Antikoagulation bei onkologischen Patienten mit Vorhofflimmern und nach thrombotischen Ereignissen: Einsatz von DOACs sinnvoll?

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Inhalt der heutigen Präsentation

- Allgemeine Gedanken
  - Vorhofflimmern (VHF) bei onkologischen Patienten
  - Krebs und Risiko für venöse Thromboembolien (VTE)
- Antikoagulation bei onkologischen Patienten
  - Datenlage/Evidenz
- Einsatz von direkten oralen Antikoagulantien (DOACs) bei onkologischen Patienten
  - Besonderheiten und persönliche Empfehlungen

Vorhofflimmern bei onkologischen Patienten

- Hohe Co-Inzidenz von Vorhofflimmern (VHF) und Krebs in einer epidemiologischen Studie (n=24 125 Patienten)
  - Prävalenz des VHF zum Zeitpunkt der Diagnose der Krebserkrankung: **2.4% („baseline" VHF**)
  - Inzidenz des Vorhofflimmerns nach Diagnose bzw. im Verlauf der Krebserkrankung: **1.8%** (**„new-onset" VHF**)
  - „new-onset" VHF mit einem 2-fach höherem Risiko für thromboembolische Komplikationen (Schlaganfälle)
  - 6-fach erhöhtes Risiko für Herzinsuffizienz

Hu et al. Int J Cardiol 2013;165:355-7

Antikoagulation bei onkologischen Patienten mit Vorhofflimmern: Eine Herausforderung!

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Krebs

- Risikoevaluierungs-Scores ($CHADS_2$ bzw. CHA_2DS_2-VASc und HAS-BLED) sind NICHT validiert für onkologische Patienten!

- Evidenz-basierte Strategien zur Antikoagulation bei onkologischen Patienten mit VHF fehlen (→individ. Vorgehen).

- Krebserkrankung →signifikanter Prädiktor einer schlechten INR-Einstellung (→Einstellung der oralen Antikoagulation mit Vitamin K Antagonisten insbesondere während einer Chemotherapie erschwert)

- Nur ganz wenige Patienten mit einer (aktiven) Krebserkrankung in SPAF-Studien mit DOACs eingeschlossen

Venous thromboembolism and Cancer

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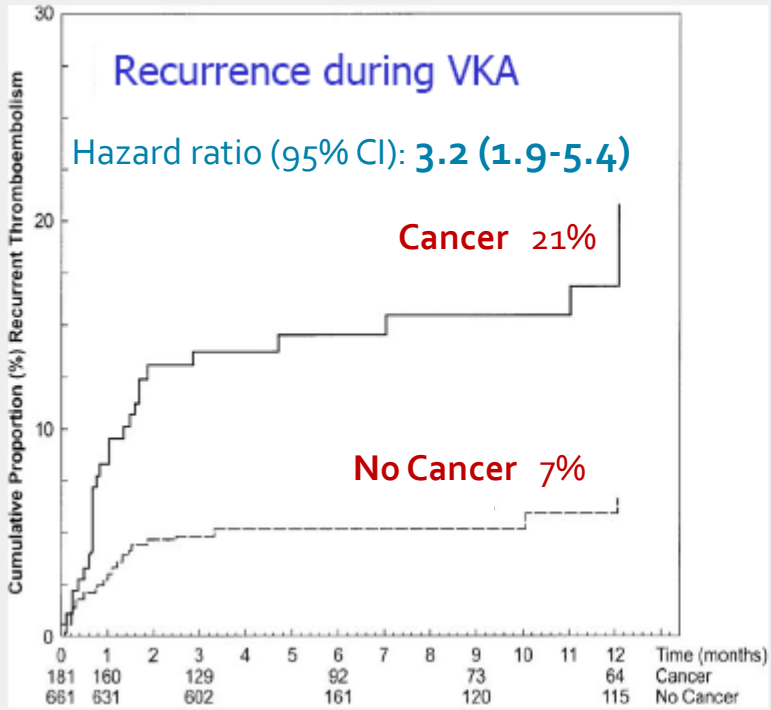
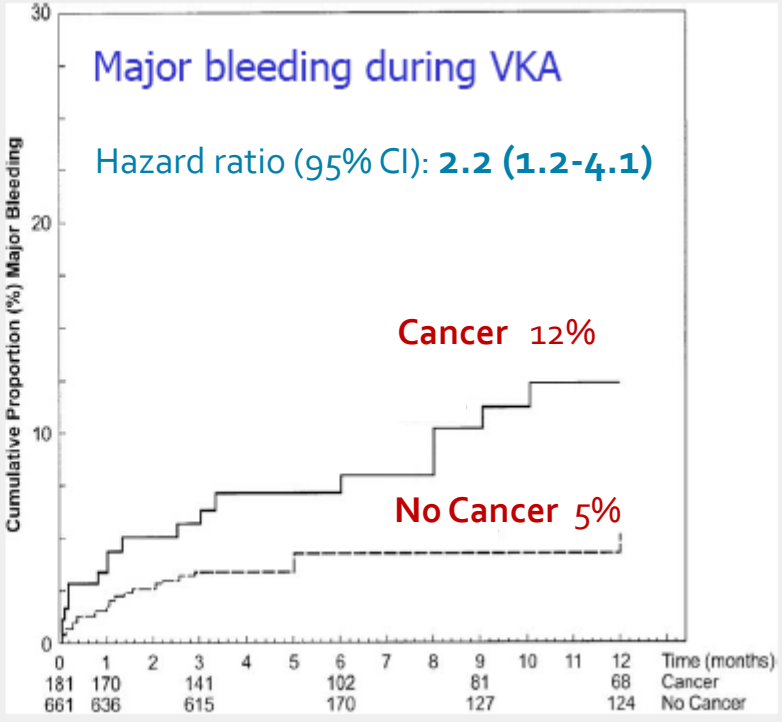
- Cancer is a strong and independent risk factor for venous thromboembolism (VTE)
  - Anti-cancer treatments (chemotherapy, hormonal therapy, anti-angiogenic/immunmodulatory drugs) and major cancer surgery are frequently complicated by deep vein thrombosis (DVT) and pulmonary embolism (PE)
  - Cancer is associated with a 4 to 6.5-fold (with chemotherapy) increased risk of VTE
- Cancer patients account for approximately 20% of all VTE events
- Management and treatment of VTE in patients with cancer is challenging in clinical practice

Heit et al, Arch Intern Med 2000; Khorana AA et al, J Clin Oncol 2009; Ay C et al, Hämostaseologie 2012

Oral anticoagulation with vitamin K antagonists (warfarin) for treatment of VTE

- High risk of recurrence of VTE and bleeding during oral anticoagulation in patients with cancer





Prandoni P, Blood 2002; 100: 3484-8

Open-label, randomized controlled trials for treatment of cancer-associated VTE

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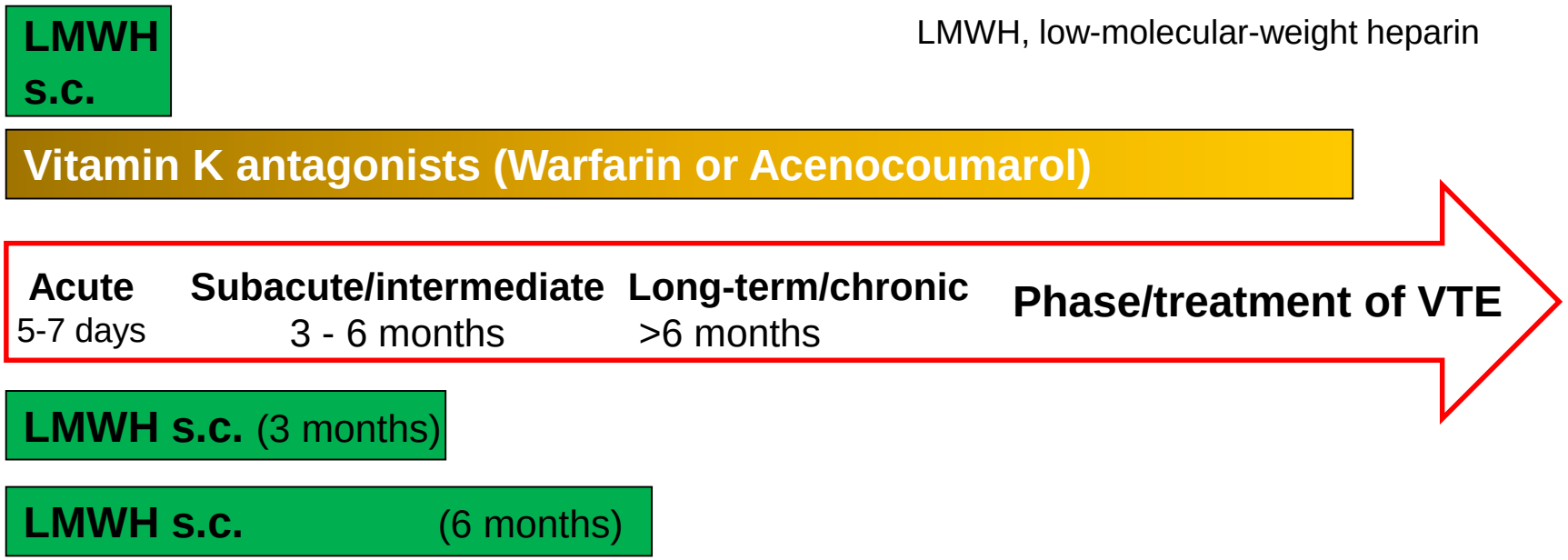
LMWH, low-molecular-weight heparin

