GFEV | GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES

Angio-Behçet

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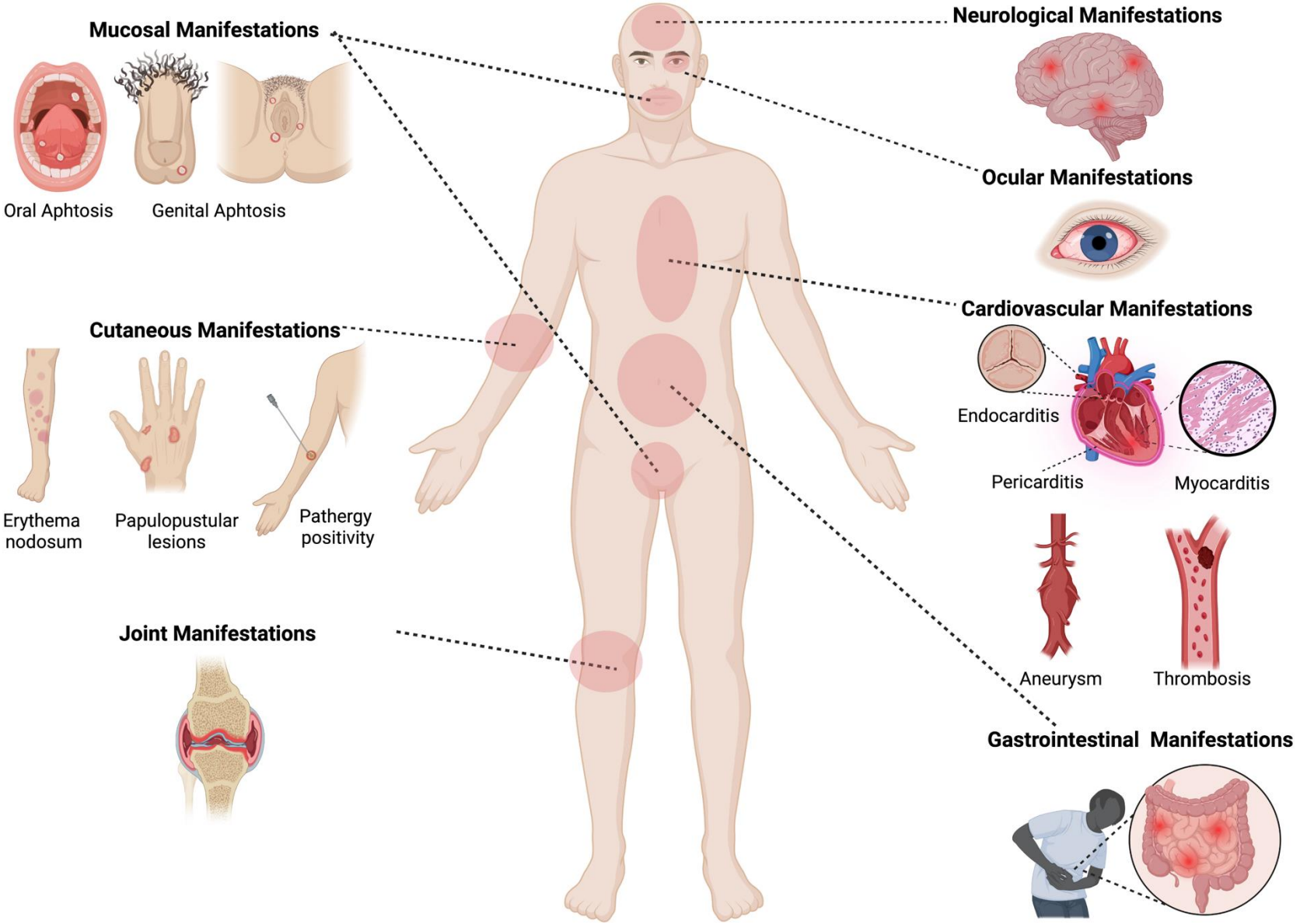
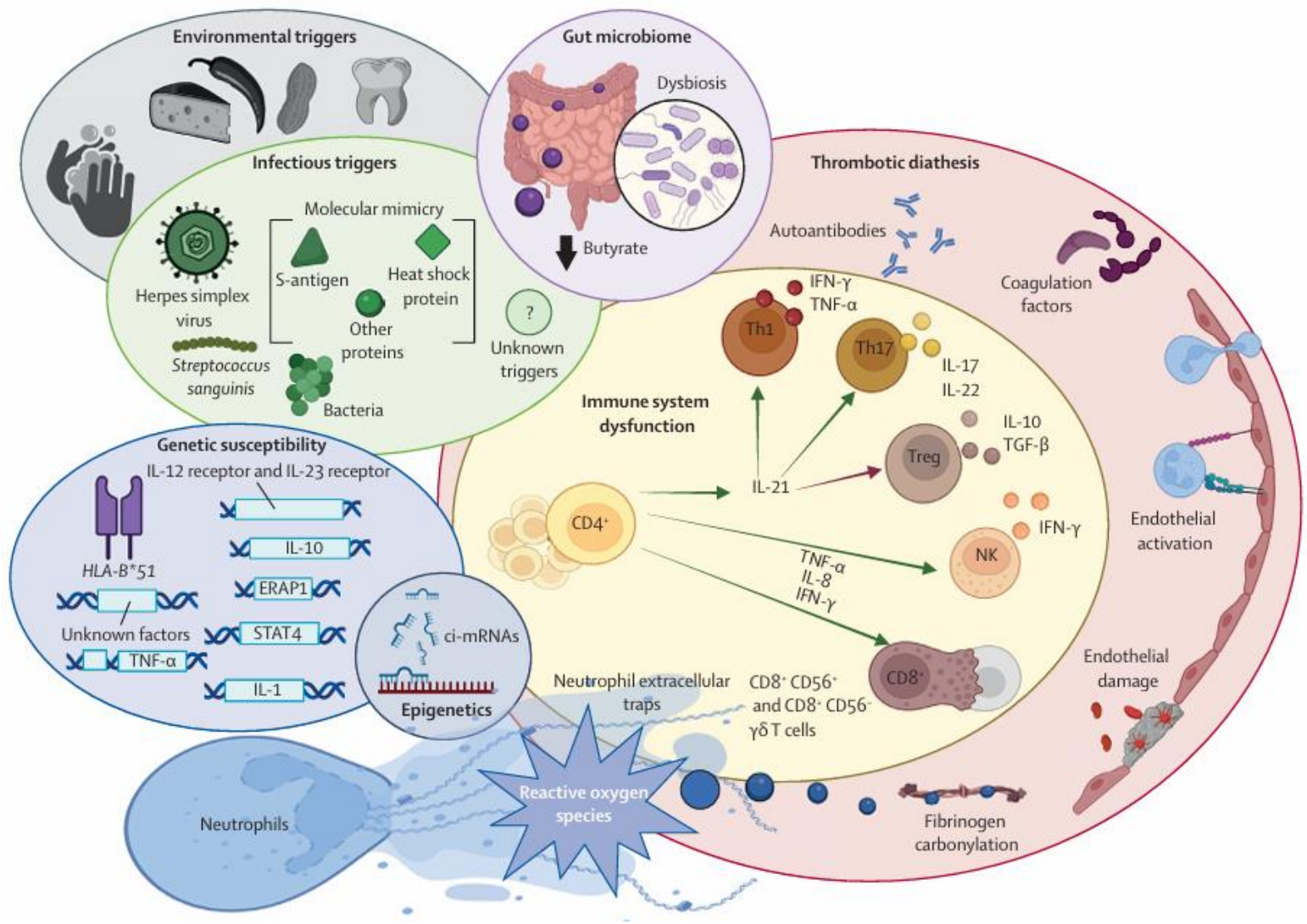
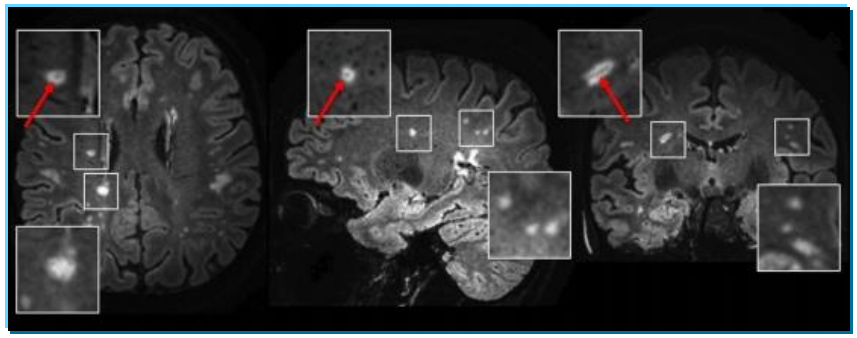
Overview on Behçet syndrome and its vascular involvement

