

Online Supplement.

Table S1. Main clinical features of the included studies.

Source and author	Mean age	Male sex (%)	Primary Vs metastasis	Histotype of cancer	Concomitant CH	Concomitant RT	Concomitant use of aspirin	ABC criteria	Overall ICH
Lee ⁹ Thromb Res 2021	62.9 (DOAC) 61.8 (LMWH)	56.4%(DOAC) 53.6% (LMWH)	Primary tumors and brain metastases.	- Primary brain tumors: anaplastic astrocytoma, anaplastic oligodendroglioma, glioma. - Brain metastases: non-small cell lung cancer, breast cancer, genitourinary, renal cell carcinoma, melanoma, gastrointestinal, other.	Yes	Yes	No	No	5/111
Jo ¹⁰ Neuro Oncol 2021	58 for LMWH group, 61 for non-AC with VTE group and 59 for non-VTE group.	58% for LMWH group, 55% for non-AC with VTE group and 52% for non-VTE group.	Primary brain tumors	Glioblastoma, anaplastic glioma.	Yes	Yes	Yes	No	22/110
Dubisnki ¹¹ Neurosurgical Review 2021	65 (DOAC), 68 (LMWH)	43% (DOAC), 38% (LMWH)	Primary brain tumors	Glioblastoma	Yes	Yes	No	No	0/46
Burth ¹² J Neurooncol. 2021	71 for GBM + AF, 70 for GBM – AF, 71 MET + AF, 71 MET - AF	76% GBM + AF, 78% GBM-AF, 67% MET + AF, 67% MET - AF	Primary tumors and brain metastases.	Glioblastoma and brain metastases.	Yes	Yes	No	No	22/172
De Melo Junior ¹³ Clin Neurol Neurosurg. 2020	62	39.6%	Primary tumors and brain metastases.	High-grade glioma, grade I meningioma, pituitary adenoma, grade II meningioma, low-grade glioma, brain metastasis.	No	No	No	No	4/53
Leader ¹⁴ Blood Adv. 2020	66 (DOAC) 55 (LMWH)	65.9: DOAC 50.9 LMWH	Brain metastases	Lung cancer, esophageal cancer.	No	Yes	No	Yes	11/96
Horstman ¹⁵ Med Oncol. 2018	61.1	45.6%	Brain metastases	Non-small cell lung cancer, breast cancer, melanoma.	Yes	Yes	No	No	12/125

Carney ¹⁶ J Thromb Haemost. 2018	-Glioma cohort: 56 years for DOAC and 61 for enoxaparin. - Brain metastases cohort: 66 years for DOAC and 62 for enoxaparin.	- Glioma cohort: 50% for DOAC and 66% for enoxaparin. -Brain metastases cohort: 48% for DOAC and 50% for enoxaparin.	Primary tumors and brain metastases	Brain metastases or a WHO grade III or IV glioma, including glioblastoma multiforme, anaplastic astrocytoma or anaplastic oligodendroglioma.	No	Yes	Yes	Yes	67/172
Gessler ¹⁷ J Neurosurg. 2018	54.8 no cerebral vein thrombosis and 47.2 with cerebral vein thrombosis	49.4%	Primary tumors and brain metastases	Meningioma, high-grade glioma, low-grade glioma, metastatic tumors and other.	No	No	No	No	3/35
Chai-Adisaksopha ¹⁸ Thromb Haemost. 2017	Non-brain tumours: 60.3 Brain tumours: 60.7	Non-brain tumours: 45.6% Brain tumours: 45.6%	Primary tumors and brain metastases	Astrocytoma, glioblastoma, oligodendroglioma, ependymoma, medulloblastoma, supratentorial, primitive neuroectodermal tumour. - Primary cancer site: brain, colorectal, lung, breast, lymphoma, ovary, bladder, stomach, head and neck, pancreas, sarcoma and others.	Yes	Yes	Yes	No	9/182
Mantia ¹⁹ Blood. 2017	62 (enoxaparin) and 61 control	66% (enoxaparin) and 58% (control group)	Primary brain tumors	Glioblastoma (84%), anaplastic oligodendroglioma (10%), anaplastic astrocytoma (5%)	No	No	Yes	Yes	25/133
Al Megren ²⁰ Thromb Res. 2017	59	72%	Primary brain tumors	Glioma	Yes	No	No	No	13/152
Khoury ²¹ Neurooncol Pract. 2016	65	61.8%	Primary brain tumors	Glioblastoma (WHO grade IV)	Yes	Yes	No	No	17/173
Donato ³ Blood. 2015	60.9 (enoxaparin) and 60 (controls)	52.9% (enoxaparin) and 49.7% (controls)	Brain metastases	Non-small cell lung cancer, breast cancer, renal cell carcinoma, melanoma, colorectal cancer, small cell lung cancer.	Yes	Yes	yes	Yes	116/293
Smith ²² J Clin Neurosci. 2015	54.2	46.8%	Primary brain tumors and brain metastases	High-grade glioma, metastases, meningioma, low-grade glioma.	No	No	Yes	No	2/69
Yust-Katz ²³ J Neurooncol. 2015	56	NR	Primary brain tumors	Glioblastoma	Yes	Yes	No	No	3/64
Chaichana ²⁴ Neurol Res.	51.6 ± 14.7	NR	Primary brain tumors and	Glioma, glioblastoma WHO grade IV, anaplastic WHO	No	No	No	No	5/126

