CASE REPORT

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Silent Danger: Dabigatran Build-up in a Frail Nonagenarian-rethinking DOAC Monitoring in Acute Care

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Abstract

Direct oral anticoagulants are widely used without routine monitoring because of their predictable pharmacokinetics and fixed dosing regimens. In acute care settings, however, situations such as bleeding, urgent procedures, or renal impairment may warrant rapid drug level testing to guide management. In a nonagenarian receiving dabigatran with acute kidney injury and clinically relevant bleeding, can early drug-level testing guide timely reversal and improve outcomes? A 91-year-old woman, taking dabigatran 110 mg twice daily, was admitted after a fall with a leg hematoma, anemia (hemoglobin 5.7 mmol/L), and acute kidney injury (creatinine 246 µmol/L). Dabigatran was initially continued but was discontinued on day 1 after the onset of rectal bleeding, which was accompanied by a hemoglobin drop to 4.9 mmol/L. The patient received one unit of packed red blood cells. A diluted thrombin time assay performed approximately 24 hours after the last dose showed a dabigatran concentration of 446 ng/mL. On day 3, with persistent anemia, prothrombin complex concentrate (Octaplex) was administered, and levels later that day were 240-270 ng/mL. Idarucizumab was not used. Following shared decision-making, the patient declined further intensive treatment, transitioned to comfort care, and died a few days later. This case highlights the importance of early recognition of possible dabigatran accumulation in a frail older adult with renal impairment. It also underscores the need for greater awareness among clinicians of the role of drug-level testing in acute care. Maintaining a low threshold for rapid assay-based testing and ensuring institutional pathways that guarantee access to validated assays may help improve safety and outcomes in this vulnerable population.

Keywords: Acute kidney injury, aging, clinical geriatrics, dabigatran, direct oral anticoagulants, drug level monitoring, drugs and aging, frailty, polypharmacy

Introduction

Direct oral anticoagulants (DOAC) are widely used for prevention of thromboembolic events and are generally prescribed without routine level monitoring because of their predictable pharmacokinetics and fixed dosing regimens. In most patients, this strategy is safe and effective (1). However, in acute care situations such as life threatening bleeding, urgent surgery or renal impairment, current guidelines emphasize that drug level measurement can provide clinically relevant information (2,3).

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Older, frail patients represent a growing proportion of those receiving anticoagulants, yet they remain underrepresented in pivotal clinical trials (4-7). Age-related changes in pharmacokinetics, comorbidities, and polypharmacy increase the risk of drug accumulation and bleeding in this population (8). Case reports, therefore, play an important role in highlighting real-world situations in which monitoring or reversal strategies are critical.

We present a case of an older, frail patient who developed persistently elevated dabigatran concentrations in the setting of acute kidney injury and bleeding. This unusual course illustrates the potential dangers of drug accumulation and underscores the importance of considering early measurement of DOAC levels in selected acute care situations.

Case Presentation

A 91-year-old frail woman with a history of atrial fibrillation, treated with dabigatran 110 mg twice daily, was referred to the emergency department (ED) with progressive pain in her left lower leg following a fall two weeks earlier. Her medical history was otherwise unremarkable. From a psychosocial perspective, she lived independently with support from a case manager and several family members who became more closely involved after her husband's passing the previous year. She remained largely independent in activities of daily living, though she required some assistance with heavier household tasks.

Upon presentation to the ED, the patient's vital signs were normal. Examination of the left lower leg revealed edema, hematomas, and a dry, superficial wound on the tibia, without clinical signs of infection (Figure 1). Movement was not overtly painful, but the skin was markedly tender.

Blood tests showed anemia (hemoglobin 5.7 mmol/L; baseline 7.3 mmol/L; normal 7.5-10.0 mmol/L), leukocytosis (19.9×10^9/L; normal $4.0\text{-}10.0\times10^9$/L), and markedly elevated C-reactive protein (329 mg/L; normal <10 mg/L). She also had acute kidney injury, with a creatinine of 246 µmol/L (baseline of 82 µmol/L; normal 45-90 µmol/L for women), and hyponatremia.

Based on these findings, the differential diagnosis included an infected hematoma, deep soft-tissue infection, compartment syndrome, and anticoagulant-related bleeding. Radiographs were obtained to exclude a fracture. An ultrasound was performed to assess for an abscess or compartment syndrome, and it confirmed the presence of a hematoma without active bleeding. No abscess or fluid collection was seen.

