Perioperative management of patients receiving anticoagulants

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INTRODUCTION — The management of anticoagulation in patients undergoing surgical procedures is challenging because interrupting anticoagulation for a procedure transiently increases the risk of thromboembolism. At the same time, surgery and invasive procedures have associated bleeding risks that are increased by the anticoagulant(s) administered for thromboembolism prevention. If the patient bleeds from the procedure, their anticoagulant may need to be discontinued for a longer period, resulting in a longer period of increased thromboembolic risk. A balance between reducing the risk of thromboembolism and preventing excessive bleeding must be reached for each patient.

Additional issues relate to the specific anticoagulant used. For those taking a vitamin K antagonist (eg, warfarin), it takes several days until the anticoagulant effect is reduced and then reestablished perioperatively; the risks and benefits of "bridging" with a shorter acting agent, such as heparin, during this time are unclear. The newer direct oral anticoagulants (eg, direct thrombin inhibitor dabigatran, factor Xa inhibitors rivaroxaban, apixaban, edoxaban) have shorter half-lives, making them easier to discontinue and resume rapidly, but the direct factor Xa inhibitors lack a specific antidote, which raises concerns about treatment of bleeding and management of patients who require an urgent procedure.

Our approach to managing ongoing anticoagulation in patients undergoing surgery or an invasive procedure is discussed here. Additional details regarding the use of specific anticoagulants and antiplatelet agents are presented separately.

- Vitamin K antagonists – (See "Warfarin and other VKAs: Dosing and adverse effects".)
- Heparins – (See "Heparin and LMW heparin: Dosing and adverse effects".)
- Direct thrombin inhibitors and direct factor Xa inhibitors – (See "Direct oral anticoagulants: Dosing and adverse effects".)
- Antiplatelet agents – (See "Perioperative medication management", section on 'Medications affecting hemostasis'.)

Perioperative venous thromboembolism prevention in patients not receiving ongoing anticoagulation is also discussed separately. (See "Prevention of venous thromboembolic disease in surgical patients".)

OVERVIEW OF OUR APPROACH

General approach — Interruption of anticoagulation temporarily increases thromboembolic risk, and continuing anticoagulation increases the risk of bleeding associated with invasive procedures; both of these outcomes adversely affect mortality [1-6]. Our approach to perioperative management of

anticoagulation takes into account these risks, along with specific features of the anticoagulant the patient is taking.

Of note, much of our approach is based on expert opinion; thrombotic and bleeding risks may vary depending on individual circumstances, and data from randomized trials are not available to guide practice in many settings. In addition, the best surrogate for complete resolution of anticoagulant effect is not always known or available for the newer direct oral anticoagulants. Thus, this approach should be used as a guideline and should not substitute for clinician judgment in decisions about perioperative anticoagulant management.

Our approach to decision making is outlined as follows:

- **Estimate thromboembolic risk** – A higher thromboembolic risk increases the importance of minimizing the interval without anticoagulation (table 1). We estimate thromboembolic risk for patients with atrial fibrillation based on age and comorbidities. For those with a recent deep vein thrombosis or pulmonary embolism, we estimate the risk based on the interval since diagnosis.
  If thromboembolic risk is transiently increased (eg, recent stroke, recent pulmonary embolism), we prefer to delay surgery until the risk returns to baseline, if possible. (See 'Estimating thromboembolic risk' below.)
  For patients with more than one condition that predisposes to thromboembolism, the condition with the highest thromboembolic risk takes precedence.
- **Estimate bleeding risk** – A higher bleeding risk confers a greater need for perioperative hemostasis, and hence a longer period of anticoagulant interruption. Bleeding risk is dominated by the type and urgency of surgery; some patient comorbidities also contribute. Procedures with a low bleeding risk (eg, dental extractions, minor skin surgery) often can be performed without interruption of anticoagulation. (See 'Estimating procedural bleeding risk'below and 'Deciding whether to interrupt anticoagulation' below.)
- **Determine the timing of anticoagulant interruption** – The timing of anticoagulant interruption depends on the specific agent the patient is receiving. As examples, warfarin requires earlier discontinuation than the shorter-acting direct oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, edoxaban) (table 2). (See 'Timing of anticoagulant interruption' below.)
- **Determine whether to use bridging anticoagulation** – For most patients, we do not use bridging anticoagulation (use of a short-acting parenteral agent to reduce the interval without anticoagulation), because it increases bleeding risk without reducing the rate of thromboembolism. However, some patients on warfarin with an especially high thromboembolic risk (eg, mechanical heart valve, recent stroke) may benefit from bridging with heparin or low molecular weight (LMW) heparin. (See 'Bridging anticoagulation' below.)

Example cases — The following examples illustrate our decision-making process using this approach in general terms; importantly, management of every case must be individualized based on the judgement of the treating clinicians:

- A 76 year old female with non-valvular atrial fibrillation, hypertension, and prior stroke three months ago, receiving warfarin, requires elective hip replacement with neuraxial anesthesia; renal function is normal, and weight is 75 kg. This patient has a very high thromboembolic risk (table 1) and a high bleeding risk (table 3).

- Stop warfarin five days before the procedure (last dose on preoperative day minus 6).
- Preoperative bridging with dose LMW heparin (eg, dalteparin, 100 units/kg [7500 units] subcutaneously twice daily) starting on preoperative day minus 3, with last dose on the morning of day minus 1.
- Resume warfarin within 24 hours after surgery (usual dose).
- Postoperative low dose LMW heparin for VTE prevention (eg, dalteparin 5000 units subcutaneously once daily) within 24 hours after surgery until postoperative bridging is started.
- Postoperative bridging on postoperative day 2 or 3, when hemostasis is secured (eg, dalteparin, 100units/kg [7500 units] subcutaneously twice daily; continue for at least four to five days, until the INR is therapeutic.

● A 70 year old male with non-valvular atrial fibrillation, diabetes, and hypertension (CHA_2DS_2-VASc score = 3) receiving dabigatran who requires a colon resection for cancer; renal function is normal. This patient has a high thrombotic risk (table 1) and a high bleeding risk (table 3).

- Stop dabigatran three days before the procedure (off dabigatran for two days before the procedure and the day of the procedure).
- No bridging.
- Resume dabigatran on day +2 or +3 after surgery, when patient is able to take medication by mouth.
- Use prophylactic dose LMW heparin for VTE prophylaxis for the first two to three postoperative days.

● A 55 year old male with an unprovoked deep vein thrombosis (DVT) four months ago, receiving apixaban 5 mg twice daily, who requires a colonoscopy because of a personal history of premalignant colorectal polyps; renal function is normal. This patient has a high thrombotic risk (table 1) and a low bleeding risk (table 3).

- Stop apixaban two days before the procedure (off apixaban for one day before the procedure and the day of the procedure).
- No bridging.
- Resume apixaban the day after the procedure, after at least 24 hours have elapsed when hemostasis secured. If the patient requires polyp removal, delay resumption of apixaban for one to two more days.

● A 68 year old female with non-valvular atrial fibrillation, hypertension, and congestive heart failure (CHA_2DS_2-VASc score = 4), receiving rivaroxaban 15 mg daily in the morning, requires a dental cleaning and two dental extractions; CrCl is 35 mL/min. This patient has a high thrombotic risk (table 1) and a low bleeding risk (table 3).

- Do not take rivaroxaban on the day of the procedure.
- Use oral tranexamic acid mouthwash just before the procedure and two to three times that day after the procedure.
- Resume rivaroxaban the day after the procedure, after at least 24 hours have elapsed (assuming the dental extractions were uneventful).

ESTIMATING THROMBOEMBOLIC RISK — The major factors that increase thromboembolic risk are atrial fibrillation, prosthetic heart valves, and recent venous or arterial thromboembolism (eg, within the preceding three months).

Atrial fibrillation — Atrial fibrillation accounts for the highest percentage of patients for whom perioperative anticoagulation questions arise. Importantly, patients with atrial fibrillation are a heterogeneous group; risk can be further classified according to clinical variables such as age, hypertension, congestive heart failure, diabetes, prior stroke, and other vascular disease (table 1) [2,7]. The CHA_2DS_2-VASc score (table 4) (calculator 1), which incorporates these variables, is discussed in detail separately; of note, use of risk scores has not been prospectively validated in the perioperative setting. (See "Atrial fibrillation: Risk of embolization".)

The magnitude of this issue was illustrated in three large trials: RE-LY (**R**andomized **E**valuation of **L**ong-Term Anticoagulant Therap**y**), ROCKET AF (**R**ivaroxaban **O**nce daily, oral direct factor Xa inhibition **C**ompared with vitamin**K** antagonism for prevention of stroke and **E**mbolism **T**rial in **A**trial **F**ibrillation), and ARISTOTLE (**A**pixaban for**R**eduction **i**n **St**roke and **O**ther **T**hromboembo**l**ic **E**vents in Atrial Fibrillation) [8-10]. These trials of each randomly assigned 15,000 to 20,000 patients to warfarin versus another oral anticoagulant (dabigatran, rivaroxaban, orapixaban, respectively). Surgical or other invasive procedures were required in one-fourth of patients in RE-LY and one-third of patients in ROCKET AF and ARISTOTLE.

