Review

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Review

Heart Failure in Elderly Patients: Medical Management, Therapies and Biomarkers

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Abstract: Heart failure (HF) is a common condition and one of the main morbidity and mortality factors in elderly patients. The incidence of HF progressively increases with age, reaching to >10% in those aged 70 years or over. In the elderly population both the diagnosis and the management of HF prove challenging, often requiring specialized care and multidisciplinary approach. In seniors atypical presentation of HF is much more common than in younger patients, thus a holistic assessment with biomarkers related to HF allows for early diagnosis and accurate risk stratification in this group of patients. This article reviews the clinical and diagnostic differences in elderly patients with HF, highlighting the presence of comorbidities, frailty, cognitive impairment and polypharmacy, as well as discusses potential biomarkers that may have clinical application in this population.

Keywords: heart failure; biomarkers; elderly patients; pharmacological treatment; comorbidities

1. Introduction

Heart failure (HF) is a leading cause of morbidity and mortality, as well as a major public health problem, generating high health-care-related costs. It is a clinical syndrome caused by structural and/or functional cardiac abnormalities, resulting in a reduced cardiac output and/or elevated intracardiac filling pressures [1]. The prevalence of HF is strongly associated with age, from around 1% for those aged <55 years to >10% in those aged 70 years or over [2]. The number of elderly patients with HF is steadily growing due to better medical care and increasing life expectancy.

Elderly patients with HF are a varied group including both patients with reduced, mildly reduced and preserved ejection fraction (HFrEF: HF with reduced ejection fraction, HFpEF: HF with preserved ejection fraction, HFmrEF: HF with mildly reduced ejection fraction). Study shows that in the patients aged ≥60 years, diastolic left ventricular dysfunction is very common, with a median prevalence of 36.0% (range 15.8–52.8%), and systolic dysfunction is less common with a median of 5.5% (range 3.3–9.2%) [2]. Thus, elderly patients with HF constitute an etiologically and functionally heterogeneous group of patients that requires an interdisciplinary approach due to comorbidities, which may additionally complicate the course of the HF. Furthermore, the clinical course and prognosis may often be difficult to predict in the elderly population. This article reviews the clinical and diagnostic differences in elderly patients with HF, highlighting the presence of comorbidities, frailty, cognitive impairment and polypharmacy, as well as discusses potential biomarkers that may have clinical application in this population.

2. Heart Failure in Elderly

In the group of patients with HF aged over 65 years old the overall course of the condition varies from other age groups. In younger age group, most patients suffer from systolic HF [1], and men are affected more often than women. In older patients, women are affected more frequently. However,

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the percentage of diastolic HF is higher in the elderly and the ratio of genders is more balanced [3]. Most common causes of HF are coronary artery disease and hypertension. However, in older patients other pathophysiological factors that contribute to development of HF can be observed, like dilatation of the left ventricle and diminished elasticity of the aorta [4]. Opposed to the general population HF etiology in the elderly is more likely to be related to valvular heart disease (VHD), with the most common VHD affecting elderly being aortic stenosis. It varies across 65-74 years old and over 75 years old groups. Patients aged 65 to 74 years more frequently had lower left ventricular ejection fraction (LVEF), an ischemic etiology of HF and required percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) before and during index hospitalization. In turn, patients aged over 75 years old had a lower percentage of ischemic etiology, and a higher average LVEF when compared to the other group [5].

Diagnosis of HF in elderly is challenging as the condition may have an unusual presentation in this group. Patients instead of typical symptoms that include dyspnea, fatigue, ankle swelling, and edema, frequently present with atypical, nonspecific symptoms such as tiredness, altered mental status, depression, and loss of appetite [6]. In the study conducted in geriatric outpatient clinic in Netherlands on 206 patients, in only 46% of geriatric patients with suspected HF could the diagnosis be confirmed, and typical signs of HF were absent in one third of patients with HF [6].

Elderly patients are more likely to have multiple comorbidities, which play an important role in the treatment, prognosis and diagnosis of HF. In the Interdisziplinäres Netzwerk Herzinsuffizienz (INH) registry, approximately 50% of the patients had seven or more comorbidities [3]. Another study investigating patients aged over 65 years old found that around 90% of older adults with HF have at least 3 other medical conditions, and over 60% have at least 5 other medical conditions [7]. Furthermore, a significant association was found between the number of comorbidities and the risk for all-cause mortality in patients with HF [8].

