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History of Atrial Fibrillation and Trajectory of Decongestion in Acute Heart Failure

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Abstract

Objectives: To characterize the course of decongestion among patients hospitalized for acute heart failure (AHF) by history of atrial fibrillation/atrial flutter (AF/AFL).

Background: AF/AFL and chronic heart failure (HF) commonly coexist. Little is known regarding impact of AF/AFL on relief of congestion among patients who develop acute heart failure (AHF).

Methods: We pooled patients from 3 randomized trials of AHF conducted within the Heart Failure Network (the Diuretic Optimization Strategies trial, the Renal Optimization Strategies Trial, and the Cardiorenal Rescue Study in Acute Decompensated Heart Failure). The association

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Tweet: New data from @nih_nhlbi RCTs: AF may make decongestion more challenging in acute HF. Should we be more aggressive with AF control in this population?

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between AF/AFL history and in-hospital changes in various metrics of congestion was assessed using covariate-adjusted linear and ordinal logistic regression models.

Results: Of 750 unique patients, 418 (56%) had a history of AF/AFL. Left ventricular ejection fraction was higher (35% vs. 27% $P<0.001$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were non-significantly lower at baseline (4210 pg/mL vs. 5037 pg/mL, $P=0.27$) in AF/AFL. After covariate adjustment, history of AF/AFL was associated with less substantial loss of weight (-5.7% vs. -6.5% , $P=0.02$) and decrease in NT-proBNP levels (-18.7% vs. -31.3% , $P=0.003$) by 72 or 96 hours. History of AF/AFL was also associated with a blunted increase in global sense of well-being at 72/96 hours ($P=0.04$). There was no association between AF/AFL history and change in orthodema congestion score ($P=0.67$) or the 60-day composite clinical endpoint (all-cause mortality or any rehospitalization) (hazard ratio 1.21, 95% confidence interval 0.92–1.59, $P=0.17$).

Conclusion: More than half of patients admitted with AHF had a history of AF/AFL. History of AF/AFL was independently associated with a blunted course of in-hospital decongestion. Further research is required to understand the utility of specific therapies targeting AF/AFL during hospitalization for AHF.

Keywords

atrial fibrillation; atrial flutter; decongestion; heart failure; body weight

Introduction

Atrial fibrillation/atrial flutter (AF/AFL) and heart failure (HF) have evolved into global, contemporary cardiovascular epidemics. Worldwide, it is estimated that over 30 million people are burdened by AF/AFL and approximately 38 million individuals carry a diagnosis of HF (1,2). Chronic AF/AFL and HF frequently coexist due to shared pathophysiology, and comorbid AF/AFL-HF carries a worse prognosis than either disease in isolation (3). Chronic AF/AFL serves as a risk factor for and a long-term consequence of both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) (4). Comorbid AF/AFL-HF is associated with both increased mortality and HF hospitalization among patients with chronic HF (5,6). The association between AF/AFL and adverse short-term clinical outcomes among those who develop acute HF (AHF) is inconsistent across multiple populations, which may lead to variability regarding management of AF in this setting (7–12). While relief of congestion through aggressive diuresis remains the mainstay of therapy in AHF (13), the influence of AF/AFL on the clinical course of decongestion is unclear. As such, we aimed to characterize the course of decongestion in patients hospitalized for AHF with a history of AF/AFL as compared with those without a history of AF/AFL in a pooled, patient-level analysis of the National Heart, Lung, and Blood Institute-sponsored Heart Failure Network (HFN).

Methods

DOSE, ROSE, and CARRESS-HF: Study Designs and Patient Selection

Patients from 3 trials conducted by the HFN were pooled for this analysis: the Diuretic Optimization Strategies Evaluation (DOSE) trial (14), the Renal Optimization Strategies Evaluation (ROSE) trial (15), and the diuretic arm of the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial (16). The study designs, protocols, and results of these trials have been previously published (14–16). All 3 trials were prospective, randomized studies which enrolled patients with AHF, regardless of left ventricular ejection fraction (LVEF), and studied the following methods of decongestion as compared with standard therapy: diuretic dosing and infusion strategies (DOSE), low-dose dopamine or nesiritide (ROSE), or ultrafiltration (CARRESS-HF). To reduce potential confounding by ultrafiltration on congestion parameters, only the diuretic (control) arm of the CARRESS-HF trial was used for this analysis. Non-duplicated patients amongst the 3 trials were included in the analysis. Patients were categorized based on history of AF/AFL as assessed at index hospitalization.

