ORIGINAL INVESTIGATIONS

Progression of Device-Detected Subclinical Atrial Fibrillation and the Risk of Heart Failure

Jorge A. Wong, MD, MPH,[a] David Conen, MD, MPH,[a] Isabelle C. Van Gelder, MD,[b] William F. McIntyre, MD,[a] Harry J. Crijns, MD,[c,d] Jia Wang, MSc,[a] Michael R. Gold, MD,[e] Stefan H. Hohnloser, MD,[f] C.P. Lau, MD,[g] Alessandro Capucci, MD,[h] Gianluca Botto, MD,[i] Gerian Grönefeld, MD,[j] Carsten W. Israel, MD,[e] Stuart J. Connolly, MD,[a] Jeff S. Healey, MD, MSc[a]

ABSTRACT

BACKGROUND Long-term continuous monitoring detects short-lasting, subclinical atrial fibrillation (SCAF) in approximately one-third of older individuals with cardiovascular conditions. The relationship between SCAF, its progression, and the development of heart failure (HF) is unclear.

OBJECTIVES This study examined the relationship between progression from shorter to longer SCAF episodes and HF hospitalization.

METHODS Subjects in ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) were ≥65 years old, had history of hypertension, no prior clinical AF, and an implanted pacemaker or defibrillator. We examined patients whose longest SCAF episode during the first year after enrollment was >6 min but ≤24 h (n = 415). Using time-dependent Cox models, we evaluated the relationship between subsequent development of SCAF >24 h or clinical AF and HF hospitalization.

RESULTS Over a mean follow-up of 2 years, 65 patients (15.7%) progressed to having SCAF episodes >24 h or clinical AF (incidence 8.8% per year). Older age, greater body mass index, and longer SCAF duration within the first year were independent predictors of SCAF progression. The rate of HF hospitalization among patients with SCAF progression was 8.9% per year compared with 2.5% per year for those without progression. After multivariable adjustment, SCAF progression was independently associated with HF hospitalization (hazard ratio [HR]: 4.58; 95% confidence interval [CI]: 1.64 to 12.80; p = 0.004). Similar results were observed when we excluded patients with prior history of HF (HR: 7.06; 95% CI: 1.82 to 27.30; p = 0.005) or when SCAF progression was defined as development of SCAF >24 h alone (HR: 3.68; 95% CI: 1.27 to 10.70; p = 0.016).

CONCLUSIONS In patients with a pacemaker or defibrillator, SCAF progression was strongly associated with HF hospitalization. (J Am Coll Cardiol 2018;71:2603–11) © 2018 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BMI = body mass index

CI = confidence interval

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

MI = myocardial infarction

SCAF = subclinical atrial fibrillation

TIA = transient ischemic attack

Atrial fibrillation (AF) is a growing global health problem and is associated with significant morbidity and mortality (1-4). Landmark clinical trials have led to significant advances in the prevention of AF-related stroke (5-9); however, other AF-related complications are important and underappreciated (10-12). Heart failure (HF) develops in up to 40% of patients with AF (13,14) and is the cause of 15% to 30% of all deaths in this patient population (10,15,16). However, most of our knowledge of the relationship between AF and HF are based on studies of overt clinical AF, and limited data exist on the association between asymptomatic, subclinical atrial fibrillation (SCAF) and HF.

SEE PAGE 2612

SCAF refers to short-lasting, asymptomatic episodes of AF that are only detected with continuous, long-term cardiac monitoring. Modern pacemakers and implantable cardioverter-defibrillators (ICD) allow for the accurate capture of SCAF episodes, which have been shown in large cohort studies to be associated with an increased risk of clinical AF and stroke (17,18). Implanted cardiac devices also allow for the precise quantification of AF episode duration. Patients with paroxysmal AF may progress from shorter episodes to more frequent, longer, and ultimately sustained episodes, and this appears to be associated with worse clinical outcomes (19-23). However, prospective data examining the clinical outcomes of AF progression have been limited, and it remains unclear whether the evolution from shorter episodes of SCAF to longer episodes is associated with worse clinical outcomes (19-23).

In this analysis of data from the ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) (18), we evaluated the predictors of SCAF progression, defined as the development of at least 1 episode of SCAF >24 h in duration or clinical AF in patients previously monitored for 1 year in which they only experienced SCAF between 6 min and 24 h, as well as the relationship between SCAF progression and HF hospitalization.

METHODS

STUDY POPULATION. The ASSERT study has been previously described (18,24). Briefly, ASSERT enrolled 2,580 participants age ≥65 years, who were on antihypertensive therapy, and had undergone implantation of a dual-chamber pacemaker or ICD within 8 weeks of enrollment. Individuals with a history of clinical AF or atrial flutter >5 min in duration or treatment with a vitamin K antagonist were excluded. All device-captured SCAF, defined as episodes lasting >6 min in duration with an atrial rate >190 beats/min, were adjudicated. Follow-up occurred at 6-month intervals after enrollment. All participants provided written informed consent.

