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*Original Article*

# A Comparative Prospective Observational Study on the Use of Direct Oral Anticoagulants after Cardiac Surgery for the Management of Atrial Fibrillation

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**Purpose: Recently, guidelines recommended the use of direct oral anticoagulants (DOACs) for the management of non-valvular atrial fibrillation (NVAF). Postoperative atrial fibrillation (POAF) is the most common post-surgical complication of cardiac surgery, but the efficacy and safety of DOAC for POAF have rarely been investigated. We conducted a prospective observational study to investigate the efficacy and safety of DOAC administered immediately after POAF.**

**Materials and Methods: In all, 135 patients that experienced POAF after cardiac surgery were treated with a DOAC. Primary endpoints were either bleeding or thromboembolic events. Secondary endpoints included changes in hemoglobin (Hb), prothrombin time (PT), activated partial thromboplastin time (APTT), serum creatinine (sCr), estimated glomerular filtration rate (eGFR), and pleural/pericardial effusion.**

**Results: Patients were treated with apixaban (n = 31), edoxaban (n = 87), and rivaroxaban (n = 17). Major bleeding (p = 0.011) and gastrointestinal (GI) bleeding (p = 0.047) were significantly more frequent in the rivaroxaban group. Stroke was observed in one rivaroxaban group patient and none in the other two groups.**

**Conclusion: DOAC as anticoagulation therapy for the early intervention of POAF following cardiac surgery is associated with a low incidence of major bleeding; a favorable safety profile and excellent efficacy were demonstrated for DOAC. Furthermore, our results indicate that the safety and efficacy of apixaban and edoxaban are better than rivaroxaban.**

**Keywords:** cardiac surgery, anticoagulation therapy, DOAC, atrial fibrillation, non-valvular atrial fibrillation

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## Introduction

Recently, new cardiovascular treatment guidelines recommended the use of direct oral anticoagulants (DOACs) for the management of non-valvular atrial fibrillation (NVAF)[1–3]; a large-scale study found that, compared to conventional warfarin therapy, the preventive effect of stroke was similar or better. In addition, intracranial bleeding was drastically decreased. Thus, favorable safety and efficacy have been reported.[4–6] The guideline recommends DOAC, as well as warfarin. Even though

several references are cited in the new guidelines, none are clinical investigations. Thus, DOACs have yet to undergo extensive investigation for use in patients with postoperative atrial fibrillation (POAF).[1)]

POAF is the most common complication following cardiac surgery, with an incidence of 16%–85%.[7,8)] Stroke is the most important clinical outcome of POAF. It also significantly affects the prognosis.[9)] POAF occurred in 24% of the 761 patients that underwent isolated coronary artery bypass grafting (CABG) at our facility, and 1.4% of these patients with POAF experienced a stroke. Thus, it is crucial to start anticoagulation therapy shortly after POAF.[10)] However, we used to begin anticoagulation therapy, which consisted of heparin and warfarin, shortly after POAF, but stroke still occurred in 1.4% of patients. Therefore, we prospectively administered edoxaban to control POAF in 15 patients, and no patients experienced postoperative bleeding.[11)] After these findings, we began to administer DOAC as the first-line anticoagulant treatment for POAF. Herein, we conducted a prospective observational study on the effects of administering DOAC immediately after the occurrence of POAF in patients who underwent cardiac surgery.

## Materials and Methods

### Study protocol

The subjects were adult patients who developed POAF following cardiac surgery (**Table 1**). POAF was defined as atrial fibrillation (Af) that occurred in patients after cardiac surgery and did not improve in 12 hours or more, despite pharmacotherapy. Patients with the following criteria were excluded: (1) artificial heart valve(s) or rheumatic mitral stenosis, (2) blood loss from the surgical drain ≥10 mL/hour, (3) unconscious, (4) inability to take oral medication, (5) infectious endocarditis, (6) creatinine clearance (CRCL) <15 mL/min, (7) hepatic disease accompanied by abnormal coagulation, (8) a history of bleeding events that included gastrointestinal (GI) bleeding, and (9) those determined unsuitable for other reasons by the attending physician.

