

## REVIEW

## Conventional Anticoagulant Therapy

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## ABSTRACT

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**KEY WORDS:** *antithrombotic therapy; heparin; low-molecular-weight heparins; heparin monitoring; heparin-induced thrombocytopenia; vitamin K antagonists*

## ABBREVIATIONS

ACCP = American College of Chest Physicians  
aPTT = activated partial thromboplastin time  
AT = antithrombin  
BCSH = British Committee for Standards in Haematology  
FFP = fresh frozen plasma  
HIT = heparin induced thrombocytopenia  
INR = international normalized ratio  
LMWH = low molecular weight heparin  
PCC = prothrombin complex concentrate  
PT = prothrombin time  
TTR = time in therapeutic range  
UFH = unfractionated heparin  
VKA = vitamin K antagonists  
VTE = venous thromboembolism

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Conventional anticoagulant regimens are the mainstay of anticoagulant therapy that have been used for over 40 years in the treatment of thrombosis before newer agents became available. They include unfractionated heparin, low-molecular-weight heparins (LMWHs) and vitamin K antagonists (VKAs). Unfractionated heparin is a glucosaminoglycan which through binding to antithrombin accelerates thrombin inhibition. It is administered parenterally and has an immediate onset of action and a variable half-life related to the dose administered. Heparin causes prolongation of the activated partial thromboplastin time (aPTT) which is the assay used to monitor its anticoagulant activity although lately anti-Xa activity assay has also been used for this purpose. The main adverse event of heparin treatment is hemorrhage. Other non-hemorrhagic serious adverse events are heparin-induced thrombocytopenia and osteoporosis. Heparin can be completely and rapidly reversed by the use of protamine sulphate. LMWHs are fragments of unfractionated heparin and act via the same mechanism. LMWHs have replaced unfractionated heparin in most indications of use because their pharmacokinetic properties allow them to be administered once or twice daily without need for routine monitoring of their anticoagulant activity. However, in situations such as renal failure, obesity and pregnancy, where clearance of the drug is altered, monitoring is required and the anti-Xa activity is the recommended test. LMWHs have the same adverse events as unfractionated heparin but to a lesser extent owing to decreased binding to platelets and osteoblasts. Protamine only partially reverses their anticoagulant effect. Vitamin K antagonists were the only orally administered anticoagulant agents until recently. They act through inhibition of the reduced form of vitamin K production which is necessary for anticoagulant factors II, VII, IX, X carboxylation and activation. Their many interactions with other drugs, foods and comorbid conditions render the stability of the anticoagulant response difficult and frequent monitoring is needed. The prothrombin time (PT) test is the most common test used to monitor VKA therapy and it is expressed as international normalized ratio (INR), a standardized ratio of patient's PT to normal PT. The lower and higher INR values beyond which the incidence of adverse events increases is defined as the therapeutic range. For most indications of VKAs the therapeutic range of INR must be 2.0-3.0. The most serious adverse event of VKAs is bleeding, with the rate increasing as the INR rises >5. When reversal of anticoagulant effect is needed vitamin K is administered and in major bleeding vitamin K along with prothrombin complex concentrates (PCC) or fresh frozen plasma (FFP) is recommended.

INTRODUCTION

The term conventional anticoagulant therapy is used to describe traditionally administered anticoagulants. These include unfractionated heparin and low-molecular-weight heparins (LMWH) and the orally administered vitamin K antagonists (VKAs). They have been the only anticoagulant drugs available for many decades and are still being widely used, despite the development of new anticoagulant agents, owing to their proved efficacy in many clinical settings.

UNFRACTIONATED HEPARIN

Unfractionated heparin is a glucosaminoglycan, consisting of alternating disaccharide and pentasaccharide units, found in the secretory granules of mast cells. The most common disaccharide unit in heparin molecule is L-iduronate - D glucosamine.<sup>1</sup> Heparin is a heterogenous molecule; the glucosaminoglycan chains vary in length, thus the molecular weight of heparin varies also, ranging from 3-30 kD, with a mean of 15 kD, which corresponds to approximately 45 saccharide units.<sup>2</sup> Commercial preparations of heparin are extracted from porcine intestinal mucosa or bovine lung which are reach in mast cells.<sup>1</sup>

MECHANISM OF ACTION

The heparin molecule does not have intrinsic anticoagulant activity, it exerts its action by binding to antithrombin, a polypeptide synthesized in the liver. Antithrombin (AT) circulates

in plasma and inhibits the activated coagulation factors of intrinsic and common pathways (factors II, X, IX, XI, XII), whereas it has little activity on factor VII (Fig. 1). Heparin binds to antithrombin by a specific pentasaccharide sequence and induces a conformational change on its molecule, thereby converting antithrombin from a progressive, slow inhibitor to a very rapid inhibitor, enhancing its effect by 1000- fold.<sup>1-3</sup> Heparin then, dissociates from the complex and can be re-used.

Thrombin and factor X are most sensitive to inhibition by heparin-antithrombin complex. For the inhibition of thrombin especially, heparin needs to be bound both to thrombin and antithrombin and this can be accomplished only by long-chain heparin molecules, with at least 18 saccharide units. With a mean molecular weight of 15000 D, almost all heparin molecules can serve this role. Consequently, by definition, heparin inhibits factor X and factor II to a similar extent (1:1).<sup>1-4</sup>

Only one-third of heparin molecules possess the unique pentasaccharide sequence and are responsible for the anticoagulant activity of heparin. The remaining two-thirds have minimal anticoagulant effect at usual therapeutic doses, but at high concentrations (rarely used in clinical practice) they catalyze the antithrombin effect of a second plasma protein, heparin-cofactor II (HC II). At even higher concentrations heparin impairs factor Xa generation by an AT and HC II independent mechanism.<sup>2,5</sup>

Heparin exerts in vitro interaction with platelets, the high-molecular weight low-AT affinity molecules being more interactive. This interaction may contribute to heparin-induced bleeding with a mechanism independent of its anticoagulant effect.<sup>2</sup> In addition to its anticoagulant effect, heparin attenuates proliferation of smooth muscle cells; it inhibits osteoblast

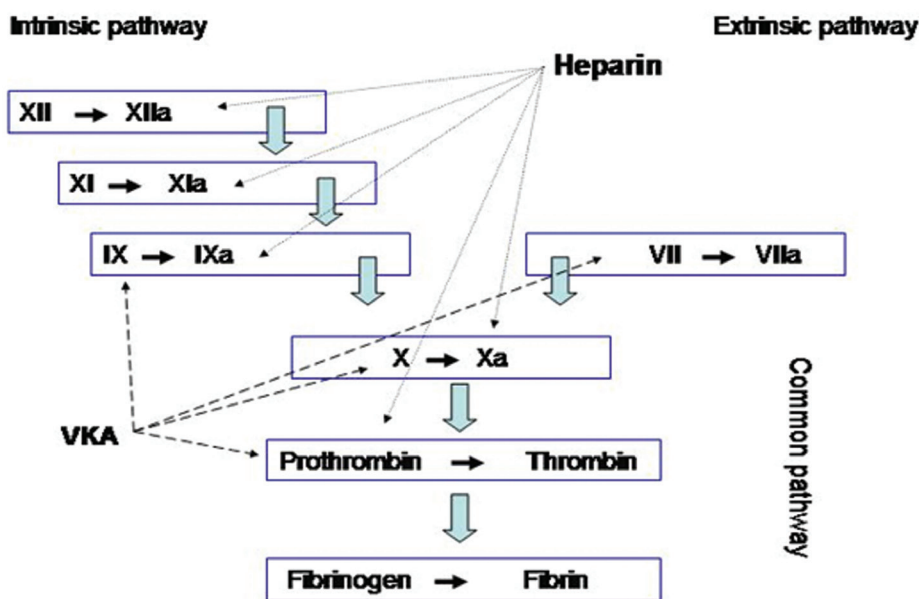


FIGURE 1. Coagulation cascade and sites of action of conventional anticoagulants.