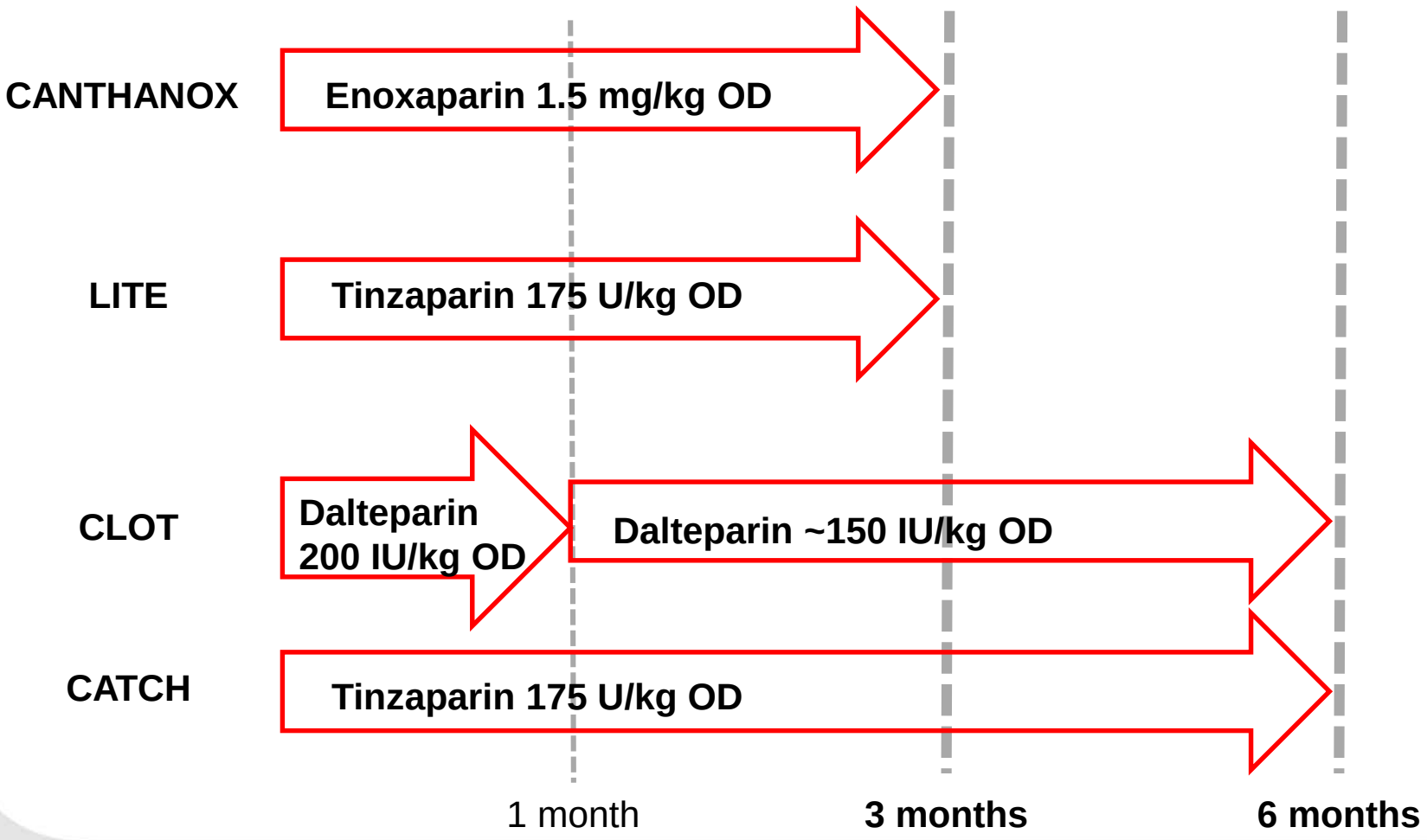


- **CANTHANOX** study: enoxaparin vs. warfarin (3 months)
- **LITE** study: tinzaparin vs. Warfarin (3 months)
- **CLOT** study: dalteparin vs. Warfarin or acenocoumarol (6 months)
- **CATCH** study: tinzaparin vs. Warfarin (6 months)

Meyer et al. Arch Intern Med 2002; 162: 1729–35.; Hull et al. Am J Med 2006; 119: 1062–72.; Lee et al. N Engl J Med 2003; 349: 146–53.; Lee et al. ASH-Meeting 2014, San Franscisco

Treatment of cancer-associated VTE

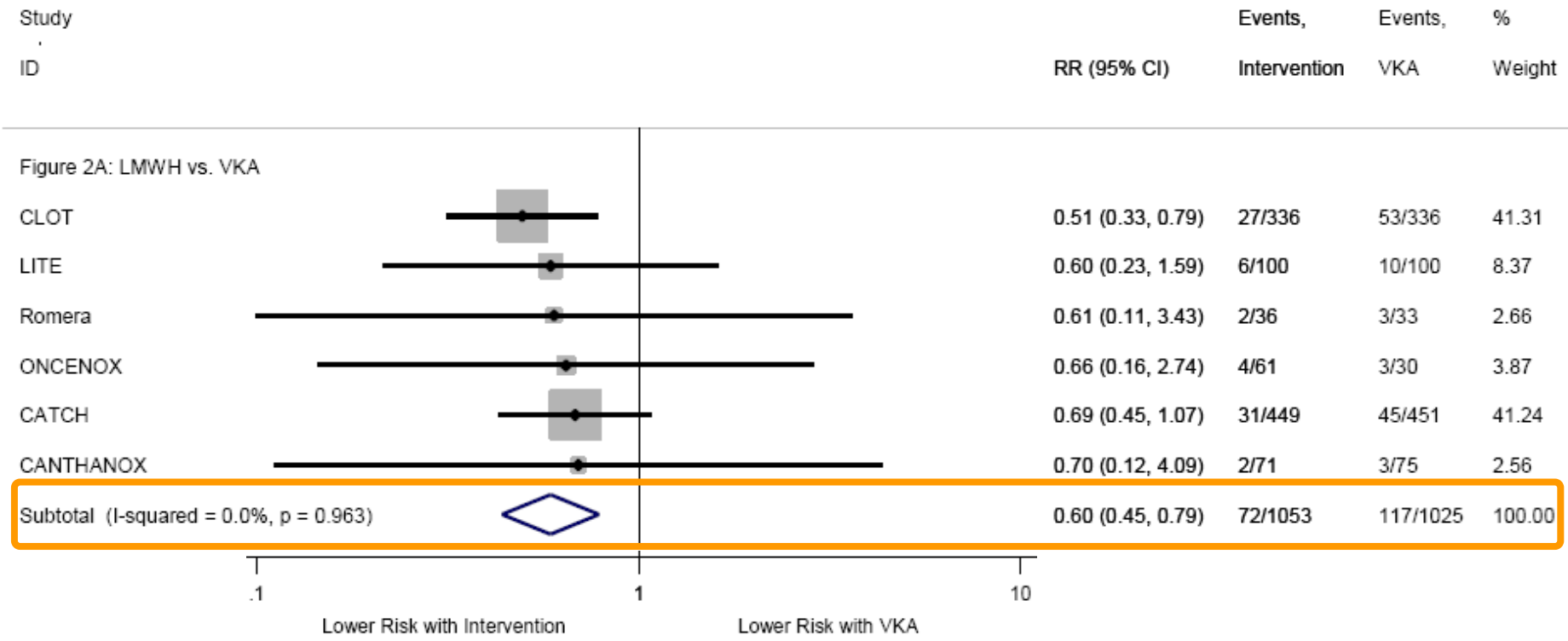
Open-label, randomized controlled trials



