

# Atrial fibrillation and stroke: what we know, what's new, and what we should do now



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## Résumé

MÊME SI L'ATTAQUE LIÉE À LA FIBRILLATION AURICULAIRE a toujours été attribuée à l'effet prothrombotique d'une stase de l'oreille gauche, on ne comprend pas entièrement l'origine de cet effet. Des données probantes récentes indiquent que l'hypercoagulabilité humorale joue un rôle. Dans le présent numéro (page 673 et 685), le Dr Susan R. Kahn et des collaborateurs appuient cette hypothèse en démontrant l'existence d'un lien entre, d'une part, les facteurs prothrombotiques et les produits de l'hémostase, et d'autre part, la fibrillation auriculaire et l'attaque. Ces constatations peuvent servir de base à l'amélioration des traitements de prévention : on pourra soit cibler avec plus de précision le traitement à la warfarine, soit mettre au point des agents pharmacologiques plus spécifiques. Néanmoins, la pratique actuelle devrait demeurer fondée sur d'importantes données de recherche qui démontrent qu'un traitement méticuleux à la warfarine prévient la plupart des attaques liées à la fibrillation auriculaire.

**I**schemic stroke is a common cause of disability, dependency and death. Stroke occurs in many people with nonvalvular atrial fibrillation,<sup>1</sup> and in the last decade we have learned much about the epidemiology and prevention of stroke in this patient group.<sup>1-9</sup> In this issue (page 673) Dr. Susan R. Kahn and colleagues address the question of why stroke is associated with atrial fibrillation and provide evidence that humoral hypercoagulability is part of the answer. It is worth reviewing these findings in the context of what we know and what we are learning about atrial fibrillation-related stroke. We should also consider carefully how to integrate new research findings in our clinical practice.

## What we know

It is now accepted that nonvalvular atrial fibrillation is an important cause of stroke. Atrial fibrillation increases the annual rate of stroke 5-fold — from 1% to 5% — in people over 65 years of age, and one-third of strokes in people older than 75 years have been attributed to atrial fibrillation.<sup>1</sup>

Most strokes in patients with nonvalvular atrial fibrillation can be prevented by warfarin therapy.<sup>3-7,9</sup> The results of randomized clinical trials are consistent and compelling: overall, treatment with warfarin sufficient to attain an international normalized ratio in the range of 2.0 to 3.0 reduced the annual rate of stroke by two-thirds — from 4.5% to 1.4% — without a substantial increase in the incidence of hemorrhage.<sup>9</sup>

Finally, we have learned that there is substantial variation in the use of warfarin therapy to prevent stroke.<sup>10-14</sup> It appears that many patients whom warfarin would likely benefit, especially those older than 75 years, are not receiving this therapy.<sup>14,15</sup>

## What's new

Given the available evidence, we know enough to act prudently. We might even argue that we ought to focus our efforts on action rather than on physiologic research, modifying clinical practice and public health initiatives to reflect

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the current understanding of how to prevent atrial fibrillation-related stroke. At the same time, we might wonder how to account for the association between atrial fibrillation and stroke. Is it attributable solely to stasis in the fibrillating left atrium, as has been held conventionally? If we had a better understanding of the humoral mediators of left atrial thrombus, could we improve prevention either by targeting warfarin therapy more precisely or by developing more specific pharmacologic agents?

Recent studies have begun to address these questions. Stroke in patients with atrial fibrillation may be attributable in part to humoral hypercoagulability as well as to stasis.<sup>16</sup> Chronic atrial fibrillation has been associated with elevated concentrations of prothrombotic factors, such as plasma fibrinogen, and the products of hemostasis, such as fibrin D-dimer (fibrin degradation fragment).<sup>17-19</sup> Moreover, cardioversion to sinus rhythm may decrease hemostatic activity, as indicated by a fall in fibrin D-dimer concentrations.<sup>20</sup> Warfarin therapy, too, may decrease hemostatic activity, as indicated by lower levels of prothrombin fragment F1+2.<sup>19</sup>

Kahn and colleagues provide further evidence that nonvalvular atrial fibrillation is associated with humoral hypercoagulability. In their comprehensive survey of humoral mediators and products of hemostasis, they took into account differences that might have been due to age, sex or concurrent warfarin therapy. Comparing patients with nonvalvular atrial fibrillation and no history of stroke with patients in sinus rhythm and no history of stroke, the investigators found that mean concentrations of hemoglobin, fibrinogen, fibrinopeptide A and tissue plasminogen activator were higher in the former group; conversely, the mean concentrations of proteins C and S and prothrombin fragment F1+2 were lower. The levels of these hemostatic factors and products were generally similar in patients with atrial fibrillation, whether or not they had a history of stroke, and in patients with a history of stroke, whether or not they had atrial fibrillation.

