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Case Report

# Asymptomatic Intracerebral Hemorrhage Under Rivaroxaban

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## Abstract

Bleeding is one of the side effects of oral anticoagulants. They need to be taken into account with a frequency of less than 1% per treatment year. They can evolve from an asymptomatic onset to a potentially life-threatening complication. In two patients, an intracerebral hemorrhage was incidentally detected before it could manifest clinically. This suggests that the actual number of anticoagulant-related complications may be higher than reported.

***Keywords:*** *Intracerebral Hemorrhage; Rivaroxaban; Apixaban*

## Introduction

With the introduction of non-vitamin K antagonist oral anticoagulants, such as Rivaroxaban (Xarelto®) and Apixaban (Eliquis®), the management of preventing cardiovascular events has become easier. However, clinicians are faced with a variety of potentially life-threatening complications. Particularly, spontaneous bleeding in body cavities often remains asymptomatic for a long time. We report on 2 cases of intracerebral hemorrhage diagnosed incidentally in previously asymptomatic patients.

## Case Reports

### Case 1

At 02:00 am, a 78-year-old man is brought in by an ambulance. He was found by his wife sitting in bed, covered in blood. He stated that he slipped in the bathroom and fell onto the back of his head. A loss of consciousness or signs of a head injury were explicitly denied.

The patient has a history of hypertension and atrial fibrillation with arrhythmia. He has been put on a medication regimen of 15 mg Rivaroxaban (Xarelto®) for 2 years.

Upon admission, the patient appeared alert and fully oriented. He could provide a detailed account of the fall incident. No neurological deficits could be observed. Arms and legs could be moved symmetrically and mobilized against resistance on both sides. A pressure bandage was applied on his head, which was already soaked in blood. There was a 5 cm deep laceration with persistent wound edge bleeding occipitally. No tenderness over the skull or signs of a skull fracture could be provoked.

The complete blood count showed no abnormalities, clinical chemistry and coagulation parameters were within the normal range. The glomerular filtration rate was reported as 55 mL/min.

First, the wound was treated, stopping the bleeding. The ECG showed the known arrhythmia due to atrial flutter. Due to the patient's oral anticoagulation therapy, a CT scan of the head was conducted.

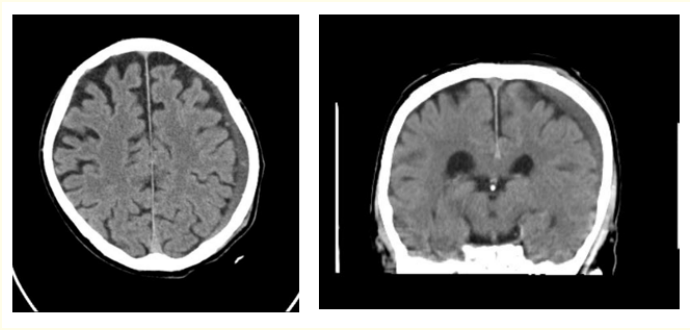

***Figure 1***

The CT scan reveals a parietotemporal chronic subdural hematoma without any midline shift.

The patient was admitted to the intermediate care unit for further observations. He received weight-adjusted 30 U/kg prothrombin complex concentrate (PPSB) and blood pressure monitoring with a target systolic blood pressure below 140 mm Hg. Additionally, the head CT scans was repeated 6 and 24 hours after admission. Both scans showed a consistent and unchanged finding. Radiologically, the density values of the bleed indicate an older hemorrhage, suggesting a chronic course. As the patient continued to be asymptomatic, he could be transferred to the general ward and discharged from the hospital after 48 hours without symptoms.

## Case 2

In the afternoon, an 82-year-old patient presents to the emergency department. He was referred by the radiology department, where an MRI of the head had been conducted prior to admission. The MRI showed a subarachnoid hemorrhage. The patient reported no symptoms.

Anamnestically, he experienced dizziness three months ago. Four weeks after the beginning of his symptoms, he visited his GP, who then ordered the MRI. The appointment for the MRI was scheduled three months after the onset of symptoms, but the initiating complaints only lasted a total of six weeks.

The patient takes Rivaroxaban (Xarelto®) for atrial fibrillation and Ramipril for known hypertension. He lived alone and was still capable of self-care.

The examination of the active patient was clinically and neurologically unremarkable.

The MRI report described a small subarachnoid hemorrhage with fresh blood components.

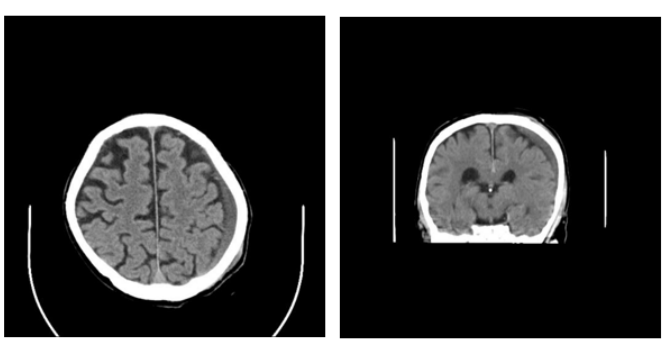

***Figure 2***

The patient was admitted for neurological observations. A head CT scan was performed according to the protocol after 6 and 24 hours. The previously described findings remained stable in size. Xarelto was paused during the hospital stay. Based on the clinical course and evaluations by internal medicine and neurology, prothrombin complex concentrate was not administered. The patient could be discharged after 48 hours. A follow-up appointment with a neurosurgeon and CT scan was scheduled. This follow-up occurred after 3 weeks and showed an increase in size. The indication for trepanation was established, but the patient declined the procedure.

