Recent Advances of DOACs

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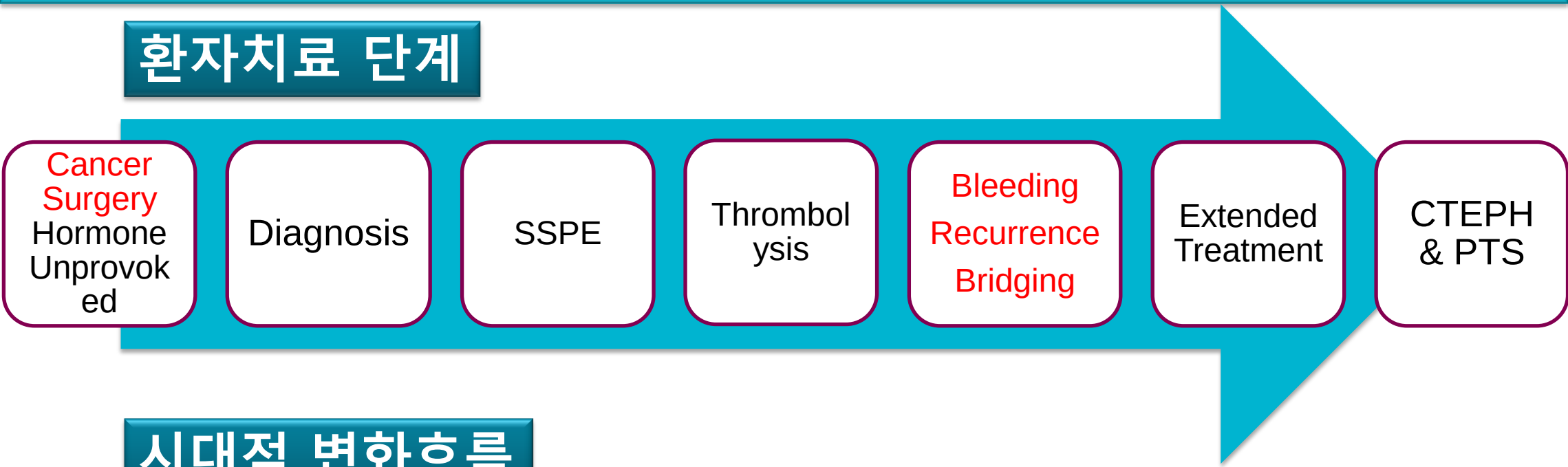
시간: 2016.11.5(토)
장소: 서울대병원 의학연구혁신센터

1

Introduction

Introduction: VTE

환자치료 단계



시대적 변화흐름

Phase III Clinical Trials → ACCP 10th guideline → Real World XALIA GARFIELD → New Agents

그리고 "한국"

Contents

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2. XALIA study
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4. Recurrence & Bleeding
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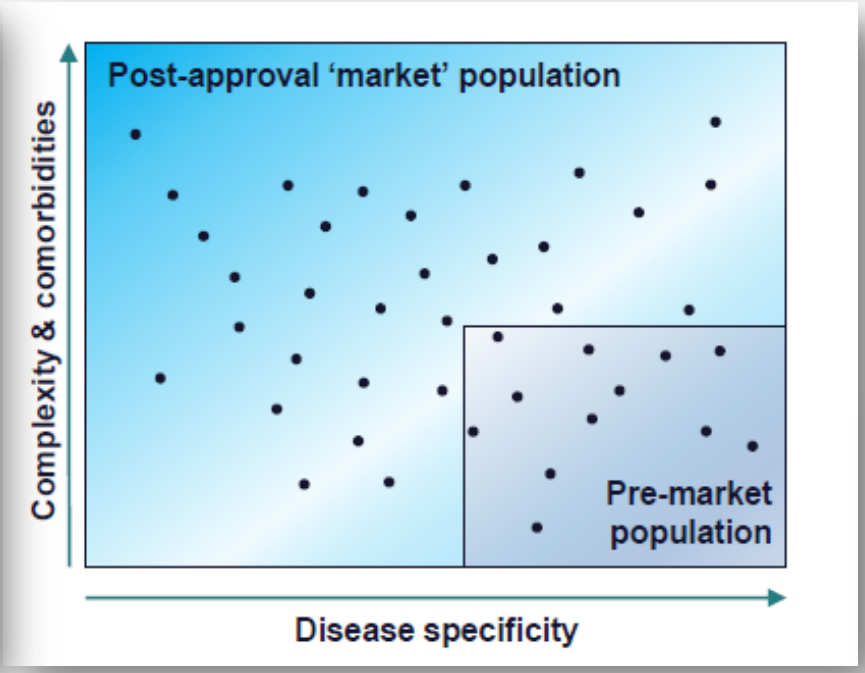
7. DOACs in Cancer patients
8. New agent in the future
9. Summary (Take-home message)

2

Prospective Registries in VTE
XALIA Study

Clinical trials versus Real world



Real World

- Unselected patient population
- Dose recommendations only
- Over- and under-reporting of events

Clinical trial

- Strict inclusion and exclusion criteria
- Strict study protocol
- Objectively adjudicated event rates

1. Ongoing prospective registries in VTE

GARFIELD-VTE [1]	Target: 10,000	• **Within 30 days** of VTE Diagnosis • 28 countries • Treated according to local standard therapy	≥ 36 mon
VTEval[2]	Target: 2000 Recruiting Until 2023	• Prospective enrollment of patients with a clinical suspicion of either **acute PE or acute DVT or with incidental Diagnosis of VTE**	5 years
PREFER-VTE[3]	Target: 3600	• Prospective evaluation of patients enrolled established acute first-time or recurrent VTE • Aim- ratio of **PE:DVT of 2:3**	≥ 12 mon
PERCEIVE[1]	To date: 4,500	• Prospective registry of cancer and events involving VTE in patients with a **newly diagnosed malignancy of the breast, colon and rectum, pancreas, lung, prostate or ovary**	10 years or until death

1. Thrombosis Research Institute
2. VTEval Project-prospective Cohort study NCT02156401, Accessed Nov 1, 2016
3. Agnelli Thromb J 2015; 13: 41

2. Ongoing prospective registries in VTE

RIETE[1,2]	To date:>45,000 (initiated 2001) Recruiting Until 2027	• Computerized registry of patients with documented symptomatic DVT or PE from 17 countries	3 years
Dresden NOAC[3,4]	Target: 2000 Last F/U: 2017	• Prospective enrollment of patients requiring anticoagulation in acute VTE for minimum 3 mon from **private practice and community hospital in Germany**. Adjusted to DOACs (**Rivaroxaban, Dabigatran, Apixaban, Edoxaban**)	Day 30±5 after procedure
XALIA[5]		• Prospective evaluation of patients with a diagnosis of actue DVT and requiring anticoagulation therapy (**rivaroxaban or standard therapy**) for ≥3 mon	1 mon after the end of treatment

1. RIETE registry website, Accessed Nov 1, 2016
2. Tzoran et al. Rambam Maimonides Med J 2014; 5: 30037
3. Dresden NOAC registry: NCT01588119
4. Beyer-Westendorf Blood 2014; 124: 955-62
5. Ageno W, et al Lancet Haematol 2016; 3:312-21

XALIA study

Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA)

