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Heart failure in elderly: progress in clinical evaluation and therapeutic approach

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Abstract

Chronic heart failure (CHF) represents a major and growing health problem, due to its high incidence and prevalence, its poor prognosis and its impact on health-care costs. Although CHF patients are mainly elderly, few studies were aimed at testing the efficacy of diagnostic and therapeutic approaches in this population. The difficulty in CHF diagnosis among the elderly is related to different factors, such as: the frequent presence of co-morbidity conditions mimicking or masking heart failure signs and symptoms; the different diagnostic cut-offs of natriuretic peptides; and the need to correctly evaluate diastolic function in order to assess CHF with preserved ejection fraction. Furthermore, the therapy of elderly CHF patients has not been well defined, considering the few studies involving very aged patients and the absence of a therapeutic strategy demonstrated to improve prognosis of CHF patients with preserved ejection fraction. The aim of this review is to focus on the most recent issues concerning the diagnosis and therapy of elderly patients affected by CHF.

1   Introduction

Chronic heart failure (CHF) represents a major and growing health problem. It has been estimated that its prevalence is 1%–2% of the population of the developed countries, with an incidence of 5–10 per 1000 persons per year.[1-2] Beside the "epidemic" proportions of the prevalence of CHF, its relevance also derives from the impact on health-care costs (around 2% of total health care budget),[3] mainly due to acute decompensated heart failure hospitalizations. The annual number of CHF related hospitalizations has been shown to be increasing[4] with a rate of rehospitalization of 50% within 6 months of discharge,[5] mostly related to worsening of previously diagnosed CHF.[6]

The prevalence and incidence of CHF progressively increase with ageing. In a US population based study, the prevalence of heart failure was 0.7% in persons aged between 45 and 54 years but it was 8.4% in those older than 75 years.[7] However, current diagnostic and therapeutic

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recommendations are based on studies not involving older patients.[1,8,9]

The aim of this review is to focus on the most recent issues concerning the diagnosis and therapy of elderly patients affected by CHF.

2   Epidemiologic aspects of heart failure in elderly

Current classification of CHF differentiates two major groups of patients, those characterised by a reduced left ventricular ejection fraction (HFREF) and those with a preserved ejection fraction (HFPEF).[1]

Recent studies state that HFPEF are more than a half of all CHF,[10] but due to the heterogeneity of its definition, it is still difficult to assess its real prevalence and incidence.[11-14] In the population of the Olmsted County Study, 2.2% of subjects were found affected by CHF and almost a half of these had a left ventricular ejection fraction (LVEF) echocardiographically assessed to be over 50%.[12] HFPEF patients are more often elderly female and obese and more frequently suffering of hypertension and atrial fibrillation (AF).[13] Moreover, the prevalence of HFPEF increases with ageing.[11,14] Investigators of Cardiovascular Health Study (CHS), affirmed that HFPEF affects the 8.8% of the geriatric population.[15] Conventionally, this population consists of

people aged more than 65 years; particularly, persons from 65 through 74 years old are termed as "early elderly", while over 75 years old as "late elderly".[16] This definition, which maybe questionable nowadays, is still considered suitable for medical contexts and also appropriate to group CHF patients.[17]

The presence of co-morbidities is one of the most important feature of the elderly population and it has a strong impact on HFPEF survival.[11,13,18] Data from the Framingham Heart Study showed that cardiovascular disease accounted for the 69.9% of HFREF deaths while cancer, infection and renal disease were recognized as causes of non-cardiac deaths for the majority of HFPEF patients.[19] Of note, data from the Acute Decompensated Heart Failure Registry (ADHERE) showed that even if HFPEF in-hospital mortality rates were lower compared to the HFREF ones (2.8% *vs*. 3.9%, $P = 0.005$), the duration of intensive care stay and total hospital stay were the same for the two syndromes.[20] However, when CHF has been investigated, patients affected by HFPEF showed a survival rate similar to those with HFREF.[21]

3 Clinical evaluation of elderly with CHF: from diagnosis to prognostic stratification.

The above mentioned epidemiologic characteristics of geriatric patients affected by CHF raise a number of issues concerning diagnostic approaches and prognostic stratification.[11]

3.1 Limited accuracy of symptoms for diagnosis of CHF in the elderly

The first step for diagnosis of CHF is based on the presence of signs and symptoms related to sodium and water retention (i.e., breathlessness) and/or fatigue.[1] However, in the elderly, these signs and symptoms are characterised by poor sensitivity and/or specificity due to the presence of co-morbid conditions mimicking or masking heart failure.[1]

