NEWER ORAL ANTICOAGULANTS

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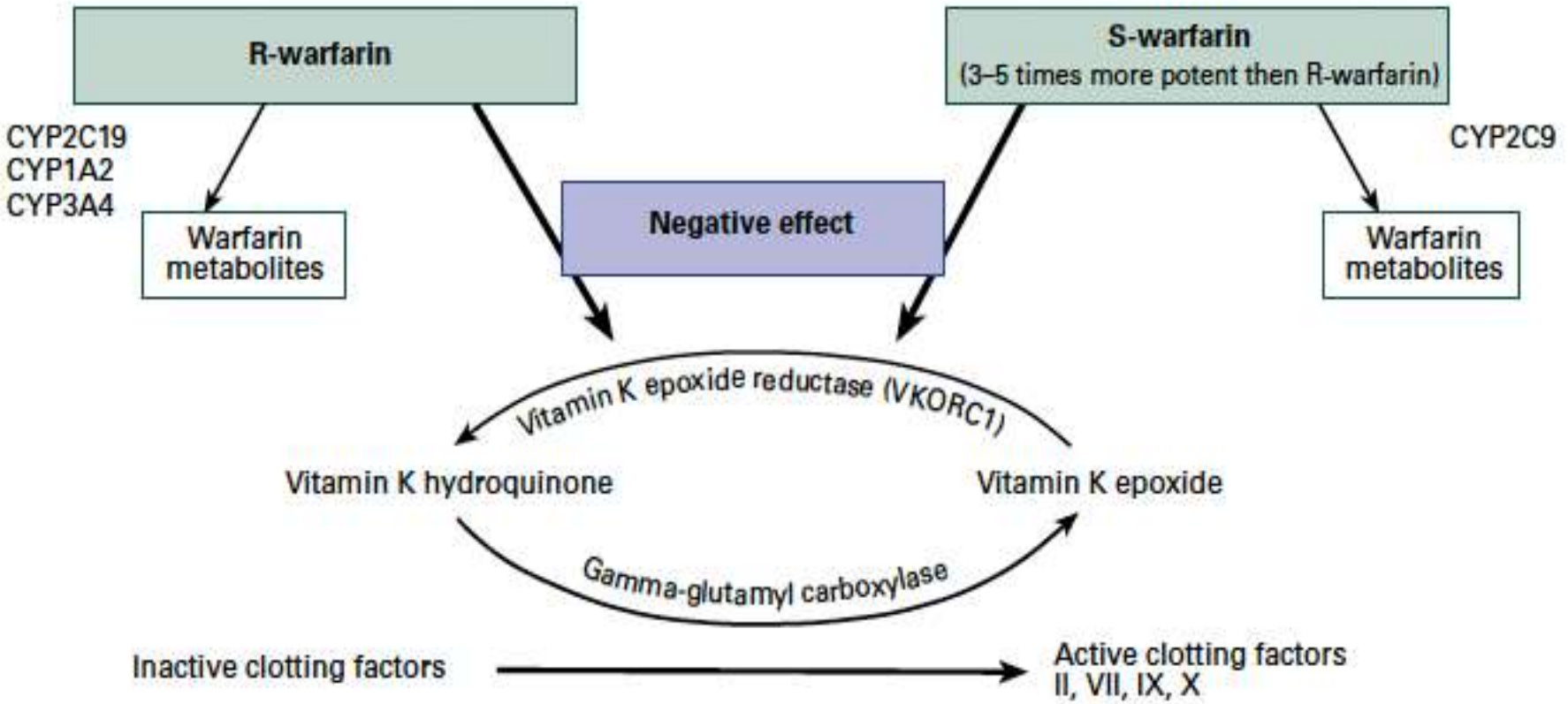
ORAL ANTICOAGULANTS CLASSIFICATION

- Vitamin K antagonists (VKA)
  - Warfarin
  - Acenocoumarol
- Non vitamin K oral anticoagulants (NOAC)
  - Direct thrombin inhibitors
    - Ximelagatran - NOT FDA APPROVED
    - Dabigatran (Pradaxa)
  - Activated Factor X inhibitors
    - Rivaroxaban (Xarelto)
    - Apixaban (Eliquis)
    - Edoxaban(Savaysa)
    - Betrixaban (Bevyxxa)

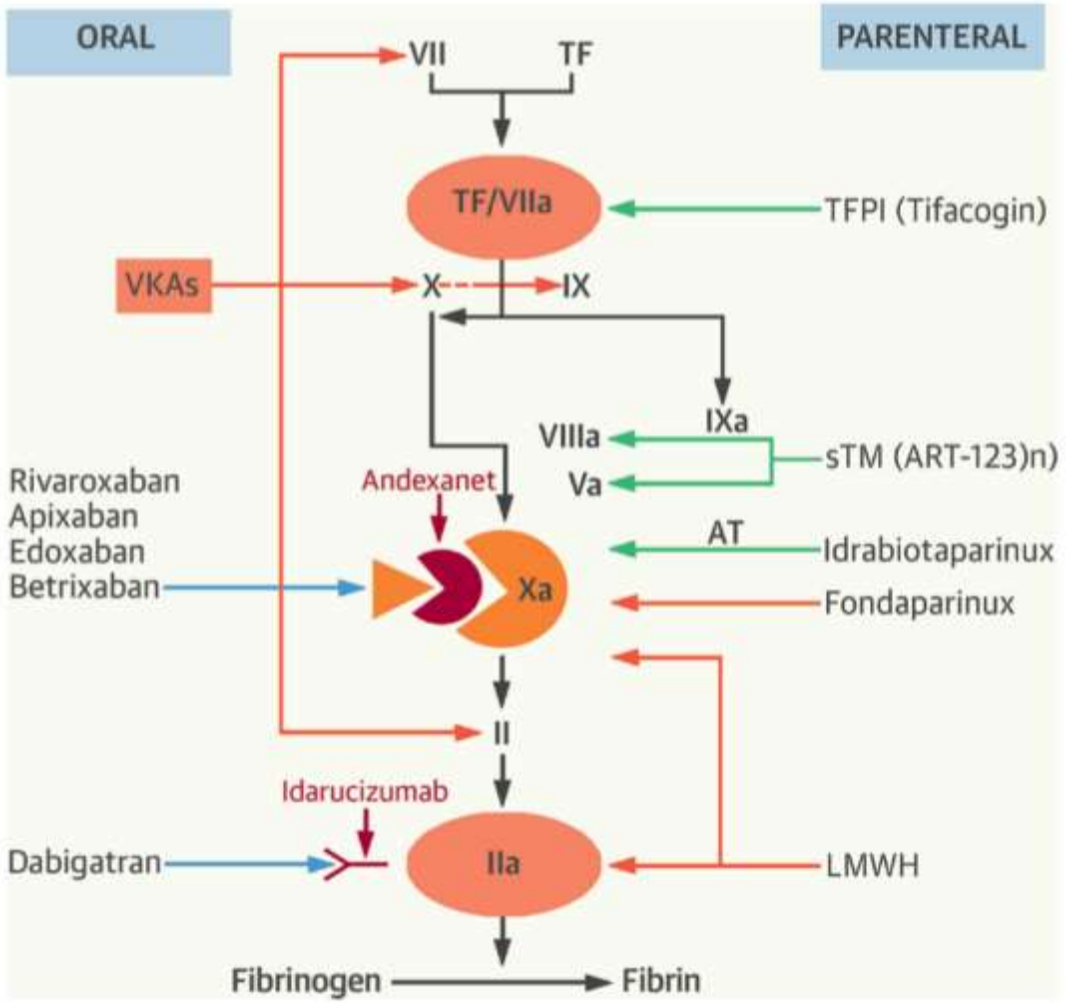
FDA APPROVED

MECHANISM OF ACTION OF VKA



VKA – VITAMIN K ANTAGONISTS

MECHANISM OF ACTION OF NOACs



DTI and Factor Xa inhibitors act on both soluble and clot bound thrombin and factor Xa respectively

TFPI-TISSUE FACTOR PATHWAY INHIBITOR

Mohammed A et al. Curr Emerg Hosp Med Rep. 2013; 1(2): 83–97
Becattini, C. et al. J Am Coll Cardiol. 2016;67(16):1941–55

WARFARIN VS ACENOCOUMAROL

PROPERTIES	ACENOCOUMAROL	WARFARIN
ORAL ABSORPTION	RAPID	RAPID
PEAK CONCENTRATION	2-3 HOURS	4 HOURS
HALF LIFE	10.9 HOURS (SHORT)	30-80 HOURS (LONG)
DURATION OF ACTION	2 DAYS	2-5 DAYS
ANTICOAGULATION STABILITY	++	+
FOOD INTERACTION	++	++
DEPENDANCE ON CYP2C9	+	++

- ACENOCOUMAROL HAS RAPID ONSET AND SHORTER DURATION OF ACTION
- REVERSAL IS RAPID WITH SMALL DOSES OF VITAMIN K

BUT BOTH REQUIRE INR MONITORING AND HAVE FOOD AND DRUG INTERACTIONS

Trailokya A et al. J Assoc Physicians India. 2016 ;64(2):88-93

IDEAL ANTICOAGULANT

1. Effective and safe as heparin and VKAs
2. Available in both a parenteral and an oral formulation
3. Rapidly acting, with excellent bioavailability
4. Low protein binding and rapid elimination
5. Free of significant food or drug interactions
6. Predictable effect and a wide therapeutic window
7. No need for close monitoring
8. Lack significant toxicities unrelated to the anticoagulant activity
9. Target a specific free and clot-bound coagulation factor
10. Have a specific antidote with rapid reversal
11. Cost effective

NO SUCH IDEAL ANTICOAGULANT AS OF NOW

NOAC VS VKA

Properties	VKA (warfarin)	NOAC
Mechanism of action	Indirect via Vitamin K Epoxide reductase	Direct target
Onset of action	Delayed (36-72 hours)	Faster (< 4 hours)
Half life	Longer (32-42 hours)	Shorter (<15 hours)
Metabolism	Hepatic	Renal/unchanged excretion in feces
Bioavailability	High	Low
Monitoring	INR –Required in all cases	Only in special circumstances
Antidote	Vitamin K (Easily available and cheap)	Idarucizumab/Andexanet alfa (Difficult to procure and costly)
Food and drug interactions	More	Less
Therapeutic window	Wide	Narrow
Cost	Cheap	Expensive
Risk of skin necrosis	Yes	No
Clinical experience	Higher	Lower

Mekaj YH et al. Ther Clin Risk Manag. 2015 ;11:967-77

PHARMACOKINETICS

PROPERTIES	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN	BETRIXABAN
PRODRUG	YES	NO	NO	NO	NO
PEAK ONSET(hours)	2	3	3	2	3.5
HALF LIFE (hours)	14-17	7-11	12	10-14	19-27
ELIMINATION	85% - Renal 15% - Stool	33% - Renal 66% - Hepatic	25% - Renal 75% - Stool	35% - Renal 65% - Stool	11%- Renal 85%- Stool Rest - hepatic
DRUG INTERACTION	P-glycoprotein inhibitors and inducers	CYP3A4 and P-glycoprotein inhibitors and inducers	Strong CYP3A4 inhibitors and inducers	Potent P-glycoprotein inhibitors	P – glycoprotein inhibitors

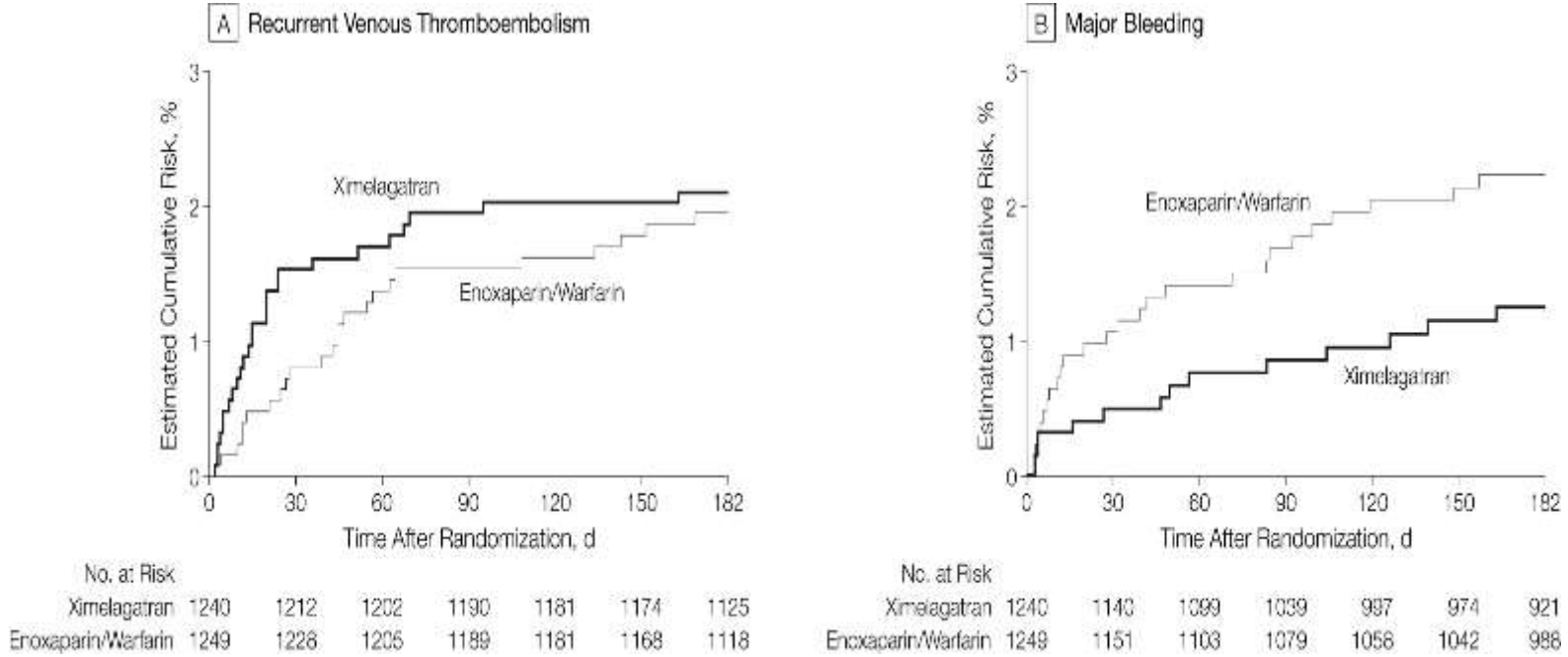
King CS et al. Chest. 2013;143(4):1106-1116

XIMELAGATRAN

- First oral DTI used in clinical trials
- THRIVE TRIAL – 2528 DVT patients
- Ximelagatran dose used 36mg BD

BLEEDING AND RECURRENT VTE – NON INFERIOR RESULTS

HEPATOTOXICITY
XIMELAGATRAN VS ENOXAPARIN/WARFARIN
9.6% vs 2%



Fiessinger JN et al. JAMA. 2005;293(6):681-689

XIMELAGATRAN

EXTEND TRIAL

- Ximelagatran vs Enoxaparin for VTE prophylaxis after hip surgery
- 1158 patients
- Significant liver toxicity with Ximelagatran

- NO FDA APPROVAL
- WITHDRAWN FROM MARKET

Agnelli G et al. Thromb Res. 2009;123(3):488-97

CLINICAL APPLICATIONS

VTE prophylaxis

VTE treatment

Stroke prophylaxis in Atrial Fibrillation

Special scenarios

VTE PROPHYLAXIS

- Trials
- Guidelines

DABIGATRAN – POST SURGERY

TRIAL	COMPARATOR	OUTCOME
BISTRO I	NO	NO MAJOR BLEEDING
BISTRO II	ENOXAPARIN 40mg OD	LOWER VTE RISK
RE-MODEL (150mg OD/220mg OD)	ENOXAPARIN 40mg OD	NON INFERIOR
RE-NOVATE I (150mg OD/220mg OD)	ENOXAPARIN 40mg OD	NON INFERIOR
RE-NOVATE II (150mg OD/220mg OD)	ENOXAPARIN 40mg OD	NON INFERIOR
RE-MOBILZE (150mg OD/220mg OD)	ENOXAPARIN 30mg BD	INFERIOR

VERDICT

- NON INFERIOR TO ENOXAPARIN (40mgOD)
- SIMILAR BLEEDING RISK

RIVAROXABAN

TRIAL	COMPARATOR	OUTCOME
ODIXa-HIP	ENOXAPARIN	NON INFERIOR
ODIXa-KNEE	ENOXAPARIN	NON INFERIOR
ODIXa-OD-HIP	ENOXAPARIN	NON INFERIOR
RECORD 1,2,3,4 (10mg) (Post surgical cases)	ENOXAPARIN (40mg)	• SUPERIOR TO ENOXAPARIN • SIMILAR BLEEDING RISK
MAGELLAN (10mg) (Medically ill patients)	ENOXAPARIN (40mg)	• SUPERIOR TO ENOXAPARIN • HIGHER BLEEDING RISK

RIVAROXABAN - MAGELLAN TRIAL

Outcome	Day 10				Day 35			
	Rivaroxaban (N=2938)	Enoxaparin (N=2993)	Relative Risk (95% CI)*	P Value†	Rivaroxaban (N=2967)	Enoxaparin–Placebo (N=3057)	Relative Risk (95% CI)*	P Value†
	no. (%)				*no. (%)*			
Composite primary efficacy outcome	78 (2.7)	82 (2.7)	0.97 (0.71–1.31)	0.003	131 (4.4)	175 (5.7)	0.77 (0.62–0.96)	0.02
Asymptomatic proximal DVT	71 (2.4)	71 (2.4)	—	—	103 (3.5)	133 (4.4)	—	—
Symptomatic proximal or distal DVT	7 (0.2)	6 (0.2)	—	—	13 (0.4)	15 (0.5)	—	—
Symptomatic nonfatal pulmonary embolism	6 (0.2)	2 (<0.1)	—	—	10 (0.3)	14 (0.5)	—	—
VTE-related death	3 (0.1)	6 (0.2)	—	—	19 (0.6)	30 (1.0)	—	—

Outcome	Rivaroxaban (N=3997)	Enoxaparin–Placebo (N=4001)	Relative Risk (95% CI)	P Value
	no. (%)			
Clinically relevant bleeding: principal safety outcome at day 10	111 (2.8)	49 (1.2)	2.3 (1.63–3.17)	<0.001
Any major bleeding	24 (0.6)	11 (0.3)	2.2 (1.07–4.45)	0.03
Major bleeding leading to fall in hemoglobin of ≥2 g/dl	17 (0.4)	7 (0.2)	—	—
Major bleeding leading to transfusion of ≥2 units of blood	15 (0.4)	5 (0.1)	—	—
Major bleeding at a critical site	5 (0.1)	1 (<0.1)	—	—
Fatal major bleeding	5 (0.1)	1 (<0.1)	—	—
Clinically relevant bleeding: principal safety outcome at day 35	164 (4.1)	67 (1.7)	2.5 (1.85–3.25)	<0.001
Any major bleeding	43 (1.1)	15 (0.4)	2.9 (1.60–5.15)	<0.001
Major bleeding leading to fall in hemoglobin of ≥2 g/dl	31 (0.8)	10 (0.2)	—	—
Major bleeding leading to transfusion of ≥2 units of blood	24 (0.6)	8 (0.2)	—	—
Major bleeding at a critical site	9 (0.2)	4 (0.1)	—	—
Fatal major bleeding	7 (0.2)	1 (<0.1)	—	—
Other safety outcomes				
Any cardiovascular event during treatment†	51 (1.3)	49 (1.2)	—	—
Any adverse event during treatment, excluding bleeding	2616 (65.4)	2607 (65.2)	—	—
Any serious adverse event during treatment, excluding bleeding	616 (15.4)	569 (14.2)	—	—

Rivaroxaban superior than enoxaparin for VTE prophylaxis but with higher bleeding risk in medically ill patients

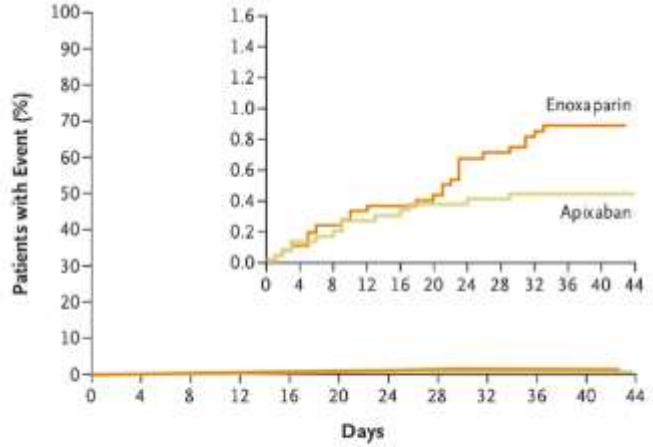
Cohen AT et al. N Engl J Med. 2013 Feb 7;368(6):513-23

APIXABAN - POST SURGERY

TRIAL	COMPARATOR	DURATION OF PROPHYLAXIS	OUTCOME
ADVANCE 1 (2.5mg BD)	ENOXAPARIN 30mg BD	12 DAYS	INFERIOR, LESSER BLEEDING
ADVANCE 2 (2.5mg BD)	ENOXAPARIN 40 mg OD	12 DAYS	NON INFERIOR, SIMILAR BLEEDING
ADVANCE 3 (2.5mg BD)	ENOXAPARIN 40mg OD	5 WEEKS	SUPERIOR, SIMILAR BLEEEDING

FDA APPROVED FOR VTE PROPHYLAXIS AFTER TOTAL KNEE REPLACEMENT AND TOTAL HIP REPLACEMENT

APIXABAN – MEDICALLY ILL PATIENTS (ADOPT TRIAL)

