Prevalence and determinants of systolic and diastolic cardiac dysfunction and heart failure in acute ischemic stroke patients: The SICFAIL study

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Abstract

Aims Ischaemic stroke (IS) might induce alterations of cardiac function. Prospective data on frequency of cardiac dysfunction and heart failure (HF) after IS are lacking. We assessed prevalence and determinants of diastolic dysfunction (DD), systolic dysfunction (SD), and HF in patients with acute IS.

Methods and results The Stroke-Induced Cardiac FAILure in mice and men (SICFAIL) study is a prospective, hospital-based cohort study. Patients with IS underwent a comprehensive assessment of cardiac function in the acute phase (median 4 days after IS) including clinical examination, standardised transthoracic echocardiography by expert sonographers, and determination of blood-based biomarkers. Information on demographics, lifestyle, risk factors, symptoms suggestive of HF, and medical history was collected by a standardized personal interview. Applying current guidelines, cardiac dysfunction was classified based on echocardiographic criteria into SD (left ventricular ejection fraction $< 52\%$ in men or $< 54\%$ in women) and DD (3 signs of DD in patients without SD). Clinically overt HF was classified into HF with reduced, mid-range, or preserved ejection fraction. Between January 2014 and February 2017, 696 IS patients were enrolled. Of them, patients with sufficient echocardiographic data on SD were included in the analyses ($n = 644$ patients [median age 71 years (interquartile range 60–78), 61.5\% male]). In these patients, full assessment of DD was feasible in 549 patients without SD (94\%). Prevalence of cardiac dysfunction and HF was as follows: SD 9.6\% [95\% confidence interval (CI) 7.6–12.2\%]; DD in patients without SD 23.3\% (95\% CI 20.0–27.0\%); and clinically overt HF 5.4\% (95\% CI 3.9–7.5\%)[1] with subcategories of HF with preserved ejection fraction 4.35\%, HF with mid-range ejection fraction 0.31\%, and HF with reduced ejection fraction 0.78\%. In multivariable analysis, SD and fulfilment of HF criteria were associated with history of coronary heart disease (SD: odds ratio (OR) 3.87, 95\% CI 1.93–7.75, $P = 0.0001$; HF: OR 2.29, 95\% CI 1.04–5.05, $P = 0.0406$) and high-sensitive troponin T at baseline (SD: OR 1.78, 95\% CI 1.31–2.42, $P = 0.0003$; HF: OR 1.66, 95\% CI 1.17–2.33, $P = 0.004$); DD was associated with older age (OR 1.08, 95\% CI 1.05–1.11, $P < 0.0001$) and treated hypertension vs. no hypertension (OR 2.84, 95\% CI 1.23–6.54, $P = 0.0405$).

Conclusions A substantial proportion of the study population exhibited subclinical and clinical cardiac dysfunction. SICFAIL provides reliable data on prevalence and determinants of SD, DD, and clinically overt HF in patients with acute IS according to current guidelines, enabling further clarification of its aetiological and prognostic role.

Keywords Stroke; Heart failure; Cardiac dysfunction| Brain natriuretic peptide; Troponin

Received: 26 February 2020; Revised: 24 October 2020; Accepted: 15 November 2020
Introduction

Cardiac diseases are well-established risk factors for ischaemic stroke (IS), causing about 25% of all events. In particular, the presence of heart failure (HF) increases the risk of IS. Patients with HF also have a higher incidence of recurrent stroke and higher mortality rates and may experience more severe strokes with subsequent worse functional outcome. Functional markers of cardiac dysfunction such as reduced left ventricular ejection fraction (LVEF) are also risk factors of IS, independently of the presence of clinical symptoms. Accumulating evidence suggests that cerebrovascular disorders may also alter cardiac function. For example, a recent animal study showed that cerebral ischaemia leads to the development of chronic left ventricular systolic dysfunction (SD) driven by increased sympathetic activity.

Precise estimates of frequency of different types of cardiac dysfunction and HF in patients with IS may contribute to detect cardiac co-morbidities requiring adequate action and to better estimate the extent of further cardiac investigation. However, conflicting data exist on the frequency of cardiac dysfunction in patients with IS. Previous studies reported prevalence rates of HF or reduced LVEF ranging between 3.8–17.7% and 12.6–24% respectively, but comparability is limited due to heterogeneous study designs comprising different stroke populations, various definitions of HF, and diverse rates of cardiac diagnostic uptake. Furthermore, as state-of-the-art echocardiographic examination and detailed cardiac phenotyping including blood-based biomarkers were not available in previous studies, it was not possible to reliably classify the type of SD and left ventricular diastolic dysfunction (DD) according to current guidelines. In addition, data on determinants of cardiac dysfunction in IS patients are lacking.

Therefore, we aimed to prospectively quantify the prevalence and determinants of SD, DD, and clinically overt HF in patients with acute IS applying standardized diagnostic criteria according to current guidelines.

Methods

Study design

The prospective, hospital-based Stroke-Induced Cardiac FAILure in mice and men (SICFAIL) study is an investigator-initiated cohort with ongoing long-term follow-up aiming to describe the natural course of cardiac function after IS (clinical trial registration: DRKS00011615). Consecutive patients with acute IS were recruited at the Stroke Unit of the Department of Neurology, University Hospital Würzburg, Germany, between January 2014 and February 2017. Inclusion criteria were the diagnosis of acute IS according to the World Health Organization definition, age ≥ 18 years, and provision of informed consent. Exclusion criteria were the participation in an acute interventional study and final diagnosis other than IS.

Patients with symptoms suggestive of acute IS underwent routine diagnostic and aetiological workup, including neuroimaging (computed tomography or magnetic resonance imaging), vascular imaging using ultrasound and/or computed tomography or magnetic resonance imaging angiography as judged necessary by the physician in charge, 12-lead electrocardiography, electrocardiography monitoring at the stroke unit or intensive care unit, and routine blood sampling. Thoracic and/or transoesophageal echocardiography, 24–48 h Holter monitoring, and chest X-rays were performed as part of clinical routine if clinically relevant. Stroke aetiology was independently assessed by three physicians (P. U. H., D. M., and F. A. M.) according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. Interrater reliability of the TOAST classification was good (Gwet’s AC1 coefficient: 0.83). Presence of cardiac signs and stroke severity by National Institutes of Health Stroke Scale (NIHSS) was documented on hospital admission.