The working diagnosis was a spontaneous or trauma-related leg hematoma associated with anticoagulant therapy. The patient was admitted for observation and pain control. As the hematoma appeared stable without signs of ongoing bleeding, dabigatran was initially continued. In addition, prerenal acute kidney injury secondary to poor oral intake was managed with intravenous fluids and correction of hyponatremia.

On the first day of admission, the patient experienced two episodes of rectal bleeding, accompanied by a drop in hemoglobin concentration from 5.7 to 4.9 mmol/L. The bleeding was suspected to originate from hemorrhoids or diverticular disease. Although such sources alone would not necessarily warrant discontinuation of anticoagulation, the combination of gastrointestinal bleeding, a recent large hematoma, and another hemoglobin drop prompted temporary cessation of dabigatran as a precaution. As her vital signs remained stable, one unit of erythrocyte concentrate was transfused to correct symptomatic anemia.

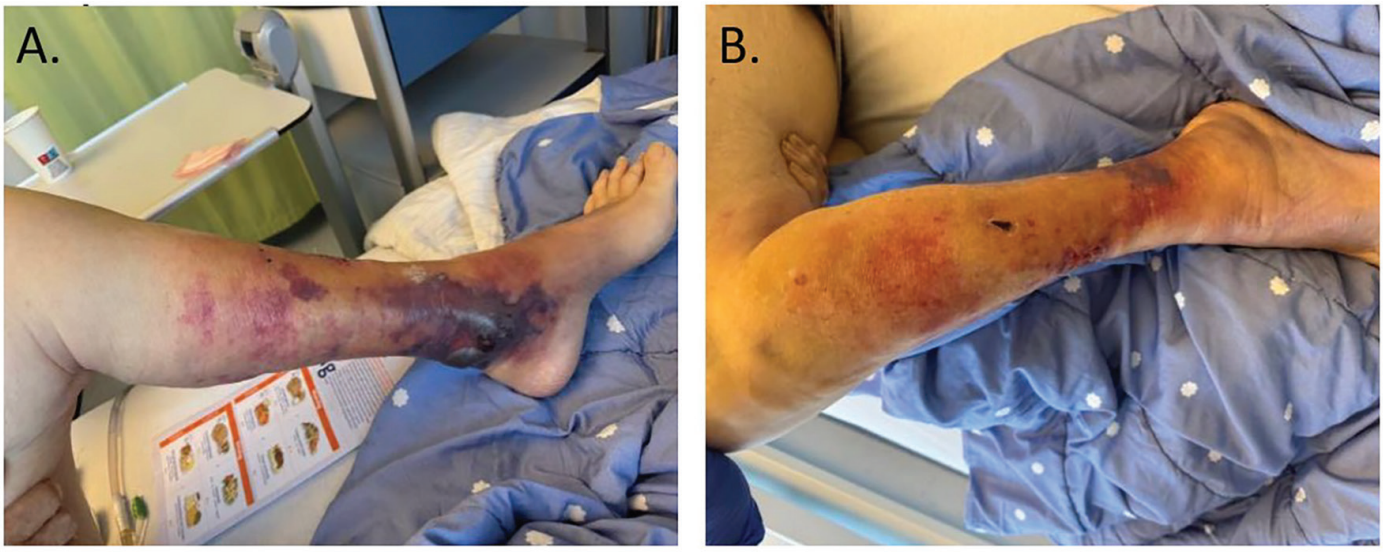

Figure 1. Clinical presentation of the patient's left lower leg. (A) Median side of the left lower leg showing extensive hematoma and edema. (B) Lateral side of the left lower leg illustrating the extent of swelling and skin discoloration.

After transfusion, her hemoglobin concentration remained stable at 5.1 mmol/L. Because the expected post-transfusion increase in hemoglobin was absent and renal function had severely deteriorated, dabigatran accumulation was suspected. Therefore, a dabigatran level determined by a diluted thrombin time (dTT) assay was obtained. Approximately 24 hours after the last dose, the measured concentration was 446 ng/mL, markedly above the expected range of 40-150 ng/mL at 12 hours post-dose (9). In line with the European Heart Rhythm Association (EHRA) 2021 Practical Guide, which supports a tailored approach to DOAC management in bleeding situations, no immediate reversal was initiated in the absence of evidence of ongoing bleeding (3).

