

Turnusärzte Fortbildung

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Etablierte Antikoagulantien

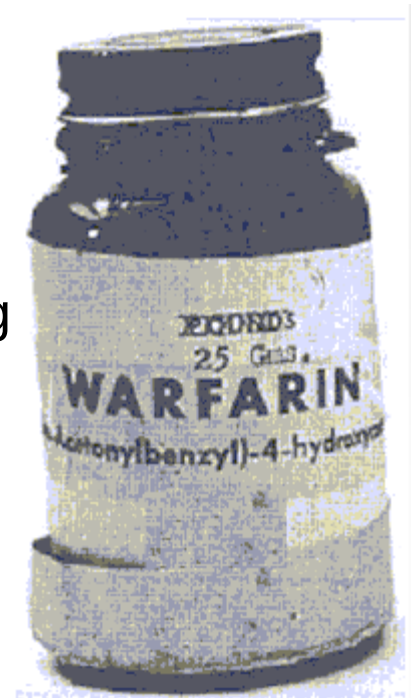
Vitamin K Antagonisten (VKA)

Vorteil

- viel Erfahrung
- Orale Einnahme – für den Patienten wenig belastend
- Billig

Nachteil

- Enges therapeutisches Fenster
- Häufige Gerinnungskontrollen
- Verzögerter Wirkungseintritt
- Verzögertes Wirkungsende
- Abhängigkeit vom Vitamin K Stoffwechsel
- Lange Halbwertszeit



Etablierte Antikoagulantien

Heparine

Unfraktioniertes Heparin

Vorteil:

- Gute Steuerbarkeit
- Völlige Neutralisierbarkeit

Nachteil:

- Parenterale Gabe
- Laborkontrollen
- Gefahr von HIT II

Niedermolekulare Heparine

Vorteil:

- Keine Routine – Laborkontrollen
- Gute Bioverfügbarkeit

Nachteil:

- Sc. Applikation (tägl. 1 bis 2 mal)
- Lange Halbwertszeit
- Nicht 100% neutralisierbar



Fondaparinux

- Präparat: **Arixtra®**
- Synthetisches Pentasaccharid
- Kleine Größe → keine Komplexbildung mit Plättchenfaktor 4 → **keine HIT**
- Einmal täglich sc.
- Halbwertszeit: 17 Stunden
- Keine routinemäßigen Laborkontrollen zur Therapiesteuerung
- **Dosierung VTE Prophylaxe:**
2.5 mg 1xtägl. sc.
- **Dosierung: VTE Therapie**
<50 kg: 5mg 1xtägl. sc
50-100 kg: 7.5 mg 1xtägl. sc.
>100 kg: 10 mg 1xtägl. sc.



Wie gut sind wir mit der VKA Therapie?

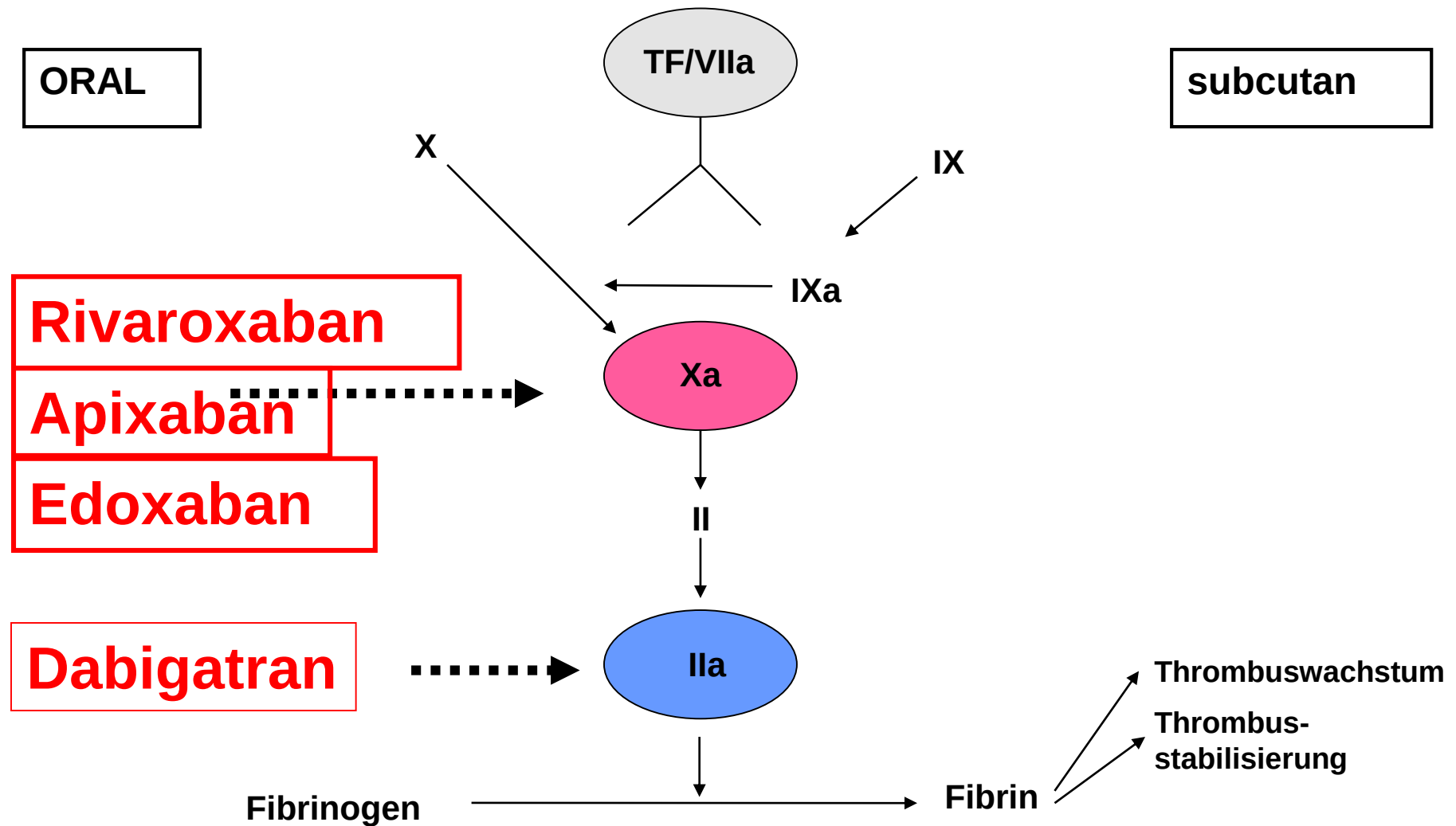
„Effect of Study Setting on Anticoagulation Control“
Van Walrasen C. Chest 2006;129:1155-66.

