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REVIEW ARTICLE

Perioperative management of patients with atrial fibrillation receiving anticoagulant therapy

Takeshi Omae[1] · Keito Koh[1] · Masateru Kumemura[1] · Sonoko Sakuraba[1] · Yosuke Katsuda[1]

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Abstract

The number of patients with atrial fibrillation (AF) and the number of patients indicated for anticoagulant therapy have been increasing because AF would affect patient survival due to thromboembolism. Once AF develops, following the disappearance of pulsation, the circumstances within the atrium become prothrombotic and thrombus formation within the left atrium occurs in patients with AF. In recent years, not only warfarin but also new oral anticoagulants were introduced clinically and have become used as oral anticoagulants. In the perioperative period, the risk of major hemorrhage needs to be reduced. On the other hand, the suspension of anticoagulant therapy and neutralization of anticoagulant effects elevate the risk of thrombosis. The perioperative management of patients receiving anticoagulant therapy is different from that of scheduled surgery and emergency surgery. In addition, knowledge of the characteristics of each oral anticoagulant is required at drug cessation and resumption. Unlike warfarin, which has been used in the past five decades, direct oral anticoagulants (DOACs) do not have sensitive indicators such as prothrombin time-international normalized ratio. To avoid major hemorrhages and thromboembolism, quantitative assays can be implemented for DOAC monitoring and for reversal therapies in perioperative settings.

Keywords Atrial fibrillation · Direct oral anticoagulants · Hemorrhage · Scheduled and emergency surgery · Thromboembolism

Introduction

Following the recent increase in the elderly population, the number of patients with atrial fibrillation (AF) and the number of patients indicated for anticoagulant therapy have been increasing. In the past five decades, warfarin was the only oral anticoagulant available for use. In recent years, new oral anticoagulants were introduced clinically and are becoming used in increasing amounts. This paper outlines the perioperative management of patients with AF receiving anticoagulant therapy, focusing on features of AF, the relationship between AF and thrombosis, drugs available for use in anticoagulant therapy, measures to be taken upon scheduled surgery for patients receiving anticoagulant therapy, and measures to be taken upon emergency surgery.

✉ Takeshi Omae
omae@za2.so-net.ne.jp

[1] Department of Anesthesiology and Pain Clinic, Juntendo University Shizuoka Hospital, Izunokuni, 1129 Nagaoka, Izunokuni, Shizuoka 410-2295, Japan

Clinical features of AF

Complication by AF can affect the prognostic factors influencing the survival of patients. In the Framingham Study (a large-scale cohort study of cardiovascular disease), 5209 patients were divided into a group with complications due to AF ($n=621$) and an AF-free group ($n=4588$), and the prognostic outcome was compared between these two groups, revealing an elevation of the death rate following complications by AF [male: odds ratio (OR) 1.5, 95% confidence interval (CI) 1.2–1.8; female: OR 1.9, 95% CI 1.5–2.2] and a twofold elevation of the incidence of cardiovascular events (cerebral infarction, heart failure, etc.) [1, 2].

Risk factors for the onset of AF include age, diabetes mellitus, hypertension, myocardial infarction, and congestive heart failure [3]. Among others, aging causes elevation in the incidence of AF, and it has been reported that the prevalence of AF is 10% or higher at age 80 and older [4].

The $CHADS_2$ score calculated from these risk factors [congestive heart failure (score 1), hypertension (score 1), age ≥ 75 (score 1), diabetes mellitus (score 1)] plus history

of stroke or transient ischemic attack (score 2) has been proposed as a tool for the identification of AF patients having a high risk for stroke. Moreover, from the viewpoint of Net Clinical Benefit, we can see that anticoagulant therapy becomes more useful if the $CHADS_2$ score exceeds 2 [5–9].

