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Venous Thromboembolism in Orthopaedic Surgery

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1. Introduction

Venous Thromboembolism (VTE) is a common complication following orthopaedic procedures. It is discussed most commonly as it relates to total hip arthroplasty (THA) and total knee arthroplasty (TKA), though this disease process can be seen after any orthopaedic surgery. It is associated with significant morbity and costs (Caprini et al., 2003). This chapter will provide an overview of the epidemiology, pathophysiology, and management of thromboembolic disease. This will include preventative strategies, evidence-based guidelines and a focus on newer drug agents currently being developed.

2. Epidemiology

Total joint arthroplasties remain some of the most common orthopaedic procedures performed worldwide. It is estimated that by 2015, over 500,000 total hip arthroplasties and 1.3 million total knee arthroplasties will be done in the United States alone (Kim, 2008). The aggregate costs in 2007 totaled over $15 billion (US Agency for Healthcare Research and Quality, 2007). Geerts et al. reported that VTE would occur in 40%-60% of the patients undergoing total joint arthroplasty if no prophylaxis was administered (Geerts et al., 2008). Despite appropriate chemophrophylaxis, one study noted asymptomatic proximal DVT found on ultrasound in 6.7% of THA and TKA patients at the time of transfer to a rehabilitation center (Schellong et al., 2005). As many as 80% of all clinical VTE events associated with arthroplasty patients occur within 3 months after surgery (Oster et al., 2004).

The costs of VTE are significant. Approximately 10% of the patients who develop VTE following THAs or TKAs require re-admission to the hospital within 3 months after their index surgery (Oster et al., 2004). The clinical sequelae are often significant and can include leg swelling, venous stasis ulcers, pulmonary hypertension, post-thrombotic syndrome, and recurrence (Heit, 2006). The one-year mortality following deep vein thrombosis (DVT) has been reported as high as 14.6%. Pulmonary embolism (PE) is associated with even higher mortality rate. Heit et al. reported as high as 52.3% in a recent cohort study (Heit et al., 1999).

3. Pathophysiology

The coagulation cascade is a complex system in which multiple components are activated to produce fibrin. An overview of the system along with the targets of various therapeutic interventions is shown in Figure 1. The coagulation pathway is separated into the intrinsic and the extrinsic pathways. The latter is activated in response to specific tissue injury. Both lead to the eventual formation of thrombin. Thrombin causes the conversion of fibrinogen to fibrin. Additionally, it activates factor XIII which stabilizes the fibrin. An endogenous fibrinolytic system balances this system. It consists of antithrombins, proteins C and S, and the plasmin-plasminogen system.
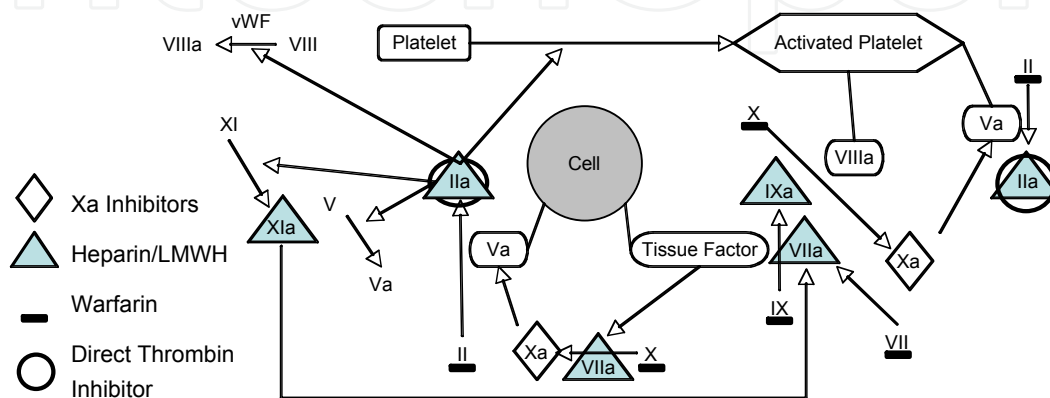