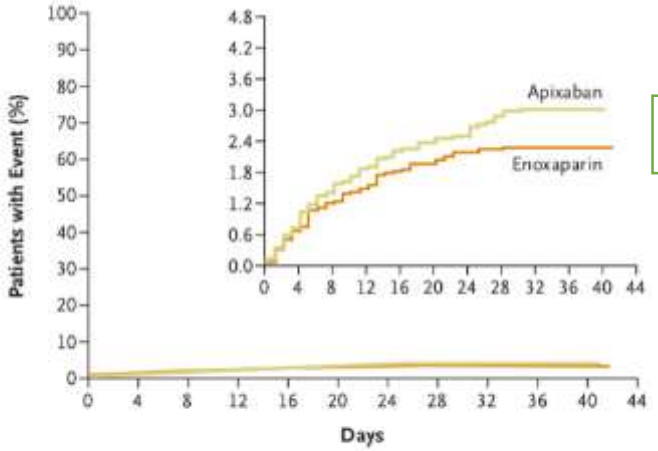


No. at Risk

Apixaban	3251	3098	2998	2935	2889	2850	2830	2810	2736	157	10	2
Enoxaparin	3266	3136	3049	2993	2946	2925	2892	2865	2783	195	12	1

1:1
APIXABAN 2.5mg OD -30 days vs
ENOXAPARIN 40 mg S/C OD -6-14 days

APIXABAN NOT SUPERIOR TO ENOXAPARIN



No. at Risk

Apixaban	3184	3042	2840	2664	2569	2493	2447	2392	1559	154	10	
Enoxaparin	3217	3078	2885	2705	2627	2562	2513	2457	1640	192	12	

SIGNIFICANTLY MORE BLEEDING EVENTS

Goldhaber SZ et al. N Engl J Med. 2011;365:2167–77

APIXABAN –METASTATIC CANCER (ADVOCATE TRIAL)

Study	Phase II
Population	Metastatic cancer on chemotherapy
Intervention	N=32, 5mg OD vs N= 30, 10 mg OD vs N=33 ,20 mg OD N=30, PLACEBO for 12 weeks
Results	Primary outcome Bleeding- 2.2 % in apixaban group

EDOXABAN – POST SURGERY

TRIAL	DOSAGE USED	COMPARATOR	RESULT
STUDY J04 (PHASE II)	5mg/15mg/30mg/60mg OD	PLACEBO	REDUCED VTE, SIMILAR BLEEDING
STUDY 011(PHASE II)	15mg/30mg/60mg/90mg OD	DALTEPARIN (2500 IU f/b 5000 IU)	REDUCED VTE
STARS E-III AND STARS J-V	30mg OD	ENOXAPARIN 20mg BD	REDUCED VTE, SIMILAR BLEEDING
STARS J-IV	30mg OD	ENOXAPARIN 20mg BD	HIGHER VTE, SIMILAR BLEEDING

BETRIXABAN – APEX TRIAL

STUDY TYPE	RCT
POPULATION	N= 7513
INTERVENTION	Enoxaparin 40mg OD vs Betrixaban 160mg -1 day f/b 80mg OD for 35-42 days

INCLUSION CRITERIA

Age > 40 years and admitted with acute medical illness with atleast one of the risk factors

- Aged 75 years or more
- 60 to 74 years old with D-dimer of two times the upper limit of normal (ULN) or more
- 40 to 59 years old with a D-dimer of at least two times the ULN and a history of VTE or history of cancer (excluding non-melanoma carcinoma of the skin

Beyer WJ et al. Eur Heart J Suppl. 2018 May;20(Suppl E):E16-E22

BETRIXABAN – APEX TRIAL

	Overall modified intent-to-treat population			Modified intent-to-treat population: patients stratified to 80 mg betrixaban dose		
	Betrixaban N = 3721 n (%)[b]	Enoxaparin N = 3720 n (%)[b]	Relative risk (95% CI)[c]	Betrixaban N = 2878 n (%)[d]	Enoxaparin N = 2926 n (%)[d]	Relative risk (95% CI)[c]
Composite outcome	165 (4.4)	223 (6.0)	0.75 (0.61-0.91) P = 0.003 NNT = 63	120 (4.2)	180 (6.2)	0.68 (0.55-0.86) P < 0.001 NNT = 50
Asymptomatic event	133 (3.6)	176 (4.7)		100 (3.5)	146 (5.0)	
Symptomatic DVT	14 (0.4)	22 (0.6)		11 (0.4)	17 (0.6)	
Non-fatal PE	9 (0.2)	18 (0.5)		4 (0.1)	14 (0.5)	
VTE-related death	13 (0.3)	17 (0.5)		8 (0.3)	12 (0.4)	
Symptomatic events[a]	35 (0.9)	54 (1.5)	0.64 (0.42-0.98)	22 (0.8)	41 (1.4)	0.55 (0.33-0.92)

FEWER THROMBOTIC EVENTS

Parameter	Safety population			Patients receiving 80 mg betrixaban		
	Betrixaban (N = 3716) n (%)	Enoxaparin (N = 3716) n (%)	RR (95% CI)	Betrixaban 80 mg (N = 2986) n (%)	Enoxaparin 40 mg (N = 2991) n (%)	RR (95% CI)
Major bleeding[a]	25 (0.67)	21 (0.57)	1.19 (0.67-2.12) P = 0.554	15 (0.50)	16 (0.53)	0.94 (0.47-1.90)
Gastrointestinal	19 (0.51)	9 (0.24)	-	-	-	-
Intracranial Haemorrhage	2 (0.05)	7 (0.19)	-	-	-	-
Intraocular	0	1 (0.03)	-	-	-	-
Fatal bleeding	1 (0.03)	1 (0.03)	-	-	-	-
CRNM bleeding[b]	91 (2.45)	38 (1.02)	2.39 (1.64-3.49) P < 0.001	66 (2.21)	33 (1.10)	2.00 (1.32-3.03)

SIMILAR BLEEDING RISK

Beyer WJ et al. Eur Heart J Suppl. 2018 May;20(Suppl E):E16-E22

GUIDELINES ON VTE PROPHYLAXIS

In acutely ill hospitalized medical patients, the ASH guideline panel recommends using LMWH over DOACs for VTE prophylaxis

Schunemann HJ et al. Blood Adv. 2018 Nov 27;2(22):3198-3225

VTE TREATMENT

TRIALS

GUIDELINES

DABIGATRAN

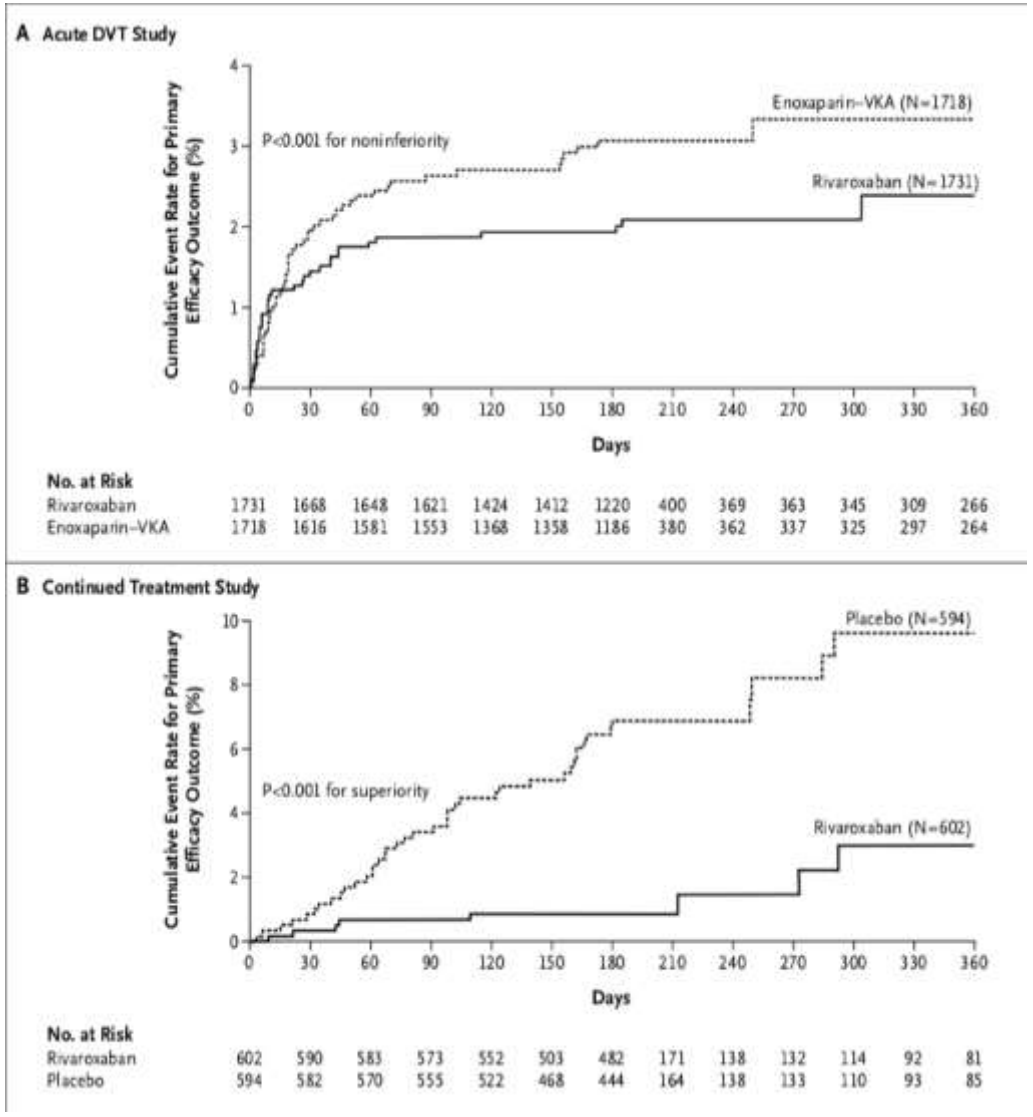
TRIAL	DOSE	COMPARATOR	OUTCOME
RECOVER	150mg BD	(Post 9 days heparin) Dabigatran vs warfarin for 6 months	• NON INFERIOR • EQUAL BLEEDING
RECOVER II	150mg BD	(Post 9.5 days of heparin) Dabigatran vs warfarin for 6 months	• NON INFERIOR • LESSER BLEEDING RISK

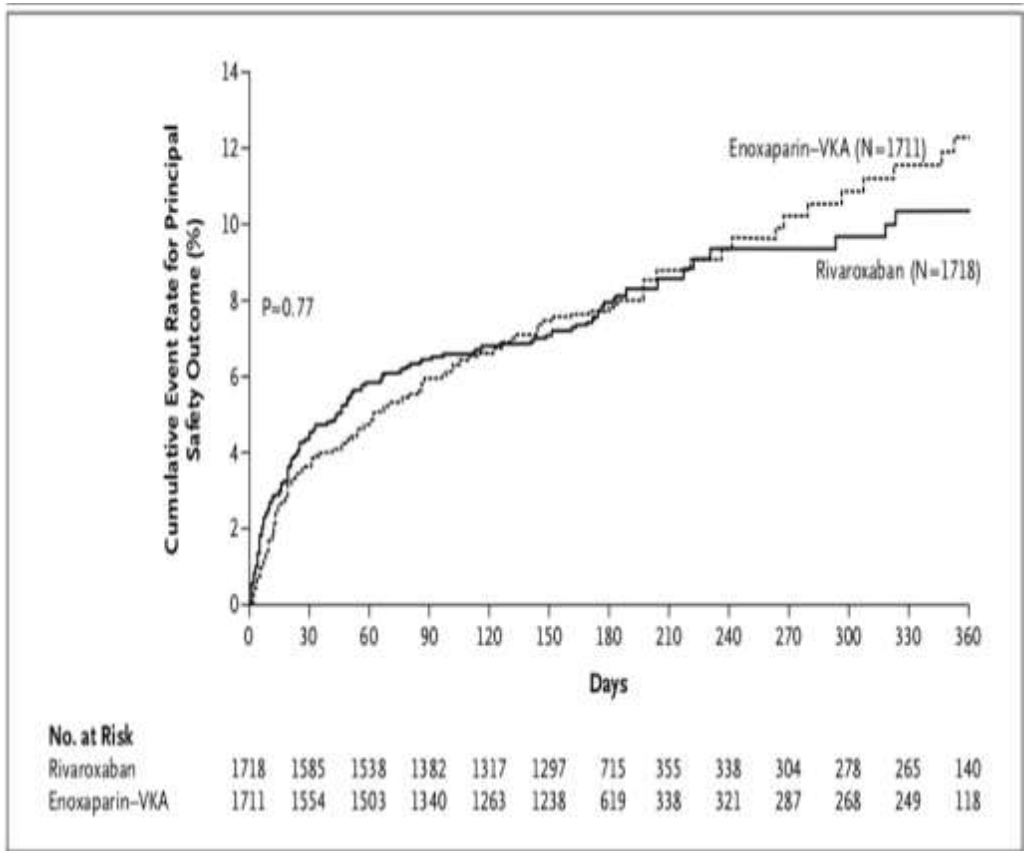
VERDICT
- NON INFERIOR TO WARFARIN
- EQUAL/LESSER BLEEDING RISK

RIVAROXABAN

TRIAL	DOSAGE USED	COMPARATOR	OUTCOME
EINSTEIN – DVT	15 mg BD for 21 days f/b 20 mg OD	ENOXAPARIN/VKA (3-6 months)	NON INFERIOR SIMILAR BLEEDING RISK
EINSTEIN - PE	Same	ENOXAPARIN/VKA	NON INFERIOR LOWER BLEEDING RISK
EINSTEIN – Ext STUDY	Same	PLACEBO	SUPERIOR TO PLACEBO HIGHER BLEEDING RISK
EISNTEIN CHOICE STUDY	10mg OD/20mg OD post 6-12 months of anticoagulation	Aspirin 100mg OD	REDUCED VTE RECURRENCE WITH RIVAROXABAN

RIVAROXABAN –(EINSTEIN DVT TRIAL)

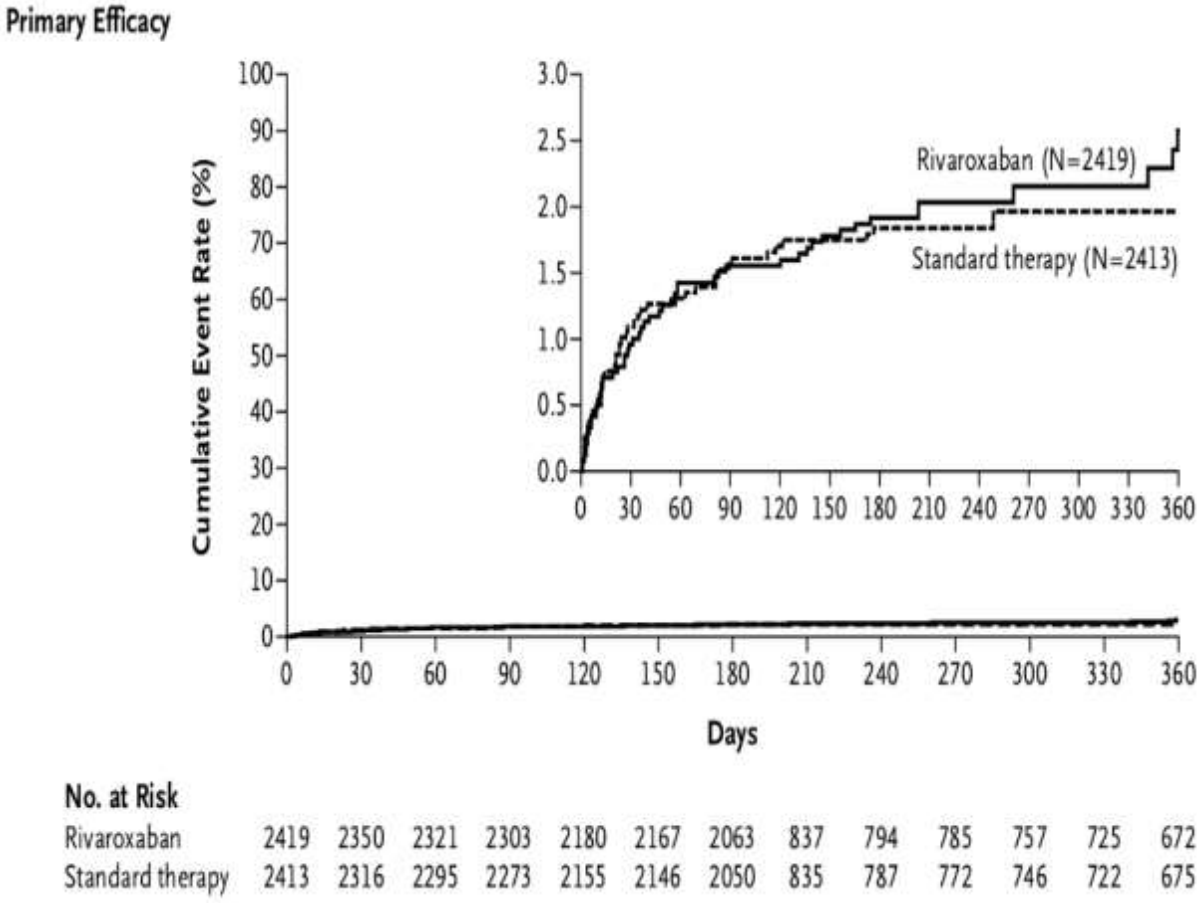


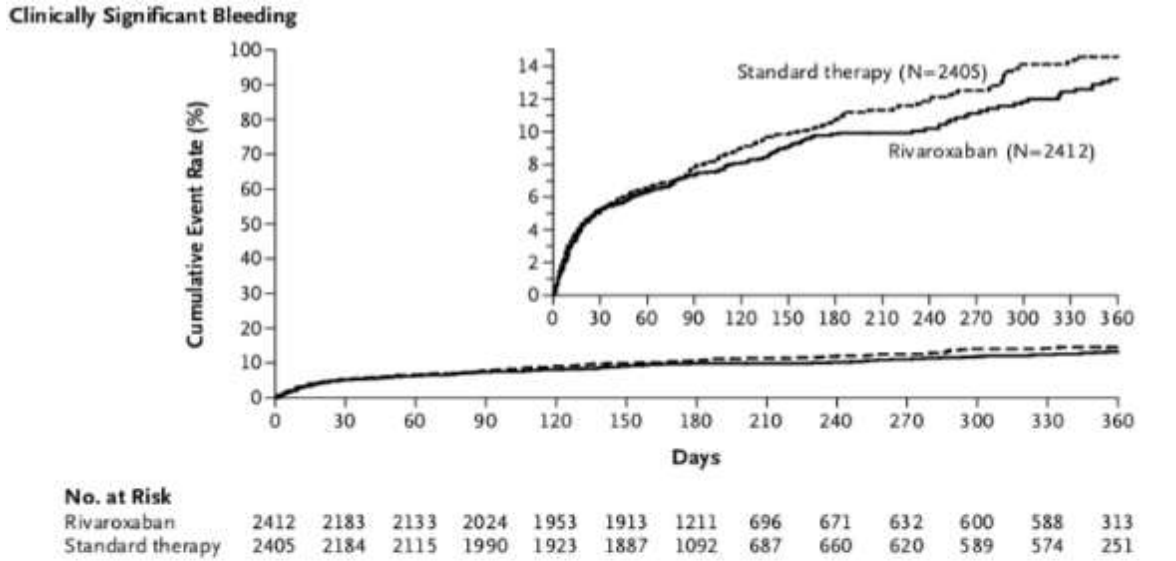


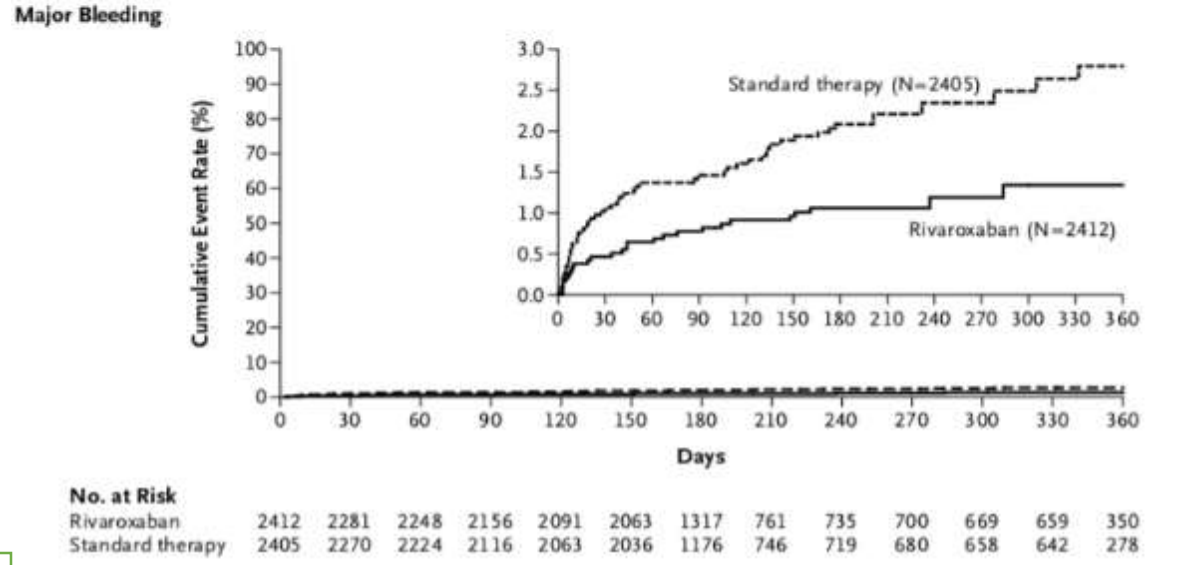
RIVAROXABAN NON INFERIOR TO ENOXAPARIN WITH SIMILAR BLEEDING RISK

Bauersachs R et al. N Engl J Med. 2010;363:2499–510

RIVAROXABAN –(EINSTEIN PE TRIAL)



