

Welkom bij sessie 8

Complement dysregulatie in
TMA/aHUS en C3 glomerulopathie

dr. Sjoerd Timmermans, Maastricht UMC
prof. dr. Nicole van de Kar, Radboudumc



NIERCONGRES
7 APRIL 2026

Dé dag voor professionals
in de **nierzorg**

the syndromes of thrombotic microangiopathy [TMA] – an old but still evolving entity

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Nephrologist/Clinical immunologist, MUMC

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Disclosure belangen Sjoerd Timmermans

Voor bijeenkomst mogelijk relevante relaties

- Sponsoring of onderzoeksgeld
- Honorarium of andere (financiële) vergoeding
- Aandeelhouder
- Andere relatie, namelijk:

Bedrijfsnamen:

- Nierstichting (Kolff Junior), Alexion
- Alexion
- /
- /

an acute febrile pleiochromic anemia with hyaline thrombosis of arterioles and capillaries

THIS case is remarkable, clinically and anatomically.

16 F w/ fever,
purpura

hemolysis, platelets[?]
SCr 1.1 mg/dL

left-sided
hemiparesis

died

d1

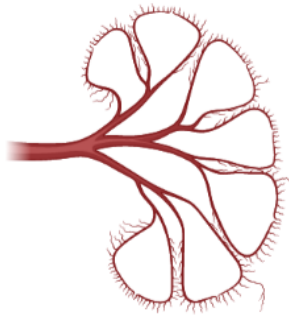
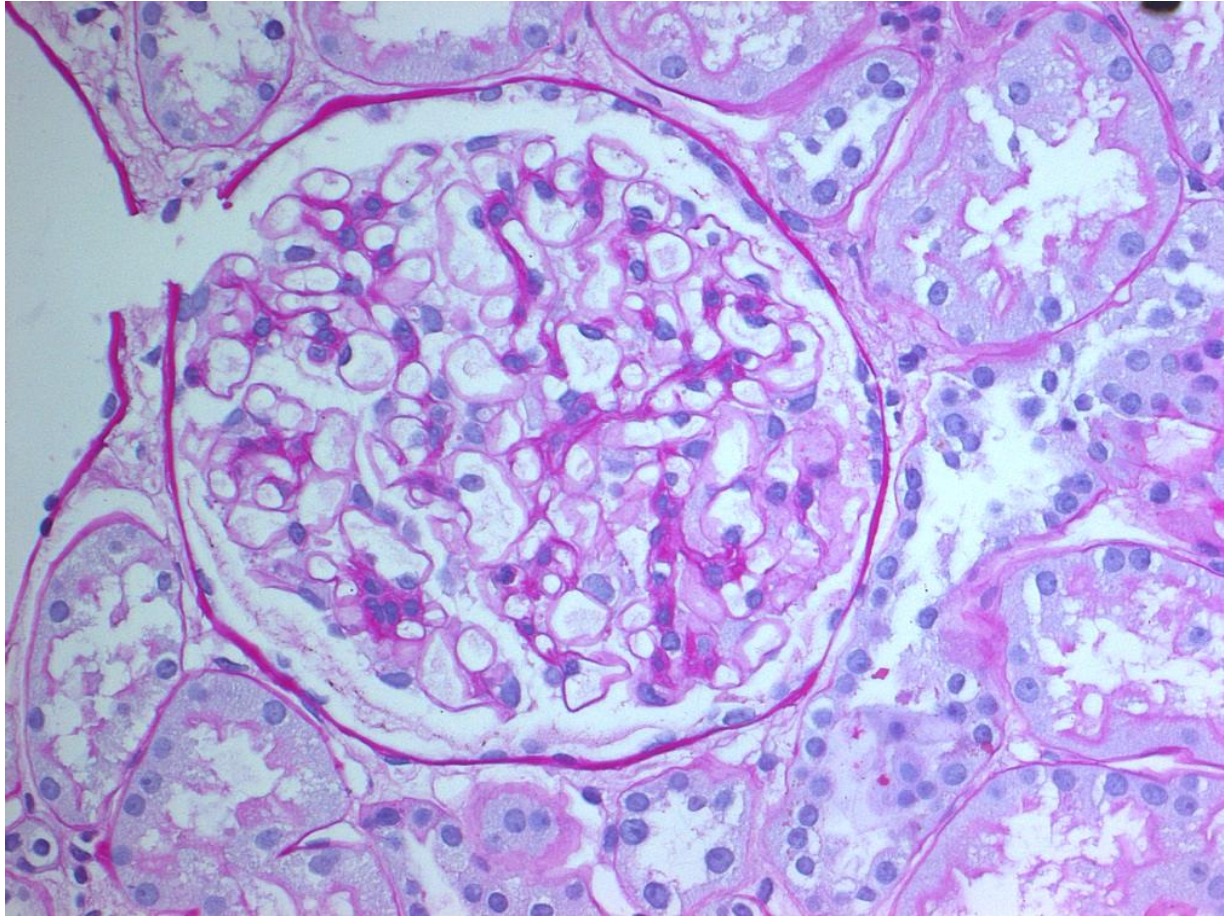
d9

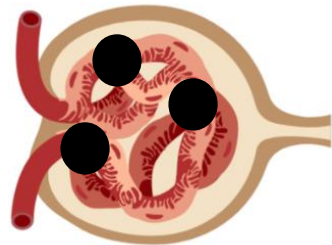
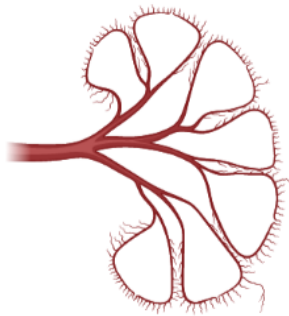
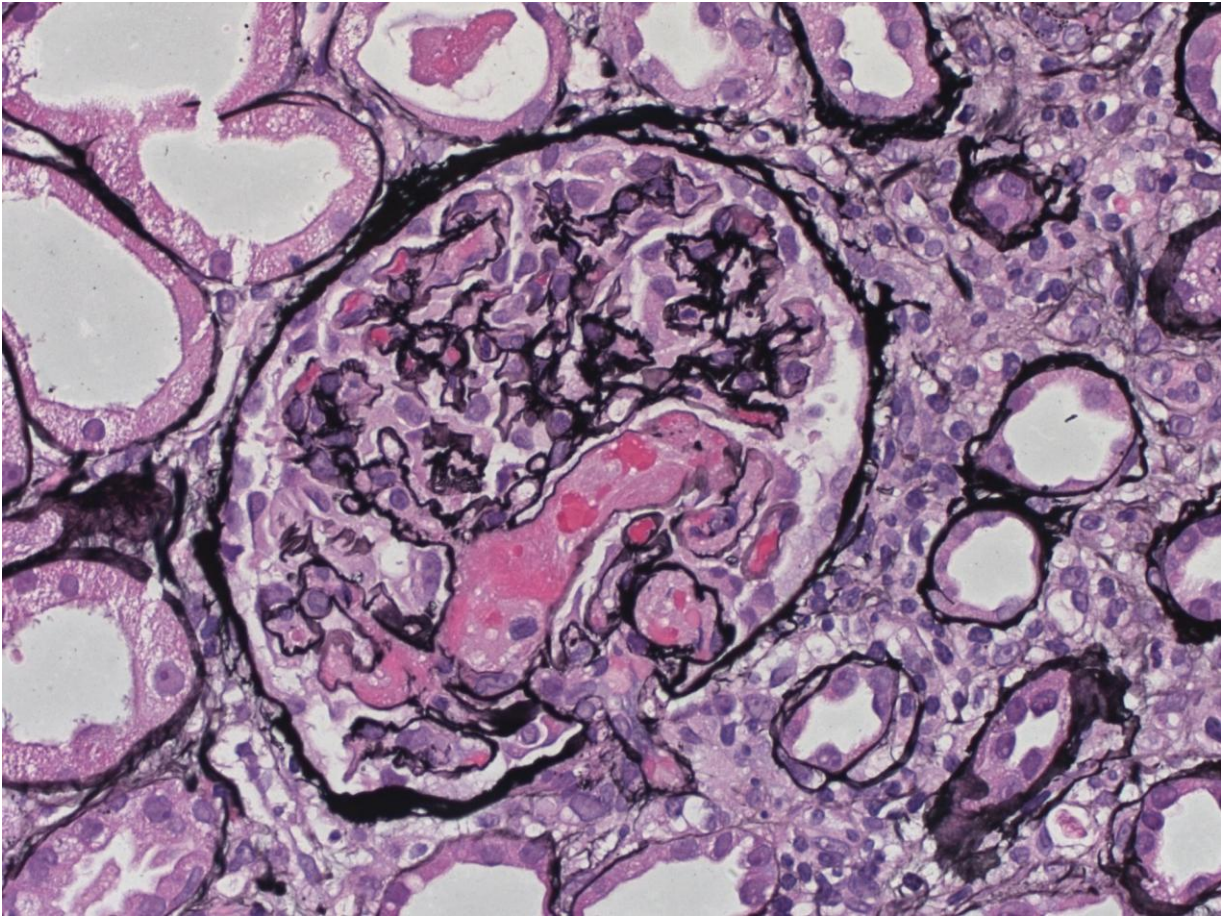
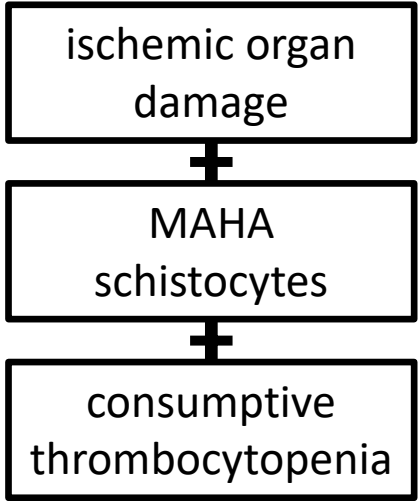
d14

d15

1924







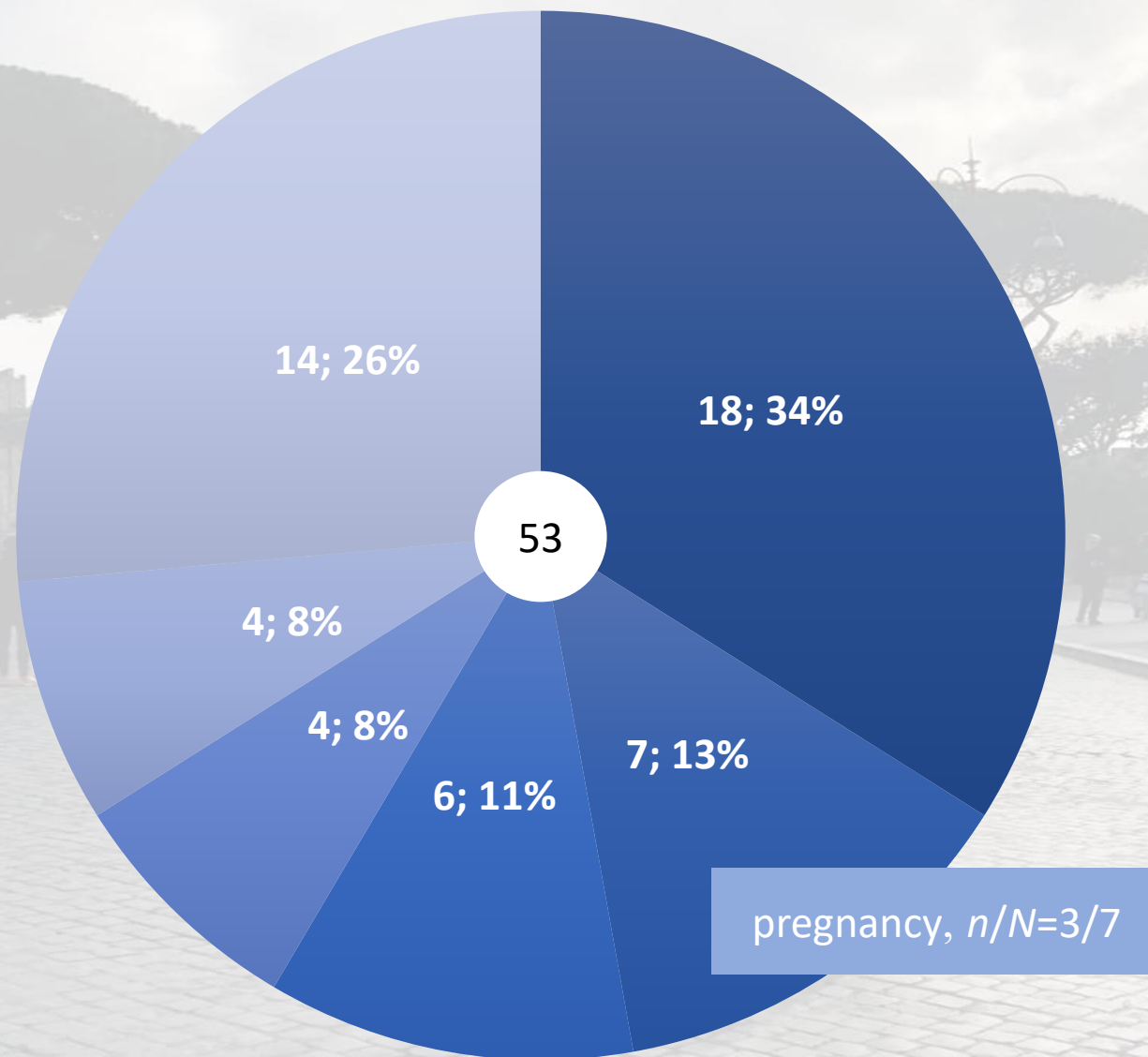
an acute febrile pleiochromic anemia with hyaline thrombosis of arterioles and capillaries

From these observations we conclude that death, in the case described, resulted from some powerful poison which had both agglutinative and hemolytic properties. If opportunity offers, further investigation will be made of this strange disease with strange pathologic morphology.



all roads lead to Rome



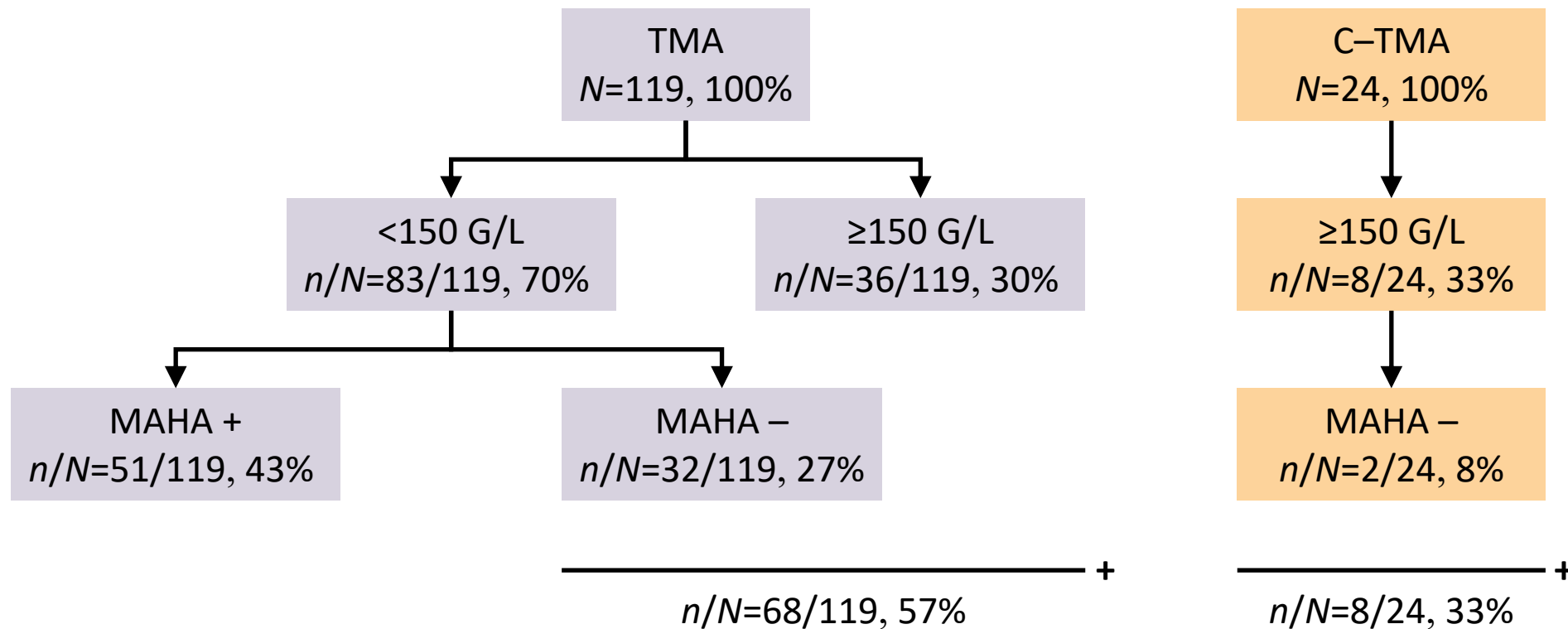


■ HT ■ complement ■ pregnancy ■ AID ■ TTP ■ others

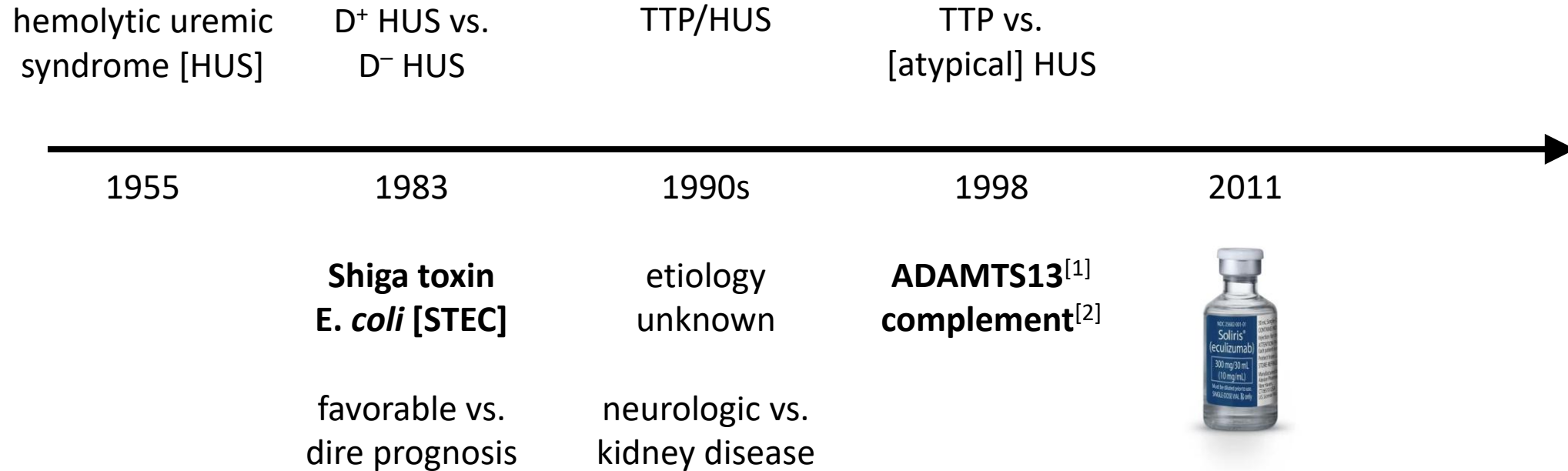




keep an eye on kidney-limited TMA ≠ HUS



a historical perspective on the nomenclature of ~~HUS~~ TMA



UPDATE

'Kiemgroente
hoogstwaarschijnlijk bron
EHEC'

