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Atrial Fibrillation Burden and Atrial Shunt Therapy in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is a common comorbidity in patients with heart failure with preserved ejection fraction (HFpEF) and in heart failure with mildly reduced ejection fraction (HFmrEF).

OBJECTIVES This study sought to describe AF burden and its clinical impact among individuals with HFpEF and HFmrEF who participated in a randomized clinical trial of atrial shunt therapy (REDUCE LAP-HF II [A Study to Evaluate the Corvia Medical, Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure]) and to evaluate the effect of atrial shunt therapy on AF burden.

METHODS Study investigators characterized AF burden among patients in the REDUCE LAP-HF II trial by using ambulatory cardiac patch monitoring at baseline (median patch wear time, 6 days) and over a 12-month follow-up (median patch wear time, 125 days). The investigators determined the association of baseline AF burden with long-term clinical events and examined the effect of atrial shunt therapy on AF burden over time.

RESULTS Among 367 patients with cardiac monitoring data at baseline and follow-up, 194 (53%) had a history of AF or atrial flutter (AFL), and median baseline AF burden was 0.012% (IQR: 0%-1.3%). After multivariable adjustment, baseline AF burden ≥0.012% was significantly associated with heart failure (HF) events (HR: 2.00; 95% CI: 1.17-3.44; $P = 0.01$) both with and without a history of AF or AFL (P for interaction = 0.68). Adjustment for left atrial reservoir strain attenuated the baseline AF burden-HF event association (HR: 1.71; 95% CI: 0.93-3.14; $P = 0.08$). Of the 367 patients, 141 (38%) had patch-detected AF during follow-up without a history of AF or AFL. Atrial shunt therapy did not change AF incidence or burden during follow-up.

CONCLUSIONS In HFpEF and HFmrEF, nearly 40% of patients have subclinical AF by 1 year. Baseline AF burden, even at low levels, is associated with HF events. Atrial shunt therapy does not affect AF incidence or burden. (A Study to Evaluate the Corvia Medical, Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure [REDUCE LAP-HF II]; NCT03088033) (J Am Coll Cardiol HF 2023;11:1351-1362) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BMI = body mass index

CV = cardiovascular

ECG = electrocardiogram

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LVEF = left ventricular ejection fraction

PA = pulmonary artery

PCWP = pulmonary capillary wedge pressure

PFO = patent foramen ovale

PVR = pulmonary vascular resistance

Atrial fibrillation (AF) is common in the setting of heart failure with preserved ejection fraction (HFpEF) or heart failure with mildly reduced ejection fraction (HFmrEF), with estimates that up to 60% of individuals with HFpEF may have comorbid AF.[1] Individuals with both AF and HFpEF have worse congestion,[2,3] reduced exercise capacity,[4] and increased risks of long-term adverse clinical outcomes compared with those without AF.[5,6] As such, AF-predominant HFpEF may be considered a particularly morbid subphenotype within the broader HFpEF syndrome, and it is characterized by marked mechanical and electrical dysfunction of the left atrium and a congested hemodynamic profile.[7]

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Despite the recognition of this clinical syndrome, several questions about AF in HFpEF remain unanswered. Traditional electrocardiogram (ECG)-based categories of AF (ie, paroxysmal, persistent, permanent) fail to capture a precise and objective burden of AF. Specifically, current societal guidelines broadly define paroxysmal AF as lasting ≤7 days and persistent AF as lasting >7 days,[8] and clinically, patients with AF are often categorized without consideration of exact time in AF. The distribution of AF burden in HFpEF, as measured using extended ambulatory rhythm monitoring that provides the percentage of time in AF, is not clear. The prevalence of subclinical AF in HFpEF, as defined by monitor-detected AF among individuals without known previous AF, is also not well understood. Finally, the potential association of subclinical AF burden with long-term clinical outcomes in HFpEF is not known.

In the recent REDUCE LAP-HF II (A Study to Evaluate the Corvia Medical, Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure), the atrial shunt (Corvia IASD System II, Corvia Medical, Inc) had no effect on a composite clinical outcome of cardiovascular (CV) mortality, nonfatal ischemic stroke, heart failure (HF) events, and health status (Kansas City Cardiomyopathy Questionnaire overall summary score [KCCQ-OSS]) in HFpEF or HFmrEF in the overall study.[9] However, atrial shunt therapy demonstrated potential efficacy in the large subset (50%; "responder population") of patients with HFpEF who had a peak exercise pulmonary vascular resistance (PVR) <1.74 WU and no pacemaker or other cardiac rhythm device at baseline.[10] The effect of the atrial shunt on AF burden over time is not known.

We evaluated the distribution of AF burden in HFpEF/HFmrEF, determined the association of baseline AF burden with long-term clinical events, and examined the effect of atrial shunt therapy on AF incidence and burden over time in the REDUCE LAP-HF II trial. We hypothesized that a higher AF burden would be associated with an increased risk of HF events.