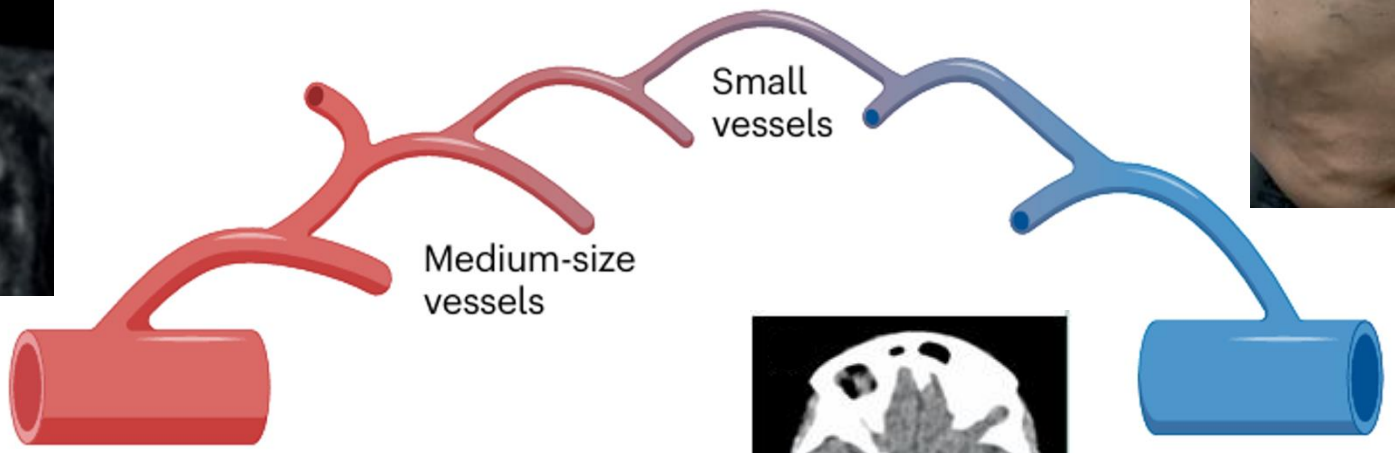


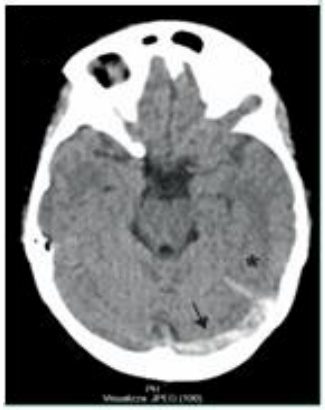
Emmi G, et al. *The Lancet*. 2024



Emmi G, et al *The Lancet*. 2024







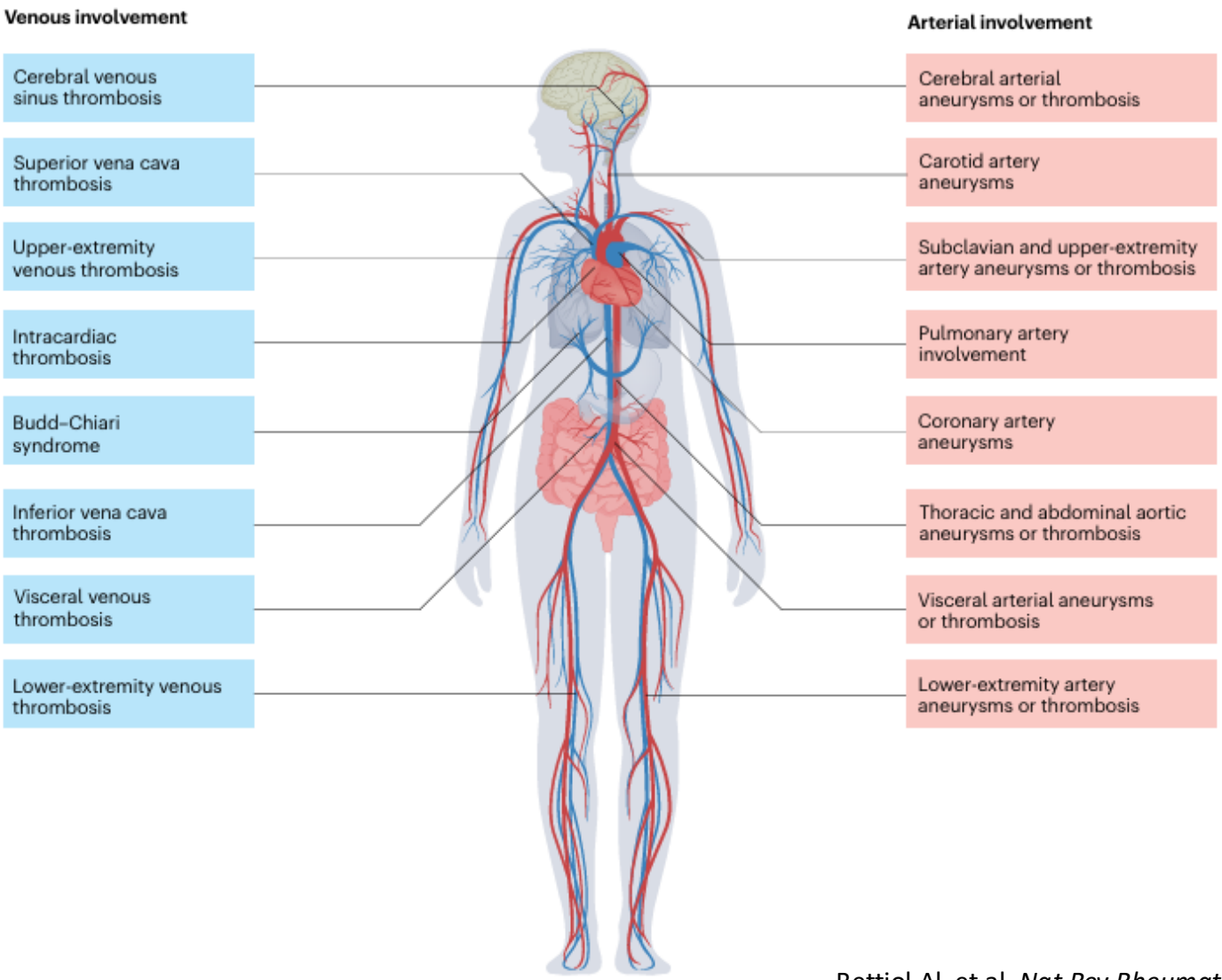
Jennette JC et al. *Arthritis Rheum*. 2013 (modified)

General features of vascular Behçet

- Vascular Behçet is more frequent and runs a severe course in the **young population, particularly among males**
- Vascular Behçet occurs early with 3/4 of the patients experiencing their first event **within the 5 years of disease onset**
- Vascular Behçet may develop **before or simultaneously with the characteristic skin-mucosa lesions** in about 1/3 of the patients
- The **vascular disease course is invariably relapsing**, and may occur at the primary site or at another vascular territory
- The vascular phenotype might be accompanied by **fever, a high acute phase response and constitutional symptoms**

Melikoglu M, et al. Clin Rev Allergy Immunol. 2008
Tascilar K, et al. *Rheumatology (Oxford).* 2014
Bettiol Al, et al. *Nat Rev Rheumatol*. 2023

Prevalence of thrombosis ranges from 15% to 40% of patients with Behçet syndrome



Bettiol Al, et al. *Nat Rev Rheumatol*. 2022

Venous thrombosis

Deep vein venous thrombosis is the main clinical vascular involvement (75%)

Superficial vein thrombosis is a characteristic feature of BS and should be considered a risk factor for the development of future vascular events. It may be a complication of venipuncture

Deep vein thrombosis is frequently the **first vascular event**, and may be later followed by arterial manifestations

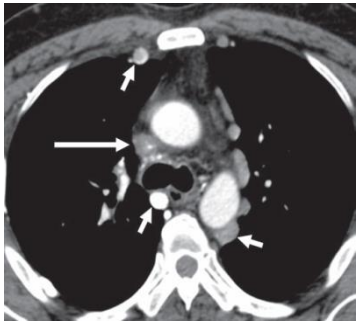
Bettiol Al, et al. *Nat Rev Rheumatol*. 2023

Seyahi E. *Best Pract Res Clin Rheumatol*. 2016

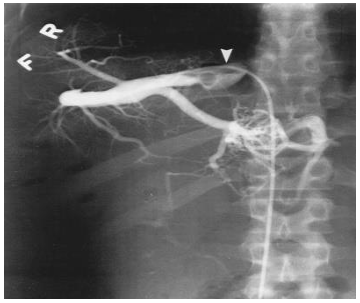
Severe post-thrombotic syndrome may develop in half the cases

Tascilar K, et al. *Rheumatology (Oxford).* 2015

Venous thrombosis at atypical sites



Superior and Inferior Vena Cava thrombosis make up 9% and 4% of all vascular complications and is sometimes associated with thrombosis of other sites



Budd-Chiari Syndrome is associated with a significant mortality rate

Cerebral Venous Thrombosis develop in about 5% of patients and in about 10 to 20% of patients with neuro-Behçet

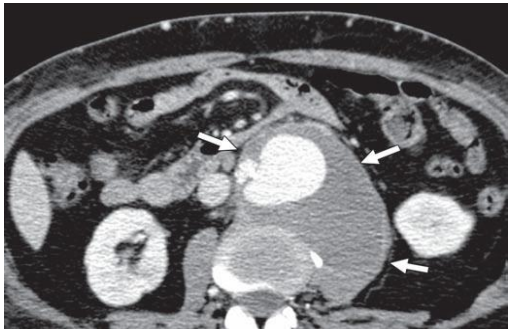
Bettiol Al, et al. *Nat Rev Rheumatol*. 2023

Seyahi E. *Best Pract Res Clin Rheumatol*. 2016

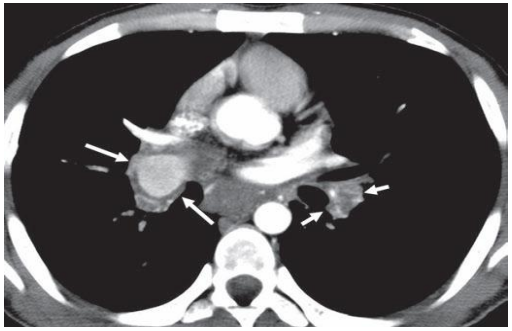
Aneurysms and Pseudoaneurysms

Arterial involvement makes up **20-25%** of all vascular complications of BS, with **aneurysms and pseudoaneurysms being the main arterial manifestations**

The long-term outcome of arterial lesions in BS is poor, especially in the case of occlusive lesions and associated venous involvement involvement



