ImmunoScience Academy

*Partnering for Education & Optimizing Treatment in ImmunoScience*

# Patients with venous thrombo - embolism and multiple myeloma

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Bristol Myers Squibb™

# Patient initial presentation, diagnosis & management

67 years

## Patient history

**Hypertension, hyperlipidemia, benign prostatic hypertrophy and sleep apnea**

## Diagnosis of multiple of myeloma

Over the past 8 months, increasing fatigue – worsening pancytopenia –
Bone marrow biopsy: 13% plasma cells, high kappa /lambda light chain ratio > 8

## Management

Lenalidomide 25 mg daily  D1 to D21 (cycles 1 - 24)

Dexamethasone dose of 40 mg on D1, 8, 15 and 22 (cycles 1 - 6) followed by 20 mg on D1, 8, 15 and 22 between cycles 7 and 12

Aspirin daily for venous thromboembolism (VTE) prophylaxis

## Follow up

Within 3 weeks of starting chemotherapy, sudden onset of exertional dyspnea

**Diagnosis of PE**

PE=pulmonary embolism; VTE= venous thromboembolism.

# Multiple myeloma

| | | | |
|---|---|---|---|
| 1 % of all cancers | 10-15% of all haematological cancers<br>3-4 cases/100.000/yr | Mainly individuals aged 70 or older | Slightly more prevalent in males (1·3:1·0) |
| Highest incidence of VTE among haematological cancers | 10% will develop VTE during the course of their disease | VTE is not associated with disease aggressiveness | Conflicting data linking VTE and inferior overall survival in MM patients |
| Adverse impacts:<br>Treatment interruption<br>Increased morbidity<br>Economic burden | Thrombogenicity in MM is multifactorial | Patients with MM are under-represented in clinical trials of thromboprophylaxis | Arterial thrombosis not unusual in patients with MM |

MM=multiple myeloma; VTE= venous thromboembolism.
Mayo Clinic proceedings volume 91 Multiple myeloma: diagnosis and treatment 2016

