Original Article

Hospital Pharmacy
1–5

DOI: 10.1177/00185787211016335
journals.sagepub.com/home/hpx
SAGE

Dabigatran-Induced Nephropathy and Gastrointestinal Bleeding and Its Successful Treatment with Idarucizumab: A Case Report

Francesca Marchesini[1*], Andrea Ossato[2*], Alberto Zendrini[1], Federica Arginelli[3], Teresa Zuppini[1], Nicola Realdon[2], Massimo Zamperini[1], and Roberto Tessari[1]

Abstract

Recently, the atrial fibrillation treatment guidelines have been updated to now recommend Non-vitamin K antagonist oral anticoagulants (NOACs) as the preferred alternative to warfarin for systemic embolism and stroke prevention in patients with non-valvular atrial fibrillation. NOACs have major pharmacologic advantages over warfarin, although the most common complications are gastrointestinal bleeding and NOAC-induced nephropathy within 6 weeks after starting therapy, as several recent case-reports stated. We are reporting for the first time a chronic delayed adverse reaction (regularly reported to Authorities) observed in an 82-year-old woman 27 months after starting dabigatran (110 mg twice a day), characterized by concomitant gastrointestinal bleeding and nephropathy. Idarucizumab administration immediately improved both bleeding and renal parameters. Moreover, we are going to highlight the importance of the compliance, the adherence to the therapeutic plan and the supervision of the Hospital Pharmacy on drug prescriptions. In fact in our case, dabigatran was firstly prescribed by the neurologist and delivered by the hospital pharmacy, but the patient continued the treatment for 27 months, prescribed by general practitioner without any laboratory control. This lack of supervision certainly contributed to the onset of the adverse reaction reported.

Keywords

dabigatran, nephropathy, gastrointestinal bleeding, idarucizumab, Non-vitamin K antagonist oral anticoagulants (NOACs)

Introduction

During the last few years, Vitamin K antagonists (VKAs; warfarin and acenocoumarol), along with the use of low molecular weight heparin (LMWH), represented the only anticoagulant drugs available for systemic embolism and stroke prevention in patients with non-valvular atrial fibrillation (NVAF).[1-3]

Recently, the atrial fibrillation (AFib) treatment guidelines have been updated to now recommend non-vitamin K antagonist oral anticoagulants (NOACs) as the preferred alternative to warfarin to reduce the risk of stroke.[2]

NOACs selectively inhibit only 1 factor of the coagulation cascade. In particular dabigatran (Pradaxa) is a direct thrombin inhibitor while rivaroxaban (Xarelto), apixaban (Eliquis) and edoxaban (Lixiana) are all Xa factor inhibitors.[2]

They have major pharmacologic advantages over warfarin, including rapid onset/offset of action, no relevant interactions with food and drugs, predictable pharmacokinetics and the possibility to avoid regular coagulation monitoring.[1]

However, the most common complications with NOACs compared to warfarin are gastrointestinal (GI) bleeding and the possible increase of their half-life due to aging and/or the reduction of the renal filtrate.[4,5]

NOACs are renally excreted to varying degrees, so the inter-individual variability in renal function, along with a renal failure status can lead to a different level of bleeding risk.[6,7]

For this reason, recently specific antidotes were developed, in order to bind the circulating NOACs stopping the

[1]IRCCS Ospedale Sacro Cuore Don Calabria, Negrar di Valpolicella, Italy
[2]University of Padova, Padova, Italy
[3]University of Modena and Reggio Emilia, Modena, Italy

*These authors contributed equally to this work.

Corresponding Author:
Roberto Tessari, Hospital Pharmacy, IRCCS Ospedale Sacro Cuore Don Calabria, Via don A. Sempreboni, 5, Negrar di Valpolicella (Verona) 37024, Italy.
Email: roberto.tessari@sacrocuore.it

