Cremona, 4 Marzo2016

A chi e quale NAO

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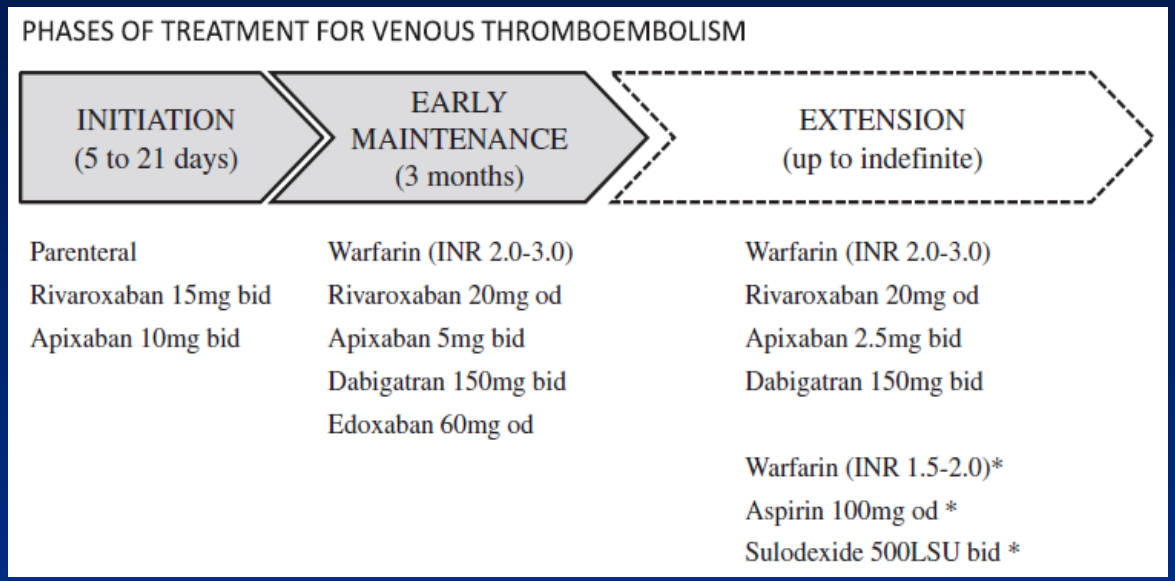
From Blondon & Bounameaux, Circulation 2015



Initial → Long-Term → Extended

From Kearon et al., Chest 2016

Terapia iniziale e lungo-termine TEV: Importanti differenze tra i NOA

- Terapia parenterale per i primi 5-9 gg poi NAO
  - dabigatran (Pradaxa) 150 mg BID
  - edoxaban (Lixiana) 60 mg OID
- Subito NAO
  - rivaroxaban (Xarelto) 15 mg BID x 21 gg poi 20 mg OID
  - apixaban (Eliquis) 10 mg BID x 7 gg poi 5 mg BID

Trial	DOAC Agent; design; no. patients; initial therapy; dosing	Rates of primary efficacy outcomes		Rates of major bleeding events	
		DOAC	Comparator	DOAC	Comparator
		Acute phase treatment			
RE-COVER [5]	Dabigatran; treatment of acute DVT or PE; 2564; initial treatment with LMWH (median 9 d.); 150 mg bid x 6 mo.	1.8 HR = 1.44 (0.78–2.64) P< 0.01 &	1.3%	1.6% HR = 0.82 (0.45-1.48)	1.9% LMWH + W
Einstein-DVT [7]	Rivaroxaban; acute and extended treatment of DVT patients; 3449, single drug treatment since the beginning (3, 6 or 12 mo.); 15 mg bid x 21 d. then 20 mg oid	2.1% HR = 0.68 (0.44-1.04) P<0.001&	3.0%	0.8% HR = 0.65 (0.33-1-30)	1.2% LMWH + W
Einstein-PE [8]	Rivaroxaban; acute and extended treatment of PE patients; 4833; single drug treatment since the beginning (3, 6 or 12 mo.); 15 mg bid x 21 d. then 20 mg oid	2.1% HR = 1.12 (0.75-1.68) P = 0.003&	1.8%	1.1% HR = 0.49 (0.31-0.79; 0.003)	2.2% LMWH + W
Amplify [9]	Apixaban; treatment of acute DVT or PE; 2609; single drug treatment since the beginning; 10 mg bid x 7 d. then 5 mg bid x 6 mo.	2.3% HR = 0.84 (0.60-1.18) P<0.001&	2.7%	0.6 RR = 0.31 (0.17-0.55) p < 0.001#	1.8% LMWH + W
Hokusai [6]	Edoxaban; acute and extended treatment of DVT or PE ; 8240; initial treatment with LMWH (median 7 d.); 60 mg oid	3.2% HR = 0.89 (0.70-1.13) P<0.001&	3.5%	1.4% HR = 0.84 (0.59-1.21)	1.6% LMWH + W

