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ORIGINAL ARTICLE

Thirty-Second Gold Standard Definition of Atrial Fibrillation and Its Relationship With Subsequent Arrhythmia Patterns

Analysis of a Large Prospective Device Database

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Jonathan S. Steinberg, MD
Heather O'Connell, MS
Shelby Li, MD, MS
Paul D. Ziegler, MS

BACKGROUND: The Heart Rhythm Society consensus statement arbitrarily defines atrial fibrillation (AF) ablation failure as any episode ≥30 seconds. However, if brief AF events are not correlated to longer events, the rationale for this end point is questionable. We determined the impact of AF episode duration threshold on AF incidence and burden.

METHODS: Patients with a pacemaker in a prospective registry with device-detected AF and follow-up >30 days were analyzed. AF patterns were calculated for various AF duration thresholds (30 s; 2 and 6 minutes; 3.8, 5.5, and 24 hours) selected based on published consensus statements, established evidence of stroke risk, and device capabilities. Freedom from AF postdevice implant at each AF episode duration threshold was assessed, as was overall AF burden.

RESULTS: Among 615 patients with pacemaker (aged 72.0±11.8 years, 54.2% male, follow-up 3.7±2.2 years) with device-detected AF, 599 had ≥1 AF episode of ≥30 seconds duration (median, 22 episodes). At 12 months, freedom from AF was 25.5%, 30.1%, 34.6%, 52.6%, 56.5%, and 73.1% for duration thresholds of 30 seconds, 2 minutes, 6 minutes, 3.8 hours, 5.5 hours, and 24 hours, respectively. Of patients with a first episode of 30 seconds to 2 minutes, 35.8% were free from subsequent episode >2 minutes at 180 days. Median AF burden was significantly less for patients with first episodes between 30 seconds and 3.8 hours versus >3.8 hours (0.2% versus 9.5%, respectively; $P<0.0001$).

CONCLUSIONS: Small differences in AF episode duration definition can significantly affect the perceived incidence of AF and impact reported outcomes, including AF ablation success. An initial AF episode of 30 seconds does not predict clinically meaningful AF patterns.

VISUAL OVERVIEW: An online visual overview is available for this article.

Key Words: ablation ■ atrial fibrillation ■ consensus ■ stroke

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WHAT IS KNOWN?

- Formal consensus documents on catheter and surgical ablation define atrial fibrillation (AF) as an arrhythmia lasting ≥30 s, assuming that a brief AF event is correlated to longer AF events or high prevalence.

WHAT THE STUDY ADDS?

- The presence of an initial AF episode of ≥30 s did not predict clinically meaningful AF patterns in a pacemaker population.
- Small differences in AF episode duration definition significantly affected the perceived incidence of AF and would impact reported outcomes, including AF ablation success.

Although seemingly a simple matter, the definition of the minimal duration of atrial fibrillation (AF) for clinical management and for determination of outcomes after interventions, such as ablation, can have profound implications. Although there is little controversy over how to define ventricular fibrillation, formally defining AF has been much more challenging.

Beginning with the 2007 Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) consensus document on catheter and surgical ablation of AF,[1] the electrophysiology community has required that AF be defined as an arrhythmia lasting ≥30 seconds or if present on the entire 10 seconds 12-lead standard ECG. Formalization of the AF definition was designed to bring coherence and consistency to the measurement of outcomes after AF ablation, a worthy and clinically relevant goal. Other measures were applied (minimum monitoring duration, blanking period, inclusion of other atrial tachyarrhythmias, etc), and indeed, the ultimate consequence was a reduction in procedural success when failure was defined as detection of at least 1 AF episode in follow-up.

An important implicit presumption of this end point definition is that the detection of a short duration event is not simply an isolated self-limited observation but would represent a greater or progressive arrhythmia burden that would become evident or would have clinical consequences. If not the case, most clinicians or patients would likely have little concern about the impact of a single ultrashort event that has no proven association with symptom burden, clinically relevant or meaningful outcomes, or rates of arrhythmia progression. Indeed, most electrophysiologists and patients would be pleased if the only AF detected after ablation was short-lived and not prevalent. Further, if brief AF events are not correlated to longer AF events or substantial prevalence, the rationale for this sensitive end point would be questionable and suggest that ablation success rates may be consistently underestimated.

