ERKNet
The European Rare Kidney Disease Reference Network

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WGIKD working group
Working Group on Inherited Kidney Disorders

WELCOME TO

ERKNet
Advanced Webinars on Rare Kidney Disorders

Date: 11 May 2021

Topic: TMA in Anti-phospholipid syndrome

Speaker: Savino Sciascia

Moderator: Jack Wetzels

AGENDA

- Definition of Antiphospholipid Syndrome
- Epidemiology
- APS and Kidney: Clinical aspects
- APS and Kidney: Diagnosis
- APS and Kidney: Therapeutic options

AGENDA

- **Definition of Antiphospholipid Syndrome**
- Epidemiology
- APS and Kidney: Clinical aspects
- APS and Kidney: Diagnosis
- APS and Kidney: Therapeutic options

Antiphospholipid syndrome and Antiphospholipid antibodies

Antiphospholipid syndrome (APS) describes a clinical autoimmune syndrome characterized by thrombosis and/or pregnancy morbidity in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL)

Thrombotic APS –patients diagnosed with APS based on **venous or arterial** thrombosis and persistent laboratory criteria for aPL.

Obstetric APS :APS-defining pregnancy morbidity:

≥3 consecutive miscarriages (<10 weeks)
≥1 foetal death (≥10 weeks)
≥1 premature birth (≤34 weeks due to severe pre-eclampsia / placental insufficiency)

Catastrophic APS – Catastrophic APS (CAPS) is a rare, severe (life-threatening) form of APS characterized by thrombotic complications, usually microvascular, affecting multiple organs that develop simultaneously or over a short period of time.

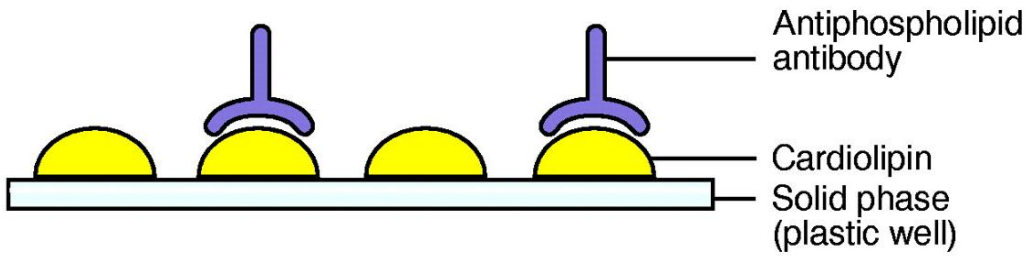
Antiphospholipid syndrome and Antiphospholipid antibodies

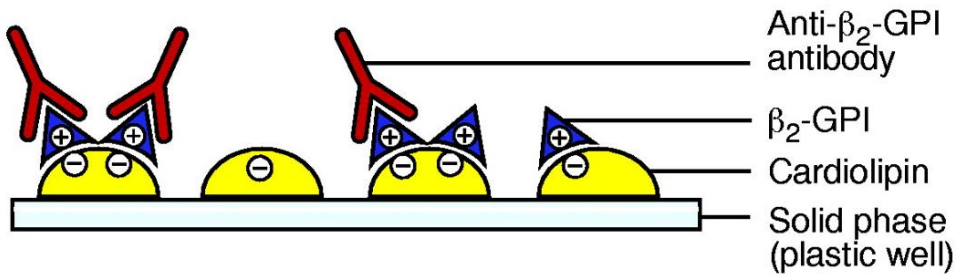
Antiphospholipid antibodies are a heterogeneous group of antibodies directed against phospholipid-binding proteins.

The aPL detection tests included in APS classification criteria are

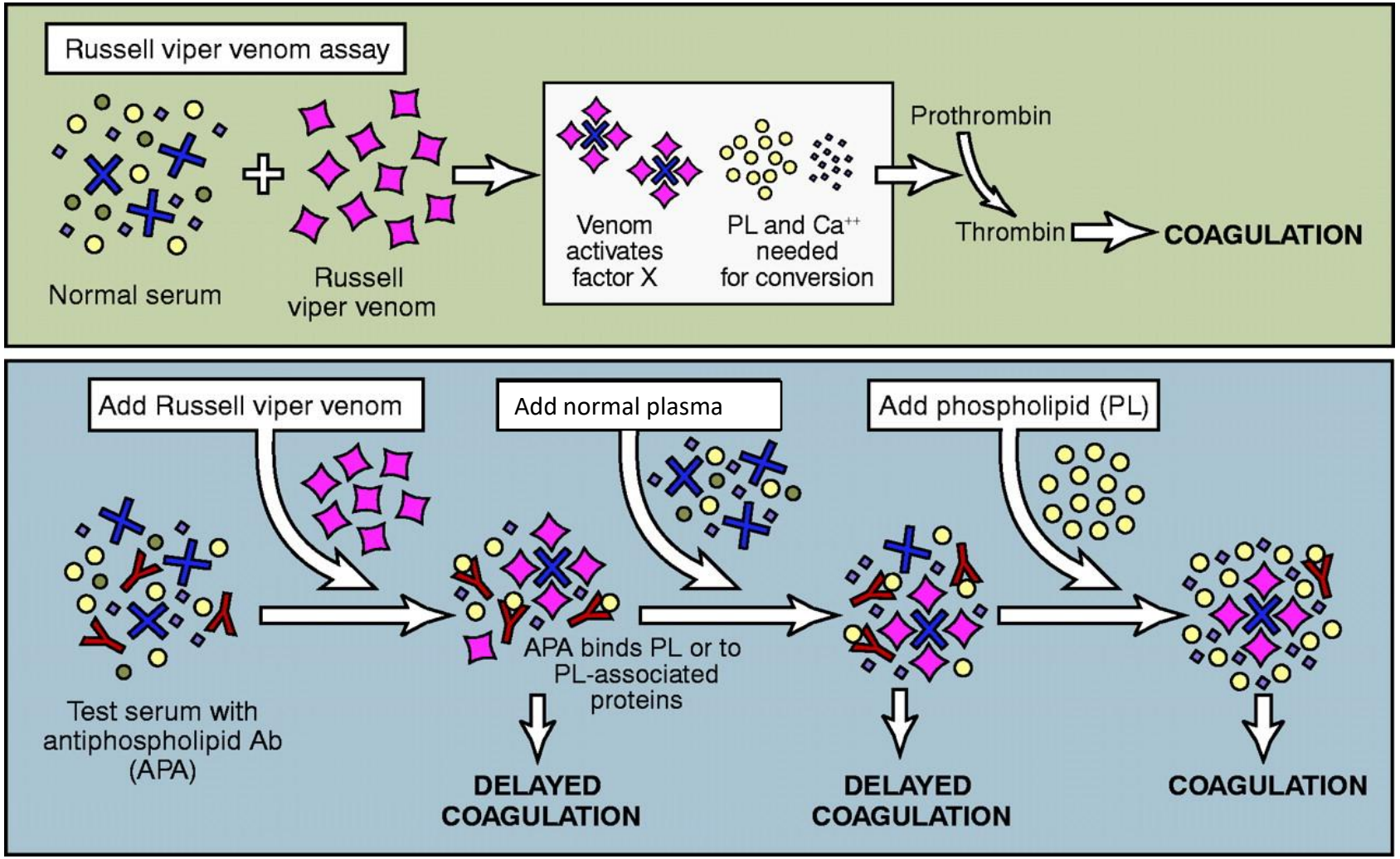
- anticardiolipin (aCL) antibody (immunoglobulin G [IgG] or IgM) enzyme-linked immunosorbent assay (ELISA),
- anti-beta2-glycoprotein (GP) I antibody (IgG or IgM) ELISA
- lupus anticoagulant (LA) assay.

Although cardiolipin is a phospholipid, most of the clinically relevant antibodies detected in this assay are actually binding to phospholipid-binding protein(s), frequently beta2-GP I, that bind to the cardiolipin in the assay.





Lupus anticoagulant



John G. Hanly CMAJ 2003;168:1675-1682

CMAJ·JAMC

EPIDEMIOLOGY

In a large retrospective analysis including patients without known autoimmune diseases, aPL were present:

9 percent of patients with pregnancy losses,
14 percent with stroke
11 percent with myocardial infarction
10 percent with deep vein thrombosis

Epidemiologic studies done in the general population from the United States and Italy determined a prevalence of APS ranging from 17 to 50 patients per 100,000

Duarte-García A, Arthritis Rheumatol. 2020
Radin M Arthritis Rheumatol. 2020

FROM TEXTBOOK TO BEDSIDE

- Most common acquired thrombophilia
- 10-20% of recurrent miscarriage
- Responsible for 1:5 strokes in under 50s
- 25-30% of patients with SLE have aPL but not all get thrombosis
- Thrombotic event can affect any vessel of any size

FROM TEXTBOOK TO BEDSIDE

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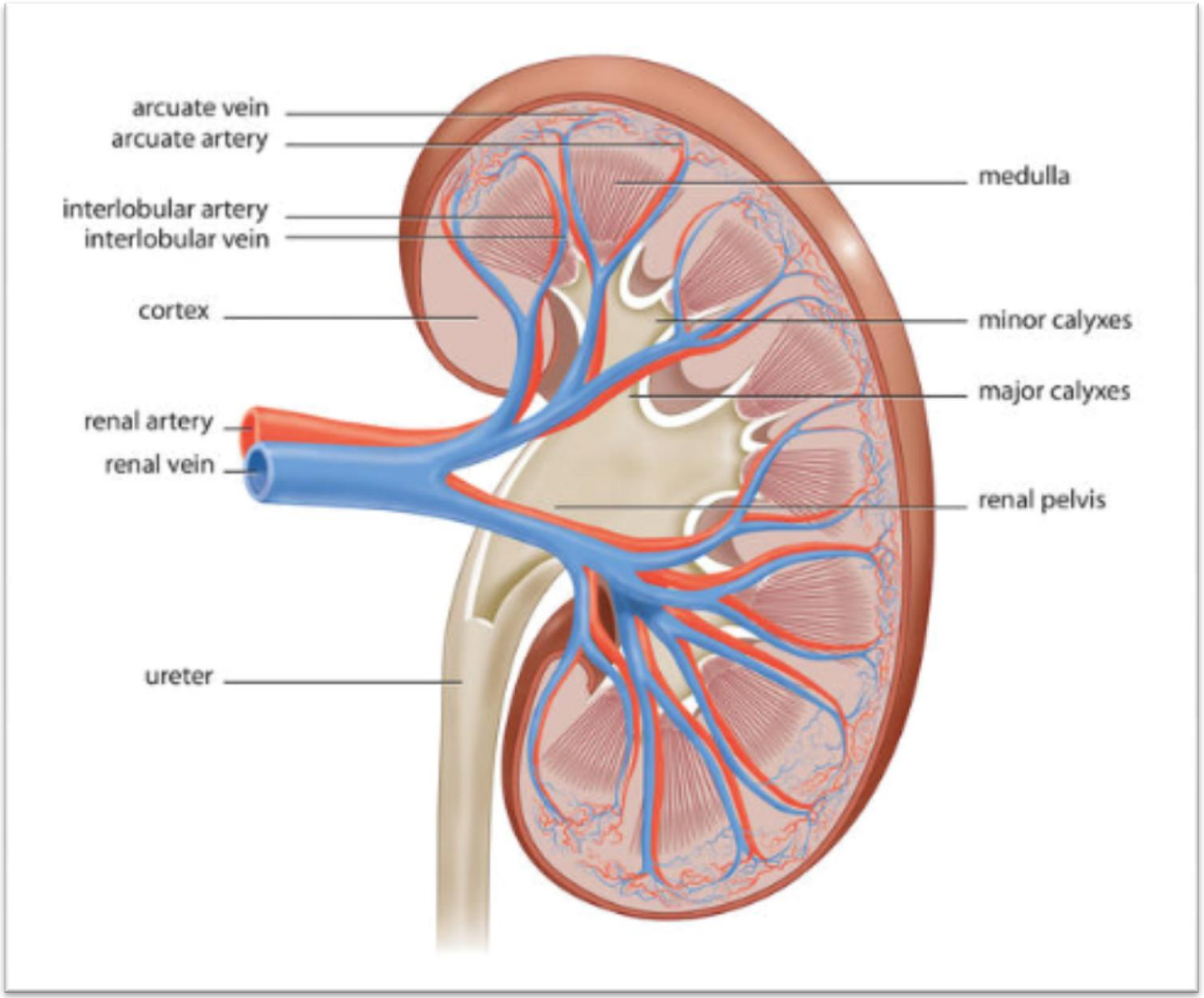
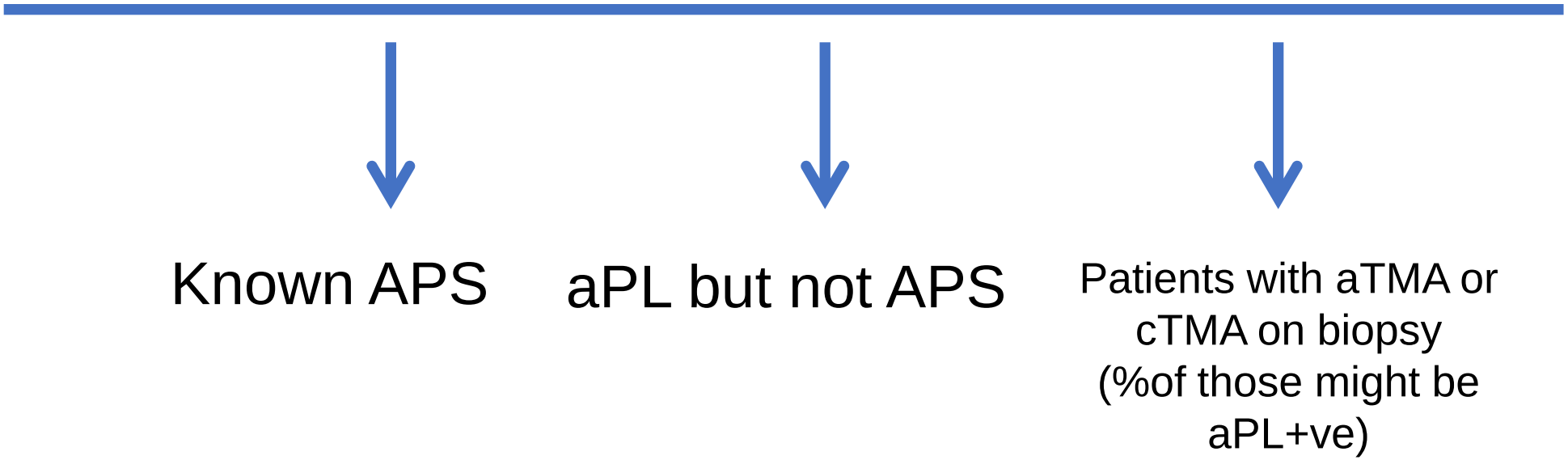
- **Thrombotic event can affect any vessel of any size**


arcuate vein
arcuate artery
interlobular artery
interlobular vein
cortex
renal artery
renal vein
ureter
medulla
minor calyxes
major calyxes
renal pelvis

Kidney manifestations in aPL+



In a cohort of 1000 patients with APS, the prevalence of renal involvement due to aPL is:

- More 5%
- Less 5%
- About 10%
- About 21%

APS and the Kidnevs

Antiphospholipid Syndrome

Clinical and Immunologic Manifestations and Patterns of Disease Expression in a Cohort of 1,000 Patients

Ricard Cervera,[1] Jean-Charles Piette,[2] Josep Font,[1] Munther A. Khamashta,[3]
Yehuda Shoenfeld,[4] María Teresa Camps,[5] Soren Jacobsen,[6] Gabriella Lakos,[7] Angela Tincani,[8]
Irene Kontopoulou-Griva,[9] Mauro Galeazzi,[10] Pier Luigi Meroni,[11]
Ronald H. W. M. Derksen,[12] Philip G. de Groot,[12] Erika Gromnica-Ihle,[13] Marta Baleva,[14]
Marta Mosca,[15] Stefano Bombardieri,[15] Frédéric Houssiau,[16] Jean-Christophe Gris,[17]
Isabelle Quéré,[17] Eric Hachulla,[18] Carlos Vasconcelos,[19] Beate Roch,[20]
Antonio Fernández-Nebro,[21] Marie-Claire Boffa,[2] Graham R. V. Hughes,[3] and
Miguel Ingelmo,[1] for the Euro-Phospholipid Project Group

n = 1000		
Renal manifestations:	27	2.7%

Cervera R. Arthritis Rheum 2002

APS and the Kidneys

Table 2 Main thrombotic manifestations related to APS associated with SLE and primary APS that appeared during the 10-year follow-up (1999–2009) of the 'Euro-Phospholipid' cohort

Thrombotic manifestations*	APS associated with SLE (n=132)† No. (%)	Primary APS (n=420)† No. (%)	p Value‡
Superficial thrombophlebitis	0	8 (1.9)	0.036
Deep vein thrombosis	4 (3.0)	18 (4.3)	
Stroke	9 (6.8)	20 (4.8)	
Transient ischaemic attacks	8 (3.1)	13 (3.1)	
Myocardial infarction	5 (3.8)	5 (1.2)	0.050
Unstable angina	4 (3.0)	10 (2.4)	
Pulmonary embolism	4 (3.0)	9 (2.1)	
Glomerular thrombosis	4 (3.0)	1 (0.2)	0.003

*Some patients had several associated presenting manifestations.
†Number of patients that continued in the study until 2009 (230 patients with APS associated with SLE were lost).
‡Pearson χ^2.
APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Cervera R. Ann Rheum Dis 2014

5 for renal involvement
(excluding CAPS)

