New Drugs in VTE (Venous Thromboembolism)

아주의대
호흡기내과
박 광 주

VTE (venous thromboembolism)

- DVT (deep vein thrombosis)
- PE (pulmonary embolism)

- Arterial thromboembolism due to Atrial Fibrillation and Coronary artery disease
- ACCP guideline: Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report 2016
- UK NICE (The National Institute for Health and Care Excellence) guideline

Indications of anticoagulation

- Prevention of CVA in (non-valvular) AF
- Prevention of VTE in major orthopedic surgery
- Treatment of acute VTE
- Secondary prevention in acute VTE (Extended treatment)
- Prevention of VTE in immobilized pts with various medical conditions
- Coronary artery disease
- Secondary prevention in CVA

Historical Perspective

- 1916, Discovery of heparin:
  Jay McLean, Johns Hopkins
- 1937, first human trial of **heparin**
- 1940, isolation of coumarin (sweet clover)
- 1941, Wisconsin Alumni Research Foundation (WARF) – **Warfarin**
- 1948, Warfarin as rat poison
- 1954, **Warfarin** for human use
- 1974 Vit K dependent carboxylase
- 1980s LMWH
- 2000s NOACs

Platelet 1882
Thrombin & Fibrin, 1905

Vitamin K 1930
factor VIII 1936

factor V 1947
factor VII, IX 1952
factor XI 1953
factor XII 1955
factor X 1957
Antithrombin III 1968

VKA (vitamin K antagonist)

- Warfarin
- Rat poison 1948, Human use 1954
- Inhibit γ-glutamyl carboxylation of II, VII, IX, X, and coagulation inhibitor proteins C and S
- Narrow therapeutic window
- Slow onset
- Frequent, routine monitoring
- Pharmacokinetic variation due to genetic and physiological factors
- Frequent interaction with other drug and foods

JAMA The Journal of the American Medical Association

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SUICIDE ATTEMPT WITH WARFARIN, A BISHYDROXYCOUMARIN-LIKE RODENTICIDE

Roy W. Holmes, (MC), U. S. N.; Julian Love, (MC), U. S. N.

JAMA. 1952;148(11):935-937. doi:10.1001/jama.1952.62930110003013a.

**warfarin:
Good and evil?**

SUICIDE ATTEMPT WITH WARFARIN, A BISHYDROXYCOUMARIN-LIKE RODENTICIDE

Lieutenant Roy W. Holmes (MC), U. S. N.
and
Captain Julian Love (MC), U. S. N., Philadelphia

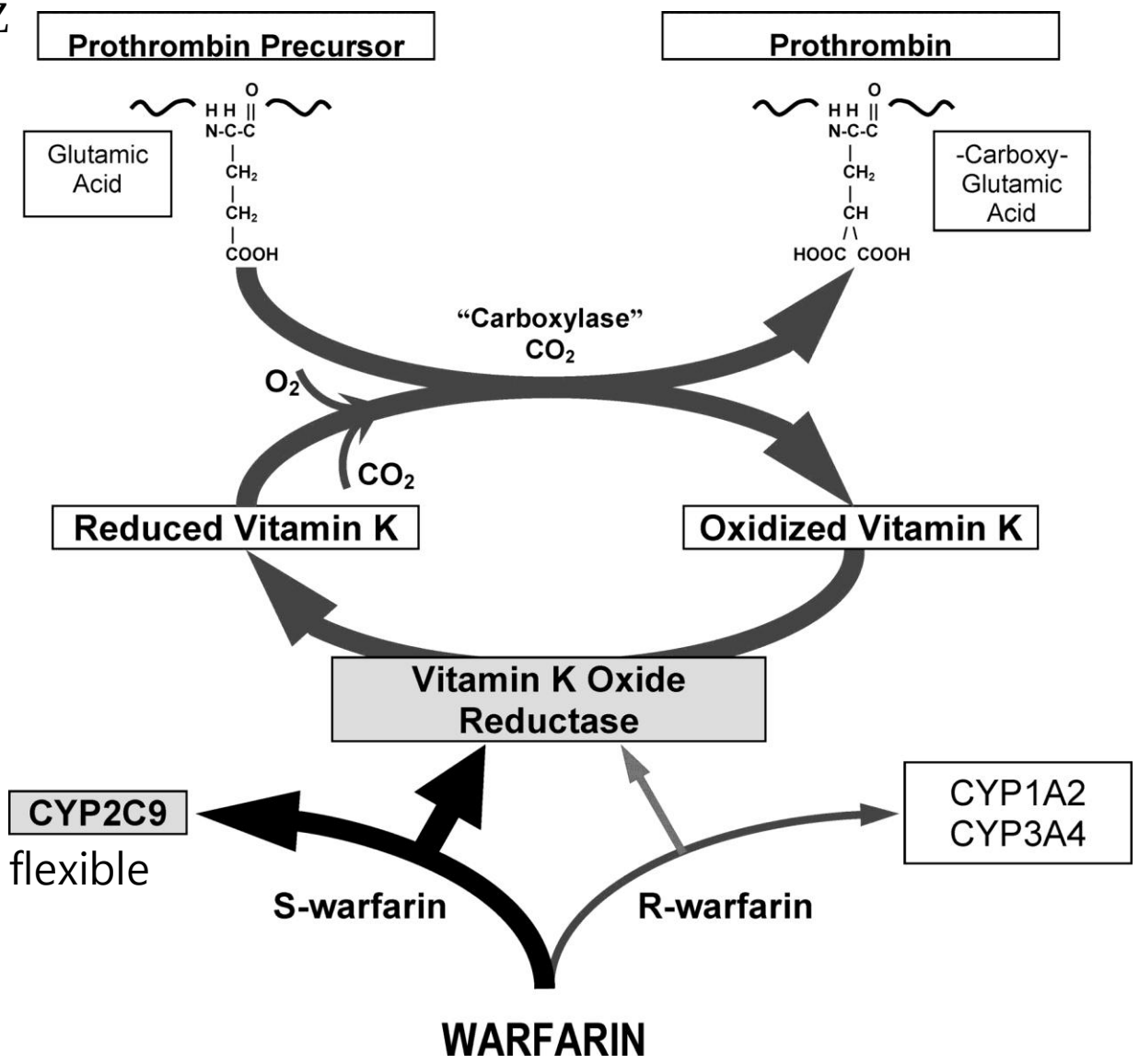
Through the ages the rat, which has caused untold amounts of sickness and death as well as property damage that far exceeds human imagination, has been a major scourge of mankind. Investigators throughout the world have searched for the ideal rat poison, which, according to O'Connor,[1] must have the following characteristics: 1. It must be surely effective in baits of small quantity so that its presence is not detected by the rodent. 2. The finished bait must not excite shyness of the rat

He noticed no ill effects of the
mission, when he began to have
kidneys and abdominal pain that
The pains continued until admis
episode of vomiting the day pric
on the day before admission he
nose would bleed for 15 to 20 m
he lay down, and the epistaxis
discharge of pinkish fluid. The p
any blood in his urine or in the
movements since he had taken th

The psychiatric component of
included, because it has no beari
port. The remainder of the his
ities and the patient had been pe
the poison.