METHODS

STUDY PATIENTS. The study protocol, description, and primary results of the REDUCE LAP-HF II trial have been previously reported.[11] Enrolled participants were at least 40 years of age, with symptomatic HF with a left ventricular ejection fraction (LVEF) of at least 40%, diastolic dysfunction, and evidence of pulmonary capillary wedge pressure (PCWP) during exercise of at least 25 mm Hg while exceeding right atrial pressure by at least 5 mm Hg. Exclusion criteria

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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included stage D HF, a cardiac index <2.0 L/min/m^2, a history of LVEF <30% within the past 3 years, a history of stroke or transient ischemic attack within the past 6 months, significant valve disease, greater than mild right ventricular dysfunction, resting right atrial pressure >14 mm Hg, PVR >3.5 WU, severe chronic obstructive pulmonary disease, a body mass index (BMI) >45 kg/m^2, or an estimated glomerular filtration rate <25 mL/min/1.73 m^2. A complete list of inclusion and exclusion criteria can be found in the study design paper.[11] All participants provided written informed consent, and the study was approved by each enrolling site's local ethics committee or Institutional Review Board. The trial is registered with ClinicalTrials.gov (NCT03088033).

STUDY PROTOCOL. REDUCE LAP-HF II was a randomized, international, multicenter, double-blind, sham-controlled trial. Eligible participants were randomly assigned at 89 institutions to receive either the atrial shunt device or a sham procedure. All participants underwent echocardiography and invasive exercise hemodynamic testing to confirm an LVEF ≥40% and a peak exercise PCWP of ≥25 mm Hg. Independent core laboratories, blinded to treatment assignment, were used for both echocardiographic and invasive hemodynamic measurements. Participants also underwent KCCQ-OSS determination at baseline. Participants randomized to the treatment arm underwent placement of the IASD System II atrial shunt device (Corvia Medical, Inc). Patients assigned to the sham control group underwent femoral venous puncture and imaging of the interatrial septum and left atrium. Follow-up visits occurred at 6, 12, and 24 months by clinicians masked to treatment allocation.

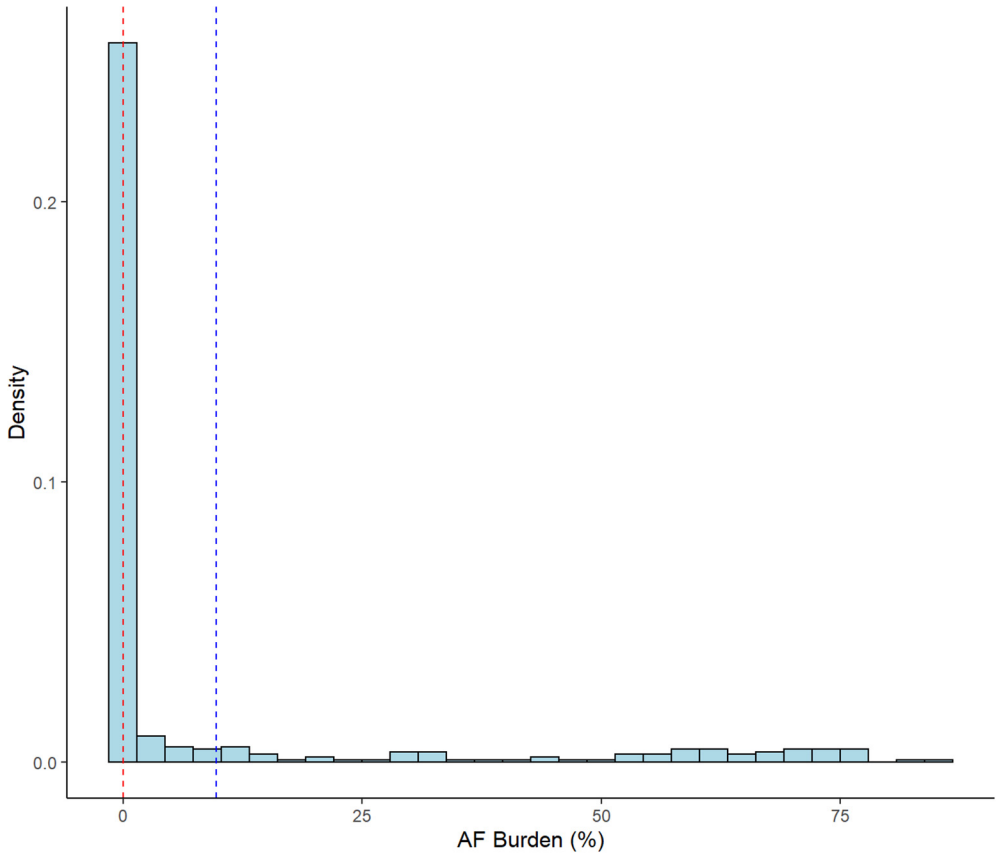
EXTENDED AMBULATORY RHYTHM MONITORING. A subset of REDUCE LAP-HF II participants were invited to wear an extended ambulatory cardiac monitor both at baseline and during a 12-month follow-up period. Participants wore an ambulatory cardiac monitoring patch (VitalPatch RTM, VitalConnect) that provided continuous single-lead ECG data. Before randomization, participants were requested to wear the patch for 4 to 6 days. For the first 3 months after randomization, participants were asked to wear the patch as much as possible (5-6 days on, 1-2 days off). For the subsequent 9 months, participants were asked to wear the patch for 1 week per month. Rhythm data were transmitted electronically, and participants did not have to ship the patch back for analysis. AF was determined using a U.S. Food and Drug Administration–approved, automated intelligence AF detection algorithm (PhysIQ). The primary AF variable of interest was time-normalized AF burden, defined as percentage of time in AF, and it was calculated by the minutes of patch-detected AF divided by the total minutes of patch wear time for each participant. Secondary AF variables of interest were as follows: 1) AF duration >6 minutes; 2) any AF; and 3) new onset AF. AF duration >6 minutes was chosen because of its association with stroke risk, and it was defined as total AF duration >6 minutes during a single 24-hour period.[12] Any AF was defined as AF burden >0%. New onset AF was determined as AF noted on patch monitoring among patients without a baseline clinical history of AF. Primary and secondary AF variables were determined both at baseline and during follow-up.

