



Etiologies and predictors of mortality in an all-comer population of patients with non-ischemic heart failure

S. Göbel^{1,2} · A. S. Braun¹ · O. Hahad^{1,2} · U. von Henning¹ · M. Brandt^{1,2,3} · K. Keller^{1,2,3} · M. M. Gaida^{4,5} · T. Gori^{1,2} · H. P. Schultheiss⁶ · F. Escher^{7,8} · T. Münzel^{1,2} · P. Wenzel^{1,2,3} 

Received: 23 March 2023 / Accepted: 29 November 2023
© The Author(s) 2024

Abstract

Background Despite progress in diagnosis and therapy of heart failure (HF), etiology and risk stratification remain elusive in many patients.

Methods The My Biopsy HF Study (German clinical trials register number: DRKS22178) is a retrospective monocentric study investigating an all-comer population of patients with unexplained HF based on a thorough workup including endomyocardial biopsy (EMB).

Results 655 patients (70.9% men, median age 55 [45/66] years) with non-ischemic, non-valvular HF were included in the analyses. 489 patients were diagnosed with HF with reduced ejection fraction (HFrEF), 52 patients with HF with mildly reduced ejection fraction (HFmrEF) and 114 patients with HF with preserved ejection fraction (HFpEF). After a median follow-up of 4.6 (2.5/6.6) years, 94 deaths were enumerated (HFrEF: 68; HFmrEF: 8; HFpEF: 18), equating to mortality rates of 3.3% and 11.6% for patients with HFrEF, 7.7% and 15.4% for patients with HFmrEF and 5.3% and 11.4% for patients with HFpEF after 1 and 5 years, respectively. In EMB, we detected a variety of putative etiologies of HF, including incidental cardiac amyloidosis (CA, 5.8%). In multivariate logistic regression analysis adjusting for age, sex and comorbidities only CA, age and NYHA functional class III + IV remained independently associated with all-cause mortality (CA: HR_{perui} 3.13, 95% CI 1.5–6.51; $p = 0.002$).

✉ P. Wenzel
wenzelp@uni-mainz.de

¹ Cardiology I – Department of Cardiology, University Medical Center Mainz (Johannes Gutenberg University Mainz), Langenbeckstr. 1, 55131 Mainz, Germany

² German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Mainz, Germany

³ Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz (Johannes Gutenberg-University Mainz), Mainz, Germany

⁴ Institute of Pathology, University Medical Center Mainz (Johannes Gutenberg University Mainz), Mainz, Germany

⁵ TRON, Translational Oncology at the University Medical Center Mainz, Mainz, Germany

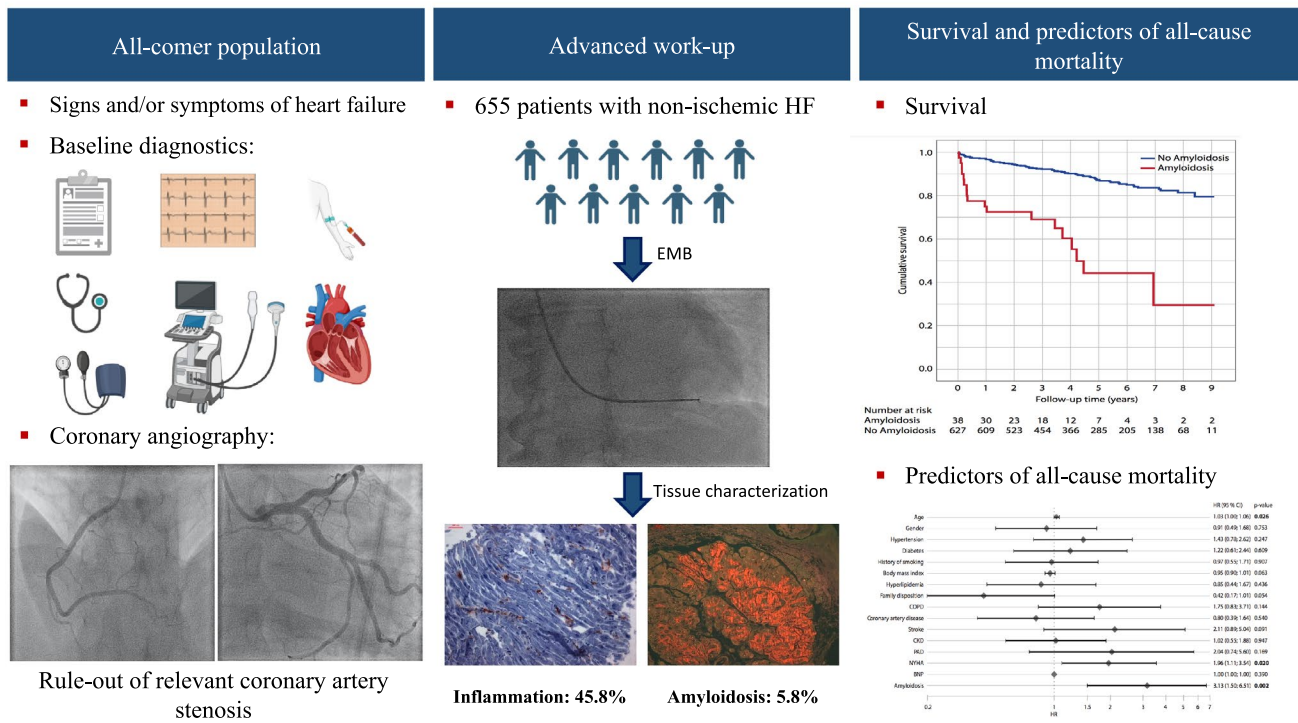
⁶ Institute of Cardiac Diagnostics and Therapy (IKDT), Berlin, Germany

⁷ Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Campus Virchow Klinikum, Berlin, Germany

⁸ German Center for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany

Conclusions In an all-comer population of patients presenting with HF of unknown etiology, incidental finding of CA stands out to be independently associated with all-cause mortality. Our findings suggest that prospective trials would be helpful to test the added value of a systematic and holistic work-up of HF of unknown etiology.

Graphical abstract



Keywords Heart failure · Endomyocardial biopsy · All-cause mortality · Cardiac amyloidosis

Abbreviations

AL	Immunoglobulin light chain amyloidosis
ATTRh	Hereditary transthyretin amyloidosis
ATTRwt	Wild-type transthyretin amyloidosis
CA	Cardiac amyloidosis
CAD	Coronary artery disease
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVRF	Cardiovascular risk factors
EMB	Endomyocardial biopsy
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrfEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
LV	Left ventricular
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association

Introduction

Coronary artery disease and arterial hypertension are the predominant risk factors for the development of heart failure (HF) [1]. In cases of non-ischemic and non-valvular HF, the underlying etiology is likely to be multifactorial and cannot always be detected by established diagnostic procedures such as coronary angiography, echocardiography, cardiac magnetic resonance imaging (cMRI) or additive genetic testing. Considering recent advances in the development of new therapies for specific myocardial diseases, an accurate and early diagnosis is mandatory to provide the most appropriate therapy for the patient and improve survival. Endomyocardial biopsy (EMB) integrated into the diagnostic work-up may improve diagnostic accuracy of unexplained HF [2] as it enables detailed tissue characterization. A search for etiologies is recommended in current guidelines for HFpEF [3] and with less stringency also for HFrfEF [4, 5]. Initially, EMB was predominantly used for monitoring of heart transplant rejection [6, 7]. EMB has been demonstrated to be a safe procedure if performed in high volume centers by

experienced operators [8–11]. Until today, it remains controversial, if routine EMB helps to risk-stratify patients with HF of unknown etiology or predict their outcomes. We therefore set out to investigate the long-term follow-up in an all-comer population with HF of unknown etiology that had undergone a structured diagnostic workup including routine EMB, and identify factors that may predict outcomes.

