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## Evidence-based focused review

# Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach

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### Case presentations

**Case 1:** A 69-year-old woman with chronic atrial fibrillation and hypertension requires a dental restoration procedure that will need local anesthetic injections.

**Case 2:** A 77-year-old, 100-kg man with chronic atrial fibrillation, stable coronary artery disease, hypertension, and a previous transient ischemic attack that occurred 2 years ago after warfarin interruption for colon polypectomy now requires colon resection for stage I adenocarcinoma of the bowel.

The management of patients who are receiving anticoagulants and require surgery or an invasive procedure is a common clinical problem that, paradoxically, is both trivial and complex.<sup>1,2</sup> It is trivial because stopping and resuming an anticoagulant is simple enough: wait until the anticoagulant effect wears off and resume it when there is adequate hemostasis. It is complex because of the wide range of perceived thromboembolic risks during anticoagulant interruption. Consider that in a prospective cohort study assessing warfarin interruption in 535 low- to moderate-risk patients with atrial fibrillation who interrupted warfarin and did not receive heparin bridging, the incidence of arterial thromboembolism was 0.7% (95% confidence interval [CI]: 0.2-1.9).<sup>3</sup> The authors concluded that "... for many patients receiving warfarin who need a minor procedure, a brief (5 day) interruption of therapy is associated with a low risk of thromboembolism." Now consider a retrospective cohort study that estimated a risk for thrombotic events of 1 per 6219 (0.016%) during warfarin interruption in a broad spectrum of warfarin-treated patients.<sup>4</sup> The authors concluded that "with no documented increase in severe bleeding during perioperative continuation of warfarin, these data provide a compelling argument to maintain patients on warfarin during cutaneous operations." Thus, one group considered that a risk for thromboembolism of 0.7% associated with simply stopping and restarting warfarin was acceptable, obviating the need for heparin bridging, whereas another group thought a risk of 0.016% was too high and justified perioperative continuation of warfarin. Added to these varied perceptions of thromboembolic risk is the wide range of surgical and other invasive procedures that patients undergo and clinicians' differing perceptions of associated bleeding risk.<sup>5,6</sup> Overall, the perceived risk for thromboembolism will likely drive patient management,<sup>6</sup> and if it is perceived to be greater than the risk for bleeding, this will determine whether heparin bridging is administered during warfarin interruption.

Caught between these varied, and at times extreme, perceptions of risks to patients is the practicing clinician who seeks a practical but evidence-based approach to patient management. Addressing

this need is problematic, as high-quality evidence from randomized trials of perioperative anticoagulation is lacking.<sup>7</sup> In an attempt to bridge this disparity between clinical need and limited evidence, the approach herein aims to update the best available evidence on perioperative anticoagulant management, using the GRADE working group's approach to evidence appraisal,<sup>8</sup> and is framed on the following key clinical questions:

1. How to stratify patients according to risk for thromboembolism and bleeding?
2. When is perioperative interruption of warfarin therapy not required?
3. If warfarin interruption is required, when should it be stopped and resumed?
4. If warfarin therapy is stopped, when is heparin bridging required?
5. How should heparin bridging be given before and after surgery, and at what dose?

In the practice recommendations mentioned herein, attention should be given to the wording. In accordance with the GRADE system, a recommendation statement with the wording "*clinicians should*" reflects a strong recommendation, which may be applied to most patients. A statement with the wording "*clinicians may consider*" reflects a weak recommendation, which would be applied to many patients but may not be applied to many other patients; in such circumstances, clinicians should consider individual patient characteristics and patients' values and preferences to decide on the treatment and/or management course taken. An overview of the perioperative management of warfarin-treated patients is provided in Figure 1.

