2021

Progetto Ematologia Romagna

Anticoagulazione: vecchi e nuovi farmaci a confronto

Marco Marietta – Modena

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Il sottoscritto **Marco Marietta,** in qualità di relatore all'evento ***"Progetto Ematologia-Romagna" 16 ottobre 2021***, ai sensi dell'art. 3.3 sul Conflitto di Interessi, dell'Accordo Stato-Regione del 19 aprile 2012, dichiaro che negli ultimi due anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- **Relazioni a convegni:** Novo-Nordisk, Octapharma, Werfen

e che detti rapporti non sono tali da poter influenzare l'attività di docenza espletata nell'ambito dell'Evento nel senso di pregiudicare la finalità esclusiva di educazione/formazione dei professionisti della Sanità nell'attività formativa

"What's in a name?
That which we call a rose
By any other name would smell as sweet."

William Shakespeare
Romeo and Juliet (II,ii,1-2)

- ✓ NAO = Nuovi Anticoagulanti Orali
- ✓ NOA = Novel Oral Anticoagulants
- ✓ DOAC = Direct Oral AntiCoagulants
- ✓ AVK = Anti Vitamin K

Agenda

- ✓ Perchè occuparsi dei DOAC?

DOAC IN ITALIA

Circa 1.100.000 pazienti in DOAC per FA

(stima basata sulla prevalenza d'uso in Emilia-Romagna)

Circa 2% paz. /anno con emorragia maggiore

Circa 10% paz con manovre invasive /anno

Circa 22.000 emorragie maggiori / anno in DOAC

Circa 110.000 manovre invasive in DOAC

Agenda

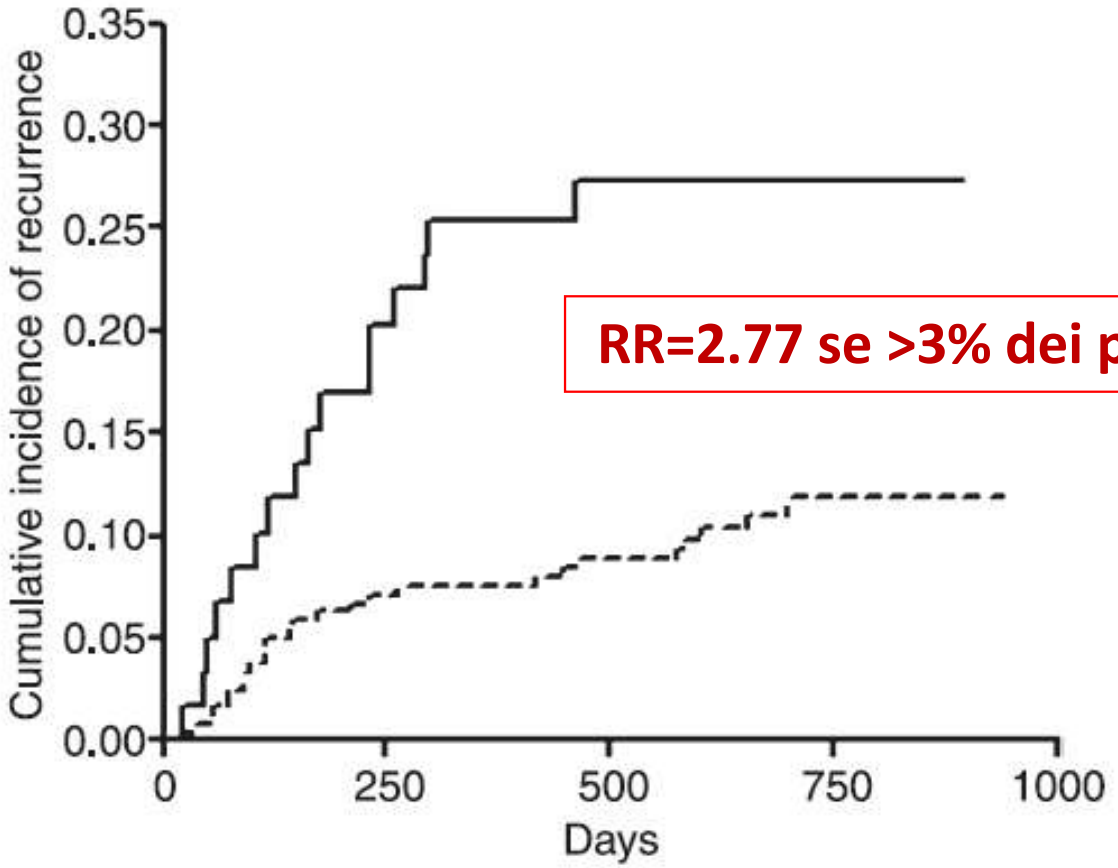
- ✓ Perchè occuparsi dei DOAC?
- ✓ Avevamo bisogno dei DOAC?

Qualità terapeutica ed efficacia nella FA

Rischio relativo di stroke in relazione al controllo INR (% tempo in range)			
	Totale	$CHA_2DS_2VASc \geq 1$	$CHA_2DS_2VASc \geq 2$
No antitrombotici	1 (Ref)	1 (Ref)	1 (Ref)
< 30%	3.08	3.07	2.74
31-40%	1.65	1.65	1.56
41-50%	1.36	1.35	1.24
51-60%	1.08	1.09	1.00
61-70%	**0.67**	**0.65**	**0.60**
>70%	**0.68**	**0.67**	**0.62**