Volkskrant, 2011



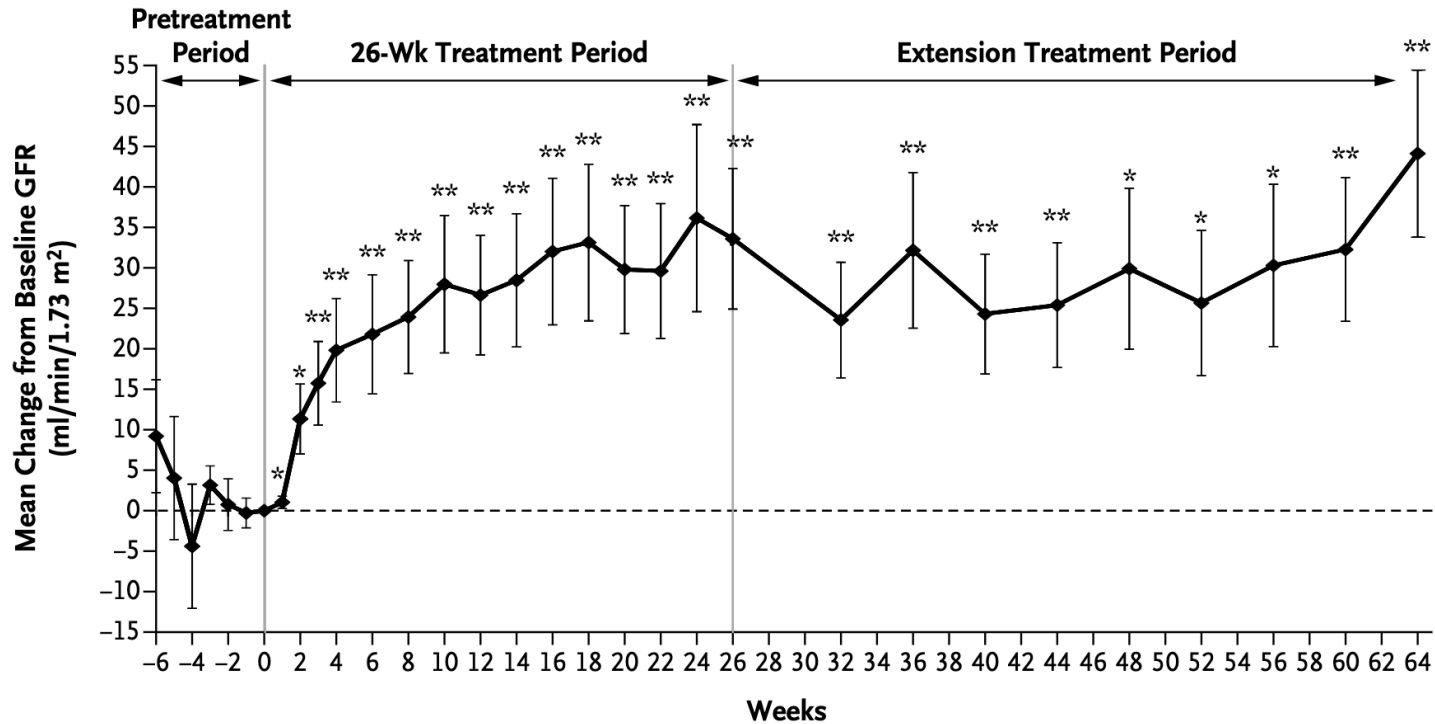
The NEW ENGLAND
JOURNAL of MEDICINE

^[1]Furlan *et al.* 1998

^[2]Warwicker *et al.* 1999



the renaissance of therapeutic complement inhibition



	Ecu ^[1]	BSC ^[2]
PR/CR	≥80%	?
ESKD	<20%	~65%

meningitis is rare



^[1]Licht *et al.* *Kidney Int.*, 2015; ^[2]Frémeaux–Bacchi *et al.* *Clin J Am Soc Nephrol*, 2013

COREIUS

prof. Bouts
drs. Dorresteyn
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Erasmus MC
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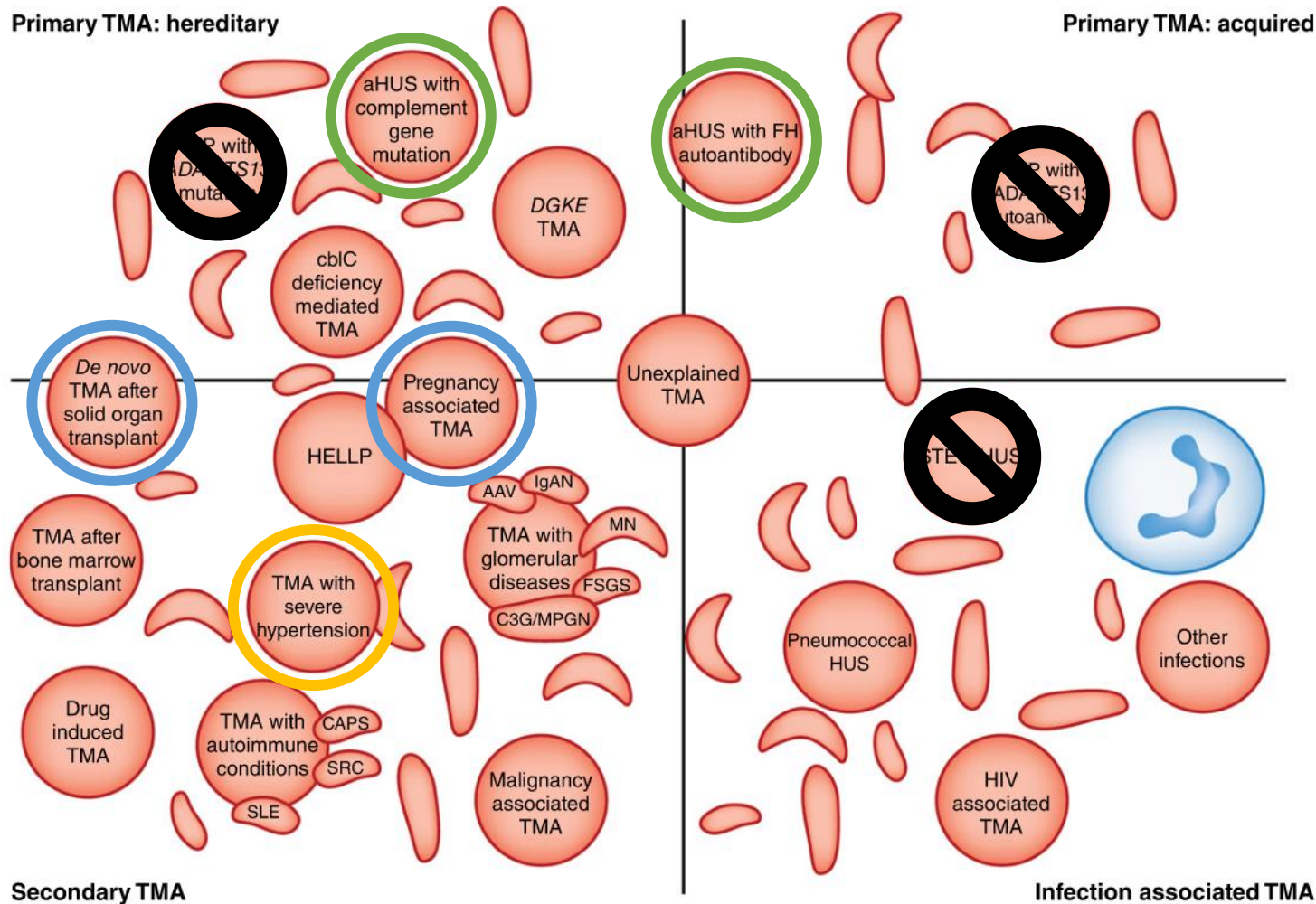


all roads to TMA – atypical HUS as a diagnosis per exclusion

Fakhouri *et al.*, 2010
n/N=18/21, **86%** pregnant women carried variants

Le Quintrec *et al.*, 2008
n/N=7/24, **29%** kidney recipients carried variants

“additional work is required to define the impact of complement risk factors in these subgroups” [KDIGO]



the coexisting conditions are diverse and so are the outcomes

564 patients with TMA, incl. TTP [$n=18$, 3%] and primary atypical HUS [$n=15$, 3%]

	infection	STEC	HT emergency	pregnancy	transplan- tation	DITMA	cancer	auto- immunity	other[s]
<i>N</i>	184	35	20	197	96	144	105	48	31
low platelets	93%	97%	86%	93%	90%	91%	95%	92%	84%
→ SCr, mM	150	424	486	71	168	159	114	194	97
dialysis	26%	66%	60%	4%	27%	24%	12%	25%	10%



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SCr, mM	150	424	486	71	168	159	114	194	97
dialysis	26%	66%	60%	4%	27%	24%	12%	25%	10%
ESKD risk ^[1]	variable	low	high	variable	variable	low	low	variable	N/a

akin to primary atypical HUS, suggesting complement dysregulation



^[1]Timmermans *et al.* J Clin Med, 2021; Bayer *et al.* Clin J Am Soc Nephrol, 2019



patients with TMA and hypertensive emergency may have C-TMA

patient no.	BP	SCr, μmol/L	MAHA	plts, *10 ⁹ /L	C3, g/L	CH50, %	variant[s]	ESKD
1	184/140	1,730	Y	224	0.69	95	<i>C3</i>	Y
2	205/114	1,195	Y	158	WNR	97	<i>CD46</i>	Y
3	200/120	586	Y	100	WNR	94	<i>C3</i>	Y
4	180/120	1,138	Y	142	0.63	104	<i>CFH</i>	Y
5	195/105	162	N	98	WNR	99	None	N
6	180/120	334	N	285	WNR	97	<i>CFI</i>	Y
7	224/122	1,065	N	228	0.72	110	<i>C3</i>	Y
8	240/150	673	N	133	WNR	90	None	Y
9	220/120	649	N	340	WNR	113	None	Y



Gili Trawangan, Indonesia;
summer of 2017



Sjoerd... good day. My name is salvatore chillemi, I'm a nephrologist in the Atlanta georgia area (USA) and have recently come across a gentleman living in holland (actually from New Zealand but married a Dutch woman and kids are In holland) who was/is here on business.... came into hospital with malignant hypertension, creatinine of 30, BUN of 300 and on dialysis now.. he was intubated and the whole spero!

Genetics here in USA cost \$4000 and he doesn't have insurance to cover this. So I would hope you all can order it on him.

Dr Laurence email makes me skeptical of my decision to treat with ecu.. 😞

47y-old male was found unconscious
BP >220/120 mmHg
hypertensive retinopathy III/IV

SCr 1,980 $\mu\text{mol/L}$; anuria/dialysis
pK 2.9 mmol/L
platelets 270,000 $/\mu\text{L}$, mild MAHA

Atlanta, GA



NETHERLANDS

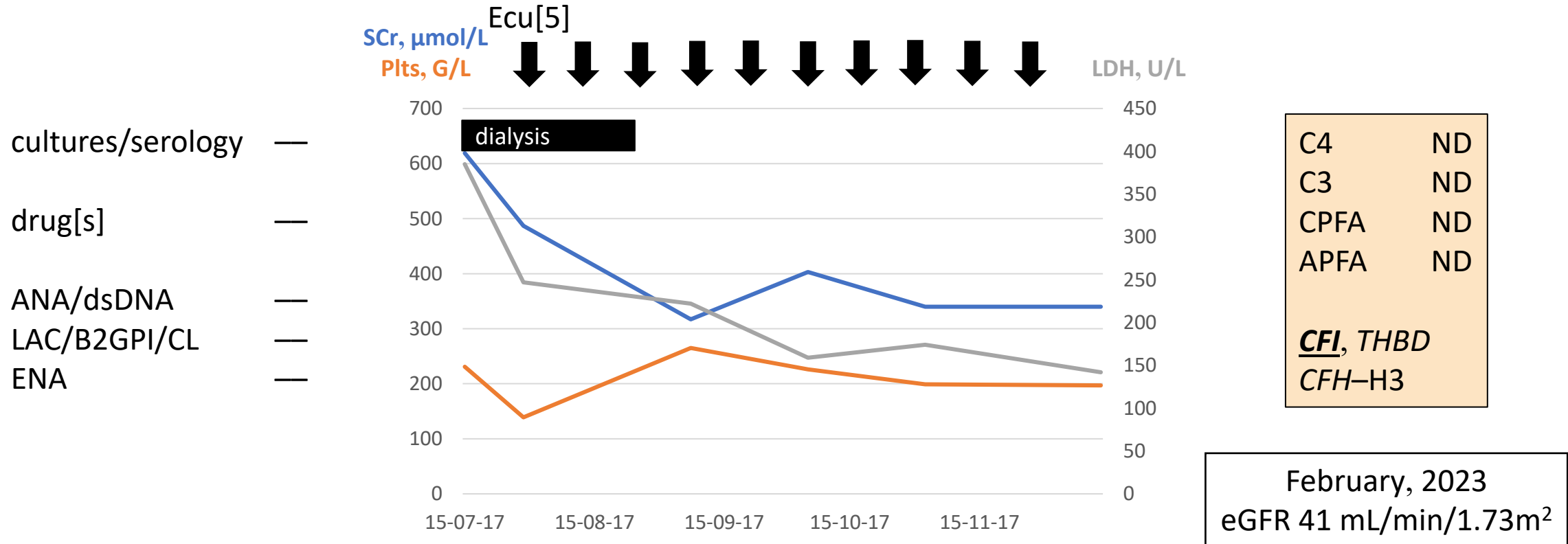


Pompeii

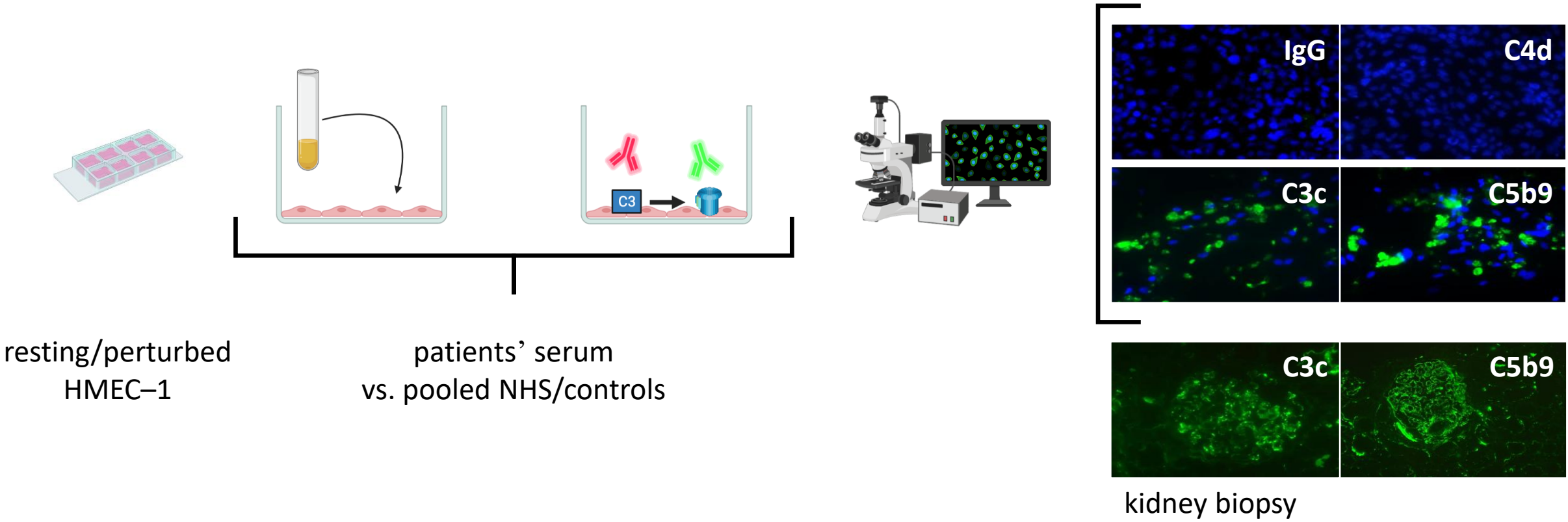


47^y-old male presented w/ TMA and coexisting hypertensive emergency

ADAMTS13 42%; no diarrhea; no response despite BP control

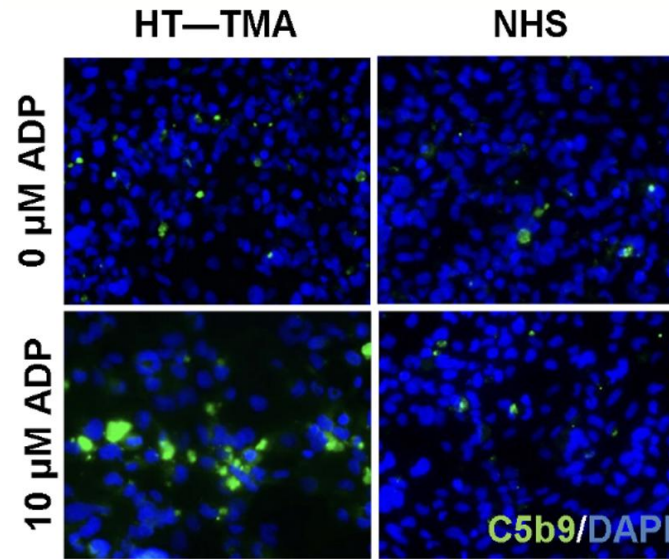
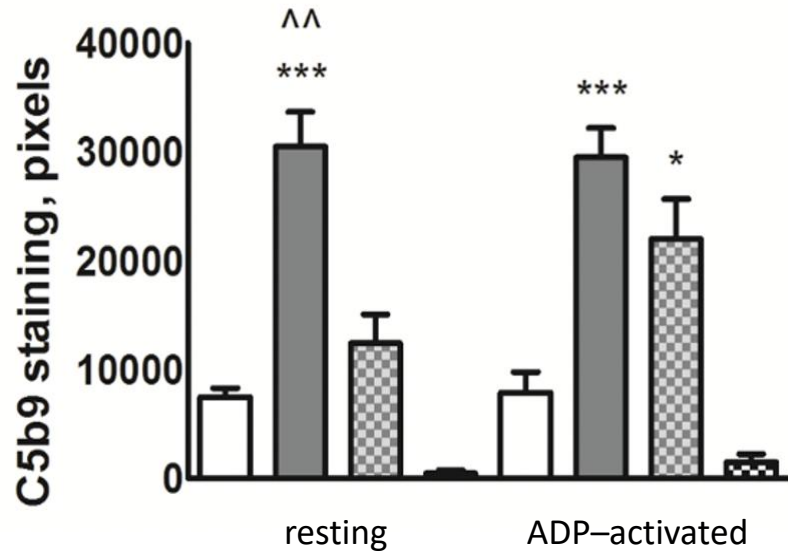


can we better detect complement-mediated TMA?

