Current Pain and Headache Reports (2019) 23: 13
https://doi.org/10.1007/s11916-019-0747-3

OTHER PAIN (A. KAYE AND N. VADIVELU, SECTION EDITORS)

Perioperative Considerations in the Management of Anticoagulation Therapy for Patients Undergoing Surgery

Alice M. Kai[1] · Nalini Vadivelu[2] · Richard D. Urman[3] · Shikha Shukla[2] · Rob Schonberger[2] · Trevor Banack[2]

Published online: 22 February 2019

Abstract

Purpose of Review As ambulatory surgery has become increasingly more common, the appropriate management of anticoagulation therapy in patients undergoing invasive procedures has become progressively more relevant to healthcare professionals. The purpose of this literature review is to provide an overview of current common anaticoagulants and their pharmacological properties and to evaluate recent relevant literature and bridging therapy and provide recommendations on risk-guided therapy.

Recent Findings With the development of new drugs and the advancing study and practice of anticoagulation use, clinicians must keep up-to-date on the optimal management of patients requiring anticoagulation. NOACs and warfarin continue to be the mainstays of treatment, with varying timelines regarding when to hold administration of the different agents within the perioperative period.

Summary There are numerous factors that are considered in patients with multiple comorbidities including the risk for stroke on long-term anticoagulation and risk for thromboembolism, particularly in the perioperative setting when certain medication regimens may be altered and/or briefly held. There is ongoing investigation whether certain NOACs have more efficacy or greater safety profiles, depending on the degree of surgical intervention.

Keywords Anticoagulation · Thromboembolism · Perioperative · Warfarin · Novel anticoagulants

Introduction

The management of anticoagulation therapy in patients undergoing surgery has become increasingly important and relevant to become familiar with, as ambulatory surgery has become gradually more common. Healthcare professionals including surgeons, anesthesiologists, cardiologists, and nurse practitioners must be knowledgeable regarding the current literature and findings to guide appropriate perioperative anticoagulation strategies in patients who require long-term anticoagulation. This encompasses a broad range of patients, including those who are at risk of stroke due to atrial fibrillation, atrial flutter, or mechanical heart valves, or in patients with history of thromboembolic events who are at risk of a recurrence in a venous thromboembolism. Anticoagulation recommendations become more complex when these patients on long-term anticoagulation present for elective surgical or invasive procedures, and decisions need to be made regarding their perioperative anticoagulation regimen. The purpose of this review is to provide an overview of the common anticoagulants currently in use, evaluate recent relevant literature, and summarize current recommendations in their management in the perioperative setting.

This article is part of the Topical Collection on *Other Pain*

✉ Alice M. Kai
Alice.Kai@nyulangone.org

[1] Department of Internal Medicine, NYU-Winthrop Hospital, 222 Station Plaza North Suite 598, Mineola, NY, USA

[2] Department of Anesthesiology, Yale University School of Medicine, TMP3 333, Cedar Street, New Haven, CT, USA

[3] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA, USA

Common Anticoagulants

Patients are placed on anticoagulation therapy in order to prevent or treat venous thromboembolism (VTE), or to prevent stroke associated with arrhythmias such atrial fibrillation, or postoperatively following heart valve replacement or stent placement. Patients with atrial flutter and atrial fibrillation are at an increased risk for stroke and require preoperative prophylaxis [1]. Patients with these conditions are commonly on factor Xa inhibitors, vitamin K antagonists, or direct thrombin inhibitors. Between 1964 and 2010, warfarin was the only anticoagulant approved by the US Food and Drug Administration until the approval of dabigatran in 2010 and rivaroxaban among other direct factor Xa inhibitors in 2011 [2]. Collectively, this newer category of drugs is referred to as novel oral anticoagulants (NOACs) or non-vitamin K antagonists. Since then, the use of NOACs has rapidly increased. There are now more anticoagulation options for patients, and individualized factors clinicians consider to determine the anticoagulation of choice in patients. In order to understand when to hold and resume anticoagulation with care, it is important to review the pharmacokinetics of the anticoagulant medications.

Warfarin

Since being approved in 1954, warfarin remained the mainstay of therapy for thrombotic therapy for more than half of a century [3]. Despite the introduction of numerous new anticoagulants, warfarin remains the gold standard by which every new drug is compared, given its tried and tested safety profile, as well as its proven efficacy in decreasing the risk for recurrent thrombosis and fatal pulmonary embolisms [3]. Warfarin interrupts the conversion of vitamin K to 2,3-epoxide, thereby inhibiting the activity of vitamin K–dependent factors II, VII, IX, and X and decreasing the anticoagulant activity of proteins S and C [4, 5].

