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AF and Venous Thromboembolism – Pathophysiology, Risk Assessment and CHADS-VASc score

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Abstract

Atrial fibrillation (AF) and venous thromboembolism (VTE) are the two most common medical conditions managed with anti-coagulation therapy. Not all the patients with decreased mobility or AF have a similar risk for thromboembolism. The risk factors for venous thromboembolism and thromboembolism associated with AF are described in various studies. Considering that the two conditions have similar pathophysiologic basis of clot formation, one could imply that the risk factors for the occurrence of thrombosis could be similar. The present review focuses on the similarities and differences in the clinical risk factors of VTE and AF related thromboembolism. We will also be discussing the role of $CHADS_2$-VASc scoring system in the risk assessment of VTE.

Introduction

In the mid eighteenth century, Virchow proposed a triad for the cause of venous thrombosis. This was constituted by stasis of blood, changes in the vessel wall and blood coagulability. Atrial fibrillation (AF), the most common sustained cardiac arrhythmia is associated with an increased risk of thromboembolism. In AF, all the changes occur in the atrium to fulfill Virchow's triad for thrombogenesis.[1] It is also noted that stroke patients suffering from AF have a higher incidence of venous thromboembolism (VTE).[2] Several factors have been studied and established as risk factors for developing VTE and thromboembolism in patients with AF. We will review the similarities and differences in these factors.

Epidemiology

An estimated 200,000 people in the United States are diagnosed with VTE annually.[3-7] This includes 106,000 patients with deep venous thrombosis (DVT) and 94,000 with pulmonary embolism (PE).[3-7] The incidence of VTE occurring for the first time in about 100 per 100,000 people.[6] VTE contributes to about 300,000 to 600,000 hospitalizations and 100,000 deaths annually. Death occurs in about 6% of patients with DVT and 12% of PE cases within a month of diagnosis.[6] In the International Cooperative Pulmonary Embolism Registry (ICOPER), all-cause mortality rate at 3 months, associated with PE was 17%.[8] In the Worcester, Massachusetts metropolitan area study, patients with PE had mortality rate of 11.1%.[9]

AF is the commonest sustained cardiac arrhythmia, which is associated with significant risk of morbidity and mortality resulting from thromboembolism.[10] Approximately 2.2 million Americans suffer from AF.[11-12] By 2050, an estimated 16 million Americans are predicted to have AF.[13] On

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screening of patients with ischemic stroke, AF is recognized in 6.7% of patients on routine electrocardiogram, 10.6% on 24 hour Holter and 15.6% with 7 day event monitor.[14] While the stroke risk is increased by 5 folds by AF, this risk is not homogeneous as it is altered by other stroke risk factors.[10]

Pathophysiology

Hemostasis is primarily a protective mechanism of reducing bleeding after vascular injury. In situations of endothelial dysfunction, stasis or hypercoagulability, there is increased activation of this protective mechanism resulting in thrombosis. Arterial and venous thromboses are two pathophysiologically distinct entities with different clinical presentations and management strategies. Arterial thrombosis generally develops as a result of underlying vascular abnormalities, typically atherosclerotic disease and is largely a phenomenon of platelet activation. Unlike arterial thrombosis, venous thrombosis occurs in regions of sluggish blood flow and is largely a matter of activation of the clotting system.[15] The venous clots are relatively larger in size compared to arterial clots and are composed predominantly of fibrin enmeshed with cellular components including red blood cells. Activation of the coagulation system is the primary cause of venous thrombosis and precedes platelet activation and aggregation.[16] Surgery or trauma may cause direct injury to the vessels resulting in exposure of the subendothelial tissue factor (TF). This however, is not common in non-surgical patients with VTE. Venous stasis promotes thrombus formation by not flushing out the activated coagulation factors from endothelial dysfunction. Circulating TF-bearing microparticles are also suggested to play an important role in VTE. These particles attach to activated endothelial cells and transfer TF to them initiating coagulation reactions and clot formation.[17-18] This is different from thrombus formation in the arterial system. The TF-bearing micro-particles may also contribute to the hypercoagulable state associated with disease conditions with an increased risk of DVT.[17-19] In patients with AF, there is abnormal stasis of blood in the atrium with endothelial dysfunction, and hypercoagulable states resulting in thrombus formation.[1,20] Systemic fibrinogen and fibrin D-dimer levels are elevated in patients with persistent and paroxysmal AF which increases the procoagulant state.[1] Both von Willebrand factor and TF are also over expressed in the atrial endothelium of patients with AF who have a history of thromboembolism.[1] AF seems to fulfill the Virchow's triad for thrombogenesis, and the thrombus formed has a 'venous-type clot'. These findings are suggestive of similar pathophysiologic basis for clot formation for VTE and AF, which may imply similar risk factors for the occurrence of thrombosis. This could also explain for the success of anticoagulants and not antiplatelets in the prevention of VTE and AF related strokes.[21-23]

