JACC: CLINICAL ELECTROPHYSIOLOGY VOL. ■, NO. ■, 2019

PUBLISHED BY ELSEVIER

Are Atrial High-Rate Episodes Associated With Increased Risk of Ventricular Arrhythmias and Mortality?

Pasquale Vergara, MD, PhD,[a] Francesco Solimene, MD,[b] Antonio D'Onofrio, MD,[c] Ennio C. Pisanò, MD,[d] Gabriele Zanotto, MD,[e] Carlo Pignalberi, MD,[f] Saverio Iacopino, MD,[g] Giampiero Maglia, MD,[h] Paolo Della Bella, MD,[a] Valeria Calvi, MD,[i] Antonio Curnis, MD,[j] Gaetano Senatore, MD,[k] Mauro Biffi, MD,[l] Alessandro Capucci, MD,[m] Quintino Parisi, MD,[n] Fabio Quartieri, MD,[o] Fabrizio Caravati, MD,[p] Massimo Giammaria, MD,[q] Massimiliano Marini, MD,[r] Antonio Rapacciuolo, MD, PhD,[s] Michele Manzo, MD,[t] Daniele Giacopelli, MSc,[u] Alessio Gargaro, MSc,[u] Renato P. Ricci, MD[v]

ABSTRACT

OBJECTIVES This study evaluated the temporal association between atrial high-rate episodes (AHREs) and sustained ventricular arrhythmias (VAs) in a remotely monitored cohort with implantable cardioverter-defibrillators (ICD) with and/or without cardiac resynchronization therapy with a defibrillator (CRT-D).

BACKGROUND Clinical relevance of AHREs in terms of VA rate and survival has not been outlined yet.

METHODS This study analyzed data of patients with ICDs and CRT-Ds from the nationwide Home Monitoring Expert Alliance network. The cohort included 2,435 patients with a median follow-up of 25 months (interquartile range: 13 to 42 months) and age 70 years (range: 61 to 77 years); 19.7% were women, 51.4% had coronary artery disease, and 45.2% had a CRT-D. There were 3,410 appropriate VA episodes; 498 (14.6%) were preceded by AHREs within 48 h; in 85.5% of this group, AHREs were still ongoing at episode onset. In a longitudinal analysis, the odds ratios (ORs) of experiencing any VA in a 30-day interval with AHREs versus intervals without AHREs were 2.35 (95% confidence interval [CI]: 1.86 to 2.97; $p < 0.001$) for ventricular tachycardia (VT), 3.06 (95% CI: 2.35 to 3.99; $p < 0.001$) for fast VT, 1.84 (95% CI: 1.36 to 2.48; $p < 0.001$) for self-extinguishing ventricular fibrillation (VF), and 2.31 (95% CI: 1.17 to 4.57; $p = 0.01$) for VF. ORs decreased with increasing AHRE burden. Patients with AHREs 48 h before VAs were more likely to experience VA recurrences (adjusted hazard ratio [HR]: 1.78; 95% CI: 1.41 to 2.24; $p < 0.001$) and had higher overall mortality (HR: 2.67; 95% CI: 1.68 to 4.23; $p < 0.001$).

CONCLUSIONS AHREs were not uncommon 48 h before VAs, which tended to be distributed around intervals with AHREs. Temporal connection between AHREs and VAs was a marker of increased risk of VA recurrence and a poorer prognosis. (J Am Coll Cardiol EP 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

From the [a]Arrhythmias and Cardiac Electrophysiology, Ospedale San Raffaele, Milan, Italy; [b]Electrophysiology Lab, Clinica Montevergine, Mercogliano (AV), Italy; [c]Electrophysiology and Cardiac, Pacing Unit, Ospedale Monaldi, Naples, Italy; [d]Cardiology, Department, Ospedale Vito Fazzi, Lecce, Italy; [e]Cardiology Department, Ospedale Mater Salutis, Legnago, Italy; [f]Cardiology Department, Ospedale San Filippo Neri, Rome, Italy; [g]Arrhythmias and Cardiac Electrophysiology, Villa Maria Care & Research, Cotignola (RA), Italy; [h]Electrophysiology, Cardiac Pacing, and Arrhythmias, Azienda Ospedaliera Pugliese Ciaccio, Catanzaro, Italy; [i]Electrophysiology and Cardiac Pacing, Policlinico Vittorio Emanuele PO Ferrarotto, Catania, Italy; [j]Cardiology Division, Spedali Civili, Brescia, Italy; [k]Cardiology Division, Ospedale di Ciriè, Ciriè (TO), Italy; [l]Institute of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, Policlinico Sant'Orsola-Malpighi, Bologna, Italy; [m]Cardiology Department, Ospedali Riuniti, Ancona, Italy; [n]Cardiology Department, Fondazione di Ricerca e Cura Giovanni Paolo II, Campobasso, Italy; [o]Department of Interventional Cardiology, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; [p]Department of Cardiology I, Ospedale di Circolo e Fond. Macchi, Varese, Italy; [q]Department of Cardiology, Ospedale Maria Vittoria, Torino, Italy; [r]Department of Cardiology, Ospedale Santa Chiara, Trento, Italy; [s]UNINA Department of Advanced Biomedical Sciences, Azienda Ospedaliera Universitaria Federico II, Naples, Italy; [t]Department of Cardiology, Azienda Ospedaliera Universitaria S.Giovanni di Dio e Ruggi D'Aragona, Salerno, Italy; [u]Department of Clinical Research, BIOTRONIK Italia, Vimodrone (MI), Italy; and [v]Department of Arrhythmias, CardioArrhythmology Center, Rome, Italy. Dr. Vergara has been a consultant for Biosense Webster and Boston Scientific. Dr. Della Bella has received consultancy fees from Abbott, Biosense Webster, and Boston Scientific. Dr. Ricci has received consultancy fees from Medtronic and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2019.06.018

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AHRE = atrial high-rate episode

AHRE-48-VA = ventricular arrhythmia preceded by AHREs within 48 h

CRT-D = cardiac resynchronization therapy with defibrillator

CI = confidence interval

EGM = electrogram

GEE = generalized estimating equations

HMEA = Home Monitoring Expert Alliance

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

OR = odds ratio

RM = remote monitoring

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Sudden cardiac death is responsible for approximately 25% of deaths related to cardiovascular diseases (1). Ventricular arrhythmias (VAs) or any shockable rhythm by external defibrillators are the initial recorded cardiac rhythm in 20% of treated out-of-hospital cardiac arrests (2). In the last 3 decades, the prognosis of patients who experienced or were at high risk of developing VAs profoundly changed, due to the introduction of implantable cardioverter-defibrillators (ICDs) and catheter ablation of ventricular tachycardias (VTs) (3-6).

Although VA is an independent risk factor for cardiac mortality, only a few studies have provided significant insight into the predictors of VAs and their onset (7,8). The association between VA and atrial fibrillation (AF) has been documented in some series, but little is known about the underlying mechanisms (9,10).

The aim of the present analysis was to investigate the temporal association between device-detected atrial high-rate episodes (AHREs), including AF, atrial flutter, and atrial tachycardias, and the risk of VA in patients with remotely monitored implantable cardioverter-defibrillators (ICD), with or without cardiac resynchronization therapy with a defibrillator (CRT-D).

