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The Dilemma of Edoxaban Interruption and Heparin Bridging Before Upgrading to Cardiac Resynchronization Therapy in an Older Patient with Atrial Fibrillation, Chronic Kidney Disease, and a Mitral Bioprosthesis

Atriyal Fibrilasyon, Kronik Böbrek Hastalığı ve Mitral Biyoprotezli Yaşlı Bir Hastada Kardiyak Resenkronizasyon Terapisine Yükseltme İşleminden Önce Edoksaban Kesintisi ve Heparinle Köprüleme İkilemi

ABSTRACT

The peri-procedural management of novel oral anticoagulants (NOAC) should be individualized based on patient-specific factors (age, body weight, renal function, concomitant medications, history of thromboembolic or bleeding events, and the presence of prosthetic valve) as well as procedural characteristics (bleeding risk). Less invasive procedures carry a relatively low bleeding risk and may be performed with minimal or no interruption of NOAC therapy. However, upgrading from an implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy (CRT) is more complex than initial implantation. Therefore, the timing of the last NOAC dose before an elective procedure requires careful judgment, balancing individual risks and benefits. Herein, we present the case of an elderly patient with atrial fibrillation, grade IIIb chronic renal disease, low body weight, and a bioprosthetic mitral valve, who underwent an upgrade from an implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy with a defibrillator (CRT-D). The patient developed bioprosthetic valve thrombosis 24 hours after edoxaban interruption without heparin bridging, which was successfully treated with ultraslow tissue plasminogen activator (tPA) therapy.

Keywords: Edoxaban, interruption, novel oral anticoagulant, thrombosis

ÖZET

Yeni oral antikoagülanların (NOAK) girişimsel işlemlerden önce yönetimi, hastaya (yaş, vücut ağırlığı, böbrek fonksiyonu, ilaçlar, önceki tromboembolik/kanama olayı, protez kapak varlığı) ve işlemin (kanama riski) özelliklerine göre kişiselleştirilmelidir. Daha az girişimsel işlemler nispeten düşük kanama riski taşır ve minimal veya kesintisiz NOAK tedavisi altında gerçekleştirilebilir. Ancak, implante edilebilir defibrilatörden (ICD) kardiyak resenkronizasyon tedavisine (KRT) yükseltme, ilk implantasyon işleminden daha karmaşıktır. Bu nedenle, elektif bir prosedürden önce son NOAK alımının zamanlaması, bireysel fayda/risk oranına dayalı karar vermeyi gerektirir. Burada, atriyal fibrilasyon, evre 3b kronik böbrek hastalığı, düşük vücut ağırlığı ve biyoprotez mitral kapağı olan ve ICD'den KRT-D'ye yükseltme işlemi sürecinde, heparin köprülemesi olmadan edoksaban tedavisinin kesilmesinden 24 saat sonra biyoprotez kapak trombozu yaşayan ve ultra yavaş tPA tedavisiyle başarılı bir şekilde tedavi edilen yaşlı bir hastanın yönetimini sunduk.

Anahtar Kelimeler: Edoksaban, ara verme, yeni oral antikoagülan, tromboz

Physicians must carefully balance the risk of thromboembolic events and bleeding during the peri-procedural management of novel oral anticoagulants (NOACs). Many low bleeding-risk procedures can be performed with minimal or no interruption of NOAC therapy. However, both patient-specific factors (such as age, body weight, renal function, concomitant medications, history of thromboembolic or bleeding events, and the presence of a prosthetic valve) and procedural characteristics

CASE REPORT
OLGU SUNUMU

Mert Doğan

Uğur Canpolat

Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Corresponding author:
Uğur Canpolat
✉ dru_canpolat@yahoo.com

