Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.04.019

Clinical Classifications of Atrial Fibrillation Poorly Reflect Its Temporal Persistence

Insights From 1,195 Patients Continuously Monitored With Implantable Devices

Efstratios I. Charitos, MD,* Helmut Pürerfellner, MD,† Taya V. Glotzer, MD,‡ Paul D. Ziegler, MS§

Luebeck, Germany; Linz, Austria; Hackensack, New Jersey; and Minneapolis, Minnesota

Objectives This study aimed to identify how accurately the current clinical atrial fibrillation (AF) classifications reflect its temporal persistence.

Background Clinical classification of AF is employed to communicate its persistence, to select appropriate therapies, and as inclusion criterion for clinical trials.

Methods Cardiac rhythm histories of 1,195 patients (age 73.0 ± 10.1 years, follow-up: 349 ± 40 days) with implantable devices were reconstructed and analyzed. Patients were classified as having paroxysmal or persistent AF by physicians at baseline in accordance with current guidelines. AF burden, measured as the proportion of time spent in AF, was obtained from the device. Additionally we evaluated the agreement between clinical and device-derived AF classifications.

Results Patients within the same clinical class were highly heterogeneous with regards to AF temporal persistence. Agreement between the clinical AF classification and the objective device-derived assessments of AF temporal persistence was poor (Cohen's kappa: 0.12 [95% CI: 0.05 to 0.18]). Patient characteristics influenced the clinical decision to classify AF as paroxysmal or persistent. Higher ejection fraction (odds ratio: 0.97/per unit [95% CI: 0.95 to 0.98/per unit]; $p < 0.0001$) and presence of coronary artery disease (odds ratio: 0.53 [95% CI: 0.32 to 0.88]; $p = 0.01$) were independently associated with a lower probability of being classified as persistent AF for the same AF burden level.

Conclusions The currently used clinical AF classifications poorly reflect AF temporal persistence. Patient characteristics significantly influence the physician's classification of AF. Patients classified in identical clinical categories may be inherently heterogeneous with regard to AF temporal persistence. Further study is required to determine if patient selection on the basis of objective criteria derived from rigorous AF monitoring can improve reported outcomes and better identify responders and non-responders to treatments. (OMNI Study–Assessing Therapies in Medtronic Pacemaker, Defibrillator, and Cardiac Resynchronization Therapy Devices; NCT00277524; TRENDS: A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics; NCT00279981) (J Am Coll Cardiol 2014;63:2840–8) © 2014 by the American College of Cardiology Foundation

The clinical classifications of atrial fibrillation (AF) are employed to communicate the persistence of AF, to select appropriate candidates for therapies, and as inclusion criterion for patients in clinical trials. Therefore it is important for these classifications to accurately characterize the magnitude and scale of the arrhythmia.

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The 2006 American Heart Association (AHA) guidelines (1) classify AF as *first detected episode of AF*, *paroxysmal* (spontaneously terminating AF sustained for <7 days), *persistent* (when episodes are sustained for >7 days), and *permanent* (when cardioversion attempts have failed or have been foregone). In a manner similar to the AHA guidelines (1), the European Society of Cardiology guidelines (2) distinguish between *first diagnosed AF*, *paroxysmal* (self-terminating AF lasting no longer than 7 days), *persistent* (AF episode lasting >7 days or requiring some form of

From the *Department of Cardiac and Thoracic Vascular Surgery, University of Luebeck, Luebeck, Germany; †Department of Cardiology, Elisabethinen University Teaching Hospital, Linz, Austria; ‡Cardiac Research, Hackensack University Medical Center, Hackensack, New Jersey; and the §Department of Diagnostics and Monitoring Research, Medtronic Inc., Minneapolis, Minnesota. Presented at the 2013 American Heart Association Scientific Sessions, Dallas, Texas, November 16 to 20, 2013. Dr. Pürerfellner is a consultant for Medtronic. Mr. Ziegler is a stockholder and full-time employee of Medtronic (>$10,000). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 17, 2014; revised manuscript received March 2, 2014, accepted April 3, 2014.

pharmacological or electrical cardioversion), *long-standing persistent* (AF lasting ≥1 year and a rhythm control strategy is decided), and *permanent* (when the arrhythmia is accepted and rhythm control is no longer pursued). Both statements recognize the high uncertainty in diagnosing AF on the basis of symptoms (1–4) or intermittent rhythm monitoring (1,2,5,6).

These clinical classifications are used to individualize the choice of rate or rhythm control strategies and to select appropriate medical or interventional therapies for each AF patient. For example, although patients classified as having paroxysmal or persistent AF are generally indicated for rhythm control, patients with permanent AF are usually treated with rate control strategies. Additionally, the success of cardioversion efforts has been shown to be related to the duration of AF, which is partly communicated through the AF classification (1,7).

The clinical AF classifications are also employed to select patients for inclusion in clinical trials (8) with the primary intention to build groups of patients with similar arrhythmia magnitude and persistence in order to draw valid inferences regarding the effect of a treatment between the control and the treatment group.

The aim of the present study was 2-fold. First, we sought to assess how accurately the clinical AF classifications ("paroxysmal," "persistent") reflect the temporal persistence of AF (i.e., how much time a patient is in AF). Second, we assessed the homogeneity of patients classified in the same clinical AF classification. To accurately evaluate the temporal persistence of AF, we analyzed patients who were continuously monitored via implantable devices.