Baseline investigation

Demographic characteristics, self-reported co-morbidities, pre-stroke functional status, lifestyle factors, pre-stroke HF symptoms, and family history of cardiovascular diseases were documented at baseline (for definitions, see Supporting Information, Appendix S1). Information was collected from the patients themselves or from a next of kin knowledgeable about patient’s history in cases of aphasia or disturbed consciousness. Hypertension was defined as self-reported history of hypertension or intake of antihypertensive medication. Coronary heart disease (CHD) was defined as history of myocardial infarction or angina. Smoking was defined as current or former tobacco smoking. Pre-stroke dependency was defined as any need for assistance in daily life. Previously diagnosed HF was defined as the listing of HF as a co-morbidity in the medical record of the index event. Atrial fibrillation was defined as either (i) the listing of atrial fibrillation as a previously existing co-morbidity in the medical record of the index event or (ii) a new diagnosis of atrial fibrillation during the index stay based on electrocardiography, stroke unit monitoring, or Holter records.
Echocardiography

Standardized transthoracic echocardiography (TTE) was performed as part of the routine diagnostic workup according to current recommendations by an expert sonographer of the Comprehensive Heart Failure Center Würzburg on a high-end ultrasound device (Vivid E9®, GE Healthcare, Horten, Norway, GE M5S-D matrix single-crystal phased array transducer). Sonographers underwent internal certification in the frame of the quality assurance programme of the Characteristics and Course of Heart Failure Stages A–B and Determinants of Progression (STAAAB) study. The results of the certification have been published elsewhere. A minimum of three electrocardiography-triggered cardiac cycles were recorded for analysis and stored digitally. Left ventricular end-diastolic and end-systolic volumes (LVVed and LVVes) were measured using the biplane disc summation method (i.e. modified Simpson’s rule) from 2D images of apical four-chamber and two-chamber views, and LVEF was calculated accordingly using the formula: (LVVed – LVVes)/LVVed x 100. In case of suboptimal imaging conditions, LVEF was assessed from the apical four-chamber view according to Simpson’s monoplane method. Transmirtal inflow pattern with E-wave and A-wave velocities was obtained by pulsed-wave Doppler with the sample volume positioned at the mitral leaflet tips. Pulsed-wave tissue Doppler imaging was obtained at the septal and lateral mitral annulus in the apical four-chamber view, and peak early (e’) diastolic lengthening velocities were measured, respectively. Systolic tricuspid pressure gradient was assessed using continuous-wave Doppler through the tricuspid valve in an apical four-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was assessed using M-mode, aligned perpendicularly to tricuspid annular systolic movement. Left atrial volume was assessed from the apical four-chamber and two-chamber views. In case of suboptimal image quality, left atrial area was assessed from the apical four-chamber view only. Parameters for SD, DD, and HF were assessed according to current recommendations.

Blood-based biomarkers

Fasting blood samples were collected the morning after enrolment [median 3 [interquartile range (IQR) 2–4] days after symptom onset] in different tubes prepared with ethylenediaminetetraacetic acid and coagulation-promoting reagent. After centrifugation at 2500 g for 10 min, serum and plasma were collected in new tubes and stored at −80°C in the Interdisciplinary Bank of Biomaterials and Data Würzburg following standard operating procedures established in accordance to guidelines of the Organisation for Economic Co-operation and Development. The following assays were used to determine serum concentrations of high-sensitive troponin T (hs-TnT), N-terminal pro B-type natriuretic peptide (NT-proBNP), and creatinine: Elecsys Troponin T high-sensitive STAT (Roche Diagnostics, Mannheim, Germany; range 3–10 000 ng/L, 99th percentile upper reference limit 14 ng/L); Elecsys proBNP II (Roche Diagnostics; range 5–35 000 pg/ml, functional sensitivity 50 pg/ml); and Creatinine plus ver. 2 (Roche Diagnostics; range 0.06–30.5 mg/dl). Cut-off values for NT-proBNP (≥125 pg/ml) and hs-TnT (≥14 ng/L) were predefined according to current guidelines (NT-proBNP) or the respective assay’s validation study (hs-TnT). Measurements were performed by an operator blinded to all clinical data. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Definition of cardiac dysfunction and heart failure

Left ventricular SD and DD were defined according to current recommendations from the American Society of Echocardiography and European Association of Cardiovascular Imaging for cardiac chamber quantification and for echocardiographic evaluation of left ventricular diastolic function (Table 1). If DD was present, DD grades were defined based on E-wave and A-wave velocities in patients without atrial fibrillation and E/e’ ratio in patients with atrial fibrillation as proposed by Nagueh et al. HF was defined according to current guidelines of the European Society of Cardiology for diagnosis and treatment of acute and chronic HF and required simultaneous fulfilment of clinical, echocardiographic, and biomarker criteria (Table 2). Clinical signs and symptoms of HF were ascertained using a modified version of the Framingham criteria. Right ventricular systolic function was assessed using TAPSE, and TAPSE < 17 mm was considered as an indicator of reduced right ventricular systolic function.

Statistical analysis

According to the distribution of the variables, differences between groups were tested using the $\chi^2$ test, Student’s t-test, ANOVA, Mann–Whitney U test, or Kruskal–Wallis test. In case of HF, P-values were only presented for clinically overt HF (defined as heart failure with preserved ejection fraction (HFpEF), heart failure with mid-range ejection fraction (HFmrEF), or heart failure with reduced ejection fraction (HFrEF)) vs. no HF as the sample size was too small for further comparisons. We used multivariable logistic regression analyses to determine variables associated with SD, DD, or HF and present odds ratios (ORs) with 95% confidence intervals (CI). We selected a priori variables for the multivariable logistic regression analyses based on clinical background knowledge and adjusted the models block-wise in three additional
blocks: (i) demographics (age and sex); (ii) co-morbidities (hypertension, CHD, and diabetes); and (iii) clinical characteristics of index event (NIHSS score at admission, insular lesion yes/no, and hs-TnT).

Concentrations of NT-proBNP and hs-TnT were logarithmically transformed due to skewed distribution. We excluded NT-proBNP from the multivariable analyses as it is included in the definition of HF and was collinear with hs-TnT and NIHSS score. Frequencies were reported for patients with complete information regarding the specified criteria. Several sensitivity analyses were performed considering different diagnostic scenarios: (i) estimation of maximum DD prevalence, when all missing parameters were assumed as positive criteria; (ii) estimation of HF prevalence without considering NT-proBNP as prerequisite; (iii) estimation of HF prevalence without considering clinical symptoms and NT-proBNP in patients with previous HF diagnosis, under the assumption that HF-specific treatment might have masked clinical symptoms and reduced NT-proBNP levels; and (iv) estimation of the association of hs-TnT levels ≥ 14 ng/L with SD, DD, and HF. Sample size calculation was based on previously published estimates of 10–24%. We aimed to recruit 750 patients to reach prevalence estimates of 10% with a precision of 8.1–24% or of 24% with a precision of 21.1–27.2%. Data analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined at an α level of 0.05 (two-tailed).