The drugs tested in this study were apixaban, edoxaban, and rivaroxaban; the attending physician at intensive care unit selected the drug for each patient, and it was administered for 2 months. It was continued even when POAF recovered to sinus rhythm. We continued treatment for the patients with Af after the study ended. DOAC was administered 12 hours after the onset of POAF if it occurred. In addition, if patients with chronic Af underwent Maze surgery, then treatment initiation followed the same criteria as POAF treatment. If Maze surgery was not conducted or if Af persisted after Maze surgery, then treatment started 2 days after the surgery. The patient was assigned treatment and dosage if they met the criteria for that particular drug. The criteria for the low dose of apixaban (2.5 mg, twice daily) was: 80 years or older, bodyweight <60 kg, or serum creatinine (sCr) level >1.5 mg/dL; all other patients received the high dose (5 mg, twice daily). The low dose of edoxaban (30 mg, once daily) was assigned if one of the following was met: bodyweight <60 kg, CRCL (mL/min) level <50 mL/min, or concomitant use of P glycoprotein inhibitor; all other patients received the high dose (60 mg, once daily). The low dose of rivaroxaban (10 mg, once daily) was administered if CRCL was <50 mL/min; all other patients received the high dose (15 mg, once daily).

This study was conducted in an open-label manner. The details of the study were explained, and informed consent was obtained from each patient. Our institutional review board approved this study, and it was registered with the University Hospital Medical Information Network (study ID: UMIN000030851).

We defined the primary endpoints: major bleeding events that required a blood transfusion such as major postoperative bleeding, GI bleeding, or cerebral hemorrhage; minor bleeding events that were clinically significant; thromboembolic events; and the last day of the 2-month treatment period. The secondary endpoints were as follows: hemoglobin (Hb), sCr and CRCL were at baseline levels on days 1 and 3, week 1, and month 1; prothrombin time (PT) was at baseline levels on day 1, week 1, and month 1; and activated partial thromboplastin time (APTT) was at baseline levels on day 1, week 1, and month 1. For blood sampling for coagulation tests, day 0 was defined as immediately before the administration of DOAC, day 1 as the first 24 hours, and day 3 as the first 72 hours after the start of DOAC. Thereafter, blood sampling was conducted at 8:00 in the morning.

After the administration of DOAC, patients underwent chest X-rays the next day and then once-a-week to identify intrathoracic bleeding or pericardial bleeding. The presence or absence of pericardial effusions was evaluated by echocardiography at week 1. If chest X-rays indicated increased pleural effusion, decreased Hb, or worsening respiratory functions; or if echocardiography showed pericardial effusions of 10 mm or larger and was associated with decreased Hb and negative hemodynamic influences; then invasive interventions, such as

drainage or re-thoracotomy, were conducted. Liver dysfunction was defined as a twofold increase in aspartate transaminase (AST) and alanine aminotransferase (ALT) from baseline, and renal dysfunction was defined as either sCr of 2.0 mg/dL or CRCL of 15 mL/min or less.

**Statistical analysis**

For parametric data, results were expressed as the mean ± standard error. The comparison test between the three groups was performed by Fisher's exact test. For time-course analysis, repeated measures of analysis of variance (ANOVA) with Fisher's protected least-squares difference test was used. The Kaplan–Meier method determined event-free rates. For all analyses, $p<0.05$ was considered statistically significant.

