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EXPERTS OPINION

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Anticoagulation in patients at high risk of stroke without documented atrial fibrillation. Time for a paradigm shift?

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Atrial fibrillation (AF) is currently considered a risk factor for stroke. Depending on the severity of clinical factors (risk scores) a recommendation for full anticoagulation is made. Although AF is most certainly a risk factor for ischemic stroke, it is not necessarily the direct cause of it. The causality of association between AF and ischemic stroke is questioned by the reported lack of temporal relation between stroke events and AF paroxysms (or atrial high-rate episodes detected by devices). In different studies, only 2% of patients had subclinical AF > 6 minutes in duration at the time of stroke or systemic embolism. Is it time to consider AF only one more factor of endothelial disarray rather than the main contributor to stroke? In this "opinion paper" we propose to consider not only clinical variables predicting AF/stroke but also electrocardiographic markers of atrial fibrosis, as we postulate this as a strong indicator of risk of AF/stroke. We ask if it is time to change the paradigm and to consider, in some special situations, to protect patients (preventing stroke) who have no evidence of AF.

1 | ATRIAL FIBRILLATION AND STROKE. THE ROLE OF ANTICOAGULATION THERAPY

Atrial fibrillation (AF) is frequently a progressive disease that starts as paroxysmal and later evolves into persistent and permanent forms (Jahangir et al., 2007). Its prevalence increases with age and the presence of associated risk factors. The Framingham study (Kannel, Abbott, Savage, & McNamara, 1982) showed that patients with permanent AF present higher mortality, six fold excess of strokes and three fold risk of congestive heart failure. Initially, treatment was directed to preventing the occurrence of AF by modifying risk factors such as diabetes, hypertension, and heart failure whenever possible (Benjamin et al., 1994). However, in the late 80s and early 90s, different studies consistently demonstrated that oral anticoagulation therapy decreased the risk of stroke in patients with AF by approximately 70%, at the expense of a small increase in the frequency of major bleeding (Atrial Fibrillation Investigators, 1994). Oral anticoagulation therapy was especially indicated in older patients with valvular heart disease, heart failure or ischemic heart disease. These AF risk factors are now part of the scores endorsed by scientific societies worldwide, including the most universally accepted, the CHA_2DS_2-VASc (Kirchhof et al., 2016). Due to the associated risk of bleeding and unproven benefit, anticoagulation therapy is not indicated in young people with isolated AF, and should be used with caution in patients at high risk of bleeding (HAS-BLED score ≥3).

2 | EPIDEMIOLOGY OF ATRIAL FIBRILLATION. ASSOCIATION WITH EMBOLIC STROKE AND COGNITIVE IMPAIRMENT

The public health burden of AF is enormous, and expected to continue increasing in the future (Martínez-Sellés, Massó-van Roessel, et al., 2016). Currently, the prevalence of AF in the developed world is of 2% in the general population, with a clear age-related increase, affecting about 5 million people in the United States, and a similar number in Europe (Svennberg et al., 2015; Kirchhof et al., 2016; Martínez-Sellés, Massó-van Roessel, et al., 2016). About 30% of strokes have an embolic origin (Atrial Fibrillation Investigators, 1994), and this rate also increases with age. The incidence of AF-related ischemic stroke is about 0.2% per year in a population-based cohort older than 65 years (Yiin et al., 2014). Around 5%–10% of patients that already presents AF

have an embolic stroke in 2–3 years, 2% during the first year, and this rate that may even be >4% in patients with advanced age and structural heart disease (Atrial Fibrillation Investigators, 1994). Ischemic stroke associated to AF is nearly twice as likely to be fatal as non-AF stroke and stroke may be the first manifestation of AF (Potpara & Lane, 2014). Therefore, diagnosing AF before the first stroke occurs is critical for reducing disability and mortality. However AF may be asymptomatic in up to 30%–40% of the patients (Healey et al., 2012; Potpara & Lane, 2014). Finally, AF has been also associated to cognitive impairment (Horstmann et al., 2014; Hui et al., 2015).