Multicenter, prospective, non-interventional, observational study

21 countries

Observational study of 5142 patients with acte VTE

Treatment at treating physician’s discretion

Ageno Lancet Haematol 2016; 3(1): 312-21

XALIA study: Results

	Rivaroxaban XALIA (EINSTEIN DVT)	Standard therapy XALIA (EINSTEIN DVT)	HR	P value
Major bleeding	0.8% (0.8%)	2.1% (1.2%)	0.77 (0.4-1.50)	0.44
Recurrent VTE	1.4% (2.1%)	2.3% (3.0%)	0.91 (0.54-1.54)	0.72
Mortality	0.4% (2.2%)	3.4% (2.9%)	0.51 (0.24-1.07)	0.074

Ageno Lancet Haematol 2016; 3(1): 312-21

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GARFIELD-VTE

GARFIELD-VTE

10,000 patients from ~500 sites in 28 countries
Patients must be assessed for eligibility within 30 days of diagnosis

Global, observational, Non-interventional
Prospective, multi-center

Will be managed according to local practices
And followed for at least 3 years.
Not interfering with patient treatment at any time

Weitz Thromb Haemost 2016 Sep 22; 116(6) [Epub ahead of print]

GARFIELD-VTE

Assessment of recurrent VTE

Bleeding events

Assessment of Stroke/TIA, MI/ACS, cancer

PTS (Villalta score)

Diagnosis of CTEPH

Weitz Thromb Haemost 2016 Sep 22; 116(6) [Epub ahead of print]

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Recurrence & Bleeding

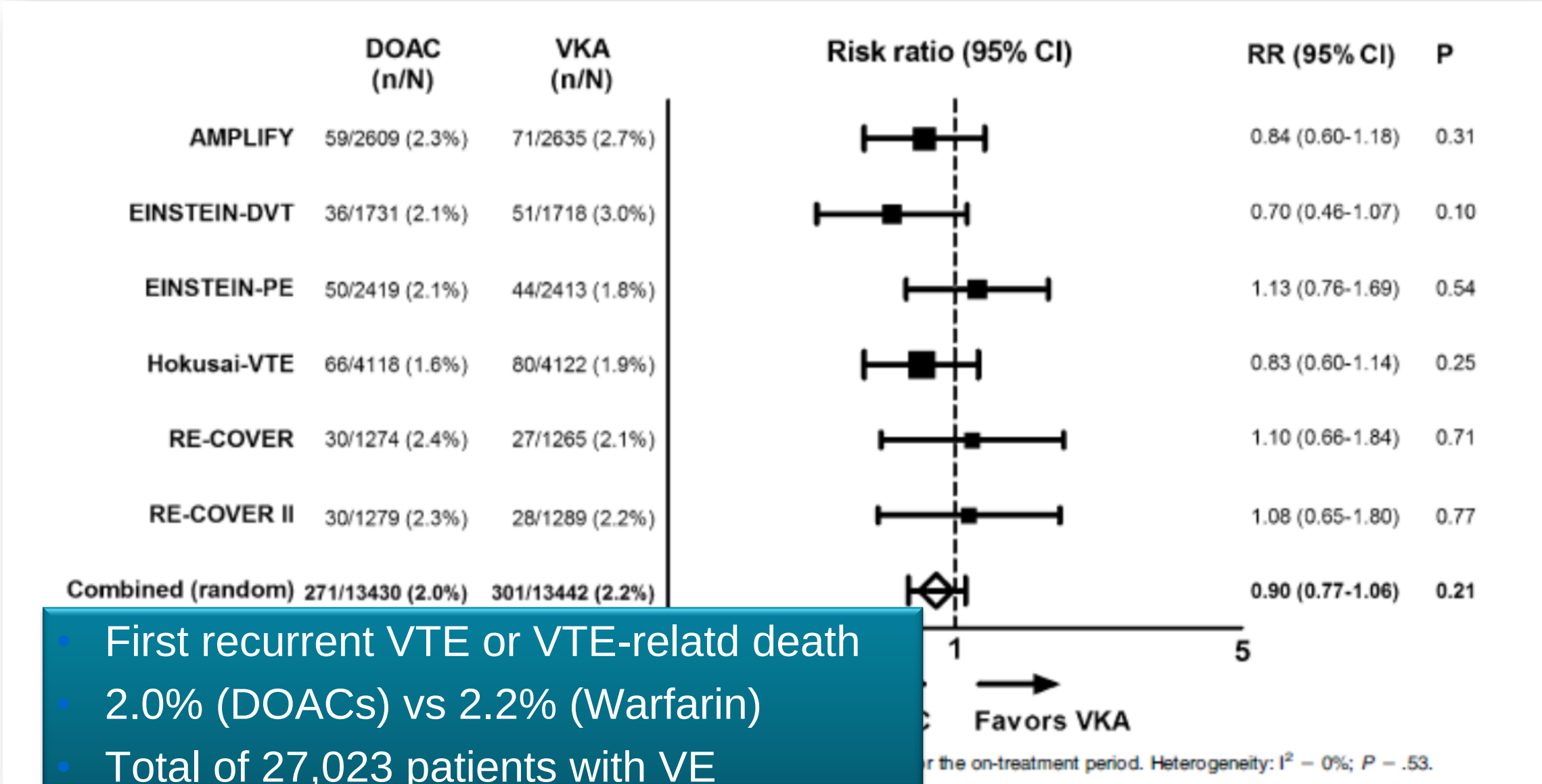
Phase 3 Clinical trials

Real world (XALIA)

Real world in Korea

Meta-analysis of efficacy and safety in phase 3 trials

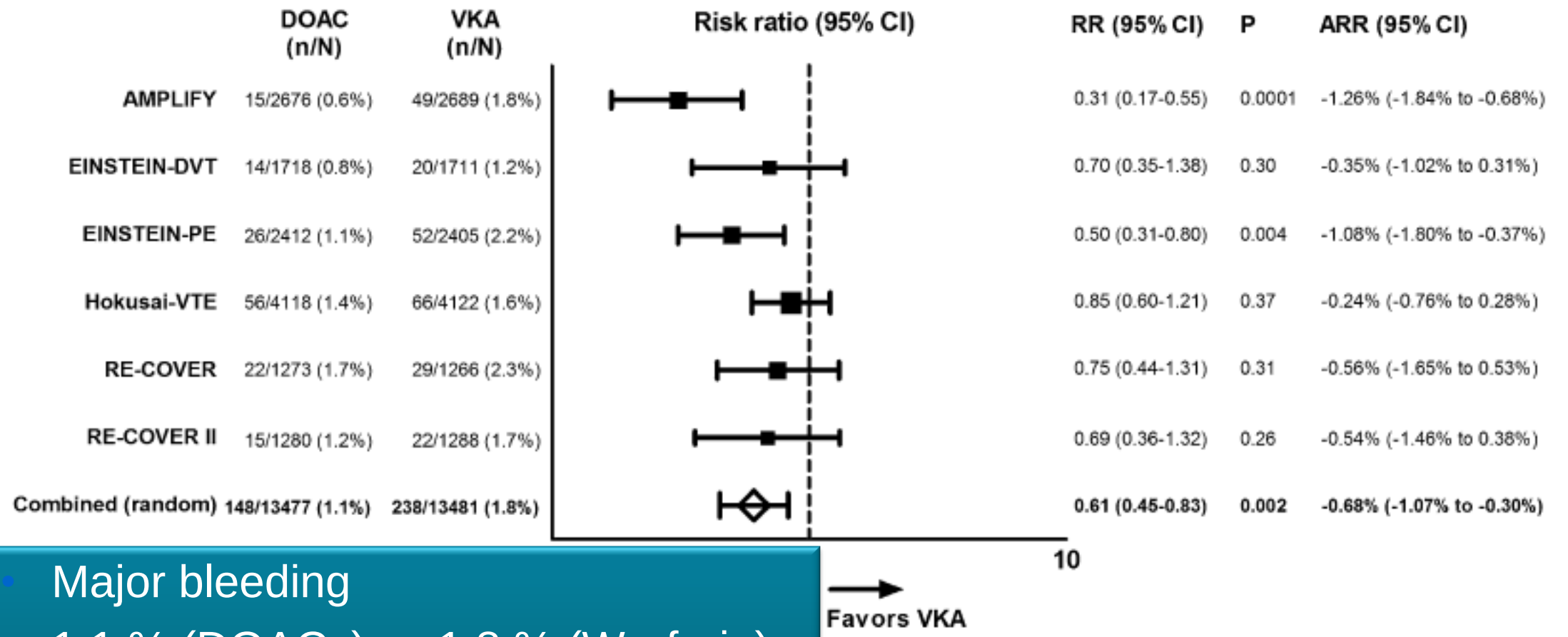
Efficacy with DOACs compared with VKA for acute VTE in 6 phase 3 trials