# Multiple myelomas: key features

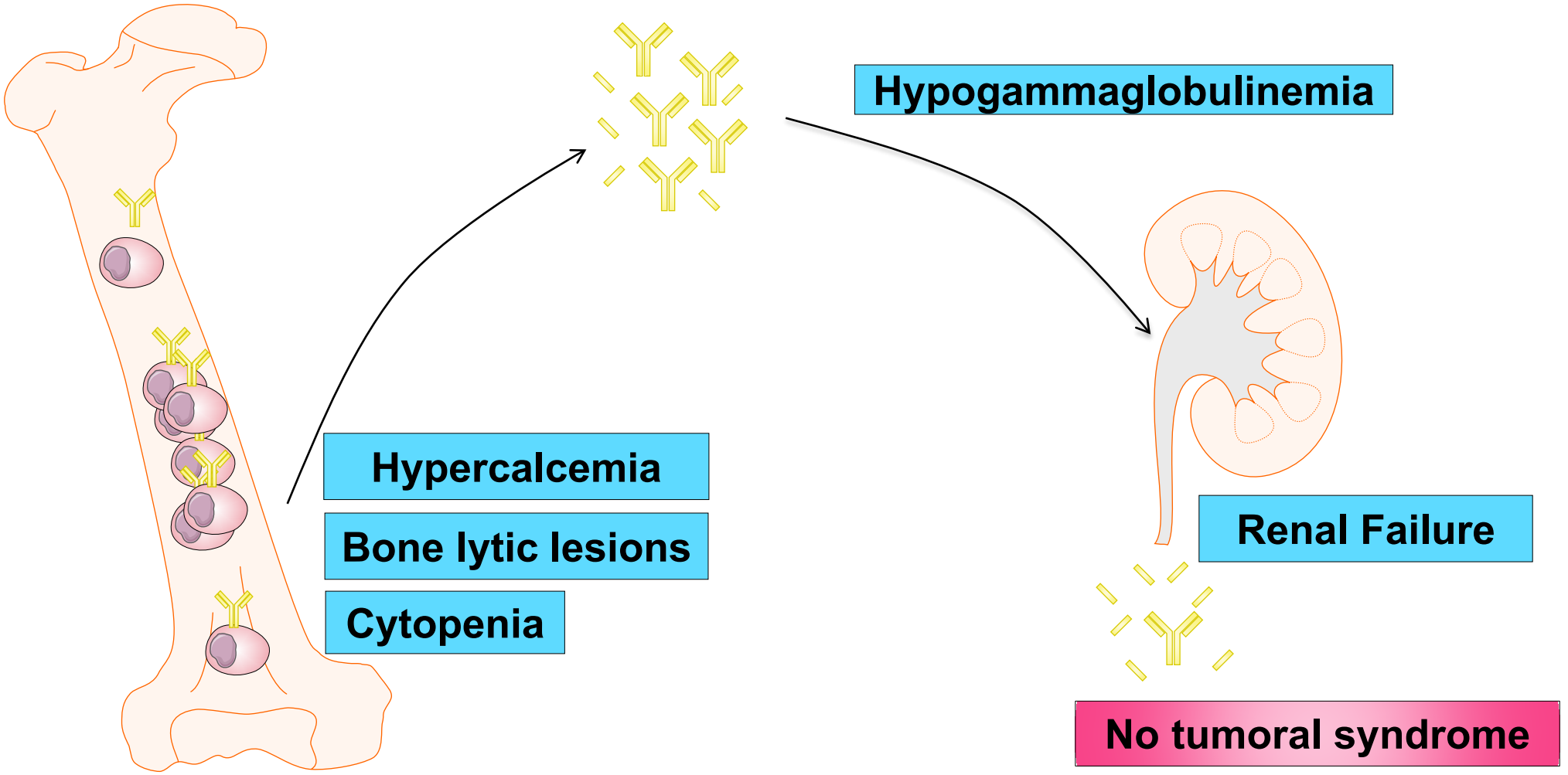



Figure by C. Hermans

# Cancers and thrombotic adverse events

| Thrombotic risk categories by cancer type | | |
|---|---|---|
| **Very high risk[a]** | **High risk[b] (select example)** | **Modest risk[c]** |
| Pancreas | Gynecological<br>(Clear cell carcinoma) | Breast[e] |
| Stomach | Lung<br>(Mucinous adenocarcinoma) | Prostate |
| Metastatic | Brain<br>(High-grade gliomas) | Colon |
| | Hematological<br>(Multiple myeloma; high-grade/ bulky lymphomas) | |
| | Genitourinary[d]<br>(Renal cell carcinoma) | |

[a]Reported 'Very high risk' thrombotic presentations include; migratory thrombophlebitis (prostate), portal vein thrombosis (prostate) and thrombophlebitis (stomach)
[b]Reported 'High risk' thrombotic presentations include; pelvic venous obstruction (clear cell carcinoma), post operative venous thromboses (high grade gliomas) and renal vein and caval tumor invasion and thrombosis (renal cell carcinoma)
[c]Modest risk thrombotic presentations are high prevalence with modest to low thrombosis risk
[d]Excluding prostate
[e]Highly prevalent, with modest/low thrombotic risks

Table adapted from Mosarla RC et al. *J Am Coll Cardiol*. 2019 March 26; 73(11): 1336–1349. doi:10.1016/j.jacc.2019.01.017

# Risk factors associated with the development of VTE in different haematological cancers

Increasing risk of venous thromboembolism

**AML**
DIC score
Advanced age
Co-morbidities
Use of central venous device
Female gender

**ALL**
Use of L-asparaginase
Advanced age
Co-morbidities
Use of central venous device

**APL**

**MPNs**
Age ≥ 60
Previous history of VTE
JAK2V617F mutation
Male gender
Leukocytosis

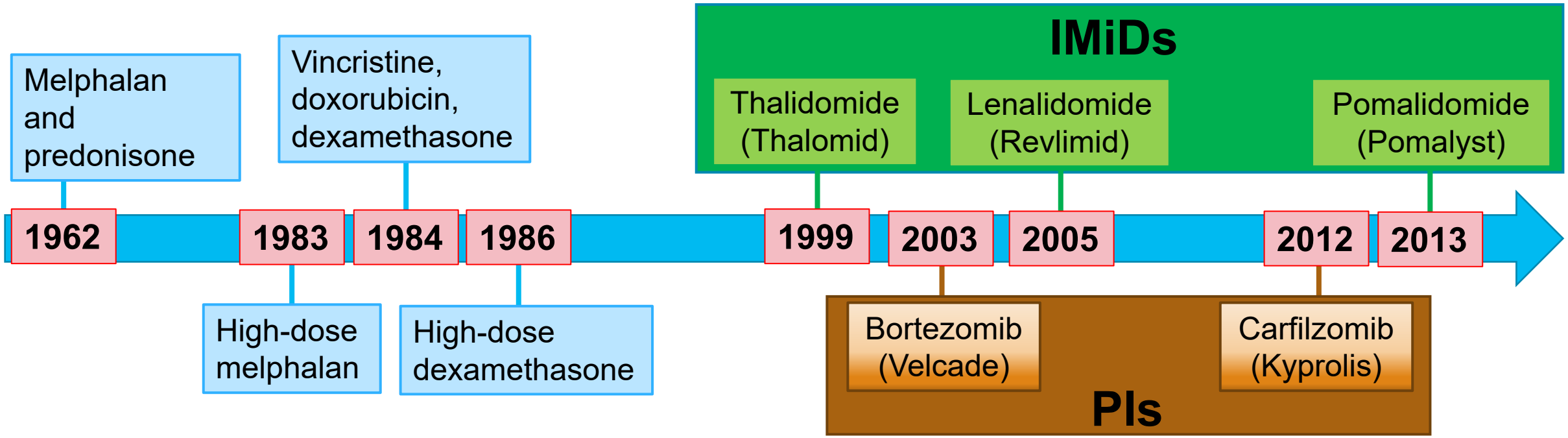
**Lymphomas**
Primary CNS or primary mediastinal B cell lymphoma
Previous VTE
Obesity
Immobility
Extranodal disease
Neutropenia
Hemoglobin ≤10g / dL

