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Clinical Characteristics and Outcomes of Young and Very Young Adults With Heart Failure

The CHARM Programme (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity)

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Objectives This study sought to determine the characteristics and outcomes of young adults with heart failure (HF).

Background Few studies have focused on young and very young adults with HF.

Methods Patients were categorized into 5 age groups: 20 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years.

Results The youngest patients with HF were more likely to be obese (youngest vs. oldest: body mass index ≥35 kg/m^2: 23% vs. 6%), of black ethnicity (18% vs. 2%), and have idiopathic-dilated cardiomyopathy (62% vs. 9%) (all $p < 0.0001$). They were less likely to adhere to medication (nonadherence in youngest vs. oldest: 24% vs. 7%, $p = 0.001$), salt intake, and other dietary measures (21% vs. 9%, $p = 0.002$). The youngest patients were less likely to have clinical and radiological signs of HF during hospitalization. Quality of life was worse, but all-cause mortality was lowest in the youngest age group (3-year mortality rates across the respective age categories: 12%, 13%, 13%, 19%, and 31%, respectively). Compared with the referent age group of 60 to 69 years, both all-cause and cardiovascular mortality were lower in the youngest group even after multivariable adjustment (hazard ratio: 0.60, 95% confidence interval: 0.36 to 1.00; $p = 0.049$, and hazard ratio: 0.71, 95% confidence interval: 0.42 to 1.18, $p = 0.186$, respectively). Three-year HF hospitalization rates were 24%, 15%, 15%, 22%, and 28% in ages 20 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years, respectively ($p < 0.0001$).

Conclusions Beyond divergent etiology and comorbidities, younger patients exhibited striking differences in presentation and outcomes compared with older counterparts. Clinical and radiological signs of HF were less common, yet quality of life was more significantly impaired. Fatal and nonfatal outcomes were discordant, with better survival despite higher hospitalization rates. (J Am Coll Cardiol 2013;62:1845–54) © 2013 by the American College of Cardiology Foundation

Because heart failure (HF) predominantly affects the elderly, most reports have appropriately focused on older patients (1–3). However, HF also afflicts younger patients, although little is known about the characteristics of these patients and their outcomes. Existing studies have largely defined "younger" as ages <65 or 60 years, probably because most studies have small numbers of adults in the third to sixth decades of life (4–6). As a result, there are few data

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Abbreviations and Acronyms

ACEI = angiotensin-enzyme converting inhibitor
ARB = angiotensin receptor blocker
CI = confidence interval
HF = heart failure
HF-PEF = heart failure with preserved ejection fraction
HF-REF = heart failure with reduced ejection fraction
HR = hazard ratio
HRQL = health-related quality of life
IDCM = idiopathic-dilated cardiomyopathy
LVEF = left ventricular ejection fraction
MLwHF = Minnesota Living with Heart Failure
NYHA = New York Heart Association

describing the symptom burden, quality of life, and hospitalization and mortality rates in HF patients ages 20 to 60 years, although it is in these patients where estimates of prognosis may be most keenly sought by patients and their families.

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Additionally and related to the latter, the most invasive and expensive therapeutic interventions are most commonly considered for younger patients (7,8). Consequently, knowledge of the causes, characteristics, and consequences of HF in young patients is clinically important. We therefore analyzed the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity programme) study database to provide a comprehensive description of HF in younger patients, comparing them with older participants.

The CHARM programme enrolled a broad spectrum of patients with chronic HF who were 18 years or older. Detailed information was collected on symptoms, signs, quality of life, treatment, precipitants of hospitalization, and nonfatal and fatal outcomes.

Methods

The rationale, design, and baseline characteristics of patients in the CHARM programme and the primary analyses have been published in detail elsewhere (9–14). Patients with symptomatic HF (New York Heart Association [NYHA] classes II to IV) for at least 4 weeks, who were 18 years or older and receiving standard therapy (beta-blockers, diuretics, digitalis, and spironolactone), were enrolled into 1 of 3 parallel clinical trials according to left ventricular ejection fraction (LVEF) and angiotensin-converting enzyme inhibitor (ACEI) treatment: LVEF $\leq$40% and not receiving an ACEI due to previous intolerance (CHARM-Alternative); LVEF $\leq$40% receiving ACEI treatment (CHARM-Added), and LVEF >40% (CHARM-Preserved). Exclusion criteria included serum creatinine $\geq$265 μmol/l, serum potassium $\geq$5.5 mmol/l, known bilateral renal artery stenosis, symptomatic hypotension, women of childbearing age potentially not using adequate contraception, critical aortic and mitral stenosis, myocardial infarction, stroke, or open heart surgery in the previous 4 weeks, use of angiotensin-receptor blocker (ARB) in the previous 2 weeks, any noncardiac disease judged likely to limit 2-year survival, and unwillingness to consent. All participating centers received approval from local ethics committees, and all patients gave written consent before enrollment.