METHODS

ANALYSIS OBJECTIVE AND PROJECT DESIGN. Data from the Home Monitoring Expert Alliance (HMEA) database were analyzed (11). HMEA is an independent project that pools remote monitoring (RM) data from cardiac implantable electronic devices during routine follow-up for specific analyses on investigators' demand. The present analysis was proposed by the first author and approved by an executive committee consisting of 7 members from sites that contributed the highest data volumes with 2-year renewal. Forty-one HMEA centers listed in the Online Appendix contributed to data pooling. All patients gave written informed consent before RM activation. The HMEA project was approved by competent ethics committees.

RM SYSTEM AND DIAGNOSTIC DATA. RM data were generated during ordinary medical practice from ICD and CRT-D devices equipped with home monitoring technology (Biotronik SE KG & Co., Berlin, Germany), based on daily Global System for Mobile (GSM) communications from the device to a central service center through a mobile patient unit.

VAs were evaluated by intracardiac electrogram (EGM) registrations. EGM recordings included pre-episode, detection, and post-therapy sections with 3-channel signals from the atrial, right ventricular, and left ventricular electrodes, or the far-field signal (**Figure 1**).

AHRE detection was based on the high atrial rate criterion programmed with nominal settings (200 beats/min threshold rate). For each patient, we retrieved AHRE burden, defined as the percentage of time spent in AHREs in a single day. Persistent forms of AHREs were included in the analysis.

ANALYSIS ENDPOINTS. The primary endpoint of the analysis was the frequency of VA episodes preceded by AHREs within 48 h (AHRE-48-VA). Multiple VA episodes that occurred within the same day were aggregated.

Further endpoints were the association between VA occurrence and AHRE incidence, and the rate of VA recurrences in the groups of patients with and without AHRE-48-VA episodes.

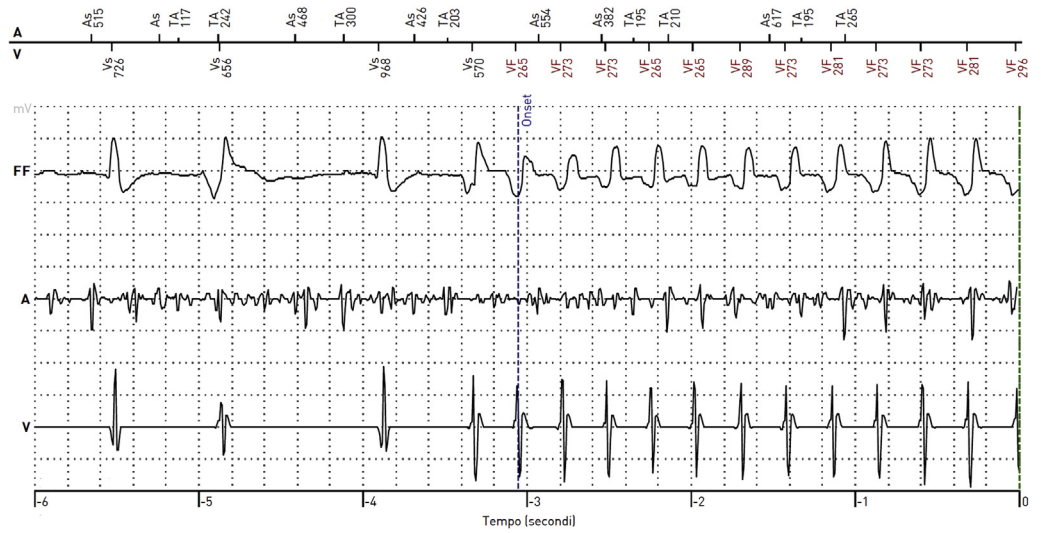
Association of VA occurrence with AHRE incidence was investigated by dividing individual follow-up periods in 30-day intervals and modeling the risk of VA occurrence in each interval as a function of AHRE occurrence in the same interval. A schematic representation of the analysis is provided in **Figure 2**. Measure of association was expressed as the odds ratio (OR) of VA occurrence in a 30-day interval with AHREs versus a 30-day interval without AHREs. Several cumulative daily AHRE burden cutoffs were used for the analysis (any duration, ≥3, ≥6, ≥12, ≥18, and 24 h). Age, sex, ischemic cardiomyopathy, beta-blockers at baseline, secondary prevention of sudden death, left ventricular ejection fraction, history of paroxysmal and persistent AF, and indication for CRT were included as adjusted model covariates. Further details are reported in the Online Appendix.

Patients with appropriate VA detections were divided into 2 groups according to whether they had at least 1 AHRE-48-VA episode. Time to first VA

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 *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received January 24, 2019; revised manuscript received June 28, 2019, accepted June 28, 2019.

FIGURE 1 **Intracardiac Electrogram Registration of Arrhythmic Episode Remotely Transmitted**



Onset of ventricular tachycardia with a mean cycle length of 280 ms during ongoing atrial fibrillation. Signals are from atrial (A), right ventricular (V), bipolar electrodes, and ventricular coil to device can far-field (FF) electrodes.

recurrence was then calculated in both groups to investigate whether the presence of temporal connections between AHREs and VAs could predict an increased risk of subsequent VA recurrences. The all-cause mortality rate was also evaluated in these 2 subgroups.

PATIENT SELECTION. At the time of the present analysis, 2,971 patients with ICDs or CTR-D devices were included in the HMEA database. Of those, we selected only first-implant devices with atrial sensing capabilities. Patients with permanent AF at time of RM activation were excluded. Eventually, 2,435 patients who underwent implantation from 2007 to 2017 were eligible for the analysis.

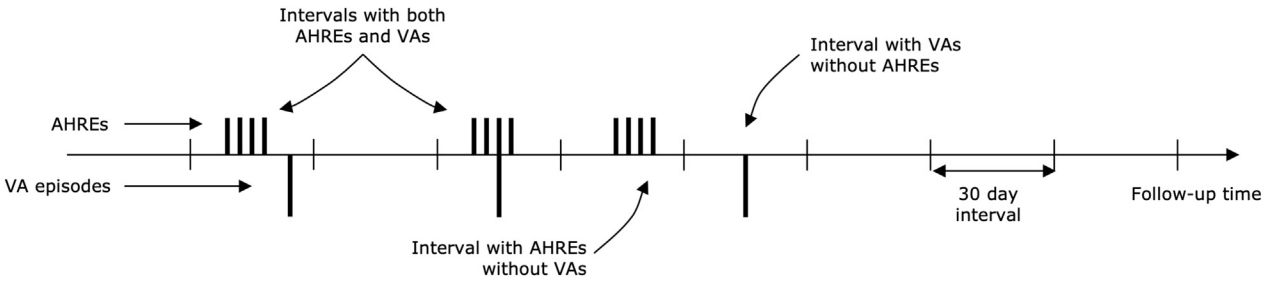
CLASSIFICATION OF VA EPISODES AND METHOD OF ADJUDICATION. As a large registry design, VA detection was programmed according to routine care in all devices. However, it reflected standard programming schemes with limited interindividual variability. The ventricular fibrillation (VF) detection zone was programmed between 270 and 300 ms in 91% of patients; 98% of devices had at least 1 active VT detection zone (including monitoring zones), 80% of which were programmed within the 50 ms range from 350 to 400 ms. Median Detection counters were 28 (interquartile range: 26 to 40) for device VT zones and 12 (8 to 18) of 16 (12 to 24) for VF zones.