- RE-LY (dabigatran versus warfarin) – Of the 4591 patients who underwent elective procedures or surgery in the RE-LY trial, the perioperative thromboembolic risk was 1.2 percent, based on a composite endpoint of stroke, cardiovascular death, and pulmonary embolus [8]. There were no differences in thromboembolic risk with dabigatran versus warfarin, or with the high versus the low dabigatran dose. However, urgent surgery was associated with a higher risk of ischemic stroke or systemic embolism than elective surgery (warfarin: 1.8 versus 0.4 percent; dabigatran 150 mg twice daily: 1.4 versus 0.4 percent; dabigatran 110 mg twice daily: 2.8 versus 0.3 percent).
- ROCKET AF (rivaroxaban versus warfarin) – Of the 4692 anticoagulant interruptions in this trial, 40 percent were for surgery or invasive procedures [10]. The thromboembolic risk during anticoagulant interruption was similar for rivaroxaban and warfarin (0.3 and 0.4 percent).
- ARISTOTLE (apixaban versus warfarin) – During 9260 procedures performed on patients in the ARISTOTLE trial, the perioperative thromboembolic risk was 0.57 percent for warfarin and 0.35 percent for apixaban [9].

Bleeding risk in these trials and registries are presented below. (See 'Overview of whether to interrupt' below.)

Prosthetic heart valve — The risks of thromboembolism and perioperative management of patients with prosthetic heart valves are discussed separately. (See "Complications of prosthetic heart valves", section on 'Valve thrombosis and thromboembolism' and "Complications of prosthetic heart valves", section on 'Thromboembolism' and"Antithrombotic therapy for prosthetic heart valves: Management of bleeding and invasive procedures", section on 'Management of antithrombotic therapy for invasive procedures'.)

Recent thromboembolism — Thromboembolic risk is greater in the immediate period following a thromboembolic event and declines over time. Individuals with a recent thromboembolic event are likely to benefit from delaying surgery, if possible. If emergent surgery is required (eg, acute cholecystectomy), bridging anticoagulation may be used to reduce the interval without an anticoagulant. (See 'Bridging anticoagulation' below.)

Venous — The perioperative risk of venous thromboembolism (VTE) is greatest in individuals with an event (eg, deep vein thrombosis, pulmonary embolus) within the prior three months and those with a

history of VTE associated with a high-risk inherited thrombophilia (table 1). However, many patients with VTE do not require thrombophilia testing, and we do not perform this testing specifically to evaluate perioperative thrombotic risk in patients who otherwise do not warrant screening. Appropriate use of thrombophilia screening is discussed separately. (See"Approach to the diagnosis and therapy of lower extremity deep vein thrombosis", section on 'Screening for a hypercoagulable state'.)

Individuals with cancer have a moderate risk, and those with a provoked event more than one year ago have a low risk of VTE complications.

Thus, patients who require surgery within the first three months following an episode of VTE are likely to benefit from delaying elective surgery, even if the delay is only for a few weeks. This approach is supported by data showing that the recurrence risk for individuals with a recent VTE is highest within the initial three to four weeks and diminishes over the following two months [11-13]. Without anticoagulation, the early risk of recurrent VTE was approximately 50 percent; treatment with warfarin for one month reduced this risk to 8 to 10 percent, and after three months of warfarin therapy the risk declined to 4 to 5 percent [13-15].

Arterial — The risk of recurrent arterial embolism from any cardiac source is approximately 0.5 percent per day in the first month after an acute event [16]. The vast majority of cases are due to atrial fibrillation; other less common cardiac sources include paradoxical embolism, non-bacterial thrombotic endocarditis in a patient with malignancy, dilated or poorly contractile left ventricle, or left ventricular aneurysm (table 5) [17-19].

Thus, patients with a recent arterial embolism are likely to benefit from delaying elective surgery, if such a delay is possible.

ESTIMATING PROCEDURAL BLEEDING RISK — The risk of bleeding is dominated by the type of surgery or invasive procedure. Patient comorbidities (eg, older age, decreased renal function) and medications that affect hemostasis may also contribute [3,20,21].

As a general guideline, we divide procedures into high and low bleeding risk (two-day risk of major bleeding 2 to 4 percent or 0 to 2 percent, respectively); examples of high bleeding risk procedures include coronary artery bypass surgery, kidney biopsy, and any procedure lasting >45 minutes; low bleeding risk procedures include cholecystectomy, carpal tunnel repair, and abdominal hysterectomy (table 3) [2]. Importantly, these categories do not substitute for clinical judgement or consultation between the surgeon and other treating clinicians. Neuraxial, intracranial, and cardiac procedures are especially concerning because the location of potential bleeding increases the risk of serious complications. (See "Neuraxial (spinal, epidural) anesthesia in the patient receiving anticoagulant or antiplatelet medication".)

Major bleeding is generally defined as bleeding that is fatal, intracranial, requires surgery to correct, lowers the hemoglobin by ≥2 g/dL, or requires transfusion of ≥2 units packed red cells; however, there is heterogeneity in definitions used by different clinicians [22].

The risks of some specific types of procedures are also discussed in detail separately in the following topic reviews, along with management issues specific to those procedures:

- **Neuraxial anesthesia** – (See "Neuraxial (spinal, epidural) anesthesia in the patient receiving anticoagulant or antiplatelet medication".)
- **Gastrointestinal procedures** – (See "Management of anticoagulants in patients undergoing endoscopic procedures", section on 'Elective procedures in anticoagulated patients'.)

- **Percutaneous coronary intervention (eg, angioplasty, atherectomy, stenting)** – (See "Triple antithrombotic therapy in patients with cardiovascular disease", section on 'Dosing' and "Management of antithrombotic therapy in patients receiving long-term oral anticoagulation undergoing percutaneous coronary intervention", section on 'Elective patients'.)
- **Ophthalmologic procedures** – (See "Diabetic retinopathy: Prevention and treatment", section on 'Patients taking antiplatelet or anticoagulant medication' and "Age-related macular degeneration: Treatment and prevention", section on 'Safety in patients taking anticoagulants or antiplatelet drugs' and "Cataract in adults", section on 'Antithrombotic agents'.)

Dental and cutaneous procedures are generally associated with a low risk of bleeding. (See 'Settings in which continuing the anticoagulant may be preferable' below.)

Patient factors can also contribute to bleeding risk; these patient-related risks can be quantified using bleeding risk scores. An example is the HAS-BLED score (calculator 2), which was used in the **B**NK **O**nline B**r**i**d**ging **Re**gist**r**y (BORDER), an observational registry that assessed perioperative outcomes in outpatients undergoing invasive cardiac procedures (eg, cardiac catheterization, pacemaker implantation, cardiac surgery) [23]. Nearly all of the patients were receiving a vitamin K antagonist, which was interrupted for the procedure and replaced with a bridging agent, usually a low molecular weight (LMW) heparin. There were 35 clinically relevant bleeding episodes during 1000 procedures (3.5 percent). A HAS-BLED bleeding risk score ≥3 was the most predictive variable for bleeding (HR 11.8, 95% CI 5.6-24.9). The HAS-BLED score assigns one point each for **h**ypertension, **a**bnormal renal or liver function (two points for both), **s**troke, **b**leeding tendency, **l**abile INRs, **e**lderly age, and antiplatelet **d**rugs or alcohol (table 6).

DECIDING WHETHER TO INTERRUPT ANTICOAGULATION

Overview of whether to interrupt — Once the thromboembolic and bleeding risks have been estimated, a decision can be made about whether the anticoagulant should be interrupted or continued. Data comparing the relative benefits of continuing anticoagulation versus interrupting an anticoagulant are limited, and decisions that balance thromboembolic and bleeding risks must be made on a case-by-case basis. No scoring system can substitute for clinical judgment in this decision making.

- In general, the anticoagulant must be discontinued if the surgical bleeding risk is high. Those at very high or high thromboembolic risk should limit the period without anticoagulation to the shortest possible interval; in some cases this involves the use of a bridging agent. (See 'Settings requiring anticoagulant interruption' below and 'Whether to use bridging' below.)
- In contrast, individuals undergoing selected low bleeding risk surgery often can continue their anticoagulant; in certain cases, continuation of the anticoagulant may preferable. (See 'Settings in which continuing the anticoagulant may be preferable' below.)

Practices to reduce bleeding and thromboembolic risks should be employed regardless of whether the patient's anticoagulant is interrupted or continued. Examples include the following:

- Agents that interfere with platelet function should be avoided for routine analgesia (eg, non-steroidal antiinflammatory drugs [NSAIDs], aspirin) unless the benefit outweighs the increased risk of bleeding, and routine perioperative use of aspirin should be avoided due to an increased risk of bleeding and lack of benefit. In contrast, if these agents are administered for a separate indication (eg, recent stroke, acute coronary syndromes, implanted coronary stent) they can (and generally should) be continued [24]. Issues associated with perioperative aspirin use are discussed in detail

separately. (See "Perioperative medication management", section on 'Medications affecting hemostasis' and "Management of antithrombotic therapy in patients receiving long-term oral anticoagulation undergoing percutaneous coronary intervention".)

- For those not receiving an anticoagulant in the immediate postoperative period, thromboprophylaxis to reduce the risk of venous thromboembolism should be used when appropriate. (See "Prevention of venous thromboembolic disease in surgical patients".)

Settings requiring anticoagulant interruption — Individuals undergoing surgery with a high risk of bleeding will require interruption of their usual anticoagulant perioperatively, putting them at higher risk of thromboembolic complications related to their underlying condition.

- If the very high risk of thromboembolism is **transient** (eg, ischemic stroke within the previous month), attempts should be made to delay elective surgery, if possible, until the thromboembolic risk has returned to baseline.

