Perioperative Anticoagulation Management in Patients who are Receiving Oral Anticoagulant Therapy: A Practical Guide for Clinicians

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Abstract

The management of patients who require temporary interruption of oral anticoagulant therapy because of surgery or other invasive procedures is a clinically important topic because of the increasing prevalence of patients who are receiving oral anticoagulants, and the availability of low-molecular-weight heparins, which allow out-of-hospital perioperative anticoagulation. The optimal management of such patients has been hampered by the lack of well-designed prospective studies investigating the efficacy and safety of different perioperative management strategies. The two main issues that need to be considered in perioperative anticoagulant management is the patient's risk of thromboembolic event when anticoagulant therapy is interrupted, and the risk of bleeding that is associated with the surgery or procedure. An assessment of these factors will determine the perioperative management approach. The objectives of this review is to focus on practical issues relating to perioperative anticoagulation; and the implementation of a perioperative anticoagulation management approach that can be used in everyday clinical practice.

Case Presentation

A 60 year-old woman, weighing 70 kg, with rheumatic valvular heart disease and a mechanical bileaflet mitral valve is scheduled to undergo elective sub-total colectomy for adenocarcinoma of the sigmoid colon. Her past medical history includes chronic atrial fibrillation, hypertension, and steroid-dependent chronic obstructive pulmonary disease. Her medications are aspirin, warfarin, diltiazem, ramipril, prednisone, and inhaled bronchodilators. There is no previous history of stroke, other cardiovascular events, or renal insufficiency.

Introduction

The management of patients, as described above, who require temporary interruption of oral anticoagulant therapy because of surgery or an invasive procedure is a frequently encountered but under-investigated clinical problem. In North America, there are over one million people with a mechanical prosthetic heart valve, chronic atrial fibrillation, or venous thromboembolism who are receiving long-term warfarin therapy (1). With an aging population, the number of warfarin-users will increase (2), and since elderly people over 65 years of age are two times more likely to require surgery than non-elderly people (3), the clinical scope of perioperative anticoagulant management will increase considerably.

Surprisingly, few studies have investigated the efficacy and safety of different perioperative anticoagulant management strategies (4-12). The traditional approach is to hospitalize patients for 3 to 4 days before and 3 to 4 days after surgery to administer intravenous unfractionated heparin (UFH) during the period that warfarin therapy is temporarily interrupted and the international normalized ratio (INR) is subtherapeutic (13-15). The emergence of low-molecular-weight heparins (LMWHs), which can be administered in a fixed, weight-adjusted, subcutaneous dose and without laboratory monitoring (16), obviates the need for in-hospital perioperative anticoagulation. This approach is appealing because of its convenience, and the potential to substantially reduce health care costs (17).

The rationale for administering full-dose (or therapeutic-dose) LWMH or UFH as bridging anticoagulant therapy while warfarin is temporarily interrupted is to shorten the time period that patients are not receiving therapeutic anticoagulation and, therefore, to minimize the risk of thromboembolic events (13-15). In addition, after warfarin or antiplatelet therapy is stopped, a transient hypercoagulable state may develop due to a rebound increase in thrombin generation (18,19), or platelet activation (20). Despite these considerations, the efficacy, in terms of preventing perioperative thromboembolism, and safety, in terms of minimizing postoperative bleeding, of bridging anticoagulant therapy has been neither substantiated nor challenged by well-designed clinical trials. Authorities that include the American College of Cardiology /American Heart Association Task Force on Practice Guidelines and the American College of Chest Physicians recommend that bridging anticoagulant therapy with UFH or LMWH should be considered for most patients who require temporary interruption of warfarin therapy (21,22).

However, the need for bridging anticoagulant therapy is not universally accepted. Some authorities have argued that, with the exception of a minority of high-risk 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 (23,24). Other authorities do not specify which patients should receive bridging anticoagulant therapy (25).

The lack of consistent recommendations regarding perioperative anticoagulant management is reflected in the variability of physicians' practice patterns. In a recent survey of perioperative anticoagulation practices of 473 Canadian internists (26,27), full-dose intravenous UFH was preferred by 60% of respondents, full-dose LWMH was preferred by 15% of respondents, and several other anticoagulation strategies were preferred by the remaining respondents. It is noteworthy that the physicians' management preferences were driven more by the need to prevent perioperative thromboembolism than concerns about postoperative bleeding.

