



**LEARNING OBJECTIVE:** Readers will individualize their management of anticoagulation for patients with atrial fibrillation or venous thromboembolism

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# Navigating the anticoagulant landscape in 2017

## ABSTRACT

Several questions remain regarding anticoagulant management: What is the best strategy for managing acute venous thromboembolism? How should patients on a direct oral anticoagulant or on warfarin be managed when they need elective surgery? When is heparin bridging necessary?

## KEY POINTS

Venous thromboembolism has a myriad of clinical presentations, warranting a holistic management approach that incorporates multiple antithrombotic management strategies.

A direct oral anticoagulant is an acceptable treatment option in patients with submassive venous thromboembolism, whereas catheter-directed thrombolysis should be considered in patients with iliofemoral deep vein thrombosis, and low-molecular-weight heparin in patients with cancer-associated thrombosis.

Perioperative management of direct oral anticoagulants should be based on the pharmacokinetic properties of the drug, the patient's renal function, and the risk of bleeding posed by the surgery or procedure.

Perioperative heparin bridging can be avoided in most patients who have atrial fibrillation or venous thromboembolism, but should be considered in most patients with a mechanical heart valve.

This article is based on an edited transcript from a Heart and Vascular Institute Grand Rounds presentation at Cleveland Clinic. It was approved by the author but not peer-reviewed.

doi:10.3949/ccjm.84gr.17005

**T**HIS ARTICLE reviews recommendations and evidence concerning current anticoagulant management for venous thromboembolism and perioperative care, with an emphasis on individualizing treatment for real-world patients.

## TREATING ACUTE VENOUS THROMBOEMBOLISM

### Case 1: Deep vein thrombosis in an otherwise healthy man

A 40-year-old man presents with 7 days of progressive right leg swelling. He has no antecedent risk factors for deep vein thrombosis or other medical problems. Venous ultrasonography reveals an iliofemoral deep vein thrombosis. How should he be managed?

- Outpatient treatment with low-molecular-weight heparin for 4 to 6 days plus warfarin
- Outpatient treatment with a direct oral anticoagulant, ie, apixaban, dabigatran (which requires 4 to 6 days of initial treatment with low-molecular-weight heparin), or rivaroxaban
- Catheter-directed thrombolysis followed by low-molecular-weight heparin, then warfarin or a direct oral anticoagulant
- Inpatient intravenous heparin for 7 to 10 days, then warfarin or a direct oral anticoagulant

All of these are acceptable for managing acute venous thromboembolism, but the clinician's role is to identify which treatment is most appropriate for an individual patient.

### Deep vein thrombosis is not a single condition

Multiple guidelines exist to help decide on a management strategy. Those of the American College of Chest Physicians (ACCP)<sup>1</sup> are used most often.

That said, guidelines are established for “average” patients, so it is important to look beyond guidelines and individualize management. Venous thromboembolism is not a single entity; it has a myriad of clinical presentations that could call for different treatments. Most patients have submassive deep vein thrombosis or pulmonary embolism, which is not limb-threatening nor associated with hemodynamic instability. It can also differ in terms of etiology and can be unprovoked (or idiopathic), cancer-related, catheter-associated, or provoked by surgery or immobility.

Deep vein thrombosis has a wide spectrum of presentations. It can involve the veins of the calf only, or it can involve the femoral and iliac veins and other locations including the splanchnic veins, the cerebral sinuses, and upper extremities. Pulmonary embolism can be massive (defined as being associated with hemodynamic instability or impending respiratory failure) or submassive. Similarly, patients differ in terms of baseline medical conditions, mobility, and lifestyle. Anticoagulant management decisions should take all these factors into account.

### Consider clot location

Our patient with iliofemoral deep vein thrombosis is best managed differently than a more typical patient with less extensive thrombosis that would involve the popliteal or femoral vein segments, or both. A clot that involves the iliac vein is more likely to lead to postthrombotic chronic pain and swelling as the lack of venous outflow bypass channels to circumvent the clot location creates higher venous pressure within the affected leg. Therefore, for our patient, catheter-directed thrombolysis is an option that should be considered.

