MEDICAL THERAPY FOR ADVANCED HEART FAILURE
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University of Arizona College of Medicine
Director, Center for Advanced Heart Disease
Banner University Medical Center
Phoenix, AZ
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Disclosure

None
• Recognizing transition to advanced heart failure from chronic heart failure.
• Current status of medical therapy for heart failure – medications, effectiveness and performance.
• Calibrating medical therapy for stage “C” ambulatory and hospitalized patients with heart failure.
• When to refer to a disease management program.
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
CHRONIC HF VERSUS ADVANCED HF

Stage A
High risk with no symptoms

Stage B
Structural heart disease, no symptoms

Stage C
Structural disease, previous or current symptoms

Stage D
Refractory symptoms requiring special intervention

- Hospice
- VAD, transplantation
- Inotropes
- Aldosterone antagonist, nesiritide
- Consider multidisciplinary team
- Revascularization, mitral-valve surgery
- Cardiac resynchronization if bundle-branch block present
- Dietary sodium restriction, diuretics, and digoxin
- ACE inhibitors and beta-blockers in all patients
- ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
- Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
- Risk-factor reduction, patient and family education

Jessup, NEJM 2003; 348:20
ACC/AHA Practice Guidelines
Pyramid Approach to HF Therapy

A
- Treat HTN, lipids;
- smoking cessation, exercise, limit alcohol,
- ACE-I in appropriate populations

Clinical Class remains the #1 predictor of mortality in Heart failure

Classification of HF: ACC/AHA stage vs NYHA class

<table>
<thead>
<tr>
<th>ACC/AHA HF stage</th>
<th>NYHA functional class</th>
<th>Hospital Admission</th>
<th>Annual Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>A At high risk for HF but without structural heart disease or symptoms</td>
<td>None</td>
<td>Rare</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>B Structural heart disease but without HF</td>
<td>I Asymptomatic</td>
<td>≤ 1</td>
<td>10-15%</td>
</tr>
<tr>
<td>C Structural heart disease with prior or current HF symptoms</td>
<td>II Sympt. with moderate exertion</td>
<td>2 – 4</td>
<td>20%</td>
</tr>
<tr>
<td>D Refractory HF requiring specialized interventions</td>
<td>IV Symptomatic at rest</td>
<td>&gt;4</td>
<td>35-50%</td>
</tr>
</tbody>
</table>

MEDICAL THERAPY FOR ADVANCED HEART FAILURE
CHRONIC HF VERSUS ADVANCED HF

ACE inhibitor, ARB or ARNI use is indicated in the following HF population:

A. ACC stage C heart failure patients
B. ACC stage B heart failure patients
C. ACC stage A patients with hypertension
D. All of the above
<table>
<thead>
<tr>
<th>INTERMACS PROFILE-LEVEL</th>
<th>NYHA</th>
<th>Official Shorthand</th>
<th>Modifier options</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS 1</td>
<td>D - IV</td>
<td>“Crash and burn”</td>
<td>+ Arrhythmia, + Temporary Circ Support</td>
</tr>
<tr>
<td>INTERMACS 2</td>
<td>D - IV</td>
<td>“Sliding fast” despite inotropic support</td>
<td>+ Arr, TCS</td>
</tr>
<tr>
<td>INTERMACS 3</td>
<td>D - IV</td>
<td>Stable but inotropic therapy-dependent, in hosp or home</td>
<td>+ Arr + Frequent Flyer</td>
</tr>
<tr>
<td>INTERMACS 4</td>
<td>D, Amb.IV</td>
<td>Resting symptoms on oral therapy at home.</td>
<td>+ Arr + FF</td>
</tr>
<tr>
<td>INTERMACS 5</td>
<td>D, Amb.IV</td>
<td>“Housebound”, Comfortable at rest, symptoms with minimal daily activity</td>
<td>+ Arr + FF</td>
</tr>
<tr>
<td>INTERMACS 6</td>
<td>D, Amb.IV</td>
<td>“Walking wounded”- ADL possible but meaningful activity limited</td>
<td>+ Arr + FF</td>
</tr>
<tr>
<td>INTERMACS 7</td>
<td>C, D III, IIIB</td>
<td>Advanced Class III</td>
<td>+ Arr</td>
</tr>
</tbody>
</table>