50208 Patienten

2/3 im therapeutischen Bereich

**= 1/3 nicht im therapeutischen
Bereich**

Wirkungsweise neuer Antikoagulantien

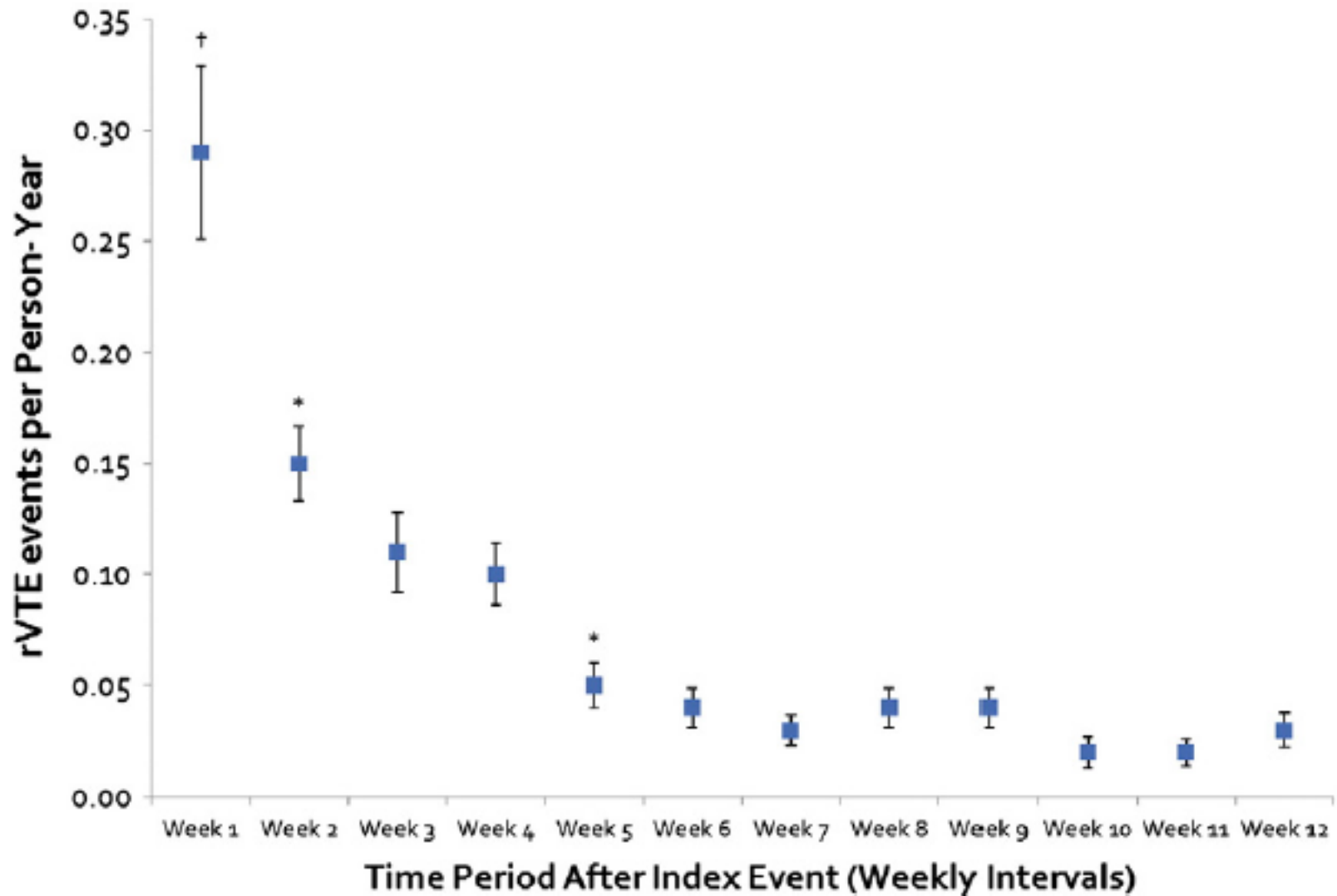


Pharmakokinetik

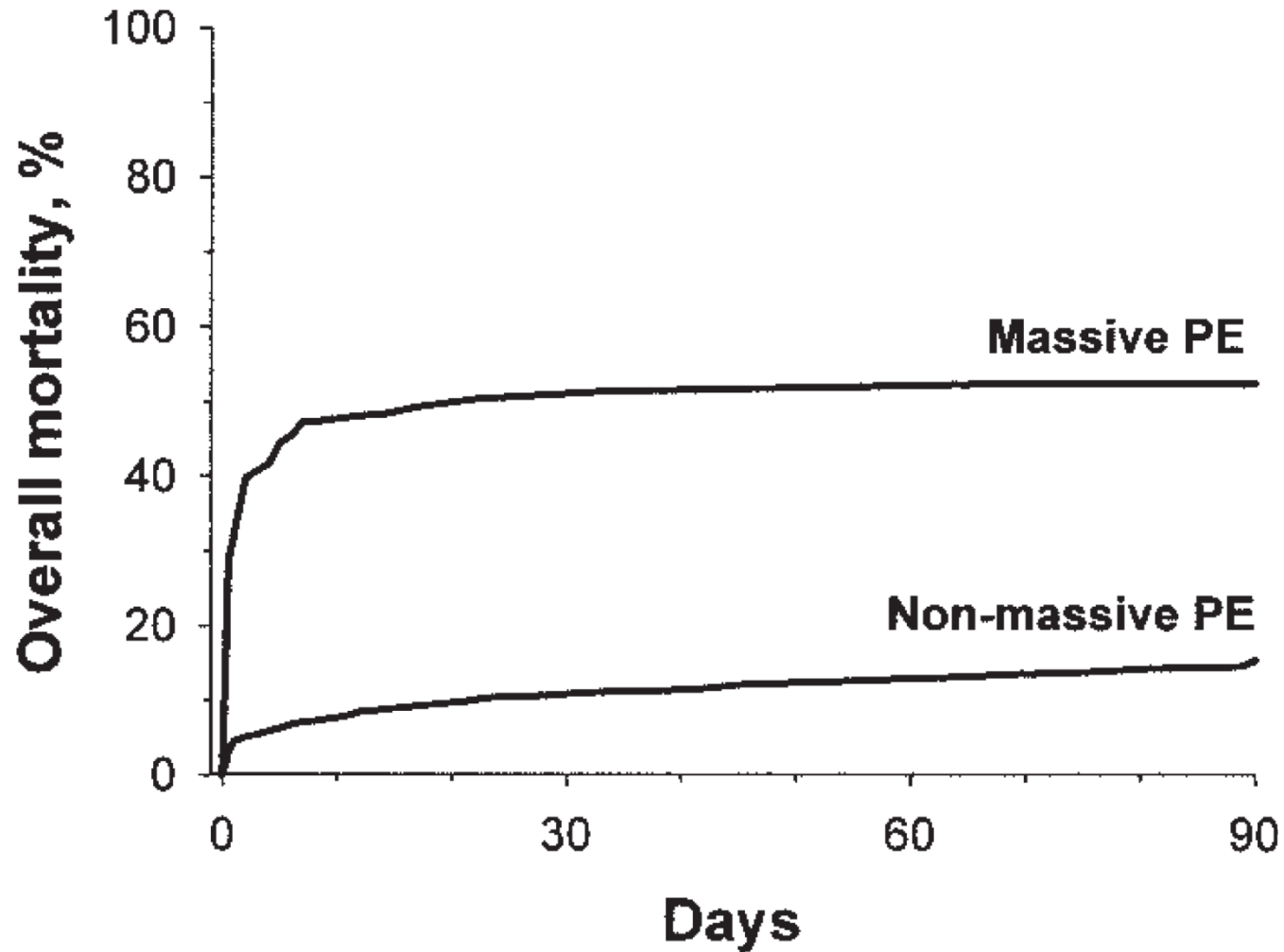
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Zielgerinnungsfaktor	IIa	Xa	Xa	Xa
Anflutung in h	1.25-3	2-4	3-4	1-2
Renale Elimination	80%	33%	25%	50%

Therapie der VTE

Rezidivereignisse nach VTE - Metaanalyse

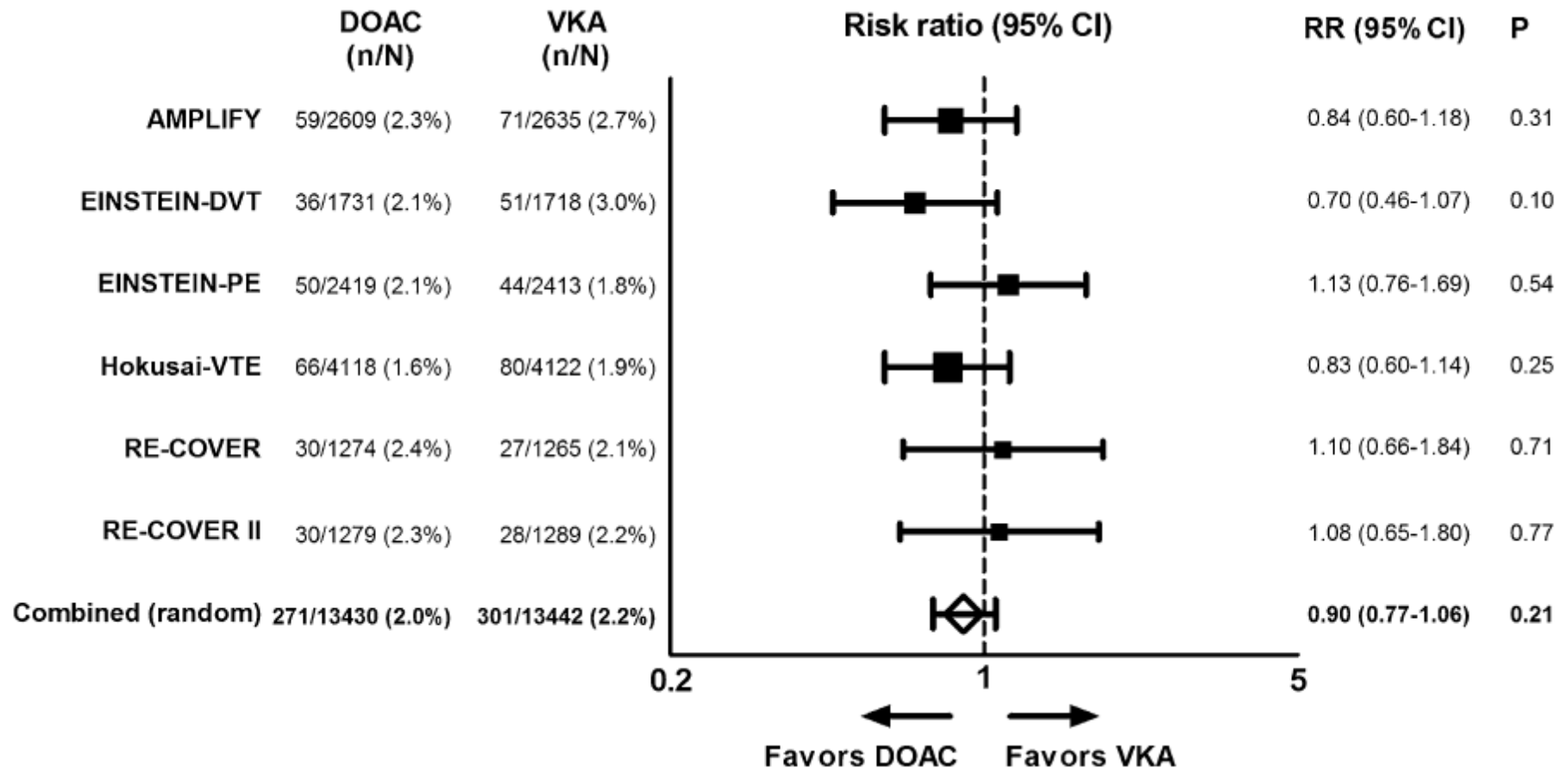


PAE-Mortalität



Substanz	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Handelsname	Pradaxa	Xarelto	Eliquis	Lixiana
Gerinnungsfaktor	II	X	X	X
Renale Elimination	80%	35%	27%	50%
Standardddosis	150 mg 1-0-1	15 mg 1-0-1 für 3 Wochen; danach 20 mg 0-1-0, Einnahme zum Essen! Optional nach 6 Monaten Reduktion auf 10 mg 0-1-0 je nach Blutungsrisiko	10 mg 1-0-1 für 1 Woche; danach 5 mg 1-0-1 für 6 Monate; danach 2.5 mg 1-0-1	60 mg 0-1-0; 30 mg bei Crea Cl 30-50 ml/min oder bei KG unter 60 kg
Reduzierte Dosis	110 mg 1-0-1	15 mg 0-1-0	Siehe oben	Siehe oben
Dosisreduktion bei	>80a oder gleichzeitig Verapamil, sonst individuell (Nierenfunktion etc.)	bei hohem Blutungsrisiko	Siehe oben	Siehe oben
Nicht bei...	CrCl <30 ml/min	CrCl <15 ml/min	CrCl <15 ml/min	CrCl <15 ml/min
Heparin Lead in (mind. 5 Tage)	ja	nein	nein	ja
Antidot	ja (Praxbind 2 mal 2.5g als KI)	nein	nein	nein
Blutungsmanagement	Antidot geben	50IE/kgKG Faktorenkonzentrat	50IE/kgKG Faktorenkonzentrat	50IE/kgKG Faktorenkonzentrat

Rezidiv VTE – Alle DOAK-VTE-Studien zusammengefasst



S2-Leitlinie 2015 Therapie der Venenthrombose

Kriterien für bzw. gegen eine verlängerte Antikoagulation nach 3-6 Monaten	FÜR	GEGEN
Risikofaktor	fortbestehend	passager
Genese	unklar	getriggert
Rezidiv	ja	nein
Blutungsrisiko	gering	hoch
Bisherige Antikoagulationsqualität	gut	schlecht
D-Dimere (nach Therapieende)	erhöht	normal
Residualthrombus	vorhanden	fehlend
Geschlecht	Mann	Frau
Thrombus-Ausdehnung	langstreckig	kurzstreckig
Thrombus-Lokalisation	proximal	distal
Schwere Thrombophilie	ja*	Nein**
Patientenpräferenz	dafür	dagegen

* z.B. Antiphospholipid-Syndrom,

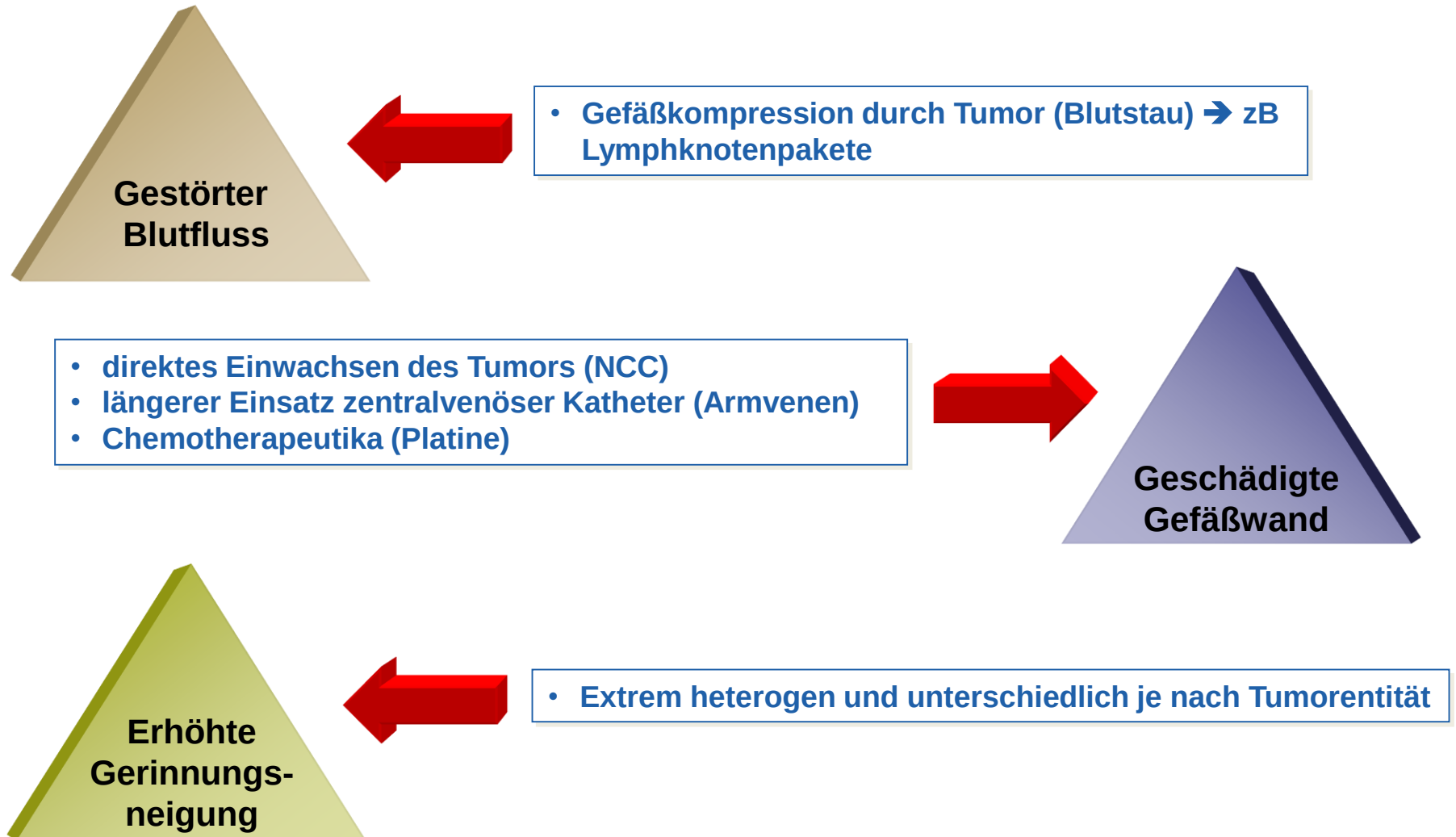
** z.B. Heterozygote Faktor V- oder heterozygote Prothrombinmutation

