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Systematic Review/Meta-analysis

Association of Inflammatory and Hemostatic Markers With Stroke and Thromboembolic Events in Atrial Fibrillation: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Atrial fibrillation (AF) increases the risk of stroke and thromboembolic events. Recently, biomarkers have been proposed as a practical tool to predict adverse outcomes in patients with AF. The prognostic value of inflammatory and hemostatic markers in AF has been widely studied; however, the results of previous studies have been inconclusive.

Methods: We conducted a systematic review and meta-analysis to evaluate the association of inflammatory and hemostatic markers with stroke and thromboembolic events in patients with AF.

Results: A total of 27 studies including 22,176 participants met our inclusion criteria for the systematic review. Our meta-analysis determined that elevated circulating plasminogen activator inhibitor-1 (PAI-1) and thrombin-antithrombin (TAT) were significantly associated with increased risk of stroke in patients with AF (standardized mean difference [SMD], 0.89; 95% confidence interval [CI], 0.20-1.59 and 1.43; 95% CI, 0.40-2.47, respectively). Higher levels of D-dimer were associated with increased subsequent thromboembolic event risk with

RÉSUMÉ

Introduction : La fibrillation auriculaire (FA) augmente le risque d'accident vasculaire cérébral (AVC) et d'événements thromboemboliques. Récemment, des biomarqueurs ont été proposés comme outil pratique pour prédire les effets indésirables chez les patients atteints de FA. La valeur pronostique de marqueurs inflammatoires et hémostatiques dans la FA a été largement étudiée ; toutefois, les résultats des études précédentes n'ont pas été concluants.

Méthodes : Nous avons effectué une revue systématique et une méta-analyse pour évaluer l'association de marqueurs inflammatoires et hémostatiques avec les AVC et les événements thromboemboliques de patients atteints de FA.

Résultats : Un total de 27 études incluant 22 176 participants répondaient à nos critères d'inclusion pour la revue systématique. Notre méta-analyse a déterminé qu'un taux circulant élevé d'inhibiteur de l'activateur du plasminogène 1 (PAI-1) et du complexe thrombine-antithrombine (TAT) étaient significativement associés à un risque accru d'AVC chez les patients atteints de FA (différence moyenne

Atrial fibrillation (AF) is the most common arrhythmia. The prevalence of AF is approximately 0.4%-1.0% among the general population and is estimated to double in the next 50 years as the population ages.[1] The presence of AF independently increases the risk of peripheral embolism and stroke by approximately 5-fold across all age groups, although this level may be substantially underestimated because of the frequently asymptomatic nature of AF.[2] The American Heart Association recently estimated that AF is associated with an increased risk of mortality in both men (odds ratio [OR], 1.5; 95% CI, 1.2-1.8) and women (OR, 1.9; 95% CI, 1.5-2.2).[3] This increased mortality risk is partly because of stroke or thromboembolism. These fatal or disabling complications lead to impaired quality of life and higher medical care costs in patients with AF.[4]

Optimal treatment of complications in patients with AF requires prediction of adverse outcomes at an early stage when severe damage has not occurred.[5] To identify patients with AF who are at high risk of stroke and eligible for optimal anticoagulant therapy, 2 stroke risk stratification schemes have been developed and applied widely in clinical practice, including the

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a pooled hazard ratio of 2.90 (95% CI, 1.22-6.90) for cohort studies and an SMD of 0.93 (95% CI, 0.36-1.50) for case-control studies. There was also very limited evidence indicating that other biomarkers—such as interleukin-6, von Willebrand factor, P-selectin, and mean platelet volume—could predict adverse outcomes in AF.

Conclusions: In conclusion, increased circulating PAI-1 and TAT levels were significantly associated with subsequent stroke in patients with AF, and high levels of D-dimer were associated with thromboembolic events in AF. Further epidemiologic studies are needed to accumulate more evidence on the prognostic role of inflammatory and hemostatic markers in AF.

standardisée [DMS], 0,89; Intervalle de confiance [IC] à 95 % 0,20-1,59 et DMS, 1,43; IC à 95 %, 0,40-2,47, respectivement). Des niveaux plus élevés de D-dimères étaient associés à un risque accru d'événements thromboembolique ultérieurs avec un rapport groupé des risques instantanés de 2,90 (IC à 95 %, 1,22-6,90) pour les études de cohorte et d'un DMS de 0,93 (IC à 95 %, 0,36-1,50) pour les études cas-témoins. Il y avait également très peu de preuves indiquant que d'autres biomarqueurs tels que l'interleukine-6, le facteur de von Willebrand, la P-sélectine, et le volume moyen plaquettaire, pourraient prédire des répercussions défavorables dans la FA.