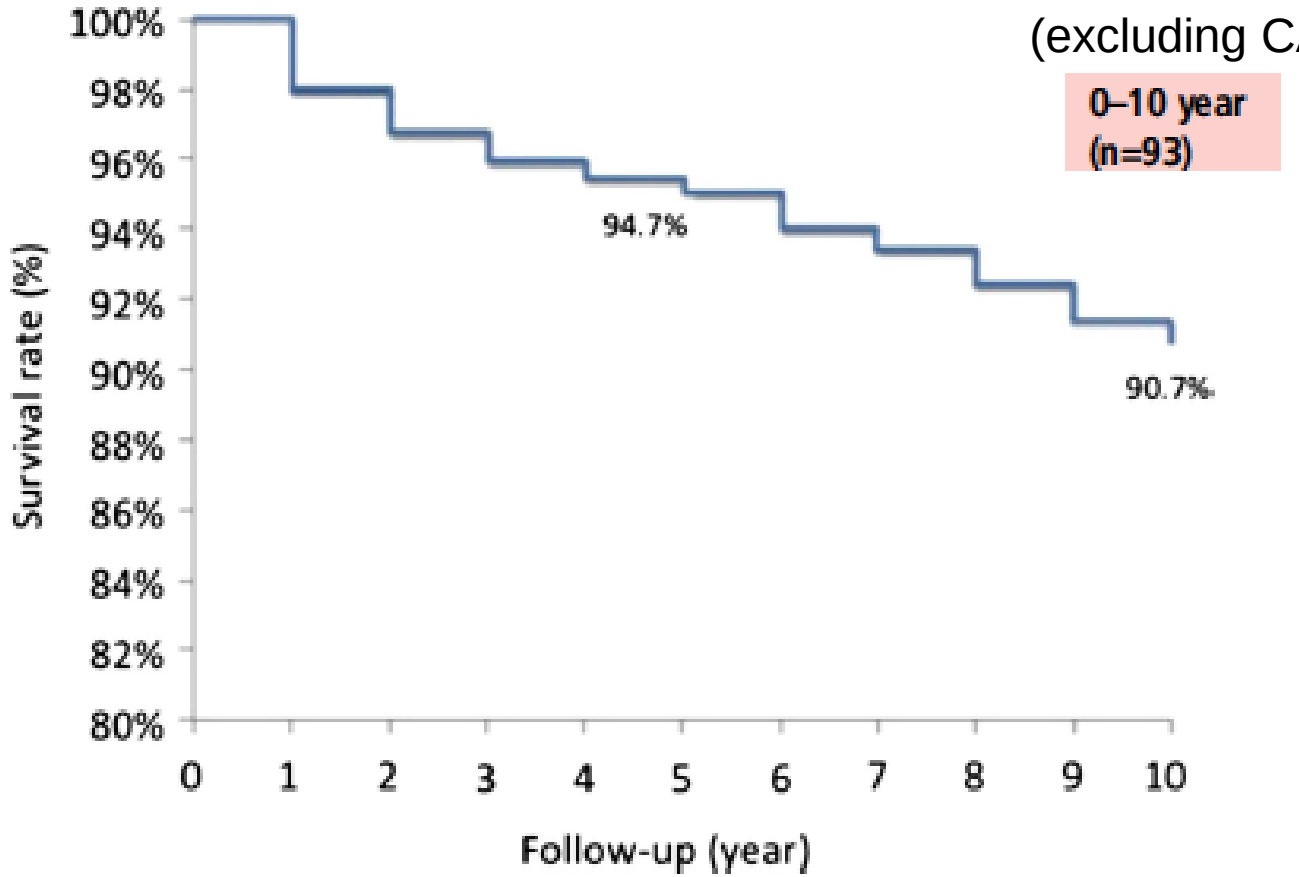


Figure 1 Kaplan–Meier survival curve of the total cohort showing a 94.7% probability of remaining alive at 5 years and 90.7% at 10 years from the time of entry into the study.

Cervera R. Ann Rheum Dis 2014

AGENDA

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- APS and Kidney: Therapeutic options

APS and the Kidneys

- Renal artery stenosis and thrombosis
- Renal vein thrombosis
- Renal infarction
- So called “APS Nephropathy”
- CAPS

Sciascia S, Nat Rev Neph 2014

CONCISE REPORT

Renal artery stenosis in the antiphospholipid (Hughes) syndrome and hypertension

S R Sangle, D P D'Cruz, W Jan, M Y Karim, M A Khamashta, I C Abbs, G R V Hughes

Ann Rheum Dis 2003;**62**:999–1002

Group 1: 77 patients with aPL
60 with SLE and APS
11 with primary APS,
and 6 with aPL only

} uncontrolled hypertension

Group 2: patients with uncontrolled hypertension.

Group 3: 92 healthy, normotensive, aPL antibody

Sangle S, Ann Rheum Dis, 2003

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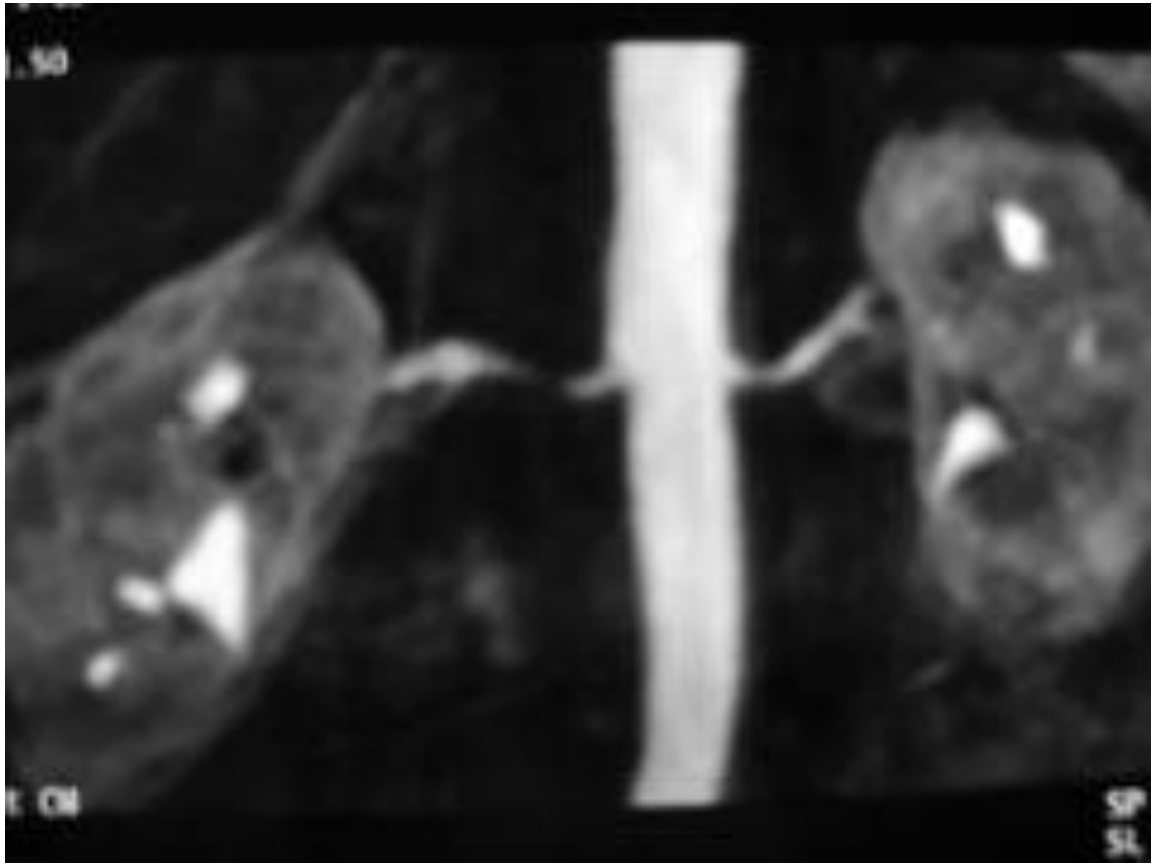
FINDINGS

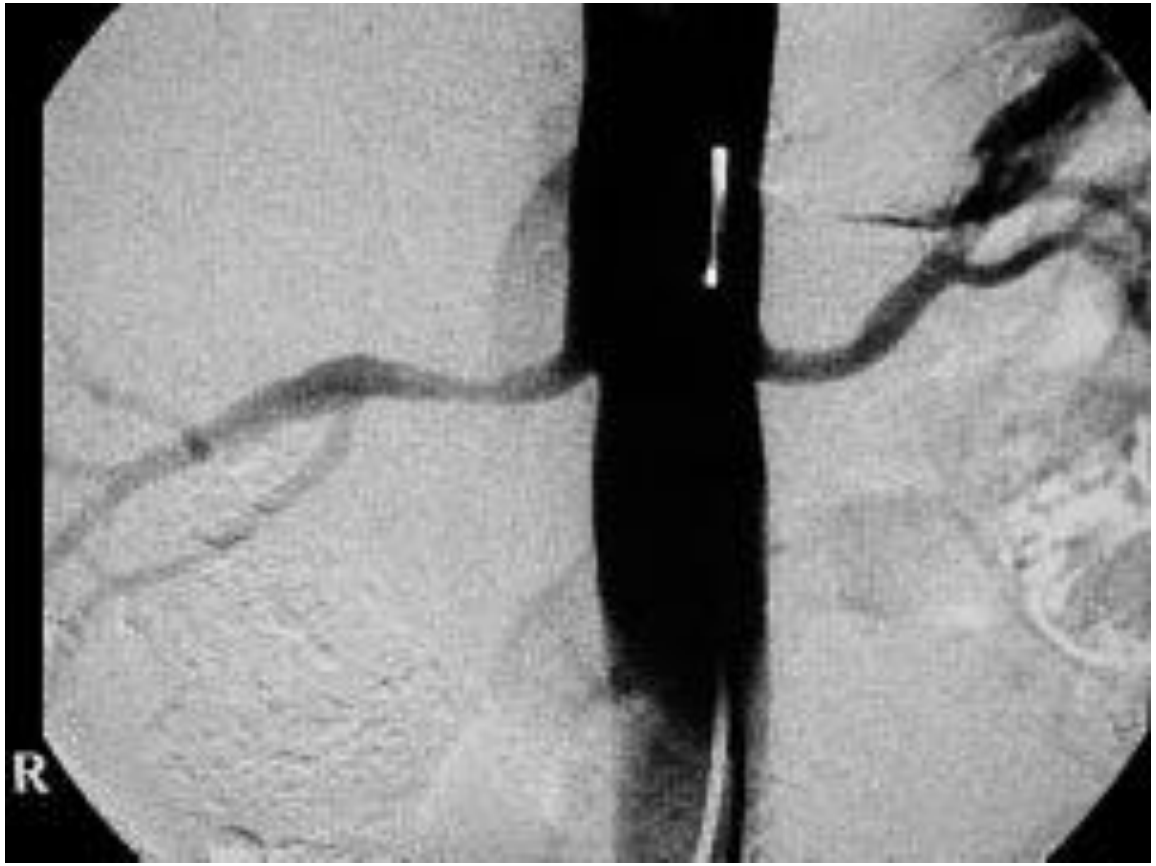
A **significantly increased prevalence of renal artery stenosis (26%)** was found in patients with APS and hypertension, compared with relatively young (<50 years) hypertensive controls and healthy potential donors.

Sangle S, Ann Rheum Dis, 2003

Magnetic resonance angiography showing renal artery stenosis in a patient with APS and hypertension.



RAS confirmed on arteriography. The lesion is a long smooth stenosis with no evidence of atheroma.



Sangle S, Ann Rheum Dis, 2003

Concise Report

Renal artery stenosis in hypertensive patients with antiphospholipid (Hughes) syndrome: outcome following anticoagulation

S. R. Sangle, D. P. D'Cruz, I. C. Abbs, M. A. Khamashta and G. R. V. Hughes

- They studied 23 patients retrospectively with renal artery stenosis (RAS).
- Fourteen received oral anticoagulation for more than 1 yr.
- Five patients had primary APS.
- Patients were divided into two groups based on their INR (<3.0 and 3.0).
- Nine patients had repeat magnetic resonance angiography (MRA) or an
- angiogram of the renal arteries after 2 yr.

Sangle S, Rheumatology, 2005

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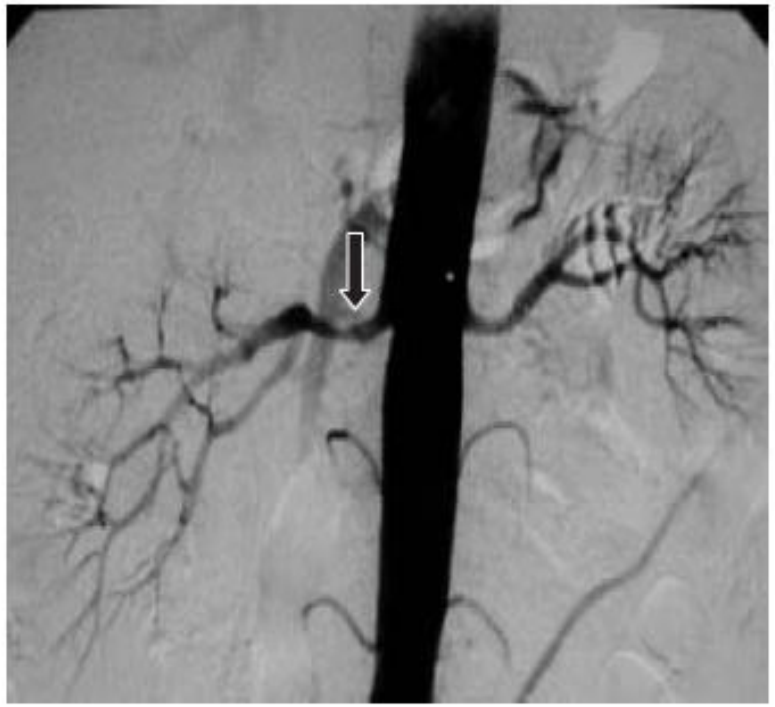
FINDINGS

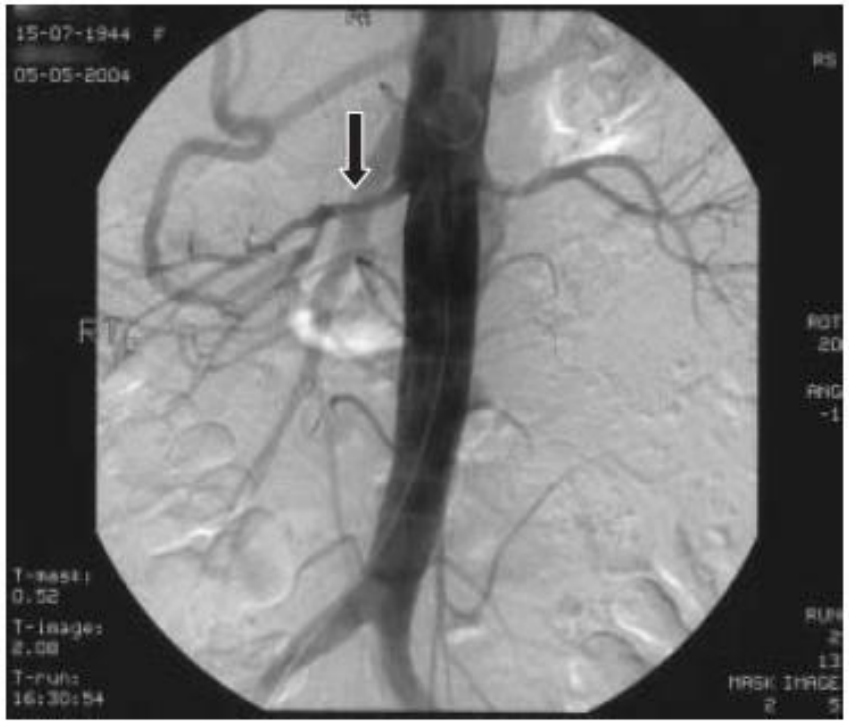
Anticoagulation with INR maintained 3.0 helped to control the blood pressure and prevent the progression of renal disease.

Sangle S, Rheumatology, 2005

DSA angiogram 2002



DSA angiogram 2004



Target INR 3.0–4.5

Recanalization of right renal artery stenosis in a patient APS with hypertension on anticoagulation (median INR 3.3).

Sangle S, Rheumatology, 2005

So-called “APS Nephropathy” or aPL-associated nephropathy

Thrombotic microangiopathy involving both arterioles and glomerular capillaries *and/or*

One or more of:

- Fibrous intimal hyperplasia involving organized thrombi with or without recanalization
- Fibrous and/or fibrocellular occlusions of arteries and arterioles
- Focal cortical atrophy
- Tubular thyroidization (large zones of atrophic tubules containing eosinophilic casts)

Miyakis S, J Thromb Haemost. 2006;

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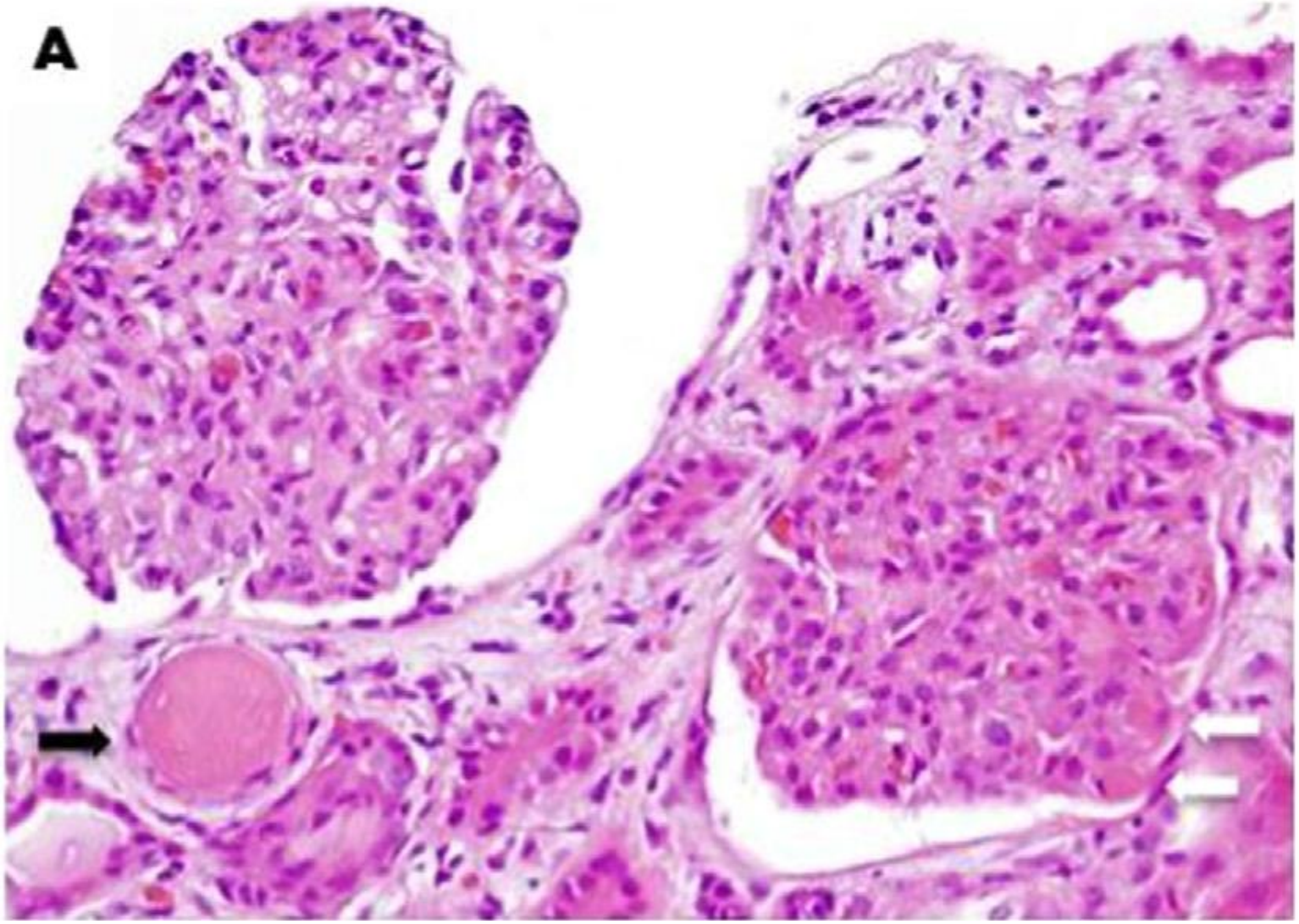
Vasculitis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, malignant hypertension, and other reasons for chronic renal ischemia are exclusions.

