LE RAGIONI DEL RISCHIO TROMBOTICO NEI PAZIENTI CON CANCRO: PRINCIPI DI TERAPIA

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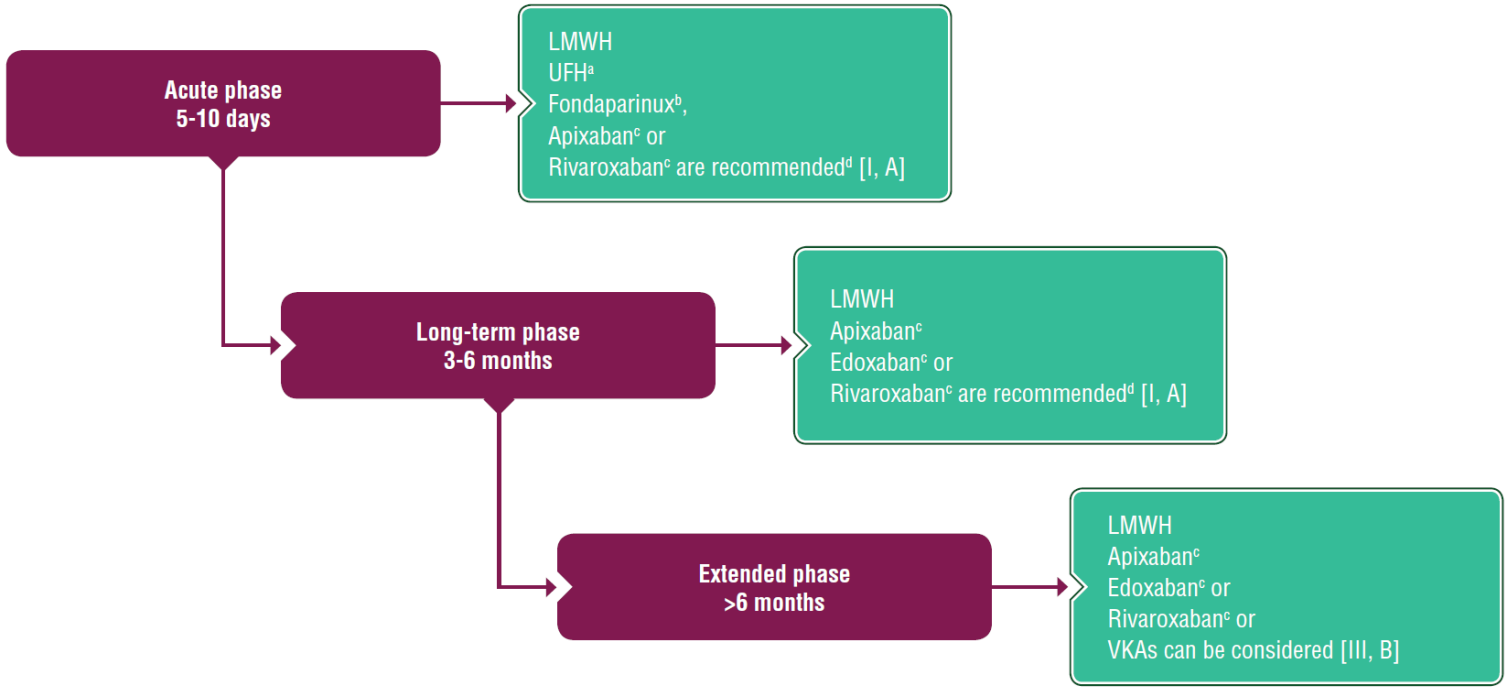
Verona 14.05.2024

VTE TREATMENT

Figure 3. Treatment of CAT.

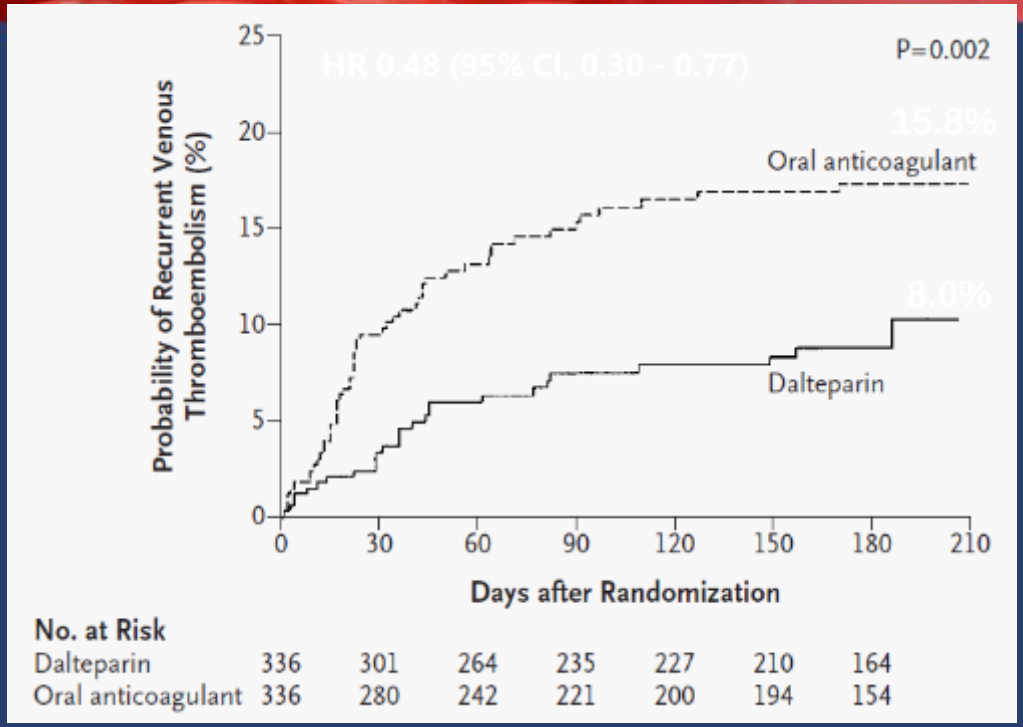


The CLOT study

Randomized open trial of 672 patients with cancer-related venous thrombosis.

