Not So Benign Hematology

Aplastic anemia, Paroxysmal Nocturnal Hemoglobinuria, atypical Hemolytic Uremic Syndrome, Thrombotic Thrombocytopenic Purpura

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Disclosures

- Dr. Brodsky serves as a Scientific Advisory Board member to:
  - Alexion Pharmaceuticals
  - Achillion Pharmaceutical

- Grant funding:
  - NHLBI
  - Alexion

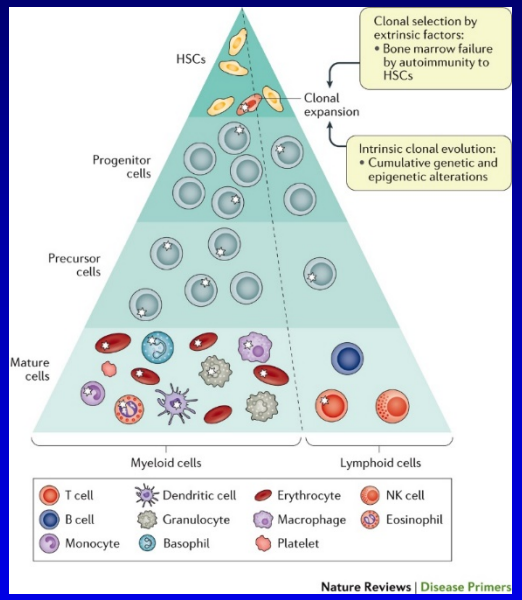
Aplastic Anemia
Diagnosis And Nomenclature

- SAA
  - Bone marrow (< 25% cellular)
  - Peripheral cytopenias (at least 2 of 3)
    - ANC < 500 per μl
    - Platelets < 20,000 per μl
    - Absolute retic < 60,000 or corrected retic < 1%
- VSAA: as above, but ANC < 200

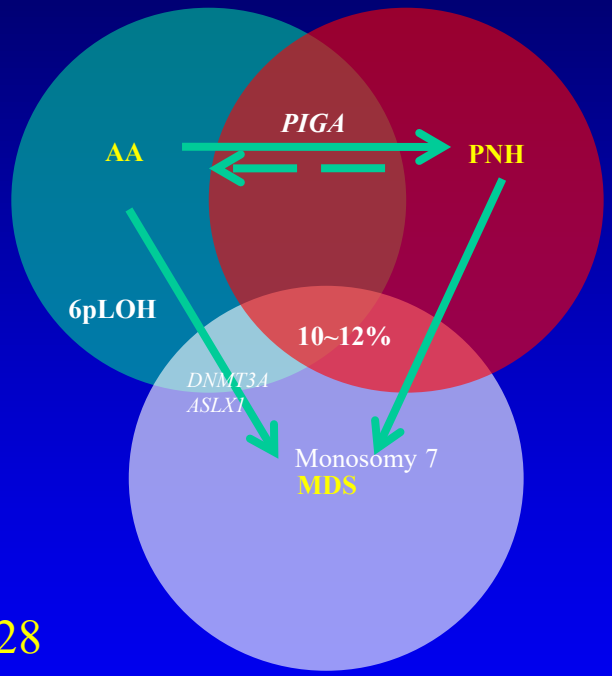
2 year mortality > 70%

- Moderate AA or (NSAA)
  - Hypocellular marrow but does not meet criteria for SAA

SAA: An Acute and Chronic Illness



Nat Rev Dis Primers. 2017 May 18;3:17028



CHIP + *PIGA*

↓

CLASSICAL PNH

Acquired AA

↓

PIGA clonal escape
AA/PNH

Take Home:
Autoimmune attack on stem cells
Predisposes to clonal escape/malignancy

