OBJECTIVES

- By the end of this presentation attendees will be able to:
  - Understand the epidemiology and pathophysiology of heart failure
  - Describe the challenges of managing heart failure in elderly patients
  - Summarize the literature regarding the controversy behind achieving target doses of beta blockers in elderly heart failure patients

DEFINITION OF ELDERLY

- According to the World Health Organization (WHO), most developed countries have accepted the chronological age of ≥65 years as a definition of “elderly” or older persons
- A consensus definition does not exist
  - May vary in underdeveloped countries
Heart failure (HF) is defined as a complex clinical syndrome caused by structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

**Figure 1.**

**Definitions**

- **HF reduced ejection fraction (HFrEF):**
  - Systolic dysfunction
  - Secondary to dilated ventricles
  - Left ventricular ejection fraction (LVEF) ≤40%
  - Randomized controlled trials have mostly enrolled these patients

- **HF preserved ejection fraction (HFpEF):**
  - Diastolic dysfunction
  - Secondary to impaired ventricular filling
  - LVEF ≥50%
  - Currently, efficacious therapies have not shown proven mortality benefits


### CLASSIFICATIONS

<table>
<thead>
<tr>
<th></th>
<th>ACCF/AHA</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs and symptoms of HF</td>
<td>I</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease but with prior or current symptoms of HF</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
<td>IV</td>
</tr>
</tbody>
</table>

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### EPIDEMIOLOGY

#### Prevalence
- Lifetime risk of developing HF is 20% for patients ≥40yo
- >650,000 new HF cases each year

#### Mortality
- 50% within 5 years of diagnosis

#### Hospitalizations
- 75% occur in patients >65yo
- Leading cause of readmissions
- >$30 billion for HF care annually

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### PREVALENCE OF HF IN THE ELDERLY

- Factors contributing to the rise and incidence of HF
  - Age-related cardiovascular changes
  - High prevalence of cardiovascular disease
  - Improved therapies for coronary heart disease

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**PATHOPHYSIOLOGY**

**Figure 3.**

Myocardial Injury →

- **SNS**
  - Vasosecretion
  - Norepinephrine, adrenaline, BP, HR, contractility, etc.

- **RAAS**
  - Vasosecretion
  - BP, sympathetic tone, aldosterone, hypertrophy, fibrosis, etc.

- **NPS**
  - Vasodilation
  - BP, hypertrophy, fibrosis, sympathetic tone, etc.

**CLINICAL PRESENTATION/RISK FACTORS**

**Primary Symptoms**
- Dyspnea
- Fatigue
- Edema
- Exercise intolerance

**Risk Factors**
- Coronary artery disease (CAD)
- Valvular heart disease
- Uncontrolled chronic disease (i.e. Hypertension)
- Cardiomyopathy
- Pericardial disease

**CHALLENGES OF MANAGING HF IN THE ELDERLY**

- **Physiological age-related changes**
  - Influence drug pharmacokinetics and dynamics

- **More complex comorbidities**
  - Higher risk for drug-related side effects
  - Polypharmacy

- **Social issues**
  - Limited access to caregivers and specialists
  - Cognitive impairment
  - Financial problems affect therapy adherence
NON-PHARMACOLOGIC RECOMMENDATIONS

- Patient education
- Restrict sodium intake (1.5-2 grams/day)
- Weight control
- Manage/control underlying causes
- Intensive follow-up
- Smoking cessation
- Restrict alcohol

PHARMACOLOGIC RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Goal</th>
<th>Medication Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage A</td>
<td>Prevent structural heart damage and promote heart healthy lifestyle</td>
<td>ACEI/ARB in patients with vascular disease or DM</td>
</tr>
<tr>
<td>Stage B</td>
<td>Prevent HF symptoms and further cardiac remodeling</td>
<td>ACEI/ARB and beta blockers as appropriate</td>
</tr>
<tr>
<td>Stage C</td>
<td>Control symptoms, prevent morbidity and mortality and slow progression of worsening cardiac function</td>
<td>Diuretics, ACEI/ARB, ARNI, beta blockers, aldosterone antagonists, hydralazine/isosorbide dinitrate, digoxin, nondihydropyridine CCBs</td>
</tr>
<tr>
<td>Stage D</td>
<td>Control symptoms, improve quality of life, reduce hospital admissions, establish end-of-life goals</td>
<td>Advanced care measures, heart transplants, chronic intravenous inotropes, implantable cardiac device, palliative care</td>
</tr>
</tbody>
</table>
BETA BLOCKERS (BBs)
BACKGROUND AND ROLE IN HF

