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Abbreviations

aPTT  activated partial thromboplastin time
ASA  acetylsalisylic acid
CBC  complete blood count
DVT  deep vein thrombosis
INR  international normalized ratio
IU  international units
LMWH  low-molecular-weight heparin
NSAID  non-steroidal anti-inflammatory drug
TIA  transient ischemic attack
UFH  unfractionated (standard) heparin
VTE  venous thromboembolism (includes deep vein thrombosis and pulmonary embolism)
Overview

The clinical management of patients who require temporary interruption of warfarin or other coumarin derivatives because of surgery or a non-surgical invasive procedure is a common and challenging clinical problem. There are approximately 4 million people in Europe and North America who are receiving long-term treatment with an oral anticoagulant such as warfarin. It is estimated that approximately 10% of such patients (or 400,000) are assessed annually for temporary interruption of oral anticoagulant therapy and possible ‘bridging anticoagulation’.

Bridging anticoagulation with a short-acting heparin preparation, such as unfractionated heparin (UFH) or low-molecular-weight heparin (LWMH), is administered to minimize the period of time before and after surgery that patients are not receiving therapeutic anticoagulation and, thereby, minimize the risk of thromboembolism. Although the risk for thromboembolic events during temporary warfarin interruption is considered low (i.e., <3%), these events can have devastating clinical consequences: thrombosis of a mechanical heart valve is fatal in 15% of patients, and embolic stroke results in a major neurological deficit or death in 70% of patients.

There are no universally accepted recommendations regarding bridging anticoagulation, and the aggressiveness of anticoagulation strategies varies in published reviews of this topic. In general, most experts recommend that patients at high risk for thromboembolic events should receive therapeutic-dose (or full-dose) anticoagulant therapy during the period before and after surgery, whereas recommendations in patients at low or moderate risk for thromboembolism are less consistent. Recent surveys of physicians’ current practice patterns regarding bridging anticoagulation reflect these recommendations: over 90% of physicians prefer bridging anticoagulation in patients at high risk for thromboembolism whereas 50-80% of physicians prefer bridging anticoagulation to patients at lower risk.

The overall objective of this monograph is to provide a practical guide for the assessment and management of patients who require temporary interruption of oral anticoagulant therapy for surgery or a non-surgical invasive procedure. We acknowledge there are no randomized controlled trials of bridging anticoagulation to provide definitive, evidence-based practice recommendations. Nonetheless, there is evidence from recent non-randomized trials of bridging anticoagulation that help to inform clinical practice. Our suggested guidelines are based on these studies and on our clinical experience in managing patients who are considered for bridging anticoagulation.

As a convention in this monograph, the term ‘surgery’ refers to patients who are undergoing a surgical procedure that requires an anesthetic, or a non-surgical invasive procedure, such as gastrointestinal endoscopy or a dental procedure, in which a general anesthetic is not required. In addition, we will use warfarin to represent oral anticoagulants (vitamin K antagonists).
Objectives

1) To provide a practical guide that clinicians and other health care providers can use for the management of patients who require temporary interruption of warfarin for surgery.

2) To identify patient groups at increased risk for thromboembolic events, in whom peri-operative bridging anticoagulation with LWMH or UFH should be considered.

3) To identify patient groups who are at increased risk for post-operative bleeding in whom anticoagulation should be used with caution.

4) To address frequently encountered questions in patients who are receiving warfarin therapy and require management of peri-operative anticoagulation.
Frequently-Asked Questions

General Issues

1) What is ‘bridging anticoagulation’?

Bridging anticoagulation refers to the administration of therapeutic-dose (or full-dose) anticoagulant therapy with LMWH or UFH for the 8 to 10 day period before and after surgery, during which time warfarin therapy is interrupted and its anticoagulant effect is below the target therapeutic range. The use of a short-acting anticoagulant, such as LMWH or UFH, in the peri-operative period allows an anticoagulant effect to be present until just before surgery, and allows the resumption of therapeutic anticoagulation within 24 hours after surgery, at the earliest. This management approach minimizes the time period that patients are not receiving therapeutic-dose anticoagulation in the peri-operative period and, therefore, is intended to minimize the risk of potentially devastating thromboembolic events due to sub-therapeutic anticoagulation, such as a stroke, systemic embolism or prosthetic heart valve thrombosis.

2) In which patients should bridging anticoagulation be considered?

There are no universally accepted guidelines as to which patients who require interruption of warfarin therapy should receive bridging anticoagulation. In general, bridging anticoagulant should be considered in patients at moderate or high risk for developing a thromboembolic event. Bridging anticoagulation is optional in patients at low risk for a thromboembolic event.

3) Can patients undergo surgery or other invasive procedure without interruption of warfarin therapy?

Although there are no clinical trials addressing this issue, most surgeons prefer that warfarin therapy is interrupted prior to a surgical or other non-surgical invasive procedure to allow normal or near-normal hemostasis at the time of the procedure and, thereby, minimize the risk for bleeding. However, some physicians consider that the risk for bleeding has been overstated and suggest that warfarin therapy does not require interruption prior to many procedures. Ultimately, a discussion with the attending surgeon or interventionist will guide whether interruption of warfarin is required since for many procedures, such as cataract surgery or dental extractions, warfarin therapy can be continued without interruption.

4) What is the traditional approach to bridging anticoagulation?

This involves hospitalizing patients 4-5 days before surgery to stop warfarin and start intravenous UFH while the anticoagulant effect of warfarin recedes. UFH is stopped, typically, 3-4 hours before the procedure to avoid a residual anticoagulant effect at the time of the procedure. After the procedure, warfarin and UFH are resumed within 24 hours, the later for 4-5 days until therapeutic anticoagulation with warfarin is re-established. Because of unpredictable pharmacokinetics, use of UFH requires once- or twice-daily laboratory monitoring with activated partial thromboplastin time (aPTT) testing. Intravenous UFH is no longer widely used for bridging anticoagulation because of constraints on hospital bed availability and the increasing number of surgical and other invasive procedures performed without hospitalization or with a short, overnight, hospitalization.
5) **Why is a more novel approach to bridging anticoagulation with LMWH more appealing?**

LMWH therapy is more convenient for peri-operative anticoagulant management because it can be administered as a fixed, weight-adjusted subcutaneous injection, without the need for laboratory monitoring. Consequently, the use of LMWH as bridging anticoagulant therapy obviates the need for hospitalization for peri-operative anticoagulation, and can simplify patient care. Furthermore, this strategy has the potential to substantially reduce health care costs.

6) **What are current consensus recommendations regarding bridging anticoagulation?**

Consensus groups that include the American College of Cardiology /American Heart Association Task Force on Practice Guidelines and the American College of Chest Physicians recommend bridging anticoagulant therapy in patients at 'high risk' for thromboembolism, although the definition of such 'high-risk' patients is not clear. In patients at low or moderate risk for thromboembolism, there are no clear guidelines regarding the need for bridging anticoagulation.

