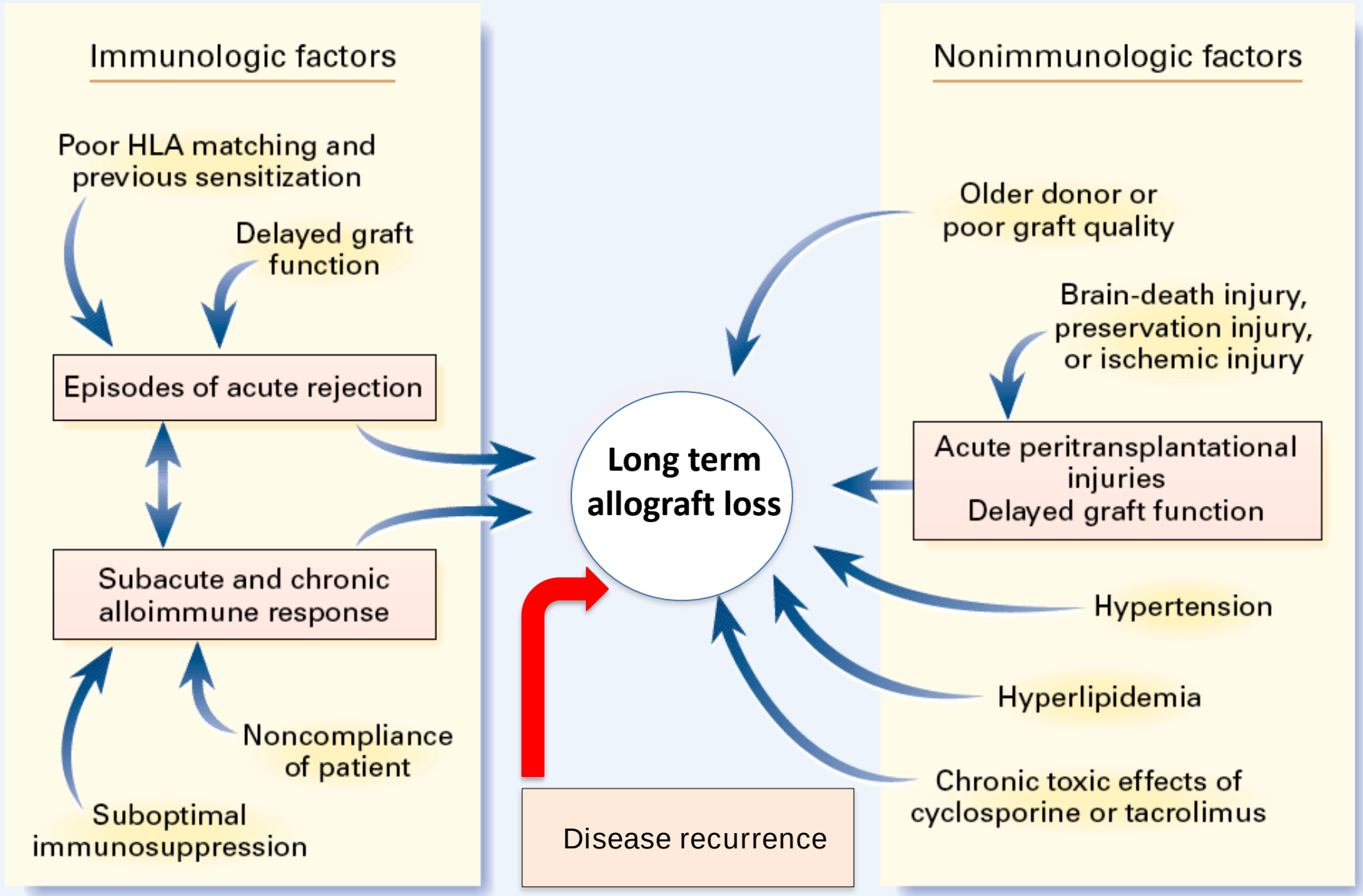
Récidives en transplantation.

Christophe Legendre, Hôpital Necker
& Université Paris Descartes, Paris

Fondation
Day-Solvay



M Pascual et al, N Engl J Med 2002

Post-transplant kidney disease recurrence

Primary glomerular diseases

Systemic diseases

Metabolism diseases

Classifications of recurrent glomerular diseases

- **Clinical classification**:
  - True recurrence: native and recurrent disease are the same confirmed by histology,
  - Potential recurrence: occurrence of a post-transplant glomerular disease confirmed by biopsy without histological knowledge of native kidney disease,
  - De novo glomerulonephritis: occurrence of a new glomerular disease in the transplant kidney.

Limitations in recurrent glomerular disease Δ

- **Native kidney disease**:
  - Unknown in many patients with ESRD,
  - Difficulties at late stage of chronic kidney disease,
  - Primary versus secondary FSGS.
- **Indication for post-transplant renal biopsy**:
  - Protocol versus for cause biopsy,
  - Immunofluorescence and EM not routinely applied.

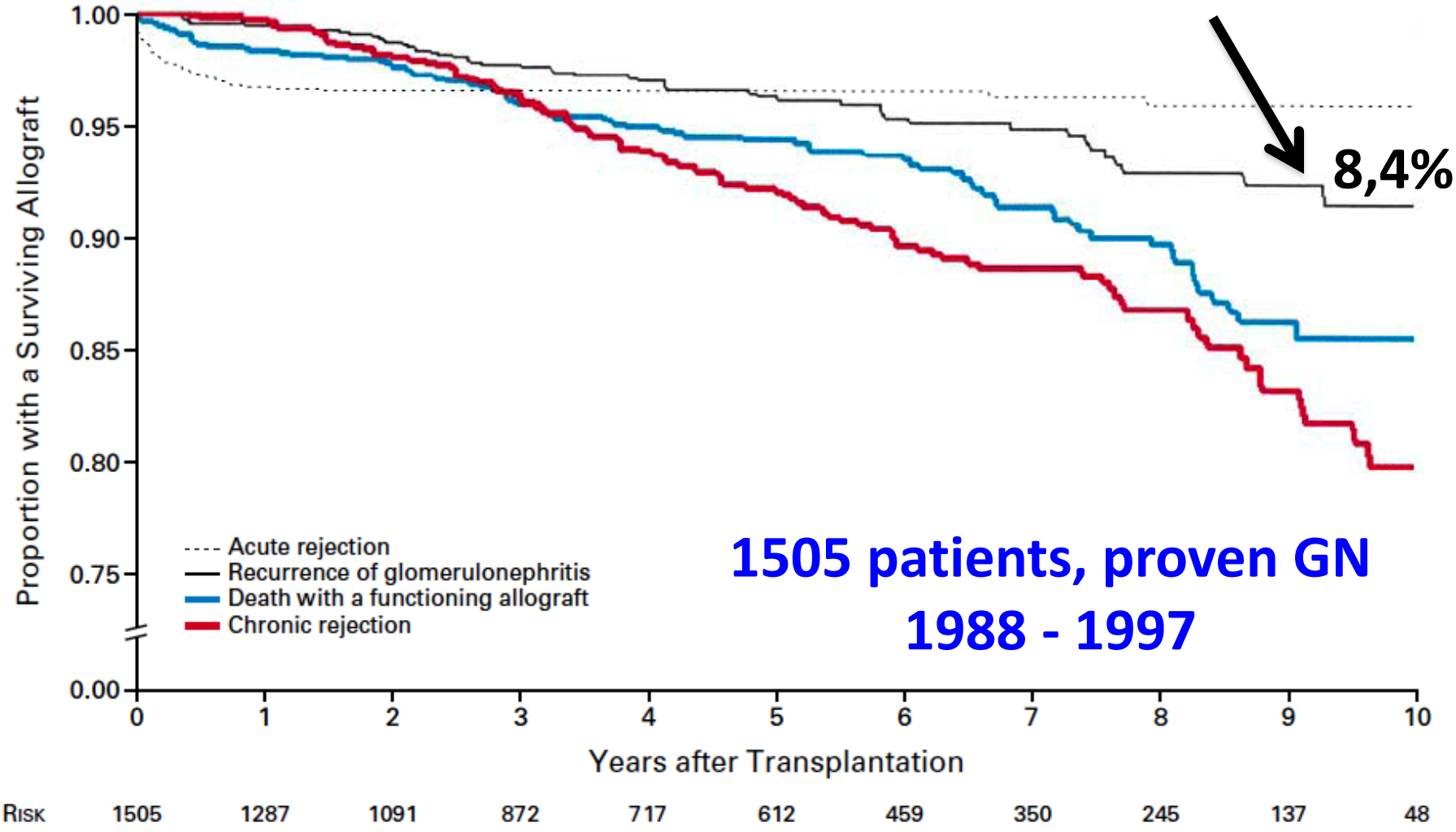
WA Golgert et al, Clin J Am Soc Nephrol 2008

Table 2. Risk of glomerulonephritis recurrence and graft loss after kidney transplantation

Type of glomerulonephritis	Risk of recurrence (% of patients)	Risk of graft failure, 5–10 years (% of patients)
IgA	50– 60 (Histologic), 7 – 30 (clinical)	1.6–19.1
FSGS	20–40 (Early)	20–27
Membranous nephropathy	10–40	20–50
MPGN, type I	20–60 (monoclonal-related)	70–100
MPGN, type II	50–90	34–66
ANCA-associated glomerulonephritis	0– 0	0–10
SLE	2.4– 41.6	14.3
Anti-GBM	<5	Rare
Fibrillary and immunotactoid	>50	Lack of data

CD Blosser et al, Cur Op Nephro Hypertension 2017

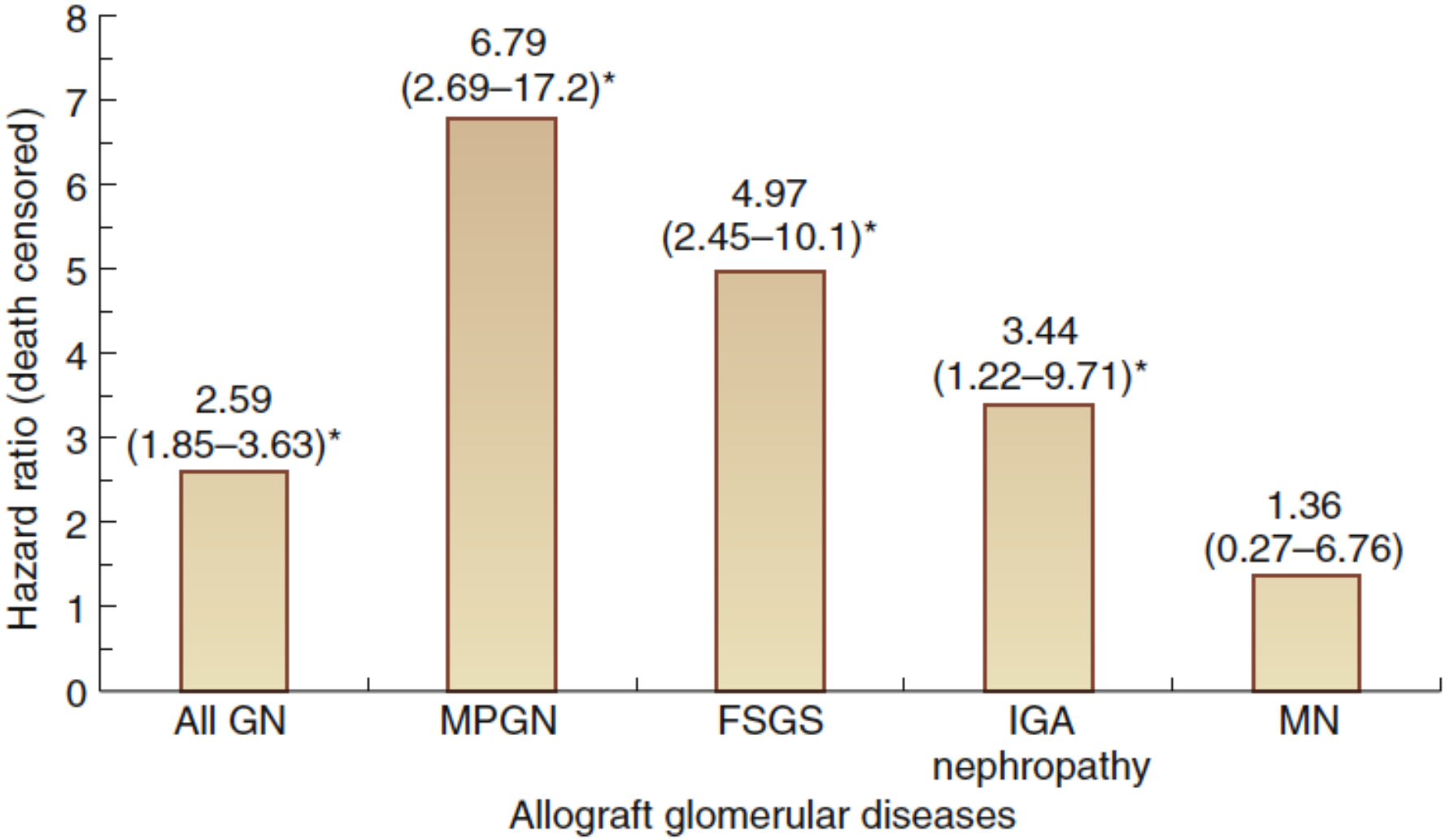
Graft loss due to recurrent GN



S Hariharan et al, Transplantation 1999

EM Briganti et al, N Engl J Med 2002

Graft loss due to post-RT disease recurrence

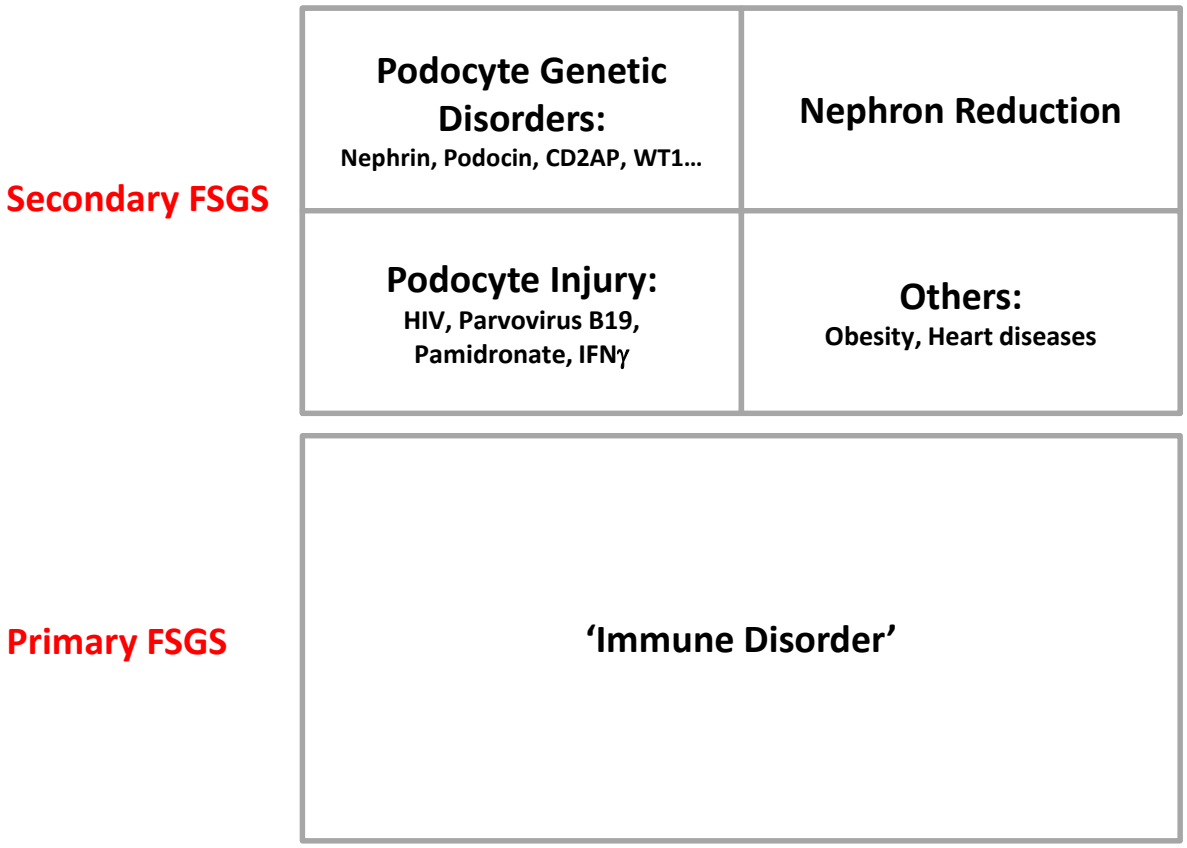


FG Cosio , DC Cattran, Kidney Int 2016

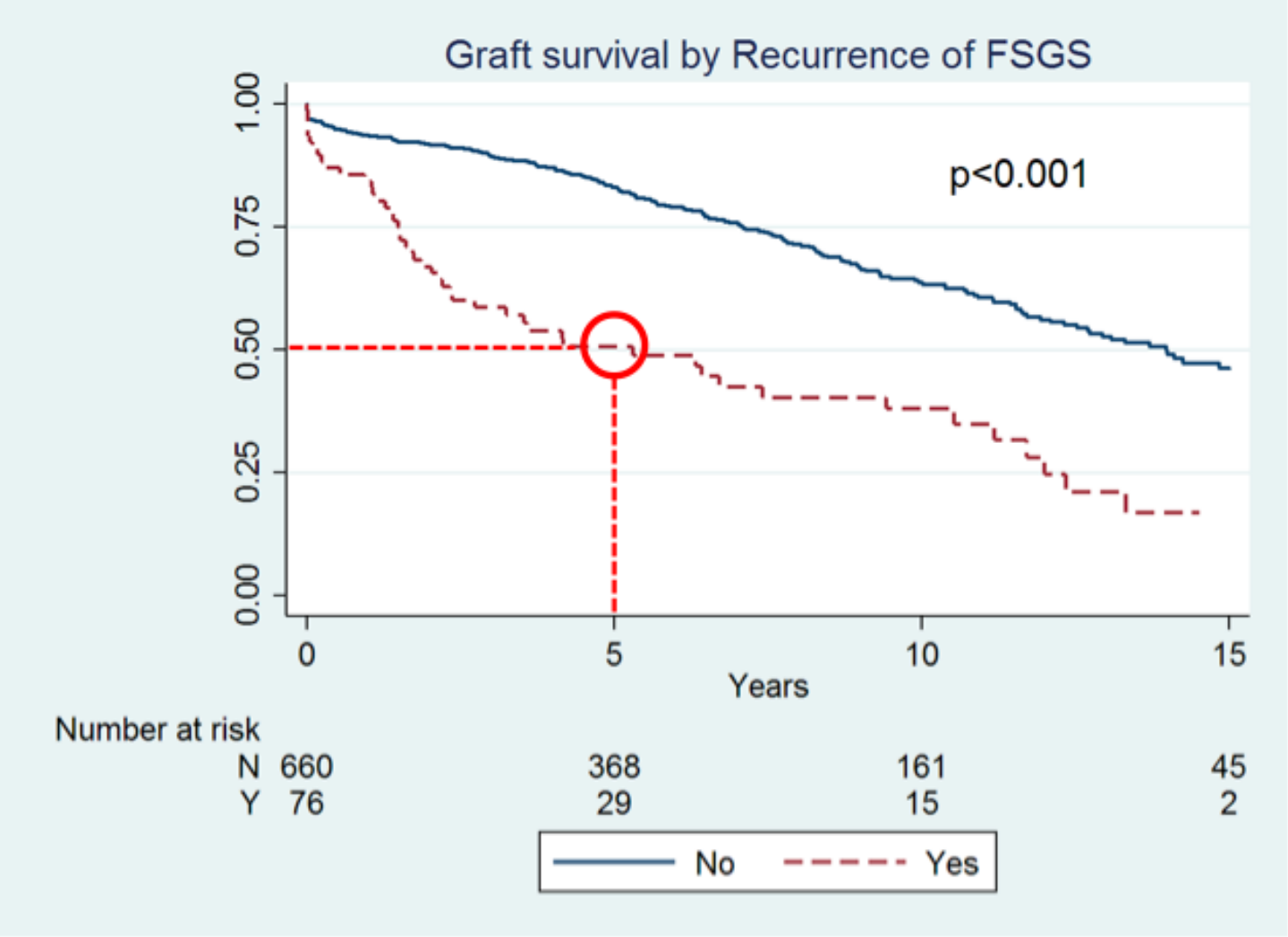
Post-transplant glomerulonephritis recurrence

- **Focal and segmental glomerulosclerosis (FSGS)**
- Atypical Hemolytic Uremic Syndrome (aHUS)
- Antiphospholipid syndrome (APS)
- Membranous nephropathy (MN)
- Membranoproliferative glomerulonephritis (MPGN)
- IgA nephropathy