Methods

Study population

The Mainz Endomyocardial Biopsy in Heart Failure Study (My Biopsy-HF Study; German Clinical Trials Register number: 22178) is a retrospective monocentric study conducted at the University Medical Center Mainz (Germany) to investigate the etiology of HF in an all-comer population of patients with non-ischemic and non-valvular HF [2]. Patients presenting with symptoms and/or signs of HF at the Heart Failure Outpatient Clinic, the emergency department or the chest pain unit of the University Medical Centre Mainz between 14/10/2012 and 01/03/2021, who underwent endomyocardial biopsy (EMB) were available for the present analysis. Decision to obtain EMB of the patients was based on current guidelines of the American Heart Association (AHA), the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) in 2007 [4]. Prior to EMB, echocardiography was performed to rule out valvular heart disease, as well as a left heart catheterization to rule out ischemic heart disease. Based on the patients' medical reports, the following data were included in the present analysis: personal history, clinical presentation, medication, laboratory results, electrocardiogram, echocardiographic findings as well as the results of EMB and genotyping. Informed consent was obtained from all included individuals to use EMB tissue samples for further scientific purpose.

Echocardiography

A comprehensive standardized echocardiographic examination was performed by trained and certified medical staff in all patients in the echocardiographic laboratory of the University Medical Center Mainz using either a Philips ie33, a GE E9 or Siemens Acuson s2000 machine according to standard operating procedures (SOP). Routinely 2–4 cardiac cycles were obtained at frame rates of 50–100 fps and digitally transferred into a picture archiving and communication system (Xcelera) for offline analysis. All structural and functional measurements were made according to current ASE/EACVI recommendations [12].

Detailed information on the assessment of systolic and diastolic function is provided in the Supplementary Appendix.

Endomyocardial biopsy

Endomyocardial biopsy is described in detail in the Supplementary Appendix.

Tissue processing, polymerase chain reaction, histology and immunohistochemistry

Information on tissue processing, histology and immunohistochemistry is provided in detail in the Supplementary Appendix.

Genotyping

Technical aspects of genotyping are described in detail in the Supplementary Appendix.

Outcome measures

Mortality

All-cause mortality was defined as the main study outcome. Follow-up was performed through March 2022 using the medical record system. In addition to death notes in clinical care, information on death/survival was also regularly obtained and updated from the mortality registry of the state of Rhineland-Palatinate (“Mortalitätsregister Rheinland Pfalz”). Information on the date of death was available, however, the underlying cause could not be provided, so that we can solely report on all-cause mortality.

Ethics approval

The retrospective monocentric Mainz Endomyocardial Biopsy in Heart Failure Study (My Biopsy-HF Study, German Clinical Trials Register number: 22178) was approved by the Ethics Committee of Rhineland Palatinate to be in accordance with the legal regulations and the declaration of Helsinki.

Statistical analysis

Univariate and multivariate logistic regression models were used to analyze predictors of all-cause mortality in patients with HF. Results are presented as odds ratio (OR) and 95% confidence intervals (CI). The multivariate regression models were adjusted for age and sex, classical cardiovascular risk factors (i.e. history of smoking, arterial hypertension, diabetes mellitus, hyperlipidemia, obesity,

family disposition) as well as several comorbidities (chronic obstructive pulmonary disease, chronic kidney disease, coronary artery disease, stroke peripheral artery disease and amyloidosis). A probability value of $p < 0.05$ was considered statistically significant. Overall survival was estimated by the Kaplan–Meier method and tested for differences in survival between groups by the log-rank test. All statistical analyses were performed with SPSS (version 22.0; IBM Corp.).

Results

Sample characteristics stratified for phenotype of heart failure

The analysis sample comprised 655 patients (70.9% men) who presented with symptoms and/or signs of HF at the outpatient clinic, the emergency department or the chest pain unit of the University Medical Centre Mainz between October 2012 and March 2021. 378 (57.7%) presented in New York Heart Association (NYHA) functional class I or II and 277 (42.3%) with NYHA functional class III or IV. 489 (74.7%) patients were diagnosed with HF with reduced ejection fraction (HFrEF), 52 (7.9%) patients with HF with mildly reduced ejection fraction (HFmrEF) and 114 (17.4%) patients with HF with preserved ejection fraction (HFpEF). Patients with HFrEF were older compared to patients with HFmrEF and HFpEF (HFrEF vs. HFmrEF vs. HFpEF: 56 [47/65] vs. 53 [43/65] vs. 53 [39/67]) and were more likely to present in NYHA functional class III or IV (47.1% vs. 25% vs. 29.8%). The expression of natriuretic peptides (i.e. BNP) was highest amongst patients with HFrEF (597 [184/1266] vs. 152 [35/527] vs. 159 [31/411] pg/ml), whereas the expression of high-sensitive cardiac troponin I was highest in patients with HFmrEF (21 [9/53] vs. 55 [3/224] vs. 29 [7/176] pg/ml). A detailed sample characterization including comorbidities, cardiovascular risk factors as well as functional parameters and biomarker expressions stratified for phenotypes of our cohort of non-ischemic and non-valvular HF is provided in Table 1.

Etiology of heart failure based on endomyocardial biopsy findings

Based on the results of both histological and immunohistochemical analyses of endomyocardial biopsy specimens including virus detection, virus-negative cardiomyopathy was detected in 218 patients (33.3%) being the most common EMB-finding in the present analysis sample. According to the phenotype of HF, patients with evidence of virus-negative cardiac inflammation predominantly presented with HFrEF (77.5% of all patients with virus-negative cardiac

inflammation). Active virus replication was detected in 10 patients with cardiac inflammation (1.5% of the whole study population). 7 patients (1.1% of the whole study population) were diagnosed with active myocarditis and 6 patients (0.9% of the whole study population) with giant cell myocarditis. Equivalent to patients with virus-negative cardiac inflammation, patients with the aforementioned types of inflammatory cardiomyopathies also presented mostly with HFrEF.

Overall, 38 patients (5.8%) had histological evidence of cardiac amyloidosis (CA). Further histological sub-specification revealed that 15 (2.3%) CA patients were diagnosed with immunoglobulin light chain cardiac amyloidosis (AL-CA) and 23 (3.5%) with transthyretin cardiac amyloidosis (ATTR-CA). Histological analysis revealed unspecific findings in overall 160 patients (24.4%). A detailed overview of all EMB findings in our patient population is depicted in Table 2, stratified for phenotype of HF.

Genotyping

All patients with ATTR-CA underwent additional genotyping to further analyze the underlying cause of ATTR-CA, revealing 17 patients with wild-type transthyretin amyloidosis (ATTRwt) and 6 patients with variant transthyretin amyloidosis (ATTRv). Besides patients with histological proven transthyretin amyloidosis, genotyping was also performed in 84 additional patients in whom a genetic cause was suspected following detailed counselling. Supplemental Table 1 provides an overview of the total numbers of performed genotyping stratified for EMB-based diagnosis. All detected mutations stratified for phenotype of HF are depicted in detail in Supplemental Table 2.

