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Case Report



# Hemoptysis in Quadriplegia with Atrial Fibrillation Who Was Taking Edoxaban: a Case Report

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## HIGHLIGHTS

- The direct oral anticoagulant may induce major bleeding.
- For anticoagulation, the restarting point of anticoagulation remained unclear.
- We present a case with severe anemia and massive hemoptysis after taking direct-acting oral anticoagulants (DOACs).
- The optimal regimen and time for restarting anticoagulation were discussed.

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**Conflict of Interest**
The authors have no potential conflicts of interest to disclose.

## ABSTRACT

The direct-acting oral anticoagulants (DOACs) would be the standard treatment for the prevention of stroke and thromboembolism in nonvalvular atrial fibrillation patients. The adverse effects of greatest concern are bleeding especially major bleeding. We present a case of a patient with a history of nonvalvular atrial fibrillation and pacemaker, who developed severe anemia after massive hemoptysis while taking DOAC; however, he has continued taking DOAC. Through this case, we have summarized the current management of major bleeding associated with anticoagulation and discuss the optimal regimen for restarting of anticoagulation therapy.

**Keywords:** Direct-acting Oral Anticoagulants; Atrial Fibrillation; Hemoptysis; Quadriplegia

## INTRODUCTION

Nowadays, the direct-acting oral anticoagulants (DOACs, non-vitamin K-dependent oral anticoagulant) as direct thrombin inhibitor (dabigatran) and Factor Xa inhibitor (rivaroxaban, apixaban, edoxaban) would be the standard treatment for prevention of stroke and thromboembolism in nonvalvular atrial fibrillation patients or other primary diseases [1,2].

According to a recent 1 year follow up study of 1,807 patients with nonvalvular atrial fibrillation taking DOAC, major bleeding (involves major organs, drops hemoglobin level more than 2 g/dL, requires massive transfusion or another fatal bleeding) occurred in 34 patients (1.9%), and among them, only 2 cases are pulmonary origin bleeding [3]. In the real-world, a research demonstrated a major bleeding occurred in 25 patients (3.1%) among the total of 799 patients with DOAC [4]. The annualized rate of major bleeding is approximately 2.75% for patients with daily 60mg of edoxaban and 1.61% with 30mg of edoxaban [5].

We present a case of a patient with a history of nonvalvular atrial fibrillation, subarachnoid hemorrhage (SAH), and pacemaker, who developed severe anemia after massive hemoptysis while taking DOAC, however, he has continued taking DOAC.

## CASE REPORT

A 77-year-old man with severe cognitive dysfunction and quadriplegia due to SAH was referred to the emergency center with hemoptysis and abruptly decreased serum hemoglobin level. He had taken an in-patient rehabilitation program at a local rehabilitation center for 3 months after SAH onset, and the baseline score of cognitive function was 8 out of 30 in Korean version of the Mini-Mental State Examination (K-MMSE). He was not able to sit up independently with poor truncal control, and he was total dependent in activity of daily living with scored 0 out of 100 in Korean Version of Modified Barthel Index (K-MBI). And he was prescribed edoxaban (60 mg, once daily) for nonvalvular atrial fibrillation and had a cardiac pacemaker implanted 10 years ago.

On routine examination at the local rehabilitation center, he developed abrupt anemia, with a decrease in his hemoglobin level from 12 to 7.5 g/dL. After arriving at our emergency center, his heart rate was elevated to 132 bpm, and the hemoglobin level was 5.5 g/dL. A chest posterior-anterior X-ray revealed widespread air space opacification in both lungs (Fig. 1), and a subsequent chest computed tomography scan revealed spontaneous massive hemorrhage (Fig. 2), which was attributed to anticoagulant use triggered by pneumonia. Other causes of pulmonary hemorrhage, such as pulmonary tuberculosis, bronchiectasis or endobronchial cancer, were ruled out with bronchoscopy showing no endobronchial lesion with no pathogenic microorganism in washing fluid. Also, on his laboratory findings, there is not enough evidence of coagulopathy or decreased renal function.

Edoxaban therapy was therefore stopped. Acute management for major bleeding was done including hydration, transfusion and tranexamic acid IV injection. Fortunately, his vital sign stabilized without surgical or interventional procedure such as bronchial artery embolization. He was at high risk for thrombosis and needed to resume the anticoagulate treatment when vital signs stabilized, but he was also at high risk for re-bleeding. Thus, the anticoagulation therapy was discontinued for just 3 days and restarted with the half dose for 5 days. After then, he has taken the standard dose of edoxaban despite recent massive hemoptysis. He resumed rehabilitation in 7 days with stable vital signs, and no additional bleeding occurred during the 3 months before discharge and during the 3 months of the outpatient visit after discharge.

