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A Clinician's Guide to Perioperative Bridging for Patients on Oral Anticoagulation

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Abstract

Updates in recent clinical guidelines have led to a change in the management of perioperative anticoagulation for patients on oral anticoagulant therapy. No standardized bridging consensus exists in the literature. The necessity for bridging therapy is determined based on careful consideration of the thrombosis risk versus the bleeding risk of the procedure. Risk stratification will aid the decision to bridge or not to bridge. Patients are bridged with agents with appropriate kinetics to allow for their elimination prior to the time of the procedure in order to decrease the risk of hemorrhage during invasive procedures. This intent of this article is to discuss perioperative bridging therapy and provide a practical guide for the clinician.

Keywords

bleeding, bridging anticoagulation, low molecular weight heparin, perioperative, thromboembolism

Continuing Education Learning Objectives

By the end of the article, the reader should be able to:

1. Evaluate bleeding risk based on patient characteristics and specific procedures.
2. Assess thrombotic risk based on patient characteristics.
3. List the preferred anticoagulant agents for perioperative bridging.
4. Determine correct timing for cessation and resumption of anticoagulation relative to the procedure.
5. Recognize patient characteristics that affect preferred anticoagulation agent, dose, and monitoring parameters.

Introduction

Controversy surrounds the appropriate periprocedural management of patients on chronic oral anticoagulation therapy and in need of surgical intervention or invasive procedures. Due to high inter-patient variability in both thromboembolic and bleeding risk, the literature lacks conclusive data and guidance to support standardized perioperative procedures in the chronically anticoagulated patient. Vitamin K antagonists (VKAs) are the most commonly used oral anticoagulants in the United States. These agents must be discontinued several days prior to surgery due to their long elimination half-lives and the long half-lives of the clotting factors whose product the VKAs inhibit, in order to avoid bleeding complications during the procedure. Anticoagulant agents with shorter half-lives such as low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are the preferred agents for periprocedural bridging therapy. The heparins are used after discontinuation of therapeutic VKA treatment as "bridging" therapy prior to surgical procedures. These agents are also used after the resumption of VKAs postprocedurally until therapeutic oral anticoagulation is achieved.

The decision to bridge a patient who is receiving a VKA depends on the evaluation of the risk of a thrombotic event from periprocedural interruption of anticoagulant therapy versus the risk of bleeding with the use of bridging therapy.[1] In Europe and North America, an estimated 4 million people are treated with long-term anticoagulation for atrial fibrillation (AF), mechanical heart valve (MHV), or venous thromboembolism

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Table 1. Risk of Thromboembolism With Cessation of Vitamin K Antagonist Therapy Based on Indication[a]

Indication	High Risk	Moderate Risk	Low Risk
Atrial fibrillation	Recent stroke/TIA (<3 months) $CHADS_2$ score 5-6 Rheumatic heart disease	$CHADS_2$ score 3-4	$CHADS_2$ score 0-2 (no prior stroke/TIA)
Mechanical heart valve	Any mitral valve Older (caged-ball or tilting disc) aortic valve Recent (< 6 months) stroke/TIA	Bileaflet aortic valve and one of following (A fib; prior stroke/TIA; HTN, DM, CHF or age >75 years)	Bileaflet aortic valve without AF and no other risk factors for stroke
Venous thromboembolism	Recent VTE (<3 months) Severe thrombophilia (protein C, protein S, or antithrombin deficiency, antiphospholipid antibodies, or multiple conditions)	VTE within past 3-12 months Nonsevere thrombophilic condition (heterozygous factor V Leiden mutation, heterozygous factor II mutation) Recurrent VTE Active cancer (treated within 6 months or palliative	Single VTE occurred >12 months ago and no other risk factors

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; DM = diabetes mellitus; HTN = hypertension; TIA, transient ischemia attack; VTE = venous thromboembolism; $CHADS_2$ = see text and Table 2.
[a] Adapted from *Chest*. 2008;133(6 suppl):299-339.[1]

Table 2. $CHADS_2$ Scoring[a]

	Risk Factor	Point Value
C	CHF, recent	1
H	Hypertension	1
A	Age > 75 years	1
D	Diabetes Mellitus	1
S_2	Stroke or TIA	2

Abbreviations: CHF, congestive heart failure; TIA, transient ischemic attack.
[a] Adapted from *JAMA*. 2001;285(22):2864-2870.[3]