Novel Oral Anticoagulants

The use of NOACs has increased significantly over the past 10 years [6•]. They are approved for the treatment of deep vein thrombosis, pulmonary embolism, prevention of stroke in non-valvular atrial fibrillation, and for DVT prophylaxis for select surgical procedures [6•]. This class of anticoagulants was introduced as an alternative to warfarin, driven by cost-effectiveness. Initially called NOACs, they are also increasingly interchangeably referred to as direct oral anticoagulants (DOACs). NOACs provide rapid onset of therapeutic effect, do not necessitate as frequent monitoring, decrease complications, and confer fewer dietary and drug interactions relative to warfarin [7]. Despite the convenience that this class of medications offers, the disadvantage to NOACs compared to warfarin is the relative lack of randomized controlled trials demonstrating the safety in performing surgical procedures, and that there are no specific reversal agents for the NOACs. Although the use of NOACs has shown superior efficacy in the prevention of systemic embolism resulting in strokes compared to warfarin, it has not demonstrated significant difference in the rate of prevention of myocardial infarction or ischemic strokes [8].

Antiplatelet Agents (P2Y12-Receptor Antagonists)

Antiplatelet agents irreversibly inhibit ADP receptors on platelets, by binding to P2Y12 receptors, which prevents the aggregation of platelets [6•]. Antiplatelets are commonly given to patients with history of cerebral vascular accidents, coronary artery disease with stent placement, and peripheral vascular disease. They are most frequently used in conjunction with aspirin as thrombosis prophylaxis.

Aside from aspirin, clopidogrel is the most commonly utilized antiplatelet agent. It is a second-generation thienopyridine and has demonstrated greater efficacy in decreasing ischemic stroke, MI, and vascular mortality compared to aspirin [9]. It is activated in vivo in a dual-step process requiring CYP2C19, CYP450, and CYP3A enzymes [10].

Prasugrel is another antiplatelet agent in the thienopyridine family, which in contrast to clopidogrel, only requires a single-step metabolic activation via the CYP450 system [6•]. Prasugrel reaches peak plasma concentrations 30 min following absorption and has prolonged duration of action of approximately 3 days [11].

Ticagrelor is an antiplatelet agent in the cyclopentyl triazolopyrimidine family, in contrast to prasugrel and clopidogrel. It is absorbed orally and does not require enzymatic activation, with peak platelet inhibition demonstrated at 2–4 h [12] with terminal half-life of approximately 7 h [13].

Factor Xa Inhibitors

Currently, there are four factor Xa inhibitors available on the market: rivaroxaban, apixaban, betrixaban, and edoxaban. This class of anticoagulants binds to factor Xa bound to the prothrombinase complex and to free factor Xa, thereby preventing the formation of thrombin by interrupting the extrinsic and intrinsic coagulation cascades [6•].

Rivaroxaban was the initial factor Xa inhibitor that was available on the market. It is presently approved in the USA for the treatment of VTE, prevention of VTE following orthopedic surgery, and for stroke and VTE prophylaxis in patients with non-valvular atrial fibrillation [6•]. The drug has a rapid onset of action—peak plasma concentrations are achieved within 2.5 to 4 h of oral dosing. In healthy patients, its maximum effects are achieved at around 3 h and its effects last for

approximately 12 h [14]. The terminal half-life of rivaroxaban is 5.7 to 9.2 h; however, it is extended in the elderly population due to age-related renal decline [14, 15]. Due to the involvement of hepatic metabolism via CYP2C8-independent, CYP3A4-independent, and CYP-independent mechanisms, it is contraindicated in patients with severe liver dysfunction [16]. It is also contraindicated in patients with a creatinine clearance below 30 mL/min, as it is renally excreted [17]. Rivaroxaban can be reversed with 4-factor prothrombin complex or if active charcoal is administered within 8 h of ingestion [18]. There is no standardized mechanism of rivaroxaban monitoring; however, it can be watched via prothombin time (it only prolongs PT during peak drug concentrations) or antifactor Xa levels [19]. Of note, activated partial thromboplastin time (aPTT) and international normalized ratio (INR) are not reliable methods to monitor the effects of this drug [6•].