**Ethics**

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Medical Faculty of the University of Würzburg (176/13). All patients or their legal representatives provided written informed consent.

**Results**

Overall, 2,154 patients were screened; of 1,192 eligible patients with suspected IS, 750 patients were recruited. After exclusion of dropouts [stroke mimics (n = 41) or withdrawal of consent (n = 13)] and patients without valid echocardiography (n = 52), 644 patients were included in the present analysis (Figure 2). Median age was 71 years (IQR 60–79), and 396 patients (61.5%) were male. Median NIHSS score on admission was 3 (IQR 1–5). Baseline characteristics are shown in Table 2. Patients underwent TTE at median of 4 (IQR 2–5).

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**Table 1** Definitions of systolic dysfunction, diastolic dysfunction, and heart failure

| Systolic dysfunction |
|----------------------|
| LVEF < 52% (men) and <54% (women) |

| Diastolic dysfunction (≥ 3 criteria fulfilled in patients without systolic dysfunction) |
|----------------------------------|
| LAVI > 34 mL/m² OR LA area > 30 cm² (if LAVI not available) |
| Average E/e’ > 14 |
| Lateral e’ < 10 cm/s OR septal e’ < 7 cm/s |
| Tricuspid regurgitation maximal flow velocity > 2.8 m/s |

| Heart failure |
|---------------|
| Heart failure with preserved ejection fraction |
| LVEF ≥ 50% |
| At least one of the following: |
| LAVI > 34 mL/m² |
| LVMI ≥ 115 g/m² (men) and ≥95 g/m² (women) |
| Average E/e’ ≥ 13 |
| Lateral e’ < 9 OR septal e’ < 9 |

| Clinical signs and symptoms (2 major criteria or 1 major and 2 minor criteria) |
|----------------------------------|
| Pre-stroke paroxysmal nocturnal dyspnoea |
| Pre-stroke orthopnoea (sleeping with the upper body at an angle > 45°) |
| Pre-stroke dyspnoea on mild exertion |
| Rales on admission |
| Acute pulmonary oedema (chest X-ray) |
| Cardiomegaly [LVED > 58.4 mm (men) or >52.2 mm (women)] |
| Third heart sound on admission |

| Not required |
|----------------------------------|
| Pre-stroke lower limb oedema as assessed on admission |
| Pleural effusion (chest X-ray) |
| Heart rate ≥ 120 b.p.m. at Day 3 |
| Nycturia (>2 times/night) |
| Pre-stroke dyspnoea on moderate or intense exertion |

LA, left atrium; LAVI, left atrial volume index; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide.
Prevalence and determinants of systolic dysfunction

The prevalence of SD was 9.6% (95% CI 7.6–12.2%). In the final model, reduced LVEF was significantly associated with previous history of CHD (OR 3.87; 95% CI 1.93–7.75) and higher levels of log hs-TnT (OR 1.78; 95% CI 1.31–2.42) (Table 3). Levels of hs-TnT ≥ 14 ng/L were also significantly associated with SD (OR 3.23; 95% CI 1.55–6.75). No patient was found with a typical Takotsubo syndrome. Almost 40% of patients with SD also had reduced right ventricular systolic function, as assessed by TAPSE.

Prevalence and determinants of diastolic dysfunction

Among 549 patients with normal LVEF and sufficient data on diastolic function, 23.3% (95% CI 20.0–27.0%) fulfilled ≥3 DD criteria and, hence, were classified as having DD. In these patients, information on sinus rhythm was available in 96.9%. Of them, 81.5% were in sinus rhythm during TTE with 95.0% having sufficient information on mitral flow velocities to assess the severity of DD: we observed Grade 1 in 4.2%, Grade 2 in 84.4%, and Grade 3 in 11.4% of these patients. Of patients with arrhythmia during TTE, 39.1% had sufficient information on mitral E and annular e’ velocities. All of these patients presented with elevated left ventricular filling pressures (E/ere’ ≥ 11).

The proportion of patients fulfilling ≥3 DD criteria would increase up to 38.7% if all missing information was assumed indicative of DD. In the final model, patients with DD were significantly older (OR 1.08; 95% CI 1.05–1.11) and more likely to have a history of untreated or treated hypertension (OR 3.15; 95% CI 0.98–10.17 and OR 2.84; 95% CI 1.23–6.54, respectively). While the levels of log hs-TnT were statistically not significantly associated with DD (OR 1.16; 95% CI 0.86–1.56), levels of hs-TnT ≥ 14 ng/L reached statistical significance (OR 1.91; 95% CI 1.05–3.45). About 19% of patients with DD without SD presented with reduced right ventricular systolic function.

Prevalence and determinants of heart failure

Overall, 35 patients (5.4%; 95% CI 3.9–7.5%) fulfilled HF criteria during the acute IS phase. Distribution of the different HF types was HFpEF 4.35%, HFmrEF 0.31%, and HFrEF 0.78%. No substantial differences in demographics, risk factors, medical history, and clinical characteristics were observed between patients categorized as HFP EF and patients presenting HFmrEF and HFrEF (see Supporting Information, Table S3). Patients fulfilling HF criteria were more likely to have symptomatic pre-stroke CHD.
Table 2  Study population by prevalence of systolic dysfunction, diastolic dysfunction, and symptomatic heart failure after ischaemic stroke

