Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2024 San Diego

Hämostaseologie

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Universitätsklinikum
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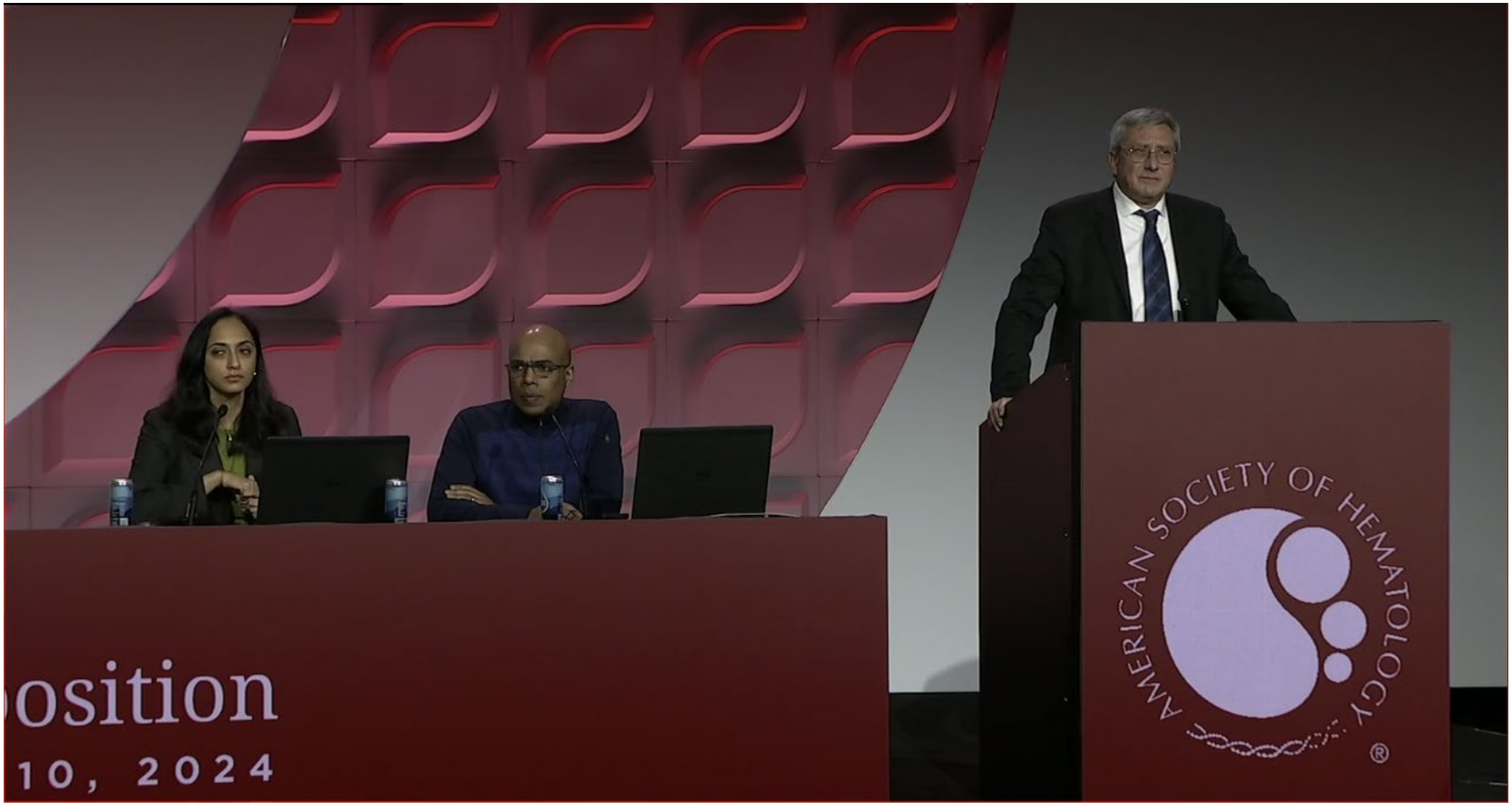
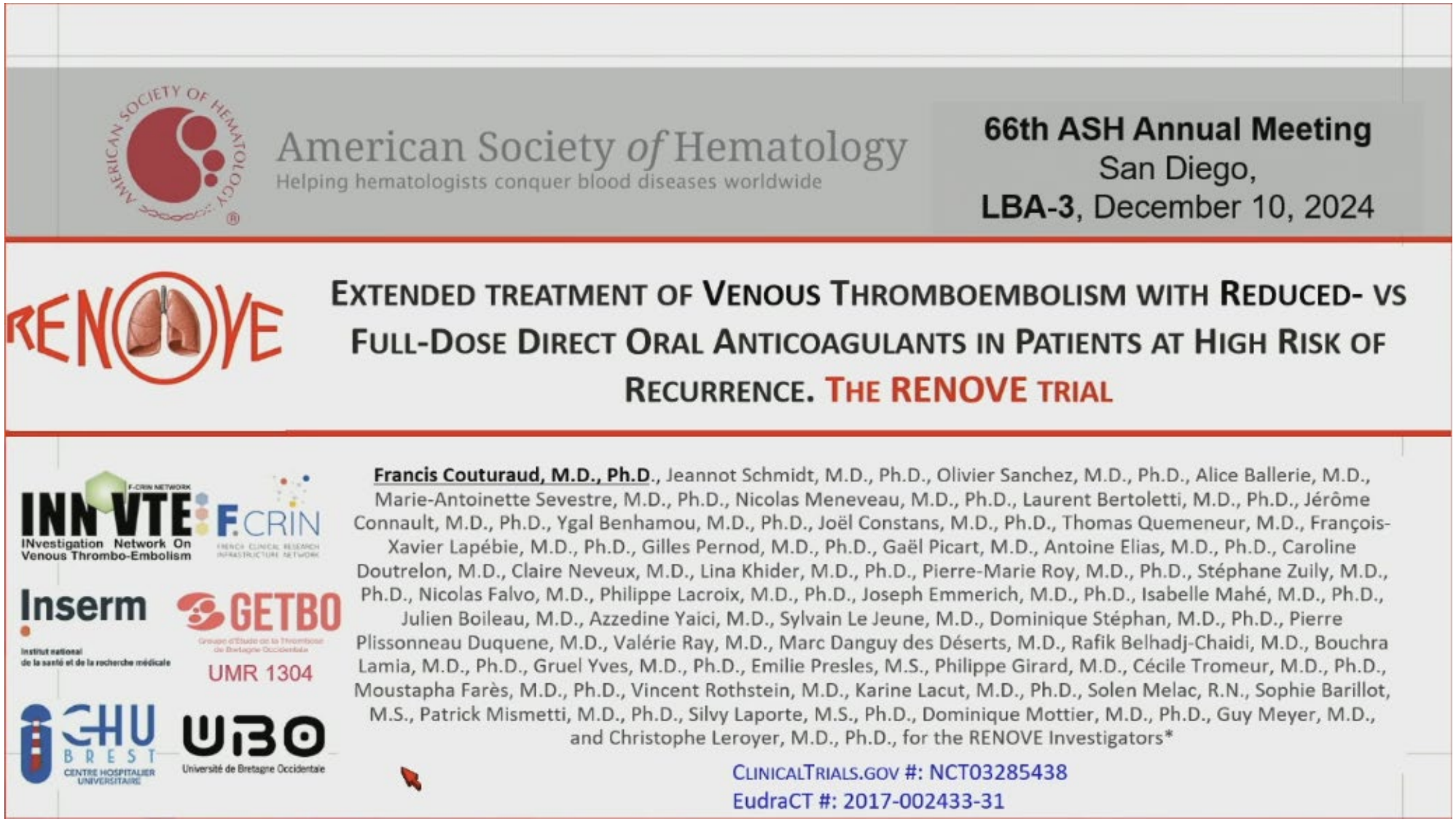
Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK



Francis Couturaud. LBA-3 Extended Treatment of Venous Thromboembolism with Reduced- Vs Full-Dose Direct Oral Anticoagulants in Patients at High Risk of Recurrence.

Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK



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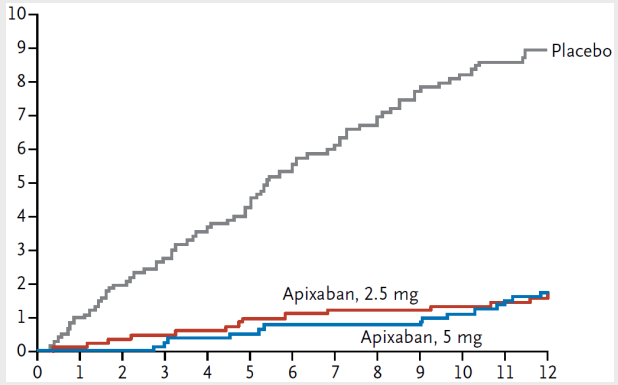
Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

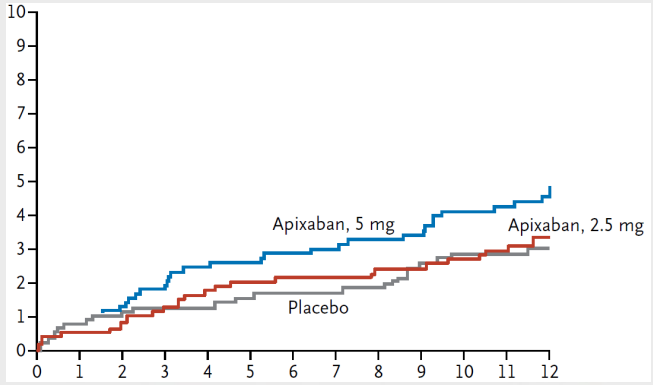
Rationale

Amplify-Ext

Symptomatic Recurrent VTE or VTE-Related Death

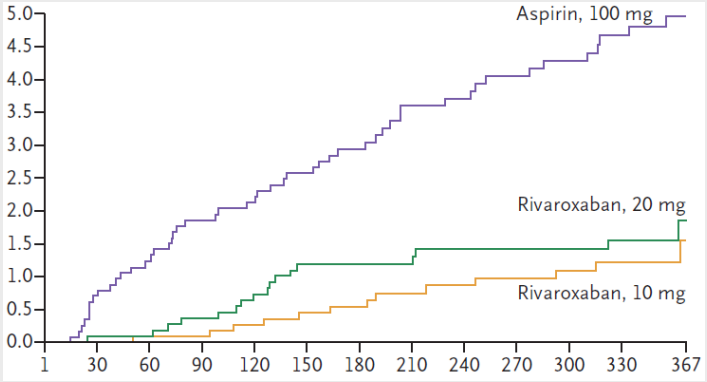


Major or Clinically Relevant Nonmajor Bleeding

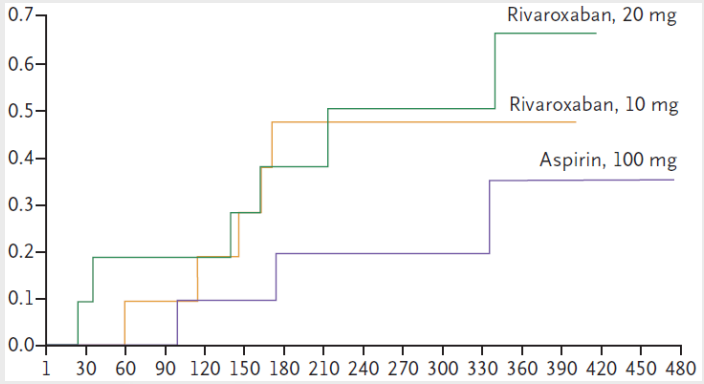


Einstein-Choice

Fatal or Nonfatal Venous Thromboembolism



Major Bleeding



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Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

Rationale

However, these two studies[1,2]:

- were neither designed nor powered to demonstrate similar efficacy and improved safety with the reduced dose,
- with the inclusion of placebo[1] or aspirin[2] control groups, enrolled patients with uncertain need for extended anticoagulation.