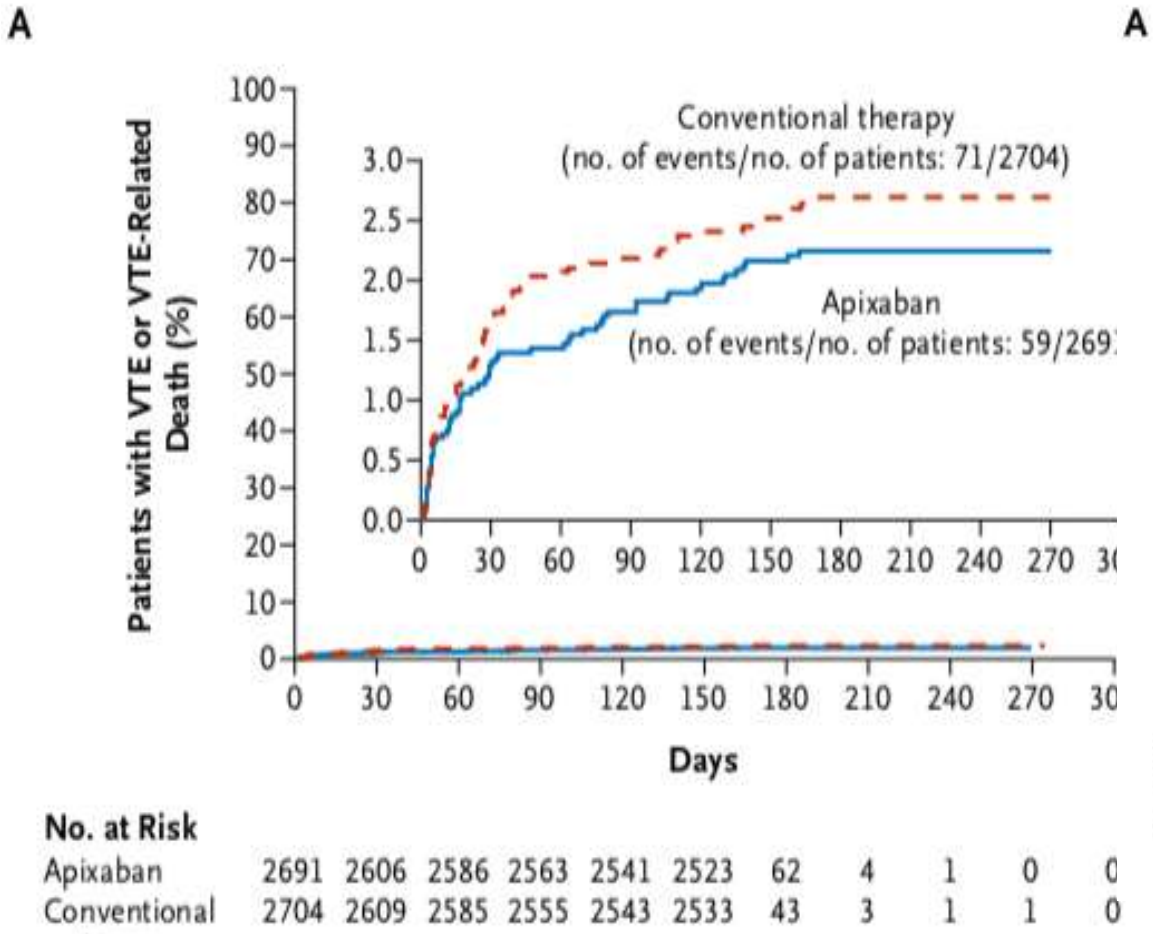




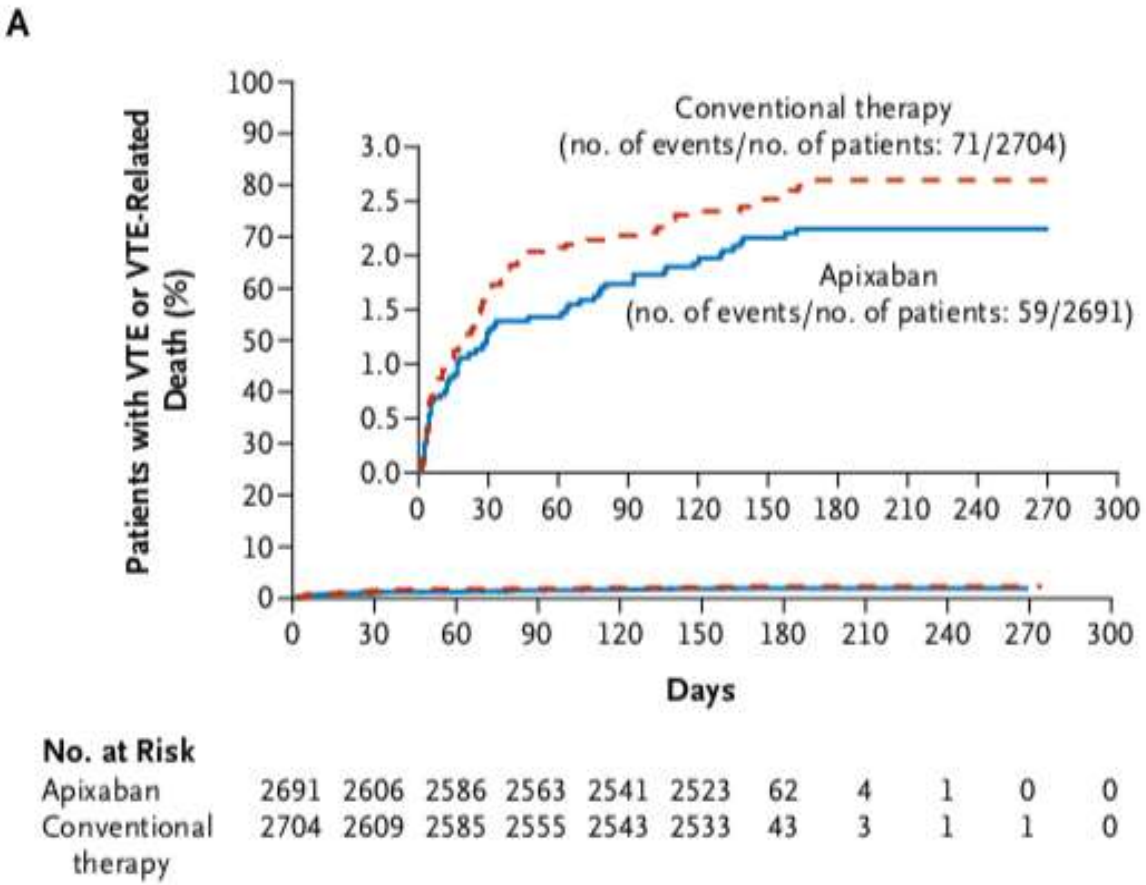
NON INFERIOR TO ENOXAPARIN WITH LOWER BLEEDING RISK

Buller HR et al. N Engl J Med. 2012 Apr 5;366(14):1287-97

APIXABAN- AMPLIFY TRIAL – 10mg BD -7days f/b 5mg BD



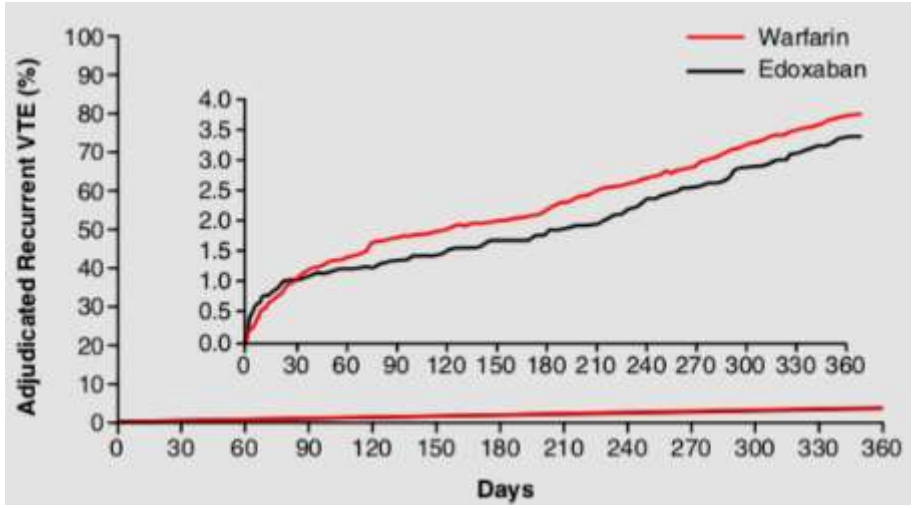
NON INFERIOR FOR VTE : P<0.001

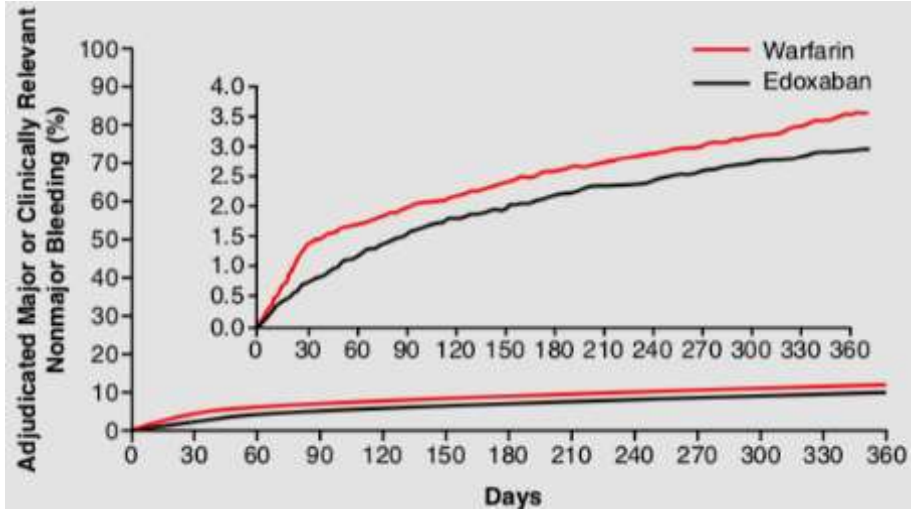


SUPERIOR FOR BLEEDING RISK: P<0.001

Agnelli G et al. N Engl J Med. 2013;369:799–808

EDOXABAN – HOKUSAI VTE TRIAL

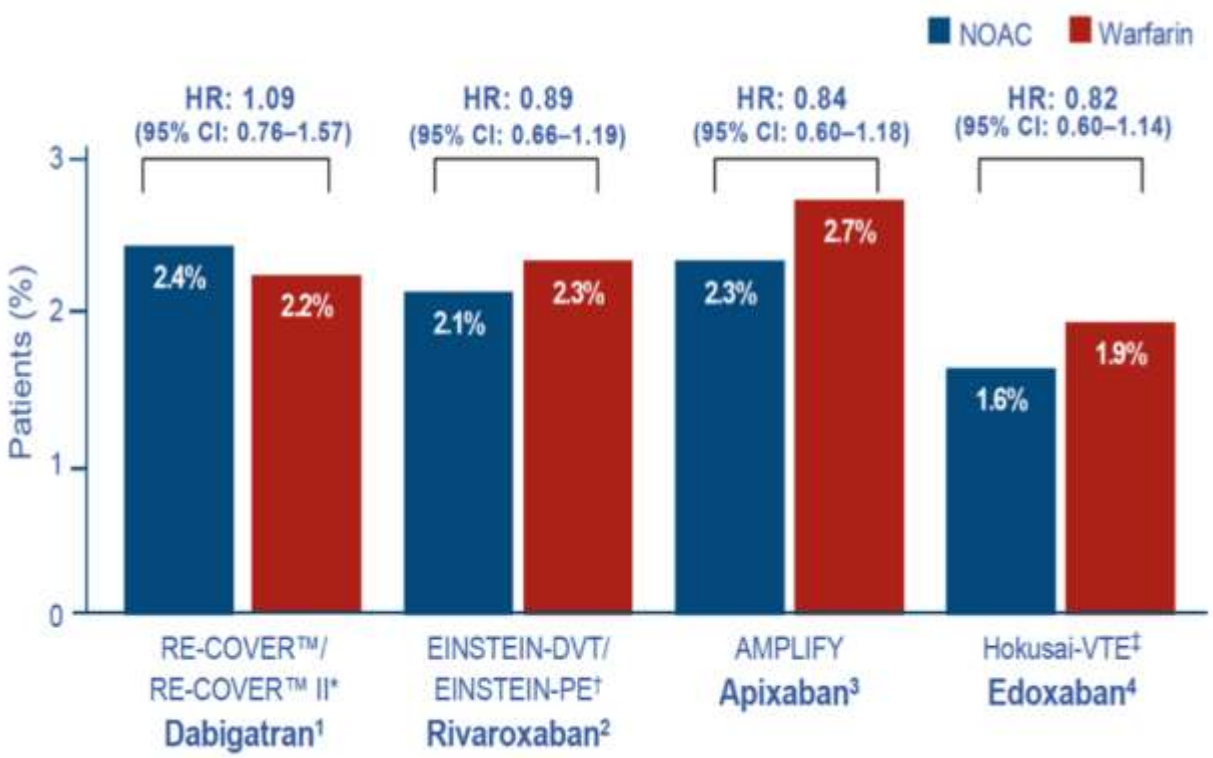


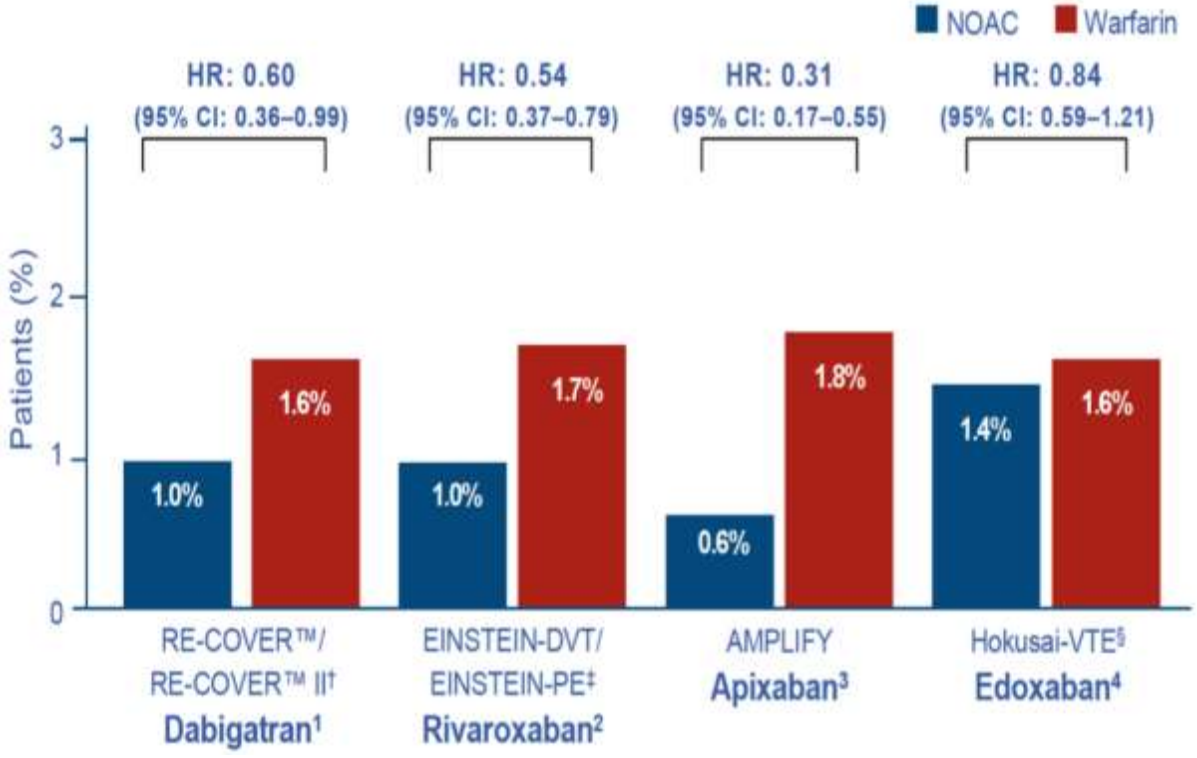


STUDY	PHASE 3
POPULATION	N= 8292
INTERVENTION	HEPARIN FOR ≥ 5 DAYS F/B EDOXABAN 60mg OD or WARFARIN, 12 months
OUTCOME	SYMPTOMATIC RECURRENT VTE – NON-INFERIOR (P<0.001) BLEEDING RISK –SUPERIOR (P=0.004)

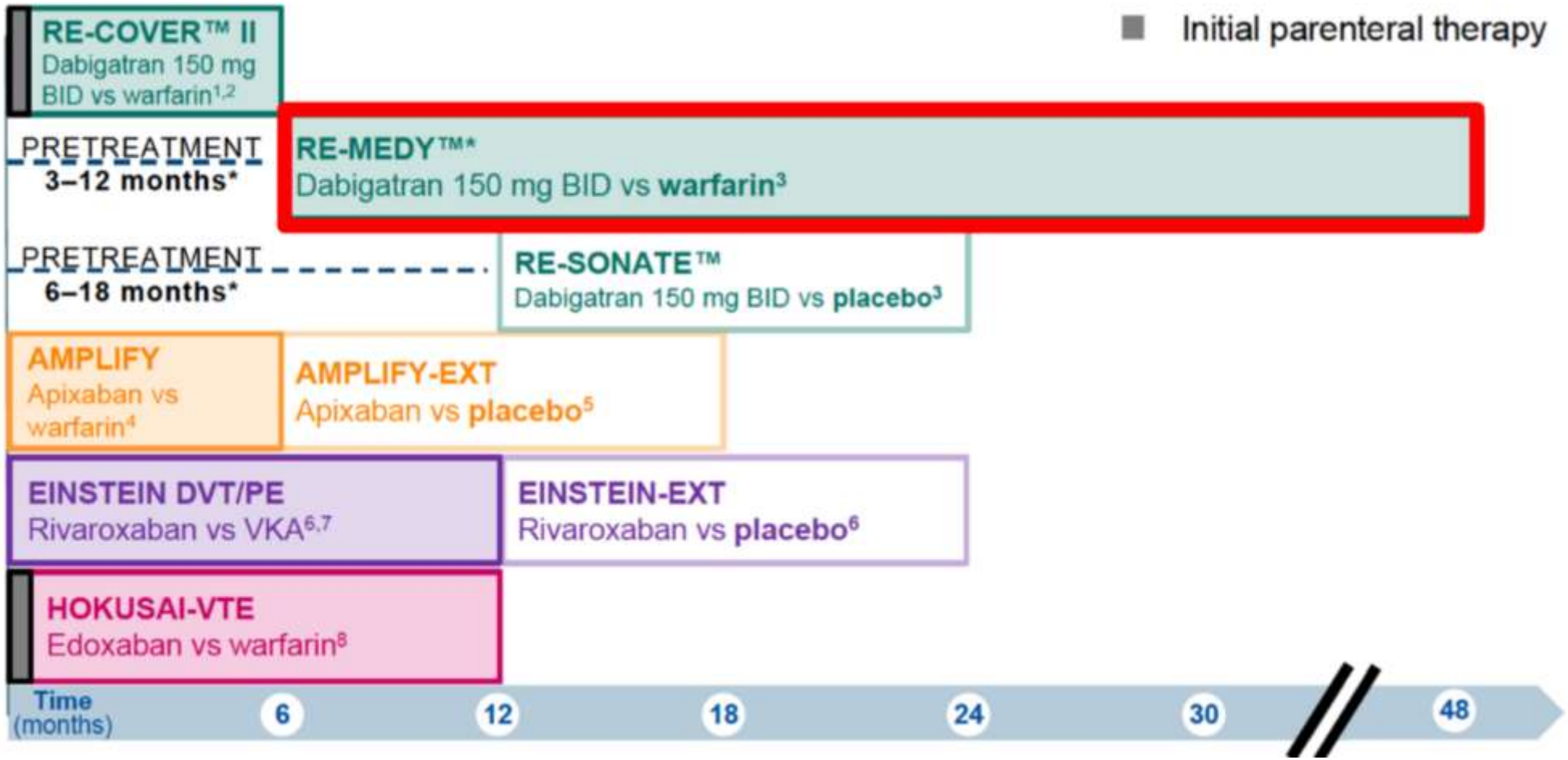
Buller H et al. N Engl J Med.