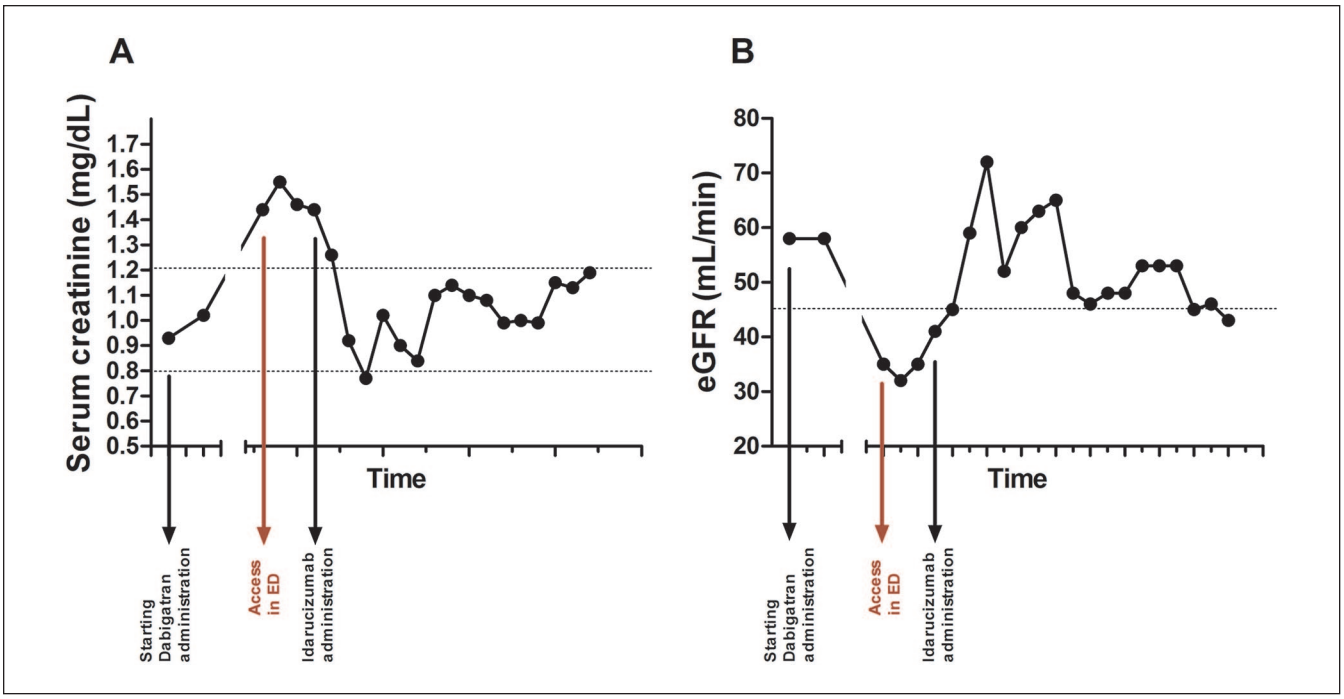

Figure 1. Renal function trends, respectively serum creatinine expressed as mg/dL (sCR, panel A) and estimated glomerular filtration rate expressed as mL/min (eGFR, panel B) during hospitalization.

anticoagulant effect. Idarucizumab (Praxbind) works as dabigatran antagonist and is the first antidote that obtained marketing authorization in Italy. Adexanet alfa (Ondexxya) is the new available antidote for rivaroxaban, edoxaban, and apixaban.[8]

Interestly, in recent years several case-reports put the light on NOAC induced-nephropathy[9-17]: according to them, it seems that NOACs can cause an acute kidney injury (AKI) with a histological damage similar to the 1 evoked by warfarin, despite their difference in pharmacodynamics.[7,18]

All the adverse reactions analyzed and cited in previous works, happened within 6 weeks after starting NOACs. Otherwise, in this report, we present for the first time a chronic delayed adverse reaction (regularly reported to Authorities) associated with the use of dabigatran, characterized by concomitant gastrointestinal bleeding and nephropathy.

Case Description

An 82-year-old Caucasian woman affected by non-valvular atrial fibrillation with a history of ischemic stroke, started dabigatran (Pradaxa Boehringer) 110 mg twice a day in February 2016 as prescribed by the neurologist. Her medical history included non-valvular atrial fibrillation, Type II diabetes, arterial hypertension, moderate obesity (class II), severe depressive syndrome, rheumatoid arthritis, serious spine arthrosis, hypothyroidism, insomnia and gout.

