2018
28-30 JUNE
VIENNA

MASCC/ISOO
ANNUAL MEETING
SUPPORTIVE CARE IN CANCER

# Common Bleeding Disorders in Cancer Patients

(June 29, 2018)

**Thein Hlaing Oo, MD, FRCPE, FACP**
**Professor of Medicine / Consultant Hematologist**
**The University of Texas M. D. Anderson Cancer Center, Houston, USA**

# Faculty Disclosure

| | |
|---|---|
| | No, nothing to disclose |
| X | Yes, please specify: |

| *Company Name* | *Honoraria/ Expenses* | *Consulting/ Advisory Board* | *Funded Research* | *Royalties/ Patent* | *Stock Options* | *Ownership/ Equity Position* | *Employee* | *Other (please specify)* |
|---|---|---|---|---|---|---|---|---|
| Diichi-Sankyo | | | x | | | | | |
| Janssen Pharmaceuticals | | | x | | | | | |
| Medical Education Speakers Network | x | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

- The Scope of the problem of cancer and bleeding
- Common Causes of Bleeding in Cancer
- Management of Bleeding in Cancer Patients

# Cancer and Bleeding: The Scope of the Problem

# Cancer Associated Bleeding

- **Gastrointestinal Bleeding**
  > 300,000 hospitalizations (1 - 2% of all US hospitalizations)
  Upper : 50-100/100,000 persons per year
  Lower : 30 – 36/100,000 persons per year
  **10%** cancer (cancer per se or therapy-related)

- **Hemoptysis**
  100/100,000 persons per year
  Cancer discovered in 8% in men and 4.3% in women

- **Hematuria**
  Cancer discovered in 8% in men and 3.7% in women

- **Postmenopausal Bleeding**
  5% of all gynecological consultations
  7 -10% found to have cancer

El-Tawil et al. World J Gastroenterol 2012;18:1154; Ghassemi et al. Curr Gastroenterol Rep 2013;15:333; Chung P et al. Acute Gastrointestinal Bleeding – Diagnosis & Treatment; p3-7; Jones et al. BMJ 2009;339; Yafi et al. Can Urology Assoc J 2011;5:97; Grossfeld. Urology 2001;57:604; Johnson. J Urol 2008;72:498

# Anticoagulant – associated Bleeding

- **Atrial Fibrillation**
  Prevalence: 2.7 – 6.1 millions

- **Coronary Heart Disease**
  Prevalance: 15 millions ( ≥ 20 years old)

- **Venous Thromboembolism**
  Annual incidence: 104 – 183 /100,000 person-years
  20% of all VTE due to cancer

- **CKD stage 3 (eGFR 30 – 59)**
  Prevalence 6% of general population

- **Bleeding rates (6-12 months):**
  **Major: 2.4 – 10.2%**
  **Clinically Relevant Nonmajor Bleeding: 15 – 20%**

www.cdc.gov, accseeed 6/24/2018; Westendorf: Blood 2014;124:955-962; Eikelboom. Am J Med 2016;129:533; Lee AY: N Engl J Med 2003;349:146; Lee AY. JAMA 2015;314:677; Raskob GE. N Engl J Med 2018;378:615; Young AM. J Clin Oncol 2018 [Epub]; Writing Group Members. Circulation 2016;133:447; Heit JA. Nat Rev Cardiol 2015;12:464-474 ; Ross JA. Thromb Res 2017:150:86; Francis CW, J Thromb Haemost 2015;13:1028

# Major Bleeding vs Clinically Relevant Nonmajor Bleeding

**Major Bleeding**

- Fatal bleeding
- Bleeding in a critical area or organ; intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular with compartment syndrome
- Fall in Hb ≥ 2g/dL or leading to transfusion of ≥ 2 units whole blood or packed RBCs

**Clinically Relevant Nonmajor Bleeding**

- Any signs or symptoms of hemorrhage that does not fit the criteria for major bleeding
- a face-to-face evaluation
- and/or hospitalization or increased level of care
- And/or requires medical intervention

Schulman et al. J Thromb Haemost 2005;3:692-694
Kaatz et al. J Thromb Haemost 2015;13:2119-26

# Major Bleeding & CRNMB rates in Cancer VTE Trials

| Trials | Major Bleeding (%) | | CRNMB (%) | |
|---|---|---|---|---|
| **CLOT**<br>NEJM 2003<br>6 months | Dalteparin | VKA | Dalteparin | VKA |
| | 4 | 6 | 10 | 13 |
| **CATCH**<br>JAMA 2015<br>6 months | Tinzaparin | VKA | Tinzaparin | VKA |
| | 2.7 | 2.4 | 10.9 | 15.3 |
| **DALTECAN**<br>J Thromb Haemost 2015<br>(12 months) | Dalteparin<br>10.2 | | | |
| **Houkusai Cancer VTE**<br>NEJM 2018<br>(12 months) | Dalteparin | Edoxaban | Dalteparin | Edoxaban |
| | 4 | 6.9 | 11.1 | 14.6 |
| **SELECT-D**<br>J Clin Oncol 2018<br>(6 months) | Dalteparin | Rivaroxaban | Dalteparin | Rivaroxaban |
| | 4 | 6 | 4 | 13 |