NOAC VS VKA –VTE TREATMENT





NOAC – LONGTERM STUDIES



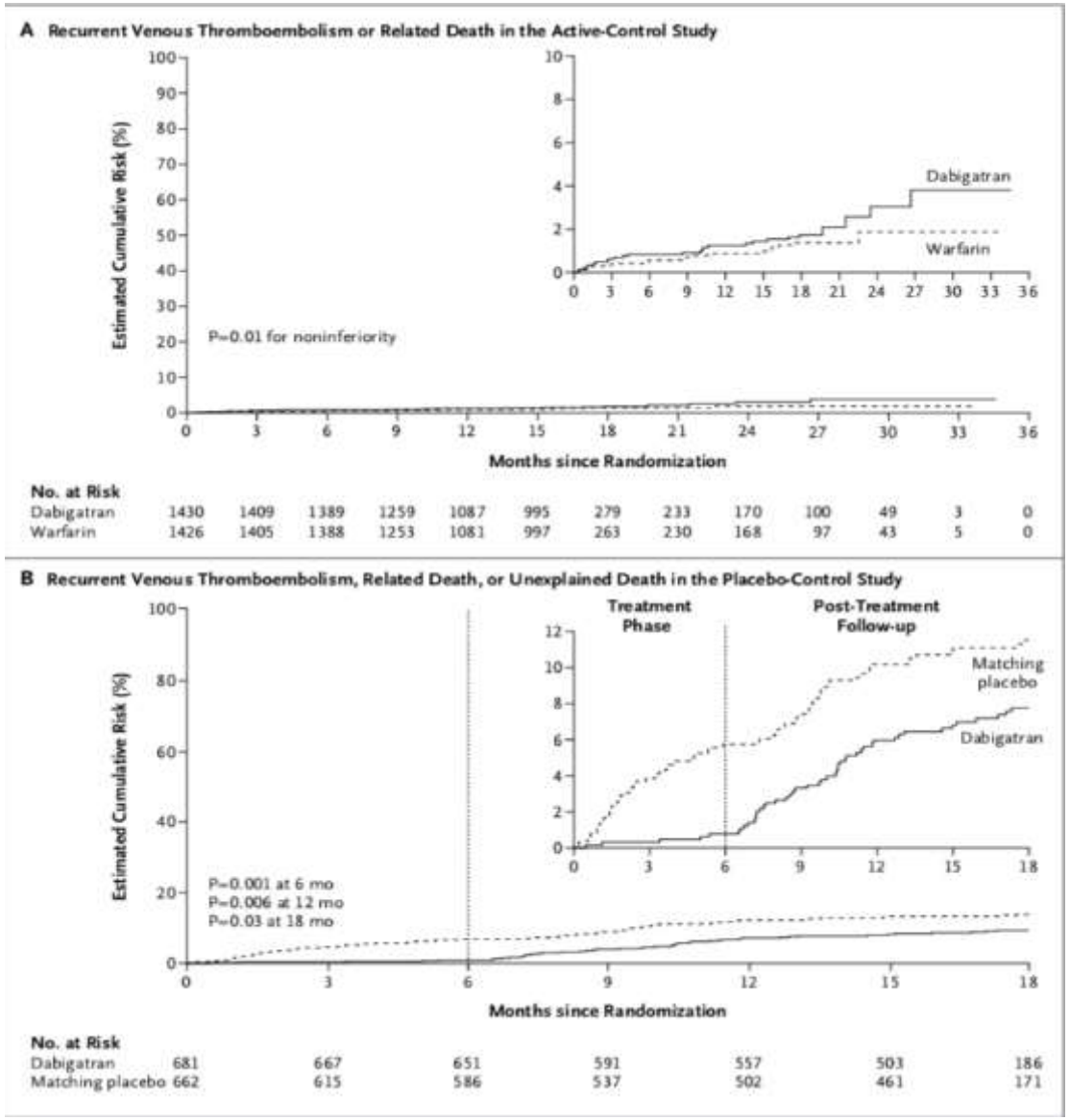
DABIGATRAN – PREVENTING VTE RECURRENCE

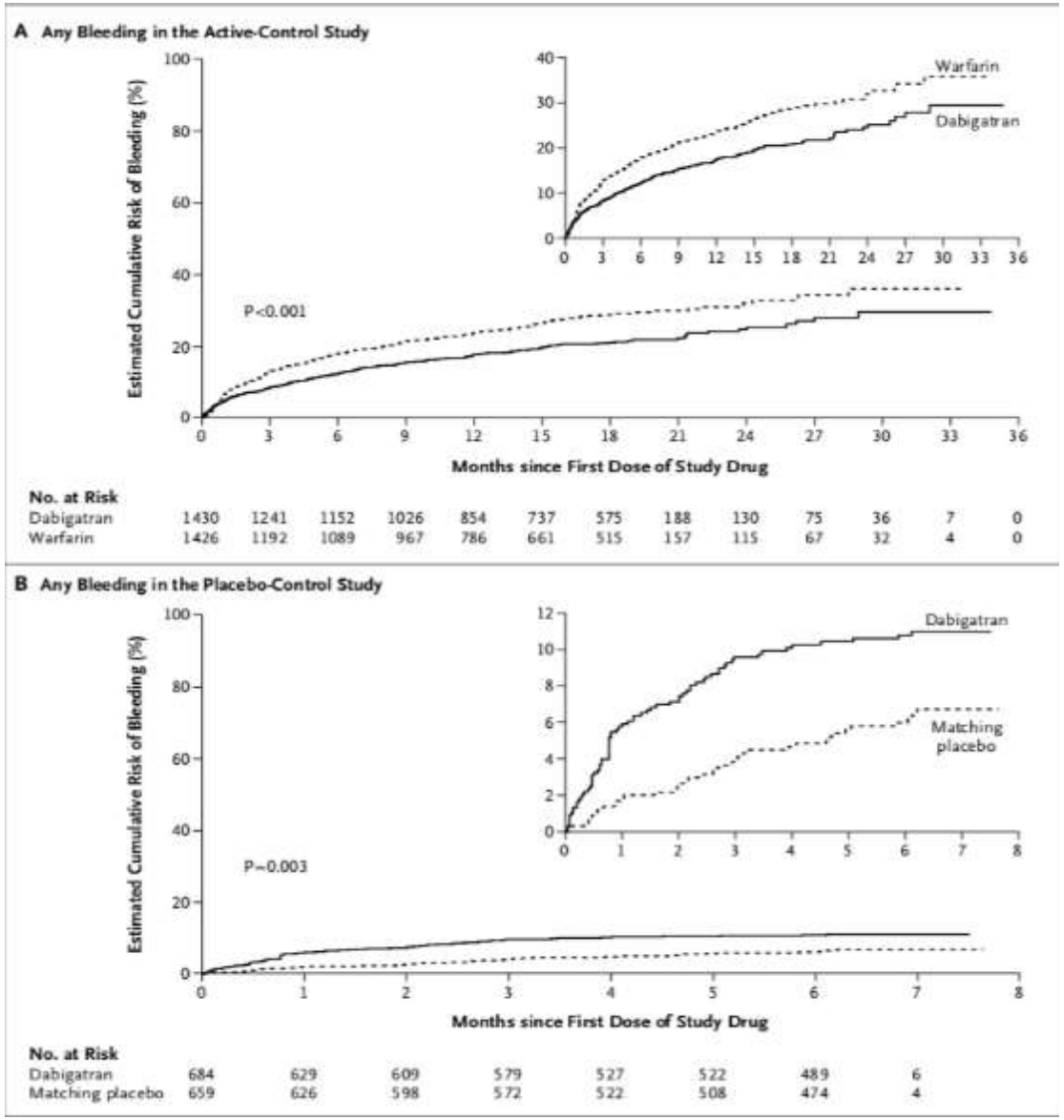
TRIAL	DOSE	COMPARATOR	OUTCOME
RESONATE	150mg BD	(Post 12 months of approved anticoagulation) Placebo	• LOWER RECURRENT VTE • HIGHER BLEEDING
RE-MEDY	150mg BD	(post 3 months of approved anticoagulation) Warfarin	• NON INFERIOR • LESSER BLEEDING

- VERDICT
- NON INFERIOR TO WARFARIN
- LESSER BLEEDING RISK

Schulman et al. N Engl J Med. 2013 Feb 21;368(8):709-18

RE-MEDY TRIAL

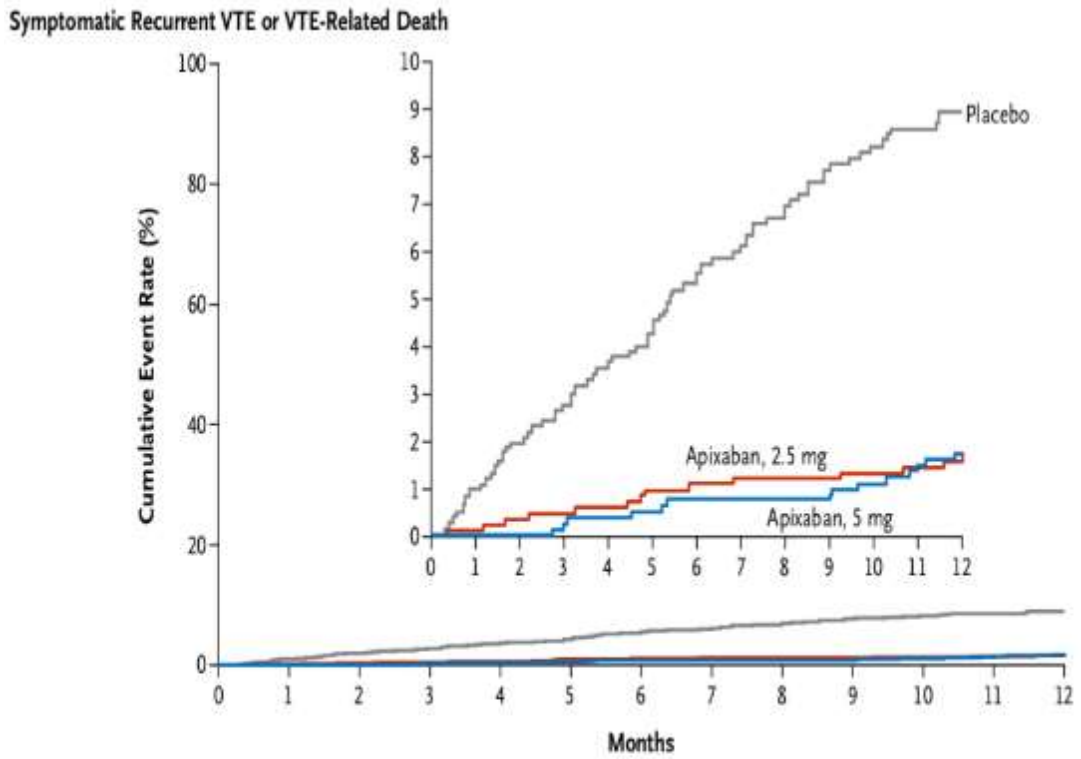




RESONATE TRIAL

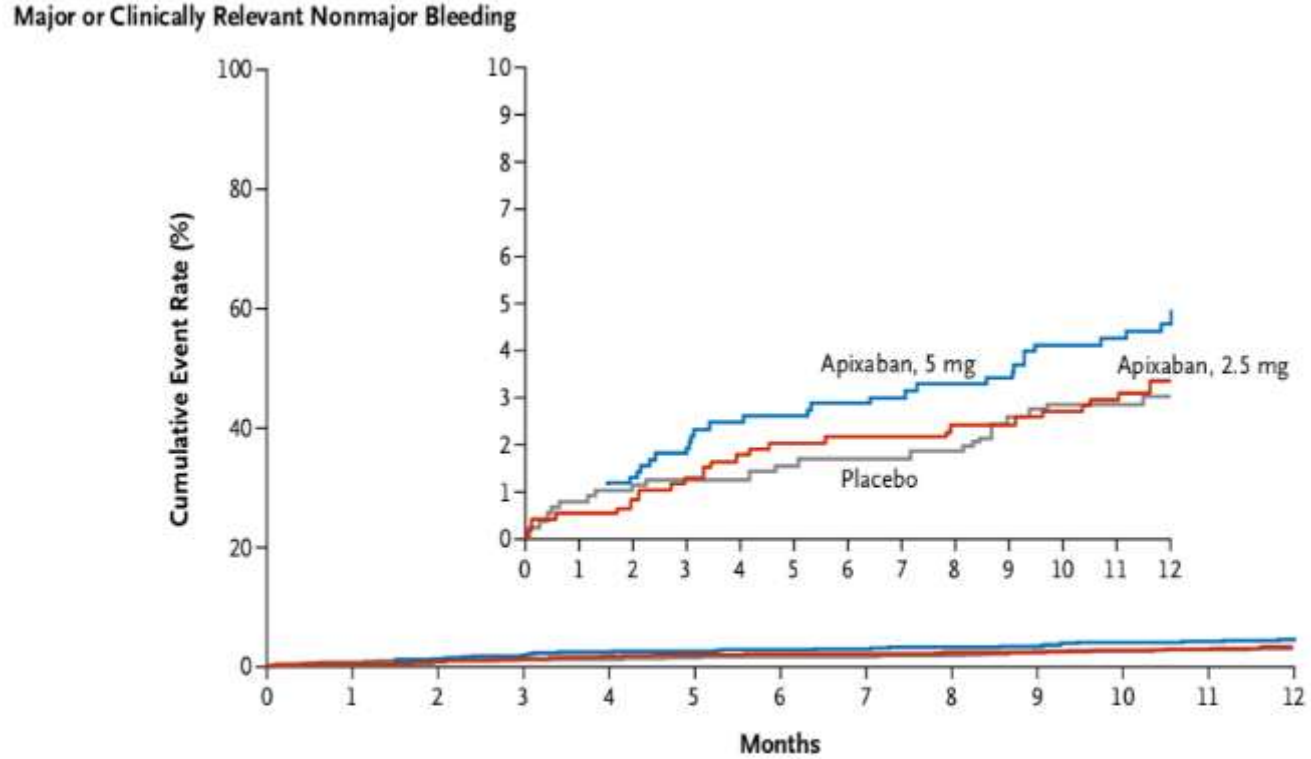
Schulman et al. N Engl J Med. 2013 Feb 21;368(8):709-18

APIXABAN – VTE RECURRENCE PREVENTION(post 6 months treatment)
AMPLIFY EXT TRIAL – 2.5mg BD vs 5mg BD vs Placebo



No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

NON INFERIOR

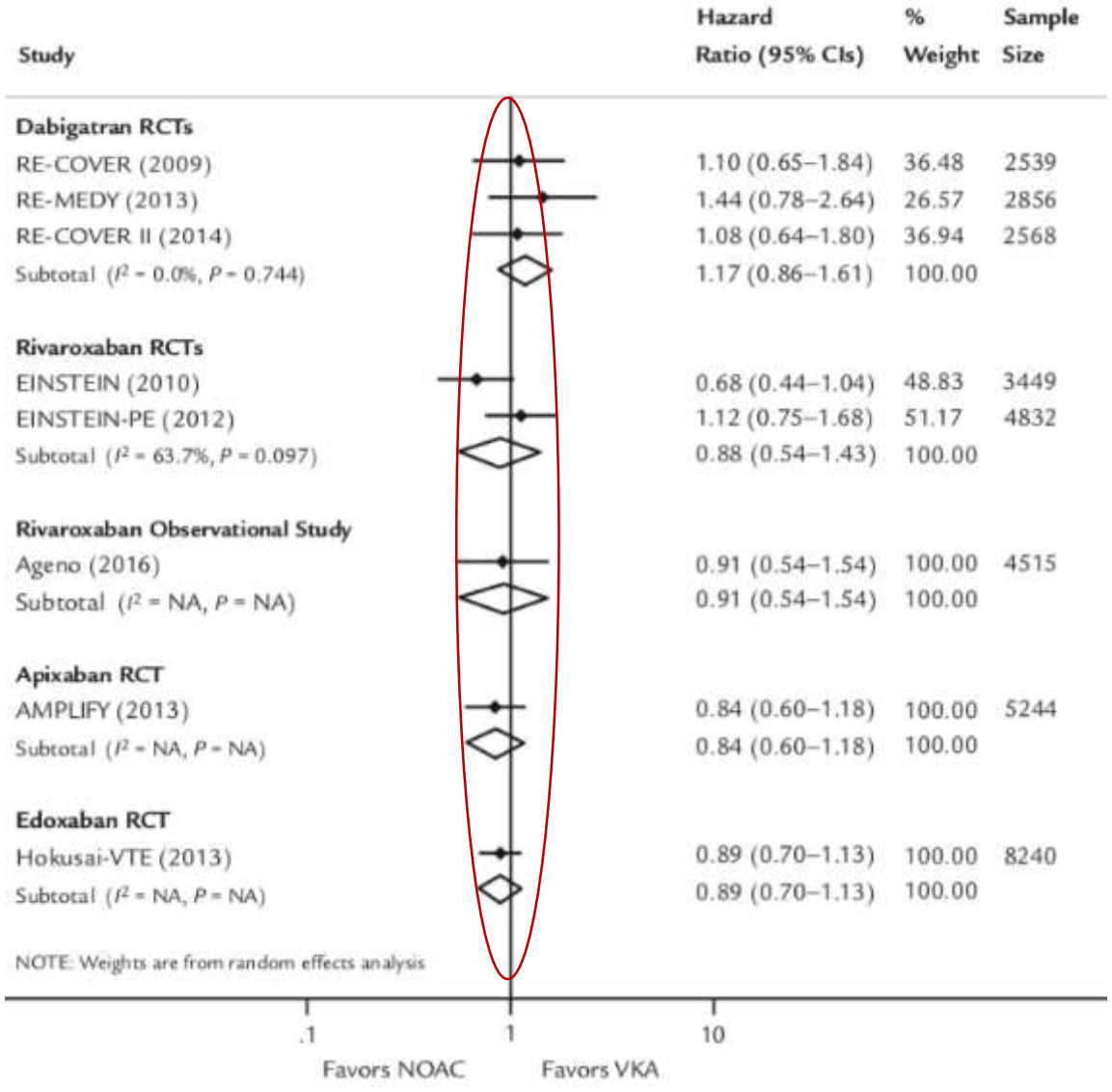


No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

SIMILAR BLEEDING RISK

Agnelli G et al. N Engl J Med. 2013;368:699-

NOACs IN VTE TREATMENT - METAANALYSIS

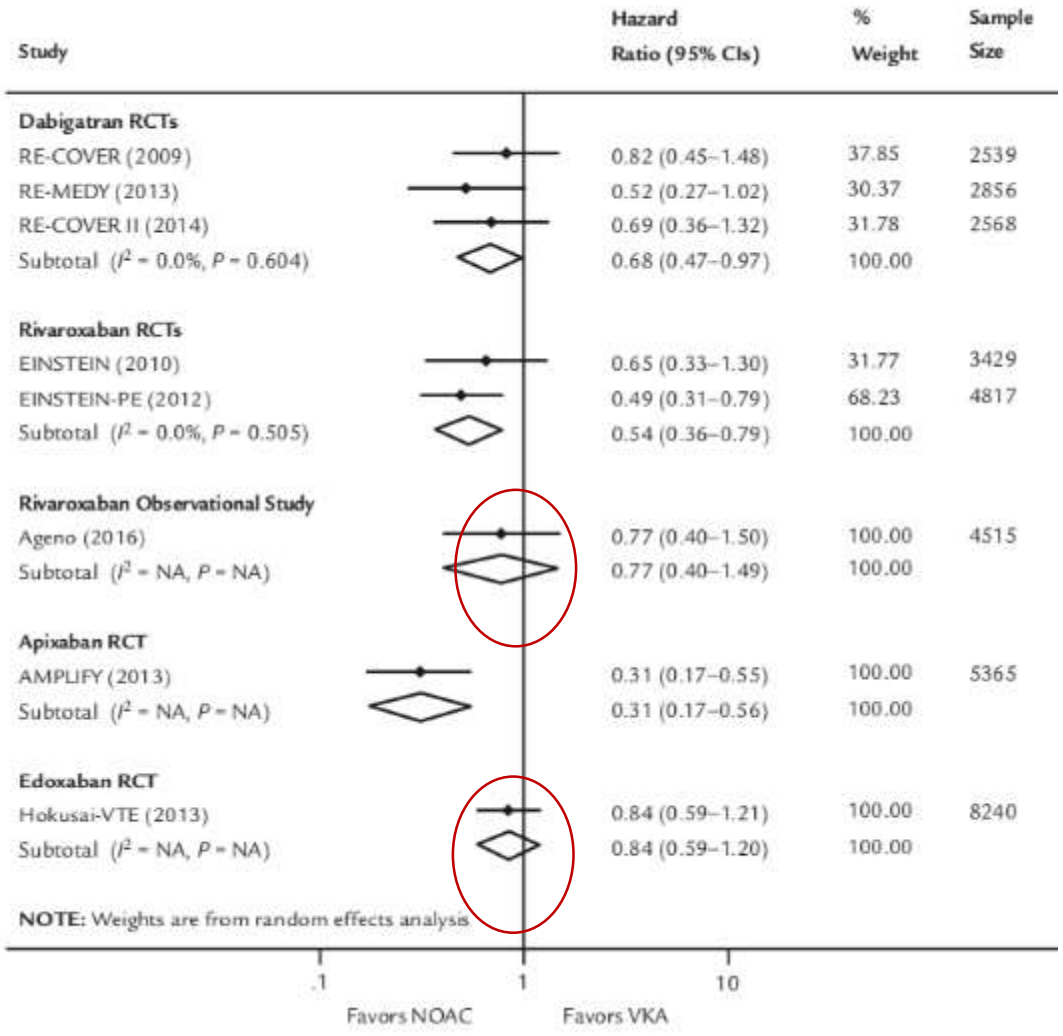


FOREST PLOT

NOACs and VKAs had no difference in risk reduction of recurrent VTE/fatal PE

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

NOACs IN VTE TREATMENT - METAANALYSIS



RIVAROXABAN AND EDOXABAN HAVE NOT SHOWN CONSISTENTLY REDUCED MAJOR BLEEDING RISK COMPARED TO VKA

DABIGATRAN, APIXABAN – 32-69% REDUCED BLEEDING RISK COMPARED TO VKA

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

Secondary Outcomes

- Recurrent DVT, nonfatal PE, or all-cause mortality – No difference
- Gastrointestinal bleeding – Dabigatran 38% more risk than VKA, Apixaban and Rivaroxaban have reduced risk
- Intracranial bleeding – Rivaroxaban and Edoxaban –reduced risk, Dabigatran and Apixaban – similar risk as VKA