Survival of patients and predictors of all-cause mortality

After a median follow-up of 4.6 (2.5/6.6) years, 94 deaths were enumerated (HFrEF: 68; HFmrEF: 8; HFpEF: 18). This equated to mortality rates of 3.3% and 11.6% for patients with HFrEF, 7.7% and 15.4% for patients with HFmrEF and 5.3% and 11.4% for patients with HFpEF after 1 and 5 years, respectively (Fig. 1). The corresponding annualized event rates were 16 events/1 year and 57 events/5 years for patients with HFrEF, 4 events/1 year and 8 events/5 years for patients with HFmrEF and 6 events/1 year and 13 events/5 years for patients with HFpEF, respectively. Overall, 25 patients died out of hospital and 69 during hospitalization. All-cause mortality was significantly higher in patients presenting in NYHA functional class III or IV compared with patients presenting in NYHA functional class I or II as indicated by a hazard ratio of 2.18 (hazard ratio [HR] per unit increase [ui], 2.18, 95% CI, 1.41–3.37). After adjustment for age,

Table 1 Baseline characteristics stratified for phenotype of heart failure

Characteristics	HFrEF N=489	HFmrEF N=52	HFpEF N=114
Age [years]	56 (47/65)	53 (43/65)	53 (39/67)
Sex (female)—% (n)	29.7% (145)	34.6% (18)	24.6% (28)
BMI	27 (24/30.8)	27 (23/31.9)	26.1 (24.2/29.7)
<i>Cardiovascular risk factors</i>			
Diabetes—% (n)	17.6% (86)	23.1% (12)	12.3% (14)
Arterial hypertension % (n)	51% (249)	50% (26)	50.9% (58)
Dyslipidemia—% (n)	20.1% (98)	19.2% (10)	22.8% (26)
Family history of cardiovascular disease—% (n)	19.6% (96)	25% (13)	22.8% (26)
Smoking—% (n)	45.2% (221)	30.8% (16)	42.1% (48)
<i>Comorbidities</i>			
Atrial fibrillation—% (n)	14.5% (71)	9.6% (5)	7.1% (8)
Coronary artery disease ¹ —% (n)	14.9% (73)	9.6% (5)	18.4% (21)
Stroke—% (n)	4.5% (22)	9.6% (5)	4.4% (5)
Peripheral artery disease—% (n)	3.1% (15)	1.9% (1)	0.9% (1)
COPD—% (n)	9.4% (46)	0% (0)	4.4% (5)
Chronic kidney disease—% (n)	14.1% (69)	7.7% (4)	22.8% (26)
<i>Left ventricular structure/function</i>			
LV ejection fraction [%]	25 (20/35)	45 (45/45)	55 (55/60)
LV end-diastolic pressure (mmHg)	18 (13/26)	16 (12/23)	19 (13/23)
Troponin I [pg/ml]	21 (9/53)	55 (3/224)	29 (7/176)
BNP [pg/ml]	597 (184/1266)	152 (35/527)	159 (31/411)
<i>Signs and symptoms at presentation</i>			
NYHA I/II—% (n)	52.9% (259)	75% (39)	70.2% (80)
NYHA III/IV—% (n)	47.1% (230)	25% (13)	29.8% (34)
Angina pectoris—% (n)	22.9% (112)	30.8% (16)	32.5% (37)
Oedema—% (n)	23.1% (113)	11.5% (6)	18.4% (21)

Data are presented as relative and absolute frequencies of subjects for binary variables and median with 1st and 3rd quartile for continuous traits

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *BNP* brain natriuretic peptide, *LV* left ventricular, *NYHA* New York Heart Association

¹No history of myocardial infarction, and no relevant coronary stenosis requiring revascularization revealed by invasive coronary angiography

classical cardiovascular risk factors and comorbidities, only CA, age and NYHA functional class were independently associated with increased all-cause mortality (CA: HR_{perui} 3.13 [1.5–6.51]; $p=0.002$; Age: HR_{perui} 1.03 [1.00–1.06]; $p=0.026$; NYHA functional class III/IV: HR_{perui} 1.96 [1.11–3.54]; $p=0.02$) (Fig. 2). As cardiac inflammation in general as defined according to Caforio et al. [13] was not associated with all-cause mortality, we performed a subgroup analysis of patients with inflammatory cardiomyopathy (i.e. composite of active myocarditis; erythroparvovirus with inflammation; coxsackie with inflammation; giant cell myocarditis; virus-negative cardiac inflammation). Stratification of this subgroup according to markers of inflammation revealed that perforin-positive inflammation (compared with perforin-negative inflammation) was significantly associated with all-cause mortality in univariate regression analysis (HR_{perui} 2.28

95% [CI 1.04/4.95]; $p=0.038$), as well as after adjustment for age and sex (HR_{perui} 2.29 [95% CI 1.04/5.06]; $p=0.04$) (Supplemental Fig. 1).

Patient characteristics and outcome stratified for the presence of amyloidosis

We next stratified the study population for the presence of CA. Patients with CA were older compared to patients without CA (70 [65/76] vs. 55 [44/64]; $p<0.001$), had a higher prevalence of comorbidities like chronic kidney disease (44.7% vs. 13.7%; $p<0.001$) and history of stroke (13.2% vs. 4.5%; $p=0.023$) and showed a higher left ventricular ejection fraction based on echocardiographic examination (50% [40/55] vs. 30% [20/40]; $p<0.001$) as well as inter-ventricular septal thickness (1.6 cm [1.4/2.1] vs. 1.1 cm [1.0/1.5]; $p=0.002$). A detailed sample characterization

Table 2 Diagnosis based on EMB findings stratified for phenotype of heart failure

Characteristics	HFrEF N=489	HFmrEF N=52	HFpEF N=114
Unspecific finding—% (n)	24.3% (119)	26.9% (14)	23.7% (27)
Dilative Cardiomyopathy—% (n)	15.3% (75)	1.9% (1)	1.8% (2)
Hypertrophic cardiomyopathy—% (n)	1.2% (6)	1.9% (1)	7% (8)
Hypertensive heart disease—% (n)	0.6% (3)	0% (0)	0.9% (1)
ARVD—% (n)	0.2% (1)	1.9% (1)	0% (0)
Amyloidosis—% (n)	2.7% (13)	11.5% (6)	16.7% (19)
Sarcoidosis—% (n)	0.4% (2)	1.9% (1)	1.8% (2)
Post myocarditis—% (n)	9.4% (46)	11.5% (6)	6.1% (7)
Active myocarditis—% (n)	1% (5)	0% (0)	1.8% (2)
Erythroparvovirus without inflammation—% (n)	4.7% (23)	11.5% (6)	1.8% (2)
Erythroparvovirus with inflammation—% (n)	1.2% (6)	0% (0)	2.6% (3)
Coxsackie without inflammation—% (n)	0.6% (3)	1.9% (1)	0% (0)
Coxsackie with inflammation—% (n)	0.2% (1)	0% (0)	0% (0)
Erythroparvovirus/HHV reactivation without Inflammation—% (n)	1.8% (9)	5.8% (3)	1.8% (2)
Giant cell myocarditis—% (n)	0.8% (4)	0% (0)	1.8% (2)
Toxic cardiomyopathy—% (n)	0.8% (4)	0% (0)	0% (0)
Virus negative cardiac inflammation—% (n)	34.6% (169)	23.1% (12)	32.5% (37)

Data are presented as relative and absolute frequencies of subjects for binary variables. ARVD, arrhythmogenic right ventricular dysplasia

including comorbidities, cardiovascular risk factors as well as functional parameters and biomarker expressions stratified for the presence of amyloidosis, is provided in Table 3.

