Données du registre international du SHU atypique

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Conflicts of interest

- Alexion:
  - Expertises;
  - Research grants;
  - Clinical trials;

Aims of the International aHUS Registry

launched in April 2012 and funded by Alexion Pharmaceutical

- To improve knowledge about the natural history and evolution of aHUS
- To evaluate
  - the efficacy of and tolerance of treatments, including eculizumab
  - the quality of life of aHUS patients
- To collect prospectively clinical and biological data in aHUS patients treated by eculizumab in real life for reglementary authorities

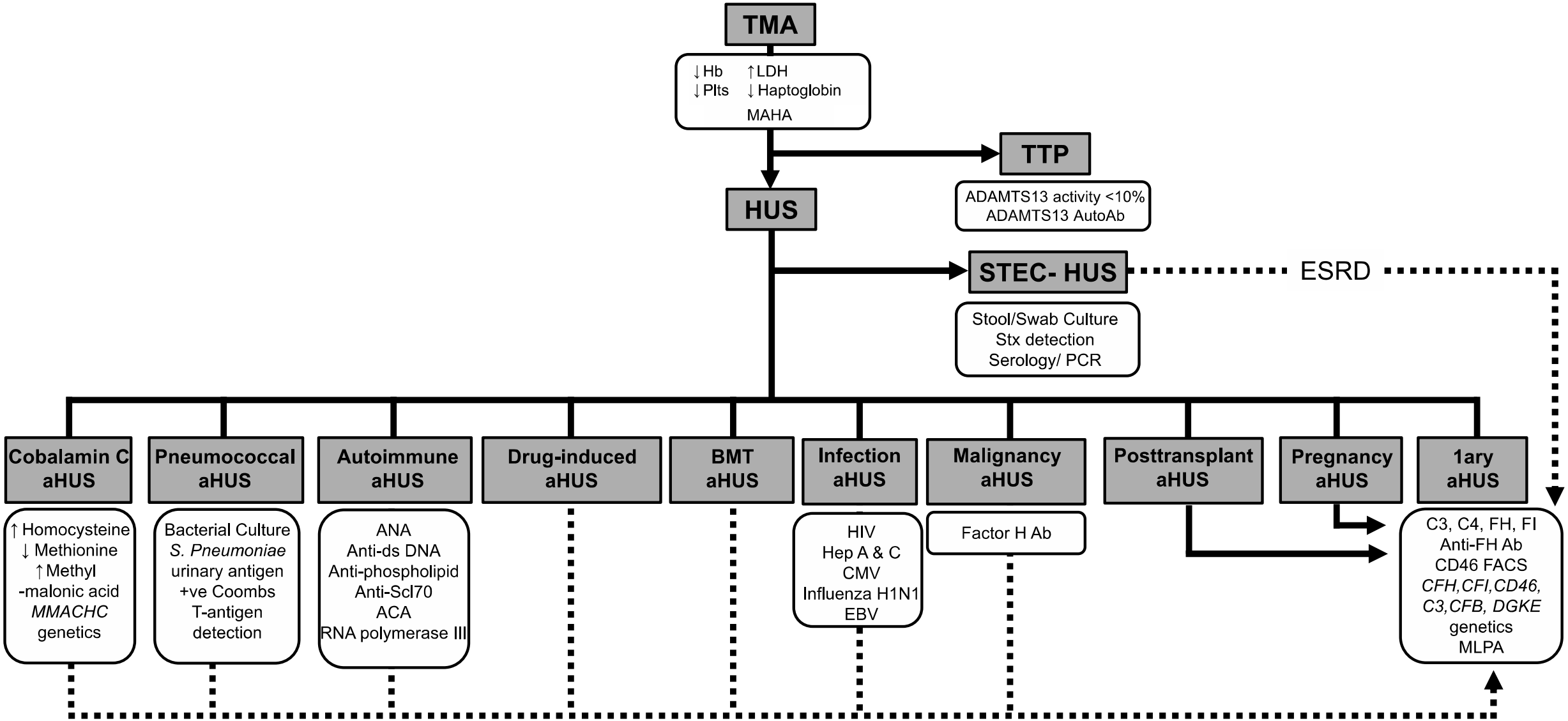
Schema

- Observational, non interventional study
- International
- Multi-centric
- Retro and prospective
- For a minimal 5 years of recruitment
- And 5 year of prospective follow up per patient

TMA diagnostic flow chart

aHUS and C3 glomerulopathy: a KDIGO conference report

Kidney Int., 2016



Methods (1)

- **Inclusion/exclusion criteria**
  - Every patient with a diagnosis of aHUS can be included:
    - With or without identified mutation, or anti-CFH antibody
    - Treated or not with eculizumab
  - Patients with STEC-induced HUS and those with ADAMTS-13 < 5% (TTP) are excluded
- **Data collection**: at inclusion and then every 6 months
  - Demographics, past medical history and current disease history
  - Clinical signs and biological results
  - TMA-related signs, tolerance of eculizumab, or other treatments
  - Auto-evaluation of the clinical status by the patients

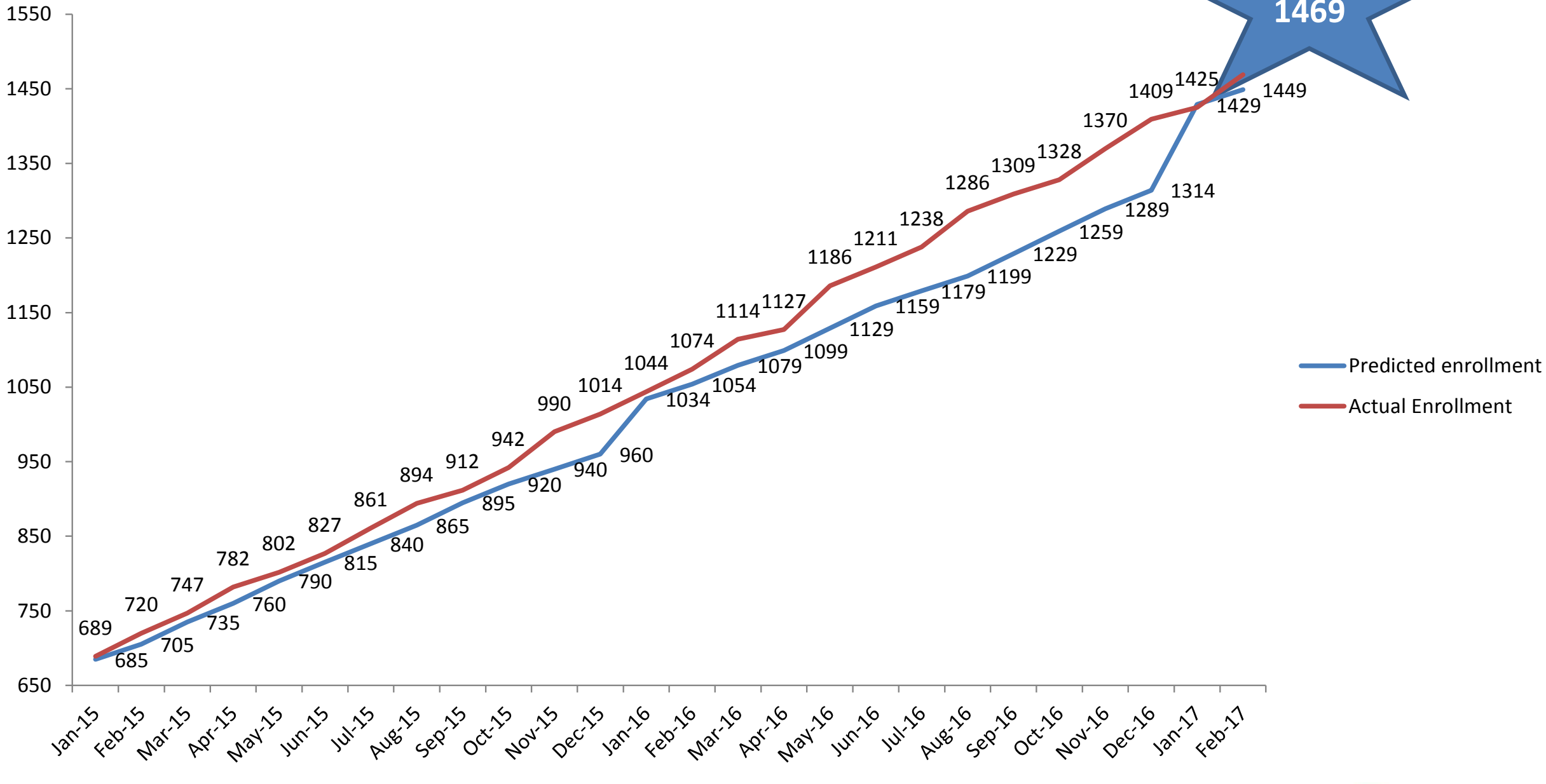
Methods (2)

