Webinars

Thrombotic Microangiopathies

Hemolytic uremic syndrome and other thrombotic microangiopathies

EuroBloodNet Topic on Focus

Organ Dysfunction in Thrombotic Thrombocytopenic Purpura

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the Health Programme
of the European Union

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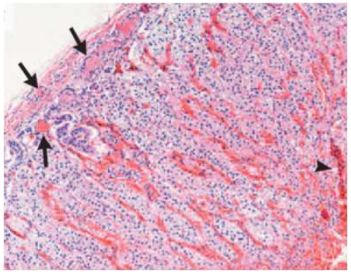
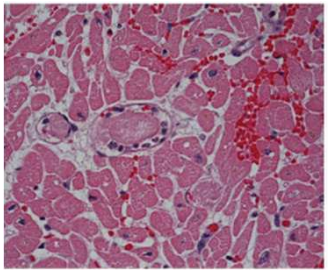
Network Hematological Diseases (ERN EuroBloodNet)

- **Lecture fees from Sanofi**

Webinar rules

- **30-35min presentation (30 slides max) + 15 min Q&A session**
- **Microphones will be muted by host to avoid back noise**
- **Please, stop your video to improve internet conexion**
- **Send your questions during the presentation through the chat**

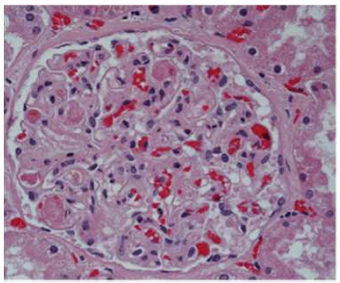


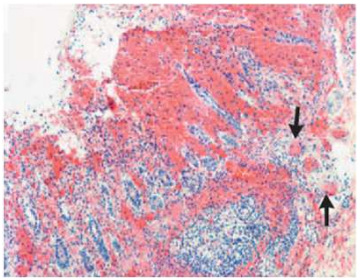


1. Know the spectrum and mechanisms of organ involvement in TTP

2. Understand the pronostic value of specific organ involvement

3. Learn the risk of long term sequellae in TTP patients





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TTP

HUS

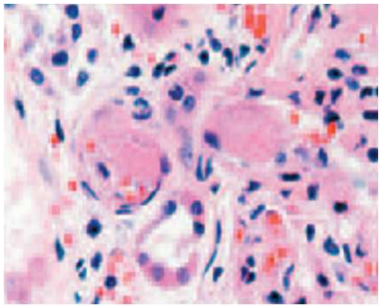
DIC

Malignant hypertension

Vasculatis

GVHD

Metastatic cancer



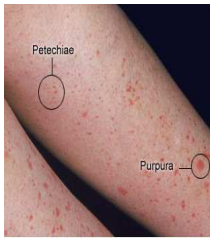
TMA syndrome

= Microvascular thrombosis

Mechanical hemolytic anemia

Visceral ischemia

Peripheral thrombocytopenia



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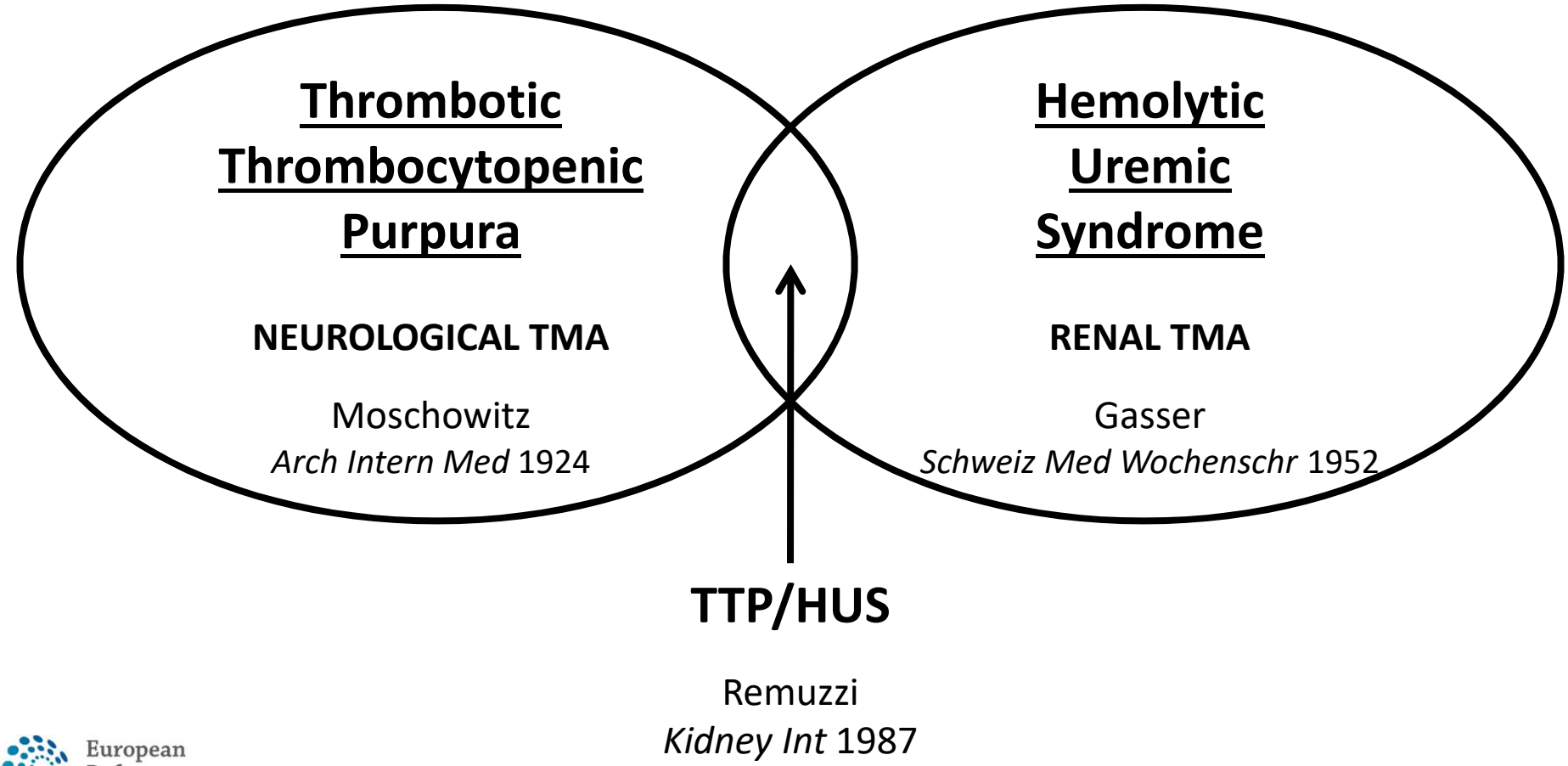
From a clinical classification of TMA syndromes…



