**Research Report Template**
**Rhys Axon, Ph.D. Updated 20 November 2020**

## PROJECT TITLE & AUTHORS

| | | |
|---|---|---|
| Project Title: | **Therapeutic Inertia in Blood Pressure Control and Heart Failure** | |
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## PROPOSAL CHECKLIST

| Completed (Y) | Checklist item |
|---|---|
| Y | Project title is clear and concise. |
| Y | Names and emails for project advisor(s) and up to five students per group are provided. |
| Y | Abstract is no more than 250 words and retains headings |
| Y | Introduction provides a definition of the topic under study, importance of the topic, and the issue addressed by the study and is no more than one single-spaced page. |
| Y | There is NO literature review section |
| | Purpose of project is clearly and concisely stated |
| Y | Methods section uses headings and represents a summary of the methods used. (Actual methods used should be described if they were modified from the proposal.) |
| Y | Data analysis described is appropriate and responds to the purpose. |
| Y | Appropriate tables are included in the results section. |
| Y | Text of results section interprets the findings reported in the tables, not repeating them. |
| Y | The discussion section includes a description of the most important findings, and relates findings to the literature. |
| Y | The final section of the discussion is the limitations section. |
| Y | The conclusions respond to the purpose statement. |
| Y | Reference list is complete and contains appropriate references, and reference style is applied correctly and consistently. |
| Y | Data collection/recording form(s) and/or questionnaire(s) are included in the appendix. |
| Y | Information is placed in the appropriate section—introduction, methods, results, etc. |
| Y | Template structure is maintained and all required sections are included. Red |

| | |
|---|---|
| | text instructions/examples are removed. Proposal is written in Times New Roman 12-point font and does not exceed 10 single-spaced pages (excluding appendices). Proposal has been spell-checked and grammar-checked. |

**ABSTRACT**

**Specific Aims:** To analyze therapeutic inertia as it relates to blood pressure control in patients with heart failure in an ambulatory care setting compared to American College of Cardiology/American Heart Association (ACC/AHA) guidelines and landmark trial recommended therapy.

**Methods:** Data were collected via retrospective chart review using the electronic record in Cerner from a local patient cohort. Data were collected for over a year and included the two most recent blood pressure measurements. Patients included were part of a dual eligible cohort and identified using Cerner Dynamic Worklist coding for a diagnosis of heart failure. Therapeutic inertia was analyzed with current doses of heart failure medications compared to the landmark trials. Evaluation of blood pressure control was based on the ACC/AHA guideline goal of less than 130/80 mmHg. Data were analyzed using a chi-square test and t-test. The level of significance (p) was set at 0.05.

**Results:** A total of 55 patients were evaluated, and two blood pressure readings were collected for each (17 male, 38 female). Overall 56% of all patients had controlled blood pressure. Analysis of systolic and diastolic blood pressures were statistically different with a p-value of <0.01. Although therapeutic inertia was observed in 54% of patients no statistically significant difference was found between blood pressure control and therapeutic inertia

**Conclusions:** Therapeutic inertia was common, and blood pressure was often higher than the ACC/AHA recommendation for heart failure.

## INTRODUCTION

Providers' failure to increase therapy when treatment goals are unmet is known as therapeutic inertia (TI). TI is one of the contributors to the high prevalence of uncontrolled blood pressure (BP) ≥ 140/90 mm Hg.[1] High risk patients with a diagnosis of diabetes, heart failure (HF), or other manifestations of cardiovascular disease (CVD) could certainly benefit greatly from adequate treatment whether this includes a proper titration regimen or additional pharmacotherapies[2]. These patients face greater morbidity/mortality compared to patients who suffer from high BP alone. BP control is essential in patients with comorbidities like HF because there are a number of factors that contribute to their health. One of the gaps between guideline-recommended treatment and clinical practice is appropriate pharmacotherapy titration/escalation.