From Palareti G., Semin Hematol 2014

Trial	DOAC Agent; design; no. patients; initial therapy; dosing	Rates of primary efficacy outcomes		Rates of major bleeding events	
		DOAC	Comparator	DOAC	Comparator
		Extended treatment			
RE-MEDY RE-SONATE [10]	Dabigatran; Extended treatment after the first 3 mo.; 150 mg bid				
	RE-MEDY: 2866; comparator W;	1.8% HR = 1.44 (0.78–2.64) P<0.01&	1.3% W	0.9% HR = 0.52 (0.27-1.02) P = 0.06#	1.8% W
	RE-SONATE: 1363; comparator placebo;	0.4 HR = 0.08 (0.02–0.25) p<0.001#	5.6 placebo	0.3%	0 placebo
Amplify Extension [11]	Apixaban; Extended treatment with 2 different doses: 2.5 mg bid or 5 mg bid; 2482; comparator placebo;	2.5 mg bid = 3.8 HR= 0.33 (0.22–0.48) 5 mg bid = 4.2 HR = 0.36 (0.25–0.53) P<0.001# for both comparisons	11.6 placebo	2.5 mg bid = 0.2% HR = 0.49 (0.09-2.64) 5 mg bid = 0.1% HR = 0.25 (0.03-2.24)	0.5% placebo

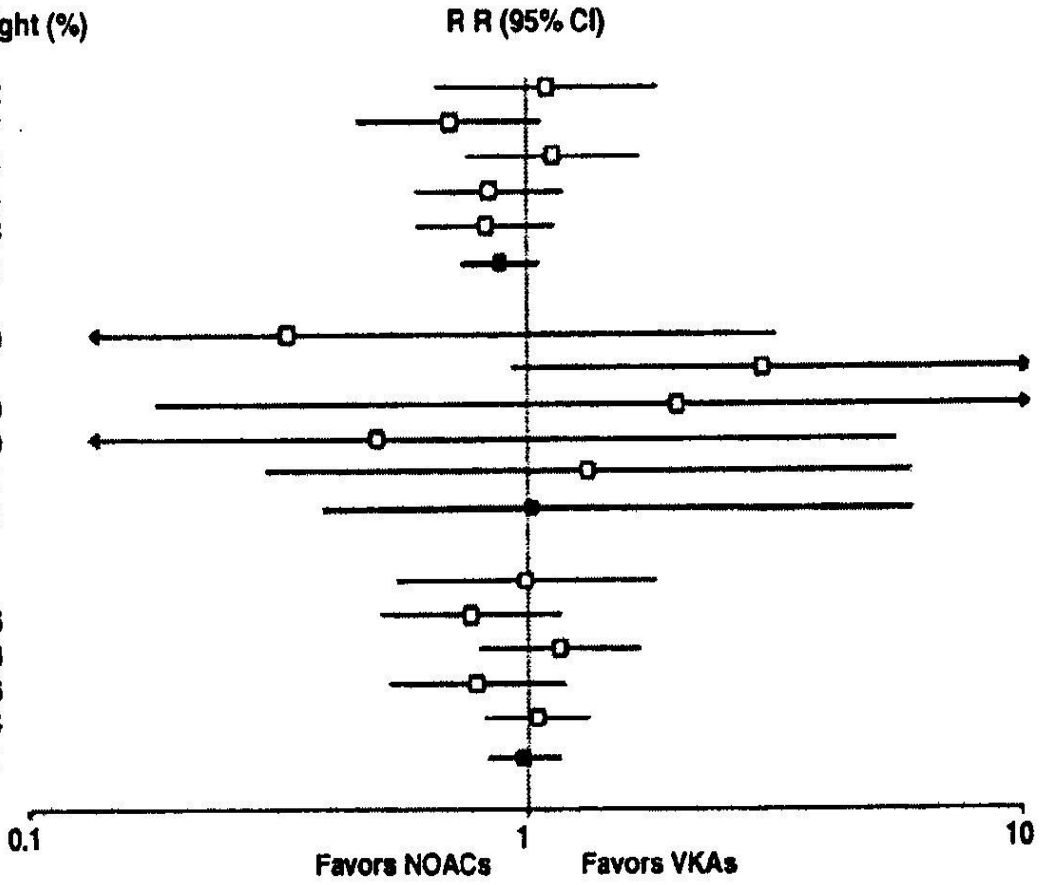
& = statistical significance for non-inferiority; # = statistical significance for superiority

