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Managing antithrombotic medication in thrombocytopenic cancer patients

Moderator
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Conflict of Interest Disclosure Form

In accordance with the rules of the Health Care Inspectorate (IGZ)

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☑☐ I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
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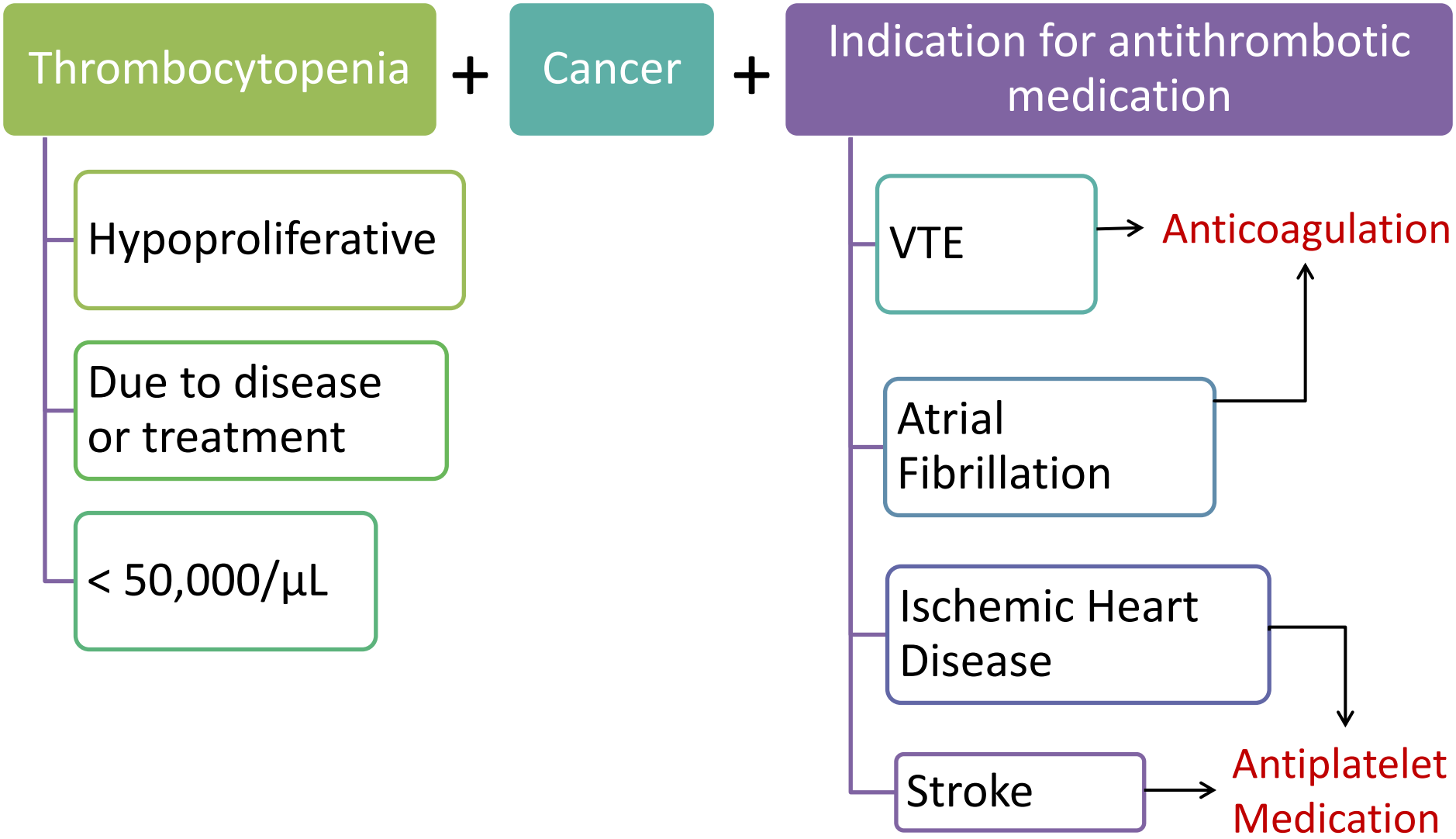
Scientific advisory board	Bayer

Who?


