Perioperative management of patients receiving vitamin K antagonists

[Prise en charge périopératoire des patients traités aux antagonistes de la vitamine K]

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Purpose: As the number of patients taking vitamin K antagonists (VKA) is growing, the clinician is increasingly faced with having to make decisions regarding anticoagulation therapy before, during and immediately after surgery. In this article we review the indications for VKA and assess their use in the perioperative period based on available pharmacological and clinical data.

Source: An on-line computerized search of Medline was conducted limited to English and French language articles. The bibliographies of relevant articles and additional material from other published sources were retrieved and reviewed.

Principal findings: Assessment of patients taking VKA who need surgery must include three factors: 1) the indication for anticoagulation, which determines the thromboembolic risk; 2) the pharmacokinetics of VKA, which determine the moment at which treatment should be discontinued; and 3) the type of surgery, which determines the hemorrhagic risk. Some patients will need to stop VKA treatment and start a substitution or "bridging" anticoagulant therapy, such as unfractionated heparin or low molecular weight heparin, prior to and after surgery. In patients requiring emergency surgery, prothrombin complex concentrate can be used to improve coagulation and is preferable to, although more expensive than fresh frozen plasma.

Conclusions: For the perioperative setting, further studies are required to determine the optimal substitution ("bridging") regimen and the clinical circumstances that necessitate substitution therapy.

Objectif : Comme le nombre de patients qui prennent des antagonistes de la vitamine K (AVK) augmente, le clinicien a de plus en plus de décisions à prendre sur l'anticoagulothérapie avant, pendant et immédiatement après une opération. Dans le présent article, nous revoyons les indications pour les AVK et évaluons leur usage périopératoire en nous inspirant des données pharmacologiques et cliniques existantes.

Source : Une recherche directe informatisée dans Medline a été menée, limitée aux articles parus en anglais et en français. Les bibliographies des articles pertinents et des documents additionnels d'autres sources ont été trouvés et passés en revue.

Constatations principales : L'évaluation des patients qui prennent des AVK et qui doivent être opérés doit comprendre trois facteurs : 1) l'indication pour l'anticoagulation qui détermine le risque thromboembolique; 2) la pharmacocinétique des AVK qui détermine le moment où le traitement doit être interrompu et 3) le type de chirurgie qui détermine le risque hémorragique. Certains patients devront arrêter le traitement aux AVK et commencer un traitement anticoagulant de substitution ou de transition, comme l'héparine non fractionnée ou de bas poids moléculaire, avant et après l'opération. Chez les patients qui doivent être opérés d'urgence, un concentré de complexe prothrombique, plus cher que le plasma frais congelé mais préférable, peut être utilisé pour améliorer la coagulation.

Conclusion : D'autres études sont nécessaires pour déterminer, dans le cadre périopératoire, les circonstances cliniques qui nécessitent un traitement de substitution et son dosage optimal.

THE temporary interruption of anticoagulation for surgery or other invasive procedures is seen increasingly as greater numbers of patients are treated with oral anticoagulants. In this article, we review the perioperative use of vitamin K antagonists (VKA) based on available pharmacological and clinical data.

1 Pharmacology of VKA

1.1 Mechanism of action

Vitamin K antagonists produce their anticoagulant effect by inhibiting vitamin K epoxide reductase and possibly vitamin K reductase.¹ They reduce vitamin

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TABLE I Characteristics of VKA

VKA	Drug	Half-life (hr)	Onset of action (hr)	Duration of action (hr)	Delay (days) to normal	Mean dose (mg·day ⁻¹)
Short half life	Acenocoumarol (Sintrom®, Novartis Pharma, Bruxelles, Belgium)	24 hr	24-36	48-96	2-3	2-10
Long half-life	Fuindione (Previscan®, Procter & Gamble Pharmaceuticals, France)	31 hr	48-72	48	3-4	20-40
	Warfarin (Marevan®, Therabel Pharma, Bruxelles, Belgium)	35-45 hr	24-72	96-120	4	2-15
	Phenprocoumon (Marcoumar®, Roche, Bruxelles, Belgium)	5-4 days	96-120	48-72	2-4	2-8

VKA = vitamin K antagonists.

