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CASE REPORT
Electrophysiology

Minimizing drug-drug interactions between dabigatran and levetiracetam through clinical management: a case report

Danilo Menichelli [1], Daniele Pastori [1]*, Pasquale Pignatelli [1], and Arianna Pani [2]

[1]Department of Clinical, Internal, Anesthesiologic and Cardiovascular Sciences, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy; and [2]Department of Oncology and Hemato-oncology, Postgraduate School of Clinical Pharmacology, University of Milan, Via Festa del Perdono 720122 Milano, Italy

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Background Direct oral anticoagulants (DOACs) are useful for stroke prevention in atrial fibrillation (AF) patients. However, the concomitant administration of Levetiracetam limited their use in clinical practice, although some authors raise doubts about clinical relevance of the interaction.

Case summary We report a case of a 54-year-old male with AF, cirrhosis, and seizures, in which the assessment of Dabigatran plasma concentration was needed due to the concomitant use of Levetiracetam. In this case, no relevant reduction of trough Dabigatran plasma concentration was found. An increased peak serum level of dabigatran may be obtained delaying levetiracetam administration. The patient was then followed in our clinic and during 32 months of follow-up no ischaemic or haemorrhagic events occurred.

Discussion The evaluation of DOACs concentration could be helpful to start a tailored therapy in frailty patients.

Keywords Dabigatran • Levetiracetam • DOAC serum level • Drug interaction • Atrial fibrillation • Case report

ESC Curriculum 5.3 Atrial fibrillation • 8.5 Primary prevention

Learning points

- Drug-drug interactions (DDIs) should always be evaluated in patients with multimorbidities taking multiple drugs
- The use of laboratory monitoring of direct oral anticoagulants may be helpful to manage DDIs.
- A tailored therapy may enhance the compliance of patients and reduce adverse events

Background

The introduction of direct oral anticoagulants (DOACs) has simplified the management of antithrombotic therapy in atrial fibrillation (AF) patients, providing an effective and safer therapeutic option for patients on warfarin, especially those with low time in therapeutic range (TiTR).[1] However, there are still some subgroups of patients in whom the use of DOACs is not well established or contraindicated, such as those with liver cirrhosis Child-Pugh C, patients with end-stage renal disease, and morbid obese patients.[2] Furthermore, drug-drug interactions (DDIs) with medications interfering with the membrane permeability glycoprotein (p-gp) should be considered in DOAC-treated patients. In particular, in 2018, the European Heart Rhythm Association (EHRA) Practical Guide on the use of DOACs in patients with AF,[1] the authors advise against the concomitant use of dabigatran and levetiracetam, based on the supposed modulation of p-gp protein

* Corresponding author. Tel: +0649970893, Fax: +0649972309, Email: daniele.pastori@uniroma1.it
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by levetiracetam as substrate. However, some authors raised doubts on the clinical relevance of the DDI of levetiracetam with DOACs.[3] This indication was then changed in the most recent version of the EHRA Guide that now indicates that despite a DDI between Dabigatran and Levetiracetam is expected, these may be used with caution.[1] In addition, DDI should be put in the context of the benefit of an effective thromboprophylaxis strategy. Very few evidence regarding this topic do exist in the literature.