CAT – Cancer Associated Thrombosis

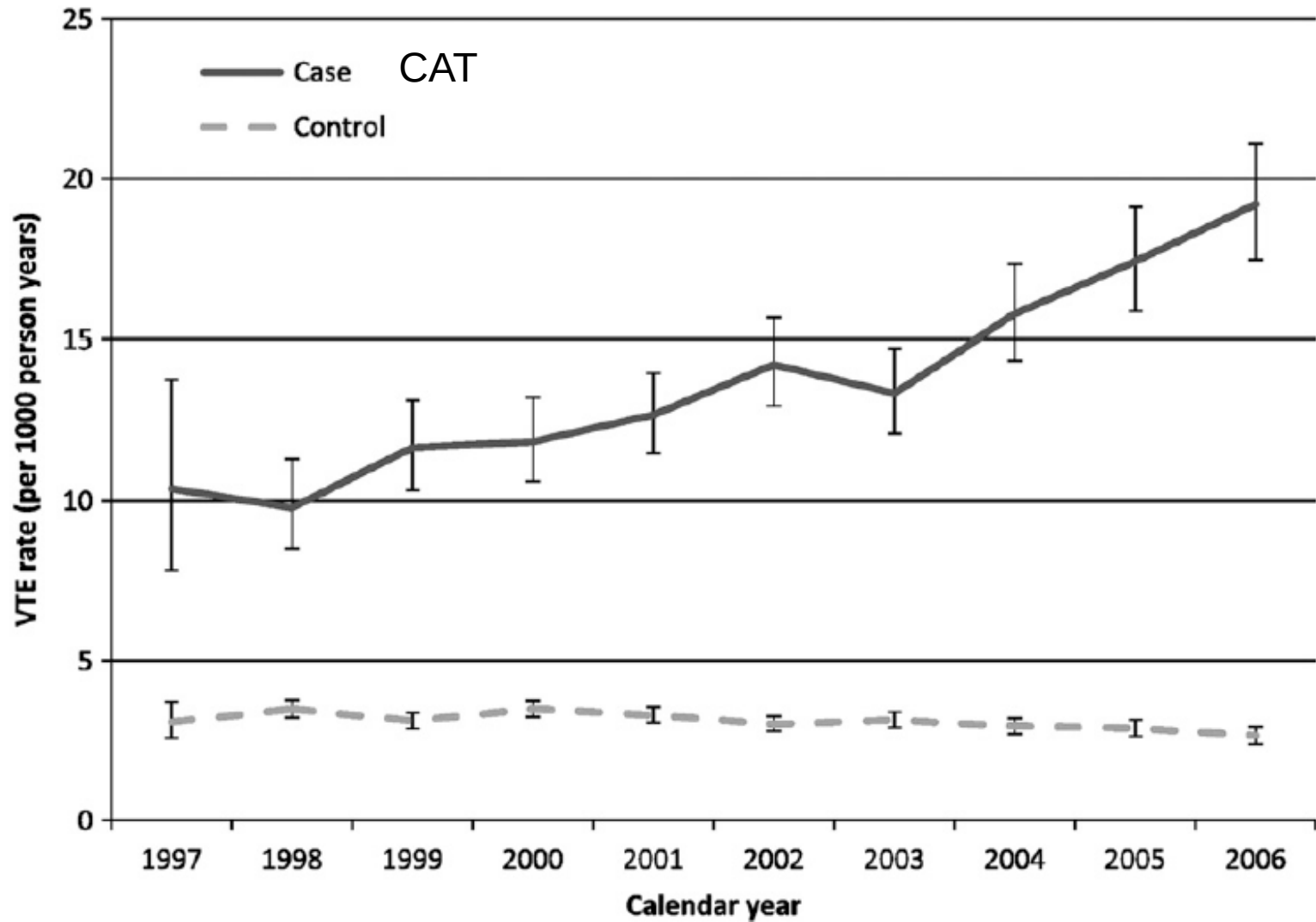
Tumor und Thrombose – Fakten

- rd. **1/5** aller VTE werden durch **Tumorerkrankungen** verursacht
- Thromboembolien → **2.häufigste Todesursache** für Tumorpatienten (nach dem Tumor selbst)
- eine **Chemotherapie** erhöht das **VTE-Risiko** zusätzlich um **ca. 60%**

