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▶ To cite this version:

George Markousis-Mavrogenis, Waldemar B Minich, Ali A Al-Mubarak, Stefan D Anker, John G F Cleland, et al.. Clinical and prognostic associations of autoantibodies recognizing adrenergic/muscarinic receptors in patients with heart failure. Cardiovascular Research, 2023, 119 (8), pp.1690-1705. 10.1093/cvr/cvad042 . hal-04023791

HAL Id: hal-04023791 https://hal.univ-lorraine.fr/hal-04023791

Submitted on 10 Mar 2023

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Clinical and prognostic associations of autoantibodies recognizing adrenergic/muscarinic receptors in patients with heart failure

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33 Short Title: Autoantibodies in Heart Failure

- 34 Keywords: beta 1, beta 2, beta 3, M2, immune system, autoimmunity
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3 Abstract

Aims. The importance of autoantibodies (AABs) against adrenergic/muscarinic receptors in heart failure
(HF) is not well-understood. We investigated the prevalence and clinical/prognostic associations of four
AABs recognizing the M2-muscarinic receptor or the β1-, β2-, or β3-adrenergic receptor in a large and wellcharacterized cohort of patients with HF.

Methods and Results. Serum samples from 2256 patients with HF from the BIOSTAT-CHF cohort and 8 9 299 healthy controls were analyzed using newly established chemiluminescence immunoassays. The primary outcome was a composite of all-cause mortality and HF-rehospitalization at 2-year follow-up, and 10 each outcome was also separately investigated. Collectively, 382 (16.9%) patients and 37 (12.4%) controls 11 were seropositive for ≥ 1 AAB (p=0.045). Seropositivity occurred more frequently only for anti-M2 AABs 12 (p=0.025). Amongst patients with HF, seropositivity was associated with the presence of comorbidities 13 14 (renal disease, chronic obstructive pulmonary disease, stroke, atrial fibrillation), and with medication use. Only anti-β1 AAB seropositivity was associated with the primary outcome [hazard ratio (95% confidence 15 interval): 1.37 (1.04-1.81), p=0.024] and HF-rehospitalization [1.57 (1.13-2.19), p=0.010] in univariable 16 analyses, but remained associated only with HF-rehospitalization after multivariable adjustment for the 17 BIOSTAT-CHF risk model [1.47 (1.05-2.07), p=0.030]. Principal component analyses showed considerable 18 overlap in B-lymphocyte activity between seropositive and seronegative patients, based on 31 circulating 19 biomarkers related to B-lymphocyte function. 20

Conclusions. AAB seropositivity was not strongly associated with adverse outcomes in HF and was mostly
 related to the presence of comorbidities and medication use. Only anti-β1 AABs were independently
 associated with HF-rehospitalization. The exact clinical value of AABs remains to be elucidated.w

1 Translational Perspective.

Currently, little is known regarding the clinical/prognostic associations of ANS-AABs in patients with HF.
We show that out of four investigated ANS-AABs, only anti-β1 AAB seropositivity was independently
associated with HF-rehospitalization. Seropositivity for any of the investigated AAB was not associated
with changes in circulating B-lymphocyte-related markers. Seropositivity was highly similar when
compared to healthy controls. These findings support a limited prognostic role for ANS-AABs in the general
HF population and suggest that ANS-AAB generation may be constitute a previous event unrelated to HF.
Future studies should investigate specific target groups such as Chagas cardiomyopathy, non-hereditary

N'

9 DCM and PPCM.

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11 Abbreviation list

| | ABBREVIATION | DEFINITION |
|----|--------------|--|
| | HF | Heart failure |
| | AAB | Autoantibody |
| | ANS-AAB | Autoantibodies against autonomic nervous system receptors |
| | DCM | Dilated cardiomyopathy |
| | BIOSTAT-CHF | A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure |
| | LVEF | Left ventricular ejection fraction |
| | BNP | Brain natriuretic peptide |
| | NT-PROBNP | N-terminal pro-brain natriuretic peptide |
| | ACEI/ARB | Angiotensin converting enzyme inhibitor/angiotensin receptor blocker |
| | BB | β-adrenoreceptor blocker |
| | CRP | C-reactive protein |
| | HS-CTNT | High-sensitivity cardiac troponin-T |
| | EGFR | Estimated glomerular filtration rate |
| | MDRD | Modification of Diet in Renal Disease |
| | HR | Hazard ratio |
| Χ. | 95% CI | 95% confidence interval |
| | IL-6 | Interleukin-6 |
| | ANOVA | Analysis of variance |
| | PCA | Principal component analysis |
| | COPD | Chronic obstructive pulmonary disease |
| | AF | Atrial fibrillation |
| | MRA | Mineralocorticoid receptor antagonist |

PPCM

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Peripartum cardiomyopathy

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2 Introduction

Many studies have demonstrated the intricate relationship between immune activation and pathophysiological mechanisms in HF.¹ Nevertheless, direct immunomodulatory interventions have as of yet no established role in the clinical management of HF.

Antibodies are soluble forms of the B-cell receptor that are secreted by activated plasma cells and 6 7 constitute an important part of the adaptive immune response.² The generation of an effective immune response requires a broad antibody repertoire, which is achieved with impressive efficiency by 8 recombination of immunoglobulin genes.³ This permits the generation of antibodies with potentially infinite 9 specificities. Unavoidably, this process also leads to the generation of antibodies against self-antigens. 10 Specialized regulatory mechanisms have evolved to eliminate self-reactive lymphocytes⁴; nevertheless, 11 these do not always function optimally. Accordingly, self-reactive lymphocytes and autoantibodies (AABs) 12 feature prominently in numerous autoimmune rheumatic diseases ⁵ and other disease states.⁶ 13

A relationship between AABs against autonomic nervous system receptors (ANS-AABs) and HF has been described previously, particularly in patients with non-hereditary dilated cardiomyopathy (DCM)⁷ and Chagas cardiomyopathy.⁸ However, to our knowledge, most reports are limited to small cohorts and no data from large, well-characterized, and diverse populations currently exist in the literature. We thus aimed to investigate the prevalence of ANS-AAB seropositivity in patients with HF, and to determine its clinical associations and potential relationships with outcomes.

1 Methods

2 <u>Patients</u>

We performed a post-hoc analysis of the BIOSTAT-CHF index cohort (n=2516), which has been 3 described previously.⁹ Briefly, BIOSTAT-CHF was a multi-center study enrolling patients from 11 4 5 European countries. Participants were aged ≥ 18 years, had symptoms of new-onset or worsening HF, combined with a left ventricular ejection fraction (LVEF) $\leq 40\%$ or brain-type natriuretic peptide (BNP) 6 and/or N-terminal pro-BNP (NT-proBNP) plasma levels >400 pg/mL or >2,000 pg/mL, respectively. 7 Participants were either not previously treated with angiotensin converting enzyme inhibitors/angiotensin 8 receptor blockers (ACEi/ARB) and/or β -adrenoreceptor blockers (BB) or were receiving $\leq 50\%$ of guideline-9 10 recommended target doses and anticipated their initiation or up-titration. All patients were treated with loop diuretics. Participants could be enrolled as inpatients or outpatients. The primary outcome was a composite 11 12 of all-cause mortality and rehospitalization for HF censored at 2-year follow-up, with each component separately constituting a secondary outcome. The study protocol was approved by local and national ethics 13 committees (EudraCT 2010-020808-29; R&D Ref Number 2008-CA03; MREC Number 10/S1402/39) and 14 all participants provided written informed consent. The study was performed according to the principles 15 outlined in the Declaration of Helsinki. 16

17 <u>Autoantibody Measurements</u>

Measurements of autoantibody titers against β1-, β2- and β3-adrenergic receptors, as well as M2muscarinic receptors were performed using chemiluminescence immunoassays (ImmunometriX, Berlin,
Germany) on blood serum samples from 2256/2516 (89.7%) patients from the BIOSTAT-CHF index cohort,
and in 299 controls that self-identified as healthy [acquired commercially from in.vent Diagnostica (Berlin,
Germany)]. Assay development and calculation of binding indices are described in the Supplementary
Methods. For quality control of the anti-β1 AAB assay, one negative and one positive sample from the

control group (binding index below the median and higher than 10 respectively) was measured in duplicate 1 2 in all microtiter plates during analysis (n=26 duplicates each). As there is no prior knowledge on the threshold for relevant AABs concentrations, the 99th percentile value of negative controls (1.3883) was used 3 4 to define a cut-off under which an assay would be considered definitively negative (henceforth 5 "seronegative"), while the 1st percentile value of positive controls (7.3818) was similarly used to define a cut-off above which, an assay would be considered definitively positive (henceforth "seropositive") 6 7 (Supplementary Figure 1). Patients with assay results in-between the two cut-off values were labelled 8 "intermediate". The same cut-offs were also applied for defining subgroups in the remaining AAB assays.

9 <u>Laboratory Indices</u>

Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal
disease (MDRD) formula. NT-proBNP and hs-cTnT were measured using sandwich immunoassays (Roche
Inc.), and CRP was measured using competitive immunoassays on a Luminex platform (Alere Inc.). Anemia
was defined according to the World Health Organization definition.

14 Biomarker Measurements

Plasma biomarkers were determined using the proximity extension assay technology (Olink 15 proteomics Inc.), as part of four biomarker panels involving 92 biomarker measurements each 16 (Cardiovascular-II, Cardiovascular-III, Immune Response and Oncology II panels), thus 368 biomarkers in 17 total. The complete list of available biomarkers has been reported previously.¹⁰ Overlapping biomarkers 18 between the four panels were amphiregulin, c-kit ligand and tissue factor pathway inhibitor-2 (measured 19 20 twice), as well as interleukin-6 (IL-6) (measured three times). For overlapping biomarkers, the mean of all measurements was used, leaving a total of 363 unique biomarkers. Additionally, eight biomarkers were 21 22 excluded from analyses because >10% of measurements were outside the assay's limit of detection. Thus, 23 in total, 355 biomarkers were available for further analysis.

CVR-2022-1307

1 <u>Pathway Over-representation Analysis</u>

Pathway over-representation analysis of the 355 biomarkers was performed using the "GProfiler" 2 pathway analyzer (version e104 eg51 p15 3922dba).¹¹ The results of the analysis were classified based on 3 4 the gene ontology classification of biological processes (annotation 2022-01-13).¹² Corrections for multiple testing were performed using the built-in g:SCS algorithm, using a false discovery rate threshold of 5%. 5 Only significantly over-represented processes that included ≥ 5 of their constituents, were included in the 6 final selection. The biomarker corneodesmosin could not be analyzed by GProfiler, and since the biomarkers 7 8 BNP and NT-proBNP share the same protein designation, the effective number of analyzed biomarkers was 9 eventually 353.

10 Selection of GO Biological Processes Related to B-lymphocytes and Antibodies

11 The pathway over-representation analysis of the 353 biomarkers yielded 768 over-represented 12 biological processes. Of these, 13 contained the terms "B cell" and "immunoglobulin". To eliminate 13 potential data redundancies due to member overlap between processes¹⁰, the 13 selected processes were 14 visualized in a directed acyclic graph, and the most distal non-redundant processes were selected (**Figure** 15 **1A, Figure 1B, Supplementary Figure 2**). This yielded five processes related to B-lymphocytes and 16 antibodies, represented by different combinations of 31 biomarkers (**Figure 1C**).

17 <u>Statistical Analysis</u>

18 Statistical analyses were conducted using R-studio (R version 4.2.0). Normality of continuous 19 variables was determined by visual inspection of histograms and Q-Q plots. Baseline characteristics were 20 compared for each of the four investigated AABs between seronegative, intermediate, and seropositive 21 patients. Normally distributed variables were compared using one-way analyses of variance (ANOVA), not-22 normally distributed continuous variables using Kruskal-Wallis tests, and categorical/binary variables using 23 Chi-square tests. In case of a significant ANOVA result, pairwise post-hoc testing with independent t-tests

1 using Bonferroni correction was performed. Chemiluminescence assay results for each AAB were compared 2 between patients with HF and healthy controls when considering the corresponding binding index as 3 continuous variable using the Mann-Whitney U test, and when classified based on the previously defined 4 groups by using Chi-square tests. Associations between autoantibody status and the primary outcome and 5 all-cause mortality were investigated using Kaplan-Meier curves, while associations with hospitalization 6 were investigated using cumulative incidence function curves while considering all-cause mortality a 7 competing risk. Univariable associations were investigated with log-rank tests, while multivariable corrections for previously published risk models for this cohort ⁹ were performed using Cox regression, 8 when statistical assumptions were met. These included, among others, age, comorbidities, measures of 9 congestion, NT-proBNP, and renal function⁹. Statistical testing in survival analyses was performed using 10 the log-rank test. Statistical significance was considered as $p \le 0.05$, considering the exploratory character of 11 12 this study.

Significant findings from survival analyses were further verified with propensity-score matching (MatchIt package v. 4.5.0) based on the aforementioned variables of BIOSTAT-CHF risk model. Seropositive patients were matched 1:1 to seronegative patients. A nearest-neighbor matching algorithm with a caliper of 0.2 and without replacement, taking into account the region of common support, was used for this purpose.¹³ Unmatched observations were discarded. Statistical as well as graphical balance diagnostics tools were performed in order to evaluate the matching process.