For the purposes of this analysis, the study population included all ASSERT participants who had episodes of SCAF lasting >6 min, but not longer than 24 h in the first year after enrollment (n = 415) (**Figure 1**). Participants who only had ≤6 min of SCAF (n = 125) were excluded because not all of these episodes were adjudicated, and the rate of false-positive SCAF is high when episode duration is this brief (18). The upper limit of 24 h was selected because episodes of greater duration appear to be associated with an increased risk of stroke (25) and are considered to be clinically important by expert guidelines (26). SCAF progression was defined as the development of SCAF lasting >24 h or presentation with overt clinical AF in a patient previously shown to have SCAF lasting from >6 min to 24 h during the initial year of follow-up. Clinical AF was defined as AF detected by 12-lead electrocardiography or surface electrocardiography rhythm strip >6 min.

ASSESSMENT OF COVARIATES. Pre-specified covariates evaluated in this analysis were assessed at study entry and included age, sex, weight, height, body mass index (BMI), systolic and diastolic blood pressure, heart rate, history of diabetes,
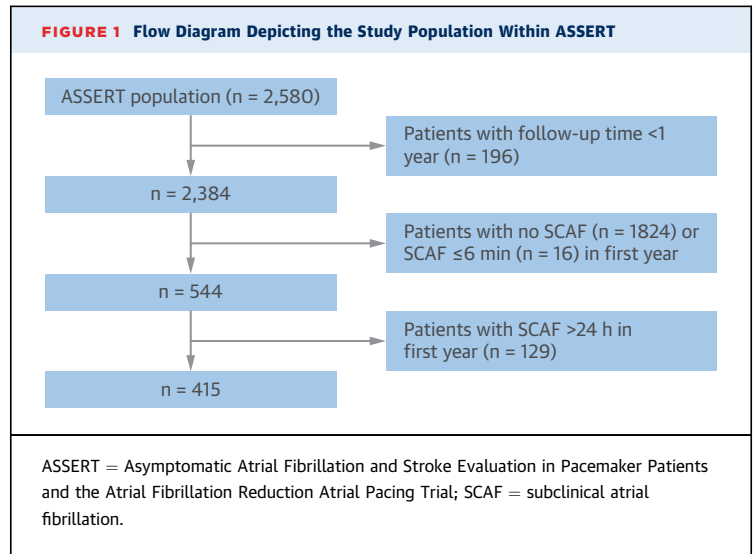
hypercholesterolemia, HF, left ventricular ejection fraction, prior stroke/transient ischemic attack (TIA), prior myocardial infarction (MI), CHA$_2$DS$_2$-VASc (stroke risk index [Congestive Heart Failure/Left Ventricular Dysfunction, Hypertension, Age ≥75 Years (2 points), Diabetes, History of Stroke/TIA (2 points), Vascular Disease, Age 65 to 74 Years, and Female Sex (if ≥65 years or other risk factor)]) scores, presence of sinus node disease, left ventricular hypertrophy, and medication use including use of acetylsalicylic acid, statins, beta-blockers, angiotensin antagonists, and antiarrhythmic drugs.

OUTCOMES FOR ANALYSIS. The incidence and clinical predictors of SCAF progression were studied. In this analysis, the primary outcome was the relationship between SCAF progression and HF hospitalization. HF hospitalization was defined as a minimum of an overnight stay in hospital of an individual who presented with signs and symptoms of HF and had radiologic evidence of HF or received intravenous diuretics or inotropes. The association between SCAF progression and stroke, cardiovascular death, and MI were assessed as secondary outcomes.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD, unless not normally distributed, in which case medians and interquartile ranges (IQR) were used. Categorical variables were expressed as frequencies and proportions. Normally distributed continuous variables were compared using the independent Student's *t*-test, otherwise the Wilcoxon rank sum test was used. The chi-square test or Fisher exact test was used to compare categorical variables. Independent predictors of SCAF progression were identified using Cox proportional hazards models, with all models including age, systolic blood pressure, BMI, prior stroke/TIA, and prior HF as they were clinically suspected to be associated with SCAF progression (see Methods in the Online Appendix).

The relationships between SCAF progression and individual outcomes were examined by modeling the occurrence of SCAF progression during the study as a time-dependent covariate in multivariable Cox models. SCAF episodes were classified into 2 categories based on episode length (>6 min to 24 h, >24 h). All participants started as having SCAF >6 min to 24 h, and if patients developed a SCAF episode >24 h or clinical AF, participants would be reclassified to the corresponding category and remain there. Only clinical events occurring after development of SCAF >24 h or clinical AF were

FIGURE 1 Flow Diagram Depicting the Study Population Within ASSERT

ASSERT = Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; SCAF = subclinical atrial fibrillation.

attributed to SCAF progression. Events occurring prior to progression were counted toward the SCAF progression absent group. Baseline covariates were used for multivariable model adjustment on the basis of prior literature (18) and included age, sex, history of diabetes, HF, MI, and prior stroke/TIA as well as the logarithm of the longest SCAF episode duration within the first year of enrollment. To rule out potential model overfitting in this setting, a propensity score method to adjust for the above-mentioned potential confounders was also used (see Methods in the Online Appendix) (27). A competing risk analysis using the method of Fine and Gray was also performed to assess all-cause mortality as a competing event for the clinical outcomes of interest (28).