Table 3. Stroke Risk With Atrial Fibrillation Using $CHADS_2$ Score[a]

Risk Level	$CHADS_2$ Score	Adjusted Stroke Rate (%/year)
Low	0	1.9
	1	2.8
	2	4.0
Moderate	3	5.9
	4	8.5
High	5	12.5
	6	18.2

[a] Adapted from *JAMA*. 2001;285(22):2864-2870.[3]

(VTE), and an estimated 10% of these patients have interruptions in VKAs annually for procedures.[2] This article will provide a review of the estimated risk of thrombosis and the definition of bleeding severity and its risk after commonly performed procedures based on the available literature. Recommendations from the literature will be offered to assist in developing an individualized bridging plan. Several tables in this article are offered to aid the clinician in tailoring treatment to individual patient cases.

Assessment of Thromboembolic Risk

A patient's risk of thromboembolism (TE) during a brief interruption in anticoagulant therapy is dependent on his or her indication for anticoagulation and the overall likelihood of thrombus formation from the procedure or surgery. This article will focus on thromboembolic risk stratification based on indication for anticoagulation. Table 1 illustrates the level of risk of TE with cessation of VKA therapy based on indication for anticoagulation.[1]

Without therapeutic anticoagulation, patients with AF have a variable risk of stroke. The well-validated $CHADS_2$ scoring system's name is derived from 5 patient risk factors for stroke. Point values are assigned to each risk factor, and the summation of points equals the $CHADS_2$ score (see Table 2). The score reflects an estimation of the percentage of thromboembolic risk for 100 patient years and allows the scores to be categorized as high, moderate, and low risk for stroke (see Table 3).[3] Because embolic stroke is fatal or associated with severe neurological deficits in 70% of patients, this risk must be seriously considered when compared to a patient's risk of bleeding.[1,4] Anticoagulation is recommended for high-risk patients ($CHADS_2$ score 5-6), should be considered in moderate-risk patients ($CHADS_2$ score 3-4), and is not indicated in low-risk patients with AF ($CHADS_2$ score 0-2).[3]

The thromboembolic risk for patients with MHVs depends both on the type and position of the valve. As a general rule, mitral valves are more thrombogenic than aortic valves, and "older" type mechanical valves (ie, caged-ball, tilting disk) are more thrombogenic than some of the more recent valve models (ie, St. Jude). The risk of embolism or valve thrombosis is greater with the St. Jude valve in the mitral position (22% per year) compared to the aortic position (12% per year).[1,5] A prosthetic mitral valve confers twice the yearly risk of thrombosis (20%) of a valve in the atrial position, which is closer to 10%[6] (Table 1).

The risk of a recurrent VTE is usually higher within the first few months of an initial event. Without anticoagulation, the risks of TE at 1 and 3 months post event are 40% and 10%, respectively. The risk decreases significantly after 3 months

Table 4. Risk of Bleeding From Select Procedures[a]

High Risk of Bleeding (2-Day Risk of Major Bleed = 2%-4%)	Low Risk of Bleeding (2-Day Risk of Major Bleed = 0%-2%)
Abdominal aortic aneurysm repair	Abdominal hernia repair
Any major operation (>45-minute duration)	Abdominal hysterectomy
Bilateral knee replacement	Axillary node dissection
Coronary artery bypass	Bowel polypectomy
Endoscopically guided fine needle aspiration	Bowel resection
Heart valve replacement	Bronchoscopy ± biopsy
Kidney biopsy	Carpal tunnel repair
Laminectomy	Cataract and noncataract eye surgery
Multiple tooth extractions	Central venous catheter removal
Neurosurgical/urologic/head and neck/abdominal/breast cancer surgery	Cholecystectomy
PEG placement	Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilation	Dilatation and curettage
Transurethral prostate resection	Endartectomy or carotid bypass surgery
Vascular and general surgery	GI endoscopy ±biopsy, enteroscopy, biliary/pancreatic stent without sphinecterotomy, endonosonography, without fine needle aspiration
	Hemorrhoidal surgery
	Hydrocele repair
	Knee/Hip replacement and shoulder/foot/hand surgery and arthroscopy
	Noncoronary angiography
	Pacemaker and cardiac defibrillator insertion and electrophysiologic testing
	Simple dental extractions
	Skin cancer excision
	Sternotomy wire removal

[a] Adapted from *Dis Mon* 2005;51(2-3):183-93.[6]

to 15% per year.[6] Significant recurrent VTE is fatal in 4% to 9% of patients.[1,7]

Other risk factors for VTE include hypercoagulable states, such as factor V Leiden, antiphospholipid syndrome, and malignancy (see Table 1).