**Inotrope/MCS/TX**

**Medical therapy**
54 year old man referred as outpatient with 4 years of HF from DCM. NYHA III-IV, 3 ADHF admissions in 9 months

- Echo EF 15%, EDD 7.4, Mod MR, Mod TR, Mod RV dysfunction
- Cr 1.6, Na 136

- Physical Exam:
  Comfortable at rest. BP 100/75, HR 94, JVD 12, clear lungs, +S3, +S4, P2, Palpable liver, Cool ext. 2+ bilateral edema
- Meds:
  Carvedilol, Lisinopril, Aldactone, Digoxin, Lasix
  6MWD = 265 meters
## MEDICAL THERAPY FOR ADVANCED HEART FAILURE

What clinical hemodynamic profile?

### Congestion at rest?
(e.g. orthopnea, elevated jugular venous pressure, pulmonary rales, S3 gallop, edema)

<table>
<thead>
<tr>
<th>Low perfusion at rest?</th>
<th>No</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td>No</td>
<td>Warm and Dry</td>
<td>Warm and Wet</td>
</tr>
<tr>
<td>Yes</td>
<td>Cold and Dry</td>
<td>Cold and Wet</td>
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</tbody>
</table>

Profile?
# Medical Therapy for Advanced Heart Failure

What clinical hemodynamic profile?

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<td></td>
<td></td>
</tr>
<tr>
<td>Cold and Dry</td>
<td></td>
<td>Cold and Wet</td>
</tr>
</tbody>
</table>

- Low perfusion at rest?:
  - Narrow pulse pressure, cool extremities, hypotension

- Congestion at rest?:
  - Low perfusion at rest: Warm and Dry
  - High perfusion at rest: Cold and Dry

<table>
<thead>
<tr>
<th>BP 100/75 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP 25 mm Hg</td>
</tr>
<tr>
<td>Cool Ext.</td>
</tr>
<tr>
<td>JVD 12</td>
</tr>
<tr>
<td>S3</td>
</tr>
<tr>
<td>2+ Edema</td>
</tr>
</tbody>
</table>
MEDICAL THERAPY FOR ADVANCED HEART FAILURE

What clinical hemodynamic profile?

Congestion at rest?
(e.g. orthopnea, elevated jugular venous pressure, pulmonary rales, S3 gallop, edema)

Low perfusion at rest?
(e.g. narrow pulse pressure, cool extremities, hypotension)

BP 100/75 mm Hg
PP 25 mm Hg
Cool Ext.

JVD 12
S3
2+ Edema

Assessing hemodynamic profile is inadequate.
Ascertain chronic stable versus advanced HF

Warm and Dry
Cold and Dry

Cold and Wet
1. **NYHA Class III-IV Symptoms**
2. **Episodes of volume overload and/or peripheral hypo-perfusion**
3. **Objective evidence of severe cardiac dysfunction**
   (EF<30%, Doppler Pseudonormal or Restrictive filling pattern, PCWP>16mmHg or RAP >12 mmHg)
4. **Severely impaired functional capacity**
   (Inability to exercise, 6MWD<300m, Peak VO2<12-14 ml/kg/min)
5. **HF Hospitalizations**
   (≥1 in past 6 months)
6. **Above occurring despite attempts to optimize diuretics, RAAS antagonists, BB, CRT or in the setting of intolerance to OMT**
54 year old man referred as outpatient with 4 years of HF from DCM. NYHA III-IV, 3 ADHF admissions in 9 months

- Echo EF 15%, EDD 7.4, Mod MR, Mod TR, Mod RV dysfunction
- Cr 1.6, Na 136

Physical Exam:
Comfortable at rest. BP 100/75, HR 94, JVD 12, clear lungs, +S3, +S4, P2, Palpable liver, Cool ext. 2+ bilateral edema

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6MWD = 265 meters

Advanced HF?
54 year old man referred as outpatient with 4 years of HF from DCM. NYHA III-IV, 3 ADHF admissions in 9 months

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Meds:
Carvedilol, Lisinopril, Aldactone, Digoxin, Lasix

6MWD = 265 meters
WHAT CONSTITUTES CLASSIFICATION OF A PATIENT INTO COLD AND WET HEMODYNAMIC PROFILE?

