A Survey of Direct Oral Anticoagulant Cessation in General Surgery and Outcomes in Patients with Nonvalvular Atrial Fibrillation

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Summary

There is little data on management and outcomes of atrial fibrillation (AF) patients on direct oral anticoagulants (DOAC) undergoing general surgery.

We retrospectively assessed 98 surgeries in 85 nonvalvar AF patients aged 73 ± 8 (59 men) receiving DOACs. Cardiac, emergency, and minimally invasive surgeries were excluded.

The CHA2DS2-VASc score ranged from 0 to 8. The DOACs being given were: dabigatran, 16; rivaroxaban, 25; apixaban, 28; and edoxaban, 16. While the DOACs were not suspended in 11 cases, they were interrupted for a median of 2.0 days before surgery and restarted at a median of 3.0 days after surgery. There were 9 complications (9.2%), 3 instances of thromboembolism and 6 bleeding. Thromboembolism occurred at a mean of 3.0 postoperative days, all of which occurred before resumption of DOACs, while bleeding events occurred at a mean of 4.0 postoperative days. Two of the 3 patients with thromboembolism went into cardiopulmonary arrest during the event, but were resuscitated. There were significantly more patients with congestive heart failure or combined antiplatelets in the patients with complications. The complication group had a significantly higher HAS-BLED score and lower preoperative hemoglobin level. There were no significant differences in the management of DOAC interruption between those with complications and without.

The perioperative complication rate in nonvalvar AF patients undergoing elective surgery treating with DOACs was 9.2%. Patients with congestive heart failure, receiving combined therapy with antiplatelets, a higher HAS-BLED score, or lower preoperative hemoglobin level were at higher risk. Further studies evaluating the ideal perioperative DOAC protocol are warranted.

Key words: Elective surgery, Thromboembolism, Bleeding

Direct oral anticoagulants (DOACs) introduced in 2010, including the direct thrombin inhibitor dabigatran and FXa inhibitors (apixaban, edoxaban, and rivaroxaban), are increasingly being used for the prevention of thromboembolic events in patients with nonvalvar atrial fibrillation (NVAF).\textsuperscript{1,2)}

It is estimated that about 10% of AF patients receiving oral anticoagulants require treatment interruption for surgery or an invasive procedure annually.\textsuperscript{3)} The huge number of patients receiving treatment with DOACs makes management of blood coagulability during surgery and invasive procedures an important clinical endeavor. In the case of warfarin, current recommendations call for its interruption to start 3-5 days before surgery based on the value of PT-INR.\textsuperscript{4)} For DOACs, the guidelines recommend interrupting DOACs 24-48 hours before surgery depending on the bleeding risk of the particular surgery.\textsuperscript{5)} However, the guidelines for when to restart DOACs after surgery are less clear.\textsuperscript{5)} We also note that the aforementioned DOAC guideline was not developed based on clinical trials. To date, there have been few studies that have evaluated the safety of the recommended perioperative DOAC management guidelines in patients scheduled for elective surgery.\textsuperscript{6-10)}

The aim of our study was to retrospectively analyze the prevalence and prognostic factors of perioperative bleeding and thromboembolic events in NVAF patients receiving DOACs during any non-cardiac elective surgery at our hospital.

Methods

We assessed all NVAF patients with a regular DOAC prescription who underwent elective non-cardiac surgery between June 2012 and December 2018 from all clinical departments at Tokyo Medical and Dental University Hos-
hospital. We first identified AF subjects using ICD-10 codes (International Statistical Classification of Diseases and Related Health Problems - 10th revision). Medical records were reviewed to determine what anticoagulants they were on, and whether there was a history of surgery. We excluded minimally invasive surgery, such as prostate biopsy, cataract intervention, and superficial surgeries as the guidelines for the perioperative management of DOACs recommended that DOACs not be interrupted for these interventions with a minor bleeding risk.11) Cardiac surgery was excluded because transvenous anticoagulation was necessary during extracorporeal circulation. As the guidelines distinguished the perioperative management for between scheduled surgery and urgent surgery,11) we assessed only patients undergoing a planned surgery. Patients with poorly documented records regarding the timing of the preoperative cessation or postoperative resumption of DOACs were excluded. The patients were followed until March 2019, although some patients were lost to follow-up earlier due to transferal to another hospital or due to the occurrence of clinical events.

