

# **Evaluation of Different Protocols for Management of Thrombotic Disorders**

Essay

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## Summary and Conclusion

Better understanding of the molecular mechanisms underlying thrombogenesis, advances in recombinant DNA technology, isolation and characterization of antithrombotic proteins from hematophagous organisms, and improvements in structure-based drug design have accelerated the pace of drug discovery. With these advances, we now have an array of new antithrombotic drugs.

Limitations of the currently available anticoagulants have fanned the continuing search for new anticoagulants with improved pharmacological and biosafety profile, and equal, if not superior efficacy. Targets of inhibition include the factor VIIa/tissue factor pathway (recombinant nematode anticoagulant peptide c2, tissue factor pathway inhibitor), factor Xa (fondaparinux, idraparinux, razaxaban), factor Va and VIIIa

pathway (recombinant activated protein C, soluble thrombomodulin) and thrombin (hirudin, bivalirudin, argatroban, ximelagatran, dabigatran). Irrespective of their mode of action, bleeding complications are invariable with all anticoagulants. Conventional assessment and measures should remain as first-line responses to bleeding complicating the use of these anticoagulants. Antidotes do not exist for the overwhelming majority of these agents. The role of recombinant activated factor VIIa in controlling bleeding is still investigational. Definitive haemostatic strategies for bleeding

# *List of Contents*

Title	Page
• <b>List of Abbreviations</b> .....	<b>II</b>
• <b>List of Figures</b> .....	<b>VI</b>
• <b>List of Tables</b> .....	<b>VIII</b>
• <b>Introduction</b> .....	<b>1</b>
• <b>Aim of the Work</b> .....	<b>5</b>
• <b>Review of Literature:</b>	
➤ <b>Chapter 1:</b> Coagulation pathway and physiology .....	<b>7</b>
➤ <b>Chapter 2:</b> The aetiology of Thrombosis .....	<b>31</b>
➤ <b>Chapter 3:</b> Different presentations of Thrombosis .....	<b>47</b>
➤ <b>Chapter 4:</b> Traditional Antithrombotics .....	<b>66</b>
➤ <b>Chapter 5:</b> New Antithrombotic Agents .....	<b>89</b>
➤ <b>Chapter 6:</b> Different Protocols For thrombotic management, Controversies and Challenges....	<b>129</b>
• <b>Summary and Conclusion</b> .....	<b>178</b>
• <b>References</b> .....	<b>180</b>
• <b>Arabic Summary</b> .....	

## *List of Abbreviations*

<b>ACT</b>	Activated clotting time
<b>APC</b>	Activated protein c
<b>APTT</b>	Activated partial thromboplastin time
<b>ATIII</b>	Antithrombin III
<b>BRVO</b>	Branch retinal vein occlusion
<b>CAST</b>	Chinese acute stroke trial
<b>CI</b>	Confidence interval
<b>COX</b>	Cyclooxygenase
<b>CrCl</b>	Creatinine clearance
<b>CS</b>	Cystathionine synthase
<b>CT</b>	Computed tomography
<b>CURE</b>	Clopidogrel in unstable angina to prevent recurrent events
<b>CVT</b>	Cerebral vein thrombosis
<b>Da</b>	Daltons
<b>DNA</b>	Deoxyribonucleic acid
<b>DVT</b>	Deep venous thrombosis
<b>EFAT</b>	European atrial fibrillation trial
<b>ELT</b>	Euglobuline time
<b>ESPRIT</b>	Enhanced suppression of the platelet IIb/IIIa receptor with integrilin therapy
<b>FRISC</b>	Fragmin and fast revascularisation during instability in coronary artery disease