There is already some published evidence that the quality of life response to ablation is proportional to AF burden rather than to a short-lived event,[2] and stroke risk in the setting of AF is more accurately predicted by overall AF burden than the simple history of AF.[3]

We thus sought to explore the fundamental presumption of use of this definition, that is, a brief AF event is correlated to longer AF events or high prevalence, by examining a large prospective pacemaker registry with validated AF detection algorithms.

METHODS

Patient Population

The patient cohort was selected from Medtronic Product Surveillance Registry (PSR), which is a platform that collects longitudinal real-world observational data for patients treated with at least 1 Medtronic product. The Cardiac Rhythm PSR platform enrolls and follows patients prospectively from device implant and includes both patient- and device-detected information. The registry protocol was approved by local Institutional Review Boards, and patients provided consent to release their data as required by their Institutional Review Boards. Patients enrolled in the registry were treated and followed per standard practice. From this large, observational registry, the derivation of the analysis cohort is presented in Figure 1. Patients implanted between 2005 and 2016 with dual-chamber pacemakers capable of detecting atrial arrhythmias were selected, regardless of AF or ablation history. All patients were required to have ≥30 days of device data and ≥1 detected AF episode postimplant.

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Data Collection

Baseline data were collected in an electronic data capture system. Given the longevity and change in PSR data collection over time, complete baseline data were not available for all patients for each variable of interest. Procedural information, device details, and electrical measurements were captured at the implant procedure. Patients were followed in office in accordance with standard of care practices and could be monitored via remote data transmissions. At each follow-up, device electrical measurements were captured in addition to assessing the patient's status and adverse events. Electrical measurements, including AF episodes and arrhythmia burden summaries, were collected on the patient's device and reported through save-to-media, or transmitted via Medtronic CareLink system, which is a secure system for transmission of stored medical device data to clinics, physicians, and Medtronic. Programming of the atrial tachycardia (AT)/AF detection interval was left to the discretion of the treating physicians. Approximately three quarters of patients were programmed to the nominal AT/AF detection interval of 350 ms at baseline (79%) and end of follow-up (74%). AF burden sensitivity and specificity in Medtronic devices has been previously shown to exceed 95%,[4–6] so the pacemaker represented a reliable source for continuous AF monitoring.

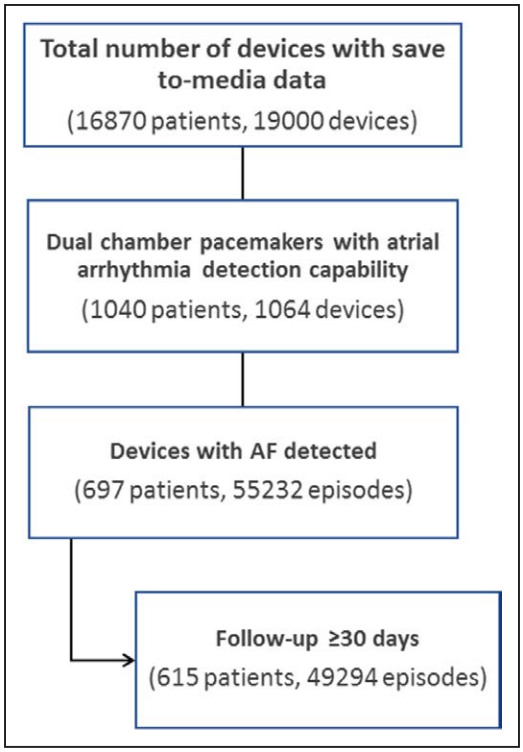

Figure 1. Derivation of analysis cohort.
AF indicates atrial fibrillation.

Statistical Analysis

Data from the PSR electronic case report forms were merged with the CareLink or save-to-media device data to generate the analysis data set. Descriptive statistics for baseline characteristics and distribution and frequency of episodes were calculated.

