Pharmacotherapy of Chronic Heart Failure in the Elderly: A Review of the Evidence

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Abstract: Heart failure (HF) is a very prevalent disease in the United States and in Europe, with the highest prevalence among older patients. Population estimates suggest substantial growth among the elderly over the next four decades. However, older patients are underrepresented in clinical trials evaluating HF therapies and are less likely to receive the medications shown in these trials to reduce the morbidity and mortality associated with HF. Age-related differences exist in cardiovascular function that may affect disease progression, clinical presentation, and/or response to therapy. Further, medication use in older patients is complicated by physiologic changes in pharmacokinetics and the presence of multiple co-morbidities, which leads to polypharmacy and the related complications. We reviewed the pharmacotherapy clinical trials in HF to review the results specifically in older patients. Trials were included in this review if clinical endpoints were evaluated, if data regarding the participants’ age was reported, and if the intervention studied was in a medication class that is generally recommended for patients with HF by published guidelines. Although some non-randomized data shows benefits of standard therapies may be maintained among patients with HF ≥ 60 years old, the randomized controlled trials that have been published to date showed no benefit and no harm in this group. Cautious HF management among older patients is critical as additional evidence is pursued.

Keywords: heart failure, elderly, older patients, pharmacotherapy
Introduction
Heart failure (HF) affects more than 5 million people in the United States and between 2%–3% of the population in Europe. The prevalence of HF increases with increasing age; approximately 12.2%–13.8% of the women and men, respectively, over the age of 80 have HF compared to 4.8%–9.3% of the women and men, respectively, between 60–79 years old. The incidence and prevalence of HF is increasing and is expected to double in the United States by 2037, largely because of the growing elderly population. In fact, in the United States, the population over the age of 65 is expected to double by 2050; however, the population over the age 85 is growing even faster and is expected to quadruple. Simply put, there are currently approximately 5 million adults over the age 85; by 2050, it is expected this group will have grown to almost 20 million. In spite of these trends, the elderly are historically under-represented in clinical trials and are less likely to be treated with life-saving medications. The American College of Cardiology and American Heart Association joint HF Guidelines recommend applying evidenced-based therapy to the elderly patient, while acknowledging the uncertainties regarding safety and efficacy. Given the population and HF trends, a comprehensive review of the evidence for managing HF in older patients is justified. This review will provide a focused summary of the data specifically for use of pharmacotherapy of HF in older patients (≥60 years).

Methods
A MedLine search was done to identify studies published between 1980 and November 2009 in patients with chronic, symptomatic HF. Trials were included if clinical endpoints were evaluated (mortality and/or morbidity), if the trial reported a descriptor of the patients’ age (mean, median, or distribution), and if the intervention studied was in an approved medication class that is considered beneficial for HF according to published guidelines. Trials were excluded if not fully published (i.e. in abstract form only) or not in English. Meta-analysis, retrospective, and cohort studies were included if the investigators’ primary objective was to evaluate age-related outcomes. Trials evaluating device therapy have been reviewed by others and is not included in the present review.

Pathophysiology
HF is a progressive disease that results from a hostile cardiovascular environment. Cardiovascular injury from heart diseases, such as ischemic disease, hypertension, or valvular disease, typically start the process; this stress leads to structural damage and ensuing neuroendocrine activation. Myocardial scar tissue and fibrosis develop, leading to dilatation, hypertrophy, and, ultimately, systolic and/or diastolic dysfunction; this compromises cardiac output and organ perfusion. The compensatory response to reduced cardiac output starts with renin release and subsequent activation of the renin-angiotensin-aldosterone system. This increases aldosterone and norepinephrine release, which facilitates organ perfusion via sodium and water retention and enhanced cardiac output. However, chronic adrenergic activation increases cardiac workload and vascular and ventricular pressures, thus further contributing to the adverse environment and destructive cycle.