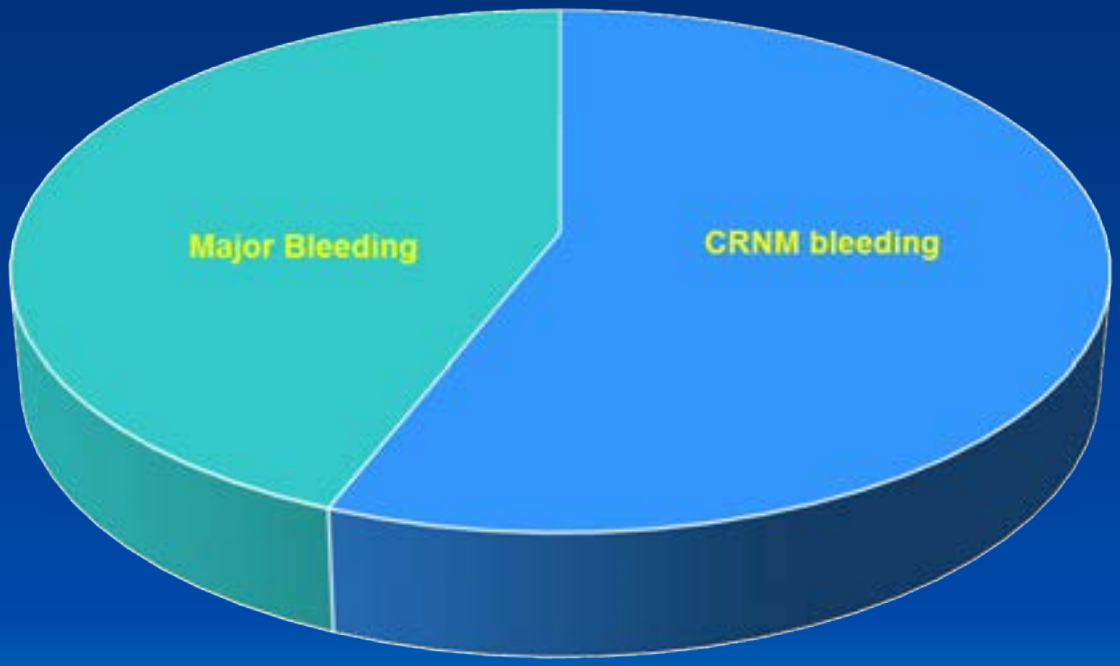
# Common Causes of Bleeding in Cancer Patients

University of Texas M.D. Anderson Cancer Center Experience

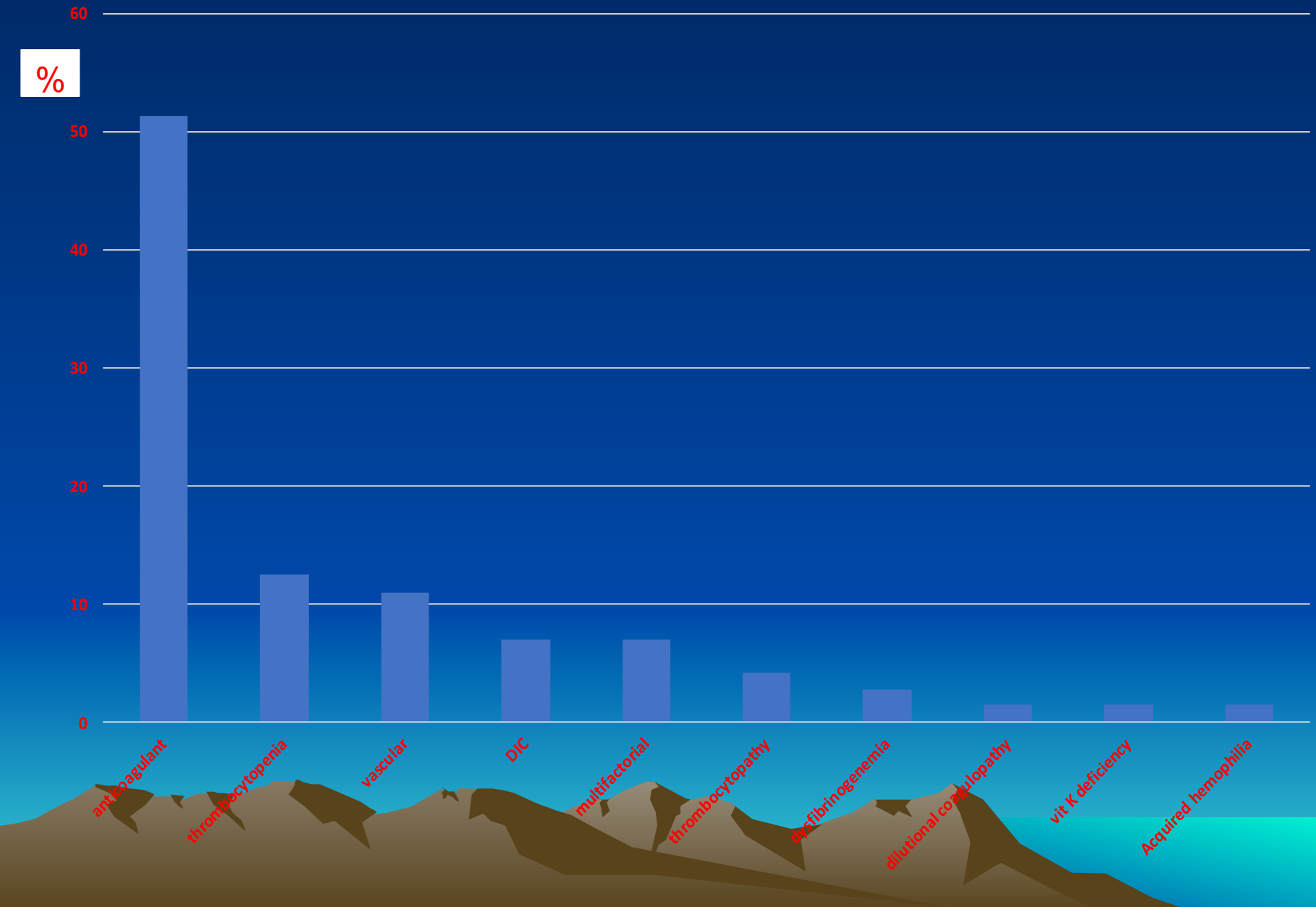
# Vascular Bleeding (Tumor erosion & others)