A. Hypotension, warm extremities with JVP of 8 cm.

B. Cold extremities, narrow pulse pressure, elevated JVP and rales.

C. Normotension, peripheral edema and rales along with elevated JVP.

D. Hypertension, rales, lower extremity edema and shortness of breath.
Recognizing transition to advanced heart failure from chronic heart failure.


Calibrating medical therapy for stage “C” ambulatory and hospitalized patients with heart failure.

When to refer to a disease management program.
**MEDICAL THERAPY FOR ADVANCED HEART FAILURE**

**Stage “C” - 2013**

**HFpEF Stage C**
**NYHA Class I – IV**

*Treatment:*

- **Class I, LOE A**
  - ACEI or ARB **AND**
  - Beta Blocker

  **For all volume overload, NYHA class II-IV patients**
  - Add
    - **Class I, LOE C**
      - Loop Diuretics

  **For persistently symptomatic African Americans, NYHA class III-IV**
  - Add
    - **Class I, LOE A**
      - Hydral-Nitrates

  **For NYHA class II-IV patients. Provided estimated creatinine >30 mL/min and K+ <5.0 mEq/dL**
  - Add
    - **Class I, LOE A**
      - Aldosterone Antagonist

Clyde W. Yancy et al. JACC 2013;62:e147-e239
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Stage “C” - 2017

Step 1
Establish Dx of HFrEF; assess volume; initiate GDMT

Step 2
Consider the following patient scenarios

- NYHA class II–IV, provided est. CCl >30 mL/min & K+ <5.0 mEq/L
  Aldosterone antagonist (COR I)

- NYHA class II–III HF, Adequate BP on ACEI or ARB*, No C/I to ARB or sacubitril
  Discontinue ACEI or ARB, initiate ARNI* (COR I)

- NYHA class III–IV, in black patients
  Hydral-Nitrates† (COR I)

- NYHA class II–III, LVEF ≤35%; (caveat: >1 y survival, >40 d post MI)
  ICDE (COR I)

- NYHA class II–IV, LVEF ≤35%, NSR & QRS ≥150 ms with LBBB pattern
  CRT or CRT-D† (COR I)

- NYHA class II–III, NSR, heart rate ≥70 bpm on maximally tolerated dose beta blocker
  Ivabradine (COR IIA)

Step 3
Implement indicated GDMT. Choices are not mutually exclusive, and no order is inferred

- NYHA class III–IV
  Palliative care‡ (COR I)

- Refractory NYHA class III–IV
  Transplant‡ (COR I)

- LVAD‡
  Symptoms improved (COR IIA)

- Investigational studies§

Step 4
Reassess symptoms

Step 5
Consider additional therapy

Continue GDMT with serial reassessment & optimized dosing/adherence

What do we know from CHAMP HF registry?
CHAMP HF (2018)

- ACEI/ARB/ARNI Target dose = 16.7%
- BB Target dose = 27.5%
- MRA Target dose = 76.6%
- Eligible patients simultaneously receiving any dose of all 3 medications = <25%

IMPROVE HF (2010)

- ACEI/ARB Target dose = 36.1%
- BB Target dose = 20.5%
- MRA Target dose = 74.4%

MEDICAL THERAPY FOR ADVANCED HEART FAILURE
US Performance in 2018 (CHAMP HF) and comparison to prior registries (IMPROVE HF)

CHAMP HF
- ACEI/ARB/ARNI
  Target dose = 16.7%
- BB Target dose = 27.5%
- MRA Target dose = 76.6%
- Eligible patients simultaneously receiving any dose of all 3 medications = <25%

IMPROVE HF
- ACEI/ARB
  Target dose = 36.1%
- BB Target dose = 20.5%
- MRA Target dose = 74.4%

Factors reported to prevent GDMT in CHAMP HF
- Low BP
- Higher NYHA class
- CKD
- Hospitalization for HF

Recognizing transition to advanced heart failure from chronic heart failure.


