

# Beyond CHA<sub>2</sub>DS<sub>2</sub>-VASc in atrial fibrillation: the atrium and the risk of stroke

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## KEYWORDS

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Pathology affecting the atria have a significant impact on the occurrence of arrhythmias and the risk of stroke. The causal relationship between atrial fibrillation (AF) and ischaemic stroke has been challenged by the recent uncovering of the lack of temporal association between thrombo-embolic cerebral events and paroxysmal AF or tachycardia. General conditions, such as the one considered in the definition of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, or specific atrial pathology (also independently occurring), could predispose to cerebral embolism.

## Introduction

The term ‘atrial cardiomyopathy’ refers to a complex of modification affecting the structure, architecture, contractility, and electrophysiology of the atrium which could lead to relevant clinical manifestations. Prothrombotic factors expressed on the surface of atrial endothelial cells encourage adhesiveness of platelets and leucocytes to the atrial endothelium, thus promoting thrombogenesis.

A condition which specifically facilitates both prothrombotic state and atrial fibrillation (AF) is the inter-atrial block (IAB), defined as inter-atrial conduction delay, manifested by a duration of the P wave  $\geq 120$  ms in the leads II, III, and aVF. The presence of IAB increases the risk of stroke and dementia. The author’s personal experience confirms the association between IAB and AF.

Atria provide an important contribution to cardiac function. In addition to their role in ventricular filling, they serve as a volume reservoir, home to pacemaker cells, and important parts of the cardiac conduction system (e.g. sinus node, AV node) and secrete natriuretic peptides, such as atrial natriuretic peptide (ANP) and the cerebral natriuretic peptide (BNP) that regulate fluid homeostasis. Atrial myocardium is affected in many pathological, cardiac, and non-cardiac conditions and is, in many respects, more sensitive than ventricular myocardium.

The atria are activated, as well as through specialized tissue, through working cardiomyocytes, so that any alteration of the architecture or structure of the atrial myocardium can lead to significant electrophysiological disorders. Furthermore, atrial cells (both cardiomyocytes and non-cardiomyocytes such as fibroblasts, endothelial cells, and neurons) react vividly and extensively to pathological stimuli and are susceptible to a series of genetic influences. Responses include hypertrophy of atrial cardiomyocytes and contractile dysfunction, arrhythmogenic changes, fibroblast proliferation, hyper-innervation, and thrombotic changes. Thus, atrial diseases have a substantial impact on cardiac function, the onset of arrhythmias, and the risk of stroke.

The guidelines of the European Society of Cardiology of 2016 recommend the use of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score to assess the risk of stroke in patients with non-valvular AF and to initiate oral anticoagulant treatment in males with scores higher than 1 and in females with score  $>2$ .<sup>1</sup>

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score [congestive heart failure, hypertension, age  $\geq 75$  years (2 points), diabetes, stroke (2 points), vascular disease, age 65-74 years, female] is proving an important risk predictor of thrombo-embolic complications regardless of the presence of AF.<sup>2-5</sup>

These data suggest that AF is a risk factor for ischaemic stroke, but not necessarily its direct cause. The causality of the association AF–ischaemic stroke is questioned by the reported lack of temporal relationship between cerebral

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**Table 1** Histopathological classification of atrial cardiomyopathies

I	The main alterations affecting cardiomyocytes
II	Mainly fibrotic alterations
III	Combined cardiomyocytes-fibroblast alterations
IV	Non-collagen infiltration (with or without alteration of cardiomyocytes)

thrombo-embolic events and paroxysms of AF or high-frequency atrial tachycardia detected by implantable devices (loop recorder or pacemaker).<sup>6</sup>

According to some authors, the therapy can be started independently of the AF documentation in the presence of a high CHA2DS2-VASc score.<sup>7,8</sup>

These authors found that over a score of 6 the prevalence of stroke was high regardless of AF documentation.

This means that general conditions, such as those represented within the CHA2DS2-VASc score, or atrium-specific pathology conditions, even independent of these conditions, may predispose to cerebral embolism. We will therefore describe the situations of atrial pathology that can lead to an embolic risk, favoured, but not necessarily, by AF intermediation. These same conditions favour both the appearance of AF and thrombo-embolic stroke, and these are atrial cardiomyopathy and IAB.

## The atrial cardiomyopathy

The consensus document on atrial cardiomyopathy<sup>9</sup> proposes the following definition: 'Any complex of alterations of the structure, architecture, contractility, and electrophysiology of the atrium that can produce relevant clinical manifestations'.

Many diseases (such as hypertension, heart failure, diabetes, myocarditis) or conditions such as ageing and endocrine abnormalities can induce or contribute to atrial cardiomyopathy, although the alterations in the atrium that are produced are not specific to disease, so pathophysiological changes may be common under different conditions. The extent of the alterations may vary over time and in the localization within the atrium with consequent intra- and inter-individual phenotypic differences. Furthermore, while some conditions selectively affect the atrium (such as atrial remodelling), most pathological processes also involve the ventricles to varying degrees. In the absence of a histopathological classification of atrial pathologies, a histological/pathophysiological classification has been proposed (*Table 1*).

