

# Atrial fibrillation and thrombophilia. DOAC as a valid alternative? A clinical case

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## SOUHRN

Perorální antikoagulace znamenala revoluci v léčbě fibrilace síní (FS). Ve složitých případech, včetně některých typů trombofilii jako postižení zvyšujících riziko tromboembolie, může být warfarin neúčinný. Ukázalo se, že přímá perorální antikoagulancia (direct oral anticoagulants, DOAC) jsou plně hodnotnou možností léčby; jako účinný a bezpečný se osvědčil zvláště edoxaban. Popisujeme případ muže s FS a trombofilii, u něhož došlo přes antikoagulační léčbu warfarinem k vytvoření trombu v oušku levé síně; následně byla zahájena léčba edoxabanem.

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## ABSTRACT

Oral anticoagulation is a milestone in the management of atrial fibrillation (AF). In complex settings, involving some kinds of thrombophilia, a condition predisposing to higher risk of thromboembolism, warfarin can be ineffective. Direct oral anticoagulants (DOACs) demonstrated to be a valid therapeutic option; in particular edoxaban proved to be effective and safe. We show the case of a man with AF and thrombophilia who developed a thrombus in the left atrial appendage (LAA) despite anticoagulant therapy with warfarin, subsequently treated with edoxaban.

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with greater prevalence in older people.<sup>1</sup> It is associated with increased risk of mortality and morbidity especially due to stroke; in fact 20–30% of all strokes are due to atrial fibrillation.<sup>1</sup> Oral anticoagulation is a milestone in the management of AF, reducing stroke and mortality in these patients.<sup>1</sup> However, management could be challenging in particular situations such as thrombophilia, a condition predisposing to a higher risk of thromboembolism,<sup>2</sup> sometimes leading to resistance to vitamin K antagonists (VKAs).<sup>3,4</sup> Direct oral anticoagulants (DOACs) can be a therapeutic option for stroke prevention in patients with non-valvular AF.<sup>1</sup> Among these, edoxaban, a factor-

-Xa inhibitor, has demonstrated to be non-inferior to warfarin in terms of efficacy and safety.<sup>2,5,6</sup>

We show the case of a man with AF and thrombophilia who developed a thrombus in the left atrial appendage (LAA) despite anticoagulant therapy with warfarin, subsequently treated with edoxaban.

## Case report

A 76-year-old man was admitted to our hospital because of a transient ischemic attack (TIA). In his clinical history he complained at 35 years of an episode of mild psoriasis in his elbows, successfully treated with topical therapy. At 50 years he had an episode of deep vein thrombosis treated with warfarin. In the same period a stress echo-

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cardiogram, performed because of atypical chest pain, was normal. From 15 years before he had a diagnosis of hypertension and atrial fibrillation (AF), leading to persistent treatment with warfarin.<sup>7-13</sup> He was assuming a beta-blocker (bisoprolol 2,5 mg od) and an ACE-inhibitor (enalapril 10 mg od). An electrocardiogram showed AF with a mean heart rate of 100 beats per minute (Fig. 1A). Blood tests revealed an international normalized ratio (INR) of 2,3. A transthoracic echocardiography showed a normal left ventricular volume and ejection fraction (LVEF) and a dilated left atrium (LA) with severe spontaneous echocontrastographic effect. A transesophageal echocardiogram (TEE) showed a partially mobile disorganized formation (10 × 13 mm) suggestive of thrombus in the left atrial appendage (LAA) (Fig. 2A), despite anticoagulant therapy.

The checked of blood tests of the past 6 months demonstrated a time in therapeutic range (TTR)<sup>14</sup> of 69% (Fig. 1B): this excluded a poor compliance to treatment and food or drug interactions with VKAs. Therapy with intravenous heparin was started and investigations for lupus anticoagulant, anti-cardiolipin antibodies, anti beta<sub>2</sub>-glycoprotein antibodies, C protein and factor V of Leiden. A diagnosis of heterozygous factor V of Leiden was made.<sup>15-23</sup> After 1 week of treatment, we performed another TEE, which showed persistence of the thrombotic mass in the LAA (Fig. 2B). Some days after his clinical conditions improved and he was discharged with the indication to replace warfarin with edoxaban 60 mg once daily.

At the 1-month follow-up he reported no clinically relevant bleeding and a TEE revealed the absence of the thrombus (Fig. 2C). At the next follow-up he continued to be in good clinical conditions: no thromboembolic nor bleeding were reported. We suggested LAA percutaneous occlusion because of the high risk of thromboembolism but he refused.

## Discussion

This case underlines the role of thrombophilia in increasing the risk for thromboembolism. In fact our patient, who had heterozygosity for factor V Leiden mutation (a genetic disorder characterized by a low response to activated protein C),<sup>20-23</sup> developed a thrombus in the LAA despite therapy with warfarin.