ECHOCARDIOGRAPHY. Comprehensive resting, 2-dimensional, Doppler, and speckle-tracking echocardiography was performed at baseline, and all images were interpreted by a core laboratory (University of Pennsylvania, Philadelphia, Pennsylvania, USA [2D/Doppler] and Northwestern University, Chicago, Illinois, USA [strain]). Full details on the echocardiography protocol have been previously described.[11] Left atrial (LA) reservoir strain was calculated using apical 4- and 2-chamber views. R-wave gating was used to measure LA strain, which has been validated in AF.[13]

STUDY ENDPOINTS. The primary endpoint components of interest for this analysis were CV death, nonfatal ischemic stroke, time to first HF event (defined as HF hospitalization, urgent visits to a health care facility for intravenous diuresis, or outpatient intensification of oral diuretic agents), and change in KCCQ-OSS between baseline and 12 months. All events were adjudicated by a blinded clinical events committee. Additional endpoints for this analysis were the primary and secondary AF variables during the follow-up period, as defined earlier. A prespecified major secondary endpoint of the trial was newly acquired persistent or permanent AF through 12 months, which was adjudicated using clinical records that did not incorporate data from the ambulatory cardiac monitoring patch.

STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD or median (IQR), and categorical variables were reported as number and percentage of patients. Given the non-normal distribution of AF burden, we compared baseline characteristics by AF burden category (equal to or greater than the median vs less than the median) by

FIGURE 1 Distribution of Prerandomization Subclinical AF Burden



The **blue dashed line** indicates the mean, and the **red dashed line** indicates the median. AF = atrial fibrillation.

using Student's *t*-tests or Wilcoxon rank sum tests (depending upon distribution) for continuous variables and Pearson chi-square tests for categorical variables. Separate multivariable Cox proportional hazards regression models were used to evaluate associations of primary and secondary AF variables at baseline with each of the aforementioned endpoints. For these models, baseline AF burden (primary AF variable) was evaluated as a categorical variable (equal to or greater than the median vs less than the median) because of its non-normal distribution. We separately evaluated associations of primary and secondary AF variables with HF events among patients in the responder group of the REDUCE LAP-HF II trial (ie, those participants without latent pulmonary vascular disease or a cardiac rhythm device [n = 187]), as previously described.[10] Models were adjusted for age, sex, diabetes mellitus, BMI, hypertension, treatment arm, chronic kidney disease, NYHA functional class, and history of AF or AF on a baseline ECG.

In sensitivity analysis, we further adjusted for LA reservoir strain. To evaluate whether increasing AF burden (beyond a median cutpoint) was associated with HF events, we combined patients from the first and second quartiles of AF burden (because the second quartile only included 11 patients), and we then evaluated associations of third and fourth quartiles of AF burden with HF events compared with the combined first and second quartiles. These sensitivity models were adjusted for the same covariates as previously described. The proportionality of hazards assumption was confirmed for all models through numerical and graphical inspection of Schoenfeld residuals. To evaluate the association between AF burden with change in KCCQ-OSS, a multivariable linear regression model was used that additionally adjusted for baseline KCCQ-OSS scores. We

determined whether AF burden differentially predicted HF events by known history of AF by using an interaction term. We used separate logistic regression models to evaluate the effect of the atrial shunt on AF burden (above vs below median), AF duration >6 minutes, any AF, and new onset AF during follow-up among the entire REDUCE LAP-HF II cohort with cardiac ambulatory monitoring data and among those patients in the responder group alone. In sensitivity analysis, we evaluated the effect of the atrial shunt on continuous AF burden using tobit regression.

All analyses were conducted using R software version 4.0.2 (R Foundation). All statistical analyses were conducted independently at Northwestern University Feinberg School of Medicine (Chicago, Illinois, USA). A value of $P < 0.05$ was considered statistically significant.

RESULTS

AF BURDEN AT BASELINE AND PATIENT CHARACTERISTICS. Among 626 randomized patients, 394 individuals participated in the cardiac monitoring substudy of REDUCE LAP-HF II, and 367 (93%) patients had interpretable cardiac monitoring data at baseline and follow-up for analysis (Supplemental Figure 1). Compared with those patients excluded from this analysis, participants who were included were younger and had higher BMI; however, the prevalence of other comorbidities was similar (Supplemental Table 1). Over a median of 6 days (IQR: 5-6 days) of patch wear time during the prerandomization baseline period, the median AF burden (minutes of AF / minutes of patch wear time × 100) was 0.012% (IQR: 0%-1.3%), and the distribution of AF burden was non-normal (**Figure 1**). Of the 53% (194 of 367) of patients with any patch-detected AF during the baseline period, 51 (26%) did not have a clinical history of AF or AF on the baseline ECG.