Calibrating medical therapy for stage “C” ambulatory and hospitalized patients with heart failure.

When to refer to a disease management program.
MEDICAL THERAPY FOR ADVANCED HEART FAILURE

Ambulatory Patient

ACEI/ARB (Figure 3A) AND
beta blocker (Figure 3B) with diuretic (Figure 3C) as needed

- For patients with persistent volume overload, NYHA class II-IV
  - Titrate
  - Diuretics (Figure 3C)

- For persistently symptomatic African Americans, NYHA class III-IV
  - Add
  - Hydralazine + isosorbide dinitrate (Figure 3D)

- For patients stable on ACEI/ARB, NYHA class II-III
  - Switch
  - ARNI (Figure 3E)

- For patients with eGFR ≥ 30mL/min/1.72 m², K+ < 5.0 mEq/dL, NYHA class II-IV
  - Add
  - Aldosterone Antagonist (Figure 3F)

- For patients with resting HR ≥ 70, on maximally tolerated beta blocker dose in sinus rhythm, NYHA class II-III
  - Add
  - Ivabradine (Figure 3G)

Evidence

Heart Failure Pathway Writing Committee et al. JACC
2017; j.jacc.2017.11.025
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Ambulatory Patient

HFrEF Stage C Treatment

ACEI/ARB: CONSENSUS
CONSENSUS
SAVE
Solvd
VaL-HeFT
CHARM
Valiant
I-Preserve
HEAAL

ACEI/ARB (Figure 3A) and beta blocker (Figure 3B) with diuretic (Figure 3C) as needed

For patients with persistent volume overload, NYHA class II-IV

Titrated

Hydralazine + ISDN (A-HeFT)

Diuretics (Figure 3C)

For persistently symptomatic African Americans, NYHA class III-IV

Add

Hydralazine + isosorbide dinitrate (Figure 3D)

For patients stable on ACEI/ARB, NYHA class II-III

Switch

ARNI (Figure 3E)

For patients with eGFR ≥ 30mL/min/1.72 m², K⁺ < 5.0 mEq/dL, NYHA class II-IV

Add

Aldosterone Antagonist (Figure 3F)

For patients with resting HR ≥ 70, on maximally tolerated beta blocker dose in sinus rhythm, NYHA class II-III

Add

Ivabradine (Figure 3G)

ALDOSTERONE RALES
EPHESUS EMPHASIS-HF

BB:
U.S. CARVEDILOL
CIBIS-IMERIT-HF
CAPRICORN
COPERNICUS
COMET
SENIORS

Heart Failure Pathway Writing Committee et al. JACC 2017; JACC.2017.11.025
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Ambulatory Patient

A

ACEI/ARB
Select initial dose of ACEI or ARB: See Table 1 for dosing information
Consider increasing dose of ACEI/ARB every 2 weeks until maximum tolerated or target dose is achieved
Monitor blood pressure, renal function, and potassium after initiation and during titration

B

Beta blockers
Select initial dose of beta blocker: See Table 1 for dosing information
Consider increasing dose of beta blocker every 2 weeks until maximum tolerated or target dose is achieved
Monitor heart rate, blood pressure, and for signs of congestion after initiation and during titration

C

Diuretics
Select initial loop diuretic dose:
Initial dose depends on multiple factors including newness to diuretic therapy and renal function
Titrate dose to relief of congestion over days to weeks. In some instances it may be necessary to reduce diuretic dosing in the setting of increasing doses of ACEI/ARB/ARNI
Monitor blood pressure, electrolytes, and renal function after initiation and during titration
If reaching high doses of loop diuretic (i.e., equivalent of 120 mg of furosemide twice daily) consider
a. changing to a different loop diuretic or
b. adding thiazide diuretic, taken together with loop diuretic
Monitor blood pressure, electrolytes, and renal function after initiation and during titration

Benefit
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Ambulatory Patient

ACEI/ARB
- Combined mortality and hospitalization reduction 26-40%
  - Select initial dose of ACEI or ARB: See Table 1 for dosing information
  - Consider increasing dose of ACEI/ARB every 2 weeks until maximum tolerated or target dose is achieved
  - Monitor blood pressure, renal function, and potassium after initiation and during titration