Oudejans *et al*.[22] investigated a population of elderly outpatients, most of them with a number of co-morbidities, suspected of heart failure. The main symptoms these patients complained about to the clinicians were functional impairment (40%) breathlessness (35%), cognitive impairment (31%) and mobility disorders (29%). Half of them listed two or more symptoms (51%). Independent determinants of the presence of heart failure were male sex, age, nocturnal dyspnea, absence of wheezing, loss of appetite, and low Body Mass Index (BMI). The classic signs of heart failure (i.e., presence of tachycardia, tachypnea, pulmonary rales, pleural effusion, elevated jugular vein pressure (JVP), peripheral edema, or hepatomegaly) were not very sensitive,

as they were observed only in the 32% of patients with confirmed heart failure. Among the main co-morbidities influencing the accuracy of symptoms for diagnosing CHF, chronic obstructive pulmonary disease (COPD) plays a key role. Both CHF and COPD are very important in the differential diagnosis of dyspnea and their co-existence, which is observed in one third of CHF cases, leads to a higher risk for cardiac morbidity and mortality.[23]

Other diseases that can cause breathlessness are anemia, obesity, neurological or muscular disorders, and anxiety.[1] Additionally, in the geriatric population the association between CHF and cognitive impairment should always be taken into consideration.[24] Cognitive dysfunction affects patients' health behaviour and therapeutic compliance complicating diagnosis and management of the disease. It is associated with higher hospitalization and mortality rates. Results from recent studies have also shown that neuropsychological functions could improve, but not normalize, after heart failure therapy.[25,26] In this difficult clinical setting, it is particularly evident of the need for tests easily performed which could adequately screen patients with suspected CHF. Among the biomarkers which have been proposed for this goal, the plasma levels of natriuretic peptides (NP) have been recognised as the most accurate.[1]

3.2 Brain natriuretic peptide (BNP) in elderly

Since volume expansion or pressure overload produce ventricular myocardium wall stress, cardiomyocytes start synthesising pre-pro-BNP, which is then transformed in BNP a neuro-hormone whose action opposes vasoconstriction, sodium retention, and antidiuretic effects of the activated renin–angiotensin– aldosterone system.[27]

Quantitative analysis of plasma levels of NPs have been found to be helpful for triage decisions in cases of suspected CHF.[27] For this purpose, it is recommended by recent European Society of Cardiology (ESC) Guidelines to consider the exclusion cut-off points of 300 pg/mL for N-terminal-pro-Brain-Natriuretic Peptide (NT-proBNP) and 100 pg/mL for BNP in patients with acute symptoms; whereas the authors advised to establish the cut-off points of 125 pg/mL for NT-proBNP and 35 pg/mL for BNP in non-acute patients.[1] Additional benefits from combining BNP and NT-proBNP, or from using NT-proBNP/BNP are still debated.[27]

Also in elderly, the NP assays considerably improve the accuracy of CHF diagnostic process when added to the signs and symptoms evaluation.[28] However, the possible limitations of these tests in older patients should be considered because of the possibility that other factors apart from CHF could lead to a rise in NPs, as summarised in Table 1.

Table 1. Confounding factors influencing NPs serum levels. Data from Ref. #27, #29-32.

Extra-cardiac causes of increasing NP level
Ageing
Female gender
Renal dysfunction
COPD
Pulmonary hypertension
Low BMI
Pulsed pressure
Extra-cardiac causes of lowering NPs level
Obesity

BMI: body mass index; COPD: chronic obstructive pulmonary disease NPs: natriuretic peptides;

Ageing itself could explain the increase of NPs, probably due to age related myocardial fibrosis and renal impairment.[29] Renal failure is an important cause of augmented NP levels, not only because it diminishes the clearance of the peptides, but also because there is a strict relationship between the heart and the kidney in the regulation of plasma volume. Of note, NP tests for heart failure are not verified in patients on dialysis.[29]

In the healthy population of the Framingham Heart Study, plasma concentration of BNP markedly increased with age.[30] As a consequence, different age-specific reference values have been proposed in order to optimize the test accuracy.[31] Costello-Boerrigter et al.[32] additionally showed that NT-proBNP was more accurate than BNP in detecting HFREF patients among the elderly. Recent researches have studied the possible role of fibrosis related biomarkers in heart failure. Among these, Ho et al.[33] suggested the feasible use of Galectin-3, a galactoside-binding lectin secreted by macrophages, as a predictive factor of HF risk. Even if its measurement was positively correlated with age and BNP, since myocardial fibrosis is the first irreversible step for the adverse heart remodelling process, Galectin-3 could predict a very early diagnosis of heart failure before fluid overload and symptoms occur. Furthermore, Galectin-3 has also shown a prognostic value both for HFREF and HFPEF.[34,35]