19 To investigate the relative state of B-lymphocyte function in seronegative and seropositive patients, 20 principal component analyses (PCA) were conducted for each AAB, by excluding patients that were 21 categorized as intermediate. Subsequently, the results were plotted on biplots with concentration ellipses for 22 each group.

1 Results

| 2 | Baseline characteristics for the entire cohort are presented in Table 1. Mean age was 69 (12) years, |
|----|---|
| 3 | and 602 (26.7%) were women. Ischemia was the most prevalent primary etiology of HF (46%) and median |
| 4 | NT-proBNP was 2721.0 pg/mL [1204.3, 5741.8]. Median LVEF was 30% [25-37] and 216 (10.7%) patients |
| 5 | had an LVEF>40%. Healthy controls had a median age of 32 years [24, 40] (range: 18-63 years) and 134 |
| 6 | (44.8%) were women. |
| 7 | Comparison of Assay Binding Indices in Healthy Controls and Patients with Heart Failure |
| 8 | Assay binding indices for each AAB are presented as continuous variables using half-violin plots |
| 9 | with superimposed boxplots and individual data points in Figure 2A. There were no statistically significant |
| 10 | differences between healthy controls and patients with HF in median binding index for anti- β 1 AABs [1.22] |
| 11 | (1.00, 1.59) vs. 1.23 (1.01, 1.73), p=0.238], anti-β2 AABs [1.24 (0.97, 2.01) vs. 1.25 (1.01, 1.88), p=0.516] |
| 12 | and anti-M2 AABs [1.32 (1.05, 2.02) vs. 1.31 (1.00, 2.25), p=0.722]. Patients with HF had a higher median |
| 13 | binding index for anti-β3 AABs [1.10 (0.89, 1.39) vs. 1.19 (1.01, 1.46), p<0.001]. |
| 14 | Classification of Autoantibody Status |
| 15 | The relative prevalence of seronegative, intermediate, and seropositive status amongst healthy |
| 16 | controls and patients with HF are presented in Figure 2B. The prevalence of seropositivity amongst patients |
| 17 | with HF in increasing order was 1.8% (n=41) for anti- β 3, 5.1% (n=114) for anti- β 1, 5.9% (n=133) for anti- |
| 18 | β 2, and 7.6% (n=172) for anti-M2 AABs. The proportion of groups was significantly different between |
| 19 | patients with HF compared with healthy controls only for anti-M2 AABs, driven by a higher proportion of |

seropositive patients (p=0.025). In total, 382 (16.9%) patients with HF were classified as seropositive for at
least one AAB, compared with 37 (12.4%) of the healthy controls (p=0.045). Summary statistics for assay
binding indices in total and stratified by AAB status are presented in Supplementary Tables 1 and 2,
respectively.

1 The co-occurrence of either intermediate or seropositive status between the different AABs is 2 presented in **Figure 2C**, while the co-occurrence of seropositive status only is presented in **Figure 2D**. 3 Among the 382 patients that were seropositive for at least one AABs, co-occurrence of seropositivity for 4 any of the remaining AABs had a low prevalence, with the highest value being observed for seropositivity 5 for all four AABs in 15/382 (3.9%) patients. Collectively, 340/382 (89.0%) patients were seropositive for 6 only one of the studied AABs.

7 <u>Clinical Associations of Autoantibody Seropositivity</u>

8 Baseline characteristics stratified by seronegative, intermediate, and seropositive groupings for each
9 AAB are presented in Tables 1-4 for anti-β1, anti-β2, anti-β3, and anti-M2 AABs, respectively.

10 Anti-β1-Autoantibodies

Anti-β1 AAB seropositivity was associated with a lower prevalence of a primary cardiomyopathy 11 etiology [seronegative vs. intermediate vs. seropositive: 372 (27.1%) vs. 169 (23.2%) vs. 15 (13.4%), 12 p=0.002], a higher prevalence of a history of renal disease [366 (26.2%) vs. 216 (29.1%) vs. 46 (40.1%), 13 p=0.004], anemia [446 (35.1%) vs. 250 (37.0%) vs. 50 (47.2%), p=0.043], and chronic obstructive 14 pulmonary disease (COPD) [232 (16.6%) vs. 133 (17.9%) vs. 30 (26.3%), p=0.030]. These were also 15 16 mirrored by corresponding changes in serum creatinine and hemoglobin (p=0.027 and 0.047 respectively). Lastly, seropositivity was associated with a lower prevalence of mineralocorticoid receptor antagonist 17 (MRA) use [766 (54.8%) vs. 379 (51.0%) vs. 51 (44.7%), p=0.045]. Amongst patients with a primary 18 ischemic HF etiology, β 1-seropositivity did not differ significantly amongst those with and without a history 19 of MI [40 (5.2%) vs. 17 (7.0%), p=0.514]. 20

1 Anti-β2-Autoantibodies

Anti- β 2 AAB seropositivity was associated with history of stroke [129 (9.7%) vs. 63 (7.9%) vs. 20 2 3 (15.0%), p=0.027], and current smoking (p=0.021). The proportion of seropositive patients with an 4 LVEF ≥ 40% was modestly lower compared to seronegative patients [145 (12.2%) vs. 60 (8.5%) vs. 11 5 (9.2%), p=0.034]. Seropositive patients were more likely to have been recruited as outpatients rather than 6 inpatients [458 (34.6%) vs. 223 (28.0%) vs. 53 (39.8%), p=0.001]. Similar to anti-\beta1 seropositive patients, anti- β 2 seropositivity was associated with a lower prevalence of MRA use [677 (51.4) vs. 458 (57.5%) vs. 7 8 61 (45.9%), p=0.004]. Seropositive diabetics were also less likely to be using oral hypoglycemic agents 9 (p=0.042).

10 Anti- β 3-Autoantibodies

Anti-β3 AAB seropositivity was associated with a higher prevalence of atrial fibrillation (AF) and
COPD [687 (43.7%) vs. 316 (49.4%) vs. 21 (51.2%), p=0.038, and 260 (16.5%) vs. 123 (19.2%) vs. 12
(29.3%), p=0.044, respectively]. In addition, mean eGFR was lower in seropositive patients [65.92 (26.57)
vs. 62.98 (24.91) vs. 60.50 (31.33), p=0.032], with corresponding increases in serum creatinine (p=0.027).
Lastly, a greater proportion of seropositive patients was at the guideline-recommended target dose for BB
[84 (5.3%) vs. 36 (5.6%) vs. 7 (17.1%), p=0.006].

17 Anti-M2-Autoantibodies

Seropositivity for anti-M2 AABs was associated with a higher probability of being at the guidelinerecommended target dose for ACEi [157 (13.0%) vs. 105 (12.1%) vs. 33 (19.2%), p=0.040], as well as
higher probability of MRA use [615 (50.8%) vs. 477 (54.8%) vs. 104 (60.5%), p=0.026].

1 <u>Survival Analysis</u>

2 Kaplan-Meier survival curves are presented for each AAB in Figure 3A for the combined outcome, and all-cause mortality alone (Figure 3B) at 2-year follow-up. Cumulative incidence function curves for 3 4 the competing risk analysis of HF rehospitalization at 2-year follow-up with all-cause mortality as a 5 competing risk are presented in **Figure 3C**. Regarding the primary outcome, anti-B1 seropositive patients 6 trended towards a poorer prognosis, without reaching statistical significance (p=0.068). Anti- β 3 status was associated with the primary outcome, with seropositive patients having an overall better prognosis 7 (p=0.016). Anti-B2 and anti-M2 status were not significantly associated with the primary outcome. There 8 were no significant associations between AAB status and all-cause mortality. Competing risks analysis 9 revealed only a significant association between anti-ß1 seropositivity and a higher probability of HF 10 rehospitalization (p=0.029). A sensitivity analysis was performed after merging seronegative and 11 12 intermediate patients because these groups showed comparable results in previous survival analyses. This revealed that the primary outcome and HF rehospitalization alone were more frequent only in patients who 13 were seropositive for anti- β 1 AABs (p=0.023 and 0.008, respectively) (Figure 4). 14

Since the two significant comparisons for anti-\beta1 AABs in the sensitivity analysis also met the 15 criteria for the proportionality of hazards assumption, additional multivariable analyses were performed 16 17 (Cox regression for the combined outcome and competing risks regression for rehospitalization). Compared with seronegative/intermediate status, anti-ß1 seropositivity was associated with the combined outcome 18 [hazard ratio (HR), 95% confidence interval (95% CI): 1.37 (1.04-1.81), p=0.024] but ceased to be 19 20 significant when corrected for the previously published BIOSTAT-CHF risk model [HR (95% CI): 1.27 21 (0.97-1.68), p=0.087]. Anti- β 1 seropositivity was associated with HF rehospitalization both in univariable 22 analysis [HR (95%CI): 1.57 (1.13-2.19), p=0.010], and when adjusted for the BIOSTAT-CHF risk model 23 [HR (95% CI): 1.47 (1.05-2.07), p=0.030]. Additional validation was performed by means of propensity score matching as described in the methods section. All patients that were anti- β 1 seropositive except one 24

(n=113), were matched 1:1 to seronegative patients, forming well-balanced groups (standardized mean
differences <0.1, variance ratios <2). Seropositive patients had significantly higher risk for HF-
rehospitalization at 2-year follow-up (standardized HR (95% CI) 1.83 (1.08-3.10), p=0.024).

4 Because patients with intermediate AAB status seemed to have a different prognosis, particularly 5 in the case of anti- β 3 AABs (**Figure 3**), additional analyses were performed in patients with intermediate AAB status for all AABs, in order to investigate whether the AAB titer as a continuous variable was 6 associated with any of the examined outcomes (Supplementary Table 3). Intermediate patients for anti-B3 7 8 AABs showed an inverse association between anti- β 3 AAB titer and the combined outcome [HR (95% CI): 0.82 (0.71-0.94) for each 1-unit increase, p=0.006], which remained significant after adjustment for the 9 corresponding risk model [HR (95% CI): 0.83 (0.72-0.95), p=0.009]. In patients with intermediate anti-β2 10 status, AAB titers were associated with reduced all-cause mortality [HR (95% CI): 0.83 (0.72-0.95), 11 p=0.008]. However, this was no longer significant after multivariable correction for the corresponding risk 12 model (p=0.196). Patients with intermediate status for anti- β 1/anti-M2 AABs did not show associations 13 between their corresponding AAB titers and any examined outcomes. 14

15 Analysis of Circulating B-lymphocyte-Associated Markers in Relation to Autoantibody Seropositivity

PCA was used on the 31 B-lymphocyte-related biomarkers (**Figure 5**). Concentration ellipses were plotted for seropositive and seronegative individuals per AAB. All sub-analyses demonstrated considerable overlap between seropositive and seronegative patients. The relative contribution of the 31 biomarkers to the 1st and 2nd principal components is presented in **Supplementary Figure 3**.

In this post-hoc analysis of a large and heterogeneous cohort of patients with HF, 16.9% of patients were seropositive for at least one ANS-AAB. Overall, the prevalence of seropositivity did not significantly differ from that of healthy controls, with the exception of a significantly higher prevalence of seropositivity

²⁰ Discussion

for anti-M2 AABs. Seropositivity for ANS-AABs was associated with the presence of comorbidities (renal
 disease, COPD, AF, stroke), or ARB/MRA use. Only seropositivity for anti-β1 AABs was significantly
 associated with a higher probability of HF rehospitalization at 2-year follow-up. PCA revealed considerable
 overlap of B-lymphocyte activity between seropositive and seronegative patients with HF, based on 31
 circulating biomarkers.