Methods

Population characteristics. We included patients enrolled in the OMNI (9) and TRENDS (10–13) clinical trials. In brief, the inclusion criteria for the OMNI trial were the presence of a specific model of Medtronic (Minneapolis, Minnesota) device (InSync Sentry [CRT-D], EnTrust [ICD-VR and DR systems], Instrinsic [ICD-DR], and EnRhythm [IPG-DR]) in patients 18 years of age or older. Inclusion criteria for the TRENDS study were an established Class I/II indication for an implantable cardiac rhythm device capable of long-term trending of atrial tachycardia or AF burden and at least 1 of the following risk factors for stroke: congestive heart failure, hypertension, 65 years of age or older, diabetes mellitus, or prior stroke or transient ischemic attack. In the OMNI trial, single chamber devices and devices that did not have an atrial lead were excluded because of their inability to detect AF. Patients from the TRENDS trial were excluded from this analysis if they had an attempted cardioversion or AF ablation anytime during follow-up, underwent device replacements, already had permanent atrial tachycardia/AF, had known re-entrant supraventricular tachycardia, or had a terminal illness.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CRT = cardiac resynchronization therapy
LVEF = left ventricular ejection fraction
OR = odds ratio

From the initial population of the OMNI (n = 737) and TRENDS (n = 598) trials and for the purposes of the present analysis, we excluded 60 patients with AF specific treatments (medical/electrical cardioversion or catheter ablation), 27 patients with single chamber devices, and 7 patients in whom no atrial lead was implanted. The total population (n = 1,195) included patients with at least 180 days of documented rhythm history from the device trending data (Cardiac Compass, Medtronic Inc., Minneapolis, Minnesota) and the analyzed follow up duration was limited to 365 days in order to avoid having progression of AF as a confounding factor.

Clinical AF classification was performed according to AHA guidelines just prior to device implantation (1). The OMNI and TRENDS trials studied the magnitude of AF on clinical outcomes and collected data on patients' clinical management, and careful attention was paid to the clinical classification of the patients' AF according to the AHA guidelines (1).

Additionally, we sought to compare the degree of agreement between the clinical AF classifications with a device-derived AF classification on the basis of objective, device-derived criteria. For the device-derived AF classification, we used the following definitions: *no AF*: no day with >5 min of AF (11,13,14); *paroxysmal AF*: at least 1 day with >5 min of AF but <7 consecutive days with >23 h of AF; *persistent AF*: at least 7 consecutive days with >23 h of AF (15,16); *permanent AF*: All days with >23 h of AF (or >95% AF burden) (17). Although these device-based definitions may seem somewhat arbitrary, they were designed to align with published guidelines (1) and have been used in several AF trials (11,13–17). Device-derived definitions have the advantage of being consistent and reproducible, and are based on objective temporal AF indices.

AF burden was defined as the proportion of the monitored time that a patient was in AF. AF density, as described previously (6,18), characterized the temporal aggregation of the AF burden. In short, AF density is a quantitative measure of the temporal aggregation of AF burden and was calculated as an index consisting of values between 0 (AF burden evenly spread over the observation time) and 1 (maximal possible AF burden aggregation; i.e., "one continuous episode of AF"). A thorough presentation of the AF density has been reported previously (6,18). The AF detection algorithms utilized in the study devices have been evaluated extensively and have been shown to quantify AF burden with 99% accuracy (19–21).

Statistical analyses. Simple statistical tests (such as the *t* test, chi-square test, Mann-Whitney *U* test, analysis of variance, and Kruskal-Wallis tests) were employed where appropriate to identify differences in the demographics of

the patient population subgroups. The agreement between clinical and device AF classifications was evaluated using Cohen's kappa. Logistic and multinomial logistic regression was used to investigate the influence of patient demographics on the AF classification. The temporal persistence of AF as measured by the AF burden was significantly associated with the clinical AF classification and was included in subsequent models investigating the additional effect of the following variables on the clinical AF classification: age, sex, presence of coronary artery disease, presence of cardiomyopathy, functional status (New York Heart Association functional class), history of ablation for AF, history of heart surgery, AF density (6,18), and left ventricular ejection fraction (LVEF). Receiver-operating characteristic analyses were used to evaluate the performance of AF burden as a discriminator of the clinical AF classification. The p values of 2-sided tests at a significance level of 0.05 are reported.

All statistical analyses were performed with R version 3.0.1 (R Development Core Team 2013, Vienna, Austria) (22).

Results

General demographics. General demographics and characteristics for the 1,195 patients included in this study are presented in detail in Table 1. Patients clinically classified as having persistent AF were more likely to have a cardiac resynchronization therapy (CRT) device, cardiomyopathy, and lower LVEF. Patients with persistent AF also had higher AF burdens; however, a significant overlap in AF burdens was observed between the 2 clinical classification groups (Figs. 1 and 2). When the patients were classified by device-derived definitions, the increase in AF classification (no AF → paroxysmal → persistent → permanent) was accompanied by a more demarcated increase in AF burden with far less overlap between the categories (Table 1, Fig. 3).

