Recidief aHUS na Transplantatie

CUREiHUS

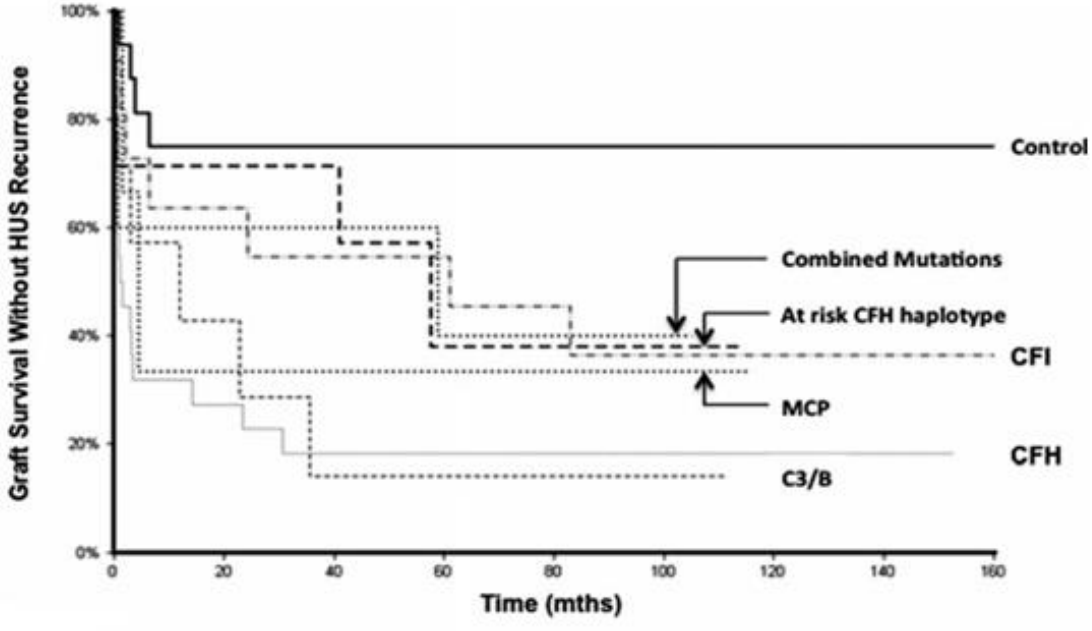
Papendal 2022

Disclosure

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	

Le Quintrec et al. Am J Trans. 2013

Hoog risico op recidief aHUS na NTx



Retrospectieve studie uit Frankrijk (1999-2005) 71 NTx, 57 patienten

Recidief risico 68%

Meestal vroeg (70% < 1 jaar)

Recidief: slechte transplantaatoverleving (na 1 jaar 44% vs 74%)

Recidief: afhankelijk van mutatie (CFH / C3 > MCP)

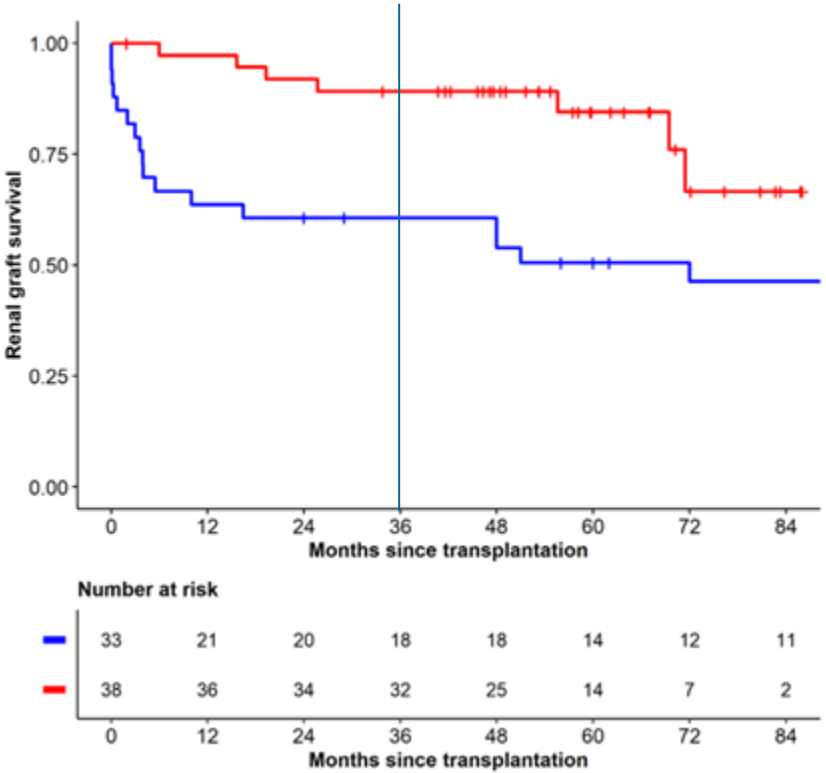
KDIGO 2016: eculizumab profylaxe

Table 4 | Prophylaxis against aHUS recurrence in allografts based on a risk-assessment strategy[a]

Recurrence risk	Treatment regimen
High risk (50-100%) • Previous early recurrence • Pathogenic mutation[a] • Gain-of-function mutation	Prophylactic eculizumab[b,c]
Moderate risk • No mutation identified • Isolated *CFI* mutations • Complement gene mutation of unknown significance • Persistent low titer FH autoantibody	Prophylactic eculizumab or plasma exchange[d]
Low risk (<10%) • Isolated *MCP* mutations • Persistently negative FH autoantibodies	No prophylaxis

- Eculizumab profylaxe indien hoog of matig risico op recidief
- Profylaxe: levenslang

