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Advanced Heart Failure and When to Refer For Advanced Therapies

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Objectives

- Review the public health crisis of heart failure (HF)
- Discuss the trajectory of HF and importance of GDMT
- Review survival trends for durable MCS and heart transplantation
- Explain the criteria for considering a referral to an advanced heart failure (AHF) program/provider

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Heart Failure in the United States

6.7 MILLION ADULTS
in the U.S. have heart failure

Expected to increase to 8.5 million by 2030

Lifetime risk of HF has increased to 24%. 1 in 4 persons will develop HF in their lifetime

After cancer,
HF is the leading cause of death

Higher incidence and prevalence in Black individuals

Mortality rates have been increasing since 2012

$70 BILLION total projected heart failure medical costs by 2030.

50% of the costs
are attributed to hospitalization

Bozkurt, B, *et al. J Card Fail* 2023

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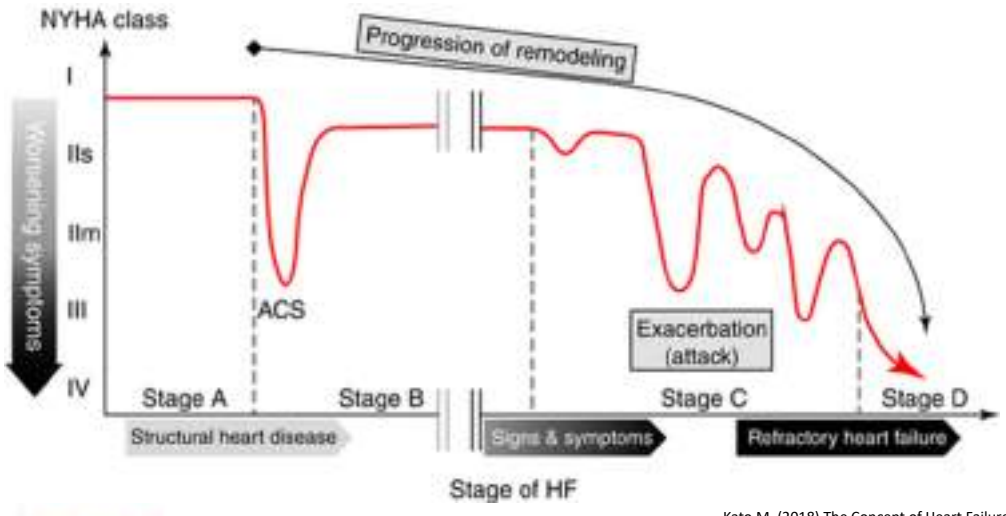
Heart Failure Disease Progression



Kato M. (2018) The Concept of Heart Failure
https://doi.org/10.1007/978-4-431-56065-4_1

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Stages of Heart Failure

TABLE 3 Stages of HF

Stages	Definition and Criteria
Stage A: At Risk for HF	At risk for HF but without symptoms, structural heart disease, or cardiac biomarkers of stretch or injury (e.g., patients with hypertension, atherosclerotic CVD, diabetes, metabolic syndrome and obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or positive family history of cardiomyopathy).
Stage B: Pre-HF	No symptoms or signs of HF and evidence of 1 of the following:
	Structural heart disease[a] ■ Reduced left or right ventricular systolic function ▸ Reduced ejection fraction, reduced stroke ■ Ventricular hypertrophy ■ Chamber enlargement ■ Wall motion abnormalities ■ Valvular heart disease
	Evidence for increased filling pressures[b] ■ By invasive hemodynamic measurements ■ By noninvasive imaging suggesting elevated filling pressures (e.g., Doppler echocardiography)
	Patients with risk factors and ■ ***Increased levels of BNP***[c] **or** ■ ***Persistently elevated cardiac troponin*** in the absence of competing diagnoses resulting in such biomarker elevations such as acute coronary syndrome, CKD, pulmonary embolus, or myopericarditis
Stage C: Symptomatic HF	Structural heart disease with current or previous symptoms of HF.
Stage D: Advanced HF	Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT.