She was on sertraline, zolpidem, quetiapine, levothyroxine, furosemide, allopurinol, and dabigatran (Pradaxa Boehringer, prescribed to prevent the thromboembolic risk due to atrial fibrillation).

Before starting the therapy, hemoglobin, and renal function were in range for age and sex: hemoglobin (Hgb) 13.30 g/dL, urea 49.06 mg/dL, serum creatinine (sCR) 0.93 mg/dL, and estimated glomerular filtration rate (eGFR) 58 mL/min (Figure 1, panel A and B). In November 2016, after 9 months therapy, the laboratory tests were still in range.

The patient took only the first NOAC package directly from the hospital pharmacy and continued the treatment without any laboratory control for 27 months, taking the drug directly from territorial pharmacies, which cannot verify the therapeutic plan, using repeated prescriptions redacted by the general practitioner.

On 7th May 2018 (27 months after starting dabigatran), the patient arrived at the emergency room at 6.47 am, reporting nocturnal rectorrhagia with abdominal pain and an episode of atrial fibrillation developed during the transport to the hospital. The clinicians reported: pallor, hypotension, tachyarrhythmia, normal abdominal examination and widespread pain on deep and superficial palpation. The rectal exploration revealed an empty ampoule with red blood on the wall.

Although the last dose was taken over 12 hours earlier, 110 mg at 7.00 pm the day before (6th May 2018), the laboratory tests revealed anemia (Hgb 9.7 g/dL) and severe renal failure with urea level of 94.38 mg/dL, sCR 1.44 mg/dL, eGFR 35 mL/min (see Figure 1, panel A and B), hematuria and a dabigatran blood value of 355.35 ng/mL (Table 1).

Table 1. Variations of Blood Dabigatran Concentration After Last Administration.

Dabigatran's blood concentration			
Day	Time since last drug administration	Blood concentration (ng/mL)	Notes
1 (07/05/18)	~12 h	355.35	—
	~23 h	261.69	22% reduction
2 (08/05/18)	~36 h	156.98	40% reduction
	~39 h	0	3 h after antidote administration

At 11.25 am, concentrated red blood cells (4 units) and plasma (3 units) were administered and the patient was clinically stabilized with a Hgb value of 12.3 g/dL with no evidence of active bleeding but with persistent severe renal failure (urea 97.88 mg/dL, sCR 1.55 mg/dL, eGFR 32 mL/min).

Rectal sigmoidoscopy and gastroscopy with sedation were performed, without finding a source of bleeding but only the presence of diverticula.

At 12.50 pm, the patient was moved to the intensive care unit. At 2.40 pm, in spite of vital and hematological parameters remaining apparently stable without signs of bleeding, the anesthesiologist decided to repeat laboratory tests with dabigatran blood concentration to monitor its variations over time. Nephropathy was still present (urea 99.51 mg/dL, sCR 1.46 mg/dL and eGFR 34 mL/min; Figure 1, panel A and B), hemoglobin showed a slight reduction to 10 g/dL and dabigatran blood value started do decrease (261,69 ng/mL; Table 1). Consequently balanced electrolyte solution was administered.

Between 5 pm and 6.45 pm another new sudden massive intestinal hemorrhage occurred. Anesthesiologist estimated a loss of about 1.1 kg of blood. The patient was urgently moved to a deep endoscopic evaluation (blind and ileal loop were also explored) but the source of bleeding was not detected, although the intestinal wall was covered by red blood and numerous diverticula were identified. Concentrated red blood cells (2 units) and plasma (3 units) were administered again.

At 10.20 am on 8th May 2018, another hemorrhage happened (about 600 g of blood) and so concentrated red blood cells (2 units) and plasma (4 units) were administered.

At 11 am laboratory tests confirmed the nephropathy (urea 99.36 mg/dL, sCR 1.44 mg/dL and eGFR 35 mL/min). Dabigatran blood concentration was still high (156.98 ng/dl, about 36 h after the last drug intake; Table 1) although no drugs that affect coagulation were administrated and the patient's partial thromboplastin time (aPTT) and Prothrombin time (PT) were respectively 1.88 and 1.5 seconds.

For this reason and considering the last recurrent bleeding episodes, at 13.30 pm on 8th May 2018 the hematology service recommended administering a single dose of 5 g I.V. idarucizumab (dabigatran antidote).

