Early is Better Than Late, but Late is Better Than Never: Referral to Advanced Heart Failure Cardiology

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The advanced heart failure cardiology practice treats a wide spectrum of patients in different stages of heart failure, including those at risk of developing heart failure syndrome; those requiring advanced heart failure therapies such as transplantation or left ventricular assist device (LVAD) placement; and those at the end of life, receiving palliative focused therapies such as inotropes. The timing of referral to advanced heart failure practices has been thoroughly discussed in the cardiology community. However, objective data to guide this timing are limited.

Heart failure is a common diagnosis affecting one in five individuals [1]; consequently, general cardiologists are both comfortable with and competent in heart failure management. Not all patients with heart failure have the same urgency for referral to an advanced heart failure practice, because many recover function and good functional capacity after treatment with guideline-directed medical therapy (GDMT) [2]. The 2022 AHA/ACC/HFSA guidelines for the management of heart failure are currently the most up-to-date, inclusive guideline for the management of heart failure [3]. These guidelines divide patients with heart failure into stages A through D. Stage A heart failure describes patients who are at risk of developing heart failure, (such as those with coronary artery disease, diabetes, family history, or exposure to cardiotoxic medications), but have normal cardiac function and no symptoms of heart failure. In Stage B, patients have no current or past symptoms of heart failure, but have structural heart disease or evidence of elevated filling pressure. Patients who have ever had signs or symptoms of heart failure are categorized as having stage C heart failure. Finally, stage D heart failure includes patients who have developed marked heart failure symptoms despite the use of GDMT. Referring patients with ACC/AHA stage D heart failure to an advanced heart failure clinic is certainly appropriate, but patients in earlier stages may also benefit from referral. Early referrals may benefit from the advanced heart failure clinic by facilitating frequent visits, titrating GDMT at a rapid pace, facilitating telemedicine and remote monitoring to discuss disease trajectory, and evaluating patients for novel therapeutic trials [3].

The criteria used to select patients for advanced heart failure therapies such as LVAD and transplantation are rigorous, requiring a committee to appropriately adjudicate a patient’s candidacy; in contrast, the indications for a referral should be much simpler, to facilitate access to these therapies [4].

The American Heart Association released a scientific statement in 2021 aimed at providing guidance for clinicians regarding the timing of referral to an advanced heart failure practice [5]. This manuscript is inclusive of many of the potential benefits that the advanced heart failure practice can provide. In addition, the scientific statement comments on the

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appropriate timing of referral to advanced heart failure clinics. A “golden window” has been suggested as the most appropriate time for referral, wherein onset of high risk features of heart failure occurs, such as the development of recurrent symptoms; inability to tolerate GDMT, including down titration; treatment for ventricular arrhythmias; and worsening of extracardiac organ function, such as renal function. The term “golden window” refers to the timeframe when patients are most likely to meet criteria for advanced therapies, but the disease process has not yet caused irreversible injury precluding therapies such as LVAD or transplantation. This timeframe varies among patients. As patients are weaned from GDMT because of hypotension or worsening renal function, the benefit from neurohormonal blockade is diminished, and further deterioration may result. If a patient develops refractory ventricular arrhythmias, clinical instability and multiorgan dysfunction could ensue. If this golden window is missed, and multiorgan system dysfunction and cardiac cachexia develop, the window may have closed, and the patient may be best served by palliative care.

When reviewing outcomes of referrals, late referrals (after the complications of long-standing heart failure manifest) are common, thus underscoring the importance of increasing early timely referral practices [6]. Many potential reasons for late referrals exist, including concerns regarding losing patients to care by another provider and concerns that standard GDMT might not have been maximally titrated before initiation of a referral. In late stages of heart failure, multiorgan dysfunction, cardiac cachexia, and frailty may preclude life prolonging therapies such as transplantation or LVAD surgery. Although these findings can sometimes be reversed to avoid multiorgan failure, patients should ideally be identified before this process starts [7]. Although referring a patient to an advanced heart failure specialist is unlikely to be futile, patients in the final stages of heart failure are likely to be treated with palliative focused care, such as inotropes or hospice referrals [8]. A recent retrospective analysis of successful heart transplant recipients, those with late referral, defined as those with the greatest markers of end stage heart failure, tended to have significantly greater resource utilization and a trend toward longer lengths of hospital stay [9].