UK cohort death censored graft survival

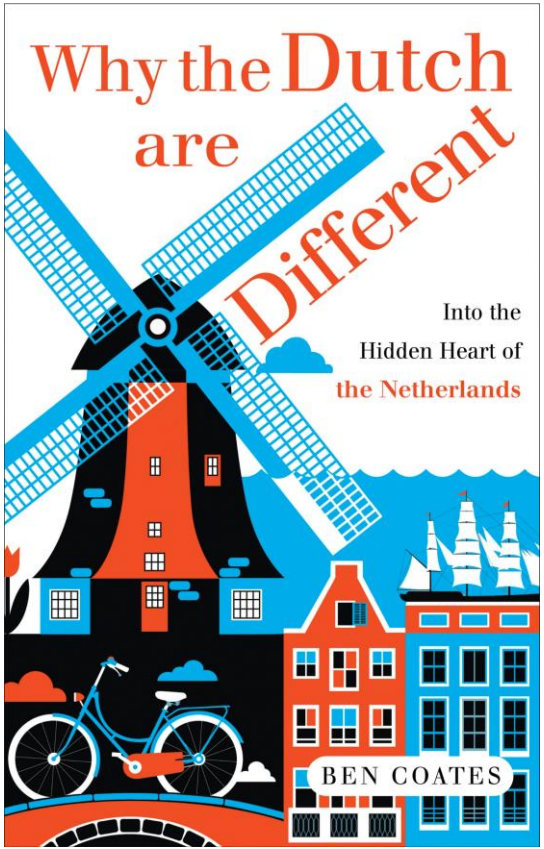


ECU profylaxe – 3j 89% survival

Geen behandeling- 3j 61% survival

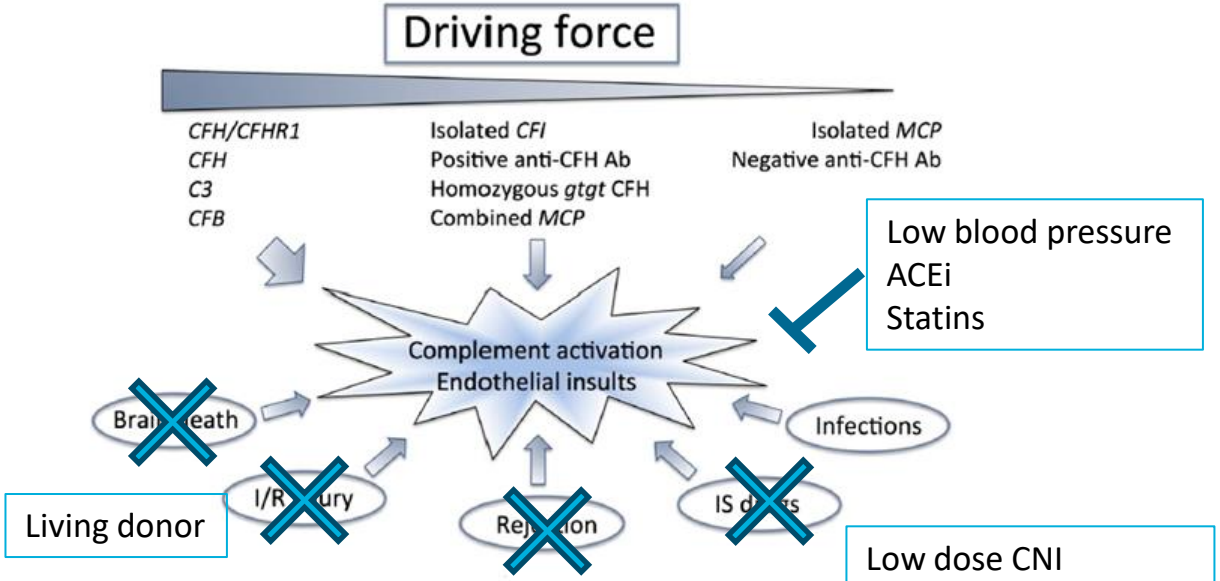
Prof ECU cohort

- Path CFH 42%
- Path C3 18%
- Hoog risico 68%
- Matig risico 32%


Why the Dutch are Different
Into the Hidden Heart of the Netherlands
BEN COATES

Biglarnia et al. Nat rev. 2018
Verhave et al. Neth J Med. 2013
Adapted from Zuber et al. Trans Rev. 2013

Niertransplantatie zonder profylaxe



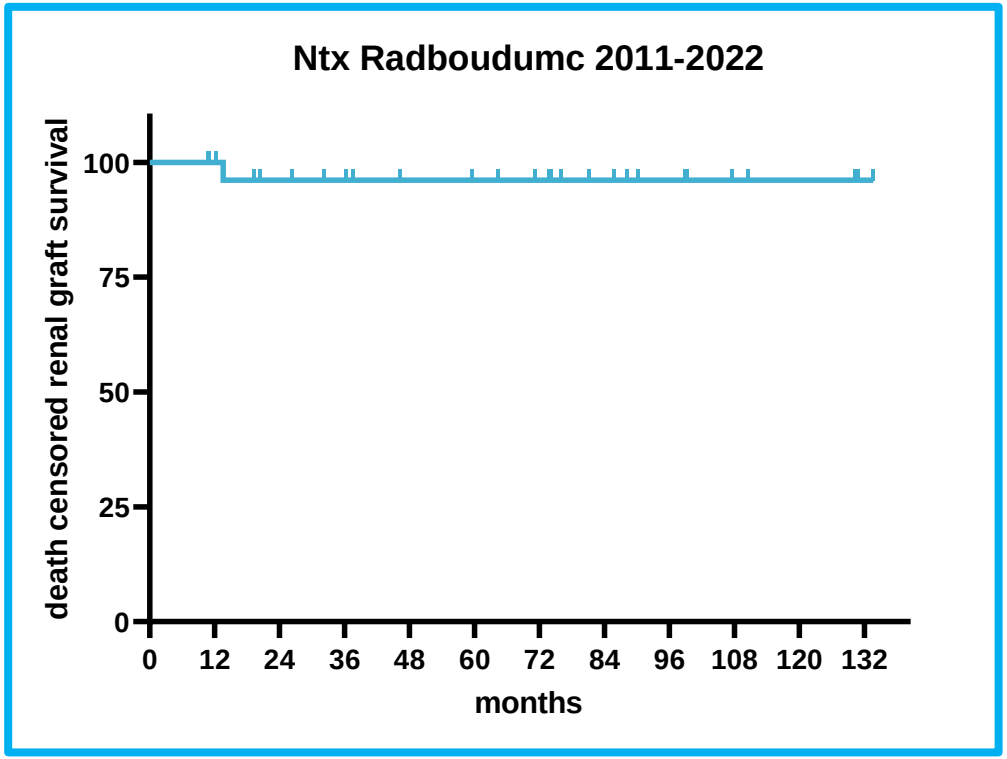
Niertransplantatie bij 29 aHUS patienten
Radboudumc 2011-2022

Levende donor	N=19
Hoog risico recidief	14/19 (74%)
Matig risico recidief	5/19 (26%)
Genetische mutatie	18/19 (95%) 19 mut
RECIDIEF (3xC3, 2xCFH)	**5/19 (26%)**

Postmortale donor	N=10
Hoog risico recidief	6/10 (60%)
Matig risico recidief	4/10 (40%)
Genetische mutatie	6/10 (60%) 8 mut
RECIDIEF (2xCFH)	**2/10 (20%)**