Fig. 1. Targets for anticoagulant drugs. LMWH = low-molecular-weight heparin. (Reference: Hoffman M, Dougald M. The action of high-dose factor VIIa in a cell-based model of hemostasis. *Disease a Month* 2003; 49: 14-21)

The primary pathophysiology factors that predispose any patient to VTE are the Virchow's Triad: endothelial injury, venous stasis (or turbulent blood flow), and hypercoagulability. Endothelial injury can occur due to manipulation, and retractor placement during surgery. Venous stasis can occur due to positioning and the use of a tourniquet. Hypercoagulability can occur as a result of depletion or dilution of endogenous anticoagulants. It is also associated with several pro-coagulant disease processes such as factor V Leiden deficiency, protein C and S deficiency, and others.

3.1 Natural history

The natural history of venous thromboembolism is variable. There are four potential outcomes when thrombosis occurs. The thrombus can propagate, embolize, organize, or undergo fibrinolysis. Proximal thrombi are more likely to propagate and embolize than the smaller distal thrombi in general. 80% of symptomatic DVTs involve the proximal veins (Conduah & Lieberman, 2007).

4. Prevention

Clinical VTEs occur due to many different causes, but one significant factor is inadequate prophylaxis (Amin et al., 2010). Several barriers exist for inadequate prophylaxis. These include: expense, bleeding concerns, availability of agents, and conflicting recommendations. The American College of Chest Physicians (ACCP) and the American

Academy of Orthopaedic Surgeons (AAOS) have each released separate guidelines regarding the prevention of VTE. This can be confusing to the providers.

Controversies exist regarding the two major practice guidelines for VTE prophylaxis. The ACCP has been updating its recommendations every 3 years for over 25 years (Hirsh et al., 2008). The AAOS guidelines have been a more recent development. Though the two have many similarities, there are a few significant differences. A major area of disagreement involves the use of DVT as a surrogate for PE in arthroplasty patients. The AAOS guidelines do not emphasize the correlation between DVT and pulmonary embolism (Eikelboom et al., 2009). In fact, the AAOS guidelines are for the prevention of PE following joint arthroplasty. The ACCP recommendations focus on the prevention of both VTE and PE as the goal rather than PE alone in the AAOS guidelines. Both guidelines focus on a balance between the risk of bleeding and the efficacy of anticoagulation. They both define risk-to-benefit ratio for different agents. Some of the most clinically relevant differences between the two guidelines are presented in Table 1. Neither guideline has been universally accepted. A recent survey was conducted by the American Association of Hip and Knee Surgeons regarding the practice standards among its member surgeons. The data demonstrated that 74% of the hospitals had adopted the ACCP guidelines, while 68% of the surgeons preferred the AAOS guidelines (Markel et al., 2010).

Furthermore, compliance with the current guidelines has been suboptimal. Many surgeons continue to under-appreciate the prevalence of VTE and remain concerned with postoperative bleeding. Additionally, patient factors can inhibit appropriate prophylactic treatment. Injectable agents are expensive. Moreover, some patients are not at ease or in compliance with their administration. Oral agents have the challenges including: titration, monitoring, and drug-drug, or drug-food interaction (Moyer et al., 2009).

4.1 Extended duration prophylaxis

The ACCP guidelines recommend the optimal duration of VTE prophylaxis to be 28 to 35 days following THAs, and 10 to 14 days following TKAs (Kolb et al., 2003). Currently, the mean length of hospital stay is between 3 to 4 days, therefore full compliance with this recommendation is difficult for both the patient and the provider. Several studies have reported that continuation of thromboprophylaxis beyond the hospitalization is efficacious and safe in the risk reduction of late VTE in surgical patients (Planes et al., 1996; Lassen et al., 1998; Comp et al., 2001; Bergqvist et al., 2002; Rasmussen et al., 2006).