With respect to outcome, 1- and 5-year mortality rates were substantially higher in patients with CA compared to patients without CA (CA: 23.7% and 52.6% vs. no CA: 3.1% and 10.4%) as outlined in Fig. 3. The annualized event rates were 9 events/1 year and 20 events/5 years for patients with CA and 19 events/1 year and 65 events/5 years for patients without CA. Stratification of patients diagnosed with CA according to the subtype of amyloidosis (i.e. ATTRwt, ATTRv and AL-CA) revealed that 10 patients diagnosed with AL-CA, 5 patients diagnosed with ATTRwt and 2 patients diagnosed with ATTRv died during the observation period. Further stratification of patients without amyloidosis according to the most recent endomyocardial biopsy diagnoses (i.e. DCM, virus-negative cardiac inflammation, unspecific findings and others) revealed no statistically significant differences with respect to median survival. None of the patients diagnosed with giant cell myocarditis died during the observation period.

Discussion

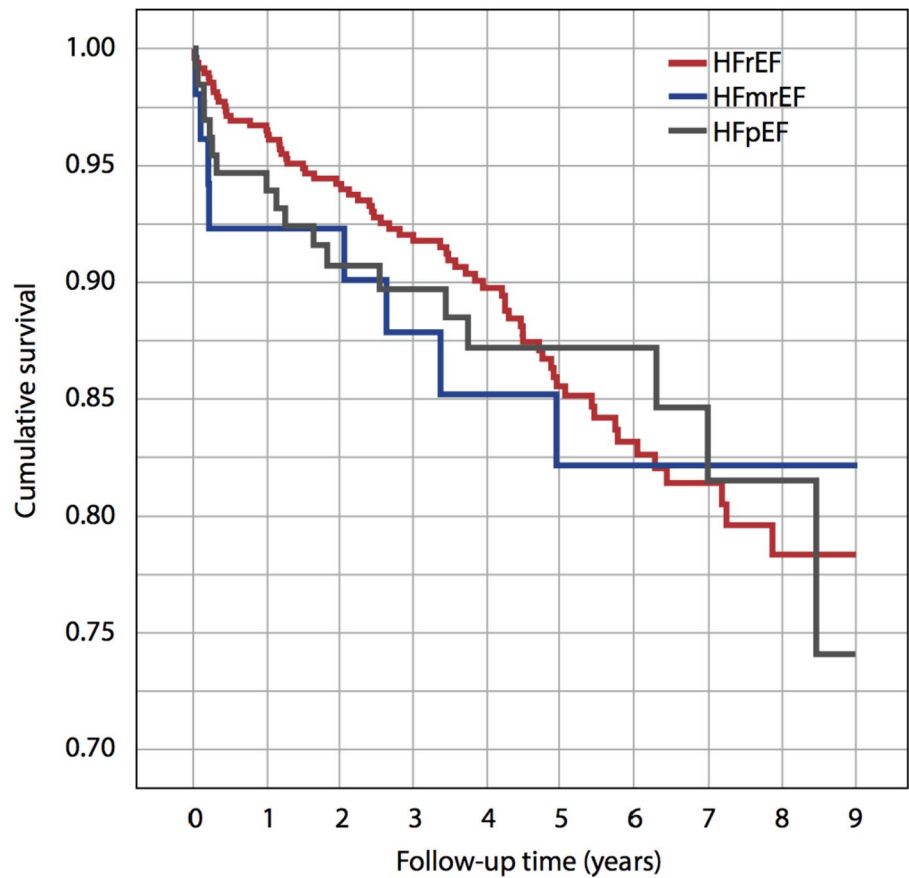
The main findings of the present analysis are: (i) EMB revealed cardiac inflammation in the majority of cases in our all-comer population of unexplained HF, mostly virus-negative; (ii) cardiac amyloidosis (including both, transthyretin

amyloidosis as well as light-chain amyloidosis) was diagnosed in 5.8% of all cases of HF of unexplained etiology; and (iii) NYHA functional class III + IV, age and cardiac amyloidosis were independently associated with all-cause mortality in our study.

Etiology of heart failure

The underlying causes of DCM-like HFrEF can be stratified in genetic and non-genetic. Since 160 patients (24.4%) showed unspecific EMB findings, genotyping might facilitate the diagnosis of the underlying cause of HF in these patients, although genetic testing is currently only recommended if a genetic cause is suspected following appropriate counselling [14]. Familial forms account for approximately 30–50% of all cases of DCM. In western populations, the genetic nature of cardiomyopathies with subsequent HF may easily be obscured considering the rather small size of contemporary families. Therefore, it is important to consider that also sporadic DCM cases can be due to (spontaneous) genetic mutations [15]. To date, variants in over 50 genes have been identified to be associated with DCM, with the evidence being strongest for titin (TTN), beta myosin heavy chain (MYH7), troponin2 (TNNT2) and the nuclear envelope gene lamin A/C (LMNA). All of these mutations accounted for the majority of detected mutations in our present analysis. Interestingly, Lota et al. recently provided evidence that DCM as well as arrhythmogenic cardiomyopathy-associated genetic variants are detectable in up to

Fig. 1 Long-term survival stratified for phenotype of heart failure. Kaplan–Meier curves indicating cumulative survival are displayed for patients with heart failure with reduced ejection fraction, heart failure with mildly reduced ejection fraction and heart failure with preserved ejection fraction



Number at risk	0	1	2	3	4	5	6	7	8	9
HFrEF	489	473	408	360	289	218	153	105	53	9
HFmrEF	52	48	43	39	30	26	22	14	6	2
HFpEF	114	107	87	69	56	46	33	22	11	2

eight percent of patients with acute myocarditis. This finding highlights the potential role of genetic sequencing in patients presenting with acute myocarditis and supports the concept that at least some genotype-positive individuals may remain phenotypically silent until the occurrence of an environmental trigger [16]. We are not able to confirm these results in our study, since patients diagnosed with acute myocarditis did not undergo additional genotyping.

Once considered an orphan disease, recent studies have indicated that CA is quite common in selected patient populations and that it increases with age [17]. Most of these studies solely focused on populations with a high pre-test probability of CA. According to the results of these studies, prevalence of ATTRwt-CA was 6.3 to 33% in elderly patients with HFpEF [18–22], 9.3 to 11% in patients with HFmrEF/HFrEF [23, 24], 4 to 16% in elderly patients with aortic stenosis referred to hospital for surgical aortic valve replacement or transcatheter aortic valve replacement [25–29], 5 to 9% in elderly patients with a phenotype of hypertrophic cardiomyopathy [30, 31] and 3 to 10% in

elderly patients undergoing carpal tunnel syndrome surgery [32–34].

Compared with the prevalence of CA reported in the above-mentioned meta-analysis [17], the prevalence detected in our study is lower (5.8%) across the whole spectrum of LVEF [18–20, 23, 24]. This is most likely attributable to the significantly younger population investigated in our study. 60.5% of our patients diagnosed with CA had ATTR-CA and 39.5% had AL-CA. This aligns with the published evidence: In six of the eight earlier studies on that topic, only ATTR-CA was detected, whereas two studies indicated that 20% [19] and 40% [22] of HFpEF patients diagnosed with CA had AL-CA, respectively.

Outcome of patients with heart failure and predictors of all-cause mortality

Considering the phenotype of HF, survival rate is equivalent to or worse than many forms of cancer [35], and slightly higher in patients with HFrEF compared to HFpEF [36, 37].