### Catheter-directed thrombolysis trials

According to the “open-vein hypothesis,” quickly eliminating the thrombus and restoring unobstructed venous flow may mitigate the risk not only of recurrent thrombosis, but also of postthrombotic syndrome, which is often not given much consideration acutely but can cause significant, life-altering chronic disability.

The “valve-integrity hypothesis” is also important; it considers whether lytic therapy

may help prevent damage to such valves in an attempt to mitigate the amount of venous hypertension.

Thus, catheter-directed thrombolysis offers theoretical benefits, and recent trials have assessed it against standard anticoagulation treatments.

**The CaVenT trial** (Catheter-Directed Venous Thrombolysis),<sup>2</sup> conducted in Norway, randomized 209 patients with midfemoral to iliac deep vein thrombosis to conventional treatment (anticoagulation alone) or anticoagulation plus catheter-directed thrombolysis. At 2 years, postthrombotic syndrome had occurred in 41% of the catheter-directed thrombolysis group compared with 56% of the conventional treatment group ( $P = .047$ ). At 5 years, the difference widened to 43% vs 71% ( $P < .01$ , number needed to treat = 4).<sup>3</sup> Despite the superiority of lytic therapy, the incidence of postthrombotic syndrome remained high in patients who received this treatment.

**The ATTRACT trial** (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis),<sup>4</sup> a US multicenter, open-label, assessor-blind study, randomized 698 patients with femoral or more-proximal deep vein thrombosis to either standard care (anticoagulant therapy and graduated elastic compression stockings) or standard care plus catheter-directed thrombolysis. In preliminary results presented at the Society of Interventional Radiology meeting in March 2017, although no difference was found in the primary outcome (postthrombotic syndrome at 24 months), catheter-directed thrombolysis for iliofemoral deep vein thrombosis led to a 25% reduction in moderate to severe postthrombotic syndrome.

Although it is too early to draw conclusions before publication of the ATTRACT study, the preliminary results highlight the need to individualize treatment and to be selective about using catheter-directed thrombolysis. The trials provide reassurance that catheter-directed lysis is a reasonable and safe intervention when performed by physicians experienced in the procedure. The risk of major bleeding appears to be low (about 2%) and that for intracranial hemorrhage even lower ( $< 0.5\%$ ).

**No single approach is preferable under all circumstances**

TABLE 1

## Deep vein thrombosis: 2016 recommendations of the American College of Chest Physicians

### Deep vein thrombosis or pulmonary embolism without cancer

For the initial 3 months, a direct oral anticoagulant (dabigatran, rivaroxaban, apixaban edoxaban) is preferable to a vitamin K antagonist (grade 2B)

If a direct oral anticoagulant is not used, a vitamin K antagonist is preferable to low-molecular-weight heparin (grade 2B)

### Deep vein thrombosis or pulmonary embolism with cancer

Low-molecular-weight heparin is preferable to a vitamin K antagonist or direct oral anticoagulant (grade 2C)

Based on information in reference 1.

### Catheter-directed thrombolysis is appropriate in some cases

The 2016 ACCP guidelines<sup>1</sup> recommend anticoagulant therapy alone over catheter-directed thrombolysis for patients with acute proximal deep vein thrombosis of the leg. However, it is a grade 2C (weak) recommendation.

They provide no specific recommendation as to the clinical indications for catheter-directed thrombolysis, but identify patients who would be most likely to benefit, ie, those who have:

- Iliofemoral deep vein thrombosis
- Symptoms for less than 14 days
- Good functional status
- Life expectancy of more than 1 year
- Low risk of bleeding.

Our patient satisfies these criteria, suggesting that catheter-directed thrombolysis is a reasonable option for him.

Timing is important. Catheter-directed lysis is more likely to be beneficial if used before fibrin deposits form and stiffen the venous valves, causing irreversible damage that leads to postthrombotic syndrome.

### Role of direct oral anticoagulants

The availability of direct oral anticoagulants has generated interest in defining their therapeutic role in patients with venous thromboembolism.