7) **What are current recommendations from experts regarding bridging anticoagulation?**

Among thrombosis experts, there is no consensus as to which patients should receive bridging anticoagulation. Some experts have argued that, with the exception of a minority of patients who have had a thromboembolic event within the preceding month, the risk of thromboembolism during the period of warfarin interruption has been overstated, and is outweighed by the risk of postoperative bleeding due to bridging anticoagulation. Other authorities do not specify which patients should receive bridging anticoagulation. There is agreement, however, on the need for randomized trials of bridging anticoagulation strategies to better inform clinical practice.

8) **What is the current practice of physicians in regards to bridging anticoagulation?**

Based on recent surveys of physician practices regarding bridging anticoagulation, as outlined in Table 1, it appears that over 90% of physicians prefer bridging anticoagulation with therapeutic-dose LMWH or UFH in 'high-risk' patients, whereas 40-80% of physicians prefer bridging anticoagulation in low to moderate risk patients.

9) **What is the evidence that temporary interruption of warfarin increases the risk for thromboembolism?**

There are no prospective trials to assess the risk for thromboembolism during temporary interruption of warfarin when bridging anticoagulation is not administered. Consequently, there are no reliable estimates of the risk for thromboembolism when warfarin is simply stopped and re-started but without intervening bridging anticoagulation. It has been postulated, however, that temporary interruption of warfarin or aspirin may result in a rebound hypercoagulable state, through mechanisms that include increased thrombin generation and platelet hyper-reactivity. Furthermore, such effects may be compounded by the prothrombotic biochemical milieu that can occur during the intra-operative and immediate post-operative period.
To date, there are no randomised controlled trials assessing different bridging anticoagulation management strategies. In recent years, however, there have been several non-randomised trials, summarized in Table 2, assessing the use of LMWH as bridging anticoagulation in patients who require temporary warfarin interruption19-23. In general, these trials found that the use of LMWH as bridging anticoagulation appears safe and there appears to be a low risk (<2%) of thromboembolic events with this management strategy. The main limitation of these studies is the lack of a comparison group in which a pre-specified bridging anticoagulation strategy, such as pre- and post-operative LMWH, is compared to other peri-operative management strategies.

Patient Stratification According to the Risk of Thromboembolism

11) What patient groups are considered to be at moderate to high risk of a thromboembolic event, in whom bridging anticoagulation should be considered?

The risk of a thromboembolic event is dependent on the underlying disease in which warfarin therapy is indicated, and the presence or absence of additional thromboembolic risk factors. Patients with a mechanical heart valve, chronic atrial fibrillation, and venous thromboembolism are classified in Table 3, Table 4, and Table 5, respectively according to the risk (i.e., high, moderate, or low) of thromboembolism during temporary interruption of warfarin therapy.

12) Should all patients with a mechanical prosthetic heart valve receive bridging anticoagulant therapy?

Bridging anticoagulant therapy should be considered in patients with a mechanical prosthetic heart valve who are at high or moderate risk for stroke or valve thrombosis (Table 3). In such patients, the risk of a thromboembolic event is determined by the type and position of the prosthetic valve, and the presence of additional risk factors for stroke and intra-cardiac thrombosis.56,14,36

In patients who are probably at high risk for thromboembolism, such as those with a recent (within 3 months) stroke or transient ischemic attack (TIA), a mitral valve prosthesis, or an older aortic valve prosthesis (e.g., caged-ball, tilting disc), bridging anticoagulation is recommended. In patients at moderate risk for thromboembolism, such as those with a newer aortic valve prosthesis (e.g., bileaflet) and ≥2 stroke risk factors, bridging anticoagulation should be considered. Finally, in patients who are probably at low risk for thromboembolism, such as those with a newer aortic or INR levels before surgery.

13) Should all patients with chronic atrial fibrillation receive bridging anticoagulant therapy?

Bridging anticoagulation should be considered in selected patients with chronic atrial fibrillation who are at high or moderate risk for stroke (Table 4). High-risk patients include those with a recent (within 3 months) stroke or TIA, and patients with rheumatic valvular heart disease.37,28 Recently, a scoring system (CHADS) was developed to assess risk for stroke in patients with nonvalvular atrial fibrillation.39 The score is calculated based on the number of risk factors a patient has: a prior stroke or TIA counts as 2
points; congestive heart failure, hypertension, diabetes, and age >75 years each count as 1 point. Bridging anticoagulation would be recommended in patients with a CHADs score of 5-6, who are at high risk for stroke, and should be considered in patients with a score of 3-4, who are at moderate risk for stroke. In low-risk patients, with a score <3, bridging anticoagulation is optional and probably not needed.

<table>
<thead>
<tr>
<th>CHADs Score</th>
<th>Risk Category</th>
<th>Annual (%) Risk for Score (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>low</td>
<td>1.9 (1.2 - 3.0)</td>
</tr>
<tr>
<td>1</td>
<td>low</td>
<td>2.8 (2.0 - 3.8)</td>
</tr>
<tr>
<td>2</td>
<td>low</td>
<td>4.0 (3.1 - 5.1)</td>
</tr>
<tr>
<td>3</td>
<td>moderate</td>
<td>5.9 (4.6 - 7.3)</td>
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<tr>
<td>4</td>
<td>moderate</td>
<td>8.5 (6.3 - 11.1)</td>
</tr>
<tr>
<td>5</td>
<td>high</td>
<td>12.5 (8.2 - 17.5)</td>
</tr>
<tr>
<td>6</td>
<td>high</td>
<td>18.5 (10.5 - 27.4)</td>
</tr>
</tbody>
</table>

14) Should all patients with venous thromboembolism receive bridging anticoagulant therapy?

Bridging anticoagulant therapy should be considered in selected patients with venous thromboembolism (deep vein thrombosis and pulmonary embolism) who are at high or moderate risk of disease recurrence (Table 5). Bridging anticoagulation would be recommended in high-risk patients who have had a recent (within 3 months) episode of venous thromboembolism, and considered in moderate risk patients who have an antiphospholipid antibody, a deficiency in protein C, protein S or antithrombin, or active malignant disease (metastatic or treated within 6 months). In low-risk patients who do not satisfy these criteria, bridging anticoagulation is optional and probably not needed.

15) What about patients who had thromboembolism during prior interruption of warfarin therapy?

Such patients may warrant special consideration despite the lack of data pertaining to the risk of thromboembolism during subsequent episodes of warfarin interruption. Patient and physician concern about recurrent thromboembolism may warrant the need for bridging anticoagulation, irrespective of the baseline risk as determined by discussed in Questions 12 to 14.

16) What patient groups are considered to be at increased risk of postoperative bleeding?