- **Data analysis**
  - Entry in the study is defined by date of inclusion if not treated by eculizumab or date just before the initiation of eculizumab
  - Patients with the following data are analyzed in the present report:
    - DOB, sex, date of inclusion
    - Treatment with eculizumab or not
    - Date of first dose of eculizumab
- **Funding and organization**: the registry is funded by Alexion Pharmaceuticals, Inc., and is supervised by an independent consultative scientific committee, and national coordinators from each participating countries

Evaluation criteria

- TMA signs and complications (see below)
- Adverse secondary events :
  - All infections, and particularly by encapsulated bacteria: Neisseria Meningitidis, Neisseria Gonorrhea, Streptococcus pneumoniae, Haemophilus influenza
  - Manifestations at infusion
  - Immunogenicity/ADA (AntiDrug Antibody)
  - Renal and liver involvment
  - cancer
  - Death
- Delay between first signs and occurrence of secondary events
- Pregnancy

Recruitment Actual vs Predicted

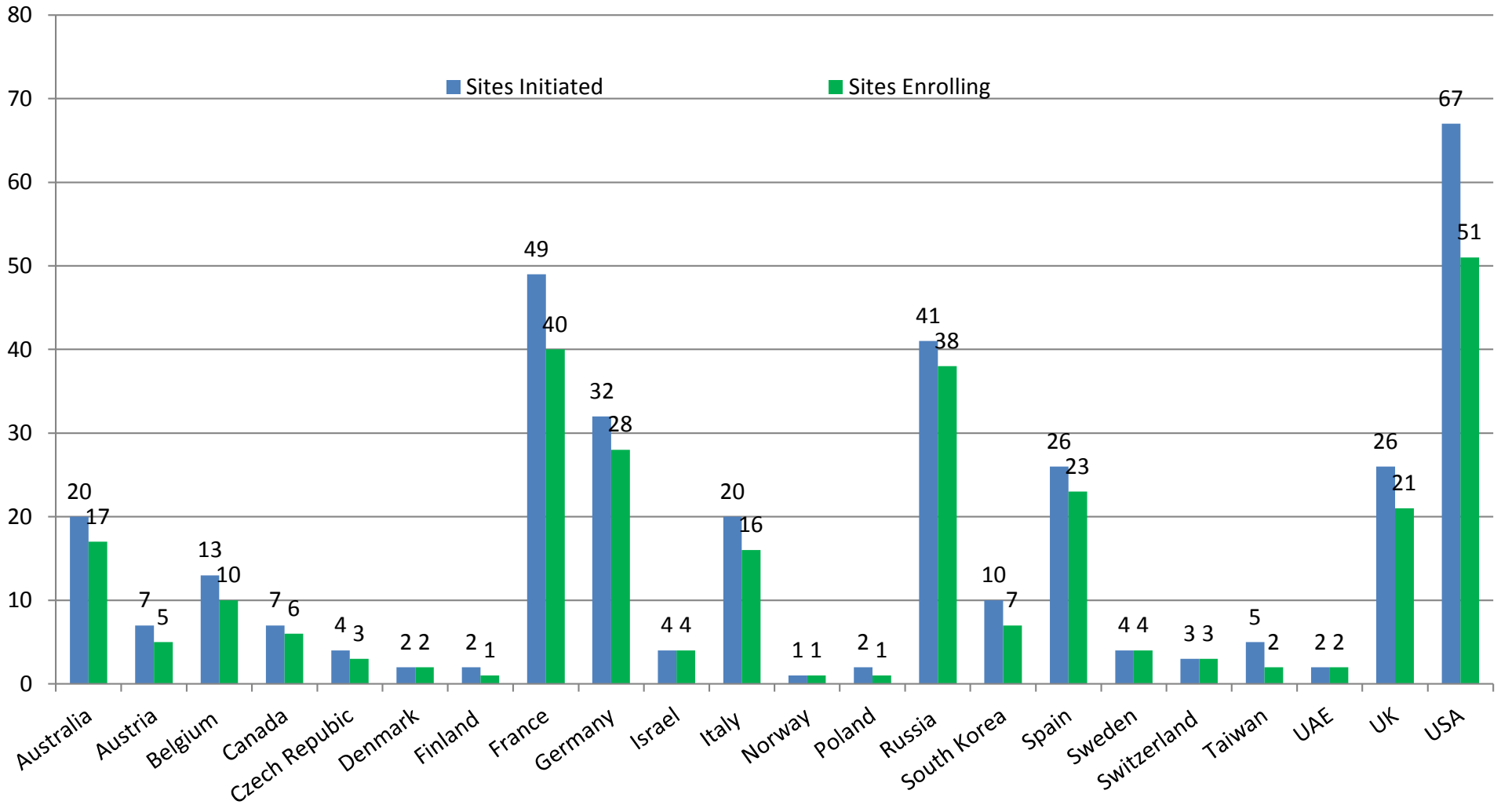


aHUS registry global status (23 february 2017)

Number of Countries Targeted		Forecasted 2017	Actual 2017
Number of Countries Open	22	0	0
Countries under setup process	Turkey	1	0
Number of sites initiated	347	Up to 35	6, initiated
Actual number of patients enrolled	1469	300	44
Number of sites with Enrolled Patients	285	90%	82.1%