## Results

Patients were classified into three drug treatment groups: apixaban (n = 31), edoxaban (n = 87), and rivaroxaban (n = 17). Among these treatment groups, no significant differences were observed in age, sex, body weight, CRCL, basic disease, risk factors, pre-surgical anticoagulation therapy, $CHADS_2$, and $CHADS_2$-$VAS_c$ (**Table 1**). No differences were observed between the groups in aortic cross-clamp times, extracorporeal circulation times, or the number of off-pump patients. However, the onset day of POAF was similar among the three treatment groups (**Table 2**). At the time of discharge, sinus rhythms were observed in the following number of patients in each group: 26 (84%) apixaban, 76 (87%) edoxaban, and 13 (76%) rivaroxaban (p = 0.446). Overall, no hospital deaths occurred, but the total number of events was significantly higher in the rivaroxaban group (p = 0.007) (**Table 3**). The overall mean number of days from the start of DOAC administration to the occurrence of an event was 6.3 ± 5.8 days (range of 1–17 days); there were no significant differences between the groups: 10.5 ± 3.2 days for apixaban, 2.5 ± 0.6 days for edoxaban, and 6.2 ± 2.7 days for rivaroxaban (p = 0.244). The overall mean number of days for the occurrence of postoperative events was 10.6 ± 5.7 days (range of 4–22 days); there were no significant differences between the groups: 13.0 ± 2.6 days for apixaban, 7.8 ± 1.6 days for edoxaban, and 11.0 ± 2.8 days for rivaroxaban (p = 0.983). Nine of the 13 patients (69%) experienced an event within 5 days after starting treatment. The dose distribution was as follows: 84% of patients received a high dose of apixaban, 82% of patients received a high dose of rivaroxaban, and 69% of patients received a low dose of edoxaban. Thus, the percentage of patients on the low dose was significantly higher in the edoxaban group than that of the other two drugs ($p<0.0001$). All patients in the apixaban and rivaroxaban groups received aspirin as an antiplatelet agent. However, patients in the edoxaban group received different antiplatelet agents, such as aspirin (n = 45), clopidogrel (n = 1), or a combination of aspirin and prasugrel (n = 1). No significant differences were observed in the use of antiplatelet agents among the study groups.

**Table 3** describes the primary endpoints experienced by patients, which included major bleeding events. We observed GI bleeding in 3% (n = 1), 1% (n = 1), and 12% (n = 2) of the apixaban, edoxaban, and rivaroxaban groups, respectively. Pleural bleeding was observed in 6% of patients in the rivaroxaban group (n = 1). Major bleeding and GI bleeding were significantly more common in the rivaroxaban group (major bleeding: p = 0.011, GI bleeding: p = 0.047). No intracranial bleeding occurred in any of the groups. One case of stroke was observed in the rivaroxaban group but not in the other groups (p = 0.125). Minor bleeding did not occur in the rivaroxaban group, while only one patient (3%) in the apixaban group and two patients (2%) in the edoxaban group experienced minor bleeding episodes (p = 1.00). The Kaplan–Meier analysis determined that the event-free rate of major bleeding on day 60 for apixaban, edoxaban, and rivaroxaban was 96.8 ± 3.2%, 98.9 ± 1.1%, and 82.4 ± 9.2%, respectively; this rate was significantly lower for rivaroxaban (p = 0.003) (**Fig. 1**). The event-free rate of GI bleeding for apixaban, edoxaban, and rivaroxaban was 96.8 ± 3.2%, 98.9 ± 1.1%, and 88.2 ± 7.8%, respectively; thus, there were no significant differences between three groups (p = 0.057). (**Fig. 1**) Finally, the event-free rate of stroke for apixaban, edoxaban, and rivaroxaban was 100%, 100%, and 94.1 ± 5.7%, respectively; the rivaroxaban group had a significantly lower event-free rate of stroke (p = 0.031) (**Fig. 1**).

**Table 4** describes the secondary endpoints experienced by patients. In all three groups, there were no significant changes in Hb from pretreatment to post-DOAC treatment (p = 0.543), but Hb did significantly increase one month after DOAC treatment began ($p<0.0001$ in each group).

Before treatment, PT was similar among the study groups (**Table 4**). PT was significantly more prolonged in apixaban than in edoxaban at week 1 and month 1 (1 week: p = 0.017, 1 month: p = 0.012). Like PT, APTT at