TABLE II Drug interactions with vitamin K antagonists

Potentialiation	Inhibition
Amiodarone	Barbiturates
Non-steroidal anti-inflammatory drugs	Carbamazepine
Antiplatelet agents	Cholestyramine
Cephalosporins	Glutethimide
Cimetidine	Griseofulvin
Erythromycin	Nafcillin
Fibrates	Estrogens
Isoniazid	Phenytoin
Omeprazole	Rifampicin
Metronidazole	Sucralfate
Miconazole (+++)	Vitamin K
Phenytoin	
Phenylbutazone	
Quinidine	
Simvastatin	
Sulfamides	
Sulfinpyrazone	
Anabolic steroids	

KH₂ (reduced form of vitamin K) levels, thereby limiting the cofactor effect of vitamin K on γ -carboxylation of the vitamin K-dependent coagulant proteins (prothrombin, factors VII, IX and X) and some anticoagulant proteins (protein C and protein S). The effects of VKA depend on the half-lives of the inhibited factors, which are as long as 72 hr for factor II and, in contrast, very short (six to seven hours) for factor VII and protein C.²

There are two pharmacological VKA families: the coumarin derivatives (warfarin, acenocoumarol, phenprocoumon) and the indane-dione derivatives (fluindione). The pharmacokinetic properties of these agents are presented in Table I. Physiological conditions (hereditary resistance) and clinical situations (fat malabsorption, poor vitamin K intake) may influence the pharmacokinetics and pharmacodynamics of oral anticoagulants. Drug interactions are described in

Table II.

1.2 Monitoring of VKA anticoagulation

The prothrombin time (PT), which assesses three of the four vitamin K-dependent clotting factors, i.e., factors II, VII and X, has been the most commonly used method to monitor the effects of VKA. This test is performed by adding calcium and thromboplastin to citrated plasma. During the initiation of treatment, PT values reflect primarily the depression of factor VII, which occurs earlier than that of factors X and II. As thromboplastins vary in their responsiveness, the expression of PT in seconds or as a percentage of normal led to confusion in determination of the therapeutic range and in interpretation of values. Therefore, the international normalized ratio (INR) was proposed in 1982 to standardize monitoring.²

$$\text{INR} = \left[\frac{\text{Patient PT}}{\text{Mean normal PT}} \right]^{\text{ISI}}$$

where ISI is the international sensitivity index, which measures the responsiveness of the thromboplastin used to measure the PT. The ISI can vary between 0.95 and 2.5. The lower the ISI, the more responsive is the reagent. The therapeutic INR range depends on the indication for treatment; in most cases, the target value ranges between 2 and 3.

The activated partial thromboplastin time (aPTT) is not used to monitor anticoagulation in patients taking oral anticoagulants, since the increase in aPTT is variable and is not well correlated to the degree of inhibition of vitamin K-dependent factors.

1.3 Clinical indications

Treatment with VKA is indicated in a variety of medical situations:

1.3.1 MECHANICAL PROSTHETIC CARDIAC VALVES AND VALVULOPATHY

Life-long anticoagulation is mandatory in patients with a mechanical prosthetic valve in order to prevent a stroke, systemic embolism or valve thrombosis. The highest risk is encountered with prosthetic valves in the mitral position, caged-ball valves or when two prosthetic valves are present. Guidelines have been developed for anticoagulation, recommending an INR between 2 and 3 for second generation aortic valve prostheses in the absence of atrial dilatation or arrhythmia. For mitral valve prostheses, and for first generation valves (*Starr-Edwards*, *Björk-Shiley standard*, *Omniscience*), the target INR is higher (INR at least 2.5, and up to 4.5 according to some recommendations.³ The most recent publications for mitral valve prostheses recommend a target INR of 2.5–3.5.^{4,5} VKA are also indicated in patients with mitral stenosis and associated atrial fibrillation (AF). The optimal therapeutic range is uncertain, an INR of 2–3 being considered reasonable. The same goal may be desirable for patients with mitral stenosis and regular sinus rhythm associated with an enlarged atrium or atrial thrombus.^{3,5,6}