HF is an important area of study due to the prevalence of the disease but also the growing impact it has on Americans. This is a growing issue in the United States; according to heart disease and stroke statistics there are 5 million individuals with HF and over 550,000 are newly diagnosed as having HF each year.[4] As these numbers continue to grow and more people are affected the impact could also pose a large financial burden due to the cost associated with HF.

The AHA projections indicate that by 2030 greater than 8 million Americans, 1 in every 33, will have HF.[3] Evaluating these rates and projecting total direct medical cost from 2012 to 2030, this would equate to direct medical cost increasing from $21 billion to $53 billion[5]. Not only does HF have large financial implications, but also has a poor prognosis for patients once diagnosed. For patients greater than 55 years old, the 15-year mortality rate was 39.1% for women and 71.8% for men.[6]

Currently, there is limited data published on TI as it relates to BP control in HF patients. The target population for this study were HF patients within Banner Healthy Together Care Partnership (HTCP) in Tucson, Arizona. The purpose of this study was to compare patients' medication therapy with guideline and landmark trial recommended therapy to evaluate TI in blood pressure control in patients with HF in an ambulatory care setting.

## METHODS

### Design

This was a retrospective cohort study comparing heart failure medication doses and BP control to determine presence of therapeutic inertia.

### Subjects

Participants were eligible if they were part of the Healthy Together Care Partnership (HTCP) cohort through Banner University Medical Group. Patients were in a dual-eligible cohort and identified using Cerner Dynamic Worklist coding with a diagnosis of HF regardless of ejection fraction (EF). Participants with no diagnosis of heart failure were excluded. The study received exemption as Human Research from the University of Arizona Human Subjects Protection Program.

### Measures

Data were collected from patient chart review using a data extraction form developed in RedCap. The form consisted of 5 variables: age, sex, heart failure type, 2 blood pressure readings, and heart failure medications (with doses). Subsequently, de-identified data was transferred to Excel for statistical analysis. The dependent variable was whether or not antihypertensive medications were titrated appropriately, this was determined by comparing current patient doses to guideline recommended target doses for BP.

### Data Collection

Data were de-identified and extracted by retrospective review of the medical record after obtaining the list of HF patients in the Healthy Together Care Partnership. This was done by using the data extraction form and codebook developed in RedCap (Appendix A).

### Data Analysis

The data were entered into a Microsoft Excel spreadsheet. The two BP readings were

averaged for analysis and were presented as mean ± standard deviation.
Data were analyzed using the Chi-Square test for categorical data and t-test assuming unequal variances for interval data with Microsoft Excel Data Analysis Tools. The a priori p-value was 0.05.

**RESULTS**

The optimal medication doses determined by ACC/AHA guidelines and clinical trials are shown in Table 1. Table 2 shows the demographic date of the 55 patients evaluated. A total of 55 patients were evaluated, and two blood pressure readings were collected for each (Table 2). There were 17 male and 38 female patients. Further evaluation by gender revealed that 47% of females and 65% of males were controlled.

Table 3 evaluates the presence of TI in the uncontrolled blood pressure and controlled blood pressure groups. Overall 56% of all patients had controlled blood pressure and 54% had TI. Yet, there was no statistically significant difference between blood pressure control and therapeutic inertia since TI was so common. An analysis of blood pressure between controlled and uncontrolled blood pressure groups is presented in Table 4. Furthermore, Table 4 shows the systolic and diastolic blood pressures were statistically different between controlled and uncontrolled patients with a p value of $<0.01$.

Table 5 compares blood pressure, dose, and medication category. A total of 34 patients received either ACEi or ARB, 41 patients received a BB, 15 patients received MRA, and 10 patients received medications from all three categories. Furthermore, 11 patients (32%) on ACEi/ARB, 10 patients (24%) on BB, and 15 patients on MRA (100%) received full dose. Moreover, Table 5 demonstrated that despite a full dose on monotherapy, 6 patients on ACEi or ARB therapy and 3 patients on BB therapy had uncontrolled blood pressure respectively.