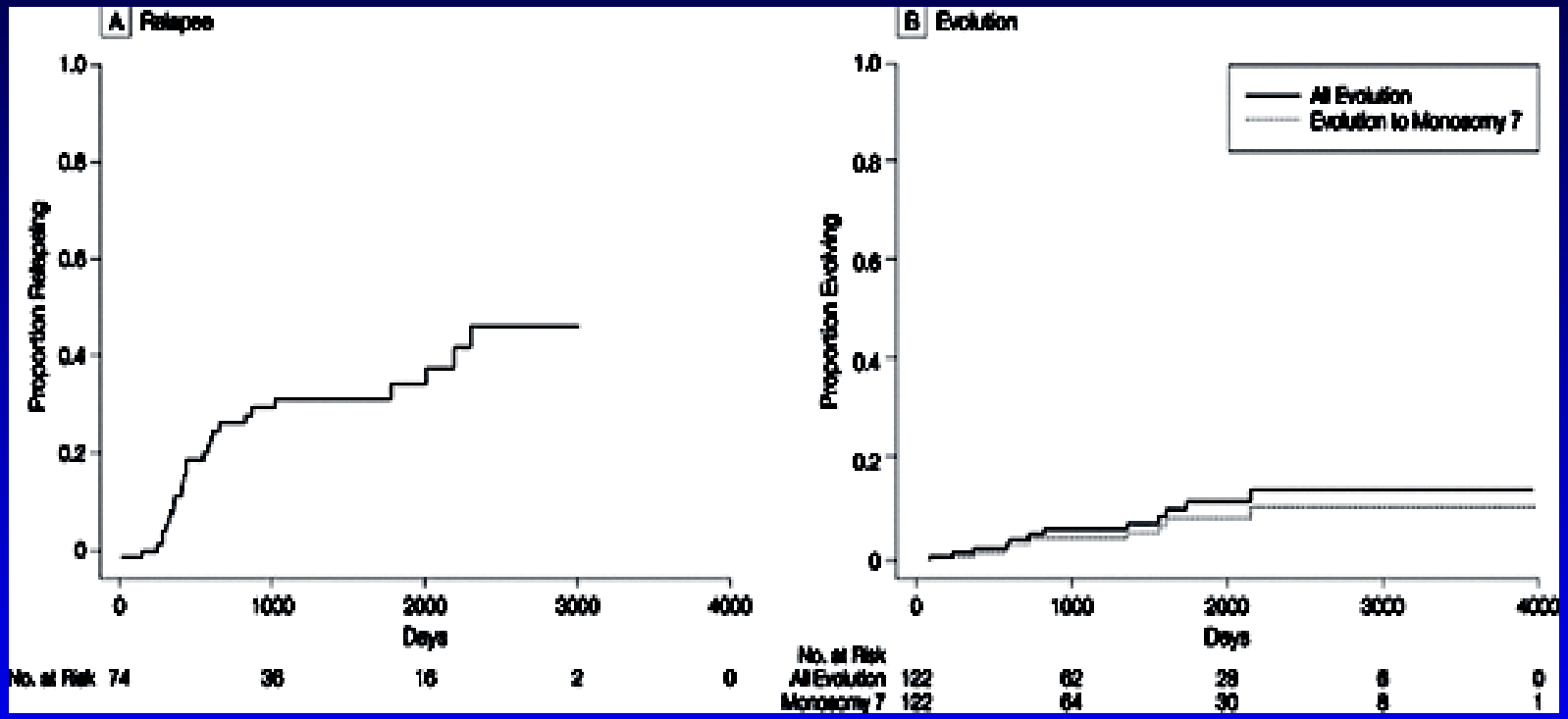
Severe Aplastic Anemia

- First line therapy
  - BMT
  - IST (ATG/CSA) +/- eltrombopag (Response rate 70%)

- Refractory Disease (poor response/prognosis)
  - Eltrombopag
  - BMT (usually from alternative donors)
  - Other IST