Gallagher AM et al. Thromb Haemost 2011; 106

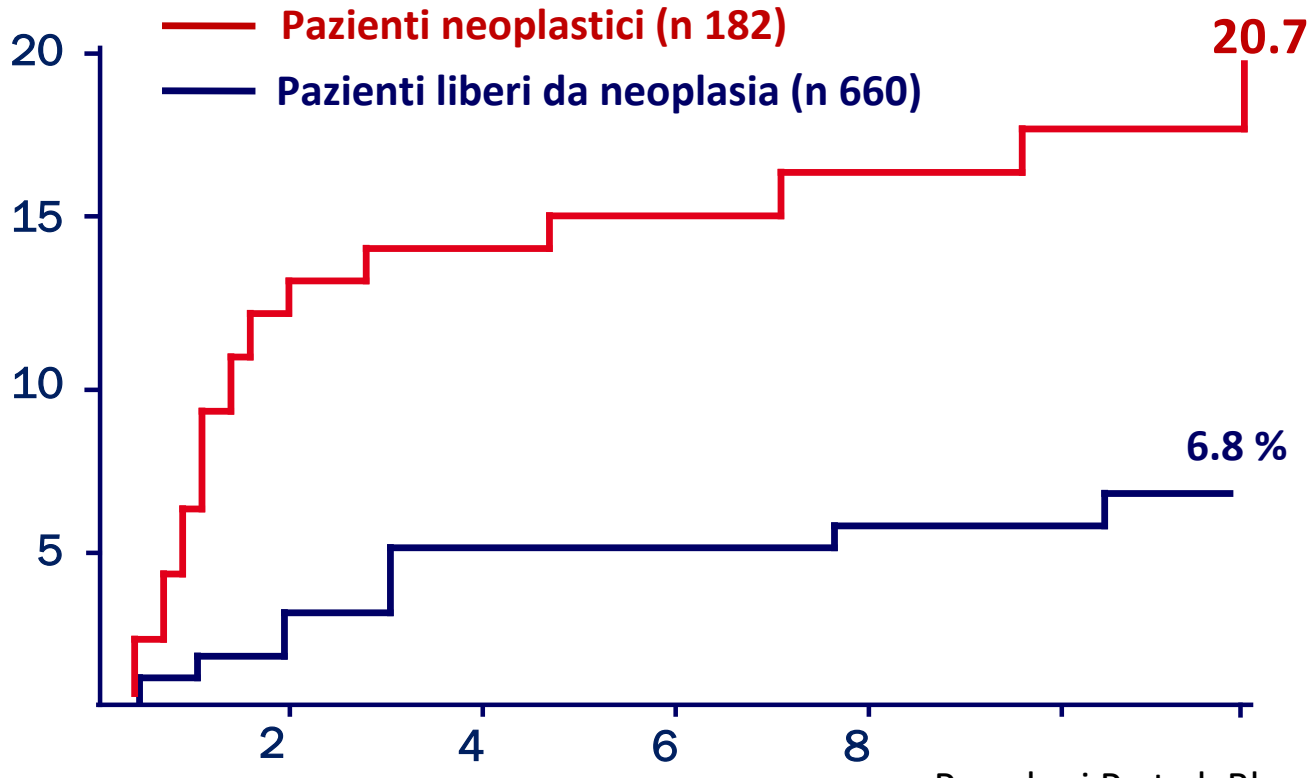
Qualità terapeutica ed efficacia nel TEV