**Myeloma**
Use of IMID +/- steroid and chemotherapy
Use of erythroid stimulating agents

ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; APL=acute promyelocytic leukemia; CNS= central nervous system; DIC= disseminated intravesicular coagulation; JAK= Janus kinase; IMiDs= immunomodulatory drugs; MPN= myeloproliferative neoplasm; MM=multiple myeloma; VTE= venous thromboembolism.
Figure adapted from https://doi.org/10.1080/17474086.2020.1751608 - Risk assessment of venous thromboembolism in hematological cancer patients: a review

# Milestones in multiple myeloma treatment

**The treatment paradigm of multiple myeloma treatment shifted with the introduction of 2 categories of novel treatment, IMiDs and PIs, which significantly improved survival in patients with MM.**



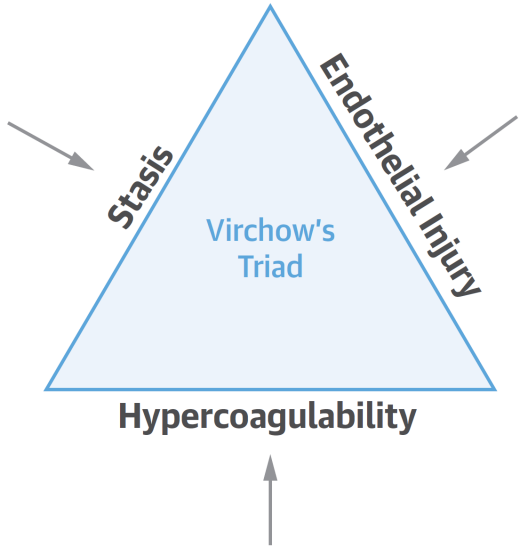

IMiDs=immunomodulatory drugs; MM=multiple myeloma; Pis=proteasome inhibitors

Figure was adapted form Weijuan Li et al. *Circulation*. 2016 Mar 1;133(9):908-12. doi:10.1161/CIRCULATIONAHA.115.018351

**Pomalidomide is approved by EC under trade name Imnovid**

# Factors contributing to increased thrombotic risks in cancer

- Immobility
- Frequent hospitalizations
- Mass effect/vascular compression from tumor
- Vascular invasion
- Blood hyperviscosity
- Volume depletion
- Arrhythmia
- Left atrial size/function




- Cancer treatment (chemotherapy, surgery, radiation)
- Central venous catheters
- Left atrial remodeling

- Local and circulating procoagulant factors
  - ↑ Tissue factor
  - ↑ Inflammatory cytokines
  - ↑ Platelet activation
  - ↓ Fibrinolysis
- Certain cancer therapies (e.g., hormonal therapies, erythropoiesis stimulating agents, proteasome inhibitors, immunomodulatory drugs, checkpoint inhibitors)
- Adjunctive therapies / blood products
- Patient factors and comorbidities

**Specific features of thrombosis in patients with MM**

Early development of VTED
No correlation with mortality
Major impact of specific treatments
Pathophysiology = different from solid cancers

MM= multiple myeloma; VTED= venous thromboembolic disease
Figure was adopted from Mosarla RC et al. *J Am Coll Caridol*. 2019 Mar 26;73(11)1336-1349

# Risk factors for venous thrombosis in patients with Multiple myeloma

**MM related factors**

- Hyperviscosity
- Newly diagnosed disease compared to relapsed patients
- Renal failure
- CRP
- Chromosome 11 abnormalities
- Light-Chain disease

