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CASE REPORT
ΕΝΔΙΑΦΕΡΟΥΣΑ ΠΕΡΙΠΤΩΣΗ

# The new oral anticoagulant agent dabigatran and acute upper gastrointestinal bleeding
## A report of three cases

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Η επίδραση του νέου από του στόματος αντιπηκτικού "dabigatran" στην αιμορραγία ανώτερου πεπτικού: Παρουσίαση 3 περιπτώσεων

*Περίληψη στο τέλος του άρθρου*

**Administration of warfarin has been the most common long-term anticoagulation treatment for patients with atrial fibrillation (AF) for many years. New oral anticoagulants (NOACs) are rapidly replacing warfarin, because they do not require frequent laboratory monitoring or dosage adjustment. They present several critical disadvantages, however; currently no reversal agent is available, they require close monitoring of renal function and, last but not least, data on their safety and bleeding risk are as yet inadequate. Three cases are presented, of an 84-year-old female, a 72-year-old female and a 79-year-old male, all with a history of AF and prophylactic administration of the NOAC dabigatran. All three patients presented with signs and symptoms of upper gastrointestinal (GI) bleeding, and endoscopic investigation of the upper GI tract revealed erosive gastritis, volvitis and duodenitis. Dabigatran may be involved in upper GI bleeding in patients treated with this agent, although the present study could not demonstrate the exact relationship. Further research is indicated for firm conclusions to be drawn.**

**Key words**

Atrial fibrillation
Dabigatran
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New oral anticoagulant agents (NOACs) such as dabigatran have recently been approved for stroke prevention in atrial fibrillation (AF) and for the prevention and treatment of venous thromboembolism.[1] These agents are as effective as warfarin, but more convenient to use, since they do not require the frequent blood examinations needed with warfarin to control and maintain the international normalized ratio (INR) within the range of 2.0–3.0.[2] Since the NOAC dabigatran is a recently developed agent, its side effects and safety are still being researched.[3] Major studies have shown a risk of gastrointestinal (GI) bleeding, especially in elderly patients and patients with renal impairment.[4–6] This is a report of three cases of upper GI bleeding in elderly patients with AF who were receiving prophylactic treatment with dabigatran.

## PRESENTATION OF CASES

### Case 1

An 84-year-old woman was admitted with upper GI bleeding. She reported melena, nausea, and dizziness for the past two days, but no other symptoms or any previous GI history. The medical history included AF and chronic renal impairment. At the time of admission she was being treated with dabigatran 150 mg twice daily, which she had been taking for 3 months. Physical examination revealed hypotension and tachycardia, and rectal examination was positive for melena. Laboratory tests revealed Ht 23%, Hb 7.1 g/dL, blood urea 92 mg/dL, and creatinine (Cr) 1.22 mg/dL. Endoscopic Gastroduodenoscopy (EGD) showed hemorrhagic erosive gastritis, volvitis and duodenitis (fig. 1a), as well as active hemorrhage, with oozing classified as Forrest 1b (fig. 1b). Hemostasis of the hemorrhagic erosions was successfully achieved by