Focal and segmental glomerulosclerosis etiology



FSGS recurrence after transplantation



A Francis et al, TTS 2016

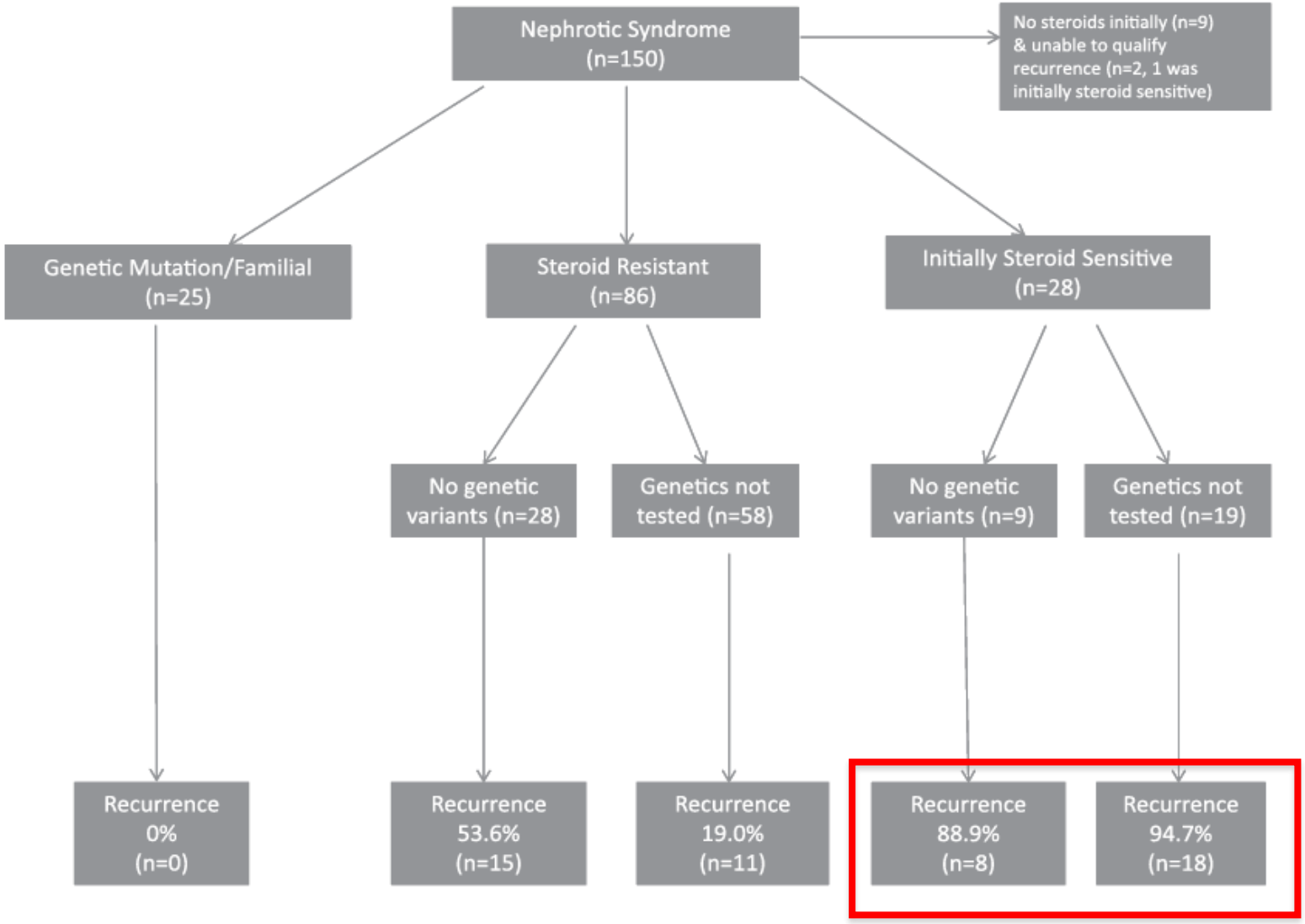
FSGS recurrence: risk factors

Table 1. Factors influencing the risk of recurrence of FSGS

Factors associated with increased risk of recurrence	Factors associated with low risk of recurrence
Second transplant after loss from recurrence	Familial FSGS
Childhood	Sporadic form with podocin mutation
Rapid progression to uraemia	Slow progression to uraemia
Mesangial proliferation in native kidneys	Non-nephronic proteinuria in the original disease
Living donation	
White race	
Elderly donor	

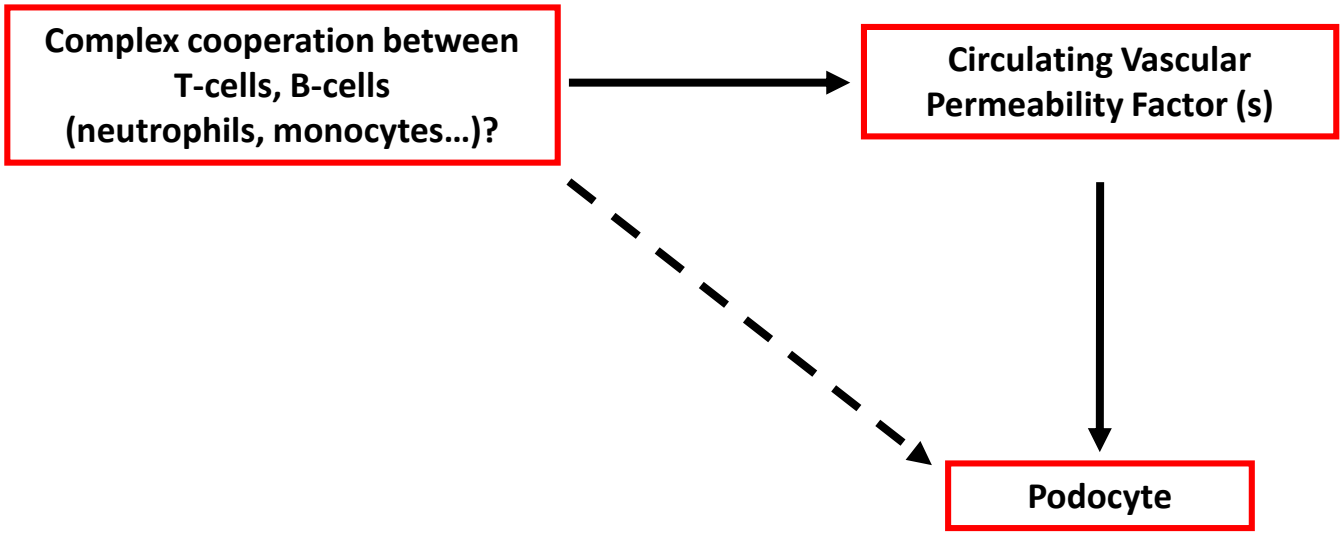
C Ponticelli et al, NDT 2010

FSGS recurrence: risk factors

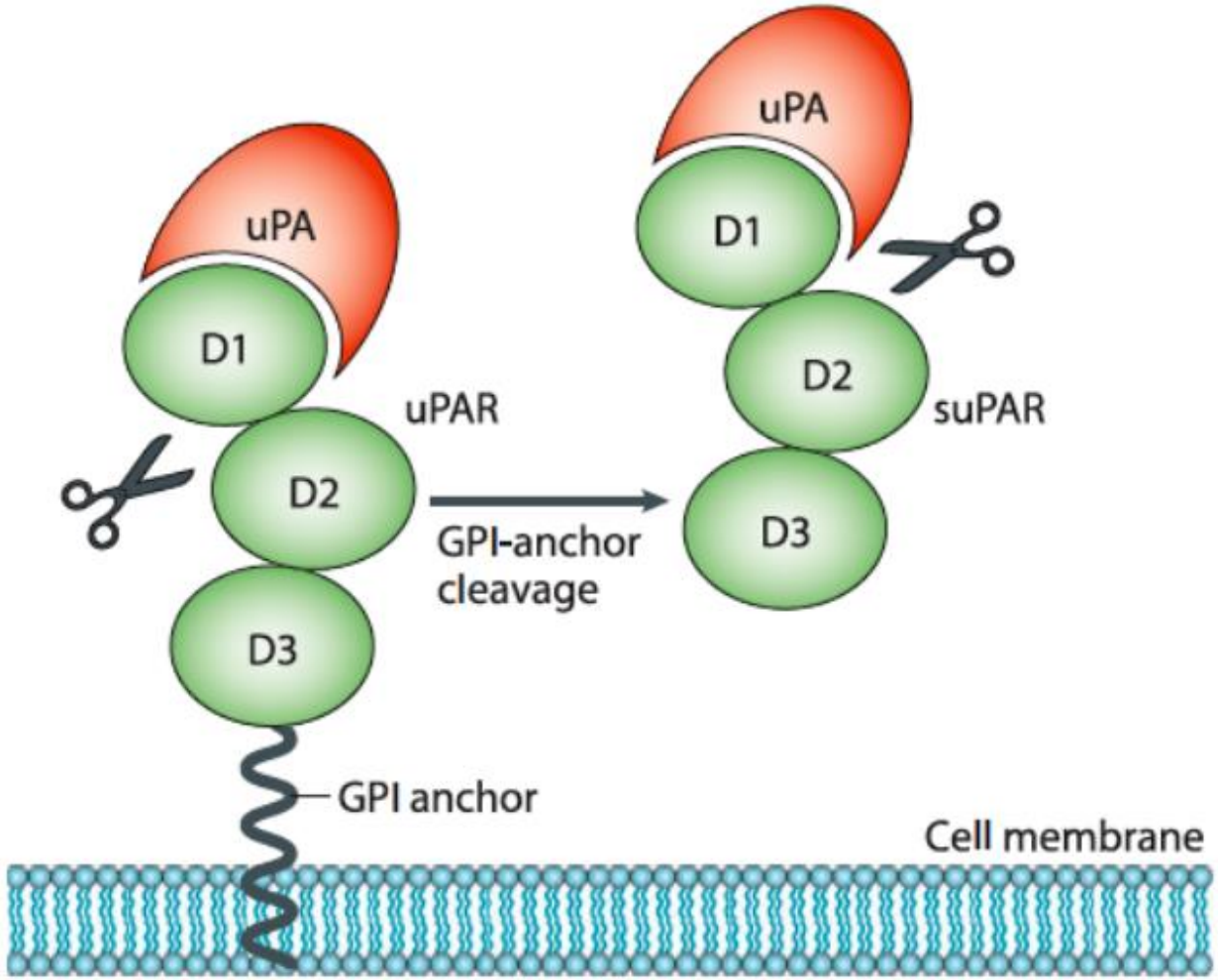


DW Ding et al, J Am Soc Nephrol 2014

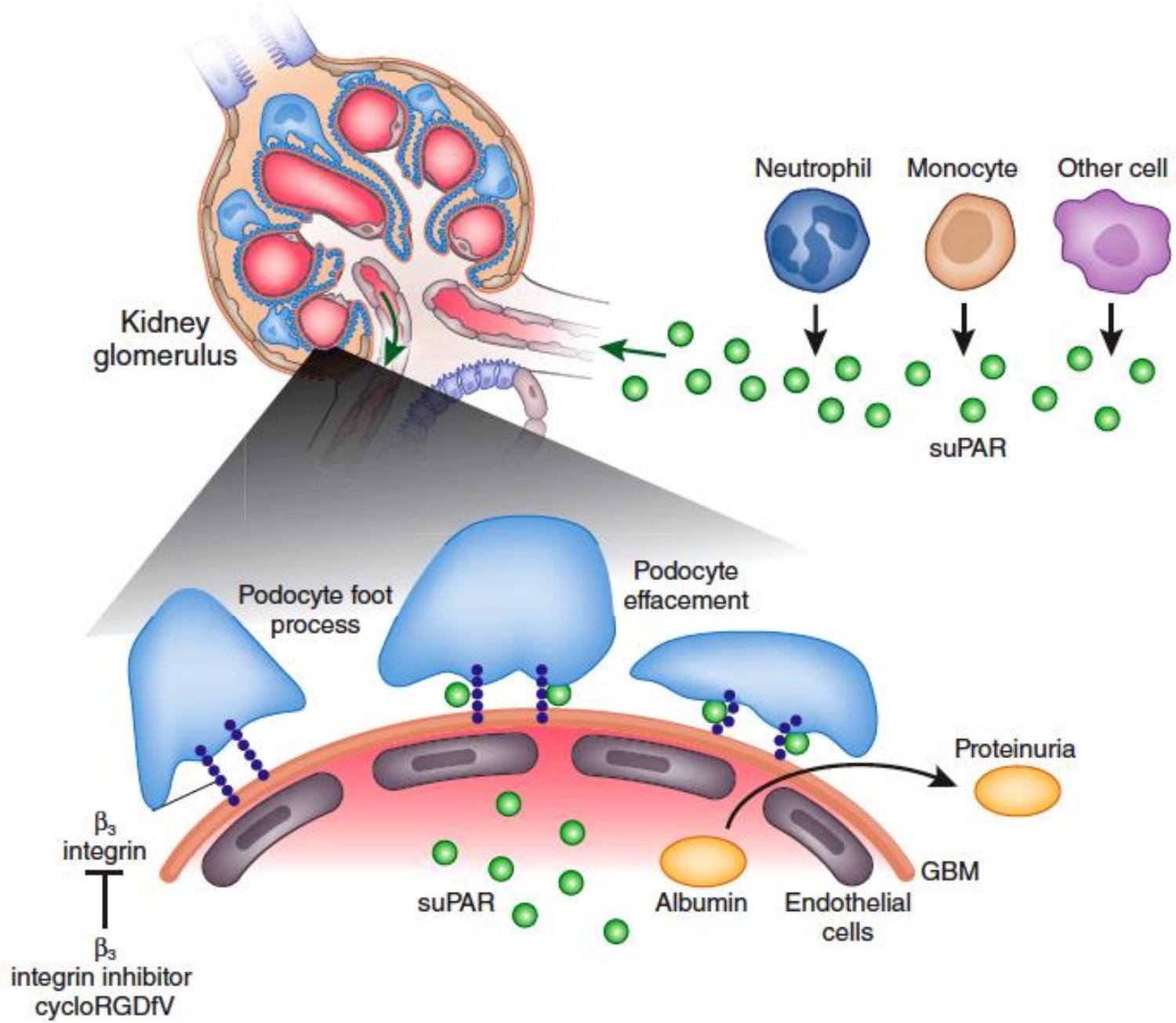
FSGS: « three players »



suPAR: the FSGS permeability factor?



Wei C et al, Nature Medicine 2011



Wei C et al, Nature Medicine 2011

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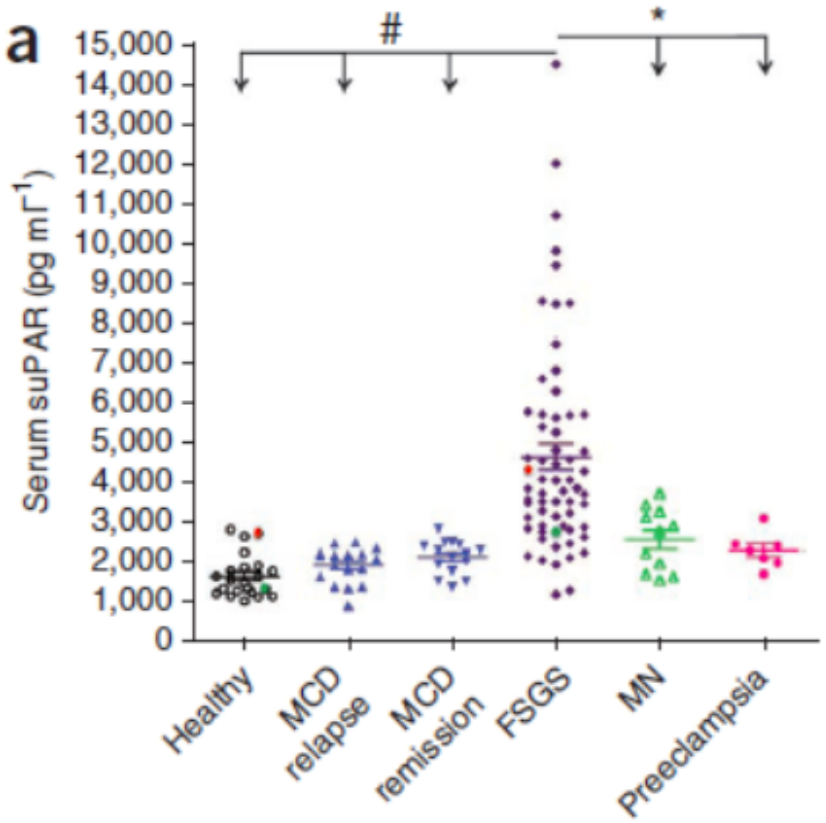
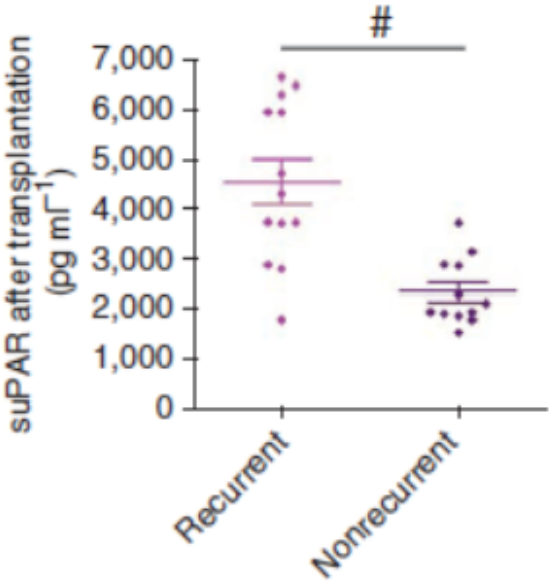


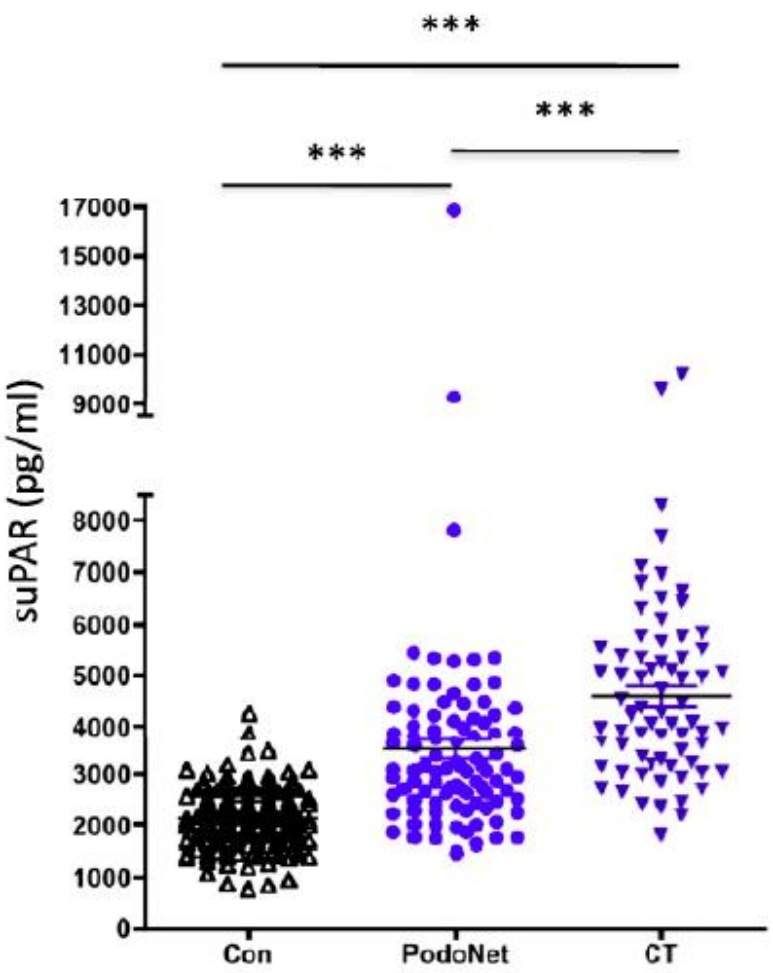


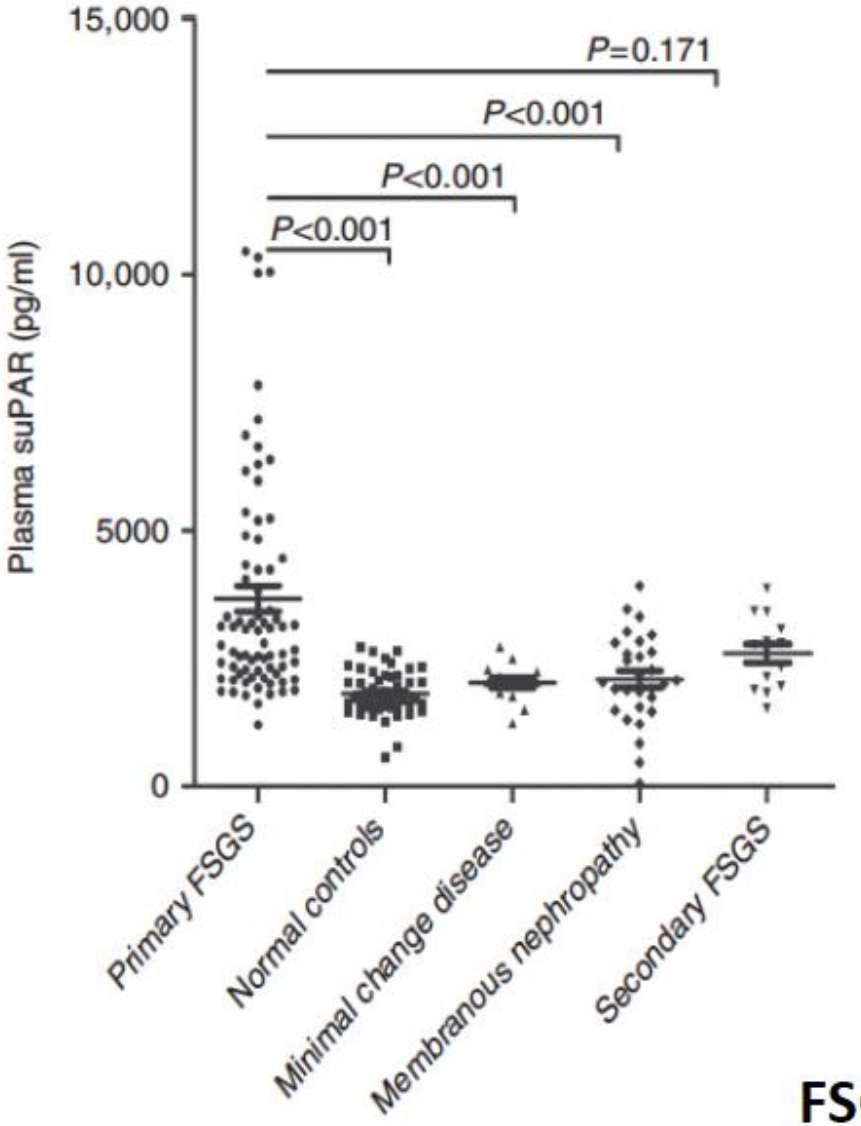
Native kidney

Transplanted kidney

Wei C et al, Nature Medicine 2011

suPAR: the FSGS permeability factor?





Wei C et al, J Am Soc Nephrol 2012
Huang J et al, Kidney Int 2013

FSGS

Pediatr Nephrol
DOI 10.1007/s00467-013-2452-5

REVIEW

Serum suPAR in patients with FSGS: trash or treasure?

