Advanced Heart Failure Definition, Epidemiology, and Clinical Course

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KEY POINTS

Advanced heart failure is characterized by a progressive worsening of symptoms that are disabling for daily life, refractory to all therapies, and with high mortality. Patients with advanced heart failure may be candidates for life-prolonging therapies, such as heart transplantation or long-term mechanical circulatory support, or just require palliative therapies. The 2018 Heart Failure Association definition of advanced heart failure requires 4 criteria that must be present despite optimal guideline-directed treatment. Timely referral of patients to advanced heart failure centers and careful selection for heart transplantation or long-term mechanical circulatory support are key to good clinical outcomes.

DEFINITION OF ADVANCED HEART FAILURE

Although medical, surgical, and device therapies, according to scientific evidence, have progressively improved the quality of life and survival of patients with heart failure (HF), some patients evolve unfavorably with a progressive worsening of symptoms that are disabling for daily life, refractory to all therapies, and with high mortality. This stage is recognized as advanced HF, also known as American College of Cardiology (ACC)/American Heart Association (AHA) "Stage D00 HF, meaning refractory HF requiring specialized interventions or end-stage HF.[1–3]

Patients at this stage may be candidates for lifeprolonging therapies, such as heart transplantation (HT) or long-term mechanical circulatory support (MCS) devices, or may just require palliative therapies (eg, intermittent ionotropic infusions, ultrafiltration, or peritoneal dialysis to control congestion or end-of-life comfort care). The 1- year survival after HT and left ventricular assist devices (LVAD) for bridge to transplant or destination therapy is approaching 80% to 90%,[4,5] being patient selection and timing critical for optimal outcomes. Each patient should be individually assessed for their specific needs, and in case of being noneligible for advanced therapies, treatment goals should be aimed at reducing symptomatic burden and improving quality of life.

The search for a definition of advanced HF has been of a great interest for clinicians, because the proper identification of patients in need of a particular treatment, especially those potentially benefiting from advanced therapies (such as HT or MCS), who are to be referred to advanced therapy centers, needs to be done at an appropriate time. Not too early, but not too late.[6]

There is no single symptom, sign, or test that can identify these patients, and this advance stage cannot be compared with patients with an acute HF hospitalization in whom, in most cases, the cause can be treated, the symptoms controlled, and the treatment implemented with improved clinical outcomes. The clinical course of patients with HF is highly unpredictable and a challenge even for experts in HF, as there are many influencing factors such as different responses to treatment or sudden instability due to pathologies and/or intercurrent circumstances, both of cardiac or extracardiac origin. Therefore, over time different scientific societies have suggested criteria to identify patients in advanced HF, which are shown in Boxes [1–3].

There are some overlaps and complementarities between them, but as a whole they gather the main clinical features that accompany patients with advanced HF and allow us to identify them with information that is easily accessible in daily clinical practice. Most of the proposed criteria are based on severity of symptoms, end-stage heart disease, absence of other treatments, recurrent hospitalizations, inability to tolerate neurohormonal activation blocking treatments such as reninangiotensin-aldosterone system inhibitors (RAASi), beta-blockers (BB), or angiotensin receptor-neprilysin inhibitor (ARNI), recurrent hospitalizations, implantable cardioverter-defibrillator shocks, refractory congestion, poor functional capacity, cardiac cachexia and progressive multiorgan impairment, especially kidney or liver dysfunction, and pulmonary hypertension.[1,3]

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles[7] were developed to classify patients who were to be considered for long-term MCS device implantation, based on the symptoms, hemodynamic compromise, and characteristics consistent with a need for advanced therapies. The classification includes 7 profiles from highest to lowest clinical severity and shorter to longer recommended maximum time frame for intervention. Profiles 1 to 3 refer to inpatients and profiles 4 to 7 to outpatients. INTERMACS profiles comprise profile 1 “Critical cardiogenic shock” in which the patient requires definitive intervention within hours, profile 2 “Progressive decline” in which definitive intervention is needed within few days, profile 3 “Stable but inotrope-dependent” in which definitive intervention elective over a period of weeks to few months, followed by profiles 4 to 6 in which the urgency for intervention is variable to profile 7 “advanced NYHA Class III” in which neither cardiac transplantation nor an MCS is yet indicated. Specific descriptions of each profile and the recommended timing of different interventions are shown in Table 1. The INTERMACS classification includes 3 modifiers for profiles: temporary circulatory support (TCS), arrhythmia (A), and frequent flyer (FF). This classification has been useful to predict outcomes after durable MCS devices implantation[8] and also for patients undergoing urgent HT.[9] It has also been found useful for risk stratifying ambulatory patients with advanced HF (profiles 4, 5, 6, and 7) and for identifying and triaging candidates for advanced therapies.[10–12]

For patients in cardiogenic shock or at risk of developing it, the Society for Cardiovascular Angiography and Interventions developed a classification in 5 stages from “A” to “E” based on physical examination, laboratory values, and hemodynamics (Fig.

