Novel Oral Anticoagulants (NOAC) or Direct Oral Anticoagulants (DOAC)

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BLOOD

- Your circulatory system contains about 5 liters of the most remarkable fluid on earth,
- traveling through 65,000 miles (104650) Kms of blood vessels to carry oxygen and nutrients to every one of your 100 trillion cells,
- and remove waste products from them.
- 45% of the volume is red blood cells (RBCs) which make round trips to your big toe about every 20 seconds,
- flowing through capillaries just 1/10th the diameter of a human hair where the transfer takes place...so small that only one RBC at a time can wriggle through.

Dr Alamzeb MBBS M.Phil
Difference between artery and vein

- Red and white thrombus
Blood endothelial contact in the various vascular regions of the circulation (ratio of endothelial surface area to blood volume). The contact between blood and endothelium is 5000 times higher in the capillaries than in the large arterioles (arteries) or venules (veins). Diameters are plotted from published data, assuming that the blood vessels are cylindric. The values in italics above/beside the columns indicate the diameters (in micrometers) of each vessel type.
Blood Pressure

- Pressure exerted by blood on walls of a vessel
  - caused by contraction of the ventricles
With injury, VWF adheres to vessel subendothelial matrix. With shear, VWF multimers uncoil, platelets adhere and become activated.

Activated platelets expose phosphatidyl serine and bind FVIII to facilitate clotting. Bleeding ceases by platelet-fibrin plug sealing vascular injury and is followed by thrombolysis and tissue repair.
“Novel” compared to heparin (discovered in 1916) and warfarin (discovered in 1941).

“Direct” compared to vitamin K antagonist, warfarin and ATIII dependent inhibition, heparin derivatives.
Prothrombin Precursor

Glutamic Acid

Prothrombin

\[ \text{\( \gamma \)-Carboxy-Glutamic Acid} \]

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Reduced Vitamin K

Oxidized Vitamin K

Vitamin K Epoxide Reductase

Cytochrome P2C9 (CYP2C9)

S-warfarin

Cytochrome P1A2 (CYP1A2)

R-warfarin

Cytochrome P3A4 (CYP3A4)

Cytochrome P2C19 (CYP2C19)

WARFARIN
Disadvantages of warfarin

- Diet and drug interactions
- INR monitoring
- < 65% within therapeutic range and narrow therapeutic index
- Partial depletion
- Wararin necrosis
Warfarin has a narrow therapeutic window
Disadvantages of heparin derivatives

- Injection
- Renal elimination
- Heparin induced thrombocytopenia
In today's NY Times: February 28, 2008
Twists in Chain of Supplies for Blood Drug
Thrombosis

Circulatory Stasis

Endothelial Injury

Hypercoagulable State
Suspected Deep Vein Thrombosis (DVT):
Pathogenesis and Complications

- **Platelet Activation**
  - Malignancy
  - Abnormal release of coagulation-promoting cytokines

- **Increased clot formation**
  - Congenital defect in coagulation (e.g., Factor V Leiden, Factor II, Protein S, C) ↑ blood clotting ability

- **Hypercoagulable State**
  - ↑ ability for the blood to coagulate upon stimulation

- **Inherited disorders**
  - Pregnancy, Oral Contraceptive (OCP)
  - Estrogen promotes hypercoagulability, esp. in presence of other risk factors

- **Obesity**
  - Fat contains aromatase, converts more androgens into estrogen

- **Hypertension**
  - Systemic injury, activation of coagulation cascade

- **Trauma/Surgery**
  - Physically damages blood vessel walls

- **Vessel Injury**
  - Exposes tissue factor on damaged cells and subendothelium for vWF binding

- **Virchow’s Triad**
  - Venous Stasis
    - Low blood flow rate over site of vessel injury, concentrating blood clotting factors at that site
    - Fat contains aromatase, converts more androgens into estrogen
  - Sedentary, poor venous return
  - Fracture, immobilization, bedrest, airplane ride

- **Clot formation typically occurs in leg veins**
  1. Deep, large veins allow for blood pooling (stasis, hypercoagulability)
  2. Venous return from legs often against gravity (stasis)
  3. Valves in leg veins prone to backflow (stasis)

- **Clot embolizes to the lungs**
- **Destruction of vein valve by clot**
- **Thromboembolus**
  - *Pulmonary embolism* (acute life threatening complication)
  - Chronic thromboembolic pulmonary HTN

- **Venous Insufficiency**
  - Clot prevents blood from returning to heart. Blood accumulating in the leg results in unilateral leg edema, venous inflammation redness, warmth, tenderness