**Table 1 Characteristics of patients who developed POAF following cardiac surgery**

| | Apixaban | Edoxaban | Rivaroxaban | p value |
|---|---|---|---|---|
| Number of patients | 31 | 87 | 17 | |
| Age (years) | 71.4 ± 1.7 | 73.4 ± 1.0 | 72.2 ± 2.0 | 0.753 |
| >65 | 25 (81%) | 73 (84%) | 14 (82%) | 0.890 |
| >75 | 11 (35%) | 44 (51%) | 8 (47%) | 0.383 |
| Gender (male: female) | 20:11 | 54:33 | 11: 6 | 1.00 |
| Body weight (kg) | 61.2 ± 2.2 | 58.3 ± 1.3 | 57.4 ± 2.9 | 0.454 |
| Creatine clearance (mL/min) | 73.6 ± 4.7 | 70.3 ± 2.3 | 67.9 ± 6.8 | 0.689 |
| Basic disease | | | | 0.323 |
| Ischemic heart disease | 15 (48%) | 29 (33%) | 8 (47%) | |
| Valvular disease | 2 (7%) | 5 (6%) | 1 (6%) | |
| Aortic disease | 10 (32%) | 48 (55%) | 7 (41%) | |
| Other | 4 (13%) | 5 (6%) | 1 (6%) | |
| Surgical procedure | | | | |
| CABG | 15 (48%) | 28 (32%) | 9 (53%) | |
| CABG+TAP | 0 | 1 (1%) | 0 | |
| Mitral annuloplasty | 1 (0.3%) | 3 (3%) | 1 (6%) | |
| Mitral annuloplasty+TAP | 1 (0.3%) | 2 (2%) | 0 | |
| Asc-Ao replacement | 5 (16%) | 20 (23%) | 2 (12%) | |
| Asc-Ao replacement +CABG | 0 | 0 | 1 (6%) | |
| Total arch replacement | 3 (1%) | 22 (25%) | 3 (18%) | |
| Total arch replacement+CABG | 2 (0.6%) | 3 (3%) | 0 | |
| Des-Ao replacement | 0 | 3 (3%) | 0 | |
| Tumor extirpation | 2 (0.6%) | 3 (3%) | 0 | |
| ASD closure | 1 (0.3%) | 1 (1%) | 0 | |
| ASD closure+TAP | 1 (0.3%) | 1 (1%) | 0 | |
| +Maze | 4 (13%) | 3 (3%) | 0 | |
| Risk factors | | | | |
| Diabetes mellitus | 10 (32%) | 26 (30%) | 5 (29%) | 0.961 |
| Hypertension | 21 (68%) | 65 (75%) | 10 (59%) | 0.400 |
| Dyslipidemia | 16 (52%) | 40 (46%) | 9 (53%) | 0.789 |
| Obesity | 6 (19%) | 10 (11%) | 2 (12%) | 0.517 |
| Cerebrovascular disease | 7 (23%) | 13 (15%) | 4 (24%) | 0.524 |
| Peripheral atrial disease | 5 (16%) | 18 (21%) | 3 (18%) | 0.946 |
| Heart failure | 5 (16%) | 9 (10%) | 2 (12%) | 0.675 |
| Preoperative anticoagulation therapy | 6 (19%) | 10 (11%) | 3 (18%) | 0.434 |
| | DOAC; 6 | DOAC; 8 warfarin; 2 | DOAC; 3 | |
| $CHADS_2$ score | 2.00 ± 0.22 | 1.94 ± 0.12 | 1.94 ± 0.42 | 0.974 |
| $CHADS_2$-VASc score | 4.03 ± 0.37 | 4.01 ± 0.18 | 4.00 ± 0.60 | 0.998 |

Asc-Ao: ascending aorta; ASD: atrial septal defect; CABG: coronary artery bypass grafting; Des-Ao: descending aorta; POAF: postoperative atrial fibrillation; TAP: tricuspid annuloplasty