AF characteristics *between* the clinical classification groups. A total of 377 patients who had been classified clinically as paroxysmal (34.5%) and 22 patients classified clinically as persistent (21.2%) did not experience *any* AF within their respective observation period (mean 349 ± 40 days, median 365 days, range 181 to 365 days) (Table 2). Twenty-two patients (2.0%) who had been classified clinically as paroxysmal and 14 patients (13.4%) classified clinically as persistent experienced *continuous atrial fibrillation* (AF burden >0.95%; all monitored days with >23 h AF) throughout their respective observation time (mean 347 ± 45 days, median 365 days, range 195 to 365 days) (Table 2).

Figure 1 shows the distribution of the AF burdens observed in the paroxysmal and persistent clinical AF classification groups. The paroxysmal group had lower AF burden (mean 0.095 ± 0.221, median 0.001, range 0 to 1) than the persistent group (mean 0.304 ± 0.385, median 0.04, range 0 to 1, $p < 0.0001$), and there was a significant overlap in the distribution of the AF burden between the 2 clinical classification groups (Figs. 1 and 2).

AF characteristics *within* the clinical classification groups. The results shown in Figures 1 and 2 depict not only that clinical AF classification poorly reflects the temporal persistence of AF but also that patients in the same AF class may vary considerably in terms of their actual temporal AF persistence (Figs. 1 and 2, Table 2). Although patients clinically classified as persistent had higher AF burden this did not result in significant discrimination ability (Fig. 4). Even at very high AF burden levels, the majority of patients were classified as having paroxysmal AF (Figs. 1 and 2, right panel). Figure 2 (right) shows that the probability of being classified in the persistent group did not increase substantially with increasing AF burden. Similarly, receiver-operator characteristic analyses (Fig. 4) revealed that the discrimination ability of AF burden, although statistically significant, was poor (area under the curve: 0.671; 95% confidence interval: 0.612 to 0.73; $p < 0.001$). Within the same clinical AF class, there was a high heterogeneity in terms of temporal AF persistence (Figs. 1 and 2, Table 2).

Factors influencing clinical AF classification. Although AF burden did influence the clinical classification of a patient as persistent AF (6.1/per unit AF burden increase; 95% CI: 3.0 to 12.3/per unit AF burden; $p < 0.0001$), additional factors independently influenced the classification of patients. Factors that were *independently* associated with a lower probability of being classified as persistent AF for the same level of AF burden included a higher LVEF (odds ratio [OR] 0.97/per unit; 95% CI: 0.95 to 0.98/per unit; $p < 0.0001$) and the presence of coronary artery disease (OR: 0.53; 95% CI: 0.32 to 0.88; $p = 0.01$) (Fig. 5). However, it should be noted that even at very high AF burden levels (Figs. 1, 2 [right], and 5), only a minority of patients were clinically classified as having persistent AF.

The effect of LVEF and the presence of coronary artery disease on the clinical AF classification did not depend on the different study (TRENDS or OMNI trials) populations (OR: 1.014; 95% CI: 0.981 to 1.049, $p = 0.40$ for the interaction between LVEF and study; OR: 0.36; 95% CI: 0.10 to 1.21, $p = 0.11$ for the interaction between presence of coronary artery disease and study).

Classification of AF on the basis of device-derived criteria. AF classification derived from continuous monitoring data reflected the temporal persistence of AF with greater accuracy and with less overlap between the AF classes. The AF burden distribution of the device-derived classification groups is more homogenous within each group and more demarcated between groups (Fig. 3, left). Additionally, the device-derived classifications more closely reflect the increases in AF burden (Fig. 3, right). As the AF burden increases, the probability of being classified in a more severe category also increases, with less overlap between categories (Fig. 3, right). Patient characteristics and demographics did not influence the device-based AF classification.

The cross tabulation of this patient population between the clinical and device AF classification schemes is displayed in Table 2. There was little agreement between the clinical AF

Table 1 Demographics, Classification, and Key Characteristics of the Patient Population and Subgroups

