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REVIEWS

Periprocedural Management of Antithrombotic Therapy in Hospitalized Patients

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The management of antithrombotic medications in patients requiring invasive procedures is a common problem in hospital medicine, for which there is limited evidence to guide clinical decision making. Existing guidelines do not address many hospital-based procedures and have not kept pace with the introduction of newer antiplatelet and anticoagulant medications. This article provides a conceptual framework for the periprocedural management of antithrombotic therapy, with a focus on the procedures that hospitalists are most likely to perform and the pharmacology of the common and newer antithrombotic medications. *Journal of Hospital Medicine* 2014;9:337–346. © 2014 Society of Hospital Medicine

The periprocedural management of antithrombotic medications is a common challenge for hospitalists, for which there is limited high-quality evidence to guide clinical decision making. The introduction of third-generation antiplatelet agents (prasugrel and ticagrelor) and the new oral anticoagulants (rivaroxaban, apixaban, and dabigatran), has added an additional layer of complexity to clinical management.

This article will provide a conceptual framework for the periprocedural management of antithrombotic therapy, with a particular focus on procedures that are considered core competencies by the Society of Hospital Medicine; these include: arthrocentesis, lumbar puncture, paracentesis, thoracentesis, and central line placement (Table 1).[1,2] The recommendations in this article are based on a review of published guidelines and consensus statements and their supporting literature.[3–8] Additional articles were identified by performing a PubMed keyword search using the terms "perioperative management" or "periprocedural management" and "anticoagulation" or "antithrombotic" or "antiplatelet" in combination with keywords relevant to the content areas (eg, arthrocentesis, lumbar puncture). Articles for inclusion were chosen based on methodological quality and relevance to hospital medicine.

There are several questions that must be addressed when developing a periprocedural antithrombotic management strategy:

1. What is the patient's risk of bleeding if antithrombotic therapy is continued?
2. What is the patient's risk of thromboembolism if antithrombotic therapy is interrupted?
3. Are there interventions that can decrease the risk of periprocedural bleeding and/or thromboembolism?

WHAT IS THE PATIENT'S RISK OF BLEEDING IF ANTITHROMBOTIC THERAPY IS CONTINUED?

Although the risk of bleeding is well described for many procedures, there are limited data on how that risk is affected by coagulopathy in general and antithrombotic medications in particular. When these data are available, they are largely derived from case series or bridging registries, which include heterogeneous patient populations and nonstandardized definitions of bleeding.[8–10] As such, few procedural or surgical professional societies have published guidelines on the periprocedural management of antithrombotic therapy,[3–5,11] and guidelines from the American College of Chest Physicians (ACCP), the American College of Cardiology (ACC), and American Heart Association (AHA) only provide specific recommendations regarding minor ambulatory procedures.[6–8]

Procedures can be categorized as low or high risk for bleeding based on the following considerations: the extent of associated tissue injury, proximity to vital organs or vascular structures, the ability to readily detect and control bleeding, and the morbidity associated with a bleeding complication (eg, a small bleed into the epidural space is potentially catastrophic, whereas a large bleed from the colon often results in no permanent harm). For procedures with a high risk or consequence of bleeding, anticoagulants must be stopped, whereas in some cases antiplatelet agents can be safely continued. For procedures with a low risk or consequence of bleeding, it may be possible to continue both anticoagulant and antiplatelet agents.

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TABLE 1. Recommended Periprocedural Management of Antithrombotic Therapy

	Antithrombotic Therapy					
Procedure	Aspirin	Thienopyridines	Prophylactic UFH or LWMH	Therapeutic UFH or LMWH	Warfarin	NOACs
Arthrocentesis[12–15]	+	+	+	+	+	+
Lumbar puncture[3]	+	±	≤5000 units UFH BID	–	–	–
Paracentesis[28–30]	+	+	+	±	±	±
Thoracentesis[37–42]	+	+	+	±	±	±
Central venous catheter insertion[48–53]	+	+	+	±	±	±

NOTE: + = safe to continue during procedure; – = unsafe to continue during procedure; ± = insufficient data, individualized approach recommended. **Abbreviations:** BID, twice daily; LMWH, low-molecular-weight heparin; NOACs, new oral anticoagulants (rivaroxaban, apixiban, dabigatran); UFH, unfractionated heparin.

Because procedures in hospitalized patients are most often performed for the purpose of diagnosing or treating an emergent condition, the risk of delaying the procedure while antithrombotic medications are held must be part of the overall risk-benefit calculation.