RR=2.77 se >3% dei primi 90 gg passati con INR<1.5

Palareti G et al. J Thromb Haemost 2005;3:955-61

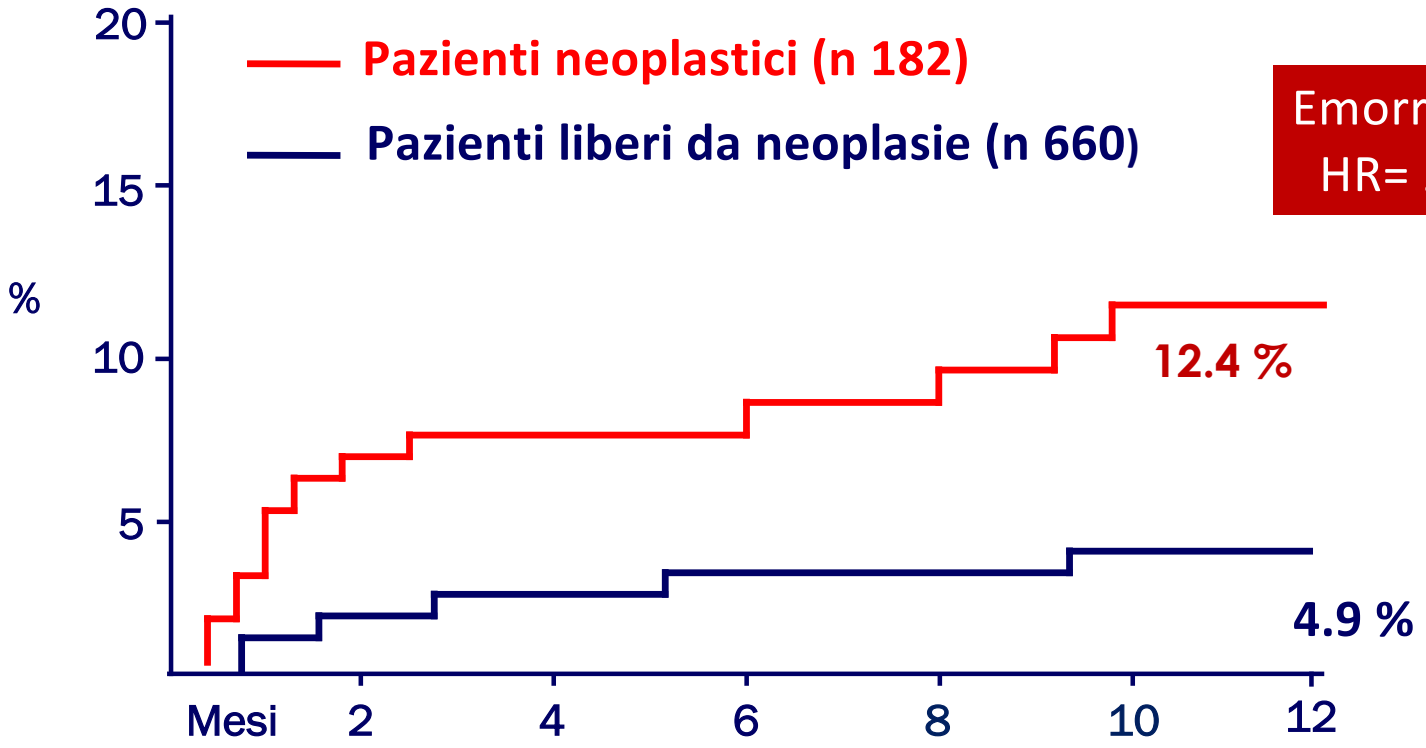
Il TEV nel paziente oncologico



Recidive di TEV
HR= 3.2; p<0.001

Prandoni P et al. Blood 2002; 100:3484-3488

Il TEV nel paziente oncologico



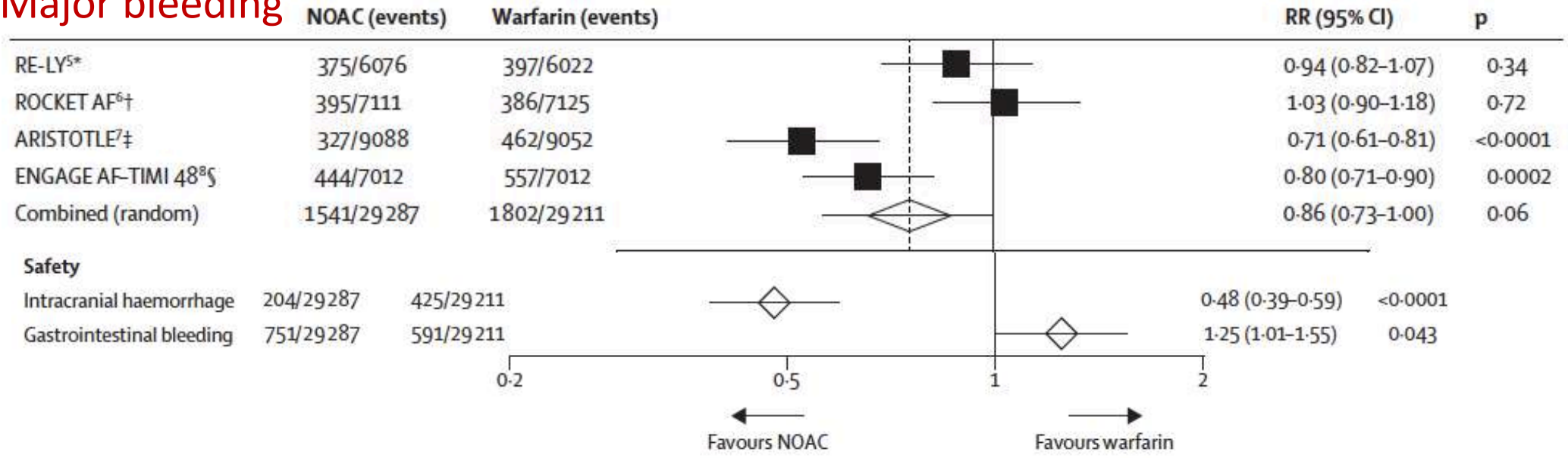
Emorragie maggiori
HR= 2.2; p=0.019

Prandoni P et al. Blood 2002; 100:3484-3488

Il rischio emorragico

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Major bleeding

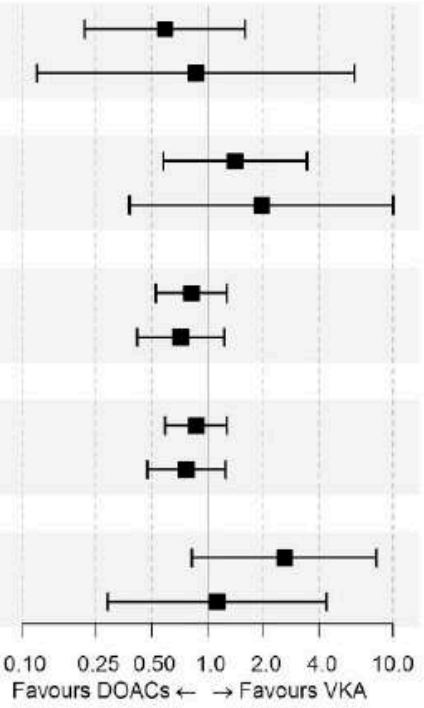


Ruff CT et al. Lancet. 2014;383:955-62.

Direct oral anticoagulants vs non-vitamin K antagonist in atrial fibrillation: A prospective, propensity score adjusted cohort study

(b) Propensity Score adjusted HR for DOACs vs VKA

OUTCOME	HR	95% CI
Stroke or Peripheral Arterial Embolism		
All patients (n=3801, e=43)	0.59	0.22 ; 1.60
Naive (n=1396, e=17)	0.86	0.12 ; 6.21
Major Bleeding		
All patients (n=3801, e=77)	1.41	0.58 ; 3.43
Naive (n=1396, e=28)	1.96	0.38 ; 10.05
AMI or other Ischemic Heart Disease		
All patients (n=3801, e=218)	0.82	0.53 ; 1.28
Naive (n=1396, e=103)	0.72	0.42 ; 1.23
Composite Outcome		
All patients (n=3801, e=320)	0.87	0.59 ; 1.27
Naive (n=1396, e=139)	0.77	0.47 ; 1.26
Death		
All patients (n=3801, e=70)	2.60	0.83 ; 8.13
Naive (n=1396, e=25)	1.13	0.29 ; 4.39



Marietta M et al. Eur J Intern Med. 2019; 62:9-16

Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

Table 2 | Number of events, and crude and weighted event rates according to initiated treatment

	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
Variables	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†
One year follow-up:												
Ischaemic stroke or systemic embolism	210	4.86	3.92	327	2.77	3.73	161	3.04	2.89	1004	3.28	3.25
Ischaemic stroke	204	4.71	3.72	321	2.72	3.68	156	2.95	2.79	920	3.00	3.01
All cause mortality	232	5.23	5.01	319	2.66	4.62	413	7.69	7.02	2652	8.52	7.41
Ischaemic stroke, systemic embolism, or death	424	9.81	8.71	623	5.28	7.92	537	10.15	9.38	3483	11.39	10.28
Any bleeding	121	3.78	3.13	253	2.77	2.85	186	5.57	4.83	959	5.53	4.71
Major bleeding	90	2.80	2.29	203	2.22	2.04	149	4.44	3.92	725	4.16	3.58
Intracranial bleeding	15	0.46	0.40	19	0.21	0.22	14	0.41	0.31	118	0.66	0.55