In the absence of evidence-based, graded, practice recommendations, several recent reviews have provided general guidelines for perioperative anticoagulation (28-32). However, perhaps what is lacking in these reviews is a practical management approach, with specific patient care guidelines that can be used by clinicians in everyday clinical practice. Therefore, the objectives of this review are: 1) to address practical issues relating to perioperative anticoagulation; and 2) to provide a perioperative anticoagulation management approach that can be integrated into everyday clinical practice.

Assessment of Perioperative Thromboembolic Risk

The assessment of a patient's baseline thromboembolic risk is based on three factors: 1) the clinical indication for anticoagulation; 2) the presence of additional thromboembolic risk factors; and 3) the clinical consequences of a thromboembolic event. This review will focus on patient groups who are frequently assessed for perioperative anticoagulation management.

Patients with a Mechanical Prosthetic Heart Valve

Anticoagulant therapy is required in patients with a mechanical prosthetic heart valve to prevent stroke and systemic embolism, and to prevent valve thrombosis, which is associated with a 15% mortality rate (33,34). Patients with a prosthetic mitral valve, a caged-ball valve, and two prosthetic heart valves are at highest risk for thromboembolic events (35). Patients with a prosthetic aortic valve and two or more thromboembolic risk factors may be considered at moderate risk for thromboembolic events, whereas patients with a prosthetic aortic valve and less than two thromboembolic risk factors are at lowest risk. The most thrombogenic prosthetic heart valve is the caged-ball type (eg., Starr-Edwards), followed by the tilting disc type (eg., Bjork-Shiley, Lillehei-Kaster), and bileaflet type (eg., St. Jude, Carbomedics), which is the least thrombogenic. Prosthetic mitral valves are more thrombogenic than aortic prostheses because of greater vascular stasis around the mitral valve (35).

Providing reliable estimates of the absolute risk of thromboembolic events in such patients during temporary interruption of warfarin therapy is problematic because most data are based on studies performed 20 to 30 years ago, and involve patients with mainly first-generation prosthetic heart valves. Nonetheless, it is estimated that the incidence of a thromboembolic event in patients with a prosthetic heart valve who are not receiving anticoagulant therapy is between 9 and 22% per year (36,37). If one interpolates this risk to a 6 to 8 day perioperative period, when warfarin therapy is interrupted, this corresponds to an absolute risk of thromboembolism of 0.17 to 0.42%. Few studies have investigated the perioperative risk of thromboembolism so as to corroborate these risk estimates **(Table 1)**. In four studies involving 271 patients with mostly first-generation prosthetic heart valves who underwent 300 procedures, 4 (1.3%) patients had a perioperative thromboembolic event despite bridging anticoagulant therapy (7-10). In a retrospective study of 235 patients with newer prosthetic valve types (191 bileaflet, 51 tilting disc), of whom 164 had bridging anticoagulant therapy with full-dose UFH or LMWH, a higher rate of thromboembolism was reported (11). In this study, 4 of 177 (2.3%) patients with a aortic valve prosthesis, 9 of 51 (18%) patients with a mitral valve prosthesis, and 3 of 7 (43%) patients with two prosthetic valves had a thromboembolic event. However, limitations of this study included inadequate information about clinical follow-up and the adequacy of perioperative anticoagulation. Two small, but well-designed, prospective cohort studies of bridging anticoagulant therapy with full-dose LMWH reported one thromboembolic event in 24 (4.2%) patients (5,6). Overall, the discrepant findings from these studies underscore the need for large, well-designed, prospective studies to provide reliable estimates of the risk of thromboembolism in patients with a mechanical heart valve who have interruption of warfarin and receive bridging anticoagulant therapy. Based on the available evidence, a classification scheme that stratifies patients with a mechanical heart valve according to the thromboembolic risk, and a suggested anticoagulation management strategy for each risk category, is provided in **Table 2**.