Patients with a baseline AF burden greater than or equal to the median were older, more likely male, had a higher prevalence of chronic kidney disease, were more likely to be in NYHA functional class II, had higher loop diuretic agent use, were less likely to have chronic obstructive pulmonary disease, and were less likely to be in the responder group (**Table 1**). N-terminal pro-B-type natriuretic peptide levels were higher, and the estimated glomerular filtration rate was lower among those participants with a baseline AF burden ≥ the median.

On echocardiography, patients with an AF burden ≥ the median had lower LVEF and tricuspid annular systolic plane excursion levels, but they had a higher LA volume index, E/e′ ratio, right ventricular volume index, and right atrial volume index compared with patients with a baseline AF burden less than the median (**Table 2**). On resting right-sided heart catheterization, patients with an AF burden equal to or greater than the median had higher PCWP and mean pulmonary artery (PA) pressure. During exercise, mean PA pressure and PVR were higher whereas cardiac output was lower among those patients with an AF burden equal to or greater than the median.

AF BURDEN AND CLINICAL OUTCOMES. Over a median follow-up monitoring period of 1.7 years (IQR: 1.0-2.0 years), a total of 13 CV deaths, 4 nonfatal ischemic strokes, and 77 first HF hospitalizations occurred. After multivariable adjustment, the baseline AF burden was not associated with either CV death or nonfatal ischemic stroke (**Table 3**). However,

TABLE 1 Baseline Clinical Characteristics by Prerandomization AF Burden Category

	AF Burden		
	(<0.012%) (n = 177)	(≥0.012%) (n = 190)	*P* Value
Age, y	68.1 ± 9.5	72.6 ± 7.7	<0.001
Female	124 (70)	94 (50)	<0.001
Diabetes	78 (44)	66 (35)	0.09
History of AF/AFL or AF/AFL on baseline ECG	53 (30)	141 (75)	<0.001
Hypertension	152 (86)	171 (90)	0.29
COPD	46 (26)	30 (16)	0.02
CKD	90 (52)	119 (63)	0.045
Ischemic heart disease	30 (17)	33 (17)	0.99
Responder group	101 (64)	86 (50)	0.02
NYHA functional class			0.01
II	29 (15)	53 (27)	
III	148 (85)	137 (73)	
BMI, kg/m^2	33.9 ± 6.5	32.7 ± 6.3	0.07
eGFR, mL/min/1.73 m^2	57.5 ± 17.4	52.5 ± 17.0	0.007
NT-proBNP, pg/mL	237 (125-443)	538 (333-1088)	<0.001
Medications			
Loop diuretic	141 (80)	171 (90)	0.009
Furosemide dose equivalent, mg	40 (40-80)	40 (20-60)	0.08
Thiazide diuretic alone	8 (5)	7 (4)	0.89
Loop and thiazide diuretic	10 (6)	12 (6)	0.96
MRA	96 (54)	100 (53)	0.84
SGLT2 inhibitor	4 (2)	3 (2)	0.92
Beta-blocker	128 (72)	131 (69)	0.55
Anticoagulant	45 (25)	129 (68)	<0.001
Aspirin	92 (52)	61 (32)	<0.001
Antiplatelet (other than aspirin)	27 (15)	18 (9.5)	0.13

Values are mean ± SD, n (%), or median (IQR).

AF = atrial fibrillation; AFL = atrial flutter; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive lung disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter 2.

TABLE 2 Baseline Echocardiographic and Hemodynamic Characteristics by Prerandomization AF Burden Category

	AF Burden		
	(<0.012%) (n = 177)	(≥0.012%) (n = 190)	*P* Value
Echocardiogram			
LVEF, %	54 ± 5	51 ± 6	<0.001
Minimum LA volume index, mL/m^2	17.5 ± 7.9	25.6 ± 11.3	<0.001
E/e′ septal	14.6 ± 6.5	16.4 ± 8.1	0.04
LA reservoir strain, %	24.3 ± 9.4	18.0 ± 7.5	<0.001
LA emptying fraction, %	40.3 ± 10.2	30.4 ± 11.6	<0.001
Mitral regurgitation, trace/mild/moderate, %	50/23/11	45/24/15	0.67
TAPSE, cm	2.1 ± 0.4	1.9 ± 0.4	0.001
RV end diastolic volume index, mL	21.6 ± 9.4	24.1 ± 9.7	0.04
RA diastolic volume index, mL	22.5 ± 8.2	30.6 ± 13.4	<0.001
Resting hemodynamics			
Heart rate, beats/min	71 ± 12	72 ± 13	0.56
Systolic blood pressure, mm Hg	143 ± 23	144 ± 25	0.64
RA pressure, mm Hg	9 ± 4	10 ± 4	0.43
PA mean pressure, mm Hg	26 ± 7	28 ± 8	0.005
PCWP, mm Hg	18 ± 6	19 ± 7	0.02
Cardiac output, L/min	5.7 ± 1.6	5.6 ± 1.8	0.69
Pulmonary vascular resistance, WU	1.59 ± 0.81	1.70 ± 0.92	0.21
Peak exercise hemodynamics			
Heart rate, beats/min	102 ± 21	103 ± 24	0.55
Systolic blood pressure, mm Hg	161 ± 31	160 ± 32	0.66
RA pressure, mm Hg	18 ± 6	19 ± 6	0.10
PA mean pressure, mm Hg	46 ± 9	48 ± 10	0.04
PCWP, mm Hg	35 ± 8	36 ± 9	0.14
Cardiac output, L/min	9.0 ± 3.0	8.4 ± 2.8	0.04
Pulmonary vascular resistance, WU	1.35 ± 0.81	1.56 ± 0.97	0.03

Values are mean ± SD.