… to a pathophysiological classification

Thrombotic Thrombocytopenic Purpura

ADAMTS13 DEFICIENCY

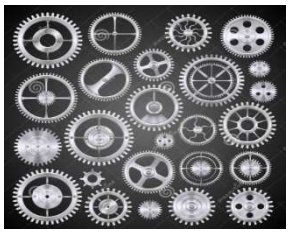
Tsaï, Furlan
N Engl J Med 1998

Hemolytic Uremic Syndrome

D+ = SHIGATOXIN

Karmali
J Infect Dis 1985

« Secondary » TMAs

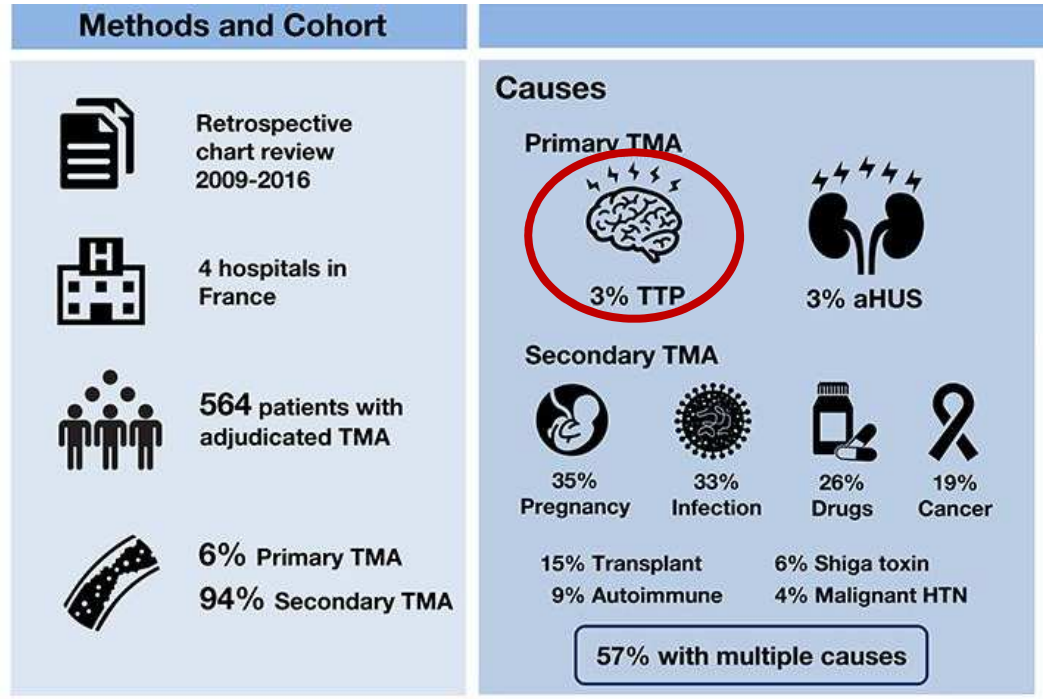


Hemolytic Uremic Syndrome

D- = ALTERNATIVE COMPLEMENT PATHWAY DEFECTS

Warwicker
Kidney Int 1998

Guillaume Bayer, Florent von Tokarski, Benjamin Thoreau, Adeline Bauvois, et al. ***Etiologies and Outcomes of Thrombotic Microangiopathies.*** CJASN doi: 10.2215/CJN.11470918. **Visual Abstract by Beatrice Concepcion, MD**



Incidence 1,5-6 new cases / million / year

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Mariotte, Lancet haematol. 2016; Miesbach, Orphanet J rare dis.2019; Page, Blood Adv. 2017; Scully, Br J Haematol 2008

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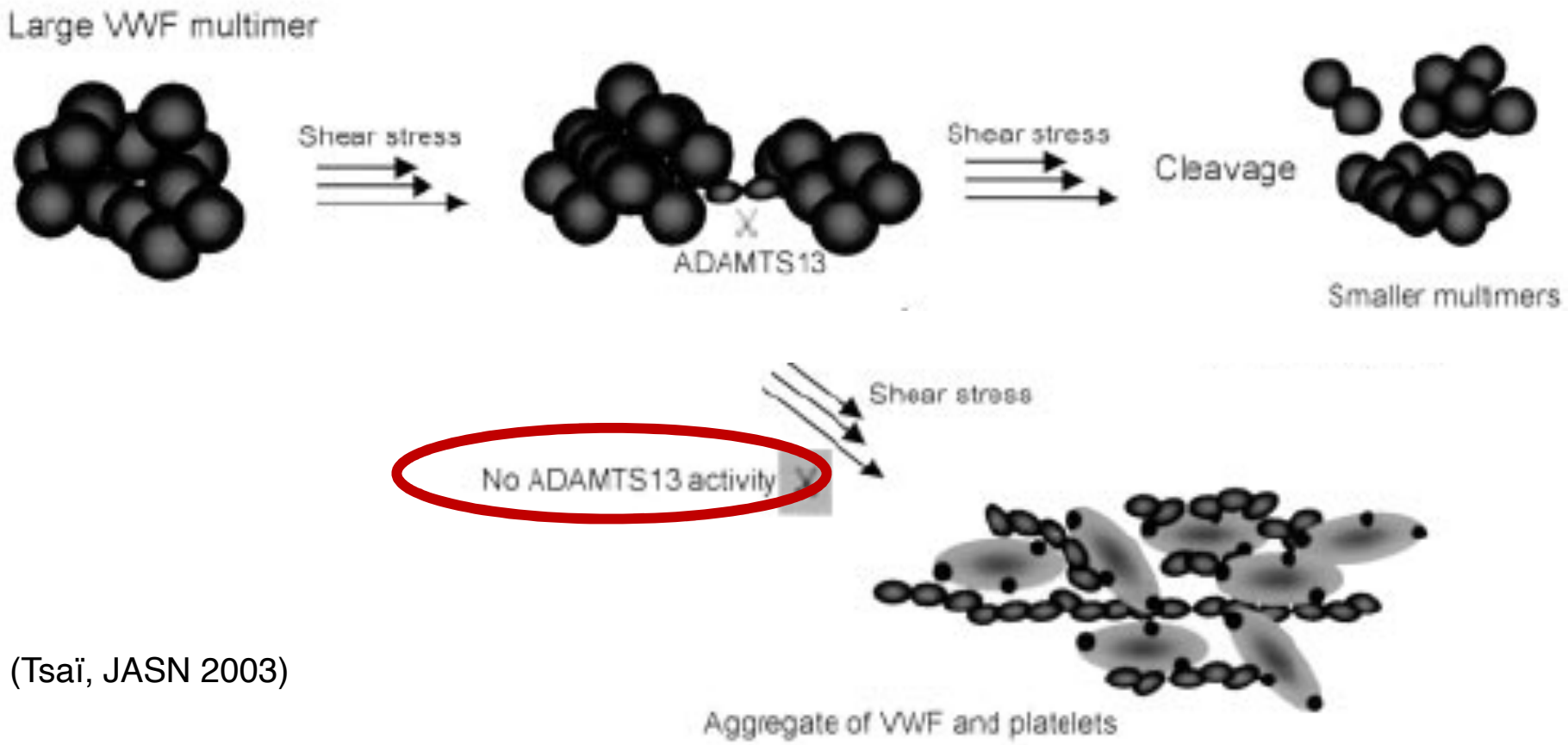
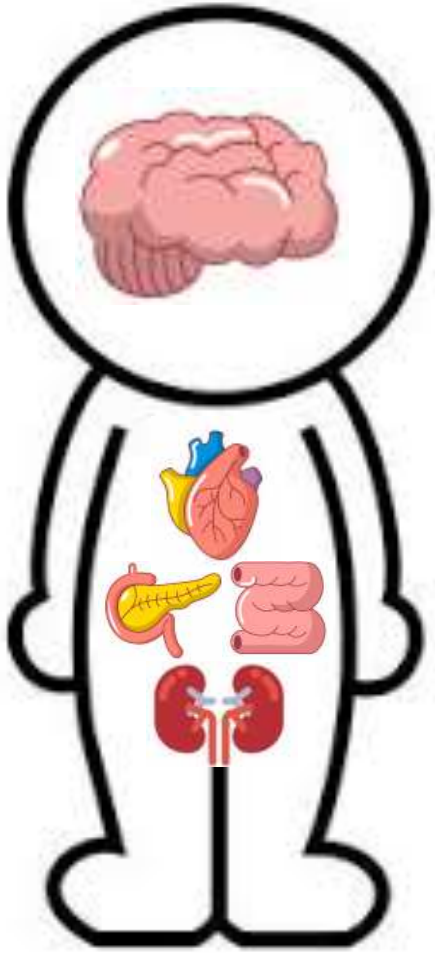
ADAMTS13 and TTP



