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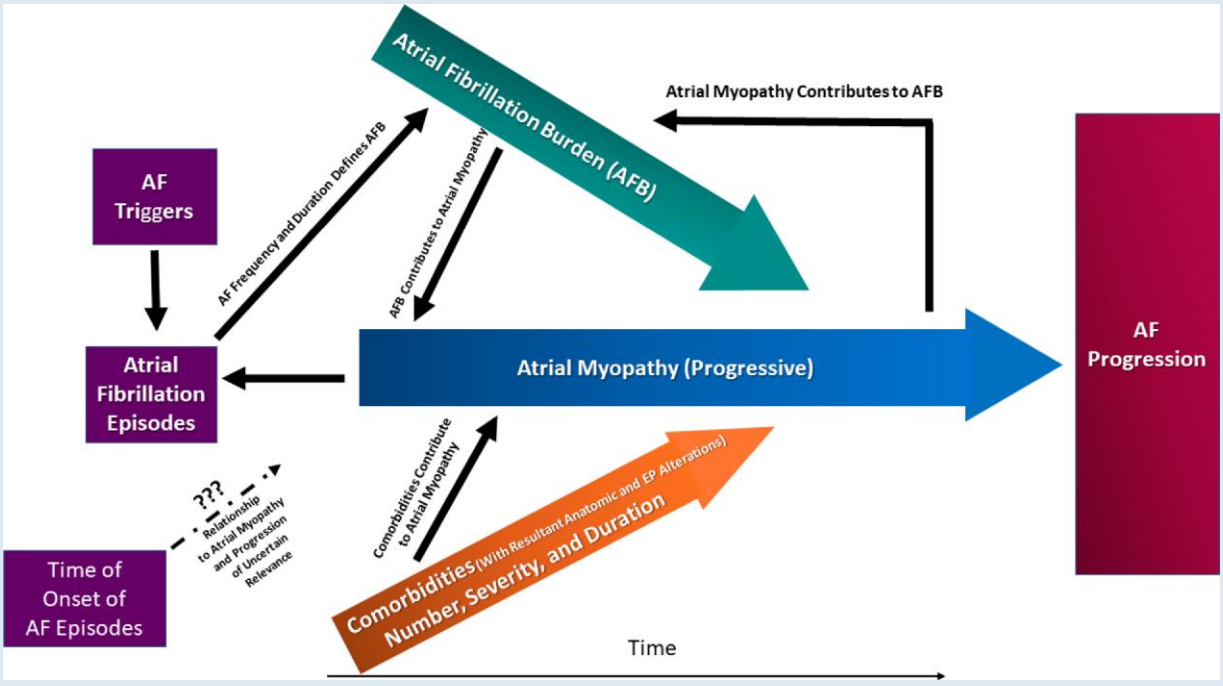
EDITORIAL

Atrial fibrillation progression: another step in the RACE to full understanding

Alessandro Capucci [1] **and James A. Reiffel** [2]*

[1]Director of Clinica di Cardiologia Institute, Ospedali Riuniti di Ancona, Polithecnic Marche University, Ancona, Italy; and [2]Department of Medicine, Division of Cardiology, Columbia University Vagelos College of Physicians & Surgeons, c/o 202 Birkdale Lane, Jupiter, Florida 33458, USA

Graphical Abstract



Atrial fibrillation progression: a clinical consequence of atrial fibrillation burden, concomitant comorbidities, and their duration.

This editorial refers to 'Time of onset of atrial fibrillation and atrial fibrillation progression data from the RACE V study', by M.E. van de Lande *et al.*, https://doi.org/10.1093/europace/euad058.

