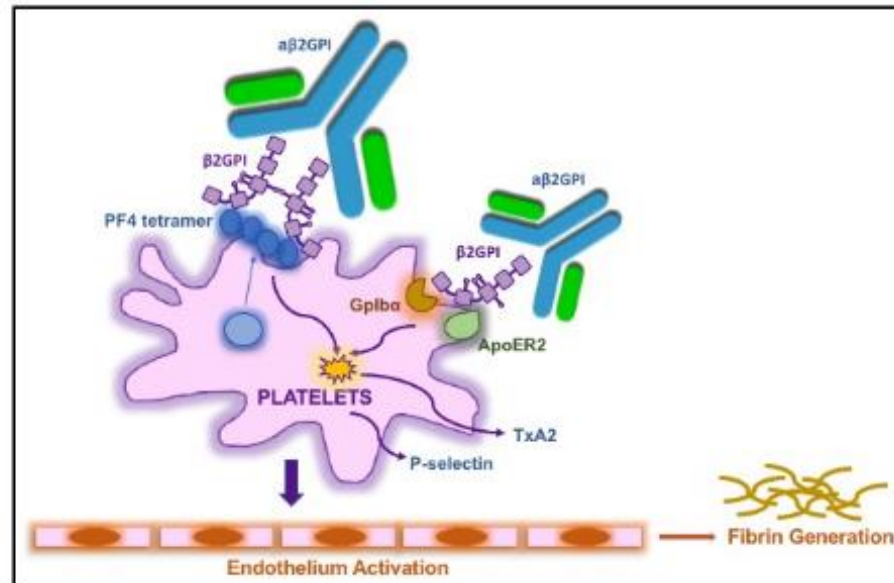


# The role of platelets and thrombocytopenia in APS

Vittorio Pengo (Italy)

# APS pathophysiology: platelets

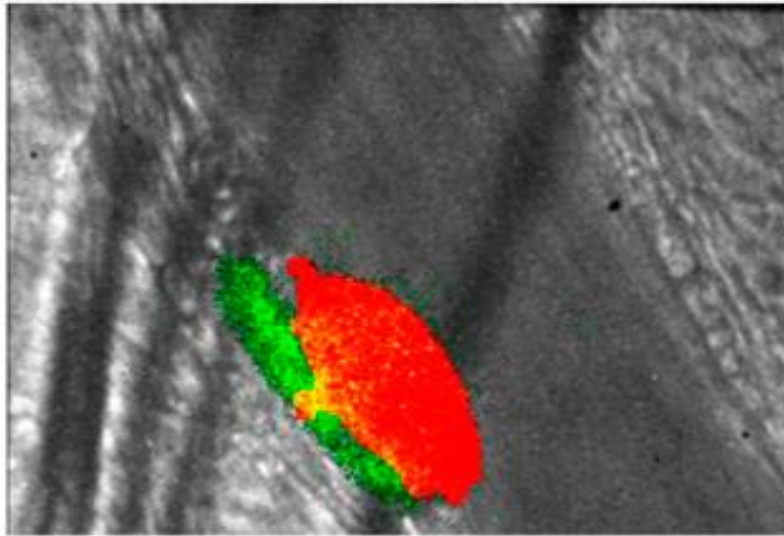
- Binding of  $\beta$ 2GPI-antibody complexes to platelets results in platelet activation, P-selectin expression, and thromboxane B2 production (TXB2): Zhang 2016
- PF4 tetramers can bind two  $\beta$ 2GPI molecules simultaneously allowing their dimerization Sikara 2010



