

Behandlung der venösen Thrombose bei Thrombozytopenie

Prof. Dr. med. Amin Polzin

Herz- und Gefäßzentrum Düsseldorf

Klinik für Kardiologie, Pneumologie und Angiologie

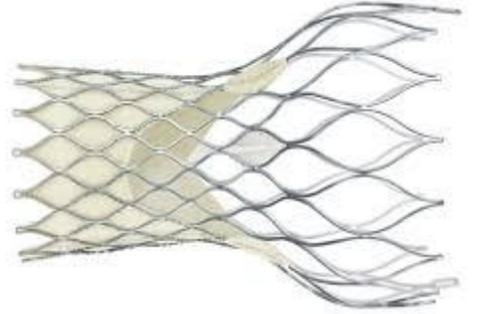
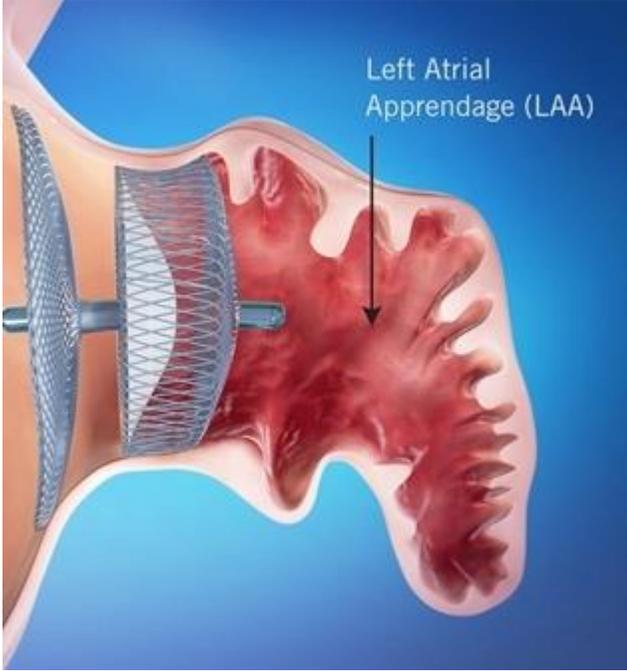
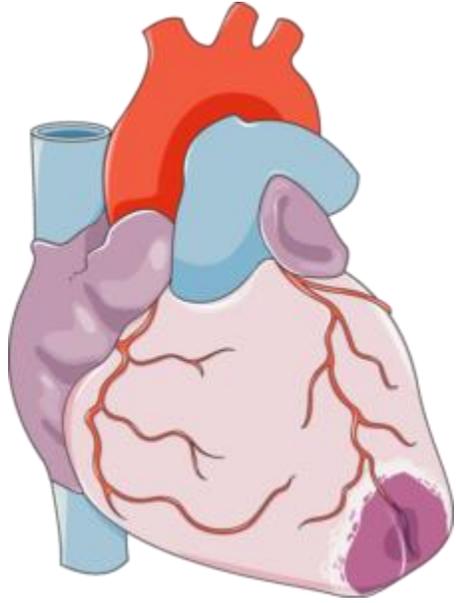
Cardiovascular Research Institute Düsseldorf

Disclosures:

- Speakers honoraria: Abbott, Abiomed, Amarin, AstraZeneca, Bayer, BMS, CorviaMedical, Daiichi Sankyo, Edwards, Medtronic, Occlutech, Pfizer, Philips
- Advisory Board: Bayer, BMS, BoehringerIngelheim, Edwards, Pfizer, Sanofi
- Clinical trials: Abbott, Abiomed, Bayer, BMS, Boston Scientific, CorviaMedical, Daiichi Sankyo, Medtronic, Novartis, Occlutech, Pfizer, Philips
- Research grants: Abiomed, Bayer, DFG, DZHK, DAAD, BMBF

Antithrombotische Therapie für kardiologische Eingriffe bei hämatologischen PatientInnen mit Thrombozytopenie

Konsensuspapier der Arbeitsgruppe „Kardiovaskuläre Hämostase und antithrombotische Therapie“ (AG19) der Deutschen Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V. (DGK), der Deutschen Gesellschaft für Transfusionsmedizin und Immunhämatologie (DGTI), der Deutschen Gesellschaft für Hämatologie und Medizinische Onkologie e. V. (DGHO) und der Gesellschaft für Thrombose- und Hämostaseforschung (GTH)



ACS mit Koronarintervention	50.000 – 100.000/ μ l	30.000 – 50.000/ μ l	< 30.000/ μ l	< 10.000/ μ l
	ASS + Clopidogrel für bis zu 6 Monate	ASS + Clopidogrel für 1 Monat	ASS für 1 Monat	Keine antithrombotische Therapie
	1 Monat			
	3 Monate			
	6 Monate			
12 Monate				

Relevanz?

5% aller kardiologischen Patienten weisen eine
Thrombozytopenie auf

Decreased Production



Bone Marrow Disorders

Increased Destruction



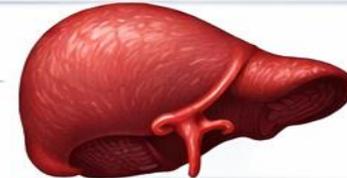
Autoimmune Diseases

Medication-Induced



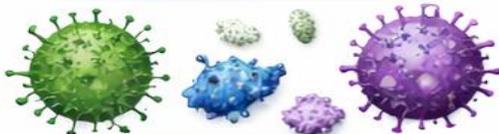
Drug Side Effects

Splenic Sequestration



Enlarged Spleen

Infections

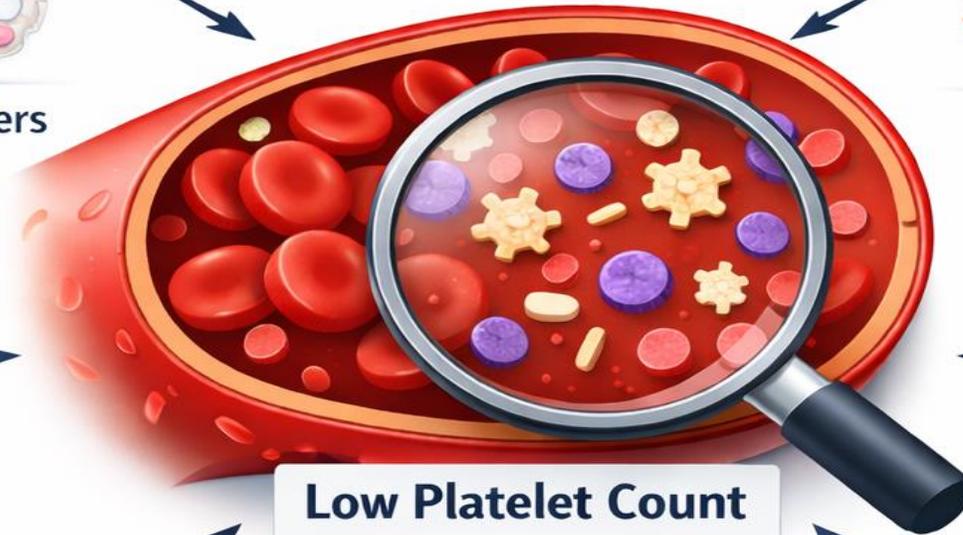


Viral or Bacterial

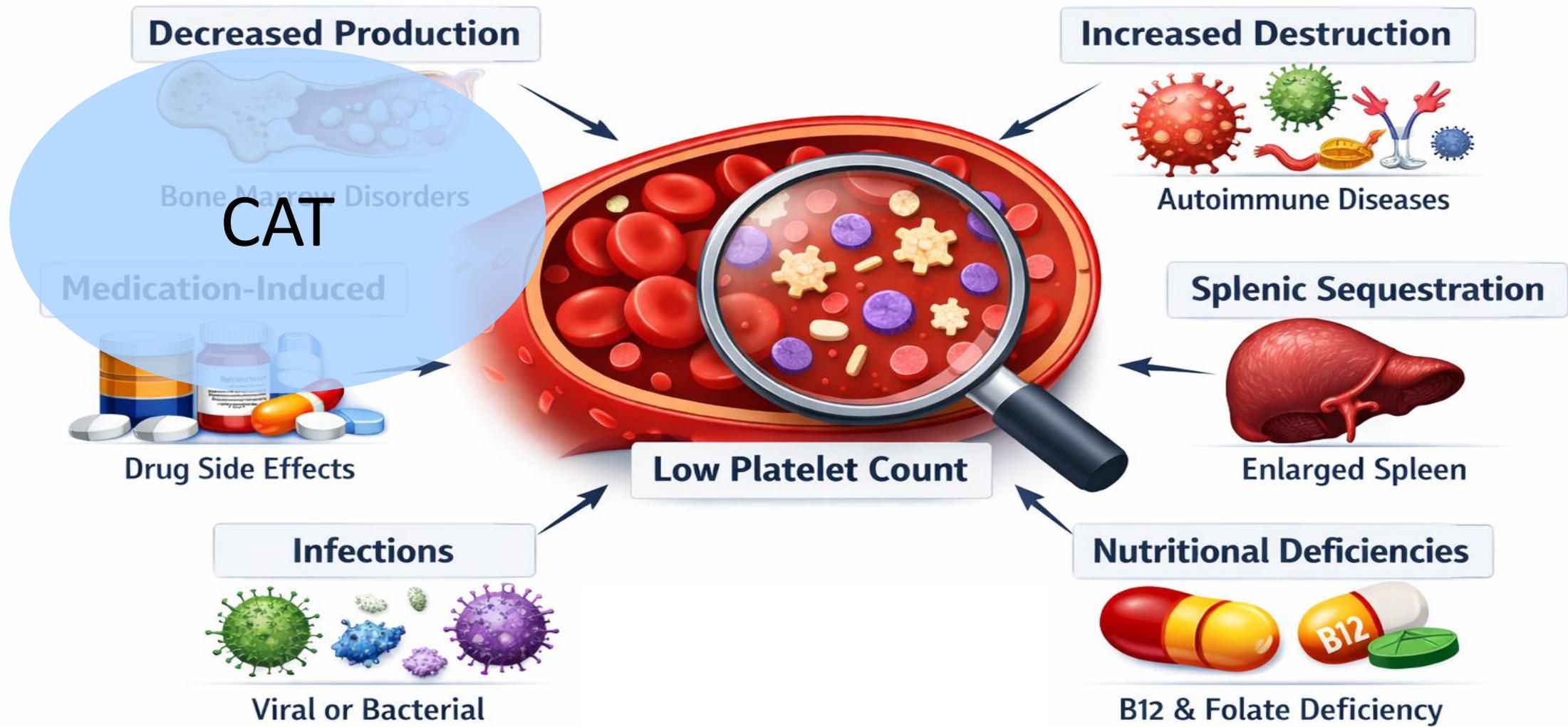
Nutritional Deficiencies



B12 & Folate Deficiency



Low Platelet Count



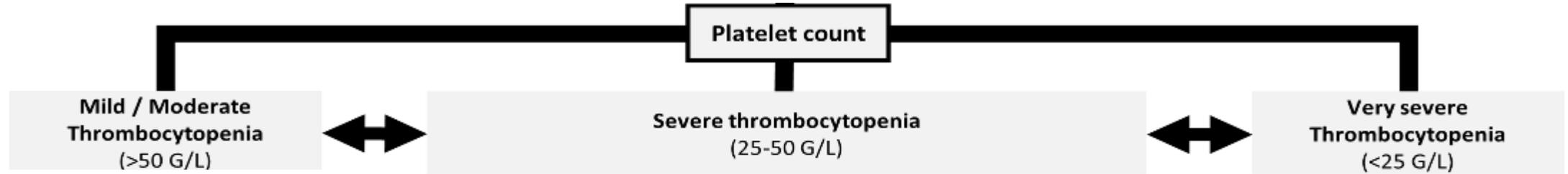
Behandlung der venösen Thrombose bei *Cancer-Associated Thrombosis und* Thrombozytopenie

