

Heart failure in younger patients: the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC)

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Aim

Our understanding of heart failure in younger patients is limited. The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) database, which consisted of 24 prospective observational studies and 7 randomized trials, was used to investigate the clinical characteristics, treatment, and outcomes of younger patients.

Methods and Results

Patients were stratified into six age categories: <40 ($n = 876$), 40–49 ($n = 2638$), 50–59 ($n = 6894$), 60–69 ($n = 12\,071$), 70–79 ($n = 13\,368$), and ≥ 80 years ($n = 6079$). Of 41 926 patients, 2.1, 8.4, and 24.8% were younger than 40, 50, and 60 years of age, respectively. Comparing young (<40 years) against elderly (≥ 80 years), younger patients were more likely to be male (71 vs. 48%) and have idiopathic cardiomyopathy (63 vs. 7%). Younger patients reported better New York Heart Association functional class despite more severe left ventricular dysfunction (median ejection fraction: 31 vs. 42%, all $P < 0.0001$). Comorbidities such as hypertension, myocardial infarction, and atrial fibrillation were much less common in the young. Younger patients received more disease-modifying pharmacological therapy than their older counterparts. Across the younger age groups (<40, 40–49, and 50–59 years), mortality rates were low: 1 year 6.7, 6.6, and 7.5%, respectively; 2 year 11.7, 11.5, 13.0%; and 3 years 16.5, 16.2, 18.2%. Furthermore, 1-, 2-, and 3-year mortality rates increased sharply beyond 60 years and were greatest in the elderly (≥ 80 years): 28.2, 44.5, and 57.2%, respectively.

Conclusion

Younger patients with heart failure have different clinical characteristics including different aetiologies, more severe left ventricular dysfunction, and less severe symptoms. Three-year mortality rates are lower for all age groups under 60 years compared with older patients.

Keywords

Heart failure • Ejection fraction • Young

Introduction

Although the overall prevalence of heart failure (HF) in the general adult population is 1–2%,^{1,2} the majority of those affected is elderly.³ Prior studies on the epidemiology and prognosis of HF have focused on older individuals.^{4–7} There is limited information on the causes and consequences of HF in younger patients (<60 years), especially those aged <40 years.^{8,9} This is primarily because

no single epidemiological study, registry, or clinical trial have included sufficient numbers of such individuals to draw robust conclusions. Yet, it is often in these younger patients that the most searching questions about aetiology and prognosis are asked.

The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) has collated individual patient data from 31 studies (24 observational studies including the Euro Heart Failure Survey¹⁰ and 7 randomized controlled trials of either pharmacotherapy or management

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interventions). These data provide an opportunity to address these deficiencies in our understanding of HF in younger patients.¹¹

Methods

The details of the rationale, methods, inclusion and exclusion criteria, and results of the meta-analysis have been published previously.¹¹ A comprehensive literature search of Embase, Medline, and PubMed was undertaken for observational studies and randomized controlled trials published at the end of 2008, using the following keywords: heart failure, left ventricle, prognosis, outcome, and preserved. The reference lists of each article and conference abstracts were scrutinized, and investigators and authors were contacted. Abstracts, unpublished studies, and articles published in languages other than English were not excluded. The inclusion criteria were that each study had a prospective study design, left ventricular ejection fraction (LVEF) was not an inclusion criterion, and all-cause mortality was reported. Each individual study was approved by the local ethics committees, and the meta-analysis was approved by The University of Auckland Human Subjects Ethics Committee.

