3° INCONTRO - Lunedì 21 settembre 2015

Eventi tromboembolici nel paziente neoplastico

Incidenza e patogenesi delle complicanze tromboemboliche

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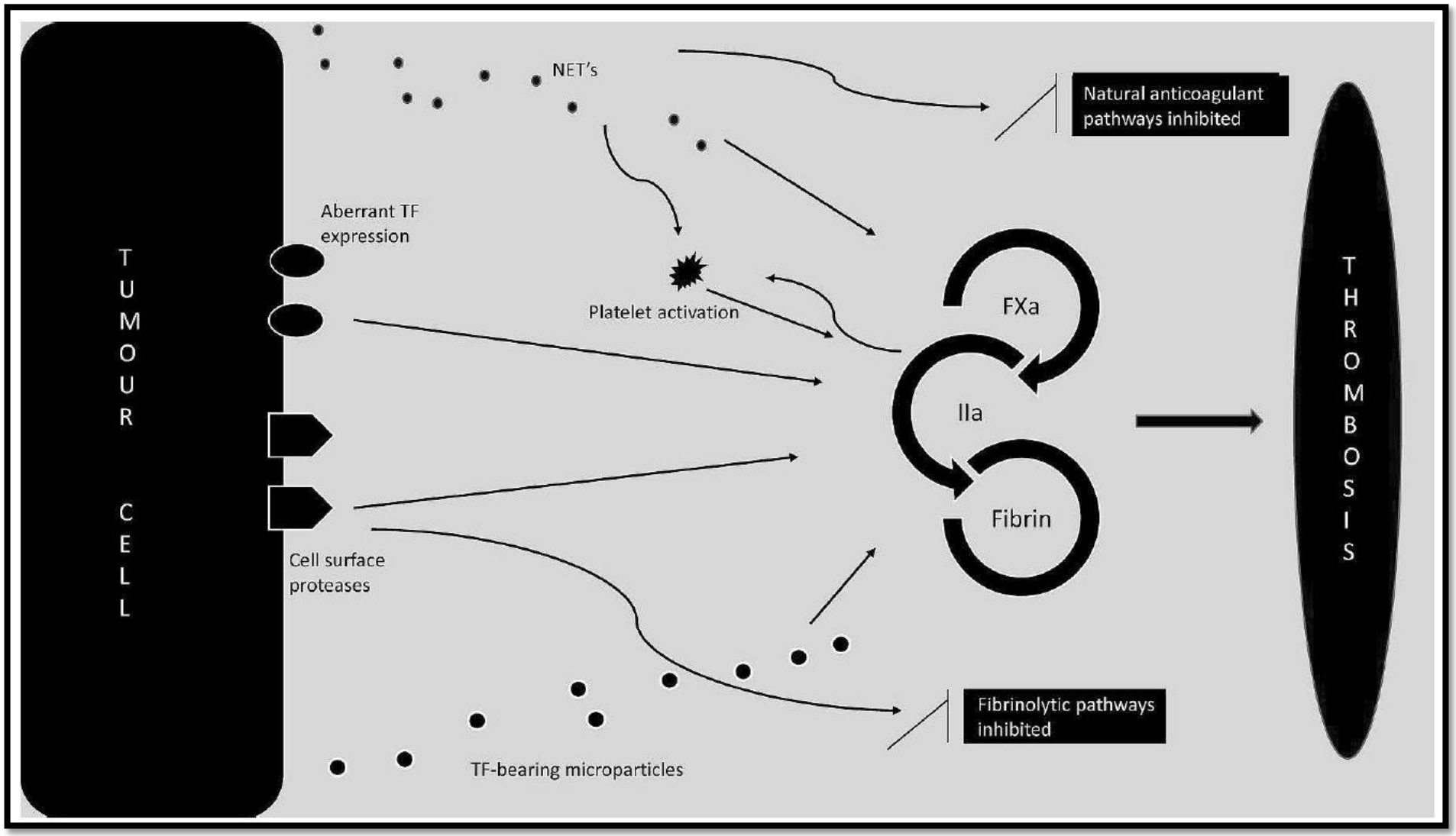
Trombosi e cancro

Armand Trousseau
(1801-1867)

Patogenesi



Donnellan et al, Curr Oncol 2014

TEV come primo segno di neoplasia

Time Point and Type of VTE	Period Prevalence of Previously Undiagnosed Cancer (95% CI), %
Baseline (≤ 1 mo)	
Overall	4.1 (3.6-4.6)
Unprovoked VTE	6.1 (5.0-7.1)
Provoked VTE	1.9 (1.3-2.5)
Baseline to 6 mo	
Overall	5.4 (4.8-6.0)
Unprovoked VTE	8.6 (7.2-10.0)
Provoked VTE	2.4 (1.4-3.4)
Baseline to 12 mo	
Overall	6.3 (5.6-6.9)
Unprovoked VTE	10.0 (8.6-11.3)
Provoked VTE	2.6 (1.6-3.6)

Diagnosi di cancro nel 10% dei pazienti con TEV idiopatica entro un anno dall'evento

Carrier et al, Ann Intern Med 2008

Screening per cancro nei pazienti con TEV idiopatica?