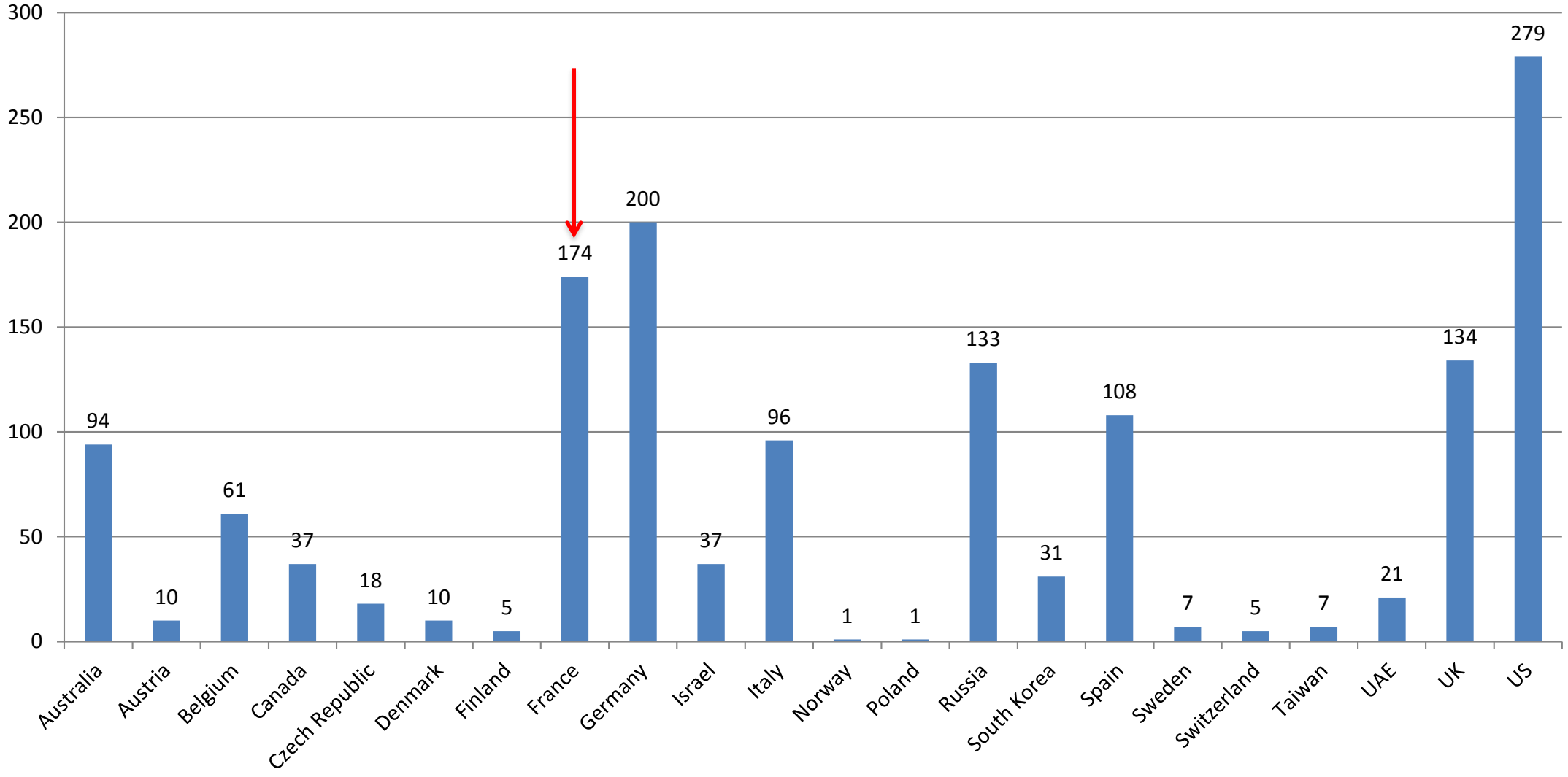
Sites Open and Enrolling by Country

as of 23 February 2017

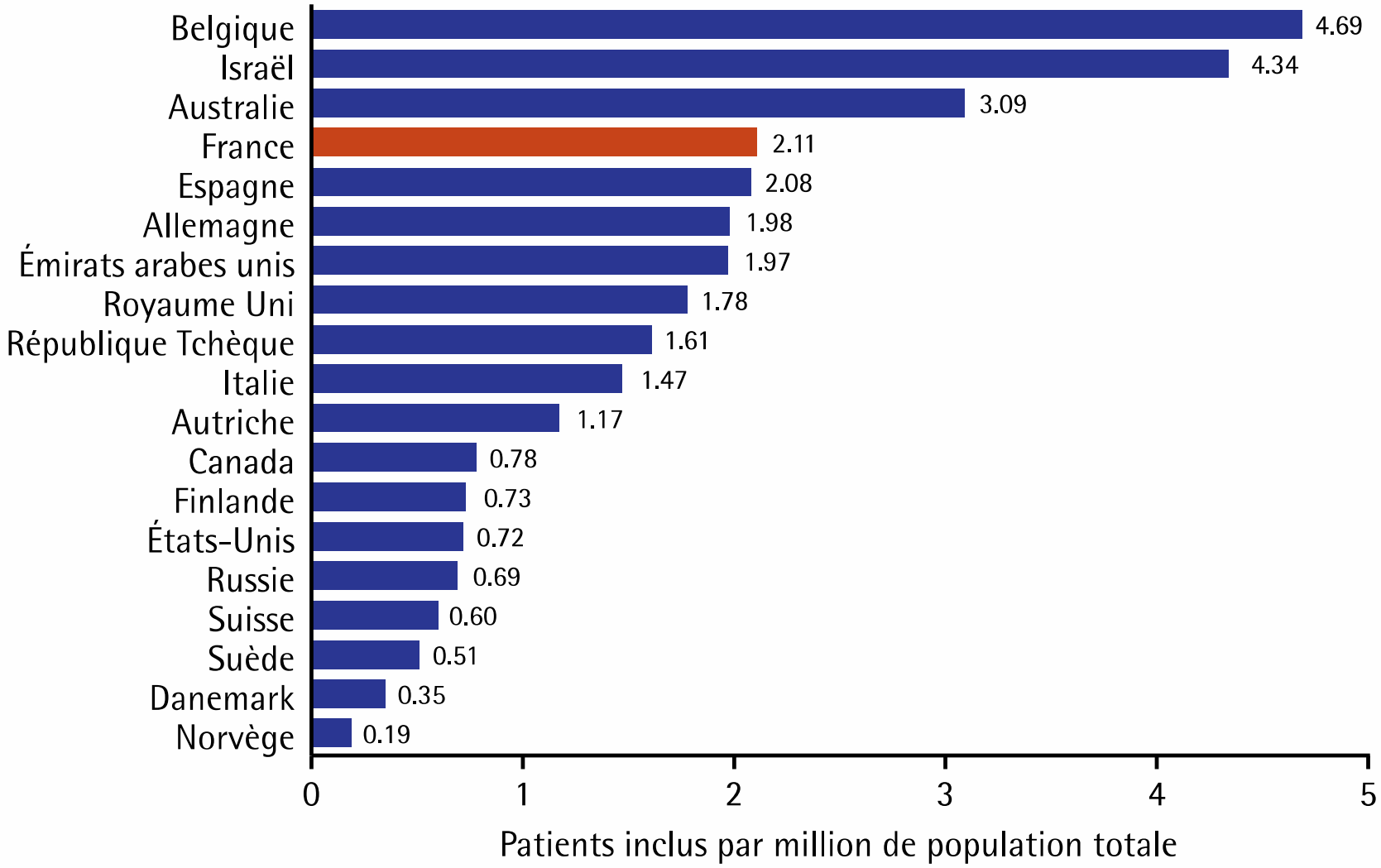


aHUS Registry Patients Enrolled by Country

as of 23 February 2017



Inclusions per countries



International registry of aHUS

On August 2017

- 22 countries
- 332 opened centers (90% active)
- Number of included patients: 1613
  - In France: 184

