COMPREHENSIVE CANCER CENTER VIENNA

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Venöse Thromboembolie

Anti-thrombotische Therapie bei onkologischen Patienten

Cihan Ay

Medizinische Universität Wien / AKH Wien
Universitätsklinik für Innere Medizin I
Klin. Abteilung für Hämatologie und Hämostaseologie
Wien, Österreich

cihan.ay@meduniwien.ac.at

Anticoagulants for treatment of venous thromboembolism (in cancer)

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- Low-molecular-weight heparins (LWMH)
  - first choice of treating cancer-associated thrombosis (CAT)
- Vitamin K antagonists (VKA)
  - alternative choice
- NOAC/DOAC
  - approved for treatment of VTE in the general population
  - only limited number of cancer patients included (subgroup analysis of highly selected, heterogeneous and poorly defined "cancer")

Lyman GH et al. JCO. 2013, Konstantinides SV et al. Eur Heart J. 2014, Mandala M et al. Ann Oncol. 2011, Farge D et al. J Thromb Haemost. 2013; Kearon C et al., CHEST 2016 (prepublished online)

Venous thromboembolism and Cancer

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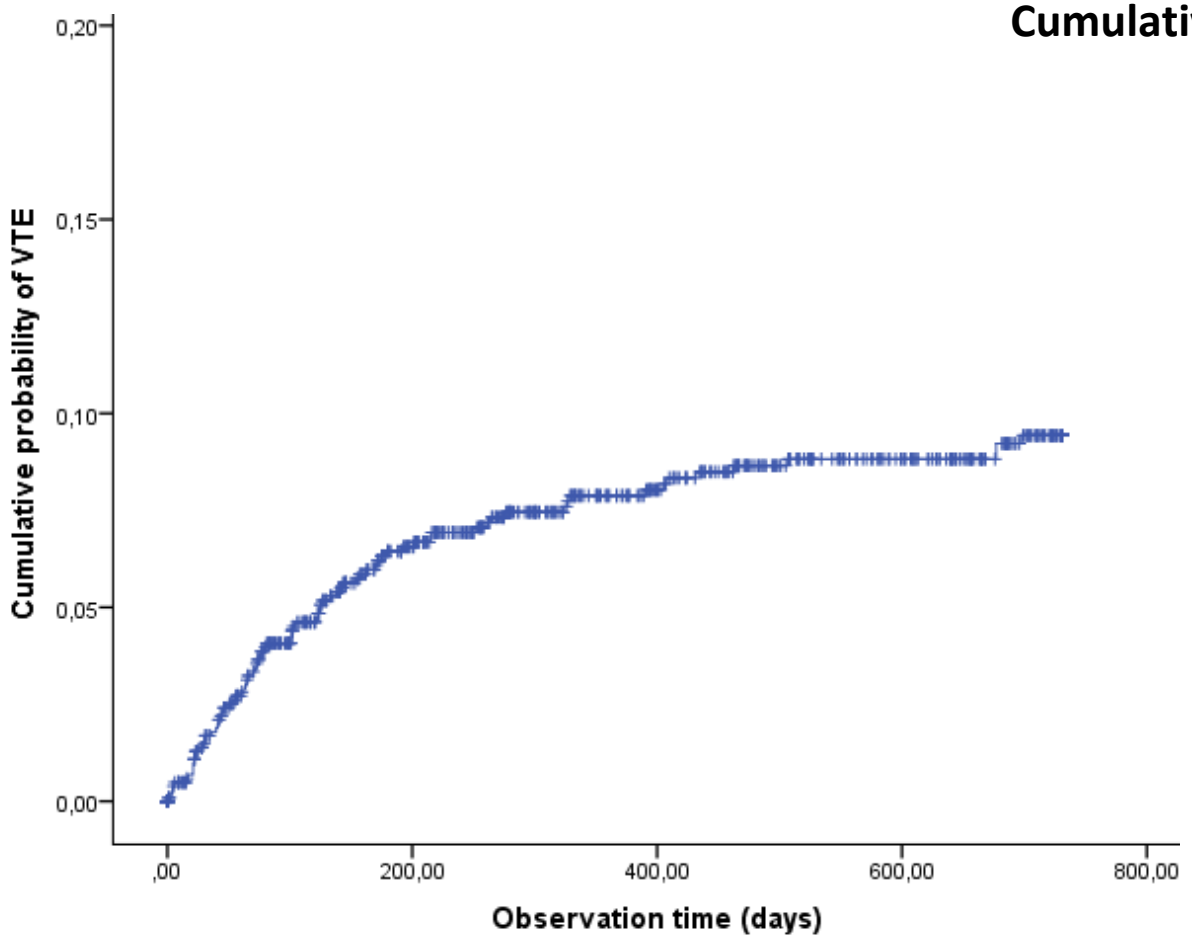
- Cancer is a strong and independent risk factor for venous thromboembolism (VTE)
- Cancer patients account for approximately 20% of all VTE events
- Management and treatment of VTE in patients with cancer is challenging in clinical practice

When do thrombotic events occur in patients with cancer?