**PATIENT related factors**

- History of VTE
- Immobility
- High age
- Obesity
- Paraplegia
- Genetic predisposition for VTE

**TREATMENT related factors**

- Multi agent chemotherapy
- Use of Thalidomide
- Use of Lenalidomide
- High-dose Dexa
- Use of Pomalidomide
- Recombinant EPO

**PROCOAGULANT changes**

- High FVIII and VWF levels
- High P-selectin levels
- Increased Fibrinogen
- Increased MP-associated TF activity
- Hypofibrinolysis
- Acquired APC resistance
- Decreased proteins

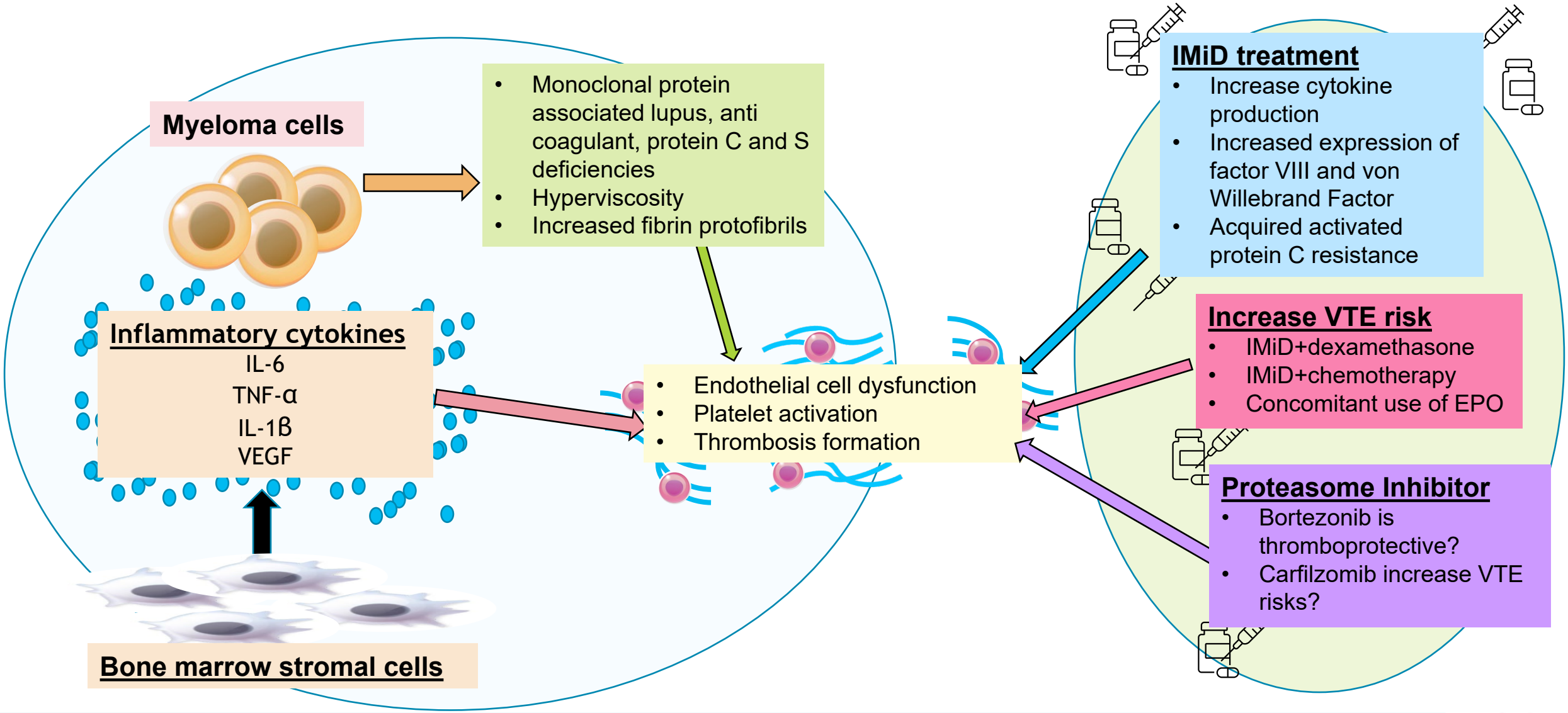
IMiDS (Thalidomide) → Thrombosis

**IMiDS + DEXA (480 mg/month) or chemotherapy** → **Thrombosis**

APC=Activated protein C; CRP= C reactive protein; DEXA=dexamethasone; EPO= erythropoietin; Fg= F gamma chain; IMiDS= immunomodulatory drugs; MP=microparticle; TF= tissue factor VTE=venous thromboembolism; VWF= von Willebrand factor