	Clinical AF Classification			Device AF Classification					
	Paroxysmal (n = 1,091)	Persistent (n = 104)	p Value	No AF (n = 399)	Paroxysmal (n = 543)	Persistent (n = 217)	Permanent (n = 36)	p Value	Total Result (n = 1,195)
TRENDS study	552 (50.6%)	35 (33.7%)		209 (52.4%)	271 (49.9%)	97 (44.7%)	10 (27.8%)		587
OMNI study	539 (49.4%)	69 (66.3%)		190 (47.6%)	272 (50.1%)	120 (55.3%)	26 (72.2%)		608
Device type									
CRT	205 (18.8%)	36 (34.6%)	<0.001	89 (22.3%)	80 (14.7%)	59 (27.2%)	13 (36.1%)	<0.001	241
ICD	316 (29%)	26 (25%)	0.45	131 (32.8%)	155 (28.5%)	46 (21.2%)	10 (27.8%)	0.02	342
IPG	570 (52.2%)	42 (40.4%)	0.02	179 (44.9%)	308 (56.7%)	112 (51.6%)	13 (36.1%)	<0.001	612
Clinical classification									
Paroxysmal	1,091	0		377 (94.5%)	509 (93.7%)	183 (84.3%)	22 (61.1%)		1,091
Persistent	0	104		22 (5.5%)	34 (6.3%)	34 (15.7%)	14 (38.9%)		104
Age, yrs	73.1 ± 10.0 (35.7–100)	71.9 ± 11.1 (21.6–92.4)	0.36	72.6 ± 10.2 (36.7–94.9)	72.7 ± 10.3 (35.7–97.6)	74.1 ± 9.8 (21.6–100)	74.8 ± 9.5 (50.1–87.5)	0.18	73.0 ± 10.1 (21.6–100)
Female	403 (36.9%)	35 (33.7%)	0.58	148 (37.1%)	214 (39.4%)	70 (32.3%)	6 (16.7%)	0.02	438
Follow-up time, days	349.3 ± 39.3 (181–365)	346.0 ± 45.1 (186–365)	0.31	348.7 ± 39.5 (181–365)	350.2 ± 38.6 (182–365)	346.9 ± 42.8 (182–365)	346.7 ± 45.1 (195–365)	0.17	349.0 ± 39.8 (181–365)
LVEF, %	43.0 ± 18.2 (10–91)	33.9 ± 17.6 (10–73)	<0.001	41.7 ± 18.1 (10–80)	43.4 ± 18.4 (10–91)	41.1 ± 19.1 (10–80)	35.5 ± 15.4 (15–60)	0.11	42.1 ± 18.4 (10–91)
AF burden	0.1 ± 0.22 (0–1)	0.3 ± 0.38 (0–1)	<0.001	0 ± 0 (0–0)	0.03 ± 0.07 (0–0.62)	0.39 ± 0.27 (0.02–0.95)	0.99 ± 0.01 (0.95–1)	<0.001	0.11 ± 0.25 (0–1)
Atrial pacing (% of time)	55.8 ± 35.2 61.8; 23.1–90.4	51.6 ± 36.5 51.0; 14.9–88.1	0.25	58.0 ± 37.3 66.5; 18.3–95.2	61.6 ± 32.7 71.9; 32.9–92.1	44.3 ± 30.0 40.6; 16.6–72.1	0.9 ± 1.2 0.5; 0–1.3	<0.001	55.4 ± 35.3 60.9; 22.5–90.1
Coronary artery disease	653 (59.9%)	53 (51%)	0.1	272 (68.2%)	282 (51.9%)	131 (60.4%)	21 (58.3%)	<0.001	706
Hypertension	817 (74.9%)	78 (75%)	0.99	295 (73.9%)	412 (75.9%)	166 (76.5%)	22 (61.1%)	0.22	895
Diabetes	294 (26.9%)	25 (24%)	0.6	115 (28.8%)	138 (25.4%)	55 (25.3%)	11 (30.6%)	0.6	319
Cardiomyopathy	537 (49.2%)	66 (63.5%)	0.01	216 (54.1%)	248 (45.7%)	118 (54.4%)	21 (58.3%)	0.02	603
History of atrial flutter	178 (16.3%)	17 (16.3%)	0.99	40 (10%)	110 (20.3%)	39 (18%)	6 (16.7%)	<0.001	195
History of atrial tachycardia	60 (5.5%)	6 (5.8%)	0.99	17 (4.3%)	37 (6.8%)	10 (4.6%)	2 (5.6%)	0.34	66
History of AF ablation	77 (7.1%)	14 (13.5%)	0.03	16 (4%)	50 (9.2%)	18 (8.3%)	7 (19.4%)	<0.001	91
History of AV node ablation	29 (2.7%)	4 (3.8%)	0.7	9 (2.3%)	17 (3.1%)	5 (2.3%)	2 (5.6%)	0.59	33
Functional status (NYHA functional class)									
None	406 (37.2%)	25 (24%)	0.01	131 (32.8%)	227 (41.8%)	67 (30.9%)	6 (16.7%)	<0.001	431
I	90 (8.2%)	5 (4.8%)	0.3	29 (7.3%)	46 (8.5%)	16 (7.4%)	4 (11.1%)	0.79	95
II	234 (21.4%)	18 (17.3%)	0.38	95 (23.8%)	108 (19.9%)	42 (19.4%)	7 (19.4%)	0.44	252
III	222 (20.3%)	37 (35.6%)	<0.001	92 (23.1%)	97 (17.9%)	58 (26.7%)	12 (33.3%)	0.01	259
IV	15 (1.4%)	4 (3.8%)	0.12	5 (1.3%)	11 (2%)	2 (0.9%)	1 (2.8%)	0.59	19
Cardiac surgery	388 (35.6%)	37 (35.6%)	0.99	164 (41.1%)	174 (32%)	72 (33.2%)	15 (41.7%)	0.02	425
CABG	336 (30.8%)	27 (26%)	0.36	146 (36.6%)	147 (27.1%)	57 (26.3%)	13 (36.1%)	<0.001	363
AVR	52 (4.8%)	5 (4.8%)	0.99	19 (4.8%)	24 (4.4%)	12 (5.5%)	2 (5.6%)	0.92	57
MVR	62 (5.7%)	7 (6.7%)	0.82	24 (6%)	30 (5.5%)	14 (6.5%)	1 (2.8%)	0.82	69
TVR	8 (0.7%)	0 (0%)	0.8	2 (0.5%)	4 (0.7%)	2 (0.9%)	0 (0%)	0.88	8

Values are n (%), mean ± SD, or median; interquartile range (first, third quartile).