GEEN profylaxe
WEL eculizumab rescue

Radboud cohort death censored graft survival

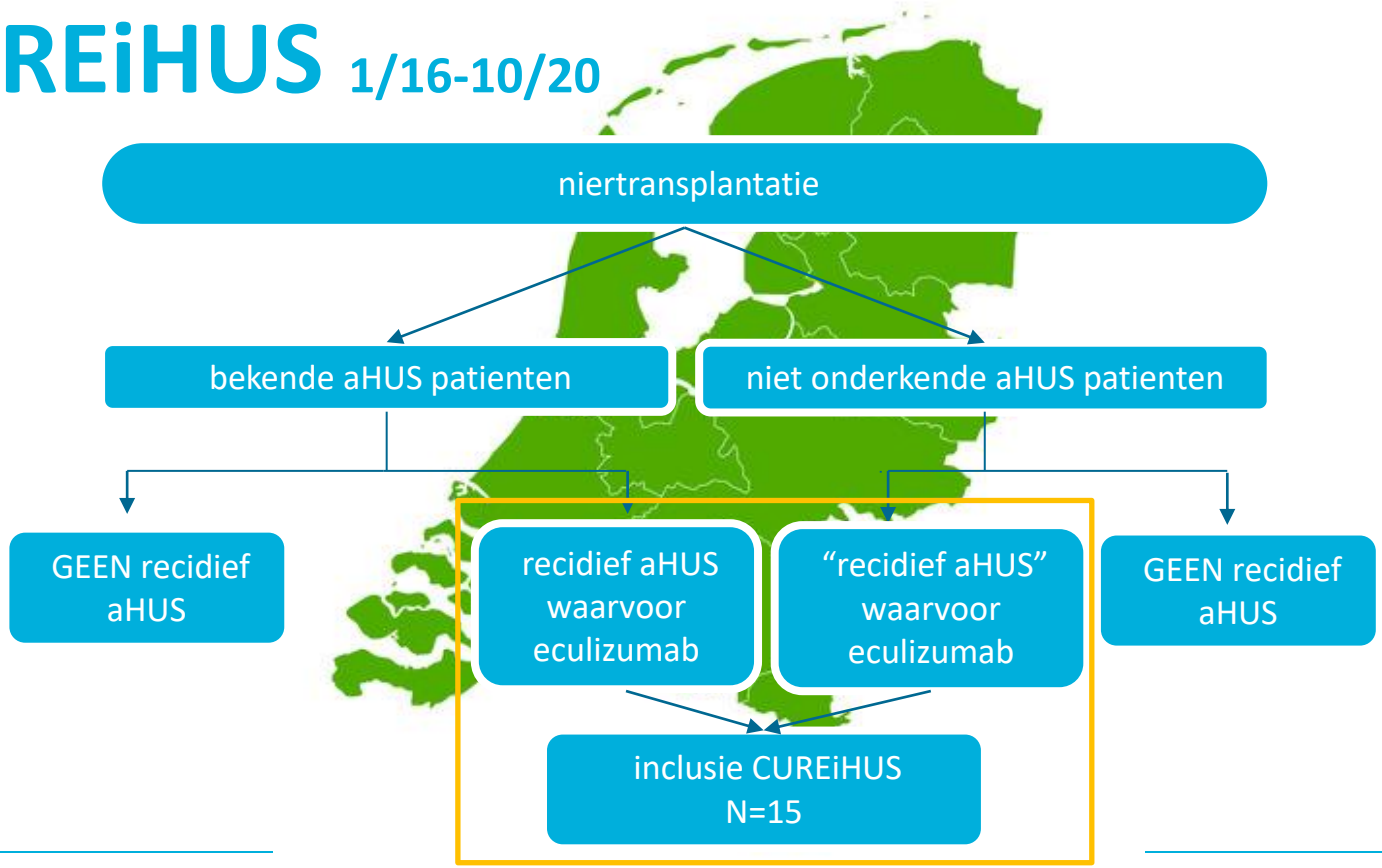


- Path CFH 17% (UK 42%)
- Path C3 52% (UK 18%)
- Hoog risico 69% (UK 68%)
- Matig risico 31% (UK 32%)

Mediane FU 73m (11-134m)
Mediane kreatinine 130 (59-500)
Mediane CKD-EPI 44 (5->90)

PROFYLAXE IS NIET KOSTEN-EFFECTIEF

CUREiHUS 1/16-10/20



Recidief aHUS na niertransplantatie
N=15

Vroeg recidief	N=7
Tijd tot recidief (maanden)	3m (0.3-8.8)
Bekend met aHUS	5/7 (71%)
Genetische mutatie	6/7 (86%) 7 mut
CFH C3	4/7 1/7
Hoog recidief risico Matig recidief risico	5 (71%) 2 (29%)

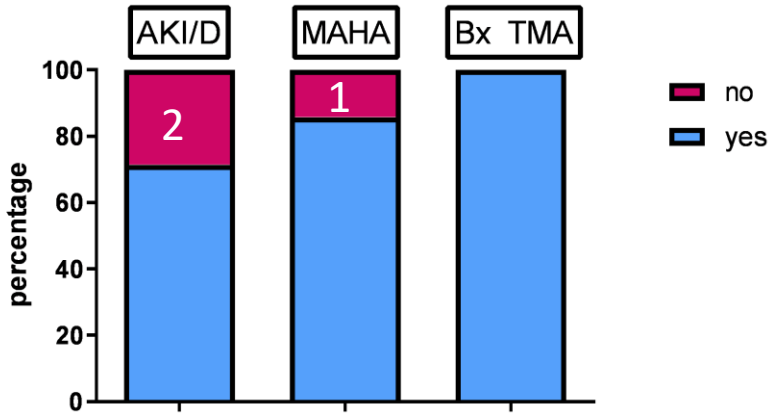
Laat recidief	N=8
Tijd tot recidief (maanden)	46m (18-69)
Bekend met aHUS	5/8 (63%)
Genetische mutatie	5/8 (63%) 7 mut
CFH C3	3/7 3/7
Hoog recidief risico Matig recidief risico	3 (38%) 5 (62%)

Mediaan, range

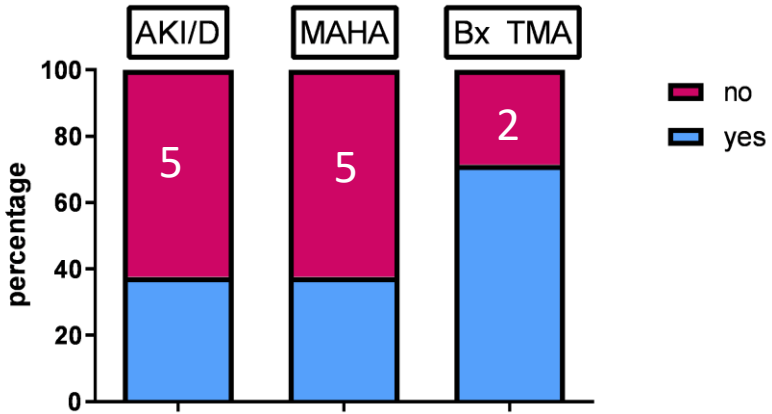
# Recidief aHUS na niertransplantatie
N=15

AKI: acute kidney injury, AKD: acute kidney disease
MAHA: microangiopatische hemolytische anemie
Bx TMA: trombose (arteriolar, glomerular) nierbiopt

