ISSN 1220-8841 (Print)
ISSN 2344-4959 (Online)

ROMANIAN
NEUROSURGERY

Vol. XXXVI | No. 1 March 2022

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Agrawal Amit,
Amrita Ghosh,
Ranabir Pal

DOI: 10.33962/roneuro-2022-010

Romanian Neurosurgery (2022) XXXVI (1): pp. 52-61
DOI: 10.33962/roneuro-2022-010
www.journals.lapub.co.uk/index.php/roneurosurgery

Planning neurosurgical interventions in patients with anticoagulant therapy

Quiñones-Ossa G.A.[1-3], Angulo-Mariño S.L.[1], Garcia-Ballestas E.[2,3], Moscote-Salazar L.R.[2-4], Agrawal Amit[5], Amrita Ghosh[6], Ranabir Pal[7]

[1] Faculty of Medicine, Universidad El Bosque.Bogotá, COLOMBIA
[2] Faculty of Medicine, Universidad de Cartagena. Cartagena, COLOMBIA
[3] Consejo Latinoamericano de Neurointensivismo- ClaNi, COLOMBIA
[4] Neurosurgeon-Critical Care. Center for Biomedical Research (CIB). Director of Research Line Cartagena Neurotrauma Research Group. Faculty of Medicine - University of Cartagena. Cartagena de Indias, Bolivar.
[5] Department of Neurosurgery, All India Institute of Medical Sciences, Saket Nagar, Bhopal 462020, Madhya Pradesh, INDIA
[6] Department of Biochemistry, Medical College, 88, College Street, Kolkata, INDIA
[7] Department of Community Medicine, MGM Medical College & LSK Hospital, Kishanganj, Bihar, INDIA

ABSTRACT

Clinical practice guideline on anticoagulation is intended to manage patients undergoing neurosurgical procedures for the best possible short and long-term outcomes. In the clinical office practice, anticoagulation is offered to prevent thromboembolism with Warfarin, Heparin, Novel Oral Anticoagulants. The management approach starts with the mitigation plans from a reversal of pre-procedural anticoagulants for impending neurosurgical procedures by estimating procedural bleeding risk on the patients. The haemorrhage criteria and the timing of procedures are best assessed by the proceduralist during and after the intervention, standing on ground situations. Yet, intra- and post-procedure anticoagulant therapy should induct a multidisciplinary consultation paradigm for the best outcome in any emergent scenario. Further, each anticoagulation event should be monitored closely with competence in the optimum reversal process. Different neurosurgical procedures also should be weighed for their inherent hazards along with the probabilities of the bleeding and thromboembolism. The treating team should also concur to suggest a resumption of the pre-procedure anticoagulant therapy which may have been in place for altogether different morbidities. Regarding the anticoagulant agent, there are special conditions and recommendations to bear in mind in the daily medical practice for patient management. In the clinical practice guidelines for neurosurgical procedures, decisions about initiation and continuation of anticoagulants require experience and thorough internalization of the planned procedure, to avoid the risks of inherent risks of bleeding and thromboembolism.

Keywords
traumatic brain injury, neurosurgery, neurosurgical procedure, neurological surgery, anticoagulant, anticoagulation agents

Corresponding author:
Amit Agrawal

MM Institute of Medical Sciences & Research,
Mullana (Ambala), India

dramitagrawal@gmail.com

ISSN online 2344-4959
© Romanian Society of Neurosurgery

First published
March 2022 by
London Academic Publishing
www.lapub.co.uk

Introduction

Human brain has poor tolerance to constant bleeding and major hemorrhage of brain occurs from non-compressible locations. In ER, the physicians are confronted with the challenging scenario of patients, requiring surgical treatments, under anticoagulant, antiplatelet or thrombolytic medications; these therapies interfere with operative hemostasis (pre-, intra-, or post-operative hemostasis). The anticoagulant therapy is the cornerstone of the standard clinical care practice to avoid of thromboembolic episodes caused by diseases viz. atrial fibrillation (AF), pulmonary embolism (PE), heart disease or deep venous thrombosis (DVT) [1-7]. Intracranial hemorrhages and the higher bleeding risks, are higher incident to the Emergency Room (ER) irrespective of the trauma characteristics (minor or high impact trauma) in those patients on anticoagulant (or over anticoagulated) [7]. Thus, anticoagulation in neurosurgical patients represents two major implications, firstly, healthcare cost, and secondly, safety as well as prognosis [6]. Rapid identification and optimum interventions of anticoagulated neurosurgical patients are related to less healthcare and system cost with improved outcomes and good prognosis [8]. The purpose of this study was to review the current literature about anticoagulation therapy before, during and after the neurosurgical procedure, while considering the co-morbidities and patient current status.