AF = atrial fibrillation; AV = aortic valve; AVR = aortic valve replacement/repair; CABG = coronary artery bypass graft surgery; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; IPG = implantable pulse generator; LVEF = left ventricular ejection fraction; MVR = mitral valve replacement/repair; NYHA = New York Heart Association; TVR = tricuspid valve replacement/repair.

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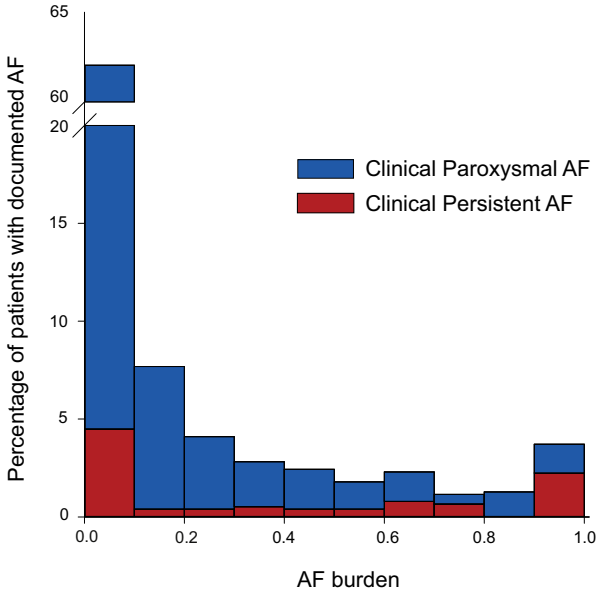

Figure 1 **Distribution of AF Burden in Patients With Documented AF According to the Clinical AF Classification**

Distribution of atrial fibrillation (AF) burden in patients with documented AF according to the clinical AF classification. The 399 patients with no documented AF (377 classified as paroxysmal and 22 classified as persistent) were excluded from this graph.

classification and the objective and quantitative measures of AF temporal persistence (Cohen's kappa: 0.12, 95% CI: 0.05 to 0.18). Overall, only 46.7% of the clinically classified paroxysmal AF patients were also classified as paroxysmal AF using the more objective device-related criteria. For the persistent AF classification this agreement dropped to 32.7%.

Discussion

The present study has 3 primary findings. First, the currently used clinical AF classifications poorly reflect the temporal persistence of AF. Second, patients classified in the same clinical AF class may be inherently heterogeneous in terms of temporal AF persistence. Third, certain clinical patient characteristics appear to influence the decision to clinically classify AF. These findings have important implications for communication, therapy selection, and clinical trials involving AF patients.

Implications for communication. Current AF classifications attempt to communicate information about the persistence and magnitude of an individual patient's AF recurrence. Our results indicate a frequent discordance between the clinical assessment of AF and the actual amount of AF, which in our patient population could be precisely measured by continuous arrhythmia monitoring.

Clinical AF classifications appear to have an element of subjectivity to them. For example, although the definition for persistent AF includes a minimal duration requirement of >7 days, it also allows for the possibility of pharmacologic or electrical cardioversion to be a component of the criteria (1,2). The threshold for seeking cardioversion may differ among patients with identical arrhythmia burden and the threshold for administering cardioversion may also differ among physicians.

The clinical AF classification is often employed not only to evaluate the magnitude and persistence of the arrhythmia but also to denote the stage or degree of disease progression, implying that patients with "paroxysmal" AF are at earlier stages of the disease than patients with "persistent" AF. It is well recognized that "atrial fibrillation begets atrial fibrillation" (23) and that in the long term there is a significant progression of AF (15,16), which manifests as a progressive increase in the temporal persistence of AF. However, the discordance that we observed between clinical AF classifications and objective temporal AF indices suggests that the clinical classification of AF is an unreliable indicator for disease progression. Our findings suggest that patients with vastly different degrees of temporal AF persistence (and stages of disease) within the same clinical classification (Fig. 2, left) may exist. Furthermore, there may also be patients that, although classified as having "paroxysmal" AF, have higher degrees of temporal AF persistence (and thus are at a later stage of the disease) than patients classified as having "persistent" AF (Fig. 2, right). If the staging of the AF disease can be reflected from its temporal persistence, then the current clinical AF classifications are unreliable indicators of the disease progression.

In contrast, although device-based definitions may seem somewhat arbitrary, they were designed to align with published guidelines (1) and have been used in several AF trials (11,13–17). Such definitions have the advantage of being consistent and reproducible, and are based on objective temporal AF indices. The AF burden distribution of the device-derived classification groups was more homogenous within each group and more demarcated between groups (Fig. 3, left) and the device-derived classifications more closely reflect the increases in AF burden (Fig. 3, right). Also as the AF burden increased, the probability of being classified in a more severe device-derived category also increased, with less overlap between categories (Fig. 3, right). Patient characteristics and demographics did not influence the device-based AF classification.

Implications for therapy selection. AF classification can strongly affect therapy selection, most importantly the decision to pursue a rhythm control or rate control strategy. Even once a particular treatment strategy has been decided, the procedural attributes of a specific therapy (e.g., AF ablation as a rhythm control strategy) can be influenced by the perceived persistence of the arrhythmia.