PROPOSED MECHANISM OF ACTION/BENEFICIAL EFFECTS

ROLE OF BETA BLOCKERS IN HF

- 2013 ACCF/AHA HF guidelines states:
  - "Use of 1 of the 3 beta blockers proven to reduce mortality (i.e. bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality."
  - Class I, Level of evidence A
  - "Clinicians should make every effort to achieve the target doses of the beta blockers shown to be effective in major clinical trials."
**Table 4.** Major Placebo-Controlled Trials of BBs Supporting HF Guideline Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Mean follow-up (mo)</th>
<th>N</th>
<th>Patient Population</th>
<th>Mean age (yo)</th>
<th>Target dose</th>
<th>% Achieved Target dose</th>
<th>Mortality/Morbidity (RRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol XL</td>
<td>MERIT-HF (1999)</td>
<td>14</td>
<td>3991</td>
<td>NYHA II-IV; LVEF &lt;40%</td>
<td>64</td>
<td>200 mg daily</td>
<td>64%</td>
<td>↓ 34% / ↓ 18%</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>CIBIS-II (1999)</td>
<td>15.6</td>
<td>2647</td>
<td>NYHA class III-IV; LVEF &lt;35%</td>
<td>61</td>
<td>10 mg daily</td>
<td>48%</td>
<td>↓ 34% / ↓ 28%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>COPERNICUS (2002)</td>
<td>10.4</td>
<td>2289</td>
<td>NYHA class IV; LVEF &lt;25%</td>
<td>63</td>
<td>25 mg BID</td>
<td>65%</td>
<td>↓ 35% / ↓ 20%</td>
</tr>
</tbody>
</table>

*Not approved in the US*

RRR = Relative Risk Reduction

**BACKGROUND: BETA BLOCKERS IN THE ELDERLY**

**Do Elderly Systolic Heart Failure Patients Benefit from Beta Blockers to the Same Extent as the Non-Elderly? Meta-Analysis of >12,000 Patients in Large-Scale Clinical Trials**

Brian R. Dolin, MD, Steven J. Hass, MD, John B. Baker, MD, Wilton T. Abrams, MD, and Harry Krum, MBBS, PhD

**RESULTS**

![Graph showing results for Elderly and Non-Elderly populations](image-url)
BETA BLOCKER CLINICAL TRIALS INVESTIGATED

<table>
<thead>
<tr>
<th>BB</th>
<th>Trial</th>
<th>N</th>
<th>Patient Population</th>
<th>Mean</th>
<th>follow-up (mo)</th>
<th>N (Patient)</th>
<th>% ≥70yo</th>
<th>% Mortality/Morbidity (RRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>MERIT-HF (1999)</td>
<td>12,399</td>
<td>NYHA ll-lV; LVEF &lt;40%</td>
<td>64</td>
<td>12</td>
<td>0.2%</td>
<td>▼34%</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>CIBIS-II (1999)</td>
<td>15.6, 2647</td>
<td>NYHA class III-lV; LVEF &lt;35%</td>
<td>61</td>
<td>15.6</td>
<td>0.2%</td>
<td>▼34%</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>COPERNICUS (2002)</td>
<td>10.4, 2289</td>
<td>NYHA class IV; LVEF &lt;25%</td>
<td>63</td>
<td>10.4</td>
<td>0.2%</td>
<td>▼35%</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Carvedilol U.S. Trials (1996)</td>
<td>6.5, 1094</td>
<td>NYHA ll-lV; LVEF &lt;35%</td>
<td>59</td>
<td>6.5</td>
<td>0.2%</td>
<td>▼65%</td>
<td></td>
</tr>
<tr>
<td>Bucindolol</td>
<td>BEST (2001)</td>
<td>24, 2708</td>
<td>NYHA ll-lV; LVEF &lt;35%</td>
<td>60</td>
<td>24</td>
<td>0.2%</td>
<td>▼8%</td>
<td></td>
</tr>
</tbody>
</table>

* Not approved in the US, NS = not significant, NR = Not reported, BEST (Beta Blocker Evaluation of Survival Trial)

Is achieving target doses of beta blockers in elderly HF patients associated with better clinical outcomes?

