Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Thrombotic thrombocytopenic purpura (TTP) response following COVID-19 infection: Implications for the ADAMTS-13–von Willebrand factor axis

One of the most prominent hematologic effects of infection with coronavirus disease 2019 (COVID-19) is increased thrombotic risk.[1,2] The mechanisms of this hypercoagulable state, which defies even therapeutic anticoagulation, are under intense investigation. Autopsy studies have confirmed thrombotic disease not only at the macrovascular scale (pulmonary emboli, venous thromboses) but also with microthrombi in alveolar capillaries and severe endothelial injury.[3,4] Several studies have reported elevated levels of von Willebrand factor (VWF) activity, VWF antigen, and factor VIII levels in COVID-19, and incremental increases are reported with severity of disease.[5-7]

Most recently, Mancini et al. have added to this data by evaluating the VWF–A Disintegrin And Metalloprotease with ThromboSpondin 1-domain (ADAMTS-13) axis.[8] This cross-sectional analysis of 50 COVID-19 patients included patients on high-flow nasal cannula (low intensity, n = 14), non-invasive positive pressure (intermediate, n = 17), and invasive ventilation (high, n = 19) compared to historical controls. They found median VWF levels markedly elevated and increasing with intensity of care, and there was a relative increase of intermediate and low molecular weight VWF multimers in severe cases. ADAMTS-13 activity was mild to moderately reduced, and this inversely correlated with severity. The authors concluded that an elevated VWF antigen (VWF:Ag) to ADAMTS-13 activity ratio was strongly associated with disease severity. They hypothesize that these findings may be explained by massive release of VWF multimers by the activated endothelium with subsequent increased VWF proteolysis by ADAMTS-13, leading to consumptive reduction in its activity. In this article we wish to discuss these findings as related to a case of thrombotic thrombocytopenic purpura (TTP) with severe COVID-19 infection.

A 69-year-old African American female with a history of immune TTP presented in early 2020 with thrombocytopenia. She was initially diagnosed in 2003 and had a severe phenotype with multiple relapses treated by plasmapheresis and prednisone. Testing by next generation sequencing confirmed there were no genetic variants associated with thrombotic microangiopathy (TMA) syndromes. On diagnosis she was treated with rituximab but developed intolerance at second infusion, leading to trials of alternative immunosuppression including vincristine, cyclosporine, and cyclophosphamide, which had some effect but were also intolerable. In 2013 she developed pulmonary embolism and started anticoagulation using fondaparinux with good response, but due to patient preference she attempted to come off after 6 months. Shortly after she had a cerebral infarct in the left temporoparietal lobe and resumed fondaparinux. Four years later she again tried stopping fondaparinux but had an acute left occipital infarct and resumed anticoagulation. In 2018 she decided to continue with surveillance (no immunosuppression) and anticoagulation using fondaparinux 7.5 mg daily.

The patient had no symptoms suggestive of COVID-19, with negative testing, and was admitted for relapsed TTP (Figure 1A - Relapse 1). She responded to four sessions of plasmapheresis and prednisone, which was continued on discharge. In clinic she continued to decline other immunosuppression and tapered prednisone over a month. Five weeks later she presented with relapsed TTP again and was admitted, treated with seven sessions of plasmapheresis and steroids (Figure 1A - Relapse 2). Given relapsing disease, an inpatient trial of rituximab was recommended, but the patient developed hypotension and dyspnea during the infusion and declined further infusions. She was discharged but 3 weeks later was readmitted (Figure 1A - Relapse 3). ADAMTS-13 activity was 2.1% at this relapse; she was treated with plasmapheresis and steroids, after 3 days of steroids refused any more and asked to be discharged with outpatient surveillance and plasmapheresis as needed.

Unfortunately, 2 days after, she returned with acute hypoxic respiratory failure and was found to be COVID-19 positive on nasopharyngeal polymerase chain reaction (PCR; SARS-CoV-2 RT-PCR Assay, Roche 6800 platform). She received high flow oxygen by nasal cannula, remdesivir for 5 days, and dexamethasone 6 mg daily for 10 days and was continued on fondaparinux 7.5 mg daily. Surprisingly her platelet count increased without further immunosuppression or plasmapheresis (Figure 1A) and maintained >150 × 10^9/L several weeks out from last treatment. ADAMTS-13 activity was 2.9% at COVID-19 diagnosis. Four weeks later ADAMTS-13 activity was 16% with an inhibitor titer of 1.7 (<0.4). At this time VWF:Ag and activity (RCo:F) were checked and both were unreadably elevated (>597%); factor VIII activity was 414% (56–140). The patient's respiratory status did not improve; PCR for COVID-19 was persistently