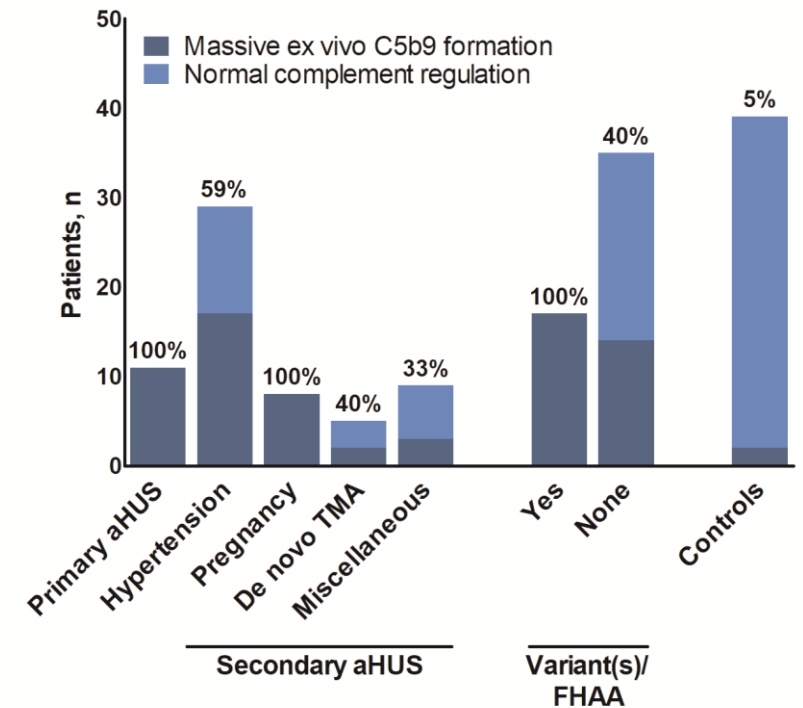


can we better detect complement-mediated TMA?

ex vivo C5b9 formation on resting and ADP-activated cells^[1]



the prevalence of complement dysregulation varies widely^[2]



^[1]Timmermans *et al.* J Am Soc Nephrol, 2018; ^[2]Kidney Int Rep, 2021

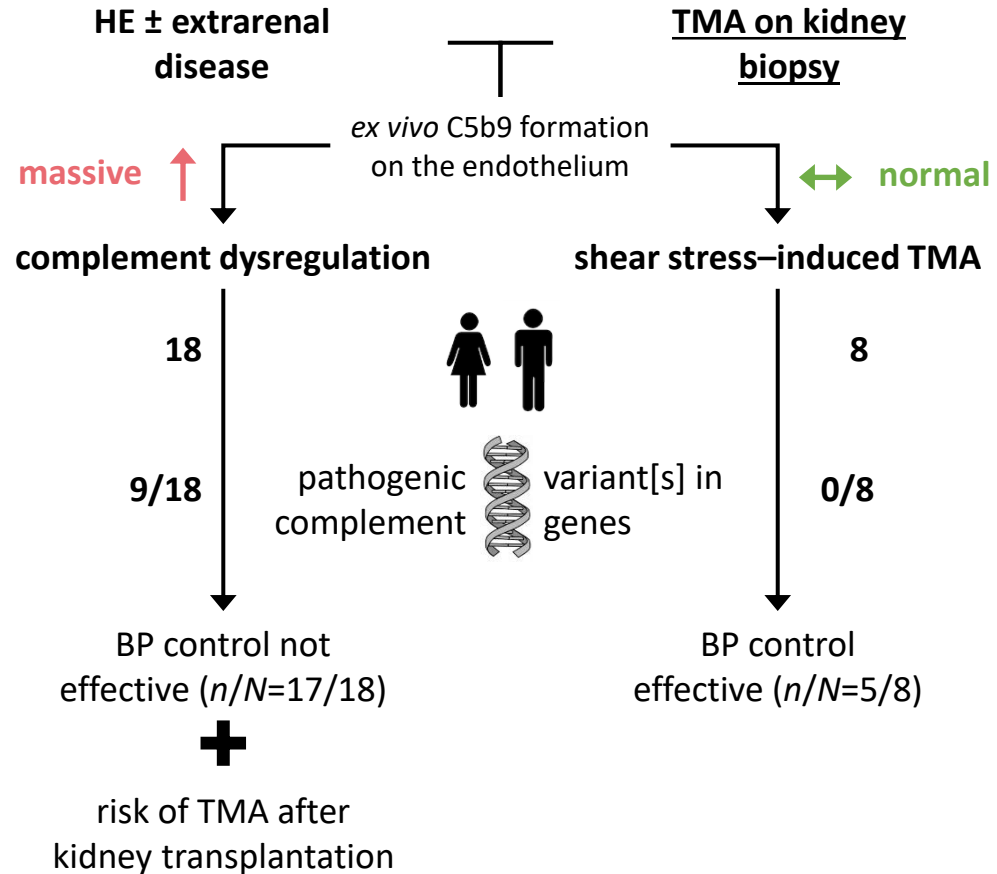
deregulated complement is prevalent in patients with hypertensive emergency



El Karoui *et al.*, 2019
HE in primary aHUS
39/76, **51%**

Cavero *et al.*, 2019
HE in primary aHUS
19/55, **35%**

Halimi *et al.*, 2022
HE in primary aHUS
40/61, **66%**

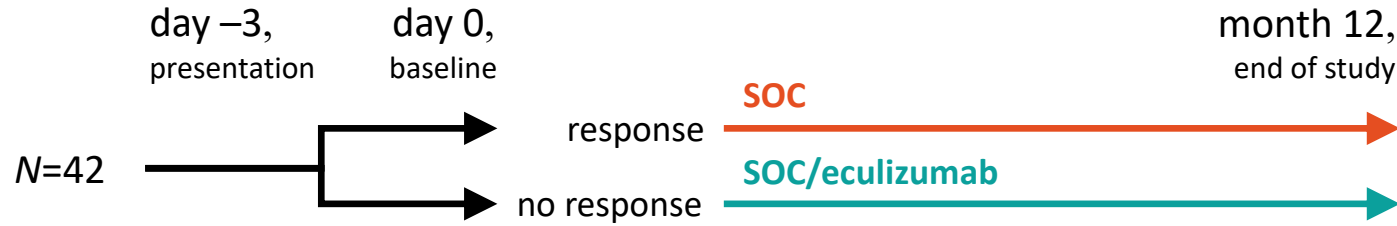


Larsen *et al.*, 2018
variants in “microangiopathy”
0/100, **0%**

Zhang *et al.*, 2020
“malignant nephrosclerosis”
7*/20, **0%**

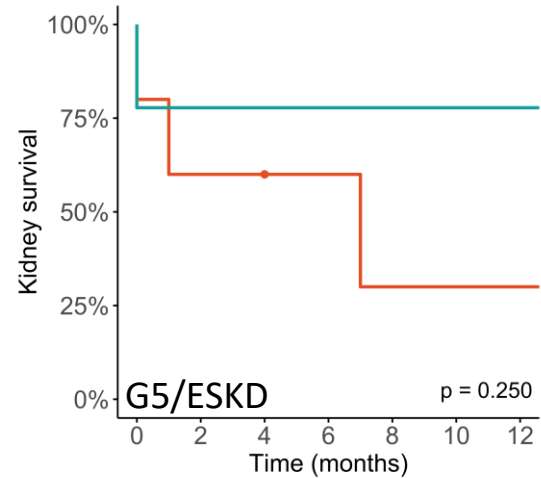


eculizumab's efficacy in TMA and hypertensive emergency

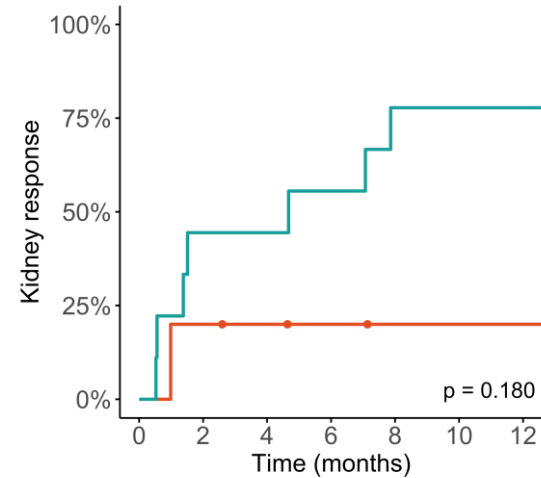


TMA on PB/KBx
eGFR <45 mL/min/1.73m²

primary aHUS
hypertensive emergency
pregnancy
dnTMA after KTx
“autoimmunity”



BSC	5	3	3	2	1	1	1
Ecu	9	7	7	7	7	7	7



BSC	5	4	3	2	1	1	1
Ecu	9	5	5	4	2	2	2

CKD	SOC*	SOC/ecu*
G2	0	1, 11%
G3	0	2, 22%
G4	2, 40%	2, 22%
G5	3, 60%	4, 44%

*similar age, SCr, plts, LDH, C3

eculizumab's efficacy in TMA and hypertensive emergency



TMA on PB/KBx
eGFR <45 mL/min/1.73m²

TMA on PB
SCr ≥354 mM; 4.0 mg/dL

primary aHUS
hypertensive emergency
pregnancy
dnTMA after KTx
“autoimmunity”

BP >180/110 mmHg
encephalopathy;
retinopathy III/IV; and/or
cardiac involvement

atrophic kidneys
“high” suspicion of C-TMA
“high” suspicion of STEC or TTP
secondary TMA
active infection
pregnancy



back to the French observations and correct interpretation

564 patients with TMA, incl. TTP [$n=18$, 3%] and primary atypical HUS [$n=15$, 3%]

	infection	STEC	malignant HT	pregnancy	transplantation	DITMA	cancer	auto-immunity	other[s]
<i>N</i>	184	35	20	197	96	144	105	48	31
low platelets	93%	97%	86%	93%	90%	91%	95%	92%	84%
SCr, mM	150	424	486	71	168	159	114	194	97
dialysis	26%	66%	60%	4%	27%	24%	12%	25%	10%
ESKD risk ^[1]	variable	low	high	variable	variable	low	low	variable	N/a

MUMC [$n=8$]

patients had moderate AKI,
but no renal sequelae
2/8 carried a *CFHR4* variant

HELLP
167/197, 85%

- 96/96 CNIs
- 54/96 infection[s]
- 32/96 cancer
- AMR[?]



^[1]Timmermans *et al.* J Clin Med, 2021; Bayer *et al.* Clin J Am Soc Nephrol, 2019

most patients with “secondary” TMA present with normal regulation

N	110
SCr, mM	344 [44–2,210]
dialysis	40%
variants	~5%
ESKD	37%
response to Ecu	—
TMA recurrence	1/73, 1%

acute, non-recurrent form of TMA^[1]

Secondary HUS

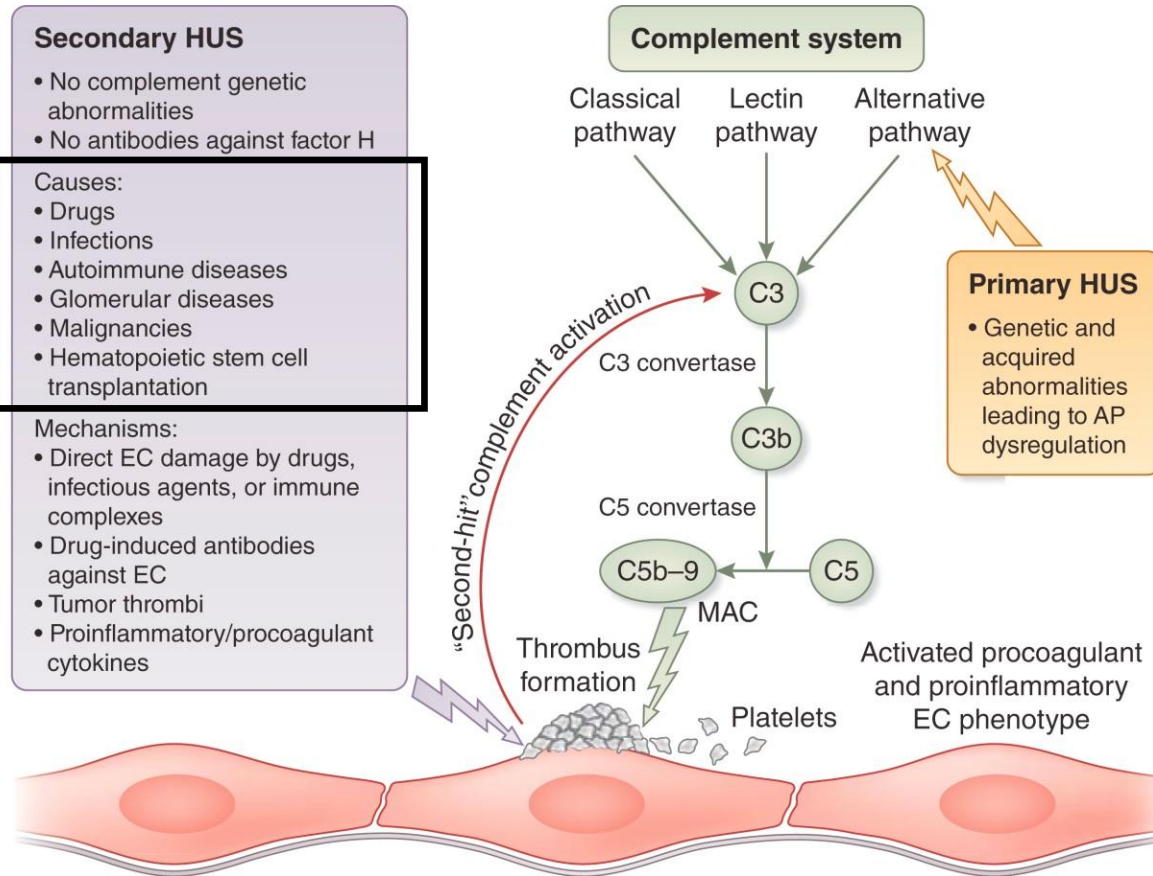
- No complement genetic abnormalities
- No antibodies against factor H

Causes:

- Drugs
- Infections
- Autoimmune diseases
- Glomerular diseases
- Malignancies
- Hematopoietic stem cell transplantation

Mechanisms:

- Direct EC damage by drugs, infectious agents, or immune complexes
- Drug-induced antibodies against EC
- Tumor thrombi
- Proinflammatory/procoagulant cytokines



3/24 “hereditary” CKD
3/24 IgAN
1/24 ANCA GN

other causes of secondary HT^[2]