Apixaban is currently approved in the USA for prophylaxis and treatment of patients with PE, or as stroke prophylaxis in patients with non-valvular atrial fibrillation [6•]. It has a rapid onset of action, with peak concentrations achieved in about 3 to 4 h. The half-life is about 12 h and just like in other NOACs; it is prolonged in patients with renal dysfunction. It is metabolized via the liver, largely through the CYP3A4 system. Approximately 25% is excreted renally, and 75% via the biliary system [6•]. Although apixaban prolongs aPTT and PT/INR in a direct dose-dependent relationship, there is inconsistent variability in lab values for consistent oral dosing, and therefore, it is not routinely utilized for the purpose of monitoring its effects [20].

Edoxaban and betrixaban are also both direct factor Xa inhibitors with the same mechanism currently under clinical investigation, yet they are not as commonly used as the two other aforementioned factor Xa inhibitors.

Direct Thrombin Inhibitor

Dabigatran remains the only oral direct thrombin inhibitor available, approved for the treatment of VTE and prevention of VTE following total joint surgery, as well as for stroke prophylaxis in non-valvular atrial fibrillation. Dabigatran etexilate reaches peak plasma concentrations in 2 h [21] and is then subsequently converted to dabigatran, the active form. Its mechanism of action is by inhibiting thrombin by binding reversibly, thereby preventing the activation of factors V, VIII, and X and preventing the conversion of fibrinogen to fibrin [6•]. In healthy adults, it has an elimination half-life of 12–17 h [21]. Currently, dabigatran is reversed with activated charcoal in 1–2 h of oral dosing or hemodialysis. A humanized monoclonal antibody fragment, idarucizumab, is now a specific antidote available for the reversal of dabigatran [22]. Currently, a newer factor Xa inhibitor reversal agent, andexanet, is undergoing late-phase clinical trials [23•].

Pharmacological Considerations

Ultimately, the timing of when anticoagulation can be held and then subsequently resumed during the perioperative period should boil down to the pharmacokinetics of each drug. In general, medications are cleared by the body after five half-lives [23•]. Compared to warfarin, NOACs have substantially shorter half-lives relative to warfarin (5 to 17 h versus 40 h, respectively) [23•]. In otherwise healthy patients, this decreased time to clearance suggests that clinicians should not need to hold NOACs for as long as warfarin preoperatively [1]. However, it is essential to consider the renal function of each individual patient, as many of the NOACs including apixaban, rivaroxaban, dabigatran, and edoxaban are renally cleared. In general, NOACs are commonly held 24 to 48 h preoperatively in patients with renal dysfunction and warfarin is held for 5 to 6 days preoperatively [1]. According to the CHEST 2016 Guidelines, anticoagulation should subsequently be restarted 12 to 24 h postoperatively once sufficient hemostasis is acquired [24].

Risk Assessment to Guide Therapy

Clinicians have several score tools that can be utilized in order to stratify individualized patient risk in order to direct management in anticoagulation. The CHA_2DS_2-VASc Score is widely used in order to assess stroke risk in patients with atrial fibrillation. This scoring system stratifies risk by evaluating patients by whether they meet any of the following criteria: congestive heart failure; hypertension defined as blood pressure > 140/90 or receiving antihypertensive therapy; age ≥ 75 years; diabetes mellitus; prior stroke, thromboembolism, or transient ischemic attack; vascular disease including aortic plaque, myocardial infarct, peripheral vascular disease; age between 65 to 74 years old; female sex. A point is assigned for each category met by each patient, with a maximum score of 10—patients who receive a score of at least 2 are routinely started on anticoagulation therapy.

Conversely, clinicians may use the HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol) score in order to assess the following criteria to determine a patient's bleeding risk in those taking warfarin: hypertension; abnormal liver or renal function lab test results; history of stroke; history of bleeding issues; labile INR; elderly (age > 65); drug and alcohol use.

After evaluating a patient's baseline risks for thrombosis and bleeding, another important consideration in determining anticoagulation therapy perioperatively is to determine bleeding risk according to procedure type. As outlined by Holbrook et al. [1], very low-risk procedures include cataract surgery, skin cancer removal or skin biopsy, single tooth extraction,

and teeth cleaning. Low-risk procedures include coronary angiography, hernia repair or laparoscopic cholecystectomy, colonoscopy, gastroenterology endoscopy, ophthalmologic, dental, and dermatological procedures. Intermediate-risk procedures include other vascular procedures, orthopedic surgeries excluding major lower limb surgery, and other intra-abdominal or intra-thoracic procedures. High-risk procedures are those that are more invasive including major thoracic, vascular, urologic, lower limb orthopedic surgeries, pacemaker and defibrillator implantations, and intestinal anastomosis procedures. Very high-risk procedures include cardiac surgery and neurosurgery.