The risk of postoperative bleeding in patients can be estimated based on surgical and non-surgical factors. Non-surgical factors include uremia, thrombocytopenia or a coagulation factor deficiency, active peptic ulcer disease and a recent bleeding episode. The type of surgery is an important consideration in determining a patient's postoperative bleeding risk. In Table 6, an overview is provided of the bleeding risk associated with different types of surgery.
Anticoagulant Management Before Surgery

17) When should patients be assessed for bridging anticoagulation?

Ideally, patients should be assessed 7-10 days prior to an elective surgical procedure to allow enough time for the warfarin anticoagulant effect to recede. Adequate time before surgery is also required to instruct patients about LMWH self-injection and to arrange for laboratory testing on the day before surgery, so as to ensure a normalized INR at the time of the procedure.

18) How many days prior to surgery should anticoagulant therapy be stopped so there is no residual anticoagulant effect at the time of surgery?

Although the pharmacokinetic properties of warfarin differ between patients, stopping warfarin 4 to 5 days before surgery will, in the vast majority of patients, ensure that there is normal hemostasis at the time of surgery; with an INR <1.3.45. Elderly patients may require a longer time for the INR to normalize after warfarin is stopped. In patients who are receiving warfarin with a target INR of 2.0 to 3.0, we recommend that warfarin is stopped 5 days before surgery (see Figure 1).

19) What about stopping warfarin in patients who have a target INR of 2.5 to 3.5?

In such patients, warfarin should be stopped 6 days before surgery, especially if the most recent INR was in the upper part of the therapeutic range or above 3.5. This will allow additional time for the INR to drift into the normal range.

20) What about patients who are receiving a coumarin derivative such as phenprocoumon?

Although there is no known therapeutic advantage to using phenprocoumon or other coumarin derivatives over warfarin, there are implications for bridging anticoagulation. Phenprocoumon has a longer half-life than warfarin (~4 days vs. ~2 days) and, consequently requires a longer time after treatment is interrupted for its anticoagulant effect to be eliminated. In patients who are receiving phenprocoumon and require surgery, this treatment should be stopped 8 to 10 days prior to the procedure, thereby warranting consideration for a longer period of bridging anticoagulation.

21) Should you always check the INR before surgery to make sure that it has normalized?

We routinely measure the INR the day before surgery to make sure that it has normalized (i.e., INR = 1.3) or is near normalized (i.e., INR = 1.4). This is done because patients with a moderately elevated INR of 1.5 or higher are at increased risk of postoperative bleeding complications. Thus, if the INR is 1.5 or higher, we administer 1 mg of vitamin K orally. This will ensure that the INR normalizes by the time of surgery. Furthermore, this small dose of vitamin K is not likely to interfere with re-anticoagulation when warfarin therapy is resumed after surgery. In patients who receive vitamin K, it is also reasonable to measure the INR on the morning of surgery to 'double-check' that the INR has normalized.
22) Why not just measure the INR on the morning of surgery?

If the INR is measured only on the morning of surgery, there is a small chance that a patient will have an INR level that is too high to allow surgery (i.e., INR = 1.5). In such patients, vitamin K will not rapidly reverse the elevated INR, and the patient will require 2 to 4 units of fresh frozen plasma to normalize the INR. However, transfusion of blood products in this circumstance is avoidable with appropriate monitoring of INR levels before surgery.

23) If patients are also receiving an antiplatelet drug, when should this be stopped?

Patients who are receiving warfarin may also be receiving treatment with an antiplatelet drug, usually ASA, 81 mg daily, or clopidogrel, 75 mg daily. Since ASA and other antiplatelet drugs such as clopidogrel irreversibly inhibit platelet function, ASA should be stopped 7-10 days (average lifespan of a platelet) prior to the planned surgery or invasive procedure to ensure normal hemostasis at the time of the procedure (see Figure 1).

24) If bridging anticoagulant therapy with LMWH is used, when should it be started before surgery?

Bridging anticoagulation with LMWH, typically, is started 3 to 4 days before surgery, when a patient's INR is below or is expected to be below the lower limit of the target therapeutic range. In most patients with a mechanical heart valve who have a target INR of 2.5-3.5, bridging anticoagulation can be started when the INR is <2.5, whereas in patients with chronic atrial fibrillation or venous thromboembolism, it can be started when the INR is <2.0.

In many instances, one will not know when the INR 'drifts below the therapeutic range', unless daily INR testing is done after stopping warfarin, which is impractical. It is reasonable to estimate when the INR will be below the therapeutic range, and when LMWH should be started. For example, if INR testing is done 5 days before the planned surgery and the INR level is 3.0 on that day, it is reasonable to assume that the INR level will be sub-therapeutic (i.e., INR <2.5) 2 days later. Thus, LMWH can be started empirically 2 days after warfarin is stopped.

LMWHs should be used with caution in patients with renal insufficiency. LMWHs are primarily cleared by the kidney and may accumulate in patients with impaired renal function, with the potential for an excessive anticoagulant effect and intra-operative bleeding. Thus, renal function should be assessed in all patients who are being considered for bridging anticoagulation with LMWH. If LMWH is to be used in such patients, tinzaparin may be the preferred LMWH based on studies in which tinzaparin was safely used for the treatment of venous thromboembolism in patients with impaired renal function. However, there are no studies assessing tinzaparin as bridging anticoagulation in patients with impaired renal function.

25) When should the last dose of LMWH be administered before surgery?

If once-daily LMWH is used as bridging anticoagulant therapy (e.g., tinzaparin, 175 IU/kg once-daily), the dose should be administered in the mornings, and with last pre-operative dose administered on the morning of the day before surgery, and at least 24 hours before surgery. If twice-daily LMWH is used (e.g., enoxaparin, 1 mg /kg twice-daily), the evening dose on the day...
before surgery should be omitted. In this way, the last dose of LMWH will be administered at least 24 hours before surgery.

26) **Should the anticoagulant effect of the LMWH be measured on the day of surgery to ensure no residual anticoagulant effect prior to surgery?**

The anticoagulant effect of LMWH is measured by the anti-factor Xa (or anti-Xa) level. The aPTT does not reliably measure the anticoagulant effect of LMWH. Anti-Xa level testing should not be routinely done in patients who are receiving LMWH because this testing is not available in many hospital or clinic laboratories and the results may not be available for several hours, which is impractical in patients who are scheduled for surgery on the same day. Furthermore, since LMWHs have a predictable pharmacokinetic profile and elimination half-lives of 3-4 hours, there should not be a clinically important residual anticoagulant when the last pre-procedure dose is administered 24 hours prior to surgery.

Anticoagulant Management After Surgery

27) **When should LMWH be restarted after surgery?**

The decision to resume LMWH after surgery is dependent on two factors: 1) Whether there is adequate postoperative hemostasis, and 2) the risk of bleeding associated with the surgical procedure. If there is ongoing bleeding after surgery, as detected by blood accumulation into a surgical drain, the start of LMWH should be deferred until the bleeding has subsided. In general, most postoperative bleeding will resolve within 24 hours after surgery.