One may speculate that, in this patient, resistance to protein C could have promoted a paradoxical pro-coagulant effect of warfarin conversely to its therapeutic anticoagulant effect.<sup>3</sup> Warfarin, as a vitamin K antagonist (VKA), works indirectly on various coagulation factors and also on protein C, that has a significant role in coagulation cascade.<sup>24</sup> A TTR almost in the range allows to exclude other possible causes but some oscillations could explain, in a case of thrombophilia, occurrence of thrombotic phenomena.<sup>20-23</sup> The choice of intravenous heparin, even if was not successful, was considered appropriate because the patient developed a thrombus despite ther-

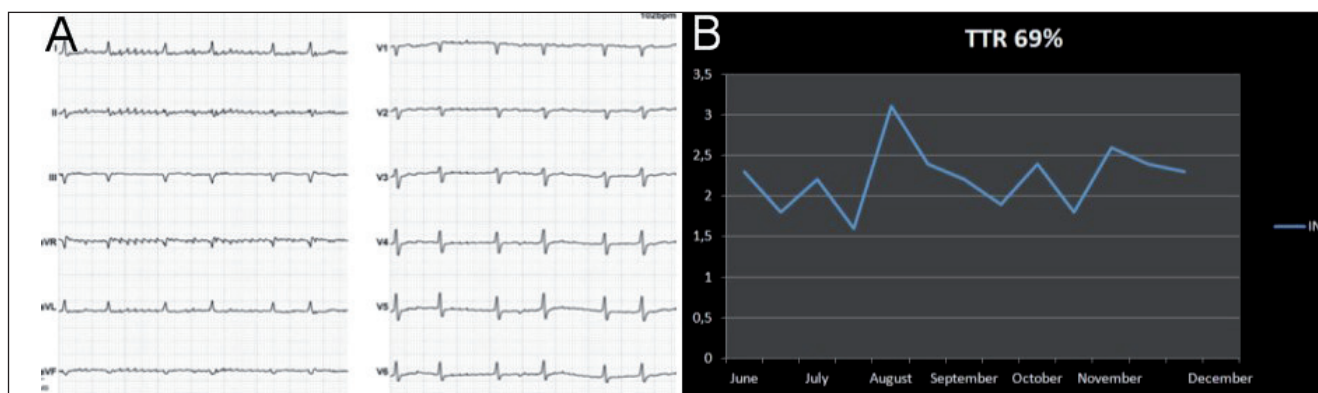


Fig. 1 – (A) Atrial fibrillation with a mean ventricular frequency 100 bpm. (B) Graphical representation of INR values in the last six months with time in therapeutic range (TTR) calculation.



Fig. 2 – (A) Transesophageal echocardiogram showing a partially disorganized mobile formation in the LAA. (B) Transesophageal echocardiogram showing permanence of the thrombotic mass in LAA after a week of heparin treatment. (C) Transesophageal echocardiogram repeated after one month revealed the thrombus disappearance after therapy with edoxaban.

apy with warfarin, needing for optimal anticoagulation control and because in literature there are several cases of low molecular weight heparin failure.<sup>15–18</sup>

DOAC are often preferred to other anticoagulants because they show rapid onset and offset of action, fewer drug interactions and dietary restriction; in addition, their predictable anticoagulant effects allow to administer fixed doses without requirement of routine coagulation monitoring.<sup>25,26</sup> These favourable characteristics, simplifying treatment, improve adherence to therapy.

We decided to switch the anticoagulant treatment from warfarin to intravenous heparin for one week and then, for long-term, to edoxaban, a DOAC introduced in 2015 and approved for the prevention of stroke and systemic thromboembolism in patients with non-valvular AF.<sup>26</sup> ENGAGE AF-TIMI 48 trial, a three-group, a randomized double blind trial, demonstrated in these patients non inferiority to warfarin of two dose regimens of edoxaban associated with a significant lower bleeding rate and lower death from cardiovascular causes.<sup>6</sup>

Little is known about the use of DOAC in thrombophilia. Some studies, such as Hokusai trial, compared warfarin with edoxaban and suggested no differences in the efficacy and safety of DOACs regardless of the type of thrombophilia.<sup>2</sup> In our case edoxaban proved to be effective not only for preventing thrombus formation but also for favouring thrombus resolution when therapy with warfarin failed. Moreover it resulted safe because of absence of haemorrhagic complications.

## Conclusions

In complex settings, involving some kinds of thrombophilia, warfarin can be ineffective. DOACs, and in particular edoxaban, demonstrated to be a safe and valid therapeutic option. Further investigations in subgroups of patients with AF and thrombophilia are needed to better understand the mechanisms that can cause the effectiveness of DOAC compared to VKA.

## Conflict of interest

None.

## Funding body

None.

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