Chronic Atrial Fibrillation

In patients with chronic atrial fibrillation, criteria for thromboembolic risk classification are well-established (38,39). Patients with a previous stroke or transient ischemic attack are at highest risk of recurrent stroke, with an incidence of 12 to 15% per year (40,41). Patients with lone atrial fibrillation, who are 65 years old or younger and have no additional stroke risk factors have the

lowest risk of stroke, with an incidence of <1% per year (42). However, such patients comprise less than 2% of all patients with chronic atrial fibrillation (42). Most patients with chronic atrial fibrillation fall between these two risk extremes, and have an incidence of stroke of 3 to 7% per year (41). In this moderate risk group, the presence of additional risk factors can be used to further stratify patients according to thromboembolic risk. There are four risk factors, in addition to a previous stroke that are associated with an increased risk of stroke (38,39): i) age >75 years; ii) hypertension; iii) diabetes mellitus; and iv) left ventricular dysfunction. These factors are similarly weighted in terms of their stroke risk **(Table 3)**.

During temporary interruption of warfarin therapy, the risk of stroke and other thromboembolic events can be interpolated from the aforementioned data, in high-, moderate-, and low-risk patients wih chronic atrial fibrillation. In high-risk patients, the absolute risk of thromboembolism is between 0.28 and 0.38%, in moderate risk patients it is 0.06, and 0.15%, and in low-risk patients it is between 0.02 and 0.04%. However, only two studies, involving 20 patients, have investigated the perioperative clinical course of such patients (5,6). Consequently, there is inadequate data to provide reliable risk estimates for perioperative thromboembolism in patients with chronic atrial fibrillation. In **Table 4**, we provide a classification scheme that stratifies patients with a chronic atrial fibrillation according to the thromboembolic risk, and a suggested anticoagulation management strategy for each risk category.

Venous Thromboembolism

In patients with venous thromboembolism, there are no data in regard to the risk of recurrent disease if warfarin therapy is temporarily interrupted. Based on studies investigating the clinical course of treated venous thromboembolism, the risk of recurrent disease is likely highest if warfarin therapy is interrupted soon after the start of treatment (43,44). In one study of 1,021 patients with venous thromboembolism, 42 of 58 (72%) recurrent events occurred during the first three weeks after diagnosis, and the incidence of recurrent disease decreased sharply thereafter (43). The risk of recurrence is higher in patients with cancer, chronic diseases, and antiphospholipid antibodies (39-42). In patients who have completed 6 to 12 weeks of anticoagulant therapy, the risk of recurrence depends mainly on the disease etiology. Idiopathic (or unprovoked) venous thromboembolism is associated with a recurrence risk of 10 to 27% per year (46,47), whereas venous thromboembolism occurring after exposure to a reversible risk factor, such as surgery, is associated with a 2 to 5% per year risk of disease recurrence (47-49). It is probable that patients with previous postoperative venous thromboembolism will be at increased risk of disease recurrence after surgery, although there are no data to provide reliable estimates of this risk. Based on these considerations, we provide a classification scheme in **Table 5** that stratifies patients with venous thromboembolism according to the risk of disease recurrence, and a suggested anticoagulation management strategy for each risk category.

Assessment of Postoperative Bleeding Risk

The assessment of postoperative bleeding risk is based the following considerations: 1) the adequacy of postoperative hemostasis; and 2) the risk of bleeding and clinical consequences of bleeding associated with surgery or an invasive procedure.

Adequacy of Postoperative Hemostasis

Determining the adequacy of postoperative hemostasis during after surgery is a subjective assessment that is based on the amount of bleeding at the surgical site, ongoing blood loss into a surgical drain, and the presence of clinical features suggestive of bleeding. Excessive wound-related bleeding is characterized by repeatedly blood-soaked wound bandages, and ongoing blood loss of >250 ml/12 hours into a surgical wound drain (50,51). In general, patients who were not receiving antithrombotic agents and had normal hemostatic function before surgery should have adequate hemostasis 12 to 24 hours after surgery.

Risk of Bleeding Associated with Surgery or an Invasive Procedure

In patients who undergo intraabdominal, intrathoracic or orthopedic surgery, there should be adequate postoperative hemostasis by 24 hours after surgical closure. However, there are several surgical procedures that can be associated with significant postoperative bleeding, despite adequate surgical technique. A bleeding risk classification scheme for various procedures is provided in **Table 6**. Urologic procedures, such as prostatectomy, bladder tumour ablation and renal biopsy, are associated with considerable postoperative bleeding, partly due to the presence of urokinase that is produced by genitourinary epithelium (52,53). Patients who undergo percutaneous renal biopsy are a particular concern because retroperitoneal bleeding may be clinically silent until there is major blood loss (54). Gastrointestinal procedures that are associated with an increased risk of bleeding include bowel resection and anastomosis, particularly in patients who are receiving corticosteroids, which may delay anastomotic wound healing (55,56). Endoscopic removal of a colonic polyp also may be associated with considerable bleeding (31,57). Coronary artery bypass surgery is associated with an increased risk of mediastinal bleeding because of coagulation factor dilution and heparinization that occurs during cardiopulmonary bypass (58,59). Neurosurgical procedures that involve the brain or spinal cord, in general, are associated with an increased risk of potentially serious intracranial or epidural bleeding (60).