If there is adequate postoperative hemostasis after surgery, the decision to resume anticoagulant therapy will depend on the bleeding risk associated with the surgical procedure. In Table 6, we classify different types of surgery according to their risk of postoperative bleeding (high, moderate, low). In patients undergoing surgery that is associated with a high risk of bleeding, such as urologic and neurosurgical procedures, the resumption of LMWH should be deferred for at least 48-72 hours after surgery and, preferably, after discussion with the attending surgeon. In patients undergoing surgery that is associated with a moderate risk of bleeding, such as intra-abdominal surgery, the resumption of LMWH should be delayed until 24-48 hours after surgery. In patients undergoing surgery that is associated with a low risk of bleeding, LMWH can be resumed 24 hours after surgery, usually the day after the procedure.

28) **What dose of LMWH should be used after surgery?**

In general, the same dose regimen used before surgery should be administered after surgery, but the timing of when LMWH is to be resumed after surgery will vary depending on whether there is adequate post-operative hemostasis and risk of bleeding associated with the procedure.

29) **Are there circumstances when LMWH should NOT be given after surgery?**

There may be patients in whom bridging anticoagulation should be considered before but not after surgery. Such patients include those who have had excessive post-operative bleeding or have undergone a procedure associated with a very high risk for bleeding (e.g., intracranial neoplasm, coronary artery bypass surgery). It is always helpful to discuss such high risk patients with the attending surgeon to better understand patient-specific issues relating to bleeding risk and to discuss the initiation of post-operative anticoagulation.
In patients who receive no post-operative LMWH as bridging anticoagulation and in those in whom post-operative LMWH is delayed for 2-3 days or longer, there may be concern that such patients may not be protected against DVT. All patients will be resuming warfarin, administered to achieve a target INR >2.0, and this treatment may be considered adequate prophylaxis against DVT [52]. However, if there are concerns that warfarin alone may be insufficient as stand-alone treatment to prevent DVT, because of a delayed anticoagulant effect, it is reasonable to administer prophylactic-dose (or low-dose) LMWH, assuming this does not pose a major bleeding risk, for the 3-5 days after surgery until the INR is within the therapeutic range.

The assessment of postoperative bleeding is subjective and will vary depending on the type of surgery [19,53]. For example, patients who undergo prostatectomy routinely have postoperative hematuria, and this may persist for 24 to 72 hours after surgery. In such patients, it is prudent to withhold LMWH until the hematuria is subsiding, that is, when the urine becomes pink-coloured. In patients who undergo neurosurgery, a small amount of bleeding may be associated with serious complications such as intracranial hemorrhage. In such patients, anticoagulation should be delayed for at least 24 to 48 hours after surgery. In general, we recommend consultation with the surgeon to assess if there is excessive bleeding after surgery, and to help guide decisions about the resumption of anticoagulant therapy.

In patients who develop postoperative major bleeding, defined by the need for transfusion of >2 units of packed red blood cells, need for re-operation or serious bleeding (eg., intra-cranial, intra-thoracic, retroperitoneal), all anticoagulants should be withheld until the bleeding source has been identified and treated. Treatment to reverse the effect of antithrombotic therapy may include one or more of the following: fresh frozen plasma; recombinant coagulation factor VII; platelets; protamine sulfate.

The resumption of anticoagulants is superseded by the need to prevent further bleeding. If the cause of the bleeding is readily reversible, as with the repair of a severed blood vessel that inadvertently occurred during surgery, anticoagulants probably can be resumed within 24 hours. On the other hand, if the bleeding is unlikely to resolve quickly, as with a large gastric ulcer, the resumption of anticoagulants should be deferred for one to two weeks, or longer, depending on the size of the ulcer and whether there was active bleeding at the time of the gastroscopy [54,55]. Repeat gastroscopy may be warranted 1-2 weeks after starting anti-ulcer therapy to ensure ulcers have healed sufficiently and are unlikely to re-bleed if anticoagulation is restarted.

30) What about preventing deep vein thrombosis in patients in whom post-operative LMWH is delayed or not given at all?

31) What is considered excessive post-operative bleeding?

32) How should patients be managed when they have unexpected postoperative bleeding?
33) *When should warfarin be restarted after surgery, assuming adequate postoperative hemostasis?*

In most patients, warfarin can be restarted on the evening after surgery. A significant anticoagulant effect of warfarin will not occur until 24 hours after the initial dose of warfarin, and a full anticoagulant effect will not occur for 4 to 5 days after the start of warfarin. Consequently, the resumption of warfarin on the evening after surgery should not affect postoperative hemostasis.

34) *What is the usual starting dose of warfarin after surgery?*

In general, we administer 5 mg of warfarin on the evening after surgery. If a patient usually receives a higher or lower daily dose of warfarin, it is reasonable to start re-anticoagulation with that dose (see Figure 1).

35) *What if a patient is using an irregular dose regimen of warfarin?*

Some patients who receive warfarin therapy require an irregular dosing regimen, such as 7.5 mg on Mondays, Wednesdays, and Fridays, and 5 mg on the other days of the week. In such patients, it is reasonable to resume warfarin so the usual day-to-day sequence of warfarin dosing is maintained. For example, if the aforementioned patient had surgery on a Tuesday, the first dose of warfarin would be 5 mg the evening after surgery, followed by 7.5 mg the next day. Resuming a patient’s usual warfarin dose regimen after surgery will minimize uncertainty about warfarin dosing for the patient, and is less likely to result in dose errors.

36) *Does the post-operative dose of warfarin change if a patient required vitamin K before surgery?*

If a patient received high-dose vitamin K before surgery (i.e., 5 to 10 mg), this may result in resistance to re-anticoagulation when warfarin is resumed. Because it is difficult to predict the warfarin dose requirements of such patients, we administer double their usual dose of warfarin for two consecutive days after surgery. In addition, we monitor the INR more frequently after surgery to detect persistently low INR levels, if they occur, and to adjust the dose of warfarin accordingly. If low-dose vitamin K is administered before surgery (i.e., 1 to 2 mg), resistance to re-anticoagulation is unlikely. Nonetheless, it is reasonable to double the first dose of warfarin in such patients, and to resume the usual dose of warfarin on the following day.

37) *When should the LMWH be stopped after surgery?*

LMWH should be stopped when a patient’s INR level is within the target therapeutic range. Preferably, INR testing should be done on day 3, and day 5 after surgery. The timing of postoperative INR testing may vary by one day earlier or later, depending on the day of the week that the surgery was done and patient availability for blood testing. In most patients, with a target INR of 2.0-3.0, LMWH will be required for 3 to 4 days after surgery, and in patients with a target INR of 2.5-3.5, 4 to 5 days of LMWH will be required.

38) *Is it necessary to measure the aPTT after surgery?*

Measuring the aPTT testing after surgery is not necessary when a patient is receiving LMWH because the aPTT test does not measure the anticoagulant effect of LMWH.
When should antiplatelet therapy be resumed after surgery?