Principal investigators from 56 potentially suitable studies were invited to participate in the meta-analysis, from which 31 investigators contributed individual patient data. These data included demographics (age, sex, and ethnicity), medical history [myocardial infarction (MI), coronary revascularization, diabetes, hypertension, atrial fibrillation, stroke, lung disease, peripheral artery disease, and smoking], aetiology (defined by individual studies; idiopathic included those labelled as idiopathic or dilated cardiomyopathy), medical treatment [angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta-blocker, diuretics, and aldosterone antagonist], symptom status [New York Heart Association (NYHA) functional class, dyspnoea, paroxysmal nocturnal dyspnoea, and oedema], clinical variables (heart rate, blood pressure, and pulmonary rates), laboratory variables [serum sodium, creatinine, and ejection fraction (EF)], and outcomes (deaths and follow-up duration). The results from the MAGGIC meta-analysis demonstrated that patients with HF with preserved LVEF (HF-PEF) have lower risk of death from any cause than patients with reduced LVEF (HF-REF).¹¹ In this study, we stratify patients into six age categories (<40, 40–49, 50–59, 60–69, 70–79, and ≥80 years) and report their clinical characteristics and outcomes.

Statistical analysis

The current analyses included all subjects in the MAGGIC data set for whom the LVEF category (HF-PEF or HF-REF) was known. Baseline characteristics are presented as means and standard deviations for continuous variables and proportions for categorical variables. Variables were compared across age categories using ANOVA for continuous variables and χ^2 for categorical variables. For all analyses, the primary outcome was rate of death from any cause at 3 years from hospital discharge or baseline study visit. Mortality estimates, stratified by age and sex, at 1, 2, and 3 years and deaths per 1000 patient-years were calculated. Baseline characteristics, mortality rates, and survival curves were stratified by EF as HF-REF and HF-PEF. Cox's proportional hazard models were used to estimate the hazard of younger age compared with the age group 50–59 years as the referent category. All models were adjusted for sex, aetiology (ischaemic vs. non-ischaemic), LVEF [reduced (defined as LVEF < 50%) vs. preserved], history of hypertension, diabetes, and atrial fibrillation, and were stratified by an individual study. Included variables were selected based on clinical relevance and where data were available for >90% of the patients in the MAGGIC data set. Data regarding NYHA functional class and medications were less complete, so models were re-analysed with these variables included as a sensitivity analysis. The presence of

an age–sex interaction was assessed in the main model. Mortality curves for each age category were created using adjusted models that were not stratified by an individual study. Analyses were performed using SAS version 9.2.

Results

Demography

Thirty-one studies contributed data on 41 926 patients whose baseline characteristics are presented in Table 1. The relative proportion of women increased with age (29% <40, 22% 40–49, 23% 50–59, 27% 60–69, 38% 70–79, and 52% ≥80 years; $P < 0.0001$).

Comorbidities

Younger patients had the lowest prevalence of comorbidities (<40 vs. ≥80 years: hypertension 22 vs. 43%, $P < 0.0001$; MI 14 vs. 35%, $P = 0.019$; AF 9 vs. 30%, $P < 0.0001$; and diabetes 9 vs. 18%, $P < 0.0001$; Table 1). The prevalence of comorbidities increased with age.

Aetiology

The aetiology of HF varied with age. Since the term 'idiopathic' may refer to dilated cardiomyopathy (typically inferring reduced EF), aetiology was examined separately in the overall population and those with HF-REF (Table 1). In both cohorts, the youngest age group had the highest proportion of 'idiopathic' cardiomyopathy, which declined sharply >40 years of age (overall 63% <40 years, 37% 40–49 years, 28% 50–59 years, 20% 60–69 years, 12% 70–79, and 7% ≥80 years; $P < 0.001$). This reflected converse parallel trends in the proportion of patients with ischaemic and hypertensive aetiology, which both increased with age: aetiology presumed to be ischaemic increased from 16% in those aged <40 to 68% in those aged ≥80 years ($P < 0.0001$); hypertensive from 5% <40 to 17% ≥80 years ($P = 0.18$). The proportion of HF attributed to alcohol was low in all age categories, ranging from 0 to 4%.

Heart failure with reduced left ventricular ejection fraction and heart failure with preserved left ventricular ejection fraction

The median EF was lowest in the youngest and progressively increased with age (31% <40, 33% 40–49, 33% 50–59, 34% 60–69, 37% 70–79, and 42% ≥80 years; $P < 0.0001$). The proportion of patients with HF-PEF (LVEF ≥50%) trebled from the youngest to oldest age groups: 14% in <40 years of age to 39% in those aged ≥80 ($P < 0.0001$; Table 1).