Overview

Anticoagulant medications increased due to higher atherosclerosis prevalence among the elderly[2, 9 8, 9] who are also at higher risk of Traumatic Brain Injuries (TBI) and Intracranial Hemorrhage (ICH) from falls or violence [10] causing huge burden of mortality, morbidity, and disability. Devastating consequences and fatal sequel have been reported after these traumas, especially when they are under anticoagulant therapy [8, 11]. So, before neurosurgical interventions, it is important to reverse or counteract the effect depending on the type of anticoagulant[1], if the patient is under anticoagulation therapy. Those who are under oral anticoagulants therapy, have worse outcomes as reversal agents for these drugs are largely not available [2].

Type of Anticoagulant

Warfarin

Warfarin, inhibits Vitamin K dependent coagulation factors viz. II, VII, IX, and X [1, 3]; takes 3 days to achieve complete inhibition of the factors in the order of VII, IX, X, and II; effect reversion also takes 3days after stoppage of doses, and is not an option when the patient needs an urgent neurosurgical procedure [1] and is linked to hematoma expansion in the ICH patient with consequent poor prognosis[12]. Warfarin advice require strict monitoring of Internationally standardized Ratio (INR) and, has known drug interactions [8, 9]. INR value reflects anticoagulant effect: <1.0= non-anticoagulant effect; 2-3 indicates active effect, >3= hemorrhage risk [1, 6, 7, 13-15], INR increase is exponential depending on the dose and individual patient response [16]. Clinico-social factors also affect these levels viz. female gender, advanced age, black race, heart diseases, substance use, psychiatric disorders, and frequent hospitalizations [16, 17]. Further, in presence of or with risk of intracranial bleeding, Prothrombin Time (PT) is strictly kept below 1[1], INR >1.2 provides poor outcomes as in ICH or a TBI [1, 6]; in neurosurgical patients a target minor of 1 to 1.5 (or 1.3) of the INR is recommended [6].

Heparin

This parenteral anticoagulant act as prophylaxis of DVT, by binding with plasma proteins and affect molecular configuration [1]. Heparin antithrombin complex rapidly interacts with circulating thrombin to inhibit the coagulation enzymes and reduce platelet aggregation by the inhibition of the Von Willebrand Factor [1]. The efficacy of heparin is measured by the partial thromboplastin time (PTT) to be 1.5-2.0 times of the patients baseline value [1]; reversal effect after stoppage of dosage administration takes up to 1 hour which is also huge time gap to start an emergency neurosurgical intervention [1]; protamine is used reversal at the dose of 1 mg per 100 units of heparin when an urgent surgery is contemplated.

Novel Oral Anticoagulants (NOACs) versus Direct Oral Anticoagulants (DOACs)

These are of two types: A) direct factor Xa inhibitors (Endoxaban, Apixaban, Rivaroxaban) and B) direct thrombin inhibitors (Dabigatran) [8]; used as first-line therapy in atrial fibrillation. There is need to review

the clinical history in absence of clear information on anticoagulant intake[16] as these increase the bleeding risk or the progression of the ICH [8]. Research groups reported reduction of venous thromboembolic episodes of NOACs used as chemoprophylactic anticoagulation therapy in TBI patients within 24 hours without Computed Tomography (CT)-Scan changes [4]. NOACs are safer and simpler alternative compared with Warfarin with shorter half/life with predictable therapeutic rapid onset effects and do not require continuing monitoring[8, 9], change the dietary pattern, less drug interactions; issues with lack of specific antidotes [3] and reversal antidotes are still evolving [8]. Few studies reported worse prognosis than Warfarin with higher progression rate of ICH and mortality after TBI[8], while others, noted lower risks against vitamin K antagonist [6,12]. NOAC used with a low aspirin dosage was reported safer and more effective than Warfarin by other researchers in preventing strokes and intracranial hemorrhage [9, 18]. During use of Dabigatran (direct thrombin inhibitor), the normal ranges of Thrombin Time (TT) or the dilute TT (dTT) is rider for associated anticoagulation effect [6]; "safe-zone" for TT before surgical interventions is <30 ng/ml; in case of a higher values (> 30 ng/ml) or with heavy bleeding, the antidote must be administered [6].