Extended duration prophylaxis for VTE requires proper selection of pharmacological agent(s). The ideal anticoagulant should have the following characteristics: standard dosing with self-administration, no requirement for monitoring, established efficacy and safety profiles, acceptable tolerability in populations with co-morbid conditions, and few drug-drug or drug-foot interactions. The ACCP guidelines currently recommend warfarin, low-molecular weight heparins (LWMH), and fondaparinux. They specifically recommend against using aspirin alone in the high-risk orthopedic patient population as there are insufficient evidence-based data.

The AAOS guidelines recommend 2 to 6 weeks of prophylaxis with warfarin, 6 weeks using aspirin, or 7 to 12 days using LMWH or fondaparinux (AAOS 2007). The ACCP guidelines,

in contrast, recommend pharmacological thromboprophylaxis for up to 35 days after THA and for 10 to 35 days after TKA. Moreover, they recommend against the use of aspirin in this patient population.

ACCP	AAOS		
Recommendation	Risk		Reccommendation
	PE	*Bleeding*	
Fondaparinux Warfarin LMWH	Standard	Standard	Aspirin LMWH Fondaparinux
	Elevated	Standard	LMWH Warfarin
	Standard	Elevated	Aspirin Warfarin Fondaparinux
	Elevated	Elevated	Aspirin Warfarin None

Table 1. Summary of ACCP and AAOS recommendations for pharmacologic thromboprophylaxis in patients undergoing elective hip or knee surgery. (Reference: Huo M. VTE prophylaxis after total joint arthroplasty: current challenges-potential solutions. *Current Orthopaedic Practice* 2011;22:193-197.)

4.2 Quality measures

Over the past 5 years, quality measures have been proposed and put into clinical application to monitor compliance with best practice guidelines in VTE prophylaxis. The Surgical Care Improvement Project (SCIP) was created in 2006 with reduction of VTE being one of its four primary focus areas. The Center for Medicare and Medicaid Services (CMS) has declared postoperative VTE as a "never event." As such, the CMS will no longer reimburse the hospital the costs associated with these complications. Other agencies and consumer groups have also declared VTE as a preventable complication.

Several important improvements have already occurred as a result of these outcome measures. Surgeons and administrators have collectively established hospital-wide or hospital system-wide prophylaxis protocols. They have also worked to establish training and education programs to deliver the best practice guidelines to all the staff involved in patient care. Several limitations still exist however. The AAOS and the ACCP guidelines should be modified to establish a consensus. Unmet needs and improvement in the safety profiles hopefully will be fulfilled by newer agents in clinical development (Huo, 2011a).

4.3 Specific modalities

A summary of specific oral pharmacologic agents currently in clinical application for orthopedic patients is in Table 2.

Drug	Mechanism	Dosing	Monitoring	Half Life	Renal Clearance
Warfarin	Vitamin K antagonist	Variable; Daily	Yes	40 hours	0%
Dabigatran etexilate	Factor IIa inhibitor	Fixed; Twice Daily	No	14-17 hours	100%
Apixaban	Factor Xa inhibitor	Fixed; Twice Daily	No	9-14 hours	25%
Rivaroxaban	Factor Xa inhibitor	Fixed; Once Daily	No	9 hours	65%

Table 2. Comparison of warfarin to new oral anticoagulants. (Reference: Eikelboom JW. Weitz JI. A replacement for warfarin: the search continues. *Circulation* 2007;116:131-133.)

4.3.1 Mechanical

Mechanical prophylaxis using sequential compressive devices (SCDs) or foot pumps can be used as a sole means of VTE prophylaxis. Their clinical efficacy and safety have been documented in multiple studies. This is particularly useful in a patient that is perceived to have an elevated bleeding risk (Geerts et al., 2008). In many practices, mechanical devices are often used in conjunction with pharmacological prophylaxis. Newer devices may be used in the outpatient setting upon hospital discharge. The clinical efficacy, safety, and compliance have been documented in a few studies. It is necessary to continue to follow larger cohorts of patients using outpatient mechanical prophylaxis alone to fully determine the efficacy and compliance.