Prof. Dr. med. Amin Polzin

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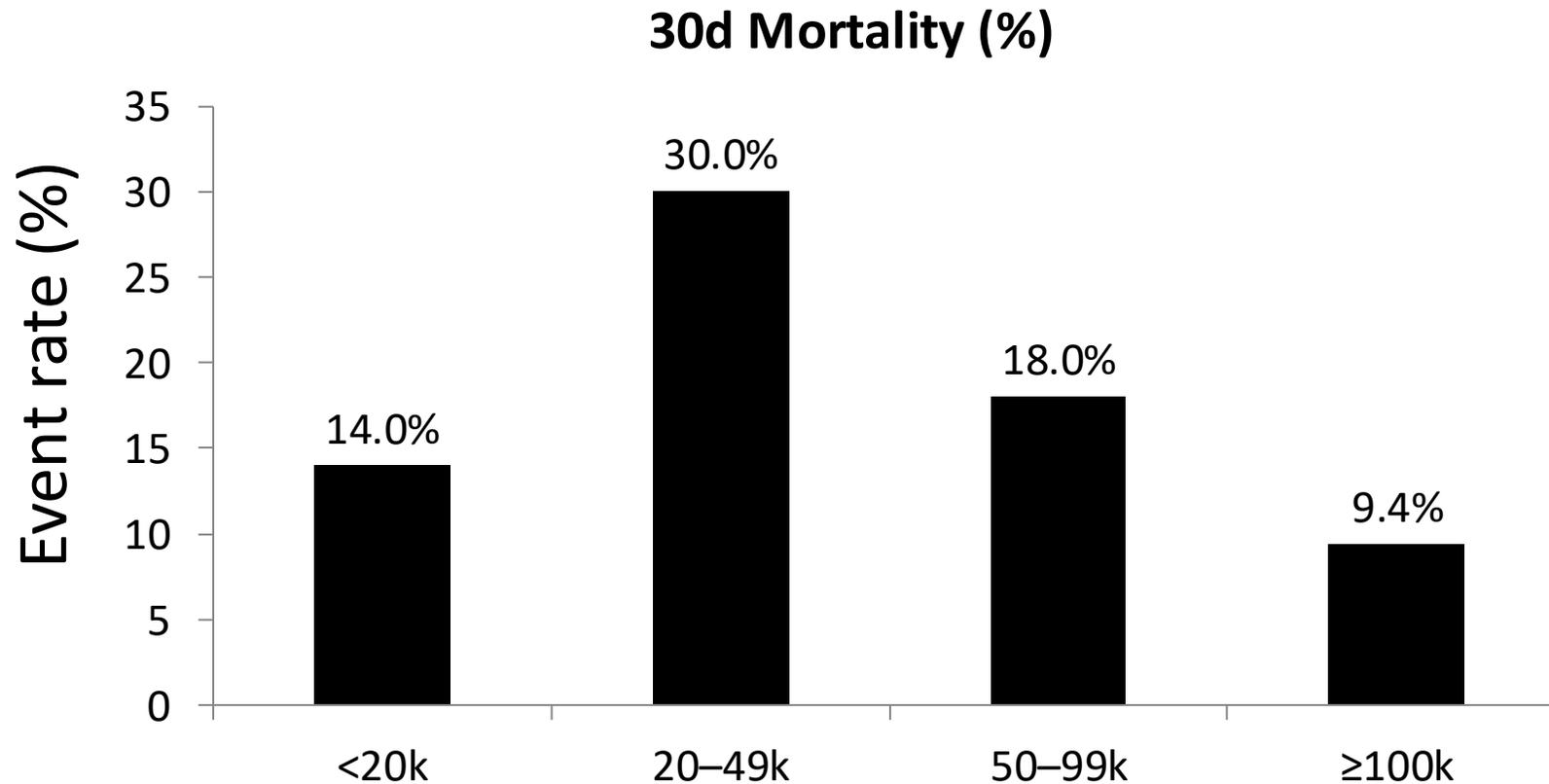
Cardiovascular Research Institute Düsseldorf



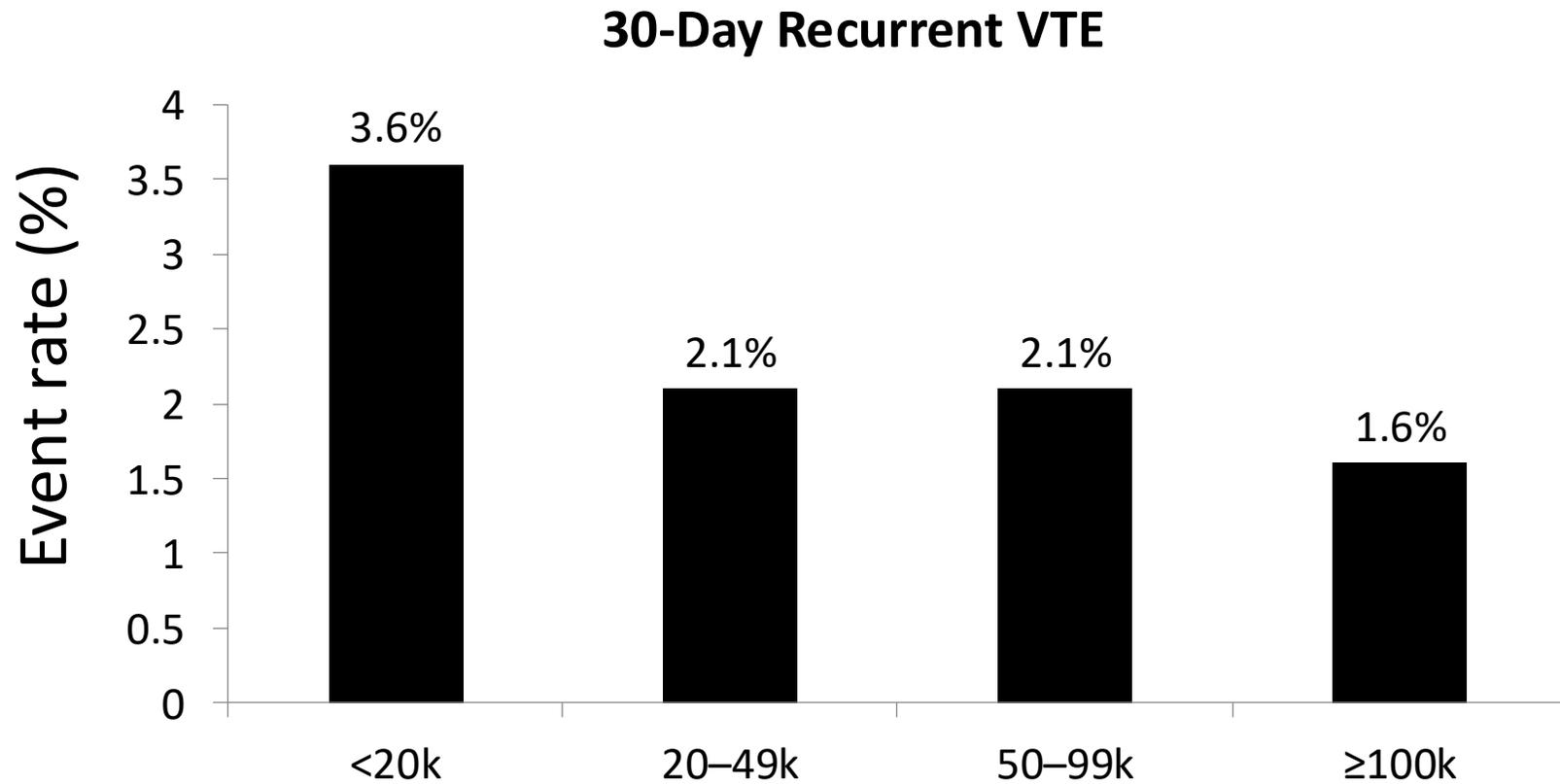
Recommendations	Class ^a	Level ^b
Apixaban, edoxaban, or rivaroxaban ^c are recommended for the treatment of symptomatic or incidental VTE in patients with cancer <i>without</i> contraindications. ^{d,578–581,584,585}	I	A



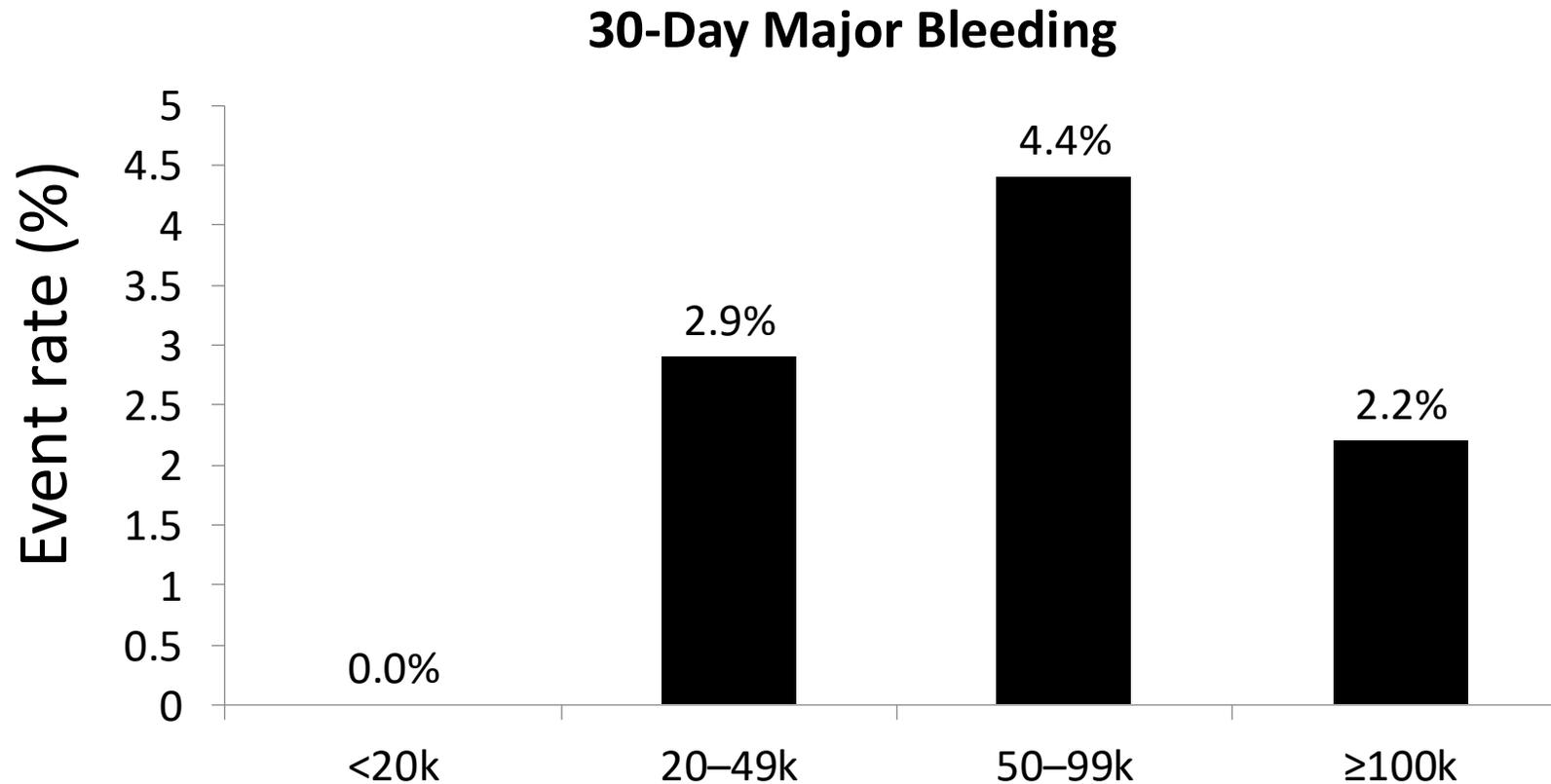
	Severe thrombocytopenia		Mild thrombocytopenia	Normal platelet count
	<20,000/ μ L	20–49,000/ μ L	50–99,000/ μ L	\geq 100,000/ μ L
Patients, N	28	138	711	14,460



