Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών
National and Kapodistrian University of Athens

Θεραπευτική Κλινική
Department of Clinical Therapeutics

The role of endothelium in Waldenström Macroglobulinemia and in AL amyloidosis

Foteini Theodorakakou

Department of Clinical Therapeutics

National and Kapodistrian University of Athens

Disclosures

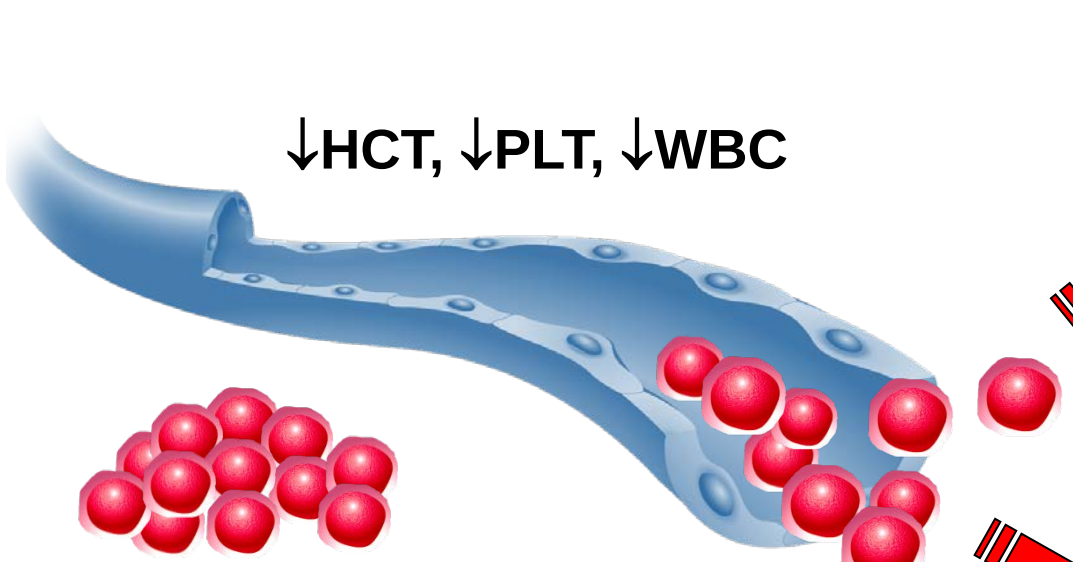
- *Consultancy (includes expert testimony): AstraZeneca*

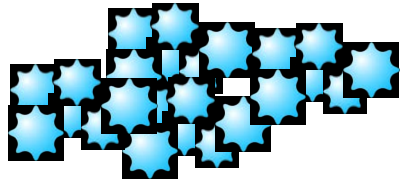
Waldenström's Macroglobulinemia (WM)

- Low-grade lymphoproliferative disorder associated with *monoclonal IgM*

- Unique disorder with symptoms and signs due to
  - Infiltration of marrow, spleen, LN
  - Amount of circulating IgM
  - Specific properties of IgM

Clinicopathologic Manifestations of WM





Hyperviscosity Syndrome: Epistaxis, HA, Impaired vision >4.0 CP

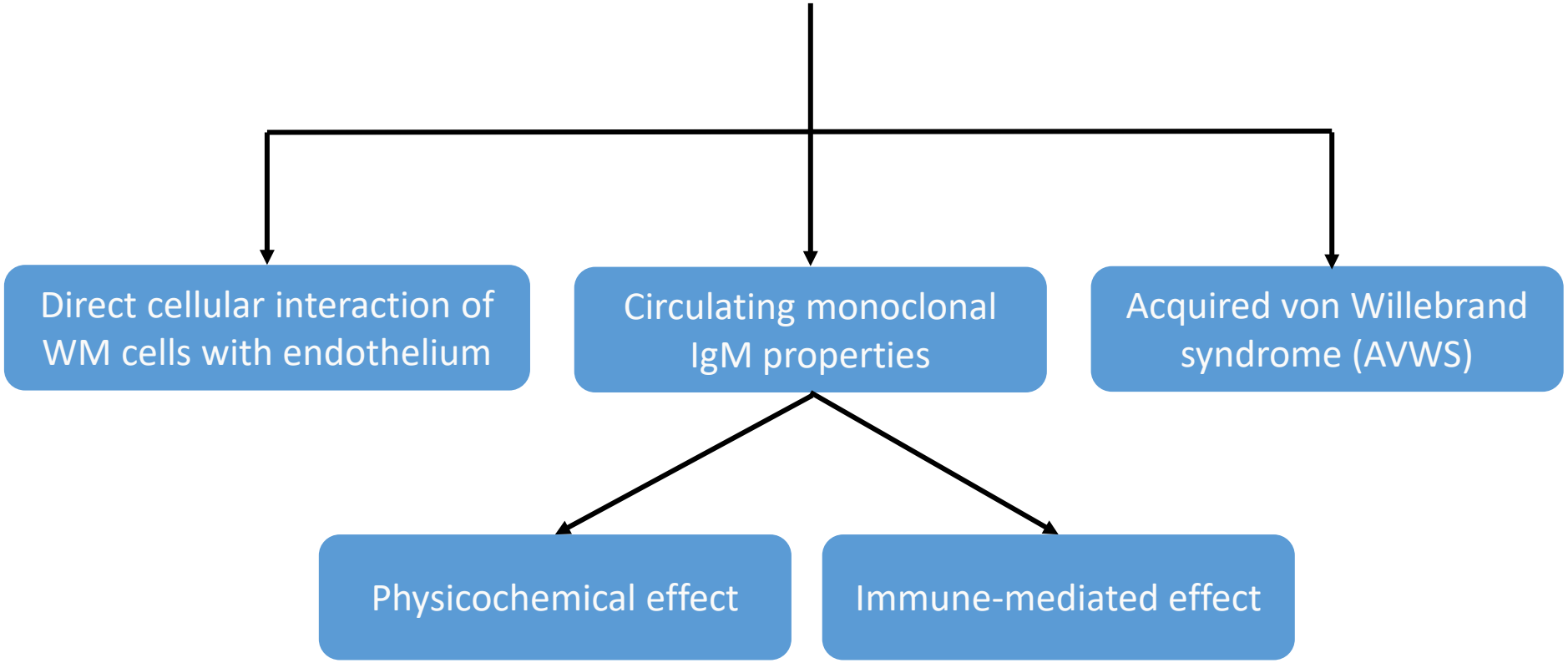
Adenopathy, splenomegaly ≤15%

IgM Neuropathy (22%)
Cryoglobulinemia (10%)
Cold Agglutinemia (5%)

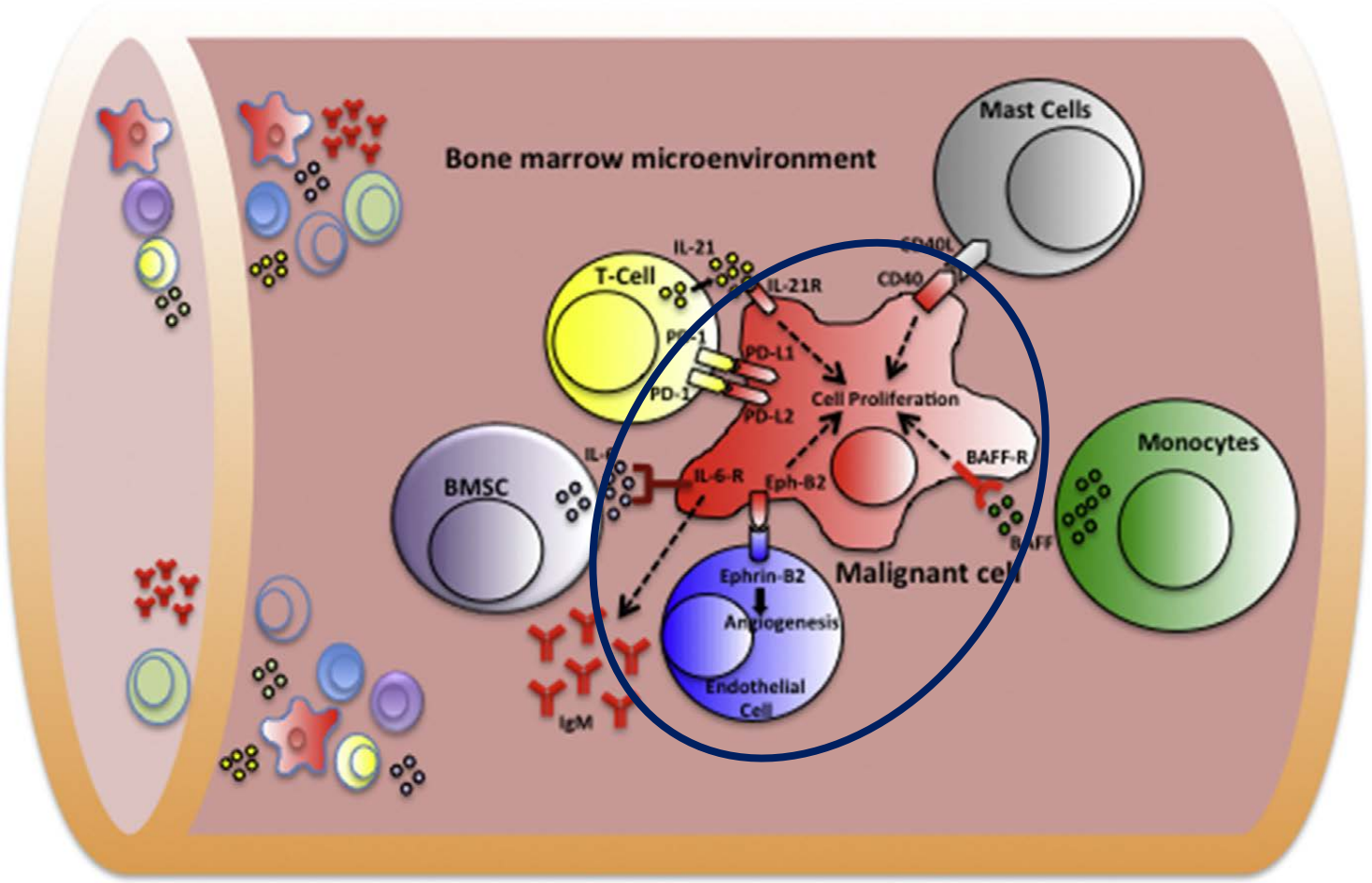
Fatigue, Constitutional Sxs
Cytokinemia?

Treon SP et al. *Cancer Treat Res.* 2008;142:211-242.