**Data extraction:** Data were extracted from the records of eligible subjects. Clinical and demographic data including age, gender, weight, medications, laboratory data, CHA2DS2-VASc score, HAS-BLED score, and clinical events were collected. Congestive heart failure (CHF) was defined arbitrarily as left ventricular systolic dysfunction.10) Renal function was evaluated using a creatinine clearance (Ccr) (mL/minute) formula developed for the Japanese population, i.e., (140-age [years]) × body weight [kg]/72/serum creatinine [mg/dL], and × 0.85 if female. The prescribed dose of the DOACs was compared to the recommended dose, in order to identify patients who were receiving inappropriately large or small doses. In some patients switching between different anticoagulant regimens had been done before the surgeries. We assessed patients with a regular DOAC prescription perioperatively in this study, however, the duration of any oral anticoagulants, DOAC or warfarin, before surgery was assessed. As current anticoagulation guidelines recommend systemic anticoagulation for at least 3 weeks prior to DC cardioversion or AF ablation,5,12) the patients who did not take any anticoagulants for at least 3 weeks before the surgeries were defined as those with a shorter duration of anticoagulation.

Perioperative complications were defined as arterial thromboembolism or bleeding that occurred within 30 days after the surgery. Arterial thromboembolic events included ischemic stroke, transient ischemic attacks, and cardiogenic systemic emboli. Bleeding events were defined as fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in the hemoglobin level of 2 g/dL or more, bleeding leading to cessation of the administration of DOACs, or a transfusion of two or more units of whole blood or red cell concentrates (RCC).13) To assess the postoperative clinical course, death, bleeding, and thromboembolic events were regarded as endpoints during the follow-up period. Patients who underwent two or more surgical procedures during the study period were categorized into the perioperative complication group if perioperative bleeding or thromboembolism occurred at least once. For those who had no complications, the latest surgical procedure was assessed for this study.

The study was approved by the Tokyo Medical and Dental University institutional review board (M2019-024). The requirement for informed consent was waived for this retrospective study.

**Statistical methods:** Normally distributed continuous variables are expressed as the mean ± standard deviation, non-normally distributed continuous variables as the median and IQR, and categorical variables as numbers and percentages. The differences between the continuous variables were assessed using Student’s t-test or the Mann Whitney U test. Categorical variables were compared using the χ²-test or Fisher’s exact test when the data were very unequally distributed among the cells of the table resulting in the expected values in any of the cells of a contingency table being below 5. P values of < 0.05 were considered statistically significant. SPSS statistics 22 software (SPSS Inc., Chicago, IL) was used for all statistical analyses.

**Results**

During the 6.5 year study period, 268 elective noncardiac surgeries were performed in NVAF patients receiving DOACs. Of those, we identified a total number of 98 eligible cases including 4 patients with 2 surgeries, 3 with 3 surgeries, and 1 with 4 surgeries. As a result, 85 individuals were included in this study (59 men, mean age, 73 ± 8 years) (Table I). The CHA2DS2-VASc score ranged from 0 to 8, and 75 patients (88%) had a score of ≥ 2. There were 42 patients with paroxysmal AF and 43 with persistent AF. There were 15 patients who were receiving some type of antiplatelet drug, including 7 patients for coronary artery disease, 4 for atherosclerosis obliterans, 2 for the prevention of cerebral infarction (CI), and old CI and canal stenosis in 1 each. These drugs were stopped 7 days before the surgery in all, as is done routinely. Forty-seven patients (55%) had an active cancer, and among them a patient was taking chemotherapy during the perioperative period.