2013			brain metastases	grade III, WHO grade II, metastatic tumours, meningiomas, schwannomas.					
Aishima ²⁵ Br J Neurosurg. 2013	50.6 ± 18.5	50.6%	Primary brain tumors and brain metastases	Glioma, lymphoma, metastatic brain tumours, meningioma, pituitary adenoma, schwannoma and other.	No	No	No	No	5/23
Alvarado ²⁶ Melanoma Res. 2012	NR	NR	Brain metastases	Melanoma	No	No	No	No	2/74
Norden ⁴ J Neurooncol. 2011	55.5	75%	Primary tumours	Glioblastoma, anaplastic astrocytoma, low-grade glioma.	No	No	No	No	13/282
Pan ²⁷ Anticancer Res. 2009	59	NR	Primary and brain metastases	High-grade gliomas.	No	No	Yes	No	3/146
Nghiempu ²⁸ Neuro Oncol. 2008	NR	NR	Primary tumors	Oligodendroglioma, glioblastomas, gliomas	Yes	No	No	No	12/265
Ghanim ²⁹ J Thromb Thrombolysis. 2007	56 ± 12 for anticoagulants group and 59 ± 15 for filter group	48.7% for anticoagulants group and 52.2% for filter group.	Primary brain tumors and brain metastases	Astrocytoma, glioblastoma and other.	No	No	No	No	51/176
Schiff ⁵ Cancer. 1994	58 (all patient), 59 (anticoagulated patients) and 55 (filter patient)	58.8%	Brain metastases	Non-small cell lung, breast, melanoma, melanoma and CML, small cell lung, renal, systemic lymphoma.	No	Yes	No	No	6/42
Quevedo ³⁰ Mayo Clin Proc. 1994	NR	NR	Primary brain tumors	Grade 3 or 4 astrocytoma, mixed astrocytoma-oligodendroglioma or gliosarcoma.	Yes	Yes	Yes	No	1/18
Altschuler ³¹ Neurosurgery. 1990	57	43.47%	Primary brain tumors.	Malignant astrocytoma, glioblastoma.	No	No	No	No	0/23
Olin ³² Arch Intern Med. 1987	52.8	60%	Primary brain tumours and brain metastases	Astrocytoma, meningioma, schwannoma, metastatic brain tumours (lung, melanoma)	Yes	No	No	No	1/49
Choucair ³³ J Neurosurg. 1987	32-66	NR	Primary tumors	Malignant gliomas	Yes	Yes	No	No	0/36
Ruff ³⁴ Ann Neurol. 1983	NR	52.23%	Primary tumors	Malignant astrocytoma or glioblastoma multiforme.	Yes	Yes	No	No	7/266

Ruff ³⁵ Trans Am Neurol Assoc. 1981	NR	NR	Primary tumors	Malignant gliomas	Yes	Yes	No	No	8/381
---	----	----	----------------	-------------------	-----	-----	----	----	-------

Abbreviations: *CH*, chemotherapy; *RT*, radiotherapy; *ICH*, intracerebral haemorrhage; *DOAC*, direct oral anticoagulant; *LMWH*, low molecular weight heparin; *AC*, anticoagulation; *VTE*, venous thromboembolism; *GMB*, glioblastoma; *AT*, atrial fibrillation; *MET*, brain metastases; *CVT*, cerebral vein and dural sinus thrombosis; *WHO*, World Health Organisation; *GB*, glioblastoma; *CNS*, Central nervous system; *CML*, chronic myelogenous leukemia; *NR*, not reported.