If SLE is also present, the above lesions should be distinguished from those associated with lupus nephropathy.

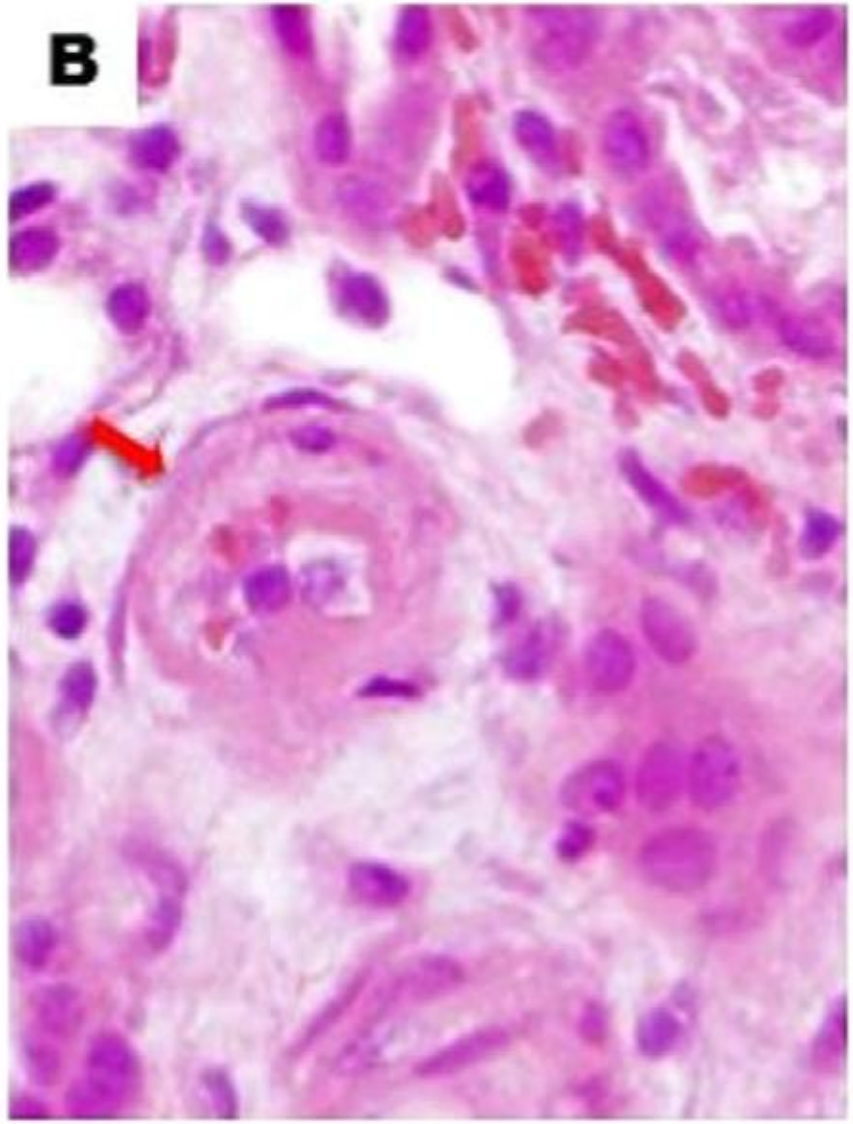
Miyakis S, J Thromb Haemost. 2006;



Intracapillary thrombi in the glomerulus on the left.

The afferent arteriole is occluded entirely by a fibrin thrombus (black arrow).

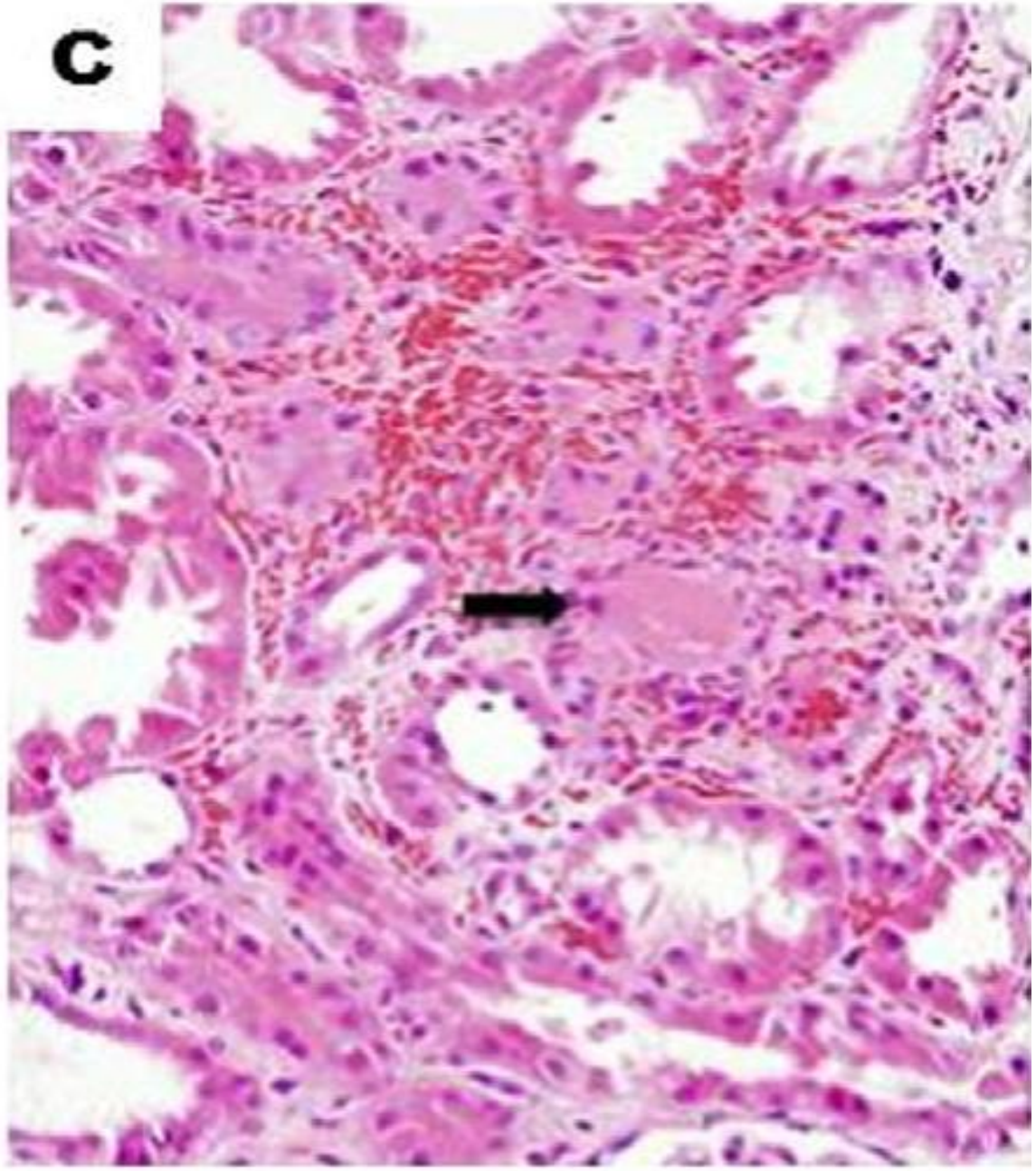
Sciascia S, Nat Rev Neph 2014



Fibrinoid necrosis and mucoid intimal edema in the intima of an arteriole (red arrow) with fragmented red blood cells.

The interstitium around the arteriole is edematous

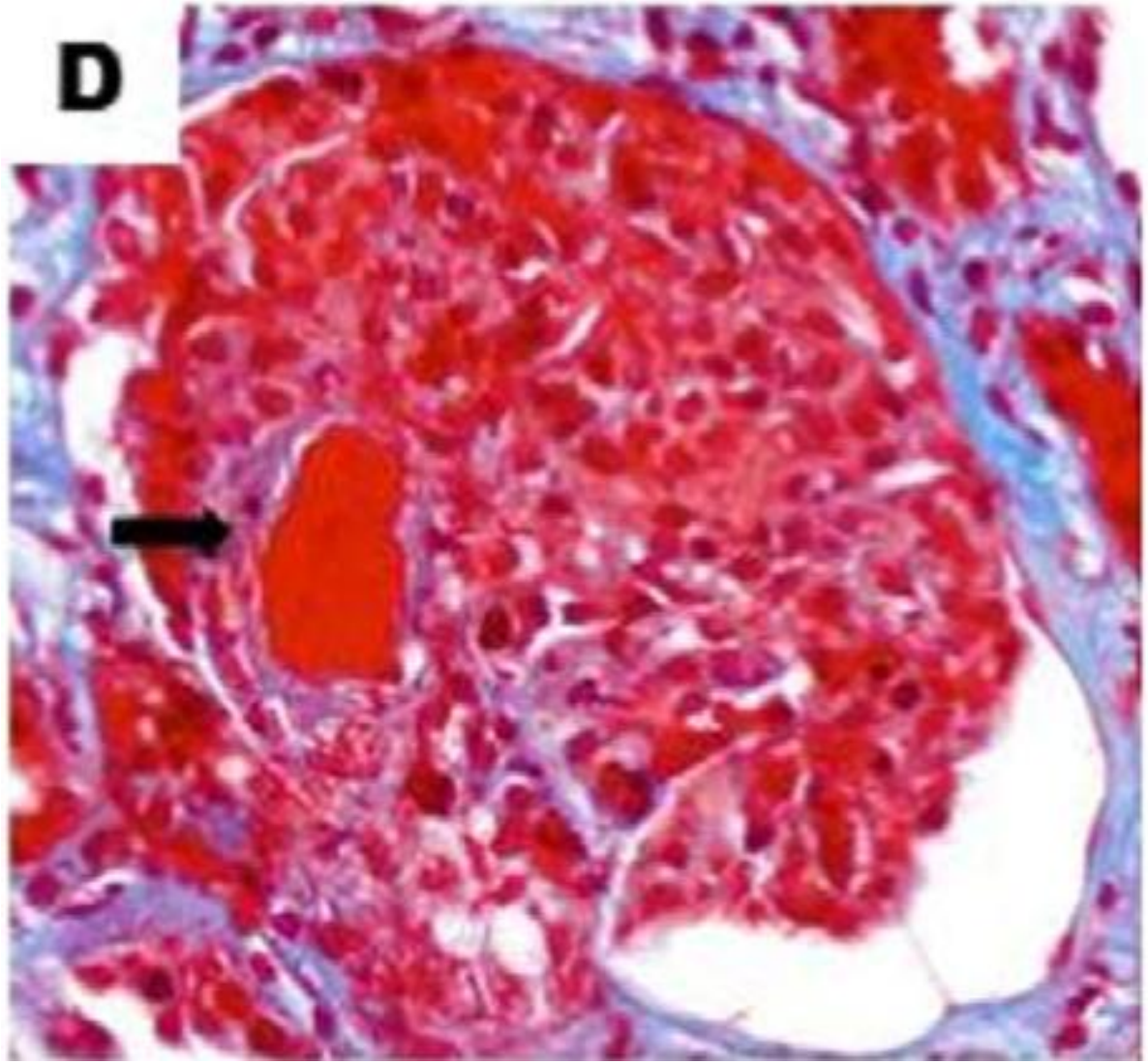
Sciascia S, Nat Rev Neph 2014



Thrombi occluding peritubular capillaries (black arrow).

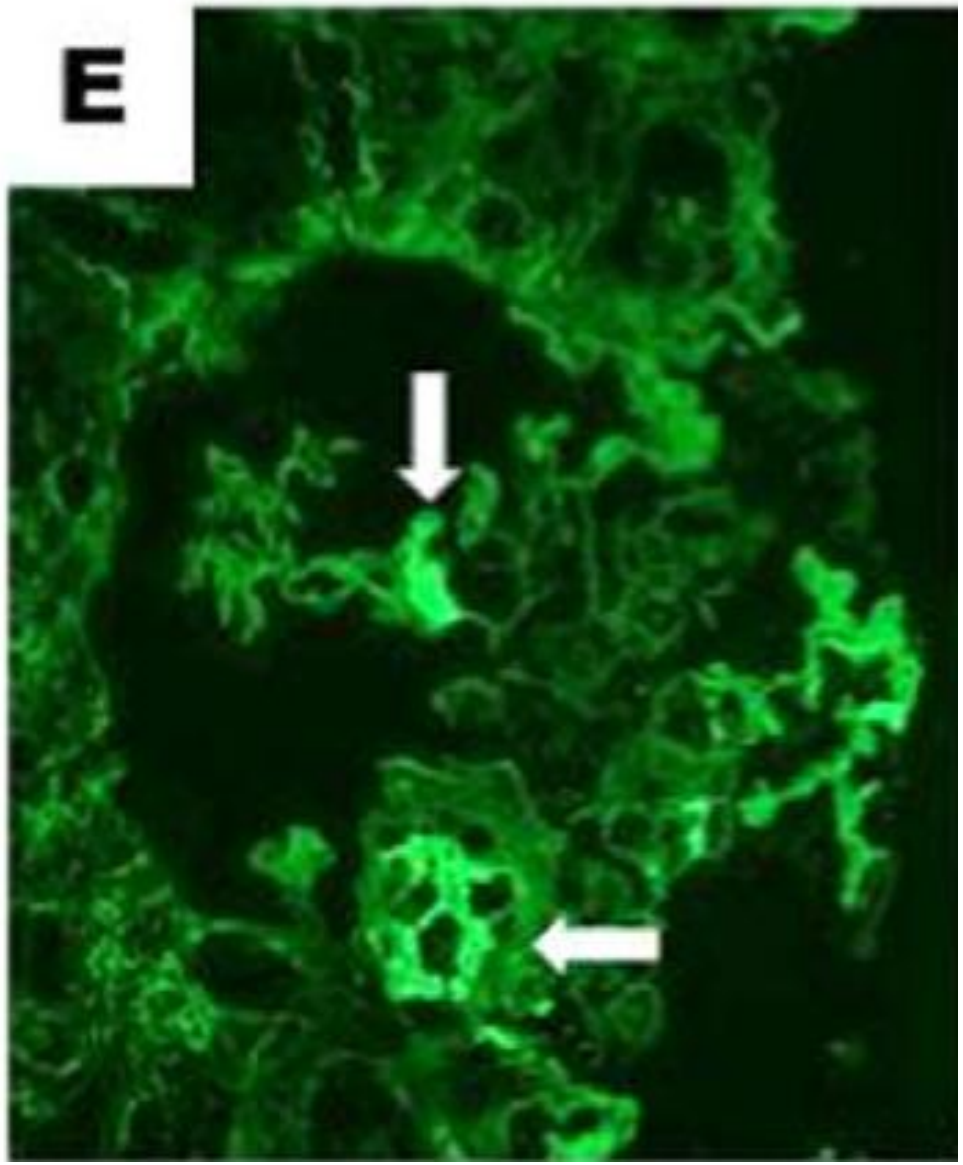
Interstitial edema, hemorrhage, and acute tubular injury might be present depending on the severity of the acute ischemic injury.

Sciascia S, Nat Rev Neph 2014



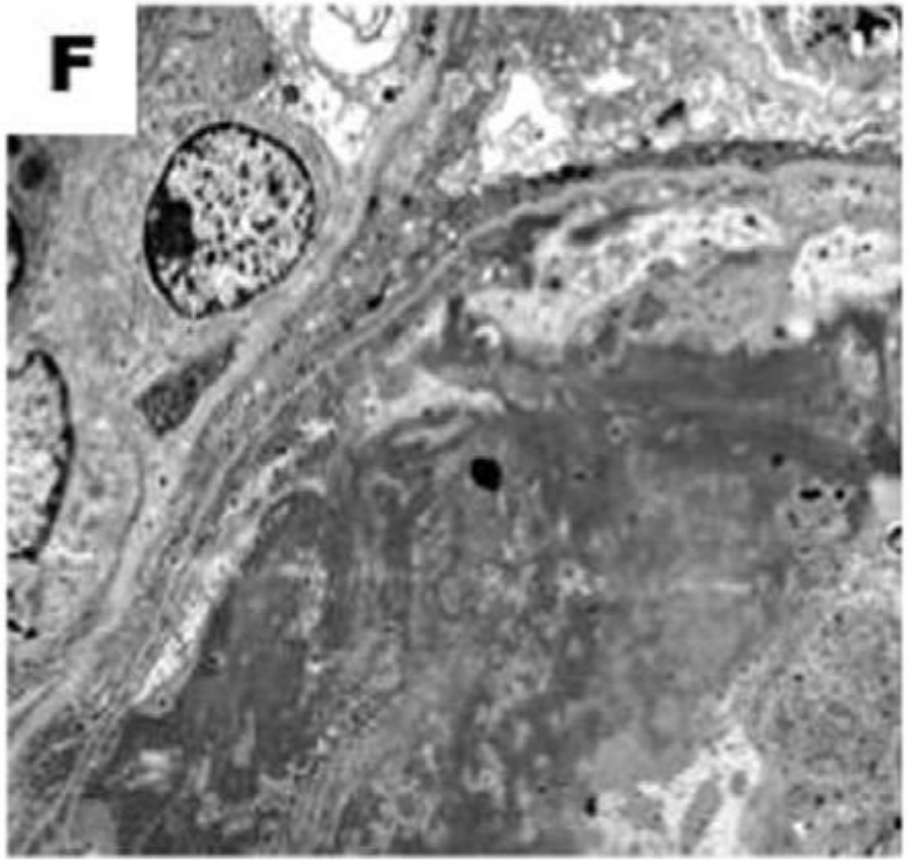
Large intravascular thrombus at the vascular pole of a glomerulus is red under trichrome staining (black arrow).