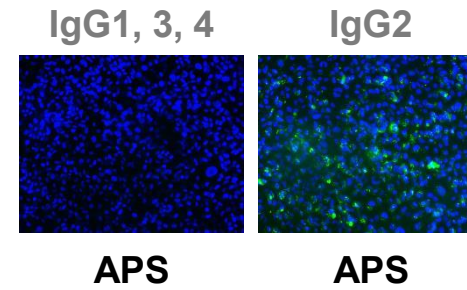
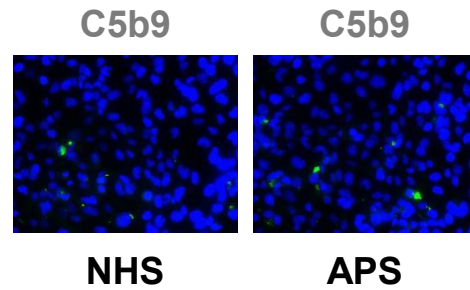
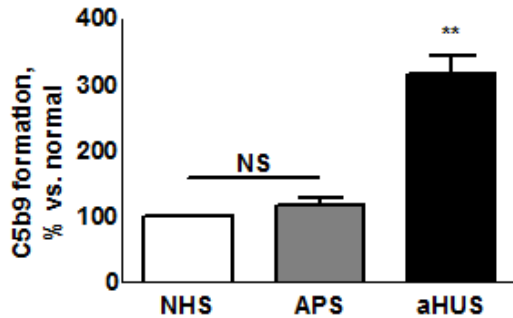
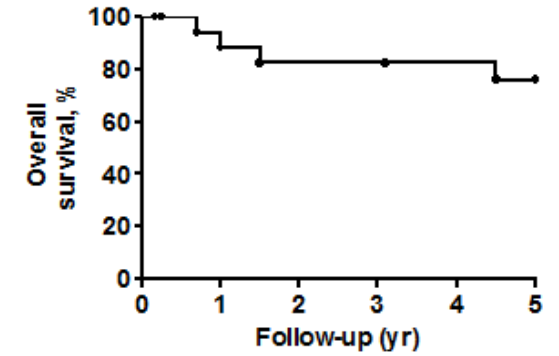
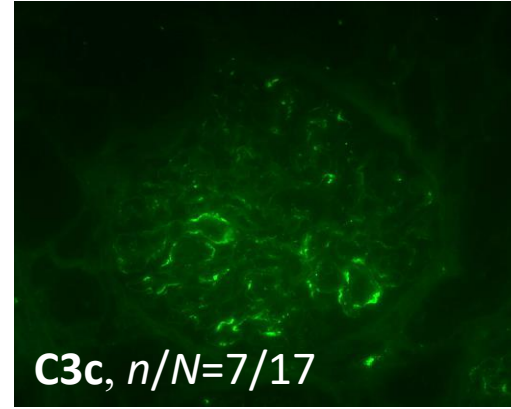
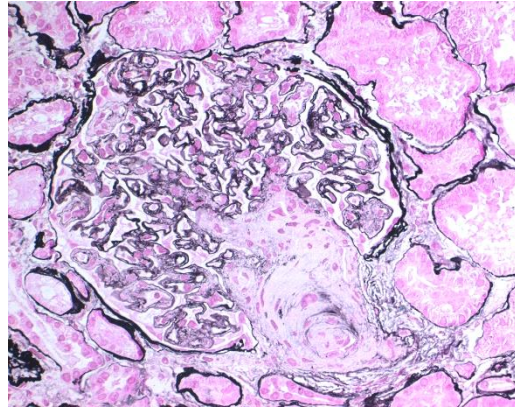
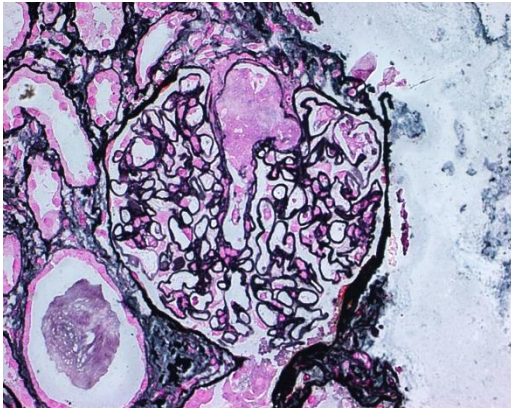
hypertensive emergency
pregnancy
kidney transplantation

acute, recurrent form of TMA

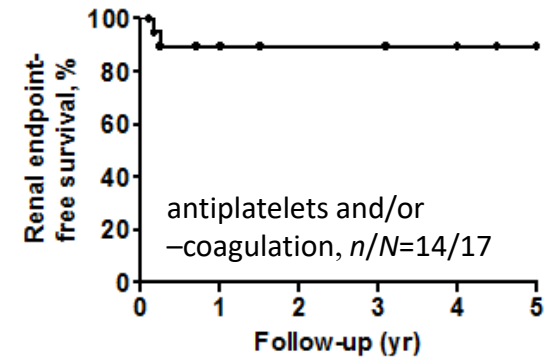


^[1]Le Clech *et al.* *Kidney Int*, 2019; ^[2]van Doorn *et al.* *Kidney Int*, 2026 [accepted]; modified from Praga *et al.* *Kidney Int*, 2019

antiphospholipid syndrome–related TMA



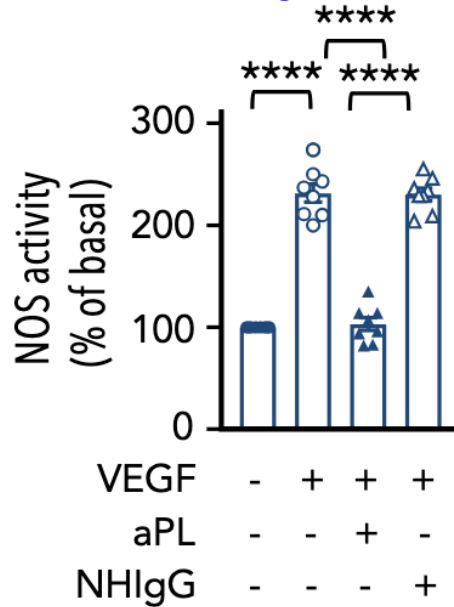
direct effect on EnC?



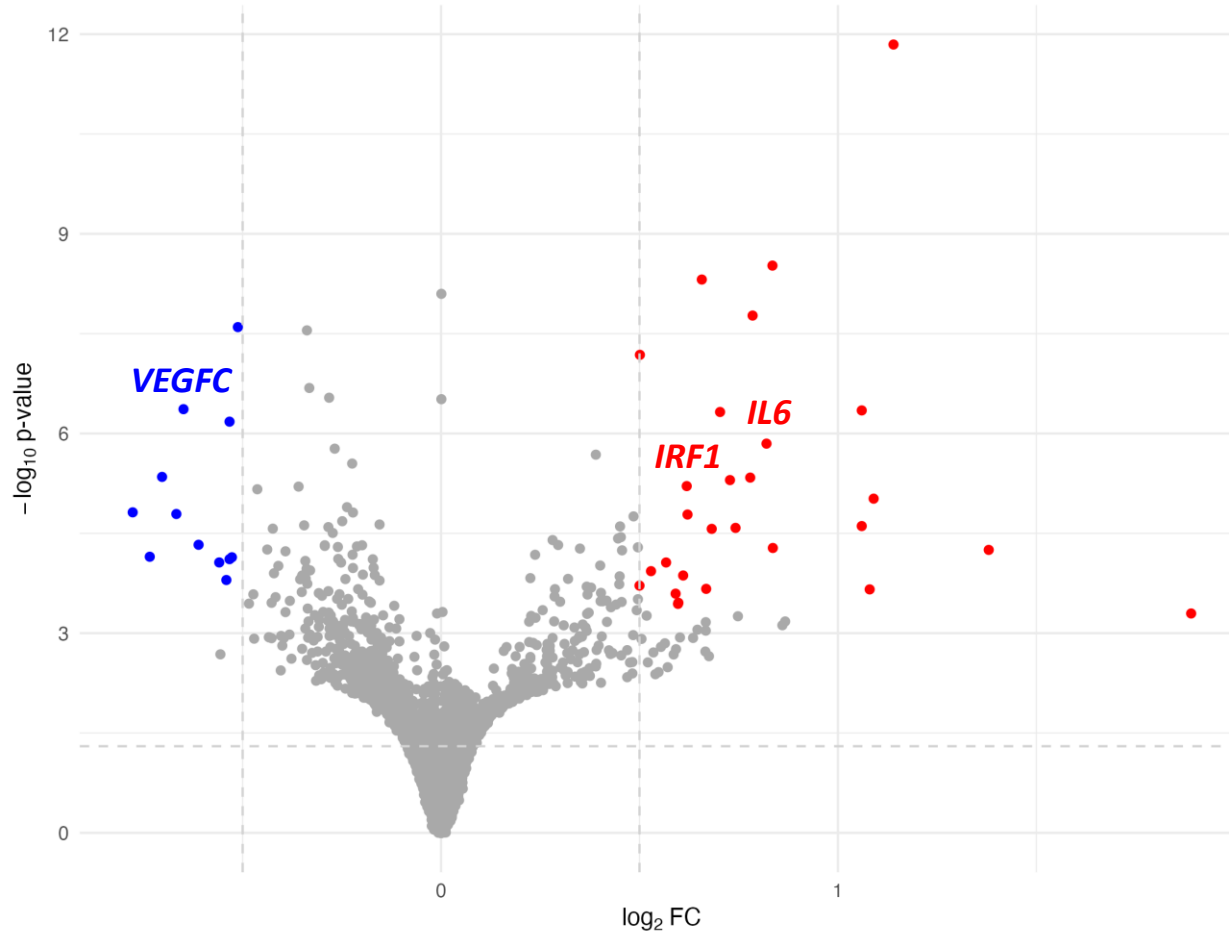
“secondary” disease [APS] versus complement-mediated TMA



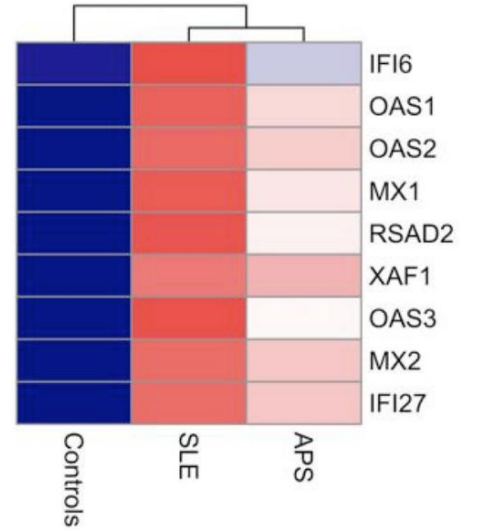
**NO stimulates VEGF
in APS**



Sacharidou *et al.* Blood, 2018



**IFN type I/II signaling,^[1, 2] IL6^[2]
in APS nephropathy**

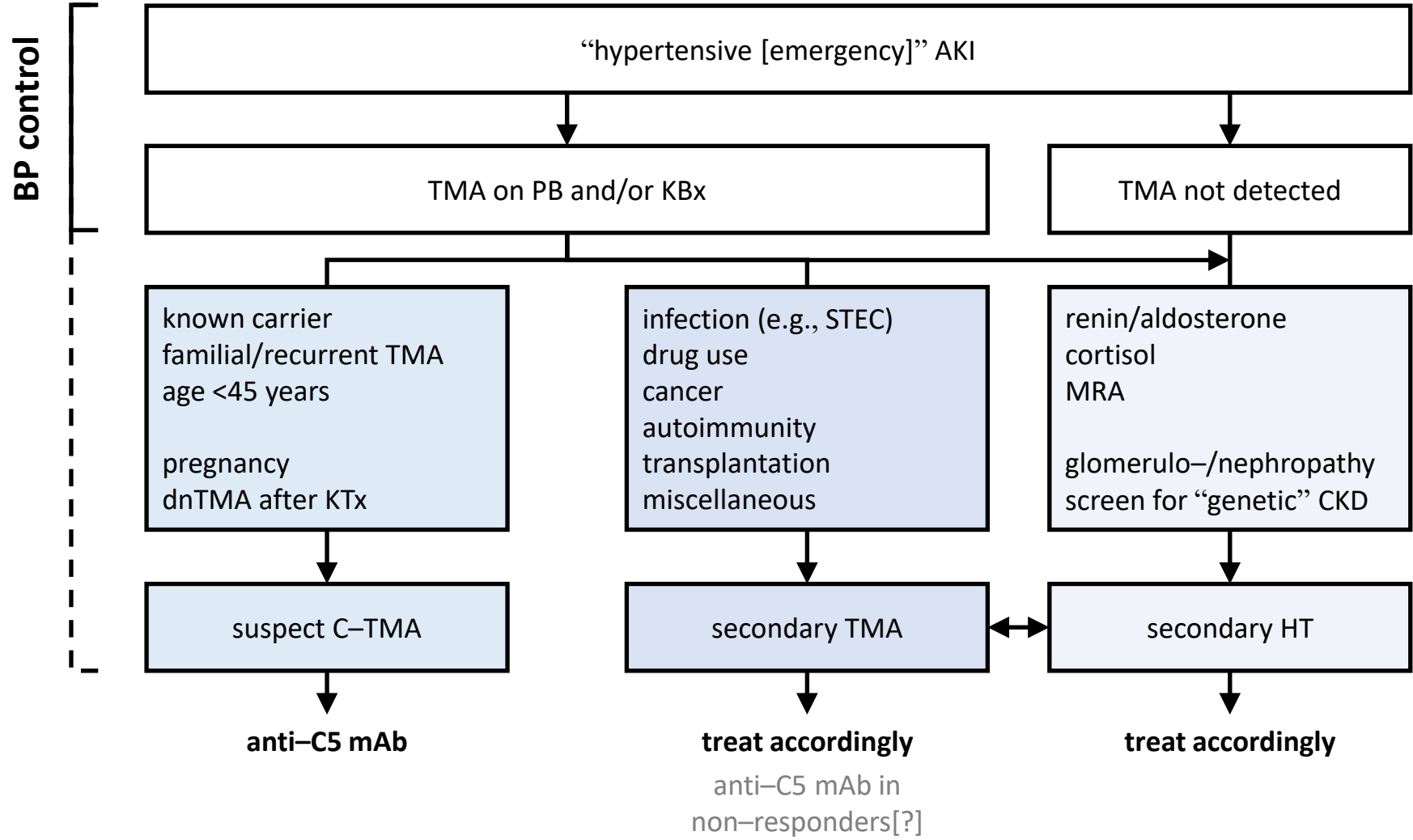


^[1]Erkan *et al.* Ann Rheum Dis, 2014

^[2]Tektonidou *et al.* Rheumatology, 2024

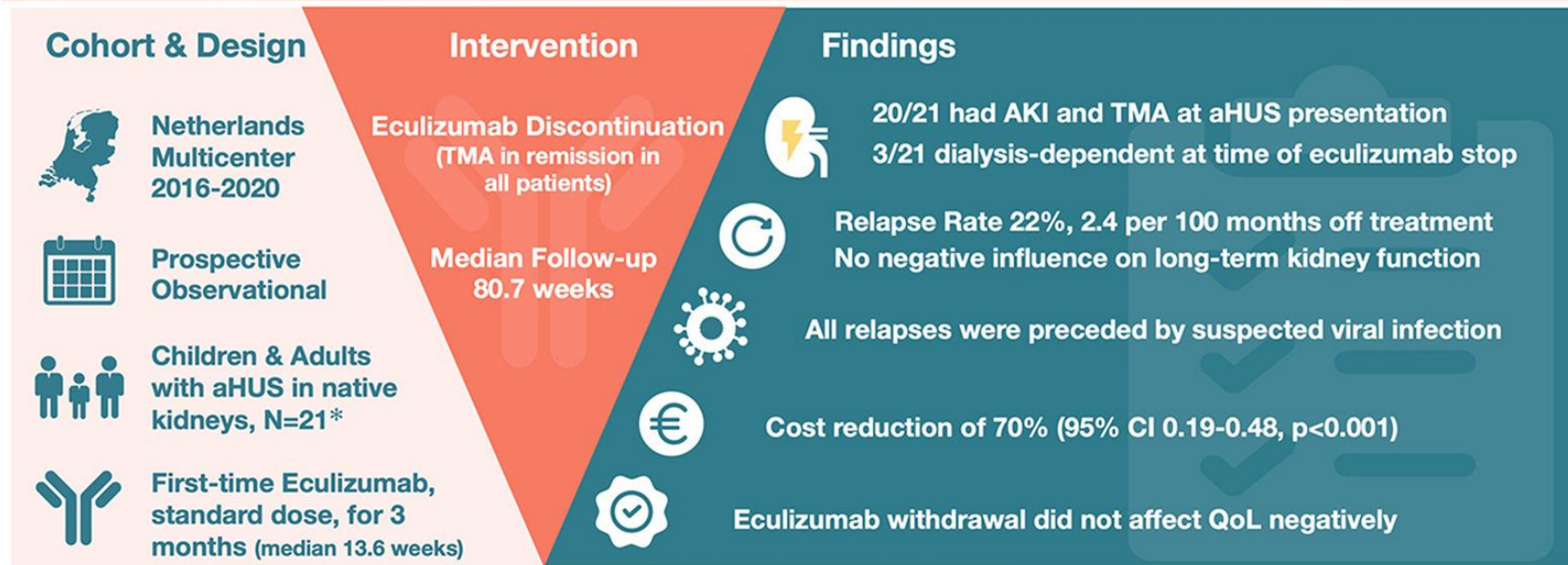


Dutch' approach for the management of TMA



enough is most of the time enough

Early Eculizumab Withdrawal in Patients with aHUS in Native Kidneys is Safe and Cost Effective: Results of the CUREiHUS study



Ecu for 13.6 wk [2.1–43.9]

aHUS, atypical hemolytic uremic syndrome; * 81% (17/21) had genetic defect in complement regulation (others classified as likely aHUS); TMA, thrombotic microangiopathy; QoL, quality of life

KIREPORTS
Kidney International Reports

Bouwmeester R, 2022
Visual abstract by:
Jade Teakell, MD PhD
 @JMTeakell

Conclusion: It is safe and (cost-)effective to discontinue eculizumab after three months of therapy in patients with aHUS. Larger data registries are needed to determine factors associated with suboptimal kidney function recovery during eculizumab treatment, factors to predict relapse(s), and long-term outcomes of eculizumab discontinuation.