Table S2. Quality assessment according to the NOS scale

Study	Selection				Comparability	Outcome			TOTAL	QUALITY
	1	2	3	4		1	2	3		
Lee, 2021	*	*	*	*	*		*	*	4,1,2	Good
Jo, 2021	*	*	*	*	*		*	*	4,1,2	Good
Dubinski, 2021	*	*	*	*	*		*	*	4,1,2	Good
Burth,2021	*	*		*	*		*	*	3,1,2	Good
De Melo Junior,2020	*	*	*	*			*		4,0,1	Poor
Leader,2020	*	*		*	*		*	*	3,1,2	Good
Horstman, 2018	*	*		*	*		*		3,1,1	Poor
Carney,2018	*	*		*	*				3,1,0	Poor
Gessler,2018	*	*	*	*	*		*		4,1,1	Poor
Chai-Adisaksopha,2017	*	*		*	*		*		3,1,1	Poor
Mantia,2017	*	*		*	*				3,1,0	Poor
Al Megren,2017	*	*		*	*		*	*	3,1,2	Good

Khoury,2016	*	*		*	*		*		3,1,1	Poor
Donato,2015	*	*		*	*		*		3,1,1	Poor
Smith,2015	*	*	*	*	*		*		4,1,1	Poor
Yust-Katz,2015	*	*		*	*				3,1,0	Poor
Chaichana,2013	*	*	*	*	*		*		4,1,1	Poor
Aishima,2013	*	*		*	*				3,1,0	Poor
Alvarado,2012	*	*		*			*		3,0,1	Poor
Norden,2011	*	*	*	*	*				4,1,0	Poor
Pan,2009	*	*		*			*		3,0,1	Poor
Nghiemphu,2008	*	*		*	*		*		3,1,1	Poor
Ghanim,2007	*	*		*	*		*		3,1,1	Poor
Schiff,1994	*	*		*	*		*	*	3,1,2	Good
Quevedo,1994	*	*		*					3,0,0	Poor
Altschuler,1990	*								1,0,0	Poor
Olin,1987	*	*		*					3,0,0	Poor
Choucair,1987	*	*		*					3,0,0	Poor
Ruff,1983	*	*		*	*		*		3,1,1	Poor
Ruff,1981	*	*							2,0,0	Poor

Table S3. Description of the studies included according to: n° of ICH according to the type of tumor, VTE progression, N° of ICH during radiotherapy.

Study Name	N° ICH according to the type of tumor	VTE progression/death from PE	N° of ICH after radiation
Lee, 2021	NR	6-month recurrent VTE: 5.6% DOAC group (55 patients) and 6.6% in LMWH group (56 patients). Any recurrent VTE event: 3 of 55 patients in the DOAC group compared to 3 of 56 patients in the LMWH group. Primary brain tumors cohort: recurrent VTE events occurred in 1/14 patients in the DOAC group and 1/12 patients in the LMWH group. Secondary brain metastases cohort: recurrent VTE events occurred in 2/41 patients in the DOAC group and 2/44 patients in the LMWH group.	55/111 received RT. Not reported N° of ICH in these patients
Jo, 2021	Only primary brain tumors	NR	NR
Dubinski, 2021	Only primary brain tumors	Re-embolism: 0/46. Re-thrombosis: 1/46.	NR
Burth,2021	NR	NR	NR
De Melo Junior,2020	NR	NR	Excluded.
Leader,2020	Lung: 7/54 Renal cell carcinoma: 2/5 Thymic NEC:1	NR	NR
Horstman, 2018	6/64 patients with NSCLC 2/4 patients with renal cell carcinoma. 2/9 patients with melanoma	NR	9/108 developed ICH with treatment (not specified type of treatment)
Carney,2018	NR	NR	NR
Gessler,2018	NR	3/35 patients with CVT died at the 3-month follow-up.	Excluded.
Chai-Adisaksopha,2017	NR.	Recurrent VTE: 11.0 per 100 patient-year in patients with brain tumors and 13.5 per 100 patient-years in those without known brain tumors.	62.5% of intracranial bleeds occurred in patients who received combination chemo-radiation therapy.
Mantia,2017	Only primary brain tumors.	NR	Excluded.
Al Megren,2017	Only primary brain tumors.	0/76	Excluded.