In a meta-analysis<sup>5</sup> of major trials comparing direct oral anticoagulants and vitamin K

antagonists such as warfarin, no significant difference was found for the risk of recurrent venous thromboembolism or venous thromboembolism-related deaths. However, fewer patients experienced major bleeding with direct oral anticoagulants (relative risk 0.61,  $P = .002$ ). Although significant, the absolute risk reduction was small; the incidence of major bleeding was 1.1% with direct oral anticoagulants vs 1.8% with vitamin K antagonists.

The main advantage of direct oral anticoagulants is greater convenience for the patient.

The 2016 ACCP guidelines<sup>1</sup> on the treatment of venous thrombosis and pulmonary embolism are summarized in **Table 1**. They suggest using direct oral anticoagulants rather than vitamin K antagonists to manage venous thromboembolism, but this is a weak (ie, grade 2B) recommendation, likely because the net clinical benefit of direct oral anticoagulants over vitamin K antagonists is modest.

### WHICH PATIENTS ON WARFARIN NEED BRIDGING PREOPERATIVELY?

Many patients still take warfarin, particularly those with atrial fibrillation, a mechanical heart valve, or venous thromboembolism. In many countries, warfarin remains the dominant anticoagulant for stroke prevention. Whether these patients need heparin during the period of perioperative warfarin interruption is a frequently encountered scenario that, until recently, was controversial. Recent studies have helped to inform the need for heparin bridging in many of these patients.

### Case 2: An elderly woman on warfarin facing cancer surgery

A 75-year-old woman weighing 65 kg is scheduled for elective colon resection for incidentally found colon cancer. She is taking warfarin for atrial fibrillation. She also has hypertension and diabetes and had a transient ischemic attack 10 years ago.

One doctor told her she needs to be assessed for heparin bridging, but another told her she does not need bridging.

The default management should be not to bridge patients who have atrial fibrillation, but to consider bridging in selected patients, such as those with recent stroke or transient isch-

**Lytic therapy may lower the risk of postthrombotic syndrome**

emic attack or a prior thromboembolic event during warfarin interruption. However, decisions about bridging should not be made on the basis of the CHADS<sub>2</sub> score alone. For the patient described here, I would recommend not bridging.

### Complex factors contribute to stroke risk

Stroke risk for patients with atrial fibrillation can be quickly estimated with the CHADS<sub>2</sub> score, based on:

- Congestive heart failure (1 point)
- Hypertension (1 point)
- Age at least 75 (1 point)
- Diabetes (1 point)
- Stroke or transient ischemic attack (2 points).

Our patient has a score of 5, corresponding to an annual adjusted stroke risk of 12.5%. Whether her transient ischemic attack of 10 years ago is comparable in significance to a recent stroke is debatable and highlights a weakness of clinical prediction rules. Moreover, such prediction scores were developed to estimate the long-term risk of stroke if anticoagulants are not given, and they have not been assessed in a perioperative setting where there is short-term interruption of anticoagulants. Also, the perioperative milieu is associated with additional factors not captured in these clinical prediction rules that may affect the risk of stroke.

Thus, the risk of perioperative stroke likely involves the interplay of multiple factors, including the type of surgery the patient is undergoing. Some factors may be mitigated:

- Rebound hypercoagulability after stopping an oral anticoagulant can be prevented by intraoperative blood pressure and volume control
- Elevated biochemical factors (eg, D-dimer, B-type natriuretic peptide, troponin) may be lowered with perioperative aspirin therapy
- Lipid and genetic factors may be mitigated with perioperative statin use.

Can heparin bridging also mitigate the risk?

### Bridging in patients with atrial fibrillation

Most patients who are taking warfarin are doing so because of atrial fibrillation, so most evidence about perioperative bridging was developed in such patients.