Congestion and Clinical Endpoints

Study visits among the 3 trials were performed during index hospitalization at baseline, 24 hours, and 48 hours. The final assessment for in-hospital data collection was 72 hours for the DOSE and ROSE trials and 96 hours for the CARRESS-HF trial. During each timepoint, the following endpoints of congestion were obtained: weight (lbs), net fluid loss (calculated at 24 hours and thereafter), and N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration. In addition, patients completed 2 distinct self-assessments at each timepoint: the global visual analog scale (VAS) and dyspnea VAS. To complete the global VAS, patients marked their global well-being on a 10-cm vertical line, the top of which was labeled “best you have ever felt” and bottom of which was labeled “worst you have ever felt” (17). The dyspnea VAS utilized a similar vertical line and concept, with the top of the line labeled “I am not breathless at all” and the bottom labeled “I am as breathless as I have ever been”. Both global VAS and dyspnea VAS were tabulated as 0 to 100 based on the measurement (in millimeters) from the patient marked site to the bottom of the vertical line (higher scores reflecting better symptoms). Finally, a 4-point “orthodema” congestion score was measured at each study assessment based on degree of orthopnea (≥ 2 pillows=2 points, <2 pillows=0 points) and peripheral edema (0–2 points) (18). For the DOSE and CARRESS-HF trials, edema was classified as none/trace (0 points), moderate (1 point), or severe (2 points). For the ROSE trial, edema was categorized as 0/1+ (0 points), 2+/3+ (1 point), or 4+ (2 points). The key clinical endpoint was the composite of all-cause mortality or any rehospitalization at 60 days post-discharge.

Statistical Analysis

Continuous variables were expressed as median (25th, 75th percentiles) and categorical variables were expressed as number (%). Pearson χ^2 analyses or Fischer’s exact tests and the Wilcoxon rank sum tests were used to compare categorical and continuous variables, respectively, by AF/AFL status. Congestion endpoints (weight, net fluid loss, NT-proBNP levels, dyspnea VAS, global VAS, and orthodema scores) were compared by AF/AFL

history at each time point (baseline, 24 hours, 48 hours, 72/96 hours) using the Wilcoxon rank sum test. To account for relative (as opposed to absolute) changes in weight and NT-proBNP levels, relative change in NT-proBNP and weight (lbs) were defined by the following formula: $(72/96\text{h value} - \text{Baseline value})/\text{Baseline value}$. General linear regression models assessed the association between AF/AFL history and change in all continuous congestion endpoints from baseline to 72/96 hours. Ordinal logistic regression models assessed the association between AF/AFL history and change in orthodema score at 72/96 hours. Models were adjusted for the following covariates, obtained at baseline and identified *a priori* by clinical relevance: age, sex, race, LVEF, heart rate, systolic blood pressure, serum creatinine, trial, and loop diuretic dose equivalent. We also explored the relationship between AF/AFL history and the primary marker of congestion (relative change in weight) in the following prespecified subgroups: 1) LVEF (LVEF $\leq 40\%$, LVEF 41–49%, LVEF $\geq 50\%$), 2) trial (DOSE, ROSE, and CARRESS-HF), and 3) baseline heart rate (above and below median value). Cox proportional hazards models were used to analyze the association between baseline AF/AFL history and the key composite clinical endpoint at 60 days. Covariates included in the clinical endpoint analysis were the same as those used in the congestion endpoint analysis. All statistical analyses were performed with SAS statistical software, version 9.1 (Cary, NC).

Results

Study Population

Of the 762 patients from ROSE (n=360), DOSE (n=308) and the diuretic arm of CARRESS-HF (n=94), 12 patients were excluded who participated in more than 1 trial. 750 unique patients were thus identified and included in the analysis. Over half of patients had a history of AF/AFL (n=418, 56%). Patients with AF/AFL history tended to be older and carried higher rates of ischemic HF etiology while patients without AF/AFL history had higher rates of diabetes mellitus and hypertension ($P < 0.05$ for all comparisons) (Table 1). In patients with AF/AFL history, EF was higher (35% vs. 27%, $P < 0.001$), the rate of HFpEF (LVEF $\geq 50\%$) was higher (35.7% vs. 23.8%, $P < 0.001$), and NT-proBNP levels were not significantly different (4210 pg/mL vs. 5037 pg/mL, $P = 0.27$) as compared with patients without AF/AFL. HFpEF and HFrEF (LVEF $< 50\%$) patients with history of AF/AFL exhibited overall similar NT-proBNP levels than their counterparts without AF/AFL (Supplemental Table 1).