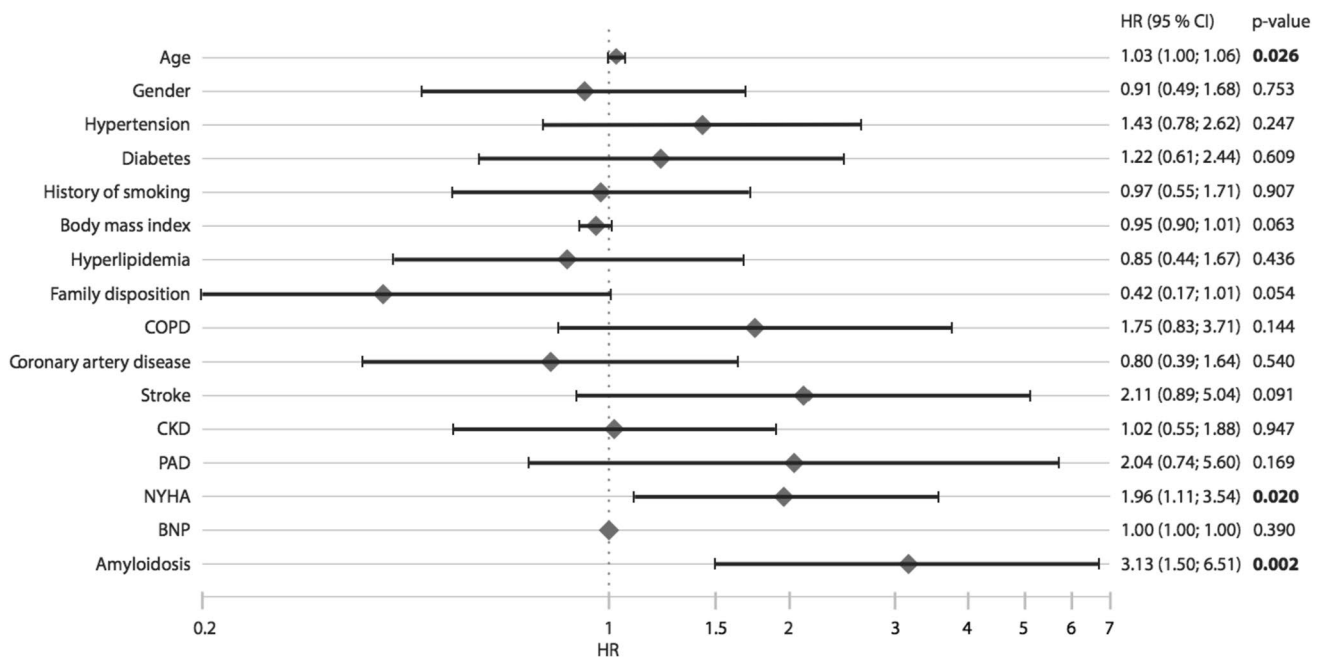


Fig. 2 Predictors of all-cause mortality. Multivariate linear regression analysis was performed to investigate the association of cardiac amyloidosis with overall mortality, adjusting for age, sex, arterial hypertension, diabetes mellitus, history of smoking, body mass index, hyperlipidemia, family disposition, chronic obstructive pulmonary disease, coronary artery disease, stroke, chronic kidney disease,

peripheral artery disease, amyloidosis and NYHA functional class. *HR* indicates hazard ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *PAD* peripheral artery disease, *BNP* brain natriuretic peptide, *NYHA* New York Heart Association functional class

Mortality rates significantly increase with age [38, 39] as indicated by 1-year and 5-year survival rates of 91.5% and 78.8% for people aged < 65 years and 83.3% and 49.5% for patients aged > 75 years [39]. Besides age, severity of HF as indicated by NYHA functional class is one of the most important clinical predictors of mortality in HF [40]. In our study, we recapitulated the importance of both age and NYHA class for outcomes. Body mass index was inversely associated with mortality, confirming the obesity paradox indicating worse outcome for individuals with low BMI [41] (see Fig. 2). The relatively young age of patients included in our analysis probably also accounts for the markedly lower prevalence of risk factors and comorbidities compared to other studies reporting on survival of patients with HF [36, 38]. This is of great importance as the burden of comorbidities in patients with HF increases with age and significantly impacts on survival [42].

With respect to non-genetic causes, chronic inflammatory responses represent a subtype of primary acquired DCM and EMB may help to detect possible underlying pathologies [43–45]. Both human herpesvirus 6 (HHV6) and erythroparvovirus B19 (B19V) account for most of virus-related inflammation, which is in line with the results of our present analysis. Development of subclinical myocarditis may be a sequel of chronic viral infection, leading to the progression from acute myocarditis to DCM.

Kühl et al. reported that in individuals with a DCM-phenotype and increased pre-test probability of a history of viral myocarditis, viral genomes could be detected in endomyocardial biopsies in almost 67% of the patients [46]. The fact that 45.8% of the present study sample were diagnosed with cardiac inflammation emphasizes the involvement of immune responses in patients with non-ischemic HF. Spontaneous resolution of acute myocarditis associated with a substantial improvement in left ventricular ejection fraction and HF can be expected in up to 60% of patients. Data regarding the development of DCM following acute myocarditis are inconsistent. Prevalence estimates range from 14 to 52% [47, 48], making an inevitable sequence of events from myocarditis to inflammatory cardiomyopathy to DCM debatable.

In our study, perforin-positive cardiac inflammation was associated with worse outcome in a multivariate analysis adjusted for sex and age, recapitulating earlier findings by Escher et al. [49] Evidence of any type of cardiac inflammation in EMB, regardless of severity, was not associated with all-cause mortality in our population which was not preselected for high pretest probability of (post)myocarditis. Immunosuppressive therapy of virus-negative inflammatory cardiomyopathy has been investigated in the TIMIC study suggesting positive effects only in selected patients [50], a concept that is supported by the results of our study.

Table 3 Patient characteristics stratified for presence of cardiac amyloidosis

Characteristics	CA N=38	No CA N=627	p value
Age [years]	70 (65/76)	55 (44/64)	<0.001
Sex (female)—% (n)	18.4% (7)	29.8% (187)	0.096
BMI	25.3 (24.1/28.7)	26.9 (24/30.9)	0.215
<i>Cardiovascular risk factors</i>			
Diabetes—% (n)	29% (11)	16.8% (105)	0.082
Arterial hypertension—% (n)	63.2% (24)	50.7% (318)	0.255
Dyslipidemia—% (n)	26.3% (10)	20.1% (126)	0.462
Family history of cardiovascular disease—% (n)	10.5% (4)	21.2% (133)	0.10
Smoking—% (n)	26.3% (10)	44.5% (279)	0.015
<i>Comorbidities</i>			
Coronary artery disease ¹ —% (n)	39.5% (15)	14% (88)	<0.001
Stroke—% (n)	13.2% (5)	4.5% (28)	0.023
Peripheral artery disease—% (n)	2.6% (1)	2.9% (18)	0.891
COPD—% (n)	13.2% (5)	8.1% (51)	0.334
Chronic kidney disease—% (n)	44.7% (17)	13.7% (86)	<0.001
<i>Left ventricular structure/function</i>			
LV ejection fraction [%]	50 (40/55)	30 (20/40)	<0.001
LV end-diastolic pressure (mmHg)	21 (17/25)	18 (13/25)	0.426
IVSED (cm)	1.6 (1.4/2.1)	1.1 (1/1.5)	0.002
Troponin I [pg/ml]	104 (45/239)	21 (8/59)	0.647
BNP [pg/ml]	456 (247/836)	408 (100/1,185)	0.352
<i>Signs and symptoms at presentation</i>			
NYHA I/II—% (n)	50% (19)	58.2% (365)	0.264
NYHA III/IV—% (n)	50% (19)	41.8% (262)	
Angina pectoris—% (n)	13.2% (5)	25.7% (161)	0.06
Oedema—% (n)	29% (11)	20.9% (131)	0.331