On the third day of admission, hemoglobin dropped to 4.1 mmol/L, while creatinine decreased from 289 to 174 µmol/L. Blood pressure was 145/80 mmHg, and heart rate was 108 bpm. Edema and pain in the left lower leg increased. Surgical consultation ruled out compartment syndrome. Because of a further decline in hemoglobin and persistent anemia despite a previous transfusion (two units of erythrocyte concentrate), prothrombin complex concentrate (PCC; Octaplex®) was administered that morning. Dabigatran levels, which had been markedly elevated at 446 ng/mL the previous day, showed a substantial decrease to 240 ng/mL at 15:30, followed by a slight increase to 270 ng/mL at 18:00 (Figure 2).

Later that day, the patient indicated that she did not wish to undergo further intensive treatment. In consultation with her family and the medical team, it was agreed not to administer additional transfusions. A psychiatric consultation was performed to exclude depression or complicated grief as the cause of her expressed wish; neither was identified. The transition to comfort care followed a shared decision-making process involving the patient, her family, and the attending physicians.

Patient Perspective

Shortly after admission, the patient clearly expressed that she did not wish to undergo further active treatment. She consistently reaffirmed this decision throughout her hospitalization and was deemed competent to do so. Her preference for comfort-focused care was respected, and both she and her family expressed relief and satisfaction with the decision to discontinue further medical interventions. Their involvement in the decision-making process ensured that care remained fully aligned with her values and previously expressed wishes.

Subsequent Course

During the following days, palliative care principles guided pain management and communication. Despite optimal analgesic treatment, her pain remained severe and became refractory. Given her advanced age, frailty, and persistent suffering, a transition to comfort-focused care was discussed with the patient and her family. In accordance with the European Association for Palliative Care framework, she met the criteria for end-of-life care, including the presence of a refractory symptom and an estimated life expectancy of less than two weeks (10).

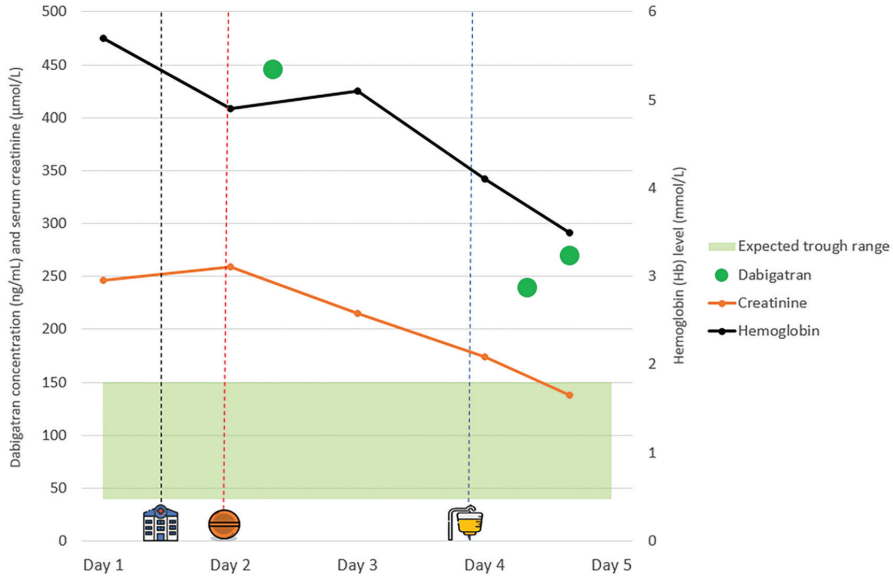

Figure 2. Dabigatran plasma concentrations, hemoglobin levels, and serum creatinine during hospitalization.

Green dots indicate dabigatran plasma concentration (ng/mL), the orange line serum creatinine (µmol/L), and the black line hemoglobin (mmol/L). The green shaded area indicates the expected trough concentration range (40-150 ng/mL). Vertical dashed lines indicate admission to the emergency department (black), last dabigatran intake (red), and administration of PCC (blue).

PCC: Prothrombin complex concentrate.

In accordance with her previously expressed wishes, the decision was made to initiate palliative sedation to alleviate suffering. She died peacefully several days later.

As shown in Figure 2, key laboratory trends included a creatinine peak of 246 µmol/L (baseline 82 µmol/L), which improved to 174 µmol/L. Dabigatran levels declined from 446 to 240 ng/mL after PCC and hemoglobin falling from 5.7 to 4.1 mmol/L despite transfusions.

Case Reflection

In this case, a 91-year-old frail patient developed persistently elevated dabigatran levels in the setting of acute kidney injury, despite discontinuation of dabigatran. Plasma levels remained markedly above the expected trough values, and reversal therapy was initiated only after a significant delay.