Rutger J. H. Maas · Jeroen K. J. Deegens · Jack F. M. Wetzels

Pediatr Nephrol
DOI 10.1007/s00467-013-2452-5

REVIEW

Urine But Not Serum Soluble Urokinase Receptor (suPAR) May Identify Cases of Recurrent FSGS in Kidney Transplant Candidates

Carlos R. Franco Palacios,[1,6] John C. Lieske,[1,2] Hani M. Wadei,[3] Andrew D. Rule,[1,4] Fernando C. Fervenza,[1] Nikolay Voskoboev,[2] Vesna D. Garovic,[1] Ladan Zand,[1] Mark D. Stegall,[5,6] Fernando G. Cosio,[1,6] and Hatem Amer[1,6,7]

Pediatr Nephrol
DOI 10.1007/s00

REVIEW

see commentary on page 499

The soluble urokinase receptor is not a clinical marker for focal segmental glomerulosclerosis

Björn Meijers[1,2], Rutger J.H. Maas[3], Ben Sprangers[1,2], Kathleen Claes[1,2], Ruben Poesen[2], Bert Bammens[1,2], Maarten Naesens[1,2], Jeroen K.J. Deegens[3], Ruth Dietrich[4], Markus Storr[4], Jack F.M. Wetzels[3], Pieter Evenepoel[1,2] and Dirk Kuypers[1,2]

[1]Department of Nephrology, UZ Leuven, Leuven, Belgium; [2]Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium; [3]Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands and [4]Department of Research and Development, Gambro Dialysatoren GmbH, Hechingen, Germany

Urin… Receptor
(suPAR) … FSGS
in …

Carlos R. Franco Palacios,[1,6] John C. Li…
Nikolay Voskoboev,[2] Vesna D. Garovic, and Hu…

Pediatr Nephrol
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REVIEW

see commentary on page 499

The soluble urokinase receptor is not a marker for focal segmental glomer

Björn Meijers[1,2], Rutger J.H. Maas[3], Ben Sprangers[1,2], Kathlee
Maarten Naesens[1,2], Jeroen K.J. Deegens[3], Ruth Dietri
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[1]Department of Nephrology, UZ Leuven, Leuven, Belgi
[3]Department of Nephrology, Radboud University
and Development, Gambro Dialysatoren Gr

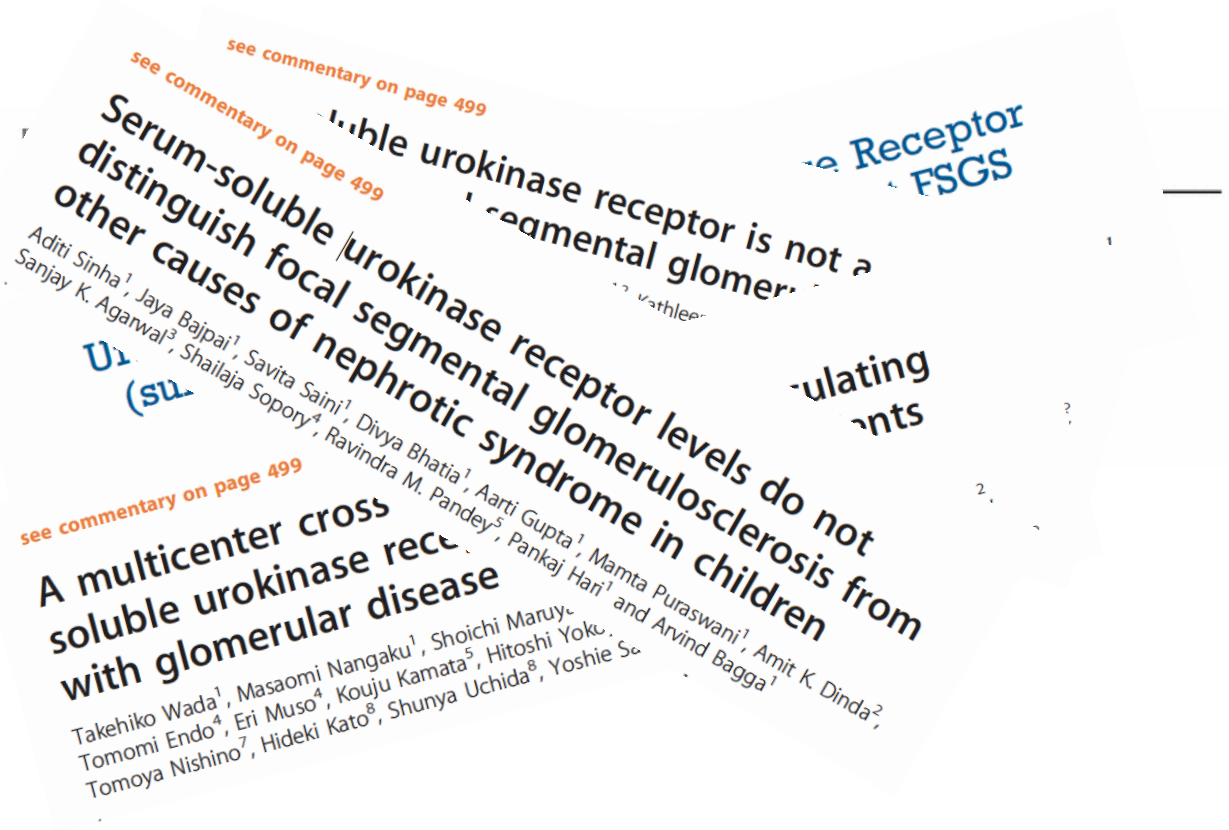
Urin
(suPAR
in

Receptor
FSGS

see commentary on page 499

A multicenter cross-sectional study of circulating soluble urokinase receptor in Japanese patients with glomerular disease

Takehiko Wada[1], Masaomi Nangaku[1], Shoichi Maruyama[2], Enyu Imai[3], Kumi Shoji[1], Sawako Kato[2], Tomomi Endo[4], Eri Muso[4], Kouju Kamata[5], Hitoshi Yokoyama[6], Keiji Fujimoto[6], Yoko Obata[7], Tomoya Nishino[7], Hideki Kato[8], Shunya Uchida[8], Yoshie Sasatomi[9], Takao Saito[10] and Seiichi Matsuo[2]



see commentary on page 499

ble urokinase receptor is not a
egmental glomer

see commentary on page 499

Serum-soluble urokinase receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children

Aditi Sinha[1], Jaya Bajpai[1], Savita Saini[1], Divya Bhatia[1], Aarti Gupta[1], Mamta Puraswani[1], Amit K. Dinda[2], Sanjay K. Agarwal[3], Shailaja Sopory[4], Ravindra M. Pandey[5], Pankaj Hari[1] and Arvind Bagga[1]

see commentary on page 499

A multicenter cross
soluble urokinase rece
with glomerular disease

Takehiko Wada[1], Masaomi Nangaku[1], Shoichi Maruy
Tomomi Endo[4], Eri Muso[4], Kouju Kamata[5], Hitoshi Yok
Tomoya Nishino[7], Hideki Kato[8], Shunya Uchida[8], Yoshie S

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

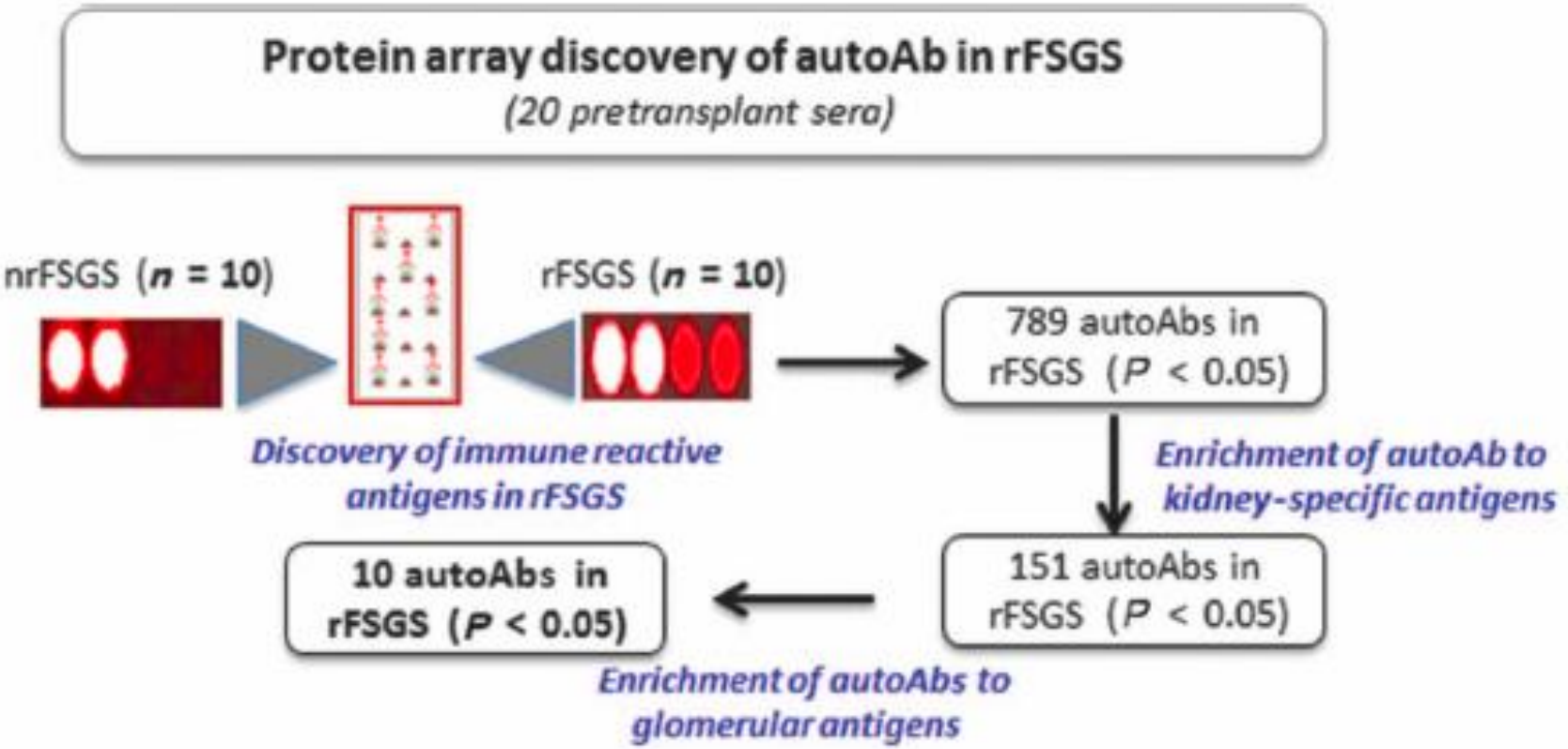
Soluble Urokinase Receptor and Chronic Kidney Disease

Salim S. Hayek, M.D., Sanja Sever, Ph.D., Yi-An Ko, Ph.D., Howard Trachtman, M.D., Mosaab Awad, M.D., Shikha Wadhwani, M.D., Mehmet M. Altintas, Ph.D., Changli Wei, M.D., Ph.D., Anna L. Hotton, Ph.D., M.P.H., Audrey L. French, M.D., Laurence S. Sperling, M.D., Stamatios Lerakis, M.D., Arshed A. Quyyumi, M.D., and Jochen Reiser, M.D., Ph.D.

CONCLUSIONS—An elevated level of suPAR was independently associated with incident chronic kidney disease and an accelerated decline in the eGFR in the groups studied. (Funded by the Abraham J. and Phyllis Katz Foundation and others.)

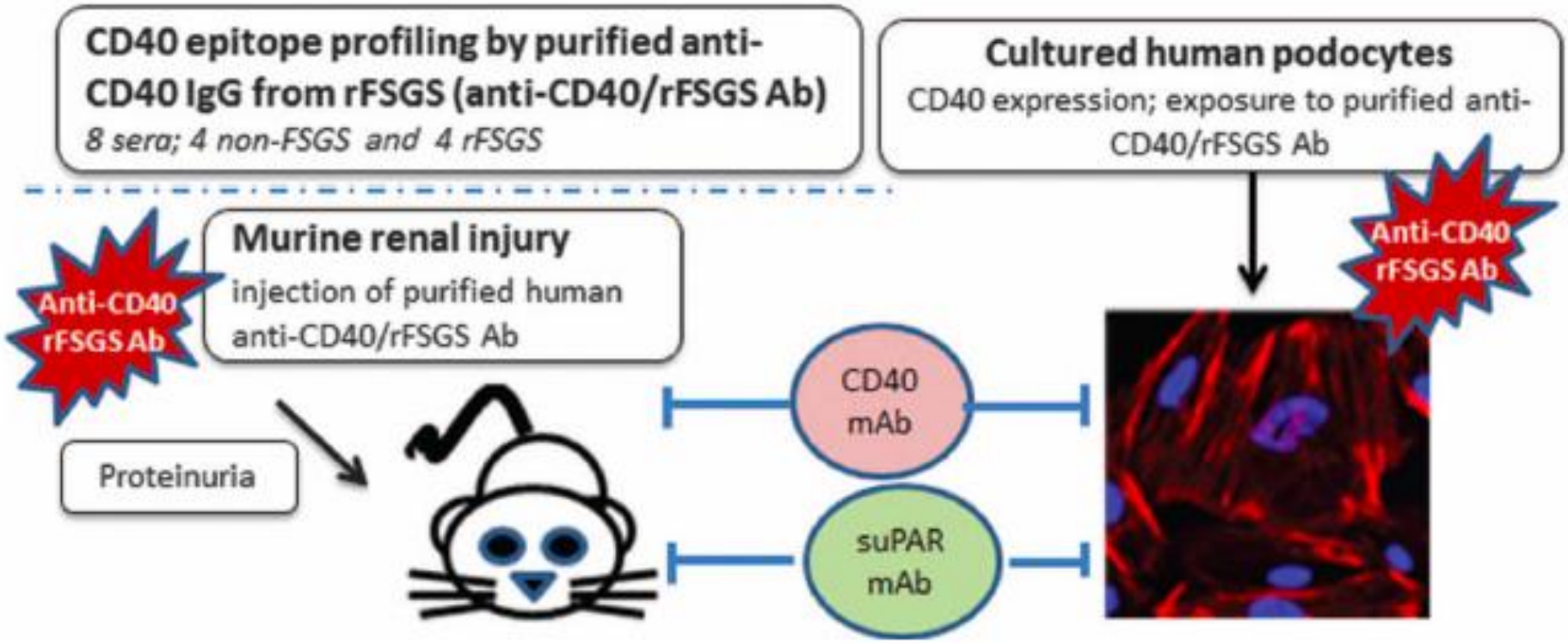
SuPAR # biomarker of chronic kidney disease

Which permeability factor?



M Delville et al, Sci Transl Med 2015

Which permeability factor?



M Delville et al, Sci Transl Med 2015

FSGS

Which permeability factor?

RESEARCH ARTICLE

Soluble CD40 ligand directly alters glomerular permeability and may act as a circulating permeability factor in FSGS

Sophie Doublier[1,2], Cristina Zennaro[3], Luca Musante[4], Tiziana Spatola[2], Giovanni Candiano[4], Maurizio Bruschi[4], Luca Besso[2], Massimo Cedrino[2], Michele Carraro[3], Gian Marco Ghiggeri[4], Giovanni Camussi[2]*, Enrico Lupia[2]*

FSGS

FSGS recurrence treatments

- **Plasma exchange**
- Anti-CD20 antibodies
- Abatacept
- Others

Table 2: Patients treated for FGGS recurrence during the1997–2005 time period (control group)

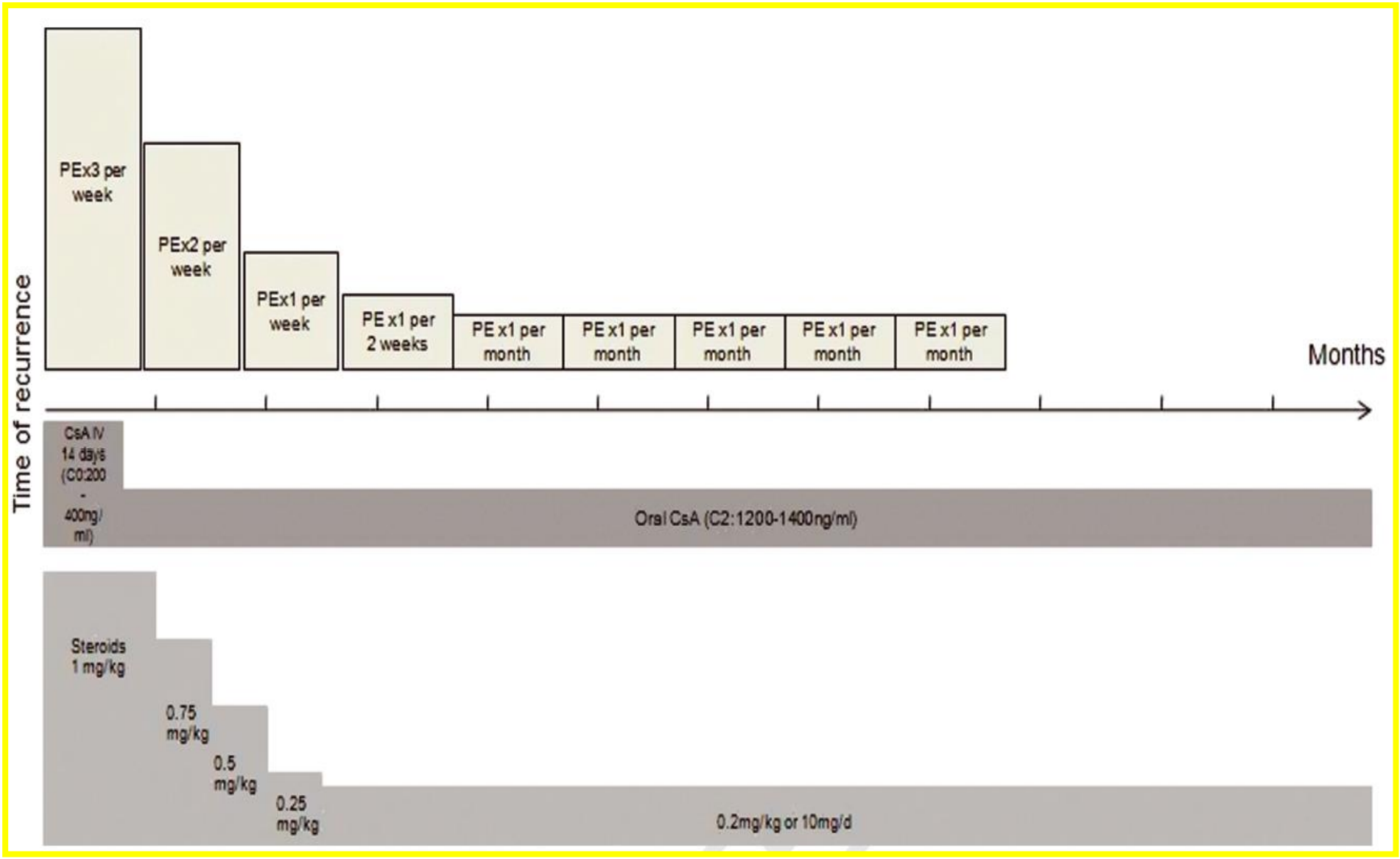
Patients	Treatment	Histological finding	Outcome	Proteinuria remission
1	CsA IV	FSGS on M12	Return on dialysis on M24	No
2	Cyc + PE	Normal kidney on light microscopy	Last follow-up M80	Complete and sustained
3	FK + PE	Normal kidney on light microscopy	Last follow-up M47	Complete and sustained
4	Steroids + FK	FSGS on M12	Last follow-up M52	No
5	CsA IV + PE	FSGS on M18	Return on dialysis on M36	No
6	Steroids + PE	Normal kidney on light microscopy	Last follow-up M61	Partial
7	CsA oral +PE	FSGS on M6	Return on dialysis M24	No
8	Steroids + PE	FSGS M12	Return on dialysis on M34	No
9	CsA oral + PE	Normal kidney on light microscopy	Last follow-up M92	Partial
10	CsA IV + PE	FSGS on M6	Return on dialysis on M6	No
11	CsA IV + PE	Normal kidney on light microscopy	Last follow-up M55	Complete and sustained
12	PE + Cyc + Rituximab	FSGS on M12	Return on dialysis M18	No
13	CsA IV	FSGS on M9	Return on dialysis on M48	No
14	CsA oral + PE	FSGS M18	Return on dialysis on M40	No
15	PE + Steroids + FK	FSGS M24	Return on dialysis on M24	No
16	FK+ PE	Normal kidney on light microscopy	Last follow-up M60	Complete and sustained
17	PE + Steroids + Rituximab	Normal kidney on light microscopy	Last follow-up M38	Partial
18	PE + Steroids	Normal kidney on light microscopy	Last follow-up M85	Complete and sustained
19	CsA IV + PE	FSGS on M24	Return on dialysis on M48	No

42% complete remission at 3 months

27% complete remission at one year

G Canaud et al, Am J Transplant 2009

FSGS



Combined IV CsA 14d + high dose steroids + plasma exchanges

G Canaud et al, Am J Transplant 2009

FSGS

Table 3: FSGS recurrence and treatment characteristics

Patient	Previous graft	Day of recurrence	Proteinuria at time recurrence (g/day)	Delay to remission (day)	Proteinuria month 3 (g/day)	Proteinuria month 12 (g/day)	loexhol GFR at 1 year (mL/min)	Follow-up after remission (months)	Total of PE sessions
1	0	2	4	18	0.05	0.05	86	21	25
2	0	12	5.4	24	0.1	0.1	58	19	25
3	0	55	7.1	28	0.3	0.3	75	16	25
4	0	1	7.9	29	0.15	0.07	84	18	25
5	0	2	5.6	18	0.20	0.05	94	17	25
6	0	4	7.7	20	0.22	0.1	41	14	25
7	0	4	22	10	0.3	0.05	61	16	25
8	2	1	8.7	23	0.04	1	85	15	39
9	0	1	40	33	0.05	0.1	56	13	25
10	0	1	12	26	0.2	0.1	45	9	25
Mean		8.3	12.0	22.9	0.16	0.19	68.5	15.8	
SD		16.8	11.1	6.7	0.09	0.29	18.6	3.3	

42% complete remission at 3 months
27% complete remission at one year

→

100% complete remission at 3 months
90% complete remission at one year
90% complete remission at 2 years