	Severe thrombocytopenia		Mild thrombocytopenia	Normal platelet count
	<20,000/ μ L	20–49,000/ μ L	50–99,000/ μ L	\geq 100,000/ μ L
Patients, N	28	138	711	14,460



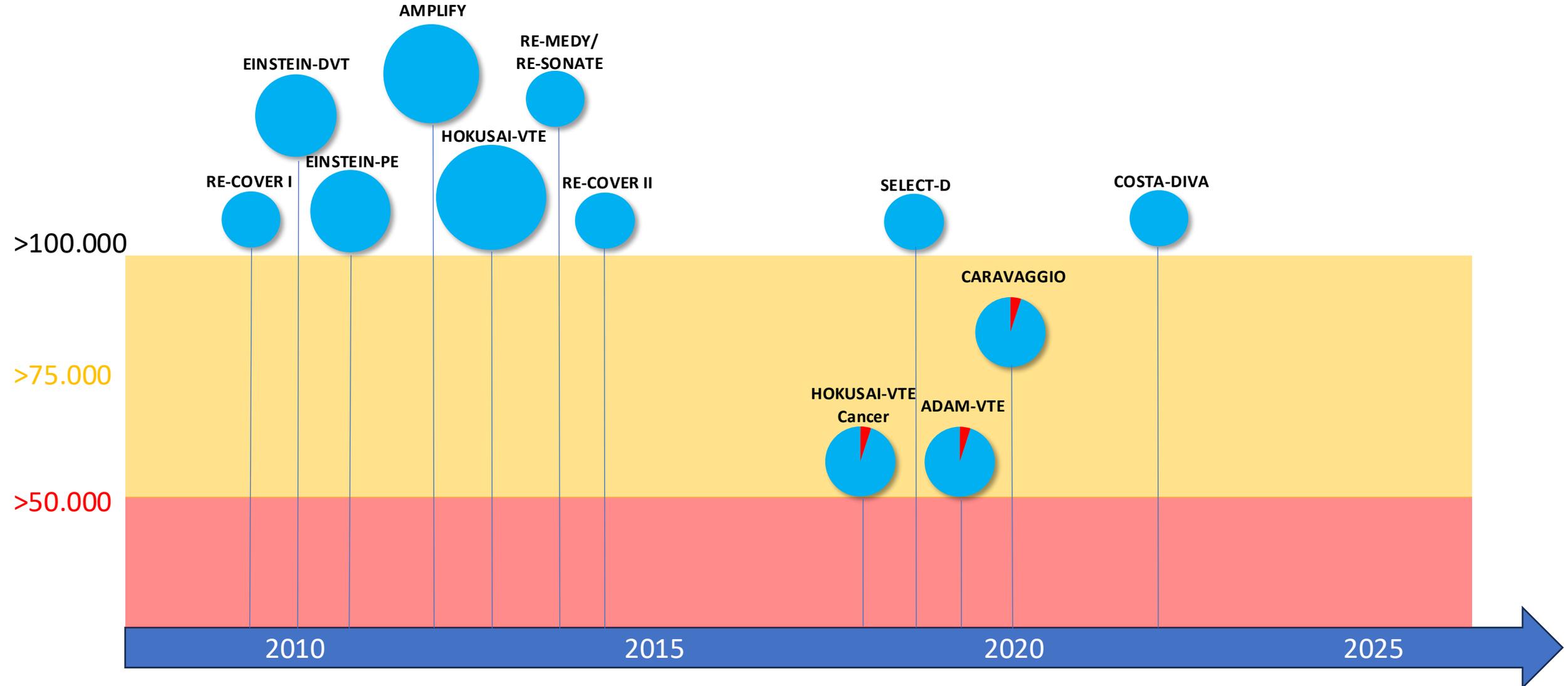
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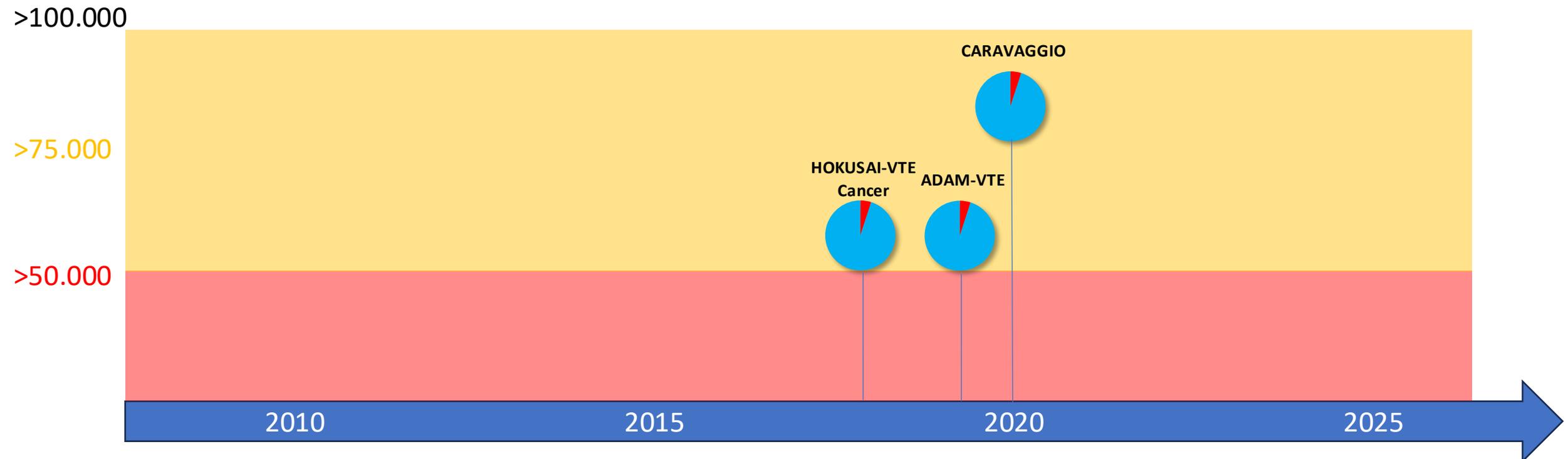
Treatment strategies.

	Severe thrombocytopenia		Mild thrombocytopenia	Normal platelet count
	< 20,000/ μ L	20–49,000/ μ L	50–99,000/ μ L	\geq 100,000/ μ L
Patients, N	28	138	711	14,460
Days of treatment (median, IQR)	58 (14–144)	64 (16–134) [‡]	109 (39–203) [‡]	137 (84–256)
Initial therapy,				
Unfractionated heparin	1 (3.6%)	14 (10%)	46 (6.5%)	703 (4.9%)
Low-molecular-weight heparin	21 (75%)	109 (79%)*	620 (87%) [‡]	13,140 (91%)
Mean LMWH dose (IU/kg/day)	95 \pm 56 [‡]	130 \pm 62 [‡]	163 \pm 48 [‡]	172 \pm 44
LMWH < 100 IU/kg/day	15 (71%) [‡]	40 (37%) [‡]	69 (11%) [‡]	885 (6.7%)
LMWH 100–150 IU/kg/day	2 (1.0%)	24 (22%)	145 (23%) [†]	2509 (19%)
LMWH > 150 IU/kg/day	4 (19%) [‡]	45 (41%) [‡]	406 (65%) [‡]	9730 (74%)
Fondaparinux	0	3 (2.2%)	20 (2.8%) [‡]	166 (1.1%)
Direct oral anticoagulants	0	0	2 (0.3%)	73 (0.5%)
Thrombolytics	0	2 (1.4%)	2 (0.3%)	103 (0.7%)
Inferior vena cava filter	3 (11%) [†]	9 (6.5%) [†]	16 (2.3%)	238 (1.6%)
No anticoagulant therapy	6 (21%) [‡]	10 (7.2%)*	21 (3.0%)	286 (2.0%)
Long-term therapy,				
LMWH	14 (54%)	85 (63%)	483 (69%)	9797 (68%)
Mean LMWH dose (IU/kg/day)	94 \pm 57 [‡]	126 \pm 49 [‡]	145 \pm 46 [†]	153 \pm 46
LMWH < 100 IU/kg/day	8 (57%) [‡]	21 (25%)	79 (16%) [†]	1137 (12%)
LMWH 100–150 IU/kg/day	3 (21%)	36 (42%)	169 (35%)	3338 (34%)
LMWH > 150 IU/kg/day	3 (21%)*	28 (33%) [‡]	235 (49%)*	5312 (54%)
Vitamin K antagonists	1 (3.8%)	13 (9.7%)	96 (14%) [‡]	3184 (22%)
Direct oral anticoagulants	0	2 (1.5%)	9 (1.3%)	234 (1.6%)
Fondaparinux	2 (7.7%)	4 (3.0%)	19 (2.7%) [‡]	156 (1.1%)

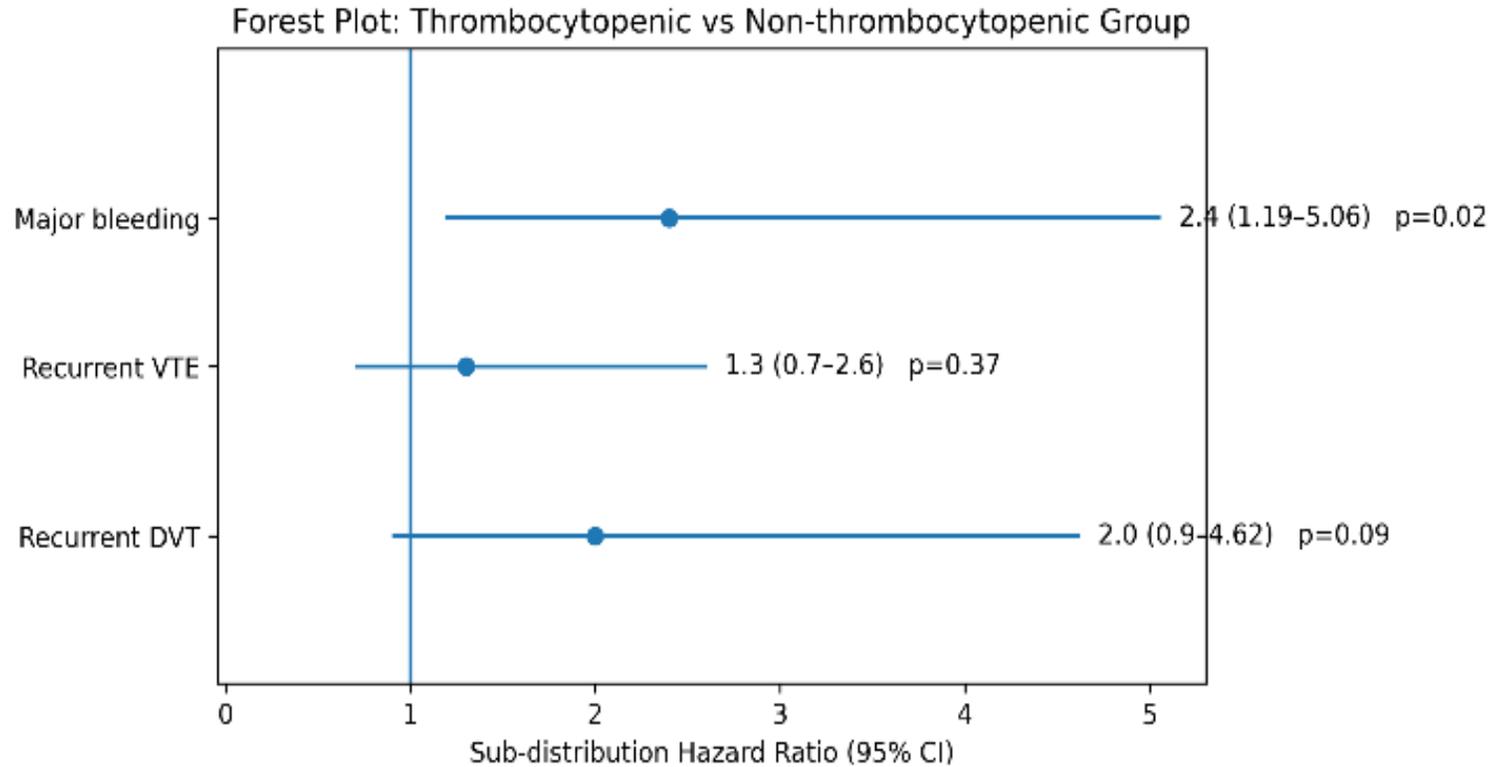
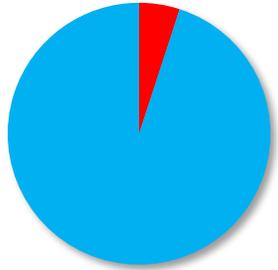
Randomisierte Studien zu NOAC und TVT/LE



