Biomarkers and heart failure events in patients with atrial fibrillation in the ARISTOTLE trial evaluated by a multi-state model

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Background Atrial fibrillation (AF) and heart failure (HF) often coexist. We investigated the prognostic impact of biomarkers on the development of HF and death in patients with AF and different left ventricular systolic function considering the influence of competing events.

Methods The study included 11,818 patients with AF from the ARISTOTLE trial who at entry had information on history of HF, an estimate of left ventricular function and plasma samples for determination of biomarkers representing cardiorenal dysfunction (NT-proBNP, troponin T, cystatin C) and inflammation (GDF-15, IL-6, CRP). Patients were categorized into: (I) HF with reduced ejection fraction (HFrEF, $n = 2,048$), (II) HF with preserved ejection fraction (HFpEF, $n = 2,520$), and (III) No HF ($n = 7,250$). Biomarker associations with HF hospitalization and death were analyzed using a multi-state model accounting also for repeated events.

Results Baseline levels of NT-proBNP, troponin T, cystatin C, GDF-15, IL-6, and CRP were highest in HFrEF and lowest in No HF. During median 1.9 years follow-up, 546 patients were hospitalized at least once for HF and 819 died. Higher levels of all investigated biomarkers were associated with both outcomes (all $P < .0001$), with highest event rates in HFrEF and lowest in No HF. The associations remained after adjustments and were more pronounced for first than for recurrent events.

Conclusions In anticoagulated patients with AF, biomarkers indicating cardiorenal dysfunction and inflammation improve the identification of patients at risk of developing HF or worsening of already existing HF. These biomarkers might be useful for targeting novel HF therapies in patients with AF. (Am Heart J 2022;251:13–24.)

Atrial fibrillation (AF) and heart failure (HF) frequently coexist and have many common risk factors and are associated with increased risks of hospitalization and death.[1] Approximately 40% of patients with either AF or HF will develop the other condition[2] and there has been little change in the magnitude of this association over the last decade.[3] Increased levels of biomarkers reflecting cardiovascular dysfunction (N-terminal B-type natriuretic peptide [NT-proBNP]), myocardial damage (cardiac troponin T), inflammation (growth-differentiation factor-15 [GDF-15], interleukin 6 [IL-6], and C-reactive protein [CRP]), and renal impairment (cystatin C) have repeatedly been shown to be associated with risk of cardiovascular events in patients with AF.[4-9] In anticoagulated patients with AF, the presence of concomitant HF, whether due to reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), is associated with a greater risk of hospitalization and death than in AF without HF.[10,11] In HF cohorts it has been reported that higher NT-proBNP levels (≥400 pg/mL) have similar predictive value irrespective of AF status in HFrEF[12] but not in HFpEF where lower risks have been observed in those with AF compared with those without AF.[13] However, the associations between cardiorenal and inflammatory biomarker levels and outcomes in patients with AF on effective oral anticoagulation treatment, considering myocardial function

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(HFrEF, HFpEF, or no HF), other predictive cardiovascular biomarkers at baseline, and the influence of competing and repeated events, have not been investigated. Identification of patients with AF at increased risk of developing or worsening HF might enable additional specific therapeutic interventions. We therefore examined the associations between cardiorenal and inflammatory biomarkers and subsequent hospitalizations for HF and for death, in patients with AF with reduced and preserved ejection fraction, in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial using a multi-state model.[14]

Methods

Study design and participants

The details of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, ClinicalTrials.gov identifier: NCT00412984) trial have been reported previoulsy.[14,15] Briefly, ARISTOTLE was a double blind, double-dummy, multi-center, event-driven clinical trial in which 18,201 patients with AF and at least 1 additional thromboembolic risk factor were randomized to apixaban or warfarin for prevention of stroke or systemic embolism. The present substudy included all patients in the ARISTOTLE trial with information on both history of HF and left ventricular systolic function as measured by echocardiography, contrast- or radionuclide ventriculography, or magnetic resonance imaging at entry and with available levels of NT-proBNP, troponin T, GDF-15, IL-6, CRP, and cystatin C in plasma samples obtained at randomization ($n = 11,818$) (Supplemental Figure 1). Information on history of HF symptoms and left ventricular systolic function was collected in the trial case report form at randomization. Patients were divided into 3 categories: (I) HFrEF ($n = 2,048$), defined as a left ventricular ejection fraction (LVEF) $\leq$40% (of if a LVEF value was not available, a report of moderately or severely reduced left ventricular systolic dysfunction) regardless of symptoms of HF; (II) HFpEF ($n = 2,520$), defined as symptomatic HF and a LVEF $>$40% (of if a LVEF value was not available, a report of normal or only mildly reduced left ventricular systolic dysfunction); (III) No HF ($n = 7,250$), defined by no symptoms of HF and a LVEF $>$40% (of if a LVEF value was not available, a report of normal or only mildly reduced left ventricular systolic dysfunction). The ARISTOTLE trial and the biomarker substudy were approved by the appropriate ethics committees at all sites and all patients provided written informed consent.

Outcomes

The outcomes examined in these analyses were hospitalization for HF and all-cause death. Hospitalization for HF was not adjudicated but designated the primary reason for admission by the trial investigators.