Meyer et al. Arch Intern Med 2002; 162: 1729–35.; Hull et al. Am J Med 2006; 119: 1062–72.; Lee et al. N Engl J Med 2003; 349: 146–53, Lee et al. ASH-Meeting 2014, San Franscisco

Meta-Analysis

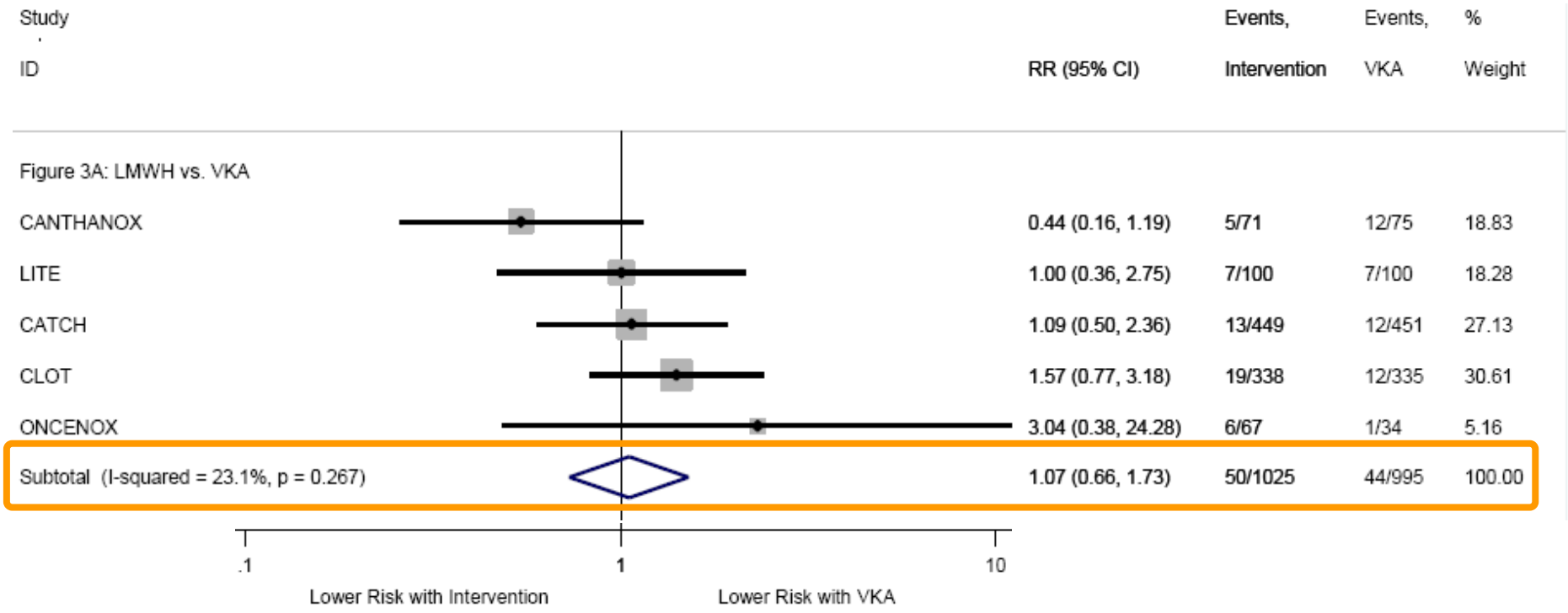
Risk of VTE recurrence in cancer patients treated with LMWH vs. Vitamin K Antagonists



Posch and Ay et al. submitted

Meta-Analysis

Risk of VTE major bleeding in cancer patients treated with LMWH vs. Vitamin K Antagonists



Posch and Ay et al. submitted

Guideline recommendations

Treatment and secondary prophylaxis of cancer-associated VTE

- All major consensus guidelines recommend monotherapy with LMWH as the preferred treatment for cancer-associated VTE
  - In the absence of contraindications, LMWH is preferred in the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE
  - For long-term anticoagulation, LMWH for at least 3 to 6 months is preferred because of improved efficacy over VKAs
    - VKAs are an acceptable alternative for long-term therapy if LMWH is not available
  - Anticoagulation beyond the initial 3 to 6 months may be considered for select patients with active cancer (e.g. metastatic disease, ongoing chemotherapy)

Kearon C et al., CHEST 2012; 141(2)(suppl):e419S-e494S; Lyman G et al., J Clin Oncol. 2013; 31:2189-2204; http://www.nccn.org/professionals/physician_gls/PDF/vte.pdf; Mandala M et al., Ann Oncol. 2011; 22(suppl 6):vi85-92; Farge D et al., J Thromb Haemost 2013; 11:56-70

DOACs
Neue Konzepte in der VTE-Therapie

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NMH s.c. ***Beginn der Therapie mit 2 Medikamenten überlappend***

Vitamin K Antagonisten (Marcoumar®, Sintrom®)

„Switching“ (Umstieg von NMH auf DOAK)

NMH s.c. **Dabigatran/Pradaxa** (150 mg Kps 2xtgl)

NMH s.c. **Edoxaban** (60 oder 30 mg 1xtgl)

„Single-drug approach“ (von Anfang an DOAK)

Rivaroxaban/Xarelto (2x15 mg tgl. für 3 Wochen, danach 1x20 mg tgl)

Apixaban/Eliquis (2x10 mg tgl. für 1 Wochen, danach 2x5 mg tgl)

Akute **Subakute/intermediäre** **Chronische** **Phase der VTE**

Direct oral anticoagulants (DOACs)
Treatment of VTE

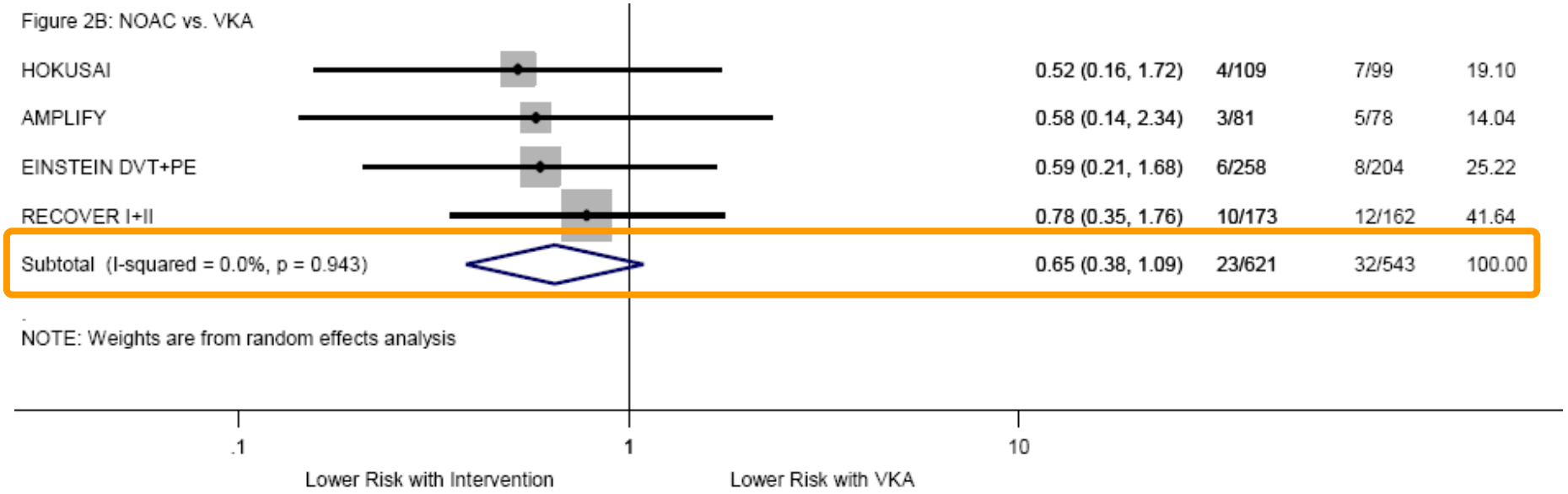
- In phase III clinical trials **dabigatran**, **rivaroxaban, apixaban** and **edoxaban** have shown non-inferiority to standard treatment (vitamin K antagonist: warfarin) in treatment of DVT and PE
    - Cancer patients comprised only ~4% to 9% of patients in these studies
    - Vitamin K antagonist (warfarin) is a known inferior agent in the treatment of VTE in cancer patients

- No studies available that have addressed specifically **DOACs** in treatment of cancer-associated VTE
    - Is it premature to use DOACs in cancer patients???