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

GUIDELINES

- *In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy*

CHEST GUIDELINES 2016

STROKE PREVENTION IN AF

TRIALS

GUIDELINES

DABIGATRAN

TRIAL	COMPARATOR	OUTCOME
PETRO	Dabigatran vs Dabigatran + Aspirin/warfarin	MORE BLEEDING IN THE COMBINATION GROUP
RE-LY	110mg BD vs 150mg BD vs warfarin (2 years follow up)	• 110mg BD GROUP – SIMILAR STROKE/EMBOLISM AND LOWER BLEEDING • 150mg BD GROUP – LOWER STROKE/EMBOLISM AND SIMILAR BLEEDING
RELY ABLE	Placebo (2.3 years post RE-LY results followup)	150mg BD GROUP – HIGHER BLEEDING THAN 110mg BD

VERDICT :
FDA APPROVED DABIGATRAN 150mg BD AS AN ALTERNATIVE TO WARFARIN IN PRIMARY OR SECONDARY PREVENTION OF STROKE IN AF

DABIGATRAN – RELY TRIAL

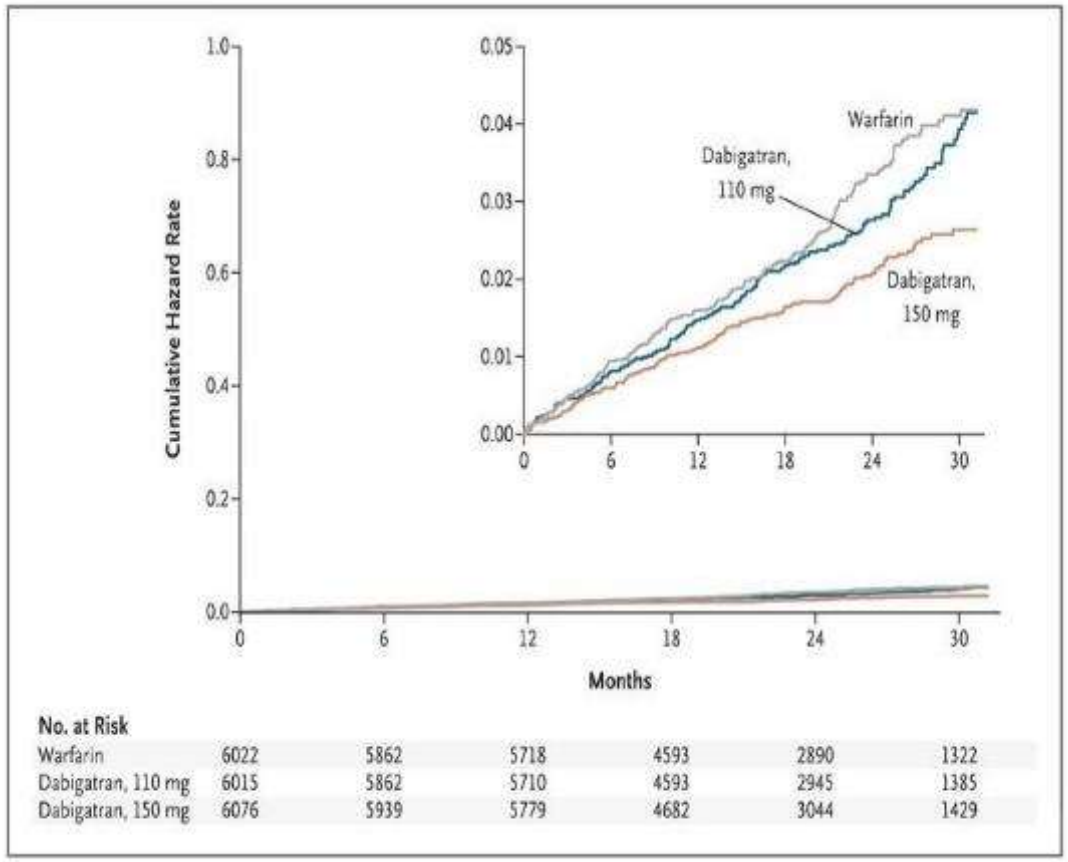


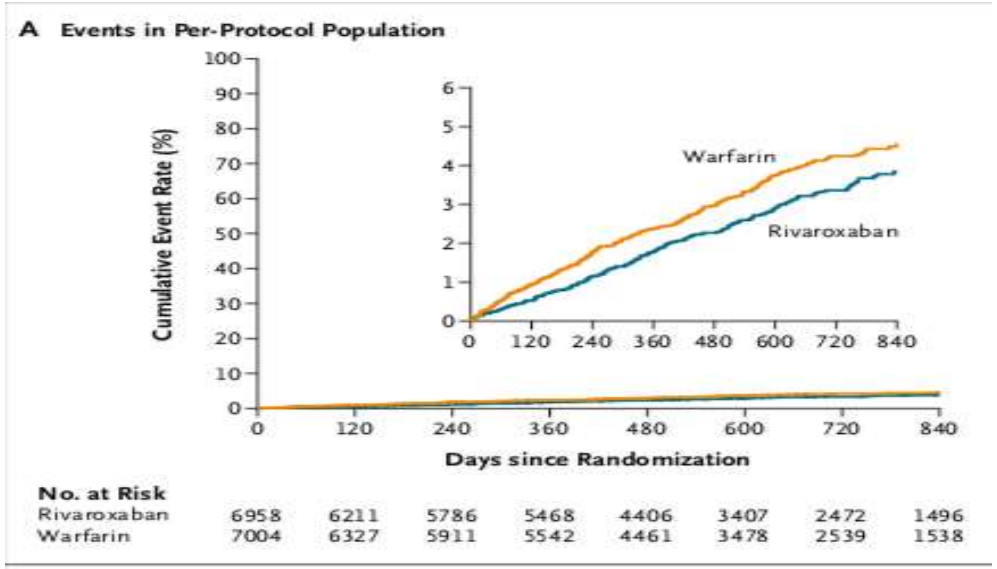
Table 3. Safety Outcomes, According to Treatment Group.*

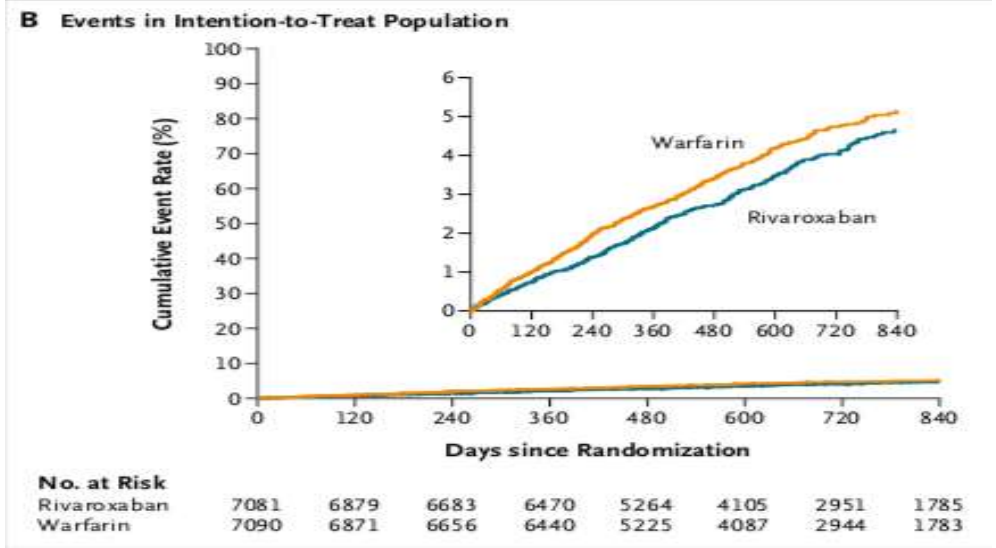
Event	Dabigatran, 110 mg		Dabigatran, 150 mg		Warfarin		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr						
Major bleeding	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31	1.16 (1.00–1.34)	0.052
Life threatening	145	1.22	175	1.45	212	1.80	0.68 (0.55–0.83)	<0.001	0.81 (0.66–0.99)	0.04	1.19 (0.96–1.49)	0.11
Non–life threatening	198	1.66	226	1.88	208	1.76	0.94 (0.78–1.15)	0.56	1.07 (0.89–1.29)	0.47	1.14 (0.95–1.39)	0.17
Gastrointestinal†	133	1.12	182	1.51	120	1.02	1.10 (0.86–1.41)	0.43	1.50 (1.19–1.89)	<0.001	1.36 (1.09–1.70)	0.007
Minor bleeding	1566	13.16	1787	14.84	1931	16.37	0.79 (0.74–0.84)	<0.001	0.91 (0.85–0.97)	0.005	1.16 (1.08–1.24)	<0.001
Major or minor bleeding	1740	14.62	1977	16.42	2142	18.15	0.78 (0.74–0.83)	<0.001	0.91 (0.86–0.97)	0.002	1.16 (1.09–1.23)	<0.001
Intracranial bleeding	27	0.23	36	0.30	87	0.74	0.31 (0.20–0.47)	<0.001	0.40 (0.27–0.60)	<0.001	1.32 (0.80–2.17)	0.28
Extracranial bleeding	299	2.51	342	2.84	315	2.67	0.94 (0.80–1.10)	0.45	1.07 (0.92–1.25)	0.38	1.14 (0.97–1.33)	0.11
Net clinical benefit outcome‡	844	7.09	832	6.91	901	7.64	0.92 (0.84–1.02)	0.10	0.91 (0.82–1.00)	0.04	0.98 (0.89–1.08)	0.66

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of intracranial bleeding.
† Gastrointestinal bleeding could be life threatening or non–life threatening.
‡ The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding.

Connolly SJ et al. N Engl J Med. 2009;361: 1139–51

RIVAROXABAN - ROCKET AF TRIAL



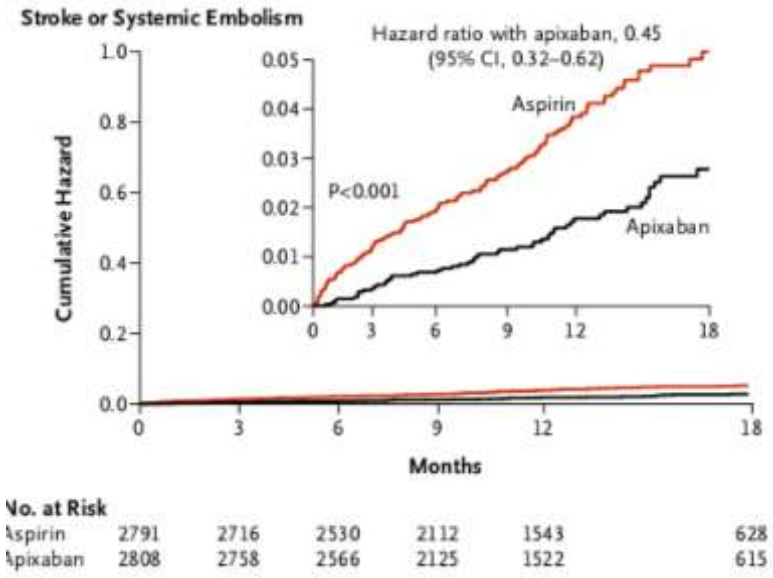


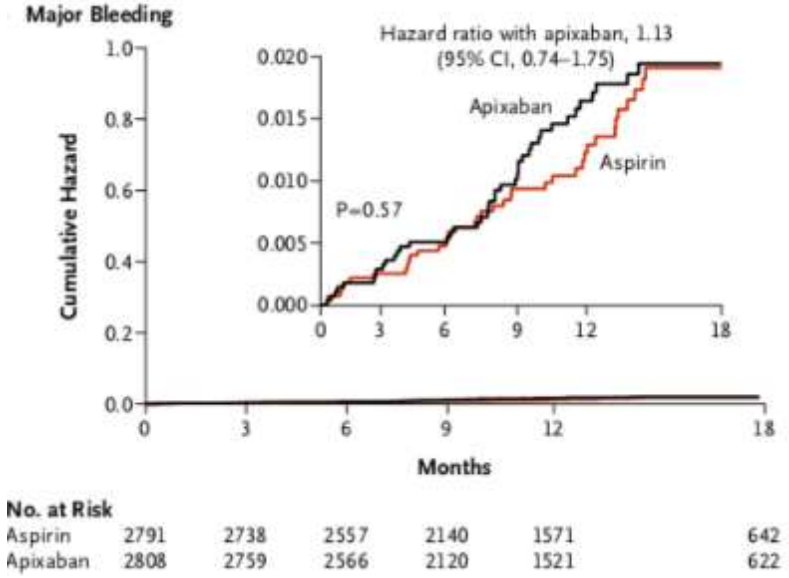
Variable	Rivaroxaban (N=7111) Events no. (%)	Rivaroxaban (N=7111) Event Rate no./100 patient-yr	Warfarin (N=7125) Events no. (%)	Warfarin (N=7125) Event Rate no./100 patient-yr	Hazard Ratio (95% CI)†	P Value‡
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

Patel MR et al. N Engl J Med. 2011; 365(10): 883-91

APIXABAN – AVERRROES TRIAL

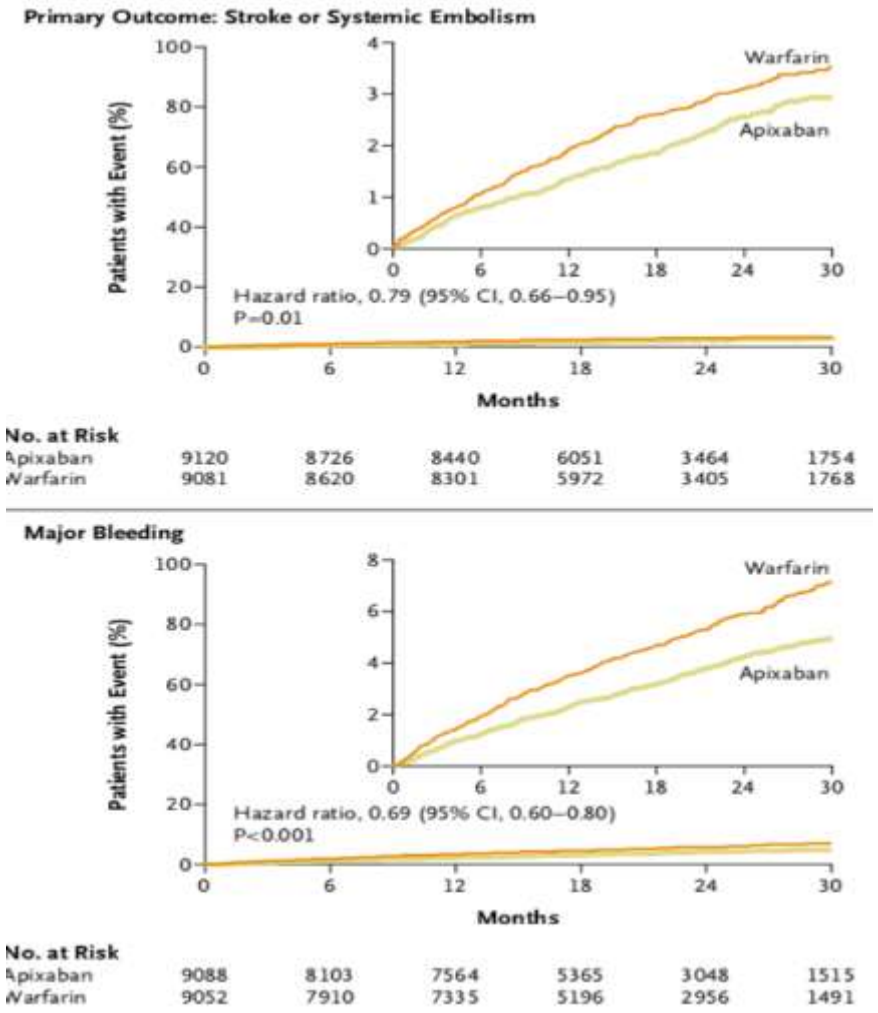
STUDY	PHASE 3
POPULATION	N=5599 , UNSUITABLE FOR WARFARIN, 2% had Mitral stenosis
METHOD	APIXABAN 5mg BD vs ASPIRIN 81-324 mg OD
RESULT	EMBOLISM LESS WITH APIXABAN (P <0.001) BLEEDING SIMILAR (P-0.57)





Connolly SJ et al. N Engl J Med. 2011;364:806-

APIXABAN – ARISTOTLE TRIAL

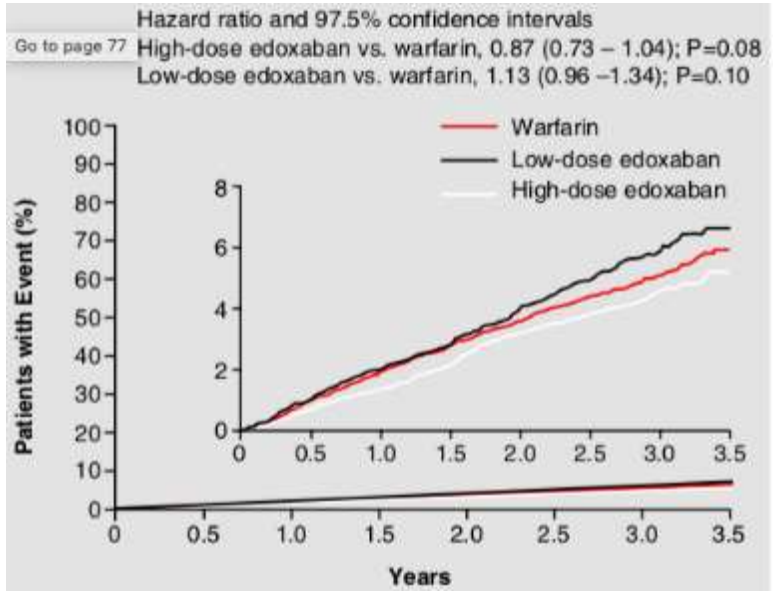


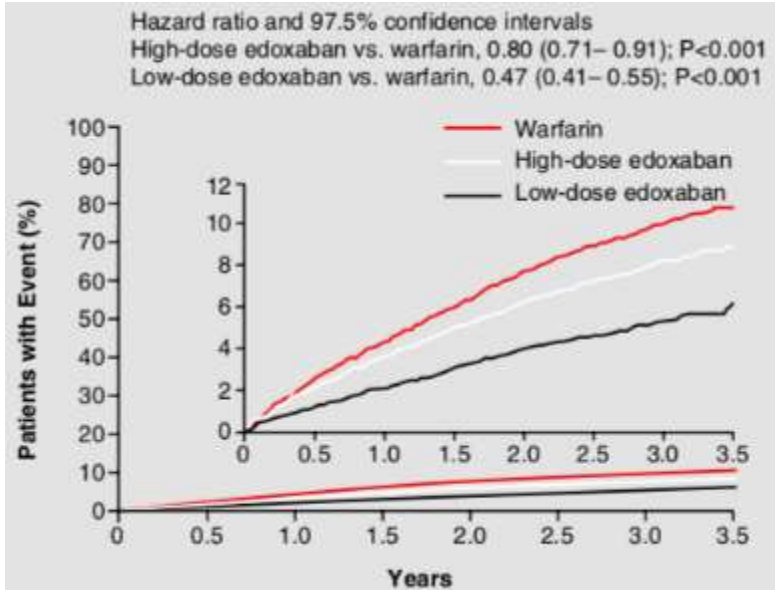
STUDY	PHASE 3
POPULATION	N=18201, AF, Mitral stenosis excluded, CHADS $\geq$ 1
INTERVENTION	1:1, APIXABAN 5mg BD vs ASPIRIN 81-324 mg OD
RESULTS	Non inferiority,P< 0.001 Superiority, P=0.01 Lesser bleeding , P< 0.001 Lesser Death P-0.047

Granger CB et al. N Engl J Med. 2011;365:981–

EDOXABAN – ENGAGE AF-TIMI TRIAL

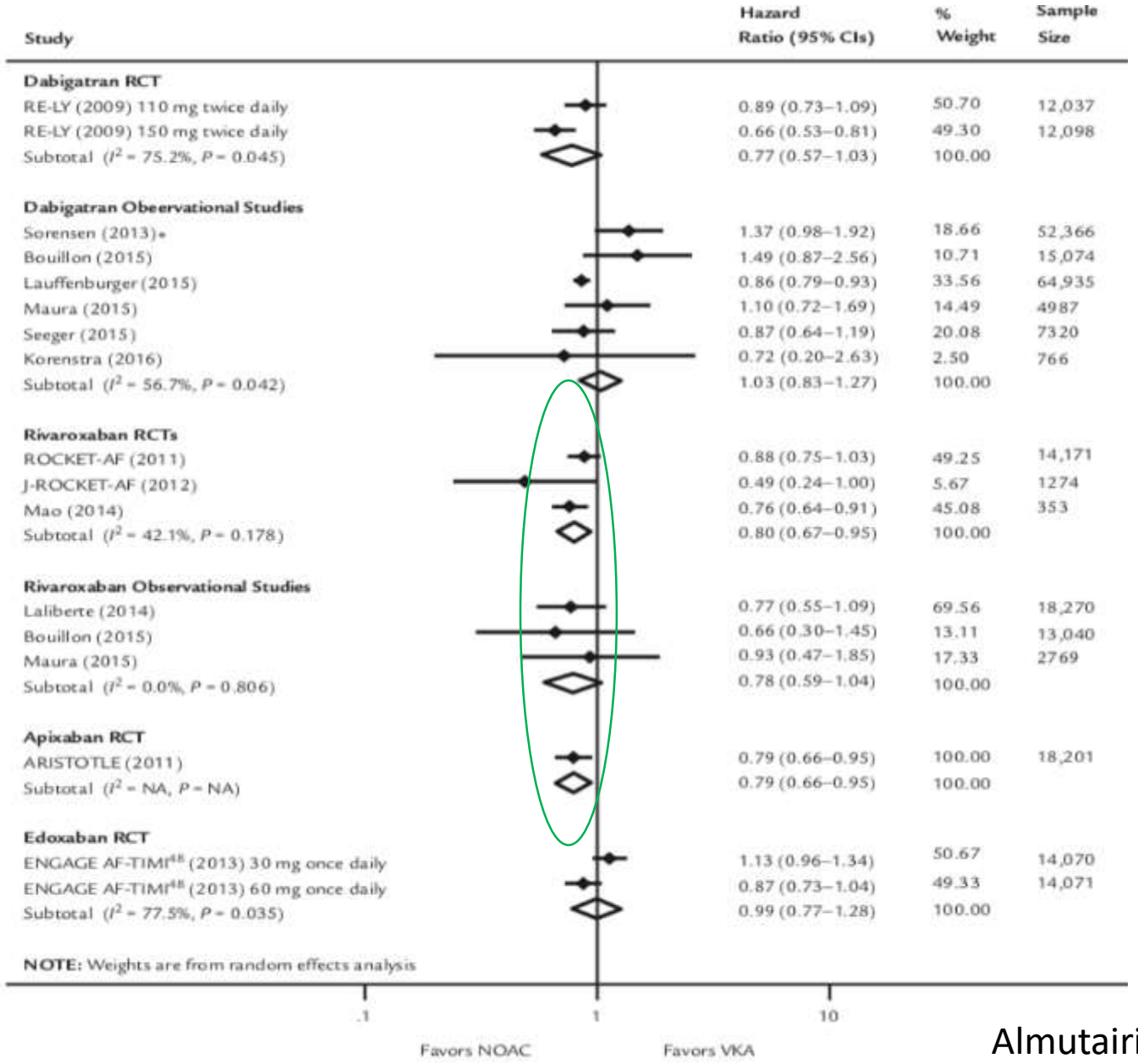
STUDY	PHASE 3
POPULATION	N= 21,105;Non valvular AF,
INTERVENTION	Edoxaban 30mg OD vs 60mg OD vs Warfarin
RESULT	EMBOLIC EVENTS – NON INFERIOR BLEEDING EVENTS - LOWER





