REVIEW ARTICLE

CURRENT CONCEPTS

Management of Antithrombotic Therapy in Patients Undergoing Invasive Procedures

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More than 6 million patients in the United States receive long-term anticoagulation therapy for the prevention of thromboembolism due to atrial fibrillation, placement of a mechanical heart-valve prosthesis, or venous thromboembolism.[1] In addition, dual antiplatelet therapy (combination treatment with aspirin and a thienopyridine) after the placement of a coronary-artery stent has dramatically increased. Annually, 10% of patients taking antithrombotic agents undergo surgical or other invasive procedures that require temporary discontinuation of therapy.[2] Although the goal is to minimize thromboembolic events and major hemorrhage in the periprocedural period, data from randomized, controlled trials in this area are limited, and many recommendations are derived from single-center cohorts, particularly with regard to bridging anticoagulation therapy. In addition, there are minimal data on procedure-specific bleeding rates in this patient population.

Guidelines from scientific societies with graded levels of evidence, as well as prior review articles, provide direction for periprocedural management of antithrombotic agents.[2-12] This review provides approaches and recommendations that are based on recent changes in national guidelines[2,13] for patients undergoing invasive procedures while receiving antithrombotic therapy, including newer antithrombotic agents.[14,15]

General Concepts

The question of whether antithrombotic therapy should be suspended in a patient who will be undergoing an invasive procedure involves balancing the risk of postprocedural bleeding with continued treatment against the thrombotic risk with suspension of treatment and use of bridging anticoagulation therapy. In general, a patient undergoing a procedure that is associated with a low risk of bleeding (low-risk procedure) can safely continue antithrombotic therapy and should do so, particularly if the patient is at high risk for a thromboembolic event (high-risk patient). Conversely, a patient undergoing a high-risk procedure can temporarily discontinue antithrombotic agents safely if the patient is at low risk for a thromboembolic event (low-risk patient).

The decision-making process is challenging when patients at moderate-to-high risk for thromboembolic events undergo high-risk procedures. Management also differs between elective and emergency procedures. A discussion among a clinician specializing in periprocedural management of antithrombotic agents and coagulation disorders, the primary provider prescribing these agents, and the proceduralist is essential. Ideally, this communication should occur well in advance of the procedure to maximize patient safety and facilitate patient education.[2] Appropriate decision making requires knowledge of thrombotic risk, procedure-related bleeding

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risk, concepts of bridging anticoagulation therapy, and timing of cessation and reinitiation of antithrombotic therapy. The first step in antithrombotic management is to assess the risk of thromboembolic events during the period when antithrombotic agents are to be discontinued.

ASSESSMENT OF THROMBOTIC RISK

ATRIAL FIBRILLATION

Periprocedural risks of discontinuing antithrombotic therapy are extrapolated from risks outside the periprocedural period. For patients with nonvalvular atrial fibrillation, important determinants of the risk of stroke include the $CHADS_2$ score[16] (Table 1) and, more recently, the CHA_2DS_2-VASc score, which includes cardiovascular atherosclerotic disease and female sex as additional risk factors.[17] Scores on the $CHADS_2$ range from 0 to 6, with higher scores indicating a greater risk of stroke; congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and prior stroke or transient ischemic attack is assigned 2 points. Scores on the CHA_2DS_2-VASc range from 0 to 9, with higher scores indicating greater risk. For the CHA_2DS_2-VASc score, an age of 65 to 74 years is assigned 1 point and an age of 75 years or older is assigned 2 points. Valvular atrial fibrillation implies the coexistence of severe valvular heart disease (mechanical valvular prosthesis or mitral-valve repair), and affected patients are at high risk for thromboembolism.

MECHANICAL HEART VALVES AND VENOUS THROMBOEMBOLISM

Risk factors for thromboembolic events in patients with one or more mechanical heart valves and venous thromboembolism are outlined in Table 2. The risk is influenced by the type, number, and location of valvular prostheses, as well as by the presence or absence of associated heart failure, atrial fibrillation, history of thromboembolism, and intracardiac thrombi.[19,20]

In patients with venous thromboembolism, the risks of recurrent thrombosis, thrombus propagation, and embolization are elevated for 3 months after the diagnosis and initiation of anticoagulation therapy.[21] The risk of recurrence differs depending on whether the venous thromboembolism was provoked (in which case the risk decreases with resolution of the underlying risk factor) or unprovoked (i.e., idiopathic) (Table 2).[22]

