# Direct oral anticoagulants in patients with atrial fibrillation following bariatric surgery: A single-center experience

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## INTRODUCTION

Obesity is associated with an increased risk of atrial fibrillation (AF) [1], which largely requires lifelong anticoagulation to reduce stroke risk. Weight loss is recommended in the prevention of thromboembolism in AF patients with obesity [2].

Bariatric surgery has been proven to result in a significant weight loss, with associated reduction of obesity-related disability and mortality [3]. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are the most common bariatric procedures [4], which alter the digestive tract function potentially affecting the pharmacokinetics of drugs, including anticoagulants [2, 5, 6]. Metabolism of vitamin K antagonists (VKA) seems to be less affected by bariatric surgery compared to direct oral anticoagulants (DOACs), and VKA may be a better choice in AF patients following such surgery [5, 6]. A few studies on the effectiveness of DOACs in post-bariatric patients with AF yielded inconsistent results [7, 8].

We investigated whether DOACs are effective and safe in AF patients following bariatric procedures as compared to VKA and if plasma concentrations of DOACs could be useful in such patients.

## METHODS

We studied 29 consecutive patients after laparoscopic SG or RYGB surgery, who developed AF thereafter and were treated with VKA from 6 months to 5 years. They were referred to the Center for Coagulation Disorders in Kraków due to their preferences to receive DOAC instead of VKA in the years 2016–2019. The choice of a specific DOAC was based on patients' preferences (the once- vs. twice-daily regimen, access to the reversal agent, and the on-treatment risk of bleeding) and left at the physician's discretion. All patients on DOAC received standard-dose regimens and were tested for knowledge of AF and anticoagulation and subsequently enrolled in an educational program [9]. The control group included well-matched patients after the same bariatric procedures, who continued VKA therapy, started at the time of AF diagnosis. The exclusion criteria were cancer, renal failure, liver disease, severe thrombocytopenia, and dual antiplatelet therapy. Patients on aspirin were eligible. We assessed the thromboembolic risk using the $CHA_2DS_2$-VASc score [2]. Data on demographics, cardiovascular risk factors, comorbidities, and current treatment were collected. Comorbidities were defined in the Supplementary materials. The study was approved by the local Research Ethics Committee, which waived the need for informed consent.

After 4–8 weeks since the initiation of a DOAC, the plasma drug concentration was measured at 4–6 hours since the last dose as described in the Supplementary material. The time in the therapeutic range (TTR) was estimated as described [10].

During the follow-up, patients had ambulatory visits or were contacted by telephone every 6–12 months. We recorded ischemic stroke, transient ischemic attack, systemic embolism, major bleeding, clinically relevant