Mechanisms of endothelial activation and injury in WM



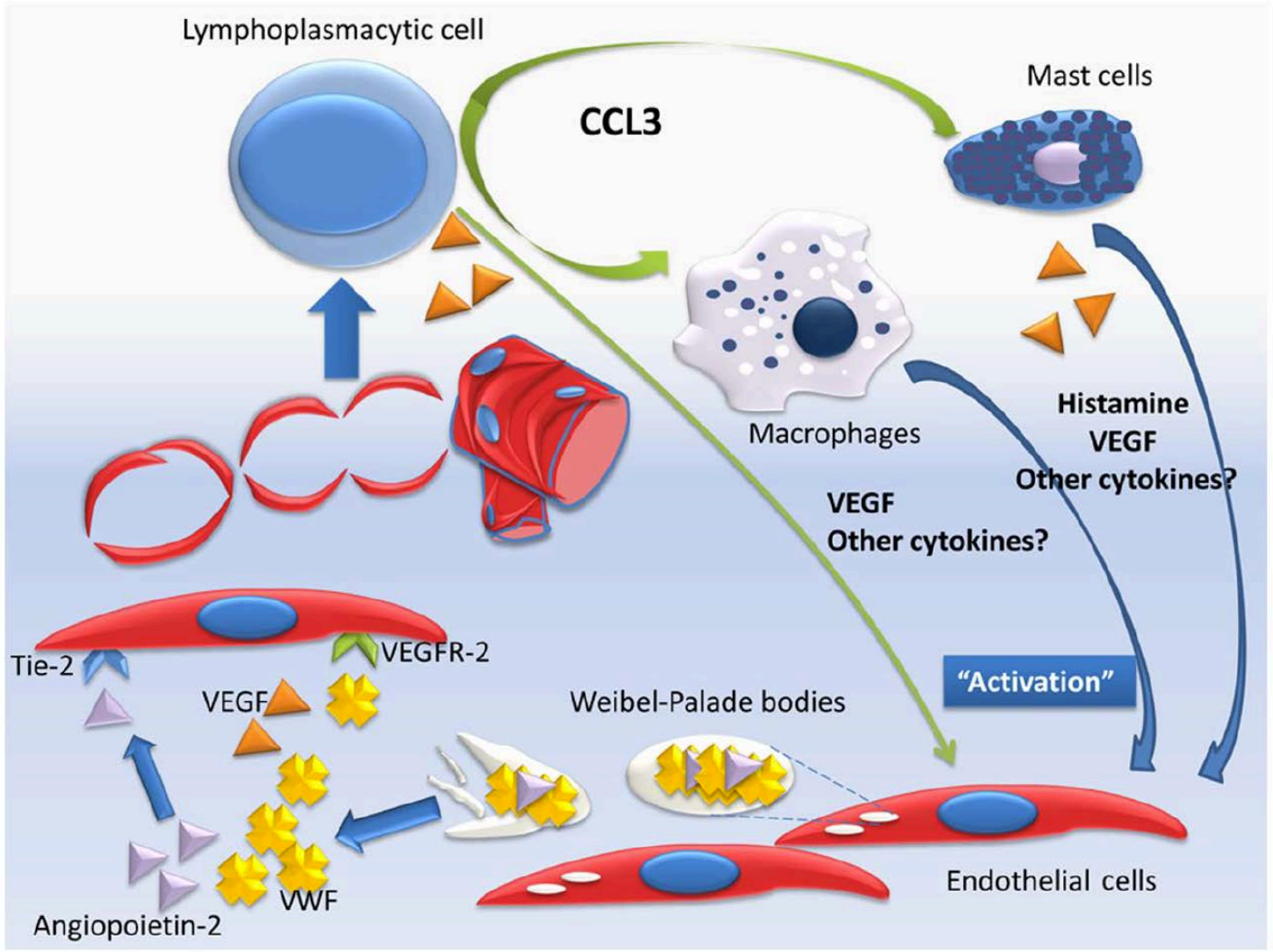
The bone marrow microenvironment in MW



- Eph-B2/Ephrin-B2 interaction plays a major role in the adhesion, proliferation, endothelial activation, vascular permeability and angiogenesis, supporting both survival of WM and microvascular dysfunction.

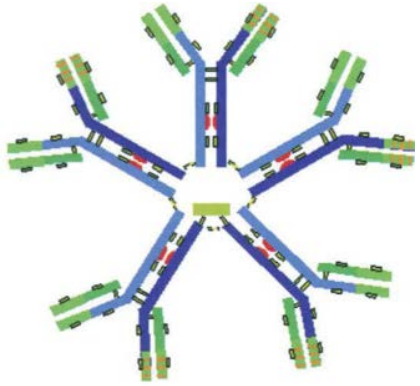
Jalali S & Ansell SM Hematol Oncol Clin N Am 32 (2018) 777–786

Angiogenesis in WM



Physicochemical properties of circulating monoclonal IgM: hyperviscosity

- IgM protein is a pentamer with high molecular weigh
- High concentration of IgM (> 6000mg/dl) increases plasma viscosity
- Hyperviscosity → shear stress, endothelial injury, impaired perfusion
- Hyperviscosity affects small vessels: headaches, visual changes (retinal hemorrhage), mucosal bleeding
- 30% of patients with WM



Pentamer
IgM

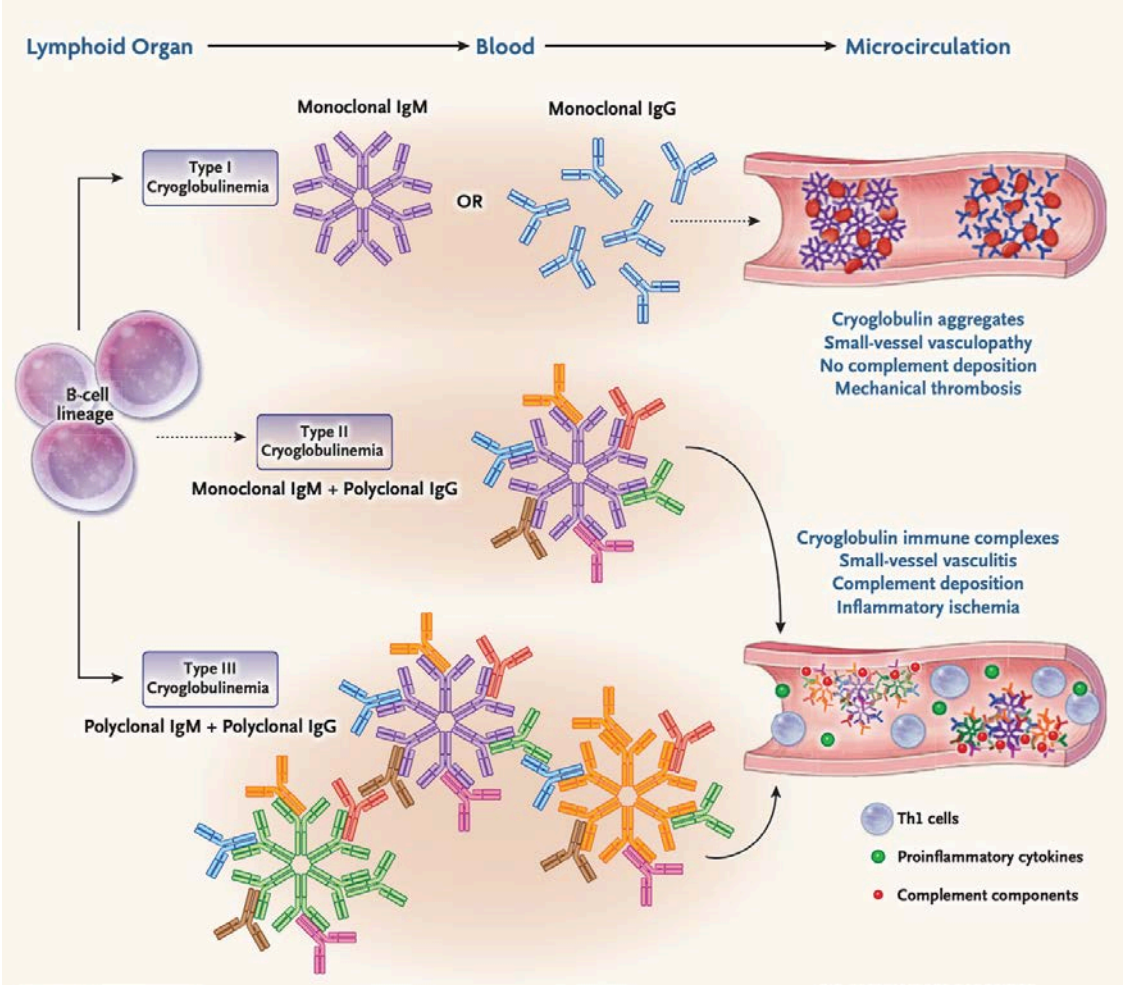
Abeykoon JP et al, *Am J Hematol*. 2018
Gustine, J.N. et al, (2017), Br J Haematol
Payandeh, M. et al. *Biomedical Research and Therapy*, *2025*

Immunological properties of circulating monoclonal IgM

- Direct endothelial activation by IgM → increased vascular permeability and is responsible for endothelial activation and tissue injury
- IgM bind to endothelial cell surface antigens and activate the classical complement pathway, resulting in local inflammation, upregulation of adhesion molecules (VCAM-1, ICAM-1), and cytokine release (notably CCL5 and IL-6), promoting endothelial activation and permeability.

