How to Approach Patients with Abnormal Bleeding or Thrombosis?

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Approach to Bleeding Disorders

- Local bleeding or systemic bleeding
- Congenital or acquired
- Primary or secondary hemostasis
Approach to Bleeding Disorders

- Local bleeding or systemic bleeding

Systemic bleeding or bleeding disorders

- Spontaneous bleeding
  - Petechiae
  - Ecchymoses
- Multiple sites (2 or more)
- Single site but 3 or more unrelated and separated occasions
- Severity more than degree of trauma, warrant blood transfusions

Approach to Bleeding Disorders

- Local bleeding or systemic bleeding
- Congenital or acquired

Family history
- X-linked recessive: hemophilia A, B
- Autosomal dominant: most of vWD

History of bleeding tendency
- Previous surgery, dental procedure
- Hypermenorrhea
- Bleeding after trauma

Approach to Bleeding Disorders

- Local bleeding or systemic bleeding
- Congenital or acquired
- Primary or secondary hemostasis

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Primary hemostasis</th>
<th>Secondary hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Petechiae, small ecchymosis</td>
<td>Large ecchymosis, hematoma</td>
</tr>
<tr>
<td>Location</td>
<td>Skin, mucous membrane</td>
<td>Muscle, joint, deep tissue</td>
</tr>
<tr>
<td>Timing</td>
<td>Immediate</td>
<td>Delayed bleeding</td>
</tr>
</tbody>
</table>
Thrombocytopenia

- Splenomegaly
  - ↓ Production
    - ↓ Proliferation
  - ↑ Destruction

- Ineffective thrombopoiesis
  - Aplastic anemia
  - Radiation
  - Infection
  - Toxin, drug
  - Marrow infiltration
    e.g. acute leukemia

- Nonimmune
  - MDS
  - Megaloblastic
  - DIC
  - TTP/HUS
  - HELLP

- Immune
  - Drug induced
  - Alloimmune
  - Autoimmune

PBS: pseudothrombocytopenia, MAHA, abnormal cells, leukoerythroblastic blood picture
ITP: Immune Thrombocytopenia

- Isolated thrombocytopenia
- Diagnosis of exclusion
  - 1) Drug-induced thrombocytopenia
ITP: Immune Thrombocytopenia

- Isolated thrombocytopenia
- Diagnosis of exclusion
  - 1) Drug-induced thrombocytopenia
    - Reported drugs
    - Occur in 2-3 weeks after exposure
    - Platelet usually < 20000/cu.mm.
    - Recovery if stop drug in 2-3 weeks
    - ± Reexposure $\rightarrow$ thrombocytopenia

# Drug-induced Thrombocytopenia

**Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.**

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Drugs Implicated in Five or More Reports</th>
<th>Other Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparins</td>
<td>Unfractionated heparin, low-molecular-weight heparin</td>
<td></td>
</tr>
<tr>
<td>Cinchona alkaloids</td>
<td>Quinine, quinidine</td>
<td></td>
</tr>
<tr>
<td>Platelet inhibitors</td>
<td>Abciximab, eptifibatide, tirofiban</td>
<td></td>
</tr>
<tr>
<td>Antirheumatic agents</td>
<td>Gold salts</td>
<td>D-penicillamine</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>Linezolid, rifampin, sulfonamides, vancomycin</td>
<td></td>
</tr>
<tr>
<td>Sedatives and anticonvulsant agents</td>
<td>Carbamazepine, phenytoin, valproic acid</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Histamine-receptor antagonists</td>
<td>Cimetidine</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Analgesic agents</td>
<td>Acetaminophen, diclofenac, naproxen</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Diuretic agents</td>
<td>Chlorothiazide</td>
<td>Hydrochlorothiazide</td>
</tr>
<tr>
<td>Chemotherapeutic and immuno-suppressant agents</td>
<td>Fludarabine, oxaliplatin</td>
<td>Cyclosporine, rituximab</td>
</tr>
</tbody>
</table>

# Drug-induced Thrombocytopenia

## Table 2. Criteria and Level of Evidence for Establishing a Causative Relationship in Drug-Induced Thrombocytopenic Purpura.*

<table>
<thead>
<tr>
<th>Criterion and Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Therapy with the candidate drug preceded thrombocytopenia, and recovery from thrombocytopenia was complete and sustained after discontinuation of therapy.</td>
</tr>
<tr>
<td>2</td>
<td>The candidate drug was the only drug used before the onset of thrombocytopenia, or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug, with a sustained normal platelet count.</td>
</tr>
<tr>
<td>3</td>
<td>Other causes of thrombocytopenia were ruled out.</td>
</tr>
<tr>
<td>4</td>
<td>Re-exposure to the candidate drug resulted in recurrent thrombocytopenia.</td>
</tr>
<tr>
<td><strong>Level of evidence</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Definite — criteria 1, 2, 3, and 4 are met.</td>
</tr>
<tr>
<td>II</td>
<td>Probable — criteria 1, 2, and 3 are met.</td>
</tr>
<tr>
<td>III</td>
<td>Possible — criterion 1 is met.</td>
</tr>
<tr>
<td>IV</td>
<td>Unlikely — criterion 1 is not met.</td>
</tr>
</tbody>
</table>

ITP: Differential Diagnosis

- Isolated thrombocytopenia
- Diagnosis of exclusion
  - 1) Drug-induced thrombocytopenia
  - Heparin induced thrombocytopenia (HIT)
    - Antibody to PF4/heparin complex
      - Platelet activation $\rightarrow$ microparticle, hypercoagulable stage, thrombocytopenia
      - Activation of endothelial cells and monocytes
    - Diagnosis: 4T scoring system, functional assay, PF4-dependent immunoassay

# 4T score for HIT

**Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Acute thrombocytopenia</strong></td>
<td>Platelet count decrease of &gt;50% and nadir ≥20,000/mm³</td>
<td>Platelet count decrease of 30–50% or nadir 10,000–19,000/mm³</td>
<td>Platelet count decrease of &lt;30% or nadir ≤10,000/mm³</td>
</tr>
<tr>
<td><strong>Timing of onset</strong></td>
<td>Day 5–10, or day 1 if recent heparin exposure</td>
<td>&gt;Day 10 or unclear exposure</td>
<td>≤Day 4 with no recent heparin exposure</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>New thrombosis or anaphylactoid reaction after heparin bolus</td>
<td>Progressive or recurrent thrombosis</td>
<td>None</td>
</tr>
<tr>
<td><strong>Other cause of thrombocytopenia</strong></td>
<td>None</td>
<td>Possible</td>
<td>Definite</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>6–8, indicating high score</td>
<td>4 or 5, indicating intermediate score</td>
<td>0–3, indicating low score</td>
</tr>
</tbody>
</table>

