Treatment Recommendations for Adults with Various Stages of Heart Failure

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Introduction
Heart failure (HF) is a progressive disease state resulting from disorders of the pericardium, myocardium, endocardium, heart valves or from certain metabolic diseases. Heart failure is the preferred term over congestive heart failure, since not every patient presents with fluid overload. Patients with heart failure will often have symptoms of left ventricular (LV) myocardium dysfunction. HF patients can have a wide range of LV functions leading to various ejection fraction (EF).

Diagnosis Classification
The two widely accepted classifications of HF are the American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) stages of HF and the New York Heart Association (NYHA) functional classifications. The ACCF/AHA stages focus on the development and progression of HF. The NYHA functional classification focuses on the symptoms of the HF and how it reflects on daily activity and exercise tolerance.

Treatment Algorithm
Treatment approaches vary depending on the patient’s clinical presentation of HF. The following table and flowchart demonstrate the treatment algorithm based on the ACCF/AHA stage and NYHA functional classification.

Treatment Options
This section provides a list of common medications used in each class of the HF treatment. It is intended to provide an overview of the treatment options, prices of medications per dose, common adverse drug reactions (ADR) and black box warnings (BBW) of each medication classes.

Table 1. Demographic characteristics of the respondents

| Stage A                                                                 | Stage B                                                                 | Stage C - HFpEF                                | Stage C - HFpEF                                | Stage D                                                                 |
|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------|
| Control BP (goal 130/80 mmHg) and lipid disorders                       | ACEI; ARB if ACEI C/I or intolerable Evident β blocker for all patients with reduced EF (EF≤40%) | ACEI or ARB and GDMT β blocker; diuretic as needed | Control BP-use β blocker, ACEI, ARB                                 | Palliative care                                                       |
| Lower other risk factors (i.e.: weight management, smoking cessation) | Statins for patients with MI history                                   | Indicated GDMT: aldosterone antagonist, ARNI, Hydral-Nitrates, Ivabradine. | Diuretics to relieve symptoms of fluid overload | Transplant                                                             |
|                                                                        |                                                                        |                                                |                                                | LVAD                                                                  |
|                                                                        |                                                                        |                                                |                                                | Investigational studies                                              |
- Avoid ACE inhibitor therapy in non-dialysis patients with creatinine clearance (CrCl)<20 mL/minute
- ARBs (Step 1 for ACCF/AHA Stage A, B, C)[8]
- Candesartan and valsartan preferred over other ARBs based on their efficacy to suppress aldosterone.[9]
- Start candesartan 4-8 mg QD and titrate up to 32 mg QD or valsartan 20 to 40 mg BID and titrate up to 160 mg BID.[10,11]

### Table 2. Definition of HFrEF and HFpEF

| Classification | EF (%) |
|----------------|--------|
| Heart failure with reduced ejection fraction (HFrEF) | ≤40 |
| Heart failure with preserved ejection fraction (HFpEF) | ≥50 |
| HFpEF, borderline | 41–49 |
| HFpEF, improved | >40 |

### Table 3. ACCF/AHA Stages of HF and NYHA Functional Classifications

| NYHA Functional Classification | Definition | ACCF/AHA Stages of HF | Definition |
|-------------------------------|------------|-----------------------|------------|
| I                             | No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. | B | Structure heart disease but without signs or symptoms of HF (i.e.: MI history, LV remodeling, asymptomatic valvular disease) |
| II                            | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. | C | Structure heart disease with prior or current symptoms of HF (i.e.: known structural heart disease with Shortness of breath and fatigue.) |
| III                           | Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity causes symptoms of HF. | | |
| IV                            | Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest. | D | Refractory HF requiring specialized interventions (i.e.: marked symptom at rest despite maximal medication treatment.) |

HTN: hypertension; DM: diabetes mellitus; ASCVD: atherosclerotic cardiovascular diseases; MI: myocardial infarction
Figure 1. Stage C and NYHA Class I-IV Medication Treatment

