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Clinical Classifications of Atrial Fibrillation Poorly Reflect Its Temporal Persistence

Insights From 1,195 Patients Continuously Monitored With Implantable Devices

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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.

See page 2849

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

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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