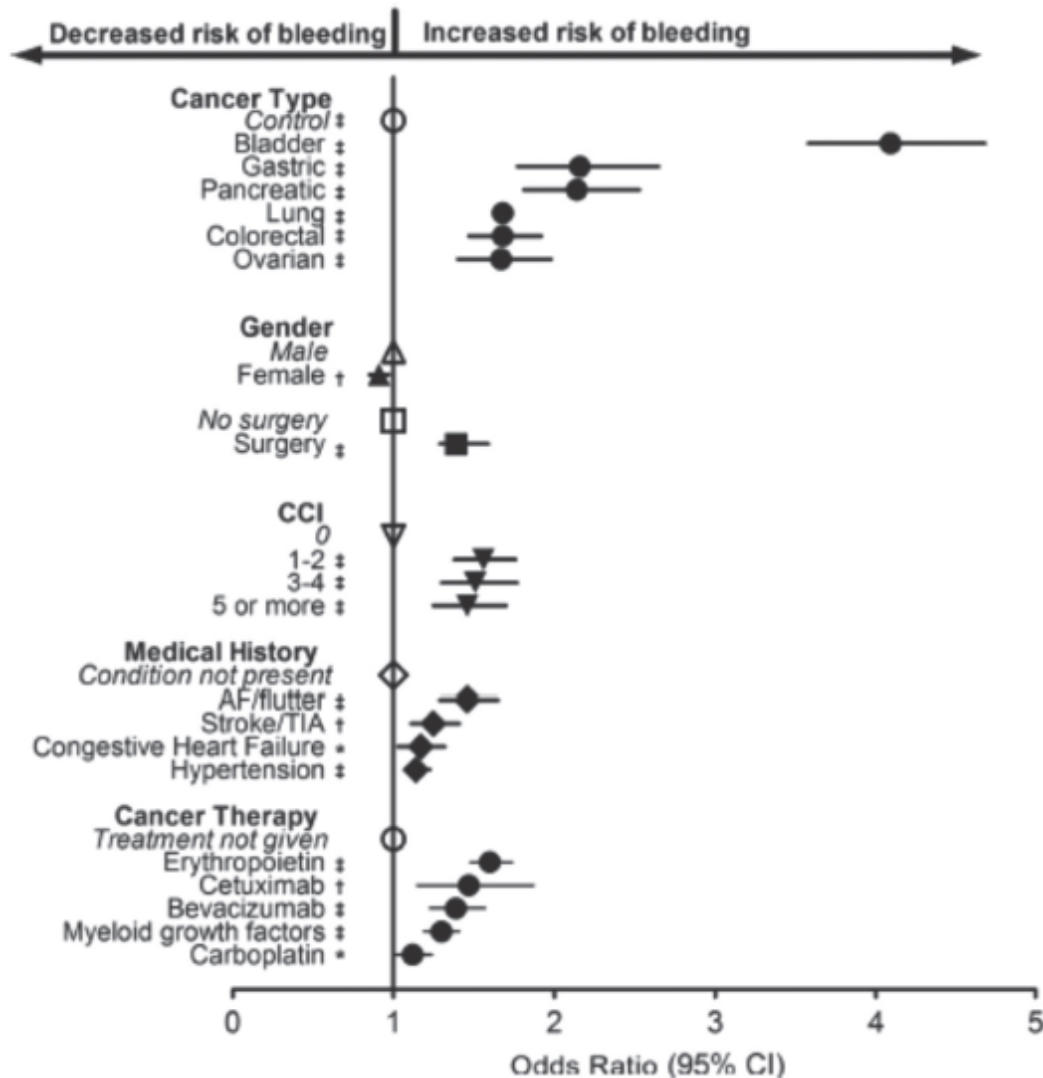
Virchow-Trias bei Krebspatienten



Häufigkeit CAT



Blutungen unter Antikoagulation bei Tumorpatienten



Symptomatische CAT-Einfluss auf Überleben

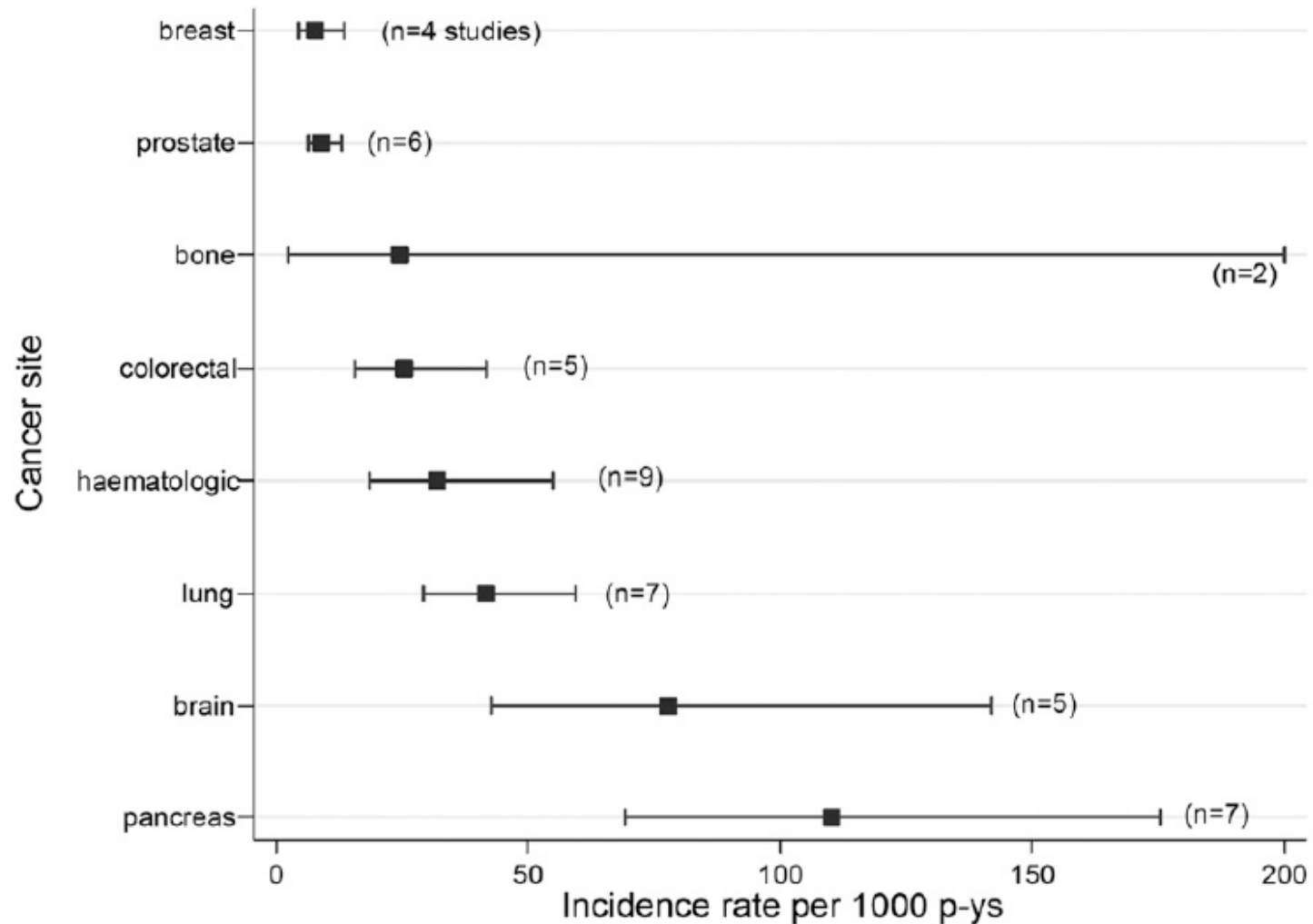
Exposure	PY	Deaths (n)	MR per 100 PY (95% CI)	HR (95% CI)
None	277 713	1750	0.63 (0.60-0.66)	1.0 (reference)
VT only	1317	67	5.1 (4.0-6.4)	2.6 (2.0-3.3)
Cancer only	5650	721	12.7 (11.9-13.7)	7.4 (6.8-8.2)
Cancer-related VT	131	72	55.0 (43.6-69.3)	31.2 (24.6-39.6)

Asymptomatische CAT-Einfluss auf Überleben

Parameter	HR	95% CI	P
Venous thrombosis	2.4	1.2–5.3	0.03
Sex	1.8	0.8–4.2	0.2
Age	1.0	0.9–1.0	0.8
Chemotherapy	1.7	0.4–7.5	0.5
Surgery	2.0	0.6–7.2	0.2
Radiotherapy	1.5	0.5–6.3	0.3
Palliative setting	1.5	0.4–5.1	0.6
Pancreatic cancer	2.5	1.1–5.4	0.02

Abbreviations: CI = confidence interval; HR = hazard ratio.