All 98 surgeries were classified as having high bleeding risk according to EHRA guidelines.10) The breakdown of the surgeries was endoscopic surgery in 32, major orthopedic surgery in 16, transurethral surgery and abdominal surgery in 9 each, and other surgeries with spinal or epidural anesthesia in 32. Among the 85 patients, dabigatran was prescribed in 16, rivaroxaban in 25, apixaban in 28, and edoxaban in 16. The prescribed dose of dabigatran was 300, 220, 150, and 75 mg/day in 5, 9, 1, and 1 cases, respectively. For rivaroxaban, doses were 15 mg/day in 12 and 10 mg/day in 13. For apixaban, the dose was 10 mg/day in 13 and 5 mg/day in 15, and for edoxaban, 60 mg/day in 5, 30 mg/day in 10, and 15 mg/day in 1. Overall, the DOAC doses were found to be appropriate in 57 cases. A less than recommended dose was prescribed in 26 (31%) with no clear indication why, and 2 (2%) received a higher than recommended dose even though clinical factors indicated otherwise. The median duration of DOAC use prior to the surgery was 181 days.
During the perioperative period, thromboembolic events occurred in 3 cases (3.1%, Table II). The thromboembolic events consisted of one each of cerebral infarction, acute embolic myocardial infarction, and internal carotid artery embolism. The first two of these were followed immediately by cardiopulmonary arrest, both of which were successfully resuscitated. The preoperative anticoagulation period was quite short in Patient 1 with persistent AF and prior stroke. He had been given an antiplatelet agent, which was then changed to rivaroxaban 17 days before the surgery. Two out of 3 patients had active cancer (Patients 1 and 2). Patient 2 with hepatocellular carcinoma had been in good control of AF and had had seldom attacks. Perioperative ECG monitoring also showed no AF. In such a situation she had acute embolic myocardial infarction. For these 3 patients, DOACs were interrupted 5.0 days preoperatively on average (range: 4-7) and the events occurred at a mean of 3.0 days after surgery (range: 2-4). They all occurred during the period before DOACs had been resumed.

During the perioperative period, bleeding events occurred in 6 (6.1%). They consisted of 3 decreases in the hemoglobin level that resulted in RCC transfusions, 2 macrohematuria events that required discontinuation of the DOACs, and 1 bloody stool that resulted in emergent clip hemostasis and RCC transfusion. The DOACs were interrupted at a mean of 2.4 days before surgery in 5 patients (range: 0-7), and the DOAC was never discontinued in 1 patient. The bleeding events occurred at a mean of 4.0 postoperative days (range: 1-8), including 2 events in which anemia progressed after the surgery before the resumption of DOACs. In the remaining 4 patients, DOACs had been restarted at a mean of 2.3 postoperative days (range: 1-3) in 3 and the DOAC had not been discontinued perioperatively in 1 (Table II).

Perioperative complications occurred in 12.5% of endoscopic surgeries and major orthopedic surgeries each,
22.2% of transurethral surgeries, 0% of abdominal surgeries, and 3.1% of other surgeries with spinal or epidural anesthesia. There was no significant difference in the incidence rate among the different types of surgeries.

The patients with perioperative complications tended to have a significantly lower hemoglobin prior to the surgery (11 versus 13 g/dL, $P = 0.028$) and higher HAS-BLED score (2.6 versus 1.6, $P = 0.004$) than those without. There were significantly more patients with CHF (56 versus 21%, $P = 0.037$) or receiving combined therapy with an antiplatelet drug (44 versus 15%, $P = 0.048$) in the patients with perioperative complications (Table I). However, there were no significant differences in the duration of anticoagulation therapy before the surgery, or the periods of DOAC interruption between those with perioperative complications and without.

Subanalyses among patients with a higher risk for perioperative complications were performed (Table III).
There were 50 patients with a HAS-BLED score higher than 2, including 3 patients with perioperative thrombosis and 4 with bleeding. Among 30 patients with a pre-hemoglobin level lower than 12 g/dL, there were 2 patients with thrombosis and 3 with bleeding, and among 21 patients with CHF, 2 with thrombosis and 3 with bleeding. In these subgroups the prevalences of perioperative bleeding and thromboembolic events were assessed according to the perioperative DOAC management. The patients were divided into 2 groups, those with shorter duration (< 21 days) of anticoagulation before surgery and longer duration (> 21 days), and those with a shorter duration (< 4 days) and a longer duration (> 4 days) of perioperative DOAC interruption. These subanalyses showed no significant differences in the prevalence of perioperative complications. Among the 25 surgeries performed after the publication of DOAC interruption guidelines recommending pausing DOACs ≥ 48 hours before the surgery, the recommendation was followed in 7 surgeries, in which there was 1 thromboembolic event.