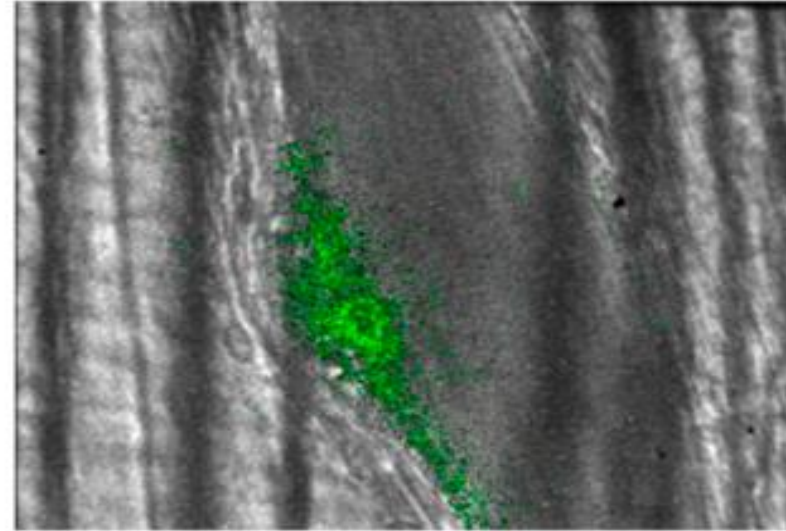
# APS: pathophysiology

- The pivotal role of platelets in the thrombotic manifestations of APS has been investigated in a mouse model (Proulle V 2014)
- Fluorescently labelled  $\beta$ 2GPI and  $\alpha\beta$ 2GPI revealed their co-localization on the laser-induced platelet thrombus but not on the endothelium.

# Animal models of APS



+ a $\beta$ 2GPI



- a $\beta$ 2GPI

Developing thrombus after laser injury in wild type mouse

Anti-b2GPI antibodies used for these experiments express anti-cardiolipin, anti-b2GPI activity, and lupus anticoagulant activity measured by the dilute Russell's viper venom time.

