Circulation: Arrhythmia and Electrophysiology

EDITORIAL

Measuring Success in Ablation of Atrial Fibrillation

Time for a Paradigm Shift?

See Article by Steinberg et al

Maria Terricabras, MD
Atul Verma, MD
Carlos A. Morillo, MD

Atrial fibrillation (AF) ablation has emerged as an effective treatment primarily for patients refractory to antiarrhythmic drugs and in selected patients as first-line therapy to improve both quality of life and potentially long-term prognosis.[1,2] Although AF ablation may almost eliminate AF in some patients, in the majority significant symptomatic improvement may still be achieved despite the persistence of a small burden of AF.[3,4] In fact, patients may continue to experience a few hours of AF per month and still report a significant improvement in quality of life, particularly if the preablation burden was substantial. The gold standard metric used in clinical trials reporting the outcome of AF ablation has been saddled with an overly stringent definition of success: freedom from AF >30 seconds.[5] This definition of failure bares no clinical impact for the patient that is seeking symptomatic relief and most would agree that a single recurrence of AF lasting 31 seconds would hardly be viewed as a failure. Notwithstanding, the 2007 Heart Rhythm Society Consensus Statement on Catheter Ablation of AF promotes >30-second cutoff as the standard for defining success in clinical trials.[5] How did we reach this point?

It is unclear when exactly did the >30-second duration was adopted as the definition of AF. Interpretation of Holter's or telemetry conventionally agreed that >30 seconds of an irregularly irregular rhythm was required to diagnose AF. Success rate of catheter ablation of supraventricular reentrant arrhythmias such as atrioventricular nodal reentrant or accessory pathway–mediated tachycardias were >90% to 95% and curative in the majority,[6] and never held to this standard. Nonetheless, after the introduction of pulmonary vein targeting for AF in 1998, the expectation of a curative procedure remained, and recurrence of the first AF episode or any atrial tachyarrhythmia post ablation was perceived as a failure.

The requirement for a definition of AF post ablation was grounded on the need for standardization in reporting of clinical trials. A wide variability in reporting outcomes for AF ablation included; only recurrent symptomatic AF, any type of atrial arrhythmias, and a 90% reduction in AF burden. This resulted in a lack of standardization in outcomes among trials making them not comparable. Thus, part of the mandate of the Heart Rhythm Society Consensus was to standardize the AF ablation outcomes in clinical trials, and the >30-second definition was adopted.

Early on the electrophysiology community realized that complete elimination of AF was untenable and that reduction in the frequency, duration, and overall symptoms associated with AF were an acceptable goal. Of note, the primary goal of AF ablation was never to reduce stroke or mortality. Significant knowledge gaps exist related with the duration of AF that increases the risk of stroke and to further complicate the issue several studies demonstrating an association between

Key Words: Editorials ■ atrial fibrillation ■ atrial flutter ■ catheter ablation ■ electrophysiology ■ quality of life

http://circep.ahajournals.org

device detection of atrial high-rate episodes (potentially a surrogate of AF) and stroke was evident, but at the same time no temporal relationship between AF and stroke has also been described.[7] The threshold to start oral anticoagulation is not well established; however, it is certainly not any AF >30 seconds. The Canadian Cardiovascular Society Guidelines only recommend prescription of oral anticoagulation in higher risk patients with AF lasting >24 hours,[8] recommendation that is in keeping with recent evidence from the ASSERT trial (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial).[9]

In this issue of *Circulation: Arrhythmia and Electrophysiology*, Steinberg et al[10] tackle the controversy around the 30-second definition of success by reporting the results of a prospective registry of 615 patients with dual chamber pacemakers capable of AF detection who had at least one episode of AF during a follow-up of 3.7 years. The authors analyzed the likelihood of having further AF by establishing different thresholds based on the patient's first AF episode duration: >30 seconds, >2 minutes, >6 minutes, >3.8 hours, >5.5 hours, and >24 hours. The probability of freedom from AF after the first 12 months showed a significant jump between the 6-minute episode cutoff with a probability of 34.6% and the 3.8-hour episode with a probability of 52.6%. Using this 3.8-hour threshold, the authors compared the AF burden during follow-up in patients with a first AF episode of >3.8 hours or less, and they reported a highly significant difference between the 2 groups (0.2% versus 9.5%, respectively). They also analyzed patients according to the likelihood of being free from AF recurrence >3.8 hours at 180 days. They found that the freedom from a >3.8-hour recurrence was 70.3% for patients with an initial AF episode of 30 seconds to 2 minutes; 54.6%, 6 minutes to 3.8 hours; and 42.8% for an initial AF >24 hours. This analysis suggested that patients with initially short episodes of AF were less likely to have longer episodes in the future compared with those with initially long AF episodes. This point was reinforced when the authors looked at freedom from persistent AF which was 97.7% for patients with initial AF duration of 30 seconds to 2 minutes, 91.2% for initial AF of 6 minutes to 3.8 hours, and 77.1% for patients with initial AF of >24 hours. Based on these results, the authors suggest that a higher cutoff for success in AF ablation (such as 3.8 hours) could better determine the risk of future higher burden AF recurrence and new prolonged episodes of AF.[10]

