CONTEMPORARY REVIEW

# New-onset atrial fibrillation and thromboembolic risk: Cardiovascular syzygy?

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Atrial fibrillation (AF) is a condition that confers increased thromboembolic risk. Oral anticoagulant (OAC) therapy can attenuate this risk. However, use of OAC therapy is determined largely by the presence of additional clinical factors (encapsulated by the $CHA_2DS_2VASc$ score) that incrementally elevate stroke risk. Currently, there is no specific recommendation regarding urgency of initiation of OAC therapy in the presence of new-onset AF, except where cardioversion is being considered. Recently, it has become increasingly apparent that there is a period immediately following the onset of AF of particularly accentuated thromboembolic risk (with respect to chronic AF): the physiological bases for this risk are as yet incompletely understood. However, given that both inflammation and impaired nitric oxide signaling are pivotally involved in the pathogenesis of AF, these factors may also mediate thrombotic risk in the context of new-onset AF. Advances in OAC therapy have recently been achieved, with development of agents that are comparable or superior to warfarin for mitigation of stroke risk, but with a safety profile similar to aspirin therapy. Thus, the incremental increase in thromboembolic risk experienced by new-onset AF patients constitutes a previously widely neglected case in favor of the rapid application of OAC therapy to such individuals. This review seeks to summarize the thromboembolic risk observed in new-onset AF and the emerging understanding of the physiological bases for this risk.

**KEYWORDS** Atrial fibrillation; New onset; Thromboembolism; Anticoagulation; Virchow

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## Introduction

Historically, atrial fibrillation (AF) was thought to arise as a result of atrial distension. It has since come to be understood that there are also significant inflammatory and biochemical mechanisms involved in the pathogenesis of AF: activation of the renin-angiotensin-aldosterone system and increased production of its effector peptide angiotensin II stimulates development of cardiac fibrosis, inflammatory activation, and increased generation of reactive oxygen species (ROS).[1] Research in animal models has also demonstrated that infusion of angiotensin II stimulates the activity of myeloperoxidase (MPO), resulting in generation of hypochlorous acid, and the activation of matrix metalloproteinases, resulting in cardiac remodeling and development of AF.[2] In human subjects, plasma MPO levels were elevated in patients with AF and clinically, the perioperative application of the hypochlorous acid scavenger, N-acetylcysteine, has been shown to attenuate development of postoperative AF in coronary artery bypass graft patients.[3]

The integrity of nitric oxide (NO) signaling has also been identified as an important factor in the development of AF: onset of AF has been linked to diminished expression and/or uncoupling of endothelial NO synthase,[4] resulting in the dual effects of increased ROS generation and loss of NO production. Additionally, MPO has been shown to impact upon NO signaling: MPO is able to interfere with the generation of NO[5,6] and diminish the availability of NO either through production of ROS or through direct catabolism.[7,8]

Recently, we demonstrated another association between AF and loss of NO effect: we observed that platelet response to NO was profoundly impaired in patients with new-onset AF, when compared with platelets of patients with chronic AF.[9] This finding corresponds with clinical data (summarized by Garcia et al[10]) identifying a period following the onset of AF of acutely elevated thromboembolic risk. Current practice regarding initiation of oral anticoagulant (OAC) therapy, tailored in accordance with the presence of cardiovascular comorbidities, does not specifically address this period of increased

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thromboembolic risk. Thus, a potentially important aspect of risk is yet to be addressed by routine therapeutic guidelines.

The physiological bases for the incremental elevation in thromboembolic risk observed in new-onset AF patients are as yet incompletely understood, though the intersection of inflammation and impaired NO signaling, both implicated in the pathogenesis of AF, remains a distinct possibility.

In this context, this review seeks to explore clinical risk specifically observed in new-onset AF and the antithrombotic strategies currently employed that may address this risk. Additionally, the physiological features that may account for this increased stroke risk will be evaluated through the prism of Virchow's triad for the pathologic development of thrombus. Based on these findings, recommendations for therapy will be made.