Abdominal aorta is the most common site of aneurysms formation



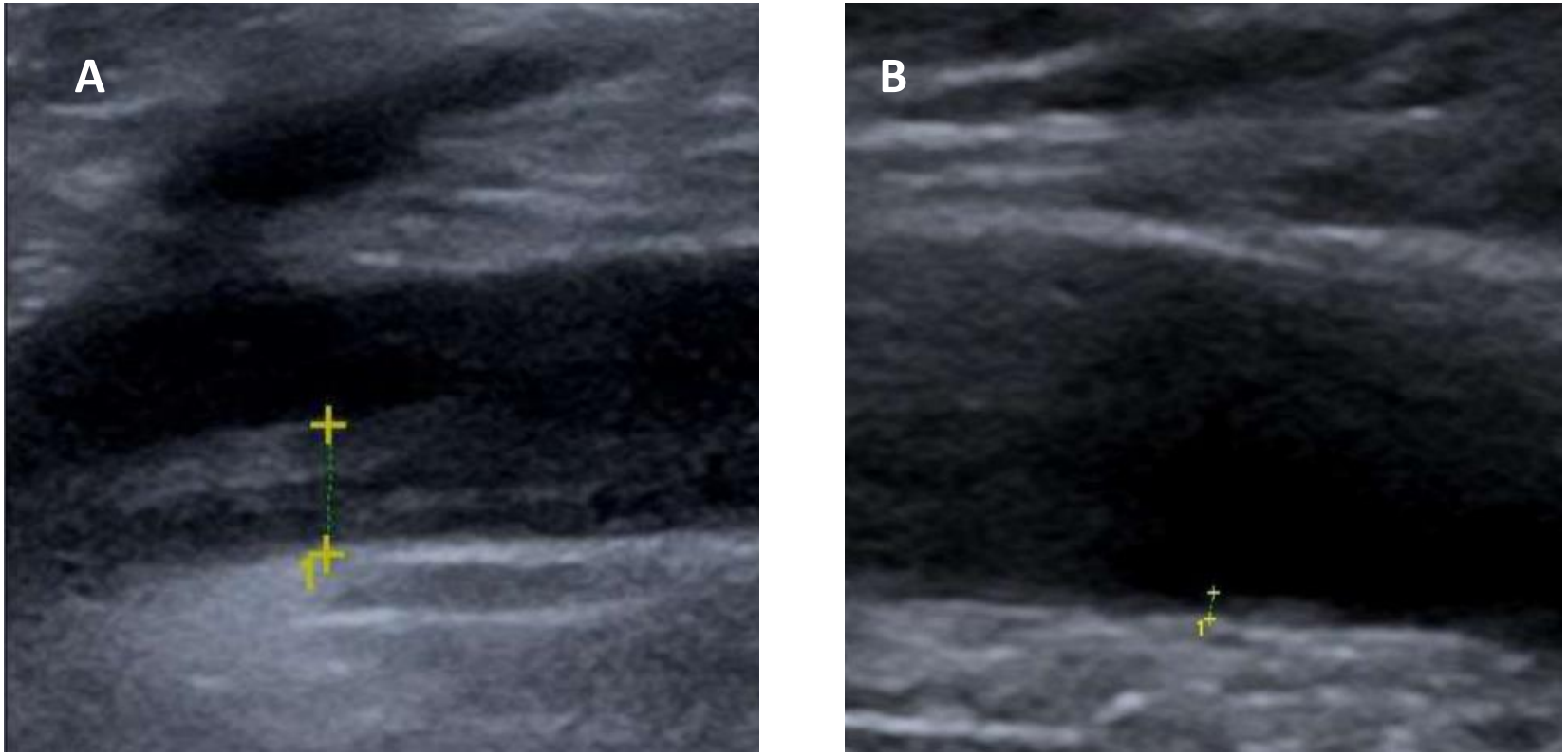
In BS both aneurysms (pulmonary artery aneurysms, PAAs) and occlusions may occur

Saadoun D, et al. *Medicine (Baltimore).* 2012

Seyahi E. *Best Pract Res Clin Rheumatol*. 2016

Emmi G, et al. *Intern Emerg Med*. 2018

Vein wall thickness in patients with Behçet's syndrome

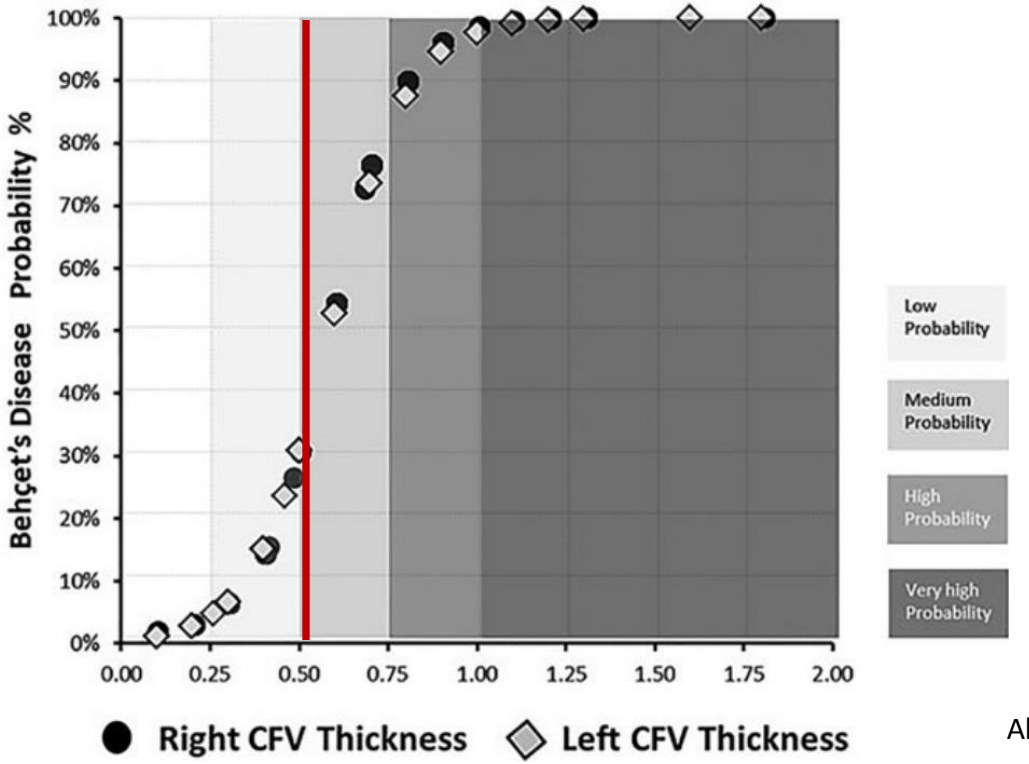


B-mode ultrasound image of a left common femoral vein on a longitudinal plane showing posterior wall vein wall thickness measurement in a patient with Behçet with chronic thrombotic changes (**A**) and without vascular involvement (**B**) [cut-off value of 0.5 mm]

Seyhai E, et al. J Vasc Surg Venous Lymphat Disord. 2019

	Behçet's disease (−), *n* (%)	Behçet's disease (+), *n* (%)
Right CFV thickness		
<0.25 mm	31 (15.7)	3 (1.9)
0.25–0.50 mm	130 (65.7)	11 (7.2)
0.50–0.75 mm	34 (17.2)	50 (32.9)
0.75–1.00 mm	3 (1.5)	71 (46.7)
≥1.00 mm	0 (0.0)	17 (11.1)
Left CFV thickness		
<0.25 mm	46 (23.2)	4 (2.6)
0.25–0.50 mm	110 (55.6)	10 (6.6)
0.50–0.75 mm	39 (19.7)	46 (30.3)
0.75–1.00 mm	2 (1.0)	70 (46.05)
≥1.00 mm	1 (0.5)	22 (14.52)

CFV: common femoral vein.



Increased CFV thickness is a distinctive feature of BS, and **can be a diagnostic tool for BS** with sensitivity and specificity rates higher than 80% for the cut-off value 0.5 mm

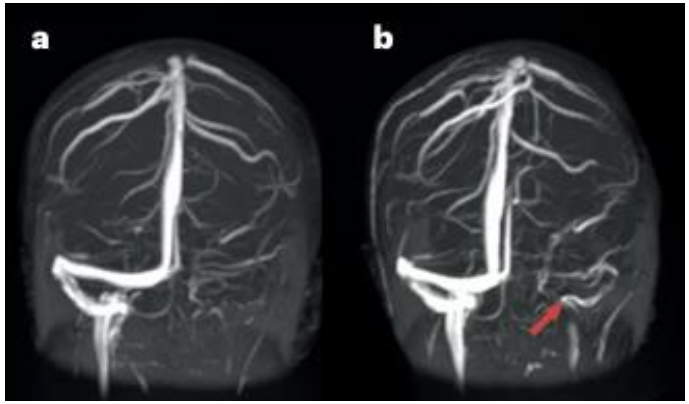
Alibaz-Oner F, et al *Rheumatology (Oxford)* 2021

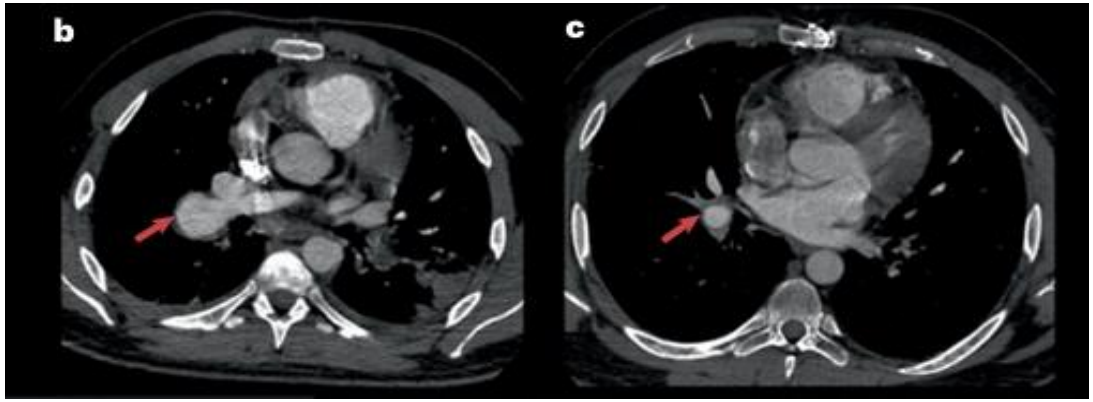
Treatment of vascular events

2025 EULAR Update on the management of Behçet Syndrome

«*For the management of acute thrombosis of deep veins, including cerebral venous sinuses, glucocorticoids and immunosuppressives, preferably monoclonal anti-TNF-antibodies, should be considered*. Immunosuppressives should be continued as maintenance»

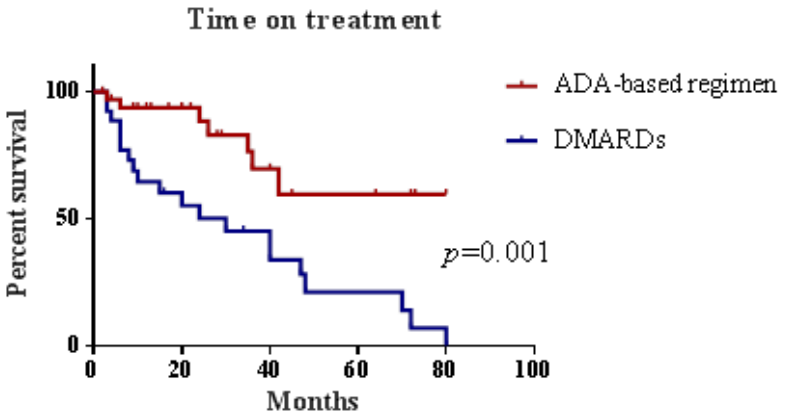
«*Anticoagulants may be added*, provided the risk of bleeding is low, and coexistent pulmonary artery aneurysms are ruled out».