G Canaud et al, Am J Transplant 2009

FSGS

FSGS recurrence treatments

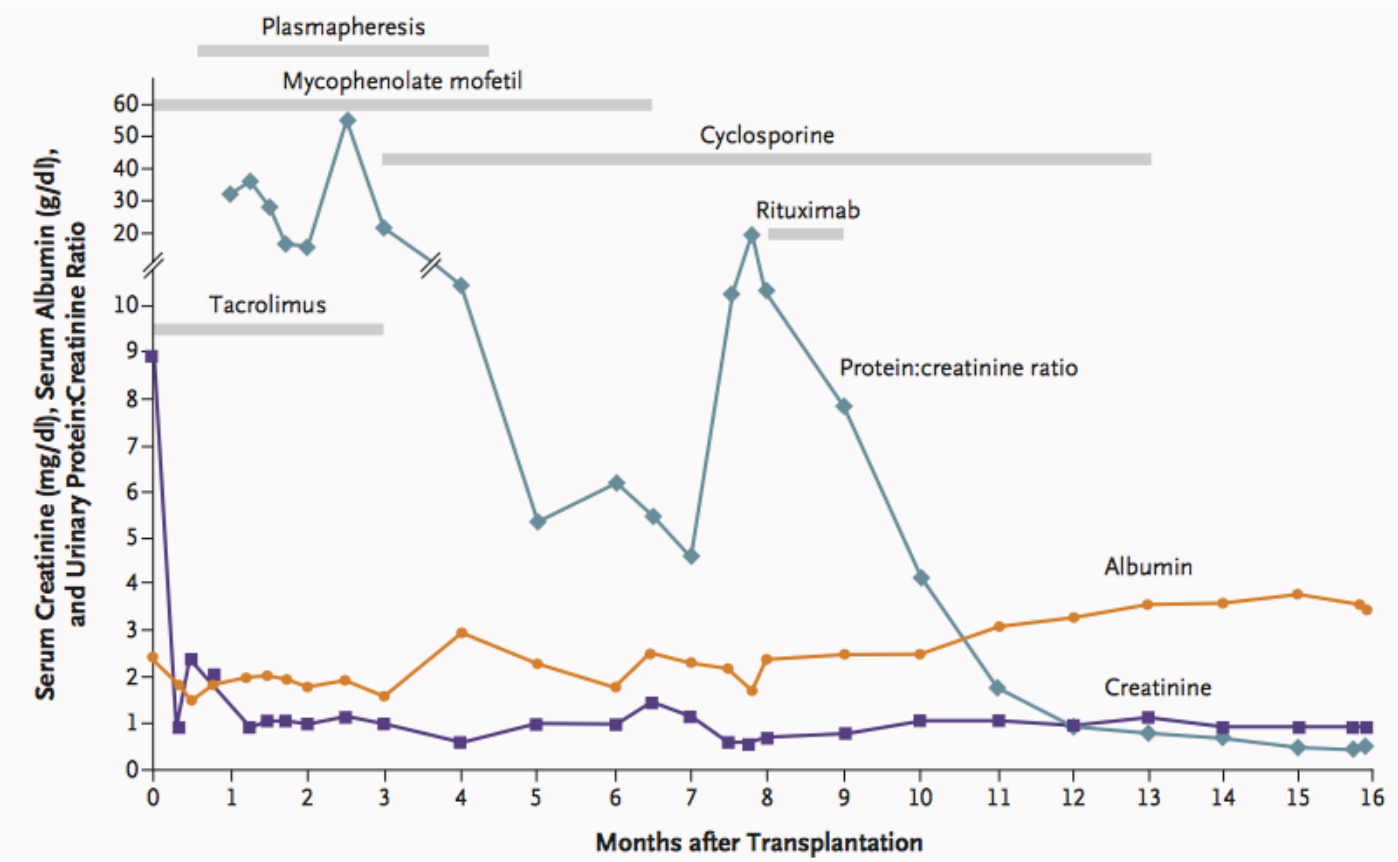
- **Preemptive plasma exchange: not convincing**
- Anti-CD20 antibodies
- Abatacept
- Others

RY Gohh et al, Am J Transplant 2005
S Alasfar et al, Transplantation 2018

FSGS recurrence treatments

- Plasma exchange
- **Anti-CD20 antibodies**
- Abatacept
- Others

FSGS recurrence and anti-CD20mab: the first case



MD Pescovitz et al, N Eng J Med 2006

FSGS recurrence and anti-CD20mab

- *Nozu K. et al, Pediatr Nephrol 2005*
- *Hristea D. et al, Transplant Int 2007*
- *Meyer TN. Et al, Transplant Int 2007*
- *Gossmann J. et al, Tansplant Int 2007*
- *Nakayama M. et al, Pediatr Nephrol 2008*
- *Bayrakci US. et al, Pediatr Transplant 2009*

Positive effect

- *Kamar N. et al, Clin Nephrol 2007*
- *Hickson LJ. et al, Transplantation 2009*
- *Dello Strologo L. et al, Transplantation 2009*
- *Canaud G. et al, Nephro Dialysis Transplant 2009*

Intermediate effect

- *Yabu JM. et al, Am J Transplant 2008*
- *Rodríguez-Ferrero M. et al, Transplant Proc 2009*

No effect

Rituximab for Recurrence of Primary Focal Segmental Glomerulosclerosis After Kidney Transplantation: Clinical Outcomes

Cyril Garrouste, MD,[1] Guillaume Canaud, MD, PhD,[2,3,4] Mathias Büchler, MD, PhD,[5,6] Joseph Rivalan, MD,[7] Charlotte Colosio, MD,[8] Frank Martinez, MD,[2] Julien Aniort, MD,[1] Caroline Dudreuilh, MD,[5] Bruno Pereira, PhD,[9] Sophie Caillard, MD, PhD,[10] Carole Philipponnet, MD,[1] Dany Anglicheau, MD, PhD,[2,3,4] and Anne Elisabeth Heng, MD, PhD[1,11]

Background. Rituximab has shown encouraging results for the treatment of kidney transplantation recipients with focal segmental glomerulosclerosis (FSGS) recurrence. However, the correct, opportune, and safe use of rituximab for this indication remains to be determined. **Methods.** This multicenter retrospective study reports on 19 new cases aged 35 (15-66) years who developed FSGS recurrence at 12 (1.5-27) days posttransplantation. Initial treatment consisted of plasma exchanges (PE), high doses of calcineurin inhibitors, and steroids. Rituximab was introduced either immediately (N = 6) or after failure of the initial treatment (N = 10) or failed attempted weaning from PE (N = 3). **Results.** Overall, we observed 9 of 19 complete remissions and 3 of 19 partial remissions. Estimated glomerular filtration rates (Modification of Diet in Renal Disease 4) were significantly higher in the responding patients than in nonresponding patients at month (M)12, M36, and M60. Overall, kidney survival at 5 years was 77.4% (95% range, 41.9-92.7). The 5-year graft survival rates in the responding patients and the nonresponding patients were 100% and 36.5%, respectively ($P = 0.01$). A further course of rituximab was required for 4 patients as a result of FSGS relapse, with good results. During the first year after renal transplantation, 14 patients developed severe infections (16 bacterial, 4 viral, 1 parasitic). **Conclusions.** In kidney transplantation recipients with recurrent FSGS, rituximab therapy may be a recommended treatment for cases that have failed either the initial treatment or weaning from PE.

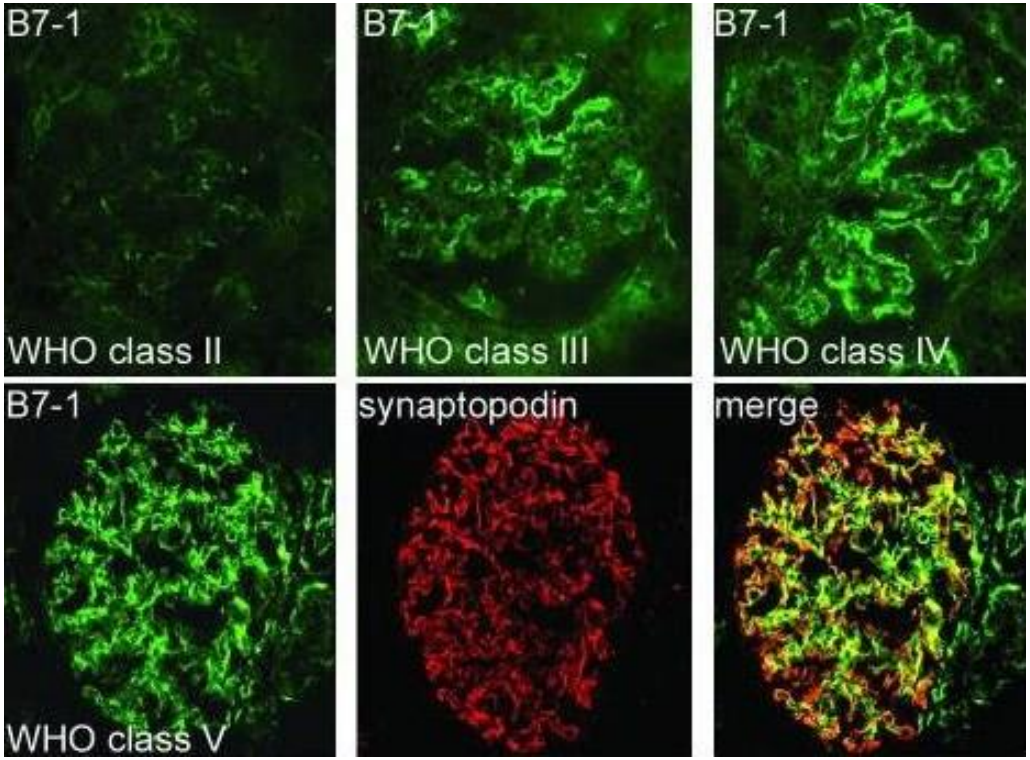
(*Transplantation* 2017;101: 649–656)

C Garrouste et al, Transplantation 2017

FSGS recurrence treatments

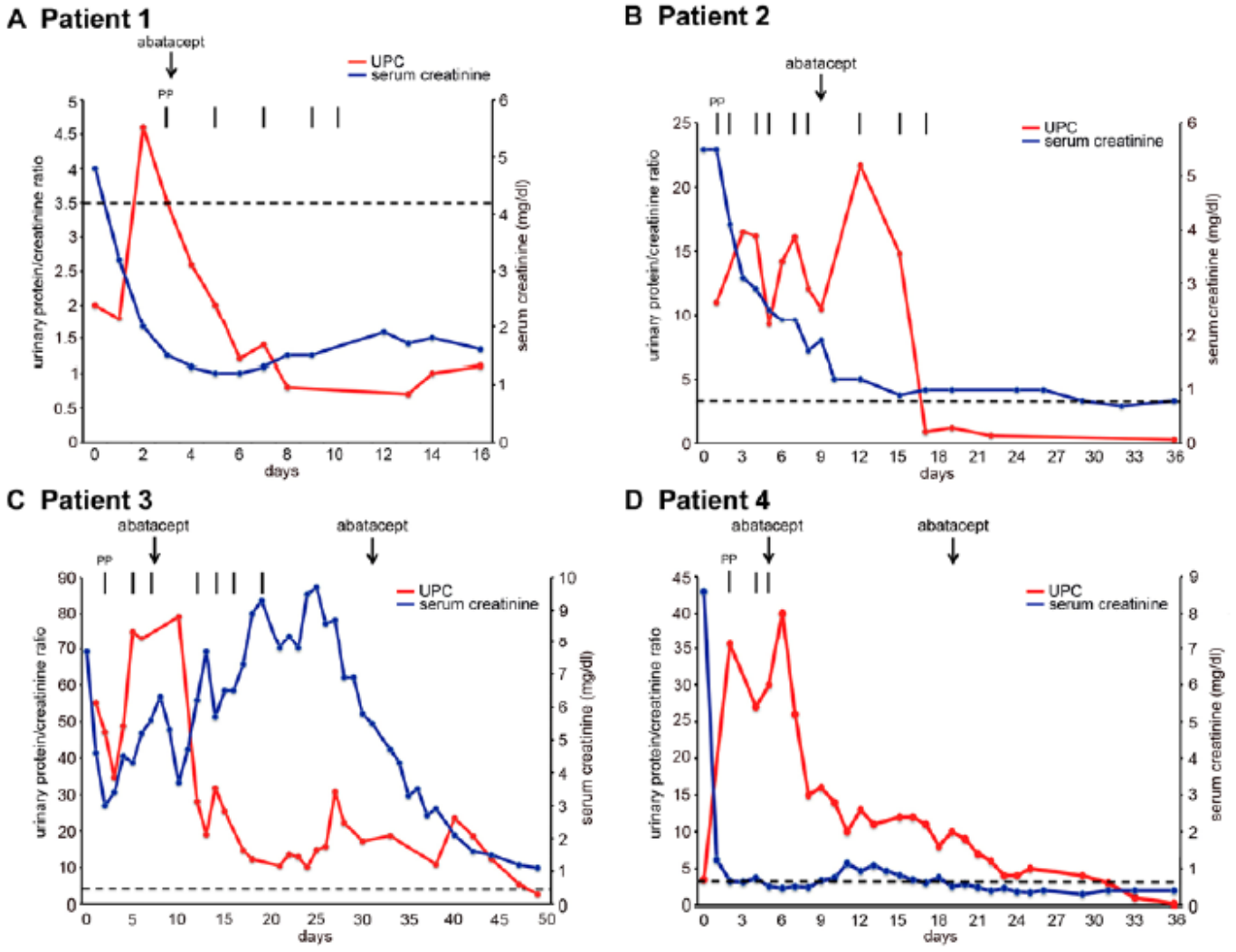
- Plasma exchange
- Anti-CD20 antibodies
- **Abatacept**
- Others

B7-1 is expressed on injured podocytes



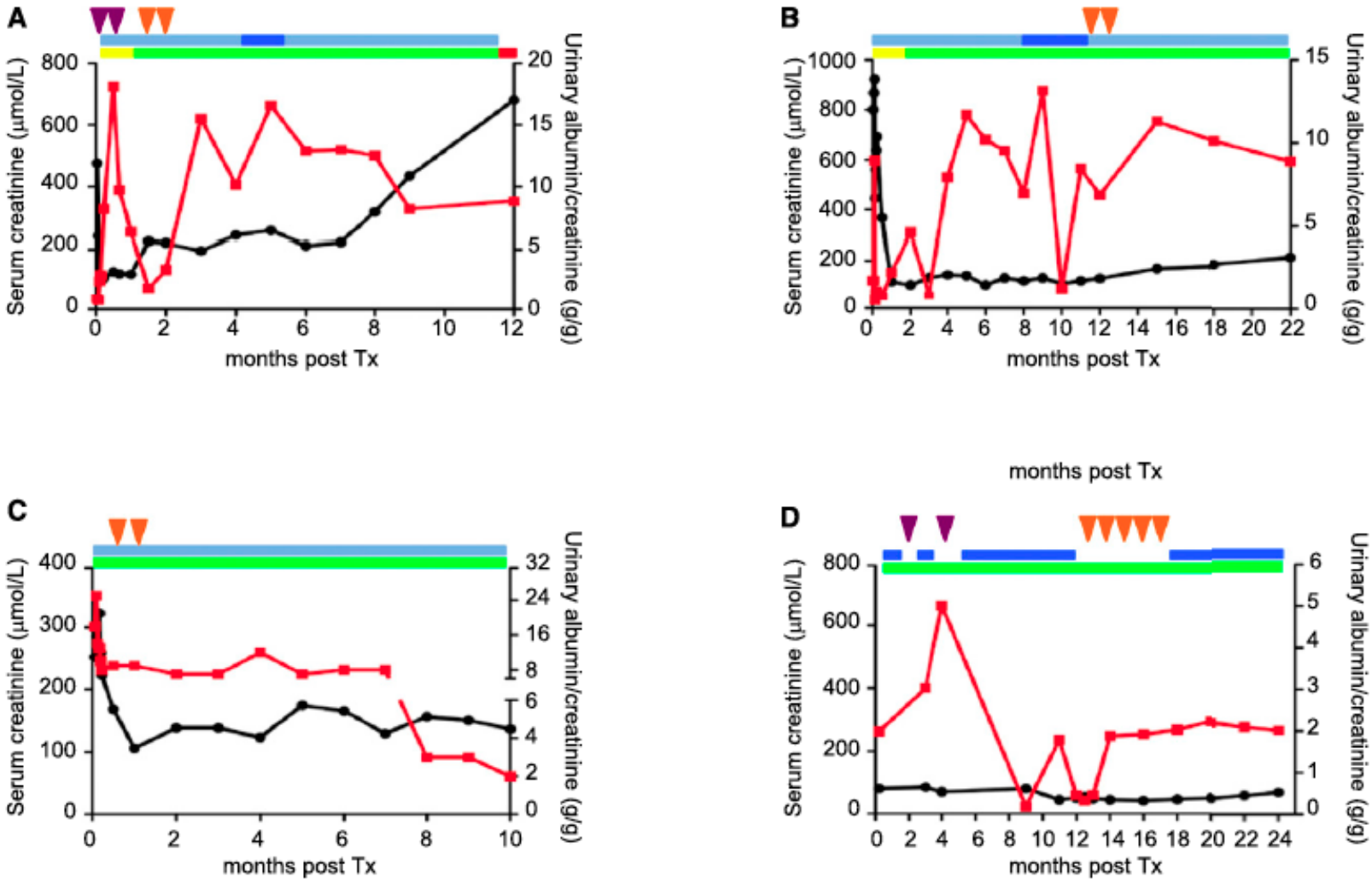
J Reiser et al, J Clin Invest 2004

Abatacept treatment = efficacy?



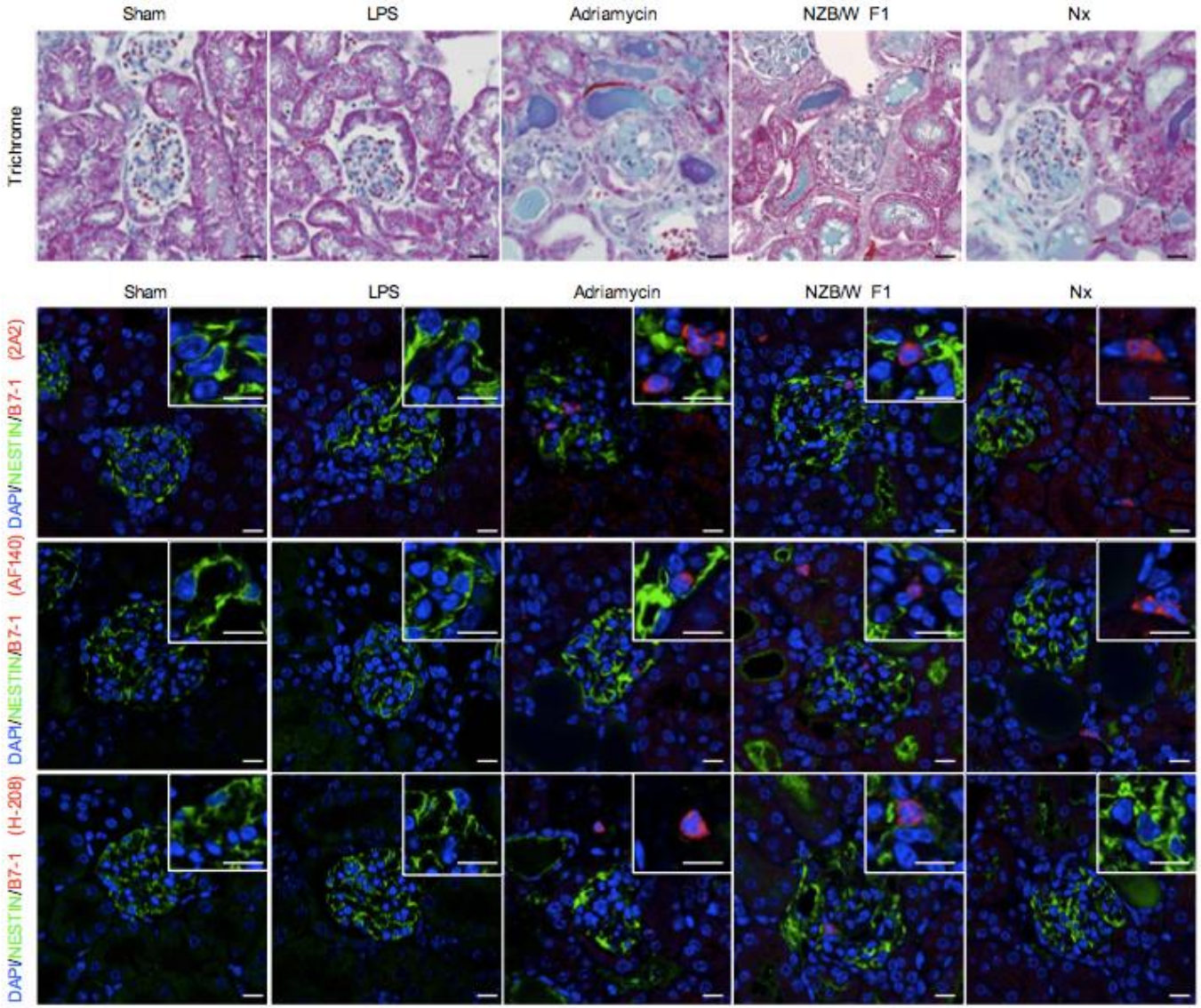
CC Yu et al, N Eng J Med 2014

Abatacept treatment = efficacy?



M Delville et al, J Am Soc Nephrol 2016

No B7-1 on injured podocytes



F Baye et al, Kidney Int 2016

FSGS treatments

- Plasma exchange
- Anti-CD20 antibodies
- Abatacept
- **Others:** galactose, anti-TNF alpha

Post-transplant glomerulonephritis recurrence

- Focal and segmental glomerulosclerosis (FSGS)
- **Atypical Hemolytic Uremic Syndrome (aHUS)**
- Antiphospholipid syndrome (APS)
- Membranous nephropathy (MN)
- Membranoproliferative glomerulonephritis (MPGN)
- IgA nephropathy

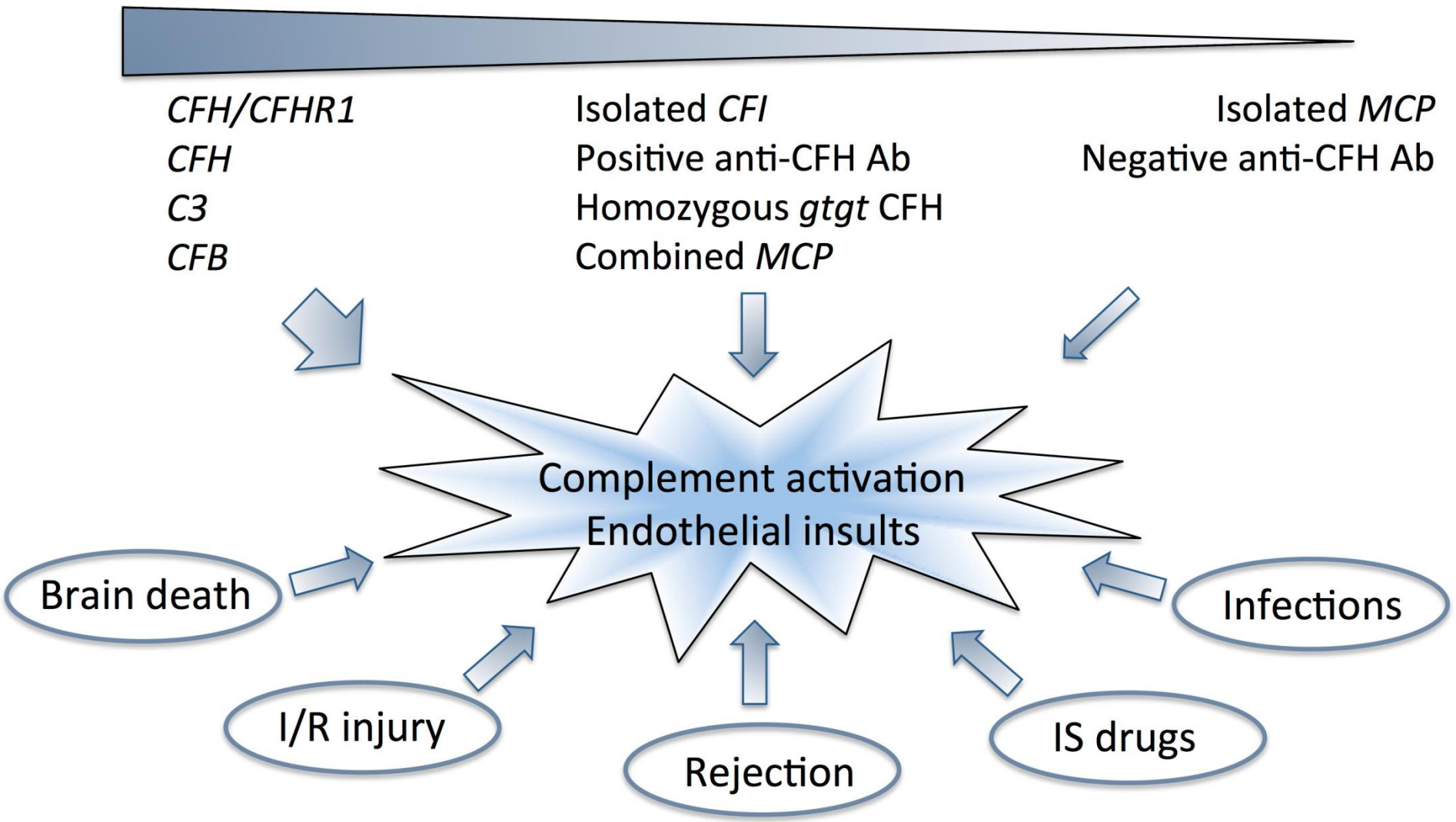
B. Atypical Hemolytic Uremic Syndromes (aHUS)

Mechanical hemolytic anemia +
Peripheral thrombocytopenia +
Acute renal failure (AKI).