From Palareti G., Semin Hematol 2014

Effectiveness and safety of NOACs as compared with VKAs in the treatment of acute symptomatic VTE: a systematic review and meta-analysis

Efficacy outcomes

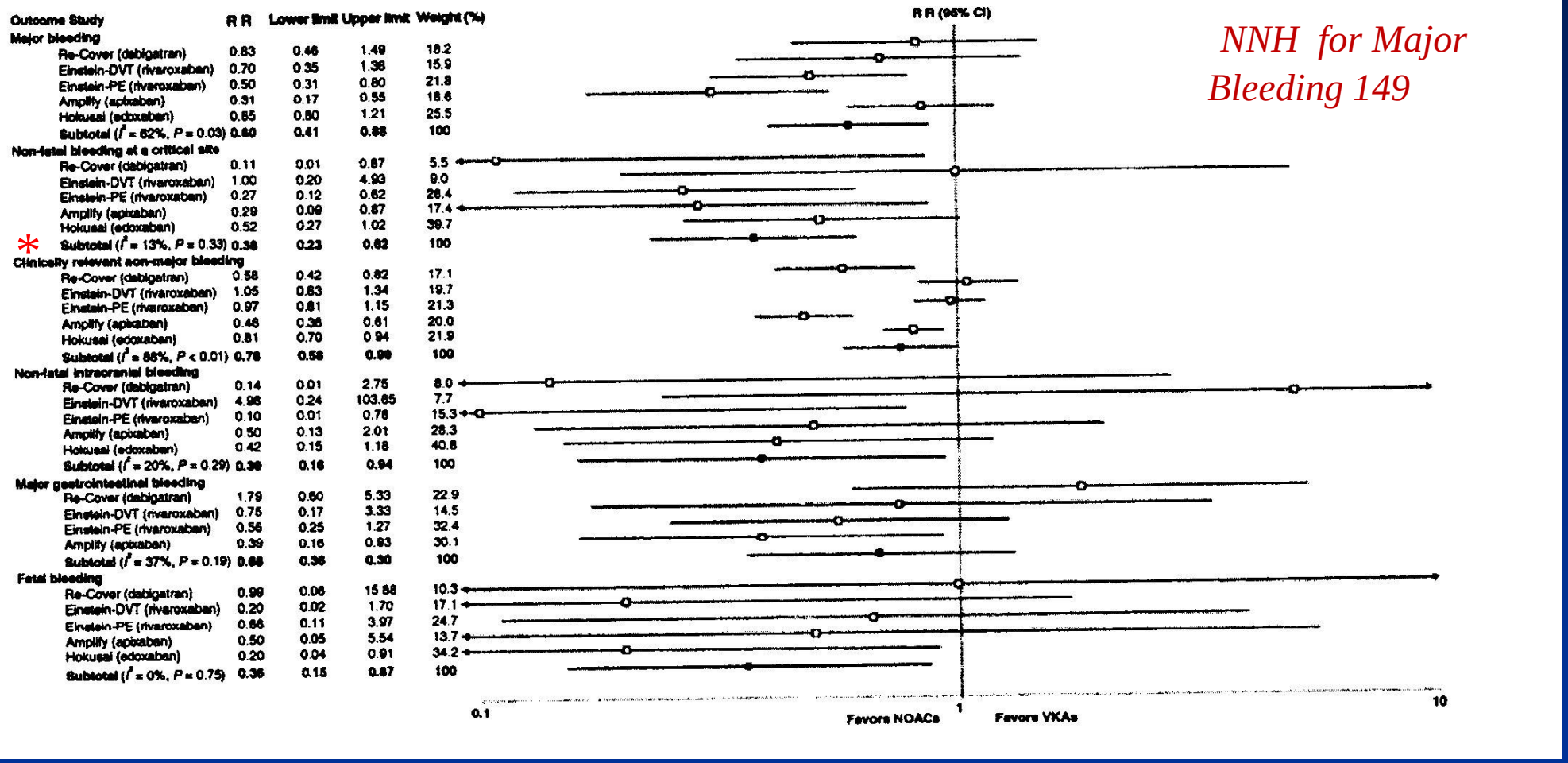
Outcome Study	R R	Lower limit	Upper limit	Weight (%)
Recurrent VTE				
Re-Cover (dabigatran)	1.10	0.66	1.84	11.2
Einstein-DVT (rivaroxaban)	0.70	0.46	1.07	16.7
Einstein-PE (rivaroxaban)	1.13	0.76	1.69	18.4
Amplify (apixaban)	0.84	0.60	1.18	25.4
Hokusai (edoxaban)	0.83	0.60	1.14	28.3
Subtotal (I^2 = 0%, P = 0.46)	**0.88**	**0.74**	**1.05**	**100**
Fatal PE				
Re-Cover (dabigatran)	0.33	0.03	3.18	18.0
Einstein-DVT (rivaroxaban)	2.98	0.12	73.04	9.0
Einstein-PE (rivaroxaban)	2.00	0.18	21.99	16.0
Amplify (apixaban)	0.50	0.05	5.57	16.0
Hokusai (edoxaban)	1.33	0.30	5.96	41.1
Subtotal (I^2 = 0%, P = 0.71)	1.02	0.39	5.96	100
Overall mortality				
Re-Cover (dabigatran)	0.99	0.55	1.81	7.1
Einstein-DVT (rivaroxaban)	0.77	0.51	1.17	14.6
Einstein-PE (rivaroxaban)	1.16	0.80	1.68	18.3