6 Most studies evaluating ANS-AABs in patients with HF have been conducted in patients with Chagas cardiomyopathy and non-hereditary DCM, mostly focusing on anti-β1 and anti-M2 AABs. 7 8 Approximately a third of patients with asymptomatic Chagas disease have detectable anti- β 1, anti- β 2 and anti-M2 AABs, while almost all who develop cardiomyopathy, are seropositive for all aforementioned 9 AABs.⁸ Among patients with non-hereditary DCM, anti-\beta1 and anti-M2 AABs were detected in 31% and 10 36-39% of patients, respectively.¹⁴ Interestingly, immunoglobulin subclasses may also be relevant, as in 11 12 patients with DCM the presence of IgG3-anti-β1 AABs was associated with a better LVEF during followup compared with seronegative patients, or those with non-IgG3-anti-β1 AABs.¹⁵ Furthermore, an increased 13 prevalence of ANS-AAB seropositivity has been reported in women with peripartum cardiomyopathy 14 (PPCM) compared with healthy pregnant controls.¹⁶ In patients with non-hereditary DCM, anti-β1 AABs 15 16 are also associated with an increased risk of ventricular tachycardia and sudden cardiac death¹⁷, while anti-M2 AABs predict rehospitalization but not all-cause mortality in PPCM.¹⁸ In our study, we only identified 17 an independent association between seropositivity for anti- β 1 AABs with HF rehospitalization at 2-year 18 follow-up, similar to a previous study in a smaller cohort.¹⁹ This might be explained by counterbalance of 19 anti- β 1 AAB actions by anti- β 2 AABs,²⁰ although their co-occurrence was limited. Conversely, 20 21 seropositivity for anti-β3 AABs trended towards an association with better prognosis. However, the low seroprevalence of anti-\beta3 AABs made additional analyses difficult. 22

ANS-AABs can potentially influence cardiac function by causing inappropriate positive or negative
 chronotropic or inotropic effects, by inducing cardiomyocyte apoptosis, or by activating the complement

cascade.^{14,21-23} Other authors reported that anti-B1 AABs from patients with DCM enhanced T-cell 1 proliferation via PKA/MAPK-signaling, which was prevented by metoprolol.²⁴ They also reduced 2 interferon- γ production, while increasing IL-4 production by T-cells.²⁴ Anti- β 1 AABs also impaired 3 endothelial function in In Wistar rats by negatively affecting NO signaling.²⁵ In contrast, anti-B3 AABs from 4 patients with HF protected rats with abdominal aortic banding from developing LV dysfunction and 5 dilation.²⁶ Anti-β1 and anti-M2 AABs have been found to induce HF in rodents, which could be reversed 6 upon their removal.^{27,28} This suggests a drug-like function on their corresponding target receptors.²⁸ 7 However, the pharmacology governing these interactions is as of yet unclear²⁸ and the agonist or antagonist 8 characteristics of anti-\beta1 AABs can also be of interest with regard to whether their removal would lead to 9 clinical benefit.27 10

Extensive studies in the setting of autoimmunity have led to the identification of numerous 11 12 mechanisms underlying the generation of AABs. One such mechanism has been termed "molecular mimicry", which describes the process of antibody generation against microbial proteins, which are also 13 structurally homologous to self-peptides.²⁹ A search of the literature did not reveal the presence of any 14 structural homologues of ANS receptors; still, structural similarities between microbial peptides and ANS 15 16 receptors cannot be ruled out. A different mechanism involves the generation of AABs against strictly 17 intracellular antigens, as often occurs in autoimmune diseases (e.g. anti-nuclear antibodies, anti-cytoplasmic antibodies. etc.).³⁰ The latter is less likely in this case, considering that ANS receptors are transported to the 18 cell membrane. An additional explanation could be that B-lymphocytes expressing B-cell receptors that 19 20 recognize self-antigens with high affinity are efficiently depleted or functionally silenced, while Blymphocytes with medium- or low-affinity receptors may escape tolerance mechanisms and give rise to 21 antibody-producing plasma cells.³¹ Collectively, circulating markers of B-lymphocyte function did not 22 23 differ significantly between seropositive and seronegative patients in our PCA analyses, suggesting that 24 ANS-AAB generation was not an acute process.

Autoreactive B-lymphocytes and plasma cells also occur in the general population and 1 2 seropositivity for AABs associated with thyroid disorders or autoimmune diseases does not per se lead to 3 clinical manifestations.^{14,32,33} Yet, both within the field of cardiovascular disease, as well as in other disease 4 states, circulating ANS-AABs have been implicated in the pathophysiology of various diseases. The reasons 5 behind the differential effects of circulating AABs in the general population and in specific disease processes remain unknown. Natural autoreactive immunoglobulin-M (IgM) antibodies may protect from autoimmune 6 disease³⁴, while the subtype of circulating IgG antibodies as well as the glycosylation and sialylation status 7 of their Fc-segments regulate higher affinity binding to inhibitory Fcy receptors (FcyRIIA, FcyRIIB).³¹ 8 Interestingly, animal studies have shown that the generation of IgG antibodies with pro-inflammatory 9 profiles requires a T-lymphocyte-dependent immune response³⁵, which is in agreement with previous 10 findings by our group underlying the important prognostic role of T-lymphocyte activation in HF.¹⁰ 11 Furthermore, anti-\beta1 AABs from patients with HF lead to cardiac fibrosis, cardiomyocyte apoptosis, LV 12 dilatation, and increases in LV mass in wild-type mice, which was not observed in mice lacking T-13 lymphocytes.³⁶ The same study showed that blockade of IL-6 production using small interfering RNA in 14 wild-type mice ameliorated cardiomyocyte apoptosis, and that anti- β 1 AABs upregulated IL-6 production 15 in T-lymphocytes from patients with HF.³⁶ These findings illustrate the interplay between T-lymphocytes 16 and ANS-AABs and are further supported by the prognostic value of IL-6 in HF.37 17

18 Limitations

19 The post-hoc character of this study and the relatively low prevalence of AAB seropositivity suggest 20 that some analyses may have been underpowered, particularly in the case of anti- β 3 AABs. Additional 21 characteristics for the healthy control population were not available and could thus not be accounted for in 22 statistical analyses. Additionally, the control population was significantly different from the examined 23 patients (younger, more women) and our findings could suggest potential age-dependency of AAB 24 formation. Extensive antibody repertoire mapping was not performed, which might have led to the identification of AABs with greater prognostic implications. In addition, our study did not include any
patients with Chagas cardiomyopathy or PPCM and lacked the necessary data to determine the presence of
non-hereditary DCM. The BIOSTAT-CHF cohort included patients that were suboptimally treated for HF
and might thus not be representative of the general HF population. Furthermore, it could be hypothesized
that the uptitration of HF treatments after initial blood sampling could have masked or attenuated the effects
of AABs on outcomes. Lastly, we did not evaluate the functional characteristics of measured AABs (e.g.,
inhibitory, stimulatory) and the specific isotype/class, subclass and allotype of AABs were not determined.

8 Conclusion

In a large and heterogeneous population of patients with HF, seropositivity for ANS-AABs was not
 strongly associated with adverse outcomes and was mostly related to existing comorbidities and medication
 use, while only seropositivity for anti-β1 AABs was independently associated with rehospitalization for HF.
 Further studies are necessary to better elucidate the potential prognostic significance and clinical
 associations of ANS-AABs in patients with non-hereditary DCM, Chagas cardiomyopathy or PPCM.

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15 Acknowledgements: No acknowledgements to disclose.

Funding: BIOSTAT-CHF was funded by the European Commission [FP7-242209-BIOSTAT-CHF;
EudraCT 2010-020808-29]. The analytical work was supported by the German Federal Ministry for
Economic Affairs and Energy (BMWi) and the European Social Fund (ESF); EXIST-Project "BridgeART", FKZ: 03EFLBE114.

Statement of contribution: GMM (design, analysis, interpretation, drafting, revision), WBM (analysis,
 revision), AAaM (design, analysis, interpretation, revision), SDA (acquisition, revision), JGFC (acquisition,
 revision), KD (acquisition, revision), CCL (acquisition, revision), LLN (acquisition, revision), NJS

 (acquisition, revision), FZ (acquisition, revision), MM (acquisition, revision), PS (design, acquisition, analysis, revision), AH (design, acquisition, analysis, revision), PL (design, acquisition, analysis, revision),
 DJvV (acquisition, revision), RAdB (acquisition, revision), AAV (acquisition, revision), PvdM (acquisition, revision), LS (conception, design, analysis, interpretation, revision), NB (conception, acquisition, analysis, interpretation, revision)

6 Disclosures: AAV received consultancy fees and/or research grants from AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cytokinetics, Merck, NovoNordisk, Novartis, and Roche diagnostics. PvdM received 7 consultancy fees and/or grants from Novartis, Corvidia, Singulex, Servier, Vifor Pharma, Astra Zeneca, 8 9 Pfizer and Ionis. R.A.d.B. received grants from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche and speaker fees from 10 Abbott, AstraZeneca, Bayer, Novartis, and Roche. F.Z. received personal fees for trial oversight 11 12 committees, advisory boards, or speakers' bureau from Acceleron, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer, Cardior, Cereno Scientific, Cellprothera, CVRx, G3 Pharmaceuticals, 13 Merck, Merck AG, Novartis, NovoNordisk, Pfizer, Servier, Vifor Fresenius, and is Co-Founder of 14 CardioRenal, CVCT. JGFC received consultancy fees and/or research grants from Abbott, Amgen, Astra-15 16 Zeneca, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Cytokinetics, Idorsia, Johnson & Johnson, 17 Medtronic, Myokardia, Novartis, NI Medical, Pharmacosmos, Pharma Nord, Philips, Respicardia, Servier, Torrent, Vifor, Viscardia. M.M. reports fees from Actelion, Amgen, Astra-Zeneca, Livanova, Servier, Vifor 18 19 pharma and WindTree Therapeutics as member of clinical trials committees or advisory boards and from 20 Abbott vascular, Bayer, Boheringer Ingelhelm and Edwards Therapeutics for speeches at sponsored 21 meetings in the last three years. W.B.M., P.S. and P.L. are founders of ImmunometriX. W.B.M. and L.S. 22 are listed as inventors on a patent application. All other authors have no relationships to disclose that could 23 be construed as a conflict of interest with regard to this manuscript.

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1 Figure legends

Figure 1. A. Directed acyclic graph displaying the 13 over-represented GO biological processes containing
the terms "B cell" and "immunoglobulin". Non-redundant children terms selected for further analysis are
highlighted in blue. A higher resolution version of this image is presented in Supplementary Figure 2. B.
Detailed results of pathway over-representation analysis for the 13 selected biological processes, including
the p-value, intersection size and term size. C. Network denoting biomarker membership to the 5 GO
biological processes that were used for further analyses. GO gene ontology; ID identifier; HGNC HUGO
Gene Nomenclature Committee.

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Figure 2. A. Half-violin plots and boxplots with individual data points of assay binding indices for all investigated autoantibodies, presented separately for healthy controls and patients with HF. B. Relative prevalence of seronegative, intermediate and seropositive status for each autoantibody in healthy controls and patients with HF. C. Venn diagram illustrating the co-occurrence of intermediate and/or seropositive status for each autoantibody in patients with HF. D. Venn diagram illustrating overlapping seropositivity

15 for each autoantibody in patients with HF. HF heart failure

16

Figure 3. Kaplan-Meier curves for the combined outcome (all-cause mortality and rehospitalization for HF) censored at 2 years (**row A**), and for all-cause mortality alone (**row B**), as well as cumulative incidence function curves for rehospitalization for HF only with all-cause mortality as a competing risk (**row C**). From left to right, results of univariable analyses for anti- β 1, anti- β 2, anti- β 3, and anti-M2 autoantibodies. HF

21 heart failure

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Figure 4. Sensitivity analyses of the results presented in Figure 3, by stratifying categories as seronegative/intermediate and seropositive. Kaplan-Meier curves for the combined outcome (all-cause mortality and rehospitalization for HF) censored at 2 years (row A), and for all-cause mortality alone (row B), as well as cumulative incidence function curves for rehospitalization for HF only with all-cause mortality as a competing risk (row C). For anti- β 1 autoantibodies, Cox regression analyses for the combined outcome and competing risks analyses for HF-related rehospitalization (both univariable and multivariable) are presented in the results section. HF heart failure

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Figure 5. Biplot of principal component analysis of the 31 biomarkers involved in B-lymphocyte-associated biological processes. The intermediate group for each AAB was excluded to accentuate potential differences. Considerable overlap is seen between groups in all comparisons. For optimal visualization, only the top fifteen biomarkers that contributed the most to the first principal component are shown. The relative contribution of all examined biomarkers is shown in **Supplementary Figure 3**). AAB autoantibody