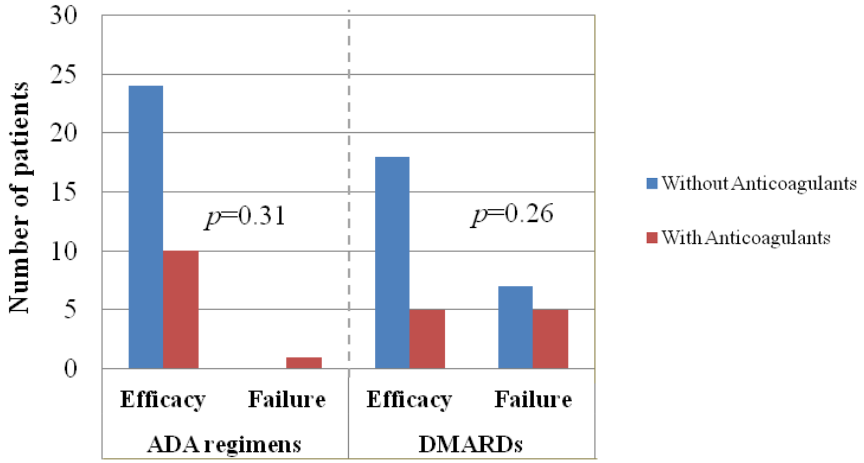


Hatemi G, et al. *manuscript in preparation*

Anti-TNF monoclonal antibodies for DVT in Behçet Syndrome

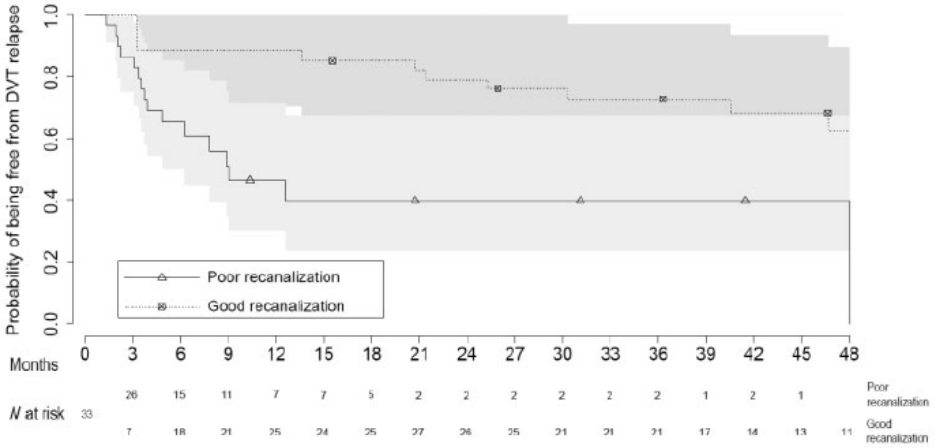


ADA-based regimen induced clinical and imaging improvement of DVT more frequently (p=0.001) and rapidly (p<0.0001) than DMARDs



Emmi G, et al *Arthritis Rheumatol* 2018

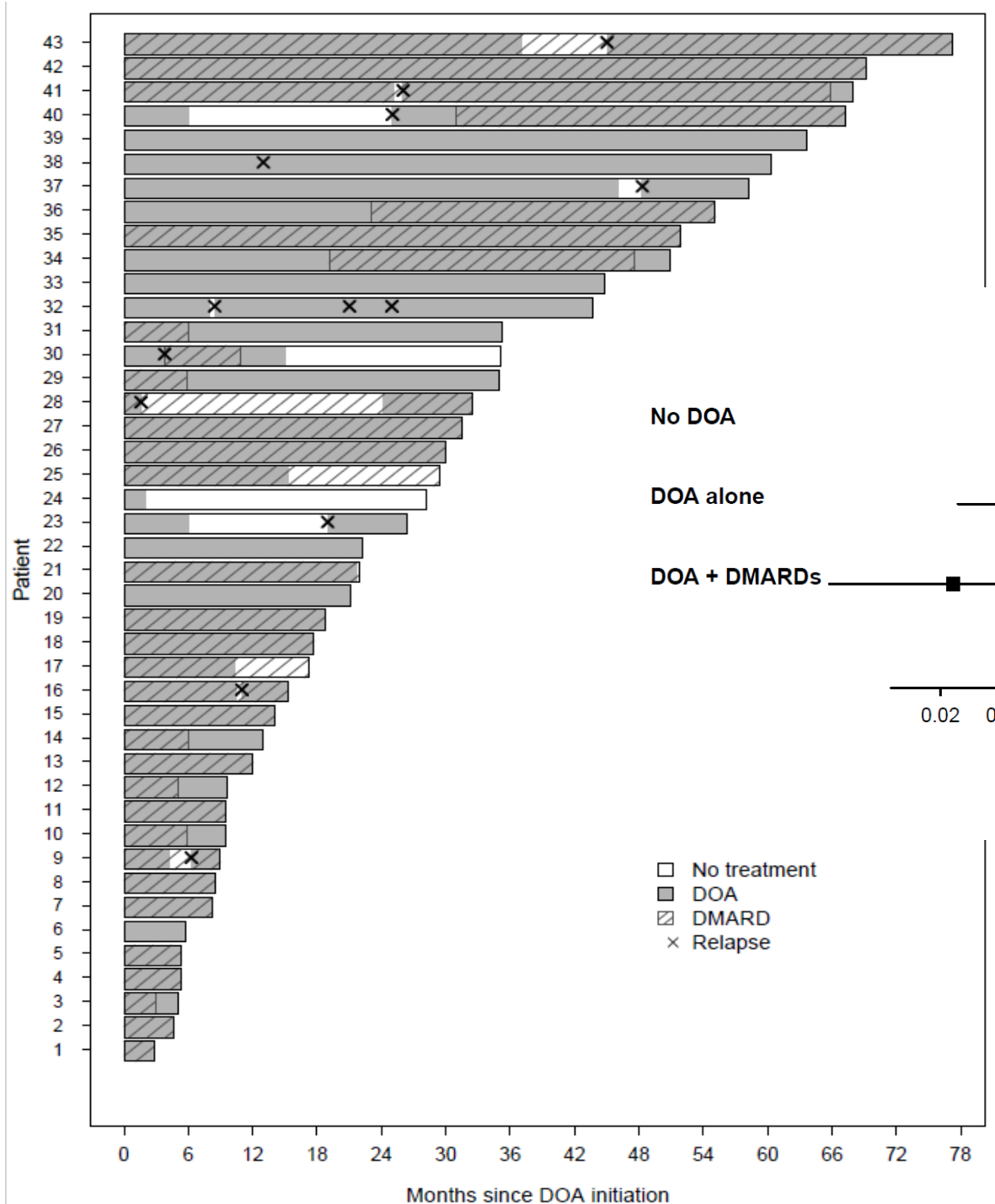
Relapse rate for DVT

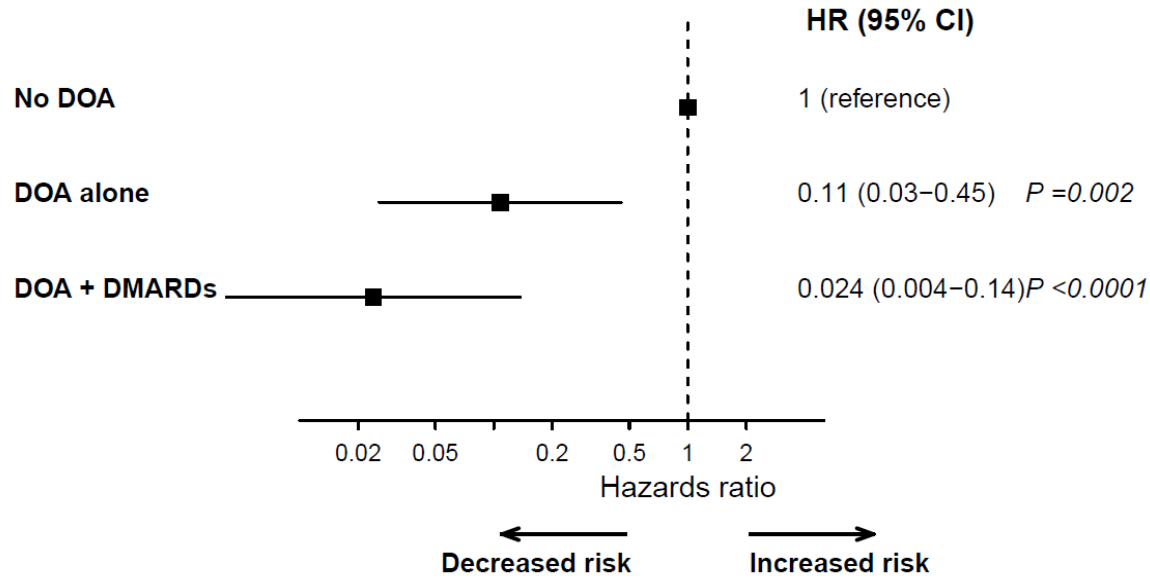


The relapse rate for DVT was high despite AZA treatment. IFN-alpha seemed to be a promising agent for preventing DVT relapses and achieving good recanalization

Ozguler Y, et al *Rheumatology* (Oxford) 2019

Direct oral anticoagulant for prevention of venous thrombosis relapse in Behçet's syndrome





