 Updates in Advanced Heart Failure 2019

Sandra Chaparro, MD
Associate Professor
Director Mechanical Circulatory Program,
Director Heart Failure/Transplant Fellowship Program
Statistics

Prevalence

About 6.5 million Americans have HF.¹

Incidence

There are 960,000 new cases of HF diagnosed annually in the USA¹

Mortality

Approximately 50% of HF patients die within 5 years of diagnosis¹,³

Outcomes with each hospitalization

Median survival (50% mortality)

Approach to HFrEF

NYHA Class I

- ACEI, ARB’s, beta blocker. Diuretics if volume overload
- Treat hypertension, diabetes mellitus, coronary artery disease, dyslipidemia.
- Use ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB)

NYHA Class II-III

- Mineralocorticoid receptor antagonist
- Refer for cardiac rehabilitation
- Evaluate for iron deficiency
- Hydralazine-nitrates in African Americans
- Consider cardiac resynchronization therapy and/or ICD
- Consider sacubitril/valsartan (LCZ696)

NYHA Class III - IV

- Consider ivabradine
- Assess biomarkers, evaluate risk
- Consider implantable monitoring device
- End of life discussions
- Transplant
- Palliative care

NYHA Class IV

Owens et al. Circ Research 2016;118:480-495
Strategies by INTERMACS Level

INTERMACS, interagency registry for mechanically assisted circulatory support
Lietz, Miller Curr Opin Cardiol. 2009;24:246-251
New Classification of cardiac shock

EXTREMIS
A patient being supported by multiple interventions who may be experiencing cardiac arrest with ongoing CPR and/or ECMO.

DETERIORATING
A patient who fails to respond to initial interventions. Similar to stage C and getting worse.

CLASSIC
A patient presenting with hyperfusion requiring intervention beyond volume resuscitation (inotrope, pressor, or mechanical support including ECMO). These patients typically present with relative hypotension.

BEGINNING
A patient who has clinical evidence of relative hypotension or tachycardia without hyperfusion.

AT RISK
A patient with risk factors for cardiogenic shock who is not currently experiencing signs or symptoms. For example, large acute myocardial infarction, prior infarction, acute and/or acute on chronic heart failure.

Guidelines

• 2013 ACCF/AHA Guideline for the Management of Heart Failure

• 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure

• 2017 ACC/AHA/HFSA Focused Update Guideline for the Management of Heart Failure

• 2018 Canadian Guidelines and Australian Guidelines

• 2016 ESC Guidelines
### Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ACE: A</td>
<td>The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors <em>(Level of Evidence: A)</em> (9-14), OR ARBs <em>(Level of Evidence: A)</em> (15-18), OR ARNI <em>(Level of Evidence: B-R)</em> (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23, 24), is recommended for patients with chronic HFREF to reduce morbidity and mortality.</td>
</tr>
<tr>
<td>I</td>
<td>ARB: A</td>
<td>In patients with chronic symptomatic HFREF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).</td>
</tr>
</tbody>
</table>

ARNI: angiotensin receptor neprilysin inhibitors
Guidelines

2017 ACC/AHA/HFSA
Focused Update Guideline for the Management of Heart Failure
1. Biomarkers
2. New therapies indicated for stage C HF with reduced ejection fraction (HFrEF)
3. Updates on HF with preserved ejection fraction (HFpEF)
4. New data on important comorbidities, including sleep apnea, anemia, and hypertension
5. And new insights regarding the prevention of HF

Yancy et al. JACC 2017 8:70(6):776-803
Top Clinical Trials in Heart Failure 2019

1. SGLT-2 inhibitors in HFrEF
2. Transcatheter mitral valve repair for functional mitral regurgitation
3. Magnetically levitated circulatory pump for advanced heart failure
4. Tafamidis in ATTR amyloid cardiomyopathy
5. Cardiac Contractility modulation in HFrEF
6. Sacubitril-valsartan therapy in acute heart failure and HFpEF
7. Atrial fibrillation in heart failure
8. Hospital readmission reduction program increases HF mortality
9. Rivaroxaban in HFrEF without atrial fibrillation
10. Intra-atrial shunting device for HFpEF
Sodium Glucose Cotransporter-2 Inhib in HF

Clinical Trials: Dapa HF

Dapagliflozin vs with placebo in HFrEF.

Dapagliflozin 10 mg daily (2,373) versus placebo (2,371).