### How to stratify patients according to risk for thromboembolism and bleeding?

There are no validated risk stratification schemes to estimate risk for perioperative stroke or thromboembolism as is the case with the CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc prediction guides, which are used in a nonperioperative clinical setting.<sup>9,10</sup> The suggested risk stratification scheme in Table 1 is an empiric formulation derived largely from indirect evidence of risk in a nonperioperative setting. In patients with atrial fibrillation, additional evidence from a large, linked administrative database that gathered data from 1996 to 2001 (during a prebridging era) suggests that the CHADS<sub>2</sub> score may estimate postoperative risk for stroke (Table 2).<sup>11</sup> The 30-day postoperative incidence of stroke appeared higher than expected based on the annual risk if prorated over a 30-day period, in turn supporting the premise that the perioperative milieu is

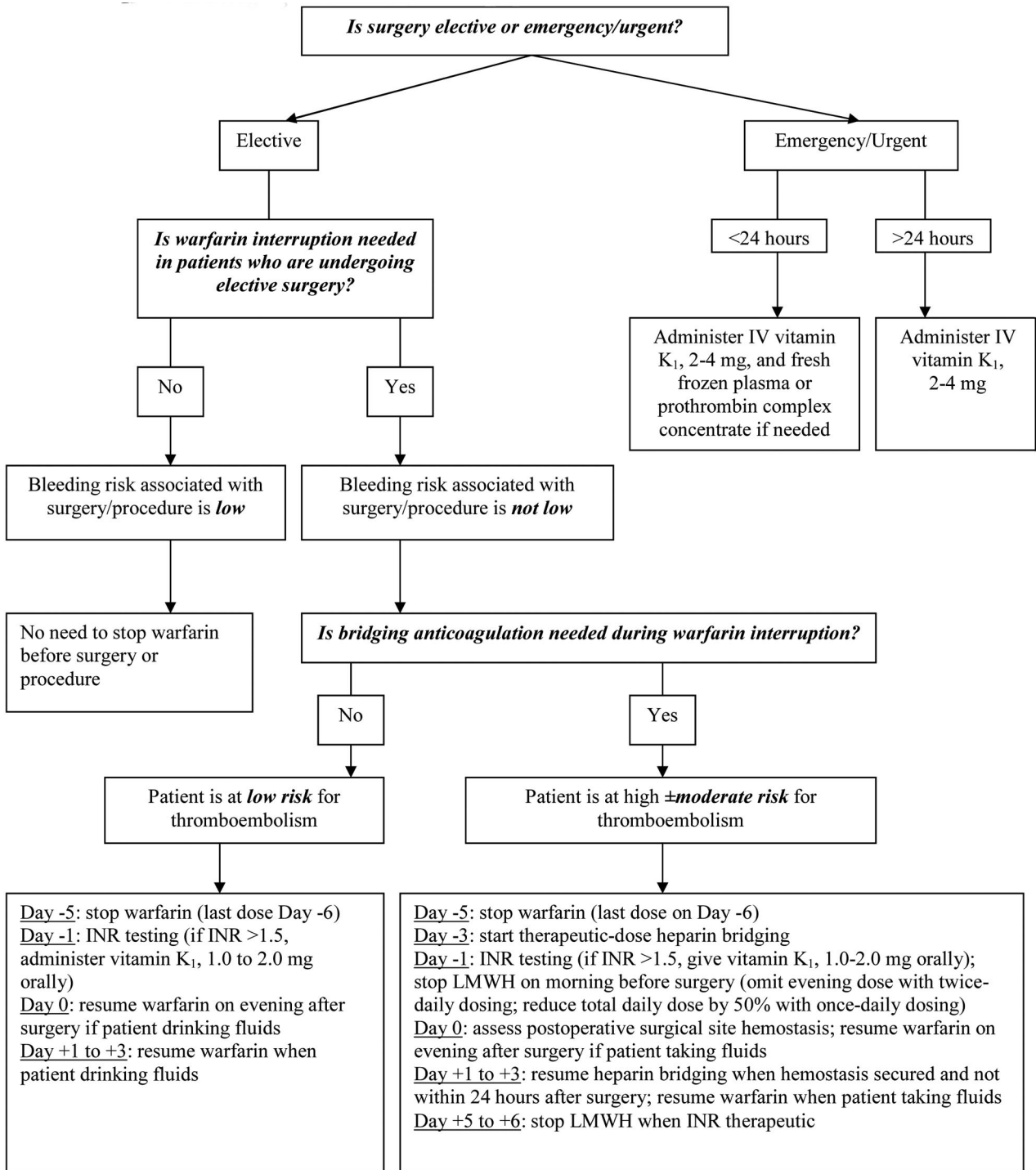


Figure 1. Overview of perioperative management of warfarin therapy and heparin bridging before and after surgery/procedure.