Relationship between AF and thrombosis

The living body rapidly recognizes an injured site and activates the clotting system (platelet system and coagulation system) at that site alone. As a result, hemostasis can be achieved immediately. Erroneous functioning of the clotting system within blood vessels can directly lead to pathologic thrombosis. To avoid this, the vascular endothelial cells usually control the clotting system and prevent thrombosis within the closed circulating system [10]. In other words, hemostasis occurs only at sites where the vascular endothelial cells have been injured or have disappeared, i.e., at injured sites. This antithrombotic function of endothelial cells involves multiple mechanisms, including the following: (1) prevention of platelet activation by prostacyclin, nitric oxide (NO), and adenosine diphosphatase; (2) binding of antithrombin and tissue factor pathway inhibitor to the heparin-like molecule on the endothelial cells; and (3) tissue plasminogen activator (t-PA) secretion and plasmin formation [11–16]. However, metabolic syndrome, involving diabetes mellitus, hypertension, and hyperlipidemia among others, causes oxidative stress to the vascular endothelial cells, resulting in NO synthesis and reduced synthesis of thrombomodulin and t-PA, thereby changing the antithrombotic conditions to prothrombotic within the closed circulating system [17–20]. These changes are intensified by aging [1, 21]. The endocardium, like vascular endothelial cells, also possesses antithrombotic activity but, following the disappearance of pulsation, etc., the circumstances within the atrium become increasingly more prothrombotic. In this way, thrombus formation within the left atrium occurs in patients with AF. Blood retention within the left atrium also plays a large role in thrombus formation there in such cases [22–24]. The percentage of AF patients showing thrombus formation within the left atrium has been reported to be 14% (76/549 cases) by the ACUTE Study, involving observation by transesophageal echocardiography during outpatient clinic visits [25].

Anticoagulant therapy

Until the 1980s, aspirin was the major drug used for antithrombus therapy. Nowadays, anticoagulant therapy is playing a central role. This was endorsed also by the meta-analysis of 12 randomized control trials (RCTs) comparing the cerebral infarction-preventive effect between warfarin and aspirin in 12,963 patients with AF [relative risk (RR) reduction 0.39; 95% CI 0.22–0.52; $p < 0.001$] [26].

Warfarin

Warfarin is a vitamin K antagonist whose action targets vitamin K epoxide reductase (VKOR). Unbound warfarin inhibits this enzyme to suppress the vitamin K recycling circuit. In this way, this drug manifests its pharmacological activity through inhibiting the active forms of clotting factors (Fig. 1) [27, 28]. Warfarin shows quite numerous interactions with concomitantly used drugs. Drugs known to require particular caution include macrolide antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), statins, amiodarone, antiplatelet drugs, cimetidine, and omeprazole [29]. Natto (fermented soybeans) is rich in vitamin K and can change PT-INR even after a single dose, thus requiring caution [30].

The American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guideline for the Management of Patients with Atrial Fibrillation recommends the PT-INR to be controlled between 2.0 and 3.0 during use of warfarin for AF patients with risk factors [Class I, level of evidence (LOE) A] [31].

Differences in the efficacy of warfarin among races have also been reported [32–36]. Particularly because many cases of major hemorrhage were reported among elderly people, the current Japanese guidelines (Guidelines for Pharmacotherapy of Atrial Fibrillation) divides patients into two groups according to age (< 70 and ≥ 70 years) and recommends anticoagulation management with the use of

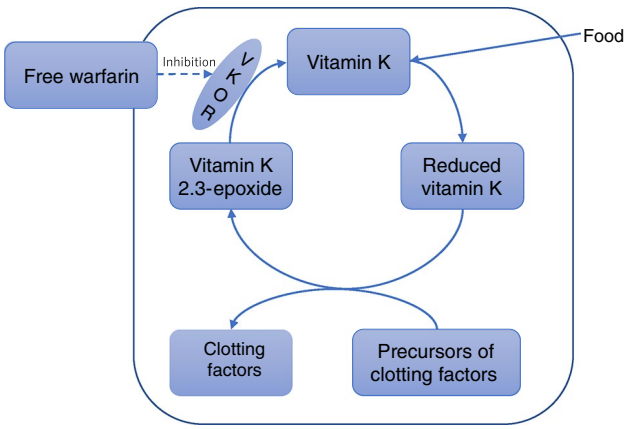

Fig. 1 Vitamin K cycle and action site of warfarin. Warfarin is a vitamin K antagonist whose action targets vitamin K epoxide reductase (VKOR). Unbound warfarin inhibits this enzyme to suppress the vitamin K recycling circuit. After that, it inhibits Vitamin K-dependent clotting factors (factors II or prothrombin, VII, IX, and X)

