Treatment of heart failure in the elderly: never say it’s too late

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This editorial refers to ‘Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II’, by M. Komajda on page 478

Komajda et al. have provided very important information on an essential and relatively unstudied group of heart failure (HF) patients—those 80 years of age and older.¹ Their findings from the Euro Heart Failure Survey (EHFS) II provide unique information on the characteristics and outcomes in this group and secular trends in their management. In this editorial, we will try to place their findings in the broader context of HF management, highlighting what is known and, more importantly, what is not known about this patient group.

The background: heart failure as a disease of the elderly

HF is predominantly a disease of the elderly. The mean age of HF patients is > 70 years in most developed countries, and the prevalence of HF rises dramatically with age, from 1–2% among individuals aged 45–54 years to > 10% among those aged ≥75 years.² Ageing predisposes to HF through multiple mechanisms. First, HF is a frequent outcome of virtually all cardiovascular diseases. Hence, patients with most cardiovascular diseases (i.e. hypertension, acute coronary syndromes, cardiac surgery, etc.) are prone to developing ventricular remodelling and HF when elderly. Secondly, even in the absence of any cardiovascular event, ageing is associated with reduced aortic and left ventricular (LV) compliance, with increased aortic impedance and abnormal LV diastolic function. These conditions lower the threshold for the development of HF when the heart is exposed to precipitating factors such as hypertension and/or tachyarrhythmias (especially atrial fibrillation).

These last mechanisms explain why the clinical picture of HF in older patients differs substantially from that of the syndrome usually described and studied in randomized clinical trials (RCTs). Elderly patients with HF are more likely to be women (as their life span is longer), as well as more likely to suffer from hypertension, have a normal LV ejection fraction (EF), and suffer from co-morbidities.³,⁴ Compared with younger patients, elderly patients often have an inadequate assessment while in hospital, with underprescription and underdosing of recommended, life-saving therapies. Age has been repeatedly shown to be an independent predictor of increased mortality and hospitalization rates.²,⁵

Which are the desired effects?

What is the evidence for treatment in the elderly?

Ageing is clearly attended by a shift in the primary aim of treatment from duration of life to quality of life. However, duration of life remains an important target in elderly patients too. The benefits of recommended therapies are, however, not so clearly shown by RCTs, and there is a discrepancy between the patients studied in these trials and real patients with HF.⁶ Even if patients with HF have a mean age of 75 years, the evidence for current treatment is based on RCTs including patients with a mean age of ~60 years, with generally only < 30% of the patients older than 70 years.

With respect to the first cornerstone of medical treatment of HF, the angiotensin-converting enzyme inhibitors (ACEIs), the results in elderly patients with HF are rather controversial. A relatively recent meta-analysis failed to show a significant effect of ACEIs on outcomes in the subgroup of patients aged > 75 years.⁷ This result, however, appears to be a function of the low number of elderly patients included in trials since no significant interaction between age and the benefits of ACEIs was found.

Results have also been disappointing in a further prospective RCT comparing perindopril with placebo in HF patients aged ≥70 years, with an LVEF > 40% and echocardiographic signs of
LV diastolic dysfunction. In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, the incidence of the primary endpoint of all-cause death or HF hospitalization tended to be reduced, with perindopril vs. placebo, at 1 year (hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.47–1.01; P=0.055), although the wide CIs reflect the small number of events, and this trend was not present at the end of the study (HR 0.92, 95% CI 0.70–1.21). These results were probably affected by the high incidence of withdrawals from the study drug and of starting open-label ACEIs (>35% in both cases) as well as by the low severity of the condition in a significant proportion of patients included, as shown by their low B-type natriuretic peptide (BNP) levels. In any case, a definitive demonstration of the efficacy of ACEIs in elderly HF patients is still lacking.

Similarly, the two major RCTs with angiotensin receptor blockers (ARBs) in patients with HF included patients with a mean age of 63 ± 11 years with 47% of the patients older than 65 years in the Valsartan Heart Failure Trial (VAL-HeFT), and of 66 ± 11 years with 23% of the patients aged ≥75 years in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) trial. Subsequent analyses showed similar beneficial effects of ARBs on outcomes in patients aged <65 or ≥65 years. It is, however, clear that such a cut-off point provides little information about the population over 80 years of age. More recently, attention has focused on elderly patients with HF and ‘preserved’ EF (HFPEF), which has been variously defined as an EF >40–50%, since these comprise the large majority of this patient group. Unfortunately, in two large trials, addition of an ARB failed to improve patient outcomes or quality of life. These findings raise the possibility that the underlying pathophysiology in HFPEF patients, especially in those with EF ≥50%, differs from that in those with low a EF. The latter speculation is consistent with their relatively infrequent ischaemic aetiology, absence of LV dilation, and nearly universal underlying hypertension, as well as the much higher prevalence of women among the patients with HFPEF. Thus, at least in the HFPEF group, one cannot assume that the treatments recommended for low EF HF will be effective in the former group.