Cumulative probability of VTE

3 months: 4.2%

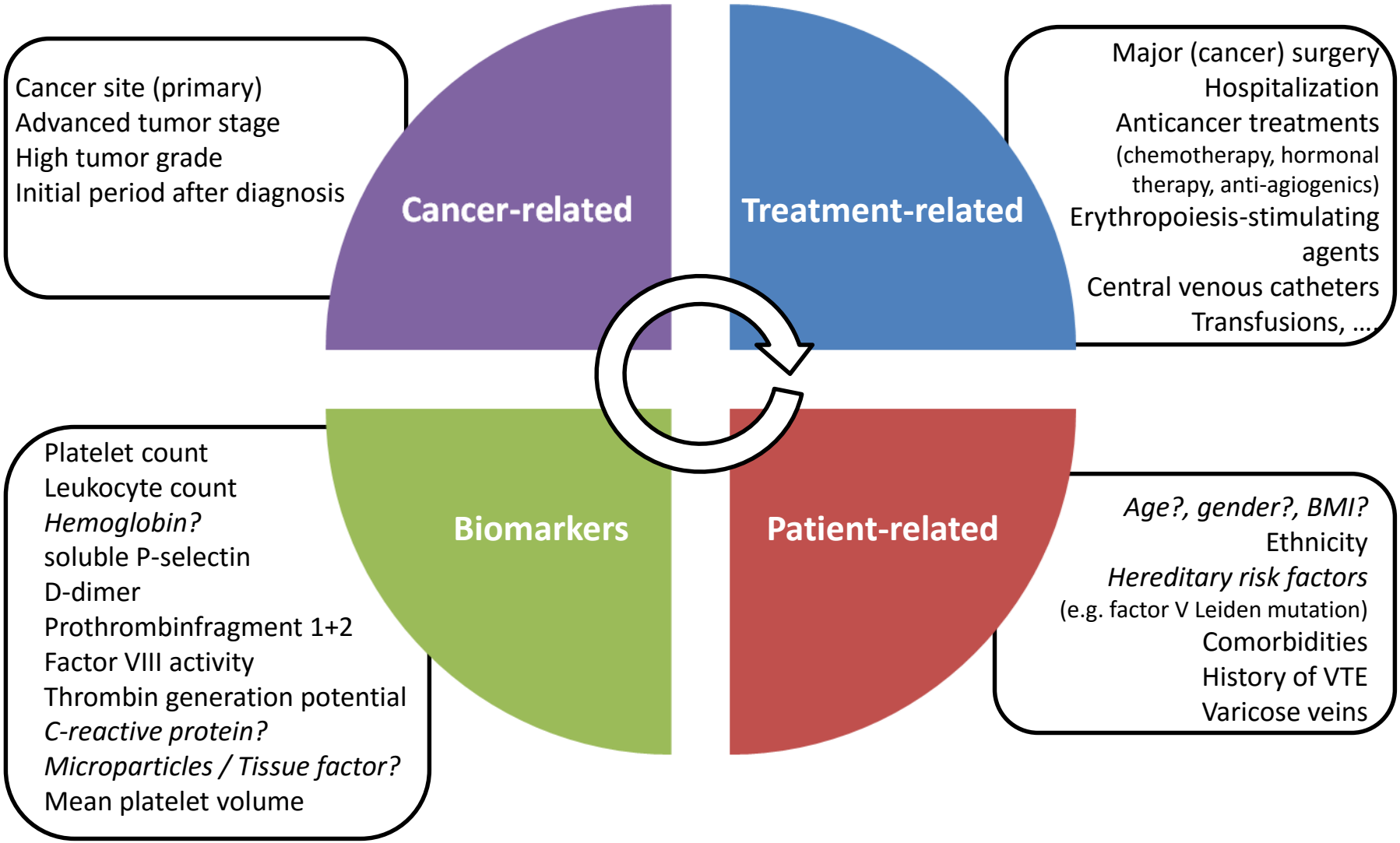
6 months : 6.1%

12 months : 8.1%

2 years: 9.4%

Ay et al (CATS, unpublished)

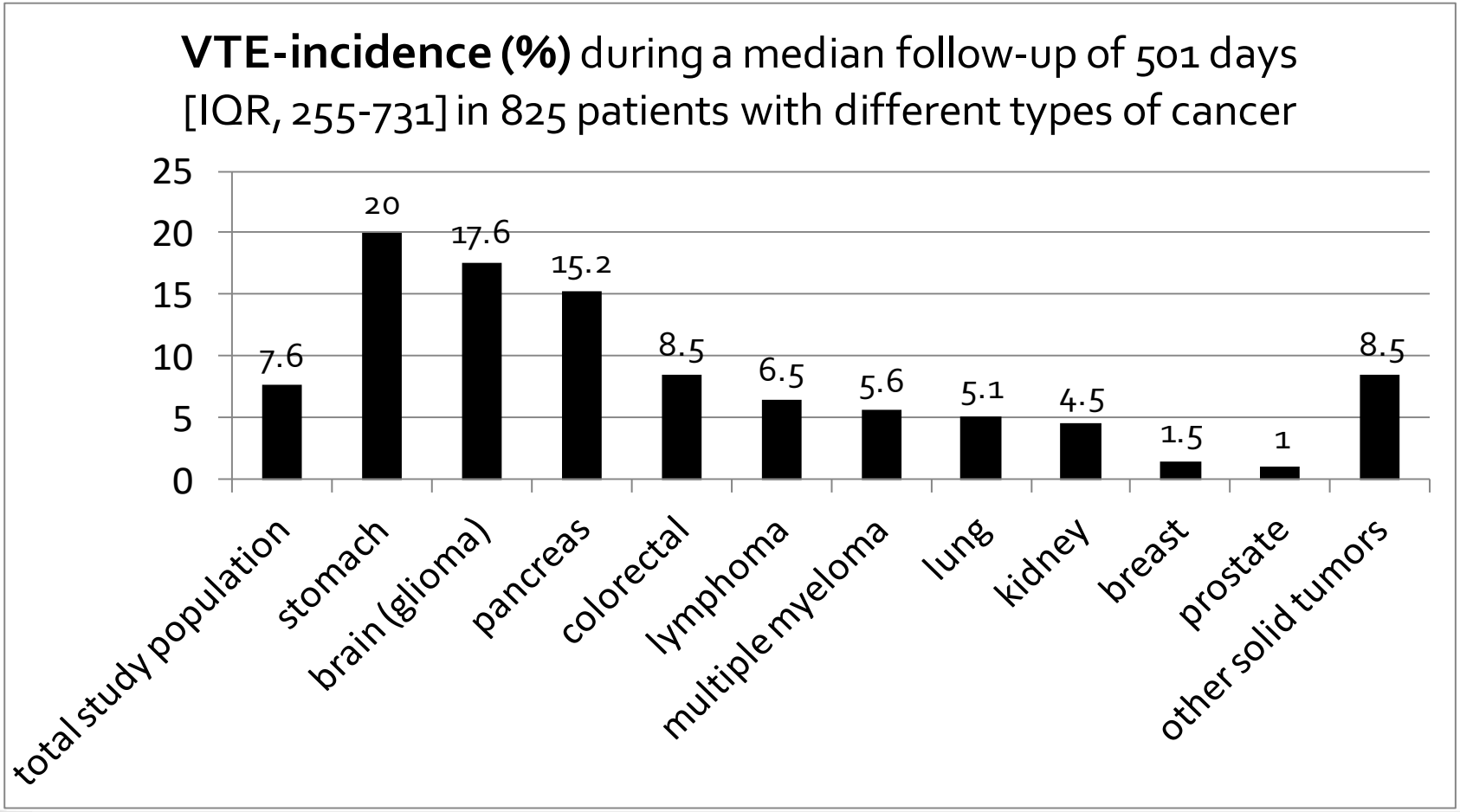
Risk factors for VTE in patients with cancer