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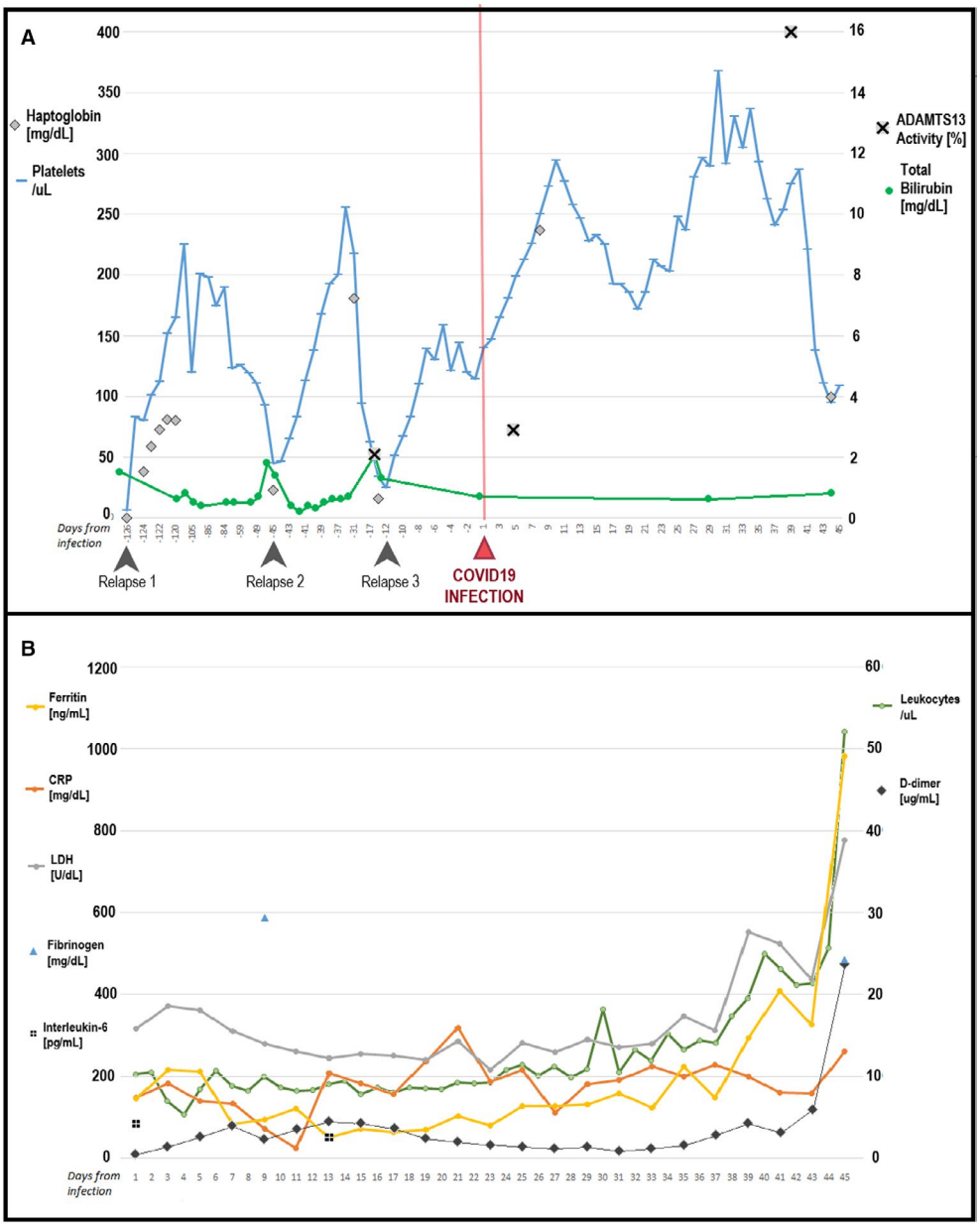

FIGURE 1 A, Response in platelets and hemolytic indices leading up to and following infection with COVID-19. B, Trends in inflammatory markers after infection

positive and inflammatory markers worsened over time (Figure 1B). She was intubated 2 weeks after diagnosis. At the same time she was found to have deep venous thrombosis at the site of a left femoral central venous catheter. The catheter was removed and anticoagulation switched to heparin. After 5 weeks the patient had hypoxia refractory to all management and severe multi-organ dysfunction syndrome; this continued for 1 more week and she died 6 weeks following COVID-19 infection.

It has been suggested that TTP, cerebral malaria, and severe COVID-19 all share similar TMA pathophysiology.[9] Recent research suggests that the VWF–ADAMTS-13 axis has a central role in COVID-19 vasculopathy. These studies seem consistent but there are still unexplained in vivo hematologic aspects of severe COVID-19. Highlighted by our recent case is the question of why despite having markedly increased VWF:Ag to ADAMTS-13 ratio there was improvement in platelet count and no evident hemolysis or TMA progression. Interestingly, looking at the study by Mancini et al., there was no thrombocytopenia, and in fact patients at intermediate and high intensity care (severe COVID-19) who had reduced ADAMTS-13 and elevated VWF had increasingly elevated platelet counts.[8] These observations combined with the case above lead us to think that several pathways in severe COVID-19 interact with the VWF–ADAMTS-13 axis and modify the classical TTP/TMA response. These interactions mitigate some effects that would lead to platelet consumption and result in fulminant TMA, but still drive a hypercoagulable state. It would be interesting to see reports of cases from other centers and as iterated by all, ongoing research to define the mechanisms of COVID-19 hypercoagulability need to be supported.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

SM, RX, and AR were involved in direct care of the patient. All authors conceptualized the idea for the study and contributed to data collection. SM wrote the manuscript. RX and AR contributed to and edited the manuscript. All authors approved the final version.