Immunological properties of circulating monoclonal IgM: Type I cryoglobulinemia

- Cryoglobulins precipitate at temperature < 37°C
- The main mechanism in Type I cryoglobulinemia is mechanical obstruction in small vessels by cold-induced aggregates leading to thromboses and endothelial injury
- Clinical manifestations: skin changes (acral necrosis or Raynaud's) and cryoglobulinemic glomerulonephritis
- Observed in approximately 5% of WM patients



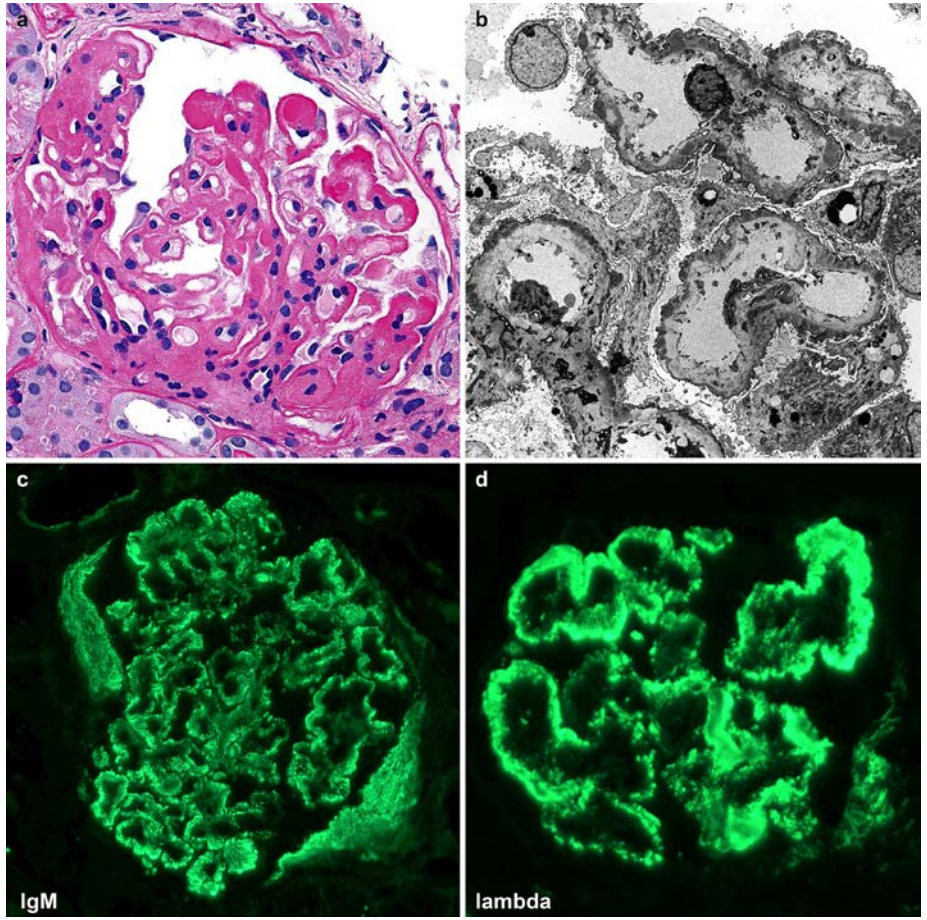
Thrombotic microangiopathy (TMA) in WM

Monoclonal IgM protein may trigger the pathogenesis of endothelial injury with one of the following mechanism:

- mechanical injury by monoclonal IgM, hyperviscosity or cryoglobulins
- monoclonal IgM has auto-antibody activity against alternative complement pathway component (Factor H)
- monoclonal IgM auto-antibody activity against ADAMTS13

➢ Renal biopsy findings: Intracapillary IgM thrombi, endothelial swelling, mesangiolysis, and subendothelial accumulation of fluffy and cellular material

➢ Low levels of complement may be present



Tan, S.Y.S. *et al. J Nephrol* (2018)

von Willebrand factor

- von Willebrand factor (vWF) is a large multimeric glycoprotein mainly produced, stored and secreted by endothelial cells
- vWF participates in primary hemostasis, inflammation, and angiogenesis.
- Circulating vWF is a marker of endothelial activation and endothelial damage.

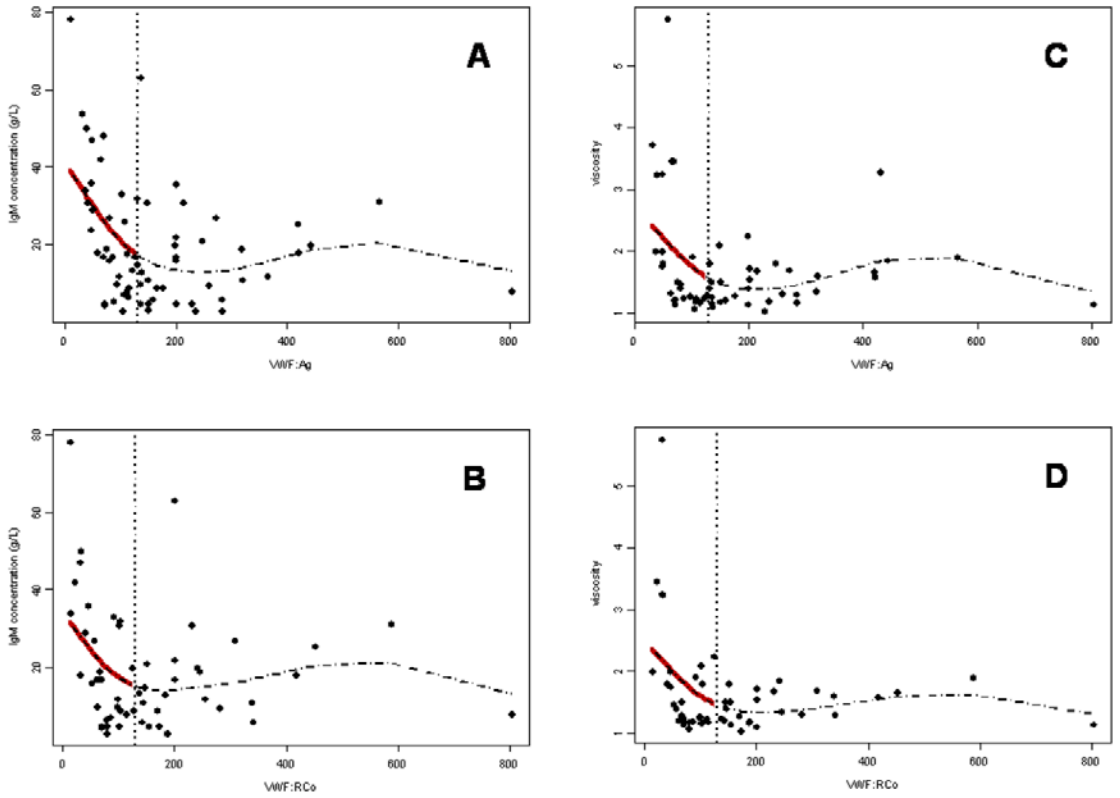
Acquired vWF syndrome in WM

- A variety of mechanisms have been proposed to cause structural or functional loss of vWF:
  - Deactivation by monoclonal IgM that binds to vWF and accelerate its clearance
  - Specific autoantibody-mediated destruction
  - Absorption by malignant cells
  - Increased fluid shear stress resulting in vWF multimer unfolding and proteolysis by ADAMTS-13.

Hivert, et al Blood.2012
How I treat AVWS, 2011 Blood
Mayerhofer et al European Journal of Clinical Investigation, 2009
Castillo, J.J. et al (2019), Br J Haematol

Acquired vWF syndrome in WM

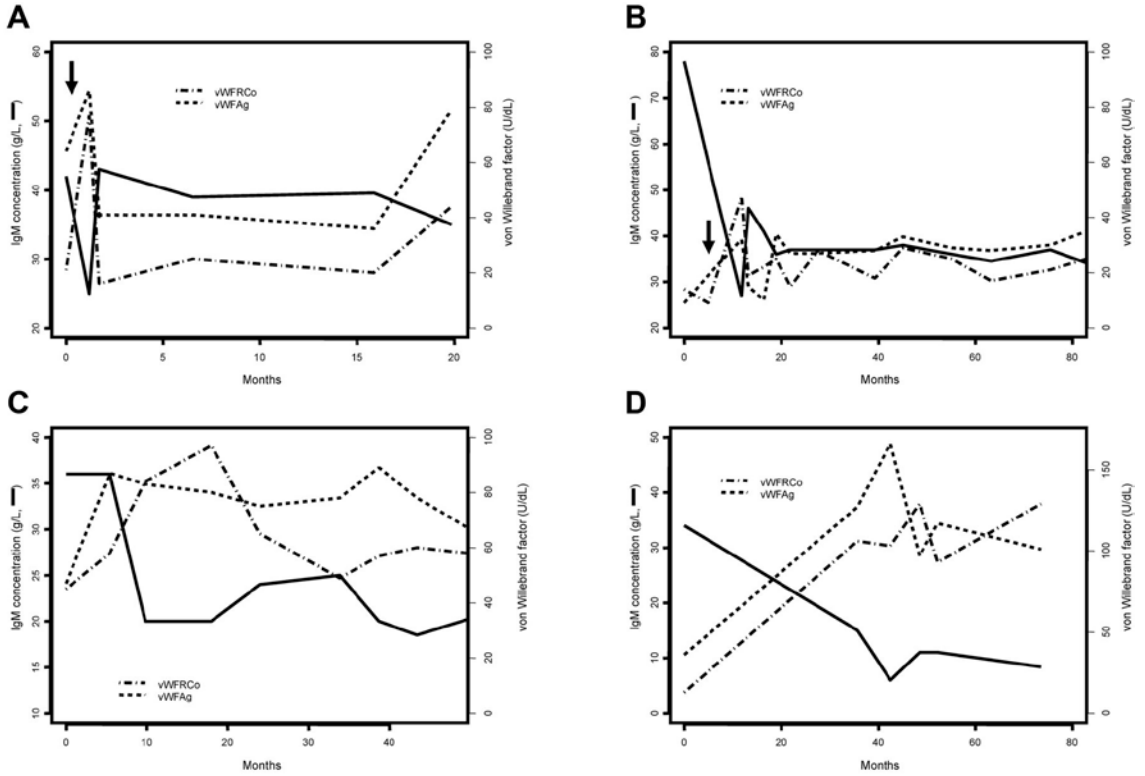
- 14% of patients with WM fulfill criteria for AVWS
- Inverse correlation has been found between vWF:Ag and monoclonal IgM or serum viscosity.



Hivert, et al Blood.2012;120(16):3214-3221.