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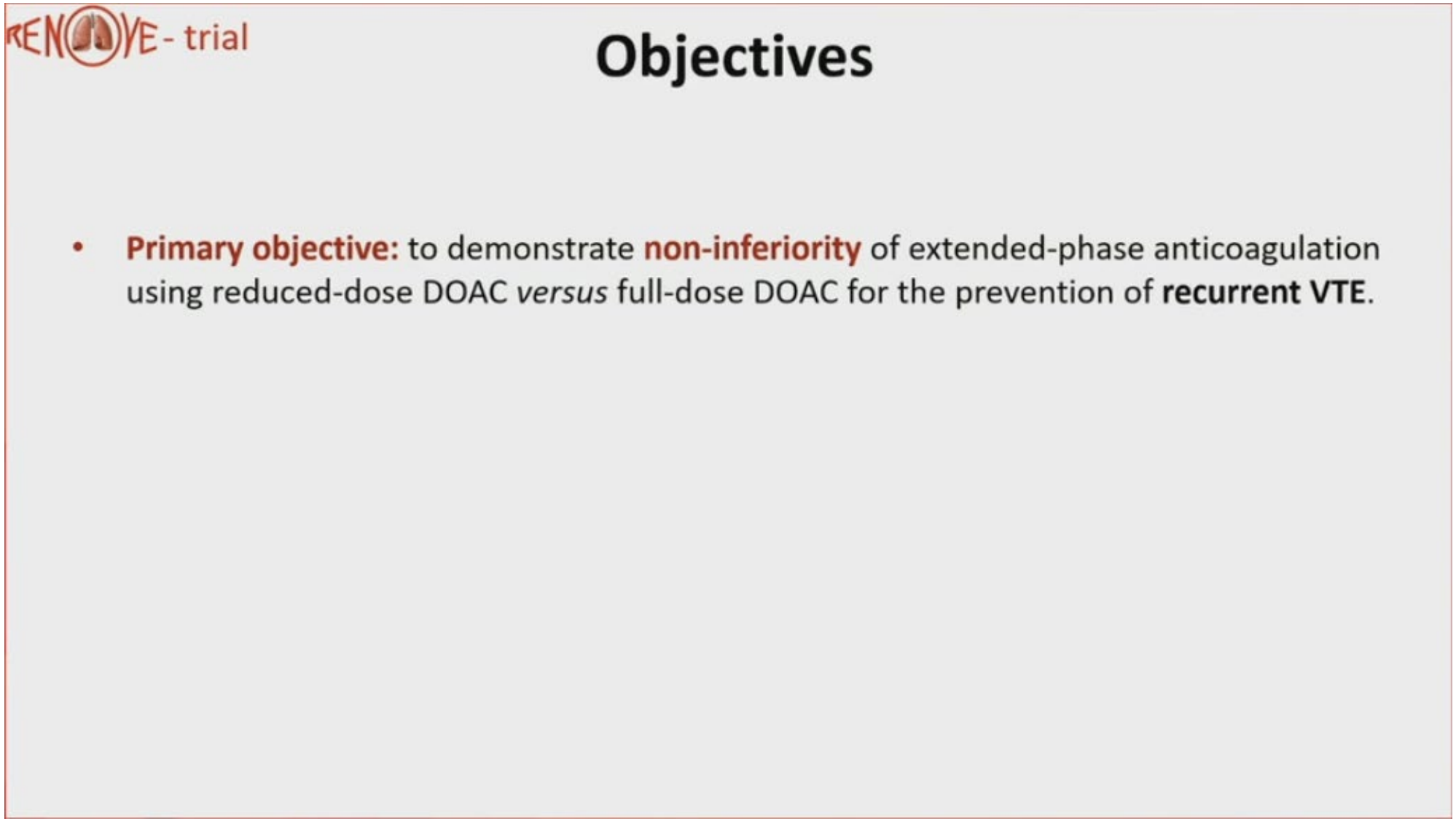

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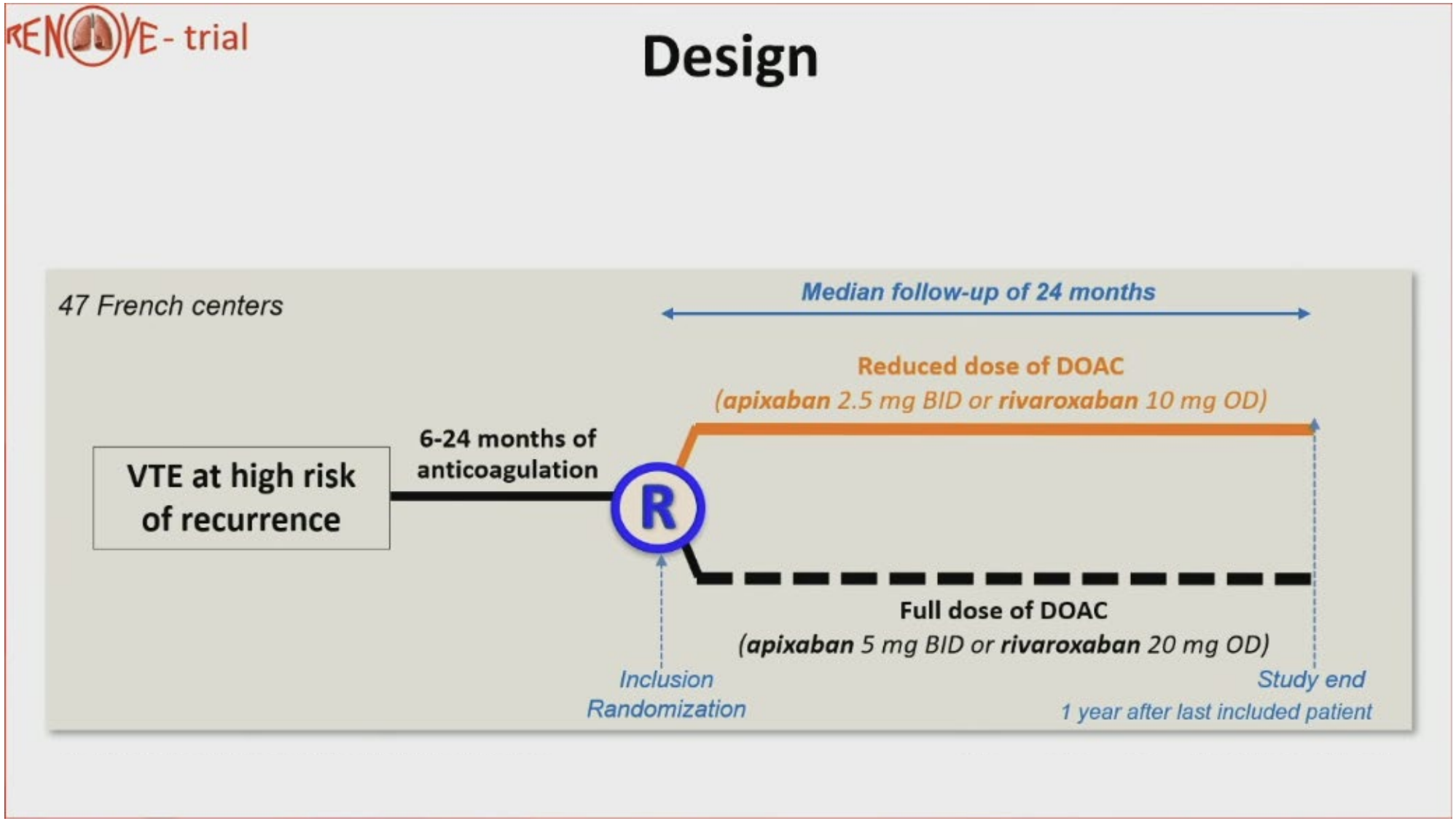

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Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

Primary outcome

5-year cumulative incidence

	Reduced Dose (N=1383)	Full Dose (N=1385)	Adjusted HR (95% CI)	P-Value
Primary outcome				
Symptomatic recurrent VTE - no. (%)	**19** (2.2)	**15** (1.8)	**1.32** (0.67 - 2.60)	**0.23**
Symptomatic recurrent PE	11	13		
Fatal PE	3	3		
Symptomatic isolated proximal DVT	9	2		

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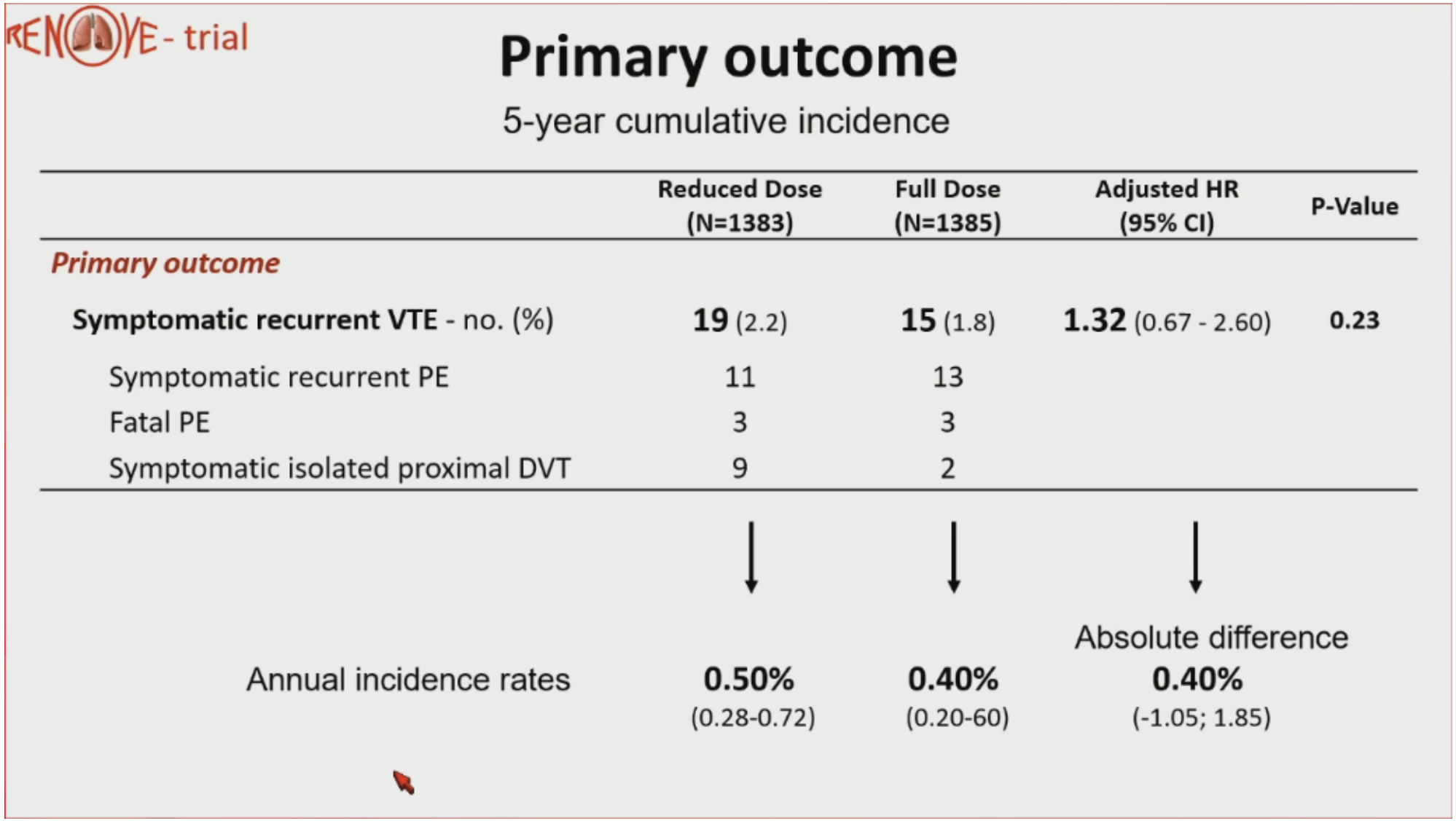

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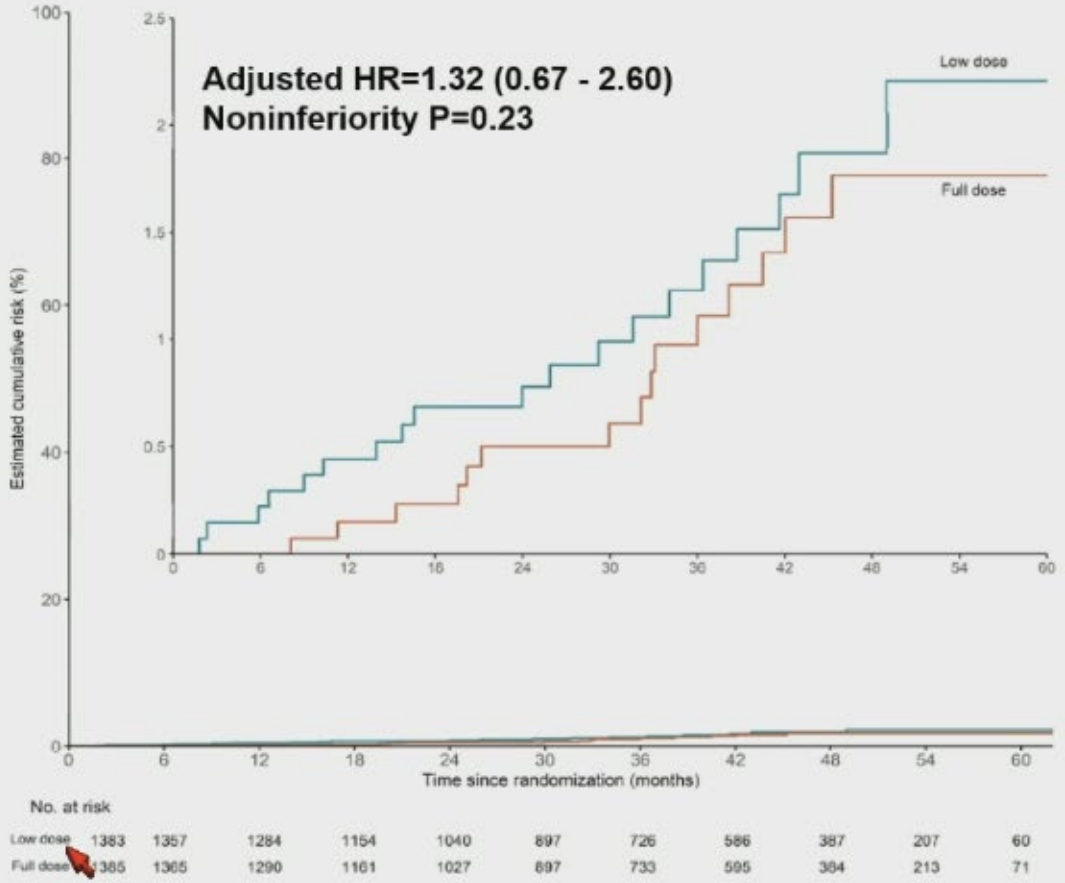
Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