Risk Factors for VTE and AF Thromboembolism

Systematic reviews of epidemiologic cohorts and clinical trials have identified various risk factors associated with AF and their impact on stroke.[24-25] The risk factors and their adjusted relative risk (RR) as described by the Stroke in AF Working Group are: previous stroke/transient ischemic attack (TIA) (RR 2.5), age (RR 1.5/decade), hypertension (RR 2.0), diabetes (RR 1.8) and female gender (RR 1.6).[24-25] Congestive heart failure (CHF) history was not associated with stroke risk in this study, although moderate systolic dysfunction was still an independent predictor. In a systemic review by the National Institute of Health and Clinical Evidence (NICE), history of stroke or TIA, advanced age, hypertension and structural heart disease were predictors of stroke.[25] Diabetes mellitus and gender were not significant factors to predict stroke risk in this review. The $CHADS_2$ score was derived by adding the AF investigators and Stroke Prevention in AF (SPAF) -1 trials.[26] The factors included were CHF, hypertension, age > 75 years, diabetes mellitus, and prior stroke/TIA. This scoring was simple and was validated in assessing the risk of thromboembolic stroke in patients with AF. However, it could not differentiate very low risk group from low risk and intermediate risk groups.[26] To further refine and define the risk of stroke in AF patients, the European Society of Cardiology came up with the CHADS-VASc score to complement the CHADS2 scheme.[27] In this the major risk factors were age > 75 years and previous stroke/TIA (with allocated two points); the non-major risk factors were CHF, hypertension, diabetes mellitus, age between 65 years and

75 years, vascular disease and female gender (with allocated one point for each) (see Table 1).[28] The CHADS-VASc score has also been well validated and is efficient in identifying patients at high and moderate risk of thromboembolic events.[28-29] Absence of the risk factors as defined by the CHADS-VASc score identifies patient who are at very low risk of thromboembolism or stroke.[30] In low risk patients (CHADS-VASc score = 0), the rate of thromboembolism per 100 person-years was 1.67 [95% confidence interval (CI) 1.47–1.89].[30] Presence of any of the minor risk factors significantly increased the risk of stroke (absolute risk 2.01; 95% CI 1.70–2.36). The negative predictive value (i.e. the percent categorized as not being at higher risk, actually being free from thromboembolism) for CHADS-VASc was 99.5% suggesting that other clinical or laboratory factors may not have significant contribution to thromboembolic risk.

Table 1 Factors and adjusted thromboembolic stroke risks in patients with atrial fibrillation (CHADS-VASc scoring)

Major risk factors (assigned 2 points)	
Aged >/= 75 years Stroke/Transient ischemic stroke	
Minor risk factors (assigned 1 point)	
Congestive heart failure Hypertension Diabetes mellitus Vascular disease (prior myocardial infarct, peripheral arterial disease) Aged 65–74 years Sex category (female gender)	
Score	**Adjusted stroke rate (% per year)**
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Adapted from European Heart Rhythm Association Guidelines [27] and Lip GY, et al.[28]