In the elderly, age-related changes in cardiovascular function contribute to the development and progression of HF. Isolated systolic hypertension, the most common form of hypertension in those over the age of 50, occurs as a consequence of connective tissue deposition, increased vascular thickness and stiffness, endothelial dysfunction and elevated pulse pressure; these predispose patients to developing left ventricular hypertrophy and impaired diastolic function. Autopsy studies of those without evident cardiovascular disease show a decrease in ventricular mass, an increase in cardiac interstitial collagen content, an increase in myocyte apoptosis, and development of reactive myocyte hypertrophy; these changes further contribute to the impairment of ventricular compliance. Additionally, various electrophysiologic changes occur in older patients, including the involution of the sinoatrial node, which may lead to the loss of up to 75% of its cells. Age-related changes to neurotransmitter release, clearance, and response also exist. Older patients have higher levels of norepinephrine and epinephrine, but reduced norepinephrine uptake and desensitization of postsynaptic signaling has been demonstrated. This truncated response to
β-adrenergic stimulation could influence the response to compensatory mechanisms, progression of disease, and/or response to therapeutic interventions. Many of these changes are mediated at a fundamental molecular level; in fact, investigations have shown the myocyte action potential duration is increased with aging, likely related to defects in calcium sequestration.\textsuperscript{15,16}

The above pathophysiologic processes manifest as the clinical syndrome of HF when the patient develops symptoms, often months to years after cardiac remodeling has occurred.\textsuperscript{7} The principal symptoms of HF include dyspnea, fatigue, and exertional intolerance. Older patients often experience these typical symptoms, but uncommon symptoms, such as confusion, irritability, somnolence, and anorexia, may manifest more frequently in this population.\textsuperscript{3}

Management with Pharmacotherapy

Drug therapy is a cornerstone for management of HF. However, physiologic differences among older patients could influence the safety and efficacy of pharmacotherapy. Some of the most clinically relevant changes are related to drug distribution, metabolism, and clearance.\textsuperscript{17} Older patients experience a reduction in lean body mass and total body water, which increases concentrations of hydrophilic drugs such as digoxin and angiotensin converting enzyme inhibitors (ACE-inhibitors); this is accompanied by an increase in body fat, which decreases blood levels of highly lipophilic drugs, such as beta-blockers.\textsuperscript{17} Older patients may also metabolize drugs less efficiently, especially for those drugs undergoing oxidation reactions, and may not eliminate drugs as well, especially those drugs that are renally cleared.\textsuperscript{17} Medication use in the elderly is further complicated by multiple co-morbidities, which predisposes to use of multiple medications. Polypharmacy is well recognized as increasing the risk of adverse events in older patients,\textsuperscript{18,19} but data are now starting to accumulate to suggest polypharmacy may be a surrogate marker for increased mortality as well, even after adjustment for co-morbidities.\textsuperscript{20,21} Older patients with cardiovascular disease are particularly prone to orthostatic hypotension, as the cardiovascular disease impairs baroreflex sensitivity and ventricular compliance; this effect is augmented by anti-hypertensives.\textsuperscript{22} These issues must be considered in weighing the relative risks and benefits of using “evidence-based” medicine that was evaluated in studies that predominantly included younger patients; the net clinical impact of an intervention will likely be altered by these confounders.

Clinical trials have clearly shown the benefits of pharmacotherapy that intercepts the neurohormonal activation with ACE-inhibitors,\textsuperscript{23,24} angiotensin receptor blockers (ARBs),\textsuperscript{25–27} and beta-blockers.\textsuperscript{28–31} These therapies are given the highest level recommendation for use in patients with systolic dysfunction by multiple expert HF groups.\textsuperscript{2,7,32} Other treatments that have shown morbidity and mortality benefit in specific populations or provide symptomatic benefit include diuretics,\textsuperscript{33} digoxin,\textsuperscript{34,35} aldosterone blockers,\textsuperscript{36,37} and hydralazine/nitrate combination.\textsuperscript{38} The specific data of each of these drug classes in older patients will be reviewed.

ACE-inhibitors

Randomized controlled trials of ACE-inhibitors presented some of the earliest data about the morbidity and mortality benefits of neurohormonal intervention. However, these early studies did not clearly address the influence of age on outcomes. In one trial, the average age was 59 and 61 years in the placebo and enalapril groups, respectively;\textsuperscript{24} another trial included patients who were older, with an average age of 70 and 71 in the placebo and enalapril groups, respectively.\textsuperscript{23} There was a 16%–27% relative risk reduction in death with ACE-inhibition, but neither trial reported results based on age.\textsuperscript{23,24} Systematic reviews of ACE-inhibitors in HF were conducted to address deficits in the individual trial data, such as the effect based on age. One review found ACE-inhibitors maintained the mortality and hospitalization benefit among those over 60 years old,\textsuperscript{39} but another review found the statistical benefit of ACE-inhibitors disappeared in those over 75 years old (Table). A retrospective review among Medicare recipients reported treatment with ACE-inhibitors was associated with reduced mortality among elderly patients (p = 0.03).\textsuperscript{41} Although average age was not reported in this evaluation, the reported age distribution was as follows: 53% (49 out of 92) of the study group was over the age 75 and 20.6% (19 out of 92) was over age 85.