Thrombocytopenia
+
Cancer
+
Indication for antithrombotic medication
Hypoproliferative
Due to disease or treatment
< 50,000/µL
VTE
Anticoagulation
Atrial Fibrillation
Ischemic Heart Disease
Stroke
Antiplatelet Medication

How common is it?

In cancer

- **Antithrombotic medication often indicated**[1,2,3]
- **Thrombocytopenia common**
- **Thrombocytopenia & antithrombotic indication not uncommon**
  - As high as 45% [4]
  - Median 5 patients per month [5]

[1]Fitzpatrick, Thr Res 2017; [2]Falanga, Crit Rev Oncol Hematol 2017;
[3] Navi, JACC 2017; [4]Vinholt, Platelets, 2016; [5]Leader, ICTHIC 2018

Antithrombotics in thrombocytopenia and cancer: Key Questions

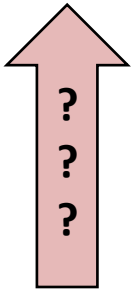
1. Does thrombocytopenia protect against thrombosis?
2. At which platelet count should changes be made?
3. What is the bleeding risk?
4. When is the risk of thrombosis high *vs.* low ?
5. Is it safe to reduce doses or increase the platelet transfusion threshold?
6. Can DOACs be safely used for CAT or AF in thrombocytopenia?
7. How to manage antiplatelet medication in acute coronary syndrome?

Does thrombocytopenia protect against thrombosis?

#1

- **Does not protect** against VTE[1,2,3] or ischemic arterial events[5]

- **Adverse short and long term outcomes**[4,5]



  - Discontinuation of antithrombotic medication[4,6]

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[1]Gerber, Blood 2008; [2]Labrador, Haematologica 2013; [3]Khanal, Am J Hem 2016; [4]Feher, Oncologist 2017; [5]Del Prete, Clin Lymphoma Myeloma Leuk 2018; [6]Sundstrom, Circulation 2017

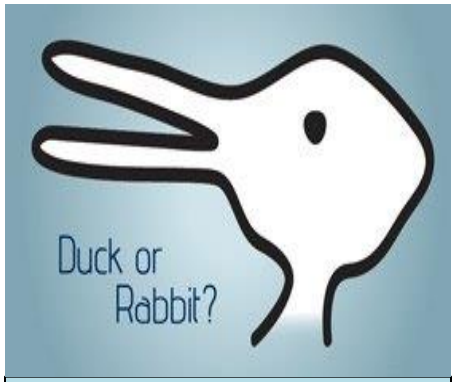
High risk scenario

- **Increased risk of thrombosis in cancer**[1,2]
  - High CAT recurrence (4-17% within 6 months of VTE)
  - Ischemic stroke/MI (4.7% within 6 months of diagnosis[2])

- **Significant bleeding risks**
  - Anticoagulation in cancer[1]
  - Chemotherapy induced thrombocytopenia[3]