Clinical Decongestion by AF/AFL Status and Clinical Outcomes

Comprehensive trends in markers of congestion over the course of HF hospitalization are displayed in Figure 1. Creatinine trend did not differ between the two groups by 72/96 hours (median increase: +0.02 mg/dL in AF/AFL, +0.01 mg/dL in no AF/AFL, $P = 0.95$). There was no significant difference in median baseline weight (AF/AFL: 200 lbs, no AF/AFL 208 lbs, $P = 0.17$), which decreased by 7 pounds in both groups by 72/96 hours (Figure 1A). Patients with AF/AFL history had lower overall net fluid loss by 72/96 hours compared with those without AF/AFL history (4018 mL vs. 4466 mL, $P = 0.02$). Similarly, while NT-proBNP levels were comparable in the two groups at baseline (AF/AFL: 4210 vs. No AF/AFL: 5037 pg/mL, $P = 0.27$), the overall in-hospital decrease in NT-proBNP was blunted in

the AF/AFL history group at 72/96 hours (-732 vs. -1409 pg/mL, $P<0.001$, Figure 1C). Dyspnea VAS scores were similar between both groups at baseline (AF/AFL=54, no AF/AFL=52, $P=0.69$). There was a trend toward more appreciable increase in dyspnea VAS scores by 72/96 hours in those without AF/AFL (median change [25th–75th percentiles]: $+18$ [1–40] vs. $+15$ [0–32], $P=0.06$, Figure 1D). Likewise, global VAS scores were similar at baseline (AF/AFL=50, no AF/AFL=49, $P=0.13$), but increased more substantially by 72/96 hours in the cohort without AF/AFL history (median change [25th–75th percentiles]: $+21$ [5.5–41.5] vs. $+16.5$ [0–34], $P=0.003$, Figure 1E). The median orthodema congestion score was 3 at baseline in both groups ($P=0.20$) and decreased similarly in both groups by 72/96 hours (median change [25th–75th percentiles]: -1 [$-2 - 0$] vs. -1 [$-2 - 0$], $P=0.54$).

After covariate adjustment, baseline history of AF/AFL was associated with less substantial loss of relative weight (-5.7% vs. -6.5% , $P=0.02$) and decrease in relative NT-proBNP levels (-18.7% vs. -31.3% , $P=0.003$) at 72/96 hours (Table 2). The association between history of AF/AFL and blunted average net fluid loss was attenuated after covariate adjustment (adjusted average net fluid loss: 9655.5 mL vs. 10079.6 mL adjusted $P=0.12$). History of AF/AFL was associated with a blunted increase in global VAS at 72/96 hours (mean increase: $+31$ vs. $+35.9$, $P=0.04$). After multivariable adjustment, there was no significant association between AF/AFL history and change in orthodema congestion score or dyspnea VAS at 72/96 hours (Table 2). In subgroup analyses, the association between AF/AFL history and change in relative weight did not differ significantly by LVEF, clinical trial, or median heart rate (Table 3). At 60-day followup, 167 (40%) patients with AF/AFL history and 121 (36%) of patients without AF/AFL history had experienced the key composite clinical endpoint (**Figure 2, Graphical Abstract**). After covariate adjustment, AF/AFL history was not significantly associated with the key composite clinical endpoint (hazard ratio: 1.21, 95% confidence interval: 0.92 – 1.59, $P=0.17$).

Discussion

In a pooled, patient-level analysis of 3 HFN trials of patients hospitalized for AHF, we define the relationship between AF/AFL history, course of decongestion, and short-term postdischarge clinical outcomes. History of AF/AFL was present in $>50\%$ of patients hospitalized for AHF and represented an older cohort with higher prevalence of ischemic heart disease. History of AF/AFL was associated with blunted decongestion as evidenced by diminished changes in weight and natriuretic peptides during hospitalization in both HFrEF and HFpEF. History of AF/AFL was not independently associated with adverse clinical outcomes at 60 days after hospital discharge.

Comorbid AF/AFL and Acute HF

History of AF/AFL was present in most patients with AHF in this pooled trial population and rates were slightly higher than observed in other trials and registries of AHF (7,19). Similar to other AHF populations, AF/AFL patients tended to be older and carry higher rates of ischemic heart disease. Consistent with prior studies (7,19), the AF/AFL cohort was more likely to have HFpEF than HFrEF, which may partially account for lower NT-proBNP levels

at the time of presentation for AHF. Natriuretic peptides are lower in HFpEF, both during periods of stability and acute decompensation as compared with HFrEF (20).

