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Editorial

Stroke risk assessment in atrial fibrillation: Beyond atrial rhythm

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and is responsible for at least 20% of all strokes. Moreover, strokes associated to AF are largely avoidable, as the use of anti-vitamin K drugs can prevent >65% of all strokes, and direct oral anticoagulants can reduce the rate of stroke by a further 19% [1].

The results of large cohort studies in cardiac implantable electronic device (CIED) patients [2] demonstrate that many patients with atrial tachycardias (AT), including AF, have no symptoms during brief or even extended periods of the arrhythmia, suggesting that the true burden of arrhythmias in this population is much greater than previously documented, and making detection in subjects at risk for stroke challenging.

By definition: atrial high rate events (AHRE) are atrial tachyarrhythmia episodes with rate >190 beats/min detected by a CIED, and subclinical atrial fibrillation (SCAF) is an AHRE (>6 min and <24-h) with lack of correlated symptoms in patients with CIEDs, detected with continuous ECG monitoring (intracardiac) and without prior diagnosis (ECG or Holter monitoring) of AF. SCAF (either asymptomatic or which evades clinical detection) often precede the development of clinical AF [2].

A meta-analysis on those studies also show that SCAF is associated with up to a 2.4-fold increase in the risk of stroke [3], highlighting the importance of recognizing this condition in patients with CIEDs.

Li et al. [4] presented a further study on 594 consecutive CIED patients, without history of AF and without anticoagulation at baseline: 175 (29.5%) developed AHRE, of those 33 experienced thromboembolic events (TEs) (IR 1.38% per patient-year). Incidence of TEs was lower in low-risk patients having a CHA_2DS_2-VASc score <2 (male)/<3 (female) (AHRE vs. no-AHRE, 0.60% vs. 0.00% per patient-year, p = 0.469), and higher in high-risk patients with CHA_2DS_2-VASc score ≥2 (male)/≥3 (female) (AHRE vs. no-AHRE, 2.12% vs. 1.36% per patient-year, p = 0.209), regardless of the AHRE presence. Unlike previous study, AHRE was not significantly associated with TEs (HR, 1.46 [0.64–3.33]). In agreement with previous studies, there was no temporal relationship between AHRE and TEs. Baseline CHA_2DS_2-VASc score, but not AHRE, was independently associated with TEs (HR, 1.41 [1.13–1.75]) on multivariate analysis.

The precise mechanisms that could explain the association between AHRE in subjects with CIED and the increased thromboembolic risk in those patients is yet to be determined. Three different issues need to be discussed.

First, the association of AHRE and thromboembolic risk is evident from several trials [3] but, for instance in the ASSERT trial [5], all the patients included were at high risk for stroke (CHA_2DS_2-VASc score ≥2, or arterial hypertension and age ≥65 years) and AHREs were clearly associated with thromboembolic risk (HR, 2.49; 95% CI, 1.28–4.85). These results are concordant with those in the Italian AT-500 Registry cohort of elderly patients with bradycardia and antitachycardia pacemakers, in whom the adjusted thromboembolic risk was increased 3.1-fold in patients with device-detected AHRE of >24 h [6]. In the study of Li et al. [4], the inclusion of low-risk patients in the study population and, as a consequence, the relatively low number of TEs might have limited the chance to draw a strict relationship between AHRE and the risk of thromboembolism. However a trend in favour of the association between AHRE and TEs is clearly evident.

Second, AHRE and TEs are temporally disconnected. In a subanalysis of the ASSERT study [7] 51 patients experienced TEs after 3-month visit, among those 25 (49.1%) had no AHRE during the follow-up, 8 (15.6) had AHRE after the TE, and among 18 patients with AHRE prior to the TE, only 4 (8%) had AHRE within 30 days before the target TE. Since very few patients had AHRE in the month before their event is possible that AHRE could be a thromboembolic modulator rather than risk factor per se. In the IMPACT study [8], TE were not preceded by AHRE or clinical AF, and the arrhythmia usually occurred after it. Causality regarding the role of AT/AF in generating TEs remains debatable, and AHRE might not be the immediate cause for TEs.

Finally, the study from Li et al. [4] clearly suggested that TEs are mainly driven by clinical risk factors.

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The incidence of TE events was very low in low-risk group, regardless of AHRE presence, while in high-risk group, both subjects with and without AHRE were at risk for TEs. In another analysis of the Italian AT-500 Registry cohort [9] the rate of TEs, was a function of the $CHADS_2$ score, and progressively increased ($R2 > 0.85$) from 1.2% in $CHADS_2$ score 0 patients to 17.6% in $CHADS_2$ score ≥3 patients. Similarly, the TE risk increased with the duration of the AT/AF episode. Combining the data on AF presence/absence, duration, and $CHADS_2$ score demonstrated that patients with $CHADS_2$ score $= 0$ are at low risk for TEs, even if they have long-lasting AF episodes; by contrast, patients with $CHADS_2$ score ≥3 should be considered at very high risk for TEs even when AF is no longer detected. The same analysis restricted to patients with moderate risk ($CHADS_2$ score $= 1$ or 2); combining AF presence/duration with $CHADS_2$ score still yields a significantly different risk in the subgroups identified (0.6%vs4%).

The underlying mechanisms that could explain the thromboembolic phenomenon in AF is only partially understood but the mechanisms are known to be related to the atrial rhythm as well as the atrial substrate. The temporal dissociation between timing of AF and occurrence of TEs has led to the "atrial myopathy" hypothesis that fibrotic, prothrombotic atrial tissue is an important cause of thrombus formation in patients with AF, independent of the atrial rhythm [10].

Stroke prediction might be improved by the addition of emerging risk factors, many of which are expressions of atrial fibrosis. The use of novel parameters, to be added to clinical criteria, biomarkers, and imaging data, might improve stroke risk prediction and inform on optimal treatment for patients with AF and perhaps individuals without atrial arrhythmias, only at risk of AF.

Conflict of Interest

GLB and FMAB no conflict of interest to declare.

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