Typical
Shiga toxin

Atypical
Complement

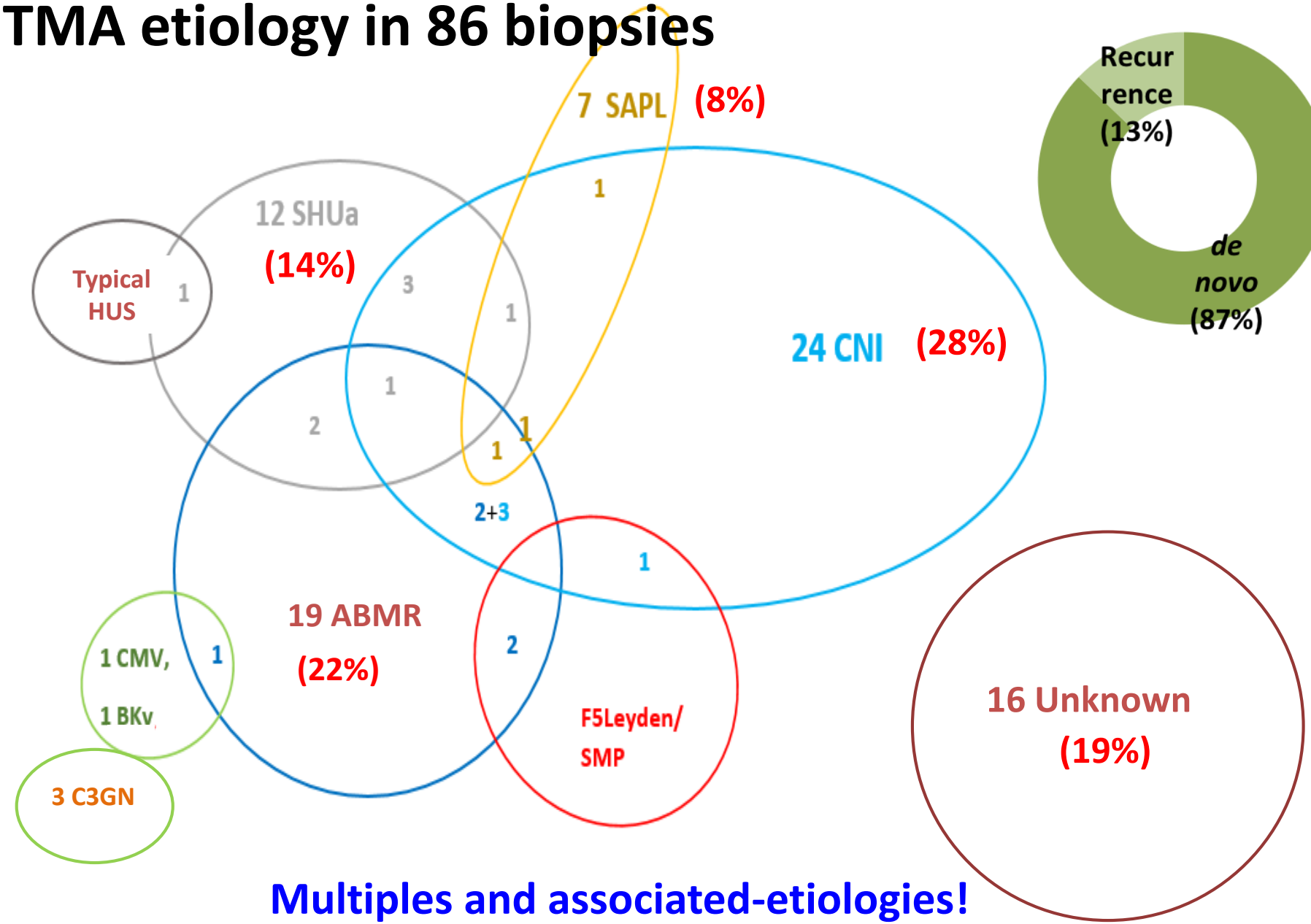
Driving force



Precipitating factors

J Zuber et al, Nat Rev Nephrol 2011, 7: 23-35.

TMA etiology in 86 biopsies



Multiples and associated-etiologies!

K Dessaix et al, Manuscript in preparation

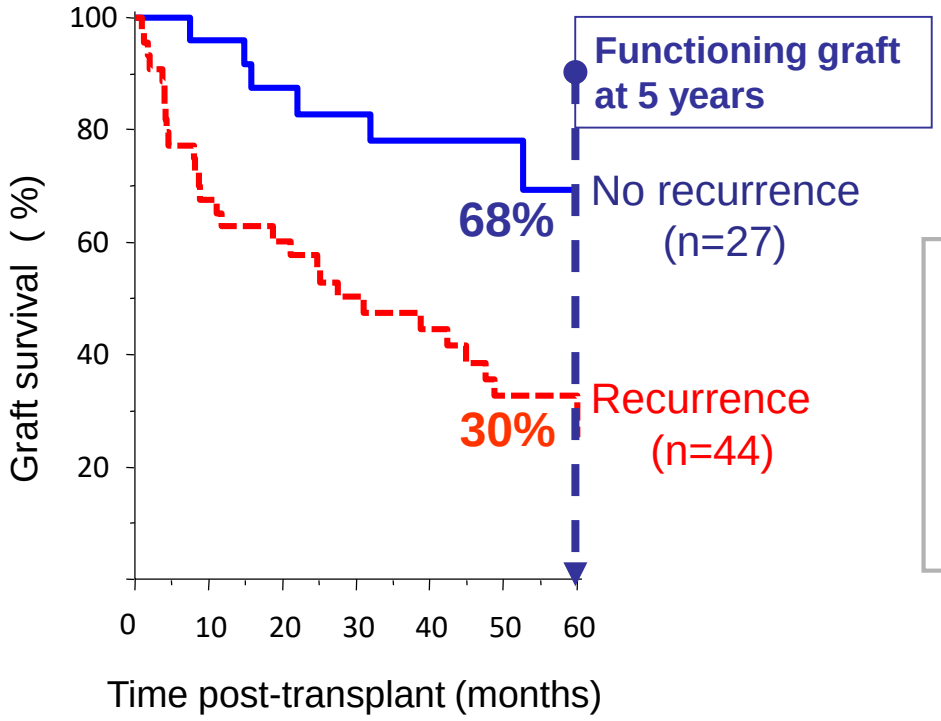
Table 1 | Risk of aHUS recurrence according to the implicated genetic abnormality

Gene	Protein location	Functional impact	Mutation frequency in aHUS (%)	Recurrence frequency after transplantation (%)
Mutation				
CFH	Plasma	Loss	20–30	75–90
CFI	Plasma	Loss	2–12	45–80
CFB	Plasma	Gain	1–2	100
C3	Plasma	Gain	5–10	40–70
MCP	Membrane	Loss	10–15	15–20
THBD	Membrane	Loss	5	1 case
Genetic polymorphism (frequency in control populations)				
Homozygous *CFHR1*del (3–8%)	Circulating	Undetermined	14–23 (>90% in patients with anti-CFH antibodies)	NA

J Zuber et al, Nat Rev Nephrol 2011, 7: 23-35.

2/3 of aHUS patients experienced post-transplant recurrence which significantly impaired graft outcome

71 kidney grafts in 57 aHUS patients (>18 y at onset) transplanted in France between 1995 and 2009

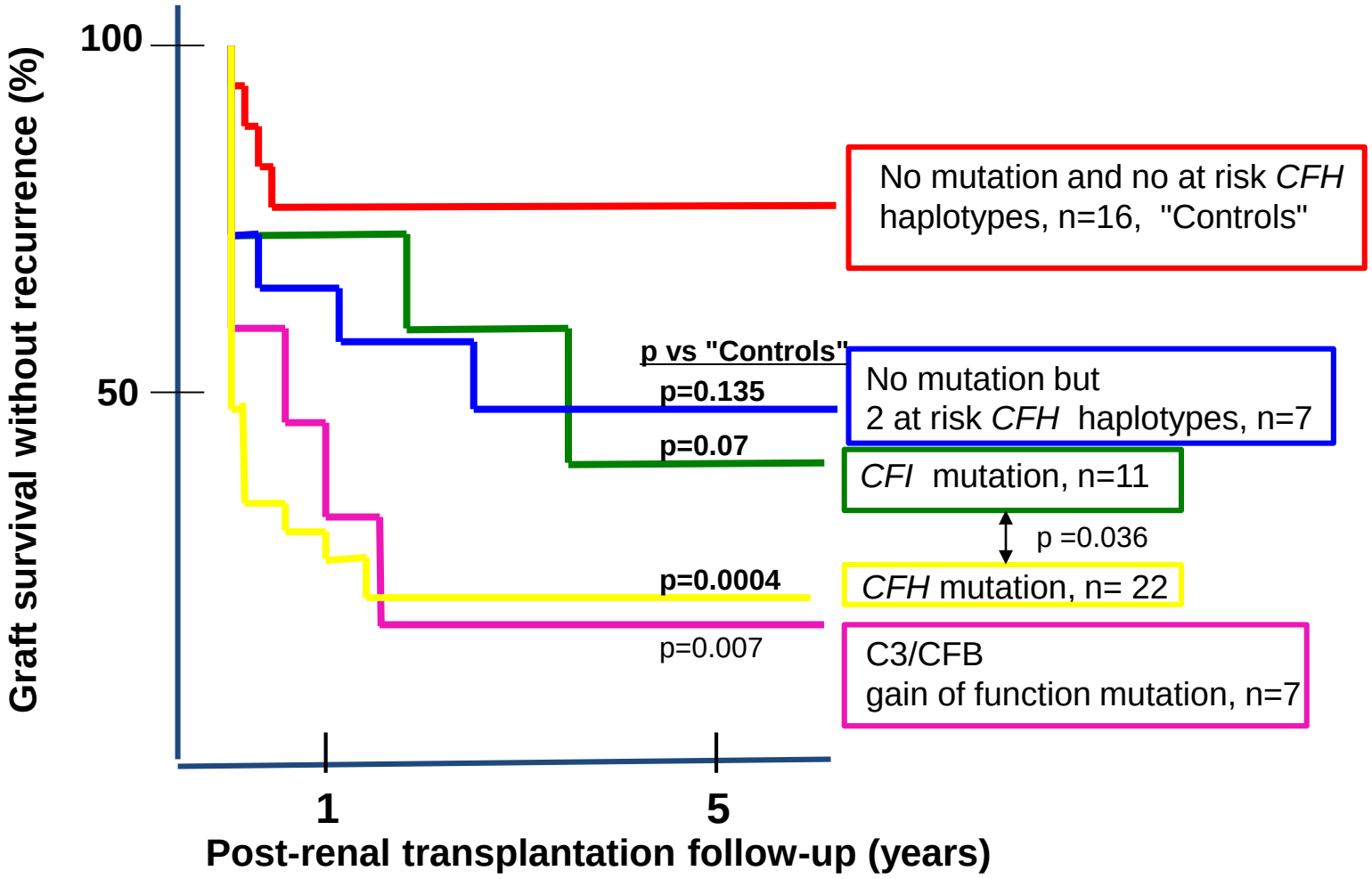


- **Post-transplant recurrence occurred in 44/71 grafts (62%)**
- **At 5 years, graft survival was 30% in patients with recurrence versus 68% in patients without recurrence**
  RR 4.89 (1.30-13.81), p=0.001

France

M Le Quintrec et al, Am J Transplant 2013, 13: 663-675.

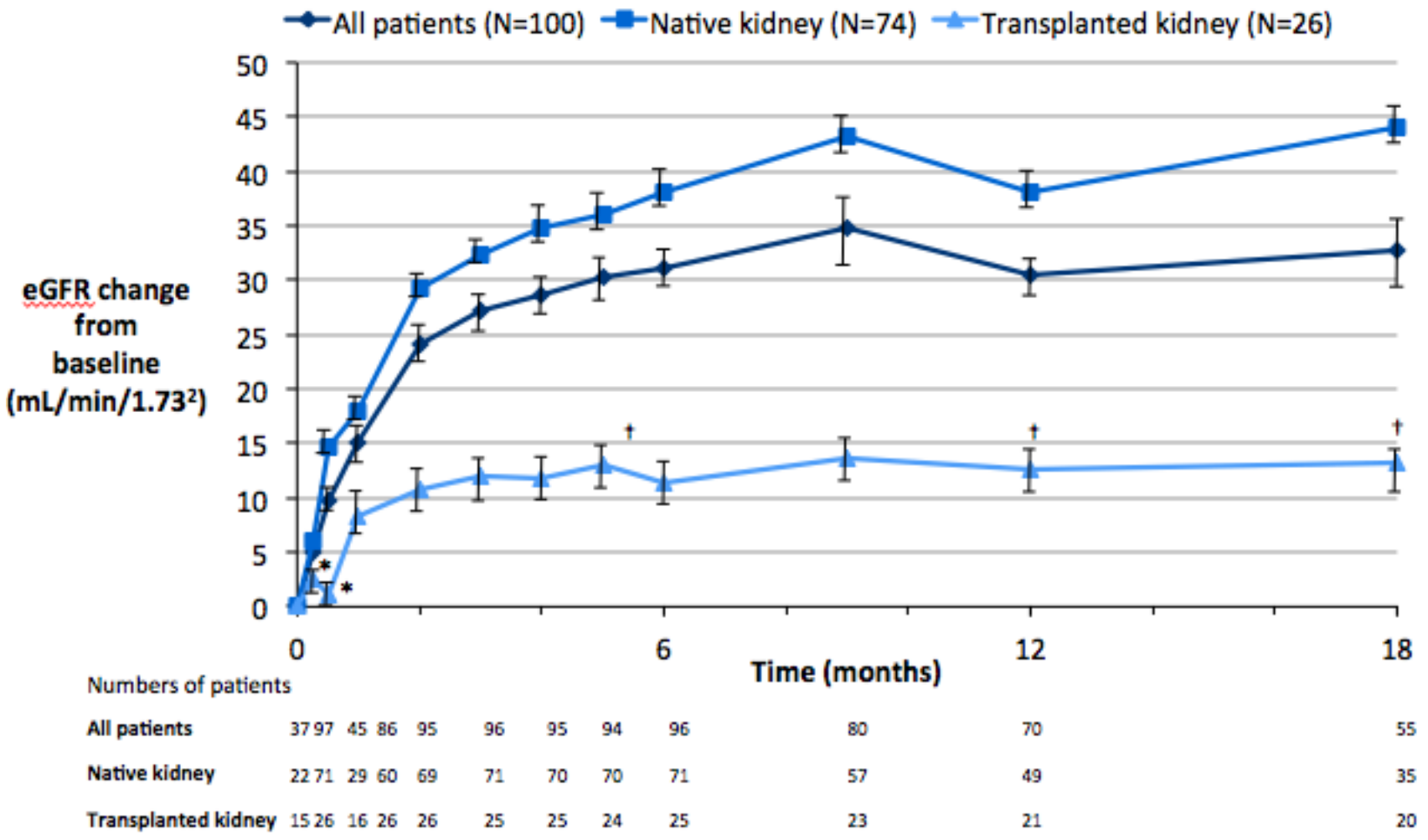
Pre-transplant assessment of post-transplant recurrence risk relies on genetics



M Le Quintrec et al, Am J Transplant 2013, 13: 663-675.

France

Atypical Hemolytic Uremic Syndrome: renal function

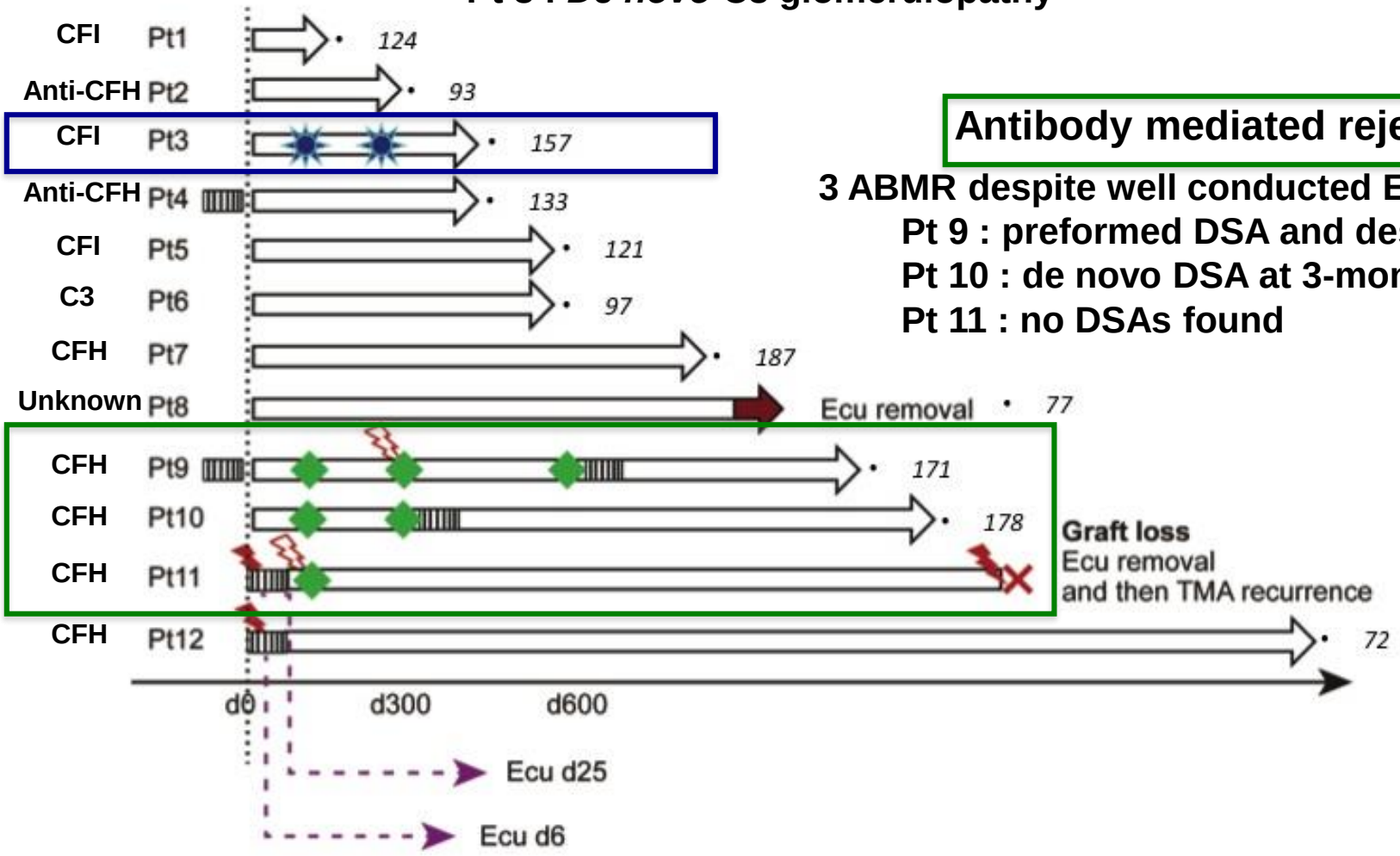


Ch Legendre et al, N Engl J Med 2013, 368: 2169-2181.
F Fakhouri et al, AJKD 2016, 68: 84-93.

Necker's experience

De novo C3 glomerulonephritis

Pt 3 : *De novo* C3 glomerulopathy



Antibody mediated rejection

3 ABMR despite well conducted Eculizumab

Pt 9 : preformed DSA and desensitizati

Pt 10 : de novo DSA at 3-months

Pt 11 : no DSAs found

C Levi et al, Transplantation 2017 (Epub ahead of print))

No prevention with eculizumab?

