Treatment of heart failure in the elderly: Which drugs are essential and which should be avoided

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Abstract

With improved health care and with population aging, heart failure (HF) has become a common disease among the elderly and is one of the principal causes of mortality in elderly age. But the pharmacological management of HF in the elderly has still not yet been defined, as the clinical context is complicated by comorbidities, and differs from that of younger adults. In general, elderly patients with HF should be treated according to current guideline recommendations, for which ACE-I, beta-blockers and anti-aldosterones constitute the cornerstone of therapy. Interesting prospects are opening up with the use of new drugs such as neprilysin inhibitors, which appear to reproduce in the elderly the positive effects observed in the young adult population, and ivabradine, which may substitute the traditional use (now probably obsolete) of digitalis. Currently, however, treatment of HF in elderly patients is characterized by insufficient drug titration and by a habitual underuse of the recommended therapies - this is partly due to prescription inertia and in part to the negative effect of polypharmacotherapy on patient adherence. Even if HF therapy is similar in older and younger patients, the presence in older patients of more comorbidities, and frailty, functional status, and socio-environmental factors related to aging require a multidisciplinary approach to care and, above all, an additional assessment aimed at personalizing the treatment.

Introduction

Heart failure (HF) is one of the principal causes of morbidity and mortality in elderly patients [1]. Despite the high prevalence and ever rising incidence, elderly patients are underrepresented as a category in large randomized clinical trials, and there are to date no specific guidelines for this age-group, the only references to the elderly being limited to the sections devoted to "gaps in evidence". This limitation is all the more serious because HF management differs in the elderly from that in younger patients in many respects, both as regards general characteristics and in specific regard to therapy. Even if in the very elderly, as is often noted, quality of life is more important than simply prolonging it, the main objectives of HF therapy are to alleviate symptoms, maintain or improve functional capacity and quality of life, preserve independence and lengthen survival. This statement is conditioned by the fact that in elderly patients HF is associated with a high burden of comorbidity, the cause-and-effect relation of which is still not completely clear. Moreover, there is a huge difference between the "average" geriatric patient and the average patient in a large clinical trial: it is not so easy to utilize evidence-based medicine (EBM) in treating elderly patients with HF because this population is characterized by marked heterogeneity in terms of lifestyle, personal goals and prospects, and by a close link between HF and the cognitive-psychological profile, whose deterioration is an important independent risk factor for adverse events. Considering just the pharmacological aspect, the response to medications can be different in an elderly patient with respect to a younger one; drug interactions and side effects can be higher; comorbidities often necessitate the administration of polypharmacy, as a consequence of which treatment adherence is reduced making the treatment less effective.

Even if there is rarely a "cure" for HF in the elderly population and notwithstanding the fact that many of the problems that geriatricians encounter in their clinical practice have not been - and are unlikely to be - investigated in controlled trials, there is no plausible reason to exclude the elderly from the use of HF drugs, and so current guideline recommendations [2] need to be generalized to include also this patient subgroup.

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Treatment of heart failure with reduced systolic function

Angiotensin-converting enzyme inhibitors and AT-1 angiotensin II receptor blockers

Angiotensin-converting enzyme inhibitors (ACE-I) have demonstrated their ability to reduce mortality and morbidity in patients with decreased left ventricular (LV) systolic function [3,4], and so unless contraindications or intolerance are present they should be used in all symptomatic patients. Although no recent data are available on the use of ACE-I or AT-1 angiotensin II receptor blockers (ARBs) in elderly patients with reduced systolic function, their use is essential in HF management regardless of age. It is widely demonstrated that in clinical practice the majority of patients receive suboptimal doses of ACE-I [5]; on the contrary, the dose should be titrated up to the maximum tolerated dose in order to obtain an adequate inhibition of the renin-angiotensin-aldosterone system

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(RAAS), paying particular attention to the secondary effects of the drug and to the coexistence of eventual comorbidities. ARBs represent the alternative to ACE-I in the case of their contraindication or intolerance [2]. In special circumstances, a combination of ACE-I and ARBs can be considered, but the association is not recommended in elderly patients due to a high risk of hypotension, deterioration of renal function and hyperkalemia.