**Notes:**
- Venous thrombus causes PE, Arterial thrombus causes Stroke
- Previous DVT is risk factor for current DVT

**Legend:**
- = pathophysiology
- = mechanism
- = sign/symptom/lab finding
- = complications

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Blood coagulation *in vivo*

**Initiation phase**
- Platelets
- TF (tissue factor) → TF-VIIa
- IXa
- X
- Xa
- Prothrombin → Thrombin

**Amplification phase**
- Xla → XIa
- IXa
- (αTHR) → Xla
- (APC) → VIIIa
- Va → Va
- (αTHR) → Va
- (αTHR) → Xla
- (αTHR) → XIa
- XIa
- XI
- VIII
- V
- Fibrinogen → Fibrin
- Fibrin → Fibrin clot
- XIIIa
- XIII
Intrinsic Pathway

Surface contact (collagen, platelets)
Prothrombin

XII → XIIa
Platelet surface (?)

XI → Xla

Activated Partial Thromboplastin Time or aPTT

Extrinsic Pathway

Tissue injury

VII → VIIa
Tissue factor

VIIa

VIIIa
PL
Ca++

Xa

IIa
Va
PL
Prothrombin (II)
Thrombin (IIa)
Fibrinogen → Fibrin

Final Common Path
Vascular endothelium

- Fibrinogen
- TAFI
- Platelet
- Activated protein C
- TM
- P-selectin
- t-PA
- ICAM-1
- Leukocyte
- Thrombin

Proteins and pathways involved in vascular endothelial function.
Intravascular Hemolysis and Thrombosis

- Mechanical valve
- Sickle cell crisis
- PNH
- Microangiopathic hemolytic anemia
Consequences of Chronic Hemolysis and Free Hemoglobin

Normal RBCs are protected from complement attack by a shield of terminal complement inhibitors. Without this protective complement inhibitor shield, PNH red blood cells are destroyed.

New Frontiers and Evolving Paradigms in Cancer and Thrombosis
Focus on the Complex Interfaces Among Thrombosis, Anticoagulation, and Malignancy

Program Chairman: PROFESSOR the LORD AJAY KAKKAR, MBBS (Hon)
Clinical Presentation

OTHERS

- Depression
  - More common in pancreatic cancer than other abdominal tumors
  - 11 times increase risk of suicide especially early postoperative period

- Migratory thrombophlebitis
  - Trousseau sign of malignancy OR
  - Trousseau syndrome
  - Seen in 10% cases
  - Due to release of PAF (Platelet aggregating factors) from tumor or its necrotic material

* Trousseau himself died of CA pancreas who had migratory thrombophlebitis
Why VKA is less effective in cancer-associated thrombosis?
GENERATION OF MICROPARTICLES

Endothelium

WBC

RBC

μp

Pla.

EC

Stimulus

DISEASE
Formation of a Hemostatic Plug

Primary Hemostasis

Platelet adhesion
- Platelet glycoprotein Ib
- von Willebrand factor

Platelet aggregation
- Platelet glycoprotein Ib-IIIa
- Fibrinogen

Platelet shape change

Platelet secretion
- ADP
- Thromboxane A2

Secondary Hemostasis

Activation of the coagulation cascade
H$_2$N-Pro-Arg$_4$-Ser-Arg-Pro-Val-Arg$_5$-Pro-Arg$_2$-Pro-Arg$_2$-Val-Ser-Arg$_6$-Gly-Arg$_4$-COOH

PROTAMINE

HEPARIN

PROTAMINE-HEPARIN COMPLEX
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.
DE, dabigatran etexilate; dTT, diluted thrombin time; RI, renal impairment (CLcr: mild RI ≥ 60–< 90 mL/min; moderate RI ≥ 30–< 60 mL/min); TT, thrombin time.
MANY CHOICES
The coagulation cascade is complex, but anticoagulant drugs in late-stage development hit it at just two points, Factor Xa or thrombin.
Characteristics of Betrixaban

- Orally-active and selective fXa inhibitor
  - Oral bioavailability 34%,

- Peak to trough concentration profile 2.5 : 1
  - ~20 hour effective half-life

- No dose adjustment expected for renal impairment
  - Excreted mostly unchanged through bile with minimal renal excretion (<5%)

- Antidote in development

- No major drug interactions expected
  - Not substrate for CYP450 system
  - Substrate for efflux proteins including P-glycoprotein

Direct oral anticoagulants (DOAC)

• Efficacy
• Safe
• Convenience
• Cost
• Flexibility
• Antidotes
• More choice
• More indications
• Questionable in case of thromboembolisms associated with intravascular hemolysis, such as mechanical valve