## Management of thromboembolic risk in atrial fibrillation

The need for chronic anticoagulation in AF has been established for some time,[11] while the concept that AF itself is an independent risk factor for thromboembolism was established somewhat later.[12,13] Given the hazards associated with chronic warfarin therapy, efforts were undertaken in order to identify clinical factors associated with elevated stroke risk in AF,[14–17] resulting in the eventual development of the $CHADS_2$ and $CHA_2DS_2VASc$ stroke risk scores.[18,19]

The evolution of these clinical schemes for determining thromboembolic risk saw their inception from a desire to tailor chronic OAC therapy (ie, warfarin) appropriately on a "risk-versus-reward" basis; classically, this has resulted in OAC therapy being underused in chronic AF,[20] a pattern also apparent for patients with new-onset AF.[21–25] With the development of newer anticoagulant therapies that display much-improved safety profiles with respect to warfarin,[26,27] this traditional concept of restricting OAC therapy on the basis of limited benefit versus risk is being reevaluated.[28]

## High-risk status of new-onset atrial fibrillation

A number of studies have reported findings suggesting that AF of recent onset is a period of particularly elevated thromboembolic risk (supplementary material available online). For example, Wang et al[17] observed that 13% of a warfarin-naïve cohort experienced stroke and/or death within 30 days following onset of AF; this equates to a crude incidence rate for stroke and/or death of 153 events per 100 person-years, as compared to 13.4 events per 100 person-years in the main study, suggesting exceptionally high risk during this period. Similarly, the first 4 months following de novo detection of AF has been associated with disproportionately high mortality rates, with a reported hazard ratio (HR) of 9.62 (95% confidence interval [CI], 8.93–10.32) for mortality within the first 4 months, declining to 1.66 (95% CI, 1.59–1.73) from that point on.[29] A large Swedish case-control study observed significantly elevated mortality rates in AF patients, particularly within the initial 12 months following AF diagnosis.[30] Conen et al,[31] examining event rates in the Women's Health Study, observed that new-onset AF, developing in 2.9% of this group, carried an increased risk of cardiovascular (HR 4.18 [95% CI, 2.69–6.51]) and total mortality (HR 2.14 [95% CI, 1.64–2.77]); in 6.3% of these individuals, mortality occurred within 30 days of AF onset. However, this study does not permit analysis regarding the possible role of gender in predisposing to such complications.

The development of new-onset AF following hospital admission for acute coronary syndromes also results in significantly poorer prognoses than those with pre-existing or no AF. Analyses of the ACACIA[32] and PRACSIS[33] studies both observed increased 30-day and/or in-hospital mortality, while similar evaluation of the OPTIMAAL[34] and GRACE[35] studies documented increased 30-day and/or in-hospital mortality and stroke risk.

Historically cardioversion has only been advocated for patients with recent-onset AF, and cardioversion without prior OAC therapy for patients with AF of less than 48 hours duration;[24,28,36,37] thus, data regarding thromboembolism rates following cardioversion are also relevant here. Thromboembolic risk in patients undergoing direct current cardioversion with or without OAC therapy was retrospectively investigated in a Danish population.[36] It was observed that the incidence of thromboembolism at 30-day and 1-year follow-up periods was greatly increased in the population without OAC therapy (Figure 1), despite lower conventional clinical risk indices. Similarly, anticoagulation during cardioversion has been advocated by another study,[38] on the observed basis that short-term (30-day) thromboembolic risk following cardioversion increases with presence of clinical risk factors for thromboembolism; subsequent analyses by the same group observed that AF arrhythmia lasting more than 12 hours was a significant, independent predictor for thromboembolism.[39] Admittedly, the cardioversion procedure itself is a potentially confounding factor in assessing thromboembolic risk in the context of new-onset AF: the occurrence of "atrial stunning" (discussed later) and/or dislodgment of pre-existing atrial thrombi are possibilities; the routine use of transesophageal echocardiography to discriminate for the presence of thrombus[40] would presumably mitigate this risk.

It might be argued that in many cases the onset of asymptomatic paroxysmal AF substantially precedes that of clinically overt arrhythmia; hence, newly detected AF may not really be "new onset."[41,42] Various studies have evaluated the prognostic implications of AF episodes detected by implanted devices for the occurrence of stroke,[41–44] and have generally noted that nonsustained asymptomatic AF is rapidly followed by sustained AF in about half of cases.[45] In one such case-crossover study, episodes of AF were documented to increase in frequency from 120 days to 30 days preceding the stroke event.[44] In a smaller study, Martin et al[43] observed no benefit from anticoagulant therapy in patients with "device-detected" AF; however, there was substantial potential for type 2 error in this study. Finally, in the ASSERT trial,[41] it was indeed