  It may also be advisable to delay elective surgery in a patient with atrial fibrillation who has had inadequate anticoagulation in the preceding month. This is based on the observation that among patients with nonvalvular atrial fibrillation, over 85 percent of thrombi resolve after four weeks of warfarin therapy [25]. (See "Atrial fibrillation: Risk of embolization", section on 'Imaging predictors'.)

- Individuals with a temporarily very high or high thromboembolic risk in whom surgery cannot be delayed (eg, potentially curative cancer surgery) should limit the interval without an anticoagulant to minimize the risk of thromboembolism. This generally involves stopping the usual anticoagulant as close to surgery as possible, restarting it as soon as possible, and using a bridging agent before and/or after surgery while the usual anticoagulant is not therapeutic, especially for those on warfarin. (See 'Timing of anticoagulant interruption' below and 'Bridging anticoagulation' below.)

  In the setting of acute venous thromboembolism within the past three to four weeks and surgery that cannot be delayed, we also place a temporary vena caval filter that can be removed after surgery, especially for patients anticipated to have a longer interval of anticoagulant interruption (eg, extensive surgery with long recovery period).

- For individuals with a chronically elevated thromboembolic risk, we often use bridging anticoagulation to minimize the period when anticoagulation is not being used. (See 'Appropriate settings for bridging' below.)

- Individuals with a moderate thromboembolic risk generally can interrupt their anticoagulant for surgery without bridging. The bleeding risk from bridging may outweigh any potential benefit, especially in those with low-risk nonvalvular atrial fibrillation [26,27].

Settings in which continuing the anticoagulant may be preferable — For individuals undergoing selected surgery that confers a low risk of bleeding (eg, cataract extraction) it may be preferable for them to continue their anticoagulant, depending on patient factors and the judgement of the treating clinician. Continuing the anticoagulant likely reduces the risk of thromboembolism, and in some settings (eg, cardiac implantable electronic device) it actually reduces the risk of bleeding as well. For those receiving warfarin or another vitamin K antagonist, it is important to confirm that the INR is not above the therapeutic range at the time of the procedure.

- **Dental procedures** – Dental procedures are generally considered to confer a low risk of bleeding, and anticoagulation can be continued in most patients during these procedures. The evidence for the safety of continuing anticoagulation comes from patients receiving warfarin with an INR in the

therapeutic range [28-34]. In the ARISTOTLE trial, which included patients anticoagulated with warfarin versus apixaban for atrial fibrillation, perioperative bleeding rates were approximately 1 percent in patients undergoing dental and other low bleeding risk procedures. Bleeding can be further reduced with the use of topical hemostatic agents (eg, tranexamic acidor aminocaproic acid mouthwash, used three to four times daily for one to two days) [7,33,35-38].

An exception is multiple tooth extractions, which we consider high bleeding risk. (See 'Settings requiring anticoagulant interruption' above.)

- **Cutaneous procedures** – Cutaneous procedures (eg, skin biopsy, tumor excision) are also generally considered to confer a low bleeding risk of bleeding; the potential for local control measures further reduces concerns about bleeding risk.
- **Selected cardiac procedures** – For certain cardiac procedures, there is evidence that continuing anticoagulation is safe (and in some cases associated with better outcomes) compared with stopping and restarting the anticoagulant.
    - **Cardiac implantable devices** – We agree with a position document from the European Heart Rhythm Association (EHRA) that states the majority of patients undergoing implantation of a cardiac electronic device (eg, pacemaker, cardioverter-defibrillator) should continue their anticoagulant perioperatively [39]. This is based on data from the BRUISE CONTROL trial, which randomly assigned patients on warfarinundergoing implantation of a cardiac implantable electronic device to continuation of warfarin or heparin bridging, as well as other smaller trials [40]. This trial found a lower risk of bleeding in patients who continued warfarin. Potential explanations for the increased bleeding in the heparin bridging arm include initiation of postprocedure bridging too early (eg, within 24 hours after the procedure) or better identification of surgical bleeding sites that could be addressed during the procedure in patients receiving continued warfarin. An exception is a patient with a low risk of thromboembolic events, in whom warfarin may be discontinued, or a patient receiving a direct oral anticoagulant, for whom temporary discontinuation is likely to be appropriate [39]. Bridging anticoagulation is not recommended in such individuals.
    - **Endovascular procedures** – Endovascular procedures include a variety of venous and arterial interventions such as angioplasty, catheter ablation, and atherectomy. In a meta-analysis of randomized trials involving over 20,000 patients undergoing these procedures, uninterrupted warfarin therapy was associated with equivalent or lower rates of complications [41]. As an example, a benefit of warfarin continuation rather than discontinuation with bridging was reported in the COMPARE trial, which randomly assigned patients with atrial fibrillation undergoing catheter ablation to continued warfarin or discontinuation of warfarin with bridging [42]. In this trial, patients randomized to continue warfarin had a lower risk of stroke and less bleeding. (See "Catheter ablation to prevent recurrent atrial fibrillation: Anticoagulation", section on 'Patients taking long-term vitamin K antagonist'.)

      We also agree with the EHRA position document statement that all patients undergoing catheter ablation for atrial fibrillation should receive full anticoagulation with heparin in addition to continuing their oral anticoagulant [39].

If a decision is made to discontinue the anticoagulant (eg, patient with renal insufficiency), bridging is reserved for those with a high-very high thromboembolic risk, and not used for those with a moderate thromboembolic risk. (See'Appropriate settings for bridging' below.)

TIMING OF ANTICOAGULANT INTERRUPTION — If a decision has been made to interrupt the anticoagulant for surgery with high or moderate bleeding risk, the agent should be stopped in sufficient time to allow anticoagulation to resolve. For some agents, laboratory testing is a reliable indicator that the anticoagulant effect has resolved after discontinuation (eg, warfarin); for others, well-validated and easily accessible testing is not always available. If a moderate or high bleeding risk surgery is required urgently or emergently, reversal of the anticoagulant may also be required. (See 'Urgent anticoagulant reversal' below.)

Data to guide the timing of anticoagulant interruption are evolving, and much of our practice is based on expert opinion as we await results from ongoing trials. Risks of bleeding with neuraxial anesthesia and risks of thrombosis in patients with prosthetic heart valves are especially concerning; these issues are discussed in detail separately. (See "Neuraxial (spinal, epidural) anesthesia in the patient receiving anticoagulant or antiplatelet medication" and "Antithrombotic therapy for prosthetic heart valves: Indications".)

Typical durations of anticoagulant interruption are illustrated by the RE-LY trial, which randomized individuals with nonvalvular atrial fibrillation to warfarin or dabigatran for prevention of thromboembolism [8]. In this trial, nearly half of patients treated with dabigatran had surgery within 48 hours of stopping the drug, whereas only approximately 1 in 10 patients treated with warfarin had surgery within 48 hours of drug discontinuation. The incidence of thromboembolism was low (<1 percent), and bleeding rates were similar for those receiving warfarin or either dabigatran dose. (See'Atrial fibrillation' above.)

Warfarin — Warfarin blocks a vitamin K-dependent step in clotting factor production; it impairs coagulation by preventing synthesis of factors II (prothrombin), VII, IX, and X. Resolution of warfarin effect is determined by measurement of the prothrombin time, which is standardized across institutions using an international normalized ratio(PT/INR).

- **Discontinuation** – If it has been determined that warfarin discontinuation is appropriate, we typically discontinue warfarin five days before elective surgery (ie, last dose of warfarin is given on day minus 6) and, when possible, check the PT/INR on the day before surgery [7,13,43,44]. If the INR is >1.5, we administer **low** dose oral vitamin K (eg, 1 to 2 mg) to hasten normalization of the PT/INR and recheck the following day. We proceed with surgery when the INR is ≤1.4. An INR in the normal range is especially important in patients undergoing surgery associated with a high bleeding risk (eg, intracranial, spinal, urologic) or if neuraxial anesthesia is to be used. (See 'Estimating procedural bleeding risk' above and 'Neuraxial anesthesia' below.)

  This timing of warfarin discontinuation is based on the biological half-life of warfarin (36 to 42 hours) and the observed time for the PT/INR to return to normal after stopping warfarin (eg, two to three days for the INR to fall to below 2.0; four to six days to normalize) [43]. Normalization of the INR may take longer in patients receiving higher-intensity anticoagulation (INR 2.5 to 3.5), and in elderly individuals [45]. Half-lives of other vitamin K antagonists also differ (eg, 8 to 11 hours for acenocoumarol; three to five days for phenprocoumon; approximately three days for fluindione). (See "Warfarin and other VKAs: Dosing and adverse effects", section on 'Warfarin administration'.)

  For a procedure that requires more rapid normalization of the INR, additional interventions may be needed to actively reverse the anticoagulant. (See 'Urgent anticoagulant reversal' below.)

  This discontinuation schedule will produce a period of several days with subtherapeutic anticoagulation. As an example, it is estimated that if warfarin is withheld for five days before surgery and is restarted as soon as possible afterwards, patients would have a subtherapeutic INR

for approximately eight days (four days before and four days after surgery) [13]. Thus, for patients at very high or high thromboembolic risk, bridging may be appropriate.

●**Use of bridging preoperatively** – We generally reserve bridging for individuals considered at very high or high risk of thromboembolism (eg, recent stroke, mechanical heart valve, $CHADS_2$ score of 5 or 6) if they require interruption of warfarin. In these cases, the bridging agent (eg, therapeutic dose subcutaneous low molecular weight [LMW] heparin) is started three days before surgery. (See 'Bridging anticoagulation' below.)