In general, antiplatelet therapy such as ASA can be resumed on the same day as warfarin.

Specialized Patient Groups

How do I manage anticoagulation in a patient who has an indwelling epidural catheter that is used to administer analgesia after surgery?

The anticoagulant management of patients with an indwelling epidural catheter is problematic because of concerns that such patients might develop an epidural haematoma, which is a rare but devastating complication. In general, the epidural catheter should be removed before LMWH is started after surgery. In our practice, we are comfortable administering LMWH while a patient is also receiving continuous epidural analgesia through an indwelling epidural catheter if the following criteria are satisfied:

i) epidural catheter placement was not traumatic

ii) only low-dose, once-daily, LMWH is administered (as outlined in Table 5)

iii) warfarin therapy is not started until after the epidural catheter is removed

iv) the epidural catheter is removed during the trough anticoagulant effect of the LMWH, corresponding to 18 to 22 hours after the preceding dose

v) other drugs that impair haemostasis, such as aspirin or NSAIDs, are avoided until the epidural catheter is removed

What about anticoagulant management in patients who receive spinal (regional) anaesthesia and have the epidural catheter removed immediately after surgery?

If the epidural catheter was used only to administer intra-operative anaesthesia and was removed after surgery, it is safe to resume anticoagulant therapy within 12 hours of surgery. However, if the epidural catheter placement was traumatic, the resumption of anticoagulant therapy probably should be delayed for at least 24 hours after surgery.

Are there patients in whom one should consider UFH (standard heparin) instead of LMWH for bridging anticoagulant therapy?

In patients with moderate-to-severe renal insufficiency, defined by a serum creatinine >150 mmol/L or a creatinine clearance <40 mL/min, UFH is the anticoagulant of choice because its clearance will not be significantly impaired in the presence of renal insufficiency. On the other hand, LMWH is eliminated primarily by the kidney and, therefore, can accumulate in patients with renal insufficiency, with the potential to cause bleeding complications after surgery.

If LMWH must be used in such patients with moderate-to-severe renal insufficiency, the anticoagulant effect of LMWH should be measured with anti-Xa levels done 4 hours after the LMWH dose. The targeted therapeutic anti-Xa level with LMWH is 0.5 to 1.0 anti-Xa units/mL. In regard to the choice of a LMWH, there are differences in LMWH preparations that may favour the use of tinzaparin in such patients. In 2 studies of elderly patients with age-associated renal impairment, treatment with tinzaparin 175 IU/kg for 10 days was not associated with an excessive anticoagulant effect or an increased risk for bleeding complications. This observation is in contrast to findings reported with other LMWH preparations, suggesting that the renal clearance differs between LMWH preparations.
43) **How does one manage peri-operative anticoagulation in a patient with renal insufficiency?**

If UFH is used for bridging anticoagulant therapy, the conventional approach is to administer UFH intravenously in the peri-operative period, which requires that patients are hospitalized for about 3 to 4 days before and 3 to 4 days after surgery. If intravenous UFH is used pre-operatively, the infusion should be stopped at least 4 hours before surgery. In the post-operative period, intravenous UFH can be resumed 12 to 24 hours after surgery. However, we avoid using a standardized heparin nomogram because of the unpredictable dose-response effect with UFH and the potential that patients will develop a very high aPTT (i.e., >150 seconds) that might increase the risk of bleeding complications [63]. Instead, we use a more conservative dosing regimen of intravenous UFH, with a target aPTT of 45 to 60 seconds rather than the target aPTT of 60 to 80 seconds as used with a heparin nomogram.

The disadvantage of this approach is that it requires physician adjustment of the UFH infusion rate. An alternative approach for peri-operative UFH administration is to administer UFH with twice-daily subcutaneous injections, which would allow outpatient treatment. However, this management approach also requires daily aPTT testing 6 hours after the morning UFH dose to monitor the anticoagulant effect, and to adjust the dose of subcutaneous UFH.

44) **What about the patient with renal insufficiency in whom intravenous UFH is not feasible?**

In such patients, management options include the use of subcutaneously administered UFH. This can be done with by using a standard dose of 15,000 to 17,500 IU twice-daily and measuring the mid-interval aPTT 6 hours after preceding dose of UFH, with the target aPTT 1.5-2.0 times the control value. An emerging alternative approach to administer UFH is a weight-based, fixed-dose regimen of UFH, 250 IU/kg, without the need to aPTT monitoring.

LMWHs can be administered with caution in patients who have impaired renal function and, probably, with laboratory monitoring of anti-Xa levels 4 hours after the LWMH dose and with the anti-Xa level to not exceed 1.0 anti-Xa units/mL. If this is done, there is evidence that tinzaparin is the LMWH-of-choice since it appears to be safer in patients with impaired renal function, possible because it is less dependent on renal elimination than other LMWHs.

45) **What about LMWH dosing in the obese patient?**

In obese patients, who typically weigh >100 kg, there is uncertainty as to whether the dose of LMWH for bridging anticoagulation should be 'capped' at a maximum dose or if the dose should be based on body weight without capping. For example, in a 120 kg person, the capped dose of the LMWH tinzaparin would be 18,000 IU whereas the weight-based dose would be 21,000 IU. Although there are no studies comparing 'capped' vs. 'weight-based' dosing in obese patients, recent trials have found 'weight-based' dosing with tinzaparin (175 IU/kg) was safe, with no increase in bleeding, and not associated with an excessive anticoagulant effect. In the peri-operative setting, most trials have used a 'capped' dosing, possibly because of concerns of an excessive anticoagulant effect in a susceptible patient group that is undergoing surgery.
Heparin-induced thrombocytopenia (HIT) is an immune-mediated thrombocytopenia that occurs in patients who have received UFH and is associated with thrombotic complications that include venous limb gangrene, stroke, and myocardial infarction. In patients with prior HIT, all heparin preparations, including LMWHs, should be avoided. In such patients, danaparoid, a low-molecular-weight heparinoid that has minimal cross-reactivity with UFH is a safe alternative anticoagulant. The dose of danaparoid is 1250-2500 IU twice-daily subcutaneously, starting on the day after surgery. One limitation of danaparoid is that, like LMWHs, it is cleared by the kidneys and should be avoided or used with caution in patients with renal insufficiency.

Since danaparoid is not available in some countries, there are 2 alternative anticoagulants for the treatment of HIT: argatroban and lipirudin.

Argatroban is a direct thrombin inhibitor that is given intravenously, with a starting dose of 2 mg/kg/min, to achieve a target aPTT of 1.5- to 3.0-times the baseline aPTT. Argatroban is cleared by the liver and should be avoided or used with caution in patients with impaired hepatic function. It has a half-life of 40-50 minutes, thereby allowing rapid elimination from the circulation after the infusion is stopped. Because argatroban prolongs the INR, care should be taken when argatroban is used as bridging anticoagulant after temporary interruption of warfarin.