[1]Prandoni, Blood 2002; [2]Navi, JACC 2017; [3]Stanworth, NEJM 2013

Quite common



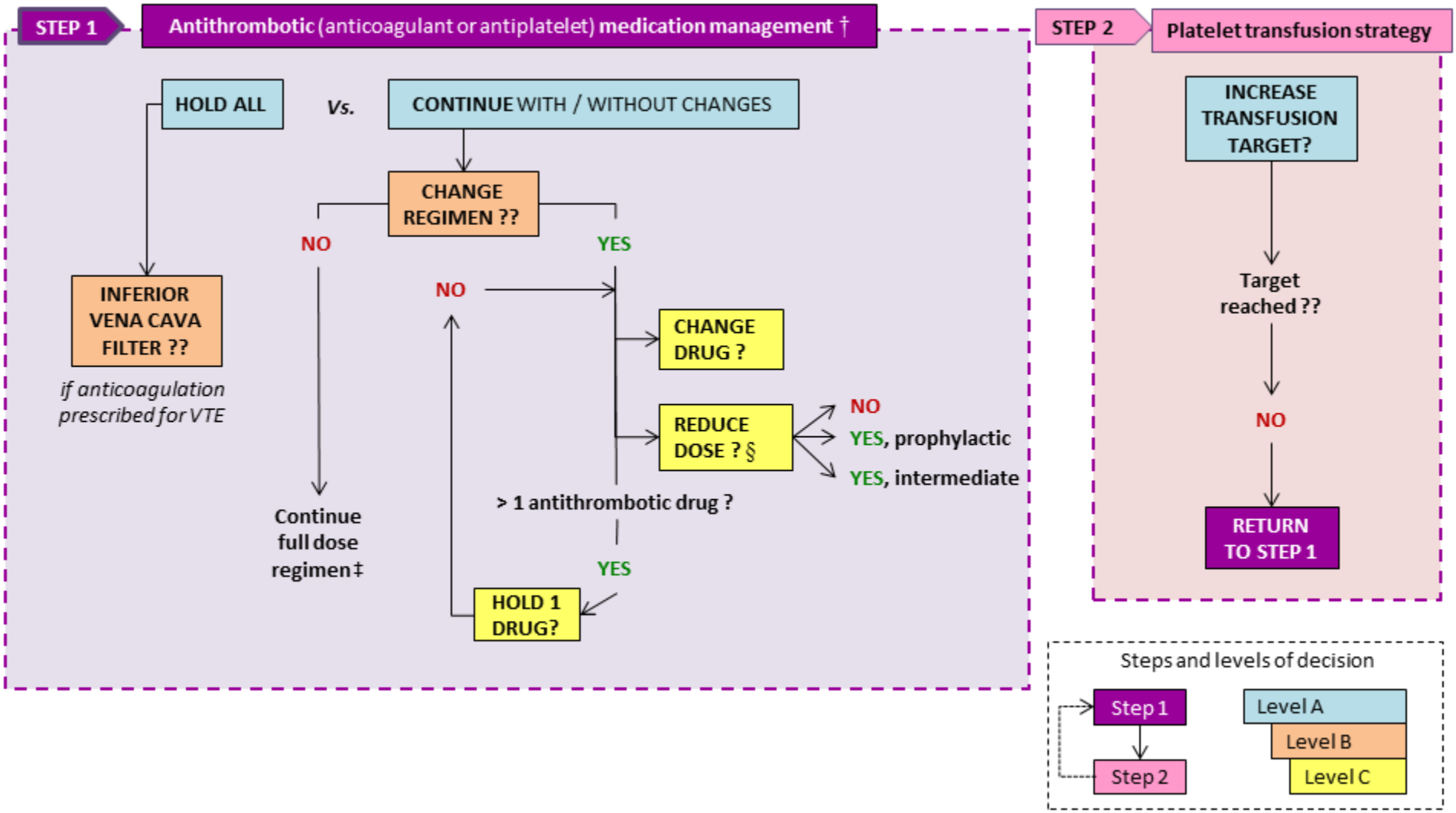
Poor Evidence

Balancing act

Difficult decisions

Evidence → Guidelines

Flow of management choices



Leader, Critical Reviews Oncology / Hematology, 2018

At which platelet count should changes be made?

#2

- Platelets **> 50,000/µL: Full dose** anticoagulation **safe** [1]

