

# Drug therapy in elderly heart failure patients

Ewa A. Jankowska<sup>1,2\*</sup>, Cristiana Vitale<sup>3</sup>, Izabella Uchmanowicz<sup>4</sup>,  
Michał Tkaczyszyn<sup>1,2</sup>, Marcin Drozd<sup>1,2</sup>, and Piotr Ponikowski<sup>1,2</sup>

<sup>1</sup>Department of Heart Diseases, Wrocław Medical University, Borowska 213, 50-556 Wrocław, Poland;

<sup>2</sup>Centre for Heart Diseases, University Hospital, Borowska 213, 50-556 Wrocław, Poland;

<sup>3</sup>Department of Medical Sciences, IRCCS San Raffaele Pisana, Centre for Clinical and Basic Research, Via della Pisana 235, 00163 Rome, Italy; and

<sup>4</sup>Department of Clinical Nursing, Wrocław Medical University, K. Bartla 5, 51-618 Wrocław, Poland

## KEYWORDS

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Although heart failure (HF) is considered as a cardiogeriatric syndrome, elderly and very elderly patients are under-represented in the vast majority of clinical trials investigating novel drugs and therapies in this population. The homeostatic systems of elderly subjects are very fragile, and the management of HF accompanied by numerous comorbidities requires a holistic approach towards the patient, with special emphasis not only on psychosomatic problems but also on the individual (including social) needs of each particular patient, along with the support for the family and/or caregivers. In this article, we summarize current evidence regarding pharmacotherapy of elderly patients with HF and summarize the clinical problems occurring in this population.

## Introduction

Heart failure (HF) is considered as a cardiogeriatric syndrome. The prevalence of HF in a general population increases with age, from 1% among those aged 45-55 years to 10% among those aged 80 years and more.<sup>1</sup> Among patients aged over 65 years supervised by general practitioners presenting with exercise dyspnoea, HF would be diagnosed in one-sixth of them.<sup>2</sup> Finally, the mortality of patients with HF increases with age.<sup>3,4</sup>

## Evidence-based pharmacotherapy in elderly patients with heart failure

In the vast majority of clinical trials executed in patients with heart failure with reduced ejection fraction (HFrEF), elderly subjects are underrepresented.<sup>5,6</sup> However, pre-specified subgroup analyses in the major clinical trials investigating angiotensin-converting enzyme (ACE) inhibitors,<sup>7</sup> beta-blockers,<sup>8,9</sup> mineralocorticoid receptor

antagonists,<sup>10</sup> and ivabradine<sup>11</sup> in patients with HFrEF have shown that older subjects benefit from certain drug interventions to an analogous extent as do younger subjects. Very few studies have been based on an a priori investigation of particular drugs in relatively elderly patients (e.g. nebivolol in the SENIORS trial,<sup>12</sup> bisoprolol and carvedilol in the CIBIS-ELD trial<sup>13</sup>). In the PARADIGM-HF trial, a sacubitril-valsartan combination brought clinical benefits over an enalapril therapy (including the longer lifetime free of clinical endpoints, such as cardiovascular death and HF hospitalization) across all investigated age groups.<sup>14</sup> Similarly, in the DAPA-HF trial, dapagliflozin compared with placebo reduced the risk of primary composite endpoint (worsening HF or cardiovascular death) in both younger and older patients with HFrEF.<sup>15</sup>

Therefore, the pharmacotherapy of HFrEF in elderly patients is recommended to be the same as for patients in all other age groups according to the ESC/HFA guidelines,<sup>2</sup> and is based on ACE inhibitors (or angiotensin receptor antagonists [ARB] or angiotensin receptor-neprilysin inhibitors [ARNI]), beta-blockers, mineralocorticoid receptors (MRA), ivabradine to improve clinical outcomes, along with loop diuretics, and sometimes digoxin to further alleviate HF symptoms.<sup>16,17</sup>

\*Corresponding author. Tel: + 48 71 733 11 12,  
Email: ewa.jankowska@umed.wroc.pl

**Table 1** Side-effects associated with heart failure treatment requiring a special attention in the elderly

1. Diuretics—a risk of hypovolaemia, hyponatraemia, which may lead to pre-renal kidney failure, delirium, and orthostatic hypotension
2. Beta-blockers—a risk of vertigo, bradycardia/atrioventricular block, chronotropic incompetence, bronchial constriction, depression, and cognitive impairment
3. Ivabradine—a risk of bradycardia/atrioventricular block, chronotropic incompetence, and photopsia
4. ACE inhibitors (or ARB), ARNI, and MRA—a risk of hyperkalaemia, hypotension, and worsening of renal function
5. Digoxin—a risk of overdosing with development of delirium, depression, anxiety, nausea, vomiting, and diarrhoea
6. Spironolactone—a risk of hypogonadism, catabolism, and impairment of glycaemic control
7. Amiodarone—a risk of hyper- or hypothyroidism, polyneuropathy, and interstitial pulmonary fibrosis