prothrombotic.<sup>12</sup> There are also emerging data that the type of surgery influences the risk for stroke, as is already established for cardiac bypass and carotid endarterectomy.<sup>11,13,14</sup> Overall, an assessment of the absolute risk for thromboembolism should consider (1) the underlying disease requiring anticoagulation, (2) presence of concomitant cardiovascular risk factors, and (3) type of surgery.

Estimating the risk for perioperative bleeding also lacks a prediction guide, such as the HAS-BLED score in the nonperioperative setting,<sup>15</sup> and is driven by the type of surgery. Rather than

attempt a bleeding risk classification to encompass all surgery types, clinicians may focus on surgeries associated with a high risk of bleeding, as listed here, in which perioperative anticoagulation should be used with caution<sup>7</sup>:

- coronary artery bypass, heart valve replacement, intracranial surgery, or intraspinal surgery, in which surgical site bleeding can have serious consequences
- major vascular surgery such as aortic aneurysm repair and peripheral artery bypass, in which extensive vascular tissue damage predisposes to bleeding

**Table 1. Suggested risk stratification scheme for perioperative arterial and venous thromboembolism**

Thromboembolic risk category	Clinical indication for warfarin therapy		
	Atrial fibrillation	Mechanical heart valves	Venous thromboembolism
High	<ul style="list-style-type: none"> <li>● CHADS<sub>2</sub> score: 5 or 6</li> <li>● Recent (&lt; 3 months) stroke/TIA</li> <li>● Rheumatic valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>● Any mechanical mitral valve</li> <li>● Older aortic mechanical valve (caged-ball, tilting disk)</li> <li>● Recent (&lt; 3 months) stroke or TIA</li> </ul>	<ul style="list-style-type: none"> <li>● Recent (&lt; 3 months) VTE</li> <li>● Severe thrombophilia*</li> </ul>
Moderate	CHADS <sub>2</sub> score: 3 or 4	Bileaflet aortic valve prosthesis with at least one risk factor†	<ul style="list-style-type: none"> <li>● VTE within past 3-12 months</li> <li>● Non-severe thrombophilia‡</li> <li>● Recurrent VTE</li> <li>● Active cancer</li> </ul>
Low	CHADS <sub>2</sub> score: 0-2 (without previous stroke or TIA)	Bileaflet aortic bileaflet without any risk factors†	VTE > 12 months ago

Adapted with permission from Douketis J, et al. *Chest*. 2008;133(6 suppl):299S-339S.<sup>7</sup>

CHADS<sub>2</sub> indicates Cardiac failure-Hypertension-Age-Diabetes-Stroke; VTE, venous thromboembolism; and TIA, transient ischemic attack.

\*Severe thrombophilia: deficiency of protein C, protein S, or antithrombin; antiphospholipid syndrome, or multiple abnormalities.

†Risk factors: atrial fibrillation, cardiac failure, hypertension, age > 75 years, diabetes, stroke, or TIA.

‡Non-severe thrombophilia: heterozygous factor V or factor II mutation.