Nevertheless, the state of the art diagnostic algorithms still propose exclusively the NP measurement. In order to diagnose HFPEF, Paulus et al.[36] suggested the use of cut off values of 100 pg/mL for BNP and 120 pg/mL for NT-proBNP, in order to exclude HFPEF in symptomatic patients. On the other hand, NPs tests need the implementation of other investigation techniques to differentiate HFPEF from HFREF and among these, the echocardiographic examination is the principal recommended technique.[1,36]

3.3 Echocardiographic approach for diagnosis of HFPEF

Over the last years, different criteria have been proposed in order to define HFPEF,[1,36,37] as summarized in Table 2. Although slight differences can be observed among the recommended criteria, a common strategy in order to detect diastolic dysfunction can be considered.

After first establishing the presence of signs or symptoms of CHF, the finding of "normal" LVEF is a fundamental feature of the syndrome. The cut-off value for normal LVEF is 50%. In order to exclude eccentric remodelling, a normal left ventricular dimension should be also observed.

The echocardiographic detection of diastolic function is based on pulsed Doppler flow recorded at the level of the mitral annulus and the pulmonary veins outlet and on pulsed Doppler by Tissue Doppler Imaging recorded at the level of the mitral annulus (Table 2). However, the evaluation of left atrial dimensions, of left ventricular mass index (LVMI), and presence at ECG of AF may also represent useful parameters in order to better identify HFPEF patients. Finally, in equivocal cases invasive measures should be considered.

3.4 Prognostic stratification in the elderly: from BNP to the multidimensional approach

A number of variables influence the prognosis of patients with CHF. Many scoring systems have been created to guide treatment options and predict patients' mortality and/or hospitalization.[1] Recently, the application of some of them, such as the SHFM[38] and the SENIORS risk model,[39] has also been evaluated for very aged patients.

BNP is widely included in the major part of survival scores. Moreover, it has been independently demonstrated that from the baseline values, the change of NT-proBNP plasma levels occurring over time correlates also with all-cause mortality and cardiovascular mortality in people aged more than 70 years.[40]

As shown in SENIORS risk model,[39] left atrial volume is another strong prognostic index for both HFREF and HFPEF. In another study, also Tsang et al.[41] identified a left atrial (LA) volume index > 32 mL/m² as an independent predictor of cardiovascular events in a population aged ≥ 65 years was more powerful than other echocardiographic indices, such as left ventricular mass index or left ventricular diastolic dysfunction. Analogously, in Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) echocardiographic substudy,[42] LA enlargement had a more significant prognostic value than Doppler indices of diastolic dysfunction. The relevance of left atrium dimension is due to the fact that it is load independent and reflects the

Table 2.   Recommended parameters for diagnosis of HFPEF.

	Task Force ESC for diagnosis of HFPEF (2007)[36]	EAE/ASE for the evaluation of Diastolic dysfunction (2009)[37]	ESC Guidelines criteria for HFPEF diagnosis (2012)[1]
Systolic function and remodelling			
LVEF (%)	> 50	-	> 50
LVEDVI (ml/m²)	< 97	-	< 97
LVEDDI (mm/m²)		-	< 32
Invasive evaluation of diastolic function			
τ (ms)	> 48	> 48	-
Echocardiographic evaluation of diastolic function			
Transmitral pulsed Doppler			
- E/A ratio: Mild dysfunction	< 1 (< 0.5 if > 50 years)	< 0.8	< 1
Moderate	1–2 (Pseudonormal)	0.8–1.5	1–2
Severe	> 2 (Restrictive)	> 1.5	> 2
- DTE (msec): Mild dysfunction	> 280	> 200	
Severe dysfunction	< 200	< 160	
Pulmonary vein pulsed Doppler			
- S/D	< 1	< 1	< 1
- Ar-A duration duration (ms)	≥ 30	≥ 30	≥ 30
TDI mitral pulsed Doppler			
- E'(cm/s)	-	< 8 (septal E')	< 9 (average E')
- E/E':			
Abnormal if associated with	8–15*	9–13# (average E')	8–15† (average or septal E')
Abnormal	> 15	> 13	> 15
Atrial volume index (mL/m²)	> 40	> 34	> 34
Left ventricular mass index (g/m²)	> 149 (> 122 in women)	-	> 115 (> 95 in women)
Heart rhythm	Atrial fibrillation		Atrial fibrillation
Natriuretic peptide			
BNP (pg/mL)	> 200	-	> 35
NT-proBNP (pg/mL)	> 220	-	> 125