A bridging agent may also be appropriate if there is a prolonged period during which the patient cannot take oral medications (eg, postoperative ileus).

●**Restarting warfarin and postoperative bridging** – We resume warfarin 12 to 24 hours after surgery, typically the evening of the day of surgery or the evening of the day after surgery, assuming there were no unexpected surgical issues that would increase bleeding risk and the patient is taking adequate oral fluids [7]. We use the same dose the patient was receiving preoperatively.

After warfarin is restarted in the perioperative setting, it takes 5 to 10 days to attain a full anticoagulant effect as measured by an INR above 2.0. Thus, we generally treat individuals at very high risk and some individuals with a high risk of thromboembolism with a heparin bridging agent during this period. (See 'Bridging anticoagulation'below.)

Dabigatran — Dabigatran is a direct thrombin inhibitor; it reversibly blocks the enzymatic function of thrombin in converting fibrinogen to fibrin (factor IIa).

●**Discontinuation** – Dabigatran can be discontinued two to three days before a surgical procedure in patients with normal or mildly impaired renal function (ie, creatinine clearance >50 mL/minute), and two to four days before the procedure in those with more severe renal insufficiency (eg, creatinine clearance between 30 and 50 mL/minute),with the longer intervals used for higher bleeding risk procedures and the shorter interval for surgeries with less bleeding risk.

As an example, in a patient with normal renal function undergoing a high bleeding risk procedure, the patient will skip four doses of dabigatran, and not receive any doses on surgical days minus 2, minus 1, or the day of surgery (table 2). Longer intervals for interruption are required for patients with impaired renal function and in other situations in which the risk for bleeding is high. (See 'Neuraxial anesthesia' below.)

The last preoperative day on which dabigatran is administered can be more closely estimated based on the elimination half-life of dabigatran, which varies according to renal function (eg, 12 to 14 hours in patients with normal renal function) [2,46-49]. A protocol incorporating bleeding risk and creatinine clearance was tested in a prospective cohort of 541 dabigatran-treated patients undergoing surgery and was found to be effective in minimizing bleeding and thrombotic complications [49].

Unlike the PT/INR for warfarin, routine coagulation tests have not been validated for ensuring that dabigatraneffect has resolved. A normal or near-normal aPTT may be used in selected patients to evaluate whether dabigatran has been adequately cleared from the circulation prior to surgery (eg, patients at high risk of surgical bleeding) (table 7). Importantly, the reliability of aPTT testing may depend on the specific assay used; if available, a diluted plasma thrombin time may be preferable [47,50,51]. (See "Direct oral anticoagulants: Dosing and adverse effects", section on 'Dabigatran' and "Clinical use of coagulation tests".)

●**Use of bridging** – In general, the rapid offset and onset of dabigatran activity obviates the need for bridging anticoagulation. We reserve bridging anticoagulation for selected individuals who are at very high risk for postoperative thromboembolism **and** require extended interruption of dabigatran.

Examples include postoperative bridging in patients who are unable to take oral medications postoperatively due to intestinal ileus from gastrointestinal surgery. (See 'Bridging anticoagulation' below.)

●**Restarting** dabigatran – Dabigatran should be resumed postoperatively when hemostasis has been achieved, at the same dose the patient was receiving preoperatively. Since dabigatran has a rapid onset of action, with peak effects occurring two to three hours after intake, caution should be used in patients who have had major surgery or other procedures associated with a high bleeding risk.

We often delay resumption of dabigatran for two to three days after high bleeding risk procedures and, if needed, administer a lower dabigatran dose for the initial two to three postoperative days (eg, 110 mg once daily) or use prophylactic dose LMW heparin for this period. We generally restart dabigatran one day after low bleeding risk surgery (if it was interrupted) and two to three days after high bleeding risk surgery.

Rivaroxaban — Rivaroxaban is a direct factor Xa inhibitor; it reversibly blocks the enzymatic function of factor Xa in converting prothrombin to thrombin.

●**Discontinuation** – Rivaroxaban can be discontinued approximately two to three days before a procedure, with the longer interval for higher bleeding risk procedures and the shorter interval for lower bleeding risk procedures (table 2). Thus, for high bleeding risk procedures, the patient will skip two doses of rivaroxaban, and not receive any doses on surgical days minus 2, minus 1, or the day of surgery. These intervals are based on the elimination half-life of 5 to 9 hours and apply to individuals with normal renal function or mild renal insufficiency (eg, creatinine clearance >50 mL/minute), who are likely to be receiving the 20 mg once daily dose; and to those with moderate renal insufficiency (eg, creatinine clearance between 30 and 50 mL/minute), who are likely to be receiving the 15 mg once daily dose.

Longer intervals for interruption may be required for situations in which the bleeding risk is very high. (See'Neuraxial anesthesia' below.)

Rivaroxaban interacts with dual inhibitors of CYP-3A4 and P-glycoprotein (eg, systemic ketoconazole, ritonavir); dose adjustment or substitution of heparin may be appropriate if these dual CYP-3A4 and P-glycoprotein inhibitors are used perioperatively. Interactions with drugs that inhibit only one of these enzymes do not seem to alter rivaroxaban anticoagulant effect.

Unlike the PT/INR for warfarin, routine coagulation tests have not been validated for ensuring that therivaroxaban anticoagulant effect has resolved. A normal or near-normal anti-factor Xa activity level may be used in selected patients to evaluate whether rivaroxaban has been adequately cleared from the circulation prior to surgery (eg, patients at high risk of surgical bleeding) (table 7) [2]. Of note, the reliability of anti-factor Xa activity testing may depend on the specific assay used, and clinicians are advised to speak with their clinical laboratory to determine whether this assay is available at their institution and whether it has been validated for direct factor Xa inhibitors.

●**Use of bridging** – In general, the rapid offset and onset of rivaroxaban obviates the need for bridging anticoagulation. In rare cases bridging may be required, such as the use of postoperative bridging in individuals who have a very high thromboembolic risk and are unable to take oral medications postoperatively due to intestinal ileus from gastrointestinal surgery. (See 'Bridging anticoagulation' below.)

●**Restarting** rivaroxaban – Rivaroxaban can be resumed postoperatively when hemostasis has been achieved, at the same dose the patient was receiving preoperatively. Since rivaroxaban has a

rapid onset of action, caution should be used in patients who have had major surgery or other procedures associated with a high bleeding risk.

We often delay rivaroxaban for two to three days after high bleeding risk procedures and, if needed, use prophylactic dose LMW heparin for this period. We generally restart rivaroxaban one day after low bleeding risk surgery (if it was interrupted) and two to three days after high bleeding risk surgery.

Apixaban — Apixaban is a direct factor Xa inhibitor; it reversibly blocks the enzymatic function of factor Xa in converting prothrombin to thrombin.

●**Discontinuation** – Apixaban can be discontinued approximately two to three days before a procedure, with the longer interval for higher bleeding risk procedures and the shorter interval for lower bleeding risk procedures (table 2). Thus, for high bleeding risk procedures, the patient will skip four doses of apixaban, and not receive any doses on surgical days minus 2, minus 1, or the day of surgery. These intervals are based on the apixaban elimination half-life of 8 to 15 hours. These intervals apply to individuals with normal renal function or mild renal insufficiency (eg, creatinine clearance >50 mL/minute), who are likely to be receiving the 5 mg twice daily dose; and to those with moderate renal insufficiency (eg, creatinine clearance between 30 and 50 mL/minute), who are likely to be receiving the 2.5 mg twice daily dose.

Longer intervals for interruption may be required for situations in which the bleeding risk is very high. (See'Neuraxial anesthesia' below.)

Unlike the PT/INR for warfarin, routine coagulation tests have not been validated for ensuring that apixaban effect has resolved. A normal or near-normal anti-factor Xa activity level may be used in selected patients to evaluate whether apixaban has been adequately cleared from the circulation prior to surgery (eg, patients at high risk of surgical bleeding) (table 7). Of note, the reliability of anti-factor Xa activity testing may depend on the specific assay used, and clinicians are advised to speak with their clinical laboratory to determine whether this assay is available at their institution and whether it has been validated for direct factor Xa inhibitors.

●**Use of bridging** – In general, the rapid offset and onset of apixaban obviates the need for bridging anticoagulation. In rare cases, bridging may be required, such as the use of postoperative bridging in individuals who have a very high thromboembolic risk and are unable to take oral medications postoperatively due to intestinal ileus from gastrointestinal surgery. (See 'Bridging anticoagulation' below.)

●**Restarting** apixaban – Apixaban can be resumed postoperatively when hemostasis has been achieved, at the same dose the patient was receiving preoperatively. Since apixaban has a rapid onset of action, caution should be used in patients who have had major surgery or other procedures associated with a high bleeding risk.

We often delay apixaban for two to three days after high bleeding risk procedures, and if needed use prophylactic dose LMW heparin for this period. We generally restart apixaban one day after low bleeding risk surgery (if it was interrupted).

Edoxaban — Edoxaban is a direct factor Xa inhibitor; it reversibly blocks the enzymatic function of factor Xa in converting prothrombin to thrombin.