Acquired vWF syndrome in WM

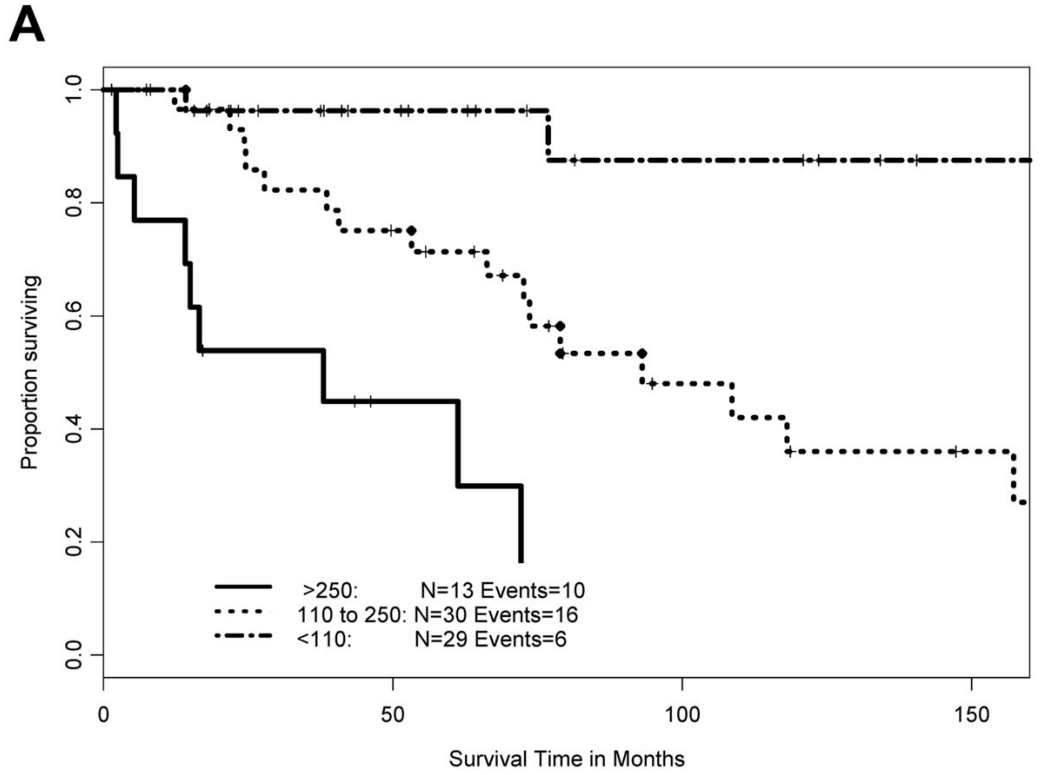
- Acquired vWS in WM poorly responds to vWF concentrates, desmopressin or high dose immunoglobulins.
- Treatment of the underlying disorder is the first choice, and reduction in monoclonal IgM is associated with increase in vWF levels.



Hivert, et al Blood.2012;120(16):3214-3221.

Elevated levels of vWF in WM

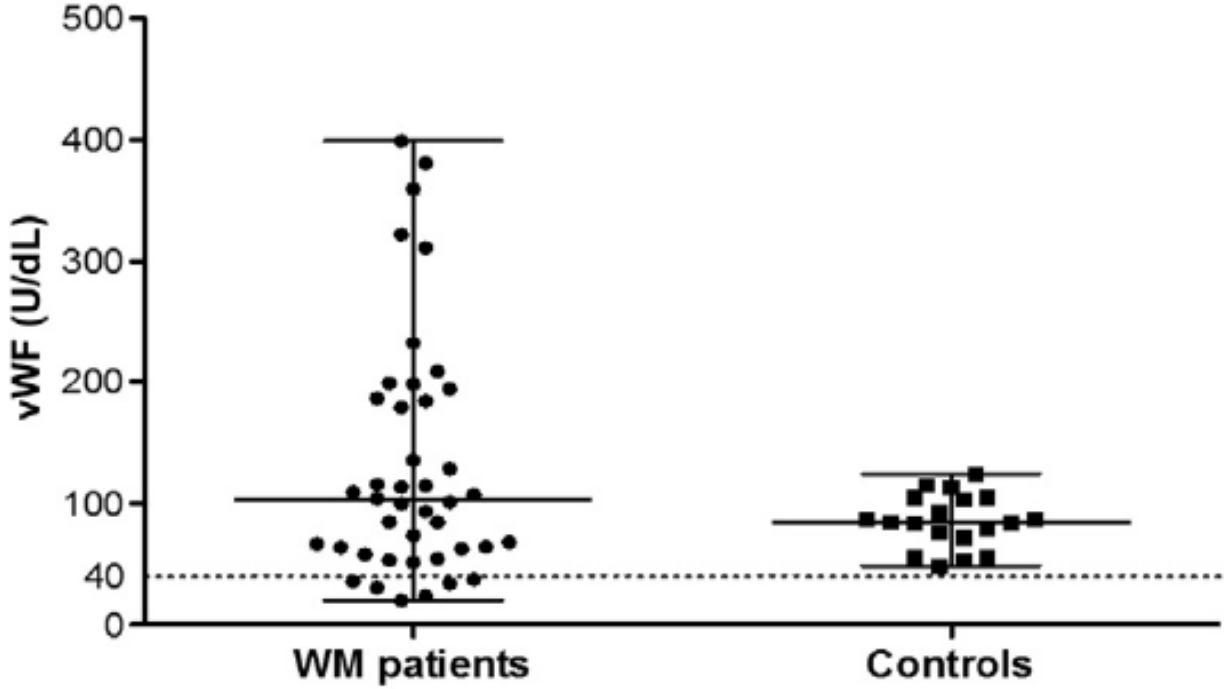
- 59% of patients had elevated levels of vWF:Ag (> 110 U/dL)
- Five-year survival rates of patients with vWF:Ag < 110 U/dL, between 110 U/dL and 250 U/dL, and > 250 U/dL were 96%, 71%, and 44% (p < 0.0001)



Hivert, et al Blood.2012;120(16):3214-3221.

Elevated levels of vWF in WM

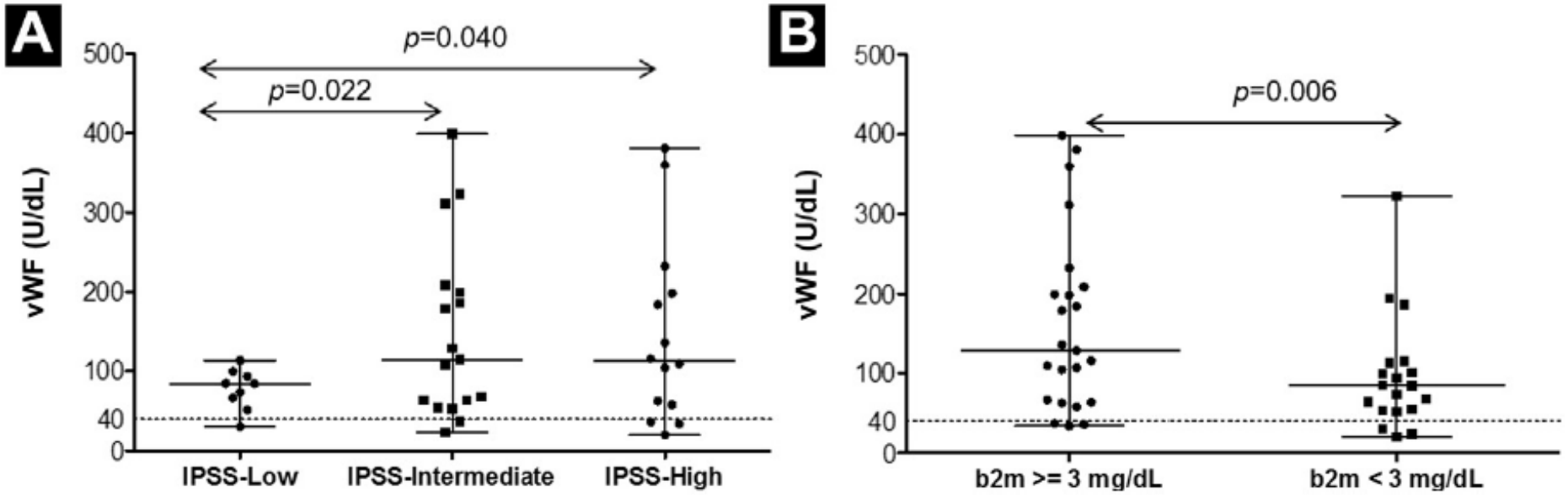
- The median serum level of vWF antigen was 101 U/dL (range, 19.9-399 U/dL) and was slightly greater than the serum level of the healthy controls (median, 85 U/L; range, 48-124 U/L).



Gavriatopoulou et al, Clin Lymphoma Myeloma Leuk. 2019

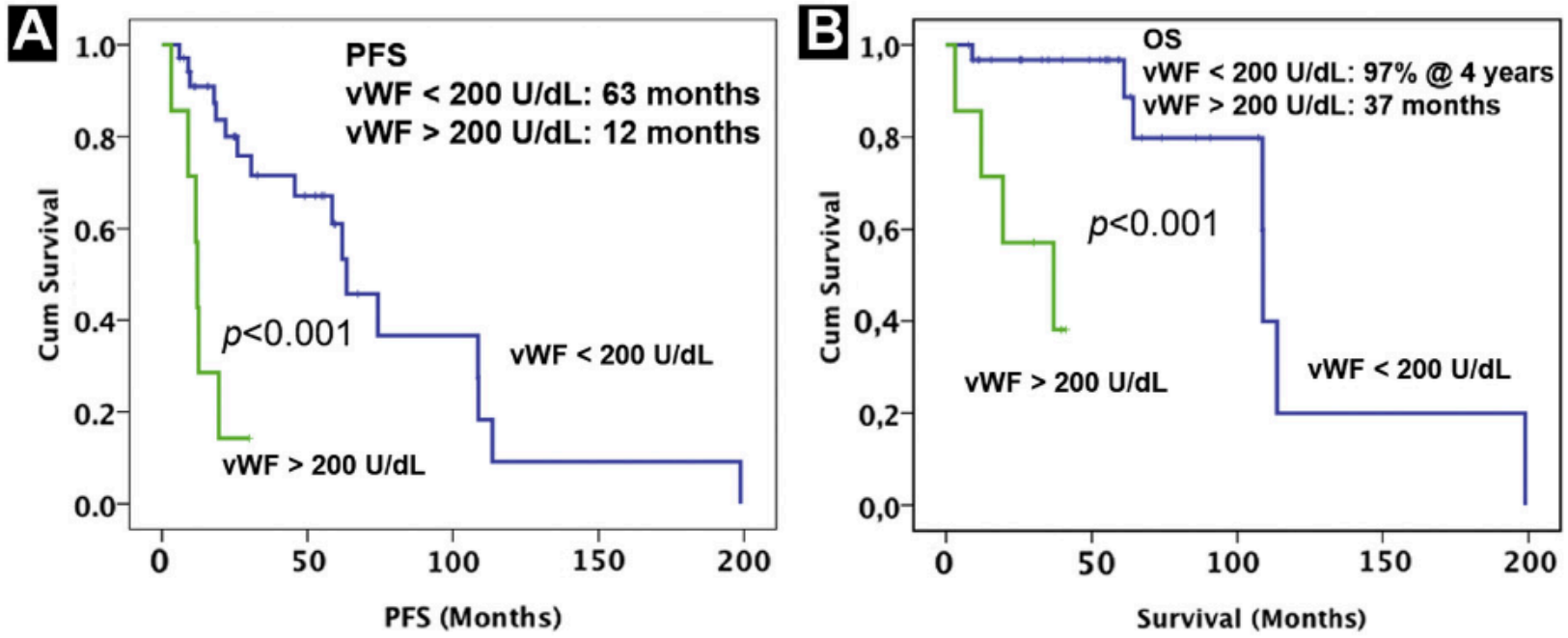
Elevated levels of vWF in WM

- No correlation was found between the vWF:Ag and IgM levels or the extent of bone marrow infiltration.
- Higher vWF:Ag levels were more frequent in patients with intermediate-risk (59%) or high-risk (62%) disease vs low-risk (11%) using the IPSS.
- Higher vWF:Ag levels were more frequent in patients with b2-microglobulin (b2m) > 3 mg/L.