| Demographics                        | All patients<sup>a</sup> (n = 644) | With SD (n = 62) | Without SD (n = 582) | P-value | With DD (n = 128) | Without DD (n = 421) |
|-------------------------------------|------------------------------------|------------------|----------------------|---------|-------------------|----------------------|
| **Age, years, median (IQR)**        | 71 (60–78)                         | 73 (65–79)       | 71 (60–78)           | 0.1894  | 79 (75–84)        | 67 (57–76)           |
| **Male**                            | 396 (61.5)                         | 44 (71.0)        | 352 (60.5)           | 0.1067  | 67 (52.3)         | 270 (64.1)           |
| **Dependency pre-stroke**           | 80 (12.8)                          | 10 (16.9)        | 70 (12.3)            | 0.3135  | 30 (24.2)         | 33 (8.0)             |
| **Risk factors**                    |                                    |                  |                      |         |                   |                      |
| **Heart failure**                   |                                    |                  |                      |         |                   |                      |
| Pre-stroke self-reported            | 62 (9.6)                           | 14 (22.6)        | 48 (8.2)             | 0.0003  | 14 (10.9)         | 31 (7.4)             |
| Pre-stroke recorded in medical records | 34 (5.3)                           | 13 (21.0)        | 21 (3.7)             | <0.0001 | 8 (6.3)           | 10 (2.4)             |
| Atrial fibrillation                 | 143 (22.2)                         | 18 (29.0)        | 125 (21.5)           | 0.1736  | 51 (39.8)         | 68 (16.2)            |
| Coronary heart disease              | 102 (16.2)                         | 21 (35.6)        | 81 (14.2)            | <0.0001 | 19 (15.3)         | 58 (14.1)            |
| **Hypertension**                   |                                    |                  |                      |         |                   |                      |
| No hypertension                     | 157 (24.5)                         | 12 (19.4)        | 145 (25.1)           | 0.3327  | 12 (9.4)          | 126 (30.1)           |
| Untreated hypertension              | 50 (7.8)                           | 3 (4.8)          | 47 (8.1)             | 9 (7.1) | 37 (8.9)          |                      |
| Treated hypertension                | 433 (67.7)                         | 47 (75.8)        | 386 (66.8)           | 106 (83.5) | 255 (61.0)    |                      |
| **Previous stroke or TIA**          | 123 (24.7)                         | 12 (29.3)        | 111 (24.3)           | 0.4838  | 28 (30.1)         | 77 (22.9)            |
| Peripheral artery occlusive disease | 33 (5.4)                           | 3 (5.4)          | 30 (5.4)             | 0.9927  | 10 (8.3)          | 18 (4.5)             |
| Hyperlipidaemia                     | 177 (28.5)                         | 19 (32.2)        | 158 (28.1)           | 0.5026  | 35 (28.7)         | 111 (27.1)           |
| Diabetes mellitus, self-reported    | 140 (22.3)                         | 17 (28.8)        | 123 (21.6)           | 0.2035  | 30 (24.2)         | 82 (19.9)            |
| Tobacco smoking                     | 343 (54.6)                         | 35 (59.3)        | 308 (54.1)           | <0.0001 | 58 (14.1)         | 244 (59.2)           |
| Family history of cardiovascular diseases | 463 (84.3)                         | 40 (78.4)        | 423 (84.9)           | 0.2233  | 79 (78.2)         | 318 (87.1)           |
| HF signs and symptoms               | 48 (7.5)                           | 9 (14.5)         | 39 (6.7)             | 0.0259  | 16 (12.5)         | 18 (4.3)             |
| **Index event**                     |                                    |                  |                      |         |                   |                      |
| TOAST classification                | 0.6703                             |                  |                      |         |                   |                      |
| Large artery atherosclerosis        | 72 (11.2)                          | 6 (9.7)          | 66 (11.4)            | 11 (8.6) | 51 (12.1)         |                      |
| Cardioembolism                      | 192 (29.9)                         | 22 (35.5)        | 170 (29.3)           | 50 (39.1) | 115 (27.4) |                      |
| Small artery occlusion              | 93 (14.5)                          | 6 (9.7)          | 87 (15.0)            | 17 (13.3) | 67 (16.0) |                      |
| Other determined cause              | 18 (2.8)                           | 1 (1.6)          | 17 (2.9)             | 3 (2.3) | 13 (3.1) |                      |
| Undetermined aetiology              | 268 (41.7)                         | 27 (43.5)        | 241 (41.5)           | 47 (36.7) | 174 (41.4) |                      |
| **NIHSS at admission**              |                                    |                  |                      |         |                   |                      |
| Median (IQR)                        | 3 (1–5)                            | 3 (2–6)          | 3 (1–5)              | 0.0816  | 3 (1–5)          | 3 (1–4)              |
| ≤4                                 | 468 (72.9)                         | 40 (65.6)        | 428 (73.7)           | 0.1762  | 88 (69.3)        | 318 (75.5)           |
| Insular lesion                      | 82 (12.7)                          | 12 (19.4)        | 70 (12.0)            | 0.0999  | 13 (10.2)        | 52 (12.4)            |
| **Laboratory values**               |                                    |                  |                      |         |                   |                      |
| NT-proBNP, pg/mL, median (IQR)      | 268 (97–906)                       | 1038 (643–3594)  | 217 (81–709)         | <0.0001 | 732 (304–1835)  | 154 (62–445)         |
| hs-TnT, ng/L                        |                                    |                  |                      |         |                   |                      |
| Median (IQR)                        | 11 (5–20)                          | 19 (11–28)       | 10 (5–19)            | <0.0001 | 16 (9–28)        | 8 (5–14)             |
| hs-TnT ≥ 14                         | 187 (36.7)                         | 33 (62.3)        | 154 (33.8)           | <0.0001 | 56 (58.3)        | 85 (25.4)            |
| Impaired kidney function<sup>c</sup> | 61 (12.0)                          | 9 (17.0)         | 52 (11.4)            | 0.2341  | 20 (20.6)        | 29 (8.7)             |
| **TAPSE**                           |                                    |                  |                      |         |                   |                      |