### Discussion

In this retrospective single center study, we found that the perioperative complication rate (bleeding and thrombosis) in the DOAC-treated NVAF patients undergoing elective non-cardiac surgery was 9.2% (3.1% thromboembolism and 6.1% bleeding). Patients with CHF, receiving combined therapy with antiplatelets, a higher HAS-BLED score, or lower preoperative hemoglobin level were at higher risk for perioperative complications.

In recent years, DOACs are increasingly being used for the prevention of thromboembolic events in NVAF patients. Their advantages are predictable pharmacokinetics which lead to simplified dosing, fewer interactions with other drugs and food, and that routine monitoring of the coagulation status is not necessary.10 However, a disadvantage of DOACs is that conventional coagulation assays such as the activated partial thromboplastin time (APTT) and prothrombin time (PT) are known to have poor sensitivity and specificity for assessing the anticoagulant effect of DOACs.13,16)

It is estimated that about 10% of AF patients receiving oral anticoagulants require treatment interruption for surgery or an invasive procedure annually.15 Guidelines for the perioperative management of DOACs already exist, in which it is recommended that DOACs not be interrupted for interventions with a minor bleeding risk. For procedures with a low bleeding risk, the recommendation is to take the last dose of a DOAC 24 hours before the surgery, and for procedures with a high bleeding risk, 48 hours before or longer.16 Concerning resumption of DOAC therapy after surgery, the guidelines state that DOACs should be resumed after 1-5 days dependent on the risk of secondary bleeding, but conclude that uncertainties exist regarding the optimal timing. Obviously, resumption should begin when the risk of postoperative bleeding is considered to be under control with certainty. Unfortunately, with DOACs, it is impossible to accurately calculate the residual anticoagulant effect using common laboratory testing at a given time.13,16 In the case of emergent surgeries in patients receiving DOACs, risk of bleeding is of primary concern. At the present time, dabigatran is the only DOAC that has an antidote in Japan. However, in our recent study of patients who underwent elective surgery, the perioperative thromboembolic events led to more critical outcomes, with 2 of 3 patients going into cardiopulmonary arrest, while the patients with perioperative bleeding

| Table III. Incidence of Perioperative Complications According to DOAC Usage Among Patients with a Higher Risk for Perioperative Complications |
|---------------------------------------------------------------|
| Patients with HAS-BLED score higher than 2 (n = 50)          |
| Duration of anticoagulation before surgery                  |
| Number of patients                                           |
| Number of complications                                     |
| Periods of perioperative DOAC interruption                   |
| Number of patients                                           |
| Number of complications                                     |
| Patients with preoperative hemoglobin level lower than 12 g/dL (n = 30) |
| Duration of anticoagulation before surgery                  |
| Number of patients                                           |
| Number of complications                                     |
| Periods of perioperative DOAC interruption                   |
| Number of patients                                           |
| Number of complications                                     |
| Patients with congestive heart failure (n = 21)              |
| Duration of anticoagulation before surgery                  |
| Number of patients                                           |
| Number of complications                                     |
| Periods of perioperative DOAC interruption                   |
| Number of patients                                           |
| Number of complications                                     |
| DOAC indicates direct oral anticoagulants.                   |

| Duration | Shorter duration | Longer duration | P value |
|----------|------------------|-----------------|---------|
| < 21 days| 4                | 46              | 0.625   |
| ≤ 4 days |                  |                 |         |
| ≥ 21 days| 0                | 7               |         |
| > 4 days |                  |                 |         |
| Number of complications | 30 | 20 | 0.416 |
| Number of complications | 3  | 4  |     |
| Number of complications | 14 | 5  | 0.513 |
| Number of complications | 2  | 3  | 0.743 |
| Number of complications | 1  | 20 | 0.567 |
| Number of complications | 0  | 5  |     |
| Number of complications | 12 | 9  | 0.882 |
| Number of complications | 3  | 2  |     |

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sustained no fatal bleeding. Although thromboembolism and bleeding are two sides of the same coin, our results suggest that it is more important to prevent thromboembolism for elective surgeries.