(Tsaï, JASN 2003)

Central nervous system
43-80%



Heart
10-42%

Gut
35%

Kidneys
18-76%

Autopsic data: adrenal glands, spleen, skin, bone marrow, lung…

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Hassan 2015; Mancini 2019; Mariotte 2016; Matsumoto 2010; Page 2017

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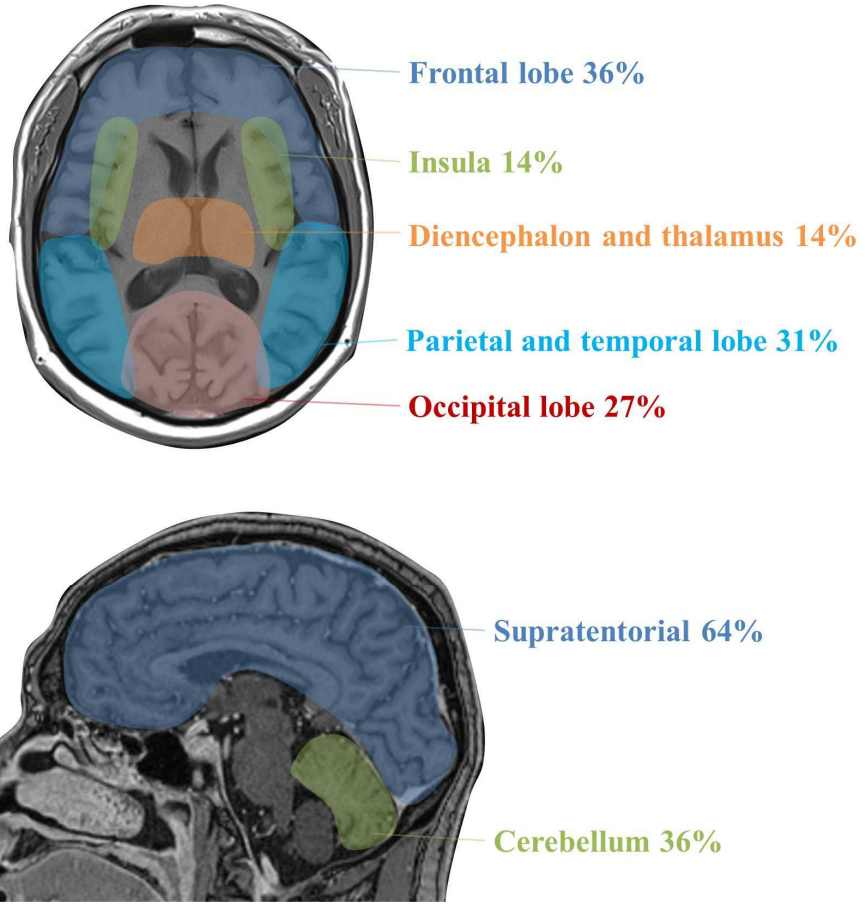
Table I. Presenting symptoms necessitating MRI scanning and the frequency of abnormal scans by indication.

Symptom	Frequency	% Abnormal MRI
Aphasia	3 (2%)	100%
Confusion and agitation	12 (9%)	83%
Headaches only	50 (38%)	18%
Expressive dysphasia	8 (6%)	63%
Reduced GCS beyond confusion	4 (3%)	50%
Seizures	9 (7%)	89%
TIA/Stroke	39 (30%)	85%
Vacant episodes	1 (1%)	100%
Visual disturbance (loss or diplopia)	5 (4%)	60%

Brain imaging

Changes on CT-scan (/performed)	9/48 (19%)
Changes on MRI (/performed)	27/67 (40%)



Mirouse and al, under press

Neurological involvement in TTP

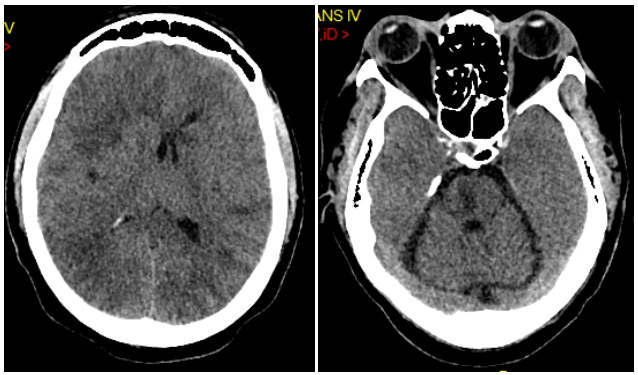
Ischemic stroke

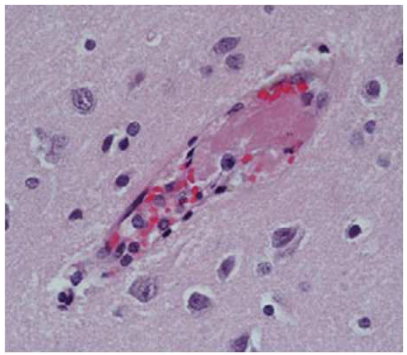
Hemorrhage

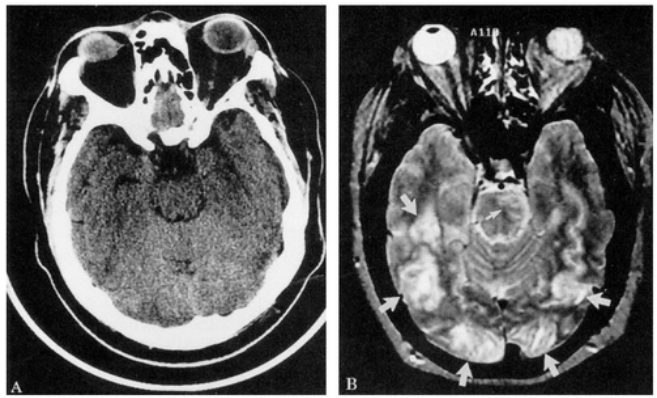
PRES

Transient ischemia

RVCS







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Guzzini F Haematologica 1998