| Median (IQR)                        | 21 (18–24)                         | 18 (15–20)       | 21 (18–24)           | <0.0001 | 21 (18–24)       | 21 (18–24)           |
| TAPSE < 17 mm                       | 96 (15.6)                          | 23 (39.7)        | 73 (13.1)            | <0.0001 | 28 (18.8)        | 66 (15.0)            |
| Risk factors                          | P-value   | Without HF (n = 609) | With HFpEF (n = 28) | With HFmrEF (n = 2) | With HFrEF (n = 5) | P-value<sup>b</sup> |
|--------------------------------------|-----------|----------------------|---------------------|---------------------|-------------------|-------------------|
| Age, years, median (IQR)             | <0.0001   | 70 (60–78)           | 79 (70–82)          | 73 (72–73)          | 71 (55–86)        | 0.0038            |
| Male                                 | 0.0164    | 377 (61.9)           | 14 (50.0)           | 2 (100.0)           | 3 (60.0)          | 0.3677            |
| Dependency pre-stroke                | <0.0001   | 71 (12.0)            | 7 (25.0)            | 1 (50.0)            | 1 (20.0)          | 0.0183            |
| Heart failure                        |           |                      |                     |                     |                   |                   |
| Pre-stroke self-reported             | 0.1968    | 49 (8.0)             | 9 (32.1)            | 2 (100.0)           | 2 (40.0)          | <0.0001           |
| Pre-stroke recorded in medical records | 0.0323   | 29 (4.8)             | 4 (14.3)            | 0 (0.0)             | 1 (20.0)          | 0.0154            |
| Atrial fibrillation                  | <0.001    | 131 (21.5)           | 10 (35.7)           | 0 (0.0)             | 2 (40.0)          | 0.0770            |
| Coronary heart disease               | 0.7290    | 89 (15.0)            | 9 (32.1)            | 1 (50.0)            | 3 (60.0)          | 0.0006            |
| Hypertension                         | <0.0001   |                      |                     |                     |                   | 0.0247            |
| No hypertension                      | 154 (25.5) | 3 (10.7)             | 0 (0.0)             | 0 (0.0)             | 0 (0.0)           |                   |
| Untreated hypertension               | 49 (8.1)  | 1 (3.6)              | 0 (0.0)             | 0 (0.0)             | 0 (0.0)           |                   |
| Treated hypertension                 | 402 (66.4) | 24 (85.7)            | 2 (100.0)           | 5 (100.0)           | 0 (0.0)           | 0.9767            |
| Previous stroke or TIA               | 0.1535    | 117 (24.7)           | 5 (25.0)            | 1 (100.0)           | 0 (0.0)           | 0.3744            |
| Peripheral artery occlusive disease  | 0.0972    | 29 (5.0)             | 3 (10.7)            | 1 (100.0)           | 0 (0.0)           | 0.1976            |
| Hyperlipidaemia                      | 0.7366    | 165 (28.1)           | 9 (32.1)            | 1 (50.0)            | 2 (40.0)          | 0.3774            |
| Diabetes mellitus, self-reported      | 0.2970    | 128 (21.5)           | 9 (32.1)            | 1 (50.0)            | 2 (40.0)          | 0.0783            |
| Tobacco smoking                      | 0.0021    | 325 (54.8)           | 13 (46.4)           | 2 (100.0)           | 3 (60.0)          | 0.8232            |
| Family history of cardiovascular diseases | 0.0257 | 435 (84.1)         | 22 (88.0)           | 2 (100.0)           | 4 (80.0)          | 0.6118            |
| HF signs and symptoms                | 0.0007    | 13 (2.1)             | 28 (100.0)          | 2 (100.0)           | 5 (100.0)         | <0.0001           |
| TOAST classification                 | 0.1512    |                      |                     |                     |                   | 0.7720            |
| Large artery atherosclerosis         | 70 (11.5) | 1 (3.6)              | 0 (0.0)             | 1 (20.0)            |                   |                   |
| Cardioembolism                       | 180 (29.6) | 9 (32.1)             | 0 (0.0)             | 3 (60.0)            |                   |                   |
| Small artery occlusion               | 87 (14.3) | 6 (21.4)             | 0 (0.0)             | 0 (0.0)             |                   |                   |
| Other determined cause               | 18 (3.0)  | 0 (0.0)              | 0 (0.0)             | 0 (0.0)             |                   |                   |
| Undetermined aetiology               | 253 (41.6) | 12 (42.9)           | 2 (100.0)           | 1 (20.0)            |                   |                   |
| NIHSS at admission                   |           |                      |                     |                     |                   |                   |
| Median (IQR)                         | 0.2111    | 3 (1–5)              | 3 (2–5)             | 2 (1–3)             | 6 (4–8)           | 0.5145            |
| ≤4                                   | 0.1593    | 443 (73.0)           | 21 (75.0)           | 2 (100.0)           | 2 (40.0)          | 0.8407            |
| Insular lesion                       | 0.5008    | 74 (12.2)            | 5 (17.9)            | 0 (0.0)             | 3 (60.0)          | 0.0646            |
| Laboratory values                    |           |                      |                     |                     |                   |                   |
| NT-proBNP, pg/mL, median (IQR)       | <0.0001   | 234 (83–760)         | 1135 (539–2728)     | 1297 (959–1635)     | 7885 (1038–8189)  | <0.0001           |
| hs-TnT, ng/L                         |           |                      |                     |                     |                   |                   |
| Median (IQR)                         | <0.0001   | 10 (5–19)            | 23 (12–37)          | 20 (14–27)          | 23 (15–64)        | <0.0001           |
| hs-TnT ≥ 14                          | <0.0001   | 163 (34.4)           | 19 (67.9)           | 1 (50.0)            | 4 (80.0)          | <0.0001           |
| Impaired kidney function<sup>c</sup> | 0.0011    | 48 (10.1)            | 11 (39.3)           | 1 (50.0)            | 1 (20.0)          | <0.0001           |
| TAPSE                                |           |                      |                     |                     |                   |                   |
| Median (IQR)                         | 0.3739    | 21 (18–24)           | 20 (17–25)          | 17 (15–19)          | 13 (10–17)        | 0.0156            |
| TAPSE < 17 mm                        | 0.2747    | 89 (15.3)            | 3 (11.5)            | 1 (50.0)            | 3 (75.0)          | 0.0049            |

