



What's the Best Anticoagulation Management for Deep Venous Thrombosis?

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Abstract

Management of Deep Venous Thrombosis has dramatically changed with implication of endovascular techniques. Mechanical thrombectomy and Catheter directed thrombolysis have become the treatment of choice for proximal (femoro-iliac) disease giving excellent long lasting results. Anticoagulation remains crucial treatment for distal disease and even patients post successful proximal recanalizations require long term anticoagulation afterwards. The duration of the treatment suppose to follow the guidelines, but choice of medication is usually left on the physician and the circumstances. In our article we describe all available anticoagulant agents with detailed analysis.

Keywords: Deep venous thrombosis; Pulmonary embolism; Anticoagulation

Introduction

Anticoagulants are commonly called "blood thinners". They are used to help preventing new clots from forming rather than actually dissolving the clot itself [1]. All Deep Venous Thrombosis (DVT) cases are initiated on anticoagulant therapy as much evidence support the use of it and have been recommended by all major medical bodies [2]. If anticoagulants are contraindicated, the placement of a Vena Cava Filter (IVC filter) should be considered [3].

Contemporary trend is to treat majority of cases on outpatient basis. Therefore, there is no need to admit all patients, especially those with distal disease in which there is plan for any further interventions to take place. However, we have to be cautious in making the decision since there is a group of patients that are not fit for outpatient regiment, such as: patients recently post-surgery (less than 7 days), patients with extensive DVT and high risk of PE, unstable patients or patients with serious co-morbidities, thrombocytopenic patients, patients not able to co-operate or difficult to reach from various reasons, patients with thrombocytopenia, poor kidney or liver functions.

Multiple anticoagulant options are available at present, and each is considered at a given setting that fits the management mostly. Hospitalized patient can be started on Unfractionated Heparin (UFH) or Low Molecular Weight Heparin (LMWH) as both have shorter elimination half-life, which can serve the peri-procedural management. It's been suggested that UFH may be preferable for inpatients with planned invasive procedures, recent major bleeding episodes or severely impaired renal function as well as underweight or morbidly obese patients. UFH and LMWH require routine coagulation monitoring thus, Direct Oral Anticoagulants (DOAC) can be also considered in hospitalized patients. However, the downside of DOAC is that it is not easily reversible as it has a longer elimination half-life (7-15 hrs) and has limited experience with perioperative management. Thus, DOAC are optimized for outpatient more than inpatient use [4,5].

Using anticoagulant only 75% of patient with DVT symptoms experience post thrombotic syndrome in 5-10 years. However, only 5% will experience venous ulceration [6-8].

Traditionally has been used Warfarin with proven benefits. It is factor K dependent factors inhibitor. It requires frequent INR monitoring and has higher risk of bleeding in compare with DOAC. However, in case of life-threatening bleeding the effect of warfarin can be easily reversed using its antidote (Vitamin K) (Table 1) [5,9].

NOAC

Novel Oral Anticoagulants (NOAC) are used as an alternative to Vitamin K Antagonist (VKA). The European Society of Cardiology guidelines recommend the use of NOACs as alternatives to VKA anticoagulation for secondary prevention of Venous Thromboembolism (VTE). NOAC

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Table 1: Recommended duration of anticoagulation therapy.

Clinical Scenario	Recommended duration of therapy (months)
Provoked leg DVT or PE	
Provoked by surgery	3
Provoked by nonsurgical transient risk factor	3
Unprovoked leg DVT or PE	
Low or moderate bleeding risk	>3
High bleeding risk	3
Leg DVT or PE and active cancer	>3 (no scheduled stop date)

DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism

help in overcoming the complications of overlapping a parenteral anticoagulant with a VKA. NOACs have been shown to be effective in the prevention and treatment of VTE and in the prevention of stroke and systemic embolism in patients with Non-Valvular Atrial Fibrillation (NVAF) [10-12].

