Newer oral anticoagulants for VTE and their relevance in India

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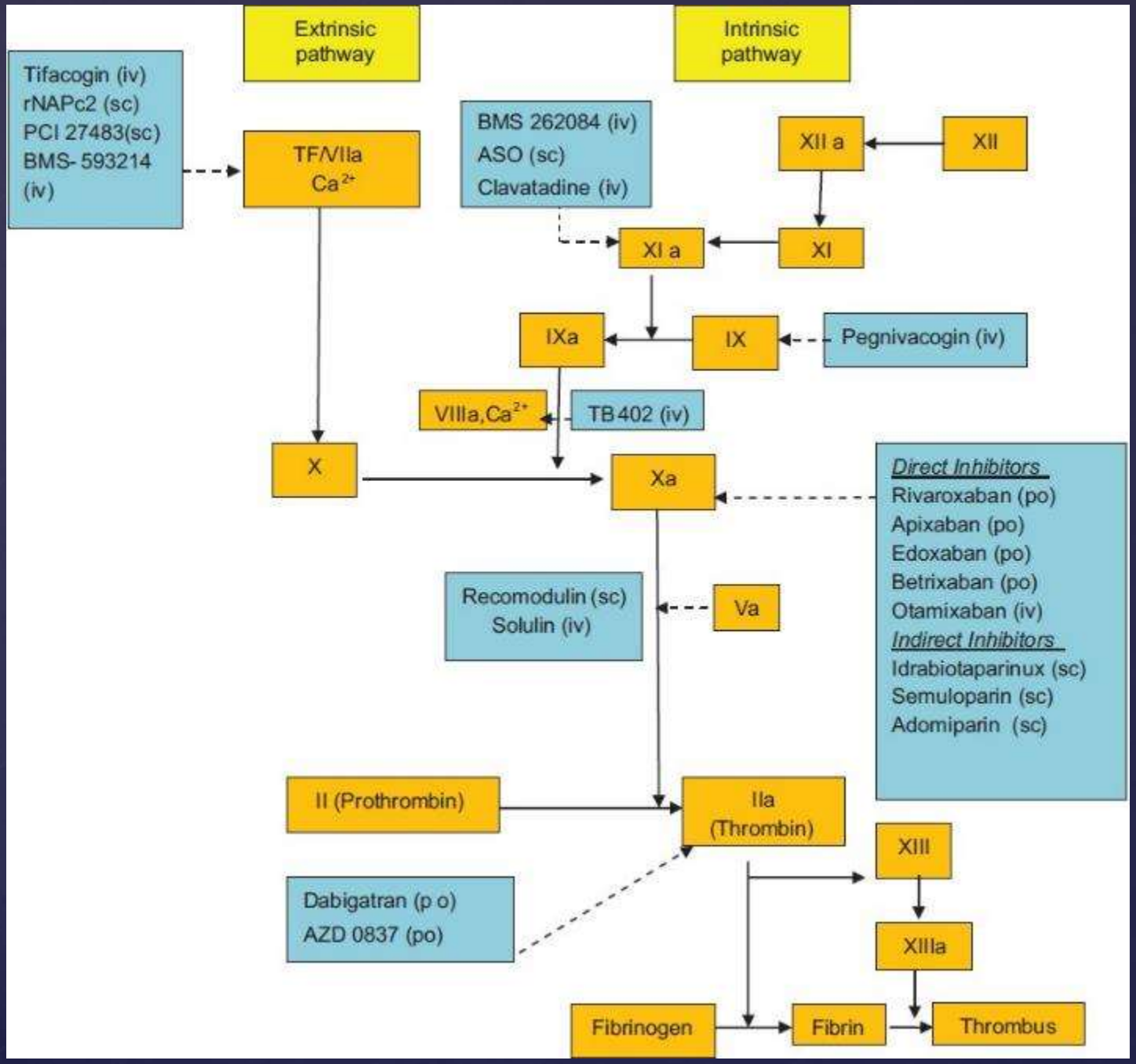
Objectives

- Need for new drugs
- Individual drugs and their evidences
- Evidence for NOAC in specific situations
- Risks associated with these newer agents
- Challenges in India