Activated Partial Thromboplastin Time (APTT) help approximate time since the last dose[19] as prolongation result due to the anticoagulant effect[3] and suggest risk of bleeding if the value is twice the normal ratio[19]; not done in lupus syndrome or clotting factors deficiency disorders due to the intrinsic prolonged effect of APTT that may mask the true effects[3]. Reversal with Idarucizumab depends on the available tests; in absent of testing facilities and with active bleeding doses have to be repeated [6]. Studies reported rapid hematoma expansion and bad prognosis in ICH patients with NOACs intake even with minor intracranial bleeding [8, 20, 21]. For the X-factor inhibitor, anticoagulants activity evaluation involves Anti-activated factor X (Anti-Xa) calibrated to LMWH or the corresponding "xaban" available on limited scale[6]. NOACs usage has increased in a colossal way in the last years replacing conventional anticoagulants especially in patients with trauma in ER[8]. Patients with ICH, regardless of the origin, under Dabigatran require urgent reversal, should be treated with idarucizumab[3]; on factor Xa inhibitors intake to be treated with PCC [3]. NOACs use may need observation [6]in circumstances viz. normal CCT-Scan and GCS, an open head injury with injured scalp reflecting normal coagulation status and with unilateral chronic subdural hematoma without neurological deterioration or red flags or minimal neurological symptoms[6].

Management approach in anticoagulated patients

ER personnel should assess clinical status, triage and neurosurgical intervention with review of clinical records for co-morbidities, medications and anticoagulant use in TBI cases or with ICH suspects followed by Cranial Computed Tomography (CCT) as the anamnesis or neurological status in anticoagulated patients is usually attributed to vascular origin[3]. The latter has high sensitivity for extent of intracranial damage with acute onset of the hemorrhage [6]; contrast enhanced CT helps to identify the risk of bleeding expansion within the hematoma (spot signs)[3]. The prognosis of ICH varies on age, clinical status, volume of hematoma and degree of anticoagulant activity[7]. Regardless of the type of bleeding and anticoagulant agent, every life-threatening hemorrhage should be managed initially with basic ABC resuscitation protocol[3]; no uniform recommendation in the primary ICH exists for NOACs,[3]; ICH is 11times worst compared to extracranial with VKA therapy [3]. Even with normal CCT on anticoagulant medication, patients should be observed in-hospital for 24 hours to exclude delayed intracranial hemorrhage; repeat CCT scan needed in neurological deterioration[6]; with intubation, sedation, neurological concomitant disease, follow-up to be made by CCT-Scan [6].

There is need to optimize neurosurgical procedure, reversal agents, risk of thromboembolism versus anticoagulation and re-induction of anticoagulation after procedure [3]; correct management of blood pressure is related to a less neurological damage, hematoma expansion and unfavorable outcomes including improvement in functional recovery[3]. Total correction of VKA is achieved with a PCC infusion (20 UI/kg) or a bolus of 25 IU/kg and a single dose of 5 mg of Vitamin K in order to get a value from 1.2-1.5 with an approximate 6hours effect [16]; neurosurgical procedures require INR <1.3 [16]. [Table 1] The surgical procedures can be unscheduled invasive surgery or emergency surgery, semi-urgent, relative delayable surgery, urgent diagnosis procedures (e.g. lumbar

puncture) or scheduled invasive procedures than can present high or moderate risk of hemorrhage, each needs special recommendations (Table 2.)[16]

Table 1. Major hemorrhage criteria[16]

- Excessive/fatal bleeding
- Symptomatic hemorrhage with a critical organ compromise (intracranial, spinal, intraocular, pericardial, intramuscular hemorrhage with a compartment syndrome, retroperitoneal hemorrhage).
- A drop in hemoglobin levels that requires transfusion of more than two units of packed red blood cells or whole blood compounds.
- Damaged organ or special location (intracranial, spinal, digestive, thorax, pericardium, abdominal cavity).
- Massive hemorrhage that cannot be managed with conventional procedures.
- Requirement of invasive treatment (surgery, interventional radiology or endoscopy).