Physical examination on admiss
well-nourished young white man
thermore, he was obviously menta
to elaborate about his symptoms,

Factor VII, IX, X
Protein C, S, Z



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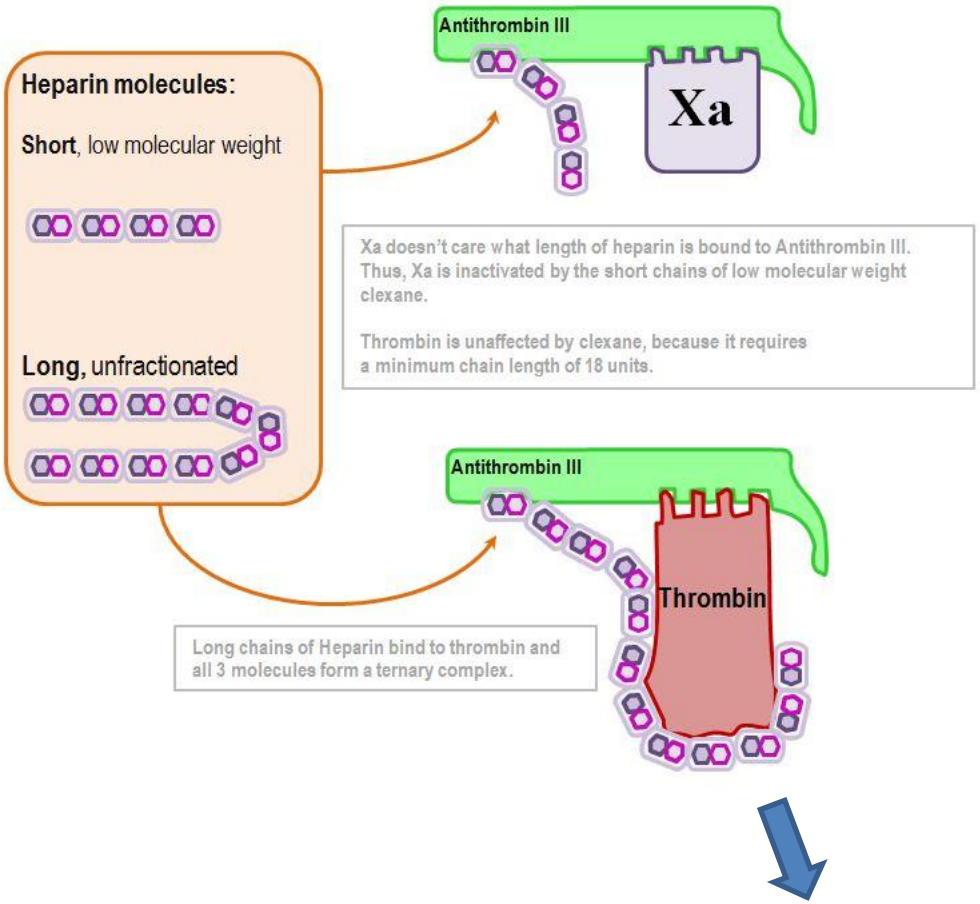
Other anticoagulants

- LMWH: dalteparin, enoxaparin
  stable and predictable anticoagulation
  unpredictable bioavailability (obese,
  renal failure)
- Indirect acting factor Xa inhibitors: Fondaparinux (Arixtra®), Idraparinux
- Hirudin: parenteral direct thrombin inhibitor
- Ximelagatran: oral direct thrombin inhibitor

LMWH



- Inhibit Clot-bound Xa
- Longer half life

More predictable anticoagulant response

- Binds to plasma proteins including acute phase reactant and vascular and blood cells
- Neutralized by platelet factor 4

NOAC

- Novel (New) oral anticoagulants
- Non-vitamin K anticoagulants
- DOAC: direct oral anticoagulants
- TSOAC: target-specific oral anticoagulants
- Predictable pharmacokinetic profiles
- Simple dosing
- No routine coagulation monitoring
- Lack of antidote
- **Difficult names**

NOAC

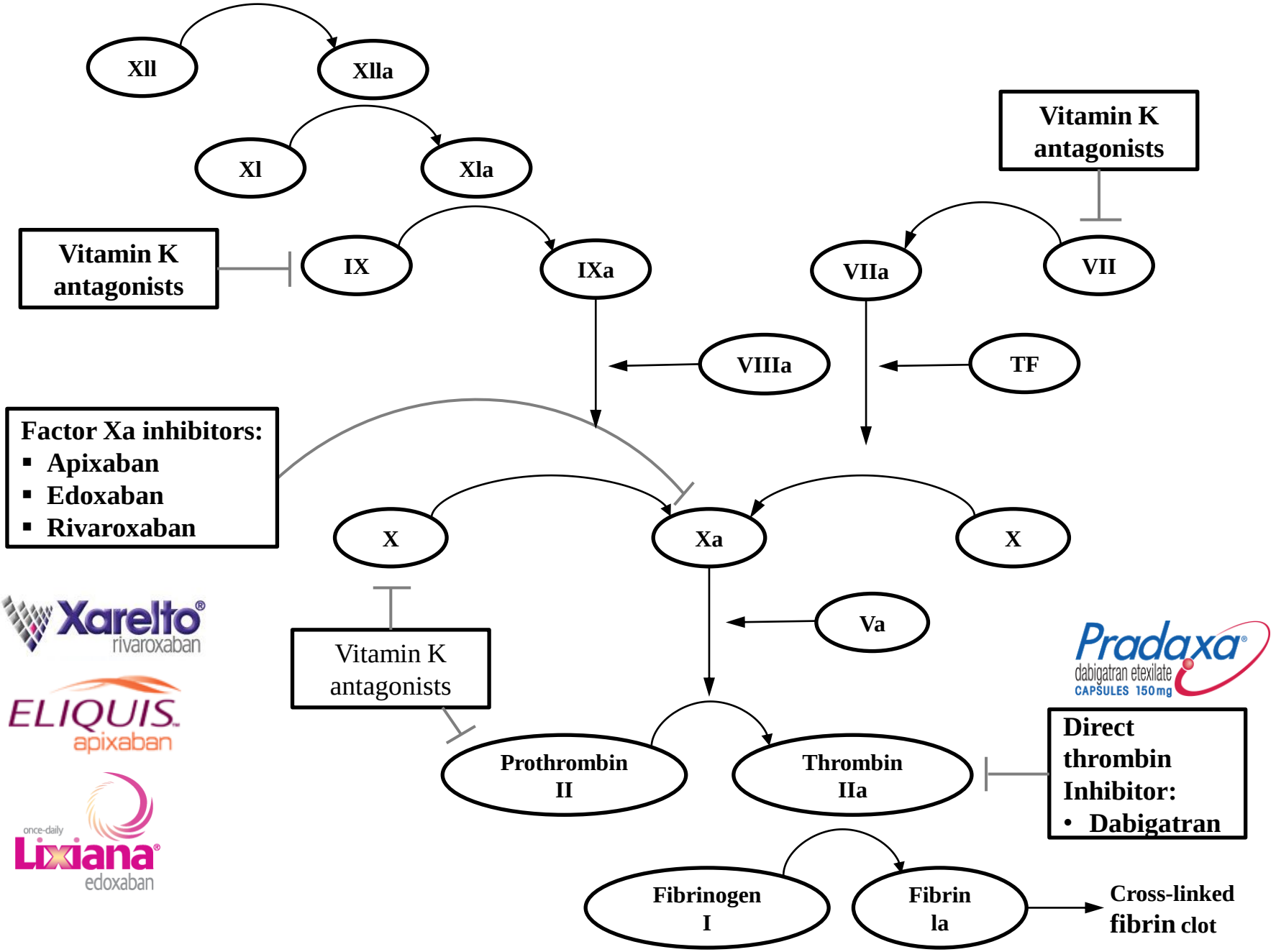
- Direct thrombin inhibitor: Dabigatran etexilate (dabigatran; Pradaxa® , Boehringer Ingelheim)
- Direct factor Xa inhibitor:

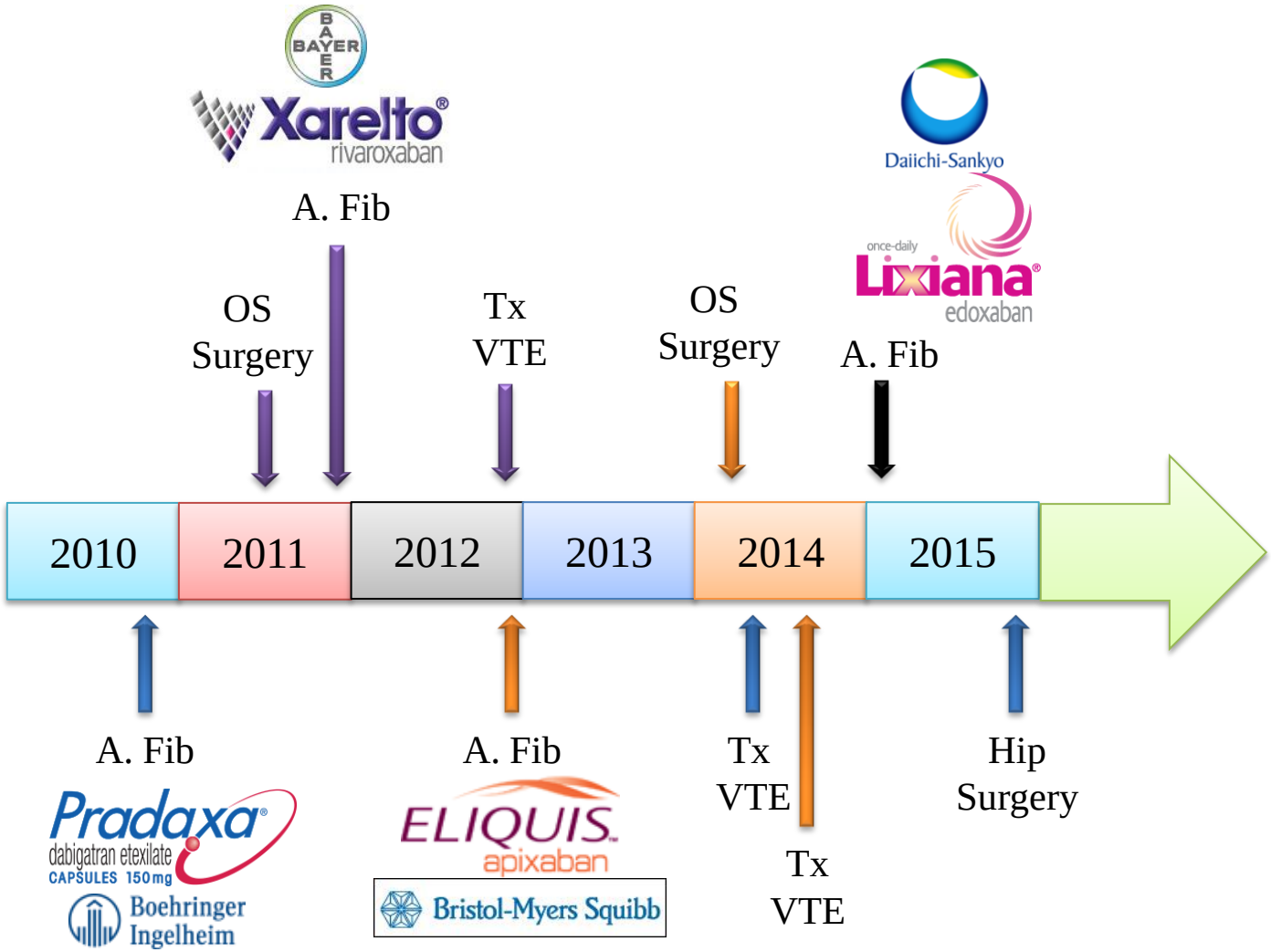
  Rivaroxaban (Xarelto® , Bayer & Janssen)

  Apixaban (Eliquis® , Bristol-Myers-Squibb)

  Edoxaban (Lixiana® , Daiichi Sankyo)

Rivaro-Xa-ban


XII
XIIa
XI
XIa
Vitamin K antagonists
IX
IXa
Vitamin K antagonists
VIIa
VII
VIIIa
TF
Factor Xa inhibitors:
▪ Apixaban
▪ Edoxaban
▪ Rivaroxaban
X
Xa
X
Va
Vitamin K antagonists
Prothrombin II
Thrombin IIa
Direct thrombin Inhibitor:
• Dabigatran
Fibrinogen I
Fibrin Ia
Cross-linked fibrin clot
Xarelto rivaroxaban
ELIQUIS apixaban
once-daily Lixiana edoxaban
Pradaxa dabigatran etexilate CAPSULES 150mg



FDA approval of NOAC

Summary of Recommendations ACCP guideline, 2016

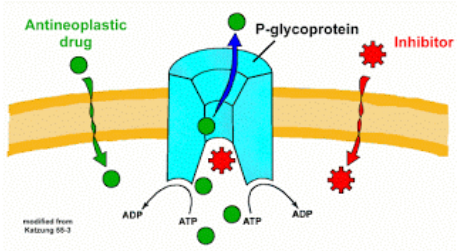
1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).

2. 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 (all Grade 2B).

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	Direct thrombin (lla) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Bioavailability	3-7%	63-79%	66%	50%
Half-life	12-17h	7-13h	8-15h	9-11h
Time to peak effect	2-3h	2-4h	1-3h	1-3h
Metabolism	80% renal 20% liver	1/3 renal 2/3 liver	25% renal 75% fecal	35% renal 63% liver
Protein binding	35%	92-95%	87%	40-59%
Drug interactions	P-glycoprotein	CYP3A4, P-glycoprotein	CYP3A4, P-glycoprotein	CYP3A4, P-glycoprotein

Dabigatran (Pradaxa)

- 2002, Boehringer Ingelheim, Germany
- Dabigatran etexilate: prodrug
- Inhibits free thrombin, fibrin-bound thrombin, clot-bound thrombin and thrombin-induced platelet aggregation.
- Efflux transporter P-glycoprotein (P-gp): Amiodarone, Azithromycin, Captopril, Clarithromycin, Cyclosporine, Quinidine, Verapamil.
- Asian ethnicity: dyspepsia 25%



Recent issues

- Re-Ly substudy: plasma dabigatran levels can vary up to fivefold (2014, BMJ)
- In 2011, 3,781 reports of serious adverse events (uncontrolled bleeding), 542 fatal events.
- Paid $650 million to settle thousands of claims brought by patients
- Pradaxa topped $1 billion in sales in 2012
- Pradaxa sales reached $1.19 billion in 2013 and $1.2 billion in 2014.

Factor Xa inhibitors

- Rivaroxaban, Apixaban, Edoxaban
- Partly metabolized via cytochrome P450 3A4 and P-glycoprotein
- Inhibit prothrombinase, clot-associated factor Xa
- Fxa: production of hundreds of thrombin molecules
- Preserve high-affinity platelet thrombin receptor
- All approved for VTE prevention and treatment

Drug interaction

Recommendation	Drug group	Reason
Avoid concurrent use	Ketoconazole, itraconazole, voriconazole, posaconazole, HIV protease inhibitors	Strong CYP3A4 and P-gp Inhibitors (increased xaban concentration, increased bleeding risk)
Avoid Concurrent Use	Dronedarone Amiodarone	P-gp inhibitor
Caution	Carbamazepine, Phenytoin Rifampicin Phenobarbitone St Johns Wort	CYP3A4 and P-gp inducers (reduced rivaroxaban concentration)
Caution	NSAIDs including aspirin Platelet aggregation inhibitors Macrolide antibiotics	Increased bleeding risk, pharmacodynamic interaction

Rivaroxavan

- Janssen Pharma.
- First oral factor Xa inhibitor
- No parenteral lead, Once a day prescription
- Orthopedic prophylaxis: 6-10 h after surgery, and 10mg/d, knee 12d, hip 25d
- EINSTEIN program 2009
  1. Acute DVT Study (n = 3,499)
  2. Acute PE Study (n = 4,832)
  3. Continued Treatment Study

Apixaban

- 2001 Bristol-Myers Squibb, 2007 Pfizer
- Renal 25%, Faecal 50%, partially P450 3A4
- Preferred in renal insufficiency
- BID dosing: lower peak–trough ratio
- Potent indirect antiplatelet effect
- ADOPT trial in acute medical illness: higher incidence of major bleeding