reviewed in: Pabinger, Thaler and Ay, Blood 2013; Königsbrügge, Pabinger and Ay, Thromb Res 2014

Rates of VTE in patients with cancer

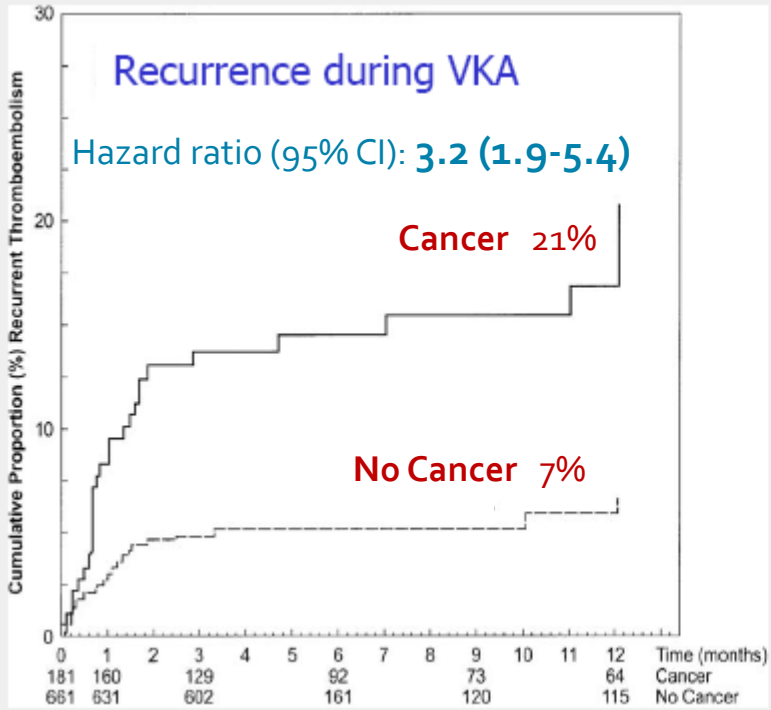
- 1 - 20% of patients with cancer develop VTE during the course of their disease

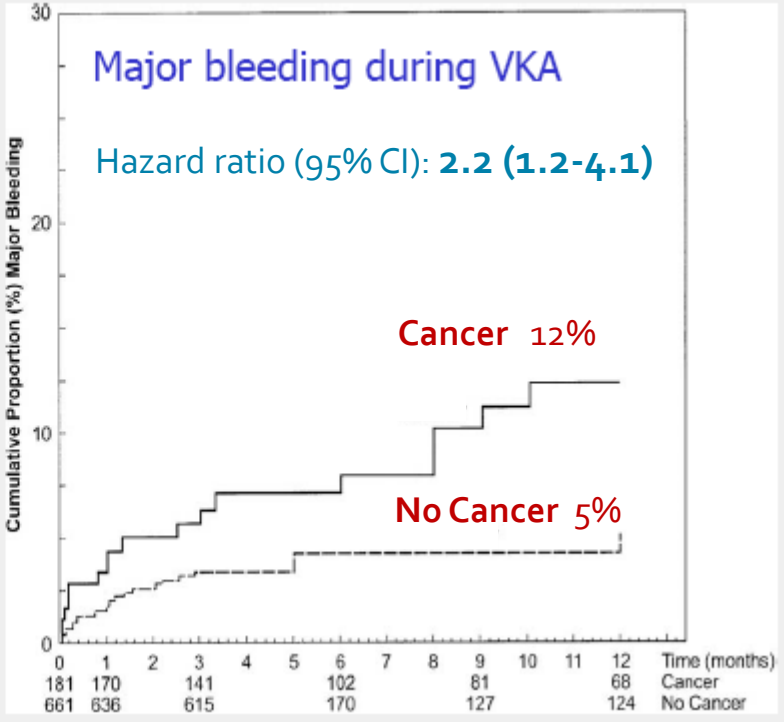


Ay C et al, J Clin Oncol 2009

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

Recurrence of VTE and major bleeding in relation to INR

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INR (range)	Recurrent VTE		Major Bleeding	
	Cancer	No Cancer	Cancer	No Cancer
< 2.0	54	15.9	30.6	0
2.0–3.0	18.9	7.2	11.2	0.8
> 3.0	18.4	6.4	0	6.3
Overall	27	9	13.3	2.1
Number of events per 100 patients/yrs				