DD, diastolic dysfunction; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-TnT, high-sensitive troponin T; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, systolic dysfunction; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

<sup>a</sup>n (%) if not otherwise indicated.

<sup>b</sup>P-value for comparison of HF vs. no HF.

<sup>c</sup>Impaired kidney function defined as glomerular filtration rate < 60 mL < 60 mL/min/1.73 m².
### Table 3: Association of demographic and clinical characteristics with (A) systolic dysfunction, (B) diastolic dysfunction, and (C) clinically overt heart failure in univariable and multivariable logistic regression analysis

|                         | Univariable | Model 1* | Model 2* | Model 3* |
|-------------------------|-------------|----------|----------|----------|
|                         | OR (95% CI) | P-value  | OR (95% CI) | P-value  | OR (95% CI) | P-value  |
| **(A) Systolic dysfunction** |             |          |          |          |
| Demographics            |             |          |          |          |
| Age, per year           | 1.02 (1.00–1.04) | 0.1218 1.02 (1.00–1.04) | 0.0714 1.01 (0.99–1.03) | 0.4336 1.00 (0.97–1.03) | 0.9627 |
| Male                    | 1.60 (0.90–2.83) | 0.1092 1.72 (0.97–3.10) | 0.0642 1.54 (0.84–2.82) | 0.1627 1.63 (0.82–3.26) | 0.1652 |
| Risk factors            |             |          |          |          |
| Hypertension            | 1.00        | 0.3393   | 1.00     | 0.8506   | 1.00     | 0.5219   |
| No hypertension         |             |          |          |          |          |          |
| Treated hypertension    | 1.47 (0.76–2.85) | 0.95 (0.44–2.04) | 0.60 (0.25–1.45) |
| Untreated hypertension  | 0.68 (0.18–2.57) | 0.69 (0.17–2.78) |
| Coronary heart disease  | 3.33 (1.86–5.96) | <0.0001 3.86 (1.93–7.75) | 0.0001 |
| Diabetes mellitus       | 1.47 (0.81–2.67) | 0.2057 1.18 (0.63–2.23) | 0.6027 1.20 (0.58–2.49) | 0.6326 |
| **Index event**         |             |          |          |          |
| NIHSS at admission >4   | 1.47 (0.84–2.57) | 0.1782 1.47 (0.75–2.89) | 0.2661 |
| Insular lesion          | 1.76 (0.89–3.46) | 0.1037 1.08 (0.46–2.53) | 0.8675 |
| Log (hs-TnT), ng/L      | 1.71 (1.32–2.21) | <0.0001 1.78 (1.31–2.42) | 0.0003 |
| **(B) Diastolic dysfunction** |             |          |          |          |
| Demographics            |             |          |          |          |
| Age, per year           | 1.10 (1.07–1.12) | <0.0001 1.09 (1.07–1.12) | <0.0001 1.09 (1.06–1.12) | <0.0001 1.08 (1.05–1.11) | <0.0001 |
| Male                    | 0.61 (0.41–0.92) | 0.0169 0.87 (0.56–1.35) | 0.5318 0.96 (0.61–1.52) | 0.8701 1.07 (0.63–1.84) | 0.7990 |
| Risk factors            |             |          |          |          |
| Hypertension            | <0.0001     |          | <0.0001 0.0595 | 0.0405 |
| No hypertension         | 1.00        | 1.00     | 1.00     |          |          |          |
| Treated hypertension    | 4.37 (2.32–8.23) | 2.19 (1.09–4.39) | 2.84 (1.23–5.64) |
| Untreated hypertension  | 2.75 (1.00–7.54) | 3.15 (0.98–10.17) |
| Coronary heart disease  | 1.10 (0.63–1.94) | 0.7290 0.72 (0.39–1.35) | 0.3043 0.65 (0.31–1.34) | 0.2421 |
| Diabetes mellitus       | 1.29 (0.80–2.08) | 0.2977 0.93 (0.55–1.56) | 0.7776 0.81 (0.44–1.50) | 0.5020 |
| **Index event**         |             |          |          |          |
| NIHSS at admission >4   | 1.37 (0.88–2.12) | 0.1602 1.38 (0.77–2.46) | 0.2792 |
| Insular lesion          | 0.80 (0.42–1.53) | 0.5016 0.45 (0.19–1.11) | 0.0819 |
| Log (hs-TnT), ng/L      | 1.84 (1.44–2.34) | <0.0001 1.16 (0.86–1.56) | 0.3334 |
| **(C) Heart failure**   |             |          |          |          |
| Demographics            |             |          |          |          |
| Age, per year           | 1.04 (1.01–1.07) | 0.0710 1.04 (1.01–1.07) | 0.0115 1.03 (0.99–1.06) | 0.1102 1.01 (0.98–1.05) | 0.4841 |
| Male                    | 0.73 (0.37–1.45) | 0.3692 0.85 (0.43–1.72) | 0.6589 0.74 (0.36–1.51) | 0.4041 0.71 (0.34–1.49) | 0.3636 |
| Risk factors            |             |          |          |          |
| Hypertension            | 0.0402      |          | 0.4030   | 0.5290   |          |          |
| No hypertension         | 1.00        | 1.00     | 1.00     |          |          |          |
| Treated hypertension    | 3.96 (1.19–13.14) | 2.21 (0.61–7.97) | 1.97 (0.53–7.37) |
| Untreated hypertension  | 1.05 (0.11–10.30) | 1.03 (0.10–10.29) | 1.00 (0.10–10.50) |
| Coronary heart disease  | 3.35 (1.63–6.89) | 0.0010 2.63 (1.23–5.63) | 0.0126 2.29 (1.04–5.05) | 0.0406 |
| Diabetes mellitus       | 1.90 (0.92–3.92) | 0.0828 1.36 (0.64–2.89) | 0.4261 1.57 (0.72–3.43) | 0.2570 |
| **Index event**         |             |          |          |          |
| NIHSS at admission >4   | 1.08 (0.51–2.29) | 0.8407 0.72 (0.31–1.70) | 0.4546 |
| Insular lesion          | 2.14 (0.94–4.89) | 0.0705 1.93 (0.76–4.93) | 0.1683 |
| Log (hs-TnT), ng/L      | 1.71 (1.32–2.21) | <0.0001 1.66 (1.17–2.33) | 0.0040 |

CI, confidence interval; hs-TnT, high-sensitive troponin T; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

*Model 1: demographics; Model 2: demographics + risk factors; Model 3: demographics + risk factors + characteristics of index event.

(OR 2.29; 95% CI 1.04–5.05) and higher levels of log hs-TnT during the acute stroke phase (OR 1.66; 95% CI 1.17–2.33). When NT-proBNP was not considered as a prerequisite, HFrEF prevalence was 5.4%, while rates of HFmrEF and HFrEF were unchanged. Assuming all patients presenting clinical signs and symptoms of HF had fulfilled additional criteria, prevalence was 7.5% (see Supporting Information, Appendix S1). Thirty-four patients had a previous diagnosis of HF in their medical records. Of those, 29 (85%) did not fulfill HF criteria, mostly due to the lack of documented clinical symptoms (93%). Overall, only 9 acute IS patients with SD (14%) and 13 patients without SD and ≥3 DD criteria (10%) fulfilled HF criteria (see Supporting Information, Table S2).

When HF diagnoses in medical records were included, total HF prevalence was 9.9%. Based on echocardiographic criteria only, 52% of 34 patients with previous HF diagnosis in medical records would qualify for HFrEF, 14% for HFmrEF, and 21% for HFrEF, and 21% would not fulfill echocardiographic HF criteria.