Strengths of care included timely recognition of bleeding, transfusion support, and involvement of the patient and her family in shared decision-making, resulting in a transition to palliative care consistent with her wishes. However, important limitations included the delayed measurement of dabigatran levels and the postponement of reversal, which may have contributed to further clinical deterioration. Dabigatran was initially continued because hemodynamics remained stable. In retrospect, given the presence of acute kidney injury and a progressive drop in hemoglobin, earlier discontinuation of dabigatran and measurement of plasma levels might both have been appropriate. These steps might have prevented further accumulation and guided an earlier reversal.

When bleeding recurred and markedly elevated dabigatran plasma levels were identified, reversal was still postponed for the same reason. At that stage, earlier use of idarucizumab might have been a more appropriate choice, given its rapid and specific reversal effect. Only after a third episode of hemoglobin drop, PCC was ultimately administered after multidisciplinary discussion, since the bleeding was not considered immediately life-threatening and the patient remained hemodynamically stable, in line with current guideline recommendations that reserve specific reversal agents for life-threatening or uncontrolled major bleeding events (3,11). Nonetheless, idarucizumab would have offered more targeted reversal and might have limited further accumulation.

Discussion

DOACs, including dabigatran, apixaban, rivaroxaban, and edoxaban, are widely prescribed for the prevention and treatment of thromboembolic disorders, including non-valvular atrial fibrillation and venous thromboembolism. Their predictable pharmacokinetics and fixed dosing regimens eliminate the need for routine coagulation monitoring, unlike vitamin K antagonists (2). In acute clinical scenarios, however, guidelines note that measurement of DOAC plasma levels may provide clinically relevant information. The EHRA specifically highlights scenarios such as life-threatening bleeding (for example, uncontrolled bleeding), urgent surgical interventions (for example, emergency surgery), uncertain drug intake, and urgent reversal (3,12). EHRA also addresses the use of DOACs in older and frail patients, recognizing their particular vulnerability to both thromboembolic and bleeding complications. Older individuals, especially those aged 75 years or older, are more susceptible to drug accumulation due to age-related changes such as decreased renal clearance, lower lean body mass, polypharmacy, and a higher comorbidity burden (8). Ultimately, current guidelines leave it to the treating physician to determine whether DOAC level measurement is clinically useful in such acute scenarios.

In emergency situations, the ability to accurately assess DOAC activity can be crucial. Interpretation of intermediate values can be challenging, as no universally established therapeutic ranges exist and concentrations are influenced by age, renal function, and frailty. By contrast, markedly elevated levels, as in our patient, are clearly abnormal and clinically relevant (13). Standard coagulation tests such as prothrombin time and activated partial thromboplastin time may provide some indication of an anticoagulant effect, but are unreliable for quantifying DOAC levels. Specific assays are required. For dabigatran, a direct thrombin inhibitor (DTI), the dTT and the ecarin chromogenic assay are the most extensively validated assays, showing a strong linear correlation with plasma concentrations. For factor Xa inhibitors, such as apixaban, chromogenic anti-Xa assays calibrated for each DOAC are preferred. A negative result (i.e., absence of anti-Xa activity) effectively rules out clinically significant levels. Turnaround times can be under 30 minutes in equipped laboratories, making them feasible for use in acute care (2,14).

Reversal Strategies for Direct Oral Anticoagulants

In cases of life-threatening bleeding or urgent surgical intervention, prompt reversal of DOAC activity may be required. Reversal therapy is most effective when significant drug levels are present, but offers little benefit when circulating levels are minimal or absent (15). Several pharmacological options are available, though their efficacy, availability, and costs vary substantially.

For DTIs, such as dabigatran, the specific antidote idarucizumab provides immediate and complete neutralization through high-affinity binding. It acts within minutes after intravenous administration and has been shown to rapidly restore hemostasis in patients with major bleeding or those requiring urgent surgery (15-17).