**The BRIDGE trial** (Bridging Anticoagu-

lation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery)<sup>6</sup> was the first randomized controlled trial to compare a bridging and no-bridging strategy for patients with atrial fibrillation who required warfarin interruption for elective surgery. Nearly 2,000 patients were given either low-molecular-weight heparin or placebo starting 3 days before until 24 hours before a procedure, and then for 5 to 10 days afterwards. For all patients, warfarin was stopped 5 days before the procedure and was resumed within 24 hours afterwards.

A no-bridging strategy was noninferior to bridging: the risk of perioperative arterial thromboembolism was 0.4% without bridging vs 0.3% with bridging ( $P = .01$  for noninferiority). In addition, a no-bridging strategy conferred a lower risk of major bleeding than bridging: 1.3% vs 3.2% (relative risk 0.41,  $P = .005$  for superiority).

Although the difference in absolute bleeding risk was small, bleeding rates were lower than those seen outside of clinical trials, as the bridging protocol used in BRIDGE was designed to minimize the risk of bleeding. Also, although only 5% of patients had a CHADS<sub>2</sub> score of 5 or 6, such patients are infrequent in clinical practice, and BRIDGE did include a considerable proportion (17%) of patients with a prior stroke or transient ischemic attack who would be considered at high risk.

Other evidence about heparin bridging is derived from observational studies, more than 10 of which have been conducted. In general, they have found that not bridging is associated with low rates of arterial thromboembolism ( $< 0.5\%$ ) and that bridging is associated with high rates of major bleeding (4%–7%).<sup>7–12</sup>

### Bridging in patients with a mechanical heart valve

Warfarin is the only anticoagulant option for patients who have a mechanical heart valve. No randomized controlled trials have evaluated the benefits of perioperative bridging vs no bridging in this setting.

Observational (cohort) studies suggest that the risk of perioperative arterial thromboembolism is similar with or without bridging

**The main advantage of direct oral anticoagulants is convenience**



TABLE 2

## Bridging for patients taking warfarin

### Preoperatively

Give last warfarin dose on day –6

Start bridging on day –3 with one of the following:

Enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily

Dalteparin 100 IU/kg twice daily or 200 IU/kg once daily

Tinzaparin 175 IU/kg once daily

Nadroparin 85 IU/kg twice daily

Give last bridging dose on the morning of day –1

Do not routinely check the international normalized ratio on the day before surgery (> 90% will be < 1.5) except for very high-risk cases or patients having neuraxial anesthesia

Do not continue aspirin; stop 7 days preoperatively, and resume 7 days postoperatively

Give the patient precise instructions for the bridging plan

### Postoperatively

Give double dose of warfarin on the first 1–2 days postoperatively

Resume bridging when hemostasis is secured:

24 hours after low-bleeding-risk surgery

48–72 hours after high-bleeding-risk surgery

Do not use therapeutic-dose bridging at all for:

Cardiac surgery

Intracranial or spinal surgery

Cancer surgery (eg, Whipple procedure)

Reconstructive surgery (eg, skin grafting)

anticoagulation, although most patients studied were bridged and those not bridged were considered at low risk (eg, with a bileaflet aortic valve and no additional risk factors).<sup>13</sup> However, without stronger evidence from randomized controlled trials, bridging should be the default management for patients with a mechanical heart valve. In our practice, we bridge most patients who have a mechanical heart valve unless they are considered to be at low risk, such as those who have a bileaflet aortic valve.

### Bridging in patients with prior venous thromboembolism

Even less evidence is available for periprocedural management of patients who have a history of venous thromboembolism. No randomized controlled trials exist evaluating bridging vs no bridging. In 1 cohort study in

which more than 90% of patients had had thromboembolism more than 3 months before the procedure, the rate of recurrent venous thromboembolism without bridging was less than 0.5%.<sup>14</sup>

It is reasonable to bridge patients who need anticoagulant interruption within 3 months of diagnosis of a deep vein thrombosis or pulmonary embolism, and to consider using a temporary inferior vena cava filter for patients who have had a clot who need treatment interruption during the initial 3 to 4 weeks after diagnosis.