warfarin if 2.0 < PT-INR < 3.0 at age < 70 and if 1.6 < PT-INR < 2.6 at age ≥ 70 (Class I, LOE B) [37].

DOAC

At present, four vitamin K non-antagonizing oral anticoagulants are used clinically. These new oral anticoagulants exert their pharmacological activity by directly inhibiting thrombin or activated clotting factor X (factor Xa) (Fig. 2) [38–44]. For this reason, they are called direct oral anticoagulants (DOACs). These DOACs have features not seen in warfarin such as less inter-individual differences in efficacy, less interactions with meals or concomitantly used drugs and more stable pharmacokinetics [38–44]. Warfarin suppresses the formation of four clotting factors (factors II, VII, IX, and X), whereas DOACs suppress only one clotting factor (Fig. 2) [38–46]. As a result, despite the same outcome (suppressed formation of fibrin), the way of suppression differs markedly in terms of the relationship to blood drug level between warfarin and DOACs [38–46]. When warfarin is used, the elevation of the blood drug level affects the four clotting factors [45, 46]. As a result, the elevation of the blood drug level works in a synergistic manner, leading to a sharp increase of the drug's efficacy [45, 46]. With DOACs, by contrast, blood drug level elevation does not work in a synergistic manner, leading to a more gentle increase in drug efficacy [38–44]. This explains why DOACs, which suppress a single molecule, are more stable in terms of pharmacokinetics than is warfarin, which suppresses multiple molecules [38–46].

DOACs are roughly divided into thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) [38–44, 47].

Dabigatran

Dabigatran is the first clinically introduced DOAC for the prevention of stroke and systemic embolism associated with non-valvular AF [38]. The fraction of dabigatran excreted via the kidneys is high (80%) (Table 1) [48, 49]. Therefore, adequate care must be taken when this drug is prescribed to patients with compromised renal function. A correlation between activated partial thromboplastin time (APTT) and diluted thrombin time (diluted TT) for dabigatran has been reported [39, 50–55] (Table 2). The International Society on Thrombosis and Haemostasis (ISTH) guideline recommends APTT and the American College of Chest Physicians (ACCP) guideline recommends diluted TT as the appropriate screening marker for dabigatran [56, 57]. Dabigatran can be well quantified by using specific parameters, including diluted TT, ecarin chromogenic assay (ECA), and ecarin clotting time (ECT) [51–61]. The ISTH guideline recommends diluted TT, and the ACCP guideline recommends ECT for the quantification of dabigatran [56, 57].

Factor Xa inhibitors

Factor Xa inhibitors are DOACs that were clinically introduced after dabigatran was. The excretion rate of factor Xa inhibitors via the kidneys is lower than that of dabigatran, especially that of apixaban (24–28%). Rivaroxaban is contraindicated in individuals with moderately compromised hepatic function because two-third of the drug's excretion/degradation depends on the liver [49]. However, the influence of hepatic function on apixaban is relatively small during treatment [62].