formation and activates osteoclasts. These last two effects promote bone loss.<sup>2,5</sup>

#### PHARMACOKINETICS

Heparin is not absorbed from the gastrointestinal tract, and it is administered intravenously or subcutaneously. The onset of action is immediate when given intravenously, whereas it needs 1-2 hours when given subcutaneously. Subcutaneous route of administration decreases the bioavailability of heparin and larger doses (about 10% higher) are needed to overcome this reduction.<sup>1,2,4</sup> Because heparin binds not only to antithrombin but to other plasma proteins too, which neutralize its anticoagulant effect, its bioavailability varies among patients. Elevated levels of these proteins in patients with inflammatory and malignant conditions contribute to heparin resistance.<sup>2</sup> Heparin's binding to endothelial cells and macrophages further complicates its pharmacokinetics.

The elimination of heparin follows two different pathways: one readily saturable, by internalization and depolymerization into endothelial cells and macrophages and a slower one which is largely renal. The complex kinetics of heparin render the dose-anticoagulant response non-linear, the half-life of heparin rising disproportionately with increasing doses. At usual doses the half-life of heparin is approximately 45-90 min.<sup>2,6</sup>

#### DOSING

Randomized controlled trials have shown a relationship between heparin dose, efficacy and safety. Patients treated with lower starting doses had higher recurrence rates of thromboembolism, as also patients treated with standard dosing of heparin versus weight-based dosing. Those patients that achieved a therapeutic activated partial thromboplastin time (aPTT) during 24 hours had lower mortality rates.<sup>2</sup> The recommended dose for intravenously given heparin is 80 units/kg bolus infusion followed by 18 u/kg/h for venous thromboembolism. Lower initial dose is recommended for cardiac patients, 70 u/kg bolus infusion followed by 15 u/kg/h. A fixed dose of 5000 u followed by 1000 u/h is an alternative dosing scheme. For subcutaneous use of heparin the recommended initial dose is 333 u/kg and 250 u/kg thereafter without monitoring.<sup>7</sup>

#### MONITORING

Given the relationship of heparin dose with efficacy and safety and the variability of anticoagulant response among different patients, it became a standard practice to monitor heparin response and to adjust the dose according to the anticoagulation tests. Heparin results in amplification of antithrombin-mediated inhibition of factors II, IX, X, XI and XII. Therefore heparin therapy at usual doses is associated with significant prolongation of the thrombin clotting time, aPTT and little, if any, prolongation of prothrombin time (PT); most PT reagents contain heparin neutralizer.<sup>8,9</sup> Unfractionated heparin at prophylactic doses does not prolong the aPTT.

For over 30 years the aPTT has been the assay used to monitor heparin therapy and the recommended therapeutic range was determined as 1.5-2.5 times the control value. Its use was based on a single observational study of 234 patients with venous thromboembolism (VTE)<sup>10</sup> and its clinical relevance has not been confirmed by randomized trials.<sup>2</sup> The measured response to aPTT varies between reagents and instruments used to measure the aPTT and the reagents and instruments used have changed over the last 25 years. The American College of Chest Physicians (ACCP) and the College of American Pathologists (CAP) recommend that the therapeutic ranges of aPTT for a given institution must be determined by setting an aPTT range that correlates with an unfractionated heparin (UFH) activity of 0.3-0.7 units/ml by factor-Xa inhibition assay.<sup>2,11</sup> For those heparin levels, modern aPTT reagents and coagulometers produce aPTT ratios that are 1.6-2.7 to 3.7-6.2 times the control values. Therefore, the therapeutic aPTT range should be determined by each laboratory according to the responsiveness of the specific reagent being used. Like aPTT assays, anti-Xa assays also vary in their responsiveness to heparin; therefore standardization of aPTT ratios by reference to anti-Xa levels is also problematic.<sup>2</sup>

Thus, despite its standard use in monitoring unfractionated heparin, aPTT has certain drawbacks as a monitoring method: (1) There is need for aPTT standardization for each laboratory and each lot of testing reagent, because results are not equivalent to the same result from another laboratory. Anti-Xa-related aPTT method does not appear to enhance inter-laboratory agreement.<sup>2,12</sup> (2) The aPTT is affected by many preanalytic, analytic and biologic variables. Examples of preanalytic factors are the underfilling of the tube or the extreme erythrocytosis of the patient. The aPTT can be prolonged in benign factor deficiencies such as factor XII or prekallikrein deficiencies or in the presence of lupus anticoagulant, which neither increases the risk of bleeding nor provides protection from thrombosis but may lead to heparin under-anticoagulation. On the other hand, antithrombin deficiency and increases in factors like VIII and fibrinogen, which are acute phase reactants, in certain inflammatory conditions, may blunt the expected prolongation of aPTT after heparin therapy (a phenomenon referred as 'heparin resistance'), leading to over-anticoagulation and increased bleeding risk. In addition, aPTT is influenced by other conditions (liver dysfunction or vitamin K deficiency, or concomitant warfarin therapy) which may have a synergistic response to prolongation of aPTT beyond the one expected from the given heparin concentration.<sup>11-13</sup> For all these reasons, aPTT has a low specificity in predicting the risk of bleeding.