VAs were a posteriori reclassified as follows: 1) any VA episode detected in 1 of the 2 available VT detection zones was classified as VT; 2) any VA episode detected in the device VF zone, but still showing regular cycles (≤25% stability limit) was classified as fast VT; 3) any VA episode with an irregular cycle detected in the VF zone, followed by a an aborted shock, was classified as a self-extinguishing VF; and 4) any VA episode detected in the VF zone with an irregular cycle and treated with delivered shocks was classified as VF.

All available 3-channel EGM recordings relative to VA episodes, as well as to AHREs detected within 1 month before VA episodes, were adjudicated by a 3-member board blinded to investigational sites. A 2-stage adjudication process was applied during EGM visual inspection: the first stage consisted of an algorithmic application of objective electrophysiological criteria, including comparison of atrial and ventricular cycle length; atrioventricular decoupling; and unstable ventricular rhythm during supraventricular tachyarrhythmias. The second stage was adjudication by majority vote, whenever objective criteria were not possible or uncertain.

STATISTICAL ANALYSIS. Continuous variables were reported as median (interquartile range), binary or categorical variables as percentages, and rates as 100 patient-years. Between-group comparisons were

FIGURE 2 Representation of the Analysis of Temporal Connection of AHREs to VAs



After dividing follow-up into 30-day intervals, probability of ventricular arrhythmia (VA) occurrence in any interval was modeled conditional for the presence of atrial high-rate episodes (AHREs) in the same interval using multivariable logit generalized estimating equations with an exchangeable correlation matrix and several covariates (including age, sex, ischemic cardiomyopathy, beta-blockers at baseline, secondary prevention of sudden death, left ventricular ejection fraction, and history of paroxysmal and persistent atrial fibrillation). We reported the model conditional probability in terms of the odds ratio of VA occurrence in any 30-day interval with AHREs versus intervals without AHREs. We used several daily cutoffs for cumulative daily AHRE burden to be included in the model as potential risk predictors (any duration, ≥3, ≥6, ≥12, ≥18, and ≥24 h).

performed with the Mann-Whitney U-test for continuous variables, and with Pearson's chi-square or Fisher's exact tests for binary or categorical variables. Comparisons of frequency of AHREs 48 h before a VA episode among VA types was performed with generalized estimating equations (GEE) using the logit link function and exchangeable "sandwich" correlation matrix. GEEs were also used to evaluate association of VA occurrence and AHREs, reporting odds ratios (ORs) and 95% confidence intervals (CIs) of experiencing any VA episode in a 30-day interval with AHREs versus intervals without AHREs, adjusting by several model covariates as described previously. Kaplan-Meier curves were used to plot VA recurrence-free rates calculated with the product-limit method and compared between groups with the log-rank test. Sex- and beta-blocker–adjusted hazard ratios (HRs) and 95% CIs were estimated with proportional hazard shared-frailty Cox regression models using the investigational site as random effect variable. Statistical significance was set at $p = 0.05$ and adjusted with Bonferroni's correction in case of multiple comparisons. All analyses were performed with Stata software version 11.1 SE (StataCorp, College Station, Texas).

RESULTS

PATIENT POPULATION. The 2,435 patients included in the analysis were remotely monitored for a median of 25 months (interquartile range: 13 to 42 months), during which 734 patients experienced at least 1 appropriately detected VA episode and 153 patients (20.8% of patients with ≥1 VA occurrence) had at least 1 AHRE-48-VA episode. Complete patient characteristics are reported in the Table 1 for the following groups: 1) the whole population; 2) patients without any VA recurrence; 3) patients with VA occurrences never preceded by AHRE within 48 h; and 4) patients with at least 1 AHRE-48-VA episode. Most characteristics were not significantly different between patients with and without VA occurrences, although patients with VAs were younger, were more frequently male, and received an ICD device, likely due to higher prevalence of secondary prevention indication. The pharmacological therapy was also not significantly different among the latter groups. Conversely, patients with AHRE-48-VA episodes were older, had a higher prevalence of AF history, were in a higher New York Heart Association functional class, and had a higher percentage of CRT-D devices compared with patients with VAs never preceded by an AHRE within 48 h.

VA EPISODE OCCURRENCE. Of 4,205 days with ≥1 ventricular episodes detections, EGM recordings were available for 3,591 days (85.4%) and underwent the adjudication process. After the exclusion of 795 episodes (18.9% of all VA detections), a total of 3,410 episodes were classified as appropriate VAs (Figure 1): 1,670 episodes were VT (49.0%); 1,050 episodes were fast VT (30.8%); 613 episodes were self-extinguishing VF (18.0%), and 77 episodes were VF (2.2%). VT episodes were appropriately treated with 12,840 antitachycardia pacing bursts or ramps, of which 7,225 (56.3%) were successful. One-shot antitachycardia pacing bursts were attempted 2,693 times in fast VT, with 1,846 (68.5%) successes preventing as many full capacitor charging cycles. Globally, 8,455 appropriate

TABLE 1 Patient Characteristics

	All	Patients Without VAs	p Value*	Patients With VAs Never Preceded by AHRE within 48 h	p Value†	Patients With VAs Preceded by AHREs within 48 h
N	2,453	1,701 (69.8)		581 (23.9)		153 (6.3)
Median age (yrs)	70 (61-77)	70 (61-77)	0.006	68 (59-76)	<0.001	74 (67-78)
Sex (female)	20.4	21.5	0.02	17.0	0.001	10.5
NYHA functional class						
I	9.4	9.6	0.81	11.0	0.04	3.3
II	62.7	63.4		61.7		62.0
III	26.7	26.0		25.7		34.8
IV	1.1	1.0		1.6		0.0
LVEF (%)	30 (28-35)	30 (28-35)	0.88	30 (25-35)	0.62	30 (27-34)
QRS duration (ms)	120 (100-142)	120 (100-143)	0.25	120 (100-140)	0.32	122 (103-142)
CRT devices	45.2	47.6	<0.001	37.5	0.02	47.7
Comorbidities						
Diabetes	23.8	25.9	0.001	18.3	0.85	19.1
Chronic obstructive pulmonary disease	10.9	11.4	0.24	9.2	0.09	14.5
Stroke/TIA	8.9	8.7	0.43	9.9	0.70	8.7
Chronic kidney disease	12.8	13.1	0.49	11.8	0.90	12.3
Vascular disease	8.6	8.7	0.96	8.6	0.80	7.8
Cardiomyopathy						
CAD	51.4	52.2	0.20	48.7	0.36	53.6
Nonischemic DCM	35.1	34.4	0.25	37.4	0.57	34.5
Valvular	6.3	5.3	0.22	6.9	0.14	11.1
Hypertrophic	3.6	3.9	0.22	2.6	0.94	2.8
Congenital	2.3	2.4	0.72	2.7	0.09	0.0
History of arrhythmias						
Ventricular fibrillation	7.3	6.7	0.047	9.6	0.23	5.8
Sustained VT	14.4	11.4	<0.001	21.8	0.89	21.1
Non-sustained VT	19.0	18.6	0.60	19.7	0.74	21.1
Paroxysmal AF	8.1	8.4	0.01	4.7	<0.001	19.8
Persistent AF	5.1	5.0	0.06	2.9	<0.001	15.6
Therapy						
ACE inhibitors	55.1	56.5	0.17	52.8	0.30	47.4
Beta-blockers	75.9	75.6	0.78	76.2	0.51	79.1
Sartans	9.3	9.7	0.27	7.9	0.37	10.6
Diuretics	71.5	71.1	0.22	71.3	0.26	76.5
Calcium antagonists	5.7	5.9	0.72	5.5	0.73	4.6
Spironolactone	16.6	16.5	0.65	15.5	0.07	22.9
Digitalis	4.9	4.3	0.57	5.0	0.02	11.0
Ivabradine	6.7	7.2	0.29	5.7	0.59	4.3
Anticoagulants	24.2	23.6	0.46	22.0	<0.001	40.5
Antiplatelet	46.7	47.8	0.32	47.8	0.36	40.3
Amiodarone	13.9	13.0	0.09	16.1	0.91	16.5
Sotalol	1.5	1.2	0.58	1.6	0.16	3.8