# Thrombocytopenia and APS

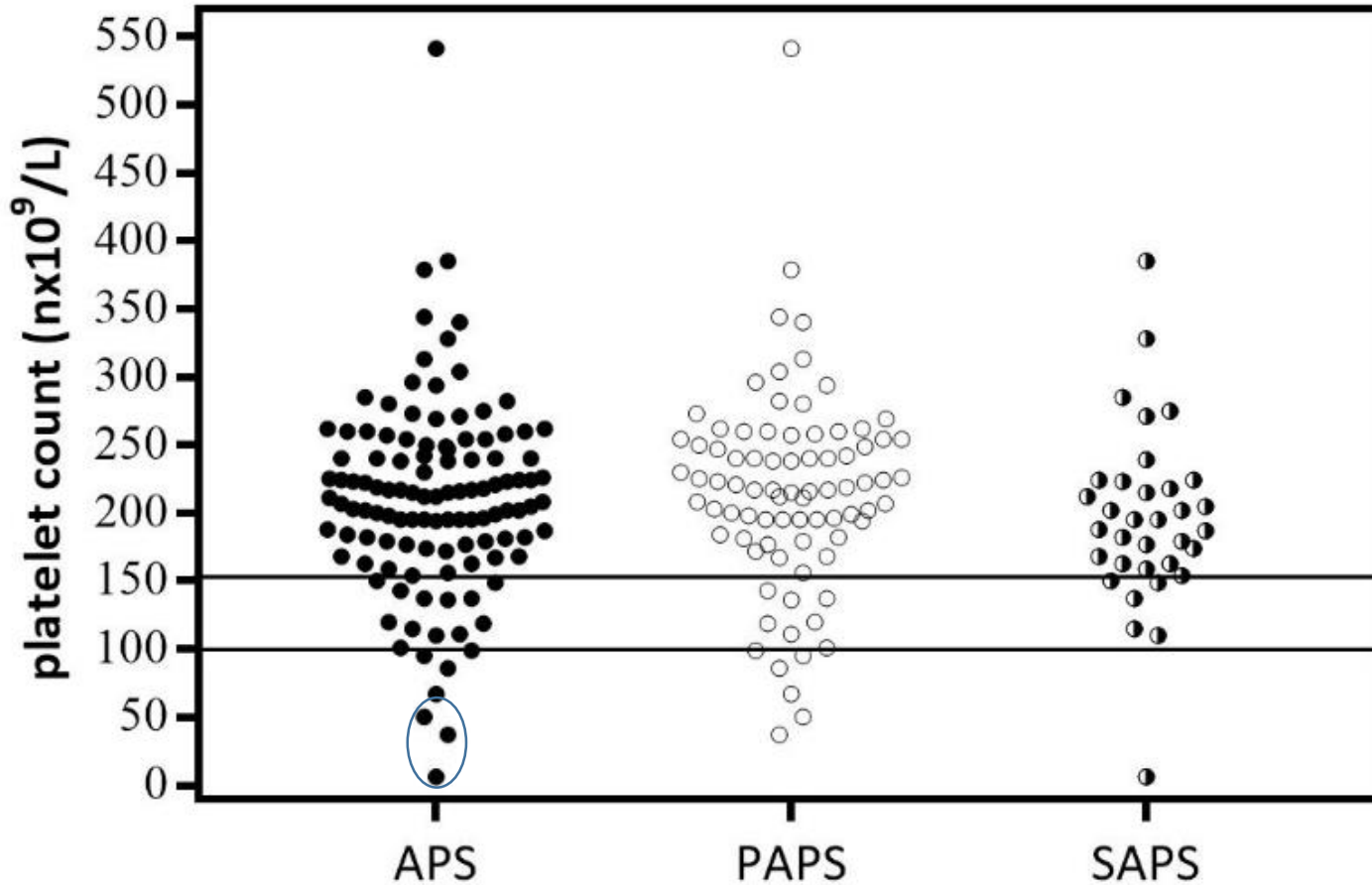
- Thrombocytopenia is defined as a platelet count of less than  $150 \times 10^9 \text{ L}^{-1}$ .
- Thrombocytopenia may be caused by direct binding of anti- $\beta 2$ -GPI antibodies or anti- $\beta 2$ -GPI- $\beta 2$ -GPI complexes.
- It is assumed to be the most common non-criteria manifestation of APS, with a frequency of occurrence reported in 20–50% of cases  
[Cervera R et al. Arthritis Rheum 2002;46(4):1019–1027.27]