Burrus T Neurology 2009

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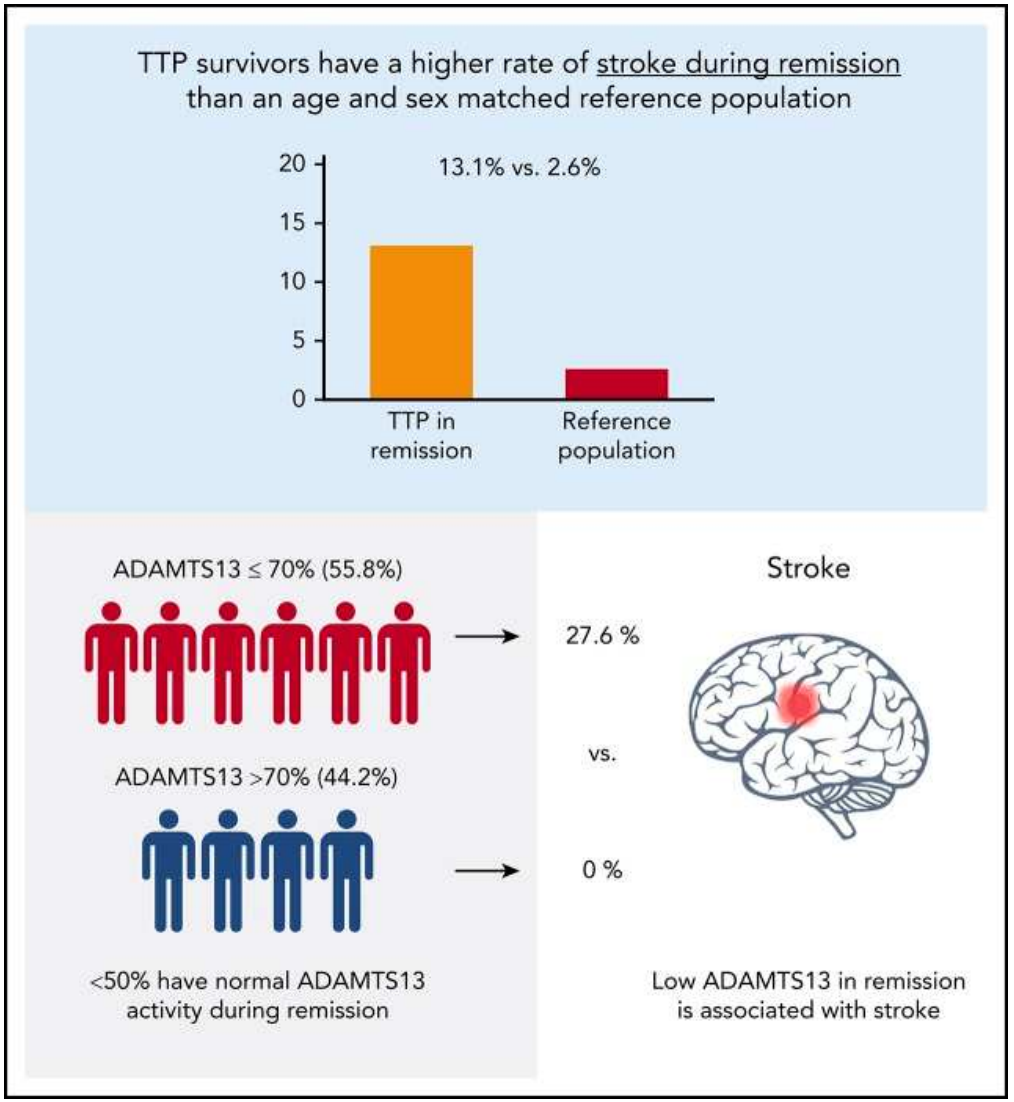

TTP survivors have a higher rate of stroke during remission than an age and sex matched reference population
20
15
10
5
0
13.1% vs. 2.6%
TTP in remission
Reference population
ADAMTS13 ≤ 70% (55.8%)
ADAMTS13 >70% (44.2%)
<50% have normal ADAMTS13 activity during remission
27.6 %
vs.
0 %
Stroke
Low ADAMTS13 in remission is associated with stroke

Headache prevalence following recovery from TTP and aHUS

Table 3 Summary of HIT-6 score by disease (aHUS vs. TTP)

TTP-aHUS	Number	Mean	SD	*p* value[a]
aHUS	10	51.9	9.9	–*
TTP	21	59.9	9.6	0.002
Total	31	57.3	10.2	0.005

**p* value for aHUS patients not calculated given normative patient data for mean HIT-6 of 51.7

[a] *p* value based on one-sample *t* test comparing the HIT-6 score to the female US norm value of 51.74 for HIT-6. *p* values have been adjusted in ordered to conserve the overall type I error rate at 0.05

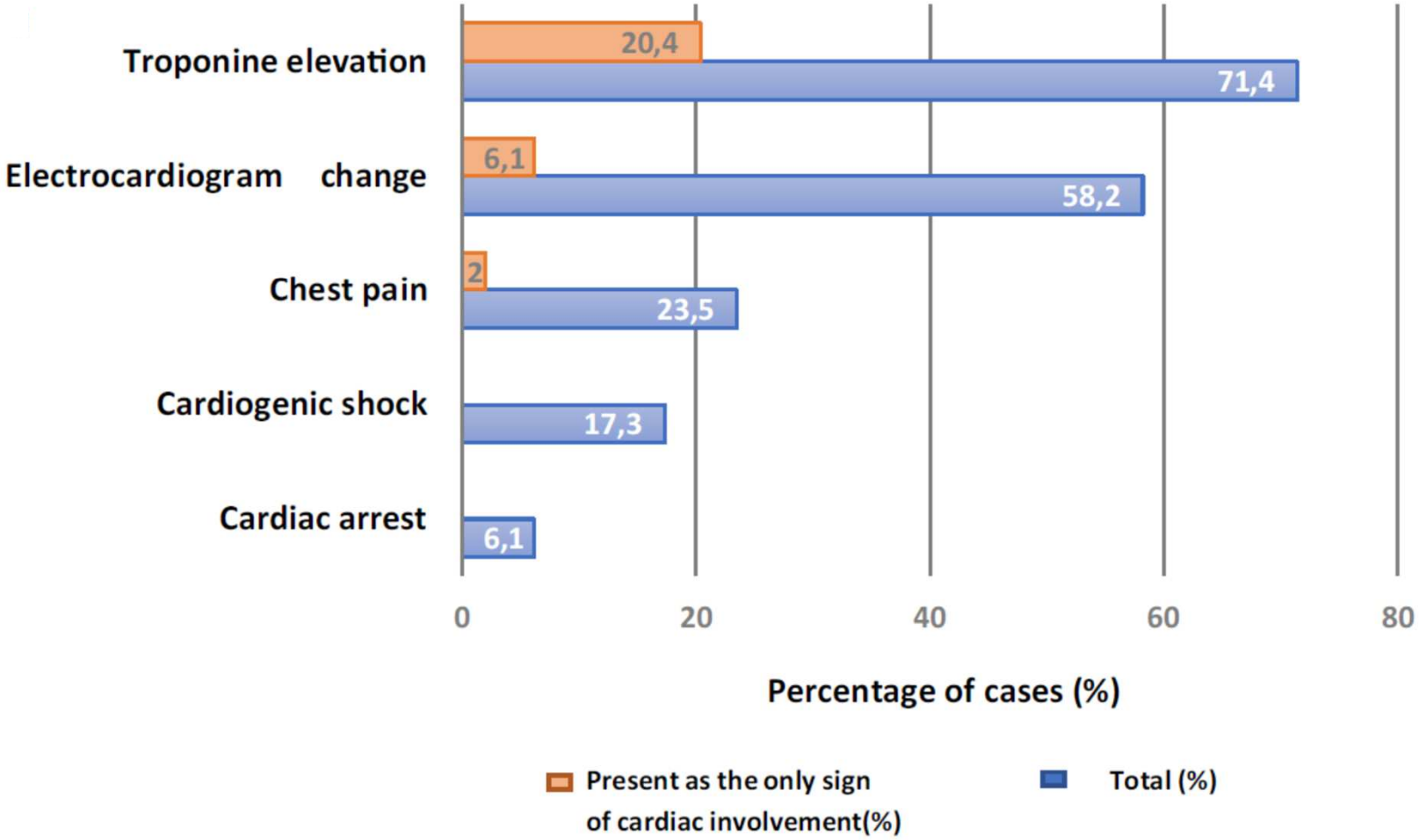
- Standard cognitive performances are usually preserved
- « Infra-clinical » cognitive performances are durably altered in TTP patients
- Depressive symptoms / depressions more frequent in this population