Atrial fibrillation (AF) is one of the most common comorbidities coexisting with HF. The proportion of patients with HF who develop AF increases with age and HF severity making it especially prevalent in elderly. Studies conducted on the Polish population show that nearly 40% of patients with HF also have AF [9,10]. Patients with AF have higher short- and long-term mortality after hospital discharge and higher risk of readmission. Mean age of studied patients with both AF and HF was 72 (62–79) [5]. In a group of patients aged over 75 years old AF often leads to stroke, as this group is less frequently treated with anticoagulants, because of a higher risk of bleeding [9].

Another important comorbidity in elderly patients with HF is diabetes mellitus type 2 (DM-2). DM-2 and HF often occur concomitantly, and each disease independently increases the risk for the other. In HF cohorts, including both HFrEF and HFpEF, the prevalence of DM-2 ranges from 10% to 47%. Hyperglycemia and hyperinsulinemia accelerate atherosclerosis via vascular smooth muscle cell proliferation and inflammation [11]. DM-2 can also cause cardiovascular autonomic neuropathy, which has potentially life-threatening complications including arrhythmias and silent myocardial ischemia [12]. It is important to note that treatment of HF is similar in patients with and without diabetes. Sodium-glucose cotransporter 2 inhibitors (SLGT2i) such as empagliflozin or dapagliflozin initially demonstrated to reduce HF hospitalizations in diabetic patients and after multiple trials became an important pharmacological group in HF treatment even in patients without DM-2 [1]. Despite the potential need for additional hypoglycemic agents the possibility to better optimize pharmacological therapy is particularly beneficial to the older patients with HFrEF.

3. Pharmacotherapy in Elderly

Elderly patients are underrepresented in most trials investigating drug treatment of HF. Therefore, the recommendations for treatment in this group are more or less based on subgroup analysis and expert opinions. However, the majority of trials have not demonstrated age-dependent heterogeneity in the efficacy or safety of medical treatment for HF [13]. The pre-specified subgroup analyses in the major clinical trials investigating angiotensin-converting enzyme inhibitors (ACEI) [14], beta-blockers (BB) [15], mineralocorticoid receptor antagonists (MRA) [16], and SGLT2i [17,18] show that in patients with HFrEF, both in elderly and other age groups, the therapy yields similar results. Thus, pharmacotherapy in elderly is recommended to follow the guidelines established for other age groups.

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Current treatment regimen assumes fastest possible initiation and rapid escalation of ACEI, BB, and MRA dosage, simultaneously with the initial optimal dose of SGLT2i [1,19]. Simultaneous initiation takes place at the initial (low) doses recommended for HFrEF (except for SGLT2i, which are dosed from the beginning at the optimal dose) [1,19]. Especially in older patients monitoring of potency and side effects (including kidney function) is of great importance in establishing the optimal regimen for each individual.

Out of the four main groups of drugs used in HF treatment, ACE -Is were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF. They are recommended in all patients unless contraindicated or not tolerated. However, the 2021 guidelines strengthen indication for angiotensin receptor-nephrilysin inhibitor (ARNI) as a replacement in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment with ACEI/ARB (angiotensin receptor bloker) [1]. It is important to note that no randomized controlled studies that focused on elderly patients with ACEi or ARB were conducted. A meta-analysis of five randomized controlled trials with ACEIs in patients with ischemic etiology of HF or left ventricular systolic dysfunction reports that there was a nonsignificant age-by-treatment interaction for mortality, reinfraction and rehospitalisation [20]. When it comes to ARNI, a subgroup analysis of the PARADIGM – HF trial demonstrated consistent risk reduction in the primary endpoint of CV mortality or hospitalization for HF regardless of age [21].

Beta blockers play a major role in HF treatment. Controlled prospective clinical studies documented the efficacy of bisoprolol, carvedilol (the only non-cardioselective BB used in HF), and prolonged-release metoprolol succinate, as included in both the European and American guidelines [1,19]. The fourth BB used in HF is nebivolol, similarly to carvedilol it has a vasodilatory effect. What is interesting, nebivolol is included as an evidence-based beta-blocker in the ESC guidelines, but not the CCS or AHA/ACC/HFSA guidelines [1,19]. All of those drugs are eligible for treatment in elderly patients, as stated in the following trials. In the SENIORS trial, therapy with nebivolol was compared with placebo, in patients aged ≥70 years. Therapy with nebivolol led to a significant reduction of the primary endpoint all-cause mortality and cardiovascular hospitalizations regardless of the ejection fraction value [22]. Similar trial, including a considerable percentage of elderly patients, was conducted with metoprolol succinate, comparing its effect with placebo. A retrospective subgroup analysis found a comparable reduction regarding mortality and morbidity in patients aged over 69 and younger participants [23]. The CIBIS-ELD trial was a superiority trial comparing therapy with the beta-blockers bisoprolol and carvedilol in older patients. It found no difference regarding tolerance or achieved target dose between the two [24]. However, patients with bisoprolol more often suffered from bradycardia whereas carvedilol led to a reduction in the forced expiratory volume (FEV1) [24]. It shows the importance of individual approach to pharmacotherapy, as the choice of suitable BB should be tailored to patients' needs and comorbidities.