Arthrocentesis

Bleeding complications from arthrocentesis are very rare, and there are few data on the additional risk associated with antithrombotic therapy.[12–14] In a retrospective cohort study, investigators determined the incidence of clinically significant bleeding (defined as bleeding requiring reversal of anticoagulation, prolonged manual pressure, surgical intervention, hospital admission, or delay in hospital discharge) and procedure-related pain among 514 patients on antithrombotic therapy referred for arthrocentesis or injection of the hip, shoulder, or knee. Four hundred fifty-six procedures were performed in patients without interrupting warfarin therapy, all of whom maintained an international normalized ratio (INR)≥2, and 184 procedures were performed in patients who had stopped their warfarin to achieve an INR <2. Antiplatelet therapy was routinely continued in both groups, with 48% of patients taking aspirin and 9% clopidogrel. There was 1 bleeding complication (0.2%) in a patient with an INR of 2.3 who was also taking aspirin, and 2 patients developed procedure-related pain (INR 3.3 and 5.3, neither taking antiplatelet medications).[15]

Based on the available evidence, arthrocentesis appears to be safe in patients on therapeutic warfarin, with or without aspirin and/or clopidogrel. At present, there are no published studies that address the risk of arthrocentesis in patients taking other antiplatelet or anticoagulant medications, but given the low overall risk of this procedure, it is reasonable to infer that these medications can also be safely continued.

Lumbar Puncture

The incidence of bleeding complications from diagnostic lumbar puncture is unknown, but is likely similar to that seen with spinal anesthesia, where in a large retrospective observational study, spinal hematoma occurred in ~1:165,000 spinal block procedures.[16] Factors associated with an increased risk of spinal hematoma include traumatic tap, advanced age, female gender, spinal cord or vertebral column abnormalities, coagulopathy, and not allowing sufficient time between stopping and restarting antithrombotic therapy.[3,17–20]

Therapeutic anticoagulation must be stopped and prophylactic anticoagulation delayed before performing a lumbar puncture. The 1 exception is low-dose unfractionated heparin (UFH), which the American Society for Regional Anesthesia (ARSA) recommends continuing in patients undergoing neuraxial procedures, provided the total dose is ≤5000 U twice daily. This assessment is based on observational data, surveys of practice patterns, and decades of use without evidence of complications; in fact, there are only 5 case reports of spinal hematomas in this population.[3] However, because these data are from surgical populations, in which heparin thromboprophylaxis is typically dosed at 5000 units twice daily, there are limited data on the safety of higher or more frequent doses of heparin. In a retrospective cohort study of 928 patients who received thoracic epidural analgesia in conjunction with UFH dosed at 5000 U, 3 times daily, there were no cases of neuraxial bleeding, but given the rarity of neuraxial hematoma, it is not possible to draw any conclusions from this relatively small sample size.[21]

In November 2013, based on surveillance data showing increased risk for spinal or epidural hematoma associated with low-molecular-weight heparin (LMWH), the US Food and Drug Administration (FDA) issued a drug safety communication recommending that neuraxial procedures be delayed for 12 hours after prophylactic LMWH and 24 hours after therapeutic LMWH, and that LMWH not be restarted for at least 4 hours after catheter removal.[20] These recommendations are largely consistent with existing guidelines[3,22] but are not explicitly stated in the package insert for any of the LMWHs available in the United States,[23–25] and the FDA is working with the manufacturers to add this information.

Nonsteroidal anti-inflammatory drugs (NSAIDs), dipyridamole, and aspirin do not appear to increase the risk of spinal hematoma and are considered safe to continue.[11,26] There are limited data on the safety of thienopyridine medications in neuraxial anesthesia, but based on case reports and increased bleeding rates seen in surgical populations, it is generally

recommended that these medications be discontinued before performing a lumbar puncture.[3,22,27]

The optimal time to restart anticoagulation after a lumbar puncture is unknown. The ARSA recommends a minimum of 1 hour for UFH and 2 hours for LMWH after neuraxial catheter removal, and provides no specific guidance about other anticoagulants,[3] whereas the European Society of Anesthesiology recommends a minimum of 1 hour for UFH, 4 hours for LMWH, 4 to 6 hours for rivaroxaban and apixiban, and ≥6 hours for dabigatran and fondaparinux.[22] Longer time periods should be considered after a traumatic tap, and postprocedure monitoring of neurological function is recommended for all patients.