This classification can be useful to describe the histological alterations of biopsies and to correlate the pathologies with the alterations detected with imaging techniques and could help in the future to customize the treatment of AF.

There are many conditions that determine histopathological alterations of atrial walls and predispose to AF and therefore to cardio-embolic stroke (*Table 2*).

### Prothrombotic indexes: coagulation, platelets

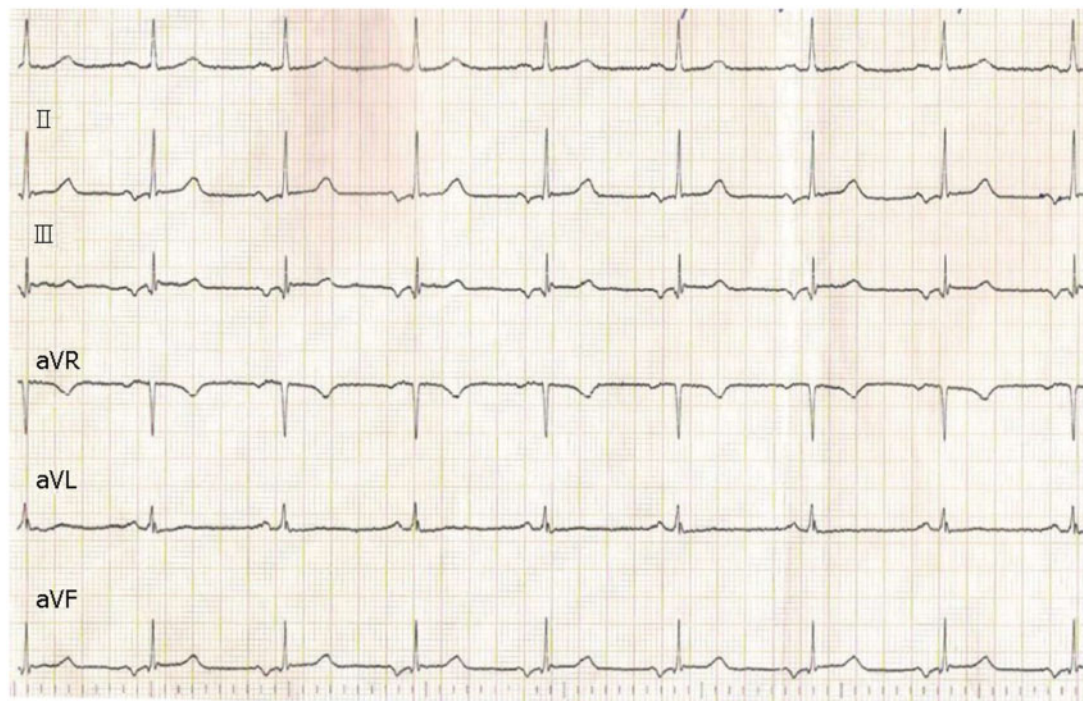
Over 150 years ago Virchow proposed a triad of anomalies predisposing to the formation of the thrombus, that is,

**Table 2** Conditions determining histopathological alterations of atrial walls

Isolated FA (lone): when predisposing pathologies are not recognizable. In this condition there may be a genetic predisposition 10, with recognizable histopathological alterations of Class II and III
Isolated atrial amyloidosis
Abnormal ANP production: present in some forms of atrial tachyarrhythmias and atrial cardiomyopathies
Hereditary muscular dystrophies
Atrial cardiomyopathy due to heart failure
Obstructive apnoea syndrome
AF-induced remodelling
Drug-induced AF
Myocarditis
Atrial cardiomyopathies due to genetic alterations of repolarization
Ageing
Hypertension
Obesity
Diabetes
Valvular heart disease

pathology of the vascular wall, slowing of the flow, and haematic hyper-viscosity. In the context of AF, thromboembolism coexists with structural cardiopathies (e.g. mitral stenosis) and endothelial damage/dysfunction, detectable by biomarkers (Von Willebrand factor), by tissue plasminogen activator, by immuno-histochemical studies of the atrial wall, electron microscopy, or functional studies (e.g. flow-mediated dilation). Flow anomalies in the atrium as in auricula can be highlighted with spontaneous echo-contrast in cavity and with Doppler flowmetry. In AF the abnormalities of blood constituents are evident, with alterations of coagulation, platelets, fibrinolysis, presence of markers of inflammation, and other signs directly or indirectly associated with thrombogenesis or predisposition to it. Platelet abnormalities, often evident during AF, may be more a reflection of associated vascular pathologies than AF itself. The thrombus that develops in AF is typically rich in fibrin (red thrombus), while the arterial thrombus is particularly rich in platelets (white thrombus), which explains the role of anticoagulation rather than antiplatelet in the prevention of thromboembolism in AF.