Burden of VTE

- Common in surgical patients, hospitalised medically ill and cancer patients. Incidence of phlebographic DVT 40-60% , symptomatic DVT 5-36% during the post operative period J Orthop Sci 2008;13:442–51.
- Risk of pulmonary embolism is 0.9 to 28 % in hip arthroplasty and 1.5 to 10% in knee arthroplasty

Prevention of VTE.ACCP guidelines. Chest 2008; 133: 3815-453



Aditya S. Oral and parenteral anticoagulants: New kids on the block. *J Postgrad Med 2012;58:275-85*

VKAs (Warfarin)

- Act by inhibiting synthesis of vitamin k dependent factors, II,IV, IX, X, protein C and S.
- Time-tested anticoagulants
- Economical
- More than five decades of experience in using the drug

Why not warfarin?

Limitation	Clinical Implications
Slow onset and offset of action	Need for bridging with a rapidly acting anticoagulant
Interindividual variability in anticoagulant effect	Variability in dosing requirements
Narrow therapeutic index	Need for routine coagulation monitoring
Food and drug interactions	Dietary precautions; need for routine coagulation monitoring
Reduced synthesis of all vitamin K–dependent proteins	Risk of skin necrosis in patients with protein C or S deficiency; potential for osteoporosis*

Hankey GJ, Eikelboom JW. Circulation. 2011; 123:1436-1450

Why not warfarin?

- Wide intra and inter individual variability
- Even in trials INR has been noted to be in the therapeutic range for about 50-60% of the times
- Both sub therapeutic and supra therapeutic anticoagulation are harmful

Search for an ideal anticoagulant

- Oral anticoagulant
- Fixed dosing
- No monitoring required
- No interaction with food or diet
- Safe
- Wide therapeutic index
- An effective antidote should be available

Study design in most of these trials

- Multi center randomized control trial, double blind study
- Non inferiority when compared to warfarin, superiority over placebo
- Patient population – acute symptomatic VTE (DVT,PE)
- Primary outcome : recurrent symptomatic objectively confirmed VTE or death due to VTE

Study design (safety outcomes)

- Major and clinically relevant non major bleed
- *Major bleed* – hemoglobin drop 2 g/dL or more, 2 units transfusion, bleeding in critical site or fatal bleed
- *Clinically relevant non major bleed* : bleed requiring medical intervention. Spontaneous hematoma >25 cm^2 , gingival or epistaxis >5 mts, spontaneous hematuria, rectal bleed and in surgical patients wound hematoma 100 cm^2,