| 1 | | | | | | | | | |
|--|-------------------------|-------------------------|-------------------------|-------------------------|------------------------------|--|--|--|--|
| Table 1 . Baseline characteristics for the entire patient cohort and stratified according to anti-61-adreneraic receptor autoantibody status. | | | | | | | | | |
| Variable | Whole Cohort | Anti-β1 Seronegative | Anti-β1 Intermediate | Anti-B1 Seropositive | p-value | | | | |
| Group Size | 2256 | 1399 | 743 | 114 | N/A T | | | | |
| Demographics | | | | | ht | | | | |
| Age (Years) | 69 (12) | 69 (12) | 69 (11) | 70 (12) | 0.568 ਰ | | | | |
| Female sex | 602 (26.7%) | 401 (28.7%) | 167 (22.5%) | 34 (29.8%) | 0.006* | | | | |
| Recruited as outpatient | 822 (32.6%) | 455 (32.6%) | 242 (32.6%) | 37 (32.5%) | 0.999 🖁 | | | | |
| Primary HF Etiology | | | | | de | | | | |
| Cardiomyopathy | 556 (25.1%) | 372 (27.1%) | 169 (23.2%) | 15 (13.4%) | 0.002* 🗎 | | | | |
| Hypertensive | 233 (10.5%) | 137 (10.0%) | 85 (11.7%) | 11 (9.8%) | 0.468 o | | | | |
| Ischemic | 1018 (46.0%) | 619 (45.1%) | 342 (47.0%) | 57 (50.9%) | 0.402 b | | | | |
| Valvular Disease | 167 (7.5%) | 104 (7.6%) | 49 (6.7%) | 14 (12.5%) | 0.099 8 | | | | |
| Previous History and | | | | | n/c | | | | |
| Comorbidities | | | | | ard | | | | |
| AF | 1024 (45.4%) | 636 (45.5%) | 331 (44.5%) | 57 (50.0%) | 0.549 | | | | |
| DM | 732 (32.5%) | 459 (32.9%) | 237 (31.9%) | 36 (31.6%) | 0.884 ឆ្ល | | | | |
| HT | 1398 (62.0%) | 868 (62.1%) | 458 (61.6%) | 72 (63.2%) | 0.944 <u>କ</u> | | | | |
| RD | 628 (27.9%) | 366 (26.2%) | 216 (29.1%) | 46 (40.4%) | 0.004* 0 | | | | |
| Anemia | 746 (36.4%) | 446 (35.1%) | 250 (37.0%) | 50 (47.2%) | 0.043* | | | | |
| COPD | 395 (17.5%) | 232 (16.6%) | 133 (17.9%) | 30 (26.3%) | 0.030* and | | | | |
| IVII Charles | 864 (38.3%) | 525 (37.6%) | 297 (40.0%) | 42 (36.8%) | 0.525 | | | | |
| Stroke | 212 (9.4%) | 133 (9.5%) | 70 (9.4%) | 9 (7.9%) | 0.849 a | | | | |
| HF Hospitalization during | /11 (31.5%) | 439 (31.4%) | 242 (32.6%) | 30 (26.3%) | 0.404 | | | | |
| previous year | | | | | /dc | | | | |
| Smoking | 824 (26 6%) | E24 (28 29/) | 252 (24 0%) | 28 (22 6%) | oi/1 | | | | |
| Past | 1105 (49 1%) | 656 (47.0%) | 202 (54.0%) | 59 (52.0%) | 0.16 - | | | | |
| Current | 322 (14 3%) | 206 (14.8%) | 100 (13 5%) | 16 (14 2%) | 0.10 00 | | | | |
| Clinical Characteristics | 522 (11.576) | 200 (11.07.0) | 100 (10.070) | 10 (11.270) | 3/c | | | | |
| NYHA Functional Class | | | | | vr/c | | | | |
| | 209 (10.6%) | 132 (10.9%) | 66 (10.1%) | 11 (10.8%) | ova | | | | |
| II | 1014 (51.6%) | 644 (53.2%) | 323 (49.6%) | 47 (46.1%) | 0.226 | | | | |
| | 663 (33.8%) | 391 (32.3%) | 236 (36.3%) | 36 (35.3%) | 42/ | | | | |
| IV | 78 (4.0%) | 44 (3.6%) | 26 (4.0%) | 8 (7.8%) | 70 | | | | |
| | | | | | 723 | | | | |
| NYHA Class III or IV | 741 (37.7%) | 435 (35.9%) | 262 (40.2%) | 44 (43.1%) | 0.095 员 | | | | |
| BMI (kg/m ²) | 27.1 [24.1, 30.5] | 27.2 [24.2, 30.8] | 27.2 [24.0, 30.5] | 25.9 [23.6, 29.1] | 0.089 ರ | | | | |
| HR (beats/min) | 76 [67, 90] | 76 [67, 88] | 76 [67, 90] | 75 [67, 85] | 0.813 0 | | | | |
| SBP (mm Hg) | 125 (22) | 125 (22) | 125 (23) | 126 (21) | 0.907 🖯 | | | | |
| DBP (mm Hg) | 75 (13) | 75 (13) | 75 (14) | 73 (14) | 0.179 Z | | | | |
| Pulmonary Crackles | 1156 (52.8%) | 716 (52.7%) | 381 (53.1%) | 59 (53.2%) | 0.984 🛓 | | | | |
| 6MWT Successfully Completed | 1413 (64.8%) | 888 (65.7%) | 459 (64.2%) | 66 (58.4%) | 0.266 $\stackrel{()}{\prec}$ | | | | |
| 6MWT Distance (m) | 220 [0, 350] | 222 [0, 356] | 216 [0, 350] | 160 [0, 328] | 0.685 _ | | | | |
| LVEF (%) | 30 [25, 36] | 30 [25, 35] | 30 [25, 37] | 33 [25, 40] | 0.052 🖉 | | | | |
| LVEF > 40% | 216 (10.7%) | 122 (9.8%) | 77 (11.7%) | 17 (16.7%) | 0.062 | | | | |
| Laboratory Indices | | | | | | | | | |
| NI-proBNP (pg/mL) | 2/21.0 [1204.3, 5741.8] | 2608.5 [1204.3, 5337.5] | 2/98.0 [11/0.0, 6460.0] | 3144.0 [1513.0, 6073.0] | 0.289 0 | | | | |
| CRP (mg/L) | 13.0 [5.8, 26.4] | 12.5 [5.8, 26.4] | 13.5 [5.8, 26.6] | 15.1 [4.8, 26.6] | 0./11 | | | | |
| eGFK (ML/MIN/1./3 M²) | | | | L() 1 / 10/ 11 | | | | | |
| Croatining (um -1/1) | 65.0 (26.2) | 65.5 (25.7) | 64.8 (26.6) | 60.1 (29.2) | 0.108 9 | | | | |

| Medications | | | | | |
|----------------------------------|-------------------|-------------------|-------------------|-------------------|---------|
| BB | 1880 (83.4%) | 1159 (83.0%) | 624 (84.0%) | 97 (85.1%) | 0.737 |
| BB at target dose | 127 (5.6%) | 74 (5.3%) | 43 (5.8%) | 10 (8.8%) | 0.295 |
| BB Fraction of Target Dose | 0.25 [0.06, 0.50] | 0.25 [0.06, 0.48] | 0.25 [0.06, 0.50] | 0.25 [0.06, 0.50] | 0.527 |
| ACEi/ARB | 1615 (71.7%) | 1011 (72.4%) | 531 (71.5%) | 73 (64.0%) | 0.163 |
| ACEi/ARB at target dose | 295 (13.1%) | 181 (13.0%) | 99 (13.3%) | 15 (13.2%) | 0.971 🛓 |
| ACEi/ARB Fraction of Target Dose | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.267 😡 |
| MRA | 1196 (53.1%) | 766 (54.8%) | 379 (51.0%) | 51 (44.7%) | 0.045* |
| Digoxin | 424 (18.8%) | 259 (18.5%) | 149 (20.1%) | 16 (14.0%) | 0.283 🚊 |
| Oral hypoglycemic agents** | 457 (62.4%) | 290 (63.2%) | 150 (63.3%) | 17 (47.2%) | 0.155 |

| - / / / / / / / / / / | | |
|---|--|-----------------------------------|
| Lable 1 Daceline characteristics strat | tiod according to anti K1 adrong | raic recenter autoantibodu ctatur |
| | ()P() ()(())())()() () () ()())-() /-()()(P()P | |
| | | |