Between March 1999 and March 2001, 7,599 patients (3,803 on candesartan, 3,796 on placebo) were randomized to candesartan 4 or 8 mg once daily or matching placebo. The dosage was doubled every 2 weeks, as tolerated, to a target dose of 32 mg once daily, with recommended monitoring of blood pressure, serum potassium, and creatinine. Visits were scheduled for every 4 months for a minimum duration of 2 years after the initial dose titration. The program was concluded, as planned, 2 years after the final patient was randomized, with a median duration of follow-up of 37.7 months.

The present analysis groups patients into 5 age categories: 20 to 39 years (n = 120), 40 to 49 years (n = 538), 50 to 59 years (n = 1,527), 60 to 69 years (n = 2,395), and $\geq$70 years (n = 3,019). The investigator-reported primary etiology of HF was systematically collected using a case report form that consisted of 8 options (ischemic heart disease, idiopathic-dilated cardiomyopathy [IDCM], hypertension, valvular heart disease, diabetes mellitus, alcohol-related, atrial fibrillation, and other). Adherence to study drug was assessed at each follow-up visit. At each visit, investigators assessed adherence based on the patient's report, the investigator's inspection of pill bottles, and a tablet count in cases of uncertainty. The investigators were asked to estimate compliance with study drug by selecting 1 of the pre-defined categories (>80%, 20% to 80%, and <20% adherence) on the case report form. We calculated adherence as the number of visits when pills were taken as prescribed >80% of the time divided by the number of visits actually made × 100 (15). Patients recruited at the 243 sites in the United States and Canada were prospectively asked to participate in the CHARM Health-Related Quality of Life (HRQL) study. Enrolled patients completed the Minnesota Living with Heart Failure (MLwHF) questionnaire at baseline. The questionnaire contains 21 disease-specific items, with a score for each item ranging from 0 to 5 and a summary score of 0 to 105 (higher score represents worse quality of life). Data regarding acute episodes of decompensation after randomization were prospectively collected using a specifically designed endpoint form documenting evidence of worsening HF, precipitating or aggravating factors, and intravenous treatment.

Baseline characteristics are reported as mean ± SD for continuous variables and proportions for categorical variables. Variables were compared across age categories using analysis of variance for continuous variables and chi-square or Fisher exact tests for categorical variables. A conservative significance level of $p < 0.0001$ was adopted for the comparison of baseline characteristics, given the retrospective nature of the study and the multiple comparisons made. All-cause mortality (the primary endpoint of the overall program), the composite endpoint of cardiovascular death or HF hospitalization (the primary outcome of the 3 component trials), and the secondary pre-specified endpoints were

analyzed by age group. Kaplan-Meier survival curves were plotted by age category, and event-free survival was estimated at 1, 2, and 3 years. Cox's proportional hazard models were used to estimate the hazard of younger age compared with the age group of 60 to 69 years as the referent category, adjusted for the previously published predictors of mortality and morbidity specific to each endpoint in the CHARM trial (16). For the survival analyses and multivariable models, a conventional level of significance was used ($p < 0.05$), and the results are presented with 95% confidence intervals (CIs).

Results

Demography, etiology, and ejection fraction. Baseline characteristics stratified by age are presented in Table 1. Younger patients were less often of European origin (youngest vs. oldest: 73% vs. 95%, $p < 0.0001$), but more often of black ethnicity (18% vs. 2%, $p < 0.0001$), had a higher body mass index (29.8 kg/m^2 vs. 27.0 kg/m^2, $p < 0.0001$) and were more likely to be obese (body mass index $\geq$35 kg/m^2: 23% vs. 6%, $p < 0.0001$). All age groups were predominantly male, with the proportion of females increasing with age, especially in the oldest age group (71%, 77%, 76%, 71%, and 61% male in age groups 20 to 39, 40 to 49, 50 to 59, 60 to 69 years, and $\geq$70 years, respectively, $p < 0.0001$).

In the youngest age group, the most common investigator-reported etiology of HF was IDCM, followed by a presumed ischemic etiology and hypertension. The proportion of patients with a presumed ischemic and hypertensive etiology increased progressively with age (ischemic from 15% to 66% and hypertensive from 5% to 15%), comparing youngest and oldest patients, respectively ($p < 0.0001$). The relative proportion of patients with IDCM declined with age, from 62% in those ages 20 to 39 years to 9% in those ages $\geq$70 years ($p < 0.0001$). Alcohol-related HF was more common in the youngest age group than in the oldest age group (3% vs. 0%, $p < 0.0001$).

The mean ejection fraction was lowest in the youngest age group and increased steadily with age (34%, 37%, 38%, 38%, and 40% in ages 20 to 39, 40 to 49, 50 to 59, 60 to 69, and $\geq$70 years, respectively; $p < 0.0001$). Across the same age bands, the prevalence of HF with reduced ejection fraction (HF-REF) (LVEF $\leq$40%) was greatest in young patients and declined with age (70%, 66%, 64%, 63%, and 55%, respectively; $p < 0.0001$).