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REFERENCES

1. Lodigiani C, Iapichino G, Carenzo L, et al. Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9-14.
2. Middeldorp S, Coppens M, van Happs TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18:1995-2002.
3. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020;77(2):198-209.
4. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383:120.
5. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol*. 2020;7(8):e575-e582.
6. Peyvandi F, Artoni A, Novembrino C, et al. Hemostatic alterations in COVID-19. *Haematologica*. 2020. http://doi.org/10.3324/haematol.2020.262634. Epub ahead of print. PMID: 32855280.
7. Rauch A, Labreuche J, Lassalle F, et al. Coagulation biomarkers are independent predictors of increased oxygen requirements in COVID-19. *J Thromb Haemost*. 2020;18(11):2942-2953.
8. Mancini I, Baronciani L, Artoni A, et al. The ADAMTS13-von Willebrand factor axis in COVID-19 patients. *Journal of Thrombosis and Haemostasis*. 2020. http://doi.org/10.1111/jth.15191. Epub ahead of print. PMID: 33230904.
9. O'Sullivan JM, Gonagle DM, Ward SE, Preston RJS, O'Donnell JS. Endothelial cells orchestrate COVID-19 coagulopathy. *Lancet Haematol*. 2020;7(8):e553-e555.

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Thrombotic thrombocytopenic purpura as the initial presentation of COVID-19

We read the article "The ADAMTS13-von Willebrand factor axis in COVID-19 patients"[1] with interest and hereby present a relevant clinical case.

Thromboembolism predominates coronavirus disease 2019 (COVID-19)'s coagulopathy, but there is a paucity of reported arterial events and microangiopathy.[2] Acute infections are associated with thrombotic thrombocytopenic purpura (TTP), caused by an autoantibody that inhibits the ADAMTS-13 metalloprotease, responsible for cleaving von Willebrand factor (VWF).[3] We describe the case of an asymptomatic patient positive for severe acute respiratory coronavirus 2 (SARS-CoV-2) presenting with TTP.

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A 70-year-old man known for peripheral artery disease and dyslipidemia presented to the hospital for confusion. Home medication were aspirin and a statin. He had tested positive for COVID-19 19 days prior, based on nasopharyngeal reverse transcription polymerase chain reaction that had detected SARS-CoV-2. He was completely asymptomatic for COVID-19 upon presentation to the emergency room, where he thereafter had a prolonged seizure requiring sedation and intubation. Physical examination revealed no purpura or other relevant findings. A computed tomography of the head and a chest radiograph were normal. The initial complete blood count showed a platelet count of 18 × 10^9/L (normal value: 130-400 × 10^9/l) and hemoglobin of 60 g/l (normal value: 130-170 g/l). Features of hemolysis were found (high total bilirubin, high lactate dehydrogenase, and low haptoglobin) with schistocytes on the blood smear. Renal function and coagulation parameters were

TABLE 1 Evolution of laboratory findings from presentation until the end of plasma exchange therapy

	Day 1	Day 2	Day 3	Day 4	Day 7	Day 9
Plasma exchange	+	+	+	+	+	–
Hemoglobin (g/l) (130-170)	60	74	73	75	81	79
Platelets ($\times 10^9$/l) (130-400)	18	49	115	200	367	405
Leukocytes ($\times 10^9$/l) (4-10)	8	10.5	13.7	10.6	7.7	6.2
Reticulocytes ($\times 10^9$/l) (20-84)	—	—	—	254.5	207.9	169.6
Schistocytes on blood smear	+	+	+	—	—	—
Creatinine (µmol/l) (53-112)	106	102	91	77	76	67
LDH (U/l) (104-205)	1422	417	—	295	232	183
Total bilirubin (µmol/l) (7-23)	38	23	—	14	—	—
Haptoglobin (g/l) (0.46-1.46)	<0.3	0.48	—	0.79	0.67	0.69
Fibrinogen (g/l) (2-4.5)	5.35	2.3	—	—	—	—
ADAMTS-13 (%) (56-133)	<10	—	—	—	—	43
ADAMTS-13 IgG antibody	+ Titer 1/2	—	—	—	—	—
INR (0.8-1.15)	1.07	1.05	1	1	0.93	0.98
PTT (22-31)	24	23	22	22	22	23
SARS-CoV-2 (negative)	+	—	—	—	—	—

Abbreviations: ADAMTS-13, disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time.

normal. He later mentioned having had dark urine 5 days before hospitalization (Table 1).