Assessment of Bleeding Risk

The risk of bleeding associated with a given procedure must be weighed against the risk of thrombosis to determine if the provision of bridging therapy is appropriate. A patient's medications, prior medical history, and the inherent bleeding risk associated with the procedure contribute to the overall intra- and postprocedure bleeding risk. Table 4 lists some common procedures and the associated bleeding risk.[6] This list is not exhaustive, and no validated bleeding risk index for bridging therapy is available in the literature. Uncertainty about the bleeding risk of a specific procedure should be clarified with the surgeon or physician performing the procedure. Invasive procedures have a greater risk of bleeding complications with bridging anticoagulation.[6] Further studies are needed in order to clarify and classify the bleeding risk associated with various procedures.

Bleeding complications are often separated into the following categories in the literature: major, minor, and clinically significant nonmajor. The International Society on Thrombosis and Haemostasis suggested the following definitions for the constituents of a major bleed: (1) fatal bleeding, (2) symptomatic bleeding in the following areas: intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome, or (3) bleeding that causes a drop in hemoglobin that necessitates transfusion of $\geq$2 units of whole blood or red blood cells.[8] Minor bleeding is self-limiting. Clinically significant nonmajor bleeding requires medical attention but does not fit the requirements for major bleeding. Examples include bleeding which would require intervention with wound dressing or sutures.[8] The goal of proper perioperative anticoagulation is to reduce the risk of these bleeding complications while also reducing the risk of thrombosis.

Recent Clinical Studies Evaluating the Role and Feasibility of Bridging Therapy

The provision of periprocedural bridging therapy is highly controversial due to the difficulty of balancing the thrombosis and bleeding risk in each specific patient scenario. One school of thought proposes that if a patient has a low to moderate risk for TE, the patient should not be given bridging therapy periprocedurally in order to avoid the anticoagulation-associated risk of bleeding. In contrast, the other philosophy emphasizes that the serious consequences of a major thromboembolic event may outweigh those of a bleed and that use of bridging therapy is the preferred strategy. A multitude of clinical trials addressed the appropriateness and feasibility of perioperative bridging therapy. The following section and Table 5 summarize the major findings of selected recent clinical trials.

Dunn et al published a systematic review of the literature in 2003 that summarized the efficacy and safety of various methods for perioperative management. Among the 1868 patients in the 31 reports identified, 4 major bleeding events and 29 thromboembolic events occurred. They concluded that VKAs could be continued with minor procedures and that the decision to use LMWH or UFH as bridging therapy in patients undergoing invasive procedures must be individualized. They concluded that more rigorous studies were needed to address the decision to implement bridging therapy.[10]

The authors of a prospective observational cohort study concluded that a brief (<5 day) interruption of warfarin therapy posed a low risk of TE in 1293 episodes of warfarin interruptions