CANCER

Patients with cancer have an increased risk of periprocedural thrombosis owing to cancer-specific prothrombotic activity, hormonal therapy, angiogenesis inhibitors, radiotherapy, and the presence of indwelling central venous catheters.[23] Concurrently, there is an increased risk of bleeding[24] because of the administration of prophylactic agents for the prevention of venous thromboembolism, chemotherapy-related hepatic and renal dysfunction and thrombocytopenia, and tumor friability. An increasing number of outpatients with cancer-related thrombosis and a history of recurrent thrombosis before the cancer diagnosis are receiving long-term parenteral anticoagulation therapy.[25]

CORONARY STENTS

Some patients with coronary stents may require dual antiplatelet therapy indefinitely. Premature discontinuation of antiplatelet therapy in antici-

Table 1. $CHADS_2$ Scoring System for Assessing the Risk of Stroke among Patients with Atrial Fibrillation.*

$CHADS_2$ Score or Assessment	Risk of Stroke	Stroke Rate per 100 Patient-Yr *range (95% CI)*
Score of 0, 1, or 2	Low	1.9–4.0 (1.2–5.1)
Score of 3 or 4	Moderate†	5.9–8.5 (4.6–11.1)
Score of 5 or 6, stroke or TIA within previous 3 mo, or severe valvular heart disease	High	12.5–18.2 (8.2–27.4)

* Scores on the $CHADS_2$ range from 0 to 6, with higher scores indicating a greater risk of stroke; the categories of congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and the category of prior stroke or transient ischemic attack (TIA) is assigned 2 points. CI denotes confidence interval.

† If the risk of stroke is moderate, assessment of the patient's individual risk–benefit tradeoff for the discontinuation of antithrombotic agents is particularly important.

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Table 2. Risk Factors for Thromboembolic Events in Patients with a Mechanical Heart Valve or History of Venous Thromboembolism.

Patient History	Risk Factors for Thromboembolism*		
	Low Annual Risk	Moderate Annual Risk	High Annual Risk
Mechanical heart valve	Bileaflet aortic-valve prosthesis without atrial fibrillation, prior stroke or thromboembolic event, or known intracardiac thrombus	Bileaflet aortic-valve prosthesis and atrial fibrillation	Any mitral-valve prosthesis, any caged-ball or tilting-disk aortic-valve prosthesis, multiple mechanical heart valves, or stroke, TIA, or cardioembolic event
Venous thromboembolism	Venous thromboembolism >12 mo previously and no other risk factor (e.g., provoked and transient)	Venous thromboembolism within previous 3–12 mo, nonsevere thrombophilia†, or recurrent venous thromboembolism	Venous thromboembolism within previous 3 mo, severe thrombophilia,‡ unprovoked venous thromboembolism, or active cancer (cancer diagnosed ≤6 mo or patient undergoing cancer therapy)

* Annual-risk categories for thromboembolism are defined as follows: low, an annual rate of less than 5%; moderate, an annual rate of 5 to 10%; and high, an annual rate of more than 10%. The assessment of a patient's individual risk–benefit tradeoff for discontinuation of antithrombotic agents is particularly important in patients at moderate risk.

† Nonsevere thrombophilia is diagnosed if the patient is heterozygous for factor V Leiden or heterozygous for a mutation in the prothrombin gene G20210A.[18]

‡ Severe thrombophilia is diagnosed if the patient has a protein C, protein S, or antithrombin deficiency; has the antiphospholipid syndrome (presence of antiphospholipid antibodies or lupus anticoagulant); is homozygous for factor V Leiden; is homozygous for a mutation in the prothrombin gene G20210A; or has compound heterozygous mutations of these two genes.[18]

pation of a surgical or other invasive procedure may lead to stent thrombosis[26,27] and precipitation of myocardial infarction, with a mortality rate of 50% or higher.[2]

The risk of stent thrombosis differs between bare-metal stents and drug-eluting stents. The risk of thrombosis is highest within 6 weeks after the placement of a bare-metal stent and within 3 to 6 months after the placement of a drug-eluting stent[28]; antiplatelet therapy is required for at least 1 month after placement of a bare-metal stent and for 1 year after placement of a drug-eluting stent.[29] After acute coronary syndromes, continuation of dual antiplatelet therapy is recommended for up to 12 months in patients with bare-metal stents and for at least 12 months in patients with drug-eluting stents, unless the risk of bleeding is excessive.[30] The optimal duration of dual antiplatelet therapy for patients with coronary stents remains unknown. However, recent studies suggest that 6 to 12 months may be appropriate, with little to gain from a longer duration.[31,32]

ASSESSMENT OF PERIPROCEDURAL BLEEDING RISKS

The risk of major periprocedural bleeding depends on the type of procedure, and additional risk factors include residual effects of antithrombotic agents, active cancer and chemotherapy, history of bleeding, and reinitiation of antithrombotic therapy within 24 hours after the procedure.[33] Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, shows commonly performed procedures and associated bleeding risks; classification into high-risk and low-risk categories is based on guidelines and reviews coupled with expert opinion within our institution.

