blood advances

TO THE EDITOR:

Direct oral Xa inhibitors for the treatment of venous thromboembolism after bariatric surgery

Margarita Kushnir, Radhika Gali, Mariam Alexander, and Henny H. Billett

Division of Hematology, Department of Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY

More than 250 000 people underwent weight loss surgery in the United States in 2018.[1] Although direct oral anticoagulants (DOACs) have replaced vitamin K antagonists (VKAs) as standard of care for the treatment of venous thromboembolism (VTE), data on their use in the setting of bariatric surgery remain scarce.

The absorption of oral anticoagulants may be altered in patients after bariatric procedures, because gastrointestinal absorptive surface, food volume, gastric pH, and gastrointestinal transit time all affect bioavailability.[2,3] Although there is some evidence on the efficacy of DOACs in preventing stroke in atrial fibrillation, data on VTE recurrence are limited to 9 patients.[4,5]

Updated 2021 International Society on Thrombosis and Haemostasis guidelines suggest not using DOACs for the treatment or prevention of VTE in the first 6 to12 months after bariatric surgery, a recommendation based on data limited to pharmacokinetic (PK)/pharmacodynamic (PD) studies with small numbers of patients.[6] Therefore, we set out to determine whether DOACs are safe and effective in preventing recurrent VTEs in patients who have undergone bariatric surgery.

Using our institutional database, we identified all adult patients (age ≥18 years) with a history of bariatric surgery who were started on anticoagulation for the treatment of VTE with apixaban or rivaroxaban between 1 July 2013 and 30 June 2018. We performed retrospective review of charts to obtain detailed information on patients and clinical outcomes of recurrent VTEs and bleeding from the first prescription date to the earliest of the following: thrombotic event, discontinuation of medication, death, or end of study period (30 June 2018). Type of surgery, body mass index (BMI), age, sex, type of surgery, race, and indication for anticoagulation were verified. VTEs were confirmed by review of imaging studies (compression ultrasonography, ventilation/perfusions scans, computed tomography scans, and magnetic resonance imaging). Bleeding events were included if they met criteria for clinically relevant nonmajor bleeding (CRNMB) and/or major bleeding according to the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[7,8] The study was approved by the Montefiore Medical Center and Albert Einstein College of Medicine Institutional Review Board.

All analyses were performed in samples stratified by medication separately. Means and standard deviations, medians and interquartile ranges, or counts and percentages of baseline demographic and clinical characteristics (age, sex, race, BMI, and follow-up time in days) were tabulated by anticoagulant cohorts (apixaban vs rivaroxaban). Time to event was defined as the time from first prescription date (baseline) to VTE recurrence or bleeding event, respectively. Patients who had not experienced a specific event were censored at the time of death, last confirmed date on anticoagulant, or end of the study period (30 June 2018).

We identified 102 post–bariatric surgery patients who were started on anticoagulation with rivaroxaban (60 patients) or apixaban (42 patients) for the treatment of VTE. As depicted in Table 1, our cohort was predominantly female (82.4%) and had a mean age of 48.5 years and median BMI of 35.7 kg/m^2 at initiation of anticoagulation. The most common bariatric surgery in both anticoagulant groups was gastric bypass (51%), followed by sleeve gastrectomy (SG; 37.3%) and adjustable gastric banding

Submitted 24 November 2021; accepted 27 May 2022; prepublished online on *Blood Advances* First Edition 31 May 2022. https://doi.org/10.1182/bloodadvances.2021006696.

For original data, please contact margarita.kushnir@bannerhealth.com.

Table 1. Demographics and outcomes for study population

Patients	Apixaban (n = 42)	Rivaroxaban (n = 60)	Total (N = 102)
Age, y			
Mean	49.0	48.3	48.5
SD	10.7	12.4	11.6
Sex			
Female	33 (78.6)	51 (85.0)	84 (82.4)
Male	9 (21.4)	9 (15)	18 (17.6)
BMI, kg/m^2			
Median	36.3	35.5	35.7
IQR	28.4-41.5	31.5-43.7	30.1-43.1
BMI group, kg/m^2			
≤30	12 (28.6)	12 (20.0)	24 (23.5)
30-40	16 (38.1)	28 (46.7)	44 (43.1)
≥40	12 (28.6)	18 (30.0)	30 (29.4)
Race			
White	6 (14.3)	10 (16.7)	16 (15.7)
Black	15 (35.7)	25 (41.7)	40 (39.2)
Other/declined	21 (50.0)	25 (41.7)	46 (45.1)
Bariatric surgery procedure			
Gastric banding	4 (9.5)	8 (13.3)	12 (11.8)
SG	18 (42.9)	20 (33.3)	38 (37.3)
Gastric bypass	20 (47.6)	32 (53.3)	52 (51.0)
Indication for anticoagulation			
Acute VTE	33 (78.6)	42 (70)	75 (73.5)
Chronic VTE	9 (21.4)	18 (30)	27 (26.5)
Follow-up duration, d			
Median	137	240	187.5
IQR	61.5-375.8	97.8-652.0	82.5-627.5
Recurrent VTE	0 (0)	1 (1.7)	1 (1.0)
Major bleeding	0 (0)	3 (5.0)	3 (2.9)
CRNMB	1 (2.4)	0 (0)	1 (1.0)