Group	N	Cancer diagnosed with screening	Cancer become symptomatic during follow-up^	Mean delay to diagnosis^^	Cancer-related mortality
Extensive screening*	99	13.1%	1.0%	1.0 mo	2.0%
Control	102	-	9.8%	11.6 mo	3.9%

^ $p<0.01$; ^^ $p<0.001$

***Extensive screening:** US of the abdomen, including the pelvis, followed by CT-scan of these areas, gastroscopy or double contrast barium swallowing, colonoscopy or sigmoidoscopy followed by barium enema, hemoccult, sputum cytology and tumor markers including CEA, a-FP and CA125; mammography and Pap smear for women; transabdominal US of the prostate (performed before the CT scan) and total PSA for men

Non è stata dimostrata una significativa riduzione della mortalità con lo screening

Piccioli et al, J Thromb Haemost 2004

La TEV nei pazienti oncologici

Study Population	Design	Number of patients	Proportion of cancer-associated VT cases
Olmsted county population [1]	Nested case-control	625/625	18%
California discharge dataset[2]	Cohort	21002	21%
Worcester metropolitan area, outpatient setting[3]	Cohort	1399	29%
RIETE Registry[4]	Cohort	35539	17%
Tromsø Study[5]	Cohort	462	23%

Circa il 20-30% delle TEV si verificano in pazienti oncologici

1. Heit et al, Arch Intern Med 2002; 2. White et al, Thromb Haemost 2005;
3. Spencer et al, Arch Intern Med 2007; 4. Gussoni et al, Thromb Res 2013;
5. Braekkan et al, Am J Epidemiol 2010

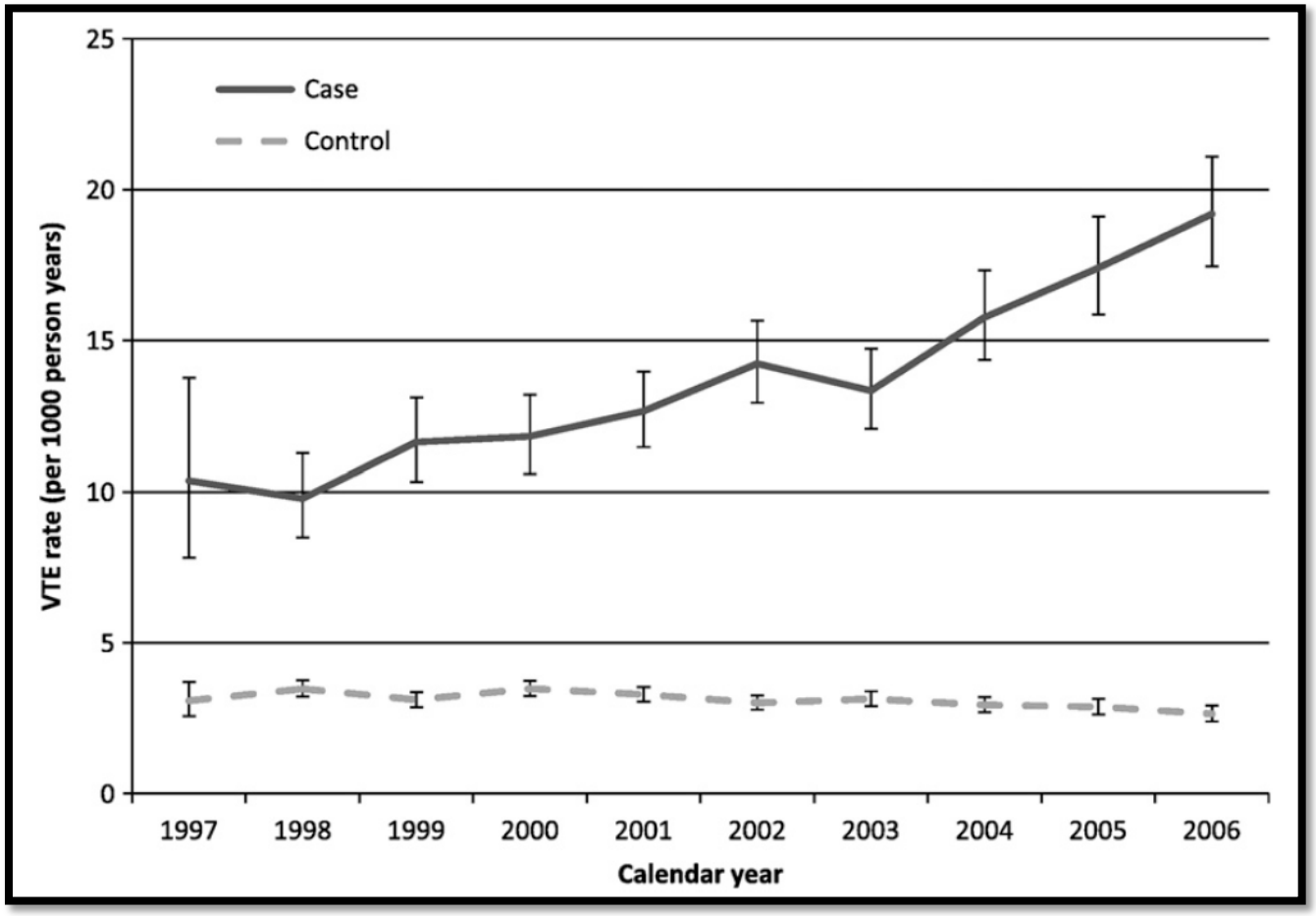
Rischio di TEV nei pazienti oncologici

Study Population	Design	Number of patients	Relative risk
MEGA study[1]	Case-control	2131/3220	OR 6.7
Olmsted country population[2]	Nested case-control	625/625	OR 4.1
Linked UK database[3]	Cohort	82203/577207	HR 4.7
Danish population-based registry[4]	Cohort	57591/287476	HR 4.7