We tested various AF episode duration thresholds, including the HRS consensus definition based on current consensus statements (eg, 30 s[7]), established clinical evidence for stroke risk (eg, 6 minutes,[8] 3.8 hours,[9] 5.5 hours,[10] and 24 hours[11]), and device capabilities (eg, 2 minutes[12]). Kaplan-Meier curves were generated for freedom from AF using the thresholds above for time to first event. AF burden was calculated for each patient, based on total hours of AF detected burden divided by total hours of device follow-up. Descriptive statistics for % AF burden per patient were obtained for different subgroups based on the first AF episode duration threshold according to published literature, as defined above. Further, we examined the likelihood of patient's experiencing subsequent arrhythmias using the Kaplan-Meier survival analysis method. To measure the probability of subsequent events, we defined the first AF episode duration as in all the other analyses based on definitions above.

RESULTS

Baseline Patient Characteristics

Of the 1064 patients with dual pacemakers with atrial arrhythmia sensing capability, 697 (65.5%) patients had at least 1 device-detected AT/AF episode (Figure 1). The final analyzed cohort of 615 patients had at least 30 days of follow-up. The average age was 72.0±11.8 years, and 333 (54.2%) were male. The QRS duration was 105.6±28.1 ms for the 369 patients in which it was available. Left ventricular ejection fraction was available in 354 patients and was 58.1±9.6%. Patients were followed an average of 3.7±2.2 years.

Probability, Distribution, and Frequency of AF Episodes

The likelihood that at least 1 AF episode was detected was highly dependent on the definition of AF. Of the 615 patients who had at least 1 atrial arrhythmia episode recorded throughout the entire follow-up, 599 (97.4%) had at least 1 AF episode ≥30 seconds and of those, >528 (88.0%) had AF episodes in each episode duration category up to 6 minutes. For the categories between 3.8 and 5.5 hours, the prevalence drops off to 61.1% to 65.5%, and only 44.9% of patients had an AF episode >24 hours.

The definition of shorter durations of AF resulted in a greater frequency of AF episodes per patient (Table). The median number of AF episodes per patient ranged between 13 and 22 for the follow-up period based on patients with any episode >30 seconds through >6 minutes. The median number of episodes for patients with any episode between 3.8 to 24 hours was substantially less, at 3 to 7 per patient, during the course of follow-up. When the entire cohort was subdivided into individual subgroups, the composition was as follows: ≥30 seconds to 2 minutes (n=163, 26.5%); >2 to 6 minutes (n=89, 14.47%); >6 minutes to 3.8 hours (n=160, 26.02%); >3.8 to 5.5 hours (n=25, 4.07%); >5.5 to 24 hours (n=62, 10.08%); and >24 hours (n=100, 16.26%).

Bearing in mind that almost all patients had at least 1 episode of AF of 30-second duration throughout the 3.7 years of follow-up, the probability of patient freedom from AF at 12 months was estimated using the Kaplan-Meier survival method (Figure 2). At 12 months, the probabilities of freedom from an AF episode were 25.5%, 30.1%, 34.6%, 52.6%, 56.5%, and 73.1%, when using episode duration thresholds of >30 seconds, >2 minutes, >6 minutes, >3.8 hours, >5.5 hours,

Table. Frequency and Median Number of Atrial Arrhythmia Episodes by Episode Duration

Episode Duration	n	Proportion, %	Episodes*
≥30 s	599	97.40	22 (4–79)
>2 min	561	91.22	17 (5–59)
>6 min	528	85.85	13 (4–43)
>3.8 h	403	65.53	7 (2–18)
>5.5 h	376	61.14	6 (2–17)
>24 h	276	44.88	3 (1–9)

*Median (interquartile range).