More recently, the efficacy of perindopril in elderly patients with preserved systolic ventricular function...
## Table. Summary of Key Trials*

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Included age</th>
<th>Age descriptors</th>
<th>HF Type</th>
<th>Design</th>
<th>Results*</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE-Inhibitors</strong></td>
<td></td>
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<tr>
<td>Consensus21</td>
<td>253 N</td>
<td>≥60 only</td>
<td>Mean 70–71 years RE</td>
<td>RCT, PC</td>
<td>40% RRR in mortality</td>
<td>P = 0.002</td>
<td></td>
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<tr>
<td>SOLVD22</td>
<td>2569 N</td>
<td></td>
<td>Mean 59–61 years RE</td>
<td>RCT, PC</td>
<td>No sub-group analyses for age reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEP-CHF40</td>
<td>850 Y</td>
<td></td>
<td>Mean 75 years PR</td>
<td>RCT</td>
<td>No difference all-cause mortality or unplanned HF hospitalization</td>
<td>HR 0.92, 95% CI (0.70–1.21), P = 0.545</td>
<td></td>
</tr>
<tr>
<td>Havranek39</td>
<td>1016 Y</td>
<td></td>
<td>Mean 74 on ACE-I Mean 80 not on ACE-I 53% &gt; 75 years 20.6% &gt; 85 years NR Retro Cohort</td>
<td>12% absolute reduction in 1 year mortality</td>
<td>P = 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garg37</td>
<td>NA N</td>
<td></td>
<td>NR</td>
<td>SR</td>
<td>Sub-group: &gt;60: No significant effect on total mortality 21% RRR in total mortality or hospitalization for HF mortality</td>
<td>OR 0.94, 95% CI (0.78–1.13) OR 0.79, 95% CI (0.66–0.95)</td>
<td></td>
</tr>
<tr>
<td>Flather38</td>
<td>12,763 N</td>
<td></td>
<td>Mean 61 years RE and PR</td>
<td>SR</td>
<td>Sub-group: &gt;75, no difference in death/CHF/MI</td>
<td>HR 0.89 (0.69–1.13)</td>
<td></td>
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<tr>
<td><strong>Angiotensin Receptor Blockers</strong></td>
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<tr>
<td>ELITE II23</td>
<td>3152 Y</td>
<td></td>
<td>Mean 71.4 Y</td>
<td>RE RCT, AC</td>
<td>No difference in all cause mortality</td>
<td>HR 1.13, 95% CI (0.95–1.35), P = 0.16</td>
<td></td>
</tr>
<tr>
<td>Val-HeFT24</td>
<td>5010 N</td>
<td></td>
<td>Mean 62.4–63.0 RE</td>
<td>RCT, PC</td>
<td>Sub-group: ≥65, no significant difference in primary combined endpoint</td>
<td>Detailed statistics not provided</td>
<td></td>
</tr>
<tr>
<td>CHARM-overall25</td>
<td>7601 N</td>
<td></td>
<td>Mean 65.9–66.0 22.8% ≥ 75 years RE and PR</td>
<td>RCT, PC</td>
<td>Sub-group: ≥65&lt;75 and ≥75—candesartan reduced CV death or CHF admission</td>
<td>Detailed statistics not provided</td>
<td></td>
</tr>
<tr>
<td>VALIDD44</td>
<td>384 N</td>
<td></td>
<td>Mean 60.2–61.1 years PR</td>
<td>RCT, AC</td>
<td>No sub-group analyses for age reported</td>
<td></td>
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<tr>
<td>I-Preserve43</td>
<td>4128 Y</td>
<td></td>
<td>Mean 72 years 60.3% ≥ 75 years PR</td>
<td>RCT, PC</td>
<td>No difference in all-cause death or CV hospitalization</td>
<td>HR 0.95, 95% CI (0.86–1.05)</td>
<td></td>
</tr>
<tr>
<td>HEAAL42</td>
<td>3834 N</td>
<td></td>
<td>Mean 66.0 RE</td>
<td>RCT, AC</td>
<td>Sub-group: ≥65, No difference in death or HF hospital admission</td>
<td>HR 0.95, 95% CI (0.84–1.07)</td>
<td></td>
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<tr>
<td><strong>Beta-Blockers</strong></td>
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<tr>
<td>US Carvedilol trials27</td>
<td>1197 N</td>
<td></td>
<td>Mean 58 years RE</td>
<td>RCT, PC</td>
<td>Sub-group: ≥59, 62% RRR in mortality with carvedilol</td>
<td>HR 0.38, 95% CI, 0.19–0.77</td>
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</tr>
<tr>
<td>COBRA28</td>
<td>1140 N</td>
<td></td>
<td>Mean 70–71 years RE</td>
<td>RCT, AC</td>
<td>No difference in all-cause mortality</td>
<td>P = 0.37</td>
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<tr>
<td>VALIANT29</td>
<td>12,664 N</td>
<td></td>
<td>Mean 70–71 years RE</td>
<td>RCT, PC</td>
<td>No difference in all-cause mortality</td>
<td>P = 0.76</td>
<td></td>
</tr>
<tr>
<td>DIG main23</td>
<td>21,184 N</td>
<td></td>
<td>Mean 59–61 years RE</td>
<td>RCT, PC</td>
<td>No difference in all-cause mortality</td>
<td>HR 1.02, 95% CI (0.98–1.06), P = 0.22</td>
<td></td>
</tr>
<tr>
<td>DIG substudy32</td>
<td>2118 N</td>
<td></td>
<td>Mean 59–61 years RE</td>
<td>RCT, PC</td>
<td>No difference in all-cause mortality</td>
<td>HR 1.02, 95% CI (0.97–1.07), P = 0.31</td>
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</tr>
<tr>
<td>BB cohort47</td>
<td>15,509 N</td>
<td></td>
<td>Mean 59–61 years RE</td>
<td>RCT, PC</td>
<td>No difference in all-cause mortality</td>
<td>HR 1.00, 95% CI (0.98–1.03), P = 0.68</td>
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<tr>
<td><strong>Diuretics</strong></td>
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</tr>
<tr>
<td>US Carvedilol trials27</td>
<td>1197 N</td>
<td></td>
<td>Mean 58 years RE</td>
<td>RCT, PC</td>
<td>Sub-group: ≥59, 62% RRR in mortality with carvedilol</td>
<td>HR 0.38, 95% CI, 0.19–0.77</td>
<td></td>
</tr>
</tbody>
</table>