Study Population	Design	Number of patients	Absolute risk
Patients with solid tumors[5]	Cohort	1041	7.8% (median follow-up 26 mos)
CATS study[6]	Cohort	840	8% within 1 year
38 papers on cohorts with cancer patients[7]	Meta-analysis	NA	13/1000 PY for average-risk pts 68/1000 PY for high-risk pts

1. Blom et al, JAMA 2005; 2. Heit et al, Arch Intern Med 2000; 3. Walker et al, Eur J Cancer 2003;
4. Cronin-Fenton et al, Br J Cancer 2010; 5. Sallah et al, Thromb Haemost 2002;
6. Vormittag et al, Arterioscler Thromb Vasc Biol 2009; 7. Horsted et al, PloS Med 2012

L’incidenza di TEV è destinato ad aumentare



Walker et al, Eur J Cancer 2013

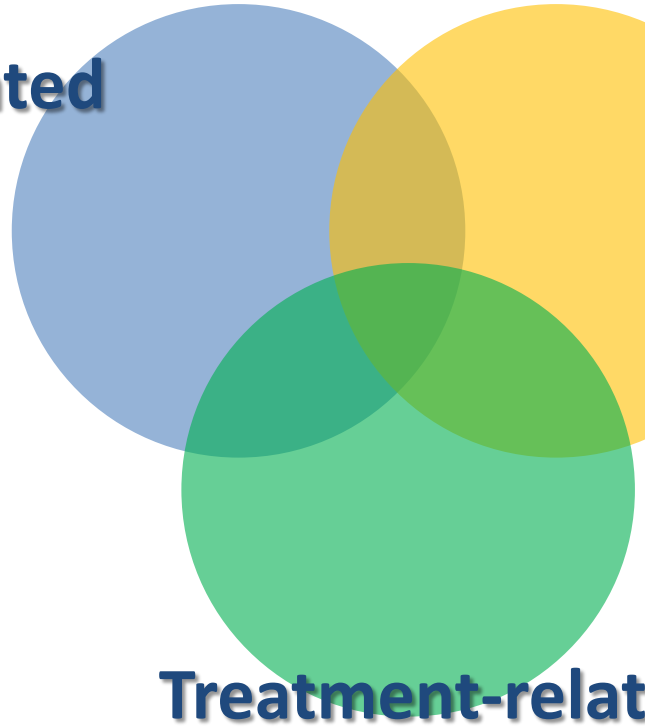
Mortalità

Exposure	Pts	Deaths (n)	MR per 100 PY (95% CI)	HR (95%)
None	277713	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	71	55.0 (43.6-69.3)	31.2 (24.6-39.6)