Comorbidities. Myocardial infarction, angina, stroke, hypertension, diabetes, atrial fibrillation, previous coronary revascularization, and a pacemaker were less common in younger patients and increased in prevalence with advancing age (all $p < 0.0001$) (Table 1). The prevalence of a previous HF hospitalization was similar in all age categories, likely reflecting the inclusion criteria in CHARM Added (patients in NYHA class II required hospitalization for a cardiac condition within the past 6 months) and CHARM Preserved (patients required previous hospitalization for a cardiac condition at any time). The prevalence of smoking peaked in the age group 40 to 49 years (30%) and declined thereafter (8% in the elderly).

Symptoms and signs. The association between age and present symptoms (i.e., at randomization) was inconsistent (Table 2). In the youngest patients, dyspnea on level ground was less frequent (45% <40 years vs. 68% in $\geq$70 years, $p < 0.0001$), yet paroxysmal nocturnal dyspnea was more prevalent (22% <40 years vs. 12% $\geq$70 years, $p = 0.001$). The prevalence of dyspnea at rest, dyspnea on climbing, and orthopnea was similar across all age categories. The youngest patients reported the worst quality of life scores, which improved with increasing age (mean MLwHF scores 52.6, 50.8, 47.1, 38.9, and 35.3 in age groups 20 to 39, 40 to 49, 50 to 59, 60 to 69, and $\geq$70 years, respectively; $p < 0.0001$).

Past signs and present signs (i.e., reported before and at the time of randomization) were consistent. The prevalence of jugular venous pressure elevation was similar across age categories. An S3 gallop and hepatomegaly were more common in younger patients (youngest vs. oldest patients: S3 gallop 46% vs. 20% previously and 31% vs. 11% at randomization; hepatomegaly 28% vs. 14% previously and 10% vs. 7% at randomization; all $p < 0.0001$). In contrast, signs of fluid extravasation (peripheral edema and basilar pulmonary crackles) were less common in the younger patients. Systolic blood pressure was lowest and mean heart rate highest in younger patients (121 mm Hg vs. 134 mm Hg and 78 beats/min vs. 72 beats/min comparing those ages <40 years against those ages 70 years, respectively, $p < 0.0001$).

Investigations. A normal electrocardiogram was uncommon, irrespective of age (9% vs. 8% youngest vs. oldest) (Table 3). Specific abnormalities were significantly less common in younger patients and increased with age, including atrial fibrillation or flutter (4% vs. 20%), bundle branch block (22% vs. 26%), paced rhythm (1% vs. 10%), and pathological Q waves (10% vs. 23%) (all $p < 0.0001$). The exception was left ventricular hypertrophy, which occurred most frequently in the youngest age group (24% vs. 15%, $p = 0.032$).

Radiological changes at randomization were uncommon. Previous radiological abnormalities, however, exhibited a similar pattern to clinical signs (Table 3). Cardiomegaly was more common and fluid extravasation was less common in the young (interstitial pulmonary edema 20% vs. 28%, bilateral effusions 6% vs. 19%; $p < 0.0001$). Mean sodium, potassium, urea, and creatinine levels were lower in younger patients, whereas the mean hemoglobin, white cell, and platelet count were higher.

Medications. Compared with the oldest patients, the youngest patients were more likely to receive an ACEI (53% vs. 35%, $p < 0.0001$), a beta-blocker (62% vs. 48%, $p < 0.0001$), spironolactone (20% vs. 17%, $p = 0.097$), and digoxin (64% vs. 42%, $p < 0.0001$) (Table 1). Diuretic use was lowest in those ages 40 to 49 years and increased with age (80%, 77%, 78%, 82%, and 87% in age groups 20 to 39, 40 to 49, 50 to 59, 60 to 69, and $\geq$70 years, respectively; $p < 0.0001$). These overall percentages might be confounded