AF/AFL and In-Hospital Decongestion

Although multiple prior studies have explored the association between AF/AFL and clinical outcomes among patients hospitalized for HF (7,9), the implications of AF/AFL on the in-hospital trajectory of decongestion has been poorly characterized. In the present study, the cohort of patients with a history of AF/AFL experienced significantly less in-hospital reduction in 2 markers of congestion (relative weight and NT-proBNP levels). Furthermore, differences in the rate of decongestion between the two groups became more apparent after the initial 24 hours of diuresis. Thus, AF/AFL history appears to be associated with a reduction in sustained decongestion over the course of the latter 48 to 96 hours of hospitalization. Diminished rates of decongestion in those with AF/AFL history may be associated with lower overall well-being and quality of life, as evidenced by decreased global VAS scores among the AF/AFL cohort.

Notably, history of AF/AFL was not associated with changes in the 4-point orthodema congestion score. This score has proved useful in risk stratifying patients with AHF for postdischarge events (18). In our population, orthodema scores, while initially elevated, dropped significantly in the first 24 hours from baseline and remained relatively low in most patients, regardless of AF/AFL history.

The finding of numerically lower NT-proBNP levels among patients with a history of AF/AFL on admission for AHF is not consistent with the chronic HF population and requires further attention. Higher rates of HFpEF in the AF/AFL cohort may only partially explain diminished natriuretic peptide levels, as history of AF/AFL was associated with numerically lower NT-proBNP levels even when compared across similar EF subtypes (i.e. HFrEF and HFpEF). This paradoxical finding has been noted in prior AHF trial populations of HFrEF (21). Among patients with AF/AFL, less myocardial stretch may be required to promote congestive symptoms that ultimately “tip over” such patients into AHF as compared to those without AF/AFL, leading to paradoxically lower natriuretic peptides on admission. Additionally, symptoms of AF/AFL and AHF are often overlapping, posing a clinical challenge to discern the primary etiology of dyspnea among patients with comorbid AF/AFL and HF. Given numerically lower baseline weight and natriuretic peptide levels, it is possible that arrhythmia is the primary etiology of symptoms in the AF/AFL cohort as opposed to progressive volume overload. Further investigation using invasive or non-invasive (e.g., echocardiographic) hemodynamic data on hospital presentation is required to understand the true congestive status of patients with AF/AFL-HF who present with dyspnea.

Mechanisms of Blunted Decongestion in AF/AFL

Mechanisms driving blunted decongestion in AF/AFL are not well understood. AF/AFL resulting in rapid ventricular rate leads to decreased diastolic left ventricular filling time and may ultimately limit diuresis (22). However, the baseline heart rate among patients with and without AF/AFL were similar in our study. In addition, there was no difference in

association of AF/AFL and relative change in weight when patients were categorized based on resting heart rate. Abnormal left ventricular myocardial mechanics in AF/AFL may also predispose patients to decreased overall systemic circulatory flow and impaired diuresis. Finally, left atrial mechanical dysfunction may hinder decongestion in HF. Marked anatomic and physiologic changes occur to the left atrium in the setting of AF/AFL, particularly among patients with HF (23,24).

Progressive left atrial fibrosis, abnormalities in calcium handling, and increased sympathetic tone through upregulation of the renin-angiotensin-aldosterone system lead to mechanical dysfunction of the left atrium and are associated with poor clinical outcomes (25–27). Specifically, AF/AFL perturbs left atrial contraction (booster function) (28) and filling (reservoir function) (29,30), which together may promote the development of AHF and hinder the efficacy of traditional strategies to achieve decongestion.

AF/AFL in Acute HF: A Target for Therapy?