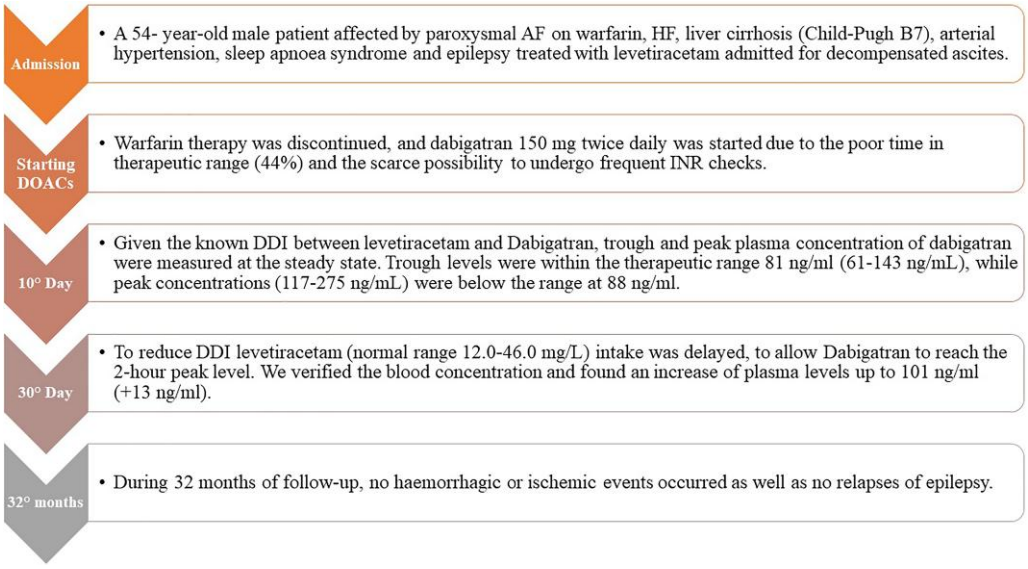
We hereby report a case of a patient taking dabigatran and levetiracetam in whom we managed the DDI through clinical management and blood drug concentration monitoring.[4]

Timeline

Case report

A 54-year-old man was admitted to our department due to the worsening of clinical conditions and onset of diffuse oedema and ascites. A diagnosis of liver cirrhosis was made (Child-Pugh B7. MELD Na^+ 9) during hospitalization. The patients had a history of paroxysmal AF, heart failure, metabolic syndrome (with severe obesity, BMI 41 Kg/m^2), previous pancreatic **cured** tail carcinoma (2013), hypothyroidism, arterial hypertension, sleep apnoea syndrome, and epilepsy. The CHA_2DS_2-VASC score was 2 (heart failure and hypertension) and the HAS BLED score was 2 (liver cirrhosis and labile INR).

The patient was on therapy with levothyroxine 175 mcg/day, pantoprazole 40 mg/day, bisoprolol 2.5 mg/day, spironolactone 300 mg/day, furosemide 25 mg/day, warfarin with an international normalized ratio (INR) target of 2.5, levetiracetam 500 mg/BID. Daily schedule of



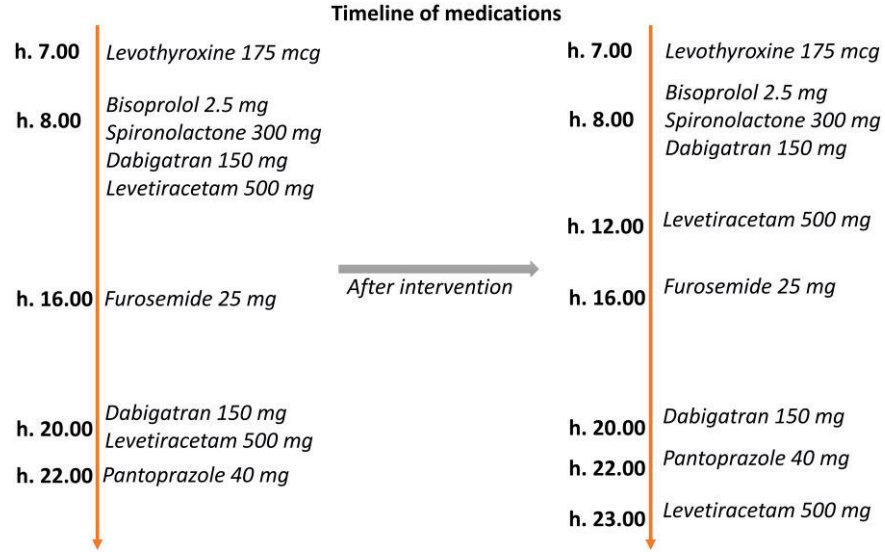


Figure 1 Medications' schedule of patient at admission.