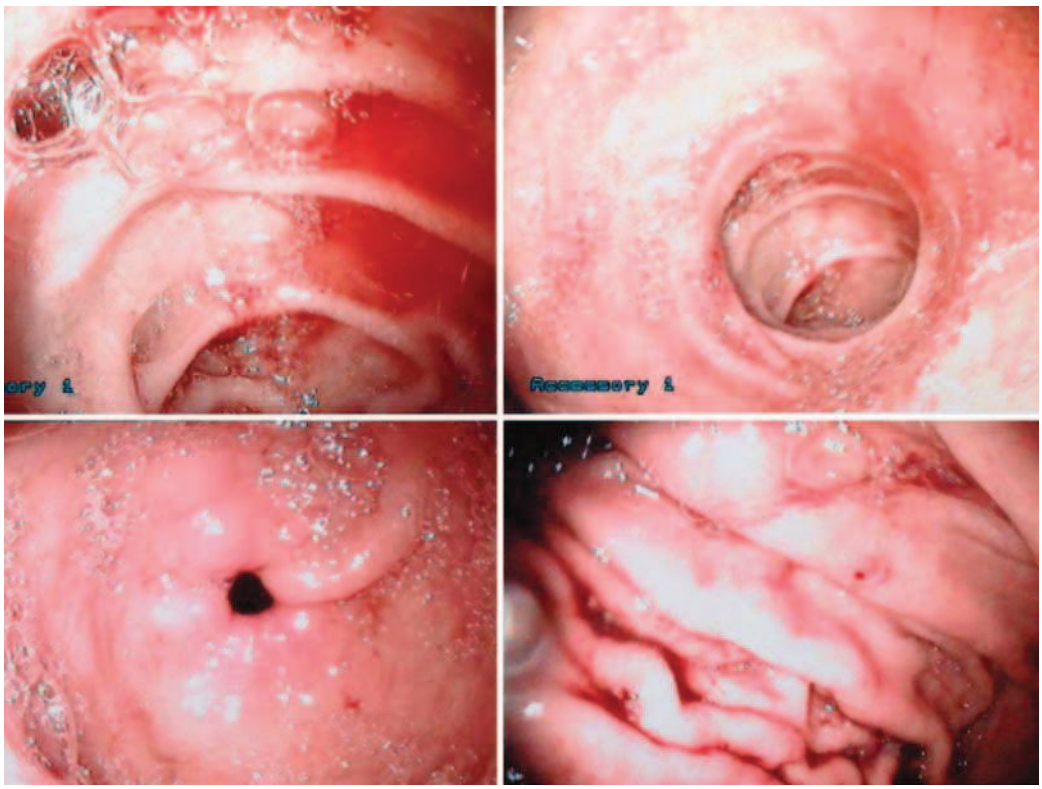

**Figure 1a.** Endoscopic findings in an 84-year-old woman with gastrointestinal bleeding, showing hemorrhagic erosive gastritis, volvitis and duodenitis.