All patients in Stage C

1. ACEI or ARB
2. GDMT β blocker
3. Diuretic as needed

4. Aldosterone antagonist
5. Discontinuous ACEI/ARB
6. ARNI

7. Ivabradine

Figure 2. Stage A, B and D Treatment

All patients in Stage A

1. Lifestyle modification
2. ACEI or ARB
3. Statins as needed

All patients in Stage B

1. ACEI or ARB
2. Evident β blocker
3. Statins as needed

All patients in Stage D

1. Surgical intervention
2. Palliative care
Table 4. Cost of Treatment Per Dose

| Medication            | Frequency | Dose (initial) | Note                                      | Cost per initial dose* |
|-----------------------|-----------|----------------|-------------------------------------------|------------------------|
| ACE Inhibitors        |           |                |                                           |                        |
| BBW: Fetal/neonatal morbidity and mortality |           |                |                                           |                        |
| Captopril             | TID       | 6.25 mg        | Smallest tablet is 12.5 mg Max dose: 50 mg TID | $0.64–$0.86            |
| Enalapril             | BID       | 2.5 mg         | Max dose: 10-20 mg BID                    | $0.52–$1.46            |
| Fosinopril            | QD        | 5–10 mg        | Max dose: 40 mg QD                        | $0.22–$1.19            |
| Lisinopril            | QD        | 2.5–5 mg       | Max dose: 20-40 mg QD                     | $0.08–$0.97            |
| Perindopril           | QD        | 2 mg           | Max dose: 8-16 mg QD                      | $1.90–$1.97            |
| Quinapril             | BID       | 5 mg           | Max dose: 20 mg BID                       | $1.22                  |
| Ramipril              | QD        | 1.25–2.5 mg    | Max dose: 10 mg QD                        | $1.46–$1.53            |
| Trandolapril          | QD        | 1 mg           | Max dose: 4 mg QD                         | $1.21–1.24             |
| ARBs                  |           |                |                                           |                        |
| BBW: Fetal/neonatal morbidity and mortality |           |                |                                           |                        |
| Candesartan           | QD        | 4–8 mg         | Max dose: 32 mg QD                        | $3.06–$3.31            |
| Losartan              | QD        | 25–50 mg       | Max dose: 50–150 mg QD HF is not an FDA approved indication | $1.67–$3.08            |
| Valsartan             | BID       | 20–40 mg       | Smallest tablet is 40 mg Max dose: 160 mg BID | $0.09–$4.06            |

*Cost is obtained from the lowest AWP of the generic formulation from Lexicomp on 09/09/2019.

**Loop diuretics. QD: once daily; BID: twice daily; TID: three times daily; AF: atrial fibrillation; SrCr: serum creatinine level; N/A: not applicable.
Table 4 (continued). Cost of Treatment Per Dose

| Medication                  | Frequency | Dose (initial) | Note                                                                                           | Cost per initial dose* |
|-----------------------------|-----------|----------------|------------------------------------------------------------------------------------------------|------------------------|
| ARNI - Common ADR: hypotension, renal impairment, hyperkalemia, angioedema BBW: Fetal/neonatal morbidity and mortality |           |                |                                                                                                |                        |
| Sacubitril/ Valsartan       | BID       | 49/51 mg       | May also be initiated at 24/26 mg BID Max dose: 97/103 mg BID • Not to be used in patients with a history of angioedema • Not to be used within 36 hours of the last dose of an ACEI Valsartan in Entresto vs generic Valsartan: • 26 mg=40 mg • 51 mg=80 mg • 103 mg=160 mg | $10.18                 |
|                             |           |                |                                                                                                |                        |
| If channel inhibitor Common ADR: bradycardia, hypertension, AF Decrease HF hospitalization for patients with NYHA II-III stable chronic HFrEF receiving GDMT |           |                |                                                                                                |                        |
| Ivabradine                  | BID       | 5 mg           | Max dose: 7.5 mg BID                                                                           | $8.85                  |
| Aldosterone antagonists – Common ADR: gynecomastia, hyperkalemia (monitor K and SrCr) |           |                |                                                                                                |                        |
| Spironolactone              | QD        | 12.5-25 mg     | Max dose: 25 mg QD or BID                                                                   | $0.08–$0.46           |
| Eplerenone                  | QD        | 25 mg          | Max dose: 50 mg QD                                                                          | $4.17–$4.34           |
| β blockers - Common ADR: fatigue, bradycardia, hypotension |           |                |                                                                                                |                        |
| Bisoprolol                  | QD        | 1.25 mg        | Max dose: 10 mg QD HF is not an FDA approved indication                                      | $1.22–$2.25           |
| Carvedilol                  | BID       | 3.125 mg       | Max dose: 50 mg BID                                                                         | $0.03–$2.14           |
| Carvedilol ER               | QD        | 10 mg          | Max dose: 80 mg QD                                                                          | $9.91–$10.32          |
| Metoprolol Succinate ER     | QD        | 12.5–25 mg     | Smallest tablet is 25 mg Max dose: 200 mg QD                                                 | $1.05–$1.28           |