Perioperative Management with Bridging Anticoagulant Therapy

This section will focus on how to implement bridging anticoagulant therapy with out-of-hospital full-dose LMWH and will refer to a suggested perioperative patient care path outlined in the **Figure**. The use of in-hospital intravenous UFH as an alternative to LMWH also will be discussed. In general, bridging anticoagulant therapy should be considered in patients at high-risk for thromboembolic events and, possibly, for moderate-risk patients. In patients at low-risk for thromboembolic events, in whom bridging anticoagulant therapy is optional, the patient care path can be used but with omission of the section on full-dose LMWH or UFH administration.

Preoperative Anticoagulation Management

i) *Stopping antithrombotic drugs*. There is a increased risk of intra- and post-operative bleeding when surgery is performed in patients who are receiving an anticoagulant (61,62), or antiplatelet drug (63-65). To ensure normal hemostatic function at the time of surgery, antiplatelet drugs should be stopped 7 to 10 days before surgery, as aspirin, ticlopidine and clopidogrel all irreversibly inhibit platelet function for the 7 to 10 day lifespan of a platelet (66). In patients who are receiving warfarin therapy with a target INR of 2.0 to 3.0, stopping warfarin 5 days before surgery will, in the vast majority of cases, ensure a normal INR at the time of surgery (67). Elderly patients appear to require a longer time for the INR to normalize after warfarin is stopped (68), and in patients with a target INR of 2.5 to 3.5, it is reasonable to stop warfarin 6 days before surgery.

ii) *INR measurements before surgery*. In addition to INR testing on the day warfarin therapy is stopped, INR testing should be performed on the day before surgery to ensure that it is normal (INR $\leq$1.3) or near-normal (INR = 1.4). Patients who undergo surgery with an INR of $\geq$1.5 are at increased risk of postoperative bleeding complications (62). If the INR is $\geq$1.5 on the day before surgery, administering low-dose oral vitamin K (i.e., 1 to 2 mg) will ensure a normal INR at the time of surgery, and is unlikely to cause resistance to re-anticoagulation when warfarin is resumed after surgery (69,70).

iii) *Preoperative bridging anticoagulant therapy*.

Bridging anticoagulant therapy with LWMH is started, typically, 3 to 4 days before surgery, when a patient's INR is below or is expected to be below the lower limit of the therapeutic range. In patients who are receiving warfarin with a target INR of 2.5 to 3.5, bridging anticoagulant therapy is started when the INR is <2.5, and in patients with a target INR of 2.0 to 3.0, it is started when the INR is <2.0. In many instances, however, the caregiver will not know when the INR drifts below the therapeutic range unless daily INR testing is performed, which is impractical. Thus, it is reasonable to empirically start LMWH therapy two days after warfarin is stopped. If once-daily LMWH is used as bridging anticoagulant therapy (eg., tinzaparin, 175 IU/kg once-daily), it should be administered in the mornings, and with last preoperative dose given on the day before surgery. If twice-daily LMWH is used (eg., enoxaparin, 1 mg /kg twice-daily), the evening dose before surgery should be omitted. With either dosing regimen, the last dose of LMWH should be administered at 20 to 24 hours before surgery, to eliminate the likelihood of a residual anticoagulant effect at the time of surgery (16).