Three hours after idarucizumab administration, dabigatran blood concentration was 0 ng/dL (Table 1), aPTT and PT were respectively 0.94 and 1.09 seconds, sCR 1.26 mg/dL no hematuria was detected. After the administration of the antidote, the patient did not bleed anymore and she moved to general internal medicine where she was monitored.

On 9th May 2018, patient started treatment with calciparine 5000 UI twice a day.

An angio-CT scan without contrast medium was performed and it showed a pattern of colon diverticulosis without signs of "in progress" diverticulitis.

On 11th May, sCR, eGFR, and urea returned within the normal ranges for age and sex. About 3 weeks later, the patient left the hospital with a prescription of enoxaparin 4000 UI twice a day until further cardiological evaluations.

Discussion

Nowadays NOACs represent an opportunity to reduce thromboembolic events and, compared to warfarin, they reduce the risk of fatal bleeding, and increase compliance thanks to their fixed daily doses without any particular dietary restrictions and without International Normalized Ratio (for blood clotting time) (INR) constant monitoring.[19,20]

However, we cannot forget factors that may interfere with the metabolism of NOACs, such as: kidney dysfunction (all NOACs have renal excretion, in particular, dabigatran $>80\%$);[2] liver dysfunction, concomitant medications used to treat atrial fibrillation that could alter NOAC concentration because of interference with CYP3A4 (ie, prednisone, SSRI)[21] or P-glycoprotein (ie, verapamil and amiodarone)[2,22]; concomitant medications used to treat atrial fibrillation that could increase the bleeding risk (ie, acetylsalicylic acid, clopidogrel, ibuprofen, diclofenac).[7,21]

These are the main reasons why renal function of patients who use dabigatran should be monitored. In fact, renal function impairment as well as interactions with other therapies could lead to a prolonged half-life of dabigatran, with a consequent increased risk of bleeding.

The present case-report shows a chronic adverse reaction characterized by concomitant gastrointestinal bleeding and severe renal failure (Table 1 and Figure 1) discovered 27 months after the first dabigatran administration.

The Hospital Pharmacy investigated patient's pharmacological prescription history: the dabigatran therapy, 110 mg twice a day, was prescribed by the neurologist in February

2016 but only the first package was delivered directly from the hospital pharmacy. Subsequently, the patient never returned to the hospital either for a check-up or to take therapy. She continued the treatment without any laboratory control for 27 months, taking the drug directly from territorial pharmacies, which didn't verify the therapeutic plan, relying on repeated prescriptions redacted by the general practitioner.

This case report underlines the importance of monitoring patient compliance and adherence to the therapeutic plan and the need to perform periodic laboratory tests when assuming dabigatran. General practitioner supervision is very important, especially during this pandemic period and in particular since AIFA has definitively adopted the "Note 97."

Indeed, since October 2020, due to the pandemic emergency, AIFA definitively adopted the "Note 97" relating to the prescription of new oral anticoagulants for patients with NVAF. Therefore, medical specialists and general practitioners can continue prescribing NOACs and AVK in patients with NVAF according to the procedures set out in the before mentioned "Note 97." The paper prescription form, which replaces the AIFA Web Therapeutic Plan, is computerized since 1st December 2020 and, therefore, monitoring through the aforementioned "Therapeutic Plan" is no longer available.[23]

In this case, there are many factors that lead us to correlate this acute event with a dabigatran adverse reaction, such as: a normal renal functionality before starting dabigatran administration (February 2016), compared with renal failure at the time of hospital admission, the gastrointestinal bleeding, and the lack of patient's periodic follow-up.

The initial hypothesis was also evaluated unambiguously as "probable" according to the Naranjo algorithm (an objective assessment algorithm),[24] used and scored for both nephropathy and gastrointestinal bleeding. This test, with a value of 7 for both the effects, confirmed the probable causality of the drug-induced effect. Moreover, the diagnosis of anticoagulant-related nephropathy is highly likely, despite the INR of the patient was 1.73, because of the presence of hematuria together with unexplained severe rise of sCR and reduction of eGFR in absence of a clear acute renal injury etiology. Unfortunately, renal biopsy was avoided due to concomitantly gastrointestinal bleeding.