Demographic data (26 Feb. 2016)

Total registry (n=1054)

French registry (n=107)

	Children (n=397)	Adults (n=657)	Children (n=25)	Adults (n=82)
Female sex, n(%)	184 (46)	408 (62)	10 (40)	56 (68)
Familial history of aHUS, n (%)	60 (15)	90 (14)	9 (36)	20 (24)
Age at diagnosis, y, median (extremes)	3.8 (0-17.3)	34.4 (0.1-90.6)	0.9 (0-15.7)	32.3 (0.3-79.7)
- N (%) < 2y > 18y	 147 (38) -	 16 (3) 567 (90)	 16 (70) -	 3 (4) 60 (82)
Delay between diagnosis and inclusion, y	1.6 (0-17.1)	1.3 (0-50.6)	3.8 (0.4-15.3)	3.7 (0-32)

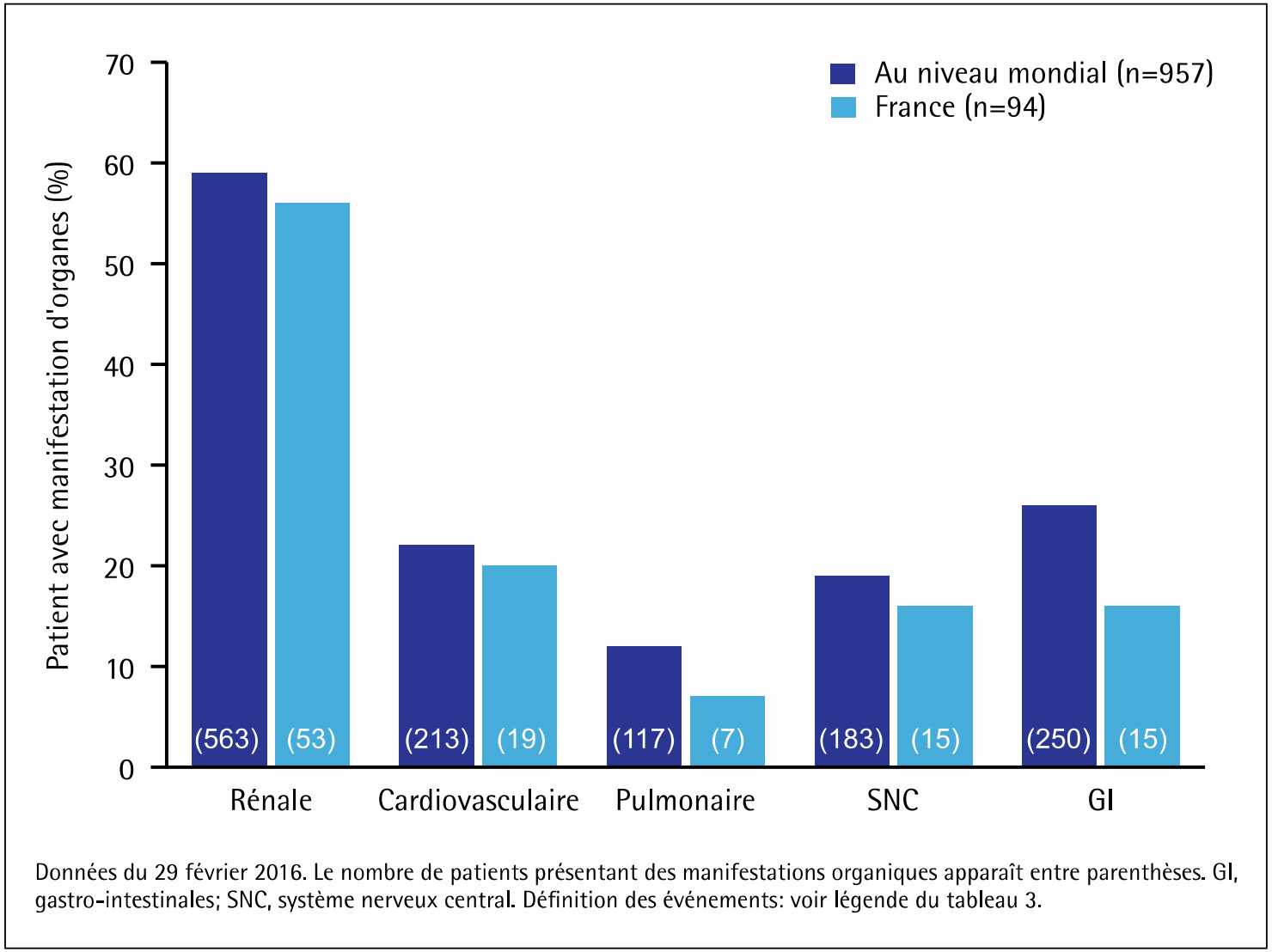
Associated diseases or precipitating factors of aHUS in 121 patients out of 851 (14%)

	None N=730	Renal transplant N=36	Cancer N=36	Pregnancy N=26	Auto Immune disease N=22	Maligant hypertension N=10
Delay between aHUS and coexisting disease (Month)	-	0.9 (0.1-10.9)	24.7 (6.6-64.9)	0.2 (0-8)	47 (4.4-147.9)	0 (0-13.6)
Mutation or anti-CFH Ab, n (%)	230 (32)	5 (14)	3 (8)	3 (12)	3 (14)	4 (40)
No mutation or anti-CFH Ab, n (%)	101 (14)	4 (11)	4 (11)	5 (19)	2 (9)	0 (0)
Unknown genetic status	399 (55)	27 (75)	29 (81)	18 (69)	17 (77)	6 (60)

Treatments and signs of TMA before inclusion in the registry (FRANCE)

	Treated with eculizumab		Never treated with eculizumab	
Treatments	**Children N=18**	**Adults N=48**	**Children N=10**	**Adults N=48**
Renal Tx, n(%)	3 (17)	16 (33)	1 (10)	6 (33)
Dialysis, n(%)	8 (44)	36 (75)	4 (40)	13 (72)
PP:PE, n(%)	9(50)	32(67)	3(30)	13(72)
Signs				
Renal	13(72)	37(77)	0(0)	3(17)
Cardiovascular	7(39)	11(23)	0(0)	1(6)
GI	3(17)	12(25)	0(0)	3(17)
CNS	5(28)	8(17)	0(0)	2(11)

Renal and extrarenal manifestations in the 6 months before inclusion



Données du 29 février 2016. Le nombre de patients présentant des manifestations organiques apparaît entre parenthèses. GI, gastro-intestinales; SNC, système nerveux central. Définition des événements: voir légende du tableau 3.