Schulman et al *NEJM* 2009, Bauersachs et al *NEJM* 2010, Buller et al *NEJM* 2012, Agnelli et al. NEJM 2013, Büller et al. NEJM 2013

Meta-Analysis

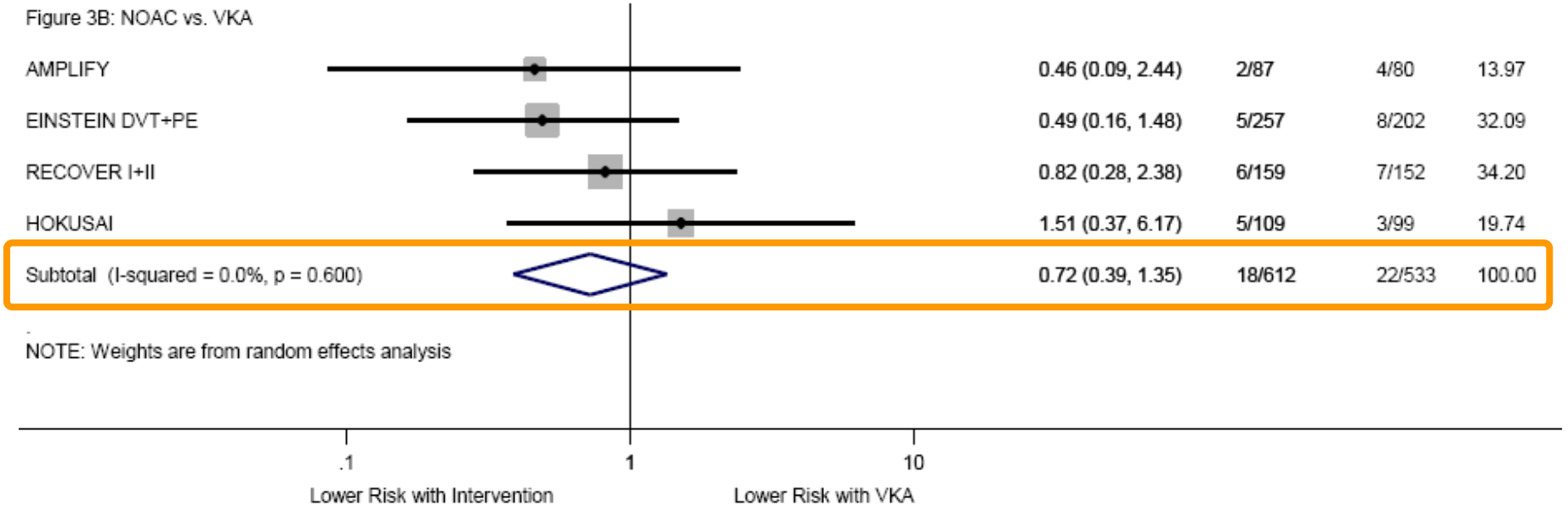
Risk of VTE recurrence in cancer patients treated with DOACs vs. Vitamin K Antagonists



Posch and Ay et al. submitted

Meta-Analysis

Risk of VTE major bleeding in cancer patients treated with DOACs vs. Vitamin K Antagonists



Posch and Ay et al. submitted

Treatment issues of oral anticoagulation (with Vitamin K Antagonists)

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- Drug interactions, malnutrition, GI disturbances and liver dysfunctions alter anticoagulant levels in an unpredictable manner (wide fluctuations of INR)

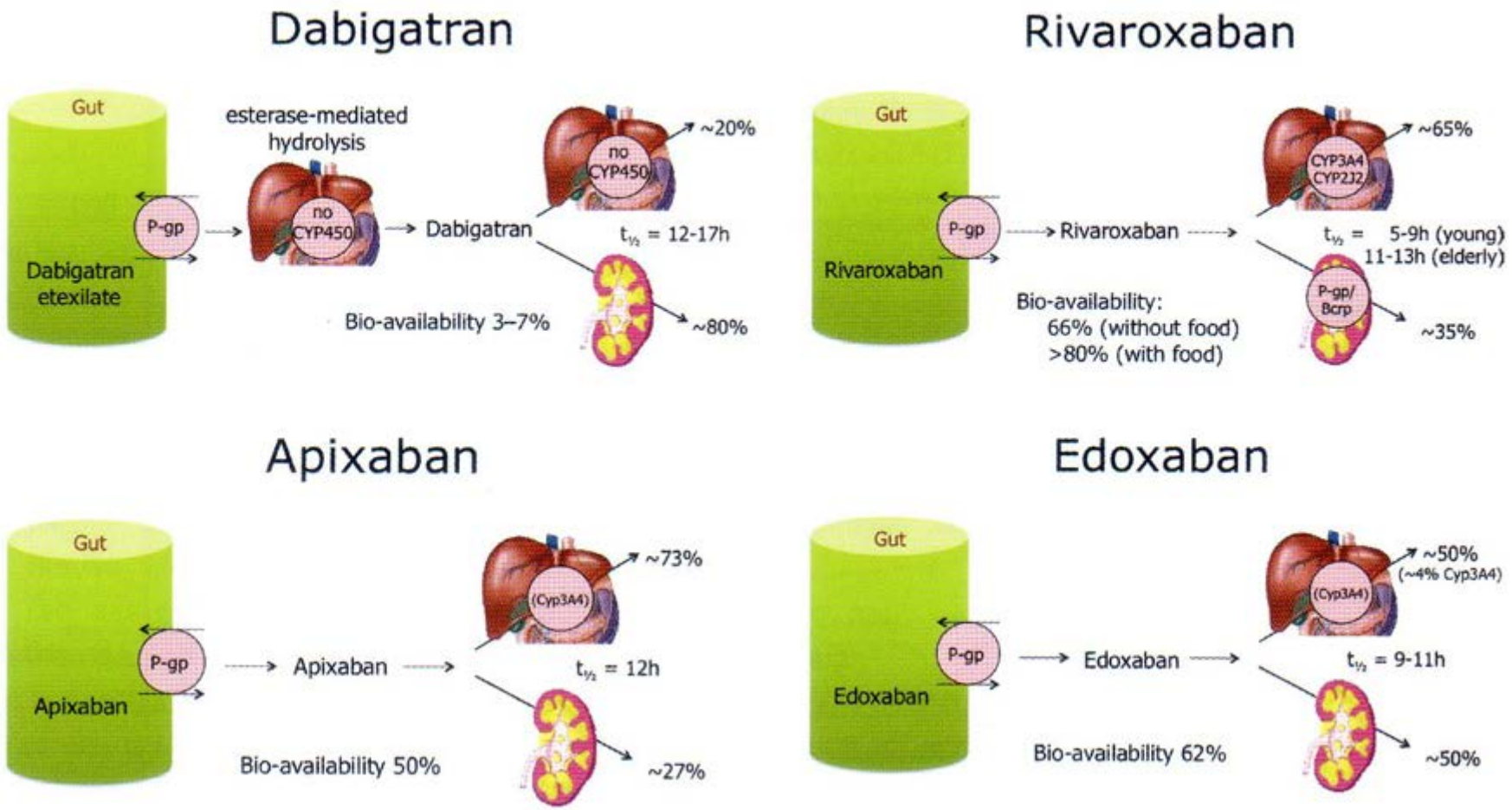
- Thrombocytopenia and invasive procedures require interruption of therapy

- Regular monitoring (INR control)

