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SHORT COMMUNICATION

# Adaptive anti-myocardial immune response following hospitalization for acute heart failure

Caroline Morbach[1,2]*, Niklas Beyersdorf[3], Thomas Kerkau[3], Gustavo Ramos[1,2], Floran Sahiti[1,2], Judith Albert[1,2], Roland Jahns[4], Georg Ertl[1], Christiane E. Angermann[1], Stefan Frantz[1,2], Ulrich Hofmann[1,2] and Stefan Störk[1,2]

[1]*Comprehensive Heart Failure Center, University and University Hospital Würzburg, Am Schwarzenberg 15, Würzburg, D-97078, Germany;* [2]*Department of Medicine I, University Hospital Würzburg, Würzburg, Germany;* [3]*Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany; and* [4]*Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw), University Hospital Würzburg, Würzburg, Germany*

## Abstract

**Aims** It has been hypothesized that cardiac decompensation accompanying acute heart failure (AHF) episodes generates a pro-inflammatory environment boosting an adaptive immune response against myocardial antigens, thus contributing to progression of heart failure (HF) and poor prognosis. We assessed the prevalence of anti-myocardial autoantibodies (AMyA) as biomarkers reflecting adaptive immune responses in patients admitted to the hospital for AHF, followed the change in AMyA titres for 6 months after discharge, and evaluated their prognostic utility.

**Methods and results** AMyA were determined in $n$ = 47 patients, median age 71 (quartiles 60; 80) years, 23 (49%) female, and 24 (51%) with HF with preserved ejection fraction, from blood collected at baseline (time point of hospitalization) and at 6 month follow-up (visit F6). Patients were followed for 18 months (visit F18). The prevalence of AMyA increased from baseline ($n$ = 21, 45%) to F6 ($n$ = 36, 77%; $P < 0.001$). At F6, the prevalence of AMyA was higher in patients with HF with preserved ejection fraction ($n$ = 21, 88%) compared with patients with reduced ejection fraction ($n$ = 14, 61%; $P$ = 0.036). During the subsequent 12 months after F6, that is up to F18, patients with newly developed AMyA at F6 had a higher risk for the combined endpoint of death or rehospitalization for HF (hazard ratio 4.79, 95% confidence interval 1.13–20.21; $P$ = 0.033) compared with patients with persistent or without AMyA at F6.

**Conclusions** Our results support the hypothesis that AHF may induce patterns of adaptive immune responses. More studies in larger populations and well-defined patient subgroups are needed to further clarify the role of the adaptive immune system in HF progression.

**Keywords** Adaptive immune response; Acute heart failure; Anti-myocardial; Autoantibody; Inflammation

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**Correspondence to: Caroline Morbach, Comprehensive Heart Failure Center, University and University Hospital Würzburg, Am Schwarzenberg 15, D-97078 Würzburg, Germany. Tel: +49 931 201 46389. Email: morbach_c@ukw.de*

## Background

Acute decompensation for heart failure (AHF) is a life-threatening condition characterized by acutely impaired cardiac function associated with profound neurohormonal, inflammatory and immune alterations, and poor prognosis.[1,2] A systemic inflammatory response[1] frequently accompanies AHF that likely primarily reflects the activation of innate immunity, although causality is debated. However, heart-specific adaptive immunity might also be critically involved in these (counter-)regulatory processes.[3–5] Circulating heart-reactive autoantibodies (anti-myocardial and anti-intercalated disc autoantibodies) have previously been described in both acute myocarditis/pericarditis and patients suffering from dilated cardiomyopathy at higher frequencies than in normal or non-inflammatory heart failure (HF) controls.[3,6] These autoantibodies are directed against multiple antigens. Some are expressed only in the myocardium (organ specific), whereas some anti-myocardial autoantibodies (AMyA) have functional effects on cardiac myocytes

*in vitro* as well as in animal models.[4,5,7] Depletion of autoantibodies by extracorporeal immunoadsorption is associated with improved ventricular function and reduced cardiac symptoms in some DCM patients, suggesting that AMyA may also have a pathogenetic role in humans.[8] Here, we explored the overarching hypothesis that an acute pro-inflammatory burst triggered by an AHF episode may boost adaptive immune responses against myocardial antigens, which might contribute to the progression of HF and worsened prognosis.