Unfractionated heparin (UFH) can also be measured using an anti-Xa assay, which may be preferable to aPTT because it provides a direct measure of heparin activity.<sup>8</sup> The test principle of anti-Xa assay is the inhibitory effect of heparin on factor Xa; reagent factor Xa in excess is added to patient plasma sample. Xa activity is neutralized in proportion to the

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amount of heparin present in the plasma. The remaining factor Xa hydrolyzes a Xa-substrate releasing a colored signal that is measured photometrically. The amount of residual factor-Xa is inversely proportional to the amount of heparin in the sample. Results are expressed as units/ml of anti-Xa activity.<sup>11,13</sup> Anti-Xa monitoring assay has its own limitations; first it is not available to all laboratories; it is poorly standardized (the inter-laboratory variation in the results is up to 30%);<sup>8</sup> it is affected by elevated bilirubin and triglyceride levels; and it cannot reflect all anticoagulant properties of heparin, nor other coagulation disorders that render the patient susceptible to adverse events.<sup>11-13</sup> Most importantly, the overall impact of monitoring with anti-Xa assay in clinical outcomes remains unclear.<sup>11</sup>

Studies attempting to evaluate the relationship between aPTT and anti-Xa assay, although with small number of patients, show that there is an overall 50% discordance between the two assays<sup>11,12,14</sup> and that monitoring patients with anti-Xa assay results in increased percentage of tests in therapeutic range, less dose modifications, fewer tests and probably less adverse events.<sup>11,13,15,16</sup> Although the 2004 American College of Chest Physicians evidence-based practice guidelines recommend aPTT for heparin monitoring, the 9<sup>th</sup> edition of Antithrombotic therapy and Thrombosis Prevention guidelines of 2012 do not make suggestions on heparin monitoring using the one over the other assay.<sup>2,5,13</sup> More research is needed to identify the optimal approach in monitoring unfractionated heparin therapy.<sup>2,13</sup>

### ADVERSE EVENTS

The major adverse event of heparin therapy is hemorrhage in 1-5% of patients.<sup>1</sup> The risk of bleeding increases with increasing dose of heparin and with co-administration of fibrinolytic agents or platelet glycoprotein IIb/IIIa inhibitors. The risk is also increased in advanced age, recent trauma or surgery.<sup>2</sup> Other serious, non-hemorrhagic complications are heparin-induced thrombocytopenia and osteoporosis, resulting from heparin's binding to platelets and osteoblasts, respectively. The incidence of heparin-induced low bone density is around 30%,<sup>17,18</sup> whereas symptomatic vertebral fracture may occur in up to 3 of every 100 people.<sup>17,19</sup> The occurrence of osteoporosis appears to be related to the duration of treatment and the daily dosage.<sup>20</sup> Other non-hemorrhagic side effects are very uncommon and include skin reactions, alopecia, hypersensitivity reactions and transient transaminasaemia.<sup>2</sup>

### REVERSAL OF THE ANTICOAGULANT EFFECT

Given the short half-time of heparin, management or prevention of bleeding can be achieved by stopping the infusion of heparin. Heparin's activity can be rapidly reversed by protamine sulphate, a protein extracted from fish sperm. Protamine binds to heparin and forms a stable inactive salt. One mg of protamine neutralizes 80-100 units of heparin. The dose of protamine is calculated according to the quantity of

heparin administered the last two hours since the half-life of heparin when given intravenously is 60-90 min. Thus, if heparin is administered with a rate of 1000 u/h, 20 mg of protamine should be given to reverse heparin's effect. For subcutaneously administered heparin, prolonged protamine administration should be considered, because protamine's half-life is only 7 min. The reversal effect of protamine can be monitored by the aPTT.<sup>1,2,21,22</sup> Protamine at high doses may exert anticoagulant activity on its own, interacting with platelets, fibrinogen and other plasma proteins.<sup>1</sup> Therefore it should be administered up to a maximum dose of 50 mg by a slow, intravenous infusion, slower than 5 mg/min, to avoid severe allergic reactions that include hypotension, bronchospasm and bradycardia,<sup>1,2,21</sup> particularly in insulin-receiving diabetic patients having already been sensitized by protamine-containing insulin preparations (use of highly purified animal insulin or human recombinant insulin has significantly reduced this occurrence).

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## LOW-MOLECULAR WEIGHT HEPARINS (LMWH)

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Like unfractionated heparin, LMWH are glucosaminoglycans. They are produced from controlled chemical or enzymatic depolymerization of heparin, a procedure that results in chains of mean molecular weight around 5000 d, one-third of that of unfractionated heparin, which corresponds to 15 saccharide units.<sup>2,3</sup>

### MECHANISM OF ACTION

The mechanism of anticoagulant activity is the same as that of heparin's: binding to and activation of antithrombin via the unique pentasaccharide sequence. Only 15-25% of LMWH molecules contain this sequence. The main difference between heparin and LMWHs is the ratio of inhibition of factor Xa/factor IIa. For thrombin (factor II) to be inhibited, simultaneously binding of heparin to antithrombin and thrombin must occur. Unfractionated heparin molecules are long enough to serve this role, but most of the low-molecular-weight-heparin chains are not. In contrast, all LMWH containing the pentasaccharide sequence can inhibit factor Xa. Thus, while heparin has equivalent activity against factor Xa and factor IIa, low-molecular-weight-heparins exert more anti-Xa activity and have anti-Xa/anti-II a ratios between 2:1 and 4:1.<sup>2,3</sup> There has been much debate about the relative importance of anti-Xa/anti-IIa activity in the anticoagulant effect of LMWHs. At present there is no evidence that differences in anti-Xa/anti-IIa activity among LMWHs influence clinical outcomes, bleeding or thrombosis.<sup>2</sup>

### PHARMACOKINETICS

Compared to heparin, LMWHs exhibit less binding to plasma proteins, a fact that results in better bioavailability;

after subcutaneous injection the bioavailability is 90% rendering the anticoagulant effect of LMWHs more predictable. Decreased binding to macrophages and endothelial cells of LMWHs results in longer half-life that is independent of dose. The elimination half-life after subcutaneous injection is 2-6 hours. These superior pharmacokinetic properties allow for once or twice daily administration and eliminates the need for anticoagulation monitoring.<sup>1-3</sup> Several studies have shown no benefit of monitoring and no association of anti-Xa levels with the rates of bleeding. Therefore monitoring is not generally recommended for the majority of patients.<sup>2</sup>

The clearance of LMWHs is mainly renal, and this limits their use in renal failure. Such cases require monitoring, as well as obese patients and pregnant women on treatment doses. Likewise, when anticoagulant effect is being questioned – occurrence of thrombosis or bleeding during therapy – monitoring is advisable.<sup>2</sup>

For monitoring the anti-Xa level is recommended. As anti-Xa levels peak in 3-5 hours after dosing the peak concentration following is approximately 4 hours after dosing. For venous thromboembolism a conservative peak anti-Xa level with twice daily enoxaparin is 0.6-1.0 u/ml. The peak anti-Xa level is different for each LMWH preparation; for a certain preparation the once or twice daily doses differentiate the peak. Thus, the target anti-Xa level for once daily enoxaparin is above 1.0 u/ml.<sup>2,23</sup>

#### DOSING IN SPECIAL SITUATIONS

Appropriate dose in patients with renal insufficiency, overweight patients and pregnant women is uncertain because such patients are excluded from large, randomized trials. Monitoring with anti-Xa assay provides some guidance to dosing.