Table 2. Recommendations according the timing of the procedure (8)

Type of procedure	Recommendation
Emergency surgery	Administration of PCC is effective in the first 30 minutes after administration and could last for 5 hours. In this case, is important to measure the INR after 5 hours after the initial dose. In neurosurgical procedures - recommended to achieve an INR <1.3.
Semi-urgent surgery	If it is performed within 24 hours the recommended values are still under 1.3 of the INR, but because of the allowed delayed time a single dose of Vitamin K (5 to 10 mg) might be effective to achieve the hemostatic safety threshold.
Invasive unscheduled procedure with a high risk of hemorrhage (e.g. lumbar puncture)	Thrombotic and hemorrhage risk should be considered, in these types of procedures, if the bleeding can be controlled with local pressure there is no need to revert the anticoagulation effect.
Scheduled invasive procedures with moderate/ high bleeding risk	In these cases, is recommended to stop VKA treatment 5 days before the procedure and monitorization the INR levels.

MINIMAL AND HIGH-RISK PROCEDURES

Neurosurgical patients under anticoagulant therapy have inherently higher risk of hemorrhages (ICH) [10] though the thromboembolic event also carry of 3-43% risk [22, 23] which should be kept in mind as 50-50 chance in order to assess the risk versus benefit [22, 23]. Neurosurgical procedures can be invasive and non-invasive, the emergency procedures with other types and sub-types [22].

A. Lumbar puncture

Lumbar Puncture (LP) is useful for therapeutic and diagnostic use in daily medical practice to help analyze Cerebrospinal Fluid (CSF) especially for suspected neuroinfection[24, 25], biomarkers for TBI prognosis [11, 26-28], to diagnose elevated Intracranial Pressure (ICP) (syn. Intracranial Hypertension) [24, 29]. After LP multiple complications can occur viz. epidurals, subarachnoid or subdural hematomas (trivial or massive) as Traumatic Lumbar Puncture (TLP) due to a direct puncture in the radicular vessels and the sliding of the arachnoid on the dura[30-32]. The diameter of needle and catheter add higher risk of bleeding, when the patients are under anticoagulant therapy [30, 33]. The spinal hemorrhages can lead to irreversible complications like paraplegia or paraparesis of lower limb[34], medullar or compressive radicular syndrome (due to exacerbated fibrinolytic property of the CSF related to a higher red blood cells count after the TLP) [33]. It is recommended to avoid anticoagulation therapy with Enoxaparin 24 hours before LP and 48 hours if under NOACs therapy [34].

B. Decompressive craniectomy

Decompressive Craniectomy (DC) is commonest treatments in treatment of high ICP since last century to maintain intracranial equilibrium[35] in high ICP from cerebral tumors, neuroinfections, TBI, ICH (whether spontaneous or traumatic)[36-39] to avoid neurological complications, secondary insults, brain herniation and unfavorable outcomes including death [40, 41]. There is a high risk of DVT after DC that need antithrombotic measurements and imaging studies [22]; patients under anticoagulation should have coagulation profile; if abnormal, suspend the therapy and/or restore the coagulation time within 48 hours[1, 22] as damaged tissues and platelets produce excessive thromboplastin and vasoconstrictors that might produce acidosis status and ischemia [22]. The preventive management are recommended to avoid hypercoagulation and thrombosis episodes, initiate mechanical

compressive; reinitiating of anticoagulant therapy done after 15 days if there is pulmonary embolism in the postoperative period [22, 42]; anticoagulation therapy are also used by others within first 24 hours; yet there is no clear consensus of the timing of the anticoagulation therapy after the surgical procedure[42, 43]. In impending risk of Cerebral Venous Thrombosis (CVT), neurological monitoring and imaging studies considered; risk of intracranial bleeding and hematoma expansion should be thought in patients under anticoagulant therapy[8, 12, 43-45].