A correlation of factor Xa inhibitors with prothrombin time (PT) has been reported [55, 63–66] (Table 2). The ISTH and ACCP guidelines recommend PT as a screening

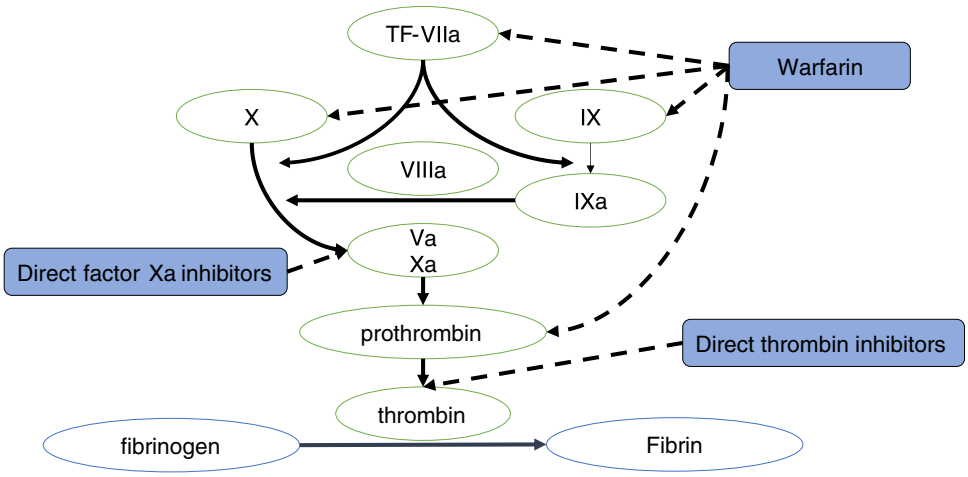

Fig. 2 Antithrombotic drug and their targets in the coagulation pathway. Warfarin inhibits Vitamin K-dependent clotting factors (factors II or prothrombin, VII, IX, and X). Direct factor Xa inhibitor (dabigatran) directly inhibits activated clotting factor X, and direct thrombin inhibitors (rivaroxaban, apixaban, and edoxaban) directly inhibit thrombin. Dotted lines, inhibition. TF-VIIa, Tissue factor and factor VIIa. After Umer Usman MH et al., with permission

Table 1 DOACs pharmacokinetic and pharmacodynamic characteristics From Cabral KP with permission

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
T_{max} (h)	1.5–3	2–4	1–3	1–2
VD (L)	50–70	50	~ 23	> 300
Half time (h)	12–17	5–9	9–14	9–11
Bioavailability	6.5%, pH sensitive	> 80%	> 50%	45%
Plasma protein binding ratio	35%	92–95%	87%	40–59%
Metabolism	Conjugation	CYP3A4, CYP2J2	CYP3A4	CYP3A4
Elimination	80% renal	66% renal (33% as active metabolites)	T_{max} delayed; C_{max} and AUC unchanged	T_{max} delayed; C_{max} and AUC unchanged
Effects of food	T_{max} delayed; C_{max} & AUC unchanged	T_{max} delayed; C_{max} & AUC increased	0.54	0.87
CYP3A4 substrate	No	Yes	Yes	Yes
P-gp substrate	Yes-dabigatran etexilate	Yes	Yes	Yes
Drug interactions	Potent P-gp inducers/inhibitors	Potent CYP3A4 inhibitors and P-gp inducers/inhibitors	Potent CYP3A4 inhibitors and P-gp inducers/inhibitors	CYP3A4 inhibitors and P-gp inducers/inhibitors

DOACs direct oral anticoagulants, *CYP* cytochrome P450, *VD* 0.3 L/kg and assuming a 75 kg patient

marker for factor Xa inhibitors [56, 57]. Factor Xa inhibitors can also be well quantified by using specific assays such as anti-FXa assays [65, 67–70]. The ISTH and ACCP guidelines recommend anti-FXa assays as the quantitative assay for factor Xa inhibitors [56, 57].

Measures to be taken upon scheduled surgery

The annual risk for onset of cerebral infarction in patients with non-valvular AF has been reported to be 5%, with the incidence of cerebral infarction induced by one-week drug cessation being about 0.1% [71–74]. In the RE-LY Trial, on the other hand, ischemic stroke developed at an incidence of 0.4% despite the application of heparin bridge therapy during the perioperative drug cessation period [38]. Thus, the risk for cerebral infarction rises several-fold during the perioperative period.