- Hematochezia, Melena Hemetemesis — Gastroenterology
- Epistaxis — ENT
- Hemoptysis — Pulmonary
- Intracranial hemorrhage — Neurosurgery
- Hematuria/GU bleeding — Urology Gynecology

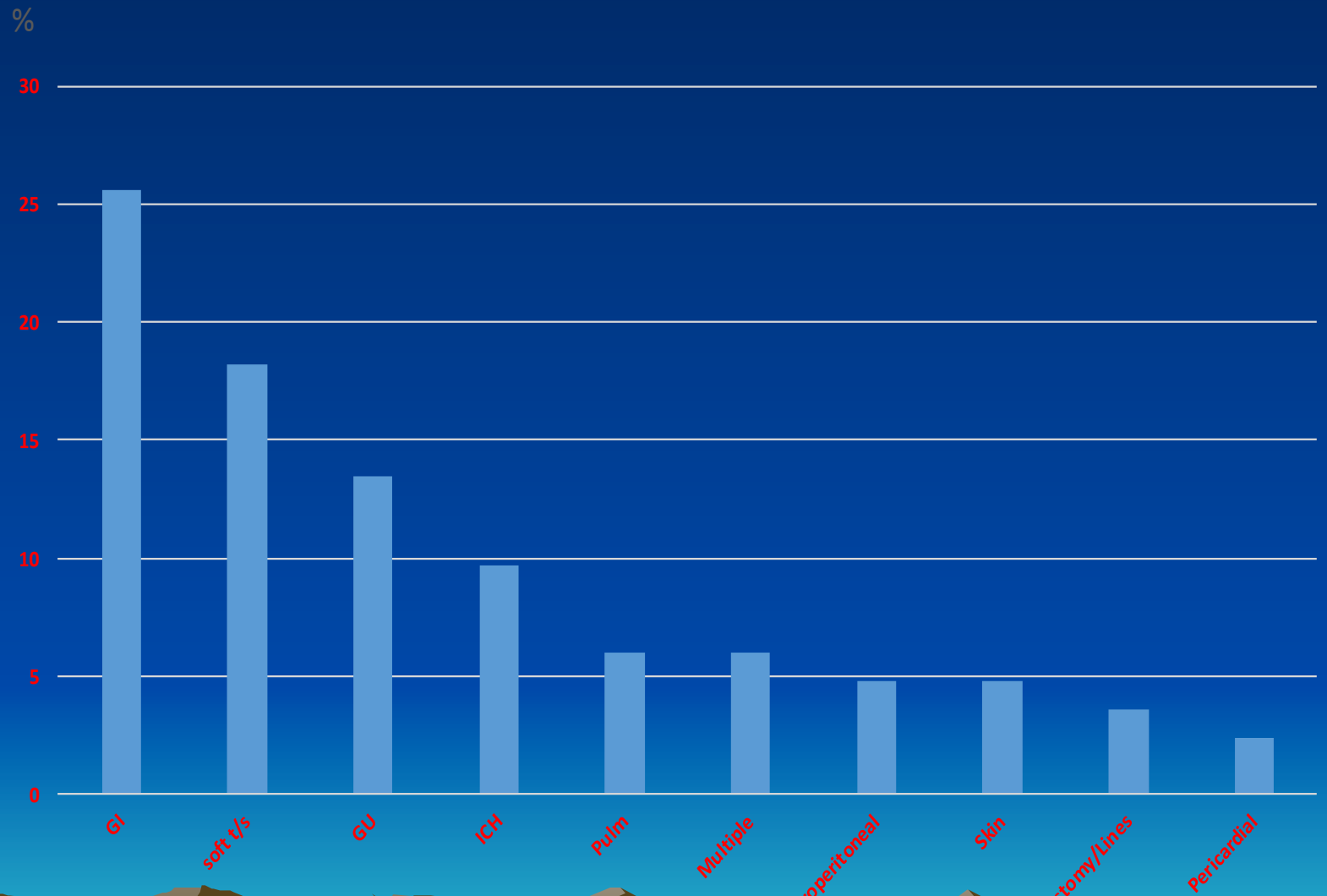
# Bleeding Consults at M.D. Anderson Cancer Center



# Bleeding Consults to Hematology



# Location of Bleeding



# Management of Bleeding in Cancer Patients

# Management

- **Assessment & treatment sometimes occur simultaneously**
- **Arrest bleeding**
- **Venous Access**
- **Stop all anticoagulants and antiplatelet drugs**
- **Volume replacement**
- **Stat Labs** : CBC, review smear, PT, PTT, fibrinogen, D-dimers, chemistry, type & crossmatch, urgent coag studies (if needed)
- Interventions

# Vascular Bleeding (Tumor erosion & others)

| | |
|---|---|
| • Hematochezia, Melena Hemetemesis | Gastroenterology |
| • Epistaxis | ENT |
| • Hemoptysis | Pulmonary |
| • Intracranial hemorrhage | Neurosurgery |
| • Hematuria/GU bleeding | Urology Gynecology |

**General Measures**

- Nonadherent dressings
- Hemostatic dressings
- Hemostastic agents
- Radiotherapy
- Surgery
- Endoscopy
- Interventional radiology
- Adjunctive therapy