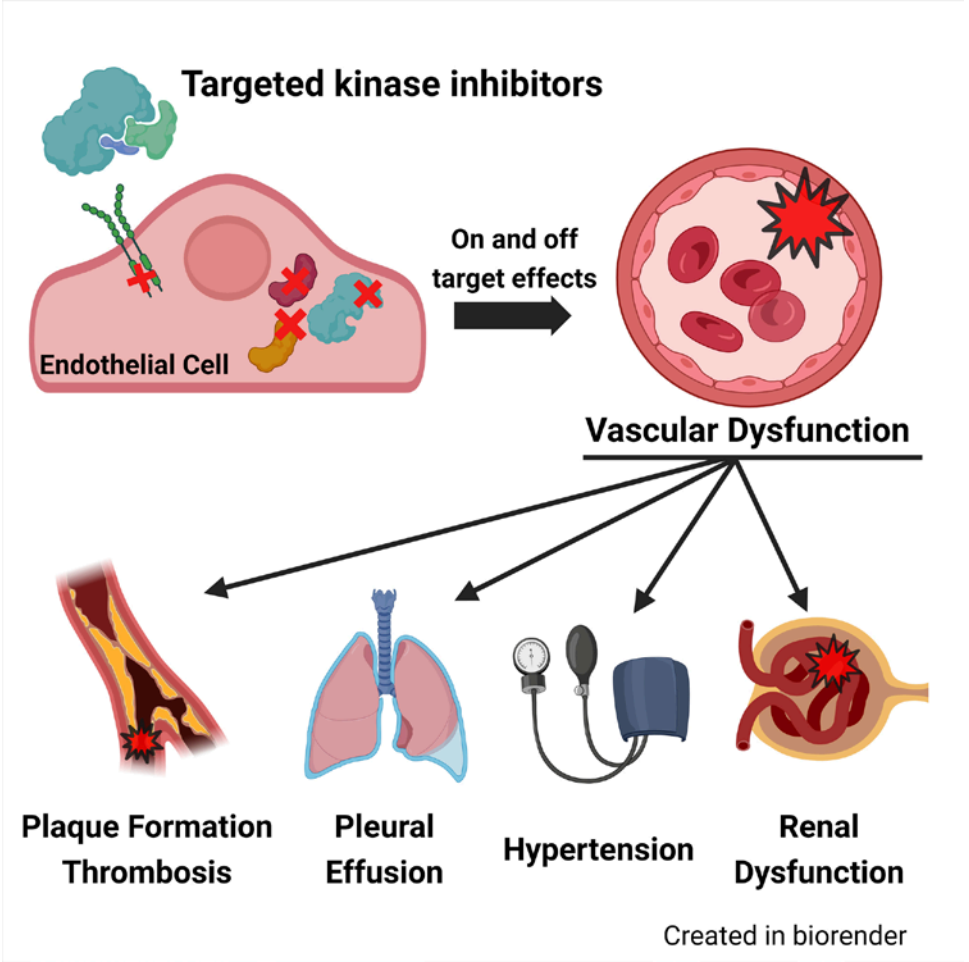
Prognostic role of vWF in WM

- Patients with vWF:Ag ≥ 200 U/dL had a median PFS of 12 months compared with 63 months for patients with vWF:Ag levels < 200 U/L (p < 0.001).
- Median OS for patients with vWF:Ag ≥ 200 U/dL was 37 months (4-year survival, 29% vs. 97% for patients with vWF:Ag < 200 U/L; p < 0.001)



Therapy-related endothelial injury

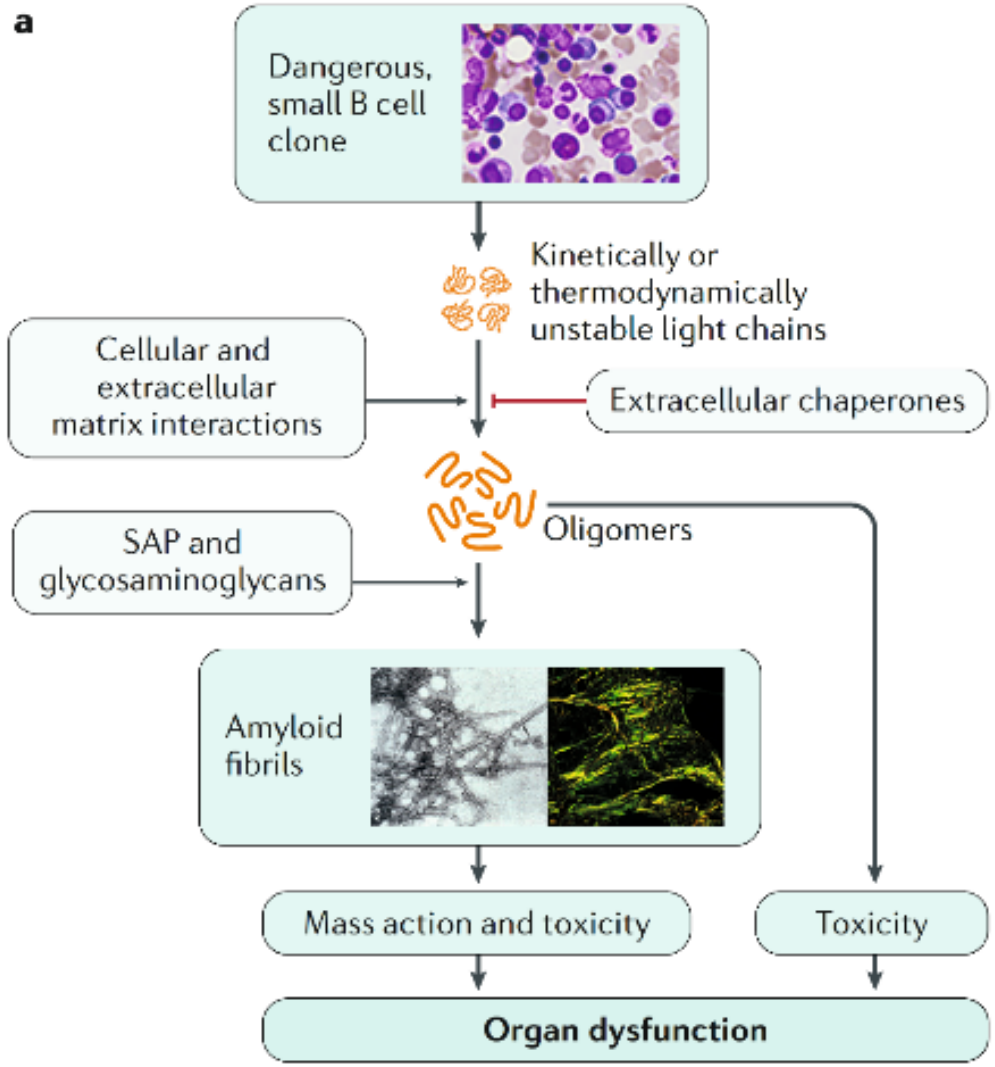
- Bruton tyrosine kinase inhibitors (BTKI), such as ibrutinib and zanubrutinib, are widely used in WM
- BTKI can cause endothelial dysfunction due to off-target inhibition of kinases critical for endothelial and platelet function
- First-generation BTKis (ibrutinib) are less selective and inhibit multiple kinases beyond BTK → TEC inhibition interferes with platelet aggregation while EGFR inhibition can affect vascular integrity
- Clinical manifestation: increased risk of bleeding, atrial fibrillation and other cardiovascular toxicities.



Travers et al AHA Journals 2025

AL amyloidosis

- Misfolding of free light chain, produced by a small B-cell clone, forms oligomers and fibrils which are deposited in tissues
- The result in disruption of architecture and function of various organs, eventually leading to organ failure
- Direct cellular toxicity of light chains or light-chain oligomers has been demonstrated in vitro and in vivo, mainly in cardiomyocytes

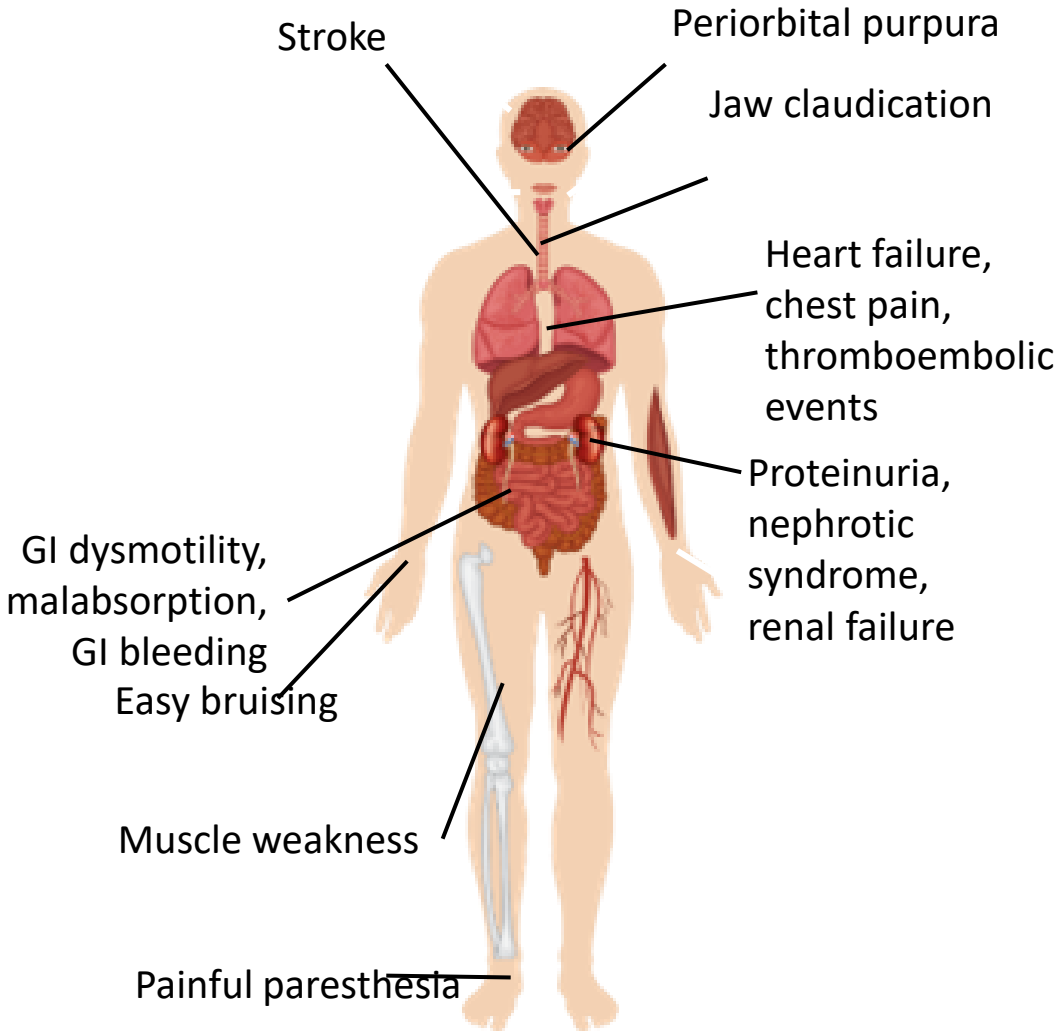


Merlini G, et al. *Nat Rev Dis Primers* 2018

Endothelial dysfunction in AL amyloidosis

- Cardiac dysfunction is the main determinant of prognosis
- However, the heart is part of an extensive vascular system covered by functionally active endothelium
- Endothelial dysfunction results from:
  - The deposition of amyloidogenic light chains as fibrils in vessel walls disrupts vascular architecture and impair tissue perfusion.
  - Circulating light chains → oxidative stress