Randomisierte Studien zu NOAC und TVT/LE



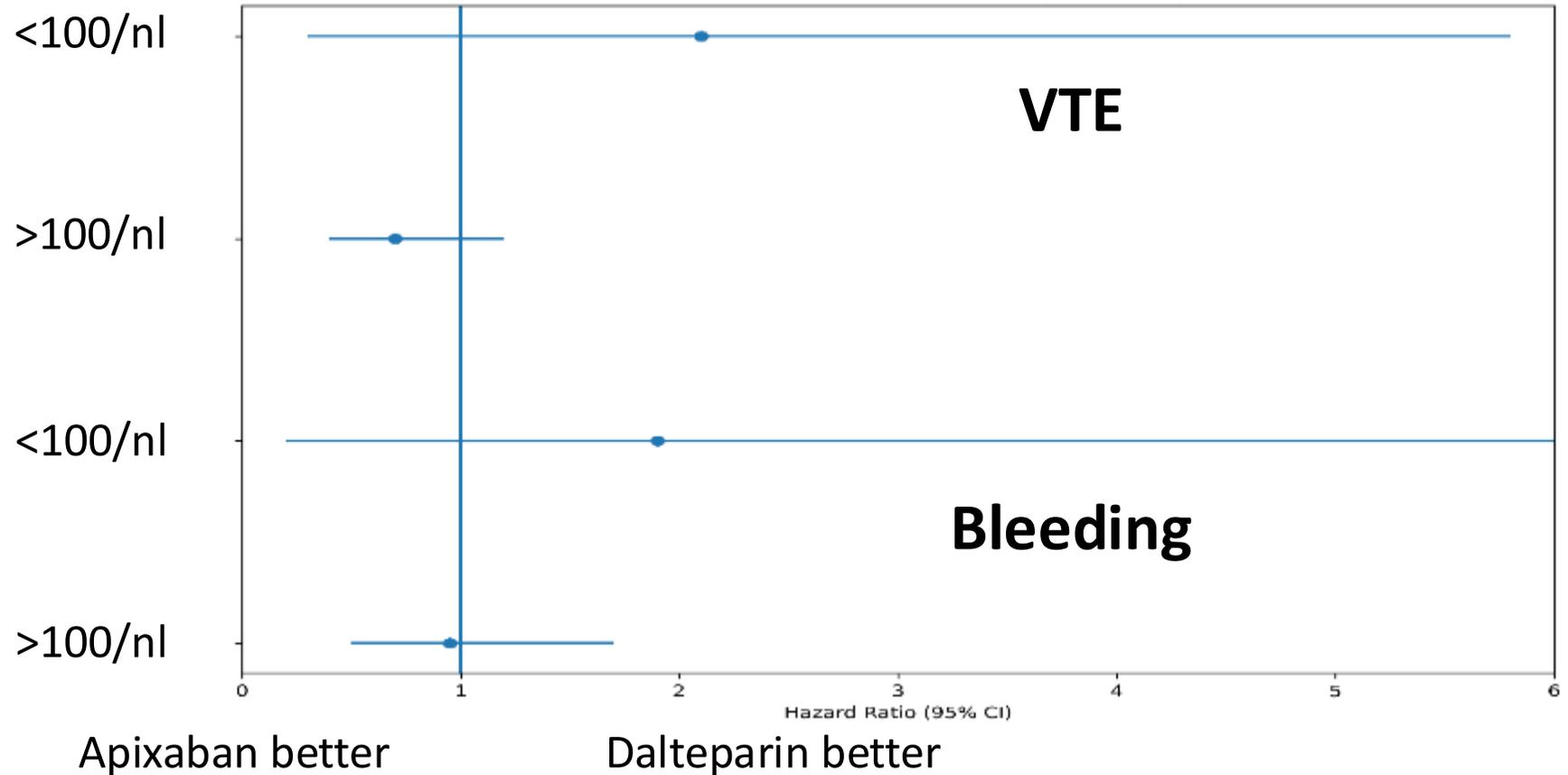
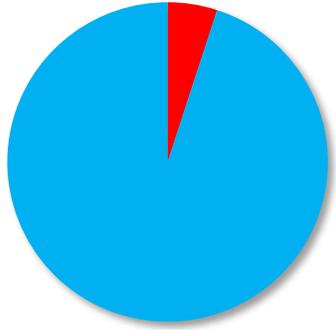
HOKUSAI-VTE Cancer



Bleeding ↑

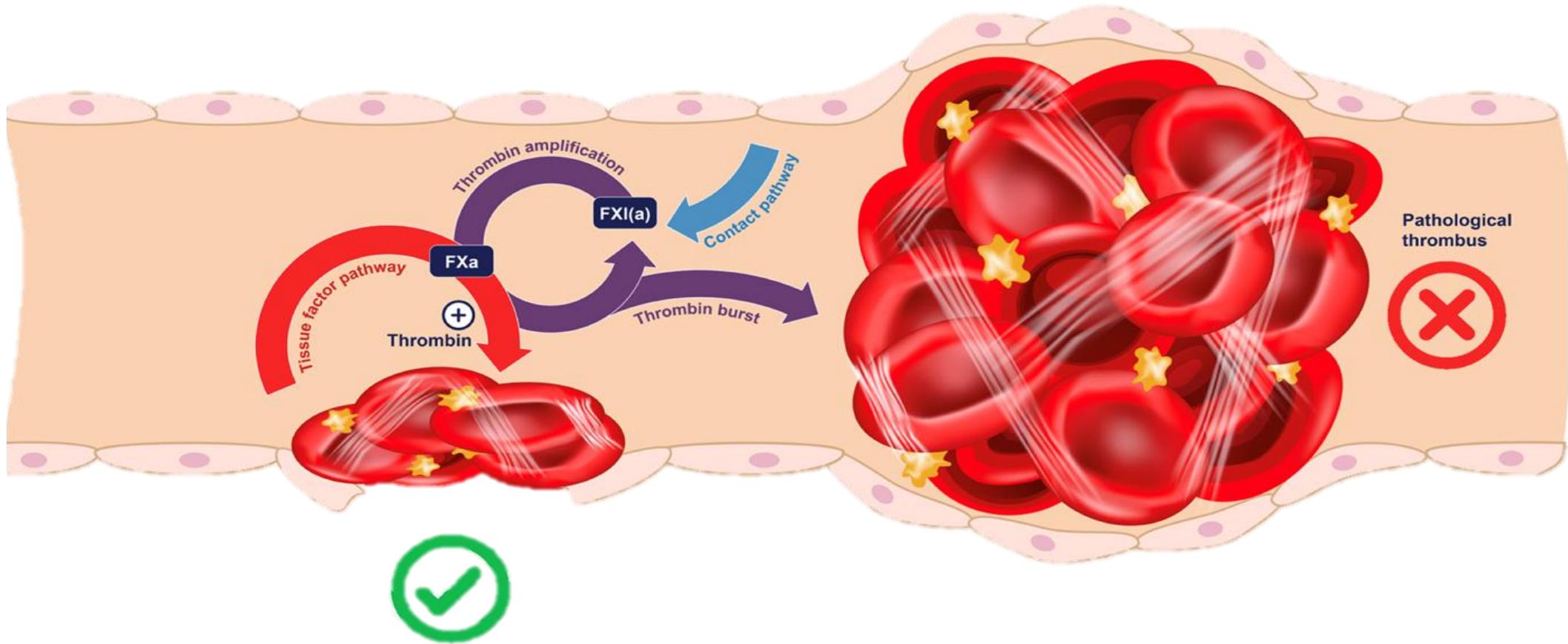
DVT ↑

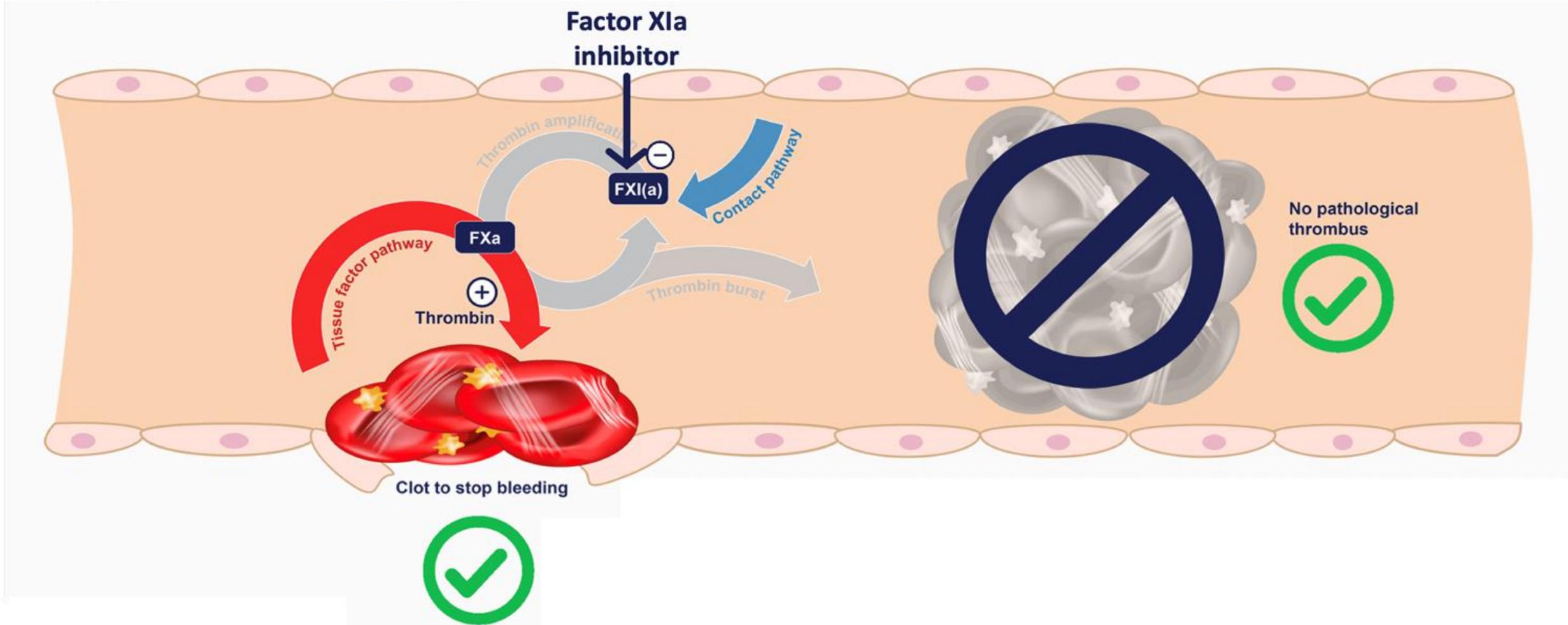
CARAVAGGIO



- CAT und Thrombozytopenie:
 - >50/nl – volle Dosis LMWH/ NOAC
 - 25-50/nl – individuelle Risikostratifizierung
 - Volle Dosis Heparin + Thrombozytentransfusion
 - Halbe Dosis oder prophylaktische Dosis Heparin
 - >25/nl – eher keine Antikoagulation
- CAVE: auch 50-100/nl mit erhöhtem Risiko

Zukunft





Vorhofflimmern

- OCEANIC-AF
- OCEANIC-AFINA
- Librexia-AF
- LILAC-TIMI 76

ACS

- Librexia-ACS

Schlaganfall

- OCEANIC-STROKE
- Librexia-Stroke



OCEANIC

AF

OCEANIC-AF Study Design



Atrial Fibrillation

Asundexian
50 mg QD

Apixaban
5 mg or 2.5 mg BID

*Randomize
Double-Blind /
Double-Dummy
(n ~ 18,000)*

Sample size of 18,000 (24 months randomization) allows for reaching 340 primary efficacy (90% power) events within 33 months for incidence rate 1.5.