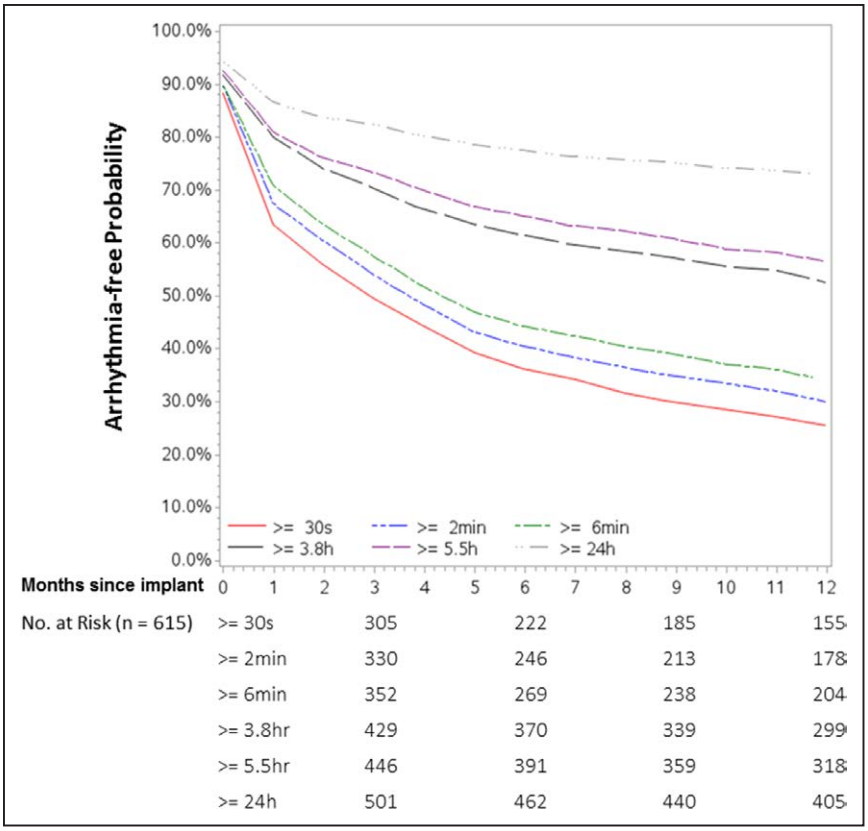

Figure 2. Probability of freedom of atrial arrhythmia by different atrial fibrillation initial episode duration thresholds.

and >24 hours, respectively. Although no statistical tests were appropriate to demonstrate this monotonic increase, the difference in the estimates between > 6-minute and >3.8-hour cutoffs was substantial, jumping from 34.6% to 52.6%, an absolute difference of 18.0%. This observation signifies the impact of AF duration definition on the reported episode rate.

AF Burden

The AF burden during the entire duration of follow-up was calculated for patients in each subgroup based on each initial AF episode duration threshold subgroup (Figure 3A). The median AF burden ranged from 0.08% to 25.0% using different threshold subgroups, with less AF burden observed when the threshold was low, despite the inclusion of more episodes. Excluding those with long (>3.8 hours) initial episodes, for patients with a first episode between ≥30 seconds and up to 3.8 hours, the median AF burden was only 0.2%. For patients with a first episode >3.8 hours, a greater median AF burden of 9.5% was observed, a difference that was highly statistically significant at $P<0.0001$ (Figure 3B).

Subsequent Arrhythmias After Initial AF Detection

The probabilities of patient freedom from a subsequent episode estimated using the Kaplan-Meier survival analysis method are displayed in Figure 4. Time 0 was defined as the onset time for the initial episode; event time is the time duration from the initial episode to the next or subsequent event using the predefined arrhythmia durations. When the subsequent event was defined as any arrhythmia of ≥2 minutes, the probability of freedom from a subsequent event at 180 days was 35.8% for patients with an initial episode of 30 s to 2 minutes, 21.7% for patients with an initial episode of 6 minutes to 3.8 hours, and 39.7% for patients with an initial episode of >24 hours. This pattern remained similar when the subsequent event is defined as any arrhythmia of ≥3.8 hours, also displayed in Figure 4. The subsequent event-free probability from arrhythmia >3.8 hours at 180 days was 70.3% for patients with an initial episode of 30 seconds to 2 minutes, 54.6% for patients with an initial episode of 6 minutes to 3.8 hours, and 42.8% for patients with an initial episode of >24 hours. These calculations implied that a high percentage of patients did not experience additional arrhythmias after initial detection during follow-up, and patients with a longer (approaching 3.8 hours) initial episode were much more likely to experience a subsequent event.