## Aims

We aimed to assess the prevalence of AMyA in patients admitted to the hospital for AHF, determine the development of AMyA within the 6 months following discharge from the hospital, and estimate their prognostic value in the subsequent year.

## Methods

From a larger registry that prospectively identifies patients admitted to our tertiary care hospital for AHF, we retrospectively selected a stratified sample consisting of 48 patients. Strata were male vs. female, chronic vs. *de novo* manifestation of AHF, and reduced left ventricular ejection fraction (LVEF $<$ 40%, HFrEF) vs. preserved LVEF (LVEF $\geq$ 50%, HFpEF). Stratification yielded eight groups of

**Figure 2** Status of expression of anti-myocardial antibodies at baseline (BL) and at the 6 month follow-up visit (F6) in patients with acute heart failure and reduced (HFrEF, *n* = 23) vs. preserved (HFpEF, *n* = 24) left ventricular ejection fraction. +/+, anti-myocardial antibodies (AMyA) titre positive at BL and F6; −/−, AMyA titre negative at BL and F6; −/+, AMyA titre newly developed between BL and F6.

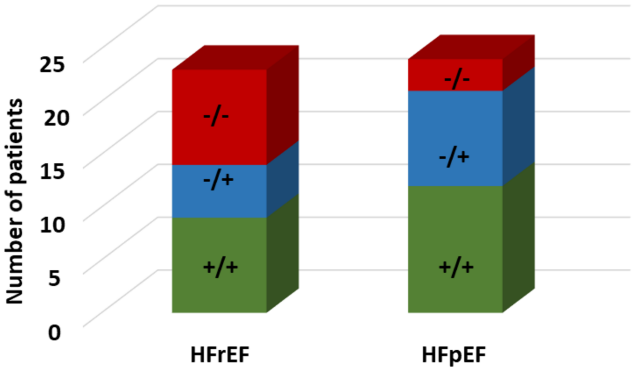


**Figure 1** Study flow. *N* = 47 patients hospitalized for acute heart failure were analysed for the presence of anti-myocardial antibodies (AMyA). The red drop symbol indicates the time points of venous blood sampling. Twenty patients provided pairs of venous samples at index hospitalization (i.e. baseline). Out of those, *n* = 12 were AMyA negative at Day 3; none of these patients exhibited altered AMyA titres *during* the index hospitalization. However, 15 patients who had been AMyA negative at baseline had generated new AMyA titres 6 months later (F6). All patients were followed for 18 months (F18) to collect endpoint information. The lower part of the figure illustrates the qualitative course of AMyA (positive +; negative −) from baseline to F6 in the total study population.