Several pre-specified sensitivity analyses were also performed, evaluating the primary outcome: 1) after excluding all patients with a history of HF; 2) after excluding all individuals with HF hospitalization within the first year of enrollment; 3) among patients whose longest SCAF was between >6 min and 12 h in duration within the first year of enrollment; and 4) among participants free of SCAF or those who had ≤24 h of SCAF in year 1. In addition, we examined the primary outcome using different definitions for progression including developing: 5) SCAF >24 h only; 6) clinical AF only; and 7) SCAF >12 h or clinical AF among participants whose longest SCAF was between >6 min and 12 h in year 1. Two-tailed p values <0.05 were considered significant. SAS version 9.4 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

TABLE 1 Study Participant Characteristics				
	Total Study Population (N = 415)	Subclinical Atrial Tachyarrhythmia Progression*		p Value
		Yes (n = 65)	No (n = 350)	
Age, yrs	76.7 ± 6.6	76.6 ± 7.2	76.7 ± 6.5	0.91
Male	227 (54.7)	42 (64.6)	185 (52.9)	0.08
Systolic blood pressure, mm Hg	139.0 ± 19.3	137.5 ± 17.1	139.3 ± 19.7	0.45
Diastolic blood pressure, mm Hg	75.7 ± 10.5	73.9 ± 10.0	76.1 ± 10.6	0.11
Pulse pressure, mm Hg	63.3 ± 17.4	63.6 ± 16.3	63.2 ± 17.6	0.86
Heart rate, beats/min	68.7 ± 11.2	67.3 ± 8.9	69.0 ± 11.6	0.18
BMI, kg/m^2	27.5 ± 5.0	28.2 ± 4.9	27.3 ± 5.0	0.21
Prior stroke/TIA	42 (10.1)	5 (7.7)	37 (10.6)	0.48
History of HF	56 (13.5)	6 (9.2)	50 (14.3)	0.27
Diabetes mellitus	97 (23.4)	16 (24.6)	81 (23.1)	0.80
MI	64 (15.4)	12 (18.5)	52 (14.9)	0.46
Peripheral vascular disease	23 (5.5)	5 (7.7)	18 (5.1)	0.38
LVEF, %	60.0 (55.0–65.0)	60.0 (50.0–65.0)	60.0 (55.0–65.0)	0.77
CHA$_2$DS$_2$-VASc score	3.9 ± 1.3	3.9 ± 1.3	3.9 ± 1.3	0.97
Pacing indication				
Sinus-node disease alone	129 (31.1)	22 (33.8)	107 (30.6)	0.6
AV node disease alone	197 (47.5)	30 (46.2)	167 (47.7)	0.82
Both sinus and AV node disease	63 (15.2)	9 (13.8)	54 (15.4)	0.74
Hypertension history >10 yrs	185 (44.6)	33 (50.8)	152 (43.4)	0.27
ECG left ventricular hypertrophy (Sokolow and Lyon index)	12 (2.9)	0 (0.0)	12 (3.4)	0.23
Device implanted				
Pacemaker	398 (95.9)	63 (96.9)	335 (95.7)	1.0
ICD	15 (3.6)	2 (3.1)	13 (3.7)	
Medications				
Aspirin	235 (56.6)	39 (60.0)	196 (56.0)	0.55
Beta-blocker	138 (33.3)	27 (41.5)	111 (31.7)	0.12
ACE inhibitor/ARB	315 (75.9)	45 (69.2)	270 (77.1)	0.17
Statin	183 (44.1)	28 (43.1)	155 (44.3)	0.86
Antiarrhythmic drug	28 (6.7)	7 (10.8)	21 (6.0)	0.18
Longest SCAF episode,† h	2.5 (0.7–6.2)	6.7 (2.5–13.4)	2.0 (0.6–5.0)	<0.001
Total SCAF duration,† h	4.0 (1.20–11.6)	14.8 (4.0–26.3)	3.2 (1.0–8.9)	<0.001

Values are mean ± SD, n (%), or median (IQR). *Defined as development of ≥1 episode of SCAF >24 h or overt clinical AF during subsequent follow-up. †During the first year from enrollment.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AV = atrioventricular; BMI = body mass index; CHA$_2$DS$_2$-VASc = stroke risk index (Congestive Heart Failure/Left Ventricular Dysfunction, Hypertension, Age ≥ 75 Years [2 points], Diabetes, History of Stroke/Transient Ischemic Attack [2 points], Vascular Disease, Age 65 to 74 Years, and Female Sex [if ≥ 65 years or other risk factor]); ECG = electrocardiography; HF = heart failure; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SCAF = subclinical atrial fibrillation; TIA = transient ischemic attack.

