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# Deep Vein Thrombosis While Still on NOAC

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**ABSTRACT**

Novel oral anticoagulation treatment has been extensively used for thromboprophylaxis in atrial fibrillation and other clinical conditions because of predicable pharmacokinetic profile and safety. However, rarely plasma drug level variation can occur that can lead to thrombotic and bleeding events. We describe a case of deep vein thrombosis in a compliant patient still on apixaban. Anticoagulation failure with NOAC is concerning and obviously there is growing need of assay in these subsets showing the activity of NOAC. Till the availability of such methods, switching back to conventional therapy with Vitamin K antagonist with accurate monitoring could be appropriate strategy.

**Keywords:** Vitamin K antagonist; Novel oral anticoagulation; deep vein thrombosis.

## INTRODUCTION

Although vitamin K antagonists (VKA) are the standard of treatment for variety of clinical conditions both as preventive and therapeutic indications, they have inherent limitations. Because of inter-individual and intra-individual differences of drug effects, they need regular monitoring in form of international normalized ratio (INR).[1] From last few decades, novel oral anticoagulation (NOAC) treatment has been used more frequently for most clinical scenarios barring exceptions as such mechanical heart valve, valvular atrial fibrillation (AF) and anti-phospholipid syndromes. Major benefits in use of NOAC over VKA lies in that fact that they have more predictable pharmacokinetics and routine monitoring is not required.[2] The efficacy and safety have been proven in multiple randomized controlled trials (RCT) and meta-analysis.[3] However, plasma drug level variation can do occur leading to both sides of adversity namely thrombotic and bleeding events.[4] Here, we describe a case of deep vein thrombosis on a complaint patient on apixaban (NOAC) for persistent non-valvular AF.

## CASE REPORT

### Case history and management

A 77 years old Asian lady came to emergency room with a medical history of hypertension and type 2 diabetes mellitus, chronic obstructive pulmonary disease, persistent AF and recent left middle cerebral artery territory infarction. She has right sided hemiparesis and residual weakness making her bed bound and complicated with decubitus ulcer over sacral region and heel of right foot. She presented with 2 days history of pain swelling and redness of right leg. She was discharged 3 weeks back on aspirin 75 mg daily, apixaban 5 mg twice daily, atorvastatin 40 mg daily, basal-bolus insulin therapy and other supportive medications. She was stable vitally with pulse rate of 80 beats per minute and irregularly irregular. An echocardiogram showed mild concentric left ventricular hypertrophy, aortic sclerosis, mild mitral annular calcification, trivial mitral regurgitation with normal left and right ventricular systolic function. There were no intracardiac mass or thrombus. Right lower limb Venous Doppler study showed only partial compressibility of superficial femoral vein and thickened walls. Arterial Doppler study revealed monophasic waveforms in posterior tibial artery and no flow in anterior tibial artery on right side. CT lower limb angiography was performed for further clarification that showed occlusive thrombus in right popliteal artery extending to tibio-peroneal trunk with muscular collateral to the distal vessels. There was high grade irregular stenoses in right anterior tibial artery. There were non-occlusive thrombi within bilateral superficial femoral veins extending contiguously into the common femoral veins.

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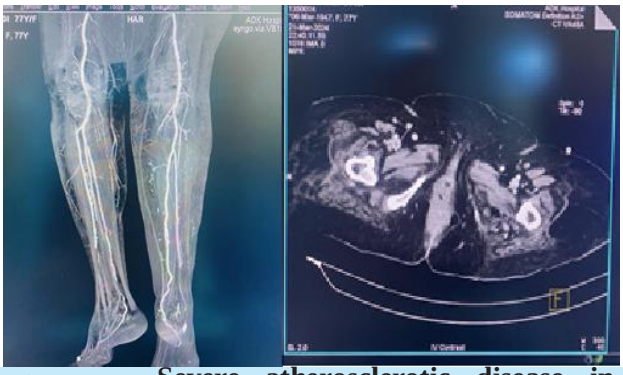