Table 5. Review of Recent Perioperative Bridging Literature

Study	N	Indication(s) for Anticoagulation, N	Procedure, N	F/U Days	Agent Evaluated, N (%) Dose	ATE, N (%)	VTE N (%)	Bleed, Major N (%)
Dunn (2003)[9]	1868	Systematic review	Major and minor surgeries	Varied	OAT continuation (237)	1 (0.4%)	0	Not specified
					OAT discontinuation (996)	6 (0.6%)	0	
					UFH (166)	0	0	
					LMWH (180)	1 (0.6%)	0	
					Not specified (263)	21 (8%)	0	
Garcia (2008)[10]	1024 1293 [a]	AF (550) VTE (144) MHV(132) CVA (93) Other (105)	Colonoscopy (324) Oral surgery (323) [a] Ophthalmic surgery (116)[a] Other (530) [a]	30	LMWH or UFH [108 (8.4%)][a] Dosing not specified	0	0	4 (3.7%)
					No bridging [1185 (91.6%)][a]	4 (0.3%)	3 (0.3%)	2 (0.2%)
Douketis (2004)[11]	650	AF (346) MHV (215) CVA (89)	High bleeding risk (108): Valve replacement (61) Other (47) Low bleeding risk (542): Pacemaker insertion (56) Angiography ± PCI (223) GI endoscopy ± biopsy (64)	10-18	Dalteparin 100 IU/kg SC q12h pre-procedure only [108 (16.6%)][b]	2 (1.8%)	0	2 (1.8%)
			Other (199)		Dalteparin 100 IU/kg SC q12h pre/post-procedure [542 (83.4%)][b]	2 (0.4%)	0	4 (0.7%)
Spyropoulos (2006)[12]	901	MHV (246) AF (349) Other arterial indication (76) Other venous Indication (230)	GI (163) IR (150) Orthopedic (118) Cardiothoracic (110) General surgery (72)	30	UFH [180 (20%)] Treatment dose IV (129) Prophylactic dose (51) Post-procedure UFH dose (164)	4 (2.4%)	0	9 (5.5%)
			Other (288)		LMWH [721 (80%)] Treatment dose SC (550) Prophylactic dose (171) Enoxaparin (83%) Dalteparin (14%) Tinzaparin (3%) Post-procedure LMWH dose (668)	4 (0.6%)	2 (0.3%)	22 (3.3%)
Spyropoulos (2008)[13]	245	MVR (93) AVR (126) AVR + MVR (25) Not specified (1)	Cardiothoracic (27) IR (29) GI (59) General Surgery (22)	30	UFH IV treatment dose (73)	1 (1.5%)	0	6 (8.8%)
			Other (108)		LMWH SC treatment dose (172) Enoxaparin mg/kg BID (76%) Dalteparin 100IU/kg BID (13%) Tinzaparin 175IU/kg daily (4%)	1 (0.6%)	0	7 (4.2%)

(continued)

Table 5 (continued)

Study	N	Indication(s) for Anticoagulation, N	Procedure, N	F/U Days	Agent Evaluated, N (%) Dose	ATE, N (%)	VTE N (%)	Bleed, Major N (%)
Pengo (2009)[14]	1262	AF (653) VTE (210) MHV (190) Valvular disease (70) Other (139)	High-bleed risk (369): Abdominal (123) Orthopedic (86) Others (160) Low-bleed risk (893): GI endoscopy (320) Cutaneous surgery (159) Cistoscopy (127) Other (247)	30	High TE risk (295): Weight-based enoxaparin or nadroparin[c] Low TE risk (967) Prophylactic enoxaparin or nadroparin	2 (0.7%) 0	3 (1%) 0	8 (2.7%) 7 (0.7%)
Daniels (2009)[15]	556	AVR (372) MVR (136) Multiple valves (48)	Lower GI endoscopy (89) IR (61) Orthopedic surgery (60) Oral surgery (54) Other (293)	90	LMWH [243 (43.7%)] Ardeparin 130IU/kg SC q 12h Dalteparin 100IU/kg SC q12h Enoxaparin 1mg/kg SC q12h UFH [99 (17.8%)] No bridging [213 (38.3%)]	2 (0.8%) 2 (3.1%) 1 (0.5%)	0 0 0	9 (3.7%) 6 (6.1%) 5 (2.4%)

Abbreviations: AF, atrial fibrillation; ATE, arterial thromboembolism;AVR, aortic valve replacement; BID, twice daily; DVT, deep vein thrombosis; F/U, follow-up; GI, gastrointestinal; IU, international units; IHD, ischemic heart disease; IR, interventional radiology; IV, intravenous; LMWH, low molecular weight heparin; MHV, mechanical heart valve; MVR, mitral valve replacement; OAT, oral anticoagulant therapy; PCI, percutaneous coronary intervention; SC, subcutaneous; TIA, transient ischemia attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a] Number of interruptions of therapy instead of number of patients.

[b] Thirty-two patients planned for postprocedural bridging actually did not receive it.

[c] Protocol violations. One patient with ATE and 1 patient with VTE did not receive bridging therapy.

in 1024 patients for common procedures such as colonoscopy, and oral and ophthalmic surgery in patients with indications including mostly AF, VTE, MHV, and stroke.[9] Seven patients who did not receive bridging experienced an event, including stroke, DVT, PE, and ischemic bowel. Six episodes of major bleeding occurred; 4 in the bridging group and 2 in the nonbridging group. The findings of this study question the need for bridging therapy with short interruptions in VKA therapy.