Vroeg recidief	N=7

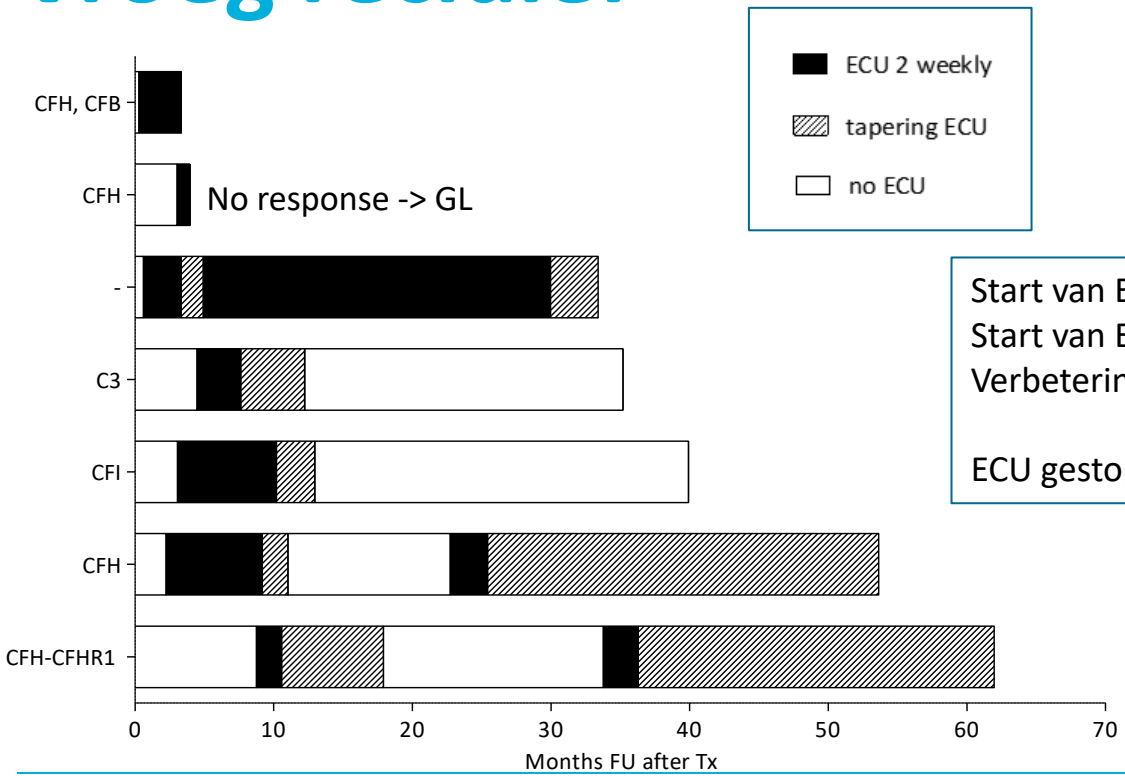


Laat recidief	N=8



Radboudumc

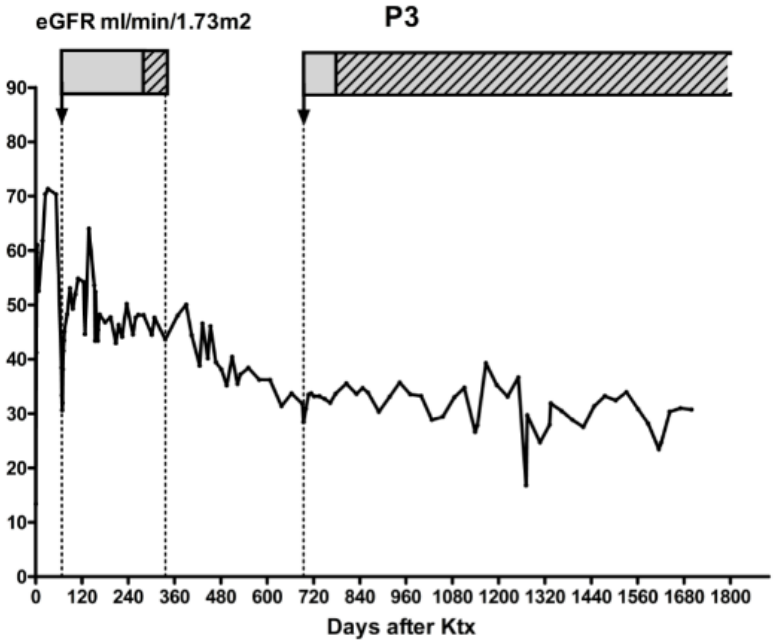
Vroeg recidief

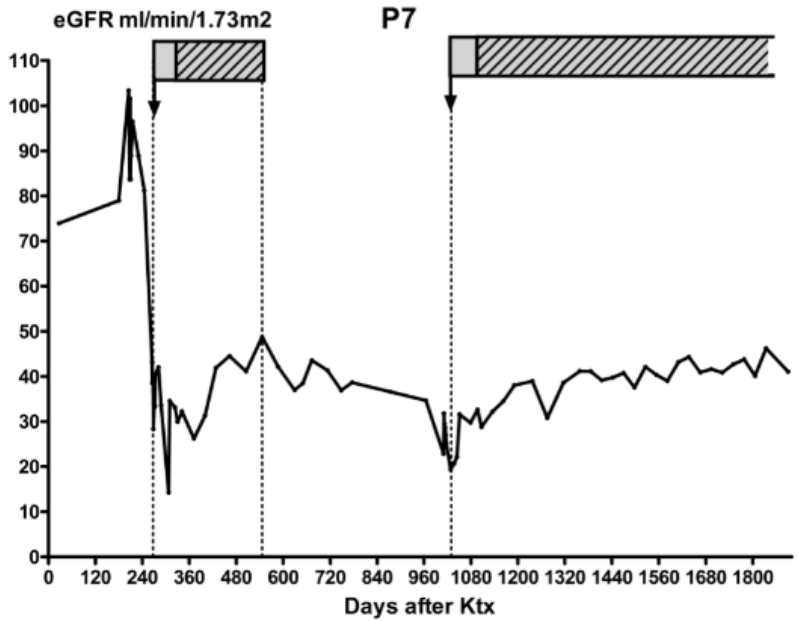


Start van ECU na detectie TMA bloed: 1d (0-4d) (n=6)
Start van ECU na laatste stabiele eGFR 14d (2-59d)
Verbetering van nierfunctie 6/7; graft loss bij 1

ECU gestopt bij 4, relapse bij 2

“Creeping creatinine”