A microangiopathic episode was confirmed and TTP was suspected. Anti-ADAMTS-13 immunoglobulin G antibody was weakly positive (titer 1/2) and ADAMTS-13 activity was low (<10%). Treatment was initiated with transfusion of 2 U of plasma before transfer to the apheresis center. Methylprednisolone was given at a dose of 1 mg/kg daily for 2 days followed by oral prednisone at 50 mg daily. Daily plasma exchange was initiated (1.5 volume exchange; Spectra Optia, TERUMOBCT) with plasma replacement. Clinically, the patient recovered rapidly without neurologic sequelae and was extubated after 24 h. Platelet count improved gradually and then rapidly after the second plasma exchange. Treatment was stopped after the seventh plasma exchange as platelet count and lactate dehydrogenase had normalized for more than 48 h. ADAMTS-13 activity at discharge normalized (43%). A diagnosis of COVID-19–induced TTP was made because no other causes could be associated with the episode.

Previous cases of COVID-19–associated TTP mostly included patients with other classic COVID-19 symptoms.[4,5] To our knowledge, this is the first case of an initial presentation of a COVID-19 infection with a severe microangiopathic episode and neurological symptoms in an otherwise asymptomatic patient. Interestingly, this severe microangiopathic activity was present despite a low titer of anti-ADAMTS-13 immunoglobulin G antibody. Studies have shown that SARS-COV-2 causes endothelial damage that could release higher amounts of VWF independently of the ADAMTS-13 activity. ADAMTS-13 activity also tends to be decreased in inflammatory states.[1,6,7] This could possibly explain the severity of the initial presentation, even with low antibody activity, as well as the fast recovery.[2,7] Full mechanisms remain incompletely understood.

In conclusion, this is a unique case of severe COVID-19–induced TTP with microangiopathy and cerebral arterial ischemic events. Pathophysiology probably implies a combination of immune dysregulation and inflammation.[1,2,8–10]

KEYWORDS
inflammation, microangiopathy, SARS-COV-2, thrombopenia, thrombotic thrombocytopenic purpura

CONFLICT OF INTEREST

The authors have no disclosures to declare.

AUTHOR CONTRIBUTION

Marie-Claude Beaulieu and Danny Sebastien Mettelus contributed to the study design, data collection, literature review, and case report redaction. Michèle Mahone and Benjamin Rioux-Massé also designed the study. They revised all intellectual content and gave their approval for final version to be submitted.

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REFERENCES

1. Mancini I, Baronciani L, Artoni A, et al. The ADAMTS13-von Willebrand factor axis in COVID-19 patients. *J Thromb Haemost*. 2020. https://doi.org/10.1111/jth.15191
2. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. *Crit Care*. 2020;24:360.
3. Saha M, McDaniel JK, Zheng XL. Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. *J Thromb Haemost*. 2017;15:1889-1900.
4. Capecchi M, Mocellin C, Abbruzzese C, Mancini I, Prati D, Peyvandi F. Dramatic presentation of acquired TTP associated with COVID-19. *Haematologica*. 2020;105(10):262345.
5. Hindilerden F, Yonal-Hindilerden I, Akar E, Kart-Yasar K. Covid-19 associated autoimmune thrombotic thrombocytopenic purpura: report of a case. *Thromb Res*. 2020;195:136-138.
6. Bockmeyer CL, Claus RA, Budde U, et al. Inflammation-associated ADAMTS13 deficiency promotes formation of ultra-large von Willebrand factor. *Haematologica*. 2008;93:137-140.
7. Katneni UK, Alexaki A, Hunt RC, et al. Coagulopathy and thrombosis as a result of severe COVID-19 infection: a microvascular focus. *Thromb Haemost*. 2020;120(12):1668-1679.
8. Colling ME, Kanthi Y. COVID-19-associated coagulopathy: an exploration of mechanisms. *Vasc Med*. 2020;25:471-478.
9. Song WC, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. *J Clin Invest*. 2020;130:3950-3953.
10. Albiol N, Awol R, Martino R. Autoimmune thrombotic thrombocytopenic purpura (TTP) associated with COVID-19. *Ann Hematol*. 2020;99:1673-1674.

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Comment on the article by Toorop et al.: "The relationship between DOAC levels and clinical outcomes: The measures tell the tale"

Dear Editor,

We read with great interest in your journal the paper by Toorop et al.,[1] who argue that "it may be worthwhile to study the relationship between direct oral anticoagulant (DOAC) concentrations and patient-important outcomes." Although we agree that research on DOAC plasma level variability according to clinical factors and its association with relevant outcomes could be informative, we would like to put the proposal by Toorop et al. in a more appropriate clinical perspective.

According to the article, this research topic would be of interest because "the overall major bleeding (MB) risk for DOAC use in observational studies remains 1% to 3% per year because of a large proportion of major extracranial bleeds."[1] This figure might look not so large compared to the rate of MB in the general population and in older subjects, which represents the majority of people receiving DOAC therapy, at least for stroke prevention in atrial fibrillation (AF). In a large study including 359,166 people without cardiovascular

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(CV) disease and not receiving antithrombotic therapies, the reported annual rate of MBs in subjects aged 70-79 years was 2.3% and 1.6% in men and women, respectively.[2] Therefore, when put in clinical context, the MB incidences observed in DOAC experimental and observational studies are quite reassuring.