E/e′ = ratio of the peak early mitral inflow velocity to the early diastolic mitral annular velocity; LA = left atrial; LVEF = left ventricular ejection fraction; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; other abbreviation as in Table 1.

the baseline AF burden was significantly associated with a greater risk of first HF events (**Table 3**, **Central Illustration**) after multivariable adjustment.

In sensitivity analysis, adjustment for LA reservoir strain slightly attenuated the association of baseline AF burden equal to or greater than the median with HF events (HR: 1.71; 95% CI: 0.93-3.14; $P = 0.08$). On evaluation of secondary baseline AF variables (AF duration >6 minutes and any AF), associations with clinical outcomes were consistent (Supplemental Table 2).

The association between AF burden greater than or equal to the median and first HF events was consistent among those with and without a clinical history of AF (P for interaction = 0.65) (**Figure 2**). On evaluation of baseline AF burden in quartiles, each of the third and fourth quartiles of baseline AF burden were significantly associated with an increased risk of first HF events compared with the combined first and second quartile, and effect sizes were similar for both the third quartile (AF burden: 0.012%-1.26%) and the fourth quartile (AF burden: >1.26%) (Supplemental Table 3). There was no association of AF burden category with change in KCCQ-OSS over time (**Table 3**).

Of 367 patients in the monitoring substudy, 187 (51%) patients had a peak PVR <1.74 WU and did not have a cardiac rhythm device at baseline (ie, responder group). The associations between baseline AF burden category and first HF events were consistent among the responder patients (Supplemental Table 4). Specifically, baseline AF duration >6 minutes was significantly associated with HF events in the responder group.

TEMPORAL EFFECT OF ATRIAL SHUNT ON AF BURDEN OVER TIME. Over a median of 125 days (IQR: 111-135 days) of patch wear time over the course of the 12-month follow-up period, the median AF burden increased from 0.012% randomization to 0.2% (IQR: 0.01%-4.6%), and the distribution of AF burden remained non-normal (Supplemental Figure 2). Over the course of follow-up, 324 of 367 patients (88%) had patch-detected AF compared with 53% pre-randomization. Of the 367 patients, 141 patients (38%) had patch-detected AF without a clinical history of AF or AF on a baseline ECG. Of these 141 individuals with subclinical AF, 102 (72%) had an AF duration of >6 minutes during the follow-up period (Supplemental Table 5). Among the 173 participants without a clinical history of AF at baseline, only 2 (1%) were adjudicated to have newly acquired persistent or permanent AF at 12 months. However, on evaluation of these same 173 patients using patch monitoring, 102 (59%) patients had an AF duration of >6 minutes at some point during monitoring. Among the 194 patients with a clinical history of AF, only 11 (5%) did not have any AF during follow-up patch monitoring.

There was no effect of the atrial shunt on AF burden category, AF duration, or new onset AF during the follow-up period (**Figure 3**). In tobit regression, there was no effect of the atrial shunt on AF burden when measured continuously (β-coefficient −1.1; SE = 2.5; $P = 0.66$). On evaluation of the responder group, atrial shunt therapy reduced AF duration >6 minutes (OR: 0.52; 95% CI: 0.27-0.99; $P = 0.05$), but not other AF endpoints (Supplemental Table 6).

DISCUSSION

In this 1-year ambulatory cardiac monitoring analysis of REDUCE LAP-HF II, we identified several key findings: 1) there is a wide range of AF burden in

HFpEF/HFmrEF, and AF was detected in 88% of patients over follow-up; 2) nearly 40% of individuals with HFpEF/HFmrEF have subclinical AF (ie, patch detected AF without a clinical history of AF), and therefore, over 90% of patients with HFpEF/HFmrEF have either subclinical AF or a history of AF; 3) a higher baseline AF burden is characterized by adverse cardiac mechanics and hemodynamics at rest and increased filling pressures and reduced cardiac output reserve in response to exercise; 4) a baseline AF burden, even at very low levels, is associated with an elevated risk of HF events in HFpEF/HFmrEF regardless of clinical history of AF; and 5) atrial shunt therapy does not increase the risk of subclinical or clinical AF, and in the atrial shunt device responder group, it may beneficially reduce AF duration >6 minutes over a 24-hour period, which is a risk factor for stroke.

AF and HFpEF commonly intersect because of shared risk factors and secondary to a cycle in which either syndrome drives the other to exist and progress. In recent clinical trials, AF affects ~50% of individuals with HFpEF/HFmrEF,[14,15] and the prevalence of AF in HFpEF within community-based cohort studies is even higher (>60%).[1] In HFpEF, the presence of AF is characterized by lower exercise capacity, a blunted course of decongestion during HF hospitalization, and worse LA mechanics.[3,4,7] Furthermore, AF has been associated with reduced overall survival and an increased risk of HF events and stroke both in patients with chronic HFpEF and in hospitalized cohorts with HFpEF/HFmrEF.[5,6,14,16] Despite our current knowledge of the shared AF-HFpEF syndrome, previous studies have defined AF using generalized clinical categories (paroxysmal, persistent, permanent) based on a single ECG, which does not measure precise AF burden or duration of AF. The current investigation furthers the understanding of AF in chronic HFpEF/HFmrEF through measurement of AF burden by continuous cardiac monitoring both at baseline and during follow-up in a randomized blinded, international trial of atrial shunt therapy as compared with a sham control procedure.