Clinical status, blood pressure, heart rate, and treatment

Younger patients were predominantly in NYHA functional class I or II. The proportion of patients in NYHA functional classes III and IV increased with age. The mean systolic blood pressure was lowest in the youngest age group (118 ± 19 mmHg <40 years vs. 137 ± 26 mmHg ≥80 years; $P < 0.0001$). Younger patients were more likely to receive disease-modifying medical therapies, including an ACEI or ARB, a beta-blocker, and spironolactone. Younger patients were also more often treated with digoxin, despite their much lower

Table 1 Baseline characteristics for patients from the MAGGIC meta-analysis by age categories

Age (years)	<40	40–49	50–59	60–69	70–79	≥80	P-value
n (31 studies)	876	2638	6894	12 071	13 368	6079	
Women (%)	29	22	23	27	38	52	<0.0001
RCTs	29	22	23	26	35	51	
Observational studies	29	22	22	29	40	53	
Medical history							
Hypertension (%)	22	37	41	44	46	43	<0.0001
MI (%)	14	38	46	50	47	35	0.019
Atrial fibrillation (%)	9	9	14	18	25	30	<0.0001
Diabetes (%)	9	18	24	27	25	18	<0.0001
Aetiology							
All patients							
Ischaemic	16	46	57	65	69	68	<0.0001
Hypertensive	5	10	9	10	13	17	0.180
Idiopathic	63	37	28	20	12	7	<0.0001
Alcoholic	3	3	2	1	1	0	<0.0001
Atrial fibrillation	9	4	4	4	5	8	<0.0001
Patients with HFREF							
Ischaemic	17	46	58	68	73	76	<0.0001
Hypertensive	4	8	8	8	9	10	0.170
Idiopathic	65	38	29	21	14	9	<0.0001
Alcoholic	3	4	2	1	1	0	<0.0001
Atrial fibrillation	11	4	3	2	3	5	<0.0001
Clinical status							
NYHA class(%) (I/II/III/IV)	21/50/25/4	14/50/31/5	11/50/34/5	10/49/35/6	9/45/38/9	9/40/37/14	<0.0001
Heart rate (b.p.m) [SD]	81 (17)	80 (16)	79 (17)	78 (17)	79 (19)	82 (22)	0.820
SBP (mmHg) (SD)	118 (19)	124 (20)	126 (21)	130 (22)	134 (23)	137 (26)	<0.0001
DBP (mmHg) (SD)	76 (12)	79 (13)	78 (12)	77 (12)	76 (13)	76 (14)	<0.0001
Medication							
All patients							
ACEI or ARB	80	77	74	71	65	53	<0.0001
Beta-blocker	45	47	47	39	34	26	<0.0001
Spironolactone	26	26	23	22	21	19	<0.0001
Digoxin	49	47	44	44	42	41	<0.0001
Diuretic	70	75	78	81	84	85	<0.0001
Patients with HFREF							
ACEI or ARB	84	82	80	77	73	63	<0.0001
Beta-blocker	47	47	48	40	39	27	<0.0001
Spironolactone	28	28	25	24	23	22	<0.0001
Digoxin	52	51	48	48	45	43	<0.0001
Diuretic	71	77	79	72	85	87	<0.0001
Ejection fraction							
Median EF (%), IQR	31 (23, 42)	33 (24, 32)	33 (24, 43)	34 (26, 46)	37 (27, 51)	42 (30, 58)	<0.0001
HF-PEF (%)	14	15	17	21	38	39	<0.0001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.p.m, beats per minute; DBP, diastolic blood pressure; HF-PEF, heart failure with preserved ejection fraction (LVEF > 50%); HF-REF, heart failure with reduced ejection fraction; IQR, inter-quartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction, NYHA, New York Heart Association functional class; SBP, systolic blood pressure; SD, standard deviation.

prevalence of atrial fibrillation. Excluding the DIG trial from the analysis, similar patterns were observed. In contrast, younger patients were less likely to receive diuretics (70% <40 years vs. 85% ≥80 years; $P < 0.0001$).