Comparison between dalteparin and warfarin.

Dalteparin 200 IU/kg for 1 month then 150 IU/kg vs. dalteparin for 5-7 days then warfarin (INR 2-3) for six months.



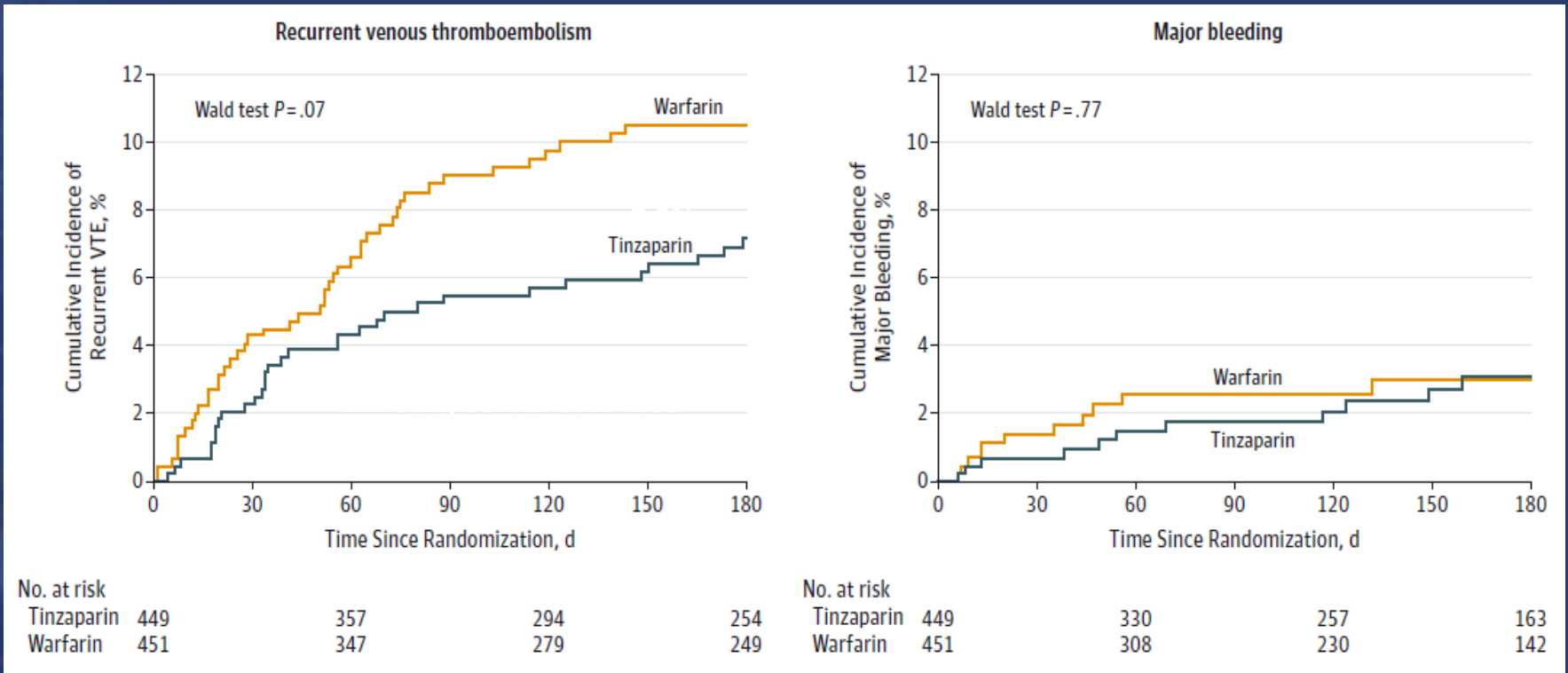
Lee AY, et al.; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003.

	Warfarin	Dalteparina	P-value
Sanguinamento maggiore	4.0%	6.0%	P=0.27

The CATCH study

Open randomized trial including 1053 patients with cancer-associated VTE.

Tinzaparin (175 IU/kg) vs tinzaparin 5-10 days then warfarin (INR 2-3) for 6 months.



Lee A, et.al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trials. JAMA 2015.

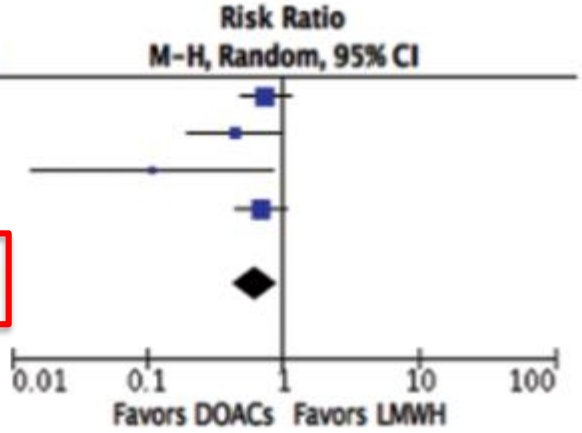
DOACs vs LMWH for the treatment of cancer-associated VTE

Recurrent VTE

Study or Subgroup	DOACs Events	DOACs Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob, 2018	34	522	46	524	40.3%	0.74 [0.48, 1.14]
Young, 2018	8	203	18	203	17.1%	0.44 [0.20, 1.00]
McBane, 2019	1	145	9	142	3.2%	0.11 [0.01, 0.85]
Agnelli, 2020	32	576	46	579	39.4%	0.70 [0.45, 1.08]
Total (95% CI)		**1446**		**1448**	**100.0%**	**0.62 [0.43, 0.91]**
Total events	75		119			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.30$, df = 3 (P = 0.23); $I^2 = 30\%$

Test for overall effect: Z = 2.46 (P = 0.01)