Beta-blockers

Beta-blockers reduce mortality and morbidity in patients with reduced symptomatic systolic function also during treatment with ACE-I and diuretics [6-8]. They should be initiated in clinically stable patients, gradually increasing the dose up to the maximum tolerated dose; in patients with acute HF, the use is advisable only after clinical stabilization. They are particularly recommended in patients with a history of myocardial infarction and asymptomatic systolic dysfunction, to reduce the risk of hospitalization for acute HF and risk of mortality. The beta-blockers which have the best evidence for proven efficacy and tolerability are bisoprolol, carvedilol and metoprolol [9]. Carvedilol is generally well tolerated in the elderly, including in the over-80 age-group, although to a lesser extent in those with advanced New York Heart Association (NYHA) class, low diastolic pressure, obstructive pulmonary disease or concomitant use of amiodarone. In studies comparing the beta-blocking effect at 24 hours, no significant difference was found between metoprolol and atenolol concerning their use in the elderly, although metoprolol has shown a better tolerability than atenolol. Likewise, no significant difference was found between carvedilol and bisoprolol in elderly patients with systolic dysfunction. Bisoprolol has been associated with a better beta-blocking effect and better tolerability in patients with chronic respiratory disease [10]. In contrast, carvedilol, due to its additional blocking of the alpha receptor and greater effect of vasodilation, could be preferable in the absence of significant obstructive pulmonary disease, especially when strict blood pressure control is necessary.

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRAs), potassium-sparing diuretics, reduce mortality and incidence of hospitalizations especially in patients with advanced NYHA class, and their benefit has been clearly demonstrated also in elderly patients with HF and reduced systolic function [11]. Despite their proven efficacy, inexplicably, they are underused, their role being seen as a "limiter" of the potassium loss induced by loop diuretics. The MRAs currently in use are spironolactone and eplerenone. It is not clear if these two agents are interchangeable or not, but particular care is needed when they are used in patients with renal failure and in those with serum potassium levels greater than 5 mmol/L.

Loop diuretics

Diuretics must be titrated in order to reduce signs and symptoms of pulmonary and systemic venous congestion and to maintain euvolemia in patients with HF with reduced systolic function, but their effects on mortality have never been investigated in randomized clinical trials. It appears from a recent meta-analysis that loop diuretics and thiazides are able to reduce the risk of mortality and deterioration of HF compared to placebo and improve functional capacity [12]. However, due to the frequent side effects such as worsening of renal function and electrolyte disorders, it has to be used, whether singly or in combination, at the lowest possible dose.

Angiotensin II AT-1 receptor/neprilysin inhibitors

LCZ696 is the progenitor of a new therapeutic class of agents acting on the RAAS which combines the action of an ARB (valsartan) with that of a neprilysin inhibitor (sacubitril). Sacubitril, as a pure inhibitor of neprilysin, promotes the activation of the natriuretic peptide system while increasing the activity of the quinine system, while the blockade of the AT1 receptor by valsartan makes it possible for angiotensin II to interact with the AT-2 receptors, with added positive effects for the decompensated patient. In the PARADIGM-HF [13] study, the effect of sacubitril/valsartan on mortality and morbidity of HF with reduced contractile function was compared to that of ACE-I. Sacubitril/valsartan (97/103 mg bid) was superior to ACE-I (enalapril 10 mg bid), drastically reducing cardiac mortality by 20% and hospitalizations for acute HF by 21% at the 3-year follow-up, with a good overall safety profile. The combination maintained its efficacy also in the over 65 years age-group. In general, sacubitril/valsartan was safe and well tolerated and although hypotension was more frequent, particularly in elderly patients, there was no increase in the rate of suspension even in this subgroup of the population.

I_f channel inhibitors: Ivabradine

Ivabradine is a specific blocker of the I_f channels of the sinoatrial node which causes a reduction in heart rate without inducing any negative inotropic effect. In the SHIFT [14] study, the addition of ivabradine to optimal therapy with beta-blockers, ACE-I and MRA in HF patients with reduced systolic function (EF <35%) and heart rate ≥70 bpm resulted in a significant positive outcome on the primary combined end-point of cardiovascular death and hospitalization for decompensation. Concerns about its use in association with beta-blockers in elderly patients at risk of sinus node dysfunction or symptomatic bradycardia have been dispelled by the demonstration that ivabradine maintains its positive effect without reducing the safety profile. The incidence of severe side effects did not vary substantially from that of younger patients, the only difference being that achieving the target dose in elderly patients was more difficult due to a greater tendency to bradycardia.