Cumulative incidence of symptomatic recurrent VTE during the treatment period (primary outcome)



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Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

Secondary outcomes

5-year cumulative incidence

	Reduced Dose (N=1383)	Full Dose (N=1385)	Adjusted HR (95% CI)	P-Value
Key secondary outcomes				
Clinically relevant bleeding - no. (%)	**96** (9.9)	**154** (15.2)	**0.61** (0.48 - 0.79)	
Major bleeding	15 (2.1)	38 (4.0)	0.40 (0.22 - 0.72)	
Fatal	2	3		
Clinically relevant non major bleeding	84 (8.6)	118 (11.5)	0.70 (0.53 - 0.93)	
Composite (recurrent VTE, or clinically relevant bleeding) - no. (%)	**113** (11.8)	**166** (16.5)	**0.67** (0.53 - 0.86)	

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Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

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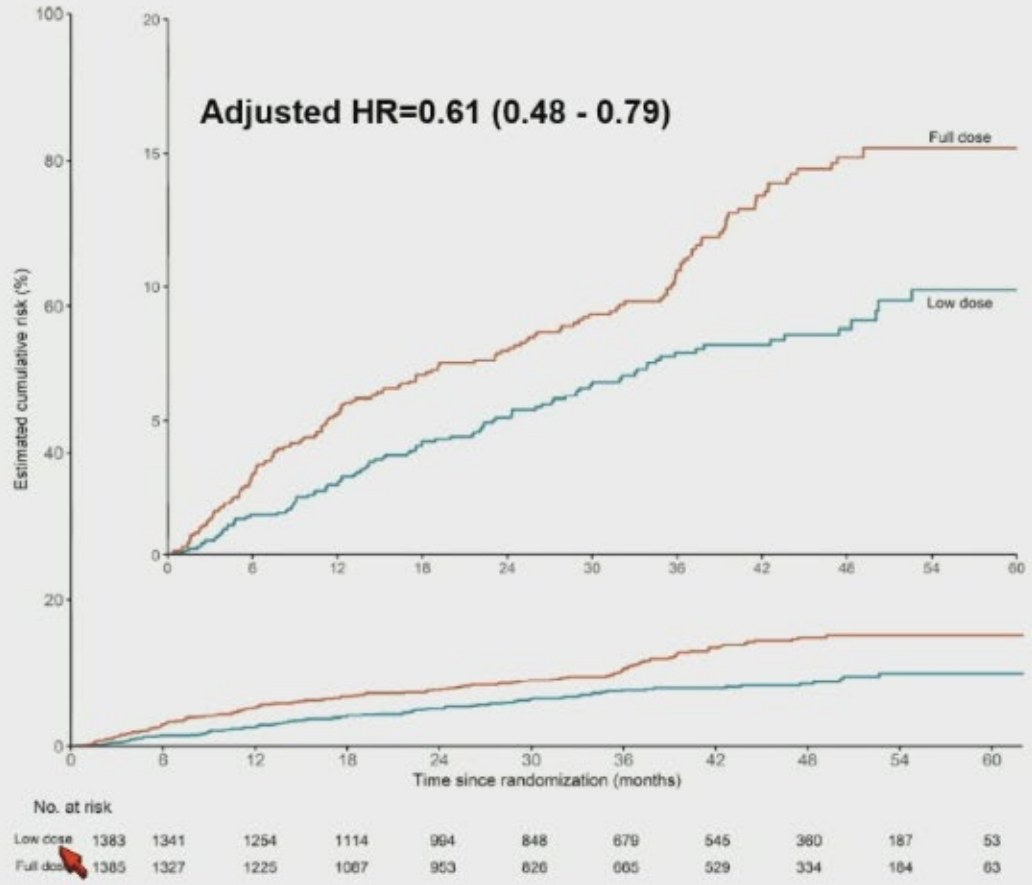
Cumulative incidence of major and clinically relevant nonmajor bleeding during the treatment period (first key secondary outcome)



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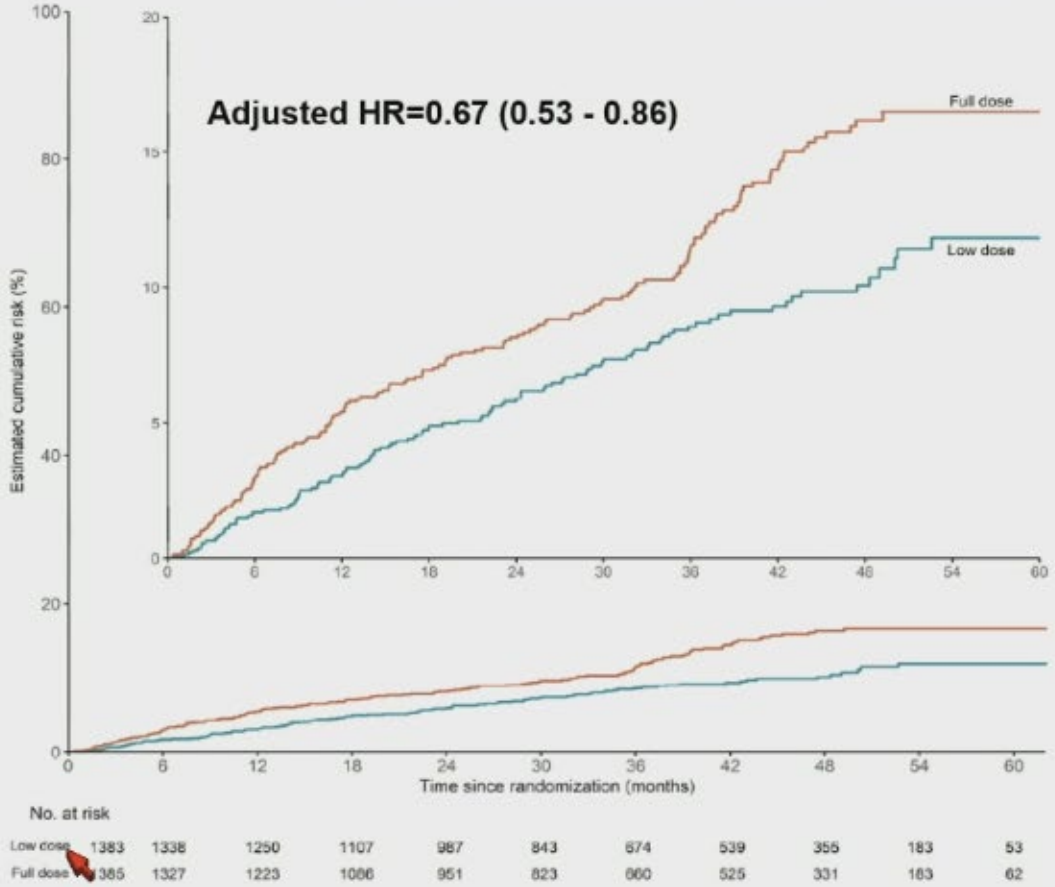
Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial **Cumulative incidence of the composite (recurrent VTE, major bleeding, or clinically relevant nonmajor bleeding) during the treatment period (second key secondary outcome)**



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Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

Secondary outcomes

5-year cumulative incidence

	Reduced Dose (N=1383)	Full Dose (N=1385)	Adjusted HR (95% CI)	P-Value
Other secondary outcomes				
All-cause death	35 (4.3)	54 (6.1)	0.67 (0.44 - 1.03)	
Arterial cardiovascular events	78 (6.2)	69 (5.5)	1.17 (0.83 - 1.64)	

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Extended Treatment of VTE with Reduced- Vs Full-Dose DOAK

RENOVE - trial

Conclusions

- DOAC dose reduction, in patients with VTE who need extended anticoagulation, **did not meet the study noninferiority** criteria.
- **Rates of recurrent VTE were low** in both the reduced- and full-dose groups.
- In the reduced-dose group, **clinically relevant bleeding** and **the composite** of recurrent VTE or clinically relevant bleeding **were lower** than in the full-dose group and did not appear to be offset by an increased risk of death or arterial thromboembolic events.
- These findings will be useful to **strengthen future guidelines and enrich shared-decision making process** for patients with VTE who need extended anticoagulation.

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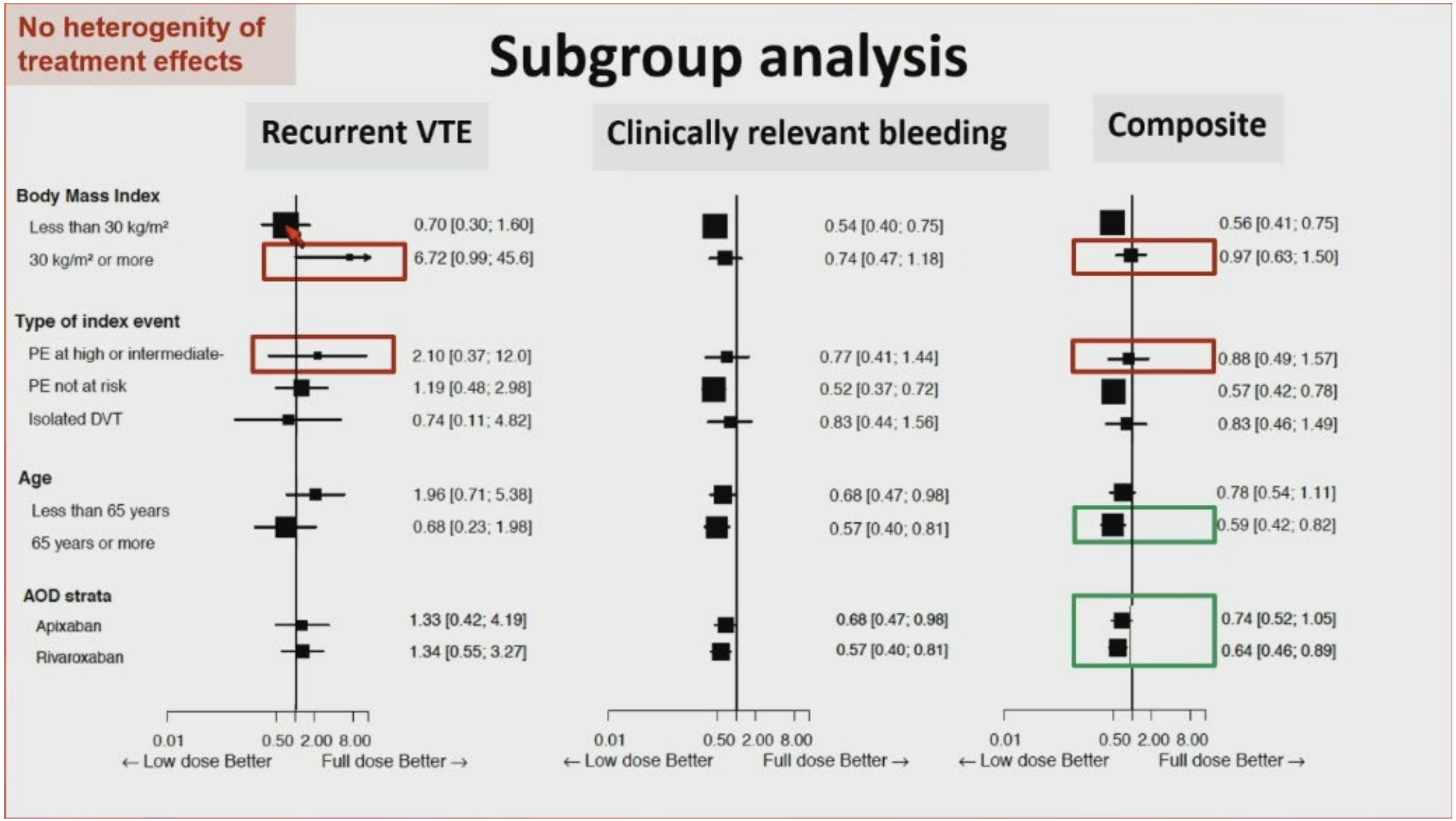