# APS and thrombocytopenia

We have analyzed platelet count:

- A) In high risk triple positive patients with APS (quiescent phase)
- B) In 6 of these patients during CAPS

## Platelet count in high risk APS (triple positive)



Mean platelet count in 119 high-risk triple positive patients was  $210 \times 10^9/L$ .

Considering a cut-off value for thrombocytopenia of  $100 \times 10^9/L$ , the prevalence of thrombocytopenia was 6% (7 patients).

Three of 7 patients had associated ITP  
No difference between primary and secondary APS.

# Catastrophic APS

- Thrombotic microangiopathy
- Differential diagnosis with other thrombotic microangiopathies may be difficult.



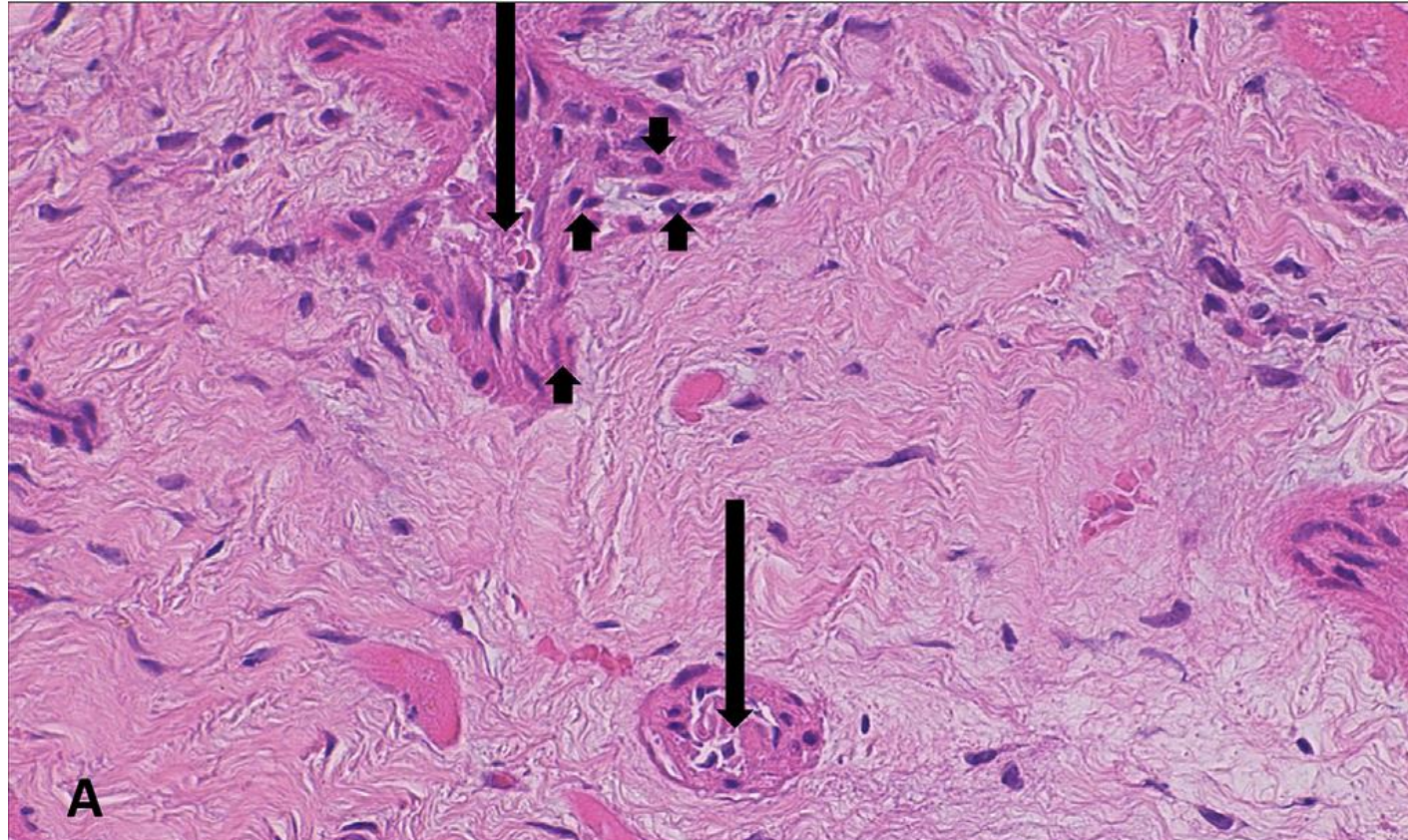
## Clinical and lab features of thrombotic microangiopathies

	Previous history of	Thrombosis of	Fibrinogen level	Haemolytic anemia	Schistocytes	Thrombocytopenia	Antibodies
<b>CAPS</b>	PAPS/ SLE	Small/ large vessels	Normal/ high	+/-	+	+	aPL
<b>TTP HUS</b>	Malignancy	Small vessels	Normal/ high	+	++	++	Anti- ADAMTS13
<b>HELLP</b>	Pregnancy	Small vessels	Normal/ high	+	+/-	++	-
<b>DIC</b>	Infection/ malignancy	Small vessels	Low	+/-	+/-	++	-
<b>HIT</b>	Heparin exposure	Large/ small vessels	Normal	-	+/-	++	Anti- HeparinPF4