Table 3. Follow-up After Kidney Transplantation

Pt No.	F/U, mo	Kidney Function at End of F/U: Scr, µmol/L	eGFR, mL/min/1.73 m^2	Proteinuria, mg/10 mmol Scr	aHUS Recurrence	Rejection	No. of Antihypertensives	Current immunosuppressive Therapy	Complications and/or Adjustment of Immunosuppressive Therapy
1	68	132[a]	39	0	No	No	2	Tac/MMF	Pred discontinued because of psychological problems
2	66	80	71	0.06	No	No	1	Tac/MMF/Pred	
3	66	106	46	0	No	No	2	Tac/Aza/Pred	MMF discontinued because of diarrhea
4	63	104	65	0.1	No	No	2	Tac/MMF/Pred	
5	45	76	72	0.07	No	No	2	Tac/Aza	MMF discontinued because of diarrhea; Pred discontinued because of weight gain and mood disturbances
6	43	158[a]	39	0.27	No	No	3	Tac/Pred	BK nephropathy; MMF discontinued
7	32	84	59	0	No	No	2	Tac/MMF/Pred	
8	32	91[a]	64	0.05	No	Yes (biopsy proven)	2	Tac/MMF/Pred	Rejection treated with methylprednisolone/ATG
9	25	166[a]	36	0.12	No	Yes (no biopsy)	3	Tac/Pred	Rejection treated with methylprednisolone; lymphocele with compression of transplant; MMF discontinued because of HSV infection
10	14	143	35	0.05	Yes	No	2	Tac/Pred	aHUS recurrence treated with eculizumab; MMF and Aza discontinued due to gastrointestinal symptoms
11	9	151[a]	30	0.14	No	Yes (biopsy proven)	3	Tac/Pred	Rejection treated with methylprednisolone/ alemtuzumab; BK nephropathy; MMF discontinued because of diarrhea; Aza discontinued because of BK nephropathy
12	7	140[a]	51	0.09	No	No	3	Tac/MMF/Pred	Hypercalcemia due to tertiary hyperparathyroidism
13	7	67	86	0.06	No	No	2	Tac/MMF/Pred	
14	13	77	76	0.31	No	No	2	Tac/MMF/Pred	
15	22	145	50	0.10	No	No	2	Tac/MMF/Pred	
16	10	79	72	0.17	No	No	2	Tac/MMF/Pred	
17	7	175[a]	28	0.44	No	No	2	Tac/Pred	Chronic norovirus infection, MMF discontinued

Abbreviations: aHUS, atypical hemolytic uremic syndrome; ATG, antithymocyte globulin; Aza, azathioprine; eGFR, estimated glomerular filtration rate; F/U, follow-up; HSV, herpes simplex virus; MMF, mycophenolate mofetil; Pred, prednisolone; pt, patient; Scr, serum creatinine; Tac, tacrolimus.

[a]These patients had complications other than aHUS and/or lower kidney function than expected (eGFR < 45 mL/min/1.73 m^2) and are described in Item S2.

C Duineveld, et al, Am J Kidney Dis 2017 (In press).

Post-transplant glomerulonephritis recurrence

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- **Antiphospholipid syndrome (APS)**
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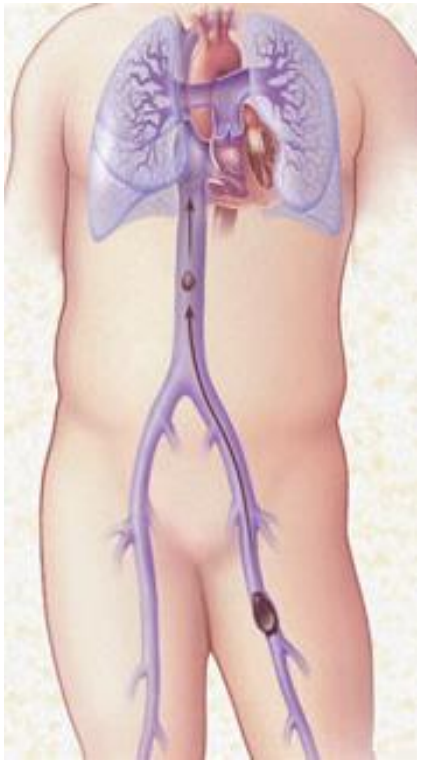
- IgA nephropathy

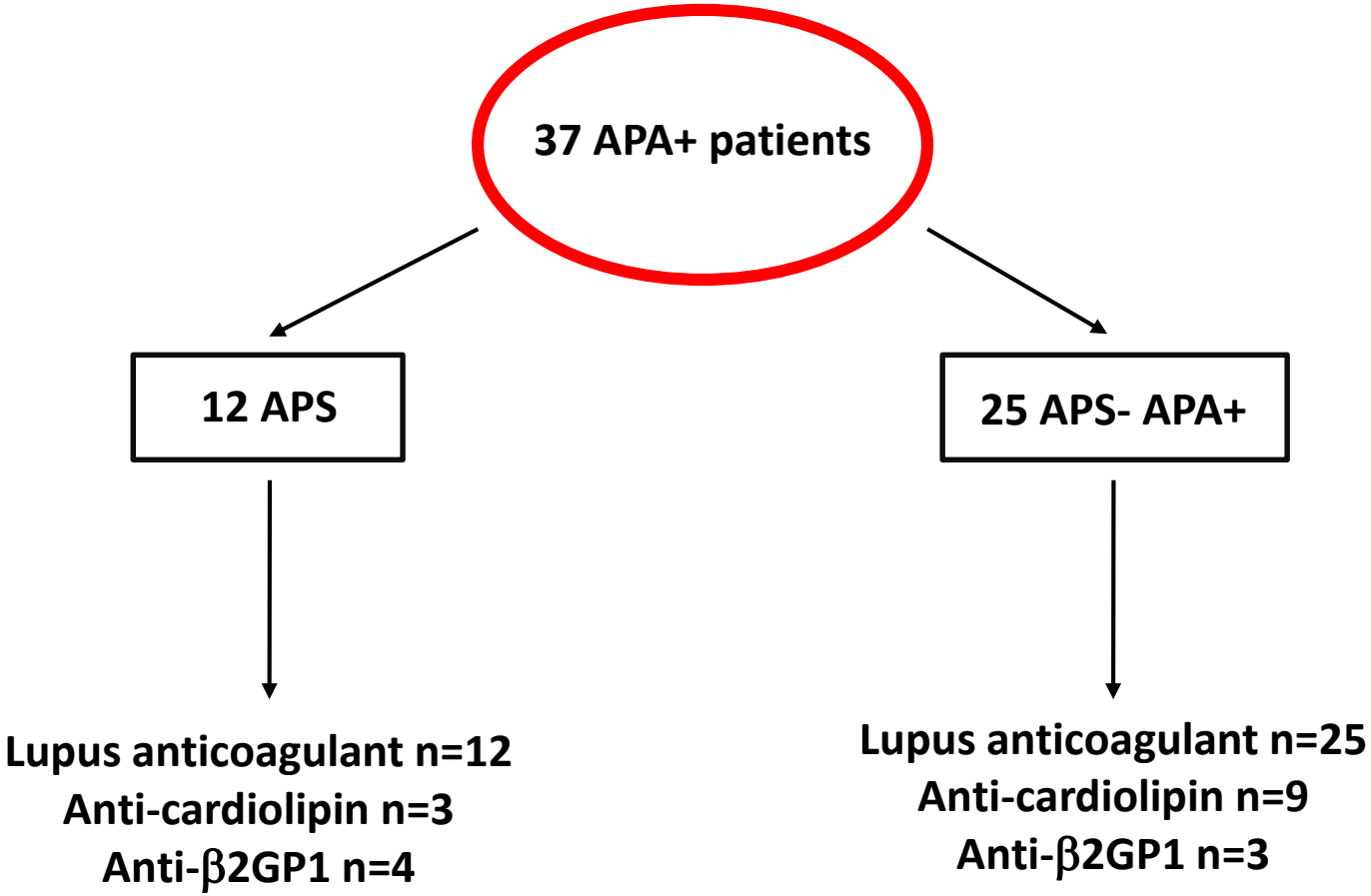
APS may recur after trasplantation



- **Thrombosis**
- **Pregnancy loss**

- **Anti-β2GPI**
- **Anti-cardiolipin**
- **Lupus Anticoagulant**

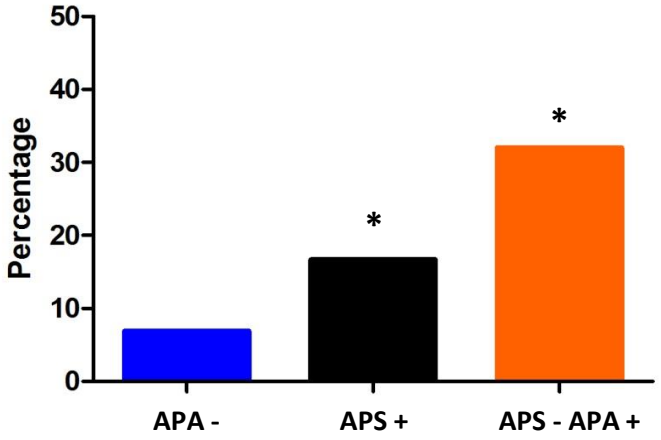
Antiphospholipid syndrome (APS)



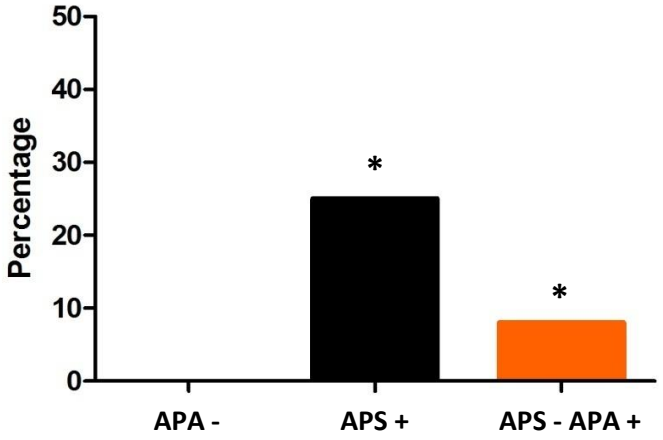
Canaud G et al, Am J Transplant 2010

Antiphospholipid syndrome (APS)

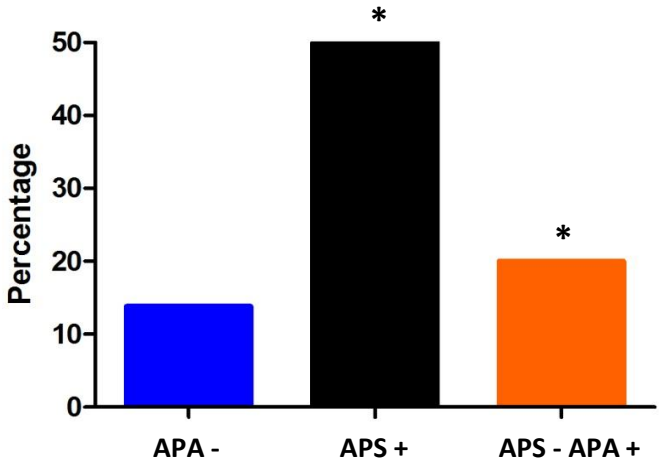
Allograft thrombosis



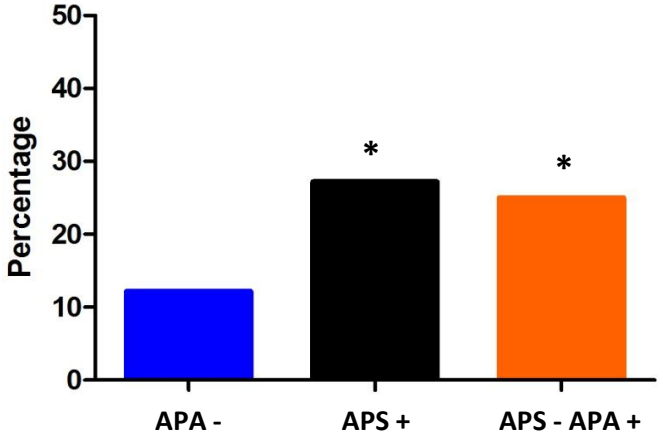
Cortical necrosis



Deep venous thrombosis post Tx



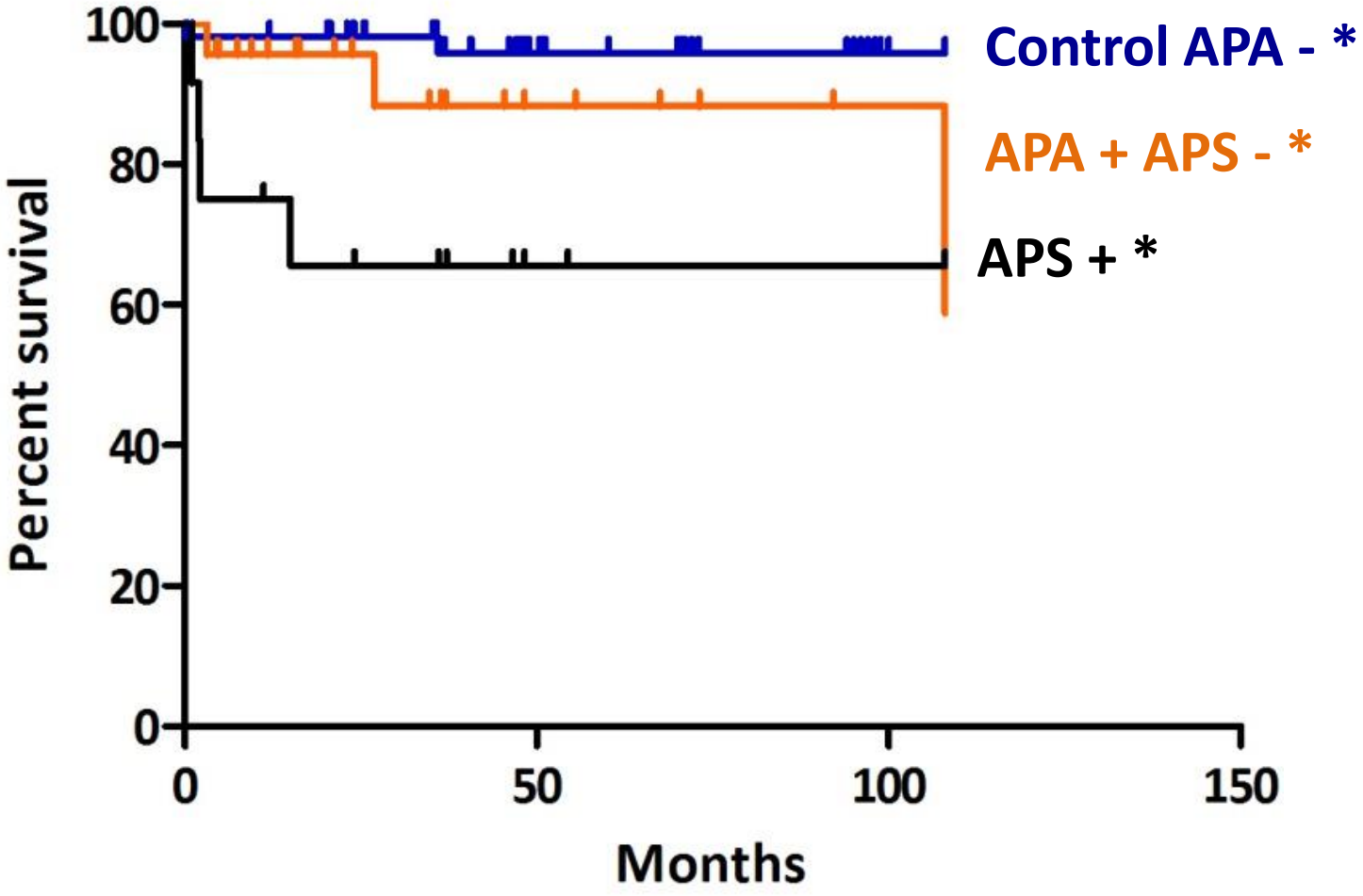
Severe hypertension



Canaud G et al, Am J Transplant 2010

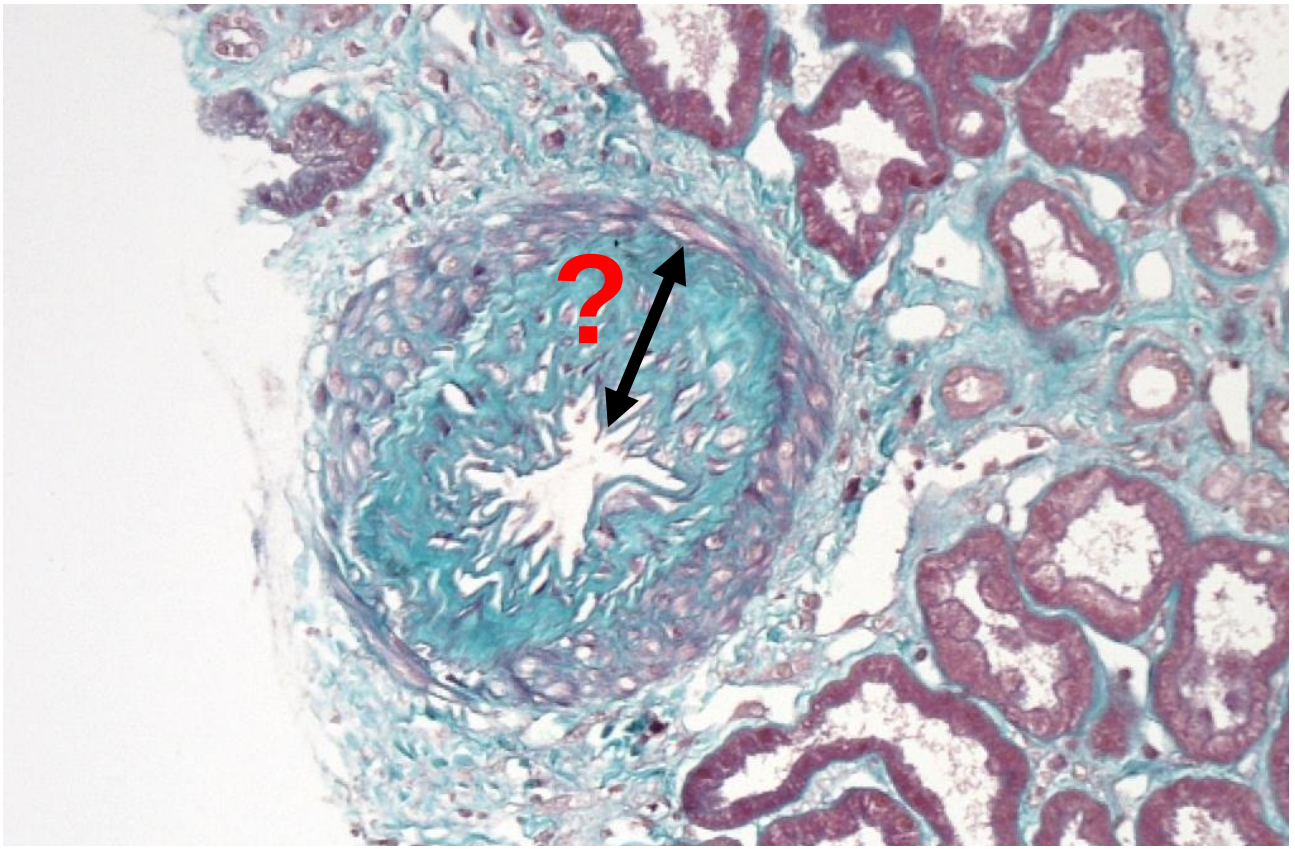
APS

Antiphospholipid syndrome (APS)