Vautier M, *Autoimmun Rev*. 2020

Infliximab versus Cyclophosphamide for Severe Behçet's Syndrome

Table 2. Primary and Secondary Outcomes at Week 22.*

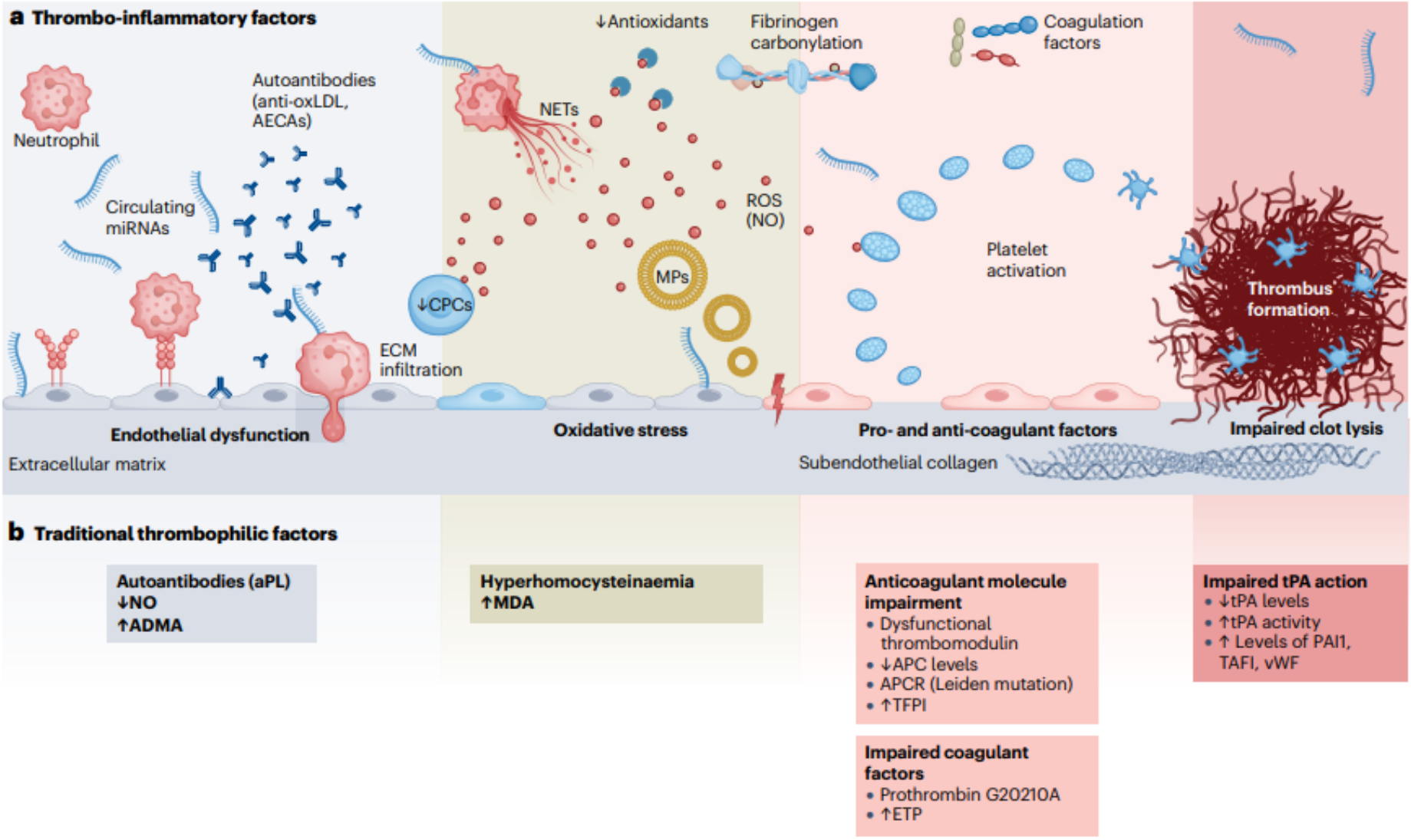
Outcome	Cyclophosphamide (n=25)	Infliximab (n=27)	Estimated difference (95% CrI)
Primary Outcome			
Overall complete response	14/25 (56)	22/27 (81)	29.8 (6.6 to 51.7)
Main Secondary Outcomes			
Vascular complete response	10/18 (56)	17/19 (94)	35.2 (9.7 to 59.2)
CNS complete response	4/7 (57)	5/8 (71)	11.4 (–31.9 to 52.3)
Relapse	4 (16)	1 (4)	–12.3 (–29.6 to 4.8)
Exploratory Secondary Outcomes			
No. of patients receiving prednisone ≤0.1 mg/kg/day	23/25 (92)	23/24 (96)	3.2 (–12.2 to 19.5)
Median prednisone doses (mg/d)	8 [5 to 8]	7 [5 to 8.3]	–0.5 (–2.1 to 1.2)
Mean CRP level, mg/l	9.4 (±12.3)	4.0 (±5.4)	–5.3 (–10.6 to –0.1)
Behçet's Disease Current Activity Form index	0 [0 to 1]	0 [0 to 1]	–0.1 (–0.6 to 0.3)
Physician's Global Assessment	10 [1.8 to 23.8]	10 [3.8 to 20]	–2.7 (–15.5 to 10)
SF-36 physical scores	41 [29 to 66.7]	56 [34.4 to 67.7]	3.8 (–12.8to 20.5)
SF-36 mental scores	57.8 [37.4 to 75.9]	58.92 [35.2 to 72.3]	3.2 (–14 to 20.4)
No. of patients with AEs	16 (64)	8 (30)	–32.3 (–55.2 to –6.6)
No. of patients with serious AEs	3 (12)	4 (14.8)	2.5 (–16.8 to 21.5)

Saadoun D, et al. *NEJM Evid*. 2024

Mechanisms of thrombo-inflammation (a few)

'In a way, phlebitis dominates all pathology… The first effect of all phlebitis is coagulation of the blood and its adherence to the walls of the vessels…'

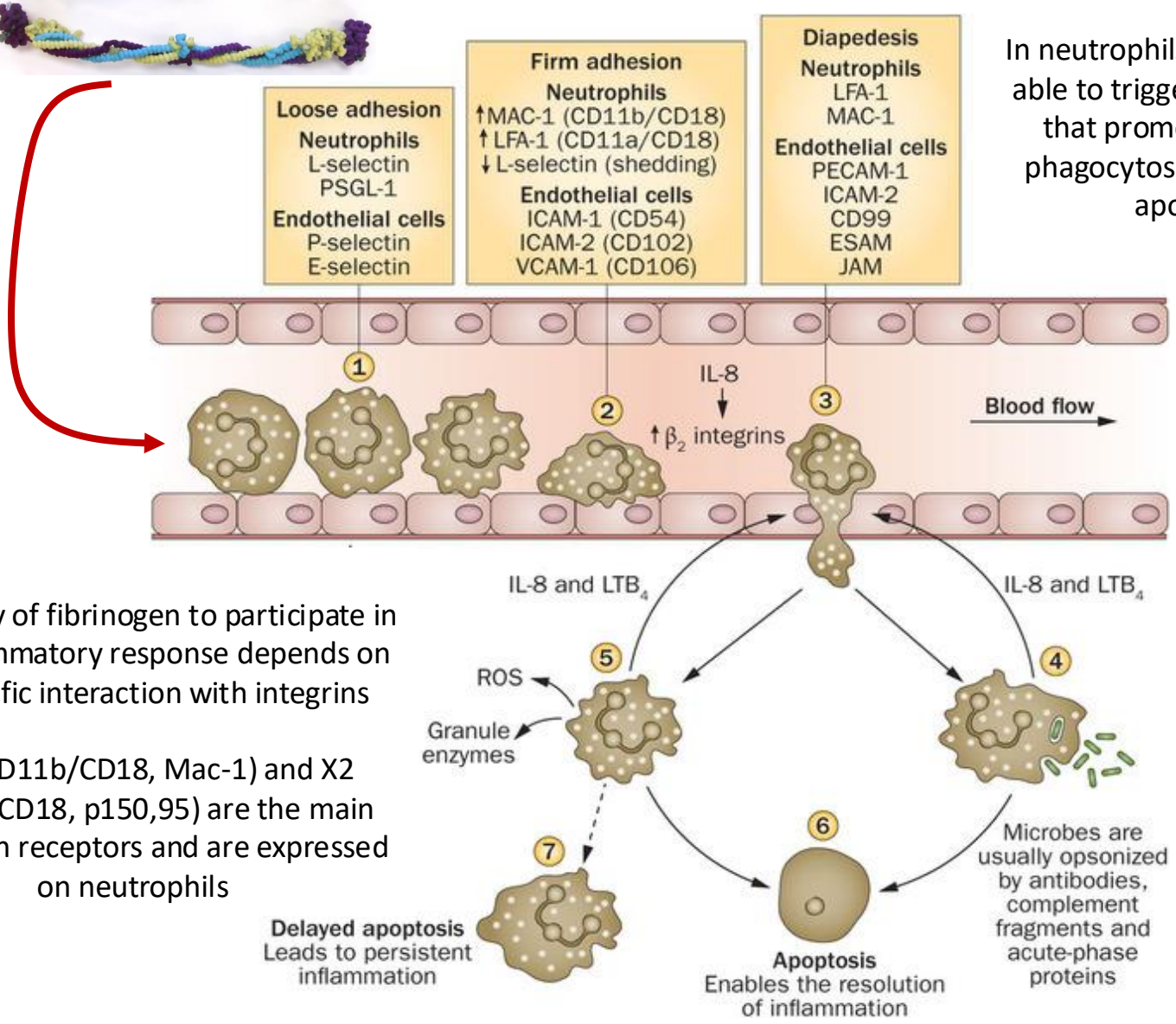
Cruveilhier J. Inflammation of the pulmonary artery and lobular pneumonia followed by phlebitis. In: Long BR, ed. Selected Readings in Pathology. London: Baillière Tindal and Cox; 1929.



Bettiol A, et al *Nat Rev Rheumatol*. 2022

Neutrophils and fibrinogen

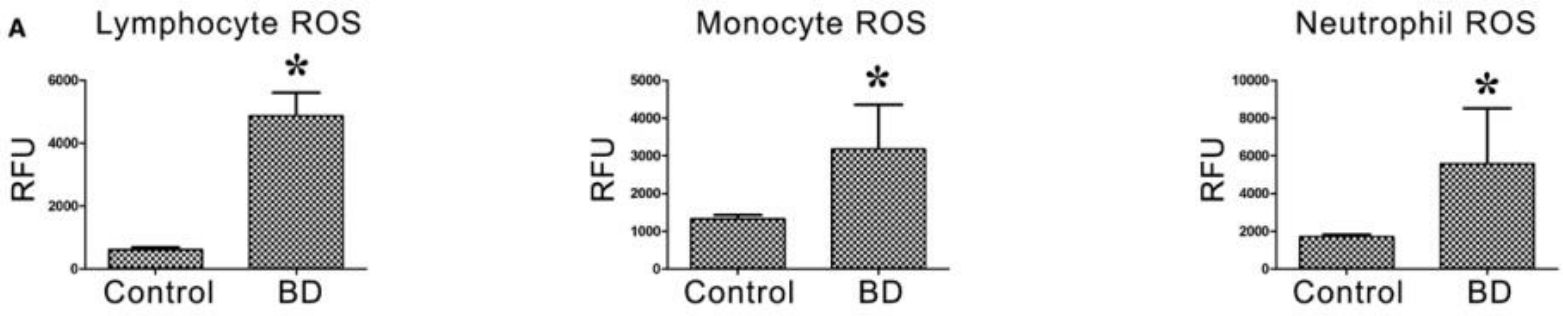
In neutrophils, soluble fibrinogen is able to trigger, an activating signal that promotes degranulation, phagocytosis enhancement, and apoptosis delay