Two classes of NOACs were introduced to overcome the limits of VKA. These agents are selective inhibitors of factor Xa (rivaroxaban, apixaban, and edoxaban) or thrombin (dabigatran). Rivaroxaban, apixaban and edoxaban are direct factor Xa inhibitors approved by FDA for the treatment of VTE. They inhibit platelet activation and fibrin clot formation via direct, selective and reversible inhibition of factor Xa (FXa) in both the intrinsic and extrinsic coagulation pathways [13].

Dabigatran is a Pro-drug converted *in vivo* by circulating esterases to the active form. It is a specific direct thrombin inhibitor. It Inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI, and XIII, and inhibition of thrombin-induced platelet aggregation.

The use of NOACs in the initial and long-term management of patients with VTE was demonstrated in large, randomized studies. These trials were designed to demonstrate non-inferior efficacy and safety of NOACs compared with standard anticoagulant treatment (LMWH followed by VKA) (Table 2).

All of the studies used recurrence and VTE-related death as the primary efficacy outcome. Major bleeding was the primary safety outcome in (AMPLIFY trail) for Apixaban, whereas major and clinically relevant non-major bleeding was the primary safety outcome in the remaining trials.

Dabigatran has been evaluated in RE-COVER I and II trials. Data from the RE-COVER II trial verified and confirmed the results of the RE-COVER trial with regard to recurrent VTE, emphasizing the non-inferiority of Dabigatran (2.3%) compared to warfarin (2.2%) (HR 1.08, 95% CI, 0.64-1.80, absolute risk difference 0.2%, 95% CI, 1.0-1.3, P=0.001). Moreover, the results of the RE-COVER II trial demonstrated that the risk for clinically relevant bleeding (Dabigatran 1.2% vs. warfarin 1.7%, HR 0.69, 95% CI, 0.36-1.32, P=0.259) or any bleeding (Dabigatran 15.6% vs. warfarin 22.1%, HR 0.67, 95% CI, 0.56-0.81, P<0.001) is significantly lower with Dabigatran to warfarin [14,15].

Rivaroxaban was compared with standard therapy for acute and short-term treatment of VTE in the EINSTEIN DVT and PE. Both EINSTEIN DVT and PE trials had a similar design.

Recurrent VTE in EINSTEIN DVT occurred in 36 Rivaroxaban

patients (2.1%) and 51 Enoxaparin/VKA patients (3.0%) (HR 0.68; 95% CI, 0.44-1.04). Major bleeding occurred in 14 Rivaroxaban patients (0.8%) and 20 Enoxaparin/VKA patients (1%) (HR 0.65; 95% CI, 0.33-1.30) [16].

The EINSTEIN PE trial had a similar design to the EINSTEIN DVT trial. Major or clinically relevant non-major bleeding occurred in 249 Rivaroxaban patients (10.3%) and 274 (11.4%) Enoxaparin/VKA patients (HR 0.90; 95% CI 0.76-1.07). Major bleeding occurred in 26 Rivaroxaban patients (1.1%) and 52 enoxaparin/VKA patients (2.2%) (HR 0.49; 95% CI 0.31-0.79). These studies suggest that Rivaroxaban is a safe and effective alternative for acute and short-term therapy of VTE [17].

In AMPLIFY Trial; Apixaban was evaluated as single-drug approach. During this trial, the dose of Apixaban was increased due to high risk for early recurrences. This increase was noted in other trials evaluating NOACs without initial heparin treatment [18,19].

Major bleeding occurred in 15 of 2676 Apixaban patients (0.6%) and 49 of 2689 conventional therapy patients (1.8%) (RR 0.31; 95% CI 0.17-0.55). Major or clinically relevant non-major bleeding was also lower in Apixaban-treated patients (4.3%) than conventional therapy patients (9.7%) (RR 0.44; 95% CI 0.36-0.55) [20].

These results indicate that Apixaban, like Rivaroxaban is an attractive single drug treatment for acute and short-term therapy of VTE compared to standard therapy.

Recent guidelines suggest use Rivaroxaban and Apixaban as an alternative to LMWH/VKA for the acute and short-term treatment of VTE in appropriate patients.