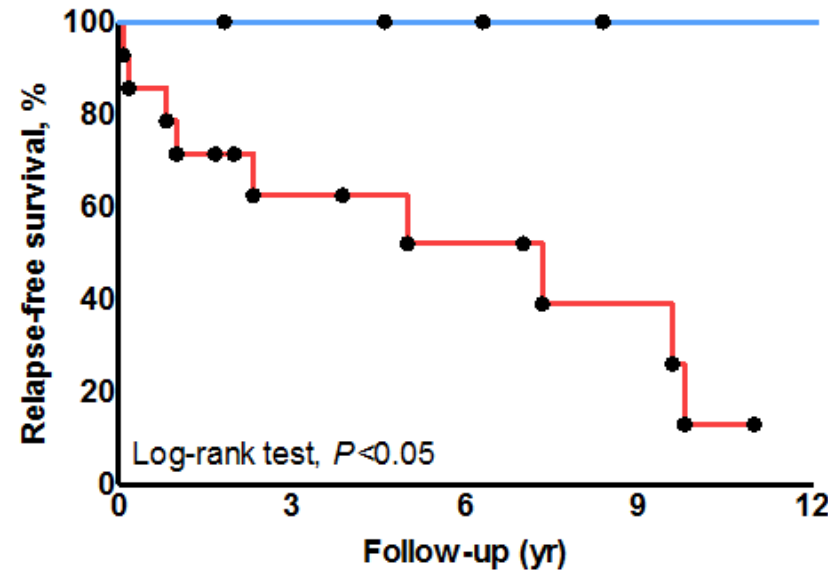
complement gene variants predict the prognosis



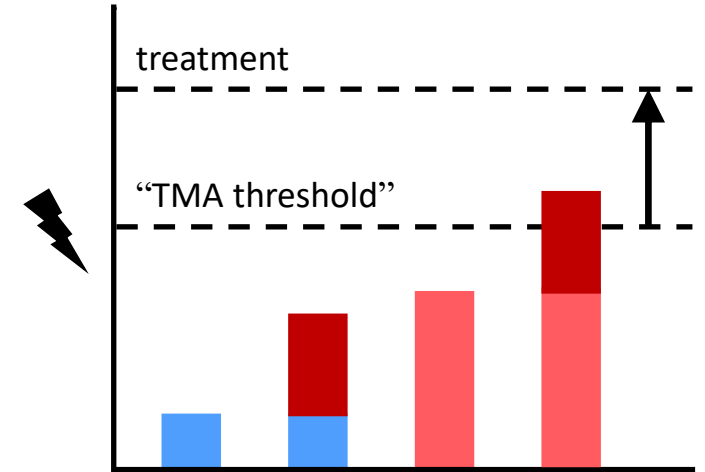
Fakhouri *et al.*, 2021
variants vs. WT after Ecu
12/28, **43%** vs. 1/27, 4%

Acosta-Medina *et al.*, 2023
variants vs. WT after Ecu
71/168, **42%** vs. 12/112, 11%

Bryant *et al.*, 2025
variants vs. WT after Ecu
4/12, **33%** vs. 0/11, 0%



Follow-up (yr)	Rare variant(s)	None
0	14	5
3	8	5
6	6	3
9	4	2
12	1	1





to treat TMA, you have to detect the TMA in the first place

**complement defects can be the key factor of ESKD in patients
with TMA and “secondary” conditions** [hypertension, pregnancy, and kidney transplantation]

**“CUREiHUS” coordinated the introduction of eculizumab in the Netherlands;
we learned a lot ever since and our approach is evolving**

Welkom bij sessie 8

Complement dysregulatie in
TMA/aHUS & C3 glomerulopathie

NIERCONGRES
7 APRIL 2026

Dé dag voor professionals
in de **nierzorg**

Sjoerd Timmermans, internist- klinisch immunoloog/nefroloog, MUMC+, Maastricht
Nicole van de Kar, kinderarts-nefroloog, Radboudumc, Nijmegen

Disclosure belangen: Nicole van de Kar

Geen (potentiële) belangenverstrengeling

Voor bijeenkomst mogelijk relevante relaties

- Sponsoring of onderzoeksgeld
- Honorarium of andere (financiële) vergoeding
- Aandeelhouder
- Andere relatie, namelijk:

Bedrijfsnamen:

Financiële vergoeding ikv adviesraad / internationale presentaties: Novartis, Samsung, Roche, Alexion, Apellis/Sobi

C3 Glomerulopathie



De diagnose



De achtergrond - pathofysiologie



De behandeling



Het vooruitzicht

Wat is C3 Glomerulopathie?



Wat is C3 Glomerulopathie?

Table 1. Table with incidence per year, showing consistent occurrence of C3G across time in the research period

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023		C3G + PI	C3G – PI
<i>n</i>	23	33	28	26	29	35	25	29	26	26	Totals	280	246
Population (million)	16.83	16.9	16.98	17.08	17.18	17.28	17.41	17.48	17.59	17.81	Mean	17.25	17.25
Incidence (<i>n</i> /million)	1.37	1.95	1.65	1.52	1.69	2.03	1.44	1.66	1.48	1.46	Mean	1.62 (\pm 0.02)	1.43 (\pm 0.03)

C3G + PI, incidence including postinfectious C3G; C3G – PI, incidence excluding postinfectious C3G; *n*, number of cases; pop., population in millions.

**ZELDZAME
NIERZIEKTEN**

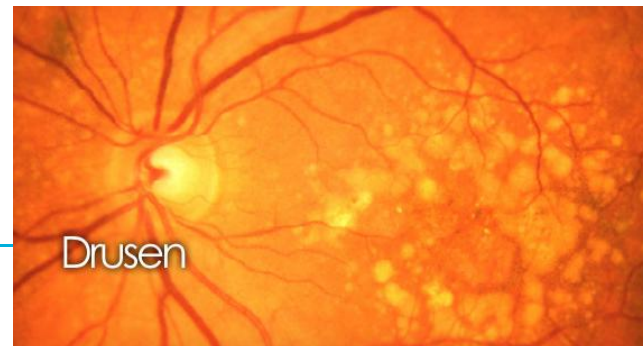
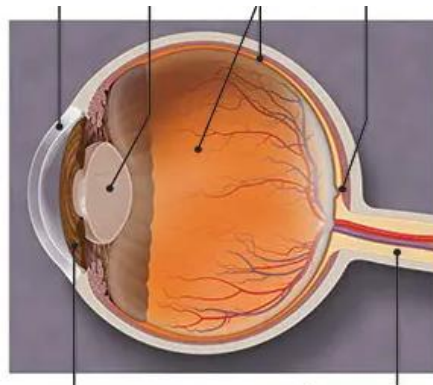
**1 - 2 C3G patiënten
per 1 miljoen mensen per jaar**

Kinderen > volwassenen

Presentatie C3G

- Algehele malaise
- Hematurie
- Proteinurie
- Nefrotisch syndroom
- Hypertensie
- Verminderde nierfunctie
- Rapidly progressive glomerulonephritis

- Drüsen

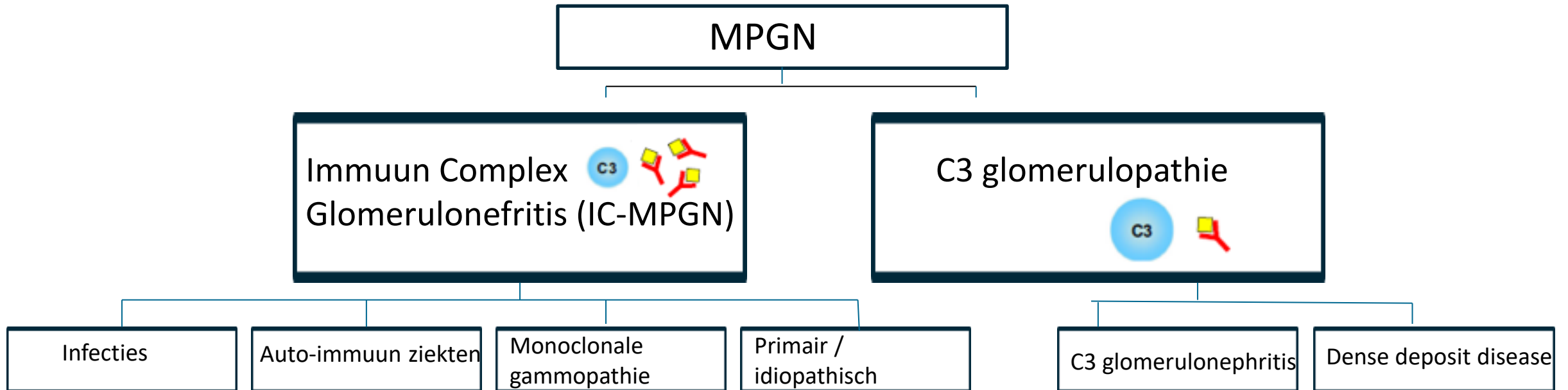


Stellen van diagnose C3G

- Symptomen bij presentatie
- Bloed- en urine onderzoek; laag C3 in bloed is verdacht
- **Nierbiopt = Gouden standaard**
- Complement onderzoek
 - C3Nef, C4ef, C5Nef, Complement eiwitten, activatie producten
- Genetisch onderzoek complement genen



Membraneuze proliferatieve glomerulonefritis- MPGN



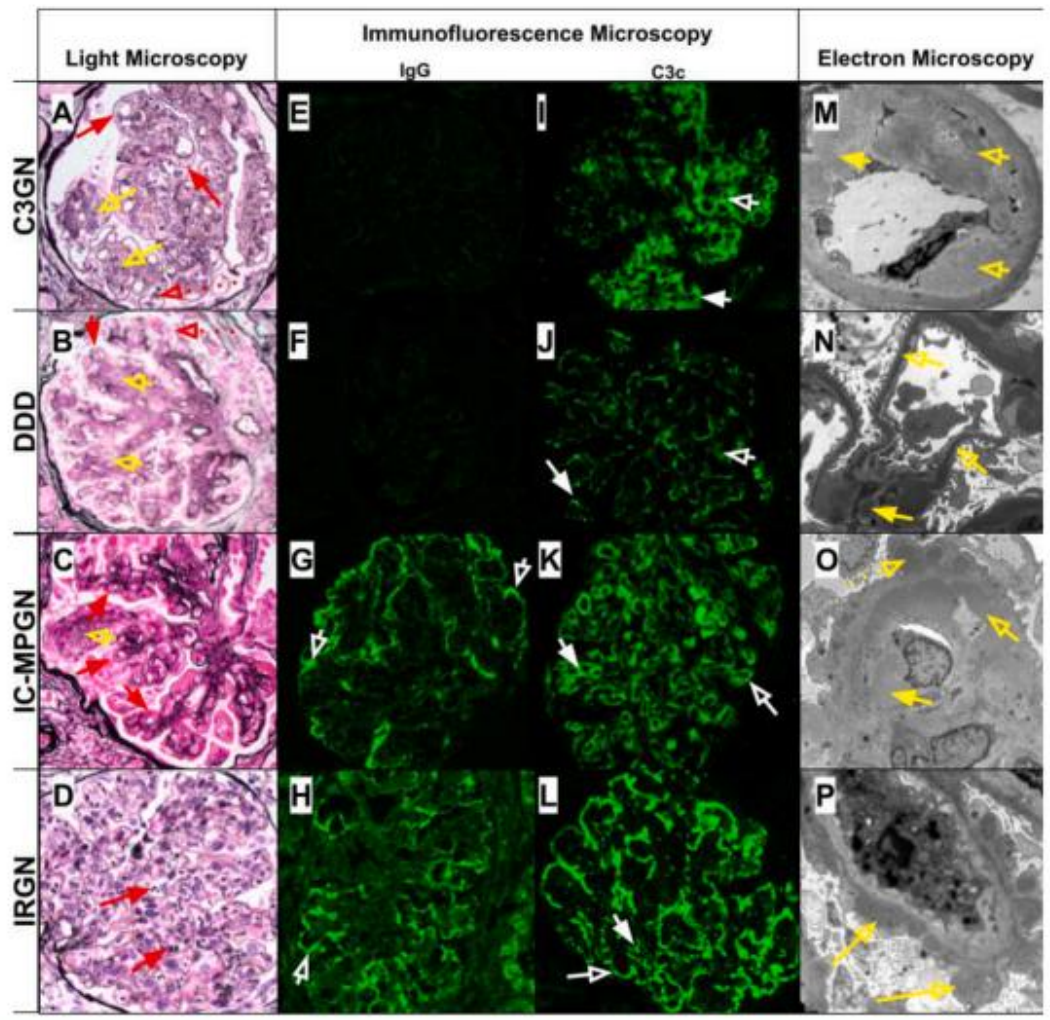
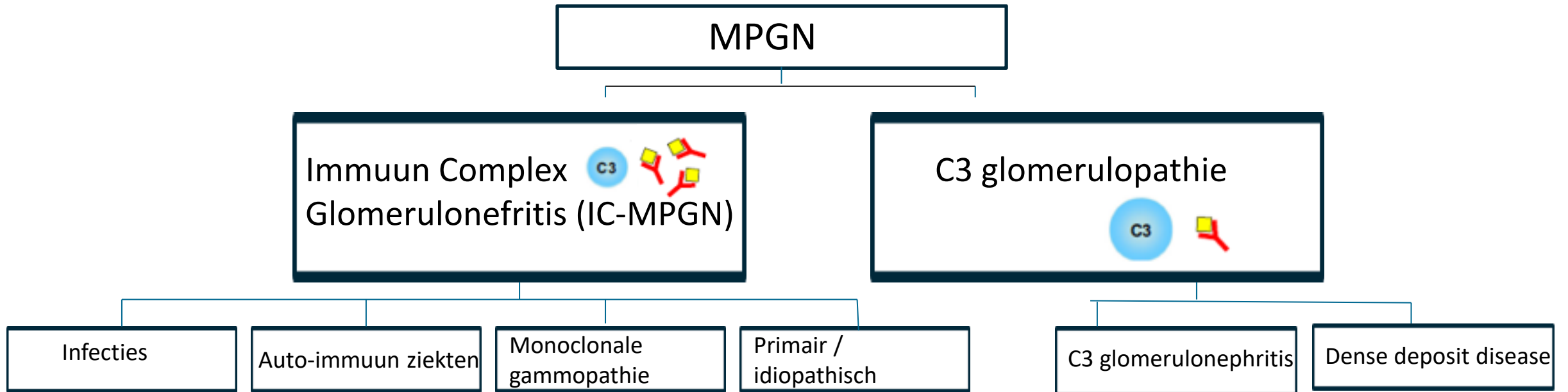


Figure 2. Histopathologic and immunofluorescence features of glomerulonephritis with dominant C3.

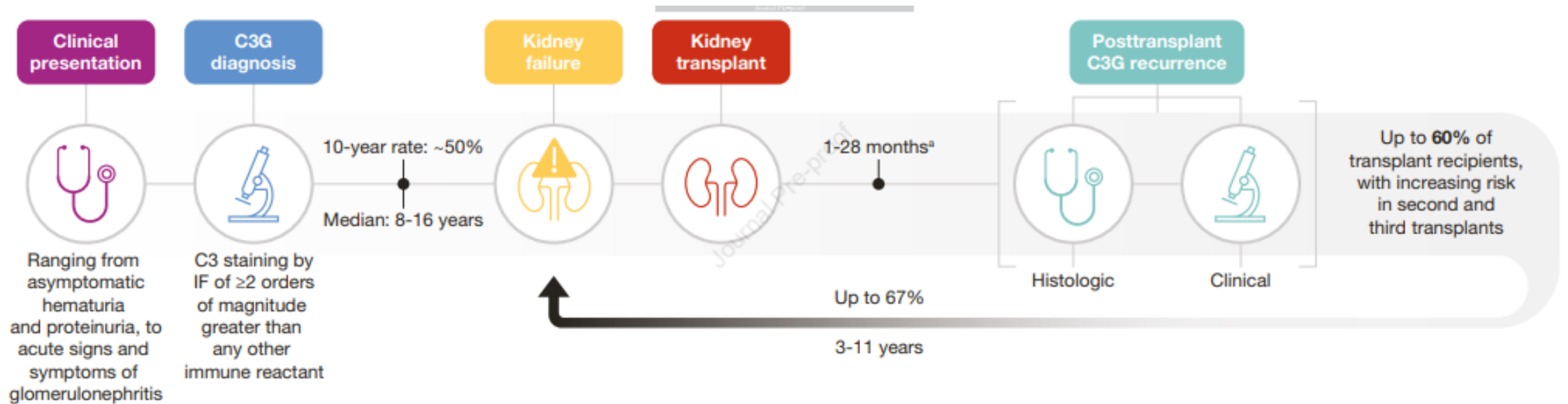


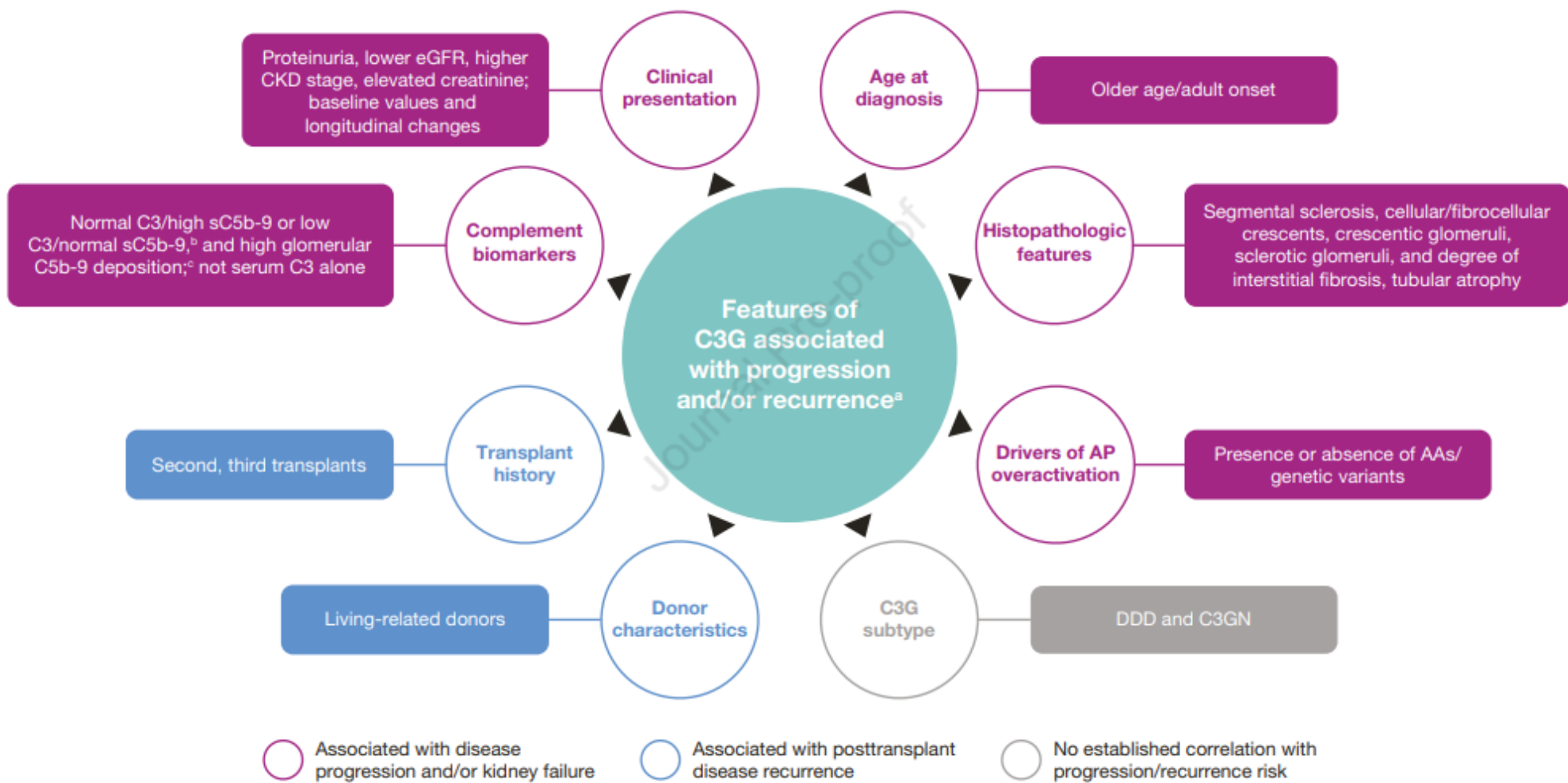
Membraneuze proliferatieve glomerulonefritis- MPGN