A p-value < 0.05 marked in bold letters suggests statistical significance

Data are presented as relative and absolute frequencies of subjects for binary variables and median with 1st and 3rd quartile for continuous traits

BMI body mass index, COPD chronic obstructive pulmonary disease, BNP brain natriuretic peptide, LV left ventricular, NYHA New York Heart Association, IVSED interventricular septal thickness end-diastolic

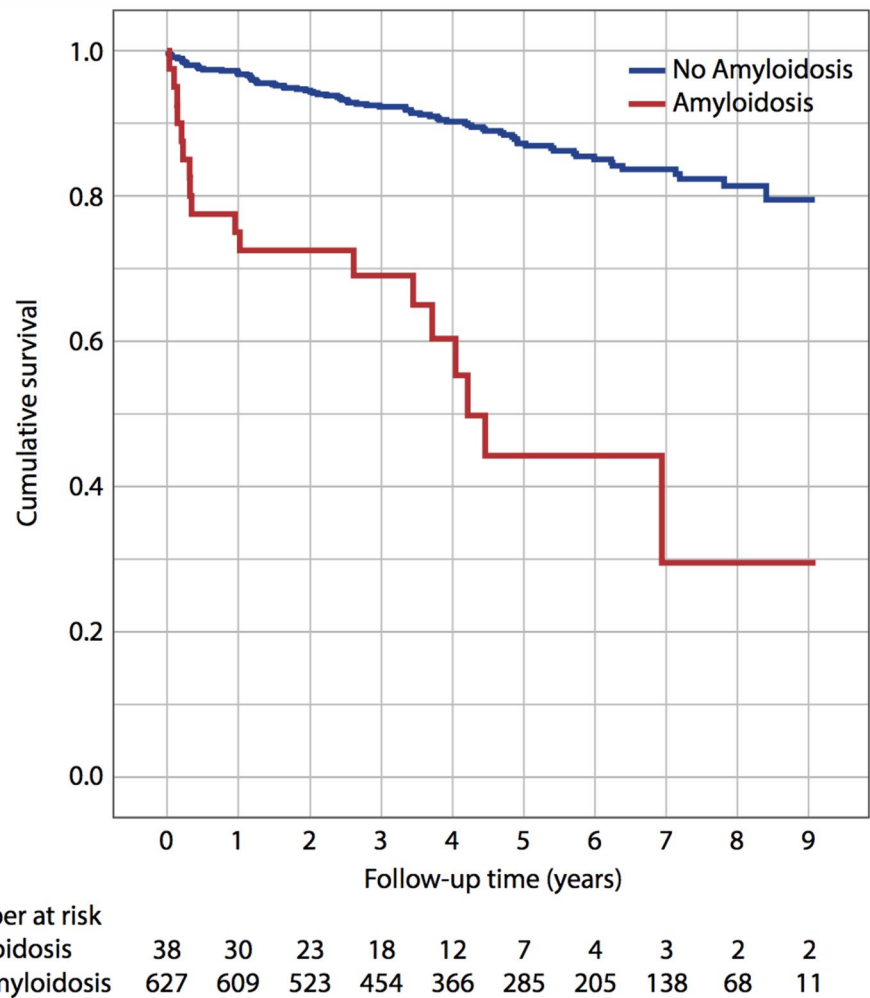
¹No history of myocardial infarction, and no relevant coronary stenosis revealed by invasive coronary angiography

Interestingly, patients with CA showed high 1- and 5-year mortality rates, and evidence of CA was independently associated with mortality in our population, even after multiple adjustments for possible confounders. As cardiac involvement has a major prognostic impact in amyloidosis, current staging systems incorporate the extent of cardiac involvement as measured by serum markers in both AL-CA [51–53] and ATTR-CA [54]. Contemporary treatment options have significantly improved survival of patients not only with AL amyloidosis [55] but also with ATTR amyloidosis [56]. Survival of patients with ATTR-CA is significantly better in patients with early-stage ATTR-CA (> 100 months) compared to more advanced stages [57]. An early diagnosis is, therefore, mandatory in both AL-CA and ATTR-CA, a concept that is further supported by our study.

Diagnostic considerations

According to current guidelines, the diagnosis of HF requires the presence of symptoms and/or signs of HF as well as objective evidence of cardiac dysfunction [3]. The proposed diagnostic algorithm includes an evaluation of risk factors, symptoms and signs of HF, electrocardiogram, measurement of natriuretic peptides (i.e. NT-proBNP or BNP), as well as echocardiographic examination to stratify for HF_rEF, HF_mrEF and HF_pEF. Further imaging modalities like cardiac magnetic resonance (CMR) as well as invasive testing (i.e. coronary angiography and endomyocardial biopsy) should only be considered under appropriate conditions. For example, invasive coronary angiography is solely recommended in patients with angina despite pharmacological therapy or symptomatic ventricular arrhythmias (class I,

Fig. 3 Long-term survival stratified for presence of cardiac amyloidosis. Kaplan–Meier curves indicating cumulative survival are displayed for patients with cardiac amyloidosis and those without cardiac amyloidosis



level of evidence B) and endomyocardial biopsy should be considered in patients with rapidly progressive HF despite standard therapy and a high probability of a specific diagnosis (class IIa, level of evidence C). In our study, indication to perform EMB was based on the EMB guidelines that date back to 2007 [4]. Given the potential impact of EMB on risk stratification and disease management of non-ischemic and non-valvular HF, the results of our study call for new prospective trials to test the usefulness of a holistic work-up of HF including EMB to increase the level of evidence.

Conclusion

The results of the present study demonstrate that incidental finding of cardiac amyloidosis represents a relevant differential diagnosis in an all-comer population with new onset of non-ischemic and non-valvular heart failure, being the underlying cause of HF in 5.8%. The relatively low 1- and 5-year mortality rates documented in the current study are probably attributable to the relatively young patient

population, the low prevalence of comorbidities compared with other HF studies, and the exclusion of patients with ischemic heart failure. As CA was independently associated with excess mortality, our study underscores the need to improve screening methods that allow the diagnosis of CA at a very early stage, especially in light of the recently established causal/specific therapeutic options, that have proven to improve outcomes of CA.

Limitations

The limitations of our retrospective monocentric study include lack of extended clinical data for all of the patients covered in this study and potential selection bias. Patients included in the present analysis were mainly of Caucasian ethnicity, which may limit the applicability of our findings to other ethnic groups. Furthermore, we were not able to provide information about causes of death and on recurrent heart failure related hospitalizations. The provided prevalence in the present study should also be interpreted with

caution considering the retrospective study design, and HF practitioners should be mindful to apply our findings to their daily practice. Instead, our study suggests that prospective trials are needed to test the added value of a systematic and holistic work-up of HF of unknown etiology to improve diagnosis and management of HF.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00392-023-02354-6>.

Acknowledgements This manuscript contains results that are part of the medical doctoral thesis work of Anne Sophie Braun. We would like to thank Irene Bell (graphic designer) and Elisabeth Bell for figure creation.

Funding Open Access funding enabled and organized by Projekt DEAL. P.W. was supported by grants from the German Federal Ministry for Education and Research (BMBF 01EO1503). T.G., T.M. and P.W. are Principal Investigators of the German Center for Cardiovascular Research (DZHK).