Although the ECG-based prevalence of clinical AF in HFpEF has been well described, less is known about the precise burden of AF and the prevalence of subclinical AF in HFpEF. To date, most studies evaluating the burden of AF have been conducted in patients with cardiac implantable electronic devices (ie, pacemakers or cardioverter-defibrillators), individuals without chronic HFpEF, or individuals after embolic stroke of undetermined source. Among patients with implanted permanent pacemakers or cardioverter-defibrillators, the prevalence of subclinical AF varies from 10% to as high as 55%.[17-19] In patients monitored after stroke of undetermined source, AF was detected in as many as 39% of individuals.[20] In a cohort of individuals without clinical AF who wore a patch monitor for 14 days, subclinical AF was detected in 4% of participants.[21] These estimates vary depending on the group under investigation and the follow-up duration. In our study of individuals with chronic HFpEF, as defined by gold standard invasive hemodynamic testing, subclinical AF was detected in 88% of individuals over a median follow-up time of 125 days, and the prevalence of subclinical AF was 38%. Furthermore, although 72% of those with subclinical AF had an AF duration of >6 minutes (over a 24-hour period) at some point during 1-year follow-up, only 1% of these patients had clinically adjudicated newly persistent/permanent AF. Among patients with cardiac implantable electronic devices, AF duration >6 minutes has been associated with an increased risk of stroke/systemic embolism and thus represents a clinically important threshold for consideration of oral anticoagulation therapy.[12,22] In combination, these findings demonstrate that subclinical AF is highly prevalent among patients with chronic HFpEF and that clinically important AF may be detected on continuous rhythm monitoring that may not be readily ascertained using standard methods.

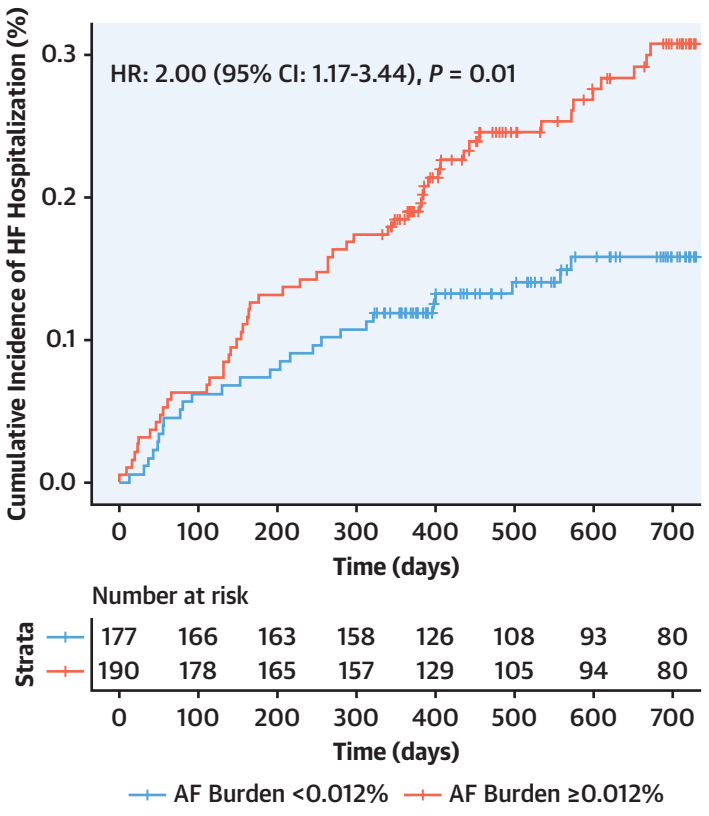
TABLE 3 Associations of Prerandomization AF Burden With Clinical Outcomes

	AF Burden	
	(<0.012%) (n = 177)	(≥0.012%) (n = 190)
HF events		
Incidence rate per 100 person-years (95% CI)	9.8 (6.4-14.3)	19.5 (14.6-25.5)
HR (95% CI)[a]	–	2.00 (1.17-3.44)
P value	–	0.01
CV death		
Incidence rate per 100 person-years (95% CI)	1.5 (0.4-3.9)	3.3 (1.5-6.3)
HR (95% CI)[a]	–	1.17 (0.32-4.27)
P value	–	0.82
Nonfatal ischemic stroke		
Incidence rate per 100 person-years (95% CI)	1.1 (0.2-3.3)	0.4 (0.01-2.10)
HR (95% CI)[a]	–	0.23 (0.02-2.74)
P value	–	0.24
Change in KCCQ-OSS		
Median 12-month change (IQR)	+11 (2-28)	8 (−4 to +22)
β-coefficient (95% CI)[b]	–	0.6 (−4.2 to +5.5)
P value	–	0.79

[a]Adjusted for age, sex, diabetes mellitus, body mass index, hypertension, treatment arm, chronic kidney disease, NYHA functional class, and history of AF or AF on the baseline electrocardiogram. [b]Additionally adjusted for baseline KCCQ-OSS score

CV = cardiovascular; HF = heart failure; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; other abbreviation as in Table 1.