ATG/CSA: Late complications

Rosenfeld et. al, Jama 2003;289: 1130-35

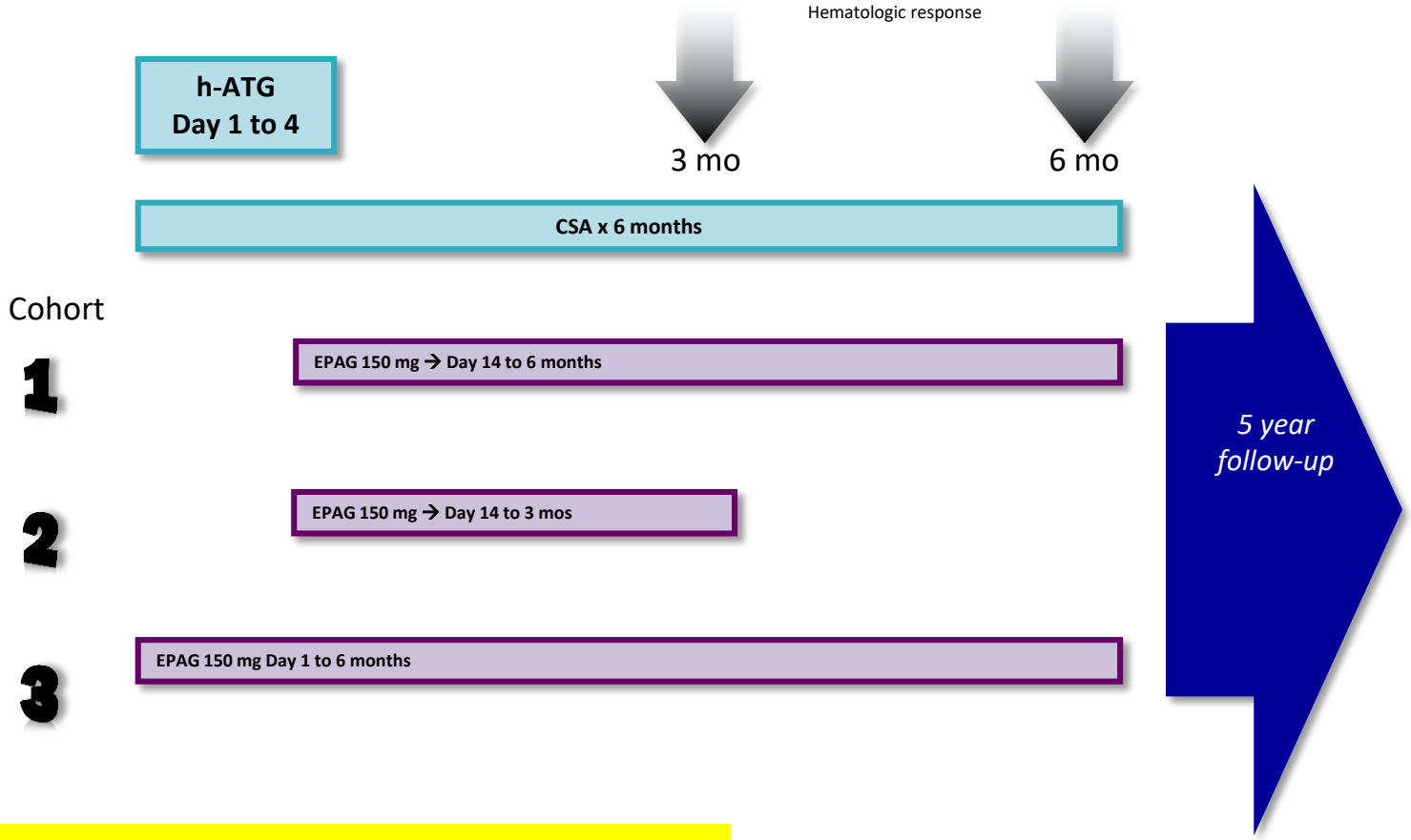


Risk of relapse > 40% in responders

Risk of clonal evolution

25-35% failure-free survival

ELTROMBOPAG ADDED TO STANDARD IMMUNOSUPPRESSION AS FIRST TREATMENT IN APLASTIC ANEMIA

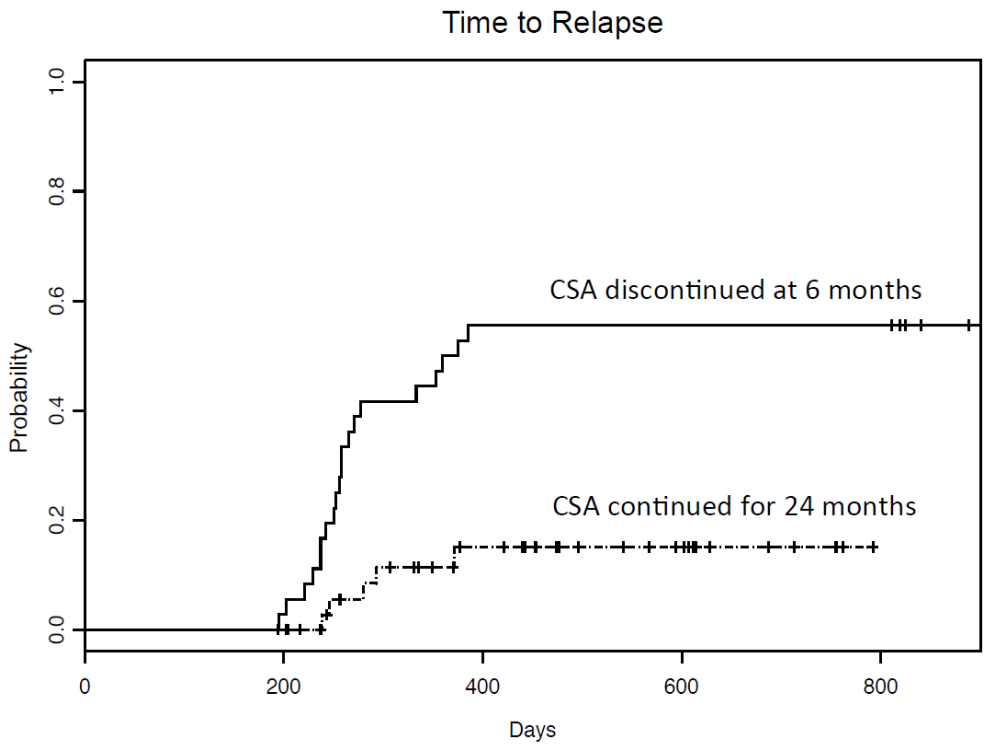


Supplemental methods:
The protocol was amended starting with subject # 46 on cohort 2, so that cyclosporine was continued at a 6 fixed daily dose, 2mg/kg/day, for an additional 18 months in order to prevent relapse.

Townsley, DM et al, *NEJM* 2017; 376:1540-50.

Supplemental Figure 4

Median follow-up 23 months



No. at risk:					
CSA discontinued	92	35	17	16	16
CSA continued	92	43	24	11	1

Cytogenetic abnormality of unclear significance					
68	CR	3	46, XX, del(13)(q12q22)[cp3]/46,XX[17]	No	Cytogenetics normalized
39	CR	30	48, XX +6 +15 [2]/ 46,XX[18]	No	CR stable
Chromosome 7 abnormality					
64	PR	3	45,XX,t(3;3)(q21;q26),-7[3]/ 46, XX[17]	Yes	AML, death post-HSCT*
72	PR	30	45, XY, -7[20]	Yes	PR stable
48	CR	6	46,XX,del (7)(p13p15)[3]/46,XX[19]	No	HSCT
61	PR	6	45, XX,-7[7]/46,XX[16]	Yes	Awaiting HSCT
16	NR	3	45, XY,-7[6]/46,XY[14]	No	HSCT*

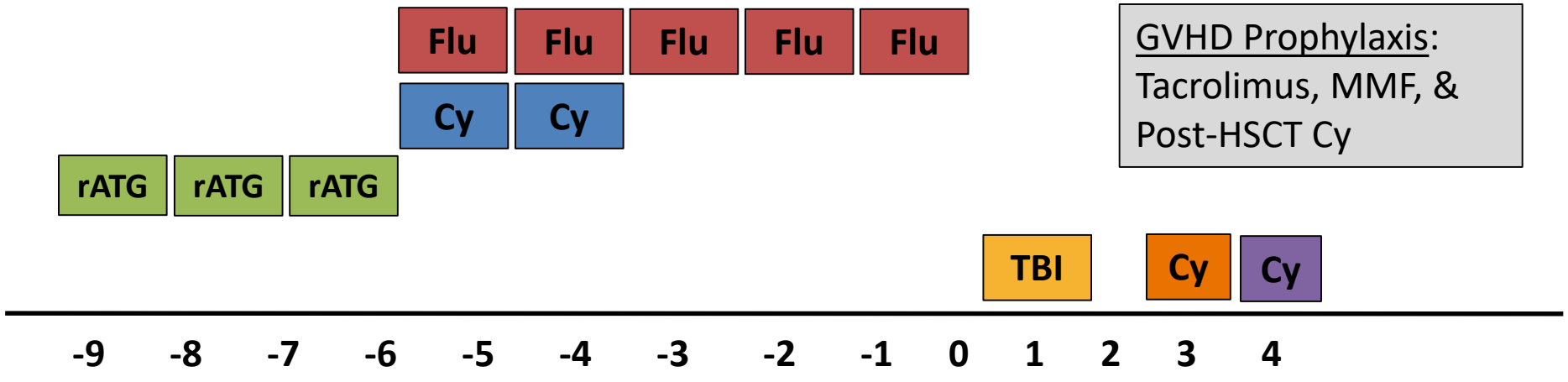
Reduced intensity haploidentical BMT with post-transplant Cyclophosphamide (CY)