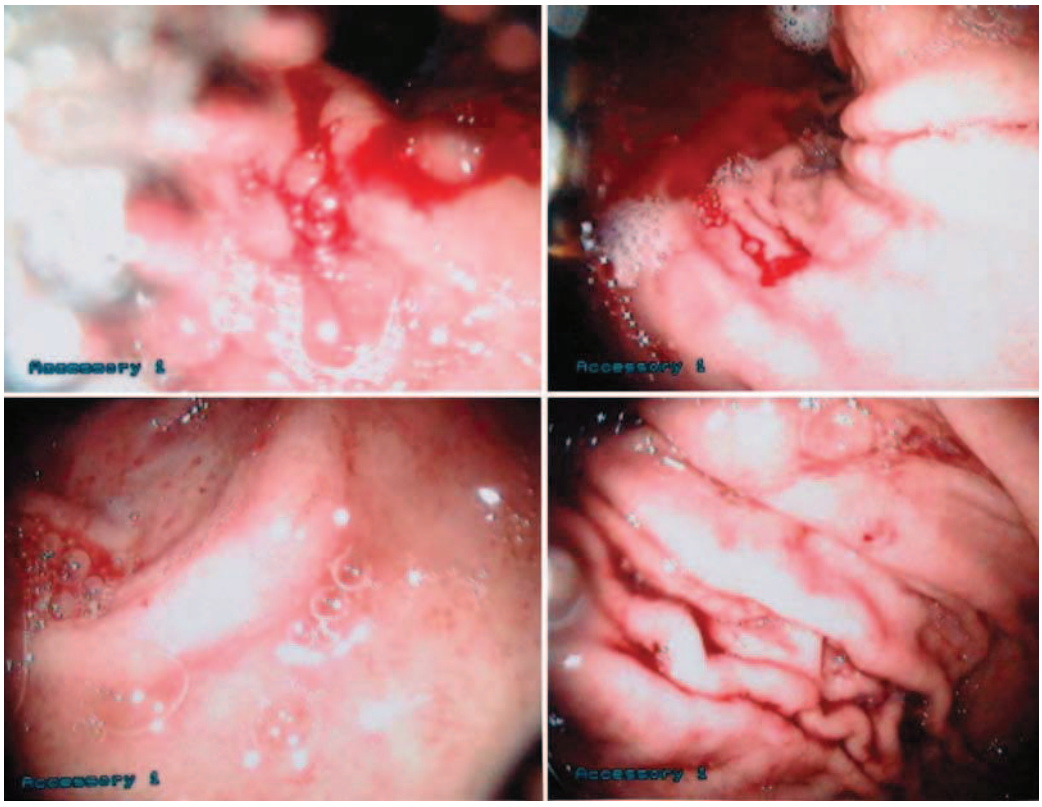

**Figure 1b.** Endoscopic findings in an 84-year-old woman with gastrointestinal bleeding, showing active hemorrhage, oozing (Forrest 1b).

injection of adrenaline 1/10,000. The patient underwent treatment with proton pump inhibitors (PPI) and was discharged after 6 days.

### Case 2

A 72-year-old woman presented with melena 2 days before admission. She had AF and was being treated with dabigatran 110 mg twice daily for stroke prevention. Her medical history included diabetes mellitus (DM), hyperlipidemia, hypothyroidism, and hypertension. She was also overweight, with a body mass index (BMI) of 29. She had no history of renal impairment, gastritis or peptic ulcer. She was hemodynamically stable on admission. Laboratory examinations revealed Ht 19.4%, Hb 6.54 g/dL, blood urea 153 mg/dL, Cr 1.30 mg/dL. The last dose of dabigatran had been taken 12 hours prior to admission. The patient underwent blood transfusion (5 units of RBCs), fluid resuscitation and PPI. EGD showed hemorrhagic erosive gastritis of the body and antrum of stomach, with mild propyloric oozing, classified Forrest 1b 9 (fig. 2). During the procedure, hemostasis with injection of adrenaline 1/10,000 was achieved. The patient remained hemodynamically stable under treatment and was discharged on day 6 of hospitalization.

### Case 3

A 79-year-old male with a history of AF and cardiac insufficiency presented with upper GI bleeding. He reported fatigue and black stools for 3 days. On admission, the patient was hemodynamically unstable. Physical examination revealed pallor, hypotension and tachycardia. Rectal examination was positive for melena. He was being treated with dabigatran 150 mg twice daily for 2 months, along with medication for cardiac insufficiency. He had no history of renal impairment, peptic ulcer or other GI lesions. Laboratory tests revealed Ht 15%, Hb 6.2 g/dL, blood urea 352 mg/dL Cr 3.09 mg/dL. After fluid resuscitation and blood transfusion, EGD showed erosive gastritis, volvitis and duodenitis (fig. 3). There was no active hemorrhage at the time of endoscopy. The patient underwent treatment with PPI and was discharged after the 3rd day of hospitalization.

## DISCUSSION

The present series comprises three patients with no previous known history of GI tract pathology, who presented with signs of upper GI bleeding (hematemesis and or melena) while being treated with a NOAC. Endoscopic findings included erosive gastritis (cases 2, 3), volvitis and duodenitis. In the first two cases, endoscopic hemostasis was required in order to prevent further hemorrhage, while in the third patient the hemorrhage was self-restricting. The

