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EDITORIAL COMMENT

Heart Failure in the Young*

Adriaan A. Voors, MD, PhD,
Peter van der Meer, MD
Groningen, the Netherlands

Heart failure (HF) is a clinical syndrome that is increasingly affecting elderly patients. Before 2000, the mean age at diagnosis of HF was 63 years, but has more recently increased to 80 years (1). Similarly, the incidence of new-onset HF is much higher in elderly patients compared with younger patients, and registry data show that the proportion of hospitalizations with a diagnosis of HF and the prevalence of HF in the general population is much higher in older patients (2).

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Consequently, most studies focused on HF in the elderly patients, traditionally defined as >65 years of age, but more recently defined as >85 years of age (3). Few studies described clinical characteristics and outcome in younger patients. However, they generally used a threshold of 65 years of age, and hardly any study focused on younger patients with HF, those <40 to 50 years of age. Interestingly, but not unexpectedly given the low number of young patients with HF, the majority of these studies are case reports. Therefore, the paper by Wong et al. (4) in the present issue in the *Journal* appears to be of particular interest.

The investigators performed a post-hoc analysis of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity programme) study. Patients with HF with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF] ≤40%) and patients with HF with preserved ejection fraction (HFpEF) LVEF >40%) were included. Less than one-third of the patients were <60 years of age, and only 2% were regarded as very young (age <40 years). As expected, idiopathic-dilated cardiomyopathy was the most common finding in the youngest age groups, and this proportion declined with age. The incidence of HFpEF increased with age, and comorbidities, including atrial fibrillation, diabetes, and hypertension, were more frequently observed in the elderly. Medication use was higher in the younger patients even after correcting for the proportion of HFpEF, but adherence was lower. Mortality increased with age, but interestingly, only in patients >60 years of age. At <60 years of age, 3-year mortality rates were not significantly different, but still were 12% to 13%. Interestingly, HF hospitalizations were significantly higher in the very young.

A large number of additional important and striking differences between different age categories were described; we would like to highlight a few.

First, there was a striking difference in signs and symptoms during presentation in younger patients versus older patients. Younger patients presented with less dyspnea, reflected by a lower New York Heart Association functional class, and they less often had peripheral edema and/or rales. In contrast, they frequently presented with signs of paroxysmal nocturnal dyspnea, increased jugular venous pressure, and hepatomegaly. These findings are important for clinicians who have to diagnose HF, because mild dyspnea and absence of peripheral edema and/or rales might easily lead to a missed diagnosis of HF in younger patients, in particular because of its low prevalence.

Second, the prevalence of black patients in the youngest age group was 8 times higher compared with the oldest age group. This finding is remarkable, but is supported by other studies. For example, in a cohort of more than 5,000 subjects, of whom half were black, new-onset HF developed in 27 patients, of whom all but 1 was black (5). These patients typically had hypertrophic hearts with a dilated ventricle and impaired systolic function. Although the cause of this higher prevalence is unclear, a higher burden of hypertension in combination with a genetic predisposition to cardiomyopathy has been postulated (5). Recent surveys from Africa showed similar results, in which black patients were young, predominantly had HF from a nonischemic cause, most commonly had hypertension, and had a high mortality (6,7). However, a recent survey indicated that lifetime risk for the development of HF was similar between white and black Americans. The greater unadjusted risk for HF in blacks and a similar adjusted lifetime HF risk might be explained by higher noncardiovascular mortality in blacks, including renal failure, homicide, and HIV (8).

Third, in patients age <40 years, 100% of deaths had a cardiovascular cause, whereas in patients in the oldest age group, 24% of all deaths was noncardiovascular. In general, once HF has been diagnosed, the majority of these patients die of a cardiovascular cause, but cardiovascular deaths occur more often in younger patients. A comparable study has been performed in young patients (age <40 years) presenting with ST-segment elevation myocardial infarction (9). All deaths except for 1 (suicide) were due to a cardiovascular origin. This indicates that if cardiac disease strikes the young, cardiovascular mortality is the leading cause of death.

Fourth, the mortality rate in the very young was similar to the mortality rate in patients age 50 to 60 years. This is

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From the Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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somewhat surprising. In the general population, all-cause mortality significantly increases with age. Similar mortality rates may be related to the fact that the very young could have had more severe HF compared with patients between 40 and 60 years of age. Inotropes were used more often in the youngest age group, and their ejection fraction was lower, although HFpEF was more prevalent in those ages 40 to 60 years. Measurements of natriuretic peptides would have been helpful to further explore this area. Furthermore, the very young were significantly more often re-hospitalized due to worsening HF, although this did not translate into higher mortality rates. Possible factors might be related to competing risks and lower treatment adherence, but could also be related to different treatment strategies for the very young (i.e., inotropes), or simply because the young have more severe HF. Follow-up time, as the investigators suggest, might be less likely because mortality rates were similar for all patient groups <60 years of age.

Next to a wealth of information, the present study by Wong et al. (4) has some limitations. First, this is a substudy of the CHARM programme, which consisted of 3 large randomized clinical trials. Patients had to be able to visit the clinic for their study visits, and therefore, patients were generally younger than the real-life HF patient population. Also, the inclusion criteria were enriched by a recent HF hospitalization. Despite this, the number of patients in the most interesting group (patients age <40 years) was very small, as was also admitted by the investigators. Nevertheless, to our knowledge, this is still the largest reported group of HF patients age <40 years so far. Second, the investigators reported a large number of striking differences among the age groups, but did not attempt to speculate on the potential clinical consequences of these differences. Also, no data were provided on the potential differential effects of candesartan among these age groups. Given the obvious difference in signs and symptoms and clinical outcome, it might be reasonable to suggest that diagnosis and treatment of younger HF patients might differ from the large group of elderly HF patients. Finally, the CHARM programme was executed in the late 1990s and early 2000s, with low prescription rates of beta-blockers, spironolactone, and device therapy, limiting the extrapolation of their data to the current era to some extent.

Nevertheless, this study is of great importance, and might stimulate other groups to study characteristics and clinical outcome in younger patients with HF, which may lead to a better diagnosis of and treatment of this small but important group of patients.

Reprint requests and correspondence: Dr. Adriaan A. Voors, Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, AB31, 9713 GZ Groningen, the Netherlands. E-mail: a.a.voors@umcg.nl.

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