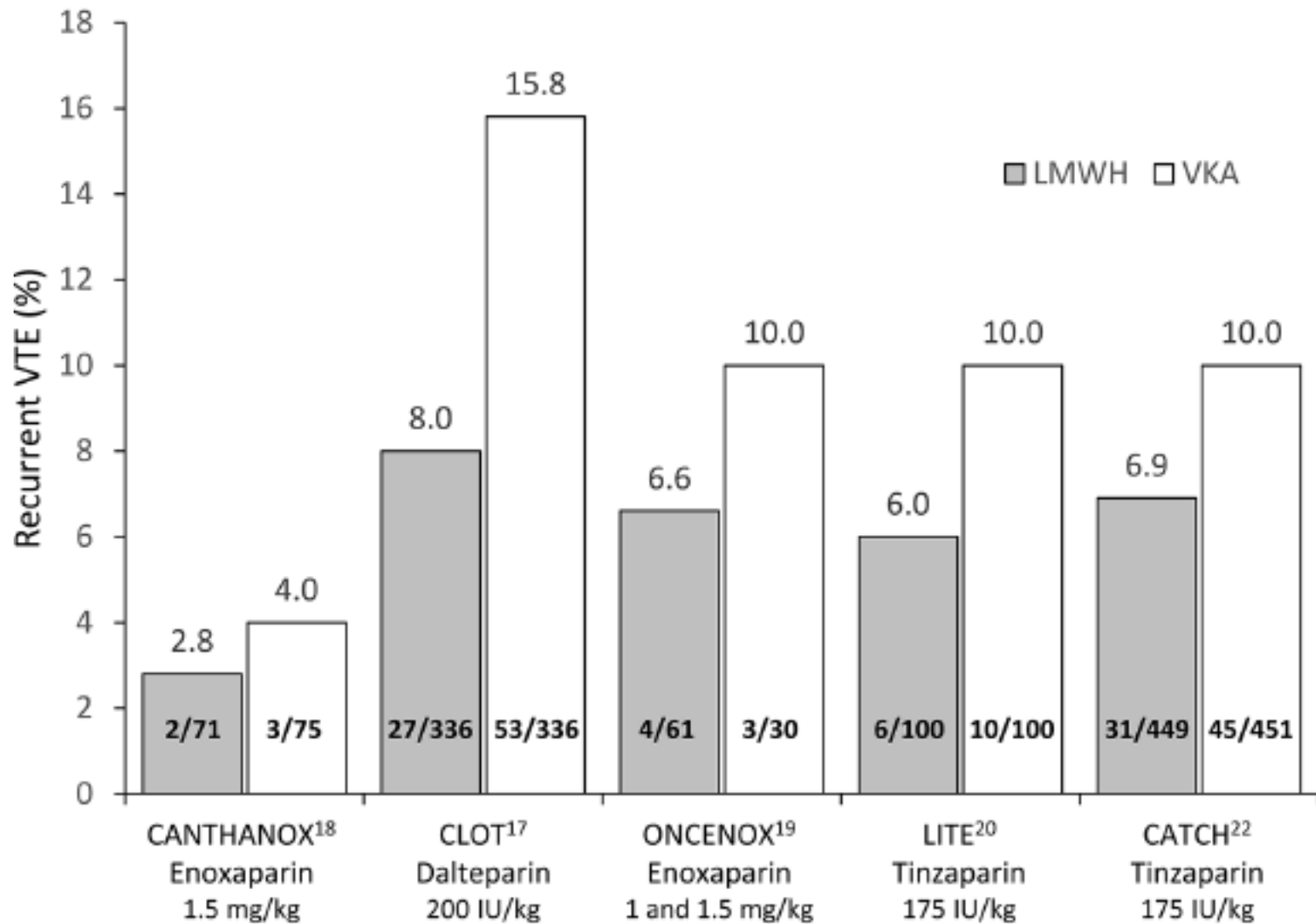
CAT-Häufigkeit je Malignom



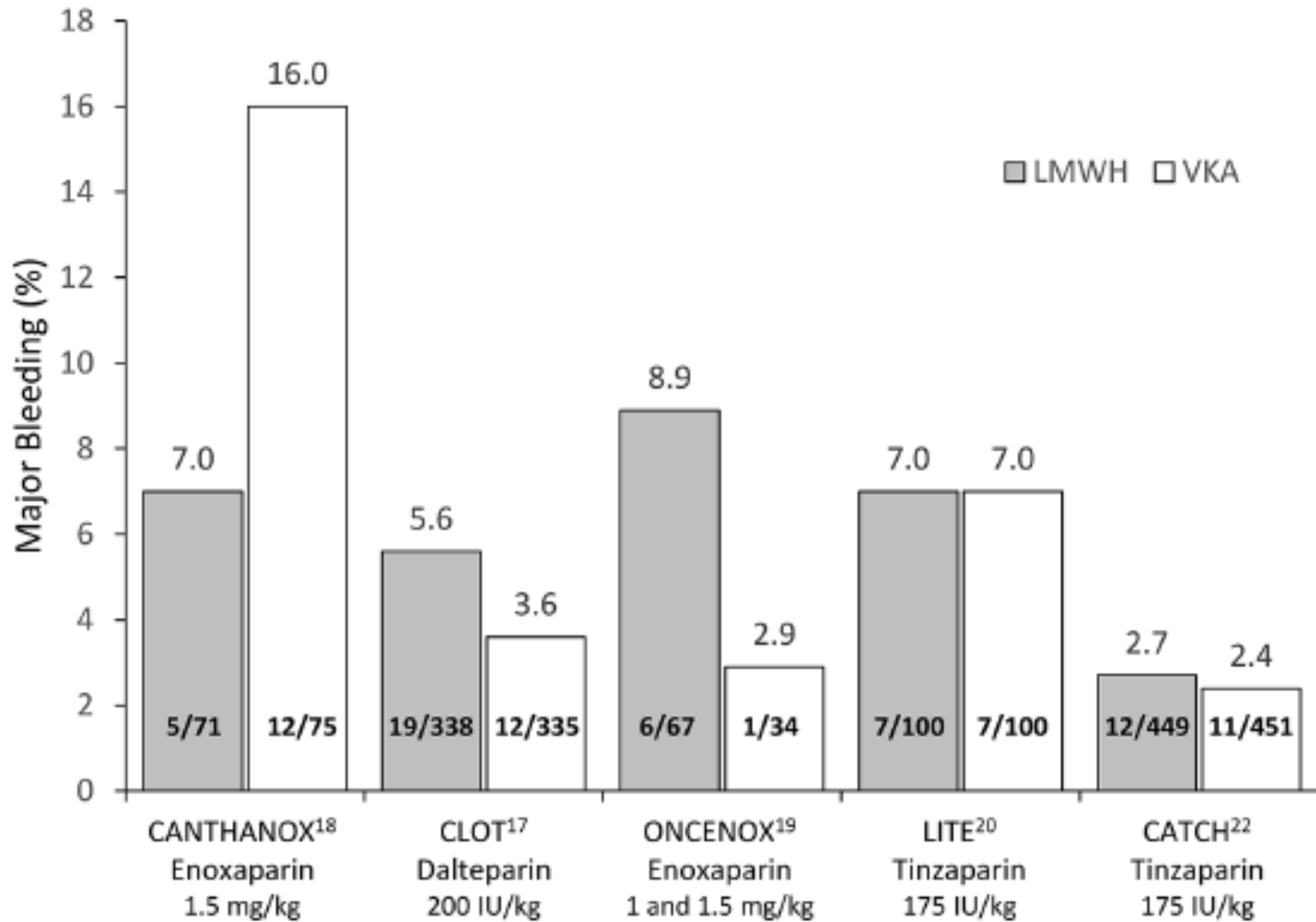
Khorana Risiko Score

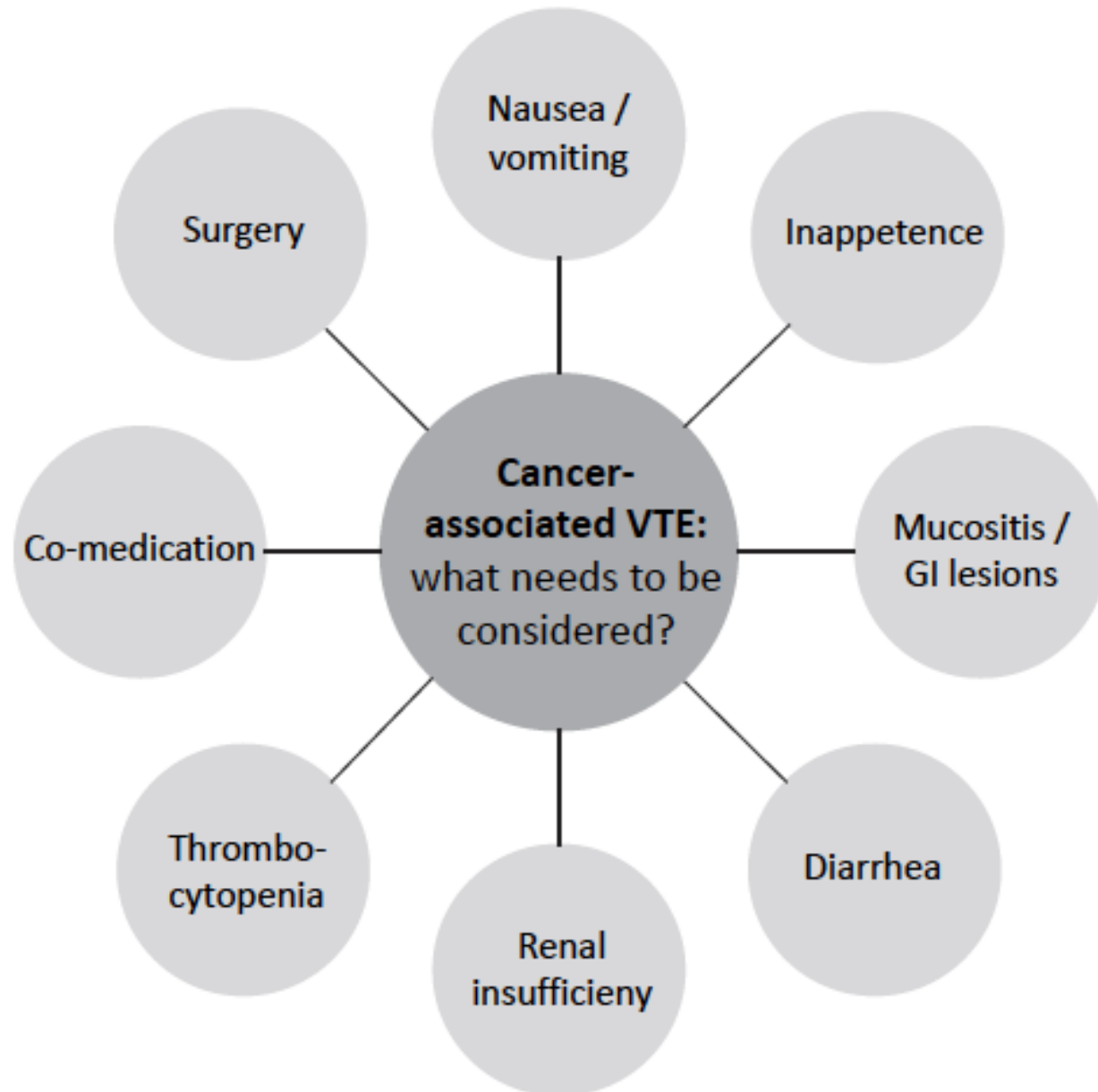
Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $\geq 350 \times 10^9/L$	1
Hemoglobin level < 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count $> 11 \times 10^9/L$	1
Body mass index ≥ 35 kg/m ²	1