1). Stage A is “at risk” for cardiogenic shock, stage B is “beginning” shock, stage C is “classic” cardiogenic shock, stage D is “deteriorating”, and E is “extremis.” The difference between stages B and C is the presence of hypoperfusion, which is present in stages C and higher. Stage D defines the patient in whom the initial set of interventions chosen have not restored stability and adequate perfusion despite at least 30 minutes of observation, and stage E is the patient in extremis, highly unstable, often with cardiovascular collapse. This classification is simple, with clinical criteria readily available to both critical care and referral center health care professionals and provides a common language for physicians and surgeons,[13] and it facilitates a paradigm shift in the care of patients in cardiogenic shock, with a focus on early identification and aggressive treatment and with important logistical implications because not all the necessary resources, in particular temporary MCS devices, are available at each center and patients need to be referred in a timely manner. The Society of Cardiovascular Angiography and Interventions classification has proved its prognostic usefulness in contemporary, real-world cohorts of patients with cardiogenic shock.[14]

For patients with less severe HF who are being followed by nonadvanced HF specialists, a useful mnemonic “I NEED HELP” has been proposed to aid in the identification of patients with advanced HF and timely referral for consideration of advanced therapies.[15] This mnemonic integrates typical features such as a decline in functional status; severe reduction in LVEF; the need for inotropes; refractory congestion; hypotension; inability to uptitrate or maintain previously welltolerated drugs such as RAASi, BB, or ARNI; hospitalizations, and electric instability or persistently high natriuretic peptide levels. Table 2.

The 2018 position statement of the Heart Failure Association of the European Society of Cardiology (HFA-ESC) on advanced HF[16] updated the 2007 criteria taking into account the availability of new therapies and emphasizing both the need for patients to be optimized on such therapies before being considered for advanced HF therapies and to refer the patient timely to advanced HF units. The updated HFA-ESC criteria are outlined in Box 4.

Compared with the former HFA-ESC definition1 the main 2 changes in 2018 were in criterion 2 and 3. Criterion 2, which refers to severe cardiac dysfunction, was based on the 2016 ESC HF guidelines.[17] The ESC criteria were considered sufficient to define

cardiac dysfunction, and they can be used for the definition of advanced HF when accompanied by other criteria that characterize patient severity. Using the ESC criteria for cardiac dysfunction gives the same importance to all patients with HF, independent of left ventricular ejection fraction (LVEF). Indeed, with a few exceptions, such as patients with hypertrophic cardiomyopathy or restrictive cardiomyopathy, most of the patients with an indication for HT or MCS have a reduced LVEF. However, at least 50% of patients hospitalized for acute HF have a preserved LVEF, and these patients can also be considered advanced, provided the other criteria outlined in the definition are present. Criterion 3 refers to HF hospitalization. In this sense, unplanned visits for HF were added and given the same value as hospital admissions. Malignant arrhythmias were added as major causes of acute events. This criterion acknowledge that acute events leading to one or more unplanned visits or hospitalizations within 12 months were the hallmark of advanced HF, independent of treatment, with emphasis placed on the instability of the clinical course and resource utilization.

This position statement on advanced HF includes proposals on triage of patients and appropriate timing of referral to advanced HF (Fig. 2).

EPIDEMIOLOGY

The prevalence of advanced HF is not well known and quite difficult to estimate. Epidemiologic studies of HF usually categorize patients according to functional status (eg, New York Heart Association [NYHA] class) and LVEF but do not according to advanced HF versus other less progressed stages.[18–20] Most of the information we have come from LVAD clinical trials and/or referral population to advanced HF centers, sometimes excluding the rest of the patients with advanced HF from the health care area, not referred to these centers, and who are, in fact, most of the patients. But even in centers with availability of advanced HF therapies, an unrecognized need for these therapies has been observed.[6]