VTE is a multifactorial disease with 2 or more risk factors being present at the same time.[31] An overview of the risk factors for VTE is provided in Table 2.[32] Genetic risk factors predisposing for VTE include deficiencies of antithrombin, protein C, protein S, and the factor V Leiden (FVL) mutation and prothrombin 20210A gene variant.[33] Genetic factors including variations in antithrombin, protein C, or protein S deficiencies are associated with approximately 5 to 10 fold, 4 to 6 fold and 1 to 10 fold increased risk of VTE respectively.[34-35] Prothrombin G20210A variant and FVL mutation are associated with 3 and 7 fold increased risk of VTE respectively.[36-37] But for these genetic risk factors, there are several acquired clinical risk factors which increase the risk for VTE. The clinical risk factors include triggering factors and demographic and chronic medical conditions. The triggering factors include immobilization, plaster casts, surgery, and trauma. The demographic and medical conditions include cancer, obesity, increasing age, hormone replacement therapy and pregnancy.[38] These acquired factors cause either stasis or hypercoagulability predisposing to VTE. Hospitalization is a risk factor for VTE considering that these patients are exposed to more than one acquired risk factor including immobility, cancer, surgery, CHF, infections and chronic kidney disease.[39]

Table 2 Risk factors for venous thrombosis and pulmonary embolism

Primary (unprovoked)
Old age (>65 years) Long-haul travel Thrombophilia (factor V Leiden or prothrombin gene mutation) Obesity Cigarette smoking Hypertension Metabolic syndrome
Secondary (provoked)
Immobilization Postoperative Trauma Oral contraceptives, pregnancy Cancer Acute medical illness (e.g. Pneumonia, congestive heart failure)

Adapted from Goldhaber SZ, et al.[32]

Relevant Risk Factors for Similarities and Differences

Similar to thrombosis in patients with AF, a com-

bination of various risk factors increases the risk for VTE episodes. Genetic risk factors (deficiency of protein C and S, and FVL mutation), and temporary triggering risk factors (trauma, surgery, pregnancy) that predispose to the development of VTE have not been studied extensively in patients with AF. Hence these factors will not be reviewed. In our discussion we will be describing the studies which have established the role of the different risk factors (i.e. CHADS-VASc score) in assessing risk of thromboembolism in patients with AF. We will also discuss the implication of these factors in assessing VTE risk.

a. Age

Levels of prothrombin activation fragment F1.2, an index of thrombin generation, increase with age in the general population[40-42] suggesting an age-related prothrombotic diathesis. In patients with AF, aging is associated with left atrial (LA) enlargement, reduced left atrial appendage (LAA) flow velocity, and spontaneous echo contrast (SEC), all of which predispose to LA thrombus formation.[43-45] The implication of aging on risk of stroke in patients with AF has been evaluated in 17 studies.[46] Twelve studies found an independent effect of age on stroke risk while five studies failed to find such an association.[46] In the analysis of pooled data from five randomized controlled trials, the annual risk of stroke increased from 15% to 20% in patients aged <65 years and >65 years with no other risk factors and from 17% to 27% in patients with one or more risk factors for stroke.[47] In this study the overall relative risk of stroke associated with every decade of life was 1.4 (95% CI 1.1-1.8). In the Framingham study, age 65 years and older was associated with a 3-fold increase in risk of stroke.[48]

VTE has an incidence of 1 to 2 cases per 1000 person-years, with age-dependent incidence ranging from 1 in 100000 in children to 1 in 100 in older individuals.[49-51] VTE rises exponentially from <5 cases per 100000 persons in younger than 15 years age to about 500 cases (0.5%) per 100000 persons at age 80 years.[6] The incidence of VTE increased significantly with age in a population based study with the noted incidence of about 100 per 100000 in people aged 50 years and more than 450 per 100000 in people aged 75 years.[52] Thus, advanced age is a risk factor for thromboembolism associated with AF as well as for development of VTE.

b. Sex (female gender)