HOKUSAI-VTE study is a large randomized double-blind non-inferiority study included 8292 patients compared Edoxaban with Warfarin in the treatment of VTE. Patients were randomized to Edoxaban 60 mg once daily (30 mg once daily if creatinine clearance 30 mL/min to 50 mL/min, body weight of 60 kg or less or concomitant therapy with a potent P-glycoprotein inhibitor) or placebo and Warfarin or matching placebo.

The primary safety outcome (major or clinically-relevant non-major bleeding) occurred in 349 (8.5%) Edoxaban patients and 423 (10.3%) warfarin patients (HR 0.81; 95% CI 0.71-0.94). Major bleeding occurred in 56 (1.4%) Edoxaban patients and 66 (1.6%) Warfarin patients (HR 0.84; 95% CI 0.59-1.21).

Among patients who fulfilled criteria for the 30 mg Edoxaban dose, 58 of 733 (7.9%) Edoxaban patients and 92 of 719 (12.8%) Warfarin patients (HR 0.62; 95% CI 0.44-0.86) developed clinically relevant non-major bleeding [21].

This study confirms that once daily Edoxaban is as effective as Warfarin in the prevention of recurrent VTE and caused significantly less bleeding following an initial course of parenteral therapy.

Recent studies suggest that factor X inhibitor exerts an anti-inflammatory property in addition to their anticoagulant effects. Several coagulation factors, including FXa, play important roles in pro-inflammatory responses through Protease-Activated Receptors (PARs) in many cell types such as endothelial cells [4,22].

Katoh conducted a study on the Anti-inflammatory effect of factor-Xa inhibitors in Japanese patients with atrial fibrillation. Selected patients with Non-Valvular Atrial fibrillation were treated with FXa inhibitors from March 2013 to March 2015. The author

Table 2: Efficacy and safety of NOACs for the treatment of VTE: Results from clinical trials.

Trial Name	Design	Treatment	Months	Patients	TTR (%)	Efficacy outcome	Safety outcome
RE-COVER, 2009	Double blind	<ul style="list-style-type: none"> Enoxa/dabigatran (150 mg BD) Enoxa/warfarin 	6	2539 acute VTE	60	Recurrent VTE or VTE-related death: <ul style="list-style-type: none"> 2.4% enoxa/dabigatran 2.1% enoxa/warfrin 	Major/clinically relevant non major bleeding: <ul style="list-style-type: none"> 5.6% dabigatran 8.8% warfarin
RE-COVER II, 2011	Double blind	<ul style="list-style-type: none"> Enoxa/dabigatran (150 mg BD) Enoxa/warfarin 	6	2539 acute VTE	57	Recurrent VTE or VTE-related death: <ul style="list-style-type: none"> 2.3% enoxa/dabigatran 2.2% enoxa/warfrin 	Major/clinically relevant non major bleeding: <ul style="list-style-type: none"> 5.0% dabigatran 7.9% warfarin
EINSTEIN-DVT 2010	Open-lable	<ul style="list-style-type: none"> Rivaroxaban (15 mg BD for 3/52 then 20 mg OD) Enoxa/VKA 	3, 6, or 12	3449 acute DVT	58	Recurrent VTE: <ul style="list-style-type: none"> 2.1% rivaroxaban; 3.0% enoxa/VKA 	Major/clinically relevant non major bleeding: <ul style="list-style-type: none"> 8.1% rivaroxaban 8.1% enoxa/VKA
EINSTEIN-PE 2012	Open-lable	<ul style="list-style-type: none"> Rivaroxaban (15 mg BD for 3/52 then 20 mg OD) Enoxa/VKA 	3, 6, or 12	4832 acute PE	63	Recurrent VTE: <ul style="list-style-type: none"> 2.1% rivaroxaban 1.8% enoxa/VKA 	Major/clinically relevant non major bleeding: <ul style="list-style-type: none"> 10.3% rivaroxaban 11.4% enoxa/VKA
AMPLIFY, 2013	Double blind	<ul style="list-style-type: none"> Apixaban (10 mg BD for 7 days then 5 mg BD) Enoxa/warfarin 	6	5395 acute VTE	61	Recurrent VTE or VTE-related death: <ul style="list-style-type: none"> 2.3% apixaban 2.7% enoxa/VKA 	Major/clinically relevant non major bleeding: <ul style="list-style-type: none"> 0.6% apixaban 1.8% enoxa/VKA
Hokusai, 2013	Double blind	<ul style="list-style-type: none"> LMWH/edoxaban (60 mg OD or 30 mg OD) UFH or LMWH/Warfarin 	≤ 12	8292 acute VTE	63	Recurrent VTE: <ul style="list-style-type: none"> 3.2% enoxa/edoxaba 3.5% enoxa/warfarin 	Major/clinically relevant non major bleeding: <ul style="list-style-type: none"> 8.5% enoxa/edoxaban 10.3% enoxa/warfarin