F. Leebeek – Update of thrombosis in multiple myeloma – Thrombosis Research 140S1 – 2016 – 576-80

# Pathophysiology of thrombosis in patients with multiple myeloma




EPO= erythropoietin; IL= interleukin; IMiDS= immunomodulatory drugs; TNF= tumor necrosis factor; VEGF= vascular endothelial growth factor; VTE=venous thromboembolism;
Figure adopted from Weijuan Li. *Circulation*. Cardiovascular Complications of Novel Multiple Myeloma Treatments, Volume: 133, Issue: 9, Pages: 908-912, DOI: (10.1161/CIRCULATIONAHA.115.018351)

# Management of DVT/PE in our patient with MM

**DVT/PE**

## DVT/PE?

- DVT: proximal/distal
- PE: limited–massive
- Provoked versus unprovoked

## Important parameters

- Renal function
- Platelet count
- Intolerance to LMWH ?
- Current antithrombotic treatment
- Patient preferences
- Drug interactions
- Risk of bleeding

Therapeutic anticoagulation
LMWH/DOAC/VKA

6 months/As long as IMiD is continued/indefinite

LMWH
- Dose reduction of 50% if platelet count <50.000/µL
- Stop LMWH if platelet count <20.000/µL

Renal function should be regularly assessed

ASA=acetylsalicylic acid; DOACs= direct-oral anti-coagulant; DVT= deep vein thrombosis; IMiDs= immunomodulatory drugs; LMWH=low-molecular-weight heparin; PE= pulmonary embolism; VKA= vitamin K antagonist.