Results from pharmacokinetic studies with therapeutic doses of enoxaparin and dalteparin show a clear relationship between anti-Xa levels and renal clearance, the anti-Xa levels rising when clearance declines to <30 ml/min. The same is observed, though less frequently, after prophylactic doses of enoxaparin. Decreased renal clearance was shown to increase the risk of bleeding in patients with creatinine clearance (CrCl) <30 ml/min treated with therapeutic enoxaparin dose. Prophylactic doses did not increase the risk of bleeding in trials even at CrCl <30 ml/min. Use of unfractionated heparin in patients with renal insufficiency is a treatment option in order to avoid the bioaccumulation that occurs with LMWHs. If LMWHs are administered, the dose should be reduced to about 50% for enoxaparin. Data are lacking for other LMWH preparations.<sup>2,23,24</sup>

Pregnancy alters renal function and fluids distribution thus affecting the clearance and distribution of the drugs. Data suggest that there is a higher LMWH turnover in pregnancy and thus higher doses are required for both treatment and prophylaxis.<sup>23,25</sup> In high-risk patients, trough anti-Xa monitor-

ing is often used to ensure constant anticoagulation, although there is no consensus on target concentration.<sup>23</sup>

Dosing in obese patients is not established. LMWHs clearance correlates with lean body mass, therefore the addition of adipose weight in weight-based calculation of dose is not justified; dosing based on total body weight may result in excessive concentrations.<sup>23</sup> However, in studies with enoxaparin but also dalteparin and tinzaparin, anti-Xa activity with total-weight-based doses increased to appropriate levels in patients up to 190 kg and there was no excess in the rate of major bleeding in obese patients over that observed in non-obese patients in total-weight-based adjusted doses.<sup>2</sup> For thromboprophylaxis with fixed-dose of enoxaparin and nadroparin there is a strong negative correlation between anti-Xa levels and total body weight; thus, a weight-based prophylactic dose over a fixed dose is suggested for obese patients.<sup>26</sup>

Aged patients may be treated with LMWH at the same weight-adjusted doses as employed in younger adults. However, in elderly underweight patients (<45-50 kg), such dosing may result in an increased incidence of bleeding, and measures for use of lower dosing should be taken.

Unfortunately there are no data on dosing modifications once the results of anti-Xa levels are known. Based on drug pharmacokinetics the dose-response is linear, and a rational approach is decreasing the dose if the clearance is in normal range or extending the frequency of administration when clearance is significantly reduced.<sup>23</sup>

#### ADVERSE EVENTS

Low molecular weight heparins cause less bleeding than unfractionated heparin in laboratory animals<sup>3</sup> and this is probably attributed to less binding with platelets and the neutral effect on vascular permeability compared to heparin. LMWHs can cause heparin-induced thrombocytopenia (HIT) and osteoporosis to a lesser extent than unfractionated heparin, because they bind less to platelets and osteoblasts, respectively.<sup>2,27</sup> Thus, the incidence of HIT is more than threefold lower with LMWHs. Osteoporosis has been studied mostly in pregnancy where it seems that with prophylactic doses the incidence of osteoporosis is low, comparable to that of non heparin-treated patients.<sup>28</sup>

#### REVERSAL OF ANTICOAGULANT EFFECT

Protamine reverses approximately 60% of the anticoagulant effect of LMWHs.<sup>21</sup> Protamine binds only to longer chain molecules of LMWHs which exert anti-II activity and fully reverses it. In contrast, anti-Xa activity which is mediated by short molecules is partially reversed by protamine.<sup>1,2,29</sup> The clinical significance of incomplete neutralization of anti-Xa activity of LMWHs is unclear. Data on LMWHs reversal effects of protamine are relatively scarce. The largest study using protamine in patients on LMWH treatment showed that it prevented excessive bleeding in surgical patients and

effectively managed active bleeding in 8 out of 12 bleeding patients. Anti-Xa levels did not correlate with the likelihood of persistent bleeding. Recombinant factor VII for the reversal of LMWHs has not been evaluated in clinical trials, but in a few case reports.<sup>2,21,29</sup>

If reversal of LMWHs activity is needed within the last 8 hours of administration, protamine sulphate is given in a dose of 1 mg for every 100 anti-Xa units of LMWH up to a maximum dose of 50 mg. A second dose of 0.5 mg of protamine per 100 anti-Xa units is considered if bleeding has not been controlled. Smaller doses are administered if LMWH was given over than 8 hours prior to the time of correction.<sup>2,21</sup>

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**CLINICAL INDICATIONS  
FOR HEPARIN USE**

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Both unfractionated and LMWHs are currently being used for prophylaxis and treatment of venous thromboembolism and pulmonary embolism in medical and surgical patients - especially orthopedic patients in hip and knee replacement operations – and also in pregnancy and peripartum. They are also administered in acute coronary syndromes and myocardial infarction<sup>30,31</sup> (Table 1). For most of these indications, LMWHs

**TABLE 1.** Current indications for the use of heparin.

Prevention of venous thromboembolism in <ul style="list-style-type: none"> <li>• Medical patients at high risk</li> <li>• Surgical patients at high risk</li> <li>• <b>Surgical patients with cancer</b></li> <li>• <b>Orthopedic surgeries (TKA, THA, HFS)</b></li> </ul>
Treatment of <ul style="list-style-type: none"> <li>• Venous thromboembolism</li> <li>• Pulmonary embolism</li> </ul>
<b>Pregnancy (for both prevention and treatment of VTE/PE)</b>
Acute coronary syndromes <ul style="list-style-type: none"> <li>• with or without STEMI</li> <li>• primary PCI or not</li> </ul>
Acute limb ischemia
Hemodialysis
Coronary artery bypass grafting surgery

Indications shown with bold letters are those for which unfractionated heparin has been replaced by LMWHs as first line treatment according to the latest ACCP recommendations.

ACCP: American College of Chest Physicians; HFS: hip fracture surgery; LMWH: low-molecular weight heparin(s); PCI: percutaneous coronary intervention; PE: pulmonary embolism; STEMI: ST elevation myocardial infarction; THA: total hip arthroplasty; TKA: total knee arthroplasty; VTE: venous thromboembolism.

have replaced unfractionated heparin due to their proven efficacy and convenience of use that includes administration once or twice daily and no need for monitoring in the majority of patients. They are also associated with fewer adverse events (major hemorrhage, osteoporosis, HIT) compared to unfractionated heparin. A limitation of LMWHs use is renal failure (CrCl <30 m/min), as they are predominately cleared by the kidneys and their biologic half-life may be prolonged in renal impairment; in such patients dose reduction or an alternative anticoagulant should be considered. Unfractionated heparin remains the drug of choice in cardiopulmonary bypass operations and hemodialysis.<sup>32,33</sup>

LMWH is the preferred agent for venous thromboembolism (VTE) prevention after a major orthopedic operation (total knee or hip arthroplasty or hip fracture surgery) and it should be administered for at least 10-14 days after the operation.<sup>32</sup> Extending thromboprophylaxis up to 35 days after surgery should be considered in these patients. For pregnant patients, LMWHs are the recommended agents for prophylaxis and treatment of VTE.<sup>32</sup>

LMWH is the drug of choice for both initial and long-term treatment of cancer-related venous thromboembolism.<sup>32,34,35</sup> Cancer patients have an increased risk of VTE recurrence and bleeding complications while receiving anticoagulant therapy. Long term anticoagulation with LMWHs is associated with a significant reduction of thrombosis recurrence without a statistical significant increase in bleeding risk compared with VKAs.<sup>35,36</sup> Treatment duration of at least 6 months or as long as the malignancy is active is recommended.<sup>34,37</sup>