These findings must be interpreted cautiously, as the authors suggest. The reason for the association between the concentrations of hemostatic factors, nonvalvular atrial fibrillation and stroke has not been established. Several alternative explanations are plausible, including: a) atrial fibrillation leads to hemostatic abnormalities, which in turn increase risk for stroke; b) underlying hemostatic abnormalities lead both to atrial fibrillation and to stroke; c) both atrial fibrillation and stroke lead to hemostatic abnormalities; or d) a common factor leads to hemostatic abnormalities, atrial fibrillation and stroke. Testing these alternative explanations will require larger longitudinal studies.

It is also unknown whether measurement of any of the hemostatic factors considered will predict either the risk

of stroke for individual patients or the probability of benefit from warfarin therapy. Even if hemostatic factors have such prognostic value, it may prove modest. Kahn and colleagues found substantial overlap between groups of patients in the concentration of each hemostatic factor measured (see Fig. 1, page 688). Thus, it is unlikely that any single hemostatic factor will discriminate precisely among patients with nonvalvular atrial fibrillation according to risk for stroke.

Although Kahn and colleagues' findings cannot be put into practice yet, they raise intriguing questions. Do concentrations of hemostatic factors, for example, explain why the rate of atrial fibrillation-related stroke increases with age, which has been associated with thrombin generation and protein C activation?<sup>21</sup> Might a profile of hemostatic activity stratify patients with atrial fibrillation according to risk for stroke precisely enough to improve targeting of warfarin therapy?

## What we should do now

Therapy should continue to be based on the substantial evidence from clinical trials.<sup>22,23</sup> For now, our clinical practice should not be affected by the hypercoagulability hypothesis — i.e., that atrial fibrillation leads to hemostatic abnormalities, which in turn predisposes to stroke.

Every patient with atrial fibrillation should be identified, and warfarin should be considered for each patient, targeting an international normalized ratio of 2.0 to 3.0.<sup>22,23</sup> Some patients — namely, those under 60 years of age without other risk factors for stroke — may be at such low risk for stroke<sup>9</sup> that warfarin will have little benefit and may be forgone. All other patients with nonvalvular atrial fibrillation, including those who are debilitated or for whom warfarin therapy presents particular risks, should be given an informed recommendation, taking into account the patient's preferences. If a therapeutic trial of warfarin is chosen and found to be acceptable, it can be continued with the expectation that atrial fibrillation-related stroke will be largely prevented. Warfarin rarely needs to be withheld altogether.

Warfarin works. However, we have yet to achieve its optimal use in everyday practice. Longitudinal studies are needed to determine the causal links between atrial fibrillation, hemostatic abnormalities and stroke. Such studies may also provide a basis for developing better strategies for preventing atrial fibrillation-related stroke. We also need to learn more about the relative risks and benefits of alternative management strategies, such as antiarrhythmic therapy. Finally, and most important, we need to learn how to facilitate the systematic and safe use of warfarin therapy to prevent atrial fibrillation-related stroke, so that it becomes more acceptable to both patients and physicians.



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## Images of embolic stroke

This patient was studied by me and colleagues in the McConnell Brain Imaging Center at the Montreal Neurological Institute. He was in the acute phase of a devastating embolic stroke. Positron emission tomography was used to measure cerebral blood flow (CBF, upper left), the cerebral metabolic rates for oxygen (CMRO<sub>2</sub>, upper right) and glucose (CMRGlu[N], lower left), and the brain pH (CPH, lower right). The intensity of any function can be estimated from the colour, with lower to higher values going from purple to blue to yellow and red. Although this patient's entire right hemisphere is suffering a drop in blood perfusion, relatively smaller brain regions are showing a drop in metabolic function, resulting from a combination of increased extraction fractions for oxygen and glucose, and a switch to anaerobic glycolysis. The latter leads to the accumulation of lactate, which results in the acidosis noted in the CPH image. Such imaging studies not only improve our understanding of stroke pathophysiology but can also be used to test the effectiveness of therapeutic measures. — Antoine Hakim, MD, PhD