Treatment by eculizumab

	World registry		French registry	
	Children (n=397)	**Adults (n=657)**	**Children (n=24)**	**Adults (n=73)**
Who received ecumizumab, n (%) - Before inclusion	247 (66) 223 (90)	400 (65) 338 (85)	14 (58) 14 (100)	55 (75) 54 (98)
Delay between aHUS diagnosis and eculizumab administration, month, (extremes)	0.72 (-1.2-204.0)	0.60 (-1.2-435.6)	1.08 (-1.2-153.6)	2.28 (0.0-320.4)
Stop eculizumab, n (%)	50 (22)	104 (27)	1 (8)	16 (30)
Resumed eculizumab after stop n (%)	12 (24)	13 (13)	1 (100)	4 (25)
Duration of treament, year (extremes)	1.5 (0.01-5.8)	1.0 (0.01-6.9)	2.1 (0.4-5.8)	1.3 (0.01-5.4)

Scientific projects

- Prognosis of aHUS according to:
  - Genetic variants
  - Treatments (plasma and/or eculizumab)
- aHUS and pregnancy
- aHUS and transplantation
- aHUS and malignant hypertension
- aHUS secondary to:
  - Chemotherapy
  - Cancer
  - Auto-immune diseases

Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome

Franz Schaefer[1], Gianluigi Ardissino[2], Gema Ariceta[3], Fadi Fakhouri[4], Marie Scully[5], Nicole Isbel[6], Åsa Lommelé[7], Varant Kupelian[8], Christoph Gasteyger[8], Larry A. Greenbaum[9], Sally Johnson[10], Masayo Ogawa[8], Christoph Licht[11], Johan Vande Walle[12] and Véronique Frémeaux-Bacchi[13]; on behalf of the Global aHUS Registry

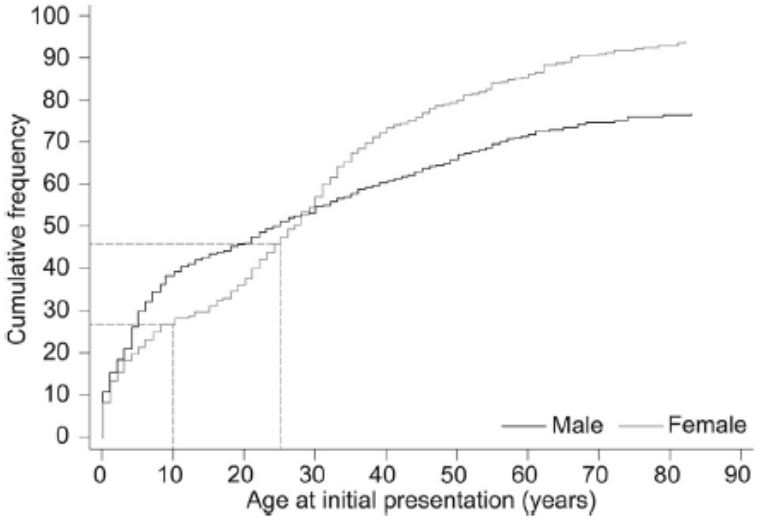
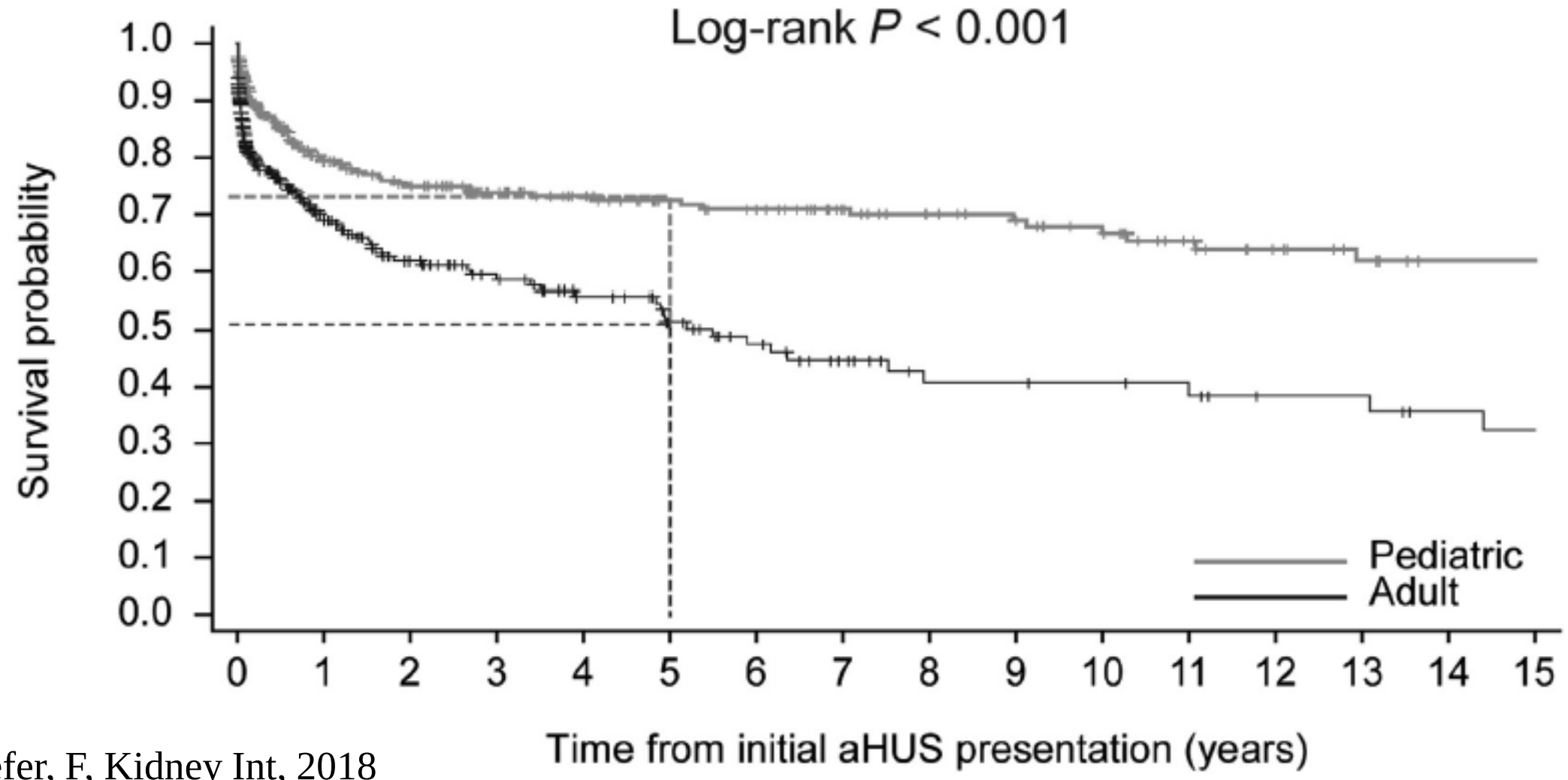