# CATASTROPHIC APS

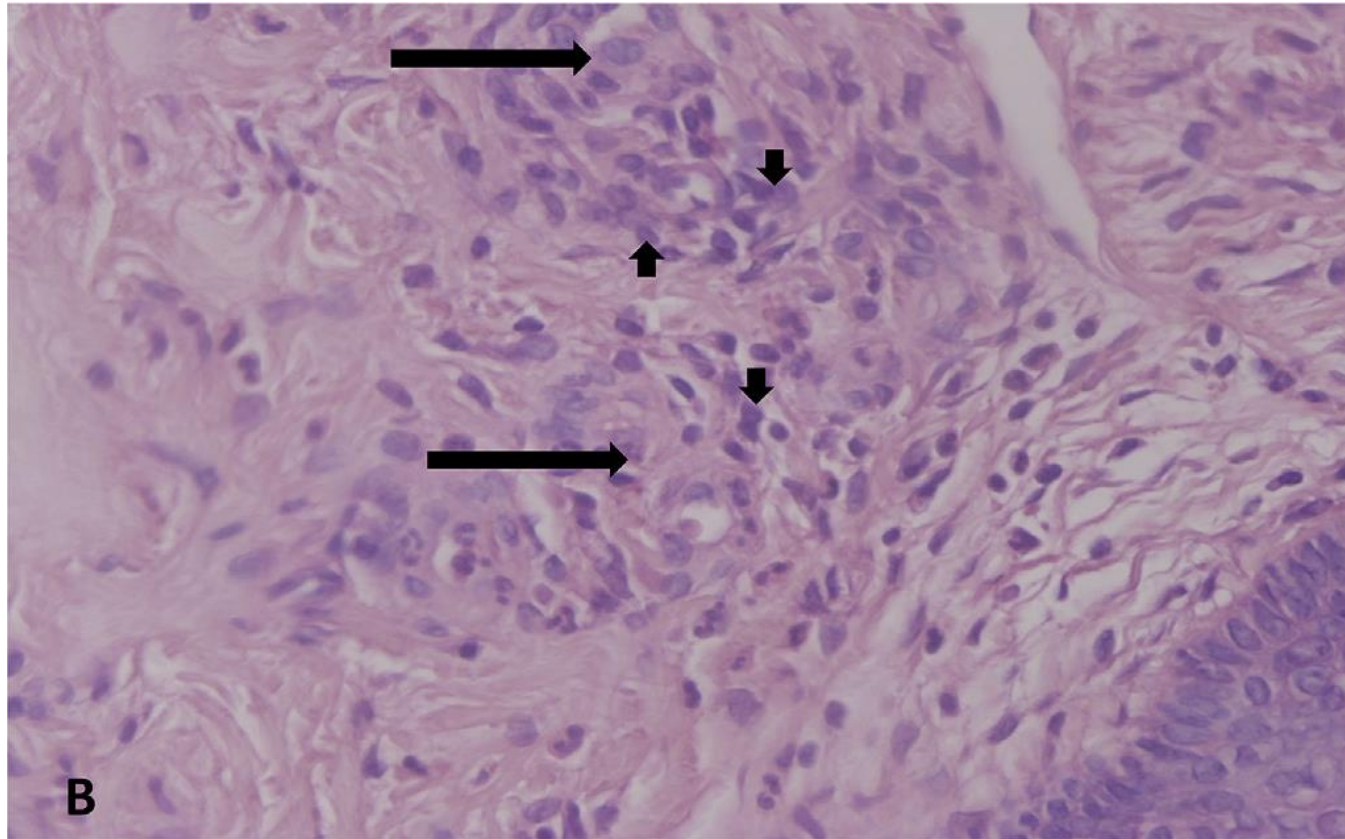
- Term proposed in 1992
- Accelerated form of APS with multiorgan thrombotic failure
- Around 50% mortality, it may show up 'ex novo'
- Trigger: infection in many cases
- 1% prevalence in APS