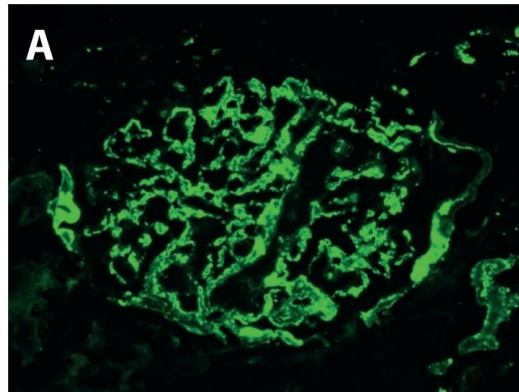
Ontregeling van het complement systeem

C3G Patient Journey

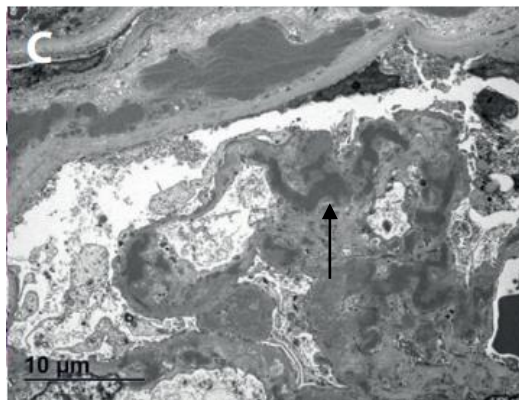




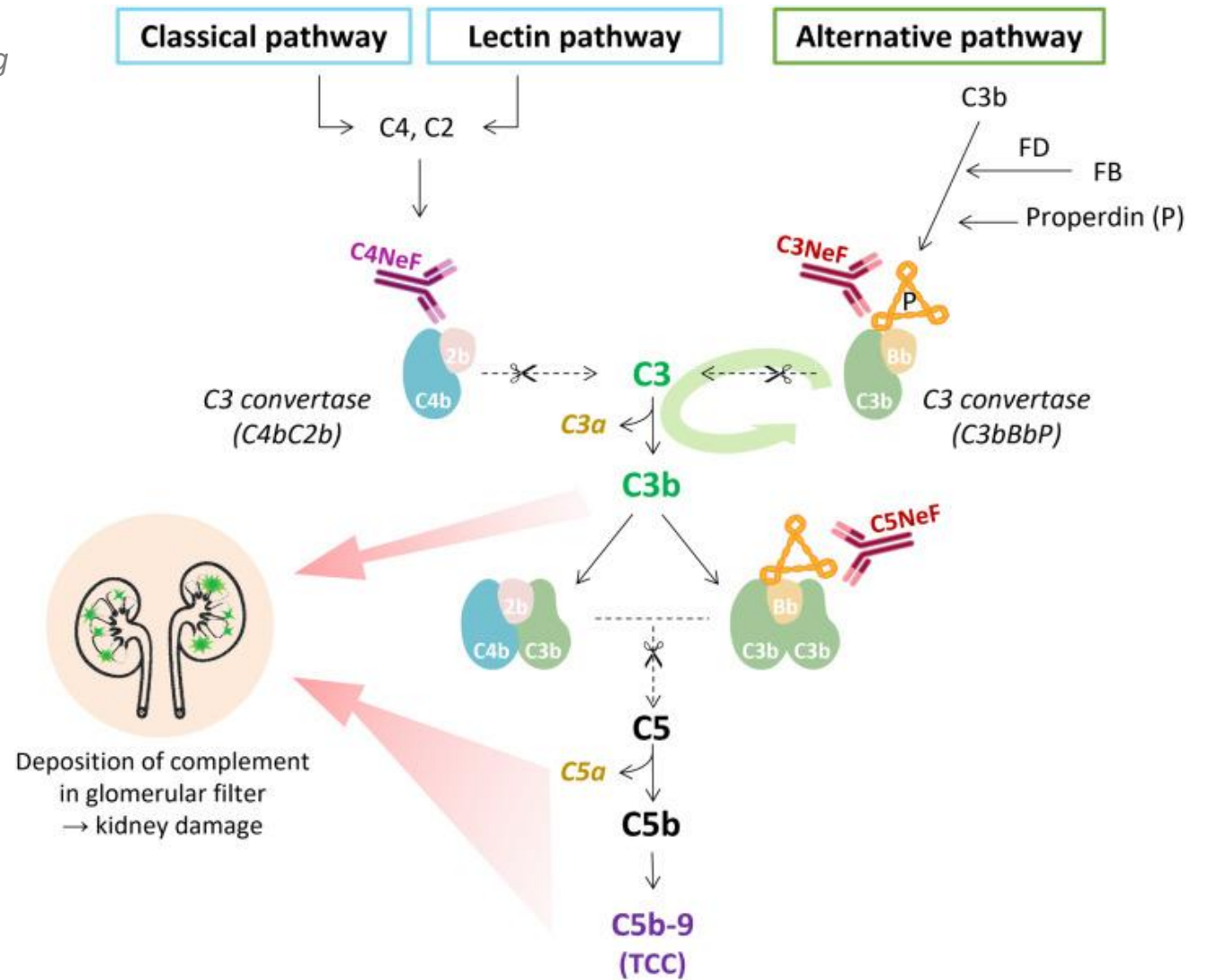
C3 glomerulopathie



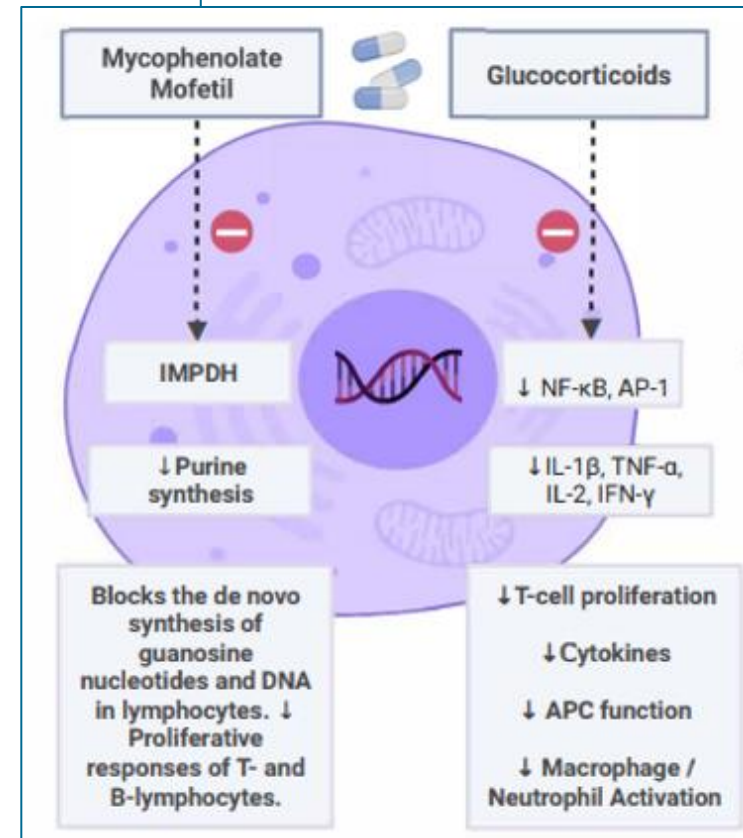
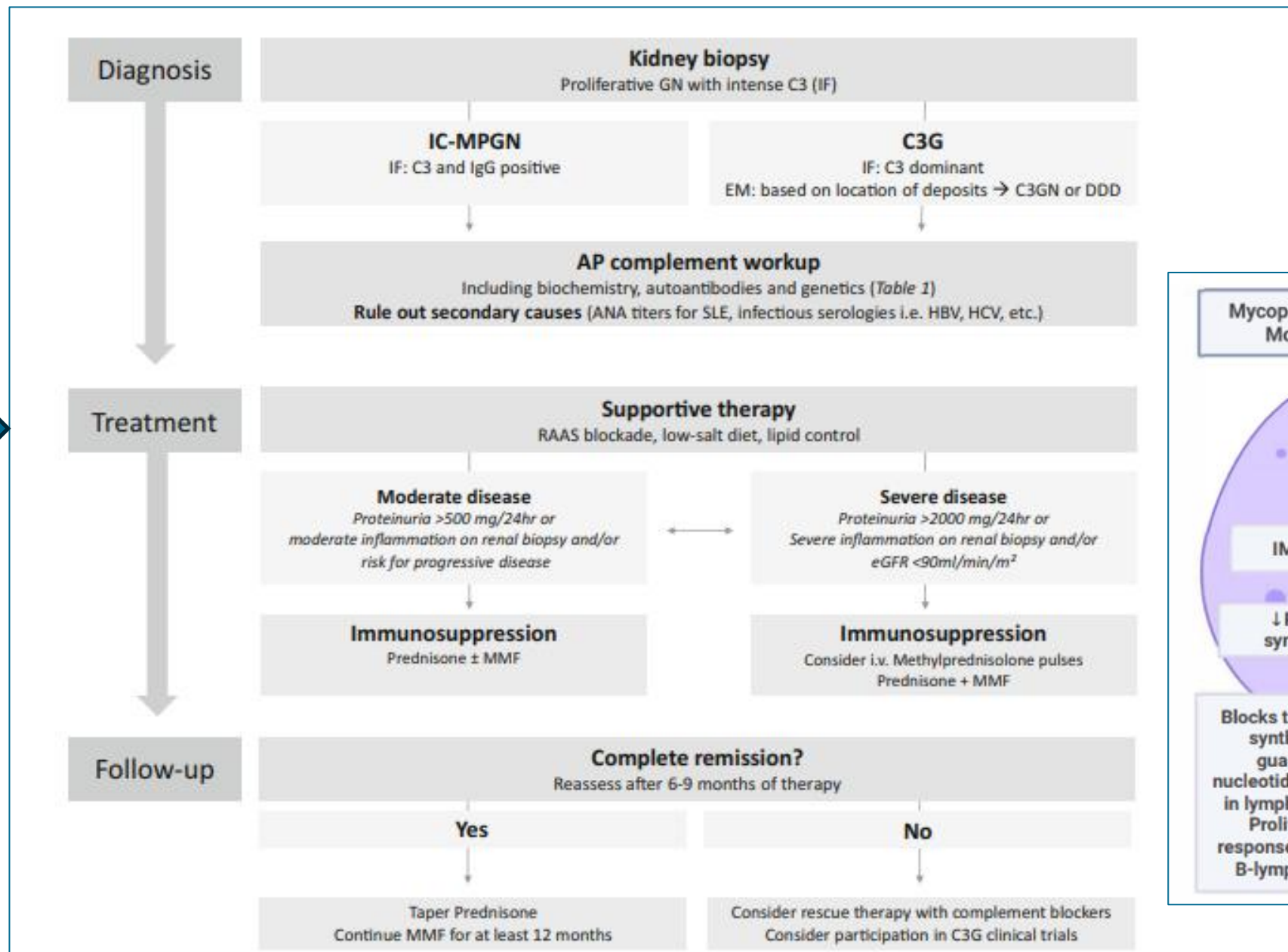
Sterke C3 aankleuring