There is limited information concerning aldosterone antagonists in elderly patients, although a subgroup analysis of the Randomized Aldactone Evaluation Study (RALES) trial showed a similar effect on outcome in patients aged <67 and ≥67 years. On the other hand, age is associated with an increased incidence of side effects, particularly hyperkalaemia, with any of these classes of agents. A trial of spironolactone in patients with an EF ≥45% is ongoing and should determine whether this therapy is effective in the HFPEF group.

With respect to β-blocker treatment, the mean age of patients enrolled in RCTs was 60–65 years, and <30% were aged >70 years, with very few ≥80 years. Subgroup analyses of these RCTs never showed a significant interaction between age and the effects of β-blockers on outcomes. However, the prospective RCT assessing the effects of the β-blocker nebivolol on outcomes in patients aged ≥70 years showed a reduction in the primary outcome (all-cause mortality or cardiovascular hospitalization) which was of lower magnitude, compared with that of previous β-blocker RCTs (HR 0.86; 95% CI 0.74–0.99; P=0.039) and, in contrast to previous trials in younger patients, did not show an effect on mortality alone (HR 0.88, 95% CI 0.71–1.08; P=0.21). At subgroup analysis, the effects of nebivolol on the primary outcome were significant in the patients aged <75 years (median value) but not in those aged ≥75 years. Age is an independent predictor of lower tolerability of β-blockers, although these agents remain tolerated in >75% of patient aged >80 years. Disease management and an education programme may substantially increase the proportion of elderly patients on β-blockers.

Lastly, the Digitalis Investigation Group (DIG) study database has provided important information regarding efficacy and tolerability in elderly patients. Increasing age had no influence on the effects of digoxin treatment on outcomes, although it was associated with increased hospitalizations for suspected digoxin toxicity and withdrawals from digoxin therapy. Interestingly, in a parallel substudy that enrolled nearly 1000 patients with HFPEF, who were generally older, digoxin showed an early favourable trend toward improved outcomes, although it is difficult to speculate about the mechanism of this finding.

Where are we now? What remains to be done?

Thus, RCTs have yielded limited evidence of the efficacy of medical treatment in elderly patients with HF. However, though there are still uncertainties regarding treatment of patients with HFPEF, we have no data suggesting that therapies shown to be beneficial in RCTs should have a different effect in elderly subjects with HF and low LVEF. Subgroup analyses have never shown a conclusive interaction between age and the effects of treatment on outcomes in RCTs. Thus, elderly patients with HF caused by LV systolic dysfunction should be treated with the same medications shown to be effective in the overall population of patients with HF. The only differences are related to the greater incidence of side effects and lower tolerability of these agents in elderly subjects and, probably more importantly, to difficulties in their administration related to lack of compliance, co-morbidities, and lack of support for some of them. More importantly, however, is that so far no treatment has been shown to improve outcomes in patients with HFPEF, who comprise the majority of elderly patients, and this remains a critical unmet need.

Komajda et al. have reported the clinical profile, outcomes, and treatment of 741 octogenarians (median age, 84 years), compared with those of 2836 younger patients (median age, 68 years) hospitalized for HF and enrolled in EHFS II. Consistently with previous studies, octogenarians were more likely to be women and had a greater prevalence of hypertension, atrial fibrillation, and non-cardiac co-morbidities, including stroke, chronic obstructive pulmonary disease, anaemia, and kidney dysfunction. As expected, a higher proportion had HFPEF. Octogenarians were less likely to undergo investigations during the hospitalization, with coronary angiography performed in only 17% of the elderly patients vs. 41% of the younger ones.

Octogenarians also had a higher prevalence of new-onset HF (45% vs. 35% in the younger patients; P <0.001). This is not unexpected since new-onset HF is known to occur more frequently in elderly patients and in females. However, its pathogenesis is probably different in younger and older patients as acute coronary
underdosage of recommended HF medications (i.e. ACEIs, ARBs, β-blockers, and aldosterone antagonists), with a greater prescription of diuretics and calcium antagonists in octogenarians vs. younger patients. Although this perhaps reflects the lack of evidence for some of these therapies in patients with HFPEF, there still may be some degree of underutilization of agents that improve outcomes in patients with a low LVEF. However, the good news is that a significant improvement compared with EHFIS I, published 5 years ago, could be shown with respect to both the prescriptions of ACEIs, ARBs, β-blockers, and aldosterone antagonists and their administration at high doses. The time course of the prescriptions of HF medications shows that all the implementation of treatment occurred during the initial hospitalization. Prescriptions remained stable during the follow-up, consistent with the good compliance of these patients. Octogenarians had poor outcomes, compared with younger patients. However, prescription of ACEIs or ARBs was an independent determinant of a better outcome, as was a prescription of β-blockers for the patients with a low LVEF.

Thus, the role of recommended medications, left somehow uncertain by RCTs, is also confirmed in elderly patients by this survey. We are left with some hope as the prescription of these medications and their dosing has improved in the last few years. We have now improved but we are far from our target. Disease management programmes, better patient education, and overcoming social deprivation may yield the needed change so that lives can be saved and quality of life be improved also in the elderly. Hopefully, more research will be devoted to this large and growing patient group.

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References