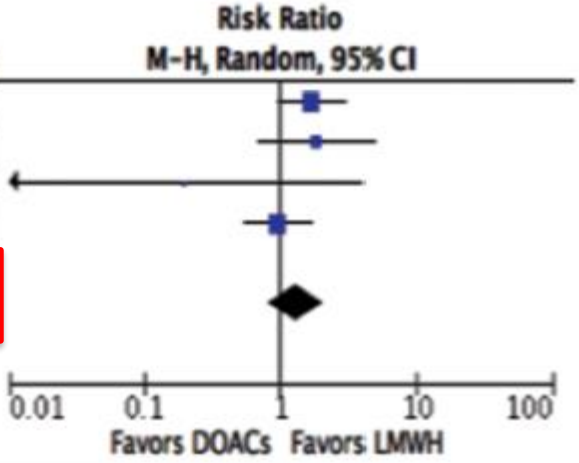


Major bleeding

Study or Subgroup	DOACs Events	DOACs Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob, 2018	29	522	17	524	39.1%	1.71 [0.95, 3.08]
Young, 2018	11	203	6	203	18.4%	1.83 [0.69, 4.86]
McBane, 2019	0	145	2	142	2.3%	0.20 [0.01, 4.04]
Agnelli, 2020	22	576	23	579	40.2%	0.96 [0.54, 1.71]
Total (95% CI)		**1446**		**1448**	**100.0%**	**1.31 [0.83, 2.08]**
Total events	62		48			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.89$, df = 3 (P = 0.27); $I^2 = 23\%$

Test for overall effect: Z = 1.14 (P = 0.25)



Giustozzi M et al. Thromb Haemost. 2020 May 4. doi: 10.1055/s-0040-1712098

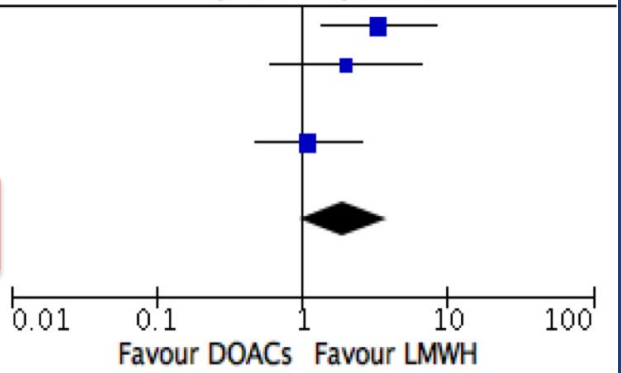
Gastrointestinal and genitourinary bleeding

a) Gastro-intestinal bleeding

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob, 2018	20	522	6	524	36.1%	3.35 [1.35, 8.26]
Young, 2018	8	203	4	203	25.0%	2.00 [0.61, 6.54]
McBane, 2019	0	145	0	142		Not estimable
Agnelli, 2020	11	576	10	579	38.9%	1.11 [0.47, 2.58]
Total (95% CI)		**1446**		**1448**	**100.0%**	**1.91 [0.96, 3.82]**
Total events	39		20			

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 3.09$, df = 2 (P = 0.21); $I^2 = 35\%$

Test for overall effect: Z = 1.84 (P = 0.07)

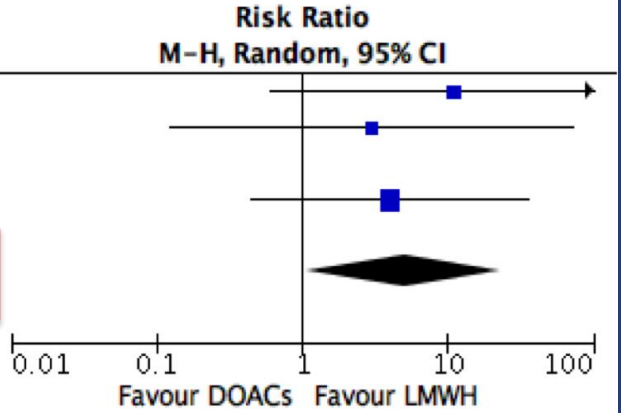


b) Genito-urinary bleeding

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Raskob, 2018	5	522	0	524	28.0%	11.04 [0.61, 199.19]
Young, 2018	1	203	0	203	23.0%	3.00 [0.12, 73.21]
McBane, 2019	0	145	0	142		Not estimable
Agnelli, 2020	4	576	1	579	49.0%	4.02 [0.45, 35.86]
Total (95% CI)		**1446**		**1448**	**100.0%**	**4.99 [1.08, 23.08]**
Total events	10		1			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0\%$

Test for overall effect: Z = 2.06 (P = 0.04)



Giustozzi M et al. Thromb Haemost. 2020 May 4. doi: 10.1055/s-0040-1712098

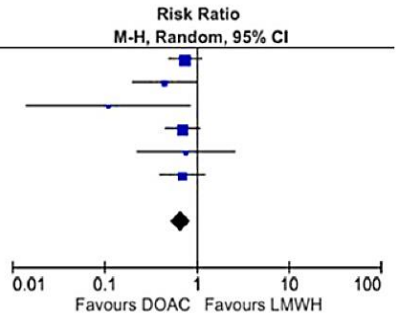
Data from RTCs comparing DOACS and LMWH in CAT

DOACs significantly decreased the risk of CAT recurrence (RR, 0.67; 95%CI, 0.52– 0.85), with a non-significant increase in the risk of major bleeding (RR, 1.17; 95%CI, 0.82–1.67).

Recurrent VTE

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	34	522	46	524	33.5%	0.74 [0.48, 1.14]
SELECT-D	8	203	18	203	9.3%	0.44 [0.20, 1.00]
ADAM-VTE	1	145	9	142	1.4%	0.11 [0.01, 0.85]
CARAVAGGIO	32	576	46	579	32.0%	0.70 [0.45, 1.08]
CASTA-DIVA	4	74	6	84	4.1%	0.76 [0.22, 2.58]
CANVAS	20	330	27	308	19.6%	0.69 [0.40, 1.21]
Total (95% CI)		**1850**		**1840**	**100.0%**	**0.67 [0.52, 0.85]**
Total events	99		152			

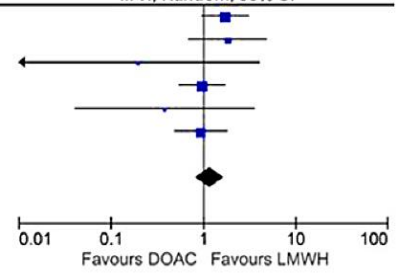
Heterogeneity: Tau² = 0.00; Chi² = 4.36, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)



