

# Lone Atrial Fibrillation Reconfirmed as Unfavorable Arrhythmia

Mitsuaki Sawano<sup>1,2</sup><sup>1</sup>Keio University School of Medicine, Department of Cardiology, Tokyo, Japan<sup>2</sup>Tokyo Dental College Ichikawa General Hospital, Department of Cardiology, Tokyo, Japan**See article vol. 28: 241-248**

Atrial fibrillation (AF) has been recognized as an intervenable risk factor for incident cardioembolic stroke in various studies. Today, patients with AF receive oral anticoagulation therapy to prevent future thromboembolic events, based on clinical risk scores such as the CHADS<sub>2</sub><sup>1)</sup> and CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>2)</sup>. Both scores incorporate risk factors such as age, sex, hypertension, diabetes mellitus, congestive heart failure, previous stroke, and other vascular diseases that incrementally increase the likelihood of incident stroke events, particularly among the Caucasian population. Similarly, in a joint cohort of five representative AF registries in Japan, previous stroke, advanced age, hypertension, low body mass index, and persistent/permanent AF were identified as independent risk factors for ischemic stroke<sup>3)</sup>. Since the majority of the cerebro-cardiovascular events have been shown to be experienced by AF patients with one or more stroke risk factors, their prognosis in the absence of these features has been long believed to be benign. In their latest article, Sairenchi *et al.* indicated that AF patients with and without traditional cerebrovascular stroke risk factors had higher risk of dying due to cerebro-cardiovascular events, in an extensive cohort of 90,629 individuals with 20 years of follow-up<sup>4)</sup>. Their observation has reinforced the underestimated risk of what has commonly been known as lone AF, that is, AF without overt cardiovascular disease or precipitating illness.

Reported prevalence of lone AF has been known to vary widely depending on the definition and cardiovascular testing modalities used to screen for sub-clinical heart disease at the study baseline. The 1948 Framingham Heart Study reported the prevalence of 0.8% (43/5,209) using the absence of coronary heart disease, congestive heart failure, rheumatic heart dis-

ease, and hypertensive cardiovascular disease as a definition. Moreover, incidence of stroke was significantly higher in the lone AF group as compared to the matched controls<sup>5)</sup>. The 1950 Olmsted County Study that also found higher risk of stroke during a 30-year follow-up and showed that lone AF was present in 2.7% (97/3,623) of those aged  $\leq 60$  years<sup>6)</sup>. In the 1993 Ibaraki Prefectural Health Study, a community-based large cohort study including individuals aged 40–79 years living in Ibaraki prefecture, lone AF was found in 0.03% (31/90,629) of the total cohort, using the definition of the absence of either hypertension, dyslipidemia, diabetes mellitus, habitual smoking, or heavy drinking. As stated in their article, patients with lone AF were at increased risk for long-term mortality, and this included both genders.

Future directions of this field are likely to involve (1) performing a more sophisticated biomarker, cardiac imaging, or genetic testing; and (2) combining various digital health data collected from various sources at serial occasions overcoming the limitations of epidemiological cohorts that rely on baseline individual evaluation. Since much of the detrimental events occur decades after an initial diagnosis of lone AF, determining the optimal strategy to recapture these patients with lone AF during the course of their lives as they transition into a higher-risk state (e.g., elevated blood pressure, glucose, structural changes of their heart chambers or valves) is crucial.

For example, a recent NIPPON DATA 2010 study showed that a subtle increase in serum B-type natriuretic peptide (BNP) was linked to electrocardiographic P-wave terminal force in lead V1 observed at baseline<sup>7)</sup>. The linkage between electrocardiographic P-wave terminal force in lead V1 and long-term outcomes remains to be confirmed. In the Japanese general population, an echocardiographic assessment utilizing speckled tracking showed that left atrial reservoir strain is an independent predictor of elevated

serum BNP levels, with both possibly being markers of increased risk of heart failure in older adults<sup>8</sup>). In a regional case registration of Japanese patients with lone AF, seven rare variants in *KCNA5*, *KCNQ1*, *KCNH2*, and *SCN5A*, involved in cardiac ion channels, and *SCN1B* genes in eight patients with lone AF, were identified as a possible contributor to the development of lone AF<sup>9</sup>). Digital health is still at its infancy; however, there is a growing interest with increasingly wearable devices now capable of detecting biometric information such as electrocardiograms, blood pressure, and blood glucose. Validation studies that can ascertain the credibility of digital health data are required prior to data-oriented health decision making of individuals such as in the case of the Apple Heart Study<sup>10</sup>).

### Conflict of Interest

Dr. M.S. received clinical research funding from Takeda Pharma outside of the submitted work.

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