*Cost is obtained from the lowest AWP of the generic formulation from Lexicomp on 09/09/2019.

**Loop diuretics. QD: once daily; BID: twice daily; TID: three times daily; AF: atrial fibrillation; SrCr: serum creatinine level; N/A: not applicable.
Table 4 (continued). Cost of Treatment Per Dose

| Medication                                      | Frequency | Dose (initial) | Note                                      | Cost per initial dose* |
|------------------------------------------------|-----------|----------------|-------------------------------------------|------------------------|
| Isosorbide Dinitrate and Hydralazine-Common ADR: hypotension, rebound hypertension, headache and dizziness Not to be taken with Phosphodiesterase-5 Enzyme Inhibitor (i.e.: Sildenafil) | TID       | 20/37.5 mg     | Max dose: 40/75 mg TID                    | $4.07                  |
| Fixed-Dose Combination                         | TID or QID| 20–30 mg/25–50 mg | Max dose: 40 mg isosorbide dinitrate TID and 100 mg hydralazine TID | $0.86–$1.31/ $0.07–$0.56 |

**Oral Diuretics:** for stage C HFrEF patients when fluid retention is observed Symptom relief. No mortality decreases.

| Medication | Frequency | Dose (initial) | Note                                      | Cost per initial dose* |
|------------|-----------|----------------|-------------------------------------------|------------------------|
| Bumetanide** | QD or BID | 0.5–1.0 mg     | Max dose: 10 mg QD                        | $1.08–$2.7             |
| Furosemide** | QD or BID | 20–40 mg       | Max dose: 600 mg QD                       | $0.14–$0.59            |
| Torsemide** | QD        | 10–20 mg       | Max dose: 200 mg QD                       | $0.7–$0.82             |
| Chlorothiazide | QD or BID | 250–500 mg     | Max dose: 1000 mg QD                      | $0.69–$1.24            |
| Chlorthalidone | QD       | 12.5–25 mg     | Max dose: 100 mg QD                       | $1.21–$2.30            |
| Hydrochlorothiazide | QD or BID | 25 mg         | Max dose: 200 mg QD                       | $0.08–$0.13            |
| Indapamide  | QD       | 2.5 mg         | Max dose: 5 mg QD                         | $0.83–$1.55            |
| Metolazone  | QD       | 2.5 mg         | Max dose: 20 mg QD                        | $1.33–$3.29            |
| Amiloride   | QD       | 5 mg           | Max dose: 20 mg QD                        | $0.27–$1.29            |
| Spironolactone | QD   | 12.5–25 mg     | Smallest tablet is 25 mg Max dose: 50 mg QD | $0.43–$0.46            |
| Triamterene | BID      | 50–75 mg       | Max dose: 200 mg QD                       | $11.50                 |

*Cost is obtained from the lowest AWP of the generic formulation from Lexicomp on 09/09/2019.