Values are n (%), median (interquartile range), and percentages. Calculations were performed with available nonmissing data. *Results of comparisons of patients without ventricular arrhythmias (VAs) versus patients with VAs never preceded by atrial high-rate episodes (AHREs) within 48 h. †Results of comparisons of patients with VAs never preceded by AHREs within 48 h versus patients with VAs preceded by AHREs within 48 h.

ACE = angiotensin-converting enzymes; AF = atrial fibrillation; CAD = coronary artery disease; CRT-D = cardiac resynchronization therapy with defibrillator; DCM = dilated cardiomyopathy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack; VT = ventricular tachycardia.

shocks were started, and 4,836 (57.1%) were eventually delivered in 725 patients.

On a per-patient analysis, 380 (15.6%) patients experienced ≥1 VT episode, 321 (13.2%) patients had fast VT, 434 (17.8%) patients experienced self-extinguishing VF, and 75 (3.1%) patients had VF. The corresponding rates were 6.5, 5.5, 7.4, and 1.3 episodes per 100 patient-years, respectively.

AHRE INCIDENCE 48 H BEFORE VA EPISODES. Of the 3,410 appropriately detected VA episodes, 498 (14.6%) were preceded by AHREs within 48 h: 219 were

TABLE 2 Incidence of VAs and AHRE Within 48 h Before Episodes in the ICD and CRT Groups

	VT	p Value	Fast VT	p Value	Self-ex VF	p Value	VF	p Value
Patients with V episodes (n/100 patient-years)								
ICD	7.3	0.54	5.5	0.72	7.3	0.77	1.3	0.54
CRT	5.4		5.4		7.5		1.2	
All	6.5		5.5		7.4		1.3	
Patients with AHREs 48 h before days with V episodes								
Rate (n/100 patient-years)								
ICD	1.3	0.045	1.1	0.27	0.7	0.14	0.3	0.78
CRT	1.4		1.3		1.1		0.3	
All	1.3		1.2		1.0		0.3	
Percentage relative to number of patients with V episodes								
ICD	17.8		20.1		11.6		20.4	
CRT	26.7		25.4		16.7		23.3	
All	21.0%		22.3		13.7		21.6	

Values are %. The p values refer to the results of comparisons between CRT and ICD groups. CRT devices: n = 1,232 median follow-up: 23 months (range: 12 to 41 months). ICD devices: n = 1,383; median follow-up: 27 months (range: 14 to 44 months). Ventricular fibrilliations (VFs) are classifications or VAs (see text for definition).

Self-ex VF = self-extinguishing VF; V = ventricular; VT = fast ventricular tachycardia; other abbreviations as in Table 1.

VT (13.1%); 177 were fast VT (16.9%); 86 were self-extinguishing VF (14.0%); and 16 were VF (20.8%). Four hundred sixty-one of the 498 (92.5%) episodes occurred the same day, and 426 (85.5%) were dual arrhythmias with AHREs still ongoing during VA onset. On average, about one fifth of patients with VAs had AHREs within the preceding 48 h: 21.0% had AHREs within 48 h before VT; 22.3% had AHREs before fast VT, 13.7% had AHREs before self-extinguishing VF; and 21.6% had AHREs before VF. Differences among VA types were not statistically significant at GEE analysis. Further details are reported in Table 2, together with comparisons between patients with CRT and ICDs with no significant results.

ASSOCIATION OF DAILY AHRE BURDEN WITH RISK OF VA EPISODES. Analyzing 30-day intervals of individual follow-ups, there were 9,551 intervals with AHRE burden, 591 of which (6.2%) included ≥1 VA episodes. Figure 3 displays examples from 5 patients who had VA episodes occurring shortly after initiation of periods with AHREs. In a longitudinal multivariable GEE analysis, AHREs of any duration were an independent predictor of an increased risk of VA occurrence in 30-day intervals. Adjusted ORs of experiencing VA episodes in any interval with AHREs ranged between 1.84 and 3.06 versus intervals without AHREs, which reached statistical significance in all VA types (Figure 4). Only secondary prevention of sudden death was significant among model covariates: the OR of experiencing any VA in secondary prevention versus primary prevention was 2.20 (95% CI: 1.77 to 2.73; $p < 0.001$). Online Table 1 provides detailed results of the GEE analysis of VA risk in 30-day intervals with AHREs versus intervals without AHREs, confirming the statistically significant association of VA with AHREs in both subgroups of primary and secondary prevention as indication for ICD.

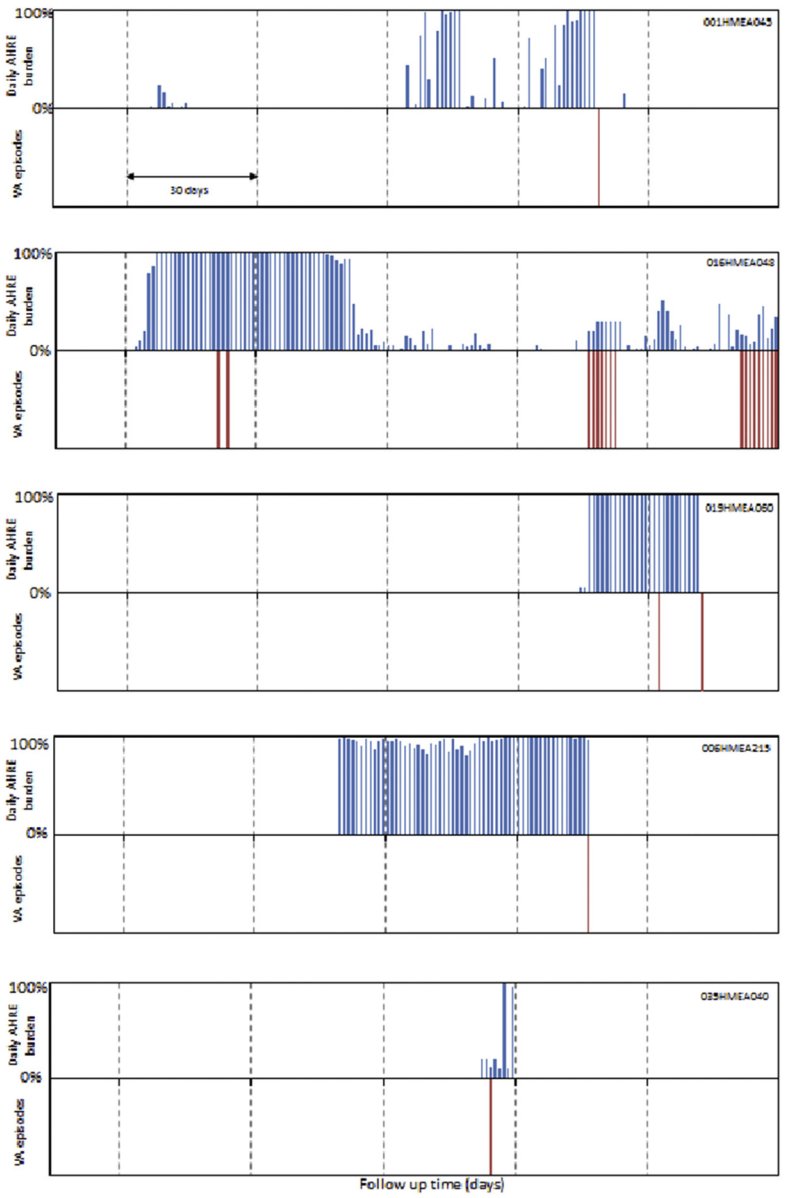
As shown in Figure 4, ORs increased with decreasing AHRE burden in all forms of VAs, consistent with shorter AHREs being more frequently associated with VA occurrences. Statistical significance was lost soon after 3-h AHRE burden for VT, whereas statistical significance in more aggressive forms of VAs, as fast VTs and self-extinguishing VFs, persisted up to ≥12-h AHREs.