Grades of bleeding severity are not standardized across specialties.[34] The American Society for Gastrointestinal Endoscopy designates low-risk procedures as those with clinical rates of bleeding of 1.5% or less.[35] In the absence of specific risk stratification, we propose that high-risk procedures are those with a rate of bleeding of more than 1.5% among patients not receiving antithrombotic agents. In addition, procedures that can result in intracranial, intraspinal, intraocular, retroperitoneal, intrathoracic, or pericardial bleeding are high-risk, with bleeding in these locations classified as major.[34] Neuraxial anesthesia is a high-risk procedure.[36,37]

For other procedures, we determine the severity of bleeding using criteria similar to those used for gastrointestinal endoscopic procedures (Table S2 in the Supplementary Appendix).[38]

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BRIDGING ANTICOAGULATION THERAPY

Bridging anticoagulation therapy is designed to minimize the risk of thromboembolism in high-risk patients when anticoagulation therapy is suspended (Tables 1 and 2) and to minimize the risk of bleeding after high-risk procedures (Table S2 in the Supplementary Appendix). The need for bridging depends on the duration of action of the anticoagulant agent and the potential for reversing anticoagulation. In most cases, bridging anticoagulation therapy is used in patients receiving warfarin. Once warfarin has been discontinued and the international normalized ratio (INR) falls below the therapeutic range, intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin is administered for 3 to 5 days. The heparin agent is withdrawn before the procedure, with the timing based on whether unfractionated heparin or low-molecular-weight heparin is used, and is usually readministered 48 hours after the procedure, if hemostasis is secured.

Although the use of bridging anticoagulation therapy in high-risk patients is considered the standard of care, it has been evaluated in only two randomized, controlled trials[39,40] and remains controversial.[41,42] The results of an ongoing trial of the use of bridging therapy in high-risk patients are awaited.[43] The available data are difficult to interpret because high-risk and low-risk patients and high-risk and low-risk procedures have been pooled. Older studies used nonperioperative data to estimate perioperative risks of stroke and thromboembolism during a period of 8 to 10 days of warfarin interruption. Rates of thrombosis were estimated to be quite low (0.1 to 0.4% among patients with a mechanical heart valve and <0.1 to 0.2% among those with atrial fibrillation[39]). However, actual overall rates (with and without bridging) are higher: 1.2% among patients with a mechanical heart valve, 0.9% among those with atrial fibrillation, and 1.8% among those with venous thromboembolism.[44] Corresponding rates of major bleeding (with and without bridging) are 2.7%, 2.0%, and 1.9%, respectively.[44]

A recent meta-analysis showed that periprocedural bridging therapy with heparin increased the overall risk of major bleeding without a significant decrease in the risk of thromboembolic events.[42] This conclusion has been affirmed in the study by Birnie et al. in this issue of the *Journal*.[40] This single-blind, randomized study involved patients at moderate-to-high risk for thromboembolic events who were undergoing pacemaker or defibrillator surgery. A clinically significant device-pocket hematoma was more common in the heparin-bridging group (16.0%) than in the continued-warfarin group (3.5%). Major surgical and thromboembolic complications were rare in both treatment groups.

When bridging therapy is required for high-risk patients with an estimated creatinine clearance of less than 30 ml per minute, the use of unfractionated heparin is preferred. High-dose unfractionated heparin (therapeutic anticoagulation)[2] is commonly used, with monitoring of the activated partial-thromboplastin time. For low-risk patients, such as those with an episode of venous

Table 3. Approach to Bridging Therapy.

Condition	Bridging Therapy Required	No Bridging Therapy	Comments
Mechanical heart valve	Mitral-valve replacement, two or more mechanical valves, nonbileaflet aortic-valve replacement, or aortic-valve replacement with other risk factors	Aortic-valve replacement, bileaflet prosthesis, and no additional risk factors	Other risk factors include prior stroke, TIA, intracardiac thrombus, or cardioembolic event
Nonvalvular atrial fibrillation	Prior stroke or embolic event, cardiac thrombus, or $CHADS_2$ score of ≥4	No prior stroke or embolic event, absence of cardiac thrombus, or $CHADS_2$ score of <4	Prior stroke, TIA, intracardiac thrombus, or cardioembolic event increases risk
Venous thromboembolism	Venous thromboembolism within previous 3 mo or severe thrombophilia	Venous thromboembolism >3 mo previously or no additional risk factors (e.g., active cancer and nonsevere thrombophilia)	Consider inferior vena cava filter if venous thromboembolism occurred <1 mo previously, if urgent or emergency surgery is required, or if there is a contraindication to anticoagulation therapy