4.3.2 Warfarin

Warfarin has been used as VTE chemoprophylaxis in high-risk orthopedic patients for decades. It is an efficacious agent. However, it requires close monitoring. It can be both difficult and costly in the outpatient setting (Eikelboom & Weitz, 2007). It also has numerous drug-drug and drug-food interactions. These interactions can be particularly challenging considering the issue of poly-pharmacy in the elderly joint arthroplasty patient population. It also has a delayed onset of action, which may require bridging with a shorter acting anticoagulant such as LMWHs or unfractionated heparin. A recent paper by Caprini et al. noted that physicians often used inadequate bridging protocols in the postoperative period. This can have important clinical implications. They found that the 30-day mortality rate was found to be 6% for DVT and 12% for PE in this cohort (Caprini et al., 2005).

4.3.3 Aspirin

The ACCP guidelines do not recommend using aspirin alone in any of the high-risk orthopedic patient populations. The AAOS guidelines do sanction its use in patients with standard risk profile for pulmonary embolism prevention (Geerts et al., 2008).

4.3.4 Unfractionated heparin

This has been included in the ACCP guidelines for patients undergoing general surgery procedures. However, the ACCP guidelines have recommended against using

unfractionated heparin alone in total joint arthroplasty or hip fracture patients due to inadequate evidence-based data to support its efficacy in these patient populations (Geerts et al., 2008).

4.3.5 Low-molecular-weight heparin

In contrast to warfarin, LMWHs have a predictable dose response with few interactions. Self-administration is generally well-tolerated and acceptable patient compliance has been documented in several studies. Additionally, there is no need for monitoring (Noble & Finlay, 2005). Dose adjustment may be necessary in the elderly, in particular in those with compromised renal clearance. LMWHs have considered to be the standard-of-care in many medical communities (Geerts et al., 2008).

5. Newer agents

There are several new oral anticoagulants in various stages of clinical development. These new classes target the inhibition of either thrombin or factor Xa. Most of the clinical trial data have demonstrated equal or even superior efficacy in comparison to LMWH. However, bleeding complications remain the primary concern. There are several other potential complications that have been reported.

5.1 Newer agents of historic importance

Ximelagatran was the first direct-thrombin inhibitor, and was approved initially by the European regulatory agencies. The initial trials showed no signs of liver toxicity in short-term use of up to 11 days (Eriksson et al., 2003). However, extended treatment (greater than 35 fays) was found to be associated with an increased risk of liver toxicity in one study (Agnelli et al., 2009). The liver toxicity was unpredictable, and the product was later withdrawn from the market (Vaughan, 2005).

Razaxaban was the first oral Factor Xa inhibitor to be developed. Data from phase I clinical trials demonstrated adequate efficacy and safety (Spyropoulos, 2007). A phase II trial involving TKA patients demonstrated significantly higher bleeding complication rates when compared with enoxaparin (Lassen et al., 2003). The trial was terminated prematurely and the drug development was discontinued.

5.2 Current oral anticoagulants

Dabaigatran etexilate is a pro-drug of the direct thrombin inhibitor, dabigatran (Eriksson et al., 2004). There have been four phase III clinical trials comparing this drug to enoxaparin. In addition, a meta-analysis of three of these has been conducted (Wolowacz et al., 2009). It demonstrated non-inferiority to once-daily enoxaparin 40mg dose in one clinical trial involving THA, but failed to do so when compared to twice-daily enoxaparin dosing with 30mg Additionally, it demonstrated non-inferiority to once-daily enoxaparin 40mg dose in two clinical trials involving THA patients (Eriksson et al., 2007a; Eriksson et al., 2007b). It was approved in the European Union and in Canada in 2008 for use in total joint arthroplasty patients as VTE prophylaxis. In the United States, it was approved for use in certain atria fibrillation patients for stroke prevention (Huo, 2011b).