In this study, one of 3 patients with perioperative thromboembolism had received DOACs for quite a short time, 17 days. Although the anticoagulant effects of rivaroxaban should have been at steady state by the time of interruption, there was a possibility that there were pre-existing left atrial appendage (LAA) thrombi at the time of surgery. Current anticoagulation guidelines for DC cardioversion in patients with AF lasting > 48 hours recommend at least 3 weeks of anticoagulation before DC. 4) Also, systemic anticoagulation for at least 3 weeks prior to AF ablation in patients with a CHA$_2$DS$_2$-VASc score of 2 or greater is recommended. 5) Based on these guidelines, it is likely that at least 3 weeks of anticoagulation would also be appropriate for the patients with NVAF before non-cardiac surgeries, however, the guidelines for surgery did not go so far as to describe the proper anticoagulation period before the surgery. In this study there were no significant differences in the duration of anticoagulation therapy before the surgery between those with perioperative complications and without, however, among 10 patients without a sufficient anticoagulation period, one patient had thromboembolism. Therefore, we thought the suitable presurgical anticoagulation period should be discussed in the future, or alternatively, ruling out of LAA thrombi using transesophageal echocardiography prior to the surgery for patients without enough anticoagulation would be recommended in the same way as for DC. 5)

We found that the patients with CHF, receiving combined therapy with antiplatelets, a higher HAS-BLED score, or lower preoperative hemoglobin level were at high risk of perioperative complications. We have previously reported that in AF patients a higher BNP level is a prognostic factor of LAA thrombi, and combined antiplatelet therapy was significantly more frequent in those with LAA thrombi than in those without despite oral anticoagulation. 6) Antiplatelet therapy is mainly given to those with ischemic heart disease, peripheral artery disease, or for prevention of thrombotic events in this study. Patients who need combined DOACs and antiplatelet treatment seem to be at risk for both bleeding and thromboembolic events. In a previous study it was also reported that treatment with concomitant blood thinners, aspirin or heparin, tended to produce a higher incidence of bleeding events in AF patients with DOACs for spine surgery. 7) Meanwhile, CHF, preoperative anemia, and prior stroke seemed to be one of the potential risk factors for perioperative complications generally. 8-10 In this study, prior stroke events were more frequent in the complication group although it did not reach a level of statistical significance.

There were no significant differences in the management of perioperative DOACs between those with and without the complication in both the whole analysis and subanalyses among patients with higher risks. These findings might mean that what regulated the perioperative complication was individual factors, and the management of DOACs might not contribute to patient outcome. Therefore, on the basis of this study we could only conclude that patients with particular factors need to be paid special attention and could not refer to the ideal DOAC management.

In our patients, 55% had an active cancer, including 2 patients among 3 with thromboembolic events. There was no significant difference in the proportion of the active cancer between the perioperative complication group and the no-complication group. Trousseau syndrome is a hypercoagulability syndrome associated with cancer which comprises thromboembolic disorders in arterial or venous systems. 11) It is not always easy to differentiate between thromboembolisms caused by AF and Trousseau syndrome in patients with both AF and a malignancy. Patient 2 with hepatocellular carcinoma had acute embolic myocardial infarction. She had taken dabigatran appropriately for paroxysmal AF for over 5 years (Table II). Although her AF was paroxysmal, her CHA$_2$DS$_2$-VASc score was as high as 6. In such a case, it is unclear which was the major cause of thromboembolism. To date, whether DOAC is effective for prophylaxis of Trousseau syndrome or not is not fully elucidated, however, the interruption of DOAC in such patients with doubled risks for thromboembolism requires close attention.