PY: person-years; MR: mortality rate; VT: venous thrombosis

Braekkan et al, Am J Epidemiol 2010

Fattori di rischio



Cancer-related

Sede
Stadio
Grading

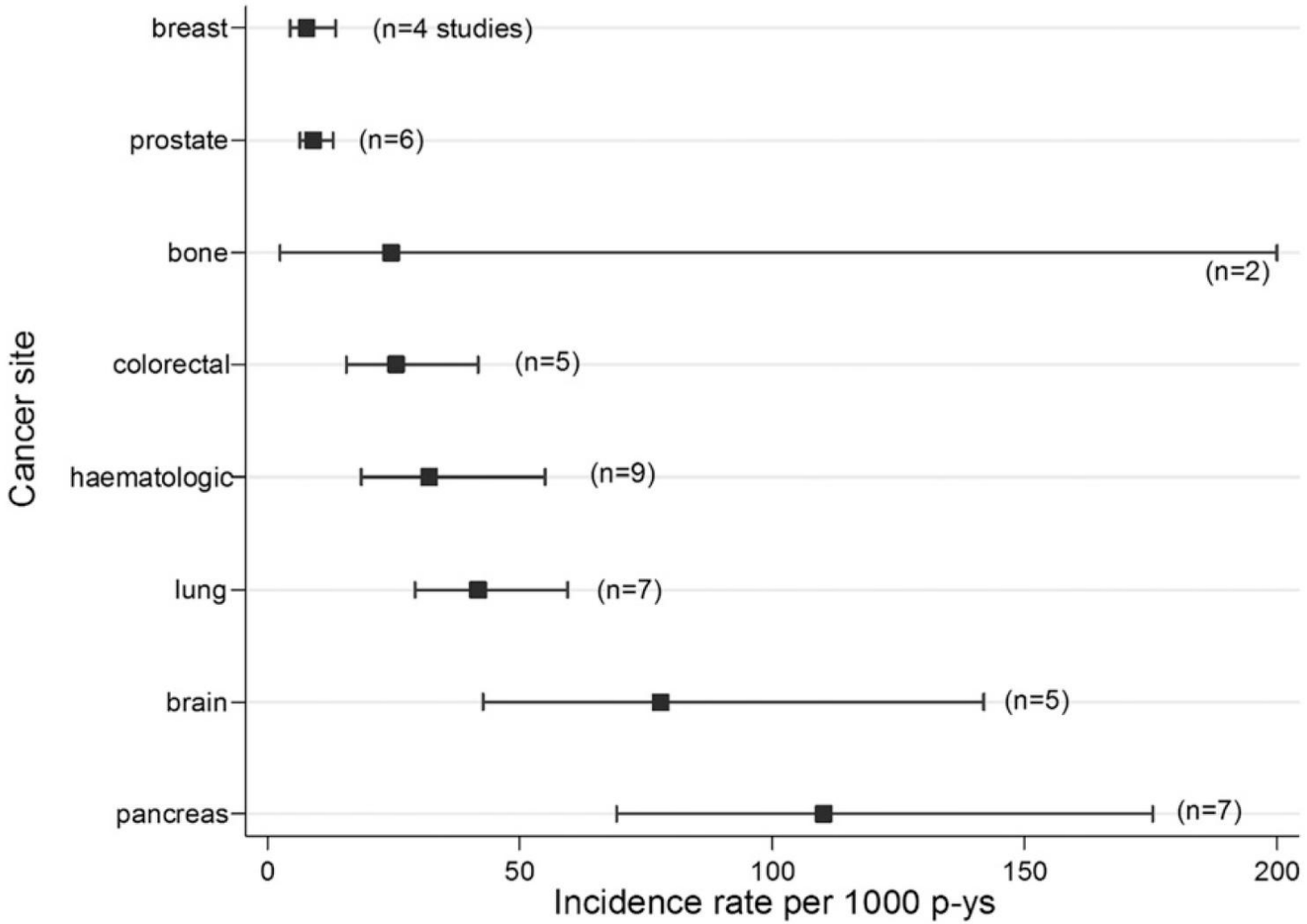
Patient-related

Età
Etnia
Sesso
Comorbidità
Allettamento
Pregressi episodi di TEV
Mutazioni pro-trombotiche

Treatment-related

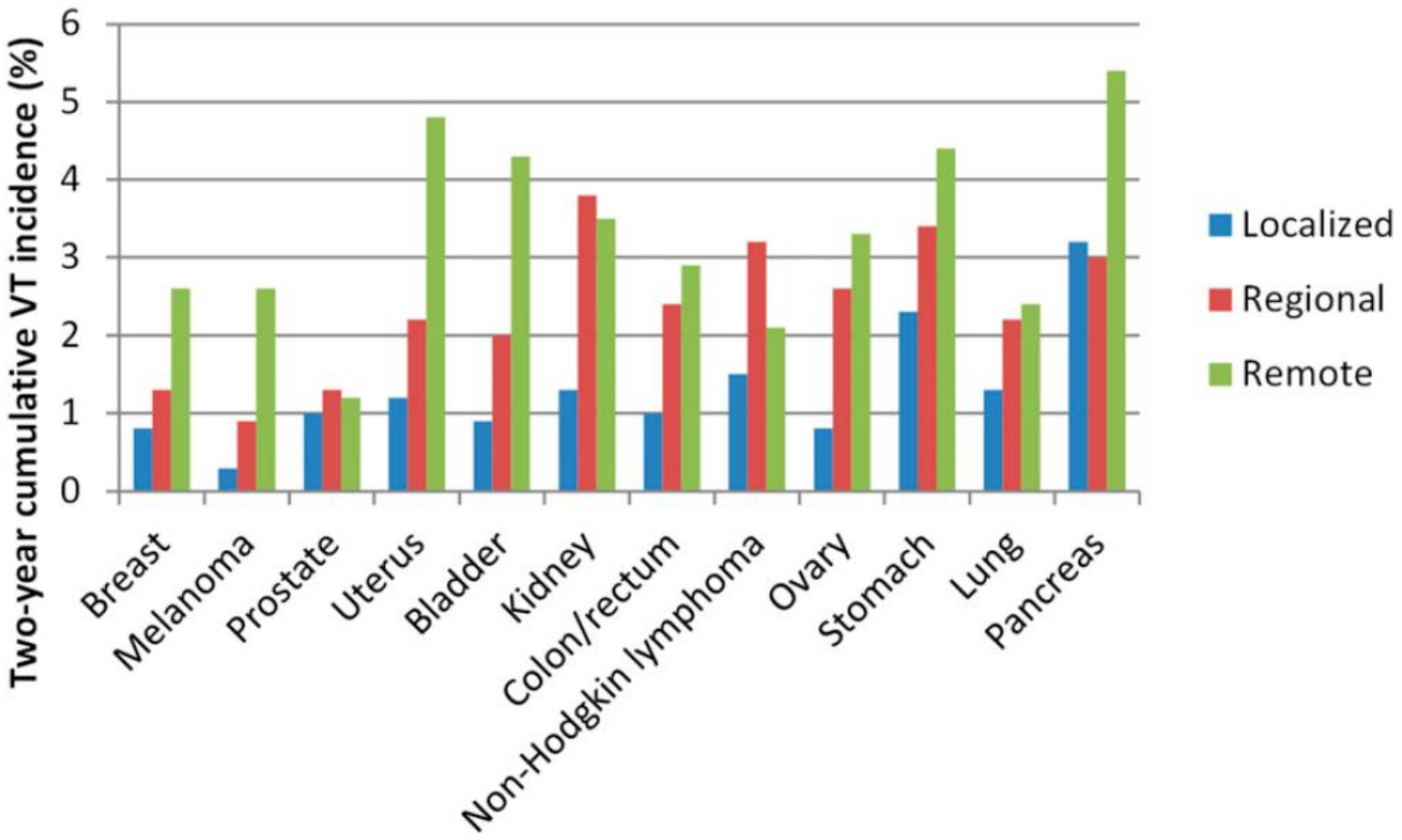
Chirurgia
Terapia endocrina
Chemioterapia
Terapia anti-vascolare