*Abnormal transmitral pulsed Doppler (E/A ratio) or pulmonary vein pulsed Doppler flow; increased LV mass or increased left atrial volume; evidence of atrial fibrillation; augmented BNP or NT-proBNP plasma levels; #Two or more than two abnormal indices among: pulmonary vein pulsed Doppler flow: changes of transmitral pulsed Doppler (E/A ratio) during Valsalva maneuver of ≥ 0.5; PA systolic pressure ≥ 35 mmHg (in the absence of pulmonary disease), LA volume enlargement; †Generic recommendation to the use of additional echo-Doppler parameters suggestive of high filling pressure. Ar-A: time difference between pulmonary vein flow A-wave duration and mitral flow A-wave duration; BNP: Brain-Natriuretic Peptide; DTE: deceleration time of E wave; E': early diastolic velocity of mitral annulus; E/A: ratio of early to late diastolic mitral inflow waves; E/E': ratio of the mitral inflow E wave to the tissue Doppler E' wave; HFPEF: heart failure with preserved ejection fraction; LVEDDI: left ventricular end-diastolic diameter index; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal-pro-Brain-Natriuretic Peptide; S/D: ratio of systolic to anterograde diastolic pulmonary flow waves; τ: Invasive measure of left ventricular relaxation rate.

results of diastolic dysfunction over a long period. Finally, in elderly patients with CHF, both frailty (defined as "decreased reserve and capacity of defending from stressors") and disability complicate therapeutic management and influence prognosis.[43] The specific characteristics of these patients imply the need of an interdisciplinary diagnostic

process in order to identify cognitive and socio-economic problems. Consistent with this aim, several approaches have been developed to perform a multidimensional evaluation. Among these, the Multidimensional Prognostic Index (MPI) is a useful tool in order to stratify prognosis of CHF patients in different clinical settings.[44] It is based on eight domains with 63 items derived from the following scales: Activities of Daily Living (ADL); Instrumental Activities of Daily Living (IADL); Short Portable Mental Status Questionnaire (SPMSQ); Mini Nutritional Assessment (MNA); Exton-Smith Scale for Risk of Pressure Sore; Cumulative Illness Rating Scale (CIRS); number of medications; social support network. It can be calculated online (http://www.operapadrepio.it/it/content/view/1091/976) and it has been demonstrated to be able to assess the risk of one-month mortality in older patients with heart failure in both men and women.

The assessment of frailty in elderly patients could also be helpful during the hospitalization to better manage the discharge planning. The BRASS Index[45] is a good instrument to detect patients at high risk of prolonged admission with the need of protected discharge. It investigates living conditions and social support, mobility, functional and cognitive abilities, sensorial impairment, behaviour, number of hospitalizations, drugs, and co-morbidities of individual patients.

4   CHF therapy in the elderly: from traditional approaches to future perspectives

4.1   HFREF in the elderly: the neuro-hormonal therapeutic approach

Over the last decades, a number of large randomised trials have demonstrated that drugs blocking sympathetic nervous system activity and of renin angiotensin aldosterone system reduce the mortality of HFREF patients. However, few studies have focused on the impact of this approach in elderly patients with HFREF.[1]

Available data suggest that the effects of angiotensin receptor blockers (ARBs) and Angiotensin-Converting Enzyme Inhibitors (ACEI) are similar in the younger and in the elderly. An overview of studies evaluating the effects of ACEI had already shown that the decline in mortality and hospitalization was consistent across all age subgroups and more evident in patients with LVEF < 35%.[46] More recently, another study demonstrated that the benefit obtained by the administration of candesartan, an ARB, in terms of the reduction of cardiovascular mortality or CHF hospitalization, did not change with age.[47] Moreover, the absolute benefit of these drugs was greater in geriatric patients because of the highest risk of decompensation they had. Finally, the proportion of patients discontinuing candesartan

for adverse effects was almost the same across all age groups, and it was small even in the very elderly.

ARBs seem to be better tolerated by elderly than ACEI The Evaluation of Losartan In The Elderly–II (ELITE II) trial compared effects of losartan or captopril in patients, most of whom aged > 65 years (mean age 71 years), with LVEF < 40%.[48] Results showed that the two drugs were similarly effective, but the ARB was better tolerated.