**Table 1.** The characteristics of patients with atrial fibrillation after bariatric surgery

| Variable | All patients (n = 29) | Patients receiving | | |
|---|---|---|---|---|
| | | DOAC (n = 14) | VKA (n = 15) | *P*-value |
| Age, years | 56.9 (4.3) | 57.0 (3.6) | 56.7 (5.0) | 0.87 |
| Female, n (%) | 7 (24.1) | 4 (28.6) | 3 (20.0) | 0.68 |
| Current smokers, n (%) | 12 (41.4) | 7 (50.0) | 5 (33.3) | 0.36 |
| Bariatric procedure | | | | |
| Prior BMI, kg/m$^2$ | 45.2 (4.0) | 45.3 (3.4) | 45.1 (4.6) | 0.86 |
| Sleeve gastrectomy, n (%) | 16 (55.2) | 8 (57.1) | 8 (53.3) | 0.84 |
| Roux-en-Y gastric bypass, n (%) | 13 (44.8) | 6 (42.9) | 7 (46.7) | 0.84 |
| Weight reduction, % | 19.3 (4.8) | 19.2 (4.9) | 19.4 (4.9) | 0.92 |
| AF | | | | |
| Time from surgery to AF diagnosis, years | 2.5 (1.0-5.0) | 2.3 (1.0–4.0) | 2.5 (1.0–5.0) | 0.91 |
| $CHA_2DS_2$-VASc score | 2.0 (2.0–3.0) | 2.0 (2.0–3.0) | 2.0 (2.0–3.0) | 0.66 |
| HAS-BLED score | 2.0 (2.0–3.0) | 2.5 (2.0–3.0) | 2.0 (1.0–2.0) | 0.06 |
| DOACs concentration after 4–6 hours | | | | |
| Apixaban (n = 7), ng/ml | | 151.3 (56.5) | | |
| Rivaroxaban (n = 4), ng/ml | | 129.8 (49.6) | | |
| Dabigatran (n = 3), ng/ml | | 87.1 (29.1) | | |
| Expected peak DOAC concentration[a] | | | | |
| Apixaban, ng/ml | | 69.0–321.0 | | |
| Rivaroxaban, ng/ml | | 178.0–343.0 | | |
| Dabigatran, ng/ml | | 52.0–383.0 | | |
| Follow-up | | | | |
| Duration, months | 29.4 (5.4) | 29.9 (6.5) | 29.0 (4.3) | 0.68 |
| Stroke, n (%) | 2 (6.9) | 1 (7.1) | 1 (6.7) | 0.96 |
| SE, n (%) | 2 (6.9) | 1 (7.1) | 1 (6.7) | 0.96 |
| Major bleeding and CRNMB, n (%) | 4 (13.8) | 2 (14.3) | 2 (13.3) | 1.00 |
| Death, n (%) | 1 (3.5) | 0 | 1 (6.7) | 1.00 |

Data are given as mean (standard deviation [SD]), median (interquartile range [IQR]), or number (percentage)

[a]Based on [5]

Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid; BMI, body mass index; CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulants; SE, systemic embolism; VKA, vitamin K antagonists

non-major bleeding, and mortality. The definitions of clinical outcomes were presented in the Supplementary materials.

Variables were presented as mean and standard deviations (SD), median (interquartile range [IQR]), or numbers (percentage) when appropriate. Normal distribution was tested using the Shapiro-Wilk test. Equality of variances was assessed using Levene's test. Differences between groups were compared using Student's, Welch's t-test, or Mann-Whitney U tests based on the distribution of variables. Nominal variables were compared by Pearson's chi-square test or Fisher's exact test. A 2-tailed *P*-value <0.05 was considered statistically significant. Statistical analyses were performed with JMP®, Version 15.2.0 (SAS Institute Inc., Cary, NC, USA).

## RESULTS AND DISCUSSION

At the enrolment, the characteristics of AF patients, who underwent bariatric surgery (SG, n = 16, and RYGB, n = 13) at the age of 53.7 (±4.5) years and either continued VKA therapy (n = 15) or were switched to DOAC (n = 14), were similar (Table 1). The most common comorbidities were dyslipidemia (86%) and type 2 diabetes (73%) (Supplementary material, *Table S1*). None of the patients had a prior stroke, diagnosed liver disease, or chronic kidney disease, stage 3 or higher. There was one major bleeding in a patient treated with acenocoumarol. After bariatric surgery, within the first year, the mean weight reduction was 19% (from a preoperative body mass index [BMI] of 45.2 ± 4.0 kg/m$^2$, min. 37.9, max. 51.4), with no difference related to the type of surgery. The median time from bariatric surgery to AF diagnosis was 2.5 (1.0–5.0) years, and persistent AF was predominant (n = 25, 86%). Twenty-five (86%) patients had $CHA_2DS_2$-VASc score ≥2 points (min. 2, max. 5), while 4 patients had 1 point in this score.

Seven patients received apixaban 5 mg twice a day, 4 rivaroxaban 20 mg once a day, and 3 dabigatran 150 mg twice a day. The peak DOAC plasma concentrations were, in most cases, within the reference range as suggested, but 2 patients receiving rivaroxaban (aged 54 and 59 years following SG and RYGB, respectively) had peak levels below the expected range (74 ng/ml and 106 ng/ml, respectively) [2]. Ten patients were treated with warfarin and five with acenocoumarol. Their mean TTR was 67 (±18) % and 53%

of patients had TTR >70%. Both DOAC levels and TTR were unrelated to the type of surgery. Five patients in both groups declared the use of aspirin 75 mg daily.