- **Mitigates GVHD**

- **Allows for greater use of alternative donors (haplo BMT)**
  - **No difference for engraftment or GVHD btw matched sibs and HLA-haplo identical donors**

- **Average person in US has >4 HLA haplo-identical donors**

Conditioning for HLA Haplo-identical BMT



GVHD Prophylaxis: Tacrolimus, MMF, & Post-HSCT Cy

Flu = Fludarabine 30 mg/m^2 IV daily

Cy = Cyclophosphamide 14.5 mg/kg IV daily

Cy = Cyclophosphamide 50 mg/kg IV daily

TBI = 200 cGy

rATG = Thymoglobulin 0.5 mg/kg (day-9) & 2 mg/kg (day -8,-7)

Mini Haplo BMT with PTCy for Refractory SAA

- **21 patients with refractory SAA (median f/u 24 mos (range 3-72)**
  - Median age: 29 years (range 5-69)
  - 15/21 had evidence of clonality (PNH and/or cytogenetic abnormality)
  - 18 haplo 1 mm URD(9/10) 2 URD (10/10)

- **Rapid and consistent engraftment**
  - Day 60 chimerism 100% in 20/21 patients
    - One primary graft failure (engrafted with 2nd BMT from different donor)
  - ANC 15 days Reds 25 days Platelets 28 days

- **Excellent Disease Free Survival**
  - All 21 alive, transfusion-independent, without clonality (KPS 100)
  - Acute GVHD grade II-IV 2/21 (9.5%)
  - Extensive chronic GVHD 0/21
  - All off IST – median f/u 30 months

Dezern et al, Biol Blood Marrow Transplant 2017, 23:498-504

Conclusions

- **SAA: IST vs BMT**
  - **BMT advancing faster than IST; solves problem of relapse and clonality**
  - **HaploBMT becoming standard of care for relapsed/refractory SAA**
  - **The future?**
    - **Upfront mini-haplo BMT if no sib match: requires increased TBI to 400: 8/8 engrafted.**