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(particularly bleeding risk) must be taken into account when deciding on the discontinuation and resumption of a NOAC. Although earlier guidelines have provided standard NOAC interruption intervals, these recommendations should be individualized based on a careful assessment of the patient's risk-benefit profile.[1] Pre-procedural heparin bridging is generally not recommended in patients receiving NOACs, as it is associated with an increased risk of bleeding.[2,3] In this case report, we present the peri-procedural management of an elderly patient with atrial fibrillation (AF), grade 3b chronic renal disease, low body weight, heart failure with reduced ejection fraction (HFrEF), and a bioprosthetic mitral valve, who underwent an upgrade from an implantable cardioverter-defibrillator (ICD) to cardiac resynchronization therapy (CRT). The patient developed bioprosthetic valve thrombosis 24 hours after edoxaban interruption without heparin bridging, which was successfully treated with ultraslow tissue plasminogen activator (tPA) therapy.

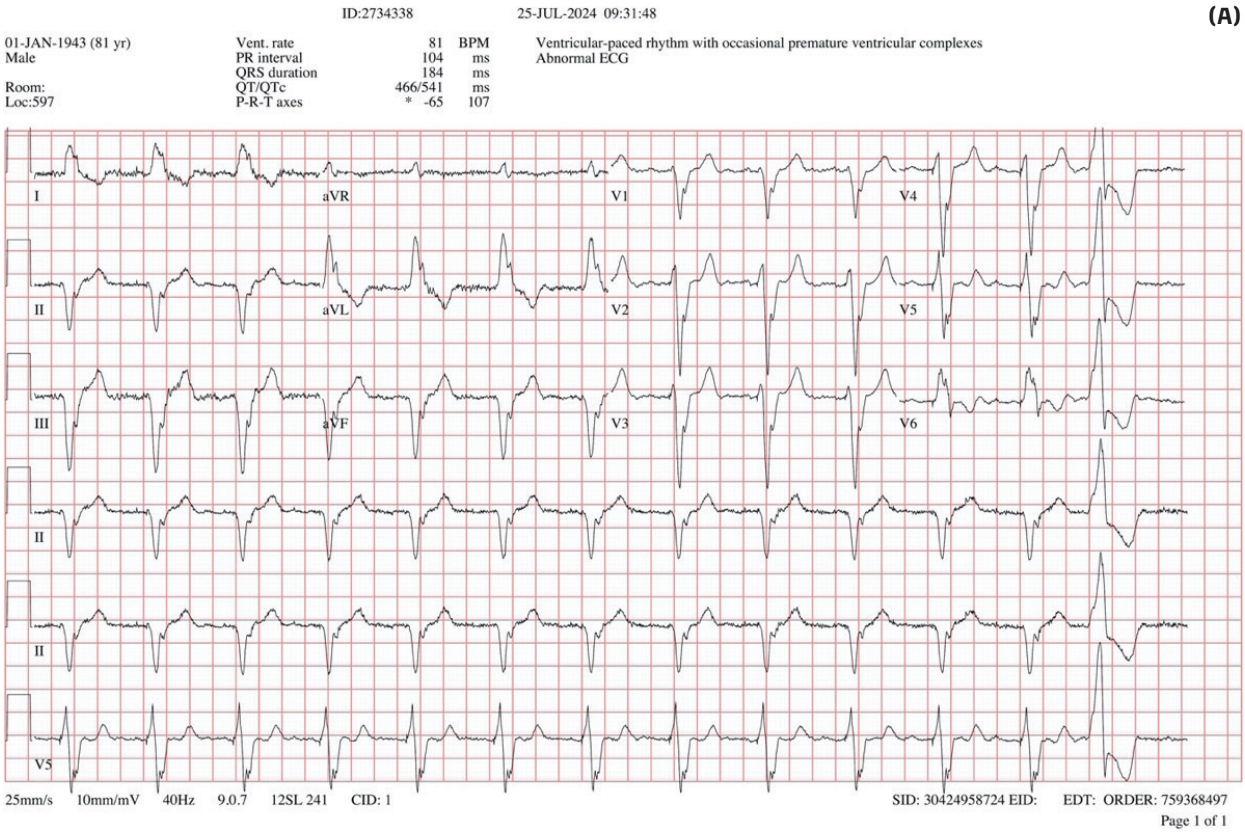
ABBREVIATIONS

BNP	Brain natriuretic peptide
CIED	Cardiovascular implantable electronic device
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with a defibrillator
ECG	Electrocardiogram
ICD	Implantable cardioverter-defibrillator
LAA	Left atrial appendage
LVEF	Left ventricular ejection fraction
NOAC	Novel oral anticoagulants
SEC	Spontaneous echo contrast
TEE	Transesophageal echocardiography
tPA	Tissue plasminogen activator
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
Vp	Ventricular pacing