Therapeutic management of AF/AFL in AHF remains challenging. Aside from limiting aggressive rate-controlling and negative inotropic therapies, current guidelines do not provide clear management suggestions in AHF (31). In this study, the presenting rhythm of patients was not captured at the time of trial inclusion and randomization and thus it is likely that a proportion of patients with a history of AF/AFL were in sinus rhythm during hospitalization for AHF. However, previous trial and registry data of AHF have revealed that 84%–86% of HF patients with history of AF/AFL present in AF/AFL at the time of hospitalization (8,32). Rhythm control with anti-arrhythmic drugs yielded neutral outcomes compared with rate-controlling therapies in the chronic HF population (33). Recently, in a modestly-sized trial of patients with chronic HFrEF, catheter ablation of AF was associated with improved clinical outcomes compared with standard medical therapy (34). Indeed, an additional trial of catheter ablation of AF is currently underway (RAFT-AF: NCT01420393), which includes patients with chronic HF, and results are expected shortly. It is not known whether the various strategies of rhythm control (cardioversion, antiarrhythmic drugs, catheter ablation, or a combination) of AF/AFL would yield benefits in promoting decongestion during hospitalization for AHF. Further research is required to address the utility of rhythm control of AF/AFL in the setting of AHF.

There are several limitations of this study. We relied on history of AF/AFL since presenting rhythm was not available at the time of AHF. As such, we were unable to determine whether atrial arrhythmia was the precipitant of AHF. Additionally, category of AF/AFL (paroxysmal, persistent, permanent) was also not recorded at randomization. While invasive hemodynamic data (right heart catheterization) is considered the “gold standard” for congestive status, these data were not captured in our study cohort. Intensity of in-hospital decongestive therapy (i.e. diuretic dose) was not uniformly collected across all 3 trials, and thus multivariable models adjusted for diuretic dose at the time of randomization. Given the retrospective nature of the analysis, the findings may be influenced by unmeasured confounders despite careful statistical accounting. Furthermore, AF/AFL is associated with elevated NT-proBNP levels in patients with chronic HF, and thus natriuretic peptides may not be truly reflective of degree of congestion in this cohort. For this reason, relative change

in weight was chosen as the prespecified primary marker of congestion. Given higher levels of congestive markers in those without history of AF/AFL at baseline, our findings may be partially explained by regression to the mean. The lack of association between AF/AFL and short-term post-discharge clinical endpoints in our pooled cohort should be interpreted with caution, as the 3 trials were each powered to detect changes in symptoms and signs of congestion, rather than clinical endpoints. This pooled analysis benefits from consistent data collection across 3 HFN trials, detailed accounting of congestion markers at multiple time-points during hospitalization for AHF, and robust representation of patients hospitalized for HFpEF.

Conclusions

In this pooled clinical trial cohort of patients hospitalized for AHF, more than half of patients had a history of AF/AFL, which was independently associated with blunted in-hospital decongestion in HFrEF and HFpEF. Further research is required to investigate the utility of rhythm-controlling therapies in promoting decongestion, relieving patient symptoms and improving clinical outcomes in the setting of concomitant AF/AFL and AHF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation List:

AF/AFL	atrial fibrillation/atrial flutter
AHF	acute heart failure
CARRESS-HF	Cardiorenal Rescue Study in Acute Decompensated Heart Failure
DOSE	Diuretic Optimization Strategies Evaluation
HF	heart failure
HF_rEF	heart failure with reduced ejection fraction
HF_pEF	heart failure with preserved ejection fraction
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-brain natriuretic peptide
ROSE	Renal Optimization Strategies Evaluation
VAS	visual analogue scale

References

1. Chugh SS, Havmoeller R, Narayanan K et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837–47. [PubMed: 24345399]
2. Braunwald E The war against heart failure: the Lancet lecture. *Lancet* 2015;385:812–24. [PubMed: 25467564]
3. Wang TJ, Larson MG, Levy D et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920–5. [PubMed: 12771006]
4. Santhanakrishnan R, Wang N, Larson MG et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. *Circulation* 2016;133:484–92. [PubMed: 26746177]
5. Zareba W, Steinberg JS, McNitt S et al. Implantable cardioverter-defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation. *Heart Rhythm* 2006;3:631–7. [PubMed: 16731460]
6. Cikes M, Claggett B, Shah AM et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction. *JACC: Heart Failure* 2018.
7. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. *Circ Heart Fail* 2012;5:191–201. [PubMed: 22361078]
8. Mentz RJ, Chung MJ, Gheorghiade M et al. Atrial fibrillation or flutter on initial electrocardiogram is associated with worse outcomes in patients admitted for worsening heart failure with reduced ejection fraction: findings from the EVEREST Trial. *Am Heart J* 2012;164:884–92 e2. [PubMed: 23194489]
9. Abualnaja S, Podder M, Hernandez AF et al. Acute Heart Failure and Atrial Fibrillation: Insights From the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) Trial. *J Am Heart Assoc* 2015;4:e002092. [PubMed: 26304935]