| Oral typegytemic agents 424 (18.8%) 229 (18.5%) 149 (20.3%) 150 (16.3%) 174 (20.3%) 150 (16.3%) 174 (20.3%) 100 (16.3%) 174 (20.3%) 100 (20.3%) 101 (20.3% | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | MRA | 1196 (53.1 | .%) | 766 (| 54.8%) | 379 (51 | 1.0%) | 51 (4 | 44.7%) | 0.045* | | |
|--|--|--|--|--------------|-----------------|-----------------|--------------------|-------------|--------------------------|-------------------|------------------------------|--|--|
| Oral hypegivemic agent** 457 (62.4%) 220 (63.2%) 150 (63.3%) 427 (47.2%) 0.155 size Herst failure, at Arial fibrillation, BM debets emettions, BX cenal dises; CCPD chronic obstructive pulmonary designed, Minocardial functions, MX and sets, WF1 effyrumettic agencin fracted in proceedings in converting exame inhibitor. 150 (63.3%) 127 (42.2%) 0.155 size Table 2. Boseline characteristics stratified according to anti-62-adtrenergic receptor automits/MC1 angoing size in position converting size in position in the proceeding in the size intermediate in the intermediate intervent size intervent in the intervent in the intervent interv | Digoxin 424 (18.8%) | | %) 259 (18.5%) | | 18.5%) | 149 (20 | 0.1%) | 16 (14.0%) | | 0.283 🛱 | | | |
| If her failure, Af attrail fibrillation; DM diabetes mellitus, IT hypertension; BD renal disease; CDPD chronic obstructive latest, USP (eff) entruition ejection fraction; NTM- MT-poRDN N-Ferminal pre-brain Natriurctic Peptide; CIP C-reactive protein; BD hemoglobin; BB padrenore-eptor antagonity, MC ingicity and converting enzyme inhibitor Alla angotenoin; MC inginistry, | Oral h | hypoglycemic agents** | 457 (62.49 | %) | 290 (| 63.2%) | 150 (63 | 3.3%) | 17 (4 | 47.2%) | 0.155 9 | | |
| New York heart association; BMI body mass index: IRR heart rate; SBP/DBP: systolic /diasolic /body pressure; 6MVT 6-minute value test: VerE Feldy vertricalar ejection fraction fr | HF heart fai | ilure; AF atrial fibrillation | n; DM diabetes mell | itus; HT hyp | ertension; RD r | enal disease; (| OPD chronic obstru | uctive pulm | ionary disease; MI r | nyocardial infarc | tion; NYH $A_{\overline{2}}$ | | |
| NT-proBP N-E-minial pro-Brain Natturetic Peptide, CBP C-reactive proteins, the hemoglobils, BB J-addrenore-eptor antagonist, ACE ingointegin converting enzyme inhibitory patients in post-hoc testing. 1 2 2 Table 2. Enseline characteristics stratified according to anti-B2-adrenergic receptor autogonitics. Not testing: Table 2. Enseline characteristics stratified according to anti-B2-adrenergic receptor autoamtbody status. Not testing: Not testing: <td cols<="" td=""><td>New York h</td><td colspan="11">New York heart association; BMI body mass index; HR heart rate; SBP/DBP; systolic/diastolic blood pressure; 6MWT 6-minute walk test; LVEF left ventricular ejection fraction</td></td> | <td>New York h</td> <td colspan="11">New York heart association; BMI body mass index; HR heart rate; SBP/DBP; systolic/diastolic blood pressure; 6MWT 6-minute walk test; LVEF left ventricular ejection fraction</td> | New York h | New York heart association; BMI body mass index; HR heart rate; SBP/DBP; systolic/diastolic blood pressure; 6MWT 6-minute walk test; LVEF left ventricular ejection fraction | | | | | | | | | | |
| Previous History and Combibilities ABB anglotensis necestories Service Stratified according to anti-82-adrenergic receptor automitbody status. 1 Table 2. Biseline characteristics stratified according to anti-82-adrenergic receptor automitbody status. Image: Status in provide in the strate in the status in th | NT-proBNP | NT-proBNP N-Terminal pro-Brain Natriuretic Peptide; CRP C-reactive protein; Hb hemoglobin; BB β-adrenoreceptor antagonist; ACEi angiotensin converting enzyme inhibitor | | | | | | | | | | | |
| 1 Table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantihody status. Table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantihody status. Table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantihody status. Table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantihody status. Table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantihody status. Table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantihody status. Primary HF Etiology Primary HF Etiology Primary HF Etiology Previous History and Comorbidities Previous History and Comorbidities Gende (45.5%) 355 (44.6%) 16 (45.9%) 355 (44.6%) 16 (45.9%) Previous History and Comorbidities Gende (45.5%) 355 (44.6%) 16 (45.9%) 355 (44.6%) 16 (45.9%) 356 (45.9%) 356 (45.9%) 356 (45.9%) 356 (46.9%) 36 (45.9%) 356 (46.9%) 356 (46.9%) 356 (46.9% | ARB angiote | ARB angiotensin receptor blocker; MRA mineralocorticoid receptor antagonist. *p≤0.05; **only for patients with diabetes mellitus; +significantly different from seronegative | | | | | | | | | | | |
| 1 Table 2. Boseline characteristics stratified according to anti-62-adrenergic receptor automatikaly status. Table 2. Boseline characteristics stratified according to anti-62-adrenergic receptor automatikaly status. Table 2. Boseline characteristics and the stratige 2 Intermediate Anti-62 Seropositive P-value forup Size April 2011 1 58 (21,01) 59 (12) 0.006* Permany HF Etiology Cardiomyopathy 375 (22,2%) 190 (23,3%) 34 (26,0%) 0.06 Primary HF Etiology Cardiomyopathy 325 (24,9%) 197 (25,3%) 34 (26,0%) 0.06 Previous History and Comorbiditie 4 58 (24,6%) 223 (28,0%) 21 (16,0%) 0.165 Valvidar Disease 96 (7,4%) 224 (24,0%) 91 (25,3%) 34 (26,0%) 0.06 Previous History and Comorbiditie 4 608 (45,9%) 0.224 (42,0%) 91 (25,3%) 0.4415 Previous History and Comorbiditie 4 608 (45,9%) 0.225 (14,0%) 0.165 (23,9%) 0.846 DM 45 (12,0%) 0.22 (14,0%) 0.91 (22,8%) 0.8422 DM 45 (12,0%) 0.22 (14,0%) 0.91 (22,8%) 0.8422 DM 45 (12,0%) 0.22 (14,0%) 0.91 (22,8%) 0.8422 DM 45 (12,0%) 0.22 (13,0%) 0.022.*% Note 125 (23,8%) 0.22 (13,7%) 0.01 (15,0%) 0.022.* HF Hospitalization during previous (vert Previous History and Comorbidities 1 121 (10,5%) 79 (11,0%) 0.101 (10,0%) 0.022.* HF Hospitalization during previous (vert Previous History and Comorbidities 1 121 (10,5%) 79 (11,0%) 0.022.* HF Hospitalization during previous (vert NHA Flincetorial (25,9%) 0.86 (13,0%) 0.22 (13,7%) 0.01 (15,0%) 0.022.* HF Hospitalization during previous (vert NHA Flincetorial (25,9%) 0.201 (12,0%) 0.21 (12,0%) 0.22 (12,0%) 0.841 H 377 (22,7%) 0.24 (23,0%) 0.26 (34,6%) 0.021* H 10377 (22,7%) 0.24 (23,0%) 0.164 (15,5%) 0.021* H 10377 (22,7%) 0.24 (23,0%) 0.75 (5,6%) 0.104 H 10377 (22,7%) 0.24 (23,0%) 0.75 (5,6%) 0.104 H 10377 (22,7%) 0.24 (23,0%) 0.75 (5,7%) 0.203 FM HE Bettymin 75 (13) 75 (13) 75 (14) 0.95 FM HE Bettymin 76 (15,2%) 0.104 (4,9%) 0.75 (5,7%) 0.203 FM HE Bettymin 76 (15,2%) 0.104 (4,9%) 0.75 (5,7%) 0.203 FM HE Bettymin 76 (15,2%) 0.104 (4,9%) 0.75 (5,7%) 0.203 FM HE Bettymin 76 (15,2%) 0.104 (4,9%) 0.75 (5,7%) 0.203 | patients in p | patients in post-hoc testing. | | | | | | | | | | | |
| Table 2. Baseline characteristics stratified according to anti-B2 intermediate Ant | 1 | | | | | | | | | | nic | | |
| Table 2: Boseline characteristics stratified according to anti-02-admenergic receptor gutdom/Bbdy/status. Variable Anti-02 seronegative Anti-02 seronegative Anti-02 seronegative Anti-02 seronegative Previous Group Size 1326 797 133 N/A Demographics Age (Years) 69 (12) + 68 (13) 69 (12) + 0.046* Primary HF Etiology 373 (28.2%) 130 (29.9%) 33 (19.3%) 0.001* Primary HF Etiology 325 (24.9%) 137 (25.3%) 34 (26.0%) 0.96 Valvalar Disease 96 (7.4%) 62 (8.0%) 9 (16.5%) 0.415 Valvalar Disease 96 (7.4%) 62 (8.0%) 9 (16.9%) 0.842 M 451 (24.9%) 235 (24.6%) 61 (45.9%) 0.842 M 608 (45.9%) 25 (28.0%) 9 (16.2%) 0.842 Valvalar Disease 96 (7.4%) 26 (8.0%) 9 (16.2%) 0.822 M 451 (24.0%) 24 (30.4%) 39 (22.8%) 0.665 N 451 (24.9%) 24 (35.7%) 46 (34.6%) | | | | | | | | | | | | | |
| Variable Anti-B2 Serongative Anti-B2 Intermediate Anti-B2 seropositive p-value Group Size 1326 '7' 133 N/A Demographics 69 (12) + 68 (13) 69 (12) + 0.04* Female sex 373 (28.2%) 190 (12,9%) 39 (29.3%) 0.076* Recruited as outpatient 458 (34.6%) 223 (28.0%) 53 (39.8%) 0.00** Primary HF Etiology 232 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Valuator Discover 666 (45.5%) 359 (46.1%) 53 (40.5%) 0.445 Valuator Discover 666 (45.5%) 355 (44.6%) 61 (45.9%) 0.846 DM 451 (24.0%) 242 (30.4%) 39 (29.3%) 0.466 MM 451 (24.0%) 242 (30.4%) 39 (62.5%) 0.842 DM 451 (24.0%) 242 (30.4%) 39 (22.4%) 0.842 M 458 (62.5%) 225 (97.7%) 130 (16.3%) 30 (22.6%) 0.829 M 525 (33.6%) 29 (37.6%) 0.46 (34.6%) 0.224 | | table 2. Baseline characteristics stratified according to anti-62-adrenergic receptor autoantibody status. | | | | | | | | | | | |
| Group Size 132 1/A Demographic Age (Years) 69 (12) 1 56 (12) 3 69 (12) 4 56 (12) 3 0.0045* Female sx 873 (12.2%) 190 (12.9%) 39 (12.3%) 0.001* Primary HF Etiology 223 (22.9%) 197 (25.3%) 34 (26.0%) 0.96 Primary HF Etiology 325 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Primary HF Etiology 325 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Valvular Disease 96 (7.4%) 62 (8.0%) 91 (6.9%) 0.346 Previous History and Comorbidies 0 0 0.415 0.96 DM 451 (24.0%) 24 (20.4%) 93 (23.2%) 0.6829 DM 451 (24.0%) 24 (20.4%) 39 (23.2%) 0.6927 MB 727 (28.3%) 248 (60.9%) 33 (12.5%) 0.6929 MA 458 (62.5%) 33 (12.5%) 0.021* MM 555 (39.6%) 29 (37.6%) 30 (22.6%) 0.2027* MM 556 (39.6%) 223 | | Varial | ble | Anti-β | 2 Seronegative | Ant | -β2 Intermediate | Ar | ti-β2 Seropositive | p-value | moc | | |
| Demographics 69 (12) 1 68 (13) 69 (12) 0.046* Female sex 373 (28.2%) 190 (23.9%) 39 (29.3%) 0.076* Recruited as outpatient 458 (34.6%) 223 (28.0%) 53 (39.8%) 0.001* Primary HF Etiology Cardiomyopathy 325 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Longit Section 666 (46.5%) 359 (46.1%) 53 (40.5%) 0.415 Valual Disease 96 (74.5%) 62 (8.0%) 91 (23.3%) 0.162 DM 451 (24.0%) 242 (30.4%) 39 (29.3%) 0.162 DM 451 (24.0%) 242 (30.4%) 39 (22.8%) 0.201 Apemia 428 (66.9%) 269 (36.6%) 30 (22.6%) 0.201 MB 50 (62.5%) 38 (16.3%) 60 (31.5%) 0.2021* | | Group Size | | | 1326 | | 797 | | 133 | N/A | I/ca | | |
| Age (Years) 69 (L2) 1 68 (L3) 69 (L2) 0.046* Recruited as outpatient 458 (34.6%) 223 (28.0%) 53 (29.3%) 0.001* Primary HF Etiology Cardiomyopathy 32 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Hyperbasics 325 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 0.415 Hyperbasics 325 (24.9%) 197 (25.3%) 53 (40.5%) 0.415 0.415 Valvular Disease 96 (7.4%) 62 (8.0%) 9 (6.5%) 9 (6.9%) 0.846 Previous History and Comorbidities 0 0 438 (36.4%) 24 (30.4%) 39 (22.3%) 0.662 M 451 (34.0%) 242 (30.4%) 39 (22.3%) 0.662 0.829 DM 451 (34.0%) 24 (30.4%) 39 (32.8%) 0.693 0.829 MA memia 438 (36.4%) 269 (35.8%) 39 (32.8%) 0.621* Mit 525 (97.7%) 130 (16.3%) 30 (22.6%) 0.621* Mit 129 (57%) 63 (17.9%) 40 (30.1%) 0. | | Demographics | | | | | | | | | ardi | | |
| Female sex 373 (28.2%) 190 (23.9%) 39 (29.3%) 0.076 Primary HF Etiology 223 (28.0%) 223 (28.0%) 53 (39.8%) 0.001* Cardiomyopathy 325 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Mypertensive 132 (10.1%) 80 (10.3%) 21 (16.0%) 0.106 Valvalar Disease 96 (2.4%) 62 (8.0%) 35 (44.6%) 0.846 Previous History and Comorbidities 66 (46.5%) 355 (44.6%) 61 (45.9%) 0.842 DM 451 (34.0%) 24 (30.4%) 39 (22.3%) 0.665 0.669 Amemia A38 (36.4%) 269 (36.3%) 39 (22.3%) 0.662 0.207 MI 453 (24.0%) 24 (30.3%) 26 (3.9%) 0.691 0.007 MI 453 (62.9%) 35 (64.6%) 63 (9.3%) 0.692 0.207 MI 453 (34.0%) 269 (36.3%) 30 (22.6%) 0.007 0.0027* MI 55 (9.9.6%) 29 (37.%) 40 (30.1%) 0.932 0.214 MI 122 | | | Age (Years) | (| 69 (12) † | | 68 (13) | | 69 (12) | 0.046* | OV | | |
| Recruited as outpatient 4458 (34.5%) 229 (28.0%) 53 (19.8%) 0.001* Primary HF Etology Cardiomyopathy Hypertensive Ischemic 325 (24.9%) 197 (25.3%) 34 (26.0%) 0.96 Maynet HS 359 (46.1%) 53 (40.5%) 0.106 0.106 Valvular Disease 96 (2.4%) 62 (80.6%) 9 (6.9%) 0.846 Previous History and Comobildities 608 (45.9%) 355 (4.6%) 61 (45.9%) 0.842 RD 75 (28.3%) 245 (27.4%) 426 (30.4%) 39 (22.8%) 0.691 Aremia 438 (36.4%) 229 (37.7%) 130 (16.5%) 30 (22.6%) 0.227* Anemia 438 (36.4%) 229 (37.7%) 130 (16.5%) 0.027* COPD 225 (37.7%) 130 (16.5%) 0.021* 0.021* HF Hospitalization during previous year 419 (31.6%) 227 (23.3%) 0.021* 0.021* Current 163 (12.3%) 30 (47.7%) 46 (44.6%) 0.021* Mil 502 (25.2%) 344 (53.7%) 46 (44.6%) 0.021* Curren | | | Female sex | 37 | 73 (28.2%) | | 190 (23.9%) | | 39 (29.3%) | 0.076 | asc | | |
| Primary HF Etiology United Stress | | Recru | uited as outpatient | 45 | 58 (34.6%) | | 223 (28.0%) | | 53 (39.8%) | 0.001* | res | | |
| Cardiomyopathy 325 (24,9%) 197(25,3%) 34 (26,0%) 0.96 Hypertensive 132 (10,1%) 180 (10,3%) 21 (16,0%) 0.105 Valvair Disease 96 (7,4%) 62 (8,0%) 9 (6,9%) 0.846 Previous History and Comorbidities | | Primary HF Etiology | | | | | | | | | s/a | | |
| Hypertensive Ischemic 132 (10.1%) 980 (10.3%) 21 (16.0%) 0.106 Valvular Disease 96 (7.4%) 62 (8.0%) 9 (6.9%) 0.346 Previous History and Comorbidities 608 (45.9%) 355 (44.6%) 61 (45.9%) 0.842 DM 451 (34.0%) 242 (30.4%) 39 (29.3%) 0.625 DM 451 (34.0%) 242 (30.4%) 39 (22.3%) 0.665 COPD 757 (28.3%) 218 (77.4%) 35 (26.3%) 0.829 Anemia 757 (28.3%) 219 (16.3%) 39 (22.6%) 0.207 MM 552 (39.6%) 299 (36.8%) 30 (22.6%) 0.207 MM 552 (39.6%) 299 (37.6%) 40 (30.1%) 0.932 Smoking Never 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* VPHA Fonctional Class I 129 (7%) 224 (35.7%) 46 (34.6%) 0.021* Smoking Never 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* III 602 (52.2%) 348 (50.1%) 64 (55.7% | | | Cardiomyopathy | 32 | 25 (24.9%) | | 197 (25.3%) | | 34 (26.0%) | 0.96 | dva | | |
| Ischemic 606 (46.5%) 353 (96.1%) 53 (40.5%) 0.415 Valvalari Disease 96 (7.4%) 62 (8.0%) 9 (6.9%) 0.846 Previous History and Comorbidities 608 (45.9%) 355 (44.6%) 61 (45.9%) 0.842 MH 78 (20.9%) 485 (60.9%) 35 (24.6%) 39 (22.3%) 0.162 MH 87 (23.3%) 218 (27.4%) 35 (26.3%) 0.829 0.842 Anemia 438 (36.4%) 269 (36.8%) 39 (32.8%) 0.691 0.003 COPD 225 (17.7%) 130 (16.3%) 30 (22.6%) 0.021* 0.033 MI 525 (39.6%) 299 (37.6%) 40 (30.1%) 0.033 0.021* Stroke 129 (9.7%) 63 (7.9%) 20 (15.0%) 0.021* 0.021* Smoking Never 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* Uried Characteristics Never 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* Uried Characteristics Never 494 (37.4%) 284 (35.7%) 46 (| | | Hypertensive | 13 | 32 (10.1%) | | 80 (10.3%) | | 21 (16.0%) | 0.106 | anc | | |
| Valvular Disease 96 (7.4%) 62 (8.0%) 9 (6.9%) 0.846 Previous History and Comorbidities AF 608 (45.9%) 355 (44.6%) 61 (45.9%) 0.842 DM 451 (34.0%) 242 (30.4%) 39 (29.3%) 0.162 0.695 MH 628 (62.5%) 485 (60.9%) 65 (63.9%) 0.695 0.695 RD 375 (28.3%) 218 (27.4%) 35 (26.3%) 0.691 0.691 COPD 235 (17.7%) 130 (16.3%) 30 (22.6%) 0.207 0.883 Stroke 129 (9.7%) 63 (7.9%) 20 (15.0%) 0.022* 0.227* Smoking Vever 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.922 Smoking Vever 494 (37.4%) 284 (35.7%) 66 (34.6%) 0.022* Vever 494 (37.4%) 380 (47.7%) 20 (15.0%) 0.022* 0.221* II 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 0.32 ViPA Fonctional Class II 602 (52.2%) 348 (50.1%) | | | Ischemic | 60 | 06 (46.5%) | | 359 (46.1%) | | 53 (40.5%) | 0.415 | e 0 | | |
| Previous History and Comorbidities AF 608 (45.9%) 355 (44.6%) 61 (45.9%) 0.842 DM 451 (34.0%) 242 (30.4%) 39 (29.3%) 0.162 0.842 DM 451 (34.0%) 242 (30.4%) 39 (29.3%) 0.162 0.695 RD 375 (28.3%) 128 (72.4%) 35 (26.3%) 0.829 0.691 Anemia 438 (36,4%) 209 (36.8%) 39 (32.8%) 0.691 0.027* MI 525 (39.6%) 299 (37.6%) 40 (30.1%) 0.028 0.0932 Stroke 1.29 (9.7%) 63 (7.9%) 20 (15.0%) 0.021* 0.932 Stroke 1.29 (9.7%) 380 (47.7%) 40 (30.1%) 0.021* Verer Past 665 (50.3%) 380 (47.7%) 60 (45.1%) 0.021* Current 163 (12.3%) 132 (16.6%) 27 (20.3%) 0.32 0.32 VHA Functional Class I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 0.32 III 377 (22.7%) 246 (35.4%) 40 (3 | | | Valvular Disease | ç | 96 (7.4%) | | 62 (8.0%) | | 9 (6.9%) | 0.846 | artio | | |
| AF 608 (45,9%) 355 (44,6%) 61 (45,9%) 0.842 0100 (45,9%) 0.421 (30,4%) 39 (22,3%) 0.162 0100 (45,9%) 0.695 HT 828 (62,5%) 485 (60,9%) 85 (63,9%) 0.695 0.683 0.695 0.695 0.695 0.683 0.695 0.683 0.695 0.681 0.695 0.681 0.695 0.683 0.695 0.621* 0.695 0.691 0.695 0.691 0.621* 0.691 0.775 | | Previous History and | Comorbidities | | | | | | | | cle/ | | |
| DM 451 (34.0%) 242 (30.4%) 39 (29.3%) 0.162 0.167 HT 626 (62.5%) 445 (60.9%) 85 (63.9%) 0.695 0.162 RD 375 (28.3%) 218 (27.4%) 35 (26.3%) 0.829 0.691 Anemia 438 (36.4%) 269 (36.8%) 39 (32.8%) 0.691 0.201 MI 525 (39.6%) 299 (37.6%) 40 (30.1%) 0.083 0.083 Stroke 129 (9.7%) 63 (7.9%) 20 (15.0%) 0.027* 0.932 Stroke 129 (9.7%) 63 (47.9%) 244 (35.7%) 40 (30.1%) 0.932 Stroke 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.021* Clinical Characteristics 1 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 III 602 (52.2%) 348 (50.1%) 64 (35.5%) 0.32 0.32 V 54 (4.7%) 22 (3.2%) 2 (1.7%) 0.32 0.32 IIII 377 (32.7%) 268 (38.6%) 42 (36.5%) 0.32 0.32 < | | | AF | 60 | 08 (45.9%) | | 355 (44.6%) | | 61 (45.9%) | 0.842 | do | | |
| HT 622 (62,5%) 445 (60,9%) 85 (63,9%) 0.695 0.695 Anemia 438 (36,4%) 269 (36,8%) 39 (32,8%) 0.691 COPD 235 (47,7%) 130 (16,3%) 30 (22,6%) 0.207 MI 525 (39,6%) 229 (37,5%) 40 (30,1%) 0.083 Stroke 129 (9,7%) 63 (7,9%) 20 (15,0%) 0.027* Smoking 494 (37,4%) 224 (35,7%) 46 (34,6%) 0.932 Smoking Never 494 (37,4%) 224 (35,7%) 46 (34,6%) 0.021* Current 163 (12,3%) 132 (16,6%) 27 (20,3%) 0.021* Virtert 163 (12,3%) 228 (35,4%) 40 (34,4%) 0.32 III 602 (52,2%) 24 (35,4%) 40 (34,4%) 0.32 V 54 (4,7%) 22 (3,2%) 2 (1,7%) 0.32 III 307 (32,78%) 266 (38,6%) 42 (35,5%) 0.841 NYHA Functional Class IV 54 (4,7%) 22 (3,2%) 0.114 MII 377 | | | DM | 45 | 51 (34.0%) | 1 | 242 (30.4%) | | 39 (29.3%) | 0.162 | i/10 | | |
| RD 375 (28.3%) 218 (27.4%) 35 (26.3%) 0.829 000000000000000000000000000000000000 | | | HT | 82 | 28 (62.5%) | | 485 (60.9%) | | 85 (63.9%) | 0.695 | 0.1 | | |
| Anemia 448 (36,4%) 269 (36,8%) 39 (32,8%) 0.691 OPP COPD 235 (17,7%) 130 (16,3%) 30 (22,6%) 0.207 OUTOR MI 525 (39,6%) 299 (37,6%) 40 (30,1%) 0.083 OU27* MI 525 (39,6%) 252 (31,7%) 40 (30,1%) 0.027* OUTOR Biology 419 (31,6%) 252 (31,7%) 40 (30,1%) 0.027* OUTOR Smoking Never 494 (37,4%) 284 (35,7%) 46 (34,6%) Outor Outor Past 665 (50,33%) 308 (47,7%) 60 (45,1%) 0.021* Outor < | | | RD | 37 | 75 (28.3%) | | 218 (27.4%) | | 35 (26.3%) | 0.829 | 000 | | |
| CUPD C25 (17.7%) 130 (18.3%) 30 (22.6%) 0.207 MI 535 (35.6%) 299 (37.6%) 40 (30.1%) 0.083 Stroke 129 (9.7%) 63 (7.9%) 20 (15.0%) 0.027* MI 535 (35.6%) 225 (31.7%) 40 (30.1%) 0.932 Smoking Vever 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* Past 665 (50.3%) 380 (47.7%) 60 (45.1%) 0.021* Clinical Characteristics 1 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 I 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 0.32 NYHA Functional Class I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 III 377 (32.7%) 224 (35.4%) 40 (43.8%) 0.32 0.32 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.34 0.35 BRI (kg/m²) 27.2 (24.2, 30.9] 27.1 [24.2, 30.4] 266 [23.5, 29.5] 0.104 HF (beats/min) | | | Anemia | 4: | 38 (36.4%) | | 269 (36.8%) | | 39 (32.8%) | 0.691 | 3/c/ | | |
| Mil 526 (39.5%) 299 (37.5%) 40 (30.1%) 0.083 Stroke 129 (9.7%) 63 (7.9%) 20 (15.0%) 0.027* HF Hospitalization during previous year 419 (31.6%) 252 (31.7%) 40 (30.1%) 0.932 Smoking | | | COPD | 2: | 35 (17.7%) | | 130 (16.3%) | | 30 (22.6%) | 0.207 | /r/c | | |
| HF Hospitalization during previous year 419 (31.6%) 252 (31.7%) 40 (30.1%) 0.932 Smoking Never 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* Current 163 (12.3%) 380 (47.7%) 66 (34.6%) 0.021* 0.021* Current 163 (12.3%) 132 (16.6%) 27 (20.3%) 0.021* 0.021* Clinical Characteristics I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 NYHA Functional Class I 121 (10.5%) 79 (11.4%) 64 (55.7%) 0.32 NYHA Class II ro IV 1 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 NYHA Class II (kg/m²) 27.2 (24.2 30.9] 27.1 (24.2 30.4] 26.6 (23.5, 29.5] 0.104 NYHA Class II (kg/m²) 27.2 (24.2 30.9] 77 (58, 90] 75 (65, 87] 0.158 BMI (kg/m²) 27.2 (24.2 30.9] 77 (124.2 30.4] 26.6 (23.5, 29.5] 0.104 MB (betrymin) 76 (66, 89] 77 (58, 90] 75 (65, 87] 0.158 BBP (mm Hg) 125 (22) 124 (22) | | | IVII Churchea | 52 | 5 (39.6%) | | 299 (37.6%) | | 40 (30.1%) | 0.083 | :va | | |
| In Problemization during previous year 7 419 (31.8%) 232 (31.7%) 40 (30.1%) 0.932 Smoking Never 494 (37.4%) 284 (35.7%) 46 (34.6%) 0.021* Past 665 (50.3%) 380 (47.7%) 60 (45.1%) 0.021* Clinical Characteristics Current 163 (12.3%) 132 (16.6%) 27 (20.3%) I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 III 307 (32.7%) 246 (35.4%) 40 (34.8%) 0.32 III 377 (32.7%) 246 (35.4%) 40 (34.8%) 0.32 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 SBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 DBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.201 GMWT Successfully Completed 837 (65.5%) 501 (6 | | UF Hernitelization du | Stroke | 1 | 29 (9.7%) | | 03 (7.9%) | | 20 (15.0%) | 0.027* | 20p | | |
| Nithing Never Past 494 (37.4%) 665 (50.3%) 284 (35.7%) 380 (47.7%) 46 (34.6%) 60 (45.1%) 0.021* Clinical Characteristics Current 163 (12.3%) 132 (16.6%) 27 (20.3%) 0.021* VIHA Functional Class I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 III 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 WHA Functional Class III 377 (32.7%) 2246 (35.4%) 40 (34.8%) V 54 (4.7%) 22 (3.2%) 2 (1.7%) 0.32 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 BBMI (kg/m²) 125 (22) 124 (22) 127 (23) 0.221 BP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 GMWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 BP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 GMWT Successfully Comp | | | uning previous year | 41 | 19 (31.0%) | | 252 (31.7%) | | 40 (30.1%) | 0.932 | 12/7 | | |
| Past 665 (50.3%) 204 (31.7%) 60 (34.5%) 0.021* Clinical Characteristics 163 (12.3%) 132 (16.6%) 27 (20.3%) 0.021* II 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 III 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 III 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 NYHA Functional Class 11 377 (32.7%) 246 (35.4%) 40 (34.8%) V 54 (4.7%) 22 (3.2%) 2 (1.7%) 0.32 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 BBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 DBP (mm Hg) 75 (13) 75 (13) 0.75 (14) 0.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 | | SHIOKINg | Novor | | A (27 A%) | | 281 (25 7%) | | 16 (21 6%) | | 707 | | |
| Current 163 (12.3%) 130 (14.7%) 30 (14.7%) 27 (20.3%) Clinical Characteristics I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 I 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 0.32 III 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 0.32 III 377 (32.7%) 246 (35.4%) 40 (34.8%) 2 (1.7%) 0.32 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 MI (kg/m ²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 (65, 87] 0.158 0.221 DBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 0.221 DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 0.787 GMWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.20 | | | Past | 43 | 55 (50 3%) | | 284 (33.7%) | | 40 (34.0%) 60 (45.1%) | 0.021* | 723 | | |
| Clinical Characteristics 120 (12.0%) 120 (12.0%) 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 II 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 <td< td=""><td></td><td></td><td>Current</td><td>16</td><td>53 (12 3%)</td><td></td><td>132 (16 6%)</td><td></td><td>27 (20 3%)</td><td>0.021</td><td>30</td></td<> | | | Current | 16 | 53 (12 3%) | | 132 (16 6%) | | 27 (20 3%) | 0.021 | 30 | | |
| NYHA Functional Class 1 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 0.32 II 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 < | | Clinical Characteristic | concili | 10 | (12.070) | | -02 (10.0/0) | | 27 (20.570) | | by | | |
| I 121 (10.5%) 79 (11.4%) 9 (7.8%) 0.32 II 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 III 377 (32.7%) 246 (35.4%) 40 (34.8%) 0.32 IV 54 (4.7%) 22 (3.2%) 2 (1.7%) 0.841 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 BMI (kg/m ²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 DBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 DBP (mm Hg) 75 (13) 75 (14) 0.95 0.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 203 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 223 6MWT Distance (m) 220 (0, 350] 224 [0, 356] 161 [0, 326] 0.237 244 [0.2%] 30 [25, 35] 0.036* 0.034* | | NYH | HA Functional Class | | | | | | | | SC | | |
| II 602 (52.2%) 348 (50.1%) 64 (55.7%) 0.32 III 377 (32.7%) 246 (35.4%) 40 (34.8%) 0 0.32 IV 54 (4.7%) 22 (3.2%) 2 (1.7%) 0.32 NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 0.221 BP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 0.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 203 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 203 6MWT Distance (m) 220 [0, 350] 224 [0, 356] 161 [0, 326] 0.237 237 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | | 12 | 21 (10.5%) | | 79 (11.4%) | | 9 (7.8%) | | B | | |
| III 377 (32.7%) 246 (35.4%) 40 (34.8%) 2000 10000 1000 10000 <th1< td=""><td></td><td></td><td>i i</td><td>60</td><td>)2 (52.2%)</td><td></td><td>348 (50.1%)</td><td></td><td>64 (55.7%)</td><td>0.32</td><td>ΔN</td></th1<> | | | i i | 60 |)2 (52.2%) | | 348 (50.1%) | | 64 (55.7%) | 0.32 | ΔN | | |
| IV 54 (4.7%) 22 (3.2%) 2 (1.7%) 20 (1.7%) 100 (1.7%) NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 000 (1.0%) BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 010 (1.0%) HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 0.021 BP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 0.95 DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 0.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 0.203 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 0.237 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | | 37 | 77 (32.7%) | | 246 (35.4%) | | 40 (34.8%) | | N | | |
| NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 SBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 023 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | IV | 5 | 54 (4.7%) | | 22 (3.2%) | | 2 (1.7%) | | Ŷ | | |
| NYHA Class III or IV 431 (37.3%) 268 (38.6%) 42 (36.5%) 0.841 001 BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 010 HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 0.104 SBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 0.211 DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 0.75 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 0.203 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 0.237 6MWT Distance (m) 220 [0, 350] 224 [0, 356] 161 [0, 326] 0.237 0.237 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | | | . , | | . , | | . , | | | | |
| BMI (kg/m²) 27.2 [24.2, 30.9] 27.1 [24.2, 30.4] 26.6 [23.5, 29.5] 0.104 Of HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 0.104 09 SBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 0.95 DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 0.76 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 0.203 023 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 0.237 0.237 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* 0.034* | | | NYHA Class III or IV | 43 | 31 (37.3%) | | 268 (38.6%) | | 42 (36.5%) | 0.841 | ser | | |
| HR (beats/min) 76 [66, 89] 77 [68, 90] 75 [65, 87] 0.158 100 SBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 0.95 DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 0.787 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 0.203 023 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 023 023 6MWT Distance (m) 220 [0, 350] 224 [0, 356] 161 [0, 326] 0.237 0.237 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | BMI (kg/m ²) | 27.2 | [24.2, 30.9] | 2 | 7.1 [24.2, 30.4] | | 26.6 [23.5, 29.5] | 0.104 | no | | |
| SBP (mm Hg) 125 (22) 124 (22) 127 (23) 0.221 March DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 90.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 90.203 90.23 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 90.237 <t< td=""><td></td><td></td><td>HR (beats/min)</td><td>7</td><td>6 [66, 89]</td><td></td><td>77 [68, 90]</td><td></td><td>75 [65, 87]</td><td>0.158</td><td>1 10</td></t<> | | | HR (beats/min) | 7 | 6 [66, 89] | | 77 [68, 90] | | 75 [65, 87] | 0.158 | 1 10 | | |
| DBP (mm Hg) 75 (13) 75 (13) 75 (14) 0.95 Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 023 6MWT Distance (m) 220 [0, 350] 224 [0, 356] 161 [0, 326] 0.237 0.30 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | Y | SBP (mm Hg) | | 125 (22) | | 124 (22) | | 127 (23) | 0.221 | M | | |
| Pulmonary Crackles 669 (52.2%) 417 (53.6%) 70 (54.3%) 0.787 57 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 023 6MWT Distance (m) 220 [0, 350] 224 [0, 356] 161 [0, 326] 0.237 0.036* LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | DBP (mm Hg) | | 75 (13) | | 75 (13) | | 75 (14) | 0.95 | arc | | |
| 6MWT Successfully Completed 837 (65.5%) 501 (64.9%) 75 (57.7%) 0.203 000000000000000000000000000000000000 | | Р | Pulmonary Crackles | 66 | 59 (52.2%) | | 417 (53.6%) | | 70 (54.3%) | 0.787 | ch . | | |
| 6MWT Distance (m) 220 [0, 350] 224 [0, 356] 161 [0, 326] 0.237 63 LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | 6MWT Succe | essfully Completed | 83 | 87 (65.5%) | | 501 (64.9%) | | 75 (57.7%) | 0.203 | 202 | | |
| LVEF (%) 30 [25, 37] 30 [24, 35] 30 [25, 35] 0.036* LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | 6 | MWT Distance (m) | 22 | 20 [0, 350] | | 224 [0, 356] | | 161 [0, 326] | 0.237 | 13 | | |
| LVEF > 40% 145 (12.2%) 60 (8.5%) 11 (9.2%) 0.034* | | | LVEF (%) | 3 | 0 [25, 37] | | 30 [24, 35] | | 30 [25, 35] | 0.036* | | | |
| | | | LVEF > 40% | 14 | 15 (12.2%) | | 60 (8.5%) | | 11 (9.2%) | 0.034* | | | |