Lewis 2007, Burrus 2009, Kennedy 2009, Cataland 2010, Deford 2013, Chaturvedi 2015, Han 2015, Saultz 2015, Falter 2017,

Beau M. Hawkins: **CARDIAC INVOLVEMENT IN TTP** **TRANSFUSION** Volume 48, February 2008

	Nb articles n=30	**Nb patients**
Cardiac symptoms	13 (43%)	**24/111 (22%)**
Cardiac events	23 (77%)	**47/86 (55%)**
Autopsy	24 (80%)	**48/48 (100%)**

- **Cardiac symptoms**:
  - Angina
  - Congestive heart failure
  - Syncope
- **Cardiac events**:
  - Myocardial infarction (enzymes, ECG)
  - Congestive heart failure
  - Arrhytmia
  - Cardiogenic shock
  - Sudden death



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Intensive Care Med (2018) 44:963–965

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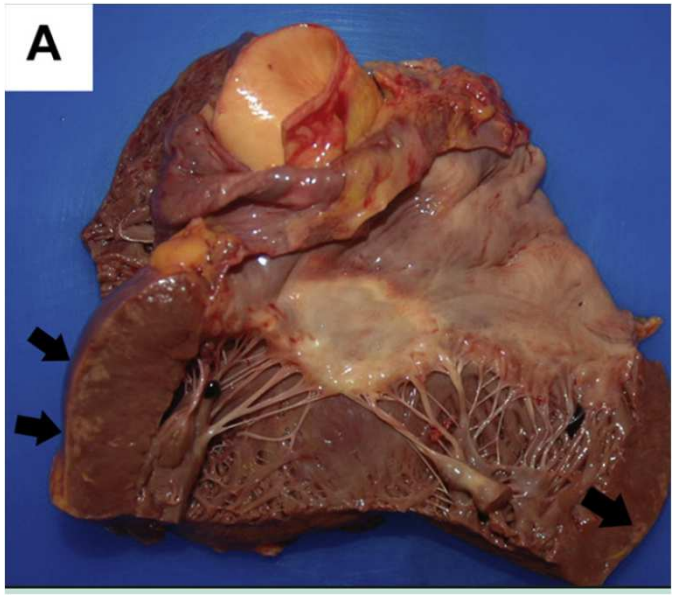
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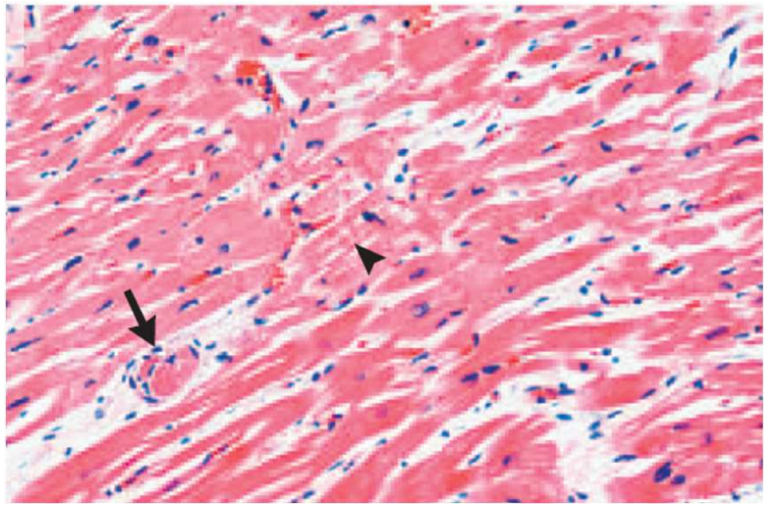
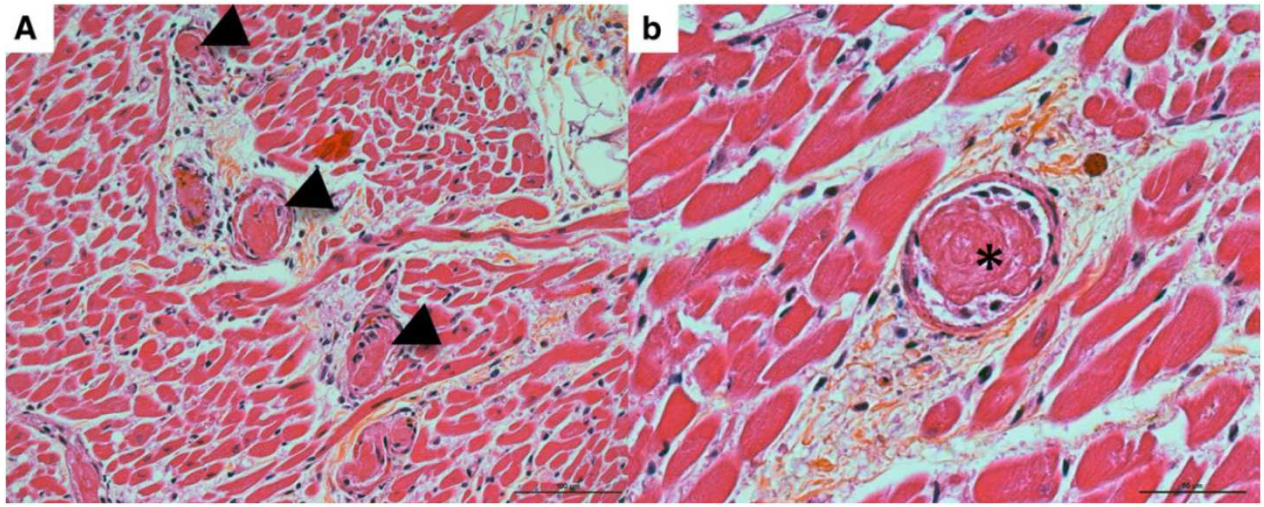