1.3.2 ATRIAL FIBRILLATION

Chronic AF may lead to stroke or transient ischemic attacks. The mean global incidence of stroke is 3–7% per year with a higher risk (12–15% per year) in patients who have already had a previous event and a lower risk (below 1% per year) in patients under 65 yr of age with no additional risk factors (such as hypertension, diabetes, left ventricular dysfunction). Acetylsalicylic acid is more often proposed in these latter cases. The target INR in patients receiving VKA is 2–3.^{3,5}

1.3.3 VENOUS THROMBOEMBOLISM (VTE)

Vitamin K antagonists are effective in preventing VTE in orthopedic surgery. Treatment can be initiated the day before surgery. This approach is not common in Europe where low molecular weight heparins (LMWH) are preferred.

Vitamin K antagonists are more often prescribed to treat established venous thrombosis.⁶ The total duration of treatment varies according to the patient's medical status and risk factors. Oral anticoagulation is indicated for six weeks to three months in patients with isolated symptomatic calf vein thrombosis. It may be prolonged to six months in idiopathic proximal vein thrombosis or recurrent venous thrombosis.

Indefinite anticoagulant therapy is indicated when recurrent thrombosis is associated with a recognized thrombophilic defect. The target INR should range between 2 and 3.^{2,7,8}

1.3.4 ACUTE MYOCARDIAL INFARCTION

Vitamin K antagonists may be effective in preventing stroke and VTE in patients with acute myocardial infarction associated with left ventricular dysfunction, myocardial wall aneurysm or extended anterior necrosis. The INR might range between 2 and 3. Beneficial effects have also been reported in the long-term management of acute myocardial infarction.^{5,9}

1.4 Adverse effects

Bleeding is the main complication of VKA therapy and the risk increases with the intensity of treatment.¹⁰ The higher the INR value, greater is the risk of hemorrhage. The concomitant use of antiplatelet agents and of other drugs, or the presence of clinical conditions that impair hemostasis, contribute to increase this risk. Skin necrosis occurs in 1/10,000 patients at the initiation of therapy. This complication is linked to the rapid decrease in protein C that leads to hypercoagulability and formation of thrombi in venules and capillaries within the *sc* fat. Therefore, treatment with VKA should be initiated under the coverage of therapeutic doses of heparin and increased gradually. Allergic reactions, hepatitis and renal insufficiency may occur rarely.

1.5 Contraindications

Vitamin K antagonists are contraindicated in cirrhosis, severe uncontrolled hypertension, recent stroke or head trauma, neurosurgery, known hemorrhagic disorder and gastric erosion. During pregnancy, VKA cross the placenta and can produce embryopathy and neurological abnormalities (first trimester) or fetal bleeding (third trimester).¹¹ In some specific situations such as mechanical heart valves, the decision to continue oral treatment when full dose heparin cannot be used may be justified. Hemorrhagic complications and thrombosis are more frequent with long-term *iv* heparin than with VKA.