Table 1 Baseline Characteristics Stratified by Age

Age Groups (yrs)	20–39 (n = 120)	40–49 (n = 538)	50–59 (n = 1,527)	60–69 (n = 2,395)	70 (n = 3,019)	p Value
Male	71	77	76	71	61	<0.0001
Ethnicity European	73	82	86	91	95	<0.0001
Ethnicity black	18	10	6	4	2	<0.0001
Body mass index (kg/m^2)	29.8 ± 7.3	30.7 ± 6.6	29.6 ± 5.9	28.4 ± 5.1	27.0 ± 4.7	<0.0001
Body mass index (kg/m^2)						
<22.5	13	7	8	10	16	<0.0001
22.5–24.9	13	10	12	17	21	
25.0–29.9	37	35	38	42	41	
30.0–34.9	15	27	26	22	17	
≥35.0	23	21	16	10	6	
HF-REF vs. HF-PEF						
EF (%)	34 (14)	37 (14)	38 (14)	38 (15)	40 (15)	<0.0001
HF-REF (EF ≤40%)	70	66	64	63	55	<0.0001
HF-PEF (EF >40%)	30	34	36	37	45	<0.0001
Primary etiology (%)						
Ischemic heart disease	15	45	58	65	66	<0.0001
Idiopathic dilated cardiomyopathy	62	35	24	17	9	<0.0001
Hypertension	5	12	11	12	15	<0.0001
Valvular heart disease	3	2	1	2	3	0.001
Alcohol-related	3	2	2	1	0	<0.0001
Atrial fibrillation	1	1	2	2	3	<0.0001
Medical history (%)						
Previous HF hospitalization	83	71	71	71	71	0.257
Myocardial infarction	16	43	51	55	55	<0.0001
Angina (present)	5	19	24	25	24	<0.0001
Stroke	3	6	6	9	11	<0.0001
Hypertension	26	48	52	56	58	<0.0001
Diabetes mellitus	15	24	30	32	26	<0.0001
Atrial fibrillation	13	13	19	26	36	<0.0001
CABG	4	14	21	27	25	<0.0001
PCI	8	19	20	17	14	<0.0001
Permanent pacemaker	3	4	5	7	12	<0.0001
Current smoker	26	30	23	15	8	<0.0001
Medications (%)						
ACE inhibitor	53	48	47	43	35	<0.0001
Beta-blocker	62	63	63	57	48	<0.0001
Spironolactone	20	19	15	17	17	0.097
Digitalis	64	46	43	43	42	<0.0001
Diuretics	80	77	78	82	87	<0.0001
Medications (EF ≤40%) (%)						
ACE inhibitor	69	64	62	57	49	<0.0001
Beta-blocker	66	63	63	56	48	<0.0001
Spironolactone	27	24	19	21	19	0.073
Digitalis	71	58	54	53	50	<0.0001
Diuretics	82	85	85	88	91	<0.0001
Adherence measure (%)						
Adherence to study drug	80	87	89	90	88	0.001

Values are % or mean ± SD.

ACE = angiotensin converting enzyme; CABG = coronary artery bypass grafting; EF = ejection fraction; HF = heart failure; PCI = percutaneous coronary intervention; PEF = preserved ejection fraction; REF = reduced ejection fraction.

by the higher proportion of HF-REF in young patients. However, similar therapeutic trends occurred comparing the youngest patients with oldest patients in HF-REF alone: ACEI (69% vs. 49%, $p < 0.0001$), beta-blockers (66% vs. 48%, $p < 0.0001$), spironolactone (27% vs. 19%, $p = 0.073$), and digoxin (71% vs. 50%, $p < 0.0001$).

Adherence measure. Adherence to study drug was the lowest in the youngest age group (80%, 87%, 89%, 90%,

Table 2 Symptoms and Signs Stratified by Age

Age Groups (yrs)	20–39 (n = 120)	40–49 (n = 538)	50–59 (n = 1,527)	60–69 (n = 2,395)	70 (n = 3,019)	p Value
NYHA class						
II	53	49	48	46	42	<0.0001
III	45	49	50	52	55	
IV	2	2	2	3	3	
Minnesota score						
Mean ± SD	52.6 ± 27.6	50.8 ± 24.9	47.1 ± 24.3	38.9 ± 23.9	35.3 ± 21.6	<0.0001
Median (IQR)	61.0 (28.0–73.0)	51.5 (32.5–72.0)	48.0 (28.0–65.0)	38.0 (18.0–58.0)	33.0 (18.0–50.0)	<0.0001
Past symptoms						
Dyspnea at rest	62	53	48	47	49	0.009
Dyspnea on flat	80	75	77	73	72	0.004
Dyspnea on climbing	79	78	78	76	72	<0.0001
Orthopnea	67	51	49	49	47	0.001
Paroxysmal nocturnal dyspnea	63	46	43	40	38	<0.0001
Present symptoms						
Dyspnea at rest	11	12	11	11	11	0.898
Dyspnea on flat	45	59	60	63	68	<0.0001
Dyspnea on climbing	93	90	92	91	91	0.790
Orthopnea	26	22	20	19	21	0.086
Paroxysmal nocturnal dyspnea	22	17	13	13	12	0.001
Heart rate and BP						
Heart rate (beats/min)	78 ± 12	76 ± 14	74 ± 14	72 ± 13	72 ± 13	<0.0001
Systolic BP (mm Hg)	121 ± 17	126 ± 18	128 ± 18	130 ± 19	134 ± 19	<0.0001
Diastolic BP (mm Hg)	78 ± 10	79 ± 11	78 ± 10	77 ± 11	75 ± 11	<0.0001
Pulse pressure (mm Hg)	43 ± 13	46 ± 12	50 ± 14	54 ± 15	59 ± 16	<0.0001
Past signs						
Jugular venous pressure >6 cm	36	27	28	25	26	0.038
Hepatomegaly	28	26	21	17	14	<0.0001
Peripheral edema	53	49	50	51	54	0.039
Basilar pulmonary crackles	49	43	47	51	54	<0.0001
S3 gallop	46	33	27	23	20	<0.0001
Present signs						
Jugular venous pressure >6 cm	10	9	9	9	10	0.719
Hepatomegaly	10	14	13	11	7	<0.0001
Peripheral edema	19	21	24	26	30	<0.0001
Basilar pulmonary crackles	8	12	12	14	19	<0.0001
S3 gallop	31	15	12	12	11	<0.0001

Values are %, mean ± SD, or median (interquartile range [IQR]).
BP = blood pressure; NYHA = New York Heart Association.

and 88% in ages 20 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years, respectively; p = 0.001).