| Laboratory Indices | | | | |
|------------------------------------|-------------------------|-------------------------|------------------------|--------|
| NT-proBNP (pg/mL) | 2798.0 [1226.5, 5738.0] | 2678.5 [1200.5, 5803.5] | 2542.0 [905.5, 5606.0] | 0.885 |
| CRP (mg/L) | 13.4 [5.8, 26.7] | 12.5 [5.9, 24.9] | 11.9 [3.7, 26.6] | 0.379 |
| eGFR (mL/min/1.73 m ²) | 64.2 (25.4) | 66.0 (27.3) | 66.2 (28.0) | 0.275 |
| Creatinine (µmol/L) | 101.7 [82.0, 128.0] | 101.3 [83.1, 131.9] | 96.8 [80.0, 118.8] | 0.638 |
| Hb (g/dL) | 13.2 (1.9) | 13.2 (1.9) | 13.4 (1.8) | 0.512 |
| Medications | | | | |
| BB | 1107 (83.5%) | 660 (82.9%) | 113 (85.0%) | 0.823 |
| BB at target dose | 79 (6.0%) | 39 (4.9%) | 9 (6.8%) | 0.497 |
| BB Fraction of Target Dose | 0.25 [0.06, 0.50] | 0.25 [0.06, 0.38] | 0.25 [0.08, 0.38] | 0.617 |
| ACEi/ARB | 941 (71.0%) | 569 (71.5%) | 105 (78.9%) | 0.153 |
| ACEi/ARB at target dose | 170 (12.8%) | 106 (13.3%) | 19 (14.3%) | 0.869 |
| ACEi/ARB Fraction of Target Dose | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.25 [0.12, 0.50] | 0.099 |
| MRA | 677 (51.1%) | 458 (57.5%) | 61 (45.9%) | 0.004* |
| Digoxin | 252 (19.0%) | 149 (18.7%) | 23 (17.3%) | 0.886 |
| Oral hypoglycemic agents** | 272 (60.3%) | 165 (68.2%) | 20 (51.3%) | 0.042* |