NMH vs. VKA

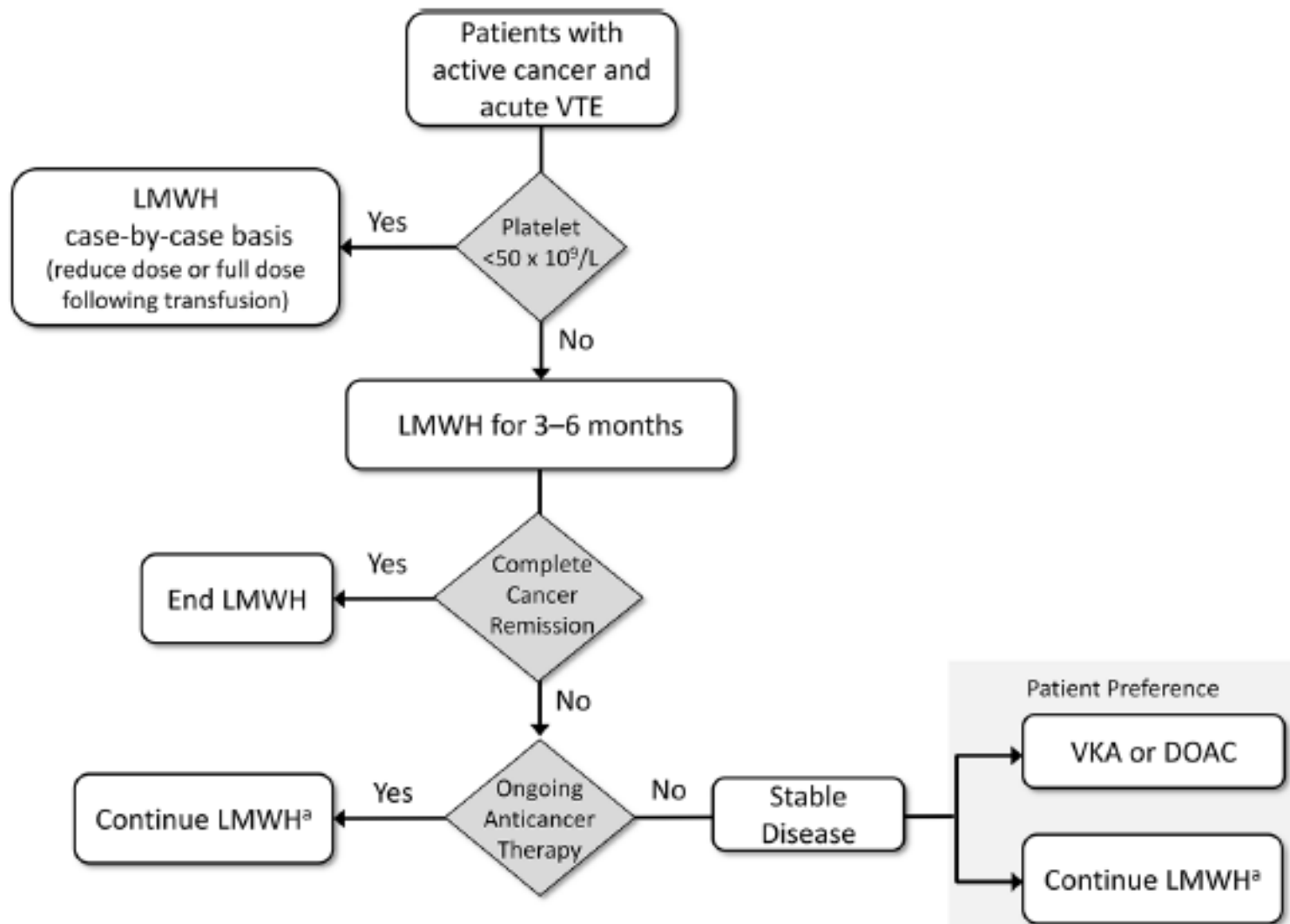


NMH vs. VKA



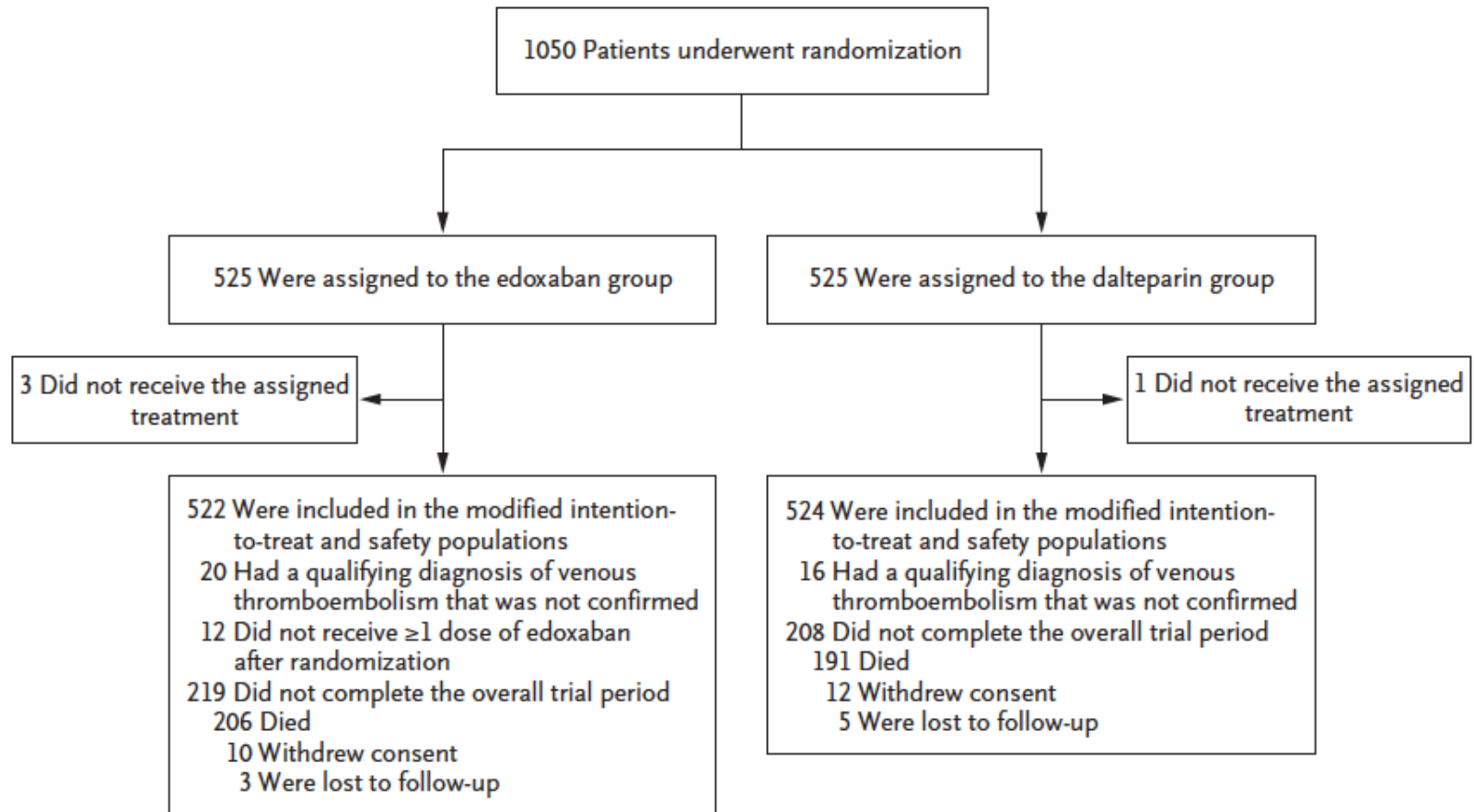


Therapie CAT bis 2018

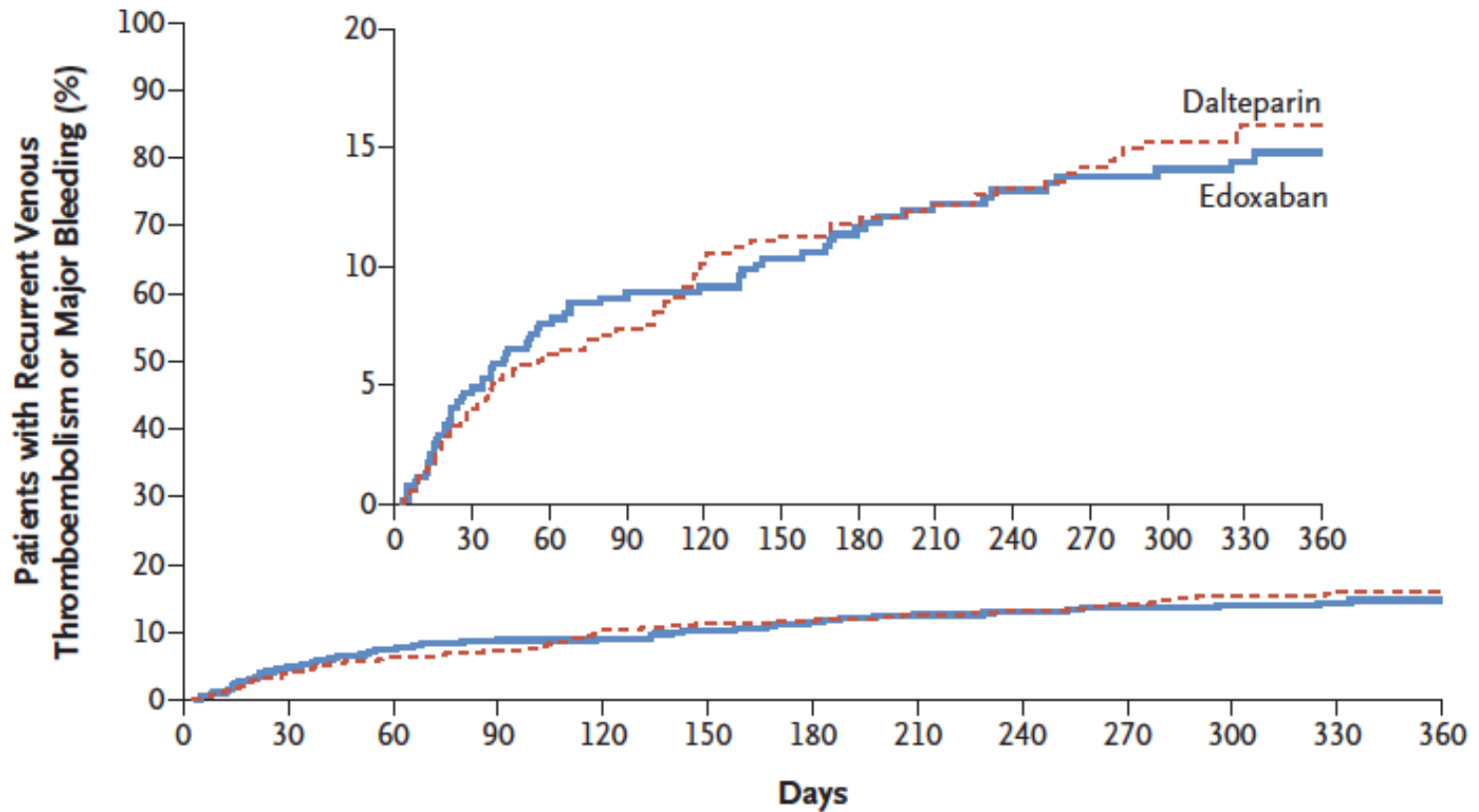


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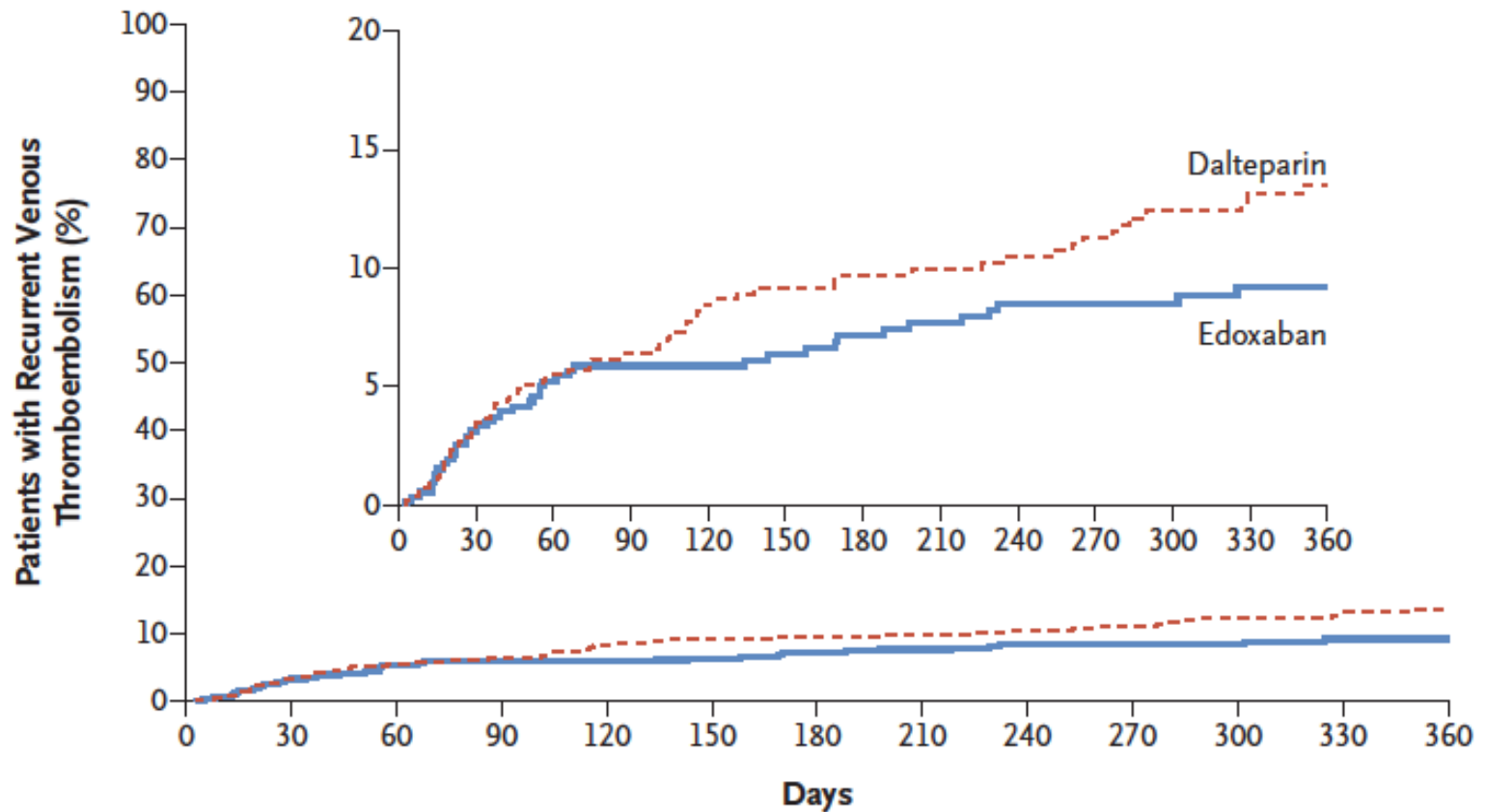
Hokusai Cancer



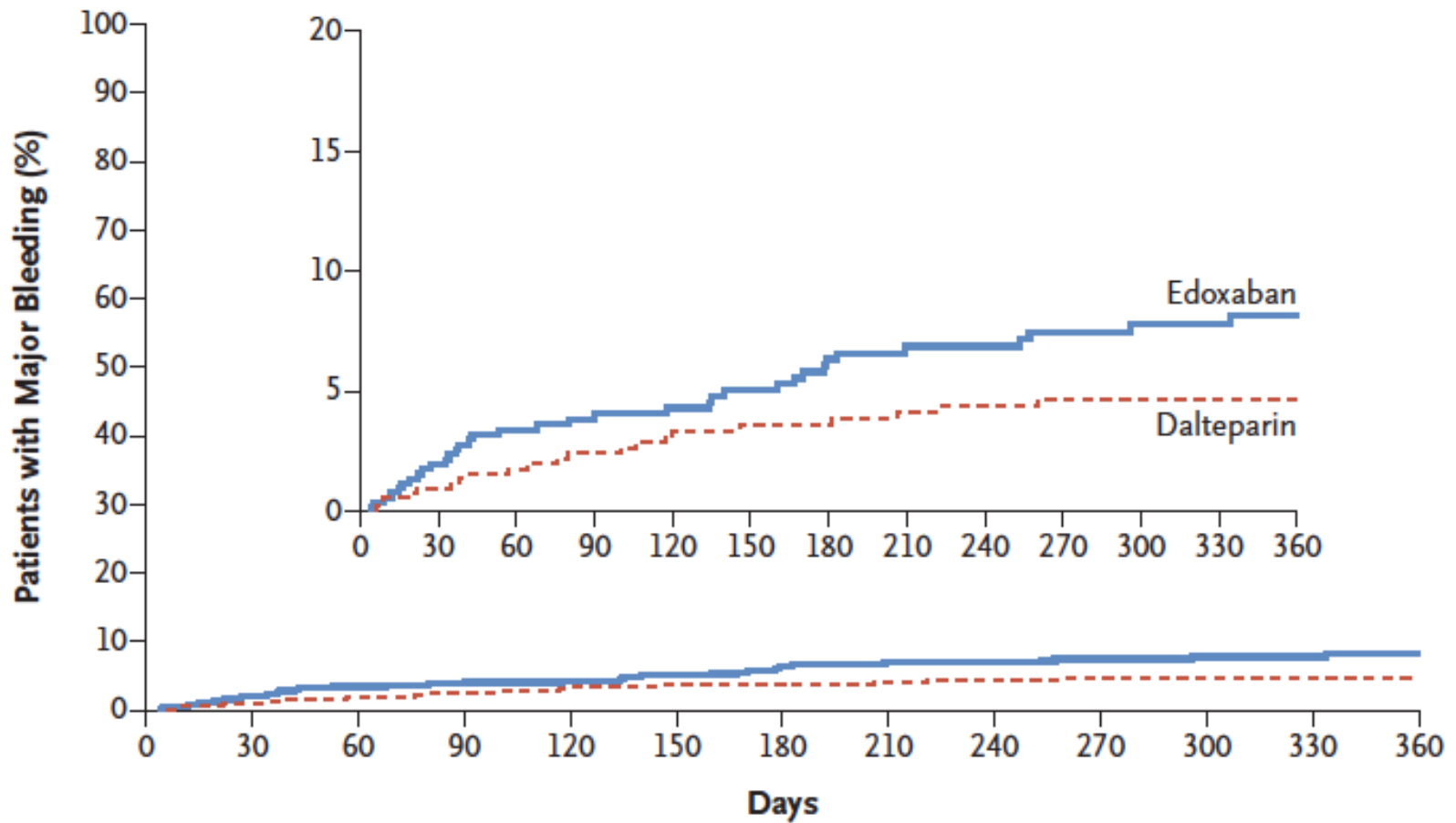
Hokusai Cancer



Hokusai Cancer



Hokusai Cancer



Hokusai Cancer

Outcome	Edoxaban (N = 522)	Dalteparin (N = 524)	Hazard Ratio (95% CI)
Primary outcome			
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)
Secondary outcomes			
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)
Recurrent pulmonary embolism — no. (%) [†]	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)
Severity of major bleeding among those with major bleeding — no./total no. (%) [‡]			
Category 1	0	0	
Category 2	24/36 (66.7)	8/21 (38.1)	
Category 3	12/36 (33.3)	12/21 (57.1)	
Category 4	0	1/21 (4.8)	