**DISCUSSION**

The current study demonstrated that therapeutic inertia was common (54% TI) and did not correlate to blood pressure control (56% controlled). Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were statistically different for those with and without BP control. The primary issue was SBP being elevated and DBP being controlled. This study highlights a missed opportunity by clinicians to optimize medication therapy for HF and hypertension.

The GUIDE-IT trial found the most common reasons for physicians not increasing the medication doses were when patients were found to be “clinically stable” and/or “already at maximally tolerated therapy.”[7] However, clinical trials showing benefit in HF titrated doses of drugs to a target dose if the patient could tolerate the higher dose and blood pressure was acceptable.

Change the Management of Patients with Heart Failure (CHANGE-HF) registry examined longitudinal titration of heart failure with reduced ejection fraction (HFrEF) medications. The analysis of this cohort found that most patients with HFrEF received less than

50% of the trial dose for beta-blockers (56.7%), ACEi/ARB (75.5%), MRA (65.3%), and ARNI (90.4%) at baseline and 12 months follow-up 1[18,19]. The present results show lower rates of dose titration for beta-blockers and ACEi/ARB.

Titration of drug doses to control BP is an opportunity for pharmacists to improve quality of care [20-22]. Future research could assess pharmacist intervention to prevent therapeutic inertia in BP control in patients with HF.

The limitations of this study include the retrospective data collection from a small sample size. The chart review was retrospective, so the intervals at which each blood pressure was collected were not the same for all patients based on the information available in the chart. There were disproportionately more female patients compared to male patients. Also, reasons for therapeutic inertia were not assessed (e.g., patient preference, intolerance).

## CONCLUSION

The aim of this study was to compare patients' medication therapy with guideline and landmark trial recommended therapy to evaluate TI in blood pressure control in patients with HF in an ambulatory care setting. The current study demonstrated that therapeutic inertia was present in 54% of the cohort and was not related to the control of blood pressure. There was a statistically significant difference between systolic and diastolic blood pressure controls for those with and without control. This study highlighted that there was a missed opportunity by clinicians to optimize medication therapy for heart failure.

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**TABLES AND FIGURES**

Table 1: Optimal Dose of Study Medications Based on ACC/AHA Guidelines and Clinical Trials[8-19]

| Drug | Target Oral Dose |
|---|---|
| Enalapril | 10-20 mg BID |
| Lisinopril | 20-40 mg daily |
| Losartan | 50-150 mg daily |
| Valsartan | 160 mg BID |
| Sacubitril/Valsartan | 97/103 mg BID |
| Bisoprolol | 10 mg daily |
| Carvedilol | 50 mg BID |
| Carvedilol ER | 80 mg daily |
| Metoprolol succinate ER | 200 mg daily |
| Eplerenone | 50 mg daily |
| Spironolactone | 25 mg daily BID |

*BID= twice daily

Table 2: Demographic Data

| | Mean ± SD | Range |
|---|---|---|

| | | |
|---|---|---|
| Age (years) | 64 ± 12.5 | 54-88 |
| Sex (M/F) | 17/38 | -- |
| EF (%) | 50.8 ±14.4 | 20-74 |
| SBP (mmHg) | 128.1 ± 15.8 | 98-165 |
| DBP (mmHg) | 72.5 ± 8.7 | 48-92 |

SD= standard deviation; M/F= male/female; EF= ejection fraction; SBP= systolic blood pressure; DBP= diastolic blood pressure

Table 3: Blood Pressure and Therapeutic Inertia (N = 55)

| Therapeutic Inertia | Uncontrolled Blood Pressure | Controlled Blood Pressure |
|---|---|---|
| Yes | 15 (27%) | 15 (27%) |
| No | 9 (16%) | 16 (29%) |
| P = 0.3* | | |

* p-value is for a 2X2 Chi square test; for uncontrolled blood pressure and controlled blood pressure