Primary outcome of cardiovascular death, hospitalization for HF, or urgent HF visit:

16.2% of the dapagliflozin group vs with 21.2% of the placebo group (p = 0.00001)

McMurray et al. NEJM. Sept 19, 2019
Clinical Trials: Mitral Clip

Death from Any Cause

Hazard ratio, 0.62 (95% CI, 0.46–0.82)
P<0.001

Control group
Device group

No. at Risk
Control group 312 294 271 245 219 176 145 121 88
Device group 302 286 269 253 236 191 178 161 124

Stone et al. NEJM Sept 2018; 379:2307-2318
Clinical Trials: Mitral Clip

COAPT vs. MITRA-FR: 12-Month Death or HF Hosp

MITRA-FR

- MitraClip + MT
- MT alone

OR [95% CI] = 1.16 [0.73–1.84]
P = 0.53

54.6% vs. 51.3%

COAPT

- MitraClip + GDMT
- GDMT alone

HR [95% CI] = 0.63 [0.49–0.82]
P < 0.001

46.5% vs. 33.9%

No. at Risk:
- Control Group: 152, 123, 109, 94, 86, 80, 73
- Device Group: 151, 114, 95, 91, 81, 73

No. at Risk:
- Control Group: 312, 244, 205, 174
- Device Group: 302, 264, 238

Obadia JF et al. NEJM Aug 2018; 379:2297-2306

CRT in Inotrope dependent patients

Hernandez et al. JACC HF 2018 Sep;6(9)734-42
Clinical Trial: Tafamidis in TTR

Amyloidosis Cardiomyopathy

Transthyretin amyloid (TTR)
Tafamidis binds to the TTR preventing tetramer dissociation and amyloidogenesis.

Lower all-cause mortality and cardiovascular related hospitalization and improve QOL
Clinical Trial: Tafamidis in TTR

A  Primary Analysis, with Finkelstein–Schoenfeld Method

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>( P ) Value from Finkelstein–Schoenfeld Method</th>
<th>Win Ratio (95% CI)</th>
<th>Patients Alive at Mo 30 no. (%)</th>
<th>Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 per patient per yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Tafamidis</td>
<td>264</td>
<td>(&lt;0.001)</td>
<td>1.70 (1.26–2.29)</td>
<td>186 (70.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Placebo</td>
<td>177</td>
<td></td>
<td></td>
<td>101 (57.1)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

B  Analysis of All-Cause Mortality

- **Pooled tafamidis**
- **Placebo**

Hazard ratio, 0.70 (95% CI, 0.51–0.96)

<table>
<thead>
<tr>
<th>Months since First Dose</th>
<th>Probability of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
</tr>
<tr>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>21</td>
<td>0.3</td>
</tr>
<tr>
<td>24</td>
<td>0.2</td>
</tr>
<tr>
<td>27</td>
<td>0.1</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
</tr>
<tr>
<td>33</td>
<td>0.0</td>
</tr>
</tbody>
</table>

No. at Risk (cumulative no. of events)

<table>
<thead>
<tr>
<th></th>
<th>Pooled tafamidis</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>264 (0)</td>
<td>177 (0)</td>
</tr>
<tr>
<td>3</td>
<td>259 (5)</td>
<td>173 (4)</td>
</tr>
<tr>
<td>6</td>
<td>252 (12)</td>
<td>171 (6)</td>
</tr>
<tr>
<td>9</td>
<td>244 (20)</td>
<td>163 (14)</td>
</tr>
<tr>
<td>12</td>
<td>235 (29)</td>
<td>161 (16)</td>
</tr>
<tr>
<td>15</td>
<td>222 (42)</td>
<td>150 (27)</td>
</tr>
<tr>
<td>18</td>
<td>216 (48)</td>
<td>141 (36)</td>
</tr>
<tr>
<td>21</td>
<td>209 (55)</td>
<td>131 (46)</td>
</tr>
<tr>
<td>24</td>
<td>200 (64)</td>
<td>118 (59)</td>
</tr>
<tr>
<td>27</td>
<td>193 (71)</td>
<td>113 (64)</td>
</tr>
<tr>
<td>30</td>
<td>99 (78)</td>
<td>111 (64)</td>
</tr>
<tr>
<td>33</td>
<td>0 (78)</td>
<td>51 (75)</td>
</tr>
<tr>
<td>33</td>
<td>0 (76)</td>
<td></td>
</tr>
</tbody>
</table>
Transthyretin Cardiac Amyloidosis