Lepirudin (recombinant hirudin) is a direct thrombin inhibitor that is given intravenously or subcutaneously with a loading dose of 0.4 mg/kg over 15 to 20 minutes followed by a continuous infusion of 0.15 mg/kg/hr for 2-10 days. Lepirudin can also be administered by subcutaneous injection. Lepirudin is cleared by the kidney and should be avoided or used with caution in patients with impaired renal function. It has a half-life of 80 minutes, thereby allowing relatively rapid elimination after the infusion is stopped.

There should be no difference in the anticoagulant management of patients who are hospitalized and those who have outpatient surgery. Hospitalized patients are likely to undergo more frequent blood testing, as part of routine postoperative care. Consequently, it is reasonable to perform more frequent INR and hemoglobin testing while a patient is hospitalized. Peri-operative management of anticoagulation in an outpatient setting has been shown to reduce health care costs.

The management of warfarin therapy in low-risk patients who do not require bridging anticoagulant therapy with LMWH is similar to that of patients who receive bridging anticoagulant therapy. Thus, warfarin should be stopped 5 to 6 days before surgery, with INR testing performed on the day before surgery. Warfarin can be restarted on the day of surgery if there is adequate postoperative hemostasis. The dose of warfarin after surgery should be the same as that which the patient was receiving before its interruption. Because the INR level will not be used to guide discontinuation of LMWH, these patients do not

46) **How do I manage the patient with a history of heparin-induced thrombocytopenia?**

Heparin-induced thrombocytopenia (HIT) is an immune-mediated thrombocytopenia that occurs in patients who have received UFH and is associated with thrombotic complications that include venous limb gangrene, stroke, and myocardial infarction. In patients with prior HIT, all heparin preparations, including LMWHs, should be avoided. In such patients, danaparoid, a low-molecular-weight heparinoid that has minimal cross-reactivity with UFH is a safe alternative anticoagulant. The dose of danaparoid is 1250-2500 IU twice-daily subcutaneously, starting on the day after surgery. One limitation of danaparoid is that, like LMWHs, it is cleared by the kidneys and should be avoided or used with caution in patients with renal insufficiency.

47) **What other approved treatment options are available for the management of patients with HIT?**

Since danaparoid is not available in some countries, there are 2 alternative anticoagulants for the treatment of HIT: argatroban and lipirudin.

**Argatroban** is a direct thrombin inhibitor that is given intravenously, with a starting dose of 2 mg/kg/min, to achieve a target aPTT of 1.5- to 3.0-times the baseline aPTT. Argatroban is cleared by the liver and should be avoided or used with caution in patients with impaired hepatic function. It has a half-life of 40-50 minutes, thereby allowing rapid elimination from the circulation after the infusion is stopped. Because argatroban prolongs the INR, care should be taken when argatroban is used as bridging anticoagulant after temporary interruption of warfarin.

**Lepirudin** (recombinant hirudin) is a direct thrombin inhibitor that is given intravenously or subcutaneously with a loading dose of 0.4 mg/kg over 15 to 20 minutes followed by a continuous infusion of 0.15 mg/kg/hr for 2-10 days. Lepirudin can also be administered by subcutaneous injection. Lepirudin is cleared by the kidney and should be avoided or used with caution in patients with impaired renal function. It has a half-life of 80 minutes, thereby allowing relatively rapid elimination after the infusion is stopped.

48) **Does the overall anticoagulant management differ in patients who have outpatient surgery and those who are hospitalized?**

There should be no difference in the anticoagulant management of patients who are hospitalized and those who have outpatient surgery. Hospitalized patients are likely to undergo more frequent blood testing, as part of routine postoperative care. Consequently, it is reasonable to perform more frequent INR and hemoglobin testing while a patient is hospitalized. Peri-operative management of anticoagulation in an outpatient setting has been shown to reduce health care costs.

49) **How should warfarin therapy be managed in patients at low risk of thromboembolism in whom LMWH is not used as bridging therapy?**

The management of warfarin therapy in low-risk patients who do not require bridging anticoagulant therapy with LMWH is similar to that of patients who receive bridging anticoagulant therapy. Thus, warfarin should be stopped 5 to 6 days before surgery, with INR testing performed on the day before surgery. Warfarin can be restarted on the day of surgery if there is adequate postoperative hemostasis. The dose of warfarin after surgery should be the same as that which the patient was receiving before its interruption. Because the INR level will not be used to guide discontinuation of LMWH, these patients do not

16
require INR monitoring as frequently after surgery. An INR test can be done 5 days after surgery to ensure that the INR is within the targeted therapeutic range, and to allow subsequent warfarin dose adjustments.

50) What is the anticoagulant management in patients who have major post-operative bleeding?

Patients who develop major postoperative bleeding while receiving bridging anticoagulation should receive a transfusion of red blood cells and other blood products as required after all anticoagulants are withheld. The source of the bleeding should be identified and corrected whenever possible. In patients who already have a prolonged INR due to postoperative warfarin, should receive 2.5-5.0 mg intravenous vitamin K in addition to fresh frozen plasma.

In patients who are receiving UFH or LMWH, protamine sulphate should be given. The dose of protamine is determined by assuming that 1 mg of protamine will neutralize the anticoagulant activity of 100 IU of UFH. In most patients who have received therapeutic-dose UFH, the dose of protamine is 25-50 mg by slow intravenous infusion. Protamine also can be given to partially reverse the anticoagulant effect of LMWH, particularly in a bleeding patient who has received a therapeutic dose of LMWH within 6 to 8 hours. Since the half-life of protamine is less than that of LMWH, additional doses of protamine may be required, every 3-4 hours, until the LMWH is cleared. LMWHs differ in their ability to be neutralized by protamine sulphate due to different degrees of sulfation content, with tinzaparin being most effectively neutralized.

Other Patient-related Issues with Bridging Anticoagulation

51) How easy is it for patients to self-inject LMWH for bridging anticoagulation?

Most patients who are assessed for bridging anticoagulation can be taught to self-inject LMWH and often find it easier than they expected. Showing patients how to administer LMWH through pictures, short videos, or demonstrations is essential to facilitate self-injection. To provide reassurance, patients may be asked to administer the first dose of LMWH under observation of the nurse to ensure that the proper technique is followed.

52) How does one manage patients who have persistently elevated INRs on the day before surgery?

INR testing should be done, whenever feasible, on the day before surgery to ensure a normal INR and to administer low-dose (1 mg) oral vitamin K in patients with an INR >1.5. To facilitate this process, we routinely provide patients with vitamin K (in tablet or liquid form). If INR testing, which is typically done outside of the hospital clinic setting, reveals an INR >1.5 the day before surgery, the patient is instructed to take the vitamin K, thereby ensuring normal hemostasis on the day of surgery and avoiding the administration of blood products or cancellation of surgery if the INR is >1.5 on the day of the procedure.