*Table includes key trials with evidence of benefit in older populations. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI) and p-values (P) where available. RRR = relative risk reduction.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Age</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS I</td>
<td>2647</td>
<td>N</td>
<td>Mean 61 years</td>
<td>RE</td>
<td>RCT, PC</td>
<td>No sub-group analyses for age reported</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>3991</td>
<td>N</td>
<td>Mean 63.7–63.9 31% ≥ 70 years</td>
<td>RE</td>
<td>RCT, PC</td>
<td>Sub-group: Upper third age group, metoprolol reduced mortality</td>
</tr>
<tr>
<td>BEST</td>
<td>2708</td>
<td>N</td>
<td>Mean 60 years 16.9% between 69–74 11.9% ≥ 75 years</td>
<td>RE</td>
<td>RCT, PC</td>
<td>No sub-group analyses for age reported</td>
</tr>
<tr>
<td>Copernicus</td>
<td>2289</td>
<td>N</td>
<td>Mean 63 years</td>
<td>RE</td>
<td>RCT, PC</td>
<td>Sub-group: ≥65, carvedilol reduced mortality</td>
</tr>
<tr>
<td>Seniors</td>
<td>2128</td>
<td>Y</td>
<td>Mean 76.1 years</td>
<td>RE and PR</td>
<td>RCT, PC</td>
<td>14% RRR in mortality and CV hospital admission</td>
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<tr>
<td>BB cohort</td>
<td>11,942</td>
<td>Y</td>
<td>Mean 79 years 30.2% between 65–79 69.8% ≥ 80 years</td>
<td>Obs Cohort</td>
<td>28% RRR in all-cause mortality</td>
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<td>Diuretics</td>
<td>Cochrane</td>
<td>525</td>
<td>N</td>
<td>Mean 59 years</td>
<td>SR</td>
<td>No sub-group analyses for age reported</td>
</tr>
<tr>
<td>Digoxin</td>
<td>DIG main</td>
<td>6800</td>
<td>N</td>
<td>Mean 63.9 years 32% ≥ 70 years 5.5% ≥ 80 years</td>
<td>RE</td>
<td>RCT, PC</td>
</tr>
<tr>
<td></td>
<td>DIG substudy</td>
<td>7788</td>
<td>N</td>
<td>Mean 63.9 years 32% ≥ 70 years 5.5% ≥ 80 years</td>
<td>RE and PR</td>
<td>Sub-study</td>
</tr>
<tr>
<td>Aldosterone Blockers</td>
<td>RALES II</td>
<td>1663</td>
<td>N</td>
<td>Mean 65 years</td>
<td>RE</td>
<td>RCT, PC</td>
</tr>
<tr>
<td></td>
<td>EPHESUS</td>
<td>6632</td>
<td>N</td>
<td>Mean 64 years</td>
<td>RE</td>
<td>RCT, PC</td>
</tr>
</tbody>
</table>