Table 1 Patient's blood sample values at admission in our clinic

		Normal value
Biochemical		
Fasting plasma glucose	97	60–100 mg/dL
Total cholesterol	126	160–220 mg/dL
HDL Cholesterol	41	35–70 mg/dL
LDL cholesterol	70	< 130 mg/dL
Triglycerides	76	40–170 mg/dL
Iron	53	50–180 µg/dL
Ferritin	9	22–320 ng/mL
Creatinine	1,0	0.70–1.20 mg/dL
AST	16	9–45 U/L
ALT	19	10–40 U/L
GGT	73	8–61 U/L
Total bilirubin	1.0	0.30–1.20 mg/dL
Conjugate bilirubin	0.4	< 0.20 mg/dL
Uric acid	6.6	0.20–0.43 mmol/L
Albumin	4.7	3.5–5 g/dL
TSH	0.97	0.45–4.78 µUl/mL
FT_3	3.43	2.30–4.20 pg/mL
Autoimmunity		
ANA	Negative 1:80	Negative 1:80
AMA	Negative 1:40	Negative 1:40
anti-LKM antibodies	Negative 1:40	Negative 1:40
Total blood count cells and coagulation		
Haemoglobin	15.51	11.0–18.0 g/dL
Platelet count	363.000	150.000–450.000/µL
Total proteins	7.3	6,4–8,3 g/dL
INR	1.35	<1.20
Virology		
HBsAg	Negative	Negative
HBeAg	Negative	Negative
HBcAb	Negative	Negative
HBeAb	Negative	Negative
HCV-Ab	Negative	Negative

INR, international normalized ratio; aPTT, activated partial thromboplastin time; AST, aspartate amino-transferase; ALT, alanine amino-transferase; GGT, gamma-glutamyl-transferase; ANA, anti-nuclear antibody; AMA; anti-mitochondrium antibodies; LKM: liver-kidney microsome

medications at admission is shown in *Figure 1*. Blood values at admission are shown in *Table 1*.

After discharge, the patient was sent to our outpatient clinic for the management of antithrombotic therapy. Patient appeared obese, awake, alert, oriented, and hydrated. No acute distress. The external chest is normal in appearance without lifts, heaves, or thrills. Heart rate and rhythm are normal. No murmurs, gallops, or rubs are auscultated. S1 and S2 are heard and are of normal intensity. A clear improvement in ascites and oedema was observed. Due to the poor TiTR of the patient (44%) during warfarin therapy and the scarce possibility to undergo frequent INR checks, warfarin was discontinued, and dabigatran 150 mg twice daily was started. However, the concomitant use of Levetiracetam and a high BMI (41 Kg/m^2) are known to reduce plasma concentrations of all DOACs[1] (a summon of potential interaction among DOACs and antiepileptic drug is shown in *Table 2*)[1]: for these reasons, we decided to measure plasmatic concentrations of dabigatran by evaluating anti-IIa levels. Blood samples were collected at dabigatran peak concentration (2 h post-intake) and trough (immediately before next intake), after 10 days from the beginning of therapy. The trough plasma concentration of dabigatran was in the normal range provided by the lab (61–143 ng/mL),[4] while peak concentrations were below range (117–275 ng/mL)[4] (*Figure 2*). As patient was taking Dabigatran and Levetiracetam at the same time in the morning and in the evening, we asked the patient to delay Levetiracetam intake at 12 a.m. and 12 p.m., respectively, to allow Dabigatran to reach a higher peak level. Indeed, dabigatran peak concentration increased from 88 to 101 ng/mL (*Figure 2*).

During 32 months of follow-up, no haemorrhagic or ischaemic events occurred. He experienced an improvement of liver cirrhosis achieving a Child-Pugh A5 class and a substantial weight loss of about 40 kg through dietary restriction (BMI: 29 Kg/m^2). Furthermore, there were no new episodes of seizures, without modification of levetiracetam posology.