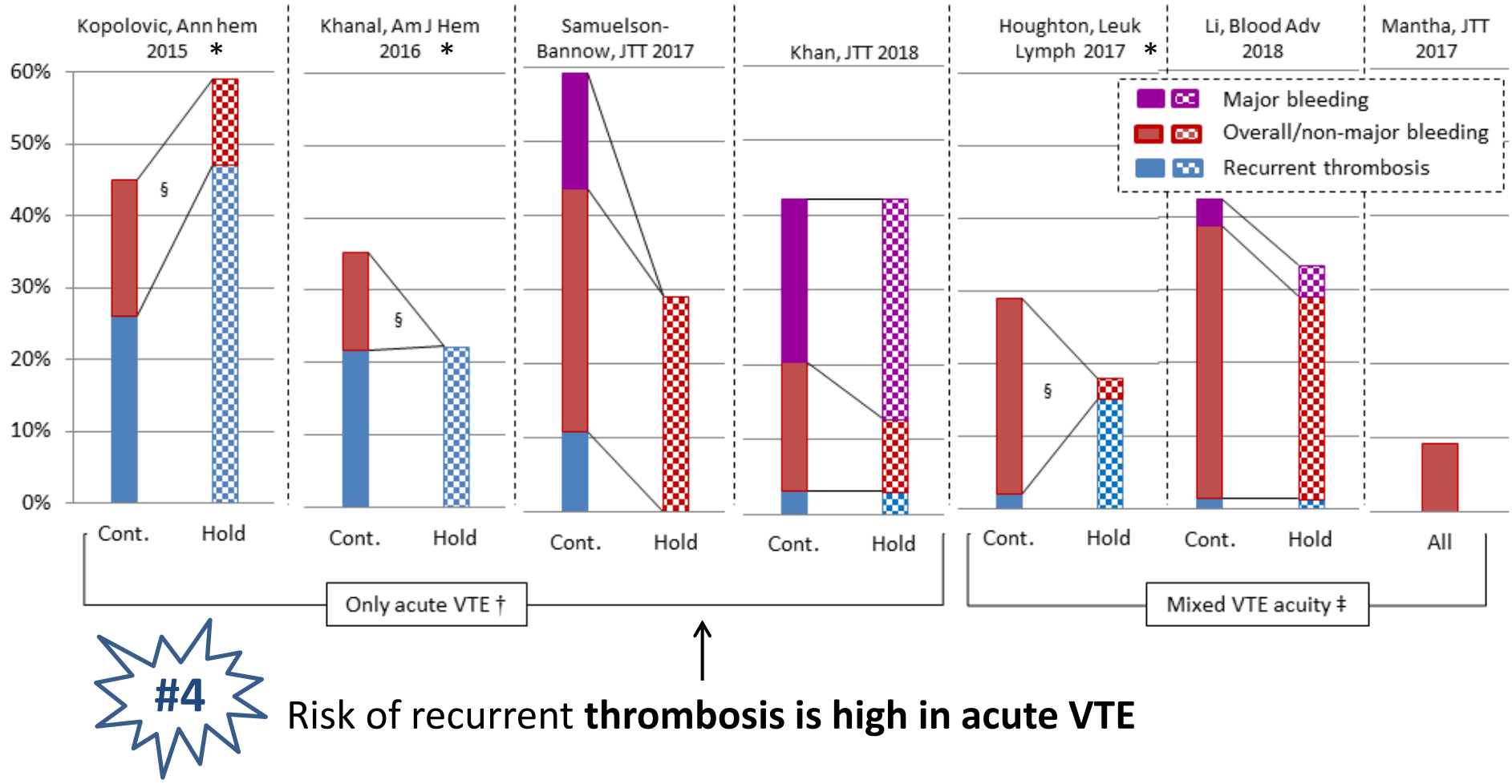
- Platelets **< 50,000/µL**
  - **Anticoagulation**: **Increase** in bleeding[2,3]
  - **Aspirin**: No increase in bleeding[4]
    - >30,000/µL

- **10,000/µL <** platelets **< 50,000/µL:**
  - No consistent evidence that counts affect bleeding[3,5,6]

[1]Khanal, Am J hem 2016; [2]Samuelson-Bannow, J Thromb Thrombolysis 2017; [3]Uhl, Blood 2017; [4]Feher, Oncologist, 2017; [5]Li, Blood Adv 2018; [6]Labrador, Haematologica 2013;