Among elderly patients with HF, women and patients with heart failure with preserved ejection fraction (HFpEF) due to mainly coronary heart disease, hypertension, and diabetes predominate.<sup>18,19</sup> In general, women have been significantly less recruited for clinical trials. For patients with HFpEF, the situation is even worse, as there is no established life-saving therapy at all, and the therapeutic strategy is focused on control of HF symptoms and treatment of comorbidities.<sup>20-22</sup>

There are some clinical scenarios that are more common in elderly patients with HF, and which require clinical experience, a watchful approach and early identification of side effects (*Table 1*). Many comorbidities, including anorexia,<sup>23</sup> iron deficiency,<sup>24,25</sup> muscle wasting,<sup>26-28</sup> and frailty<sup>29-31</sup> are all more common in the elderly<sup>32,33</sup> making drug side-effects<sup>34</sup> and poor response to therapy more likely. The majority of drugs used in HF, through a variety of mechanisms, may increase the risk of delirium, cognitive impairment, and depression, which may be difficult to distinguish from functional deficits due to cerebrovascular events.

## How to optimize pharmacotherapy globally in elderly patients with heart failure?

Homeostasis of elderly subjects is very fragile.<sup>35,36</sup> The diagnosis of HF along with accompanying comorbidities makes the global management of health problems challenging.<sup>37,38</sup> Some strategies<sup>2,5,15,39-42</sup> listed in *Table 2* are worthy to be considered to make the therapeutic strategies applied in elderly patients with HF as safe and effective as possible.<sup>43</sup>

## Final comments

Particularly for elderly patients with HF, treatment involves both the ‘art’ and the ‘science’ of good medicine. In this population, therapeutic decisions are most

**Table 2** Major instructions useful for the optimization of treatment process in elderly patients with heart failure

- Consider biological age (reflecting the status of global functioning) rather than chronological age
- Identify and eliminate the risk factors promoting frailty (in order to prevent frailty syndrome itself)
- Screen and treat malnutrition
- Screen and correct hypovolaemia along with electrolyte derangements
- Screen for asymptomatic/subclinical forms of age-related somatic comorbidities, and treat them optimally at their early stages of progression
- Screen for mild depression and dementia, which may mask the symptoms of cardiovascular disease (and vice versa), and treat them optimally at their early stages of progression
- Prioritize drugs with clear recommendation and proven efficacy/safety (ideally with evidence available for elderly cohorts), and try to limit polypharmacy
- Treat somatic and psychiatric comorbidities based on available recommendations, administer novel drugs if they are indicated, start with lower doses and increase doses slowly up to the maximal tolerated doses
- Consider factors influencing pharmacokinetics and pharmacodynamics when selecting drugs and their doses (e.g. kidney dysfunction, liver dysfunction, hypoalbuminaemia, catabolic state, hypovolaemia), and do not hesitate to ask a clinical pharmacist for advice
- Simplify pharmacotherapy daily schemes and implement other interventions improving compliance (e.g. education, smartphone applications)
- Be aware of side effects frequent in elderly patients and try to anticipate their occurrence: vertigo, instable walking, falls, gastrointestinal haemorrhage, hypovolaemia, hyponatraemia, diarrhoea, constipation, and cognitive dysfunction (including delirium)
- Treat an elderly patient with an interdisciplinary team of experts and professionals (including a cardiologist, a primary care specialist, a geriatrician, other specialists, a nurse, a dietician, a physiotherapist, a clinical pharmacist, and a social worker)
- Acknowledge the individual needs of a patient (including non-medical and social ones) and provide the broad support to the patient, his/her family members and care givers

commonly made based on clinical experience of physicians and extrapolation of data from clinical trials executed among study cohorts with no adequate representation of old and very old subjects. For patients with HFpEF (which predominate in the elderly cohorts), there is no established life-saving therapy at all, and the therapeutic strategy is focused on control of HF symptoms and treatment of comorbidities.<sup>44,45</sup>

Management of elderly patients with HF requires a holistic approach towards the patient and should consider his/her somatic and psychic problems. It is also necessary to acknowledge the individual needs (including social needs) and provide the broad support to the patient, his/her family members and care givers.<sup>46</sup>

Pharmacotherapy of elderly patients with HF must be an interdisciplinary process. It should be carefully planned and executed by a cardiologist together with a primary care specialist, with advice from a geriatrician and other specialists. The proper implementation of recommendations should also involve a nurse, a dietician, a physiotherapist, a clinical pharmacist, and a social worker.<sup>23,24,47</sup>

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