Patients fulfilling HFrEF and HFmrEF criteria presented higher rates of reduced right ventricular systolic function, compared with patients fulfilling HFrEF criteria or patients not fulfilling HF criteria.
Discussion

To the best of our knowledge, this is the first prospective study reporting on the frequency and determinants of different types of cardiac dysfunction and HF in acute IS patients defined according to current guidelines. About 10% of patients presented SD, 23% of patients without SD presented DD, and about 5% fulfilled HF criteria. The latter proportion was substantially lower compared with previous reports, with a majority of those patients classified as HFpEF. A history of CHD and increasing levels of hs-TnT emerged as independent factors associated with prevalent SD and HF. Older age and hypertension pre-stroke were independent determinants of prevalent DD in patients without SD. Elevated hs-TnT was only associated with DD when analysed as a dichotomous variable.

Our results align with a retrospective study reporting an SD (LVEF < 53%) prevalence of 12.6% among acute IS patients but significantly differ from a study reporting an SD (LVEF < 50%) prevalence of 24.1%. In the latter study, LVEF was semi-quantitatively estimated in 270 of 505 IS patients undergoing echocardiography. While the used formula might underestimate the prevalence of reduced LVEF, the limited uptake might introduce some variation in estimates. Additionally and in agreement with a study in an elderly population, one main determinant of SD was a history of CHD, which was substantially lower in our study (16% vs. 31%, respectively). Consistent with previous findings, hypertension and diabetes were not associated with SD. The association of elevated hs-TnT with SD is consistent with findings in the general population, which might reflect non-ischaemic myocardial cell loss followed by replacement fibrosis but might also result from an acute coronary syndrome occurring around the onset of neurological symptoms or even causing IS in some cases. A recent study in 29 acute IS patients with hs-TnT elevation undergoing coronary angiography identified a coronary culprit lesion in about one quarter of them. Furthermore, in patients with marked increase of hs-TnT without obstructive coronary artery disease, myocardial infarction with non-obstructive coronary arteries has been suggested as a working diagnosis encompassing many possible aetiologies (e.g. Takotsubo syndrome and coronary spasm). To note, we found no patients with a classical Takotsubo syndrome in our population.

We implemented the DD definition contained in current guidelines as the fulfilment of ≥3 DD criteria in the absence of SD, comparable with a previous study. Although patients with SD were reported to comitantly suffer from relevant DD, the special characteristics of this population justified a separate analysis. In our sample, DD was present in 23% of patients without SD. Previous retrospective studies estimated DD prevalence among IS patients between 59% and 96%. Substantial variations in the prevalence of DD have also been observed in the general population. Differences that might be largely attributed to definitions used with currently recommended criteria rendering sizeable lower DD rates than previously published definitions. A high proportion of patients (95.8%) in whom DD profiling was feasible exhibited elevated filling pressures (DD Grades 2 and 3). This is an indication of pre-existing co-morbidity, as hypertension is the major risk factor of stroke, but it might also be a transient state in certain patients, caused by volume substitution during hospital care and thus with the potential to resolve after hospital discharge. Age and hypertension were independently associated with the presence of DD, consistent with previous studies among elderly and general populations, whereas only dichotomization of hs-TnT reached statistical significance, in line with a study in elderly subjects. If this association is not spurious, this finding might be interpreted as a marker of ongoing subclinical fibrosis, a mechanism also present in the development of DD.

By applying the standardized criteria from current European Society of Cardiology guidelines, our study found a substantially lower rate of IS patients fulfilling HF criteria than previous studies in spite of high rates of NT-proBNP elevation and rather high prevalence of both SD and DD. Differing HF diagnostic criteria and variations in study populations might account for these discrepancies. For example, previous studies assessed HF in IS patients based on a previous HF diagnosis or administrative data only and were, thus, likely to overestimate its prevalence. A prospective study reported a prevalence of systolic HF (i.e. positive Framingham criteria and LVEF < 50%) of 9.7%, while a more recent retrospective study reported a 5% prevalence of clinical HF with LVEF < 53%.

Previous studies in IS patients defined HFpEF as the presence of positive Framingham criteria or ‘clinical HF’ in the absence of reduced LVEF (50–53%). Because the additional echocardiographic parameters required by current guidelines were disregarded, respective prevalences (6.7–8%) were higher than the 4.3% prevalence observed in our study. Furthermore, because the current HF definition is restricted to the stage where signs and symptoms become apparent, it is highly relevant how these are defined and assessed. In the study by Ois et al., a cardiologist diagnosed HF using the Framingham criteria. These criteria are presumably less sensitive for HF diagnosis than a cardiologist’s judgement. Thus, a clinician’s expertise might add to score performance, increasing the frequency of HF diagnosis. Li et al. used a combination of patient’s self-report and/or previous diagnosis in medical records to define HF. In our study, 34 patients (5.3%) had a previous HF diagnosis in their medical records. Of those, 29 (85%) did not fulfil HF criteria during the acute IS phase, mostly because clinical manifestations were lacking. However, adequate treatment might have masked some of the symptoms of HF, thus reducing the sensitivity of employed criteria. Elevated NT-proBNP levels are common after IS. The median NT-proBNP in a cohort including 4215 IS

ESC Heart Failure 2021; 8: 1117–1129
DOI: 10.1002/ehf2.13145
patients was 1067 pg/mL (IQR 263–3520). A smaller cohort of 250 IS patients with serial measurements reported median NT-proBNP levels consistently above the suggested threshold of 125 pg/mL during the first days after IS, even after excluding patients with HF. To mention, the positive predictive value of NT-proBNP is limited compared with its high negative predictive value, making NT-proBNP especially recommended for ruling out the diagnosis of HF.

Comparable with studies in IS patients and the general population, our data suggest that less than half of acute IS patients with SD fulfil HF criteria. Similarly, the majority of patients with DD did not fulfil HF criteria, in agreement with previous studies in elderly and general populations. This finding is of clinical relevance as both DD and SD have been associated with poor outcome 3 months after stroke, independent of clinical symptoms. Importantly, both asymptomatic SD and DD have been associated with progression to overt HF. While their optimal management is still unclear, our data underscore that a significant share of patients with IS may benefit from targeted intervention for these groups, should they further develop. Furthermore, the long-term effects of cardiac dysfunction on IS outcomes are currently unknown but will be estimated during the long-term follow-up of this cohort. Our findings suggest that the previous diagnosis or self-reported HF might be too insensitive to appropriately depict functional and structural abnormalities in IS patients, thus underscoring the need of cardiac phenotyping in these patients. Median NT-proBNP was above 125 pg/mL in all groups analysed in our cohort, suggesting that NT-proBNP may not aid to decide regarding the need of further investigation in stroke patients with suspected HF.