High bleeding risk in CAT and thrombocytopenia

#3



#4

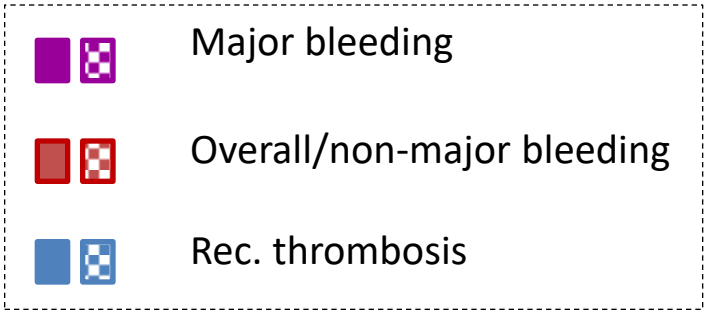
Risk of recurrent **thrombosis is high in acute VTE**

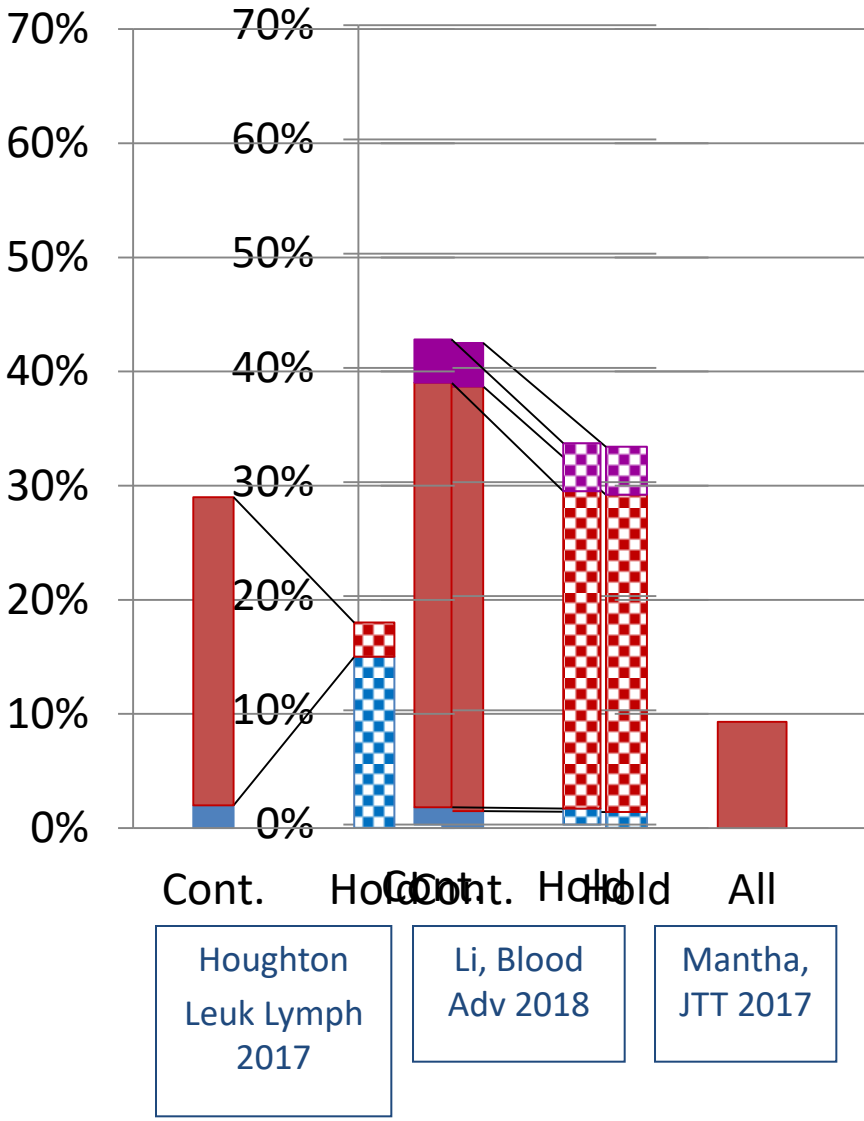
VTE

Leader, Critical Reviews Oncology / Hematology, 2018

When is the risk of recurrent thrombosis lower?