Table 2 | Prevalence of complement abnormalities

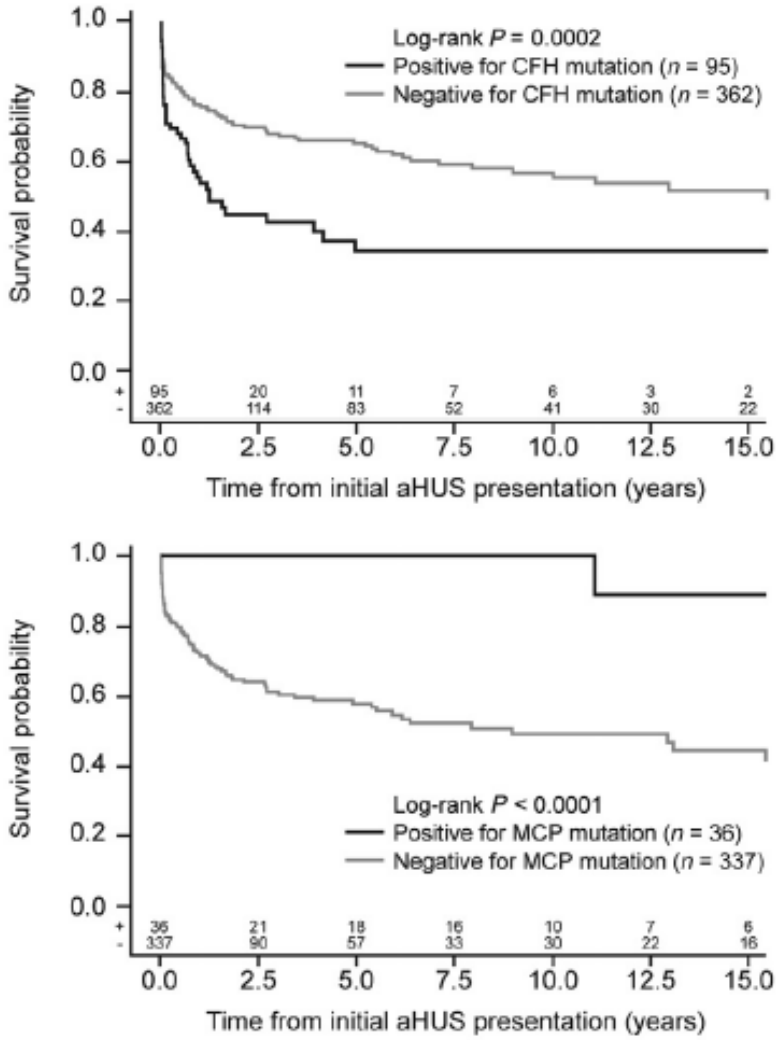
Complement abnormality	Age at presentation, yr, median (IQR)	All patients	Initial presentation in childhood	Initial presentation in adulthood	*P* value (childhood vs. adulthood)
		n with complement abnormality/*n* screened (%)[a]			
Any identified mutation[b] or anti-CFH Ab		119/267 (45)	58/136 (43)	61/131 (47)	0.5197
Any identified mutation[b]		104/267 (39)	50/136 (37)	54/131 (41)	0.4533
CFH	19.8 (1.1–30.4)	100/482 (21)	48/234 (21)	52/248 (21)	0.9020
CD46 (MCP)	5.3 (2.3–16.6)	37/395 (9)	28/196 (14)	9/199 (5)	0.0009
CFI	35.9 (21.8–48.5)	26/406 (6)	5/190 (3)	21/216 (10)	0.0036
CFB	6.0 (2.9–16.8)	4/275 (2)	3/141 (2)	1/134 (1)	0.6227
C3	22.4 (2.5–32.6)	21/331 (6)	8/166 (5)	13/165 (8)	0.2536
Anti-CFH Ab	13.1 (6.1–31.3)	86/402 (21)	47/200 (24)	39/202 (19)	0.3053

Renal survival in aHUS (international registry)



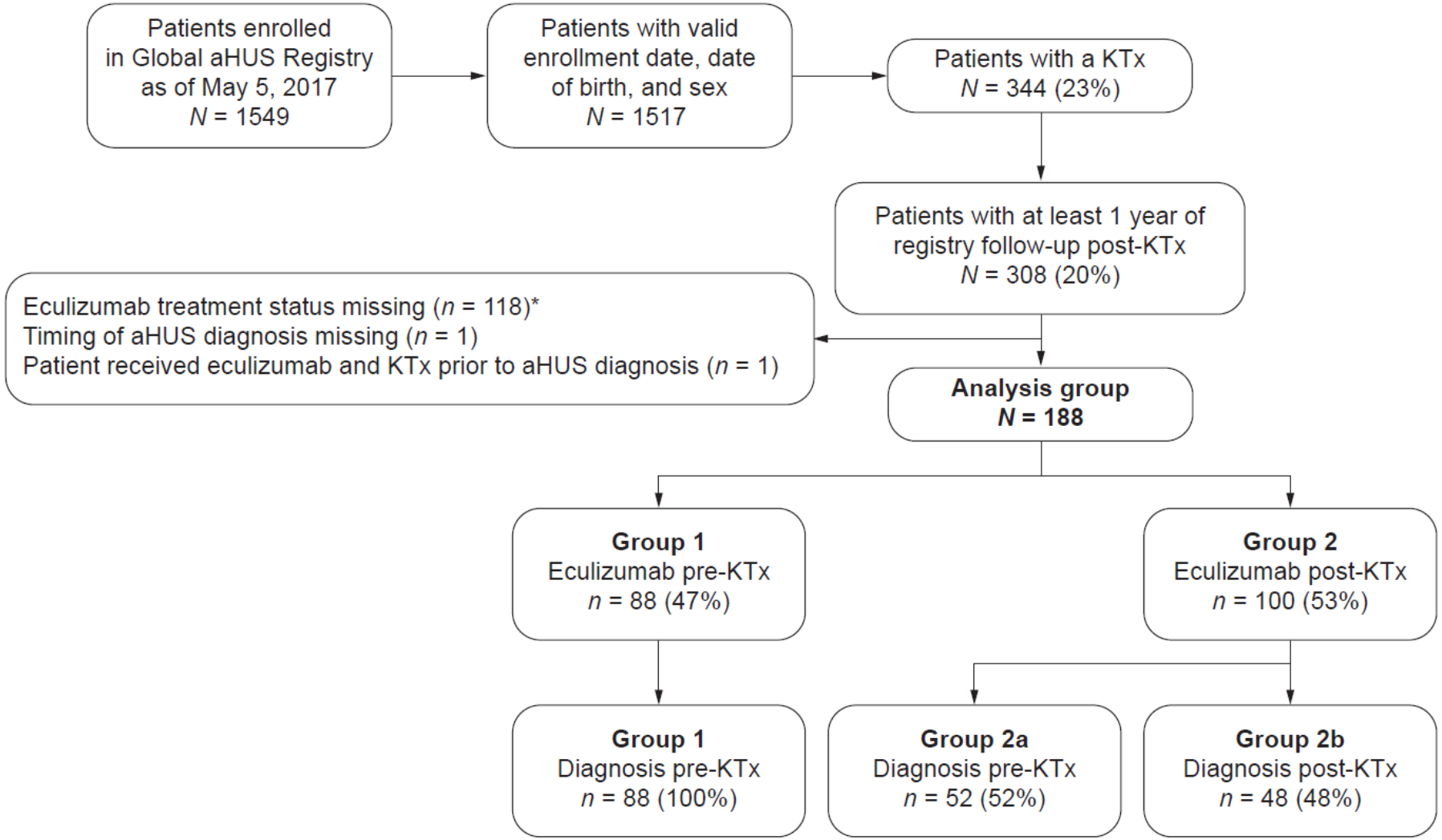
Schaefer, F, Kidney Int, 2018

Renal survival in aHUS (international registry)



Schaefer, F, Kidney Int, 2018

Kidney transplantation in patients with aHUS: data from the global aHUS registry, *KI Reports, 2018*