- major orthopedic, reconstructive plastic, and major cancer surgery, in which the extent of tissue injury predisposes to bleeding
- urogenital surgery (prostate and bladder resection), in which endogenous urokinase promotes bleeding

There are also more minor procedures that confer an increased risk for bleeding<sup>7</sup>:

- colon polypectomy, in which the polyp stalk transection site (especially if > 1 cm in diameter) may have ongoing bleeding that worsens with re-anticoagulation
- biopsy of prostate or kidney, in which endogenous urokinase may promote bleeding, possibly for several days after a procedure
- cardiac pacemaker or defibrillator implantation, in which unopposed tissue layers of the pacemaker pocket heal by secondary intent

#### When is perioperative interruption of warfarin therapy not required?

In general, interruption of warfarin is not required for minor dental, skin, and eye procedures consisting of tooth extractions or endodontic (root canal) procedures, small skin excisions (basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi), and cataract removal.<sup>7</sup>

Randomized trials and prospective cohort studies have assessed continuing warfarin around dental procedures,<sup>7,16</sup> and several

management strategies that have been assessed: (1) continuing warfarin ± co-administered prohemostatic interventions (antifibrinolytic drugs and/or sutures); (2) partial (2-3 days before procedure) warfarin interruption; and (3) complete (5-6 days before procedure) warfarin interruption. In trials that compared different strategies, continuing warfarin with a prohemostatic agent (5 mL of oral tranexamic acid, 5-10 minutes before and 3-4 times daily for 1-2 days after procedure) conferred a low risk for bleeding. Another approach associated with a low risk for bleeding is partial interruption of warfarin for 2-3 days before the dental procedure.

For skin procedures, prospective cohort studies reported a 3-fold higher incidence of minor bleeding in patients who continued warfarin compared with patients who had warfarin interruption, but most bleeds were self-limiting.<sup>17,18</sup>

For cataract removal, a common surgery among elderly warfarin-treated patients, the incidence of clinically important bleeding with continued warfarin appears low, reflecting that it is a largely avascular procedure. Thus, in a meta-analysis of warfarin-treated patients having cataract surgery, patients who continued warfarin had a 3-fold increased risk for minor bleeding (odds ratio [OR]: 3.26; CI: 1.73-6.16), with an overall incidence of bleeding of 10%, but almost all bleeds were self-limiting dot hyphemas or subconjunctival bleeds and no patient developed compromised vision.<sup>19</sup> Some clinicians may be concerned about continuing warfarin in patients undergoing cataract removal who have retrobulbar or peribulbar anesthesia, considering that periorbital bleeding may place patients at increased risk for visual loss. The risk for periorbital hemorrhage appears low (< 1%) in anticoagulated patients who have retrobulbar anesthesia, as shown in a prospective cohort study in which only 1 of 136 warfarin-treated patients developed this complication.<sup>20</sup> Nonetheless, if there is concern about retrobulbar hemorrhage, a discussion between the internist and ophthalmologist may be warranted to discuss management options, including perioperative interruption of warfarin or continuation with the cataract extraction being done using a phacoemulsification approach and topical anesthesia.

**Recommendation:** *In patients who require a minor dental procedure, clinicians either should continue warfarin with a co-administered oral prohemostatic agent or should stop warfarin 2-3 days before the procedure (aiming for a day-of-procedure INR of 1.6-1.9). In patients who require minor skin procedures, clinicians may consider continuing warfarin around the time of the*

**Table 2. Stroke risk according to CHADS<sub>2</sub> score in patients with atrial fibrillation in nonperioperative and perioperative clinical settings**

CHADS <sub>2</sub> score	Nonperioperative setting: annual stroke rate (95% CI)*	Perioperative setting: 30-day postoperative stroke rate (95% CI)†
0	1.9 (1.2-3.0)	1.01 (0.83-1.21)
1	2.8 (2.0-3.8)	1.62 (1.46-1.79)
2	4.0 (3.1-5.1)	2.05 (1.87-2.24)
3	5.9 (4.6-7.3)	2.63 (2.26-3.04)
4	8.5 (6.3-11.1)	3.62 (2.66-4.80)
5	12.5 (8.2-17.5)	3.65 (1.83-6.45)
6	18.2 (10.5-27.4)	7.35 (2.42-16.3)

CHADS<sub>2</sub> indicates Cardiac failure-Hypertension-Age-Diabetes-Stroke; and CI, confidence interval.