Bridging Therapy Perioperatively

Despite the significant portion of patients who require short-term interruption of anticoagulants for invasive procedures or elective surgical procedures, there continues to be a need for further investigation in optimization of individualized therapy. There is a lack of consistent statistics regarding the incidence of thromboembolic events associated with the interruption of warfarin [25]; however, studies have shown that an embolic stroke results in significant neurological deficit or death in 70% of patients [26], and thrombosis of a mechanical heart valve is fatal in 15% of patients [27]. During the perioperative period, one strategy that has been utilized is to administer short-acting parenteral anticoagulants to maintain anticoagulation.

Traditionally, patients with an indication for anticoagulation were bridged preoperatively to reduce the risk of thromboembolism. Warfarin would be held 5 days preoperatively, and subcutaneous LMWH or intravenous heparin was initiated once the INR was subtherapeutic and held 6 to 12 h prior to the procedure. The anticoagulant was subsequently restarted immediately postoperatively with warfarin and a bridging agent, commonly within 12 to 24 h. Currently, this holds true for the most part, especially in high-risk patients; however, there is a slight shift in management in patients with atrial fibrillation [3]. The latest American Society of Regional Anesthesia guidelines for the timing of holding and resuming anticoagulation perioperatively are summarized in Table 1 [28•].

Recently, the randomized controlled trial, Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE) [29], demonstrated that routine bridging in low-to-moderate-risk patients with atrial fibrillation on warfarin therapy may be harmful due to increased risk of major bleeding in the bridged group compared to the non-bridged group (3.2% versus 1.3%, respectively) irrespective of warfarin or dabigatran interruption. Furthermore, the study found that there were no significant differences in prevention of thromboembolism in patients who did not receive bridging therapy compared to those who did (0.4% versus 0.3%, respectively). It is now suggested that patients with atrial fibrillation with low risk of thromboembolism can forgo bridging therapies. Although a current controversial topic, some argue that those at high risk of thromboembolism may briefly discontinue anticoagulation; however, bridging therapy should be assessed on an individual basis, because studies have noted significant perioperative bleeding rates without decrease in thromboembolism when bridging therapy was employed [30, 31]. Mathew et al. [32] showed that compared to prophylactic dose bridging, therapeutic dose bridging was associated with 2.5- to 3-fold increase in risk for major bleeding after mechanical valve replacement.

Table 1 Recommendations in administration timing for warfarin [28•]

Preoperatively
- Hold warfarin at least 5 days preoperatively
- Obtain INR 1–2 days preop and if INR > 1.5, consider 1–2 mg vitamin K PO
- Consider 2.5–5 mg vitamin K PO or IV for urgent procedure reversal
- Consider fresh frozen plasma or prothrombin complex concentrate for immediate reversal
- For high-risk thromboembolism patients, bridge with unfractionated heparin IV or full dose Lovenox (hold heparin 4–6 h prior or Lovenox 24 h prior to surgery)
- Bridging is unnecessary in patients at low risk of thromboembolism

Postoperatively
- Resume warfarin on POD for those at low risk of thromboembolism
- For patients at high risk of thromboembolism, resume Lovenox 24 h postop for minor surgeries and 48–72 h postop for major procedures

In the Urgent Surgical Setting

Several publications offer recommendations when urgent surgical intervention is necessary. Sie et al. [33] recommend performing emergent surgery after allowing for at least one or two elimination half-lives of the anticoagulation administered. This suggests that patients can undergo surgery 24 to 36 h after receiving dabigatran, apixaban, and rivaroxaban. Ciurus et al. [34] advise patients under urgent procedures after a minimum of 12 h (optimally 24 h) following the last dose of anticoagulant.

Conclusion

Among the many considerations to address in patients with multiple comorbidities including risk for thromboembolism and stroke on long-term anticoagulation is how to adjust their current anticoagulation regimen in the perioperative setting. In the setting of the development of new drugs, study findings, and maturing practice of anticoagulation use, clinicians must make an effort to keep up-to-date in order to optimize the

management of patients on an individual basis. Challenges regarding what delineates the optimal regimen continue to persist, with further studies necessary to further elucidate the appropriate management in patients with varying degrees of thromboembolic and bleeding risk, for varying levels/degrees of surgical intervention.