Douketis et al prospectively evaluated a standardized LMWH bridging plan for 650 anticoagulated patients undergoing invasive procedures. Patients received the same preprocedure treatment; warfarin was stopped 5 to 6 days prior to the procedure, and dalteparin 100 IU/kg was administered twice daily starting 3 days prior to procedure. The postprocedure bridging plans were determined based on the procedure's bleeding risk, and the patient's postprocedure hemostasis. Patients undergoing non-high-bleeding-risk procedures with adequate hemostasis resumed warfarin in the evening of the day of the procedure and dalteparin the next day. Dalteparin resumption was delayed in patients that did not reach timely hemostasis after the procedure. Patients undergoing a high-bleeding-risk procedure resumed warfarin on the evening of the procedure but did not resume dalteparin postprocedurally. This study found that patients at risk of arterial TE had a low risk of TE and major bleeding with a standardized periprocedural LMWH regimen.[11]

The REGIMEN Registry was a multicenter, observational, prospective registry that enrolled 901 anticoagulated patients who required periprocedural bridging therapy. Patients received UFH or LMWH.[12] No significant differences were noted between the UFH and LMWH groups with regard to adverse events including thrombosis, major bleeding, and death (7.9% in the UFH group vs 4.2% in the LMWH group; $P = .07$). Thromboembolic rates in patients receiving UFH and LMWH was 2.4% and 0.6%, respectively (P value not reported). LMWH has an advantage over intravenous (IV) UFH due to cost savings, with the ability to treat patients in the outpatient setting and decrease the number of days of hospitalization.[12]

Spyropoulos et al conducted a prespecified subgroup analysis from the REGIMEN registry that included 245 MHV patients. Of these patients, 73 received UFH and 172 received LMWH at therapeutic doses periprocedurally. The incidence of arterial TE, death, and major bleeding was not statistically different between treatment groups. Although numerically lower rates of major bleeding were noted in the LMWH group compared to the UFH group, the difference did not reach statistical significance (4.2% vs 8.8%, respectively; $P = .17$).[13]

Pengo et al conducted a prospective inception cohort management study of 1262 patients to evaluate the efficacy and safety of an individualized bridging protocol. Patients stopped oral anticoagulants 5 days prior to procedure (369 high-bleeding risk including abdominal, orthopedic, maxillofacial, and others; and 893 low bleeding risk including endoscopy, cutaneous surgery, cistoscopy, and others), and LMWH (weight-based enoxaparin or nadroparin) was started 3 to 4 days prior to procedure. The last dose of LMWH was given at least 12 hours prior to the procedure. LMWH was resumed at least 12 hours after the procedure and continued for 6 days after surgery at 70 anti-factor Xa U/kg. Patients with high thromboembolic risk (N = 295; 52.5% with MHV) received twice daily LMWH dosing as protocol A, and low- and moderate-risk patients (N = 967; 62.2% with AF) received prophylactic once-daily LMWH doses as protocol B. Oral anticoagulation was resumed the day after the procedure. Results included 5 thromboembolic events (all in patients with high thromboembolic risk who did not receive LMWH according to the protocol) and 15 episodes of major bleeding (2.7% from protocol A vs 0.7% from protocol B; $P = .011$). The authors concluded that the individualized bridging protocol was feasible, effective, and safe for many patients. They commented that safety in MHV patients was not established by their study as it contained only a small cohort of MHV patients and it did not stratify them based on valve type.[14]

Daniels et al prospectively evaluated the 3-month cumulative incidence of TE and bleeding in 556 MHV patients on anticoagulation receiving periprocedural bridging. Patients stopped warfarin 4 to 5 days prior to the procedure (ranging from cataract surgery to endoscopy; see Table 5) and restarted postprocedural anticoagulation after hemostasis was achieved. The decision to implement bridging therapy with UFH or LMWH was made by the Mayo Clinic Thrombophilia Center or the attending physician based on individual patient characteristics and physician preference. Bleeding rates did not differ between patients who did not receive postprocedural bridging therapy versus those who received UFH or LMWH. The cumulative incidence of major bleeding at 3 months was higher than the cumulative incidence of TE (3.6% and 0.9%, respectively). The authors concluded that the risk of TE is low in MHV patients with a short interruption in anticoagulation. They recommend that postprocedural bridging should be reserved for patients with high thromboembolic risk, and that it should be started 48 hours postprocedure.[15] This delayed time period is recommended based on the low incidence of TE and the higher incidence of major bleeding. The authors acknowledge this delicate balance and severity of the consequences of these events.