Major Bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	29	522	17	524	29.2%	1.71 [0.95, 3.08]
SELECT-D	11	203	6	203	12.2%	1.83 [0.69, 4.86]
ADAM-VTE	0	145	2	142	1.4%	0.20 [0.01, 4.04]
CARAVAGGIO	22	576	23	579	30.3%	0.96 [0.54, 1.71]
CASTA-DIVA	1	74	3	84	2.5%	0.38 [0.04, 3.56]
CANVAS	17	330	17	308	24.5%	0.93 [0.49, 1.80]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.17 [0.82, 1.67]**
Total events	80		68			

Heterogeneity: Tau² = 0.02; Chi² = 5.66, df = 5 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.85 (P = 0.39)



RCT, randomized controlled trial.
Frere C, et al. J Hematol Oncol. 2022;15:69.

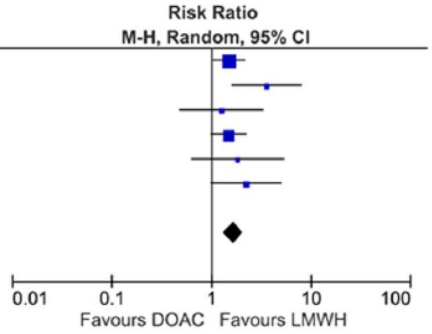
Data from RTCs comparing DOACS and LMWH in CAT

DOACS significantly increase the risk of clinically relevant nonmajor bleeding (RR 1.66; 95%CI, 1.31–2.09) and no difference in all-cause mortality rates.

C. Clinically relevant non major bleeding

Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	64	522	43	524	40.6%	1.49 [1.04, 2.16]
SELECT-D	25	203	7	203	8.2%	3.57 [1.58, 8.07]
ADAM-VTE	9	145	7	142	5.9%	1.26 [0.48, 3.29]
CARAVAGGIO	52	576	35	579	32.1%	1.49 [0.99, 2.26]
CASTA-DIVA	8	74	5	84	4.8%	1.82 [0.62, 5.31]
CANVAS	19	330	8	308	8.3%	2.22 [0.98, 4.99]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.66 [1.31, 2.09]**
Total events	177		105			

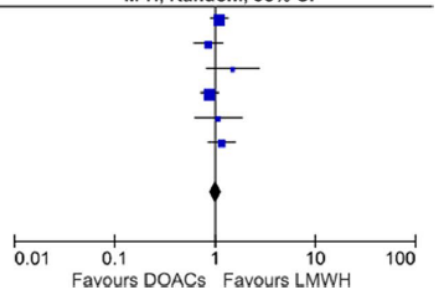
Heterogeneity: Tau² = 0.00; Chi² = 4.82, df = 5 (P = 0.44); I² = 0%
Test for overall effect: Z = 4.23 (P < 0.0001)



D. Overall Mortality

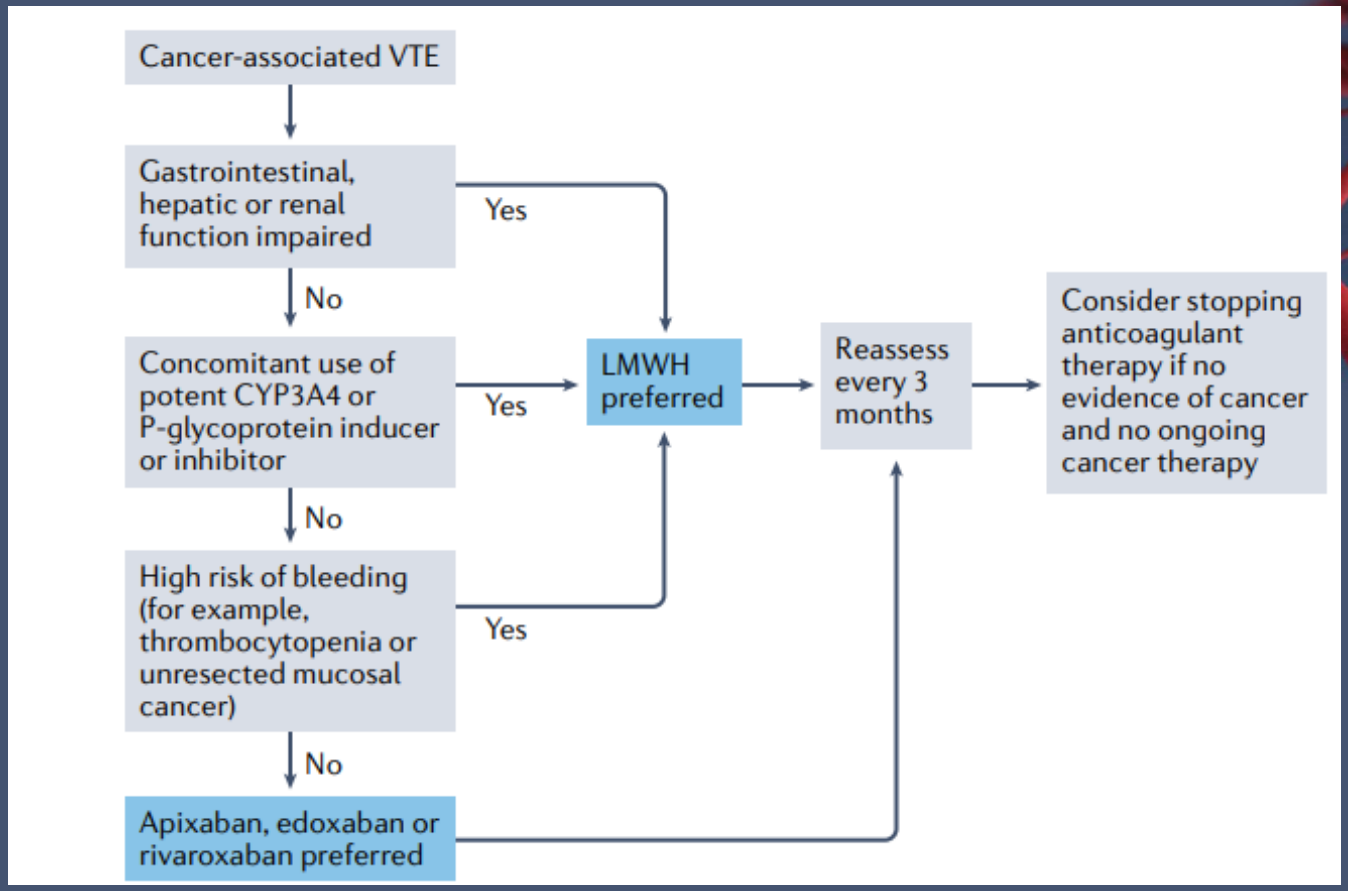
Study or Subgroup	DOAC Events	DOAC Total	LMWH Events	LMWH Total	Weight	Risk Ratio M-H, Random, 95% CI
HOKUSAI-VTE CANCER	140	522	127	524	29.9%	1.11 [0.90, 1.36]
SELECT-D	48	203	56	203	13.6%	0.86 [0.61, 1.20]
ADAM-VTE	23	145	15	142	4.4%	1.50 [0.82, 2.76]
CARAVAGGIO	135	576	153	579	31.4%	0.89 [0.73, 1.08]
CASTA-DIVA	19	74	20	84	5.5%	1.08 [0.63, 1.86]
CANVAS	71	330	57	308	15.3%	1.16 [0.85, 1.59]
Total (95% CI)		**1850**		**1840**	**100.0%**	**1.02 [0.89, 1.16]**
Total events	436		428			