Sciascia S, Nat Rev Neph 2014

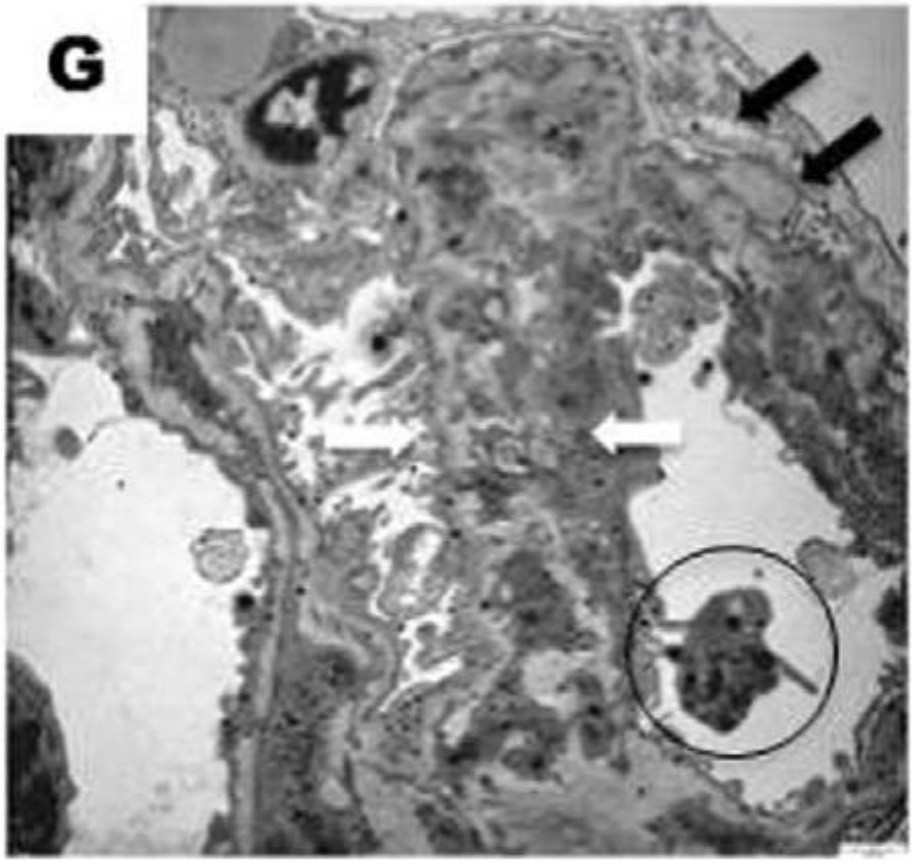


Positive staining for fibrinogen in glomerular capillary lumina and at the vascular pole (white arrows)

Sciascia S, Nat Rev Neph 2014



Fibrin occludes the capillary lumen. Endothelial cells have lost fenestration and podocytes show extensive foot process effacement.



Double contours without interposition of electron dense immune complexes can be seen (white arrow).

Sciascia S, Nat Rev Neph 2014

Is it safe for patients suspected of APS undergo to kidney-biopsy?

Open Access Research

BMJ Open

Outpatient percutaneous native renal biopsy: safety profile in a large monocentric cohort

Dario Roccatello,[1,2] Savino Sciascia,[1,2] Daniela Rossi,[1] Carla Naretto,[1] Mario Bazzan,[3] Laura Solfietti,[1] Simone Baldovino,[1] Elisa Menegatti[1]

Lupus

Safety of outpatient percutaneous native renal biopsy in systemic autoimmune diseases: results from a monocentric cohort

D Roccatello*, S Sciascia*, D Rossi, C Naretto, M Bazzan, L Solfietti, M Sandrone, M Radin, S Baldovino, E Menegatti

https://doi.org/10.1177/0961203317751645

APS and the Kidneys

- Renal artery stenosis and thrombosis
- Renal vein thrombosis
- Renal infarction
- So called “APS Nephropathy”
- CAPS
- Glomerular microthrombosis in LN related to aPL

Sciascia S, Nat Rev Neph 2014

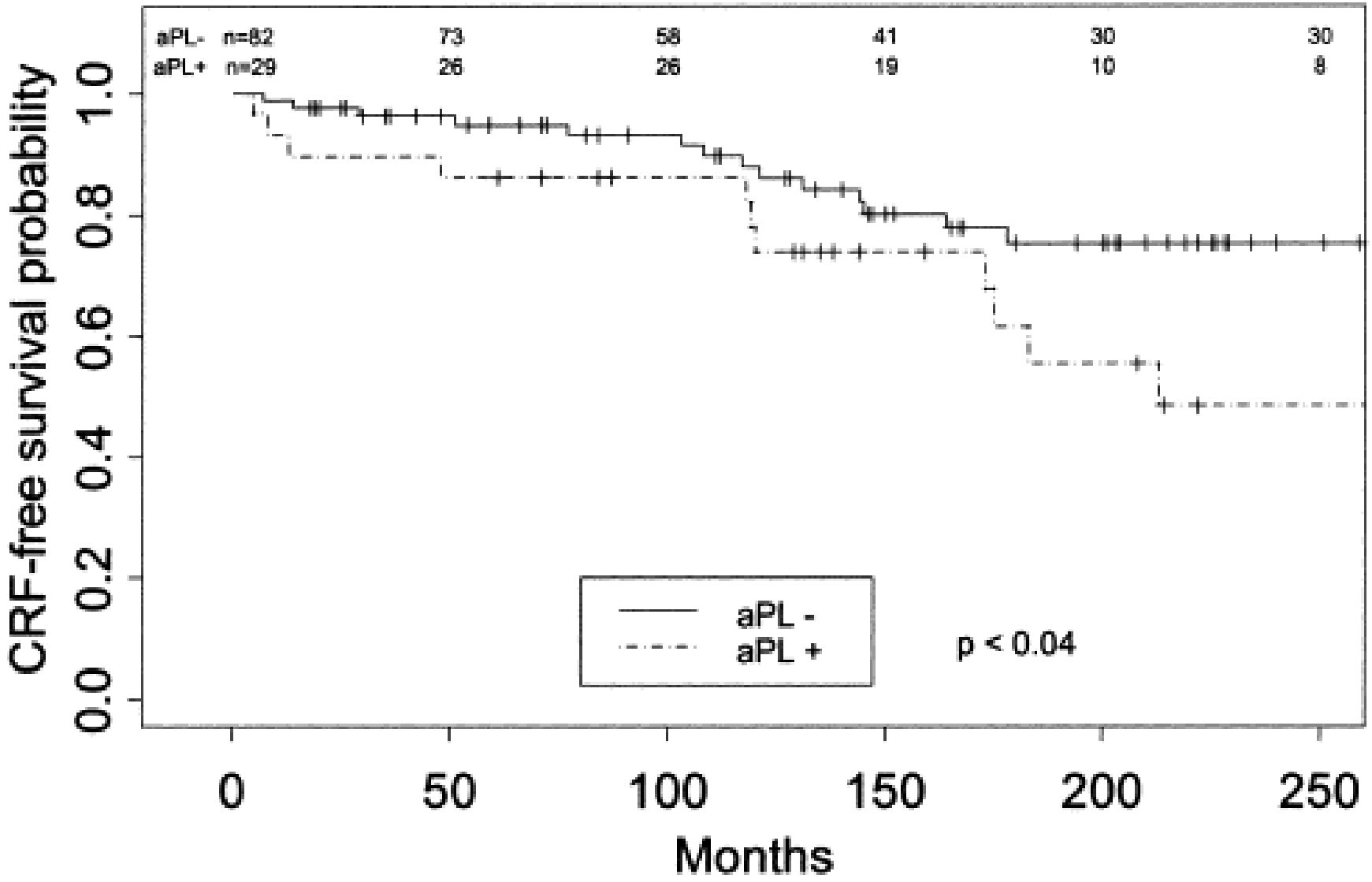
THE STORY OF LISA

RR	24 yrs
Age 14	SLE: ANA+ve, anti-Sm, skin rush, photosensitivity, arthralgia, recurrent aphthosis, aPL (LAC, aCL, anti-Beta2GPI)
10 years	HCQ, PDN 5-7.5 mg/die, azathioprine, LDA

Kidney manifestations in

aPL but not APS

Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis.

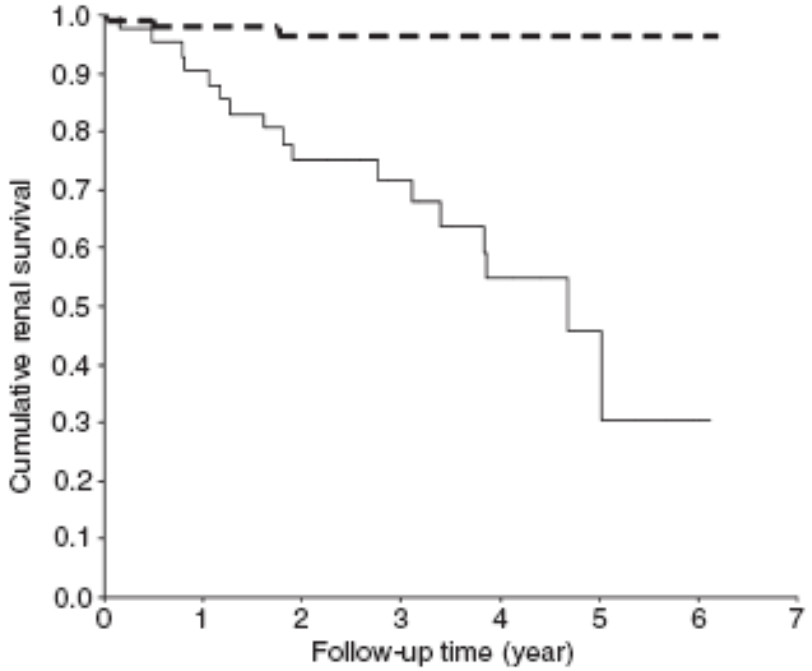


Moroni at al, Am J Kidney Dis. 2004

APSN and LN

150 SLE patients
51 (34%) APS nephropathy

More likely to have:
Hypertension
Heavy proteinuria
Renal impairment
Progression to ESRF



Cheunsuchon B et al Nephrology 2007

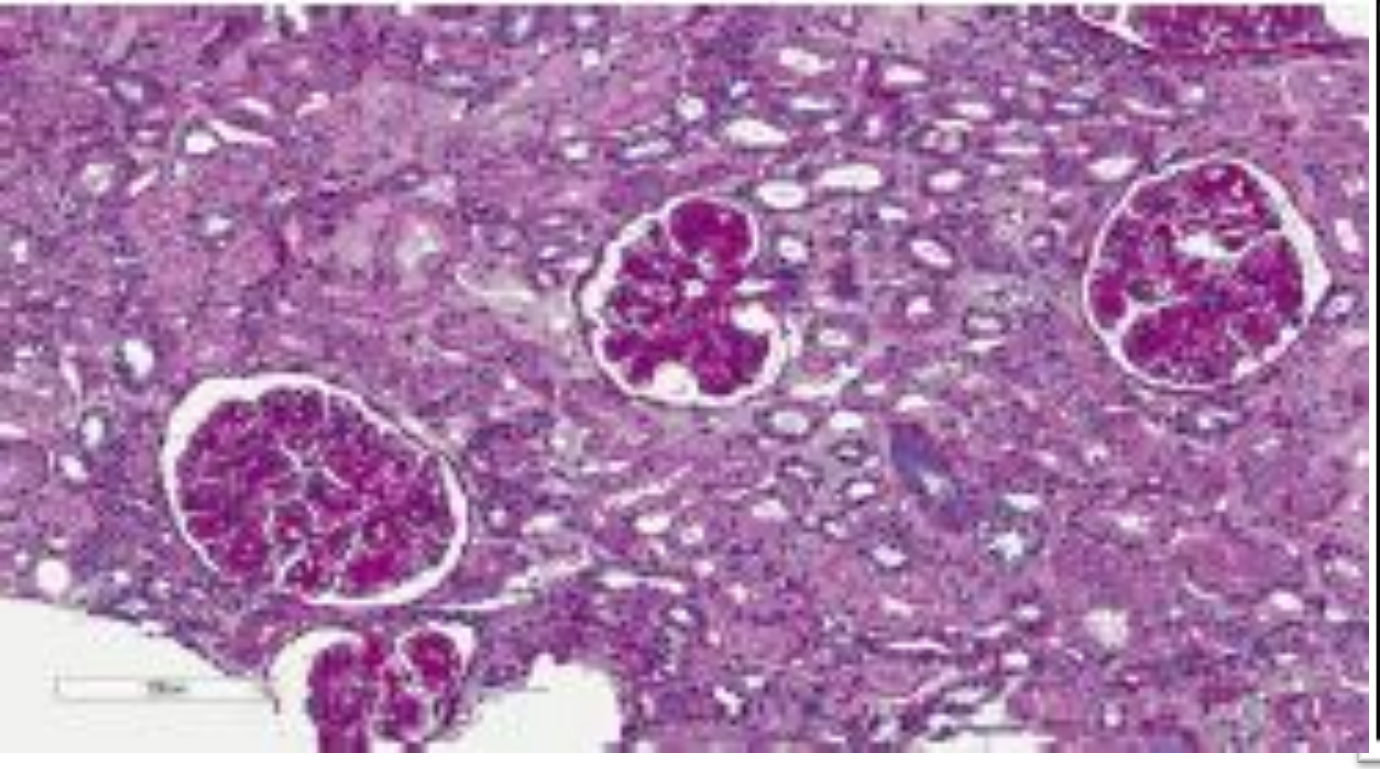
THE STORY OF LISA

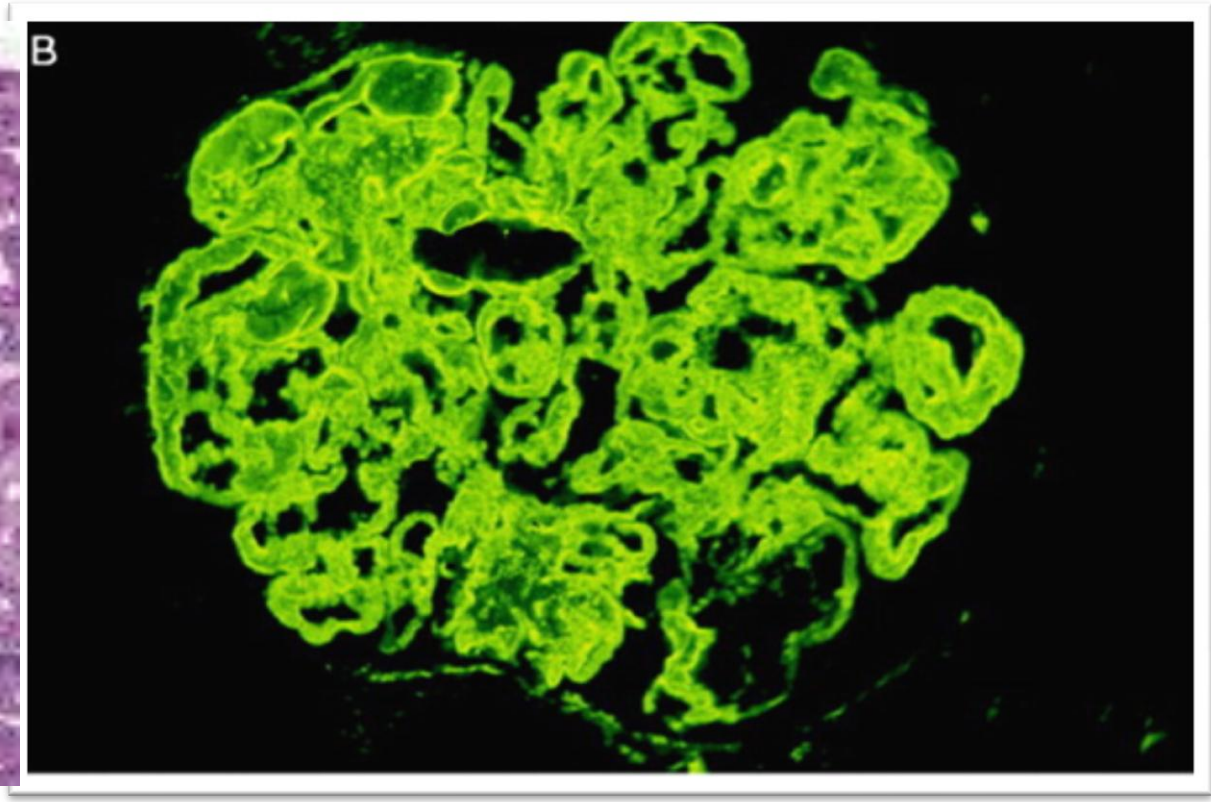
RR 24 yrs

Malaise
Nephrotic range proteinura
Newly diagnosed arterial hypertension

Ix Hb 11.0 g/dl Plts 157.000 WBC 4500
Creatinine 1.4 mg/dl
24 hour protein 4.3 g/day
active urine sediment
C3 56 C4 4
anti-DNA POS
ESR 56 mm/h; CRP negative
Renal Ultrasound and Doppler: neg

