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# The bridging conundrum: perioperative management of DOACs for venous thromboembolism

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## Summary

The majority of patients diagnosed with venous thromboembolism (VTE) are currently treated with direct oral anticoagulants (DOACs). Prior to an invasive procedure or surgery, clinicians face the decision of how to best manage DOACs. Should the DOAC be held, for how long, and are there instances where bridging with other anticoagulants should be considered? While clinical trials indicate that most patients taking DOACs for atrial fibrillation do not require bridging anticoagulation, the optimal strategy for patients with a history of VTE is undefined. In this review, we present a case-based discussion for DOAC interruption perioperatively in patients receiving anticoagulation for management of VTE.

### Keywords

bleeding; direct-acting oral anticoagulants; perioperative medicine; procedure; venous thromboembolism

## Introduction

Prior to the development of direct oral anticoagulants (DOACs), the cornerstone of anticoagulation therapy was warfarin and other vitamin K antagonists (VKAs). As such, management involved frequent decisions regarding when and how to employ bridging therapies, the use of an alternative shorter-acting anticoagulant around the time of a surgery or procedure. Bridging algorithms define a time frame to stop an oral anticoagulant, switch to a low molecular weight heparin (LMWH), and then resume this shorter-acting anticoagulant postoperatively before ultimately resuming chronic oral anticoagulation therapy. Generally, therapeutic doses of anticoagulation are used preoperatively, while postoperative anticoagulation can be at therapeutic or prophylactic doses. The need for bridging anticoagulation for warfarin interruption has diminished based on evidence that in

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atrial fibrillation that warfarin can be stopped without bridging without increasing risk of thromboembolism and with decreased risk of major bleeding.[1]

DOACs, most commonly apixaban or rivaroxaban, are now recommended first line therapy for most patients with thromboembolism (VTE).[2] DOACs are pharmacokinetically quite different from warfarin. While warfarin has a long half-life with a variable tail of efficacy after discontinuation, DOACs have a much shorter and more predictable half-life (i.e. 12 hours for apixaban, 8 hours for rivaroxaban).[3,4] As such, the strategy used with warfarin of bridging in the perioperative period with a shorter-acting anticoagulant, usually LMWH, is less intuitive for DOACs, whose half-life is often similar to that of commonly used low molecular weight heparins.

Multiple studies have concluded that temporary interruption of DOACs is safe for most patients with atrial fibrillation, with relatively low rates of major bleeding and thromboembolism seen. The PAUSE study examined a cohort of 3007 patients treated with DOACs for atrial fibrillation with standardized perioperative management strategies that did not include any pre-operative bridging of holding drug for day −1 before and the day of surgery for low-risk procedures, and day −2 before through day 1 after surgery for high-risk procedures.[5] The study found low rates of major bleeding (1.35% and 1.85%) or thromboembolic events (0.16% and 0.37%) in the apixaban and rivaroxaban arms respectively. In a recent smaller registry study following 525 patients on DOACs (comprised predominately of patients with atrial fibrillation (70%) rather than VTE (30%)), the average interruption of DOACs was 4 days.[6] In this instance, major bleeding rates were higher than a non-bridged warfarin cohort (2.9% v. 1.1%, $p = 0.01$) while thrombotic rates were similar (0.8% v. 0.5%, $p = 0.61$). Based on the emerging data, the American College of Chest Physicians advises against perioperative heparin bridging for most patients on DOACs undergoing an elective surgery or procedures.[7]

The data on safety of stopping DOAC in patients receiving anticoagulation for management of VTE are less robust. A decision on when and for how long to stop a DOAC depends both on preoperative and postoperative factors. How early to stop anticoagulation is primarily influenced by pharmacokinetics of the drugs, urgency of surgery, and bleeding risks associated with surgery, while time prior to resuming anticoagulation postoperatively depends more on the balance of VTE risks relative to bleeding. In one cohort study of 190 patients on DOACs for VTE, interruption of anticoagulation for an average of 103 hours for standard-risk procedures and 149.9 hours for high-risk procedures was associated with low rates of recurrent VTE (1.05%) and surgical major bleeding (0.53%).[8] Several VTE cohort studies report outcomes on bleeding and thrombosis but they include a variable number receiving perioperative bridging such that an optimal approach is still undefined (Table 1). In this *JTH in Clinic*, we present several clinical scenarios related to peri-procedural holding of DOACs and provide a context on how we approach decision-making in these situations.