Amplify (apixaban)	0.79	0.53	1.19	15.6
Hokusai (edoxaban)	1.05	0.82	1.33	44.4
Subtotal (I^2 = 0%, P = 0.50)	**0.97**	**0.83**	**1.14**	**100**



Van Der Tulle, J Thromb Haemost, 2014

Effectiveness and safety of NOACs as compared with VKAs in the treatment of acute symptomatic VTE: a systematic review and meta-analysis

Safety outcomes



NNH for Major Bleeding 149

Van Der Tulle, J Thromb Haemost, 2014

Accepted Manuscript

Antithrombotic Therapy for VTE Disease: CHEST Guideline

Clive Kearon, MD, PhD, Elie A. Akl, MD, MPH, PhD, Joseph Ornelas, PhD, Allen Blaivas, DO, FCCP, David Jimenez, MD, PhD, FCCP, Henri Bounameaux, MD, Menno Huisman, MD, PhD, Christopher S. King, MD, FCCP, Timothy Morris, MD, FCCP, Namita Sood, MD, FCCP, Scott M. Stevens, MD, Janine R.E. Vintch, MD, FCCP, Philip Wells, MD, Scott C. Woller, MD, Col. Lisa Moores, MD, FCCP

In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) AC therapy, we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy (all Grade 2B).