Edoxaban

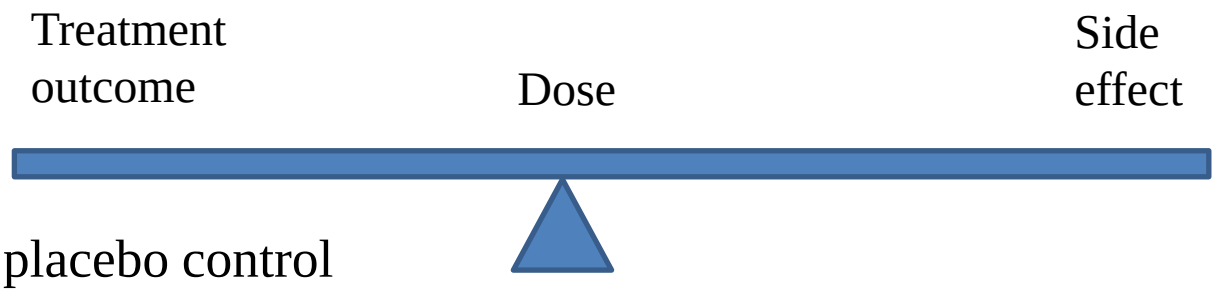
- Daiichi Sankyo, Japan　江戸, えど
- Once a day, Parenteral lead
- Approved in VTE prevention in OS surgery, Japan & U.S.A.
- ENGAGE AF TIMI 48: prevention of stroke in AF
- HOKUSAI VTE: VTE treatment with 30, 60 mg

Katsushika Hokusai

- 가츠시카 **호쿠사이** (葛飾北齋)
- 1760~1849
- Painter, and printmaker of the Edo period

Characteristic	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Clinical Trials				
AF	Re-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI
VTE prophylaxis	RE-MODEL RE-MOBILIZE RE-NOVATE I,II	RECORD I-IV MAGELLAN	ADVANCE I-III	STARS E-3 STARS J-V
VTE treatment	RE-COVER RE-COVER II	EINSTEIN-DVT EINSTEIN-PE	AMPLIFY	HOKUSAI-VTE
VTE 2ndary prevention	RE-MEDY RE-SONATE	EINSTEIN-Extension	ADOPT	
Outcomes vs. gold standard (heparin - warfarin)				
Eff, AF	Better (150 mg) Equal (110 mg)	Equal	Better	Equal
Eff, VTE prophylax.	Equal	Better	Better	Better
Eff, VTE Tx	Equal	Equal	Better	Better
Bleeding in AF	Better	Equal	Better	Better
Bleeding in VTE	Equal	Equal	Better	Equal

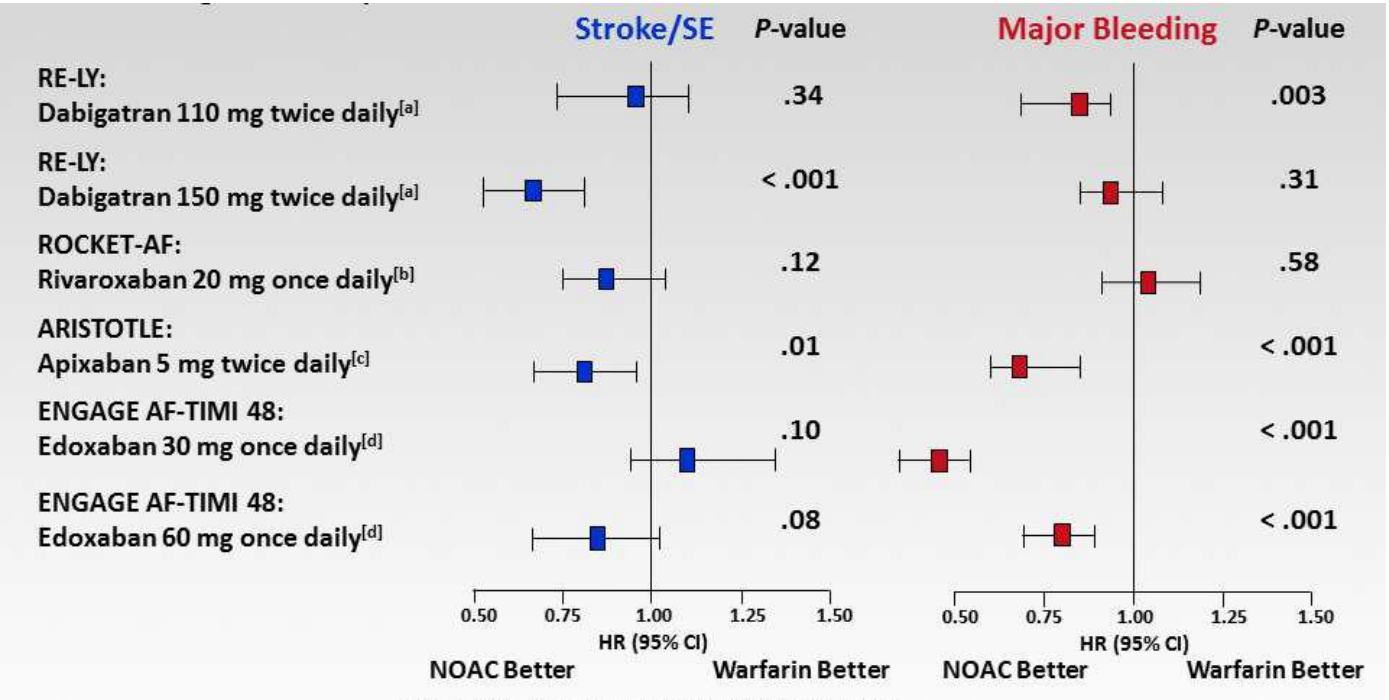
Non-inferiority Trial



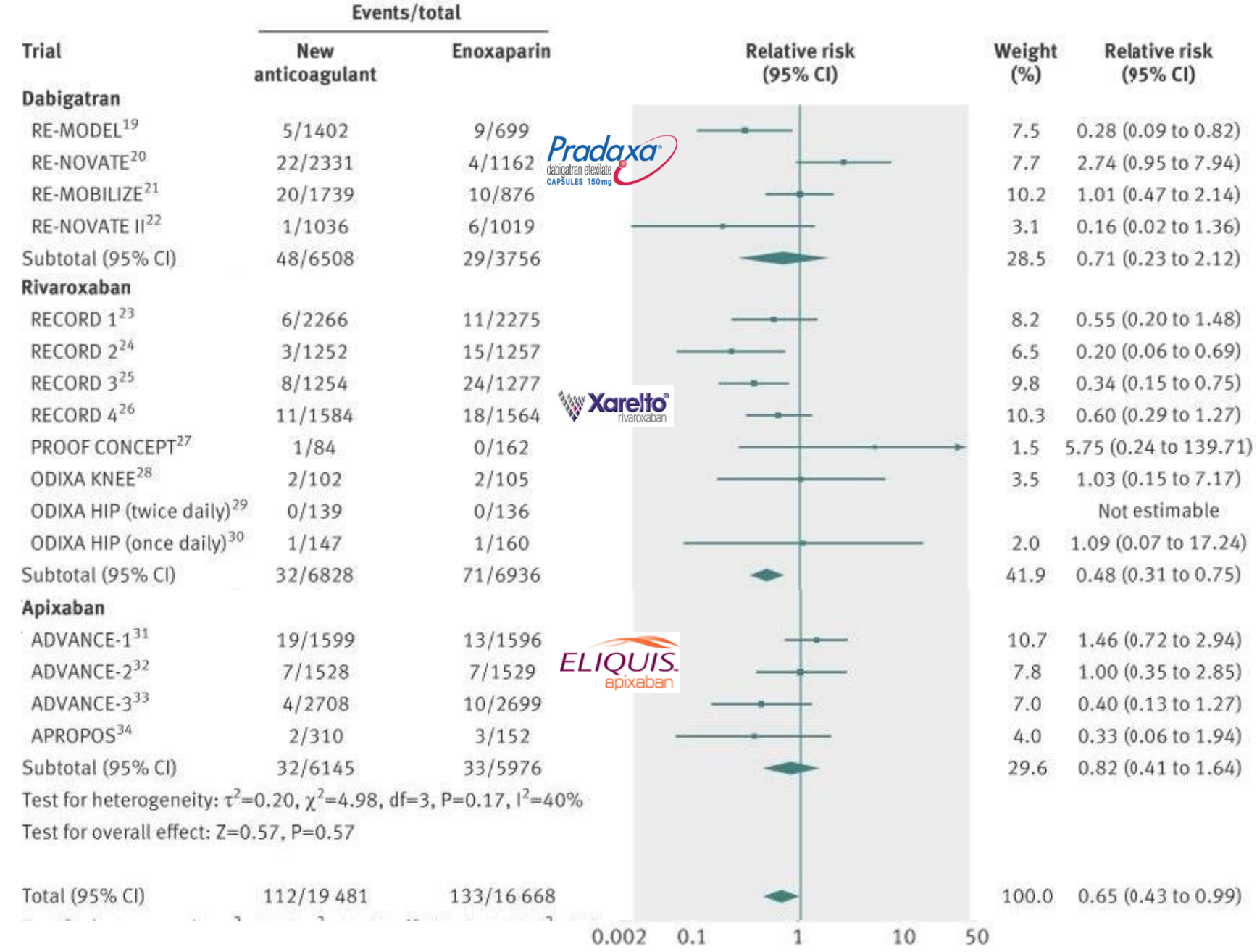
- Ethical issue of placebo control
- Well established active control
- Too strong opponent
- Important secondary end point