Beta blockers
- Overall mortality reduction 34%
  - Select initial dose of beta blocker: See Table 1 for dosing information
  - Consider increasing dose of beta blocker every 2 weeks until maximum tolerated or target dose is achieved
  - Monitor heart rate, blood pressure, and for signs of congestion after initiation and during titration

Diuretics
- Select initial loop diuretic dose:
  - Initial dose depends on multiple factors including newness to diuretic therapy and renal function
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- a. changing to a different loop diuretic or
- b. adding thiazide diuretic, taken together with loop diuretic
  - Monitor blood pressure, electrolytes, and renal function after initiation and during titration
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Ambulatory Patient

**D**

Hydralazine +isosorbide dinitrate

Select initial dose of hydralazine and
isosorbide dinitrate, either as individual
medications or fixed-dose combination:
See Table 1 for dosing information

Consider increasing dose of hydralazine
and/or isosorbide dinitrate every 2 weeks
until maximum tolerated or target dose
is achieved

Monitor blood pressure after initiation
and during titration

**E**

ARNI

Ensure 36 hours off ACEI, adequate blood pressure,
and eGFR ≥30 mL/min/1.73 m² before initiating
sacubitril/valsartan.

Select starting dose:
See Tables 1 and 3 for dosing information

If patient is taking equivalent of ≤10 mg
twice daily of enalapril
or equivalent of ≤160 mg
daily of valsartan:
24/26 mg twice daily

In 2–4 weeks, assess tolerability
If possible, increase dose stepwise to target of
97/103 mg twice daily
Monitor blood pressure, electrolytes, and renal
function after initiation and during titration

Benefit

- PARADIGM-HF: 20% reduction in cardiovascular death
  or HF hospitalization. \( P < 0.0001 \)
- A-HeFT: Mortality reduction 43%. \( p < 0.01 \)
- First HF hospitalization 33% \( P < 0.001 \)
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Ambulatory Patient

**PARADIGM-HF**
20% reduction in cardiovascular death or HF hospitalization. 
P < 0.0001

**A-HeFT**
Mortality reduction 43%.  
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First HF hospitalization 33%  
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**Hydralazine +isosorbide dinitrate**

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**ARNI**

Ensure 36 hours off ACEI, adequate blood pressure, and eGFR ≥30 mL/min/1.73 m² before initiating sacubitril/valsartan.

Select starting dose:  
See Tables 1 and 3 for dosing information

If patient is taking equivalent of ≤10 mg twice daily of enalapril or equivalent of ≤160 mg daily of valsartan:  
24/26 mg twice daily

If patient is taking equivalent of >10 mg twice daily of enalapril or equivalent of >160 mg daily of valsartan:  
49/51 mg twice daily

In 2–4 weeks, assess tolerability  
If possible, increase dose stepwise to target of  
97/103 mg twice daily  
Monitor blood pressure, electrolytes, and renal function after initiation and during titration

**Heart Failure Pathway Writing Committee et al. JACC**
2017; j.jacc.2017.11.025
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Ambulatory Patient

**Aldosterone Antagonists**
- Select initial dose of aldosterone antagonist: See Table 1 for dosing information
- Consider increasing dose of aldosterone antagonist at least every 2 weeks until maximum tolerated or target dose is achieved
- Monitor electrolytes (especially potassium) and renal function 2-3 days following initiation, and then 7 days after initiation/titration
- Then, check monthly for 3 months and every 3 months afterwards
- Clinical status may warrant closer monitoring

**Ivabradine**
- Re-assess that beta blockers are adjusted to maximally tolerated doses and/or target doses
- See Table 1 for target beta blocker doses
- See Table 2 for indications for ivabradine therapy
- Select starting dose of ivabradine: See Tables 1 and 4 for dosing information
- Age >75 years: 2.5 mg twice daily
- Age <75 years: 5.0 mg twice daily
- Re-assess heart rate in at least 2-4 weeks
- Heart rate <50 bpm or symptoms of bradycardia: Reduce dose by 2.5 mg twice daily or discontinue if already at 2.5 mg twice daily
- Monitor heart rate
- Heart rate 50-60 bpm: Maintain current dose and monitor heart rate
- Heart rate >60 bpm: Increase by 2.5 mg twice daily until reaching maximum dose of 7.5 mg twice daily
- Monitor heart rate