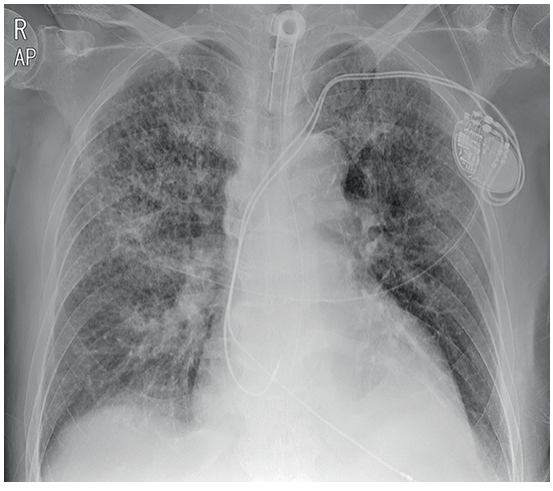


**Fig. 1.** Widespread air space opacification in both lungs caused by spontaneous hemorrhage.


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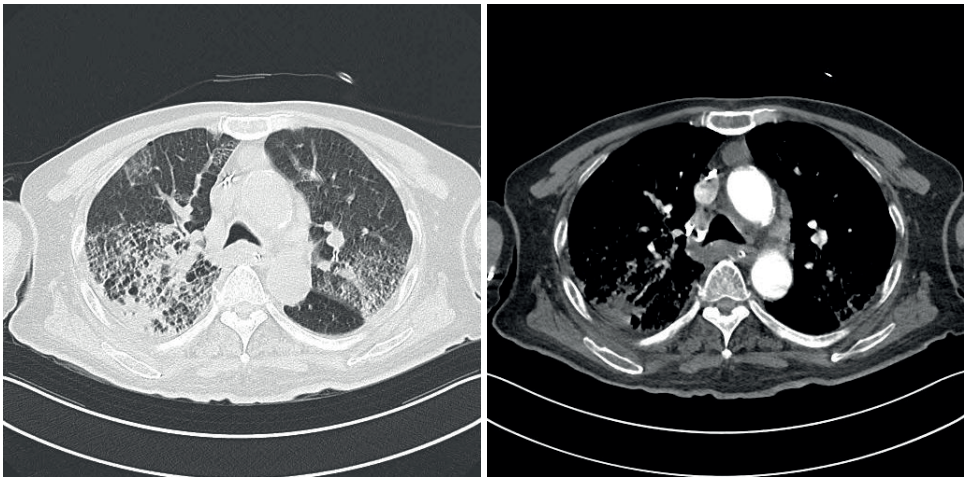

**Fig. 2.** Multifocal patchy ground glass opacity and some consolidation in right lung and left upper lobe. Considered as hemorrhagic aspiration, combined aspiration pneumonia.

## DISCUSSION

The post-major bleeding anticoagulant therapy regimen of patient with atrial fibrillation should be individualized on the basis of the patient's medical condition, especially benefits of prevention of thromboembolic event and risks of bleeding. According to the 2019 American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACC/HRS) guidelines for patients with AF, male patients with elevated CHA2DS2-VASc score of 2 or greater and female patients with 3 or greater, an oral anticoagulant is recommended [6]. In this case, the patients CHA2DS2-VASc score was 6, and without anticoagulation the ischemic stroke risk was 9.7% per year [7]. Therefore anticoagulation therapy is highly recommended. However, anticoagulation therapy should be administrated based on an assessment of the risk of bleeding. The HAS-BLED scoring system is widely used when assessing bleeding risk. In the patient previously reported, the HAS-BLED score was 4, indicating high bleeding risk; 8.7 bleeds per 100 patient per years [8]. The European Society of Cardiology (ESC) guidelines recommend that in those with a HAS-BLED score of ≥ 3, 'caution and/or regular review' in needed to minimize the risk of complication and to correct common bleeding risk factors.

Determining the risk and benefits of anticoagulation therapy is very difficult because it is impossible with simple numerical comparisons and must be determined according to the patient's individual medical condition. The CHA2DS2-VASc score has been recognized for its predictive power in several large-scale studies, and guidelines published by AHA/ACC/HRS and ESC recommend starting anticoagulant treatment based on this score. On the other hand, Several scoring systems, such as HEMORR2HAGES or ATRIA scoring system and most widely used HAS-BLED score, have been developed and used to assess the risk of bleeding, but they are all used as simple reference indicators due to their limited predictive accuracy [9]. Moreover, since these bleeding indicators share many parameters with CHA2DS2-VASc, the bleeding risk is also predicted to be high in patients with high risk of thromboembolism.

The post bleeding management of patient with atrial fibrillation includes making the decision of whether resume the anticoagulation or not, when to restart or what regimen should be administrated. All patient requires a thorough reassessment of risks and benefits


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of resuming anticoagulation. Underlying pathologic conditions such as cerebral amyloid angiopathy also must be ruled out before anticoagulation therapy.