2 Perioperative management of patients receiving VKA

In the perioperative period, management of patients receiving VKA should take two factors into account: the risk of thromboembolic events when anticoagulant therapy is interrupted and the risk of bleeding associated with the invasive procedure when VKA are continued or a substitution therapy is used.^{12–14}

The efficacy, i.e., the prevention of perioperative thromboembolism, and the safety, i.e., the reduction in perioperative bleeding, of different perioperative anticoagulation strategies have been poorly investigated. The substantial difference in the consequences of thromboembolism on the one hand and of major bleeding on the other should also be considered: permanent disability or death is common after arterial thromboembolism (75%) but is infrequent after VTE (4–10%) or major postoperative bleeding (1–6%).¹⁵ Not all patients receiving VKA will need an alternative therapy perioperatively, as the risk of thromboembolism during the interruption of treatment is low and is outweighed by the risk of perioperative bleeding.¹⁶

Several approaches are conceivable, therefore, depending essentially on three variables: 1) the indication for anticoagulation, which determines the thromboembolic risk; 2) the pharmacokinetics of VKA, which determine the moment at which treatment should be discontinued; and 3) the type of surgery, which determines the hemorrhagic risk. Assessment of these three factors will determine the perioperative management of patients receiving VKA.

1) Indication for anticoagulation

The assessment of the patient's thromboembolic risk is important in the decision to initiate therapy in the perioperative period. Kearon and Hirsh reviewed this topic and suggested therapeutic options based on estimates of the preoperative and postoperative daily risk of thrombosis and bleeding.¹⁶ Patients with a history of proximal deep vein thrombosis or pulmonary embolism within the previous month have a high risk of a VTE event. A high risk of arterial or valve thrombosis is encountered in patients with a prosthetic mitral valve, an aortic caged-ball valve or when two prosthetic valves are in place. The risk increases when AF is present, whether AF is associated or not with an enlarged atrium. Patients with a history of stroke are also at high risk. In these situations, anticoagulant substitution therapy should be strongly considered. Nevertheless, these assessments of the risk of thromboembolism were estimated from mathematical models derived from studies of patients in non-surgical settings (Table III).^{12,15,16} The ill defined duration of follow-up reported in many studies, the theoretical risk of rebound hypercoagulability after discontinuation of VKA and the hypercoagulable state induced by surgery may be implicated in an increased, although unproven, risk of thromboembolic events associated with surgery.^{15,16} Table IV provides a stratification of the thromboembolic risk according to the indication for VKA therapy and indicates when perioperative

TABLE III Annualized risk of thrombotic complications for selected conditions in the absence of anticoagulant therapy¹⁵

Conditions	%
Lone atrial fibrillation	1
Average risk atrial fibrillation	5
High-risk atrial fibrillation	12
Dual-leaflet (St Jude) aortic valve prosthesis	12
Dual-leaflet (St Jude) mitral valve prosthesis	22
Single leaflet (Bjork-Shiley) aortic valve prosthesis	23
Multiple St Jude prostheses	91

substitution therapy should be considered.

2) The pharmacokinetic properties of VKA

The period during which VKA administration should be interrupted before elective surgery may vary according to the half-life of the drug, the initial and the desired INR for that type of surgery (see below), and the age of the patient. Table I highlights the time needed to reverse anticoagulation according to the specific VKA. In order to reach a secure INR threshold of 1.5 (see below), an interruption of four to five days is necessary for warfarin, whereas 48 to 72 hr are enough for acenocoumarol. This period will need to be extended if the initial INR is high (3–3.5) and in elderly patients.^{17,18} As the decrease in INR over time is exponential and highly variable, INR testing is recommended on the day of surgery.¹⁸

When VKA with very long half-lives are used, another strategy consists of maintaining or reducing the dose of VKA while simultaneously administering vitamin K₁ and monitoring the INR.¹⁹

3) The type of surgery

The risk of adverse events is clearly associated with the type of surgery.¹⁴ The overall frequency of bleeding and thromboembolic events related to surgery was reported to be 11.9% (95% confidence interval 9.3–14.9; 9.5% for hemorrhage and 2.5% for thromboembolism) in a study of 603 patients treated with VKA for mechanical heart valve prostheses, AF or myocardial infarction. Bleeding frequencies varied from a minimum of 0 (eye and orthopedic surgery) to 34% (thoracic surgery) of procedures. Two-thirds of all events occurred within 48 hr after surgery. Bleeding complications occurred most frequently and these were more often located at the surgical site or in the gastrointestinal tract.