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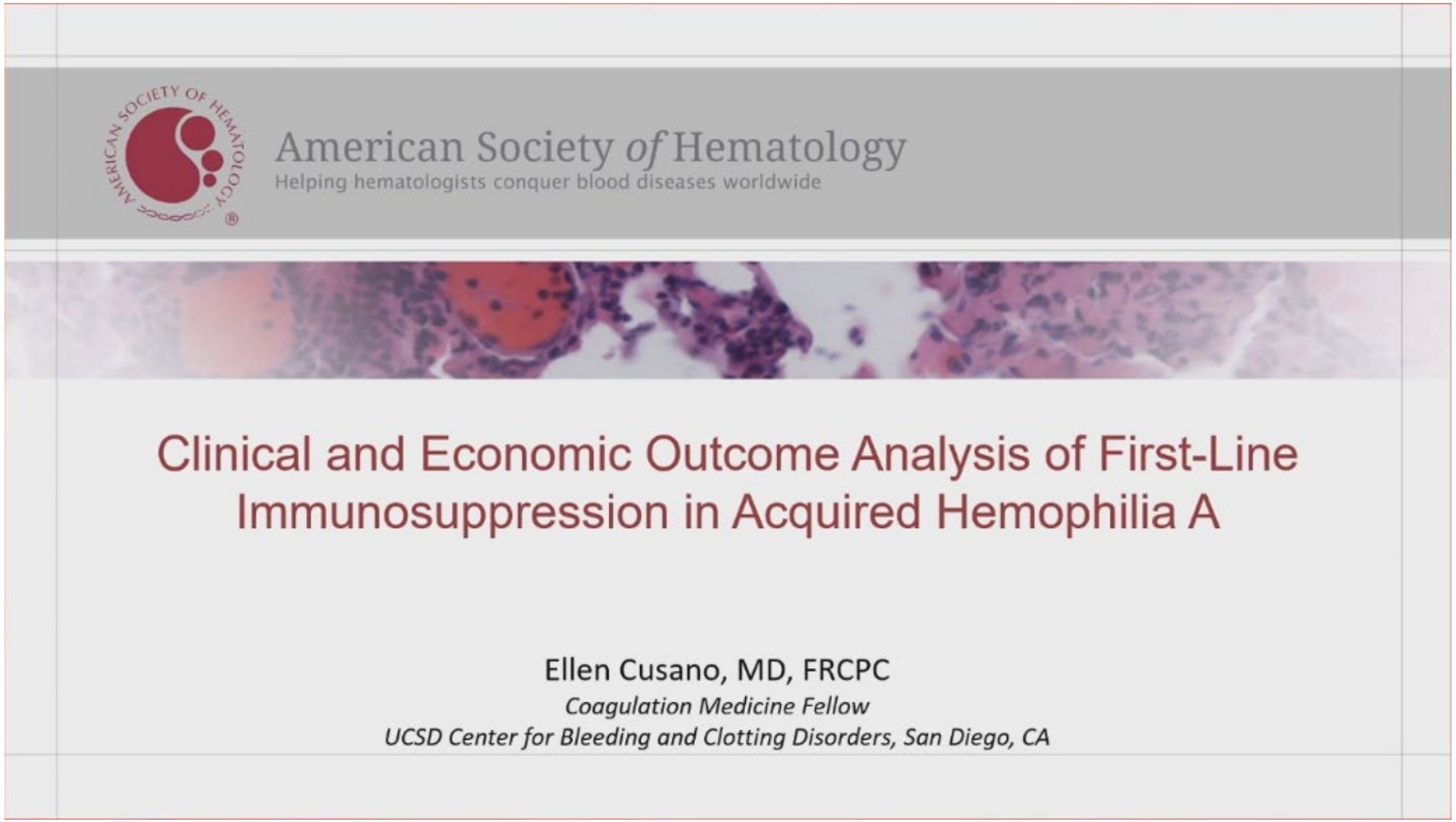
Clinical and Economic Outcome Analysis in Acquired Hemophilia A

Ellen Cusano. 554 Clinical and Economic Outcome Analysis of First-Line Immunosuppression in Acquired Hemophilia A.

Clinical and Economic Outcome Analysis in Acquired Hemophilia A



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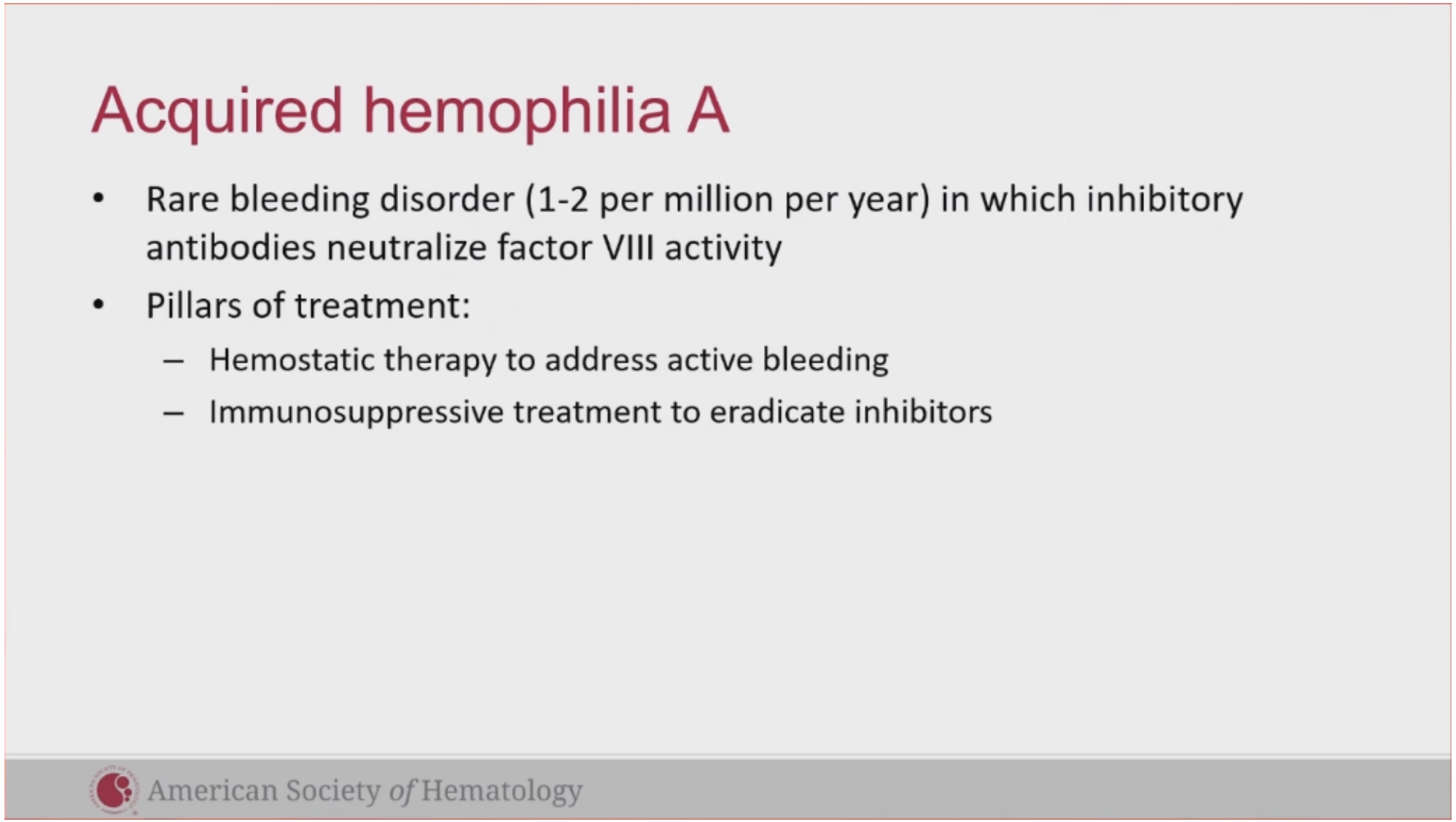

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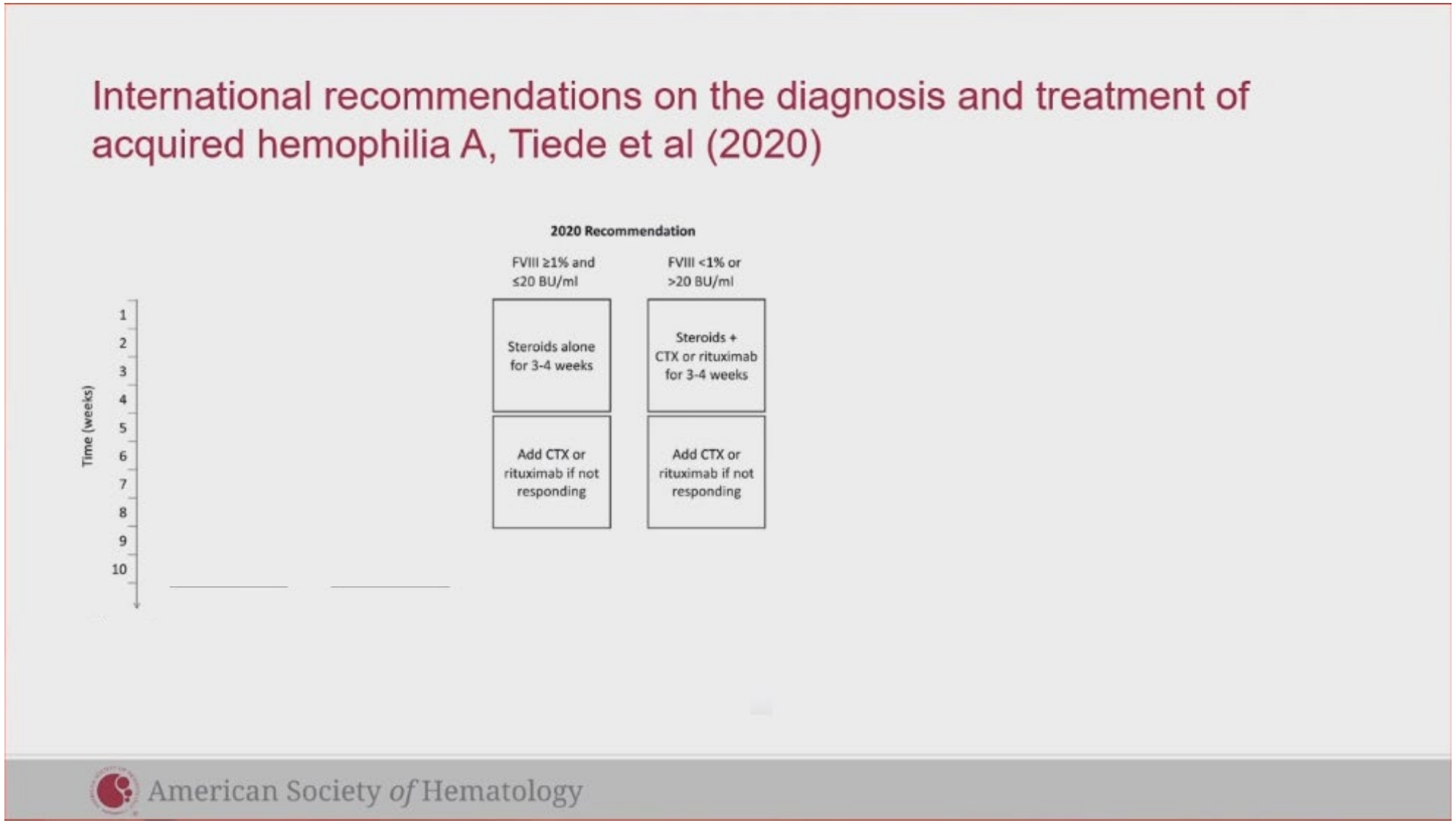

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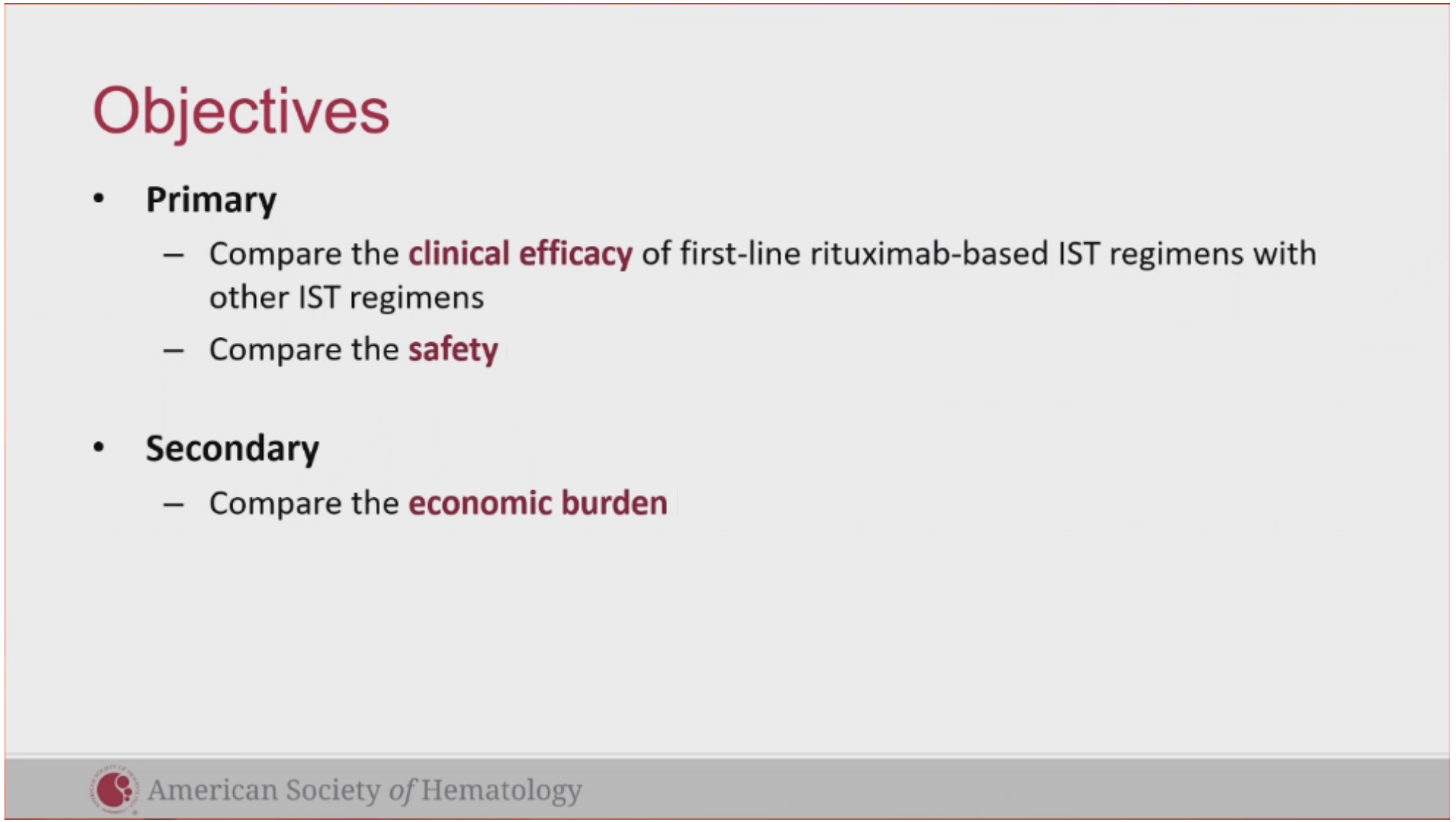