Table 2 Mortality probability estimates (%) stratified by sex and age categories at 1, 2, and 3 years, adjusted for ischaemic aetiology, diabetes, hypertension, ejection fraction group (heart failure with reduced left ventricular ejection fraction vs. heart failure with preserved left ventricular ejection fraction), and atrial fibrillation

Age groups	<40	40–49	50–59	60–69	70–79	≥80
One year						
All patients	6.7	6.6	7.5	11.2	16.7	28.2
Male	7.3	6.9	7.7	11.5	17.3	28.9
Female	5.4	5.9	7.3	10.8	15.8	26.8
Two years						
All patients	11.7	11.5	13.0	19.1	27.8	44.5
Male	12.9	12.2	13.6	19.9	29.3	46.4
Female	9.1	9.8	12.1	17.5	25.2	41.1
Three years						
All patients	16.5	16.2	18.2	26.2	37.5	57.2
Male	18.1	17.1	19.1	27.6	39.5	59.5
Female	12.6	13.7	16.7	24.0	33.8	52.9

Age–sex interaction; $P = 0.78$.

Mortality

During 3-year follow-up, 10 747 patients died. Deaths per 1000 patient-years increased with age from 64 (95% CI: 53–78) in the youngest age group to 276 (95% CI: 266–287) in the oldest age group. Likewise, the probability of death was lowest in the youngest age group and increased with age (Table 2). The estimated 3-year cumulative mortality was 16.5% <40, 16.2% 40–49, 18.2% 50–59, 26.2% 60–69, 37.5% 70–79, and 57.2% ≥80 years (Table 2). There was no significant age–sex interaction for all-cause mortality. The mortality rates in younger patients with HF-PEF were half those of patients with HF-REF [deaths per 1000 patient-years: HF-PEF vs. HF-REF: 19.3 vs. 70.9 in <40 years, 31.7 vs. 68.9 in 40–49 years, and 42.1 vs. 80.0 in 50–59 years (see Supplementary material online, Table S1)]. The deaths per 1000 patient-years were similar for patients in the randomized controlled trials (RCTs) compared with those in the observational studies (see Supplementary material online, Table S1).

After adjusting for sex, ischaemic aetiology, diabetes, hypertension, and atrial fibrillation, mortality remained lowest in the youngest patients (<60 years) in patients with both HF-REF and HF-PEF (Figure 1A and B). The hazard ratio for all-cause mortality increased with increasing age (compared with age 50–59 years as the reference group), and was lowest in those aged <60 years (Figure 2). The hazard ratios for the three youngest age groups (<40 years, 40–49, and 50–59 years) did not differ significantly. A sensitivity analysis incorporating NYHA class, ACEI, ARB, and beta-blocker did not alter the association between age and outcomes.

Discussion

Young patients with HF have different demographics, aetiology, clinical characteristics, and survival compared with the older age groups.