		There was no recurrent VTE.	
Khoury,2016	Only primary brain tumors.	NR	4/39
Donato,2015	NR	NR	NR
Smith,2015	NR	NR	Excluded
Yust-Katz,2015	Only primary brain tumors.	1/64 had 2 events (VTE).	NR.
Chaichana,2013	NR.	NR	Excluded
Aishima,2013	NR.	1 patient in group A (191 patients) died of recurrent PE and ICH.	Excluded
Alvarado,2012	NR	NR	Excluded
Norden,2011	Only primary brain tumors.	NR.	Excluded.
Pan,2009	Only primary brain tumors.	7/41 7 of the 41 VTE patients developed recurrent VTE.	Excluded.
Nghiemphu,2008	Only primary brain tumors.	NR	Excluded.
Ghanim,2007	NR	NR	Excluded.
Schiff,1994	6/42 ICH (3 symptomatic and 3 asymptomatic). 3 symptomatic: 1 patient with frontal metastasis from breast cancer treated with radiation therapy. -1 patient who had received radiation therapy for two metastases from non-small cell lung cancer. -1 patient with multiple brain metastases from non-small cell lung cancer treated with radiation therapy -3 asymptomatic: with brain metastases from melanoma, breast carcinoma and non-small cell lung carcinoma.	4/10 patients treated with Greenfield filters had recurrent nonfatal thromboembolic events (2 PE and 2 DVT). 2/51 patients were untreated for DVT and died of PE. 5/42 patients were diagnosed as having recurrent nonfatal episodes of venous thromboembolism while receiving anticoagulation (1 patient with DVT experienced a PE, 3 patients experienced recurrent DVT and 1 patient experienced both DVT and PE).	3 ICH during radiotherapy. Not reported N° of patients received radiotherapy.
Quevedo,1994	Only primary brain tumors.	NR	NR
Altschuler,1990	Only primary brain tumors.	1 patient had a PE secondary to a very extensive DVT (recurrent PE but not fatal).	Excluded.
Olin,1987	NR	NR	Excluded.

Choucair,1987	Only primary brain tumors.	10/27 patients with PE died suddenly.	0 of 6 patients had ICH during RT treatment
Ruff,1983	Only primary brain tumors.	1 patient with phlebitis taking anticoagulants developed PE (non-fatal). 3 of the 6 conservatively treated patients died of PE.	NR
Ruff,1981	Only primary brain tumors.	1/97 95 of 97 patients with phlebitis were anticoagulated. 1 of the 2 conservatively treated patients died of bilateral pulmonary emboli.	NR

Abbreviations: NR: not reported, VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, CVT: cerebral vein thrombosis, ICH: intracranial hemorrhage.

