Adherence to Guidelines in Heart Failure: Is It Valid for Elderly Patients?

Johad Khoury MD12*, Itai Gherisn MD*+, Eyal Braun MD4+, Adi Elias MD3, Doron Aronson MD5, Zaher S. Azzam MD5, and Fadel Bahouth MD7

1Pulmonary Division, Carmel Medical Center, Haifa, Israel
2Pulmonary, Critical Care and Sleep Medicine, Yale School of Medicine, New Haven, Connecticut, USA
3Departments of Internal Medicine B and Internal Medicine II, and Heart Institute, Rambam Health Care Campus, Haifa, Israel
4Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel
5Heart Institute, Bnei Zion Medical Center, Haifa, Israel

ABSTRACT
Background: Current guidelines for the treatment of heart failure with reduced ejection fraction (HFrEF) are based on studies that have excluded or underrepresented older patients.

Objectives: To assess the value of guideline directed medical therapy (GDMT) in HFrEF patients 80 years of age and older.

Methods: A single-center retrospective study included patients hospitalized with a first and primary diagnosis of acute decompensated heart failure (ADHF) and ejection fraction (EF) of ≤ 40%. Patients 80 years of age and older were stratified into two groups: GDMT, defined as treatment at hospital discharge with at least two drugs of the following groups: beta-blockers, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or mineralocorticoid antagonists; and a personalized medicine group, which included patients who were treated with up to one of these drug groups. The primary outcomes were 90-day all-cause mortality, 90-day rehospitalization, and 3-years mortality.

Results: The study included 1152 patients with HFrEF. 254 (22%) patients who were at least 80 years old. Of the group, 123 were GDMT at discharge. When GDMT group was compared to the personalized medicine group, there were no statistically significant differences in terms 90-day mortality (17% vs. 13%, P = 0.169), 90-day readmission (51% vs. 45.6%, P = 0.27), or 3-year mortality (64.5% vs. 63.3%, P = 0.915).

Conclusions: Adherence to guidelines in the older adult population may not have the same effect as in younger patients who were studied in the randomized clinical trials. Larger prospective studies are needed to further address this issue.

IMAJ 2022; 24: 757-762

KEY WORDS: adrenergic beta-antagonists, angiotensin converting enzyme inhibitor (ACEI), guideline, heart failure, older age

*These authors contributed equally to this study

Heart failure (HF) is a growing public health concern worldwide, with high morbidity, mortality, and healthcare costs. The prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people older than 70 years of age. Recent data on HF epidemiology showed that HF is increasing among elderly adults. In epidemiological studies among the general population, the mean age at first diagnosis of HF has increased over the years, now being 80 years old [1,2].

When compared to younger populations, older patient populations carry a higher incidence of HF related events, exacerbations, and hospital admissions [3]. Furthermore, advanced age has been demonstrated to be a strong predictor of poor outcomes in the settings of acute and chronic HF with subsequent higher mortality after hospitalization [1,2,4,5].

The current European Society of Cardiology (ESC) guidelines regarding treatment of heart failure with reduced ejection fraction (HFrEF) do not specifically address treatment of elderly HFrEF patients [6]. Therefore, the major studies for HF treatment have excluded or underrepresented older patients [7-10].

Hence, the aim of this study was to assess the therapeutic value of adherence to current guideline directed medical therapy (GDMT) in patients 80 years of age or older with HFrEF.

PATIENTS AND METHODS

STUDY POPULATION AND DESIGN

A retrospective observational study included all patients who were admitted for the first time with the primary diagnosis of acute decompensated heart failure (ADHF) to Rambam Health Care Campus, Haifa, Israel, between February 2008 and December 2018.

Demographic data, concomitant diseases, regular medications, laboratory results on admission and discharge, recommended treatments on discharge, and mortality data were collected by the MDClone© software (Beer Sheva, Israel) for data gathering [11].
Inclusion criteria were first admission with heart failure as the primary diagnosis, brain natriuretic peptide (BNP) level > 400 pg/mL, left ventricular ejection fraction (LVEF) ≤ 40%, and echocardiography on the index hospitalization or within 6 months prior to the admission. Exclusion criteria included primary diagnosis other than ADHF, younger than 18 years old, or missing recent echocardiographic study or without a BNP examination. Patients treated with partial doses of angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta blockers (BB), and mineralocorticoid antagonists (MRA) as dictated by the guidelines [6] were excluded from the study because the effect of a partial dose cannot be determined. To prevent chronicologic bias by available treatments, patients treated with any dose of angiotensin receptor-neprilysin inhibitors (ARNIs) or sodium-glucose cotransporter-2 (SGLT2) inhibitors were excluded from the study.