Sede primaria della neoplasia



Horsted et al, PLoS Med 2012

Stadio della neoplasia



Chew et al, Arch Intern Med 2006

Caratteristiche del paziente

Characteristic	OR (95% CI)	p
Age >65	1.08 (1.05–1.1)	<.0001
Female	1.14 (1.12–1.16)	<.0001
Comorbidities:		
Arterial thromboembolism	1.45 (1.39–1.52)	<.0001
Pulmonary disease	1.37 (1.34–1.40)	<.0001
Renal disease	1.53 (1.49–.158)	<.0001
Infection	1.77 (1.73–1.81)	<.0001
Anemia	1.35 (1.32–1.39)	<.0001

Khorana et al, Cancer 2007

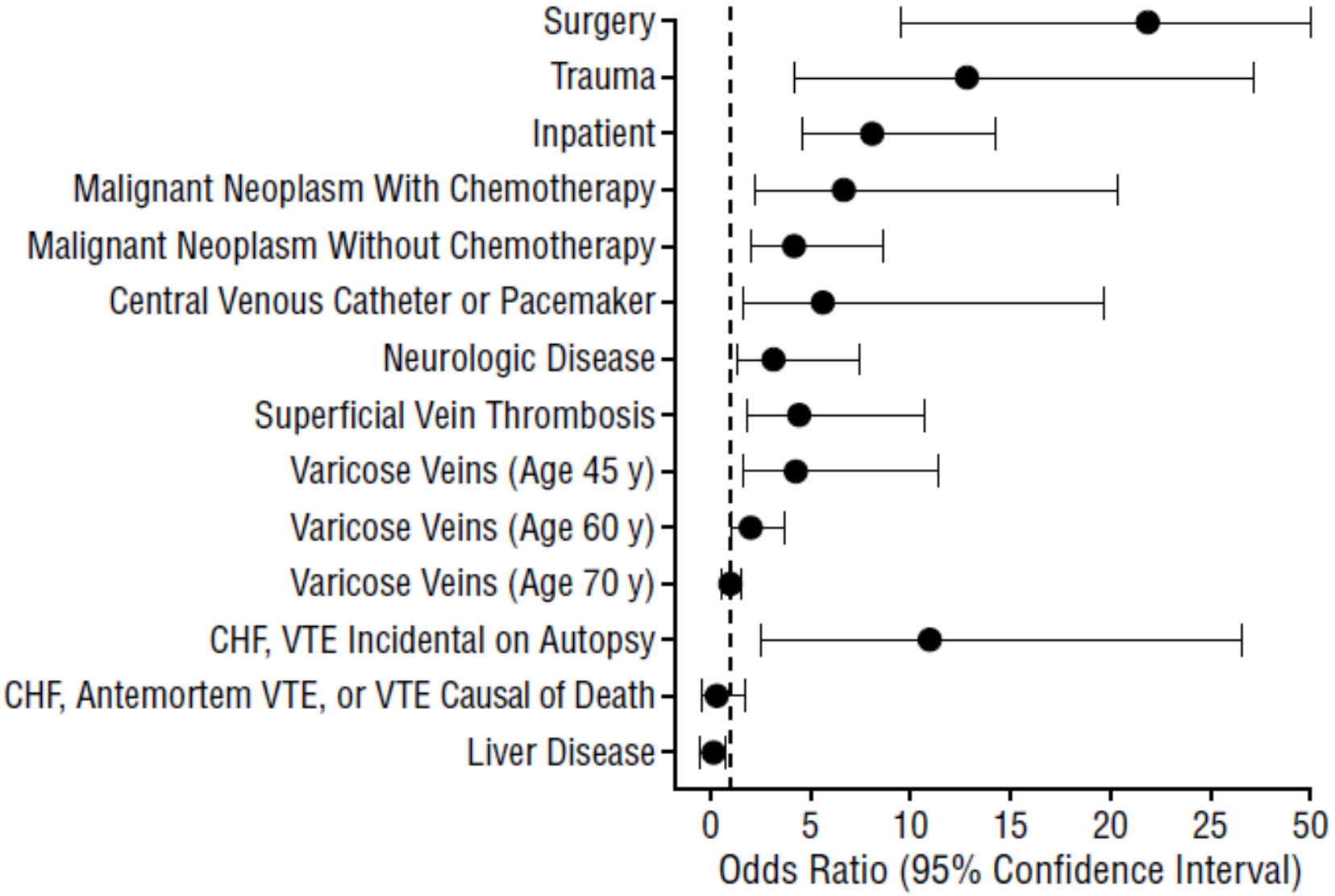
Mutazioni pro-trombotiche

Mutation	Malignancy	Patients (n = 2706)	Control Participants (n = 1757)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
Factor V Leiden					
No	No	2125	1635	1.00	1.00
	Yes	162	26	4.8 (3.2-7.3)	5.1 (3.3-7.7)
Yes	No	403	95	3.3 (2.6-4.1)	3.3 (2.6-4.1)
	Yes	16	1	11.9 (1.6-86.6)	12.1 (1.6-88.1)
Prothrombin 20210A					
No	No	2410	1694	1.00	1.00
	Yes	164	27	4.3 (2.8-6.4)	4.5 (3.0-6.8)
Yes	No	118	36	2.3 (1.6-3.4)	2.3 (1.6-3.3)
	Yes	14	0	ND	ND

Abbreviations: CI, confidence interval; ND, not determined due to 0 control participants.
*Adjusted for age and sex.