However, the issue is whether the proposed "target spot" strategy might be the best research avenue to pursue to further reduce MBs in DOAC-treated patients. Toorop et al[1] present a theoretical model (Figure 1 in their article) in which adverse events (ischemic or hemorrhagic) appear to be the direct result of the net anticoagulant effect of DOACs, implying a relatively simple relationship between DOAC plasma concentrations and outcomes. However, pharmacologists and clinicians alike know that such a balance is highly variable both within and between subjects (intra- and inter-patient variability, respectively). This is due to the action of several intrinsic and extrinsic factors that lead to rapidly evolving physio-pathological conditions, thus making the "net" anticoagulant effect practically unmeasurable. Moreover, the factors that can affect anticoagulation intensity are also independent risk factors for thromboembolic and hemorrhagic events. In fact, there are several variables other than anticoagulation intensity that prominently contribute to bleeding events in older AF patients receiving DOACs. In a Danish nationwide cohort study on 272,315 subjects with AF (median age 75 years, 47% women), 31,459 MBs occurred over a total follow-up period of 1,373,131 patient-years, with an incidence of 2.3/100 patient-years.[3] Compared to patients not receiving oral anticoagulant therapy (OAT), MB risk among those receiving either a vitamin K antagonist (VKA) or a DOAC increased only mildly (1.4 vs. 2.3 vs. 2.2 per 100 patient-years, respectively), whereas it raised dramatically with increasing number of antithrombotic drugs prescribed (up to 10.4/100 patient-years for VKA triple therapy).[3] Therefore, optimizing antithrombotic therapy and drug interactions, as well as managing modifiable risk factors for MB, represent well-recognized clinical priorities to reduce MBs during OAT. Moreover, hemorrhages occur frequently in patients with underlying pathologies predisposing to bleeding, such as colonic diverticula, angiodysplasias, peptic ulcer disease, arteriovenous malformations, inflammatory bowel disease, hemorrhoids, and malignancy. In this case, the proposed theoretical model cannot reliably identify a "target spot" to avoid a MB that primarily depends on the characteristics of the lesion itself.[4,5] Therefore, prevention of MB in DOAC-treated patients should primarily rely on a careful medical history focused on previous bleeding events and identification of risk factors, baseline and periodic evaluation of laboratory tests (hemoglobin, red blood cell number and volume, serum iron and ferritin, urinalysis, and fecal occult blood test), adoption of a risk minimization strategy, and prescription of the most appropriate drug at the correct dose according to the patient's clinical characteristics.[4-6]

In fact, the relationship between anticoagulant activity and the risk of bleeding and ischemic adverse events varies somehow among different DOAC molecules, and in any case is similar to that presented in the authors' figure.[7] Despite the fact that DOACs "have a direct effect on the hemostatic system in a bidirectional manner as has been shown for dabigatran and edoxaban (i.e, too much effect results in bleeding, too little effect in thromboembolism),"[1] in the case of dabigatran a significant treatment-by-age interaction was observed, such that, compared to warfarin, the 150 mg dose was associated with a lower risk of MB in those aged <75 years (relative risk [RR] 0.70, 95% confidence interval [CI] 0.57–0.86) and a trend toward a higher risk in those aged 75 years and older (RR 1.18, 95% CI 0.98–1.42; *p* for interaction <0.001).[4] Even if "preliminary (small-scale) studies suggest a similar bidirectional effect for rivaroxaban and apixaban,"[1] both in the ROCKET AF and in the ARISTOTLE trials, risk of MB was consistently higher among those receiving reduced doses of rivaroxaban and apixaban, respectively.[4] On-label use of reduced doses is not synonymous with low DOAC plasma concentrations; nevertheless, these findings strongly suggest that patients' characteristics (including older age, greater comorbidity burden, chronic kidney disease, previous bleedings, use of non-steroidal anti-inflammatory drugs and antiplatelets) rather than anticoagulant activity are major drivers of clinical events in this population.[4]

Toorop et al. further try to support the existence of a "target spot" of DOAC anticoagulant effect stating that "for VKAs, it is well established that adequate regulation of the international normalized ratio (INR) optimizes the risk-benefit ratio between bleeding and thromboembolic complications."[1] However, this is probably more the case for efficacy than it is for safety. Although it has been clearly demonstrated that VKA efficacy strongly depends on anticoagulation quality measured as time in therapeutic range,[8] several cohort studies have consistently shown that MB events increase with advancing age, most of them occurring in patients with well-conducted therapy, and without signals of an optimal target zone.[9,10]

We concur with the wise conclusions of Toorop et al. that some special populations and specific clinical situations may represent an interesting area of investigation. Unfortunately, the use of plasma concentrations requires consistent proof of relatively low intra-patient DOAC level variability, identification of optimal sampling time, and of one or more clinically relevant concentration cutoffs (if any). Subsequently, tailored dosing according to DOAC concentrations needs to be supported by identification of reliable dose-adjustment protocols and sound evidence that this strategy performs better than present dosing criteria in terms of net clinical benefit, and that could be cost-effective and easily implementable at least in selected patients.[4,7]

In the meantime, the undisputable overall benefit of DOACs might be improved by "measures" of well-recognized clinical utility, including careful management of patients, correction of modifiable bleeding risk factors and optimization of concomitant therapies, evaluation and promotion of therapeutic adherence, on-label dosing, and regular follow-up.