A study conducted more than 2 decades ago, in Olmstead County, Minnesota (USA), populationbased, cross-sectional design, in a random sample of 2029 residents 45 years and older, found that advanced HF (stage D) affected 0.2% of the population assessed and 2% of those with HF. However, in this study stage D was operationally defined as history of HF and functional class IV according to a self-administered questionnaire, in

which the participant was able to perform activity—less than 2 metabolic equivalents (METS).[21] Criteria for defining advanced HF have changed over time,[22] and the difficulty in making estimates is well illustrated in a systematic review by Bjork and colleagues (2016) (#7721 of criteria used in clinical trials, including 134 publications). In this study, in addition to the 2 most commonly used criteria (NYHA and LVEF), there were a wide array of criteria used such as inotrope-dependent status in 12.7%, peak oxygen consumption in 10.4%, previous hospitalizations in 10.4%, cardiac index in 10.4%, or transplant listing status in 5.2%, and it was found there is little consistency both in criteria selection and quantitative cut-off points.[20] The sequential development of more disease-modifying therapies over the past several decades has dramatically changed the prognosis of patients with HF and explain that the prevalence of advanced disease is increasing, due to growing number of patients with HF and their better treatment and survival.[23–25] Until now, none of the available therapies can cure HF. Current treatments can maintain clinical stability for a certain period of time, even with quite good quality of life, but the risk of disease progression persists over time. More recent studies estimate that patients with advanced HF account for 1% to 10% of the overall HF population[3,26] and from patients who receive care in a referral center, 4.5% progressed to advanced HF every year.[27]

In the absence of life-prolonging therapies such as HT or LVADs the prognosis of patients with advanced HF is poor. In the landmark trial REMATCH[28] in which patients ineligible for HT were randomized to first-generation LVAD implantation or optimal medical management, the 1- and 2-year survival of patients in the medical therapy group was 25% and 8%, respectively. However, since this study different criteria for defining the patient population may have modified these estimates. In addition to the poor survival and quality of life of these patients, the medical therapy is associated with significant costs and resource consumption, which increase as death approaches, as it was shown in one study that 50% of costs was spent in the last 6 months.[29]

CLINICAL COURSE

In patients with NYHA functional class III or ACC/ AHA stage C, the clinical course is mainly determined by congestion due to volume overload from LV dysfunction with elevated LV enddiastolic pressure but still normal systemic blood pressure and stroke volume. When patients progress to advanced HF a progressive reduction in stroke volume

determinates the clinical picture with consequent multiorgan damage, declining renal function, liver congestion, pulmonary hypertension, and cardiac cachexia. In patients with HF with reduced ejection fraction the reduction on stroke volume is often accompanied by LV dilation and varying degrees of secondary mitral regurgitation, which further reduces the stroke volume. In addition, the progression of HF is followed by greater electrical instability.[18,30]

The typical signs and symptoms of advanced HF include a progressive decline in functional status, with symptoms at rest or with minimal effort, refractory congestion needing escalating doses of diuretics or the use of combinations of diuretics, hypotension, inability to maintain diseasemodifying therapies, the need for inotropes, and symptomatic ventricular arrhythmias. These characteristics are well reflected in the definitions and criteria discussed earlier.

However, the clinical course of patients with advanced HF can be highly unpredictable even for experienced clinicians for many reasons, including persistent activation of disease pathways that are not fully blocked by neurohormonal antagonists, new episodes of myocardial damage or valvular dysfunction, development of pulmonary hypertension, right ventricular failure and cardiorenal syndrome, as well as the cumulative effect of multiorgan damage, environmental factors, and comorbidities.[31] Moreover, some comorbidities (renal dysfunction, pulmonary hypertension) can be consequences, as well as causes of advanced HF, and sometimes a proper treatment of the cardiac disease can lead to improvement in the comorbid condition.

Patients who are considered as potential candidates for advanced therapies should be referred in a timely manner to an Advanced HF Center, and parameters have been established to refer the patient before it is too late. The concept is that patients are not necessarily referred to receive these advanced HF therapies immediately, but they can be evaluated for a potential candidacy for HT and/or LVAD—that is, a thorough evaluation aimed to confirm indications rule out contraindications and establish the proper time of intervention—if required. Table 3 shows the suggested clinical, laboratory, and echocardiographic criteria to trigger referral, with specific comments on the prognostic scores more used in HF (Table 4), established in the 2018 HFA-ESC position statement. This document was intended primarily for professionals unfamiliar with advanced therapies who are caring for patients with HF, to correctly identify which patients are at

an advanced stage and may be candidates for specific therapies that require timely referral to centers that can offer them and suggest an operational interactional "Hub and Spoke" networking, facilitating both communication and transitional care of patients between centers with different HF resources[18] (Fig. 3).