(Continued)
Patients ≥70 years old with chronic HF were included in this study to determine the effect of perindopril on all-cause mortality or unplanned HF related hospitalization. The mean age was 75 years old. Overall, there was no difference between perindopril and placebo in the primary endpoint (Hazard Ratio HR 0.92, 95% Confidence Interval (CI) (0.70–1.21), p = 0.545). However, when the effect of age was evaluated as a prespecified subgroup analysis, younger patients (i.e. those ≤75 years old) benefited from perindopril (HR 0.53, 95% CI 0.29–0.97) while those >75 years old did not (HR 0.87, 95% CI 0.53–1.42).

Angiotensin receptor blockers

The Evaluation of Losartan in the Elderly studies (ELITE I and II) assessed the safety and efficacy of losartan compared to captopril in elderly patients with NYHA Class II–III HF and a reduced ejection fraction (HFReEF). The mean age of participants in ELITE I was slightly older than those in ELITE II (approximately 73.5 in ELITE I and 71.4 in ELITE II), but ELITE II was specifically designed to compare the effect of losartan with captopril on mortality in 3152 elderly patients with HF. No difference was found between the treatment groups in the primary endpoint of either trial, irrespective of age (HR 1.13, 95% CI (0.95–1.35), p = 0.16) (Table).

More recently, high-dose losartan (150 mg daily) was compared to low-dose losartan (50 mg daily) in 3834 patients with HFReEF. The mean age of 66.0 in participants in HEAAL was younger than previous losartan trials. The investigators reported losartan 150 mg daily reduced the primary endpoint of death or HF admission compared to losartan 50 mg daily. A sub-group analysis found there was no interaction for age (p = 0.18), but the statistical significance was lost in patients ≥65 years old (HR 0.95, 95% CI (0.84–1.07).

Irbesartan was evaluated in elderly patients with HF and preserved EF (HFPrEF). This trial enrolled 4128 patients ≥65 years old and included 2491 patients ≥75 years old; the overall mean age was 72. There was no difference between irbesartan and placebo in the primary endpoint of all-cause death or cardiovascular hospitalization (HR 0.95, 95% CI 0.86–1.05). The results remained non-significant in the prespecified sub-group analysis of three age groups (<65, 65–75, and >75). Valsartan has also been studied in...
patients with HFpEF in the Valsartan in Diastolic Dysfunction trial (VALIDD), but the patients were about 11 years younger than those in the irbesartan trial. In VALIDD, valsartan did not improve diastolic dysfunction any more than other anti-hypertensives; no results based on age were reported (Table).

Two landmark trials have shown reduced morbidity and mortality with ARBs in patients with chronic HF: the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) trials (Table). In Val-HeFT, the average age of the enrolled patients was 62.4 and 63.0 in the valsartan and placebo group, respectively. Overall, valsartan reduced the combination of morbidity and mortality by 13.2%. The patients younger than 65 years old (N = 2660) maintained this benefit, but in those ≥65 years old (N = 2350), the statistical significance was lost, though the trend was still in favor of valsartan. Detailed statistics were not provided (Table).