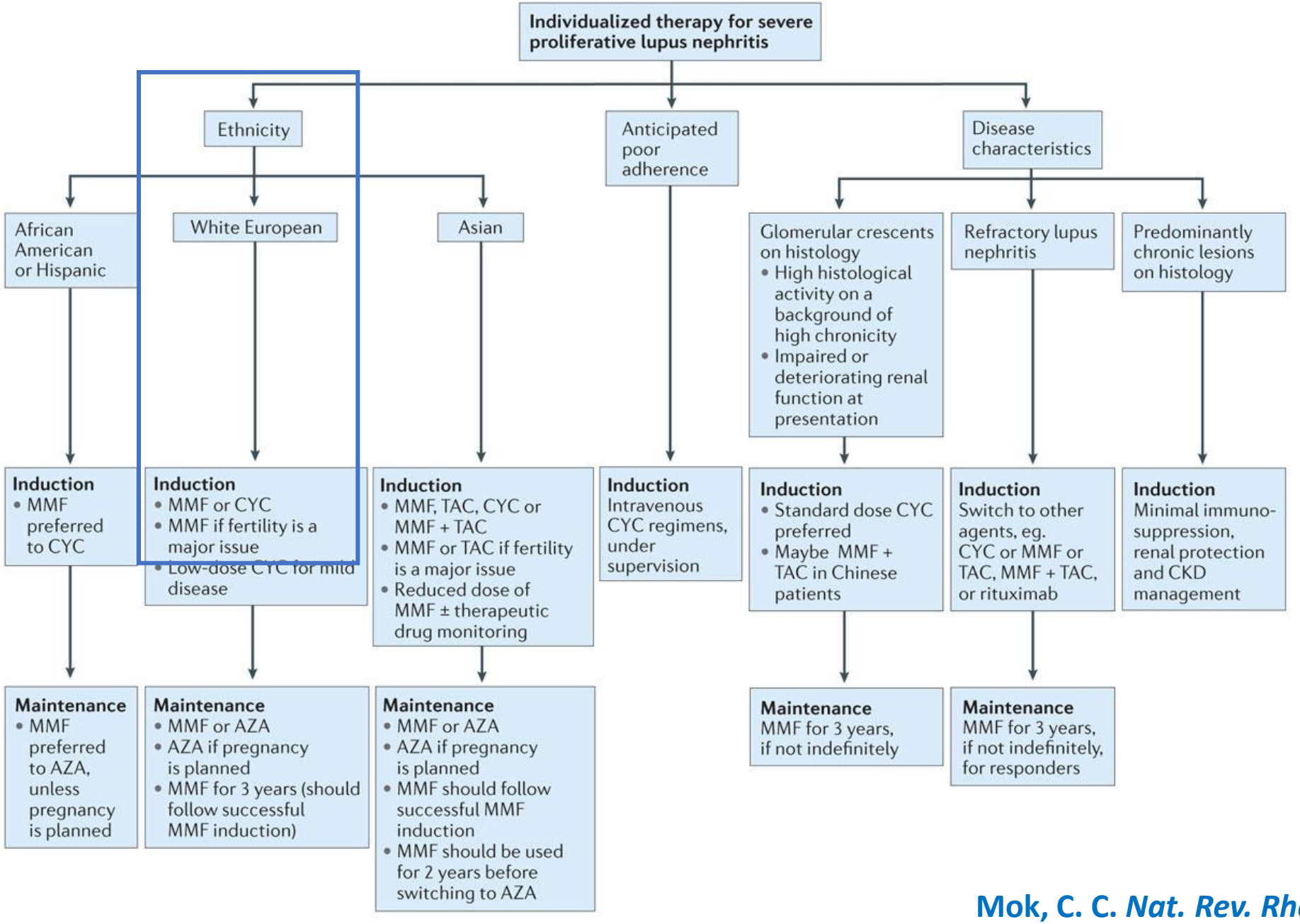
THE STORY OF LISA



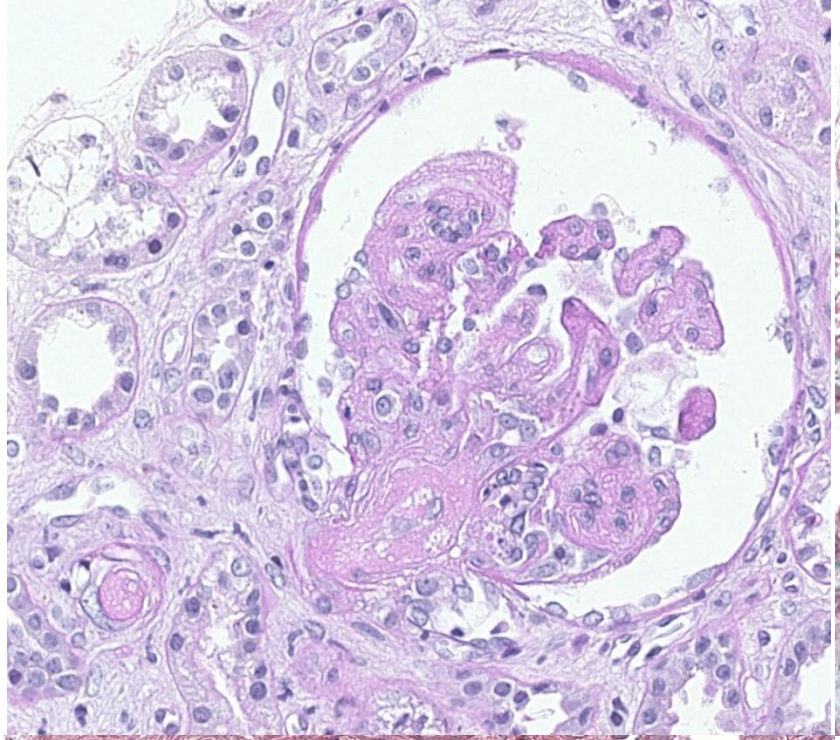


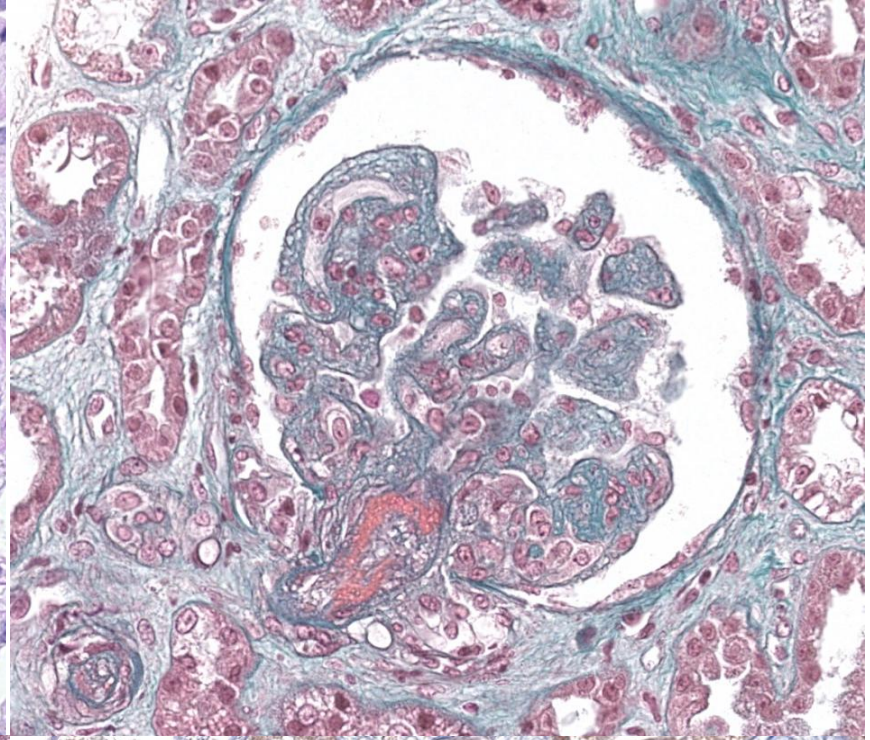
Diffuse global LN: class IV-G i.e., >50 % of the involved glomeruli showing global lesions