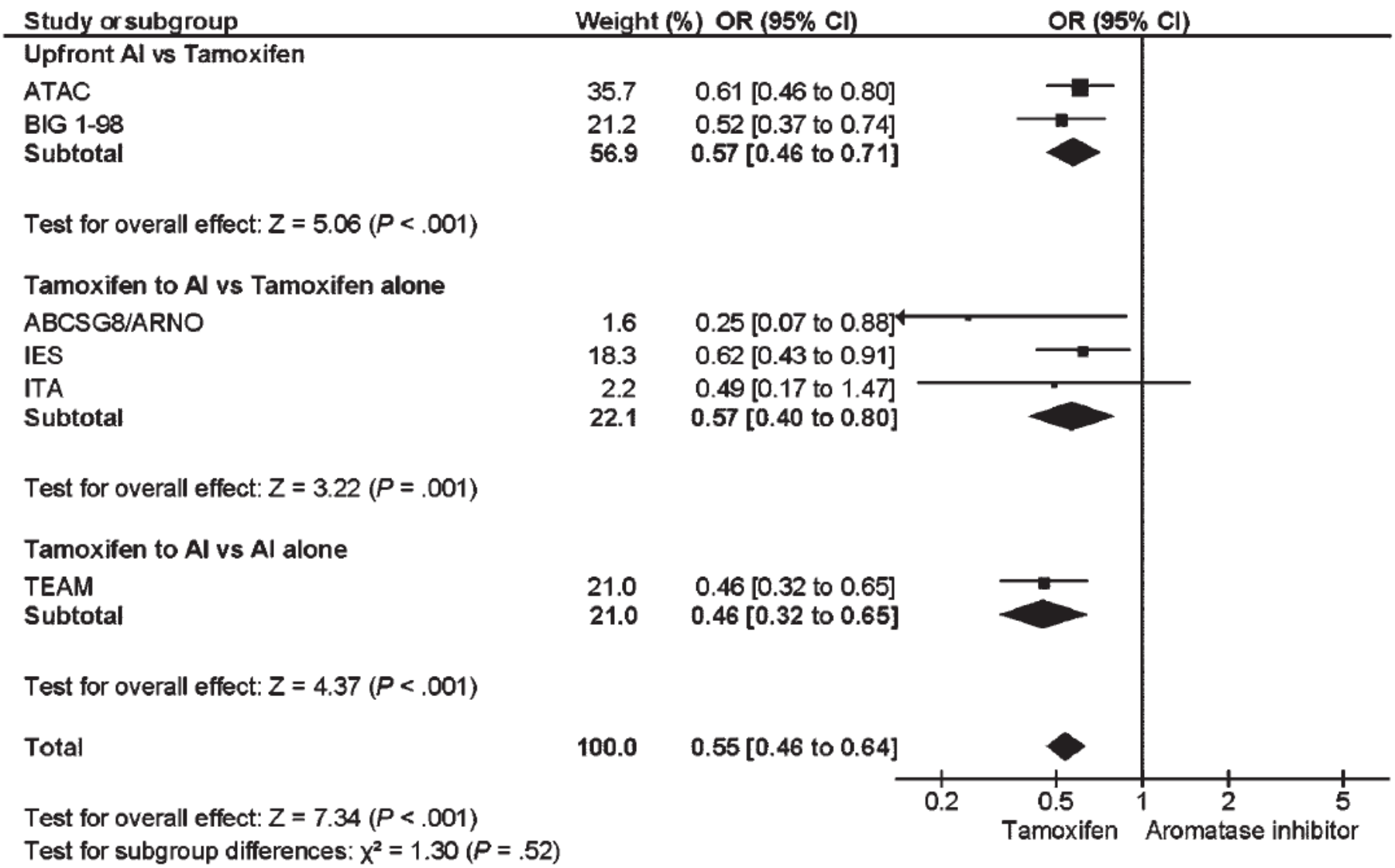
Blom et al, JAMA 2005

Chemioterapia



Heit et al, Arch Intern Med 2002

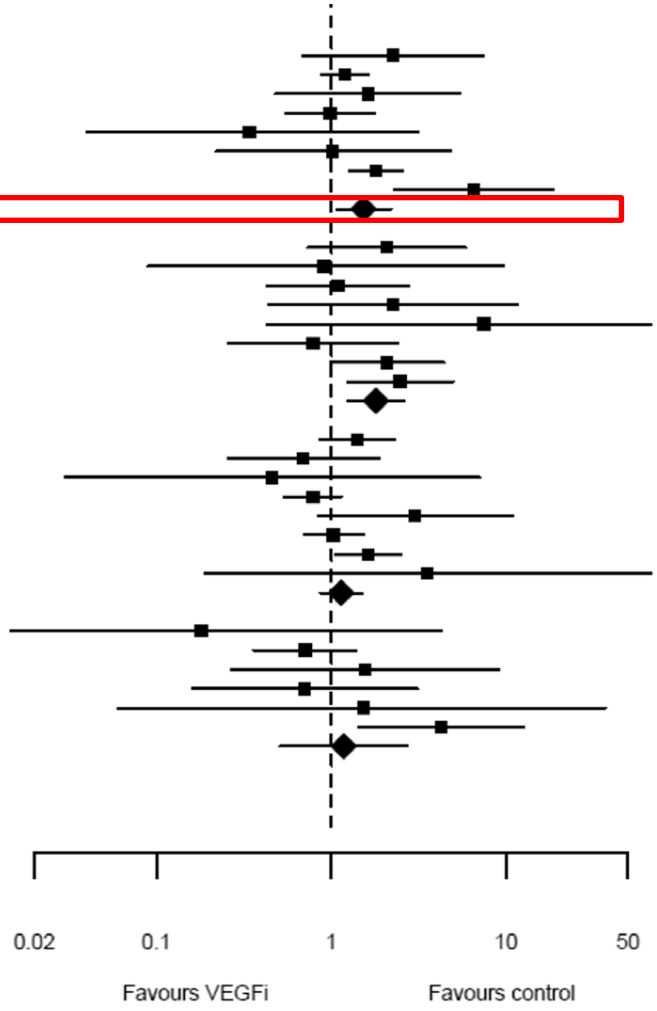
Terapia endocrina



Amir et al, J Natl Cancer Inst 2011

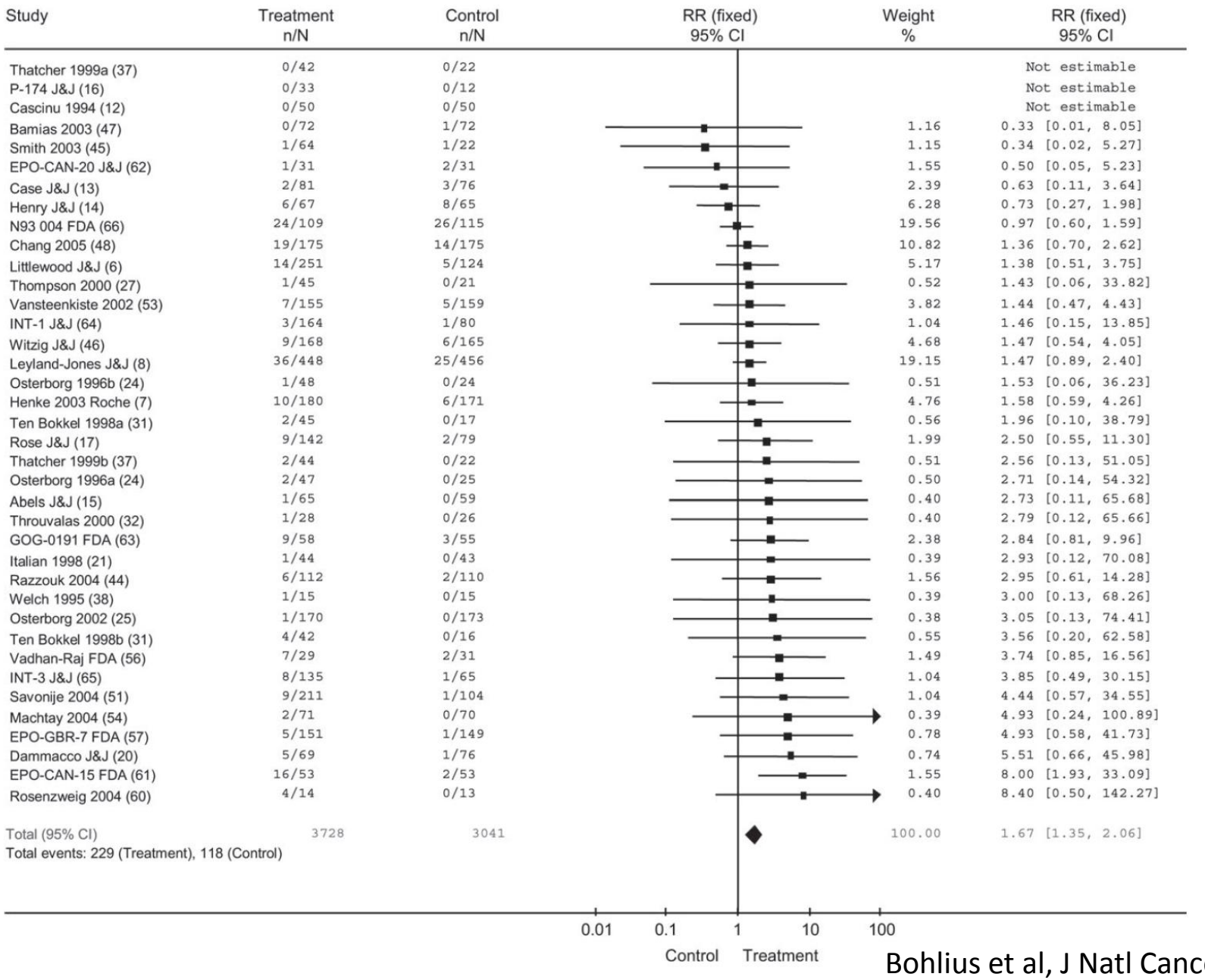
Terapia antiangiogenetica

Thrombobis			
Any thrombotic			
Kabbinavar 2003	13/67	3/35	2.26 (0.69, 7.42)
Hurwitz 2004	76/393	64/397	1.20 (0.89, 1.62)
Johnson 2004	10/66	3/32	1.62 (0.48, 5.47)
Kabbinavar 2005	18/100	19/104	0.99 (0.55, 1.77)
Arnold 2007	1/52	3/53	0.34 (0.04, 3.16)
Karrison 2007	3/47	3/48	1.02 (0.22, 4.81)
Perren 2011	80/745	45/753	1.80 (1.27, 2.55)
Van Cutsem 2011	26/427	4/428	6.52 (2.29, 18.51)
Overall (I^2 = 43; P-value = 0.07)	**227/1897**	**144/1850**	**1.53 (1.07, 2.20)**
Arterial thrombotic			
Kabbinavar 2005	10/100	5/104	2.08 (0.74, 5.87)
Spano 2008	2/68	1/31	0.91 (0.09, 9.68)
Van Cutsem 2009	9/296	8/287	1.09 (0.43, 2.79)
Escudier 2010	5/337	2/304	2.26 (0.44, 11.54)
Tebbutt 2010	7/157	0/78	7.50 (0.43, 129.65)