Some invasive procedures can be performed while patients are fully or partially anticoagulated, because

TABLE IV Stratification of the thrombotic risk according to the indication for anticoagulation with VKA^{15,19,29}

		<i>High</i>	<i>Moderate</i>	<i>Low</i>
<i>Prosthetic valve</i>	Localization	Mitral Aortic single-leaflet Two prosthetic heart valves	Aortic valve and ≥ 2 TE risk factors*	Aortic valve and < 2 TE risk factors* Bi-leaflet tilting disc type (e.g., St. Jude, Carbomedics)
	Type	First generation valve: caged-ball valve (e.g., Starr-Edwards) Single-leaflet tilting disc type (e.g., Bjork-Shiley, Medtronic-Hall)		
<i>Chronic atrial fibrillation (AF)</i>		Recent history of stroke or transient ischemic attack (TIA) Rheumatic mitral valvular heart disease	≥ 2 TE risk factors*	Lone AF, ≤ 65 yr old, and < 2 TE risk factors*
<i>Venous thromboembolism (VTE)</i>		Recent (≤ 1 month) episode of VTE Cancer Antiphospholipid antibody Chronic cardiac or pulmonary disease	VTE episode ≤ 6 months VTE recurrence associated with previous warfarin interruption	
Perioperative substitution anticoagulant therapy		Strongly recommended	Should be considered	Optional

*Thromboembolism (TE) risk factors include atrial fibrillation, atrial dilatation, left ventricular dysfunction, cardiomyopathy, history of a TE event (TIA or stroke), hypertension, diabetes mellitus, age > 75 yr.

TABLE V Type of surgery and bleeding risk

Minor surgery without interruption or reduction of VKA (INR in the therapeutic range, < 2.0)

Dental surgery
 Single or multiple extractions
Dermatological surgery
Eye surgery
 Cataract
 Eyelid
Endoscopy with or without biopsy
 Upper gastrointestinal tract
 Lower gastrointestinal tract
Joint and soft tissue injection, arthrocentesis

Surgery requiring discontinuation of VKA (INR < 1.5)

Orthopedic surgery
 Hip
 Knee
 Shoulder
Abdominal surgery
 Digestive tract
 Urology
Major surgery
 Neurosurgery
 Vascular surgery
Thoracic surgery
 Coronary artery bypass graft
 Heart valve surgery
 Lobectomy

VKA = vitamin K antagonists; INR = international normalized ratio.

bleeding is infrequent and/or easily controlled. Most patients can undergo dermatological surgery, dental procedures, cataract surgery, and diagnostic endoscopy without discontinuing anticoagulation, providing the INR is within the therapeutic range (i.e., not more than 4).^{15,20,21} For patients undergoing dental procedures, tranexamic acid mouthwash will avoid the need to interrupt VKA.²² Cataract surgery is associated with a mean incidence of perioperative bleeding of 10% (range 6 to 30%) if VKA therapy is not interrupted.¹⁵ A reduction in the daily warfarin dosage by 50% on days four, three, and two before minor surgery (to obtain a maximum preoperative INR value of 2) has been shown to be safe and inexpensive, avoiding the cumbersome shift to either *iv* or *sc* heparin.²³

An INR of 1.5 is generally considered not to increase the risk of perioperative bleeding.^{16–18} However, for neuraxial blockade, Horlocker *et al.* recommend an INR less than 1.5,²⁴ as for neurosurgical procedures a level closer to 1.0 may be advisable. The bleeding risk according to the type of surgery and the INR target value are shown in Table V.