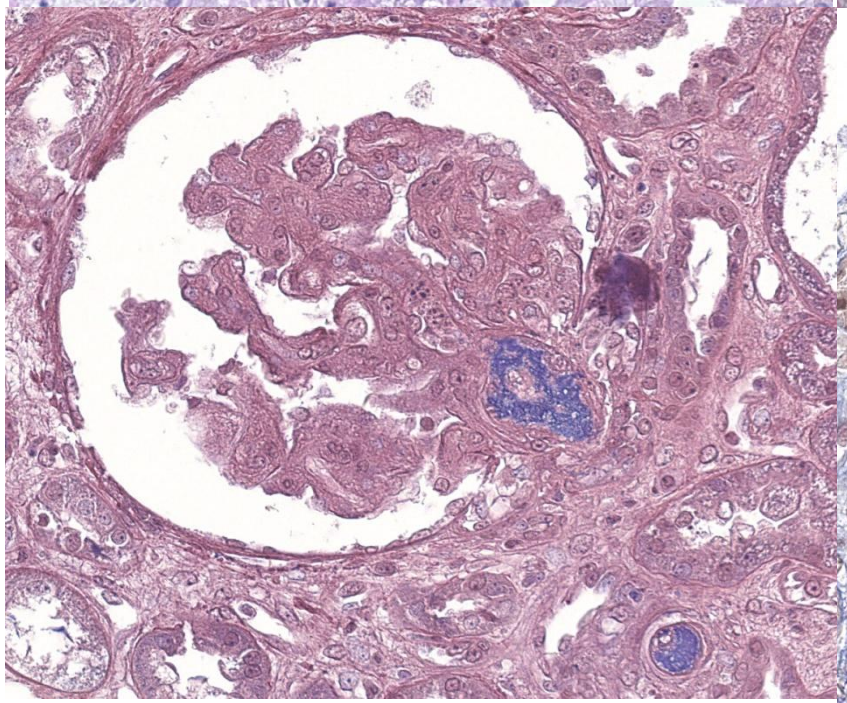
THERAPY CLASS IV LN

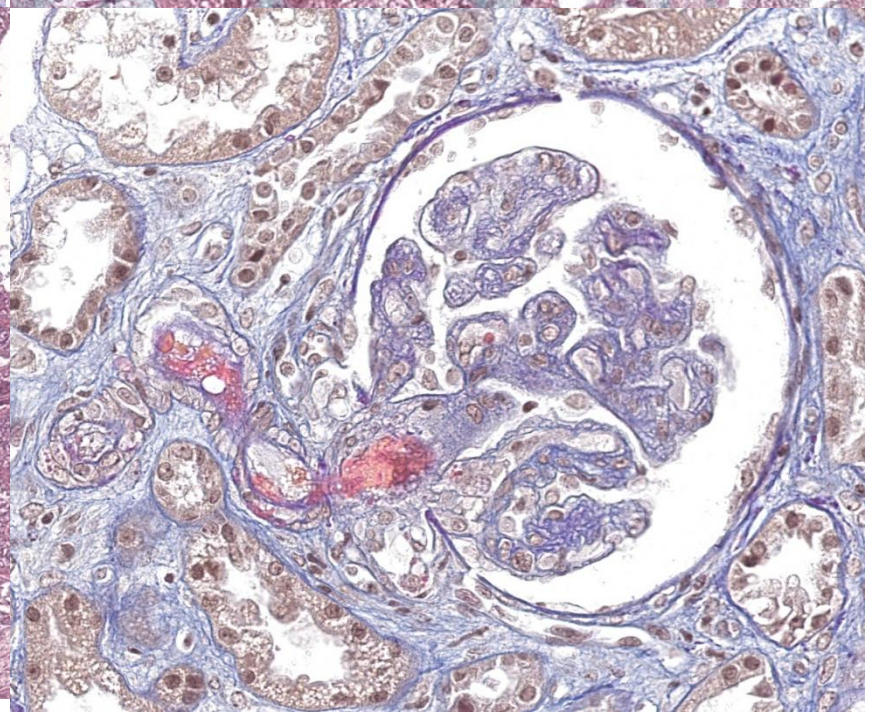


Mok, C. C. *Nat. Rev. Rheumatol.* 2015



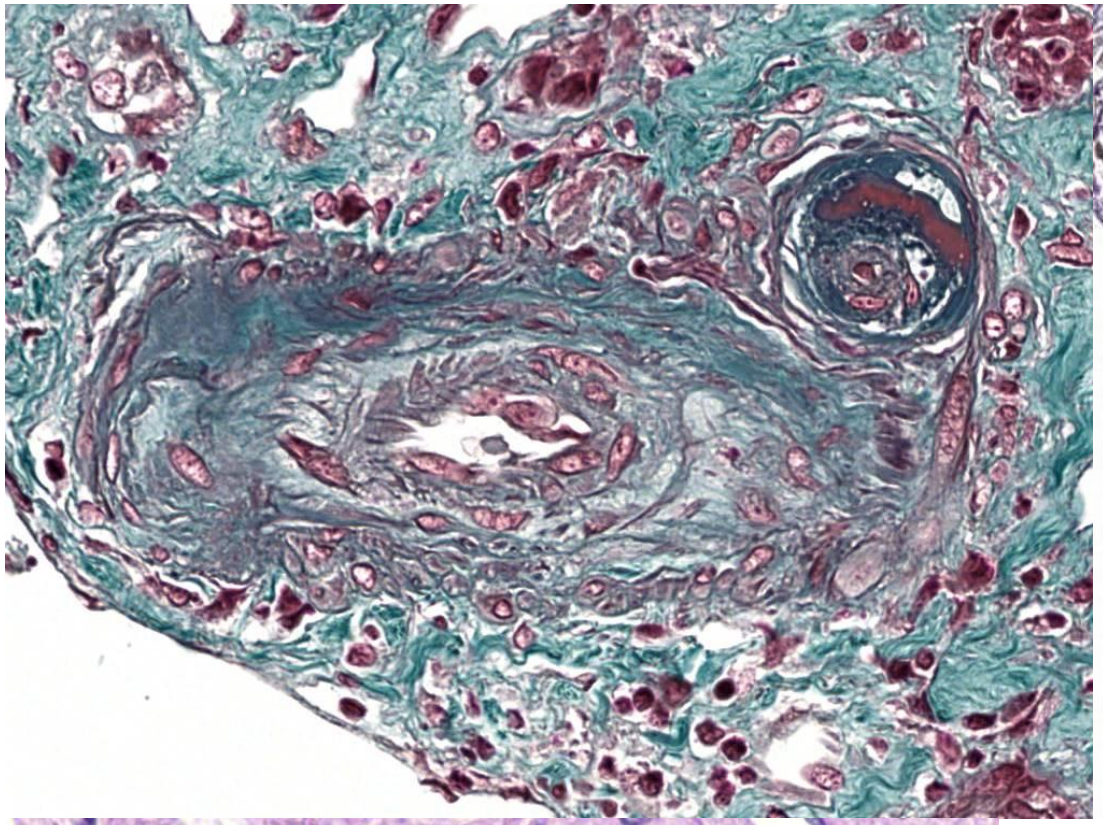


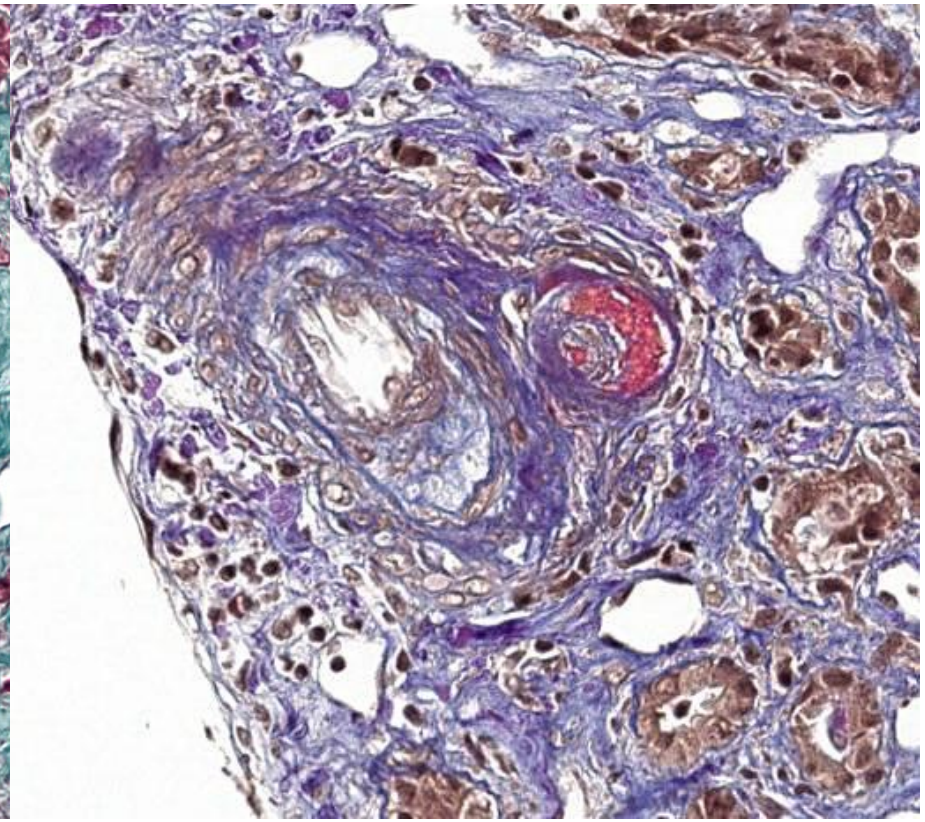


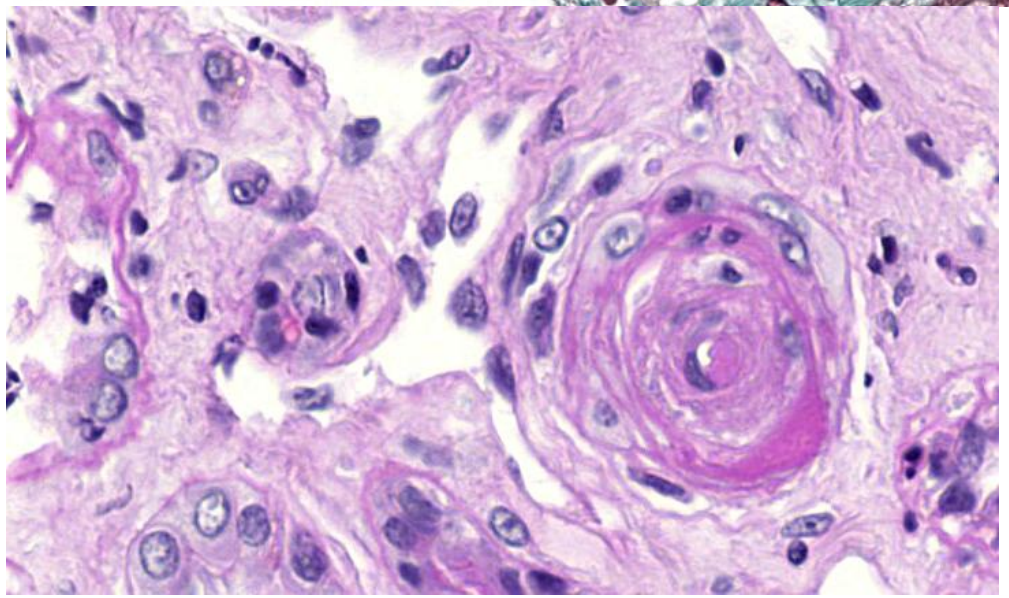


TROMBOTIC MICROANGIOPATHY

FIBRINOID NECROSIS OF PRE GLOMERULAR ARTERIOLES



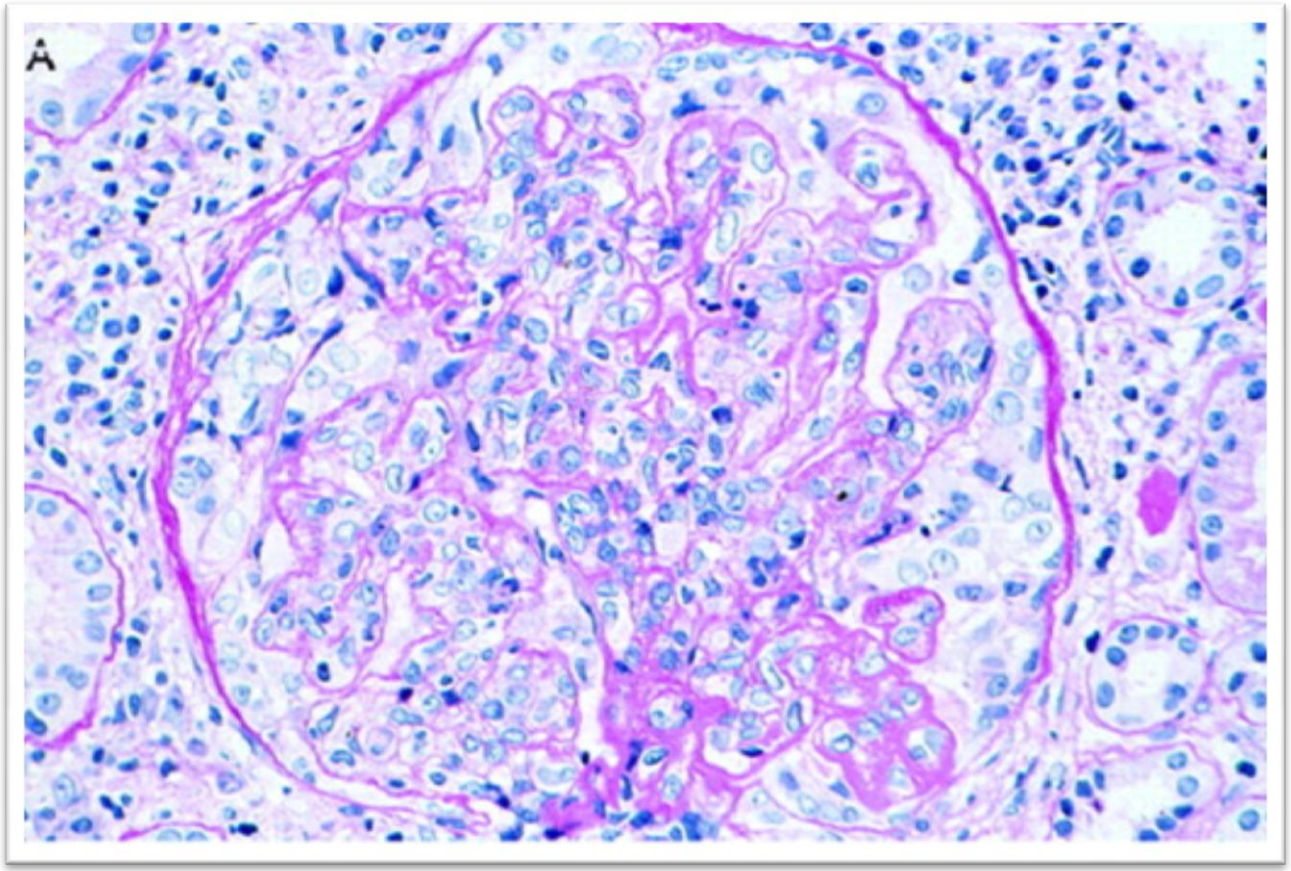


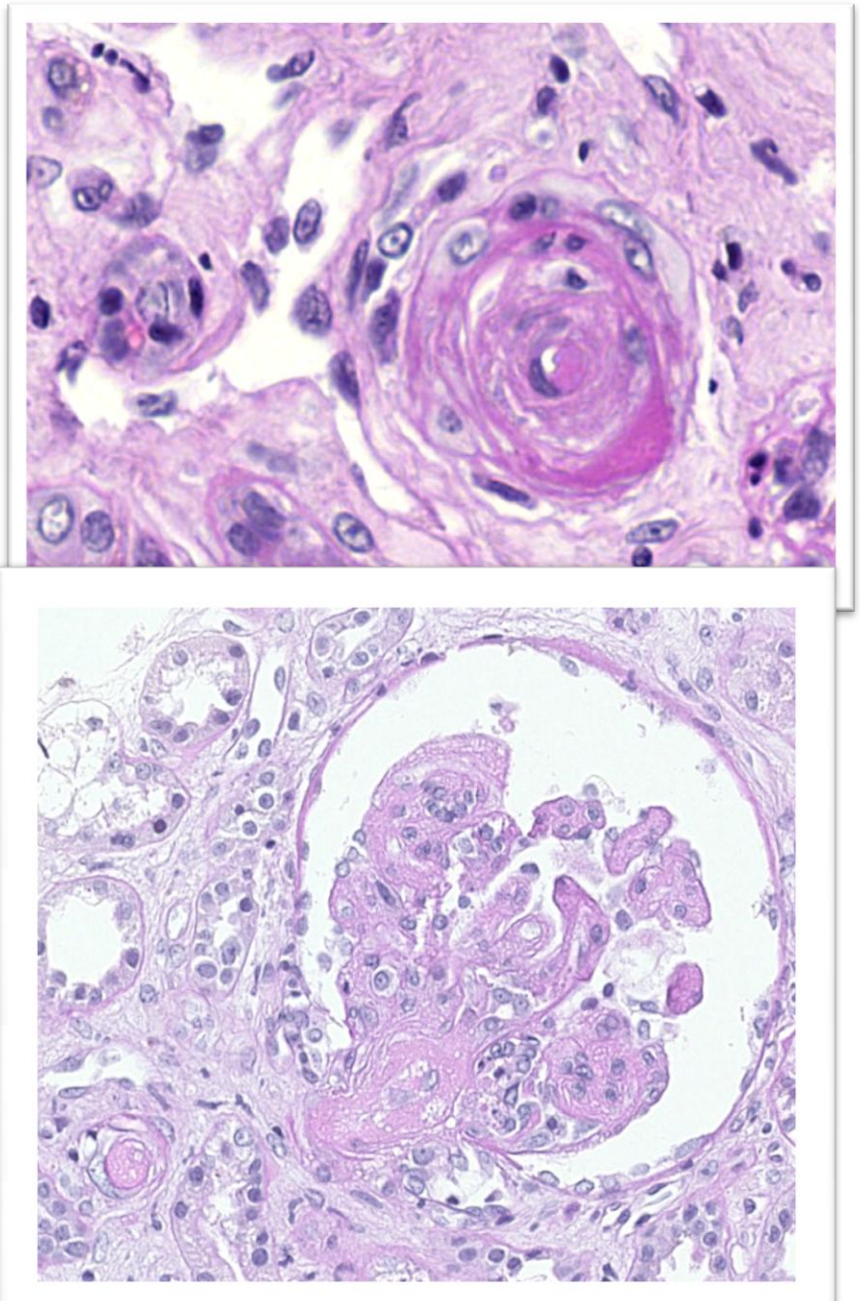


TROMBOTIC MICROANGIOPATHY

INTIMAL HYPERPLASIA AND «ONION SKIN» LESIONs WITH FIBRIN INSUDATION

WHAT WE KNOW ON TMA & LN?





WHAT WE KNOW ON TMA & LN?

- Would the presence of TMA at the biopsy change your therapeutic approach in the context of LN

- YES
- NO

WHAT WE KNOW ON TMA & LN?

- Would you…

- Use immunosuppressants alone
- Add anti-aggregants
- Add heparin
- Add VKA
- Add DOACs

AGENDA

- Definition of Antiphospholipid Syndrome
- Epidemiology
- APS and Kidney: Clinical aspects
- APS and Kidney: Diagnosis
- **APS and Kidney: Therapeutic options**

1. TMA AS A POOR PROGNOSTIC FACTOR IN LN

Table 1. Clinical and laboratory parameters

Symptom	Total (n = 197)	TMA (n = 50)	Non-TMA (n = 147)	*P* value
Pedal edema	165 (83.8%)	43 (86%)	122 (83%)	0.825
Facial puffiness	151 (76.6%)	40 (80%)	111 (75.5%)	0.567
Oliguria	48 (24.4%)	18 (36%)	30 (20.4%)	**0.035**
Oral ulcer	120 (60%)	28 (56%)	92 (62.6%)	0.502
Arthralgia	147 (74.6%)	42 (84%)	105 (71.4%)	0.092
Fever	116 (58.9%)	32 (64%)	84 (57%)	0.241
Malar rash	131 (66.5%)	36 (72%)	95 (72.5%)	0.381
Anemia (Hb < 11 g/dl)	151 (76.6%)	42 (84%)	109 (74.1%)	0.179
Thrombocytopenia (platelet count < 150,000)	62 (31.5%)	19 (38%)	43 (29.3%)	0.291
Creatinine (1.2–3 mg/dl)	47 (23.9%)	16 (32%)	31 (21.1%)	0.128
Creatinine (> 3 mg/dl)	33 (16.8%)	16 (32%)	17 (11.6%)	**0.002**
Hypoalbuminemia (Alb 3–3.5 g/dl)	39 (19.8%)	10 (20%)	29 (19.7%)	0.835
Hypoalbuminemia (Alb < 3 g/dl)	132 (67%)	31 (62%)	101 (68.7%)	0.299
Proteinuria (g/d)	2.92 ± 1.92	3.03 ± 1.76	2.89 ± 2.1	0.674
Hematuria	72 (36.5%)	18 (36%)	54 (36.7%)	1
Low C3	154 (78.2%)	41 (82%)	113 (76.9%)	0.291
Low C4	154 (78.2%)	41 (82%)	113 (76.9%)	0.554
ds DNA antibody	185 (93.9%)	48 (96%)	137 (93.2%)	0.734
ANA	196 (99.4)	50 (100%)	146 (99.3)	0.771
SLEDAI	16.2 ± 3.74	16.4 ± 3.78	16.18 ± 3.73	0.643

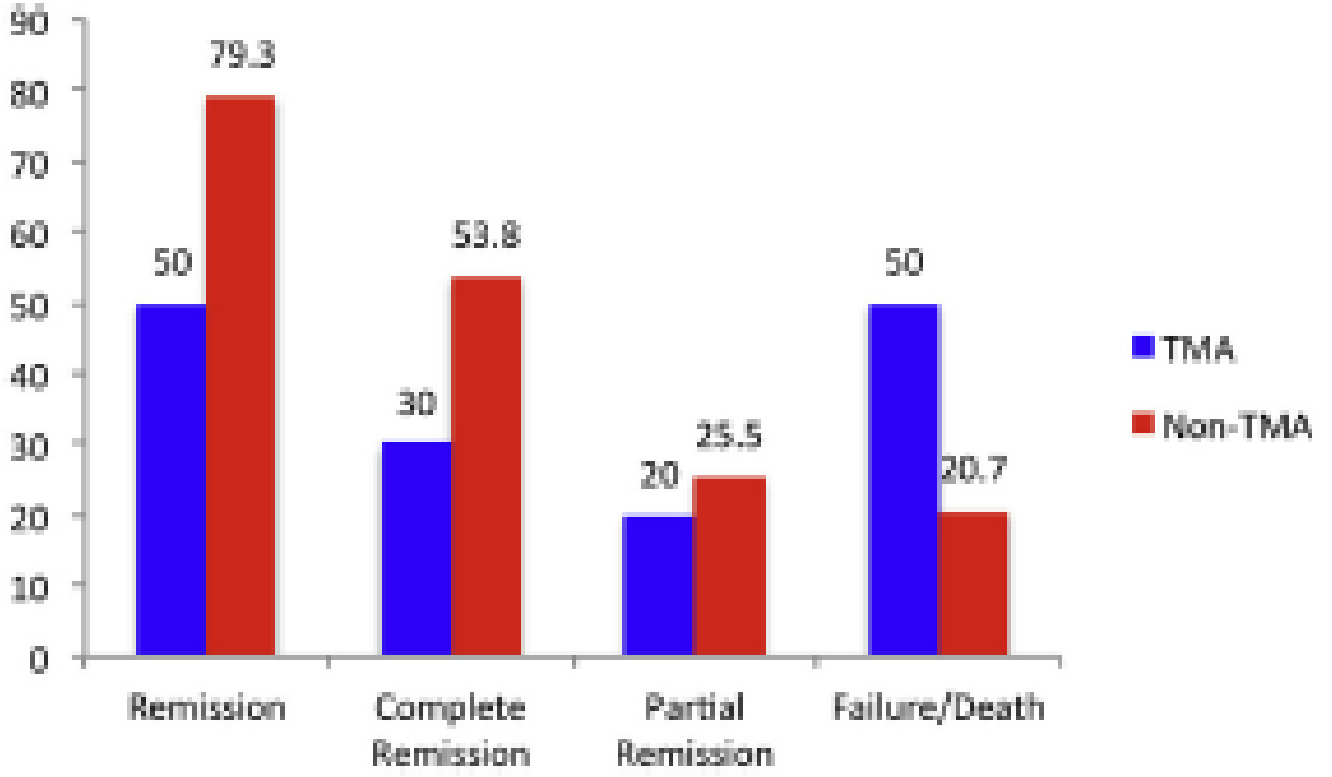


Figure 2. Comparison of outcomes between TMA and non-TMA groups of lupus nephritis. TMA, thrombotic microangiopathy.

Kidney International Reports (2017) 2, 844–849

N Pattanashetti et al.: Thrombotic Microangiopathy in Lupus Nephritis

2. TMA IN PATIENTS WITH LN IS ASSOCIATED WITH aPL

APS diagnosis (OR 5.5, 95 % CI 1–29.4, p= 0,049)

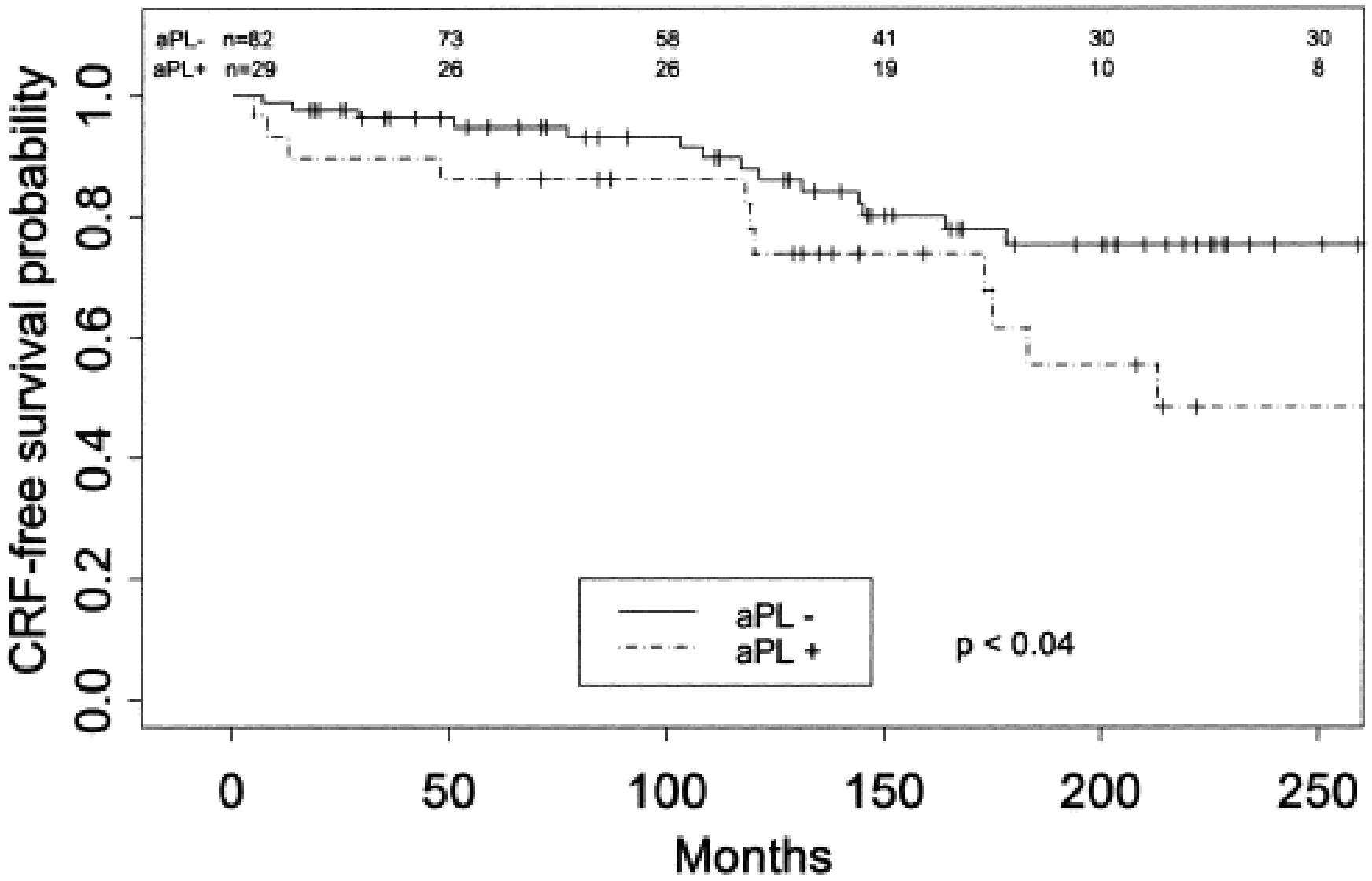
LAC positivity (OR 6.2, 95 % CI 1.4–27, p= 0.01)

Double aPLs positivity (OR 8, 95 % CI 1.7–37, p=0,008)

TMA

Erre et al, Rheumatol Int (2014)

3. aPL AS A POOR PROGNOSTIC FACTOR IN LN



aPL are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis.

Moroni at al, Am J Kidney Dis. 2004;

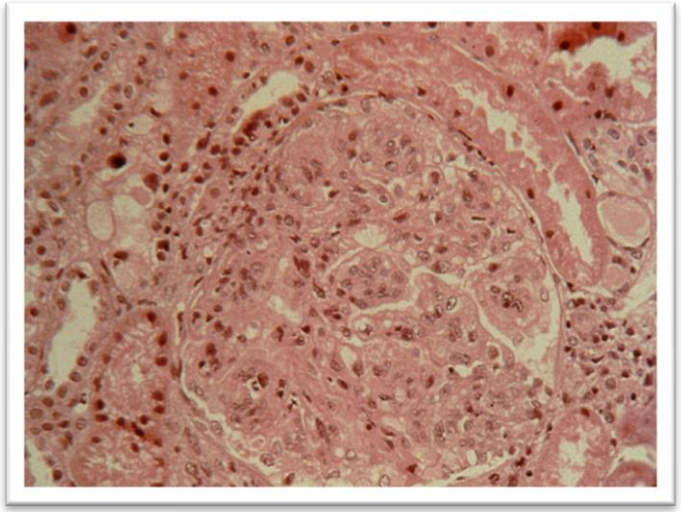
HOW SHOULD WE TREAT TMA IN LN?