Women face several unique situations during their lifetime, such as pregnancy, use of oral contraceptives and hormone replacement therapies, all of which increase their risk of thromboembolism. In AF, female gender has been observed to be a significant risk factor for thromboembolic stroke in some studies[53-57] but not in others.[58-62] In the SPAF trial, 2012 participants given aspirin were evaluated, female gender was associated with significantly higher risk of stroke with a RR of 1.6.[53] Similar to this trial, the Framingham study and the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study noted a significantly higher incidence of stroke in women with AF with the noted RR of 1.7 and 1.6 respectively.[55,63] In the AFASAK trial, female gender was not associated with occurrence of stroke. Of note, there was no association of age or left atrial size with increased incidence of stroke in this study.[59] Similar to this study, Aronow et al, did not find any association of gender with risk of thromboembolic stroke in elderly patients with chronic AF.[61]

In a Norwegian study, the incidence of first VTE events was 1.43 per 1000 person-years, with a noted slightly higher events in women than in men.[50] Contradictory to this finding, in a community-based study, incidence was higher for men than for women (1.14 per 1000 patient-years vs. 1.05 per 1000 patient-years).[64] In the Olmsted county study, the age-adjusted rates of VTE was significantly higher in males than females (130 vs. 110 per 100000 patient-years).[52] In this study it was noted that the incidence of VTE in women younger than 55 years, was higher than men. This finding may be related to the differential exposure to clinical risk factors in this specific population of women (pregnancy, postpartum state, or oral contraceptive use). In a meta-analysis of 15 studies (nine randomized controlled and six prospective observational), the estimate of the RR of recurrent VTE for men was significantly higher compared to women (RR 1.6, 95% CI 1.2-2.0).[65] In conclusion, women younger than 55 years age are at a higher risk of VTE, but with aging the risk of VTE is similar or higher in men.

c. Hypertension

Hypertension is a common risk factor for arterial thrombosis and also AF. Hypertension in patients with AF is associated with reduced left atrial appendage (LAA) flow velocity, spontaneous echocontrast (SEC), and thrombus formation.[43,44,66] Ventricular diastolic dysfunction might underlie the effect of hypertension on left atrial (LA) dynamics, but this relationship is still speculative.[67-68] Hypertension is an important predictor of stroke in patients with AF,[48,53-54,58,61,69-70] especially in those with systolic blood pressure greater than 160 mm Hg.[53-54,56] During a 2.0 year follow-up of patients with non-valvular AF, history of hypertension was associated with significantly higher risk of stroke with a RR of 2.0.[53] In a systematic review of risk factors for stroke in patients with AF, hypertension was associated with increased risk (RR 2.0, 95% CI 1.6-2.5).[24]

In a study involving the population from the Atherosclerosis Risk In Communities (ARIC) and Cardiovascular Health Study (CHS) to assess the association of established risk factors of arterial thromboembolism, hypertension was not associated with VTE.[71] The relative risk for VTE in patients with history of hypertension was 1.20 (95% CI 0.90-1.60) which was comparable to patients with normal blood pressures (RR 1.21 (95% CI 0.99-1.47). There was no difference when groups with systolic blood pressure less than 114 mmHg were compared with patients with systolic blood pressure between 114 and 130 mmHg and those with systolic blood pressure of more than 140 mmHg. In another study of patients with antiphospholipid syndrome, presence of hypertension increased the incidence of arterial thromboembolism but not VTE.[72]

d. Diabetes Mellitus

Diabetes mellitus has been associated with enhanced coagulation and reduced fibrinolytic potential which may contribute to thrombosis.[73] In the meta-analysis of independent predictors of stroke in non-anticoagulated patient with non-valvular AF by the Stroke Risk in AF Working Group, seven studies were assessed.[24] Diabetes was present in 15% of the study cohorts and was an independent risk factor for stroke. (RR 1.7, 95% CI 1.4-2.0).[24] Studies indicate that the reduction in stroke among warfarin-treated patients with diabetes was below average.[74-75]