2022 Heart Failure Guidelines; JACC VOL. 79, NO. 17, 2022

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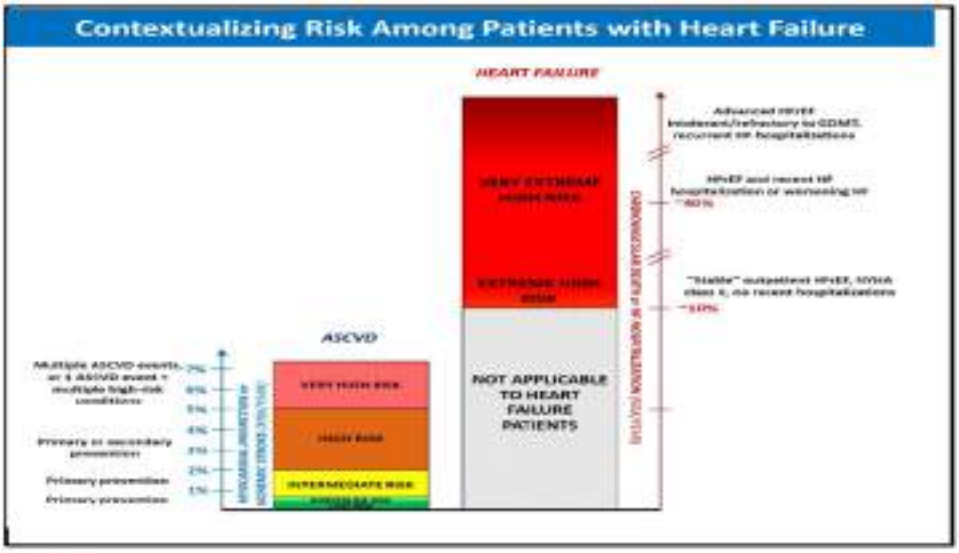
Contextualizing Risk Among Patients With Heart Failure



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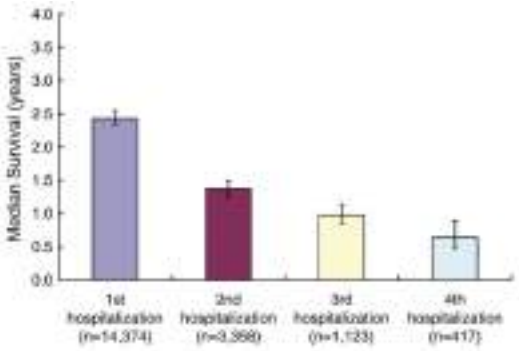
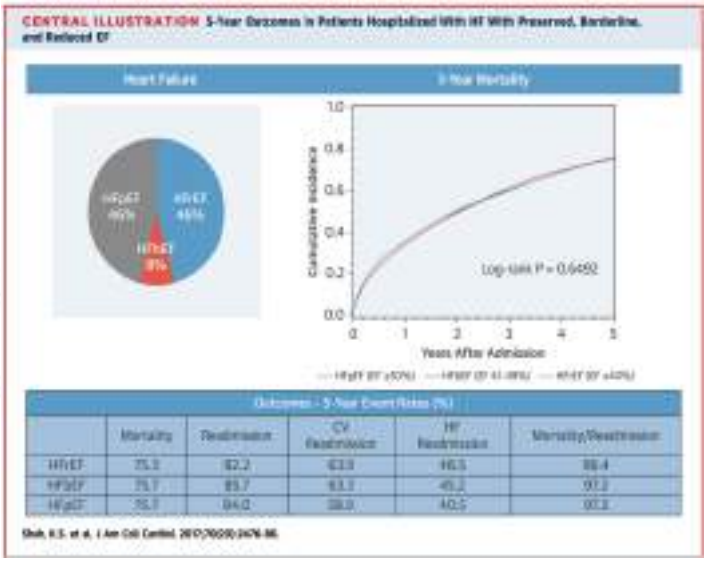
Survival after HF Hospitalization



Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.