The block of renin angiotensin aldosterone system (RAAS) should be based not only on the antagonism of renin or angiotensin receptors, but also of the aldosterone ones.[1,49] The recent Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study,[50] showed a beneficial effect of mineralocorticoid receptor antagonism even in less symptomatic patients New York Heart Association II (NYHA II). In the EMPHASIS-HF trial, the use of eplerenone reduced the risk of death from a cardiovascular cause or hospitalization for heart failure and these results were not statistically different between the subgroups of patients of older age (24% of the population studied) or less than 75 years. However, in older patients, renal function abnormalities increase the risk of hyperkalemia,[51] as well as of worsening of renal function[52] when spironolactone and eplerenone are administered. As a consequence, serum creatinine and potassium levels should be even more closely monitored in older patients. Finally, it is worth nothing that the aldosterone antagonist related gynecomastia is more common in these patients because of the age related decline in the testosterone levels.[53]

Beside RAAS block, the antagonism of sympathetic nervous system overactivity represents the other corner stone in the treatment of HFREF. Meta-analyses of beta-blocker trials have shown the possibility of this class of drugs to reduce mortality and morbidity rates by 30%.[54] The largest trial evaluating the efficacy of beta-blocker therapy in the elderly was the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) study.[55] It showed that the administration of nebivolol in a population of elderly CHF patients (all enrolled patients were > 70 years old) reduced the composite risk of all cause mortality, or cardiovascular hospital admission compared with placebo, even if it did not reduce mortality. The beneficial effects appeared after six months of treatment and the risk reduction continued to increase with longer treatment. However, the benefits of nebivolol appeared to be less in patients aged > 75 years.

Elderly patients in beta-blocker therapy also showed a higher risk of side-effects when compared with the younger cohorts. Nevertheless, 68% of patients in the nebivolol group reached the maximum dose of 10 mg (titrated over a

mean of seven weeks), with only 6% not tolerating any dose.[55] This good tolerability may, in part, be related to the vasodilating properties of nebivolol so that results may not be extended to other beta-blockers. More recently, the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD) trial[56] compared bisoprolol and carvedilol tolerability, when titrated up to their guideline-recommended target doses, found in elderly (aged > 65 years) heart failure patients with impaired and preserved LVEF, no differences in terms of achieved dosage and target dosage tolerability. However, analogously to the results from previous studies, the younger age and the lower NYHA functional class predicted the ability of patients to tolerate higher beta-blocker doses. In a sub-analysis of the CIBIS-ELD,[57] it has also been shown that heart rate reduction is both a desired effect of beta-blocker therapy and a predominant limitation for their titration. These results seem to be of particular interest considering that heart rate control has been recently proposed as a new effective therapeutic strategy in HFREF patients.

4.2   Heart rate control

The recent Systolic Heart Failure treatment with the If inhibitor ivabradine Trial (SHIFT) provided new evidence of the possible relevant role of heart rate control in improving CHF prognosis. Resting heart rate has been demonstrated to be a strong predictor of worse prognosis in patients with cardiovascular disease,[58,59] and CHF.[60] The progressive risk of increasing HR is related to a number of factors, such as a negative force-frequency relationship,[61] endothelial dysfunction,[62] and myocardial oxygen consumption.[63]

Ivabradine is a pure heart rate-slowing agent that inhibits the I_f channel in the sinus node. In the SHIFT trial,[64] 6558 patients with LVEF < 35% and resting HR > 70 beats/min were randomised to receive placebo or ivabradine in association with a standard therapy, including an ACEI or an ARB, a beta-blocker, and an aldosterone antagonist. During follow-up, a significant reduction (HR: 0.82; 95% CI: 0.75–0.90; P < 0.001) in the composite primary end-point (cardiovascular death or hospital admission) was observed in the group of patients taking ivabradine. In the same group, fewer hospital admission for the worsening of heart failure and fewer heart failure deaths were also observed. No significant reduction in cardiovascular death and death from all causes was observed. The use of ivabradine was associated not only with a significant reduction of first heart failure hospitalization, but also with a reduction in its recurrence.[65]

Finally, ivabradine has demonstrated also to be able to improve left ventricular remodelling. In an echocardiography substudy,[66] the group of patients taking ivabradine showed a significant reduction of left ventricular end-systolic volume index and a significant increase of LVEF. Although the results of SHIFT have demonstrated the possible usefulness of this new therapeutic strategy, it is worth noting that only 10% of the population was aged more than 75. Moreover, the effect of ivabradine is generally mainly related to the magnitude of HR reduction[67] while in the elderly, an age related decline in the number of sinus node pacemaker cells as well as degenerative changes in the cardiac conduction can be observed.[68,69] As a consequence, and like betablocker therapy, the use of ivabradine could easily favor the occurrence of bradiarrhythmias in this cohort of patients. Finally, no data are available about the efficacy of ivabradine in HFPEF cases.