- First recurrent VTE or VTE-relatd death
- 2.0% (DOACs) vs 2.2% (Warfarin)
- Total of 27,023 patients with VE

Nick van Es et al Blood 2014; 124 (12): 1968-1975

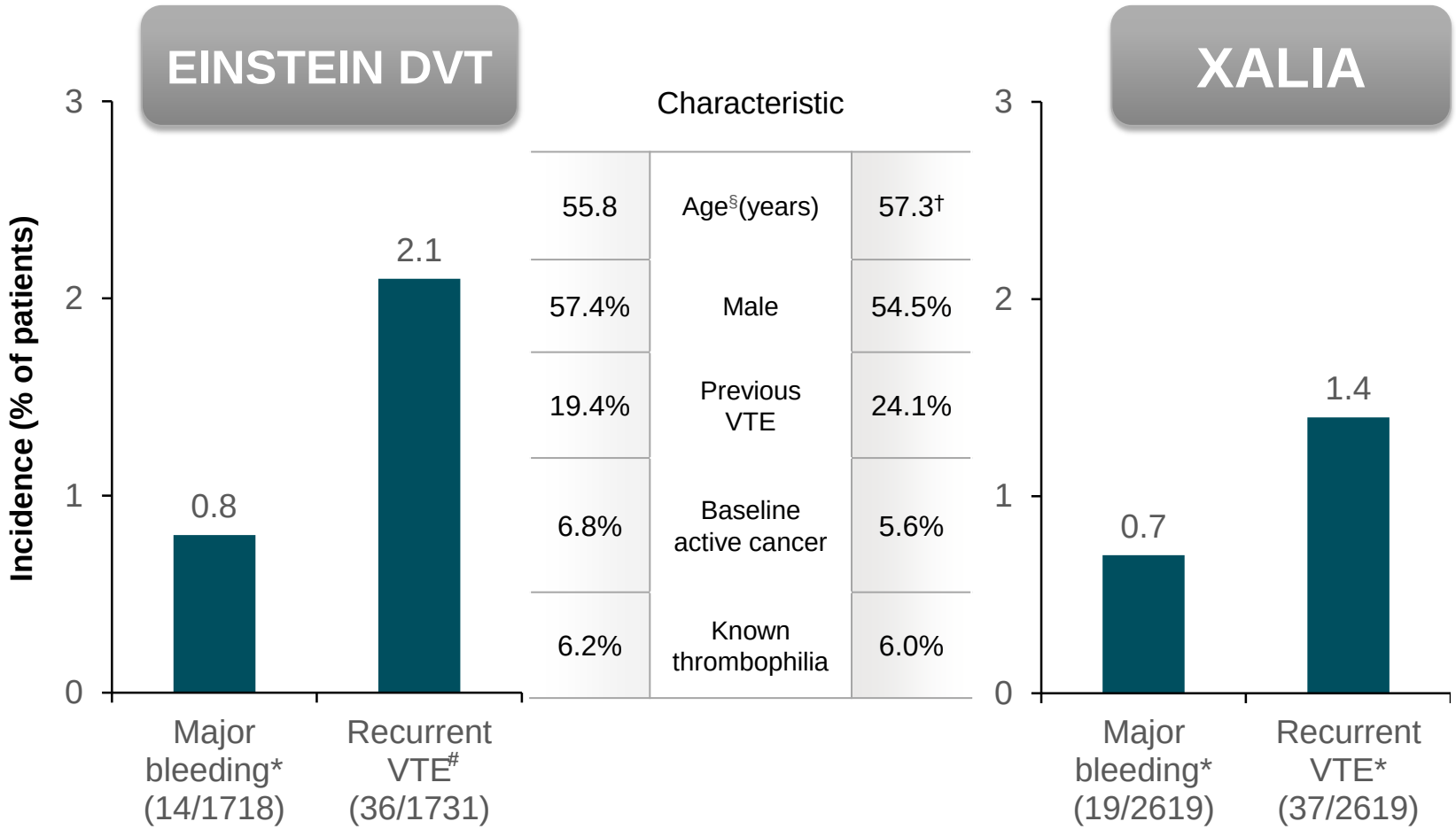
Major bleeding with DOACs compared with VKA for acute VTE in 6 phase 3 trials



- Major bleeding
- 1.1 % (DOACs) vs 1.8 % (Warfarin)
- Total of 27,023 patients with VE

Nick van Es et al Blood 2014; 124 (12): 1968-1975

EINSTEIN DVT and XALIA: Rivaroxaban Outcomes



#ITT analysis; *Safety population (patients taking ≥1 dose of study drug); §mean †ASH, USA, December 2015, A894

1. The EINSTEIN Investigators, *N Engl J Med* 2010;363:2499–2510; 2. Ageno W *et al, Lancet Haematol* 2016;3(1):e12–e21

Recurrence and bleeding in Korea

From 2005 to 2013 in single tertiary hospital, Dongsan Medical Center
Retrospective study

	Unprovoked VTE (n=239)	ACCP 9th guideline[1]	EINSTEIN-PE Standard therapy (n=2413)	RECOVER I & II Standard therapy (n=1289)
Mean age	68.4 ± 12.0		57.5 ± 7.2	54.4 ± 16.2
Major bleeding	2.9%		2.2%	1.7%
Minor bleding	19.2%		9.8%	-
Any bleeding	20.9%		11.4%	22.1%
Cumulative recurrence			1.8%	2.2%
at 1 year	8.5%	10%		
at 5 years	42.7%	30%		

1. Kearon Chest 2012; 141(2 Suppl): p.e419S-94S
2. Manuscript in progress

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Bridging
Perioperative management

Perioperative management of DOACs

- Prospective Cohort Study (n=324 procedure)
- Followup for 30 days
- Primary outcome: major bleeding,
- Secondary outcome: minor bleeding, VTE and death

Protocol

Table 1. Timing of the Last Dose of Dabigatran Before the Surgery or Invasive Procedure

Renal Function, CL_{CR}, mL/min	Estimated Half-Life, h*	Timing of Last Dose of Dabigatran Before Surgery	
		Standard Risk of Bleeding	High Risk of Bleeding†
>80	13 (11–22)	24 h=morning of day –1	2 d=morning of day –2
>50 to ≤80	15 (12–34)	24 h=morning of day –1	2 d=morning of day –2
>30 to ≤50	18 (13–23)	2 d=morning of day –2	4 d=morning of day –4
≤30‡	27 (22–35)	4 d=morning of day –4	6 d=morning of day –6