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**HEPARIN INDUCED  
THROMBOCYTOPENIA**

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Heparin induced thrombocytopenia (HIT) is a life-threatening, procoagulant disorder occurring in 0.2-5% of patients recently exposed to unfractionated or, less commonly, LMWH.<sup>38,39</sup> Patients typically present with low platelet count, and thromboembolic manifestations affecting 20-50% of patients.<sup>38,40</sup> The syndrome is associated with mortality rates of 5-10% usually as the result of thrombotic complications.<sup>41</sup>

The syndrome is caused by IgG antibodies against heparin-platelet factor 4 (PF4) complex<sup>38,39,41</sup> which binds to FcγIIa receptor on platelet surface – but also to monocytes and endothelial cells – activating them. Platelet's activation and aggregation results in thrombocytopenia and releases procoagulant microparticles that further activate the coagulation cascade with thrombin production.<sup>41</sup> Heparin-PF4 antibodies are present in all patients who develop HIT but they are also present in many patients exposed to heparin without clinical manifestations.<sup>38,41</sup> Why some antibodies are pathogenic and others not is not clear, but this may relate to the titer of the antibody or the size of heparin-PF4 complex.<sup>41</sup>

Risk factors for HIT development are drug-related and patient-related. Heparin related risk factors are type of heparin and duration of treatment. LMWH is associated with a 5-10 fold lower risk of HIT than unfractionated heparin,<sup>39</sup> and the overall incidence is 0.2-1% compared to 1-5% with UFH. The risk is higher as the duration of therapy rises to more than 5 days<sup>39,41,42</sup> and with full dose anticoagulation.<sup>42</sup> Older patients and women are at increased risk. Surgical patients have a higher risk than medical patients, orthopedic patients being at particular high risk.

Thrombocytopenia occurs usually after 4-15 days of heparin administration and may be absolute ( $<150 \times 10^9/\text{ml}$ ) or relative, with a 50% reduction from the count on the day of commencement of heparin. Platelet count rarely fall below  $20 \times 10^9/\text{ml}$ , are rarely associated with bleeding and they rise again within 4-14 days after heparin cessation.<sup>38,39</sup> In patients previously exposed to heparin (during the last 30 days) who also have heparin-PF4 antibodies, platelet count drops rapidly, within hours of heparin exposure.<sup>38,39,41</sup>

Thrombotic complications can occur simultaneously or may arise after platelet count drop.<sup>38,41</sup> In a series of patients, thrombosis appeared before any apparent fall in the platelet count.<sup>38</sup> Thrombosis can complicate the clinical course of patients with thrombocytopenia even after heparin discontinuation if an alternative antithrombotic agent is not administered.<sup>27,39</sup> The rate of venous to arterial thrombosis is 4:1. Patients typically present with deep venous thrombosis or pulmonary embolism but thrombosis in unusual sites can occur, such as splanchnic vein or cerebral venous sinuses.<sup>38,41</sup> Arterial thromboembolism, most commonly affecting the extremities is also common particularly after cardiac surgery and can progress to limb necrosis necessitating amputation.<sup>39,41</sup> Myocardial infarction and stroke are among less often manifestations.<sup>40</sup>

Establishing the diagnosis of HIT in patients with complicated clinical courses is challenging, though suspicion of the diagnosis on clinical grounds is essential for clinical outcome. HIT should be suspected in any patient exposed to heparin who presents with thrombocytopenia and thrombosis. Other causes of thrombocytopenia must be excluded to prevent unnecessary and potential harmful treatment. Several clinical scoring systems have been developed in order to help clinicians establish the probability of HIT, including the 4T score<sup>43</sup> and the Hit Expert Probability (HEP) score.<sup>41</sup> These scoring systems have high negative predictive value but low positive predictive value<sup>41,44</sup> though, and may be useful in combination with laboratory results in establishing a diagnosis.

Two general serologic assays for HIT are used: quantitative enzyme immunoassays that detect antibodies against heparin-PF4 complex and functional assays that measure platelet activation induced by these antibodies.<sup>38-41</sup> Enzyme immunoassays are readily available and have a high sensitivity, almost 100%, but low specificity. Functional assays such as serotonin-release assay or heparin-induced platelet aggregation test are both

sensitive and specific but are not widely available and their technical requirements restrict their use in reference laboratories.<sup>39,41</sup> Serologic testing for anti-heparin-PF4 antibodies is recommended in patients with a high or intermediate probability score in which strongly positive results make the diagnosis more probable and negative results precludes it.<sup>39,41</sup> In such patients functional assays further affirm the diagnosis though they are not considered necessary.<sup>41</sup> In patients with intermediate probability and positive serologic results a functional assay may help to establish the diagnosis.<sup>38,41</sup>

The goals of *management of HIT* is to reduce thrombotic risk by reducing platelet activation and thrombin production. Heparin administration must be discontinued immediately in high or intermediate clinical suspicion of HIT including heparin used to maintain patency of intravenous lines, and alternative anticoagulant therapy should be offered. LMWHs should not be used as an alternative treatment since they can form complexes with PF4 that are capable of binding HIT antibodies. Consequently in patients with HIT there is cross-reactivity of LMWHs and they should not be used.<sup>2,27</sup> The most appropriate anticoagulant for heparin induced thrombocytopenia remains uncertain. Studies evaluating the anticoagulant used for HIT suffer important methodologic limitations, including the use of historical controls, small sample sizes and inconsistencies in diagnosis.<sup>41</sup> The ACCP makes a weak recommendation for the use of argatroban or lepirudin (both direct inhibitors of thrombin) or danaparoid (antithrombin-mediated Xa inhibitor) over other non-heparin anticoagulants.<sup>32</sup> The British Committee for Standards in Haematology (BCSH) recommends danaparoid and alternatively argatroban for patients with HIT.<sup>27</sup> Lepirudin is no more available in both United States and Europe and danaparoid was withdrawn from the United States market in 2002. Fondaparinux, an indirect inhibitor of factor Xa, has been increasingly used and is an acceptable alternate although it has not been licensed for this indication.<sup>27,32,41</sup> Because HIT carries a high risk of subsequent thrombosis, long-term anticoagulation therapy is needed. Vitamin K antagonists should be administered but only after the platelet count has returned to normal levels since they have the potential of aggravating thrombosis through rapid reduction of protein C. For isolated heparin induced thrombocytopenia, anticoagulation continues for six weeks. When thrombosis has occurred duration is extended up to 3-6 months.<sup>27,32,41</sup>

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#### VITAMIN K ANTAGONISTS

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Vitamin K antagonists (VKAs) are anticoagulants that have been successfully used for many decades in a variety of clinical settings. Numerous anticoagulants have been synthesized as derivatives of 4-hydroxycoumarin or the related compound indandione. Compounds that are widely being used currently are 4-hydroxycoumarin derivatives, mainly

warfarin (Coumadin, Panwarfin), but also acenocoumarol (Sintrom) and phenprocoumon. Anisindione and phenindione (indandione derivatives) are not in use because of serious adverse effects.<sup>1</sup>