RESULTS

PATIENT CHARACTERISTICS. In the first year from enrollment, 415 patients had SCAF lasting between 6 min and 24 h. Baseline characteristics are summarized in **Table 1**. Mean age of the analysis population was 76.7 ± 6.6 years, and 13.5% had a prior history of HF. During subsequent follow-up, 65 patients (15.7%) progressed to episodes of SCAF >24 h or overt clinical AF, corresponding to a rate of 8.8% per year. Among the patients who progressed, 60 patients developed

SCAF >24 h, 25 patients developed clinical AF, and 20 patients developed both. Compared with patients who did not progress, patients with SCAF progression had greater median longest SCAF episode duration within the first year of enrollment (6.7 [IQR: 2.5 to 13.4] h vs. 2.0 [IQR: 0.6 to 5.0] h; p < 0.001). Otherwise, there were no significant differences between the groups (**Table 1**). **Figure 2** depicts the trends in the median duration of the longest SCAF episode (on a log scale) for both groups during the study period. Among the patients who progressed, the median duration of the longest SCAF episode steadily increased from 6.7 h in the first year from enrollment to a median of 153.2 h in the fourth year. In contrast, the median duration of the longest SCAF episode remained relatively stable during the study period among those who did not progress (year 1: 2.0 h and year 4: 3.3 h).

PREDICTORS OF SCAF PROGRESSION. Findings from a multivariable Cox model identifying predictors of SCAF progression are shown in **Table 2**. Every 10-year increase in age was associated with a 1.6-fold increase in the risk of SCAF progression (hazard ratio [HR]: 1.59; 95% confidence interval [CI]: 1.05 to 2.39; p = 0.028). BMI was also an independent predictor of SCAF progression, with each 10-kg/m^2 increase being associated with an HR of 1.83, 95% CI of 1.14 to 2.94, and p = 0.013. Each 1-h increase in the duration of the longest SCAF episode within the first year of enrollment was independently associated with a 13% increase in the risk of SCAF progression (HR: 1.13; 95% CI: 1.09 to 1.17; p < 0.001). None of the remaining variables, including total cumulative SCAF duration during the first year, were identified as independent risk factors of SCAF progression (**Table 2**).

SCAF PROGRESSION AND HOSPITALIZATION FOR HF. HF hospitalization occurred before and after SCAF progression in 5 and 7 individuals, respectively. The rate of HF hospitalization was 8.9% per year after progression to episodes >24 h or clinical AF compared with 2.5% per year among those who did not progress. In univariate analysis, SCAF progression was associated with an increased risk of subsequent HF hospitalization (HR: 4.10; 95% CI: 1.65 to 10.2; p = 0.002) (**Table 3**). Following multivariable adjustment, SCAF progression remained an independent predictor of HF hospitalization (HR: 4.58; 95% CI: 1.64 to 12.8; p = 0.004) (**Table 3**). Results were similar when using a propensity score model for covariate adjustment (Online Table 1) or following competing risk analysis accounting for the competing

risk of mortality (Online Table 2). **Table 4** summarizes the relationship between the covariates used in the multivariable-adjusted Cox model and the risk of HF hospitalization. In addition to SCAF progression, prior history of HF (HR: 6.34; 95% CI: 2.6 to 15.6; p < 0.001) and prior MI (HR: 2.89; 95% CI: 1.2 to 7.2; p = 0.02) were independent predictors of HF hospitalization. In exploratory analysis, prior MI appeared to be a significant predictor of HF hospitalization among those who had SCAF progression compared with those who did not (Online Table 3).

Several pre-specified sensitivity analyses were performed (Online Table 4). Adjusted HR for HF hospitalization were similar after excluding patients with a history of HF at baseline (HR: 7.06; 95% CI: 1.82 to 27.30; p = 0.005) or after exclusion of patients with HF hospitalization within the first year of enrollment (HR: 4.18; 95% CI: 1.39 to 12.6; p = 0.01). Comparable results were also observed when examining SCAF progression among the subset of participants with SCAF between 6 min and 12 h in the first year (HR: 7.73; 95% CI: 2.52 to 23.80; p < 0.001) or among participants who were either free of SCAF or had SCAF ≤24 h in year 1 (HR: 3.48; 95% CI: 1.86 to 6.51; p < 0.001). Finally, adjusted HR were similar when the definition for progression was SCAF >24 h alone (HR: 3.68; 95% CI: 1.27 to 10.70; p = 0.016), development of clinical AF alone (HR: 3.99; 95% CI: 0.85 to 18.8; p = 0.08), or development of SCAF >12 h or clinical AF among those with SCAF between 6 min and 12 h in the first year of enrollment (HR: 3.44; 95% CI: 1.15 to 10.30; p = 0.027). There was no apparent association between SCAF progression and stroke, vascular death, MI, or their composite (**Table 3**).

DISCUSSION

This study demonstrates that progression of SCAF, from shorter to longer episodes, is associated with a 5-fold increase in the risk of HF hospitalization (Central Illustration). SCAF progression to episodes >24 h was common, occurring at a rate of 9% per year, and was more frequent among older individuals, those with greater BMI and those with longer initial SCAF episodes. This study is the first to demonstrate that progression of AF, even at its asymptomatic, subclinical stage can be associated with adverse outcomes. As prior studies using implanted cardiac devices suggest that up to 85% of AF is not clinically recognized (18,29), the current analysis of SCAF adds significantly to our understanding of the relationship between AF and HF,

FIGURE 2 Trends in the Duration of the Longest SCAF Episode Over the Study Period in Patients With and Without SCAF Progression

