Omecamtiv mecarbil in chronic heart failure with reduced ejection fraction: rationale and design of GALACTIC-HF. *JACC Heart Fail*. 2020;8:329–340. doi: 10.1016/j.jchf.2019.12.001
57. Psotka MA, Abraham WT, Fiuzat M, Filippatos G, Lindenfeld J, Ahmad T, Bhatt AS, Carson PE, Cleland JGF, Felker GM, et al. Conduct of clinical trials in the era of COVID-19: JACC scientific expert panel. *J Am Coll Cardiol*. 2020;76:2368–2378. doi: 10.1016/j.jacc.2020.09.544
58. Samsky MD, DeVore AD, McIlvennan CK, Granger CB, Granger BB, Hernandez AF, Felker GM, Fonarow GC, Albert NM, Piña IL, et al. Heart failure clinical trial operations during the COVID-19 pandemic: results from a multicenter survey. *Circ Heart Fail*. 2020;13:e007456. doi: 10.1161/CIRCHEARTFAILURE.120.007456
59. Bhat RR, Schoenike MW, Kowal A, White C, Rouvina J, Hardin CC, Malhotra R, Lewis GD. Feasibility and consistency of results with deployment of an in-line filter for exercise-based evaluations of patients with heart failure during the novel coronavirus disease-2019 pandemic. *J Card Fail*. 2021;27:105–108. doi: 10.1016/j.cardfail.2020.10.005
60. Braun MU, Rauwolf T, Zerm T, Schulze M, Schnabel A, Strasser RH. Long term biventricular resynchronisation therapy in advanced heart failure: effect on neurohormones. *Heart*. 2005;91:601–605. doi: 10.1136/hrt.2003.030338
61. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Böcker D, Block M, Kirkels JH, Kramer A, et al; Pacing Therapies in Congestive Heart Failure II Study Group; Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol*. 2003;42:2109–2116. doi: 10.1016/j.jacc.2003.04.003
62. Yu CM, Chan JY, Zhang Q, Yip GW, Lam YY, Chan A, Burkhoff D, Lee PW, Fung JW. Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. *JACC Cardiovasc Imaging*. 2009;2:1341–1349. doi: 10.1016/j.jcmg.2009.07.011
63. Giallauria F, Vigorito C, Piepoli MF, Stewart Coats AJ. Effects of cardiac contractility modulation by non-excitatory electrical stimulation on exercise capacity and quality of life: an individual patient's data meta-analysis of randomized controlled trials. *Int J Cardiol*. 2014;175:352–357. doi: 10.1016/j.ijcard.2014.06.005
64. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. *Circulation*. 2018;137:148–161. doi: 10.1161/CIRCULATIONAHA.117.029058
65. Sica DA, Mannino R. Antihypertensive medications and anemia. *J Clin Hypertens (Greenwich)*. 2007;9:723–727. doi: 10.1111/j.1524-6175.2007.06296.x
66. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, et al; EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation*. 2017;136:1374–1383. doi: 10.1161/CIRCULATIONAHA.117.027497
67. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, et al; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309:1268–1277. doi: 10.1001/jama.2013.2024
68. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, Biering-Sørensen T, Böhm M, Bonderman D, Fang JC, et al; GALACTIC-HF

Investigators. Effect of ejection fraction on clinical outcomes in patients treated with omecamtiv mecarbil in GALACTIC-HF. *J Am Coll Cardiol*. 2021;78:97–108. doi: 10.1016/j.jacc.2021.04.065
69. Agostoni P, Guazzi M, Bussotti M, De Vita S, Palermo P. Carvedilol reduces the inappropriate increase of ventilation during exercise in heart failure patients. *Chest*. 2002;122:2062–2067. doi: 10.1378/chest.122.6.2062
70. Guazzi M, Agostoni P, Matturri M, Pontone G, Guazzi MD. Pulmonary function, cardiac function, and exercise capacity in a follow-up of patients with congestive heart failure treated with carvedilol. *Am Heart J*. 1999;138(3 pt 1):460–467. doi: 10.1016/s0002-8703(99)70148-1
71. Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, Medina N, Yushak M, Horn E, Katz SD. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation*. 1995;92:1499–1506. doi: 10.1161/01.cir.92.6.1499
72. Dubach P, Myers J, Bonetti P, Schertler T, Froelicher V, Wagner D, Scheidegger M, Stuber M, Luchinger R, Schwitter J, et al. Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: analysis with magnetic resonance myocardial tagging. *Am Heart J*. 2002;143:676–683. doi: 10.1067/mhj.2002.121269
73. Gullestad L, Manhenke C, Aarsland T, Skårdal R, Fagertun H, Wikstrand J, Kjekshus J. Effect of metoprolol CR/XL on exercise tolerance in chronic heart failure - a substudy to the MERIT-HF trial. *Eur J Heart Fail*. 2001;3:463–468. doi: 10.1016/s1388-9842(01)00146-5
74. Genth-Zotz S, Zotz RJ, Sigmund M, Hanrath P, Hartmann D, Böhm M, Waagstein F, Treese N, Meyer J, Darius H. MIC trial: metoprolol in patients with mild to moderate heart failure: effects on ventricular function and cardiopulmonary exercise testing. *Eur J Heart Fail*. 2000;2:175–181. doi: 10.1016/s1388-9842(00)00078-7
75. de Milliano PA, de Groot AC, Tijssen JG, van Eck-Smit BL, Van Zwieten PA, Lie KI. Beneficial effects of metoprolol on myocardial sympathetic function: evidence from a randomized, placebo-controlled study in patients with congestive heart failure. *Am Heart J*. 2002;144:E3. doi: 10.1067/mhj.2002.121807
76. Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, Krueger SK, Lejemtel T, Narahara KA, Packer M, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J Card Fail*. 1997;3:173–179. doi: 10.1016/s1071-9164(97)90013-0
77. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, Kukin ML, Kinhal V, Udelson JE, Klapholz M, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE trial. Prospective randomized evaluation of carvedilol on symptoms and exercise. *Circulation*. 1996;94:2793–2799. doi: 10.1161/01.cir.94.11.2793
78. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy. *Circulation*. 2000;101:378–384. doi: 10.1161/01.CIR.101.4.378.