Scheduled surgery for patients taking warfarin

When warfarin is used in the therapeutic range (2.0 < PT-INR < 3.0), PT-INR begins to decrease 24–36 h after drug cessation, reaching PT-INR 1.6 on average at 60 h after drug cessation [75]. This is explained by sensitive reaction of PT-INR to the clotting factor VII with short half-life [76]. If drug cessation starts at PT-INR 2.0–3.0, PT-INR decreases to 1.5 or lower in all cases four days after drug cessation [75]. The Japanese Guideline for the Management of Patients with Atrial Fibrillation recommends that minor surgery on the surface of the body be conducted with continued warfarin use after checking that PT-INR is within an appropriate therapeutic range (Class IIa, LOE C) [37]. In cases of major hemorrhage and cases in which it is difficult to deal with hemorrhage, it is recommended that warfarin is suspended 5 days before surgery and heparin treatment is started when PT-INR lowers the therapeutic range (i.e., at PT-INR < 2.0 for patients aged 70 or less and at PT-INR < 1.6 for patients aged over 70, infusing it serially intravenously until 4–6 h before surgery (Class IIa, LOE C) [37]. The dose level of heparin is adjusted so that APTT is extended to 1.5–2.5 times the control level [37].

After surgery, warfarin and heparin are resumed as soon as possible. Soon after the start of warfarin treatment, the concentration of protein C (another vitamin K-dependent clotting suppressive factor) also decreases, thus posing a risk for excessive clotting [77–79]. If warfarin use is resumed at the maintenance dose level, it takes 7–10 days until PT-INR returns to the therapeutic range [80]. Heparin is discontinued when PT-INR reaches the therapeutic range for warfarin [37].

Table 2 Summary of the usefulness common coagulation assays for assessment of anticoagulant effect of DOACs From Samuelson et al., with permission

Coagulation assay	Relationship to expected 'on therapy' range	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
APTT	Below	Normal or prolonged[a]	Normal limits	Normal limits	Normal limits
	Within	Prolonged	Normal or prolonged[b]	Normal or prolonged[b]	Normal limits
	Above	Prolonged	Normal or prolonged[b]	Prolonged	Normal or prolonged[c]
PT-INR	Below	Normal limits	Normal limits	Normal limits	Normal limits
	Within	Normal or prolonged[d]	Normal or prolonged	Normal or prolonged[e]	Normal or prolonged[f]
	Above	Normal or prolonged[d]	Normal or prolonged	Normal or prolonged[e]	Normal or prolonged[f]
TT	Below	Prolonged	Normal	Not indicated	Not indicated
	Within	Prolonged/out of range	Normal	Not indicated	Not indicated
	Above	Prolonged/out of range	Normal	Not indicated	Not indicated
Diluted TT	Below	Normal or prolonged[g]	Not indicated	Not indicated	Not indicated
	Within	Prolonged[g]	Not indicated	Not indicated	Not indicated
	Above	Prolonged[g]	Not indicated	Not indicated	Not indicated
Anti-Xa	Below	Not indicated	Normal or increased[h]	Normal or increased[i]	Normal or increased
	Within	Not indicated	Increased	Increased	Increased
	Above	Not indicated	Increased	Increased[e]	Increased[j]

APTT activated partial thromboplastin time, *DOAC* direct oral anticoagulant, *PT-INR* prothrombin time-international normalized ratio, *TT* thrombin time

[a]Results may remain within normal limits at low concentrations (< 70 ng/mL)

[b]Results may remain within normal limits above concentrations of 100 ng/mL

[c]Concentrations of 300–600 ng/mL required to double APTT

[d]Some reagents have results within normal limits at high concentrations (100–400 ng/mL)

[e]Results remain within normal limits up to a concentration of 50 ng/mL

[f]Low sensitivity at low therapeutic levels; concentrations from 163 to 406 ng/mL required to double PT, depending on reagent

[g]Highest sensitivity in the range of 50–500 ng/mL

[h]Decreased sensitivity at concentrations < 30 ng/mL and reduced accuracy at upper and lower limits of quantification with some reagents