The available evidence suggests that lumbar puncture can be safely performed in patients being treated with aspirin, NSAIDs, and UFH dosed at 5000 U twice daily; the safety of higher or more frequent doses of UFH is not known. Lumbar puncture should be delayed 12 hours after prophylactic LMWH and 24 hours after therapeutic LMWH, and LMWH should not be restarted for at least 4 hours after the procedure.[20] There are limited data on the safety of thienopyridines, but they should generally be discontinued, and all other prophylactic or therapeutic anticoagulation must be stopped prior to the procedure.

Paracentesis

Bleeding complications from paracentesis are uncommon, with abdominal wall hematoma and hemoperitoneum complicating 1% and 0.01% of procedures, respectively.[28–30] Whether antithrombotic therapy increases the risk of bleeding during paracentesis is unknown, primarily because most patients for whom the procedure is indicated have coagulopathy and thrombocytopenia from liver disease, and are therefore rarely treated with these medications.

Although patients with liver disease often have an elevated INR due to impaired hepatic synthesis of clotting factors, it is incorrect to generalize the observed rate of bleeding in this population to patients with an elevated INR from warfarin therapy who may require paracentesis for reasons unrelated to liver disease (eg, malignancy or infection). The coagulopathy of liver disease reflects deficiencies in the hepatic production of both pro- and anticoagulant proteins, and these patients develop both thrombotic and hemorrhagic complications irrespective of their in vitro coagulation indices.[31]

Although the available evidence suggests that paracentesis can be safely performed in patients with coagulopathy from liver disease, regardless of the INR,[30] little is known about the bleeding risk in other patients, with or without antithrombotic therapy. Based on indirect evidence, it is reasonable to assume that prophylactic UFH or LWMH or antiplatelet therapy would confer minimal additional risk, whereas the safety of continuing therapeutic anticoagulation is unknown.

Thoracentesis

Bleeding complications from thoracentesis are uncommon, generally occurring in <1% of procedures.[32–34] Factors associated with increased risk of overall complications include operator inexperience, large volume drainage, and lack of ultrasound guidance.[34–36] There are no studies that specifically address the risk of bleeding in patients on anticoagulant therapy, but such patients are included in studies on the risk of bleeding with coagulopathy.[37–40]

In a retrospective cohort study of 1076 ultrasound-guided thoracenteses performed by radiologists on patients with coagulopathy (defined as thrombocytopenia or an elevated INR from any cause), there were no bleeding complications (defined as anything other than minimal symptoms not requiring intervention). Among the patients in this study, 497 (46%) patients had a preprocedure INR >1.5; 198 (24%) had an INR between 2 and 3, and 32 (4%) had an INR >3.[39]

A similar study, which compared outcomes in patients with corrected and uncorrected coagulopathy, included 744 patients with an INR >1.6 (from any cause), of which 167 received preprocedural fresh-frozen plasma (FFP) and 577 did not. There was 1 (0.1%) bleeding complication in a patient who received prophylactic FFP and none in the group that was not transfused.[38]

In a prospective cohort of 312 patients at increased risk for bleeding (from coagulopathy or antithrombotic medications) who underwent ultrasound-guided thoracentesis by a pulmonologist or physician's assistant, 44 (34%) had an INR >1.5 (secondary to liver disease or warfarin therapy), 15 (12%) were taking clopidogrel, and 14 (11%) were treated with therapeutic LMWH within 12 hours or therapeutic UFH within 4.5 hours of the procedure. There were no bleeding complications in any of the patients (defined as mean change in hematocrit, chest x-ray abnormalities, hemothorax, or requirement for transfusion).[37]

Although there are no studies that specifically address the use of aspirin and bleeding complications in thoracentesis, it is generally considered safe to continue this medication,[5] and there are small studies that show that thoracentesis and small-bore chest tubes can be safely placed in patients taking clopidogrel.[41,42]

Thoracentesis is associated with a low rate of bleeding complications, and when performed by an experienced operator using ultrasound, warfarin does not appear to increase this risk. However, given the low overall complication rate, it is not known whether patients on warfarin would have worse outcomes in the event of more serious complications (eg, intercostal artery laceration). At present, there

TABLE 2. American College of Chest Physicians Stratification for Perioperative Thromboembolism[8]

	Indication for Anticoagulant Therapy		
Risk Stratum	Mechanical Heart Valve	Atrial Fibrillation	VTE
High Thrombotic Risk	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 months) stroke or TIA	• $CHADS_2$ score of 5 or 6 • Recent (within 3 months) stroke or TIA • Rheumatic valvular heart disease	• Recent (within 3 months) VTE • Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate Thrombotic Risk	• Bileaflet aortic valve prosthesis with one or more of the following risk factors: atrial fibrillation, prior stroke or TIA, hypertension, diabetes, congestive heart failure, age ≥75 years	• $CHADS_2$ score of 3 or 4	• VTE within the past 3 to 12 months • Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within six months or palliative)
Low Thrombotic Risk	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• $CHADS_2$ score of 0 to 2 (assuming no prior stroke or TIA)	• VTE >12 months previous and no other risk factors

NOTE: **Abbreviations:** $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or transient ischemic attack; TIA, transient ischemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.