EVIDENCE EVALUATING THE EFFECT OF BETA BLOCKERS ON CLINICAL OUTCOMES IN ELDERLY HF PATIENTS

Sin and colleagues, Am J Med 2002
Barywans and colleagues, Int J Cardiology 2015
Palazz and colleagues, Int J Cardiology 2016
THE EFFECTS OF BETA-BLOCKERS ON MORBIDITY AND MORTALITY IN A POPULATION-BASED COHORT OF 11,942 ELDERLY PATIENTS WITH HEART FAILURE
SIN G, MCALISTER F, ET AL, AM J MED 2002;113:650–656

**Aim**
- Evaluate the associations between BBs and outcomes in older HF patients

**Design**
- Retrospective cohort study

**Inclusion Criteria**
- All residents of Alberta, Canada ≥ 65yo who had at least 1 hospitalization for HF between 1994 and 1999

**Exclusion Criteria**
- Patients who died during the index hospitalization
- Patients who had been hospitalized for HF 2 years before the index hospitalization

**Endpoints**
- All-cause mortality
- HF hospitalizations
Methods

- Patients followed from the date of index hospitalization until the date of death, first re-hospitalization for HF, or December 31, 1999, whichever came first
- Evaluated 11,942 patients
- Divided daily dose of BBs into 3 categories:
  - Not dispensed
  - Lower dose (<50% of target dose)
  - Higher dose (≥50% of target dose)

Male (~50%)
- ≥80ys (58%)
- 2569 (22%) had Charlson comorbidity scores of ≥ 2
- Of 11,942 patients, 1162 (10%) received BB therapy
  - 519 (45%) received lower doses
  - 643 (55%) received higher doses
- Most frequently prescribed BB was metoprolol (42%)
- Median follow-up was 21 months

### Table 4. Associations between use of Beta Blockers, by dose, with All-Cause Mortality or Hospitalization for HF

<table>
<thead>
<tr>
<th>Drug</th>
<th>All-Cause Mortality</th>
<th>HF Hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Blocker</td>
<td>0.72 (0.65-0.80)</td>
<td>0.82 (0.74-0.92)</td>
</tr>
<tr>
<td>Lower Dose</td>
<td>0.77 (0.67-0.88)</td>
<td>0.91 (0.80-1.07)</td>
</tr>
<tr>
<td>Higher Dose</td>
<td>0.64 (0.55-0.75)</td>
<td>0.71 (0.60-0.83)</td>
</tr>
</tbody>
</table>

RRR = relative risk reduction
SIN 2002: AUTHOR’S CONCLUSIONS

- Benefits of BBs seen in randomized trials extend to elderly HF patients
  - 28% reduction in mortality and 18% reduction in hospitalizations were consistent with data from previous trials

- All doses of BBs were associated with benefit
  - Greater benefit seen in patients receiving higher doses

- Randomized controlled trials comparing BB doses to functional and clinical outcomes is warranted

SIN 2002: CRITIQUE

**Strengths**
- Large sample size
- Baseline characteristics similar between groups
- Evaluated BB dose associations with mortality and morbidity

**Limitations**
- Retrospective study
- Unable to monitor adherence
- Unable to capture patients without insurance
- Did not collect data on functional status/severity of HF
- Did not determine if patients had systolic or diastolic dysfunction
- Included BBs not proven to reduce morbidity and mortality in HF
- Did not report number of clinical events associated with each dosing group

BARYWANI 2015

Aim
Investigate whether patients receiving ≥50% target dose outperform those receiving <50% target dose, despite maximum up titration, and whether the target dose outperforms ≥50% or <50% target dose groups, in an elderly HF population

Design
Retrospective cohort study
2 specialized HF clinics in Gothenburg, Sweden

Inclusion Criteria
≥ 80yo
LVEF ≤40%

Exclusion Criteria
LVEF >40%

Endpoints
Primary:
All-cause mortality
Secondary:
Cardiac mortality
Hospitalization due to worsening HF

Methods
Up titrated to target dose or highest tolerated dose over 3-6 month period by HF-specialized nurse and cardiologist
Based on clinical assessment and vital signs (i.e. HR <55, SBP <100mmHg)

Definitions of groups:
Low dose: <50% of the target dose
Intermediate: ≥ 50% of target dose but less than the target dose
Highest dose: target dose
BARYWANI 2015: RESULTS

- 185 patients evaluated
- 50% received low dose
- 29% received intermediate dose
- 21% received high dose

- Most frequently prescribed BB was metoprolol succinate (84%)
- More patients with underlying CAD and HTN were in intermediate and high dose BB groups (P= 0.009 and 0.004, respectively)
- No significant differences in HF hospitalizations or non-cardiac deaths
- No significant differences in HR between all 3 groups after up-titration
Safety