The RACE V substudy in this issue of Europace[1] involving 278 patients with paroxysmal atrial fibrillation (AF) implanted with a Reveal device and with a median follow-up of 2.2 years reported that progression to persistent or permanent AF or to a greater burden of >3% was more evident in patients who initially had a mixed pattern of AF onset times compared to essentially only (>80%) nocturnal or daytime onset. However, looking at the so-called mixed population, it is clearly evident in their that these patients had: more underlying comorbidites, lower glomerular filtration rates, more diabetes, higher CHA_2DS_2-Vasc (congestive heart failure, hypertension, age 75 and above, diabetes, prior stroke, vascular disease, age 65–74, and sex category) scores, and numerically

* Corresponding author. Tel/fax: +1 561 203 2161. *E-mail address*: jar2@columbia.edu

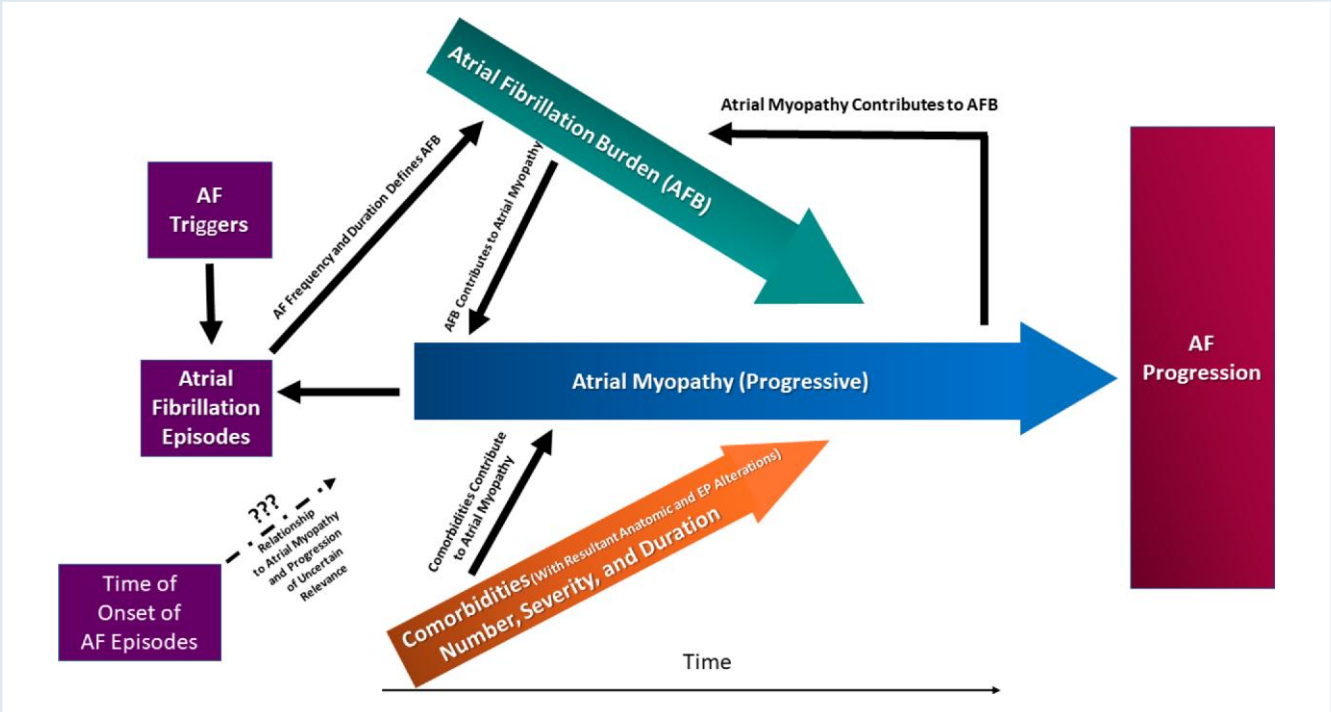


Figure 1 The figure depicts the relationships among AF events, underlying comorbidities frequent in patients with and contributing to atrial fibrillation, their combined influence on AF burden, the central role of atrial myopathy, and the contributions of each of these re: AF progression. The greater the number of comorbidites, the greater their severity, and the longer their duration all likely increase the magnitude of the atrial myopathy. Atrial myopathy is associated with structural and electrophysiological alterations that facilitate the maintenance and progression of atrial fibrillation. It appears likely that the more severe the atrial myopathy, the greater will be the atrial fibrillation burden (percentage of time atrial fibrillation is present). Concordantly, atrial fibrillation itself, through tachycardic and other actions can contribute to the presence and severity of atrial myopathy, which underlies the concept of atrial fibrillation begets atrial fibrillation and the ultimate link of greater AF burden, more atrial myopathy, and higher likelihood of AF progression (as well as greater adverse clinical outcomes). What is not clear, and hence shown with a broken arrow and several question marks, is whether the time of onset of episodes of AF (nocturnal, daytime, or mixed) has any direct relationship with atrial myopathy or atrial fibrillation progression. See text for discussion.