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Clinical and Economic Outcome Analysis in Acquired Hemophilia A

Outcomes

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	

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CR: complete remission, FVIII level >50%, negative inhibitor, cessation of IST
PR: partial remission, FVIII level <50%, negative inhibitor, cessation of IST
Persistent inhibitor: FVIII <50%, positive inhibitor, despite IST

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Outcomes

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Treatment response, n (%)						0.563
Complete remission	97 (77.0)	23 (69.7)	15 (78.9)	48 (76.2)	11 (100.0)	
Time to CR/PR, months						0.265
Median (IQR)	3.3 (2.5,4.9)	3.0 (2.3,4.8)	3.1 (2.6,3.7)	3.4 (2.4,5.5)	4.4 (3.3,4.8)	

Proportion of CR highest in combination IST group, lowest in prednisone monotherapy

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CR: complete remission, FVIII level >50%, negative inhibitor, cessation of IST
PR: partial remission, FVIII level <50%, negative inhibitor, cessation of IST
Persistent inhibitor: FVIII <50%, positive inhibitor, despite IST

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Outcomes

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Relapse, n (%)						**0.032**
Yes	22 (21.4)	11 (45.8)	1 (6.3)	8 (15.4)	2 (18.2)	
Vital status as of last follow-up, n (%)						0.090
Alive	96 (76.2)	23 (69.7)	14 (73.7)	50 (79.4)	9 (81.8)	
Cause of death, n (%)						
Infection	7 (28.0)	0 (0.0)	3 (60.0)	4 (30.8)	0 (0.0)	
Bleeding	1 (4.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	
Unrelated to AHA	14 (56.0)	2 (33.3)	3 (60.0)	9 (69.2)	0 (0.0)	

Lowest relapse proportion in rituximab group
Majority of deaths deemed unrelated to AHA

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Clinical and Economic Outcome Analysis in Acquired Hemophilia A

Bleeding events

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Major	122 (47.1)	31 (43.1)	16 (40.0)	64 (50.4)	11 (55.0)	

More major bleeds in cyclophosphamide and combination IST groups

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Bleeding events

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Mean dose of hemostatic or bypassing agent used per bleed (SD)						
rFVIIa (mg)	144.40 (190.51)	96.62 (77.43)	92.89 (151.09)	163.45 (164.06)	253.17 (423.88)	0.297
FEIBA (IU)	79113.15	71950.90	44532.14	93416.46	140403.33	0.153

More rFVIIa and FEIBA used per bleed in cyclophosphamide and combination groups

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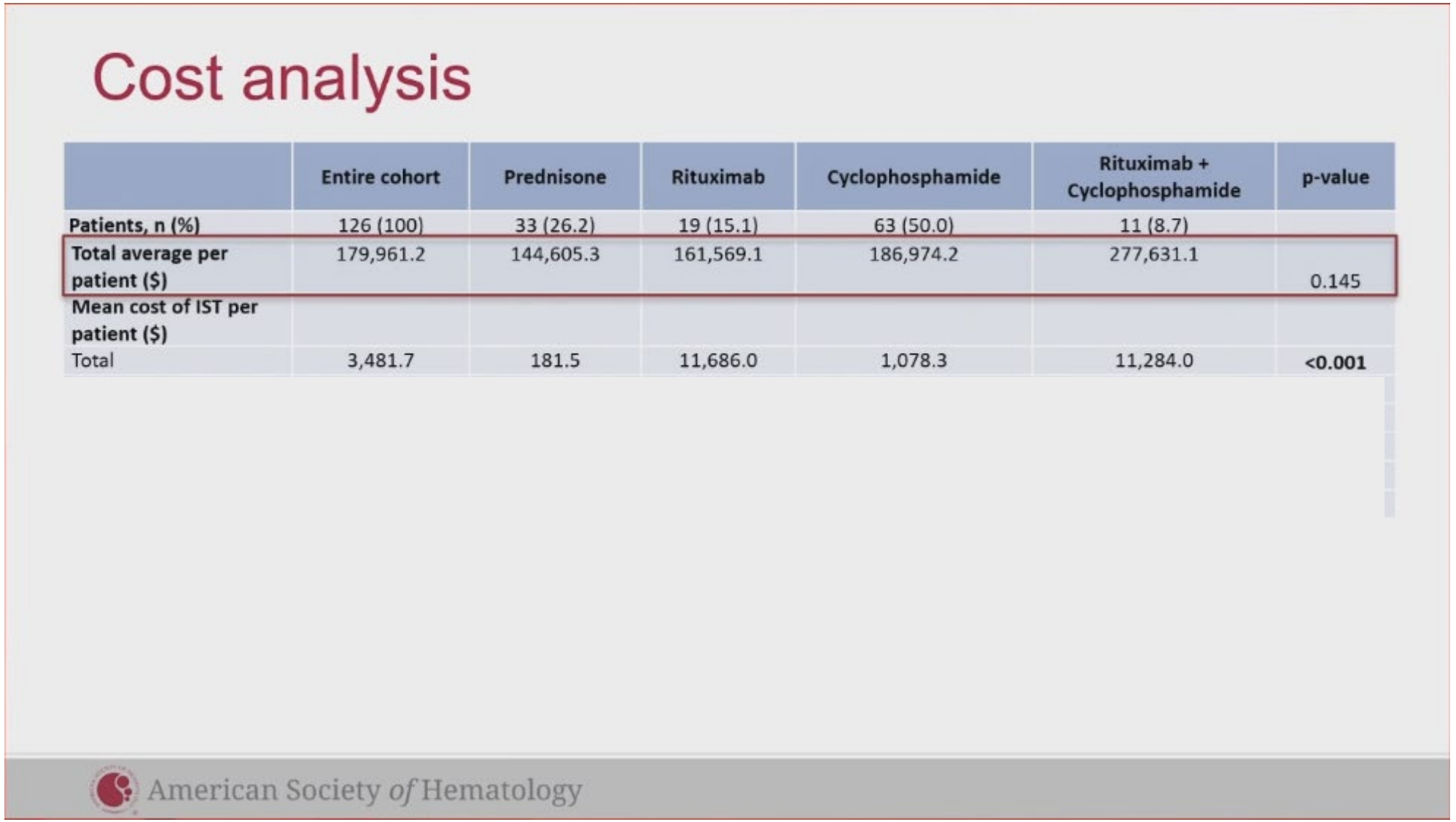

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Total average per patient ($)	179,961.2	144,605.3	161,569.1	186,974.2	277,631.1	0.145
Mean cost of IST per patient ($)						
Total	3,481.7	181.5	11,686.0	1,078.3	11,284.0	**<0.001**

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Clinical and Economic Outcome Analysis in Acquired Hemophilia A

Cost analysis

	Entire cohort	Prednisone	Rituximab	Cyclophosphamide	Rituximab + Cyclophosphamide	p-value
Patients, n (%)	126 (100)	33 (26.2)	19 (15.1)	63 (50.0)	11 (8.7)	
Mean cost of hemostatic treatment per patient ($)						
rFVIIa	176,170.5	117,876.4	113,324.3	199,411.4	308,863.3	0.297
FEIBA	158,226.3	143,901.8	8,9064.3	186,832.9	280,806.7	0.153

Greater mean cost of hemostatic treatment driven by rFVIIa and FEIBA per patient in those treated with cyclophosphamide or combination IST

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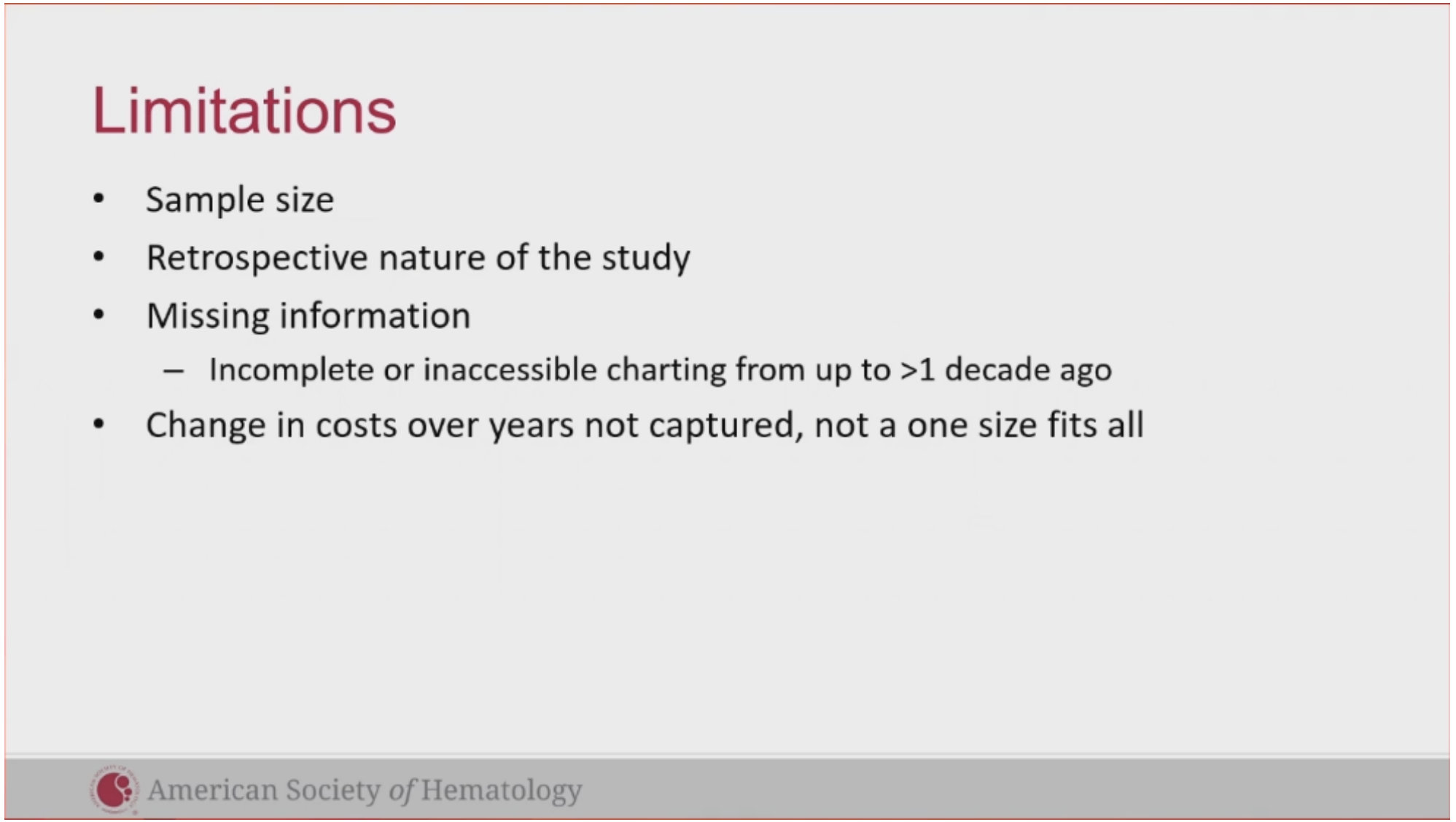