So far, there have been few reports about the postoperative thromboembolic and bleeding rates in NVAF patients treated with DOACs who undergo surgery. In the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study, a cohort study of 3,007 patients, the rate of arterial thromboembolism was < 1%. In patients with a high-bleeding-risk procedure, the rates of major bleeding were 2.96% in the apixaban cohort and 2.95% in the rivaroxaban cohort. 9) Our report was an observational study in which the management was not standardized and uniform, including perioperative heparin bridging (31.8%). In the PAUSE study they used a homogenous protocol without heparin bridging, therefore, we could not compare their results with ours. However, our results showed extremely higher rates of both bleeding and arterial thromboembolism. The incidence of active cancer was only 8.9% in the PAUSE study, which was quite lower than this study. It is speculated that the situation related with a malignant disease such as Trousseau syndrome or friability might cause the thromboembolism or bleeding. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, the rates of periprocedural major bleeding was 4.5% in patients receiving dabigatran and 4.6% in those with warfarin. 10) The incidences of stroke and all other thromboembolic complications observed were 1.4% and 1.2%. These rates are quite a bit lower compared to this study, however, most procedures performed during the RE-LY trial had minor or low bleeding risks.

**Limitations:** First, our results were obtained retrospectively from an unselected and limited population from a single institution. Multivariate analysis was not performed due to the limited patient number. In addition, to assess the management of oral anticoagulants, we excluded less invasive procedures. As a result, all surgeries in our study were categorized as high bleeding risk surgeries according to the EHRA guidelines. 5) Because our study included a
wide variety of surgical interventions each with its own bleeding risk, it was not possible to determine a standardized protocol for the perioperative management of DOACs from our study. In an ideal study, we would have collected data for each type of surgery and each DOAC. However, we believe our findings are a start to addressing real-world clinical practice. Eventually, studies with a number of homogeneous patients taking an identical DOAC undergoing the same procedure are required to establish the optimum perioperative management for NVAF patients with DOACs. Similarly, the patients in our study were not all receiving DOACs at recommended doses (31/85 = 36%), making our study less than ideal, but at the same time, reflecting real patient populations. For example, if patients were referred to our hospital for surgery, and being treated for NVAF elsewhere, their DOAC dose would likely remain untouched by the surgeon. Likewise, the duration of DOAC interruption before surgery was longer than the recommended 24-48 hours in half the patients, despite the existence of an institutional protocol for interruption of medications including DOACs before surgery, and which obviates the need for cardiology consultation. Moreover, perioperative heparin bridging was given in some patients. Second, we acknowledge that there are studies of DOAC-specific coagulation tests, such as the calibrated anti-Xa activity for factor Xa inhibitors and diluted thrombin time or ecarin-based assays for dabigatran, or the measurement of DOAC plasma concentrations.22-24)

In this study, we could not assess DOAC-specific tests, which may in the future be shown to be the best way to monitor anti-coagulation concentrations in patients receiving DOACs, helping guide perioperative management. Third, because our study found CHF to be a risk factor, BNP measurements would have been useful, but because the study was retrospective, BNP values were unavailable in many patients, precluding analysis. Lastly, we excluded intraoperative blood transfusions from the bleeding events but included post-operative transfusions. The judgement whether to give blood transfusions or not depended on each surgeon. Our definition of bleeding events was arbitrary, and selection of a different criterion might have led to different results. Our study did not provide the basis for standard guidance as to the ideal duration of DOAC interruption to minimize both ischemic events and bleeding for various patients and procedures. Future studies are warranted to determine the best practices of perioperative DOAC management.

Conclusion

The perioperative complication rate in NVAF patients undergoing elective non-cardiac surgery treated with DOACs was 9.2%. Patients with CHF, receiving combined therapy with antiplatelets, a higher HAS-BLED score, or lower preoperative hemoglobin level should receive special attention. Although both thromboembolism and bleeding should be avoided, thromboembolism seemed to cause more critical outcomes. Further studies are required to establish proper and safe protocols for the interruption of DOACs before surgery in NVAF patients.

Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

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