pretreatment was similar among the groups; but on Day 1, APTT was significantly more prolonged in apixaban than in rivaroxaban (p = 0.011). For pleural and pericardial bleeding, the number of patients who received DOAC before drainage removal in apixaban, edoxaban, and rivaroxaban was 7 (23%), 18 (21%), and 3 (18%), respectively. The length of DOAC treatment before drainage removal for apixaban, edoxaban, and rivaroxaban were 1.14 ± 0.26 days, 1.39 ± 0.24 days, and 1.33 ± 0.33 days, respectively; thus, there were no significant differences (p = 0.840). There was one patient (6%) in the rivaroxaban group with suspected pleural bleeding, so both X-ray and drainage were conducted. The number of patients with pericardial effusions that were 5mm or longer in apixaban, edoxaban, and rivaroxaban were as follows: 3 (10%), 10 (11%), and 4 (24%), respectively (p = 0.363). The number of patients with pericardial effusions that were 10 mm or larger in apixaban, edoxaban, and rivaroxaban were 0, 3 (3%, maximum 12 mm), and 1 (6%, maximum 11 mm), respectively (p = 0.434). However, when pericardial bleeding was suspected, since it negatively affects hemodynamics, no patient underwent pericardial drainage.

The renal functions, sCr and CRCL, were neither significantly different among the groups nor within each

**Table 2 Operative and postoperative characteristics of patients who underwent cardiac surgery**

| | Apixaban | Edoxaban | Rivaroxaban | p value |
|---|---|---|---|---|
| Number of patients | 31 | 87 | 17 | |
| ACCT | 83.1 ± 6.1 | 89.8 ± 5.7 | 79.5 ± 7.0 | 0.559 |
| ECCT | 124.8 ± 9.1 | 140.6 ± 9.1 | 131.3 ± 14.0 | 0.685 |
| Off pump | 5 (16%) | 16 (18%) | 2 (12%) | 0.942 |
| Onset day of POAF post-surgery | 3.90 ± 0.47 | 4.40 ± 0.30 | 4.30 ± 0.50 | |
| Dose | | | | <0.0001 |
| Low dose | 5 (16%) | 60 (69%) | 3 (18%) | |
| High dose | 26 (84%) | 27 (31%) | 14 (82%) | |
| Antiplatelet therapy | 20 (65%) | 46 (53%) | 9 (53%) | 0.537 |
| Criteria for administering DOAC | | | | |
| POAF | 27 (87%) | 78 (90%) | 14 (82%) | 0.525 |
| Chronic Af | 4 (13%) | 9 (10%) | 3 (18%) | |

ACCT: aortic cross-clamp time; Af: atrial fibrillation; DOAC: direct oral anticoagulants; ECCT: extracorporeal circulation time; POAF: postoperative atrial fibrillation

**Table 3 The primary endpoints and complications of patients who underwent cardiac surgery**

| | Apixaban | Edoxaban | Rivaroxaban | p value |
|---|---|---|---|---|
| Number of patients | 31 | 87 | 17 | |
| Total events | 4 (13%) | 4 (5%) | 5 (29%) | 0.007 |
| Major bleeding | 1 (3%) | 1 (1%) | 3 (18%) | 0.011 |
| GI bleeding | 1 (3%) | 1 (1%) | 2 (12%) | 0.047 |
| Intracranial bleeding | 0 | 0 | 0 | – |
| Pleural bleeding | 0 | 0 | 1 (6%) | 0.126 |
| Minor bleeding | 1 (3%) | 2 (2%) | 0 | 1.00 |
| Hematuria | 0 | 1 (1%) | 0 | 1.00 |
| Nasal bleeding | 1 (3%) | 0 | 0 | 0.356 |
| Pharyngeal bleeding | 0 | 1 (1%) | 0 | 1.00 |
| Cerebral infarction | 0 | 0 | 1 (6%) | 0.125 |
| Liver dysfunction | 2 (6%) | 1 (1%) | 0 | 0.173 |
| Renal dysfunction | 0 | 0 | 1 (6%) | 0.127 |

group. Due to decreased renal function, the dosage was decreased for only one patient, who was in the rivaroxaban group.

## Discussion

To the best of our knowledge, no prospective studies have been published yet on the use of DOAC after cardiac surgery. Previously, we investigated the effects of edoxaban in a limited number of patients (n = 15), but there was no incidence of either stroke or bleeding in that study. Therefore, we decided to carry out this prospective, observational study of 135 patients that received DOAC as anticoagulant therapy for the treatment of POAF after cardiac surgery. Stroke occurred in only one patient (0.7%), and the incidence of major bleeding was low, with only five patients (3.7%). Both efficacy and safety were acceptable; in particular, apixaban and edoxaban were stroke-free, and all groups had a low incidence of major bleeding. Since most events occurred shortly after surgery, we determined that these events were due to surgical-related complications rather than drug-related complications.