CLINICS CARE POINTS

Evidence-based pearls:

- The 1-year survival after HT and/or long-term MCS is approaching 80% to 90%.
- Timely referral to advanced HF centers and careful patient selection are critical for optimal outcomes.

Pitfalls

- The prevalence of advanced HF is not well known.
- The clinical course of patients with HF is highly unpredictable and a challenge even for experts in HF, as there are many influencing factors such as different responses to treatment or sudden instability due to pathologies and/or intercurrent circumstances, both of cardiac or extracardiac origin.

DISCLOSURE

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Box 1.Previous definitions or advanced heart failure: Heart Failure Association-ESC (2007)

1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)
2. Episodes of fluid retention (pulmonary and/ or systemic congestion, peripheral edema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:
    a. A low LVEF (<30%)
    b. A severe abnormality of cardiac function on Doppler-echocardiography with a pseudonormal or restrictive mitral inflow pattern
    c. High LV filing pressures (mean PCWP >16 mm Hg, and/or mean RAP >12 mm Hg by pulmonary artery catheterization)
    d. High BNP or NT-proBNP plasma levels, in the absence of noncardiac causes
4. Severe impairment of functional capacity shown by one of the following:
    a. Inability to exercise
    b. 6-MWT distance less than 300 m or less in women and/or patients older than 75 years
    c. pVO_2 less than 12 to 14 mL/kg/min
5. History of more than or equal to 1 heart failure hospitalization in the past 6 months

Presence of all the previous features despite "attempts to optimize" therapy, including diuretics, inhibitors of the renin-angiotensinaldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated

Abbreviations: 6-MWT, 6-minute walk test; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

From Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hu¨ lsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535.

Box 2 Previous definitions or advanced heart failure: American College of Cardiology/American Heart Association

1. Repeated (≥2) hospitalizations or ED visits for HF in the past year
2. Progressive deterioration in renal function (eg, increase in BUN and creatinine)
3. Weight loss without other cause (eg, cardiac cachexia)
4. Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
5. Intolerance to beta-blockers due to worsening HF or hypotension
6. Frequent systolic blood pressure less than 90 mm Hg
7. Persistent dyspnea with dressing or bathing requiring rest
8. Inability to walk 1 block on the level ground due to dyspnea or fatigue
9. Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose greater than 160 mg/d and/or use of supplemental metolazone therapy
10. Progressive decline in serum sodium, usually to less than 133 mEq/L.
11. Frequent ICD shocks

Abbreviations: ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; ED, emergency department; ICD, implantable cardioverter-defibrillator.

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Box 3 Previous definitions or advanced heart failure: Heart Failure Society of America

The presence of progressive and/or persistent severe signs and symptoms of HF despite optimized medical, surgical, and device therapy. It is generally accompanied by frequent hospitalization, severely limited exertional tolerance, and poor quality of life and is associated with high morbidity and mortality. Importantly, the progressive decline should be primarily driven by the HF syndrome.

Indicators of advanced HF in the setting of optimal medical and electrical therapies that should trigger consideration of referral for evaluation of advanced therapies include

- Need for intravenous inotropic therapy for symptomatic relief or to maintain end-organ function
- Peak VO_2 less than 14 mL/kg/min or less than 50% of predicted
- 6MWT distance less than 300 m more than or equal to 2 HF admissions in the last 12 months
- More than 2 unscheduled visits (eg, ED or clinic) in the last 12 months
- Worsening right HF and secondary pulmonary hypertension
- Diuretic refractoriness associated with worsening renal function
- Circulatory–renal limitation to RAAS inhibition or beta-blocker therapy
- Progressive/persistent NYHA functional class III–IV symptoms
- Increased 1-year mortality (eg, 20%–25%) predicted by HF survival models (eg, SHFS, HFSS, and so forth)
- Progressive renal or hepatic end-organ dysfunction
- Persistent hyponatremia (serum sodium <134 mEq/L)
- Recurrent refractory ventricular tachyarrhythmias; frequent ICD shocks
- Cardiac cachexia
- Inability to perform ADL

Abbreviations: 6MWT, 6-minute walk test; ADL, activities of daily living; ED, emergency department; HFSS, Heart Failure Survival Score; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system; SHFS, Seattle Heart Failure Score.