**Figure 1. Severe atherosclerotic disease in bilateral below knee arteries**

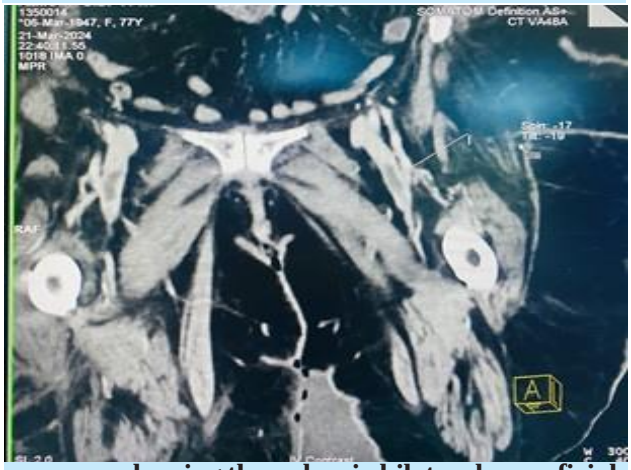

**Figure 2. showing thrombus in bilateral superficial femoral veins during venous phase of contrast**

She was admitted in high dependency unit. Cardiac examination revealed normal S1 and S2, no evidence of murmur or gallop. A 3 X3 cm gangrenous ulcer was noted over heel of right foot. There were 2 smaller pressure ulcers noted on sacral regions. Right lower extremity showed mild pitting edema upto mid shin level. Platelet count, bleeding time, INR, activated partial thromboplastin time (aPTT) were normal. Anti-factor Xa was not available in our lab. We discontinued apixaban and started on enoxaparin at 1 mg per kg dose twice daily subcutaneous injections. She was discussed for peripheral angioplasty in view of high risk for surgical intervention for arterial thrombosis. The family members opted for medical therapy alone and declined any invasive therapy. Limb viability was preserved with anticoagulation alone. After 2 days, warfarin was started and bridging was continued till 2 consecutive days of INR > 2. Her other home medications were continued with a plan to follow up in 1 week time.

## DISCUSSION

Atrial fibrillation is the most common sustained arrhythmia in adults.[5] Thromboembolic complications including ischemic stroke and systemic arterial embolization are the most significant and dreaded complication with AF.[6] It occurs due to embolization of left atrial thrombus forming as a result of stagnation of blood in left atrial appendage cavity. Based on ischemic risk and risk of bleeding associated with anticoagulation use, we must judge both benefits and risks through shared decision with the patient and care takers. Individual risk of thromboembolism is assessed most commonly nowadays with CHA2DS2Vasc score calculation.[7] HAS-BLED is one of the commonly used methods to estimate the risk of bleeding on OAC.[8] In general, a therapeutic anticoagulation (VKA or NOAC) reduced ischemic stroke and other embolic events by two-thirds compared to placebo.[9] Based on a meta-analysis including six RCT comparing VKA (Warfarin) with placebo, in 2900 participants with AF, overall stroke rate was 2.2 per 100 patient years in warfarin group compared to 6.0 per 100 patient years in placebo group.[9] On evaluating the risk of bleeding in 16,000 patients with AF, the major bleeding (including intracranial hemorrhage and gastrointestinal bleeding), annual risk of bleeding is 3.8 per 100 patient years on OAC and 2.9 per 100 patient years in control group.[10] So, the bleeding risk is double in OAC. NOAC has almost half risk of bleeding compared to VKA. While incremental absolute risk of intracranial bleeding is non-trivial (0.2 percent/year on VKA), it is substantially less than expected absolute risk reduction from ischemic stroke in patients with AF and two or more CHA2DS2Vasc risk factors, Apixaban has been tested in ARISTOTLE trial and approved by FDA for thrombo-prophylaxis in AF and at least one additional risk factor. In 18, 201 patients with median follow up of 1.8 years, the incidence of primary outcome (ischemic or hemorrhagic stroke or systemic embolism) occurred in 1.27% per year in apixaban group and 1.6% per year in warfarin group with $P < 0.001$ for non-inferiority and $P=0.01$ for superiority.[11] The rate of major bleeding was 2.13% per year in apixaban group

compared to 3.09% per year in Warfarin group[11] with P<0.001. So, NOAC are preferred over VKA due to superiority in preventing stroke or systemic embolism with less bleeding. Head-to-head comparison trial of individual NOAC are not done. However, despite adequate anticoagulation, a few patients can develop thromboembolic events known as anticoagulation failure. Ischemic stroke with non-embolic causes should not be taken as anticoagulation failure as they can occur in patients without AF. Certain risk factors increase chance of anticoagulation failure: TEE evidence dense echo contrast in left atrium,[12] decreased ejection velocity of left atrial appendage,[12]complex aortic plaque,[13] non-compliance of NOAC, sub-therapeutic INR in VKA, etc. elevated D-dimer level and von-Willebrand factor are also noted to be high in patients with anticoagulation failure[14] but routine testing is not shown to alter the outcome.Direct quantification can be done to measure the drug level and liquid chromatography tandem mass spectrometry can be used to measure the plasma concentration.[15] However, they are not available in most settings. Anti-factor Xa activity is also measured as an efficacy of anticoagulation and this is also not available widely. In our case, the patient was compliant to apixaban and she was not taking any medications that could reduce the efficacy of apixaban. In this setting, it is difficult decision to switch to another NOAC as we have no definitive method to confirm adequate anticoagulation. In the current situation, we opted to move to conventional method of VKA for ease of measuring INR.

## CONCLUSION

Anticoagulation failure with NOAC is concerning and obviously there is growing need of assay in these subsets showing the activity of NOAC. Till the availability of such methods, switching back to conventional therapy with Vitamin K antagonist with accurate monitoring could be appropriate strategy.

**Conflict of interest**: None

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