Biochemical methods

Venous blood samples were collected in EDTA plasma tubes for NT-proBNP, troponin T, GDF-15, CRP, and cystatin C, and citrate tubes for IL-6, before start of study treatment and centrifuged immediately. Plasma samples were frozen in aliquots and stored at -70 degrees Celsius until analyzed centrally at the Uppsala Clinical Research Center Laboratory, Uppsala, Sweden. As previously described the measurement of the selected biomarkers were analyzed as follows: NT-proBNP and high sensitive cardiac troponin T with the Cobas Analytics e601 Immunoanalyzer from Roche Diagnostics; GDF-15 with the Elecsys pre-commercial assay kit P03 from Roche Diagnostics; high sensitive IL-6 with ELISA technique by R&D Systems Inc.; high sensitive CRP using a immunoturbidimetric assay from Abbott Diagnostics; and cystatin C with the ARCHITECT ci8200 from Abbott Diagnostics.[4-6,8,9]

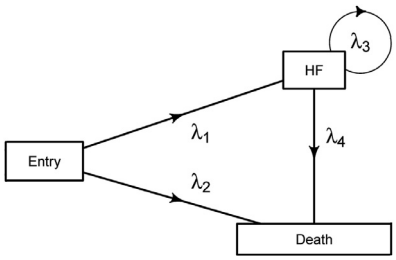
Statistical analyses

The baseline characteristics of each of the 3 groups of HFrEF, HFpEF, and No HF and for all patients were summarized using frequencies for categorical variables and median and 25th and 75th percentiles for continuous variables. Biomarker distributions were illustrated, and compared graphically between the groups, using empirical cumulative distribution function (ECDF) plots. All subjects were followed from randomization to either death or censoring at the end of study or loss to follow-up. During this time all hospitalizations due to HF were recorded.

Complete case analysis of associations with outcomes included all patients within the ARISTOTLE trial who had recorded information on symptoms of congestive HF within 3 months of randomization and measurement of left ventricular systolic function and who had levels of all biomarkers of interest (NT-proBNP, troponin T, GDF-15, IL-6, CRP, and cystatin C) available at entry. For the measurement of left ventricular systolic function, 73.3% were evaluated within 365 days and 47.9% within 90 days of randomization, respectively. The outcomes included all first and recurrent hospitalizations due to HF and all deaths. In order to account for multiple ordered events per patient, the associations between biomarker and outcomes were investigated using a multi-state model (Figure 1).[16]

This model includes separate states between which the patient can move at different rates (λ). All patients start at entry (randomization) and can then either stay at entry or go to first HF hospitalization or death. After a first HF hospitalization the patient can have recurrent HF hospitalizations or die. Movements in and out of these states are treated differently, thus the model accounts for competing risks and event history. To simplify matters, after a first HF hospitalization, all recurrent HF hospitalizations are lumped into the same state, meaning no

Figure 1



Representation of the multi-state model. Schematic for a multi-state model where all repeated heart failure (HF) hospitalizations belong to the state of one or more HF hospitalizations. The different transition rates are denoted by λ, where λ1 = from randomization to first hospitalization for HF, λ2 = from randomization to death, λ3 = from HF hospitalization to recurrent HF hospitalization/s, and λ4 = from HF hospitalization to death.

distinction is made between the risk of second, third, fourth, or more hospitalizations due to HF. The rate of transitions between the states are presented as events per 100 person-years. The event rates are estimated using a Poisson regression model. Reasons for using a Poisson model instead of a traditional Cox regression model in this analysis includes the possibility of direct modelling of the event rate in a fully parametric model as compared with the more traditional semi-parametric Cox regression model in which emphasis is more on relative effects. All models included HF status (ie, HFrEF, HFpEF, or No HF), the biomarker of interest, and the interaction between the biomarker and HF status. The biomarker was log-transformed using the natural logarithm and included as restricted cubic splines with 3 knots placed at the 10th, 50th, and 90th sample percentiles. The interaction was represented by the product of HF status and the linear part of the biomarker to save degrees of freedom in the model. Thus, this assumed that the functional form of the association with the biomarker was the same in all HF status groups but that the (linear) slope of the curves was allowed to differ. As the biomarkers were allowed to be non-linear and to interact with HF status it was not possible to give 1 single hazard ratio or incidence rate ratio to summarize the association. Instead, the association was represented graphically. The current model formulation allows for testing 4 specific hypotheses regarding each of the transition rates between the different states: (1) the overall association with HF status including the interaction with the biomarker, (2) the overall association with the biomarker including the interaction with HF status, (3) the interaction between HF status and the biomarker, and (4) the linearity assumption of the association with the biomarker. Adjustments were made in 2 steps by adding the following variables to the models: (Step 1) randomized treatment, age, sex, hypertension, diabetes mellitus, coronary artery disease (any of prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), history of stroke/transient ischemic attack (TIA), body mass index (BMI), heart rate, sinus rhythm and renal function (creatinine clearance [CrCl], was not included in the analysis of cystatin C), and (Step 2) including Step 1 + NT-proBNP and troponin T. Summary of the tested hypotheses, as specified above, in the adjusted models are presented in Table 2 and Table 3 for the outcomes from randomization and in Supplementary Table 3 and IV for the outcomes from HF hospitalization. To be able to compare the biomarkers across the adjusted models, each biomarker's partial contribution to its respective model was assessed. The contribution was measured by the partial chi-square statistic for all terms including the biomarker, ie, including interaction and spline terms, in the respective model, and larger values indicate stronger association. These partial chi-squared statistics, minus the degrees of freedom spent, were also graphically illustrated for all models.