CENTRAL ILLUSTRATION **Cumulative Incidence of Heart Failure Events According to Prerandomization AF Burden**



Patel RB, et al. J Am Coll Cardiol HF. 2023;11(10):1351–1362.

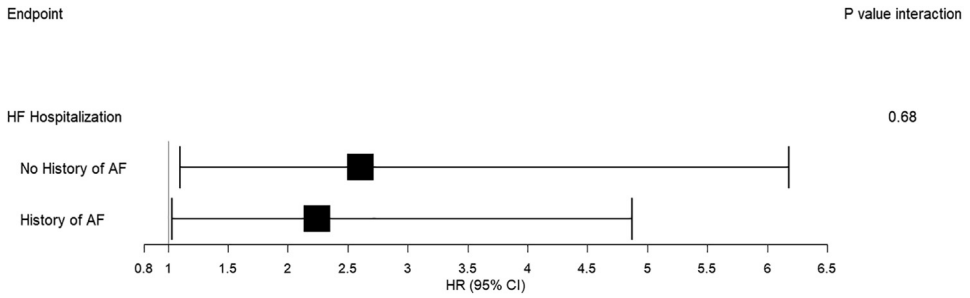
Cumulative incidence curves of heart failure (HF) events stratified by atrial fibrillation (AF) burden greater than or equal to the median (0.012%) **(red line)** vs less than the median **(blue line).**

Higher AF burden was associated with an increased risk of HF events in our study, a finding consistent among individuals with and without clinical AF. An investigation of the DELIVER (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure) trial demonstrated that paroxysmal AF was associated with worse clinical outcomes in chronic HFpEF.[14] These findings suggest that even low AF burden may carry prognostic implications in HFpEF. Our study quantifies this burden systematically and demonstrates that the threshold at which baseline subclinical AF burden was associated with HF events was low (0.012%), and this threshold was consistent for both subclinical AF and clinical AF subgroups. In REDUCE LAP HF II, AF burden was not associated with other clinical endpoints, including CV death and nonfatal ischemic stroke, a finding that may be accounted for in part by the low event rates for these outcomes in the trial. Subclinical AF burden was not associated with change in KCCQ-OSS during follow-up. Although AF itself is associated with worse health status, the relationship between AF burden and health status measures has been variable, and interventions aimed at reducing AF burden have not resulted in concomitant quality of life improvement.[23,24]

A higher baseline AF burden was characterized by marked LA dysfunction, and the association of AF burden with HF events was attenuated after adjustment for LA mechanical function (LA reservoir strain). Whether AF burden above a threshold of 0.012% in our study could be causally related to HF events is not clear, and it is as likely that this low AF burden is reflective of underlying LA myopathy.[25] The presence of LA mechanical dysfunction in HFpEF has been associated with poor hemodynamic reserve, increased congestion, reduced exercise capacity, and worse clinical outcomes, independent of AF.[26] LA reservoir strain, which represents the ability of the left atrium to stretch and fill with blood during ventricular systole is impaired in patients with AF-HFpEF.[26,27] The attenuation of the association between AF burden and HF events after adjustment for LA reservoir strain suggests that a stiffer, less compliant left atrium may be the underlying driver of elevated filling pressures, congestion, and HF events and that a low level of AF burden may be an indicator of underlying LA myopathy. Further studies are required to assess the temporal relationship of worsening of LA reservoir strain and AF burden to better understand potential mechanisms that may lead to worse clinical outcomes in HFpEF.

Atrial shunt therapy did not increase risk of AF in REDUCE LAP HF II. Because AF originates in the LA, devices placed within the atrial septum for various clinical indications may alter AF susceptibility. For example, patent foramen ovale (PFO) closure devices lead to a 5-fold increased transient risk of AF compared with medical therapy.[28] The risk of AF is highest in the first 45 days after PFO closure and appears to be consistent across various PFO closure devices.[28-30] Detection methods for AF in previous PFO trials have been variable, and few have used continuous rhythm monitors. In our study, atrial shunt therapy in HFpEF/HFmrEF did not increase AF as measured by a continuous cardiac monitoring device worn for a median of 125 days. This safety profile was consistent on various definitions of AF (ie, any AF during follow-up, newly diagnosed AF, and AF above a specific duration threshold of >6 minutes). These findings are particularly important because

FIGURE 2 Association of Prerandomization AF Burden on HF Events by History of AF



HF = heart failure; other abbreviation as in Figure 1.

several trials of atrial shunt devices are currently underway (FROST-HF [Flow Regulation by Opening the Septum in Patients With Heart Failure; NCT03751748], Relieve-HF [Reducing Lung Congestion Symptoms in Advanced Heart Failure; NCT03499236], and the Alleviate-HF-2 Study [NCT04838353]). There are several reasons that may account for differing effects of shunt devices as compared with PFO devices on AF risk. These include device material and the coincident effect of devices on LA pressure. Although PFO closure may increase LA pressure, atrial shunt devices decrease PCWP.[31] Such a pressure decrease may prevent adverse LA remodeling and be a potential trigger for AF. Our finding that AF duration >6 minutes was reduced in the atrial shunt arm of the responder cohort supports this hypothesis; further validation of this finding is required.