Discussion

Our case report shows that clinical management may help to reduce DDI without discontinuing DOAC treatment. The patient of this case report had two thromboembolic risk factors beyond sex, thus requiring long-term therapy with oral anticoagulants. According to the HAS-BLED score of 2 patient, he was classified at moderate risk of bleeding. However, a comprehensive clinical evaluation is always needed as these risk scores do not take into account other potential bleeding and thrombotic risk factors such as obesity, potential DDIs, and possible increased risk of falls in patients with epilepsy. In addition, some risk factors may increase both bleeding and thrombotic risk. For instance, aging, chronic kidney disease and liver cirrhosis may contribute to both these risks. Recent evidence however showed that liver cirrhosis may not increase *per se* bleeding risk, especially in the early stages, as INR prolongation does not reflect a true anticoagulation status of patients, as shown by the occurrence of thrombotic events in patients with elevated INR.[5] In addition, bleeding seems to be mainly related to the presence of oesophageal varices.[6] On the other side, in patients with AF liver fibrosis/cirrhosis is associated with an increased risk of cardiovascular and thrombotic events, including ischaemic stroke, venous thromboembolism and portal vein thrombosis.[7] In accordance with this evidence anticoagulant therapy in patients with liver cirrhosis is associated with a significant reduction of thrombotic complications without an increased bleeding risk.[8] Indeed, liver cirrhosis should not be considered a contraindication to anticoagulant therapy.

Current European guidelines allow the use of DOACs in patients with liver cirrhosis Child-Pugh Class A and B (apart from rivaroxaban, approved only in patients with Child-Pugh Class A).[1] Phase III clinical trials of DOACs excluded patients with advanced liver disease, but however, a recent meta-analysis of observational studies showed a potential benefit of DOAC compared with warfarin in patients with AF and advanced liver disease, also in patients with oesophageal varices.[9]

Among DOACs, we have chosen Dabigatran as it is activated by glucuronidation at liver site with no enzyme involvement and given its excretion at kidney level, making its metabolism marginally influenced by liver status.

More recently, a novel DOAC, the direct inhibitor of XIa factor, Asundexian, has been studied in a Phase 2 study.[10] However, no data were available about DDIs related to P-gp and there were no data about advanced liver disease. Indeed, patients with known significant liver disease, such as liver cirrhosis classified as Child-Pugh B or C were excluded from the phase II trial.

Table 2 **Most common interactions among antiepileptic drugs and direct oral anticoagulants (DOACs)**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban	Mechanism
			Pharmacokinetics		
P-glycoprotein			***All substrates***		
CYP3A4	***No***	***Yes***	***No***	***Yes***	
Drug interactions					
Carbamazepine	Contraindicated due to strong interaction	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	Contraindicated due to strong interaction	Strong CYP3A4/P-gp induction; CYP3A4 competition
Ethosuximide, Perampanel, Pregabalin, Lamotrigine, Gabapentin	No relevant interaction known/assumed				—
Phenytoin	Contraindicated due to strong interaction	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	Contraindicated due to strong interaction	Strong CYP3A4/P-gp induction; P-gp competition
Phenobarbital	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	Contraindicated due to strong interaction	Strong CYP3A4/ possible P-gp induction
Levetiracetam	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	Potential clinically relevant interaction expected, caution required	P-gp induction; P-gp competition
Topiramate	No relevant	Potential clinically relevant interaction expected, caution required	No relevant	Potential clinically relevant interaction expected, caution required	CYP3A4 induction; CYP3A4 competition
Valproic acid	Contraindicated due to DOACs plasma levels reduction				CYP3A4/P-gp induction/inhibition