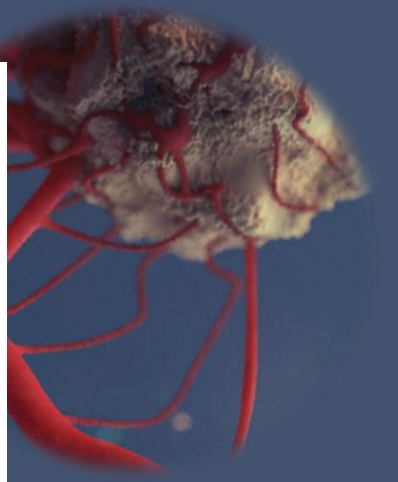
Heterogeneity: Tau² = 0.00; Chi² = 5.76, df = 5 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.25 (P = 0.80)



Frere et al., Journal of Hematology & Oncology 2022

Clinical algorithm for CAT management





Alok A. Khorana et al : NATURE REVIEWS , DISEASE PRIMERS 2022

Recommendations

ISTH 2018	LMWH. Edoxaban and rivaroxaban if low-risk of bleeding and no drug-drug interaction
ASCO 2019	• Initial: LMWH, UFH, fondaparinux, or rivaroxaban • Long-term : LMWH, edoxaban, or rivaroxaban for at least 6 months preferred over VKAs
ESC 2019	LMWH. Edoxaban and rivaroxaban alternative to LMWH if no gastrointestinal cancer
ITAC* 2019	• Initial : LMWH (preferred), UFH, fondaparinux • Early maintainance: LMWHs. DOACs (rivaroxaban, edoxaban) if no strong drug–drug interactions or GI absorption impairment • LMWH or DOACs for a minimum of 6 months
NCCN 2021	LMWH (dalteparin high level, enoxaparin, fondaparinux and UFH lower level). DOACs preferred (apixaban and edoxaban high level, rivaroxaban and dabigatran lower level) if no gastric or gastroesophageal lesions
ASH 2021	• Initial: apixaban, rivaroxaban, LMWH • Short-term: apixaban, rivaroxaban, edoxaban over LMWH or VKAs • Long-term: DOAC or LMWH
ACCP 2021	• Oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy • Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies
ESMO 2023	• LMWH, UFH, fondaparinux, apixaban or rivaroxaban recommended for the acute phase [I, A] • Anticoagulation for at least 6 mo: LMWH, apixaban, edoxaban or rivaroxaban which are preferred over VKAs [I, A] • In luminal GI cancer, LMWH is preferred for treating CAT [II, B]. Similar considerations potentially apply to urothelial K [II, B]. • High risk for GI bleeding (e.g., active ulcers or strong inhibitors/inducers of PgP and CYP3A, LMWH is preferred [IV, B]

Khorana A, *et al. J Thromb Haemost* 2018; Key NS, *et al. J Clin Oncol* 2019; Konstantinides SV, *et al. Eur Heart J* 2019; Farge D, *et al. Lancet Oncol* 2019; O'Connell C, *et al.* 2021;Oncologist 2021; Lyman G, et al. *Blood Adv* 2021; Stevens SM, et al. *Chest* 2021; Falanga A, et al. Ann Oncol 2023

DRUG-DRUG INTERACTION

European Journal of Cancer 148 (2021) 371–381

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism

Melina Verso [a,*], Andres Munoz [b], Rupert Bauersachs [c], Menno V. Huisman [d], Mario Mandalà [e], Giorgio Vescovo [f], Cecilia Becattini [a], Giancarlo Agnelli [a]

Drug-Drug Interactions (DDIs)