*Adapted from Lo et al. A low 4T score (0 to 3 points) has a high negative predictive value. The day that heparin was started is considered as day 0. The onset of heparin-induced thrombocytopenia (HIT) is defined as the day that the platelet count begins to decrease. Patients in whom the score is difficult to apply, owing to missing platelet count values or coexisting conditions causing thrombocytopenia, and those with an intermediate or high score require further evaluation. This score can be included on ordering forms for HIT laboratory testing (e.g., www2.medizin.uni-greifswald.de/transfus/fileadmin/user_upload/doku_thrombo_gerinnung/platelet_lab_request_form.pdf).*

ITP: Differential Diagnosis

- Isolated thrombocytopenia
- Diagnosis of exclusion
  - 1) Drug-induced thrombocytopenia
  - Heparin induced thrombocytopenia
    - 2 Do’s: stop all heparin, start alternative anticoagulants (fondaparinux)
    - 2 Don’ts: warfarin during acute phase, platelet
    - 2 Diagnostics: lab support, work up DVT

ITP: Differential Diagnosis

• Isolated thrombocytopenia
• Diagnosis of exclusion
  • 1) Drug-induced thrombocytopenia
  • 2) MAHA with thrombocytopenia: DIC/TTP/HUS
Thrombotic Microangiopathies (TMAs)

- DIC
- TTP
  - Hereditary TTP: mutations in ADAMTS-13
  - Acquired TTP: autoantibodies against ADAMTS-13
- HUS
  - Infection-associated HUS: shigatoxin-producing E. Coli, shigella, and pneumococci, etc.
  - Atypical HUS: complement activation, platelet activation and unknown etiology
- Other TMAs

Thrombotic Microangiopathies (TMAs)

- Medication induced: calcineurin inhibitors
- Chemotherapy associated: gemcitabine, mitomycin and anti-VEGF therapy
- Transplantation associated: solid organ and hematopoietic stem cell transplantation
- Malignancy related: disseminated breast, lung and gastric cancers
- Infections: HIV
- Pregnancy associated: HELLP syndrome and preeclampsia
- Malignant hypertension

Disseminated Intravascular Coagulation (DIC)

Underlying disorder associated with DIC

Systemic activation of coagulation

Widespread fibrin deposition

Microvascular thrombosis

Organ failure

Consumption of platelets and coagulation factors

Thrombocytopenia and coagulation factor deficiency

Bleeding

Conditions associated with DIC

- Sepsis and severe infection
- Trauma
- Organ destruction e.g. pancreatitis
- Malignancy
  - Solid tumours, leukaemia
- Obstetric
  - Amniotic fluid embolism, placental abruption, pre-eclampsia
- Vascular abnormalities
  - Large haemangiomata, vascular aneurysm
- Severe liver failure
- Toxic and immunological insults
  - Snake bites, recreational drugs, ABO transfusion incompatibility, transplant rejection

Disseminated Intravascular Coagulation (DIC)

- DIC score

Table 2. Diagnostic Scoring System for Disseminated Intravascular Coagulation (DIC).*

<table>
<thead>
<tr>
<th>Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?</th>
</tr>
</thead>
<tbody>
<tr>
<td>If yes, proceed with this algorithm</td>
</tr>
<tr>
<td>If no, do not use this algorithm</td>
</tr>
</tbody>
</table>

Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin-related marker)

Score the test results as follows:

- Platelet count: 50,000 to 100,000 per mm$^3$, 1 point; <50,000 per mm$^3$, 2 points
- Elevated fibrin-related marker (e.g., D-dimer, fibrin degradation products): no increase, 0 points; moderate increase, 2 points; strong increase, 3 points
- Prolonged prothrombin time: <3 sec, 0 points; ≥3 sec but <6 sec, 1 point; ≥6 sec, 2 points
- Fibrinogen level: ≥1 g per liter, 0 points; <1 g per liter, 1 point

Calculate the score as follows:

- ≥5 points: compatible with overt DIC; repeat scoring daily
- <5 points: suggestive of nonovert DIC; repeat scoring within next 1 to 2 days

* Data are adapted from Toh and Hoots$^{21}$ on the basis of the scoring system developed by the International Society on Thrombosis and Hemostasis.

Disseminated Intravascular Coagulation (DIC)

- Management
- Treatment of the underlying disorder
- Transfusion of platelets or plasma
  - Platelet: bleeding with platelet < 50,000/cu.mm. or platelet < 20,000/cu.mm.
  - FFP: bleeding with PT/aPTT > 1.5 times normal or fibrinogen < 1.5 g/L (may use cryoprecipitate)
- Heparin
  - Consider in cases where thrombosis predominates

Thrombotic Thrombocytopenic Purpura (TTP)

- Fever, MAHA blood picture, thrombocytopenia, neurological symptom, renal failure
- ADAMTS-13 = vWF cleaving protease deficiency
Pathogenesis of TTP

ITP: Differential Diagnosis

- Isolated thrombocytopenia
- Diagnosis of exclusion
  - 1) Drug-induced thrombocytopenia
  - 2) MAHA with thrombocytopenia: DIC/TTP/HUS
  - 3) Hypersplenism
  - 4) Infection: HIV, HCV, HBV, DHF
  - 5) Bone marrow diseases: acute leukemia, etc.
  - 6) Autoimmune diseases: SLE
  - 7) Malignancy: lymphoma

No fever, No drugs, No MAHA, No blasts, No splenomegaly, No other series
ITP: Treatment

- Platelet > 30,000/cu.mm., asymptomatic
  - Observe
- Platelet < 30,000/cu.mm. or bleeding
  - Prednisolone 1 mg/kg/day
    - Response in 4 weeks
    - Tailed steroid if platelet 100,000/cu.mm., 5-10 mg/week until 20-30 mg/day then tailed slowly 5-10 mg/month
    - Continue at least 6 months
  - Pulse dexamethasone 40 mg po or IV x 4 days
  - Pulse methylprednisolone 30 mg/kg/day

ITP: Treatment

- Not response or steroid dependent
  - Splenectomy: good response 66%
    - Age < 50, fit for surgery, no other cause e.g. SLE
- Danazol, dapsone, colchicine
- Thrombopoietic agents
  - Eltrombopag, romiprostim
- Immunosuppressive
  - Cyclophosphamide, azathioprine, cyclosporin, MMF
- Rituximab

ITP: Treatment

- **Emergency treatment**
  - High dose steroids e.g. dexamethasone 40 mg/day or IVMP 500-1000 mg/day
  - IVIG 1 g/kg/day x 1-2 days
  - Anti-D immunoglobulin
  - Emergency splenectomy
  - Platelet transfusion

Table 3: Individual agents for treatment of ITP and the time to the first and the peak response if using the reported dose range