### Practice guidelines:

#### Perioperative anticoagulation

The ACCP,<sup>15</sup> the American College of Cardiology,<sup>16</sup> and the American Heart Association<sup>17</sup> have published guidelines for perioperative management of antithrombotic therapy. Despite a paucity of evidence from randomized trials, there are sufficient data to inform clinical management. Some guidelines are complex. A simplified algorithm has been proposed that considers the type of procedure, the CHADS<sub>2</sub> score, whether the patient has a mechanical heart valve, and whether there has been a recent venous thromboembolic event.<sup>18</sup>

Guidance for preoperative and postoperative bridging for patients taking warfarin is summarized in Table 2.

### CARDIAC PROCEDURES

For patients facing a procedure to implant an implantable cardioverter-defibrillator (ICD) or pacemaker, a procedure-specific concern is the avoidance of pocket hematoma.

#### Patients on warfarin: Do not bridge

The BRUISE CONTROL-1 trial (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial)<sup>19</sup> randomized patients undergoing pacemaker or ICD implantation to either continued anticoagulation therapy and not bridging (ie, continued warfarin so long as the international normalized ratio was < 3) vs conventional bridging treatment (ie, stopping warfarin and bridging with low-molecular-weight heparin). A clinically significant device-pocket hematoma occurred in 3.5% of the continued-warfarin group vs 16.0% in the heparin-bridging group ( $P < .001$ ). Thrombo-

embolic complications were rare, and rates did not differ between the 2 groups.

Results of the BRUISE CONTROL-1 trial serve as a caution to at least not be too aggressive with bridging. The study design involved resuming heparin 24 hours after surgery, which is perhaps more aggressive than standard practice. In our practice, we wait at least 24 hours to reinstate heparin after minor surgery, and 48 to 72 hours after surgery with higher bleeding risk.

These results are perhaps not surprising if one considers how carefully surgeons try to control bleeding during surgery for patients taking anticoagulants. For patients who are not on an anticoagulant, small bleeding may be less of a concern during a procedure. When high doses of heparin are introduced soon after surgery, small concerns during surgery may become big problems afterward.

Based on these results, it is reasonable to undertake device implantation without interruption of a vitamin K antagonist such as warfarin.

### Patients on direct oral anticoagulants:

#### The jury is still out

The similar BRUISE CONTROL-2 trial is currently under way, comparing interruption vs continuation of dabigatran for patients undergoing cardiac device surgery.

In Europe, surgeons are less concerned than those in the United States about operating while a patient is on anticoagulant therapy. But the safety of this practice is not backed by strong evidence.

### Direct oral anticoagulants:

#### Consider pharmacokinetics

Direct oral anticoagulants are potent and fast-acting, with a peak effect 1 to 3 hours after intake. This rapid anticoagulant action is similar to that of bridging with low-molecular-weight heparin, and caution is needed when administering direct oral anticoagulants, especially after major surgery or surgery with a high bleeding risk.

Frost et al<sup>20</sup> compared the pharmacokinetics of apixaban (with twice-daily dosing) and rivaroxaban (once-daily dosing) and found that peak anticoagulant activity is faster and higher with rivaroxaban. This is important, because many patients will take their anti-

TABLE 3

### Periprocedural management of direct oral anticoagulants

Direct oral anticoagulant	Interruption interval	Postoperative resumption
Dabigatran	4–6 days	24 hours
Apixaban	3–5 days	24 hours
Rivaroxaban	3 days	24 hours
Edoxaban	1–2 days	24 hours

Based on information in reference 21.

coagulant first thing in the morning. Consequently, if patients require any kind of procedure (including dental), they should skip the morning dose of the direct oral anticoagulant to avoid having the procedure done during the peak anticoagulant effect, and they should either not take that day's dose or defer the dose until the evening after the procedure.

### MANAGING SURGERY FOR PATIENTS ON A DIRECT ORAL ANTICOAGULANT

#### Case 3: An elderly woman on apixaban facing surgery

*Let us imagine that our previous patient takes apixaban instead of warfarin. She is 75 years old, has atrial fibrillation, and is about to undergo elective colon resection for cancer. One doctor advises her to simply stop apixaban for 2 days, while another says she should go off apixaban for 5 days and will need bridging. Which plan is best?*

In the perioperative setting, our goal is to interrupt patients' anticoagulant therapy for the shortest time that results in no residual anticoagulant effect at the time of the procedure.