Rivaroxaban and apixabab are both inhibitors of factor Xa. Their mechanism involves the inhibition of circulating factor Xa as well as bound factor Xa within the prothrombinase complex (Weitz, 2006). There have been four phase III clinical trials comparing rivaroxaban to enoxaparin (Eriksson et al., 2008). It also is approved in the European Union and Canada for VTE prophylaxis in patients undergoing THAs and TKAs. It has recently been approved in the United States.

Apixaban has been evaluated in several phase III clinical trials as well. It has not been approved for use anywhere (Lassen et al., 2010a). It was found to be more efficacious than once-daily dosing of enoxaparin, but failed to demonstrate non-inferiority to twice daily dosing of enoxaparin (Lassen et al., 2009; Lassen et al 2010b).

5.2.1 Potential problems with the newer agents

Bleeding events are the most important complication. A recent survey reported that 50% or more orthopaedic surgeons in the United States stated that they were more concerned with bleeding than the risk of VTE (Anderson et al., 2009). Major bleeding has occurred with all of these agents as it has with other pharmacological agents. LMWHs have been studied for over 20 years, and the incidents of significant bleeding complications ranges from 0.9% to 9.3% (Leizorovicz et al., 1992). A major difference between LMWH and the newer agents is that enoxaparin can be at least partially reversed using protamine in certain situations (Crowther et al., 2002). The thrombin and factor Xa inhibitors have no such reversal agents yet (Ng & Crowther, 2006). An overview of the bleeding in clinical trials involving new agents is included in Table 3. It is also important to note the effect of drug-drug interactions. There have been trials showing prolonged bleeding when rivaroxaban was taken with clopidogrel or aspirin (Perzborn et al., 2007). Though there may be a relationship between bleeding and infection, the use of anticoagulation has not specifically been associated with a higher infection rate (Parvizi et al., 2007; Saleh et al., 2002).

Aside from bleeding risk, there are other adverse effects that have been documented with the thrombin and factor Xa inhibitors. Drug-induced liver toxicity is the most common reason cited for the withdrawal of a drug from the market (Lee, 2003). The exact mechanism has not been identified. There have been several trials with dabigatran that reported elevated liver enzymes, but all returned to baseline within 2 months (Eriksson et al., 2007b). Dabigatran is a substrate for the cellular transporter P-glycoprotein which could be a mechanism of drug interaction (Aszalos, 2007). CYP240 enzymes are involved in the metabolism of both factor Xa inhibitors (Bayer Inc, 2010). Both factor Xa and thrombin inhibitors are excreted through the renal system, so this could potentially lead to complications.

Both types of drugs are promising alternatives due to several characteristics. They have predictable pharmacokinetics, few drug interactions, and no monitoring is required (Weitz et al., 2008). It is important to note that a perfect anticoagulant does not exist at this point. The thrombin and facto Xa inhibitors have been shown to be effective and safe in multiple trials, but there still is a lack of data from community practice.