## Case #1 History of VTE (>3 months prior)

A 72-year-old man with a history of DVT in his left leg has developed osteoarthritis of the left hip and his orthopedic surgeon has recommended a total hip arthroplasty. His DVT

occurred roughly 7 months ago and was diagnosed after he developed swelling and mild pain in his leg. An ultrasound showed a thrombus extending from the left common femoral vein to the left popliteal vein; there was no extension into the iliac vein. He started on apixaban 10 mg twice daily for one week and has been on apixaban 5 mg twice daily ever since. There were no clear provoking factors for the DVT, he has no history of malignancy, and he remains on anticoagulation indefinitely. His orthopedic surgeon asks if his apixaban can be safely held around the hip replacement and if he needs any bridging therapies before or after surgery.

While many patients who develop VTE will have an identifiable risk factor, which may be either transient or ongoing, approximately two-thirds of patients have unprovoked VTE without clear risk factors.[9] A meta-analysis has shown a recurrent VTE rate of 7.4% per patient-year in patients with unprovoked VTE that discontinue anticoagulation, and as such, indefinite anticoagulation is commonly recommended.[2,10]

In determining optimal periprocedural management of DOACs, both bleeding and thrombotic risks for the patient must be considered. International Society of Thrombosis and Haemostasis (ISTH) identified important factors to consider in determining bleeding risk, based on procedure type and location. High bleeding risk procedures include major surgeries such as bowel resection or joint replacement; surgeries in locations more likely to bleed such as liver, spleen, kidney, or spine; or the requirement for neuraxial anesthesia while lower to moderate risk procedures include arthroscopy, gastrointestinal endoscopy, and coronary angiography.[11] Procedures or surgeries established to have minimal bleeding risk, such as cataract surgery and pacemaker placement often are performed without interruption of anticoagulation.[12,13] Major orthopedic surgery, as in this patient’s case, dictates the need to interrupt anticoagulation.

Studies have analyzed the risk of recurrent VTE following procedures for both bridged and non-bridged anticoagulation strategies. The risk of recurrent VTE is considered low even in the absence of perioperative bridging.[6,14] However, based on the retrospective, non-interventional nature of these studies in VTE cohorts there are insufficient data to accurately estimate the absolute risk of post-operative VTE in higher risk cohorts not receiving perioperative anticoagulation (Table 2). Recurrent VTE risk categories can be generated by extrapolating epidemiologic studies on yearly recurrence rates. As such, lower risk groups are generally considered those who have completed a therapeutic course of anticoagulation for the incident VTE (for both provoked or unprovoked VTE). For instance, among 231 patients with VTE treated for 3 months or longer, holding warfarin anticoagulation resulted in 2 VTEs (0.8%).[15]

Given the patient’s DVT was greater than 3 months prior and the absence of other additional risk factors, he was deemed to have a lower risk of recurrent thrombosis during the short period and bridging was not recommended. He took his last dose of apixaban the evening of 2 days prior to the surgery. Because he was not considered higher risk for DVT, low dose apixaban was started postoperatively and continued 48 hours with therapeutic dosing initiated at 72 hours. He did not experience bleeding or thrombotic complications.

## Case #2 Recent VTE (< 6 weeks)

A 70-year-old woman experienced a motor vehicle accident which subsequently led to an abdominal wall wound. Several days following her accident, she developed a pulmonary embolism. She started apixaban and improved clinically, with no evidence of bleeding. However, four weeks later she developed an infection of the wounded area, requiring urgent surgery for debridement. Her surgeon inquires regarding the appropriate perioperative management plan for her anticoagulation.

There are few published data on the risks of anticoagulant interruption in the setting of acute VTE, due to well-established data demonstrating substantial increases in recurrence for patients treated with less than 3 months of anticoagulation, and the extrapolation that even small periods of interruption during this initial phase of treatment carry a much higher risk.[16,17] One cohort study examined rates of thromboembolism during periprocedural interruption of warfarin anticoagulation included 53 patients with acute VTE diagnosed less than 1 month ago; there were no thrombotic events among the 47 patients who were bridged, but 1 of the 6 patients who were not bridged experienced a VTE.[15] In another similar study, only 3 patients of the 1024 patient cohort experienced an acute VTE within 30 days prior, and 1 of those 3 patients, who was not bridged, experienced a VTE.[14] While these numbers are too small to generate statistical estimates, they support the classification of patients with acute VTE into a very high risk category. As such, ideally surgeries or procedures are delayed until after a patient has received at least 3 months of anticoagulation. However, for some patients, such as the one in this case, there may be an urgent or emergent indication for surgery, and a delay may not be possible.