[i]Decreased sensitivity at concentrations < 15 and > 200 ng/mL

[j]Decreased accuracy and precision at concentrations > 200 to 300 ng/mL

Scheduled surgery for patients taking dabigatran

The Japanese Guideline for the Management of Patients with Atrial Fibrillation recommends that minor surgery on the body surface be conducted during continued dabigatran use (Class IIa, LOE C) [37, 48, 49]. Because the excretion/degradation of dabigatran depends highly on the kidneys (renal excretion rate 80%), the drug is suspended before surgery depending on creatinine clearance (Class IIa, LOE C) (Tables 3, 4) [37, 48, 49]. And heparin is serially infused until 4–6 h before surgery (Class IIa, LOE C) [37]. The cessation period for dabigatran is shorter than that for warfarin, but the incidence of perioperative complications does not differ significantly between the two drugs [38]. According to the AHA statement about DOAC issued in 2017, there is no need for heparin bridge therapy during the DOAC cessation period [81]. The recommendation of

Table 3 Last intake of dabigatran before elective surgical intervention From Heidbuchel et al., with permission

Renal function CCr (mL/min)	Low risk	High risk
80 < CCr	≥ 24 h	≥ 48 h
50 < CCr ≤ 80	≥ 36 h	≥ 72 h
30 < CCr ≤ 50	≥ 48 h	≥ 96 h
15 < CCr ≤ 30	Not indicated	Not indicated
CCr ≤ 15	No official indication for use	No official indication for use

See also Table 3

Low-risk surgery with low risk of bleeding, *high-risk* surgery with high risk of bleeding, *CCr* creatinine clearance

Table 4 Classification of elective surgical interventions according to bleeding risk From Heidbuchel et al., with permission

Interventions with low bleeding risk
Endoscopy with biopsy
Pristate or bladder biopsy
Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
Angiography
Pacemaker or ICD implantation (unless complex anatomical setting)
Interventions with high bleeding risk
Complex left-sided ablation (pulmonary vein isolation; VT ablation)
Spinal or epidural anesthesia; Lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy

For each patient, individual factors relating to bleeding and thromboembolic risk need to be taken into account and be discussed with the intervening physician

ICD implantable cardioverter-defibrillator, *VT* ventricular tachycardia

the Guideline about heparin bridge therapy during dabigatran cessation may change in the future.

Scheduled surgery for patients taking factor Xa inhibitors

The Japanese Guideline for the Management of Patients with Atrial Fibrillation recommends that surgery on the body surface be conducted during continued use of a factor Xa inhibitor [37]. In cases of major hemorrhage and cases in which it is difficult to deal with hemorrhage, it is recommended that the drug is suspended 24 h or more before surgery and heparin is serially infused until 4–6 h before surgery (Class IIa, LOE C) (Tables 4, 5) [37, 49]. Because the degree of reliance of excretion/degradation of activated clotting factor Xa inhibitors on the kidneys is low (renal excretion rate 27–50%), there is little need for adjusting the drug cessation period depending on the creatinine clearance (Table 1) [48, 49]. According to the AHA statement about DOAC issued in 2017, there is no need for heparin bridge therapy during the DOAC cessation period [81]. The recommendation of the Guideline about a heparin bridge during the cessation of factor Xa inhibitors may change in the future, as is the case with cessation for dabigatran.

Table 5 Last intake of activated clotting factor X inhibitor before elective surgical intervention. From Heidbuchel et al., with permission

Renal function CCr (mL/min)	Low risk	High risk
$80 < CCr$	≥ 24 h	≥ 48 h
$50 < CCr \leq 80$	≥ 24 h	≥ 48 h
$30 < CCr \leq 50$	≥ 24 h	≥ 48 h
$15 < CCr \leq 30$	≥ 36 h	≥ 48 h
$CCr \leq 15$	No official indication for use	No official indication for use

See also Table 3

Low-risk surgery with low risk of bleeding, *high-risk* surgery with high risk of bleeding, *CCr* creatinine clearance