●**Discontinuation** – Edoxaban can be discontinued approximately two to three days before a procedure, with the longer interval for higher bleeding risk procedures and the shorter interval for lower bleeding risk procedures (table 2). Thus, for high bleeding risk procedures, the patient will skip

two doses of edoxaban, and not receive any doses on surgical days minus 2, minus 1, or the day of surgery. These intervals are based on the edoxaban elimination half-life of 6 to 11 hours. These intervals apply to individuals with normal renal function or mild renal insufficiency (eg, creatinine clearance >50 mL/minute) and those with moderate renal insufficiency (eg, creatinine clearance between 30 and 50 mL/minute), who are likely to be receiving the 60 mg once daily or the 30 mg once daily doses, respectively.

Longer intervals for interruption may be considered for those undergoing major surgery, neuraxial anesthesia or manipulation, or other situations in which complete hemostatic function may be required. (See 'Neuraxial anesthesia' below.)

Unlike the PT/INR for warfarin, routine coagulation tests have not been validated for ensuring that edoxabaneffect has resolved. A normal or near-normal anti-factor Xa activity level may be used in selected patients to evaluate whether edoxaban has been adequately cleared from the circulation prior to surgery (eg, patients at high risk of surgical bleeding) (table 7). Of note, the reliability of anti-factor Xa activity testing may depend on the specific assay used, and clinicians are advised to speak with their clinical laboratory to determine whether this assay is available at their institution and whether it has been validated for direct factor Xa inhibitors.

●**Use of bridging** – In general, the rapid offset and onset of edoxaban obviates the need for bridging anticoagulation. In rare cases, bridging may be required, such as the use of postoperative bridging in individuals who have a very high thromboembolic risk and are unable to take oral medications postoperatively due to intestinal ileus from gastrointestinal surgery. (See 'Bridging anticoagulation' below.)

●**Restarting** edoxaban – Edoxaban can be resumed postoperatively when hemostasis has been achieved, at the same dose the patient was receiving preoperatively. Since edoxaban has a rapid onset of action, caution should be used in patients who have had major surgery or other procedures associated with a high bleeding risk.

We often delay edoxaban for two to three days after high bleeding risk procedures, and if needed use prophylactic dose LMW heparin for this period. We generally restart edoxaban one day after low bleeding risk surgery (if it was interrupted).

BRIDGING ANTICOAGULATION — Bridging anticoagulation involves the administration of a short-acting anticoagulant, typically a low molecular weight (LMW) heparin, during the interruption of a longer-acting agent, typicallywarfarin. There are no data on using the newer direct oral anticoagulants (eg, direct thrombin inhibitors, direct factor Xa inhibitors) as bridging agents; further, these agents lack a specific reversal strategy should bleeding occur. Thus, we use LMW heparin or unfractionated heparin when bridging is required. (See 'Heparin product and dose' below.)

Appropriate settings for bridging

Whether to use bridging — The intent of bridging is to minimize the time the patient is not anticoagulated, thereby minimizing the risk for perioperative thromboembolism. However, this needs to be balanced with the importance of mitigating the risk of postoperative bleeding. A slight delay in resumption of postoperative anticoagulation is preferable to premature initiation of postoperative bridging that results in bleeding, which ultimately will lengthen the period without an anticoagulant and thus increase thromboembolic risk.

The clinician needs to decide whether bridging is appropriate and, if so, whether the benefit applies preoperatively, postoperatively, or both.

Bridging anticoagulation may be appropriate in patients who will have a very high thromboembolic risk with prolonged interruption of their anticoagulant (generally a vitamin K antagonist [VKA]). Individual patient comorbidities that increase bleeding risk may also need to be considered because an increased postoperative bleeding risk may be a reason to avoid bridging. We suggest the use of bridging in individuals taking warfarin for one of the following conditions [1]:

- Embolic stroke or systemic embolic event within the previous three months
- Mechanical mitral valve
- Mechanical aortic valve and additional stroke risk factors
- Atrial fibrillation and very high risk of stroke (eg, $CHADS_2$ score of 5 or 6, stroke or systemic embolism within the previous 12 weeks)
- Venous thromboembolism (VTE) within the previous three months (preoperative and postoperative bridging) (see 'When to bridge: Preoperative, postoperative, or both' below)
- Recent coronary stenting (eg, within the previous 12 weeks) (see "Management of antithrombotic therapy in patients receiving long-term oral anticoagulation undergoing percutaneous coronary intervention")
- Previous thromboembolism during interruption of chronic anticoagulation

For most other patients on warfarin with atrial fibrillation (ie, for most individuals not included in the list of examples above), we suggest not using bridging anticoagulation. We feel more strongly about avoiding bridging the lower the patient's baseline thromboembolic risk (eg, lower $CHADS_2$ or CHA_2DS_2-VASc score (table 8)) and the higher the risk of bleeding. This practice is supported by the BRIDGE trial (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery), which randomly assigned 1884 patients with atrial fibrillation who required interruption of warfarin for an invasive procedure to receive bridging anticoagulation with the LMW heparin dalteparin versus placebo [52]. The incidence of arterial thromboembolic events 30 days after the procedure was similar in those who received dalteparin or placebo (0.3 versus 0.4 percent). The incidence of major bleeding (a secondary outcome) was higher in those who received dalteparin (3.2 versus 1.3 percent), although none of the bleeds were fatal. Patients were excluded from the trial if they had a mechanical heart valve, or a recent (within previous 12 weeks) stroke, embolism, or transient ischemic attack.

Results of a randomized trial comparing postoperative bridging versus no bridging in patients with a mechanical heart valve (PERIOP-2), where all patients receive preoperative bridging, are eagerly awaited [6,53].

Additional evidence to support our practice comes from a systematic review and meta-analysis of 34 studies in patients undergoing elective surgery or procedures [54]. All of the studies were observational except for one randomized trial in patients undergoing dental extraction. Bridging was used in 7118 patients; most received LMW heparin, at several dose levels. The large range of heparin doses and inclusion of procedures with varied bleeding risks led to a high degree of heterogeneity. There was no significant difference in the rate of thromboembolism in patients who received bridging compared with patients who did not (odds ratio [OR]: 0.80; 95% CI 0.42-1.54). Bridging was associated with a threefold increase in major bleeding compared with no bridging (OR: 3.60; 95% CI 1.52-8.50); full-dose heparin was associated with an increase in overall bleeding compared with lower heparin doses (OR: 2.28; 95% CI 1.27-4.08) (see 'Heparin product and dose' below). Bridging versus no bridging did not affect major outcomes in patients who required a major procedure during participation in large anticoagulation trials for

atrial fibrillation, including the RE-LY (warfarin versus dabigatran), ROCKET-AF (warfarin versus rivaroxaban), and ARISTOTLE (warfarin versus apixaban) trials [8-10]. In the RE-LY trial patients receiving warfarin had more thromboembolic events associated with bridging than with non-use of bridging (1.8 versus 0.3 percent); patients who received bridging also had a higher risk of major bleeding (warfarin: 6.8 percent with bridging, 1.6 percent without; dabigatran: 6.5 percent with bridging, 1.8 percent without) [55].

Additional "real world" data comes from the ORBIT-AF and Dresden registries. ORBIT-AF (**O**utcomes **R**egistry for**B**etter **I**nformed **T**reatment of **A**trial **F**ibrillation) is a community-based registry of outpatients with atrial fibrillation receiving any oral anticoagulant; in this study, 2200 of 7372 individuals (30 percent) had interruption of anticoagulation for a procedure [56]. Bridging was used in 24 percent of these interruptions, especially in patients with a history of stroke or a mechanical heart valve and/or receiving warfarin; bleeding events were more common in individuals who received bridging compared with those who did not receive bridging (5.0 versus 1.3 percent). A composite endpoint that included major bleeding, myocardial infarction, stroke, systemic embolism, hospitalization, or death within 30 days was also higher in those who received bridging (13 versus 6.3 percent). In the Dresden NOAC registry, over 800 patients who were receiving dabigatran, rivaroxaban, or apixaban for any indication and underwent an invasive procedure had similar rates of major cardiovascular events if they received bridging, no bridging, or no anticoagulant discontinuation [57]. Bridging was not an independent risk factor for major bleeding; however, individuals undergoing major procedures were more likely to receive bridging and to have major bleeding.

A potential role for bridging in reducing the risk of "rebound hypercoagulability" has also been proposed; however, this premise is not supported by data from the BRIDGE trial discussed above [52].

Of note, management of perioperative anticoagulation in patients with mechanical heart valves is discussed in detail separately. (See "Antithrombotic therapy for prosthetic heart valves: Management of bleeding and invasive procedures", section on 'Management of antithrombotic therapy for invasive procedures'.)

Bridging is generally not used for the shorter-acting direct oral thrombin inhibitors or factor Xa inhibitors. However, bridging may be appropriate for individuals on these agents who have a very high thromboembolic risk and a more prolonged interruption of their anticoagulant (eg, due to postoperative intestinal ileus that prevents oral intake). (See'Dabigatran' above and 'Rivaroxaban' above and 'Apixaban' above and 'Edoxaban' above.)

When to bridge: Preoperative, postoperative, or both — Once a decision to use bridging has been made, the next decision is whether to use bridging before the procedure, after the procedure, or both (table 9).

- **Atrial fibrillation** – As noted above, we suggest not using bridging for most patients with atrial fibrillation. (See'Whether to use bridging' above.)