Longest SCAF episode duration was log-transformed. Data presented as median and interquartile range. AF = atrial fibrillation; SCAF = subclinical atrial fibrillation.
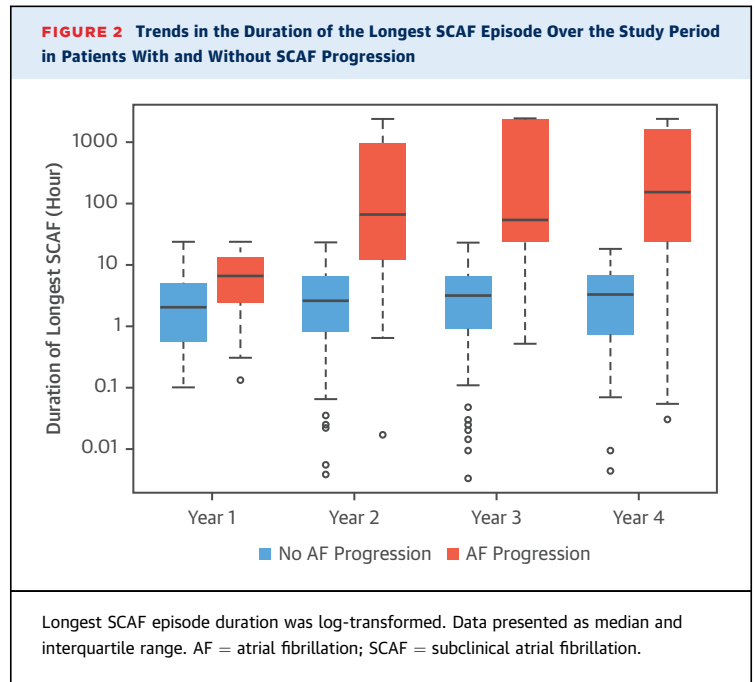
identifying a subgroup of patients who might benefit from preventive strategies (30).

In this study, increasing age and BMI were independent predictors of SCAF progression, findings consistent with prior studies of clinically overt AF (31-35). In the Women's Health Study, the risk of having nonparoxysmal AF shortly after the diagnosis of AF increased by 30% per each 10-kg increase in weight (36). Similarly, data from Olmsted County suggest that obesity and severe obesity were associated with a 30% to 50% increased risk of

TABLE 2 Independent Predictors of SCAF Progression to >24 h or Clinical AF During Follow-Up, Among Patients With SCAF Between >6 min and 24 h Within 1 Year of Enrollment

	Multivariable Adjusted Risk		
	HR	95% CI	p Value
Age, per 10-yr increment	1.59	1.05–2.39	0.028
BMI, per 10-kg/m² increment	1.83	1.14–2.94	0.013
Longest SCAF episode within 1 yr, per 1-h increment	1.13	1.09–1.17	<0.001
Beta-blocker use	1.61	0.96–2.69	0.069
Antiarrhythmic drug use	2.08	0.88–4.94	0.096
Systolic blood pressure, per 10-mm Hg increment	0.93	0.81–1.07	0.331
Prior stroke/TIA	0.48	0.17–1.35	0.164
History of HF	0.65	0.27–1.54	0.328

CI = confidence interval; HR = hazard ratio; other abbreviations as in **Table 1**.

2608   Wong et al.
Subclinical AF Progression and Heart Failure

JACC VOL. 71, NO. 23, 2018
JUNE 12, 2018:2603–11

TABLE 3 Risk of Clinical Outcomes Occurring in Patients With or Without SCAF Progression to the Combined Endpoint of SCAF >24 h or Clinical AF, Among Patients With SCAF Between >6 min and 24 h Within 1 Year of Enrollment

| | Subclinical Atrial Tachyarrhythmia Progression | | | | Unadjusted Risk* | | | Multivariable Adjusted Risk* | | |
| | Present | | Absent | | | | | | | |
	Events/Patients	% per Year	Events/Patients	% per Year	HR	95% CI	p Value	HR	95% CI	p Value
HF hospitalization	7/60	8.9	18/355	2.5	4.10	1.65–10.2	0.002	4.58	1.64–12.8	0.004
Any stroke	0/65	0	8/350	1.1	0.00	–	–	0.00	–	–
Vascular death	4/65	4.5	17/350	2.3	1.99	0.66–6.02	0.23	1.71	0.53–5.58	0.37
MI	1/65	1.1	3/350	0.4	2.40	0.21–27.1	0.48	1.94	0.15–25.1	0.61
Stroke/MI/vascular death	5/65	5.7	24/350	3.3	1.55	0.58–4.15	0.38	1.51	0.53–4.35	0.44

All outcomes adjusted for age, sex, prior diabetes, congestive HF, MI, stroke/TIA and the logarithm of longest SCAF episode within the first year of enrollment. Dashes indicate data were not available. *Where SCAF progression absent is the referent.

Abbreviations as in **Tables 1 and 2**.

progression to permanent AF (33). Taken together, these data support that weight loss and other lifestyle interventions may be useful in reducing the burden and progression of AF and the development of HF, a hypothesis worth testing in a randomized trial. Participants with longer episodes of SCAF within the first year were also more likely to progress, a characteristic that potentially identifies higher risk individuals in a patient population with few apparent baseline differences. Indeed, clinical characteristics at baseline were surprisingly not altogether different between patients who had SCAF progression and those who did not, suggesting that SCAF progression may not be entirely predicted by traditional risk factors for AF or cardiovascular disease.