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thromboembolism more than 3 months before the planned procedure, prophylactic low-dose heparin can be used for bridging.[2] In moderate-risk patients, the decision to use bridging therapy and the degree of intensity of bridging therapy should be individualized and the patient's wishes considered.[2]

Our approach to bridging therapy, shown in Table 3, is consistent with published guidelines.[2] The protocol is as follows. Stop warfarin 5 days before a high-risk procedure, and when the INR falls below the therapeutic range, begin low-molecular-weight heparin at a therapeutic dose. For patients with a mechanical heart valve or atrial fibrillation, use enoxaparin at a dose of 1 mg per kilogram of body weight, administered every 12 hours, or dalteparin at a dose of 100 IU per kilogram, administered every 12 hours. For patients with venous thromboembolism, use enoxaparin at a dose of 1.5 mg per kilogram or dalteparin at a dose of 200 IU per kilogram once daily. The final dose (either enoxaparin at a dose of 1 mg per kilogram or dalteparin at a dose of 100 IU per kilogram) should be administered 24 hours before the procedure.

Check the INR on the morning of the procedure. Restart warfarin therapy immediately after the procedure if hemostasis is secured, and reinstitute treatment with subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin at a therapeutic dose (without bolus) 48 hours after the procedure if no bleeding has occurred, with the exception that for patients undergoing endoscopic sphincterotomy, heparin therapy should be initiated after 72 hours.[45] Discontinue heparin therapy when the INR is in the therapeutic range (approximately 5 days later).

TIMING OF CESSATION OF ANTITHROMBOTIC THERAPY

When anticoagulant agents are discontinued in high-risk patients (including agents used for bridging therapy), the interval without anticoagulation therapy should be as short as possible, with the risk of thromboembolic events balanced against the risk of bleeding. The duration of action of the anticoagulant agent depends on several factors, including renal function (in the case of dabigatran, rivaroxaban, apixaban, and low-molecular-weight heparin), hepatic function (in the case of warfarin, rivaroxaban, and apixaban), and potential for reversing the effects (in the case of warfarin and heparin). Standardized monitoring recommendations are available for warfarin but not for the newer antithrombotic agents.[46,47] Suggested monitoring for older and newer antithrombotic agents is presented in Table 4.

WARFARIN

A relatively normal zone of hemostasis exists when the INR is 1.0 to 2.0, with the lower value corresponding to a coagulation factor level of 100% and the higher value corresponding to a level of 30%.[53] The INR value at which the risk of bleeding increases is unknown, but the risk is assumed not to be elevated when the INR is 1.5 or less and is assumed to be elevated when the INR is more than 2.0.[2,53] Thus, an INR of 1.5 or less is considered safe for high-risk procedures,[2,36,54] although some clinicians recommend an INR of 1.2 or less for procedures with a high risk of bleeding into closed spaces (e.g., intracranial surgery)[2] (Table S2 in the Supplementary Appendix).

An INR of 2.0 to 3.5 corresponds to therapeutic anticoagulation,[53] and 93% of patients with an INR within this range have an INR of less than 1.5 approximately 5 days after warfarin therapy has been discontinued.[48] The INR should be obtained within 24 hours before the procedure[55] and corrected with vitamin K, if needed, except in the presence of mechanical heart valves.

When warfarin therapy is continued through the procedure, it is important that the INR before the procedure not be supratherapeutic. We adjust warfarin doses over a period of 5 days to aim for an INR of approximately 2.5 by the time of the procedure.

HEPARIN

Unfractionated heparin administered intravenously has a half-life of 60 to 90 minutes, and anticoagulant effects dissipate 3 to 4 hours after discontinuation. Thus, the infusion is stopped 4 to 6 hours before high-risk procedures.[2] Low-molecular-weight heparin is administered subcutaneously at therapeutic doses for bridging and for the treatment of venous thromboembolism, with reduced doses for the prevention of venous thromboembolism in low-risk patients. The half-life of these agents is approximately 4 hours, and the last dose should be given 24 hours

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Table 4. Overview of Traditional and Newer Antithrombotic Agents.*