Patients with SD exhibited reduced values for TAPSE when compared with patients without SD, in line with a previous study. No differences regarding right ventricular systolic function were apparent between patients with DD without SD and patients without DD. Because of the low rate of patients fulfilling HF criteria in the acute IS phase, these results must be regarded as preliminary.

Our study represents one of the largest prospective cohorts with standardized echocardiographic assessment in acute IS patients. The study has, however, limitations. First, this was a single-centre cohort, which limits the generalizability of our results in other more heterogeneous populations. Second, stroke severity in our cohort was rather mild (27% of patients with NIHSS score > 4 on admission). Studies suggested that HF patients may suffer more severe strokes. As the patient or their legal representatives had to provide informed consent, this might have led to selection bias by missing severely affected patients. Third, there might be some risk for information bias introduced by patient self-reports of pre-stroke HF symptoms, because criteria such as dyspnoea on exertion might not be accurately documented after IS. Furthermore, clinical signs on admission were collected from medical records, which may have led to under-reporting. Fourth, blood samples were not available from all patients. Nonetheless, only four patients who would have otherwise fulfilled HF criteria had missing biomarker data, and thus, this factor is unlikely to have influenced HF rates substantially. Fifth, not all recruited patients underwent echocardiography, as they were performed as part of the routine diagnostic workup. We thus might have underestimated the ‘real’ prevalence of DD and HF. However, we report the prevalence of DD and HF under different diagnostic scenarios, including the maximum possible prevalence assuming that all missing information was positive. A timely performance of a standardized echocardiography is challenging, especially in the setting of acute stroke patients. We recently demonstrated good feasibility and accuracy of point-of-care echocardiography in the stroke unit setting for the detection of SD. Sixth, to enhance comparability, the same independent variables were included in all three models. Because of the small number of events of HF and SD, our models for HF and SD might have been underpowered, and the results should be interpreted with caution. However, as we included the variables block-wise, only the fully adjusted models are at risk of being underpowered. Lastly, the current classification of HF based on LVEF has been challenged, and the existence of a continuum of phenotypes with overlapping characteristics has been proposed instead. Future work in large samples of HF patients is required to establish a new classification that allows to better account for this spectrum.

Conclusions

A substantial proportion of IS patients showed echocardiographic signs of cardiac dysfunction (either SD or DD alone or in combination with HF). However, our data suggest that the prevalence of HF according to current guidelines might be lower than previously reported that might be caused by unspecific conditions used in previous reports. Age, previous CHD, and hypertension were associated to different degrees with the prevalence of cardiac dysfunction or HF. Elevated hs-TnT was consistently associated with all types of cardiac dysfunction and HF, probably depicting ongoing clinical or subclinical myocardial damage. The impact of different definitions of cardiac dysfunction and HF on outcome after IS needs to be investigated in future studies.

Acknowledgements

The authors thank Martina Bauer and Jasmin Simon for echocardiographic examinations, Melanie Roos and Heike Hergenröder for technical assistance, and study assistants for support in data collection. The authors wish to thank all
Conflict of interest

P.U.H. reports grants from the German Ministry of Education and Research, German Research Foundation, European Union, Berlin Chamber of Physicians, German Parkinson Society, University Hospital Würzburg, Robert Koch Institute, German Heart Foundation, Federal Joint Committee (G-BA) within the Innovationfond, University Hospital Heidelberg (within RASUNOA-prime; supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer Ingelheim, and Daiichi Sankyo), Charité—Universitätsmedizin Berlin (within Mondafis; supported by an unrestricted research grant to the University Hospital Heidelberg from Bayer, BMS, Boehringer Ingelheim, and Daiichi Sankyo), Charité—Universitätsmedizin Berlin (within Mondafis; supported by an unrestricted research grant to the Charité from Bayer), and University Göttingen (within FIND-AF randomized; supported by an unrestricted research grant to the University Göttingen from Boehringer Ingelheim) outside the submitted work. F.A.M. is an MD/PhD fellow of the Interdisciplinary Center for Clinical Research of the Medical Faculty of the University of Würzburg, V.R., K.U., T.L., D.M., J.A., and C.K. have nothing to disclose. S.W. reports grants from the German Ministry of Research and Education and Deutsche Herzstiftung e.V. Parts of this manuscript will be part of the medical thesis of A.Q. C.M. reports a research cooperation with the University of Würzburg and Tomtec Imaging Systems funded by a research grant from the Bavarian Ministry of Economic Affairs, Regional Development and Energy, Germany; speakers honorarium from Amgen and Tomtec; a travel grant from Orion Pharma and Alnylam; and participation in Advisory and Patient Eligibility Boards sponsored by Akcea, Alnylam, Pfizer, and EBR Systems outside the submitted work. P.K. reports fees for advisory boards from Bayer, Bristol Myers Squibb, Boehringer Ingelheim, and Daiichi Sankyo, as well as a research grant from Daiichi Sankyo, outside the submitted work. K.G.H. reports study grants by Bayer and Sanoﬁ-Aventis and lecture fees/advisory board fees from Sanoﬁ-Aventis, Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Biotronik, W. L. Gore & Associates, and Medtronic outside the submitted work. S.S. reports grants from the German Ministry of Research and Education during the conduct of the study; grants and other from Boehringer; grants and other from Bayer; grants and other from Thermo Fisher; other from AstraZeneca; other from Sanofi; other from Servier; grants, personal fees, non-financial support, and other from Novartis; grants and other from Pfizer; other from Alnylam; other from Ionis; and other from Akcea outside the submitted work. S.F. reports grants from the German Ministry of Research and Education; there is no industrial support competing with the study results.

Funding

This work was supported by the German Ministry of Research and Education within the Comprehensive Heart Failure Centre Würzburg (grant numbers BMBF 01EO1004 and 01EO1504). F.A.M. is supported by an MD/PhD fellowship of the Interdisciplinary Center for Clinical Research of the Medical Faculty of the University of Würzburg. This publication was supported by the Open Access Publication Fund of the University of Wuerzburg.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Reasons for non-classification as heart failure case among patients with clinical signs and symptoms.

Table S1 Comparison of patients with and without echocardiographic characterization (“non-responder” analysis)

Table S2. Patients fulfilling heart failure criteria by type of cardiac dysfunction

Table S3. Comparison of patients with HFpEF and patients with HFrEF or HFrEF

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