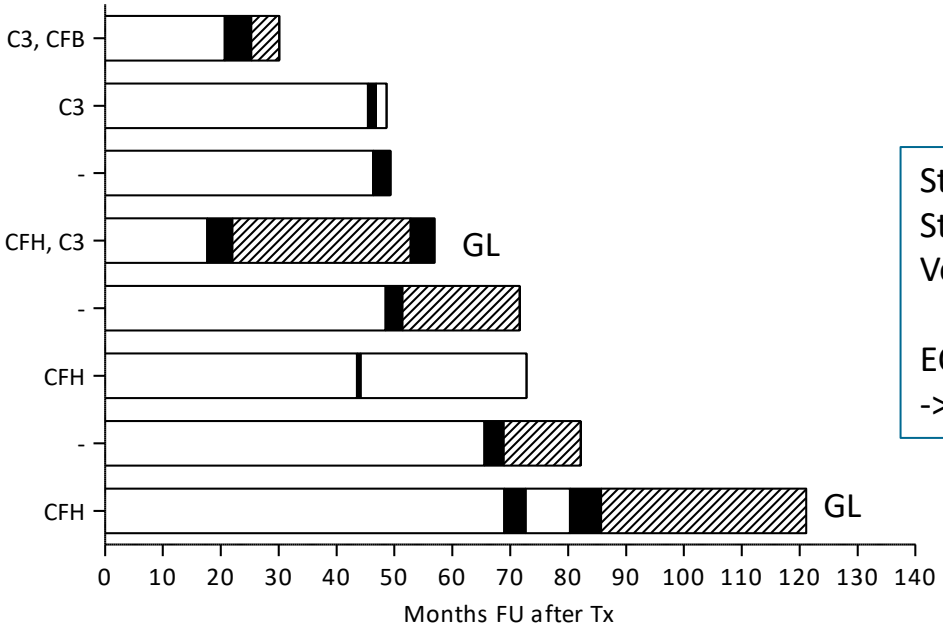


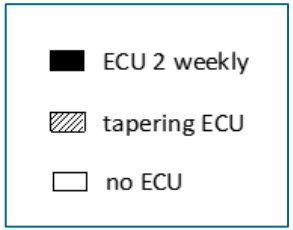


Laat recidief

- Twee “subgroepen”
  - 3 patienten met TMA in het bloed en TMA Bx en AKD
    - Trigger +
    - Snelle start na detectie TMA in het bloed
  - 5 patienten zonder TMA in het bloed en langzaam verlies eGFR
    - Vaak geen trigger, lang delay
    - 3 met TMA Bx
    - 2 (mét VG aHUS) zonder TMA Bx, wel met ABMR – is dit wel recidief?

Laat recidief





Start van ECU na detectie TMA bloed: 2d (0-5d) (n=3)
Start van ECU na laatste stabiele eGFR 285d (23-806d)
Verbetering / stabilisatie van nierfunctie 8/8

ECU gestopt bij 3 (met voldoende FU)
-> relapse bij 2 -> graft loss bij 2

Uitkomsten

Vroeg recidief	N=7	Laat recidief	N=8
FU duur na NTx (maanden)	35.2m (3-62)	FU duur na NTx (maanden)	66.9m (30-121)
FU duur na recidief (maanden)	32.8m (3-54)	FU duur na recidief (maanden)	19.8m (3-52)
Einde FU	sCr 170 (104-518) CKD-EPI 40.2 (7-51)	Einde FU	sCr 200 (84-593) CKD-EPI 30.2 (7-80)
Graft loss	1 (non-responder)	Graft loss	2

Mediaan, range

Conclusie

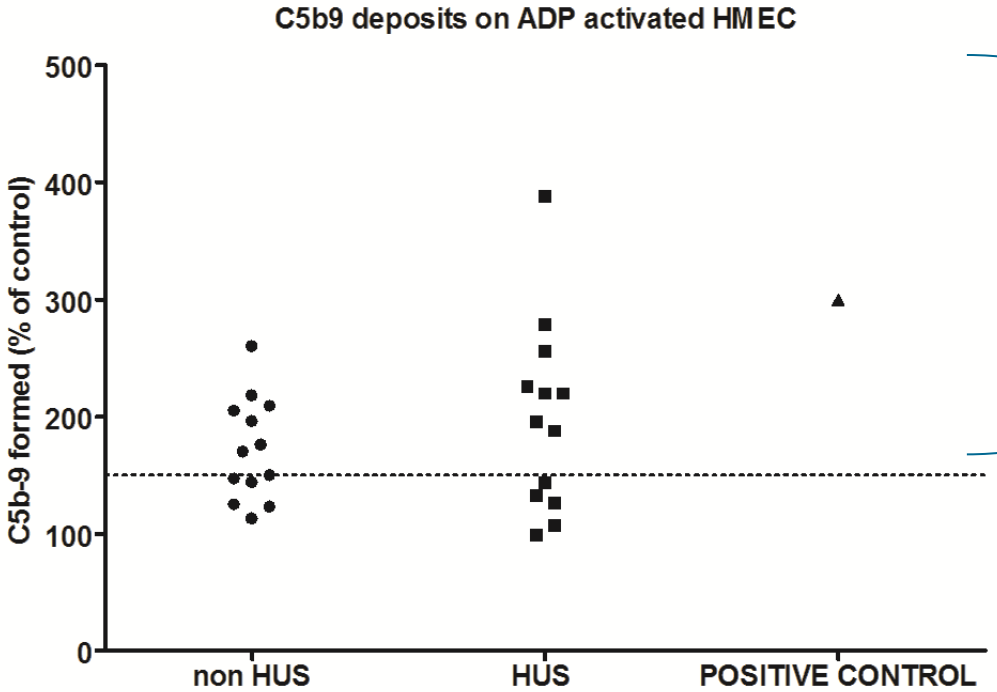
- Vroege aHUS recidieven zijn herkenbaar (AKI/AKD, MAHA, TMA Bx), resulterend in snelle start eculizumab
- Late aHUS recidieven zijn lastig herkenbaar, door ontbreken AKI/AKD en MAHA, resulterend in delay tot start eculizumab en beperkte transplantaatfunctie
- Na staken van eculizumab regelmatig relapse aHUS, ook moeilijk herkenbaar
- Toch: substantiële groep aHUS patienten krijgt geen recidief na NTx, waardoor standaard eculizumab profylaxe niet kosten-effectief lijkt
- Toekomst: verbetering risico profiel, biomarkers voor renale aHUS activiteit

Discussie of vragen?

Mogelijkheid tot verbetering uitkomst?