Drug	Study	Number of Patients	Arthroplasty	Duration (Days)	Regimine (mg)	Major Clinically Significant Bleeding	Surgical Site Bleeding	Non-Major Clinically Relevant Bleeding
Dabigatran etexilate (Dab)	BISTRO I (Eriksson, 2004)	289	Hip	6-10	Dab 12.5-, 25-, 50-, 100-, 150-, 200-, 300-BID; and 150-, 300-QD	2.4% Dab 150-QD	N/A	2.4% Dab 150-QD
	BISTRO II (Eriksson, 2005)	1949	Hip and Knee	6-10	Dab 50-, 150-, 225-BID; and 300-QD; Enox 40-QD	8.2% Dab 150-BID; 8.3% Dab 300-QD; 4.6% Enox	N/A	4.1% Dab 150-QD; 4.9% Dab 300-QD; 2.6% Enox
	RE-NOVATE (Eriksson, 2007a)	3463	Hip	28-35	Dab 150-, 220-QD; Enox 40-QD	6.0% Dab 150-QD; 6.2% Dab 220-QD; 5.1% Enox	N/A	4.7% Dab 150-QD; 4.2% Dab 220-QD; 3.5% Enox
	RE-MODEL (Eriksson, 2008b)	2076	Knee	6-10	Dab 150-, 220-QD; Enox 40-QD	8.1% Dab 150-QD; 7.4% Dab 220-QD; 6.6% Enox	N/A	6.8% Dab 150-QD; 5.9% Dab 220-QD; 5.3% Enox
	RE-MOBILIZE (Ginsberg, 2009)	2596	Knee	12-15	Dab 150-, 220-QD; Enox 30-BID	3.1% Dab 150-QD; 3.3% Dab 220-QD; 3.8% Enox	N/A	2.5% Dab 150-QD; 2.7% Dab 220-QD; 2.4% Enox
Rivaroxaban (Riv)	ODIXa-KNEE (Turpie, 2005)	613	Knee	5-9	Riv 2.5-, 5-, 10-, 20-, 30-BID; Enox 30-BID	2.9% Riv 5-BID; 4.8% Enox	0% Riv 5-BID; 1.9% Enox	2.9% Riv 5-BID; 2.9% Enox
	ODIXa-OD-HIP (Eriksson, 2006a)	845	Hip	5-9	Riv 5-, 10-, 20-, 30-, 40-QD; Enox 40-QD	2.8% Riv 10-QD; 5,1% Enox	N/A	2.1% Riv 10-QD; 3.2% Enox
	ODIXa-HIP (Eriksson, 2006b)	704	Hip	5-9	Riv 2.5-, 5-, 10-, 20-, 30-BID; Enox 40 QD	8.1% Riv 5-BID; 1.5% Enox	2.2% Riv 5-BID; 0.8% Enox	5.9% Riv 5-BID; 0% Enox
	Dose-escalation study (Eriksson, 2007c)	625	Hip	5-9	Riv 2.5-, 5-, 10-, 20-, 30-BID; 30-QD; Enox 40 QD	3.8% Riv 5-BID; 1.9% Enox	2.5% Riv 5-BID; 0% Enox	1.3% Riv 5-BID; 1.9% Enox
	RECORD1 (Eriksson, 2008)	4433	Hip	31-39	Riv 10-QD; Enox 40-QD	3.2% Riv; 2.5% Enox	N/A	2.9% Riv; 2.4% Enox
	RECORD2 (Kakkar, 2008)	2457	Hip	31-39 Riv; 10-14 Enox	Riv 10-QD; Enox 40-QD	3.4% Riv; 2.8% Enox	N/A	3.3% Riv; 2.7% Enox
	RECORD3 (Lassen, 2008)	2459	Knee	10-14	Riv 10-QD; Enox 40-QD	3.3% Riv; 2.8% Enox	N/A	2.7% Riv; 2.3% Enox
	RECORD4 (Turpie, 2009)	3034	Knee	10-14	Riv 10-QD; Enox 30-BID	3.0% Riv; 2.3% Enox	N/A	2.6% Riv; 2.0% Enox
	RECORD1-3 (Eriksson, 2009)	9349	Hip and Knee	10-39	Riv 10-QD; Enox 40-QD	3.3% Riv; 2.7% Enox	N/A	3.0% Riv; 2.5% Enox
	RECORD1-4 (US FDA, 2009)	12383	Hip and Knee	10-39	Riv 10-QD; Enox 40-QD or 30-BID	3.19% Riv; 2.55% Enox	1.8% Riv; 1.37% Enox	N/A
Apixaban (Apix)	APROPOS (Lassen, 2007)	1217	Knee	10-14	Apix 5-, 10-, 20-QD; 2.5-, 5-, 10-BID; Enox 30-BID or Warfarin (INR 1.8-3.0)	0% Apix 2.5-BID; 1.3% Enox; 0% Warfarin	N/A	N/A
	ADVANCE-1 (Lassen, 2009)	3184	Knee	10-14	Apix 2.5-BID; Enox 30-BID	2.9% Apix; 4.3% Enox	0.5% Apix; 0.9% Enox	2.2% Apix; 3.0% Enox
	ADVANCE-2 (Lassen, 2010b)	3009	Knee	10-14	Apix 2.5-BID; Enox 40-QD	3.5% Apix; 4.8% Enox	0.5% Apix; 0.7% Enox	2.9% Apix; 3.8% Enox
	ADVANCE-3 (Lassen, 2010a)	5332	Hip	N/A	Apix 2.5-BID; Enox 40-QD	4.8% Apix; 5.0% Enox	0.7% Apix; 0.6% Enox	4.1% Apix; 4.5% Enox