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Table 1 Interagency Registry for Mechanically Assisted Circulatory Support profile descriptions in patients with advanced heart failure

Profile	Time Frame for Intervention
Profile 1: Critical cardiogenic shock Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. “Crash and burn.”	Definitive intervention needed within hours.
Profile 2: progressive decline Patient with declining function despite intravenous inotropic support may be manifested by worsening renal function, nutritional depletion, or inability to restore volume balance. “Sliding on inotropes.” Also describes declining status in patients unable to tolerate inotropic therapy.	Definitive intervention needed within few days.
Profile 3: stable but inotrope dependent Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both) but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. “Dependent stability.”	Definitive intervention elective over a period of weeks to few months.
Profile 4: resting symptoms Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADL. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.	Definitive intervention elective over a period of weeks to few months.
Profile 5: exertion intolerant Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patients may be more at risk than INTERMACS 4 and require definitive intervention.	Variable urgency, depends on maintenance of nutrition, organ function, and activity.

Profile 6: exertion limited Patient without evidence of fluid overload is comfortable at rest and with ADL and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment "walking wounded."	Variable, depends on maintenance of nutrition, organ function, and activity level.
Profile 7: advanced NYHA class III A placeholder for more precise specification in future; this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Transplantation or circulatory support may not currently be indicated.

Modifiers for Profiles	Possible Profiles to Modify
TCS: temporary circulatory support can modify only patients in hospital (other devices would be INTERMACS devices). This includes IABP, ECMO. TandemHeart, Levitronix, BVS 5000 or AB5000, Impella.	1, 2, 3 in hospital.
A: arrhythmia can modify any profile. Recurrent ventricular tachyarrhythmias that have recently contributed substantially to clinical compromise. This includes frequent ICD shocks or requirement for external defibrillator, usually more than twice weekly.	Any profile.
FF: frequent flyer can modify only outpatients, designating a patient requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary intravenous vasoactive therapy.	3 if at home, 4, 5, 6. A Frequent Flyer would rarely be profile 7.

Abbreviations: ADL, activities of daily living; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association.

From Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, et al. INTERMACS profiles of advanced heart failure: the current picture. J Heart Lung Transplant. 2009;28:535-41; with permission.

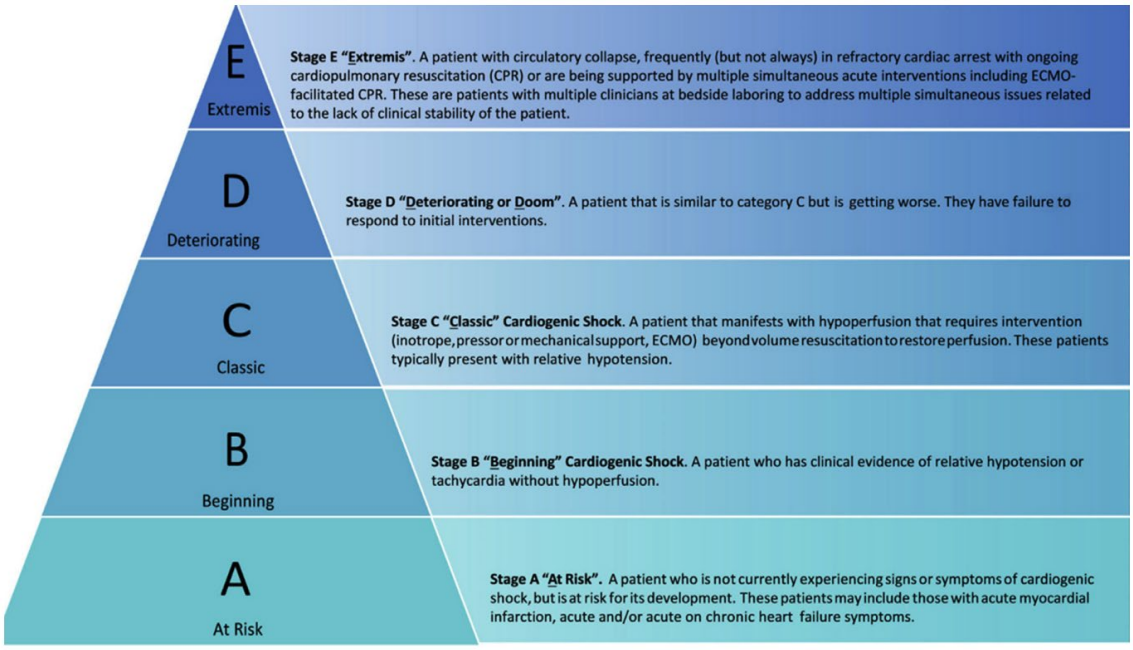

Fig. 1. Society for the cardiovascular angiography and intervention classification of cardiogenic shock. (From Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv. 2019;94(1):29-37.)