53) How does one facilitate communication between caregivers involved in a patient who requires temporary interruption of warfarin and is receiving bridging anticoagulation?

The care of patients who require temporary interruption of warfarin for surgery
may involve one or more of the following health care providers: internist, family physician, surgeon, anesthetist, nursing and other allied health care staff. One way to maintain good communication is to transmit a record of the patient assessment to these individuals promptly after the patient is assessed. The increasing availability of an electronic medical record may facilitate this process.

One approach is the use of a standardized computerized patient record which can be completed while the patient is being assessed. This record estimates the patient’s risk for thromboembolism and bleeding and outlines the bridging anticoagulation management plan. This record can be sent by e-mail or fax to all caregivers. A sample medical record is provided in Figure 2. This approach also streamlines care for patients who are seen on multiple occasions for bridging anticoagulation (e.g., yearly surveillance colonoscopy).

54) **How can one ensure that patients follow the instructions for bridging anticoagulation?**

Having patients understand bridging anticoagulation can be challenging as they must understand when to start and stop warfarin, as well as when to start and stop LMWH the timing of the LMWH doses. To facilitate this and minimize patient error, a patient instruction sheet can be provided. As outlined in Figure 1, this provides explicit instructions as to the timing and dose warfarin and LMWH dose to be administered before and after surgery.
### Suggested Bridging Anticoagulation Patient Instructions

<table>
<thead>
<tr>
<th>Date (d/m/y)</th>
<th>Days in relation to surgery</th>
<th>Anticoagulant Management</th>
<th>Blood testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7</td>
<td></td>
<td>STOP aspirin/clopidogrel/ticlopidine</td>
<td></td>
</tr>
<tr>
<td>-6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5</td>
<td></td>
<td>STOP warfarin (i.e., no warfarin on this day)</td>
<td>INR</td>
</tr>
<tr>
<td>-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily</td>
<td></td>
</tr>
<tr>
<td>-2</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily (last dose 24 hours before surgery)</td>
<td>INR</td>
</tr>
<tr>
<td></td>
<td>SURGERY (at bedtime, when there is adequate postoperative hemostasis)</td>
<td>warfarin ____ mg</td>
<td></td>
</tr>
<tr>
<td>+1</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily (at least 24 hours after surgery, when there is adequate postoperative hemostasis)</td>
<td>warfarin ____ mg</td>
</tr>
<tr>
<td>+2</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily</td>
<td>warfarin ____ mg</td>
</tr>
<tr>
<td>+3</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily</td>
<td>warfarin ____ mg</td>
</tr>
<tr>
<td>+4</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily (if required)</td>
<td>warfarin ____ mg</td>
</tr>
<tr>
<td>+5</td>
<td></td>
<td>LMWH ____ units, once- or twice-daily (if required)</td>
<td>warfarin ____ mg</td>
</tr>
</tbody>
</table>
Figure 2. Sample Medical Record

St. Joseph's Healthcare Hamilton McMaster University

Perioperative Bridging Anticoagulation Programme
St. Joseph's Healthcare, Hamilton

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Today's Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referring MD</td>
<td>ID:</td>
</tr>
<tr>
<td>Family MD</td>
<td>DOB:</td>
</tr>
<tr>
<td>Health Card #</td>
<td>INR Lab:</td>
</tr>
<tr>
<td>Telephone #</td>
<td>Allergies:</td>
</tr>
</tbody>
</table>

Date of surgery/procedure

History of presenting illness

Reason for Anticoagulation

<table>
<thead>
<tr>
<th>DVT or PE</th>
<th>Coronary Artery Disease</th>
<th>Peripheral Artery Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>Stroke/Systemic Embolism</td>
<td>Bioprosthetic Heart Valve</td>
</tr>
<tr>
<td>Mechanical Heart Valve</td>
<td>Aortic</td>
<td>Mitral</td>
</tr>
<tr>
<td></td>
<td>Aortic + Mitral</td>
<td></td>
</tr>
</tbody>
</table>

Valve type and insertion date

Start of anticoagulation

Risk Factors for Thromboembolism

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Congestive Heart Failure</th>
<th>Thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>Peripheral Arterial Disease</td>
<td>Age &gt;75 years</td>
</tr>
<tr>
<td>DVT</td>
<td>Coronary Artery Disease</td>
<td>Diabete Mellitus</td>
</tr>
<tr>
<td>PE</td>
<td>Hypertension</td>
<td>Systemic Embolism</td>
</tr>
<tr>
<td>Prior TE in association with warfarin interruption</td>
<td>Active Cancer</td>
<td></td>
</tr>
</tbody>
</table>

Remarks
Risk Factors for Bleeding

<table>
<thead>
<tr>
<th>recent (&lt;6 mos) GI bleed</th>
<th>chronic renal disease</th>
<th>active peptic ulcer disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>recent bleed (other)</td>
<td>chronic liver disease</td>
<td>prior peptic ulcer disease</td>
</tr>
<tr>
<td>prior bleed (any kind)</td>
<td>thrombocytopenia (&lt;100)</td>
<td>age &gt;75 years</td>
</tr>
<tr>
<td>prior bleed in association with surgery/bridging therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>potential for spinal anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>potential for post-procedure epidural analgesia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remarks

Other Relevant Past Medical History

Antithrombotic Therapy

<table>
<thead>
<tr>
<th>ASA</th>
<th>clopidogrel</th>
<th>ticlopidine</th>
<th>ASA-dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td></td>
<td>Other:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>warfarin (current dose)</th>
</tr>
</thead>
</table>

Other Medications

Physical Examination

H&N:
CHEST:
CVS:
ABD:
CNS:
SKIN:

<table>
<thead>
<tr>
<th>Height:</th>
<th>Weight:</th>
</tr>
</thead>
</table>

Remarks
LMWH Administration

| self inject | family member | requires nursing agency |

Laboratory Results

<table>
<thead>
<tr>
<th>Date</th>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td></td>
</tr>
</tbody>
</table>

Thromboembolism Risk Assessment

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding Risk Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
</table>

Assessment and Summary

Bridging Anticoagulation Recommendations

<table>
<thead>
<tr>
<th>No bridging</th>
<th>Last antiplatelet dose</th>
<th>Last warfarin dose</th>
</tr>
</thead>
</table>

Pre-procedure Anticoagulation

Post-procedure Anticoagulation

Signature

James D. Douketis MD, FRCP(C)
Table 1. Physician Practice Patterns for Bridging Anticoagulation