Based on the absence of data demonstrating benefit and potential for increased hemorrhage as demonstrated in the atrial fibrillation literature, in the majority of cases bridging anticoagulation is not indicated for perioperative management of DOACs prescribed for treatment of VTE. However, we consider acute VTE (within 6 weeks of VTE) to be very high risk of recurrent VTE such that perioperative bridging should be considered. Another instance where we will consider on a case-by-case basis are those groups deemed “high” risk for recurrence who previously developed recurrent VTE after short interruptions.

In most scenarios, the DOAC is held 48-72 hours prior to surgery. LMWH is often the preferred anticoagulant for bridging owing to its relatively short half-life and lack of monitoring. Intravenous unfractionated heparin (UFH) can also be considered especially in patients with renal failure. A common regimen is a twice daily dose of low molecular weight heparin (LMWH), e.g. 1 mg/kg enoxaparin, with the last dose the morning of the day prior to surgery, as administered in the BRIDGE and PERIOP2 studies.[1,18] The goal is minimizing time without anticoagulation to less than 36 hours, from when the last dose is no longer therapeutic, the evening prior to surgery, to the evening afterwards when anticoagulation can be resumed. In cases of very-high-risk acute thrombosis, intravenous UFH can be administered and owing to its shorter half-life, can be stopped 4-6 hours prior to surgery. However, bridging with UFH can be challenging due to potential for residual effects of DOACs that can impact both anti-Xa levels and partial thromboplastin times (PTT).[19] Some guideline statements recommend that at the time of transition from DOACs to UFH

clinicians should either use an UFH-calibrated thrombin time test or neutralizing agents to remove the DOAC, while other guidance recommends PTT monitoring in place of anti-Xa monitoring during the first 24-48 hours of overlap.[19,20]

Another important consideration when faced with a patient with an acute DVT and need for emergent surgery is whether that patient should have an inferior vena cava (IVC) filter placed. There are no high-quality data to speak to the benefit of IVC filter placement in this population. The recommendations on the role of IVC filters varies between different society guidelines.[21–25] We typically reserve IVC filter placement for the very high risk VTE category when the VTE occurred within the last 4 weeks, especially if there is residual proximal DVT or instances where resumption of anticoagulation is contraindicated during the early postoperative period.[26]

After the surgery, when to resume full-dose anticoagulation with a DOAC depends on overall bleeding risk. In patients undergoing surgeries with high bleeding risk, as described in the ISTH guidance document, DOAC should be resumed on day 2 or 3 after surgery, while in patients undergoing surgeries with moderate or low bleeding risk, DOAC can be resumed on day 1 after surgery.[11] In patients undergoing surgery with high bleeding risk, if they have a moderate or very high risk of thrombosis, it is reasonable to treat with prophylactic-dose LMWH starting the evening of or day 1 after surgery until full dose anticoagulation can be safely resumed.

In this case, DOAC was held day −2 and enoxaparin 1 mg/kg for a single dose was administered day −1 before surgery. She underwent the surgery without complications and resumed prophylactic LMWH the morning after surgery and was transitioned back to therapeutic anticoagulation 24 hours later.

## Case #3 Cancer-associated VTE

A 65-year-old woman with locally advanced lung adenocarcinoma developed a pulmonary embolism with proximal DVT in the absence of other provoking factors outside of her malignancy. She started apixaban and clinically improved. Seven weeks later, she is planned to undergo a wedge resection of her lung. A lower extremity ultrasound re-demonstrates her known DVT. Her anticoagulation requires interruption, and the thoracic surgery team requests guidance on appropriate interruption and whether bridging is indicated.