In addition to the studies discussed above, many smaller studies evaluated perioperative bridging therapy in specific groups of patients with various anticoagulation indications, procedure types, and bridging protocols.[16–18]

Alternatives to Bridging

Methods other than bridging can also be used to balance the risk of thrombosis versus bleeding in certain dental procedures such as complicated extractions and gingival and alveolar surgeries. Instead of stopping VKA therapy preprocedurally, some dentists give antifibrinolytic agents such as tranexamic acid as a 5% mouthwash for 2 minutes 4 times daily to control local bleeding postsurgically.[19] A consensus group in the United Kingdom recommended a 2-day course of this regimen with a grade A, level 1b evidence.[20] Patients can continue VKA

Table 6. Bridging Recommendation Based on Indication for Anticoagulation and Thrombotic Risk Level[a]

Indication	Risk Level	Bridging Recommendation[b]
Mechanical heart valve, atrial fibrillation, venous thromboembolism	High	1) Therapeutic dose SC LMWH 2) IV UFH
	Moderate	1) Therapeutic dose SC LMWH 2) IV UFH 3) Prophylactic dose SC LMWH
	Low	1) Prophylactic dose SC LMWH or no bridging

Abbreviations: LMWH, low molecular weight heparin; IV, intravenous; SC, subcutaneous.
[a] Adapted from *Chest*. 2008;133(6 suppl):299-339.[1]
[b] Recommendation 1) is the preferred bridging recommendation in all risk levels.

therapy periprocedurally to prevent TE, while these agents can be used to prevent excessive bleeding from the surgical site.

Management of Perioperative Bridging

If it is determined that the benefit of bridging therapy outweighs the risk of bleeding, the clinician must determine the most appropriate bridging plan for the patient. Issues that need to be considered include: preprocedural discontinuation of VKAs, preprocedural bridging therapy, postprocedural resumption of VKAs, and postprocedural bridging therapy, and monitoring (See Tables 6-8).

Preprocedural Discontinuation of VKAs and Antiplatelet Agents

Antiplatelet agents (aspirin, clopidogrel) should be discontinued 7 to 10 days prior to the procedure to allow adequate time for elimination of the medications based on their half-life and their pharmacodynamic effect on platelets. However, patients who have had a bare metal stent placed in the previous 6 weeks or a drug-eluting stent placed in the previous 12 months, or patients who have had a myocardial infarction in the previous 3 months should continue aspirin and clopidogrel periprocedurally.[1] VKAs should be discontinued at least 5 days prior to procedure to allow the international normalized ratio (INR) to normalize. This time frame accounts for the elimination of warfarin and the reaccumulation of the 4 vitamin K-dependent clotting factors which warfarin inhibits, and should result in an INR < 1.5 prior to the procedure. If the INR is still elevated (>1.5) 1 to 2 days prior to the surgery, a small (1-2 mg) dose of oral vitamin K has been shown to be effective at lowering the INR sufficiently without causing excessive resistance to re-anticoagulation postoperatively.[1]

Preprocedural Bridging Therapy

Table 6 lists the preferred bridging strategy based on the risk level for patients with MHV, AF, or VTE. LMWH is preferred over IV UFH for outpatient care due to convenience and ease of administration.[1] Suggested therapeutic and prophylactic dosing for UFH and LMWH agents are listed in Table 7.

Table 8 provides an algorithm to further assist clinicians in stopping and restarting specific anticoagulants relative to the date of the procedure. Bridging with LMWH should begin 36 to 48 hours after the last dose of VKA is given prior to the procedure. The last dose of therapeutic-dose LMWH should be administered 24 hours preprocedurally, at half the daily dose to accommodate for the 3.5- to 5-hour half-life of the agents and to allow for weaning of the therapeutic effect. Patients with impaired renal function will need longer times for elimination of LMWH.[21] If the therapeutic-dose IV UFH is used, the last dose should be given 4 hours preprocedurally to account for its 45-minute half-life.[1]

Postprocedural Resumption of VKAs and Bridging Therapy

The preferred time to restart anticoagulation postprocedure is determined by the risk of bleeding of the procedure and during surgery and the hemostatic status of the patient. Practice guidelines recommend restarting antiplatelet agents 24 hours (or the next morning) after the procedure if hemostasis has been achieved. VKAs take at least 48 to 72 hours to reach partial anticoagulant effect. Provided that hemostasis is achieved, current guidelines recommend restarting VKAs in the evening on the day of the procedure, or the evening following the procedure if there are complications or if the procedure was a high-bleed risk. This is up to the discretion of the practitioner based on the overall postprocedure bleeding risk.[1]