Clinical manifestations of vascular amyloidosis

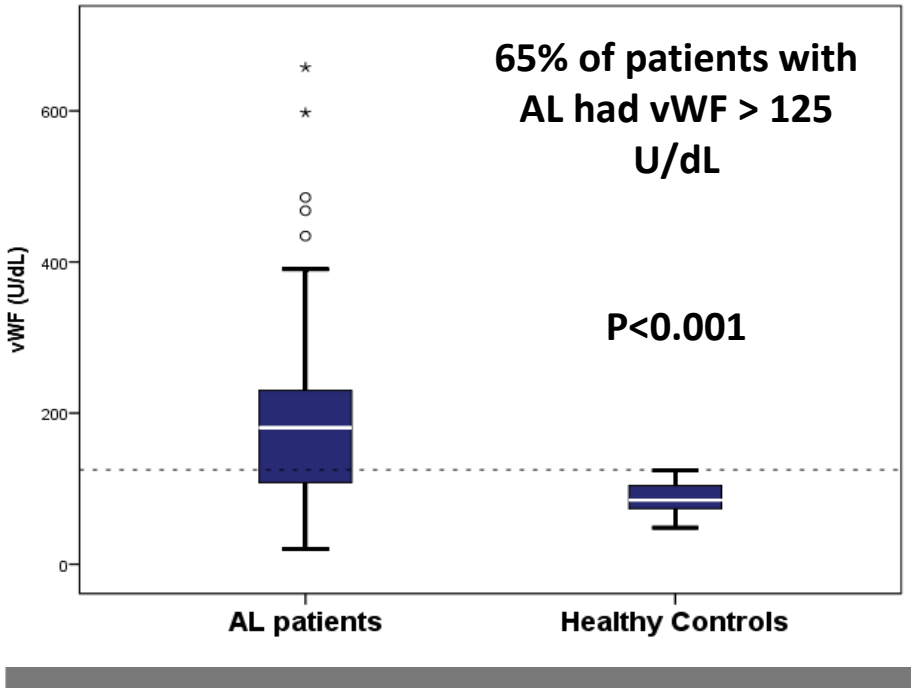


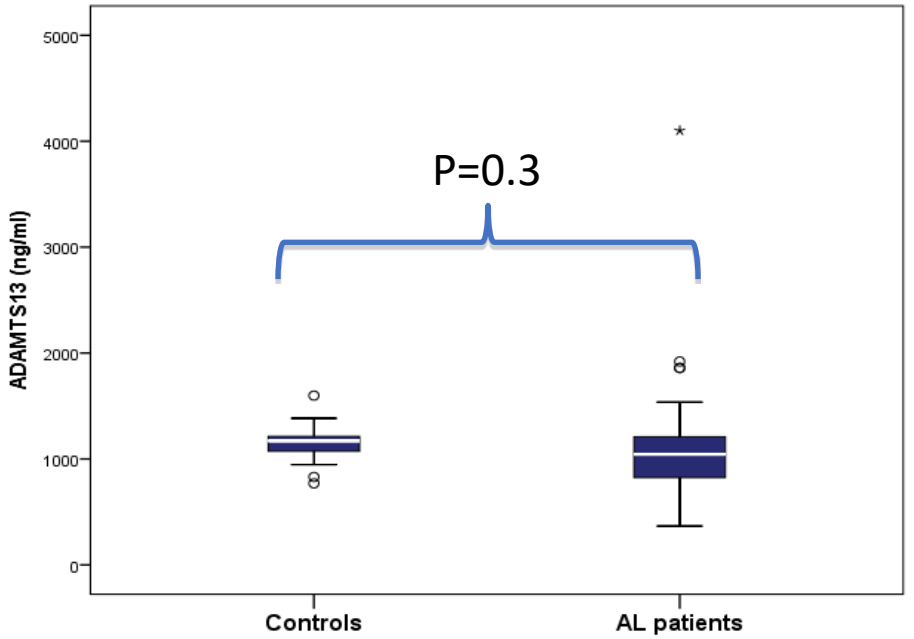
Gertz. JAMA. 2020. Adapted from Muchtar. J Intern Med. 2021.

Slide credit: clinicaloptions.com

Elevated von Willebrand factor antigen is a marker of endothelial activation in AL amyloidosis.

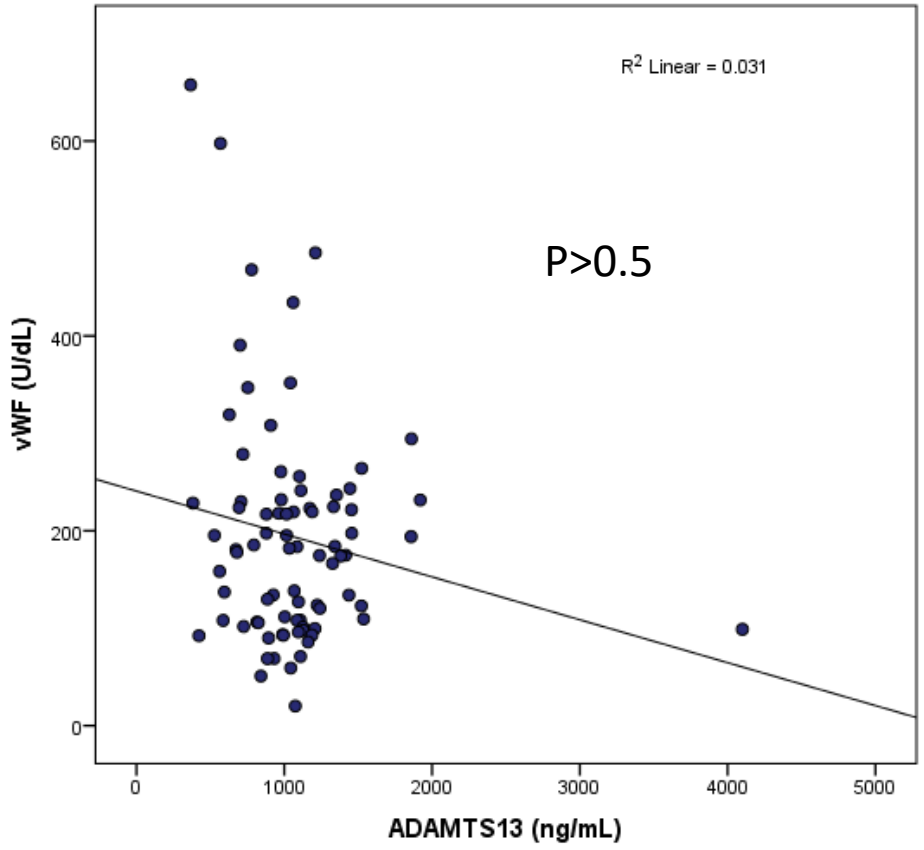
	AL patients (N=111)	Healthy controls (N=40)
vWF (median / range) (U/dL)	181 (20-657)	84 (48-124)
ADAMTS-13 (median / range) (ng/ml)	1044 (770-1600)	1170 (770-1600)





Kastritis E et al Blood 2016.

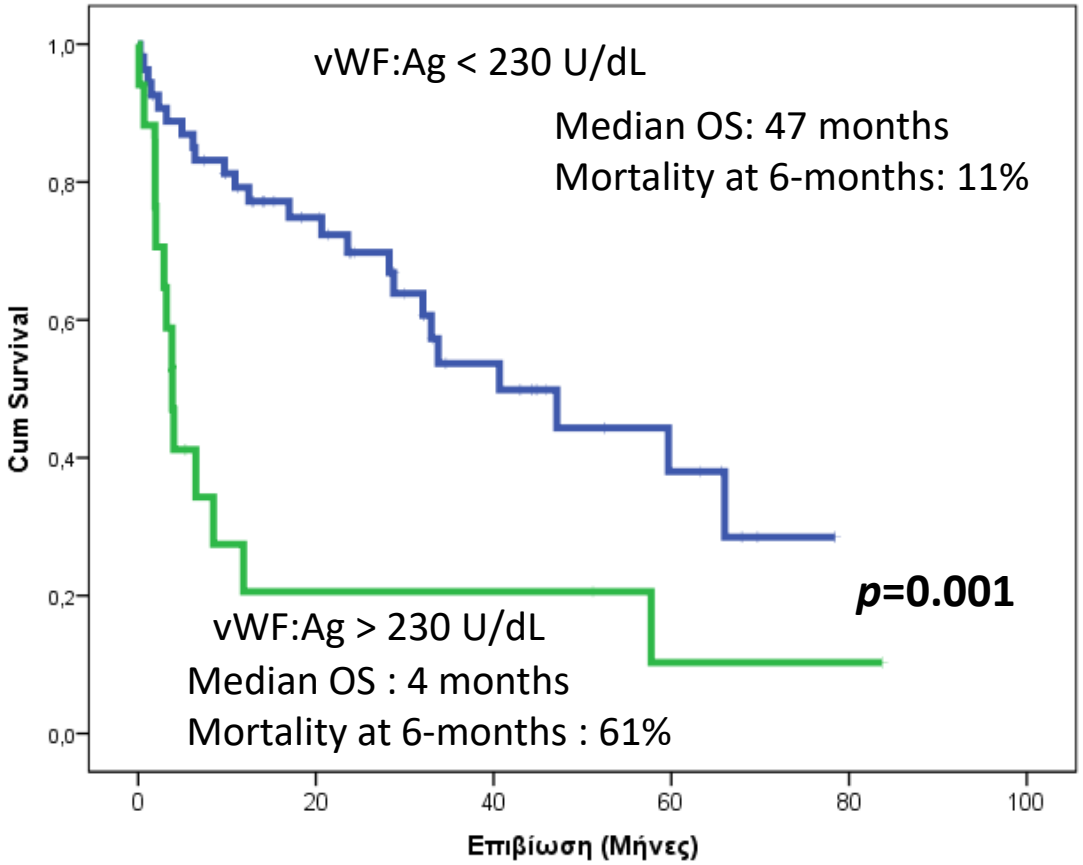
No correlation was found between vWF:Ag and ADAMTS-13 levels



Kastritis E et al Blood 2016.