Agent	Route of Administration	Mechanism of Action	Recommended Interval between Last Dose and Procedure
Anticoagulant agents			
Warfarin (Coumadin, Bristol-Myers Squibb)	Oral	Inhibition of vitamin K–dependent factors II, VII, IX, and X for γ-carboxylation; and proteins C and S	1–8 days, depending on INR and patient characteristics; INR decreases to ≤1.5 in approximately 93% of patients within 5 days[48]
Unfractionated heparin	Intravenous or subcutaneous	Antithrombin activation (inhibition of factors IIa, IXa, Xa, XIa, and XIIa)	Intravenous, 2–6 hr, depending on dose; subcutaneous, 12–24 hr, depending on dose
Low-molecular-weight heparins (enoxaparin [Lovenox, Sanofi Aventis] and dalteparin [Fragmin, Eisai])	Subcutaneous	Antithrombin activation (inhibition of factor Xa and, to a lesser extent, factor IIa)	24 hr
Fondaparinux (Arixtra, GlaxoSmithKline)	Subcutaneous	Antithrombin activation (factor Xa inhibitor)	36–48 hr
Dabigatran (Pradaxa, Boehringer Ingelheim)	Oral	Direct thrombin inhibitor	1 or 2 days with creatinine clearance rate of ≥50 ml/min; 3–5 days with creatinine clearance rate of <50 ml/min
Rivaroxaban (Xarelto, Bayer HealthCare)	Oral	Direct factor Xa inhibitor	≥1 day when renal function is normal; 2 days with creatinine clearance rate of 60–90 ml/min; 3 days with creatinine clearance rate of 30–59 ml/min; and 4 days with creatinine clearance rate of 15–29 ml/min[52]
Apixaban (Eliquis, Bristol-Myers Squibb)	Oral	Direct factor Xa inhibitor	1 or 2 days with creatinine clearance rate of >60 ml/min; 3 days with creatinine clearance rate of 50–59 ml/min; and 5 days with creatinine clearance rate of <30–49 ml/min
Desirudin (Iprivask, Canyon Pharmaceuticals)	Subcutaneous	Direct thrombin inhibitor	2 hr
Antiplatelet agents			
Aspirin	Oral	Cyclooxygenase inhibitor (irreversible effect)	7–10 days
Aspirin and dipyridamole (Aggrenox, Boehringer Ingelheim)	Oral	Phosphodiesterase inhibitor	7–10 days
Cilostazol (Pletal, Otsuka Pharmaceutical)	Oral	Phosphodiesterase inhibitor	2 days
Thienopyridine agents (clopidogrel [Plavix, Sanofi Aventis], ticlopidine [Ticlid, Roche], prasugrel [Effient, Eli Lilly], and ticagrelor [Brilinta, AstraZeneca])	Oral	ADP receptor antagonist	5 days (clopidogrel and ticagrelor), 7 days (prasugrel), or 10–14 days (ticlopidine)

* ADP denotes adenosine diphosphate, aPTT activated partial thromboplastin time, FDA Food and Drug Administration, INR international normalized ratio, and PCC prothrombin complex concentrate.
† PCCs are either 3-factor or 4-factor concentrates. Nonactivated 4-factor PCCs contain factors II, VII, IX, and X and proteins C and S, and nonactivated 3-factor PCCs contain factors II, IX, and X and only small amounts of factor VII. For details, see the Supplementary Appendix.
‡ Factor VIII inhibitor bypass activity provides both factor II (prothrombin) and factor Xa for rapid and sustained thrombin generation. For details, see the Supplementary Appendix.