KEYWORDS

anticoagulants, atrial fibrillation, dabigatran, factor xa inhibitors, pharmacology

CONFLICTS OF INTEREST

M.B. reports receiving consulting fees from Bayer, Boehringer, BMS-Pfizer, and Daiichi-Sankyo. E.B. has no relevant conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

M.B. wrote the original draft of the paper, M.B. and E.B. critically revised and approved the final version of the manuscript.

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REFERENCES

1. Toorop MMA, Lijfering WM, Scheres LJJ. The relationship between DOAC levels and clinical outcomes: the measures tell the tale. *J Thromb Haemost*. 2020;18:3163-3168.
2. Selak V, Kerr A, Poppe K, et al. Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. *JAMA*. 2018;319:2507-2520.
3. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation*. 2019;139:775-786.
4. Bo M, Corsini A, Brunetti E, et al. Off-label use of reduced dose direct oral factor Xa inhibitors in subjects with atrial fibrillation: a review of clinical evidence. *Eur Heart J Cardiovasc Pharmacother*. 2020:pvaa103. [Online ahead of print]. https://doi.org/10.1093/ehjcvp/pvaa103.
5. Lanas-Gimeno A, Lanas A. Risk of gastrointestinal bleeding during anticoagulant treatment. *Expert Opin Drug Saf*. 2017;16:673-685.
6. Bo M, Marchionni N. Practical use of direct oral anti coagulants (DOACs) in the older persons with atrial fibrillation. *Eur J Intern Med*. 2020;71:32-38.
7. Eikelboom JW, Quinlan DJ, Hirsh J, Connolly SJ, Weitz JI. Laboratory monitoring of non-vitamin K Antagonist oral anticoagulant use in patients with atrial fibrillation: a review. *JAMA Cardiol*. 2017;2:566-574.
8. Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa T-P. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost*. 2011;106:968-977.
9. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet*. 1996;348:423-428.
10. Poli D, Antonucci E, Testa S, Tosetto A, Ageno W, Palareti G. Italian Federation of anticoagulation clinics. bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for Anticoagulation. *Circulation*. 2011;124:824-829.

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The relationship between DOAC levels and clinical outcomes: The measures tell the tale–Response from original authors Lijfering et al

Brunetti and Bo[1] raised a number of comments to our recently published Forum Article[2] on the potential benefits of measuring anticoagulation levels in patients who use direct oral anticoagulants (DOACs). We would like to respond to these comments. First, Brunetti and Bo argue that "major bleeding incidences observed in DOAC experimental and observational studies are quite reassuring", thereby referring to major bleeding rates (1.6%–2.3% per year) among elderly individuals not receiving antithrombotic therapies.[3] We agree that major bleeding is a multicausal disease and that DOACs are not the only factor that can induce bleeding. Still DOACs have, like all anticoagulants, the side effect of bleeding, as for instance has been shown in placebo-controlled trials in which the risk of major or clinically relevant bleeding is elevated for DOAC use.[4] In a recent trial among elderly Japanese patients who were not appropriate candidates for standard doses of DOAC therapy for atrial fibrillation due to various reasons (impaired kidney function, major

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bleeding history, low body weight, or continuous use of nonsteroidal anti-inflammatory drugs or antiplatelet drugs), patients were randomized to a low dose (15 mg once daily) of edoxaban or placebo.[5] The annualized rate of major bleeding was 3.3% in the low-dose edoxaban group and 1.8% in the placebo group (hazard ratio, 1.87; 95% confidence interval [CI], 0.90–3.89), emphasizing the contribution of even low-dose edoxaban to a substantial increased risk of the annual major bleeding rate.[5] As such, there is room for improvement in decreasing the number of bleeds (and herewith associated mortality, comorbidity, and health-care costs) among patients who are anticoagulated with DOACs. Second, we agree with the authors that a careful medical history and identification and management of risk factors for bleeding are important in the individual patient. In fact, we stress this issue in our Forum Article by arguing that measuring DOAC may be most optimal in patients who are at a priori high risk of bleeding such as patients with impaired kidney function. The presence of such risk factors, however, does not imply the absence of a potential relationship between DOAC plasma concentrations and outcomes. In the cohort study mentioned by Brunetti and Bo,[6] the risk of major bleeding among atrial fibrillation patients receiving no anticoagulation, vitamin K antagonists (VKA), or DOAC increased "only mildly (1.4 vs. 2.3 and 2.2 per 100 patient-years, respectively)." What remains unknown, however, is whether there were differences in DOAC plasma concentrations between patients who had a major bleeding event versus those without. Several studies have shown that there is a dose response between DOAC plasma concentrations and major bleeding events.[7-10] We agree with the authors that a focus on modifiable risk factors is a priority, and dose-adjustments based on DOAC drug levels[11] could potentially be one of those.