The severity of major bleeding at clinical presentation was adjudicated by an independent clinical events committee (whose members were unaware of the treatment assignments) according to the following prespecified categories: category 1 included bleeding events that were not considered to be a clinical emergency; category 2 included bleeding events that could not be classified in any of the other categories because they led to some treatment but were not considered to be a clinical emergency; category 3 included bleeding events that were considered to be a clinical emergency, such as bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms; and category 4 included bleeding events that led to death before or almost immediately after the patient entered the hospital.¹²

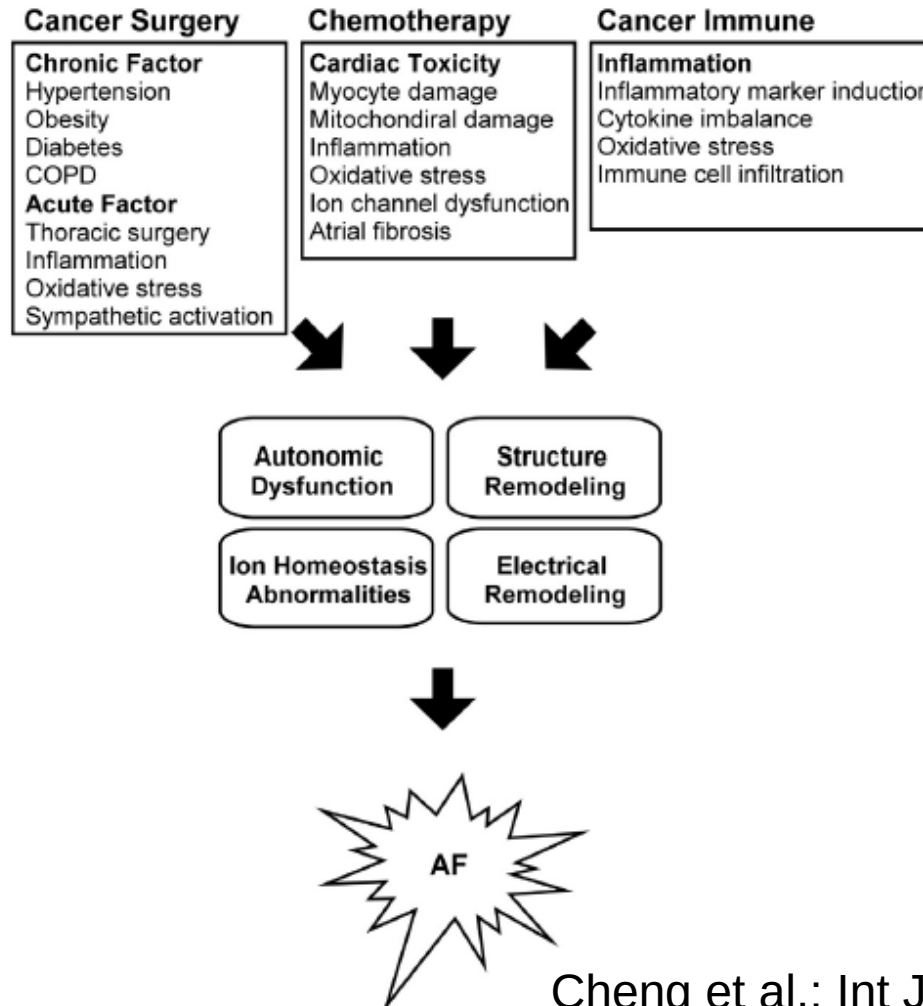
VHFA bei Tumorpatienten??

AF Prävalenz bei Malignompatienten

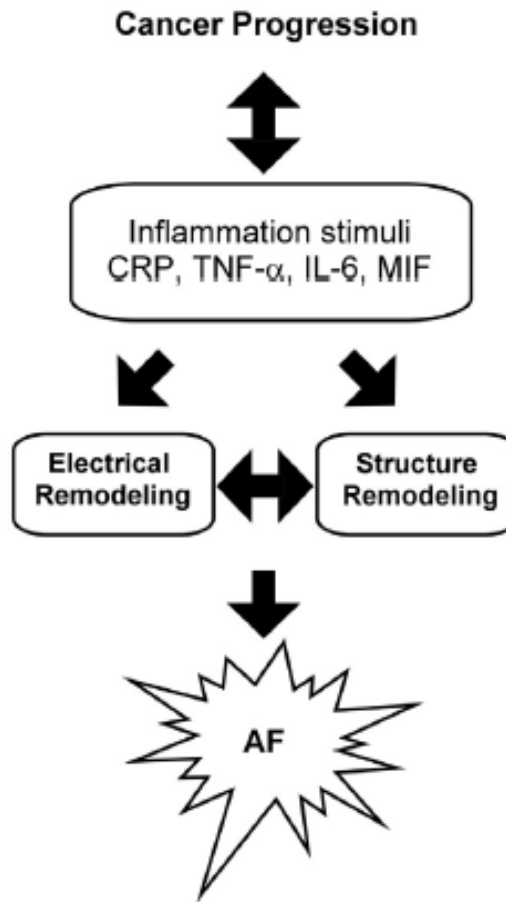
Type of study, year	First author	Type of cancer	Number of patients	HR	OR	SIRs	AF prevalence	95% CI	References
Prospective single-center study 2005	Roselli et al.	Lung cancer resection	604	UK	UK	UK	19%	UK	[9]
Prospective single-center study 2012	Imperatori et al.	Lung cancer resection	454	UK	UK	UK	9.9%	UK	[12]
Retrospective study 2005	Siu et al.	Elective surgery for colorectal cancer	563	UK	UK	UK	4.4%	UK	[10]
Prospective single-center study 2013	Ojima et al.	Esophagealcancer resection	207	UK	UK	UK	9.2%	UK	[11]
Case-control study 1994	Muller AD et al.	Colon cancer	12,304	1.34	UK	UK	UK	1.16–1.55	[13]
Case-control study 2002	Guzzetti et al.	Colorectal cancer	456	UK	3.5	UK	5.2%	1.6–7.2	[14]
Prospective single-center study 2008	Guzzetti et al.	Colorectal or breast cancer	1317	UK	3.3	UK	3,6%	1.67–6.61	[15]
Case-control study 2012	Erichsen et al.	Colorectal cancer	28,333	UK	7	UK	0.59%	6.3–7.8	[16]
Cohort study 2012	Hu et al.	All cancers combined	24,125	UK	UK	UK	2.4% at cancer diagnosis/1.8% after cancer diagnosis	UK	[17]
Cohort study 2014	Ostenfeld et al.	All cancers combined	269,742 with new-onset AF	UK	UK	5.11	UK	4.99–5.24	[18]
Cohort study 2016	Conen et al.	All cancers combined	34,961	1.58	UK	UK	4.2%	1.34–1.87	[2]

Mery et al.; Int J Cardiol 2017

Mögliche Ursachen von AF bei Malignompatienten



AF und Malignom



Gibt es Daten aus den großen Zulassungsstudien der DOACs für Malignompatienten?

- ➔ Aristotle trial (Apixaban bei VHFA)
- ➔ 1236 pts mit Malignom anamnestisch
- ➔ Davon hatten 12.7% einen aktiven Tumor (157 pts)

	Active Cancer		
	Event (Rate*)		
	Apixaban (n = 76)	Warfarin (n = 81)	HR (95% CI)
Ischemic outcomes			
Stroke or SE	0 (0)	5 (3.8)	NA
Death from any cause	5 (3.7)	11 (8.1)	0.45 (0.16-1.29)
Ischemic stroke	0 (0)	3 (2.3)	NA
MI	0 (0)	1 (0.8)	NA
PE/DVT	0 (0)	1 (0.8)	NA
Bleeding outcomes			
ISTH major bleeding	1 (0.8)	5 (4.5)	0.19 (0.02-1.59)
Major or CRNM bleeding	6 (5.2)	10 (9.5)	0.56 (0.20-1.54)
Any bleeding	27 (31.4)	30 (34.9)	0.93 (0.55-1.56)
Intracranial bleeding	0 (0)	2 (1.8)	NA
Net composite end point			
Composite efficacy end point†	5 (3.7)	16 (12.1)	0.30 (0.11-0.83)
Composite end point§	6 (4.4)	18 (13.9)	0.32 (0.13-0.81)

AF = atrial fibrillation; CI = confidence interval; CRNM = clinically relevant nonmajor bleeding; MI = myocardial infarction; PE = pulmonary embolism; SE = systemic embolism.

*Event rate = events per 100 patient-years of follow up.

†P value for the randomized treatment-by-cancer interaction.

‡Stroke/SE, MI, and death.

§Stroke/SE, MI, death, and ISTH major bleeding.

Was sagen aktuelle Guidelines?

Table 16 Atrial fibrillation and malignancy

Interdisciplinary teamwork
(1) Estimate individual patient risk profile ● AF-related risk factors (CHA₂DS₂-VASc, bleeding risk) ● Cancer-related risk factors (type, liver metastases, coagulopathy, renal/hepatic function etc.) ● Treatment-related risk factors (thrombocytopenia, surgery, radiation, central lines etc.) (2) Choose anticoagulant ● Current standard of care: VKA/(LMWH)^a ● NOACs: Available data scarce, but encouraging ● Consider patient preference (VKA vs. NOAC) (3) Protect the patient ● Gastric protection (PPI/H2 blockers) ● Beware of drug–drug interactions (Table 4) ● Dose reduction/treatment interruption (if platelets <50k, renal dysfunction, bleeding, . . .)
Beware ● Risk of thromboembolism ↑ ● Risk of bleeding ↑

^aIf oral therapy is not possible reversion to LMWH is reasonable.

EHRA practical guidelines; European Heart 2018

Achtung NOAK und PCT!

	Via ¹⁴²	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Antimitotic agents					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Antimetabolites					
Metotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated				
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; No relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Anthracyclines/Anthracenediones					
Doxorubicin	Strong P-gp induction, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Idarubicin	Mild CYP3A4 inhibition; P-gp competition				

Tyrosine kinase inhibitors

Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition				
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				

Vorsicht Thrombopenie bei CAT

- ➔ Therapie über 50 000 Thrombos möglich (NMH oder Edoxaban)
- ➔ Zwischen 25 000 und 50 000 Thrombos NMH halbtherapeutisch
- ➔ Unter 25 000 keine Antikoagulation

Perioperative Vorgehen bei DOACs

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥ 12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50–80 mL/min	≥ 36 h	≥ 72 h	≥ 24 h	≥ 48 h
CrCl 30–50 mL/min ^a	≥ 48 h	≥ 96 h	≥ 24 h	≥ 48 h
CrCl 15–30 mL/min ^a	Not indicated	Not indicated	≥ 36 h	≥ 48 h
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥ 24 h low risk, ≥ 48 h high risk.