79. Bristow MR, O'Connell JB, Gilbert EM, French WJ, Leatherman G, Kantrowitz NE, Orie J, Smucker ML, Marshall G, Kelly P. Dose-response of chronic beta-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Bucindolol Investigators. *Circulation*. 1994;89:1632–1642. doi: 10.1161/01.cir.89.4.1632
80. Guazzi M, Palermo P, Pontone G, Susini F, Agostoni P. Synergistic efficacy of enalapril and losartan on exercise performance and oxygen consumption at peak exercise in congestive heart failure. *Am J Cardiol*. 1999;84:1038–1043. doi: 10.1016/s0002-9149(99)00495-6
81. Dickstein K, Barvik S, Aarsland T. Effect of long-term enalapril therapy on cardiopulmonary exercise performance in men with mild heart failure and previous myocardial infarction. *J Am Coll Cardiol*. 1991;18:596–602. doi: 10.1016/0735-1097(91)90619-k
82. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation*. 1999;100:1056–1064. doi: 10.1161/01.cir.100.10.1056
83. Ellis GR, Nightingale AK, Blackman DJ, Anderson RA, Mumford C, Timmins G, Lang D, Jackson SK, Penney MD, Lewis MJ, et al. Addition of candesartan to angiotensin converting enzyme inhibitor therapy in patients with chronic heart failure does not reduce levels of oxidative stress. *Eur J Heart Fail*. 2002;4:193–199. doi: 10.1016/s1388-9842(02)00002-8
84. De Bock V, Mets T, Romagnoli M, Derde MP. Captopril treatment of chronic heart failure in the very old. *J Gerontol*. 1994;49:M148–M152. doi: 10.1093/geronj/49.3.m148
85. Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo ME. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo controlled trial. *Heart*. 2002;88:373–377. doi: 10.1136/heart.88.4.373
86. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol*. 1983;2:755–763. doi: 10.1016/s0735-1097(83)80316-7.
87. Piepoli MF, Hussain RI, Comin-Colet J, Dosantos R, Ferber P, Jaarsma T, Edelmann F. OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. *Eur J Heart Fail*. 2021;23:127–135. doi: 10.1002/ejhf.2076
88. Metra M, Eichhorn E, Abraham WT, Linseman J, Böhm M, Corbalan R, DeMets D, De Marco T, Elkayam U, Gerber M, et al; ESSENTIAL Investigators. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J*. 2009;30:3015–3026. doi: 10.1093/eurheartj/ehp338
89. Lowes BD, Higginbotham M, Petrovich L, DeWood MA, Greenberg MA, Rahko PS, Dec GW, LeJemtel TH, Roden RL, Schleman MM, et al. Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group. *J Am Coll Cardiol*. 2000;36:501–508. doi: 10.1016/s0735-1097(00)00759-2
90. Szabó BM, van Veldhuisen DJ, van der Burgh PH, Kruik J, Girbes AR, Lie KI. Clinical and autonomic effects of ibopamine as adjunct to angiotensin-converting enzyme inhibitors in chronic heart failure. *J Card Fail*. 1996;2:185–192. doi: 10.1016/s1071-9164(96)80040-6
91. Dei Cas L, Metra M, Visioli O. Effects of acute and chronic ibopamine administration on resting and exercise hemodynamics, plasma catecholamines and functional capacity of patients with chronic congestive heart failure. *Am J Cardiol*. 1992;70:629–634. doi: 10.1016/0002-9149(92)90203-b
92. Barabino A, Di Benedetto G, Musso N, Vergassola C, Azzolini A, Lotti G, Pizzorni C. Neurohormonal evaluation and long-term treatment of mild congestive heart failure in elderly patients with ihopamine: a double-blind, placebo-controlled study. *Am J Noninvasive Cardiol*. 1991;5:23–31. doi: 10.1159/000470496.