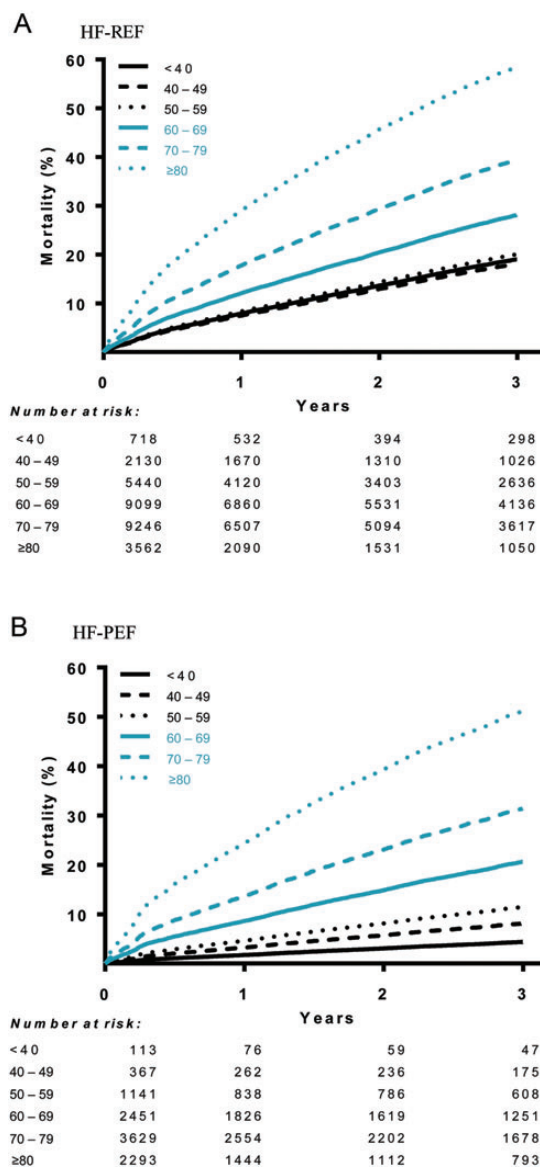
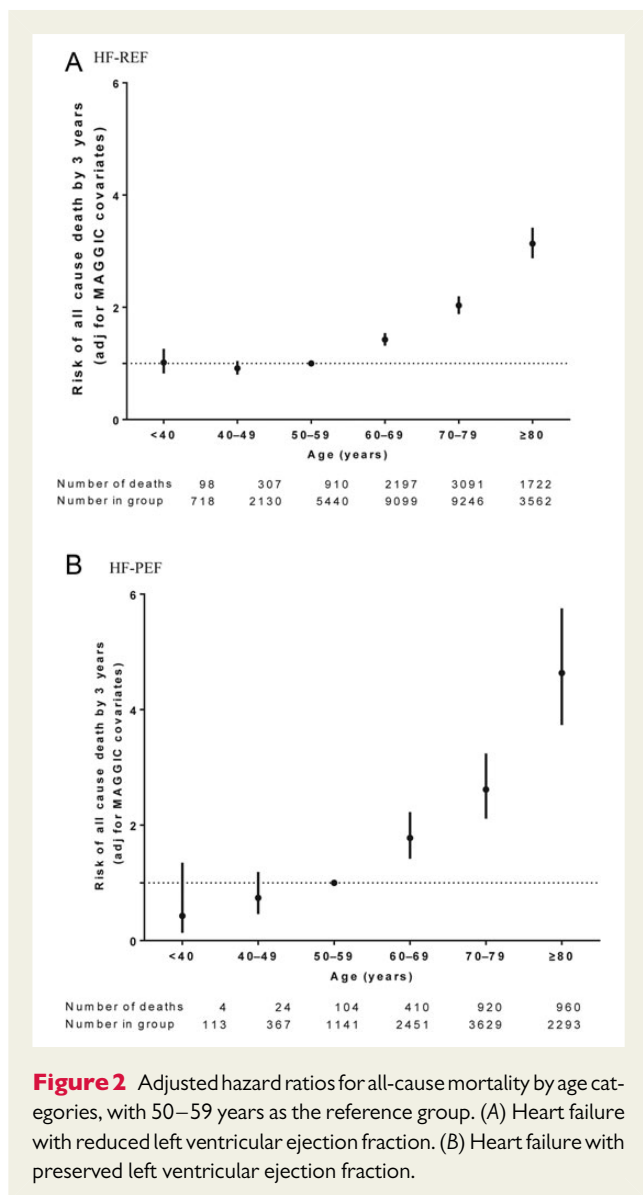


Figure 1 Mortality curves adjusted for sex, ischaemic aetiology, diabetes, hypertension, and atrial fibrillation stratified by age for (A) heart failure with reduced left ventricular ejection fraction and (B) heart failure with preserved left ventricular ejection fraction.