**Loop diuretics. QD: once daily; BID: twice daily; TID: three times daily; AF: atrial fibrillation; SrCr: serum creatinine level; N/A: not applicable.
Beta Blockers (Step 2 for ACCF/AHA Stage B, C)

- For all patients with reduced ejection fraction.
- Start with carvedilol 3.125 mg BID titrate up every two to four weeks as tolerated up to 25 mg BID or 50 mg BID if patient (pt)>85kg for a greater improvement in LVEF comparing to metoprolol succinate and a greater effect on overall mortality comparing to bisoprolol.\(^{(15-17)}\)
- If 25 mg carvedilol not tolerable then use one of the following:
  - Bisoprolol 1.25 mg QD titrate up every two or more weeks as tolerated up to 10 mg QD.\(^{(16)}\)
  - Metoprolol succinate 12.5 to 25 mg QD every two or more weeks as tolerated up to 200 mg QD.\(^{(18)}\)
- Switching among the three recommended beta blockers not recommended.
- Watch for signs of resistant edema for possible dose adjustment or discontinuation.
- Contraindication
  - 2nd or 3rd degree atrioventricular heart block without pacemaker
  - Heart rate<50 bpm without pacemaker
  - Asthma
ARNI (Step 2 for ACCF/AHA Stage C, HFrEF NYHA Class II-III)\(^{20}\)

Used for its benefit of reducing left atrial size, reverse left atrial remodeling and improve in NYHA class.\(^{21}\)

- If patient with adequate BP (Systolic Blood Pressure>100 mmHg) and eGFR≥30 mL/min on moderate to high dose ACEI or ARB,
  - Start Sacubitril/Valsartan (Entresto) at 49 mg/51 mg BID, titrate up by doubling dose every two to four weeks until 97 mg/103 mg BID.
- If patient with adequate BP on low dose ACEI or ARB or no ACEI or ARB,
  - Start Sacubitril/Valsartan (Entresto) at 24 mg/26 mg BID, titrate up by doubling dose every two to four weeks until 97 mg/103 mg BID.
- Contraindication
  - Angioedema

Aldosterone antagonists (Step 3 for ACCF/AHA Stage C)

- Eplerone is preferred over spironolactone due to the endocrine related adverse effects.

Diuretic (Step 3 for ACCF/AHA Stage C)\(^{22}\)

- Start with furosemide 20 mg QD, titrate up to BID. Use the lowest possible dose to achieve goal.
- BID dosing to avoid post-diuretic rebound sodium retention.
- If loop diuretic resistance, add Hydrochlorothiazide 25-100 mg to achieve sequential blockade.

Statins (primary/secondary prevention for cardiovascular disease for ACCF/AHA Stage A, B, C, NYHA class II to IV, EF<35\%)\(^{8,23}\)

- Initiate atorvastatin 10-20 mg (moderate statin therapy) for patients:
  - Low density lipoprotein cholesterol (LDL-C)<190 mg/dL and 10-year cardiovascular disease (CVD) risk of 10 percent or greater
- Initiate atorvastatin 80mg (high intensity statin therapy) for patients:
  - LDL-C≥190 mg/dL without familiar hypercholesterolemia.
- Do not initiate statin therapy with patients with LDL-C<190 mg/dL and 10-year cardiovascular disease (CVD) risk of less than 5 percent.
- LDL fewer than 30 leads to higher cardiovascular risk.

Abbreviations

ACCF: American College of Cardiology Foundation
ACEI: angiotensin-converting enzyme inhibitors
ADR: adverse drug reactions
AF: atrial fibrillation
AHA: American Heart Association
ARB: angiotensin-receptor blockers
ARNI: angiotensin receptor-neprilysin inhibitors
ASCVD: atherosclerotic cardiovascular diseases
BBW: black box warnings
BID: twice daily
BP: blood pressure
BPM: beats per minute
C/I: contraindicated
CrCl: creatinine clearance
CVD: cardiovascular disease
DM: diabetes mellitus
EF: ejection fraction
eGFR: estimated Glomerular filtration rate
GDMT: guideline-directed medical treatment
HF: heart failure
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
HTN: hypertension
LDL-C: low density lipoprotein cholesterol
LV: left ventricular
LVAD: left ventricular assist device
LVEF: left ventricular ejection fraction
MAP: mean arterial pressure
MI: myocardial infarction
N/A: not applicable
NYHA: New York Heart Association
Pt: patient
QD: once daily
SrCr: serum creatinine level
SV: stroke volume
TID: three times daily
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