<table>
<thead>
<tr>
<th>Agent/Treatment</th>
<th>Reported Dose Range*</th>
<th>Time to Initial and Peak Responses§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone⁴,⁴⁴</td>
<td>1-4mg/kg po daily x 1-4 weeks</td>
<td>4-14 days 7-28 days</td>
</tr>
<tr>
<td>Dexamethasone⁴⁸,⁴⁹</td>
<td>40 mg po or iv daily x 4 days for 4-6 courses every 14-28 days</td>
<td>2-14 days 4-28 days</td>
</tr>
<tr>
<td>IVIG⁴¹,⁴⁶,⁶⁰</td>
<td>0.4-1g/kg/dose iv (1-5 doses)</td>
<td>1-3 days 2-7 days</td>
</tr>
<tr>
<td>IV anti-D⁴²,⁴⁷</td>
<td>75 µg/kg/dose iv</td>
<td>1-3 days 3-7 days</td>
</tr>
<tr>
<td>Rituximab⁴⁰,⁵¹,¹⁰</td>
<td>375 mg/m²/dose iv (4 weekly doses)</td>
<td>7-56 days 14-180 days</td>
</tr>
<tr>
<td>Splenectomy⁴³</td>
<td>laparoscopic</td>
<td>1-56 days 7-56 days</td>
</tr>
<tr>
<td>Vincristine⁴</td>
<td>up to 2mg/dose iv (4-6 weekly doses)</td>
<td>7-14 days 7-42 days</td>
</tr>
<tr>
<td>Vinblastine⁴⁶,⁴</td>
<td>0.1 mg/kg/dose iv (6 weekly doses)</td>
<td>7-14 days 7-42 days</td>
</tr>
<tr>
<td>Danazol⁵²,⁴</td>
<td>400-800 mg po daily</td>
<td>14-90 days 28-180 days</td>
</tr>
<tr>
<td>Azathioprine⁵²</td>
<td>2 mg/kg po daily</td>
<td>30-90 days 30-180 days</td>
</tr>
<tr>
<td>AMG531⁹,⁶,⁷</td>
<td>3-10 µg/kg/weekly sc</td>
<td>5-14 days 14-60 days</td>
</tr>
<tr>
<td>Eltrombopag⁸</td>
<td>50-75mg po daily</td>
<td>7-28 days 14-90 days</td>
</tr>
</tbody>
</table>
Acquired Disorders of Platelet Function

- Drug-induced platelet dysfunction
  - Analgesics: NSAIDs
  - Antibiotics
  - Cardiovascular drugs
  - Psychototropic drugs
- Secondary platelet dysfunction
  - Uremia
  - Paraproteinemia
  - Myelodysplastic syndrome (MDS)
  - Myeloproliferative neoplasms (MPNs)
- Acquired von Willebrand disease
# Platelet dysfunction

## Bleeding time
- Functional test for primary hemostasis
  - Platelet
  - Blood vessel
- Lack accuracy in determining risk of bleeding
- Poorly reproducible
- Time consuming

## Platelet function test
- Platelet Function Analyzer-100 (PFA-100)
- Platelet aggregation test
  - ADP, epinephrine, collagen, arachidonic acid (AA), ristocetin, thrombin

Approach to Coagulopathy
Coagulation Test
Approach to Coagulopathy

Isolated PTT prolonged

Bleeding

- Mixing test
  - Correct: Hemophilia A
  - Not correct: FVIII inhibitor, FIX inhibitor, FXI inhibitor

No bleeding

- Mixing test
  - Correct: Contact factor deficiency
  - Not correct: Lupus anticoagulant

Approach to Coagulopathy

- Isolated PT prolonged
  - Vitamin K deficiency or vitamin K antagonist
  - Liver disease
  - FVII deficiency (rare)
  - FVII inhibitor (extremely rare)
Approach to Coagulopathy

• Combined PT and PTT prolongation
• Inherited
  • Deficiency of FV, X, fibrinogen, prothrombin
• Acquired
  • Moderate to severe liver disease
  • DIC
  • Warfarin and heparin
  • Vitamin K deficiency
  • Primary amyloidosis associated FX deficiency
  • Paraproteinemia
  • Dilutional coagulopathy
  • Inhibitor of FV, X, fibrinogen, prothrombin

Approach to Coagulopathy

- TT prolonged
  - Hypofibrinogenemia: congenital, DIC
  - Dysfibrinogenemia
  - Thrombin inhibitors: heparin, FDP
Approach to Coagulopathy

- Bleeding with normal platelet and coagulogram
  - Mild bleeding disorders: vWD, hemophilia
  - FXIII deficiency: clot solubility test
  - Hyperfibrinolysis: euglobulin lysis time
    - Cirrhosis – increased fibrinolytic activity
    - PAI-1 deficiency, α2-antiplasmin deficiency
- Vascular disease
- Platelet dysfunction
Hemophilia

- X-linked congenital bleeding disorder
  - Hemophilia A: FVIII deficiency (80-85%)
  - Hemophilia B: FIX deficiency
- Clinical suspicious
  - Easy bruising in early childhood
  - Spontaneous bleeding, particularly into the joints, muscles, and soft tissues
  - Excessive bleeding following trauma or surgery
- A definitive diagnosis: factor assay to demonstrate deficiency of FVIII or FIX

Severity & Symptoms

- Severe: factor activity < 1%
  - Onset in childhood
  - Hemarthrosis
  - Spontaneous bleeding
- Moderate: factor activity 1-5%
  - Abnormal bleeding after minor surgery or trauma
- Mild: factor activity 5 - 20%
  - Abnormal bleeding after major surgery or trauma