# Which antithrombotic in MM patients?

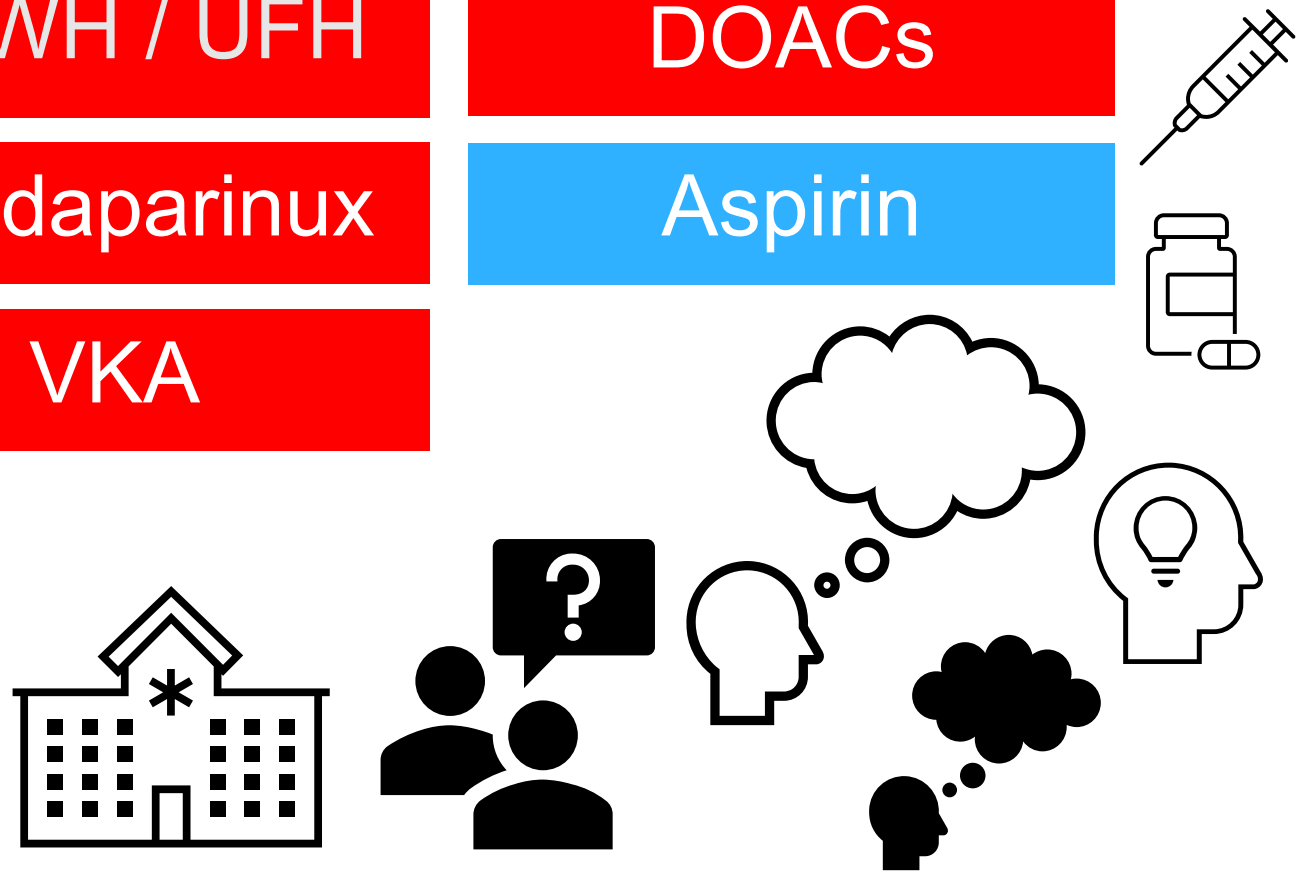
LMWH / UFH

Fondaparinux

VKA

DOACs

Aspirin



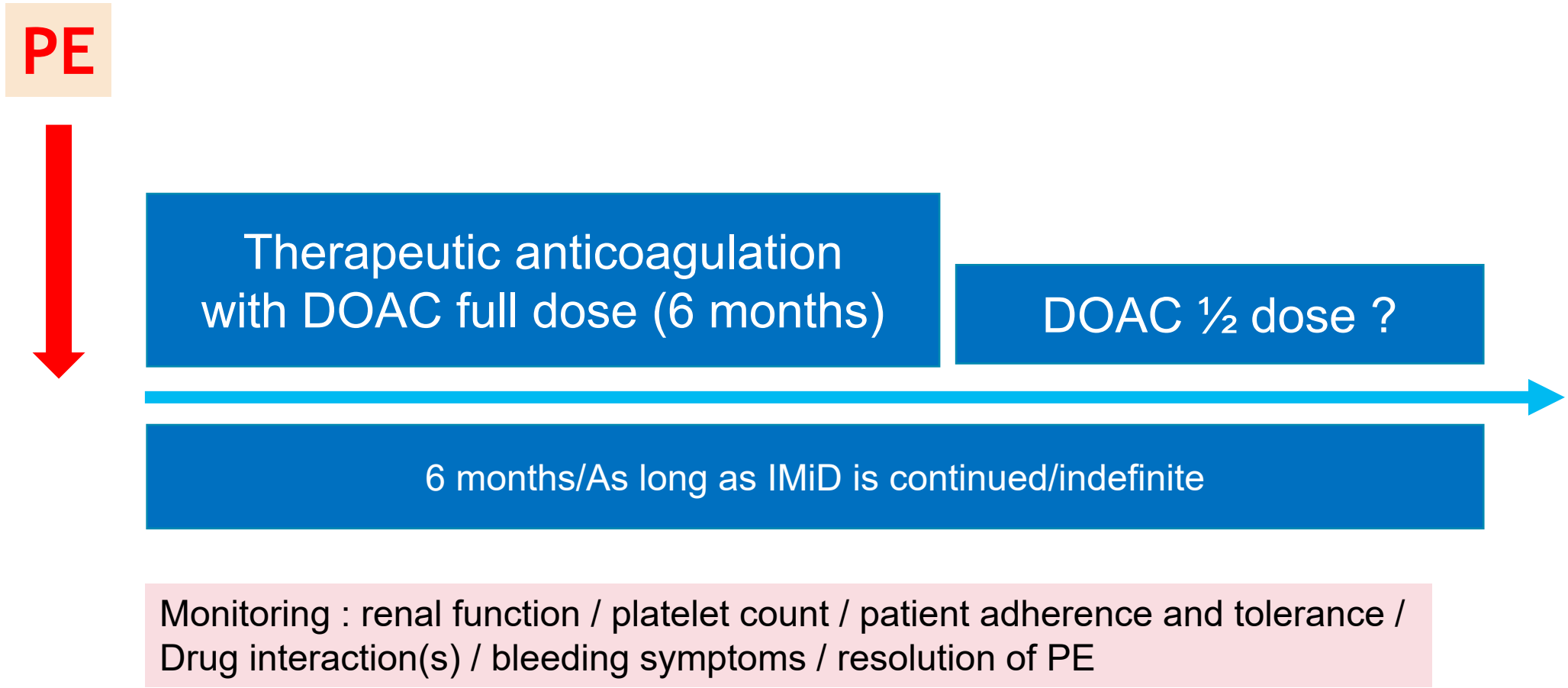
DOACs= direct-oral anti-coagulant; LMWH=low-molecular-weight heparin; UFH=unfractionated heparin; VKA= vitamin K antagonist.