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Approved Indications	Laboratory Monitoring	Reversal Agents (in cases of severe bleeding)	Comments
Prevention and treatment of venous thrombosis and pulmonary embolism, prevention and treatment of thromboembolic complications of atrial fibrillation or cardiac-valve replacement, and prevention of recurrent myocardial infarction and associated thromboembolic events	INR	Oral or intravenous vitamin K, with or without fresh-frozen plasma; 4-factor PCCs preferred over 3-factor PCCs[49,50]†	Reversal with PCCs requires lower volume than fresh-frozen plasma but is more expensive
Prevention and treatment of arterial embolism, prevention or treatment of venous thrombosis and extension, and treatment of atrial fibrillation with embolization, among other indications	aPTT	Protamine sulfate	—
Prevention and treatment of deep-vein thrombosis and prevention of ischemic complications of unstable angina and non–Q-wave myocardial infarction	None, except anti–factor Xa antibody levels in selected patients	Protamine sulfate (only partially reverses anticoagulation)	Elimination is impaired in patients with stage IV or V chronic kidney disease
Prophylaxis for deep-vein thrombosis and pulmonary embolism in patients undergoing repair of hip fracture, hip replacement, knee replacement, or abdominal surgery; treatment of acute deep-vein thrombosis and treatment of acute pulmonary embolism when administered with warfarin	None, but consider fondaparinux-specific anti-Xa assays	None, but consider recombinant factor VIIa only in high-risk patients with major bleeding[51]	Elimination is impaired in patients with stage IV or V chronic kidney disease
Prophylaxis for thromboembolic complications of nonvalvular atrial fibrillation	aPTT or thrombin time can be used to rule out substantial residual effect	None, but consider factor VIII inhibitor bypass activity or recombinant activated factor VIIa, and hemodialysis[51]‡	Consider withholding for longer period before high-risk bleeding procedures
Prophylaxis for deep-vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement, prophylaxis for stroke in patients with nonvalvular atrial fibrillation, and immediate treatment of venous thromboembolism	Prothrombin time or anti–factor Xa antibody; normal value may rule out clinically relevant residual anticoagulant effect	None, but consider PCCs[51,53]	Consider withholding for longer period before high-risk bleeding procedures
Prophylaxis for thromboembolic complications of nonvalvular atrial fibrillation	Anti–Xa antibody; normal level may rule out clinically relevant residual anticoagulant effect	None, but consider charcoal hemoperfusion or PCCs, particularly 4-factor†	—
Prophylaxis for deep-vein thrombosis and pulmonary embolism in patients undergoing elective hip replacement	aPTT, thrombin time, or ecarin clotting time; normal value rules out clinically relevant residual anticoagulant agent	None	—
Not FDA-approved; used for platelet inhibition in multiple conditions	None, but consider platelet-function testing	Platelet transfusion	Platelet turnover for repletion
Secondary prophylaxis for ischemic stroke	None, but consider platelet-function testing	Platelet transfusion	—
Intermittent claudication	None	Platelet transfusion	—
Prevention and treatment of acute coronary syndrome, secondary prevention of coronary-artery and stent thrombosis and thrombotic cerebrovascular accident, treatment of peripheral vascular disease, and prevention of TIA	None, but consider platelet-function testing	Consider platelet transfusion, but efficacy may be limited	Precise FDA indications vary according to the specific drug

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before the anticipated procedure at 50% of the total daily dose (i.e., enoxaparin at a dose of 1 mg per kilogram or dalteparin at a dose of 100 IU per kilogram).[2]

NEWER ANTICOAGULANT AGENTS

Direct factor Xa inhibitors include the oral agents rivaroxaban and apixaban. The timing of discontinuation of both agents before high-risk procedures depends on the creatinine clearance.[53] The recommended durations are taken from package inserts, if the information is provided, or are derived from guidelines and drug pharmacokinetics (Table 4). However, because of the lack of available reversal agents, we prefer to take a more conservative approach, withholding these agents for slightly longer periods than those based on package inserts, guidelines, or pharmacokinetic data (i.e., 1 to 2 days longer than the specifications outlined in Table 4).[44] Future studies should focus on more precise laboratory monitoring and reliable reversal of the newer anticoagulant agents.

Fondaparinux is a subcutaneously administered direct factor Xa inhibitor approved for the prevention and treatment of venous thromboembolism, with a half-life of 17 hours. It has been shown to be associated with acceptable rates of bleeding when discontinued more than 36 hours before cardiopulmonary bypass surgery.[56]

Direct thrombin inhibitors can be administered orally (dabigatran), subcutaneously (desirudin), and intravenously (argatroban and bivalirudin). Bivalirudin is used primarily during acute coronary interventions. Argatroban is used for the treatment of heparin-induced thrombocytopenia. Dabigatran is approved for the prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation, and the timing of discontinuation is based on the creatinine clearance (Table 4).[57,58] Desirudin is used postoperatively for prophylaxis against deep-vein thrombosis in patients undergoing hip replacement. It has a half-life of 2 hours and should be discontinued 10 hours before high-risk procedures.