Monthly Monitoring
Adherence to standard-of-care guidelines

Primary Efficacy Endpoint: Stroke or Systemic Embolism

Primary Safety Endpoint: ISTH Major Bleeding

Primary Net Clinical Benefit Endpoint: Stroke or Systemic Embolism and ISTH Major Bleeding

IDMC Recommends Stopping OCEANIC-AF

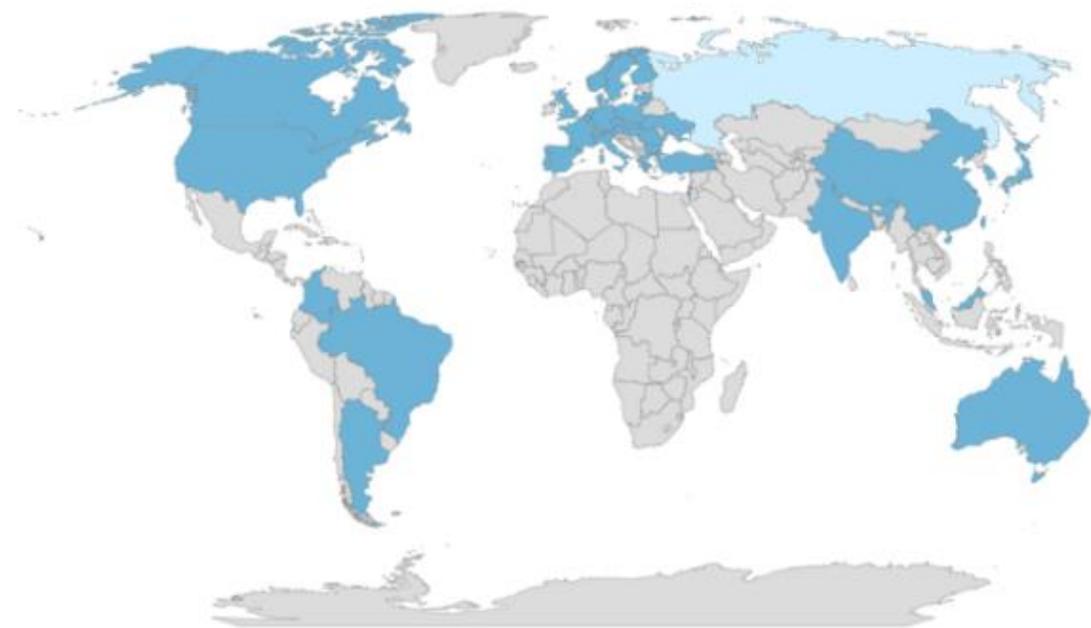


From December 2022 to November 2023, 14,830 of the planned 18,000 patients had been randomized

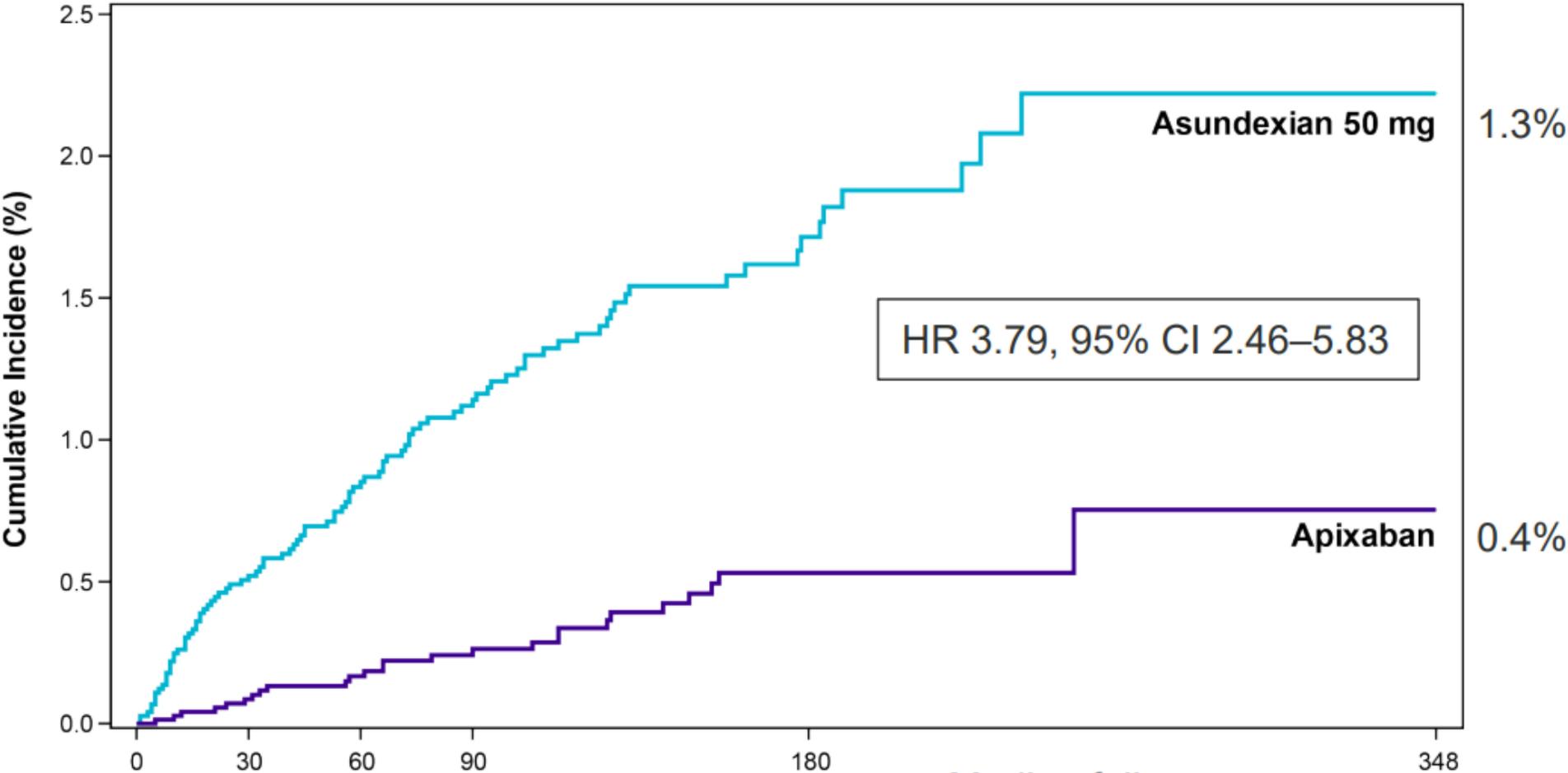
IDMC recommended stopping OCEANIC-AF to the EC and study team due to inferiority of Asundexian to Apixaban for the prevention of stroke and systemic embolism

November 19th, 2023: Sites notified worldwide

// Patients transition to open-label therapy and close-out visits conducted across the world



Cumulative Event Rate for the Primary Efficacy Endpoint



	Number of participants at risk				Days
	0	30	60	90	180
Asundexian 50 mg	7415	6564	5574	4622	1958
Apixaban	7395	6596	5624	4657	1979

1
0

Efficacy Events

Efficacy Events According to ITT	Asundexian (N=7415)	Apixaban (N=7395)	Total (N=14,810)	csHR (95% CI)*
Stroke or SE	98 (1.3%)	26 (0.4%)	124 (0.8%)	3.79 (2.46–5.83)
Ischemic stroke or SE	96 (1.3%)	22 (0.3%)	118 (0.8%)	4.38 (2.76–6.96)
All-cause mortality	60 (0.8%)	71 (1.0%)	131 (0.9%)	0.84 (0.60–1.19)
Ischemic stroke	85 (1.1%)	21 (0.3%)	106 (0.7%)	4.06 (2.52–6.54)
CV death	48 (0.6%)	44 (0.6%)	92 (0.6%)	1.09 (0.72–1.64)
CV death, MI, or stroke	155 (2.1%)	77 (1.0%)	232 (1.6%)	2.02 (1.54–2.66)

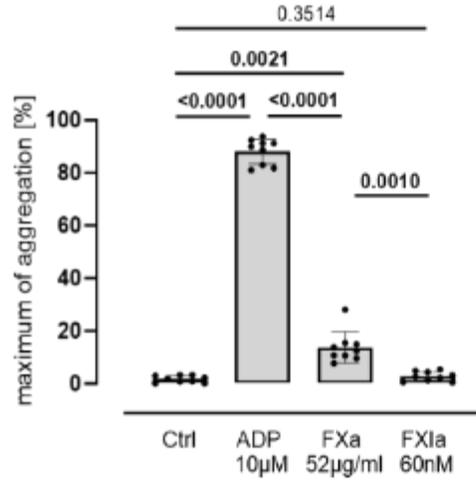
*Derived from a stratified cause-specific Cox proportional hazards regression model. Cumulative Incidence Rates provided
 CI indicates confidence interval; csHR, cause-specific hazard ratio; CV, cardiovascular; ITT, intention to treat; MI, myocardial infarction; SE, systemic embolism.

Safety Events

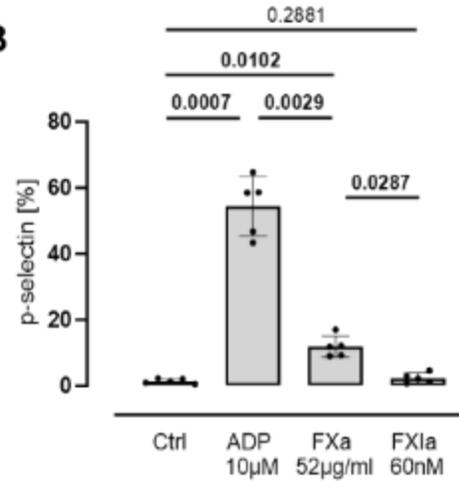


	Asundexian 50 mg (N=7373)	Apixaban (N=7364)	Total (N=14,737)	csHR (95% CI)[†]
ISTH major bleeding	17 (0.2%)	53 (0.7%)	70 (0.5%)	0.32 (0.18–0.55)
ISTH major and CRNM bleeding	83 (1.1%)	188 (2.6%)	271 (1.8%)	0.44 (0.34–0.57)
ISTH CRNM bleeding	67 (0.9%)	140 (1.9%)	207 (1.4%)	0.48 (0.36–0.64)
Hemorrhagic stroke	1 (<0.1%)	6 (0.1%)	7 (<0.1%)	0.17 (0.02–1.42)
Symptomatic intracranial hemorrhage	3 (<0.1%)	18 (0.2%)	21 (0.1%)	0.16 (0.05–0.55)
Fatal bleeding	0 (0%)	4 (0.1%)	4 (<0.1%)	Not calculated
ISTH minor bleeding	187 (2.5%)	317 (4.3%)	504 (3.4%)	0.59 (0.49–0.70)
Stroke, SE, or ISTH major bleeding (net clinical benefit endpoint)	120 (1.6%)	75 (1.0%)	195 (1.3%)	1.61 (1.21–2.15)