4.3   Therapy of HFPEF

Over the last decade, whether a significant reduction in death from HFREF has been observed due to advances in pharmacotherapy, the mortality rate from HFPEF is unchanged.[12] This is due to the fact that no controlled randomised trial has demonstrated the possibility of improving survival in HFPEF patients. In particular, trials which tested the efficacy of a therapeutic approach based on the antagonisms of the neurohormonal system failed to demonstrate any benefit in reducing mortality of HFPEF. The Perindopril for Elderly People With Chronic Heart Failure (PEP-CHF) trial compared the effects of perindopril (up to 4 mg/d) with placebo in a group of HFPEF patients aged > 70 years.[70] In this trial, no reduction in mortality was found, whereas a first-year follow-up reduction of heart failure hospitalizations was observed. It should be noted that inclusion criteria of the trial considered a low cut-off of LVEF (EF ≥ 40%) and a significant proportion of patients had coronary artery disease and eccentric LV remodelling.[71] Also the trials testing the effects of angiotensin receptor blockers failed to demonstrate the efficacy in improving the prognosis of patients. Candesartan in heart failure Assessment of Reduction in Mortality and morbidity (CHARM) preserved study[72] randomised more than 3000 subjects with NYHA Class II to IV symptoms and LVEF > 40% to receive candesartan, or placebo. During follow-up, there was a no significant reduction in death, or heart failure admission. More recently, the I-PRESERVE trial[73] showed that Irbesartan therapy administered in CHF patients with LVEF > 45% and 34% aged > 75%, was not able to reduce primary (death or cardiovascular hospitalization) as well as secondary outcomes when compared to placebo. In comparison with previous studies, the I-PRESERVE has the merit of having enrolled patients whose clinical characteris-

tics are more similar to those expected in HFPEF; they were predominantly elderly females affected by hypertension who showed a lower prevalence of prior myocardial infarction and eccentric left ventricular remodelling.[73]

Also, the use of beta-blockers has not been found to be associated with an improvement in the prognosis of patients. The SENIORS trial tested the efficacy of nebivolol in elderly patients with a broad range of LVEF. Although the beneficial effects in terms of reduction of primary end-point were similar in patients with LVEF above and below 35%, only few patients had an LVEF greater than 50%.[74] Moreover, whether a beneficial effect was observed in patients with reduced LVEF in terms of left ventricular remodelling and LVEF improvement, no significant changes were observed when echocardiographic parameters reflecting diastolic function were considered.[75]

On the other hand, in the Swedish Doppler- Echocardiographic Study (SWEDIC) trial,[76] the efficacy of beta-blocker therapy was tested in HFPEF patients selected on the basis of strict echocardiographic criteria. The results of the study did not show any efficacy in modifying the composite primary endpoint, but an improvement in E/A ratio was observed, particularly in patients with higher heart rate.

Preliminary results suggest that the use of an aldosterone antagonist could be useful in order to improve diastolic dysfunction.[77] This is due to the role played by this molecule in inducing hypertrophy and fibrosis. On the basis of these considerations, a National Institutes of Health (NIH) sponsored trial, the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOP-CAT) study is currently ongoing and it is aimed at testing the effects of chronic administration of spironolactone in HFPEF patients.[78]

The absence of a demonstrated benefit from the class of drugs antagonising RAAS and sympathetic nervous system highlights the question, if HFPEF is a disease fundamentally different from HFREF.[79] This is even more relevant considering the increased percentage of CHF patients with preserved ejection fraction in the different age decades.[80] This strengthens the need of new trials aimed to define the best therapeutic approach to HFPEF. However, these trials should be designed considering all the biases of previous studies that can, in part, explain the lack of efficacy in prior experimental therapy. First of all, HFPEF patients are grouped persons with very heterogeneous forms of cardiac diseases. Following, the trials which tried to assess the efficacy of HFPEF therapy considered different cut-off of LVEF in order to exclude systolic dysfunction. On the other hand, in the studies with lower cut-offs, there was a greater prevalence of patients with previous myocardial infarction

and with eccentric remodelling. As a consequence, in these studies, the positive effects of drugs could be due to the action on pathophysiological mechanisms more similar to those of HFREF patients. Moreover, few trials evaluated diastolic function by echo-Doppler indices during the enrolment and, analogously, few trials considered the improvement of these parameters as an end-point. This issue appears to be very important if considering results from the CHARM-preserved trial, in which less than half of enrolled patients showed moderate to severe diastolic dysfunction, whose presence was associated with a worse prognosis.[81]

The last relevant point about the difficulties in therapeutic approach of HFPEF concerns the frequent presence of co-morbid status in this group of patients. There is the need for performing multimodality treatment interventions, as already applied successfully in other chronic syndromes. Arterial pressure, myocardial ischemia, ventricular rate, and diabetes are considered very important targets for HFPEF treatment and non-pharmacologic interventions, such as diet and exercise have seemed to be promising in some small clinical investigations.[82]