## *List of Abbreviations (Cont.)*

<b>FV</b>	Factor V
<b>GPIb</b>	Glycoprotein Ib
<b>GUSTO</b>	Global utilization of streptokinase and tissue plasminogen activator for occluded coronary artery
<b>HCII</b>	Heparin cofactor II
<b>HIT</b>	Heparin induced thrombocytopenia
<b>HMWK</b>	High molecular weight kininogen
<b>HRG</b>	Histidine rich glycoprotein
<b>HRT</b>	Hormonal replacement therapy
<b>INR</b>	International normalized ratio
<b>ISAR-CHOICE</b>	Intracoronary stenting and antithrombotic regimen: choose between 3 high doses for immediate clopidogrel effect
<b>ISIS</b>	International study for infarct survival
<b>IV</b>	Intravenous
<b>LMWH</b>	Low molecular weight heparin
<b>Lpa</b>	Lipoprotein a
<b>MEDAL</b>	Multinational etoricoxib and diclofenac arthritis long term
<b>MI</b>	Myocardial infarction
<b>MRI</b>	Magnetic resonance imaging
<b>MTHFR</b>	Methylene tetrahydrofolate reductase
<b>MW</b>	Molecular weight
<b>OR</b>	Odds ratio

## *List of Abbreviations (Cont.)*

<b>PAI</b>	Plasminogen activator inhibitor
<b>PaO<sub>2</sub></b>	Partial pressure of arterial oxygen
<b>PC</b>	Protein C
<b>PCI</b>	Percutaneous coronary intervention
<b>PE</b>	Pulmonary embolism
<b>PF4</b>	Platelet factor 4
<b>PG</b>	Prostaglandin
<b>PNH</b>	Paroxysmal nocturnal hemoglobinuria
<b>PRISM-PLUS</b>	Platelet receptor inhibition in ischemic syndrome management in patients limited by unstable signs and symptoms
<b>PS</b>	Protein S
<b>PT</b>	Prothrombin time
<b>PTT</b>	Partial thromboplastin time
<b>RR</b>	Relative risk
<b>RVO</b>	Retinal vein occlusion
<b>RVT</b>	Retinal vein thrombosis
<b>SALT</b>	Swedish aspirin low dose trial
<b>SBP</b>	Systolic blood pressure
<b>Sc</b>	Subcutaneous
<b>SLE</b>	Systemic lupus erythromatosis
<b>SVT</b>	Splanchnic vein thrombosis
<b>TAFI</b>	Thrombine activatable fibrinolytic inhibitor
<b>TARGET</b>	Therapeutic arthritis research and gastrointestinal event trial

## *List of Abbreviations (Cont.)*

<b>TCT</b>	Thrombin clotting time
<b>TEG</b>	Thromboelastography
<b>TF</b>	Tissue factor
<b>TFPI</b>	Tissue factor pathway inhibitor
<b>TIMI</b>	Thrombolysis and thrombin inhibition in myocardial infarction
<b>TM</b>	Thrombomodulin
<b>TTP</b>	Thrombotic thrombocytopenic purpura
<b>TX</b>	Thromboxane
<b>U/d</b>	Unit per day
<b>UA</b>	Unstable angina
<b>UFH</b>	Unfractionated heparin
<b>US FDA</b>	United States Food and Drug Administration
<b>V/Q</b>	Ventilation-perfusion
<b>VKA</b>	Vitamin K antagonist
<b>VTE</b>	Venous thromboembolism
<b>vWF</b>	von Willebrand factor
<b>WHO</b>	World health organization
<b>WRIGHT</b>	WHO Research into global hazards of travel