TTR: Time in Therapeutic Ran

Table 3: Risk stratification of bleeding risk with anticoagulation following therapy.

Bleeding risk category	Type of surgery or procedure	Anticoagulation recommendation
Very high	<ul style="list-style-type: none"> Neurosurgical procedure (Intracranial or spinal) Prostatectomy or partial nephrectomy, bladder surgery Heart valve replacement Coronary artery bypass grafting 	<ul style="list-style-type: none"> Can initiate prophylactic dose anticoagulation at 24 hour Consider therapeutic dose anticoagulation no sooner than 72 hours
High	<ul style="list-style-type: none"> Pacemaker or AICD Placement Major cancer surgery Major vascular surgery (AAA repair, peripheral artery bypass) Reconstructive plastic surgery Renal or hepatic biopsy Bowel polypectomy (Assume this will be part of colonoscopy) Major orthopedic surgery 	<ul style="list-style-type: none"> Can initiate prophylactic dose anticoagulation within 12-24 hour Consider therapeutic dose anticoagulation no sooner than 48-72 hours
Moderate	<ul style="list-style-type: none"> Major intra- abdominal surgery Major intra- thoracic surgery 	<ul style="list-style-type: none"> Can initiate prophylactic dose anticoagulation within 12-24 hour Consider therapeutic dose anticoagulation no sooner than 24-48 hours
Low	<ul style="list-style-type: none"> Laparoscopic cholecystectomy or hernia repair Coronary angiography Arthroscopy Biopsy (prostate, bladder, thyroid, lymph node) Bronchoscopy +/- biopsy Central venous catheter removal Multiple dental extraction or gum surgery 	<ul style="list-style-type: none"> Can initiate prophylactic dose anticoagulation within 12 hour Consider therapeutic dose anticoagulation 24-48 hours
Very low	<ul style="list-style-type: none"> Minor dental procedures (Single tooth extraction or root canal) Minor dermatologic procedures (Excision of basal and squamous cell carcinomas, actinic keratosis , and malignant or premalignant nevi) Cataract removal Electroconvulsant Therapy (ECT) Arthrocentesis Joint or soft tissue injections GI endoscopy without biopsy 	<ul style="list-style-type: none"> Interruption of anticoagulation typically not necessary

concluded that plasma concentrations of pentraxin 3 and FDP D-dimer decreased and thrombomodulin increased after the initiation of treatment with FXa inhibitors hence supporting the anti-inflammatory effects [5].

In vitro study published in elsevier on the anti-inflammatory effect of apixiban on Mesangial cells. This study suggests that apixiban prevent plasma-evoked oxidative stress generation, increase in MCP-1 and ICAM-1 mRNA levels in, and THP-1 cell adhesion to, mesangial cells. Therefore exerts anti-oxidative and anti-inflammatory reactions in plasma-exposed mesangial cells by inhibiting the formation of

thrombin from prothrombin via blockade of Xa and subsequently suppressing the thrombin-PAR-1 system [23].

Aspirin

It is an antiplatelet agent, and it showed efficacy in patients who are not suitable for anticoagulant use. A prospectively planned combined analysis of the WARFASA and ASPIRE trials reported that aspirin as compared with placebo, significantly reduced the rate of VTE recurrence by 32% no excess risk of bleeding [24,25].

Guidance for the treatment of Deep vein thrombosis and pulmonary embolism (Table 3).

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