  However, for those for individuals for whom bridging is used due to a very high risk of thromboembolism, we use bridging both preoperatively and postoperatively [13]. Warfarin is usually resumed within 24 hours after surgery, which may be the evening of the day after surgery or postoperative day two, as long as adequate hemostasis has been achieved. (See 'Warfarin' above.)
- **Venous thromboembolism**

•**First three months** – For individuals within the first three months after an acute episode of VTE, we use bridging both preoperatively and postoperatively, typically with therapeutic-dose LMW heparin (eg, enoxaparin 1 mg/kg twice daily) [13]. This practice is based on the high incidence of recurrence without anticoagulation. While postoperative intravenous heparin doubles the rate of bleeding, there is a net reduction in serious morbidity in such patients because the risk of postoperative recurrent VTE is high (see 'Preoperative timing of bridging' below and 'Postoperative timing of bridging' below) In selected patients in whom surgery cannot be delayed beyond the first month after the diagnosis of an acute VTE, it may be appropriate to use a temporary inferior vena cava (IVC) filter, especially if bridging anticoagulation cannot be used postoperatively due to high bleeding risk. (See "Overview of the treatment of lower extremity deep vein thrombosis (DVT)", section on 'Patients with contraindications to anticoagulation' and "Overview of the treatment, prognosis, and follow-up of acute pulmonary embolism in adults", section on 'Inferior vena cava filters'.)

•**Greater than three months** – For individuals greater than three months after an acute episode of VTE, we generally use postoperative bridging, typically with a low dose LMW heparin regimen (eg, enoxaparin 40 mg daily), but not preoperative bridging [58]. For patients who are undergoing a minor procedure or day surgery, bridging is probably not justified. This practice is based on the significantly reduced risk of VTE recurrence after the first month [59,60]. (See 'Postoperative timing of bridging' below.)

Heparin product and dose — Two types of heparin products are available: LMW heparins and unfractionated heparin. LMW heparins have similar efficacy compared with unfractionated heparin, are more convenient to use, and generally do not require monitoring. Intravenous unfractionated heparin is less costly and can be reversed more rapidly than subcutaneous LMW heparin; it may be a reasonable alternative in some individuals.

●We prefer LMW heparin for bridging anticoagulation in individuals with a very high risk of arterial thromboembolism (eg, rheumatic heart disease, atrial fibrillation with recent embolic stroke, high-risk mechanical heart valve) and those with a moderate risk of thromboembolism (eg, active cancer) [26,27,61].

Perioperative anticoagulation management in individuals with prosthetic heart valves is discussed in detail separately. (See "Antithrombotic therapy for prosthetic heart valves: Management of bleeding and invasive procedures", section on 'Management of antithrombotic therapy for invasive procedures'.)

●For individuals with renal insufficiency and/or those requiring hemodialysis, intravenous or subcutaneous unfractionated heparin can be used more easily because dosing is unaffected by renal clearance [62]. (See "Heparin and LMW heparin: Dosing and adverse effects", section on 'Dosing'.)

We do **not** use any of the newer direct oral anticoagulants (eg, dabigatran, rivaroxaban, apixaban, edoxaban) for bridging, as there are no data on the safety or efficacy of these agents for perioperative bridging.

Heparins can be dosed at prophylactic doses, therapeutic doses, or doses intermediate between the two. Of note, the term "therapeutic dose" refers to doses typically used for treatment of thromboembolic disease, despite the fact that in this case it is being used prophylactically (ie, to prevent thromboembolism). There are no clinical trial data or practice standards to guide dosing, and clinical judgment is required to determine the appropriate dose for each patient [54,63,64].

- **Therapeutic dosing** – Therapeutic dosing (also called "full dose") is appropriate for bridging anticoagulation for individuals with a potential arterial thromboembolic source (eg, atrial fibrillation, mechanical heart valve) or VTE within the preceding month. Typical regimens include enoxaparin, 1 mg/kg subcutaneously twice daily ordalteparin, 100 units /kg subcutaneously twice daily.
- **Intermediate dosing** – Intermediate dose anticoagulation may be appropriate for individuals with atrial fibrillation or VTE within the preceding month when bridging is needed but concerns about bleeding are greater. Typical regimens include enoxaparin, 40 mg twice daily, or dalteparin, 5000 units subcutaneously twice daily
- **Prophylactic dosing** – Prophylactic dose anticoagulation (also called "low dose") generally is not used for bridging in patients with atrial fibrillation, because there is no evidence that prophylactic dose heparin prevents stroke in this setting. This dose level may be reasonable in patients who have had a VTE event between within the preceding 3 to 12 months. Typical prophylactic regimens include enoxaparin, 40 mg once daily, or dalteparin5000 units subcutaneously once daily.
  The use of prophylactic dose heparin for postoperative VTE prevention in patients not receiving ongoing anticoagulation is discussed separately. (See "Prevention of venous thromboembolic disease in surgical patients".)

Additional details regarding heparin products, including dose adjustments for obesity and renal impairment are provided separately. (See "Heparin and LMW heparin: Dosing and adverse effects".)

Timing of bridging

Preoperative timing of bridging — We generally initiate heparin bridging three days before a planned procedure (ie, two days after stopping warfarin), when the PT/INR has started to drop below the therapeutic range.

- **LMW heparin** – We discontinue LMW heparin 24 hours before the planned surgery or procedure, based on a biologic half-life of most subcutaneous LMW heparins of approximately three to five hours [7,61,65]. If a twice-daily LMW heparin regimen is given, the evening dose the night before surgery is omitted, whereas if a once-daily regimen is given (eg, dalteparin 200 international units/kg), one-half of the total daily dose is given on the morning of the day before surgery. This ensures that no significant residual anticoagulant will be present at the time of surgery, based on studies that have shown a residual anticoagulant effect at 24 hours after stopping therapeutic-dose LMW heparin, and it is consistent with the 2012 ACCP Guidelines [7,11,66,67].
- Unfractionated heparin – For therapeutic dose unfractionated heparin, we continue the intravenous infusion until four to five hours before the procedure, based on the biologic half-life of intravenous unfractionated heparin of approximately 45 minutes [7,65,66]. If subcutaneous unfractionated heparin is used, typically with a dose of approximately 250 international units/kg twice daily, the last dose can be given the evening before the procedure.

Postoperative timing of bridging — Postoperative resumption of unfractionated heparin and LMW heparin is similar, based on the onset of anticoagulation at approximately one hour after administration for both forms of heparin, and peak anticoagulant activity at approximately three to five hours.

- The resumption of bridging, especially when given as a therapeutic-dose regimen, should be delayed until there is adequate hemostasis based on a clinical assessment of the wound site, drainage fluid amount, and expected postoperative bleeding; coupled, where appropriate, with hemoglobin levels [68]. This assessment will vary depending on the surgery type and individual

patient considerations, and it may be difficult for surgery where ongoing bleeding is not readily apparent (eg, cardiac, intracranial).

- For those undergoing major surgery or those with a high bleeding risk procedure, therapeutic-dose unfractionated heparin or LMW heparin should be delayed for 48 to 72 hours after hemostasis has been secured [7].
- For most minor procedures associated with a low bleeding risk in which bridging is used (eg, laparoscopic hernia repair), therapeutic-dose unfractionated heparin or LMW heparin can usually be resumed 24 hours after the procedure.

Resumption of bridging anticoagulation too early, especially the use of therapeutic dose heparin within 24 hours after surgery, is associated with a two- to fourfold increased risk for major bleeding compared with no bridging or prophylactic dose heparin. The increased bleeding risk was demonstrated in the **Pros**pective **p**eri-operative **e**noxaparin **c**ohort **t**rial (PROSPECT), which evaluated bleeding risk in a cohort of 260 patients undergoing major surgery whose treating physicians used bridging anticoagulation [69]. In this trial, nine patients had major postoperative bleeding (3.5 percent), most on postoperative day 0, and 19 (7.3 percent) had minor bleeding.

Postoperatively, warfarin is generally resumed on the same postoperative day as the heparin. Heparin can be discontinued when the INR reaches the therapeutic range for individuals at moderate thromboembolism risk.

Individuals with heparin-induced thrombocytopenia — Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening condition in which heparin-induced antibodies to platelets can cause thrombocytopenia and/or venous or arterial thrombosis. (See "Clinical presentation and diagnosis of heparin-induced thrombocytopenia".)

Patients with HIT should not receive any heparin (eg, they should not receive heparin flushes, unfractionated heparin, or LMW heparin). Non-heparin anticoagulants that can be used in patients with HIT are discussed separately. (See"Management of heparin-induced thrombocytopenia", section on 'Initiation of a non-heparin anticoagulant'.)

URGENT ANTICOAGULANT REVERSAL — Reversal of the patient's usual anticoagulant may be required for more urgent or emergent surgery or procedures, or to treat perioperative bleeding. Agents with a potential prothrombotic effect (eg, prothrombin complex concentrates [PCCs], plasma products, immediate reversal agents) should be reserved for the treatment of severe bleeding or anticipated severe bleeding (eg, intracranial hemorrhage, emergent major surgery with elevated prothrombin time/international normalized ratio [PT/INR]). Agent-specific strategies include the following:

- Warfarin – For individuals who require reversal of warfarin or other vitamin K antagonists, the appropriate reversal strategy is determined by the degree of anticoagulation (eg, PT/INR, clinical bleeding), urgency of the procedure, and degree of bleeding risk (table 10).
  - If semi-urgent reversal of warfarin is required (eg, within one to two days), warfarin should be withheld andvitamin K administered (eg, 2.5 to 5.0 mg of oral or intravenous vitamin K). (See "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Urgent surgery/procedure'.)
  - If immediate reversal is required (eg, for emergent surgery or active bleeding), this can be achieved via the use of prothrombin complex concentrates (PCCs) or plasma products (eg, Fresh Frozen Plasma [FFP]; Plasma Frozen Within 24 Hours After Phlebotomy [PF24]) along

with vitamin K (table 11) [70,71]. Four-factor PCCs contain adequate amounts of all vitamin K-dependent clotting factors, whereas three-factor PCCs may require supplementation with FFP for adequate factor VII (table 12). Of note, there is a thrombotic risk associated with these products, and they should be used only if there is life-threatening bleeding and prolongation of the INR by a vitamin K antagonist [71]. (See "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Serious/life-threatening bleeding'.)