<table>
<thead>
<tr>
<th>Survey Year (reference)</th>
<th>Patient Group</th>
<th>Pre-procedure preference</th>
<th>Post-procedure preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998¹</td>
<td>mech. mitral valve mec. aortic valve</td>
<td>89–92% 61–66%</td>
<td>89–90% 51–72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>1998¹⁶</td>
<td>atrial fibrillation</td>
<td>n/a 55–80%</td>
<td>n/a 38–77%</td>
</tr>
<tr>
<td>2002¹⁷</td>
<td>mech. mitral valve mec. aortic valve</td>
<td>95–96% 67–76%</td>
<td>61–89% 61–72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2003¹⁸</td>
<td>mech. mitral valve mec. aortic valve</td>
<td>94–95% 53–65%</td>
<td>75–81% 32–45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Table 2. Arterial Thromboembolism and Major Bleeding in Uncontrolled Trials of Bridging Anticoagulation with LMWH

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Number of patients</th>
<th>Patient follow-up (months)</th>
<th>LMWH</th>
<th>Reason for anticoagulation</th>
<th>Incidence of ATE</th>
<th>Incidence of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis¹⁹</td>
<td>650</td>
<td>0.5</td>
<td>dalteparin</td>
<td>AF, MHV</td>
<td>0.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Kovaes²⁰</td>
<td>224</td>
<td>3</td>
<td>dalteparin</td>
<td>AF, MHV</td>
<td>1.3%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Dunn²¹</td>
<td>200</td>
<td>1</td>
<td>enoxaparin</td>
<td>AF</td>
<td>2.3%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Spyropoulos²²</td>
<td>595</td>
<td>1</td>
<td>tinzaparin, dalteparin, enoxaparin</td>
<td>AF, MHV</td>
<td>0.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Turpie²³</td>
<td>220</td>
<td>3</td>
<td>enoxaparin</td>
<td>MHV</td>
<td>0.5%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
Table 3. Perioperative Anticoagulant Management in Patients with a Mechanical Heart Valve

<table>
<thead>
<tr>
<th>Thromboembolism Risk Category</th>
<th>Patient Characteristics</th>
<th>Suggested Anticoagulant Management</th>
</tr>
</thead>
</table>
| High Risk                     | - recent (within 3 months) stroke or TIA  
- any mitral valve  
- caged-ball* or tilting-disc† aortic valve | - bridging anticoagulant therapy strongly recommended |
| Moderate Risk                 | - bileaflet‡ aortic valve and ≥ 2 stroke risk factors | - bridging anticoagulant therapy should be considered |
| Low Risk                      | - bileaflet‡ aortic valve and <2 stroke risk factors | - bridging anticoagulant therapy is optional |

Legend:
*Starr-Edwards valve; †Bjork-Shiley, Medtronic-Hall or Omnicarbon valve; ‡St.Jude or Carbomedics valve.

Stroke Risk Factors
- chronic atrial fibrillation  
- left ventricular dysfunction  
- age > 75 years  
- hypertension  
- diabetes mellitus

Table 4. Perioperative Anticoagulant Management in Patients with Chronic Atrial Fibrillation

<table>
<thead>
<tr>
<th>Thromboembolism Risk Category</th>
<th>Patient Characteristics</th>
<th>Suggested Anticoagulant Management</th>
</tr>
</thead>
</table>
| High Risk                     | - recent (within 3 months) stroke or TIA  
- rheumatic mitral valvular heart disease  
- CHADS score of 5 or 6 | - bridging anticoagulant therapy strongly recommended |
| Moderate Risk                 | - CHADS score of 3 or 4 | - bridging anticoagulant therapy should be considered |
| Low Risk                      | - chronic AF and CHADS score of <3 | - bridging anticoagulant therapy is optional |

Legend:
AF = atrial fibrillation, *stroke risk factors (see below).

Stroke Risk Factors
- previous stroke or transient ischemic attack  
- left ventricular dysfunction  
- age > 75 years  
- hypertension  
- diabetes mellitus
### Table 5. Perioperative Anticoagulant Management in Patients with Venous Thromboembolism

<table>
<thead>
<tr>
<th>Thromboembolism Risk Category</th>
<th>Patient Characteristics</th>
<th>Suggested Anticoagulant Management</th>
</tr>
</thead>
</table>
| High Risk                     | - recent (within 1 month) episode of VTE  
- active cancer* or antiphospholipid antibody†  
- VTE within 6 months  
- previous VTE occurring after surgery  
- none of the above factors present | - bridging anticoagulant therapy strongly recommended |
| Moderate Risk                 | - VTE within 6 months  
- previous VTE occurring after surgery | - bridging anticoagulant therapy should be considered |
| Low Risk                      | - none of the above factors present | - bridging anticoagulant therapy is optional |

**Legend:**  
VTE = venous thromboembolism (includes deep vein thrombosis and pulmonary embolism); *cancer that has been treated within the past 6 months or is palliative; †anticardiolipin antibody or lupus anticoagulant.

### Table 6. Surgery Bleeding Risk Classification and Postoperative Anticoagulation

<table>
<thead>
<tr>
<th>Bleeding Risk Category</th>
<th>Surgery or Invasive Procedure</th>
<th>Timing of Postoperative Anticoagulation</th>
<th>Warfarin</th>
<th>LMWH</th>
</tr>
</thead>
</table>
| Very High Risk         | - intracranial surgery  
- spinal surgery  
- coronary artery bypass surgery  
- heart valve replacement | first or second day after surgery >72 hours after surgery or consider no post-operative LMWH | first or second day after surgery >72 hours after surgery or consider no post-operative LMWH |
| High Risk              | - major vascular surgery  
- permanent pacemaker insertion  
- internal defibrillator placement  
- prostatectomy  
- bladder tumour resection  
- lung resection surgery  
- hip/knee joint replacement surgery  
- intestinal anastomosis surgery  
- bowel polypectomy  
- kidney or prostate biopsy  
- cervical cone biopsy | evening of the day of surgery 24 to 48 hours after surgery | evening of the day of surgery 24 to 48 hours after surgery |
| Moderate Risk          | - other intra-abdominal surgery  
- other intra-thoracic surgery  
- other orthopaedic surgery  
- dental surgery | evening of the day of surgery 24 to 48 hours after surgery | evening of the day of surgery 24 to 48 hours after surgery |
| Low Risk               | - cataract extraction  
- most cutaneous surgery  
- laparoscopic cholecystectomy or hernia repair  
- single dental extraction | evening of the day of surgery 24 after surgery (i.e., day after surgery) | evening of the day of surgery 24 after surgery (i.e., day after surgery) |
Table 7. Low-molecular-weight Heparin Dose Regimens

<table>
<thead>
<tr>
<th>LMWH (generic name)</th>
<th>LMWH (proprietary name)</th>
<th>Dose (subcutaneous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>100 IU/kg, twice-daily</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Lovenox</td>
<td>1 mg/kg, twice-daily</td>
</tr>
<tr>
<td>Nadroprin</td>
<td>Fraxiparine</td>
<td>171 IU/kg, once-daily</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Innohep</td>
<td>175 IU/kg, once-daily</td>
</tr>
</tbody>
</table>

References