Figure S1. The flow-diagram of the research strategy

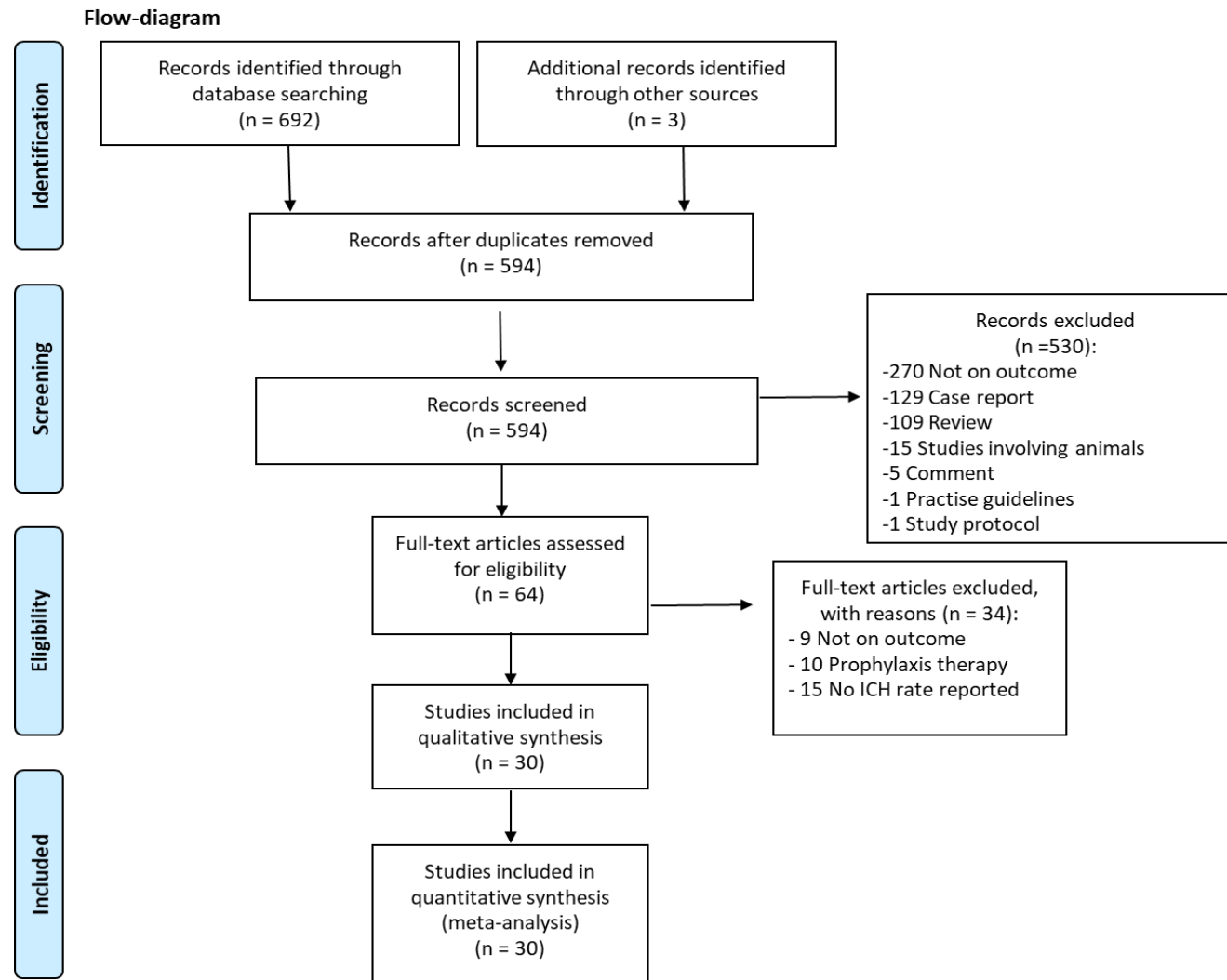