HF heart failure; AF atrial fibrillation; DM diabetes mellitus; HT hypertension; RD renal disease; COPD chronic obstructive pulmonary disease; MI myocardial infarction; NYHA New York heart association; BMI body mass index; HR heart rate; SBP/DBP; systolic/diastolic blood pressure; 6MWT 6-minute walk test; LVEF left ventricular ejection fraction; NT-proBNP N-Terminal pro-Brain Natriuretic Peptide; CRP C-reactive protein; Hb hemoglobin; BB β-adrenoreceptor antagonist; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; MRA mineralocorticoid receptor antagonist. *p≤0.05; **only for patients with diabetes mellitus; †significantly different from intermediate patients in post-hoc testing.

Table 3. Baseline characteristics stratified according to anti-63-adrenergic receptor autoantibody status.

| Group Size 1575 640 41 N/A Demographics Age (Years) Female sex 69 (12) 69 (12) 71 (11) 0.346 Recruited as outpatient 504 (32.0%) 160 (25.0%) 12 (29.3%) 0.495 Primary HF Etiology Cardiomyopathy Hypertensive Ischemic 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.532 Valvular Disease 113 (7.3%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 MH 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.83 MD 516 (32.8%) 325 (0.2%) 25 (61.0%) 0.502 MI 611 (38.8%) 222 (38.9%) 11 (29.7%) 0.248 Apernia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 Apernia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) | Variable | Anti-β3 Seronegative | Anti- ^{β3} Intermediate | Anti-β3 Seropositive | p-value |
|---|---|----------------------|----------------------------------|----------------------|---------|
| Demographics Age (Years) 69 (12) 69 (12) 71 (11) 0.346 Female sex 430 (27.3%) 160 (25.0%) 12 (29.3%) 0.495 Recruited as outpatient 504 (32.0%) 213 (33.3%) 17 (41.5%) 0.402 Primary HF Etiology 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.532 Mypertensive 154 (10.0%) 76 (12.0%) 3 (7.7%) 0.322 Ischemic 716 (46.5%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities 716 (32.8%) 202 (31.6%) 14 (34.1%) 0.838 DM 516 (32.8%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 325 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Aremia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 </td <td>Group Size</td> <td>1575</td> <td>640</td> <td>41</td> <td>N/A</td> | Group Size | 1575 | 640 | 41 | N/A |
| Age (Years) Female sex 69 (12) 69 (12) 71 (11) 0.346 Female sex 430 (27.3%) 160 (25.0%) 12 (29.3%) 0.495 Recruited as outpatient 504 (32.0%) 213 (33.3%) 17 (41.5%) 0.405 Primary HF Etiology 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.322 Mypertensive 154 (10.0%) 76 (12.0%) 3 (7.7%) 0.322 Ischemic 716 (46.5%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.0444 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.4243 GOPD 260 (16.5%) 55 (8.6%) 6 (14.6%) 0.331 | Demographics | | | | |
| Female sex Recruited as outpatient 430 (27.3%) 504 (32.0%) 160 (25.0%) 213 (33.3%) 12 (29.3%) 17 (41.5%) 0.495 0.402 Primary HF Etiology 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.532 0.532 Lypertensive Ischemic 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.322 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.833 MT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.0442 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.0442 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.0442 MI 611 (38.8%) 241 (37.7%) | Age (Years) | 69 (12) | 69 (12) | 71 (11) | 0.346 |
| Recruited as outpatient 504 (32.0%) 213 (33.3%) 17 (41.5%) 0.402 Primary HF Etiology 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.532 Hypertensive 154 (10.0%) 76 (12.0%) 3 (7.7%) 0.322 Ischemic 716 (46.5%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.833 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 COPD 260 (16.5%) 123 (19.2%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.443 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.443 MH 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.443 | Female sex | 430 (27.3%) | 160 (25.0%) | 12 (29.3%) | 0.495 |
| Primary HF Etiology Cardiomyopathy 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.532 Hypertensive 154 (10.0%) 76 (12.0%) 3 (7.7%) 0.322 Ischemic 716 (46.5%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.833 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 | Recruited as outpatient | 504 (32.0%) | 213 (33.3%) | 17 (41.5%) | 0.402 |
| Cardiomyopathy Hypertensive 393 (25.5%) 156 (24.6%) 7 (17.9%) 0.532 Hypertensive 154 (10.0%) 76 (12.0%) 3 (7.7%) 0.322 Ischemic 716 (46.5%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.833 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Aremia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.0443 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 MF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | Primary HF Etiology | | | | |
| Hypertensive Ischemic 154 (10.0%) 76 (12.0%) 3 (7.7%) 0.322 Valvular Disease 113 (7.3%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.833 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke <t< td=""><td>Cardiomyopathy</td><td>393 (25.5%)</td><td>156 (24.6%)</td><td>7 (17.9%)</td><td>0.532</td></t<> | Cardiomyopathy | 393 (25.5%) | 156 (24.6%) | 7 (17.9%) | 0.532 |
| Ischemic 716 (46.5%) 284 (44.9%) 18 (46.2%) 0.794 Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.833 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | Hypertensive | 154 (10.0%) | 76 (12.0%) | 3 (7.7%) | 0.322 |
| Valvular Disease 113 (7.3%) 50 (7.9%) 4 (10.3%) 0.732 Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.83 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | Ischemic | 716 (46.5%) | 284 (44.9%) | 18 (46.2%) | 0.794 |
| Previous History and Comorbidities AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.83 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | Valvular Disease | 113 (7.3%) | 50 (7.9%) | 4 (10.3%) | 0.732 |
| AF 687 (43.7%) 316 (49.4%) 21 (51.2%) 0.038 DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.83 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | Previous History and Comorbidities | | | | |
| DM 516 (32.8%) 202 (31.6%) 14 (34.1%) 0.83 HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | AF | 687 (43.7%) | 316 (49.4%) | 21 (51.2%) | 0.038* |
| HT 988 (62.8%) 385 (60.2%) 25 (61.0%) 0.502 RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | DM | 516 (32.8%) | 202 (31.6%) | 14 (34.1%) | 0.83 |
| RD 419 (26.6%) 196 (30.6%) 13 (31.7%) 0.142 Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 Smoking K K K K K K K K K | HT | 988 (62.8%) | 385 (60.2%) | 25 (61.0%) | 0.502 |
| Anemia 513 (35.5%) 222 (38.9%) 11 (29.7%) 0.248 COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 | RD | 419 (26.6%) | 196 (30.6%) | 13 (31.7%) | 0.142 |
| COPD 260 (16.5%) 123 (19.2%) 12 (29.3%) 0.044 MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 Smoking | Anemia | 513 (35.5%) | 222 (38.9%) | 11 (29.7%) | 0.248 |
| MI 611 (38.8%) 241 (37.7%) 12 (29.3%) 0.423 Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 Smoking | COPD | 260 (16.5%) | 123 (19.2%) | 12 (29.3%) | 0.044* |
| Stroke 151 (9.6%) 55 (8.6%) 6 (14.6%) 0.391 HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 Smoking | MI | 611 (38.8%) | 241 (37.7%) | 12 (29.3%) | 0.423 |
| HF Hospitalization during previous year 482 (30.6%) 215 (33.6%) 14 (34.1%) 0.374 Smoking | Stroke | 151 (9.6%) | 55 (8.6%) | 6 (14.6%) | 0.391 |
| Smoking | HF Hospitalization during previous year | 482 (30.6%) | 215 (33.6%) | 14 (34.1%) | 0.374 |
| | Smoking | | | | |
| Never 575 (36.6%) 236 (37.0%) 13 (31.7%) | Never | 575 (36.6%) | 236 (37.0%) | 13 (31.7%) | |
| Past 765 (48.7%) 321 (50.3%) 19 (46.3%) 0.453 | Past | 765 (48.7%) | 321 (50.3%) | 19 (46.3%) | 0.453 |
| Current 232 (14.8%) 81 (12.7%) 9 (22.0%) | Current | 232 (14.8%) | 81 (12.7%) | 9 (22.0%) | |