Paroxysmal Nocturnal Hemoglobinuria

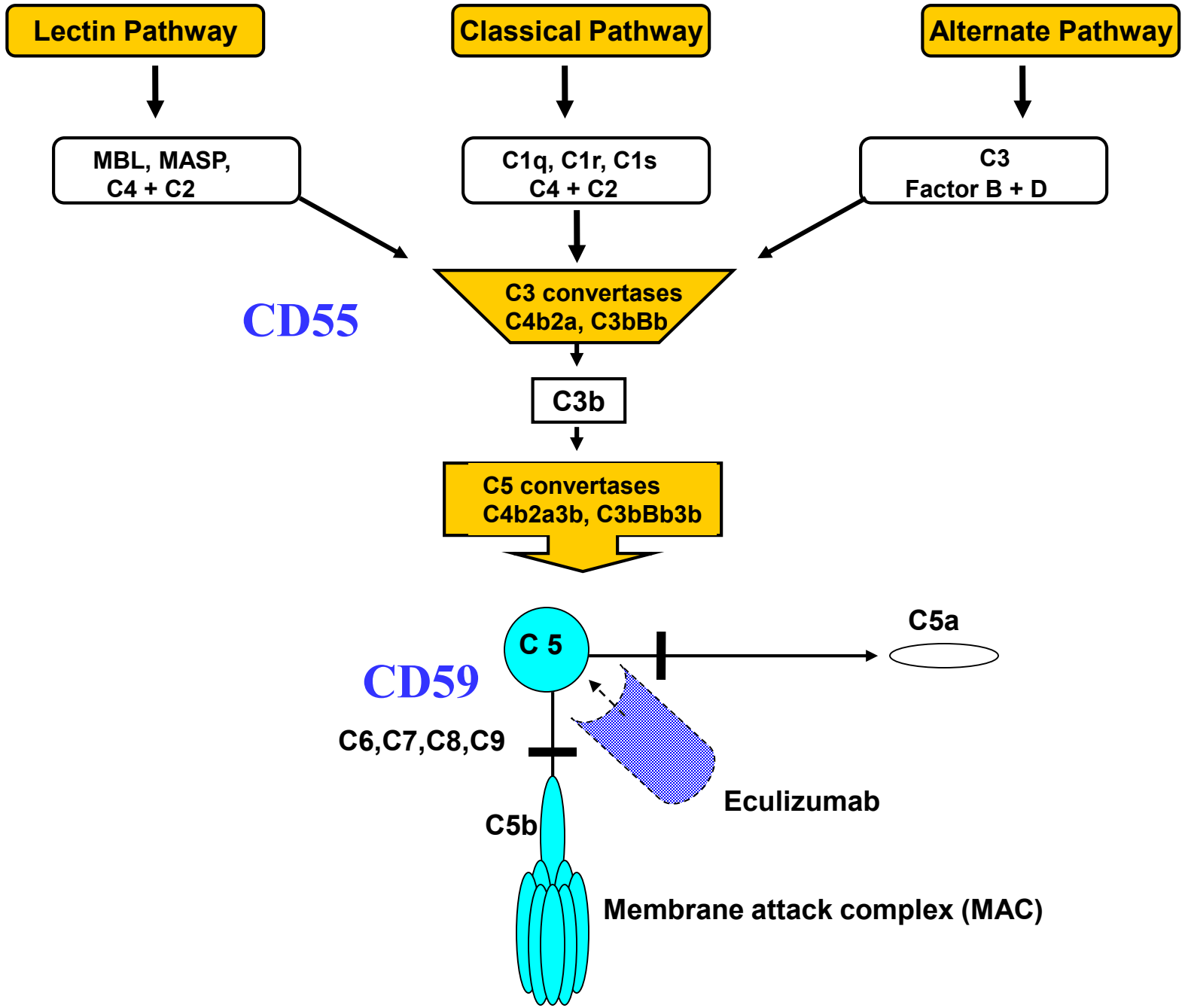
Biology

- Acquired Clonal Hematopoietic Stem Cell Disease
- *PIGA* mutation
  - X(p22.1)
- PIGA gene product necessary for 1st step in the biosynthesis of GPI anchors
- PNH cells have deficiency or absence of all GPI anchored proteins

PNH

Pathogenesis of hemolytic anemia

- CD59
  - Membrane inhibitor of reactive lysis
  - Prevents incorporation of C9 into C5b-8; thus, MAC does not form
- CD55
  - Decay accelerating factor
  - Block C3 convertase
- Protect cells from complement-mediated destruction


Lectin Pathway
Classical Pathway
Alternate Pathway
MBL, MASP,
C4 + C2
C1q, C1r, C1s
C4 + C2
C3
Factor B + D
CD55
C3 convertases
C4b2a, C3bBb
C3b
C5 convertases
C4b2a3b, C3bBb3b
C 5
C5a
CD59
C6,C7,C8,C9
Eculizumab
C5b
Membrane attack complex (MAC)

Lessons from Eculizumab Trials

- Safe
  - Mild side-effects
  - Increased risk for Neisserial infections (~0.5% per year)

- Effective
  - Decreases intravascular hemolysis
  - Decreases (>90%) or eliminates (70%) need for PRBC
  - Improves quality of life
  - Reduces the risk for thrombosis by >90%

Hillmen et al, NEJM 2006, 355:1233-43
Brodsky et al, Blood 2008, 111: 1840-47

Lessons from Eculizumab Trials – cont.

- **Drawbacks**
  - Lifelong therapy intravenous therapy
  - Cost (> 500K a year)
  - Some patients have a lot of extravascular hemolysis

Hillmen et al, NEJM 2006, 355:1233-43
Brodsky et al, Blood 2008, 111: 1840-47

Next Generation Complement Inhibitors

- **Ravulizumab** (Abstracts 625,626,627,2330)
  - **Anti-C5 monoclonal antibody (non-inferior to ecu in randomized phase III trial)**
  - **Intravenous every 8 weeks**
  - **FDA approved**

- **SKY59** (Abstracts 535,3611)
  - **Anti-C5 monoclonal antibody**
  - **Subcutaneous (monthly) terminal ½ life of 25 days**

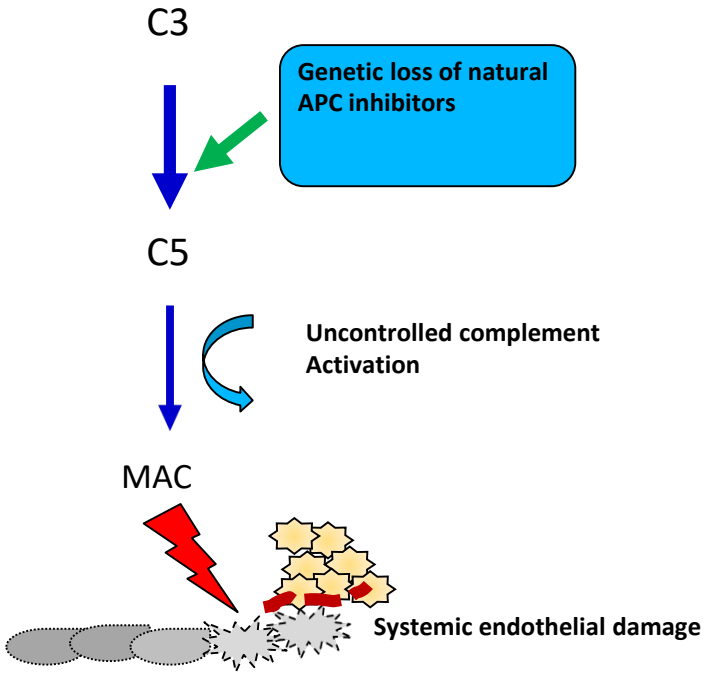
- **APL2** (Abstract 2314)
  - **C3 inhibitor**
  - **Daily subcutaneous**

- **ACH4471**
  - **Factor D inhibitor**
  - **TID oral**

Atypical hemolytic uremic syndrome (aHUS)

- **Clinical Presentation**: MAHA, renal failure, and thrombocytopenia
- **Pathophysiology**: excessive activation of alternative complement pathway (APC)
- **Treatment:** Eculizumab -- Monoclonal Ab that blocks terminal complement activation (FDA approved 2011)
- **Diagnosis:** Clinical – must exclude TTP and typical HUS (shiga toxin)
  - Often leads to reluctance to initiate expensive therapy