Since the release of 2021 ESC guidelines MRAs (eplerenone and spironolactone) are recommended in all patients with HFrEF. Their use is associated with a reduction in

HF symptoms, risk of hospitalization for HF, and mortality. MRAs block receptors that bind aldosterone and other steroid hormones (e.g. corticosteroid and androgen) receptors, with different degrees of affinity. Eplerenone is more selective to aldosterone receptor, thus causes less gynaecomastia, than spironolacton [1]. Similarly to ACEI their impact on elderly is based on prespecified subgroup analyses. Both in the RALES and in the EMPHASIS-HF the analysis concluded that older HF patients benefit from treatment with an MRA to a similar extent as younger patients [25,26]. The most important adverse effect of MRA treatment is hyperkaliemia, which is more common in elderly, especially with concomitant medication with an ACEI or an ARB, thus in this group renal function and electrolytes should be controlled regularly.

SGLT2i were introduced to the pharmacotherapy of HF fairly recently. The current guidelines [1,19] strongly recommend (class I) dapagliflozin or empagliflozin in patients with HF (NYHA class II-IV) with reduced left ventricular ejection fraction (LVEF ≤40%) to reduce the risk of hospitalization for HF and death. Both drugs according to sub analysis have no evidence of heterogeneity in treatment effects according to age [17,18].

Due to the complexity of pharmacotherapy patients with HF are at higher risk of adverse reactions. Furthermore, there is a number of commonly used medications thar are relatively or absolutely contraindicated in patients with HF, because they can cause exacerbations of HF or cause

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harmful interactions with the administered drugs [27]. That makes drug-induced exacerbation or decompensation of established HF a relatively common occurrence. It is important to acknowledge the usual mechanisms by which drugs can exacerbate HF, which is sodium retention, negative inotropic effect and direct cardiotoxicity. Nonsteroidal antiinflammatory drugs deserve special attention, as they are one of the most common groups taken by patients worldwide. They are relatively contraindicated as they may precipitate acute decompensation in patients with HF [28]. As some patients with HF may also suffer from angina it is important to note that verapamil and diltiazem increase HF-related events in patients with HFrEF and therefore should be substituted by other safer alternatives such as ivabradine and trimetazidine [1,29]. In the treatment of hypertension aside from non-dihydropyridine calcium channel blockers (diltiazem and verapamil), centrally acting agents, such as moxonidine, are contraindicated as they are associated with worse outcomes [30]. On the other hand, alpha blockers according to ESC guidelines have no effects on survival and are therefore not indicated, while 2022 AHA guidelines indicate that they may cause or exacerbate HF and should be avoided [1,19]. In case of diabetes and HF coincidence treatment should avoid thiazolidinediones (glitazones), as they cause sodium and water retention and an increased risk of worsening HF and hospitalization [31], also sulfonylureas were associated with a higher risk of HF events in some analyses [1].

4. Polypharmacy and Its Impact on Elderly

In HF, the progressive use of multiple drugs and a complex therapeutic regimen is common and is recommended by ESC guidelines for the diagnosis and treatment of acute and chronic HF [32]. Adequate pharmacotherapy is also crucial to controlling comorbidities, lowering mortality and potentially improving the quality of life. In elderly where the number of comorbidities is usually greater, each could require additional specific treatment, thus further increasing the number of drugs prescribed. Study shows that the vast majority (84% at admission and 95% at discharge) of older patients take at least 5 different medications and nearly half of the investigated population (42% at admission and 55%) at discharge took over 10 different ones [33]. Elderly patients are particularly vulnerable to the adverse effects of polypharmacy due to age-related alterations in pharmacokinetics and pharmacodynamics [34] and coexisting conditions like frailty and mental impairment.

Among the drugs used in elderly patients with HF, warfarin could be especially harmful in polypharmacy due to its multiple potential interactions [35]. The last guidelines for atrial fibrillation [36] recommend direct oral anticoagulants (DOAC) as a first-line drug but many erderly patients are still taking warfarin due to its high price point [37]. Furthermore, there are also some conditions that still require vitamin K antagonists (VKA) usage. Patients with mechanical valves or left ventricular assist device are treated with VKA in long term oral anticoagulation therapy. Both patients with those conditions or atrial fibrillation make up for a significant number of elderly patients still taking warfarin, therefore at higher risk of adverse drug reactions [38]. Unfortunately, almost 50% of optimally treated HF patients were additionally taking medications and supplements for self-treatment, such as analgesics, herbal products and mineral products further increasing the probability of interactions [39].