NOACs for prevention of systemic embolism or stroke in non-valvular AF

Drug Dose (mg)	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF
	Dabigatran 110 bid 150 bid	Rivaroxaban 20 mg OD	Apixaban 5 mg bid	Edoxaban 30, 60 mg OD
Study design	Randomized open label	Randomized double-blind, double-dummy	Randomized control double-blind parallel arm	Three-group, randomized, double-blind, double-dummy
No. patients	18,113	14,264	18,201	21,105



Gomez-Outes A, et al. NOAC vs. enoxaparin after total hip or knee replacement. BMJ. 2012; 344:e3675.

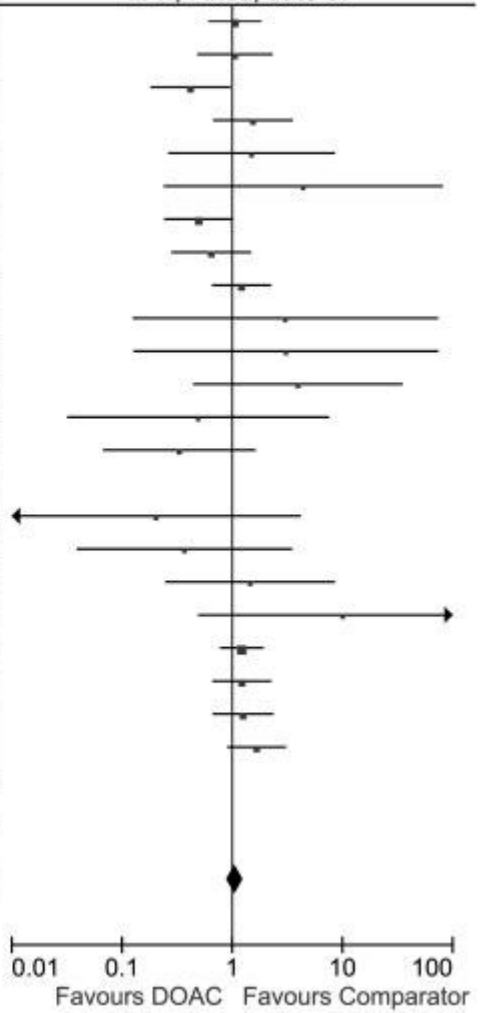


VTE prevention in major orthopedic surgery

Study or Subgroup	DOAC Events	DOAC Total	LMWH/fondaparinux Events	LMWH/fondaparinux Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RE-NOVATE	38	2309	18	1154	11.0%	1.06 [0.60, 1.84]
RE-MODEL	19	1382	9	694	5.5%	1.06 [0.48, 2.33]
RE-MOBILIZE	10	1728	12	868	7.3%	0.42 [0.18, 0.97]
RE-NOVATE II	14	1010	9	1003	4.1%	1.54 [0.67, 3.55]
Mirdamadi	3	45	2	45	0.9%	1.50 [0.26, 8.55]
APROPOS	4	305	0	149	0.3%	4.41 [0.24, 81.41]
ADVANCE-1	11	1596	22	1588	10.1%	0.50 [0.24, 1.02]
ADVANCE-2	9	1501	14	1508	6.4%	0.65 [0.28, 1.49]
ADVANCE-3	22	2673	18	2659	8.3%	1.22 [0.65, 2.26]
Raskob	1	170	0	172	0.2%	3.04 [0.12, 73.98]
STARS J-2	1	85	0	87	0.2%	3.07 [0.13, 74.32]
STARS E-3	4	354	1	349	0.5%	3.94 [0.44, 35.11]
STARS J-4	1	59	1	29	0.6%	0.49 [0.03, 7.58]
STARS J-5	2	303	6	301	2.8%	0.33 [0.07, 1.63]
Fuji	0	22	0	20		Not estimable
ODIXa-KNEE	0	102	2	104	1.1%	0.20 [0.01, 4.20]
ODIXa-OD-HIP	1	142	3	157	1.3%	0.37 [0.04, 3.50]
ODIXa-HIP 2006	3	136	2	132	0.9%	1.46 [0.25, 8.57]
ODIXa-HIP 2007	2	80	0	162	0.2%	10.06 [0.49, 207.14]
RECORD1	40	2209	33	2224	15.0%	1.22 [0.77, 1.93]
RECORD2	22	1228	18	1229	8.2%	1.22 [0.66, 2.27]
RECORD3	21	1220	17	1239	7.7%	1.25 [0.67, 2.37]
RECORD4	27	1526	16	1508	7.4%	1.67 [0.90, 3.08]
NCT01205932 (R1)	0	298	0	98		Not estimable
NCT01206972 (R2)	0	224	0	74		Not estimable
Total (95% CI)		**20707**		**17553**	**100.0%**	**1.07 [0.89, 1.29]**
Total events	255		203			

Heterogeneity: $Chi^2 = 24.14$, $df = 21$ ($P = 0.29$); $I^2 = 13\%$

Test for overall effect: $Z = 0.74$ ($P = 0.46$)