For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban or edoxaban, we suggest VKA therapy over LMWH (Grade 2C).

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Reasons for the preference:

1) Similar risk reduction for recurrent VTE with NOACs and VKA;
2) Similar risk reduction with different NOACs (indirect comparisons);
3) Less risk of bleeding with NOACs than with VKA (particularly ICH)
4) Less bleeding with NOACs and greater convenience for patients and healthcare providers.

NAO: Attesa migliore qualità nella fase iniziale del trattamento del TEV

(opinione personale!)

Journal of Thrombosis and Haemostasis, 3: 955–961

ORIGINAL ARTICLE

Poor anticoagulation quality in the first 3 months after unprovoked venous thromboembolism is a risk factor for long-term recurrence

G. PALARETI, C. LEGNANI, B. COSMI, G. GUAZZALOCA, M. CINI and S. MATTAROZZI
Department of Angiology & Blood Coagulation "Marino Golinelli", University Hospital S. Orsola-Malpighi, Bologna, Italy

2005

Table 3 Quality of oral anticoagulation control (percentage of time spent at different INR classes during anticoagulant treatment period for all individual subjects whether they experienced recurrent venous thrombo-embolic events or not [median values (range)]

	Subjects without VTE recurrence	Subjects with VTE recurrence	*P*-value
<1.5 INR	0 (0–40.2)	1.4 (0–14)	0.009
1.5–1.99 INR	13.3 (0–86.9)	15.3 (0–97.8)	0.202
2.0–2.9 INR	74.1 (3.6–100)	66.2 (2.2–90.6)	0.0093
≥3.0 INR	7.9 (0–76.2)	12.2 (0–82.6)	0.277
Median OAT duration (days)	176 (70–903)	169 (92–435)	0.584

2005

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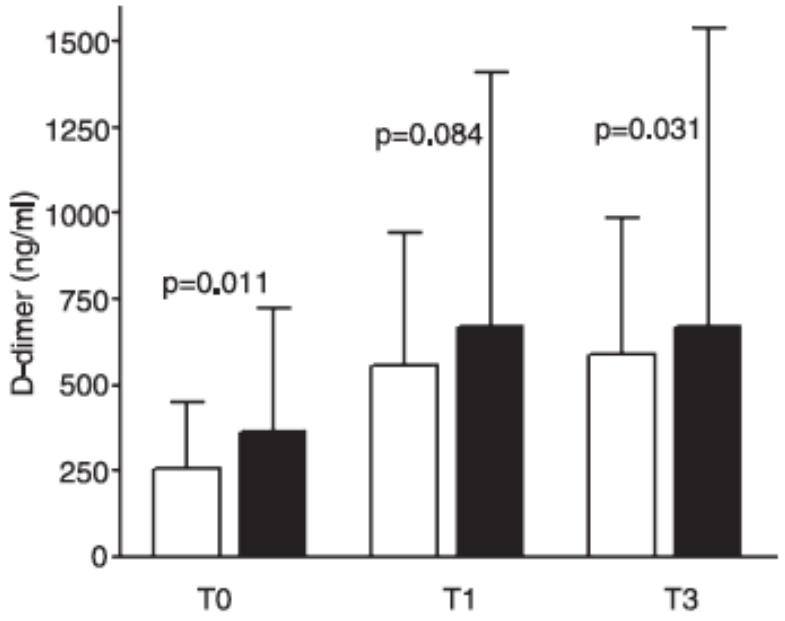

Fig. 1. D-dimer results (median and interquartile range) obtained in subjects whose percentage of time spent at < 1.5 INR was distributed in the first to fourth quintiles (≤3.1%) (open bars) or in the fifth quintile (> 3.1%) (black bars). The test was performed on venous blood sampled the day oral anticoagulation was discontinued (T0), 21–37 days (T1) and 3 months (±10 days) (T3) afterwards.