SHIFT
Reduction in HF admissions
Reduction in HF death
[HR 0.74 (P<0.014)]

RALES
RR in mortality 30% (P<0.001)

Benefit
**SHIFT**
Reduction in HF admissions
Reduction in HF death
[HR 0.74 (P=0.014)]

**RALES**
RR in mortality 30% (P<0.001)
Right heart catheterization shows:

- BP 95/65/75 mm Hg
- RA 10 mm Hg
- PA 65/24/35 mm Hg
- PCWP 16 mm Hg
- CO 3.5 L/min
- SVR 1440 dynes/sec
- PVR 435 dynes/sec (5.4WU)

- Acute testing was not successful - admitted to telemetry on IV Milrinone.
- No absolute contraindications for transplant.
- Develops VT and received ICD shock 3 times.
- Placed on IV Amiodarone, and given volume for hypotension.
- The following clinical picture ensues after 2 days despite maximal medical therapy...
Right heart catheterization shows:

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MEDICAL THERAPY FOR ADVANCED HEART FAILURE
Hospitalized Patient

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock pending definitive therapy or resolution</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>BTT or MCS in stage D refractory to GDMT</td>
<td>IIa</td>
<td>B</td>
<td>647, 648</td>
</tr>
<tr>
<td>Short-term support for threatened end-organ dysfunction in hospitalized patients with stage D and severe HF/EF</td>
<td>IIb</td>
<td>B</td>
<td>592, 649, 650</td>
</tr>
<tr>
<td>Long-term support with continuous infusion palliative therapy in select stage D HF</td>
<td>IIb</td>
<td>B</td>
<td>651–653</td>
</tr>
<tr>
<td>Routine intravenous use, either continuous or intermittent, is potentially harmful in stage D HF</td>
<td>III: Harm</td>
<td>B</td>
<td>416, 654–659</td>
</tr>
<tr>
<td>Short-term intravenous use in hospitalized patients without evidence of shock or threatened end-organ performance is potentially harmful</td>
<td>III: Harm</td>
<td>B</td>
<td>592, 649, 650</td>
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<thead>
<tr>
<th>MCS</th>
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<tr>
<td>MCS is beneficial in carefully selected* patients with stage D HF in whom definitive management (eg, cardiac transplantation) is anticipated or planned</td>
<td>IIa</td>
<td>B</td>
<td>660–667</td>
</tr>
<tr>
<td>Nondurable MCS is reasonable as a “bridge to recovery” or “bridge to decision” for carefully selected* patients with HF and acute profound disease</td>
<td>IIa</td>
<td>B</td>
<td>668–671</td>
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<tr>
<td>Durable MCS is reasonable to prolong survival for carefully selected* patients with stage D HF/EF</td>
<td>IIa</td>
<td>B</td>
<td>672–675</td>
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<th>Cardiac transplantation</th>
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<td>Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management</td>
<td>I</td>
<td>C</td>
<td>680</td>
</tr>
</tbody>
</table>

*Although optimal patient selection for MCS remains an active area of investigation, general indications for referral for MCS therapy include patients with LVEF <25% and NYHA class III–IV functional status despite GDMT, including, when indicated, CRT, with either high predicted 1- to 2-year mortality (eg, as suggested by markedly reduced peak oxygen consumption and clinical prognostic scores) or dependence on continuous parenteral inotropic support. Patient selection requires a multidisciplinary team of experienced advanced HF and transplantation cardiologists, cardiothoracic surgeons, nurses and ideally, social workers and palliative care clinicians.