Table 3. Major bleeding rates in VTE prophylaxis clinical trails in THA and TKA. (Reference: Huo, M. New oral anticoagulants in venous thromboembolism prophylaxis in orthopaedic patients: Are they really better? *Thromb Haemost* 2011;106:45-57.

6. Conclusion

VTE remains a challenging problem that complicates many orthopaedic procedures. The incidence has been found to be particularly high following TKA and THA. Governmental and consumer governing bodies are beginning to recognize it as a "never-event" indicating that increased emphasis will be placed on prophylaxis in the years to come. Recommendations have been released by both the ACCP and the AAOS and there remains some disagreement as to the optimal management of VTE. Warfarin and LMWH remain the standard of care in many practices, but newer agents show increasing promise.

The authors have several recommendations regarding the duration and type of therapy. Patients should be anticoagulated for 25-30 days postoperatively following total hip arthroplasty and for 14 days following a total knee arthroplasty. Certain patients with high risk of VTE (obese, low mobility, prior VTE, family history of VTE, or protein C/S deficiency) should be treated for 25-30 days as well following hip or knee replacement. At our institution, we generally use enoxaparin for postoperative anticoagulation. For inpatients, either 30mg twice daily or 40mg daily may be used following total hip arthroplasty. The FDA has approved only the twice daily dosing after total knee arthroplasty. For outpatients, enoxaparin 40mg daily is our regimen of choice.

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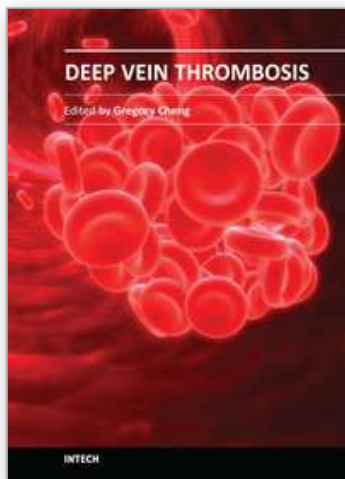
Deep Vein Thrombosis

Edited by Dr. Gregory Cheng

This book provides a comprehensive review of deep vein thrombosis. There are chapters on risk factors for DVT, post thrombotic syndrome and its management, vena cava malformation as a new etiological factor and thrombosis in the upper limbs. DVT is usually seen in patients undergoing major surgeries. The guidelines for thrombo-prophylaxis in orthopaedic patients, radical pelvic surgeries, laparoscopic operations and risks versus benefits in regions with a low prevalence of DVT are thoroughly addressed. Cancer and its treatment are recognized risk factors for VTE and extended prophylaxis in ambulatory cancer patients is reviewed. The role of imaging and endovascular therapies in acute DVT, hypercoagulabilty in liver diseases and the challenges in developing countries are discussed.

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