Unfortunately, there is no consensus for post-major bleeding anticoagulation therapy. According to several systematic reviews and meta-analyses, resuming anticoagulation after intracranial hemorrhage can effectively lower the risk of thromboembolism, and there is no evidence of increased risk of intracranial hemorrhage recurrence [10-12]. And a recent retrograde cohort study reports that either warfarin or DOAC resumption after major gastrointestinal bleeding was associated with a decreased risk of thromboembolism, whereas warfarin and rivaroxaban resumption was associated with an increased risk of recurrent gastrointestinal bleeding [13]. Another meta-analysis of restarting of anticoagulation in patients with atrial fibrillation after major bleeding, published in 2020 and including 7 retrospective cohort studies enrolling total 12,197 patients, showed that restarting anticoagulation reduced risks of thromboembolism and mortality without increasing reoccurrence of bleeding [14]. Taken together with the previous studies, it seems the benefit of restarting anticoagulation after major bleeding exceeds the risk of massive re-bleeding or other fatal complications.

The optimal discontinuation period before resuming anticoagulant therapy after anticoagulation-associated major bleeding is also not clear [15]. In a recent meta-analysis study about restarting of oral anticoagulants after major bleeding in AF patients, the optimal timing for restarting cannot be analyzed because of the wide variation of restart timing among the included studies [14]. In a systematic review study conducted by Hawryluk et al. [16], it was concluded that restarting anticoagulation 72 hours after ICH is a cut-off timing that separates the risks and benefits of ICH recurrence and thromboembolic complications. On the other hand, in a retrospective cohort study, there was an increased reoccurrence of gastrointestinal bleeding when the resumption of anticoagulation therapy in less than 7 days [17].

The optimal dose of edoxaban should be taken into consideration when restarting anticoagulation. The therapeutic dose of edoxaban is 60 mg or 30 mg once daily. Both regimens were non-inferior to warfarin [5,18]. The annualized rate of systemic embolism and stroke was 1.2% and 1.6%, respectively, with 60 mg and 30 mg of edoxaban, whereas 1.5% with warfarin. And the rate of major bleeding was 2.8% with 60 mg of edoxaban and 1.6% with 30 mg of edoxaban, whereas 3.4% with warfarin [6]. There was a significant difference between the 2 regimens in the rate of stroke, systemic embolic event, and bleeding. Patient with 30 mg of edoxaban has less bleeding event, but more stroke or systemic embolic event than with 60 mg of edoxaban [5]. Currently, The FDA approved only 60 mg once daily regimen and the standard dose according to ESC guideline is also 60 mg once daily [15]. However, there are limited clinical trials of which regimen is preferable to a patient recovering from major bleeding.

Therefore, the physician's decision with which regimen anticoagulation should be restarted is required in the context of the clinical setting. In this case, the patient's vital sign and medical condition had getting stabilized without sign of additional bleeding in a short clinical course. Also, there is no lesions with high bleeding risk were found on bronchoscopy or cerebral angiogram, so the additional bleeding potency is not expected to be significant, although he had previous bleeding history; SAH and pulmonary hemorrhage. On the other hand, we determined the actual thromboembolic complication risk is significantly higher than the risk assessed according to CHA2DS2-VASc, based on the clinical situation that the patient had a


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cardiac pacemaker, that he had been on anticoagulation for a long time, and that his mobility was severely impaired. Immobility can easily cause deep vein thrombosis and pulmonary thromboembolism. Based on the clinical considerations described earlier, we judged that the benefits of resuming anticoagulation treatment on the patient outweigh the risks.

However, since his risk of bleeding is also high, resuming anticoagulation with standard dose of 60 mg edoxaban once daily from the beginning requires careful consideration. As mentioned about previously, half-dose regimen also has therapeutically effect, so we decided to restart the anticoagulant regimen with a sub-standard dose of 30 mg of edoxaban for 5 day after 3 days of interruption.

Rehabilitation program of patient with atrial fibrillation and anticoagulation is not seemed to increase bleeding risk. Rather, early ambulation is recommended in patients using anticoagulation after venous thrombosis, and acute physical exercise is safe [19,20]. Therefore, in our opinion, it is recommended to start exercise therapy from gentle range of motion exercise and proceed slowly and carefully to resistance exercise that can potentially cause trauma or injury.

In conclusion, there is no consensus as to when anticoagulant therapy should be resumed and at what dose. According to several large studies, resuming anticoagulant therapy after major bleeding does not appear to increase the risk of additional bleeding. Therefore, clinicians should consider the patient's medical situation and carefully re-administer with extra caution. Also, further studies for optimal regimen and timeframe of restarting anticoagulation would be needed.

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