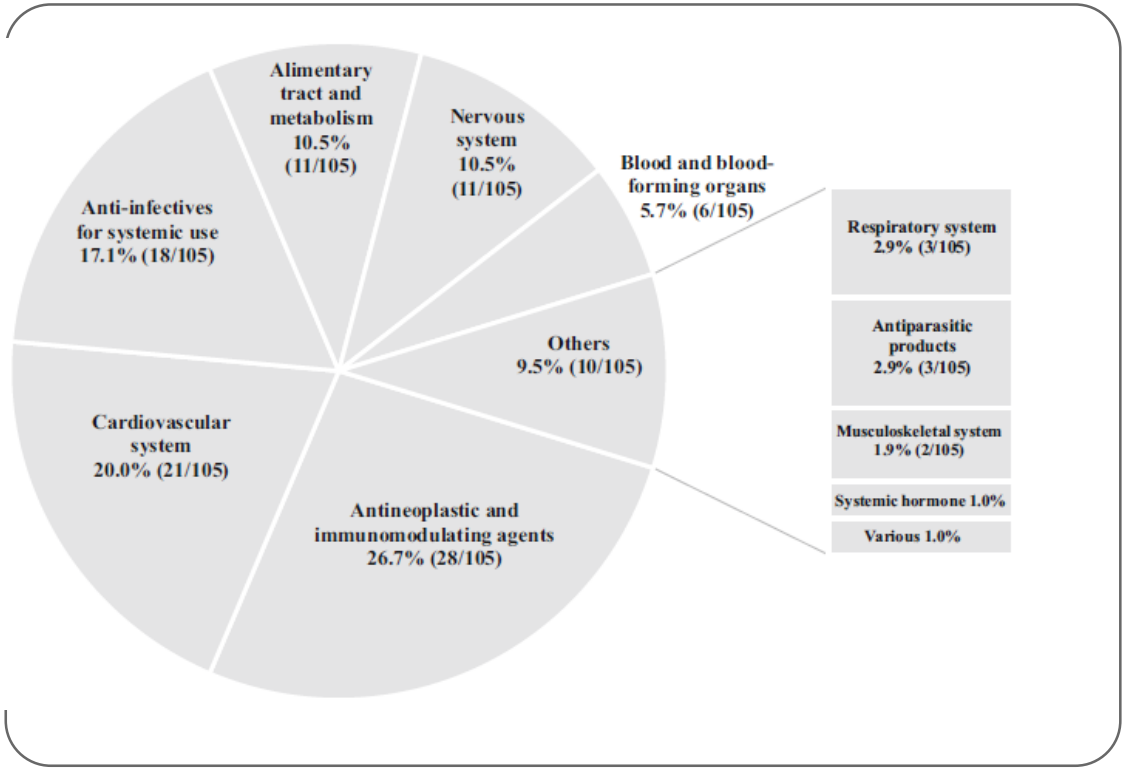
Cancer therapy specific inhibitors and inducers of CYP3A4 and P-glycoprotein

Cancer-related therapies	Cytochrome p450 CYP3A4	P-glycoprotein
Anthracyclines		
Doxorubicin	↓	↑
Idarubicin	↓	
Antimycotic agents		
Vinblastine	↓	↑
Vincristine	↓	
Vinorelbine	↓	
Paclitaxel	↑	
Topoisomerase inhibitors		
Topotecan	↓	
Etoposide	↓	↑
Alkylating agents		
Cyclophosphamide	↓	
Ifosfamide	↓	
Lomustine	↓	
Tyrosine kinase inhibitors		
Afatinib		↓
Alectinib		↓
Ceritinib	↓	
Crizotinib	↓	↓
Dasatinib	↓	
Ibrutinib		↓
Idelalisib	↓	↓
Imatinib	↓	↓
Lapatinib	↓	↓
Nilotinib	↓	↓
Osimertinib	↓	
Vemurafenib	↑	↓
Lenvatinib	↑	↑
Sunitinib		↓
Vandetanib		↓
Immune-modulating agents		
Cyclosporine	↓	↓
Sirolimus	↓	
Temsirolimus	↓	
Tacrolimus	↓	↓
Methylprednisolone	↑	
Dexamethasone	↑	↑

Cancer-related therapies	Cytochrome p450 CYP3A4	P-glycoprotein
Supportive care		
Aprepitant	↑↓	
Fosaprepitant	↑↓	
Fentanyl	↓	
Methadone	↓	
Acetaminophen	↓	
Other		
Bortezomib	↓	
Bexarotene	↑	
Venetoclax		↓
Hormonal agents		
Tamoxifen	↓	↓
Anastrozole	↓	
Bicalutamide	↓	
Enzalutamide	↑	↓
Abiraterone	↓	↓
Mitotane	↑	

Blood. 2019;133(4):291-298

A growing concern in cancer : DDIs



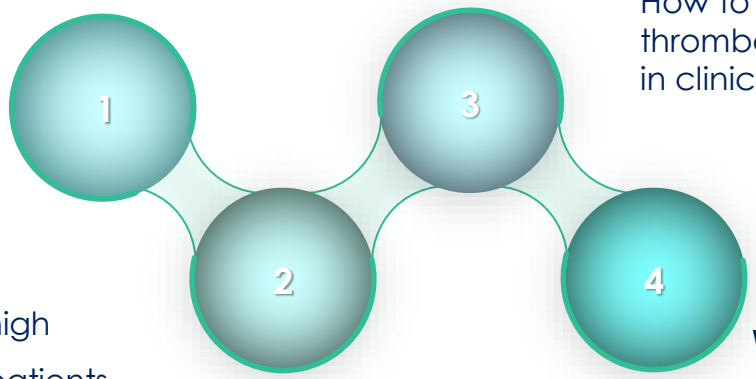
Studies on anticancer drugs (26.7%) contributed the most to published PBPK models, followed by cardiovascular (20.0%) and anti-infective (17.1%) drugs

Min JS. Arch Pharm Res 2017
PBPK: Physiologically Based PharmacoKinetic
PBPK definition: PBPK modeling is a mathematical modeling technique that uses a series of mass balance differential equations to predict the ADME characteristics of drugs in humans

Concerns for thromboprophylaxis in patients with active cancer

Why CAT should be prevented?

How to integrate thromboprophylaxis in clinical practice?