Table 2 I NEED HELP. Markers of advanced heart failure

I	Inotropes	Previous or ongoing requirement for dobutamine, milrinone, dopamine, or levosimendan
N	NYHA class/ natriuretic peptides	Persisting NYHA class III or IV and/or persistently high BNP or NTproBNP
E	End-organ dysfunction	Worsening renal or liver dysfunction in the setting of heart failure
E	Ejection fraction	Very low ejection fraction <20%
D	Defibrillator shocks	Recurrent appropriate defibrillator shocks
H	Hospitalizations	More than 1 hospitalization with heart failure in the last 12 mo
E	Edema/escalating diuretics	Persisting fluid overload and/or increasing diuretic requirement
L	Low-blood pressure	Consistently low BP with systolic <90-100 mm Hg
P	Prognostic medication	Inability to uptitrate (or need to decrease/cease) ACEI, betablockers, ARNIs, or MRAs

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor.

From Baumwol J. "I Need Help"-A mnemonic to aid timely referral in advanced heart failure. J Heart Lung Transplant. 2017;36(5):593-4; with permission.

Box 4 Heart Failure Association of the European Society of Cardiology 2018 criteria for defining advanced heart failure

All the following criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of heart failure (NYHA class III [advanced] or IV).
2. Severe cardiac dysfunction defined by a reduced LVEF less than or equal to 30%, isolated RV failure (eg, ARVC) or nonoperable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.[9]
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing more than 1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin.

In addition to the aforementioned criteria, extracardiac organ dysfunction due to heart failure (eg, cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present but are not required.

Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2) but who also have substantial limitation due to other conditions (eg, severe pulmonary disease, noncardiac cirrhosis, or most commonly by renal disease with mixed etiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

Abbreviations: 6MWTD, 6-minute walk test distance; ARVC, arrhythmogenic right ventricular cardiomyopathy; BNP, B-type natriuretic peptide; ESC, European society of cardiology; HFA, heart failure association; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO2, peak exercise oxygen consumption; RV, right ventricular.

From Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hu¨ lsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535.

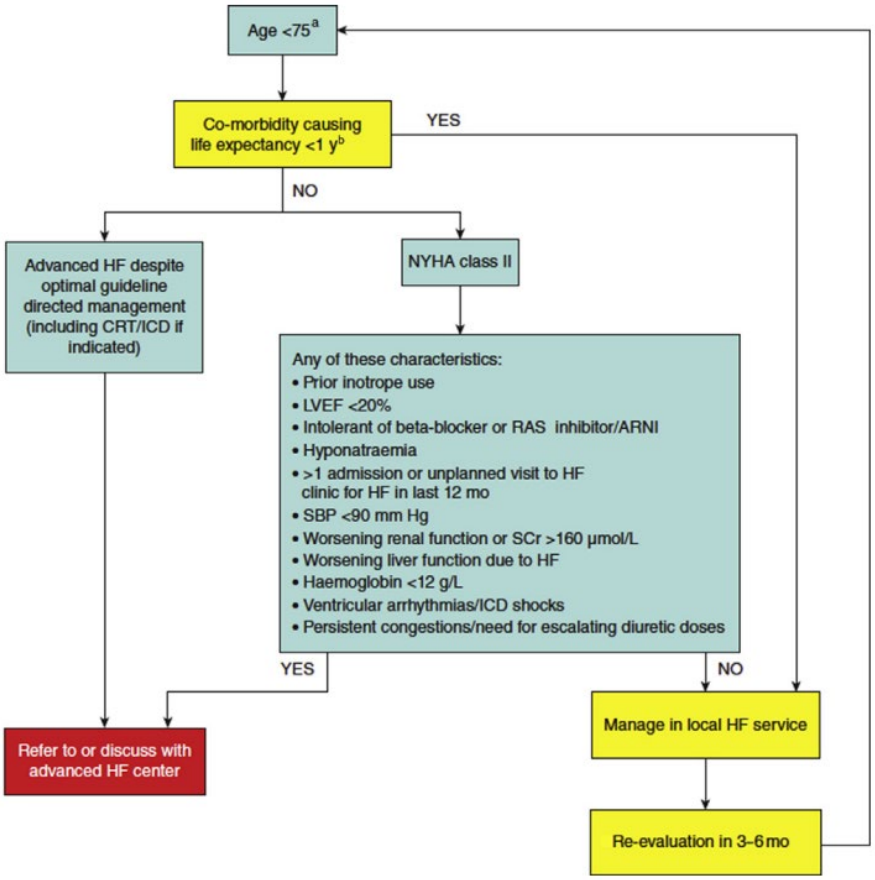

Fig. 2. Triage of patients with advanced HF and appropriate timing of referral.[a] >75 years if good functional status apart from HF (mono-organ disease). [b]e.g. untreatable cancer, dementia, severe COPD (*From* CrespoLeiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hu¨ lsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, StraburzynskaMigaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535.)