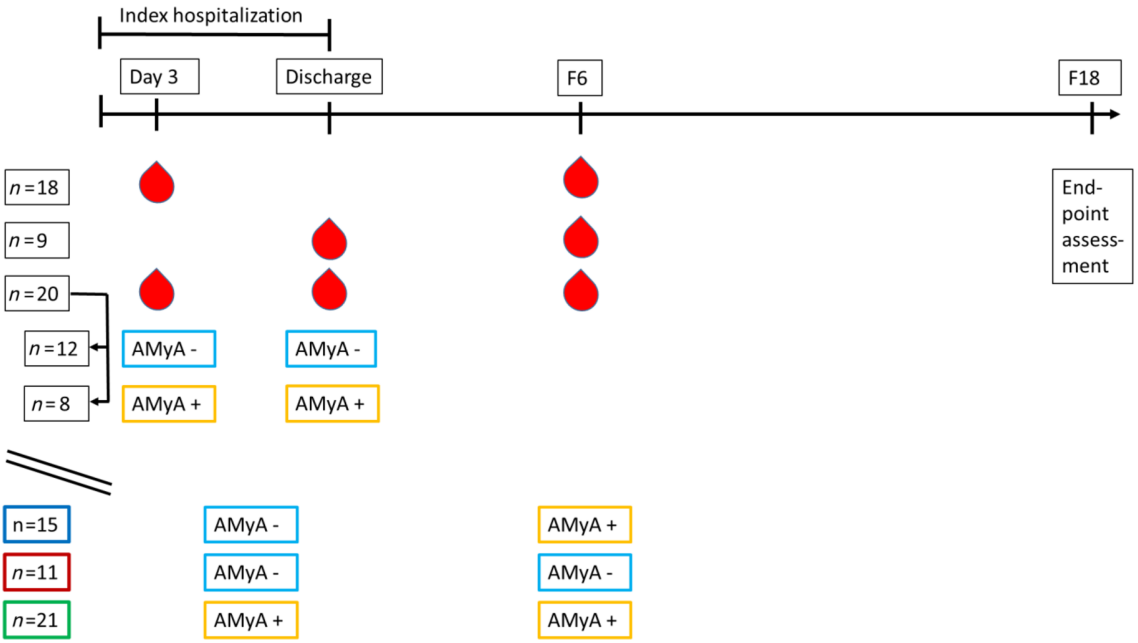



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**Table 1** Baseline characteristics and laboratory parameters assessed during index hospitalization in the total sample and in subgroups according to the presence of antimyocardial autoantibodies (AMyA) at baseline (BL) and 6 month follow-up visit (F6), respectively