4.4 Diuretic therapy and cardiorenal syndrome

In HFREF as well as in HFPEF treatment, the use of diuretics plays a key role in order to control signs and symptoms related to volume overload. However, elderly patients taking diuretics showed a significant increased risk of death, or hospitalization (as shown in secondary analysis of DIG trial[83]), and the administration of high doses of diuretics has been found to be associated with an increased risk of mortality.[84]

The possible negative effects of diuretics in CHF patients could be related to their influence on the complex pathophysiologic link between heart and kidney. Through a number of direct and indirect effects, each of these organs can induce and perpetuate any dysfunction on the other one.[85] In order to better classify this relationship, the term of cardio-renal syndrome[85] has been recently introduced. In CHF outpatients, the use of high dose of loop diuretics has been demonstrated to be associated with a significant worsening of renal function, i.e., of the cardio-renal syndrome.[86] This detrimental effect is even more evident when central venous pressure remains high despite the administration of high doses of a loop diuretic and a vicious circle takes place; high central venous pressure dictates the increase of the diuretic dose to keep patients stable, thus making a further worsening of the renal function more probable.

It is worth noting that in the elderly, the adverse effects of diuretics can be due to the co-presence of renal function abnormalities. The age related decline of glomerular filtra-

tion rate and the impaired renal tubular capacity in concentrating and diluting urine[87] increases the propensity of elder patients taking diuretics to develop electrolyte disturbances. Moreover, in the elderly, a reduction in the thirst mechanism[81] may predispose patients to dehydration. This condition is even more harmful in HFPEF patients in which the presence of diastolic dysfunction implies the need of higher left ventricular filling pressure in order to maintain cardiac output.[9] On the other hand, the loss of renal function could be also associated with a reduced response to diuretic therapy and to an increased risk of volume overload and heart failure decompensation.

On the basis of these considerations, in older patients chronically taking diuretics, a close monitoring of their hydration status and electrolyte serum levels should be done. In addition, when there are difficulties in reaching a good balance between renal insufficiency and hemodynamic status, it could be reasonable to accept some degree of volume overload with slight worsening of renal function.[8,88]

4.5 Treatment of AF

AF is the most common arrhythmia in CHF patients with an incidence rate of up to 30%–40% and is even more common in patients with HFPEF. Ageing is another risk factor of developing AF, because of atrial remodelling with fibrosis and dilatation.[89] AF leads to worsening the quality of life, and increasing mortality and morbidity rates because of thromboembolic and stroke risks. Treating AF, clinicians should always identify the arrhythmia's correctable causes (e.g., hyperthyroidism, electrolyte disorders, uncontrolled hypertension, mitral valve disease) and potential precipitating factors (e.g., acute myocardial ischemia). After that, both rhythm and rate control are possible therapeutic options beside the prevention of the thromboembolic risk.[1]

Many studies have shown that primary rate control is not inferior to rhythm control. Usually in the symptomatic elderly CHF patients, the administration of digitalis or amiodarone to slow heart rate is preferred.[89] The potential toxicity of these drugs imposes one to exercise in caution in their use. Recently, dronedarone has been proposed as an alternative to amiodarone to provide rhythm and rate control. Dronedarone has a minor extracardiac toxicity, but it is contraindicated in patients with NYHA III–IV, or recently (within the previous 4 weeks) decompensated heart failure.[90]

In selected patients, ablation of the atrioventricular node and ventricular pacing should be considered when pharmacological rate control, including a combination of drugs, has failed, or rhythm control is contraindicated, or has failed.[91]

In CHF patients who suffer of symptomatic AF recur-

rences despite conventional therapy, catheter ablation may be indicated to improve AF-related symptoms (European Heart Rhythm Association score II–IV).[89] Nonrandomized studies involving symptomatic drug refractory AF patients showed that age is not a contraindication to perform catheter ablation; success and complication rates were similar between patients over 65 years of age and younger patients (70% vs. 74% for success rate) and even patients aged 80 years and older had no increased risk of periprocedural complications.[91] However, randomised controlled trials are still needed to verify these data and clarify not only the safety, but also the long-term efficacy of the ablation therapy for geriatric patients.

Finally in the elderly, oral anticoagulation therapy is an important tool in preventing AF-related ischemic events, but it has a narrow therapeutic window. If oral vitamin K antagonists are contraindicated, antiplatelet therapy can be administered, but their efficacy is much less.[89]

4.6 Implantable cardioverter defibrillator and cardiac resynchronization therapy

Current Guidelines recommend the implantation of a cardioverter defibrillator (ICD) in order to prevent sudden death and/or electrical cardiac resynchronization therapy (CRT) to improve cardiac remodelling, as well as functional status, quality of life, and prognosis in HFREF patients. The growing proportion of older CHF patients leads one to suppose that the number of cases with indication to ICD or CRT is increasing and will further increase in the future.