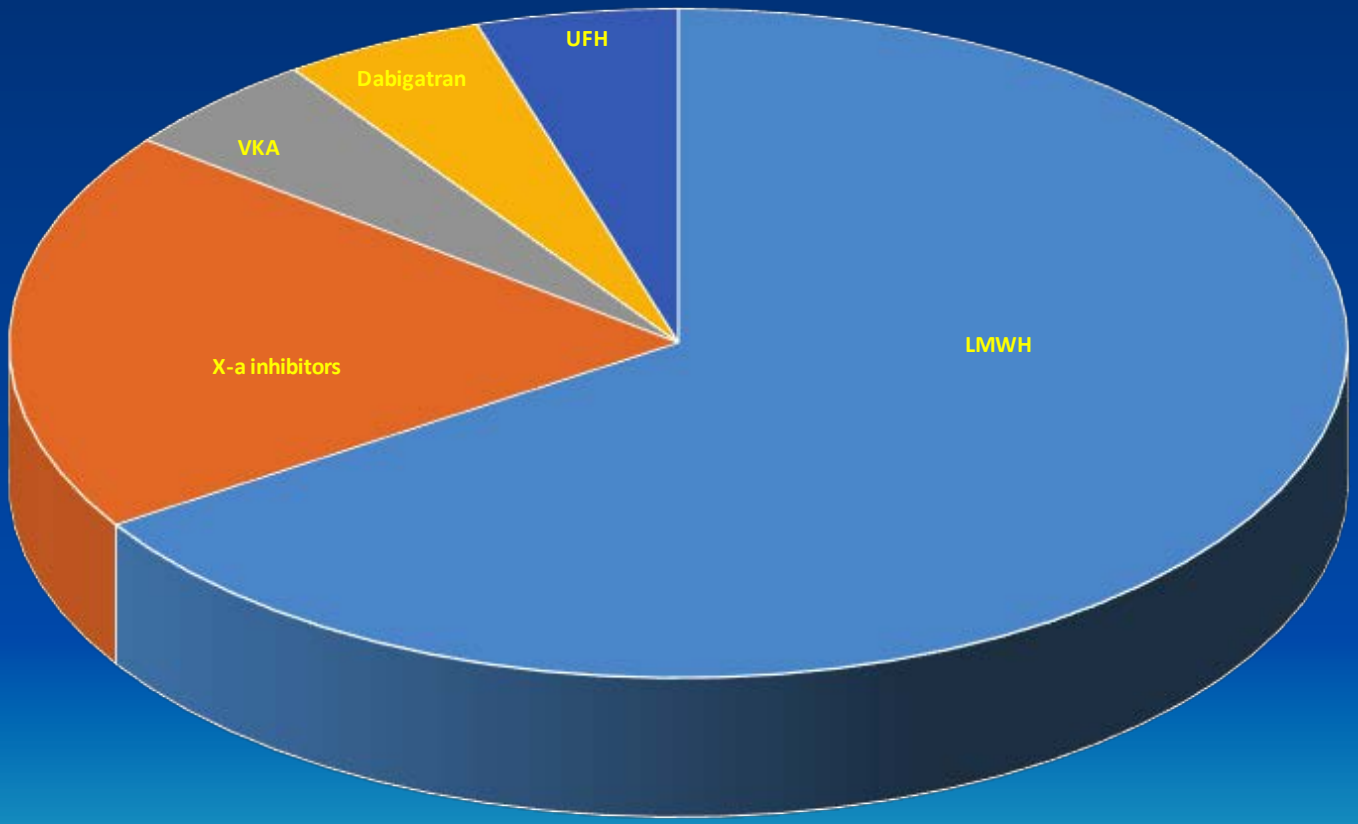
Adapted from Pereira J et al. The Oncologist, 2004:9:561-570

# Medical Bleeding

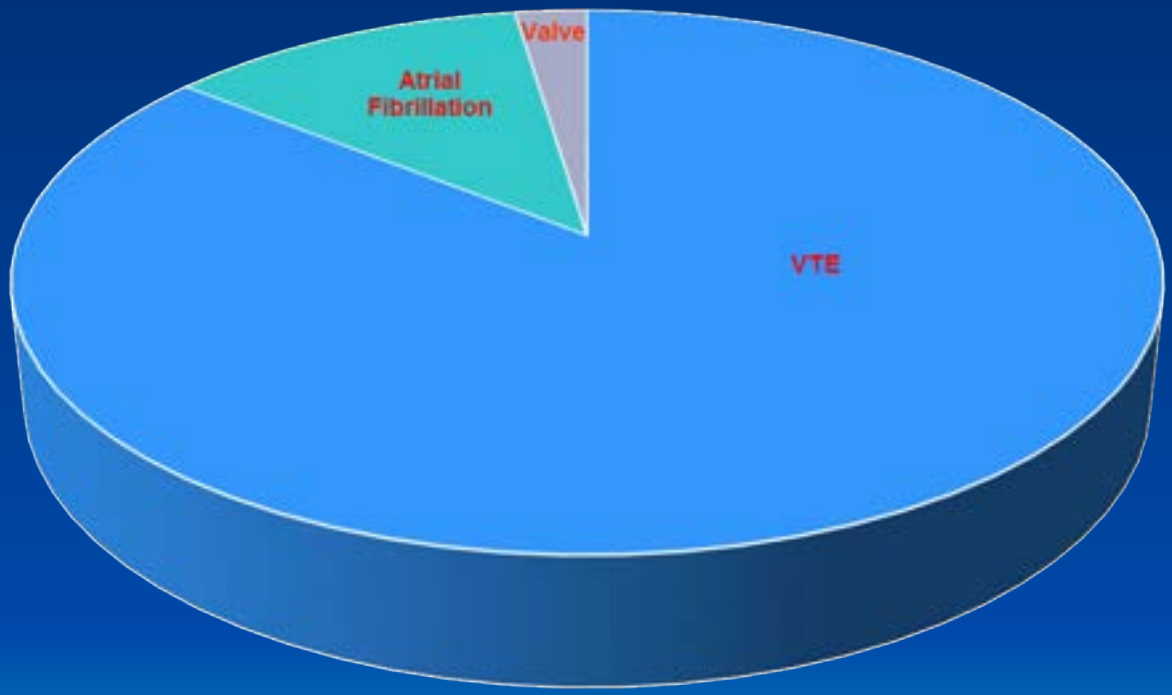
- Platelet Defect
  - Quantitative (Thrombocytopenia)
  - ~~Qualitative (NSAIDs, M-protein)~~
- Coagulation Factor Defect
  - Deficiency
  - Inhibitors (esp. anticoagulants)
- Fibrinolysis Defect
  - Hyperfibrinolysis