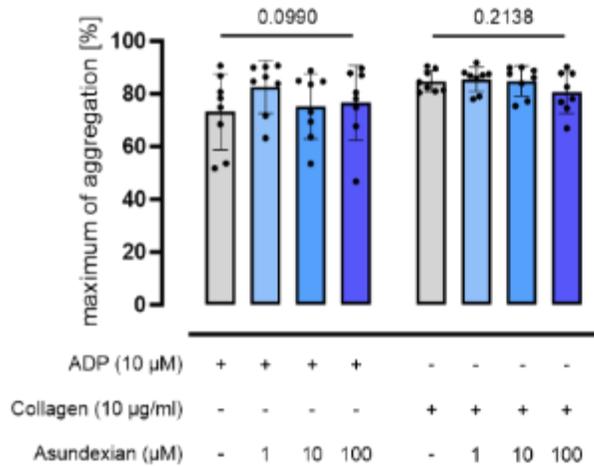
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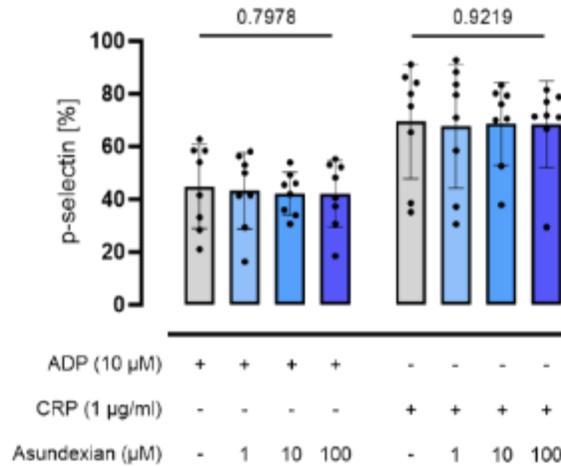
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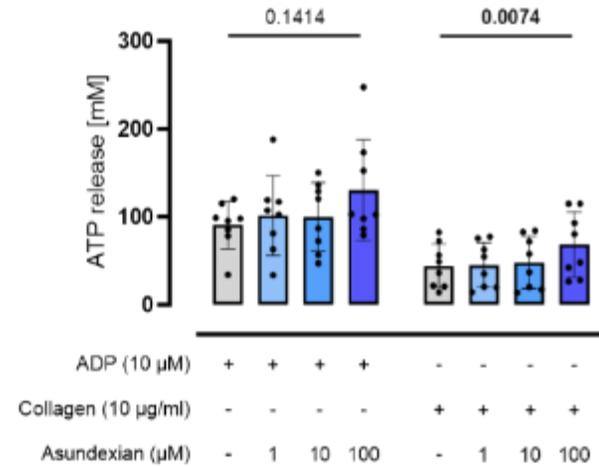
C



D



E



Vorhofflimmern

- ~~OCEANIC-AF~~
- OCEANIC-AFINA
- Librexia-AF
- LILAC-TIMI 76

ACS

- Librexia-ACS

Schlaganfall

- OCEANIC-STROKE
- Librexia-Stroke



**Population Health
Research Institute**
HEALTH THROUGH KNOWLEDGE



**International
Stroke
Conference**

FACTOR XIa INHIBITION WITH ASUNDEXIAN IN ACUTE NON-CARDIOEMBOLIC STROKE OR HIGH-RISK TRANSIENT ISCHEMIC ATTACK: PRIMARY RESULTS OF THE OCEANIC-STROKE TRIAL

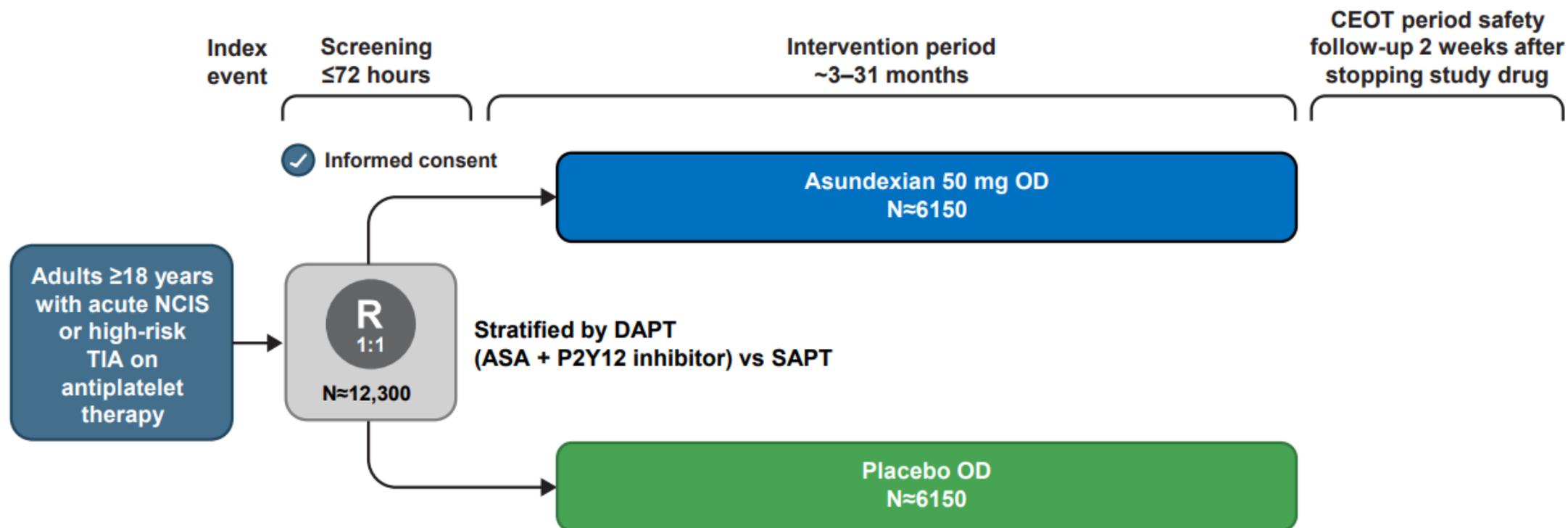
M. Sharma, Q. Dong, T. Hirano, S. Kasner, J. Saver, J. Masjuan, A. Demchuk, C. Cordonnier, D. Bereczki, G. Tsivgoulis, R. Veltkamp, I. Staikov, H-J. Bae, B. Campbell, A. Zini, I-H. Lee, S. Ameriso, M. Kovar, R. Mikulik, R. Lemmens, J. Ferro, T. Robinson, H. Christensen, S. Ozturk, R. Leker, P. Turcani, A. Slowik, P. Amaya, F.K. Hoo, G.M. De Marchis, M. Knoflach, P.N. Sylaja, J. Putaala, J.M. Coutinho, H.B. van der Worp, E. Miglane, V. Matijosaitis, A.G. Lindgren, G. Sampaio Silva, E. Sandset, S. Turuspekova, P. Amarenco, K. Sheth, E.E. Smith, J. Eikelboom, R. Joundi, K. Schulze, L. Xu, L. Heenan, C. Neumann, J. Gilbride, E. Muehlhofer, P. Colorado, L. Keller, H. Mundl, A. Shoamanesh for the OCEANIC-STROKE Steering Committee and Investigators



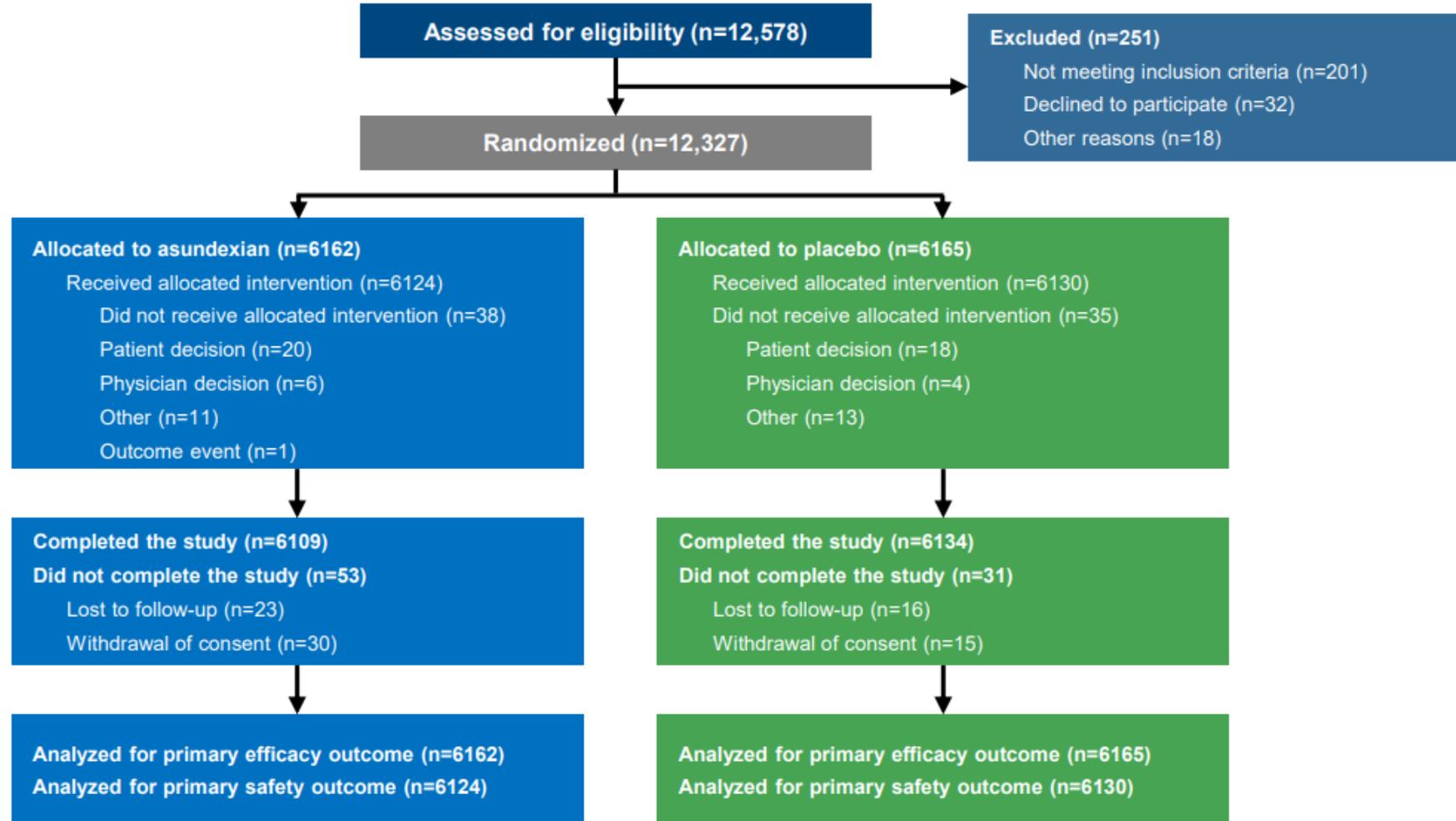
**American
Stroke
Association.**
*A division of the
American Heart Association.*