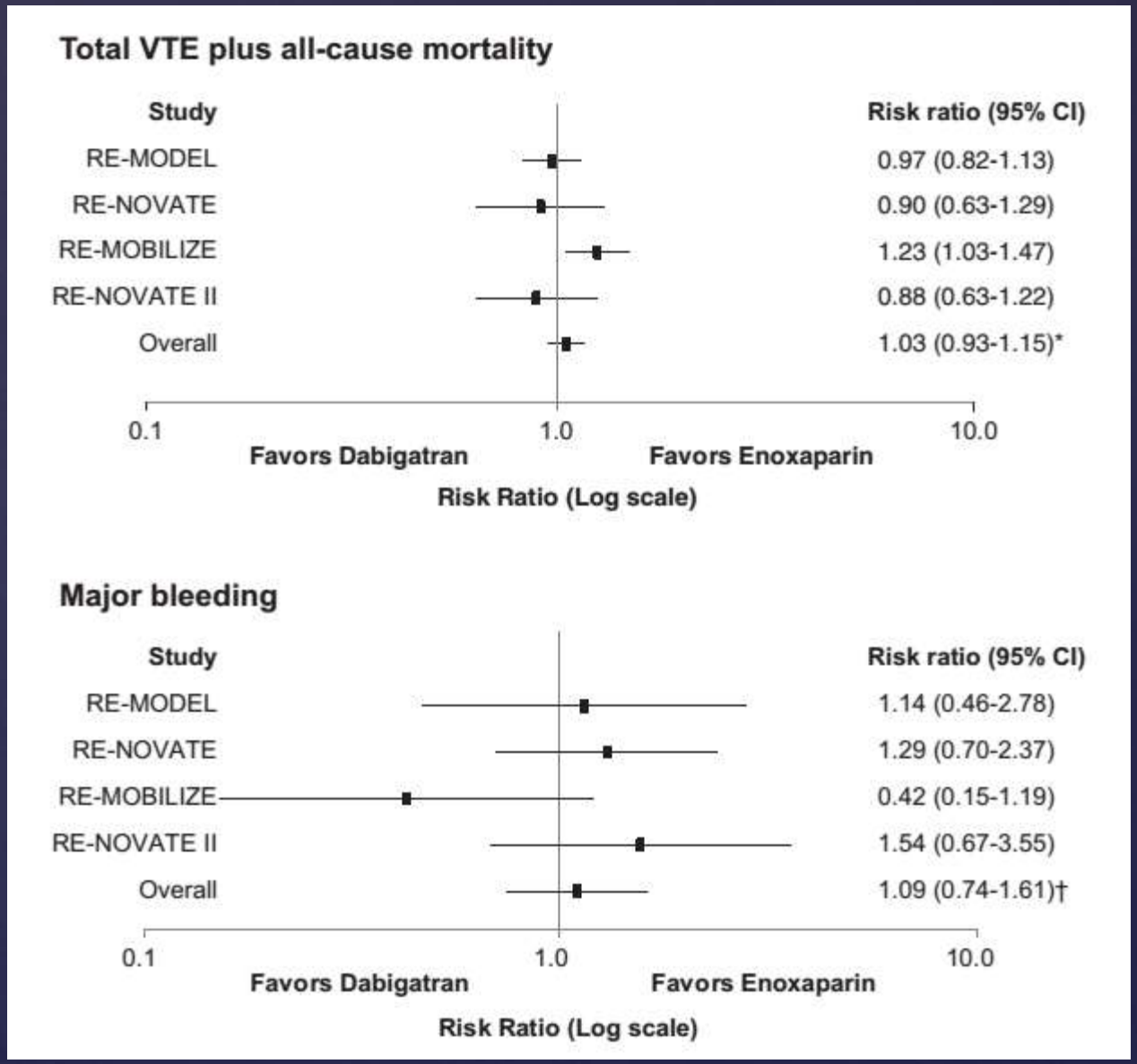
Dabigatran

- Orally active pro-drug
- 6-7% bioavailability
- No cyp3A4 interaction
- Contra indicated in severe renal dysfunction
- Individual trials and meta analysis have shown dabigatran to be equally effective as enoxaparin for preventing VTE and mortality in orthopedic surgeries

Dabigatran in VTE

Trial	Patients	No.	Intervention	Duration of Treatment	Primary Outcome, % or %/y (n/N)	Rate Ratio (95% CI)	Absolute Risk Difference (95% CI), %	Major Bleed, % or %/y (n/N)	Rate Ratio (95% CI)
Prevention of VTE					Total VTE and death				
RE-MODEL[41]	TKA	2101	Enoxaparin SC 40 mg OD	6–10 d	37.7% (193/512)			1.3% (9/694)	
			Dabigatran 220 mg OD		36.4% (183/503)	0.97 (0.82–1.13)	−1.3 (−7.3–4.6)	1.5% (10/679)	1.14 (0.46–2.78)
			Dabigatran 150 mg OD		40.5% (213/526)		2.8 (−3.1–8.7)	1.3% (9/703)	
RE-NOVATE[42]	THA	3494	Enoxaparin SC 40 mg OD	28–35 d	6.7% (60/897)			1.6% (18/1154)	
			Dabigatran 220 mg OD		6.0% (53/880)	0.90 (0.63–1.29)	−0.7 (−2.9–1.6)	2.0% (23/1146)	1.29 (0.70–2.37)
			Dabigatran 150 mg OD		8.6% (75/874)		1.9 (−0.6–4.4)	1.3% (15/1163)	
RE-MOBILIZE[43]	TKA	2615	Enoxaparin SC 30 mg BID	12–15 d	25.3% (163/643)			1.4% (12/868)	
			Dabigatran 220 mg OD		31.1% (188/604)	1.23 (1.03–1.47)	5.8 (0.8–10.8)	0.6% (5/857)	0.42 (0.15–1.19)
			Dabigatran 150 mg OD		33.7% (219/649)		8.4 (3.4–13.3)	0.6% (5/871)	
RE-NOVATE II[44]	THA	2055	Enoxaparin SC 40 mg OD	28–35 d	8.8% (69/785)			0.9% (9/1003)	
			Dabigatran 220 mg OD		7.7% (61/792)	0.88 (0.63–1.22)	−1.1 (−3.8 to 1.6)	1.4% (14/1010)	1.54 (0.67–3.55)
Treatment of VTE					Recurrent VTE and related death				
RE-COVER[45]	Acute VTE	2564	Warfarin (INR 2.0 to 3.0)	6 mo	2.1% (27/1265)			1.9% (24/1265)	
			Dabigatran 150 mg BID		2.4% (30/1274)	1.10* (0.65–1.84)	0.4 (−0.8–1.5)	1.6% (20/1274)	0.82* (0.45–1.48)