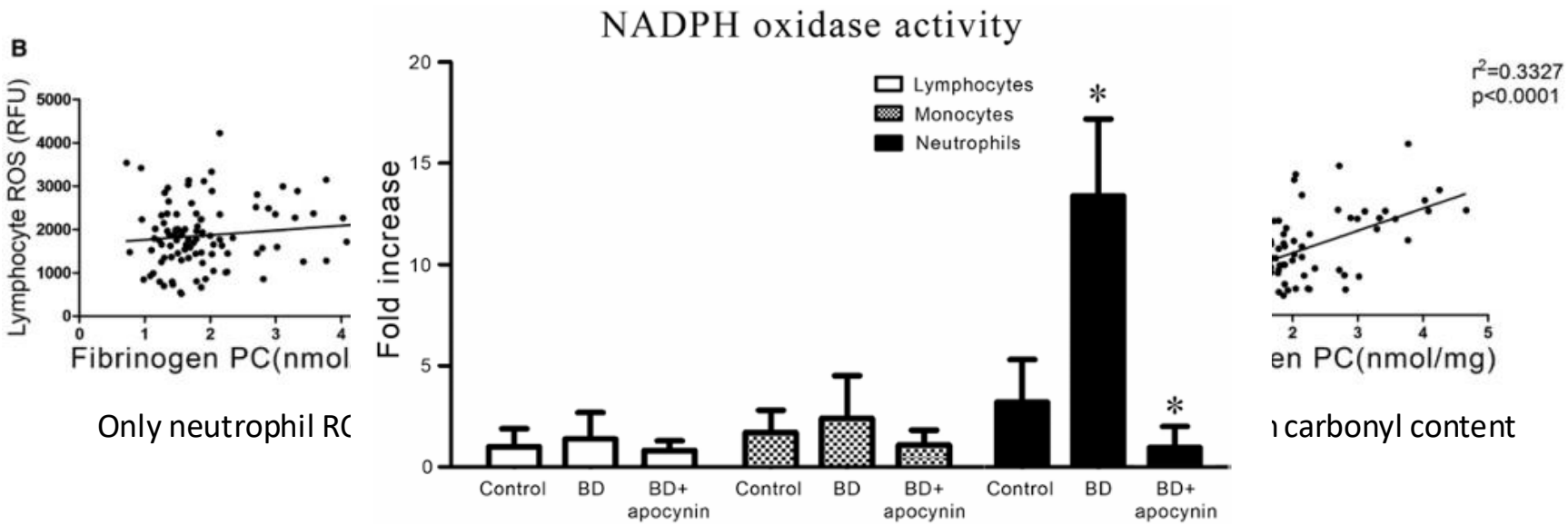
The ability of fibrinogen to participate in the inflammatory response depends on its specific interaction with integrins

M2 (CD11b/CD18, Mac-1) and X2 (CD11c/CD18, p150,95) are the main fibrinogen receptors and are expressed on neutrophils

Leucocyte ROS production and NADPH activity



ROS production in Behçet patients in lymphocyte and monocyte fractions was almost 2-fold and in neutrophils was 3-fold compared with healthy controls

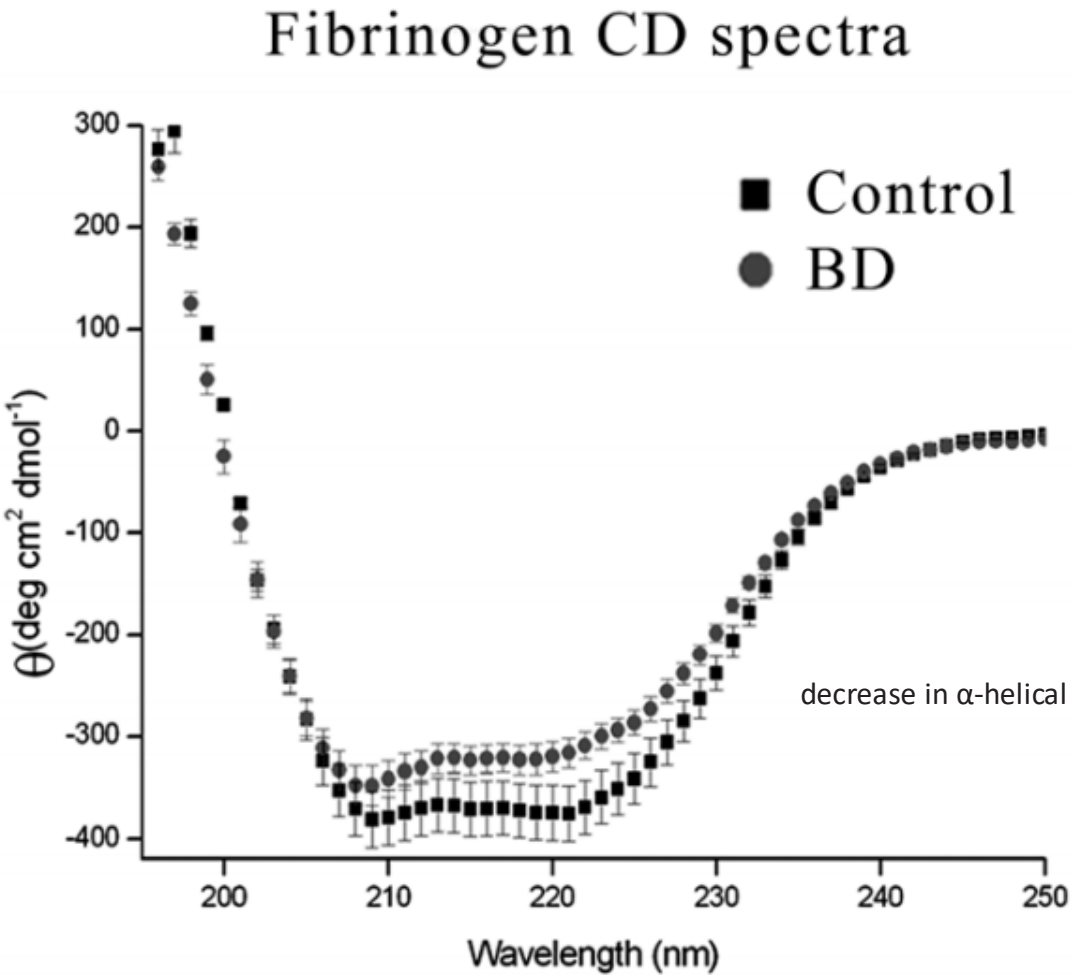


Only neutrophil RC

carbonyl content

Becatti M, et al. *Circulation* 2016

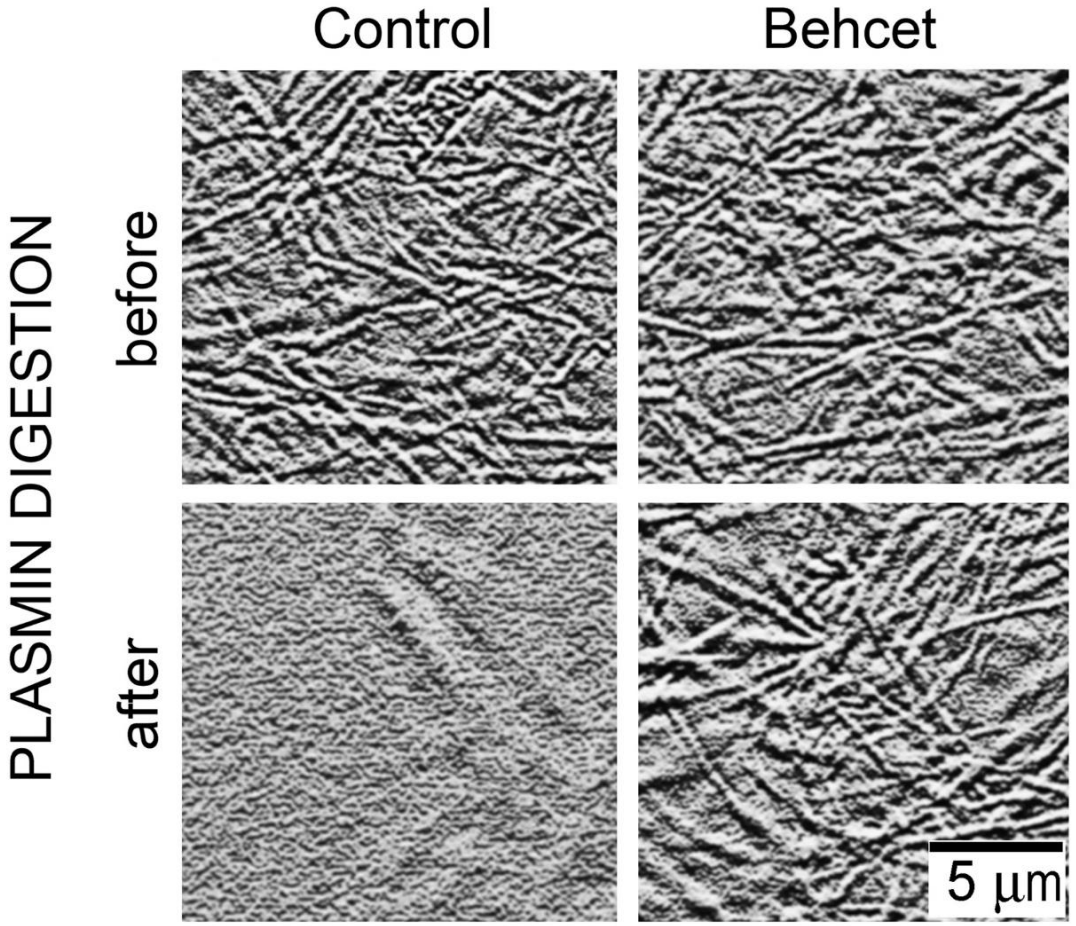
Spectroscopy analysis of fibrinogen secondary structure



decrease in α-helical content

Becatti M, et al. *Circulation*. 2016

Fibrin Susceptibility to Plasmin-Induced Lysis



Differential interference contrast microscopy

Plasmin-induced lysis in fibrin obtained from Behçet patients compared with controls is significantly impaired