Rhythm control is generally attempted as first line therapy in patients with paroxysmal AF. As the disease progresses to persistent and permanent AF, a rate control approach is often adopted. A recent survey from the European Heart Rhythm Association showed that a patient's clinical AF

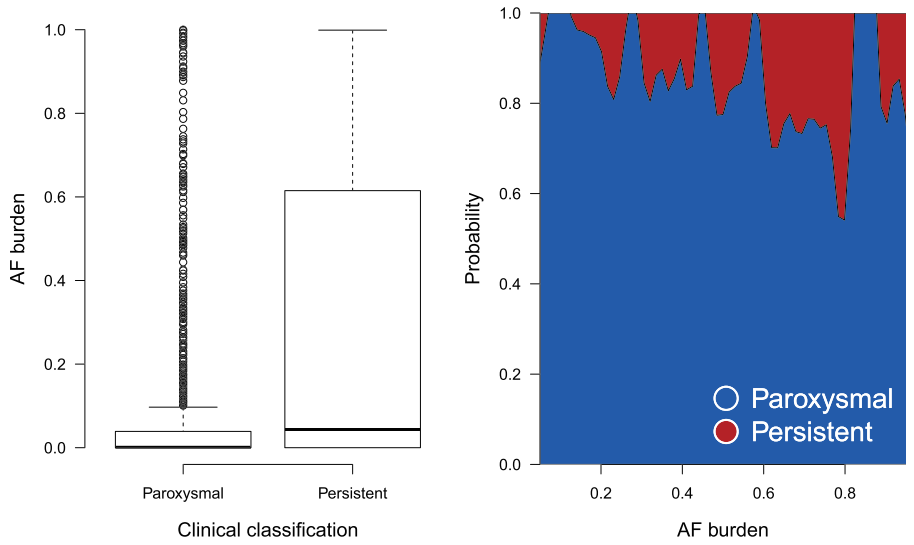

Figure 2 **Clinical AF Classification**

(Left) Distribution of the atrial fibrillation (AF) burden in the clinical classification groups (paroxysmal, persistent) ($p < 0.001$). **(Right)** The probability of being in either of the clinical classification groups at any given AF burden level (conditional density plot). For example, at an AF burden of 0.2, the probability of being classified as "paroxysmal" or "persistent" was approximately 0.8 and 0.2, respectively. As the AF burden increases, intuitively one would expect that the probability of being classified as "paroxysmal" AF decreases and the probability of being classified as "persistent" increases. Unexpectedly, at AF burdens of 0.9, the probability of being classified as "paroxysmal" or "persistent" was also approximately 0.8 and 0.2, respectively, showing the disconnection between clinical classification and temporal persistence. Even at very high burdens the vast majority of patients were classified as having "paroxysmal" AF.

classification can affect the choice of therapeutic treatment (7). For example, only 3.1% of patients deemed to be in persistent AF were selected to undergo "upstream" therapy, whereas 3 times as many patients (9.4%) classified as having paroxysmal AF were selected for this therapy. Furthermore, the choice of therapy had a strong influence on the subsequent rigor of arrhythmia monitoring.

Imprecise AF classification may also affect the perceived and reported efficacy of specific rhythm control procedures. In the case of AF ablation for rhythm control, it is generally

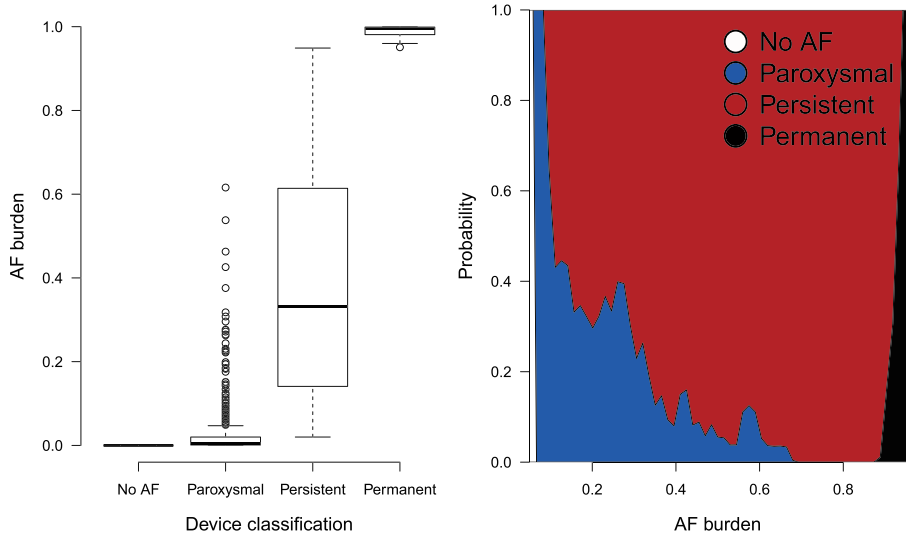

Figure 3 **Device-Derived AF Classification**

(Left) Distribution of the atrial fibrillation (AF) burden in the device classification groups (no AF, paroxysmal, persistent, permanent). **(Right)** The probability of being in any of the device classification groups at any given AF burden level (conditional density plot). As AF burden increases, the probability of being classified in a progressively more severe classification (no AF → paroxysmal → persistent → permanent) increases. This is in contrast to the clinical AF classification (Fig. 2, right panel).