The study population was divided into two main groups: 80 years or older as the study group, and younger than 80 as a validation group. We compared HFpEF patients who were 80 years of age or older and treated by GDMT to HFrEF patients who were 80 years of age or older who did not receive GDMT. We referred to the latter group as the personalized medicine group, as it was treated based on the clinician's decision and not based on the common practice recommended by the guidelines. GDMT was defined as the use of a recommended dose of at least two of the following drug classes that are considered the cornerstone treatments according to the guidelines: ACEI, ARB, BB, and MRA [6].

FOLLOW-UP
Follow-up and data collection took place up to 36 months after the last patient was admitted to our center. Mortality data were available through a government registry and were available for all the patients in the study.

STUDY ENDPOINTS

Primary endpoint
The primary endpoint was all-cause 90-day mortality, 90-day re-admission, and 3-year mortality among patients 80 years of age or older.

Secondary endpoints
The secondary endpoints were all-cause mortality at 90 days, 6 months, and 3 years among patients younger than 80 years of age.

STATISTICAL ANALYSIS
Patients were stratified into two age groups: younger than 80 years old and 80 years or older.

The calculated sample size to detect between-group difference with 80% power, 0.05 significance level, and 0.35 effect size, considering one tail, is 204 (102 patients in each group).

Continuous variables are presented as either means ± standard deviation or medians (with interquartile range) and categorical variables as numbers and percentages. Baseline characteristics of the groups were compared using the unpaired t-test for continuous variables and by chi-square statistic for categorical variables.

Univariate and multivariate Cox proportional hazard analyses were performed to determine the relationship between candidate variables, including age and the risk of primary endpoint occurrence. We also performed multivariable logistic regression analyses to determine independent predictors for the group age strata.

Differences were considered statistically significant at the one-sided $P < 0.05$ level. Statistical analyses were performed using SPSS statistical software version 15.0 (SPSS Inc, Chicago, Illinois, USA). The study was approved by the institutional review board (IRB).

RESULTS
A total of 3537 patients with ADHF were noted; 1152 HFrEF met the inclusion criteria and were included in the study. Among them, 254 patients (22%) were 80 years of age or older. Of those, 123 patients (48%) were treated with at least two evidence-based medicine drugs for HFrEF, and 131 (52%) where treated with one drug at most [Figure 1], of whom 16 were treated with ACEI or ARBs, 74 with BB, 5 with MRA, and 36 were not treated with any of these drugs.

The baseline characteristics of the study patients are shown in Table 1.

There were some notable differences in the baseline characteristics of the two age groups (younger and older than 80 years). There were more patients with diabetes mellitus in the younger population (51.67% vs. 40%, $P = 0.004$). Similarly, the younger population presented with more ischemic heart disease (IHD) and atrial fibrillation (AF). In the older population, significantly more patients had chronic kidney disease (CKD), hypertension, and pulmonary hypertension [Table 1].

Figure 1. Study flow chart

EBM = evidence-based medicine, HF = heart failure, HFrEF = heart failure with reduced ejection fraction

<table>
<thead>
<tr>
<th>3575 HF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1152 HFrEF patients</td>
</tr>
<tr>
<td>898 patients &lt; 80 years</td>
</tr>
<tr>
<td>254 patients &gt; 80 years</td>
</tr>
<tr>
<td>131 patients received at most 1 EBM drug</td>
</tr>
<tr>
<td>123 patients received at least 1 EBM drug</td>
</tr>
</tbody>
</table>
Figure 2. Comparison of the personalized medicine group and GDMT group. 90-day mortality

ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin, receptor blocker BB = beta blockers

Personalized medicine = 0–1 drug, GDMT = guideline directed medical treatment, defined as treatment at hospital discharge with at least two drugs of the following groups: BB, ACEI, ARB, or mineralocorticoid antagonists

** statistically significant

Table 1. Baseline characteristics of the study patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age &lt; 80 years</th>
<th>Age &gt; 80 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>898</td>
<td>254</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>75.5</td>
<td>66</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>51.67</td>
<td>40</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>70.8</td>
<td>84</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (%)</td>
<td>15.14</td>
<td>9</td>
<td>0.023</td>
</tr>
<tr>
<td>Peripheral arterial disease (%)</td>
<td>11.8</td>
<td>14</td>
<td>0.698</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>22</td>
<td>32</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>32.4</td>
<td>26</td>
<td>0.006</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>71</td>
<td>52</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>19.9</td>
<td>22</td>
<td>0.004</td>
</tr>
</tbody>
</table>