### Guideline for Factor Replacement

<table>
<thead>
<tr>
<th>Type of hemorrhage</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desired level (IU dL⁻¹)</td>
<td>Duration (days)</td>
</tr>
<tr>
<td>Joint</td>
<td>40–60</td>
<td>1–2, may be longer if response is inadequate</td>
</tr>
<tr>
<td>Superficial muscle/no NV compromise (except iliopsoas)</td>
<td>40–60</td>
<td>2–3, sometimes longer if response is inadequate</td>
</tr>
<tr>
<td>Iliopsoas and deep muscle with NV injury, or substantial blood loss</td>
<td>80–100</td>
<td>1–2</td>
</tr>
<tr>
<td>Initial</td>
<td>80–100</td>
<td>1–2</td>
</tr>
<tr>
<td>Maintenance</td>
<td>30–60</td>
<td>3–5, sometimes longer as secondary prophylaxis during physiotherapy</td>
</tr>
<tr>
<td>CNS/head</td>
<td>80–100</td>
<td>1–7</td>
</tr>
<tr>
<td>Initial</td>
<td>50</td>
<td>8–21</td>
</tr>
<tr>
<td>Maintenance</td>
<td>80–100</td>
<td>1–7</td>
</tr>
<tr>
<td>Throat and neck</td>
<td>50</td>
<td>1–7</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>80–100</td>
<td>7–14</td>
</tr>
<tr>
<td>Initial</td>
<td>50</td>
<td>8–14</td>
</tr>
<tr>
<td>Maintenance</td>
<td>80–100</td>
<td>3–5</td>
</tr>
<tr>
<td>Renal</td>
<td>50</td>
<td>5–7</td>
</tr>
<tr>
<td>Deep laceration</td>
<td>50</td>
<td>5–7</td>
</tr>
<tr>
<td>Surgery (major)</td>
<td>80–100</td>
<td>1–3</td>
</tr>
<tr>
<td>Pre-op</td>
<td>60–80</td>
<td>1–3</td>
</tr>
<tr>
<td>Post-op</td>
<td>40–60</td>
<td>4–6</td>
</tr>
<tr>
<td>Surgery (minor)</td>
<td>30–50</td>
<td>7–14</td>
</tr>
<tr>
<td>Pre-op</td>
<td>50–80</td>
<td>1–5, depending on type of procedure</td>
</tr>
<tr>
<td>Post-op</td>
<td>30–80</td>
<td>1–5, depending on type of procedure</td>
</tr>
</tbody>
</table>
Guideline for Factor Replacement

<table>
<thead>
<tr>
<th>Indication</th>
<th>Desired level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening hemorrhage or major surgery</td>
<td>80 -100%</td>
</tr>
<tr>
<td>Major-bleeding or minor surgery</td>
<td>50 – 80%</td>
</tr>
<tr>
<td>Mild bleeding</td>
<td>30 – 40%</td>
</tr>
</tbody>
</table>

- Consider DDAVP for mild to moderate bleeding in hemophilia A
- Consider antifibrinolytic drugs for mucosal bleeding
How to Calculate Factor Replacement

- **Factor VIII**
  - 1U/kg of FVIII infusion increases 2% activity
  - One half of the initial dose is given every half-life (q 12-24 hr)

- **Factor IX**
  - 1U/kg of FIX infusion increases 1% activity
  - Repeated dose q 24 hr

Blood Component Therapy for Hemophilia A

- **Factor VIII concentrates**
  - 1 vial containing 250-500 U of factor VIII

- **FFP**
  - Containing all coagulation factors
  - 1 ml containing 1U of factor VIII, IX

- **Cryoprecipitates**
  - Containing FVIII, fibrinogen, FXIII, vWF
  - 1 bag of cryoprecipitate containing 80-100 U of FVIII

Acquired Hemophilia A

- Rare disease resulting from autoantibodies against endogenous FVIII
- Median age 64–78 years
- Cause
  - Idiopathic (50%)
  - Malignancy
  - Autoimmune disorders e.g. RA
  - Others: infections, dermatologic conditions, medications
- > 80% Subcutaneous bleeding

Acquired Hemophilia A

- **Diagnosis**
  - Screening test
    - Isolated prolonged aPTT
    - Not correct by aPTT mixing study with 2 hrs incubation at 37°C
  - Confirmation test: FVIII inhibitor

Acquired Hemophilia A

- **Diagnosis**
- **Screening test**
  - Isolated prolonged aPTT
  - Not correct by aPTT mixing study with 2 hrs incubation at 37°C
- **Confirmation test: FVIII inhibitor**

Acquired Hemophilia A

• Management

1. Controlling and preventing bleeding
   • Low inhibitor titers (< 5 BU): FVIII replacement
   • High inhibitor titers (> 5 BU): bypassing therapy e.g. aPCC, rFVIIa

2. Eradication of the inhibitor
   • Immunosuppressive therapy: corticosteroids +/- cyclophosphamide

3. Treatment of the underlying disease
von Willebrand disease

• Inherited quantitative and/or qualitative abnormalities in vWF
  • Most = autosomal dominant
  • Commonly associated with mucosal hemorrhages
• vWF: large, multimeric plasma protein
  • Recruitment of circulating platelets at sites of vascular injury under high shear conditions
  • Protecting FVIII from rapid degradation or cellular uptake

Ng C. Blood 2015;125:2029-37.
von Willebrand disease

- **Phenotypic classification**

<table>
<thead>
<tr>
<th>vWD type</th>
<th>Pathophysiologic mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of vWF and/or FVIII</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative defects of vWF</td>
</tr>
<tr>
<td>2A</td>
<td>Decrease platelet-dependent vWF function, lack of HMWM</td>
</tr>
<tr>
<td>2B</td>
<td>Increase platelet-dependent vWF function, lack of HMWM</td>
</tr>
<tr>
<td>2M</td>
<td>Decrease vWF function, normal multimers</td>
</tr>
<tr>
<td>2N</td>
<td>Decrease binding vWF to FVIII, normal multimers</td>
</tr>
<tr>
<td>3</td>
<td>SevereCOMPLETE deficiency of vWF and moderately severe decrease of FVIII</td>
</tr>
</tbody>
</table>

Ng C. Blood 2015;125:2029-37.
Type 2 vWD

VWD Type 2A
Decreased platelet binding
Loss of HMWM

VWD Type 2N
Decrease FVIII binding
Low FVIII levels

VWD Type 2B
Increased platelet binding
Thrombocytopenia

VWD Type 2M
Decreased platelet binding
Normal multimers

Ng C. Blood 2015;125:2029-37.
RIPA, ristocetin induced platelet aggregation

Ng C. Blood 2015;125:2029-37.
Management of vWD

• ddAVP
  • Induces exocytosis of Weibel-Palade bodies
  • Dose 0.3 µg/kg diluted in 50 mL saline over 30 min repeated every 12 to 24 hours
  • Typically increases plasma levels of VWF 3-5 fold over baseline within the first hour
  • A test infusion is recommended
  • Not used in type 2B and type 3

Management of vWD

- Replacement therapy
  - VWF/FVIII concentrates
  - Cryoprecipitate
- For vWD type 3, 2B or patients who are not response to ddAVP
- Calculation as FVIII repeat q 12-24 hr

Acquired vWD

• Pathogenesis

1) Antibody-mediated clearance or functional interference
   - Autoimmune disease
   - Lymphoproliferative disorders: MGUS, MM

2) Adsorption to surfaces of transformed cells or platelets
   - MPNs
   - Malignancy

3) Increased shear stress and subsequent proteolysis
   - Cardiovascular disorders e.g. AS