EFFECT OF AHRE ON VA RECURRENCE AND SURVIVAL. Patients with any AHRE preceding VA were more likely to experience VA recurrences (HR: 1.78; 95% CI: 1.41 to 2.24; $p < 0.001$) after adjusting for sex and beta-blocker therapy. In patients with AHRE-48-VAs, median time to subsequent VA episode was 4.5 months (95% CI: 1.9 to 6.5 months), whereas in patients without AHREs 48 h before VAs, the median time to a subsequent episode was 21.1 months (95% CI: 13.9 to 38.9 months); the Kaplan-Meier plot is shown in Figure 5A. The group of patients with AHRE-48-VAs also showed a decreased 5-year survival (Figure 5B) compared with the group with VAs never preceded by AHREs within 48 h (all-cause mortality rate of 5.9 per 100 patient-years vs. 2.5 per 100 patient-years; sex- and beta-blocker–adjusted HR: 2.67; 95% CI: 1.68 to 4.23; $p < 0.001$). Differences in survival persisted after excluding patients with a history of AF (4.8 × 100 patient-years vs. 2.6 × 100 patient-years; $p = 0.004$).

DISCUSSION

In a large series of patients with RM ICD and CRT-D devices, we detected a temporal relationship between VAs and AHREs in approximately 20% of patients who experienced a sustained VA. On a longitudinal analysis, 30-day intervals with AHREs were associated with a 2- to 3-fold increased risk of VA occurrence compared with AHRE-free intervals, with the association decreasing with higher AHRE burdens. Patients with AHREs 48 h before any VA episode had 78% increased risk of experiencing VA recurrences, with a median time to recurrence of 4.5 months, and lower 5-year survival compared with patients who never presented with AHREs 48 h before a ventricular episode (Central illustration).

FIGURE 3 **Temporal Distribution of VAs Relative to AHREs**

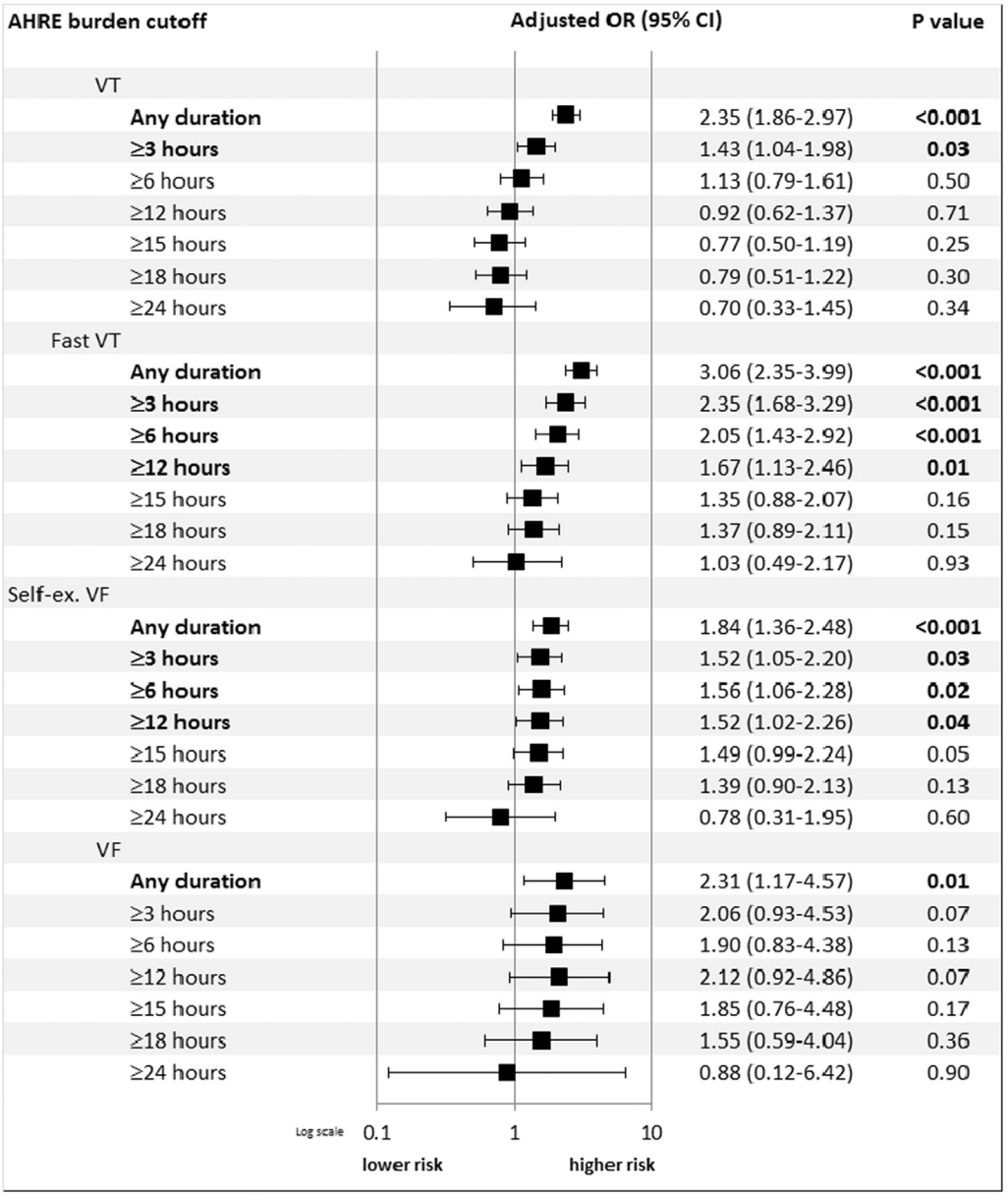


Examples from 5 patients with VA episodes **(red vertical lines)** and daily percentage with AHRE burden **(blue vertical lines)** reported along the horizontal time axis (follow-up days). Segments of 30 days are highlighted. The plots show several AHRE burden days distributed around VA episodes. Abbreviations as in Figure 2.