- Dabigatran – Dabigatran is an oral direct thrombin inhibitor; a reversal product was approved for use in the setting of emergency surgery or urgent procedures (or life-threatening bleeding) in 2015. Potential strategies for treating bleeding in individuals receiving dabigatran are presented separately. (See "Management of bleeding in patients receiving direct oral anticoagulants".)
- Rivaroxaban**,** apixaban**, and** edoxaban – Rivaroxaban, apixaban, and edoxaban are oral direct factor Xa inhibitors; there are no specific reversal agents for this class of anticoagulants. Potential strategies for treating bleeding in individuals receiving these agents are presented separately. (See "Management of bleeding in patients receiving direct oral anticoagulants".)

Additional discussions of postoperative bleeding are presented separately. (See "Postoperative complications among patients undergoing cardiac surgery", section on 'Hematologic dysfunction'.)

NEURAXIAL ANESTHESIA — Neuraxial (ie, spinal or epidural) anesthesia should **not** be used in anticoagulated individuals, due to the risk of potentially catastrophic bleeding into the epidural space. The increased risk of bleeding applies both at the time of catheter placement and the time of removal.

If neuraxial anesthesia is considered for surgical anesthesia or postoperative pain control, the timing of anesthesia and anticoagulant administration should be coordinated to optimize the safe use of both. Early consultation with the anesthesiologist is advised. This subject is discussed in detail separately. (See "Neuraxial (spinal, epidural) anesthesia in the patient receiving anticoagulant or antiplatelet medication".)

The timing of anticoagulant use in patients receiving neuraxial anesthesia is illustrated by evidence-based guidelines from the American Society of Regional Anesthesia (ASRA), which suggest the following [72,73]:

- **Prophylactic dose** LMW heparin (eg, enoxaparin 40 mg once daily):
  - Before surgery, wait at least 10 to 12 hours after the last dose of LMW heparin is administered before aspinal/epidural catheter is placed.
  - After surgery, when there is adequate surgical site hemostasis, wait at least six to eight hours after catheter removal before resuming treatment with LMW heparins.
- **Therapeutic** dose LMW heparin (eg, enoxaparin, 1 mg/kg twice daily):
  - Before surgery, wait at least 24 hours after the last dose of LMW heparin is administered before aspinal/epidural catheter is placed.
  - After surgery, when there is adequate surgical site hemostasis, for twice daily dosing, wait at least 24 hours after catheter removal before resuming therapeutic-dose LMW heparin. For once daily dosing, wait at least six to eight hours after catheter removal before the first dose; the second postoperative dose should occur no sooner than 24 hours after the first dose.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have

about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Anti-clotting medicines: Dabigatran, rivaroxaban, apixaban, and edoxaban (The Basics)" and "Patient information: Anti-clotting medicines: Warfarin (Coumadin) (The Basics)")
- Beyond the Basics topics (see "Patient information: Warfarin (Coumadin) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Interruption of anticoagulation temporarily increases thromboembolic risk, and continuing anticoagulation increases the risk of bleeding associated with invasive procedures; both of these outcomes adversely affect mortality. We take into account these risks, along with specific features of the anticoagulant the patient is taking. Case examples are provided above. (See 'Overview of our approach' above.)
- **Thromboembolic risk** – Those at very high or high thromboembolic risk should limit the period without anticoagulation to the shortest possible interval. The major factors that increase thromboembolic risk are atrial fibrillation, prosthetic heart valves, and recent venous or arterial thromboembolism (eg, within the preceding three months) (table 1). If thromboembolic risk is transiently increased (eg, recent stroke, recent pulmonary embolism), we prefer to delay surgery until the risk returns to baseline, if possible. (See 'Estimating thromboembolic risk'above.)
  - **Atrial fibrillation** – In the RE-LY trial, the perioperative thromboembolic risk was 1.2 percent based on a composite endpoint of stroke, cardiovascular death, and pulmonary embolus. We estimate thromboembolic risk for patients with atrial fibrillation based on clinical variables including age and comorbidities. (See 'Atrial fibrillation' above and "Atrial fibrillation: Anticoagulant therapy to prevent embolization".)
  - **Prosthetic heart valve** – The risks of thromboembolism and perioperative management of patients with bioprosthetic and mechanical heart valves are discussed separately. (See "Complications of prosthetic heart valves", section on 'Valve thrombosis and thromboembolism' and "Complications of prosthetic heart valves", section on 'Thromboembolism' and "Antithrombotic therapy for prosthetic heart valves: Management of bleeding and invasive procedures", section on 'Management of antithrombotic therapy for invasive procedures'.)
  - **Recent thromboembolism** – The perioperative risk of venous thromboembolism (VTE) is greatest in individuals with an event within the prior three months, and those with a history of VTE associated with a high-risk inherited thrombophilia. Patients who require surgery within the first three months following an episode of VTE are likely to benefit from delaying elective surgery, even if the delay is only for a few weeks. The risk of recurrent arterial embolism from any cardiac source is approximately 0.5 percent per day in the first month after an acute event. (See 'Recent thromboembolism' above.)

●**Bleeding risk** – A higher bleeding risk confers a greater need for perioperative hemostasis, and hence a longer period of anticoagulant interruption. Bleeding risk is dominated by the type and urgency of surgery (table 3); some patient comorbidities (eg, older age, decreased renal function) and medications that affect hemostasis also contribute. (See 'Estimating procedural bleeding risk' above and 'Deciding whether to interrupt anticoagulation'above.)

- **High risk** – High bleeding risk procedures include coronary artery bypass surgery, kidney biopsy, and any procedure lasting >45 minutes. In general, the anticoagulant must be discontinued if the surgical bleeding risk is high. (See 'Settings requiring anticoagulant interruption' above.)
- **Low risk** – Low bleeding risk procedures include dental extractions, minor skin surgery, cholecystectomy, carpal tunnel repair, and abdominal hysterectomy. Individuals undergoing selected low bleeding risk surgery often can continue their anticoagulant. (See 'Settings in which continuing the anticoagulant may be preferable' above.)
- **Cardiac implantable device or catheter ablation for atrial fibrillation** – Continuing warfarin was associated with a **lower** risk of bleeding in patients on the BRUISE CONTROL trial who were undergoing implantation of a cardiac implantable electronic device (eg, pacemaker, implantable cardioverter-defibrillator) and patients on the COMPARE trial who were undergoing catheter ablation for atrial fibrillation. (See 'Overview of whether to interrupt' above and "Catheter ablation to prevent recurrent atrial fibrillation: Anticoagulation", section on 'Patients taking long-term vitamin K antagonist'.)

●**Timing of interruption** – If a decision has been made to interrupt the anticoagulant, the timing of discontinuation and reinitiation depends on the specific agent used (table 2). (See 'Timing of anticoagulant interruption' above and 'Warfarin' above and 'Dabigatran' above and 'Rivaroxaban' above and 'Apixaban' above and 'Edoxaban'above.)

●**Bridging** – Bridging anticoagulation involves the administration of a short-acting anticoagulant, typically a low molecular weight (LMW) heparin, during the interruption of a longer-acting agent, typically warfarin. The intent is to minimize the risk of perioperative thromboembolism.

For selected patients on warfarin (eg, mechanical mitral valve; stroke, systemic embolism, or transient ischemic attack within the previous 12 weeks; mechanical aortic valve and additional stroke risk factors; atrial fibrillation and very high risk of stroke [eg, $CHADS_2$ score of 5 or 6]; venous thromboembolism within the previous 12 weeks; recent coronary stenting; previous thromboembolism during interruption of chronic anticoagulation), we suggest the use of bridging (**Grade 2C**).

For most other patients on warfarin with atrial fibrillation or VTE, we suggest not using bridging (**Grade 2B**). We feel more strongly about avoiding bridging the lower the baseline thromboembolic risk and the higher the bleeding risk.

In contrast to individuals on warfarin, bridging usually is not required for individuals receiving a direct thrombin inhibitor or factor Xa inhibitor, because these agents have shorter half-lives (table 2). (See 'Appropriate settings for bridging' above.)

- **Agent** – When bridging is used, we prefer LMW heparin for most patients. An exception is an individual with renal insufficiency and/or hemodialysis requirement, for whom intravenous or subcutaneous unfractionated heparin can be used more easily. We do **not** use dabigatran, rivaroxaban, apixaban, or edoxaban for bridging. Non-heparin

anticoagulants that can be used in patients with heparin-induced thrombocytopenia are discussed separately. (See 'Heparin product and dose' above.)

•**Timing** – Bridging can be used preoperatively, postoperatively, or both, depending on the underlying condition for which the patient is being anticoagulated (table 9). The timing depends on the heparin product used and the procedural bleeding risk. Importantly, resumption of bridging anticoagulation too early is associated with an increased risk for major bleeding. (See 'When to bridge: Preoperative, postoperative, or both' above and 'Timing of bridging' above.)