larger (though not statistically) left atria than the other two groups. This is in accordance with previous papers where the basal clinical setting has been considered the crucial point for progression.[2,3] Similar to virtually all other recent large AF trials, hypertension was present in the majority of the AF population (more than 80% in the present cases). Accordingly, this study is consistent with the belief that progression is linked to associated clinical contributors.[4] Moreover, early treatment of both the AF and the comorbidities has been associated with reduced progression and reduction of adverse clinical outcomes.[5] The timing of episode onsets appears to us to be of less certain contributory significance at this point (*Graphical Abstract*, *Figure 1*; and, see more below). Confounding the present analysis, the nocturnal and daytime onset groups had a significantly higher use of antiarrhythmic drugs than the mixed group, which could certainly have been an additional factor in their lower likelihood of developing progressive AF. The report did not make clear why this imbalance was present.

A second point for discussion is whether a 3% longer burden should really be considered a sign of AF progression independent of being related to its casuality. The cited Nguyen paper where the concept of 3% is advanced is also a RACE V substudy with few patients taken from the same cases; therefore, it is not supported by larger experiences. Many studies have provided evidence for the concept of atrial cardiomyopathy and its progression as a marker for AF progression. That is, AF could be only the tip of the iceberg with the associated cardiovascular contributors as the main basis for AF development and progression.[6] While high AF burden itself can alter the atria and co-contribute to the development and progression of atrial cardiomyopathic alterations and consequences, this is less clear for infrequent or short periods of AF.

A third point worthy of discussion is related to the mechanisms causing nocturnal AF episodes vs. daytime or mixed onset episodes. In the present study, the nocturnal onset AF group involved people with less comorbidities, aside from the finding of a higher obesity level in the nocturnal ones (apnoea/hypopnoea syndrome likely). Although Coumel has suggested in case reports that nocturnal AF is mainly due to nocturnal parasympathathetic dominance, in other studies using continuous cerebral monitoring during sleep it has been demonstrated that a high percentage of nocturnal AF ensues in the arousal or REM (rapid eye movement) state (not in the vagal Phase 3–4), therefore outlining a sympathetic/vagal interaction more than a purely parasympathetic influence.[7] For the mainly daytime only episodes, it is highly possible that a prevalent sympathetic dominance could be present, which might be demonstrable by studying such patients' heart rate variability with appropriate monitoring approaches.

Finally, one might postulate the possibility that the mixed onset AF group had greater progression not only because of more contributory comorbidities to the associated atrial myopathy but because mixed onset might be a consequence of a longer AF history and more resultant already advanced atrial myopathy.[8] That is, might predominantly nocturnal or daytime AF be earlier forms which, as the atrial myopathy progresses, evolve into more episodes in which a mixed onset pattern

develops. In this construct, which we believe is the more likely, the mixed time of onset would be a marker of more advanced atrial myopathy rather than a contributor to it. The Van de Lande *et al.* paper[1] did not investigate the duration of AF history in the three groups (nocturnal onset, daytime onset, mixed onset), so we do not know if this consideration holds truth. However, the possibility that the duration of AF history is an important link between the type of AF onset and the further progression of AF should be considered and might therefore be appropriate for subsequent investigation.

In conclusion, this RACE V study supports the belief that AF progression is not a phenomenon of mainly electrophysiologic evolution but is a consequence of an underlying atrial organic disease that evolves over time—especially if early and appropriate therapeutic intervention is not provided. Whether the time of episode onsets during the diurnal cycle is another major factor will require additional studies to evaluate.

Conflict of interest: A.C.: Scientific Consultant of Italian Biotronick. J.A.R.: Investigator and/or Consultant for J&J, Sanofi, Acesion, Amarin, InCarda Therapeutics; Speakers Bureau for Sanofi.

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