*High-risk patients may also include those with a prior stroke or TIA occurring >3 months before the planned surgery and a $CHADS_2$ score <5, those with prior thromboembolism during temporary interruption of VKAs, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

are no published studies that address the risk of thoracentesis in patients taking new oral anticoagulants (NOACs).

Central Venous Catheter Insertion

The incidence of bleeding complications from central venous catheter (CVC) placement varies depending on the site of insertion and definition of bleeding, with hematoma and hemothorax occurring in 0.1% to 6.9%, and 0.4% to 1.3% of procedures, respectively.[43–45] Factors that increase the likelihood of complications include operator inexperience, multiple needle passes, and lack of ultrasound guidance.[46,47] There are no studies that specifically address the risk of bleeding from CVC placement in patients on anticoagulant therapy, but such patients are included in studies of CVC placement in patients with coagulopathy, which report similar complication rates as seen in patients with normal hemostasis.[48–53]

In a retrospective cohort study, investigators collected information on CVC-associated bleeding complications in 281 medical and surgical intensive care patients with coagulopathy (INR ≥1.5 from any cause) after they adopted a more conservative approach to plasma transfusion in their intensive care unit; specifically, the routine use of prophylactic FFP to correct coagulopathy was discouraged for patients with an INR <3 (vs usual practice using an INR cutoff of 1.5), but the final decision was left to the discretion of the attending performing or supervising the procedure. Bleeding was defined as insertion-site hematoma, interventions other than local manual pressure, and the need for blood transfusion. One case of bleeding (hematoma) was observed in a patient with an INR of 3.9, who received FFP before the procedure. There were no complications among those with uncorrected coagulopathy, including 66 patients with an INR between 1.5 and 2.9, and 6 with an INR ≥3.0. Ultrasound guidance was used in ~50% of CVCs placed in the internal jugular vein.[54]

Although there are no studies that specifically address the use of antiplatelet drugs and bleeding complications in CVC placement, aspirin is generally considered safe to continue,[5] and by inference, thienopyridines are expected to add minimal additional risk.

CVC placement is associated with a variable rate of bleeding complications, with hematoma being relatively common. Based on the available literature, warfarin does not appear to increase this risk, but there are limited data from which to draw firm conclusions. A femoral or jugular approach may be preferable because they allow for ultrasound visualization and are amenable to manual compression. There are no published studies that address the risk of CVC placement in patients taking NOACs, and although the risk of bleeding is probably similar to patients receiving warfarin, the lack of effective reversal agents for these medications should be part of any risk-benefit calculation.[55]

WHAT IS THE PATIENT'S RISK OF THROMBOEMBOLISM IF ANTITHROMBOTIC THERAPY IS INTERRUPTED?

Anticoagulants

If it is determined that a procedure cannot safely be performed while continuing antithrombotic therapy, one must then consider the patient's risk of thromboembolism if these therapies are temporarily interrupted. Unfortunately, there are few robust clinical studies from which to make this assessment, and therefore most clinicians rely on the risk stratification model proposed by the ACCP, which divides patients into 3 tiers (low, moderate, high), based on their indication for anticoagulation and risk factors for thromboembolism (Table 2)[8]. The ACCP model is largely based on indirect evidence from antithrombotic

therapy trials in nonoperative patients, and its application to perioperative patients necessitates several assumptions that may not hold true in practice.

