



Atrial Fibrillation Progression: New Insight in The Natural History of This Arrhythmia

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The past decade has witnessed a dramatic shift in our approach to the management of atrial fibrillation (AF).¹ This can largely be attributed to the advent of catheter ablation therapy which has proven to be significantly more efficacious in achieving arrhythmia control than antiarrhythmic drugs.²⁻⁴ However, despite these developments, there is a paucity of data on the natural history of this arrhythmia and studies that have been conducted so far to evaluate this aspect of AF behavior, are mostly retrospective.⁵⁻⁷ Thus, there is a growing need to assess AF progression on a prospective basis.

In response to this emerging need, Pappone et al report on the natural history of arrhythmia progression in a heterogeneous population of patients presenting with the first episode of AF that were prospectively followed for 5 years.⁸ Although this was an observational study, the prospective design ensured exclusion of subjects where AF was attributable to a reversible etiology. Thus over a 6 month period, 402 patients were screened of which, 106 were selected for participation. For the next 5-years, enrolled subjects were followed by multiple clinic visits, holter monitors and transthoracic echocardiograms (at 1, 3, 6 months and then annually) as well as trans-telephonic monitors which the patients were required to transmit from 5 days

a week for the study duration. Additionally, all patients underwent transesophageal echocardiogram (TEE) at baseline and these were repeated annually in the subgroup of patients who had comorbidities.

The initial AF episode was not treated in any consistent way. However, for subsequent recurrences, antiarrhythmic drug (AAD) therapy was initiated with class IC and / or class III agents. Patients that failed and / or were intolerant to AADs were offered catheter ablation. The primary study end-point was assessment of long-term AF progression. Thus over the 5-year follow-up period, almost half the patients (n=50) maintained sinus rhythm without any intervention. In the remaining 56 subjects that experienced AF recurrence, 11 patients were treated with catheter ablation and the rest (45 subjects) with AADs. In the latter group, AF remained paroxysmal in 21 and became persistent in 24 (16 of these progressed to a permanent stage). Patients demonstrating AF recurrence and / or AF progression were older and had more co-morbidities especially diabetes and heart failure. Other interesting observations included 19% incidence of silent AF and occurrence of cardiovascular / cerebrovascular events exclusively in patients with more established forms of AF.

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This is an interesting study which provides us insight on the natural history of AF progression. However, there are some limitations both in the study design and the reported outcomes. Over a 6-month period, 402 eligible subjects (presenting with 1st episode of paroxysmal AF with no prior history of the arrhythmia) were identified from a single hospital. This is an inordinately high number which may reflect unique referral patterns to a tertiary center that is well recognized for its expertise in the management of AF. This raises the issue of whether these data can be “generalized”. Perhaps the prospective study design and pre-specified inclusion criteria help mitigate this concern. The follow-up schedule for patients participating in the study was quite intense: 5 days per week of 3-minute TTMs for the entire study duration as well as frequent (n=7) TTE, clinic visits and holoers and all patients with co-morbidities (roughly 50% of the cohort) underwent annual TEEs. This latter requirement seems rather aggressive and without precedence. However, despite this arduous schedule, patient follow-up was 100% which makes results of the study compelling. The outcome data reveals dichotomous AF progression. Approximately half the patients presenting with the first episode of AF did not experience future arrhythmia recurrences whereas in the remainder, AF recurrences were common despite AADs. In the latter group, half the patients progressed to more established forms of AF within 2 years with the majority (67%) eventually developing permanent AF. Such dichotomous nature of AF progression as observed in this study seems unique and inconsistent with prior reports.^{5-7,9} There are several possible explanations for the discrepancy: prior studies were largely retrospective with variable patient follow-up, current study design may have overestimated certain AF categories, 5-year prospective follow-up while long may still be insufficient to truly gauge the natural history of AF in a heterogeneous population, etc.

A major criticism of the current study is that the category of permanent AF as defined by the investigators may have included patients considered “long persistent” as per the most recent HRS/EHRA/ECAS consensus statement.^{10,11} However, even if we reclassify the groups, the observation that 20% of patients experiencing AF for the first time will progress to a persistent state within 5

years, despite AADs is sobering. In this context, the authors’ observation of no AF recurrence / progression in subjects who underwent AF ablation is reassuring.

However, one has to be appropriately cautious in interpreting these data because of the very small numbers (only 11 patients underwent AF ablation) and lack of randomization. Nevertheless these observations are consistent with the results of recent prospective randomized multi-center studies that compared catheter ablation with AADs and found the latter significantly less useful in restoring / maintaining sinus rhythm long-term.^{2,4} Another interesting observation in the current study is the high occurrence (39%) of side effects in patients treated with AADs. This seems excessive and inconsistent with observations of prior studies.^{9,12} Since the investigators of the current study do not describe the criteria used for adverse event characterization, it can be speculated that they may have overestimated the problem. These investigators also found association between AF progression and the presence of co-morbidities. However, it is interesting to note that in patients demonstrating AF progression, the co-morbidities remained relatively stable over the study duration. Thus it is difficult to elicit a direct “cause and effect” relationship. One way to sort this out may be perhaps in a future trial to control for different co-morbidities by aggressive treatment while monitoring AF progression. However, such an exercise can be time consuming and could potentially be viewed as unethical if done in a prospective manner.

So for now we have to remain content with the important information that has been revealed in this painstakingly conducted study which offers new insight in the natural history of AF progression. As shown in this study, AF progression can be dichotomous, may be predicated by the presence of co-morbidities and can be arrested by catheter ablation. This latter observation is consistent with data from prior studies and supports utilizing a more aggressive strategy in the initial management of this arrhythmia.

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