Hutten BA, J Clin Oncol. 2000; 18: 3078-83

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

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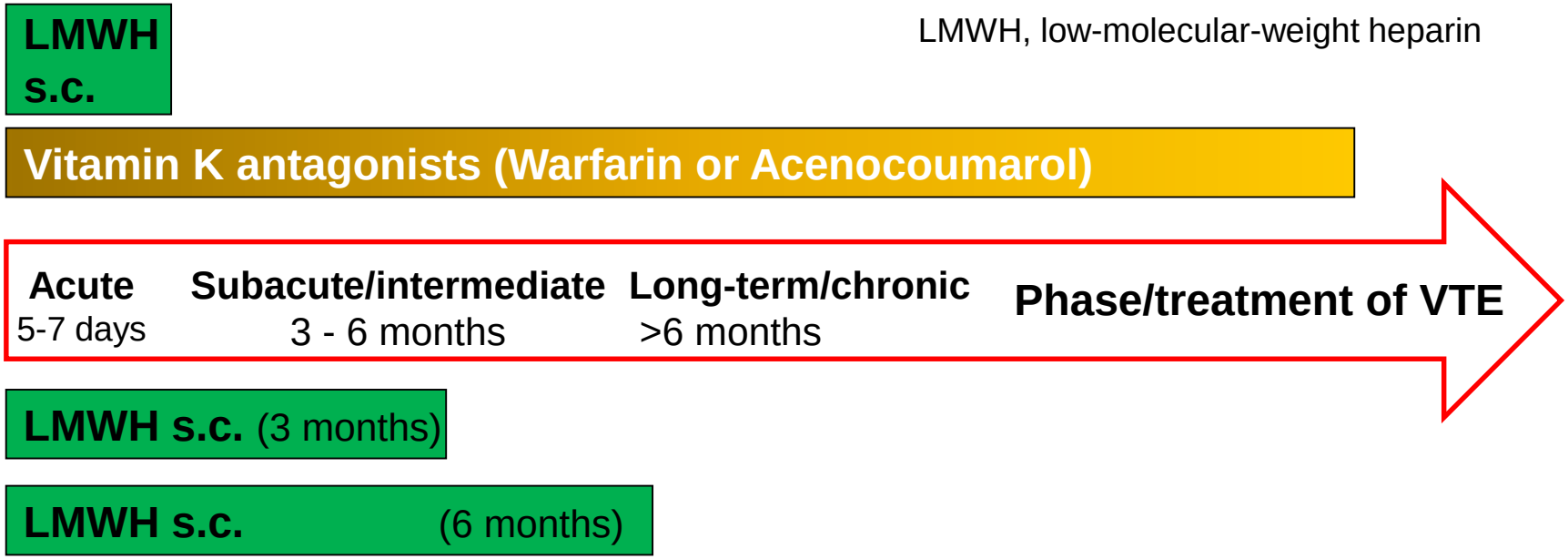
LMWH, low-molecular-weight heparin