Case Report

An 81-year-old male patient presented to our clinic with complaints of exertional dyspnea, classified as New York Heart Association class II. His medical history included AF, with a CHA2DS2-VASc score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke/transient ischemic attack) of 4 and a HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol) of 3, chronic kidney disease, a diagnosis of non-ischemic dilated cardiomyopathy ten years earlier, and implantation of a dual-chamber ICD. Ten months prior, the patient had undergone mitral valve replacement with a bioprosthesis (Hancock II Bioprosthesis, size 27, Medtronic, USA) and tricuspid Kay annuloplasty. On physical examination, his body weight was 57 kg. Bilateral rales were heard at the lung bases, and +2 pitting edema was observed in the pretibial region bilaterally. A 12-lead electrocardiogram (ECG) revealed a ventricular paced (Vp) rhythm at 81 beats per minute. The patient remained in AF, with a paced QRS duration of 184 msec (Figure 1A). Device interrogation of the ICD showed a ventricular pacing (Vp) burden of 92.6%. Laboratory findings included a hemoglobin level of 15.0 gr/dL, serum creatinine of 1.58 mg/dL (corresponding to an estimated glomerular filtration rate [eGFR] of 40 mL/min), and a brain natriuretic peptide (BNP) level of 743.52 pg/mL. Transthoracic echocardiography (TTE) revealed a left ventricular (LV) end-diastolic diameter of 56 mm, a left ventricular ejection fraction (LVEF) of 21%, and a left atrial diameter of 45 mm. The bioprosthetic mitral valve was functioning with a mean transvalvular gradient of 3 mmHg. The repaired tricuspid valve showed moderate tricuspid regurgitation, and systolic pulmonary artery pressure was estimated at 45 mmHg. One year earlier, the patient's LVEF had been 38%, with a Vp burden of 31.2%. Given the current findings, right ventricular pacing-induced cardiomyopathy was suspected. Therefore, an upgrade from ICD to CRT-D was planned. The patient had been on edoxaban 30 mg/day as oral anticoagulation therapy. Due to advanced age, impaired renal function, low body weight, and the anticipated complexity of the procedure, edoxaban was interrupted for 48 hours without bridging with heparin prior to the CRT-D upgrade. Upon hospitalization the day before the procedure, 24 hours after edoxaban interruption, a follow-up TTE was performed. There was a three-day interval between the two echocardiographic assessments. A 13 × 16 mm hyperechogenic mobile mass, moving toward the left atrium and ventricle, was detected on the posterior leaflet of the mitral bioprosthetic valve (Figure 2A-C, Video 1). This mass had not been present prior to the interruption of edoxaban therapy. An increase in the mean transvalvular gradient to 8 mmHg was also observed. Transesophageal echocardiography (TEE) confirmed the presence of the hyperechogenic mobile mass attached to the mitral bioprosthetic valve.