## Catastrophic APS



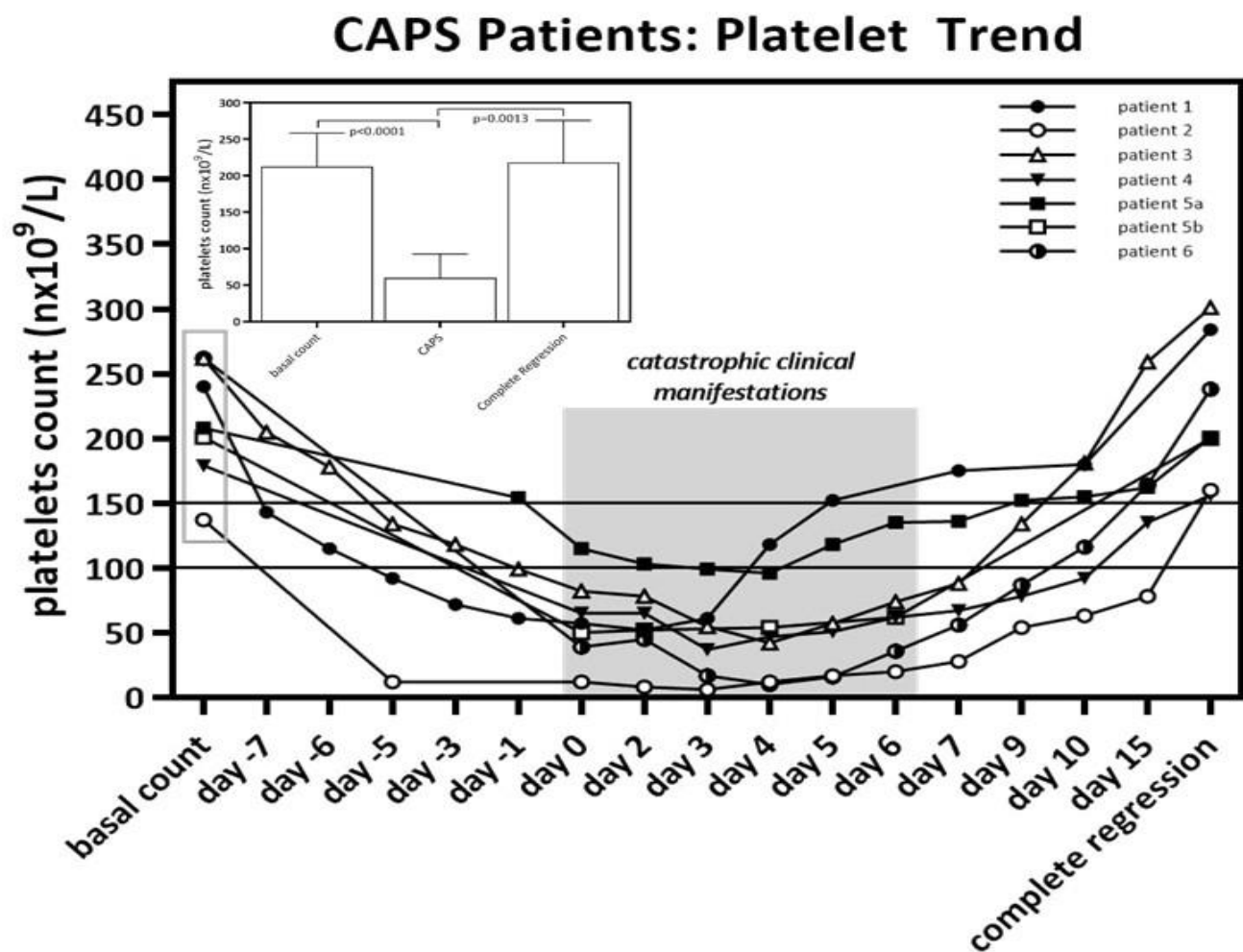
Endomyocardial histology: small vessels with endoluminal thrombosis (long arrows) and perivascular/intramural inflammatory cells (short arrows).

## Catastrophic APS



Histology of a cutaneous lesion of the right hand:  
thrombosis of small vessels of the dermis (long arrows) and  
granulocytic infiltrate (short arrows).