# I. Anticoagulant-associated Bleeding

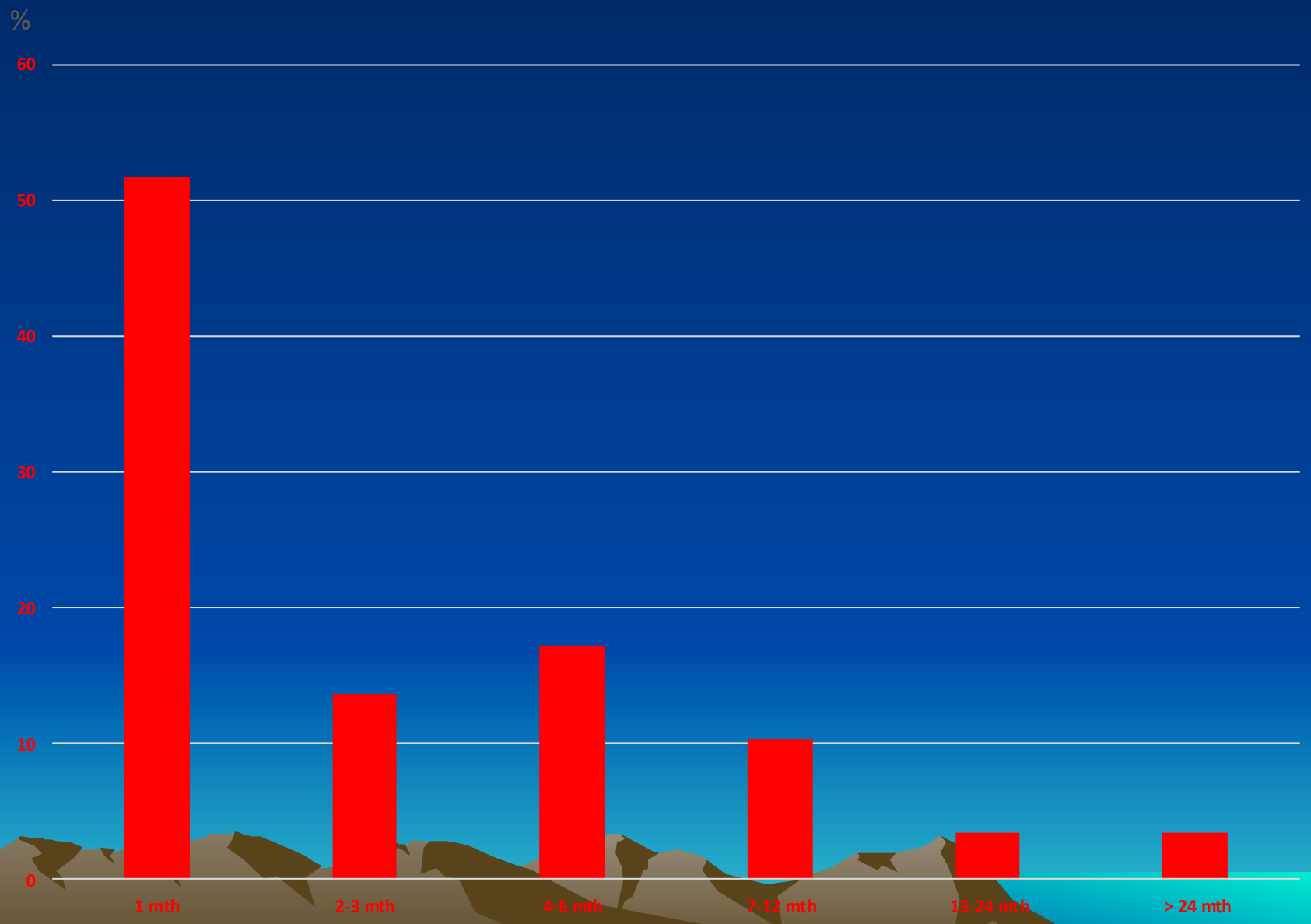
# MD Anderson Experience: Anticoagulant – Associated Bleeding



# Anticoagulation Indications



# Onset of Bleeding Complications in VTE patients



# Management of Anticoagulant-Associated Bleeding

- General & local measures and stop anticoagulants

## Unfractionated Heparin (UFH)

- UFH ½ life = 60- 90 minutes
- 1mg of protamine neutralizes 100 IU of UFH

| Time elapsed since heparin dose | Dose of protamine (mg) to neutralize 100 IU of UFH |
|---|---|
| Immediate | 1.0 – 1.5 mg/100 IU of UFH |
| 30 – 60 min | 0.5 – 0.75 mg/100 IU of UFH |
| > 2 hrs | 0.25 – 0.375 mg/100 IU of UFH |

- Not ≥ 50 mg of protamine
- Monitor APTT
- Second dose may be necessary

https://reference.medscape.com/drug/protamine-343746, accessed June 3, 2018

# Management of Anticoagulant-Associated Bleeding

## Low-molecular weight heparins (LMWH)

- LMWH ½ life = 4-7 hours
- Protamine neutralizes 60 % of anti-Xa activity

| LMWH | Time elapsed since LMWH dose | Protamine dose (mg) |
|---|---|---|
| Enoxaparin | < 8 hrs | 1mg/ 1mg enoxaparin |
| | 8 – 12 hrs | 0.5 mg/1 mg enoxaparin |
| Dalteparin<br>Tinzaparin | < 8 hrs | 1mg/ 100 anti-Xa units |
| | 8 -12 hrs | 0.5 mg/100 anti-Xa units |