[8] Subgroup analysis for patients with or without co-morbidities

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>GDMT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With co-morbidities</td>
<td>16.8%</td>
<td>13%</td>
</tr>
<tr>
<td>Co-morbidities-free</td>
<td>18.6%</td>
<td>15.8%</td>
</tr>
<tr>
<td>90-day readmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With co-morbidities</td>
<td>50.8%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Co-morbidities-free</td>
<td>52.5%</td>
<td>43.1%</td>
</tr>
<tr>
<td>6-month mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With co-morbidities</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>Co-morbidities-free</td>
<td>25%</td>
<td>23%</td>
</tr>
</tbody>
</table>

GDMT = guideline directed medical treatment

Co-morbidities include one or more of the following: diabetes mellitus, hypertension, chronic kidney disease, or atrial fibrillation and/or renal disease.
ADHERENCE TO GUIDELINES IN THE ELDERLY GROUP

Short-term mortality and readmission

When comparing the GDMT group to the personalized medicine group, multivariate analysis showed no statistically significant differences in terms of 90-day mortality (16.7% vs. 13%, \( P = 0.169 \)) [Figure 2], 90-day readmission (51% vs. 45.6%, \( P = 0.27 \)), or 6-month mortality (27% vs. 21%, \( P = 0.215 \)).

Treatment for other indications were administered to distinguish between patients being treated with ACE-I, ARBs, BB, or MRA for HF or for other indications such as hypertension, diabetic nephropathy with proteinuria, or rate control. A subgroup analysis was conducted for patients with or without co-morbidities (one or more of: diabetes mellitus, hypertension, chronic kidney disease, or atrial fibrillation).

In multivariate analysis, there was no difference between GDMT and personalized medicine in terms of 90-day or 6-month mortality, nor in 90-day readmission in patients with or without co-morbidities [Table 1].

Long-term mortality

The 3-year mortality rate was 64.5% and 63.3% in the personalized medicine and GDMT groups respectively, resembling non-significant statistical difference. Similar mortality rates were seen throughout the whole follow-up period [Figure 3]. Similarly, subgroup analysis for patients with or without co-morbidities was conducted long-term as well.

In patients with HFrEF and co-morbidities, the GDMT patients showed better survival than the personalized medicine group. However, for patients without concomitant co-morbidities, no difference was seen in all-cause mortality between the GDMT and personalized medicine groups [Figure 3].

Validation

To validate our data, the same analysis was conducted on patients under 80 years of age. In these younger patients, 90-day mortality was 7.5% vs. 3.4% among the personalized medicine and GDMT groups, respectively; and 6-month mortality was 14.2% vs. 8.5%, respectively, all statistically significant. The long-term mortality was higher in the personalized medicine group [Figure 3]. In a subgroup analysis for patients with or without co-morbidities (one or more of: diabetes mellitus, hypertension, chronic kidney disease, or atrial fibrillation), better survival was seen in the GDMT group than in the personalized medicine group, regardless of co-morbidities [Figure 3].

DISCUSSION

The prevalence of heart failure has significantly increased in the older population [12-14]. This may be in part explained by improved management of acute conditions such as acute myocardial infarction, myocarditis, valvular diseases, and co-morbidities [15,16].

Figure 3. Mortality rates throughout the whole follow-up period

Patients < 80 years of age without recommended medications, patients < 80 years of age with recommended medications, patients > 80 years of age without recommended medications, patients > 80 years with recommended medications

[A] Survival analysis over time for patients over 80 years of age

[B] Survival curves in different patient groups with heart failure and reduced ejection fraction without co-morbidities

[C] Survival curves in different patient groups with heart failure and reduced ejection fraction with co-morbidities
Based on the ESC guidelines for the diagnosis and treatment of acute and chronic HF published in 2021 [6], HF patients are categorized into three groups based on LVEF: HFrEF that is LVEF < 40%, HF with mildly reduced EF (HFrEF) LVEF range 40–49%, and HF with preserved EF (HFpEF) when LVEF ≥ 50%. Distinguishing between patients with HF based on LVEF is important due to differing underlying etiologies, demographics, co-morbidities, and response to therapies.

Overall survival of HFrEF patients has substantially improved with evidence-based medical therapies including ACEI, ARB, BB, and MRA [16-18]. Although it is well established that adherence to GDMT improves clinical outcomes in patients with HF [6,19], many of the landmark trials that formed the basis for current treatment guidelines tended to exclude older adult patients with HF and did not focus specifically on the effects of these therapeutic modalities on the older adult population [7-10].

Older HF patients differ from younger HF patients by pathophysiology, medication tolerance, and an increased rate of co-morbidities including AF, hypertension, CKD, and malignancies [1,2,4,5].

In this study we showed that older adult patients do not appear to benefit from treatment with at least two recommended drugs in terms of 90-day mortality, 90-day rehospitalization, or long-term mortality. These results may be partially explained by adverse events of medications, such as hypotension, acute kidney injury, and hyperkalemia, as older adult patients may be at increased risk of developing these adverse events [20-23].