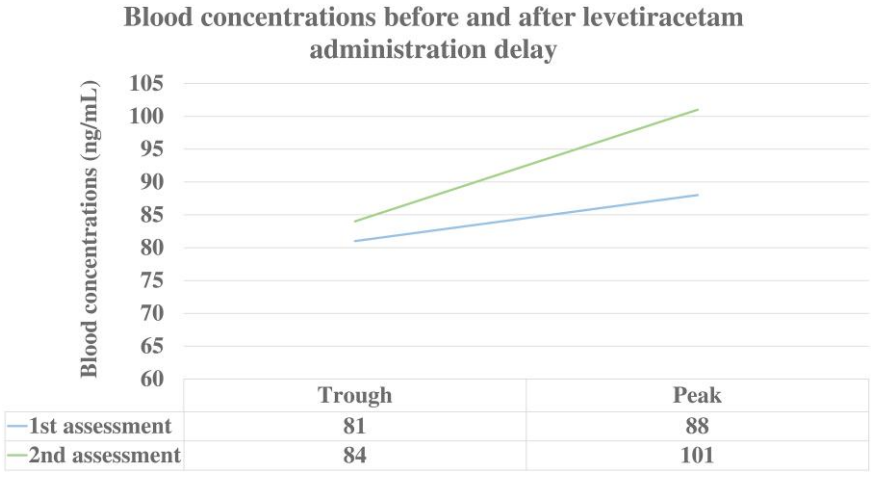


Figure 2 Dabigatran peak and trough concentrations before and after levetiracetam administration delay.

In addition to liver cirrhosis, our patient was on treatment with levetiracetam for the treatment of epilepsy. Recently, a prospective study including 91 AF patients evaluated the incidence of ischaemic stroke and major bleeding in patients taking both DOACs and antiepileptic drugs; the study showed an increased risk of ischaemic stroke in this cohort of patients.[11] Here, we present a case of concomitant use of dabigatran and levetiracetam and propose a plasma-level driven approach to patient management. Plasma levels of anti IIa activity may help clinician to check whether despite a known DDI, Dabigatran may reach effective peak and through levels. Thus, we found that in range therapeutic through plasma concentrations were achieved in our patient, which was reassuring given the association between through levels and ischaemic events.[12] Conversely peak levels, which are associated with bleeding,[13] were below the lower limit of therapeutic range. Since therapy with Levetiracetam was well tolerated and led to good seizure control, and Dabigatran was chosen based on the presence of comorbidities, we decided to continue both drugs.

Delaying the levetiracetam dose was a good option for this patient who was on the scheduled minimum dose of levetiracetam. Furthermore, recent studies on the ABC pathway[14] have shown that an inappropriate dose of DOACs (the 'A' component) resulted in suboptimal anticoagulant therapy and to an increased risk of cardiovascular events.

In our case, the laboratory measurement of plasma levels of Dabigatran helped us to verify the existence of DDI. Although the routine measurement of DOAC plasma levels is not recommended for all patients in clinical practice,[1] it may be useful in particular situations such as extreme bodyweights, potential and multiple expected/known DDI, severe kidney disfunction or, in the emergency setting, during acute stroke requiring thrombolysis or severe bleeding potentially candidate to reversal agents.[1] What it should be however underlined is that the majority of evidence regarding DDIs come from pre-clinical/pharmacological studies and for some of them, there is no firm evidence that this laboratory interaction directly translates into a clinically relevant interaction.[3] This is also due to multiple interactions that are frequently in patients taking many drugs at the same time.

Our results showed a minimal DDI between Levetiracetam and Dabigatran that may be reduced just delaying Levetiracetam administration compared with that of Dabigatran. However, this type of clinical management may be challenging for some fragile patients taking many drugs for whom it may be difficult to follow a rigorous schedule for drugs assumption, such as very elderly patients or those with dementia without social care/support.

Our case highlights some relevant aspects for patients' management. First, DDIs are very often under evaluated and misdiagnosed, being responsible for a significant proportion of hospitalizations related to side effects of drugs. Thus, DDIs may lead to an underrecognized under or over concentration of some medications affecting their therapeutic effect. Second, in anticoagulated patients, the dosage of DOACs should be tailored based not only on clinical and biochemical characteristics (e.g. body weight, renal function, age) but also considering DDI. Finally, despite DOACs do not require routine laboratory monitoring, assessment of plasma levels of DOACs may be useful in specific situations.