| Baseline values | Total cohort *N* = 47 | AMyA (BL/F6) −/+ *N* = 15 | AMyA (BL/F6) −/− *N* = 11 | AMyA (BL/F6) +/+ *N* = 21 |
|---|---|---|---|---|
| Age, median (Q1; Q3) | 71 (60; 80) | 70 (63; 80) | 77 (45; 80) | 71 (60; 78) |
| Female sex, *n* (%) | 23 (49) | 6 (40) | 5 (45) | 12 (57) |
| HFrEF, *n* (%) | 23 (49) | 6 (40) | 8 (73) | 9 (43) |
| HFpEF, *n* (%) | 24 (51) | 9 (60) | 3 (27) | 12 (57) |
| *De novo* heart failure, *n* (%) | 23 (49) | 6 (40) | 6 (55) | 11 (52) |
| History of coronary disease, *n* (%) | 16 (34) | 8 (53) | 2 (18) | 6 (29) |
| History of diabetes mellitus, *n* (%) | 25 (53) | 11 (73) | 6 (55) | 8 (38) |
| History of hypertension, *n* (%) | 45 (96) | 15 (100) | 11 (100) | 19 (90) |
| Duration of index hospitalization (days), median (Q1; Q3) | 9 (7; 15) | 10 (7; 23) | 8 (7; 13) | 9 (7; 12) |
| Main cause of AHF | | | | |
| Myocarditis, *n* (%) | 1 (2) | 0 | 0 | 1 (5) |
| Acute coronary syndrome, *n* (%) | 6 (13) | 1 (7) | 3 (27) | 2 (10) |
| Hypertension, *n* (%) | 4 (9) | 3 (20) | 0 | 1 (5) |
| Rhythm disorder, *n* (%) | 10 (21) | 6 (40) | 1 (9) | 3 (14) |
| Infectious disease, *n* (%) | 1 (2) | 0 | 0 | 1 (5) |
| Cardiomyopathy, *n* (%) | 8 (17) | 0 | 2 (18) | 6 (29) |
| Valvular disease, *n* (%) | 7 (15) | 1 (7) | 0 | 6 (29) |
| Renal failure, *n* (%) | 4 (9) | 2 (13) | 1 (9) | 1 (5) |
| Other, *n* (%) | 6 (13) | 2 (13) | 4 (36) | 0 |
| Admission | | | | |
| Haemoglobin (g/dL), median (Q1; Q3) | 12.8 (11.4; 14.3) | 13.0 (11.4; 13.8) | 12.6 (12.0; 14.1) | 12.8 (10.7; 14.5) |
| Leucocytes (× 1000/μL), median (Q1; Q3) | 8.4 (7.2; 9.9) | 8.1 (7.0; 10.4) | 8.9 (7.0; 9.7) | 8.4 (7.4; 9.6) |
| Creatinine (mg/dL), median (Q1; Q3) | 1.3 (1.1; 1.6) | 1.3 (1.1; 1.7) | 1.2 (1.1; 1.5) | 1.2. (0.9; 1.6) |
| eGFR (mL/min/1.73 $m^2$), median (Q1; Q3) | 55 (47; 66) | 52 (43; 64) | 54 (49; 71) | 56 (39; 74) |
| CRP (mg/dL), median (Q1; Q3) | 0.9 (0.3; 2.5) | 1.0 (0.6; 1.9) | 0.5 (0.3; 3.0) | 1.2 (0.3; 3.0) |
| NT-proBNP (pg/mL), median (Q1; Q3) | 4513 (2729; 8255) | 3995 (2159; 6618) | 4243 (3316; 6152) | 6362 (2729; 10 677) |
| CK (U/L), median (Q1; Q3) | 78 (51; 120) | 69 (48; 109) | 80 (43; 109) | 96 (54; 168) |
| Discharge | | | | |
| Haemoglobin (g/dL), median (Q1; Q3) | 12.8 (11.7; 14.0) | 12.1 (11.3; 14.0) | 12.8 (11.7; 13.8) | 12.9 (11.7; 14.3) |
| Leucocytes (× 1000/μL), median (Q1; Q3) | 8.0 (6.8; 9.3) | 7.8 (6.3; 10.4) | 7.4 (6.7; 8.7) | 8.3 (7.0; 9.4) |
| Creatinine (mg/dL), median (Q1; Q3) | 1.2 (1.0; 1.5) | 1.4 (1.0; 1.6) | 1.3 (0.9; 1.5) | 1.2 (1.0; 1.5) |
| eGFR (mL/min/1.73 $m^2$), median (Q1; Q3) | 54 (48; 69) | 51.7 (41.5; 66.5) | 60 (51; 69) | 53 (45; 71) |
| CRP (mg/dL), median (Q1; Q3) | 0.5 (0.3; 0.9) | 0.6 (0.4; 0.9) | 0.4 (0.3; 0.7) | 0.5 (0.3; 1.0) |
| NT-proBNP (pg/mL), median (Q1; Q3) | 1447 (740; 2274) | 1113 (740; 1730) | 1058 (824; 2445) | 1492 (580; 2685) |
| CK (U/L), median (Q1; Q3) | 75 (61; 100) | 64 (51; 100) | 76 (64; 102) | 78 (64; 109) |
| Echocardiography[a] | | | | |
| Baseline | | | | |
| LVEDD (mm), median (Q1; Q3) | 54 (50; 61) | 53 (50; 56) | 56 (53; 60) | 53 (48; 63) |
| LVEF (%), median (Q1; Q3) | 34 (24; 61) | 52 (27; 61) | 26 (21; 51) | 55 (24; 64) |
| 6 month follow-up | | | | |
| LVEDD (mm), median (Q1; Q3) | 55 (47; 65) | 57 (46; 65) | 58 (48; 65) | 55 (47; 67) |
| Change from BL (mm), median (Q1; Q3) | +3 (−12; +15) | +11 (−11; +16) | +3 (−13; +12) | +1.0 (−15; +17) |
| LVEF (%), median (Q1; Q3) | 43 (29; 55) | 45 (30; 62) | 45 (37; 53) | 37 (28; 51) |
| Change from BL (%), median (Q1; Q3) | +1 (−20; +24) | −13 (−25; +37) | +22 (−3; +24) | +/−0 (−20; +19) |

AHF, acute heart failure; AMyA, anti-myocardial autoantibodies; BL, baseline; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.
Results are displayed as median (Q1; Q3) or *n* (% in the respective (sub)group).
[a]Echocardiography was available in *n* = 46 patients at BL and in *n* = 42 patients at F6.

six patients each. In addition, all patients had undergone a 6 month follow-up visit (F6) in our outpatient department and had complete information regarding hospitalization(s) or death for a follow-up period of 18 months after discharge from index hospitalization (F18). The study complies with the Declaration of Helsinki and was approved by the local ethics committee; patients provided informed consent regarding study participation. AMyA were determined in prospectively collected blood samples taken at baseline and visit F6 employing 'NOVA Lite® Heart (Primate) IFA Slides' together with anti-human IgG-FITC and standard positive and negative controls (Inova Diagnostics, San Diego, CA, USA). Serum dilutions of 1:20 were used for screening, and individual AMyA titres were determined by limiting dilution (two-fold dilution steps: 1:20, 1:40 etc.; highest titre: 1:1280). All slides were independently assessed by three observers for fluorescence of myofibrils. Titres of ≥1:20 were classified as positive. Statistical analyses were performed using SPSS® (IBM, Armonk, NYok, USA) Version 26. Continuous variables are reported as median