\*Based on risk for stroke in untreated patients.<sup>8</sup>

†Based on linked administrative database from 1996-2001 of patients with atrial fibrillation who were hospitalized for surgery, but no information on perioperative anticoagulation is available (adapted with permission from Kaatz S, et al. *J Thromb Haemost*. 2010;8(5):884-890<sup>11</sup>).

**Table 3. Suggested perioperative anticoagulation management in patients who receive heparin bridging**

Patient group	Preoperative management	Postoperative management
Low-bleeding-risk surgery	Stop therapeutic-dose LMWH on morning (20-24 h) before surgery <ul style="list-style-type: none"> <li>● Omit evening dose with BID regimen</li> <li>● Give 50% total dose with OD regimen</li> </ul>	Resume therapeutic-dose LMWH* approximately 24 h after surgery (eg, the following day), when there is adequate hemostasis.
High-bleeding-risk surgery	Stop therapeutic-dose LMWH on morning (20-24 h) before surgery <ul style="list-style-type: none"> <li>● Omit evening dose with BID regimen</li> <li>● Give 50% total dose with OD regimen</li> </ul>	Delay resumption of therapeutic-dose LMWH for 48-72 h after surgery, when hemostasis is secured <p>OR</p> administer only low-dose LMWH† when hemostasis is secured or avoid the use of LMWH altogether.

LMWH indicates low-molecular-weight heparin; BID, twice daily; and OD, once daily.

\*Therapeutic-dose regimen refers to a weight-adjusted regimen, for example, enoxaparin 1 mg/kg BID or dalteparin 100 IU/kg BID.

†Low-dose regimen refers to a fixed-dose (not weight-adjusted) regimen, for example, enoxaparin 40 mg OD or dalteparin 5000 IU OD.

*procedure and optimizing local hemostasis. In patients who require cataract surgery, clinicians may consider continuing warfarin around the time of the surgery.*

#### **If warfarin interruption is required, when should it be stopped and resumed?**

The current recommendation to stop warfarin 5 days before surgery, intended to provide normal or near-normal hemostasis at surgery, is based on 3 data sources. The first relates to the pharmacodynamic properties of warfarin, namely the synthesis rate of functional coagulation factors II and X after warfarin interruption. Assuming first-order pharmacokinetics for warfarin elimination, each half-life elapsed after stopping warfarin leads to a 50% reduction in the residual anticoagulant effect; thus, 50%, 25%, 12.5%, 6.25%, and 3.125% after 1, 2, 3, 4, and 5 half-lives elapsed, respectively.<sup>21</sup> At least 5 days would be needed for the INR to normalize after stopping warfarin. The second source comes from studies assessing perioperative warfarin interruption. In a key prospective cohort study of 224 patients who stopped warfarin 5 days before surgery, only 15 (7%) patients had an INR > 1.5 on the day of surgery.<sup>22</sup> Further, in a randomized trial in which patients stopped warfarin 5 days or 1 day before surgery (the latter group also received 1 mg of vitamin K), the mean INR at surgery in the 5-day interruption group was 1.2.<sup>23</sup> Finally, the 5-day warfarin interruption period corresponds to approximately 2 half-lives of factor II, allowing time for this pivotal factor to be sufficiently replenished.<sup>21</sup>

Resuming warfarin after surgery is feasible and safe for most patients on the evening of or the morning after surgery. This practice is supported by several prospective cohort studies, totaling more than 2500 patients who had perioperative management (typically with heparin bridging), in which warfarin was resumed within 24 hours of surgery.<sup>7</sup> In a 650-patient prospective cohort study in which warfarin was resumed within 24 hours of surgery at patients' usual maintenance dose, the mean time to attaining an INR  $\geq$  2.0 was 5.1 days.<sup>24</sup> Another cohort study found that resuming warfarin with a doubling of patients' usual dose for the initial 2 postoperative days conferred a mean duration to attain an INR  $\geq$  2.0 of 4.6 days.<sup>25</sup> The early (within 24 hours) postoperative resumption of warfarin is unlikely to incur an increased risk for bleeding compared with delayed re-initiation because it takes 2-3 days after resuming warfarin to attain a measurable anticoagulant effect (ie, INR > 1.3) and 5-7 days to attain a therapeutic anticoagulant effect (ie, INR > 1.9).<sup>21,22</sup>