Hankey GJ, Eikelboom JW. Circulation. 2011; 123:1436-1450



$I^2 = 49\%$

$I^2 = 28\%$

Hankey GJ, Eikelboom JW. Circulation. 2011; 123:1436-1450

Treatment of Acute Venous Thromboembolism with Dabigatran or Warfarin and Pooled Analysis

Sam Schulman, Ajay K. Kakkar, Samuel Z. Goldhaber, Sebastian Schellong, Henry Eriksson, Patrick Mismetti, Anita Vedel Christiansen, Jeffrey Friedman, Florence Le Maulf, Nuala Peter and Clive Kearon
for the RE-COVER II trial investigators

Circulation. published online December 16, 2013;

	Study Design	Intervention	Primary outcome	Safety outcome
RE-COVER 2 (Circulation Dec 2013)	Acute VTE 2589 patients (20% Asians) Randomized Double blind Double dummy Non-inferiority trial	UFH or LMWH for 5 to 11 days f/b Dabigatran 150mg BD 0r warfarin (INR 2-3)	2.3% In dabigatran group 2.2% in warfarin group	Any bleed 15.6% vs. 22.1% Major bleed 1.2% vs. 1.7%

Schulman S et al. **Circulation**. 2014 Feb 18;129(7):764-72

- Pooled analysis of RECOVER I and II – Hazard ratio for

  recurrent VTE 1.09

  major bleed 0.79

  any bleed 0.7

- Dabigatran is non-inferior to warfarin in preventing VTE recurrence, with a reduced risk of bleeding

Schulman S et al. **Circulation**. 2014 Feb 18;129(7):764-72

Dabigatran vs Enoxaparin: is dabigatran always better?