A
b

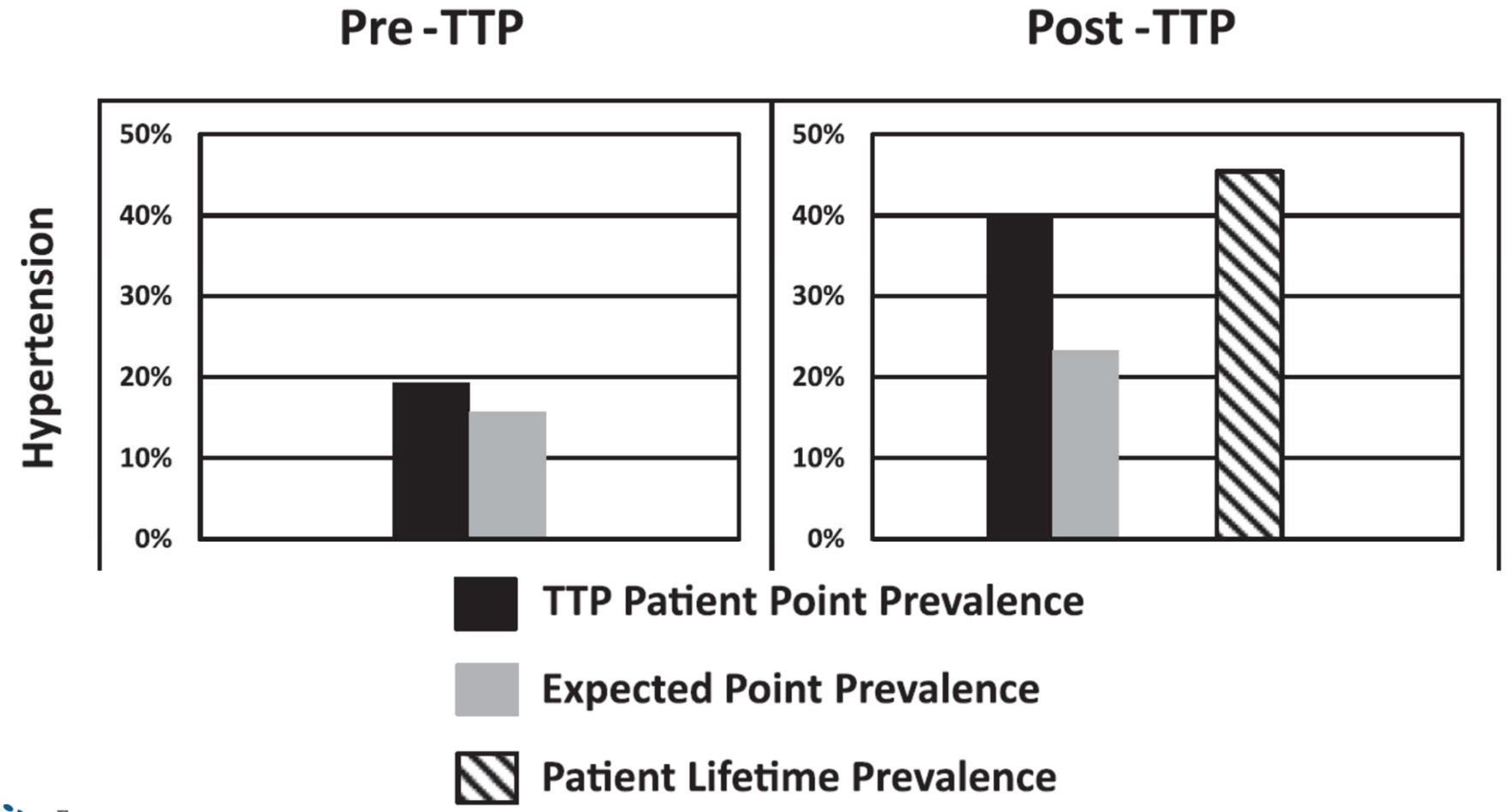
ORIGINAL ARTICLE

Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center

Table 3 Association between patients' characteristics and death by multivariable analysis

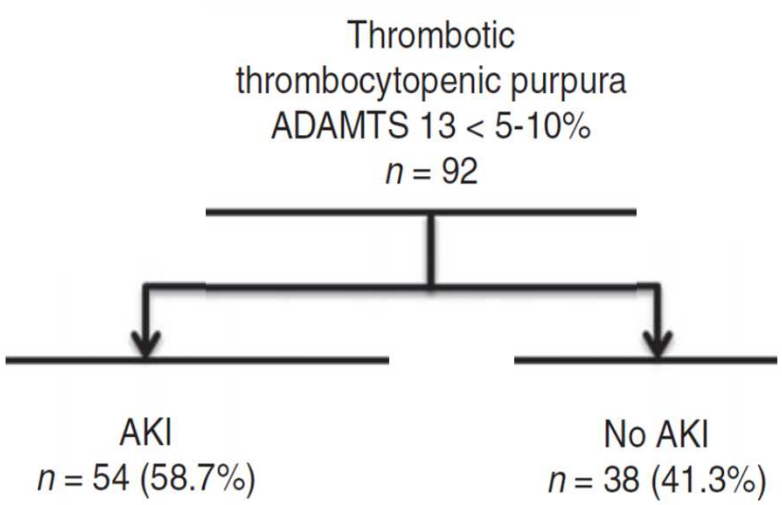
	Odds ratio (95% CI)	*P*
Troponin-I > 0.25 μg L^{-1}	**2.86 (1.13–7.22)**	**0.024**
Age (years)		
≤ 40	1	0.7
41–60	1.54 (0.49–4.87)	
> 60	1.76 (0.48–6.54)	
Neurologic involvement	1.66 (0.58–4.78)	0.4
eGFR	0.61 (0.23–1.63)	0.32

Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura



BLOOD, 19 SEPTEMBER 2013 • VOLUME 122, NUMBER 12

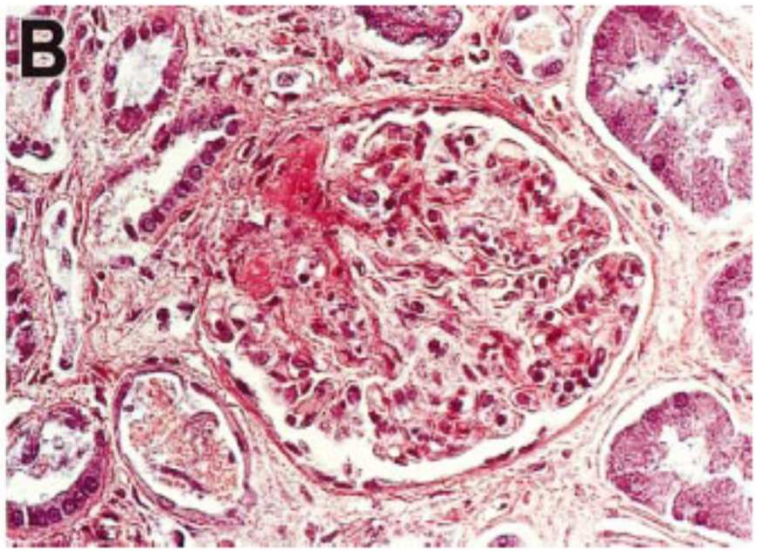
Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity



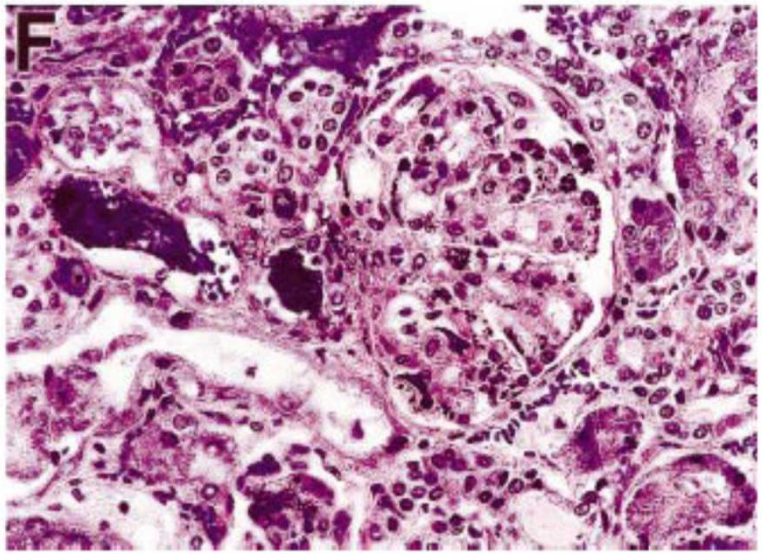
Variables	*n* (%) or median [IQR]
AKI staging	
Stage 1	24 (44.4)
Stage 2	9 (16.7)
Stage 3	25 (46.3)
Oliguria, *n* (%)	9 (16.7)
Median Scr mg dL^{-1} before ICU admission	0.78 [0.68–0.86]
Median MDRD before ICU admission (mL min^{-1} per 1.73 m^2)	111.5 [79–127]
Median Scr mg dL^{-1} at ICU admission	1.6 [1.2–2.3]
Median blood urea nitrogen (mg dL^{-1}) at ICU admission	37 [24–54]
Hypertension, *n* (%)	41 (75.9)
Renal replacement therapy (RRT) during ICU stay, *n* (%)	14 (25.9)

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome Are Distinct Pathologic Entities

A Review of 56 Autopsy Cases



TTP



HUS

Variables	*n* (%) or median [IQR]
RRT at ICU discharge	6 (11.1)
Scr (mg dL^{-1}) at month 6 in RRT-free patients	0.87 [0.8–1]
MDRD at month 6 in RRT-free	93 [68.8–110]
Renal failure at month 6	
CKD stage 2	11 (20.4)
CKD stage 3	8 (14.8)
CKD stage 4	1 (1.9)
CKD stage 5	3 (5.6)

Glomerular filtration rate	No difference compared to age/sex/race/BMI-matched controls (P = 0.387) at 90 months	Deford [24]
Urine albumin:creatinine ratio	No difference compared to age/sex/race/BMI-matched controls (P = 0.793) at 90 months	Deford [24]
Mild-moderate renal impairment[a]	Incidence: 2/10 (20%) at 16 months	Breckenridge [28]
	Incidence: 5/52 (10%) at 34 months	Hayward [31]
	Incidence: 1/72 (1%) at 30 months	Zhan [46]
	Incidence: 4/19 (21%) at 156 months	Falter [27]
Chronic dialysis dependence	Incidence: 4/52 (8%) at 34 months	Hayward [31]
	Incidence: 3/17 (18%) at 60 months	Basic [39]
	Incidence: 1/31 (3%) at 42 months	Zeitler [42]

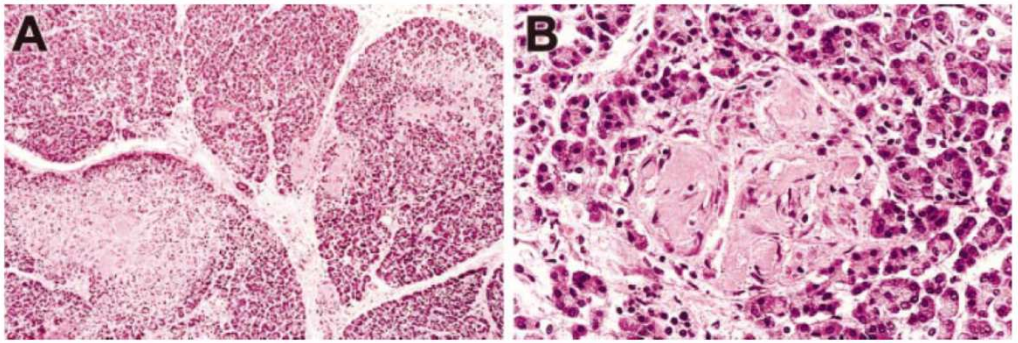
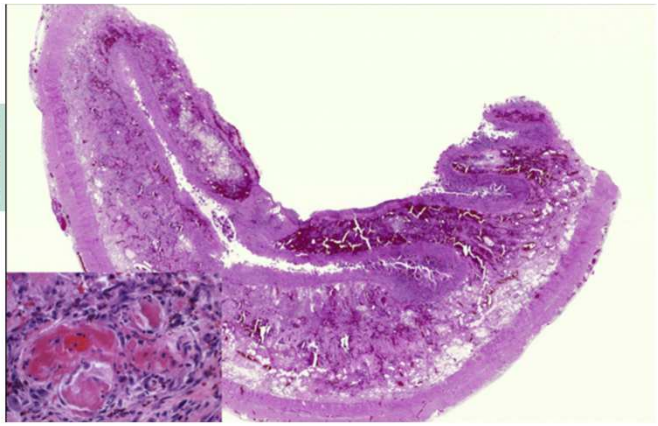


Figure 4. *A, The pancreas may show extensive arterial thrombi in the interstitium, exocrine pancreas, and islets of Langerhans (hematoxylin-eosin, original magnification ×20). One islet centered in a focal necrosis is seen at the lower left. B, In some patients, there appears to be preferential involvement of islets (hematoxylin-eosin, original magnification ×100).*

Arch Pathol Lab Med—Vol 127, July 2003

- Abdominal pain present around 1/3 patients at diagnosis, presumably secondary to gut ischemia
- Pancreatic microvascular thrombosis frequently found at autopsy
  - Clinical pancreatitis is rare in TTP
  - TTP-like syndrome secondary to acute pancreatitis have been described