Anticoagulant therapy based on warfarin is recommended for POAF following cardiac surgery, irrespective of whether heparin bridging is performed or not.[12] However, it takes several days before warfarin reaches its full therapeutic potential. According to the results of a meta-analysis and several large-scale studies, heparin bridging is associated with a threefold to fivefold higher incidence of bleeding.[13,14] Anticoagulation therapy using DOAC was recently recommended for the management of NVAF. Although DOAC is commonly used in clinical practice,[1–3] few studies have investigated its role in cardiac surgery. According to the 2014 ESC/EACTS Guideline and the 2012 Guideline Revised Version,[15] either

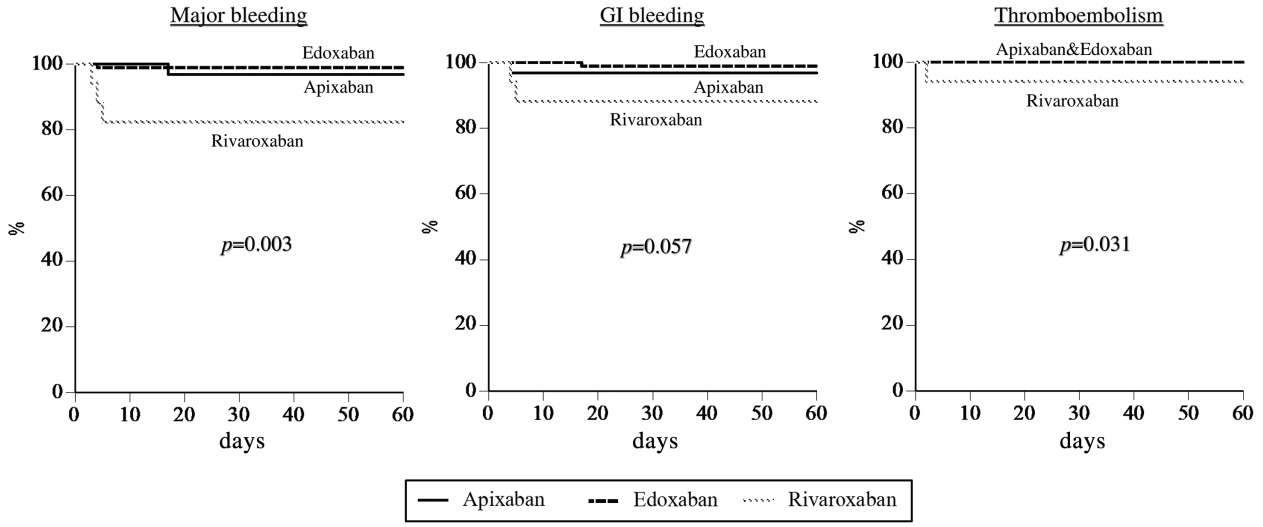


**Fig. 1** Event-free rates of major bleeding, GI bleeding, and thromboembolism. GI: gastrointestinal

heparin or NOAC for 4 weeks is recommended for the management POAF lasting more than 48 hours to prevent strokes;[16] these recommendations were updated in 2018 to include use of the CHA2DS2-VASc score, warfarin, and NOAC for POAF management. However, there were no relevant clinical studies cited for either the 2014 or 2018 guidelines;[17] but there were several reports involving databases and questionnaires cited. For instance, Beller et al. reviewed the Society of Thoracic Surgeons' database and found that 18% of 34,188 patients were prescribed anticoagulants at discharge, and 23% of those were prescriptions for DOAC. Interestingly, the number of prescribed DOACs increased rapidly from 10.3% in 2011–2014 to 35.4% in 2015–2018. Others reported that the number of patients with POAF using non–vitamin K oral anticoagulants increased after undergoing bioprosthetic valve replacement and isolated CABG from 6.3% to 35.4% and from 12.3% to 40.3%, respectively (both $p < 0.01$); furthermore, DOAC resulted in a significantly shorter postoperative hospital stay ($p < 0.01$).[18] Vranckx et al. conducted questionnaires at 16 clinical sites in 14 countries where DOAC was initiated within 24 hours after cardiac surgery at 12 institutions, but only 3 sites used heparin prior to DOAC; they concluded that the incidence of postoperative pericardial bleeding, which required pericardiocentesis or re-intervention, was from 0% to 6.5% with an average incidence rate of 2.4%. Additionally, the same article stated that "the optimal postoperative antithrombotic treatment for Af patients is not guided by randomized controlled trials in general, and there is a lack of data concerning the use of DOACs in early postoperative Af in particular"; thus, it emphasized the necessity of a controlled clinical study of DOAC for POAF management.[19] Yu et al. conducted a retrospective analysis of anticoagulation therapy in 246 patients who underwent CABG (warfarin [n = 182], NOAC [n = 64], 38 rivaroxaban, 22 apixaban, 4 dabigatran); the incidence of invasive intervention for pericardial or pleural effusion was 26.6% in NOAC patients and 13.2% in warfarin patients. DOAC patients were reported to be significantly higher ($p < 0.014$).[20]

Anderson et al. reported a retrospective study of POAF following isolated CABG. Warfarin (27 patients received low molecular weight heparin as a bridging) was used in 45 patients and DOAC (apixaban 21 patients, dabigatran 1 patient, rivaroxaban 5 patients) was used in 27 patients. There were no strokes and no differences in the incidence of bleeding during the hospitalization period between two groups. However, delayed major bleeding after discharge occurred in two warfarin group patients and no incidences in the DOAC group. The therapeutic potential time range was significantly prolonged in the warfarin group. Moreover, drug costs were significantly higher in the NOAC group; however, if international normalized ratio (INR) tests are included inpatient treatment, then the 30-day anticoagulant costs were significantly more expensive in the warfarin group. Ultimately, they concluded that DOAC provided quick therapeutic effects at a cheaper cost than did warfarin.[21] There are several concerns with warfarin therapy that include a long time to provide therapeutic anticoagulation, an increased incidence of bleeding when used

**Table 4 The changes in the secondary endpoints of patients who underwent cardiac surgery**

| | Day 0 | Day 1 | Day 3 | Day 7 | Day 30 |
|---|---|---|---|---|---|
| Hemoglobin (g/dL) | | | | | |
| Apixaban | 10.9 ± 0.2* | 11.0 ± 0.2 | 11.1 ± 0.2 | 11.2 ± 0.3 | 12.0 ± 0.2* |
| Edoxaban | 11.1 ± 0.1* | 11.1 ± 0.1 | 11.1 ± 0.1 | 11.0 ± 0.2 | 11.7 ± 0.1* |
| Rivaroxaban | 10.8 ± 0.3* | 10.9 ± 0.3 | 10.9 ± 0.3 | 11.1 ± 0.3 | 11.4 ± 0.3* |
| PT (sec) | | | | | |
| Apixaban | 13.9 ± 0.3 | 16.5 ± 1.0 | – | 17.8 ± 0.8** | 19.7 ± 1.5** |
| Edoxaban | 13.4 ± 0.2 | 15.6 ± 0.5 | – | 16.0 ± 0.3** | 16.5 ± 0.5** |
| Rivaroxaban | 13.9 ± 0.7 | 16.3 ± 0.9 | – | 16.6 ± 1.1 | 19.1 ± 1.5 |
| APTT (sec) | | | | | |
| Apixaban | 34.7 ± 1.1 | 36.2 ± 1.2# | – | 35.4 ± 0.8 | 37.3 ± 1.3 |
| Edoxaban | 34.4 ± 1.0 | 34.2 ± 0.6 | – | 34.1 ± 0.5 | 36.4 ± 0.5 |
| Rivaroxaban | 33.5 ± 1.3 | 31.9 ± 0.7# | – | 33.5 ± 0.7 | 36.8 ± 1.3 |
| sCr (mg/dL) | | | | | |
| Apixaban | 0.84 ± 0.07 | 0.86 ± 0.06 | 0.86 ± 0.06 | 0.88 ± 0.07 | 0.90 ± 0.05 |
| Edoxaban | 0.81 ± 0.03 | 0.81 ± 0.03 | 0.81 ± 0.03 | 0.82 ± 0.03 | 0.90 ± 0.03 |
| Rivaroxaban | 0.91 ± 0.10 | 0.92 ± 0.08 | 0.89 ± 0.08 | 0.88 ± 0.07 | 0.96 ± 0.08 |
| CRCL (mL/min) | | | | | |
| Apixaban | 73.6 ± 4.7 | 68.7 ± 3.6 | 67.6 ± 3.3 | 64.7 ± 3.1 | 62.7 ± 3.4 |
| Edoxaban | 70.3 ± 2.3 | 70.0 ± 2.2 | 69.7 ± 2.0 | 67.5 ± 2.1 | 61.7 ± 2.0 |
| Rivaroxaban | 67.9 ± 6.8 | 65.3 ± 6.8 | 66.9 ± 6.3 | 64.9 ± 5.3 | 60.7 ± 5.2 |