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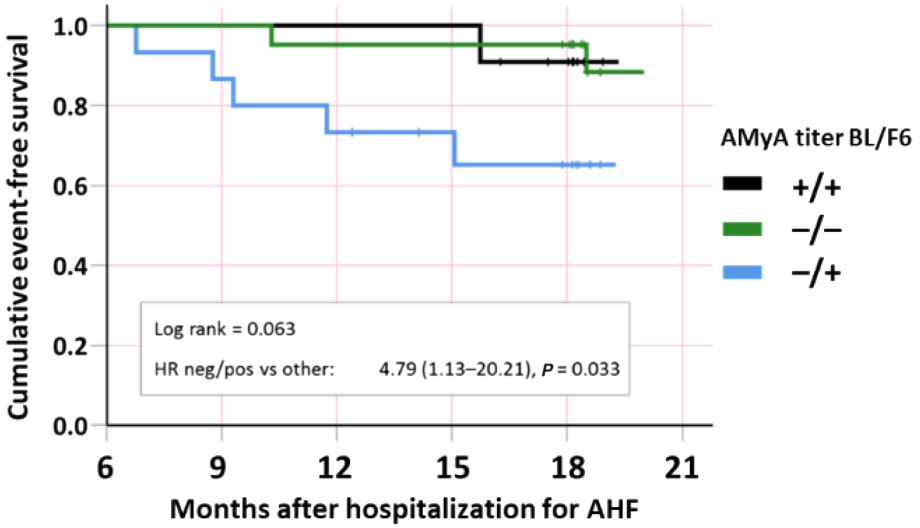
**Figure 3** Event-free survival (hospitalization for heart failure or death) observing the 12 month period between 6 (F6) and 18 months (F18) after discharge from the index hospitalization. Groups composed by the presence of anti-myocardial autoantibodies (AMyA) at baseline (BL) and F6 in *n* = 47 patients, who had been hospitalized for acute heart failure (AHF) at baseline (index hospitalization). HR, hazard ratio.




(quartiles) and categorical variables as frequency (per cent). Groupwise differences were calculated using $\chi^2$ and Kruskal–Wallis tests, as appropriate. Prognostic information is displayed using Kaplan–Meier survival curves and log-rank test. The prognostic yield of AMyA was assessed using Cox proportional hazard regression analyses, and hazard ratios with 95% confidence intervals are reported.

## Results

For the present analysis, serum samples of 47 patients hospitalized for AHF (index hospitalization; May 2015–March 2017) and at F6 were analysed (one female patient with *de novo* HFrEF yielded insufficient blood quality and thus did not enter analyses). Sampling at index hospitalization had been performed on Day 3 (*n* = 38) and on the day of discharge (*n* = 29; *Figure 1*). The median age of these patients was 71 (60; 80) years, and *n* = 23 (49%) were female. The median duration of index hospitalization was 9 (7; 15) days. Sixteen (34%) patients had known coronary disease, and 14 (30%) patients were in atrial fibrillation. At baseline, 21 (45%) patients exhibited AMyA within a range of 1:20–1:80. There was no difference in the prevalence of AMyA in HFrEF (*n* = 9, 39%) vs. HFpEF (*n* = 12, 50%; *P* = 0.454), in *de novo* (*n* = 11, 48%) vs. chronic HF (*n* = 10, 42%; *P* = 0.671), and in male (*n* = 9, 38%) vs. female patients (*n* = 12, 52%; *P* = 0.312). In 20 patients with blood samples from both Day 3 and the day of discharge, 12 (60%) were AMyA negative at Day 3 and remained negative until discharge (*Figure 1*). We found an increase in the prevalence of AMyA from baseline (*n* = 21, 45%) to F6 (*n* = 36, 77%; $P < 0.001$) and a higher prevalence of AMyA in HFpEF (*n* = 21, 88%) than in HFrEF at F6 (*n* = 14, 61%; *P* = 0.036; *Figure 2*). One male patient, who had an AMyA titre of 1:20 at baseline, was negative at F6 (assuming persistence of AMyA; this patient was considered +/+ for further analyses). All other patients with positive AMyA titres at baseline remained positive at F6. Fifteen (32%) patients newly developed positive AMyA titres, and 11 (23%) patients remained negative. *Table 1* illustrates baseline characteristics and laboratory parameters according to the prevalence of AMyA at baseline and F6.