- Increased risk of recurrence and bleeding

DOACs – Interaktionspotential

Absorption, Metabolismus und Elimination



EHRA Guide: Heidbuchel H, et al. Europace (2013) 15, 625–651

DOACs/NOACs
Interactions with anti-cancer therapies

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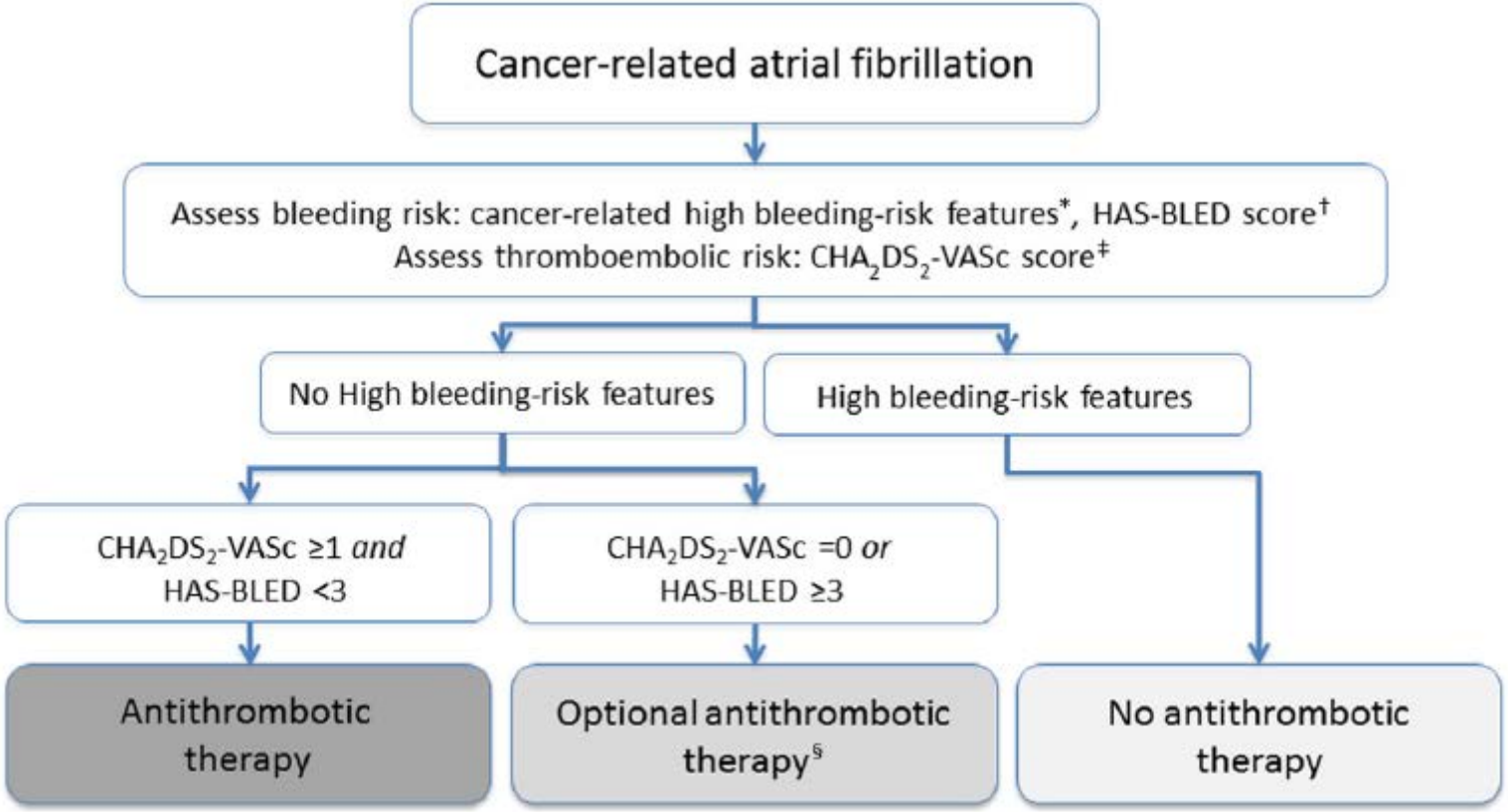
Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein CYP3A4
Increases NOAC plasma levels† (INHIBITORS)	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
Reduces NOAC plasma levels‡ (INDUCERS)	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

DOACs may not be suitable for use in some cancer patients because they share metabolic pathways.

Further research is needed to find out more about the impact of the interaction!

Zusammenfassung

Algorithmus zur Antikoagulation bei onkologischen Patienten mit Vorhofflimmern

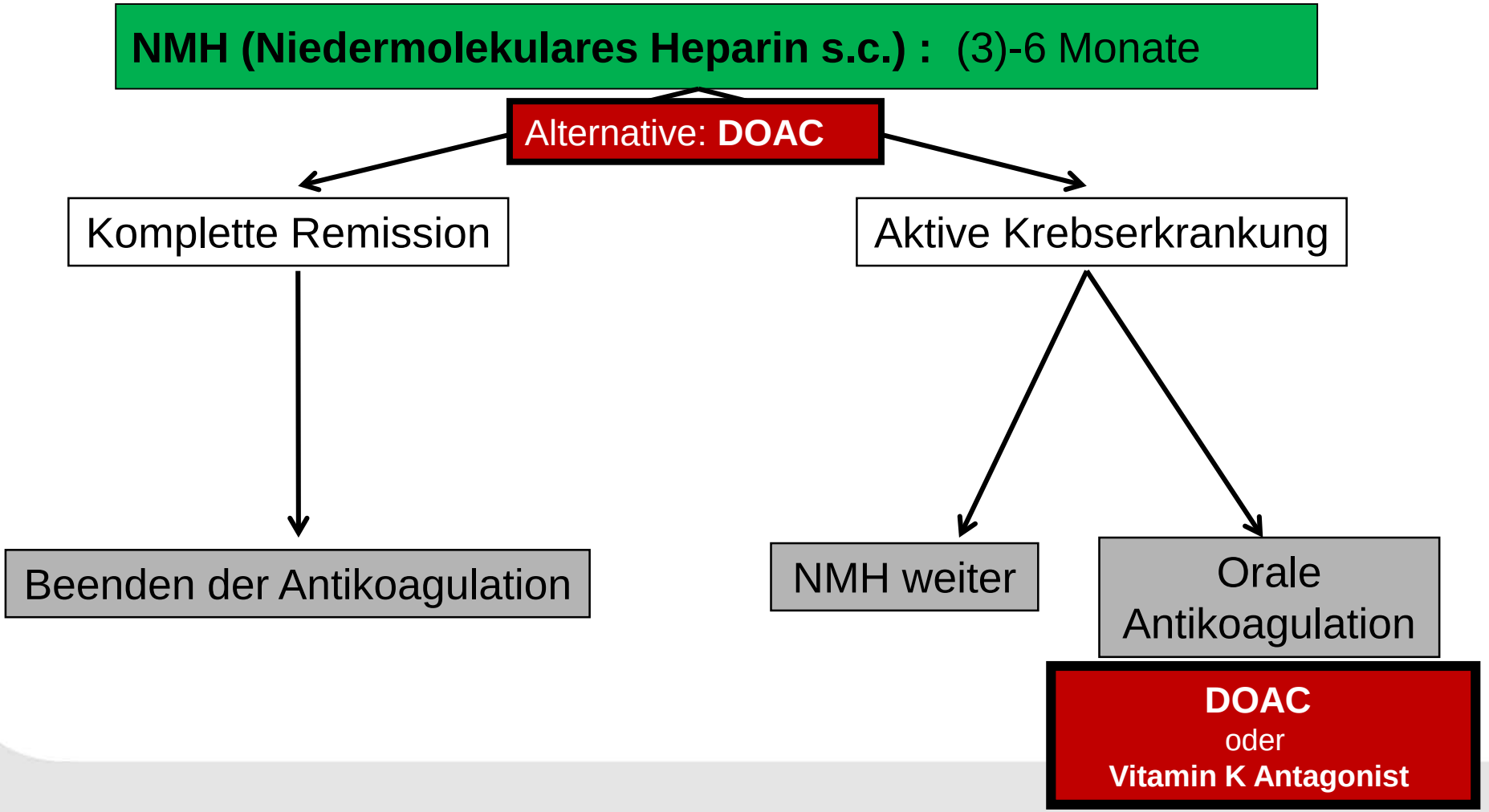


*Intracranial tumor, hematologic malignancies with coagulation defects, cancer therapy induced thrombocytopenia, severe metastatic hepatic disease etc.

Farmakis et al. J Am Coll Cardiol 2014;63:945-53

Zusammenfassung

Wie behandle ich eine krebs-assoziierte VTE



Ay C et al.; Hämostaseologie 2012; 32: 139–44.

Evaluierung der Patienten für Einsatz von DOACs

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Kriterien für Einsatz von DOACs bei onkologischen Patienten

- **Risikofaktoren für Blutungen**
  - Keine großen Blutungsereignisse (innerhalb der letzten 2 Monate)
  - Nichtvorhandensein intrakranieller oder viszeraler Malignome mit einem erhöhten Blutungsrisiko
- **Thrombozyten**
  - Thrombozytenzahl >50 G/l
  - Abfall der Thrombozyten nicht zu erwarten (aufgrund der Grunderkrankung oder Chemotherapien)
- **Normale plasmatische Gerinnung (PTZ, aPTT, Fibrinogen)**
- **Normale Leberfunktionsparameter**
  - Keine signifikante Hepatopathie (z.B. CHILD-Pugh B oder C Zirrhose)
- **Nierenfunktion**
  - CrCl >30 ml/min
  - Nicht zu erwartende Fluktuation aufgrund nephrotoxischer Chemotherapien oder anderer Medikamente
- **(Co-)Medikamente**
  - Kein gleichzeitiger Gebrauch mit starken Inhibitoren/Induktoren von CYP3A4 oder P-glycoprotein über eine lange Dauer

Short et al. The Oncologist 2014;19:82-93

Vielen Dank für Ihre Aufmerksamkeit!