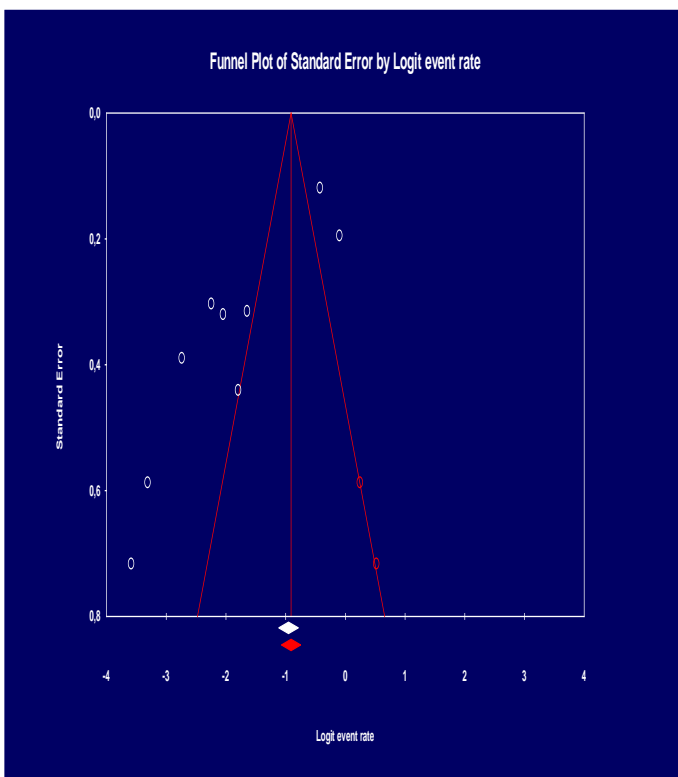
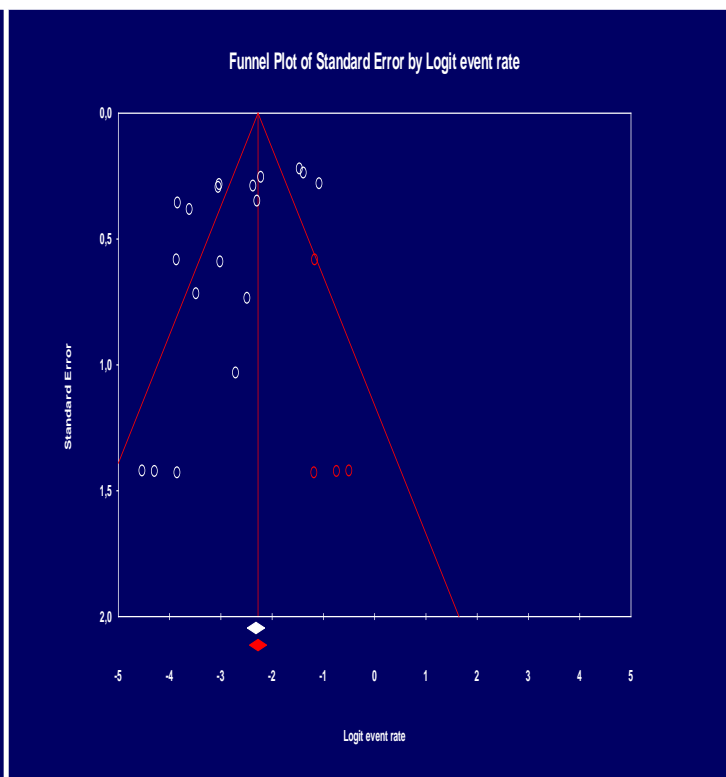