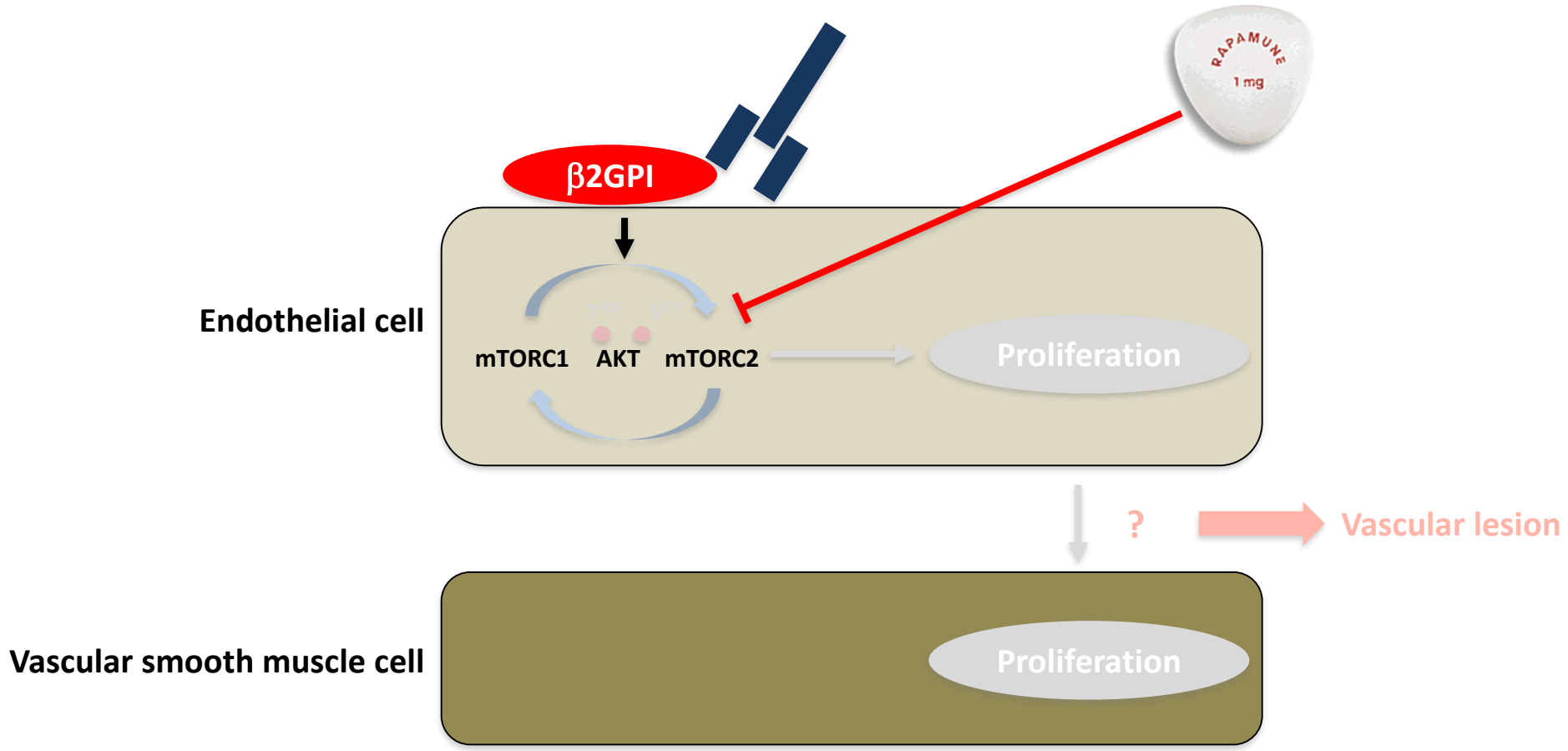
Canaud G et al, Am J Transplant 2010

Mechanisms and pathway



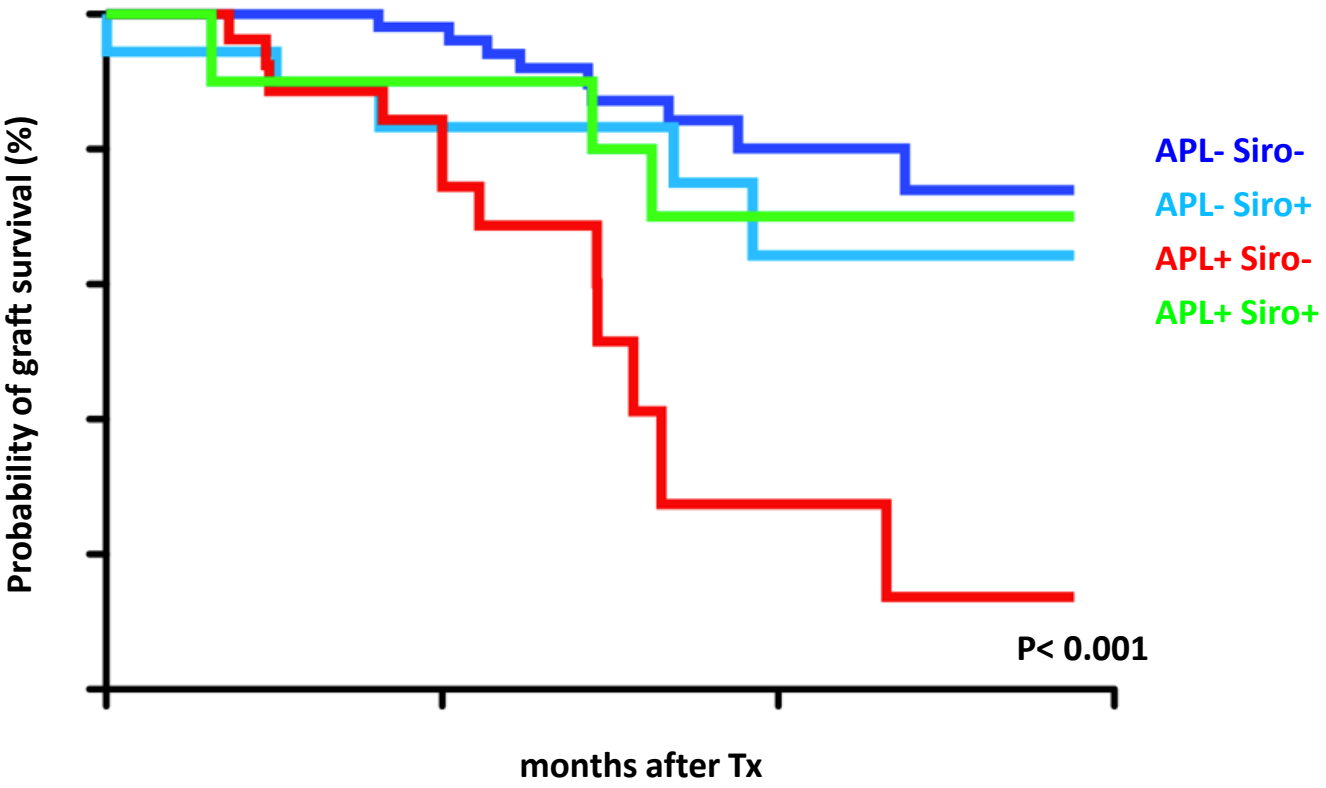
Proliferation and Hypertrophy

Mechanisms and pathway

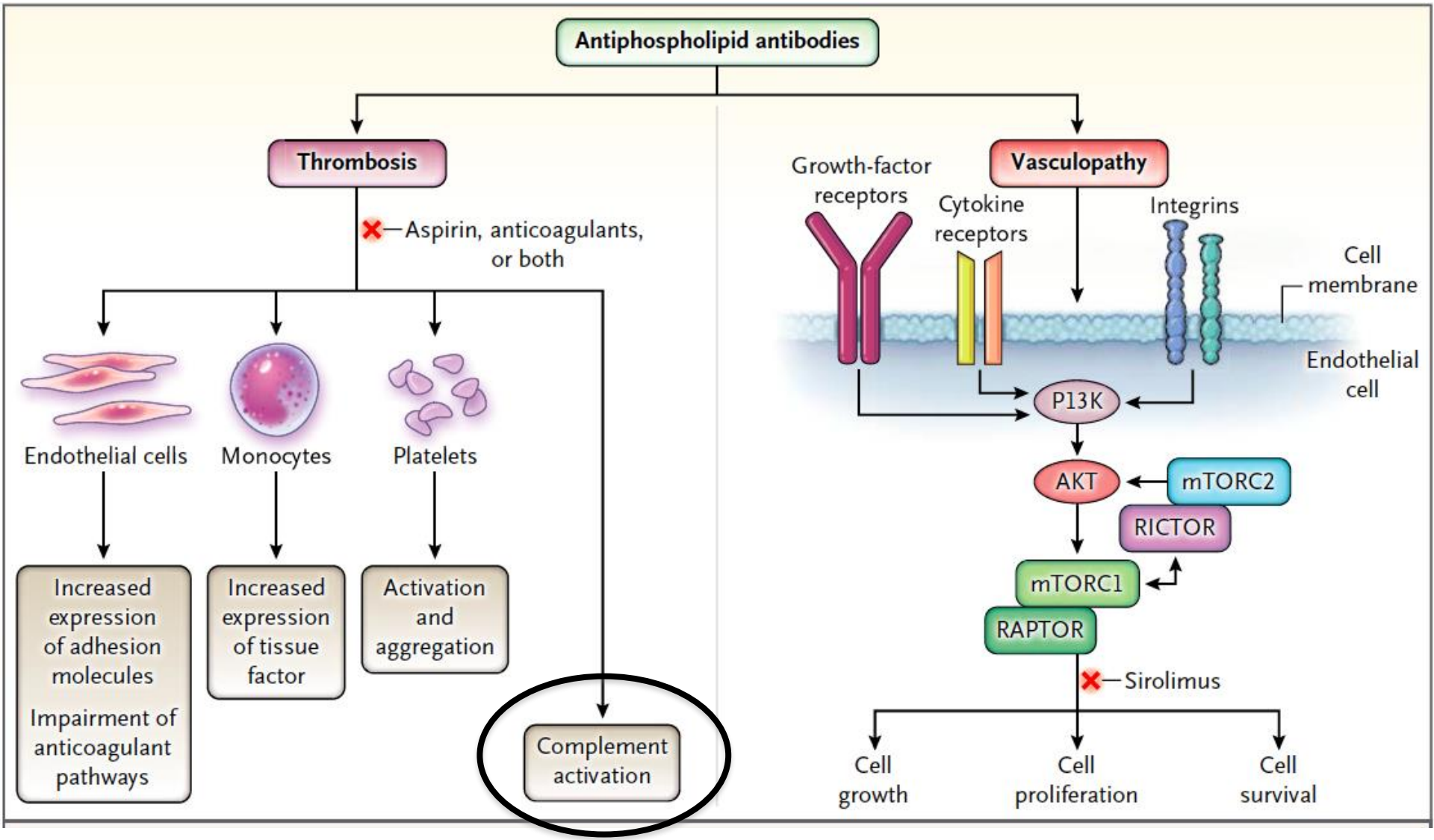


G Canaud et al. N Eng J Med 2014

Sirolimus improves graft survival

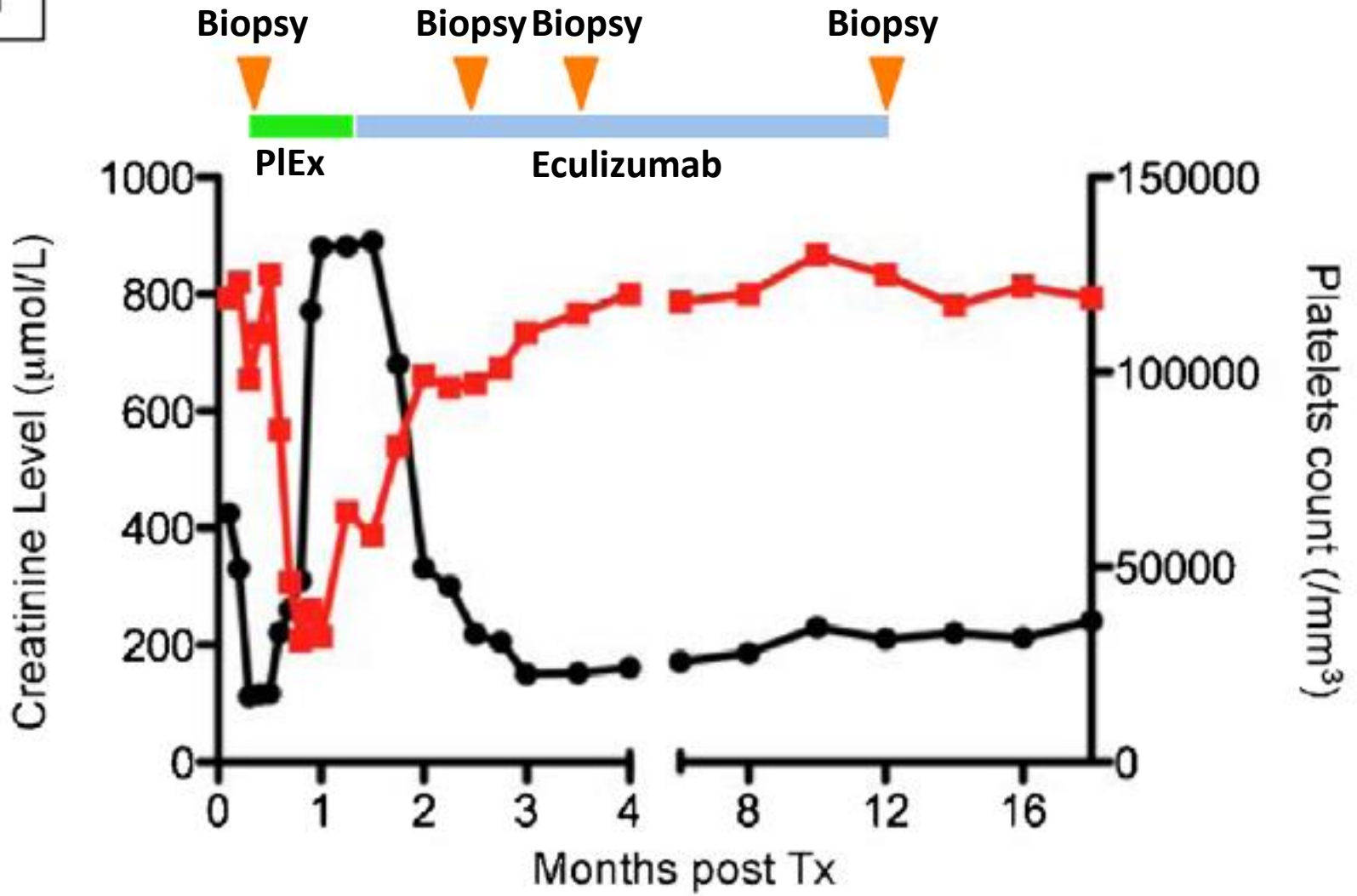


G Canaud et al. N Eng J Med 2014



JW Eikelboom et al, N Engl J Med 2014

Patient 1



G Canaud et al, Am J Transplant 2013
BE Lonze et al, Am J Transplant 2014

Post-transplant glomerulonephritis recurrence

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Membranous nephropathy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 2, 2009 VOL. 361 NO. 1

M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Human Idiopathic Membranous Nephropathy — A Mystery Solved?

Richard J. Glassock, M.D.

Beck L et al, N Engl J Med 2009

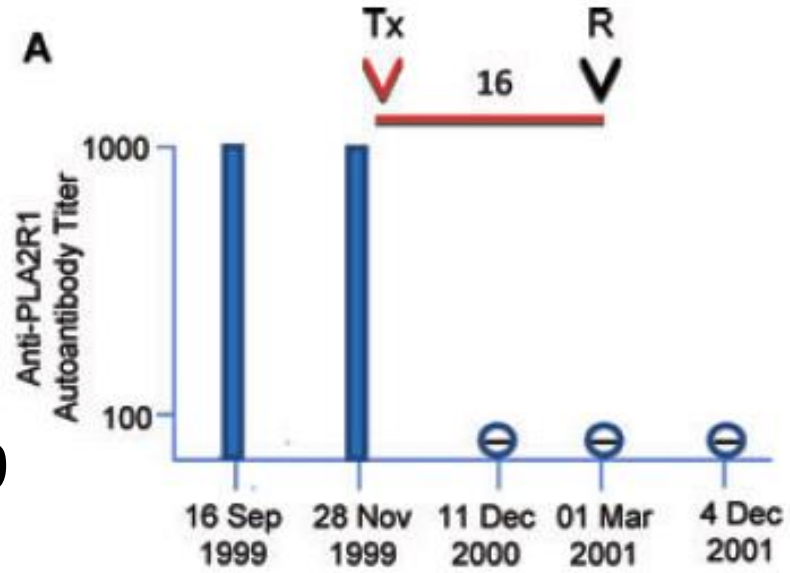
MN

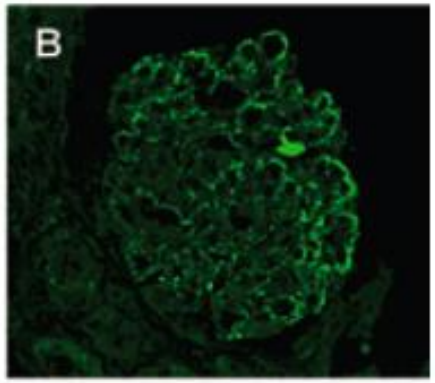
Rec MN n = 10

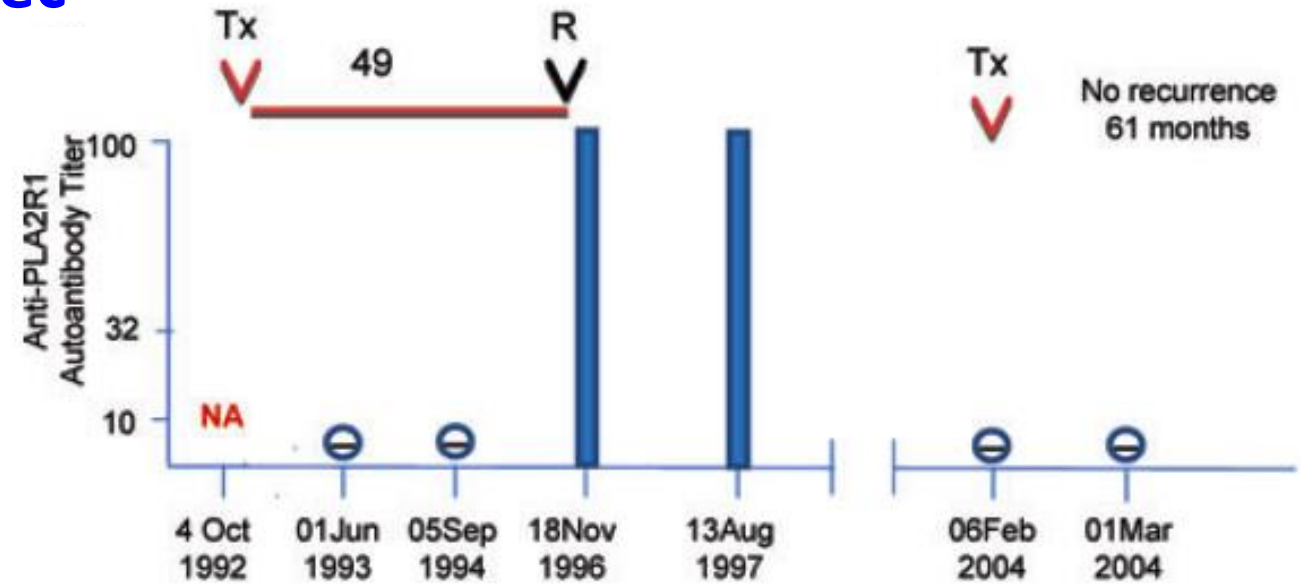
De novo MN n = 9

PLA2R1 in 5/10 Rec

None in de novo

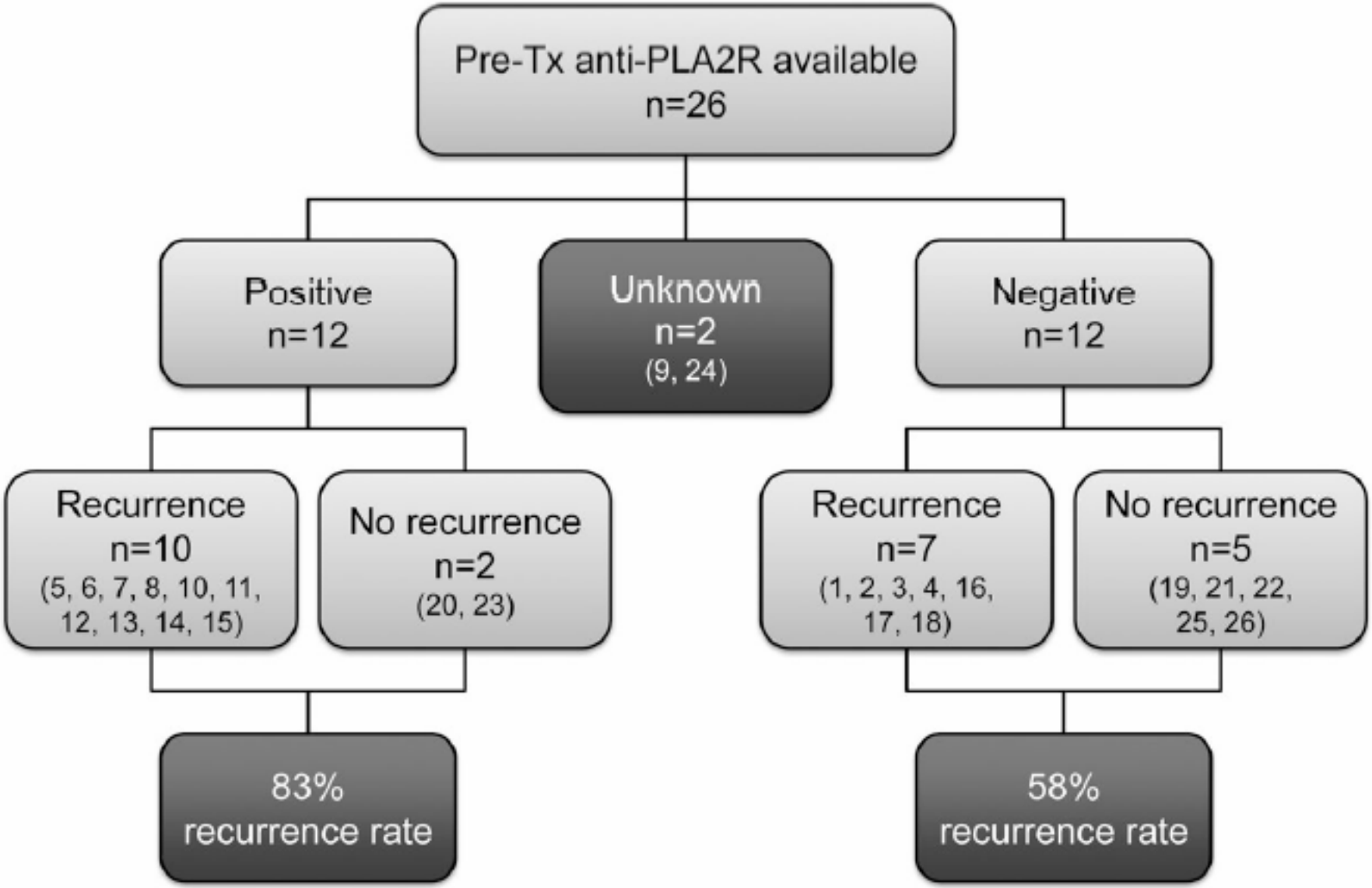






Debiec H et al, Am J Transplant 2011

MN



A Kattah et al, Am J Transplant 2015

Membranous nephropathy recurrence

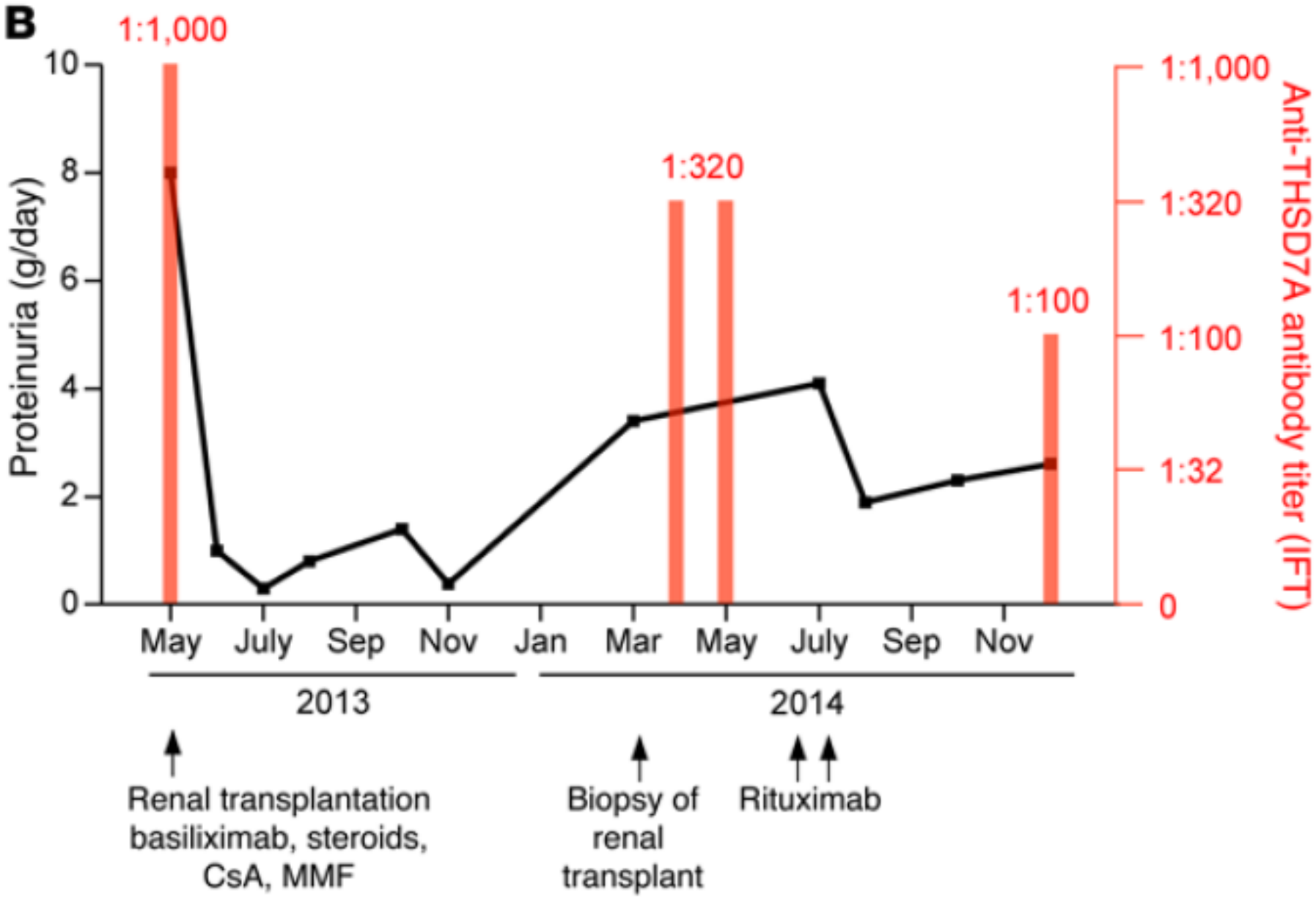
The Journal of Clinical Investigation

RESEARCH ARTICLE

Autoantibodies against thrombospondin type 1 domain–containing 7A induce membranous nephropathy