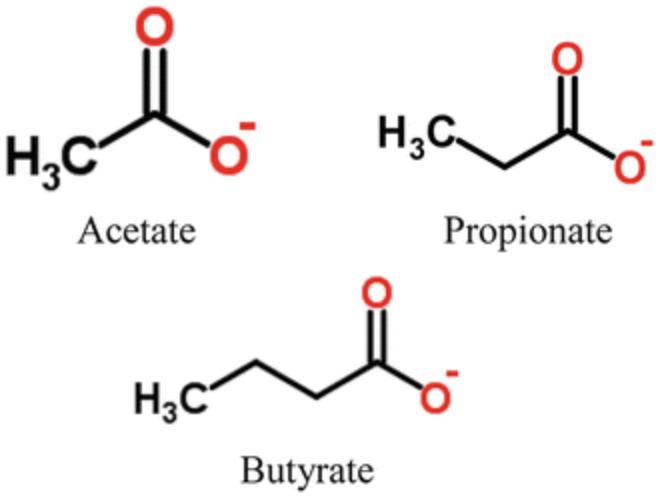
Becatti M, et al. *Circulation*. 2016

The gut microbiome in Behçet

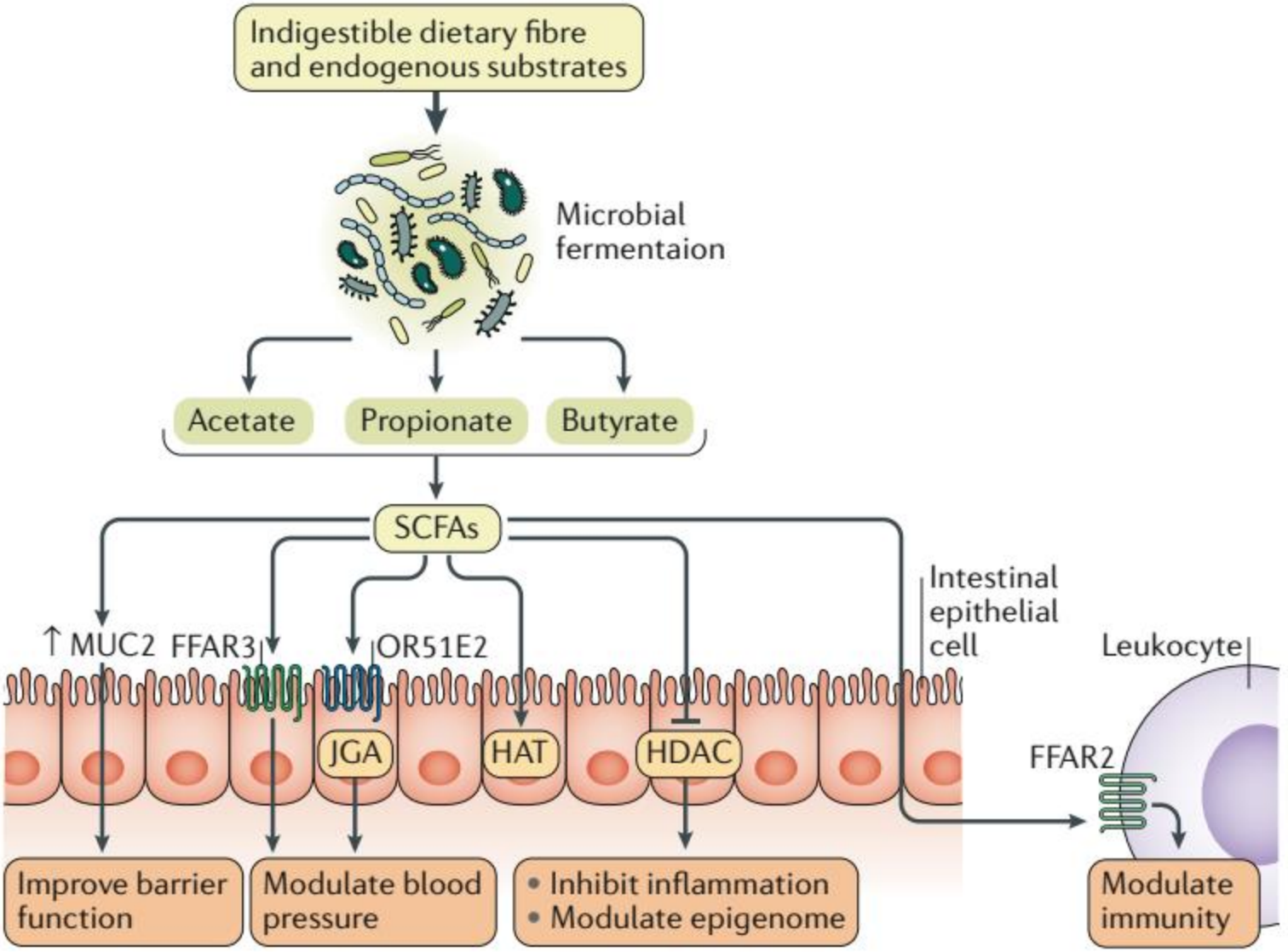
Behçet's patients have a reduced alfa-diversity as compared to healthy controls

Behçet's patients have a significant depletion of Roseburia and Subdoligranulum, (Clostridium cluster) involved in the production of butyrate

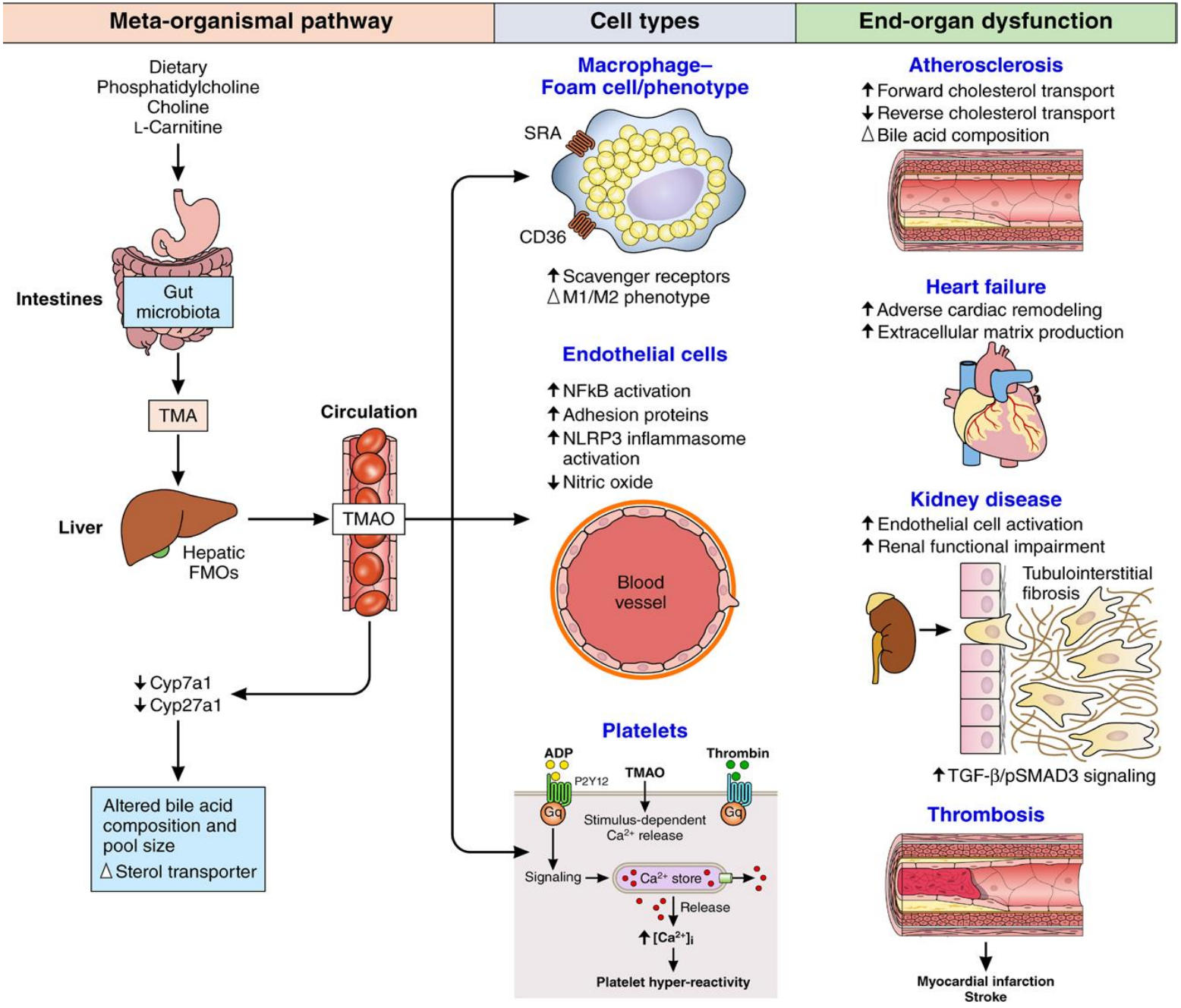
In patients with Behçet, a significant reduction in butyrate production was found



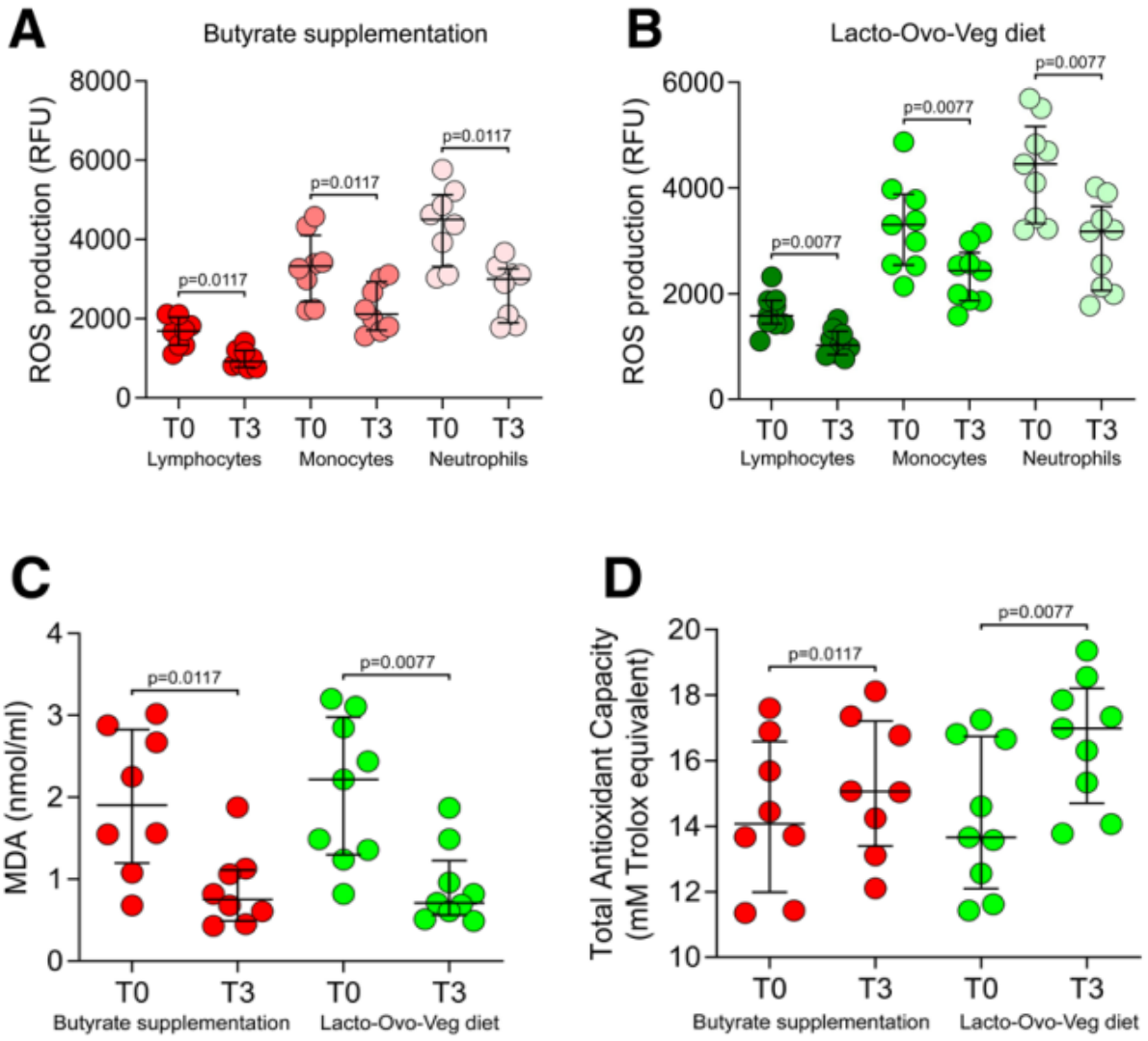
Consolandi C, et al. *Autoimmun Rev*. 2014
Bettiol A, et al. *Clin Immunol*. 2023