We further examined the probability of freedom from persistent AF (≥7 days) after the initial episodes per defined arrhythmia duration. For patients with an initial arrhythmia of duration 30 s to 2 minutes, persistent AF-free probability was 97.7% in the following 180

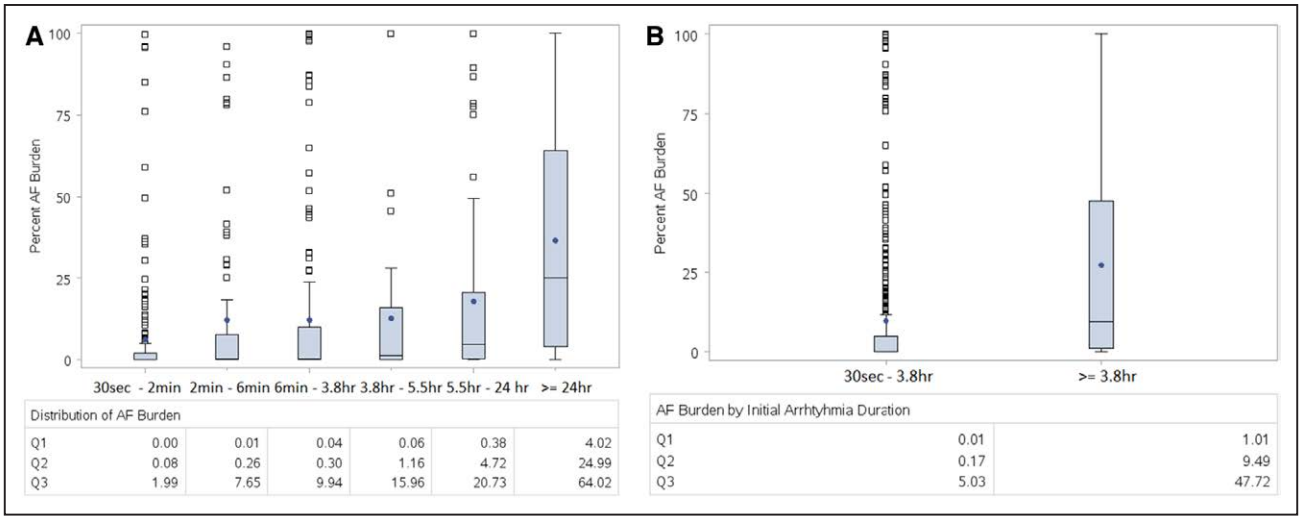

Figure 3. Atrial fibrillation (AF) burden during follow-up.
A, AF burden box-plot by different AF initial episode duration threshold subgroups; (**B**) AF burden box-plot by clinically relevant AF initial episode duration threshold subgroups.

days, compared with 91.2% for 6 minutes to 3.8 hours and 77.1% for the >24-hour subgroup (P<0.0001).

DISCUSSION

Several years after the use of catheter ablation for AF became widespread, the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up[1] was published and explicitly defined AF as lasting at least 30 seconds without a reversible cause. The 2012 updated consensus statement[13] further refined the usage of the definition such that any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long enough for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm strip, should be considered an AF episode. The consequences of this formalized consensus were profound. The definition was widely accepted and was required usage in most published studies and in the United States by the Food and Drug Administration. Success rates following ablation declined from >90% to 50% to 80%, and the lexicon was altered such that cure virtually vanished from the ablation literature. This definition has been retained in the recent 2017 guidelines[7] that reiterated that the definition derives from previously published consensus statements but acknowledged has not been linked to a specific outcome of AF.

The same definition was also adopted outside the original ablation application. For example, AF duration >30 seconds was used or proposed for evaluation of cryptogenic stroke,[14,15] ECG surveillance of asymptomatic AF in high-risk populations,[16,17] and generic trials of AF.[18]

An important implicit presumption of this end point definition was that the detection of a short duration event was not simply an isolated self-limited observation but would represent a greater or progressive arrhythmia burden that could become evident or have clinical consequences. We thus sought to explore the fundamental relationship of minimal AF duration threshold and AF incidence and patterns during a mean follow-up of 3.7 years by examining a large mixed device prospective registry with formalized AF detection systems. We used various AF episode duration thresholds based on current consensus statements,[1,7,13] established clinical evidence for stroke risk,[8–11] and device capabilities.[12] Our data analyses concluded the following: (1) the duration definition of AF, not surprisingly, had a large impact on AF event frequency and cumulative AF burden as assessed in this device population; and (2) notably, the presence of an initial AF episode of 30 seconds (HRS definition) did not portend clinically meaningful AF patterns.