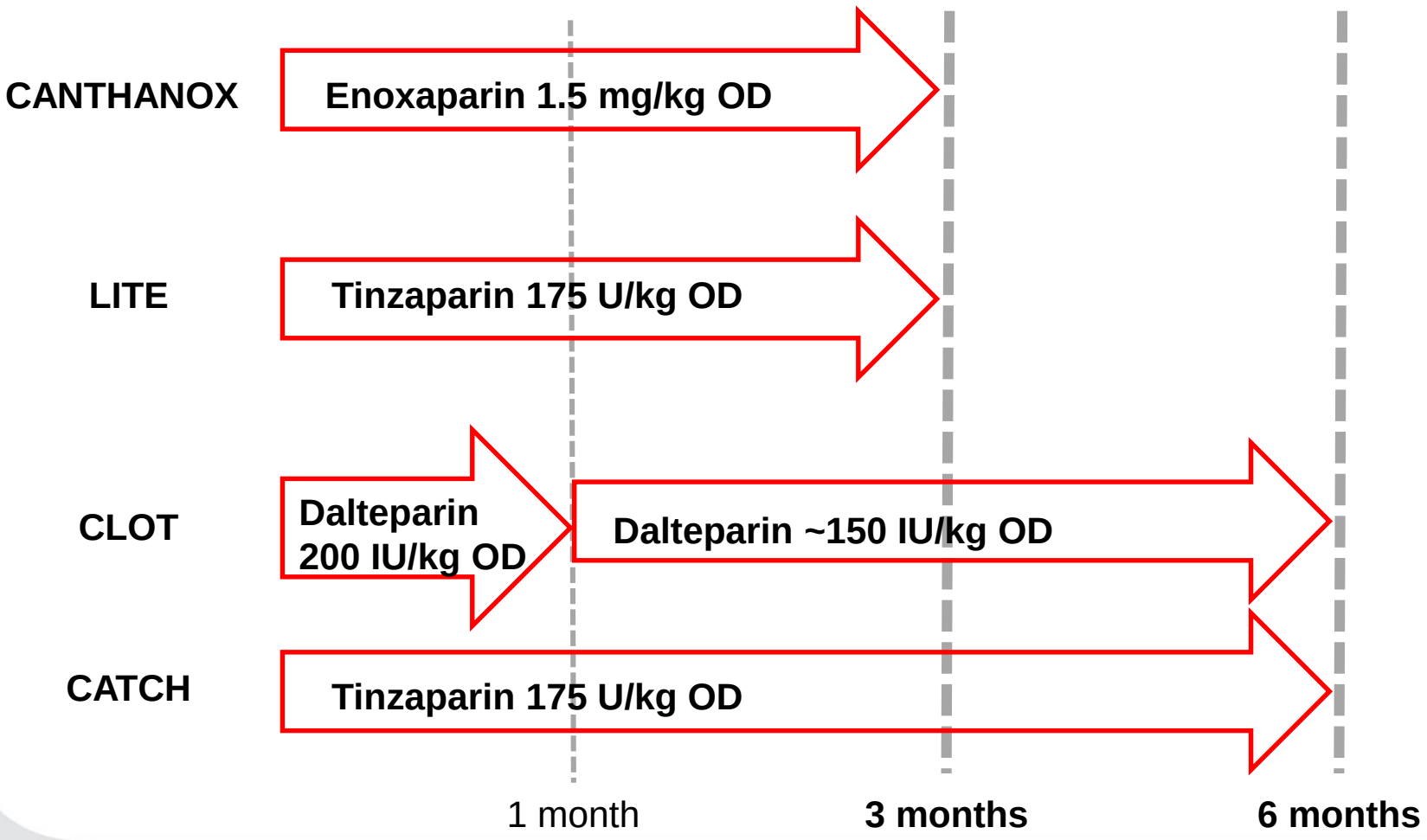


- **CANTHANOX** study: enoxaparin vs. warfarin (3 months)
- **LITE** study: tinzaparin vs. Warfarin (3 months)
- **CLOT** study: dalteparin vs. Warfarin or acenocoumarol (6 months)
- **CATCH** study: tinzaparin vs. Warfarin (6 months)

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. JAMA. 2015;314:677-86.

Treatment of cancer-associated VTE

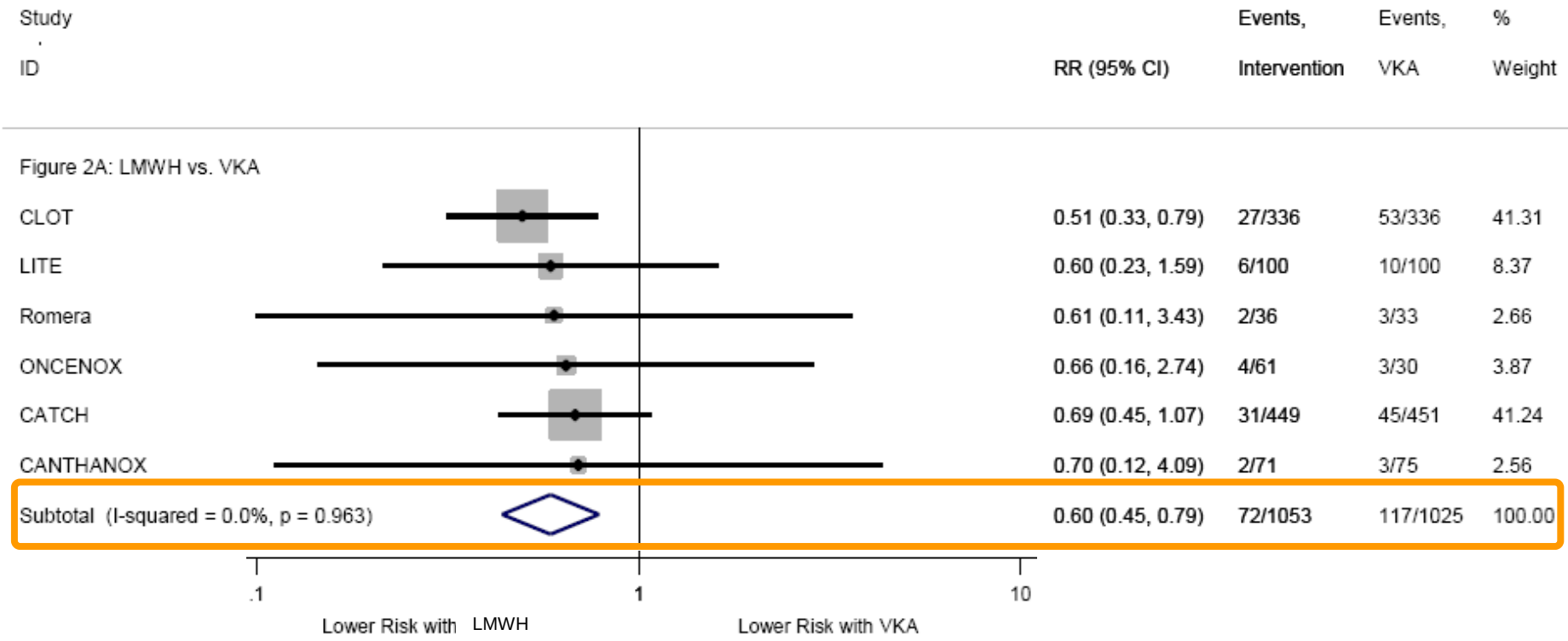
Open-label, randomized controlled trials



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. JAMA. 2015;314:677-86.