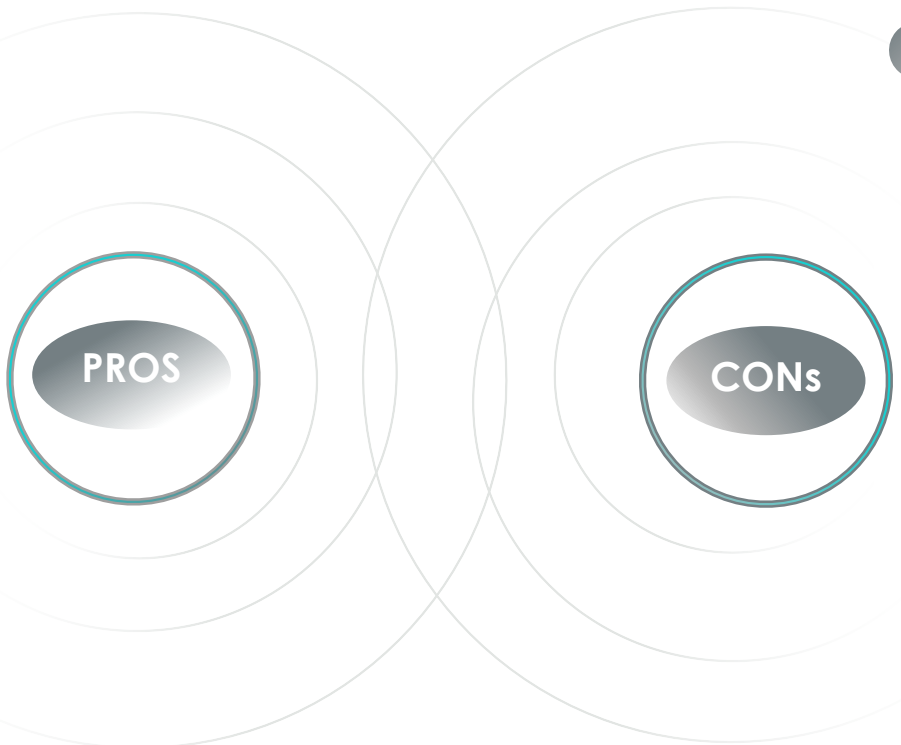
How to identify the high thrombotic burden patients with active cancer ?

What to consider when choosing anticoagulant in patients with active cancer ?

Anticoagulation Agents for patients with active cancer

Farmakis D. European Journal of Preventive Cardiology doi:10.1093/eurjpc/zwaa087

VKAs



- indicated for valvular Atrial Fibrillation

- Drug-drug interactions
- Narrow therapeutic window
- Low TRR due to malnutrition vomiting & hepatic disfunction
- Difficult handling peri-operatively

Farmakis D. European Journal of Preventive Cardiology doi:10.1093/eurjpc/zwaa087

DOACs

- Low risk of intracranial hemorrhage
- Trials for cancer & VTE (rivaroxaban, endoxaban, apixaban)

- Drug-drug interactions
- Poor monitoring of anticoagulant activity by standard assays
- Increased risk of GI bleeding
- Increased risk of GU bleeding
- Unpredictable absorption due to vomiting
- Not Reversal agent (dabigatran)

Farmakis D. European Journal of Preventive Cardiology doi:10.1093/eurjpc/zwaa087

LMWHs

- Long-term experience in CAT
- Indicated for CAT (dalteparin, tinzaparin)
- Not known interactions

- Parenteral route

Farmakis D. European Journal of Preventive Cardiology doi:10.1093/eurjpc/zwaa087

LONG TERM DURATION OF THROMBOPROPHYLAXIS OPEN QUESTIONS

NO EVIDENCE BEYOND 6 MONTHS

COMPLIANCE IS A CONCERN

HIGH RISK PATIENTS WITH BRAIN MET

HOW TO MANAGE PATIENTS WITH THROMBOCYTOPENIA

BURDEN OF THE DISEASE

INCIDENCE (USA)

- 25000 Primary brain cancers
- 200.000 brain metastases

MAIN METASTATIC CANCERS

- NSCLC
- Breast
- Melanoma

NCI SEER 2022

EPIDEMIOLOGY OF VTE IN "BRAIN CANCER"