3 | ATRIAL FIBRILLATION IS NOT THE FINAL CAUSE OF STROKE. IT IS JUST ANOTHER RISK FACTOR

The documentation of AF and the evaluation of its impact on prognosis relies on the methodology of AF screening. Implantable loop recorders allow for extended monitoring up to 3 years, increasing the detection of silent AF (Gladstone et al., 2014; Reiffel et al., 2014; Sanna et al., 2014). Detection of atrial high rate episodes by analyzing the information stored in pacemakers or implantable cardioverter defibrillators, allows more extended monitoring and further improve AF screening even though atrial high-rate episodes represent only indirect indicators of AF (Gladstone et al., 2014; Sanna et al., 2014). However, although AF is most certainly a risk factor for ischemic stroke, it is not necessarily the direct cause of it. The causality of association between AF and ischemic stroke is questioned by the reported lack of temporal relation between stroke events and AF paroxysms or atrial high-rate episodes detected by implantable loop recorders or devices (Hohnoloser et al., 2006; Glotzer et al., 2009; Benezet-Mazuecos, Rubio, & Farré, 2014; Gladstone et al., 2014; Reiffel et al., 2014; Sanna et al., 2014). In different studies, only 2% of patients had subclinical AF >6 min in duration at the time of stroke or systemic embolism (Martin et al., 2015). Among the plausible explanations for this change of paradigm is the recently proposed concept of fibrotic atrial cardiomyopathy (Kottkamp, 2013; Hirsh, Copeland-Halperin, & Halperin, 2015), according to which AF may result from an underlying progressive disease affecting atrial myocardium and resulting in replacement of myocardium with fibrosis and fat (Daccarett et al., 2011; Platonov, Mitrofanova, Orshanskaya, & Ho, 2011; Akoum et al., 2013; Kottkamp, 2013; Marrouche et al., 2014; Hirsh et al., 2015).

4 | ADVANCED INTERATRIAL BLOCK AS A RISK MARKER OF AF AND STROKE

The idea that the easily available surface ECG could help to predict AF risk is attractive. The rationale for this emerges from the notion that the surface ECG is a good reflection of the anatomical substrate of AF that is atrial fibrosis (Kottkamp, 2013; Hirsh et al., 2015). The ECG is a simple and reliable technique to detect the presence of conduction

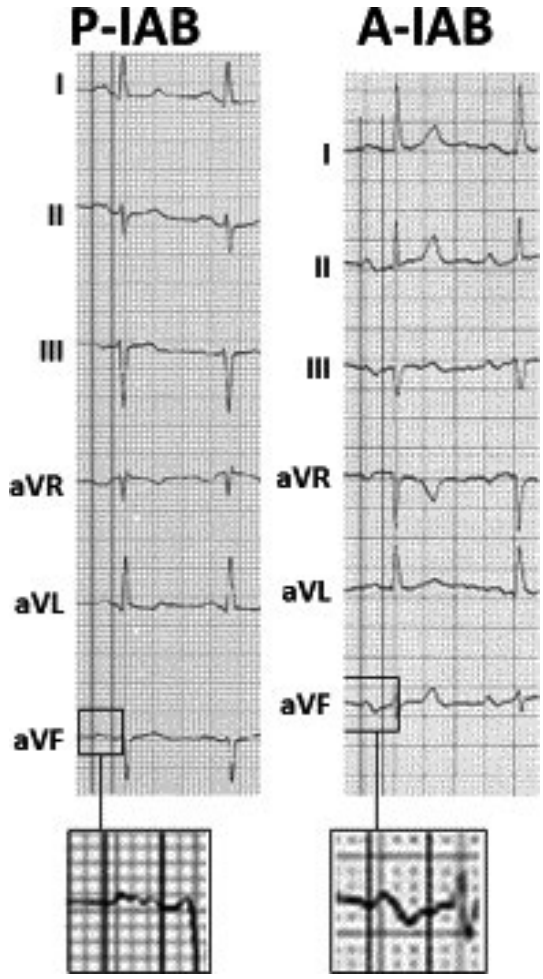

FIGURE 1 Examples of partial interatrial block (P-IAB) (P wave duration ≥120 ms, positive in leads II, III, and aVF), and of advanced interatrial block (A-IAB) (P wave duration ≥120 ms with plus/minus morphology in leads II, III, and aVF)

delay in the atria (Bayés de Luna et al., 1985; Bayés de Luna, 2012; Conde, Baranchuk, & Bayés de Luna, 2015). Few years ago, a consensus document (Bayés de Luna et al., 2012) standardized the classification of interatrial blocks (IAB), facilitating its rapid identification as partial (P-IAB) (P wave ≥120 ms) or advanced (A-IAB) (P wave ≥120 ms plus biphasic (±) morphology in leads II, III, aVF) (Figure 1). The diagnosis of A-IAB can be done by a quick look at ECG tracings, and provides us information regarding the possible risk of AF/stroke in the future. The presence of A-IAB indicates a chain of events summarized in Figure 2 that include: (1) Delayed and abnormal left atrium activation with consequently abnormal contraction against a closed (closing) mitral valve (Goyal & Spodick, 2001), (2) Increased left atrium pressure, wall stress and dilation, (3) Damage to the endocardium and progressive atrial fibrosis (Kottkamp, 2013; Hirsh et al., 2015).