Recently, different evidences showed apixaban,[9,10] rivaroxaban,[11] and mostly dabigatran[12-17] induced-nephropathy. This adverse effect with dabigatran was also demonstrated in preclinical studies, in rat model.[25]

The real mechanism of dabigatran-evoked AKI is not yet clear but there are mainly 2 proposed mechanisms which could explain it: the first one is characterized by obstruction of renal tubules by erythrocytes[14] while the second one is due to the diminished thrombin activity that induces glomerular filtration barrier abnormalities.[18]

Considering the absence of renal parameters close to the acute event, we cannot completely exclude that the nephropathy was due to other concomitant factors. Moreover, renal failure could justify the high blood dabigatran concentration even if the patient had taken the last dose many hours before bleeding. In addition, she was treated with sertraline (SSRI) for depression and this association could increase dabigatran blood concentration and so the bleeding risk.[21]

Finally, in this case-report, the patient was treated with idarucizumab that reversed the hemorrage and the nephropathy evoked by dabigatran (see Table 1 and Figure 1).

The right dabigatran blood dosage to use dabigatran antidote is still unclear and the role of time from the last drug administration is not yet well determined.

As previously highlighted in other case-reports, idarucizumab administration in patients suffering from life threatening bleeding with renal injury, improved the sCR and urine output level (Table 1 and Figure 1).[15]

Conclusion

Some drug categories require close clinical and pharmacological monitoring; NOACs, as EMA and AIFA said, are part of these drugs. Their safety profile is better than AVK ones, but we should not consider them as "totally safe." The risk of bleeding and renal failure is present, especially in patients with comorbidities. This report demonstrates that renal function needs to be monitored in patients taking NOACs, to avoid drug accumulation and subsequent uncontrolled bleeding.[26]

In our case, a close renal and dabigatran monitoring over time would have avoided its accumulation and perhaps it would have prevented bleeding.

We also put in evidence the importance of respecting the therapeutic plan along with the supervision of the Hospital Pharmacy. In fact, in our case, the therapy with dabigatran was prescribed for the first time by neurologist in February 2016 but only the first package was delivered directly from the hospital pharmacy. The patient continued the treatment without any laboratory control for 27 months, taking the drug directly from territorial pharmacies, which didn't verify the therapeutic plan, using repeated prescriptions redacted by the general practitioner. This lack of supervision certainly contributed to the onset of the adverse reaction reported.

We conclude that it is important that general practitioners strictly monitor patient parameters (renal function, presence of dehydration, weight loss) and prescriptions during NOAC therapy, respecting the paper prescription form.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Roberto Tessari https://orcid.org/0000-0001-5933-8063