Our study is the first to use continuous, long-term monitoring to prospectively examine the outcomes of AF progression and addresses many of the limitations of prior studies. Although several studies have suggested that progression of paroxysmal to nonparoxysmal AF is associated with worse
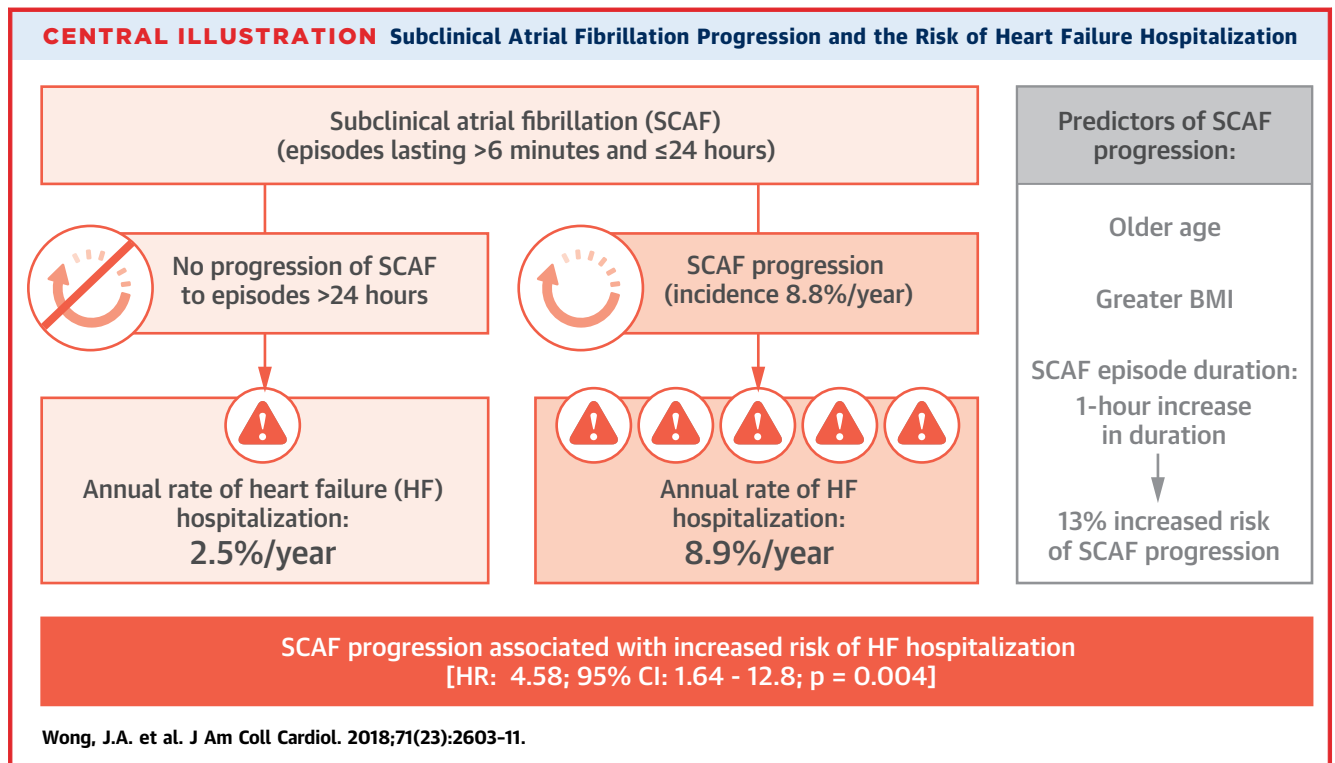
outcomes, these observations were primarily based on cross-sectional analyses with few prospective data available; raising concerns about residual confounding (19–22,31,33). Previous reports have also been limited by small numbers of participants, single-center design, short follow-up duration, and incomplete ascertainment of AF (31,37). Finally, prior studies are also based on a clinical classification for the pattern of AF, which has been found to correlate poorly with the temporal persistence of the arrhythmia (38).

The mechanisms linking AF progression with HF are incompletely understood. Patients pre-disposed to HF may not tolerate prolonged, rapid ventricular rates during SCAF, leading to the clinical unmasking of HF (39). Furthermore, tachycardia-induced cardiomyopathy due to prolonged episodes of SCAF may be an important factor in some patients (40). Atrial systole can contribute a considerable proportion of the cardiac output in patients pre-disposed to HF, and its loss during episodes of SCAF might also account for some of the observed increase in HF risk (39). There may also be shared pathophysiology between these conditions, with myocardial inflammation and fibrosis pre-disposing to diastolic dysfunction, atrial stiffness, and AF (41,42). Finally, abnormal calcium handling, activation of the renin-angiotensin-aldosterone system, and the modulation of natriuretic peptides during prolonged episodes of SCAF may also pre-dispose to HF (40,41,43). Interestingly, in exploratory analysis, prior MI was a strong predictor of HF hospitalization in the SCAF progression group, whereas it was not an independent predictor among those who did not progress. Whereas this data suggest that prior MI, presumably via ischemia-induced left ventricular dysfunction or impaired left ventricular filling, may be more