DOES AF TRIGGER VENTRICULAR ARRHYTHMIAS?

In our study, AHREs frequently occurred during the 48 h preceding VAs, and were detected by the RM system in approximately 20% of patients with VAs. Similarly, Stein et al. (12) showed that 8.6% of VT/VF episodes in their cohort of ICD recipients occurred during ongoing atrial tachycardias or AF episodes, and 20% of the patients with VT/VF events had at least 1 dual tachycardia episode. Our results were in line with these data, because we observed that 14.5% of VAs was preceded by AHRE episodes within 48 h, as well as 6.2% of 30-day intervals with AHRE episodes presented with at least 1 VA episode. However, our findings were additive because we showed that, although AHREs could not be considered efficient predictors due to low specificity, AHREs were an

FIGURE 4 VA Risk in 30-Day Intervals With AHREs



Forest plot showing the results of a longitudinal analysis reporting adjusted odds ratio of VA occurrence in 30-day intervals with AHREs versus intervals without AHREs. CI = confidence interval; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Figure 2.

independent risk factor of VA occurrence. Although most VAs were not preceded by AHREs and most AHREs were not associated with VAs, our analysis showed that temporal connection between AHREs and VAs was not rare in patients with VAs. When present, the temporal connection was associated with increased risk of subsequent VA recurrences with shorter recurrence time and worse prognosis. We used GEEs to reflect the longitudinal structure of the data and to model the probability of finding a VA episode in any 30-day interval marginal to the presence of AHREs in the same interval. The AHRE component in the model was statistically significant, independent of the adjusting covariates, including history of paroxysmal and persistent AF, which was relatively more frequent in the group with AHREs

preceding VAs (Table 1). Our analysis showed that the probability of experiencing a ventricular episode was higher in 30-day intervals with AHREs compared with intervals without AHREs, even after adjusting for a history of AF, thus providing evidence that VAs tend to be distributed in days with AHREs.

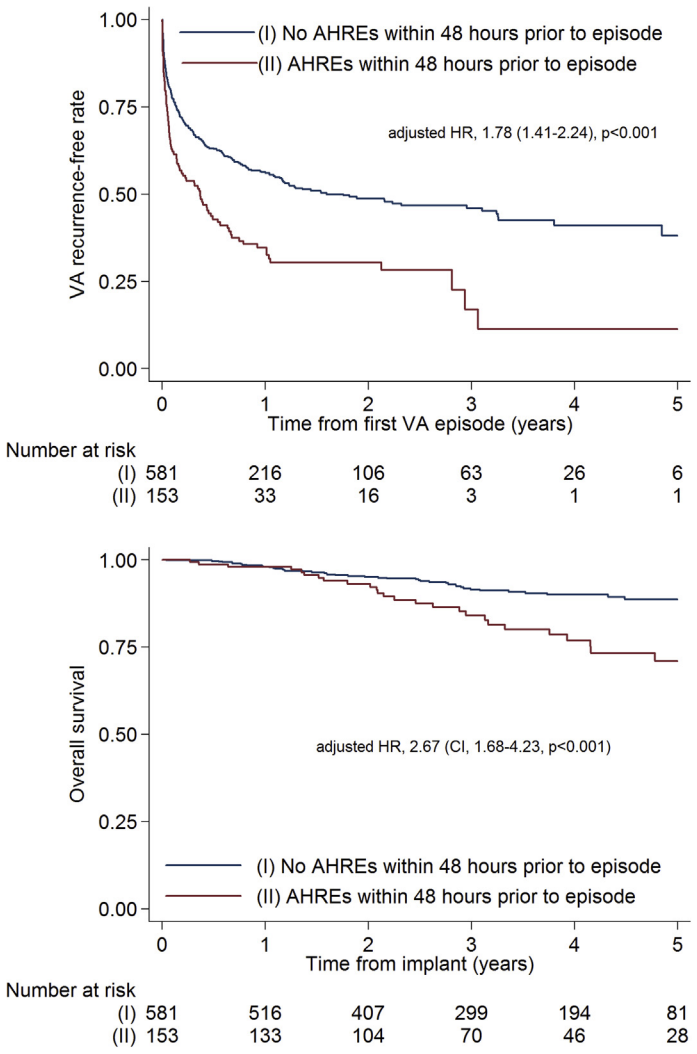
Risk of VAs was higher during the first hour after AHREs onset, as shown by the decreasing VA risk with higher AHRE burden cutoffs. Risk of fast forms of VA (VF and self-extinguishing VF) persisted up to 12 h from AHRE onset, whereas it faded after 3 h in VTs. Although a complete explanation of the underlying mechanism was not straightforward, the finding did not support the hypothesis of a dose-dependent relationship between AF and VA in the short term, and it might suggest a rapid effect of atrial arrhythmias on the ventricular arrhythmic substrate. Ventricular rate immediately after AF onset is usually faster than that in the subsequent hour. This might be due to a shift toward a lower level of sympathetic activity after the initial increase (13) or activation of compensatory molecular mechanisms, such as the progressive reduction of fully active calcium ions observed in permanent AF (14).

MECHANISM OF VA ONSET DURING AHREs. Several electrophysiological mechanisms have been proposed to explain the onset of VA during AHREs. Rapid ventricular rates during an atrial tachyarrhythmia directly reduce ventricular refractoriness, and the irregular rhythm of AF leads to short-long-short sequences that may be pro-arrhythmic (15). Gronefeld et al. (16) noticed an arrhythmia onset pattern with a typical short-long-short sequence in which the short-coupled beat was morphologically different from sinus rhythm; this indicated a triggered ventricular activation that is more frequently observed in patients with AF compared with patients in sinus rhythm. Atrial tachyarrhythmias may also indirectly affect ventricular electrophysiology through pro-arrhythmic hemodynamic and neurohormonal changes, such as altered mechano-electrical coupling (17), increased sympathetic tone (18), and ischemia.

Our analysis could not provide evidence of any causal relationship between AHREs and VA onset. Beyond purely electrophysiological or neurological mechanisms, AHREs temporally close to VAs may certainly relate to clinical events, such as worsening cardiomyopathy and heart failure decompensation that likely predispose to ventricular arrhythmias.

Distinguishing between AHREs that are temporally closed but are still separate and AHREs that are ongoing during VA onset might be potentially important, because in the former case, it would suggest that there might be a common mechanism (ultimately related to worsening cardiomyopathy or exacerbating heart failure) that triggers both arrhythmias independently. However, in the latter case, the linkage might be more causal, with AHREs providing an electrophysiological trigger for VA onset. Whether the latter mechanism is prevalent could not be assessed by our analysis, but the hypothesis would be consistent with the observation