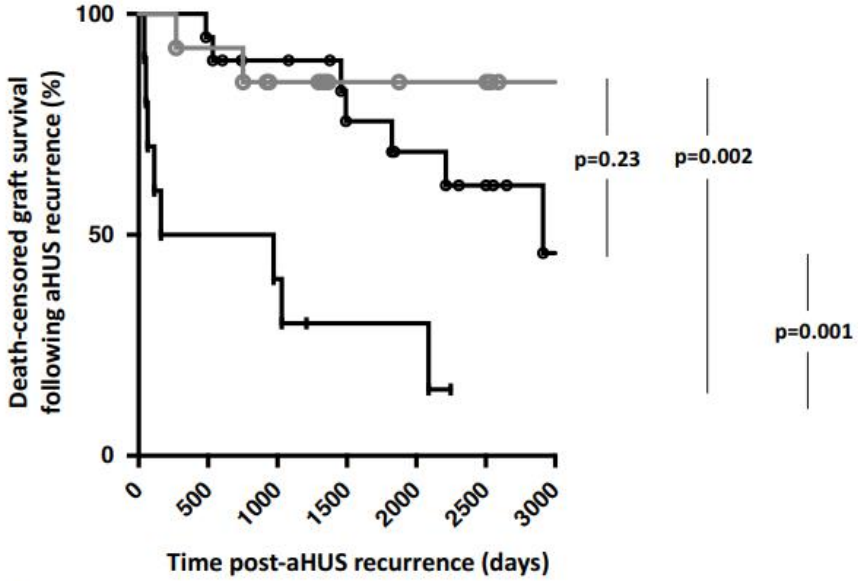
- Bij alle bekende aHUS patienten met achteruitgang van transplantaatfunctie (zoals DGF) 1 gift eculizumab geven, terwijl er diagnostisch onderzoek gedaan wordt
- Bij creeping creatinine zonder MAHA -> nierbiopt. Indien geen histologische oorzaak voor achteruitgang is: proefbehandeling eculizumab
  - Uitleesmaat? Nierfunctie? Biomarkers?
- Eculizumab niet meer staken na posttransplantatie aHUS?
- Pten met pathogene CFH variant wel profylaxe geven?
- In het transplantatie centrum vervolgen door aHUS arts

C5b-9 assay?



Actieve aHUS?

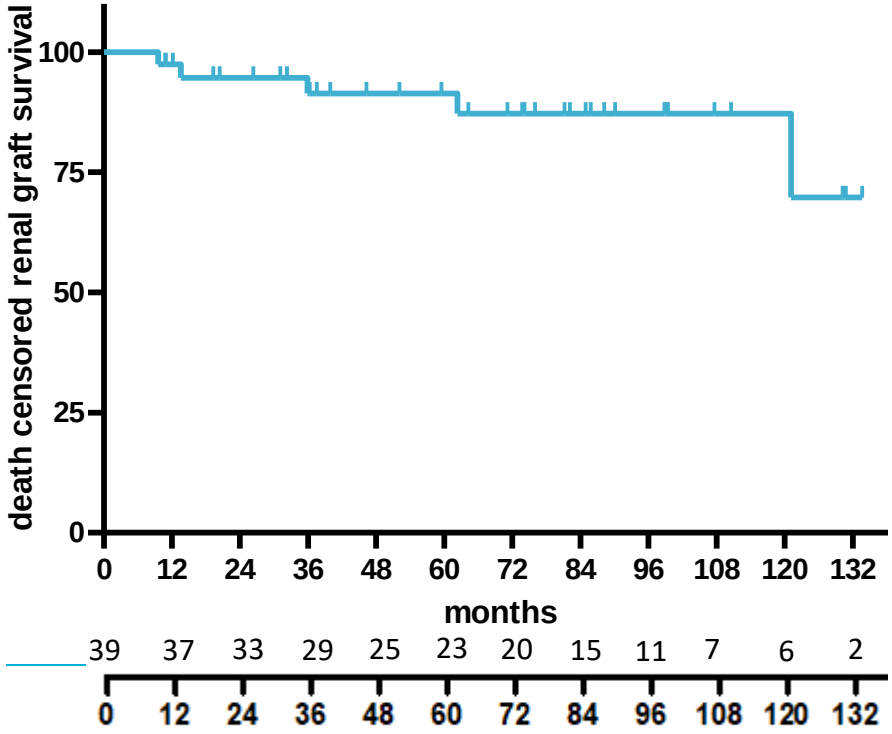
Survival Frankrijk rescue therapie

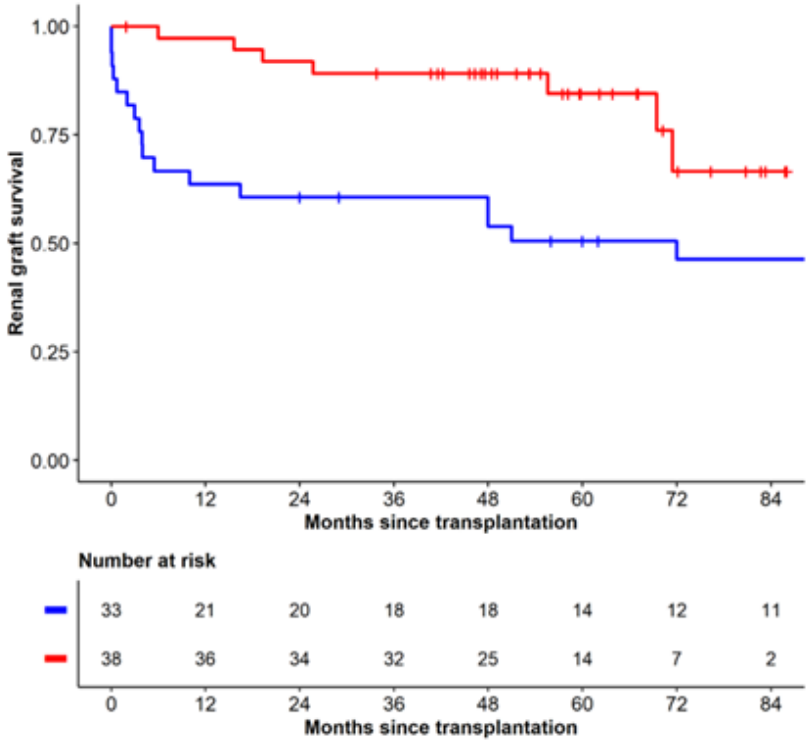


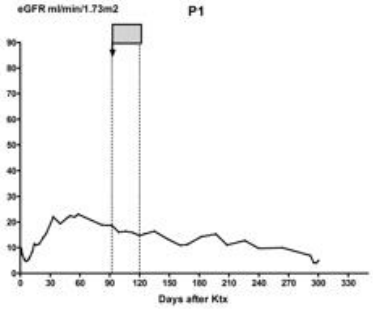
		At risk						
Eculizumab	● > 1 week	19	19	16	12	10	8	4
	⊖ ≤ 1 week	13	13	10	5	5	5	2
No Eculizumab	+	10	6	5	3	3	0	0