In conclusion, with our clinical case, we wish to emphasize that a personalized approach to anticoagulant therapy[15] may help reducing DDI in patients requiring specific drugs and who are unable to tolerate or have very low-quality warfarin therapy.

Lead author biography

Daniele Pastori is an Associate Professor at Sapienza University of Rome, specialist in internal medicine, PhD in Experimental And Clinical Hepato-Gastroenterology. Senior visiting research fellow at the Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Chest & Heart Hospital, Liverpool, UK. His research fields include atrial fibrillation, the use of direct oral anticoagulants and vitamin K antagonists, antiphospholipid syndrome, cardioncology, non-fatty liver alcoholic (NAFLD), and cardiac valvulopathies.

Supplementary material

Supplementary material is available at European Heart Journal—Case Reports

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: Written informed consent in accordance with COPE guidelines was obtained from the patient for publication of this case report and any accompanying images.

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References

1. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, *et al.* 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612–1676.
2. Menichelli D, Ettorre E, Pani A, Violi F, Pignatelli P, Pastori P, *et al.* Update and unmet needs on the use of nonvitamin K oral anticoagulants for stroke prevention in patients with atrial fibrillation. *Curr Probl Cardiol* 2021;**46**:100410.
3. Mathy FX, Dohin E, Bonfitto F, Pelgrims B. Drug-drug interaction between levetiracetam and non-vitamin K antagonist anticoagulants. *Eur Heart J* 2019;**40**:1571.
4. Tripodi A. The laboratory and the direct oral anticoagulants. *Blood* 2013;**121**:4032–4035.
5. Buresi M, Hull R, Coffin CS. Venous thromboembolism in cirrhosis: a review of the literature. *Can J Gastroenterol* 2012;**26**:905–908.
6. Rodriguez-Castro KI, Antonello A, Ferrarese A. Spontaneous bleeding or thrombosis in cirrhosis: what should be feared the most? *World J Hepatol* 2015;**7**:1818–1827.
7. Kuo L, Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, *et al.* Liver cirrhosis in patients with atrial fibrillation: would oral anticoagulation have a net clinical benefit for stroke prevention? *J Am Heart Assoc* 2017;**6**.
8. Loffredo L, Pastori D, Farcomeni A, *et al.* Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. *Gastroenterology* 2017;**153**:480–487 e481.
9. Menichelli D, Ronca V, Di Rocco A, Pignatelli P, Podda GM, CAR, *et al.* Direct oral anticoagulants and advanced liver disease: a systematic review and meta-analysis. *Eur J Clin Invest* 2021;**51**:e13397.

10. Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, *et al.* Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet* 2022;**399**:1383–1390.
11. Giustozzi M, Mazzetti M, Paciaroni M, Agnelli G, Becattini C, Vedovati MC, *et al.* Concomitant use of direct oral anticoagulants and antiepileptic drugs: a prospective cohort study in patients with atrial fibrillation. *Clin Drug Investig* 2021;**41**:43–51.
12. Testa S, Paoletti O, Legnani C, Dellanoce C, Antonucci E, Cosmi B, *et al.* Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost* 2018;**16**:842–848.
13. Reilly PA, Lehr T, Haertter S, Connolly SL, Yusuf S, Eikelboom JW, *et al.* The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 2014;**63**:321–328.
14. Pastori D, Menichelli D, Violi F, Pignatelli P, Lip GYH. ATHERO-AF The atrial fibrillation better care (ABC) pathway and cardiac complications in atrial fibrillation: a potential sex-based difference. The ATHERO-AF study. *Eur J Intern Med* 2021;**85**:80–85.
15. Pastori D, Menichelli D, Gingis R, Pignatelli P, Violi F. Tailored practical management of patients with atrial fibrillation: a risk factor-based approach. *Front Cardiovasc Med* 2019; **6**:17.