Burger 2011	8/1215	5/601	0.79 (0.26, 2.41)
Hecht 2011	21/585	10/583	2.09 (0.99, 4.41)
Perren 2011	27/745	11/753	2.48 (1.24, 4.97)
Overall (I^2 = 0; P-value = 0.67)	**89/3503**	**42/2741**	**1.80 (1.24, 2.59)**
Venous thrombotic			
Hurwitz 2004	35/393	25/397	1.41 (0.86, 2.32)
Kabbinavar 2005	6/100	9/104	0.69 (0.26, 1.88)
Spano 2008	1/68	1/31	0.46 (0.03, 7.05)
Van Cutsem 2009	43/296	53/287	0.79 (0.54, 1.14)
Escudier 2010	10/337	3/304	3.01 (0.84, 10.82)
Burger 2011	73/1215	35/601	1.03 (0.70, 1.53)
Perren 2011	50/745	31/753	1.63 (1.05, 2.52)
Rugo 2011	3/111	0/56	3.56 (0.19, 67.79)
Overall (I^2 = 33; P-value = 0.16)	**221/3265**	**157/2533**	**1.14 (0.87, 1.50)**
Pulmonary embolism			
Yang 2003	0/76	1/40	0.18 (0.01, 4.26)
Hurwitz 2004	14/393	20/397	0.71 (0.36, 1.38)
Kabbinavar 2005	3/100	2/104	1.56 (0.27, 9.14)
Miller 2005	3/229	4/215	0.70 (0.16, 3.11)
Rugo 2011	1/111	0/56	1.53 (0.06, 36.89)
Van Cutsem 2011	17/427	4/428	4.26 (1.45, 12.56)
Overall (I^2 = 48; P-value = 0.09)	**38/1336**	**31/1240**	**1.18 (0.51, 2.73)**



Faruque et al, PloS One 2014

Eritropoietina



Bohlius et al, J Natl Cancer 2006

Take home messages

- Il cancro determina uno stato di ipercoagulabilità per attivazione delle pathways pro-coagulanti ed inibizione di quelle anti-coagulanti
- La TEV è a volte la prima manifestazione del cancro
- I pazienti oncologici hanno un rischio di TEV circa 5 volte maggiore dei soggetti non oncologici
- Fattori di rischio per TEV nei pazienti oncologici sono: fattori legati al tumore (sede primaria della neoplasia, stadio, grado) fattori legati al trattamento (chirurgia, ormonoterapia, chemioterapia, terapia anti-vascolare, EPO), fattori legati al paziente (età, comorbidità, allettamento)
- La TEV si associa ad aumentata mortalità nel paziente oncologico

Ospedale
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PRESIDIO OSPEDALIERO ACCREDITATO - REGIONE VENETO

GRAZIE

PER L'ATTENZIONE