Keeping in mind that patients were required to demonstrate at least 1 brief AF episode during follow-up of 3.7 years, the prevalence of AF in our study cohort fell from nearly 100% based on the 30-second definition, to 45% using a 24-hour definition. The median number of events per patients similarly declined based on AF duration definition. Given that a variety of trials use ECG detection of AF end points, we also constructed hypothetical survival analyses based on various definitions and observed that freedom from AF varied between 25.5% and 73.1% at 12 months. These latter findings would be akin to data collected in drug and device trials of AF therapy and highlight the extreme variation of time to first event within the range of definitions that were used in our data analyses (nearly 3-fold).

To determine what the most relevant threshold might be, it is also important to assess their clinical relevance for patients. AF burden most accurately

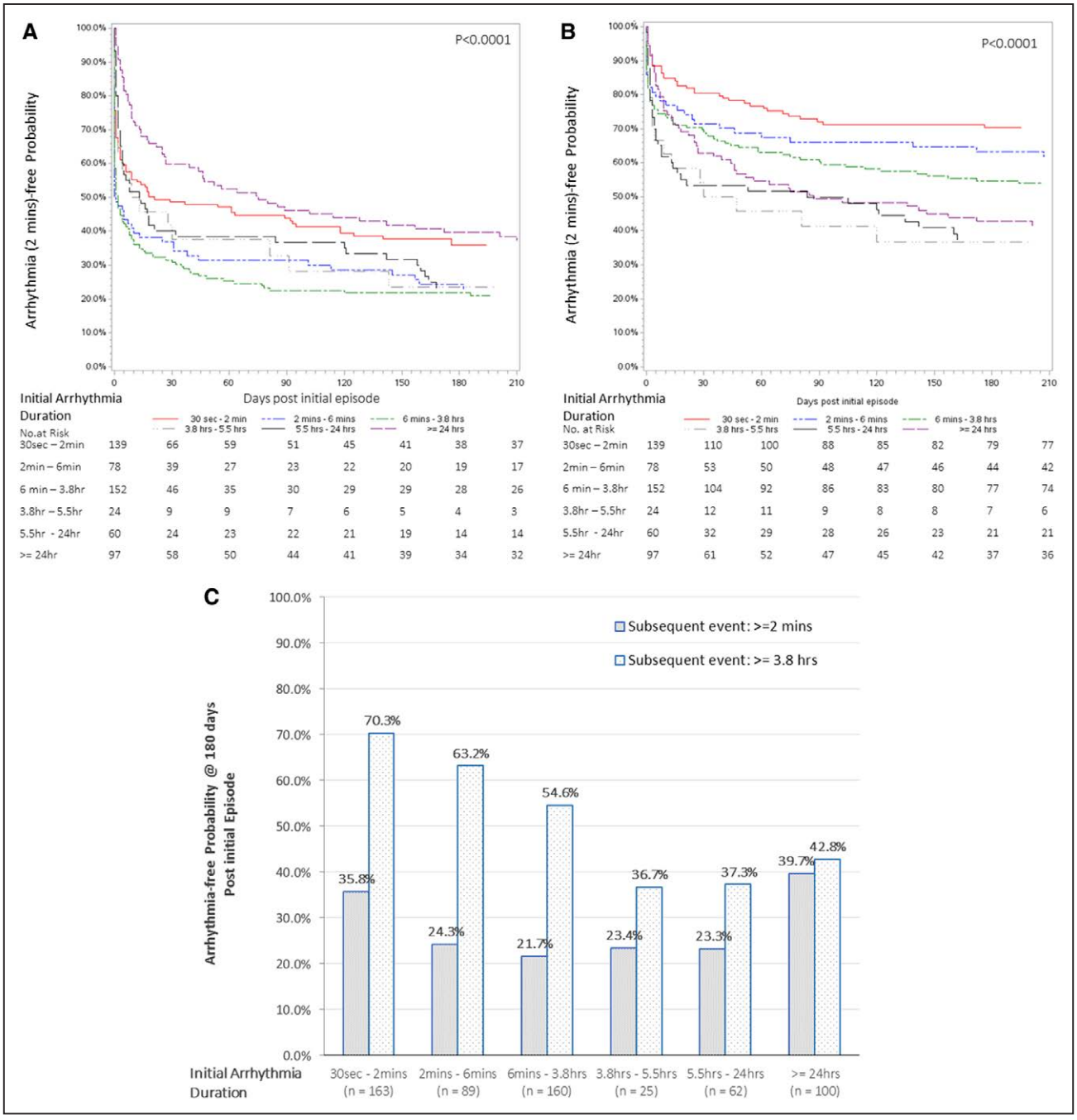

Figure 4. Analysis of subsequent atrial arrhythmia events.
Computed at 180 d using different definitions of initial atrial fibrillation (AF) event and subsequent AF event; (**A**) Kaplan-Meier plot with subsequent AF event defined as ≥2 min; (**B**) Kaplan-Meier plot with subsequent AF event defined as ≥3.8 h; (**C**) and Summary of results with both end points at 180 d of follow-up.

reflects clinically relevant AF for patients as it reflects the overall time in AF,[19] and higher burdens of AF have been shown to increase stroke risk[3,9–11]; however, the precise threshold that confers an increased risk is not completely understood and likely depends on other risk factors.[20] Although technology exists today that is effective in monitoring continuously for AF episode recurrence and overall burden postablation[21] (eg, Reveal LINQ, pacemakers, etc), there are cost, clinical indication, and patient preference barriers to perform this type of monitoring on all patients. Therapeutic success could be defined by a prespecified reduction in AF burden in response to an intervention. In the absence of this technology for all patients, most patients are observed at specific time points (typically 3, 6, and 12 months) for at least 24-hour duration to test for a single episode and then extrapolate that this 24-hour period reflects the patient's AF burden; however, intermittent monitoring is not accurate for estimating true AF burden.[22] Because the cohort in this