Measures to be taken upon emergency surgery

Emergency surgery for patients taking warfarin

In cases where a major hemorrhage is developed during the use of anticoagulants or in cases requiring emergency surgery during the use of anticoagulants, correction of the anticoagulant's effect is needed. For patients taking warfarin, the Japanese Guideline for the Management of Patients with Atrial Fibrillation recommends the administration of vitamin K (Class I, LOE C), fresh frozen plasma (FFP), or clotting factor IX complex (Class IIa, LOE C) [37]. After the administration of vitamin K, it takes 3 h until the blood level of reduced vitamin K (acting on the target VKOR) reaches a peak and 12 h until the blood level of factor VII (the clotting factor with the shortest half-life) reaches a peak [82]. For this reason, the administration of a plasma preparation is needed. According to the Guideline on the use of FFP based on scientific evidence prepared by the Japan Society of Transfusion Medicine and Cell Therapy, FFP has little effect in correcting warfarin and the use of FFP as a means of emergency correction is not recommended. The said Guideline recommends the use of prothrombin complex as a means of emergency correction of warfarin. The prothrombin complex preparation contains vitamin K-dependent clotting factors (factors II, VII, IX, and X) and vitamin K-dependent clotting suppressive factors (protein C and protein S) [83, 84]. In an RCT in which 181 patients requiring correction of hemorrhagic tendencies due to warfarin during emergency surgery were divided into two groups (the prothrombin complex group and the FFP group) and the hemostatic effect and rapid PT-INR correction were compared between the two groups, the non-inferiority and superiority of Four-Factor Prothrombin Complex Concentrate (4F-PCC) to/over FFP was demonstrated in both the hemostatic

effect (4F-PCC 90% vs FFP 75%; difference 14.3%, 95% CI 2.8–25.8) and rapid PT-INR correction (4F-PCC 55% vs FFP 10%; difference 45.3%, 95% CI 31.9–56.4) [85]. Also, in a meta-analysis of the data from 19 studies (1 RCT and 18 cohort studies) involving 2878 cases in total, rapid PT-INR correction was achieved (4F-PCC 65 min vs FFP 256 min, $p < 0.0001$) without elevation in the incidence of complications by thromboembolism (4F-PCC 2.5% vs FFP 6.5%, $p = 0.54$) [86]. The Chest Guideline also recommends the use of 4F-PCC during emergency surgery, because 4F-PCC can correct PT-INR 4–6 times more rapidly in patients taking warfarin [87]. Although 4F-PCC can correct PT-INR rapidly, the PT-INR-correcting effect lasts only for a short period after a dose of only 4F-PCC (which is a clotting factor itself) [81]. Simultaneous administration of vitamin K can extend the duration of the corrective effect of PT-INR [88].

Emergency surgery for patients taking dabigatran

For patients taking dabigatran, the Guideline recommends suspension of dabigatran use and implementation of an appropriate drip infusion to promote excretion of the drug through diuresis (Class IIa, LOE C) [37]. It additionally describes the need to consider administrating factor IX, factor VII, and FFP as well as utilizing hemodialysis in view of the drug's high renal excretion rate (Table 1) [48, 49]. Although blood dabigatran levels are known to correlate with APTT, this relationship has not been standardized and if APTT is in the normal range, this shows that dabigatran has not reached its therapeutic range [81]. Diluted TT in the normal range indicates that dabigatran has not reached its therapeutic range [55]. Diluted TT and ECT are strongly correlated with plasma concentrations of dabigatran, and they are useful markers for the evaluation of the risk of bleeding following dabigatran administration [50–57] (Table 2). Idarucizumab is a drug created for the rapid neutralization of dabigatran's anticoagulant effect [89–91]. In a cohort study analyzing the neutralization rate for dabigatran's anticoagulant effect at 4 h after a dose of idarucizumab in 302 cases of serious hemorrhage and 210 cases undergoing emergency surgery, the maximum neutralization rate was 100% (95% CI 100–100) in terms of both the diluted TT and the kaolin clotting time, and the median time until hemostasis was 2.5 h for the serious hemorrhage group and 1.6 h for the emergency surgery group, thus endorsing the usefulness in neutralizing dabigatran's anticoagulant effect [92]. Idarucizumab is a monoclonal antibody fragment that neutralizes the anticoagulant effect by binding specifically to dabigatran. Its affinity for dabigatran is about 350 times higher than that of thrombin, but it is free of proclotting and anticlotting activities. Its half-life is 12 h, with the effect lasting for 24 h [89–93]. Inducing thrombocytopenia has been suggested to be a risk. Furthermore, since idarucizumab neutralizes dabigatran's anticoagulant activity, it elevates the risk for thrombosis [91, 94]. Dabigatran use may be resumed 24 h after an idarucizumab dose. The other anticoagulants can be administered immediately after a dose of idarucizumab [93, 94].