Results

Baseline characteristics and demographics

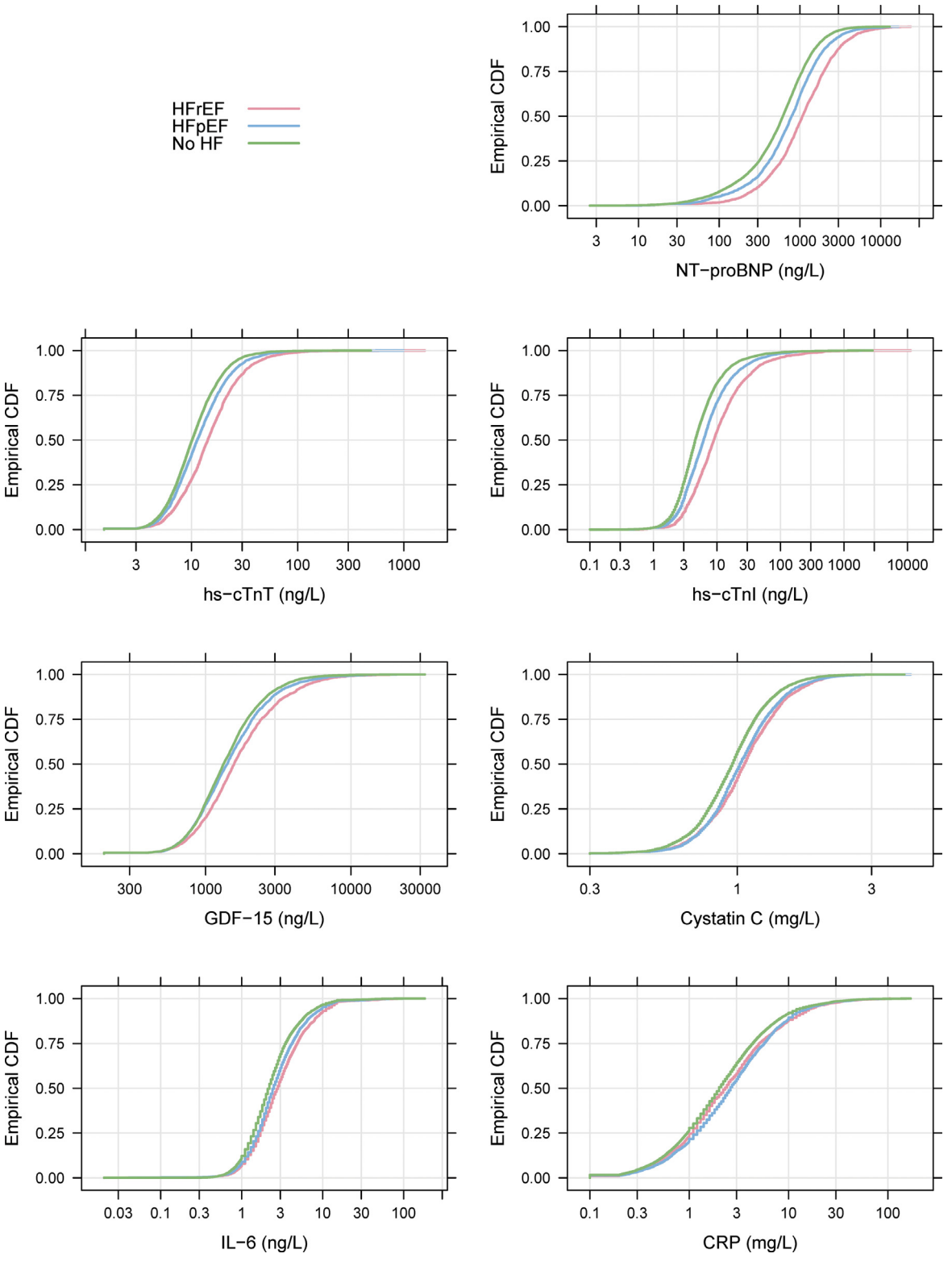
Baseline characteristics by the 3 groups of HFrEF, HFpEF, and No HF are presented in Table 1. Data for the total 11,818 patients are presented in Supplementary Table 1. Overall, the median age was 70 years (interquartile range [IQR] 62-76) and approximately 35% were women. The proportion of women in the groups of HFrEF, HFpEF, and No HF were 21%, 43%, and 36%, respectively. Compared with No HF, patients with HFrEF and HFpEF were more likely to smoke and have persistent or permanent AF, prior myocardial infarction, prior vascular disease, and prior coronary heart disease. Comparison between the 2 HF groups showed that hypertension was more common in HFpEF (89%) than in HFrEF (75%), whereas coronary artery disease was more common in HFrEF (34%) than in HFpEF (22%).

Biomarker distributions

The median levels and distributions of the biomarkers concentrations in the HFrEF, HFpEF, and No HF groups are presented in Table 1 and in Figure 2. The shape of the distribution for each biomarker was similar for the 3 groups, with, in general, higher levels in the HFrEF group followed by the HFpEF group and lowest in the No HF group, for all biomarkers, except for CRP that was higher in the HFpEF group. The difference between the biomarker distributions for the 3 groups were all statistically significant (Kruskal-Wallis test, $P < .001$) (Figure 2).

Empirical cumulative distribution function for different biomarkers. For each value of the biomarker on the x-

Figure 2



Distributions of biomarker concentrations by HF status. HF, heart failure.