A potentially greater challenge is identifying patients in the ideal range for referral. Symptoms of advanced heart failure are often small insidious, incremental changes that elude the patient and practitioner as concerning features. Although these changes are easily mistaken for innocuous events, decreasing heart failure therapies because of patient intolerance or hypotension may lead to clinical deterioration. A key challenge is identifying whether an individual patient has progressed from heart failure to advanced heart failure and may potentially need therapies beyond standard medical therapies. In an effort to shift the paradigm from late to early referral patterns, in 2017, Jay Baumwol described the I NEED HELP acronym [10] (Table 1). This acronym identifies nine clinical parameters indicating advancing heart failure; each parameter is associated with elevated risk of all-cause mortality in patients with heart failure. If a patient meets any of the nine parameters, referral to an advanced heart failure clinic should be strongly considered. The acronym is aimed at identifying high yield patient characteristics. Although some characteristics are subtle, they should lead clinicians to consider referral to an advanced heart failure clinic. Inotropes are used when clinical findings suggest a low cardiac output state and should be reserved for high risk patients [11]. Outpatients receiving these agents have a particularly high risk of morbidity; therefore, expedited evaluation should be performed in an advanced heart failure clinic [12]. Persistent heart failure symptoms at rest or with usual activity, as well as high natriuretic peptide levels despite medical therapy, indicate some degree of failure of conventional therapies, and that patients are at risk of hospitalization for heart failure as well as death from cardiovascular causes [13, 14]. Worsening liver and renal function are easily measured, objective markers of multiorgan system involvement that suggest that an individual is not being optimally managed with the current strategy [15, 16]. Similarly, ongoing symptoms of congestion and recurrent hospitalization suggest a trend toward decompensation and a need to change therapy course [17]. Patients with higher ejection fractions, in contrast with an ejection fraction less than 20%, may be more likely to recover with GDMT and less likely to benefit from an advanced heart failure referral, because left
ventricular ejection fraction has been demonstrated to be a strong predictor of cardiovascular outcomes [18]. Recurrent appropriate defibrillator shocks occur in patients with end stage heart failure for a variety of reasons; however these events are generally associated with poorer prognosis and may lead to further clinical deterioration [19]. Finally, consistently low blood pressure, or inability to increase GDMT suggests that there is a limitation in standard medical therapies for an individual and is associated with worse prognosis [20].

Socioeconomic barriers may also have roles in the feasibility and timeliness of referrals. A study from Denmark has found that in heart failure patients household income, location of index diagnosis, and index admission at a tertiary care center were associated with invasive hemodynamic testing [21]. Patients belonging to minority racial and ethnic groups have elevated likelihood of being referred to a non-cardiology service after being admitted for heart failure exacerbations, thus potentially leading to delays in advanced heart failure evaluation [22].

Worldwide, many patients with heart failure are managed most acutely by a primary care physician—a practice that has been in place for many years [23, 24]. Although the acuity varies among practices, patients referred for evaluation of advanced heart failure therapies from cardiology practices appear to be more likely to have more advanced disease at the time of referral. Although heart failure referral patterns worldwide are not well described, the practice patterns for advanced heart failure vary substantially among countries, particularly in terms of the use of IV inotropes [25].

The clinical course of patients with heart failure and the development of end stage heart failure can be difficult to predict [26]. Although tools such as cardiopulmonary exercise testing can aid in predicting the need for advanced heart failure therapies, patients with heart failure may show rapid alterations in the clinical course; therefore, frequent reevaluation of patients may be necessary to avoid missing patients as the disease progresses [27].

Many advanced heart failure practices facilitate the implantation and management of Cardiomems (Abbot Cardiovascular Plymouth, MN), which can facilitate medication adjustments and decrease heart failure hospitalization in patients with prior hospitalization or elevated natriuretic peptide levels [28]. However, these devices are specifically intended for individuals at elevated risk of future hospitalization who are in end stage heart failure. Implantable hemodynamic monitoring may help clinicians define the disease trajectory of these higher risk patients, and guide future referral for LVAD or transplant evaluation.

Although patients with heart failure with preserved ejection fraction (HFpEF) are not typically candidates for heart transplantation or mechanical circulatory support, select individuals may benefit
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from referral to an advanced heart failure specialist. Patients with HFpEF with high risk features or uncertain diagnosis may benefit from the multidisciplinary heart failure team’s approach and resources that may not be available elsewhere. To identify patients with HFpEF who may benefit from advanced heart failure referral, the INHALE acronym (Table 2) was developed. This acronym guides general practitioners and cardiovascular specialists deciding when to refer patients to an advanced heart failure clinic [18], which may be able to facilitate diagnostic testing and therapeutics for HFpEF mimickers, such as cardiac amyloidosis and other rarer diseases.

Advanced heart failure clinics may be able to offer patients without an option to receive standard medical therapies a possibility of enrolling in clinical trials that might provide benefits after other options are exhausted. Although the benefits of these trials may be uncertain, these trials are usually grounded in strong preclinical science and may offer potential benefits in the absence of other routes to improve clinical outcomes.

The shared care model is a practice model aiming to maintain primary cardiologists’ involvement in patient care after transplantation. The aim of this model is to enable patients to be treated by local cardiologists in tandem with a transplant team, and to communicate with local providers at regular intervals. The most recent version of the International Society of Heart Lung Transplant guidelines for the care of heart transplant recipients recommends this care model in the 2023 guideline update [29]. Modalities of communication may vary among programs; however, the guidelines recommend periodic conference calls. At our institution, direct communication with individual providers has become standard practice and typically occurs on the day of the patient encounter.

In referring patients to advanced heart failure clinics, a good general rule might be that early is better than late, but late is better than never.

Conflict of Interests

The authors declare no conflicts of interest.

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<th>Table 2</th>
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<tr>
<td>I</td>
<td>In need of a diagnosis</td>
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<tr>
<td>N</td>
<td>Nonresponder to diuretic agents or medical therapy</td>
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<tr>
<td>Natriuretic peptides extremely high</td>
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<td>H</td>
<td>Hospitalizations</td>
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<tr>
<td>A</td>
<td>Acute or chronic end-organ dysfunction</td>
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<td>L</td>
<td>Low blood pressure</td>
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<td>E</td>
<td>Evidence of HFpEF mimics</td>
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BNP, B-type natriuretic peptide; NT-ProBNP, N-terminal pro-B-type natriuretic peptide.


REFERENCES


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