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Table 2 Cross Tabulation of the Clinical and Device-Derived AF Classifications

Clinical AF Classification	Device Classification: No AF AF Burden <0.001 (n = 399)	Paroxysmal At Least 1 Day With >5 Min AF But <7 Consecutive Days With >23 H of AF (n = 543)	Persistent At Least 7 Consecutive Days With >23 H AF (n = 217)	Permanent All Monitored Days With >23 H AF (n = 36)
Paroxysmal (n = 1,091)	377	509	183	22
Persistent (n = 104)	22	34	34	14

AF = atrial fibrillation.

accepted that pulmonary vein isolation alone is sufficient for paroxysmal AF patients whereas additional lesions are also required to maintain sinus rhythm in patients with more advanced, persistent AF. A potential explanation for lack of complete efficacy with the pulmonary vein isolation only approach is that some of the patients perceived to have paroxysmal AF may actually have a more persistent form of the disease. Likewise, performing additional lesions in patients thought to have persistent AF could expose them to unnecessary increased risk if in fact they have a more paroxysmal form of the disease. More accurate classification may allow us to better align appropriate therapies to appropriate patients and balance the respective risks and benefits of these therapies.

Implications for clinical trials. Accurate categorization of patients into the various clinical AF classifications affects both our ability to study a homogenous cohort, as well as our ability to precisely assess the treatment effects when AF recurrence or progression is an endpoint. Clinical trials frequently attempt to enroll patients with only paroxysmal AF (8,24), only persistent AF (25), or both types of AF (26) with the goal of evaluating the effect of a therapy within a specific patient population or comparing the effect between patient populations. Therefore it is important that these study cohorts are as uniform as possible with respect to the magnitude of AF as a disease. Our results suggest that there may be significant "blurring" of these AF classifications in clinical practice, thereby making the interpretation of such

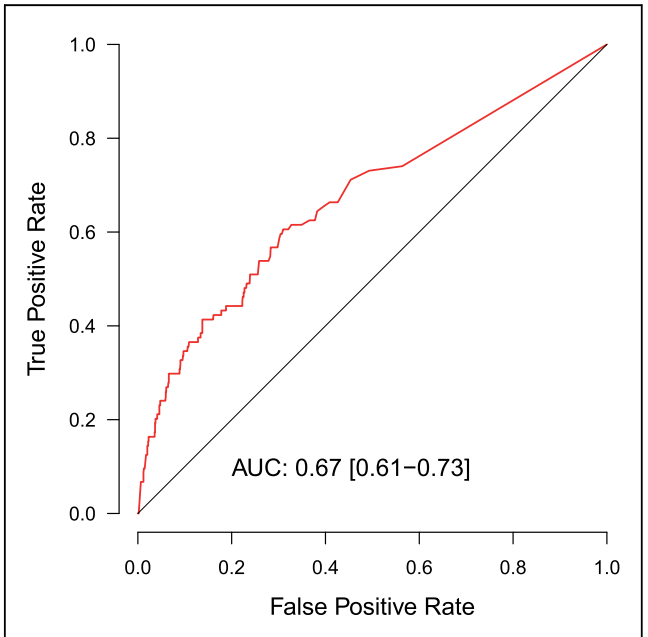

Figure 4 Receiver-Operating Characteristic Curve for the Discrimination Ability of AF Burden on Clinical AF Classification

Receiver-operating characteristic curve for the discrimination ability of atrial fibrillation (AF) burden on clinical AF classification. AF burden has a statistically significant, albeit poor, discrimination ability (area under the curve [AUC]: 0.67; 95% confidence interval: 0.61 to 0.73; $p < 0.001$).

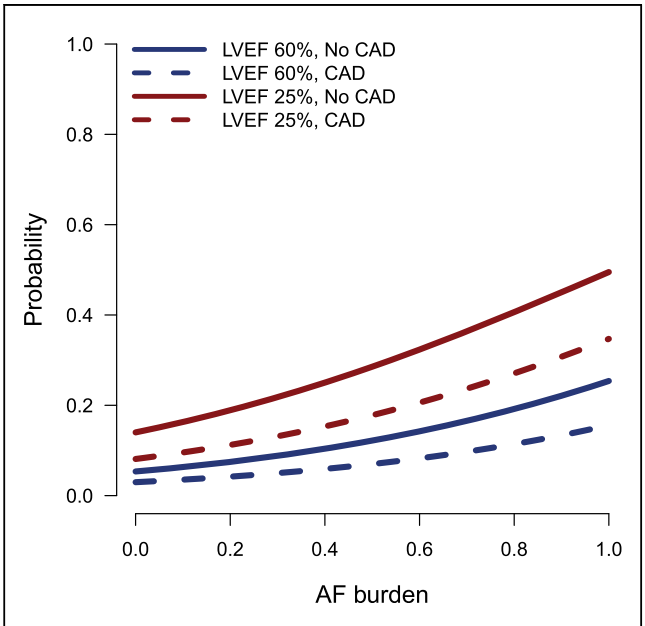

Figure 5 The Logistic Regression Model Evaluating the Effect of LVEF and CAD on the Clinical AF Classification

The logistic regression model evaluating the effect of left ventricular ejection fraction (LVEF) and coronary artery disease (CAD) on the clinical AF classification. Both LVEF and the CAD significantly and independently influenced the clinical atrial fibrillation (AF) classification. At the same level of AF burden, patients with different LVEF and presence or absence of CAD were classified differently. It should also be noted that even at very high AF burdens, only a minority of patients was classified as having persistent AF.

studies a challenge. For example, we observed that 54% of patients classified as having persistent AF at baseline did not meet the threshold of having at least 7 consecutive days of AF despite an mean follow-up of almost 1 year.