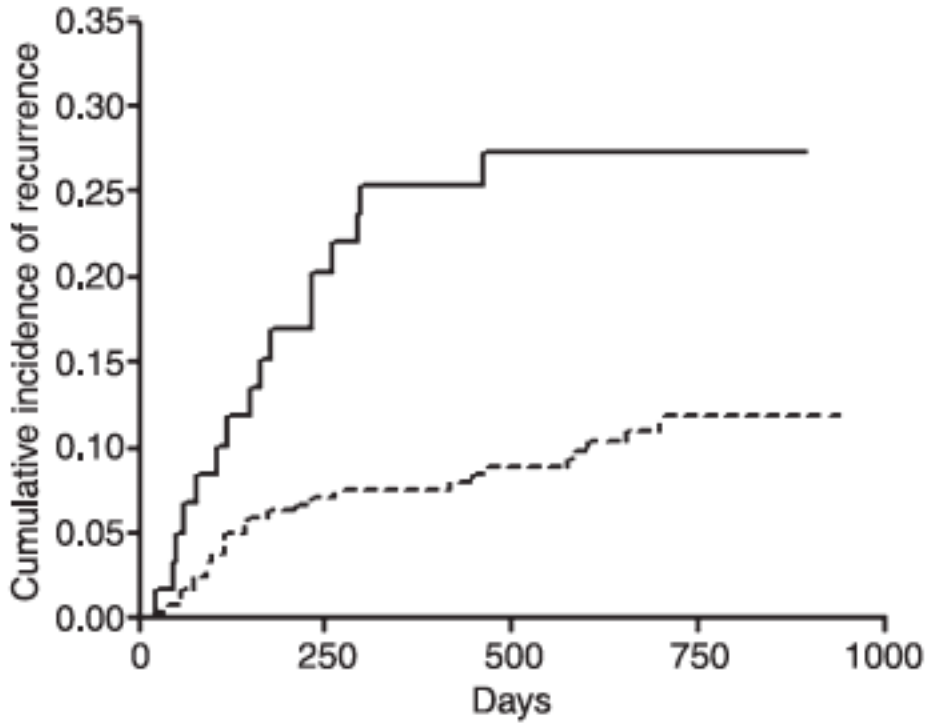

Fig. 2. Cumulative incidence of recurrence after oral anticoagulation interruption in subjects with a previous unprovoked venous thromboembolic event who were in the upper quintile of the percentage of time spent at INR values < 1.5 (continuous line) vs. those in all the other quintiles (dashed line). In each subject the first 90 days of the oral anticoagulant course were considered for analysis, after exclusion of the initial days of anticoagulation induction during treatment with unfractionated or low-molecular-weight heparin. The hazard ratio was 2.77 (95% CI 1.75–8.40).

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2005

Table 4 Relative risk of venous thromboembolism recurrence according to percentage of time spent <1.5 INR

Percentage of time spent <1.5 INR	No. of subjects	No. of recurrences (%)	Univariate relative risk (95% CI)	Multivariate relative risk* (95% CI)
(a) During the first 90 days of oral anticoagulation treatment				
1st–4th quintiles (≤ 3.1%)	238	26 (10.9)	1 (reference)	1 (reference)
5th quintile (>3.1%)	59	16 (27.1) $P = 0.0036$	2.77 (1.49–5.18) $P = 0.001$	2.70 (1.39–5.25) $P = 0.003$
(b) Throughout anticoagulation treatment				
1st–4th quintiles (≤ 3.1%)	238	29 (12.2)	1 (reference)	1 (reference)
5th quintile (>3.1%)	59	13 (22.0) $P = 0.088$	2.05 (1.07–3.96) $P = 0.031$	1.98 (0.98–4.0) $P = 0.056$