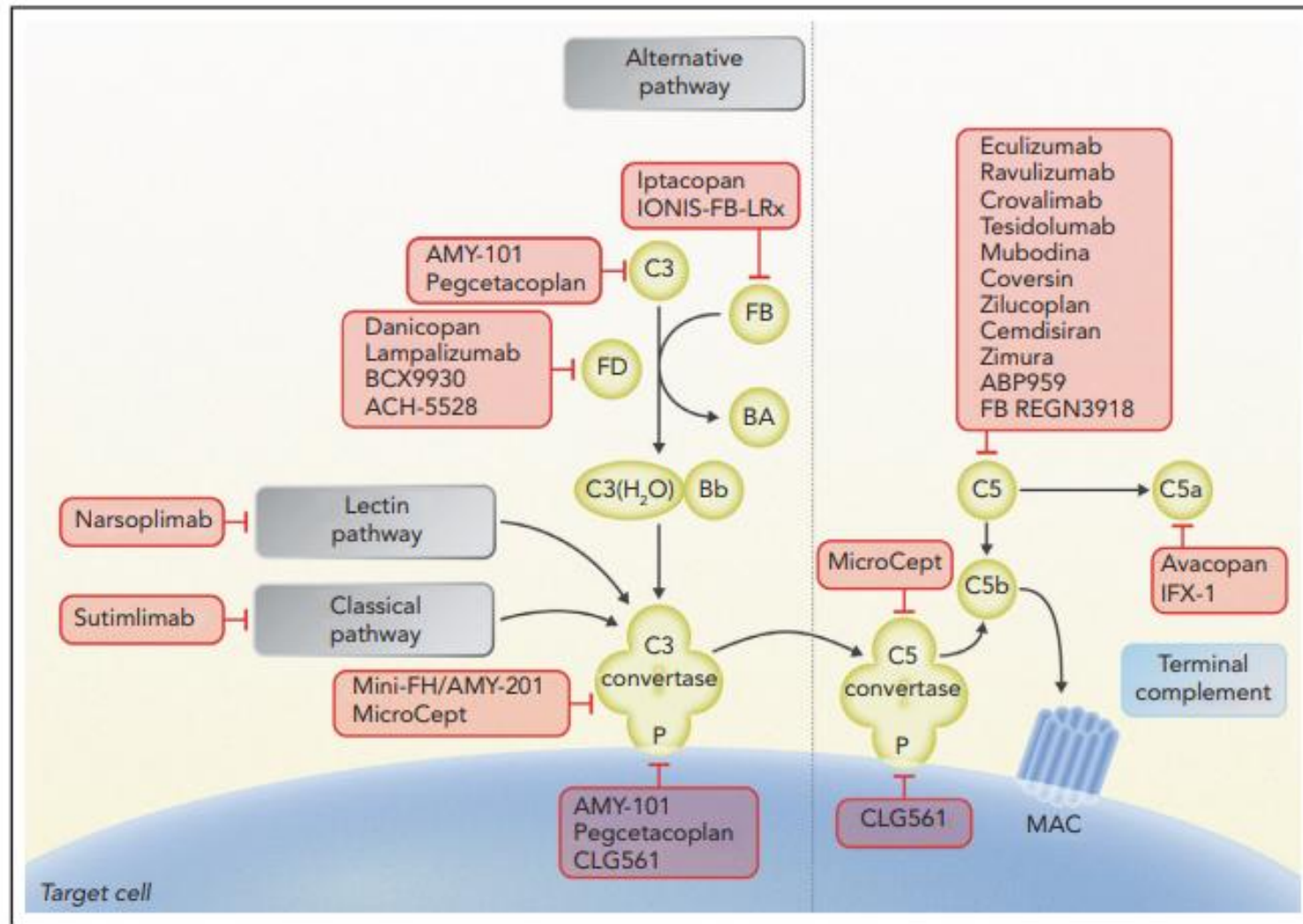


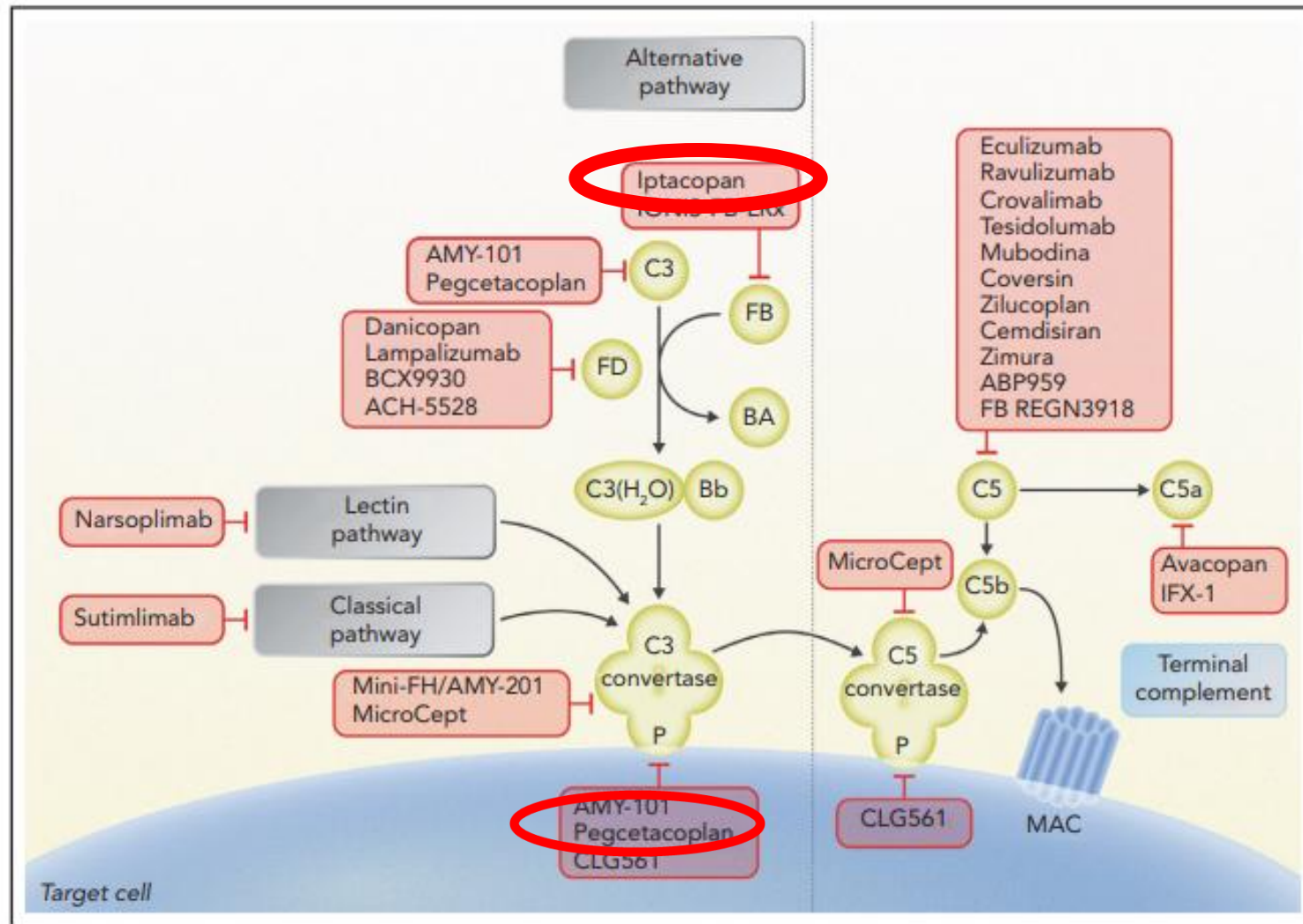
"Dense deposits"



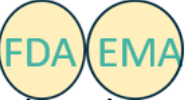

- Verworven (±70%)
- Aangeboren (±10%)







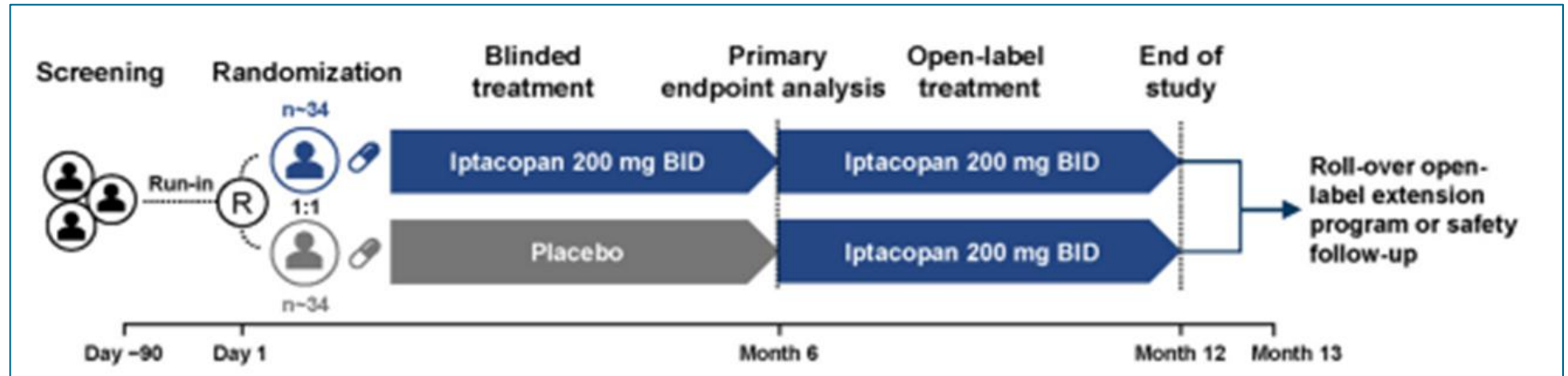
Op weg naar gerichte behandeling C3G

- Complement remmers
 - **Eculizumab**
 - Nooit officieel effectiviteit getoetst in C3G, geen trial
 - In NL: vergoedings-mogelijkheid voor kinderen, maar niet voor volwassenen
 - **Iptacopan,**
 - Internationaal onderzoek bij volwassen met C3G in eigen nieren is klaar 
 - Internationaal onderzoek bij kinderen vanaf 12 jaar met C3G in eigen nieren is gaande
 - Nog geen vergoedingsstatus in Nederland
 - **Pegcetacoplan**
 - Internationaal onderzoek bij volwassenen / kinderen >12 jaar met C3G / IC-MPGN in eigen nieren / transplantaat nier is afgerond. 
 - Nog geen vergoedingsstatus in Nederland

Phase 3

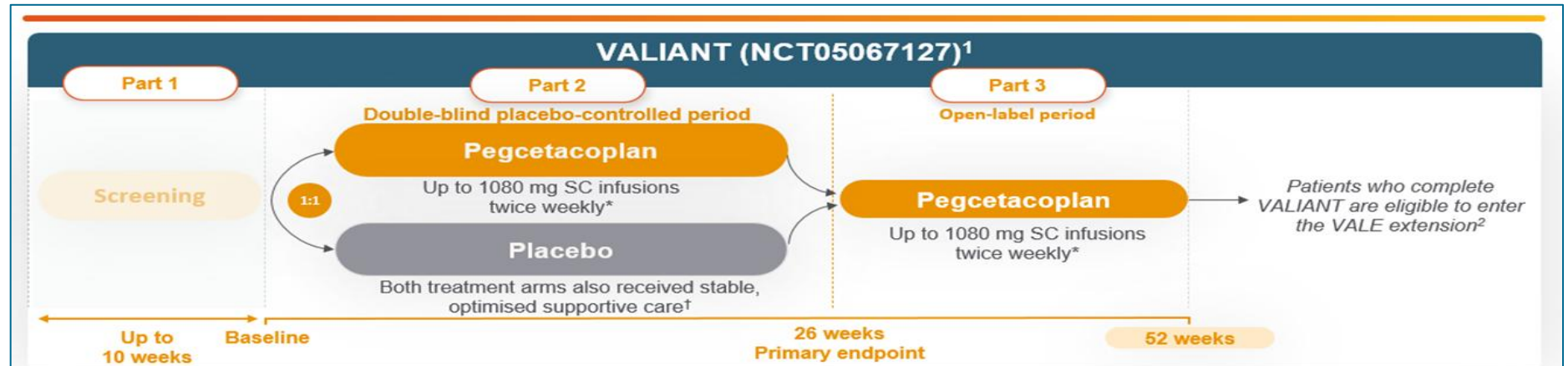
IPTACOPAN
Remmer van factor B
C3G,
age >18

APPEAR studie
2 keer per dag tabletje

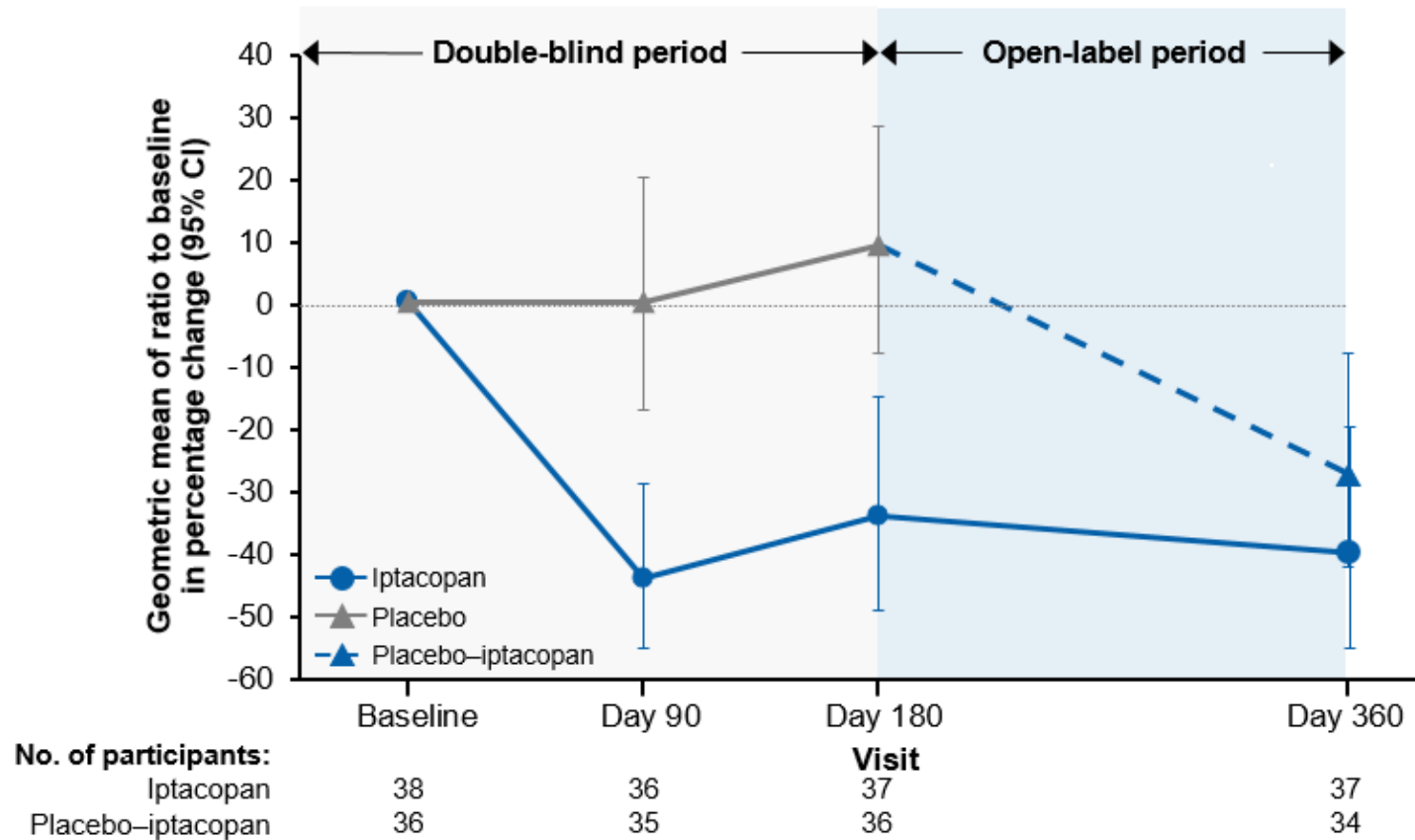


PEGCETACOPLAN
Remmer van C3 en C3b
C3G, p IC-MPGN,
age >12
native /Tx

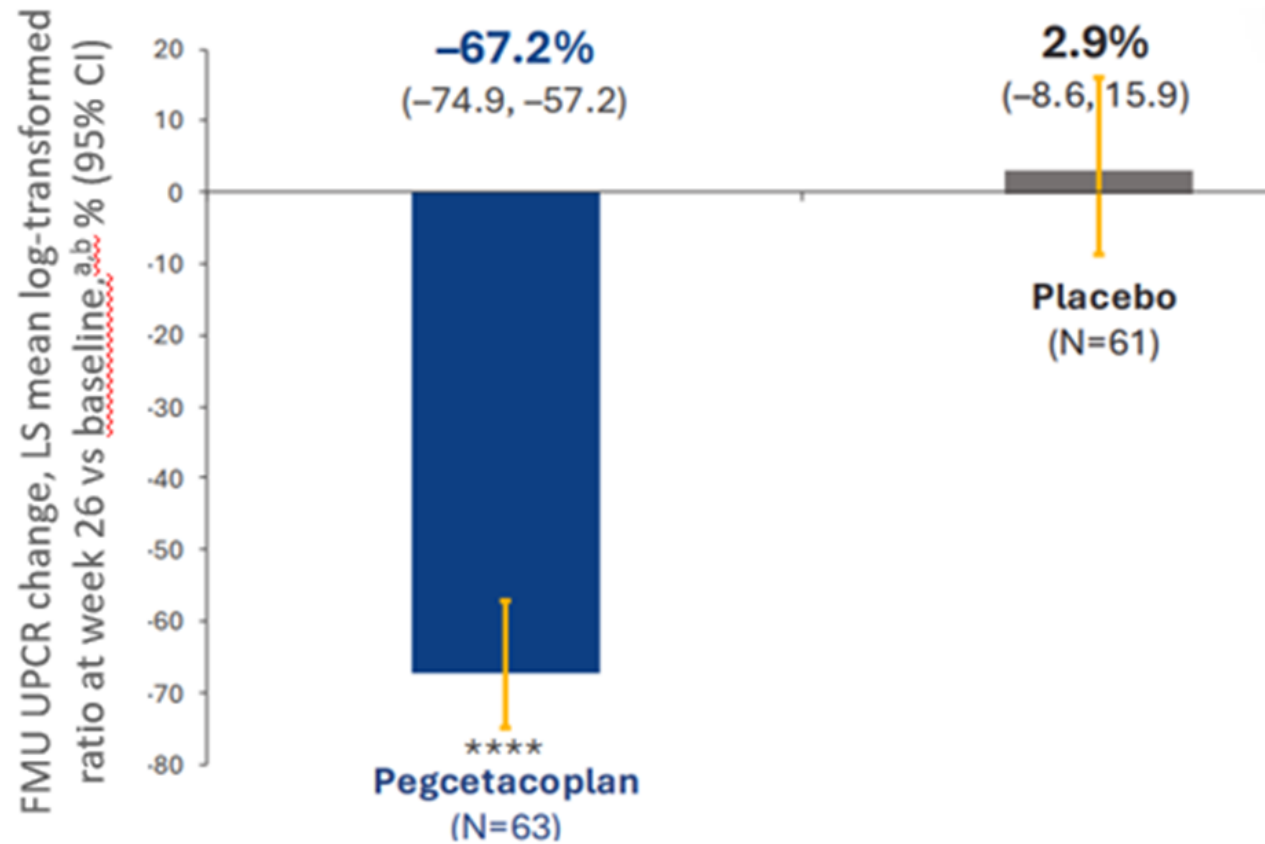
VALIANT studie
2 keer per week sc



Iptacopan in C3G



Pegcetacoplan in C3G

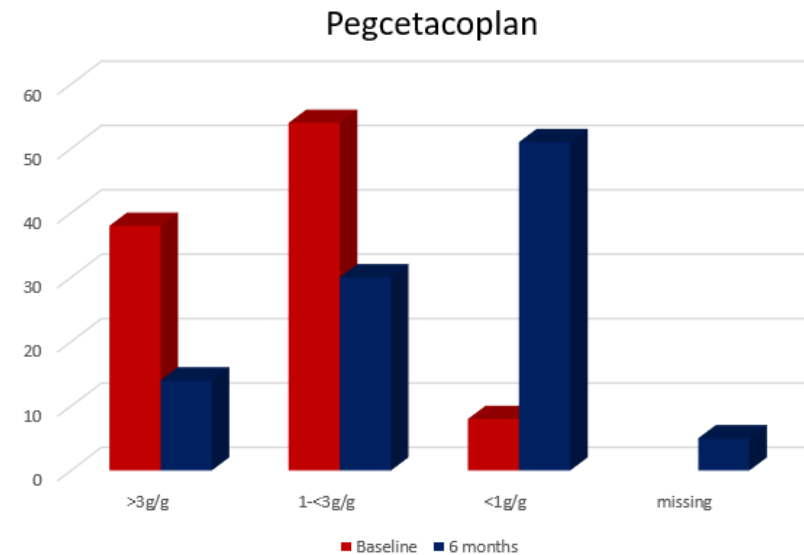
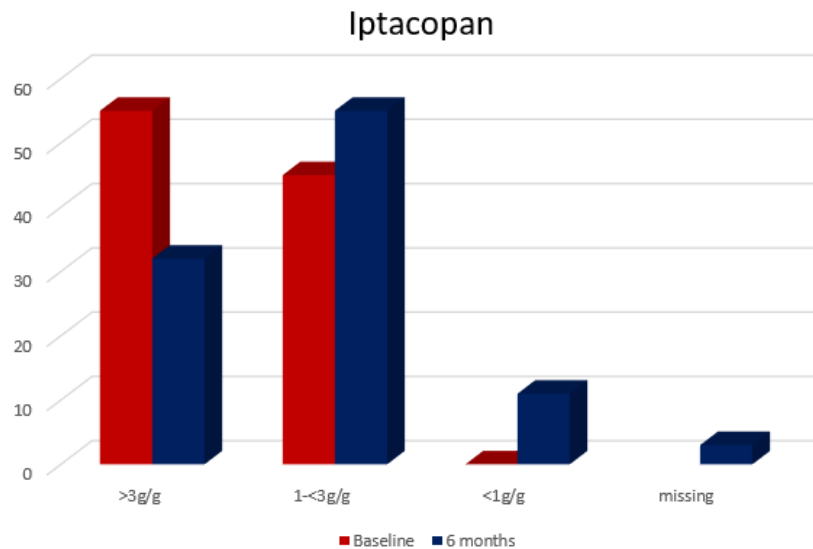






Hoe goed is goed genoeg?