Setoguchi et al. *Am Heart J* 2007



Heart Failure with Reduced Ejection Fraction (HFrEF)

- Systolic dysfunction
- EF <50%
- Goals of treatment: slow progression, control symptoms, decrease morbidity and mortality
  - Guideline Directed Medical Therapy (GDMT) to improve survival and symptoms
  - ACEi/ARB/ARNI
    - McMurray JJ et al, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004. doi: 10.1056/NEJMoa1409077. Epub 2014 Aug 30. PMID: 25176015.
  - Hydralazine and long-acting nitrates
  - Beta Blockers
  - Mineralocorticoid Receptor Antagonists (MRAs)
  - Sodium-glucose cotransporter-2 inhibitors (SGLT2i)
    - Fitchett D, et al, EMPA-REG OUTCOME® trial investigators. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. Eur Heart J. 2018 Feb 1;39(5):363-370. doi: 10.1093/eurheartj/ehx511. PMID: 29020355.
    - McMurray JJV et al, DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.
- Loop and thiazide diuretics
- Digoxin
- EP devices: ICD, CRT
- Advanced Cardiac Therapies: LVAD, heart transplantation, continuous inotropes and palliative care

The Four Pillars of HFrEF

- Angiotensin receptor neprilysin inhibitor (ARNI)
- Beta blocker (BB)
- Aldosterone antagonist (AA)
- Sodium glucose cotransporter-2 inhibitor (SGLT2i)

- Cumulative reduction in all-cause mortality if ALL FOUR evidence-based medical therapies are used:
  - Relative risk reduction: 72.9%
  - Absolute risk reduction: 25.5%
  - Number needed to treat (NNT) = 3.9, over 24 months

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GDMT and 2-year survival in RCT

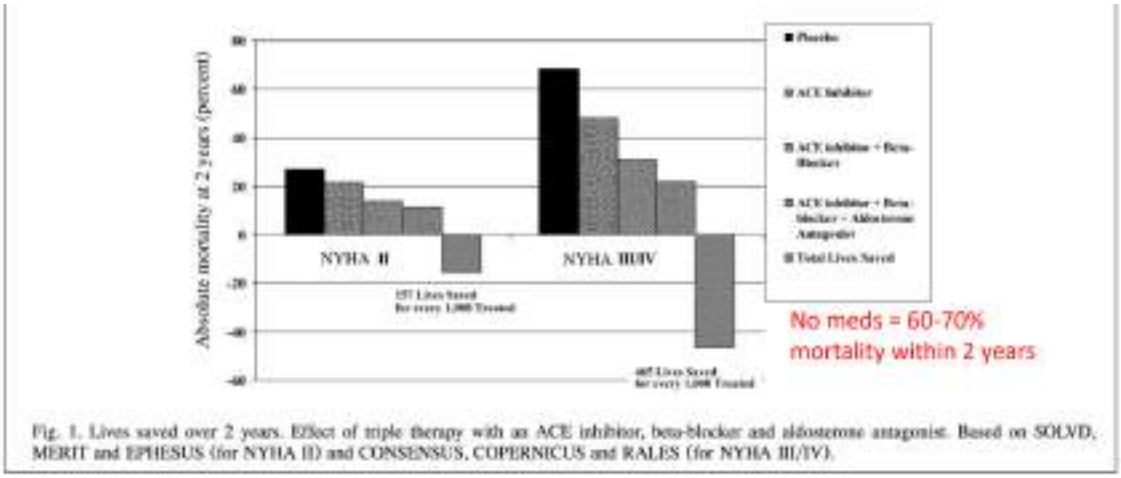

Fig. 1. Lives saved over 2 years. Effect of triple therapy with an ACE inhibitor, beta-blocker and aldosterone antagonist. Based on SOLVD, MERIT and EPHESUS (for NYHA II) and CONSENSUS, COPERNICUS and RALES (for NYHA III/IV).

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CHAMP-HF

- N=2588 (Dec '15 – Oct '17), LVEF ≤ 40%
- At baseline on class
  - MRA: 34%
  - BB: 80%
  - ACEi/ARB: 66%
  - ARNI: 14%
- At baseline on target
  - MRA: 25%
  - BB: 20%
  - ACEi/ARB: 11%
  - ARNI: 2%

MHI
34%
73%
83%

MHI HF
56%
78%
91%

- 12-months initiation or dose increase:
  - MRA: 6%
  - BB: 10%
  - ACEi/ARB: 7
  - ARNI: 10%
- 12-months discontinuation or dose decrease:
  - MRA: 4%
  - BB: 7%
  - ACEi/ARB: 11%
  - ARNI: 3%

12 months: <1% on target of all

Greene SJ et al, *JACC* 2019 May 21.