Nicola M. Tomas,[1] Elion Hoxha,[1] Anna T. Reinicke,[1] Lars Fester,[2] Udo Helmchen,[3] Jens Gerth,[4] Friederike Bachmann,[5] Klemens Budde,[5] Friedrich Koch-Nolte,[6] Gunther Zahner,[1] Gabriele Rune,[2] Gerard Lambeau,[7] Catherine Meyer-Schwesinger,[1] and Rolf A.K. Stahl[1]

NM Tomas et al, J Clin Invest 2016



NM Tomas et al, J Clin Invest 2016

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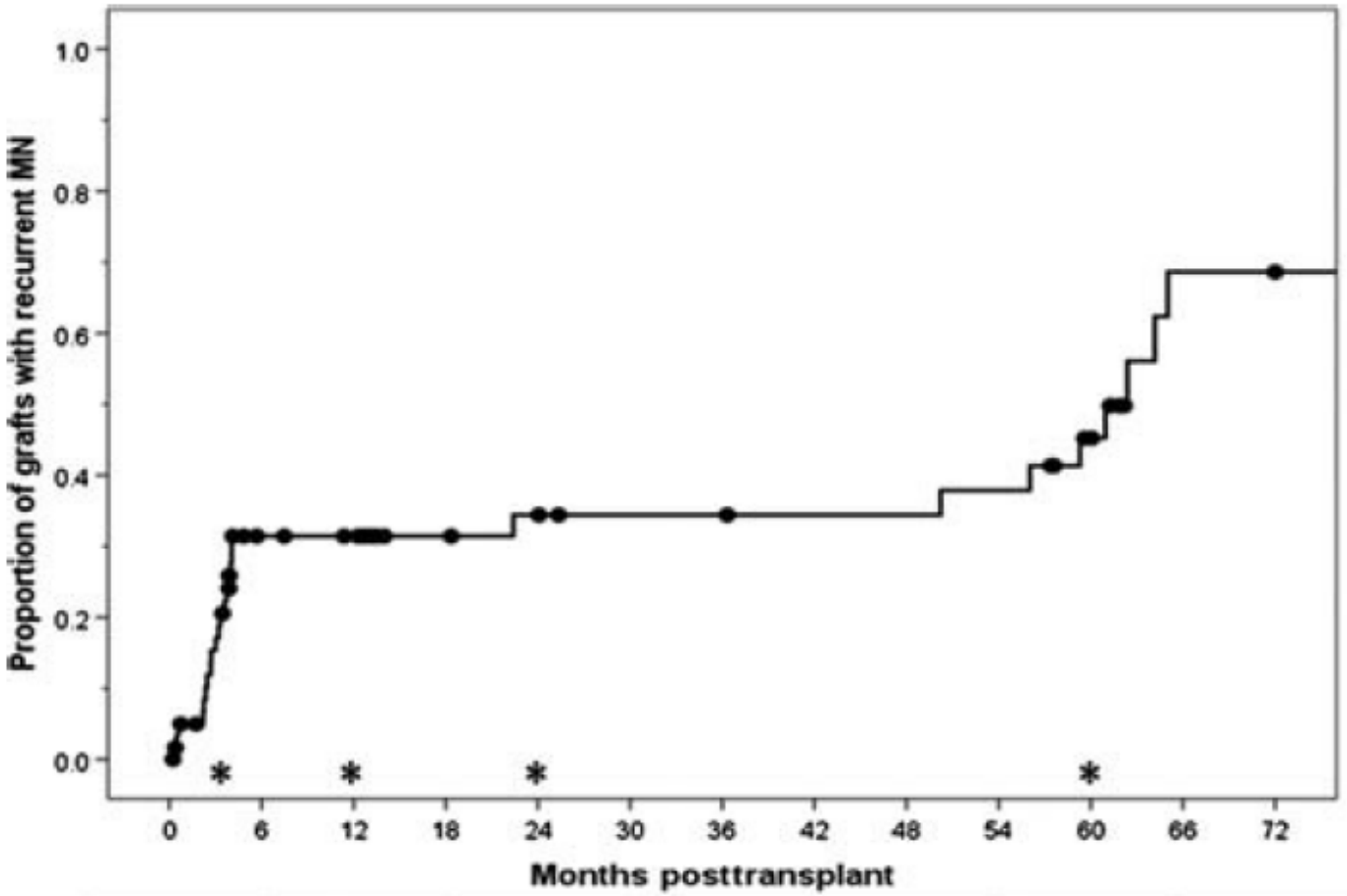
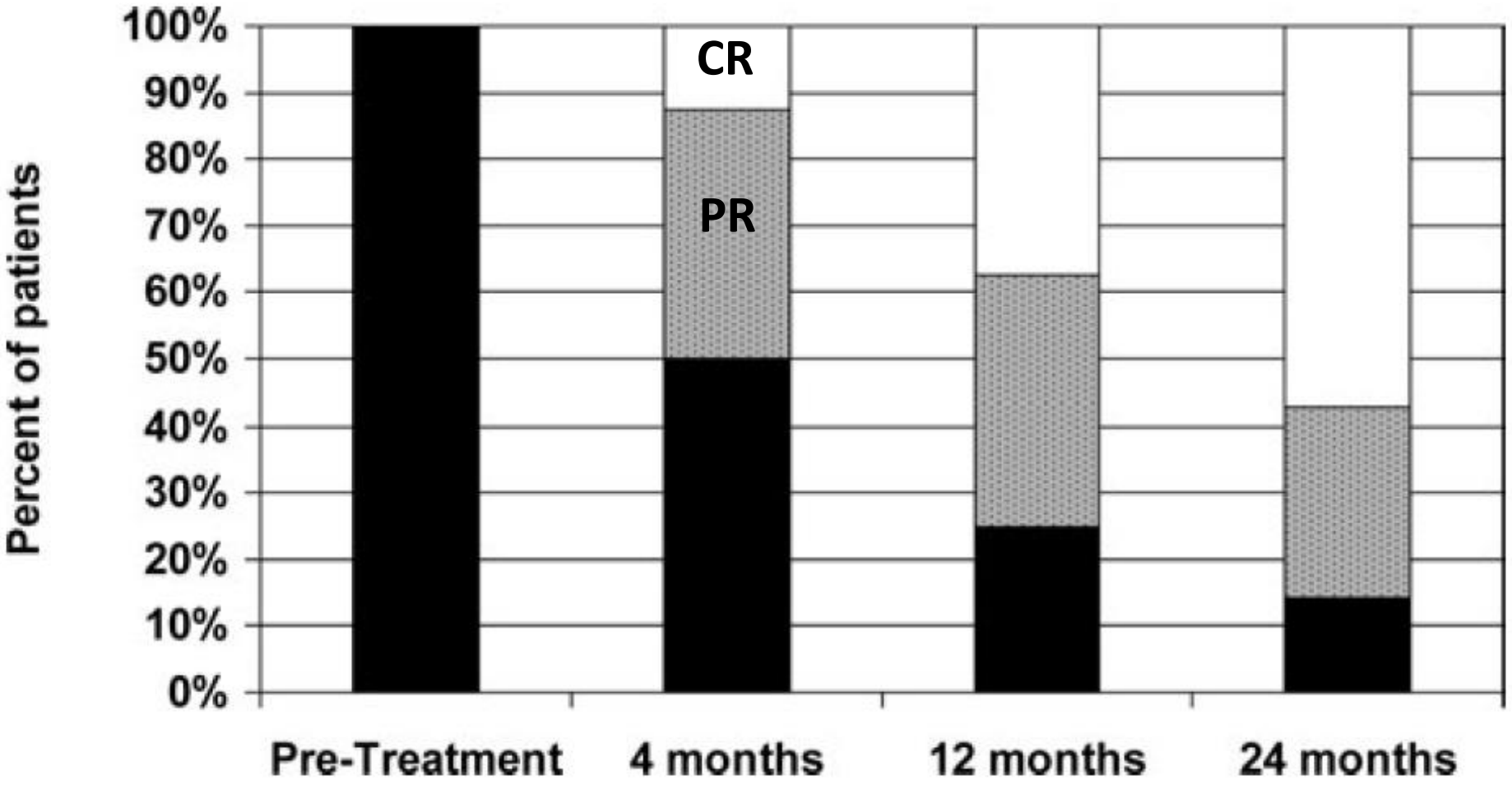
Membranous nephropathy recurrence



Months	12	24	36	48	60	72
N	58	54	51	40	39	32

A Grupper et al, Transplantation 2015

Membranous nephropathy: tt anti-CD20



EL-Zoghby ZM et al, Am J Transplant 2009

MN

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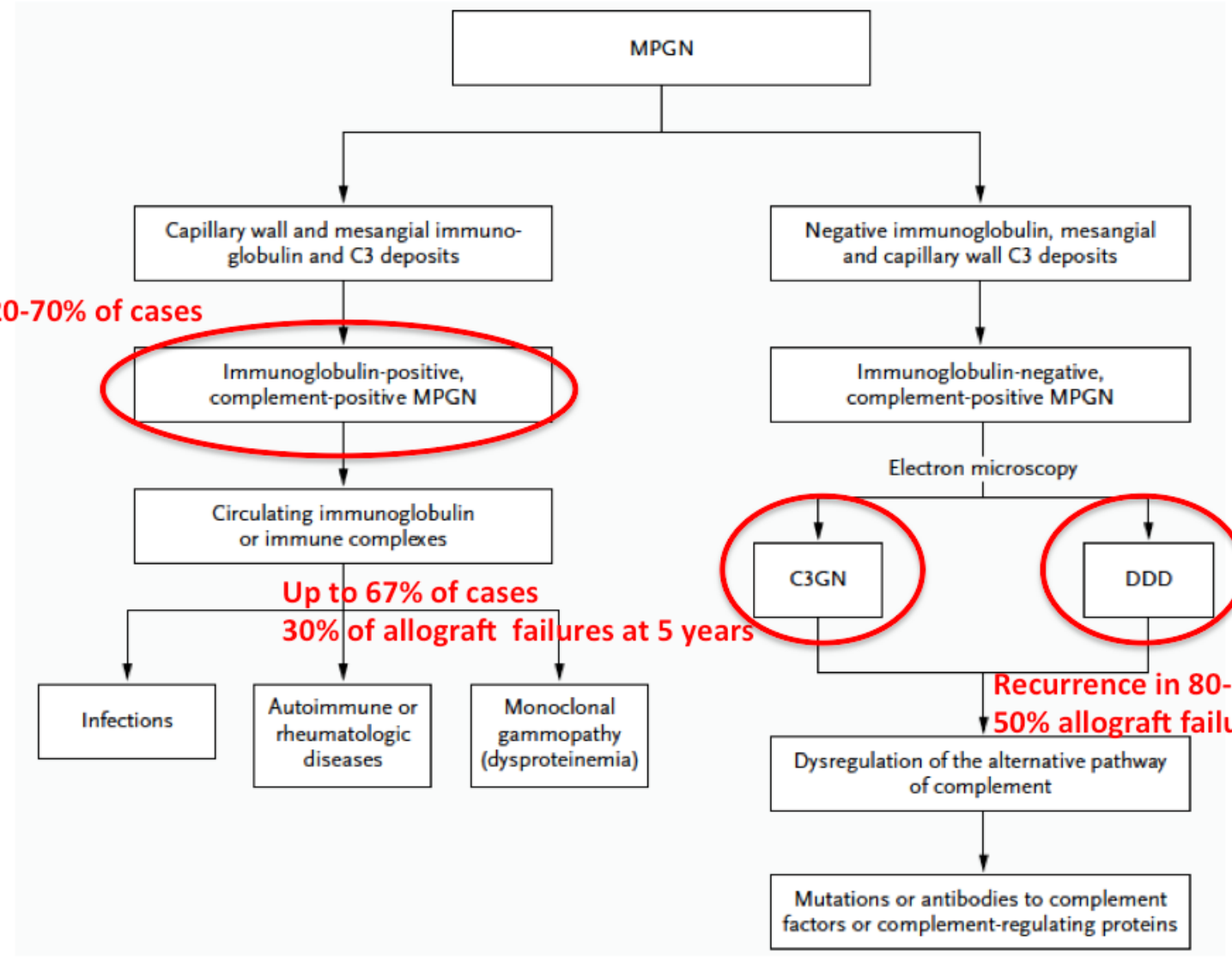
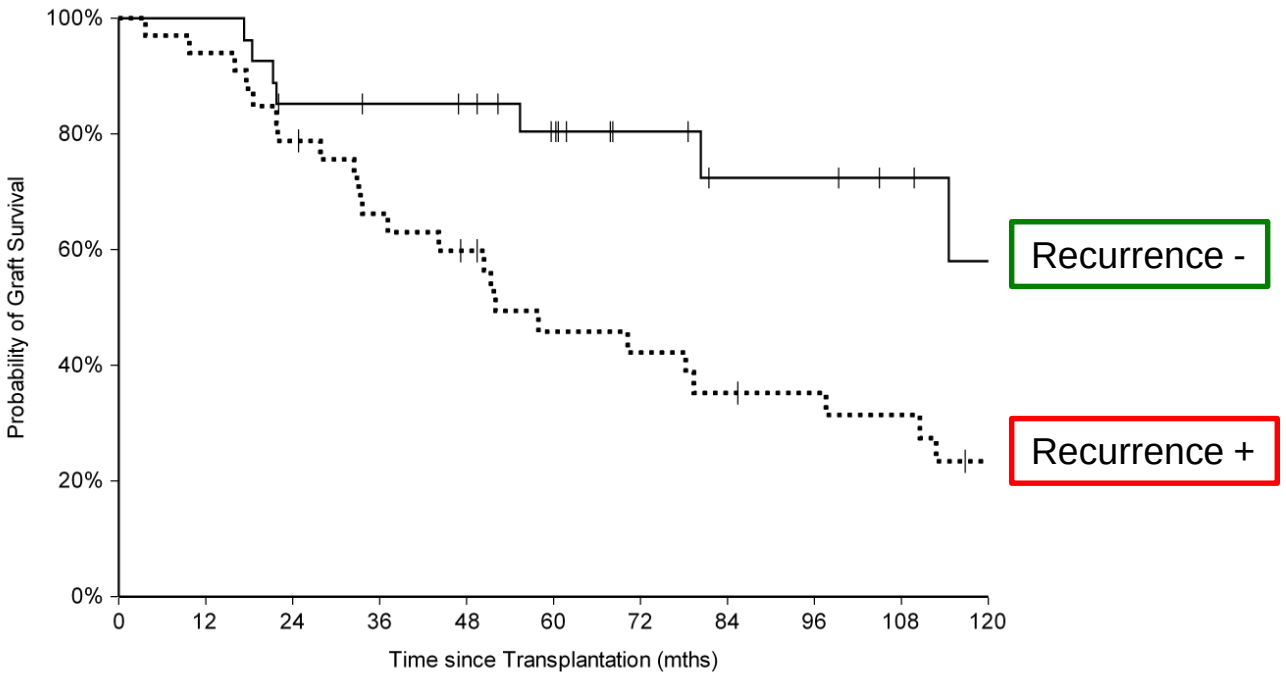


S Sethi et al , N Engl J Med 2012

Graft Survival according to MGN Recurrence



Time (mths)	0	12	24	36	48	60	72	84	96	108	120
N at risk R-	27	25	25	25	21	16	16	10	10	7	4
N at risk R+	33	28	28	28	20	13	13	10	10	8	5

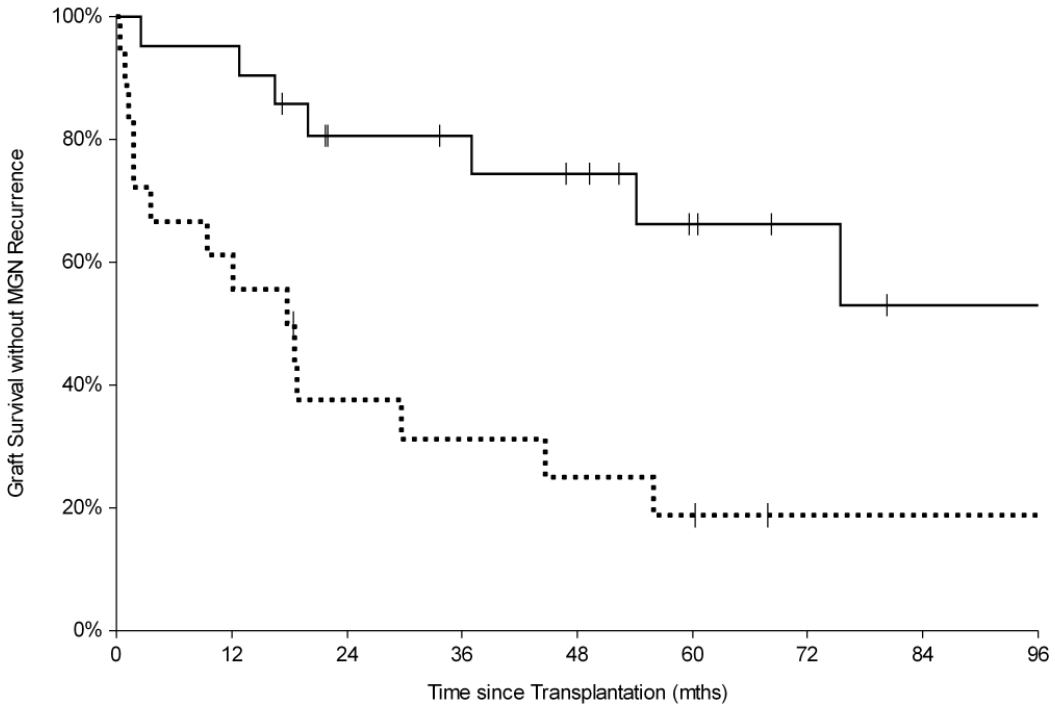
5 years graft survival = 0,46 (0,28 – 0,63) vs 0,80 (0,65 – 0,96)
Logrank test : p = 0,0128
Cox-Mantel Hazard Ratio HR = 2.49 (1,28-4,84)

R- : median survival = 128 mths (80 - 149)

R+: median survival = 52 mths (34 – 79)

M Lequintrec et al, Manuscript in preparation

Recurrence according to pre-transplant C5b-9



C5B9 ≤ 460

C5B9 > 460

P = 0,002 (Logrank)

HR = 3,55 (1,46-8,63)

Median Survival Time 18 (4-30) vs 123 (75 – 123) mths

M Lequintrec et al, Manuscript in preparation

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- **IgA nephropathy**

American Journal of Transplantation 2011; 11: 1645–1649
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03667.x

Steroids and Recurrent IgA Nephropathy After Kidney Transplantation

P. Clayton[a,b,*], S. McDonald[a,c] and S. Chadban[a,b,d]

Received 15 October 2010, revised 08 February 2011 and accepted for publication 27 February 2011

1521 patients proven IgA nephropathy

1988 – 2007

54 graft losses attributed to recurrence

Clayton P et al, Am J Transplant 2011

IgAN

Table 2: Predictors of graft loss due to IgAN recurrence

	SHR[1]	95% CI	p-Value
Use of steroids	0.50	0.30, 0.84	0.009
Age (per decade)	0.87	0.67, 1.13	0.31
Male sex	1.46	0.72, 2.95	0.30
Any HLA mismatch	0.46	0.23, 0.90	0.02
Dialysis duration			0.18
0 to <6 months	1[2]	–	
6 months to <1 year	0.73	0.35, 1.49	
1 to <5 years	0.50	0.25, 0.98	
≥5 years	0.40	0.09, 1.74	
Era			0.02
1988–1992	1[2]	–	
1993–1997	0.80	0.45, 1.42	
1998–2007	0.26	0.10, 0.66	

[1]SHR subhazard ratio.
[2]Referent

IgA nephropathy

- Recurrence is common, 13-53% of patients (according to biopsy policy),
- Ten-year incidence of graft loss is 9.7% (CI= 4.7-19.5%)
- Risk of recurrence: living related donor, SNP IL-10 and SNP TNFa
- Treatment: angiotensin converting enzyme inhibitor and angiotensin receptor blocker
- 117 recipients with IgAN: ATG reduced allograft recurrence from 41% to 9% compared to IL-2R antagonist

BY Choi et al, Am J Transplant 2006
K Oka et al, NDT 2006
F Berthoux et al, Transplanatation 2008

Type of glomerulonephritis	Treatment options	
	Standard practice	Variable evidence
IgA	Control proteinuria with RAAS blockade	Tonsillectomy Rituximab Eculizumab
FSGS		Plasmapheresis Rituximab
Membranous nephropathy	Control proteinuria with RAAS blockade Rituximab	Calcineurin inhibitors Cyclophosphamide Chlorambucil Corticosteroids
MPGN, type I	Target cause Control proteinuria with RAAS blockade	
DDD	Eculizumab Control proteinuria with RAAS blockade	Rituximab
C3 glomerulonephritis	Control proteinuria with RAAS blockade	Eculizumab

CD Blosser et al, Cur Op Nephro Hypertension 2017

Conclusions

- Post-transplant disease recurrence is a **significant cause of graft loss,** specially in younger recipients.
- Modern immunosuppression has **not changed** these figures in the last decade.
- However, there are efficient **therapeutical options**:
  - Combined IV-CSA/high dose steroids/PE = FSGS
  - Eculizumab = aHUS
  - Anti-CD20 = MN.
- New perspectives: CD40L, anti-CD20

Botanical garden, Padova 2016