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« Fallpräsentation »

Ein 68-jähriger Mann präsentiert sich mit folgenden Symptomen: Appetitlosigkeit, Fieber, Gewichtsverlust und Nachtschweiß seit einem Monat

Anamnese: « immer gesund »
Status: palpable Lymphknoten inguinal, Beinödeme; ECOG 2
Blutbild: Hb 10.2 G/l, PLT 98 G/l, WBC 3.9 G/l
eGFR 48 ml/min, gamma-GT und LDH sind mäßig erhöht
CT-Hals/Thorax : Pleuraergüsse, mediastinale Lymphknotenvergrößerung, retroperitoneale Lymphadenopathie, « Lymphknotenbulk » in der Fossa iliaca links

« Fallpräsentation »

Weitere Abklärung mit Lymphnotenbioposie und BKP:
Diffus großzelliges B-Zell-Lymphom (DLBCL), Stadium IIIB

Therapieempfehlung: Immun-/Chemotherapie nach dem R-CHOP Protokoll

Nach 3 Zyklen R-CHOP erfolgt ein Re-Staging (PET-CT)
→dabei findet sich eine sog. « asymptomatische » bzw. zufällig entdeckte Pulmonalembolie (Unterlappen links)

Blutbild zu diesem Zeitpunkt: Hb 9.8 G/l, PLT 68 G/l, WBC 3.1 G/l

« Fragen »

Würden Sie diesen Patienten (bei einer asymptomatischen Pulmonalembolie) überhaupt behandeln?

Sind direkte orale Antikoagulantien (DOACs) eine geeignete Behandlungsoption für diesen Patienten?

Welche Bedenken haben Sie sonst?

Potentielle Interaktionen der DOACs mit der Chemotherapie

	P-glycoprotein	CYP 3A4
Rituximab	keine	keine
Doxorubicin	**Induktion**	**Inhibitor**
Vincristin	keine	**Inhibitor**
Cyclophosphamid	keine	**Inhibitor**
Prednison	keine	**Inhibitior**

Management of cancer-associated VTE in patients with high risk of bleeding

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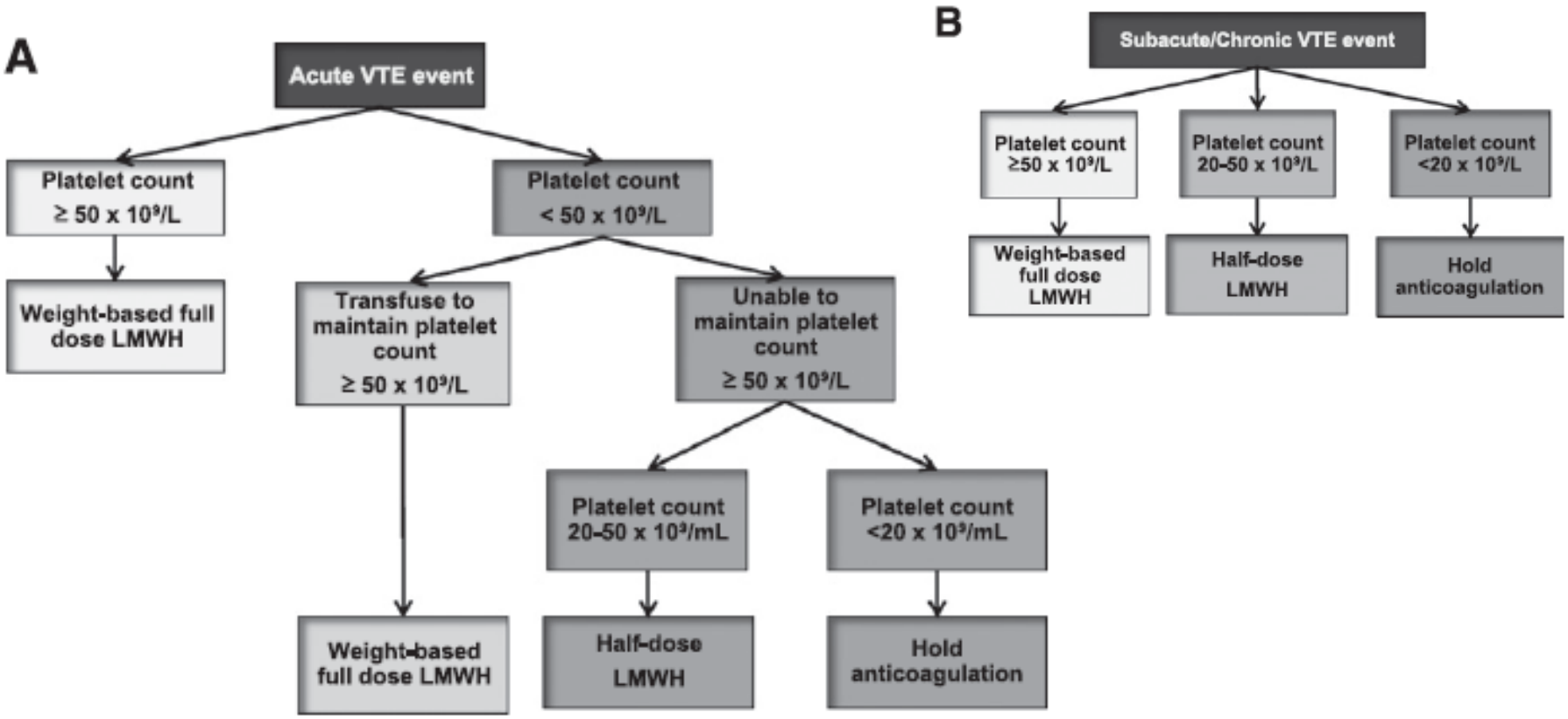
- Cancer- and chemotherapy induced **thrombocytopenia**

- LMWH is cleared by the kidneys →accumulation in patients with impaired renal function (creatinine clearance <30 ml/min).
  - Increased risk for major bleeding in patients with a creatinine clearance of <30 ml/min treated with therapeutic doses of LMWH
  - In patients with severe renal failure (creatinine clearance <25–30 ml) →anti-Xa activity monitoring is recommended
  - Elevated levels of anti-Xa activity →dose reduction of LMWH

Management algorithm of VTE in patients with cancer and thrombocytopenia



Acute VTE (<1 month) and subacute or chronic VTE (>1month)

Lee AY. Blood 2013

Treatment of thrombosis associated with central venous catheters in patients with cancer

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Journal of Thrombosis and Haemostasis, 11: 71–80

DOI: 10.1111/jth.12071

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer

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Debourdeau P et al.; J Thromb Haemost 2013; 11: 71–80.

Catheter-related thrombosis (CRT)
Therapy

• For the treatment of symptomatic CRT in cancer patients, **anticoagulant treatment** is recommended for a minimum of **3 months**; in this setting, **LMWHs** are suggested. **Oral VKA can also be used**, in the absence of direct comparisons of these two types of anticoagulants in this setting *[Best clinical practice]*.

• The CVC can be kept in place if it is functional, well-positioned and non-infected with good resolution of symptoms under close surveillance; whether the CVC is kept or removed, no standard approach in terms of duration of anticoagulation is established *[Best clinical practice]*.

Debourdeau P et al.; J Thromb Haemost 2013; 11: 71–80.

Catheter-related thrombosis (CRT)
Prophylaxis and general recommendations

- Use of **anticoagulation for routine prophylaxis of CRT is not recommended** *[Grade 1A].*

Values and preferences: bleeding risk with anticoagulants.

- Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium *[Grade 1A]*.

Debourdeau P et al.; J Thromb Haemost 2013; 11: 71–80.

Major guidelines

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Table 1. Consensus guidelines on treatment of deep vein thrombosis or pulmonary embolism in patients with cancer

	ACCP 2012[21]	NCCN 2011[13]	ASCO 2013[14]
Initial/acute treatment	Not addressed in cancer patients.	LMWH Dalteparin 200 U/kg OD Enoxaparin 1 mg/kg BID Tinzaparin 175 U/kg OD Fondaparinux 5 mg (<50 kg), 7.5 mg (50-100 kg), or 10 mg (>100 kg) OD APTT-adjusted UFH infusion	LMWH is preferred for initial 5-10 d of treatment in patients with a CrCl >30 mL/min.
Long-term treatment	LMWH preferred to VKA [2B].*	LMWH is preferred for first 6 mo as monotherapy without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer.	LMWH is preferred for long-term therapy.
	In patients not treated with LMWH, VKA therapy is preferred to dabigatran or rivaroxaban [2C].* Patients receiving extended therapy should continue with the same agent used for the first 3 mo of treatment [2C].*	Warfarin 2.5-5 mg every day initially with subsequent dosing based on INR value targeted at 2-3.	VKAs (target INR, 2-3) are acceptable for long-term therapy if LMWH is not available.
Duration of treatment	Extended anticoagulant therapy is preferred to 3 mo of treatment [2B].*	Minimum 3 mo. Indefinite anticoagulant if active cancer or persistent risk factors.	At least 6 mo duration. Extended anticoagulation with LMWH or VKA may be considered beyond 6 mo for patients with metastatic disease or patients who are receiving chemotherapy.