Schulman Criculation 2015; 132: 167-173

Perioperative management of DOACs

Table 2. Characteristics of the Patients Included

Characteristic	Patients Included (n=541)
Age, mean (SD), y	72.2 (10.8)
Male sex, n (%)	379 (70)
Body weight, mean (SD), kg	87.3 (20.8)
Creatinine clearance, n (%)	
≤30 mL/min	4 (0.7)
>30–≤50 mL/min	86 (16)
>50–≤80 mL/min	213 (39)
>80 mL/min	238 (44)
Indication for anticoagulation, n (%)	
Atrial fibrillation	524 (97)
Venous thromboembolism	10 (1.8)
Stroke or TIA*	4 (0.7)
Other	3 (0.6)
Maintenance dose of dabigatran, n (%)	
75 mg twice daily	1 (0.2)
110 mg twice daily	229 (42)
150 mg twice daily	311 (57)
Risk factors for bleeding, n (%)†	
None	482 (89)
Bleeding with hospitalization	24 (4.4)
Gastrointestinal bleeding	22 (4.1)
Gastrointestinal, nonbleeding ulcer	18 (3.3)
Thrombocytopenia	1 (0.2)
Bleeding risk of the planned procedure, n (%)	
Standard bleeding risk	324 (60)
High bleeding risk	217 (40)

Table 3. Number of Invasive Procedures and Surgeries by Bleeding Risk.

	Bleeding Risk, n		
Procedure	Standard	High	Total
Abdominal surgery	7	21	28
Ankle/knee/hip/shoulder surgery	10	19	29
Biopsy	8	16	24
Brain surgery	0	3	3
Cardiac catheterization	67	0	67
Dental	7	2	9
EPS and ablation therapy	78	1	79
Ear surgery	4	1	5
Endoscopy, bronchoscopy*	84	34	118
Epidural/spinal injection	1	4	5
Eye surgery	20	1	21
Gynecological surgery	4	2	6
Hand or wrist surgery	6	1	7
ICD or pacemaker insertion†	0	52	52
Kidney surgery	0	5	5
Lung surgery	0	7	7
Neck surgery	1	6	7
Skin surgery	13	3	16
TURP/TURBT	2	15	17
Vascular surgery	6	13	19
Other‡	6	11	16
Total, n (%)	324 (60)	217 (40)	541

Bleeding risk in 541 cases

- 324 (60%) standard risk
- 217 (40%) increased risk

Schulman Circulation 2015; 132: 167-173

Perioperative management of DOACs

	24 hr	48hr	96hr before surgery
Last dose of Dabigatran	46%	37%	6%

- Stopping adherence is 89%
- Resumption was timed as the **first dose on the day of procedure** in **40%** of the patients
- Resumption occurred **after 0 to 2 days in 73%** of patients

	Results in Dabigatran	In VKA	Afib, 110	Afib 150
Major bleeding	10 patients (1.8%; 95% CI 0.7-3.0)	2.94%	2.8%	3.8%
Minor bleeding	28 patients (5.2%; 95% CI, 3.30-7.0)			
Transient ischemic attack	1 patient (0.2%; 95% CI, 0-0.5)			
Death	4 deaths unrelated to bleeding or thrombosis			

Schulman Criculation 2015; 132: 167-173

Perioperative management of DOACs

	No Bridging	Perioperative bridging
Major bleeding in RE-LY trials (Douketis et al)	1.8	6.5

No Need for Bridging

Schulman Criculation 2015; 132: 167-173

Perioperative management in Korea

Number	49
Male, n (%)	25 (51)
Age, mean (range)	63 (19-84)
Indication of anticoagulation, n (%)	
Venous thromboembolism	34 (69)
Atrial fibrillation	9 (18)
Replacement of cardiac valve (mechanical)	3 (6)
Others	3 (6)
Reasons of bridging anticoagulation, n (%)	
Major surgery/procedure	29 (59)
Minor surgery/procedure	20 (41)
Experience on warfarin, n (%)	
Warfarin naïve (≤90days)	20 (41)
Warfarin experienced (>90 days)	21 (59)
Duration on warfarin, days, median (range)	122 (6-6016)
Comorbid condition, n (%)	
Active malignancy (within 6 months)	16 (33)
CHF	3 (6)
CVA or TIA	3 (6)
Ischemic heart disease	4 (8)
Renal insufficiency (GFR <30 mL/min)	10 (20)

Manuscript in progress

Perioperative management in Korea

Efficacy outcome measure (30-day)	
Recurrent VTE, n (%)	0 (0)
All-cause mortality, n (%)	0 (0)
Safety outcome measure (30-day)	
Major bleeding, n (%)	2 (4.1)

Manuscript in progress

VTE following OS surgery in Korea

- Retrospective study
- After hip and knee replacement arthroplasty
- January 1 and December 31, 2010
- Health Insurance Review and Assessment Service (HIRA)
- HRA: 22,127
- KRA: 52,882

Table 1. Baseline characteristics of patients with hip and knee replacement

Parameters	Patients with hip replacement			Patients with knee replacement		
	Chemoprophylaxis (-) (n = 13,868) No. (%)	Chemoprophylaxis (+) (n = 8,259) No. (%)	*P* value*	Chemoprophylaxis (-) (n = 27,305) No. (%)	Chemoprophylaxis (+) (n = 25,577) No. (%)	*P* value*
Gender			0.001			0.001
Male	5,445 (39.3)	3,052 (37.0)		3,553 (13.0)	2,927 (11.4)	
Female	8,423 (60.7)	5,207 (63.0)		23,752 (87.0)	22,650 (88.6)	
Age (yr)‡						
Mean ± SD	68.6 ± 15.2	69.6 ± 14.2	< 0.001	68.5 ± 7.7	68.6 ± 7.0	0.333
≤ 44	1,145 (8.3)	547 (6.6)	< 0.001†	141 (0.5)	36 (0.1)	< 0.001†
45 ≤ age ≤ 64	3,433 (24.8)	1,900 (23.0)		7,070 (25.9)	6,595 (25.8)	
65 ≤ age ≤ 74	3,456 (24.9)	2,254 (27.3)		14,222 (52.1)	13,860 (54.2)	
75 ≤ age ≤ 84	4,077 (29.4)	2,572 (31.1)		5,700 (20.9)	4,939 (19.3)	
≥ 85	1,757 (12.7)	986 (11.9)		172 (0.6)	147 (0.6)	

Lee J Korean Med Sci 2016; 31: 80-88

VTE following OS surgery in Korea

HRA	VTE	DVT	PE
Overall incidence during 90 days after HRA (n=22,127)	3.9%(n=853)	2.7%(n=597)	1.5%(n=327)
Incidence after HRA in western	7.0	5.1	2.5
Western population-based registry after HRA	2.3		

KRA	VTE	DVT	PE
Overall incidence fter KRA (n=52,882)	3.8% (n=1,990)	3.2% (n=1,699)	0.7% (n=355)
Incidence after KRA in western	6.2	5.4	1.0
Western population-based registry after KRA	1.8		

Lee J Korean Med Sci 2016; 31: 80-88

VTE following OS surgery in Korea: Risk factors

	Odd ratio after HRA	Odd ratio after KRA
Previous VTE history	10.8	8.5
Chronic heart failure	2.1	1.3
Arrhythmia	1.8	1.7
Atrial fibrillation	3.4	2.1

Incidence of VTE, DVT and PE was not low compared that in other Asian or Western population.