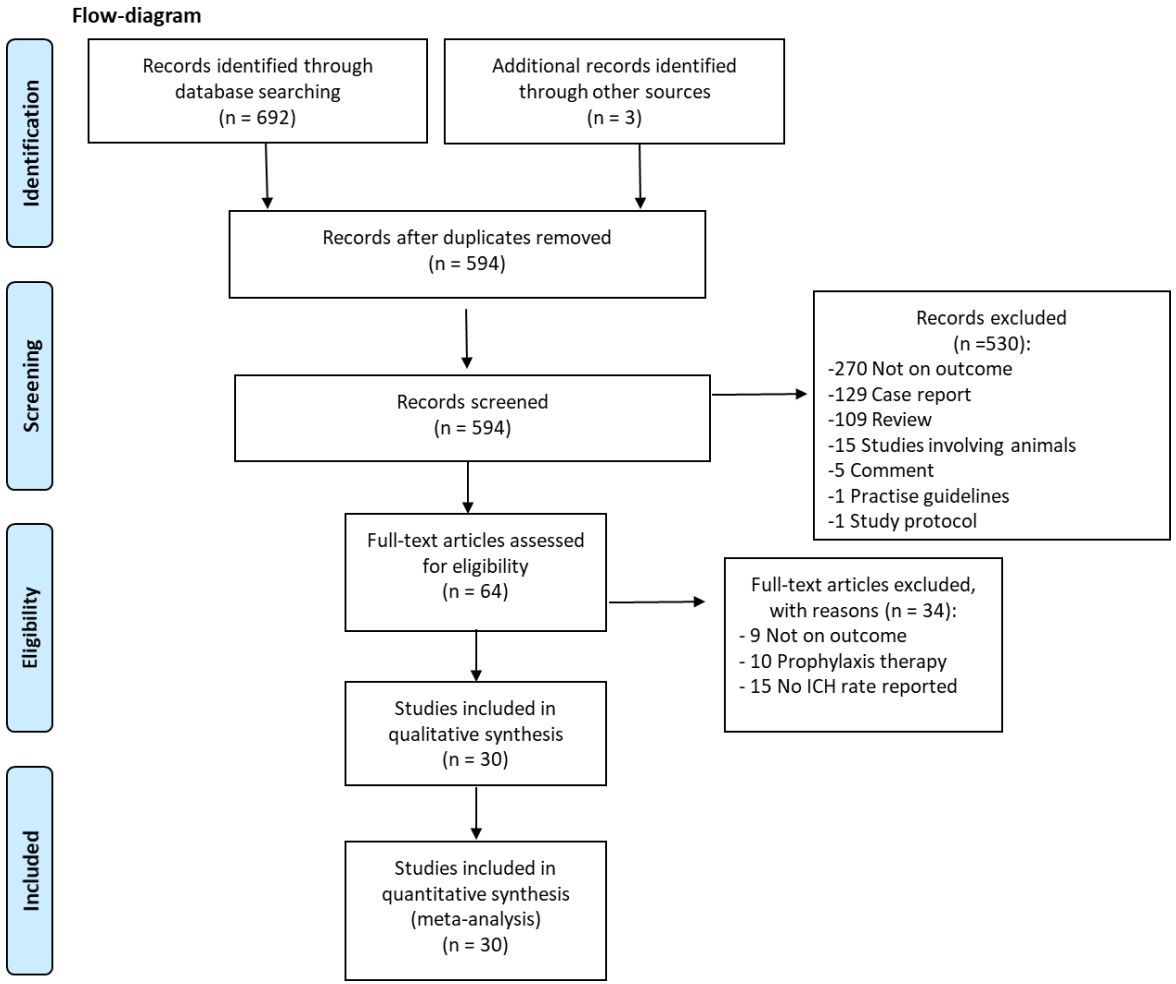
VTE: High incidence

- Glioblastoma 40%
- NSCLC 10%

VTE: Low Incidence

- Breast 2-3%
- Renal 2-3%
- Melanoma 2-3%

The flow-diagram



Main clinical features of the studies included

- 30 studies (3,893 patients) were included.

15 studies (2,353 pts) included patients with primary brain cancer only

6 studies (1,009 pts) included patients with brain metastases only

9 studies included both patients with primary brain cancer and patients with brain metastases

- All studies included were retrospective.

- The main indication for anticoagulant treatment was acute VTE (25 studies, 3,313 patients), followed by atrial fibrillation (2 studies, 268 patients), cerebral vein thrombosis (2 studies, 187 patients) or any indication for anticoagulant treatment (1 study, 125 patients).

Results

Outcomes	N° of studies	N° of ICH/ N° of patients	Rate	95% CI	I squared
Overall ICH	30	445/3,893	7.7%	5.1-11.5	92.8%
Major ICH	7	117/1,287	6.2%	2.8-13.0	91.5%
Fatal ICH	11	13/764	2.9%	1.7-4.7	0%
ICH in PBC patients	18	156/2,353	6.4%	4.1-9.9	84.4%
ICH in MBC patients	9	218/1,009	13.0%	6.5-24.2	93.7%
Major ICH* in PBC patients	4	30/793	3.9%	1.3-11.6	87.6%
Major ICH in MBC patients	3	87/494	15.4%	9.4-24.2	74.6%
ICH in pts with VTE	25	384/3,313	7.1%	4.4-11.5	93.7%

* Major ICH: Any hemorrhage that was≥10 ml in volume, required surgical intervention, or was associated with clinical symptoms, such as nausea and vomiting, or focal neurologic deficit.

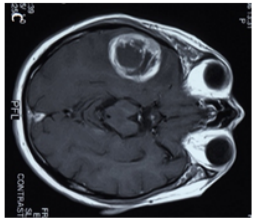
Results

	N° of studies	N° of ICH/ N° of patients treated	Anticoagulant therapy %	N° of ICH/ N° of patients not treated	No anticoagulant therapy %	RR	95% CI	P-value	I^2
Overall patients	17	152/1,072	11.5% (95% CI 7.4-17.6)	177/1,824	6.0% (95% CI 3.0-11.5)	1.81	1.15-2.84	0.001	60.3%
Patients with PBC	11	80/659	12.5% (95% CI 8.0-18.8)	50/1,346	4.4% (95% CI 2.5-7.7)	2.58	1.59-4.19	<0.001	45.5%
Patients with MBC	4	61/265	14.7% (95% CI 4.4-39.2)	81/301	15.4% (95% CI 5.3-37.2)	0.86	0.45-1.65	0.287	0%
Patients treated with DOACs vs LMWH	5	12/172	8.3% (95% CI 4.4-15.3)	71/278	11.7% (95% CI 2.9-37.0)	0.44	0.25-0.79	0.007	0%
Patients treated with LMWH vs warfarin	4	15/211	5.9% (95% CI 1.5-20.5)	8/198	5.4% (95% CI 1.5-17.3)	1.45	0.56-3.79	0.185	0%
Overall major ICH	4	33/239	10.4% (95% CI 4.0-24.5)	47/734	3.4% (95% CI 0.6-17.6)	1.93	0.79-4.73	0.001	38.7%
Major ICH in patients with PBC	3	9/135	6.3% (95% CI 1.7-20.3)	9/545	1.8% (95% CI 0.9-3.4)	3.75	1.6-4.5	0.003	0%

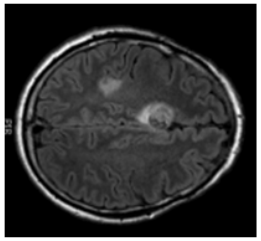
SUMMARY

Incidence of ICH in patients with primary vs metastatic brain cancer treated or not with anticoagulant therapy

ICH primary vs metastases: 6.4% vs 13.0%, RR 3.26 (2.69-3.94)



Primary brain cancer



Metastatic brain cancer

	Treated with anticoagulants	Without anticoagulants	DOACs vs Heparin
Primary brain cancer	**12.5%** (95% CI 8.0-18.8)	**4.4%** (95% CI 2.5-7.7)	**RR 0.19** (95% CI 0.04-0.99)
	RR 2.63 (95% CI 1.48-4.67)		
Metastatic brain cancer	**14.7%** (95% CI 4.4-39.2)	**15.4%** (95% CI 5.3-37.2)	**RR 0.65** (95% CI 0.36-1.16)
	RR 0.92 (95% CI 0.43-1.93)		

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CONCLUSIONS

VTE TREATMENT: LMWH AND DOAC

DDI TO BE ADDRESSES

ROOM FOR IMPROVEMENT