Conclusions : En conclusion, l'augmentation du taux circulant de PAI-1 et des niveaux de TAT étaient significativement associés à un AVC subséquent chez les patients atteints de FA, et des niveaux élevés de D-dimères ont été associés à des événements thromboemboliques en cas de FA. D'autres études épidémiologiques sont nécessaires pour accumuler plus de preuves sur le rôle pronostique des marqueurs inflammatoires et hémostatiques dans la FA.

$CHADS_2$ [**C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack] score[6] and the CHA_2DS_2-VASc VASc [**C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female)] score.[7] However, these 2 schemes have only modest predictive value for predicting "high-risk" patients, with a c-statistic of approximately 0.6.[8]

Recently, several studies have identified some biomarkers that may play important roles in predicting stroke or thromboembolic events in patients with AF, which is an appealing strategy for managing these patients. These studies have focused mainly on inflammatory and hemostatic factors, and most were case-control or cohort studies with small sample sizes. Recently, several large prospective cohort studies were published; however, the results remain controversial. Although some studies found that D-dimer, prothrombin fragment 1+2 (F1+2), fibrinogen, plasminogen activator inhibitor (PAI-1) and C-reactive protein (CRP) were associated with subsequent stroke or thrombotic events in patients with AF,[9-12] other studies failed to demonstrate these associations.[13-15] We therefore conducted a systematic review and meta-analysis to provide an overview of the association of inflammatory and hemostatic factors with stroke and thromboembolic events in patients with AF.

Methods

Search strategy

We used electronic databases and manual searches to identify relevant studies. The PubMed, EMBASE, Web of Science, and Chinese Biomedical Literature databases were systematically searched for studies published up to September 2014 using a web-based search engine. The search terms were "platelet," "platelet factor-4," "β-thromboglobulin," "P-selectin," "D-dimer," "fibrinogen," "prothrombin fragment 1+2," "thrombin-antithrombin," "antithrombin-III," "a_2-antiplasmin," "fibrinopeptide A," "tissue-type plasminogen activator," "urokinase-type plasminogen activator," "plasminogen activator inhibitor," "plasmin-antiplasmin complex," "von Willebrand factor," "soluble thrombomodulin," "hemostatic markers," "C-reactive protein," "interleukin-1," "interleukin-6," "interleukin-8," "interleukin-10," "interleukin-18," "tumor necrosis factor," "human transforming growth factor," "white blood cell," "inflammatory markers," "biomarker," "prognosis," "prognostic," and "atrial fibrillation." We also manually searched journals and the reference lists of all retrieved articles. Additionally, relevant review articles were also cross-referenced. The literature retrieval was performed in duplication by 2 independent reviewers (N.W. and Y.L.). The meta-analysis was performed according to the guidelines presented by the Meta-analysis of Observational Studies in Epidemiology Group.[16]

Study selection

Human studies, regardless of sample size, were included if they met the following criteria: (1) the study design was a case-control study (retrospective or nested case-control study) or cohort study (retrospective or prospective cohort study) and (2) the study investigated the association between circulating biomarkers (inflammatory and hemostatic factors) and stroke or thromboembolic events in patients with AF. If multiple publications were based on the same or overlapping data, we used the most recent or largest population as recommended by Little et al.[17]

Quality assessment

Two reviewers (N.W. and Y.L.) independently assessed the study quality using the primary criteria for nonrandomized studies described in the Newcastle-Ottawa scale.[18] A "scoring system" was developed based on the Newcastle-Ottawa criteria (Supplemental Table S1). The total scores ranged from 0 (worst) to 9 (best) for case-control or cohort studies. A consensus on scoring was reached after discussion to resolve any disagreements.

Data extraction

Using standard data extraction forms, 2 reviewers (N.W. and Y.L.) extracted data from the relevant studies. The data extracted included publication information (first author's name, publication year, country, and study design), sample size, mean age of participants, mean follow-up time, adverse outcomes, and information related to effect size. If the study provided the