STUDY LIMITATIONS. REDUCE LAP HF II participants were enrolled on the basis of invasive hemodynamic testing and had high rates of HF events. It is unclear whether our findings extend to other HFpEF cohorts who have lower rates of HF events or whose diagnosis was established through noninvasive measures. The event rates for CV death and nonfatal stroke were low, and power to detect associations between AF burden and these clinical outcomes was insufficient. Patches were worn continuously during the first 3 months of follow-up compared with the subsequent 9 months, and this may have decreased detection of AF during the later follow-up. Participants of REDUCE LAP HF II were invited to participate in the extending cardiac monitoring substudy, which may lead to selection bias. Despite this, event rates among the extended monitoring subset were similar to those of the overall cohort. AF categories (paroxysmal/persistent/permanent) were not captured in REDUCE LAP HF II. Further studies are required to evaluate the longitudinal relationships among LA dysfunction, AF burden, and clinical outcomes in HFpEF/HFmrEF.

CONCLUSIONS

We characterized AF burden in REDUCE LAP HF II, a randomized trial of atrial shunt therapy compared with a sham procedure in chronic HFpEF. AF was detected in 88% of patients with HFpEF, and nearly 40% of patients with HFpEF had subclinical AF on continuous cardiac monitoring during the trial period. Higher baseline subclinical AF burden, even at low levels, was associated with increased filling pressures and risk of HF events, LA mechanical dysfunction, and poor cardiac output reserve to exercise. Atrial shunt device therapy does not increase the risk of AF and may decrease the risk of clinically significant AF burden. Further efforts are required to mitigate risk among patients with AF burden, even at low levels, in patients with HFpEF and HFmrEF.

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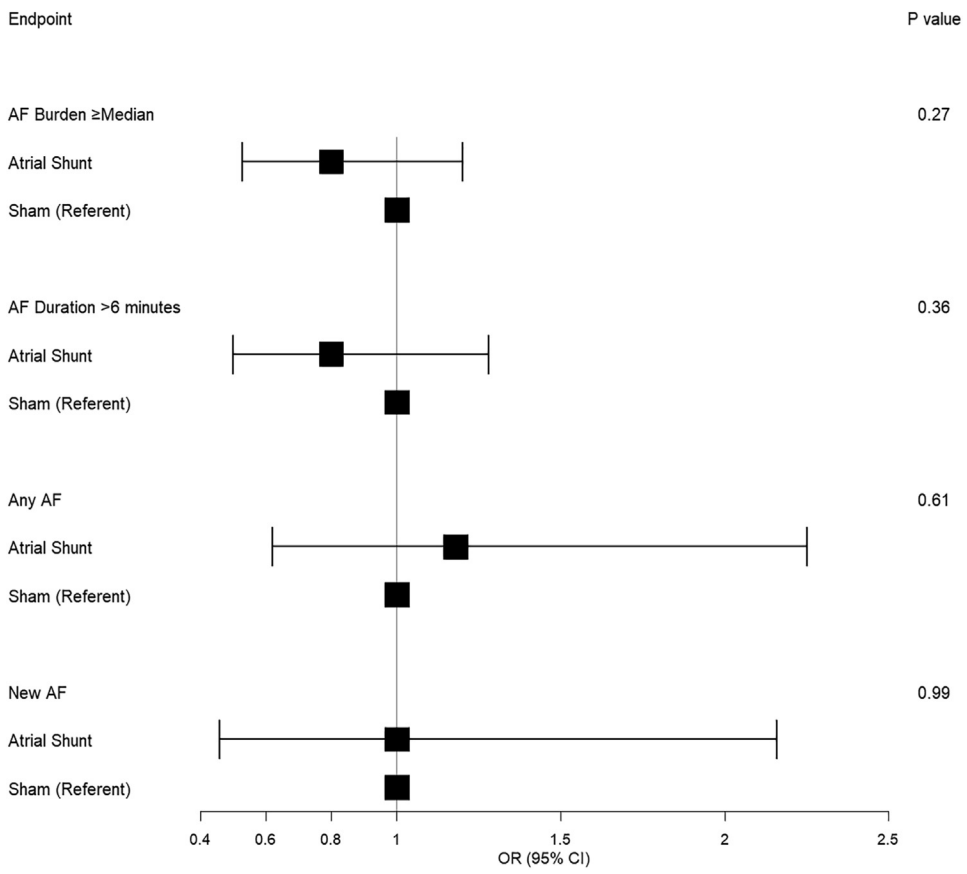
FIGURE 3 Effect of Atrial Shunt Therapy on AF Over Time



Forest plot demonstrating associations of atrial shunt therapy on the primary and secondary AF endpoints. OR <1.00 indicates that the shunt device is favorable, and OR >1.00 indicates that the sham procedure is favorable. Abbreviation as in Figure 1.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF burden, even at very low levels, is associated with an increased risk of HF hospitalization in HFpEF and HFmrEF.

TRANSLATIONAL OUTLOOK: Further studies are needed to elucidate whether AF burden or LA mechanical dysfunction drives poor prognosis among patients with both AF and HFpEF or HFmrEF.

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KEY WORDS atrial fibrillation, burden, clinical trial, heart failure, shunt

APPENDIX For supplemental tables and figures, please see the online version of this paper.