3. van den Berg G, Moorman AF. Development of the pulmonary vein and the systemic venous sinus: an interactive 3D overview. PLoS One 2011; 6: e22055.
4. Tosun Ö, Saygı M, Kasar T, Ayyıldız P, Türkvatan A, Ergül Y, et al. A rare pathology: Levoatriocardinal vein. Turk Kardiyol Dern Ars 2016; 44: 315-9.
5. Pinto CA, Ho SY, Redington A, Shinebourne EA, Anderson RH. Morphological features of the levoatriocardinal (or pulmonary-to-systemic collateral) vein. Pediatr Pathol 1993; 13: 751-61.

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# Apixaban successfully resolved a warfarin-resistant left atrial appendage thrombus in a patient with end-stage renal disease on hemodialysis

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## Introduction

The left atrial appendage (LAA) is the major source of thromboembolism in patients with atrial fibrillation (AF). Warfarin or new oral anticoagulants (NOACs) have been used to treat the LAA thrombus; however, the use of NOACs is limited in patients with renal dysfunction. Here, we report the case of a patient with paroxysmal AF and end-stage renal disease (ESRD) requiring hemodialysis, in whom apixaban successfully and safely resolved a LAA thrombus refractory to warfarin.

## Case Report

A 62-year-old female with a history of ESRD and on hemodialysis was referred to our electrophysiology department due to paroxysmal AF. Anticoagulation therapy with warfarin was started because her CHADS2-VASc score was 4 (hypertension, diabetes, congestive heart failure, and female gender), as well as amiodarone therapy for rhythm control. Transthoracic echocardiography demonstrated enlarged left atrium (LA) with a reduced left ventricular ejection fraction (25%). The coronary angiogram demonstrated no significant stenosis at the epicardial coronary artery. Transesophageal echocardiography (TEE) revealed a thrombus in the LAA (Video 1 & Fig. 1a). We targeted an INR of 2.0–2.5 with a monthly check up; however, labile INR was documented with time in a therapeutic range (TTR) of 45.8%. With maintaining warfarin and amiodarone, the patient experienced syncope. Tachycardia–bradycardia syndrome was documented, and therefore, a catheter ablation was planned. However, after approximately 2 years of warfarin anticoagulation therapy, TEE detected remaining thrombus (Fig. 1b). Therefore, warfarin was switched to a direct factor Xa inhibitor, apixaban at 5mg bid. Patient's PT and INR values were 19.4 and 1.78, respectively, at the time of replacement. Apixaban was initially prescribed at 2.5 mg bid as opposed to 5 mg bid recommended by the package labeling for fear of bleeding complications, and it was increased to 5 mg bid a month later. After 4 months of apixaban treatment, TEE revealed complete resolution of the LAA thrombus (Video 2 & Fig. 1c). Finally, catheter ablation was performed without complications, and the patient has since been in the sinus rhythm under continued anticoagulant treatment with apixaban. No thromboembolic or bleeding event occurred during the 26 months of the follow-up after the catheter ablation.

## Discussion

Randomized controlled trials evaluating warfarin and NOACs have generally excluded patients with ESRD undergoing hemodialysis. Based on current guidelines, warfarin remains the anticoagulant of choice in these patients. However, a low TTR is the problem most likely intrinsic to hemodialysis patients due to multiple factors, which include drug interactions, high comorbidity burden, frequent interventions requiring interruption of anticoagulation, and subclinical vitamin K deficiency (1).

In a previous evaluation of the pharmacokinetics, pharmacodynamics, and safety of apixaban in eight patients with ESRD undergoing hemodialysis, it was demonstrated that the area under the curve (AUC) of apixaban was 36% higher for the ESRD patients than for those with normal renal function. The AUC decreased by 14% when apixaban was administered prior to hemodialysis. However, the calculated hemodialysis extraction ratio was negligible, with only 0.33 mg of the dose being removed (2). In another study, the AUC of apixaban was found to be increased by 44% in seven individuals with severe renal impairment (creatinine clearance ≤15 mL/min); however, the apixaban exposure (C max) was not affected by the presence of renal impairment (3). This information led to a labeling change approved by the FDA in 2014 to an apixaban dose of 5 mg bid in hemodialysis patients without dose adjustment necessary for renal impairment alone. In a recent retrospective study, the bleeding rates were similar in ESRD patients undergoing hemodialysis who were either on apixaban or on warfarin for the treatment or prevention of venous thromboembolism (4).