For factor Xa inhibitors, andexanet alfa is available as a targeted reversal agent. It is a modified, inactive version of factor Xa that binds factor Xa inhibitors with high affinity, thereby sequestering them and restoring normal thrombin generation. Although it effectively reverses the anticoagulant effect, evidence that this translates into improved clinical outcomes remains limited. The most recent ANNEXA-I trial, conducted in patients with intracerebral hemorrhage, demonstrated a reduction in hematoma expansion compared with standard care but did not demonstrate a clear clinical benefit (18). Its use is further limited by high costs, restricted availability, and an increased risk of thromboembolic events. Although andexanet alfa would theoretically bind other factor Xa inhibitors, it has only been studied and approved for apixaban and rivaroxaban, leaving edoxaban without a specifically approved antidote. In clinical practice, PCCs are often used as nonspecific reversal agents when specific antidotes are unavailable. PCCs replenish vitamin K-dependent clotting factors and can improve hemostasis, although supporting evidence is stronger for factor Xa inhibitors than for dabigatran (15-17).

According to the 2021 EHRA Practical Guide, idarucizumab is recommended as the first-line therapy for dabigatran reversal in cases of life-threatening bleeding or when urgent surgery is required; andexanet alfa may be considered for apixaban- or rivaroxaban-associated bleeding when available. In the absence of a specific antidote, for example, in patients treated with edoxaban or when andexanet alfa is not available for apixaban- or rivaroxaban-associated bleeding, the guideline advises the use of 4-factor PCC (19). These recommendations underscore the importance of availability and logistics in acute care, which frequently determine real-world management choices.

The economic implications are considerable: idarucizumab is estimated at ~€2,500 per treatment, PCCs at ~€750, and andexanet alfa may exceed €18,500 in certain settings (10-12). Based on current European price estimates, these differences highlight the need for more accessible and scalable reversal strategies in acute care. An overview of available agents, including their mechanisms, onset of action, limitations, and estimated costs, is provided in Table 1.

Future Perspectives

DOAC reversal is a rapidly evolving field, with new agents and strategies under development to address limitations of current therapies. Future directions focus on developing universal, safer, and more accessible reversal agents, optimizing clinical protocols, and expanding options for new classes of anticoagulants. Two investigational reversal agents for factor Xa inhibitors are currently under development. Ciraparantag is a small molecule that reverses the effects of direct and indirect FXa inhibitors through charge-based binding. It acts rapidly after intravenous administration and produces sustained reversal of effects for up to 24 hours. Early-phase studies in healthy volunteers have demonstrated dose-dependent reversal of apixaban, rivaroxaban, and edoxaban, with good tolerability. A phase II trial is ongoing. VMX-C001 is a modified recombinant factor X that restores thrombin generation without excessive rebound. Preclinical studies show a favorable safety profile, and a phase I trial is underway to evaluate its efficacy in reversing FXa inhibitors in humans (23).

Take-away Lesson

This case underscores the need for greater awareness among clinicians regarding the potential value of DOAC- level measurement in frail older patients presenting with bleeding or renal impairment. Although DOACs are generally considered safe and predictable, measurement can provide critical information to guide decisions about discontinuation, reversal, and individualized management. Older and frail patients, often underrepresented in pivotal trials, are particularly vulnerable to drug accumulation and bleeding due to age-related pharmacokinetic variability, comorbidities, and polypharmacy.

Furthermore, the case highlights the importance of familiarity with available reversal strategies and their appropriate indications. Broader awareness of both diagnostic and therapeutic options may support earlier recognition of DOAC-related complications and safer, more tailored care in this population.

Table 1. Overview of currently available DOAC reversal strategies.

Agent	Target DOAC(s)	Mechanism of action	Onset of effect	Limitations	Approximately cost (per treatment)
Idarucizumab	Dabigatran	Monoclonal antibody fragment. Binds to dabigatran	Immediate, complete	Only for dabigatran	~ €2,500 (20)
Andexanet alfa	Apixaban, rivaroxaban (not edoxaban)	Recombinant modified factor Xa decoy	Rapid, short half-life	Limited availability, ↑ thrombosis risk	~ €18,500 (21)
PCCs (e.g. Octaplex)	All DOACs (non-specific)	Replenish vitamin K-dependent clotting factors	Rapid (minutes-hours)	Evidence stronger for FXa inhibitors than dabigatran	~ €750 (22)

DOAC: Direct oral anticoagulant, PCC: Prothrombin complex concentrate.

Ethics

Informed Consent: Written informed consent for publication of this case report and any accompanying images was obtained from the patient's legal representatives.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.R.D.W., A.M.L.O.L., Concept: F.J.H.M., Design: F.J.H.M., Data Collection or Processing: I.S.F., S.R.D.W., Analysis or Interpretation: I.S.F., Literature Search: I.S.F., Writing: I.S.F., S.R.D.W., M.J.D.J., A.M.L.O.L., K.W., F.J.H.M.

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