Patients with cancer were excluded or underrepresented in many of the trials exploring the role of bridging, comprising only 8% of patients in the PAUSE trial and 12% of those in the BRIDGE trial.[1,5] In a previously-mentioned cohort study, cancer emerged as an independent risk factor for thrombosis during periprocedural holding of anticoagulation, with a hazard ratio of 4.86 (1.63 - 14.50).[15] Certain malignancies are particularly prothrombotic.[27] Even when receiving appropriate anticoagulation, the rates of recurrent thrombosis in patients with cancer are much higher than recurrence rates among the general population while on anticoagulation.[28–30] Thus, periprocedural management of patients with malignancy requires an even greater awareness of various risk factors than for patients without malignancy.[31]

This case, similar to that of the patient with acute VTE, occupies a space with relatively limited data to provide guidance. Patients with cancer-associated VTE clearly have higher risks of recurrent and break-through thrombosis, and in one retrospective analysis were shown to have both higher bleeding and thrombotic events after anticoagulation interruption for surgery than a similar cohort of patients with non-cancer-associated VTE.[32] The decision to bridge with LWMH or UFH in patients with a cancer diagnosis on DOACs is influenced by several factors. Timing of VTE is often the critical factor, and as above, if the event is recent (i.e. <6 weeks) we typically recommend bridging anticoagulation. In some instances where the underlying malignancy is poorly controlled, especially with concomitant risk factors such active chemotherapy and recurrent VTE, we discuss with the patient and surgeon the risks and benefits of bridging anticoagulation during a period of holding DOAC anticoagulation.

Given the subacute nature of the VTE (7 weeks), progression of underlying malignancy, and presence of proximal DVT, bridging was advised for this patient. As she was admitted for the surgery, she was transitioned from apixaban to an enoxaparin bridge, with last dose the morning of day −1 prior to surgery. She received prophylactic low molecular weight heparin the evening of the procedure and resumed apixaban on day 2 after surgery.

## Case #4 High-bleeding risk procedure

A 35-year-old woman on rivaroxaban indefinitely due to two prior VTE events has severe, chronic back pain which requires a surgical operation. Initially, she had an unprovoked deep vein thrombosis of the left popliteal vein while taking combined estrogen and progesterone oral contraceptives. She switched to an alternative non-hormonal form of birth control and was anticoagulated with warfarin for one year and then stopped. Subsequently, 3 years later, she experienced an unprovoked pulmonary embolism of the segmental and subsegmental arteries of the right lower lobe of her lung. She was started on rivaroxaban indefinitely. She presents 2 years after her second VTE with severe lower back pain which has not responded to conservative management such that the orthopedic surgeon is recommending a spinal surgery with vertebral fusion. Her surgeon requests guidance in perioperative management of her rivaroxaban and the need for bridging.

Procedures that involve the spinal space are defined as having high bleeding risk, based on the severity of morbidity were bleeding to occur. Data from the time of warfarin use found a 20% risk of bleeding in major surgeries with high bleeding risk when anticoagulation was resumed within 1 day of the procedure, although this was only a small proportion of the patients (40 patients) in the overall study.[33] The PAUSE trial demonstrated that holding DOACs for 2 days prior to a procedure with high bleeding risk, and resuming DOAC on postoperative day 2, allowed for manageable bleeding rates.[5] However, it is important to acknowledge that other groups and societies recommend different durations of holding anticoagulation and ultimately decisions must be individualized. While the decision of whether to use post-procedural prophylactic (i.e. 30-40 mg once daily of enoxaparin) or intermediate-dose (i.e. 1 mg/kg once daily of enoxaparin) anticoagulation was left up to the primary clinician in most of these protocols, these techniques are used much more frequently in patients with high bleeding risk procedures, likely due to the longer time off

of full-dose anticoagulation. For example, in the PAUSE trial, 35% of patients undergoing high-bleeding-risk procedures had prophylactic LMWH postoperatively while only 2% of patients undergoing low-bleeding-risk procedures. Unsurprisingly, major bleeding rates were higher (2.4% v. 0.9%) in patients undergoing high bleeding risk procedures compared to low bleeding risk procedures, but it is impossible to distinguish what of this is due to prophylactic LMWH and what is inherent to the procedure. That said, it is a reasonable option for patients with higher thrombotic risk undergoing high bleeding risk procedures to use postoperative prophylactic dosing of LMWH.

In this patient's case, given moderate thrombotic risk, there was not felt to be a role for pre-procedural bridging. The last dose of rivaroxaban was given on day −3 prior to the surgery, and she underwent the surgery without complication. On day 2 after surgery, she started prophylactic-dose (40mg once daily) low molecular weight heparin for 3 days, and then subsequently resumed full anticoagulation with rivaroxaban on day 5 after surgery.