References

1. Chan N, Sager PT, Lawrence J, et al. Is there a role for pharmacokinetic/pharmacodynamic-guided dosing for novel oral anticoagulants? *Am. Heart J*. 2018;199:59-67. doi:10.1016/j.ahj.2017.10.002
2. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace*. 2018;20(8):1231-1242. doi:10.1093/europace/euy054
3. Chao TF, Nedeljkovic MA, Lip GYH, Potpara TS. Stroke prevention in atrial fibrillation: comparison of recent international guidelines. *Eur Heart J*. Dec 2020;22(suppl O):O53-O60. doi:10.1093/eurheartj/suaa180
4. Brodsky SV. Anticoagulants and acute kidney injury: clinical and pathology considerations. *Kidney Res Clin Pract*. 2014;33(4):174-180. doi:10.1016/j.krcp.2014.11.001
5. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol*. 2017;83(9):2096-2106. doi:10.1111/bcp.13299
6. Kitchen S, Gray E, Mackie I, Baglin T, Makris M. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: guidance from the British Committee for Standards in Haematology. *Br J Haematol*. 2014;166(6):830-841. doi:10.1111/bjh.12975
7. Dempfle CE. Direct oral anticoagulants–pharmacology, drug interactions, and side effects. *Semin Hematol*. 2014;51(2):89-97. doi:10.1053/j.seminhematol.2014.03.005
8. Ojetti V, Saviano A, Brigida M, Saviano L, Migneco A, Franceschi F. A review on the use of reversal agents of direct oral anticogulant drugs in case of gastrointestinal bleeding. *Rev Recent Clin Trials*. 2020;15(4):309-320. doi:10.2174/1574887115666200624193938
9. Abdulhadi B, Mulki R, Goyal A, Rangaswami J. Novel oral anticoagulant and kidney injury: apixaban-related acute interstitial nephritis. *BMJ Case Rep*. 2017;2017:1-2. doi:10.1136/bcr-2017-221641
10. DiMaria C, Hanna W, Murone J, Reichart J. Direct oral anticoagulant and AKI: apixaban-induced acute interstitial nephritis. *BMJ Case Rep*. 2019;12(6):e230371. doi:10.1136/bcr-2019-230371
11. Monahan RC, Suttorp MM, Gabreëls B. A case of rivaroxaban-associated acute tubulointerstitial nephritis. *Neth J Med*. 2017;75(4):169-171.
12. Basetty P, Keith B. A cautionary tale: dabigatran toxicity associated with allergic interstitial nephritis. *Am J Kidney Dis*. 2013;61(4):B24.
13. Shafi ST, Negrete H, Roy P, Julius CJ, Sarac E. A case of dabigatran-associated acute renal failure. *WMJ*. 2013;112(4):173-175; quiz 176.
14. Escoli R, Santos P, Andrade S, Carvalho F. Dabigatran-related nephropathy in a patient with undiagnosed IgA nephropathy. *Case Rep Nephrol*. 2015;2015:298261. doi:10.1155/2015/298261
15. Awesat J, Sagy I, Haviv YS, et al. Dabigatran-induced nephropathy and its successful treatment with Idarucizumab—case report and literature review. *Thromb Res*. 2018;169:120-122. doi:10.1016/j.thromres.2018.07.019
16. Patel S, Hossain MA, Ajam F, et al. Dabigatran-induced acute interstitial nephritis: an important complication of newer oral anticoagulation agents. *J Clin Med Res*. 2018;10(10):791-794. doi:10.14740/jocmr3569w
17. Zeni L, Manenti C, Fisogni S, et al. Acute kidney injury due to anticoagulant-related nephropathy : a suggestion for therapy. *Case Rep Nephrol*. 2020;2020:8952670. doi:10.1155/2020/8952670
18. Narasimha Krishna V, Warnock DG, Saxena N, Rizk DV. Oral anticoagulants and risk of nephropathy. *Drug Saf*. 2015;38(6):527-533. doi:10.1007/s40264-015-0290-z
19. Lip GY, Mitchell SA, Liu X, et al. Relative efficacy and safety of non-Vitamin K oral anticoagulants for non-valvular atrial fibrillation: network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups. *Int J Cardiol*. 2016;204:88-94. doi:10.1016/j.ijcard.2015.11.084
20. Almutairi AR, Zhou L, Gellad WF, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants for atrial fibrillation and venous thromboembolism: a systematic review and meta-analyses. *Clin Ther*. 2017;39(7):1456-1478 e1436. doi:10.1016/j.clinthera.2017.05.358
21. Lee MT, Park KY, Kim MS, You SH, Kang YJ, Jung SY. Concomitant use of NSAIDs or SSRIs with NOACs requires monitoring for bleeding. *Yonsei Med J*. 2020;61(9):741-749. doi:10.3349/ymj.2020.61.9.741
22. Sandhu RK, Islam S, Dover D, et al. Real world data on the concurrent use of P-glycoprotein or cytochrome 3A4 drugs and non-vitamin K antagonist oral anticoagulants in non-valvular atrial fibrillation. *Eur Heart J Qual Care Clin Outcomes*. Published online January 22, 2021. doi:10.1093/ehjqcco/qcab002
23. Agenzia Italiana del Farmaco (AIFA). 2020. Accessed February 15, 2021. https://www.aifa.gov.it/documents/20142/1180832/Determina_DG-1034-2020_Adozione_definitiva_Nota-97.pdf
24. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. doi:10.1038/clpt.1981.154
25. Ryan M, Ware K, Qamri Z, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. *Nephrol Dial Transplant*. 2014;29(12):2228-2234. doi:10.1093/ndt/gft380
26. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. *J Thromb Haemost*. 2016;14(3):461-467. doi:10.1111/jth.13229