Presumed 'idiopathic' dilated cardiomyopathy is relatively more common in young patients. The relative frequency of DCM is nearly ten times higher in the youngest age group (<40 years) compared to the oldest age group (7 vs. 63%). These findings expand upon the previous clinical trials^{12–14} and registries,^{8,9,15,16} which reported a higher prevalence of presumed non-ischaemic (25–58%) or idiopathic dilated aetiology (6–40%) in those aged <50–65 years, compared with 2–36% in those aged ≥70–80 years. In both the current analysis and previous reports, whether patients truly had non-ischaemic aetiology is unknown, as routine coronary angiography



or testing for myocardial ischaemia was not mandated. Thorough investigation for the cause of HF (e.g. with genetic testing and cardiac magnetic resonance imaging) was likewise uncommon.

The preponderance of men in the younger age groups was striking, with at least 70% males in every age category below 70 years, and was apparent in both cohort studies (52% of our patients) and RCTs (48%). More than half of the observational patient data originate from the Euro Heart Failure Survey and Italian Network on Congestive Heart Failure registry, which are broadly representative of patients hospitalized with HF or referred to HF clinics.^{10,17} Peripartum cardiomyopathy should increase the proportion of women in the younger age groups, although it may have been underrepresented in cohort studies from hospitals without maternity services. Furthermore, pharmacological trials often excluded pregnant or lactating women. Young women with HF are thus most likely underrepresented.

The preponderance of men in younger age groups is also reported in community echocardiographic studies,^{3,18–21} epidemiology and large cohort studies of cardiomyopathy,^{22,23} cardiomyopathy registries,^{24,25} and genetic studies in patients with cardiomyopathy.^{26–28} X-linked laminopathies and dystrophin defects, such as Becker's and Duchenne's muscular dystrophy, must contribute.^{29,30} Dystrophin defects are most prevalent in younger (<30 years) men.³¹ Certain mutations in cardiac troponin T or cardiac β -myosin heavy chain in patients with DCM result in early-onset ventricular dysfunction and HF.^{32,33} In patients with hypertrophic cardiomyopathy, men have more hypertrophy and a higher risk of left ventricular systolic dysfunction.³⁴ Arrhythmogenic right ventricular cardiomyopathy likewise exhibits a male preponderance with greater right ventricular dilatation.³⁵ A male preponderance of occult coronary disease and excess alcohol consumption is also possible. No matter the explanation, clinicians investigating young men with symptoms compatible with HF should be mindful to exclude the diagnosis.

Young patients with HF have more severe left ventricular systolic dysfunction than their elderly counterparts, mandating therapy with ACEI, beta-blockers, and spironolactone in most cases. Among the youngest patients in MAGGIC, prescribing rates of ACEI were 50% greater and beta-blocker rates were almost double than those observed in the elderly. While these differences are multifactorial, indication, and contraindication to prescribing likely contribute: the prevalence of HF-REF is highest in the youngest age group, while comorbidities precluding therapy (e.g. chronic kidney disease and severe obstructive airways disease) are least prevalent in these patients. There are no evidence-based pharmacological treatments with prognostic benefit in HF-PEF.¹ Heart failure with reduced LVEF is also more frequently managed in specialist cardiology services, which are associated with higher levels of pharmacotherapy.^{10,36}

Despite having more severe left ventricular systolic dysfunction, younger patients in MAGGIC reported less marked symptoms as represented by NYHA class III/IV. NYHA functional class increased progressively with every decade. The DIG study reported similar findings (i.e. worse left ventricular systolic function but fewer symptoms in the young), albeit in a randomized clinical trial.¹³ A small number of young patients with severe symptoms may have been excluded from our analysis and DIG due to listing for cardiac transplantation. Alternate reasons why younger patients have better NYHA functional class are incompletely understood, but may partly reflect fewer comorbidities such as atrial fibrillation or airways disease.