study had continuous monitoring via their pacemaker devices, we correlated initial AF episode durations with AF burden during the course of the study. In fact, using a short duration for AF detection resulted in a smaller percentage of AF burden; patients grouped between 30 seconds and 3.8 hours had a median AF burden of only 0.2%, which was statistically lower than the 9.5% median AF burden in the group with an initial AF episode >3.8 hours ($P<0.0001$). This observation implied an important correlation between AF detection threshold and AF burden. AF symptoms were not documented in the study, so it is not clear what symptoms were experienced. Previous studies have indicated that AF burden of 0.5% should be used as the definition of responder after ablation,[23] that 4.5% predicts subsequent AF after the blanking period,[24] and that >2 hours per day has a deleterious impact on quality of life.[25] The present study data would suggest that in a study where continuous monitoring was not feasible to directly measure AF burden, a more clinically meaningful AF episode duration threshold might be an initial episode of at least 3.8 hours in duration. Further, the advent of smartphone ECG recorders may present a reasonable, efficient, and scalable alternative for some long-term studies of AF patterns. More frequent ambulatory ECG recordings and multiweek Holters may be options as well.

We further tested the likelihood of a patient not experiencing a subsequent episode using the various cutoff thresholds. For patients with shorter initial episodes (30 s–2 minutes), the estimated probability of not having a longer episode (≥3.8 hours) in the following 180 days was 70%; whereas the probability was 37% for patients with initial episodes of 3.8 to 5.5 hours. In fact, for patients with an initial AF episode of 30 s to 2 minutes, 36% of the patients had no subsequent episode of ≥2 minutes in follow-up (Figure 4). These patients would be classified as being an AF end point in clinical trials, despite the absence of another AF event. Even though this study was conducted exclusively in a patient population of patients with an AF diagnosis, the data demonstrate that a single episode of AF does not reliably predict future episodes. As expected, stricter (longer) duration thresholds resulted in lower recurrence rates, and there were statistically different recurrence rates between episode duration categories 30 s and 3.8 hours and ≥3.8 hours.