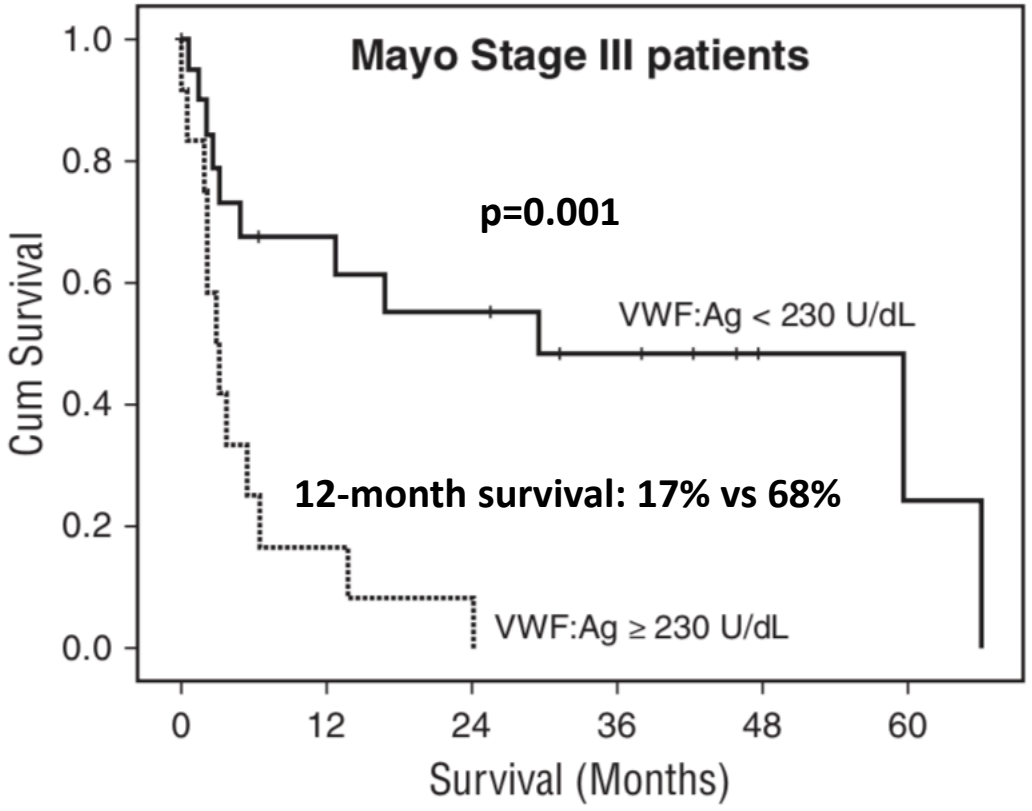
vWF levels in AL amyloidosis

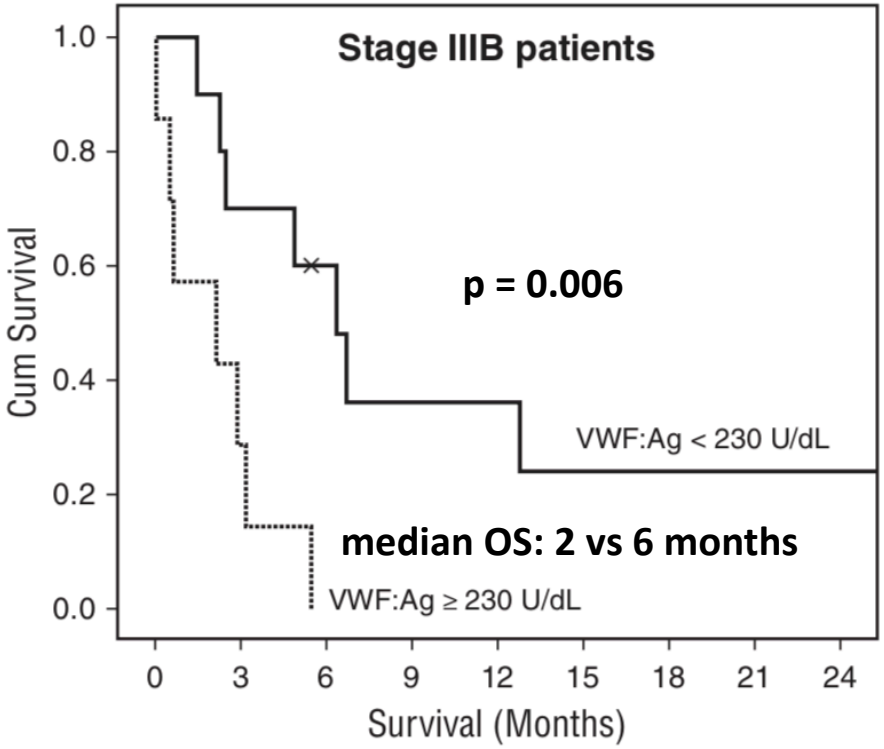
- Elevated levels of serum vWF:Ag (≥ 230 U/dL) were associated with inferior survival and with higher rates of early mortality at 6 months (11% vs 61%, p= 0.001)



Kastritis E et al Blood 2016.

Among patients with Mayo stage III or stage IIIB (that is stage III with NTproBNP > 8500 pg/mL) disease, VWF:Ag identified subgroups of patients with very poor outcome.





Kastritis E et al Blood 2016.

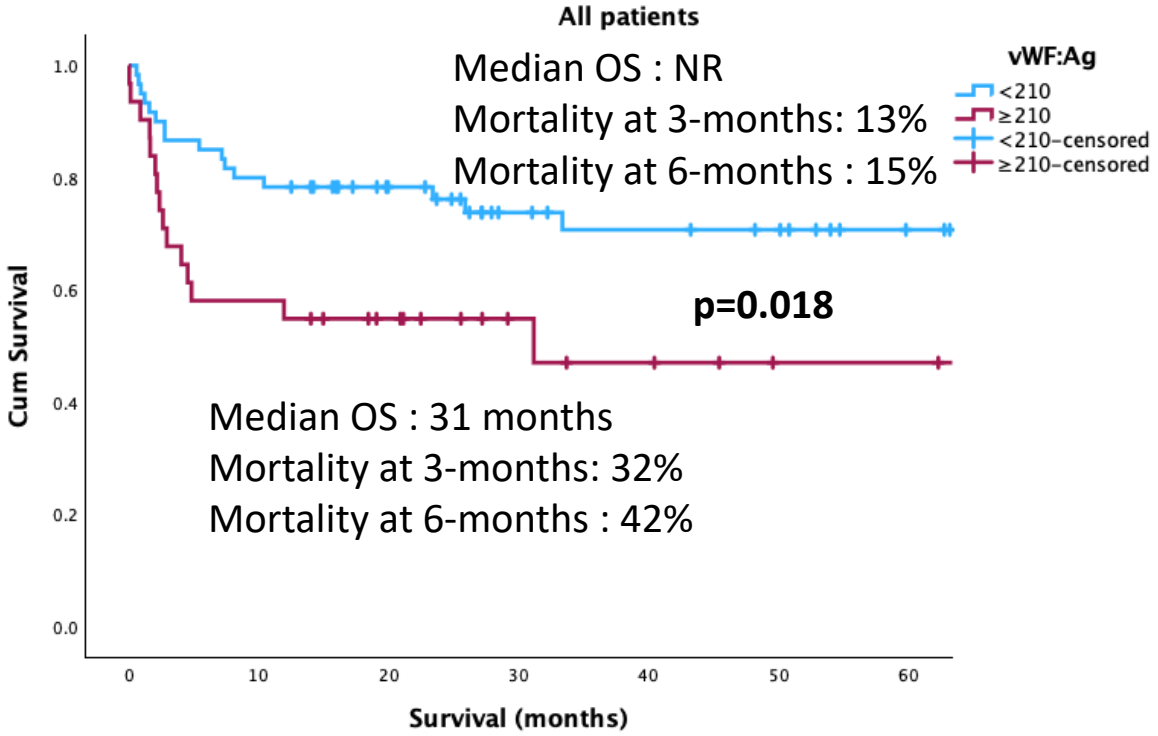
vWF levels in AL amyloidosis

- In order to validate the prognostic role of vWF in patients with AL amyloidosis treated in the modern era we analyzed the data of patients that received daratumumab-based therapies.
- Median serum levels of vWF:Ag was 201 U/dL (range 70-1151 U/dL)
- There was no association with Mayo stage or heart involvement or clonal markers (iFLC, BMPC infiltration).