Table 4: Blood Pressure Analysis

| Blood Pressure (mm Hg) | Uncontrolled (N = 24) | Controlled (N = 31) |
|---|---|---|
| Systolic | 141 ± 12 * | 117 ± 8 * |
| Diastolic | 76 ± 8 * | 69 ± 8 * |
| Range | 123-165/65-92 | 98-129/48-80 |

*P < 0.01 for systolic and diastolic BP for a student's t-test

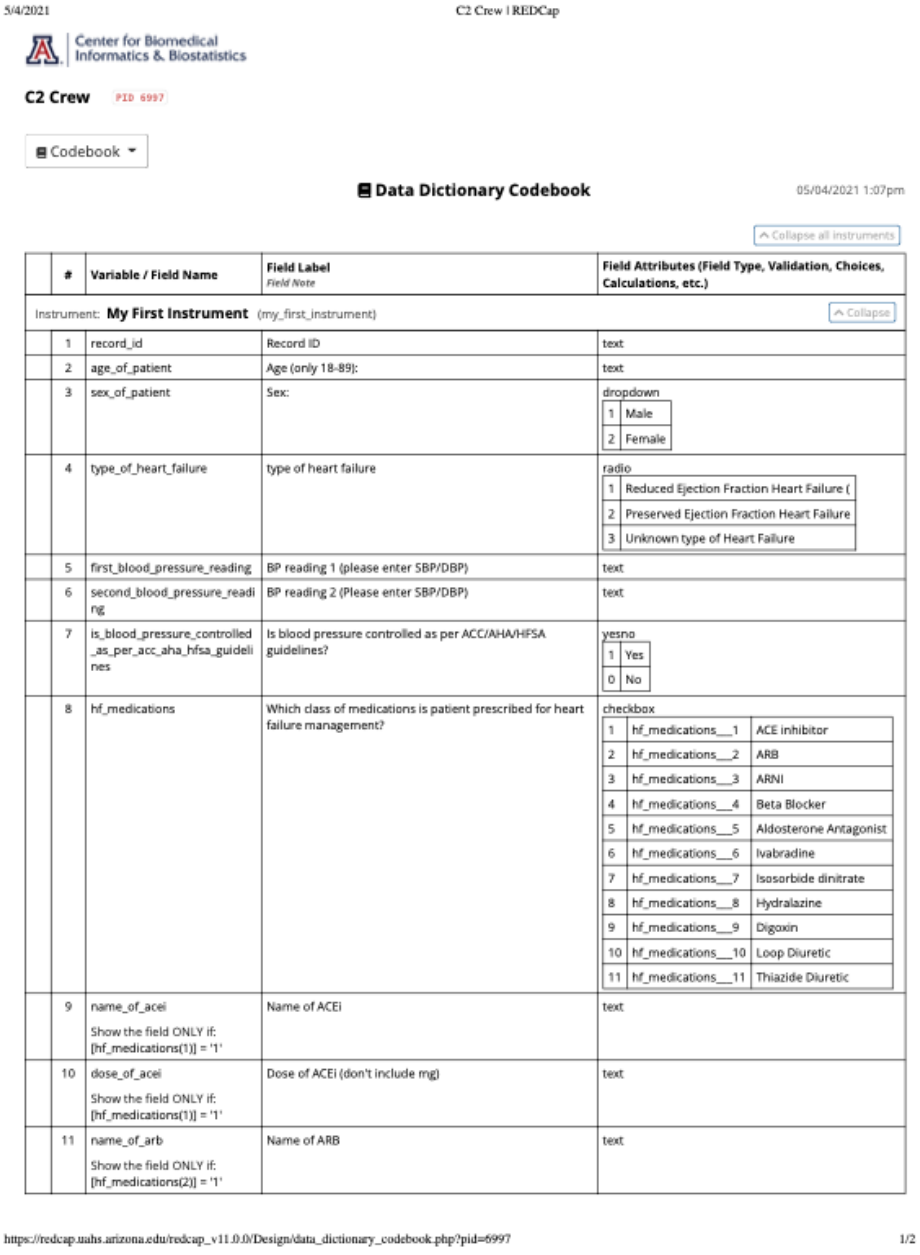
Table 5: Comparison of Blood Pressure and Dose