Postoperative Anticoagulation Management

i) *Resumption of LMWH*. The decision to resume LMWH after surgery is based on whether there is adequate postoperative hemostasis and the bleeding risk associated with surgery. If there is ongoing bleeding, detected by accumulation of blood into a surgical drain, the resumption of LMWH should be deferred until the bleeding has subsided. Most postoperative bleeding that is due to delayed wound healing will resolve within 24 hours of surgery. If there is adequate postoperative hemostasis, the decision to resume anticoagulant therapy is based on the bleeding

risk associated with the surgical procedure. In patients undergoing surgery that is associated with a high risk of bleeding **(Table 6)**, the resumption of LMWH should be deferred for at least 24 to 48 hours after surgery and, preferably, after consultation with the surgeon. The initial treatment of LMWH should be low-dose, which is used as prophylaxis against deep venous thrombosis **(Table 7)**. This low-dose regimen can be started on the first or second day after surgery. The use of full-dose (therapeutic-dose) LMWH should be avoided for 48 to 72 hours after surgery, or may not be used at all if there is ongoing concern about postoperative bleeding. In patients undergoing surgery that is associated with a moderate or low risk of bleeding, low-dose LMWH can be resumed on the evening after surgery. If this treatment is well-tolerated, and without bleeding complications, subsequent doses of LMWH can be administered with a full dose regimen, starting 24 to 48 hours after surgery **(Table 8)**.

ii) *Resumption of warfarin*. In most patients, warfarin can be restarted the evening after surgery. A minimal anticoagulant effect of warfarin will not occur for at least 24 hours after the initial dose of warfarin, and a therapeutic anticoagulant effect will not occur for 4 to 5 days after the start of warfarin therapy (67). The dose of warfarin can correspond to the dose the patient usually receives on that day of the week. If a patient received high-dose vitamin K (i.e., 5 to 10 mg) before surgery, this may result in resistance to re-anticoagulation when warfarin is resumed. Because it is difficult to predict the warfarin dose requirements of patients who have received a high dose of vitamin K, it is reasonable to double the patient's warfarin dose for two consecutive days after surgery. In addition, INR monitoring can be performed more frequently after surgery to detect persistently low INR levels and to adjust the warfarin dose accordingly. If low-dose vitamin K (i.e., 1 to 2 mg) is administered before surgery, resistance to re-anticoagulation is unlikely (69,70). Nonetheless, it is reasonable to double the first dose of warfarin in such patients, and to resume the patient's usual dose of warfarin on the following day.

iii) *Stopping LMWH*. LMWH should be stopped when the INR is within the target therapeutic range. In most patients with a target INR of 2.0 to 3.0, LMWH or UFH will be required for 3 to 4 days after surgery, and in most patients with a mechanical heart valve and a target INR of 2.5 to 3.5, LMWH or UFH will be required for 4 to 5 days after surgery.

iv) *Patients with unexpected postoperative bleeding*. Major bleeding, defined as bleeding associated with transfusion of $\geq$2 units of packed red blood cells, re-operation, or bleeding into the intracranial, intrathoracic or retroperitoneal cavity (71), can be separated into surgical and non-surgical bleeding. Surgical bleeding at the wound site is the most common source of bleeding (72-74), and usually results from delayed wound healing or intraoperative blood vessel injury. Bleeding also can occur from stress-induced peptic ulceration or a hemorrhagic stroke. The anticoagulant management in such patients depends on the cause and location of bleeding although, in general, anticoagulants should be withheld until the bleeding source has been identified and treated. If the cause of bleeding is reversible, as with the repair of a severed blood vessel that inadvertently occurred during surgery, anticoagulant therapy can be resumed probably within 24 hours. In patients with gastrointestinal bleeding, anticoagulants can be withheld for as little as two days in patients with a self-limiting Mallory-Weiss tear, to as long as 21 days in patients with a large gastric ulcer (75,76). In patients with intracranial bleeding, resumption of anticoagulants can occur within one to four weeks, depending on the extent of bleeding and

radiologic evidence of healing (77-79).

Unfractionated Heparin as Bridging Anticoagulant Therapy

If UFH is used for bridging anticoagulant therapy, the conventional approach is to hospitalize patients for 3 to 4 days before and 3 to 4 days after surgery to administer intravenous UFH, with dose adjustments to achieve a targeted activated partial thromboplastin time (aPTT) of 1.5- to 2-times the control aPTT (80). The preoperative infusion of UFH should be stopped at least four hours before surgery, and resumed 12 to 24 hours after surgery when there is adequate postoperative hemostasis. To minimize the risk of postoperative bleeding, it is reasonable to avoid the use of a standardized heparin nomogram because of the unpredictable dose-response of UFH, and the potential that patients may have persistently high aPTT levels (i.e., >150 seconds). Instead, one might consider 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 that used with the standardized heparin nomogram (80). Although this approach has not been tested in prospective clinical trials, there is evidence that a persistently increased aPTT in heparin-treated patients is associated with an increased risk of bleeding (81,82). A drawback of this approach is the need for periodic adjustment of the UFH infusion rate. An alternative management approach is out-of-hospital, twice-daily subcutaneous injections of UFH (83). However, this approach requires daily, mid-interval, aPTT testing to be performed 6 hours after the morning dose of UFH to monitor the anticoagulant effect and make dose adjustments as required.