Meta-Analysis

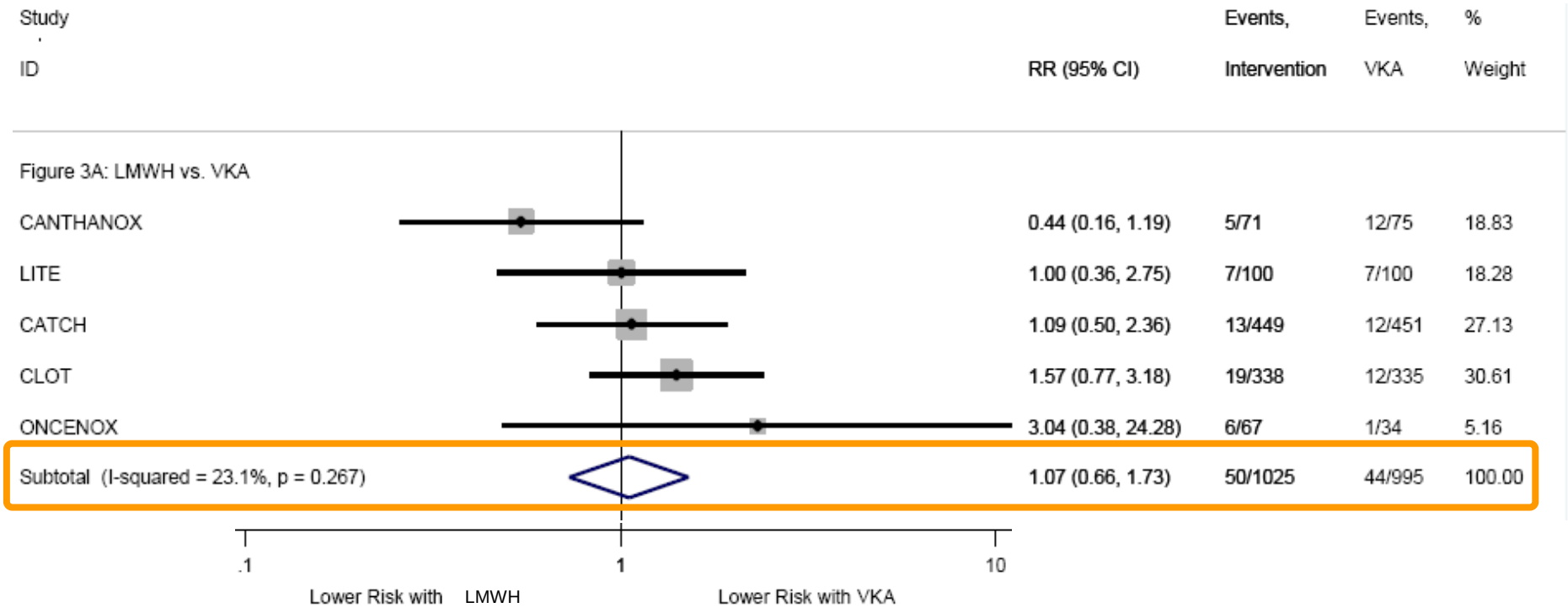
Risk of VTE recurrence in cancer patients treated with LMWH vs. Vitamin K Antagonists



Posch and Ay et al. Thromb Res. 2015 Sep;136(3):582-9.

Meta-Analysis

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



Posch and Ay et al. Thromb Res. 2015 Sep;136(3):582-9.

NOACs
New options for treatment of DVT/PE

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„Conventional“ treatment

NMH s.c.

Vitamin K Antagonist

„Switching“

NMH s.c. **Dabigatran/Pradaxa®** (150 mg BID)

NMH s.c. **Edoxaban** (60 or 30 mg OD)

„Single-drug approach“

Rivaroxaban/Xarelto® (15 mg BID for 3 weeks, followed by 20 mg OD)

Apixaban/Eliquis® (10 mg BID for 1 week, followed by 5 mg BID)

acute **subacute/intermediate** **chronic/long-term** **Phase of DVT/PE**

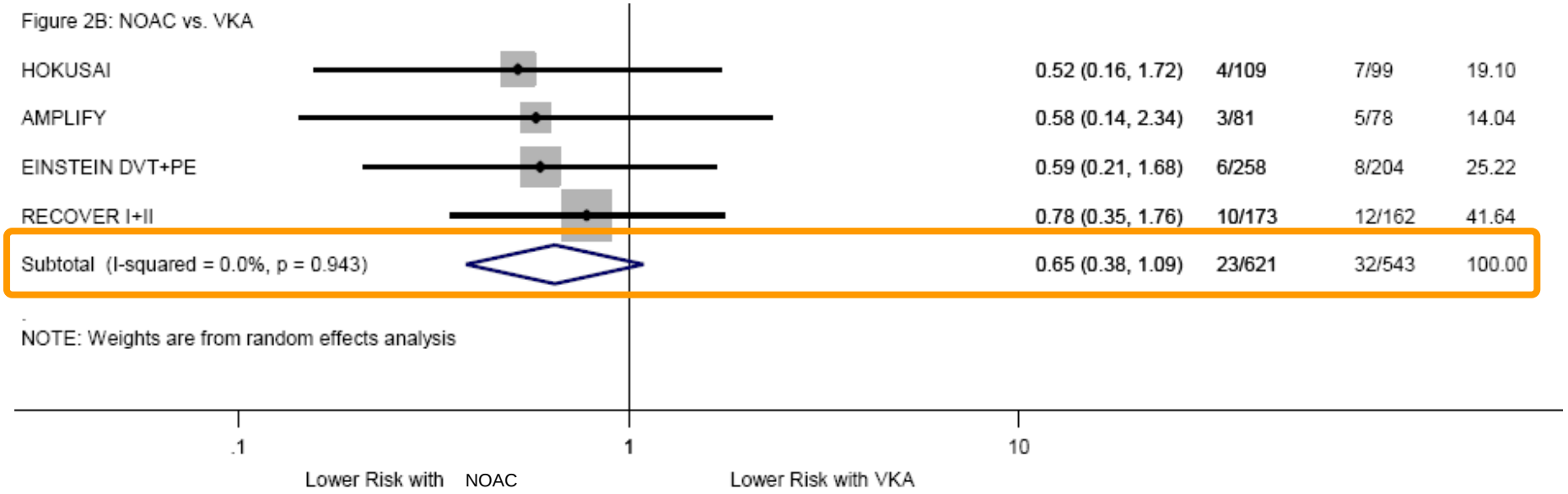
NOACs
Treatment of VTE

- In phase III clinical trials **dabigatran**, **rivaroxaban, apixaban** and **edoxaban** have shown non-inferiority to standard treatment (LMWH/vitamin K antagonist: warfarin) for treatment of DVT and PE
    - Cancer patients comprised only ~4% to 9% of the population 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 specifically addressed the efficacy and safety of **NOACs** in treatment of cancer-associated VTE
    - Is it premature to use NOACs 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 NOACs vs. Vitamin K Antagonists