| | Total number of patients | Target dose | BP High | BP High and target dose |
|---|---|---|---|---|
| RAS | 34 | 11 | 11 | 6 |
| BB | 41 | 10 | 15 | 3 |
| RAS + BB | 26 | 5 | 10 | 4 |
| MRA | 15 | 15 | 5 | 5 |
| All 3 agents | 10 | 3 | 2 | 2 |

BP = blood pressure; MRA= either eplerenone or spironolactone; RAS = renin-angiotensin system inhibitor (either ACEi, ARB, ARNi); BB = beta blocker; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI= angiotensin receptor neprilysin inhibitor

## APPENDICES

### Appendix A: Data Extraction Form and Codebook



5/4/2021 C2 Crew | REDCap

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**C2 Crew** PID 6997

Codebook

**Data Dictionary Codebook** 05/04/2021 1:07pm

Collapse all instruments

| | # | Variable / Field Name | Field Label *Field Note* | Field Attributes (Field Type, Validation, Choices, Calculations, etc.) |
|---|---|---|---|---|
| Instrument: **My First Instrument** (my_first_instrument) Collapse | | | | |
| | 1 | record_id | Record ID | text |
| | 2 | age_of_patient | Age (only 18-89): | text |
| | 3 | sex_of_patient | Sex: | dropdown<br>1, Male<br>2, Female |
| | 4 | type_of_heart_failure | type of heart failure | radio<br>1, Reduced Ejection Fraction Heart Failure (<br>2, Preserved Ejection Fraction Heart Failure<br>3, Unknown type of Heart Failure |
| | 5 | first_blood_pressure_reading | BP reading 1 (please enter SBP/DBP) | text |
| | 6 | second_blood_pressure_reading | BP reading 2 (Please enter SBP/DBP) | text |
| | 7 | is_blood_pressure_controlled_as_per_acc_aha_hfsa_guidelines | Is blood pressure controlled as per ACC/AHA/HFSA guidelines? | yesno<br>1, Yes<br>0, No |
| | 8 | hf_medications | Which class of medications is patient prescribed for heart failure management? | checkbox<br>1, hf_medications___1, ACE inhibitor<br>2, hf_medications___2, ARB<br>3, hf_medications___3, ARNI<br>4, hf_medications___4, Beta Blocker<br>5, hf_medications___5, Aldosterone Antagonist<br>6, hf_medications___6, Ivabradine<br>7, hf_medications___7, Isosorbide dinitrate<br>8, hf_medications___8, Hydralazine<br>9, hf_medications___9, Digoxin<br>10, hf_medications___10, Loop Diuretic<br>11, hf_medications___11, Thiazide Diuretic |
| | 9 | name_of_acei<br>Show the field ONLY if: [hf_medications(1)] = '1' | Name of ACEi | text |
| | 10 | dose_of_acei<br>Show the field ONLY if: [hf_medications(1)] = '1' | Dose of ACEi (don't include mg) | text |
| | 11 | name_of_arb<br>Show the field ONLY if: [hf_medications(2)] = '1' | Name of ARB | text |

https://redcap.uahs.arizona.edu/redcap_v11.0.0/Design/data_dictionary_codebook.php?pid=6997 1/2

## Appendix B: Appropriate HF Medication Doses

- Will utilize chart from Pharmacist's Letter to determine appropriate medication doses and TI

Christopher Fuentes, Xenia Leon, Belle Soyfer

*~This Clinical Resource gives subscribers additional insight related to the Recommendations published in~*

trc pharmacist's letter ~ trc prescriber's letter ~ trc pharmacy technician's letter ~ trc nurse's letter ~

December 2017 ~ Resource #331202

## Target Doses of Meds for Systolic Heart Failure

When dosing medications for chronic systolic heart failure (i.e., heart failure with reduced ejection fraction [HFrEF]), doses associated with cardiovascular outcome benefit in clinical trials should be targeted.[1,4] To this end, initial and target doses of heart failure medications are provided in the table below. For an overview of heart failure treatment, including place in therapy of each medication, see our chart, *Heart Failure Treatment at a Glance*.