If the INR remains higher than 2.0 on the day before the operation, administration of a low dose of vitamin K₁ can reverse anticoagulation; doses as low as 1 to 2 mg have been shown to reduce anticoagulation effects adequately.²⁵ Intravenous administration of vitamin K₁ offers a more predictable and rapid reversal of VKA than the *sc* route when a timely correction is needed (within eight hours).²⁶ However, the *iv* route has been associated with the development

of anaphylaxis.²⁷ Alternatively, the oral administration of phytonadione has similar efficacy and safety to *iv* vitamin K₁.^{25,28} Importantly, higher doses of vitamin K₁ are useless, and even harmful, as they can induce resistance to anticoagulation in the postoperative period.¹⁶ For surgery with a moderate bleeding risk, administration of vitamin K₁ 24 to 48 hr before surgery, while maintaining the same dose of VKA, has been proposed.^{12,19}

3 Perioperative substitution (“bridging”) anticoagulant therapy

The perioperative management of the patient receiving VKA ranges between two extremes: a minimalist strategy of withholding VKA without any substitution of anticoagulant therapy and an aggressive strategy of withholding VKA with full substitutive anticoagulation. Substitutive anticoagulation is usually achieved with *iv* unfractionated heparin (UFH) although interest in the use of *sc* LMWH has increased, as LMWH are much less expensive and more convenient to use. However, recommendations may vary from country to country.

Intravenous UFH

Bridging therapy during interruption of VKA may involve the administration of full-dose *iv* UFH, in order to assure readily reversible anticoagulation before and after an invasive procedure. However, this schedule is complex and rather expensive, since *iv* UFH is usually started two days after VKA withdrawal (about three to four days before surgery for warfarin, two to three days for acenocoumarol), while patients are in the hospital. Heparin infusion (initial dose 10 UI·kg⁻¹·hr⁻¹) has to be adjusted periodically to a target aPTT 1.5 to two times the normal range.²⁹ The therapeutic level varies according to the reagent used in the laboratory and should be calibrated in order to correspond to a heparin concentration of 0.2 to 0.4 UI·mL⁻¹ (anti-Xa or anti-IIa activity). Intravenous UFH is usually interrupted a least four hours before surgery and resumed 12 to 24 hr after surgery according to the bleeding risk.^{6,16,18} Vitamin K antagonists are resumed as rapidly as possible postoperatively according to the bleeding risk. Intravenous UFH can be discontinued when the INR again reaches the target therapeutic range, generally three to four days later (for INR 2.0–3.0; four to five days to reach a target INR between 2.5–3.5). Intravenous UFH is often preferred for high bleeding risk surgery because of its short duration of action and the possibility to reverse the anticoagulant effect with protamine.

Subcutaneous UFH

In order to avoid hospitalization, UFH can also be administered *sc* (400 UI·kg⁻¹·day⁻¹ to achieve full anticoagulation), in two or three injections a day. The major drawbacks of this approach are the need for repeated injections and the difficulty adjusting the dose because of the low bioavailability of UFH along with a poorly predictable anticoagulant effect.

Subcutaneous LMWH

Low molecular weight heparins often offer a better benefit/safety ratio (as compared to UFH), and have been proposed as an attractive substitutive anticoagulant therapy.^{16,29,30} Limited studies support the conclusion that outpatient administration of LMWH for bridging anticoagulant therapy is simple, effective, safe and much less expensive.^{13,16,31–37} Depending on the type of surgery, Amorosi *et al.* showed that the cost of bridging therapy can be reduced by 65 to 85% with patient-administered LMWH at home and by 63 to 77% with nurse-administered LMWH compared with the in-hospital, continuous infusion of *iv* UFH.³¹ Nevertheless, more studies are needed to determine whether outpatient perioperative *sc* LMWH therapy should be a recommended alternative to hospitalization and *iv* UFH in high-risk patients.¹²

The main advantages of LMWH are their high bioavailability (better pharmacokinetic predictability, less inter-patient variability), the possibility of treatment on an out-of-hospital basis, a once or twice daily administration, and no need for monitoring. Iterative plasma measurements of anti-FXa activity following therapeutic doses of LMWH may be helpful in pregnant women,³⁸ in small children, in obese patients or in patients with renal failure.³⁹ In line with this recommendation, a substantial proportion of patients older than 70 yr could benefit from monitoring of anti-FXa activity as creatinine clearance is frequently reduced in these patients. An anti-Xa activity of 0.5–1 UI·mL⁻¹ measured four hours after the administration of LMWH should be expected. Otherwise, the administration of aPTT-guided anticoagulation with UFH may represent a more realistic option in these situations.⁴⁰ Finally, as for UFH, a platelet count should be obtained at regular intervals to detect heparin-induced thrombocytopenia.