The association between the presence of interatrial block and the extent of atrial fibrosis has been confirmed in a detailed *post mortem* histology study. (Platonov et al., 2011) In clinical settings, the exact quantification of atrial fibrosis by imaging is more problematic, although pioneering studies that have used magnetic resonance imaging with gadolinium enhancement have shown promising results

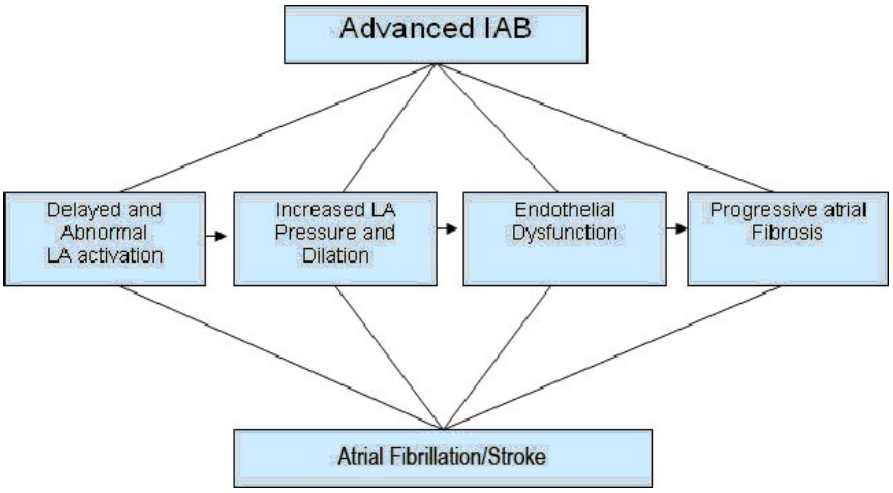

FIGURE 2 Physiopathological relation between advanced interatrial block (IAB) and atrial fibrillation

(Daccarett et al., 2011; Akoum et al., 2013). The presence of fibrotic atrial cardiomyopathy (Kottkamp, 2013; Hirsh et al., 2015) implies a stagnant and sluggish left atrium favouring the appearance of stasis-induced thrombosis especially in the left atrial appendage. This may be, at least in part, the physiological rationale for the previously described association between IAB, AF and stroke.

Several studies have looked into the ability of IAB to predict AF. Bayés de Luna et al. (1988, 1999) published a few decades ago that 80% of patients with A-IAB advanced heart disease and ambient arrhythmias, presented AF or atrial flutter after 3 years of follow-up. CHA_2DS_2-VASc score (≥3) and the P wave duration ≥160 ms were also presented in 80% of these patients. The association of A-IAB with AF has been recently named Bayés Syndrome (Conde & Baranchuk, 2014a,b; Bacharova & Wagner, 2015).

It has also been reported that A-IAB may predict AF in different clinical scenarios. P wave prolongation has shown strong association with incident AF in epidemiological studies such as Aric cohort (O'Neal, Zhang, Loehr, Chen, Alonso, & Soliman, 2016), Copenhagen cohort (Nielsen et al., 2015) and in patients with a CHA_2DS_2 (Wu et al., 2016b). ECG signs of abnormal atrial conduction were predictive of new onset AF in patients with advanced heart disease (Caldwell et al., 2014; Wu et al., 2016a). A-IAB also predicts AF recurrence after pulmonary vein isolation (Agarwal, Aronow, Levy, & Spodick, 2003; Holmqvist et al., 2009; Holmqvist et al., 2010), and after atrial flutter ablation (Enriquez et al., 2015). In patients with atrial flutter ablation, recognizing A-IAB could be a reason to consider extending the anticoagulation treatment to cover for possible AF episodes after the ablation of the cavotricuspid isthmus. A-IAB has also identified patients at risk of developing AF after pharmacological cardioversion (Enriquez, Conde, Hopman, et al., 2014), and it remains to be investigated whether these patients should be considered for pulmonary vein isolation earlier. A-IAB was found a predictor of new onset AF in a series of patients with severe heart failure receiving cardiac resynchronization (Sadiq Ali et al., 2015). In patients with advanced Chagas' disease A-IAB was also able to predict new onset AF (Enriquez, Conde, Femenia, et al., 2014). Finally, a study performed in centenarians also concluded that IAB, particularly A-IAB, is a pre-AF condition associated with premature atrial beats (Martínez-Sellés, Massó-van Roessel, et al., 2016).