Larsen TB et al. *BMJ 2016;353:i3189*

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

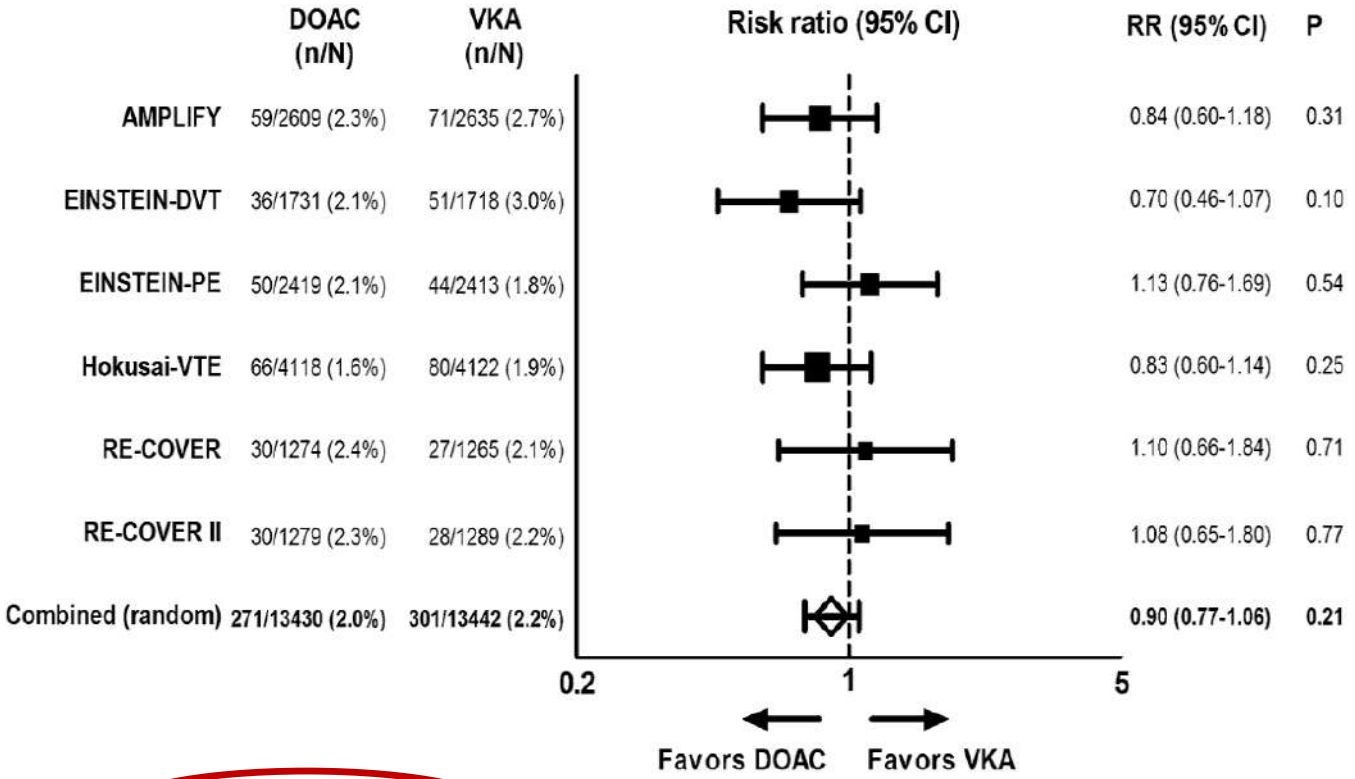


Figure 1. First recurrent VTE or VTE-related death. For Hokusai-VTE, we used event data for the on-treatment period. Heterogeneity: $I^2 = 0\%$; $P = .53$.

Van Es N et al. Blood. 2014;124:1968-1975

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

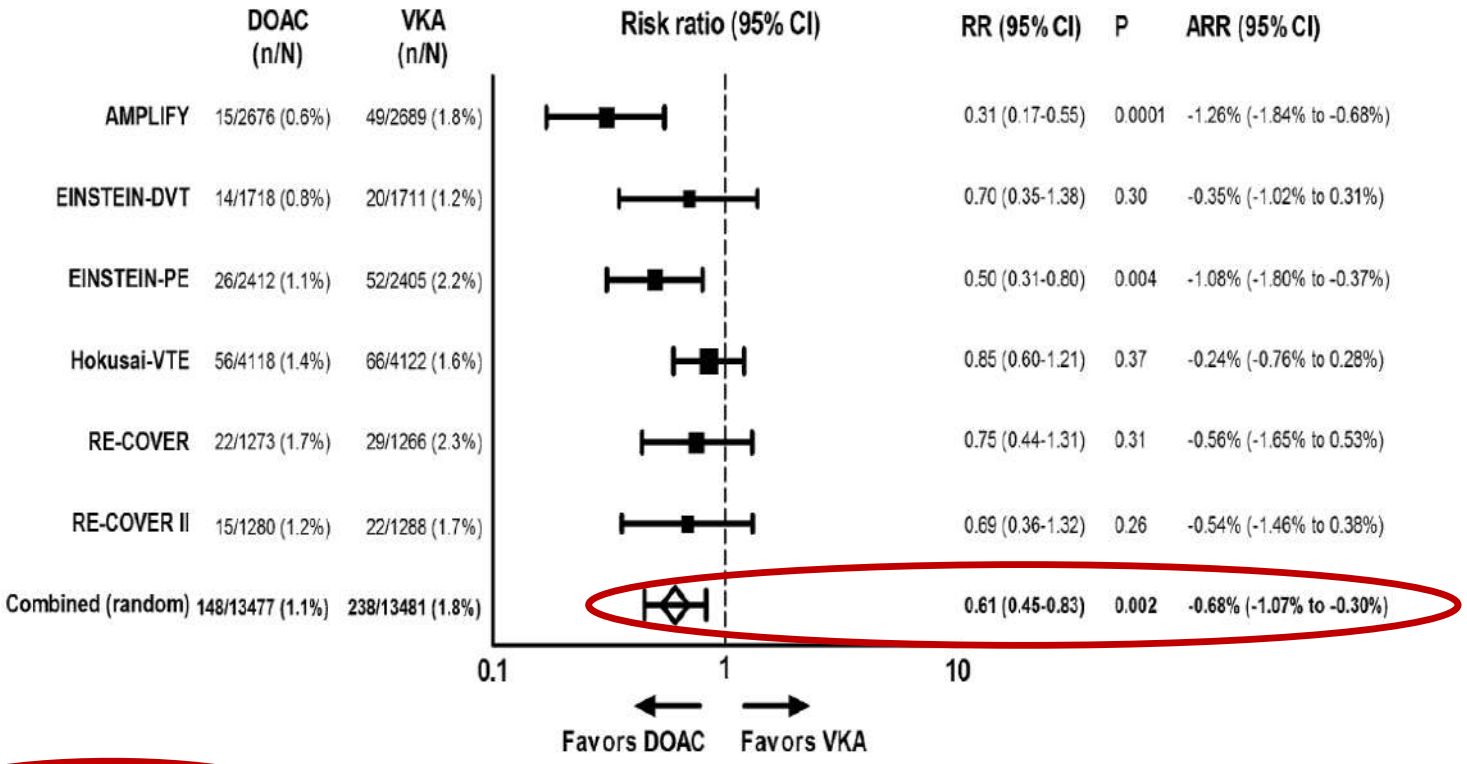
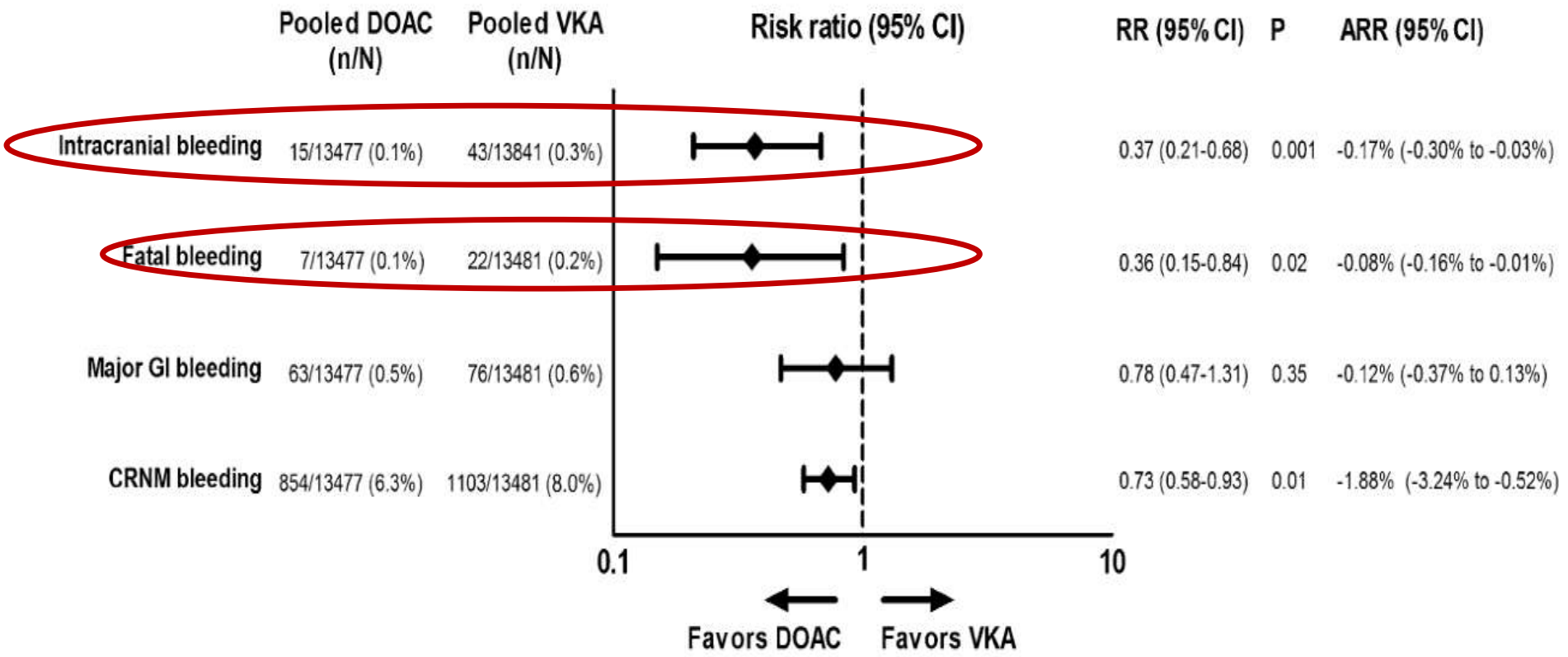