In the CHARM-Overall program, the average age of patients was 65.9 and 66.0 in the candesartan and placebo group, respectively. There were 1736 (22.8%) patients ≥75 years old. The primary endpoint of the overall program was all-cause death, which was significantly reduced with candesartan by 10% after statistical adjustment (HR 0.90, 95% CI 0.82–0.99, P = 0.032). The investigators reported no interaction for age on this endpoint (p = 0.26) and demonstrated that the benefit was maintained in those patients between 65–75 years old and in those ≥75 years old; however detailed HR and CIs were not reported in numeric form. The individual trials from the CHARM program did not report detailed sub-groups analysis of the effect of age, but investigators stated there were similar effects in all their prespecified sub-groups. Of particular importance are the results from the CHARM-Preserved program, which included older patients than the other CHARM programs. In CHARM-Preserved, the average age was 67.2 and 67.1 in the candesartan and placebo groups, respectively. There were 407 (26.9%) and 400 (26.5%) patients ≥75 years old in the candesartan and placebo groups, respectively. The primary outcome of the CHARM-Preserved program, cardiovascular death or unplanned admission to the hospital for the management of worsening HF, was not significant (adjusted HR 0.86, 95% CI 0.74–1.00, p = 0.051).

Beta-blockers
Randomized controlled trials have demonstrated that neurohormonal intervention with beta-blockers also provides substantial improvements in mortality in patients with HFpEF; a 34%, 35%, and 65% relative risk reduction in death was shown among bisoprolol, extended release metoprolol, and carvedilol, respectively. However, these trials generally included patients between 58 and 64 years old. The Cardiac Insufficiency Bisoprolol II study (CIBIS II) excluded patients >80 years old and did not report any findings based on age. The Beta-Blocker Evaluation of Survival Trial (BEST) did not exclude the very elderly, but did not have a large proportion of older patients (16.9% (458) were between the ages of 69–74 and 11.9% (322) were 75 years or older); no sub-group or interaction analysis based on age was reported. However, BEST did not find a benefit of using bucindolol in patients with advanced chronic heart failure. The United States Carvedilol HF Study included the youngest patients, with an average age of 58 years. The investigators presented sub-group analyses based on age <59 or ≥59; both age groups showed similar improvements in the primary endpoint of survival (<59 HR 0.30, 95% CI, 0.11–0.80; ≥59 HR 0.38, 95% CI 0.19–0.77). Another carvedilol trial evaluated the effect in slightly older patients (mean age 63) with severe HF on death from any cause in 2289 patients. Overall, there was a 35% reduction in mortality with carvedilol; a sub-group analysis showed similar results on the primary endpoint, as well as the combined secondary endpoint of risk of death or all-cause hospitalization, for patients <65 years old or ≥65 years old (Table). The MERIT-HF study, which showed the benefit of using extended release (ER) metoprolol in chronic HF, included approximately 31% of patients ≥70 years old. A sub-group analysis done on the upper tertile age group revealed that this age group had a similar benefit from ER metoprolol as was seen in the participants collectively, but detailed statistics were not provided (Table).

The SENIORS study was a randomized, placebo controlled trial specifically designed to study the efficacy of nebivolol, a third generation beta-blocker, in patients ≥70 years old with both HFpEF and
HFPrEF. The patients’ mean age was 76.1 and median age was 75.2 and 75.3 in the nebivolol and placebo group, respectively. The mean ejection fraction (EF) was 36%, with approximately 35% of the population having an EF > 35%. The primary endpoint of all-cause mortality or cardiovascular hospital admission was reduced by 14% in the overall study (HR 0.86, 95% CI 0.74–0.92, p = 0.039). Several ad-hoc analyses were performed to determine effects of nebivolol based on EF and/or age. In patients less than the median age of 75.2 with an EF ≤ 35%, the benefit was maintained and revealed a 27% reduction in the risk of the primary endpoint (HR 0.73, 95% CI 0.56–0.96) and a 38% reduction in all-cause mortality alone (HR 0.62, 95% CI 0.43–0.89). However, if the EF threshold used was ≤ 40% rather than ≤ 35%, the significance was lost in spite of increasing the power of the analysis. Another ad-hoc analysis evaluated the effect of nebivolol in patients between the median age of 75.2 years and 85 years, as well as for those > 85 years; there was no significant effect of nebivolol in either of these groups (Table). Adverse events in the SENIORS trial were similar to adverse events in other beta-blocker trials; no analysis was reported about the effect of age on these events.

One large observational cohort study did find significant benefit of using beta-blockers in elderly patients with HF. Patients included in this study were at least 65 years old; 30.2% (N = 3602) were between 65–79 years and 69.8% (N = 8340) were ≥ 80 years of age. Although only 10% (1162) of the cohort received a beta-blocker, there was a 28% reduction in all-cause mortality (HR 0.72, 95% CI 0.65–0.80) and 18% reduction in HF hospitalizations (HR 0.82, 95% CI 0.74–0.92).