Another important issue is adherence to therapy. Study by Giardini et al. shows that adherence is usually low in the elderly (below 45%) and further decreases with an increasing number of medications administered [40]. This problem is exacerbated in patients with dementia. According to the study conducted on the Polish population nearly 60% of patients forget to take their medications. In this group, 70% of patients declared they did not take a medication dose that had been forgotten, and 29% took such a dose as soon as they remembered. This may lead to reduced levels of the active substance reducing treatment efficiency or lead to adverse reaction when the level of active substance increases beyond safety threshold [39]. Complexity of the treatment regimen and introduction of non-pharmacological guidelines may also pose a problem. Geriatric patients do not often comply with physicians guidelines because of a too complex treatment regimen, long treatment duration or introduction of constant changes that are difficult to be remembered by the elderly. Furthermore, patients are required to change their previous habits and to introduce new ones such as a limited intake of salt and fluids, tobacco smoking cessation, reduced alcohol consumption, performing physical exercises of moderate activity and daily body weight monitoring [41]. Those non-pharmacological guidelines are usually regarded by patients as difficult to introduce or hardly

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significant, which is a challenge especially in elderly patients who have been accustomed to their own lifestyle for many years.

5. Frailty Syndrome in Elderly Patients

Frailty is defined as an age-associated clinical syndrome characterized by a decrease in physiological reserve in situations of stress, constituting a state of vulnerability that entails a higher risk of adverse events [42]. Frailty has over 70% prevalence in patients aged over 70 years old hospitalized for HF [43]. Furthermore, patients affected by frailty have an overall increased risk of 1.5 for hospitalization and mortality in chronic HF. Studies also suggest that stratification of patients with HF by frailty status provides prognostic information and may inform priorities for HF interventions and management [44]. Thus, it is essential to recognize and characterize frailty status in patients with HF in order to minimize the significant negative impact of frailty on chronic HF. There are multiple scales for frailty assessment and the major ones (frailty index by Rockwood and Mitnitski, Fried phenotype from the Cardiovascular Health Study, FRAIL scale, and the Hubbard modified frailty score) perform similarly in predicting death and physical limitation in a geriatric study population [45]. Cardiac rehabilitation plays an important role in evaluating and treating frailty. With proven beneficial effects on muscle mass and strength, mobility, habitual physical activity, social interaction, cognitive performance, mood, and vitality it may be considered as (one of the only) comprehensive antidotes available in clinical practice with the potential to counteract frailty and its downstream consequences [46].

6. Neurohormones in HF

6.1. Natriuretic Peptides

Neurohormones play a major role in cardiology largely due to their diagnostic and prognostic values in the setting of a variety of cardiovascular conditions including acute coronary syndromes (ACSs) and congestive HF. Among neurohormones, both natriuretic peptides including N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) have become established diagnostic and prognostic markers [47]. Plasma concentrations of natriuretic peptides are recommended as initial diagnostic tests in patients with symptoms suggestive of HF to rule out the diagnosis [1]. However, levels of natriuretic peptides increase with age and may vary in the presence of comorbidities such as obesity, kidney disease, thyroid disease or atrial fibrillation [3]. Therefore, the usefulness of natriuretic peptides in elderly patients may be limited. The BED (BNP Usefulness In Elderly Dyspnoeic Patients) study showed that BNP was not useful for discriminating between cardiac and respiratory origin of acute dyspnea in patients ≥ 60 years [48]. In a meta-analysis of BNP-guided therapy in patients with HF where two cohorts divided by age were investigated and compared similar correlation was observed. It was found that in patients under 75 years of age, NT-proBNP-guided therapy led to a decrease in mortality and hospitalization rates, there was no improvement in patients over 75 years of age [49]. While data from the TIME-CHF (Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure) study showed that NT-proBNP guided therapy is safe in elderly and highly co-morbid HF patients [50].

6.2. Copeptine in Elderly Patients

Neurohormones in the cascade of the arginine vasopressin (AVP) system including AVP and copeptin have also been investigated in elderly patients with HF as potentially useful in clinical practice. AVP is a conventional neurohormone that is well known to be released from hypothalamus in response to hypovolemia and increased plasma osmolality. AVP concentration is increased in patients with chronic HF partially as a response to a high osmolality. The release of AVP in HF is mainly stimulated by reduced cardiac output, and in turn insufficient filling of arteries leads to carotid sinus and aortic baroreceptor's activation. Hyponatremia, which is often present in patients with HF, might also stimulate the release of AVP. It is also known that angiotensin II increases concentration of AVP [51].