ACCP, American College of Chest Physicians; BID, twice-daily dosing; NCCN, National Comprehensive Cancer Network; OD, once-daily dosing.
*ACCP adaptation of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group evidence-based recommendations: 2B, weak recommendation, moderate-quality evidence; 2C, weak recommendation, low- or very-low-quality evidence.[16]

Lee AY. Blood 2013

Risk factors for VTE in patients with cancer

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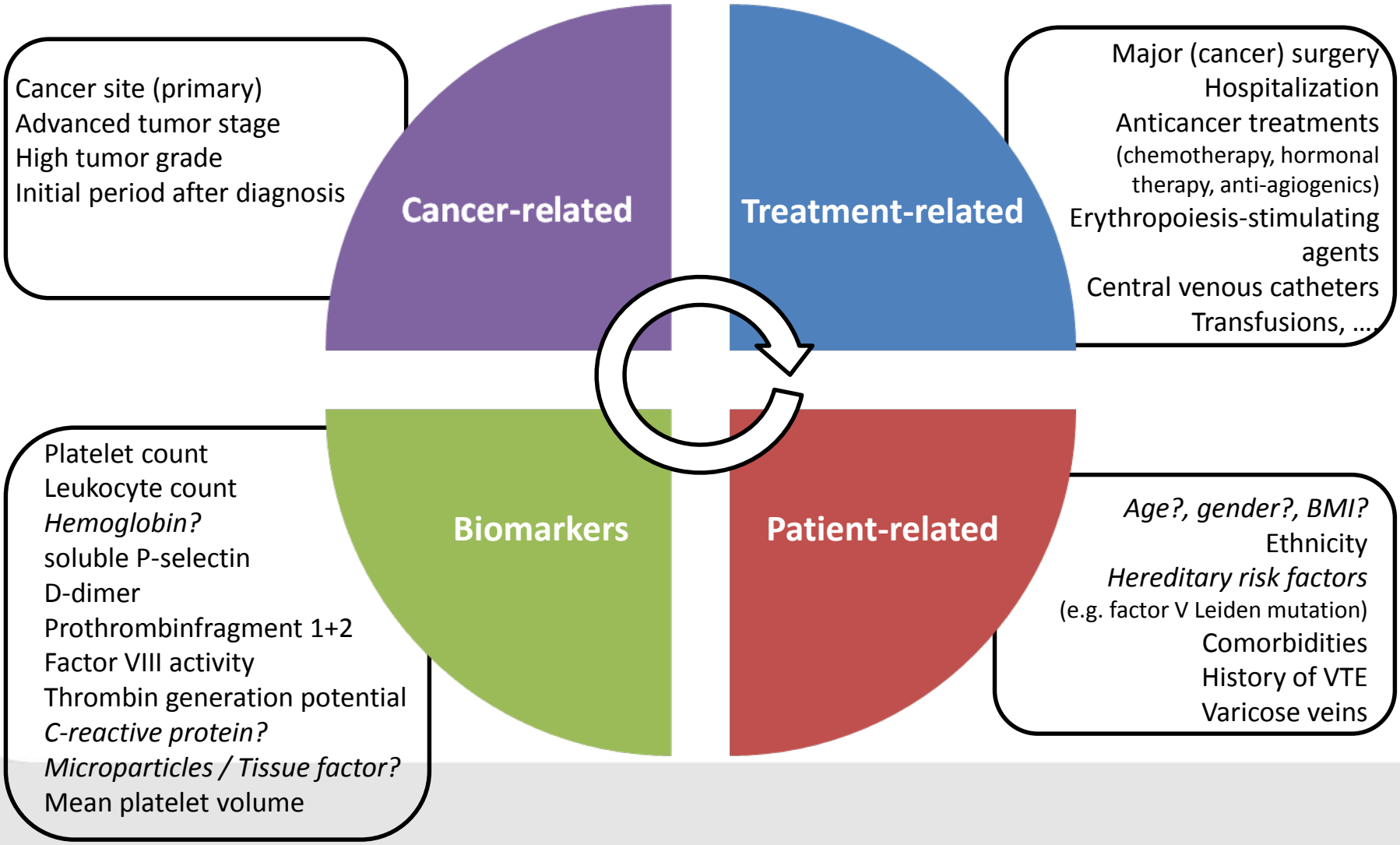
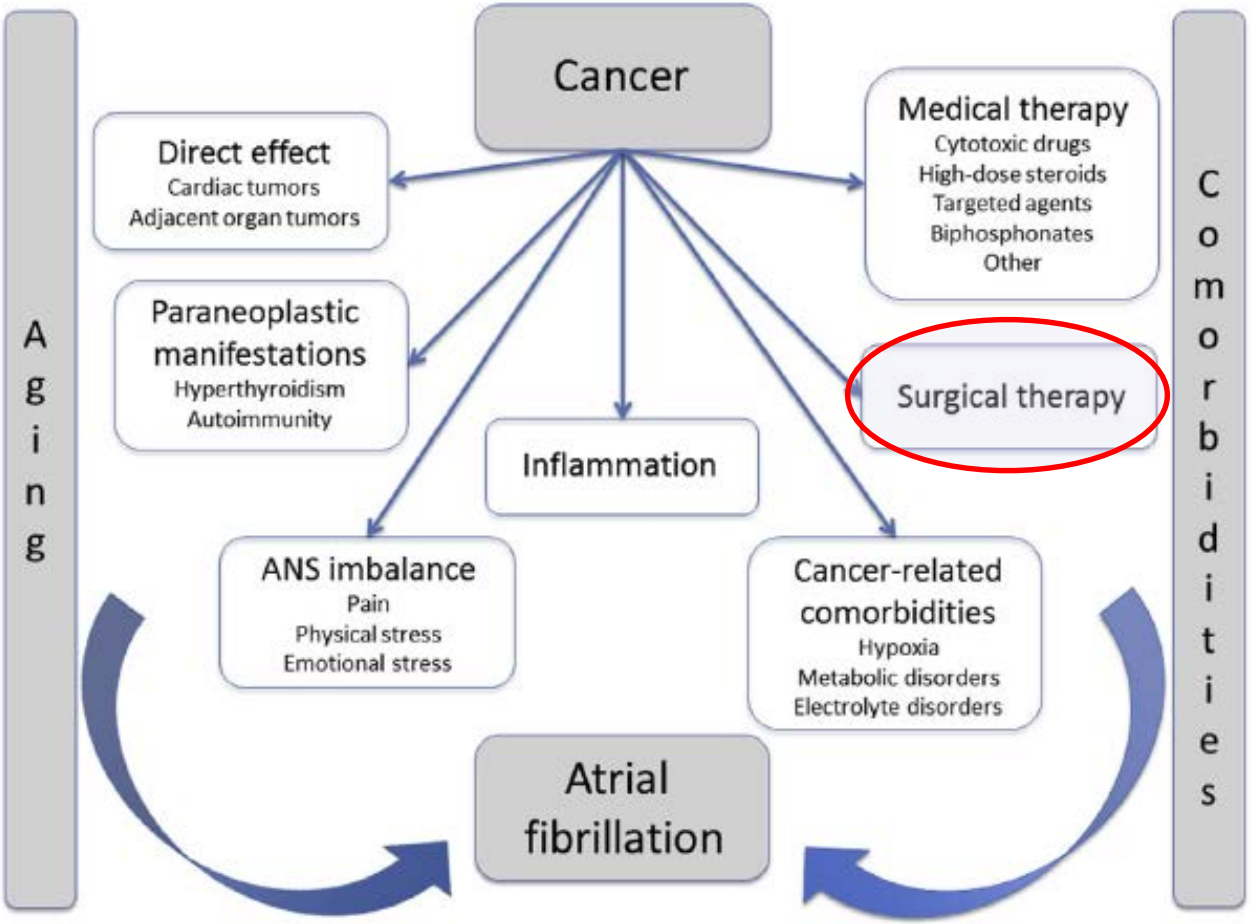