***Information in chart may differ from product labeling. Doses for adults with normal renal/hepatic function, unless otherwise noted.***

**Abbreviations:** BP = blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure; SCr = serum creatinine

| Angiotensin-Converting Enzyme Inhibitors (ACEIs) | | | |
|---|---|---|---|
| **Drug** | **Starting Dose for HFrEF** | **Target Dose for HFrEF** | **Comments** |
| Captopril | 6.25 mg three times daily[5] | 50 mg three times daily[5] | • May increase dose after 1 to 2 weeks.[3] If target dose cannot be reached, patients probably receive some benefit from lower doses.[1]<br>• Avoid abrupt discontinuation when possible.[1,4]<br>• Use caution with hypotension, hyponatremia, diabetes, volume depletion, renal disease, potassium use, potassium >5 mEq (mmol)/L, and advanced age.[1,3]<br>• Check potassium, serum creatinine, and BP within a week of initiation or dosage increase in the elderly, and within 1 to 2 weeks of initiation or dose increase in others.[1,3,6,7] (Canada: check potassium and serum creatinine in the first week, fourth week, fourth month, and when clinically indicated.[4]) Recheck in 3 to 4 weeks if stable. If SCr increases <30%, recheck potassium, SCr, and BP after 2 to 3 weeks and again in 3 to 4 weeks.[3] Increases up to 30% that stabilize within 2 to 3 weeks are acceptable.[3,4] Evaluate for hypoperfusion (e.g., volume depletion, NSAID use), then bilateral renal artery stenosis if SCr increases more than 30% within 1 month of starting therapy.[3] SCr increases of 30% to 50% may respond to a 50% dosage decrease.[3] Discontinue if SCr increases more than 1 mg/dL (88.4 umol/L), SCr increases more than 30% within the first 2 months of therapy despite dosage decrease, and perhaps if potassium is >5.5 mEq (mmol)/L.[3,4] If stable, recheck SCr and potassium once or twice yearly, or if patient condition or meds change.[2,3,8]<br>• See footnote "a" regarding hyperkalemia management. |
| Enalapril (*Vasotec*, generics) | U.S.: 2.5 mg twice daily[5]<br>**Canada:** 1.25 to 2.5 mg twice daily[4] | U.S.: 10 mg to 20 mg twice daily[5]<br>**Canada:** 10 mg twice daily, or 20 mg twice daily for NYHA Class IV[4] | |
| Fosinopril | 5 to 10 mg once daily[5] | 40 mg once daily[5] | |
| Lisinopril (*Prinivil*, *Zestril*, generics) | 2.5 to 5 mg once daily[4,5] | U.S.: 20 to 40 mg once daily[5]<br>**Canada:** 20 to 35 mg once daily[4] | |
| Perindopril (*Aceon* **[U.S.]**, *Coversyl* [Canada], generics) | U.S.: 2 mg once daily[5]<br>**Canada:** 2 to 4 mg once daily[4] | U.S.: 8 to 16 mg once daily[5]<br>**Canada:** 4 to 8 mg once daily[4] | |
| Quinapril (*Accupril*, generics) | 5 mg twice daily[5] | 20 mg twice daily[5] | |