- Not ≥ 50 mg of protamine per dose
- Second dose may be necessary

https://reference.medscape.com/drug/protamine-343746, accessed June 3, 2018; clincalc.com/Protamine/, accessed June 3, 2018

# Management of Anticoagulant-Associated Bleeding

## Vitamin K Antagonists (VKA)

- Warfarin ½ life:  20-60 hours

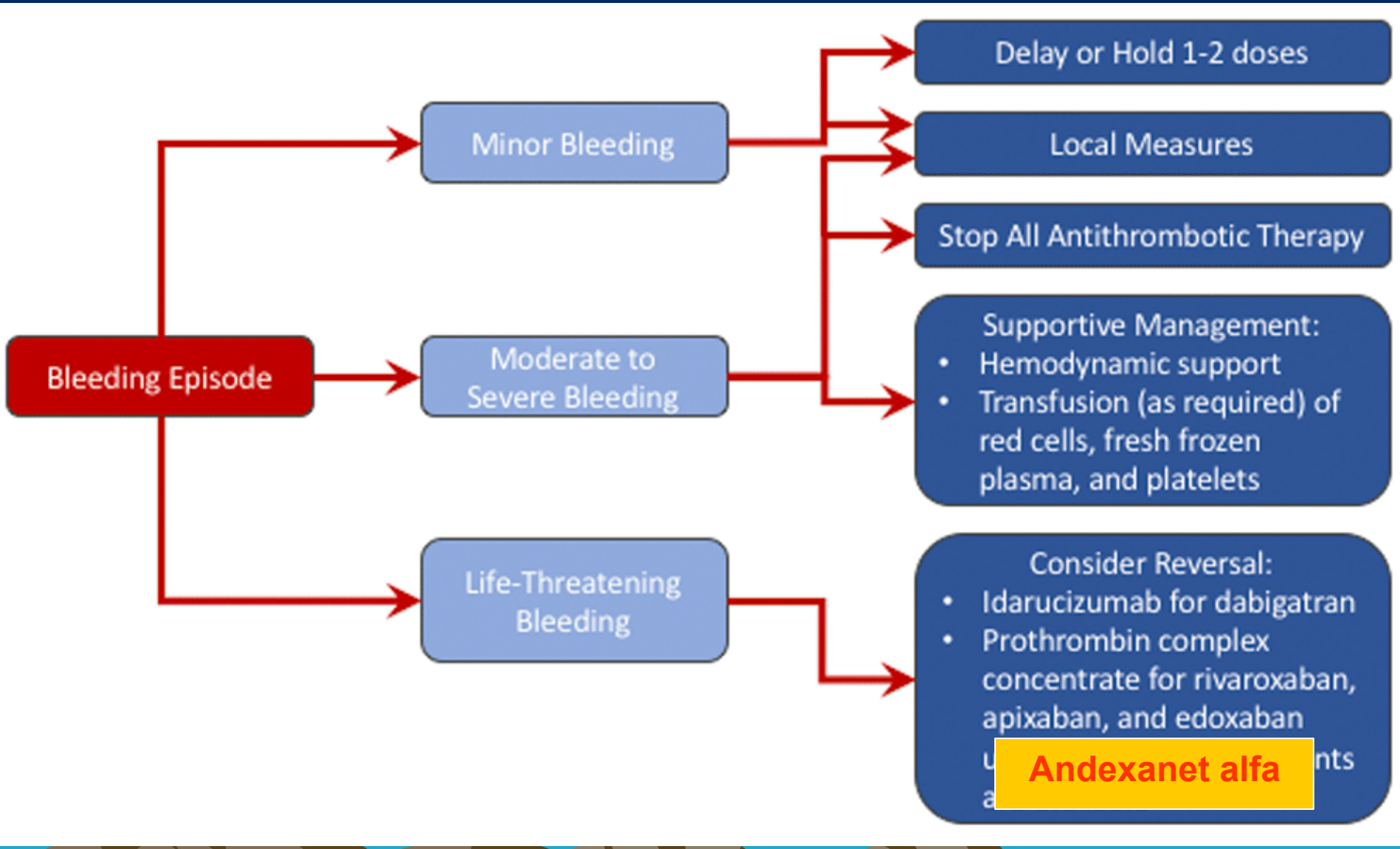
- IV Vitamin K 5-10 mg

- 4F- Prothrombin Complex Concentrate (PCC)
  - INR 2 - 4: 25 IU/kg
  - INR 4 - 6: 35 IU/kg
  - INR > 6  : 50 U/kg

- If 4F-PCC not available, fresh frozen plasma 10-15 ml/kg

Adapted from Tomaselli et al. J Am Coll Cardiol 2017;70:3042-3067

# Figure 1. Management of direct oral anticoagulant-associated bleeding.




Weitz JI, Jaffer IH and Fredenburgh JC. Recent advances in the treatment of venous thromboembolism in the era of the direct oral anticoagulants [version 1]. F1000Research 2017, 6:985 (doi: 10.12688/f1000research.11174.1)

# II. Thrombocytopenia

# Mechanisms of Thrombocytopenia

- **Decreased bone marrow production of platelets**
  marrow failure : aplastic anemia, myelodysplasia
  marrow infiltration : leukemias, myeloma, myelofibrosis
  myelosuppression : cytotoxic drugs and radiotherapy