Association of biomarkers with risk of VTE in patients with cancer

Biomarkers and laboratory tests investigated for prediction of cancer-associated VTE in CATS		
Platelet count	Simanek et al, JTH 2009	+
soluble P-selectin	Ay et al, Blood 2008	+
D-Dimer		+
Prothrombinfragment 1+2	Ay et al, J Clin Oncol 2009	+
C-reaktive Protein	Kanz et al, JTH 2011	(+)
Factor VIII activity	Vormittag et al, ATVB 2009	+
Thrombin Generation Assay	Ay et al, J Clin Oncol 2011	+
Microparticles/Tissue factor bearing microparticles	Thaler et al, JTH 2012	-/+ ?
Fibrinogen	Tiedje et al, Thromb Haemost 2011	--

Reviewed in: Ay and Pabinger, Thromb Res 2012

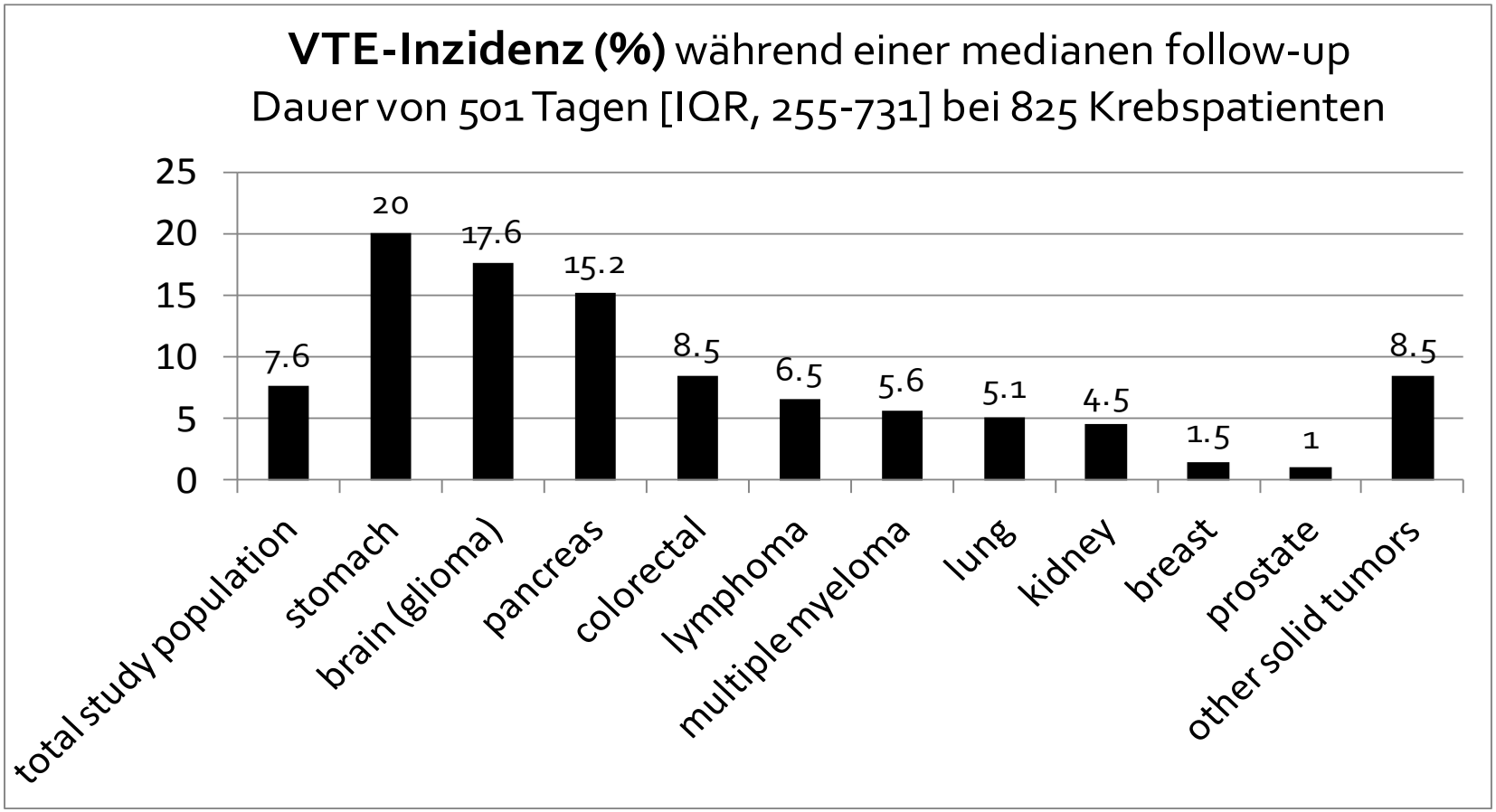
Mögliche pathogenetische Mechanismen zwischen Krebs und Vorhofflimmern



Farmakis et al. J Am Coll Cardiol 2014;63:945-53

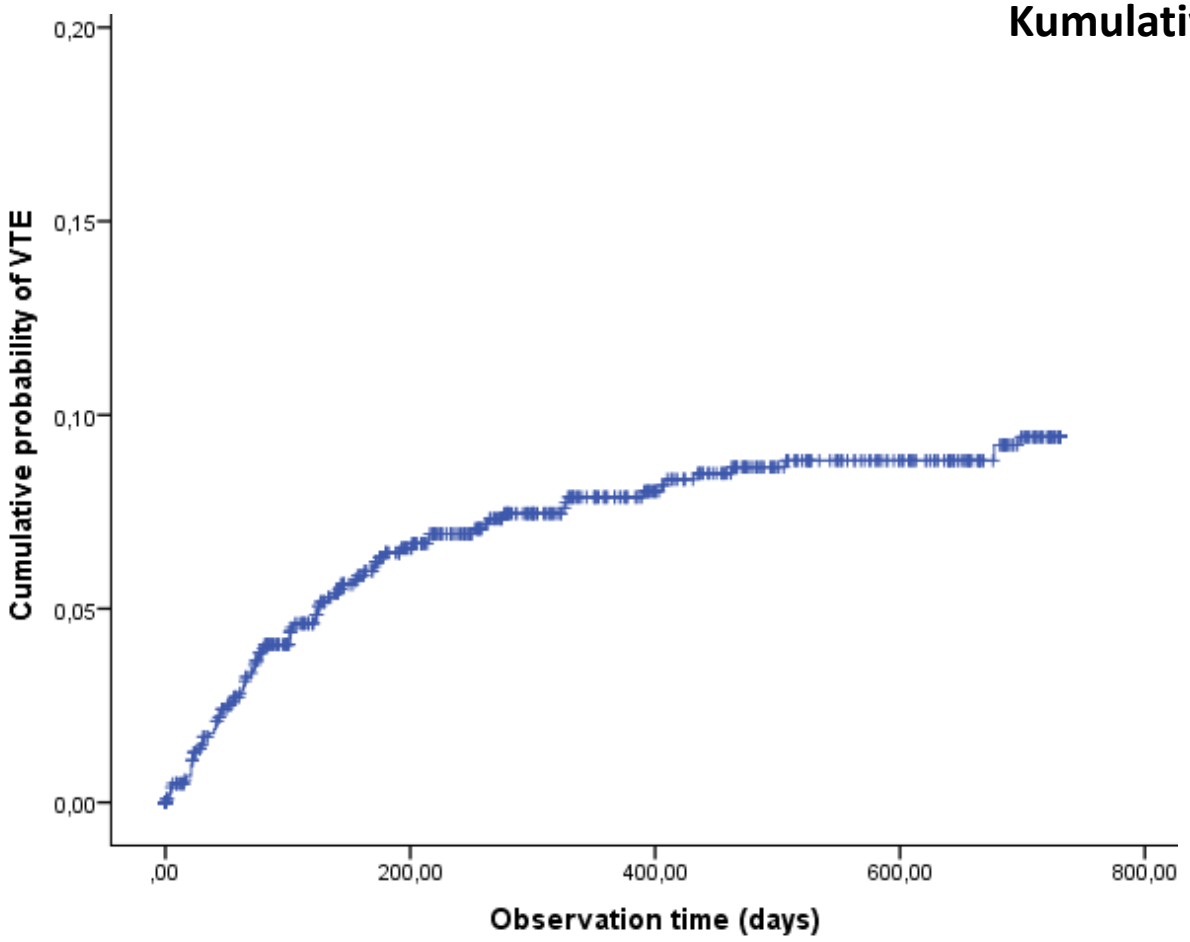
Vienna Cancer and Thrombosis Study

- VTE-Inzidenz bei verschiedenen Tumorentitäten in einer prospektiven Kohortenstudie



Ay C et al, J Clin Oncol 2009

Wann tritt die VTE bei Krebspatienten auf?



Kumulative Wahrscheinlichkeit

3 Monate: 4.2%

6 Monate: 6.1%

12 Monate: 8.1%

2 Jahre: 9.4%

CATS (unpublished)