Copeptin, the C-terminal portion of provasopressin, is a novel neurohormone of the AVP system co-secreted with AVP from hypothalamus, it reflects vasopressin concentration in human plasma and serum. Because copeptin is secreted in equimolar amounts to AVP and more stable than AVP, it has

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been gradually replaced AVP in the clinical setting [47], and accordingly studies investigating the association between AVP system and various clinical conditions have particularly focused on copeptin rather than AVP [52]. Previous study showed that copeptin was an independent predictor of mortality and rehospitalization in patients with advanced HF [53]. Similar findings were reported in a study on elderly patients, showing an association between copeptin levels and mortality [54].

Combined use of copeptin with other biomarkers may also appear to have strong prognostic value. In a study on 470 elderly patients with symptoms of HF the association between plasma concentrations of copeptin combined with concentrations of the NT-proBNP, and mortality was investigated. The study found that in this group both increased copeptin levels and combination of increased levels of copeptin and NT-proBNP were associated with enhanced risk of all-cause mortality during a median period of 13 years in these patients [54]. Similarly among 172 patients suffering from chronic HF, survival analysis demonstrated that both copeptin and high sensitivity cardiac troponin T were excellent predictors of outcome during long-term follow-up [55].

6.3. Other Biomarkers

New biomarkers are being evaluated for their ability to advance the management of patients with HF, but only few have shown their usefulness for the elderly patients.

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin 1 receptor family with 2 main isoforms: transmembrane or cellular (ST2L) and soluble or circulating (sST2) forms. ST2 is a marker associated with inflammatory disease and fibrosis, and its concentration was found to not be affected by age, renal function, or body mass index [56]. ST2L is a membrane bound receptor for which IL-33 is the functional ligand. IL-33/ST2L signaling leads to inflammatory gene transcription which results in the production of inflammatory cytokines/chemokines and induction of immune response. Depending on several co-stimulatory factors, IL-33 can either act as a pro- or anti-inflammatory cytokine. In the context of the heart and HF, IL-33 is considered to exert cardioprotective effects. sST2 is secreted into the circulation and functions as a decoy receptor for IL-33, inhibiting the effects of IL-33/ST2L signaling. Thus, increased concentrations of sST2 in the circulation attenuate the systemic biologic effects of IL-33 [57]. ST2 demonstrates predictive value for 30-day and 1-year outcomes in comorbid frail elderly patients with HFpEF in a study comparing four different markers. In this study the value of early post-discharge circulating levels of ST2, NT-proBNP, cancer antigen 125 (CA125), and high-sensitive cardiac troponin T (hs-cTnT) was assessed. ST2 outperformed NT-proBNP for risk prediction of the composite primary endpoint (all-cause mortality or HF-related rehospitalization). Thus, establishing its role as predictive marker in high-risk HFpEF [56].

Another interesting one is hs-cTnT, as mentioned earlier its combined use with copeptin was an excellent prognostic marker for patients with stable HF. Testing for hs-cTnT is commonly performed in patients with HF, particularly in those with acute HF syndromes, where cardiac troponin I (cTnI) or cTnT measurement is recommended to establish the presence of type 1 myocardial infarction (MI) or acute HF-related injury [57]. However, sensitive troponin levels have also been found to be associated with prognosis in patients with chronic heart failure, and changes in cTnT concentrations over time, as measured with a hs-cTnT, were shown to predict cardiovascular events in these patients. In elderly hs-cTn has also shown its usefulness. In the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial elevated hs-cTnT levels in elderly patients with chronic HF of ischemic cause provided independent prognostic and discriminating information beyond that of established risk markers [58].

7. Conclusions

HF in elderly is a nuanced and varied problem in clinical practice. The clinical profiles of elderly patients differ from those of younger ones and non-specific symptoms of HF in this group of patients are associated with a later diagnosis and consequently significantly worse prognosis. To improve on the prognosis, a holistic approach is recommended. Addressing the issue of polypharmacy, specific and frequent aging particularities such as frailty and other geriatric conditions and proper management of comorbidities are vital steps in HF treatment in this group. Natriuretic peptides

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commonly used in HF have limited clinical utility in elderly patients. Other biomarkers including copeptin, ST2 and high-sensitive troponin may be useful prognostic tools in this population.

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