Data are presented as n (%) unless otherwise indicated.
SD, standard deviation.

(11.8%). Anticoagulation was started within 6 months after bariatric surgery in 7 (11.7%) of 60 rivaroxaban patients (4 patients within 30 days and 2 patients between 60 and 90 days) and 5 (11.9%) of 42 apixaban patients (4 patients within 30 days and 1 patient at 49 days). Anticoagulation was initiated for acute VTE in 73.5% of patients; 26.5% of patients were switched from another anticoagulant for chronic VTE. Follow-up duration was longer with rivaroxaban (240 days) compared with apixaban (137 days).

There were no recurrent VTE events in the apixaban group. Among patients receiving rivaroxaban, one recurrent VTE (1.7%) occurred in a patient with remote history of gastric bypass, chronic venous insufficiency requiring treatment with Unna boot for ulcers, and BMI of 54 kg/m^2 at the time of recurrent event. She developed acute deep vein thrombosis (DVT) in the left common femoral vein while receiving rivaroxaban.

In the rivaroxaban group, one patient had CRNMB (menorrhagia leading to cessation of anticoagulation) and three patients, all after Roux-en-Y gastric bypass (RYGB), had major bleeding events: one episode of gastrointestinal bleeding, one instance of hemarthrosis, and one admission for unexplained acute anemia requiring transfusion of two units of blood. No major bleeds occurred and only one CRNMB event was recorded in the apixaban group. There was no statistically significant difference in composite bleeding rates between patients receiving apixaban (2.4%) and those receiving rivaroxaban (6.7%; $P = .3$).

Although the altered PDs and PKs of warfarin were demonstrated after bariatric surgery, international normalized ratio monitoring allows easy dose adjustments to ensure that patients remain in the desired therapeutic range.[9] Apixaban is mainly absorbed in the proximal small intestine. It is unclear whether the lower portion of the small intestine can compensate if absorption is impaired at this site as a result of altered anatomy.[10-12] Rivaroxaban seems to be absorbed primarily in the stomach. Studies of rivaroxaban have shown reduced absorption (29% decrease in area under the curve and 56% decrease in maximum concentration) when the drug is released into the proximal small intestine, with further reduction as the drug is released more distally into the small intestine and colon.[13,14] Therapeutic doses of rivaroxaban also depend on food to increase absorption.[15]

PD studies have reported varied results. A 2017 study of 6 patients found no significant difference in the PDs of rivaroxaban before and after RYGB procedure, after a 10-mg dose of rivaroxaban.[16] In another study, a single 10-mg dose of rivaroxaban was administered to 12 patients 1 day before and 3 days after bariatric surgery (6 RYGB and 6 SG patients). Area under the plasma-concentration time curve, peak plasma concentration, time to peak plasma concentration, and terminal half-life were found to be similar between preoperative and postoperative patients. The study was limited by the single dose of 10 mg (less affected by food intake) and short interval between surgery and administration of rivaroxaban.

Results of another 2017 study were contradictory.[17] When DOAC levels (9 apixaban, 7 rivaroxaban, and 2 dabigatran) in 18 post–bariatric surgery patients were compared with levels in 18 control participants (matched by age, sex, BMI, creatinine, and dose), apixaban levels in all 9 patients were found to be within the expected range. However, in 5 of 7 patients who received rivaroxaban, levels were below the expected range (4 after SG and 1 after adjustable gastric banding).