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HF should be treated more like cancer

- "Intentionally waiting until a cancer becomes metastatic before referral to oncologist would be indefensible"
- "The moment a cancer is even suspected, a seek-and-destroy mission is launched"
- "For a disease with mortality rates rivaling many deadly cancers, the call to action…is comparatively subdued and haphazard."
- Mainstay of therapy is GDMT – BUT adherence as low as 20-30%
- Many providers 'know how to treat heart failure' and referral to AHF is salvage and patients/families are overwhelmed at that point

From Brian Lima, MD (CV Surgeon) from kevinmd.com (2019). https://www.kevinmd.com/2019/05/its-time-we-approach-heart-failure-like-cancer.html

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Why refer to an AHF Specialist/Program?

- Multidisciplinary, proactive approach, shared decision making
- Optimization of GDMT
- Assessment of type of cardiomyopathy and prognosis
- HF staging
- Access to specialized devices to treat HF and clinical trials
- Provide options for advanced therapies:
  - LVAD
  - Heart transplant
  - Palliative inotropes
  - Hospice

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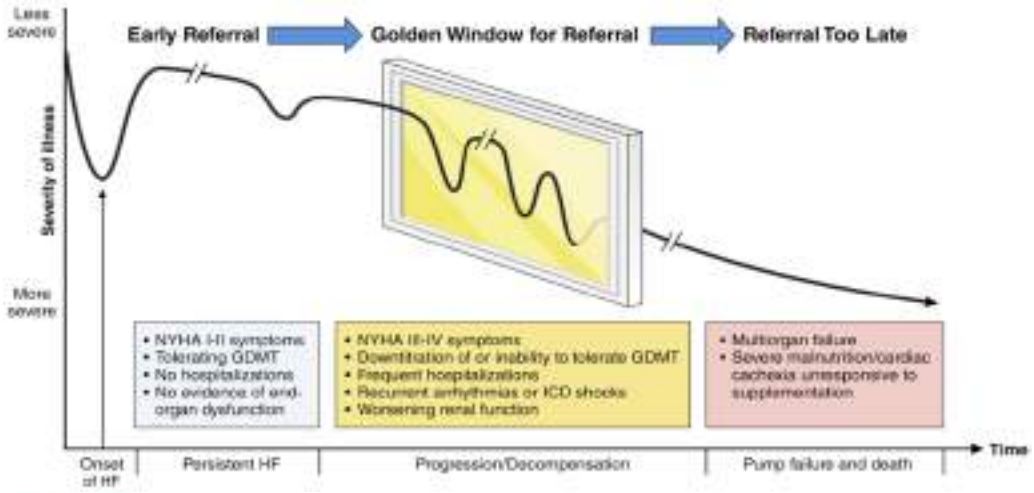
When to Refer: The Goldilocks Scenario



There is never a referral that is "too early"

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INTERMACS Profiles

Profiles	Brief Description	Details
INTERMACS 1	Critical cardiogenic shock (crash and burn)	Life-threatening hypotension despite rapidly escalating inotropic support.
INTERMACS 2	Progressive decline (Sliding fast on inotropes)	Declining function despite intravenous inotropic support.
INTERMACS 3	Stable but inotrope dependent (Dependent stability)	Stable on continuous intravenous inotropic support.
INTERMACS 4	Resting symptoms on oral therapy at home	Patient experiences daily symptoms of congestion at rest or during activities of daily living.
INTERMACS 5	Exertion intolerant	Patient is comfortable at rest and with activities of daily living but unable to engage in any other activity.
INTERMACS 6	Exertion limited (Walking wounded)	Patient has fatigue after the first few minutes of any meaningful activity.
INTERMACS 7	Advanced NYHA class III (Placeholder)	Patients living comfortably with meaningful activity limited to mild physical exertion.

Includes temporary MCS

Ann Thorac Surg. 2024 Jan;117(1):33-44. doi: 10.1016/j.athoracsur.2023.11.004. Epub 2023 Nov 8.