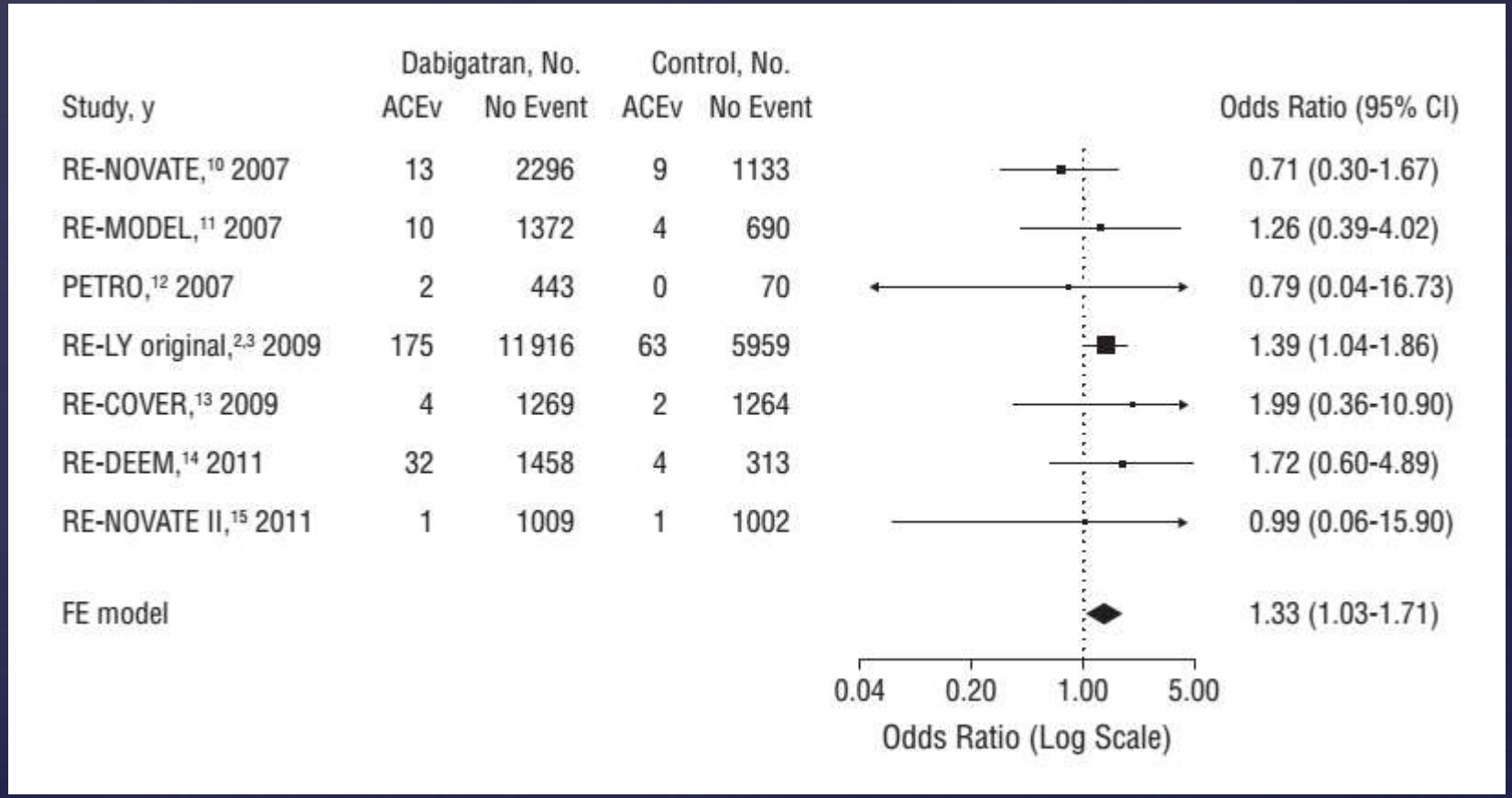
Trial	Design	Comparison	VTE rates	Bleeding
RE-MOBILIZE J arthroplasty 2009 Jan	1896 orthopedic patients during post op period 12-15 days	Dabigatran 220 mg BD or Dabigatran 110 mg BD or Enoxaparin 30mg BD	31% (p 0.02) 34% (p 0.001) 25%	Bleeding rates were similar

Dabigatran and bleeding

- Patients with major bleed on dabigatran had –
  - Older age
  - Reduced creatinine clearance
  - Received more NSAIDS
- Bleed in patients receiving dabigatran was a/w less 30 d mortality (9.1%) as compared to bleed in patients receiving warfarin (13%)
- Less ICU stay for patients on dabigatran on comparison with warfarin induced bleed

Majeed A et al.Circulation. 2013 Nov 19;128(21):2325-32

Dabigatran & ACS/MI



Uchino K et al. Arch Intern Med. 2012 Mar 12;172(5):397-402

Dabigatran & ACS/MI

- Meta analysis however was largely contributed by the original RE-LY trial
- RE-LY comprised 59% weightage and 74% of the events
- Median 2 years of follow up
- May be due to unfavourable effects on atherosclerosis

Uchino K et al. Arch Intern Med. 2012 Mar 12;172(5):397-402

Dabigatran & ACS

- Contradicting results from another meta analysis
- Data from four phase three trials pooled, RE-MOBILIZE, RE-MODEL, RE-NOVATE, RENOVATE II.
- No difference noted between dabigatran and the comparator drug with regards to ACS

Eriksson BI et al. Thromb Res. 2012 Sep;130(3):396-402.