4) Decreased synthesis
   - Hypothyroidism

# Approach to Thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Arterial thrombosis</th>
<th>Venous thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormalities of</td>
<td>Platelet activation</td>
<td>Hypercoagulable state</td>
</tr>
<tr>
<td>blood</td>
<td>Thrombocytosis</td>
<td>Thrombocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormalities of</td>
<td>Turbulence</td>
<td>Venous stasis</td>
</tr>
<tr>
<td>blood flow</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperviscosity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormalities of</td>
<td>Atherosclerosis</td>
<td>Trauma/erosion</td>
</tr>
<tr>
<td>vessel wall</td>
<td>Trauma/erosion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Differential diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Vascular or cardiac embolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

**Risk Factors for Thrombosis**

**“Thrombophilia”**

<table>
<thead>
<tr>
<th>Hereditary factors</th>
<th>Acquired factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>Provoked</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>◦  Immobilization, major surgery, trauma, central venous catheterization</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>◦  Pregnancy &amp; postpartum</td>
</tr>
<tr>
<td>Factor V Leiden (FVL)</td>
<td>◦  Oral contraceptives, hormone-replacement therapy</td>
</tr>
<tr>
<td>Activated protein C resistance</td>
<td>Unprovoked</td>
</tr>
<tr>
<td>without FVL</td>
<td>◦  Cancer</td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>◦  MPN: PV, ET</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>◦  Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>◦  PNH</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>◦  DIC, TTP</td>
</tr>
<tr>
<td></td>
<td>◦  Drugs: chemotherapy, heparin</td>
</tr>
<tr>
<td></td>
<td>◦  Nephrotic syndrome</td>
</tr>
</tbody>
</table>

Heit JA. Hematology 2007;127-135.
# Risk Factors for Thrombosis “Thrombophilia”

<table>
<thead>
<tr>
<th>Hereditary factors</th>
<th>Acquired factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
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</tr>
<tr>
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<td>◦ Immobilization, major surgery, trauma, central venous catheterization</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>◦ Pregnancy &amp; postpartum</td>
</tr>
<tr>
<td>Factor V Leiden (FVL)</td>
<td>◦ Oral contraceptives, hormone-replacement therapy</td>
</tr>
<tr>
<td>Activated protein C resistance without FVL</td>
<td><strong>Unprovoked</strong></td>
</tr>
<tr>
<td>Prothrombin gene mutation</td>
<td>◦ Cancer</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>◦ MPN: PV, ET</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>◦ Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>◦ PNH</td>
</tr>
<tr>
<td></td>
<td>◦ DIC, TTP</td>
</tr>
<tr>
<td></td>
<td>◦ Drugs: chemotherapy, heparin</td>
</tr>
<tr>
<td></td>
<td>◦ Nephrotic syndrome</td>
</tr>
</tbody>
</table>

**Arterial or venous thrombosis**

Heit JA. Hematology 2007;127-135.
Antiphospholipid Syndrome

• Clinical criteria
  • Vascular thromboses
    • One or more episodes of arterial or venous thrombosis
  • Pregnancy morbidity
    • GA > 10 week : fetal death ≥ 1
    • GA < 10 week : abortion ≥ 3
    • GA < 34 week : premature births from preeclampsia or placental insufficiency
• Laboratory criteria: ≥ 2 at least 12 week apart
  • Lupus anticoagulant
  • Anticardiolipin Ab IgG and/or IgM
  • Anti-β2 glycoprotein I IgG and/or IgM

## Risk Factors of Cerebral Venous Sinus Thrombosis

### Table 1. Causes of and Risk Factors Associated with Cerebral Venous Sinus Thrombosis.

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic prothrombotic conditions</td>
<td>Antithrombin deficiency&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Protein C and protein S deficiency&lt;sup&gt;6-8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Factor V Leiden mutation&lt;sup&gt;9-11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Prothrombin mutation (the substitution of A for G at position 20210)&lt;sup&gt;9,11,12&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Homocysteinemia caused by gene mutations in methylenetetrahydrofolate reductase&lt;sup&gt;13,14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acquired prothrombotic states</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipid antibodies&lt;sup&gt;7,15&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Homocysteinemia&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Pregnancy&lt;sup&gt;16,17&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Puerperium&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infections</td>
<td>Otitis, mastoiditis, sinusitis&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Systemic infectious disease&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Inflammatory disease</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Wegener’s granulomatosis&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>Behçet’s syndrome&lt;sup&gt;19,20&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hematologic conditions</td>
<td>Polycythemia, primary and secondary</td>
</tr>
<tr>
<td></td>
<td>Thrombocythemia</td>
</tr>
<tr>
<td></td>
<td>Leukemia&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Anemia, including paroxysmal nocturnal hemoglobinuria&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drugs</td>
<td>Oral contraceptives&lt;sup&gt;9,23&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Asparaginase&lt;sup&gt;8,21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mechanical causes, trauma</td>
<td>Head injury&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Injury to sinuses or jugular vein, jugular catheterization</td>
</tr>
<tr>
<td></td>
<td>Neurosurgical procedures</td>
</tr>
<tr>
<td></td>
<td>Lumbar puncture&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Dehydration, especially in children&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cancer&lt;sup&gt;1,6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Risk Factors of SVT

**Local precipitating factors**
- Abdominal cancer
- Cirrhosis

**PVT**
- Acute pancreatitis
- Abdominal cancer

**Isolated SpVT**
- Splenectomy

---

Riva N. Thromb Res 2012;130:S1–S3.
Diagnosis of VTE: DVT and PE

Figure 1: A diagnostic algorithm for clinically suspected deep vein thrombosis or pulmonary embolism. Use of CUS with suspected deep vein thrombosis, and of multidetector CT angiography with pulmonary embolism. CUS=compression ultrasonography. MDTCA=multidetection CT angiography.
Diagnosis of VTE: Clinical Probability Score