Diuretics
Overall, the evidence regarding diuretics in HF is scant; this is even more so in patients ≥ 65 years of age. A Cochrane review summarized the evidence for diuretics in HF and found the average age of the patients in the diuretic studies was 59 years. This analysis demonstrated that diuretic therapy was associated with a 70% relative reduction in mortality, but this was based on only 15 deaths out of 221 participants, as there were only a small number of placebo controlled trials that reported the effect on mortality. No age-related results were reported. In spite of the paucity of evidence, most elderly patients with HF will require diuretics to manage hypervolemia; it is likely this group will be at risk for adverse events given the age-related changes described above. Elderly patients are not only at higher risk for metabolic abnormalities, such as hyponatremia and hypokalemia, but also for related complications. Elderly patients may also experience an altered pharmacodynamic response to diuretics because of age-related reductions in the number of nephrons; this results in the need for higher diuretic doses to achieve a similar diuretic effect. Likewise, older patients are more susceptible to volume depletion and related complications, such as bone fractures from a fall. These issues must be balanced when using diuretics in older patients; frequent monitoring of both safety and efficacy is essential.

Digoxin
A randomized, placebo-controlled study demonstrated that digoxin reduced the rate of HF hospitalizations, but did not reduce mortality in patients with HF in the Digitalis Investigative Group (DIG) Study. A post-hoc analysis on this data was conducted to determine the effect of age on mortality, hospitalizations, and response to digoxin. The mean age was 63.9 years approximately 32% were 70 years or older (N = 1839), with 5.5% ≥ 80 years old (N = 425). In the sub-study, patients were groups by age (≤ 50 = 841; 50–59 = 1545; 60–69 = 2885; 70–79 = 2092; ≥ 80 = 425); no interaction was found between age and mortality, all-cause hospitalization, HF hospitalization, or HF death or hospitalization (P > 0.05 on all). The benefits of digoxin on HF death or hospitalization were maintained across all age groups (Table) P = 0.0001. There were similar results for safety. Adverse events were more frequent in elderly patients (atrioventricular block, supraventricular arrhythmias, nausea/vomiting, withdrawal due to side effects, and hospitalization for suspected digoxin toxicity), but there was no interaction between digoxin treatment and age (P > 0.1 for all).

Although the DIG sub-study provides evidence that benefits of digoxin can be appreciated in older patients, clinicians must diligently apply caution when using this drug in the elderly. In the DIG study, patients were started on a digoxin dose that took
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into account several factors per protocol, including age and renal function. The dose of digoxin was lower in each incrementally evaluated age group, yet, the mean digoxin serum levels increased with increasing age; this reflects the volume of distribution and clearance changes expected with digoxin in older patients. The DIG investigators applied this information and maintained safety; this data supports that prudent use of digoxin in older patients can be safe and effective.

Aldosterone blockers
Two large randomized, placebo-controlled trials have shown the benefit of using spironolactone and eplerenone in HFReEF, the RALES II and EPHESUS trials, respectively. The mean age in RALES II was 65 and in EPHESUS was 64 years old. Both trials performed a sub-group analysis that evaluated the benefit of the aldosterone blocker based on age. In RALES II, the benefit of spironolactone was maintained, but eplerenone’s benefit was no longer significant in patients ≥ 65 years old; detailed statistics were not reported in either study. Neither trial reported the number of patients in the cohort of older patients.

A retrospective study evaluated the safety of spironolactone in elderly patients with HF. Sixty-six patients ≥ 75 years old taking both ACE-inhibitors and spironolactone with both reduced and preserved EFs were retrospectively identified. The average age of the cohort was 85, approximately 20 years older than the average age in RALES II. The rate of renal insufficiency was 37.5%, hyperkalemia (K ≥ 5.5 mmol/L) was 36% and severe hyperkalemia (K ≥ 6.0 mmol/L) was 11%. No significant relationship was found between the occurrence of adverse effects from spironolactone (namely, renal insufficiency and hyperkalemia) and age. However, there was a relationship with the presence of another illness (sepsis or dehydration) and hyperkalemia.

Nitrate-hydralazine
The African-American Heart Failure Trial (A-HeFT) was a randomized, placebo-controlled study that showed significant improvements in a scored primary composite endpoint that included death, hospitalizations, and quality of life with the combination of isosorbide dinitrate (ISDN) and hydralazine in 1050 black patients with chronic HFReEF. Patients taking the ISDN-hydralazine combination experienced a 43% relative risk reduction in mortality compared to placebo, leading to early termination of the trial. The mean age of the patients enrolled in this study was 56.7 and 56.9 years in the treatment and placebo groups, respectively. No age-related results were reported.