First, it assumes that the annualized risk of a thrombotic event in nonoperative patients can be prorated to determine the short-term risk of discontinuing antithrombotic therapy in the perioperative period. For example, it has been estimated that the risk for perioperative stroke in a patient with atrial fibrillation who temporarily interrupts anticoagulation for 1 week would be ~0.1% (5% per year ÷ 52 weeks),[56,57] and yet we know from observational data that the actual risk of perioperative stroke in similar patients is 5 to 7 times higher.[58,59] Second, it assumes that bridging therapy will decrease the risk of thromboembolism in high-risk patients when warfarin therapy is interrupted, a premise that is logical but has not been subject to randomized controlled trials.[60] Third, it does not take into account the surgery-specific risk for thromboembolism, which varies significantly, with arterial thromboembolism being more common in cardiac valve, vascular, and neurologic procedures, and venous thromboembolism (VTE) being more likely in orthopedic, trauma, and cancer surgery.[61,62] These limitations notwithstanding, the ACCP model still offers the best available framework for thrombotic risk assessment and a reasonable starting point for clinical decision making.

Antiplatelet Agents

Patients with coronary artery stents who undergo noncardiac surgery are at increased risk for adverse cardiovascular events, including acute stent thrombosis, which carries a risk of myocardial infarction and death of 70% and 30%, respectively.[63] This risk is highest during the period between stent implantation and endothelialization, a process that takes 4 to 6 weeks for bare-metal stents (BMS) and 6 to 12 months for drug-eluting stents (DES). Premature discontinuation of dual antiplatelet therapy is the most important risk factor for stent thrombosis during this time.[64] Although the optimal perioperative strategy for these patients is unknown, there is general agreement that elective surgery should be delayed for at least 4 weeks in patients with a BMS and 12 months for patients with a DES. If a procedure or surgery is required during this time period, every effort should be made to continue dual antiplatelet therapy; if this is not possible, aspirin should be continued, and thienopyridine therapy should be interrupted as briefly as possible (Table 3).

ARE THERE INTERVENTIONS THAT CAN DECREASE THE RISK OF PERIPROCEDURAL BLEEDING AND/OR THROMBOEMBOLISM?

Mitigating the Risk of Bleeding

Bleeding complications can be reduced by allowing a sufficient time for the effects of antithrombotic medications to wear off before performing a procedure. This requires an understanding of the pharmacology of these medications, with particular attention to patients in whom these medications are less well studied, including the elderly, patients with renal insufficiency, and those with very high or low body mass index. Table 3 provides recommendations for when to stop antithrombotic therapy prior to an invasive procedure. The intervals are based on the time needed to achieve a minimal antithrombotic effect, which is generally 4 to 5 half-lives for anticoagulants and 7 to 10 days for irreversible antiplatelet agents. Shorter intervals may be appropriate for procedures with low risk or consequence of bleeding, but there are insufficient data to make specific recommendations regarding this strategy.

It is equally important to ensure that there is adequate time for postoperative hemostasis prior to restarting antithrombotic therapy. Data from VTE prophylaxis trials and bridging studies consistently show that bleeding complications occur more frequently when anticoagulation is started too early, and antithrombotic therapy should generally be delayed 24 hours in patients at average risk and 48 to 72 hours in patients at high risk or consequence for postoperative bleeding.[8,60,65]

Aspirin increases the risk of surgical blood loss and transfusion by up to 20%, and by up to 50% when given in combination with clopidogrel, but with the exception of intracranial surgery, there does not appear to be an increase in perioperative morbidity or mortality with either of these agents.[66]

Mitigating the Risk of Thromboembolism

Once the decision has been made to temporarily discontinue warfarin, the next consideration is whether to bridge with a short acting anticoagulant (typically subcutaneous LMWH or intravenous UFH) during the period of time when the INR is subtherapeutic. Conceptually, one would expect this strategy would minimize the risk of thromboembolism, but its efficacy has never been clearly demonstrated. In fact, in a systematic review and meta-analysis of 34 studies that compared the rates of thromboembolism among bridged and nonbridged patients, heparin therapy did not reduce the risk of thromboembolic events (odds ratio: 0.80; 95% confidence interval: 0.42–1.54), but did result in higher rates of periprocedural bleeding.[60]

The applicability of these results to clinical practice are limited by the heterogeneity of the data used in the analysis; specifically, bridging strategies varied (including therapeutic, intermediate, and prophylactic dose regimens), there was wide variation in the types of surgery (and therefore bleeding risk), and because the majority of studies were observational, there is a significant likelihood of confounding by indication (ie, patients at high risk for thromboembolism are more likely to receive bridging therapy), and thus the benefit

TABLE 3. Recommended Timing for Periprocedural Interruption and Initiation of Antithrombotic Therapy