- Sub-acute and remote VTE
- Autologous SCT
  - Mainly remote VTE (>3 mo.)
- Catheter related thrombosis[1]
  - Contradictive data exists[2]





VTE

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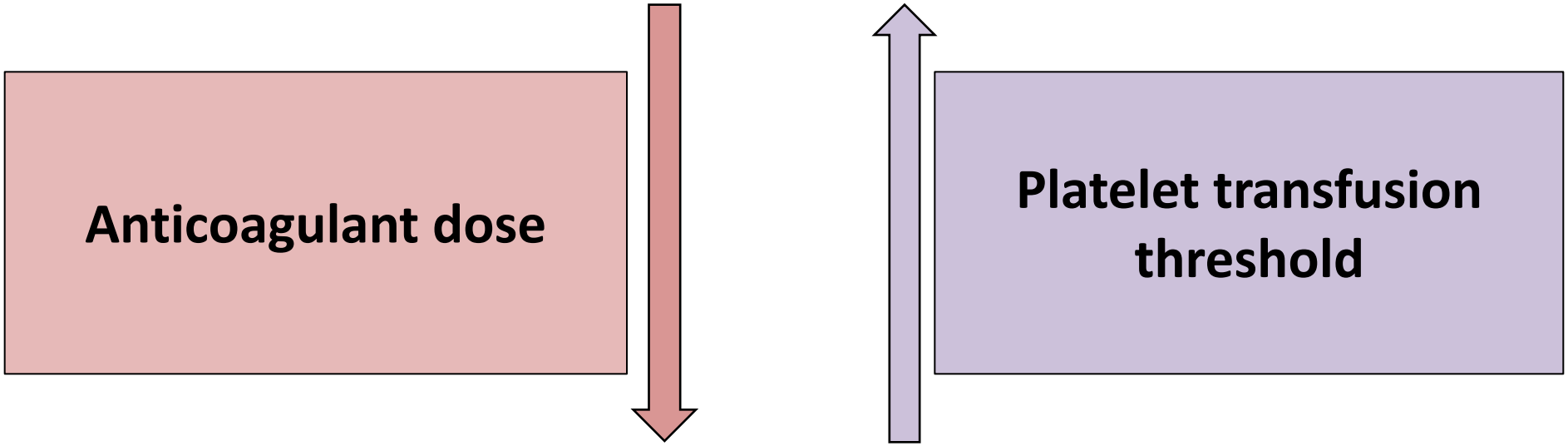
[1]Htun, J Thrombosis Thrombolysis 2018; [2]Kopolovic, Ann Hem 2015

Reducing the high bleeding risk



Is it safe (and effective) **to reduce LMWH doses?**

- **Conflicting** results in 2 small cohorts[1,2,3]
- Bridging with reduced dose LMWH in cancer → safe and feasible[4]
- Prophylactic LMWH doses safe in veno-occlusive disease[5,6]
- **Safety promising** but **efficacy unclear**

VTE

[1]Kopolovic, Ann hem 2015; [2]Khanal, Am J Hem 2016; [3]Samuelson-Bannow, RPTH 2018; [4]Or, Transplantation 1996; [5]Simon, BMT 2001; [6]Saccullo, Am J Hem 2002

Is it safe to increase platelet transfusion threshold?

#5

- **Efficacy not proven**[1]

- The **ideal target is not known**[1]
  - Consider platelet function ??? [2]

- **Not without risk**
  - Transfusion-related adverse events, including thrombosis[3,4]
  - Platelet transfusion refractoriness
    - Discontinuation of anticoagulation[1,4,5]
  - Economic toxicity

VTE

[1]Li, Blood adv 2018; [2]Baaten, Haematologica 2018; [3]Khorana, Arch Int Med 2008; [4]Samuelson-Bannow, J Thromb Thrombolysis 2017; [5]Houghton, Leuk Lymph 2017

CAT and thrombocytopenia, ISTH guidelines (1)