10. Arrigo M, Gayat E, Parenica J et al. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail* 2017;19:201–208. [PubMed: 27790819]
11. Platz E, Jhund PS, Claggett BL et al. Prevalence and prognostic importance of precipitating factors leading to heart failure hospitalization: recurrent hospitalizations and mortality. *Eur J Heart Fail* 2018;20:295–303. [PubMed: 28872259]
12. Fonarow GC, Abraham WT, Albert NM et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med* 2008;168:847–54. [PubMed: 18443260]
13. Mentz RJ, Kjeldsen K, Rossi GP et al. Decongestion in acute heart failure. *Eur J Heart Fail* 2014;16:471–82. [PubMed: 24599738]
14. Felker GM, Lee KL, Bull DA et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;364:797–805. [PubMed: 21366472]
15. Chen HH, Anstrom KJ, Givertz MM et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA* 2013;310:2533–43. [PubMed: 24247300]
16. Bart BA, Goldsmith SR, Lee KL et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;367:2296–304. [PubMed: 23131078]
17. Ambrosy AP, Bhatt AS, Gallup D et al. Trajectory of Congestion Metrics by Ejection Fraction in Patients With Acute Heart Failure (from the Heart Failure Network). *Am J Cardiol* 2017;120:98–105. [PubMed: 28479167]
18. Lala A, McNulty SE, Mentz RJ et al. Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). *Circ Heart Fail* 2015;8:741–8. [PubMed: 26041600]
19. O'Connor CM, Starling RC, Hernandez AF et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;365:32–43. [PubMed: 21732835]
20. Shah KS, Xu H, Matsouka RA et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol* 2017;70:2476–2486. [PubMed: 29141781]
21. Greene SJ, Fonarow GC, Solomon SD et al. Influence of atrial fibrillation on postdischarge natriuretic peptide trajectory and clinical outcomes among patients hospitalized for heart failure: insights from the ASTRONAUT trial. *Eur J Heart Fail* 2017;19:552–562. 22. [PubMed: 27748006]
22. DiMarco JP. Atrial fibrillation and acute decompensated heart failure. *Circ Heart Fail* 2009;2:72–3. [PubMed: 19808318]
23. Kuppahally SS, Akoum N, Burgon NS et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging* 2010;3:231–9. [PubMed: 20133512]
24. Rossi A, Ciccoira M, Zanolli L et al. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2002;40:1425. [PubMed: 12392832]
25. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J* 2015;36:3250–7. [PubMed: 26419625]
26. Patel RB, Vaduganathan M, Shah SJ, Butler J. Atrial fibrillation in heart failure with preserved ejection fraction: Insights into mechanisms and therapeutics. *Pharmacol Ther* 2017;176:32–39. [PubMed: 27773787]
27. Hsu PC, Lee WH, Chu CY et al. Prognostic role of left atrial strain and its combination index with transmitral E-wave velocity in patients with atrial fibrillation. *Sci Rep* 2016;6:17318. [PubMed: 26833057]
28. Saraiva RM, Demirkol S, Buakhamsri A et al. Left atrial strain measured by twodimensional speckle tracking represents a new tool to evaluate left atrial function. *J Am Soc Echocardiogr* 2010;23:172–80. [PubMed: 20152699]
29. Blume GG, McLeod CJ, Barnes ME et al. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr* 2011;12:421–30. [PubMed: 21565866]

30. Santos AB, Kraigher-Krainer E, Gupta DK et al. Impaired left atrial function in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014;16:1096–103. [PubMed: 25138249]
31. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:e1–76. [PubMed: 24685669]
32. Piccini JP, Hernandez AF, Zhao X et al. Quality of care for atrial fibrillation among patients hospitalized for heart failure. *J Am Coll Cardiol* 2009;54:1280–9. [PubMed: 19778670]
33. Roy D, Talajic M, Nattel S et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;358:2667–77. [PubMed: 18565859]
34. Marrouche NF, Brachmann J, Andresen D et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *N Engl J Med* 2018;378:417–427. [PubMed: 29385358]

Clinical Perspectives**Competency in Medical Knowledge.**

History of AF/AFL is a common comorbidity among patients hospitalized for AHF, representing an elderly, frail cohort with high comorbidity burden.

Translational Outlook 1:

History of AF/AFL is associated with a blunted course of decongestion among patients hospitalized for AHF. Further research is required to better understand the hemodynamic effects of AF/AFL in the setting of AHF and the mechanisms that may influence decongestion.