Ruff CT et al. Am Heart J. 2010; 160:635–41

METAANALYSIS OF NOAC IN AF



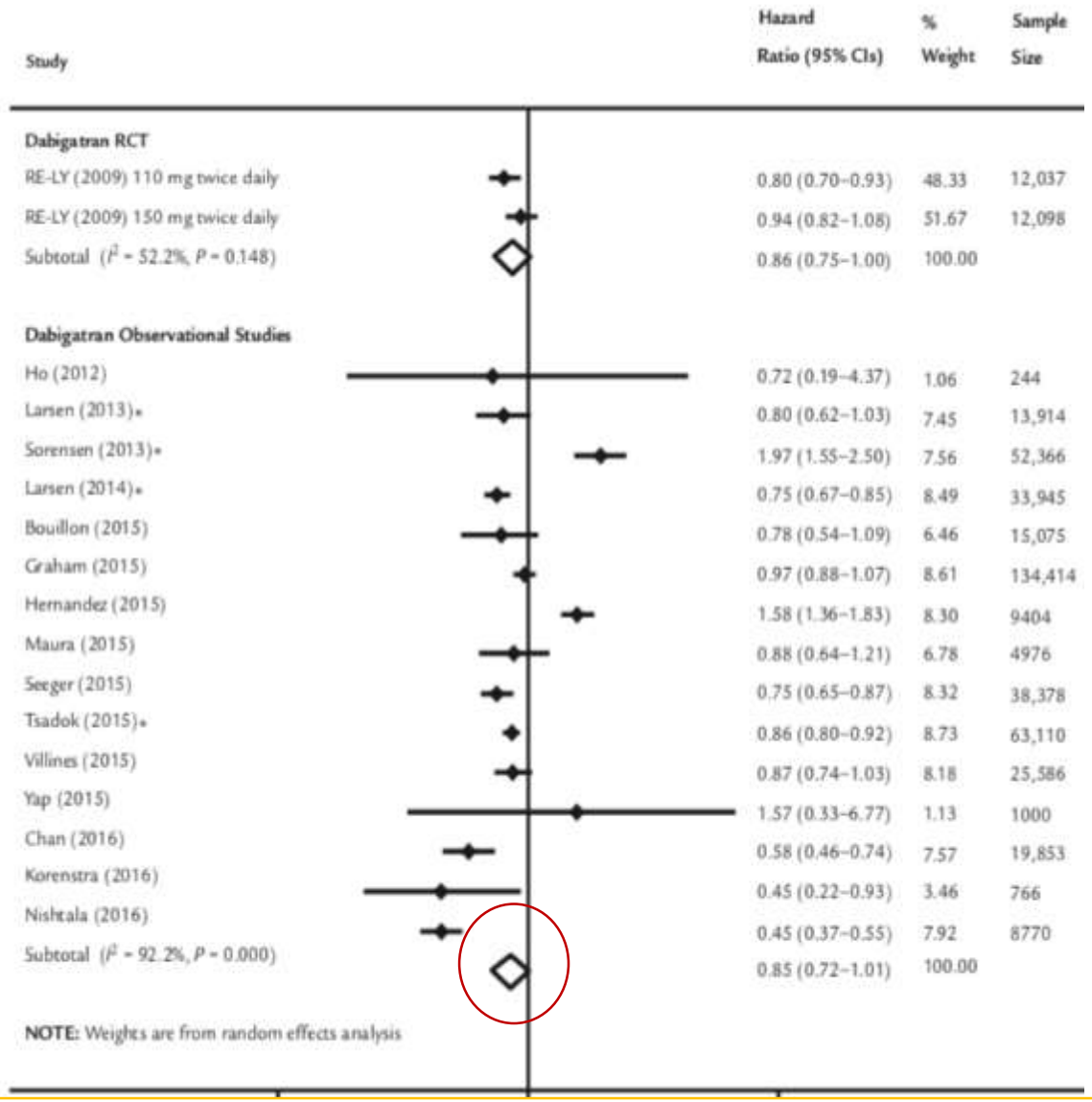
13 RCTs and 27 observational studies- FOREST PLOT

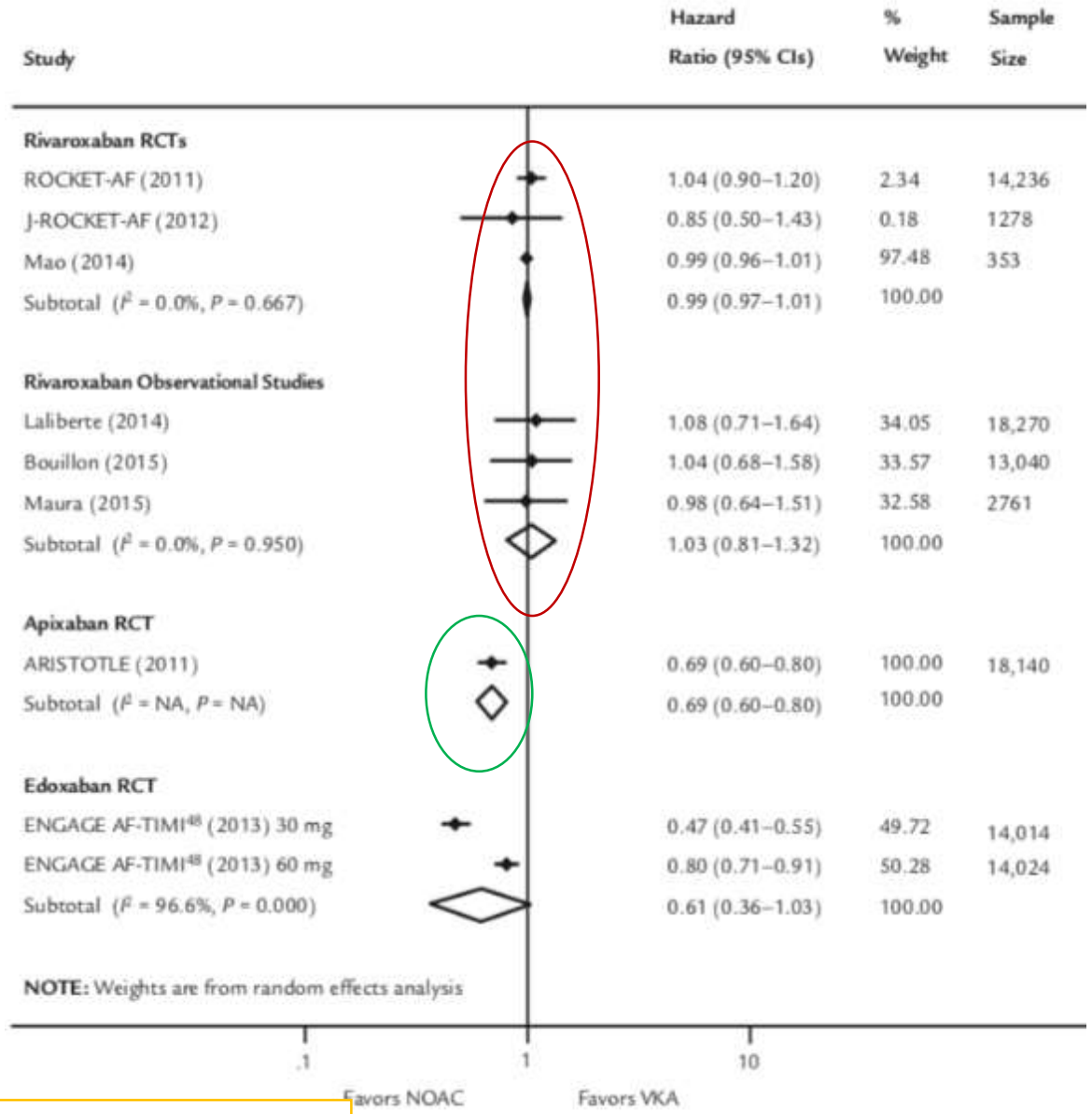
STROKE AND EMBOLIC EVENTS

1. DABIGATRAN AND EDOXABAN – EQUAL TO VKA
2. RIVAROXABAN AND APIXABAN REDUCE THE EMBOLISM RISK BY 20 % MORE COMPARED WITH VKA

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

METAANALYSIS OF NOAC IN AF – MAJOR BLEEDING





BLEEEDING RISK OF DABIGATRAN, RIVAROXABAN AND EDOXABAN SIMILAR TO VKA
APIXABAN -31% LOWER BLEEDING RISK

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

Secondary outcomes:

- Ischemic stroke : NOACs – similar to VKA
- MI – Dabigatran -36 % increased risk , no increased risk with other NOACs
- All cause mortality – Reduced with Dabigatran, Apixaban and Edoxaban

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

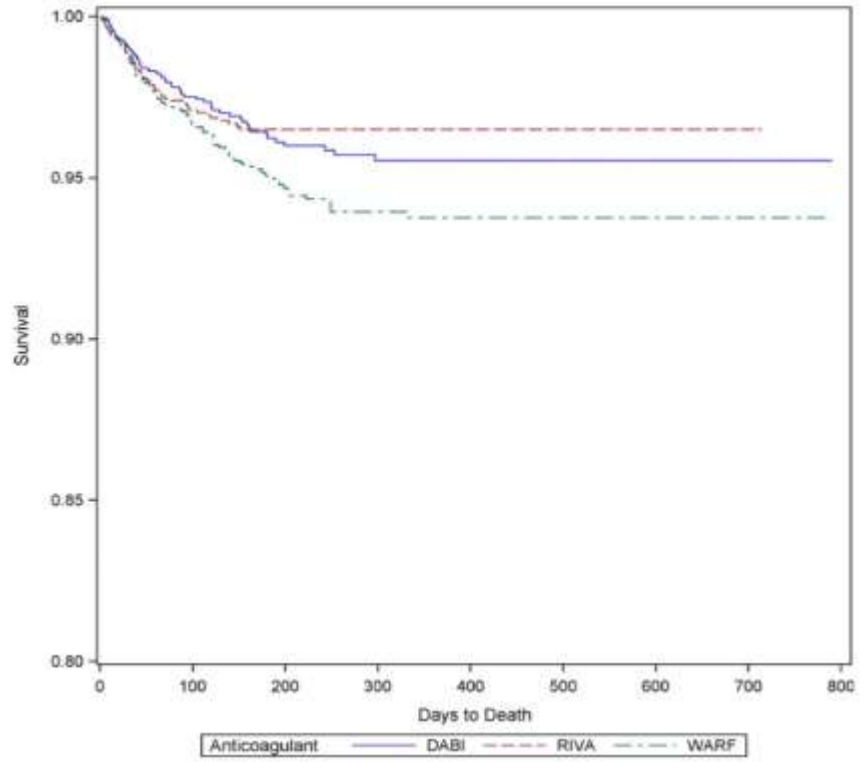
Safety Outcomes :

- Gastrointestinal bleeding – No risk difference compared to VKA
- Intracranial haemorrhage - Dabigatran, apixaban and edoxaban reduced risk compared to VKA

Almutairi AR et al. Clin Ther 2017 Jul;39(7):1456-1478

NOAC IN VALVULAR AF

STUDY	OBSERVATIONAL STUDY
POPULATION	18,137 patients with VHD (Dabigatran- 1,979; Rivaroxaban- 2,027; Warfarin-14,131) 85,596 patients without VHD (Dabigatran- 13 522; rivaroxaban, 14,257; warfarin;57,817]



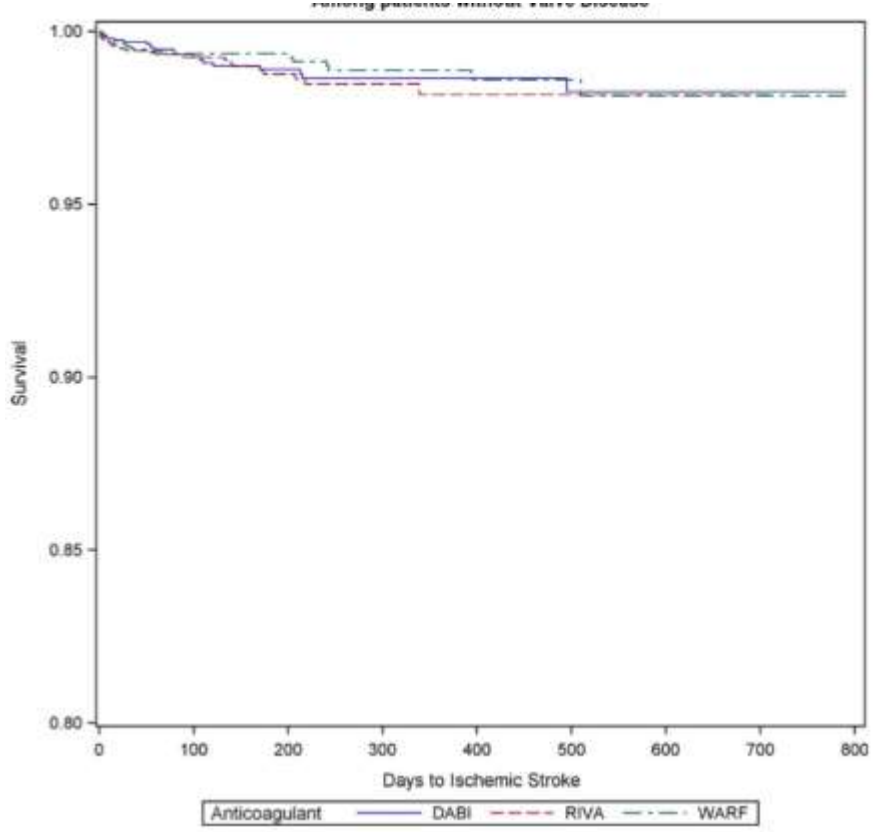
ALL CAUSE MORTALITY
Dabigatran vs warfarin: 0.71 (0.52–0.98; P=0.038)
Rivaroxaban vs warfarin: 0.68 (0.49–0.95; P=0.022)
Rivaroxaban vs dabigatran: 0.96 (0.67–1.37; P=0.82)

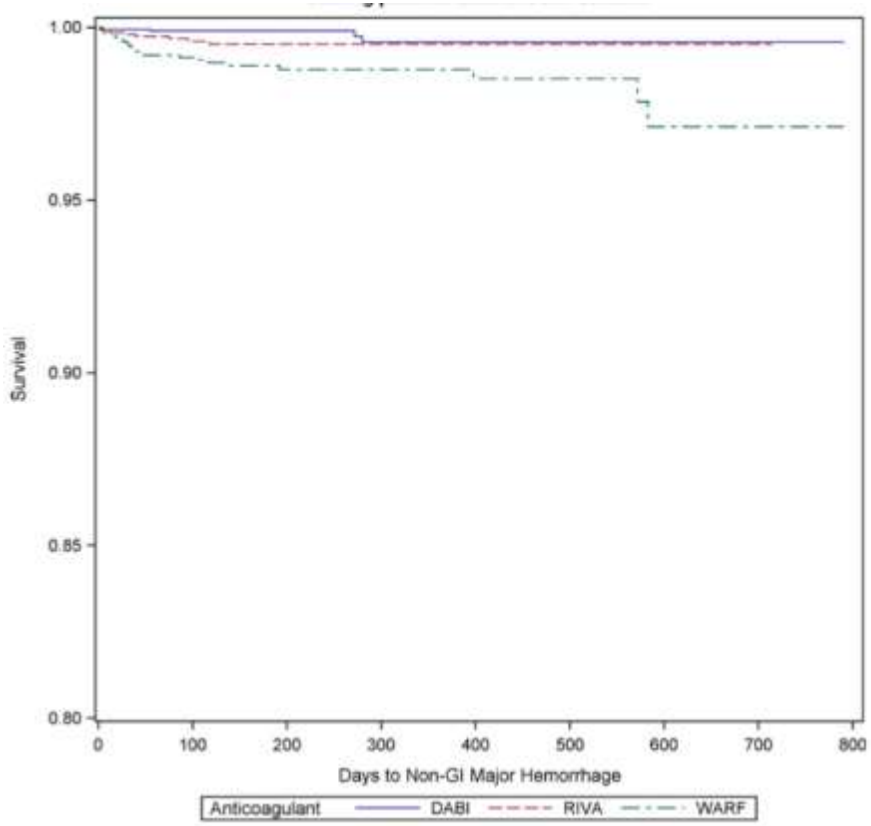
ISCHEMIC STROKE
ANY BLEEDING
MYOCARDIAL INFARCTION
GI BLEEDING

} *NO DIFFERENCE BETWEEN NOAC and VKA*

Briasoulis A et al. J Am Heart Assoc. 2018: 5;7(8): e008773

NOAC IN VALVULAR AF





STROKE
Dabigatran vs warfarin: 1.12 (0.59–1.1; P=0.7)
Rivaroxaban vs warfarin: 1.3 (0.7–2.4; P=0.4)
Rivaroxaban vs dabigatran: 1.1 (0.64–2.1; P=0.62)

NONGASTROINTESTINAL BLEEDING
Dabigatran vs warfarin: 0.17 (0.06–0.49; P=0.001)
Rivaroxaban vs warfarin: 0.37 (0.17–0.84; P=0.017)
Rivaroxaban vs dabigatran: 2.2 (0.66–7.3; P=0.2)

Briasoulis A et al. J Am Heart Assoc. 2018: 5;7(8): e008773

NOAC IN ATRIAL FIBRILLATION - GUIDELINES

- CHA2DS2-VASc
  - Score – Males -0 ; Females-1 : No antithrombotic
  - Score $\geq$ 1 (non sex risk factor +) – suggest oral anticoagulation
  - Score – Males $\geq$ 2 ;Females $\geq$ 3 – Recommend oral anticoagulation
- *Suggest using a non-vitamin K antagonist oral anti- coagulant drug rather than adjusted-dose vitamin K antagonist therapy*
- *Aim for TTR(Time in therapeutic range) > 70%*
- *If TTR < 65%, Consider switch to NOAC*

CHEST 2018 GUIDELINES

NOAC IN ATRIAL FIBRILLATION-GUIDELINES

- *Patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding - suggest using apixaban, edoxaban, or dabigatran 110 mg*
- *Patients with prior gastrointestinal bleeding - apixaban or dabigatran 110 mg bid preferable*
- *Patients at high risk of ischemic stroke- Dabigatran 150 mg twice daily recommended*
- *Patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion – NOAC/VKA recommended for 3 weeks before procedure and atleast 4 weeks after the procedure*

CHEST 2018 GUIDELINES

NOAC IN ATRIAL FIBRILLATION

1. *For patients with AF and an elevated CHA2DS2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended*
    1. *Warfarin*
    2. *Dabigatran*
    3. *Rivaroxaban*
    4. *Apixaban*
    5. *Edoxaban*
2. *NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve)*

AHA 2019 GUIDELINES

NOAC IN ATRIAL FIBRILLATION

- For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended
- In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended

AHA 2019 GUIDELINES

ACUTE CORONARY SYNDROME

Trials

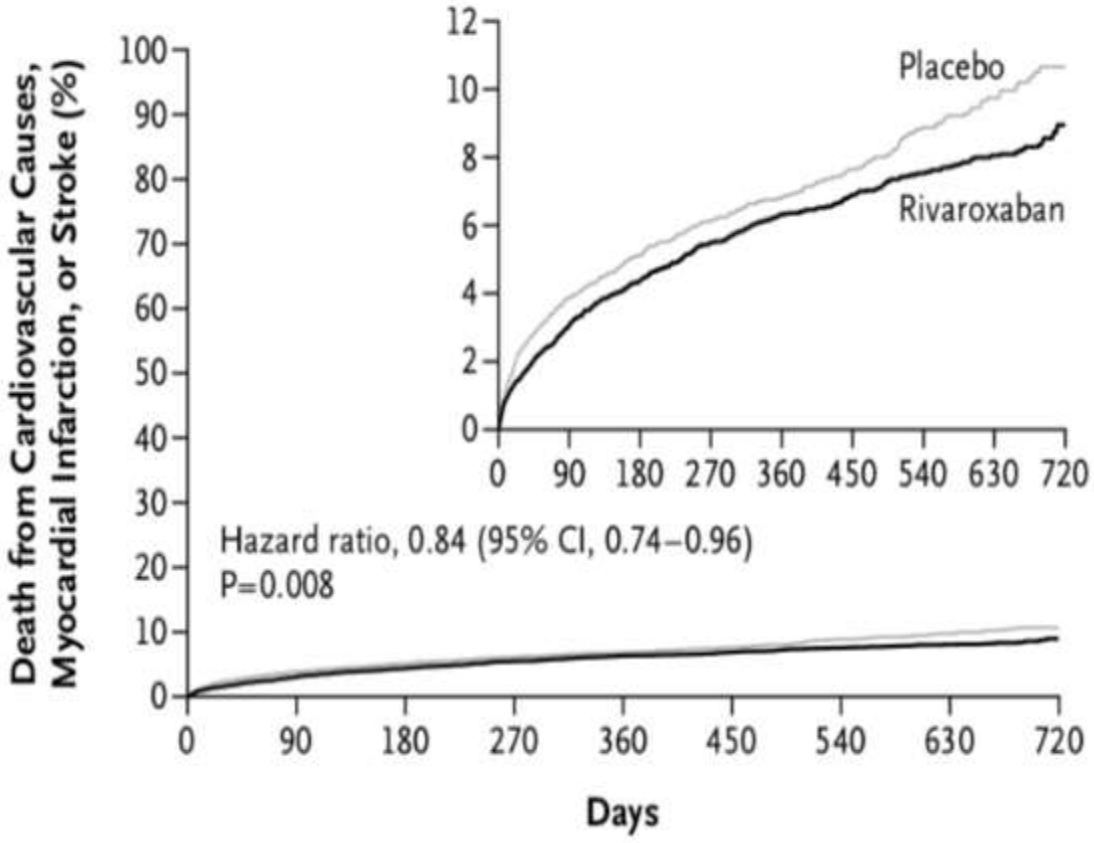
DABIGATRAN IN ACUTE CORONARY SYNDROME

TRIAL	COMPARATOR	OUTCOME
RE-DEEM	DABIGATRAN + DAP vs DAP (6 months)	HIGHER BLEEDING
D-fine	DABIGATRAN + DAP vs UFH + DAP during PCI	INADEQUATE ANTICOAGULATION

VERDICT
DABIGATRAN – NOT USEFUL IN ACS

Vranckx P et al. Euro Intervention. 2013;8:1052–60
Oldgren J et al. Eur Heart J. 2011;32:2781–9

RIVAROXABAN IN ACUTE CORONARY SYNDROME (ATLAS ACS 2–TIMI 51)

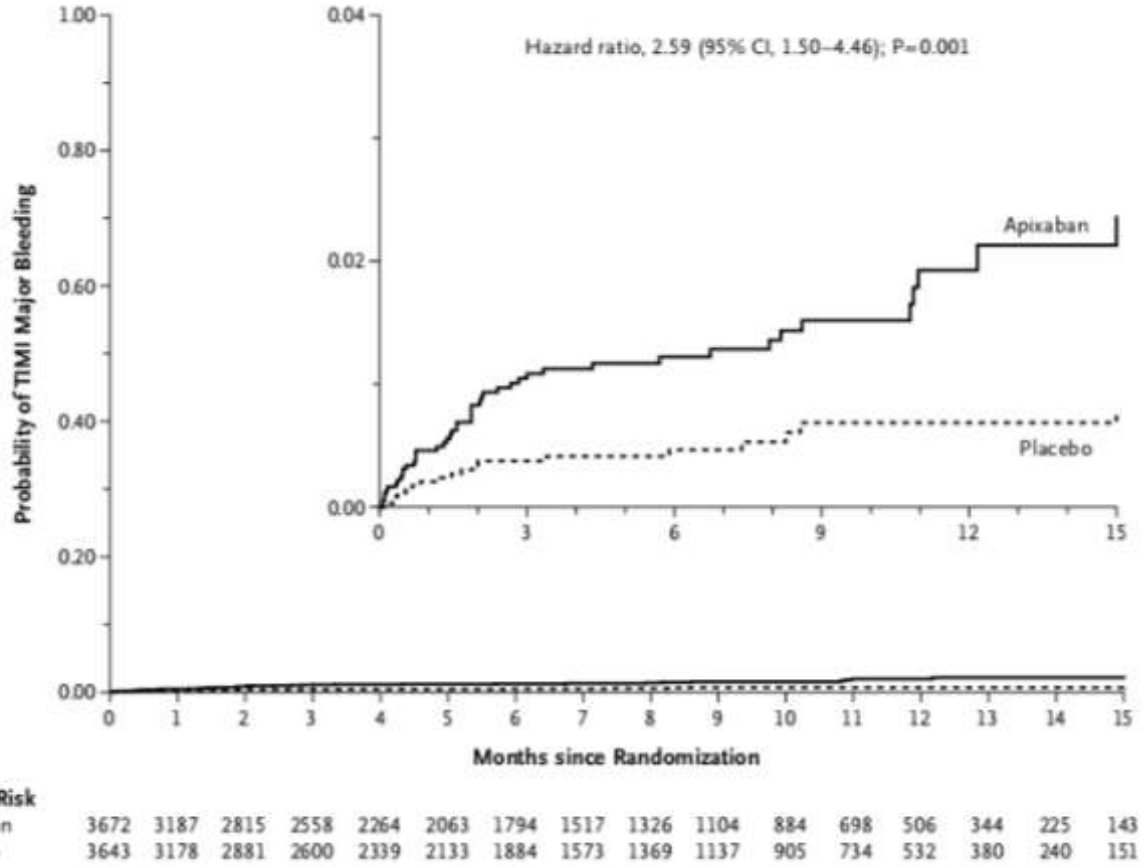


TIMI major bleeding not associated with CABG	65 (1.8)	82 (2.4)	147 (2.1)	19 (0.6)
TIMI minor bleeding	32 (0.9)	49 (1.6)	81 (1.3)	20 (0.5)
TIMI bleeding requiring medical attention	492 (12.9)	637 (16.2)	1129 (14.5)	282 (7.5)
Intracranial hemorrhage	14 (0.4)	18 (0.7)	32 (0.6)	5 (0.2)
Fatal bleeding	6 (0.1)	15 (0.4)	21 (0.3)	9 (0.2)

BETTER THAN PLACEBO
SIMILAR FATAL BLEEDING EVENTS

Mega JL et al. N Engl J Med. 2012;366:9–19.

APIXABAN IN ACUTE CORONARY SYNDROME(APPRAISE 2 TRIAL)



STUDY	PHASE 3
POPULATION	N=7392, POST ACS
INTERVENTION	1:1 , APIXABAN 5mg BD +DAP vs PLACEBO+DAP
OUTCOME	NO SIGNIFICANT CARDIOVASCULAR EVENT REDUCTION (P=0.51) MORE FATAL BLEEDING EVENTS (P=001)

NOT APPROVED

Alexander JH et al. N Engl J Med. 2011;365:699–708

SPECIAL SCENARIOS

ELDERLY POPULATION (≥ 75 years)

- Predisposing factors such as high frequency of renal failure, low body mass index, differed body composition of muscle and fatty tissue in the elderly
- All NOACs:
  - Efficacy is same as in younger individuals
  - Higher risk of Gastrointestinal bleeding
- Dabigatran –
  - 150mg BD dose has higher risk of GI bleeding than 110mg BD
  - No dose modification necessary

Karamichalakis et al. Journal of Geriatric Cardiology (2016) 13: 718-723

ELDERLY POPULATION(≥ 75 years)

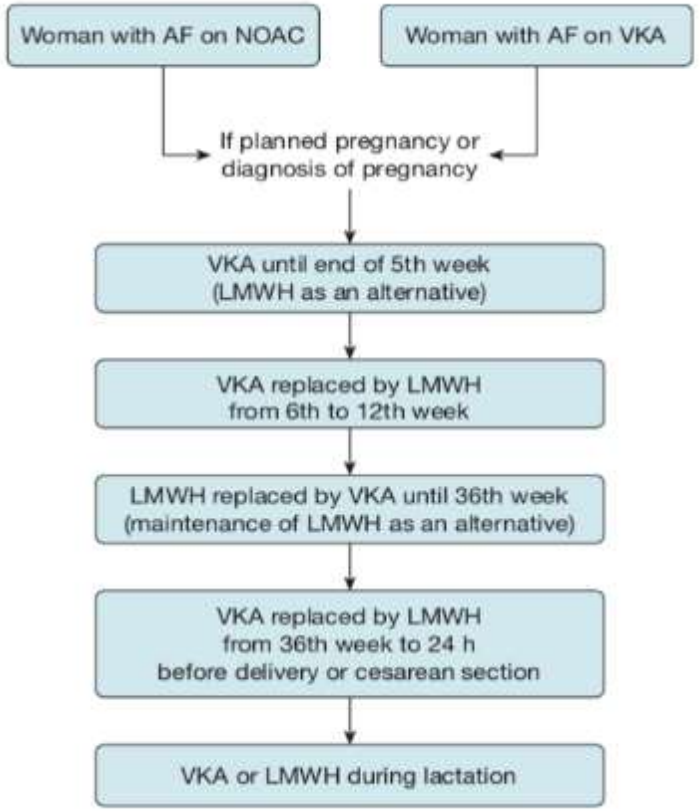
- Rivaroxaban - No dose modification necessary
- Apixaban
    - Age ≥ 80 years
    - Cr ≥ 1.5 mg/dl
    - Body weight ≤ 60 kg

  } If (2/3) Present - Dose reduced to 2.5mg BD
- Edoxaban – No dose modification necessary

Karamichalakis et al. Journal of Geriatric Cardiology (2016) 13: 718-723

PREGNANCY AND LACTATION

- *Pregnant women - suggest avoiding the use of NOACs – VKA preferred*
- *Breast-feeding women- suggest alternative anticoagulants rather than NOACs*



CHEST 2018 GUIDELINES

RENAL DYSFUNCTION

CrCl	≥ 50 (No modification)	30-49	15-29	<15
DABIGATRAN	150mg BD	110mg BD	CI	CI
RIVAROXABAN	20mg OD	15 mg OD	15 mg OD	CI
APIXABAN	5 mg BD	5mg BD	2.5 mg BD	CI
EDOXABAN	60mg OD	30mg OD	30mg OD	CI

Dabigatran has been approved in USA at CrCl 15-29 – 75mg BD
Apixaban has been approved in USA at CrCl <15.– 5mg BD

CI –CONTRAINDICATED
CrCl- CREATININE CLEARANCE

CHEST 2018 GUIDELINES

LIVER DYSFUNCTION

PROPERTIES	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
HEPATIC DYSFUNCTION (Dose adjustment)				
CTP A	No	No	No guidance	No guidance
CTP B	No	Contraindicated	No guidance	
CTP C	Contraindicated	Contraindicated	No guidance	

BODY MASS INDEX

- No effects on efficacy and safety were observed in subgroup analyses for body weight categories in the dabigatran, rivaroxaban, apixaban, and edoxaban studies
- However, patients with body weight <50 kg were marginally represented in all trials
- Caution is recommended with the use of NOACs in patients with body weight <50 kg and >150 kg

Becattini C et al. J Am Coll Cardiol. 2016 Apr 26;67(16):1941-55

GENDER

STUDY	METAANALYSIS
POPULATION	N=17,305 (3 RCTs), Medically ill
INTERVENTIONs	NOAC in males vs females for VTE prophylaxis
RESULT	VTE • Males OR 0.79 • Females OR 0.63 BLEEDING • Males OR 1.34 • Females OR 2.74

FEMALES HAVE FEWER VTE EVENTS WITH NOACs BUT WITH HIGHER BLEEDING RISK THAN MALES

Jackson C et al. CHEST. 2018. 154(4); 1051A

HAEMORRHAGIC RISK

- History of GI bleed – Apixaban/Dabigatran 110mg BD
- Major GI symptoms/dyspepsia – Apixaban/Rivaroxaban/Edoxaban
- High risk of bleeding (HAS-BLED $\geq$ 3)- Apixaban/Dabigatran110mg BD/Edoxaban

CHEST 2018 GUIDELINES

THROMBOPHILIC STATES

STUDY (n=1994)	METAANALYSIS (8 phase II/III RCT studies)
Population	Inherited and acquired thrombophilias with thrombotic events
Intervention	Rivaroxaban/dabigatran/edoxaban
Result	Risk of VTE recurrence similar to those without thrombophilias(RR, 0.70; 95% CI, 0.34-1.44) Limited data on high risk Antiphospholid syndrome

Cohen H et al. J Thromb Haemost. 2018 Jun;16(6):1028-1039

THROMBOPHILIC STATES

- Only exception is Antiphospholipid syndrome

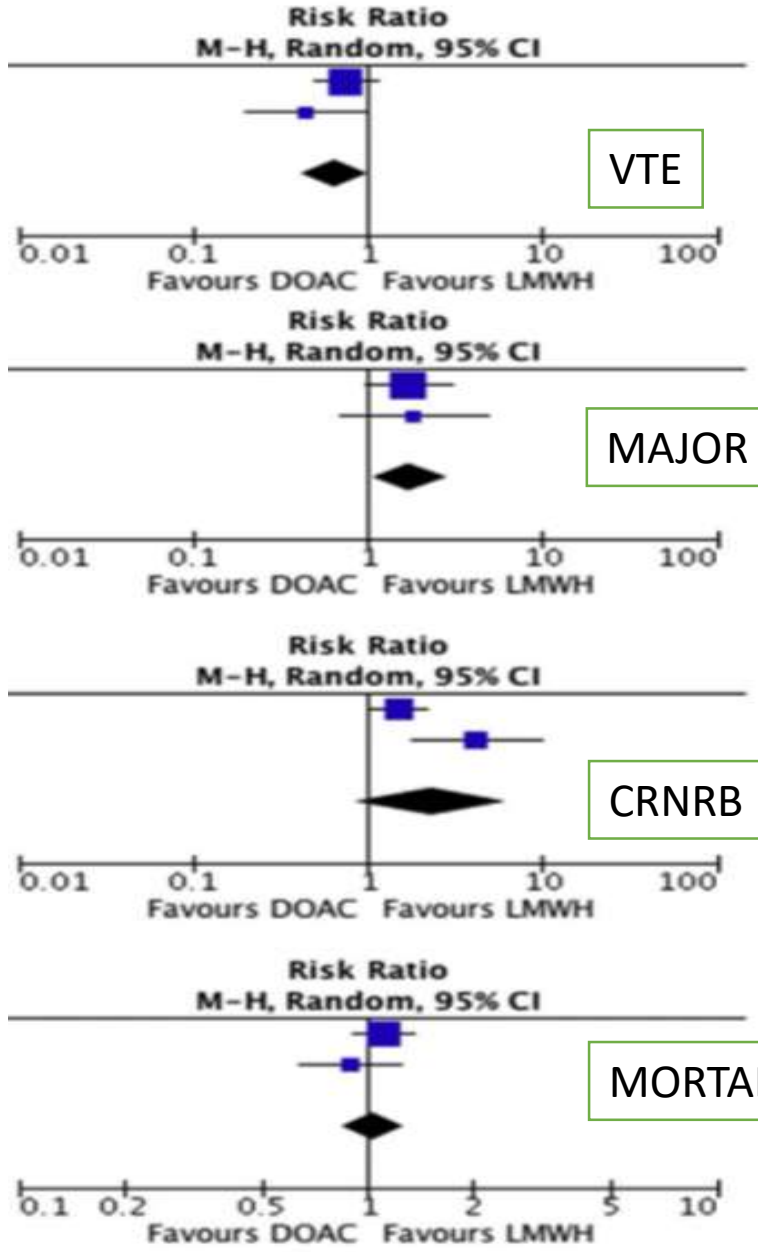
STUDY (n=120)	Randomized, open-label, multicenter, non-inferiority study
Population	High risk Thrombotic APS (Triple antibody +ve)
Intervention	Rivaroxaban 20mg OD vs warfarin
Result	Thromboembolic events 12 % vs 0%

NOACs not advised in high risk thrombotic APS

Pengo V et al. Blood 2018 ;132(13):1365-1371

MALIGNANCY – VTE TREATMENT

STUDY	METAANALYSIS
POPULATION	2 RCTs –Metastatic cancer patients with VTE *HOKUSAI-Cancer TRIAL* Edoxaban vs Dalteparin *SELECT-D TRIAL* Rivaroxaban vs Dalteparin
RESULT	• *NOACs - Lower risk of recurrent VTE in 6 months* RR: 0.65 (95% CI: 0.42–1.01) • *NOACs - Higher incidence of 6-month major bleeding when compared to LMWHs* RR: 1.74 (95% CI: 1.05–2.88) • *Mortality – no difference* RR: 1.03 (95% CI: 0.85–1.26)



A Li et al. Thrombosis Research. 2019: 173; 158–163

MALIGNANCY – VTE TREATMENT

- *Though statistically important, the absolute risk differences between treatments with DOACs versus LMWHs are small for both recurrent VTE (−3% (−6% to 0%)) and major bleeding (+2% (0 to +4%)*
- *Major bleeding episodes related to DOACs seems to be limited to the upper gastrointestinal tract*
- *Bleeding more in those with gastrointestinal cancers*

A Li et al. Thrombosis Research. 2019: 173; 158–163

MALIGNANCY RELATED VTE

In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban

CHEST GUIDELINES VTE 2016

MALIGNANCY - VTE PROPHYLAXIS (AVERT TRIAL)

STUDY	RCT
POPULATION	N=563, intermediate to high risk cancer patients, started on chemotherapy
INTERVENTION	Apixaban 2.5mg BD vs Placebo, 180 days

INCLUSION CRITERIA

Newly diagnosed cancer or progression of known cancer after complete or partial remission and who were initiating a new course of chemotherapy with a minimum treatment intent of 3 months with Khorana score ≥ 2

EXCLUSION CRITERIA

1. *Life expectancy of less than 6 months*
2. *Renal insufficiency with a glomerular filtration rate of less than 30*
3. *Platelet count of less than 50,000*
4. *Body weight < 40kg*

KHORANA SCORE

Variable	Score
Very high-risk tumor (stomach, pancreas)	2
High-risk tumor (lung, gynecologic, genitourinary excluding prostate)	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 × 10^9/L	1
Prechemotherapy platelet count 350 × 10^9/L or greater	1
Body mass index 35 kg/m^2 or greater	1

A score of 0 = low-risk category. A score of 1–2 = intermediate-risk category. A score of >2 = very high-risk category.