The European Society of Regional Anesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine<sup>21</sup> recommend an extended period of interruption of direct oral anticoagulants (Table 3)

They further recommend that if the risk of venous thromboembolism is high, low-molecular-weight heparin bridging should be done while stopping the direct oral anticoagulant,

**Pacemaker or ICD implantation typically does not require interrupting anticoagulation**

TABLE 4

### When to interrupt direct oral anticoagulants: A simplified approach

Direct oral anticoagulant	Surgery or procedure bleeding risk	
	Low	High
<b>Dabigatran</b> (creatinine clearance $\geq$ 50 mL/min) (creatinine clearance $<$ 50 mL/min)	1 day off 2 days off	2 days off 4 days off
<b>Rivaroxaban</b>	1 day off	2 days off
<b>Apixaban</b>	1 day off	2 days off
<b>Edoxaban</b>	1 day off	2 days off
No direct oral anticoagulant on day of surgery or procedure		

Based on information in reference 26.

with the heparin discontinued 24 hours before the procedure. This recommendation seems counterintuitive, as it is advising replacing a short-acting anticoagulant with low-molecular-weight heparin, another short-acting anticoagulant.

The guidelines committee was unable to provide strength and grading of their recommendations, as too few well-designed studies are available to support them. The doctor in case 3 who advised stopping apixaban for 5 days and bridging is following the guidelines, but without much evidence to support this strategy.

#### Is bridging needed during interruption of a direct oral anticoagulant?

There are no randomized, controlled trials of bridging vs no bridging in patients taking direct oral anticoagulants. Substudies exist of patients taking these drugs for atrial fibrillation who had treatment interrupted for procedures, but the studies did not randomize bridging vs no bridging, nor were bridging regimens standardized. Three of the four atrial fibrillation trials had a blinded design (warfarin vs direct oral anticoagulants), making perioperative management difficult, as physicians did not know the pharmacokinetics of the drugs their patients were taking.<sup>22–24</sup>

We used the database from the Randomized Evaluation of Long-Term Anticoagu-

lation Therapy (RE-LY) trial<sup>22</sup> to evaluate bridging in patients taking either warfarin or dabigatran. With an open-label study design (the blinding was only for the 110 mg and 150 mg dabigatran doses), clinicians were aware of whether patients were receiving warfarin or dabigatran, thereby facilitating perioperative management. Among dabigatran-treated patients, those who were bridged had significantly more major bleeding than those not bridged (6.5% vs 1.8%,  $P < .001$ ), with no difference between the groups for stroke or systemic embolism. Although it is not a randomized controlled trial, it does provide evidence that bridging may not be advisable for patients taking a direct oral anticoagulant.

The 2017 American College of Cardiology guidelines<sup>25</sup> conclude that parenteral bridging is not indicated for direct oral anticoagulants. Although this is not based on strong evidence, the guidance appears reasonable according to the evidence at hand.

The 2017 American Heart Association Guidelines<sup>16</sup> recommend a somewhat complex approach based on periprocedural bleeding risk and thromboembolic risk.

#### How long to interrupt direct oral anticoagulants?

Table 4 shows a simplified approach to interrupting direct oral anticoagulants that we use in Canada. The approach takes into account the type of surgery and kidney function for patients taking dabigatran, a drug that depends more on renal clearance than the other direct oral anticoagulants do.<sup>26</sup>

Evidence for this approach comes from a prospective cohort study<sup>27</sup> of 541 patients being treated with dabigatran who were having an elective surgery or invasive procedure. Patients received standard perioperative management, with the timing of the last dabigatran dose before the procedure (24 hours, 48 hours, or 96 hours) based on the bleeding risk of surgery and the patient's creatinine clearance. Dabigatran was resumed 24 to 72 hours after the procedure. No heparin bridging was done. Patients were followed for up to 30 days postoperatively. The results were favorable with few complications: one transient ischemic attack (0.2%), 10 major bleeding episodes (1.8%), and 28 minor bleeding episodes (5.2%).