- Platelets **≥ 50,000/µL: Full** therapeutic anticoagulation; **No** platelet transfusion

- **Acute** CAT and platelets < **50,000/µL**
  - and **high risk** of thrombus progression:

    Full anticoagulation (LMWH/UFH); **With** platelet Tx (target **≥ 40-50,000/µL**)

  - and **lower risk** of thrombus progression:
    - IF platelets **25-50,000/µL**: **Reduce** LMWH dose (50%/prophylactic)
    - IF platelets **< 25,000/µL**: **Hold**

Samuelson-Bannow, JTH 2018

CAT and thrombocytopenia, ISTH guidelines (2)

- **Sub-acute or chronic** CAT and platelets < **50,000/µL**
    - Same as acute CAT and lower risk for thrombus progression
- When platelets **> 50,000/µL: Resume full dose** without transfusion support, if no CI
- **IVC filters:** Only **if absolute contra-indication** to anticoagulation
- **DOACs** when platelets < **50,000/µL :** May **not** be appropriate

Samuelson-Bannow, JTH 2018

Thrombocytopenia in clinical trials of DOACs in cancer patients

Study name	Study population and treatment	DOAC type	PLT inclusion criteria (x 10^9/L)	DOAC use in TCP		Median baseline PLT (x 10^9/L)
				PLT threshold (x 10^9/L)	Change	
Hokusai Cancer[1]	• **Treatment** of CAT • DOAC *vs.* Dalteparin	Edoxaban	≥ 50	NS	NS	50-100 in 6.1%
Adam VTE[2]		Apixaban	≥ 50	NS	NS	NS
Select_d[3]		Rivaroxaban	≥ 100	< 50	Hold [a]	NS
Avert[4]	• **Prophylaxis** in cancer outpatients • DOAC *vs.* placebo	Apixaban	≥ 50	NS [b]	NS	NS
Cassini[5]		Rivaroxaban	≥ 50	< 25 for > 1 week	Hold [a]	NS

[a] Resume when platelets above the prespecified threshold

[b] Only 1/105 (1%) had apixaban discontinued due to TCP

CAT, cancer associated thrombosis; DOAC, direct oral anticoagulant; NS, not specified; PLT, platelet count

VTE

[1]Raskob, NEJM 2018; [2]McBane, #421 ASH 2018; [3]Young, JCO 2018; [4]Carrier, NEJM 2018; [5]Khorana, #LBA-1 ASH 2018

Can DOACs be safely used for CAT in thrombocytopenia?

#6

We really don't know, and there is **reason to exercise caution**, because:

1. **Increased clinically rel. and/or major bleeding** with edoxaban and rivaroxaban[1,2]
   - ISTH guidance suggests **LMWH over DOAC** for CAT with **high risk of bleeding**[3]

2. **Increased major bleeding with prophylactic DOAC doses** vs. placebo in cancer[4,5]

3. No cohorts of DOAC use in CAT and thrombocytopenia

[1]Young, JCO 2018; [2]Raskob, NEJM 2018; [3]Khorana, JTH 2018;
[4]Carrier, NEJM 2018; [5]Khorana, #LBA-1 ASH 2018

Anticoagulation management: Atrial fibrillation, evidence

- **Extrapolate**:
  - **High bleeding** risk (VTE in thrombocytopenia & cancer)
  - **Low** absolute risk of **thrombosis???** (non-cancer LMWH bridging) [4]
    - *But*: Cancer is different[4]

- **No cohorts of AC in AF with platelets < 50,000/µL**[1]
  - **DOAC vs. VKA** in AF with **platelets < 100**,000/µL [2]
    - Trend toward better safety with DOAC; equivalent effectiveness
  - **Reduced-dose rivaroxaban** may be safe & effective if platelets 50-100,000/µL [3]
    - Cancer patients excluded

AF

[1]Caro, Am J Hem 2018; [2]Wang, J Thromb Thrombolysis 2018; [3]Janion-Sadowska, J Cardiovasc Pharmacol 2018; [4]Douketis, NEJM 2015; [4]Navi, JACC 2017