Management of Specialized Patient Groups

Patients with Renal Insufficiency

In patients with significant renal insufficiency, defined by a serum creatinine >150 mmol/L or a creatinine clearance <40 ml/min, UFH is the anticoagulant of choice because it is not cleared primarily by the kidney (16). LMWH should be avoided in patients with renal insufficiency because it is cleared primarily by the kidney. Furthermore, if LMWH is used, its bioaccumulation of LMWH may be undetected, as the aPTT will not be increased, thereby increasing the risk of intra- and post-operative bleeding (16,84). If LMWH is used in patients with renal insufficiency, the anticoagulant effect of LMWH should be measured with an anti-factor Xa level done 4 hours after the LMWH dose, with a targeted therapeutic anti-factor Xa level of 0.5 to 1.0 units/ml (16).

Patients with Previous Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a rare but serious complication of UFH therapy, and to a lesser extent LMWH therapy, that is associated with venous limb gangrene, stroke and myocardial infarction (85). UFH and LMWH should be avoided in patients with HIT. Danaparoid, a low-molecular-weight heparinoid with minimal cross-reactivity with UFH, can be safely administered in patients with HIT. The initial low dose of danaparoid is 750 IU, administered subcutaneously on the evening after surgery, with subsequent doses increased to 1,250 IU, twice-daily. Alternatively, lepirudin, a direct thrombin inhibitor, can be administered to patients with HIT. Lepirudin is given initially as a loading dose, 0.4 mg/kg intravenously over 15

to 20 minutes, followed by a continuous infusion at 0.15 mg/kg/hr for 2 to 10 days, and can also be administered subcutaneously (86).

Patients with Spinal Anesthesia or Continuous Epidural Analgesia

The anticoagulant management in patients who had a spinal puncture before surgery is problematic because of the risk of a spinal epidural hematoma, a rare but devastating complication (87,88). In patients who have spinal anesthesia, with epidural catheter removal immediately after surgery, it is safe to resume anticoagulant therapy within 12 hours after surgery. If the epidural catheter placement was traumatic, the resumption of anticoagulants should be delayed for at least 24 hours after surgery. In patients who have an indwelling epidural catheter after surgery to administer analgesia, anticoagulants, in general, should be withheld until the epidural catheter is removed. However, co-administration of LMWH and continuous epidural analgesia may be considered if the following criteria are satisfied (89): i) epidural catheter placement was non-traumatic; ii) low-dose, once-daily, LMWH is administered; iii) warfarin is started after the epidural catheter is removed; iv) the epidural catheter is removed during the trough anticoagulant effect of LMWH, corresponding to 18 to 22 hours after the preceding dose; v) other drugs that effect haemostasis, such as aspirin or NSAIDs, are avoided until the epidural catheter is removed.

Case Discussion

This case represents a patient who is considered at high risk for perioperative thromboembolic events because of a mitral valve prosthesis, and two additional risk factors (chronic atrial fibrillation, hypertension). The surgery is associated with a moderate bleeding risk. However, corticosteroid use may impair wound healing, particularly at the colostomy site, with the potential to increase wound-related bleeding. The overall management approach consists of bridging anticoagulant therapy with out-of-hospital , full-dose, LMWH, and cautious resumption of anticoagulants after surgery.

Preoperative management. The patient is instructed to stop aspirin 10 days before surgery, and to have INR testing 6 days before surgery. One that day, the INR level is 3.9, and the patient is instructed to stop warfarin. Rather than repeating the INR daily to determine when the INR drifts below the therapeutic range (i.e., INR <2.5), out-of-hospital LMWH is started empirically 3 days before surgery, with dalteparin 100 IU twice-daily, subcutaneously. INR testing is repeated the day before surgery, and is elevated at 1.6. To ensure the INR has normalized by the time of surgery, the patient receives vitamin K, 1 mg, orally. The last preoperative dose of dalteparin is administered on the morning of the day before surgery to ensure no residual anticoagulant effect at the time of surgery. The INR is re-checked and is 1.3 on the morning before surgery.