It is easy to forget how potent direct oral anticoagulants are

TABLE 5

**When to interrupt direct oral anticoagulants based on drug pharmacokinetics**

Direct oral anticoagulant	Drug half-life	Renal clearance	Days before surgery
<b>Apixaban</b>	9–12 hours	25%	2
<b>Dabigatran</b>			
(creatinine clearance $\geq$ 50 mL/min)	12–14 hours	80%	2
(creatinine clearance < 50 mL/min)	18–24 hours	80%	4
<b>Rivaroxaban</b>	8–12 hours	33%	2
<b>Edoxaban</b>	10–14 hours	50%	2

A subgroup of 181 patients in this study<sup>28</sup> had a plasma sample drawn just before surgery, allowing the investigators to assess the level of coagulation factors after dabigatran interruption. Results were as follows:

- 93% had a normal prothrombin time
- 80% had a normal activated partial thromboplastin time
- 33% had a normal thrombin time
- 81% had a normal dilute thrombin time.

The dilute thrombin time is considered the most reliable test of the anticoagulant effect of dabigatran but is not widely available. The activated partial thromboplastin time can provide a more widely used coagulation test to assess (in a less precise manner) whether there is an anticoagulant effect of dabigatran present, and more sensitive activated partial thromboplastin time assays can be used to better detect any residual dabigatran effect.

Dabigatran levels were also measured. Although 66% of patients had low drug levels just before surgery, the others still had substantial dabigatran on board. The fact that bleeding event rates were so low in this study despite the presence of dabigatran in many patients raises the question of whether having some drug on board is a good predictor of bleeding risk.

An interruption protocol with a longer interruption interval—12 to 14 hours longer than in the previous study (3 days for high-bleed risk procedures, 2 days for low-bleed risk procedures)—brought the activated partial thromboplastin time and dilute thrombin time to normal levels for 100% of patients with the protocol for high-bleeding-risk surgery. This study was based on small numbers

and its interruption strategy needs further investigation.<sup>29</sup>

**Case 3 continued**

Based on the current empiric evidence, we recommend interrupting direct oral anticoagulants for 2 days (or approximately a 60-hour interval between the last dose and surgery) for this 75-year-old woman who is taking apixaban (Table 5). This interruption interval corresponds to 5 elimination half-lives for apixaban, which should result in little to no residual anticoagulant and will facilitate major surgery and, if indicated, neuraxial anesthesia.

The PAUSE study (NCT02228798), a multicenter, prospective cohort study, is designed to establish a safe, standardized protocol for the perioperative management of patients with atrial fibrillation taking dabigatran, rivaroxaban, or apixaban and will include 3,300 patients.

### **■ PATIENTS WITH A CORONARY STENT WHO NEED SURGERY**

**Case 4:****A woman with a stent facing surgery**

A 70-year-old woman needs breast cancer resection. She has coronary artery disease and had a drug-eluting stent placed 5 months ago after elective cardiac catheterization. She also has hypertension, obesity, and type 2 diabetes. Her medications include an angiotensin II receptor blocker, hydrochlorothiazide, insulin, and an oral hypoglycemic. She is also taking aspirin 81 mg daily and ticagrelor (a P2Y<sub>12</sub> receptor antagonist) 90 mg twice daily.

Her cardiologist is concerned that stopping an-

**Parenteral bridging is not indicated for direct oral anticoagulants**



TABLE 6

### Overall management recommendations

#### How should acute venous thromboembolism be managed?

Direct oral anticoagulants are first-line treatment, but based on a weak recommendation

Low-molecular-weight heparin and warfarin are acceptable alternatives

Low-molecular-weight heparin is recommended for cancer-associated venous thromboembolism

Catheter-directed lysis should be considered for iliofemoral deep vein thrombosis.