Atypical Hemolytic Uremic Syndrome: excessive activation of the APC



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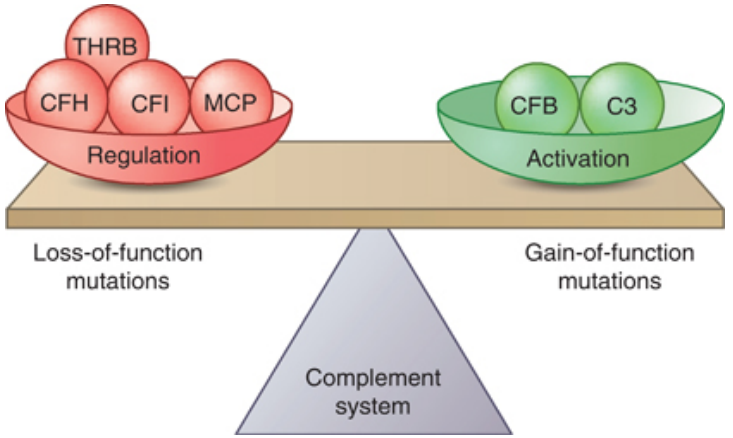

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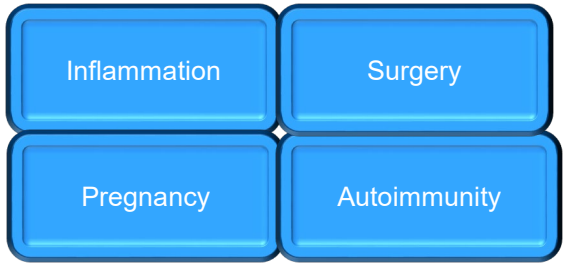


Modified from Gros, Nat. Struct. Mol. Biol. 2011 and Goioechea de Jorge, Kidney International. 2010.

Eculizumab Cessation in aHUS

- 17 patients (76% female, 70% white)
  - ADAMTS13: 60% (15-102); Hgb 8.3 (3.3-13.3)
- Initial PLEX 64%. All with active aHUS at initiation of ecu
- Median duration of ecu: 90 (14-545) days before stopping ecu
- 2 deaths: 1 while on ecu; 1 with non-adherence

Merrill et al, Blood 2017; 130:368-72

Johns Hopkins Criteria Used for Stopping Eculizumab

- aHUS in complete remission
  - ➢ Normalization of LDH, Platelets, TMA symptoms, renal function normal or plateaued at new baseline.
  - ➢ Resolution of trigger
  - ➢ Informed/Compliant patient

Eculizumab Cessation Offered to aHUS patients in CR with Mitigation of Putative Trigger

(94% TMA-free and 82% dialysis independent)

- 15 patients stopped ecu
  - 13 planned
  - 2 Non-adherence

- Relapses: 3 (20%)
  - 2 non-adherent patients (not in CR)
  - 1 planned (7%)
  - No patient required resumption of dialysis

Eculizumab can be Discontinued in Many aHUS Patients

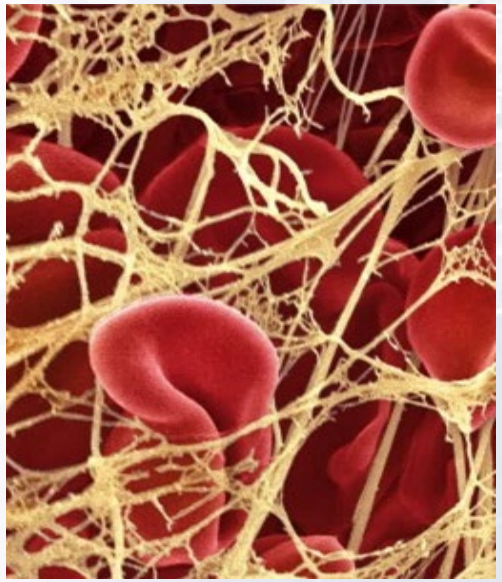
- Updated Unpublished Data
  - 20 patients have discontinued eculizumab
- Still only 3 relapses (1 planned discontinuation)
- Median time since discontinuation now 30 months
  - Estimated cost savings over $40 million