Intraoperative course. Intraoperative spinal epidural anesthesia is administered, and the surgery is uneventful. Because of concerns with parenteral analgesia use in a patient with chronic obstructive lung disease, the epidural catheter remains is place to administer epidural analgesia.

Postoperative management. In the immediate postoperative period, there appears to be adequate hemostasis although there is ongoing drainage of serosanguinous fluid from an abdominal drain,

with 250 ml having accumulated within 6 hours after surgical closure. The indwelling epidural catheter is to be removed the day after surgery. Warfarin is resumed on the evening of the day of surgery, with sips of water, starting with the patient's usual dose for that day of the week. On the 1st postoperative day, low-dose LMWH is administered (i.e., dalteparin 5,000 IU once-daily), three hours after removal of the epidural catheter. On the 2nd postoperative day, there is no ongoing blood loss from the intraabdominal drain, and LMWH is increased to full-dose treatment (i.e., dalteparin 7,000 IU twice-daily). Aspirin is also restarted on this day. On the 5th postoperative day, when the INR is 2.5, full-dose LMWH is stopped after the evening dose.

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Table 1. Thromboembolic Events in Patients with a Mechanical Heart Valve after Temporary Interruption of Warfarin Therapy

Study (reference)	Number of Patients (procedures)	Number of Patients Receiving Bridging Anticoagulant Therapy	Thromboembolic Events/Patients at Risk (percent)		
			Aortic Valve Prosthesis	Mitral Valve Prosthesis	Double-Valve Prosthesis
Katholi (7)	44 (44)	6 with aortic prosthesis, 3 with mitral prosthesis*	0/31	2/13 (15)	n/a
Katholi (8)	39 (39)	1 with aortic prosthesis, 21 with mitral prosthesis*	0/18	0/21	n/a
Tinker (9)	159 (180)	23**	0/105	0/75	n/a
Darmon (10)	37 (45)	39†	0/18	2/11 (18)	0/8
Carrel (11)	235 (235)	190†	4/177 (2.2)	9/51 (18)	0/7
Spandorfer (5)	12 (12)	12‡	0/10	0/2	none
Tinmouth (6)	12 (12)	12¶	1/7 (14.3)	0/3	0/2
Kuwada (75)	17	none§	0/6	0/9	1/2 (50)
Ananthasubra-maniam (76)	25	none§	0/9	0/12	0/4
Total	580		5/381 (1.2)	13/197 (6.6)	1/23 (4.3)

Legend: *Intravenous UFH (unspecified dose); **no perioperative warfarin withdrawal; †subcutaneous or intravenous UFH (dose unspecified) or no warfarin withdrawal; ‡enoxaparin 1 mg/kg twice-daily; ¶dalteparin 100 IU/kg twice-daily; §anticoagulants withheld because of bleeding episode.

Table 2. Perioperative Anticoagulant Management in Patients with a Mechanical Prosthetic Heart Valve

Thromboembolism Risk Category	Patient Characteristics	Suggested Anticoagulant Management
High Risk	- recent (within 1 month) stroke or transient ischemic attack - any mitral valve - caged-ball* or tilting-disc† aortic valve	bridging anticoagulant therapy strongly recommended
Moderate Risk	- bileaflet‡ aortic valve and 2 or more 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: atrial fibrillation, previous stroke, transient ischemic attack or systemic embolism, left ventricular dysfunction, age >75 years, hypertension, diabetes mellitus.

Table 3. Risk Factors for Stroke in Patients with Chronic Atrial Fibrillation

Risk Factor	Relative Risk (Atrial Fibrillation Investigators)*	Relative Risk (SPAF Investigators)†
Previous stroke, transient ischemic attack or systemic embolism	2.5	2.9
Age (decade increment)	1.6	1.8
Hypertension	1.6	2.0
Diabetes mellitus	1.7	1.6‡
Left ventricular dysfunction	2.5	n/a

Legend: *Ref. 38; †ref. 39; ‡statistically significant in univariate analysis only; n/a, not available.

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

Thromboembolism Risk Category	Patient Characteristics	Suggested Anticoagulant Management
High Risk	- recent (within 1 month) stroke or transient ischemic attack - rheumatic mitral valvular heart disease	bridging anticoagulant therapy strongly recommended
Moderate Risk	- chronic atrial fibrillation and 2 or more stroke risk factors*	bridging anticoagulant therapy should be considered
Low Risk	- chronic atrial fibrillation and <2 stroke risk factors*	bridging anticoagulant therapy optional

Legend: *Stroke risk factors: previous stroke, transient ischemic attack or systemic embolism, left ventricular dysfunction, age >75 years, hypertension, diabetes mellitus.