- Main reasons for not reaching target doses
  - Symptomatic bradycardia (33%)
  - Symptomatic hypotension (46%)
  - Worsening pulmonary symptoms (1%)

Clinical outcomes of BB therapy is independent of BB dose when the target HR is achieved

Randomized controlled trials are needed to confirm results

- Evaluated elderly patients with multiple comorbidities
- Evaluated optimal clinical outcomes
- Optimally titrated medications at HF clinic
- Used guideline recommended BBs

Strengths:
- Small sample size
- Retrospective study
- Differences in baseline characteristics
**Aim**
- To determine the impact of different doses of BBs on survival and admission for HF in elderly patients with reduced ejection fraction (REF).

**Design**
- Single-center observational study
- Madrid, Spain

**Inclusion Criteria**
- Age ≥ 75yo
- LVEF ≤ 35%

**Exclusion Criteria**
- Patients who died or suffered a major cardiovascular event (HF admission requiring intravenous diuretics or sustained ventricular arrhythmia)

**Endpoints**
- **Primary**: Time to all-cause death
- **Secondary**: Time to first HF admission requiring intravenous diuretics
**Methods**

- 784 patients assessed for eligibility
- Maximal tolerated doses of carvedilol, bisoprolol, metoprolol succinate, and nebivolol were recorded
- Six months after diagnosis, patients were divided into 3 groups depending on BB dose:
  - No BB (NBB)
  - Low dose (LD): <50% of target dose
  - High dose (HD): ≥50% of target dose

**PELAEZ 2016: RESULTS**

- 559 patients included
- Median age ~80yo
- Significant differences baseline characteristics in regards to age, QRS complex width, resting HR, COPD, cognitive impairment, functional disability, ischemic etiology of REF, NYHA class, in the use of implantable cardioverter defibrillator (ICD), and ivabradine
- 24% received NBB
- 46% received LD
- 30% received HD
- Bisoprolol (59%) was the most prescribed BB
- Median follow-up was ~30 months

**Figure 7.**
PELAEZ 2016: AUTHOR’S CONCLUSION

- BB therapy is associated with a significant reduction in mortality among elderly patients with REF, regardless of dose.
- BB therapy may not be associated with a decrease in HF admissions in this patient population.
- Further studies needed to determine optimal doses and their association with clinical outcomes.

PELAEZ, ET AL. 2016: CRITIQUE

Strengths:
- Appropriate statistics
- Patient population was a reflection of real-world clinical practice
- Assessed appropriate clinical outcomes

Limitations:
- Single-center observational study
- Excluded patients with serious events in the first 6 months after diagnosis
- Did not collect data on changes in BB doses during follow-up
- Included BB (nebivolol) not shown to reduce mortality
- Did not evaluate safety

LITERATURE SUMMARY

Sin 2002
- ≥ 65yo HF patients
- All BB doses are associated with benefit (reduction in morbidity and mortality)
- Greater benefit seen with higher doses

Barywani 2015
- ≥ 80yo HF-REF patients
- Highest tolerable doses of BB achieved similar mortality and morbidity outcomes to target doses

Pelaez 2016
- ≥ 75yo HF-REF patients
- All BB doses improved survival
- Found no relationship between BB intake and HF hospitalizations
CONCLUSION
- Up-titration of BBs to target doses in the elderly is challenging
- According to current literature:
  - Survival is independent of BB dose
  - Benefit on morbidity is inconsistent
- Common reasons for up-titration failure:
  - Symptomatic bradycardia, symptomatic hypotension, worsening pulmonary symptoms
- Randomized controlled trials are needed to determine the optimal BB doses
- Would recommend to initiate BBs in this patient population at low doses and titrate up to the highest tolerated dose based on HR and BP

ACKNOWLEDGEMENTS
- Evaluator: Jason Jokerst, PharmD, BCPS
- Committee:
  - April Hinds, PharmD, BCACP
  - Lindsay Vasquez, PharmD, BCPS, BCACP, CDE
  - Maaya Srinivasa, PharmD, BCACP, CDE

QUESTIONS
Target Dose vs Highest Tolerated Dose: Beta-Blocker Therapy in Heart Failure in the Elderly

JASMINE PETERSON, PHARMD
PGY-2 AMBULATORY CARE RESIDENT
COMMUNITY CARE CLINIC
UNIVERSITY OF TEXAS COLLEGE OF PHARMACY AT AUSTIN
OCTOBER 7, 2016