Figure 3 The surgically resected small bowel showed submucosal hemorrhage and acute inflammation consistent with acute ischemic injury (hematoxylin & eosin stain, 20×)



The American Journal of Medicine, Vol 130, No 8, August 2017

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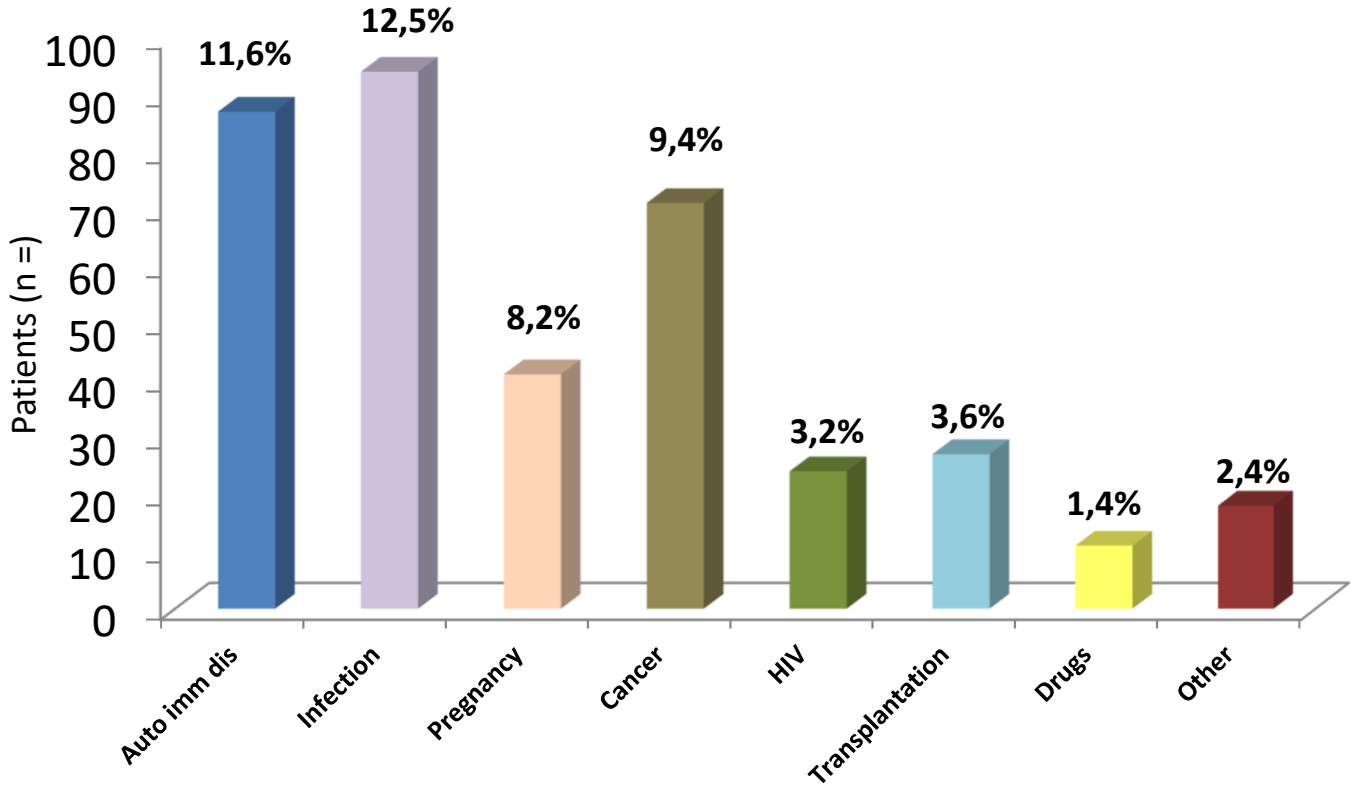
751 patients with adult acquired TTP (ADAMTS13<10%)

- Idiopathic : 50,3% (n=378)

- Associated condition : 49,7% (n=373)



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Lancet Haematol 2016; 3: e237–45

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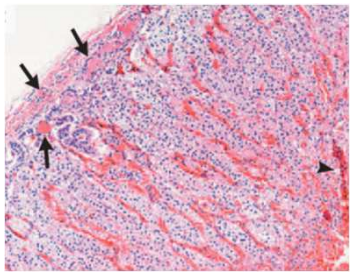
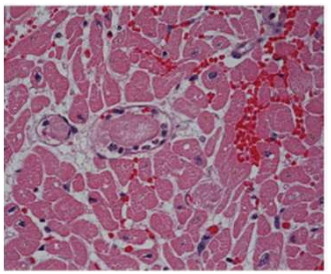
Macrovascular thrombosis in critically ill patients with thrombotic micro-angiopathies

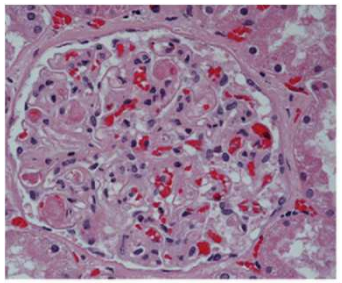
Table 2 Clinical site of thrombosis according to ADAMTS13 status

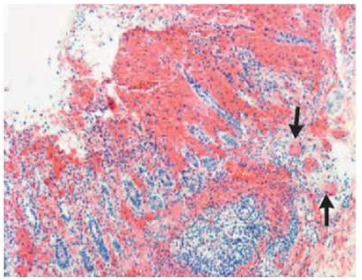
Site	Detectable ADAMTS13, ($n = 19$)	Undetectable ADAMTS13 ($n = 36$)
Arterial cerebral infarcts	3 (16 %)	4 (11 %)
Deep vein thrombosis or Pulmonary embolism	0	8 (22 %), including 4 DVT and 4 pulmonary embolism
Catheter-related thrombosis	3 (16 %)	10 (28 %)





1. **Organ involvement is highly variable in TTP and is not restricted to the CNS**
2. **Cardiac involvement has been associated with worse short term outcome**
3. **Neurological involvement has been associated with worse long term neurological/neuropsychological outcome**





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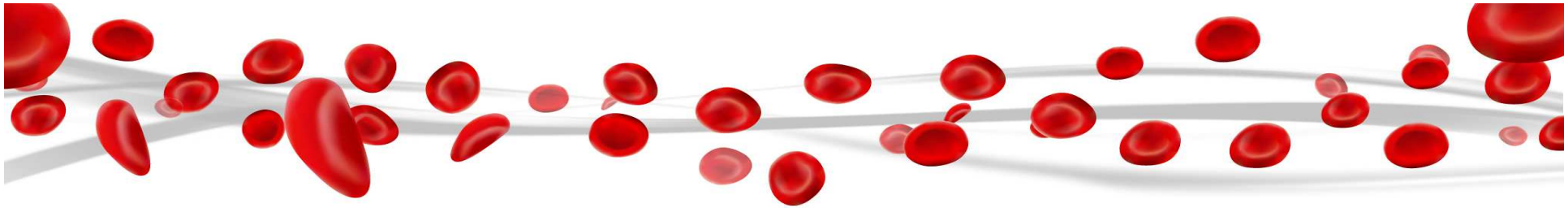

Discussion