LMWH should be restarted 24 hours postprocedurally if the patient has achieved hemostasis and the procedure has a low-to-moderate bleed risk. With major surgery and a high-bleed risk, restarting therapeutic-dose LMWH should be delayed 48 to 72 hours postprocedurally, or the patient should be given prophylactic-dose LMWH, or LMWH and UFH should be avoided postprocedurally.[1]

Monitoring

Safety considerations for LMWH bridging include monitoring platelet counts every 3 days due to the concern of heparin-induced thrombocytopenia (HIT).[1] In addition, renal function has to be evaluated and monitored for the appropriate dosing of LMWHs. Monitoring the anti-factor-Xa activity in special populations could be considered but is not routinely performed when patients are renally stable and will be on the agent only for the course of bridging (typically 7-14 days).[1]

Table 7. Prophylactic and Treatment Doses for Select Bridging Agents

Bridging Agent	Prophylactic Dose	Treatment Dose
Dalteparin	5000 IU SC every 24 hours	100 IU/kg SC every 12 hours or 200 IU/kg SC every 24 hours
Enoxaparin	30 mg SC every 12 hours or 40 mg SC every 24 hours	1 mg/kg SC every 12 hours or 1.5 mg/kg SC every 24 hours
Tinzaparin	4500 IU SC every 24 hours	175 IU/kg SC every 24 hours
Unfractionated heparin	5000 IU SC every 12 hours	IV Titrated to aPTT correlated with an anti-factor-Xa level of 0.3-0.7 units/mL

Abbreviations: aPTT, activated partial thromboplastin time; IU, international units; IV, intravenous; SC, subcutaneous.

Table 8. Perioperative Bridging Timeline Relative to Day of Procedure

	Recommended Action		
Day	Oral Anticoagulant/Antiplatelet	Bridging Agent	Laboratories
Day −10 to Day −7	Stop antiplatelet agents (aspirin, clopidogrel)	NA	
Day −5	Stop warfarin	NA	
Day −4	No warfarin	Start LMWH	
Day −3 to Day −2	Stop NSAIDs with long half-life (naproxen, sulindac, celecoxib, diflunisal)	LMWH	
Day −2 to Day −1	Stop NSAIDs with short half life (ibuprofen, diclofenac, ketoprofen, indomethacin)	Last dose of LMWH[a] 24-36 hours prior to procedure (at ½ of the treatment dose)	INR, CBC with PLT
Day 0 (procedure)	No anticoagulation before procedure. Resume warfarin at the maintenance dose in the evening if low-bleeding risk and hemostasis has been achieved	No anticoagulation before procedure	
Day 1	Resume warfarin at maintenance dose if not started in the evening after procedure due to high-bleeding risk. Resume aspirin, clopidogrel, 24 hours after procedure	Resume LMWH if minor surgery or low-bleeding risk procedure	
Day 2	Warfarin	Resume LMWH[b] if major surgery or high-bleeding risk procedure	
Day 3 to Day 4	Warfarin	LMWH	CBC with PLT
Day 6 to Day 7	Warfarin	Discontinue LMWH when INR is therapeutic	INR, CBC with PLT

Abbreviations: CBC, complete blood count; INR, international normalized ratio; LMWH, low molecular weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; PLT, platelet count.
[a] The last dose of LMWH given 24 hours prior to procedure should be half the daily treatment dose
[b] Plan to be determined if patient will resume therapeutic or prophylactic dose of LMWH based on the bleeding risk postprocedure.

Special Populations

Obesity

Dosing of LMWH in obese and renally impaired patients is controversial. A review article by Nutescu et al summarizes current recommendations.[21] VTE prophylactic doses for enoxaparin may be increased by 30% in morbidly obese patients (body mass index [BMI] $\geq$40 kg/m^2) to give a dose of 40 mg subcutaneously (SC) every 12 hours (Q12h).[22] Treatment doses should be based on total body weight, as capping enoxaparin doses at 150 mg may lead to underdosing and a subsequent increase in the risk of thrombosis. For patients who weigh over 190 kg, the initial dosing should be based on total body weight, and monitoring anti-Xa levels will guide dose adjustments if necessary. If anti-Xa monitoring is not available, the clinician may decrease the dose based on bleeding complications. In the obese patient, once daily dosing for enoxaparin should be avoided due to the evidence suggesting an increased thrombosis rate. However, dalteparin (200 IU/kg daily) and tinzaparin (175 IU/kg daily) may be dosed once daily.[21]