Table 3 Suggested clinical, laboratory, and echocardiographic criteria to trigger referral

Clinical[a]	Laboratory	Imaging	Risk Score Data
• >1 HF hospitalization in last year • NYHA class III–IV • Intolerant of optimal dose of any GDMT HF drug • Increasing diuretic requirement SBP ≤ 90 mm Hg • Inability to perform CPET • 6MWT • CRT nonresponder clinically • Cachexia, unintentional weight loss • KCCQ • MLHFQ	• eGFR <45 mL/min • SCr ≥160 mmol/L • K >5.2 or <3.5 mmol/L • Hyponatraemia • Hb ≤120 g/L • NT-proBNP ≥1000 pg/mL • Abnormal liver function test • Low albumin	• LVEF ≤30% • Large area of akinesis/ dyskinesis or aneurysm • Moderate[b]–severe mitral regurgitation • RV dysfunction • PA pressure ≥50 mm Hg • Moderate-severe tricuspid regurgitation • Difficult to grade aortic stenosis • IVC dilated or without respiratory variation	• MAGGIC predicted survival ≤80% at 1 y • SHFM predicted survival ≤80% at 1

Abbreviations: 6MWT, 6-minute walk test; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; Hb, hemoglobin; HF, heart failure; IVC, inferior vena cava; K, potassium; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MLHFQ, Minnesota Living with Heart Failure Questionnaire; Na, sodium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; RV, right ventricular; SCr, serum creatinine; SBP, systolic blood pressure; SHFM, Seattle Heart Failure Model.

[a] Note that this table reflects many clinically relevant but sometimes subjective and nonspecific criteria. With these criteria, sensitivity has been prioritized over specificity, that is, many criteria may be present in patients who do not need referral, but by considering these criteria in a comprehensive assessment, there is a lower risk that high-risk patients may be missed or referred too late. Although cut-offs exist for transplantation listing or LVAD implantation, there are no data to support specific cut-offs for referral to an HF center.

[b] Moderate MR alone is not sufficient, but moderate MR is one factor suggesting risk of progression and should be considered together with other variables.

From Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hu¨ lsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535.

Table 4 Prognostic scores in heart failure

Score	Components	Comments
HFSS	• Presence/absence coronary artery disease • Resting heart rate • Left ventricular ejection fraction • Mean arterial blood pressure • Presence/absence of intraventricular conduction delay • Serum sodium • Peak oxygen uptake HFSS = [(0.0216 * resting HR) + (−0.0255 * mean BP) + (−0.0464 * LVEF) + (−0.047 * serum sodium) + (−0.0546 * peak VO_2) + (0.608 * presence or absence of IVCD) + (0.6931 * presence or absence of ischemic heart disease)]	Score is based on a sum of these variables multiplied by defined coefficients Low risk: ≥8.1 Medium-risk: HFSS 7.20–8.09 High-risk: HFSS ≤7.1
SHFM	• Demographics • Clinical characteristics • Medications • Laboratory data • Devices www. seattleheartfailuremodel.org/	Incorporates impact of interventions (medical and device) and provides estimates of 1, 2, and 5-y survival
MECKI	• Percent predicted peak VO_2 • VE/VCO_2 slope • Hemoglobin • Serum sodium • LVEF	Incorporates data from the CPET as well as kidney function

MAGGIC	• eGFR by MDRD • Age • Gender • Left ventricular ejection fraction • Systolic blood pressure • Body mass index • Serum creatinine • NYHA class • Smoking history • Comorbidities (eg, diabetes, COPD) • Length of heart failure diagnosis • Medications www. heartfailurerisk.org/	Risk model converted into integer score Generalizable to broad spectrum of patients

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Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; eGFR, estimated glomerular filtration rate; HFSS, Heart Failure Survival Score; HR, heart rate; IVCD, intraventricular conduction defect; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; SHFM, Seattle Heart Failure Model, VE/VCO2, minute ventilation carbon dioxide production relationship; VO2, oxygen consumption.

From Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hu¨ lsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535.

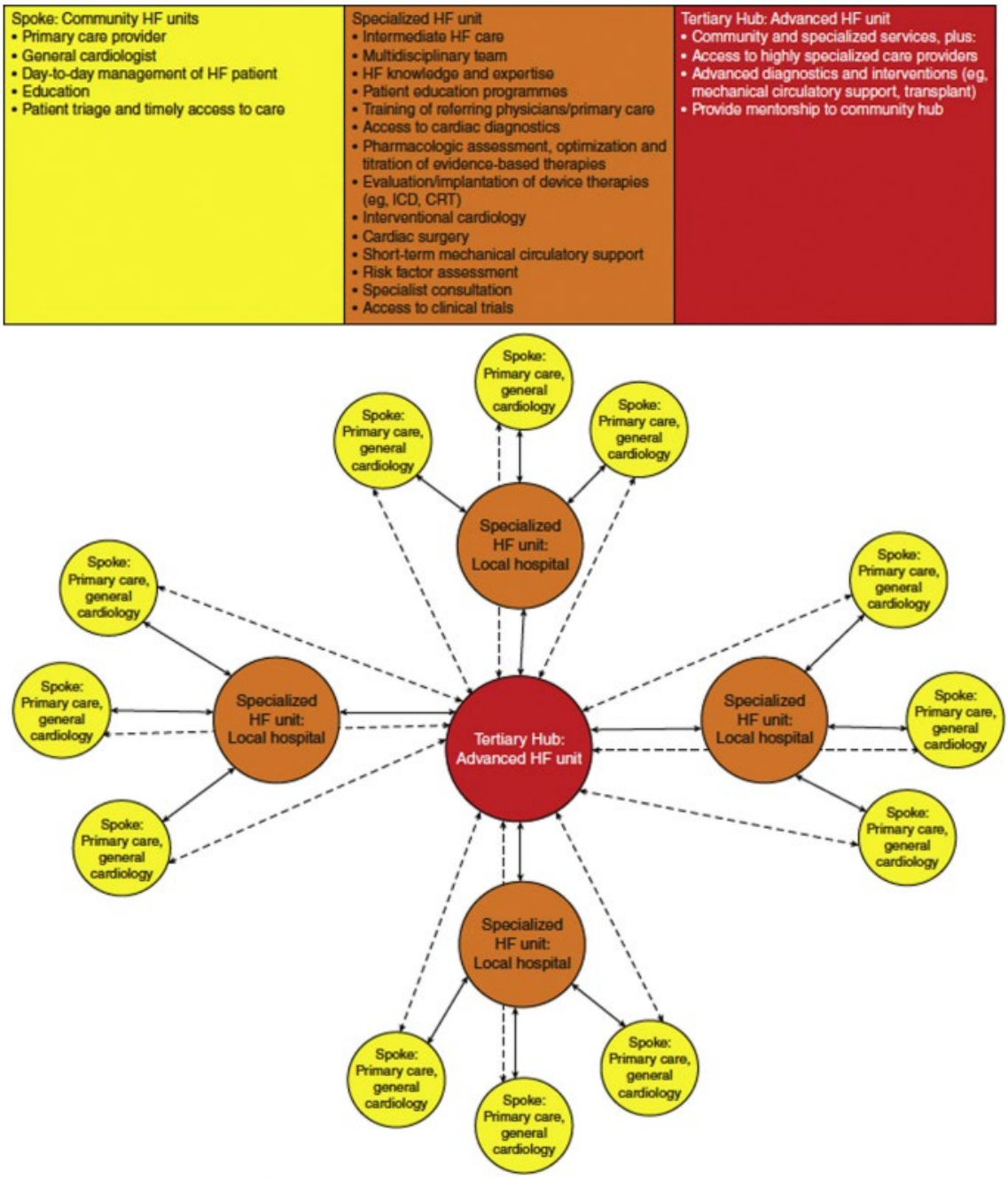

Fig. 3. Conceptual structure of a hub and spoke model of care for patients with advanced HF. (*From* Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, Gustafsson F, Tsui S, Barge-Caballero E, De Jonge N, Frigerio M, Hamdan R, Hasin T, Hu¨ lsmann M, Nalbantgil S, Potena L, Bauersachs J, Gkouziouta A, Ruhparwar A, Ristic AD, Straburzynska-Migaj E, McDonagh T, Seferovic P, Ruschitzka F. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018 Nov;20(11):1505-1535.)