It is, therefore, possible, that within the same study, the selection of AF episode duration definition alone could result in statistically different freedom from AF recurrence results. In a similar analysis of different cutoff durations on study results from the STAR AF II trial (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II), significant differences were also found between 30-second and 2-minute and 6-minute, 1-hour, and 24-hour time points.[26] Indeed, for that trial, whereas the reported freedom from AF/atrial flutter/AT was 25.5% based on the 30-second definition, alternative study efficacy rates increased to 73.1%, if 24 hours had been used as the definition.[26] The results of our study firmly indicate that clinical trial success could be consistently underestimated with the current definition of ≥30 seconds.

Certainly, clinical trials can and have used a variety of secondary end points, but by definition these do not define the study's interpretation and do not carry the weight of a succinct primary outcome analysis. There is evidence that, at least in the ablation literature, other symptom-oriented end points/instruments are better correlated to overall quality of life,[27] hospitalization,[28] and emergency room visits,[29] but are sensitive to placebo effect.

Study Limitations

The 30-second definition was proposed in an era of intermittent monitoring. Therefore, if 30 seconds of AF was detected via intermittent monitoring, it may have been assumed that the patient was likely having longer episodes of AF during periods in which the patient was not monitored. We have shown that patients with 30 seconds of AF often do not have longer episodes of AF, despite continuous monitoring with implantable devices. Medtronic PSR was selected as an appropriate source to evaluate this question from an existing database that combines patient characteristics and long-term device-detected AF captured electronically via Medtronic CareLink system. Continuous monitoring is the optimal method for monitoring AF[30,31] with device sensitivity of 95%[4] compared with 24-hour Holter device sensitivity of 44%.[21] Although the PSR was selected as a source to address this question, there are several limitations to its use. First, because we started with a cohort of patients eligible for dual-chamber pacemakers, they are not representative of the general population that is studied in some clinical trials, where the definition of AF episode duration is in question. For example, this cohort is older than most AF ablation clinical trials, which could have an effect on AF patterns, as age is a powerful and influential factor. However, in lieu of conducting a prospective trial with continuous monitoring of AF patients, this provides a good surrogate population that demonstrates some shared clinical characteristics. In addition, symptoms and clinical AF diagnosis status were not tracked for all patients at each follow-up visit; therefore, we are not able to correlate device data with symptoms and subsequent treatment. In addition, the clinical data consistently collected were limited, including treatment for AF that could affect arrhythmia patterns. Also, patient characteristics and comorbidities may have confounded the results, and

no analysis was conducted adjusting for these. We acknowledge that the 30-second threshold detection may have different predictive implications when detected on an intermittently recorded ECG or ECG monitor rather than an implanted device, but the issue has been unaddressed at this stage. Finally, AF episodes were not independently adjudicated, so there is the possibility that some AF episodes, especially of shorter duration, could contain artifact and therefore overestimate the incidence.

Conclusions

The presence of an initial AF episode of 30 seconds did not predict clinically meaningful AF patterns in a pacemaker population. It is likely that small differences in AF duration threshold could dramatically impact reported clinical or procedural outcomes, most notably AF ablation success rates. A consistent, uniformly measurable definition with clinical significance would be valuable to allow meaningful conclusions and implications of the results of observational and interventional investigations. In the future, reporting AF outcomes with different duration thresholds may be of value to clinicians and thereby facilitate comparison to older literature yet also provide alternative analyses of potential clinical impact.

ARTICLE INFORMATION

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Correspondence

Jonathan S. Steinberg, MD, Director, SMG Arrhythmia Center, Summit Medical Group, 85 Woodland Rd, Short Hills, NJ 07078. E-mail jsteinberg@smgnj.com

Affiliations

Heart Research Follow-up Program, University of Rochester School of Medicine and Dentistry, NY (J.S.S.). SMG Arrhythmia Center, Summit Medical Group, Short Hills, NJ (J.S.S.). Medtronic Cardiac Rhythm Heart Failure (CRHF), Minneapolis, MN (H.O., S.L., P.D.Z.).

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Disclosures

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