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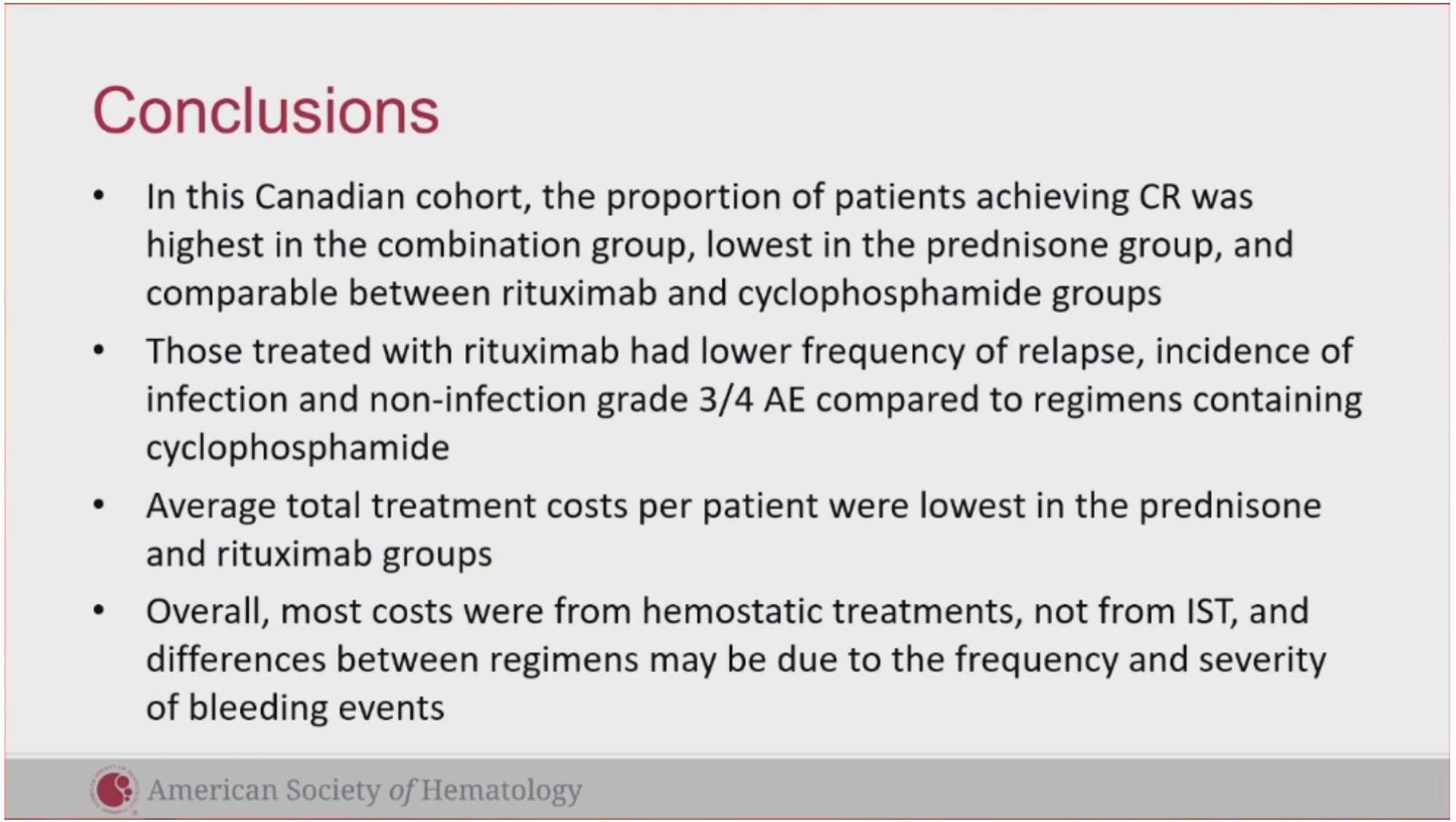

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Zwei randomisierte Studien - Cyclophosphamid vs Rituximab

Cyclophosphamide vs rituximab for eradicating inhibitors in acquired hemophilia A: A randomized trial in 108 patients

	Prednisone + Cyclophosphamide	Prednisone + Rituximab	*P*	Odds ratio [95 % CI][+]
Complete remission				
All patients — n (%)	N = 58	N = 50		
Month 3	41 (70.7)	34 (68.0)		[0.57;
Patients with poor prognosis i. e., titer > 20 BU/mL and FVIII < 1 IU/dL — n (%)	N = 28	N = 25		
Month 3	21 (75.0)	13 (52.0)	0.0204*	3.97
Time to 1st complete remission — days	N = 45	N = 41		
Median (Q1;	46 (43; 59)	48 (45; 52)		

 L´evesque H et al. Thromb Res 2024;237:79-87. Wang PJ. Am J Hematol. 2024;99:28–37.

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Month 3	21 (75.0)	13 (52.0)	0.0204*	3.97
Time to 1st complete remission — days	N = 45	N = 41		
Median (Q1;	46 (43; 59)	48 (45; 52)		

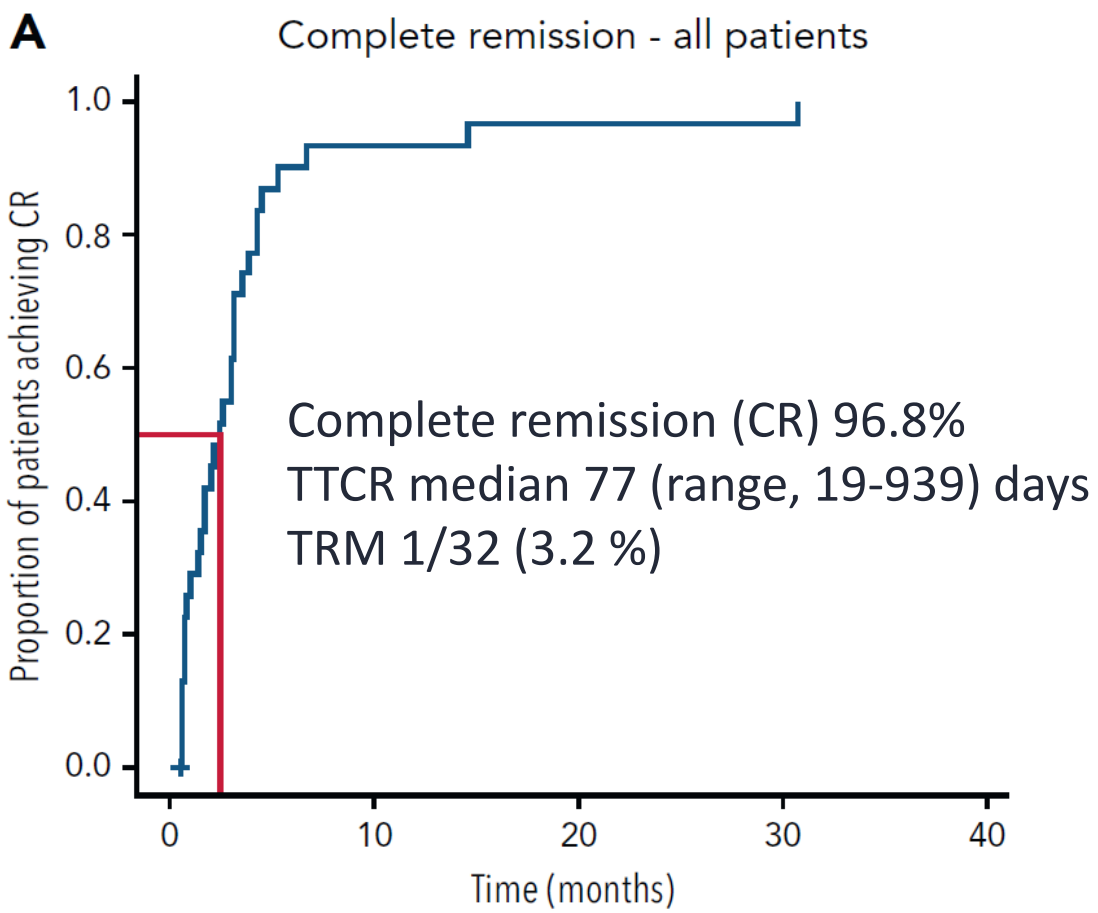
Single-dose rituximab plus glucocorticoid versus cyclophosphamide plus glucocorticoid in patients with newly diagnosed acquired hemophilia A: A multicenter, open-label, randomized noninferiority trial

	RTX + Glucocorticoid (*n* = 31)	CTX + Glucocorticoid (*n* = 32)	*p* value
Primary endpoint			
CR—no. (%)	24 (77·4)	22 (68·8)	·005
Secondary endpoints			
Median time to CR [IQR]—days	28·0 [20·8, 52·5]	36·0 [23·8, 50·3]	·41

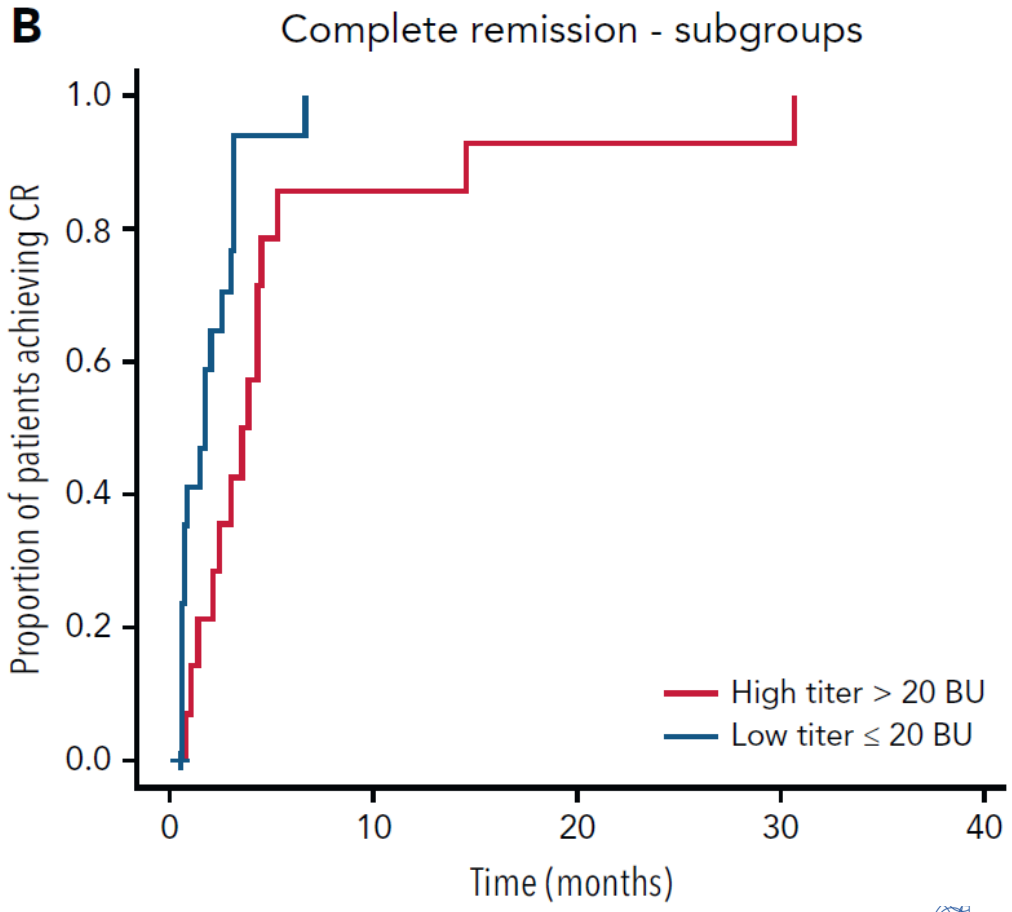
L´evesque H et al. Thromb Res 2024;237:79-87. Wang PJ. Am J Hematol. 2024;99:28–37.

Immunsuppressive Therapie - CyDRi

32 patients with AHA: cyclophosphamide 1000 mg on days 1 and 22
dexamethasone 40 mg on days 1, 8, 15, and 22
rituximab 100 mg on days 1, 8, 15, and 22



Complete remission (CR) 96.8%
TTCR median 77 (range, 19-939) days
TRM 1/32 (3.2 %)



 Simon B et al. Blood 2022;140;1983-1992

Sustained Improvement of Survival in Patients Receiving Emicizumab

Inga M. Schimansky. 555 Sustained Improvement of Survival in Patients Receiving Emicizumab Prophylaxis Instead of Immunosuppression during Early Management of Acquired Hemophilia a (AHA).

