https://doi.org/10.1093/europace/euac208

Estimated incidence of previously undetected atrial fibrillation on a 14-day continuous electrocardiographic monitor and associated risk of stroke: comment—Authors' reply

This is a response to the Letter to the Editor, 'Estimated incidence of previously undetected atrial fibrillation on a 14-day continuous electrocardiographic monitor and associated risk of stroke: comment' by Adithya Sreeniva and Mahmood Ahmad https://doi.org/10.1093/europace/euac206, about the article, 'Estimated incidence of previously undetected atrial fibrillation on a 14-day continuous electrocardiographic monitor and associated risk of stroke' by William F. McIntyre *et al.* https://doi.org/10.1093/europace/euab324.

We thank Sreenivas and Ahmad for their interest in our work.

We used pacemaker data from participants in asymptomatic atrial fibrillation and stroke evaluation in pacemaker patients and the atrial fibrillation reduction atrial pacing trial (ASSERT) to simulate 14-day Holter monitors used for atrial fibrillation (AF) screening in patients aged ≤65 with hypertension.[1] The proportion of patients who would have a total duration of AF ≥6 min was estimated at 3.1%. This finding was associated with a tripling of the hazard for stroke.

The readers request exploration of the relationship between CHA_2DS_2-VASc and stroke/systemic emboli in ASSERT patients without any AF. A previous analysis of ASSERT reported that among patients with no subclinical AF during follow-up, 19 strokes or systemic emboli occurred in 1811 patients, corresponding to an event rate of 0.54%/year.[2] With so few clinical events, we would not have the power to appropriately investigate this relationship. Moreover, we would have no ability to test whether such events in high CHA_2DS_2-VASc patients without AF would be sensitive to oral anticoagulation (OAC). Larger, observational data sets with contemporary monitoring are better suited to answer the question of baseline risk and appropriately designed randomized trials would be required to assess the role of OAC in this population. Two large randomized trials have already failed to show that OAC was superior to aspirin for the prevention of recurrent stroke in patients with a prior history of embolic stroke of undetermined source (ESUS). Among these, rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent embolic stroke of undetermined source (NAVIGATE-ESUS) showed that OAC increased bleeding.[3] The readers also asked about the relationship between the burden of premature atrial contractions (PACs) and the risk of stroke/systemic embolism. The pacemakers used in ASSERT did not collect these data. Interestingly, a sub-study of NAVIGATE-ESUS showed that high PAC counts did not predict response to OAC in patients with ESUS but without AF[4]

The readers wonder about the relationship between AF episodes that lasted <6 min and stroke. ASSERT began in 2000, when device-based AF detection algorithms were less sophisticated compared with today's technology. In ASSERT, physicians reviewed all device-detected AF lasting ≥6 min, and 50% of shorter episodes.[5] Of the more than 10 000 adjudicated episodes lasting <6 min, only 50% were actually AF; these episodes were totally impractical for clinical or research use. As a result, ASSERT focused on device-detected AF episodes that lasted ≥6 min, where the positive predictive value was 83%, although physician review was still necessary. Although the readers are concerned about the risk associated with short AF episodes, it was uncommon for individuals with device-detected AF to have only short episodes. The average and median AF burdens over 14 days of simulated monitoring were 55.3 ± 104.7 h and 6.1 (interquartile range 1.1–38.3) hours, respectively.

Each data set has its strengths and weaknesses. Ten years after the original publication, the strengths of ASSERT remain the completeness of monitoring and the very low rate of OAC use. Unfortunately, it cannot tell us about AF events that were shorter than 6 min and the relatively small number of events makes subgroup analyses challenging. We believe the questions raised by Sreenivas and Ahmad are interesting and important but are best left to other studies.

Conflict of interest: The authors have no conflicts of interest to declare.

References

1. McIntyre WF, Wang J, Benz AP, Johnson L, Connolly SJ, Van Gelder IC *et al.* Estimated incidence of previously undetected atrial fibrillation on a 14-day continuous electrocardiographic monitor and associated risk of stroke. *Europace* 2022;**24**:1058–64.
2. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR *et al.* Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;**38**:1339–44.
3. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD *et al.* Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–201.
4. Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE *et al.* Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. *JAMA Neurol* 2019;**76**:764–73.
5. Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH *et al.* Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm* 2012;**9**:1241–6.