| Clinical Characteristics | | | | |
|----------------------------------|-------------------------|-------------------------|-------------------------|--------|
| NYHA Functional Class | | | | |
| 1 | 142 (10.4%) | 64 (11.3%) | 3 (8.3%) | |
| II | 717 (52.6%) | 276 (48.9%) | 21 (58.3%) | 0.599 |
| 111 | 448 (32.8%) | 205 (36.3%) | 10 (27.8%) | |
| IV | 57 (4.2%) | 19 (3.4%) | 2 (5.6%) | |
| | | | | |
| NYHA Class III or IV | 505 (37.0%) | 224 (39.7%) | 12 (33.3%) | 0.465 |
| BMI (kg/m ²) | 27.2 [24.2, 30.8] | 26.9 [23.8, 30.2] | 26.6 [24.2, 29.1] | 0.224 |
| HR (beats/min) | 76 [67, 89] | 76 [67, 90] | 72 [63, 87] | 0.494 |
| SBP (mm Hg) | 125 (22) | 124 (22) | 123 (19) | 0.609 |
| DBP (mm Hg) | 75 (13) | 75 (13) | 73 (11) | 0.432 |
| Pulmonary Crackles | 789 (51.5%) | 344 (55.8%) | 23 (56.1%) | 0.178 |
| 6MWT Successfully Completed | 997 (65.4%) | 394 (64.1%) | 22 (56.4%) | 0.456 |
| 6MWT Distance (m) | 225 [0, 360] | 215 [0, 344] | 197 [0, 314] | 0.39 |
| LVEF (%) | 30 [25, 36] | 30 [24, 36] | 30 [25, 35] | 0.553 |
| LVEF > 40% | 147 (10.5%) | 64 (11.2%) | 5 (13.9%) | 0.737 |
| Laboratory Indices | | C | | |
| NT-proBNP (pg/mL) | 2600.0 [1158.0, 5581.0] | 2950.0 [1296.5, 5995.5] | 2685.5 [1356.5, 5958.8] | 0.153 |
| CRP (mg/L) | 12.8 [5.7, 26.2] | 13.2 [6.0, 26.8] | 19.2 [6.9, 32.6] | 0.23 |
| eGFR (mL/min/1.73 m²) † | 65.9 (26.6) | 63.0 (24.9) | 60.5 (31.3) | 0.032* |
| Creatinine (µmol/L) | 100.0 [80.9, 126.0] | 102.8 [86.0, 133.0] | 112.0 [84.0, 140.6] | 0.027* |
| Hb (g/dL) | 13.2 (1.9) | 13.1 (2.0) | 13.4 (1.8) | 0.401 |
| Medications | | | | |
| BB | 1307 (83.1%) | 538 (84.1%) | 35 (85.4%) | 0.808 |
| BB at target dose | 84 (5.3%) | 36 (5.6%) | 7 (17.1%) | 0.006* |
| BB Fraction of Target Dose | 0.25 [0.06, 0.48] | 0.25 [0.08, 0.50] | 0.25 [0.05, 0.50] | 0.351 |
| ACEi/ARB | 1137 (72.3%) | 446 (69.7%) | 32 (78.0%) | 0.309 |
| ACEi/ARB at target dose | 201 (12.8%) | 87 (13.6%) | 7 (17.1%) | 0.654 |
| ACEi/ARB Fraction of Target Dose | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.25 [0.12, 0.50] | 0.324 |
| MRA | 835 (53.1%) | 339 (53.0%) | 22 (53.7%) | 0.996 |
| Digoxin | 293 (18.6%) | 122 (19.1%) | 9 (22.0%) | 0.85 |
| Oral hypoglycemic agents** | 322 (62.4%) | 127 (62.9%) | 8 (57.1%) | 0.912 |

HF heart failure; AF atrial fibrillation; DM diabetes mellitus; HT hypertension; RD renal disease; COPD chronic obstructive pulmonary disease; MI myocardial infarction; NYHA New York heart association; BMI body mass index; HR heart rate; SBP/DBP; systolic/diastolic blood pressure; 6MWT 6-minute walk test; LVEF left ventricular ejection fraction; NT-proBNP N-Terminal pro-Brain Natriuretic Peptide; CRP C-reactive protein; Hb hemoglobin; BB β-adrenoreceptor antagonist; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; MRA mineralocorticoid receptor antagonist. *p<0.05; **only for patients with diabetes mellitus; †no significant between-group differences in post-hoc testing.

1

 Table 4. Baseline characteristics stratified according to anti-M2-muscarinic receptor autoantibody status.

| | Variable | Anti-M2 Seronegative | Anti-M2 Intermediate | Anti-M2 Seropositive | p-value |
|-----------------|--------------------------------|----------------------|----------------------|----------------------|---------|
| Group Size | | 1213 | 871 | 172 | N/A |
| Demographics | | | | | |
| | Age (Years) | 69 (12) | 69 (13) | 70 (11) | 0.260 |
| | Female sex | 338 (27.9%) | 215 (24.7%) | 49 (28.5%) | 0.224 |
| | Recruited as outpatient | 403 (33.1%) | 276 (32.0%) | 55 (32.0%) | 0.862 |
| Primary HF Etic | ology | | | | |
| | Cardiomyopathy | 301 (25.3%) | 214 (25.1%) | 41 (24.0%) | 0.935 |
| VY | Hypertensive | 116 (9.7%) | 102 (12.0%) | 15 (8.8%) | 0.195 |
| | Ischemic | 539 (45.3%) | 399 (46.9%) | 80 (46.8%) | 0.750 |
| | Valvular Disease | 87 (7.3%) | 66 (7.8%) | 14 (8.2%) | 0.881 |

| Previous History and Comorbidities | | | | |
|---|--------------------------|-------------------------|--------------------------------|---------|
| AF | 540 (44.6%) | 400 (45.9%) | 84 (48.8%) | 0.539 |
| DM | 376 (31.0%) | 296 (34.0%) | 60 (34.9%) | 0.289 |
| HT | 733 (60.5%) | 555 (63.7%) | 110 (64.0%) | 0.289 |
| RD | 329 (27.2%) | 255 (29.3%) | 44 (25.6%) | 0.449 |
| Anemia | 409 (36.9%) | 286 (36.1%) | 51 (33.6%) | 0.704 |
| COPD | 204 (16.8%) | 152 (17.5%) | 39 (22.7%) | 0.170 |
| MI | 454 (37.5%) | 345 (39.6%) | 65 (37.8%) | 0.611 |
| Stroke | 122 (10.1%) | 79 (9.1%) | 11 (6.4%) | 0.275 |
| HF Hospitalization during previous year | 383 (31.4%) | 276 (32.0%) | 52 (30,2%) | 0.895 |
| Smoking | | | | |
| Never | 436 (36.0%) | 332 (38,2%) | 56 (32,6%) | |
| Past | 606 (50.1%) | 405 (46.6%) | 94 (54 7%) | 0 308 |
| Current | 168 (13 9%) | 132 (15.2%) | 22 (12.8%) | 0.000 |
| Clinical Characteristics | 100 (10.570) | 132 (15.270) | 22 (12.0)0) | |
| NVHA Eurotional Class | | | | |
| | 109 (10.4%) | 84 (11 0%) | 16 (10 5%) | |
| 1 | EC1 (E2 4%) | | 82 (54.2%) | 0 5 1 0 |
| | 220 (22.2%) | 370 (46.0%) | 65 (54.2%) 47 (20.7%) | 0.510 |
| | 555 (52.5%) 41 (2.0%) | 277 (30.4%) | 47 (30.7%) | |
| IV | 41 (3.9%) | 30 (3.9%) | 7 (4.0%) | |
| NVUA Class III or IV | 280 (26.2%) | 207 (40.2%) | F4 (2F 29/) | 0 1 6 1 |
| | | 307 (40.3%) | 54 (55.5%) 27 2 [24 5 20 5] | 0.101 |
| BIVII (Kg/m²) | 27.0 [24.0, 30.5] | 27.2 [24.2, 30.8] | 27.3 [24.5, 30.5] | 0.382 |
| HR (beats/min) | 76 [66, 90] | 76 [67, 90] | 75 [69, 88] | 0.898 |
| SBP (mm Hg) | 125 (23) | 124 (21) | 123 (20) | 0.131 |
| DBP (mm Hg) | 75 (14) | 75 (13) | 74 (12.2) | 0.407 |
| Pulmonary Crackles | 615 (52.3%) | 454 (54.0%) | 87 (50.6%) | 0.634 |
| 6MWT Successfully Completed | 765 (65.3%) | 552 (65.6%) | 96 (57.8%) | 0.142 |
| 6MWT Distance (m) | 230 [0, 350] | 217 [0, 350] | 167 [0, 360] | 0.539 |
| LVEF (%) | 30 [25, 37] | 30 [25, 36] | 30 [25, 35] | 0.832 |
| LVEF > 40% | 119 (11.1%) | 82 (10.6%) | 15 (9.3%) | 0.775 |
| Laboratory Indices | | | | |
| NT-proBNP (pg/mL) | 2711.0 [1157.5, 5460.0] | 2879.0 [1268.0, 6066.0] | 2356.0 [1231.8, 5396.8] | 0.253 |
| CRP (mg/L) | 13.1 [5.7, 25.0] | 13.0 [5.9, 27.1] | 13.2 [5.5, 27.1] | 0.847 |
| eGFR (mL/min/1.73 m ²) | 65.4 (25.8) | 64.4 (26.8) | 65.0 (26.3) | 0.664 |
| Creatinine (µmol/L) | 100.0 [82.0, 126.4] | 104.2 [83.0, 132.6] | 99.5 [83.7, 132.2] | 0.167 |
| Hb (g/dL) | 13.2 (1.9) | 13.2 (1.9) | 13.3 (2.0) | 0.826 |
| Medications | | | | |
| BB | 1020 (84.2%) | 715 (82.1%) | 145 (84.3%) | 0.410 |
| BB at target dose | 69 (5.7%) | 45 (5.2%) | 13 (7.6%) | 0.457 |
| BB Fraction of Target Dose | 0.25 [0.06, 0.50] | 0.24 [0.06, 0.48] | 0.25 [0.06, 0.50] | 0.347 |
| ACEi/ARB | 866 (71.5%) | 625 (71.8%) | 124 (72.1%) | 0.984 |
| ACEi/ARB at target dose | 157 (13.0%) | 105 (12.1%) | 33 (19.2%) | 0.040* |
| ACEi/ARB Fraction of Target Dose | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.25 [0.00, 0.50] | 0.956 |
| MRA | 615 (50.8%) | 477 (54.8%) | 104 (60.5%) | 0.026* |
| Digoxin | 223 (18.4%) | 169 (19.4%) | 32 (18.6%) | 0.848 |
| Oral hypoglycemic agents** | 227 (60.4%) | 191 (64.5%) | 39 (65.0%) | 0.496 |

HF heart failure; AF atrial fibrillation; DM diabetes mellitus; HT hypertension; RD renal disease; COPD chronic obstructive pulmonary disease; MI myocardial infarction; NYHA New York heart association; BMI body mass index; HR heart rate; SBP/DBP; systolic/diastolic blood pressure; 6MWT 6-minute walk test; LVEF left ventricular ejection fraction; NT-proBNP N-Terminal pro-Brain Natriuretic Peptide; CRP C-reactive protein; Hb hemoglobin; BB β-adrenoreceptor antagonist; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; MRA mineralocorticoid receptor antagonist. *p<0.05; **only for patients with diabetes mellitus.











Clinical and Prognostic Associations of Autoantibodies Recognizing Adrenergic/Muscarinic Receptors in Patients with Heart Failure