Lee J Korean Med Sci 2016; 31: 80-88

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Post thrombotic syndrome

PTS in real world

- Sam Schulman: **New Project to see PTS at 5 years** in patients on Dabigatran in **RECOVER I & II**
- Expecting the result in **GARFIELD-VTE**
- **XALIA (-)**

Thrombolytic therapy in proximal DVT
Systemic or catheter-directed

- Extensive iliofemoral or proximal DVT
- High risk of limb ischemia

- **CaVent trial[1]:** open-label randomized
- 209 patient with first iliofemoral DVT
- Included within 21 days from symptom
- Catheter directed therapy (alteplase) vs anticogualtion (101 vs 108)
- Outcome: PTS at 2 years (Villalta score)

	CDT	Anticoagulation	P-value
PTS at 2 years, n(%)	37(41)	55 (55.6)	0.047

- Large multicenter trial (the ATTRACT trial[2]) is underway
  - (n=692) since 2013
  - Pharmaco-mechanical catheter-directed thrombolysis(PCDT) vs standard only
  - Outcome: PTS at 2 years (Villalta score)

1. Isolated thrombolysis with oscillating wire
2. PowerPulse thrombolysis (25mg of rt-PA)
   - Powerful pulse-spray from AngioJet catheter
3. Infusion: 0.01mg/kg/hr for up to 30 hrs

1. Enden et al. Lancet 2012; 379(9810): 31-8
2. Vedantham et al. Am Heart J 2013; 165(4): 523-530.e3

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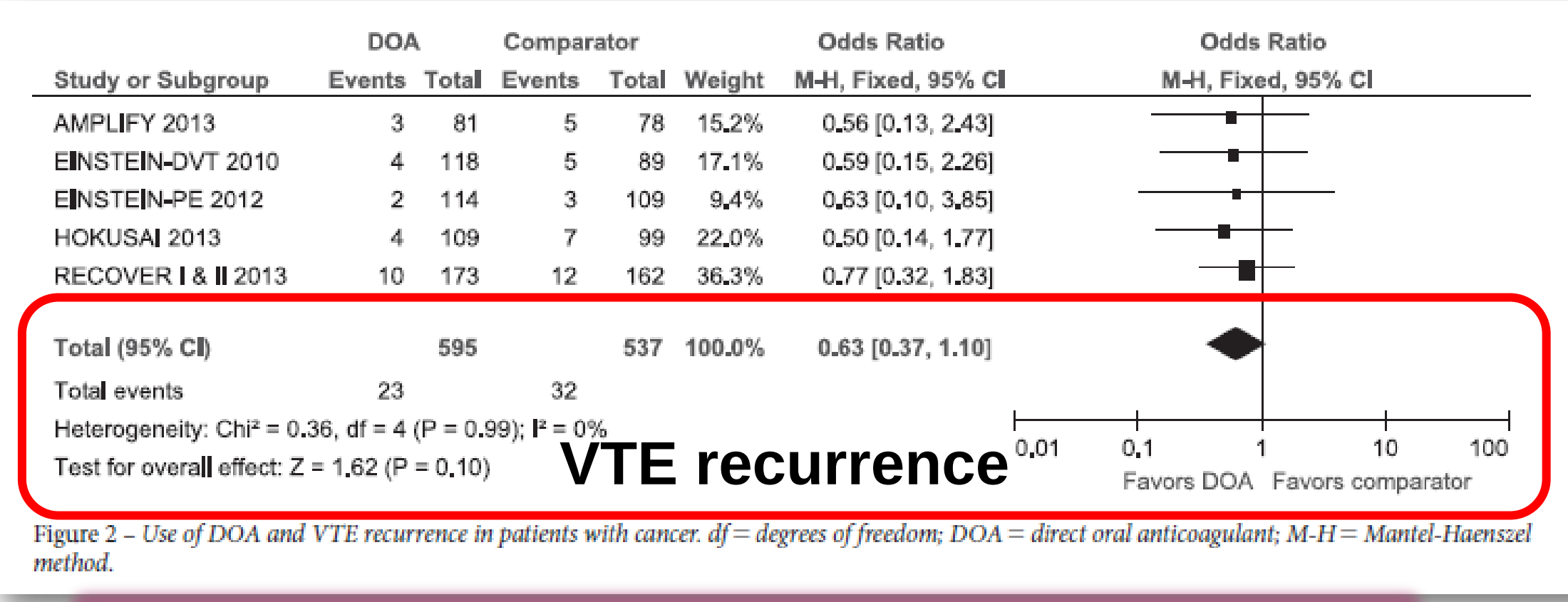
DOACs in VTE & Cancer

LMWH versus Warfarin in VTE and cancer

Trial Name	CLOT	CATCH
Year of Publication	2003	2015
Design	Open-label	Open-label
Number of Patients	676	900
Treatment Protocol	**Dalteparin 200 IU/kg once daily for the first month then 150 IU/kg for 5 months**	**Tinzaparin 175 IU/kg once daily**
Duration of Therapy (months)	**6**	**6**
Primary Efficacy Outcome LMWH vs VKA (%)	**Recurrent symptomatic VTE: 9[a] vs 17**	**Composite of recurrent symptomatic VTE, fatal PE, or incidental VTE: 7.2 vs 10.5 (p=0.07)**
Safety Bleeding Outcomes LMWH vs VKA (%)	Major bleeding: 6 vs 4 Any bleeding: 14 vs 19	**Major bleeding: 2.7 vs 2.4** **CRNM bleeding: 10.9[a] vs 15.3**

DOACs for the treatment of VTE in cancer patients



Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		595		537	100.0%	0.63 [0.37, 1.10]
Total events	23		32			

Heterogeneity: Chi² = 0.36, df = 4 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.62 (P = 0.10)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favors DOA Favors comparator

VTE recurrence

Figure 2 – *Use of DOA and VTE recurrence in patients with cancer. df = degrees of freedom; DOA = direct oral anticoagulant; M-H = Mantel-Haenszel method.*

Total (95% CI)	595	537	100.0%	0.63 [0.37, 1.10]	
Total events	23	32			

Vedovati et al. Chest 2015; 147(2): 475-483

DOACs for the treatment of VTE in cancer patients

Vedovati et al. Chest 2015; 147(2): 475-483

A

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		587		527	100.0%	0.77 [0.41, 1.44]
Total events	19		22			

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favors DOA Favors comparator

Major bleeding

B

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	11	87	18	80	21.0%	0.50 [0.22, 1.13]
EINSTEIN-DVT 2010	17	118	14	88	17.6%	0.89 [0.41, 1.92]
EINSTEIN-PE 2012	14	114	10	108	11.5%	1.37 [0.58, 3.24]
HOKUSAI 2013	20	109	25	99	27.4%	0.67 [0.34, 1.29]
RECOVER I & II 2013	23	159	20	152	22.4%	1.12 [0.59, 2.13]
Total (95% CI)		587		527	100.0%	0.85 [0.62, 1.18]
Total events	85		87			

Heterogeneity: Chi² = 4.04, df = 4 (P = 0.40); I² = 1%

Test for overall effect: Z = 0.96 (P = 0.34)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favors DOA Favors comparator

CRNMB

VTE and Cancer versus VTE and no Cancer
ACCP 10th guideline

	VTE and cancer	VTE and no cancer
LMWH	2B	---
Dabigatran	2C over VKA	2B over VKA
Rivaroxaban	2C over VKA	2B over VKA
Apixaban	2C over VKA	2B over VKA
Edoxaban	2C over VKA	2B over VKA