However, the trials demonstrating the beneficial effect of electrical therapy in HFREF enrolled only a minor percentage older patients. Mean age of patients in Multicenter Automatic Defibrillator Implantation Trial (MADIT) was 62 years,[92] in MADIT II [93] 64 years, and in Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) 60 years.[94] Moreover, whether MADIT II showed a similar mortality reduction in patients ≥ 75 years when compared to those < 75 years,[95] SCD-HeFT failed to demonstrate the ability of ICD in improving survival of patients older than 65 years.[94] Analogously, a meta analysis, including three large trials, failed to demonstrate a significant survival benefit in the elderly.[96] Furthermore, it has been demonstrated that mobility and mortality rates related to device implantation are higher in patients older than 80 years.[97] A recent large observational study,[98] evaluated patients who underwent ICD implantation for primary prevention of sudden cardiac death at the Leiden University Medical Center. These data confirmed the increased proportion of older implanted patients. In fact, before 2005, no patient older than 75 years was implanted, and after 2005 implanted patients aged > 75 years

represented 16%. Five-year cumulative incidence of appropriate shock was 19% for patients < 65 years, 23% for patients 65–74 years, and 13% for patients ≥ 75 years. At one year following appropriate shock, the cumulative incidence for death was 35% for patients ≥ 75 years compared to 7% for patients < 65 years ($P < 0.01$). But it is important to note that more than one third of patients ≥ 75 years died within the one year follow-up. This could reflect the fact that in patients with worse cardiac conditions, there is a greater risk of experiencing ventricular arrhythmias, but also a higher risk of heart failure events and non-arrhythmic death. In these patients, the prevention of sudden death could probably result in only a minimal prolongation of life.

As a consequence, the need of implanting with an ICD in these older CHF patients is still debated. It should be carefully evaluated in patients older than 80 years, also considering their life expectancy, co-morbidity status, as well as the risk of a worsening quality of life due to inappropriate shocks.

Another relevant issue concerning ICD is related to its influence on quality of life in older patients with non-cardiac severe or terminal hill. CHF patients and, more frequently, elderly CHF patients can be affected by advanced non-cardiac diseases which can favour conditions such as hypoxia, sepsis, pain, heart failure and electrolyte serum level abnormalities which lead to an increased frequency of shock therapy. In these cases, the occurrence of shock has the only effect of worsening the quality of life without improving life expectancy. Therefore, the deactivation of the ICD in the terminal stage of diseases, when death has been estimated to be near, could be appropriated.[99,100] The recent EHRA expert consensus statement underlines that this decision should be taken with the patient who is carefully informed about the consequences of the ICD deactivation, and only after having well discussed all legal and ethical issues of the matter.[100]

Whether ICD implantation is able only to improve survival, CRT has been demonstrated to be able to improve quality of life. A systemic review of studies evaluating the effects of CRT,[101] concluded that this tool can reduce all cause mortality by 22% and hospitalizations by 37%. Also for CRT, few trials evaluated the effects in elderly patients. In a recent observational study involving patients who underwent CRT,[102] a similar improvement in left ventricular remodelling and functional capacity was observed in patients aged < 70 years, those between 70 and 79 years, and in those > 80 years. Analogously, the time to the first hospitalization was similar in the three groups. On the other hand, a higher annualized mortality was observed in patients older than 80 years.

CRT could be considered an effective strategy in order to improve the quality of life for elderly CHF patients. However, as for ICD, in very old patients it should be considered only in the presence of few co-morbidities and a related good life expectancy.

5   Conclusions

CHF represents a major and growing health problem due to its high incidence and prevalence, its worse prognosis, and its impact on health-care costs. The relevance of this syndrome is even greater in the elderly considering its higher prevalence and the little evidence about the best diagnostic and therapeutic approaches to use in this group of patients.

Actually, it is generally accepted as a common treatment strategy for younger and older patients affected by HFREF and is based on the block of RAAS and sympathetic nervous system activities. The control of heart rate based on ivabradine administration could be an additional therapeutic tool. The implantation of ICD and the use of CRT should be carefully considered on the basis of co-morbidities and the estimation of life expectancy in order to maximise their effectiveness.

The diagnostic and therapeutic approach to HFPEF is still an open challenge. In these patients, the diagnosis should be supported by echocardiographic evaluation of their diastolic function. Current therapy only pursues the relief of symptoms and the control of co-morbidity status, due to the failure of the available randomised trials in demonstrating the possibility of improving patients' survival.

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