BTT indicates bridge to transplant; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; HF/EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; N/A, not applicable; and NYHA, New York Heart Association.
## Medical Therapy for Advanced Heart Failure

### Hospitalized Patient

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF patients hospitalized with fluid overload should be treated with intravenous diuretics</td>
<td>I</td>
<td>B</td>
<td>737, 738</td>
</tr>
<tr>
<td>HF patients receiving loop diuretic therapy should receive an initial parenteral dose greater than or equal to their chronic oral daily dose; then dose should be serially adjusted</td>
<td>I</td>
<td>B</td>
<td>739</td>
</tr>
<tr>
<td>HF/EF patients requiring HF hospitalization on GDMT should continue GDMT except in cases of hemodynamic instability or where contraindicated</td>
<td>I</td>
<td>B</td>
<td>195, 735, 736</td>
</tr>
<tr>
<td>Initiation of beta-blocker therapy at a low dose is recommended after optimization of volume status and discontinuation of intravenous agents</td>
<td>I</td>
<td>B</td>
<td>195, 735, 736</td>
</tr>
<tr>
<td>Thrombosis/thromboembolism prophylaxis is recommended for patients hospitalized with HF</td>
<td>I</td>
<td>B</td>
<td>21, 770–774</td>
</tr>
<tr>
<td>Serum electrolytes, urea nitrogen, and creatinine should be measured during titration of HF medications, including diuretics</td>
<td>I</td>
<td>C</td>
<td>N/A</td>
</tr>
</tbody>
</table>

When diuresis is inadequate, it is reasonable to:
- give higher doses of intravenous loop diuretics; or
- add a second diuretic (e.g., thiazide)

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<tbody>
<tr>
<td>Low-dose dopamine infusion may be considered with loop diuretics to improve diuresis</td>
<td>Ila</td>
<td>B</td>
<td>38, 739, 740–743</td>
</tr>
<tr>
<td>Ultrafiltration may be considered for patients with obvious volume overload</td>
<td>lib</td>
<td>B</td>
<td>744, 745</td>
</tr>
<tr>
<td>Ultrafiltration may be considered for patients with refractory congestion</td>
<td>lib</td>
<td>C</td>
<td>N/A</td>
</tr>
<tr>
<td>Intravenous nitroglycerin, nitroprusside, or nesiritide may be considered an adjuvant to diuretic therapy for stable patients with HF</td>
<td>lib</td>
<td>A</td>
<td>760–763</td>
</tr>
<tr>
<td>In patients hospitalized with volume overload and severe hyponatremia, vasopressin antagonists may be considered</td>
<td>lib</td>
<td>B</td>
<td>787, 788</td>
</tr>
</tbody>
</table>

COR indicates Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF/EF, heart failure with reduced ejection fraction; LOE, Level of Evidence; and N/A, not available.

MEDICAL THERAPY FOR ADVANCED HEART FAILURE

Back to the hospitalized patient....

- Patient on mechanical ventilator
- Vitals: BP 90/55, HR 104, JVD 12, clear lungs, +S3, +S4, Palpable liver, Cool ext. 2+ edema
- Meds: Milrinone @ 0.5 mcg/kg/min, Amiodarone 0.5mg, Lasix
- Hemodynamics: CO -3.8, CI – 1.8, RA – 14, PCW – 18, SVR – 1108, PVR- 3.1
### MEDICAL THERAPY FOR ADVANCED HEART FAILURE

#### ADVANCED HF AND INTERMACS PROFILES: TRANSITION AMONG PROFILES – A COMMON OCCURRENCE

<table>
<thead>
<tr>
<th>INTERMACS PROFILE-LEVEL</th>
<th>NYHA</th>
<th>Official Shorthand</th>
<th>Modifier options</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMACS 1</td>
<td>D - IV</td>
<td>“Crash and burn”</td>
<td>+ Arrhythmia, + Temporary Circ Support</td>
</tr>
<tr>
<td>INTERMACS 2</td>
<td>D - IV</td>
<td>“Sliding fast” despite inotropic support</td>
<td>+ Arr, TCS</td>
</tr>
<tr>
<td>INTERMACS 3</td>
<td>D - IV</td>
<td>Stable but inotropic therapy-dependent, In hosp or home</td>
<td>+ Arr + Frequent Flyer</td>
</tr>
<tr>
<td>INTERMACS 4</td>
<td>D, Amb.IV</td>
<td>Resting symptoms on oral therapy at home.</td>
<td>+ Arr + FF</td>
</tr>
<tr>
<td>INTERMACS 5</td>
<td>D, Amb.IV</td>
<td>“Housebound”, Comfortable at rest, symptoms with minimal daily activity</td>
<td>+ Arr + FF</td>
</tr>
<tr>
<td>INTERMACS 6</td>
<td>D, Amb.IV</td>
<td>“Walking wounded” - ADL possible but meaningful activity limited</td>
<td>+ Arr + FF</td>
</tr>
<tr>
<td>INTERMACS 7</td>
<td>C,D III, IIIIB</td>
<td>Advanced Class III</td>
<td>+ Arr</td>
</tr>
</tbody>
</table>