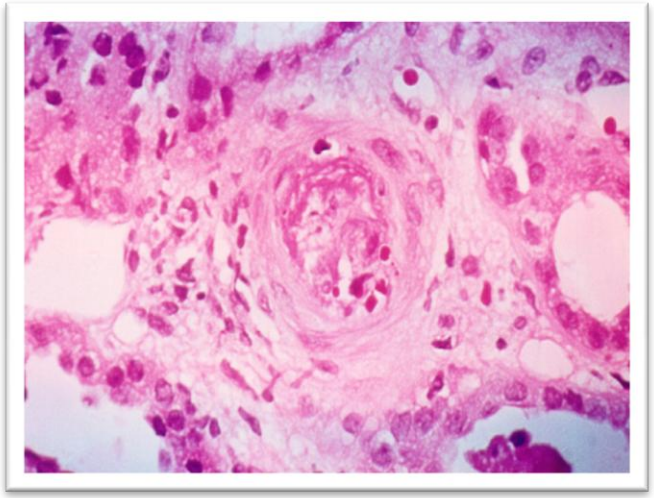
SLE

- Small vessels
- Immune complex mediated
- **Immunosuppression**

APS

- Large and small vessels
- Thrombotic nature
- Coagulation disorder
- **Anticoagulation**





Should we use anti-thrombotic therapy in pts with concomitant TMA and LN?

No changes rather than conventional IS protocol for LN

Anti-platelets

Anti-coagulation

TMA AND LN

We sought to assess kidney outcomes and response to anti-thrombotic treatments in addition to conventional immunosuppression in patients with biopsy proven LN and TMA.

METHODS

- Data of patients with biopsy-proven LN and TMA were retrospectively searched (2007-2017)
- Antibody profiles, induction and maintenance therapies for LN, and anti-thrombotic treatments were collected.
- TMA lesions were classified into acute and chronic.

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International Society on Thrombosis and Haemostasis

METHODS: Acute Vs. Chronic TMA lesions

Glomerular Acute lesions

- Endothelial swelling with partial or complete occlusion of lumina
- Microthrombi, focal or global
- Fragmented RBC on glomerular subendothelial space and/or mesangial areas
- Mesangiolysis, focal, segmental/global
- Glomerular congestion with efferent arteriolar occlusion

Arteriolar Acute lesions in TMA

- Endothelial swelling with partial or complete occlusion
- Fibrin/platelet thrombi, segmental/partialor occlusive
- Fragmented RBC in subendothelial space

Arterial Acute lesions in TMA

- Endothelial separation with intimal mucoid degeneration
- Intravascular thrombi, segmental/partial orocclusive
- Fragmented RBC in subendothelial space

Glomerular Chronic lesions

- Capillary wall thickening with double contours
- Organizing capillary thrombi
- Glomerular ischemic collapse with afferent arteriolar occlusion
- Segmental/global glomerulosclerosis

Arteriolar Chronic lesions in TMA

- Organizing thrombi, partial or occlusive
- Fibromyointimal thickening/ proliferation

Arterial Chronic lesions in TMA

- Organizing thrombi, partial or occlusive
- Fibromyointimal thickening/ proliferation

TMA AND LN

- Clinical and histopathological data for 97 patients with biopsy-proven LN and TMA were retrospectively analyzed.

- Mean age was 38.9±15.2 years (range, 13–69 years) with 85 females (87.6 %).

- The clinical presentations:

  nephrotic syndrome 39.2%

  nephritic syndrome 20.6%

  asymptomatic urinary abnormalities 40.2%

TMA AND LN: Patients Characteristics

- LN Class III: 9 pts (including 2 as Class III + V)
- LN Class IV: 82 pts

(10 as Class IV-segmental(IV-S), 72 as Class IV-global (IV-G), including 4 as Class IV-G + V)

- LN Class V: 6 pts

TMA features:

42 pts acute TMA

55 pts chronic TMA

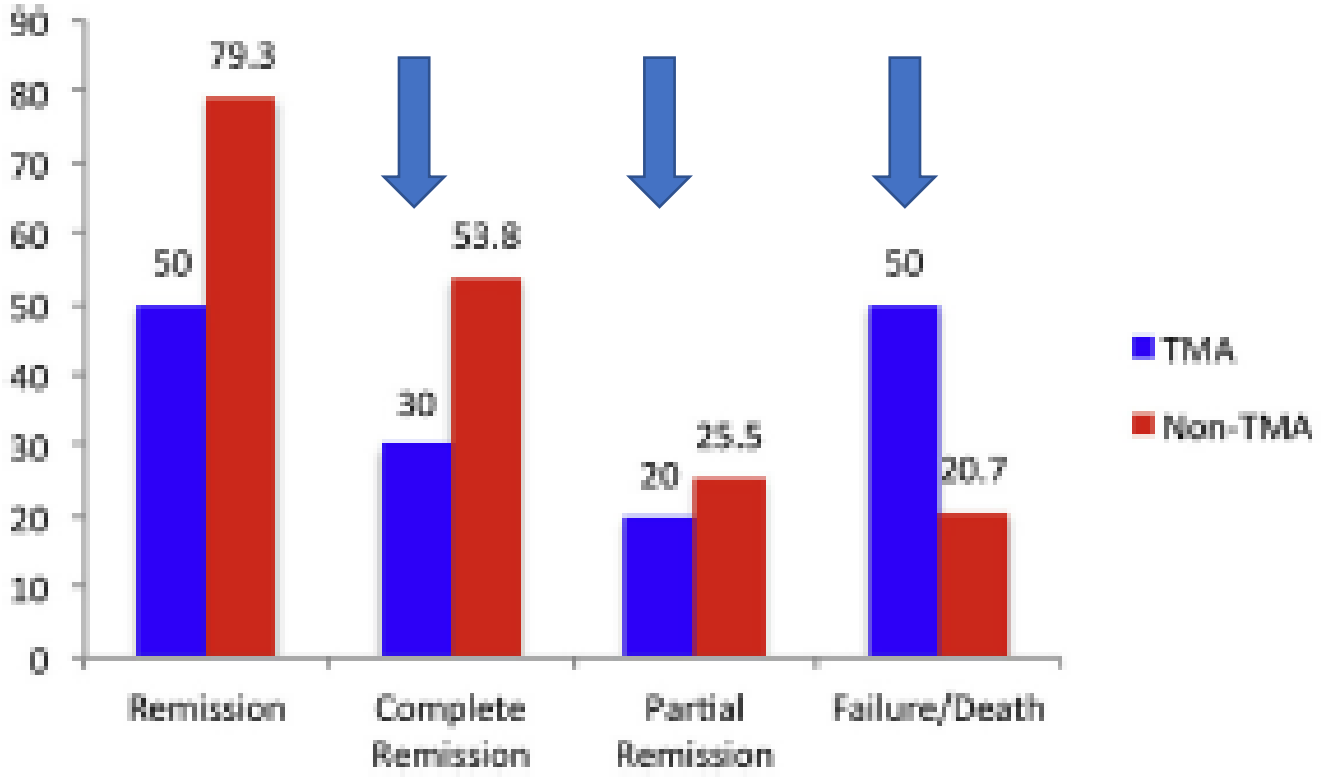
All patients had received treatment with steroids and standard immunosuppressants

- 55% mycophenolate
- 39% cyclophosphamide
- 6% other regimen

TMA AND LN: Renal Response

Renal outcome at 12 month

- CR 37 pts (38.1%)
- PR 22 pts (22.6%)
- NR 38 pts (39.1%)



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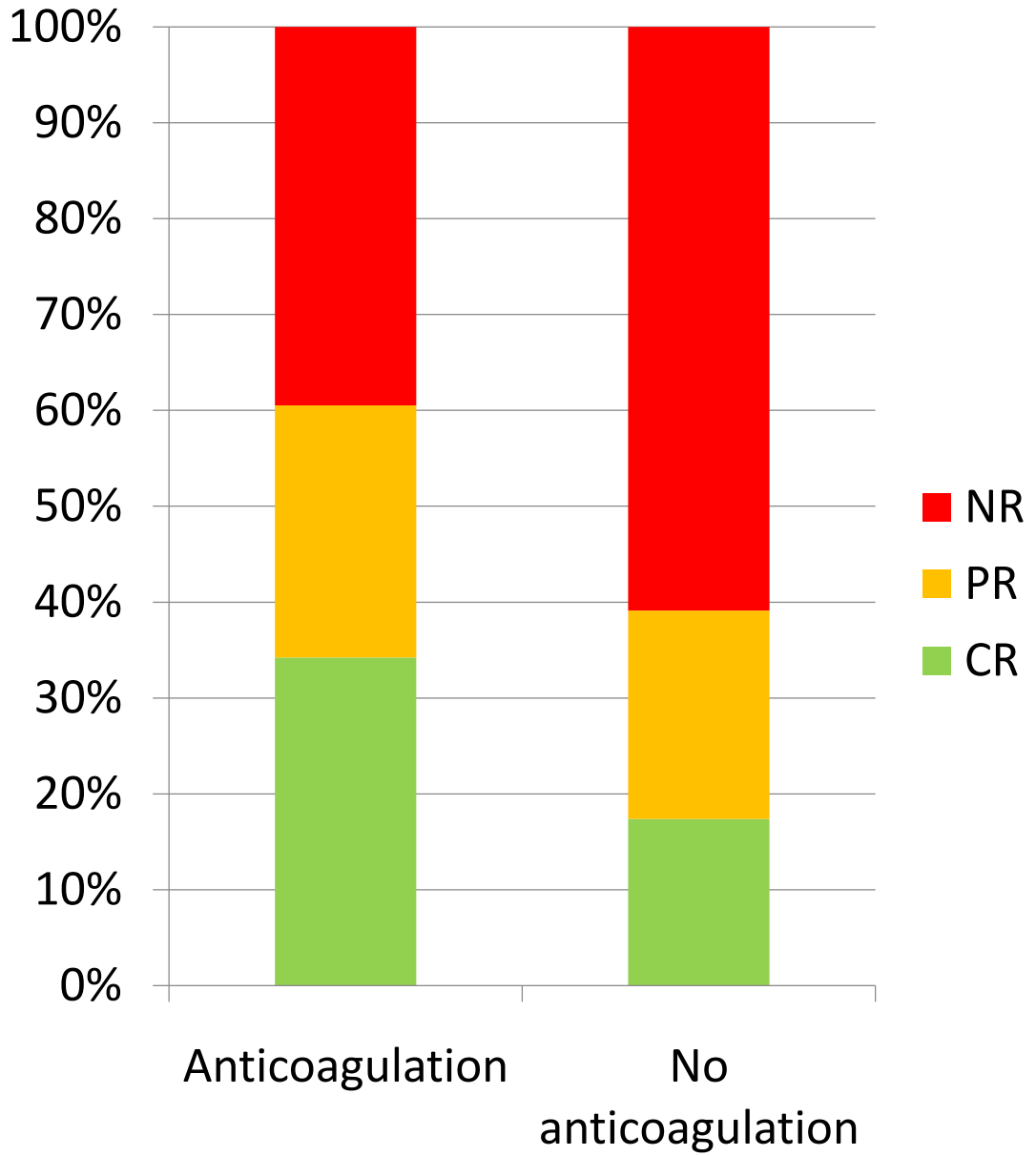
TMA and LN: aPL positivity

- 61 patients (62.9%) were aPL positive
- 37 (38.1%) of these patients received anticoagulation with a VKA and/or heparins .

- Mean duration of anticoagulation therapy after TMA and LN diagnosis was 7.7 months (3-12).



Prognostic Factors

- POOR prognostic factors associated with No Renal Response:

  anti-DNA positivity (OR, 12.8; 95% CI 3.0–71.3; p = 0.002)

  aPL positivity (OR, 2.4; 1.2–7.3; p = 0.03)

  chronic features of TMA (OR 3.0; 95% CI 1.2–17.5; p = 0.04)

Prognostic Factors

In the aPL positive patients, FAVOURABLE prognostic factors:

- acute TMA rather than chronic (OR, 8.62; 95% CI 1.4–97.1; p = 0.03)
- VKA*/heparins (OR, 2.1; 95% CI, 1.02–16.2; P = 0.046)

after adjusting for type of immunosuppressant therapy and LN class

*For patients receiving VKA, mean TTR 72±7.3%.

KEY MESSAGES

In patients with concomitant LN and TMA:

the presence of aPL
chronic features of TMA

} Poor kidney outcomes

KEY MESSAGES

In patients with concomitant LN and TMA:

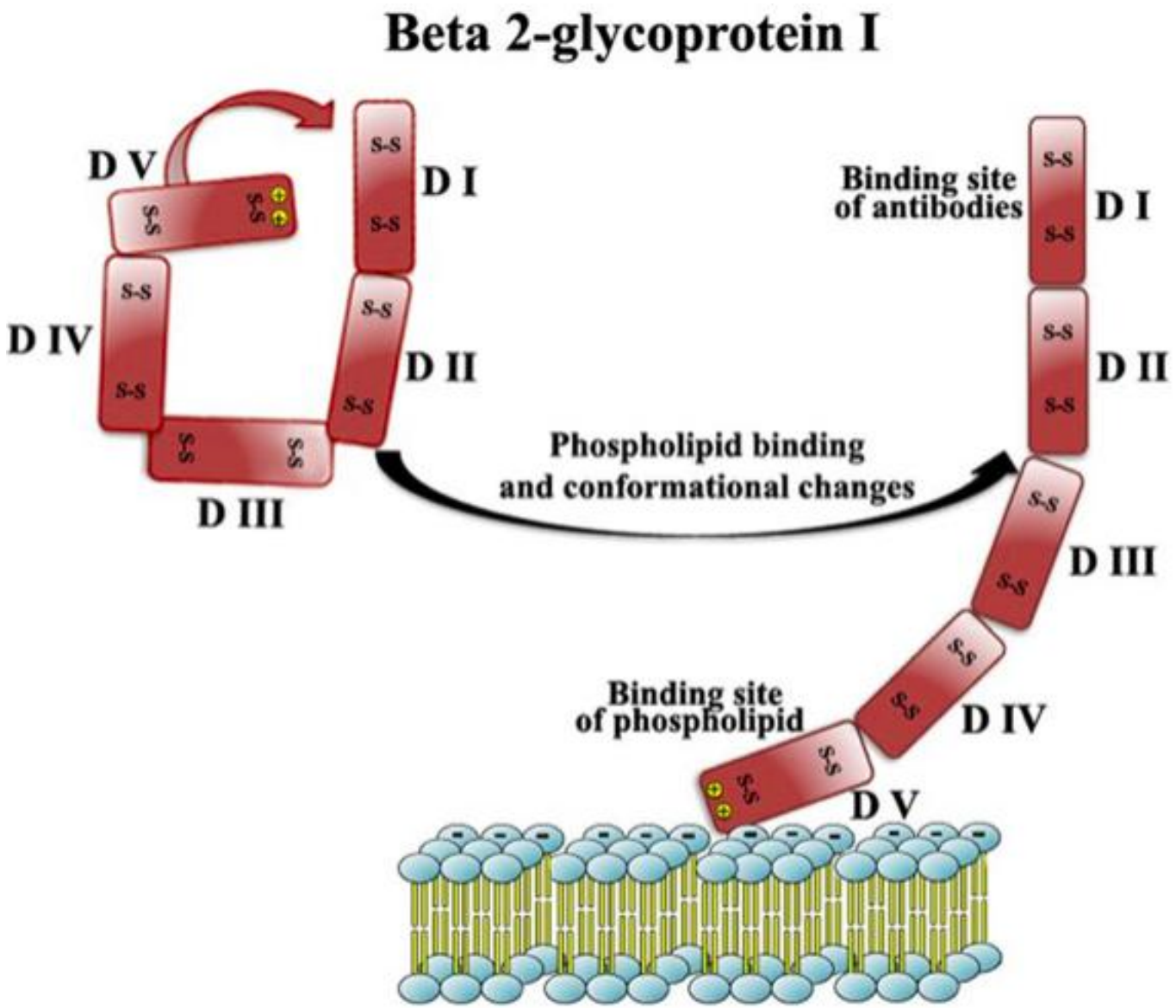
the presence of aPL
chronic features of TMA
} Poor kidney outcomes

In patients with aPL, the use of anticoagulation appeared protective, especially in the setting of acute TMA

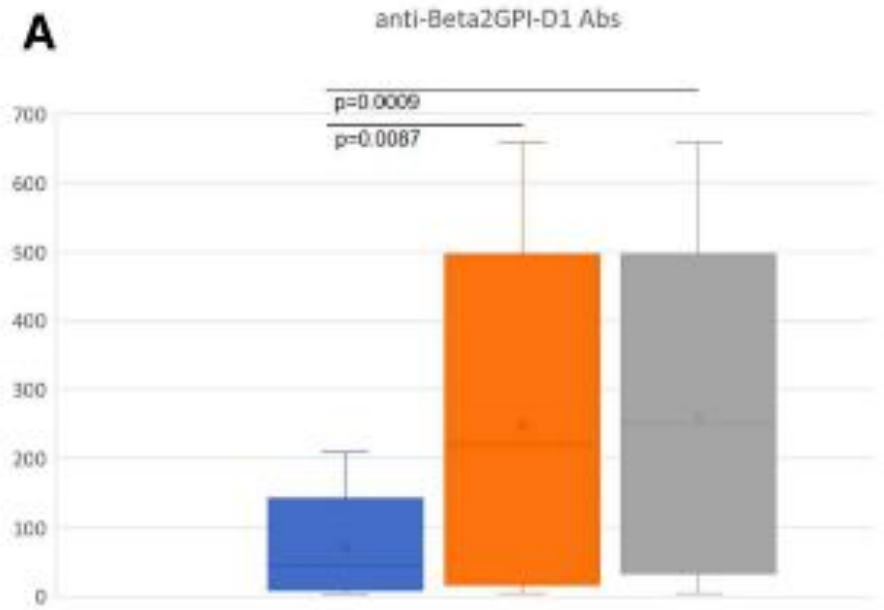
FUTURE PERSPECTIVE

- IDENTIFYING NEW PATHOGENIC MECHANISMS

- TARGET THERAPY in aPL-RELATED MANIFESTATIONS BEYOND ANTICOAGULATION

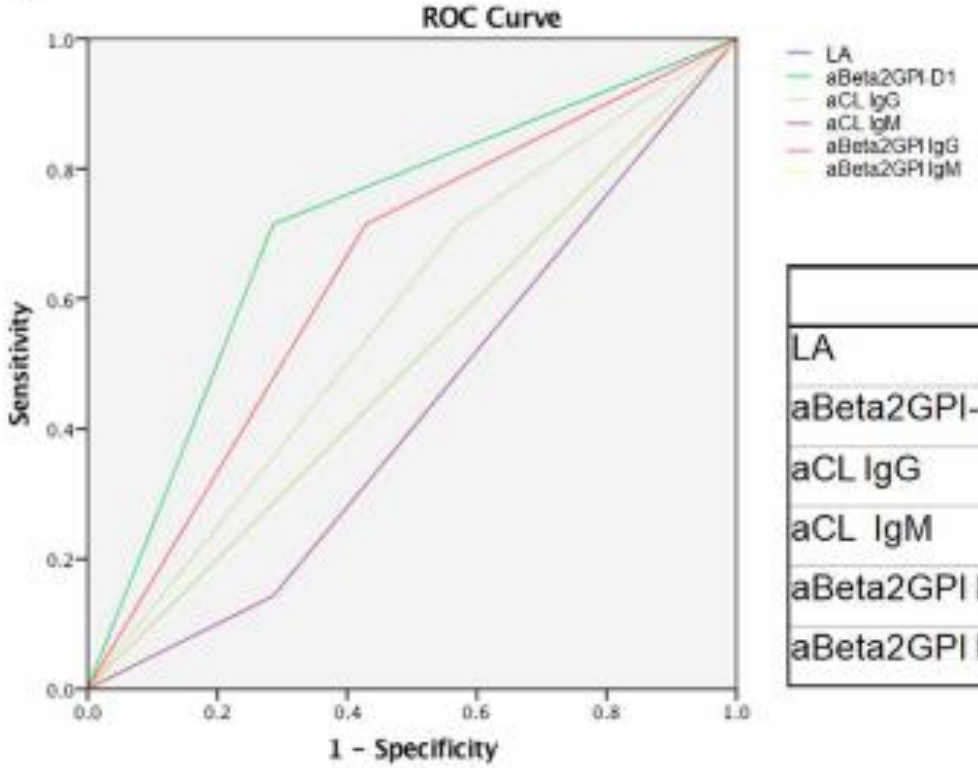

Beta 2-glycoprotein I
D V
D I
D IV
D II
D III
S-S
Phospholipid binding
and conformational changes
Binding site
of antibodies
Binding site
of phospholipid