	Recommended Interval Between Last Dose of Medication and Procedure	Recommended Interval Between Procedure and First Dose of Medication, h	
		Low Risk or Consequence of Postprocedure Bleeding	High Risk or Consequence of Postprocedure Bleeding
Antiplatelet Medications*			
Aspirin (81–325 mg daily ± dipyridamole)	7–10 days (skip 6–9 doses)	24	48
Ticlodipine (250 mg twice daily)	10–14 days (skip 19–26 doses)	24	48
Clopidogrel (75 mg once daily)	7–10 days (skip 6–9 doses)†	24	48
Prasugrel (10 mg once daily)	7–10 days (skip 6–9 dose)‡	24	48
Ticagrelor (90 mg twice daily; t $\frac{1}{2}$ = 8 hours)	5 days (skip 8 doses)§	24	48
Cilostazol (100 mg twice daily; t $\frac{1}{2}$ = 11 hours)	3 days (skip 4 doses)	24	48
Anticoagulant Medications‖			
Warfarin (t $\frac{1}{2}$ = 36–42 hours, but highly variable)	6 days (skip 5 doses)¶	12	24
Intravenous UFH (t $\frac{1}{2}$ ~60 minutes)	4–6 hours	24	48–72
LMWH (t $\frac{1}{2}$ = 3–7 hours)			
Prophylactic dosing	12 hours#	12	24–36
Therapeutic dosing			
Once daily	24 hours (give 50% of last total dose)#	24	48–72
Twice daily	24 hours (skip 1 dose)#	24	48–72
Fondaparinux (t $\frac{1}{2}$ = 17 hours, any dose)	3–4 days (skip 2–3 doses)**	24	48–72
Dabigatran (150 mg twice daily)			
CrCl > 50 mL/min (t $\frac{1}{2}$ = 14–17 hours)	3 days (skip 4 doses)	24	48–72
CrCl 30–50 mL/min (t $\frac{1}{2}$ = 16–18 hours)	4–5 days (skip 6–8 doses)	24	48–72
CrCl 15–30 mL/min (t $\frac{1}{2}$ = 16–18 hours)††	4–5 days (skip 6–8 doses)	24	48–72
Rivaroxaban (20 mg once daily)			
CrCl > 50 mL/min (t $\frac{1}{2}$ = 8–9 hours)	3 days (skip 2 doses)	24	48–72
CrCl 30–50 mL/min (t $\frac{1}{2}$ = 9 hours)	3 days (skip 2 doses)	24	48–72
CrCl 15–29.9 mL/min (t $\frac{1}{2}$ = 9–10 hours)‡‡	4 days (skip 3 doses)	24	48–72
Apixiban (5 mg twice daily)			
CrCl > 50 mL/min (t $\frac{1}{2}$ = 7–8 hours)	3 days (skip 4 doses)	24	48–72
CrCl 30–50 mL/min (t $\frac{1}{2}$ = 17–18 hours)	4 days (skip 6 doses)	24	48–72

NOTE: **Abbreviations:** CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

*Assuming minimal platelet effect by 7 days and no effect by 10 days for (irreversible) agents: aspirin, ticlodipine, clopidogrel, and prasugrel. Ticlodipine drug clearance is prolonged by an additional 4 days after repeated dosing.

Ticagrelor and cilostazol half-life depends on rate of drug clearance.

†Five days is sufficient for cardiac surgery.[94]

‡Seven days per manufacturer[91]; drug effect may persist up to 10 days.

§Five days per manufacturer[93]; a shorter interval is expected based on half-life.

‖Intervals based on 4–5 drug half-lives to achieve minimal residual anticoagulant effect; shorter intervals may be appropriate for procedures with low risk or consequence of bleeding. Adapted from Spyropoulos and Douketis.[95]

¶More than 90% of patients will achieve an international normalized ratio <1.5 after skipping 5 doses.[8]

#Longer intervals are recommended for patients with CrCl <30 mL/min.[96]

**Longer intervals are recommended for patients with CrCl <50 mL/min.[96]

††Patients receiving dabigatran 75 mg twice daily.

‡‡Patients receiving rivaroxaban 15 mg daily.

of this strategy may be underestimated. It is also important to note that in the majority studies anticoagulation was restarted <24 hours after the procedure, which likely contributed to the increased rate of bleeding.