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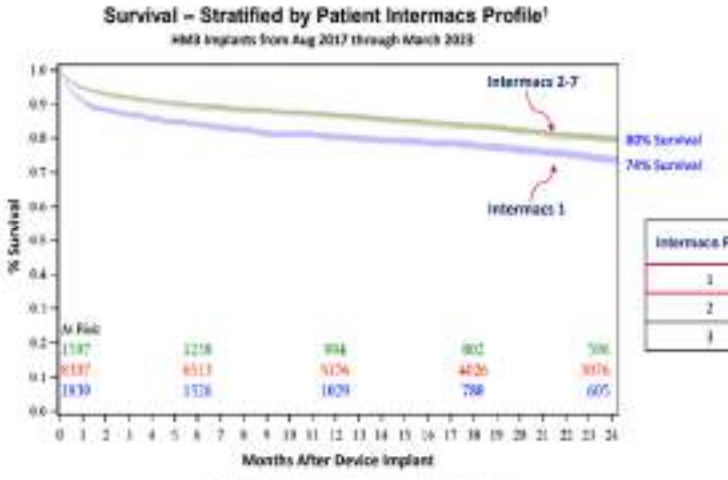
HM3 Survival Stratified by INTERMACS Profile



Intermacs Profile	MOM 3 (%)²	CAP (%)³	STS Intermacs¹
1	2.3%	4.1%	15.7%
2	30.3%	31.0%	33.1%
3	52.8%	50.5%	37.7%

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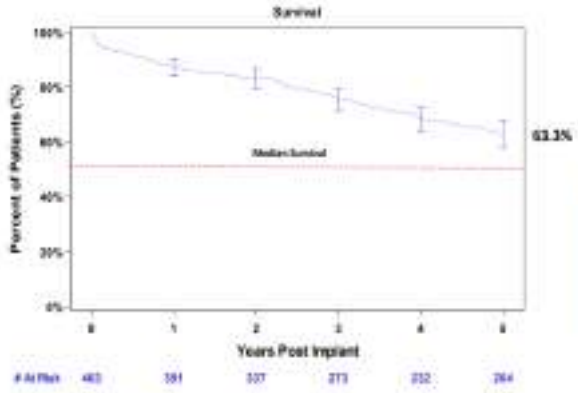
Heartmate 3 Survival

MOMENTUM 3 5-YEAR FOLLOW-UP

Overall Survival: Primary Implant Cohort



A total of 540 patients implanted at 26 centers were included between January 2015 and February 2017.

Overall Survival – Primary Implant Cohort
- HeartMate 3 LVAD 5-year survival 63.3%
- Median survival exceeding 5 years

Mehra et al; JAMA. 2022 Sep 27;328(12):1233-1242. doi: 10.1001/jama.2022.16197.

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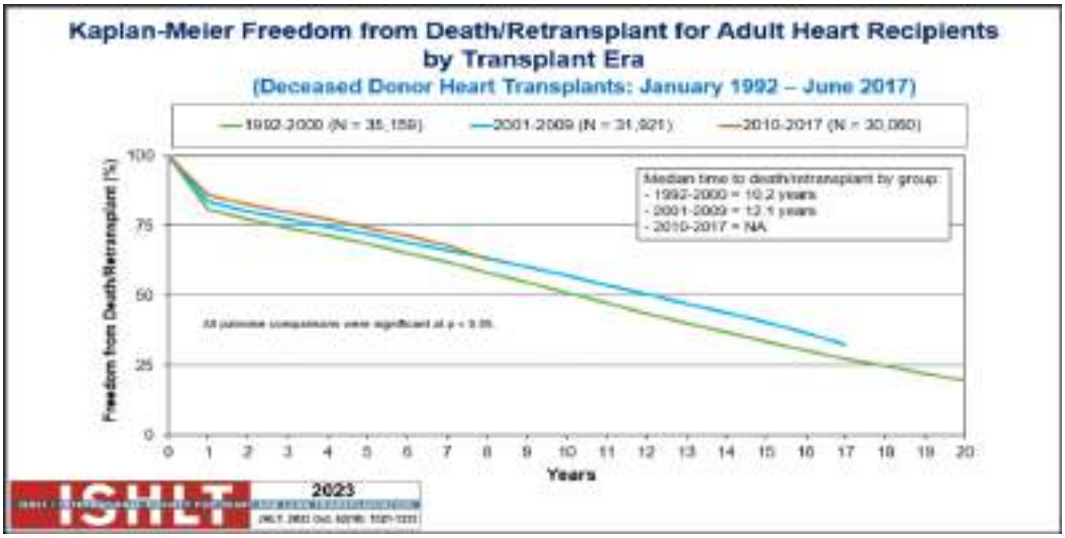
Heart Transplant Survival