The key limitation of this analysis was that it was performed in a population of older AF patients with pacemakers with incomplete baseline data. No information was available about the management of AF (ie, antiarrhythmic medications or ablation). Treatment can substantially alter the pattern of AF recurrence after an initial episode. If many of the study patients were treated with rate control only (a fairly safe assumption), then the authors' conclusions may not be applicable to a population that has undergone ablation and continues to receive rhythm control medication which can alter the pattern and duration of AF recurrence. Postablation, long-persisting episodes of atrial flutter/AF may arise in patients with low burdens of AF preablation because of iatrogenic reentry caused by incomplete lesions. However, patients may not develop any AF recurrence long-term even with a prolonged initial AF episode, particularly if it occurred during the first 3-month blanking period.

The lack of baseline data also limits how much we can rely on the study patients to reflect a patient population undergoing AF ablation mainly because device-detected AF is usually subclinical. The authors do not provide information on whether the initial AF episode detected by the device was actually the patient's first ever AF. If the patients had a preexisting history of AF, more information is needed about prior AF episode durations to better assess their relevance to future AF recurrence. Several other factors may influence the duration and occurrence of AF and include left atrial size and volume, prior duration of AF, and clinical components of the HATCH score (Hypertension, Age, Transient Ischemic Attack or Stroke, Chronic Obstructive Pulmonary Disease and Heart Failure).[11] This information was not provided, further limiting the comparability of this cohort with previously reported AF ablation studies.

Finally, the cutoffs proposed by the authors are no less arbitrary than the 30-second cutoff supported by the Heart Rhythm Society Consensus. The authors make a laudable effort to define cutoffs for AF duration based on the stroke literature. However, few of these studies included patients that are reflective of an AF ablation population. The 3.8-hour cutoff was derived from a study showing that 3.8 hours of device-detected AF was associated with a significant increase in thromboembolic event rate in 560 patients with heart failure and cardiac resynchronization therapy, which is quite different from the majority of patients receiving AF ablation today.[12] The TRENDS study (The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk) was the basis for the 5.5-hour cutoff, but about half of the patients in this study also had implantable defibrillators and/or resynchronization devices, around 60% had a history of congestive heart failure and a little more than one-third had a $CHADS_2$ score of >3.[13] Although the 6-minute cutoff comes from the ASSERT study, a recent subanalysis demonstrates that only patients with >24-hour AF duration had an increased risk of stroke or systemic embolism (hazard ratio, 3.24; [95% confidence interval, 1.51–6.95]; P=0.003).[9] Furthermore, whether it is duration or burden of AF episodes that determines risk of thromboembolic complications remains to be determined. The recently reported KP-RHYTHM study (Kai-

ser Permanente Real-World Heart Monitoring Strategy Evaluation, Treatment Patterns, and Health Metrics in Atrial Fibrillation) suggests that a burden of AF >11% was associated with a 3-fold increase in stroke and systemic embolism, after adjusting for either ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) or CHA_2DS_2-VASc stroke risk scores.[14]

Two ongoing large-scale trials are underway to assess whether oral anticoagulation is even warranted in patients with low-burden AF detected by implantable cardiac devices (ARTESIA: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01938248; and NOAH: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02618577).[15] What is the threshold of AF that increases the risk of stroke remains highly debated and therefore defining a relevant cutoff for AF success in a postablation population is certainly an important goal? Trials are underway to answer this question as well (OCEAN: URL: http://www.clinicaltrials.gov. Unique identifier: NCT02168829). Finally, great discussion is taking place between clinicians and clinical trialists about the most appropriate and relevant outcomes that should be reported. Should mortality, heart failure or simply significant AF recurrence reduction be defined on the basis of stroke? Real world registries[16] indicate that we are primarily performing ablations to alleviate symptoms, that is, improve quality of life. First-line and early AF ablation are proposed primarily to reduce the risk of AF progression, therefore choosing a cutoff that predicts AF progression should be a desirable outcome in this population. Adopting a definition of success as arbitrary as the >30-second cutoff has only ensured ongoing controversy and fails to resolve the debate on what is the most pragmatic definition of success and what are the outcomes of relevance in trials evaluating AF ablation.

Does the study by Steinberg et al[10] change the definition of clinical success post-AF ablation? This is unlikely mostly because these definitions have been arbitrarily chosen and not validated in the context of a randomized clinical trial. The 2017 Heart Rhythm Society Consensus statement continued to adopt the 30-second definition of success mainly because any other number chosen would be equally arbitrary and we would also lose the ability to compare contemporary clinical trial results to older ones designed since the 2007 statement that set the 30-second rule.[17] Nonetheless, more studies like Steinberg et al[10] in populations undergoing AF ablation or antiarrhythmic treatment are direly needed. Is the time ripe for a paradigm shift about the definition of AF ablation success and selection of outcomes that are clinically relevant? Clearly, outcomes that include AF burden, quality of life, and health resource utilization may be suffice in patients at low risk of thromboembolic complications. However, mortality, heart failure, stroke, and bleeding should be the target in moderate–high-risk AF patients with underlying left ventricular dysfunction. Steinberg et al[10] should be congratulated for diving head first into this topic that will certainly add to the ongoing debate of where should we draw the line on defining success post-AF ablation.