The 3-year mortality rate was relatively low in all age groups under the age of 60 years: 16.5, 16.2, and 18.2% in those aged <40, 40–49, and 50–59 years, respectively. Prior epidemiological studies have reported worse 3-year outcomes in younger age groups compared with our findings. In patients with HF aged 45–54 years in UK primary care followed from 1991, the 3-year mortality was 47 and 24% in men and women, respectively.⁴ Five-year mortality in patients aged <55 years was 39.4% in a previously hospitalized Scottish population studied from 1986 to 2003.³⁷ Conversely, the mortality rate in younger patients with HF is still significantly higher than the general population in the same age categories (death per 1000/year: 0.2–1.2 <40 years, 1.1–2.5 40–49 years, and 2.6–6.2 in 50–59 years

compared with our study (64.2 < 40 years, 60.1 40–49 years, and 73.2 50–59 years).^{38,39}

The MAGGIC data set includes 31 studies without EF as an inclusion criterion conducted over several decades. The deaths/1000 patient-years for the younger patients in the current analysis were similar among the RCTs and observational studies. The lower mortality rates in our data set could reflect improved pharmacotherapies, but are unlikely to be a consequence of device-based therapies, as most of the included studies predate the increased uptake of device-based therapies for HF. The clinical relevance of our observations is clear. Clinicians managing young patients with HF can inform and counsel patients appropriately, rather than citing outcomes from elderly cohorts. Patients need to know their predicted longer-term prognosis with modern medical and device therapy.

Limitations

A number of limitations merit consideration. The meta-analysis included individual patients' data from 31 randomized trials and observational studies, the variables collected being determined by each original study. Data on medications, NYHA functional class, and echocardiographic and laboratory variables were not universally available in all patients. However, only variables with data available for at least 90% of the patients were included. Other important prognostic variables were not selected due to missing data that could bias the analysis. The primary outcome, all-cause mortality, increases with age in part due to greater cardiovascular and non-cardiovascular comorbidity. However, too few studies provided cause-specific death to analyse cardiovascular death as opposed to all-cause mortality. The balance and competing risks between pump failure, sudden cardiac death, other cardiovascular death (e.g. MI), and non-cardiovascular death are likely age dependent.

Conclusion

Younger patients with HF have different clinical characteristics including different aetiologies, more severe left ventricular dysfunction but less severe symptoms, and have much lower 3-year mortality. These differences are of practical importance both to clinicians investigating and managing younger patients with HF and also to patients themselves who can be reassured by their dramatically better outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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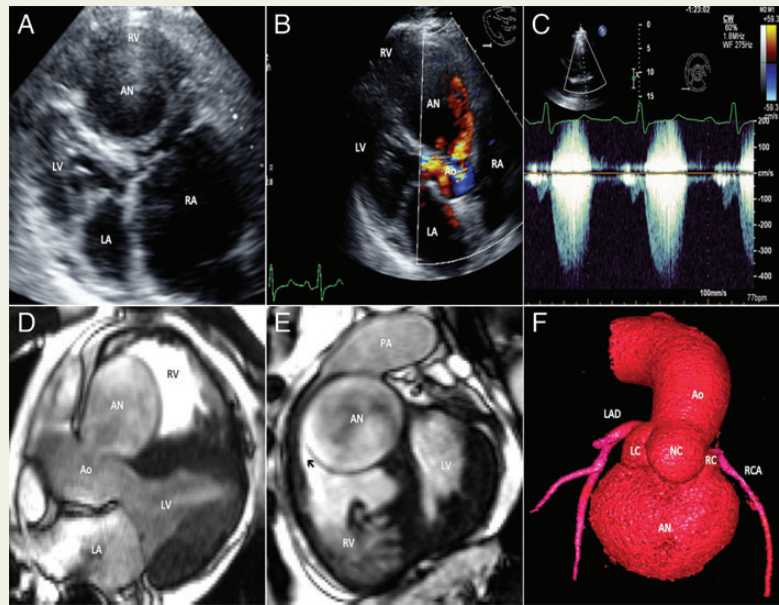
An unusual case of right-sided heart failure caused by giant sinus of Valsalva aneurysm obstructing right ventricular outflow tract