Theodorakakou F et al ASH 2025

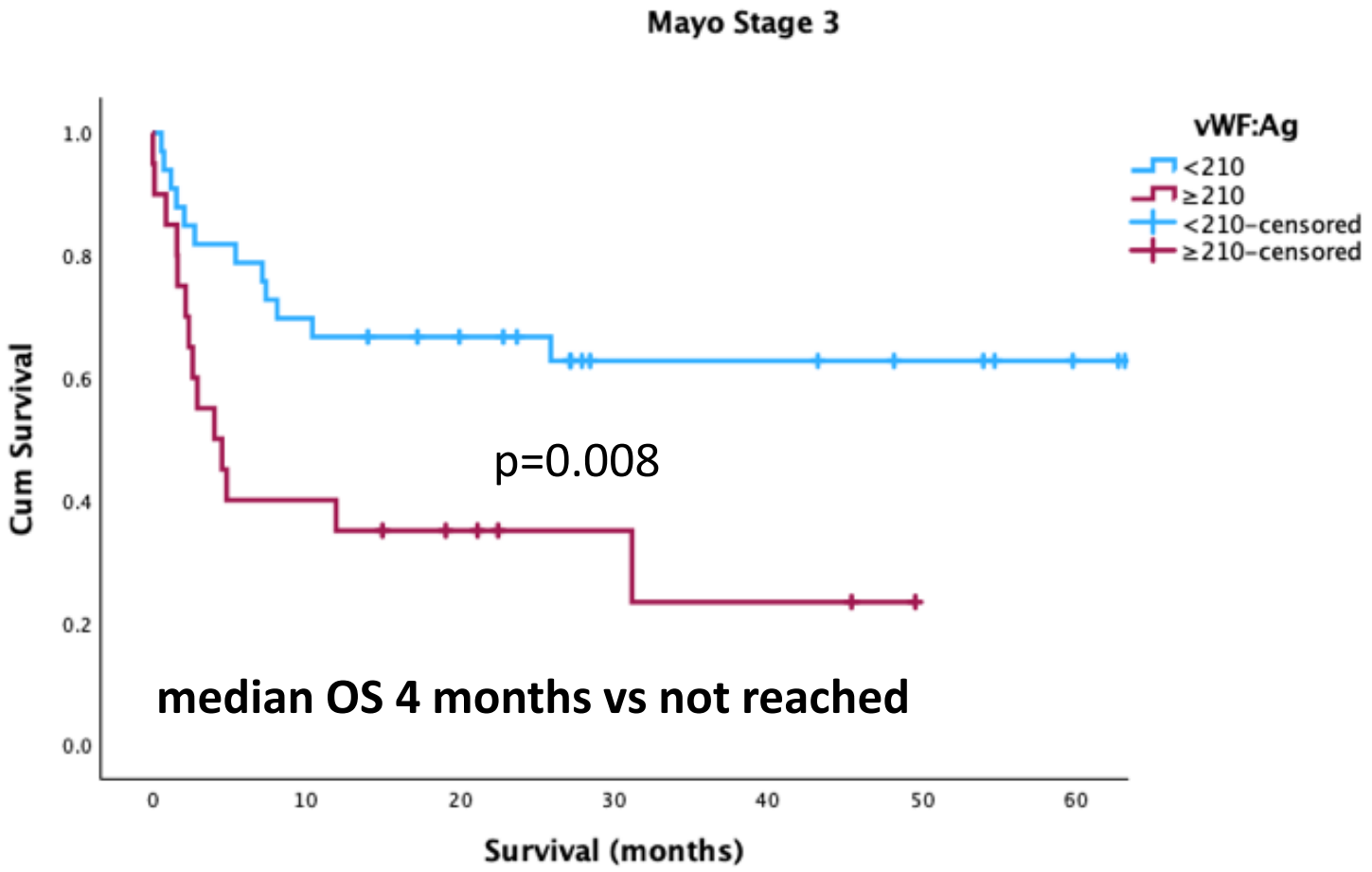
Among patients treated with daratumumab elevated vWF:Ag was associated with higher rates of early mortality

- Patients with vWF:Ag ≥210 U/dL had 3-month mortality of 32% vs 13% for vWF:Ag <210 U/dL (p=0.032) and 6-month mortality of 42% vs 15% (p=0.004).
- Median OS for pts with vWF:Ag ≥ 210 U/dL was 31 months but was not reached for vWF:Ag <210U/dl (p=0.018).



Theodorakakou F et al ASH 2025

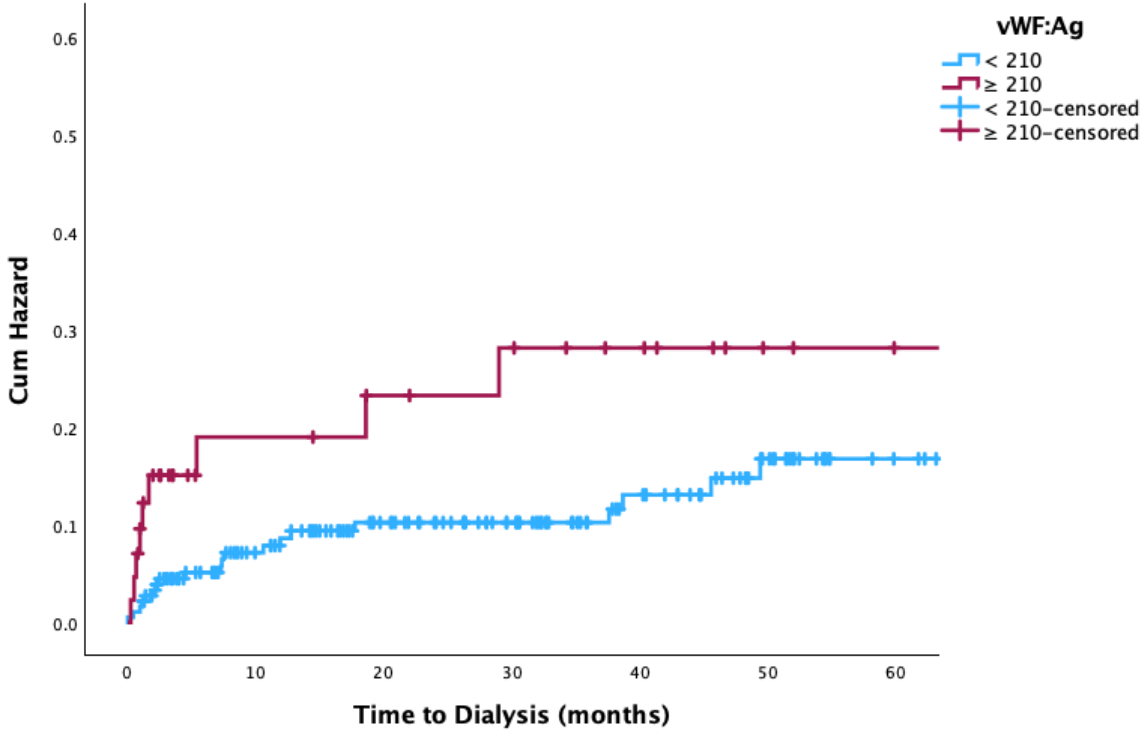
Among Dara-treated patients with Mayo stage 3, those with vWF:Ag ≥ 210 U/dL had significantly worse outcome



Theodorakakou F et al ASH 2025

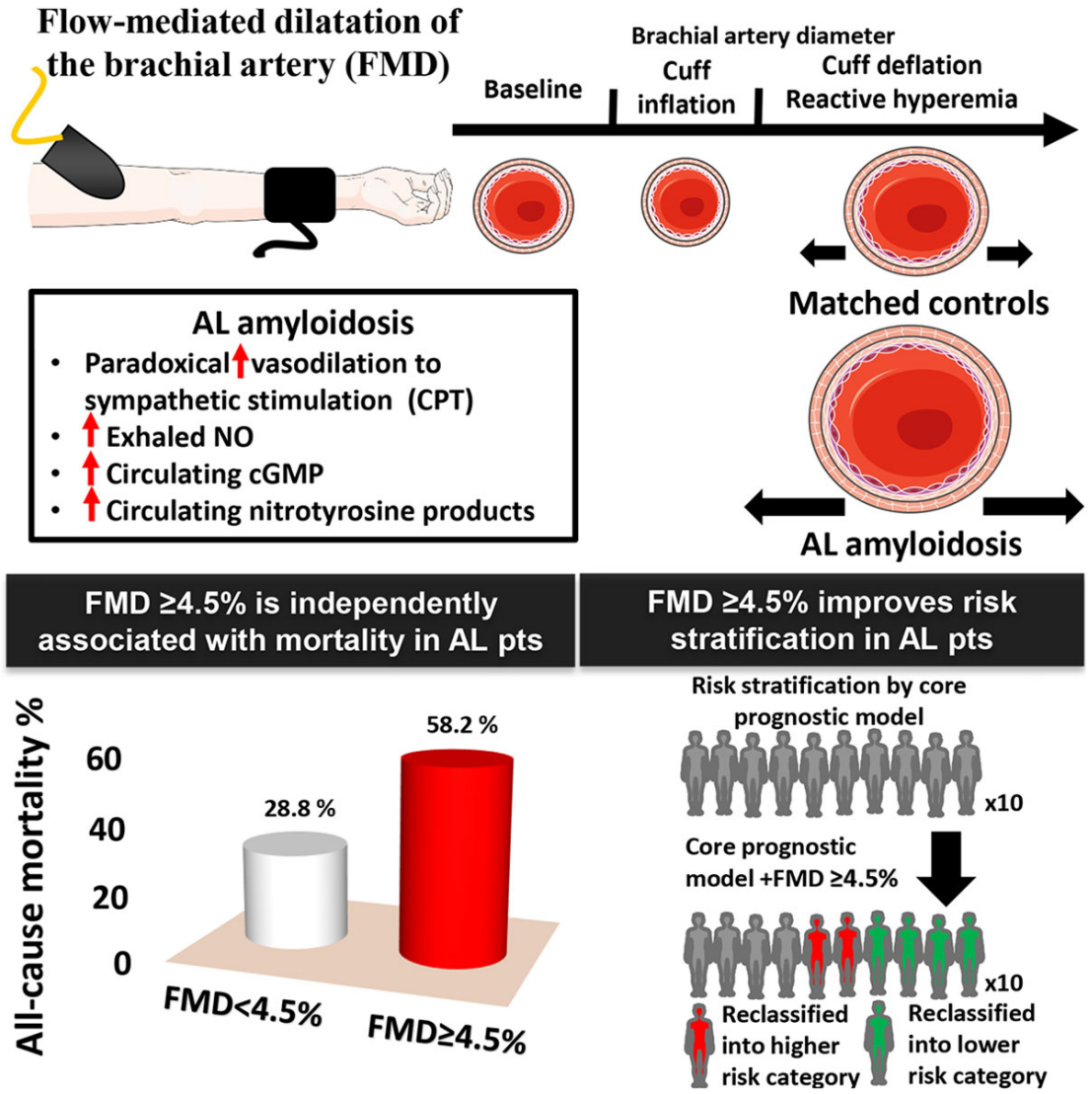
Renal outcomes

- Endothelial dysfunction may also be related to renal dysfunction, so we also evaluated renal outcomes.
- Patients with vWF:Ag ≥ 210 U/dl had a 2-year dialysis rate of 35% vs 6%
- Increased risk of progression to dialysis (HR 7.44, 95% CI 1.34-41.34, p=0.022).



Theodorakakou F et al ASH 2025

Reactive Vasodilation Predicts Mortality in Primary Systemic Light-Chain Amyloidosis



Stamatelopoulos et al 2019

Take home messages

- Endothelial dysfunction is a recognized complication in WM, mediated by **direct cellular interaction in the bone marrow microenvironment, physicochemical properties of circulating monoclonal IgM and immune-mediated mechanism of circulating monoclonal IgM**
- In AL amyloidosis **amyloid deposits and light chain toxicity induce direct endothelial injury**
- vWF:Ag is elevated in both WM and AL suggesting endothelial activation and dysfunction
- High vWF:Ag levels is an adverse prognostic factor for WM patients and a strong predictor of early mortality for AL amyloidosis patients independently of cardiac involvement.

Thank you