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Sustained Improvement of Survival in Patients Receiving Emicizumab

Infection as a major risk for patients with AHA

	UK[1]	EU[2]	FR[3]	DE/AT[4]	ES[5]	NL[6]
Year of publication	2007	2012	2013	2015	2021	2021
Fatal bleeding (%)	9.1	4.5	3.5	2.9	3.3	2.9
Fatal infection (%)	11	4.2	12	16	10	7.3

1. Collins PW, et al. Blood 2007; 109: 1870-7
2. Knöbl et al. J Thromb Haemost 2012; 10: 622–31
3. Borg et al. Haemophilia 2013; 19: 564-70
4. Tiede et al. Blood 2015; 125:1091-7
5. Minot-Castellano et al. Blood Adv 2021; 5: 3821-9
6. Schep et al. Am J Hematol 2021; 96: 51-9

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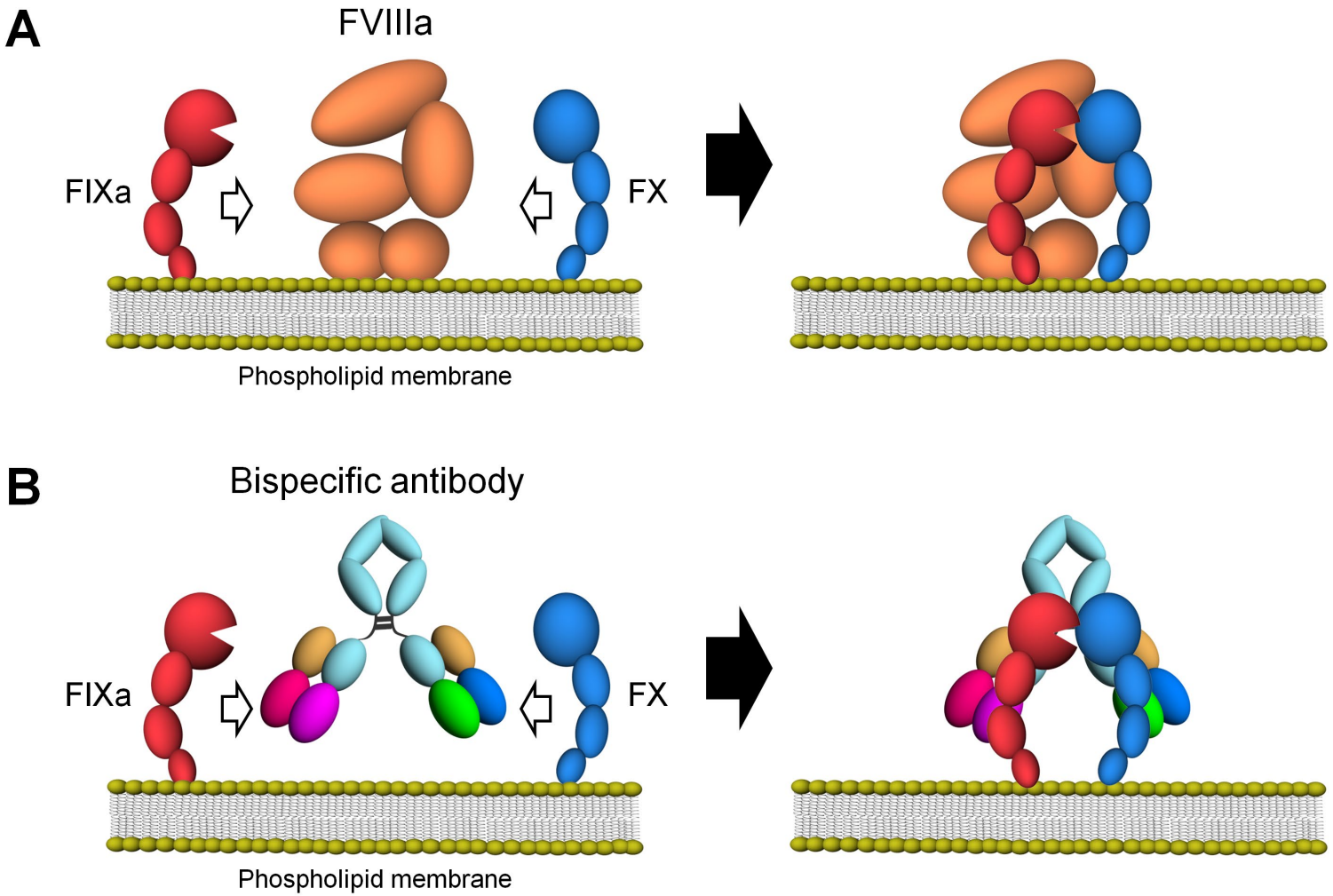
Emicizumab

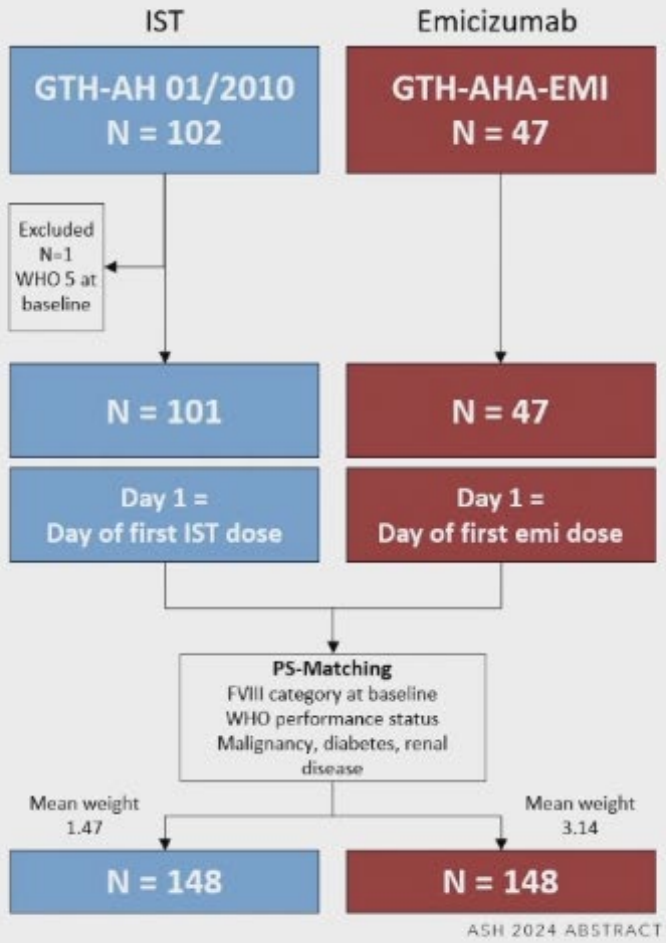


 Sampei Z et al. PLoS ONE 8(2): e57479. https://doi.org/10.1371/journal.pone.0057479

Sustained Improvement of Survival in Patients Receiving Emicizumab

Methods

- 2-year follow-up information was collected using an electronic case report form
- Sites reported data from last regular patient visit and additionally planned visits on site or over the telephone
- The matching strategy was predefined in the GTH-AHA-EMI study protocol and already reported for a short-term analysis[1]



1. Hart, Klamroth, Sachs et al. J Thromb Haemost. 2024; 22 (10): 2692-2701

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Sustained Improvement of Survival in Patients Receiving Emicizumab

Overall survival

1-year OS

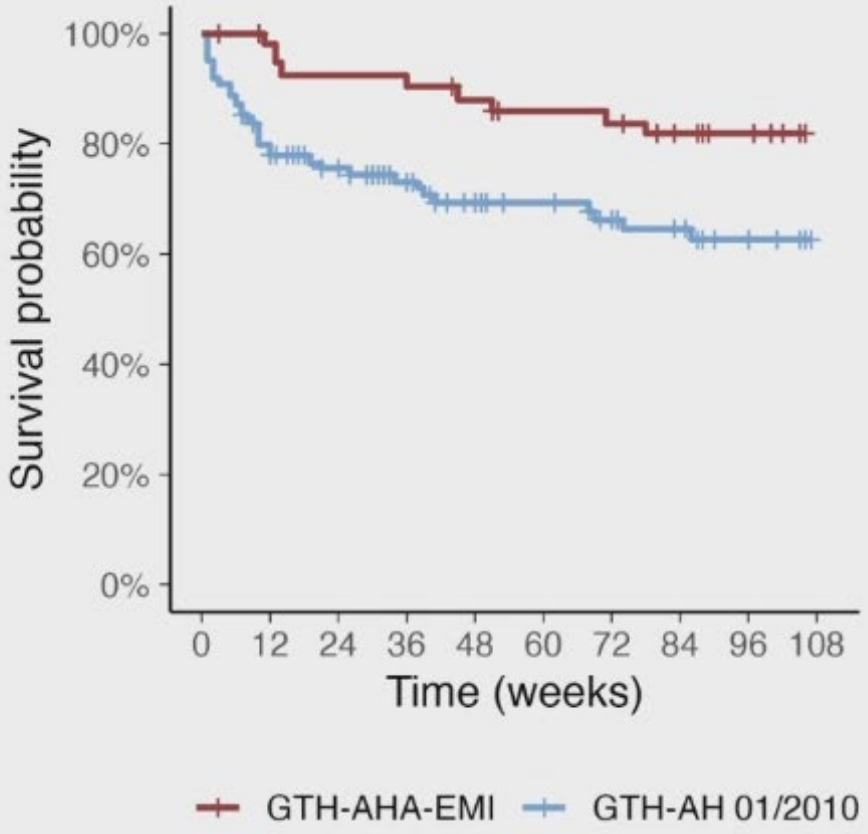
86% vs. 69% (Δ +17%)

2-year OS

82% vs. 63% (Δ +19%)

Relative risk of mortality reduced by 61%

HR 0.39 (95% CI 0.19-0.80, p<0.01)



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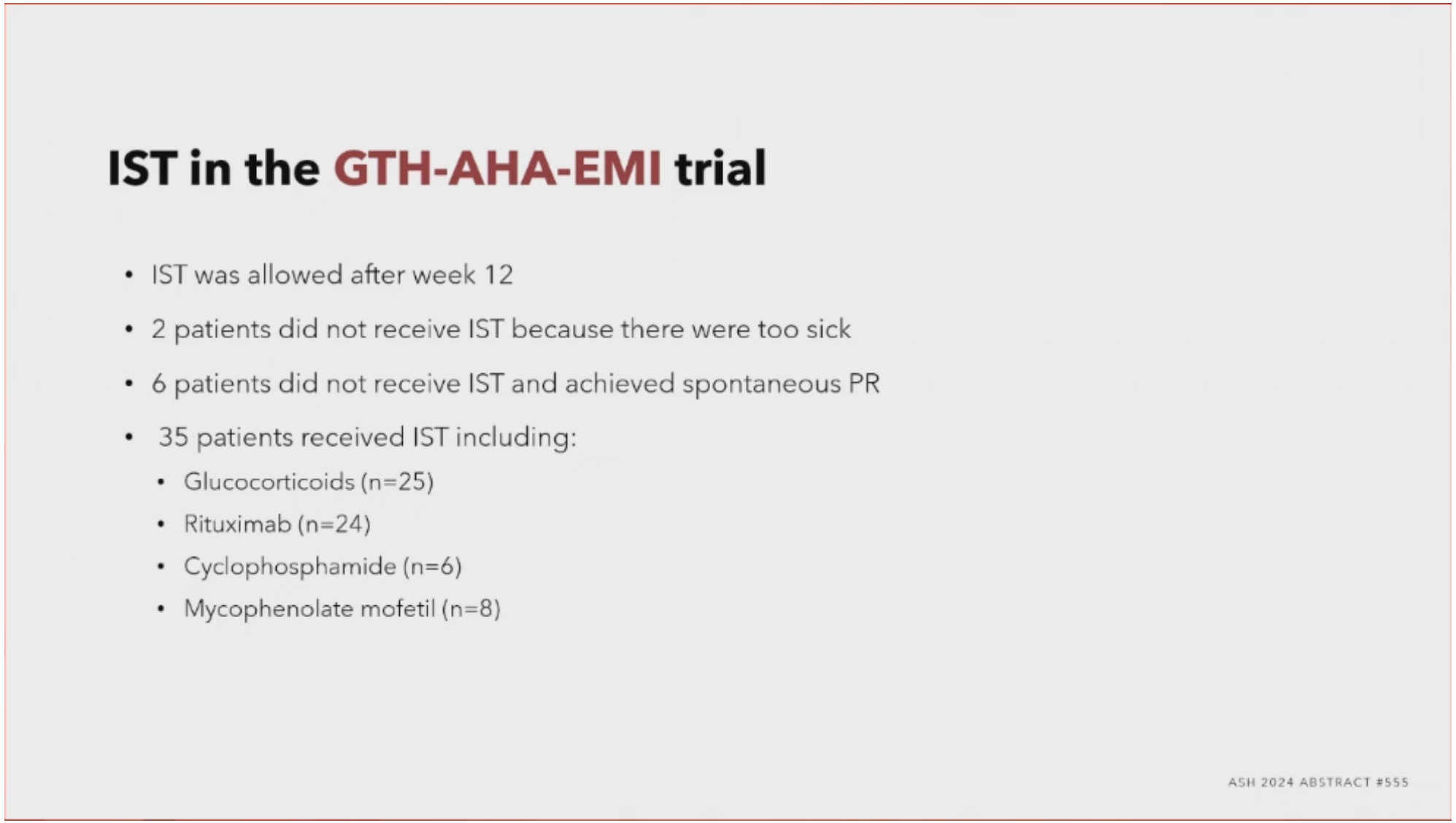