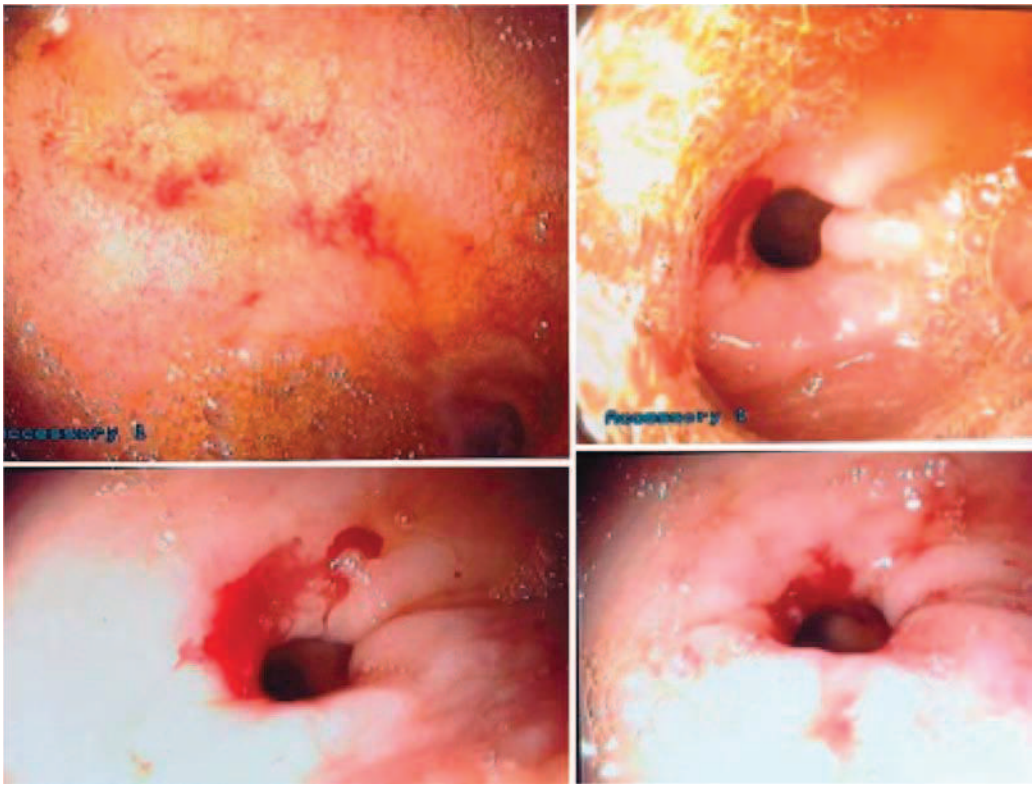

**Figure 2.** Endoscopic findings in a 72-year-old woman with gastrointestinal bleeding, showing hemorrhagic erosive gastritis of the body and antrum of stomach, with mild propyloric oozing (Forrest 1b).