ANTIPLATELET AGENTS

TRADITIONAL ANTIPLATELET AGENTS

Aspirin is used alone or in combination with other antiplatelet agents. Low-dose aspirin alone does not substantially increase the risk of clinically important bleeding after invasive procedures.[59-62]

Dipyridamole reversibly inhibits platelet aggregation. It has an elimination half-life of 12 hours and a duration of action of approximately 2 days after discontinuation. Aspirin and dipyridamole individually do not substantially increase the risk of clinically important postprocedural bleeding but are sometimes discontinued before certain elective high-risk procedures. Administration of aspirin and dipyridamole together (i.e., Aggrenox [Boehringer Ingelheim]) probably increases the risk of postprocedural bleeding.[63]

Cilostazol, a phosphodiesterase inhibitor, is approved for the treatment of claudication and is used off-label in combination with antiplatelet drugs for patients with coronary artery disease[64] and for those with ischemic cerebrovascular disease.[65] Cilostazol does not increase the risk of bleeding when used alone. Platelet function returns to normal approximately 2 days after discontinuation.[15]

OTHER ANTIPLATELET AGENTS

Orally administered inhibitors of the adenosine diphosphate receptor $P2Y_{12}$ include clopidogrel, ticlopidine, prasugrel, and ticagrelor (Table 4).[15] The period during which therapy should be suspended ranges from 5 to 7 days for clopidogrel, ticagrelor, and prasugrel and possibly longer for ticlopidine (10 to 14 days).

INFERIOR VENA CAVA FILTERS

We do not recommend the routine placement of inferior vena cava filters for bridging.[23] Whenever feasible, we suggest delaying elective surgical procedures until patients have received at least 3 months of anticoagulation therapy. The placement of an inferior vena cava filter (which should be removable, whenever possible, because of the risks of long-term adverse events with permanent filters) may be indicated if pulmonary thromboembolism or proximal deep-vein thrombosis has occurred within the previous 4 weeks and an urgent procedure is required. In such cases, filters can prevent pulmonary embolic events and allow the temporary discontinuation of anticoagulation therapy.[66]

PHARMACOLOGIC REVERSAL OF ANTICOAGULATION

When urgent or emergency procedures are required, there are various options for the manage-

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ment of antithrombotic agents. In some patients, a low-risk temporizing procedure may be carried out to delay the need for a definitive higher-risk procedure. When this approach is not possible, the administration of reversal agents may be considered if the risk of bleeding outweighs the risk of thrombotic events. Several reversal agents are available (Table 4). Further discussion of plasma and prothrombin complex concentrates is provided in the Supplementary Appendix.[49,51]

ANTITHROMBOTIC AGENTS WITH REVERSIBLE EFFECTS

In patients with an INR that is not supratherapeutic, the effect of warfarin can be reliably reversed within 24 to 48 hours by administering intravenous vitamin K. Reversal occurs within a few hours after the infusion of vitamin K and fresh-frozen plasma.[53,67] The administration of either vitamin K or fresh-frozen plasma may cause clinical problems. High-dose vitamin K will delay the response to warfarin therapy when it is reinstituted. The administration of fresh-frozen plasma may lead to volume overload in patients with advanced cardiac or kidney disease.[68] Prothrombin complex concentrates are preferred in cases of bleeding related to vitamin K antagonist treatment,[49] particularly for patients with heart failure, valvular heart disease, or renal failure, in whom a large-volume infusion of fresh-frozen plasma may result in volume overload.

Because unfractionated heparin has a short duration of action, reversal is not usually required. Protamine can completely reverse the action of unfractionated heparin and can partially reverse the action of low-molecular-weight heparin.

ANTITHROMBOTIC AGENTS WITH NONREVERSIBLE EFFECTS

Reliable reversibility of the effects of newer anticoagulant agents (direct thrombin inhibitors and direct factor Xa inhibitors) has not been proved.[53] There is no clinical evidence that prothrombin complex concentrates effectively reverse major bleeding induced by these agents. The effects of rivaroxaban but not dabigatran were reversed in 12 healthy volunteers after the administration of 4-factor prothrombin complex concentrates,[69] which contain factors II, VII, IX, and X and proteins C and S (see the Supplementary Appendix). It is unknown whether these data are applicable to patients undergoing invasive procedures.

In patients receiving dabigatran who have life-threatening bleeding that cannot be managed with supportive care and local hemostatic measures, hemodialysis or charcoal hemoperfusion can be considered.[70] However, these interventions may not be feasible, given the bleeding risks associated with dialysis-catheter placement. Moreover, hemodialysis may not increase drug elimination in the absence of renal failure. Unlike dabigatran, rivaroxaban and apixaban are not dialyzable.

For patients receiving treatment with newer anticoagulant agents, when surgery is imminent but the timing is unpredictable (e.g., organ transplantation), we recommend switching to warfarin because its effects can be rapidly and reliably reversed.

RESUMPTION OF ANTITHROMBOTIC THERAPY

The reinitiation of antithrombotic therapy, particularly full-dose therapy, is a major determinant of the bleeding risk after invasive procedures. In contrast to full-dose anticoagulation therapy, prophylactic anticoagulation therapy is resumed once hemostasis is secured. In patients receiving bridging therapy, heparin at a therapeutic dose should be withheld for 48 hours after the procedure. If the risk of postprocedural bleeding is deemed acceptably low, full-dose anticoagulation therapy may be initiated after a shorter interval.