*More . . .*





| Angiotensin-Converting Enzyme Inhibitors (ACEIs), continued | | | |
|---|---|---|---|
| **Drug** | **Starting Dose for HFrEF** | **Target Dose for HFrEF** | **Comments** |
| Ramipril (*Altace*, generics) | U.S.: 1.25 to 2.5 mg once daily[5]<br>**Canada:** 1.25 to 2.5 mg twice daily[4] | U.S.: 10 mg once daily[5]<br>**Canada:** 5 mg twice daily[4] | |
| Trandolapril (*Mavik*, generics) | U.S.: 1 mg once daily[5]<br>**Canada:** 1 to 2 mg once daily[4] | 4 mg once daily[4,5] | |
| **Angiotensin II Receptor Blockers (ARBs) with the best evidence for heart failure.** | | | |
| Candesartan (*Atacand*, generics) | 4 to 8 mg once daily[4,5] | 32 mg once daily[4,5] | • Cautions and monitoring as per ACEIs, above.<br>• In general, uptitrate by doubling the dose.[1]<br>• *Entresto* also contains the **neprilysin inhibitor** sacubitril.<br>• For *Entresto*, Canadian guidelines provide dosing and titration specific to comorbidities and pretreatment ACEI/ARB/aldosterone antagonist doses. See table 14 of the guidelines at http://heartfailure.onlinecjc.ca/wp-content/uploads/2017/11/HEART_FAILURE_GUIDELINES-CDN_JRNL_CARDIO-EZEKOWITZ-OCT_2017.pdf. |
| Losartan (*Cozaar*, generics) | 25 to 50 mg once daily[5] | 50 to 150 mg once daily[5] | |
| Valsartan (*Diovan*, generics) | U.S.: 20 to 40 mg twice daily[5]<br>**Canada:** 40 mg twice daily[4] | 160 mg twice daily[4,5] | |
| Sacubitril/valsartan (*Entresto*) | 24/26 to 49/51 mg twice daily[4,5] | 97/103 mg twice daily[4,5] | |
| **Beta-Blockers with the best evidence for heart failure.** | | | |
| Bisoprolol | 1.25 mg once daily[4,5] | 10 mg once daily[4,5] | • Bisoprolol and metoprolol are beta-1 selective; carvedilol blocks beta-1, beta-2, and alpha-1 receptors.[1]<br>• Principal adverse effects: fluid retention, worsening heart failure, fatigue, bradycardia, heart block, and hypotension.[1]<br>• Monitor vitals closely during uptitration.[1] Do not increase dose until any adverse effects have resolved.[1]<br>• Use diuretics to manage fluid retention.[1] |
| Carvedilol (*Coreg*, generics) | 3.125 mg twice daily[4,5] | U.S.: 50 mg twice daily[5]<br>**Canada:** 25 mg twice daily<br>(50 mg twice daily if >85 kg)[4] | |