Table 1. Clinical probability scores for PE and DVT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
<th>PE: Wells</th>
<th>Points</th>
<th>DVT: Wells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 y or older</td>
<td>1</td>
<td>Signs or symptoms of DVT</td>
<td>3</td>
<td>Active cancer (treatment ongoing or within previous 6 mo or palliative)</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>3</td>
<td>Alternative diagnosis is less likely than PE</td>
<td>3</td>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
</tr>
<tr>
<td>Surgery or fracture within 1 mo</td>
<td>2</td>
<td>Heart rate &gt; 100 bpm</td>
<td>1.5</td>
<td>Recently bedridden for more than 3 d or major surgery within 4 wk</td>
</tr>
<tr>
<td>Active malignant condition</td>
<td>2</td>
<td>Immobilization/surgery in previous 4 wk</td>
<td>1.5</td>
<td>Localized tenderness along distribution of the deep venous system</td>
</tr>
<tr>
<td>Unilateral lower limb pain</td>
<td>3</td>
<td>Prior history of DVT or PE</td>
<td>1.5</td>
<td>Entire leg swollen</td>
</tr>
<tr>
<td>Pain or deep palpitation of lower limb and unilateral edema</td>
<td>4</td>
<td>Hemoptysis</td>
<td>1</td>
<td>Calf swelling by more than 3 cm compared with asymptomatic leg (measured 10 cm below tibial tuberosity)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>0</td>
<td>Active cancer</td>
<td>1</td>
<td>Fitting edema (greater in the symptomatic leg)</td>
</tr>
<tr>
<td>Heart rate 75-94 bpm</td>
<td>3</td>
<td></td>
<td></td>
<td>Collateral superficial veins (nonvalvocoe)</td>
</tr>
<tr>
<td>Heart rate 95 bpm or more</td>
<td>5</td>
<td></td>
<td></td>
<td>Past history of DVT</td>
</tr>
<tr>
<td>Modified Geneva</td>
<td></td>
<td></td>
<td></td>
<td>Alternative diagnosis as likely or greater than that of DVT</td>
</tr>
<tr>
<td>&lt;3 points = low</td>
<td></td>
<td>Traditional</td>
<td></td>
<td>-2</td>
</tr>
<tr>
<td>4-10 points = Intermediate</td>
<td></td>
<td>Original score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 points = high</td>
<td></td>
<td>&lt;0 points = low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simplified</td>
<td></td>
<td>0-2 points = intermediate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2 points or less = PE unlikely</td>
<td></td>
<td>&gt;2 points = high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simplified</td>
<td></td>
<td>Dichotomized score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4 = PE likely</td>
<td></td>
<td>≤1 = DVT unlikely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 or less = PE unlikely</td>
<td></td>
<td>≥2 = DVT likely</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

bpm indicates beats per minute.

History (risk factors) + Physical examination

Wells P. Hematology 2013:457-463.
Cerebral Venous Sinus Thrombosis

Clinical features
Headache 90%
Neurological deficit 50%
Seizure 40%
Behavioral symptoms
Coma

Diagnosis
CT-CTV
MRI-MRV

Splanchnic Vein Thrombosis

• Portal vein thrombosis (PVT), Budd-Chiari syndrome (BCS), mesenteric vein thrombosis (MVT), and splenic vein thrombosis (SpVT)
• Heterogeneous clinical presentations
  • Abdominal pain: most frequent (40-60%)
  • Intestinal infarction (30% of acute MVT)
  • GI bleeding (25% of PVT)
  • Ascites (25% of BCS)
  • Asymptomatic (18%)
• Diagnosis: imaging studies e.g. CT

Riva N. Thromb Res 2012;130:S1–S3.
Thrombophilia Testing

- **Indication**
  - Idiopathic or recurrent VTE
  - First episode in < 40-50 year
  - Family history of VTE esp. 1st degree relative
  - VTE at unusual sites
  - Unexplained recurrent (≥3 in first trimester) pregnancy loss
  - Neonatal purpura fulminans
  - Warfarin induced skin necrosis

Heit JA. Hematology 2007;127-135.
# Thrombophilia Testing

## Venous thrombosis
- Protein C
- Protein S
- Antithrombin
- CBC (MPN, PNH, DIC)
- Cancer screening
- Antiphospholipid antibody
- Serum homocysteine
- \textit{JAK2} mutation (splanchnic vein thrombosis)

## Arterial thrombosis
- CBC (MPN, PNH, DIC)
- Cancer screening
- Antiphospholipid antibody
- Serum homocysteine

Heit JA. Hematology 2007;127-135.
Thrombophilia Testing

First VTE

- Provoked by strong triggers
  - No role for testing
  - Consider testing for FVL and PTG, protein S, protein C, antithrombin
  - Consider aPL testing in the case of extensive DVT or PE

- Provoked by weak triggers in a young patient with strong family history and female family members of childbearing age
  - Determine role of testing

- Unprovoked
  - Determine role of testing
  - Consider aPL testing, especially in the case of arterial or recurrent events

- Unusual site
  - Cerebral veins
    - Test for FVL, PTG, protein S, protein C, antithrombin, and aPL
  - Splanchnic veins
    - Test for inherited thrombophilias, aPL, MPN, and PNH

If patient is young and has a strong family history or a female family member of childbearing age, consider testing for FVL, PTG, protein C, protein S, and antithrombin

Thrombophilia Testing

- **Acute thrombosis**
  - Decrease: antithrombin, proteins C and S
  - Increase: fibrinogen and factor VIII
  - Delaying testing for at least 6 weeks

- **Heparin and warfarin therapy**
  - Heparin therapy: lower antithrombin levels and impair interpretation of lupus anticoagulant
  - Warfarin therapy: reduces proteins C and S (4 to 6 weeks after stop)
  - Delaying testing until the effects of heparin and warfarin therapy have resolved

Heit JA. Hematology 2007;127-135.
Antithrombotic Therapy for VTE

Phases of anticoagulation

- **Initial** (0 to ~7 days)
- **Long-term** (~7 days to ~3 months)
- **Extended** (~3 months to indefinite)

- Parenteral*: Heparin, LMWH, fondaparinux
- Vitamin K antagonist or other agent†: Includes LMWH, dabigatran, rivaroxaban

* Heparin, LMWH, fondaparinux; † Includes LMWH, dabigatran, rivaroxaban

**Figure 1.** Phases of anticoagulation. LMWH = low-molecular-weight heparin.
# Direct oral anticoagulants (DOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability (%)</strong></td>
<td>7</td>
<td>80</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>BID</td>
<td>OD (BID)</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td><strong>Time-to-peak effect</strong></td>
<td>1-3 hr</td>
<td>2-4 hr</td>
<td>1-2 hr</td>
<td>1-2 hr</td>
</tr>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>14-17</td>
<td>7-11</td>
<td>8-14</td>
<td>5-11</td>
</tr>
<tr>
<td><strong>Renal clearance as unchanged drug (%)</strong></td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>P-gp</td>
<td>3A4/P-gp</td>
<td>3A4/P-gp</td>
<td>P-gp</td>
</tr>
</tbody>
</table>

OD, once daily; BID, twice daily; P-gp, P-glycoprotein; 3A4, cytochrome P450 3A4 isoenzyme

Antithrombotic Therapy for VTE

- **Initial treatment**¹
- **Parenteral anticoagulant**
  - Low-molecular-weight heparin (LMWH)
  - Fondaparinux
  - Unfractionated heparin (UFH): IV or SC
    - Renal failure or initial risk of bleeding/urgent surgery
- **Direct oral anticoagulants (DOACs)**
  - Rivaroxaban 15 mg twice-daily for 3 weeks²
  - Apixaban 10 mg twice-daily for 7 days³