Heart failure hospitalization after randomization. Patients ages 40 to 59 years had the lowest HF hospitalization rate at 1, 2, and 3 years (Table 4). The youngest patients had similar HF hospitalization rates to the oldest patients (20 to 39 years vs. ≥70 years: 1 year, 15% vs. 14%; 2 years, 20% vs. 22%; 3 years, 24% vs. 28%). HF hospitalization rates at 3 years were 24%, 15%, 15%, 22%, and 28% in ages 20 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years, respectively. Younger patients were more likely to present with exertional dyspnea, orthopnea, nocturnal dyspnea, and fatigue at the time of HF hospitalization. As with clinical signs and past investigations, pulmonary edema and radiological signs of HF were again less common in younger patients (youngest vs. oldest 24% vs. 35% and 28% vs. 53%, respectively).

Lifestyle factors were often thought to have contributed to HF hospitalization in younger patients, who were 2 to 3 times less likely to adhere to their medications and dietary restrictions. Comparing youngest patients (20 to 39 years) with oldest patients (≥70 years), medication nonadherence was 24% vs. 7% (p = 0.001), dietary adherence was 21% vs. 9% (p = 0.002), and reported alcohol excess was 3% vs. 1% (p < 0.0001). No significant difference was observed among age groups in acute treatment with intravenous diuretics, inotropes, or vasodilators.

Mortality and cardiovascular outcomes. Crude mortality for any cause at 3 years was lowest in the youngest age group and increased with age, although only markedly above 60 years (12%, <40 years; 13%, 40 to 49 years; 13%, 50 to 59 years; 19%, 60 to 69 years; and 31%, ≥70 years; p < 0.0001) (Fig. 1, Table 5). This remained the case after adjusting for previously published predictors of mortality

Table 3 Investigative Findings Stratified by Age

Age Groups (yrs)	20–39 (n = 120)	40–49 (n = 538)	50–59 (n = 1,527)	60–69 (n = 2,395)	70 (n = 3,019)	p Value
Electrocardiogram						
Normal	9	12	13	9	8	<0.0001
Atrial fib/flutter	4	7	11	14	20	<0.0001
Bundle branch block	22	17	22	25	26	<0.0001
Paced rhythm	1	3	3	5	10	<0.0001
Pathological Q waves	10	26	27	28	23	<0.0001
Left ventricular hypertrophy	24	17	16	16	15	0.032
Other abnormality	53	46	42	41	42	0.051
Chest x-ray						
Interstitial pulmonary edema	20	18	22	24	28	<0.0001
Bilateral effusion	6	7	11	13	19	<0.0001
Cardiomegaly	51	39	39	37	39	0.020
Ejection fraction (%)	34 (14)	37 (14)	38 (14)	38 (15)	40 (15)	<0.0001
Biochemistry						
Sodium (mmol/l)	139.5 ± 3.7	139.5 ± 3.4	140.2 ± 2.8	140.4 ± 2.9	140.5 ± 3.1	<0.0001
Potassium (mmol/l)	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	<0.0001
Urea (mg/dl)	14.7 ± 6.8	17.2 ± 14.9	16.6 ± 11.4	18.6 ± 12.5	19.8 ± 13.1	<0.0001
Creatinine (mg/dl)	1.0 ± 0.3	1.1 ± 1.6	1.1 ± 0.4	1.2 ± 0.4	1.3 ± 0.7	<0.0001
Hematological						
Hemoglobin (g/dl)	14.2 ± 1.5	14.1 ± 1.6	13.9 ± 1.5	13.6 ± 1.7	13.3 ± 1.6	<0.0001
White cell count (10^3/mm^3)	7.6 ± 2.5	7.9 ± 2.4	7.5 ± 2.1	7.3 ± 2.1	7.2 ± 2.3	0.001
Platelet count (10^3/mm^3)	223.2 ± 105.4	192.8 ± 127.1	171.7 ± 132.7	150.7 ± 126.4	130.8 ± 114.5	<0.0001
Mean corpuscular volume (μm^3)	89.0 ± 5.9	89.9 ± 5.3	91.5 ± 5.3	92.0 ± 6.1	92.6 ± 6.0	<0.0001

Values are % or mean ± SD.

and morbidity (Fig. 2). The inclusion of ethnicity (European origin, black, South Asian, Arab/Middle Eastern, Oriental, Malay, or other) and the patients' geographic regions into the model made little difference to the adjusted outcomes, and there was no interaction between age and ethnicity ($p = 0.71$) or age and regions ($p = 0.28$). The respective hazard ratios [HR] for ages <40, 40 to 49, and 50 to 59 years, referenced to 60 to 69 years, were 0.60 (95% CI: 0.36 to 1.00; $p = 0.049$), 0.63 (95% CI: 0.50 to 0.81; $p < 0.0001$), and 0.64 (95% CI 0.54 to 0.75; $p < 0.0001$) for all-cause mortality. For cardiovascular death, the HRs were 0.71 (95% CI: 0.42 to 1.18; $p = 0.186$), 0.78 (95% CI: 0.60 to 1.00; $p = 0.054$), and 0.70 (95% CI: 0.59 to 0.84; $p < 0.0001$).