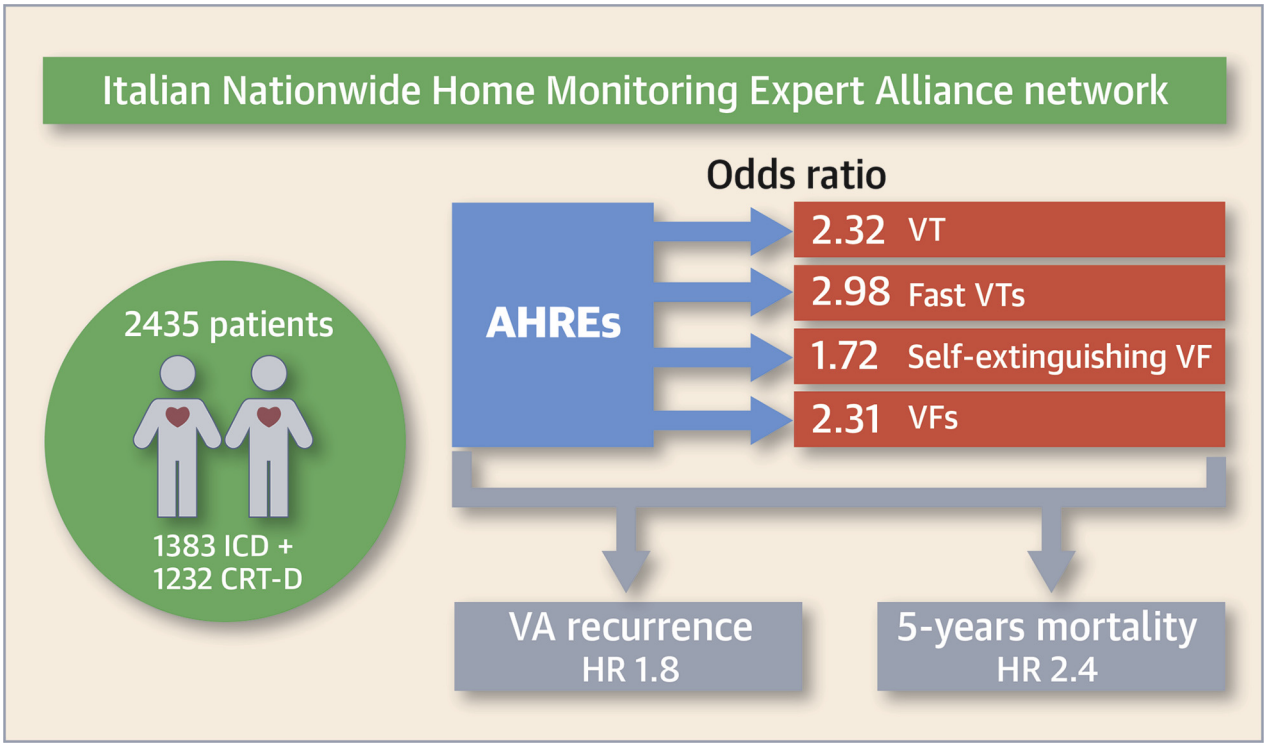
FIGURE 5 Kaplan-Meier Plots and Survival Estimates



(A) Kaplan Meier plots of time to VA recurrence after a first episode. Times were rescaled at first VA episode. **(B)** Kaplan-Meier survival estimates. The 734 patients with ventricular episodes were divided into **(I)** the group of patients who never experienced AHREs in 48 h before ventricular episodes (n = 581; **blue line**) and **(II)** patients who experienced at least1 ventricular episode with AHREs in the preceding 48 h (n = 153; **red line**). HR = hazard ratio; other abbreviations as in Figure 2.

print & web 4C/FPO

CENTRAL ILLUSTRATION **Clinical Relevance of the Association Between AHREs and VAs**



Vergara, P. et al. J Am Coll Cardiol EP. 2019;■(■):■–■.

In a cohort of 2,435 patients with implantable cardioverter-defibrillator (ICD) and/or cardiac resynchronization therapy with defibrillator (CRT-D) devices, temporal connection of atrial high-rate episodes (AHREs) with ventricular arrhythmias (VAs) was statistically significant. Thirty-day intervals with AHREs were associated with 1.84 to 3.06 adjusted odds ratio of VA versus intervals without AHREs. Patients with VAs preceded by AHREs within 48 h were exposed to a high risk of VA recurrence and 5-year mortality. HR = hazards ratio; VF = ventricular fibrillation; VT = ventricular tachycardia.

that AHREs were still ongoing in 85% of VAs with detections of AHREs within the preceding 48 h.

AF AND MORTALITY. For decades, the main clinical risk of AF was considered related to thromboembolic events. However, in Olmsted County adult residents (19), 4,500 patients with AF showed a 2-fold higher mortality risk than control subjects; the risk was highest within the first 4 months after the first AF diagnosis and decreased thereafter. In patients with severe left ventricular dysfunction, history of AF was also associated with significant comorbidities that translated into higher long-term risks of adverse events (20,21). These observations raised the question whether the increase in mortality was linked to the effects of comorbidities or if there was any independent effect of AF itself. Data provided by Bunch et al. (22) favored the latter hypothesis, showing that, in patients with no history of AF, the risk for death dramatically increased from 3.2% to 8.9% when they developed AF shortly after receiving an ICD. AF and ejection fraction were independent predictors of overall and arrhythmic mortality also in patients with heart failure. Patients with new-onset AF had a higher mortality rate (42% over 2.6 years) compared with both no AF (10%) and persistent AF (16%) groups (23).

Our data were in line with these observations because we found that patients with AHRE-48-VAs showed more than double 5-year mortality compared with patients with ventricular episodes that never preceded by AHREs.

CLINICAL IMPLICATIONS OF AF ONSET IN HEART FAILURE PATIENTS. In a time when the scientific debate is under way on the clinical relevance of AHREs in relation to the risk of stroke (24–27), our results brought to light an additional aspect—warning against underestimating AHREs when temporally connected to VAs. Patients with heart failure and AHREs (including short episodes) might still be

exposed to higher risk of ventricular arrhythmias, despite a relatively lower risk of stroke compared with clinical AF.

Patients with AHRE preceding a VA showed a 78% increased risk of VA recurrences in our study, which was again consistent with previous observations (12,28). These findings reinforced the importance of RM for continuous surveillance and early alerts in patient management and identification of the most suitable therapeutic intervention, including start of oral anticoagulation, antiarrhythmic therapy optimization and, when appropriate, non-pharmacological rhythm control strategies. AF catheter ablation was shown to reduce ICD therapies, improve ejection fraction (29), survival (30), reduce hospitalization for worsening heart failure, and deaths from cardiovascular causes (31).

STUDY LIMITATIONS. This study was observational and retrospective; therefore, it had several limitations, including lack of uniform procedures. Although we detailed clinical information at the time of device implantation, we did not have data about changes in patient status and medical therapy during follow-up. However, our analysis was based on a large data repository generated by daily RM of devices that provided comprehensive information on arrhythmias, which reduced the risks of underreporting and reflected current medical care in ordinary settings. Also, the adjudication process was extended to available EGM recordings of AHREs that occurred at onset and during up to 1 month before all appropriate VAs. Full EGM review of all AHREs over complete episode duration was definitely not possible with any currently available cardiac implantable electronic device and RM technology, because AHRE duration could range from a few minutes to several days, whereas EGM recordings were available for seconds at AHRE onset and during VA episodes. However, RM was shown to be a reliable tool for monitoring atrial arrhythmias. It is a class I indication for early detection and quantification of AF (32).

Finally, it should be also emphasized that we studied a particular population with current indications for ICD and/or CRT; therefore, extrapolation to other populations is not straightforward.

CONCLUSIONS

In our analysis, patients having AHREs 48 h before any ventricular episode showed a higher ventricular recurrence rate and poorer prognosis. Although our results could not prove a causal relationship, the observed temporal connection between AHREs and VAs might point to a pro-arrhythmic effect of AHREs as well as a marker of a period of both atrial and ventricular arrhythmia susceptibility.