Similarly, trials using AF recurrence (27) or the progression to persistent AF (28) as study endpoints are prone to error in the absence of comprehensive rhythm monitoring. AF recurrence and progression are typically assessed via intermittent periods of external monitoring and/or patient-reported symptoms. It is well established that these brief monitoring snapshots do not accurately capture the true arrhythmia status (5,6,29) and that relying on patient symptoms can lead to both under-reporting and over-reporting of AF (3,4,30). Long-term arrhythmia monitoring helps to mitigate these errors by providing objective measures of the arrhythmia persistence (31). A more accurate classification of patients on the basis of objective criteria of AF persistence may lead to better identification and selection of patients that will more likely respond to the appropriate therapy. The advent of smaller implantable monitoring devices (32,33) and more comfortable external patches (34) is likely to increase the number of patients in whom this type of data is available in the future.

Role of patient characteristics. One striking finding of this study was that patients' clinical characteristics appear to have influenced the clinical AF classification. In particular, patients with reduced LVEF were more likely to be characterized as having persistent AF for the *same level* of AF burden. Additionally, patients with coronary artery disease were more likely to be classified as having paroxysmal AF, for the *same level* of AF burden and LVEF. An interpretation of this finding can only be speculative at this point. Perhaps in sicker patients (with low LVEF), the perception of AF may be more prominent, or the same amount of AF may generate a more severe symptomatology, causing physicians to subsequently classify the patient's AF as more severe. In contrast, patients with coronary artery disease were less likely to be classified as having persistent AF for the *same level* of AF burden and LVEF. A potential explanation for this finding could be that in some patients with coronary artery disease, the occurrence of AF may be more likely attributed to the underlying coronary artery disease and not to the "AF process" itself. Regardless of the explanation for the above findings, it remains true that clinical patient factors other than the temporal persistence of AF influenced the clinical classification of AF.

The influence of symptomatology on AF classification. Although the guidelines do not explicitly take the degree of AF-related symptomatology into consideration, patient symptoms may influence the clinical AF classification. Patients with higher symptomatology regardless of the temporal AF persistence may seek medical attention more frequently, thus allowing for more frequent documentation of their rhythm status. Patients with other co-morbidities such as low ejection fraction may exhibit more severe symptomatology for the same level of temporal AF persistence. Furthermore, the degree of AF-related symptoms may influence the physician's decision to attempt cardioversion which, when performed, simultaneously reclassifies a patient to the "persistent" AF class regardless of the degree and magnitude of the temporal AF persistence. If the degree of AF disease is reflected by the temporal AF persistence, the patient's symptomatology has been shown to poorly correlate with the AF temporal persistence (4) and may significantly influence and blur the clinical AF classification.

Study limitations. AF is not a static disease and therefore it is possible that although the physician assessment of rhythm status was accurate at the time it was made, AF may have progressed over time. However, the relatively brief follow-up period of <1 year should have minimized the extent of AF progression. Furthermore, AF progression cannot account for patients who "improved" their AF classification (e.g., a patient deemed to have persistent AF who was found to not have any AF).

We did not have thorough reporting of all interventions and changes in medical regimens, and therefore AF may have improved in some patients due to implementation of effective therapies. However, we attempted to minimize this issue by including patients from observational (noninterventional) studies and excluding patients with obvious AF treatments.

All patients had clinical indications for a pacemaker or implantable cardioverter-defibrillator. Therefore these results theoretically may not apply to the broader population of patients without an implantable device indication. However, small subcutaneous devices are now available which provide similar AF monitoring capabilities to patients without traditional implantable device indications (33).

In the present study, the AF classification was performed before the observation period and therefore the physicians were not able to re-evaluate the AF classification on the basis of new information. AF classifications were not assessed at the end of the study. Although this is a limitation, the design of the present study design is appropriate to investigate the disconnect between AF classification and AF temporal persistence when the AF classification is used as an inclusion criterion as in clinical trials (such as the present study where AF classification was performed before the observation period), as well as the disconnect between the clinical classification as a "belief" on the staging of the AF disease, and the objective temporal AF persistence.

Conclusions

Clinical AF classifications poorly reflect its temporal persistence and clinical patient characteristics significantly influence the clinical categorization of AF. Our results demonstrate that patients classified in identical traditional clinical AF categories may be inherently heterogeneous with regards to AF temporal persistence. Further study is required to determine if classifying AF on the basis of rigorous arrhythmia monitoring can improve clinical outcomes relative to traditional clinical assessments.

Acknowledgment

The authors wish to thank Jodi Koehler for her assistance in data preparation and formatting.

Reprint requests and correspondence: Dr. Efstratios I. Charitos, Department of Cardiac and Thoracic Vascular Surgery, University of Luebeck, Ratzeburger Allee 160, 23568 Luebeck, Germany. E-mail: efstratios.charitos@gmail.com.

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Key Words: arrhythmia ■ atrial fibrillation ■ monitoring.