Thrombotic thrombocytopenic purpura

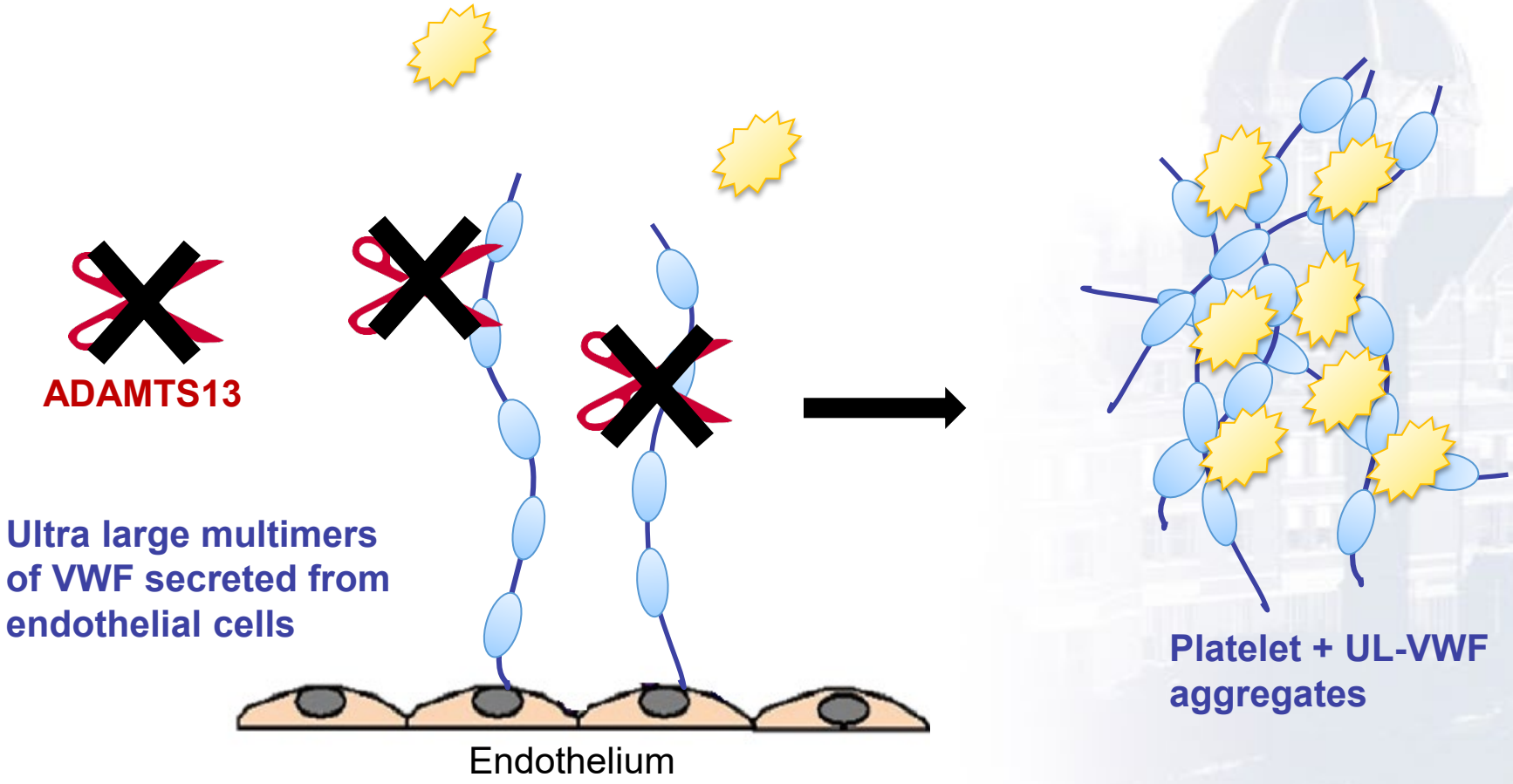
- TTP is a potentially fatal disorder characterized by acute episodes of systemic microvascular thrombosis.
- Mortality 90% untreated, 10-15% with treatment.

EPIDEMIOLOGY

- 1.7-3 per 1 million per year
- Peak incidence between ages 30 - 50 years
- Higher in women and AA race
- Pregnancy may precipitate episode