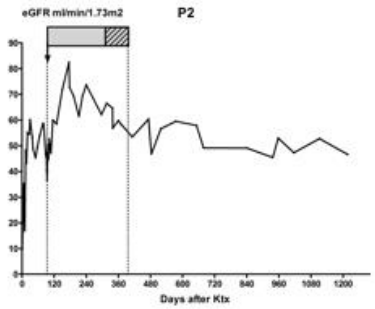
Graft survival + CUREiHUS data

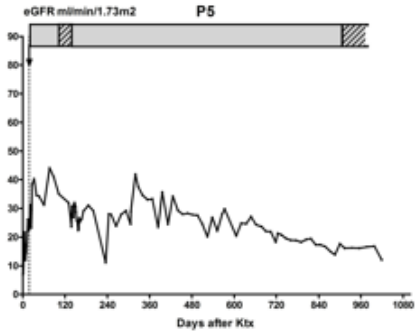
Ntx Radboud 2011-2022 plus CUREiHUS

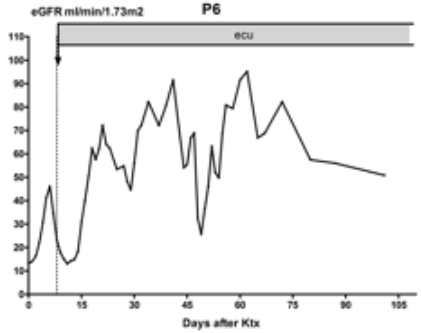


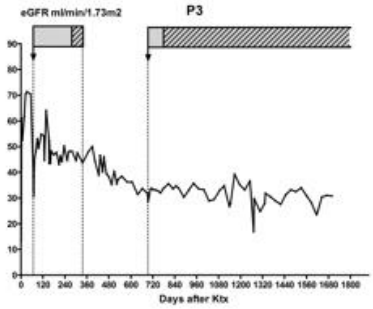


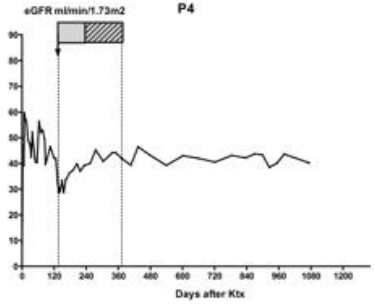

eGFR ml/min/1.73m2
P1
Days after Ktx

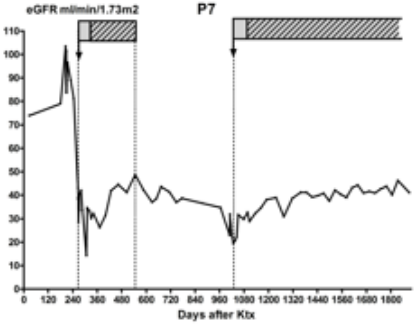

eGFR ml/min/1.73m2
P2
Days after Ktx

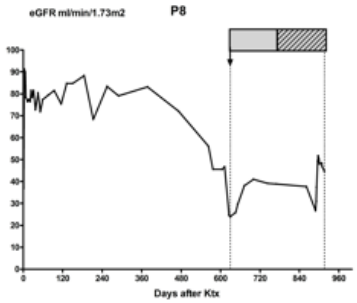

eGFR ml/min/1.73m2
P5
Days after Ktx

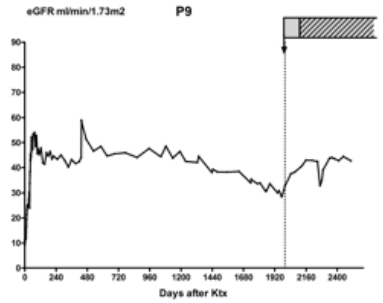

eGFR ml/min/1.73m2
P6
ecu
Days after Ktx

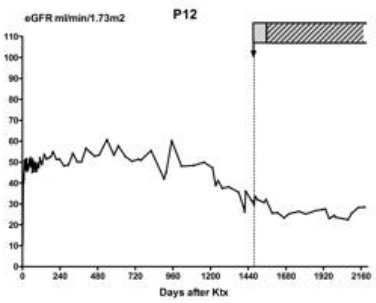

eGFR ml/min/1.73m2
P3
Days after Ktx

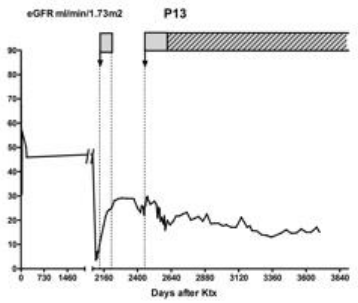

eGFR ml/min/1.73m2
P4
Days after Ktx

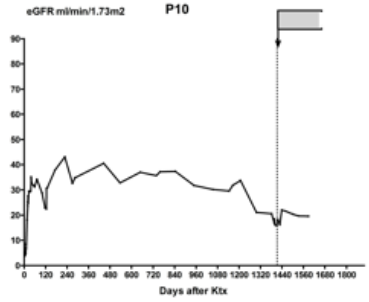

eGFR ml/min/1.73m2
P7
Days after Ktx


eGFR ml/min/1.73m2
P8
Days after Ktx


eGFR ml/min/1.73m2
P9
Days after Ktx


eGFR ml/min/1.73m2
P12
Days after Ktx


eGFR ml/min/1.73m2
P13
Days after Ktx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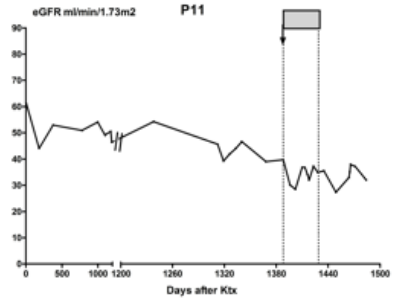
P10
Days after Ktx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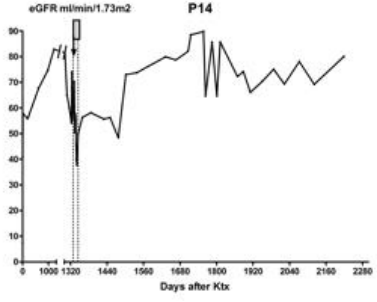
P11
Days after Ktx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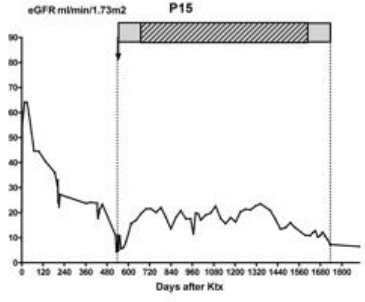
P14
Days after Ktx


eGFR ml/min/1.73m2
P15
Days after Ktx

Supplemental Table 1: characteristics of patient (N=15) with CKD stage ≤3 and stage ≥4 at end of the CUREiHUS study

Variables	eGFR ≥30 ml/min/1.73m² (n=9)	eGFR <30 ml/min/1.73m² (N=6)
Female	6/9	6/6
Age at Ktx (years)	42.1 (24.4-58.2)	42.4 (22.0-66.3)
Early recurrence	5/9	2/6
KDIGO high recurrence risk	7/9	1/6
Genetic variant	8/9	3/6
(Likely) pathogenic genetic variant	6/8	0/3
Laboratory signs of TMA	6/9	3/6
TMA kidney biopsy	6/7	5/6
Last stable eGFR (ml/min/1.73m²)	58.5 (46.1-88.9)	41.7 (21.7-49.9)
Interval from last stable eGFR to start ECU (days)	37.0 (2-806)	176.5 (4-569)
eGFR at start of ECU (ml/min/1.73m²)	33.4 (32.2-60.1)	18.3 (3.8-29.4)
UPCR at start of ECU (ml/min/1.73m²)	2.2 (0.31-11.9) (n=8)	1.6 (0.5-11.8)

Values are given as median (range)

Abbreviations: ECU: eculizumab, eGFR: estimated glomerular filtration rate (CKD-EPI), Ktx: kidney transplantation, RRT: renal replacement therapy, TMA: thrombotic microangiopathy, UPCR: urine protein-creatinine ratio.