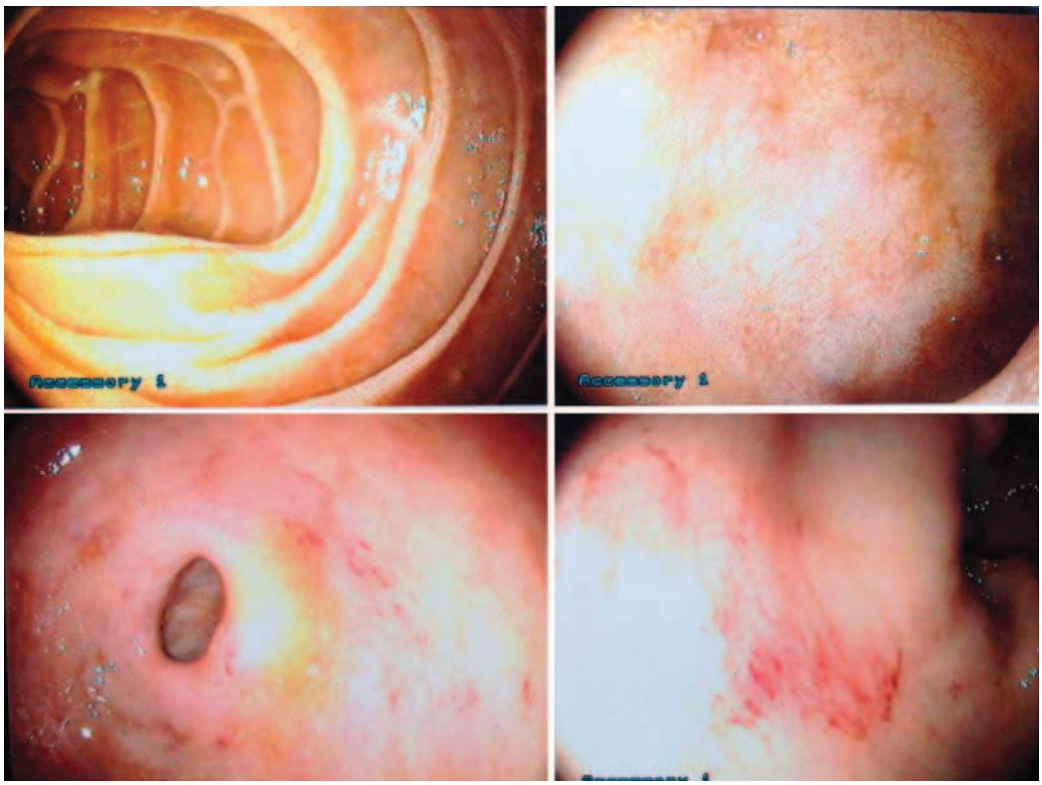

**Figure 3.** Endoscopic findings in a 79-year-old male with gastrointestinal bleeding, showing duodenitis, erosive volvitis, and erosive gastritis, with signs of recent hemorrhage.

mean length of hospital stay was 5 days. All three patients presented with a slightly raised serum level of Cr, which suggests that older patients should always be monitored for renal function when taking NOACs.

AF is the most common supraventricular arrhythmia, with an increased incidence after the seventh decade of life. The treatment goals include restoration and maintenance of sinus rhythm, as well as prevention of thromboembolic complications. Patients with paroxysmal, persistent or permanent AF should be treated prophylactically with anticoagulants such as warfarin, unless contraindicated. The next generation of oral anticoagulants, the NOACs such as dabigatran have recently been proposed as alternative to warfarin in the treatment of non-valvular AF, and also for the prevention and treatment of venous thromboembolism. Unlike warfarin, the pharmacodynamics of dabigatran appear to be predictable and therefore frequent blood testing for maintenance of the INR is not required.[7] Dabigatran appears relatively free of drug and food interactions and offers efficacy similar to that of warfarin in preventing ischemic events.[7] In addition, it provides rapid onset and offset of action in patients with normal renal and hepatic function.[8]

Patients using warfarin have a higher risk of life-threatening bleeding, such as cranial hemorrhage, than dabigatran-using patients. Recent studies, however, document higher rates of GI bleeding in patients using dabigatran, especially those aged over 75 years, with the risk estimated to be 0.3–0.5% per year.[9,10]

Discontinuation of dabigatran because of bleeding, one of the most frequent adverse reactions, is reported in more than 10% of patients. Dabigatran inactivates both fibrin bound and free thrombin, while heparin cannot act in fibrin bound thrombin and continues to trigger thrombus expansion.[10,11] Compared with warfarin, dabigatran at a dose of 150 mg twice daily increases the risk of major GI bleeding approximately 1.5-fold, while 110 mg twice daily does not significantly alter the risk.

Dabigatran is available in the form of dabigatran etexilate in capsules which contain also tartaric acid, with the aim of lowering gastric pH to ensure adequate absorption. As a result, its absorption is independent of GI tract acidity and is not affected by co-administration of PPI. Tartaric acid is associated with dyspepsia and, by lowering gastric pH, could be a possible trigger for GI bleeding. Such a

hypothesis is speculation, as antiplatelet agents, such as aspirin and dipyridamole, which are administered in a similar way, with comparable quantities of tartaric acid, have not been associated with increased GI bleeding.[12,13] GI bleeding could possibly be attributed to incomplete absorption of dabigatran across the GI tract which may allow localized drug activity in addition to the systemic drug activity. The bioavailability of orally administered dabigatran is 6%, and the remainder travels through the GI tract and is excreted in feces.