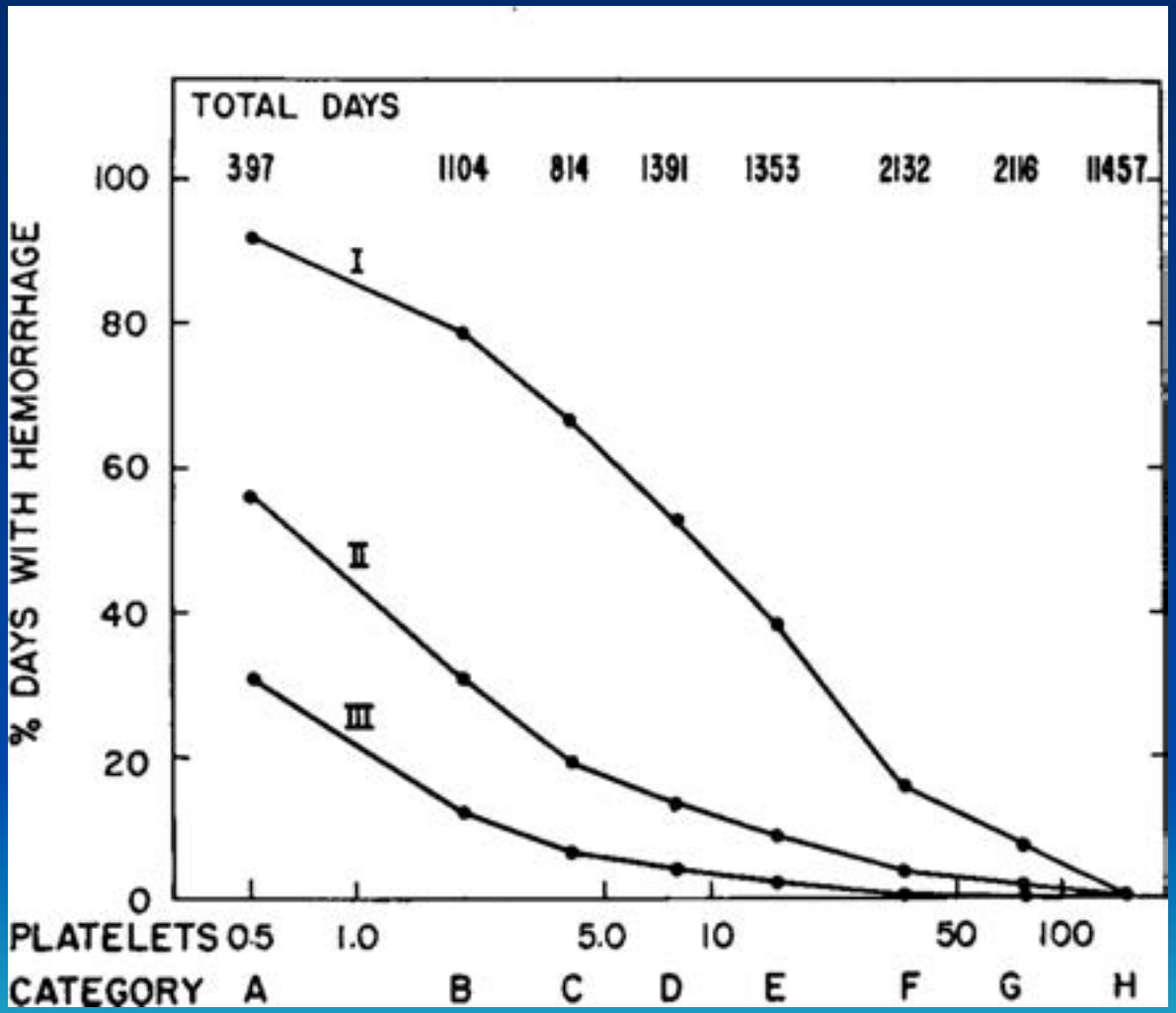
- **Increased peripheral destruction of platelets**
  immune thrombocytopenic purpura ( ITP )

- **Consumption thrombocytopenia**
  heparin-induced thrombocytopenia, DIC, TTP/HUS, HELLP

- **Platelet sequestration**
  hypersplenism

# *Relation between Hemorrhage and Platelet Count (92 patients with acute leukemia)*

| Category | PLT count/cmm |
|---|---|
| A | < 1,000 |
| B | 1,000 – 3,000 |
| C | 3,000 – 5,000 |
| D | 5,000 – 10,000 |
| E | 10,000 – 20,000 |
| F | 20,000 – 50,000 |
| G | 50,000 – 100,000 |
| H | > 100,000 |
| Curve I | All hemorrhage |
| Curve 2 | Skin hemorrhage & epistaxis excluded |
| Curve 3 | Grossly visible hemorrhage |




Gaydos LA et al. N Engl J Med 1962;266:905-909.

# Platelet Transfusion Guidelines (ASCO)

| Conditions | Platelet K/cmm | Comment |
|---|---|---|
| Hematologic malignancies | < 10 | Transfuse at higher count – bleeding, fevers, hyperleukocytosis, clotting abnormalities, invasive procedures |
| Stem cell transplantation | < 10 | Transfuse at higher levels based on judgement |
| Chronic, stable, severe thrombocytopenia (not on therapy, e.g. MDS, Aplastic anemia) | | Consider observation; reserve transfusion for episodes of bleeding or during therapy |
| Solid tumors | < 10 | Transfuse at higher levels if bleeding |
| Invasive procedures | | 40-50K for major procedures<br>≥ 20K for bone marrow biopsy, central line, etc |