ARTICLE INFORMATION

Correspondence

Carlos A. Morillo, MD, Department of Cardiac Sciences, University of Calgary, Foothills Medical Centre, Room C823, 1403 29th St NW, Calgary, AB T2N 2T9, Canada. E-mail carlos.morillo@ucalgary.ca

Affiliations

Southlake Regional Health Centre, Newmarket, ON, Canada (M.T., A.V.). Department of Surgery, University of Toronto, ON, Canada (M.T., A.V.). Foothills Medical Centre and Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, University of Calgary, Canada (C.A.M.).

Disclosures

Dr Verma reports research grants from Biosense Webster, Medtronic, Bayer, and Biotronik. Dr Morillo reports grants from Bayer, and Pfizer, and consulting fees from Abbott, Biosense Webster, Boston Scientific, Bayer, Medtronic, Pfizer, and Servier. The other author reports no conflict.

REFERENCES

1. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378:417–427. doi: 10.1056/NEJMoa1707855.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210.
3. Wokhlu A, Monahan KH, Hodge DO, Asirvatham SJ, Friedman PA, Munger TM, Bradley DJ, Bluhm CM, Haroldson JM, Packer DL. Long-term quality of life after ablation of atrial fibrillation the impact of recurrence, symptom relief, and placebo effect. *J Am Coll Cardiol*. 2010;55:2308–2316. doi: 10.1016/j.jacc.2010.01.040.
4. Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Khaykin Y, Guerra PG, Nair G, Torrecilla EG, Verma A. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol*. 2013;29:1211–1217. doi: 10.1016/j.cjca.2013.06.006.
5. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ; Heart Rhythm Society; European Heart Rhythm Association; European Cardiac Arrhythmia Society; American College of Cardiology; American Heart Association; Society of Thoracic Surgeons. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace*. 2007;9:335–379. doi: 10.1093/europace/eum120.
6. Calkins H, Yong P, Miller JM, Olshansky B, Carlson M, Saul JP, Huang SK, Liem LB, Klein LS, Moser SA, Bloch DA, Gillette P, Prystowsky E. Catheter

ablation of accessory pathways, atrioventricular nodal reentrant tachycardia, and the atrioventricular junction: final results of a prospective, multicenter clinical trial. The Atakr Multicenter Investigators Group. *Circulation*. 1999;99:262–270.
7. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, Khokhar KB, Thiyagarajah A, Middeldorp ME, Nalliah CJ, Hendriks JML, Kalman JM, Lau DH, Sanders P. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J*. 2018;39:1407–1415. doi: 10.1093/eurheartj/ehx731.
8. Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, McMurtry MS, Connolly S, Cox JL, Dorian P, Ivers N, Leblanc K, Nattel S, Healey JS; CCS Atrial Fibrillation Guidelines Committee. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2014;30:1114–1130. doi: 10.1016/j.cjca.2014.08.001.
9. Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser SH, Gold MR, Capucci A, Lau CP, Morillo CA, Hobbelt AH, Rienstra M, Connolly SJ. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. 2017;38:1339–1344. doi: 10.1093/eurheartj/ehx042.
10. Steinberg JS, O'Connell H, Li S, Ziegler PD. Thirty-second gold standard definition of atrial fibrillation and its relationship with subsequent arrhythmia patterns: analysis of a large prospective device database. *Circ Arrhythm Electrophysiol*. 2018;11:e006274. doi: 10.1161/CIRCEP.118.006274.
11. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol*. 2010;55:725–731. doi: 10.1016/j.jacc.2009.11.040.
12. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK, Bauer WR, Paul V, Sack S. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace*. 2012;14:230–237. doi: 10.1093/europace/eur293.
13. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2:474–480. doi: 10.1161/CIRCEP.109.849638.
14. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, Harrison TN, Liu TI, Solomon MD. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation: the KP-RHYTHM study [published online ahead of print May 16, 2018]. *JAMA Cardiol*. doi: 10.1001/jamacardio.2018.1176.
15. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120–129. doi: 10.1056/NEJMoa1105575.
16. Arbelo E, Brugada J, Blomström-Lundqvist C, Laroche C, Kautzner J, Pokushalov E, Raatikainen P, Efremidis M, Hindricks G, Barrera A, Maggioni A, Tavazzi L, Dagres N; on the behalf of the ESC-EHRA Atrial Fibrillation Ablation Long-term Registry Investigators. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J*. 2017;38:1303–1316. doi: 10.1093/eurheartj/ehw564.
17. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14:e275–e444. doi: 10.1016/j.hrthm.2017.05.012.

Measuring Success in Ablation of Atrial Fibrillation: Time for a Paradigm Shift?

Maria Terricabras, Atul Verma and Carlos A. Morillo

Circ Arrhythm Electrophysiol. 2018;11:
doi: 10.1161/CIRCEP.118.006582
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084