Table 1. Baseline characteristics by HF status

	HFrEF (*N* = 2,048)	HFpEF (*N* = 2,520)	No HF (*N* = 7,250)
Randomized to Warfarin	50.4 (1,033)	49.4 (1,246)	50.1 (3,631)
Age (years)	67.0 (60.0 - 74.0)	69.0 (61.0 - 74.0)	70.0 (63.0-76.0)
Gender: Female	20.6 (422)	42.7 (1076)	35.7 (2,588)
BMI (kg/m^2)	28.1 (24.5 - 32.0) [14]	29.4 (25.9 - 33.6) [7]	28.5 (25.3 - 32.6) [30]
Systolic blood pressure (mm Hg)	125.0 (113.0 - 138.0) [6]	130.0 (120.0 - 140.0) [5]	130.0 (120.0 - 140.0) [13]
Diabetes	25.9 (531)	24.8 (626)	25.2 (1828)
Hypertension	74.8 (1,531)	88.5 (2,231)	89.9 (6,515)
Current smoker	11.0 (225) [1]	8.2 (207) [3]	7.4 (534) [5]
Alcohol	3.0 (61)	1.4 (35)	2.8 (202)
Permanent or persistent AF	89.6 (1,835)	85.0 (2,141) [2]	81.5 (5,909) [1]
Prior stroke/TIA	14.9 (305)	17.2 (434)	19.7 (1,426)
Prior bleeding	16.4 (336)	14.7 (370)	19.1 (1,385)
Prior anemia	7.4 (151) [2]	7.7 (194) [3]	7.6 (554) [5]
Symptomatic HF within 3 months	65.0 (1,331)	100.0 (2,520)	0.0 (0)
Prior coronary artery disease	34.3 (703) [1]	21.7 (548)	19.4 (1,410)
Prior myocardial infarction	25.8 (528) [1]	16.0 (404)	9.7 (701)
Prior PCI	13.6 (278)	7.2 (182)	10.4 (751)
Prior CABG	12.4 (253)	5.4 (136)	6.9 (500)
Prior peripheral arterial disease	4.8 (99) [1]	6.3 (160)	4.9 (357)
Prior vascular disease	36.9 (756)	28.9 (729)	23.7 (1,717)
Warfarin within 7 days of randomization	57.3 (1,171) [5]	47.1 (1,185) [2]	59.5 (4,306) [17]
Antiplatelet/NSAID	39.8 (815)	37.3 (941)	39.4 (2,859)
Prior Digitalis	50.7 (1,038)	43.1 (1,085)	26.4 (1,911)
Prior Diuretic	3.4 (70)	3.2 (80)	1.3 (95)
Prior Betablocker	76.7 (1,570)	71.2 (1,794)	63.8 (4,622)
Prior ACEi/ARB	83.0 (1,699)	78.5 (1,978)	67.9 (4,922)
Heart rate	77 (67-88) [7]	76 (67-87) [5]	74 (64-84) [16]
Sinus rhythm	6.3 (129) [7]	12.1 (303) [6]	14.2 (1,031) [12]
LV ejection fraction (%)	35.0 (29.0-38.0) [158]	56.0 (50.0-62.0) [191]	60.0 (55.0-65.0) [992]
LV dysfunction classification*:			
Normal	4.2 (24) [1,478]	60.4 (496) [1,699]	85.3 (2012) [4,892]
Mild	11.4 (65)	31.9 (262)	13.1 (310)
Moderate	49.1 (280)	7.4 (61)	1.4 (33)
Severe	35.3 (201)	0.2 (2)	0.1 (3)
Biomarkers			
Hemoglobin (g/dL)	14.3 (13.2-15.4) [12]	14.2 (13.0 - 15.3) [10]	14.2 (13.2-15.2) [32]
NT-proBNP (ng/L)	1074.5 (585.0-1,975.8)	791.0 (417.0 - 1371.2)	615.0 (312.0-1,069.5)
hs-cTnT (ng/L)	14.2 (9.4-21.8)	11.3 (7.7 - 17.4)	10.1 (7.2-15.0)
GDF-15 (ng/L)	1572.0 (1090.2-2413.0)	1409.0 (970.0-2,091.0)	1,328.0 (957.2-1,930.0)
IL-6 (ng/L)	2.8 (1.7 - 4.9)	2.5 (1.6 - 4.2)	2.2 (1.4 - 3.5)
CRP (mg/L)	2.3 (1.1 - 5.1)	2.6 (1.2 - 5.7)	2.0 (1.0 - 4.4)
CrCl (mL/min)	73.5 (55.9 - 95.5) [7]	75.6 (56.9 - 97.4) [4]	74.5 (57.4 - 95.5) [26]
Cystatin C (mg/L)	1.1 (0.9 - 1.3)	1.0 (0.9 - 1.2)	1.0 (0.8 - 1.2)

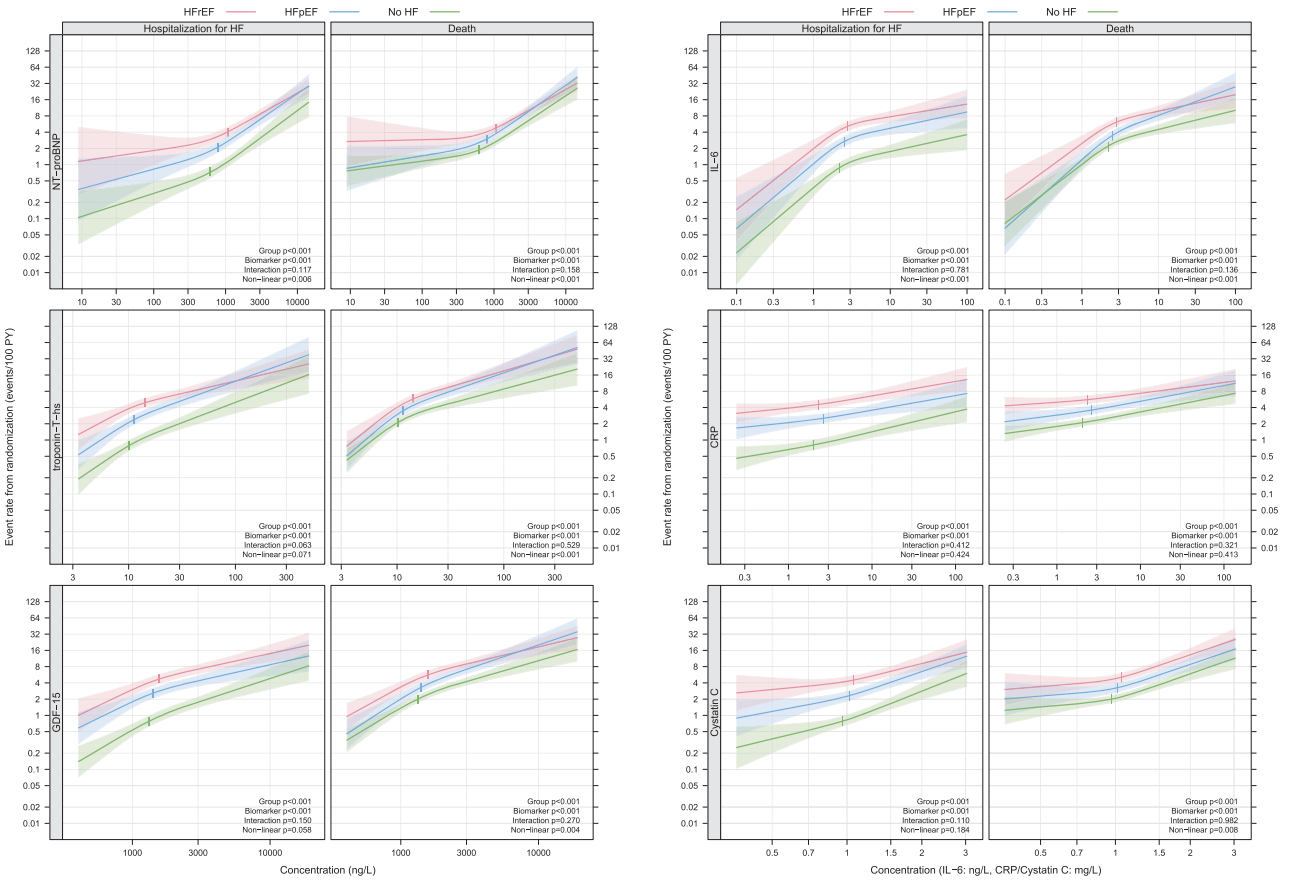
m (a - b) represents median (Q1 - Q3). p (n) represent percentage (frequency). Percentages computed by group. [M] represents number of missings. HF, heart failure; rEF, reduced ejection fraction; pEF, preserved ejection fraction; BMI, body mass index; AF, atrial fibrillation; TIA, transient ischemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NSAID, nonsteroidal anti-inflammatory drugs; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NT-proBNP, N-terminal B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; GDF-15, growth-differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein; CrCl, creatinine clearance. *If both LV ejection fraction (%) and LV dysfunction classification (normal, mild, moderate, severe) were reported in a patient, only LV ejection fraction (%) was counted in the analyses.

axis the proportion of subjects with a value less than or equal to that value can be read on the y-axis. HF, heart failure; rEF, reduced ejection fraction; pEF, preserved ejection fraction; NT-proBNP, N-terminal B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; hs-cTnI, high-sensitivity cardiac troponin I; GDF-15, growth-differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein.

Associations with first hospitalization for HF or death

During follow-up, 546 patients were hospitalized for HF and a total of 819 deaths occurred of which 709 died without a preceding hospitalization for HF (Supplemental Table 2). The median duration of follow-up was 1.9 years. The event rates of both HF hospitalization and death were higher in the HFrEF group than in the HFpEF group and lowest in the No HF group, independent of

Figure 3



Associations between biomarkers and first outcome event according to HF status. HF, heart failure; rEF, reduced ejection fraction; pEF, preserved ejection fraction; NT-proBNP, N-terminal B-type natriuretic peptide; hs, high-sensitivity; GDF-15, growth-differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein.

biomarker level (Figure 3). There were positive associations between baseline concentration of each biomarker and the probability of both HF hospitalization and death after randomization (Figure 3). These associations were consistent across the groups of HFrEF, HFpEF, and No HF for each biomarker and were more pronounced for first time events than for recurrent events (compare Figure 3 and Supplemental Figure 2). There were strong indications of non-linear associations between log biomarker levels and the log rate of first occurrence of either hospitalization for HF or death, except for cystatin C for HF hospitalization and CRP for both outcomes (Figure 3).

All associations remained similar after adjustments for the other predictive clinical risk factors. The associations between each of GDF-15, IL-6, and CRP and both outcomes remained statistically significant even when extending the adjustments with NT-proBNP and troponin T to the clinical risk factors. The associations with cystatin C were non-significant in presence of NT-proBNP and troponin T (Table 2 and III and Figure 4).

Associations with subsequent events after HF hospitalization

In addition to the traditional analyses above concerning time to first event, we also evaluated the associations between baseline biomarkers and subsequent events in relation to HF status. The maximum number of hospital admissions for HF noted in a patient was 7. In total, there were 173 additional hospitalizations for HF (a total of 107 patients had at least 2 HF hospitalizations) and 110 deaths subsequent to hospitalization for HF (Supplemental Table 2). In general, event rates were higher but associations weaker between baseline biomarker levels and events occurring after HF hospitalization (Supplemental Figure 2). These associations were consistent for all biomarkers across the 3 groups with 2 exceptions: (i) the association between IL-6 and death after HF hospital-

Table 2. Significances of associations between HF status, biomarkers and first hospitalization for heart failure (HF)

	HF status			Biomarker			Interaction			Non-linear		
	χ^2	df	*P*	χ^2	df	*P*	χ^2	df	*P*	χ^2	df	*P*
NT-proBNP												
Unadjusted	148	4	<.0001	268.2	4	<.0001	4.30	2	.1167	7.65	1	.0057
Adj step 1	133	4	<.0001	178.6	4	<.0001	2.97	2	.2268	6.45	1	.0111
Adj step 2	116	4	<.0001	101.6	4	<.0001	2.74	2	.2547	4.69	1	.0303
Troponin T												
Unadjusted	200	4	<.0001	172.5	4	<.0001	5.54	2	.0626	3.25	1	.0714
Adj step 1	171	4	<.0001	104.4	4	<.0001	3.41	2	.1813	2.75	1	.0972
Adj step 2	117	4	<.0001	36.1	4	<.0001	6.19	2	.0454	1.81	1	.1789
GDF-15												
Unadjusted	225	4	<.0001	154.1	4	<.0001	3.79	2	.1503	3.61	1	.0575
Adj step 1	194	4	<.0001	71.1	4	<.0001	2.75	2	.2526	3.32	1	.0683
Adj step 2	110	4	<.0001	20.2	4	.0005	5.72	2	.0573	2.83	1	.0926
IL-6												
Unadjusted	232	4	<.0001	98.9	4	<.0001	0.49	2	.7810	11.99	1	.0005
Adj step 1	192	4	<.0001	65.6	4	<.0001	0.34	2	.8435	7.91	1	.0049
Adj step 2	103	4	<.0001	23.2	4	.0001	1.86	2	.3940	4.71	1	.0301
CRP												
Unadjusted	261	4	<.0001	59.0	4	<.0001	1.78	2	.4116	0.64	1	.4243
Adj step 1	209	4	<.0001	42.5	4	<.0001	1.48	2	.4773	0.05	1	.8157
Adj step 2	108	4	<.0001	14.3	4	.0065	2.37	2	.3061	0.27	1	.6044
Cystatin C												
Unadjusted	238	4	<.0001	103.0	4	<.0001	4.41	2	.1103	1.77	1	.1839
Adj step 1	208	4	<.0001	55.8	4	<.0001	3.30	2	.1922	0.90	1	.3430
Adj step 2	111	4	<.0001	4.4	4	.3509	3.79	2	.1504	0.15	1	.6946

The columns show the results from testing the 4 specific hypotheses of (1) overall association with HF status including the interaction with the biomarker, (2) the overall association with the biomarker including the interaction with HF status, (3) the interaction between HF status and the biomarker and (4) the linearity assumption of the biomarker association. The results are presented as the partial χ^2 value, the number of degrees of freedom, and the corresponding *P*-value for the respective test as specified above.

Adjustments were made in 2 steps by adding the following variables to the models: (Step 1) randomized treatment, age, sex, hypertension, diabetes mellitus, coronary artery disease (any of prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), history of stroke/transient ischemic attack (TIA), body mass index (BMI), heart rate, sinus rhythm and renal function (creatinine clearance [CrCl], will not be included when we study cystatin C), and (Step 2) including Step 1 + N-terminal B-type natriuretic peptide (NT-proBNP) and troponin T. GDF-15, growth-differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein.

ization was stronger in the No HF group ($P = .004$ for test of no interaction), and (ii) the association between CRP and subsequent hospitalization for HF was stronger in the HFpEF group ($P = .001$ for test of no interaction) (Supplemental Figure 2).

Discussion

In patients with AF on effective oral anticoagulation, the median levels of cardiorenal (NT-proBNP, troponin T, cystatin C) and inflammatory (GDF-15, IL-6, CRP) biomarkers were higher in patients with HFrEF, than in patients with HFpEF, and lower in those without HF than in both HF subgroups. The event rates of HF hospitalization and death was highest in patients with HFrEF, followed by HFpEF and lowest in those without HF. Higher levels of all the analyzed cardiorenal and inflammatory biomarkers measured (NT-proBNP, troponin T, cystatin C, GDF-15, IL-6, and CRP) were independently associated with higher probability of both hospitalization for HF and death, regardless of HF status at baseline. These findings show that cardiorenal and inflammatory biomarkers may add important prognostic information for both incident HF hospitalization and death in patients with AF without known HF and with progression of existing HF, irrespective of left ventricular systolic function. Utilizing a multistate model, the results displayed more pronounced associations between baseline biomarker levels and first events than recurrent events.

The prevalence of HF increases with age, reaching ≥10% among persons 70 years or older[17] and is expected to reach even higher levels in the future due to an aging population. A similar trend is seen for AF with an estimated lifetime risk of 33% and an expected 2-fold rise in prevalence.[1] In patients with AF, concomitant HF is present in up to 40% of the patients, and vice versa, and the coexistence of both conditions constitutes a major risk factor for both hospitalization and mortality.[2,10,11] While strategies to prevent stroke in patients with AF has improved substantially during the last decade with better antithrombotic agents, hospitalization for HF and death remain substantial problems with event rates surpassing those for ischemic stroke,[18] even in patients with AF without concomitant HFrEF or HFpEF treated with oral anticoagulation.[11] Although stroke continues to be a feared complication of AF, the rates of HF hospitaliza-

Table 3. Significances of associations between HF status, biomarkers and death

	HF status			Biomarker			Interaction			Non-linear		
	χ^2	df	*P*	χ^2	df	*P*	χ^2	df	*P*	χ^2	df	*P*
NT-proBNP												
Unadjusted	42	4	<.0001	267	4	<.0001	3.69	2	.1581	25.52	1	<.0001
Adj step 1	52	4	<.0001	126	4	<.0001	2.13	2	.3440	11.34	1	.0008
Adj step 2	42	4	<.0001	61	4	<.0001	2.08	2	.3541	7.29	1	.0069
Troponin T												
Unadjusted	59	4	<.0001	220	4	<.0001	1.27	2	.5294	11.90	1	.0006
Adj step 1	67	4	<.0001	127	4	<.0001	2.34	2	.3096	6.72	1	.0096
Adj step 2	39	4	<.0001	56	4	<.0001	1.41	2	.4934	5.99	1	.0144
GDF-15												
Unadjusted	85	4	<.0001	248	4	<.0001	2.62	2	.2697	8.23	1	.0041
Adj step 1	85	4	<.0001	129	4	<.0001	1.99	2	.3691	4.52	1	.0336
Adj step 2	41	4	<.0001	46	4	<.0001	2.61	2	.2708	2.70	1	.1001
IL-6												
Unadjusted	92	4	<.0001	174	4	<.0001	3.99	2	.1357	13.19	1	.0003
Adj step 1	86	4	<.0001	130	4	<.0001	4.10	2	.1290	10.21	1	.0014
Adj step 2	38	4	<.0001	69	4	<.0001	4.46	2	.1075	5.40	1	.0202
CRP												
Unadjusted	113	4	<.0001	60	4	<.0001	2.27	2	.3210	0.67	1	.4129
Adj step 1	101	4	<.0001	65	4	<.0001	2.10	2	.3505	0.28	1	.5945
Adj step 2	43	4	<.0001	29	4	<.0001	3.31	2	.1909	0.09	1	.7669
Cystatin C												
Unadjusted	90	4	<.0001	115	4	<.0001	0.04	2	.9815	7.02	1	.0081
Adj step 1	93	4	<.0001	50	4	<.0001	0.16	2	.9242	5.86	1	.0155
Adj step 2	39	4	<.0001	3	4	.5507	0.49	2	.7828	2.66	1	.1027

The columns show the results from testing the 4 specific hypotheses of (1) overall association with heart failure (HF) status including the interaction with the biomarker, (2) the overall association with the biomarker including the interaction with HF status, (3) the interaction between HF status and the biomarker and (4) the linearity assumption of the biomarker association. The results are presented as the partial χ^2 value, the number of degrees of freedom, and the corresponding p-value for the respective test as specified above.

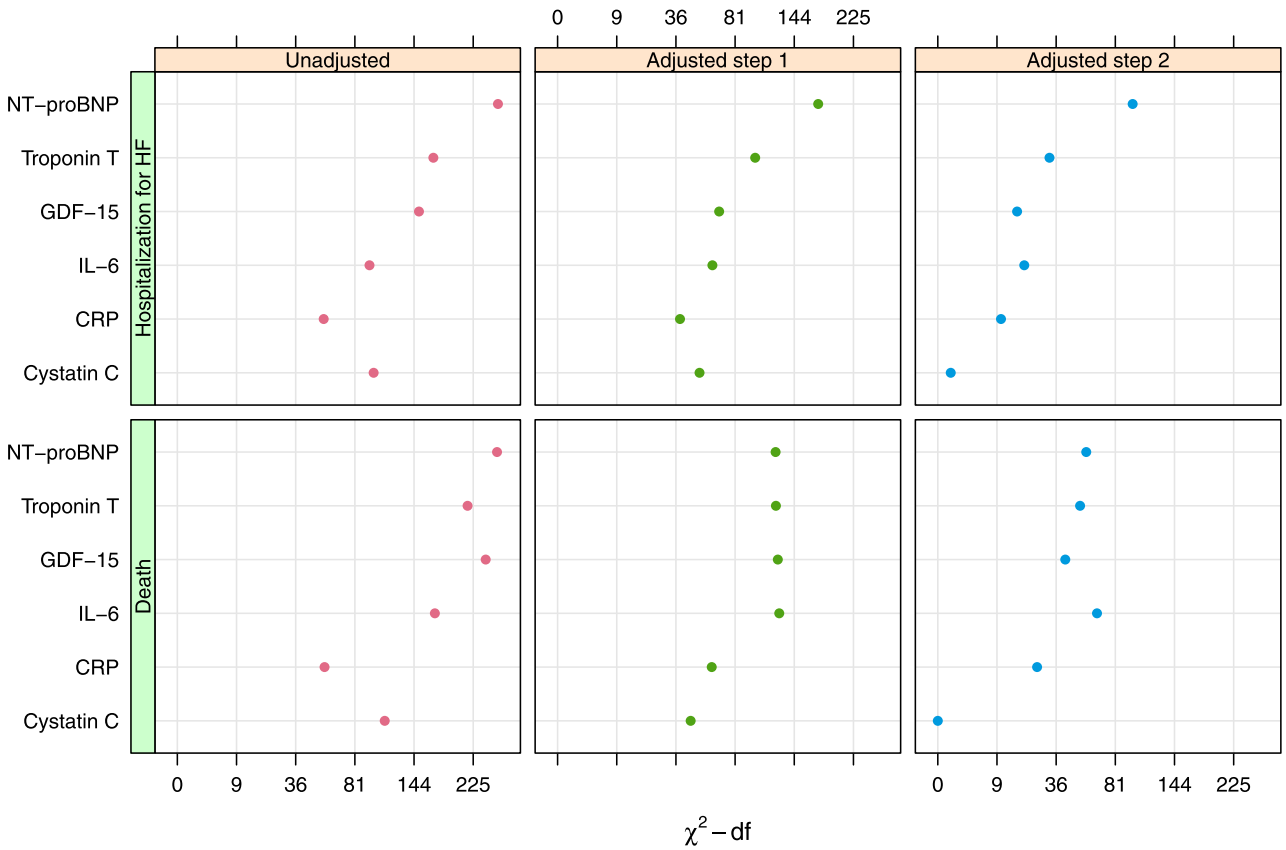
Adjustments were made in 2 steps by adding the following variables to the models: (Step 1) randomized treatment, age, sex, hypertension, diabetes mellitus, coronary artery disease (any of prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), history of stroke/ transient ischemic attack (TIA), body mass index (BMI), heart rate, sinus rhythm and renal function (creatinine clearance [CrCl], will not be included when we study cystatin C), and (Step 2) including Step 1 + N-terminal B-type natriuretic peptide (NT-proBNP) and troponin T. GDF-15, growth-differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein.