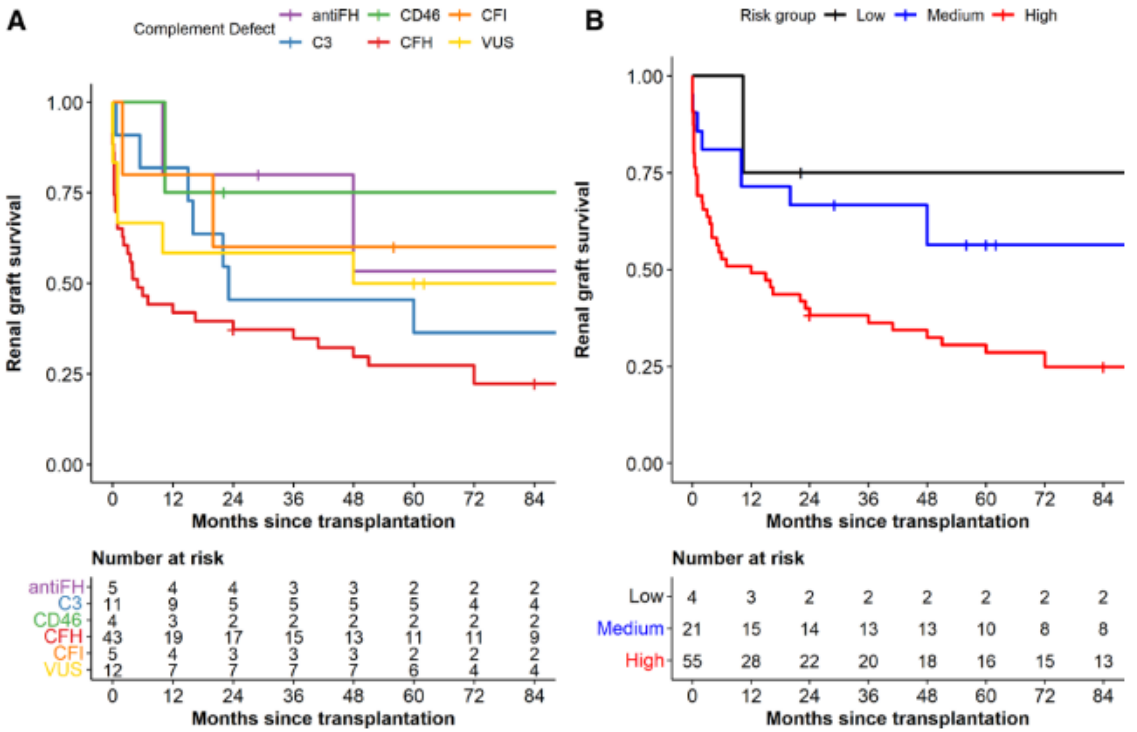
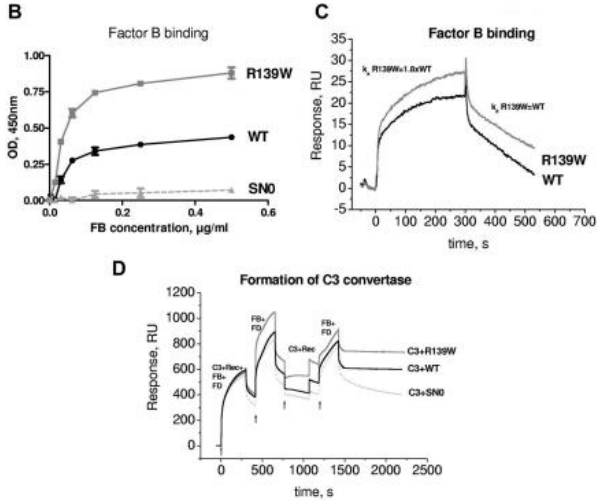
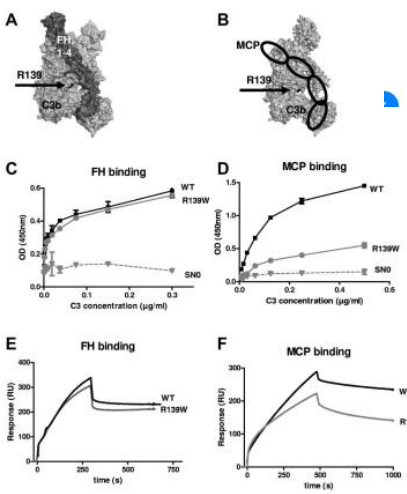


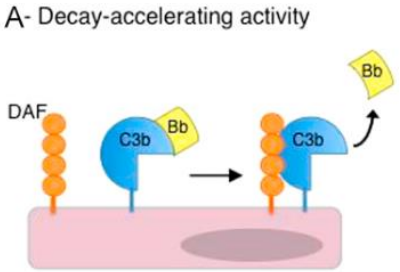
FIGURE 3. Death-censored renal graft survival without eculizumab treatment. Kaplan-Meier analysis of overall renal graft survival in recipients transplanted between 1978 and 2016 for atypical hemolytic uremic syndrome who did not receive eculizumab treatment with the transplant. Survival is censored for patient death with a functioning graft and for functioning graft at last follow-up. Numbers at risk in each group at 12 monthly time points are detailed below the graph. A. Graft survival by complement defect. Grafts grouped by presence of autoantibodies against Factor H (anti-FH), variant of uncertain significance (VUS) or pathogenic variant in complement factor I (CFI), complement factor H (CFH), membrane cofactor protein (CD46), or C3 in recipient. B. Graft survival by risk of relapse. Grafts grouped by low, medium, or high risk of atypical hemolytic syndrome recurrence (as stratified by KDIGO)[3] in the recipient.

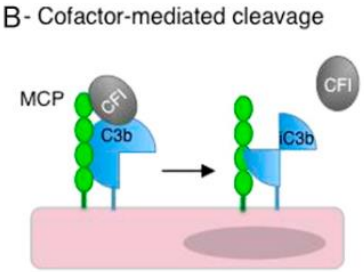
R161W

- Gain of function mutatie -> hyperactief C3 convertase
  - Verhoogd affiniteit voor factor B
  - Verminderde binding van MCP
  - Normale factor H regulatie









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