**Recommendation:** *In patients who require temporary interruption of warfarin before surgery, clinicians should stop vitamin K antagonists approximately 5 days before surgery to allow adequate*

*time for the INR to normalize. Clinicians may consider resuming warfarin 12-24 hours (evening or next morning) after surgery and when there is adequate hemostasis.*

#### **If warfarin therapy is stopped, when is heparin bridging required?**

The need for heparin bridging during warfarin interruption is driven largely by patients' estimated risk for perioperative thromboembolism, which, in turn, is determined by the indication for warfarin and, to a lesser extent, by the type of surgery. Ideally, randomized trials that allocate patients to a heparin bridging or no bridging strategy should be used to determine best perioperative anticoagulation practices, and such trials are in progress.<sup>2</sup> A suggested approach for heparin bridging is provided in Table 3.

Among patients classified as "high risk," observational studies have assessed heparin bridging typically with a therapeutic-dose low-molecular-weight heparin (LMWH) regimen such as enoxaparin 1 mg/kg SC twice daily. Such heparin bridging regimens are associated with a 1%-2% incidence of thromboembolism and a 2%-4% incidence of major bleeding, the latter typically defined as bleeding associated with a symptomatic > 2-g/dL decrease in hemoglobin or need for transfusion of 2 or more units of packed red blood cells.<sup>7</sup> Heparin bridging with intravenous unfractionated heparin (UFH) has also been studied in such patients, with rates of thromboembolism and bleeding comparable with that of LMWH bridging,<sup>26</sup> but it is infrequently used.<sup>7</sup>

Among "moderate-risk" patients, observational studies have assessed different bridging regimens, including therapeutic-dose LMWH, intermediate-dose LMWH (eg, enoxaparin, 40 mg SC twice daily) and, in a minority of patients, no heparin bridging. Irrespective of the anticoagulation strategy used, the incidence of thromboembolic events was ~ 1%.<sup>27</sup> Given the uncertainty about which patients can be managed with a bridging or no bridging strategy, the decision about perioperative anticoagulation should be based on individual patient- and surgery-related factors. Patients groups within this risk stratum in whom bridging may be considered include

- patients with previous stroke or systemic embolism
- patients with active coronary artery disease or peripheral vascular disease
- patients with previous thromboembolism during interruption of warfarin
- patients undergoing major cardiac or vascular surgery

For patients at moderate to high risk for thromboembolism in whom heparin bridging is being considered in an attempt to mitigate this risk, a 2%-4% risk for major bleeding should not be

overlooked, especially because major bleeding in the perioperative setting can have serious consequences if emergency reoperation is needed. It is likely, although not shown by randomized trials, that the 2%-4% risk for major bleeding can be reduced if postoperative resumption of heparin bridging is done carefully, with either a delay in its resumption for 48-72 hours after surgery or a reduction in its dose.<sup>24,25</sup>

Among "low-risk" patients, observational studies that included such patients consisting of low-risk atrial fibrillation, isolated mechanical bileaflet aortic valves, or previous remote venous thromboembolism have assessed a wide range of bridging regimens (therapeutic dose, intermediate dose, low dose) and no heparin bridging. Rates of thromboembolism in patients who did not receive heparin bridging were < 1%, thereby suggesting that bridging in such patients is unnecessary.<sup>3,27,28</sup>

**Recommendation:** *In patients at high risk for thromboembolism, clinicians may consider using heparin bridging during interruption of warfarin therapy; in patients at moderate risk, clinicians may consider a bridging or no bridging approach based on an assessment of individual patient- and surgery-related factors; in patients at low risk for thromboembolism, clinicians may consider no heparin bridging during interruption of warfarin.*