Schiffer CA et al. J Clin Oncol 2017;36:283-301

# III. Disseminated Intravascular Coagulation

# Disseminated Intravascular Coagulation

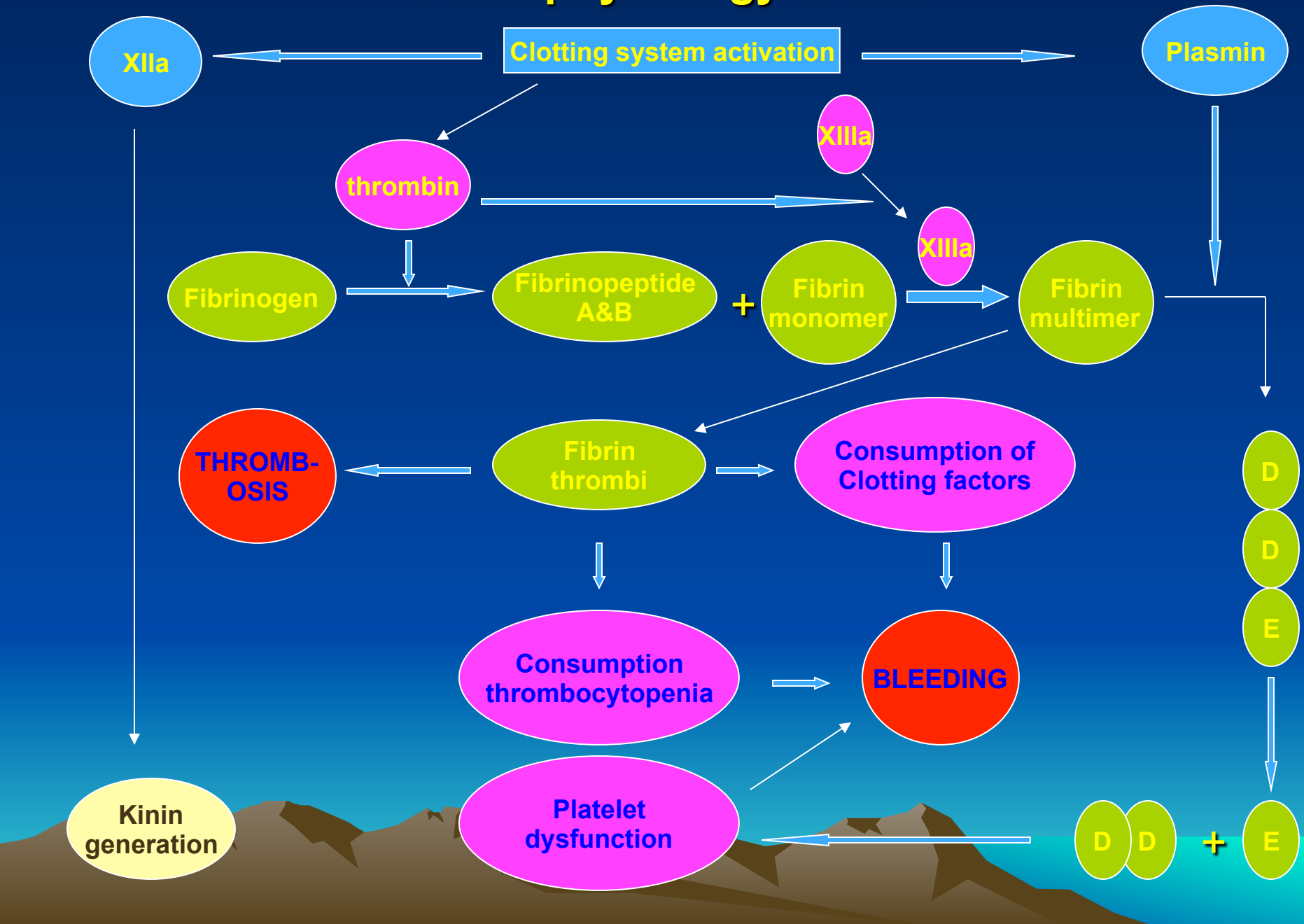
- **Pathophsiolgy**

  (1) extensive endothelial injury
  (2) release of thromboplastin-like substances and activation of coagulation cascade
  (3) activation of fibrinolysis

- **Causes**:

  *tissue damage* ( eg. trauma )
  *complications of pregnancy* ( release of tissue factor)
  *neoplasia* ( tissue factor, protease, TNF, etc )
  *infection*
  *vascular disorders*
  *immunological (*complement activation, tissue factor)

# Pathophysiology of DIC



# Cancer-associated DIC

| | Procoagulant | Hyperfibrinolytic | Subclinical |
|---|---|---|---|
| Predominant type of cancer | Pancreatic cancer, adenocarcinoma | Acute promyelocytic leukemia (APL), metastatic prostate Ca | Many solid cancers |
| Predominant clinical symptom | thrombosis | bleeding | neither |
| Different clinical presentations | Features of arterial ischemia<br>DVT, PE<br>Marantic endocarditis | Bruising, mucosal and internal bleeding, trauma sites bleeding.<br>Hemorrhage – most common cause of induction mortality in APL | Only laboratory abnormalities ( ↓ PLT, ↓ fibrinogen, ↑ PT/APTT, microangiopathic hemolytic anemia)<br>May remain long-standing; worsen or improve depending on cancer |
| Treatment | Treat underlying cancer<br>Anticoagulation with heparin | Treat underlying cancer<br>Supportive care with blood products | Treat underlying cancer<br>? Anticoagulation with heparin |

Adapted from Thachil et al. J Thromb Haemost 2015;13:671-675

# Management of Acute (Hyperfibrinolytic) DIC

- Supportive therapy as required ( e.g. volume replacement )

- Replacement therapy
  - platelet transfusion
    < 50 (if bleeding ) or
    < 30 in APL or < 20 in other cancers (at high risk of bleeding)

  - cryoprecipitate/fibrinogen concentrate to replace fibrinogen
  - FFP to replace other factors

- Monitor response with CBC, PTT, PT, fibrinogen

- Specific therapy : eg. *All trans-retinoic acid in APL*

Levi M et al. Br J Haematol 2009;145:24-33; Thachill et al. J Thromb Haemost 2015;13:671-5

# Conclusion

- Bleeding is common in cancer, due to cancer per se or due to antineoplastic therapy or antithrombotic therapy.
- Vascular bleeding due to cancer invasion or therapy-related complications is very common.
- Medical causes of clinically relevant bleeding in cancer include the use of antithrombotics, thrombocytopenia, qualitative defect in platelets, coagulation defects and sometimes multifactorial etiologies.
- Management of bleeding requires quick evaluation, arresting bleeding, replacement/supportive therapy and specific management.

Thank you for your attention !