Figure S2. Bias assessment plot in Panel A (rate of ICH in primary and metastases brain cancers), Panel B (rate of ICH in primary brain cancer), Panel C (rate of ICH in brain metastases).

Panel A



Panel B



Panel C

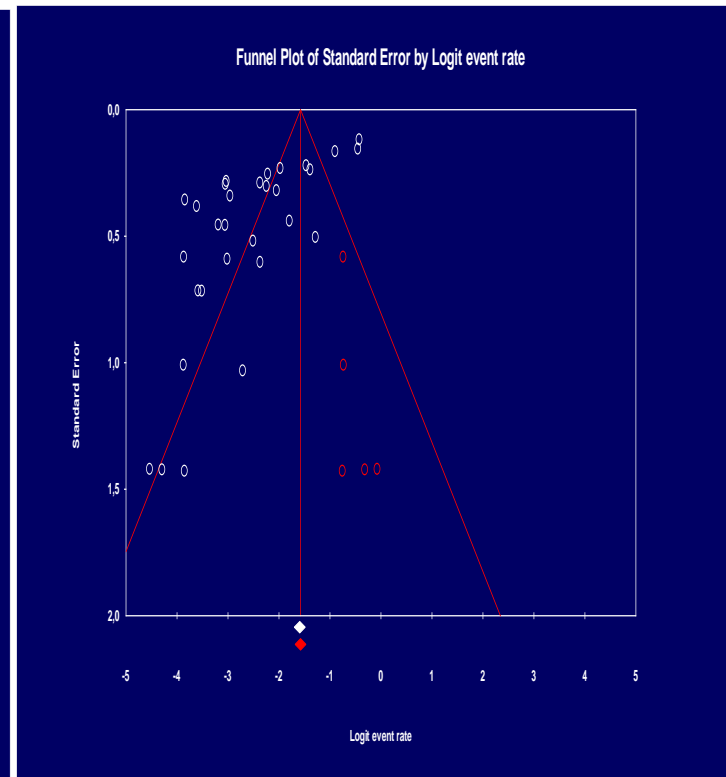
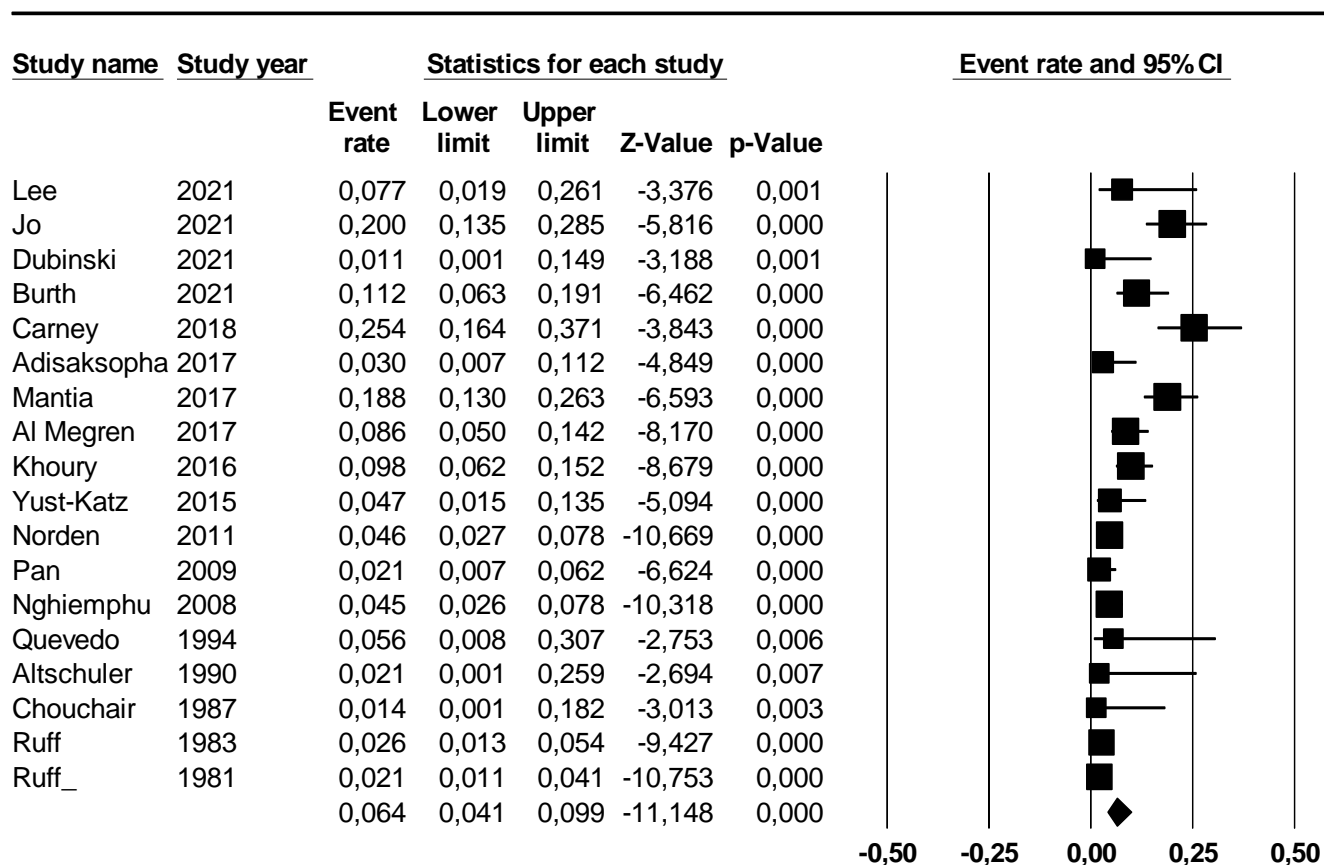


Figure S3. Rate of ICH in primary brain cancer only (panel A) and rate of ICH in metastatic brain tumors (panel B)