Kearon Chest 2016; 149(2): 315-352

VTE-cancer : clinical trials

- Open-label trial underway (NCT02073682)
- Edoxaban versus Dalteparin

Rank	Status	Study
1	Not yet recruiting	Direct Oral Anticoagulants (DOACs) Versus LMWH +/- Warfarin for VTE in Cancer **Conditions:** Cancer; Venous Thromboembolism; Deep Vein Thrombosis (DVT); Pulmonary Embolism (PE); Blood Clot; VTE **Interventions:** Drug: Rivaroxaban; Drug: Apixaban; Drug: Edoxaban; Drug: Dabigatran; Drug: Warfarin; Drug: Dalteparin; Drug: Enoxaparin; Drug: Fondaparinux
2	Recruiting	Cancer Venous Thromboembolism (VTE) **Conditions:** Venous Thromboembolism (VTE); Deep Vein Thrombosis (DVT); Pulmonary Embolism (PE); Cancer **Interventions:** Drug: edoxaban; Drug: Dalteparin

ClinicalTrials.gov, Accessed November 2016

8

New Agent in Future

Emerging anticoagulants Strategies

Factor XII and XI

- Naturally occurring polyphosphates activate the contact system.
- **Contact system** is critical for thrombus stabilization and growth.
- Factors (F) XII and FXI as targets for new anticogulants

Aspirin & Anticoagulants

- There is evidence that platelets contribute to venous thrombosis
- Primary prevention & Secondary prevention

Fredenburg Blood Oct 2016

Emerging anticoagulants

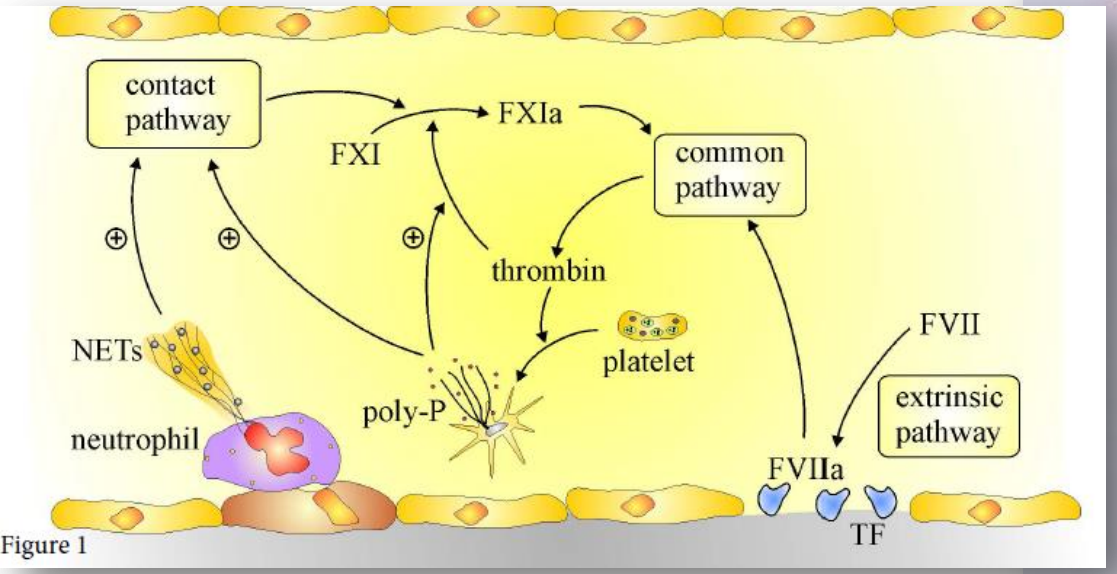
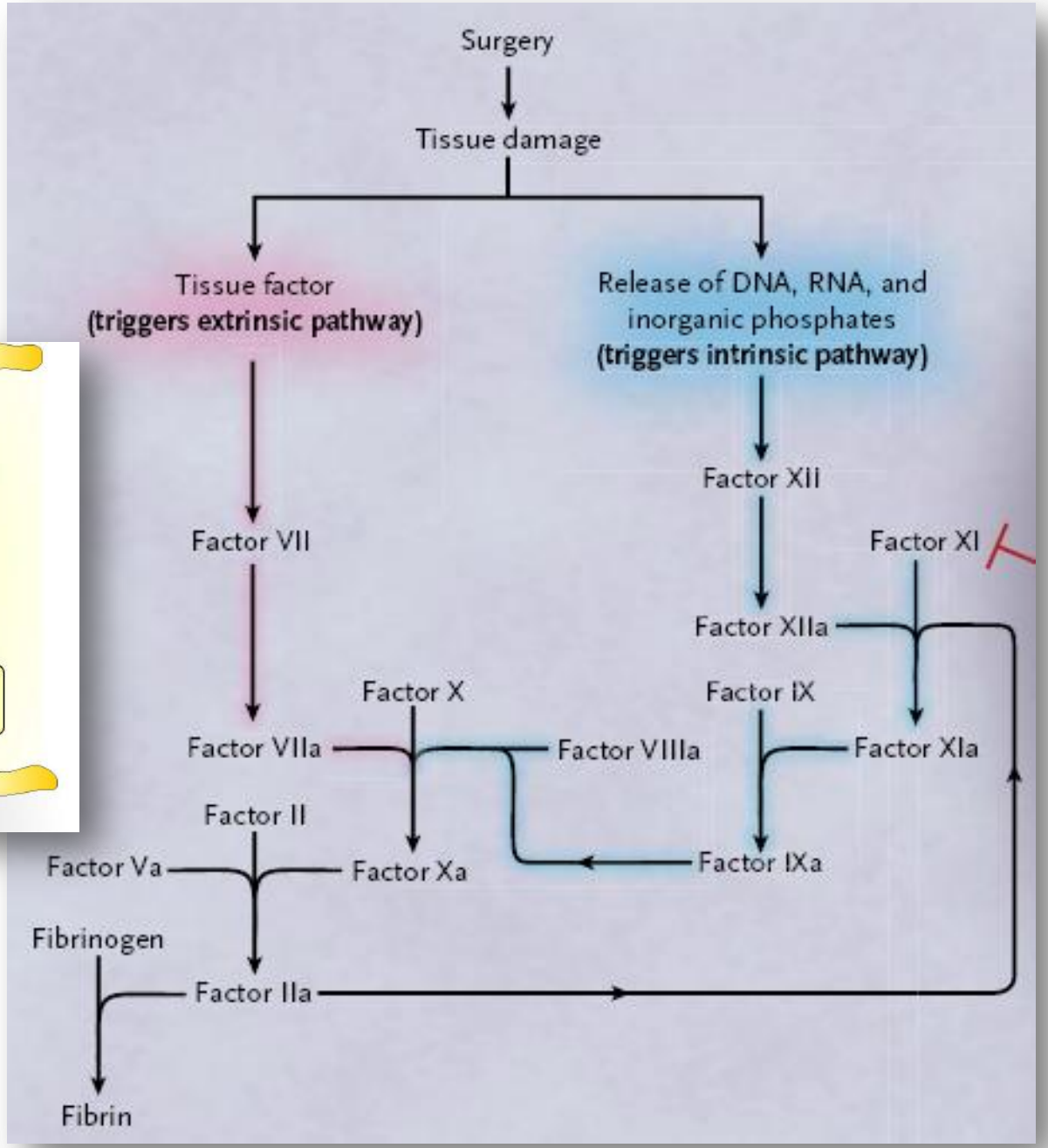


Figure 1



Buller N ENGL J MED 2015; 372:3 232-240
Fredenburg Blood Oct 2016

Emerging anticoagulants

Venous thrombosis is attenuated
- in mice rendered thrombocytopenic,
- in those deficient in VWF,
- or in those treated with antiplatelet agents.