¹ Kearon C. Chest 2016;149:315-52.
Antithrombotic Therapy for VTE

- **Initial treatment**
- **If use VKA:**
  - Recommend early initiation of VKA
  - Continuation of parenteral anticoagulation for a minimum of 5 days and until INR 2.0 or above for at least 24 h

Kearon C. Chest 2012;141(suppl 2):e419S-e494S.
Antithrombotic Therapy for VTE

- **Initial treatment**
- **Thrombolytic therapy**
  - Patients with acute PE associated with hypotension (e.g., systolic BP < 90 mmHg) who do not have a high bleeding risk
  - Selected patients with acute PE who deteriorate after starting anticoagulant therapy have a low bleeding risk
Antithrombotic Therapy for VTE

- **Long-term and extended treatment**
- **Vitamin K antagonist (VKA)**
  - Target INR 2-3
  - Reduces recurrent VTE by 90%
- **Direct oral anticoagulant (DOACs)**
  - Dabigatran, rivaroxaban, apixaban, edoxaban
- **LMWH**
  - More effective than a VKA in cancer patients

Kearon C. Chest 2012;141(suppl 2):e419S-e494S.
### DOACs in Initial, Long-term, and Extended Phase

<table>
<thead>
<tr>
<th>DOACs</th>
<th>Bridging with heparin</th>
<th>Initial phase dose</th>
<th>Long-term phase dose</th>
<th>Extended phase dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran(^1)</td>
<td>Yes</td>
<td></td>
<td>150 mg twice-daily</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban(^2,3)</td>
<td>No</td>
<td>15 mg twice-daily for 3 weeks</td>
<td>20 mg daily</td>
<td>10-20 mg daily</td>
</tr>
<tr>
<td>Apixaban(^4)</td>
<td>No</td>
<td>10 mg twice-daily for 1 week</td>
<td>5 mg twice-daily</td>
<td>2.5-5 mg twice-daily</td>
</tr>
<tr>
<td>Edoxaban(^5,6)</td>
<td>Yes</td>
<td>60 mg daily or 30 mg daily in case of CrCl 30-50 ml/min or BW &lt; 60 kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antithrombotic Therapy for VTE


Dabigatran, edoxaban
Rivaroxaban, apixaban
DOACs in VTE: Efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>59/2609 (2.3%)</td>
<td>71/2635 (2.7%)</td>
<td></td>
<td>0.84 (0.60-1.18)</td>
<td>0.31</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>36/1731 (2.1%)</td>
<td>51/1718 (3.0%)</td>
<td></td>
<td>0.70 (0.46-1.07)</td>
<td>0.10</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>50/2419 (2.1%)</td>
<td>44/2413 (1.8%)</td>
<td></td>
<td>1.13 (0.76-1.69)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>66/4118 (1.6%)</td>
<td>80/4122 (1.9%)</td>
<td></td>
<td>0.83 (0.60-1.14)</td>
<td>0.25</td>
</tr>
<tr>
<td>RE-COVER</td>
<td>30/1274 (2.4%)</td>
<td>27/1265 (2.1%)</td>
<td></td>
<td>1.10 (0.66-1.84)</td>
<td>0.71</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>30/1279 (2.3%)</td>
<td>28/1289 (2.2%)</td>
<td></td>
<td>1.08 (0.65-1.80)</td>
<td>0.77</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>271/13430 (2.0%)</td>
<td>301/13442 (2.2%)</td>
<td></td>
<td>0.90 (0.77-1.06)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Figure 1. First recurrent VTE or VTE-related death. For Hokusai-VTE, we used event data for the on-treatment period. Heterogeneity: $I^2 = 0\%$; $P = .53$. van Es N. Blood 2014;124:1968-75.
DOACs in VTE: Major Bleeding

<table>
<thead>
<tr>
<th>Study</th>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>ARR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>15/2676 (0.6%)</td>
<td>49/2689 (1.8%)</td>
<td>0.31 (0.17-0.55)</td>
<td>0.0001</td>
<td>-1.26% (-1.84% to -0.68%)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>14/1718 (0.8%)</td>
<td>20/1711 (1.2%)</td>
<td>0.70 (0.35-1.38)</td>
<td>0.30</td>
<td>-0.35% (-1.02% to 0.31%)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>26/2412 (1.1%)</td>
<td>52/2405 (2.2%)</td>
<td>0.50 (0.31-0.80)</td>
<td>0.004</td>
<td>-1.08% (-1.80% to -0.37%)</td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>58/4118 (1.4%)</td>
<td>86/4122 (1.6%)</td>
<td>0.85 (0.60-1.21)</td>
<td>0.37</td>
<td>-0.24% (-0.76% to 0.28%)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>22/1273 (1.7%)</td>
<td>29/1266 (2.3%)</td>
<td>0.75 (0.44-1.31)</td>
<td>0.31</td>
<td>-0.56% (-1.65% to 0.53%)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>15/1280 (1.2%)</td>
<td>22/1288 (1.7%)</td>
<td>0.69 (0.36-1.32)</td>
<td>0.26</td>
<td>-0.54% (-1.46% to 0.38%)</td>
<td></td>
</tr>
<tr>
<td>Combined (random)</td>
<td>148/13477 (1.1%)</td>
<td>238/13481 (1.8%)</td>
<td>0.61 (0.45-0.83)</td>
<td>0.002</td>
<td>-0.68% (-1.07% to -0.30%)</td>
<td></td>
</tr>
</tbody>
</table>

CHEST Guideline

• For VTE and no cancer, as long-term anticoagulant therapy, suggest
  • Dabigatran (Grade 2B)
  • Rivaroxaban (Grade 2B)
  • Apixaban (Grade 2B)
  • Edoxaban (Grade 2B)

  Over VKA therapy

• VKA therapy over LMWH (Grade 2C)

# Treatment of Cancer-associated Thrombosis

## Table 1. Consensus guidelines on treatment of deep vein thrombosis or pulmonary embolism in patients with cancer

<table>
<thead>
<tr>
<th></th>
<th>ACCP 2012(^2)</th>
<th>NCCN 2011(^3)</th>
<th>ASCO 2013(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial/acute treatment</strong></td>
<td>Not addressed in cancer patients.</td>
<td>LMWH Dalteparin 200 U/kg OD Enoxaparin 1 mg/kg BID Tinzaparin 175 U/kg OD Fondaparinux 5 mg (&lt;50 kg), 7.5 mg (50-100 kg), or 10 mg (&gt;100 kg) OD APTT-adjusted UFH infusion</td>
<td>LMWH is preferred for initial 5-10 d of treatment in patients with a CrCl &gt;30 mL/min.</td>
</tr>
<tr>
<td><strong>Long-term treatment</strong></td>
<td>LMWH preferred to VKA [2B].*</td>
<td>LMWH is preferred for first 6 mo as monotherapy without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer.</td>
<td>LMWH is preferred for long-term therapy.</td>
</tr>
<tr>
<td>In patients not treated with LMWH, VKA therapy is preferred to dabigatran or rivaroxaban [2C].*</td>
<td></td>
<td>Warfarin 2.5-5 mg every day initially with subsequent dosing based on INR value targeted at 2-3.</td>
<td>VKAs (target INR, 2-3) are acceptable for long-term therapy if LMWH is not available.</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>Extended anticoagulant therapy is preferred to 3 mo of treatment [2B].*</td>
<td>Minimum 3 mo. Indefinite anticoagulant if active cancer or persistent risk factors.</td>
<td>At least 6 mo duration. Extended anticoagulation with LMWH or VKA may be considered beyond 6 mo for patients with metastatic disease or patients who are receiving chemotherapy.</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; BID, twice-daily dosing; NCCN, National Comprehensive Cancer Network; OD, once-daily dosing.