# Indirect and direct anticoagulants: multiple - versus single-factor inhibition

| | Vitamin K Antagonists (VKA) | Heparins (UFH-LMWH) | DOACs Anti-Xa Anti-IIa |
|---|---|---|---|
| Mode of action | • Interference with vitamin K recycling | • Potentiation of antithrombin | • Direct inhibition of FXa or FIIa |
| Targets | • FII, FVII, FIX, FX<br>• Reduced synthesis | • Indirect inhibition of FXa and FIIa | • Selective inhibition of FXa or FIIa |
| Indication | • Universal anticoagulants including mechanical cardiac valve | • Universal anticoagulants<br>• Acute phase of PE | • Prevention and treatment of VTE (DVT/PE)<br>• Prevention of stroke in AF |

AF=atrial fibrillation; DOACs= direct-oral anti-coagulant; DVT= deep vein thrombosis; FXa=factor Xa; LMWH=low-molecular-weight heparin; NOACs= novel oral anti-coagulants; PE= pulmonary embolism; UFH=unfractionated heparin; VKA= vitamin K antagonist; VTE= venous thromboembolism.
Refer to respective Smpc

# Management of DVT/PE in our patient with MM




ASA=acetylsalicylic acid; DOACs= direct-oral anti-coagulant; DVT= deep vein thrombosis; IMiDs= immunomodulatory drugs; LMWH=low-molecular-weight heparin; PE= pulmonary embolism; VKA= vitamin K antagonist.

# Prevention of DVT/PE in patient with MM ?

## *Still open/evolving question...*

MM diagnosis
Treatment initiation
Thrombosis Risk Assessment

How can the risk be assessed?

Treatment choice?

**Antithrombotic treatment**
**AAS/LMWH/DOACs/VKA ?**

**LMWH**

- Dose reduction of 50% if platelet count <50.000/µL
- Stop LMWH if platelet count <20.000/µL

Renal function should be regularly assessed

ASA=acetylsalicylic acid; DOACs= direct-oral anti-coagulant; DVT= deep vein thrombosis; LMWH=low-molecular-weight heparin; PE= pulmonary embolism; VKA= vitamin K antagonist.

# Prediction of the risk of thrombosis in MM

| IMWG score[a] |
|---|
| **Individual risk factors**<br>Obesity (BMI≥30kg/m$^2$)<br>Previous venous thromboembolism<br>Central venous catheter or pacemaker |
| **Associated disease**<br>Cardiac disease<br>Chronic renal disease<br>Diabetes<br>Acute infection<br>Immobilization<br>Blood clotting disorders |
| **Surgery**<br>General surgery<br>Any anesthesia<br>Trauma |
| **Medicatoin**<br>Erythropoetin |
| Myeloma-related risk factors<br>Diagnosis<br>Hyperviscosity |
| **Myeloma therapy**<br>High-dose dexamethasone (≥480mg /month)<br>Doxorubicin |

| IMPEDE score<br>Predictor (acronym/score) | |
|---|---|
| **Immunomodulatory Drug** | (A/+4) |
| **Body Mass Index ≥ 25kg/m$^2$** | (M/+1) |
| **Pelvic, Hip or Femur Fracture** | (P/+4) |
| **Erythropoiesis-Stimulating Agent** | (E/+1) |
| **Doxorubicin** | (D/+3) |
| **Dexamethasone** | |
| • High-Dose (>160mg monthly) | (D/+4) |
| • Low-Dose (≤160mg monthly) | (D/+2) |
| **Ethnicity/Race = Asian/Pacific Islander** | (E/-3) |
| **History of Venous Thromboembolism before MM** | (V/+5) |
| **Tunneled Line/Central venous Catheter** | (T/+2) |
| **Existing Thromboprophylaxis:** | |
| • **Therapeutic LMWH or Warfarin** | (E/-4) |
| • **Prophylactic LMWH or Aspirin** | (E/-4) |

[a]Recommendations from IMWG; if no risk factor or any one risk factor present, Aspirin 81-325mg OD. If two or more risk factors are present LMWH (enoxaparin 40mg OD), full dose warfarin (target INR 2-3)
IMWG score table adapted from Palumbo A et al.*Leukemia*.2008 .IMPEDE score table adopted from Li A et al.*J Natl Compr Canc Netw*.2019, Covut F et al.*Br J Haematol*.2021