ACKNOWLEDGMENTS The authors would like to thank Paolo Ballati for essential assistance in data management and Xenia Antoniou for text revision and scientific advice. And the authors are grateful to all field engineers of BIOTRONIK Italia for their continuous technical support.

ADDRESS FOR CORRESPONDENCE: Dr. Pasquale Vergara, Arrhythmia Unit and Electrophysiology Laboratory, Department of Cardiology and Cardiothoracic Surgery, Ospedale S. Raffaele, Milano, Italy. E-mail: pasqualevergara@hotmail.com.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AF is known to be associated with increased risk of thromboembolic events. RM of cardiac implantable electronic devices has been shown to favor early detection and quantification of AHREs and arrhythmia burden. Early reactions guided by alerts from a RM system based on daily transmissions resulted in lower all-cause mortality in patients with heart failure.

TRANSLATIONAL OUTLOOK 1: In patients with ventricular dysfunction, the risk of sustained VAs was significantly higher in periods with AHREs, including short (<12 h) episodes.

TRANSLATIONAL OUTLOOK 2: Patients with VAs preceded by or during AHREs are exposed to an increased risk of VA recurrences and overall mortality. Future studies are needed to evaluate whether a timely treatment of VAs preceded by AHREs improves patients' outcomes.

REFERENCES

1. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al., ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015;36:2793–867.

2. Benjamin EJ, Virani SS, Callaway CW, et al., American Heart Association Council on

Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018; 137:e67–492.

3. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933–40.

4. Bardy GH, Lee KL, Mark DB, et al., Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.

5. Sapp JL, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. N Engl J Med 2016;375:111–21.

6. Tung R, Vaseghi M, Frankel DS, et al. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: An International VT Ablation Center Collaborative Group study. Heart Rhythm 2015;12:1997–2007.

7. Lee H, Shin SY, Seo M, Nam GB, Joo S. Prediction of ventricular tachycardia one hour before occurrence using artificial neural networks. Sci Rep 2016;6:32390.

8. Ulus T, Kudaiberdieva G, Gorenek B. The onset mechanisms of ventricular tachycardia. Int J Cardiol 2013;167:619–23.

9. Andersson T, Magnuson A, Bryngelsson IL, et al. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. Eur Heart J 2013;34:1061–7.

10. Botto GL, Dicandia CD, Mantica M, et al. Clinical characteristics, mortality, cardiac hospitalization, and ventricular arrhythmias in patients undergoing CRT-D implantation: results of the ACTION-HF study. J Cardiovasc Electrophysiol 2013;24:173–81.

11. Rovaris G, Solimene F, D'Onofrio A, et al. Does CHA2DS2-VASc Score reliably predict atrial arrhythmias? Analysis of a nationwide database of remote monitoring data daily transmitted from cardiac implantable electronic devices. Heart Rhythm 2018;15:971–9.

12. Stein KM, Euler DE, Mehra R, et al., Jewel AF Worldwide Investigators. Do atrial tachyarrhythmias beget ventricular tachyarrhythmias in defibrillator recipients? J Am Coll Cardiol 2002;40: 335–40.

13. Uradu A, Wan J, Doytchinova A, et al. Skin sympathetic nerve activity precedes the onset and termination of paroxysmal atrial tachycardia and fibrillation. Heart Rhythm 2017;14:964–71.

14. Workman AJ, Kane KA, Rankin AC. The contribution of ionic currents to changes in refractoriness of human atrial myocytes associated with chronic atrial fibrillation. Cardiovasc Res 2001;52:226–35.

15. Denker S, Lehmann MH, Mahmud R, Gilbert C, Akhtar M. Facilitation of macroreentry within the His-Purkinje system with abrupt changes in cycle length. Circulation 1984;69:26–32.

16. Gronefeld GC, Mauss O, Li YG, Klingenheben T, Hohnloser SH. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. J Cardiovasc Electrophysiol 2000;11: 1208–14.

17. Lerman BB. Mechanoelectrical feedback: maturation of a concept. J Cardiovasc Electrophysiol 1996;7:17–9.

18. Lown B, Verrier RL. Neural activity and ventricular fibrillation. N Engl J Med 1976;294: 1165–70.

19. Miyasaka Y, Barnes ME, Bailey KR, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol 2007;49:986–92.

20. 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.

21. Dries DL, Exner DV, Gersh BJ, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1998;32:695–703.

22. Bunch TJ, Day JD, Olshansky B, et al., INTRINSIC RV Study Investigators. Newly detected atrial fibrillation in patients with an implantable cardioverter-defibrillator is a strong risk marker of increased mortality. Heart Rhythm 2009;6:2–8.

23. Corell P, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail 2007;9: 258–65.

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

25. Mahajan R, Perera T, Elliott AD, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. Eur Heart J 2018;39:1407–15.

26. Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. Am Heart J 2017;189: 137–45.

27. Kirchhof P, Blank BF, Calvert M, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. Am Heart J 2017;190:12–8.

28. Borleffs CJ, Ypenburg C, van Bommel RJ, et al. Clinical importance of new-onset atrial fibrillation after cardiac resynchronization therapy. Heart Rhythm 2009;6:305–10.

29. Kosiuk J, Nedios S, Darma A, et al. Impact of single atrial fibrillation catheter ablation on implantable cardioverter defibrillator therapies in patients with ischaemic and non-ischaemic cardiomyopathies. Europace 2014;16:1322–6.

30. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. Circulation 2016;133:1637–44.

31. Marrouche NF, Brachmann J, Andresen D, et al., CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417–27.

32. Slotwiner D, Varma N, Akar JG, et al. HRS Expert Consensus Statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. Heart Rhythm 2015;12:e69–100.

KEY WORDS **atrial fibrillation, atrial high rate episodes, implantable cardioverter-defibrillator, ventricular arrhythmias, ventricular tachycardia**

APPENDIX **For a list of investigational sites and a supplemental table, please see the online version of this manuscript.**

Are Atrial High-Rate Episodes Associated With Increased Risk of Ventricular Arrhythmias and Mortality?

Pasquale Vergara, Francesco Solimene, Antonio D'Onofrio, Ennio C. Pisanò, Gabriele Zanotto, Carlo Pignalberi, Saverio Iacopino, Giampiero Maglia, Paolo Della Bella, Valeria Calvi, Antonio Curnis, Gaetano Senatore, Mauro Biffi, Alessandro Capucci, Quintino Parisi, Fabio Quartieri, Fabrizio Caravati, Massimo Giammaria, Massimiliano Marini, Antonio Rapacciuolo, Michele Manzo, Daniele Giacopelli, Alessio Gargaro, Renato P. Ricci

This study interrogated the database of the Home Monitoring Expert Alliance network to analyze data from 2,435 patients with remotely monitored implantable cardioverter-defibrillator and cardiac resynchronization therapy devices to evaluate the temporal association between atrial high-rate episodes (AHREs) and ventricular arrhythmias (VAs). AHREs were ongoing 48 h before or during VAs in 14.6% of all VA episodes. Thirty-day intervals with AHREs were associated with 2- to 3-fold increased risk of VAs versus intervals without AHREs. Patients with AHREs 48 h before VAs had a higher VA recurrences rate and overall mortality. Our findings might help outlining clinical relevance of AHREs when temporally associated with VAs in patients with ventricular dysfunction.

oooo