Additionally, a fresh thrombus in the form of sludge was observed in the left atrial appendage, along with grade III spontaneous echo contrast (SEC) in the left atrium (Video 2). The patient had no fever or signs of systemic infection. Acute-phase reactant levels were within normal limits, and blood cultures were negative. Given the rapid appearance of the mass and other findings suggestive of blood stasis on TEE, a diagnosis of mitral bioprosthetic valve thrombosis was considered. Although the patient experienced no clinical thromboembolic events or further deterioration after hospitalization, and despite current guideline recommendations favoring anticoagulation with a vitamin K antagonist (VKA) or unfractionated heparin (UFH) prior to re-intervention, we opted for thrombolytic therapy to minimize the time to treatment of bioprosthetic valve thrombosis. The patient's clinical status (critically ill due to decompensated heart failure), the size of the thrombus (>10 mm), the high surgical risk associated with advanced heart failure, and the increased mean transvalvular gradient were the primary factors influencing the decision to initiate thrombolytic therapy at the first-line option. Tissue plasminogen activator was administered via an ultraslow protocol (25 mg of tPA infusion over 25 hours). On follow-up TTE after the first tPA infusion, the mass on the mitral bioprosthesis valve had completely resolved, and the mean mitral transvalvular gradient had decreased to 4 mmHg (Figure 2D, Video 3). The sludge and fresh thrombus in the left atrial appendage (LAA) also disappeared after the tPA infusion, as confirmed by follow-up TEE. The CRT implantation procedure was performed six hours after completion of thrombolytic treatment. UFH