## Choice of Anticoagulant

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug of choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive DVT or massive PE</td>
<td>Heparin</td>
</tr>
<tr>
<td>High initial risk of bleeding</td>
<td></td>
</tr>
<tr>
<td>Active cancer</td>
<td>LMWH</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance &lt; 30 mL/min</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Liver dysfunction with increased PT/INR at baseline</td>
<td>Warfarin, LMWH</td>
</tr>
<tr>
<td>Limited access to anticoagulation clinic</td>
<td>DOACs</td>
</tr>
<tr>
<td>All-oral therapy</td>
<td>Rivaroxaban or apixaban</td>
</tr>
<tr>
<td>Poor compliance with long-term twice-daily dosing</td>
<td>Rivaroxaban or edoxaban</td>
</tr>
</tbody>
</table>

Thrombosis

Yes

Proximal DVT or PE
- Warfarin (INR 2.0-3.0)
  - No transient risk factor: long term anticoagulation
  - Transient/reversible risk factor: 3-6 months

Arterial thrombosis
- Cerebral
- Non-cerebral
  - Cardiac
  - Non-cardiac
    - Aspirin + Clopidogrel +/- stent
    - Warfarin (INR 2.0-3.0)
      - Warfarin (INR 2.0-3.0) or Clopidogrel or Aspirin +/- Dipyridamole
  - UFH or LMWH plus Aspirin

No

Pregnant
- Therapeutic LMWH +/- monitor Anti-FXa
- Change to Warfarin (INR 2.0-3.0) post-partum
- Prior pregnancy morbidity satisfying APS classification criteria

No treatment

Recurrent episode while receiving Warfarin
- Warfarin (INR 3.0-4.0) or Warfarin (INR 2.0-3.0) + low dose Aspirin or if unstable INR LMWH

## Duration of Treatment of VTE

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked DVT/PE</td>
<td></td>
</tr>
<tr>
<td>- Surgery</td>
<td>3 months</td>
</tr>
<tr>
<td>- Non-surgical transient risk factors</td>
<td></td>
</tr>
<tr>
<td>Unprovoked DVT/PE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At least 3 months then evaluate the risk and benefit of extended therapy</td>
</tr>
<tr>
<td></td>
<td>- Low to moderate bleeding risk: extended therapy</td>
</tr>
<tr>
<td></td>
<td>- High bleeding risk: 3 months</td>
</tr>
<tr>
<td>Second unprovoked DVT/PE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Low to moderate bleeding risk: extended therapy</td>
</tr>
<tr>
<td></td>
<td>- High bleeding risk: 3 months</td>
</tr>
</tbody>
</table>

Duration of Treatment of VTE

- **VTE due to major transient risk factor**
  - 3 months
  - Woman with VTE on hormones
  - Non-major transient risk factor
  - Woman with unprovoked VTE
    - DVT
    - PE
  - Man with unprovoked VTE
    - DVT
    - PE

- **Thrombophilia**
  - ACCP, AHA, ISTH, BJH, ACF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inherited conditions†</strong></td>
<td></td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>25</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>5</td>
</tr>
<tr>
<td>Homozygous</td>
<td>50</td>
</tr>
<tr>
<td>G20210A prothrombin-gene mutation (heterozygous)</td>
<td>2.5</td>
</tr>
<tr>
<td>Dysfibrinogenemia</td>
<td>18</td>
</tr>
<tr>
<td><strong>Acquired conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Major surgery or major trauma</td>
<td>5–200‡</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>50</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>Elevated anticardiolipin antibody level</td>
<td>2</td>
</tr>
<tr>
<td>Nonspecific inhibitor (e.g., lupus anticoagulant)</td>
<td>10</td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
</tr>
<tr>
<td>Major medical illness with hospitalization</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>5</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>10</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>7</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>5</td>
</tr>
<tr>
<td>Hormone-replacement therapy</td>
<td>2</td>
</tr>
<tr>
<td>Selective estrogen-receptor modulators</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>5</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>3</td>
</tr>
<tr>
<td>Obesity</td>
<td>1–3</td>
</tr>
</tbody>
</table>

Management of DOACs-associated Bleeding

Risk stratification

Minor bleeding
- Local hemostatic measures
- Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)

Moderate bleeding
- General measures
  - Anticoagulant withdrawal
  - Mechanical compression
  - Monitor hemodynamic status
  - Volume replacement
  - Definitive interventions
- Blood product transfusion
  - RBC transfusion for anemia
  - Plasma for coagulopathy (e.g., DIC, dilutional)
  - Consider platelets for patients on antiplatelet agents

Severe/life-threatening bleeding
- General measures and blood product transfusion as per moderate bleeding
  - Intensive care setting
  - Hemodynamic support
  - Consider: 4-factor PCC (50 U/kg)*
    - Activated PCC (80 U/kg)**
- Adjunctive therapies
  - Oral charcoal for dabigatran ingestion within 2 hours
  - Hemodialysis for dabigatran removal
  - Desmopressin
  - Antifibrinolytic agents

# Antidote of DOACs

<table>
<thead>
<tr>
<th></th>
<th>Idarucizumab(^1)</th>
<th>Andexanet alfa(^2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidote</td>
<td>Direct thrombin inhibitor (dabigatran)</td>
<td>Direct factor Xa inhibitor (rivaroxaban, apixaban)</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Monoclonal antibody of dabigatran</td>
<td>Recombinant modified human factor Xa decoy protein</td>
</tr>
<tr>
<td>Dose</td>
<td>5 gm IV</td>
<td>Less than 7 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800 mg IV followed by 8 mg/min for 120 min (total 960 mg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than 7 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg IV followed by 4 mg/min for 120 min (total 480 mg)</td>
</tr>
</tbody>
</table>

Thank You for Your Attention