Riva, et al. Semin Thromb Hemost 2016;42:42–54

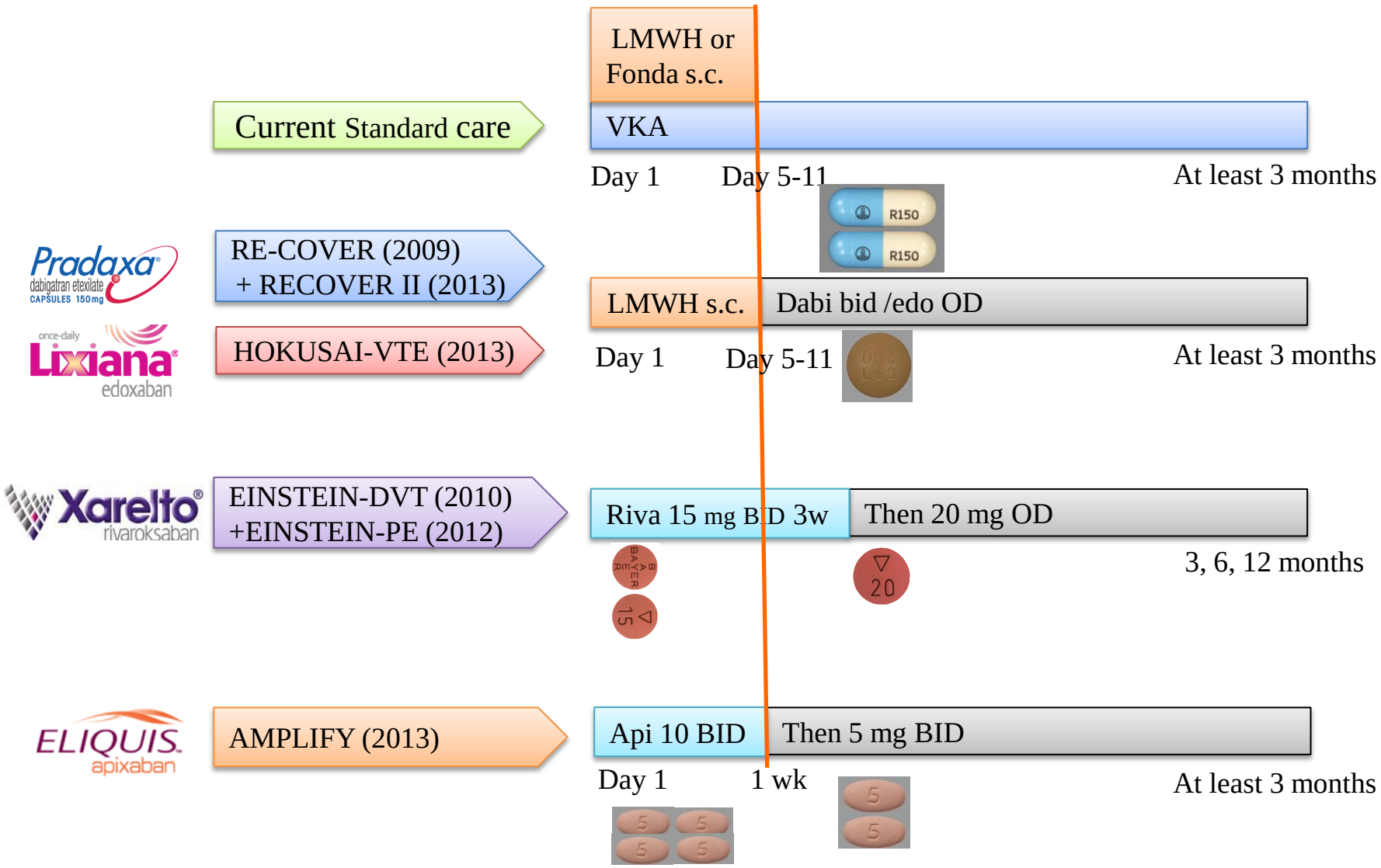
RCTs of NOACs for the treatment of acute VTE

	RE-COVER	RE-COVER II	EINSTEIN-DVT	EINSTEIN-PE	AMPLIFY	HOKUSAI
Medication	Dabigatran vs. Warfarin	Dabigatran vs. Warfarin	Rivaroxaban vs. Warfarin/ Acecoumarol	Rivaroxaban vs. Warfarin/ Acecoumarol	Apixaban vs. Warfarin	Edoxaban vs. Warfarin
Studydesign	randomized double blind non-inferiority	randomized double blind non-inferiority	randomized open label non-inferiority	randomized open label non-inferiority	randomized double blind non-inferiority	randomized double blind non-inferiority
Patients	1749 DVT	1750 DVT	3449 DVT	4832 PE	3532 DVT	4921 DVT only
	541 PE	595 PE			1359 PE	3319 PE
	245 both	221 both			477 both	
Initial treatment	LMWH/UFH for ≥ 5 days	LMWH/UFH for ≥ 5 days	2 × 15 mg for 3 weeks	2 × 15 mg for 3 weeks	2 × 10 mg for 7 days	LMWH/UFH for > 5 days
Further treatment	2 × 150 mg	2 × 150 mg	1 × 20 mg	1 × 20 mg	2 × 5 mg	1 × 60/1 × 30 mg[1)]
Duration of treatment	6 months	6 months	3 – 12 months	3 – 12 months	6 months	3 – 12 months
% time in therapeutic range (average)	59.9 %	57 %	57.7 %	62.7 %	61 %	63.5 %

DVT … deep venous thrombosis, PE … pulmonary embolism, LMWH…low molecular weight heparin, UFH … unfractionated heparin
[1)] lower dose if body weight < 60 kg or creatinine clearance 30 – 50 ml/min or treatment with potent P-glycoprotein inhibitors

Hirschl et al. *Vasa 2014; 43: 353 – 364*

NOAC Phase III VTE treatment



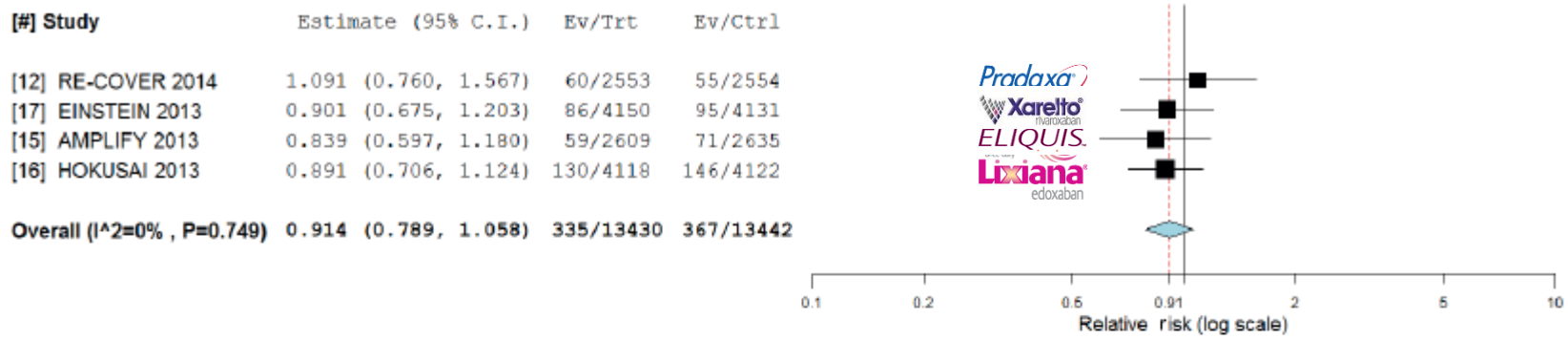


Figure 2: Forest plot for relative risk of recurrent symptomatic VTE, NOACs against VKAs. Relative risks and 95 % confidence intervals are shown. Number of events and number at risk for NOACs (Trt) and VKAs (Ctrl) are listed. Homogeneity test (I^2 and p-value) as well as overall relative risk estimate are displayed in the last line.

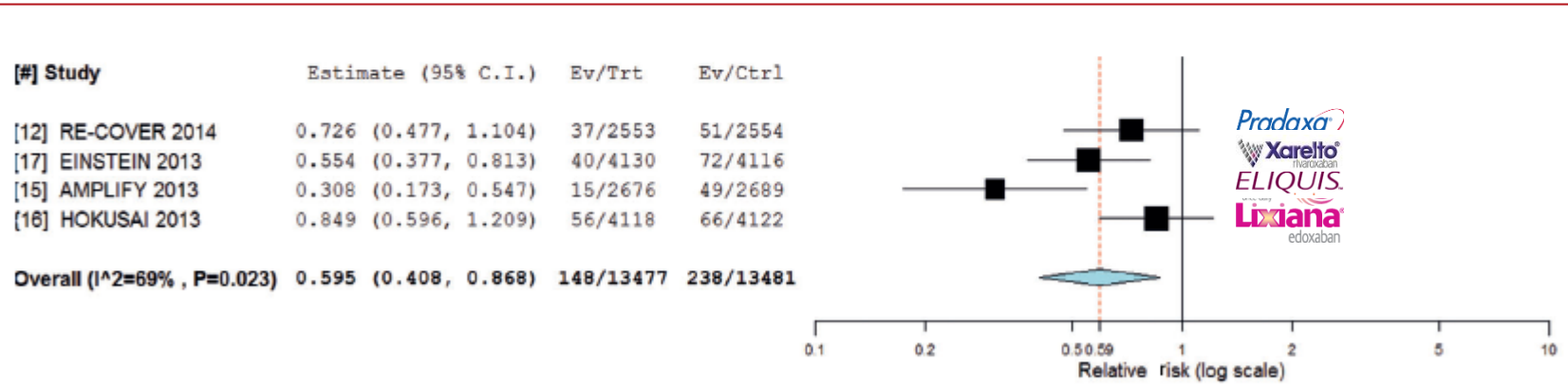


Figure 3: Forest plot for relative risk of major bleeding, NOACs against VKAs. Relative risks and 95 % confidence intervals are shown. Number of events and number at risk for NOACs (Trt) and VKAs (Ctrl) are listed. Homogeneity test (I^2 and p-value) as well as overall relative risk estimate are displayed in the last line.