The prothrombotic factors that are expressed on the surface of the endothelial cells of the atrium favour an increase in the adhesion of the platelets and leucocytes to the atrial endocardium. This phenomenon initiates thrombogenesis at the level of the atrial endocardium. Several clinical factors, such as those present in the CHA2DS2-VASc score, but not only those, favour molecular alterations (oxidative stress) at the level of myocytes and endothelial cells, increasing the expression of prothrombotic factors. These alterations are not directly correlated with the presence or absence of AF at the surface ECG and help to understand why thrombogenesis is enhanced even in the presence of sinus rhythm. A particular condition favouring both the prothrombotic state and AF, which has been well defined over the last few years, is the IAB.



**Figure 1** Electrocardiogram of a patient with advanced inter-atrial block (P wave of 120 ms duration with negative final component in DII, DIII, and aVF).

## The inter-atrial block

In 1979, Bayés de Luna<sup>11</sup> described the atrial conduction blocks classifying them as atrial and inter-atrial. The IAB was defined as a conduction delay between the atria in the area of the Bachmann bundle, with P wave duration  $\geq 120$  ms in the II, III, and aVF derivations. Inter-atrial block was defined as advanced in the presence of a negative final component of the P wave (*Figure 1*). IAB is a frequent condition in old age, reaching 40% in the over 70-year-old.<sup>12</sup> Inter-atrial block is strongly associated with supraventricular arrhythmias, particularly with AF in many clinical contexts, and this association has been called ‘Bayés syndrome’.

Furthermore, IAB increases the risk of stroke<sup>13</sup> and appears to be associated with dementia. The association of IAB with the incidence of AF was confirmed in different contexts,<sup>14-23</sup> including the general population, centenarians, patients with previous AF, after ablation of the cavatricuspid isthmus, patients with high CHADS2 score, patients with structural cardiopathies, heart failure, and Chagas cardiomyopathy. In most cases, the risk was higher in patients with advanced IAB. Although the reasons for these associations are not clear, probably the key factor in the chain of events leading to atrial fibrosis is atrial remodeling due to delayed and abnormal atrial activation, especially in the case of advanced IAB. This delayed activation produces an abnormal contraction against a closed mitral valve, with increased pressure in the left atrium. The end result is damage to the atrial wall, progressive dilation, and fibrosis. Indeed, patients with advanced grade IAB present an abundant fibrosis with reduced atrial mobility and reduced strain as verifiable with the echo speckle-tracking.<sup>24,25</sup>

This has its importance in the management of patients with AF, since it has been shown that the magnitude of fibrosis is more important than the clinical phenotype of AF (paroxysmal vs. permanent). As mentioned above, elderly patients with IAB have not only an increase of the risk of developing AF but also thrombo-embolic stroke. This association has also been demonstrated in different contexts, including the general population, centenarians, hospitalized patients, and patients with high CHA2DS2-VASc score and appears to be related in particular to hypercoagulation and fibrosis induced by blood stasis as a result of an abnormal activation of the left atrium. In fact, it is probably the physiopathological context of the left atrium that favours the state of hyper-coagulation, more than the presence of AF.

In patients without documented arrhythmias, anticoagulant drugs for stroke prevention are generally not recommended. However, anticoagulation may play a role in patients with IAB. The data that support this potential role are stronger in patients with high CHA2DS2-VASc,<sup>3</sup> and in those of global cohort with advanced IAB, in order to prevent cognitive deterioration and embolic stroke. This option seems particularly interesting in the elderly with structural heart disease. The Inter-atrial Block and Yearly Events (BAYES) registry focuses on these patients<sup>26</sup> and will help to assess the influence of IAB as a precursor to AF, stroke, and cognitive impairment. If the role of IAB is confirmed, the next step would be to perform a clinical trial comparing anticoagulation and placebo, with the prospect of changing the current paradigm that necessitates the documentation of AF to prescribe anticoagulant therapy. This would answer the question of whether elderly patients at high risk of AF, but without this being documented, benefit from anticoagulant treatment.



## Our experience

We verified the prevalence of IAB and the incidence of AF in the population with IAB in the subjects enrolled in the PREDICTOR study<sup>27</sup> followed for a period of 6.6 years. In 1626 subjects IAB was present in 415 (25.5%). In the general population, IAB was associated with the appearance of AF with hazard ratio (HR) equal to 1.5, while in normal-weight subjects, the presence of IAB tripled the risk of AF (HR 3.05). This association was independent of a history of ischaemic heart disease, left ventricular hypertrophy, CHA2DS2-VASc score, atrial size, and NT-proBNP, indicating that IAB is a predictor of AF independent of structural alterations of the heart. Furthermore, the CHA2DS2-VASc score was able to predict cardio-embolic stroke independently of the incident FA demonstration (data being published).

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