Figure 2. Major bleeding. The sums of numbers of events from RE-COVER and RE-COVER II with respect to major bleeding slightly differ from those in the pooled analysis. We used data from the pooled analysis because these were most accurate. Heterogeneity: $I^2 = 51\%$, $P = .07$. ARR, absolute risk reduction.

Van Es N et al. Blood. 2014;124:1968-1975

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials



Van Es N et al. Blood. 2014;124:1968-1975

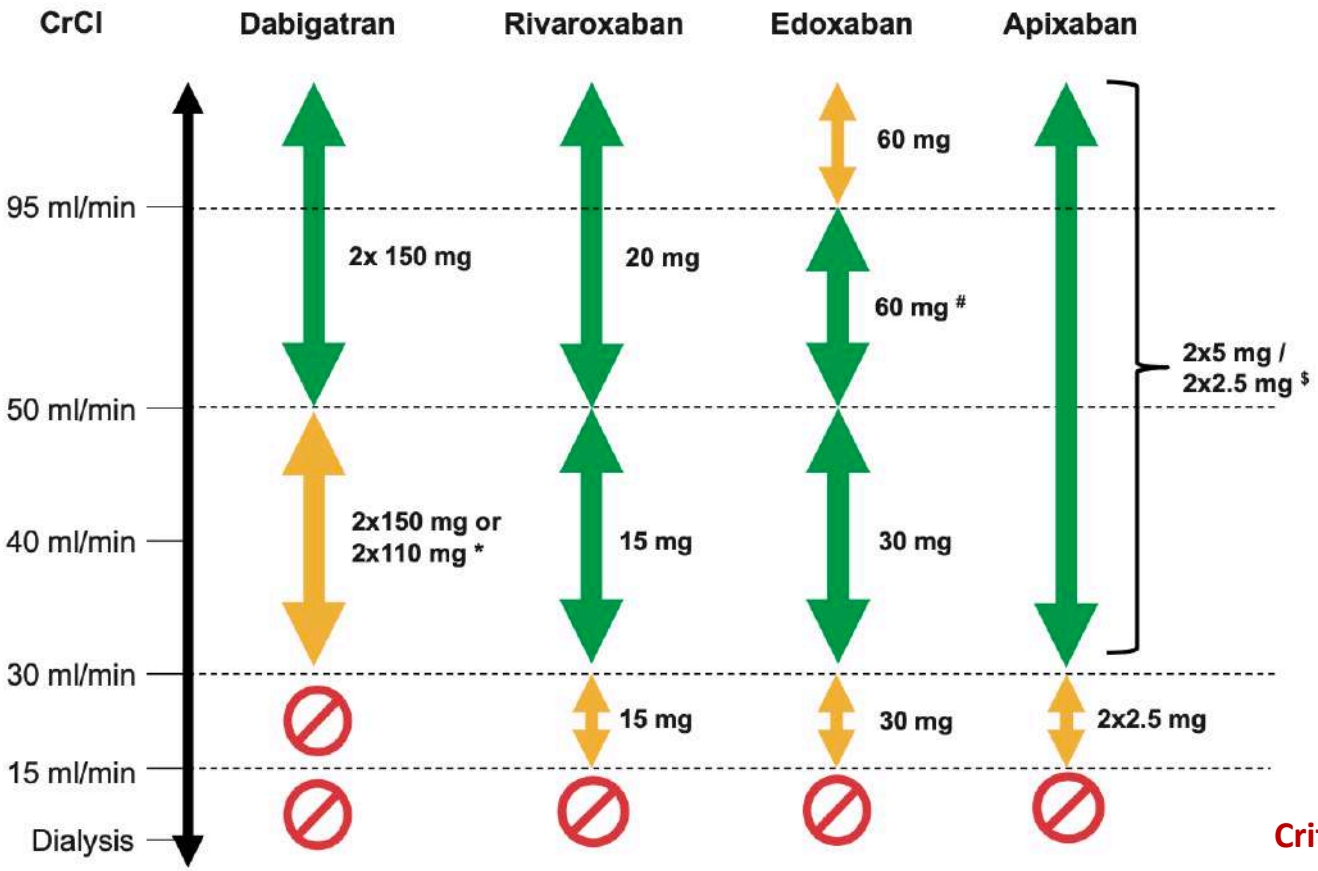
Agenda

- ✓ Perchè occuparsi dei DOAC?
- ✓ Avevamo bisogno dei DOAC?
- ✓ Farmacologia minima dei DOAC

Tab. 3 Caratteristiche farmacologiche a confronto di AVK e NAO[1,2,3]

	AVK	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	fatt vit. K dip: (VII, IX, X, II)	fatt. IIa (trombina)	fatt. Xa	fatt. Xa	fatt. Xa
Pro farmaco	no	sì	no	no	no
Biodisponibilità	elevata	3-7%	66% a digiuno 100% coi pasti	50%	62%
Eliminazione renale	60-90% inattivo	80-85%	33%	27%	35%
Dializzabilità	--	Si	Parziale	No	No
Metabolizzazione da citocromo CYP3A4	Si	No	Si (32%)	Si (15%)	<10%
Effetto del cibo sull'efficacia	forte	assente	presente assumere col pasto)	assente	assente
Emivita Plasmatica T1/2	8-11 h (aceno-cumarina) 20-60 h (warfarin)	12-17 ore	5-9 ore (giovane) 11-13 ore (anziano)	8-15 ore	10-14 ore
Dosi giornaliere	1	2	1	2	1
Legame (%) con le proteine plasmatiche	98	35	85	90	55
Tmax (h) per raggiungere il picco di concentrazione	~ 72 (warfarin)	~ 2	2-4	1-4	1-2
Tempo medio scomparsa di effetto (con normale funzione renale)	3-5 giorni	~ 24 h	~ 24 h	~ 24 h	~ 24 h