Hazard ratio, relative risk or odds ratio of selected outcomes for the novel oral anticoagulants in comparison to a vitamin K antagonist

	Dabigatran (RE-COVER I, II combined)			**Rivaroxaban** (EINSTEIN-DVT and EINSTEIN-PE combined)			**Apixaban** (AMPLIFY)			**Edoxaban** (Hokusai-VTE)		
	HR	95 % CI	p	HR	95 % CI	p	RR	95 % CI	p	HR or OR[e]	95 % CI	p
Recurrent VTE	1.09	0.76–1.57	NA	0.89	0.66–1.19	0.41	**0.84**	0.60–1.18	<0.001	0.89	0.70–1.13	<0.001
Major bleeding	0.73	0.48–1.11	NA	0.54	0.37–0.79	0.002	**0.31**	0.17–0.55	<0.001	0.84	0.59–1.21	0.35
Major or clinically relevant nonmajor bleeding	0.62	0.50–0.76	NA	0.93	0.81–1.06	0.27	**0.44**	0.36–0.55	<0.001	0.81	0.71–0.94	0.004
Death	1.0	0.67–1.51	NA	0.89	0.67–1.18	0.43	0.79	0.53–1.19	NA	1.05[e]	0.82–1.35[e]	0.70

Manth S, et al. J Thromb Thrombolysis (2015) 39:155–165

Secondary Prevention

- Extended VTE therapy
- Prevent recurrence vs. Risk of bleeding
- No definite indication and duration
- Un-provoked VTE: at least 3 months
- Indefinitely in permanent risk factor (cancer, antiphospholipid syndrome)

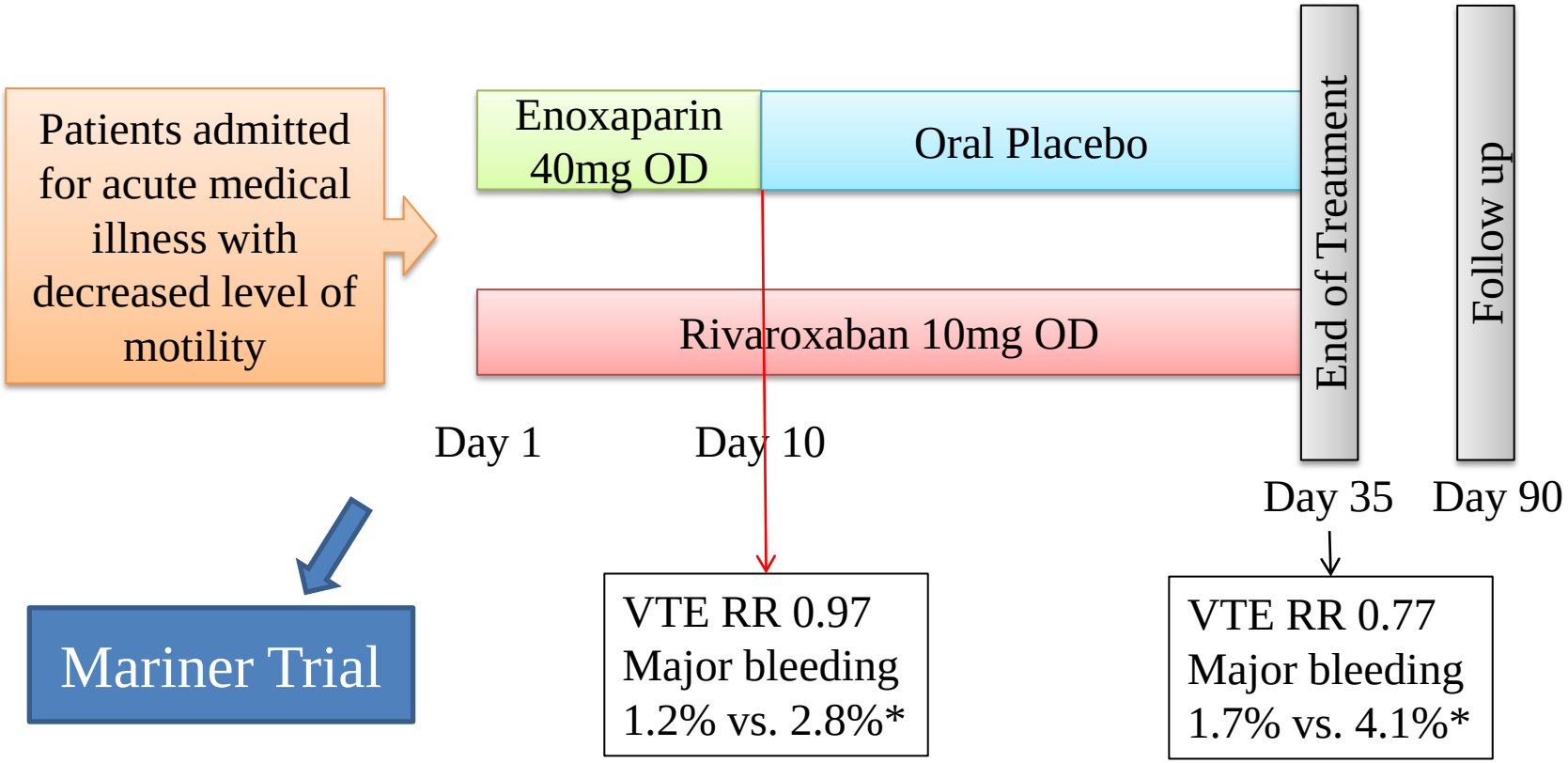
Phase III clinical trials of novel OACs for 'Extended' VTE therapy

Trial	Study design	Patients	Recurrent VTE	Major bleeding
Apixaban (2.5mg or 5.0mg twice daily) vs placebo				
AMPLIFY-EXT	Randomized, double-blind, superiority, intention to treat analysis	Completed 6-12 m of anticoagulation *n*=2,482	1.7% (2.5mg) 1.7% (5.0mg) vs 8.8% *P*<0.001 (superiority)	0.2% (2.5mg) RR 0.49 0.1% (5.0mg) RR 0.25 vs 0.5%
Dabigatran (150mg twice daily) vs warfarin and placebo				
RE-MEDY	Randomized, double-blind, active-controlled, noninferiority	Completed 3 m of anticoagulation *n*=2,856	1.8% vs 1.3% *P*=0.03	0.9% vs 1.8% *P*=0.06
RE-SONATE	Randomized, double-blind,placebo-controlled, Noninferiority	Completed 3 m of of anticoagulation *n*=1,343	0.4% vs 5.6%	0.3% vs 0.0%
Rivaroxaban alone (15mg BID for 3 weeks, followed by 20mg OD vs placebo)				
EINSTEIN-EXT	Randomized, double-blind superiority	Completed 6-12 m of anticoagulation *n*=1,196	1.3% vs 7.1% *P*=0.001 (superiority)	0.7% vs 0.0% *p*=0.11

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
VTE prophylaxis		신기능정상: 수술후 1-4h 시작 220mg QD 28-35 일 CCl <50ml/min: 150mg QD	수술후 6-10h 시작 10mg QD 12 일 (knee) 25 일 (hip surgery)	수술후 12-24h 시작 2.5mg BID 10-14 일 (knee) 32-38 일 (hip surgery)	30 mg QD
VTE Treat-ment	Load	주사 항응고제 최소 5일	15mg BID 3주	10 mg BID 7일 후	주사 항응고제 최소 5일
	Main-tenanc	150 mg BID	20mg QD	5 mg BID	60 mg QD
VTE 2ndary prevention A. Fib CVA 2nd		150 mg BID	20mg QD	5 mg BID	60 mg QD