## *List of Figures*

Fig. No	Title	Page
<b>Figure (1):</b>	Basic representation of the elements of hemostasis ( <i>Goodnight, 2001</i> ). ....	7 -
<b>Figure (2):</b>	A stylized view of endothelial functions related to procoagulation and anticoagulation. ( <i>Steffel, 2006</i> ). ....	8 -
<b>Figure (3):</b>	Classic theory of coagulation as proposed by Paul Morawitz, in which the prothrombin, by calcium activation yielded thrombin, converting fibrinogen to fibrin ( <i>Hoffbrand et al., 2005</i> ). ....	13 -
<b>Figure (4):</b>	The coagulation cascade model. The point of integration between the intrinsic and extrinsic pathways in this model occurs with factor IX activation. HMWK, high molecular weight kininogen ( <i>Hoffman et al., 2005</i> ). ....	16 -
<b>Figure (5):</b>	Diagram of leg veins (anterior view of right leg).....	53 -
<b>Figure (6):</b>	Diagnostic algorithm using D-dimer testing and ultrasound imaging in patients with suspected DVT ( <i>Wells, 2003</i> ). ....	54 -
<b>Figure (7):</b>	CT Scans obtained 1 hour 40 minutes after the onset of symptoms suggestive of cortical stroke in the territory of the right middle cerebral artery.....	63 -
<b>Figure (8):</b>	Fibrinolytic agents ( <i>Martin, 2006</i> ). ...	79 -



<b>Figure (9):</b> Comparative properties of fibrinolytics ( <i>Martin, 2006</i> ). .....	- 80 -
<b>Figure (10):</b> Classification of new anticoagulants. ( <i>Jeffery et al., 2008</i> ). .....	- 90 -
<b>Figure (11):</b> Mechanism of action direct thrombin inhibitors ( <i>Lefkovits and Topol, 1994</i> ). ....	- 104 -

## *List of Tables*

Tab. No	Title	Page
<b>Table (1):</b>	Proteins involved in the formation of clot ( <i>Butenas et al., 2007</i> ). .....	11 -
<b>Table (2):</b>	Summary of the Phases of coagulation, as proposed by the current cell-based theory of coagulation ( <i>Loscalzo et al., 2003</i> ). .....	20 -
<b>Table (3):</b>	Clinical model for predicting pretest probability of deep-vein thrombosis (DVT)* ( <i>Wells,</i> <i>2003</i> ). .....	52 -
<b>Table (4):</b>	Protocol for heparin dose adjustment ( <i>Bates et</i> <i>al., 2001</i> ). .....	69 -
<b>Table (5):</b>	Methods for preparation of LMWHs and danaparoid ( <i>Hirsh et al., 1992</i> ). .....	72 -
<b>Table (6):</b>	Factors IXa inhibitors ( <i>Cohen et al., 2006</i> ). ....	94 -
<b>Table (7):</b>	Indirect factor Xa inhibitors ( <i>Yusuf et al.,</i> <i>2006</i> ). .....	94 -
<b>Table (8):</b>	Direct factor Xa inhibitors ( <i>Jeffery et al.,</i> <i>2008</i> ). .....	97 -
<b>Table (9)</b>	General approach in treating patients with cancer who developed VTE ( <i>Pallavi et al.,2010</i> ):	142 -
<b>Table (10):</b>	Optimal duration of anticoagulation following DVT( <i>Buller et al., 2005</i> ). .....	145 -
<b>Table (11):</b>	Summary of current data for antiplatelet therapy in stroke prevention: ( <i>Sacco et al., 2008</i> ) .....	160 -

**Table(12):**Risk stratification, recommended thromboprophylaxis and optimal duration of prophylaxis by patient group(*Geerts et al., 2008*) ..... - 171 -

## **Introduction**

Thrombosis is the formation of a blood clot (thrombous) inside a blood vessel, obstructing the flow of blood through the circulatory system. When a blood vessel is injured, the body uses platelets and fibrin to form a blood clot, as the first step in repairing it (hemostasis) to prevent loss of blood. If that mechanism causes too much clotting, and the clot breaks free, a thrombous is formed (*Furie and Furie, 2008*).

Intravascular thrombous formation present the greatest challenge in the field of cardiovascular disease. Within the arterial tree, it is the culprit including clinical presentation in the majority of patients presenting with acute coronary syndrome (ACS). Thrombous formation within the venous circuit also results in substantial morbidity and mortality. Despite significant advances in prevention and treatment of venous thromboembolism (VTE), pulmonary embolism (PE) remains a common preventable cause of hospital death (*Horlander et al., 2003*).