C. Craniotomy in Tumor Resection

Cerebral tumors have frequent post-operative complications due to high risk of DVT (27-45%) or prothrombotic status related to the tumor itself [22]. Tumors predispose to a venous stasis and atherosclerosis by the intimal dysfunction, disturbance of vessels and major procoagulant factors[22, 44] add higher risk of thromboembolic events. The enoxaparin or NOACs treatment lead to major ICH; it is better to use mechanical measurements to prevent thrombosis to decrease post-surgical bleeding[22, 46]. Chronic anticoagulant treatment has not been associated with a post-surgical hemorrhage recurrence within first 72 hours compared to non-anticoagulated patients[46, 47]. LMWH usage in the first 48 hours after the procedure as a prophylactic therapy is recommended to avoid the thrombotic complications[46, 47].

D. Ventriculoperitoneal Shunt and Ventriculostomies

Ventriculoperitoneal shunt (VPS) is used treat high ICP especially in hydrocephalies[48]. External Ventricular Drainage system drains CSF and reduces ICP; the hemorrhage risk is 7% but a significant hemorrhage reported in minority (0.8%); Heparin is recommended in VPS [9, 49, 50]

Dose adjustment

No clinical practice guideline can replace clinical acumen and judgment on ground situations though many standard office procedures are based on 2012 ACCP guidelines for antithrombotic therapy and discussions are needed regarding different qualitative and quantitative approaches [51].

Warfarin

In Warfarin over-anticoagulated patients with high INR, 5-10mg Vitamin K (oral or intravenous) is administered; takes up to 24 hours to full reversal [1, 6]. Thus in ER, Vitamin K as antidote or reversal agent is not recommended in hemorrhagic TBI or urgent surgery; useful as an adjunct therapy[6]. Prothrombin Complex Concentrate (PCC) dosage depends on initial INR value, has the advantage of immediate reversal effect, Vitamin K can be used to maintain effect [6]. Plasma transfusion therapy require high volumes and can lead to circulatory overload, pulmonary edema, congestive heart failure and immune-suppression; also takes longer time compared to PCC to reverse and normalize INR[6]. Warfarin use causes higher postoperative bleeding than NOACs[3].

Pre-operative and peri-operative thromboembolism vs. bleeding risk prediction

At first, bleeding versus embolism risk stratification needed using CHA2DS2-VASc and HAS-BLED scores are user-friendly for rapid assessment of thrombotic and hemorrhagic risk respectively [3, 52, 53]. Additionally, we have to consider risk factors of ICH viz. older age, hypo- or hypertension, micro-bleeds on echo-magnetic resonance imaging gradient, and ICH in lobar location[3]. To reach at correct treatment strategy, every patient under anticoagulation treatment requires an evaluation and categorization on urgency of the invasive procedure with a special consideration of thrombotic and hemorrhagic risk [16]; otherwise carry risk of thrombosis or pulmonary embolism (PE) in 25-60% [52]. Other researchers prefer initiation of thromboembolism prophylaxis after first 24 hours only in radiographically and neurological stable TBI [6]; restart of antithrombotic prophylaxis within first 72 hours has lower incidence of DVT and PE [6].

Post-operative management – when to restart anticoagulation therapy?

Intracranial bleeding represents a special condition for resumption of anticoagulation as in hemispheric location of hemorrhage the VKA therapy should be permanently discontinued[16] Resumption of anticoagulation regimen is a clinical dilemma in ICH or any neurosurgical procedure[3, 9]; after hemostasis achieved and ICH has stopped, the resumption of

anticoagulants can add risk of bleeding or a future re-bleeding in TBI [6]. ICH management guidelines indicates that therapeutic anticoagulation should be reinitiated after 2 weeks post-trauma with stable injury and high cerebral ischemia risk secondary to mechanical valve prosthesis or atrial fibrillation with a high a CHA2DS2VASc score[6, 54, 55]; with low risks of thromboembolism, anticoagulation therapy are reinitiated after 8 weeks [6]. Literature reports that VKA's therapy might be initiated within 7 days and with heparin after 3 days in ICH without re-bleeding complications[56] but others recommend anticoagulation therapy after the first 2 weeks to avoid hemorrhagic complications[57]. Restarting the anticoagulation with Warfarin within 14 days is associated with an increased hemorrhagic complications, thus anticoagulation after 2weeks is recommended[16]; some studies reported as ideal time to reinitiate Warfarin after a week of the procedure[9, 58].