Epidemiology

Recognition of ATTR-CM

Noninvasive-Scintigraphy

Diagnosis

Emerging Treatment Options

TAFAMIDIS
Under review by FDA

TAFAMIDIS
Under review by FDA

TAFAMIDIS
Under review by FDA

PATISIRAN

PATISIRAN

INOTERSEN

INOTERSEN

PATISIRAN

INOTERSEN

DIFLUNISAL
Off-label usage

DIFLUNISAL
Off-label usage

DIFLUNISAL
Off-label usage

DIFLUNISAL
Off-label usage

Ruberg et al. JACC 2019;73(22):2872-91
Clinical Trials: FIX HF

Cardiac Contractility Modulation (Optimizer Device)
166 patients with EF between 25 and 45%
NYHA 3 and 4

Abraham et al. JACC Heart Failure. 2018 Oct;6(10):874-883
Clinical Trials: Pioneer HF Trial

![Graph showing change in NT-proBNP from baseline over weeks since randomization for Enalapril and Sacubitril-valsartan. No. at Risk:
- Enalapril: 394, 359, 351, 350, 348
- Sacubitril-valsartan: 397, 355, 363, 365, 349]

Velazquez et al, NEJM 2019; 380:539-548
Clinical Trials: Pioneer HF Trial

**Effect through Week 8**

HR 0.58 (95% CI: 0.40, 0.85)

p = 0.005

**A**

Cumulative Incidence of Serious Composite Endpoint (%)

Days from Randomization

- Enalapril
- Sacubitril/Valsartan

**B**

Cumulative Incidence of CV Death or Rehospitalization for HF (%)

Days from Randomization

- Enalapril
- Sacubitril/Valsartan

**Effect through Week 8**

HR 0.58 (95% CI: 0.39, 0.87)

p = 0.007

Morow et al, Circulation. 2019;139:2285–2288
Sacubitril/valsartan Mortality

Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Clinical Trials: Reduce LAP HF

Interatrial Device in HFpEF

Randomized sham-controlled trial.

In 44 patients with HF and EF ≥40%.

Unloads the left atrium and reduces pulmonary capillary wedge pressure during exercise.

Clinical Trials: TREAD HF Trial

Clinical Trials: TREAD HF Trial

Event rate 45.7% (95% CI 28.5–67.2); p=0.0001

Number at risk
- Control group: 26 (0), 26 (1), 26 (2), 26 (3), 26 (4), 26 (5), 26 (6)
- Treatment withdrawal group: 25 (0), 22 (1), 22 (2), 21 (3), 16 (4), 16 (5), 13 (6)

Duration of Support

Percutaneous

Paracorporal

Implanted
Types of Continuous Flow Devices

Mancini, JACC. 2015;65(23):2542-2555
Use of LVADs and Disease Severity

Mancini et al. JACC. 2015;65(23):2542-2555
LVAD Survival

*82% 2-year survival for heart transplant patients between 2009 and 2015.*

LVAD complications

Continuous Flow LVAD/BiVAD Implants: 2008 – 2013, n = 9372

Instantaneous Death Rate (Hazard) for selected causes

Causes of Death
- Infection
- Bleeding
- RHF
- Neurological
- Device Malfunction
- MSOF

Deaths/Month

Months post implant

Intermacs JHLT 2014;33, 555–564
Quality of life with LVAD

- 100% of HeartMate II DT patients were NYHA Class III/IV status at baseline\(^1\)
- 81% of patients improved to NYHA Class I or II by 24 months\(^1\)

At 6 months, patients are able to walk 377 yards – the length of almost 4 football fields – in 6 minutes

Clinical Trial: Heart Mate 3

- Randomized non inferiority and superiority trial.
- HM2 vs HM3.
- The composite primary end point was survival at 2 years free of disabling stroke or survival free of reoperation to replace or remove a malfunctioning device.
Clinical Trials: Heart Mate 3