The relation between the HR for cardiovascular death or HF hospitalization and age was nonlinear. The youngest age group had a similar risk of cardiovascular death or HF hospitalization compared with the referent age group of 60 to 69 years (HR: 0.99, 95% CI: 0.71 to 1.38; $p = 0.930$). This was driven by the aforementioned higher risk of HF hospitalization in the youngest age group (Fig. 2). However, the absolute number of events in this group was small, resulting in wide CIs.

Discussion

With nearly 2,200 patients younger than 60 years (and almost 660 younger than 50 years), we demonstrated some striking differences from older patients with HF, in terms of demographics, etiology, comorbidity, symptoms, signs, quality of life, investigative findings, treatment adherence, potential precipitants of decompensation, and nonfatal and fatal outcomes. We are not aware of any similarly comprehensive study of younger patients with HF.

That more younger patients were black is consistent with epidemiological studies in the United States showing that African Americans have a higher risk of developing HF than do whites, and do so at an earlier age (17). Similarly, the finding that a higher proportion of younger patients had an investigator-reported etiology of IDCM (and a smaller proportion of ischemic etiology) is consistent with the occurrence of symptomatic coronary heart disease later in life (2,18). Previous clinical trials (19–22) and surveys and/or registries (6,23,24) reported a higher proportion of IDCM in younger patients with HF. Interpretation of this apparent association between age and etiology requires consideration of both the numerator and denominator. The incidence and prevalence of IDCM increase steadily with age in the general population (25,26). However, the incidence and prevalence of the 2 most common alternative etiologies (ischemia and hypertension) rise even more rapidly with age, thus diminishing the relative frequency of IDCM in patients with an established diagnosis of HF.

The lower prevalence of all comorbidities, including diabetes mellitus, hypertension, and stroke, likewise reflects these conditions occurring beyond middle age (2,6,27). Because comorbidities (along with age) are among the most

Table 4 Clinical Presentation, Precipitating Factors, and Treatment Related to Unplanned Hospitalization for Heart Failure Occurring After Randomization

Age Groups (yrs)	20–39 (n = 120)	40–49 (n = 538)	50–59 (n = 1,527)	60–69 (n = 2,395)	70 (n = 3,019)	p Value
Hospitalization rates, % (95% CI)						
1 yr	15 (9–22)	8 (6–11)	7 (6–8)	11 (10–12)	14 (13–15)	<0.0001
2 yrs	20 (12–27)	12 (9–15)	12 (10–13)	18 (16–19)	22 (20–23)	<0.0001
3 yrs	24 (17–32)	15 (12–18)	15 (13–17)	22 (20–24)	28 (27–30)	<0.0001
Hospital stay						
Bed days, median (IQR)	12 (6–33)	8 (4–21)	10 (4–21)	12 (6–25)	11 (5–21)	0.007
Clinical presentation						
Increasing dyspnea on exertion	93	92	85	86	82	0.016
Orthopnea	62	52	58	48	48	0.018
Nocturnal dyspnea	48	48	42	36	36	0.051
Increasing peripheral edema	41	51	52	46	45	0.052
Increasing fatigue or decreasing exercise tolerance	62	66	60	54	51	0.005
Renal hypoperfusion	7	11	18	20	20	0.051
Clinical pulmonary edema	24	19	32	35	35	0.022
Radiological sign of heart failure	28	43	46	48	53	0.005
Precipitating factors						
Nonadherence with cardiac medications	24	13	15	7	7	0.001
Excessive salt intake/ dietary nonadherence	21	24	17	12	9	0.002
Alcohol excess	3	4	4	1	1	<0.0001
Inappropriate decrease of antifailure therapy	7	5	3	6	6	0.055
Cardiac arrhythmias	17	22	26	29	28	0.002
Acute myocardial ischemia	3	1	3	5	8	0.014
Intravenous treatment						
Diuretic	93	94	92	90	92	0.085
Inotropic agent	24	20	17	22	17	0.042
Vasodilator	10	15	13	17	17	0.072

Values are % unless otherwise indicated.
CI = confidence interval; IQR = interquartile range.

powerful predictors of prognosis, these findings are central to the much better survival of younger patients (see the following) (4,28). Atrial fibrillation was also significantly less common in younger patients, whether identified by medical history at baseline (13% vs. 36% youngest vs. oldest) or on the baseline electrocardiogram (4% vs. 20%). This suggests that atrial fibrillation may be an age-related comorbidity in HF, rather than just a consequence of HF, especially because severity of HF (associated with the prevalence of atrial fibrillation) did not differ greatly across age groups (6,27,29). Interestingly, the youngest age group had the lowest prevalence of atrial fibrillation but had the highest prescribing rate of digoxin. Trial enrollment from 1999 closely followed publication of the Digitalis Investigation Group trial. Most likely, the aforementioned higher hospitalization rates, nonischemic etiology, radiological cardiomegaly, and worse LVEF and quality of life prompted physicians to prescribe digoxin more frequently in younger patients (30).