#### INDICATIONS FOR USE

Vitamin K antagonists are currently used for primary and secondary prophylaxis from venous and arterial thromboembolism. In particular, they are administered for **thromboprophylaxis** after orthopedic procedures, in patients with thrombophilia and for the prevention of arterial thromboembolism in patients with atrial fibrillation, prosthetic heart valves and rheumatic mitral valve disease. They have been the treatment of choice for long-term therapy of venous thromboembolism and pulmonary embolism.<sup>32</sup>

#### MECHANISM OF ACTION

VKAs interfere with vitamin K oxidation-reduction cycle. Coagulation factors II, VII, IX, X (Fig. 1) and anticoagulant proteins C and S are synthesized in the liver and they are not effective unless they undergo a carboxylation to form calcium binding sites. The carboxylation procedure requires the reduced form of vitamin K. Oral anticoagulants exert their anticoagulant effect by targeting Vitamin K Oxidase Reductase (VKOR) an enzyme responsible for the reduction of vitamin K in vitamin K cycle.<sup>1,45</sup> Thus, the coagulation factors are produced in the liver but they have reduced anticoagulant activity by 10-40%.<sup>1</sup>

#### PHARMACOKINETICS

*Warfarin* is water soluble and it is rapidly absorbed from the gastrointestinal system. Food can decrease the rate of absorption. It is usually detectable in the plasma after one hour of its administration and reaches maximum concentration in about 2 hours.<sup>1,45</sup> It is almost completely (98%) bound to plasma proteins, mainly albumin, and it is rapidly distributed in plasma. Fetal plasma concentrations are almost equal to maternal concentrations, therefore it is contraindicated in pregnancy.<sup>1</sup> VKAs are metabolized in the liver. Most of them are racemic mixtures of R and S enantiomers. For warfarin the S-enantiomer and for *acenocoumarol* the R-enantiomer are the most potent isomers and they are both metabolized by CYP2C9 enzyme of P450 cytochrome. Warfarin has a half-life of 36-42 hours; acenocoumarol 10-24 hours.<sup>1,45</sup>

Pharmacokinetics and pharmacodynamics of VKAs can be modified by genetic polymorphisms in CYP2C9 and VKORC1 genes. Most common polymorphisms of CYP2C9 gene is CYP2C9\*2 CYP2C9\*3. About 20% of Caucasians and less than 5% of African-Americans and Asians carry these polymorphisms.<sup>1</sup> People who carry them tend to have increased levels of S-warfarin because of impaired ability to metabolize it. These individuals need lower doses of warfarin; heterozygotes may need 20-30% and homozygotes up to 50-70% dose

reduction.<sup>1,45</sup> Some have shown that genetic polymorphisms are also related to high rates of bleeding.<sup>45</sup> VKORC1 variants are more common than CYP2C9 ones. The prevalence is higher in Asian-Americans. People with polymorphisms have altered sensitivity to inhibition of VKORC1 by warfarin and probably need from 20% to 50% dose reduction (for heterozygotes and homozygotes respectively).<sup>1,7,45</sup>

Studies that have attempted to compare time in therapeutic range (TTR) in patients treated with genetic-based and clinical-based dose strategies gave inconsistent results.<sup>7,45</sup> The pharmacogenetic-based dosing scheme was better in predicting TTR in people requiring very high or very low weekly doses but it did not affect dosing calculation in intermediate doses. As yet, it is not proven that genetic testing is related to better clinical outcomes. The 9<sup>th</sup> edition of ACCP guidelines do not recommend pharmacogenetic testing for guiding dose.<sup>7,45</sup> Randomized controlled trials gave inconsistent results of pharmacogenetic based dose over clinical-based dose in TTR.<sup>46-48</sup> None of these trials was designated to address the influence of pharmacogenetic testing in the rate of bleeding/thrombosis. A meta-analysis of studies published recently have shown a 50% reduction of serious bleeding events by approximately 50% with pharmacogenetic-guided dosing.<sup>49</sup> The Genetics InFormatics Trial (GIFT) may give convincing evidence. This is an ongoing randomized controlled trial, assessing the safety and effectiveness of pharmacogenetic guided warfarin dosing for the reduction of deep vein thrombosis compared with clinical algorithm dosing following total hip or knee repair. The primary end-point is a composite of venous thromboembolism, hemorrhage, INR >4 or death.<sup>50</sup>

#### DRUG AND FOOD INTERACTIONS

VKAs are very sensitive to drug-drug interactions, thus making the anticoagulation management troublesome in routine practice. The mechanisms by which drugs interact with VKAs include: reduction of their absorption in the gastrointestinal tract (cholestyramine), increased clearance by liver enzyme induction (carbamazepine, rifampicin, barbiturates), decreased clearance by CYP2C9 inhibition (amiodarone, antifungals, clopidogrel, metronidazole), inhibition of vitamin K cycle (cephalosporins) or elimination of bacteria flora (sulfonamides, broad spectrum antibiotics), enhancement of clearance of vitamin K dependent coagulation factors (thyroxine) or interference with other hemostatic parameters (antiplatelets, non-steroidal anti-inflammatory drugs - NSAIDs).<sup>1,7,45</sup> The most effective way to avoid drug interaction is to avoid co-administration. If that is not possible a more frequent monitoring of the anticoagulant effect may help avoiding adverse events.<sup>45</sup> Hemorrhagic episodes have been shown to increase when VKAs are administered along with antiplatelet agents, antibiotics and NSAIDs, therefore according to 9<sup>th</sup> ACCP recommendation the concomitant use of these drugs should be avoided whenever possible.<sup>7</sup>

Patients taking VKAs are sensitive to fluctuations of dietary vitamin K which is derived from plants. An increased oral intake of vitamin K that is sufficient to reduce the anticoagulant response to warfarin can occur in patients consuming green vegetables or vitamin-K containing supplements, or those on weight reduction diets. More sensitive are vitamin-K deficient patients. In general, a consistent intake of vitamin K is recommended, and no specific restrictions or additions are recommended in patients with stable anticoagulant control.<sup>7,45</sup>

#### ANTITHROMBOTIC EFFECT

By reducing anticoagulant factors' activity, VKAs induce prolongation of both PT and aPTT. Vitamin K antagonists have no effect on already carboxylated factors in the circulation, which sustain their anticoagulant activity for some time related to their half-lives. Half-lives of these factors (in hours) are approximately as following: factor VII: 6; factor IX: 24; factor X: 36; factor II: 50; protein C: 8; protein S: 30 hours. Therefore, although the prolongation of PT occurs relatively soon after administration of VKAs, reflecting reduction of coagulation factors with short half-life (such as factor VII), the full antithrombotic effect which is mainly attributed to reduction of factor II<sup>1,45</sup> is not established until several days have passed. This is the basis for overlapping the administration of VKAs with parenteral agents when rapid anticoagulation is needed. According to latest recommendation, VKAs are administered one or two days after initiation of LMWH or UFH.<sup>7</sup>