## Conclusion

Bridging is a practice which began in the use of oral vitamin K antagonists that required multiple days of administration before reaching therapeutic levels. Given the pharmacokinetics of DOACs, with relatively quick time-to-anticoagulation as well as shorter half-lives, bridging is now a much smaller part of perioperative anticoagulation management than it once was. While recent guidelines from ASH and ACCP generally advise against bridging, they combine both patients with AF and VTE into a single recommendation whereas the relative risks and benefits are not the same in these two populations.[7]

In patients with extremely high thrombotic risk, generally those with acute VTE, bridging anticoagulation after holding DOAC can be considered. On a case-by-case basis we consider other high risk groups such as those with recurrent thrombosis or strongly prothrombotic risk factors. Bridging may be done with either LMWH, or in highest-risk situations with admission to the hospital and intravenous heparin.

In patients with moderate-to-very high thrombotic risk and very high bleeding risk procedures, postoperative bridging with prophylactic or intermediate-dose LMWH may be considered prior to resumption of full dose anticoagulation.

In each of these cases, any data to support the suggestion of considering bridging is of low-quality and inferred from other situations. While these situations raise the highest risk of anticoagulation, it is not conclusively known that bridging reduces the risk of recurrent thrombosis, and it is possible that the bleeding risks associated outweigh the benefits as evidenced by studies conducted in atrial fibrillation.[34] Further research is needed to inform bridging practices and guide clinicians on management of competing risks in these particularly complex patients during the perioperative period.

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**Table 1 -**

Complications of DOAC Interruption

| Study | # of pts on DOACs* | Proportion of patients with AF* (%) | Proportion of Patients with VTE* (%) | Major bleed rate | Thrombosis rate | Use of bridging |
|---|---|---|---|---|---|---|
| Shaw RPTH 2020[35] | 325 | 100% | **0%** | 0.57% | 0.57% | 23.9% perioperative prophylactic AC |
| Garcia Blood 2014[36] | 5439 | 100% | **0%** | 1.62% | 0.35% | 11.7% bridging |
| Douketis JAMA IM 2019 (PAUSE)[5] | 3007 | 100% | **0%** | 1.43% | 0.33% | 12.6% perioperative prophylactic AC |
| Douketis TH 2015 (Bridged cohort)[37] | 418 | 100% | **0%** | 6.5% | 1.2% | 100% bridging |
| Douketis TH 2015 (Unbridged cohort)[37] | 2291 | 100% | **0%** | 1.8% | 0.6% | 0% bridging |
| Colonna Clin Card 2020[38] | 1155 | 92.6% | **8.6%** | 0.4% | 0.6% | Perioperative prophylactic AC allowed; rates not provided |
| Beyer-Westendorf EHJ 2014[39] | 595 | 81.1% | **17.1%** | 1.2% | 1% | 22.5% bridging with therapeutic heparin; 7.3% with perioperative prophylactic AC |
| Lee JTH 2022[6] | 525 | 70.7% | **29.3%** | 2.9% | 0.8% | Rates of bridging not provided |
| Shaw JTH 2019[32] | 146 | 0% | **100%** | 4.1% | 4.1% | Rates of bridging not provided |
| Shaw JTH 2017[8] | 190 | 0% | **100%** | 0.53% | 1.05% | 41.1% perioperative prophylactic AC |

DOAC=Direct Oral Anticoagulant, AF = Atrial Fibrillation, VTE = Venous Thromboembolism

**Table 2 -**

Thrombotic Recurrence Risk After Primary Anticoagulation

| VTE Risk Category | Risk Factors | VTE rate off anticoagulation (per year) | Bridging anticoagulation? | Ref |
|---|---|---|---|---|
| **Low** | History of provoked VTE (> 3 months) | <4% | No | [40] |
| **Moderate** | History of idiopathic VTE (>3 months prior) | 4-10% | No | [40,41] |
| **High** | Active cancer<br>Recent VTE (6 weeks to 3 months)<br>Antiphospholipid antibody syndrome | 10-15% | Occasionally | [41–43] |
| **Very high** | Recent VTE (<6 weeks of anticoagulation)<br>History of recurrent VTE during short anticoagulation interruptions | >20% | Commonly (consideration of IVC filter placement) | [41] |