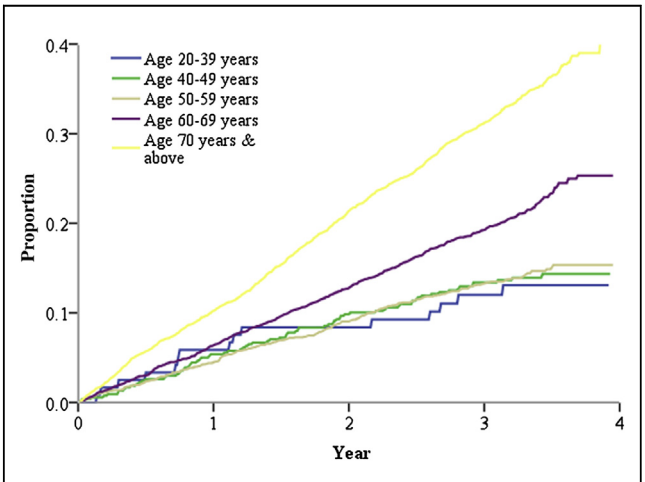

Figure 1 Kaplan-Meier Mortality Curves in Age Categories for All-Cause Mortality

Although younger patients had a slightly, but significantly more favorable NYHA class profile (i.e., a greater proportion were in NYHA class II and/or smaller proportion were in NYHA class III and/or IV) than older participants, they had strikingly worse HRQL, as assessed by the MLwHF. This disconnect between NYHA class and MLwHF score is of interest, and may in part, reflect the difference between a physician-based assessment (NYHA class) and a patient-reported one (MLwHF). That younger patients reported worse HRQL has been reported before and likely reflects the

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Table 5 Kaplan-Meier Mortality Rates for Each Age Category

Age Categories (yrs)	1 Year	2 Years	3 Years
20–39	6 (2–10)	8 (3–13)	12 (6–18)
40–49	5 (4–7)	10 (7–12)	13 (11–16)
50–59	5 (4–6)	9 (8–11)	13 (12–15)
60–69	6 (5–7)	13 (11–14)	19 (18–21)
≥70	10 (9–11)	21 (20–23)	31 (30–33)

Values are cumulative mortality rate (95% confidence interval).

greater impact of HF symptoms and functional limitation in an age group that is more active (or desires to be more active) in meeting the demands of employment and family and/or social commitments (31,32). Of interest, in connection with this, younger patients reported more HF-related symptoms in the past. Although this finding was not clear for the current symptoms reported by patients at baseline, the difference in symptoms between younger and older patients was also noted during episodes of decompensation after randomization.

The pattern of HF signs also differed strikingly between younger and older patients. In particular, younger patients seemed less likely to develop peripheral or pulmonary edema. Evidence for this was seen in previous and current signs and in chest radiographic findings (less frequent pulmonary edema and effusions) collected at baseline; the same differences were noted during episodes of decompensation reported after randomization. Intriguingly, less peripheral edema was noted in younger patients despite a higher prevalence of an elevated jugular venous pressure and hepatomegaly in these patients (compared with older patients) and less pulmonary edema despite a lower LVEF and higher prevalence of a third heart sound. This suggests, perhaps, that peripheral and pulmonary endothelial integrity diminishes with age, leading to increasing capillary "leakiness." These findings also have potential clinical importance for the recognition of HF in younger patients. HF is unlikely to be high on the list of differential diagnoses in young patients with breathlessness, and if the most easily detectable and commonly recognized signs of HF (i.e., peripheral and