Renal Impairment

In patients with renal impairment, creatinine clearance should be estimated based on the Cockcroft-Gault equation rather than calculating the glomerular filtration rate (GFR) until trials demonstrate the superiority of the latter equation for the purposes of dose modification. For VTE prophylaxis in patients with mild-to-moderate renal impairment (CrCl 30-60 mL/min), dosage adjustments are generally not needed for LMWH.[23–26] In patients with CrCl <30 mL/min, prophylactic-dose enoxaparin may be decreased to 30 mg daily; dosage adjustments may not be needed with dalteparin or tinzaparin if used for less than 10 days. With longer term use, anti-factor-Xa monitoring may be considered.[21] UFH is an acceptable alternative to LMWH for most renally impaired patients; it should be considered for treatment doses for patients with CrCl <20 mL/min. Several trials have demonstrated an increase in anti-Xa factor activity in patients receiving treatment doses of enoxaparin with renal impairment compared to those with normal renal function.[25,27] In patients with CrCl < 30 mL/min, enoxaparin dosing should

be reduced to 1 mg/kg daily as recommended by the manufacturer. No significant difference has been observed with dalteparin between CrCl <40 mL/min or >80 mL/min in 1 small study.[28] Two studies of tinzaparin showed no correlation between anti-Xa activity and renal function.[29,30] This suggests that dosage reduction for these 2 agents may not be required.[21]

Elderly

Since renal function decreases with increasing age, many elderly patients require smaller doses of LMWH to avoid accumulation. In a study of patients over 75 years receiving enoxaparin 30 mg or 40 mg daily, 4% had a peak anti-Xa level greater than 1 unit/mL. A subanalysis of ExTRACT-TIMI-2 trial noted that a dose reduction in enoxaparin prevented an increase in bleeding rate compared to UFH. Based on that study, elderly patients with STEMI should receive enoxaparin 0.75 mg/kg every 12 hours, and each dose should be capped at 75 mg.[31] Renal function should be carefully monitored in elderly patients and adjustments should be made based on the individual's bleeding risk.[21]

Heparin-Induced Thrombocytopenia

Some clinicians use fondaparinux (a synthetic pentasaccharide) as a bridging agent for patients who have previously tested positive for HIT, although this is not a Food and Drug Administration–approved indication. Due to its long half-life (17-21 hours), preprocedural use may lead to accumulation. If this agent is to be used, it may be prudent to only administer it postprocedurally. Dosing strategies in patients with renal dysfunction or obese patients is generally lacking.

Emergency Surgery

For patients requiring emergent surgeries and rapid reversal of the anticoagulant state due to VKAs, no randomized trials have been conducted. Observational studies have included the administration of fresh frozen plasma, prothrombin concentrates, and recombinant factor VIIa. Patients should also receive 2.5 or 5 mg phytonadione by mouth or intravenously.[1] If the procedure can be delayed, phytonadione will effectively reduce the INR within 12 to 24 hours. If this time course for reversal is not available (ie, surgery is required sooner), fresh frozen plasma can be administered. No agent is available for immediate reversal of antiplatelet agents (aspirin, clopidogrel, or ticlopidine). Platelet transfusion should be reserved for excessive or life-threatening bleeds.[1] Prohemostatic agents might be an alternative to platelet transfusion. Epsilon aminocaproic acid and tranexamic acid (both antifibrinolytic agents) and 1-deamino-8-D-arginine vasopressin (which increases von Willebrand factor and factor VIII) have been used with cardiac surgery. In situations apart from cardiac surgery, these agents should be reserved for excessive or life-threatening bleeds.[1] Protamine is available for immediate reversal of UFH; it offers only partial neutralization of LMWH.[1]

Discussion

Bridging anticoagulation remains controversial due to the unknown absolute reduction in risk of TE, and the risk of intra- and postprocedural bleeding. In order to determine whether or not to bridge a patient periprocedurally, a clinician must properly assess the bleeding risk of the procedure and the potential for thrombosis based on individual patient characteristics. Ongoing studies such as the PERIOP 2 will continue to address the issues of safety with LMWH bridging.[32] The tables and tools provided in this article can guide a clinician through the periprocedural management of a patient's anticoagulation. All recommendations must be applied judiciously with respect to the specific patient scenario.

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