BMI= body mass index; IMWG= international myeloma working group; IMPEDE=?;INR=international normalized ratio; LMWH=low-molecular-weight heparin; OD= once daily, INR : international normalized ratio
1 Palumbo A et al.*Leukemia*.2008. 2 Li A et al. *J Natl Compr Canc Netw*.2 019. 3 Covut F et al. *Br J Haematol*. 2021

# Algorithm for risk stratification and choice of anticoagulants for patients with MM

***(Still open/evolving question... What are the guidelines saying?)***

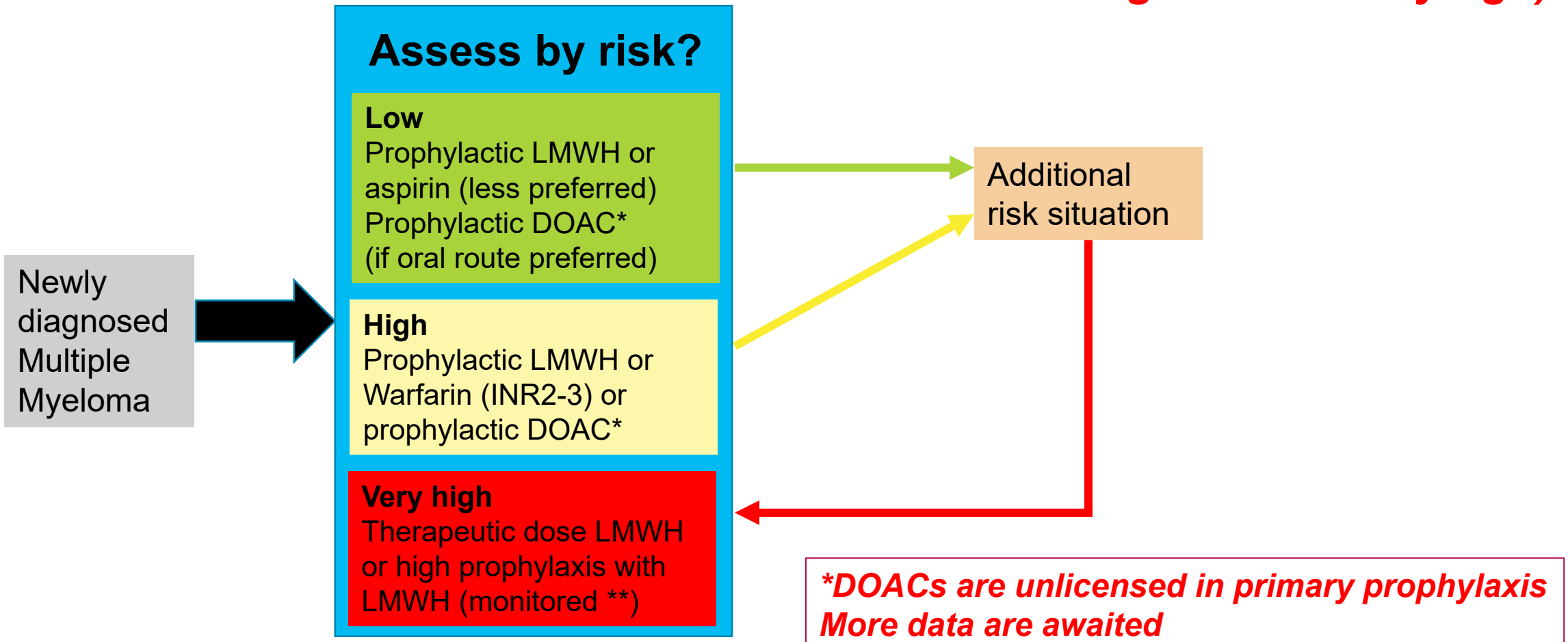



Figure adopted from Swan D et al.*Br J Haematol*. 2018 Nov;183(4):538-556. ** High prophlaxis indicates anti-Xa level at the higher end of prophylactic range eg 0.4iu/ml

DOAC= direct-oral anti-coagulant; INR=international normalized ratio; LMWH=low-molecular-weight heparin; MM=multiple myeloma

# Thrombosis and Multiple Myeloma: Conclusions

- Patients with MM are at high risk of thrombotic complications
- Thrombotic complications in patients with MM have specific features
  - Early development in the disease
  - Specific pathophysiology
  - No apparent correlation with survival
  - Several impacts on the disease management
- Assessment of the risk of thrombosis in each MM patient=mandatory
- Different antithrombotic strategies can be used
- Underlying evidence is limited
- Role and validation of DOACs in this setting ? (Evolving evidence)

DOACs= direct-oral anti-coagulant; MM=multiple myeloma