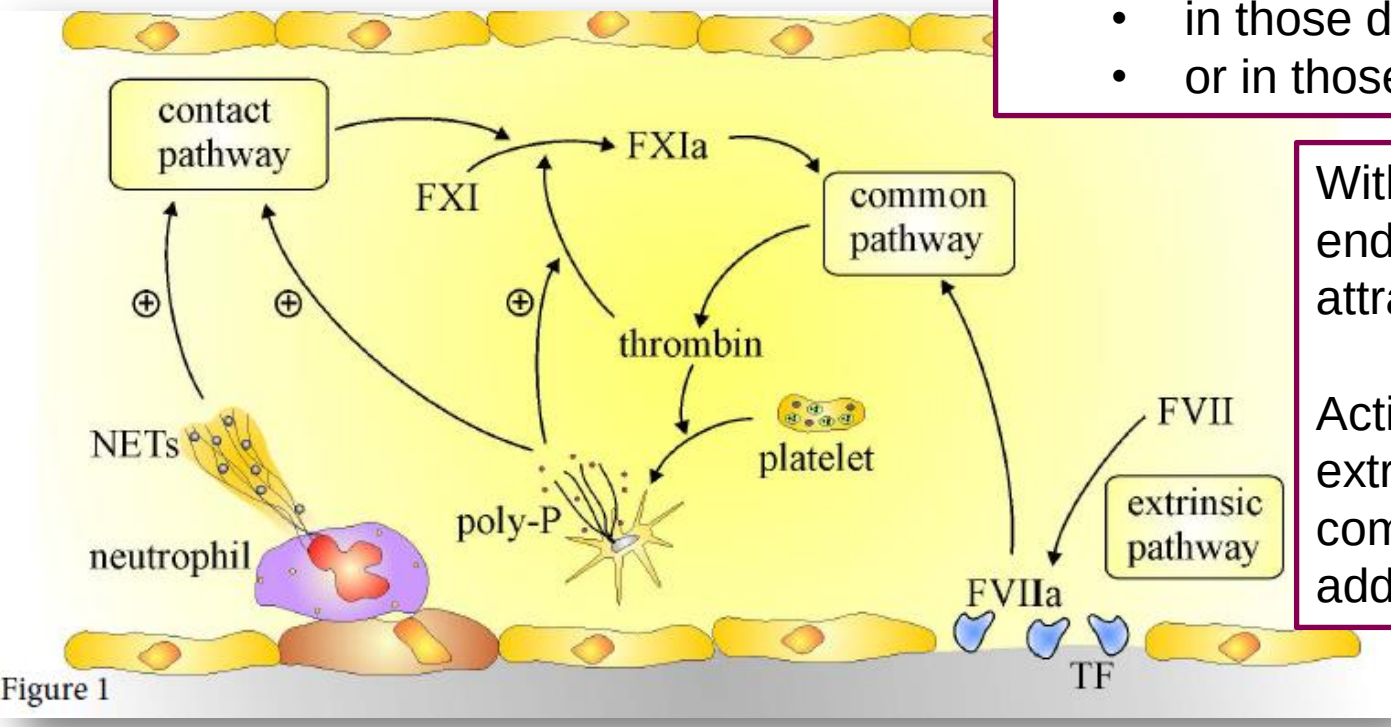


Figure 1

With venous flow restriction, endothelial cells become activated and attract platelets and neutrophils.

Activated neutrophils release neutrophil extracellular traps (NETs), lattices composed of DNA and histones, to which additional platelets adhere

Clotting factors assemble on their surface to generate thrombi
Release of inorganic polyphosphate from platelet dense granule triggers activation of the contact system, which amplifies thrombin generation.

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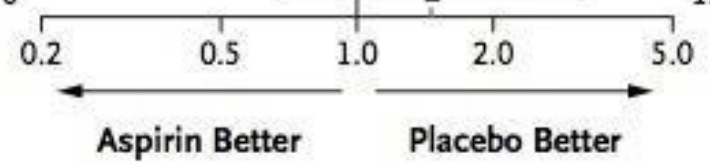
Aspirin vs placebo

- ASPIRE[1]: Recurrent VTE in first unprovoked VTE, to receive aspirin at a dose of 100mg daily or placebo for up to 4 years
- WARFASA[2]: Aspirin, 100mg daily or placebo for 2 years

Outcome and Study	Placebo	Aspirin	Hazard Ratio (95% CI)	P Value	P Value for Heterogeneity
	no. of events/total no. of patients				
Venous thromboembolism					0.42
ASPIRE	73/411	57/411	0.74 (0.52–1.05)	0.09	
WARFASA	43/197	28/205	0.58 (0.36–0.93)	0.02	
Pooled	116/608	85/616	0.68 (0.51–0.90)	0.007	
Major vascular events					0.96
ASPIRE	88/411	62/411	0.66 (0.48–0.92)	0.01	
WARFASA	48/197	36/205	0.67 (0.43–1.03)	0.06	
Pooled	136/608	98/616	0.66 (0.51–0.86)	0.002	
Clinically relevant bleeding					0.50
ASPIRE	8/411	14/411	1.72 (0.72–4.11)	0.22	
WARFASA	4/197	4/205	0.98 (0.24–3.96)	0.97	
Pooled	12/608	18/616	1.47 (0.70–3.08)	0.31	



1. Brighton NEJM, 2012
2. Becattini NEJM, 2012

DOACs versus Aspirin in VTE

New Indications for DOACs

Indication	Trial No	Intervention	Control	Duration	Sample size	Efficacy outcome	Safety outcome
Primary prevention	EPCAT II 01720108	Rivaroxaban 10mg od	Aspirin 81mg	10 or 30 days	3,426	Symptomatic VTE	Major or CRNMB
Secondary prevenditon	EINSTEIN Choice 02064439	Rivaroxaban 10mg OD or 20mg OD	Aspirin	1 year	3,399	Recurrent VTE	Major bleeding

Extended VTE prophylaxis comparing rivaroxaban to aspirin following THA and TKA

EINSTEIN Choice: multicenter, randomized, double blind, event-driven, superiority study for efficacy

Eligibility: Patients with symptomatic DVT or PE who completed 6 or 12 mo of Tx of anticoagulation