*More . . .*





| Beta-Blockers with the best evidence for heart failure, continued | | | |
|---|---|---|---|
| **Drug** | **Starting Dose for HFrEF** | **Target Dose for HFrEF** | **Comments** |
| Carvedilol extended-release (*Coreg CR* [U.S. only]) | 10 mg once daily[5] | 80 mg once daily[5] | • Decrease dose in the event of bradycardia associated with dizziness or lightheadedness, or second- or third-degree heart block.[1]<br>• If hypotension occurs, separate beta-blocker from other hypotensive agents (e.g., ACEI), or decrease diuretic dose.[1]<br>• For clinical hypoperfusion, decrease dose or discontinue.[1]<br>• Fatigue blamed on beta-blockers may actually be caused by overdiuresis, sleep apnea, or depression.[1]<br>• Avoid abrupt discontinuation when possible.[1,4]<br>• Continue beta-blocker even if it does not seem to improve heart failure symptoms.[1] |
| Metoprolol succinate extended-release (*Toprol-XL*, generics [U.S. only]) | 12.5 to 25 mg once daily[5] | 200 mg once daily[5] | |
| **Aldosterone Antagonists** | | | |
| Eplerenone (*Inspra*, generics) | 25 mg once daily[4,5] (every-other-day if eGFR 30 to 49 mL/min/1.73 m$^2$)[1] | 50 mg once daily[4,5] (25 mg once daily if eGFR 30 to 49 mL/min/1.73 m$^2$,[1] or with moderate CYP3A4 inhibitors[11,12] [Canada: not recommended in moderate renal impairment if taking a moderate CYP3A4 inhibitor[12]]) | • Do not start if baseline creatinine is 2.5 mg/dL (221 umol/L) or higher in men or 2 mg/dL (176.8 umol/L) or higher in women, eGFR is 30 mL/min/1.73 m$^2$ or less, or potassium is 5 mEq (mmol)/L or higher.[5] (Canadian labeling: contraindicated if eGFR <30 mL/min/1.73m$^2$.)[13,14]<br>• Patients with eGFR <60 mL/min/1.73m$^2$ might not tolerate the max dose.[10]<br>• Use particular caution in ACEI or ARB users with eGFR <45 mL/min/1.73m$^2$ or baseline potassium >4.5 mEq (mmol)/L.[13]<br>• Discontinue or reduce dose of potassium supplements.[1] Counsel patients to avoid high-potassium foods and NSAIDs.[1] For more information on meds that cause hyperkalemia, see our commentary, *Trimethoprim, Hyperkalemia, and Meds that Increase Potassium*.<br>• Hold in the event of diarrhea, dehydration, or loop diuretic interruption.[1]<br>• Check potassium and renal function on day three to seven, at one month, then every three months and when clinically indicated (e.g., ACEI or ARB initiation or dosage increase, renal function insult, etc).[1,9] (Canadian guidelines: in the first week, fourth week, fourth month, and when clinically indicated.[4])<br>• Increase to target dose after four weeks if potassium is 5 mEq (mmol)/L or less.[1] |
| Spironolactone (*Aldactone*, generics) | U.S.: 12.5 to 25 mg once daily[5]<br>**Canada:** 12.5 mg once daily[4]<br>(12.5 mg once daily or every-other-day if eGFR 30 to 49 mL/min/1.73 m$^2$)[1] | U.S.: 25 mg once or twice daily[5]<br>**Canada:** 50 mg once daily[4]<br>(12.5 to 25 mg once daily if eGFR 30 to 49 mL/min/1.73 m$^2$)[1] | |

*More . . .*

| Aldosterone Antagonists, continued | | | |
|---|---|---|---|
| **Drug** | **Starting Dose for HF*r*EF** | **Target Dose for HF*r*EF** | **Comments** |
| | | | • If potassium increases to over 5.5 mEq (mmol)/L, or renal function worsens, decrease dose, hold, or stop. If potassium is 6 mEq (mmol)/L or less, may hold and restart at reduced dose if hyperkalemia and renal insufficiency resolve and are stable for at least 72 hours.[1]<br>• See footnote "a" for a link to additional advice regarding hyperkalemia management.<br>• Eplerenone contraindicated with strong CYP3A4 inhibitors.[11,12] |
| **Vasodilators** | | | |
| Hydralazine and Isosorbide Dinitrate | **Hydralazine**<br>**U.S.:** 25 to 50 mg three to four times daily[5]<br>**Canada:** 37.5 mg three times daily[4] PLUS<br>**Isosorbide dinitrate**<br>**U.S.:** 20 to 30 mg three to four times daily[5]<br>**Canada:** 20 mg three times daily[4] | **Hydralazine**<br>**U.S.:** 100 mg three times daily[5]<br>**Canada:** 75 to 100 mg three to four times daily[4] PLUS<br>**Isosorbide dinitrate**<br>40 mg three times daily[4,5] | • Adherence is poor.[1]<br>• Titrate slowly to improve tolerability.[1]<br>• Principal adverse effects: headache, dizziness, gastrointestinal side effects.[1] |
| Isosorbide Dinitrate 20 mg/Hydralazine 37.5 mg (*BiDil*)(U.S.) | 20/37.5 mg three times daily[5] | 40/75 mg three times daily[5] | |