The therapeutic anticoagulation effect of this NOAC is achieved within 2–4 hours of administration and its half-life ranges from 12 to 17 hours. Circulating dabigatran is eliminated primarily via the kidneys, and its half-life may therefore be prolonged when renal impairment is present. As a result, renal impairment (Cr clearance <30 mL/min) and other underlying conditions, such as malignancies, active ulcers, hepatic impairment, co-administration of antiplatelet agents and NSAIS, may increase the risk of bleeding.[6] Age over 75 years, moderate renal impairment with Cr clearance 30–50 mL/min, and conditions such as thrombocytopenia, recent biopsy, recent GI bleeding and other coagulation disorders, can all pose an additional predisposition to bleeding.

Unlike that for warfarin, no antidote is currently available to reverse the anticoagulant effect of dabigatran in the case of bleeding. The half-life of dabigatran in healthy individuals ranges from 12 to 17 hours while the INR remains unaffected when measured. The most sensitive tests used to monitor the effect of dabigatran include thrombin clotting time (TT), ecarin clotting time (eTT), the Hemoclot test and aPTT. The majority of these blood markers, claimed to be the most reliable, are measured in specialized laboratories, which is a limitation in the monitoring of patients taking dabigatran.[13] A time of aPTT over 80 sec measured before the next dose administration is considered to be associated with a higher bleeding risk.

Appropriate selection of patients and periodic monitoring of the renal function, especially in elderly patients, are crucial precautions in treatment with dabigatran. The use of dabigatran in patients with fluctuating renal function should be considered carefully. Routine endoscopic examination of the upper GI tract is of paramount importance in older patients on long-term dabigatran treatment.

## ΠΕΡΙΛΗΨΗ

**Η επίδραση του νέου από του στόματος αντιπηκτικού "dabigatran" στην αιμορραγία ανώτερου πεπτικού: Παρουσίαση 3 περιπτώσεων**

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Μέχρι πρόσφατα, οι ασθενείς με κολπική μαρμαρυγή αντιμετωπίζονταν με βαρφαρίνη ως μακροχρόνια αντιπηκτική θεραπεία. Τα νεότερα από του στόματος αντιπηκτικά έχουν αντικαταστήσει τη βαρφαρίνη καθ' ότι δεν απαιτούν τακτικό εργαστηριακό έλεγχο και προσαρμογή δόσης. Αντίθετα, για τα συγκεκριμένα αντιπηκτικά είναι απαραίτητο να διενεργείται έλεγχος νεφρικής λειτουργίας επειδή δεν υπάρχει ακόμη αναστρέψιμος παράγοντας, καθώς και επαρκή δεδομένα για την ασφάλειά τους και τον κίνδυνο αιμορραγίας. Παρουσιάζονται 3 περιπτώσεις, δύο γυναικών, ηλικίας 84 ετών και 72 ετών, καθώς και ενός άνδρα 79 ετών με ιστορικό κολπικής μαρμαρυγής, που εκδηλώθηκαν με συμπτώματα και σημεία αιμορραγίας ανώτερου πεπτικού μετά από λήψη του νέου από του στόματος χορηγούμενου αντιπηκτικού νταμπιγκατράνη (dabigatran). Η ενδοσκόπηση του ανώτερου πεπτικού ανέδειξε διαβρωτική γαστρίτιδα, βολβίτιδα και δωδεκαδακτυλίτιδα σε όλους τους ασθενείς. Το νεότερο από του στόματος αντιπηκτικό dabigatran μπορεί να εμπλέκεται σε αιμορραγίες ανώτερου πεπτικού σε ασθενείς που αντιμετωπίζονται με αυτόν τον παράγοντα. Η περαιτέρω έρευνα σε αυτό το πεδίο θα συμβάλλει στην εξαγωγή οριστικών συμπερασμάτων.

**Λέξεις ευρετηρίου:** Αιμορραγία ανώτερου πεπτικού, Ενδοσκόπηση πεπτικού, Κολπική μαρμαρυγή, Dabigatran

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