#### How should heparin bridging be given before and after surgery, and at what dose?

Before surgery, heparin bridging is started on the third day before surgery. With LMWH bridging, because the elimination half-life of LMWHs is ~ 4-5 hours, the last dose should be given on the morning of the day (20-24 hours) before surgery. Two cohort studies have shown that preoperative, therapeutic-dose LMWH is associated with a detectable anticoagulant effect during surgery (in more than 50% of patients) if the last dose is given on the evening before surgery.<sup>29,30</sup> Thus, on the day before surgery patients should receive only the morning dose if a twice-daily LMWH regimen is used or 50% of the total dose if a once-daily LMWH regimen is used.

After surgery, assessing the risk for bleeding depends on the anticipated surgery-specific risk and the evaluation of wound hemostasis. Consequently, the assessment of bleeding risk, which drives the decision about when (and if) to resume heparin bridging in the postoperative period, is largely subjective and individualized. The judicious resumption of anticoagulants postoperatively is critical to prevent serious bleeding. Three factors may be considered to minimize postoperative bleeding:

**Time interval since surgery.** No trials have compared an early (within 24 hours after surgery) or late (more than 24 hours after surgery) resumption of therapeutic-dose LMWH bridging after surgery. In a prospective cohort study in which all patients received enoxaparin, 1.5 mg/kg, at a fixed time period, 12-24 hours after surgery, the incidence of major bleeding was 20% (8 of 40) after major surgery and 0.7% (1 of 148) after minor surgery.<sup>31</sup> Other studies that allowed a flexible postoperative bridging regimen in high-bleeding risk patients, with either delayed resumption of

therapeutic-dose LMWH or substitution of a low-dose regimen, found a low incidence of major bleeding (< 5%).<sup>24,25</sup> Overall, these findings suggest that when resuming therapeutic-dose LMWH, it should be delayed for at least 24 hours and probably longer (48-72 hours) in patients having major surgery. In patients having minor surgery who received therapeutic-dose LMWH bridging started ~ 24 hours (on the morning of the day after surgery), the incidence of major and nonmajor bleeding was < 5%.

**Heparin dose when bridging is resumed.** Therapeutic-dose LMWH (and UFH) has been shown to be associated with a higher risk of major bleeding compared with low-dose LMWH or UFH regimen or no bridging (OR: 4.4; 95% CI: 1.5-14.7) in a prospective multicenter registry.<sup>5</sup> Consequently, its perioperative use should be judicious and tailored to the type of surgery so as to minimize bleeding risk.

**Flexibility in postoperative resumption of anticoagulant therapy.** Several studies demonstrate a low (1%-3%) risk for major bleeding after major surgery if the timing of resumption of anticoagulation is not fixed but varies according to the anticipated bleeding risk and observed intra- and postoperative bleeding.<sup>1,24</sup> This also makes clinical sense because the time needed for wound-healing will vary depending on the degree of tissue damage associated with different types of surgery. Further, there will be variability as to postoperative bleeding among individual patients having the same surgery.

#### Back to the cases

**Case 1:** *This patient can be considered at "low risk" for thromboembolism. Either continuing warfarin with tranexamic acid or a 2- to 3-day warfarin interruption (given the patient's low risk for thromboembolism) around the time of the dental procedure would be reasonable.*

**Case 2:** *This patient can be considered at "high risk," based on the risk factor profile, especially previous thromboembolism during warfarin interruption. Before surgery, warfarin is stopped 5 days before surgery and LMWH bridging is reasonable, for example, enoxaparin 100 mg SC twice daily, to start 3 days before surgery, with the last dose on the morning of the day before surgery. After surgery, assuming there is no excessive bleeding, LMWH can be resumed 48 hours after surgery on the morning of the third postoperative day, as there is likely to be adequate hemostasis by this time.*

#### Authorship

Contribution: J.D.D. developed and wrote the manuscript.

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