In a study of assessing the association of traditional cardiovascular risk factors on occurrence of VTE, diabetes and obesity were each associated with significant increase in events even in age, race and sex adjusted models.[71] In this study the incidence of VTE increased from 0.83 events per 1000 person-years in non-diabetics to 2.12 events per 1000 person-years among diabetics (RR 1.70, 95% CI: 1.20-2.40).[71] On adjusting for body mass index (BMI), diabetes still persisted to be significantly associated with VTE though the risk for events was attenuated (HR 1.46, 95% CI 1.03-2.05). Diabetic patients also had higher secondary events of VTE as compared to patients with idiopathic VTE (HR 1.62 vs. 1.27 respectively).

e. Congestive Heart Failure

CHF is a prothrombotic state resulting from impaired blood flow due to poor myocardial contraction. This is compounded by endothelial dysfunction, abundance of adhesion molecules and an imbalance of procoagulants and anticoagulants.[76] Patients with CHF have abnormally elevated von Willebrand factor levels, soluble thrombomodulin (indexes of endothelial damage/dysfunction) and soluble E-selectin (an index of endothelial activation).[8] It is well established that AF and CHF are inter-related in a varieties of ways with each predisposing to the occurrence of other. In regards to the risk of stroke in patients with both AF and CHF, there are different studies noting variable association. In the SPAF trial, recent (within 3 months) history of CHF was independently associated with a substantial risk for thromboembolism (greater than 7% per year).[69] In contrast to this study, the Embolism in Left Atrial Thrombi (ELAT) study did not find an association of CHF with occurrence of stroke. However, in this study there was significant relation of CHF with all cause mortality.[77] In the Stroke in AF Working Group assessment, CHF was not significantly associated with stroke. The presence of moderate systolic left ventricular dysfunction was still an independent marker.[24] In the National Institute for Health and Clinical Evidence (NICE) review, structural heart disease was independently associated with stroke occurrence.[25]

Stasis of blood in the lower extremities in patients with CHF activates coagulation system, leading to fibrin formation which results in thrombus formation in the extremities. The reported incidence of DVT in patients with CHF ranges from 1% to 59% and that for PE from 1% to 39%.[3,78-81] In a review of the US National Hospital Discharge Survey, the incidence of PE and DVT were significantly higher in patients with diagnosis of CHF than those without CHF. The noted relative risks of 2.15 and 1.21 respectively.[82] In a study addressing the out-patient risk, CHF was an independent risk factor for VTE with an adjusted OR of 2.6 (95% CI, 1.4-4.7).[83]

f. Stroke

Stroke is a consequence of a prothrombotic state resulting in occlusion of the cerebral arteries. Stroke is the most feared complication of AF. History of stroke/TIA in turn increases events of thromboembolism associated with AF and hence secondary event of strokes. Several studies have found a previous history of stroke or TIA to be a significant independent risk factor for secondary stroke.[53-55,62,69] AF increases the risk of stroke by five-fold, and the use of anticoagulation reduces this risk by two-thirds whilst antiplatelet therapy reduces stroke by one-fifth.[84-85] In a systematic evaluation of risks, prior stroke/TIA had the higher risk association for stroke occurrence in patients with AF (RR 2.5, 95% CI: 1.8-3.5).[24] Stroke patients are at high risk for VTE due to immobility caused by stroke.

Patients with stroke have several related risk factors including immobility, hypertension, diabetes, hospitalization which increase the incidence of VTE. The incidence of DVT within the first 2 weeks after stroke ranges from 10% to 75%, depending on the diagnostic method and timing of evaluation.[86] In patients with acute hemiplegic stroke, the incidence of DVT is approximately 50% within 2 weeks in the absence of prophylaxis.[87] In another study, among patients who were not on any prophylactic precautions, the incidence of DVT was found to be 53% in the paralyzed leg and 5% in the non-paralyzed leg.[88] In a MRI based direct thrombus imaging study, of the 102 unselected patients with acute ischemic stroke, the prevalence of all VTE, DVT, and PE after 21 days were 40%, 18%, and 12% respectively.[89] In this study, non-ambulatory status of patients around the time of admission to the hospital was found to predict higher risk of VTE. In the International Stroke Trial (IST), the incidence of PE in patients with stroke was 0.8% at 2 weeks in patients not receiving heparin prophylaxis and 0.5% in patients receiving heparin prophylaxis.[90] This relatively lower incidence of PE reported in the IST study could be due to under-reporting or to early mobilization of patients not described in the study.