Therefore, although bridging therapy is not indicated for patients at low risk, it is premature to conclude that it should be avoided in patients at moderate or high risk for thromboembolism. The results of 2 ongoing, randomized, placebo-controlled trials of bridging therapy in patients taking warfarin for atrial fibrillation (Effectiveness of Bridging Anticoagulation for Surgery [BRIDGE]) or mechanical heart values (A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism [PERIOP-2]) should help to answer this question.[67,68]

The uncertainty regarding the benefits of bridging therapy is reflected in the changes to the most recent ACCP guidelines. In 2008, the ACCP recommended low-dose LMWH or no bridging for patients at low risk (grade 2C), therapeutic-dose bridging for patients at moderate risk (grade 2C), and therapeutic-dose bridging for patients at high risk for thromboembolism (Grade 1C).[56] In 2012, the ACCP recommended *against* bridging for low-risk patients (grade 2C), made no specific recommendation regarding moderate-risk patients, and offered a less robust recommendation for bridging in high-risk patients (grade 2C).[8]

Until the results of the BRIDGE and PERIOP-2 trials are available, the author still favors therapeutic bridging for patients at high risk and selected patients at moderate risk for thromboembolism, provided sufficient time is allowed for postoperative hemostasis before anticoagulation is restarted. For procedures with a high risk or consequence of bleeding, intravenous UFH (without a bolus) is a reasonable initial postoperative strategy to insure that anticoagulation is tolerated before committing to LMWH. Indirect evidence supports the use of prophylactic or intermediate-dose bridging regimens in patients for whom the primary consideration is the prevention of recurrent VTE, but data to show that this strategy is effective for the prevention of arterial thromboembolism are lacking.

Intravenous glycoprotein IIb/IIIa inhibitors are sometimes used to bridge high-risk patients with coronary artery stents who must stop antiplatelet therapy prior to a procedure, but the data to support this practice are limited and observational in nature.[69,70]

STARTING AND STOPPING ANTITHROMBOTIC THERAPY

Warfarin

For patients on warfarin, the INR at which it is safe to perform invasive procedures is unknown. Normal hemostasis requires clotting factor levels of approximately 20% to 40% of normal,[71] which generally corresponds to an INR of <1.5, whereas for most indications, therapeutic anticoagulation is achieved when the INR is between 2.0 and 3.5. However, because the relationship between the INR and the levels of clotting factors is nonlinear, for a given patient, the INR may be "abnormal" (ie, >1) despite levels of clotting factors that are sufficient for periprocedural hemostasis.[72–75] Because of its relatively long half-life (36–42 hours), warfarin should be stopped 6 days (skip 5 doses) prior to a procedure to achieve an INR of <1.5, but can safely be restarted the same day in most patients.

Heparins

The half-life of intravenous heparin is dose dependent, and at therapeutic levels is approximately 60 minutes; therefore, it should be discontinued 4 to 6 hours (~5 half-lives) before performing an invasive procedure.[76] The half-life of subcutaneous LMWHs ranges from 3 to 7 hours in healthy volunteers,[23–25] and is often longer in patients for whom these medications are commonly prescribed.[77,78] Therefore, when administered at therapeutic doses twice daily, the last dose should be given in the morning the day before the procedure, and for therapeutic once-daily regimens, the last dose should be reduced by 50%.[8] The optimal time to discontinue prophylactic doses of LWMH prior to an invasive procedure is unclear, but a minimum of 12 hours is recommended.[22,79] Because LWMHs are renally cleared, longer intervals are needed for patients with impaired renal function.[76,80]

New Oral Anticoagulants

The manufacturer of rivaroxaban recommends that if anticoagulation must be discontinued, it be stopped at least 24 hours before the procedure.[81] Although this may be sufficient for procedures with a low risk or consequence of bleeding, the half-life of rivaroxaban is between 8 and 10 hours, and therefore 48 hours (4–5 half-lives) is required to ensure minimal residual anticoagulant effect.

Apixaban has a clearance half-life of ~6 hours, but displays prolonged absorption such that its effective half-life is ~12 hours after repeated dosing. The manufacturer recommends that it be stopped at least 24 hours prior to a procedure with a low risk or consequence of bleeding, and 48 hours prior to a procedure with a high risk or consequence of bleeding.[82]

The manufacturer of dabigatran recommends that the drug be discontinued 1 to 2 days (creatinine clearance (CrCl) ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures, and that longer times be considered when complete hemostasis is required.[83] Given that the half-life of dabigatran is 14 to 17 hours, the author recommends that it be stopped at least 2 days (~3 half-lives) prior to a procedure with a low risk or consequence of bleeding, and 3 days (4–5 half-lives) prior to a procedure with a high risk or consequence of bleeding.

The clearance of all the NOACs is significantly prolonged in patients with renal impairment, and a longer interval between the last dose and the procedure is necessary in patients with renal failure to ensure normal hemostasis (Table 3).