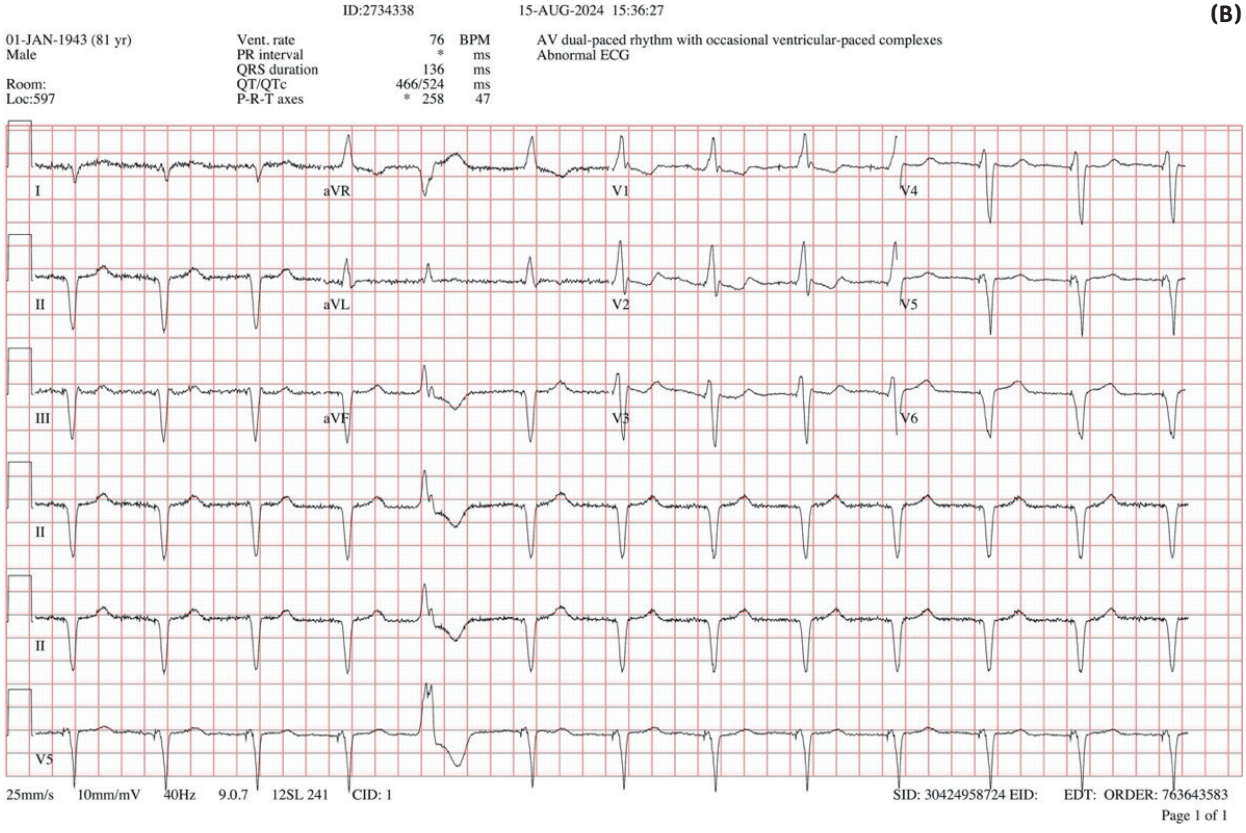


Figure 1. (A) On admission, a 12-lead electrocardiogram (ECG) revealed a right ventricular paced (Vp) rhythm at 81 beats per minute. The patient remained in AF, with a paced QRS duration of 184 msec. (B) The biventricular paced QRS duration on the postprocedural ECG was 136 milliseconds.

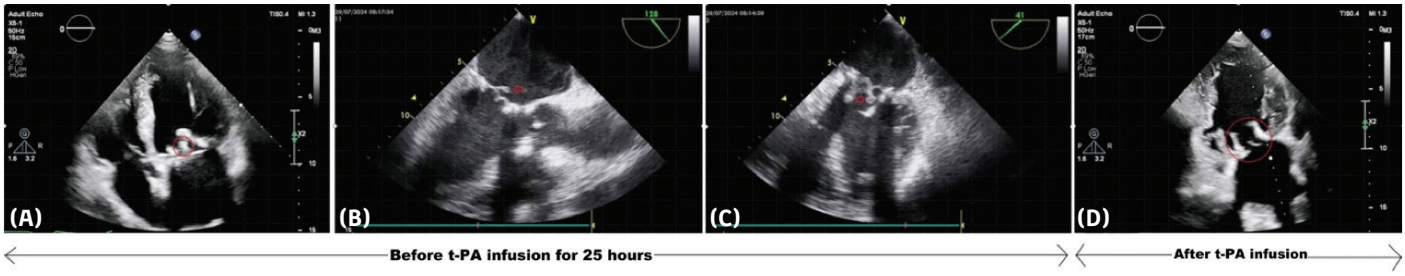


Figure 2. Transthoracic echocardiography (A) and transesophageal echocardiography (B–C) showed a hyperechogenic, mobile mass on the posterior leaflet of the bioprosthetic mitral valve 24 hours after edoxaban interruption. The mass disappeared following ultraslow tissue plasminogen activator (tPA) therapy (D).

bridging was used during this interval and was discontinued two hours before the procedure. The patient was then taken to the catheterization laboratory for the CRT-D upgrade. After a single axillary vein puncture, the coronary sinus was cannulated using a delivery sheath (Selectra Catheter Extended Hook-45 Lead Delivery System, Biotronik), and a coronary sinus electrode (Sentus ProMRI OTW QP S-xx/49, Biotronik) was positioned in the posterolateral branch of the coronary sinus. The CRT-D generator (Inlexa 3 HF-T, Biotronik) was successfully implanted. Electrical cardioversion was performed, and sinus rhythm was achieved following the procedure. The paced QRS duration on the postprocedural ECG was 136 milliseconds (Figure 1B). Edoxaban 30 mg was reinitiated six hours after the CRT-D upgrade procedure. The remainder of the hospital stay was uneventful. The patient was discharged on edoxaban 30 mg orally once daily, acetylsalicylic acid 100 mg orally once daily, amiodarone 200 mg orally once daily, along with optimized heart failure therapy.