DOAC e Insufficienza Renale



Criterio di esclusione da studi registrativi

Come calcolare la funzionalità renale nei pazienti i DOAC: la formula di Cockroft-Gault

Table 1 Validated equations allowing estimation of renal function

2009 CKD-EPI creatinine equation	$141 \times \min(SCr/k, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [x1.018 if female] [x1.159 if black]
	Where SCr is serum creatinine (in mg dl^{-1}), κ is 0.7 for women and 0.9 for men, a is -0.329 for women and -0.411 for men, min is the minimum of SCr/κ or 1, and max is the maximum of SCr/κ or 1.
MDRD eGFR (ml min^{-1} per 1.73 m^2)	$186 \times$ [serum creatinine (mg dl)]$^{-1.154} \times$ (age)$^{-0.203} \times$ (0.742 if female) $\times$ (1.212 if black)
Cockcroft and Gault formula	[(140-age) $\times$ weight (kg)]/(72 $\times$ creatinine (mg dl^{-1}))(x 0.85 if woman)
2012 CKD-EPI cystatin C equation	$133 \times \min(SCysC/0.8, 1)^{-0.499} \times \max(SCysC/0.8, 1)^{-1.328} \times 0.996^{Age}$ [x 0.932 if female]
	Where SCysC is serum cystatin C (in mg l^{-1}), min indicates the minimum of SCysC/0.8 or 1, and max indicates the maximum of SCysC/0.8 or 1
Cockcroft and Gault formula with ideal body weight (IBW)	IBW for men = 50 + 0.9 $\times$ [length (in cm) − 152]
	IBW for women = 45.5 + 0.9 $\times$ [length (in cm) − 152]

- ✓ All formulae have their limitations
- ✓ Regulatory authorities have to set up guidelines for kidney function estimation in clinical trials and to promote the use of the most appropriate GFR equation for drug dosing
- ✓ Limitations of the CG equation: failure to normalise for body surface area, not validated in a broad sample of patients with CKD
- ✓ CG has the greatest accuracy for patients who are underweight

Ahmed A et al; ESA Guidelines on perioperative venous thromboembolism prophylaxis. Eur J Anesthesiol 2017;34:1-12

Agenda

- ✓ Perchè occuparsi dei DOAC?
- ✓ Avevamo bisogno dei DOAC?
- ✓ Farmacologia minima dei DOAC
- ✓ Quando usare i DOAC?

DOAC nella Fibrillazione Atriale

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose standard	**150 mg x2**	**20 mg x1** **Stomaco pieno**	**5 mg x2**	**60 mgx1**
Dose ridotta	**110 mg x2 se:** **OBBLIGATORIO** Età >80 anni Tp. con verapamil **FACOLTATIVO** ALTO RISCHIO EMORRAGICO	15 mg x1 se: CrCl 30-49 ml/min (cautela 15-30)	2.5 mg x 2 se **ALMENO 2 di:** ≥80 anni ≤ 60 kg Creatinina ≥ 1.5 **OPPURE** CrCl 15-29 ml/min	30 mg x1 se: CrCL 15-50 ml/min < 60 kg Inibitori della P-gp
	110 mg x 2 + SAP (inibitore $P2Y_{12}$) se FA + PCI + stent	15 mg x 1 + SAP 2.5 mg x 1 + DAPT se FA + PCI + stent	5 mg x 2 (riduzione secondo criteri) + inibitore $P2Y_{12}$	

DOAC nel TEV

INDICAZIONE	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
TERAPIA DEL TEV ACUTO Dose standard	**5 gg di EPARINA, poi 150 mgx2**	**- 15 mg x2 per 21 gg poi 20 mg x1**	**- 10 mg x2 per 7 gg poi 5 mgx2**	**5 gg di EPARINA poi 60 mgx1**
Dose ridotta	-	15 mg x2 per 21 gg Poi ↓ se CrCl 30-49 ml/min + rischio emorragico	-	5 gg di EPARINA poi 30 mgx1 se CrCL 15-50 ml/min < 60 kg Inibitori della P-gp
TERAPIA DEL TEV (dopo 6 mesi)	-	10 mg x 1	2.5 mgx2	-

Direct Oral Anticoagulants for the Treatment of Acute Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis

Outcomes	DOACs % (95% CI)	Dalteparin % (95% CI)	RR	95% CI	I^2
Recurrent VTE	5.2% (4.2–6.5)	8.2% (6.9- 9.8)	0.62	0.43–0.91	30%
Major bleeding	4.3% (3.4–5.5)	3.3% (2.5–4.4)	1.31	0.83–2.08	23%
Recurrent PE	3.2% (2.4–4.2)	4.6% (3.6–5.8)	0.71	0.49–1.03	0%
Recurrent DVT	2.2% (1.6–3.1)	3.8% (2.9–4.9)	0.60	0.36–1.00	16%
Fatal PE	0.3% (0.2–0.8)	0.3% (0.1–0.7)	1.25	0.34–4.67	0%
CRNMB	10.4% (8.912.1)	6.4% (5.2–7.7)	1.65	1.19–2.28	29%
CRB	13.7% (12.0–15.6)	9.3% (7.8–10.9)	1.51	1.09–2.09	49%
Fatal bleeding[a]	0.2% (0.07–0.6)	0.3% (0.2–0.8)	0.37	0.07–2.00	0%
All-cause death	23.9% (21.8–26.2)	24.2% (22.1–26.5)	0.99	0.83–1.18	37%