Interatrial blocks is also an independent risk factor for stroke and also cognitive impairment. Spodick's group was the first to publish this association in patients hospitalized (Ariyarajah, Puri, Apiyasawat, & Spodick, 2007). In a cohort of global population O'Neal, Kamel, Zhang, Chen, Alonso, & Soliman, (2016) recently confirmed the association of A-IAB with incident ischemic stroke. Wu et al. (2016c) also found this association between IAB and stroke in patients with high CHA_2DS_2-V score. Finally, Martínez-Sellés, Massó-van Roessel, et al., 2016 found that centenarians with IAB presented a higher prevalence of cognitive impairment and previous stroke than centenarians with normal P wave.

5 | THE MAIN AIM SHOULD BE TO REDUCE THE RISK OF STROKE

The present strategy to reduce the incidence of ischemic stroke is focused on the documentation of AF in those with high risk of stroke, especially in after ischemic stroke and no known AF. This approach demands development of cost-efficient and minimally invasive ECG monitoring techniques as likelihood of AF detection is related to the duration of ECG monitoring, being the highest using implantable loop recorders, or availability of the on-demand AF screening options such as thumb-ECG recorded using hand-held devices. The drawbacks of this approach are the associated costs and uncertainty in regard to the causal relationship between ischemic cerebral events and ultrashort AF episodes, which appear to be common in patients with cardiovascular comorbidities (Gaita et al., 2013). A recent randomized study found no temporal relation between atrial tachyarrhythmias and stroke; and the strategy of early initiation and interruption of anticoagulation based on remotely detected atrial tachyarrhythmias did not prevent thromboembolic events (Martin et al., 2015).

However, we think our aim has to be to prevent embolic stroke. We propose a different strategy based on the findings of the strong association between the high CHA_2DS_2-VASc score, the presence of ambient

arrhythmias, and the risk of AF, which was repeatedly documented in the cohorts of ischemic stroke survivors, and in selected cohorts of patients evaluated for palpitations (Henriksson et al., 2011; Suzuki et al., 2013; Zuo et al., 2013; Acharya et al., 2015). It is therefore plausible to suggest that patients with high CHA_2DS_2-VASc score may benefit from anticoagulation without need for documentation of AF. This approach is based on the earlier discussed value of IAB as an ECG-based AF-marker, and the well-known association of the CHA_2DS_2-VASc score association with both AF and ischemic stroke events. It is necessary to emphasize that the vast majority of patients with A-IAB have at the same time a CHA_2DS_2-VASc score ≥2 and therefore, if AF is documented, the patients would fulfil conventional indications for oral anticoagulation. Consequently, one could argue that given the association of A-IAB with AF, there is a possibility that many strokes would be avoided if patients with high CHA_2DS_2-VASc score and A-IAB, were treated with anticoagulation regardless of the documented evidence of AF (Chhabra & Gowdar, 2016; Hughes & Worrall, 2016; Martínez-Sellés, Fernández Lozano, Baranchuk, Bayes-Genis, & Bayés de Luna, 2016). Of course, the possible benefits derived from this hypothesis; need to be counter balanced with the possible side effects of anticoagulation. Fortunately the incidence of cerebral haemorrhage as a consequence of treatment is low. The results of five randomized trials (Atrial Fibrillation Investigators, 1994) showed that it was 1% in the placebo arm, and 1.3% in patients under warfarin. The new oral anticoagulants are even associated with less risk of bleeding (Heidbuchel et al., 2016) and their benefits could be expanded to some patients with A-IAB, even if they had no documented AF. Whether any of these approaches is superior to others is not known and can only be tested in a clinical trial. In order to advance knowledge in this topic, and International Registry (BAYES Registry) was launched on October 1, 2016 with a follow-up estimated in 3 years (Martinez-Selles, Baranchuk, Elousa, & Bayes de Luna, 2016). The beneficial efficacy and safety profile of the new oral anticoagulants together with insufficient efficacy of the current primary stroke prevention strategies indicate that the paradigm of having to document AF in order to start anticoagulation may need to be broken.

6 | CONCLUSIONS

We suggest a new step in the prevention of ischemic stroke: to use anticoagulation therapy in sinus rhythm patients if they are at high risk of AF and stroke, even without documentation of AF. The subgroup of patients suitable for this approach may be represented by those with A-IAB, structural heart disease, CHA_2DS_2-VASc score ≥3, and frequent premature atrial contractions. Prospective validation of this approach in a controlled interventional study is ultimately needed; however, the expected benefits would be further reducing embolic stroke and/or cognitive impairment in high risk patients not fulfilling conventional indications for anticoagulation today. It remains to be seen whether this benefit may compensate for the well-established side effects of anticoagulation, which should be tested in prospective studies.

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