It has been shown before that strict glycemic control in older adult patients may lead to adverse events due to hypoglycemia. Likewise, strict control of hypertension in older patients correlated with a higher incidence of hypotension related sequelae [24,25].

As BB, ACEI, ARBs, and/or MRA may also be prescribed in treating other condition like hypertension, rate control, or proteinuria, we sub-divided the cohort into co-morbidity-complicated and co-morbidity-free patients. We noted that co-morbidity-free older patients did not benefit from these drugs; hence, treatment did not improve mortality when it is prescribed for HF. However, a survival benefit was seen in older patients with co-morbidities, which may be related to control of these co-morbidities and not necessarily to HF. However, short-term survival did not improve significantly in the latter group, probably because co-morbidity control affected the long-term outcome only.

The validation conducted on the younger patients showed, as expected, a survival benefit using GDMT in both short and long-term, with or without co-morbidities. These points suggest that what is valid in the younger age is not necessarily applicable in the elderly adults.

Co-morbidities may result in conflicting treatment recommendations. Polypharmacy frequently includes drugs that may themselves contribute to worsening of HF (e.g., non-steroidal anti-inflammatory drugs) or increasing the risk of drug–drug interactions (e.g., antidepressants and antiarrhythmics, antibiotics and anti-coagulants).

LIMITATIONS
Our study was a retrospective single center study. The GDMT group contained different drug combinations; however, we do not know the impact of the various combinations of the recommended drugs according to current guidelines on outcome. While the study is powered to detect difference between the GDMT and personalized medicine groups, some of the subgroup analysis might be underpowered. Moreover, the study followed the guidelines available in 2008, which are still valid but do not include newer drugs or protocols that were added to the guidelines later, such as ARNIs and SGLT2 Inhibitors. In this study, 22% of the patients were 80 years or older, this is because we included patients with first diagnosis of HF, and most of these patients are diagnosed earlier in life; on the other hand, including every patient with ADHF may include misleading data such as adverse effects of treatment, temporary withholding of treatments because of adverse events, drug–drug interaction etc.

CONCLUSIONS
Older adults represent a large proportion of HF patients and have worse outcomes when compared to younger patients. Treatment with GDMT does not appear to improve their outcome. Thus, we believe treatment decisions in older HFrEF patients should be individualized. Larger prospective trials are needed to settle this issue.

Correspondence
Dr. J. Khoury
Pulmonary, Critical Care and Sleep Medicine, Yale School of Medicine, New Haven, 06520, Connecticut, USA
Phone: (12 203) 737-6419
email: joshua.khoury@yale.edu

References
Capsule

Impact of vaccination on post-acute sequela of SARS CoV-2 infection in patients with rheumatic diseases

Vaccination decreases the risk of severe COVID-19 but its impact on post-acute sequela of COVID-19 (PASC) is unclear among patients with systemic autoimmune rheumatic diseases (SARDs) who may have blunted vaccine immunogenicity and be vulnerable to PASC. Patel et al. prospectively enrolled SARD patients from a large healthcare system. These patients survived acute infection and completed surveys. Among 280 patients, the mean age was 53 years, 80% were female, and 82% were white. The most common SARDs were inflammatory arthritis (59%) and connective tissue disease (24%). Those with breakthrough infection had more upper respiratory symptoms, and those with non-breakthrough infection had more anosmia, dysgeusia, and joint pain. Compared to those with non-breakthrough COVID-19 infection (n=164), those with breakthrough infection (n=116) had significantly more symptom-free days over the follow-up period (+28.9 days, 95% confidence interval [95%CI] 8.83–48.89, P = 0.005) and lower odds of PASC at 28 and 90 days (adjusted odds ratio aOR 0.49, 95%CI 0.29–0.83 and aOR 0.10, 95%CI 0.04–0.22, respectively).

Capsule

Antibiotics shape lifetime health

Premature infants are vulnerable to infection and consequently are frequently given antibiotics prophylactically. However, antibiotic treatment in the very young can interfere with the establishment of a complete gut microbiota community. Poon et al. investigated the longer-term consequences of vancomycin treatment on neonatal mice. In addition to sustained disruption to the microbiota, the authors also noted changes in gut transit times, and found that the activity of myenteric and submucosal neurons differed between treated and untreated mice as they reached adulthood. Furthermore, neonatal vancomycin treatment was associated with lifetime depletion of mucosal serotonin levels. Although male mice showed greater myenteric neural disruption, serotonin depletion was seen in both sexes. Such profound physiological changes in response to early life antibiotic treatment may have sex-specific and lifetime consequences for mammalian health.