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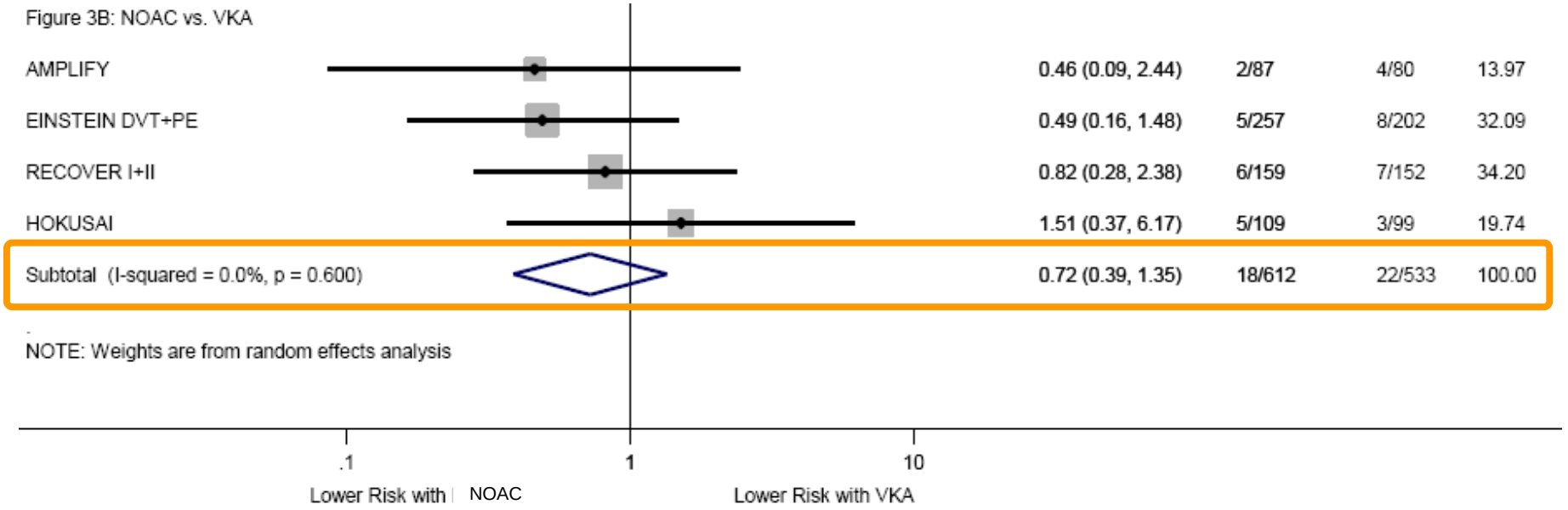
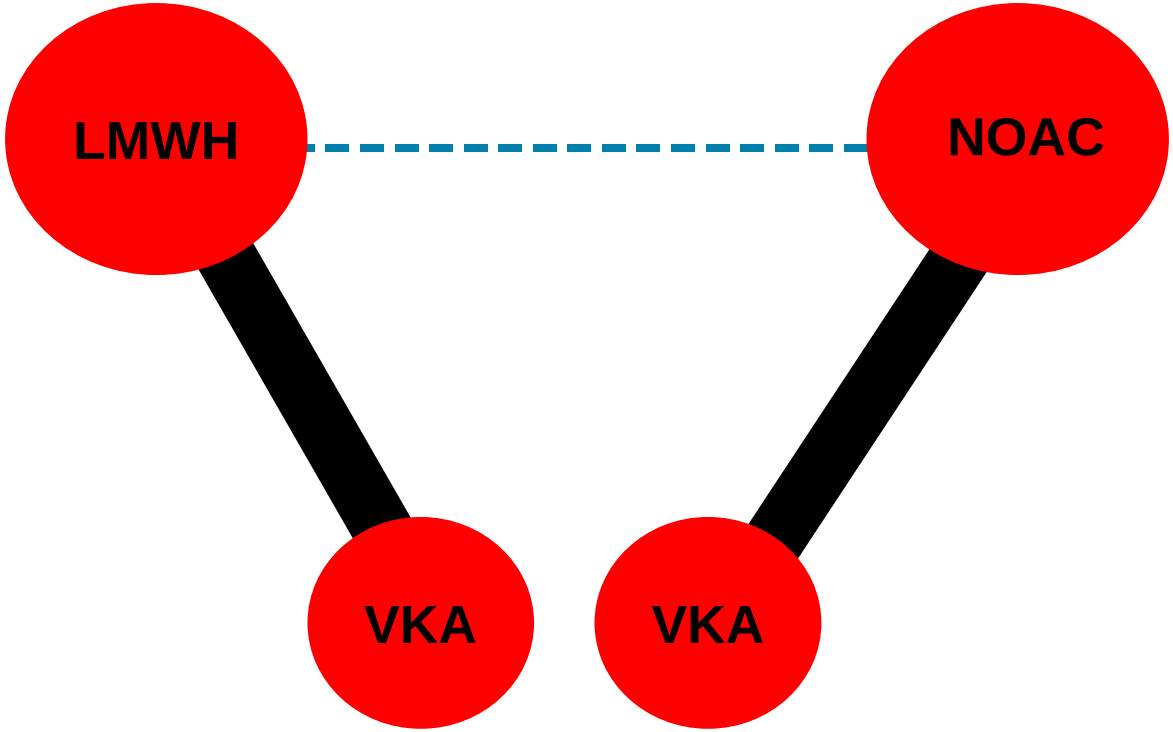
Meta-Analysis

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



Posch and Ay et al. Thromb Res. 2015 Sep;136(3):582-9.