#ISC26

OCEANIC-STROKE: STUDY DESIGN



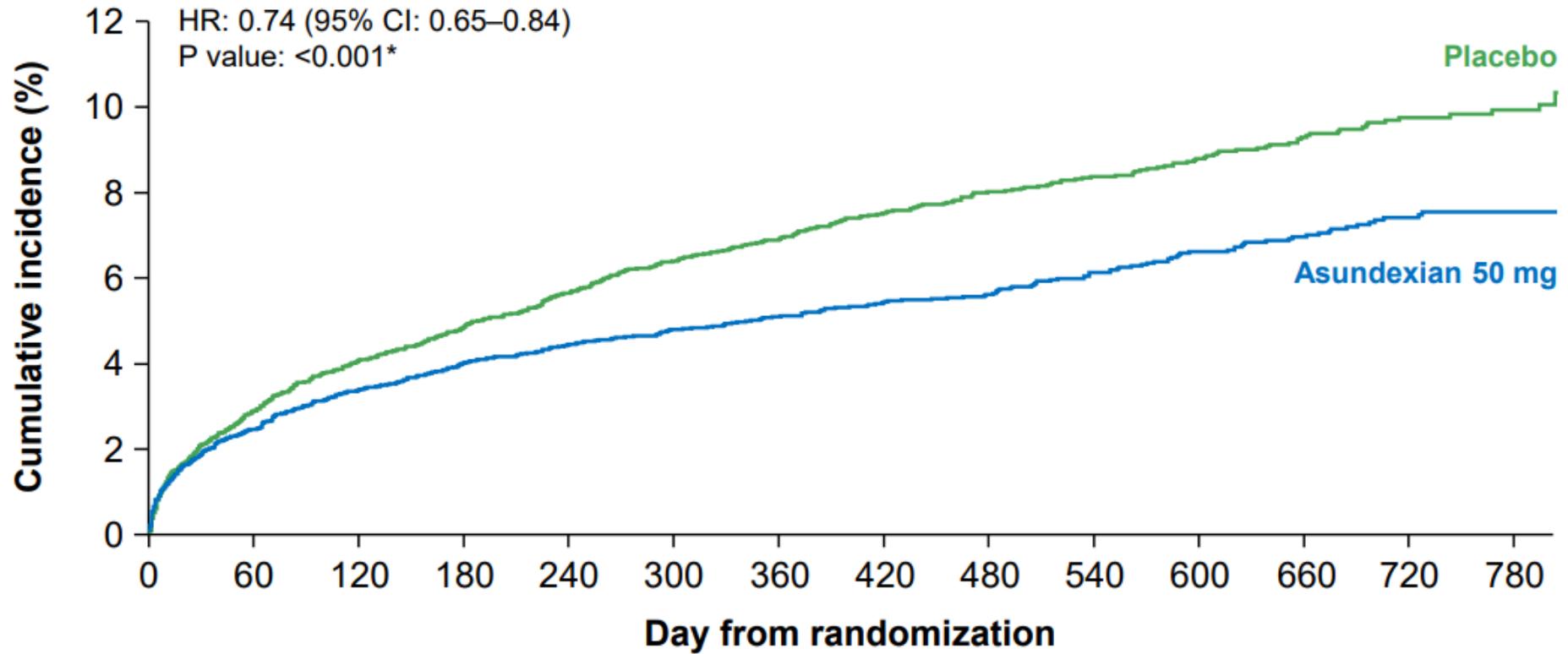
CONSORT DIAGRAM



INDEX EVENT CHARACTERISTICS

Characteristics	Asundexian 50 mg	Placebo
Index event, n (%)		
Ischemic stroke	5839 (94.8)	5838 (94.7)
High-risk TIA	323 (5.2)	325 (5.3)
TOAST subtype of index event,[†] n (%)		
Large-artery atherosclerosis	2512 (43.0)	2484 (42.5)
Stroke of undetermined etiology	1786 (30.6)	1710 (29.3)
Small-vessel occlusion	1290 (22.1)	1349 (23.1)
Stroke of other etiology	161 (2.8)	188 (3.2)
Cardioembolic	89 (1.5)	107 (1.8)
NIHSS at randomization,[†] median (IQR)	2 (1, 4)	2 (1, 4)
NIHSS at randomization,[†] n (%)		
≤3	4087 (70.0)	4079 (69.9)
4–7	1385 (23.7)	1375 (23.6)
≥8	365 (6.3)	382 (6.5)
Dual antiplatelet therapy	3859 (62.6)	3853 (62.5)

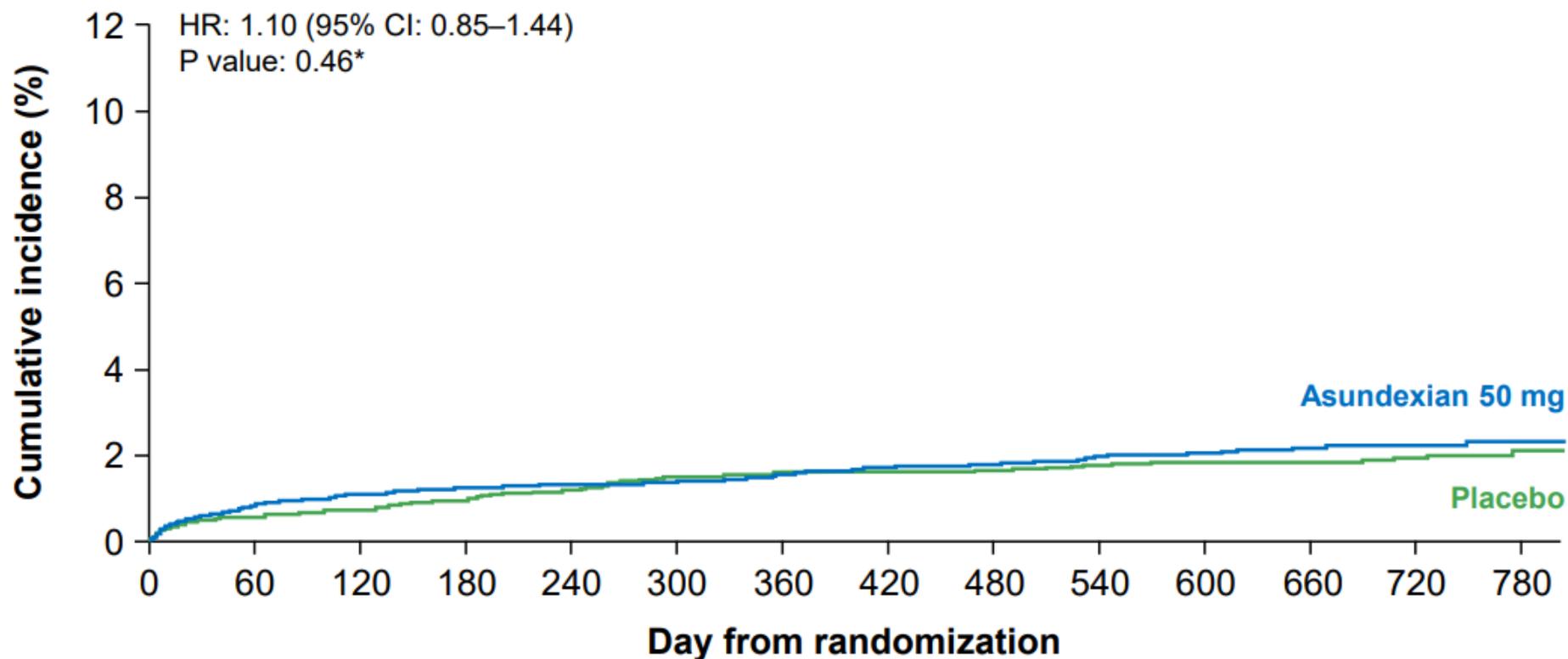
CUMULATIVE INCIDENCE OF ISCHEMIC STROKE



No. at risk

Placebo	6165	5949	5853	5754	5370	4840	4406	3990	3497	3070	2564	1961	1410	792
Asundexian 50 mg	6162	5958	5859	5763	5384	4876	4463	4033	3543	3101	2588	2004	1428	810

CUMULATIVE INCIDENCE OF ISTH MAJOR BLEEDING



No. at risk

Placebo	6130	5391	5021	4833	4415	3944	3572	3165	2775	2441	2026	1549	1121	618
Asundexian 50 mg	6124	5354	4968	4807	4366	3900	3547	3104	2699	2374	1943	1508	1082	613

Vorhofflimmern

- ~~OCEANIC-AF~~
- OCEANIC-AFINA
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- LILAC-TIMI 76

ACS

- Librexia-ACS

Schlaganfall

- OCEANIC-STROKE
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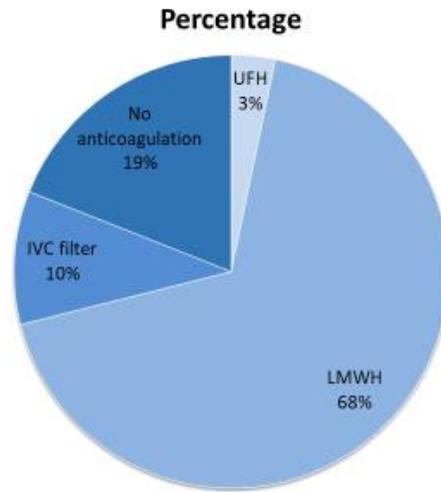


- CAT und Thrombozytopenie:
 - Komplex
 - Interdisziplinäre Diskussion
 - Es gibt noch viel zu lernen

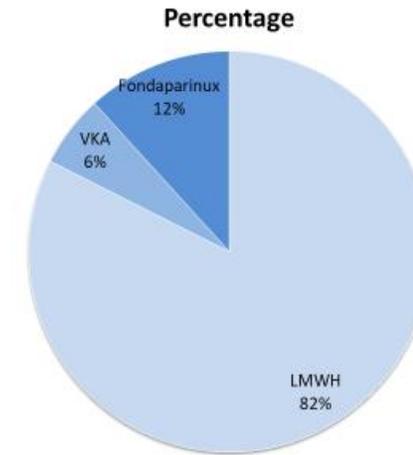


Treatment

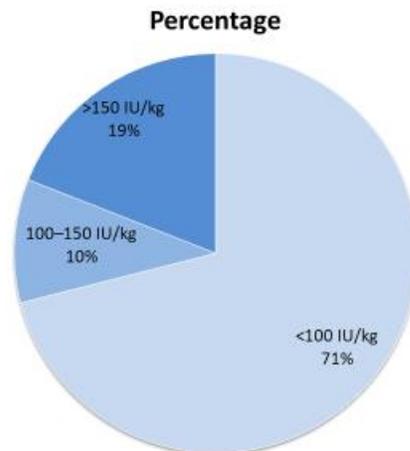
<20k – Acute therapy



<20k – Long-term therapy



<20k – Acute LMWH dose



Register

Severe thrombocytopenia

Mild thrombocytopenia

Normal platelet count

< 20,000/ μ L

20–49,000/ μ L

50–99,000/ μ L

\geq 100,000/ μ L

Patients, N

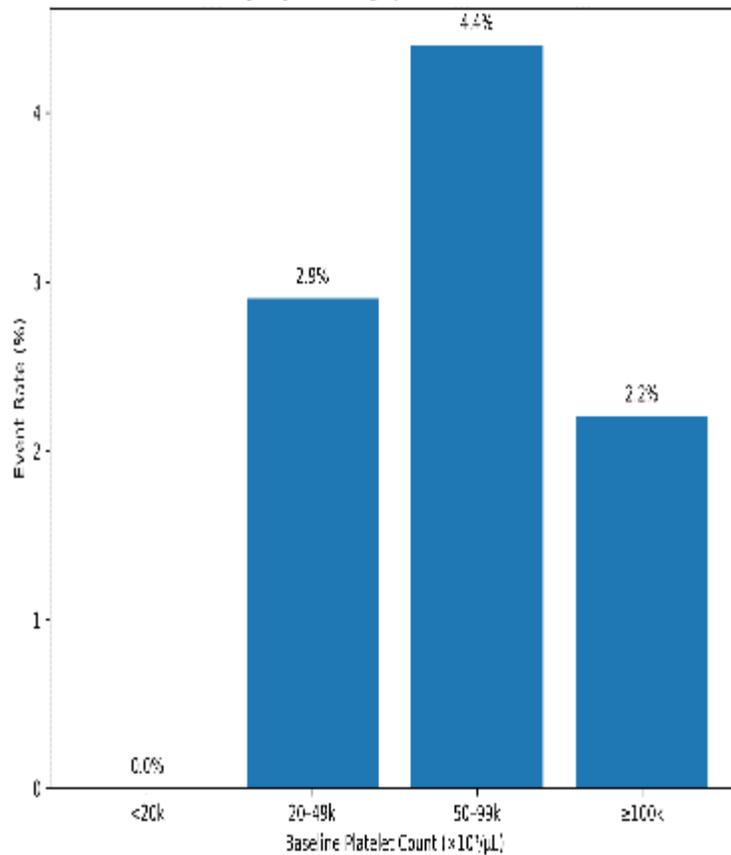
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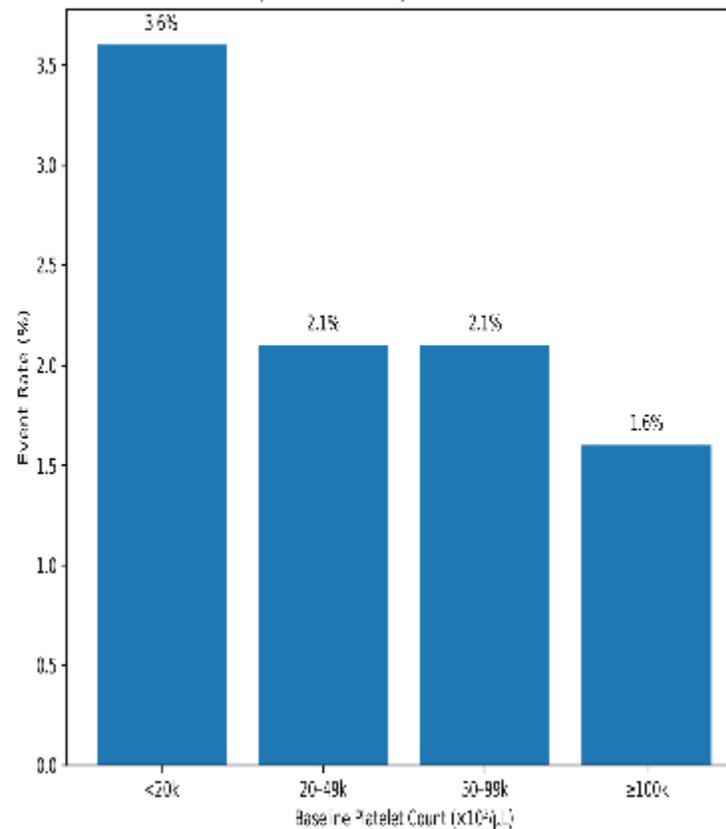
711