#### MONITORING

The prothrombin time (PT) is the test used to monitor the anticoagulant effect of VKAs. PT is performed by adding thromboplastin and calcium to citrated plasma. The ability of each thromboplastin to prolong the PT for a given reduction of coagulation factors varies among different reagents, thus when PT is expressed in seconds or as a ratio of patient / mean normal, PT is not standardized. Comparison of the thromboplastin used in a laboratory to the International Reference Thromboplastin used by the World Health Organization gives the International Sensitivity Index (ISI) of the reagent; the more responsive the reagent the lower the ISI value which ideally is equal to 1. A model adopted in 1982 for standardizing PT results is converting PT to INR (International Normalized Ratio) according to the following equation:  $INR = (\text{patient's PT}/\text{mean normal PT})^{ISI}$ .<sup>1,45</sup>

Although introduction of the INR system has improved the laboratory monitoring of patients on oral anticoagulant therapy, the INR will not be identical with different thromboplastins. ISI values of each thromboplastin reagent, as well as mean normal PT determined with the reagent, should be provided by the manufacturer of thromboplastin reagent. Several studies have shown that the ISI and the mean normal PT are not a function of thromboplastin alone but also of the method

and coagulometer used. Thus, the mean normal PT and the instrument-specific ISI for each reagent should be determined locally. In general, the College of American Pathologists has recommended that laboratories should use thromboplastin reagents that are at least moderately responsive (ISI <1.7) and reagent/instrument combinations for which the ISI has been established and validated.<sup>45</sup>

The INR is based on ISI values derived from the plasma of patients who had received stable anticoagulant doses for at least 6 weeks; thus, the validity of INR in the early course of warfarin therapy as well as in patients with other condition of coagulation impairment (i.e. liver disease) has not been adequately evaluated. Another issue is that INR values can be affected by collection tube underfilling because of higher citrate concentrations.<sup>45</sup>

Initial testing is usually performed after 2-3 doses in outpatients. Frequency of monitoring depends on patient's compliance, comorbid conditions, concomitant use of drugs interacting with VKAs or changes in diet and whether the patients have demonstrated stable INR. If two consecutive weekly INR values are within range, the interval between draws could be extended to monthly.<sup>51</sup> The INR is considered particular stable if the results are consistent for at least 3 months without dose adjustments. Retrospective and observational studies have generally shown that increasing monitoring intervals may either increase or decrease the time in therapeutic INR range but three randomized studies demonstrated that in stable patients, the monitoring frequency can be extended to every 4 weeks or even more (12 weeks in particularly stable patients) without the rates of bleeding or thrombosis being increased.<sup>7,45</sup> Factors that have been shown to influence long-term INR stability are age >70 years, comorbid conditions, physical activity, vitamin K deficiency but most importantly patient's adherence to treatment.

Numerous studies have shown that patient self-testing (self-testing and informing the treating physician) or self-monitoring (self-testing and self-deciding dose management) using one of the approved point-of-care INR measurement devices are related to greater INR stability and decrease of adverse events.<sup>7,45,52,53</sup> However, these practices may not be suitable to most patients and their implementation requires high patient motivation and training.<sup>7,45,52</sup>

Therapeutic range is the range of INR levels beyond which the rate of adverse events increases. Time in therapeutic range (TTR) serves as a function of anticoagulant treatment quality and has been consistently related to fewer adverse events in trials in diverse clinical settings.<sup>45</sup> When moderate intensity INR (2.0-3.0) was compared to high-intensity oral anticoagulation, the former proved to be related to fewer bleeding rates without reducing efficacy. In a systematic review of 19 studies, with more than 80,000 patients reporting clinical outcomes in three different INR ranges, the lower rate for composite outcomes of major bleeding and thromboembolism was seen in INR range

2.0-3.0.<sup>7</sup> Low-intensity (INR <2.0) anticoagulation in patients with venous thromboembolism or atrial fibrillation was inferior to moderate intensity treatment in terms of efficacy without protecting patients from major bleeding. Therefore the optimal INR range recommended by ACCP and BCSH for patients on VKA treatment for most clinical indications is 2.0-3.0, including patients with thrombophilia. A possible exception are patients with mechanical mitral valve for whom therapeutic INR range is recommended to be 2.5-3.5.<sup>7,52,54</sup>

#### ADVERSE EVENTS

*Bleeding* is the most common adverse event of VKAs, occurring with an incidence of 1.5-3.0% annually.<sup>7,29</sup> The most important risk factor for bleeding is treatment intensity; risk is substantially increased when INR rises >4.5.<sup>1,7,45</sup> Several patient characteristics are associated with higher rates of bleeding during anticoagulation, with history of bleeding being the most consistent predictive factor,<sup>45</sup> necessitating searching for a potential anatomic source of hemorrhage especially in the gastrointestinal tract. Other patient-related factors are advanced age and comorbid conditions.

Apart from hemorrhage, thrombotic complications such as skin necrosis and limb gangrene are important side effects of VKAs but uncommon. They occur on 3-8<sup>th</sup> day of therapy and they are probably attributed to rapidly decline levels of protein C in deficient individuals, however this complication occurs also in non deficient patients. Management is difficult, requiring discontinuation of VKA and substitution by a parenteral anticoagulant agent. Re-initiation of VKA treatment for long-term anticoagulation is attempted under heparin coverage with small, gradually increased doses.<sup>45</sup>

A very rare adverse event is the purple toe syndrome, developing 3 to 8 weeks after initiation of therapy with sudden appearance of painful, bilateral, purple lesions of the toes that blanch with pressure.<sup>45</sup>

#### REVERSAL OF ANTICOAGULANT EFFECT

*Vitamin K* can reverse the anticoagulant effect of VKAs, promoting the reduction of vitamin K epoxide via a reductase enzyme insensitive to VKAs. Orally administered vitamin K starts to correct INR in about 12-16 hours, whereas intravenously administered has a more rapid effect, the reduction starts at 2 hours and the INR value returns to normal in approximately 24 hours.<sup>45</sup> In urgent situations like major bleeding or an invasive procedure, where rapid reversal of anticoagulation is required, vitamin K serves as a maintenance treatment, with infusion of coagulation factors being the cornerstone of management. Traditionally, *fresh frozen plasma* (FFP) is widely being used but it has certain limitations: thawing time makes it not readily available, it partially corrects the INR, it can cause volume overload and carries all the adverse events of a transfusion, including infection transmission and transfusion related acute lung injury (TRALI) risk.<sup>22,45</sup> *Prothrombin*

*complex concentrate* (PCC) is recommended over FFP<sup>7,21,22</sup> for anticoagulation reversal because it is administered in a small volume of fluid, it fully corrects the INR in less than 30 min<sup>21</sup> without the risk of infection transmission although it has not been compared with FFP in adequately powered randomized trials.<sup>7</sup> PCC may be classified as three-factor products (with adequate levels of factors II, IX, X and low levels of factor VII) and four-factor products containing adequate levels of all vitamin-K dependent factors plus protein C and S.<sup>21,22,45</sup> The optimal dose is not yet established; a large dose scale has been used in clinical trials ranging from 8-50 u/kg with relatively good clinical and INR outcomes with the use of any treatment protocol.<sup>55</sup> *Recombinant factor VII* can be used in life threatening bleeding but suffers lack of evidence.<sup>7</sup>