START–Register

SURVEY ON ANTICOAGULATED PATIENTS – REGISTER

Registro computerizzato per la raccolta dei dati di pazienti trattati cronicamente con anticoagulanti

Percentuale del tempo trascorso sotto, entro o sopra il range terapeutico nei primi tre mesi di trattamento in relazione alle classi di score

Score	N. of patients (%)	Percentage of time below TR	Percentage of time within TR (TTR)	Percentage of time above TR
Score Groups				
0-1	916 (70%)	31±26.7	61±26	8.4±14
≥ 2	392 (30%)	39±28	53±26	7.7±13.7
P value		p= 0.0001	p= 0.0001	p= 0.61

Palareti et al., Thromb Haemost 2016

Il caso di S.R.

- Maschio, nato 1963
- Novembre 2015 = TVP DX estesa + EP (ricovero)
- Terapia LMWH 8000 x 2 + Coumadin mg/sett. 47-55
- 11 Febbraio 2016 sostituito con Sintrom = sempre < 2.0 INR, sempre LMWH
- 16 Febbraio INR > 2; sospesa LMWH

Pazienti TEV da NON trattare con NAO (1)

- Embolie polmonari emodinamiche
- Possibili indicazioni a trombolisi o manovre invasive
- Recente chirurgia
- Piastrinopenia (salvo HIT)

Pazienti TEV da NON trattare con NAO (2)

- Gravidanza
- Allattamento
- Paziente non compliante
- Insuff. Ren. Grave (tutti); Cl.Creat. <30ml/min Pradaxa; <15 Xarelto
- Insuff. Epatica (Xarelto: Child-Pugh B e C)

Pazienti TEV: non NAO come 1° scelta

- TEV e cancro attivo (1° scelta EBPM)
- TVS (fondaparinux, EBPM)
- Trombosi in sedi inusuali (?)

Table 6: Factors that may influence which anticoagulant is chosen for initial and long-term treatment of VTE

Factor	Preferred anticoagulant	Qualifying remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban, apixaban	VKA, dabigatran and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban, edoxaban, VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised due to liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 ml/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of gastrointestinal bleeding	VKA, apixaban,	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more gastrointestinal bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	Unfractionated heparin infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, unfractionated heparin	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

Kearon et al., Chest 2016

Potenziali pro (e contro) per i pazienti

- Immediata, adeguata e persistente anticoagulazione
- Non controlli periodici e prelievi ematici
- Risparmio di tempo e meno disagi di trasporto
- Meno interferenze con farmaci (e dieta)
- Semplicità del trattamento

(contro)

- Possibili problemi di aderenza alla terapia
- Possibile mancanza di punto di riferimento per problemi intercorrenti

In chi sostituire AVK con NAO

- Instabilità (tempo nel range < 55-60 %)
- Dosi giornaliere molto basse di AVK o con problemi particolari
- Difficoltà/Impossibilità a controlli periodici e monitoraggio regolare
- Emorragie maggiori in corso di INR sovra terapeutico
- (Pazienti con particolare tendenza ad emorragie)
- Emorragie intracraniche (con alto rischio e tenendo conto degli altri fattori personali)
- Necessari farmaci associati interferenti
- Costretti a domicilio (purché ben seguiti)

Commenti personali

- Evitata l'instabilità e difficoltà iniziale degli AVK (con potenziali effetti su recidiva)
- > scelta terapeutica in generale
- > scelta per singoli pazienti (gravità del quadro clinico iniziale, compliance, ecc.)
- Tutti non inferiori per efficacia (anche per EP)
- Tendenza a < emorragie (significativa per alcuni)
- Potenziale > facilità per il trattamento esteso

Grazie