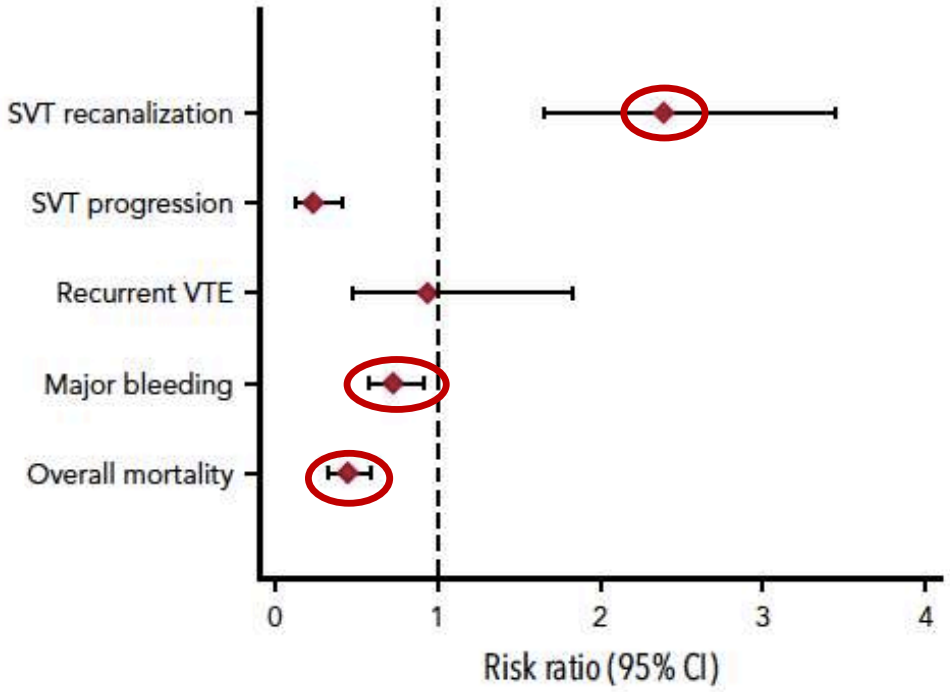
Giustozzi M et al. Thromb Haemost. 2020;120:1128-1136

Distribuzione dei tumori nei RCT su onco-TEV

	Hokusai VTE Cancer		Caravaggio	
	Edoxaban N=522	**Dalteparin N=524**	**Apixaban N=576**	**Dalteparin N=579**
Tumori Solidi – no.(%)				
Colon-retto	83 (15.9)	79 (15.1)	121 (21.0%)	113 (19.5%)
Polmone	77 (14.8)	75 (14.3)	105 (18.2%)	95 (16.4%)
Mammella	64 (12.3)	60 (11.5)	79 (13.7%)	76 (13.1%)
Genitourinari	65 (12.5)	71 (13.5)	66 (11.5%)	73 (12.6%)
Ginecologici	47 (9.0)	63 (12.0)	60 (10.4%)	59 (10.2%)
Pancreatici o epatobiliari	49 (9.4)	40 (7.6)	44 (7.6%)	43 (7.4%)
Gastrointestinali superiori	33 (6.3)	21 (4.0)	23 (4.0%)	31 (5.4%)
Cerebrali	8 (1.5)	12 (2.3)	-	-
Tumori Ematologici – no. (%)	56 (10.7)	55 (10.5)	33 (5.7%)	52 (9.0%)

Raskob G, et al. NEJM 2017; Agnelli G, et al. NEJM 2020

Anticoagulant therapy for splanchnic vein thrombosis: a systematic review and meta-analysis



Outcome	Anticoagulated: events (n/N, %)	Untreated: events (n/N, %)	Studies (n)	I^2 (%)	RR (95% CI)
SVT recanalization	381/667 (57.1)	158/710 (22.3)	25	74	2.39 (1.66-3.44)
SVT progression	16/454 (3.5)	55/383 (14.4)	20	0	0.24 (0.13-0.42)
Recurrent VTE	140/1350 (10.3)	55/498 (11.0)	18	75	0.91 (0.44-1.87)
Major bleeding	287/1927 (14.9)	154/967 (15.9)	28	0	0.73 (0.58-0.92)
Overall mortality	221/1789 (12.2)	204/913 (22.6)	39	28	0.45 (0.33-0.60)

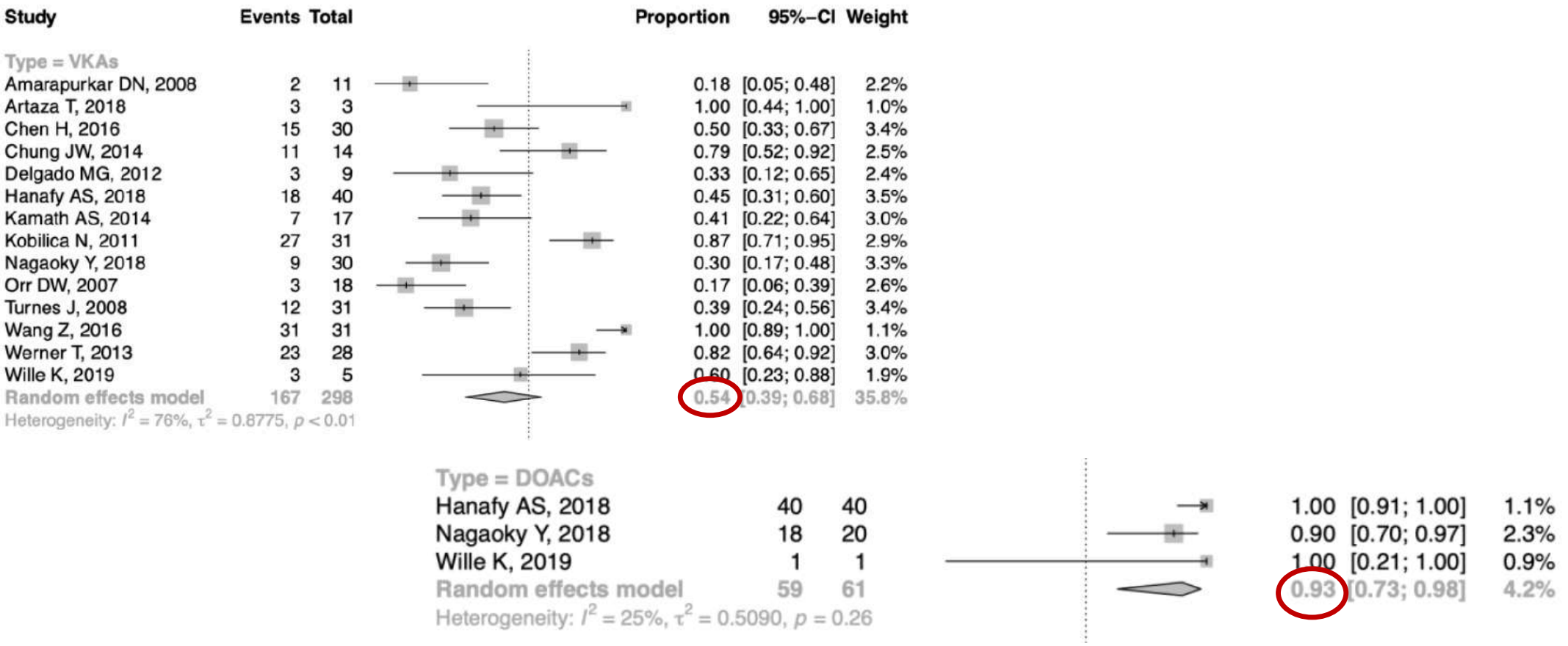
Valeriani E et al. Blood. 2021;137(9):1233-1240)

Anticoagulant therapy for splanchnic vein thrombosis: a systematic review and meta-analysis