Concepts of hemostasis and thrombosis emphasize the endothelial cells as a regulatory interface between blood and tissues. The endothelium constitutes an immense surface area ideally suited to control biologic events at the vessel surface. These include expression of membrane surface receptors for assembly of zymogens, localization of enzyme activity, orientation of adhesive glycoprotein interactions, and binding of

signals transducing ligands. In health, surface oriented interactions of endothelium serve primarily to maintain blood fluidity. In disease, disordered thromboregulation may acutely culminate in arterial and venous thrombosis (*Nachman, 1992*).

Of the three mechanisms of thrombosis defined by Virchow in the 19<sup>th</sup> century, vessel wall injury, stasis, and change in the composition of blood (hypercoagulability). Hypercoagulability can be inherited or acquired. The inherited type which is also called inherited thrombophilia, should be suspected when a patient has recurrent or life threatening venous thromboembolism, has a family history of venous thrombosis, is younger than 45 years of age, or has no apparent acquired risk factors, or if the patient is a woman who has a history of multiple abortions, stillbirth, or both. Acquired and genetic causes frequently interact (*Seligohn et al., 2001*).

By targeting the three essential components of the arterial thrombus, platelets, fibrin and thrombin, various regimens, combining antiplatelet agents (e.g. aspirin, Clopidogrel, GP IIb/IIIa inhibitors), antithrombotics (e.g. heparin, LMWH (enoxaparin), DTI (Bivalirudin) ), and either fibrinolysis have improved outcomes following acute ischemic syndromes (*de Lemos et al., 2000*).

Anticoagulant therapy remains the cornerstone of VTE treatment. Such treatment is usually divided into 2 stages. Rapid initial anticoagulation is given to minimize the risk of thrombus extension and subsequent fatal PE, whereas extended

anticoagulation is administered to prevent recurrent VTE, thereby reducing the risk of postphlebotic syndrome. With currently available drugs, immediate anticoagulation can only be effected with parenteral anticoagulants, such as heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux. Extended therapy usually involves the administration of an oral anticoagulant. Currently, the orally available anticoagulants are the vitamin K antagonists such as warfarin. LMWH and fondaparinux have simplified the initial treatment of VTE. Both agents have better bioavailability after subcutaneous injection and longer half-life than heparin. In addition, they produce a more predictable anticoagulant response. These features permit once daily subcutaneous dosing without coagulation monitoring. Consequently the majority of patients with VTE can now be treated with LMWH or fondaparinux as outpatients, an approach that reduces the health care costs and enhances the patient satisfaction (*Peter et al., 2008*).

Although LMWH and fondaparinux are important advances in VTE treatment, some difficulties persist. The need for once daily subcutaneous injections renders treatment problematic for some patients. This has prompted the introduction of longer acting parenteral anticoagulants that can be given subcutaneously on a once-weekly basis, and the development of novel oral anticoagulants with a rapid onset of action. Warfarin also problematic in the setting of VTE. Its slow onset of action necessitates overlap with a parenteral

anticoagulant for at least 5 days. The therapeutic dose of warfarin varies from patient to patient reflecting, at least in part, differences in dietary vitamin K intake, genetic polymorphisms in the enzymes involved in warfarin metabolism, and administration of concomitant medications that suppress or potentiate the anticoagulant effects of warfarin. Frequent coagulation monitoring is necessary to ensure that a therapeutic anticoagulant response is achieved with warfarin (*Ansell et al., 2004*).

The requirement of frequent coagulation monitoring is burdensome for patients and physicians and costly for the healthcare system. The difficulties surrounding warfarin administration have spurred the development of new oral anticoagulants that can be given in fixed doses with little or no coagulation monitoring. The need for such agents has increased in the recent years with emerging evidence that patients with unprovoked VTE require anticoagulation therapy for at least 6 months and possibly longer (*Kearon, 2004*).