MAGELLAN trial

- Multicenter, rAndomized, parallel Group Efficacy safety study for the prevention of venous thromboembolism in hospitalized acutely iLL medical patients comparing rivaroxabAN with enoxaparin



NOAC, prevention of VTE in medical illness

Trial	Patient population and cohort size	Dose and duration	Enoxaparin dose and duration	DVT, PE, or death (vs enoxaparin)	Major bleeding (vs enoxaparin)
MAGELLAN Rivaroxaban	Acute medical illness n = 8,101	10 mg QD 35±4 days	40 mg QD 10±4 days (Oral placebo: 35±4 days)	2.7% vs 2.7% (day 10) 4.4% vs 5.7% (day 35) P = 0.003 (noninf) P = 0.02 (super)	2.8% vs 1.2% (day 10) 4.1% vs 1.7% (day 35) P = 0.001 for both time points
ADOPT Apixaban	Medical illness n = 4,495	2.5 mg BID 30 days	40 mg twice daily 6–14 days	2.71% vs 3.06% P = 0.44 Apixaban did not achieve superiority	0.46% vs 0.19% P = 0.04

Combination with anti-PLT

- Acute MI with AF, LV thrombus 시에 antiplatelet + VKA의 복합이 권장된다.

  예) Warfarin + ASA, $P2Y_{12}$ receptor inhibitor (clopidogrel)
- Stable coronary disease, VTE 에서는 권장되지 않는다.
- Antiplatelet + NOAC 복합은 연구가 부족하다.
- NOAC은 atherothrombotic protection, coronary disease 등에서는 효과가 별로 없다.
- Dabigatran 투여 시 급성 관상 동맥 질환의 증가

Patients with cancer

- Malignancy: VTE 위험률이 4-7 배 (12-20%)
- LMWH (enoxaparin 40 mg/d, dalteparin 5,000 units/d), fondaparinux (75 IU/kg/d SQ), low-dose unfract heparin (5,000 U every 8–12 h)
- CLOT trial: LMWH > warfarin
- NOAC은 아직 RCT가 부족하다.
- ACCP guideline: 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), NOACs (Grade 2C)

Bleeding and lack of antidote

- 수술 전 최소한 24시간 전에 NOAC 중단 (75세 이상이거나 신부전 시는 1-3일 전에 중단)
- 반감기가 짧고 약물역동학적 예측성이 좋으나 역전제 (reversal agent)가 부족하다.
- Prothrombin complex concentrate (PCC): Factor Xa inhibitor에 효과
- Recombinant Factor VIIa
- Factor Xa (plasma-derived and recombinant)
- Dabigatran: hemodilaysis (esp. CRF)

NOAC and bleeding

	Dabigatran	Factor Xa inhibitor
Stop before surgery	>72 hours prior to surgeries with moderate bleeding risk	At least 24–48 hours prior to surgery with moderate bleeding risk 48–72 hours prior to surgery with high bleeding risk
Monitoring	Thrombin time (TT) Diluted TT (dTT) Ecarin clotting time (ECT) aPTT	Anti-Xa activity PT
FFP	Not effective	Not effective (minimal)
PCC	Partially effective?	Partially effective?
Target reversal	Idarucizumab Aripazine	Andexanet alfa Aripazine

Laboratory Monitoring

- Necessary in renal failure, older patients, extreme body weight, active bleeding, preoperative
- Dabigatran: aPTT > PT
- Dabigatran 150 mg bid 투여 시 aPTT: 2x control, 중단 12 시간 후 1.5x
- Factor Xa inhibitors: PT > aPTT
- aPTT normal in 18% of dabigatran
- PT normal in 32% of rivaroxaban
- Apixaban: no effect on PTT, little effect on PT

Transition

- Switching to NOAC: Warfarin 중단 후 INR<2.0에서 NOAC 시작 (rivaroxaban: INR 3, edoxaban: INR 2.5)
- Other anticoagulant to NOAC: 다음 약제 투여시간 0-2시간 전에 NOAC 시작 (unfractionated heparin 중단 0-4 시간 후)
- Switching from NOAC to warfarin: 중단 1-2일전 시작, 주사항응고제를 병용해서 전환

Idarucizumab

- Praxbind, Boehringer Ingelheim
- Humanized antibody fragment
- Dabigatran보다 350배 친화력으로 thrombin에 결합
- FDA approval October 16, 2015
- Two 2.5 g 50 mL bolus IV infusions within 15 minutes: total 5 g
- Headache, nasopharyngitis, back pain, skin irritation
- Multicenter, observational phase III trial (RE-VERSE AD)

Renal failure

- Do not use NOACs if CCL < 30 ml/min
- Severe renal failure: unfractionated heparin and LMWH
- Factor Xa inhibitor if CCL 30-50 ml/min
- Dabigatran half dose if CCL 50ml/min
- Edoxaban half dose if CCL 30-50 ml/min

  Cr 1.55 mg/dl – eGFR 50 ml/min

  Cr 2.4 mg/dl – eGFR 30 ml/min

Other conditions

- NOAC contraindicated in prosthetic (mechanical) heart valve: blood clot formation, phase II RE-ALIGN 2012
- NOAC contraindicated in pregnancy – Heparins are safe.
- NOAC not recommended in breast feeding – Heparins warfarin recommended.

Advantage of warfarin

- Long action duration
- Anti-dote
- Once a day
- Accurate monitoring
- Minimal renal effect
- Minimal side effect except bleeding
- Arterial thromboembolism: ACS, Mech. valve

NOAC의 선택

	No parenteral heparin lead	Once a day
Dabigatran (Pradaxa)		
Ribaroxaban (Xarelto)	O	O
Apixaban (Eliquis)	O	
Edoxaban (Lixiana)		O

- Efficacy, Side effect: adequate dosage
- Renal function

*Development of Better NOAC or Other Drugs

NOAC, 급여확대 후 수직상승… '자렐토' 100억 돌파

프라닥사·엘리퀴스도 3Q부터 급증…약가인하·임상데이터 발표 등 성장요인 지속 전망

이호영기자 lhy37@medipana.com 2015-12-16 06:06

포스트 와파린으로 불리며 국내 시장에 화려하게 등장했지만 고전을 면치 못했던 신규 경구용 항응고제(NOAC, New Oral Anti-Coagulant) 시장이 뜨겁게 달궈지고 있다.

16일 메디파나뉴스가 3분기 IMS데이터를 분석한 결과 국내 출시한 NOAC인 `자렐토`(리바록사반), `프라닥사`(다비가트란), `엘리퀴스`(아픽사반) 모두 처방액이 급증했다.

가장 많은 처방액을 기록한 치료제는 `자렐토`로 3분기 현재 108억원으로 지난 2013년 출시 이후 처음으로 100억원을 돌파했다.

이는 지난해 3분기 누적 처방액 63억원보다 71.6% 증가한 수치다.

`프라닥사`는 58억원, `엘리퀴스`는 37억원을 기록했지만, 성장세를 보면 향후 치열한 경쟁이 예고된다.

`프라닥사`와 `엘리퀴스`는 지난해 3분기보다 각각 94.5%, 428.5%의 처방액 증가율을 보이며 높은 성장세를 기록했다.

이 같은 성장세는 지난 7월부터 적용된 급여 확대에 힘입은 것으로 풀이된다.

제품명	2015년				2014년	증감률
	3분기(누적)	3분기	2분기	1분기	3분기(누적)	
자렐토	10,809,373,614	5,410,336,838	2,589,785,599	2,809,251,177	6,300,264,477	71.6
프라닥사	5,827,674,495	3,674,252,035	1,033,611,552	1,119,810,908	2,996,325,985	94.5
엘리퀴스	3,719,066,156	2,343,698,879	687,785,888	687,581,389	703,740,495	428.5

▲ 신규 경구용 항응고제(NOAC) 처방액 현황(IMS데이터 재구성, 단위 : 원, %)