Digoxin

Digoxin can be used to reduce the morbidity correlated to HF with reduced systolic function and in the forms with atrial fibrillation its importance has not changed as a means of modulating heart rate. However, its traditional use as a first step in patients with sinus rhythm and HF, in the beta-blocker era and with the emerging role of ivabradine, is probably now coming to an end. In fact, in patients with sinus rhythm enrolled in the Digitalis Investigation Trial (DIG) study [15], its non-effect on mortality clearly emerged, although there was an associated improvement in patients' quality of life and a significant reduction in hospital admissions. A trend towards increased mortality has been reported - although the finding is still controversial - in patients with plasma digoxin levels between 1 and 2 ng/ml compared to those with levels of 0.5-1 ng/ml [16]. For this reason, the use of digitalis in patients with HF in sinus rhythm should be limited to situations in which other drugs are insufficient, with particular attention in elderly patients and in patients with reduced renal function.

Combination of hydralazine and isosorbide dinitrate

There is no clear evidence supporting the use of this combination therapy in patients with HF with reduced systolic function. The clinical usefulness of this combination is based on the findings of a small trial

conducted exclusively in men before the spread of ACE-I and beta-blockers [17]. Historically, the association hydralazine/isosorbide dinitrate has shown an improvement in survival in the black (Afro-American) ethnic population, particularly in the elderly subgroup, but no benefit in the White ethnic group. However, at 6 months after randomization, just over 50% of patients were still able to tolerate drug administration due to the development of hypotension. The results of these findings are difficult to transfer to patients of other ethnic groups. The routine use of this combination in addition to standard treatment is therefore not recommended due to the risk of hypotension; and the eventual use in addition to beta-blockers, ACE-I or ARBs and MRAs should in any case be reserved only for the black subgroup of the population.

Treatment of heart failure with preserved systolic function

According to the latest European guidelines, the diagnosis of HF with preserved systolic function requires an LVEF ≥ 50% [2]. Age is a strong predictor of HF with preserved systolic function - in fact its prevalence is notably higher in elderly than in younger patients [18]. Probably the diagnosis, especially in the elderly population, is underestimated, and a normal contractile function does not necessarily signify a more favorable prognosis with respect to HF with reduced contractile function. To date, no clinical studies exist demonstrating the efficacy of routine therapy in HF with reduced systolic function [2]. Nevertheless, symptomatic treatment with the use of diuretics and the treatment of cardiovascular comorbidities (hypertension, atrial fibrillation and coronary artery disease) and non-cardiovascular ones (diabetes, renal insufficiency, anemia, COPD, obesity) are a key factor in the management of HF with preserved systolic function [19,20]. Even though no treatment has conclusively demonstrated the ability to reduce morbidity or mortality in patients with HF with preserved systolic function, nevertheless, given that these patients are often elderly and highly symptomatic, an important goal of therapy may be to alleviate symptoms and improve quality of life [21]. The potential efficacy of ARNIs also in HF with preserved systolic function represents an interesting prospect for elderly patients. In this regard, randomized clinical trials are already underway in patients with diastolic HF, with death and rehospitalization as the primary outcome, and the results could provide the first conclusive demonstration of the efficacy of a drug in the treatment of this type of HF, typical of the elderly, and with a similar impact on prognosis and quality of life as HF of the systolic type.

Conclusions

The pharmacological treatment of HF has made extraordinary progress in the last thirty years thanks to the introduction of ACE-I/ARBs, beta-blockers and MRAs, which have drastically reduced HF mortality independently of the disease severity and still today represent the cornerstone of the therapy for this syndrome. It is still not clear, though, whether this can be extended to include the subpopulation of the elderly, whose clinical context is characterized by a dynamic interaction between heart disease, aging, comorbidities, frailty, disability, functional status and socio-environmental factors. Population aging, the exponential increase in the prevalence and incidence of cardiovascular diseases and of HF, associated with the marked heterogeneity of older patients and the presence of multiple comorbidities are in fact generating a pathology with a distinct clinical profile of its own, *i.e.* a 'cardiogeriatric syndrome'. For this reason, optimal management of HF in the elderly requires a multidisciplinary approach and its goal is to tailor treatment - both pharmacological and non-pharmacological - to the individual patient. Currently, treatment of HF in elderly patients is characterized by widespread under-utilization of the recommended therapies and suffers from the lack of clinical trials carried out on this particular segment of the population. Subgroups of the elderly population such as the over-80s are in fact totally devoid of specific therapeutic references, and a clinical picture such as HF with preserved systolic function, which inevitably will be diagnosed more and more in the future, has not yet received adequate attention in the scientific literature. HF is associated with an unfavorable prognosis especially in older people, and there is a need for further research to develop more effective strategies for the prevention and treatment of chronic heart failure and to reduce the individual and social burden of this disease in the decades to come.

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