Table 5. Perioperative Anticoagulant Management in Patients with Venous Thromboembolism

Thromboembolism Risk Category	Patient Characteristics	Suggested Anticoagulant Management
High Risk	- recent (within 3 weeks) episode of VTE - active cancer - antiphospholipid antibody - major comorbid disease‡	bridging anticoagulant therapy strongly recommended
Moderate Risk	- VTE occurring within past 6 months - VTE occurring in association with previous interruption of warfarin therapy	bridging anticoagulant therapy should be considered
Low Risk	- none of above factors present	bridging anticoagulant therapy is optional

Legend: VTE = venous thromboembolism; *cancer that has been treated within 6 months or is palliative; †anticardiolipin antibody or lupus anticoagulant; ‡chronic cardiac or pulmonary disease.

Table 6. Bleeding Risk Classification and Postoperative Anticoagulant Management

Bleeding Risk Categtory	Surgery or Invasive Procedure	Suggested Anticoagulant Management		
		warfarin	low-dose LMWH*	full-dose LMWH†
High Risk	- neurosurgical procedure - surgical (non-laser) prostatectomy - bladder tumour resection - coronary artery bypass graft surgery - cervical cone biopsy - renal biopsy - bowel polypectomy	evening of the day after surgery	24 to 48 hours after surgery	48 to 72 hours after surgery
Moderate Risk	- major intraabdominal surgery - major intrathoracic surgery - major orthopedic surgery - multiple dental extractions	evening of the day of 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	evening of the day of surgery	24 hours after surgery

Legend: *Low-dose LMWH (see **Table 7**) is the initial dose administered, but can be continued for 24 to 72 hours in patients at increased risk of bleeding until the start of full-dose LMWH; †see **Table 8**.

Table 7. Initial Low-Dose LMWH Therapy after Surgery or Invasive Procedure

LMWH (generic name)	LMWH (proprietary name)	Dose (subcutaneous)
Dalteparin	Fragmin	5,000 IU
Enoxaparin	Lovenox	40 mg
Nadroparin	Fraxiparine	38 IU/kg
Tinzaparin	Innohep	75 IU/kg

Legend: *Administered as a single dose on the evening of the day of surgery, or for an additional 24 to 72 hours in patients at increased risk of bleeding; IU, international units.

Table 8. Full-Dose LMWH Therapy after Surgery or Invasive Procedure*

LMWH (generic name)	LMWH (proprietary name)	Dose (subcutaneous)
Dalteparin	Fragmin	100 IU/kg, twice-daily
Enoxaparin	Lovenox	1 mg/kg, twice-daily
Nadroparin	Fraxiparine	171 IU/kg, once-daily
Tinzaparin	Innohep	175 IU/kg, once-daily

Legend: *Full-dose (therapeutic-dose) LMWH to follow initial treatment with low-dose LMWH; IU, international units.

Figure. Suggested Perioperative Anticoagulation Patient Care Path

Days Relative to Surgery	Anticoagulant Management*	Blood testing
-7	STOP aspirin	
-6		
-5	STOP warfarin (i.e., no warfarin on this day)	INR
-4		
-3	LMWH _____units, once-daily	
-2	LMWH _____units, once-daily	
-1	LMWH _____units, once-daily (given 24 hours before surgery)	INR
Day of Surgery	LMWH _____units (evening dose, when hemostasis adequate) warfarin _____ mg	
1	LMWH _____units, once-daily (24 hours after surgery, when hemostasis adequate) warfarin _____ mg	
2	LMWH _____units, once-daily warfarin _____ mg	
3	LMWH _____units, once-daily warfarin _____ mg	INR CBC
4	LMWH _____units, once-daily (if required) warfarin _____ mg	
5	LMWH _____units, once-daily (if required) warfarin _____ mg	INR CBC

Legend: *The dose of LWMH will depend on the bleeding risk associated with surgery **(Table 4)**; †the first dose of LMWH should be low-dose **(Table 5)**; ‡subsequent LMWH administration can be increased to full-dose **(Table 6)**.