•**Heart valve** – Perioperative anticoagulation in individuals with prosthetic heart valves is presented separately. (See "Antithrombotic therapy for prosthetic heart valves: Management of bleeding and invasive procedures", section on 'Management of antithrombotic therapy for invasive procedures'.)

●**Urgent/Emergent procedure** – Reversal of the patient's usual anticoagulant may be required for more urgent or emergent procedures, or to treat perioperative bleeding. Agents with a potential prothrombotic effect (eg, immediate reversal agents, prothrombin complex concentrates, plasma products) should be reserved for the treatment of severe bleeding or anticipated severe bleeding (eg, intracranial hemorrhage, emergent major surgery with elevated prothrombin time/international normalized ratio (PT/INR). (See 'Urgent anticoagulant reversal' above and "Management of bleeding in patients receiving direct oral anticoagulants".)

REFERENCES

1. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. Blood 2011; 117:5044.
2. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. Blood 2012; 120:2954.
3. Torn M, Rosendaal FR. Oral anticoagulation in surgical procedures: risks and recommendations. Br J Haematol 2003; 123:676.
4. Kakkar VV, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. Lancet 1993; 341:259.
5. Jaffer AK. Perioperative management of warfarin and antiplatelet therapy. Cleve Clin J Med 2009; 76 Suppl 4:S37.
6. Gallego P, Apostolakis S, Lip GY. Bridging evidence-based practice and practice-based evidence in periprocedural anticoagulation. Circulation 2012; 126:1573.
7. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e326S.
8. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation 2012; 126:343.
9. Garcia D, Alexander JH, Wallentin L, et al. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. Blood 2014; 124:3692.
10. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). Circulation 2014; 129:1850.
11. Coon WW, Willis PW 3rd. Recurrence of venous thromboembolism. Surgery 1973; 73:823.
12. Douketis JD, Foster GA, Crowther MA, et al. Clinical risk factors and timing of recurrent venous thromboembolism during the initial 3 months of anticoagulant therapy. Arch Intern Med 2000; 160:3431.

13. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506.
14. Levine MN, Hirsh J, Gent M, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost 1995; 74:606.
15. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Research Committee of the British Thoracic Society. Lancet 1992; 340:873.
16. Cardiogenic brain embolism. Cerebral Embolism Task Force. Arch Neurol 1986; 43:71.
17. Lip GY. Intracardiac thrombus formation in cardiac impairment: the role of anticoagulant therapy. Postgrad Med J 1996; 72:731.
18. Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. N Engl J Med 1997; 336:251.
19. Nixon JV. Left ventricular mural thrombus. Arch Intern Med 1983; 143:1567.
20. Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. Blood 1991; 78:2337.
21. Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. Chest 1995; 108:276S.
22. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123:2736.
23. Omran H, Bauersachs R, Rübenacker S, et al. The HAS-BLED score predicts bleedings during bridging of chronic oral anticoagulation. Results from the national multicentre BNK Online bRiDging REgistRy (BORDER). Thromb Haemost 2012; 108:65.
24. Armstrong MJ, Gronseth G, Anderson DC, et al. Summary of evidence-based guideline: periprocedural management of antithrombotic medications in patients with ischemic cerebrovascular disease: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013; 80:2065.
25. Collins LJ, Silverman DI, Douglas PS, Manning WJ. Cardioversion of nonrheumatic atrial fibrillation. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. Circulation 1995; 92:160.
26. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:546S.
27. Salem DN, O'Gara PT, Madias C, et al. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:593S.
28. McIntyre H. Management, during dental surgery, of patients on anticoagulants. Lancet 1966; 2:99.
29. Wahl MJ. Dental surgery in anticoagulated patients. Arch Intern Med 1998; 158:1610.
30. Malden N. Dental procedures can be undertaken without alteration of oral anticoagulant regimen. Evid Based Dent 2005; 6:11.
31. Blinder D, Manor Y, Martinowitz U, Taicher S. Dental extractions in patients maintained on oral anticoagulant therapy: comparison of INR value with occurrence of postoperative bleeding. Int J Oral Maxillofac Surg 2001; 30:518.
32. Garcia-Darennes F, Darennes J, Freidel M, Breton P. [Protocol for adapting treatment with vitamin K antagonists before dental extraction]. Rev Stomatol Chir Maxillofac 2003; 104:69.
33. Perry DJ, Noakes TJ, Helliwell PS, British Dental Society. Guidelines for the management of patients on oral anticoagulants requiring dental surgery. Br Dent J 2007; 203:389.
34. Svensson R, Hallmer F, Englesson CS, et al. Treatment with local hemostatic agents and primary closure after tooth extraction in warfarin treated patients. Swed Dent J 2013; 37:71.
35. Sindet-Pedersen S, Ramström G, Bernvil S, Blombäck M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989; 320:840.
36. Webster K, Wilde J. Management of anticoagulation in patients with prosthetic heart valves undergoing oral and maxillofacial operations. Br J Oral Maxillofac Surg 2000; 38:124.
37. Souto JC, Oliver A, Zuazu-Jausoro I, et al. Oral surgery in anticoagulated patients without reducing the dose of oral anticoagulant: a prospective randomized study. J Oral Maxillofac Surg 1996; 54:27.
38. Patatanian E, Fugate SE. Hemostatic mouthwashes in anticoagulated patients undergoing dental extraction. Ann Pharmacother 2006; 40:2205.

39. Sticherling C, Marin F, Birnie D, et al. Antithrombotic management in patients undergoing electrophysiological procedures: a European Heart Rhythm Association (EHRA) position document endorsed by the ESC Working Group Thrombosis, Heart Rhythm Society (HRS), and Asia Pacific Heart Rhythm Society (APHRS). Europace 2015; 17:1197.
40. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med 2013; 368:2084.
41. Shahi V, Brinjikji W, Murad MH, et al. Safety of Uninterrupted Warfarin Therapy in Patients Undergoing Cardiovascular Endovascular Procedures: A Systematic Review and Meta-Analysis. Radiology 2016; 278:383.
42. Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation 2014; 129:2638.
43. White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med 1995; 122:40.
44. Larson BJ, Zumberg MS, Kitchens CS. A feasibility study of continuing dose-reduced warfarin for invasive procedures in patients with high thromboembolic risk. Chest 2005; 127:922.
45. Hylek EM, Regan S, Go AS, et al. Clinical predictors of prolonged delay in return of the international normalized ratio to within the therapeutic range after excessive anticoagulation with warfarin. Ann Intern Med 2001; 135:393.
46. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet 2010; 49:259.
47. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010; 103:1116.
48. Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. Circulation 2011; 123:1436.
49. Schulman S, Carrier M, Lee AY, et al. Perioperative Management of Dabigatran: A Prospective Cohort Study. Circulation 2015; 132:167.
50. Warkentin TE, Margetts P, Connolly SJ, et al. Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. Blood 2012; 119:2172.
51. Wysokinski WE, McBane RD 2nd. Periprocedural bridging management of anticoagulation. Circulation 2012; 126:486.
52. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med 2015; 373:823.
53. http://www.clinicaltrials.gov/ct2/show/NCT00432796 (Accessed on November 19, 2013).
54. Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation 2012; 126:1630.
55. Douketis JD, Healey JS, Brueckmann M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. Thromb Haemost 2015; 113:625.
56. Steinberg BA, Peterson ED, Kim S, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation 2015; 131:488.
57. Beyer-Westendorf J, Gelbricht V, Förster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J 2014; 35:1888.
58. Skeith L, Lazo-Langner A, Kovacs MJ. The equipoise of perioperative anticoagulation management: a Canadian cross-sectional survey. J Thromb Thrombolysis 2014; 37:411.
59. Skeith L, Taylor J, Lazo-Langner A, Kovacs MJ. Conservative perioperative anticoagulation management in patients with chronic venous thromboembolic disease: a cohort study. J Thromb Haemost 2012; 10:2298.
60. Clark NP, Witt DM, Davies LE, et al. Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures. JAMA Intern Med 2015; 175:1163.

61. Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:204S.
62. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA 2006; 296:935.
63. Jaffer AK, Brotman DJ, Bash LD, et al. Variations in perioperative warfarin management: outcomes and practice patterns at nine hospitals. Am J Med 2010; 123:141.
64. Tafur AJ, McBane R 2nd, Wysokinski WE, et al. Predictors of major bleeding in peri-procedural anticoagulation management. J Thromb Haemost 2012; 10:261.
65. Hirsh J, Bauer KA, Donati MB, et al. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:141S.
66. O'Donnell MJ, Kearon C, Johnson J, et al. Brief communication: Preoperative anticoagulant activity after bridging low-molecular-weight heparin for temporary interruption of warfarin. Ann Intern Med 2007; 146:184.
67. Douketis JD, Woods K, Foster GA, Crowther MA. Bridging anticoagulation with low-molecular-weight heparin after interruption of warfarin therapy is associated with a residual anticoagulant effect prior to surgery. Thromb Haemost 2005; 94:528.
68. Strebel N, Prins M, Agnelli G, Büller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? Arch Intern Med 2002; 162:1451.
69. Dunn AS, Spyropoulos AC, Turpie AG. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). J Thromb Haemost 2007; 5:2211.
70. Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. Anesthesiology 2008; 109:918.
71. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation 2013; 128:1234.
72. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010; 35:64.
73. Horlocker TT. Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy. Br J Anaesth 2011; 107 Suppl 1:i96.