Discussion

Balancing the risks of bleeding versus thromboembolic events during cardiovascular implantable electronic device (CIED) implantation in patients receiving NOACs is challenging. Patient-specific factors, such as age, body weight, renal function, concomitant medications, prior thromboembolic events, and the presence of a prosthetic valve, as well as procedural bleeding risk, are critical in the decision-making process.[1] The optimal management of NOACs during CIED implantation is uncertain. Current evidence suggests that an uninterrupted or minimally interrupted NOAC strategy, without heparin bridging, may be appropriate for NOAC-treated patients undergoing non-major surgeries such as CIED implantation.[4-7] While initial CIED implantation procedures (e.g., pacemaker or ICD) are considered low risk for bleeding, procedures involving an upgrade from ICD to CRT-D may be more complex. Due to the patient's advanced age, low body weight, grade IIIb chronic renal disease, and the anticipated complexity of the procedure, we elected to interrupt edoxaban 48 hours prior to the procedure without heparin bridging. However, a bioprosthetic valve thrombosis was detected on TTE 24 hours after edoxaban interruption. In the Global EMIT-AF/VTE (Edoxaban Management in Therapeutic Pathways for Patients With Atrial Fibrillation or Venous Thromboembolism) study, Santamaria et al.[8] identified predictors of edoxaban interruption, the use of heparin bridging strategies, and associated adverse clinical outcomes. Heparin bridging was used in approximately 15% of patients whose edoxaban therapy was interrupted. The study results showed that a HAS-BLED score greater than 3 and high European Heart Rhythm Association (EHRA) procedural risk predicted both edoxaban interruption and the use of a heparin bridging strategy. In contrast, the CHA2DS2-VASc score was not a significant predictor. Peri-procedural heparin bridging in this study was associated with a two-fold increase in bleeding risk without a corresponding reduction in thromboembolic events. Therefore, Santamaria and colleagues[8] concluded that patient and procedural bleeding risks influence clinicians' decisions regarding heparin bridging more than stroke risk. Due to the elevated patient- and procedure-related bleeding risks in our case, we opted to interrupt edoxaban therapy for 48 hours without heparin bridging before the procedure. However, a bioprosthetic valve thrombosis developed within a short time interval. Although the incidence of prosthetic valve thrombosis is approximately 0.4%, it is a significant, though rare, cause of morbidity and mortality.[9] Atrial fibrillation, SEC, HFrEF, and left atrial enlargement have all been identified as risk factors for thrombus formation in mitral valve prostheses, and our patient exhibited all of these risk factors.[10] Therefore, interruption of NOAC therapy with heparin bridging may be considered, particularly in patients with similar thromboembolic risk profiles. The effectiveness and safety of ultraslow thrombolytic therapy have been demonstrated in cases of prosthetic valve thrombosis.[11] In our patient, the prosthetic mitral valve thrombus was also successfully treated with an ultraslow infusion of 25 mg of tPA, without any complications. Video 2 further confirms the presence of spontaneous echo contrast, sludge, and fresh thrombus in the left atrial appendage. The presence of left atrial appendage thrombus in patients with prosthetic valve thrombosis favors surgical intervention over thrombolytic therapy.[12] While thrombolysis may be effective in patients with mitral prosthesis thrombosis,[11] only a limited number of cases have been reported,[13,14] and data regarding associated bleeding or embolic risks are scarce. Fresh and poorly organized thrombi, such as those observed in our patient, are more likely to dissolve effectively with thrombolytic therapy. In contrast, the efficacy of thrombolysis in cases involving organized or partially organized thrombi is unknown.

Although heparin bridging therapy is not routinely recommended in current practice when NOACs are interrupted, it may be considered in selected cases, such as ours, to balance the risks of thromboembolic events and bleeding.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The patient was provided with detailed information regarding the potential contribution of the case report to the medical literature. Written and verbal consent for publication was obtained from the patient.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Video 1. Transthoracic echocardiography 24 hours after edoxaban interruption revealed a hyperechogenic, mobile mass.

Video 2. Transesophageal echocardiography confirmed the presence of a hyperechogenic, mobile mass attached to the mitral bioprosthetic valve. Additionally, a fresh thrombus in the form of sludge was observed in the left atrial appendage, along with grade III spontaneous echo contrast in the left atrium.

Video 3. Transthoracic echocardiography performed immediately after ultraslow tissue plasminogen activator (tPA) therapy demonstrated complete resolution of the hyperechogenic, mobile mass on the mitral bioprosthetic valve.

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