Finally, no studies have compared bridging anticoagulation using outpatient *sc* LMWH treatment with hospital *iv* UFH during temporary interruption of VKA therapy in the perioperative setting. Based on the available evidence, UFH is recommended for the perioperative substitution of anticoagulation with VKA; however, a limited number of studies do support the

TABLE VI Perioperative substitution (“bridging”) therapy according to thromboembolic risk

<i>Thromboembolic risk</i>	<i>Stop VKA before surgery</i>	<i>Preoperative anticoagulant substitution before surgery</i>	<i>Last dose before surgery</i>	S U R	<i>Postoperative anticoagulant Depending on the bleeding risk (6 to 12 hr after surgery)</i>	<i>VKA postoperatively</i>
Low	• 4 days (warfarin)	Optional: <i>Prophylactic doses</i> Low dose UFH <i>sc</i> or LMWH (outpatient)	UFH <i>sc</i> : 4–6 hr LMWH: 12 hr	G E R Y	<i>Prophylactic doses</i> Low dose UFH <i>sc</i> or LMWH <i>sc</i>	• Resume as soon as possible depending on the bleeding risk
Intermediate	• 3 days (acenocoumarol)	LMWH (outpatient)				
	• Earlier when the INR is high and patients are older	2 days after cessation or when INR ≤ 2: <i>Prophylactic doses</i> Low dose UFH <i>sc</i> or LMWH (outpatient)	UFH <i>sc</i> : 4–6 hr LMWH: 12 hr			• Stop heparin when INR > 2
High		2 days after cessation or when INR ≤ 2: <i>Full doses</i> UFH <i>iv</i> (hospitalization) or UFH <i>sc</i> or LMWH (outpatient)	UFH <i>iv</i> 4–6 hr UFH <i>sc</i> : 6–12 hr LMWH 24 hr		<i>Full doses</i> UFH <i>sc</i> or <i>iv</i> or LMWH	

All recommendations above are grade 2C.⁹ Doses are presented in Table VII. VKA = vitamin K antagonists; INR = international normalized ratio; UFH = unfractionated heparin; LMWH = low molecular weight heparins.

use of LMWH in this context. Table VI provides an indication of perioperative bridging therapy according to the thromboembolic risk. Prophylactic and therapeutic doses of LMWH are given in Table VII.

4 Emergency surgery

In the case of an emergency or, life-threatening situation, the use of prothrombin complex concentrate (PCC) is convenient and corrects coagulation more rapidly than fresh frozen plasma (FFP). Prothrombin complex concentrate is produced by the fractionation of pooled plasma and is available in lyophilized form. The powder is reconstituted with sterile water immediately prior to administration. The recommended dose is 1.5 U·kg⁻¹ expressed in factor IX, for each 1.5 reduction in INR value. For example, in patients with an INR of 2.0–3.9 this represents a total dose of 25 U·kg⁻¹ and for an INR of 4.0–5.9, an initial dose of 35 U·kg⁻¹ is proposed. Tables for PCC dose according to body weight of the patient, initial INR and desired INR are available in the manufacturer’s brochure. In practice, the INR is measured immediately after the administration of PCC and an additional dose can be administered if necessary to reach the desired level (titrated dose). A single administration of PCC is generally sufficient, given the action of vitamin K on the vitamin K-dependent factors. In an emergency, the benefit is obvious and outweighs the disadvantages, which include a rela-

tively high cost and a potential thromboembolic risk. Thromboses have been documented in hemophiliacs after administration of PCC in acute surgical situations and for warfarin reversal. All the reported cases had risk factors for thrombosis that included cirrhosis, congestive cardiomyopathy, resuscitation and shock, and carcinoma.⁴¹ However, the thrombotic risk of the newer PCC formulations still needs to be evaluated.^{42,43}