Third, Brunetti and Bo mention that "both in the ROCKET-AF and in the ARISTOTLE trial, risk of major bleeding was consistently higher among those receiving reduced doses of rivaroxaban and apixaban, respectively." This is true. The reason for this is that patients who received reduced doses of DOAC in those trials had underlying comorbidity like impaired kidney function and being elderly people (in other words: per the protocol of these trials, these patients received a reduced DOAC dose).[12,13] Patients with impaired kidney function and elderly people have less stable and more unpredictable clearance of DOAC levels.[14,15] This was shown for instance in the RELY trial, in which the magnitude of the effect of dabigatran plasma concentrations on thromboembolism and major bleeding was strongly related to clinical characteristics like older age and impaired kidney function.[7] This does not imply that "these findings strongly suggest that patient's characteristics (including older age, […]) rather than anticoagulant activity are major drivers of clinical events in this population," for the precise reason (as Brunetti and Bo state) that "On-label use of reduced doses is not synonymous of low DOAC plasma concentrations," which is a crucial addition.

Brunetti and Bo furthermore state that "the use of plasma concentrations requires consistent proof of relatively low intra-patient DOAC level variability." Currently, it is not well known whether DOACs have a high or low between- and within-person variability, due to the lack of studies on this issue as we acknowledge in our Forum article.[2] But absence of evidence is not similar to evidence of absence. In a cohort study among atrial fibrillation patients, high between-individual variation but low within-individual variation in DOAC plasma levels was identified.[16] This suggests that DOAC plasma level measurement soon after treatment initiation could give an acceptable impression of future DOAC plasma levels, but as also stressed in our Forum article, more research on this is needed before solid conclusions can be made.

CONFLICTS OF INTEREST

The authors state that they have no conflicts of interests.

AUTHOR CONTRIBUTIONS

Myrthe M. A. Toorop, Willem M. Lijfering, and Luuk J. J. Scheres were the main investigators of the manuscript. Myrthe M. A. Toorop wrote the first draft of the manuscript and Willem M. Lijfering wrote the final version. Myrthe M. A. Toorop, Willem M. Lijfering, and Luuk J. J. Scheres were responsible for review of the manuscript.

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REFERENCES

1. Brunetti E, Bo M. ,Comment on the article by Toorop et al. "The relationship between DOAC levels and clinical outcomes: the measures tell the tale". *J Thromb Haemost*. 2020.
2. Toorop MMA, Lijfering WM, Scheres LJJ. The relationship between DOAC levels and clinical outcomes: the measures tell the tale. *J Thromb Haemost*. 2020;18:3163-3168.
3. Selak V, Kerr A, Poppe K, et al. Annual risk of major bleeding among persons without cardiovascular disease not receiving antiplatelet therapy. *JAMA*. 2018;319:2507-2520.
4. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709-718.
5. Okumura K, Akao M, Yoshida T, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation. *N Engl J Med*. 2020;383:1735-1745.

6. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation*. 2019;139:775-786.
7. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol*. 2014;63:321-328.
8. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *The Lancet*. 2015;385:2288-2295.
9. Testa S, Legnani C, Antonucci E, et al. Coordinator of SR. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost*. 2019;17:1064-1072.
10. Testa S, Paoletti O, Legnani C, et al. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost*. 2018;16:842-848.
11. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemost*. 2017;16:209-219.
12. Patel MRMK, Garg J, Pan G, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrilation. *N Engl J Med*. 2011;365:883-891.
13. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-992.
14. Derebail VK, Rheault MN, Kerlin BA. Role of direct oral anticoagulants in patients with kidney disease. *Kidney Int*. 2020;97:664-675.
15. Fava JP, Starr KM, Ratz D, Clemente JL. Dosing challenges with direct oral anticoagulants in the elderly: a retrospective analysis. *Ther Adv Drug Saf*. 2018;9:405-414.
16. Gulpen AJW, Ten Cate H, Henskens YMC, et al. The daily practice of direct oral anticoagulant use in patients with atrial fibrillation; an observational cohort study. *PLoS One*. 2019;14:e0217302.

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Making treatment decisions in hemophilia based on available safety data

The availability of emicizumab (Hemlibra) for the treatment of hemophilia A has been the most disruptive therapy to treat the condition since factor VIII (FVIII) concentrate was introduced. While for patients with antibodies to FVIII (inhibitors) this treatment has been life changing in dramatically reducing the annual bleed rate, for non-inhibitor patients on good FVIII prophylaxis the benefits are less clear. For non-inhibitor patients the benefit of emicizumab is largely that of convenience because it can be given subcutaneously every 1, 2, or 4 weeks rather than intravenously two to three times weekly.