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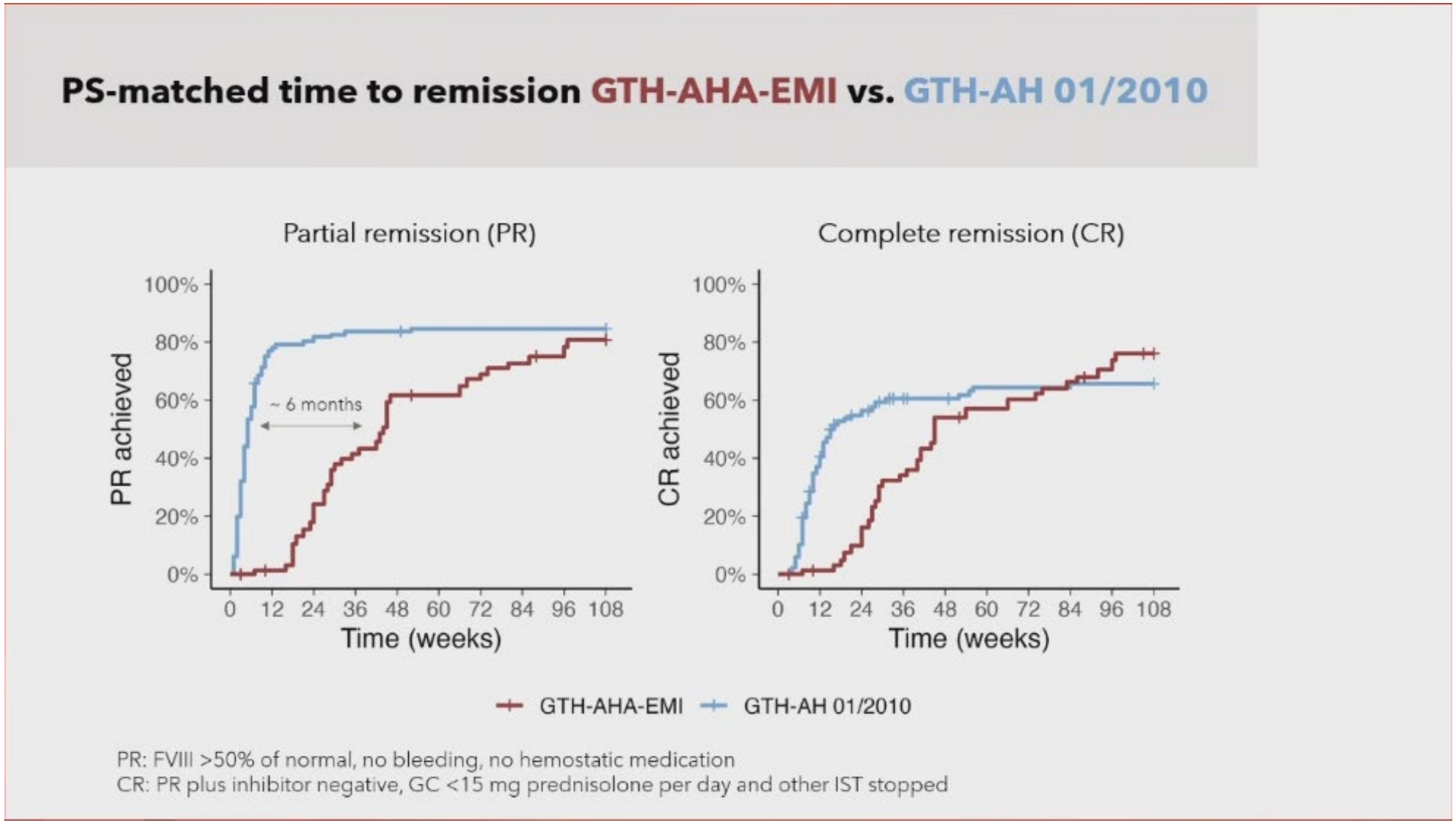

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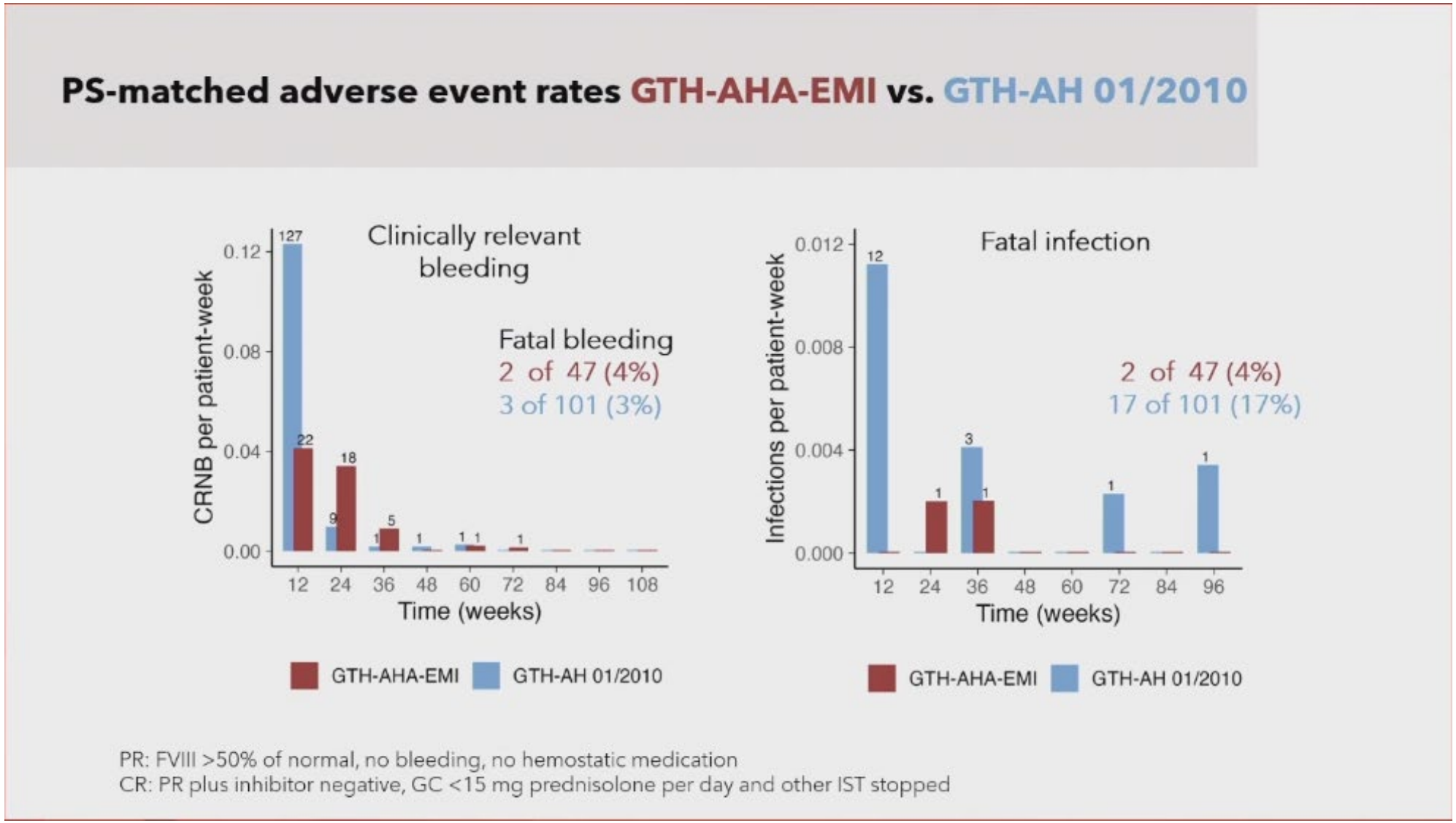

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Sustained Improvement of Survival in Patients Receiving Emicizumab

Summary

- PS-matched comparison of GTH-AHA-EMI (emicizumab, delayed IST) vs. GTH-AH 01/2010 (immediate IST) indicated
  - Overall survival improved (+ 19% absolute)
  - Fatal infection reduced (4% vs. 17%)
  - Fatal bleeding similar (4% vs. 3%)
  - Bleeding reduced in weeks 1-12, but relatively increased in weeks 13-24
  - Remission achieved later but in similar proportions at final follow-up

- Spontaneous remission occurred in 6 out of 41 (15%) patients

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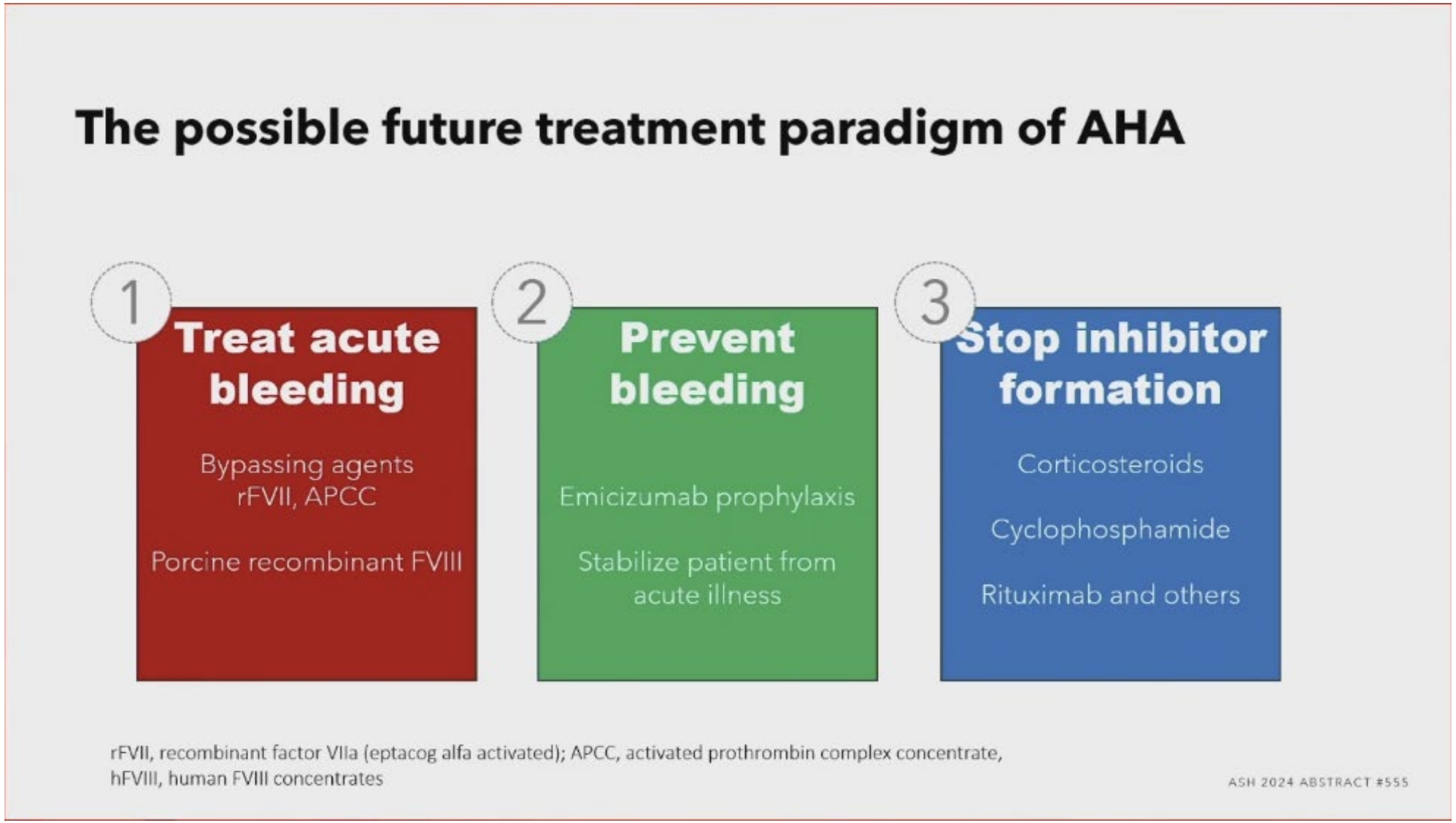

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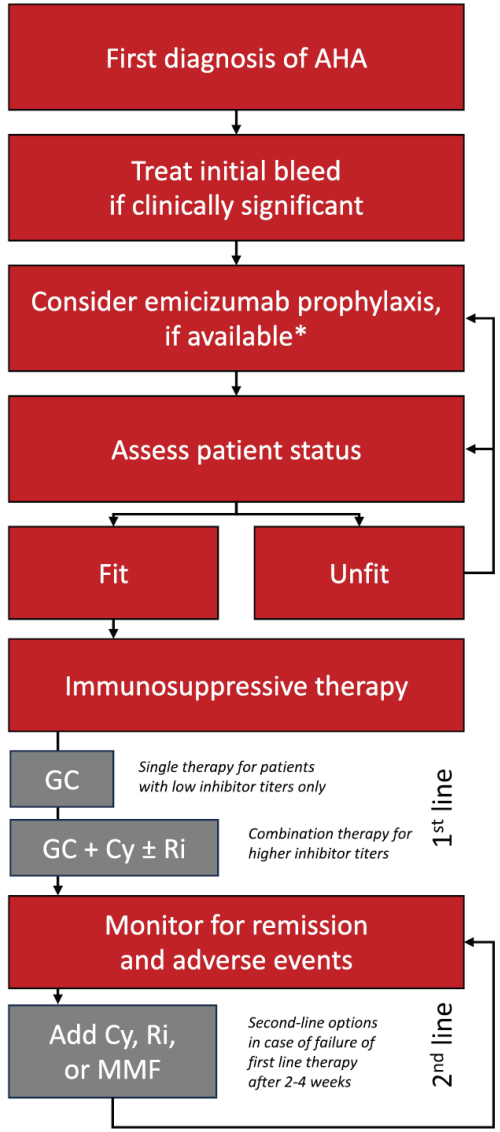
und am Ende….

Vielen Dank für Ihre Aufmerksamkeit

Universitätsklinikum Tübingen

Erworbene Hämophile - Behandlungsalgorithmus



 Tiede A. Hematology Am Soc Hematol Educ Program 2023 Vol. 2023 Issue 1 Pages 19-23

Hämostatische Therapie - Preise

	rFVIIa NovoSeven	APCC FEIBA	rpFVIII Obizur	Emicizumab Hemlibra
Offizieller Preis	0,92 €/µg	1,77 €/I.E.	2,90 €/I.E.	64,20 €/mg
ZE	0,87 €/µg	1,50 €/I.E.	3,41 €/I.E.	
NUB				60,72 €/mg
Erstdosis (75 kg)	6.204 €	6.646 € - 13.292 €	43.500 €	43.333 €
Intervalle	2 - 3 h	8 - 12 h	HWZ 10 h	7 Tage