Carrier M et al. N Engl J Med 2019; 380(8): 711-719

MALIGNANCY - VTE PROPHYLAXIS (AVERT TRIAL)

Outcome	Apixaban (N=288)	Placebo (N=275)	Hazard Ratio (95% CI)*	P Value
Venous thromboembolism — no. (%)	12 (4.2)	28 (10.2)	0.41 (0.26–0.65)	<0.001
Deep-vein thrombosis — no. (%)	7 (2.4)	12 (4.4)		
Pulmonary embolism — no. (%)†	5 (1.7)	16 (5.8)‡		
Incidental pulmonary embolism — no./total no.	3/5	6/16		
Major bleeding episode				
Any episode — no. (%)	10 (3.5)	5 (1.8)	2.00 (1.01–3.95)	0.046
Severity of episode — no./total no. (%)§				
Category 1	1/10 (10)	0		
Category 2	8/10 (80)	3/5 (60)		
Category 3	1/10 (10)	2/5 (40)		
Category 4	0	0		
Clinically relevant nonmajor bleeding — no. (%)¶	21 (7.3)	15 (5.5)	1.28 (0.89–1.84)	
Outcome occurred during the treatment period — no. (%)				
Venous thromboembolism	3 (1.0)	20 (7.3)	0.14 (0.05–0.42)	
Major bleeding episode	6 (2.1)	3 (1.1)	1.89 (0.39–9.24)	
Death from any cause — no. (%)	35 (12.2)	27 (9.8)	1.29 (0.98–1.71)	

DECREASES THE INCIDENCE AT A HIGHER RISK OF BLEEDING

Carrier M et al. N Engl J Med 2019; 380(8): 711-719

MALIGNANT-VTE PROPHYLAXIS (CASSINI TRIAL)

STUDY	RCT
DRUG	Rivaroxaban vs placebo
Population	High risk cancer patients , n=841
OUTCOME	EFFICACY : 6% vs 8.8% (p=0.10) BLEEDING :2% vs 1%

NO REDUCTION IN VTE INCIDENCE
HIGHER BLEEDING RISK

Khorana AA et al. N Engl J Med. 2019 ;380(8):720-728

ISTH GUIDELINES FOR NOAC IN CANCER RELATED VTE

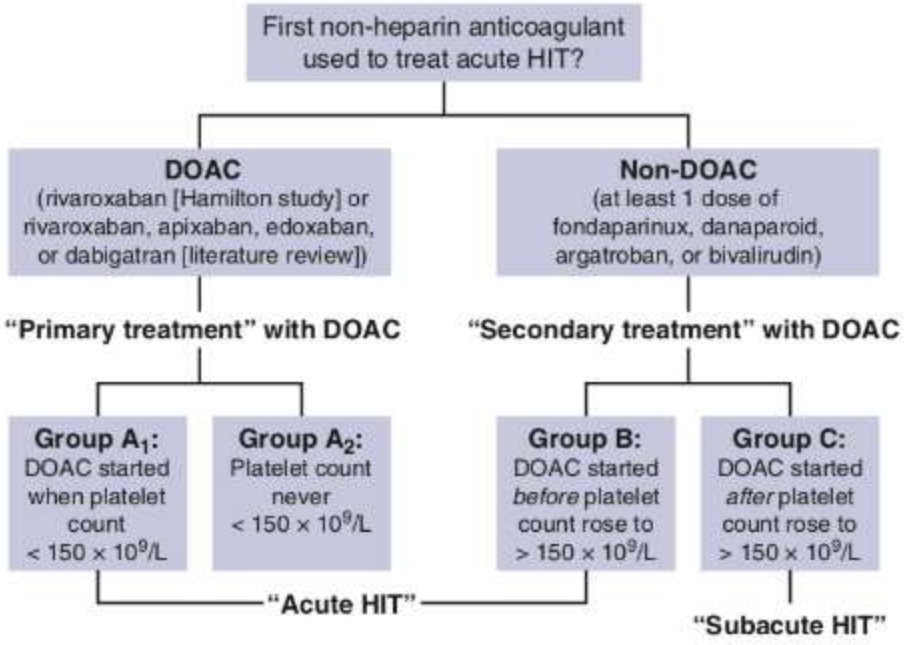
- Recommend individualized treatment regimens after shared decision-making with patients
- Suggest the use of specific DOACs for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy
- LMWHs constitute an acceptable alternative
- Edoxaban and Rivaroxaban are the only DOACs that have been compared with LMWH in RCTs in cancer populations

ISTH GUIDELINES 2018

HEPARIN INDUCED THROMBOCYTOPENIA

Study author	Reference	No. of patients	Group A_1	Group A_2	Group B	Median platelet count at rivaroxaban start	HIT-associated thrombosis* No.	HIT-associated thrombosis* %	Outcome: Thrombosis No.	Outcome: Thrombosis %	Outcome: Bleed No.	Outcome: Bleed %
Rivaroxaban-Hamilton experience												
Linkins et al	17	12	3	2	7	56	6		1		0†	
This study		10	7	1	2	64	5		0		0	
Rivaroxaban-other (non-Hamilton) centers												
Kopolovic and Warkentin	28	1	0	0	1	30	0		0		0	
Ng et al, Ong et al‡	29, 36	9	9	0	0	64	9		0		0	
Sharifi et al§	30	9‡	0	0	9	90‡	4		0		0	
Hantson et al	31	1	0	0	1	30	1		0		0	
Abouchakra et al	32	1	1	0	0	25	1		0		0	
Sartori et al	33	1	0	1	0	150	1		0		0	
Casan et al	34	1	0	0	1	48	1		0		0	
Samoš et al	35	1	1	0	0	65	1		0		0	
Summary		46	21	4	21	73	29/46‖	63.0	1/46	2.2	0/46	0

Study author	Reference	No. of patients	Group A_1	Group A_2	Group B	Median platelet count at DOAC start	HIT-associated thrombosis* No.	HIT-associated thrombosis* %	Outcome: Thrombosis No.	Outcome: Thrombosis %	Outcome: Bleed No.	Outcome: Bleed %
Apixaban												
Sharifi et al†	30	5	0	0	5	90‡	1		0		0	
Larsen et al	37	1	1	0	0	112	0		0		0	
Delgado-García et al§	38, 39	1	1	0	0	25	1		0		0	
Kunk et al	40	5	0	0	5	111	3		0		0	
Total		12	2	0	10	90‡	5/12‖	41.7	0/12	0	0/12	0
Dabigatran												
Sharifi et al†	30	6	0	0	6	90‡	2		0		0	
Annicchérico et al	41, 42	1	0	0	1	120	1		0		0	
Mirdamadi§	43	1	1	0	0	32	1		0		0	
Tardy-Poncet et al	44	1	0	0	1	56	0		0		0	
Noel et al	45	1	0	1	0	216	1		1¶		0	
Bircan and Alanoglu§	46	1	1	0	0	52	1		0		0	
Total		11	2	1	8	58	6/11‖	54.5	1/11	9.1	0/11	0



Warkentin TE et al. Blood 2017; 130(9): 1104-1113

USG GUIDED THORACENTESIS

STUDY	RETROSPECTIVE
POPULATION	NOAC patients who underwent USG guided thoracentesis, n=57
RESULTS	Overall risk of significant bleeding 0.1%

USG GUIDED THORACENTESIS CAN BE SAFELY PERFORMED IN PATIENTS ON NOACs

SURGERY

	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
CrCl, mL/min	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

NO NEED FOR ANY BRIDGING ANTICOAGULATION BEFORE OR AFTER SURGERY

Doherty et al. Journal of the American College of Cardiology. 2017; 23217

SURGERY

- *Establish that hemostasis has been achieved, procedure-specific bleeding complications have been considered, patient-specific bleeding factors have been evaluated*
- Low postprocedural bleed risk - Resume DOAC therapy at full dose on the day following the procedure
- High postprocedural bleed-risk - wait at least 48 to 72 hours before resuming DOAC therapy at full dose

Doherty et al. Journal of the American College of Cardiology. 2017; 23217

FDA APPROVED INDICATIONS

DABIGATRAN

- **Prevention of VTE post THR/TKR**
  - CrCl 30-50 : 150mg OD
  - CrCl > 50 : 220mg OD
- **Treatment of VTE**
  - Age ≥ 75 years or CrCl 30 – 50 or high bleeding risk : 110mg BD
  - Age < 75 years + CrCl > 50 + no bleeding risk : 150 mg BD
- **Prevention of stroke and systemic embolism in non-valvular AF**
  - Age ≥ 75 years or CrCl 30-50 or high bleeding risk : 110mg BD
  - Age < 75 years + CrCl > 50 + no bleeding risk : 150mg BD

APIXABAN

- **Prevention of VTE post THR/TKR**
  - CrCl ≥ 25 : 2.5 mg BD
- **Treatment of VTE**
  - CrCl ≥ 25 : 10 mg BD for 7 days f/b 5mg BD
- **Prevention of recurrent VTE**
  - CrCl ≥ 25 : 2.5mg BD (After 6 months of VTE treatment)
- **Prevention of stroke and systemic embolism in non-valvular AF**
  - CrCl ≥ 25 + alteast 2 out of the following 3 criteria : 2.5 mg BD
    - Age ≥ 80 years/Creatinine ≥ 1.5/wt ≤ 60
  - CrCl ≥ 25 and criteria not fulfilled : 5 mg BD

RIVAROXABAN

- **Prevention of VTE post THR or TKR**
  - CrCl ≥ 15 : 10mg OD
- **Treatment of VTE and prevention of recurrent VTE**
  - CrCl ≥ 30 : 15mg BD for 3 weeks f/b 20mg OD
- **Continued use to reduce the risk of VTE**
  - Post 6 months – 10mg OD for 12 extended period
- **Prevention of stroke and systemic embolism in non- valvular AF**
  - CrCl ≥ 50 : 20mg OD
  - CrCl 30 – 49 : 15mg OD

EDOXABAN

- **Prevention of stroke and systemic embolism in non- valvular AF**
  - CrCl > 50 : 60mg OD
  - CrCl 15-50: 30 mg OD
- **Treatment of VTE**
  - 5-10 days of parenteral anticoagulation
    - f/b 60 mg OD (CrCl > 50)
    - f/b 30mg OD (CrCl 15-50)

BETRIXABAN

- **Prophylaxis of VTE in medically ill patients**
  - 160mg -1st day f/b 80 mg OD for 35-42 days

CONTRAINDICATIONS

- Known hypersensitivity
- Renal dysfunction (CrCl <15ml/min) and for Dabigatran CrCl < 30ml/min
- Hepatic dysfunction with coagulopathy
- Clinically significant active bleeding
- Significant inherited or acquired bleeding disorder
- Organ lesions at risk of bleeding including intracranial haemorrhage in previous 6 months
- Indwelling spinal or epidural catheter and during the first 6 hours after removal
- Mechanical heart valve
- Pregnancy or breastfeeding mother

MONITORING

INDICATIONS:

- Patients undergoing urgent surgical procedures
- Uncovering accumulation of potentially toxic drug levels in patients with CKD or those undergoing dialysis
- Detection of potential drug–drug interactions to guide dose adjustment

AHA 2019 GUIDELINES

MONITORING

	Exclude Clinically Relevant* Drug Levels	
Drug	**Suggested Test**	**Interpretation**
Dabigatran	TT, aPTT	**Normal TT** excludes clinically relevant* levels **Prolonged TT** does not discriminate between clinically important and insignificant levels **Normal aPTT** usually excludes clinically relevant* levels, if a sensitive reagent is used.
Apixaban	None	**Normal PT and aPTT** do not exclude clinically relevant* levels
Edoxaban or rivaroxaban	None	**Normal PT and aPTT** do not exclude clinically relevant* levels

Thrombin time and prothrombin time are not good tests to assess the anticoagulant activity of NOACs

MONITORING

	Clinical Objective		
	Exclude Clinically Relevant* Drug Levels		Measure On-Therapy or Above On-Therapy Drug Levels
Drug	**Suggested Test**	**Interpretation**	**Suggested test**
Dabigatran	Dilute TT ECT ECA	Normal result probably excludes clinically relevant* levels	Dilute TT ECT ECA
Apixaban, edoxaban, or rivaroxaban	Anti-Xa	Absent chromogenic anti-Xa assay activity probably excludes clinically relevant* levels	Anti-Xa†

- *Best tests for assessing the anticoagulant activity of dabigatran include the Dilute thrombin time, Ecarin clotting time, and Ecarin chromogenic assay*
- *The preferred test for assessing the anticoagulant activity of apixaban, edoxaban, and rivaroxaban is a chromogenic anti-Xa assay*

FOLLOWUP OF PATIENTS ON NOAC

SCENARIO		STEPS ADVISED
FOLLOWUP ON NOAC	NORMAL RFT	RFT at baseline, 1st month and every 6 months
	ABNORMAL RFT	RFT at baseline, 1st month and atleast every 6 months
SWITCH FROM VKA	INR < 2	Start NOAC same day
	INR 2-2.5	Start next day
	INR >2.5	Retest INR, consider Half life of VKA

Becattini C et al. J Am Coll Cardiol. 2016 Apr 26;67(16):1941-55

WARFARIN VS NOAC – BLEEDING

STUDY	MULTICENTRE OBSERVATIONAL STUDY
POPULATION	N=2002, Bleeding on VKA/NOAC
OBSERVATION	Blood products/Reversal agents transfused and mortality
RESULTS	• Blood products transfused – equal • Reversal agents – Vit K/PCC more used in VKA cases than reversal agents PCC/rFVIIa for NOAC cases • 30 day mortality similar (12.6% - NOAC vs 16.3%- VKA)

NO DIFFERENCE IN BLEEDING RELATED MORTALITY BETWEEN VKA AND NOAC

Yan Xu et al. CHEST 2017; 152(1):81-91

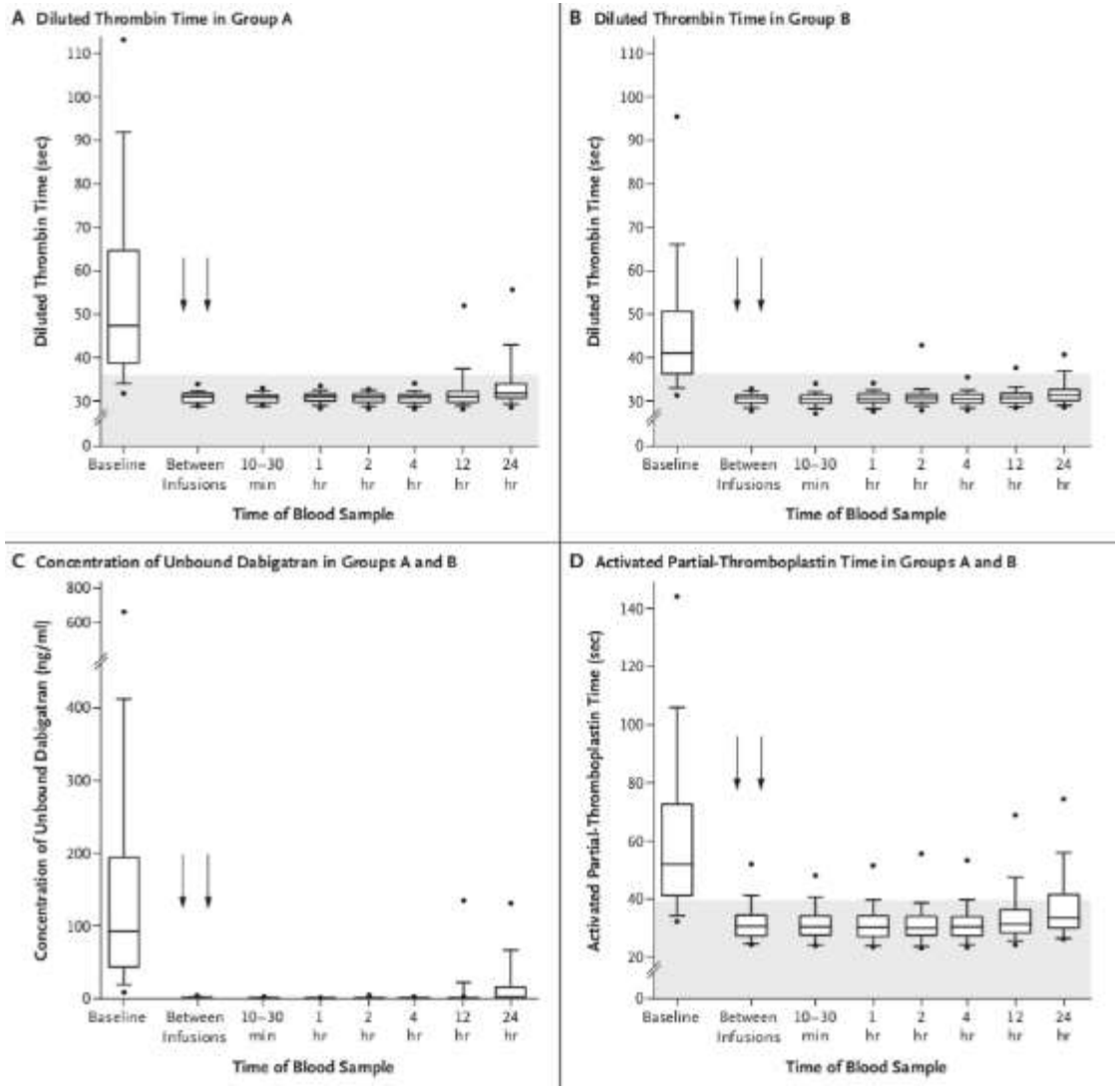
REVERSAL AGENTS

TRIALS

GUIDELINES

IDARUCIZUMAB – DABIGATRAN REVERSAL (RE-VERSE AD TRIAL)

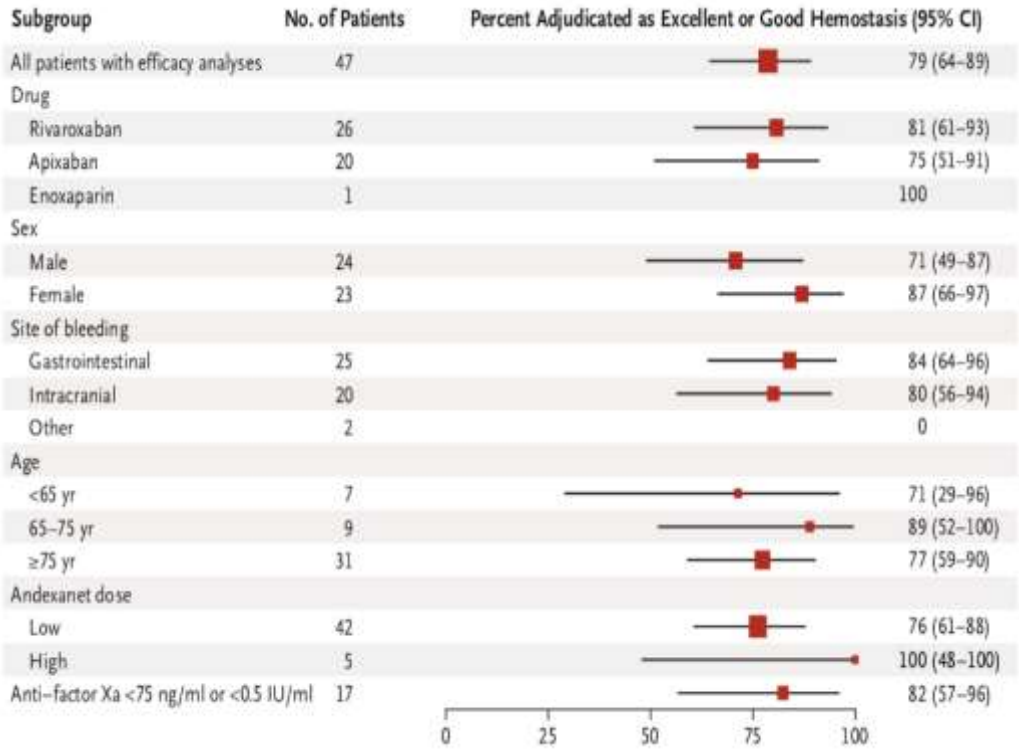
STUDY	Multicenter, prospective, open-label study
POPULATION	N=503, Group A- uncontrolled bleeding Group B- urgent surgical procedure
INTERVENTION	5g (i.v).Idarucizumab to both groups (2.5 g bolus – 2 infusions)
OUTCOME	• Group A - Median time to the cessation of bleeding was 2.5 hours • Group B – Median time to initiation of procedure 1.6 hours • Complete reversal -98% patients • Sustained for 24 hours • No serious adverse events



Pollack CV Jr et al. N Engl J Med. 2017;377:431-41

ANDEXANET ALFA – FACTOR XA REVERSAL (ANNEXA -4 TRIAL)

STUDY	Multicenter, prospective, open-label
POPULATION	N=67, Post factor Xa inhibitor bleeding
INTERVENTION	• Patients on Rivaroxaban /Apixaban before 7 hours – 400mg f/b 480 mg 2 hour infusion • Double the dose if received antifactor Xa within 7 hours
OUTCOME	Anti-factor Xa levels at 4 hours Rivaroxaban group –decreased by 39% Apixaban group –decreased by 30% At 12 hours – 79% patients achieved effective hemostasis



Connolly SJ et al. N Engl J Med. 2016;375:1131-41

COMPARING THE REVERSAL AGENTS

	IDARUCIZUMAB	ANDEXANET ALFA	Ciraparantag
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)	Synthetic water-soluble cationic small molecule
Binding	Non competitive binding to dabigatran	Competitive binding to direct factor Xa inhibitor	Covalent hydrogen bonding
Neutralise	Dabigatran	Rivaroxaban and LMWH	Factor Xa inhibitors and LMWH
Affinity	350 times	Same	-
Onset	5 mins	2 mins	5-10 mins
Half-life	Initial: 47 min Terminal: 10.3 h	Terminal : 6 hours	24 hours
Elimination	Renal	Not known	Not known
Dose	5 g administered as 2 doses of 2.5 g IV over 5-10 min, 15 min apart	400-800 mg IV bolus (30 mg/min) followed by infusion of 4-8 mg/min	100-300 mg IV bolus
Storage	Refrigerated	Refrigerated	Room temperature

REVERSAL - GUIDELINES

- *Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure*
- *Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding*

AHA 2019 GUIDELINES

ACC GUIDELINES ON REVERSAL AGENTS

Reversal Agent	Factor IIa Inhibitor (Dabigatran)	Factor Xa Inhibitor (Apixaban, Edoxaban and Rivaroxaban
4F-PCC (factor II, VII, IX, X)	Second line 50 U/kg (max dose 4,000 U)	First line
aPCC (factor II, VII, IX, X)-active +inactive forms	Second line 50 U/kg (max dose 4,000 U)	Second line
Idarucizumab	First line	-
Plasma	Not indicated	Not indicated
Vitamin K	Not indicated	Not indicated

Tomaselli GF et al. J Am Coll Cardiol. 2017; 70(24): 3042-3067

INDICATIONS OF REVERSAL AGENTS – ISTH GUIDELINES

- Life-threatening bleeding (like Intracranial bleed)
- Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome
- Persistent major bleeding despite local hemostatic measures
- Need for urgent intervention

Levy J.H et al. J Thromb Haemost 2016; 14: 623-627

REVERSAL AGENTS SHOULD NOT BE USED :

- Elective surgery
- Gastrointestinal bleeds that respond to supportive measures
- High drug levels or excessive anticoagulation without associated bleeding

Levy J.H et al. J Thromb Haemost 2016; 14: 623-627

TAKE HOME MESSAGE ON NOACs

SCENARIO	COMMENT
VTE prophylaxis in post surgical patients	NOAC > LMWH
VTE prophylaxis in medically ill patients	LMWH/Betrixaban
VTE treatment – non cancer	NOAC > LMWH
VTE treatment – Non GI tract malignancies	LMWH > NOAC
VTE treatment – GI tract malignancies	Avoid NOAC
AF (Non valvular)	NOAC > LMWH
AF (valvular)	LMWH > NOAC
VTE prophylaxis in high risk cancer patients	NOAC not to be used (higher bleeding risk)
Routine monitoring	Not needed
Monitoring	DTT/ECT/ECA/Chromogenic factor Xa assay
Renal dysfunction	Contraindicated if CrCl < 15 (Dabigatran - if CrCl < 30)
Liver dysfunction with coagulopathy	Contraindicated
Elderly and higher bleeding risk individuals	Dabigatran dose to be reduced to 110mg BD/apixaban preferred
Thrombophilic VTE	Can be used except in high risk APS
Pregnancy and lactation	Contraindicated

TAKE HOME MESSAGE

SCENARIO	COMMENT
Heparin induced thrombocytopenia	NOACs can be used
High risk of acute coronary syndrome/MI	Avoid Dabigatran
Reversal agent – Dabigatran	Idarucizumab > 4F-PCC/aPCC
Reversal agent- Factor Xa inhibitors	4F-PCC/aPCC > Andexanet alfa

THANK YOU