#### Use heparin bridging if the patient is taking warfarin and needs surgery?

No for atrial fibrillation except for patients with CHADS<sub>2</sub> > 4 or a recent stroke

Yes for patients with a mechanical heart valve, except consideration of not bridging for a patient with a bileaflet aortic valve replacement

Consider bridging for venous thromboembolism only within first 3 months of therapy.

#### How should patients be managed if they are taking direct oral anticoagulants and need surgery?

2 days off for high risk of bleeding, 1 day off for low risk (longer for dabigatran and creatinine clearance rate < 50 mL/min)

Be careful with postoperative resumption of therapy

No need to bridge

#### How should patients with a coronary stent who need surgery be managed?

Wait at least 1 to 3 months after stent implantation

If cannot wait, consider continuing aspirin with or without a P2Y<sub>12</sub> inhibitor, platelet transfusion

*tiplatelet therapy could trigger acute stent thrombosis, which has a 50% or higher mortality rate.*

*Should she stop taking aspirin before surgery? What about the ticagrelor?*

#### Is aspirin safe during surgery?

Evidence concerning aspirin during surgery comes from Perioperative Ischemic Evaluation 2 (POISE-2), a double-blind, randomized controlled trial.<sup>30</sup> Patients who had known cardiovascular disease or risk factors for cardiovascular disease and were about to undergo

noncardiac surgery were stratified according to whether they had been taking aspirin before the study (patients taking aspirin within 72 hours of the surgery were excluded from randomization). Participants in each group were randomized to take either aspirin or placebo just before surgery. The primary outcome was the combined rate of death or nonfatal myocardial infarction 30 days after randomization.

The study found no differences in the primary end point between the two groups. However, major bleeding occurred significantly more often in the aspirin group (4.6% vs 3.8%, hazard ratio 1.2, 95% confidence interval 1.0–1.5).

Moreover, only 4% of the patients in this trial had a cardiac stent. The trial excluded patients who had had a bare-metal stent placed within 6 weeks or a drug-eluting stent placed within 1 year, so it does not help us answer whether aspirin should be stopped for our current patient.

#### Is surgery safe for patients with stents?

The safety of undergoing surgery with a stent was investigated in a large US Veterans Administration retrospective cohort study.<sup>31</sup> More than 20,000 patients with stents who underwent noncardiac surgery within 2 years of stent placement were compared with a control group of more than 41,000 patients with stents who did not undergo surgery. Patients were matched by stent type and cardiac risk factors at the time of stent placement.

The risk of an adverse cardiac event in both the surgical and nonsurgical cohorts was highest in the initial 6 weeks after stent placement and plateaued 6 months after stent placement, when the risk difference between the surgical and nonsurgical groups leveled off to 1%.

The risk of a major adverse cardiac event postoperatively was much more dependent on the timing of stent placement in complex and inpatient surgeries. For outpatient surgeries, the risk of a major cardiac event was very low and the timing of stent placement did not matter.

A Danish observational study<sup>32</sup> compared more than 4,000 patients with drug-eluting stents having surgery to more than 20,000 matched controls without coronary heart disease having similar surgery. The risk of myocardial infarction or cardiac death was much

higher for patients undergoing surgery within 1 month after drug-eluting stent placement compared with controls without heart disease and patients with stent placement longer than 1 month before surgery.

Our practice is to continue aspirin for surgery in patients with coronary stents regardless of the timing of placement. Although there is a small increased risk of bleeding, this must be balanced against thrombotic risk. We typically stop clopidogrel 5 to 7 days before surgery and ticagrelor 3 to 5 days before surgery. We may decide to give platelets before very-high-risk surgery (eg, intracranial, spinal) if there is a decision to continue both

antiplatelet drugs—for example, in a patient who recently received a drug-eluting stent (ie, within 3 months). It is essential to involve the cardiologist and surgeon in these decisions.

## BOTTOM LINE

Navigating the anticoagulant landscape in 2017 is complex. Doctors should review professional society guidelines while considering the strength of evidence on which they are based and tailor management to individual patient characteristics. **Table 6** summarizes the management recommendations reviewed in this article.

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