According to the latest ACCP and BCSH guidelines, emerging reversal of anticoagulation requires administration of PCC at a dose of 25-50 u/kg and intravenous vitamin K at 5-10 mg. If PCC is not available, FFP should be given.<sup>7,21,29</sup> For non-major bleeding only vitamin K intravenously administered at a dose of 1-3 mg is recommended. Patients with INR >5 but <10 who are not bleeding should have one or two doses of VKA withheld without administration of vitamin K. For INR >10 in asymptomatic patients holding one or two doses along with oral vitamin K 1-5 mg is recommended.<sup>7,21</sup>

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#### PERIPROCEDURAL ANTICOAGULATION

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The question of whether the anticoagulant therapy should be discontinued before a planned invasive procedure involves balancing the risk of postoperative bleeding with continued treatment against the thrombotic risk with discontinuation of therapy and bridging anticoagulation.<sup>56</sup> *Bridging* anticoagulation refers to the practice of giving a short-acting blood anticoagulant, usually subcutaneous heparin, for 10-12 days around the operation, when VKAs are interrupted, in order to prevent thromboembolic events but it carries the risk of increased postoperative bleeding.

According to latest guidelines,<sup>57</sup> patients who are undergoing a minor operation with low risk of bleeding can safely continue the anticoagulant therapy especially if they are at high-thromboembolic risk. Conversely, patients planned to have a high-bleeding risk operation can discontinue the antithrombotic therapy if their thrombotic risk is low. For patients at intermediate or high risk of thrombosis undergoing high-bleeding risk procedures the decision is challenging. Assessment of thrombotic risk, type of procedure and procedure-related bleeding, duration of action of anticoagulants and time of cessation and reinstatement of antithrombotic agents should all be taken into account to help the decision-making process. An important consideration in assessing procedure-related bleeding risk is that minor procedures which are not typically associated with bleeding may be complicated by

bleeding in the context of peri-procedural administration of antithrombotic agents.<sup>57</sup>

When anticoagulant agents are discontinued in high risk patients, this must be done 5 days before the procedure and when the INR falls below therapeutic range, bridging therapy –if needed, in high risk patients- is started. Bridging therapy consists of subcutaneous low-molecular weight heparin or intravenous unfractionated heparin usually at therapeutic doses. In patients with deterioration of renal function, unfractionated heparin is given. If UFH is administered it should be stopped 4-6 hours before the operation. If LMWH is administered the last dose is given 24 hours before the procedure. If hemostasis is achieved, bridging therapy is reinitiated 48-72 hours after the procedure,<sup>52,56,57</sup> whereas VKA can be reinstated 12-24 hours postoperatively.

Although bridging anticoagulation has been considered the standard of care for high-risk patients, it has been evaluated in only a few randomized trials and its usefulness remains controversial.<sup>56</sup> Because of the paucity of high-quality evidence, available guidelines are giving weak and inconsistent recommendations for the implementation of bridging anticoagulation.<sup>57,58</sup> A recent meta-analysis showed that bridging anticoagulation is associated with more bleeding episodes with no respective reduction of thrombotic risk.<sup>59</sup> Moreover there are also other meta-analyses in patients undergoing pacemaker or implantable cardioverter defibrillator implantation surgery showing that maintenance of anticoagulant treatment is associated with significant lower bleeding postoperatively compared to heparin-based bridging anticoagulation with no difference in risk of thrombosis.<sup>60,61</sup> These results have been confirmed by a randomized trial which showed that continuing VKA therapy during implantation of cardioverter defibrillator is associated with significant reduction in the incidence of device-pocket hematoma compared to bridging anticoagulation with heparin.<sup>62</sup> A recent randomized double-blinded trial (BRIDGE) showed that in patients with atrial fibrillation who discontinued the VKA regimen in order to undergo an invasive procedure, no-bridging was not inferior to bridging anticoagulation with LMWH for the prevention of arterial thromboembolism and decreased the risk of major bleeding.<sup>63</sup> Thus, while the antithrombotic efficacy of bridging anticoagulation with LMWHs has not been demonstrated, increasing bleeding risk is observed in different types of surgery.<sup>64</sup>

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## PREGNANCY AND ANTICOAGULANTS

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During pregnancy anticoagulants are used for the following indications: (1) prevention and treatment of VTE, (2) prevention and treatment of systemic embolism in women with mechanical valves, (3) prevention of VTE in patients with thrombophilia, and (4) prevention of recurrent pregnancy loss in women with antophospholipid syndrome in combination

with aspirin.<sup>65</sup> An important issue of anticoagulation in pregnancy is both mother's and fetus's safety. LMWHs and UFH are safe for the fetus as they do not cross the placenta or enter breast milk. In contrast, VKAs are contraindicated because they cross the placenta and are associated with embryopathy, central nervous system abnormalities, pregnancy loss and fetal anticoagulation with possible bleeding. Embryopathy typically occurs after in utero exposure to VKAs during the first trimester of pregnancy.<sup>65</sup> They are considered safe during lactation. Maternal safety is mandatory since pregnancy is virtually the only indication where heparins are given over a prolonged period. The most important maternal safety issue for any anticoagulant is the risk of bleeding. LMWH is associated with less bleeding and the risk of HIT and osteoporosis appears much lower compared to UFH.<sup>25,65,66</sup> Thus, LMWH is the drug of choice for anticoagulation during pregnancy because is as effective as UFH for prevention and treatment and has better bioavailability, longer plasma half-life, more predictable dose response and improved safety profile compared to UFH.<sup>65,67,68</sup>

It should be noted, however, that the evidence guiding the use of prevention and treatment of thromboembolism in pregnancy is mostly derived from non-randomized, observational studies and from extrapolating the results of randomized trials involving non-pregnant women. Thus, there are several issues concerning the use of therapeutic and preventive doses of LMWH that remain controversial. These include the most appropriate regimen, the dose-adjustment according to the increasing body weight, the dosing schedule (once versus twice daily), the possibility of lowering the dose after initial treatment, the need for anti-Xa activity monitoring as well as the optimal duration of treatment.<sup>65,66,69</sup> Many clinicians use an once daily regimen to simplify administration and enhance compliance. Routine monitoring of therapeutic anti-Xa levels cannot be recommended and it is performed only in extremely over-weight women or those with renal impairment, while other clinicians prefer to periodically monitor anti-Xa to maintain therapeutic LMWH levels. Treatment duration should be no less than 3 months and should cover at least the first six weeks after delivery. For postpartum prophylaxis and treatment either LMWH or a VKA can be used.<sup>65,67,68</sup>

Heparin treatment should be discontinued 24 hours before planned delivery to minimize the risk of bleeding and allow the option for neuraxial anesthesia. Neuraxial anesthesia is avoided if less than 24 hours of heparin injection have elapsed because of the risk of epidural hematoma.<sup>65</sup>

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