Network-Metaanalysis
Indirekt comparison (LMWH vs. VKA vs. NOAC)

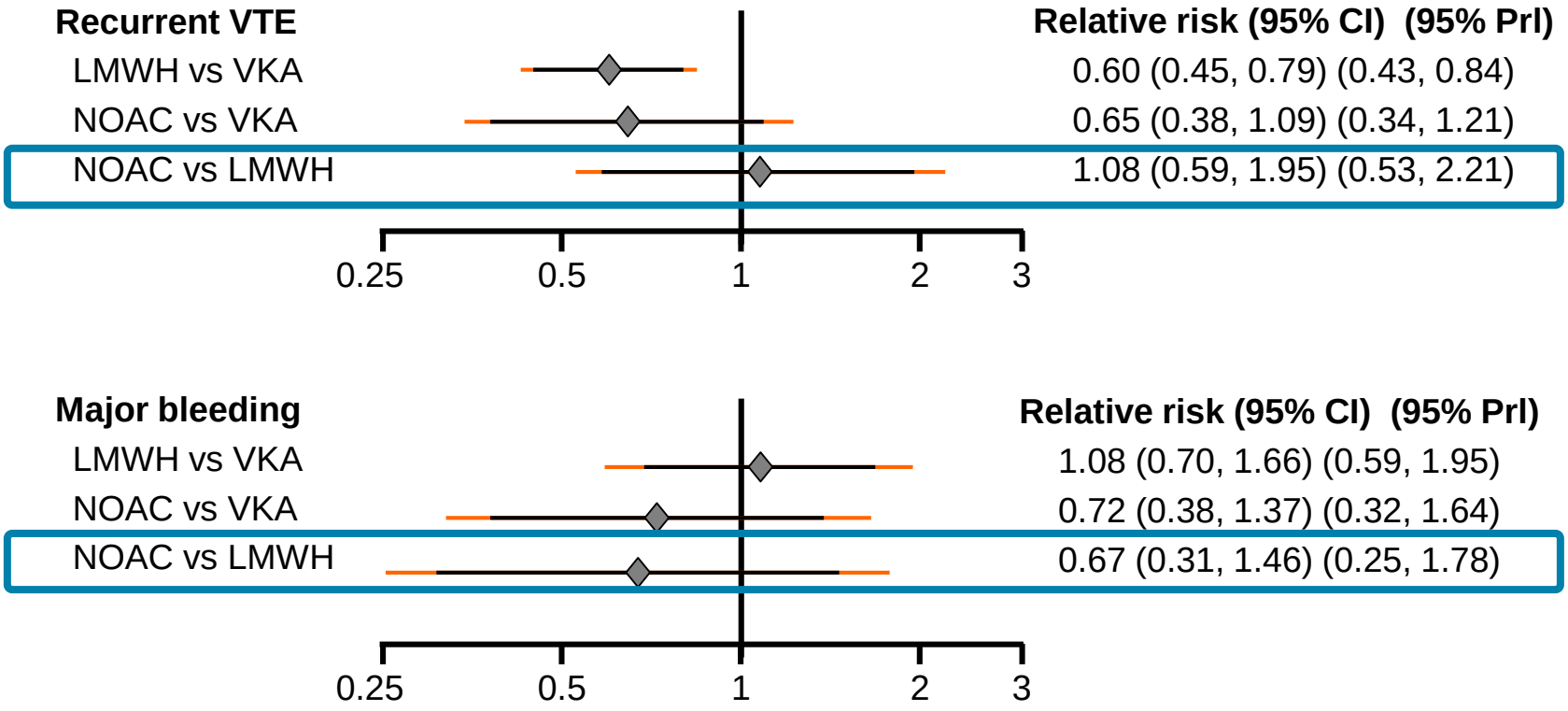


Direct Evidence from Head-to-Head Comparisons

Indirect Comparison via „Anchor“ Treatment C

Relative Risks for Recurrent VTE and Major Bleeding

- Risk of recurrent VTE was comparable between LMWH and DOACs (p=0.81)
- A non-significant reduction of major bleeding was observed with DOACs vs. LMWH (p=0.31)



95% Confidence Intervals (95% CI) are white, 95% Predictive Intervals (95% PrI) are orange
RR, relative risk (Network Meta-Analysis)

Posch F et al. *Thromb Res* 2015;136(3):582-9

HETEROGENEITY OF POPULATIONS[1,2]

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Study acronym	CANTHANOX	CLOT	ONCENOX	LITE	Romera et al.	CATCH	RECOVER I+ II	HOKUSAI	AMPLIFY	EINSTEIN DVT+PE
Cancer status definition	„STRINGENT“						„LIBERAL“			
Weighted 6-month risk of recurrent VTE in VKA arm (%)	12.6%						5.5%			
Weighted 6-month risk of major bleeding in VKA arm (%)	6.1%						4.0%			

Posch and Ay et al. Thrombosis Research 2015

[1]Carrier M et al. Thromb Res. 2014, [2]Di Minno MN et al. J Thromb Haemost. 2014

Hokusai VTE-cancer study

Design features

- Prospective, randomized, open label, blind evaluation study
- LMWH/**Edoxaban** vs. LMWH (CLOT regimen)
- Primary objective
  - Non-inferiority for combined outcome of recurrent VTE and major bleeding
- Follow-up: 12 months, 1000 pts
- Eligible patients: active cancer or diagnosed within 2 years

Conclusions

- Treatment of VTE (DVT and PE) in patients with cancer is challenging
- Low-molecular-weight heparins (LWMH)
  - first choice of treating cancer-associated thrombosis (CAT)*
- If vitamin-K-antagonist (VKA) is the treatment of choice, NOACs are acceptable treatment options
- If LMWH is standard, wait for Hokusai VTE-cancer study outcomes before routine use of NOACs

*Konstantinides S et al. Eur Heart J. 2014, *Kearon C et al., CHEST 2016 (prepublished online)

Vielen Dank für Ihre Aufmerksamkeit!

Cihan Ay

Medizinische Universität Wien / AKH Wien
Universitätsklinik für Innere Medizin I
Klin. Abteilung für Hämatologie und Hämostaseologie
Wien, Österreich

cihan.ay@meduniwien.ac.at

« 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/Abdomen : 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
eGFR: 62 ml/min

« 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**