APT may have a role in selected ACS patients with thrombocytopenia

#7

- Difficult to recruit in prospective trials (NCT00501345)

- Hematological malignancy, **acute thrombocytopenia (<50**,000/µL) & **ACS**[1]
  - Continue aspirin *vs*. Hold
    - Major **bleeding similar** (21% *vs.* 16%)
    - Recurrent MI similar (8% vs. 6%)
    - **Increased survival** and decreased cardiovascular mortality

- **PCI** in cancer patients with **chronic thrombocytopenia (<100** ,000/µL)[2]
  - No major bleeding (N=98)
  - **Overall survival highest with DAPT** > aspirin only > no APT

ACS

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[1]Feher, Oncologist 2017; [2]Iliescu, Am J Cardiol 2018

APT management: No formal guidelines

- **SCAI consensus statement** for cardio-oncology patients[1]
  - **Aspirin** if platelets **> 10,000/µL**
  - **Aspirin & clopidogrel** if platelets **> 30,000/µL**
    - ACS and/or coronary stenting

- Others suggest more conservative thresholds [2]
  - **Hold all APT** if platelets **< 50,000/µL**
  - **Restrict DAPT** if platelets **50,000/µL - 100,000/µL**
  - **Prefer clopidogrel** over ticagrelor or prasugrel
  - Protein pump inhibitors

ACS

[1]Iliescu, Catheter Cardiovasc Interv 2016; [2]McCarthy, Eur Heart J 2017)

Antiplatelet medication management: current practice

- Aspirin use is variable in ACS and thrombocytopenia[1,2,3]
- DAPT use is not uncommon in STEMI[3]
- Platelet transfusions used to support APT in 34%[3]
- APT management is complex and affected by multiple patient factors[3]:
  - Platelet count
  - APT indication
  - Time since the arterial event
  - Prior gastrointestinal bleeding
- Physician characteristics and practice settings also affect management[3]

ACS

[1]Feher, Oncologist 2017; [2]Sarkiss, Cancer 2007;
[3]Leader, Thrombosis Haemostasis 2018

MATTER study

- **Population:** Hematological malignancy, platelets < 50,000/L & antithrombotic Rx

  1. **Incidence** and predictors of bleeding and thrombosis?

  2. **Optimal management** strategy?

- **Design**: Prospective observational cohort study (FU = 30 days)

  a) Variables: Management and markers of hemostasis at baseline

  b) Primary outcome: Composite of **major bleeding and thrombosis**

- **18 Centers** in the Netherlands, Italy, Israel and USA (**80 enrolled from 11 centers**)
- Interim analysis: **August 2019 (N_target = 300)**

Take home messages (1)

1. **Thrombocytopenia does not reduce the risk** of recurrent thrombosis

2. The **threshold for changes** in anticoagulation = **50,000/µL**
   - Lower thresholds for antiplatelet drugs
   - Platelet counts remain poor predictors of bleeding

3. **High bleeding risk** with thrombocytopenia and anticoagulation in CAT or AF

4. **a) Lower thrombotic risk** in several scenarios**:**
   - Non-acute VTE, especially in autologous HSCT
   - Catheter-related thrombosis
   - Low risk atrial fibrillation

Take home messages (2)

4. **b) High thrombotic risk in acute VTE**

5. **a)** Platelet transfusion **threshold of 50,000/µL carries risks**

   b) Reducing anticoagulation **dose:**

   – **Possibly safe**, but efficacy and optimal dose not known

6. **No data on DOACs** in severe thrombocytopenia → **exercise caution**

   – Even **prophylactic dose DOACs increase bleeding risk** in cancer

7. In **acute MI**, continue/start **aspirin** in thrombocytopenia

   – Little evidence for platelets < 30,000/µL

   – DAPT may be considered in selected patients

Study collaborators

Maastricht University / MUMC+

- *Cardiovascular Research Institute (CARIM); Hematology Institute*
- *Thrombosis Expertise Center*
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