W.F. McIntyre* and J.S. Healey
Population Health Research Institute, Hamilton, ON, Canada
*Corresponding author. Tel: +1 905 521 2100 (e40631); fax: +1 905 297 3785.
E-mail address: william.mcintyre@phri.ca

https://doi.org/10.1093/europace/euac209

Arrhythmic risk assessment of mitral valve prolapse pre- and post-mitral surgery—Authors' reply

This is a response to the Letter to the Editor, 'New-onset ventricular arrhythmias after surgery for mitral valve prolapse: how to classify and manage?' by Konstantinos Tampakis *et al.* https://doi.org/10.1093/europace/euac207, about the article, 'EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC council on valvular heart disease and the European Association of Cardiovascular Imaging endorsed by the Heart Rhythm Society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society', by A. Sabbag *et al.*, https://doi.org/10.1093/europace/euac125.

We appreciate the interest of Tampakis *et al.* in our consensus document and the reemphasis on well-known knowledge gaps.[1,2] The precise mechanism leading to ventricular arrhythmia (VA) in patients with arrhythmic mitral valve prolapse (AMVP) remains a matter of speculation. There is significant heterogeneity in the arrhythmic burden observed in patients with AMVP, ranging from frequent monofocal premature ventricular contractions (PVCs), through nonsustained ventricular tachycardia, sustained monomorphic ventricular tachycardia (SMVT), multifocal PVCs and ending with PVC triggered ventricular fibrillation (VF), and polymorphic ventricular tachycardia/VF. This wide spectrum may not be explained by any single all-encompassing mechanism, particularly considering the frequent discrepancies between imaging data and arrhythmic events.

SMVT consistent with classical reentry was infrequently reported in AMVP.[3,4] Yet, there are not enough published data detailing the type of arrhythmia leading to sudden cardiac death in this newly defined subpopulation. Therefore, it would be premature to disregard reentry as an important mechanism of malignant VA, even if it accounts for only a minority of cases.

It follows that the discriminatory power of programed ventricular stimulation (PVS) would be limited in this context. While not extensively studied, the writing committee of the consensus document suggested that the induction of a SMVT may be considered an indicator of further VA.[2] However the significance of a negative study or indeed the induction of VF is less clear.

A central pillar of the consensus document was the definition of the various AMVP phenotypes. First among them is severe degenerative mitral regurgitation (MR), often accompanied by left ventricular dysfunction. The value of early mitral valve surgery in cases with at least moderate to severe MR is well established, including a reported decrease in mortality and SCD.[5] The novelty in our document was the acknowledgment of the elevated risk of SCD associated with severe myxomatous MVP phenotype irrespective of MR severity. We strive to emphasize both the critical importance of MR severity and the fact that absence of hemodynamically significant MR provides no reassurance in this unique population.

The role of mitral valve surgery in the prevention of malignant arrhythmia, in the absence of a conventional indication for surgery, is an important gap in our current understanding of AMVP. While one may conceive multiple mechanisms by which mitral valve surgery may reduce the arrhythmic risk, without solid data this is mere conjecture. Likewise, there are no robust data describing the incidence or the type of VA observed in post mitral surgery patient. It would be reasonable to assume that most would be the result of scar related reentry or bundle branch reentry, yet we may not dismiss the possibility of non-reentrant VA as a relevant mechanism. Furthermore pre-existing scar in the left ventricular myocardium is common among patient with severe MR and may support reentrant arrhythmia irrespective of surgery.

At this time, we would recommend to consider the known predictors of risk, chiefly overt arrhythmia, unexplained syncope, and the described echo/CMR features and to follow the suggested risk stratification. While it is possible that PVS yield may be notable in post mitral surgery patients, the available evidence does not support to recommend it widely or adopting a different approach in this population. We do recognize the validity and importance of the question and encourage further research.

Conflict of interest: None declared.

References

1. Tampakis K, Polytarchou K, Andrikopoulos G. New-onset ventricular arrhythmias after surgery for mitral valve prolapse: how to classify and manage. *Europace* 2022.
2. Sabbag A, Essayagh B, Barrera JDR, Basso C, Berni A, Cosyns B *et al.* EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC council on valvular heart disease and the European Association of Cardiovascular Imaging endorsed by the heart rhythm society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society. *Europace*. 2022;**24**:1981–2003.
3. Marano PJ, Lim LJ, Sanchez JM, Alvi R, Nah G, Badhwar N *et al.* Long-term outcomes of ablation for ventricular arrhythmias in mitral valve prolapse. *J Interv Card Electrophysiol* 2021;**61**:145–54.
4. Ezzeddine FM, Siontis KC, Giudicessi J, Ackerman MJ, Killu AM, Deshmukh AJ *et al.* Substrate characterization and outcomes of catheter ablation of ventricular arrhythmias in patients with mitral annular disjunction. *Circ Arrhythm Electrophysiol* 2022;**15**:e011088.
5. Grigioni F, Enriquez-Sarano M, Ling LH, Bailey KR, Seward JB, Tajik AJ *et al.* Sudden death in mitral regurgitation due to flail leaflet. *J Am Coll Cardiol* 1999;**34**:2078–85.