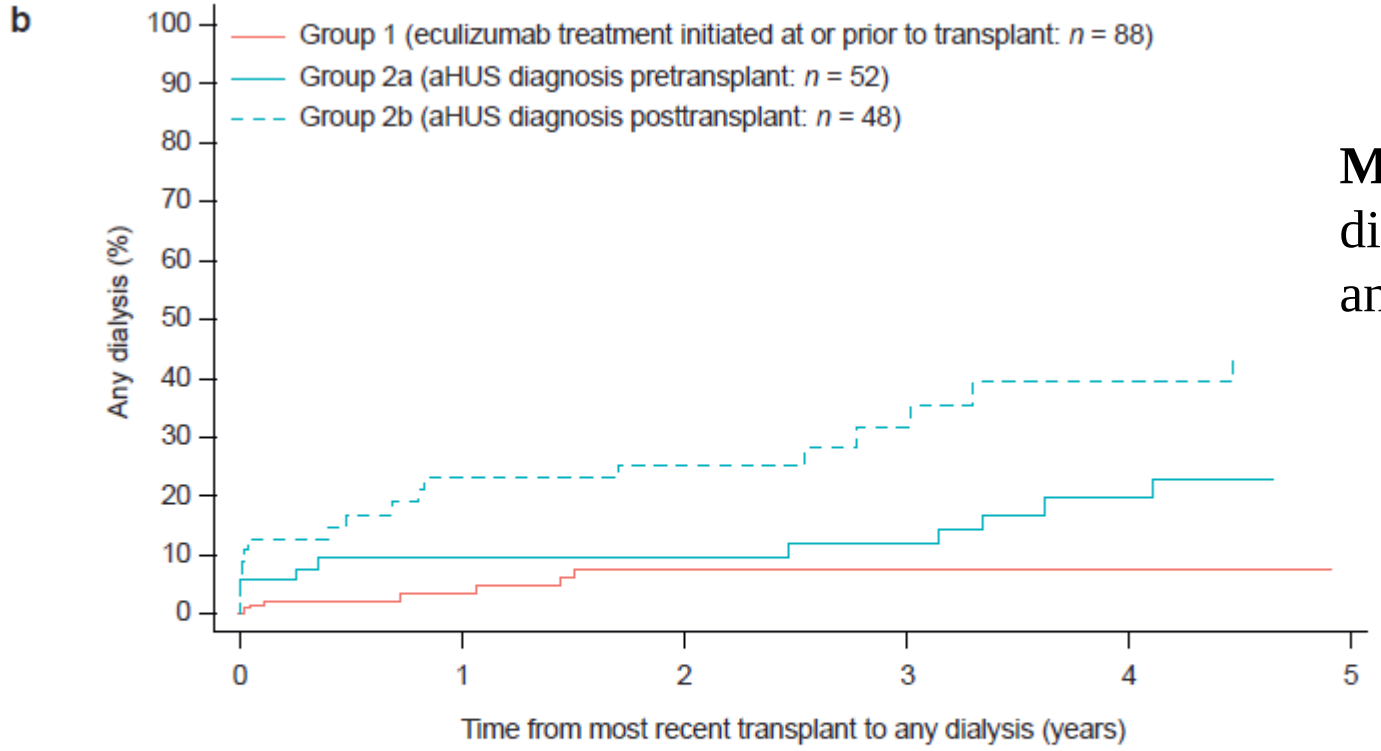
Kidney transplantation in patients with aHUS: data from the global aHUS registry

Table 1. Baseline demographics

n (%), unless stated	Group 1	Group 2 Eculizumab initiated after transplant	
	Eculizumab initiated at or before transplant ($n = 88$)	Group 2a aHUS diagnosis pretransplant ($n = 52$)	Group 2b aHUS diagnosis posttransplant ($n = 48$)
Median age at most recent KTx, y (range)	32.3 (3.0–70.2)	33.5 (2.3–67.2)	39.5 (2.9–75.3)
Age at most recent transplant, yr			
<18	27 (31)	14 (27)	8 (17)
≥18	61 (69)	38 (73)	40 (83)
Gender, female	45 (51)	29 (56)	31 (65)
Race			
Asian	0 (0)	1 (2)	3 (6)
Black	4 (5)	2 (4)	5 (10)
White	83 (94)	48 (92)	34 (71)
Other	1 (1)	0 (0)	6 (13)
Family history	25 (28)	11 (21)	2 (4)
Total number of KTx			
1	64 (73)	41 (79)	45 (94)
2	14 (16)	7 (14)	3 (6)
≥3	10 (11)	4 (8)	0 (0)
Concomitant etiologies contributing to need for transplant[a]			
Diabetes	0 (0)	1 (1)	3 (6)
Hypertension	1 (1)	0 (0)	4 (8)
Pathogenic mutation identified, *n*/*N* (%)[b]			
CFH	34/68 (50)	22/37 (60)	7/28 (25)
C3	9/42 (21)	5/22 (23)	1/21 (5)
CFI	6/53 (11)	0/26 (0)	5/26 (19)
MCP	9/54 (17)	0/23 (0)	3/24 (13)
CFB	1/41 (2)	0/18 (0)	1/19 (5)
Incidence of plasma exchange before transplant	16 (18)	13 (25)	3 (6)

KI Reports, 2018

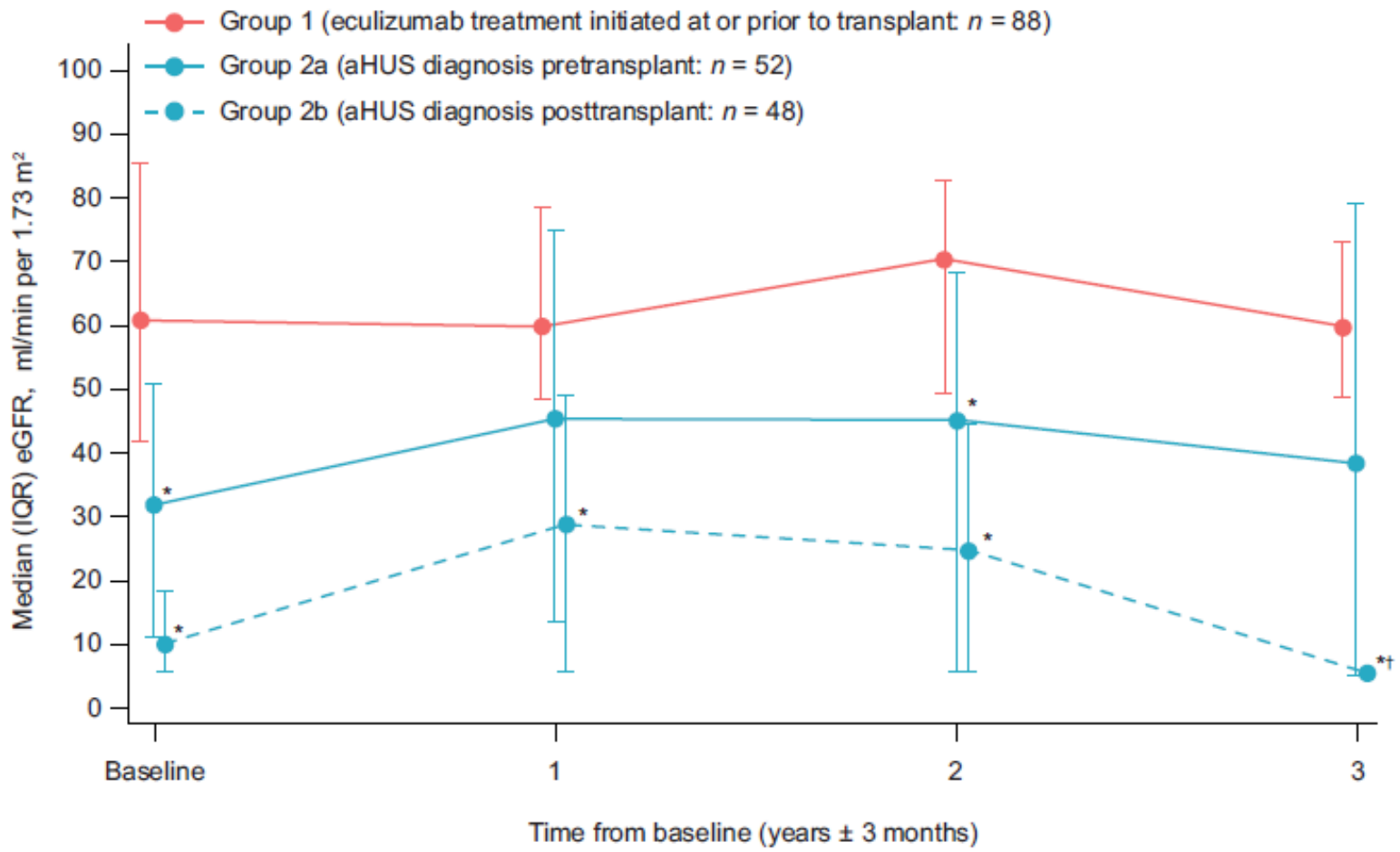
Cumulative proportion of patients receiving any dialysis post transplantation