## Discussion

An intracranial hemorrhage (ICH) describes several different conditions, including hemorrhagic stroke and subdural or epidural hematoma, and is characterized by the extravascular accumulation of blood in the skull. Subdural hematoma is located between the dura and arachnoid membranes. It is often the result of a head injury with injuries to the bridging or cortical veins, causing bleeding into the subdural space. It is defined as chronic from the 10$^{th}$ day after trauma.

Due to the increasing number of older people and the increasing use of oral anticoagulants (OAK) and antiplatelet agents, intracerebral bleeding events are a growing cause of death and disability worldwide [1]. ICH is the most serious complication of oral anticoagulant therapy. Its mortality rate of over 50% is three times higher than that of an ischemic stroke [2]. The incidence is steadily increasing due to the increasing use of oral anticoagulants [3].

Since the introduction of the new generation of non-vitamin K-dependent oral anticoagulants (NOAK), the treatment of arrhythmia-related complications, such as embolism and apoplexy, has become easier. Warfarin requires continuous monitoring, is subject to food-dependent factors, and depends on patient compliance. Rivaroxaban is a factor Xa inhibitor and only needs to be administered once a day without INR monitoring. The benefit is equivalent to that of warfarin. Intracerebral bleeding complications are even supposed to be less frequent [4]. It is estimated that intracerebral bleeding occurs with a frequency of 0,7% under warfarin as compared with 0,5% per treatment year under rivaroxaban (Sjögren 2015). However, from our own experience, significant bleeding complications occur more frequently with rivaroxaban than with warfarin and, depending on the affected body region, represent more severe to life-threatening complications. Alberts [5] for example, confirmed an increased risk of gastrointestinal bleeding compared to warfarin. In the EINSTEIN study [6], higher thrombosis and bleeding rates were found in patients over 65 years of age than in those under 65 years of age. However, among the NOAK rivaroxaban shows the highest risk of bleeding complications [7].

Findings are drawn from Medicare claims data on 581,451 adults age 65 or older with atrial fibrillation. Among every 1,000 individuals, the combined rate of major bleeding events and strokes due to clogged arteries or hemorrhage was roughly 16 per year with Xarelto versus about 13 per year with Eliquis, researchers reported on Tuesday in JAMA.

After taking participants' other risk factors into account, the overall rate of these events was 18% higher with Xarelto, they said. Xarelto was tied to a 12% higher rate of clot-related stroke, a 26% higher rate of bleeding-related stroke, a 41% higher rate of fatal non-stroke bleeding, and a roughly doubled rate of non-fatal non-stroke bleeding.

In addition, rivaroxaban has special limitations. It is contraindicated in patients with liver disease associated with coagulopathy [8]. Also, the benefit must be critically assessed in patients with reduced creatinine clearance, as the elimination time is prolonged, increasing the risk of bleeding [9-11]. The recommended maximum dose is therefore dependent on kidney function. It is 20 mg for a creatinine clearance above 50 mL/min and 15 mg for a clearance of 15 to 50 mL/min. The apparently better controllability by eliminating INR control is thus replaced by monitoring kidney function. In addition, coagulation controls are still available, as an overdose in the laboratory manifests itself as an INR increase. The risk of bleeding complications appears to be dose-dependent [12].

Another aspect is drug interactions. Nagaraja (2019) [13] emphasized the importance of drug- related side effects that can enhance the interaction with rivaroxaban, especially amiodarone [14,15], amlodipine [16] and antiplatelet agents.

The incidence of intracerebral hemorrhage without anticoagulants increases with age. Depending on the author, it varies from 0.09% to 0.65% from the age of 65 and increases to 0.38% to 0.67% in those over 75 [17-19]. Even with anticoagulation or despite it, thromboembolic events or bleeding can occur.

Among all oral anticoagulants, rivaroxaban carries the highest risk of intracerebral bleeding [20]. The complication of intracerebral bleeding under rivaroxaban was described as epidural bleeding by Lo [21] in 2014 and by Ruschel (2015) [22] and Ismail (2015) [23] in 2015. Its incidence depends on the dosage over 15 mg [24]. Cases of asymptomatic spontaneous bleeding, however, are rare. In the case of our first patient, although there was a preceding head injury, it was obviously not the cause of the subdural hematoma. This must have occurred at an earlier time and remained asymptomatic. A review of the medical records showed no previous contact, so it can be assumed to be an asymptomatic bleeding. In the second case, the bleeding caused only a short subclinical period of discomfort before becoming asymptomatic at the time of diagnosis.

## Conclusion

Intracerebral hemorrhages can occur during existing anticoagulation therapy and may remain asymptomatic or subclinical. They can be incidentally detected during routine screenings, such as after a head injury, and do not require further treatment if the patient is symptom-free. Both cases suggest that the risk of bleeding may be higher than previously estimated. Monitoring renal function while on rivaroxaban is necessary to adjust the dosage based on creatinine clearance and prevent overdosing.

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