14,460

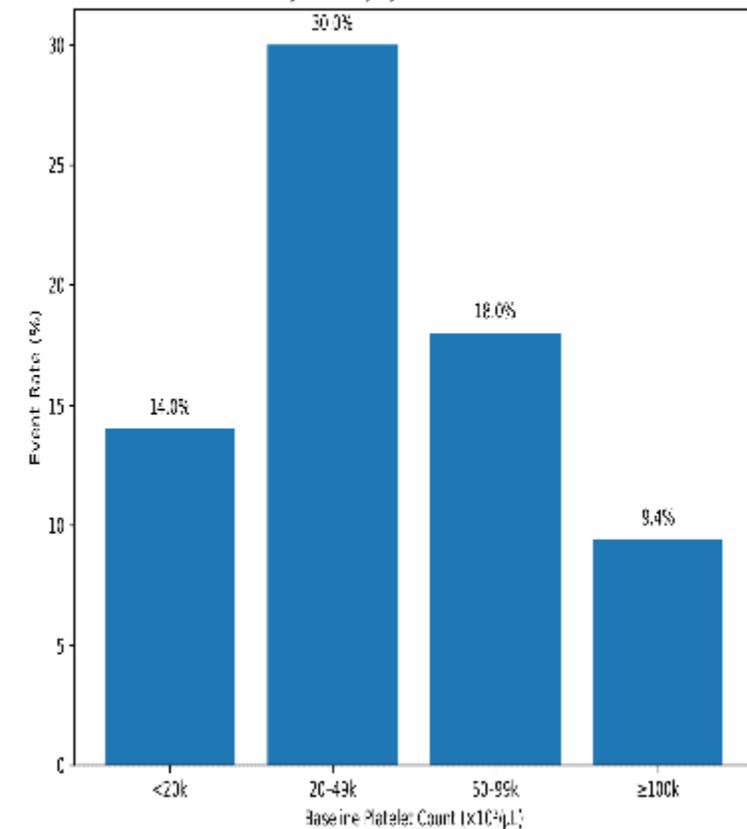
30-Day Major Bleeding by Baseline Platelet Count



30-Day Recurrent VTE by Baseline Platelet Count



30-Day Mortality by Baseline Platelet Count



Register

Severe thrombocytopenia

Mild thrombocytopenia

Normal platelet count

< 20,000/ μ L

20–49,000/ μ L

50–99,000/ μ L

\geq 100,000/ μ L

Patients, N

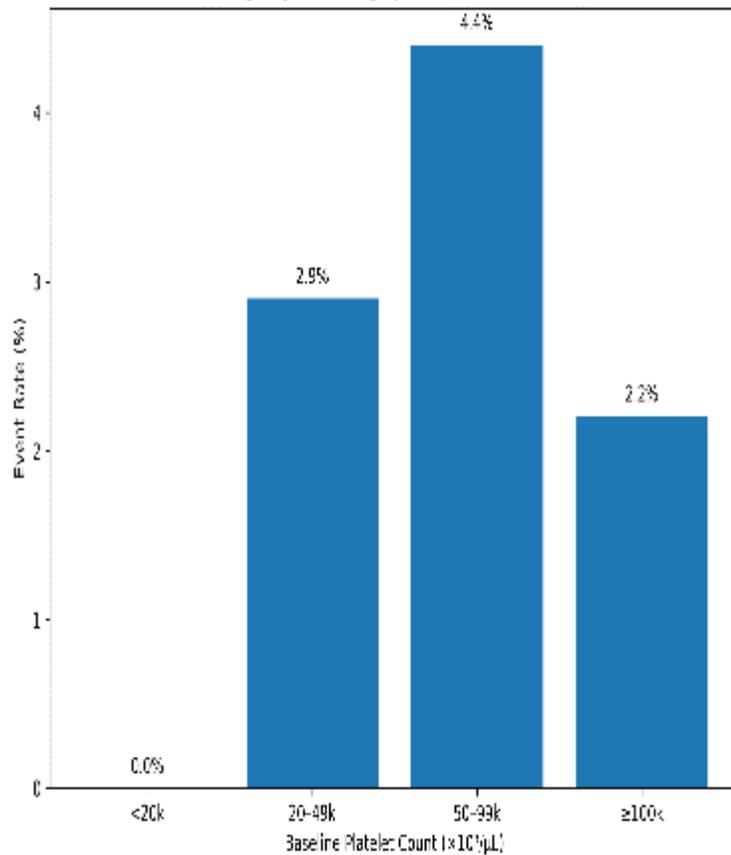
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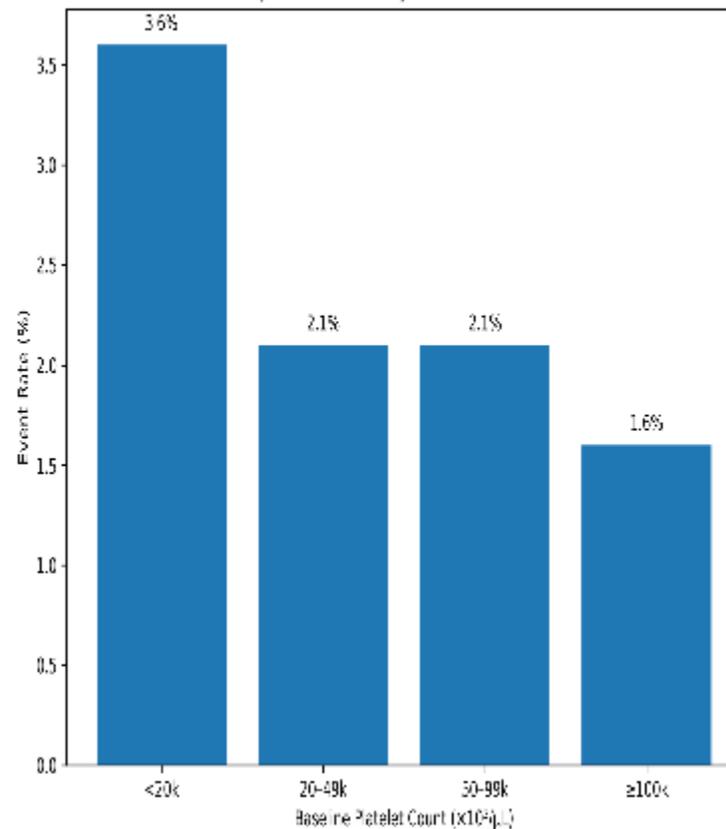
711

14,460

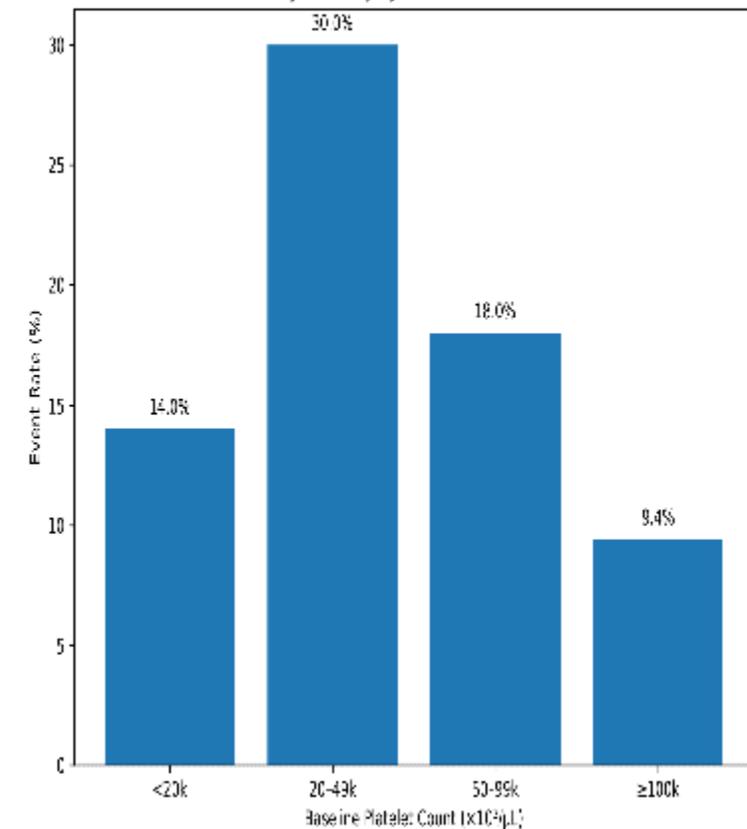
30-Day Major Bleeding by Baseline Platelet Count



30-Day Recurrent VTE by Baseline Platelet Count

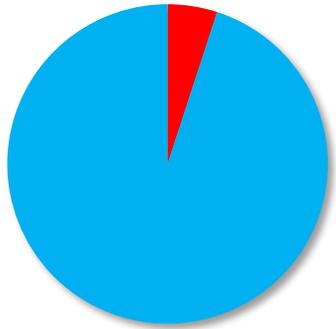


30-Day Mortality by Baseline Platelet Count



Subgruppen

CARAVAGGIO



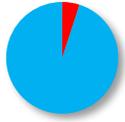
Subgroup type	Apixaban			Dalteparin			Interaction p-value	Hazard Ratio and 95% CI
	N	n	%	N	n	%		
Platelet at rand								
<=100,000 /mL	21	2	9.5	22	1	4.5		
>100,000 /mL	553	30	5.4	550	45	8.2		
Platelet at rand								
<=100,000 /mL	21	1	4.8	22	0	0		
>100,000 /mL	553	21	3.8	550	23	4.2		

Recurrent VTE

Major Bleeding

Randomisierte Studien zu NOAC und TVT/LE

ADAM-VTE



Register

	Severe thrombocytopenia		Mild thrombocytopenia	Normal platelet count
	< 20,000/ μ L	20–49,000/ μ L	50–99,000/ μ L	\geq 100,000/ μ L
Patients, N	28	138	711	14,460
30-day outcomes				
Major bleeding	0	4 (2.9%)	31 (4.4%) [‡]	322 (2.2%)
Recurrent VTE	1 (3.6%)	3 (2.1%)	15 (2.1%)	239 (1.6%)
Death	4 (1.4%)	41 (30%) [‡]	127 (18%) [‡]	1360 (9.4%)
Causes of death				
Bleeding	0	3 (2.2%)	5 (0.7%)	61 (0.4%)
Pulmonary embolism	0	4 (2.9%)	22 (3.1%)	193 (1.3%)
Respiratory insufficiency	1 (3.6%)	3 (2.2%)	8 (1.1%)	92 (0.6%)
Sudden, unexpected	0	1 (0.7%)	1 (0.1%)	22 (0.2%)