93. Lubsen J, Just H, Hjalmarsson AC, La Framboise D, Remme WJ, Heinrich-Nols J, Dumont JM, Seed P. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart*. 1996;76:223–231. doi: 10.1136/hrt.76.3.223
94. Kubo SH, Gollub S, Bourge R, Rahko P, Cobb F, Jessup M, Brozena S, Brodsky M, Kirlin P, Shanes J. Beneficial effects of pimobendan on exercise tolerance and quality of life in patients with heart failure. Results of a multicenter trial. The Pimobendan Multicenter Research Group. *Circulation*. 1992;85:942–949. doi: 10.1161/01.cir.85.3.942
95. Katz SD, Kubo SH, Jessup M, Brozena S, Troha JM, Wahl J, Cohn JN, Sonnenblick EH, LeJemtel TH. A multicenter, randomized, double-blind, placebo-controlled trial of pimobendan, a new cardiotonic and vasodilator agent, in patients with severe congestive heart failure. *Am Heart J*. 1992;123:95–103. doi: 10.1016/0002-8703(92)90752-h
96. Elborn JS, Stanford CF, Nicholls DP. Effect of flosequinan on exercise capacity and symptoms in severe heart failure. *Br Heart J*. 1989;61:331–335. doi: 10.1136/hrt.61.4.331
97. Packer M, Narahara KA, Elkayam U, Sullivan JM, Pearle DL, Massie BM, Creager MA. Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. Principal Investigators of the REFLECT study. *J Am Coll Cardiol*. 1993;22:65–72. doi: 10.1016/0735-1097(93)90816-j
98. Banning AP, Ramsey MW, Jones EA, Evans W, Carolan G, Jones CH, Henderson AH. Flosequinan in chronic heart failure: how is exercise capacity improved? *Eur J Clin Pharmacol*. 1996;51:133–138. doi: 10.1007/s002280050173
99. Hori M, Sato H, Ozaki H, Inoue M, Naka M, Fukunami M, Fukushima M, Kunisada K. Effect of flosequinan on exercise capacity and cardiac function in patients with chronic mild heart failure: a double-blind placebo-controlled study. *Heart Vessels*. 1992;7:133–140. doi: 10.1007/BF01744866
100. Likoff MJ, Weber KT, Andrews V, Janicki JS, Wilson H, Rocci ML Jr. Milrinone in the treatment of chronic cardiac failure: a controlled trial. *Am Heart J*. 1985;110:1035–1042. doi: 10.1016/0002-8703(85)90206-6
101. White HD, Ribeiro JP, Hartley LH, Colucci WS. Immediate effects of milrinone on metabolic and sympathetic responses to exercise in severe congestive heart failure. *Am J Cardiol*. 1985;56:93–98. doi: 10.1016/0002-9149(85)90573-9

102. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, Pires LA, Tchou PJ; RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med*. 2007;357:2461–2471. doi: 10.1056/NEJMoa0706695
103. De Marco T, Wolfel E, Feldman AM, Lowes B, Higginbotham MB, Ghali JK, Wagoner L, Kirlin PC, Kennett JD, Goel S, et al. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. *J Card Fail*. 2008;14:9–18. doi: 10.1016/j.cardfail.2007.08.003
104. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schöndube F, Wolfhard U, Böcker D, et al; Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:2026–2033. doi: 10.1016/s0735-1097(02)01895-8
105. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol*. 2003;42:1454–1459. doi: 10.1016/s0735-1097(03)01042-8
106. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150. doi: 10.1056/NEJMoa032423
107. Abraham WT, Young JB, León AR, Adler S, Bank AJ, Hall SA, Lieberman R, Liem LB, O'Connell JB, Schroeder JS, et al; Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter defibrillator, and mildly symptomatic chronic heart failure. *Circulation*. 2004;110:2864–2868. doi: 10.1161/01.CIR.0000146336.92331.D1
108. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, et al; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA*. 2003;289:2685–2694. doi: 10.1001/jama.289.20.2685
109. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, et al; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853. doi: 10.1056/NEJMoa013168
110. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, et al; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873–880. doi: 10.1056/NEJM200103223441202
111. Piepoli MF, Villani GQ, Corrà U, Aschieri D, Rusticali G. Time course of effects of cardiac resynchronization therapy in chronic heart failure: benefits in patients with preserved exercise capacity. *Pacing Clin Electrophysiol*. 2008;31:701–708. doi: 10.1111/j.1540-8159.2008.01073.x