During a mean follow-up of 29.4 (±5.4) months, none of the patients were lost. The two patients receiving rivaroxaban, who had too low peak drug concentrations, were switched to apixaban or warfarin.

There were 4 thromboembolic events (5.8% per year) including 2 ischemic strokes (Table 1), with no difference related to the type of anticoagulants or the surgery performed. A 56-year-old female following SG ($CHA_2DS_2$-VASc 3) experienced a stroke after cessation of apixaban therapy while on prophylactic-dose enoxaparin due to severe pneumonia. Another 62-year-old female ($CHA_2DS_2$-VASc 4) following SG was on acenocoumarol (TTR, 73%) and experienced a stroke during viral infection with fever known to de-stabilize anticoagulation with VKA [12]. We also observed 2 systemic embolism events ($CHA_2DS_2$-VASc 2, each), both in men after RYGB, one on dabigatran and the other on warfarin (TTR, 42%).

There were 2 major and 2 clinically relevant non-major bleeds (5.8 % per year); all in patients after RYGB and without previous severe bleeding. Two patients had major upper gastrointestinal bleeding, one on apixaban (plus aspirin) and one on acenocoumarol (TTR, 50%). One patient treated with dabigatran (plus aspirin) and the other with acenocoumarol (TTR, 38%) suffered from nonmajor bleeding.

Thromboembolic and bleeding events were recorded more frequently in patients following the RYGB procedure (6/8 events, including 3 on DOACs and 3 on VKA; $P = 0.04$). The TTR was lower in patients on VKA with those events (51% vs. 73%; $P = 0.03$). There were no relations in the occurrence of thromboembolic and bleeding complications among patients with TTR >70% compared to the subjects with TTR ≤70%.

One patient, free of thromboembolic or bleeding events, died of cancer after 37 months of the follow-up.

To our knowledge, this is the first Polish report on AF patients after RYGB or SG receiving DOAC, indicating that the risk of stroke/systemic embolism and bleeding is similar on DOAC versus VKA. Importantly, 6 out of 8 events were observed in patients following RYGB, therefore in our opinion, this subgroup should be closely monitored with the integrated approach by a multidisciplinary team [13]. As suggested by experts [5], the plasma DOAC concentration was measured, and the patients on apixaban and dabigatran had levels within the expected ranges with no differences related to the type of surgery. There are data suggesting caution while using rivaroxaban following RYGB [14], and, indeed, in 2 patients on rivaroxaban (one after RYGB), the peak drug concentration was below the expected value though the patients did not experience any complications and were switched to apixaban or VKA. The bioavailability of lipophilic rivaroxaban may be reduced following gastric bypass surgery when its absorption takes place distal to the stomach as discussed by Steffel et al. [5].

Hendricks et al. reported no difference in the occurrence of ischemic stroke/systemic embolism, major bleeding, and death between patients on DOAC and VKA in a bariatric cohort (n = 1673) [8]. In 29 bariatric patients on DOACs, investigators showed that bleeding events were common (29%), with a significant rate of thromboembolic events (7%); we recorded similar risks of those complications. In our study 2 outcomes were observed on apixaban and 2 on dabigatran. A relatively high risk of bleeding in bariatric patients is likely multifactorial, including over-the-counter aspirin use without a clear indication [11]. Two ischemic strokes were related to withdrawal of anticoagulation, which highlights the need for good compliance and education [2, 5, 9].

Our study has several limitations. The size of the study group was small; however, AF is relatively uncommon among middle-aged bariatric patients. DOAC levels were not routinely measured during the follow-up.

This study suggests that DOAC could represent an acceptable alternative to VKA in AF patients after bariatric surgery when supported by plasma DOAC measurements at the initiation of anticoagulation.

## Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

## Article information

**Conflict of interest:** AU received lecture honoraria from Bayer, Boehringer Ingelheim, and Pfizer. Other authors declare no conflict of interest.



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