Proteinuria

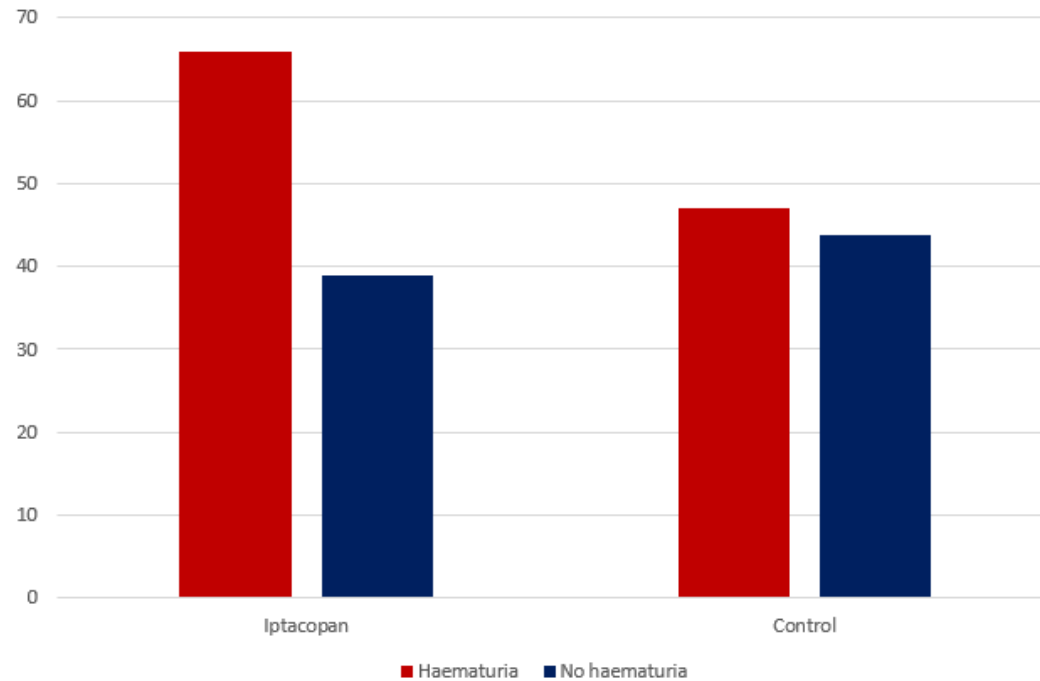


Proteinuria?- how low is good enough

Adults vs Children

Hoe goed is goed genoeg?

Haematuria

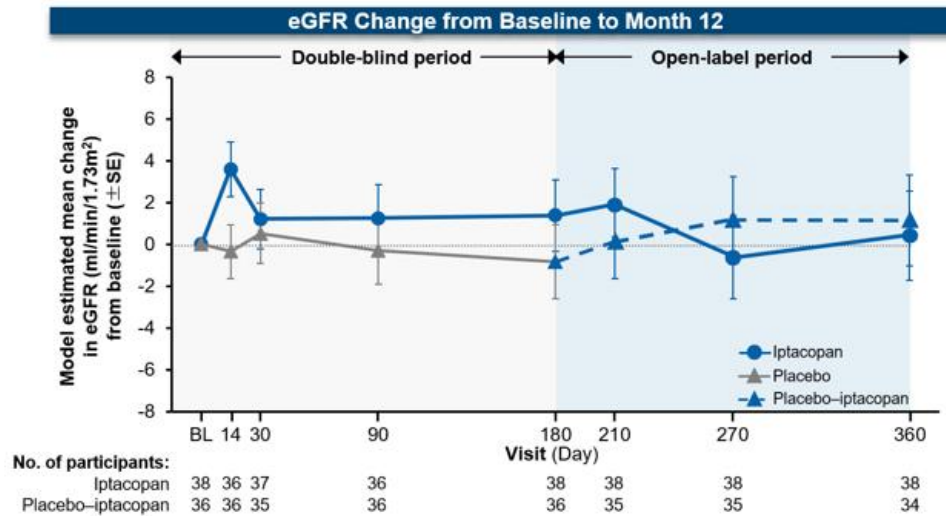


~39% have ongoing haematuria after 6 months of Iptacopan

NDT Supplement, October 2025.

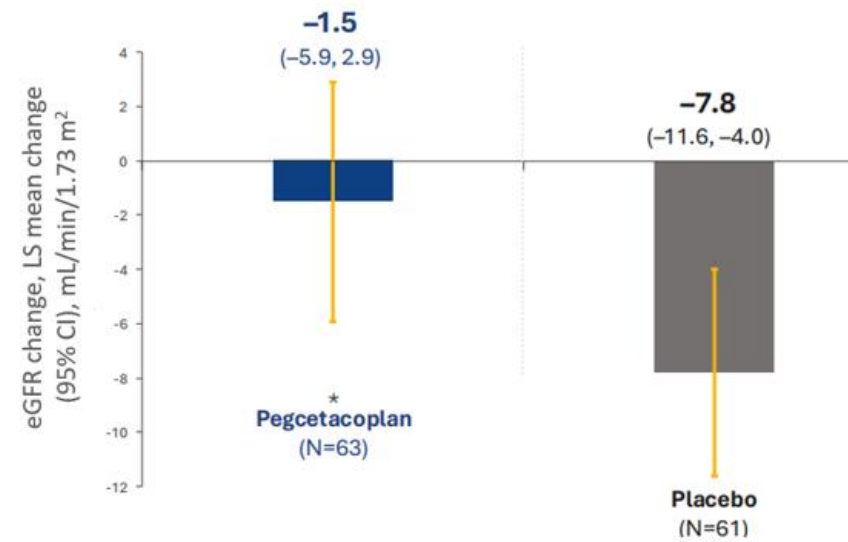
Stoppen of vertragen van de nierfunctie achteruitgang ?

Iptacopan



Pegcetacoplan

Δ eGFR (week 26 vs baseline)



Hoe monitoren we de complement inhibitie ?

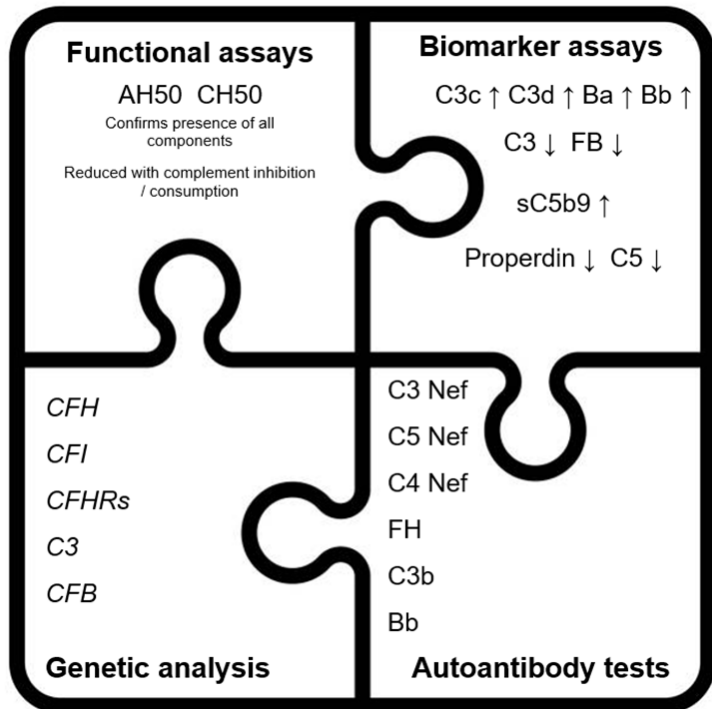
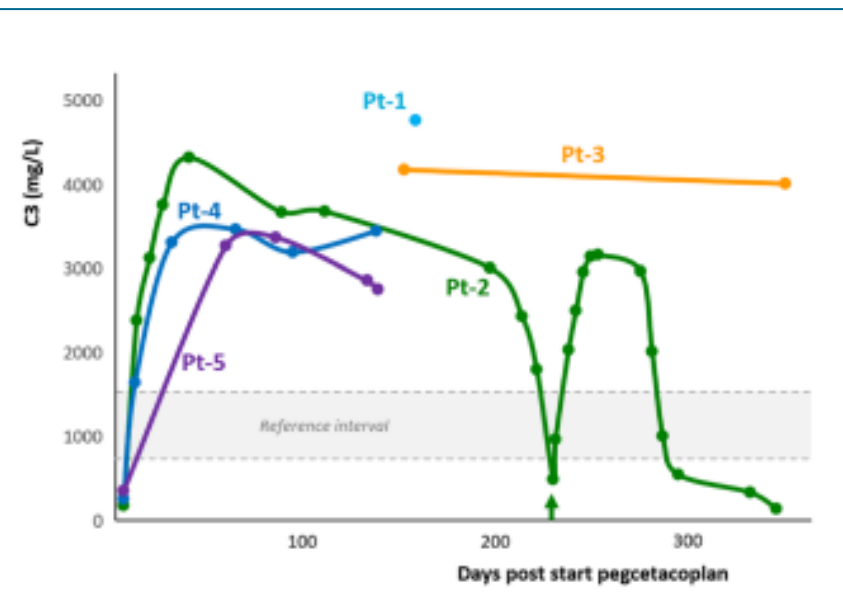


Table 3: Overview of complement diagnostics in patients treated with pegcetacoplan.

Patient	C3 mg/L (ref 700–1,500)		C3d mg/L (ref <8.3)		C3d/C3-ratio (ref <8.1)		AP % (ref 67–133)		CP % (ref 67–133)		C3bBbP CAU/mL (ref <26)	
	Before	After ^a	Before	After ^a	Before	After ^a	Before	After ^a	Before	After ^a	Before	After ^a
1.	n.t.	4,766	n.t.	n.t.	n.t.	n.t.	25	n.t.	<10	95	n.t.	n.t.
2.	180	4,863	36	12	200	4	29	30	50	63	12	65
3.	n.t.	4,100	n.t.	n.t.	n.t.	n.t.	n.t.	29	<10	68	n.t.	n.t.
4.	259	3,358	28	5	109	2	n.t.	<20	n.t.	48	14	45
5.	355	3,320	10	5	29	1	n.t.	<20	n.t.	76	39	52

^aIf more values are available, the average plateau-value is reported. n.t. = not tested.



Kan nierbioptie informatie verschaffen over gebruik van complement therapie?

- Lichtmicroscopische kenmerken gecorreleerd met proteinurie
 - Endocapillaire hypercellulariteit / dubbelcontouren capillaire vaatwand
- Mogelijk voor beoordelen effectiviteit van behandeling – Iptacopan trial : samenstellingactiviteit index nierbiopt
 - Let op processen in nierbiopt in tijd hebben verschillend herstel-vermogen: Inflammatie / C3 deposities/ vaatwand remodelling (Iptacopan trial : samenstellingactiviteit index nierbiopt)
 - Variatie beoordeling endocapillaire hypercellulariteit / inflammatie – immunohistochemie anti-CD68 (macrofagen identificatie) beter ?

Iptacopan vs Pegcetacoplan, welke?

Iptacopan (APPEAR-C3G)^{1,2}

Aged 18 yrs–60 yrs

Screening 90 days

Primary C3G only

No renal transplants

Reduced C3

>1.0 g/g

eGFR or measured GFR >30 mL/min/1.73 m²

Prednisone at a dose ≤7.5 mg/day

Pegcetacoplan (VALIANT)^{3,4}

Adolescents (12–17 yrs) and adults (≥18 yrs)

Screening 70 days

Primary C3G or IC-MPGN

Renal transplants allowed

Normal C3 allowed

>1.0 g/g

eGFR ≥30 mL/min/1.73 m²

MMF and corticosteroids (prednisone ≤20 mg/day)

Additionele immunosuppressie nodig?

	Pegcetacoplan	Placebo	Geometric Mean Ratio (95% CI)
	<i>no. of patients</i>		
Overall	63	61	0.32 (0.24–0.43)
Immunosuppressant status			
Yes	48	42	0.30 (0.21–0.42)
No	15	19	0.36 (0.20–0.63)



Toegevoegde waarde?

Subgroup	Iptacopan		Placebo		Favors iptacopan	Favors Placebo	LS Mean
	N	Adjusted geometric mean (95% CI)	N	Adjusted geometric mean (95% CI)			Geometric mean ratio (95% CI)
Overall	38	0.698 (0.572, 0.852)	36	1.076 (0.881, 1.313)			0.649 (0.489, 0.862)
CS and/or MPA treatment at randomization							
Yes	16	1.026 (0.773, 1.362)	17	1.200 (0.924, 1.558)			0.855 (0.580, 1.259)
No	22	0.504 (0.381, 0.666)	19	0.960 (0.711, 1.295)			0.525 (0.346, 0.796)



Of toch niet?

Discontinueren ja? Zo ja, wanneer?

- C3G vs aHUS
- Trials geven geen info of je kan stoppen
- Bij complete remissie van proteinurie / hematurie?
- Welke biomarkers kunnen hierbij helpen?
- Nephritic factors aanwezig ja / nee?
- Onderscheid genetische 'driver' vs auto-immunologische 'driver' ?

Hoe C3G te behandelen in niertransplantatie?

Recurrence

Up to 89% of patients with C3G/primary IC-MPGN **experience disease recurrence** following transplantation; this can occur almost immediately after transplantation in some cases

Clinical outcomes

Disease recurrence contributes to **allograft loss in ~50%** of patients 10 years post-transplant



Prophylactic vs reactive

aHUS- relapse rapid with graft rapid loss of transplant. **C3G more insidious onset with time to react** But pre-emptive study being planned.

Monitoring for relapse

Do we have a definition of what relapse is? **Protocol biopsies? If so, when? vs Reactive biopsy?**

Samenvattend C3G – targeted complement therapie

- Complement inhibitie is effectief in de behandeling van C3G
- Het is niet de perfecte behandeling voor iedere C3G
- Hoe de behandeling te monitoren?
 - Biomarkers? Welke? Proteinurie? Hematurie? Hoe laag proteinurie?
 - Wanneer biopsie?
 - Voldoende toediening geneesmiddel? Spiegel?
- Welke keuze in medicament?
 - Is de een beter dan de ander? Switchen? Icm immuno-suppressiva? Klinische trial?
- Kan complement inhibitie ook gestopt worden? Bij wie?
 - Biomarkers? Welke? Proteinurie? Hematurie? Hoe laag proteinurie? Biopt?
- Kunnen de nieuwe anti-B cel therapieën helpen om nephritic factors te verwijderen?
 - En dan stoppen met complement inhibitie?

Samenvattend C3G – targeted complement therapie


- Transplantatie?
 - Pre-emptief vs reactief?
 - Protocol biopsie vs reactief?
 - Wat wordt de definitie van relapse ? C3 deposities vs tekenen van glomerulonefritis?
- Weinig data nog van adolescenten en geen data van kinderen <12 jaar
 - Pegcetacoplan fase 3 data zijn er; Iptacopan komende
- Mogelijk toch langdurige behandeling?
 - Veiligheidsdata – op dit moment kleine aantallen in trial en korte follow up.
 - Data uit trial: biopten? PK/PD ? Wie reageert er niet en waarom niet?
- Kunnen de nieuwe anti-B cel therapieën helpen om nephritic factors te verwijderen?
 - En dan stoppen met complement inhibitie?
-  Gezien de zeldzaamheid ziektebeeld : Landelijke richtlijn / database



Table. Comparison of iptacopan and pegcetacoplan in C3G

Feature	Iptacopan (Fabhalta)	Pegcetacoplan (Empaveli)
Mechanism of action	Selective factor B inhibitor; blocks formation of the alternative pathway C3 convertase, reducing amplification of complement activation	C3/C3b inhibitor; prevents activation of all classical, lectin, and alternative complement pathways; inhibits both C3 and C5 convertases
Complement target	Alternative pathway	Central complement component C3
Route/dosing	Oral, twice daily	Subcutaneous, twice weekly
eGFR cutoff	eGFR ≥ 30 mL/min/1.73 m ²	eGFR ≥ 30 mL/min/1.73 m ²
Pivotal trial	APPEAR-C3G (phase 3, randomized, double-blind, placebo-controlled)	VALIANT (phase 3, double-blind, placebo-controlled)
Study population	74 Adults (aged ≥ 18 years) with biopsy-proven C3G, low serum C3, proteinuria despite standard therapy	124 Patients (69 adults, 55 adolescents; aged ≥ 12 years) with C3G or IC-MPGN, including post-transplant recurrence
Primary endpoint	Percent change in urine protein at 6 months	Percent change in urine protein at 26 weeks
Efficacy highlights	35% Relative reduction in proteinuria versus placebo; eGFR stabilization	68% Relative reduction in urine protein creatinine ratio (UPCR) versus placebo; $\geq 50\%$ UPCR reduction in 60% versus 5% in placebo; C3 staining clearance to 0 intensity in 71%; eGFR reduction: -1.5 versus 7.8 mL/min/1.73 m ² (consistent across subgroups: age, sex, race and ethnicity, transplant status, and immunosuppression)
Safety profile	Tolerated well through 6 months; mild to moderate adverse events; no meningococcal infections	Injection-site reactions most common; mild to moderate adverse events similar to placebo; no meningococcal infections; one COVID-19–related death; no allograft rejection or loss
Approved indication (FDA 2025)	C3G in adults	C3G and IC-MPGN in adults and adolescents aged ≥ 12 years
Monitoring/precautions	Vaccinate against encapsulated bacteria; monitor kidney function and complement markers	Vaccination against encapsulated bacteria; monitor kidney function and complement markers
Unresolved questions	Duration of remission, eGFR preservation, efficacy in dense-deposit disease, use in kidney transplantation	Long-term safety, relapse prevention, pediatric use aged < 12 years, cost/accessibility; limited transplant data; optimal treatment duration

Het **Niercongres** wordt mede mogelijk gemaakt door:



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