Because achieving full anticoagulation after the reinstitution of warfarin therapy takes several days, it can be reinstituted the evening of the day on which the procedure is performed, unless there is a substantial risk of delayed bleeding or unless reoperation is anticipated. We recommend delaying the reinitiation of treatment with dabigatran, rivaroxaban, or apixaban for at least 48 hours after high-risk procedures because the full anticoagulatory effect occurs shortly after administration and there are no reliable reversal agents for these medications.

Clopidogrel administered at maintenance doses has a delayed onset of action, and treatment can therefore be reinitiated within 24 hours after the procedure. Clopidogrel loading, which results in a rapid onset of action, can be

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used if the risk of bleeding is lower than anticipated because of a change in the procedure that was performed (e.g., endoscopic biopsy of a large colonic polyp rather than polypectomy). Treatment with other antiplatelet agents, including aspirin, can be reinitiated within 24 hours. We recommend caution when reinitiating treatment with prasugrel or ticagrelor because of their rapid onset of action, potent antiplatelet inhibition, and the lack of agents to reverse their effects.

Some gastrointestinal endoscopic procedures are associated with cautery-induced injury that may result in delayed bleeding 7 to 10 days after the procedure (e.g., polypectomy and biliary sphincterotomy). If antithrombotic therapy is reinstituted after a short interval, the full antithrombotic effects may coincide with the onset of delayed bleeding, although it is often not practical to withhold antithrombotic agents for a longer period.

RECOMMENDATIONS

For patients receiving long-term antithrombotic therapy, the approach to periprocedural use of antithrombotic agents needs to be individualized. Patients should be involved in the decision-making process,[71] especially when definitive recommendations cannot be made.

Key steps for safe and successful periprocedural management of antithrombotic therapy are outlined in the Supplementary Appendix. Communication among health care providers and a generally conservative approach are paramount. Whenever possible, procedures should be postponed until the risks associated with discontinuing anticoagulation therapy are as low as possible. Overly aggressive and premature reinstitution of antithrombotic therapy may result in bleeding.[33] This can paradoxically lead to an increase in thrombotic events because of the need to reverse the antithrombotic effects, administer blood products, and postpone the reinitiation of antithrombotic therapy.

For patients undergoing low-risk bleeding procedures (Table S2 in the Supplementary Appendix), anticoagulant agents may be continued, with the INR adjusted to the low therapeutic range (approximately 2.5). For patients undergoing high-risk procedures (Table S2 in the Supplementary Appendix) who are at low risk for thrombotic events (Tables 1 and 2), anticoagulation therapy may be temporarily discontinued at appropriate intervals (Table 4) without the use of bridging therapy. For patients undergoing high-risk procedures (Table S2 in the Supplementary Appendix) who are at high risk for thromboembolic events, anticoagulation therapy may be temporarily discontinued, but bridging therapy is strongly recommended in selected patients (Table 3). For patients with recently diagnosed venous thromboembolism, elective surgery should be delayed for 3 months. If surgery is required earlier, bridging therapy should be considered with the placement of an inferior vena cava filter if less than 1 month of anticoagulation therapy has been completed.

Most patients receiving dual antiplatelet therapy have coronary-artery stents. For these patients, an elective procedure associated with a high risk of bleeding should be postponed, if possible, for at least 6 weeks after the placement of a bare-metal stent and for at least 6 months after the placement of a drug-eluting stent.[2] Ideally, a high-risk procedure should be delayed until completion of dual antiplatelet therapy (at least 12 months after the placement of either a bare-metal or drug-eluting stent).[30] If an elective high-risk procedure must be performed (Table S2 in the Supplementary Appendix) within 6 weeks after the placement of a bare-metal stent or within 6 months after the placement of a drug-eluting stent, dual antiplatelet therapy should be continued, if possible.[2] Aspirin therapy should never be discontinued.

For patients with coronary-artery stents who are undergoing a high-risk procedure (Table S2 in the Supplementary Appendix) more than 6 weeks after the placement of a bare-metal stent or more than 6 months after the placement of a drug-eluting stent, aspirin should be continued, with thienopyridine therapy temporarily discontinued at an appropriate interval before the procedure (Table 4). For patients with coronary-artery stents and those at high risk for cardiovascular atherosclerotic events who are undergoing a low-risk procedure (Table S2 in the Supplementary Appendix), full-dose antiplatelet therapy should be continued.

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