*p <0.05: Day 0 vs. Day 30, **p <0.05: Apixaban vs. Edoxaban, #p <0.05: Apixaban vs. Rivaroxaban. APTT: activated partial thromboplastin time; CRCL: creatinine clearance; PT: prothrombin time; sCr: serum creatine

concomitantly with heparin, and the effect of various foods. However, anticoagulant therapy using DOAC will mitigate these issues related to warfarin.

Currently, four types of DOAC are used clinically; but we do not know which drug is superior in terms of efficacy and safety because direct head-to-head comparative studies have not been performed yet. Although not in direct comparison, several meta-analyses reported that DOAC significantly decreased the incidence of stroke or systemic embolic events when compared to warfarin. However, DOAC was associated with a significantly higher rate of GI bleeding than warfarin. The incidence of major bleeding was comparable between dabigatran, rivaroxaban, and warfarin; but the incidence of major bleeding in apixaban and edoxaban was significantly lower than in warfarin. Thus, they reported excellent efficacy and safety of DOAC.[22)]

Wang et al. conducted a meta-analysis of the effects of four drugs in Asians compared to non-Asians and found that Asians were more likely to have a lower incidence of stroke, systemic embolism, and major bleeding when the standard dose of DOAC was administered. Interestingly, the incidence of intracranial hemorrhage was lower with the four DOACs than with warfarin. The incidence of major bleeding and hemorrhagic stroke was lower with apixaban, dabigatran, and edoxaban than with warfarin.[23)]

In this study, rivaroxaban was associated with a higher incidence of postoperative events than either apixaban or edoxaban. However, the number of patients in this study was limited, and further investigation is necessary. Based on our study results and past reports, the administration of a low dose of rivaroxaban shortly after cardiac surgery is preferred when there is a high risk of bleeding events. Recently, we initiated a multicenter randomized controlled trial of apixaban and edoxaban for POAF to clarify the efficacy and identify potential issues related to POAF (UMIN ID: UMIN000037605).

## Limitations

This was not a randomized clinical trial, and there were some variances in the number of patients in the study groups. Also, there were a limited number of patients in this single-center study. Therefore, a randomized, multicenter clinical study is necessary to investigate the differences among DOACs and their clinical characteristics further.

## Conclusion

In this study, DOAC was used as anticoagulation therapy for patients after cardiac surgery for the management of early phase POAF. The safety of DOAC was favorable,

with a low incidence of major bleeding. Since there was only one case of stroke, our study indicates that the efficacy of DOAC is excellent. Therefore, we determined that apixaban and edoxaban were better than rivaroxaban in terms of both safety and efficacy.

## Disclosure Statement

Akira Sezai received payment for lecture fees from Bayer, Ltd.; Bristol-Myers Squibb Company; Ltd.; Chugai Pharmaceutical Company; Mitsubishi Tanabe Pharma Company; Daiichi Sankyo Company, Ltd.; and Pfizer Inc. The other authors declare no conflicts of interest associated with this study.

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