No. at risk	Group 1	88	85	59	41	22
Events		3	3	0	0	0
No. at risk	Group 2a	52	47	44	34	26
Events		5	0	1	3	1
No. at risk	Group 2b	48	37	32	18	16
Events		11	1	2	2	1

Main risk factors :
diagnosis of aHUS
and initiation of eculizumab post KT

Median estimated GFR over time in the 3 groups



n	Group 1	30	45	47	31
n	Group 2a	16	12	15	15
n	Group 2b	14	13	17	10

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Clinical Kidney Journal, 2019, vol. 12, no. 2, 196–205
doi: 10.1093/ckj/sfy035
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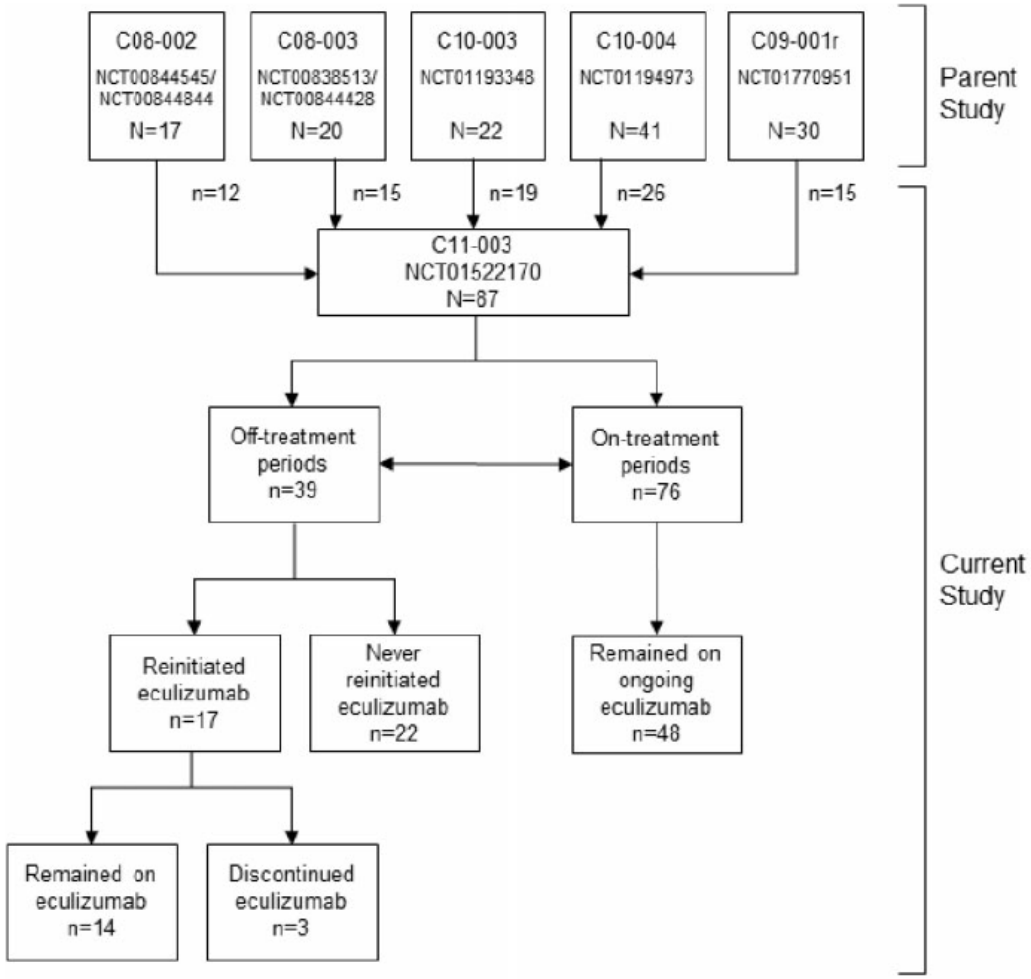
Original Article

ORIGINAL ARTICLE

Eculizumab prevents thrombotic microangiopathy in patients with atypical haemolytic uraemic syndrome in a long-term observational study

Jan Menne[1], Yahsou Delmas[2], Fadi Fakhouri[3], John F. Kincaid[4,*], Christoph Licht[5], Enrico E. Minetti[6], Chris Mix[4,*], François Provôt[7], Eric Rondeau[8], Neil S. Sheerin[9], Jimmy Wang[4], Laurent E. Weekers[10] and Larry A. Greenbaum[11]



Parameter	Eculizumab treatment status: Off treatment (n = 39)	On treatment (n = 76)
Patients with manifestation, n (%)	11 (28)	10 (13)
Total number of manifestations	14	14
Total patient-years	70.5	192.8
TMA manifestation rate/ 100 patient-years	19.9	7.3
Fold change in rate[a]	2.7	Ref
Per cent change compared with off treatment[b] (%)	Ref	−63
HR (P value)[c]	4.7 (P = 0.0008)	Ref

Rechute à l'arrêt de l'eculizumab:
44% des cas
Surtout si anomalie génétique +

Summary/conclusions 1

- Demographic characteristics for the whole registry and for french patients were quite similar
- Most of the patients, in the whole registry and in France, are adults > 18yo, and about 65% are female patients:
  - 21% of french adults however started their disease during chilhood
- Familial history of aHUS were more frequent in the french cohort than in the world cohort (27 vs 14%)
- In the whole registry, associated diseases which may cause or trigger aHUS onset, were reported in 14% (121 out of 851 patients) of the patients

Summary/conclusions 2

- Among french patients, more adults than children needed specific treatments before their inclusion in the registry:
  - 74% versus 43% who required dialysis
  - 68% versus 43% who required plasma infusion or plasma exchanges
- Patients who received eculizumab had more renal or extrarenal manifestations within the previous 6 months before inclusion
- The percentage of patients, adults or children, who did not received eculizumab was similar in the whole cohort and in the french cohort
- Among the patients who received eculizumab, most of them (87% in the world cohort and 99% in the french cohort) started their treatment before inclusion in the registry
- When eculizumab was stopped, it was resumed in 25% of the cases