If PCC is not available, FFP should be considered. However, FFP is not the optimal choice for reversing anticoagulation for several reasons: the recommended volume (10 to 15 mL·kg⁻¹) may be critical in patients with cardiovascular disease, FFP has to be blood-group specific, and thawing incurs delays in administration. Virus-inactivated plasma is secured only by a solvent-detergent technique or by the methylene blue method, which entail additional costs. Moreover, a lack of correction of factor IX may be observed, particularly in cases of over-anticoagulation (INR > 5) presenting as a hemophilia B-like syndrome.⁴⁴ It is worth mentioning that the INR is not sensitive to changes in factor IX and that the correction of anticoagulation may be underestimated.⁴⁴ Advantages of PCC over FFP administration are indicated in Table VIII. The administration of recombinant activated factor VII has also been shown to be safe, rapid and effective at correcting a critically prolonged INR and can avert or reverse bleeding associated with warfarin anticoagulation.⁴⁵

TABLE VII Prophylactic and therapeutic doses of LMWH

	<i>Prophylactic doses – sc</i>	<i>Therapeutic doses – sc</i>
<i>Enoxaparin (Clexane®, Aventis Pharma, France)</i>	40 mg once daily	1 mg·kg ⁻¹ twice daily
<i>Dalteparin (Fragmin®, Pharmacia, France)</i>	5000 IU once daily*	100 IU·kg ⁻¹ twice daily*
<i>Nadroparin (Fraxiparine®, Sanofi-Synthelabo, France)</i>	38 IU·kg ⁻¹ once daily	100 IU·kg ⁻¹ twice daily*
		171 IU·kg ⁻¹ once daily
<i>Tinzaparin (Innohep®, Leo, Denmark)</i>	75 IU·kg ⁻¹ once daily*	175 IU·kg ⁻¹ once daily*
<i>Non fractionated heparin</i>	5000 IU·day ⁻¹	3 × 500 IU·kg ⁻¹ ·day ⁻¹ adjusted to
<i>(Calparine®, Sanofi-Synthelabo, France)</i>		the aPTT with a target range of 1.5 to
		2.5 times control

*Expressed as international units anti-Xa activity. LMWH = low molecular weight heparins; aPTT = activated partial thromboplastin time.

TABLE VIII Comparison of characteristics of FFP and PCC when used to reverse anticoagulation with VKA

	<i>FFP</i>	<i>PCC</i>
<i>Volume</i>	10–15 mL·kg ⁻¹	approximately 20 mL; may have to be repeated
<i>Speed of administration of a full reversal dose</i>	Slow	Fast
<i>Virus inactivation</i>	Solvent/detergent method methylene blue	Solvent/detergent method
<i>Blood group matching</i>	Group specific	Not group specific
<i>Thrombogenicity</i>	None	Possible
<i>Cost</i>	The cost of 1 U of FFP (200 mL) is approximately \$105 CAN and the treatment will cost ± \$690 CAN for an adult patient*	The cost of 1 U FIX is approximately \$0.80 CAN and treatment will cost ± \$1650 CAN for an adult patient*

FFP = fresh frozen plasma; PCC = prothrombin complex concentrate. *Prices are indicative for Belgium, Europe.

Conclusion

The management of oral anticoagulant treatment in patients presenting for elective or emergency surgery must take into account the specific pharmacokinetic and pharmacodynamic properties of VKA, the characteristics of the patient (thromboembolic versus hemorrhagic risk), and surgical factors. Further studies are required to determine the optimal substitution (“bridging”) regimen and the clinical circumstances that necessitate substitution therapy.

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