Inotrope/MCS/TX

Medical therapy
• Recognizing transition to advanced heart failure from chronic heart failure.
• Current status of medical therapy for heart failure – medications, effectiveness and performance.
• Calibrating medical therapy for stage “C” ambulatory and hospitalized patients with heart failure.
• When to refer to a disease management program.
The determination of advanced heart failure includes consideration of following parameters despite optimal medical therapy except:

A. **NYHA Class III-IV Symptoms**

B. **Objective evidence of severe cardiac dysfunction**  
   (EF<30%, Doppler Pseudonormal or Restrictive filling pattern, PCWP>16mmHg or RAP >12 mmHg)

C. **Severely impaired functional capacity**  
   (Inability to exercise, 6MWD<300m, Peak VO2<12-14 ml/kg/min)

D. **HF Hospitalizations**  
   (≥1 in past 6 months)

E. **Ventricular tachyarrhythmia** successfully treated with antiarrhythmic and defibrillator
MEDICAL THERAPY FOR ADVANCED HEART FAILURE
DURING CALIBRATED MEDICAL THERAPY....DECIDING REFERRAL TO HF PROGRAM

Studies to Consider Initially: (see full guidelines for details)
- BNP/NT-proBNP
- CBC, basic metabolic panel, liver function, iron studies, thyroid studies, HbA1c
- EKG
- Chest X-ray
- Echocardiogram
- Coronary angiogram, cardiac MRI, biopsy, other imaging as appropriate

Serial Evaluation and Titration of Medications
- Clinic visit with history/symptoms, vitals, exam, labs
- If volume status requires treatment, adjust diuretics, follow up 1-2 weeks
- If euvoletic and stable, start/increase/switch GDMT, follow up 1-2 weeks via phone or repeat clinic visit with basic metabolic panel as may be indicated
- Repeat cycle until no further changes are possible or tolerated

Unsuccessful?

End-Intensification/maintenance
- Ongoing assessment
- Additional adjustments as indicated
- Repeat objective data as needed to reestablish prognosis

Assess response to therapy and cardiac remodeling
- Repeat laboratory tests, for example, BNP/NT-proBNP and basic metabolic panel
- Repeat echocardiogram (or similar imaging modality for cardiac structure and function)
- Repeat EKG
- Consider EP referral for those eligible for CRT or ICD

Referral to HF specialist

Heart Failure Pathway Writing Committee et al. JACC 2017;j.jacc.2017.11.025
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- If euvolemic and stable, start/increase/switch GDMT, follow up 1-2 weeks via phone or repeat clinic visit with basic metabolic panel as may be indicated
- Repeat cycle until no further changes are possible or tolerated

Lack of response/instability

End-Intensification/maintenance
- Ongoing assessment
- Additional adjustments as indicated
- Repeat objective data as needed to reestablish prognosis

Assess response to therapy and cardiac remodeling
- Repeat laboratory tests, for example, BNP/NT-proBNP and basic metabolic panel
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- Repeat EKG
- Consider EP referral for those eligible for CRT or ICD

Remember acronym to assist in decision making for referral to advanced heart failure specialist:
I-NEED-HELP (also see Table 6)
I: IV inotropes
N: NYHA III/IV or persistently elevated natriuretic peptides
E: End-organ dysfunction
D: Ejection fraction ≤35%
E: Defibrillator shocks
H: Hospitalizations >1
E: Edema despite escalating diuretics
L: Low blood pressure, high heart rate
P: Prognostic medication – progressive intolerance or down-titration of GDMT

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