Avi Sabbag [1]*, Benjamin Essayagh [2,3], Maurice Enriquez-Sarano [4], and Kristina Hermann Haugaa [5]

[1]The Davidai Center for Rhythm Disturbances and Pacing, Chaim Sheba Medical Center, Tel Hashomer, Israel and The Sakler Faculty of Medicine, Tel Aviv University, Israel; [2]Department of Cardiovascular Medicine, Simone Veil Hospital, Cannes, France; [3]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; [4]Minneapolis Heart Institute, Minneapolis, MN, USA; and [5]ProCardio Center for Innovation, Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

*Corresponding author. Tel: +972 3 5309197; fax: +972 3 5305804. *E-mail address*: avisabbag@gmail.com

https://doi.org/10.1093/europace/euac248

Prognostic value of right ventricular refractory period heterogeneity in Brugada syndrome. Independent predictor or part of something more complex?

This Letter to the Editor refers to article: 'Prognostic value of right ventricular refractory period heterogeneity in Type-1 Brugada electrocardiographic pattern' by Rossi *et al.* https://doi.org/10.1093/europace/euac168.

A response to this letter is available 'Prognostic value of right ventricular refractory period heterogeneity in Brugada syndrome. Independent predictor or part of something more complex?—Authors' response' by Alberto Giannoni *et al.* https://doi.org/10.1093/europace/euac249.

We have recently read with great interest the article by Rossi *et al.*[1] entitled 'Prognostic value of right ventricular refractory period heterogeneity in Type-1 Brugada electrocardiographic pattern'.

A prognostic stratification with electrophysiological study (EPS) was performed in 198 patients of a cohort of 372 Brugada syndrome (BrS) patients with spontaneous or drug-induced type-1 electrocardiogram (ECG) with symptoms. The primary endpoint of the study was a composite of sudden cardiac death (SCD), resuscitated cardiac arrest, or appropriate intervention by the implantable cardioverter-defibrillator. Family history of SCD, syncope, and a spontaneous Type-1 ECG pattern were univariate predictors of the primary endpoint in the whole population. From results obtained by the authors, in patients undergoing EPS, the primary endpoint was not only predicted by ventricular tachycardia (VT)/ventricular fibrillation (VF) inducibility but also by a difference in the refractory period between right ventricular outflow tract (RVOT) and right ventricle apex (ΔRPRVOT-apex) > 60 ms. For the authors, the eterogeneity of right ventricular refractory periods represents a strong, independent predictor of life-threatening arrhythmias in BrS patients, beyond VT/VF inducibility at EPS and common clinical predictors.[1]

As reported in some research, differences between shortest and longest refractory periods are not the sole indicators of the risk of developing re-entry, and the shape of the blocked zone may also be important.[2] The combined effect of three variables must compete together and exceed a threshold: the zone of unidirectional block must be large enough, conduction around this zone must be slow enough, and refractory periods proximal to the zone of block must be short enough (*Figure 1*). Even in the presence of large disparities in refractory periods but when the size of sites of prolonged refractory period is small, re-entry will not occur unless conduction is also significantly slowed.[3,4] Considering that the electrogenic alterations at the base of BrS are mainly epicardial and that EPS provide data about endocardial refractory periods is interesting to know by the authors what is in their cohort of patients the role of the other two variables listed above, so that right ventricular refractory period heterogeneity may be considered 'a strong independent predictor of life-threatening arrhythmias'. Dispersion of refractory period is a necessary but not sufficient condition for initiation of re-entry.[3]

Conflict of interest: None declared.

References

1. Rossi A, Giannoni A, Nesti M, Notarstefano P, Castiglione V, Solarino G, *et al.* Prognostic value of right ventricular refractory period heterogeneity in type-1 Brugada electrocardiographic pattern. *Europace* 2023;**25**:651-9.
2. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. II. The role of nonuniform recovery of excitability in the occurrence of unidirectional block, as studied with multiple microelectrodes. *Circ Res* 1976;**39**:168–77.
3. Burton FL, Cobbe SM. Dispersion of ventricular repolarization and refractory period. *Cardiovasc Res* 2001;**50**:10–23.
4. Dendramis G, Antzelevitch C, Brugada P. *Brugada syndrome: diagnosis, clinical manifestations, risk stratification and treatment*. New York: Nova Science Publishers; 2015.