Strategies to reduce the thromboembolism risk and non-pharmacological treatment

Thrombosis and embolism episodes are global public health problem with increasing mortality with co-morbidities the risk and incidence is doubled[59]. Risks of impending thromboembolism are well assessed by the treating physician though the multidisciplinary and integral paradigm of prevention and medical approach. Adoption of healthy lifestyle with good dietary habit, reduction of alcohol and tobacco consumption, oral anticonceptives, hormone replacement therapy is recommended [60] with non-pharmacological therapy for the patients management viz. pneumatic intermittent compression, compression stockings and drugs[52]. The prevention may start even before the surgical intervention regardless the concomitant pathologies that predispose to DVT or pulmonary embolism [22, 59]. Graduated Compression Stocking compress the lower extremities, graduated from the bottom (more intense) to the top (less compressive) to increase blood-flow; advised to use them from early deambulation till 2 years post- procedure[61, 62], the Intermittent Mechanical Compression increases blood flow in the veins of the lower limbs and is superior to graduated compression stocking to significantly reduce DVT by 7.3% and pulmonary embolism 1.2-2.8%; recommended to use it jointly with pharmacological prophylaxis. [61, 62]

Current issues with the anticoagulant therapy in anticoagulated neurosurgical patients

Anticoagulants inhibits the coagulation factors metabolism to avoid thrombotic complications including that of post-neurosurgical interventions [63, 64]. The bone of contention here is decision of precise moments of interruption or resumption of anticoagulantion after neurosurgery [62, 65, 66] where the risk-benefit analysis of the associated factors, choice of drugs, type of procedure and neurosurgeons criteria must be taken into account[63, 67]. Regarding INR measurement to analyze the effect, Thromboelastometry (viscoelastic analysis method that qualitatively assesses coagulation and fibrinolysis through rates of clot formation, resistance and degradation, and interaction of coagulation factors) is useful, yet, not established for neurosurgical use [23, 68-70].

Further, human inherent anticoagulation genetic factors with two allelic variants (2C9*2 and 2C9*3) of the CYP2C9 enzyme [71, 72] usually require a minor anticoagulant dosage. On the other hand, the variant of Vitamin K Epoxide Reductase Isoenzyme 1 (VKERI-1) generates resistance to the VKA agents requiring higher dosages o achieve the therapeutic effect [73, 74]. Non-genetic factors are associated to personal habits, adherence to therapy, preference for alternative treatments, dosage mistakes and co-morbidities the confounding variables [17].

Among the complications previously mentioned, one of the most important is the intracranial bleeding [75], followed by thrombosis that increase 2.5 times daily in anticoagulated patients whose therapy is interrupted for neurosurgical intervention; in addition the risk of developing hypercoagulability increases due to the limitation in postoperative ambulation [76-78].

Several studies recommend to avoid resumption of anticoagulation before 24 hours due to the risk of reactivation of bleeding in the intervened area, yet early restart between 4-7 days is the ideal time, with lesser complications compared to 14-day late restart, which increases the risk of cardioembolic infarction and ischemic stroke [58, 76]. Heparin use may be recommended after intracranial surgery within 24 hours with the intention to reduce DVT and PE [79, 80]. The considerations to restart anticoagulant therapy, it is important to recap type of medication, possibility of control or not with INR, cognitive deterioration or diseases associated with memory disorders, labile

INR, high risk of stroke[79, 80], and risk of bleeding or thromboembolic disease associated with non-surgical scores such as CHA2DS2-VASc and HAS-BLED [53, 81]. In addition, certain precautions should be taken in patients suffering from CKD (Chronic Kidney Disease), patients over the age of 65, on treatment with macrolides and the use of antifungals such as ketoconazole and itraconazole [80-82].

Conclusions

There is a widespread concern on the outcome of neurosurgical procedures while the patient is on anticoagulant therapy. A multipronged approach is needed involving specialities and sub-specialities ranging from Haematology, Biochemistry, Pathology, Pharmacy services, Internal Medicine, Emergency Medicine, Family Medicine, Anaesthesiology, Nephrology, and Pre-hospital consult services roped in for specific patients who need more complex continuum of care with dosing and monitoring of anticoagulant medications. There is urgent need to develop consensus guidelines for the health care professionals regarding management of anticoagulation which may be playing as double aged sword in both risk factor and outcome. Basic rules should be, while a more specific reversal agent of anticoagulant is available and approved to be used in the medical practice, antiplatelet agents can be continued throughout the perioperative period.

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