As hemophilia clinicians, we have embraced emicizumab treatment and have seen its benefits. All of our hemophilia A patients with FVIII inhibitors are now on emicizumab, as are 25% to 30% of our non-inhibitor patients. Patient-level decisions to change hemophilia treatment are based on discussion of many issues including efficacy and available safety data.

At the time of approval of a drug by the regulatory authorities, the clinical studies performed during its development are likely to have shown good efficacy and reasonable safety. It should be appreciated, however, that much of the safety data come after the drug has been released onto the market. The primary adverse events that concern treaters and patients in relation to emicizumab are thrombosis and death. Following the launch of emicizumab the manufacturer provided a website that showed three-monthly data on the number of thrombosis, thrombotic microangiopathies, and deaths occurring in patients taking emicizumab. Following the update of events to 30 June 2020 this service was discontinued, and we were informed that these data will in the future be presented in publications and at scientific meetings. The mortality issue was recently addressed by three papers in this journal.[1-3]

The first paper largely analyzes publications reporting on mortality in hemophilia since 2010.[1] As the authors identify, the cited literature shows significant heterogeneity and pooling the data can be problematic. The ideal situation in which prospective data are collected from complete populations of patients of all severities, where the primary as well as contributing causes of death are included and the data are audited, is rarely achieved. In the second paper the authors provide a framework to categorize causes of death enabling a separation into those which are related or unrelated to hemophilia.[2] This is rather artificial, and we have some issues such as the assignment of thrombosis as a hemophilia-related cause and malignancy as unrelated to hemophilia when one of the commonest malignancies in hemophilia is hepatitis C--related hepatocellular carcinoma. To us it would seem simpler to ignore the relatedness to hemophilia and simply compare the individual groups of causes between studies. The third paper describes the application of the framework algorithm[2] to the deaths of patients on emicizumab up to 15 May 2020, which are recorded on the Roche Emicizumab Global Safety Database.[3] We

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believe the way the data are presented, and the information provided, raise a number of questions.

a. In 11 (44%) of the 25 cases in which the cause of death was specified, it was reported as hemorrhage and in 5 of these (20%) cases the location was intracranial. Patients on emicizumab behave clinically (in terms of bleeding) like patients with mild hemophilia who have FVIII levels of 10% to 20% (0.10–0.20 iu/ml). To us, this is a cause of concern as intracranial hemorrhage (ICH) is rare in patients with mild hemophilia. It must be borne in mind that these are the fatal cases, and we have no information on non-fatal ICH in emicizumab-treated patients.
b. Despite the number of non-fatal thromboses including myocardial infarctions reported in patients on emicizumab, it is remarkable that none of the deaths were attributed to thrombosis. We believe this is likely due to under-reporting because the two cases of cardiac arrest could have been due to coronary thrombosis.
c. Another remarkable observation concerns relatedness. Emicizumab is a new drug for which the full safety profile remains to be established and most deaths likely occurred in patients taking the medication for less than 2 years. Despite this, the reporting clinicians felt sufficiently confident to report that in 22 (92%) of the cases in which relatedness was reported, there was no relation to emicizumab. Even in the other 2 (8%) cases, the reporting clinicians indicated unknown relatedness or identified multiple causes. In the circumstances, we feel that more doubt in relatedness could have been expressed.
d. These three papers discuss congenital hemophilia only. We are concerned about the use of emicizumab in acquired hemophilia, a condition for which the drug is not approved. The manufacturer website contained data on the number of deaths in patients with acquired hemophilia taking emicizumab, but this information is no longer available or updated. As clinicians are starting to use emicizumab for acquired hemophilia off-license, it is important that they are aware of the latest data on adverse events in this population.

The discontinuation of the three-monthly update service on thrombosis and deaths on emicizumab after June 2020 means that the next update will likely be at the ISTH meeting in July 2021, more than 1 year after the last data report. We feel that reporting data on thrombosis and death at scientific meetings should be in addition to, rather than instead of, providing the information every 3 months online as was the case until recently. We do accept that when drugs are well established, periodic presentation of data by publication or at scientific meetings is acceptable. Given the drug was launched relatively recently and large numbers of patients are considering changing to this medication, they deserve to make their decision on the most up-to-date information.

CONFLICTS OF INTEREST

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REFERENCES

1. Hay CRM, Nissen F, Pipe SW. Mortality in congenital hemophilia A – a systematic literature review. *J Thromb Haemost*. 2021;19(Suppl 1):6-20.
2. Pipe SW, Kruse-Jarres R, Mahlangu JN, et al. Establishment of a framework for assessing mortality in persons with congenital hemophilia A and its application to an adverse event reporting database. *J Thromb Haemost*. 2021;19(Suppl 1):21-31.
3. Peyvandi F, Mahlangu JN, Pipe SW, et al. Application of a hemophilia mortality framework to the Emicizumab Global Safety Database. *J Thromb Haemost*. 2021;19(Suppl 1):32-41.