In this study of clinical outcomes in post-bariatric surgery patients treated with DOACs for venous thromboembolism, the largest to date to our knowledge, we report an overall low incidence of recurrent VTEs, with no thrombotic events in patients receiving apixaban and only 1 recurrent DVT in a morbidly obese patient receiving rivaroxaban. Although we had a relatively small sample size, the incidence of VTE recurrence was comparable to that found in our previously published study of 795 patients with obesity receiving DOACs, where we noted recurrence rates of 2.1% with apixaban, 2% with rivaroxaban, and 1.2% with warfarin, with no clinically significant difference between these anticoagulants.[18]

The concern over absorption after bariatric surgery may be leading clinicians to withhold DOACs, which have fewer food and drug interactions, fixed dosing, no requirements for routine monitoring,

and decreased risk of bleeding, compared with VKAs. Prospective studies are needed to further investigate the efficacy and safety of DOACs in patients after bariatric surgery.

Contribution: M.K. was responsible for the study design, data acquisition and interpretation, and writing of the manuscript; R.G. and M.A. performed the data acquisition and chart review and contributed to the manuscript; H.H.B. was responsible for the study design, data interpretation, and writing and final approval of the manuscript; and all authors had full access to the study data.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profile: H.H.B., 0000-0001-9825-1964.

Correspondence: Margarita Kushnir, 2946 E Banner Gateway Dr, Gilbert, AZ 85234; email: margarita.kushnir@bannerhealth.com.

References

1. English WJ, DeMaria EJ, Hutter MM, et al. American Society for Metabolic and Bariatric Surgery 2018 estimate of metabolic and bariatric procedures performed in the United States. *Surg Obes Relat Dis*. 2020;16(4):457-463.
2. Steffen KJ, Wonderlich JA, Erickson AL, Strawsell H, Mitchell JE, Crosby RD. Comparison of warfarin dosages and international normalized ratios before and after Roux-en-Y gastric bypass surgery. *Pharmacotherapy*. 2015;35(9):876-880.
3. Kröll D, Nett PC, Borbély YM, et al. The effect of bariatric surgery on the direct oral anticoagulant rivaroxaban: the extension study. *Surg Obes Relat Dis*. 2018;14(12):1890-1896.
4. DeCamillo D, Haymart B, Barnes G. Adverse events in patients taking apixaban or rivaroxaban who have undergoing bariatric surgery: a retrospective case series. *J Thromb Thrombolysis*. 2022;53(3):601-606.
5. Hendricks AK, Zieminski JJ, Yao X, et al. Safety and efficacy of oral anticoagulants for atrial fibrillation in patients after bariatric surgery. *Am J Cardiol*. 2020;136:76-80.
6. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost*. 2021;19(8):1874-1882.
7. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
8. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13(11):2119-2126.
9. Strong AT, Sharma G, Nor Hanipah Z, et al. Adjustments to warfarin dosing after gastric bypass and sleeve gastrectomy. *Surg Obes Relat Dis*. 2018;14(5):700-706.
10. Frost C, Wang X, Nepal S, Shuster A, Shenker A. Assessment of the sites of gastrointestinal absorption of apixaban in healthy subjects [abstract]. *Clin Pharmacol Drug Dev*. 2013;2(suppl 1). Abstract 19.
11. Cada DJ, Levien TL, Baker DE. *Apixaban. Hosp Pharm*. 2013;48(6):494-509.
12. Byon W, Nepal S, Schuster AE, Shenker A, Frost CE. Regional gastrointestinal absorption of apixaban in healthy subjects. *J Clin Pharmacol*. 2018;58(7):965-971.
13. Mani H, Kasper A, Lindhoff-Last E. Measuring the anticoagulant effects of target specific oral anticoagulants-reasons, methods and current limitations. *J Thromb Thrombolysis*. 2013;36(2):187-194.
14. Martin KA, Lee CR, Farrell TM, Moll S. Oral anticoagulant use after bariatric surgery: a literature review and clinical guidance. *Am J Med*. 2017;130(5):517-524.
15. Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. *Thromb J*. 2013;11(1):10.
16. Kröll D, Stirnimann G, Vogt A, et al. Pharmacokinetics and pharmacodynamics of single doses of rivaroxaban in obese patients prior to and after bariatric surgery. *Br J Clin Pharmacol*. 2017;83(7):1466-1475.
17. Rottenstreich A, Barkai A, Arad A, Raccah BH, Kalish Y. The effect of bariatric surgery on direct-acting oral anticoagulant drug levels. *Thromb Res*. 2018;163:190-195.
18. Kushnir M, Choi Y, Eisenberg R, et al. Efficacy and safety of direct oral factor Xa inhibitors compared with warfarin in patients with morbid obesity: a single-centre, retrospective analysis of chart data. *Lancet Haematol*. 2019;6(7):e359-e365.