A



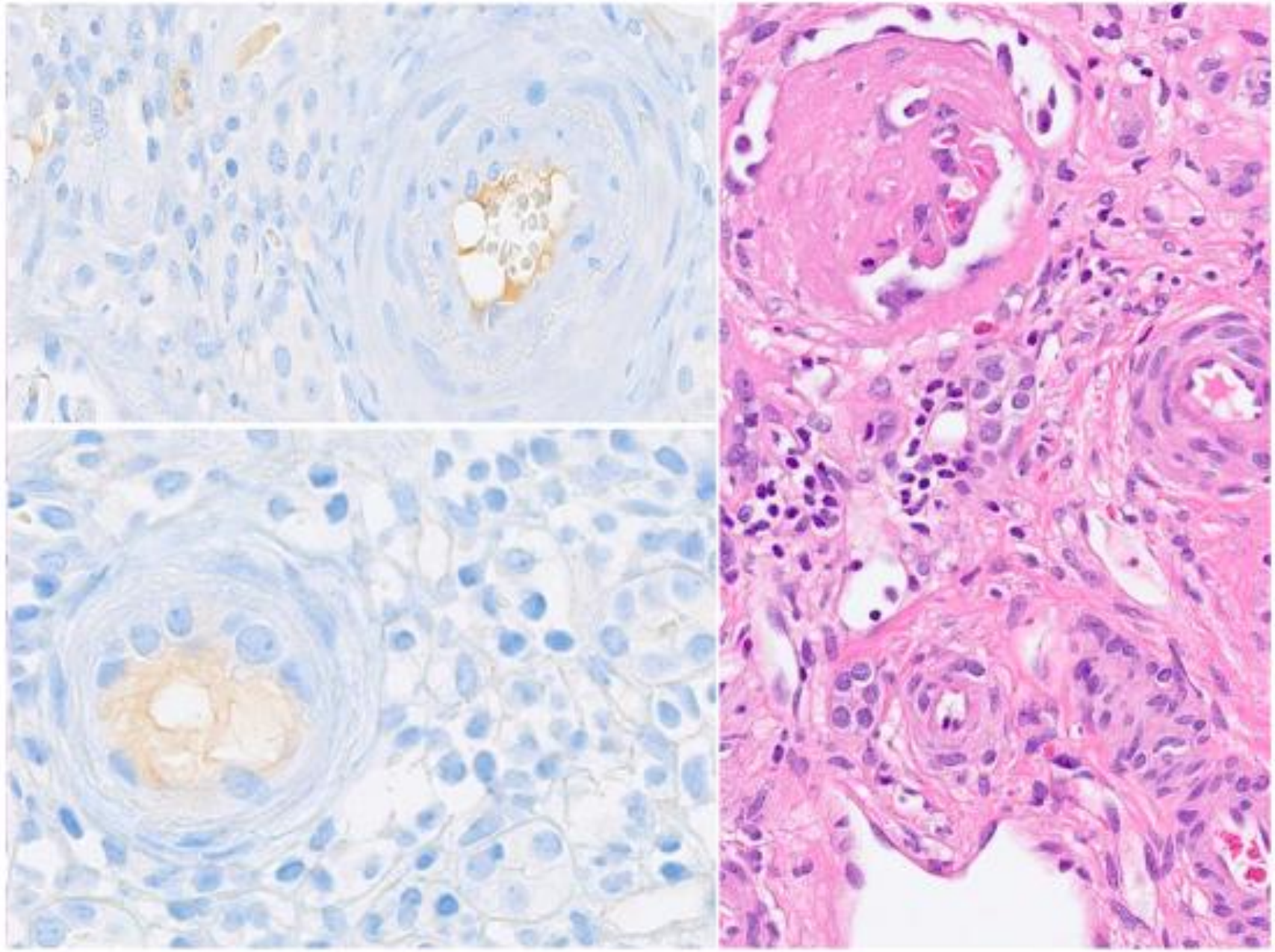
	LN		aPL-N		aTMA	
	N.	%	N.	%	N.	%
LA	7	25,9	6	50	5	71,4
aCL (IgG/M)	9	33,3	11	91,7	4	57,14
anti-Beta2GPI (IgG/M)	9	33,3	7	58,3	4	57,1
Triple Positivity	4	14,8	3	25,0	3	42,8
GAPPS ≥ 10	5	18,5	5	41,7	5	71,4
LN Class III/IV	18	66,7	11	91,7	6	85,7
LN Class V	9	33,3	1	8,3	1	14,2

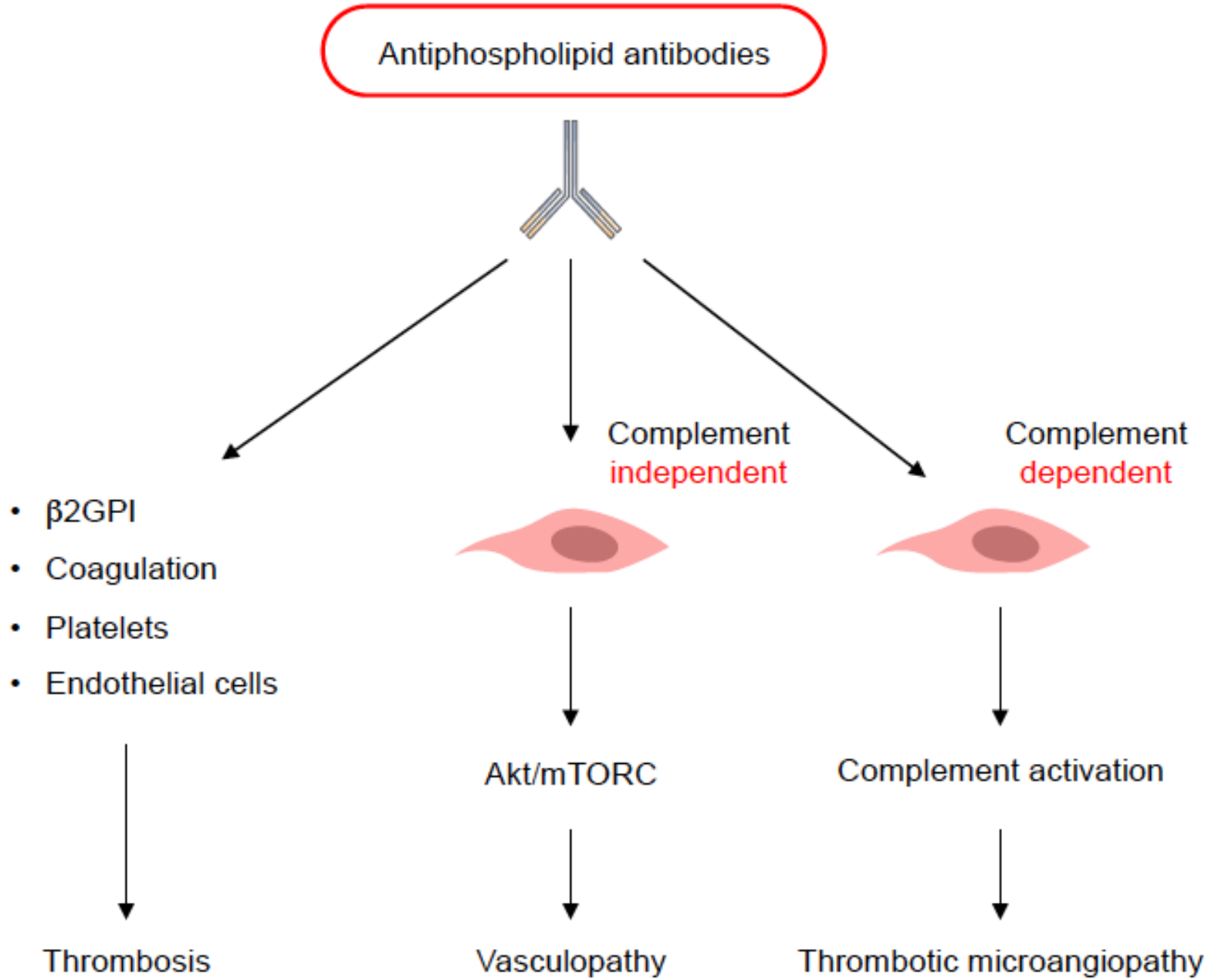
B



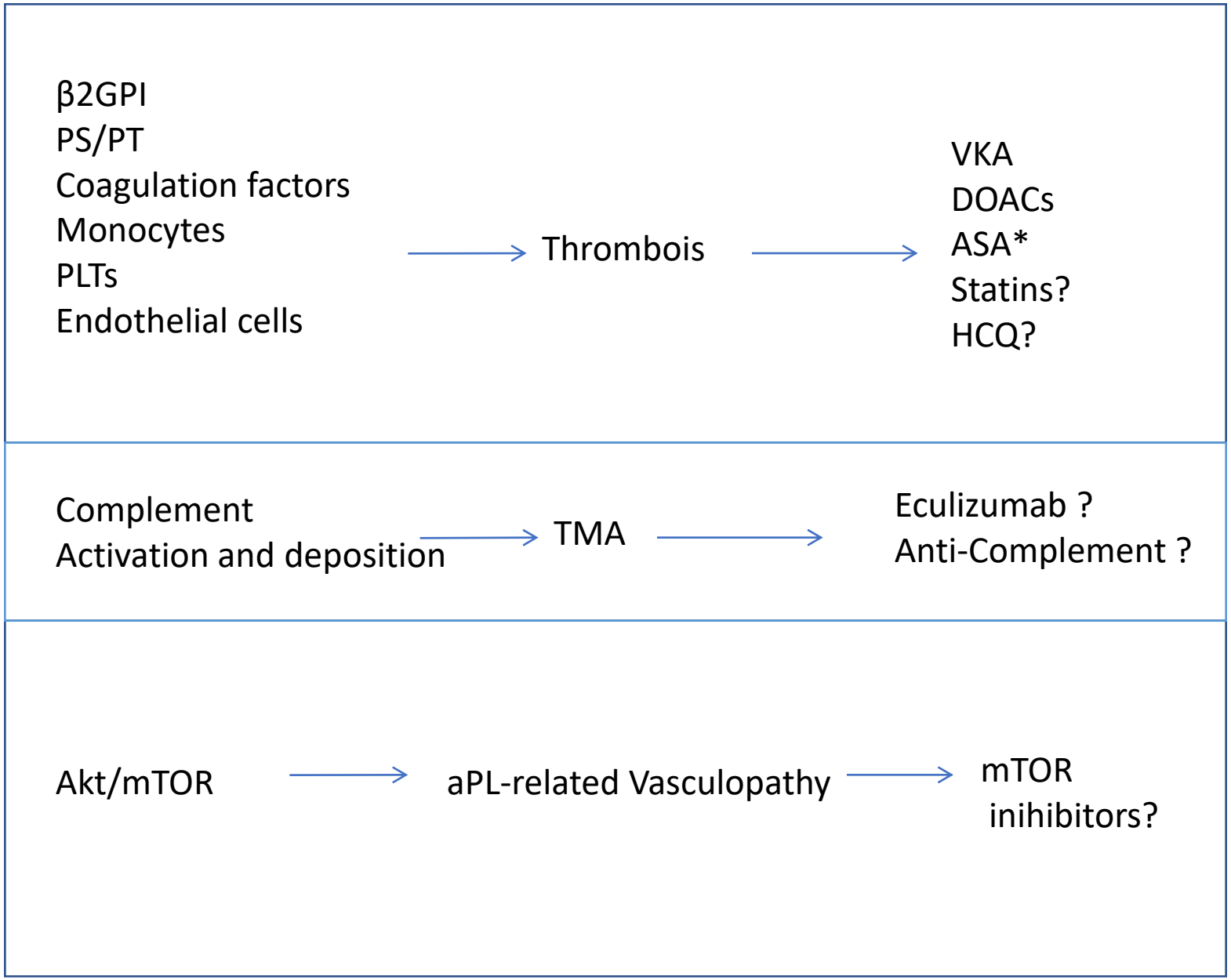
	Area
LA	.500
aBeta2GPI-D1	.714
aCL IgG	.571
aCL IgM	.429
aBeta2GPI IgG	.643
aBeta2GPI IgM	.500

Sciascia et al. JN, 2020



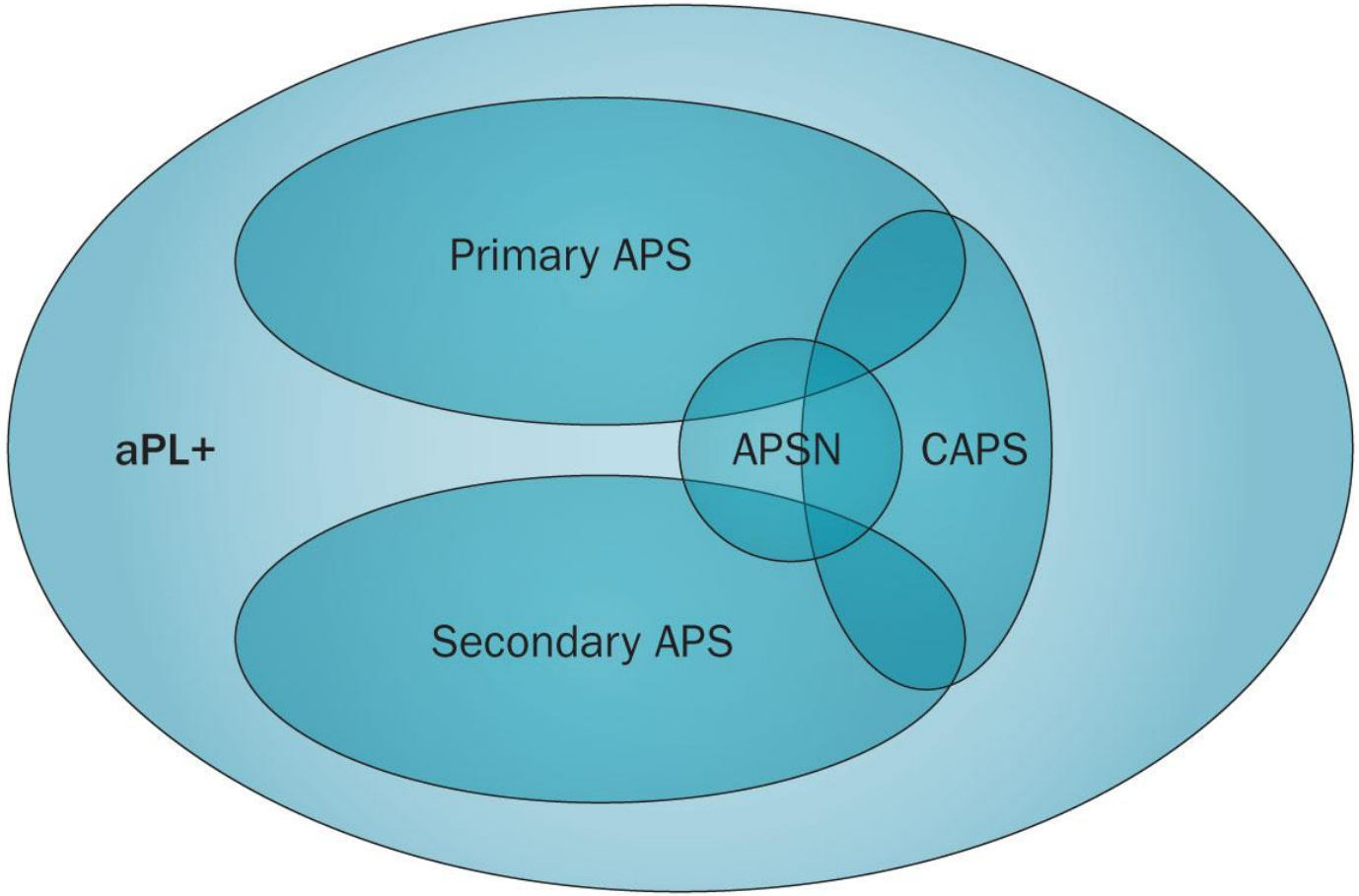

Antiphospholipid antibodies
Complement independent
Complement dependent
• β2GPI
• Coagulation
• Platelets
• Endothelial cells
Akt/mTORC
Complement activation
Thrombosis
Vasculopathy
Thrombotic microangiopathy

aPL



*as thromboprophylaxis or associated to VKA

Venn diagram of the clinical presentation of APS



Sciascia, S. *et al.* (2014) Renal involvement in antiphospholipid syndrome
Nat. Rev. Nephrol. doi:10.1038/nrneph.2014.38

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