TABLE 4 Covariates Independently Associated With Congestive HF Hospitalization in the Study Population

| | Multivariable-Adjusted Risk | | |
	HR	95% CI	p Value
SCAF progression	4.58	1.64–12.8	0.004
History of HF	6.34	2.58–15.6	<0.001
Prior MI	2.89	1.16–7.21	0.022
Age, per 10-yr increment	0.98	0.53–1.82	0.96
Male	0.86	0.38–1.95	0.71
Prior diabetes	0.84	0.33–2.12	0.72
Prior stroke/TIA	0.26	0.03–2.00	0.20
Longest SCAF episode within year 1, per 10% increment	1.02	0.99–1.04	0.27

Abbreviations as in **Tables 1 to 3**.

CENTRAL ILLUSTRATION Subclinical Atrial Fibrillation Progression and the Risk of Heart Failure Hospitalization

Subclinical atrial fibrillation (SCAF)
(episodes lasting >6 minutes and ≤24 hours)

No progression of SCAF
to episodes >24 hours

SCAF progression
(incidence 8.8%/year)

Predictors of SCAF
progression:

Older age

Greater BMI

SCAF episode duration:
1-hour increase
in duration

13% increased risk
of SCAF progression

Annual rate of heart failure (HF)
hospitalization:
2.5%/year

Annual rate of HF
hospitalization:
8.9%/year

SCAF progression associated with increased risk of HF hospitalization
[HR: 4.58; 95% CI: 1.64 - 12.8; p = 0.004]

Wong, J.A. et al. J Am Coll Cardiol. 2018;71(23):2603–11.

important in the development of HF hospitalization in patients with SCAF progression, the finding should also be interpreted with caution given the small number patients and events.

The finding that progression of SCAF is associated with an increased risk of HF adds to a growing body of published reports highlighting the clinical importance of the relationship between AF and HF. In an analysis of the ENGAGE AF–TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48) study (44), HF accounted for 23.4% of deaths during the trial. Similarly, in the RE-LY (Randomized Evaluation of Long-Term Anti-coagulation Therapy) randomized trial, sudden cardiac death and HF accounted for 37.4% of deaths (15). Finally, in a prospective registry of 15,400 individuals in 47 countries who presented to the emergency department with a diagnosis of AF, HF was the most common cause of death, accounting for 30%, and HF hospitalization was 3-fold greater than the risk of stroke (10). The identification of SCAF progression as a strong predictor of future HF in patients with continuous cardiac monitoring gives clinicians and researchers a way to identify patients at risk of HF. The application of evidence-based HF

therapies and the evaluation of risk-factor modification in this high-risk population could help prevent the adverse consequences related to HF development.

STUDY LIMITATIONS. First, our dataset contained small numbers of patients with outcomes other than HF, thus we did not have the statistical power to show associations for outcomes such as stroke. Second, our study population was composed of individuals who met criteria for pacemaker or ICD implantation, and thus our results may not be applicable to individuals who do not have cardiac device indications. However, incidence of SCAF in our study appears similar to that seen in PREDATE AF (Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events) (45) and ASSERT II (29), which examined patients with similar risk profiles who did not meet cardiac device criteria (45). Third, our results are based on a proposed definition for SCAF progression, as there is currently no widely accepted definition (46). However, this was defined a priori, and our results were similar across a range of sensitivity analyses using different definitions for progression. Finally, despite our attempts to control

for confounders, we cannot exclude the existence of residual confounding.

CONCLUSIONS

Among patients with SCAF, progression occurs at a rate of 9% per year and is independently associated with an increased risk of HF hospitalization. Progression of AF may be a suitable preventive and therapeutic target and is worthy of future studies.

ADDRESS FOR CORRESPONDENCE: Dr. Jorge A. Wong, Population Health Research Institute, 237 Barton Street East, DBCVSRI Room C3-11D, Hamilton, Ontario L8L 2X2, Canada. E-mail: Jorge.Wong@phri.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HF is a leading cause of death in patients with AF. Progression of asymptomatic, subclinical AF to increasing durations of the arrhythmia in patients with implanted pacemaker or defibrillator devices is a strong predictor of subsequent hospitalization for HF, even in patients with no history of HF.

TRANSLATIONAL OUTLOOK: Randomized studies are needed to assess whether strategies aimed at reducing the progression of AF will avoid the need for HF hospitalization and potentially decrease mortality.

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.

2. Conen D, Chae CU, Glynn RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA 2011;305:2080–7.

3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 2001; 285:2370–5.

4. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119–25.

5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

6. Granger CB, Alexander JH, McMurray JJ, et al., for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

7. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.

8. Patel MR, Mahaffey KW, Garg J, et al., for the ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

9. Active Steering Committee, ACTIVE Investigators, Connolly S, et al. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 2006;151:1187–93.

10. Healey JS, Oldgren J, Ezekowitz M, et al., for the RE-LY Atrial Fibrillation Registry and Cohort Study Investigators. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet 2016;388:1161–9.

11. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ 2016;354:i4482.

12. Vermond RA, Geelhoed B, Verweij N, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. J Am Coll Cardiol 2015;66:1000–7.