Panel A



Panel B

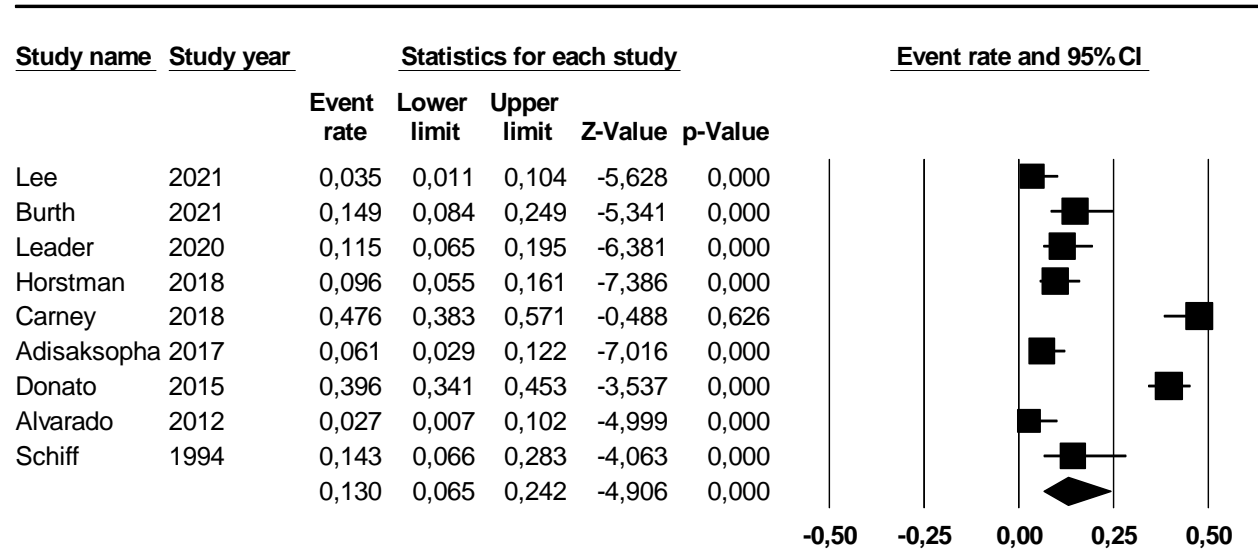
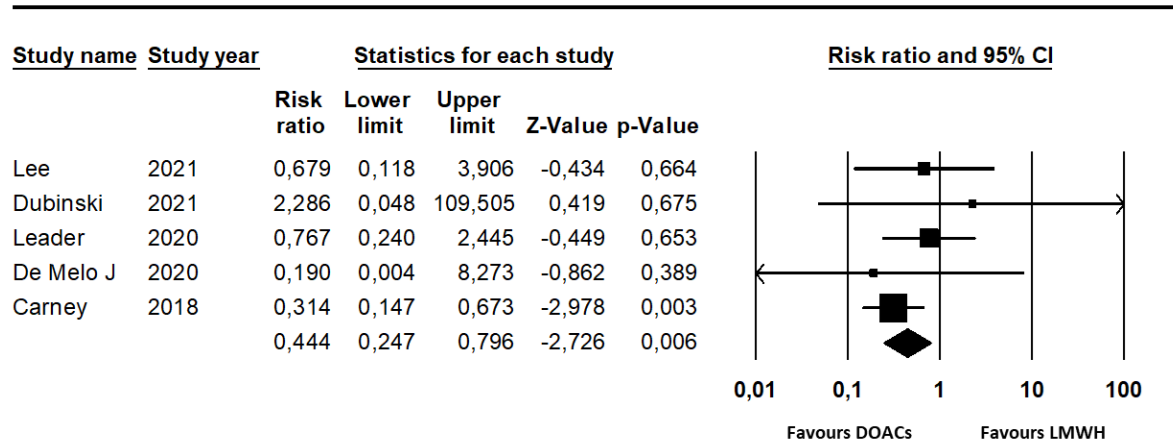


Figure S4. Risk of ICH in patients with primary and metastatic brain cancers treated with DOACs versus LMWH (Panel A) and with warfarin versus LMWH (Panel B)

Panel A



Panel B