Tang WHW, et al *Nat Rev Cardiol 2019*

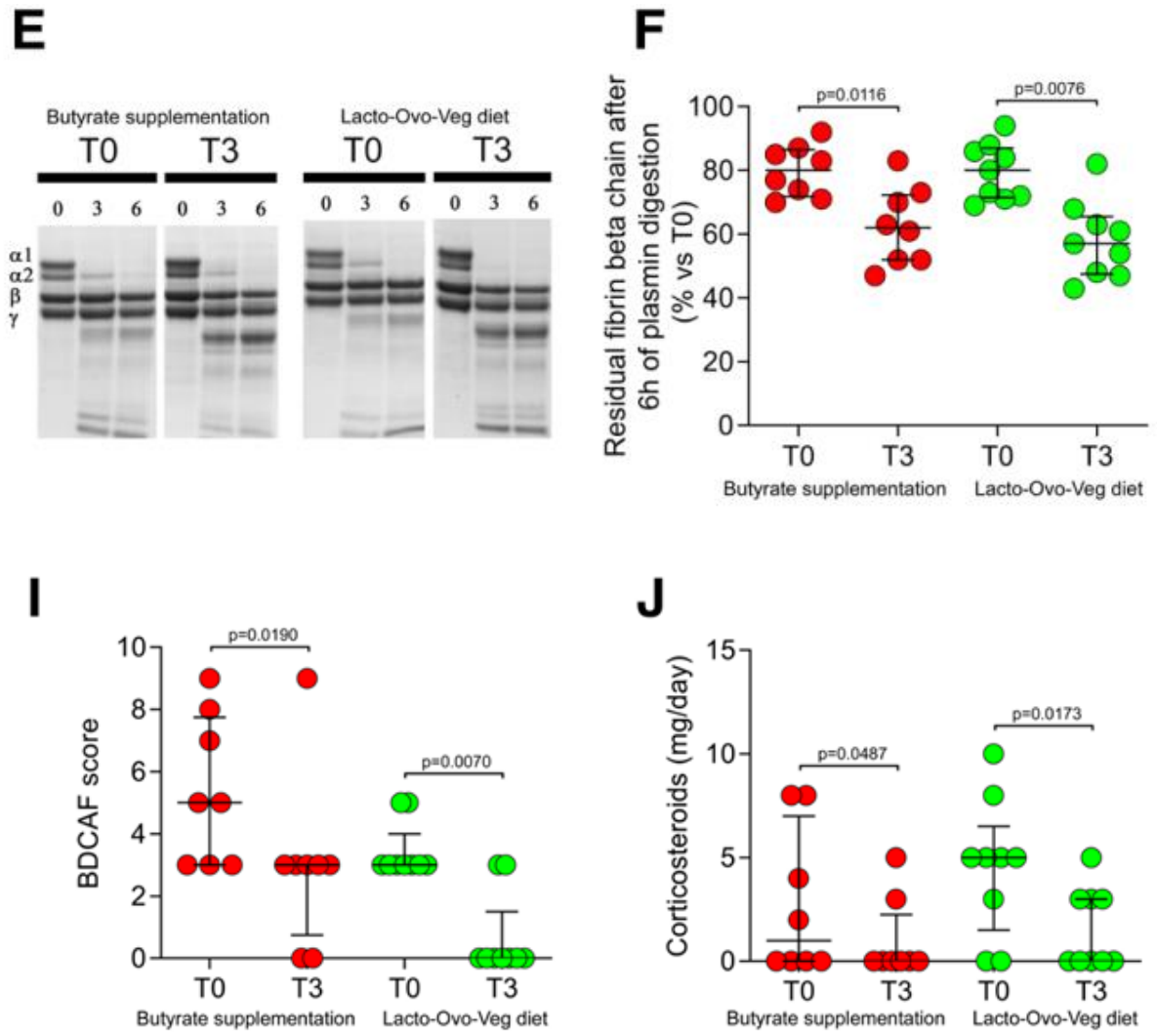

Meta-organismal pathway
Cell types
End-organ dysfunction
Dietary
Phosphatidylcholine
Choline
L-Carnitine
Intestines
Gut microbiota
TMA
Liver
Hepatic FMOs
Circulation
TMAO
↓Cyp7a1
↓Cyp27a1
Altered bile acid composition and pool size
△Sterol transporter
Macrophage–Foam cell/phenotype
SRA
CD36
↑Scavenger receptors
△M1/M2 phenotype
Endothelial cells
↑NFkB activation
↑Adhesion proteins
↑NLRP3 inflammasome activation
↓Nitric oxide
Blood vessel
Platelets
ADP
P2Y12
Gq
TMAO
Thrombin
Gq
Stimulus-dependent Ca2+ release
Signaling
Ca2+ store
Release
↑[Ca2+]i
Platelet hyper-reactivity
Atherosclerosis
↑Forward cholesterol transport
↓Reverse cholesterol transport
△Bile acid composition
Heart failure
↑Adverse cardiac remodeling
↑Extracellular matrix production
Kidney disease
↑Endothelial cell activation
↑Renal functional impairment
Tubulointerstitial fibrosis
↑TGF-β/pSMAD3 signaling
Thrombosis
Myocardial infarction
Stroke

Butyrate-riched diets improve redox *status*



Emmi G, et al *Circ Res* 2021

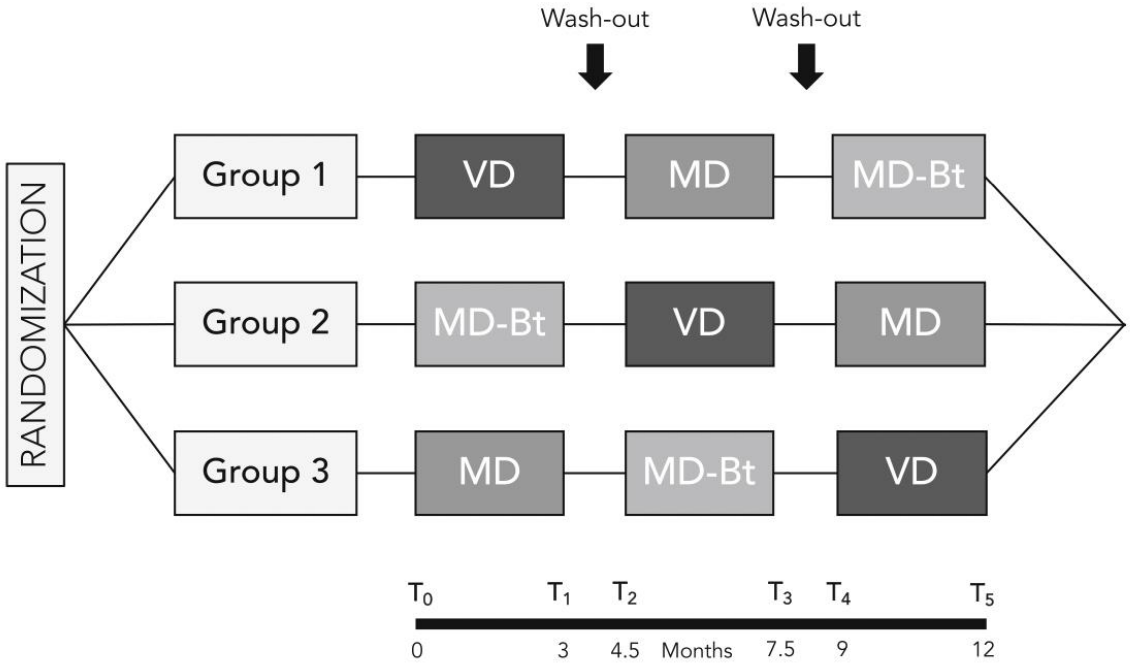
Butyrate-rich diets improve fibrin lysis and disease activity



Emmi G, et al *Circ Res* 2021

MAMBA trial: a randomized crossover study to explore nutritional modulation of gut microbiota in Behçet syndrome

90 patients with BS



Overall disease activity

Gastrointestinal symptoms

Oxidative stress

Emmi G, et al. *manuscript in preparation*

Take home messages

- ✓ Behçet syndrome is characterized by high rates of vascular events (*mostly venous*)
- ✓ Uniquely, vascular manifestations (*venous*) in Behçet are treated with immunosuppressants (e.g *anti-TNF monoclonal antibodies*)
- ✓ Neutrophil-derived ROS mediates fibrin clot resistance to plasmin degradation
- ✓ Microbiome-derived products could restore susceptibility of fibrin clot to plasmin activity

ISBD

INTERNATIONAL SOCIETY FOR BEHCET'S DISEASE

eular

EULAR Study Group on Behçet's syndrome

EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY