Gli anticoagulanti orali diretti (DOACs) per il trattamento prolungato del TEV

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Il *sottoscritto Imberti Davide*

dichiara

di aver avuto negli ultimi due anni rapporti di consulenza con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

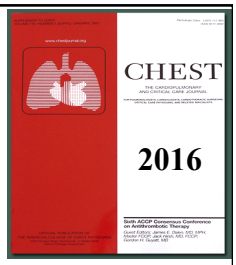
- ***ALFA WASSERMANN***
- ***BAYER***
- ***BMS-PFIZER***
- ***BOHERINGER INGELHEIM***
- ***DAIICHI-SANKYO***
- ***IL***
- ***ITALFARMACO***
- ***KEDRION***
- ***SANOFI AVENTIS***
- ***WERFEN***

Annualized recurrence rates after venous thromboembolism

	VTE recurrence at 1 year
1st VTE provoked by surgery	1%
1st VTE provoked by nonsurgical risk factor	5%
1st unprovoked VTE	10%
2nd unprovoked VTE	15%

Kearon, Chest, 2012

ACCP 2016 Treatment of VTE Secondary prevention



In patients with an unprovoked DVT of the leg or PE we recommend anticoagulant treatment for 3 months over treatment of a longer time-limited period (e.g. 6,12 or 24 months) (Grade 1B) **.**

In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE with low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B) **.**

Kearon, Chest, 2016

After acute treatment?

Stop therapy

Aspirin, Sulodexide

Extended anticoagulant therapy (VKAs, DOACs)

- D Dimer, RVO
- Risk stratification models

VTE treatment: optimal duration

4 studies, n=1184 pts	VTE recurrence at 1 year	RR (CI 95%) extended / no extended
1st VTE provoked by surgery	1%	
1st VTE provoked by nonsurgical risk factor	5%	
1st unprovoked VTE	10%	**0.12 [0.05–0.25]**
2nd unprovoked VTE	15%	

	Major bleeding at 1 year	RR (CI 95%) extended / no extended
1st VTE provoked by surgery	0.3%	
1st VTE provoked by nonsurgical risk factor	0.6%	**2.63 [1.02–6.76]**
1st unprovoked VTE	2.4%	

Kearon, Chest, 2012

Einstein, Amplify, Remedy, Resonate: EXTENSION STUDIES

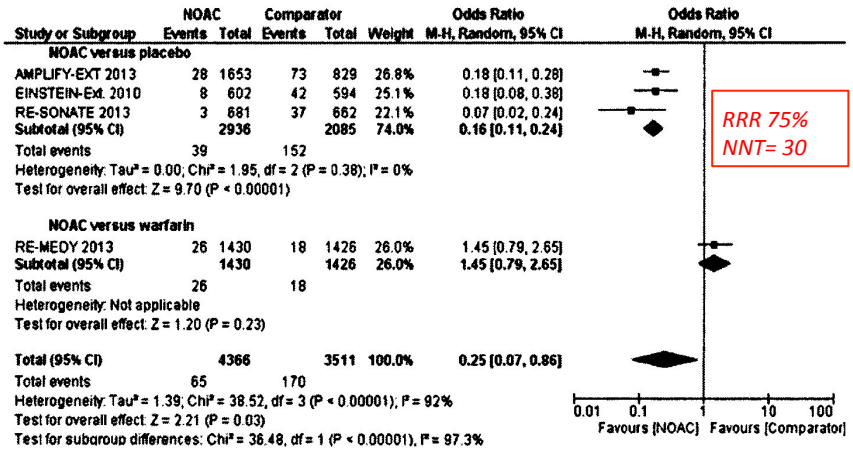
Study	Indication	Patients (n°)	Drug	Recurrent VTE (%) #	Major bleeding (%) #
EINSTEIN EXTENSION	Extension VTE	1196	Rivaroxaban 20 mg o.d. Vs placebo	1.3 vs 7.1 P<0.001**	0.7 vs 0 P=0.11*
AMPLIFY EXTENSION	Extension VTE	2486	Apixaban 2.5 mg b.d. or 5 mg b.d. Vs placebo	3.8 vs 4.2 vs 11.6 P<0.001	0.2 vs 0.1 vs 0.5
REMEDY	Extension VTE	2856	Dabigatran 150 mg b.d. Vs warfarin	1.8 vs 1.3 P=0.03*	0.9 vs 1.8 P=0.058* RRR -31%
RESONATE	Extension VTE	1343	Dabigatran 150 mg b.d. Vs placebo	0.4 vs 5.6 P<0.0001**	0.3 vs 0 P=0.996*
EINSTEIN CHOICE	Extension VTE	3396	Rivaroxaban 20 mg o.d. or 10 mg o.d. Vs ASA 100 mg	1.5 vs 1.2 vs 4.4 P<0.001	05 vs 0.4 vs 0.3

drugs vs comparator (%)
* for non inferiority, ** for superiority
≠ major and clinical relevant non major bleeding

Imberti, Internal Emerg Med, 2016 (mod)

Efficacy and safety of NOACs for extended treatment of VTE: systematic review and meta-analyses of RCTs

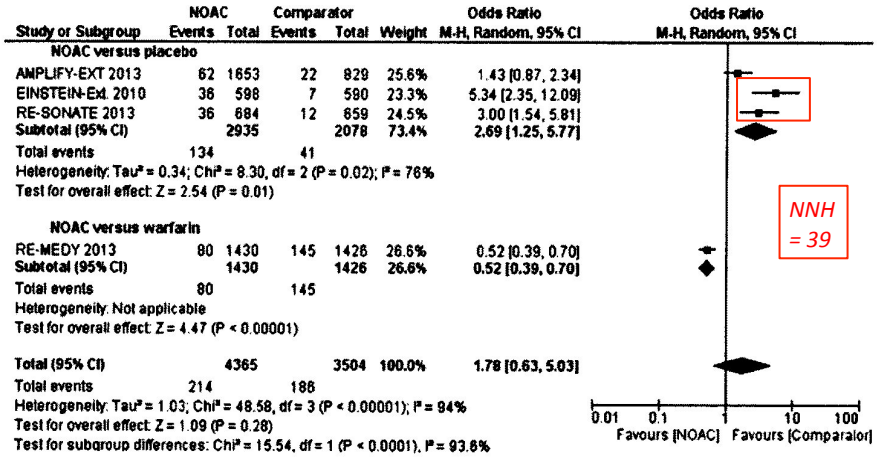
Recurrent VTE or VTE-related death



Sardar, Drugs, 2013

Efficacy and safety of NOACs for extended treatment of VTE: systematic review and meta-analyses of RCTs

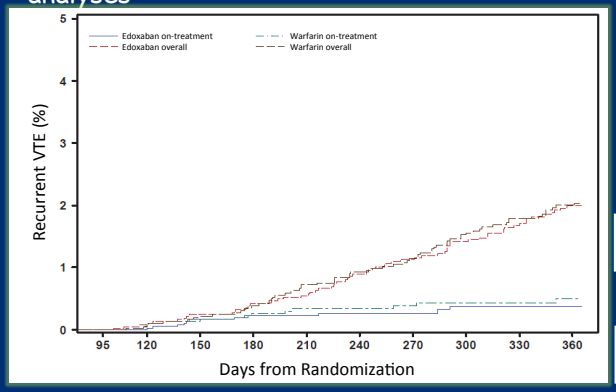
Major or CRNMB



Sardar, Drugs, 2013

HOKUSAI: Extended Treatment Period (>3 – 12 Months)

- Cumulative incidence of recurrent VTE was similar between edoxaban and warfarin for both on-treatment and overall analyses



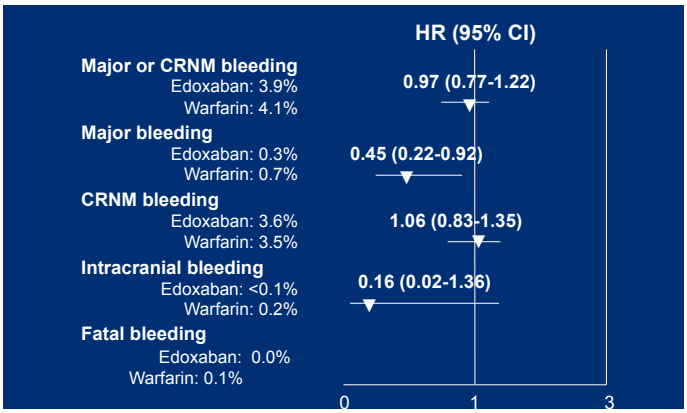
Warfarin overall
Edoxaban overall
HR 0.97
(95% CI 0.7-1.4)

Warfarin on-treatment
Edoxaban on-treatment
HR 0.78
(95% CI 0.36-1.72)

Raskob, Lancet Haematol, 2016

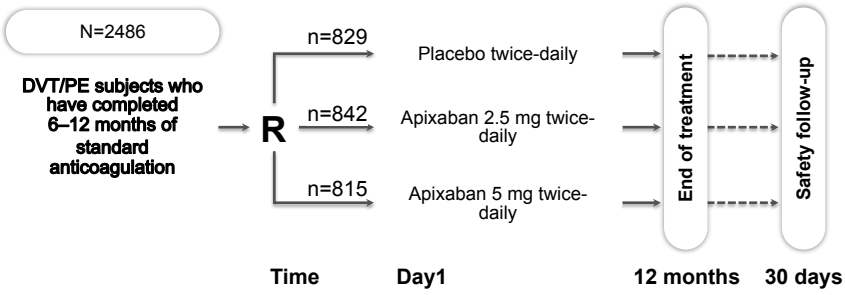
HOKUSAI: Extended Treatment Period (>3 – 12 Months)

- Significantly lower incidence of major bleeding was observed with edoxaban vs warfarin during the extended treatment period in the on-treatment analysis

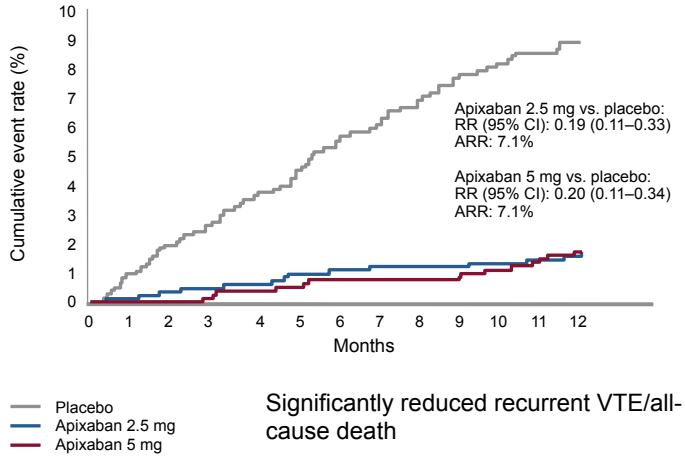


Raskob, Lancet Haematol, 2016

AMPLIFY-EXT:
12-month double-blind placebo-controlled extended treatment study



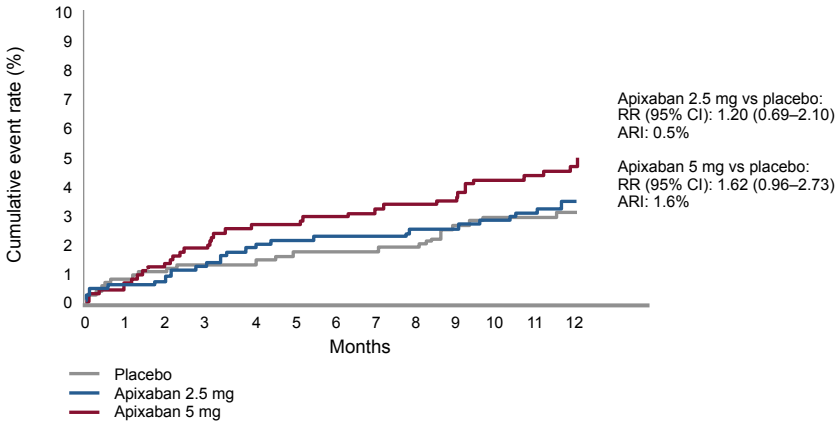
Fatal/non-fatal VTE: apixaban demonstrated superior efficacy to placebo



Significantly reduced recurrent VTE/all-cause death

Agnelli , N Engl J Med, 2013

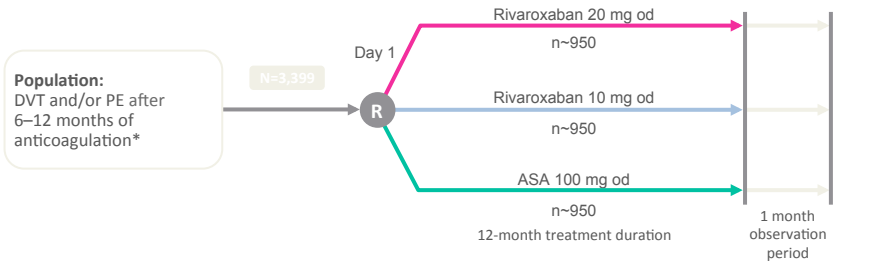
Apixaban demonstrated a similar incidence of major/CRNM bleeding as placebo



EINSTEIN CHOICE: Study Design

Official study title: Reduced-dosed Rivaroxaban and Standard-dosed Rivaroxaban Versus ASA in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis and/or Pulmonary Embolism

Objective: efficacy and safety of reduced-dosed rivaroxaban, standard-dosed rivaroxaban versus ASA for the long-term secondary prevention of recurrent symptomatic VTE in patients with symptomatic DVT and/or PE



Short design: Multicentre, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority study

Indication: VTE prevention

FPFV: Q1-14
LPLV: Q4-16

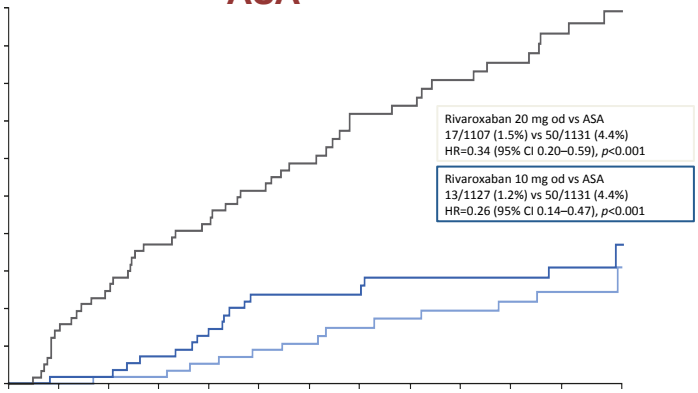
*Completed 6–12 months (±1 month) with interruption of anticoagulation ≤1 week at randomization
www.clinicaltrials.gov/ct2/show/NCT02064439; Weitz JI *et al*, *Thromb Haemost* 2015;114:645–650

Clinical Characteristics*

Outcome		Rivaroxaban 20 mg (n=1107)	Rivaroxaban 10 mg (n=1127)	Aspirin 100 mg (n=1131)
Index event, n (%)	DVT	565 (51.0)	565 (50.1)	577 (51.0)
	PE	381 (34.4)	381 (33.8)	366 (32.4)
	Both	155 (14.0)	179 (15.9)	181 (16.0)
	Asymptomatic or unconf.	6 (0.5)	2 (0.2)	7 (0.6)
Classification of index VTE, n (%)	Unprovoked	441 (39.8)	480 (42.6)	468 (41.4)
	Provoked	**666 (60.2)**	**647 (57.4)**	**663 (58.6)**
History of prior VTE, n (%)		198 (17.9)	197 (17.5)	194 (17.2)
Known thrombophilia, n (%)		79 (7.1)	74 (6.6)	70 (6.2)
Active cancer, n (%)		25 (2.3)	27 (2.4)	37 (3.3)
Study drug duration (median days, IQR)		349 (189-362)	353 (190-362)	350 (186-362)

*Differences in baseline characteristics were not significant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism, IQR, Interquartile range
Weitz JI *et al*, *N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Both Rivaroxaban Doses Provided Superior Reduction in Recurrent VTE Rates Compared with ASA



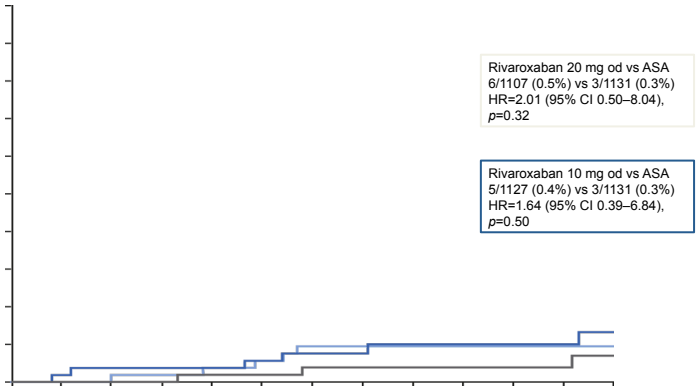
Number of patients at risk													
Rivaroxaban 20 mg od	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban 10 mg od	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
ASA 100 mg od	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

Both Rivaroxaban Doses Reduced VTE Recurrence Versus ASA in a Broad Spectrum of Patients

	Rivaroxaban 20 mg od (n=1107)	Rivaroxaban 10 mg od (n=1127)	ASA 100 mg od (n=1131)
Recurrent VTE, all patients, n/N (%)	17/1107 (1.5)	13/1127 (1.2)	50/1131 (4.4)
Risk profile, n/N (%)			
Unprovoked index event	8/441 (1.8)	7/480 (1.5)	26/468 (5.6)
Provoked index event	9/666 (1.4)	6/647 (0.9)	24/663 (3.6)
History of previous VTE, n/N (%)			
Yes	3/198 (1.5)	2/197 (1.0)	17/194 (8.8)
No	14/909 (1.5)	11/930 (1.2)	33/937 (3.5)
Duration of anticoagulation prior to randomization, n/N (%)			
<9 months	12/774 (1.6)	7/782 (0.9)	35/793 (4.4)
≥9 months	5/333 (1.5)	6/345 (1.7)	15/338 (4.4)

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

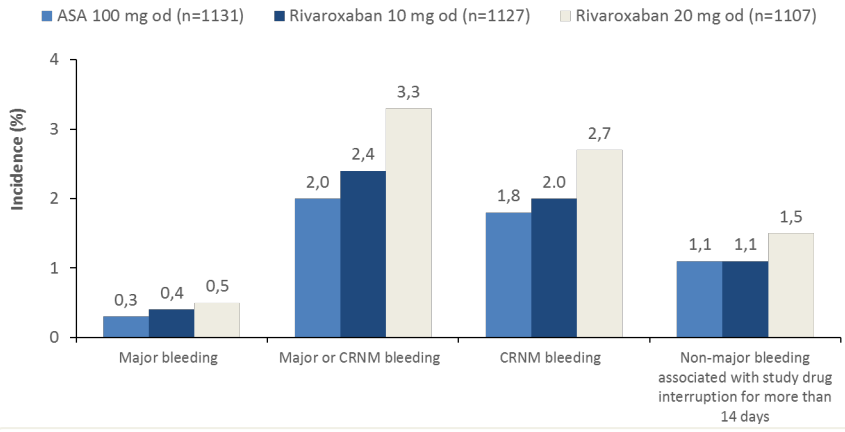
Rates of Major Bleeding Were ≤0.5% and Similar to ASA



Number of patients at risk

Rivaroxaban 20 mg od	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449
Rivaroxaban 10 mg od	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469
ASA 100 mg od	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445

Bleeding Outcome Analyses



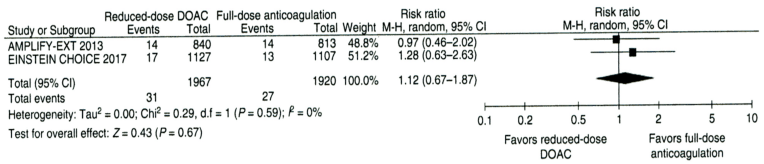
Similar rates of bleeding were observed in the rivaroxaban and ASA treatment groups

Major Bleeding Rates Were Similar Across Different Patient Subgroups

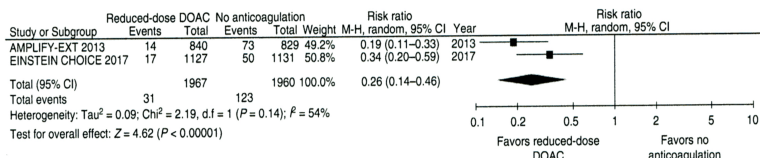
	Rivaroxaban 20 mg od (n=1107)	Rivaroxaban 10 mg od (n=1127)	ASA 100 mg od (n=1131)
Major bleeding, all patients, n/N (%)	6/1107 (0.5)	5/1127 (0.4)	3/1131 (0.3)
Risk profile, n/N (%)			
Unprovoked index event	4/441 (0.9)	2/480 (0.4)	1/468 (0.2)
Provoked index event	2/666 (0.3)	3/647 (0.5)	2/663 (0.3)
History of previous VTE, n/N (%)			
Yes	2/198 (1.0)	0/197 (0.0)	1/194 (0.5)
No	4/909 (0.4)	5/930 (0.5)	2/937 (0.2)
Duration of anticoagulation prior to randomization, n/N (%)			
<9 months	3/774 (0.4)	3/782 (0.4)	3/793 (0.4)
≥9 months	3/333 (0.9)	2/345 (0.6)	0/338 (0)

Weitz JI *et al, N Engl J Med* 2017:doi:10.1056/NEJMoa1700518

Reduced-dose DOACs in the extended treatment of VTE: a systematic review and meta-analysis



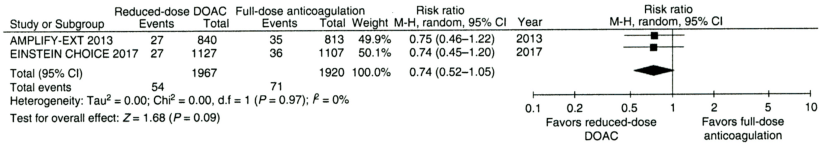
VTE recurrence with reduced dose vs full dose



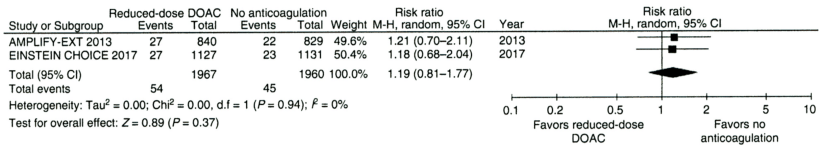
VTE recurrence with reduced dose vs no anticoagulation

Vasanthamohan, JTH, 2018

Reduced-dose DOACs in the extended treatment of VTE: a systematic review and meta-analysis



MB or CRNMB with reduced dose vs full dose



MB or CRNMB with reduced dose vs no anticoagulation

Vasanthamohan, JTH, 2018