The effect of the NOACs on the standard clotting assays are complex and vary depending on drug dose, the type of reagents used, and the calibration of the equipment. For dabigatran, the activated partial thromboplastin time (aPTT) and the thrombin time (TT) are sufficiently sensitive to allow for a qualitative assessment of drug effect, such that a normal aPTT indicates the absence, or a very low level of an anticoagulant effect, and a normal TT essentially rules out an effect. Accurate quantitative testing of dabigatran requires an appropriately calibrated dilute thrombin test or ecarin clotting time assay.[84,85]

Depending on the thromboplastin reagent used, the prothrombin time (PT) may be sufficiently sensitive to rivaroxaban that a normal level rules out a residual drug effect,[86] but this does not hold true for apixaban, which has minimal effect on the PT at therapeutic concentrations. The aPTT is insensitive to both rivaroxaban and apixaban and cannot be used for assessing residual drug effect. Accurate quantitative testing of rivaroxaban or apixaban requires an anti-factor Xa assay calibrated for use with these agents.[84]

Antiplatelet Agents

Aspirin irreversibly inhibits platelet cyclooxygenase activity, and the thienopyridines clopidogrel and prasugrel, irreversibly inhibit the platelet $P2Y_{12}$ receptor.

As such, the biological effects of these medications persist until the platelet pool has turned over, a process that occurs at 10% to 12% per day and takes 7 to 10 days to complete.[87] The minimum number of functional platelets required to ensure adequate periprocedural hemostasis is unknown, but is likely between 50 and 100,000/μL.[88] Therefore, assuming a platelet pool of 200,000/μL, most patients will regenerate an adequate number of functional platelets by 5 days after discontinuing therapy, and nearly all will have normal platelet function by 10 days. Determining the risk of bleeding prior to complete turnover of the platelet pool is further complicated by genetic variability between patients in drug metabolism and the degree of platelet inhibition by these agents.[89]

Owing to this complexity, guidelines and prescribing recommendations are inconsistent. The ACCP recommends stopping antiplatelet agents 7 to 10 days prior to an invasive procedure, and the ACC/AHA makes no specific recommendations at all.[90] Based on data from patients undergoing cardiac bypass surgery, it is recommended that clopidogrel be stopped 5 days, and prasugrel 7 days, prior to an invasive procedure.[91,92] The elimination half-life of ticlodipine is sufficiently long (up to 96 hours after repeated dosing) that it should be stopped 10 to 14 days prior to an invasive procedure.[87] Ticagrelor is a reversible $P2Y_{12}$ receptor inhibitor with a half-life of approximately 8 hours and should therefore have minimal effect by 3 days after discontinuation; however, the manufacturer recommends that it be stopped 5 days prior to an invasive procedure.[93]

The optimal time to restart antiplatelet agents after an invasive procedure is also unknown. The 2008 ACCP guidelines recommended restarting aspirin and/or clopidogrel in 24 hours, or as hemostasis allows,[56] whereas neither the 2007 or 2009 ACC/AHA guidelines,[90] or the most recent 2012 ACCP guidelines,[8] offer specific recommendations. Aspirin, prasugrel, and ticagrelor have a rapid onset of action, whereas the full antiplatelet effect of clopidogrel does not occur for several days, and for patients in whom more rapid platelet inhibition is desired, a loading dose (300–600 mg) may be appropriate.[87]

CONCLUSIONS

Deciding on an optimal periprocedural antithrombotic management strategy is a common challenge for hospitalists that requires careful consideration of both patient and procedure related-risk factors for bleeding and thrombosis, as well as the consequences of delaying or forgoing the procedure altogether. For many procedures, there is evidence that antithrombotic therapy can be safely continued, thereby obviating the risk associated with interrupting therapy. When antithrombotic therapy must be stopped, it should be done in a manner that appropriately balances the risks and consequence of periprocedural bleeding and thromboembolism. Strategies to decrease the risk of perioperative bleeding include allowing sufficient time for the effects of antithrombotic therapy to subside before starting the procedure, and ensuring adequate time for hemostasis before restarting antithrombotic therapy. Bridging therapy may provide net clinical benefit for patients at moderate to high risk for thromboembolism, but this will not be clear until the results of several ongoing bridging trials are available. The periprocedural antithrombotic management strategy should be developed in collaboration with the relevant providers and with active participation by the patient in all decisions and treatment plans. Standardized protocols and documentation can help to minimize unintended variation in practice and improve information transfer during transitions of care.

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