Mehra et al. NEJM 2019 380:1618-1627
## Clinical Trials: Heart Mate 3

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Centrifugal-Flow Pump</th>
<th>Axial-Flow Pump</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected or confirmed pump</td>
<td>7 (1.4)</td>
<td>70 (13.9)</td>
<td>0.01</td>
<td>0.12</td>
</tr>
<tr>
<td>thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any stroke</td>
<td>51 (9.9)</td>
<td>98 (19.4)</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>26 (5.0)</td>
<td>38 (7.5)</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>225 (43.7)</td>
<td>278 (55.0)</td>
<td>0.61</td>
<td>0.95</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>126 (24.5)</td>
<td>156 (30.9)</td>
<td>0.31</td>
<td>0.49</td>
</tr>
<tr>
<td>Other neurologic event</td>
<td>59 (11.5)</td>
<td>47 (9.3)</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Any major infection</td>
<td>300 (58.3)</td>
<td>285 (56.4)</td>
<td>0.82</td>
<td>0.82</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>176 (34.2)</td>
<td>143 (28.3)</td>
<td>0.27</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>185 (35.9)</td>
<td>207 (41.0)</td>
<td>0.37</td>
<td>0.45</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>111 (21.6)</td>
<td>98 (19.4)</td>
<td>0.19</td>
<td>0.17</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>73 (14.2)</td>
<td>56 (11.1)</td>
<td>0.11</td>
<td>0.08</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>25 (4.9)</td>
<td>27 (5.3)</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Clinical Trials: Lateral Trial

Lateral Thoracotomy in 144 patients
Heart Ware device

McGee et al. JHLT 2019 Apr;38(4):344-351
Clinical Trials: Lateral Trial

Lateral Thoracotomy in 144 patients
Heart Ware device

McGee et al. JHLT 2019 Apr;38(4):344-351
Clinical Trials: FIVAD

Fully Implanted Ventricular Assist Device
A Jarvik 2000 pump, powered wirelessly using both internal and external components designed by Leviticus Cardi. Allows patients to walk without any physical impediments for up to 8 hours.
Heart Transplant
Heart Transplants by Year

![Graph showing heart transplants by year](graph.png)

-JHLT. 2017 Oct; 36(10): 1037-1079
Survival by Age Group

(Transplants: January 1982 – June 2015)

Median survival (years): Adult=10.7; Conditional=13.2; Pediatric=16.1; Conditional=20.9

p<0.0001

Survival (%)

Years
Leading Causes of Death

(Deaths: January 1994 – June 2016)

- CAV
- Malignancy (non-Lymph/PTLD)
- Infection (non-CMV)
- Graft Failure
- Multiple Organ Failure
- Renal Failure

% of Deaths

0-30 Days (N=6,774)  31 Days - 1 Year (N=5,842)  >1-3 Years (N=4,129)  >3-5 Years (N=3,579)  >5-10 Years (N=9,122)  >10-15 Years (N=6,468)  >15 years (N=4,664)
Organ Preservation

Ardehali et al. Lancet 2015 June;385(9987):2577–84
Cell free DNA

- Detection of increasing amounts of the donor’s DNA in the blood of the recipient.
- The donor DNA accounted for less than 1% of all cell-free DNA in the recipient’s blood.
- During rejection episodes, the donor DNA increased to 4%.

Transplant vasculopathy

- DSE has a sensitivity of 80% and specificity of 88%.
- SPECT has a sensitivity of 21% to 92% and specificity of 55% to 100%.
- CTA has a sensitivity of 94% and specificity of 92%.

Teuterberg et al. JHLT 2015 Feb;34(2):158-60
Transplant vasculopathy

Optical coherence tomography (OCT), allows greater resolution of the coronary vasculature and plaque characterization than IVUS and it is the new gold standard.

Teuterberg et al. JHLT 2015 Feb;34(2):158-60
Heart Transplant and LVADs

Transplant

- 150K
- Waiting time 3K
- Infection
- Renal Failure
- Malignancy

LVAD

- 200K
- Unlimited supply
- Infection
- Thrombosis
- No Malignancy
Costs comparisons


What to do for HFrEF?

**Quadruple therapy:**
- ARNI
- Beta Blocker
- MRA
- SGLT2 inhibitor

Cumulative risk reduction in all-cause mortality, 74% relative, 26% absolute.
NNT 4 in just 2 years
Increase in health status, decrease in hospitalizations

Dr. Greg Fonarow, via Tweeter, Sept 19, 2019
When to Refer

I  IV inotropes
N  NYHA IIIB/IV or persistently elevated natriuretic peptides
E  End-organ dysfunction
E  Ejection fraction ≤35%
D  Defibrillator shocks
H  Hospitalizations >1
E  Edema despite escalating diuretics
L  Low BP, high heart rate
P  Prognostic medication – progressive intolerance or down-titration of GDMT

Yancy et al. JACC. 2018; 71:201-230
Heart Failure Guidelines

ACC/AHA 2016 Guideline Heart Failure and 2017 Update
- www.acc.org

Heart Failure Society of America Guideline
- www.hfsa.org

International Society of Heart and Lung Heart Transplant
- www.ishlt.org

European Society of Cardiology
- www.escardio.org
Contact Information

Sandra Chaparro, MD
schaparro@miami.edu