TTP pathogenesis: ADAMTS13 deficiency



Adapted from Bérangère S. Joly et al. Blood 2017;129:2836-2846

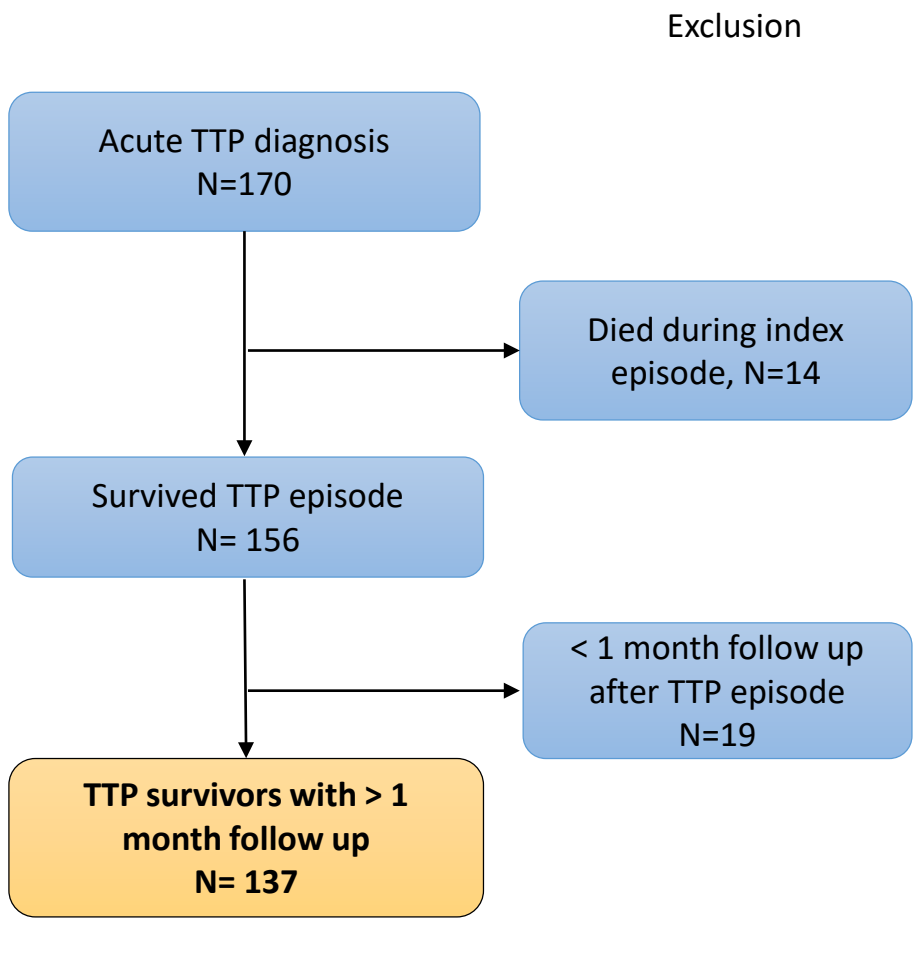
TTP IS Acute and Chronic

Patients and follow up

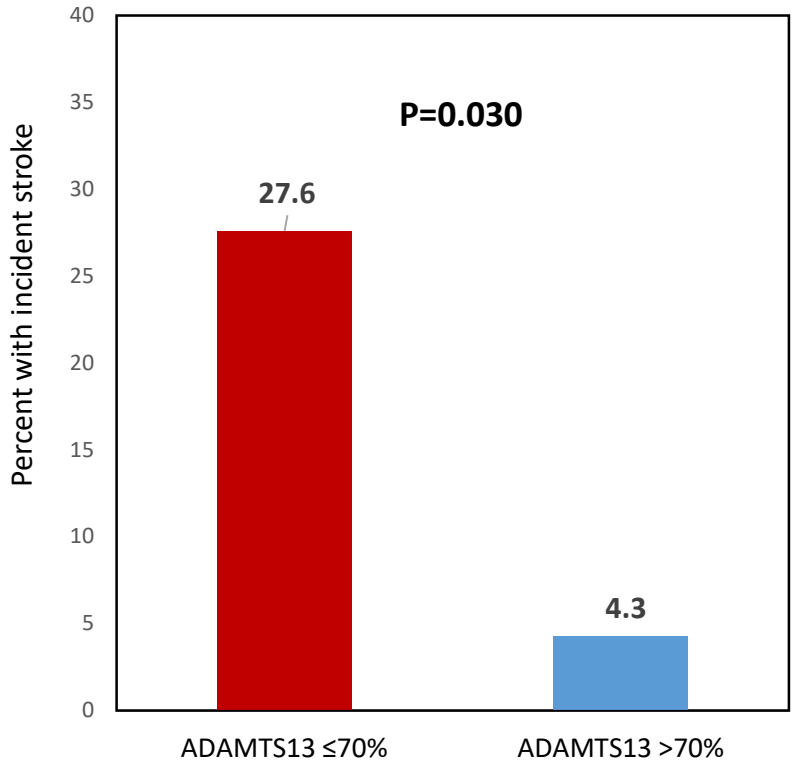
- JHH from 1990 to 2018
- 170 patients, 248 episodes of TTP

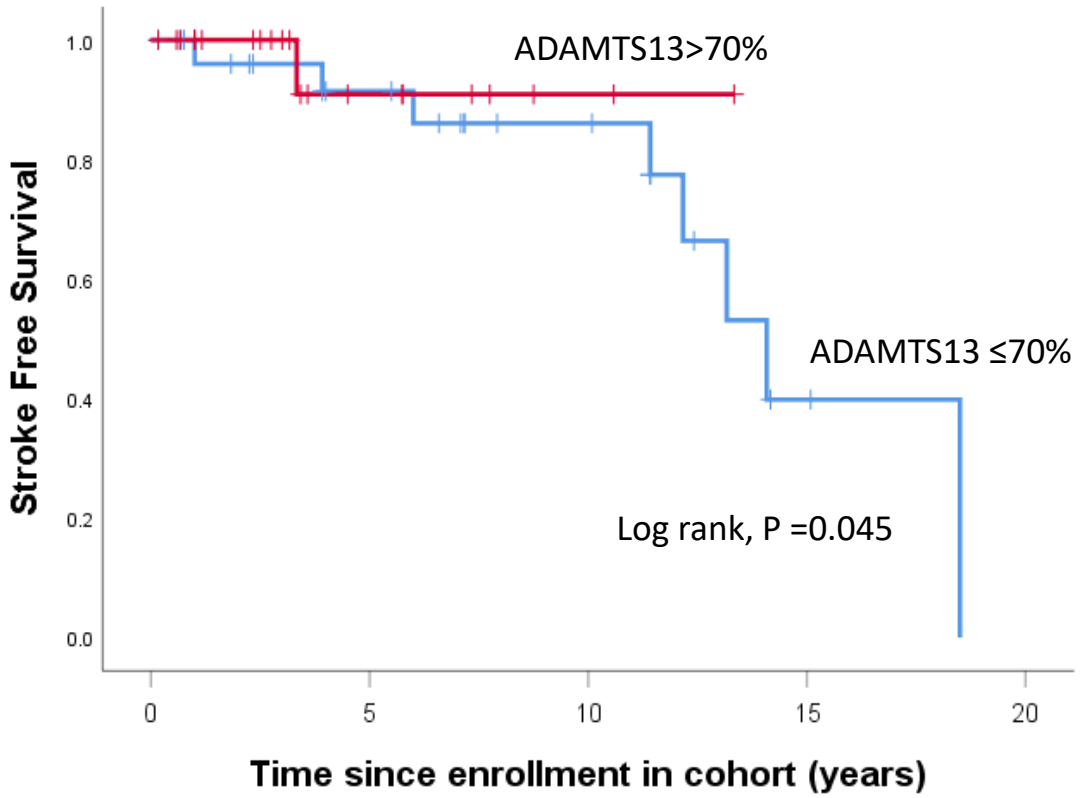
137 survivors with >1 month follow up after TTP episode included in analysis

- Follow up time
  - Median 3.08 (0.66, 7.79) years
  - 700.07 patient-years of observation
- Median age 48.8 (35.3, 60.3) years



Remission ADAMTS13 and stroke





Take Home

- **SAA: IST vs BMT**
  - Exciting clinical trials of IST and BMT
  - BMT advancing faster; solves problem of relapse and clonality

- **PNH:**
  - Novel complement inhibitors under development
  - Ravulizumab approved; more coming.

- **aHUS:**
  - Eculizumab can be discontinued in select pts
  - Must be in remission and compliant
  - Trigger should be gone

- **TTP**
  - New drugs: caplacizumab; rituxan upfront? Serologic relapse?
  - Need to think of this as a chronic disease