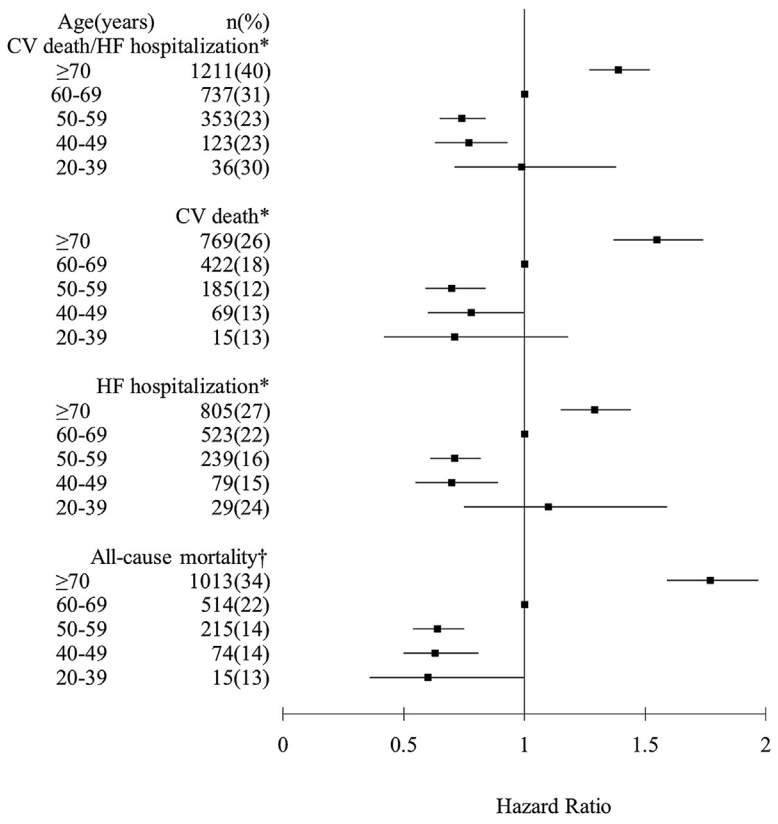

Figure 2 Adjusted Hazard Ratios for the Primary Outcome, Secondary Components and All-Cause Mortality by Age Categories, With 60 to 69 Years as the Reference Group

*Adjusted for age, diabetes: insulin-treated, diabetes: other, ejection fraction (per 5% decrease <45%), previous heart failure (HF) hospitalization, cardiomegaly, diagnosis of chronic HF more 2 years ago, New York Heart Association classes III and IV, and diastolic blood pressure. †Adjusted for age, ejection fraction (per 5% decrease <45%), diabetes: insulin-treated, diabetes: other, body mass index (per 1 kg/m^2 decreased <27.5 kg/m^2), female, New York Heart Association classes III and IV, current smoker, and bundle branch block. CV = cardiovascular.

pulmonary edema) are less common in these patients, the diagnosis may be delayed.

Other clinical and investigative findings in younger patients of relevance to patient management were lower systolic blood pressure, better renal function, and less frequent bundle branch block.

One particularly unique aspect of the present study was the prospective collection of information about acute episodes of decompensation after randomization using a specifically designed endpoint form. Nonadherence with medication and lifestyle measures was reported as a possible contributor to HF worsening significantly more frequently in younger patients than in older patients. Previous studies reported conflicting results, some supporting ours (33,34), and others not (35). The recent Get With The Guidelines-Heart Failure (GWTG-HF) program, which prospectively included 95,127 patients hospitalized with acute HF, reported patients who were nonadherent (less compliant with medication or dietary restriction, or both) were younger (nonadherence vs. adherence 64 years vs. 74 years, $p < 0.0001$) (33). After multivariate analysis, younger age was independently associated with nonadherence (odds ratio for the outcome of nonadherence in younger age [per each year decrease]: 1.022, 95% CI: 1.019 to 1.026; $p < 0.001$). Younger patients with HF may therefore merit particular attention in terms of education and other interventions to improve adherence. In keeping with their lower prevalence of comorbidity, younger patients were less likely to have decompensation attributed to myocardial ischemia or arrhythmias.

Finally, we demonstrated a possible important divergence between fatal and nonfatal outcomes in younger patients versus older patients. As expected, younger patients had a significantly lower mortality rate than older patients. However, there was a suggestion that the youngest patients (age 20 to 39 years) might have relatively high hospitalization rates, more in keeping with those ages ≥60 years than those ages 40 to 59 years. This divergence was not unexpected given the lower mortality in the youngest patients that increased the period at risk of further hospital admission. Coupled with nonadherence to study drug, cardiac medications, dietary restriction, and alcohol excess, this might explain the disconnect of higher HF hospitalization alongside lower mortality in the youngest patients compared with older patients. The modest number of patients in the youngest age group with a wide CI reduced certainty in this finding. However, the longer duration of admission experienced by these patients was consistent with the possibility that they had more severe HF, as was the greater use of digoxin (despite less atrial fibrillation) and spironolactone in this age group. Of additional interest, mortality rates appeared to be relatively flat across the age range 20 to 59 years, only increasing notably in patients ages 60 to 69 years and rising again substantially in those ages ≥70 years; this 3-step pattern was apparent for death from cardiovascular causes only and persisted after adjustment for differences in known prognostic variables that differed in frequency across the age groups.

Study limitations. A number of limitations merit consideration. The number of patients in the youngest age group was small. This resulted in wider CIs and a greater degree of uncertainty when interpreting results. Symptoms were susceptible to recall bias. The etiology of HF and electrocardiographic interpretation were reported by individual site investigators rather than by a core laboratory with standardized definitions. Systematic investigation of the etiology of HF was not mandatory in the study protocol. Serum albumin was not available for the entire cohort. The study excluded the sickest young patients who were on the heart transplant waiting list. This might have altered the mortality and morbidity outcomes. Conversely, the inclusion and exclusion criteria of a trial tend to have a greater impact on the older participants who have more comorbidities (as we have found here again in CHARM). Therefore, older participants were likely to be healthier, and consequently, we believe that the inclusion and exclusion criteria were likely to have biased the true difference between young and old patients toward the null, underestimating the difference.

Conclusions

Compared with older patients, younger patients with HF have a markedly different clinical profile, including a different pattern of symptoms and signs that could lead to delayed diagnosis, a greater reduction in HRQL, more hospitalizations attributed to nonadherence to treatment but better survival, with relatively low rates of death until the age of 60 years.

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Key Words: ejection fraction ■ heart failure ■ outcome ■ young.