13. Schnabel RB, Rienstra M, Sullivan LM, et al. Risk assessment for incident heart failure in individuals with atrial fibrillation. Eur J Heart Fail 2013;15:843–9.

14. 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.

15. Marijon E, Le Heuzey JY, Connolly S, et al., for the RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation 2013;128:2192–201.

16. Gomez-Outes A, Lagunar-Ruiz J, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Causes of death in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 2016;68:2508–21.

17. Daoud EG, Glotzer TV, Wyse DG, et al., for the TRENDS Investigators. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. Heart Rhythm 2011;8:1416–23.

18. Healey JS, Connolly SJ, Gold MR, et al., for the ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med 2012;366: 120–9.

19. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. Eur Heart J 2016;37:1591–602.

20. Al-Khatib SM, Thomas L, Wallentin L, et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. Eur Heart J 2013;34:2464–71.

21. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al., for the ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF trial. Eur Heart J 2015;36:288–96.

22. Vanassche T, Lauw MN, Eikelboom JW, et al. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. Eur Heart J 2015;36:281–287a.

23. Nieuwlaat R, Prins MH, Le Heuzey JY, et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. Eur Heart J 2008;29:1181–9.

24. Hohnloser SH, Capucci A, Fain E, et al., for the ASSERT Investigators and Committees. ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT). Am Heart J 2006;152:442–7.

25. Van Gelder IC, Healey JS, Crijns HJ, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J 2017;38:1339–44.

26. Macle L, Cairns J, Leblanc K, et al., for the CCS Atrial Fibrillation Guidelines Committee. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2016;32:1170–85.

27. Xu R, Luo Y, Glynn R, Johnson D, Jones KL, Chambers C. Time-dependent propensity score for assessing the effect of vaccine exposure on

pregnancy outcomes through pregnancy exposure cohort studies. Int J Environ Res Public Health 2014;11:3074–85.

28. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

29. Healey JS, Alings M, Ha A, et al., for the ASSERT-II Investigators. Subclinical atrial fibrillation in older patients. Circulation 2017;136: 1276–83.

30. Parkash R, Wells GA, Sapp JL, et al. Effect of aggressive blood pressure control on the recurrence of atrial fibrillation after catheter ablation: a randomized, open label, clinical trial (SMAC-AF [Substrate Modification with Aggressive Blood Pressure Control]). Circulation 2017;135:1788–98.

31. de Vos CB, Pisters R, Nieuwlaat R, et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol 2010;55:725–31.

32. Kerr CR, Humphries KH, Talajic M, et al. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. Am Heart J 2005;149:489–96.

33. Tsang TS, Barnes ME, Miyasaka Y, et al. Obesity as a risk factor for the progression of paroxysmal to permanent atrial fibrillation: a longitudinal cohort study of 21 years. Eur Heart J 2008;29:2227–33.

34. Padfield GJ, Steinberg C, Swampillai J, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. Heart Rhythm 2017; 14:801–7.

35. Tedrow UB, Conen D, Ridker PM, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (Women's Health Study). J Am Coll Cardiol 2010;55:2319–27.

36. Sandhu RK, Conen D, Tedrow UB, et al. Predisposing factors associated with development of persistent compared with paroxysmal atrial fibrillation. J Am Heart Assoc 2014;3:e000916.

37. Potpara TS, Stankovic GR, Beleslin BD, et al. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation study. Chest 2012;141:339–47.

38. Charitos EI, Purerfellner H, Glotzer TV, Ziegler PD. Clinical classifications of atrial fibrillation poorly reflect its temporal persistence: insights from 1,195 patients continuously monitored with implantable devices. J Am Coll Cardiol 2014;63:2840–8.

39. Phan TT, Abozguia K, Shivu GN, et al. Increased atrial contribution to left ventricular filling compensates for impaired early filling during exercise in heart failure with preserved ejection fraction. J Card Fail 2009;15:890–7.

40. Ellis ER, Josephson ME. Heart failure and tachycardia-induced cardiomyopathy. Curr Heart Fail Rep 2013;10:296–306.

41. Everett TH 4th, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. Heart Rhythm 2007;4 Suppl 3:S24–7.

42. Westermann D, Lindner D, Kasner M, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail 2011;4:44–52.

43. Ling LH, Khammy O, Byrne M, et al. Irregular rhythm adversely influences calcium handling in ventricular myocardium: implications for the interaction between heart failure and atrial fibrillation. Circ Heart Fail 2012;5: 786–93.

44. Eisen A, Ruff CT, Braunwald E, et al. Sudden cardiac death in patients with atrial fibrillation: insights from the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc 2016;5. pii:e003735.

45. Nasir JM, Pomeroy W, Marler A, et al. Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events (PREDATE AF) study. Heart Rhythm 2017;14:955–61.

46. Healey JS, Wong JA. Subclinical atrial fibrillation: the significance of progression to longer episodes. Heart Rhythm 2018;15:384–5.

KEY WORDS atrial fibrillation, atrial fibrillation progression, health outcome, heart failure, predictors, subclinical atrial fibrillation

APPENDIX For supplemental Methods as well as tables, please see the online version of this paper.