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When to Refer to AHF Specialist/Program

There is never a referral that is "too early"

TABLE 6 Triggers for HF Patient Referral to a Specialist/Program

Clinical Scenario	
	1. New-onset HF (regardless of EF): Refer for evaluation of etiology, guideline-directed evaluation and management of recommended therapies, and assistance in disease management, including consideration of advanced imaging, endomyocardial biopsy, or genetic testing for primary evaluation of new-onset HF
	2. Chronic HF with high-risk features, such as development or persistence of one or more of the following risk factors: ■ Need for chronic intravenous inotropes ■ Persistent NYHA functional class III-IV symptoms of congestion or profound fatigue ■ Systolic blood pressure ≤90 mm Hg or symptomatic hypotension ■ Creatinine ≥1.8 mg/dL or BUN ≥43 mg/dL ■ Onset of atrial fibrillation, ventricular arrhythmias, or repetitive ICD shocks ■ Two or more emergency department visits or hospitalizations for worsening HF in the prior 12 months ■ Inability to tolerate optimally dosed beta-blockers and/or ACEI/ARB/ARNI and/or aldosterone antagonists ■ Clinical deterioration, as indicated by worsening edema, rising biomarkers (BNP, NT-proBNP, others), worsened exercise testing, decompensated hemodynamics, or evidence of progressive remodeling on imaging ■ High mortality risk using a validated risk model for further assessment and consideration of advanced therapies, such as the Seattle Heart Failure Model
	3. Persistently reduced LVEF ≤35% despite GDMT for ≥3 months: refer for consideration of device therapy in those patients without prior placement of ICD or CRT, unless device therapy is contraindicated or inconsistent with overall goals of care
	4. Second opinion needed regarding etiology of HF, for example: ■ Coronary ischemia and the possible value of revascularization ■ Valvular heart disease and the possible value of valve repair ■ Suspected myocarditis ■ Established or suspected specific cardiomyopathies (e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, Chagas disease, restrictive cardiomyopathy, cardiac sarcoidosis, amyloid, aortic stenosis)
	5. Annual review needed for patients with established advanced HF in which patients/caregivers and clinicians discuss current and potential therapies for both anticipated and unanticipated events, possible HF disease trajectory and prognosis, patient preferences, and advanced care planning
	6. Assessment of patient for possible participation in a clinical trial

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"Rule of 3" for Timely Referral

- Any <u>one</u> of the following:
  - Repetitive hospitalizations for heart failure (≥ 2 HFH in a year)
  - Escalating diuretic requirements over time to maintain clinical stability
  - Intolerance to GDMT with onset of cardio-renal dysfunction
- Additional groups for referral if the "Rule of 3" conditions are met
  - Mitral valve regurgitation
    - moderate-severe secondary MR ineligible for a percutaneous repair
    - S/P Mitra Clip who exhibit "rule of 3" symptoms post repair
  - CRT non-responders who exhibit "Rule of 3" symptoms

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Other considerations

- Does NOT need to be someone who needs VAD/transplant imminently
  - prefer to meet more patients early in their diagnosis
  - There is never a referral that is "too early"
- Patient with persistent EF <40% and age <60 is at long-term high risk to eventually need advanced therapies and early referral is recommended
- Substance use or non-adherence is not an automatic contraindication
- OK to refer regardless of psychosocial considerations

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Conclusions

- HF has an increasing prevalence and mortality
- GDMT is a priority for improving survival
- There are markers for AHF that nurses and providers need to be aware of
- These markers are triggers for a referral to an AHF specialist/program
- There is no referral that is too early

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