In the 12 months following F6 (i.e. up to Month 18, F18), eight patients reached the combined endpoint death or rehospitalization for HF [*n* = 5 rehospitalizations for HF (with two subsequent deaths), *n* = 3 deaths]. Five of those (63%) had newly developed AMyA, two patients (25%) had persistent AMyA, and one patient (13%) had been negative for AMyA at baseline and F6. *Figure 3* illustrates event-free survival according to AMyA at baseline and F6. Prognosis differed according to AMyA status, and patients with newly developed AMyA at F6 had a significantly worse prognosis compared with the other two groups (hazard ratio 4.79, 95% confidence interval 1.13–20.21; *P* = 0.033).

## Conclusions

This pilot study analysed prospectively collected serum samples and clinical characteristics of 47 AHF patients and revealed three major findings. First, there was a high prevalence of AMyA in patients hospitalized for AHF, which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appeared independent of sex, HF phenotype, and mode of presentation. Second, an important proportion of AHF patients newly developed AMyA between baseline and the first 6 months following discharge, which was more pronounced in HFpEF compared with HFrEF. Third, we observed a worse prognosis in AHF patients with newly developed AMyA compared with those with persistent or without AMyA at F6.

The data accumulating in recent years demonstrate that elevated markers of inflammation correlate with prognosis both in HFpEF and in HFrEF patients.[2] Markers like pro-inflammatory cytokines, C-reactive protein, or galectin 3 primarily reflect innate immunity.[2] There is solid mechanistic evidence that activation of innate immunity in the myocardium contributes to myocardial fibrosis, adverse remodelling, and finally to HF progression.[2] Nevertheless, therapeutic approaches targeting inflammation in unselected HF patients were not successful in reducing HF events, so far.[9] On the other hand, circulating heart-reactive autoantibodies have been found in both acute inflammatory syndromes of the heart and in chronic HF syndromes.[3–5] Some of these autoantibodies were shown to elicit functional effects *in vitro* as well as in animal models.[8] In patients with chronic HF, antibody removal by extracorporeal immunoadsorption was associated with improved LV function and reduced clinical HF symptoms, suggesting that AMyA may also have a functional role in humans.[8] However, there is still an unmet need in defining diagnostic criteria to identify patients potentially benefitting from immunomodulatory therapy. We still lack clinical evidence on the relevance of adaptive immunity for HF progression. Therefore, we studied AMyA as biomarkers reflecting adaptive immune responses against myocardial antigens.

Our results strengthen the hypothesis that AHF, similar to acute cardiac inflammatory syndromes, may induce an adaptive immune response[8] and support further research regarding the role of the adaptive immune system in the progression of HF. However, we recognize the limitations of our approach. First, the reasons for an AMyA positive status at baseline (and, hence, a persistent AMyA positive status at F6) remain unclear. There might be pre-existing AMyA in some patients, either due to a preceding AHF episode in patients with known HF or due to a subclinical, protracted decompensation in patients with nominally '*de novo*' HF. These AMyA might be less or non-pathogenic AMyA recognizing a different set of antigens. Second, due to our aim to analyse the incidence of new AMyA development following AHF (i.e. focusing on AMyA −/+ AHF patients), we had to select patients with samples drawn at F6, hence patients who survived the first 6 months after hospitalization for acutely decompensated HF. This resulted in the selection of a relatively healthy patient group with lower event rates compared with the current literature.[1]

Larger studies including also sicker patients are needed to closely monitor the course and determinants of AMyA in acute and chronic HF as well as of the association of prevalent/incident AMyA with cardiac dimensions and myocardial function over time. Further research should investigate if AMyA as a biomarker for cardiac inflammatory processes might guide immunomodulatory therapies targeting the adaptive immune system in patients with HFrEF or HFpEF.

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## Conflict of interest

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