Emergency surgery for patients taking factor Xa inhibitors

For patients taking factor Xa inhibitors, the Japanese Guideline for the Management of Patients with Atrial Fibrillation also recommends suspension of dabigatran use and implementation of an appropriate drip infusion to promote excretion of the drug through diuresis (Class IIa, LOE C) [37]. It additionally recommends the use of clotting factor IX, factor VII, and FFP. In a randomized crossover study of 4F-PCC administration after rivaroxaban/dabigatran use in 12 healthy volunteers, Eerenberg et al. reported that extension of the APTT/thrombin time by dabigatran was not alleviated by 4F-PCC, but the PT extended by rivaroxaban was normalized rapidly by 4F-PCC [95]. The AHA statement about DOAC during acute care and the perioperative period also acknowledges the effectiveness of 4F-PCC or FFP [81]. On the other hand, hemodialysis has been reported to be ineffective because of the low renal excretion rate of the drug (Table 1) [51, 52, 81]. In the coagulation assays, prolonged PT showed that factor Xa inhibitors reached its therapeutic range or above [55]. When anti-FXa activity is not at an identifiable level, it means that the anticoagulant effect of the factor Xa inhibitor is not at an appropriate level [55, 81]. Anti-FXa activity is strongly correlated with the plasma concentrations of factor Xa inhibitors and is a useful marker to evaluate the risk of bleeding following the administration of factor Xa inhibitors [55–57, 65, 67–70] (Table 2). Andexanet alfa (a human factor Xa decoy protein) is a drug created for the rapid neutralization of the anticoagulant effect of factor Xa inhibitors [96]. In the ANNEXA-R Study, in which 101 healthy volunteers were treated with andexanet alfa or placebo after a dose of factor Xa inhibitor (apixaban or rivaroxaban), the factor Xa-inhibiting activity following an apixaban dose was reduced by 94% in the bolus andexanet alfa treatment group ($n = 24$) and by 21% in the placebo group ($n = 9$) ($p < 0.001$). The factor Xa-inhibiting activity following a rivaroxaban dose was reduced by 92% in the bolus andexanet alfa group ($n = 27$) and 18% in the placebo group ($n = 14$) ($p < 0.001$) [97]. Andexanet alfa makes up for factor Xa inhibitor at a ratio of 1:1. The binding affinity of andexanet alfa to factor Xa inhibitors is higher than the affinity of factor Xa for factor Xa inhibitors. Because its half-life in blood is about 1 h, this drug is serially infused intravenously after a bolus dose [93, 94, 97–99].

For patients taking oral anticoagulants, drug cessation and resumption based on knowledge of their pharmacokinetics

are needed during the perioperative period. Drugs for the rapid neutralization of the anticoagulant effects of both warfarin and DOACs are now available for clinical use, which reduce the risk of major hemorrhage even during emergency surgery. On the other hand, the suspension of anticoagulant therapy and neutralization of anticoagulant effects elevate the risk of thrombosis. To avoid major hemorrhages and thromboembolism, quantitative assays should be implemented for DOAC monitoring as well as reversal therapies in perioperative settings.

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Compliance with ethical standards

Conflict of interest The authors have no competing interests to declare.

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