Apixaban has the least renal excretion among four NOACs and is allowed to be used in patients requiring dialysis. Therefore, we

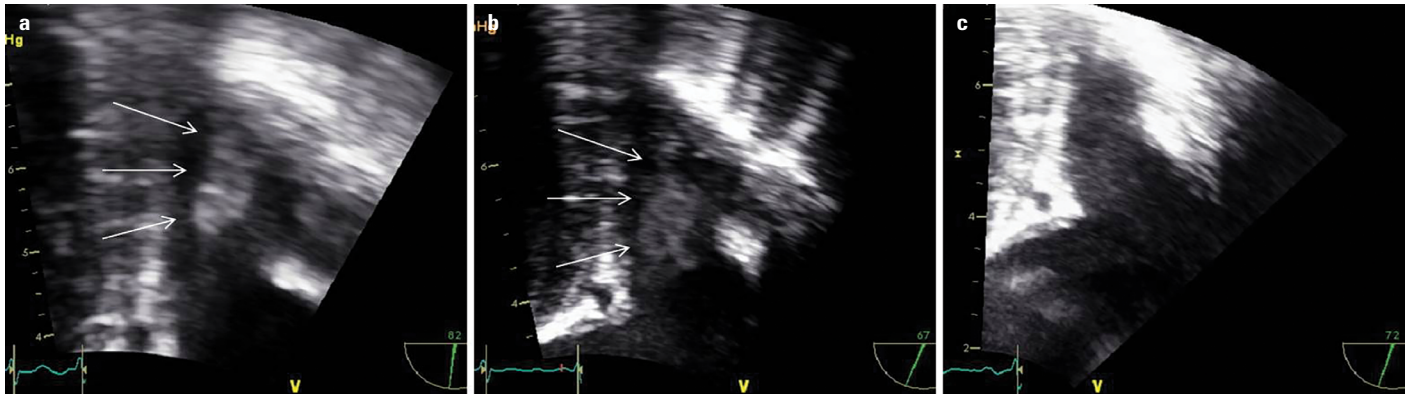


**Figure 1.** (a) TEE revealed a mobile thrombus in the LAA. (b) A follow-up TEE identified remaining thrombus almost after approximately two years of warfarin anticoagulation therapy. (c) After a total four months of apixaban treatment, TEE revealed complete resolution of the LAA thrombus
LAA - left atrial appendage; TEE - transesophageal echocardiography

chose apixaban as an alternative to warfarin in our patient. A recent case report on anti-factor Xa monitoring in a patient on hemodialysis showed peak and trough apixaban concentrations were above the upper limit of detection with apixaban at 2.5 mg bid and that the patient developed gastrointestinal bleeding (5). However, apixaban successfully resolved the LAA thrombus without any complication, including thromboembolic or bleeding events, even though therapeutic drug monitoring was not performed in our patient.

The mechanism responsible for the effect of NOACs on LAA thrombi has not been fully elucidated, although it has been suggested that the resolutions of LA and LAA thrombi by apixaban are likely to be the result of shifting the coagulation/fibrinolysis balance toward the fibrinolytic activity (6). However, oral anticoagulants are known to make thrombi mobile and/or fragile, and thus to increase the risk of thromboembolism. This is the only case report available on this topic that concerns with the use of apixaban in patients with LAA thrombi and ESRD undergoing hemodialysis. Thus, we suggest randomized comparative studies be conducted on the effectiveness of warfarin and apixaban for the treatment of LA or LAA thrombi. In addition, if patients have a poor anticoagulation quality with warfarin, like it was in our case, a switch to NOACs should be considered (7).

## Conclusion

To the best of our knowledge, we report the first case of warfarin refractory LAA thrombus resolution by apixaban in a patient with ESRD undergoing hemodialysis. We suggest that apixaban be cautiously considered as an alternative anticoagulant therapy in patients with ESRD requiring hemodialysis and warfarin refractory LAA thrombi. More clinical evidence and randomized trials are required to determine comprehensively the dose, safety, and efficacy of apixaban in patients with ESRD undergoing hemodialysis with LAA thrombi.

**Informed consent:** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

**Video 1.** TEE revealed a mobile thrombus in the LAA.

**Video 2.** After a total four months of apixaban treatment, TEE revealed complete resolution of the LAA thrombus.
LAA - left atrial appendage; TEE - transesophageal echocardiography

## References

1. Van Der Meersch H, De Bacquer D, De Vriese AS. Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation: A systematic review and meta-analysis. Am Heart J 2017; 184: 37-46. [CrossRef]
2. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Zhang D, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol 2016; 56: 628-36. [CrossRef]
3. Chang M, Yu Z, Shenker A, Wang J, Pursley J, Byon W, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. J Clin Pharmacol 2016; 56: 637-45. [CrossRef]
4. Sarratt SC, Nesbit R, Moye R. Safety Outcomes of Apixaban Compared With Warfarin in Patients With End-Stage Renal Disease. Ann Pharmacother 2017; 51: 445-50. [CrossRef]
5. Kufel WD, Zayac AS, Lehmann DF, Miller CD. Clinical Application and Pharmacodynamic Monitoring of Apixaban in a Patient with End-Stage Renal Disease Requiring Chronic Hemodialysis. Pharmacotherapy 2016; 36: e166-71. [CrossRef]
6. Miwa Y, Minamishima T, Sato T, Sakata K, Yoshino H, Soejima K. Resolution of a warfarin and dabigatran-resistant left atrial appendage thrombus with apixaban. J Arrhythm 2016; 32: 233-5. [CrossRef]
7. Yanıkoğlu A, Altıntaş MS, Ekinözü İ. Dissolution of an apical thrombus by apixaban in a patient with old anteroseptal myocardial infarction. Anatol J Cardiol 2015; 15: 671-2. [CrossRef]

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