General studies about treating HF in the elderly

The TIME-CHF study was a prospective, randomized comparison of intensive versus standard medical therapy in elderly patients with both HFReEF and HFPrEF. Standard therapy was defined as therapy targeted to symptoms, while intensive therapy was defined as directing therapy to predefined N-terminal brain natriuretic peptide (BNP) levels. Patients at least 60 years old with New York Heart Association (NYHA) Class II–IV HF were eligible if they were hospitalized for HF within the previous year. Patients were further stratified according to age, 60–74 years (n = 210) and ≥ 75 years (n = 289); the mean age in the groups was 69 and 82, respectively. While the symptom-guided and N-terminal BNP guided groups were well matched, patients in the two age groups were different in 74% of the baseline characteristics collected. Patients in the older group were more likely to be women, more were in NYHA Class III or IV HF, more had atrial fibrillation, had a higher EF, and higher systolic and diastolic blood pressure. They were also more likely to have common co-morbidities, including hypertension, prior stroke/transient ischemic attack, cancer, renal disease, or arthritis, were less likely to be on an ACE-inhibitor or ARB, beta-blocker, aldosterone blocker, but were more likely to be on a nitrate and receive higher doses of loop diuretics. Overall, there was no difference in the primary endpoint of hospital-free survival between the main treatment groups (41% for N-terminal BNP versus 40% for symptom-guided, P = 0.39). However, the N-terminal BNP group experienced more HF hospital-free survival, one of the prespecified secondary endpoints compared to the symptom managed group (HR 0.68, 95% CI 0.50–0.92, P = 0.01). An interaction between treatment and age was found to be present; in the group between 65–74 years old, N-terminal BNP-guided treatment was associated with more hospital-free
The creation of Medicare also set age 65 years as an important universal age of access to health care in the United States and it is likely cohort studies of Medicare patients have less societal bias than those of younger patients. Yet, the clinical trials’ definition of “elderly” ranged from ≥ 59 years to ≥ 75 years, based on a priori defined inclusion as well as post-hoc sub-group analyses; the most common age cut-off to define elderly in these clinical trial (including sub-group analyses) is ≥ 60–65 years. These inconsistent definitions make conclusions regarding this data difficult.

Future Directions
In spite of the need for additional investigation into treatments for elderly patients with HF, few event-driven clinical trials are underway to investigate potential pharmacologic therapies in elderly patients. One trial, the Pharmacologic Intervention in the Elderly trial, is evaluating the efficacy of spironolactone in patients at least 60 years old who have HFPrEF; another ongoing trial is evaluating spironolactone in patients at least 50 years old with HFPrEF. Many current drug therapies are targeted at either the myocyte or the arteriole whereas one of the most common events in aging is increased central arterial vascular stiffness. This leads to increased ventricular afterload related to impaired ventricular-vascular coupling. Although current therapies do not adequately address this fundamental aging process, research targeting age- and disease-related arterial stiffening is promising. In fact, one investigational drug has been shown in animals and humans to reduce this arterial stiffness by breaking crosslinks that have been shown to contribute to age- and disease-related large artery stiffening. Targeting the “vascular aging-vascular disease interaction” is likely a key area of future research.

Definition of Elderly
An important limitation of reviewing the pharmacotherapeutic management of HF in the elderly is that there is inconsistency as to how elderly has been defined. What is it to be and who is elderly is a philosophical question influenced by the epistemological perspectives and time period of the observer that we cannot definitively answer. Nonetheless the US Census bureau categorizes older patients into 65 years and older, 85 years and older, and 100 years and older. The creation of Medicare also set age 65 years as an
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Clearly, the data are insufficient to make definitive recommendations for pharmacotherapeutic interventions in older persons with HF. The limited data that does exist suggests evidence in younger patients does not translate to older patients, owing possibly to differences in pathophysiology, age-related differences, co-morbidities, medication tolerance, or other unique characteristics of older patients. However, in spite of the paucity of data, no data exists to suggest the standard HF therapies should be withheld from older patients, though careful consideration of the potential risks and benefits may lead to abstention from therapies in selected patients. Since some non-randomized data suggests a benefit, implementation of evidence-based HF therapy with close monitoring and follow up is prudent as the medical community continues to accrue evidence for management of HF in this special population.

Disclosures
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References


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