Data availability The data and methods used to conduct the research in this study will be made available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. TM, KK, MMG, OH, FE, MB and HPS report no conflict of interest. SG reports having received consultancy and lecture honoraria from Pfizer, AstraZeneca, ZOLL, Boehringer Ingelheim, Bristol-Myers Squibb, Alnylam and Novartis. TG has received grant support (CARIMA study) and speaker's honoraria from Novartis, speaker's honoraria from Boehringer Ingelheim, Daiichi-Sankyo, MSD, Pfizer, Bristol-Myers Squibb and Astra Zeneca. PW has received consultancy and lecture honoraria from Abbott, Abiomed, Astra Zeneca, Bayer, Boehringer-Ingelheim, CVRx, Daiichi-Sankyo, Novartis, Pfizer and Servier.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Disease GBD, Injury I, Prevalence C (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392:1789–1858
2. Sotiriou E, Heiner S, Jansen T, Brandt M, Schmidt KH, Kreitner KF, Emrich T, Schultheiss HP, Schulz E, Munzel T, Wenzel P (2018) Therapeutic implications of a combined diagnostic workup including endomyocardial biopsy in an all-comer population of patients with heart failure: a retrospective analysis. *ESC Heart Fail* 5:630–641
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 42:3599–3726
4. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R (2007) The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *Eur Heart J* 28:3076–3093
5. Seferovic PM, Tsutsui H, McNamara DM, Ristic AD, Basso C, Bozkurt B, Cooper LT Jr, Filippatos G, Ide T, Inomata T, Klingel K, Linhart A, Lyon AR, Mehra MR, Polovina M, Milinkovic I, Nakamura K, Anker SD, Veljic I, Ohtani T, Okumura T, Thum T, Tschope C, Rosano G, Coats AJS, Starling RC (2021) Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy. *Eur J Heart Fail* 23:854–871
6. Kawai C, Kitaura Y (1977) New endomyocardial biopsy catheter for the left ventricle. *Am J Cardiol* 40:63–65
7. Richardson PJ (1974) King's endomyocardial biptome. *Lancet* 1:660–661
8. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, Hill S, Mahrholdt H, Voehringer M, Schieber M, Klingel K, Kandolf R, Bohm M, Sechtem U (2010) Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. *Circulation* 122:900–909
9. Stiermaier T, Fahrenbach F, Klingel K, Kandolf R, Boudriot E, Sandri M, Linke A, Rommel KP, Desch S, Schuler G, Thiele H, Lurz P (2017) Biventricular endomyocardial biopsy in patients with suspected myocarditis: feasibility, complication rate and additional diagnostic value. *Int J Cardiol* 230:364–370
10. Chimenti C, Frustaci A (2013) Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. *Circulation* 128:1531–1541
11. Gobel S, Schwuchow-Thonke S, Jansen T, Karbach S, Emrich T, Gori T, Knies F, Schulz E, Munzel T, Keller K, Wenzel P (2020) Safety of transradial and transfemoral left ventricular compared with transfemoral right ventricular endomyocardial biopsy. *ESC Heart Fail* 7(6):4015–4023
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 16:233–270
13. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A,

- Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on M and Pericardial D (2013) Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 34:2636–2648
14. Catchpool M, Ramchand J, Martyn M, Hare DL, James PA, Trainer AH, Knight J, Goranitis I (2019) A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy. *Genet Med* 21:2815–2822
 15. McNally EM, Golbus JR, Puckelwartz MJ (2013) Genetic mutations and mechanisms in dilated cardiomyopathy. *J Clin Invest* 123:19–26
 16. Lota AS, Hazebroek MR, Theotokis P, Wassall R, Salmi S, Halliday BP, Tayal U, Verdonshot J, Meena D, Owen R, de Marvao A, Iacob A, Yazdani M, Hammersley DJ, Jones RE, Wage R, Buchan R, Vivian F, Hafouda Y, Noseda M, Gregson J, Mittal T, Wong J, Robertus JL, Baksi AJ, Vassiliou V, Tzoulaki I, Pantazis A, Cleland JGF, Barton PJR, Cook SA, Pennell DJ, Garcia-Pavia P, Cooper LT Jr, Heymans S, Ware JS, Prasad SK (2022) Genetic architecture of acute myocarditis and the overlap with inherited cardiomyopathy. *Circulation* 146:1123–1134
 17. Aimo A, Merlo M, Porcari A, Georgiopoulos G, Pagura L, Vergaro G, Sinagra G, Emdin M and Rapezzi C (2022) Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail* 24(12):2342–2351
 18. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P (2015) Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 36:2585–2594
 19. Hahn VS, Yanek LR, Vaishnav J, Ying W, Vaidya D, Lee YZJ, Riley SJ, Subramanya V, Brown EE, Hopkins CD, Ononogbu S, Perzel Mandell K, Halushka MK, Steenbergen C Jr, Rosenberg AZ, Tedford RJ, Judge DP, Shah SJ, Russell SD, Kass DA, Sharma K (2020) Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail* 8:712–724
 20. Lindmark K, Pilebro B, Sundstrom T, Lindqvist P (2021) Prevalence of wild type transthyretin cardiac amyloidosis in a heart failure clinic. *ESC Heart Fail* 8:745–749
 21. AbouEzzeddine OF, Davies DR, Scott CG, Fayyaz AU, Askew JW, McKie PM, Noseworthy PA, Johnson GB, Dunlay SM, Borlaug BA, Chareonthaitawee P, Roger VL, Dispenzieri A, Grogan M, Redfield MM (2021) Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. *JAMA Cardiol* 6:1267–1274
 22. Bennani Smires Y, Victor G, Ribes D, Berry M, Cagnet T, Mejean S, Huart A, Roussel M, Petermann A, Roncalli J, Carrie D, Rousseau H, Berry I, Chauveau D, Galinier M, Lairez O (2016) Pilot study for left ventricular imaging phenotype of patients over 65 years old with heart failure and preserved ejection fraction: the high prevalence of amyloid cardiomyopathy. *Int J Cardiovasc Imaging* 32:1403–1413
 23. Goland S, Volodarsky I, Fabricant Y, Livschitz S, Tshori S, Cuciuc V, Zilberman L, Fugenfirov I, Meledin V, Shimoni S, Josfberg S, George J (2021) Wild-type TTR amyloidosis among patients with unexplained heart failure and systolic LV dysfunction. *PLoS One* 16:e0254104
 24. Lopez-Sainz A, de Haro-Del Moral FJ, Dominguez F, Restrepo-Cordoba A, Amor-Salamanca A, Hernandez-Hernandez A, Ruiz-Guerrero L, Krsnik I, Cobo-Marcos M, Castro V, Toquero-Ramos J, Lara-Pezzi E, Fernandez-Lozano I, Alonso-Pulpon L, Gonzalez-Lopez E, Garcia-Pavia P (2019) Prevalence of cardiac amyloidosis among elderly patients with systolic heart failure or conduction disorders. *Amyloid* 26:156–163
 25. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, Roberts N, Hutt DF, Rowczenio DM, Whelan CJ, Ashworth MA, Gillmore JD, Hawkins PN and Moon JC (2016) Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. *Circ Cardiovasc Imaging* 9(8):e005066. PMID:27511979. <https://doi.org/10.1161/CIRCIMAGING.116.005066>
 26. Singal AK, Bansal R, Singh A, Dorbala S, Sharma G, Gupta K, Saxena A, Bhargava B, Karthikeyan G, Ramakrishnan S, Bisoi AK, Hote MP, Rajashekar P, Chowdhury UK, Devagourou V, Patel C, Ray R, Arawa SK, Mishra S (2021) Concomitant transthyretin amyloidosis and severe aortic stenosis in elderly Indian population: a pilot study. *JACC CardioOncol* 3:565–576
 27. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, Wollenweber T, Ahmed N, Thornton GD, Kelion AD, Sabharwal N, Newton JD, Ozkor M, Kennon S, Mullen M, Lloyd G, Fontana M, Hawkins PN, Pugliese F, Menezes LJ, Moon JC, Mascherbauer J, Treibel TA (2021) Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J Am Coll Cardiol* 77:128–139
 28. Castano A, Narotsky DL, Hamid N, Khaliq OK, Morgenstern R, DeLuca A, Rubin J, Chiuhan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS (2017) Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 38:2879–2887
 29. Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, Hartman N, Hawkins PN, Menezes LJ, Moon JC (2018) Prevalence of cardiac amyloidosis in patients referred for transcatheter aortic valve replacement. *J Am Coll Cardiol* 71:463–464
 30. Damy T, Costes B, Hagege AA, Donal E, Eicher JC, Slama M, Guellich A, Rappeneau S, Gueffet JP, Logeart D, Plante-Bordeneuve V, Bouvaist H, Huttin O, Mulak G, Dubois-Rande JL, Goossens M, Canoui-Poitrine F, Buxbaum JN (2016) Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J* 37:1826–1834
 31. Maurizi N, Rella V, Fumagalli C, Salerno S, Castelletti S, Dagradi F, Torchio M, Marceca A, Meda M, Gasparini M, Boschi B, Girolami F, Parati G, Olivotto I, Crotti L, Cecchi F (2020) Prevalence of cardiac amyloidosis among adult patients referred to tertiary centres with an initial diagnosis of hypertrophic cardiomyopathy. *Int J Cardiol* 300:191–195
 32. Vianello PF, La Malfa G, Tini G, Mazzola V, Miceli A, Santolini E, Briano S, Porto I, Canepa M (2021) Prevalence of transthyretin amyloid cardiomyopathy in male patients who underwent bilateral carpal tunnel surgery: the ACTUAL study. *Int J Cardiol* 329:144–147
 33. Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA, Shapiro D, Evans PJ, Maschke S, Kilpatrick SE, Tan CD, Rodriguez ER, Monteiro C, Tang WHW, Kelly JW, Seitz WH Jr, Hanna M (2018) Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol* 72:2040–2050
 34. Zegri-Reiriz I, de Haro-Del Moral FJ, Dominguez F, Salas C, de la Cuadra P, Plaza A, Krsnik I, Gonzalez-Lopez E, Garcia-Pavia P (2019) Prevalence of cardiac amyloidosis in patients with carpal tunnel syndrome. *J Cardiovasc Transl Res* 12:507–513
 35. Askoxylakis V, Thieke C, Pleger ST, Most P, Tanner J, Lindel K, Katus HA, Debus J, Bischof M (2010) Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. *BMC Cancer* 10:105

36. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 355:251–259
37. Meta-analysis Global Group in Chronic Heart F (2012) The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 33:1750–1757
38. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL (2015) A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 175:996–1004
39. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ (2019) Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 21:1306–1325
40. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Doughty RN and Meta-Analysis Global Group in Chronic Heart F (2013) Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 34:1404–1413
41. Zhang J, Begley A, Jackson R, Harrison M, Pellicori P, Clark AL, Cleland JGF (2019) Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction: a dose-response meta-analysis. *Clin Res Cardiol* 108:119–132
42. Screever EM, van der Wal MHL, van Veldhuisen DJ, Jaarsma T, Koops A, van Dijk KS, Warink-Riemersma J, Coster JE, Westenbrink BD, van der Meer P, de Boer RA, Meijers WC (2023) Comorbidities complicating heart failure: changes over the last 15 years. *Clin Res Cardiol* 112:123–133
43. Weintraub RG, Semsarian C, Macdonald P (2017) Dilated cardiomyopathy. *Lancet* 390:400–414
44. Dec GW, Fuster V (1994) Idiopathic dilated cardiomyopathy. *N Engl J Med* 331:1564–1575
45. Mahrholdt H, Wagner A, Deluigi CC, Kispert E, Hager S, Meinhardt G, Vogelsberg H, Fritz P, Dippon J, Bock CT, Klingel K, Kandolf R, Sechtem U (2006) Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. *Circulation* 114:1581–1590
46. Kuhl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, Poller W, Kandolf R, Schultheiss HP (2005) High prevalence of viral genomes and multiple viral infections in the myocardium of adults with “idiopathic” left ventricular dysfunction. *Circulation* 111:887–893
47. Dec GW Jr, Palacios IF, Fallon JT, Aretz HT, Mills J, Lee DC, Johnson RA (1985) Active myocarditis in the spectrum of acute dilated cardiomyopathies. Clinical features, histologic correlates, and clinical outcome. *N Engl J Med* 312:885–890
48. D’Ambrosio A, Patti G, Manzoli A, Sinagra G, Di Lenarda A, Silvestri F, Di Sciascio G (2001) The fate of acute myocarditis between spontaneous improvement and evolution to dilated cardiomyopathy: a review. *Heart* 85:499–504
49. Escher F, Kuhl U, Lassner D, Stroux A, Gross U, Westermann D, Pieske B, Poller W, Schultheiss HP (2017) High perforin-positive cardiac cell infiltration and male sex predict adverse long-term mortality in patients with inflammatory cardiomyopathy. *J Am Heart Assoc.* <https://doi.org/10.1161/JAHA.116.005352>
50. Frustaci A, Russo MA, Chimenti C (2009) Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 30:1995–2002
51. Dispenzieri A, Gertz MA, Kyle RA, Lacy MQ, Burritt MF, Therneau TM, Greipp PR, Witzig TE, Lust JA, Rajkumar SV, Fonseca R, Zeldenrust SR, McGregor CG, Jaffe AS (2004) Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 22:3751–3757
52. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T, Foli A, Foard D, Milani P, Rannigan L, Hegenbart U, Hawkins PN, Merlini G, Palladini G (2013) A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood* 121:3420–3427
53. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, Zeldenrust SR, Leung N, Dingli D, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Gertz MA (2012) Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 30:989–995
54. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, Quarta CC, Rezk T, Whelan CJ, Gonzalez-Lopez E, Lane T, Gilbertson JA, Rowczenio D, Petrie A, Hawkins PN (2018) A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 39:2799–2806
55. Muchtar E, Gertz MA, Kumar SK, Lacy MQ, Dingli D, Buadi FK, Grogan M, Hayman SR, Kapoor P, Leung N, Fonder A, Hobbs M, Hwa YL, Gonsalves W, Warsame R, Kourelis TV, Russell S, Lust JA, Lin Y, Go RS, Zeldenrust S, Kyle RA, Rajkumar SV, Dispenzieri A (2017) Improved outcomes for newly diagnosed AL amyloidosis between 2000 and 2014: cracking the glass ceiling of early death. *Blood* 129:2111–2119
56. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, Investigators A-AS (2018) Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 379:1007–1016
57. Law S, Bezard M, Petrie A, Chacko L, Cohen OC, Ravichandran S, Ogunbiyi O, Kharoubi M, Ganeshanathan S, Ganeshanathan S, Gilbertson JA, Rowczenio D, Wechalekar A, Martinez-Naharro A, Lachmann HJ, Whelan CJ, Hutt DF, Hawkins PN, Damy T, Fontana M, Gillmore JD (2022) Characteristics and natural history of early-stage cardiac transthyretin amyloidosis. *Eur Heart J* 43:2622–2632