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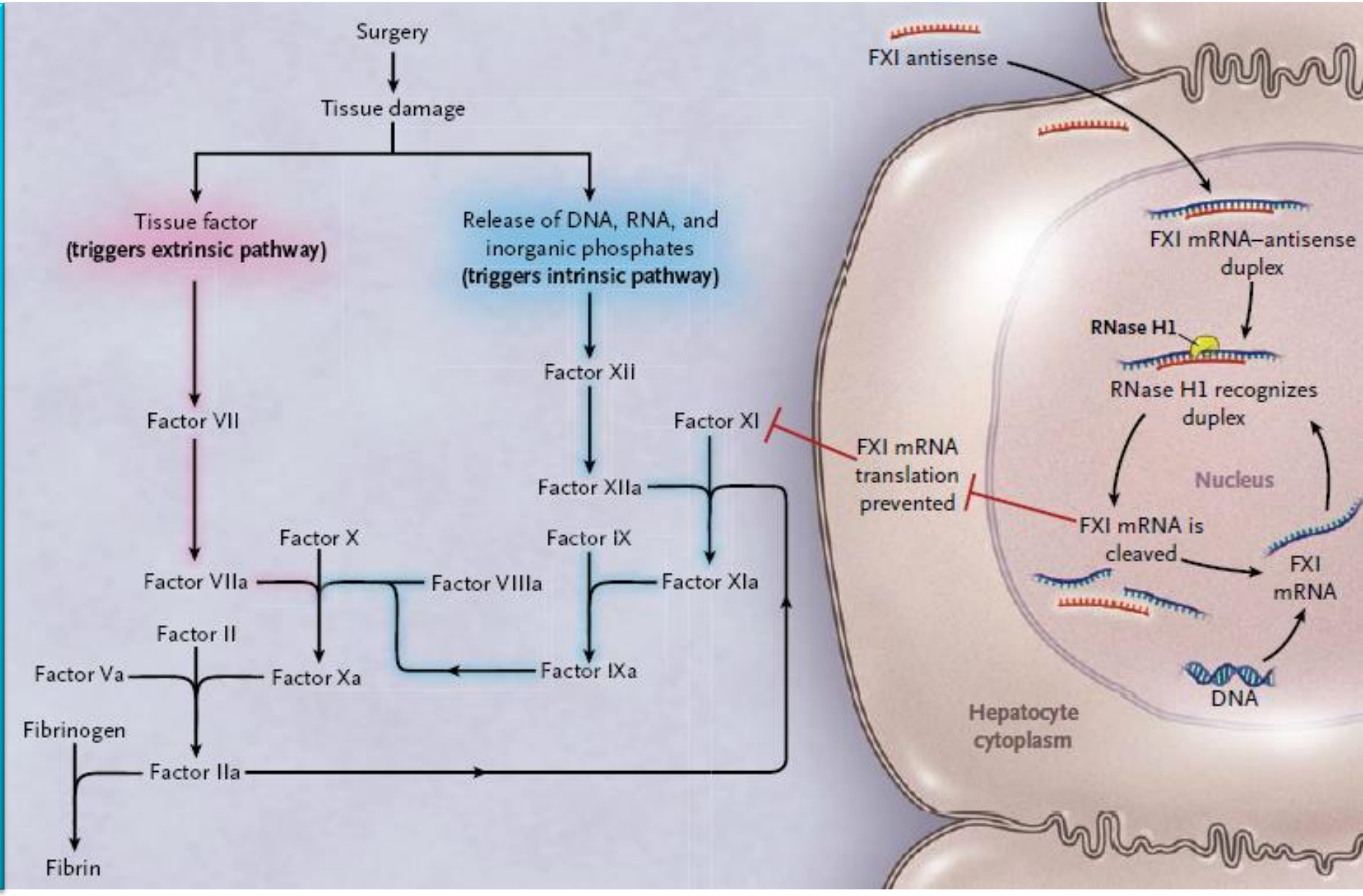
Effect of Factor XI-Antisense Oligonucleotide (ASO) on the Coagulation System



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Factor XII versus Factor XI

Relative advantages and disadvantages for new anticogulants

	Factor XII	Factor XI
Epidemiologic data	Weak	Strong
Risk of bleeding	None	Low
Level of evidence for role in thrombosis	Preclinical	Phase 2
Potensial for bypassing inhibition	Thrombin-mediated activation of factor XI could bypass factor XII inhibition	None
Potential for off target effect	May modulate inflammation by inhibiting bradykinin generation	Unlikely

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Effect of Factor XI-antisense Oligonucleotide

Phase II study	Patients undergoing total knee arthroplasty (TKA)
Open-label,	
300 patients	
Group	FXI-ASO 200mg FXI-ASO 300mg 40mg of enoxaparin once daily
Primary outcome	Incidence of venous thromboembolism
Safety outcome	Major or clinically relevant nonmajor bleeding

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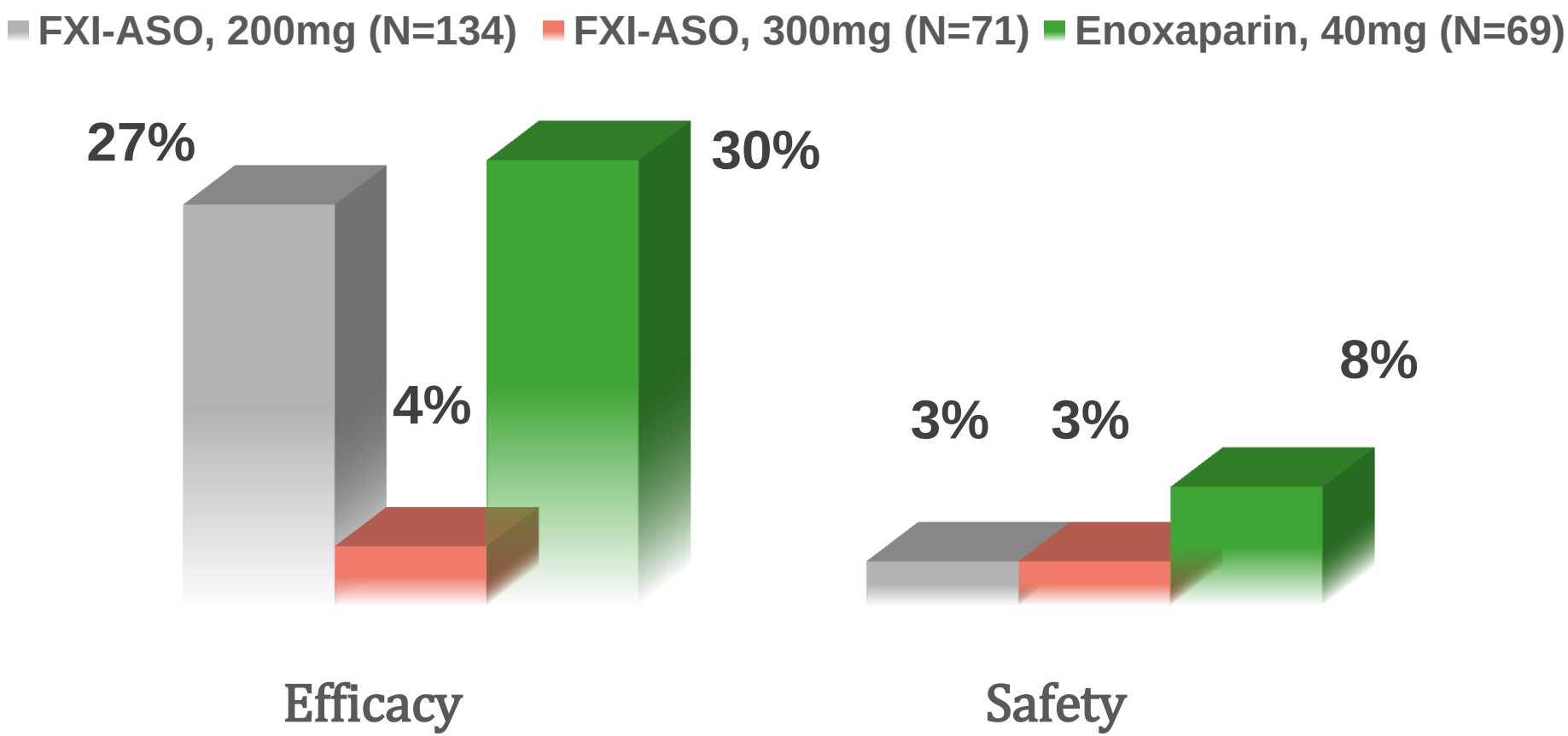
Efficacy and Safety of FXI-ASO



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Take-Home Message

Summary

1. XALIA study
2. GARFIELD-DVT
3. Recurrence & Bleeding
4. Bridging (Perioperative management)
5. Post-thrombotic syndrome
6. DOACs in Cancer patients
7. New agent in the future

경청해주셔서 감사합니다.

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