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A 63-year-old male with a previous history of leg swelling for many decades and dyspnoea on exertion for few months, presented to the local emergency department complaining of unexpected fall. He was found to have a systolic murmur and abnormal ECG for which he was referred to our clinic for further evaluation. His physical examination was significant for a loud ejection systolic murmur at the left upper sternal border, an elevated jugular venous pressure and bilateral lower extremity oedema with significant venous stasis changes. An ECG showed normal sinus rhythm with incomplete RBBB. Transthoracic echocardiography (TTE) showed a large aneurysmal vascular structure protruding into the right ventricle (RV) (Panels A and B, Supplementary material online, Videos S1 and S2) compressing the right ventricular outflow tract (RVOT) with systolic gradients across RVOT of >50 mmHg (Panel C). The left ventricular systolic function was mildly depressed and RV systolic function was severely depressed. Cardiac magnetic resonance (CMR) confirmed the presence of a giant unruptured sinus of Valsalva aneurysm (SVA) arising from the right coronary cusp causing significant RVOT obstruction (Panels D and E, arrow; Supplementary material online, Videos S3 and S4). The patient was further evaluated for the coronary arterial anatomy preoperatively by coronary computed tomography angiography (CTA), which showed normal coronary arteries (Panel F, Supplementary material online, Video S5). Patient underwent an uneventful surgery with repair of right coronary SVA. The patient was discharged from the hospital in good condition on the eleventh day of treatment.



(Panel A) Two-dimensional TTE apical four-chamber view showed a large aneurysmal vascular structure protruding into the RV. AN, aneurysm; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Panel B) Colour Doppler of aortic root (parasternal long-axis view) demonstrated flow from the aortic root into the aneurysm. AN, aneurysm; Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Panel C) Continuous wave (CW) Doppler of RVOT (parasternal short-axis view) showed the RVOT obstruction with systolic gradients across RVOT of >50 mmHg. (Panel D) Cine-CMR (three-chamber long axis) confirmed a giant unruptured sinus of Valsalva aneurysm measuring ~76 × 55 × 57 mm. AN, aneurysm; Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (Panel E) Cine-CMR of RVOT showed a giant SVA causing significant RVOT obstruction (arrow) with the interventricular septum bowing to the left during systole suggestive of RV pressure overload. AN, aneurysm; LV, left ventricle; PA, pulmonary artery; RV, right ventricle. (Panel F) Three-dimensional reconstruction of coronary CTA (posterior view) showed normal coronary arteries and a giant unruptured aneurysm of sinus of Valsalva. AN, aneurysm; Ao, aorta; LAD, left anterior-descending coronary artery; LC, left coronary cusp; NC, non-coronary cusp; RC, right coronary cusp; RCA, right coronary artery.

(Panel A) Two-dimensional TTE apical four-chamber view showed a large aneurysmal vascular structure protruding into the RV. AN, aneurysm; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Panel B) Colour Doppler of aortic root (parasternal long-axis view) demonstrated flow from the aortic root into the aneurysm. AN, aneurysm; Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Panel C) Continuous wave (CW) Doppler of RVOT (parasternal short-axis view) showed the RVOT obstruction with systolic gradients across RVOT of >50 mmHg. (Panel D) Cine-CMR (three-chamber long axis) confirmed a giant unruptured sinus of Valsalva aneurysm measuring ~76 × 55 × 57 mm. AN, aneurysm; Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (Panel E) Cine-CMR of RVOT showed a giant SVA causing significant RVOT obstruction (arrow) with the interventricular septum bowing to the left during systole suggestive of RV pressure overload. AN, aneurysm; LV, left ventricle; PA, pulmonary artery; RV, right ventricle. (Panel F) Three-dimensional reconstruction of coronary CTA (posterior view) showed normal coronary arteries and a giant unruptured aneurysm of sinus of Valsalva. AN, aneurysm; Ao, aorta; LAD, left anterior-descending coronary artery; LC, left coronary cusp; NC, non-coronary cusp; RC, right coronary cusp; RCA, right coronary artery.

Supplementary material is available at *European Heart Journal* online.