Translational Outlook 2:

Despite its high prevalence in AHF, management strategies of AF/AFL in this setting are widely variable. Further research is needed to evaluate the utility of rhythm-controlling therapies in the setting of AHF with comorbid AF/AFL.

Figure 1.
(A-E). Change in Parameters of Decongestion by AF/AFL History During Hospitalization for Acute Heart Failure. Each panel displays percentages or median values. AF/AFL= atrial fibrillation/atrial flutter; IQR= interquartile range; NT-proBNP = N-terminal pro-brain natriuretic peptide; VAS= visual analogue scale.

History of Atrial Fibrillation/Atrial Flutter and Acute Heart Failure

Figure 2.

(Graphical Abstract). History of Atrial Fibrillation/Atrial Flutter and Acute Heart Failure.

Comparisons in trajectory of markers of decongestion by 72/96h by AF/AFL status were adjusted for clinically relevant parameters as detailed in Table 2.

AHF= acute heart failure; AF/AFL= atrial fibrillation/atrial flutter; NT-proBNP = N-terminal pro-brain natriuretic peptide

Table 1.

Baseline Characteristics by History of AF/AFL.

	No AF/AFL History (N=332)	AF/AFL History (N=418)	Total Population (N=750)	P-value *
Demographics				
Age, y, median, (IQR)	63 (54 – 71)	74 (66 – 82)	69 (59 – 78)	<0.001
Male, n (%)	233 (70.2%)	315 (75.4%)	548 (73.1%)	0.11
White, n (%)	196 (59.0%)	358 (85.6%)	554 (73.9%)	<0.001
Clinical History				
NYHA classification at baseline, n (%)				0.45
I	1 (0.3%)	0 (0%)	1 (0.1%)	
II	15 (4.8%)	12 (3.1%)	27 (3.9%)	
III	200 (64.3%)	254 (65.6%)	454 (65.0%)	
IV	95 (30.5%)	121 (31.3%)	216 (30.9%)	
Ischemic Etiology of HF, n (%)	171 (51.5%)	253 (60.5%)	424 (56.5%)	0.01
Diabetes, n (%)	200 (60.2%)	213 (51.0%)	413 (55.1%)	0.01
Hypertension, n (%)	283 (85.2%)	329 (78.7%)	612 (81.6%)	0.02
COPD, n (%)	78 (23.5%)	123 (29.4%)	201 (26.8%)	0.07
ICD at index hospitalization, n (%)	126 (38.0%)	173 (41.4%)	299 (39.9%)	0.34
Hospitalization for heart failure in past year, n (%)	243 (73.9%)	284 (68.8%)	527 (71.0%)	0.13
Baseline Physical Exam and Laboratory Findings				
Heart rate (beats/min), median, (IQR)	76 (68 – 86)	75 (67 – 84)	75 (67 – 85)	0.38
Systolic Blood Pressure (mmHg), median, (IQR)	118 (106 – 134)	113 (102 – 126)	115 (104 – 130)	<0.001
Diastolic Blood Pressure (mmHg), median, (IQR)	68 (60 – 78)	64 (58 – 72)	66 (59 – 75)	0.001
Ejection Fraction (%), median, (IQR)	27 (20 – 48)	35 (23 – 55)	32 (20 – 53)	<0.001
LVEF 40% (Reduced), n (%)	224 (69.3%)	239 (57.3%)	463 (62.6%)	<0.001
LVEF 41–49% (Borderline), n (%)	22 (6.8%)	29 (7.0%)	51 (6.9%)	0.94
LVEF 50% (Preserved), n (%)	77 (23.8%)	149 (35.7%)	226 (30.5%)	<0.001
Weight (lbs), median, (IQR)	208 (172 – 254)	200 (174 – 243)	204 (173 – 248)	0.17
Body Mass Index (kg/m ²), median, (IQR)	32.0 (26.8 – 39.5)	31.1 (26.6 – 36.7)	31.6 (26.7 – 37.7)	0.09
Sodium (mg/L), median, (IQR)	139 (136 – 141)	139 (136 – 141)	139 (136 – 141)	0.89
Blood urea nitrogen (mg/dL), median, (IQR)	35 (23 – 52)	37 (27 – 53)	36 (25 – 52)	0.08
Creatinine (mg/dL), median, (IQR)	1.6 (1.2 – 2.1)	1.6 (1.3 – 1.9)	1.6 (1.3 – 2.0)	0.24
NT-pro BNP (pg/mL), median, (IQR)	5037 (2239 – 10749)	4210 (2331 – 9088)	4506 (2323 – 9856)	0.27
Medications at enrollment				
ACE inhibitor or ARB, n (%)	197 (59.3%)	217 (51.9%)	414 (55.2%)	0.04
Beta Blockers, n (%)	272 (81.9%)	345 (82.5%)	617 (82.3%)	0.83