# Platelet count in CAPS

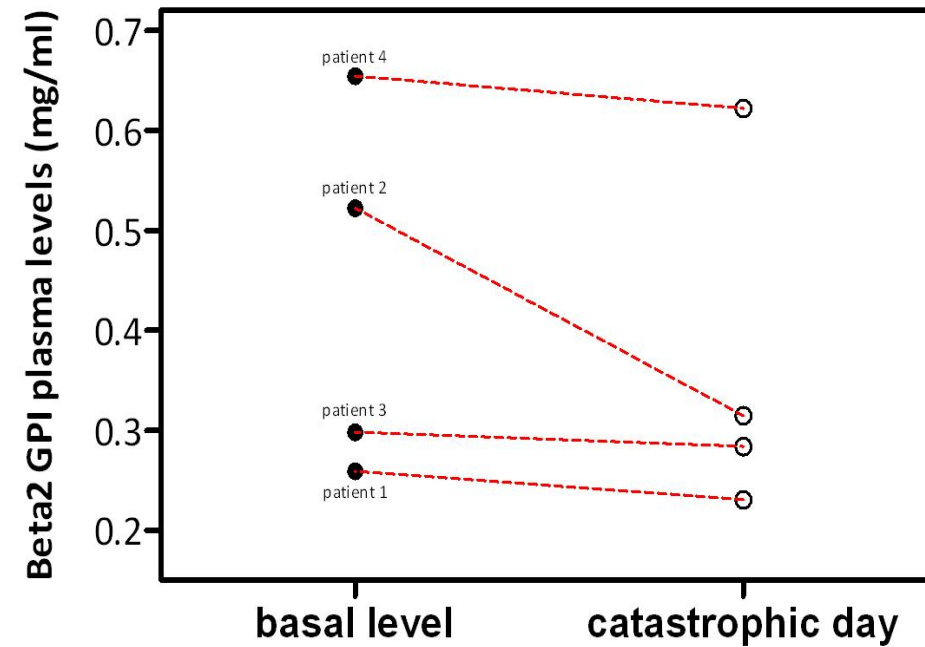


In patients who suffered from CAPS, a significant drop from the basal count ( $212 \times 10^9/L \pm 51$ ) to that at time of diagnosis ( $60 \times 10^9/L \pm 33$ ) was observed.

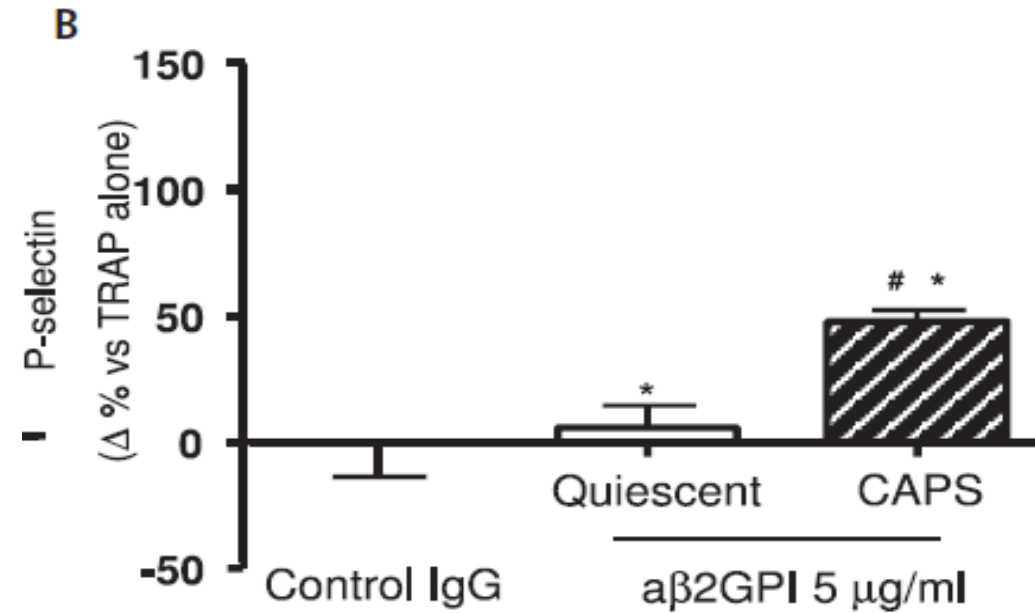
Platelet count became normal again at time of complete remission ( $220 \times 10^9/L \pm 57$ ).

A drop in platelet count always preceded the full clinical picture

## $\beta_2$ GPI concentration in quiescent and acute catastrophic APS



Higher platelet p-selectin expression in the presence of IgG anti  $\beta$ 2GP1 from a patients with cathastrophic APS than in the presence of IgG anti  $\beta$ 2GP1 from a patients with quiescent APS



# Conclusions

- Platelet count is often normal in high-risk triple-positive patients with APS in the quiescent phase. This does not exclude an increase of their turnover.
- A drop in platelet count in high-risk triple-positive patients may indicate platelet consumption/deposition in the microcirculation with consequent organ failure (CAPS)