tions are 2- to 4-fold higher than that of stroke in patients with concomitant AF and HF receiving oral anticoagulation treatment.[11] Furthermore, the majority of deaths in anticoagulated patients with AF are HF-related, either due to progressive HF (14%) or sudden cardiac death (21%), rather than due to thromboembolism (8%).[19,20] This emphasizes the need for additional preventive treatment measures beyond anticoagulation therapy to further reduce HF-related morbidity and mortality in patients with AF. Better identification of patients with AF at risk of developing new incident HF or worsening of already existing HF could enable more individually optimized treatment strategies. Accordingly, measurement of biomarker levels might contribute to identification of patients with AF suitable for more targeted upstream therapies, such as angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonist,[21] sodium-glucose cotransporter 2 (SGLT2) inhibitor,[22] and/or catheter ablation.[23,24]

Biomarkers reflecting myocardial stress and damage, inflammation, and renal impairment have previously been shown associated with increased risk of subsequent cardiovascular events in patients with AF[4-9] and in patients with HF,[25] but so far not elucidated in relation to HF status in patients with both conditions. Higher levels of BNP and troponin have previously been reported in patients with HFrEF compared with HFpEF.[26] In a recent study including more than 22,000 individuals from the general population investigating the risk of incident HF, cardiovascular biomarkers including NT-proBNP, troponin, and CRP were more strongly associated with incident HFrEF as compared with incident HFpEF during a median follow-up time of 12 years.[27] These findings are in line with our results of higher biomarker concentrations by decreasing left ventricular systolic function, and increased probability of HF progression and fatal events with increasing biomarker levels regardless of left ventricular systolic function and independent of clinical variables including heart rate and sinus rhythm.

The associations between the inflammatory biomarkers GDF-15, IL-6, and CRP and HF hospitalization and death remained significant in all 3 groups even after adjustments for the strongly predictive cardiac biomarkers NT-proBNP and troponin T, strengthening the role of the inflammatory process. In line with the present findings,

Figure 4



Strength of association between biomarkers and first heart failure (HF) hospitalization (top) and death (bottom). The strength of association was estimated by the partial chi-square minus the 4 degrees of freedom used for testing the association between the biomarker and first hospitalization for HF and mortality, respectively, in 18 different models, ie, 3 models for each of the 6 biomarkers: unadjusted (left panel), adjusted for clinical variables and renal function (middle panel), adjusted for clinical variables, renal function, N-terminal B-type natriuretic peptide (NT-proBNP), and troponin T (hs-cTnT, right panel). The models for cystatin C did not include renal function. GDF-15, growth-differentiation factor-15; IL-6, interleukin 6; CRP, C-reactive protein.

a smaller cohort study of patients with AF in Switzerland recently reported similar associations between IL-6 and CRP and HF hospitalization although without considering baseline ejection fraction or adjusting for colinearity with other prognostic cardiovascular biomarkers.[28] Inflammation is linked to AF and although the exact mechanisms remain poorly understood[29] a mechanistic link have been proposed between the NOD-like receptor protein 3 (NLRP3) inflammasome signaling, an upstream component of the IL-1β—IL-6 pathway, and the pathogenesis of AF in experimental animal models.[30] Therefore, targeting the inflammatory process with therapeutic interventions might be beneficial in patients with AF at risk of HF, as previously demonstrated in patients with coronary artery disease.[31,32]

By using a multi-state model the present study confirmed that single measurements of biomarkers provide useful information concerning the probability of the first subsequent event.[33,34] The considerably weaker association to the next events emphasizes the need to reassess biomarker concentrations after the occurrence of an event in order to maintain an accurate future risk assessment, as suggested by the current class IIa recommendation for predischarge remeasurement of biomarkers such as NT-proBNP in the 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of HF.[35]

Strengths and limitations

The strengths of this study include analyses of a large, prospective, closely monitored multinational cohort of patients with AF and minimizing of confounding by adjusting the analyses for a wide range of established prognostic variables including established cardiac biomarkers

and estimates of left ventricular function. Further, to account for multiple ordered events per patient (as subsequent events provide information on disease progression) a multi-state model was used for a more precise evaluation of the association between biomarkers and outcomes and in presence of other predictive biomarkers. This model permits incorporation of important features in the analysis reflecting the nature of the data such as repeated hospitalizations for HF, while it also accommodates for competing risks and does not waste information after first event. A limitation of the study is its basis on a clinical trial cohort of patients with AF on anticoagulation treatment with at least 1 risk factor for stroke and that the results therefore may not be directly applicable to the general AF or HF populations. Many of the biomarkers tested are not necessarily heart failure specific and may reflect a sick patient or a sick heart. Also, the outcome of HF hospitalization was not an adjudicated event but designated the primary reason for admission by the trial investigator. In addition, the time interval between measurement of the left ventricular systolic function and randomization was variable.

Conclusions

In anticoagulated patients with AF, biomarkers indicating cardiorenal dysfunction and inflammation improve the identification of patients with AF at risk of developing HF or worsening of already existing HF. These biomarkers might be useful for targeting additional HF therapies in patients with AF.

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Conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.03.009.

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