	Data	Studies reporting the variable, n
Patients characteristics		
Age, mean (SD), years	49.2 ± 10.3	91
Male sex, n/N (%)	4404/7886 (55.8)	95
Thrombophilia		
JAK2 V617F, n positive/N tested (%)	148/802 (18.5)	9
Antiphospholipid syndrome, n positive/N tested (%)	135/1064 (12.7)	20
Factor V Leiden mutation, n positive/N tested (%)	224/1938 (11.6)	28
Protein C and/or S deficiency, n positive/N tested (%)	125/1085 (11.5)	21
Prothrombin G2021A mutation, n positive/N tested (%)	112/1257 (8.9)	15
Antithrombin-III deficiency, n positive/N tested (%)	30/904 (3.3)	13
Oral anticoagulation		
LMWH→VKAs, n/N (%)	1320/2672 (49.4)	40
VKAs, n/N (%)	1892/5170 (36.6)	39
DOACs, n/N (%)	142/1125 (12.6)	9
Antiplatelet therapy	189/2569 (7.4)	15
Mixed strategies, n/N (%)	505/1817 (27.8)	22
No anticoagulation, n/N (%)	1424/5416 (26.3)	66

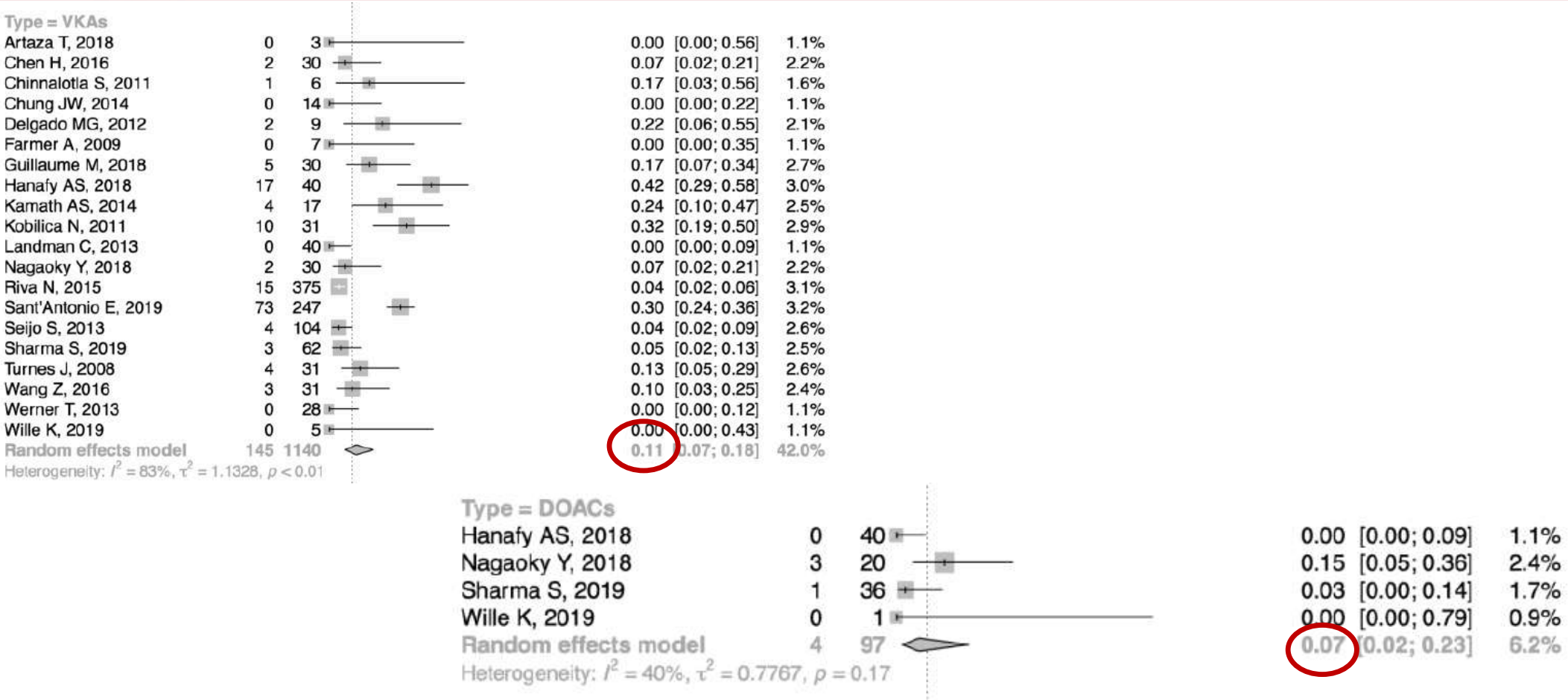
Valeriani E et al. Blood. 2021;137(9):1233-1240)

Supplemental Figure 13: SVT recanalization in patients receiving different types of anticoagulant treatment



Valeriani E et al. Blood. 2021;137(9):1233-1240)

Supplemental Figure 16: Major bleeding in patients receiving different types of anticoagulant treatment



Valeriani E et al. Blood. 2021;137(9):1233-1240)

Direct oral anticoagulants for unusual-site venous thromboembolism

DOACs in specific SVT patients

- Hepatic dysfunction
  → DOACs contraindicated if Child-Pugh class C (rivaroxaban if Child-Pugh classes B-C)
- Severe renal insufficiency
  → DOACs contraindicated if CrCl <15 mL/min* (dabigatran if CrCl <30 mL/min)
- Thrombocytopenia
  → DOACs not recommended if platelet count $<50\times10^9$/L

- Luminal GI cancer
  → Higher risk of GI bleed, poor absorption, CHT interference, vomiting/nausea
- MVT complicated by bowel ischemia
  → Potential DOACs malabsorption
- Chronic SVT or portal cavernoma
  → Case-by-case evaluation
- Gastroesophageal varices
  → Not a contraindication to anticoagulant therapy (consider EGDS, beta-blockers, EBL)
  → Frequently associated with severe liver disease

- Incidentally detected SVT
  → Similar rates of event than symptomatic SVT

Riva N, Ageno W. Res Pract Thromb Haemost. 2021;5:265–277

Addressing and proposing solutions for unmet clinical needs in the management of myeloproliferative neoplasm-associated thrombosis: A consensus-based position paper

The investigators hypothesized that the benefit/harm profile of DOAC treatment will be noninferior to, or better than, usual care with LMWH/VKAs among the MPN patients. The information gained will empower MPN patients and physicians to make more informed choices about anticoagulation strategies to manage VTE.

However, the Panel agreed that while awaiting the results of such a trial, the prevention of recurrent VTE in MPN patients should be based on VKA unless some individual factors prompt using DOACs.

Barbui T et al. Blood Cancer 2019;9:61

Agenda

- ✓ Perchè occuparsi dei DOAC?
- ✓ Avevamo bisogno dei DOAC?
- ✓ Farmacologia minima dei DOAC
- ✓ Quando usare i DOAC?
- ✓ I DOAC in pratica
  - Laboratorio?
  - Manovre invasive?
  - Emorragie maggiori?

Grazie Prof…