Compliance with Ethical Standards

Conflict of Interest Alice M. Kai, Nalini Vadivelu, Richard D. Urman, Shikha Shukla, Rob Schonberger, and Trevor Banack declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S–e84S.
2. How CH. Novel oral anticoagulants for atrial fibrillation. Singap Med J. 2015;56(12):657–8 quiz 9.
3. Smith M, Wakam G, Wakefield T, Obi A. New trends in anticoagulation therapy. Surg Clin North Am. 2018;98(2):219–38.
4. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. Lancet. 2015;386(9990):281–91.
5. Yorkgitis BK, Ruggia-Check C, Dujon JE. Antiplatelet and anticoagulation medications and the surgical patient. Am J Surg. 2014;207(1):95–101.
6. • Lemay A, Kaye AD, Urman RD. Novel anticoagulant agents in the perioperative setting. Anesthesiol Clin. 2017;35(2):305–13 **Overview of the pharmacology, pharmacokinetics, and pharmacodynamics of common NOACs.**
7. Taranu R, Redclift C, Williams P, Diament M, Tate A, Maddox J, et al. Use of anticoagulants remains a significant threat to timely hip fracture surgery. Geriatr Orthop Surg Rehabil. 2018;9:2151459318764150.
8. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.
9. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348(9038):1329–39.
10. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet. 2009;373(9660):309–17.
11. Sugidachi A, Asai F, Ogawa T, Inoue T, Koike H. The in vivo pharmacological profile of CS-747, a novel antiplatelet agent with platelet ADP receptor antagonist properties. Br J Pharmacol. 2000;129(7):1439–46.
12. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J. 2006;27(9):1038–47.
13. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral P2Y(12) receptor antagonist, in healthy subjects. Eur J Clin Pharmacol. 2010;66(5):487–96.
14. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939–an oral, direct factor Xa inhibitor–after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005;61(12):873–80.
15. Kubitza D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr Med Res Opin. 2008;24(10):2757–65.
16. Gross PL, Weitz JI. New anticoagulants for treatment of venous thromboembolism. Arterioscler Thromb Vasc Biol. 2008;28(3):380–6.
17. Kubitza D, Becka M, Roth A, Mueck W. The influence of age and gender on the pharmacokinetics and pharmacodynamics of rivaroxaban–an oral, direct factor Xa inhibitor. J Clin Pharmacol. 2013;53(3):249–55.
18. Miyares MA, Davis K. Newer oral anticoagulants: a review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health Syst Pharm. 2012;69(17):1473–84.
19. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. Clin Pharmacokinet. 2009;48(1):1–22.
20. Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol. 2013;75(2):476–87.
21. Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol. 2007;64(3):292–303.
22. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, et al. A specific antidote for dabigatran: functional and structural characterization. Blood. 2013;121(18):3554–62.
23. • Zukowski CM, Peak J. Perioperative anticoagulation management. AORN J. 2018;107(4):503–8 **Review of the management of anticoagulation therapy for patients in the perioperative period.**
24. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–52.
25. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Intern Med. 2003;163(8):901–8.
26. Longstreth WT Jr, Bernick C, Fitzpatrick A, Cushman M, Knepper L, Lima J, et al. Frequency and predictors of stroke death in 5,888 participants in the Cardiovascular Health Study. Neurology. 2001;56(3):368–75.
27. Tiede DJ, Nishimura RA, Gastineau DA, Mullany CJ, Orszulak TA, Schaff HV. Modern management of prosthetic valve anticoagulation. Mayo Clin Proc. 1998;73(7):665–80.

28.• Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43(3):263–309 **Recent guidelines on anticoagulation by the American Society of Regional Anesthesia and Pain Medicine.**

29. Douketis JD, Healey JS, Brueckmann M, Eikelboom JW, Ezekowitz MD, Fraessdorf M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. Thromb Haemost. 2015;113(3):625–32.

30. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69(7):871–98.

31. Rechenmacher SJ, Fang JC. Bridging anticoagulation: primum non nocere. J Am Coll Cardiol. 2015;66(12):1392–403.

32. Mathew JG, Spyropoulos AC, Yusuf A, Vincent J, Eikelboom J, Shestakovska O, et al. Efficacy and safety of early parenteral anticoagulation as a bridge to warfarin after mechanical valve replacement. Thromb Haemost. 2014;112(6):1120–8.

33. Sie P, Samama CM, Godier A, Rosencher N, Steib A, Llau JV, et al. Surgery and invasive procedures in patients on long-term treatment with direct oral anticoagulants: thrombin or factor-Xa inhibitors. Recommendations of the working group on perioperative haemostasis and the French study group on thrombosis and Haemostasis. Arch Cardiovasc Dis. 2011;104(12):669–76.

34. Ciurus T, Sobczak S, Cichocka-Radwan A, Lelonek M. New oral anticoagulants - a practical guide. Kardiochir Torakochirurgia Pol. 2015;12(2):111–8.