	No AF/AFL History (N=332)	AF/AFL History (N=418)	Total Population (N=750)	P-value *
Aldosterone antagonist, n (%)	88 (26.5%)	126 (30.1%)	214 (28.5%)	0.27
Furosemide-equivalent dose at randomization (mg/day), median, (IQR)	80 (40 – 160)	80 (40 – 160)	80 (40 – 160)	0.67

* Comparison of No AF/AFL history vs. AF/AFL history groups.

ACE= angiotensin converting enzyme; AF= atrial fibrillation; AFL= atrial flutter; ARB= angiotensin receptor blocker; COPD= chronic obstructive pulmonary disease; IQR= interquartile range; HF= heart failure; ICD= implantable cardioverter defibrillator; LVEF= left ventricular ejection fraction; NT-proBNP= N-terminal pro-brain natriuretic peptide; NYHA= New York Heart Association

Table 2.

Association of AF/AFL History and Parameters of Decongestion at 72/96 Hours.

	Unadjusted			Adjusted [*]		
	<i>AF/AFL History</i> Mean Difference (95% CI)	<i>No AF/AFL History</i> Mean Difference (95% CI)	pvalue	<i>AF/AFL History</i> Mean Difference (95% CI)	<i>No AF/AFL History</i> Mean Difference (95% CI)	p-value
Relative change in weight (%) [†]	−3.7% (−4%, −3%)	−4% (−4%, −4%)	0.47	−5.7% (−9.0%, −2.0%)	−6.5% (−10%, −3.0%)	0.02
Net fluid loss (mL)	4381.2 (4066.7, 4695.6)	5078.1 (4714.4, 5441.9)	0.005	9655.5 (6797.3, 12513.6)	10079.6 (7264.6, 12894.5)	0.12
Relative change in NT-proBNP (%) [†]	−14.3% (−19%, −9%)	−29.6% (−35%, −24%)	<.0001	−18.7% (−63%, +26%)	−31.3 (−75%, +12%)	0.003
Change in Dyspnea VAS	16.8 (14.0, 19.6)	21.4 (18.2, 24.5)	0.03	28.5 (3.3, 53.7)	30.4 (5.7, 55.3)	0.41
Change in Global VAS	17.8 (15.2, 20.5)	24.2 (21.1, 27.3)	0.002	31.0 (6.0, 56.0)	35.9 (11.3, 60.5)	0.04

^{*} Adjusted for age, sex, race, LVEF, baseline HR, baseline SBP, baseline serum creatinine, trial, and baseline loop diuretic dose equivalent.

[†] For parameters of weight and NT-proBNP, relative change was defined as: (72/96h value - baseline value)/baseline value.

AF= atrial fibrillation; AFL= atrial flutter; CI = confidence interval; HR= heart rate LVEF= left ventricular ejection fraction; NT-proBNP= N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure; VAS= visual analogue scale.

Table 3.

Subgroup Analysis: Association of AF/AFL History and Relative Change in Weight at 72/96 Hours.

	<i>AF/AFL History</i> Mean Relative Weight Change	<i>No AF/AFL History</i> Mean Relative Weight Change	P value interaction *
LVEF			0.39
LVEF 50% (Preserved)	−5.0%	−4.3%	
LVEF 41–49% (Borderline)	−3.0%	−5.0%	
LVEF 40% (Reduced)	−2.5%	−1.1%	
Trial			0.92
DOSE	−3.8%	−2.8%	
ROSE	−3.5%	−2.5%	
CARRESS-HF	−3.7%	−2.7%	
Heart Rate (median)			0.50
>76 bpm	−3.8%	−2.8%	
<76 bpm	−3.5%	−2.6%	

* Adjusted for age, sex, race, interaction parameter; interaction term, diabetes and creatinine at baseline

AF/AFL= atrial fibrillation/atrial flutter; bpm= beats per minute; LVEF= left ventricular ejection fraction; DOSE= Diuretic Optimization Strategies Evaluation; ROSE= Renal Optimization Strategies Evaluation; CARRESS-HF= Cardiorenal Rescue Study in Acute Decompensated Heart Failure