g. Vascular disease

Patients with peripheral vascular disease have other risk factors for the thromboembolism which include hypertension, diabetes, myocardial infarction and structural heart disease. These factors have been associated with VTE and also thromboembolism with AF. Peripheral arterial disease confers a poor prognosis in patients with AF. They have high rates of mortality, cardiovascular events, and stroke.[91-93] Lin et al[94] in their nationwide cohort study found that peripheral artery disease was an independent predictor of stroke among non-anticoagulated AF patients, with odds ratio of 1.8 (95% CI, 1.2-2.8). Vascular disease, including peripheral artery disease, was also a risk factor of subsequent stroke in AF patients age <65 years in the Loire Valley Atrial Fibrillation Project,[95] and peripheral artery disease was an independent predictor of stroke and death in the Danish Diet, Cancer, and Health Study.[96] Rasmussen et al found an incidence rate of stroke at 1-year follow-up of 10.9 per 100 person-years in patients with new-onset AF and peripheral artery disease, vs. a rate of 4.6 in new-onset AF patients without vascular disease.[96] In a Danish nationwide cohort study, the presence of vascular disease also increased the risk of thromboembolism significantly at 5 and 10 years of follow-up, with hazard ratios (HRs) of 2.04 and 2.22, respectively.[30]

In a small observation study of 176 patients, there was noted significantly higher incidence of DVT in patients admitted for arteriography, angioplasty or arterial reconstruction surgeries when compared to control patients without peripheral vascular disease.[97] In review of a large US healthcare claims database of hospitalized medically ill patients of age > 40 years age, a diagnosis of peripheral arterial disease at index admission was significantly associated with incidence of venous thromboembolism within 90 days of hospital admission (HR 1.68, 95% CI 1.28-2.21).[98]

CHAD-VASc Risk Factors and VTE

Of the CHAD-VaSc risk factors, five appear to be associated with the occurrence of VTE; these include age, CHF, diabetes, stroke and peripheral vascular disease. Patients aged over 75 years have a 5 fold increased risk when compared to patients aged <50 years. CHF also increases the incidence of VTE. The OR of DVT and PE in patients with CHF is 2.15 and 1.21 respectively. Diabetes has been noted to increase the incidence of VTE by 2 fold. Similarly, stroke significantly increases the risk of VTE. The noted incidence of DVT in patients with stroke ranges from 10% to 75%. After an index hospital admission for peripheral arterial disease, higher incidence of DVT was noted within 90 days with HR of 1.68 for the occurrence of VTE. As far as gender is concerned, women younger than 55 years of age are at a higher risk of VTE, but after 55 years, the risk of VTE is similar or higher in men. Hypertension does not seem to predispose to the development of VTE.

Conclusions

AF and VTE are two common medical conditions associated with significant morbidity and mortality. They share a similar pathophysiology for the development of thrombus and management with anticoagulants. The CHADS-VASc risk factors have been well validated in assessing the risk of thromboembolism associated with AF. Considering the similarities of AF and VTE, these factors may have a role in risk assessment of VTE. Though risk factors including age, CHF, diabetes, stroke and peripheral vascular disease predispose to the development of both conditions; factors including hypertension and sex have differential association with the two conditions. The studies in general have not been exclusively directed to assess the CHADS-VASc score risk factors on incidence of VTE and hence further studies are needed to specifically delineate these factors and the use of CHADS-VASc score for risk assessment of VTE.

Disclosures

No disclosures relevant to this article were made by the authors.

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