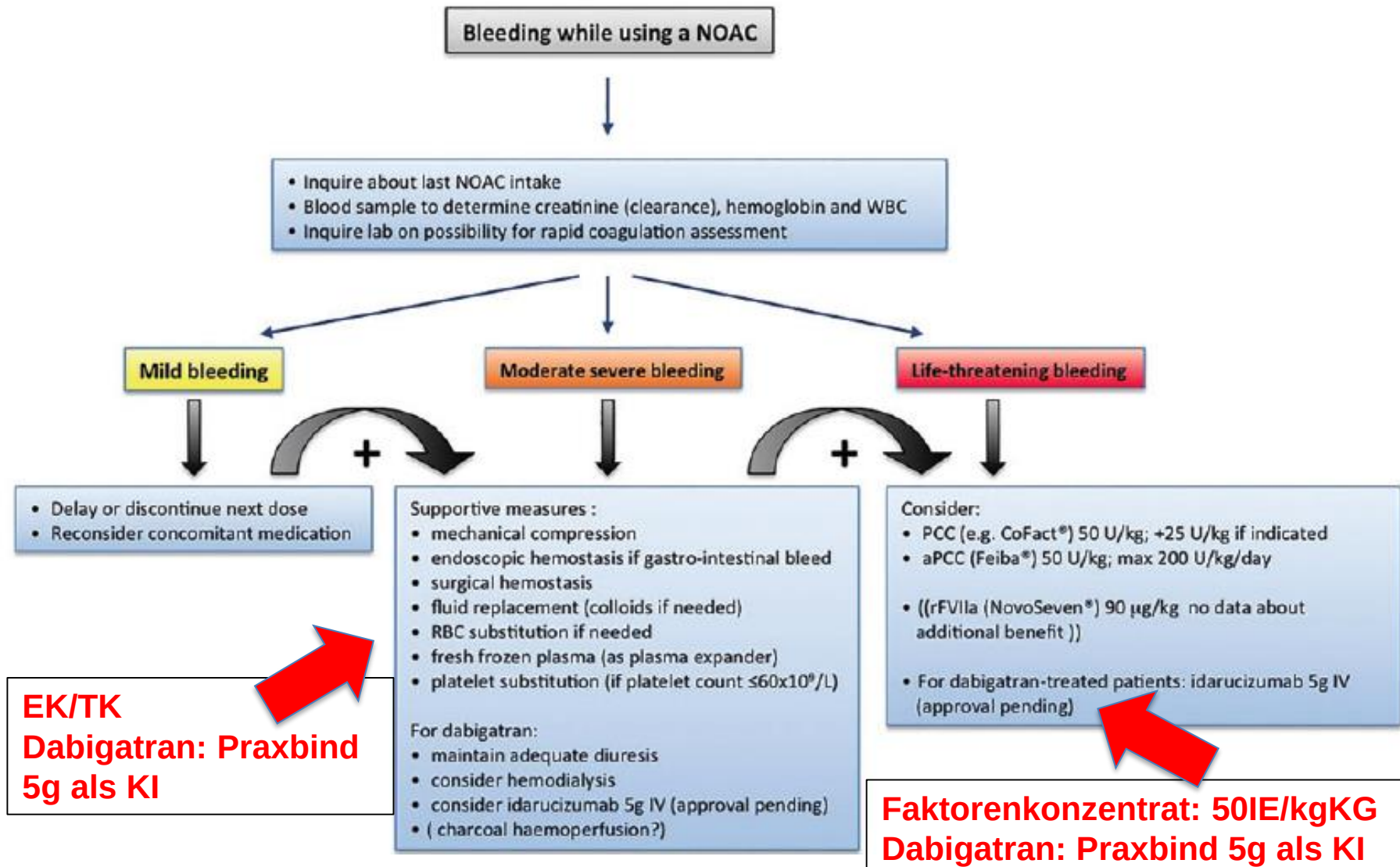
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clinical impact. See also Table 11.

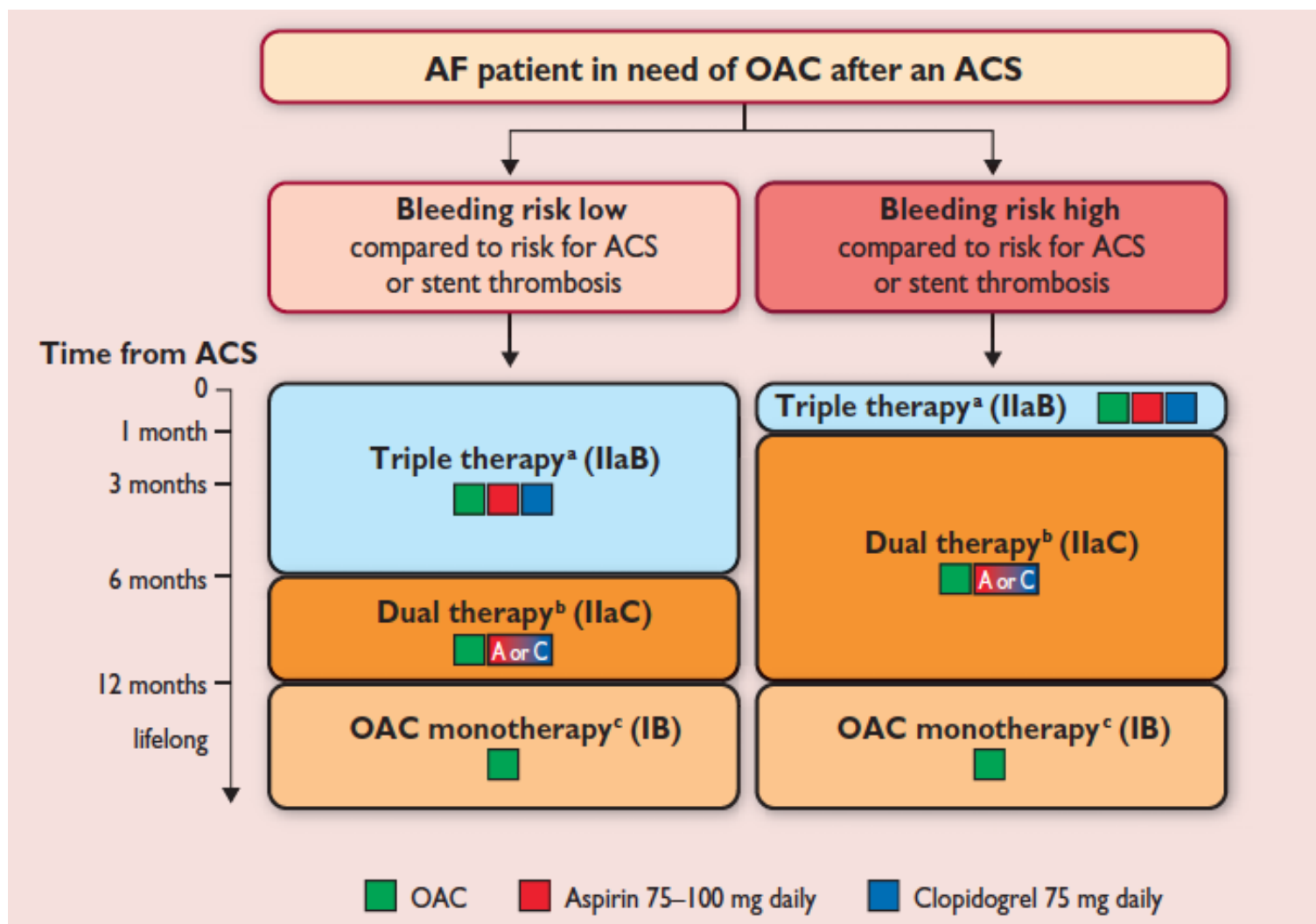
CrCl, creatinine clearance.

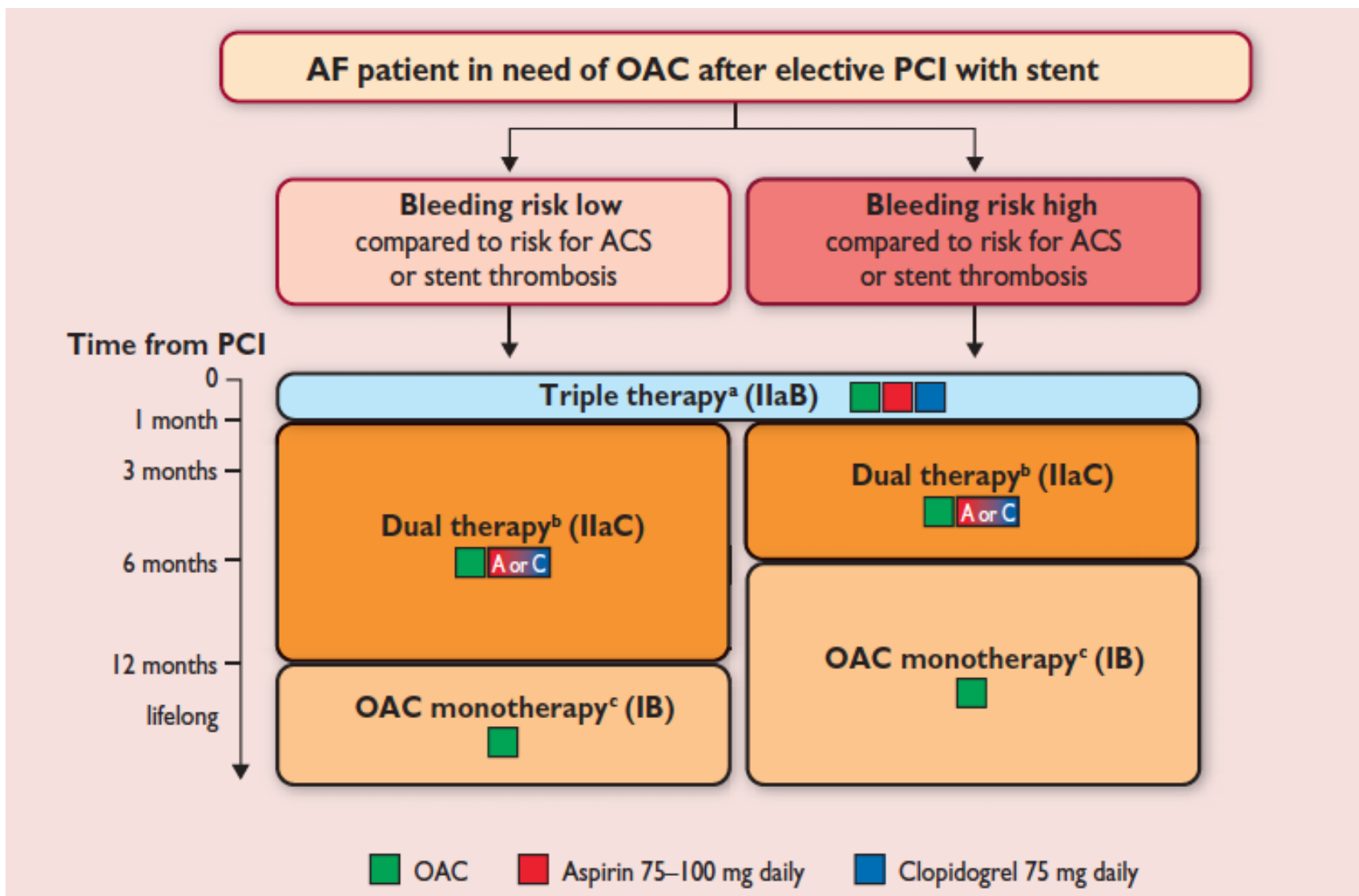
^aExamples are cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy.

[†]Examples are major cardiac surgery, insertion of pacemakers or defibrillators (resulting from the risk for pocket hematoma), neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery.

Blutung unter DOAK Therapie







Danke für Ihre Aufmerksamkeit

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