A word of caution

- The above analysis was on patients undergoing orthopedic surgery and hence on dabigatran for short duration (6-35days)
- Meanwhile, the analysis which included RELY trial where patients received dabigatran for AF and followed up to a median of two years had increased risk of ACS/MI
- Is short term therapy safe and not long term therapy ?

Rivaroxaban

- Direct factor Xa inhibitor
- Selective, competitive and reversible inhibitor of factor Xa
- Free factor Xa as well those bound to the prothrombinase complex
- The bound factor Xa is protected from antithrombin and antithrombin-dependent anticoagulants

Rivaroxaban

- Water insoluble
- 90-95% albumin/protein bound
- Does not affect bleeding time and platelet aggregation whereas aPTT, PT, heparin clotting time are prolonged
- A single fixed dose can be administered irrespective of age, sex, weight

Rivaroxaban

- Dose – 10 mg in orthopedic surgery for VTE prevention

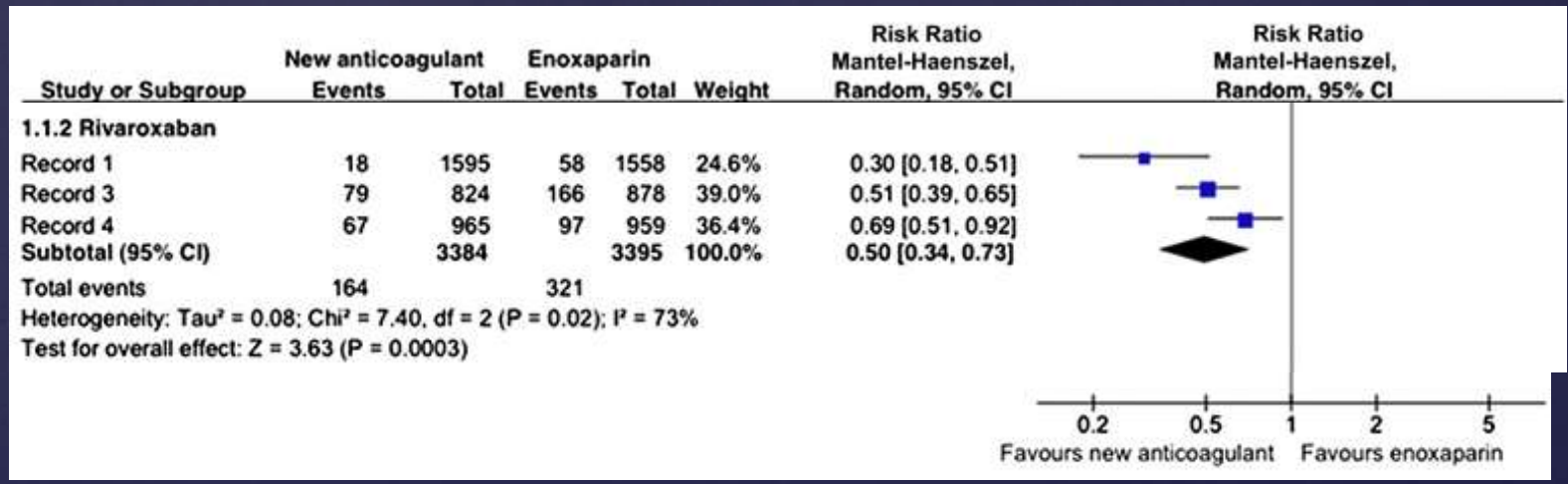
  20 mg OD in secondary VTE prevention
- 1/3 is excreted unchanged by kidneys
- 2/3 is by hepatic metabolism
- CYP3A4 interaction – Quinidine, verapamil, amiodarone and other P-glycoprotein inhibitors are contraindications

	Study Design	Intervention	1 ^{0} outcome	Safety outcome
RECORD 1 Eriksson BI et al. N Engl J Med 2008; 358:2765-2775	THR 4541 patients Randomised Double blind Double dummy Non-inferiority trial	Rivaroxaban 10 mg OD post-op Vs. Enoxaparin 490 mg OD	1.1% In Rivaroxaban group 3.7% in enoxaparin group	Any bleed 15.6% vs. 22.1% Major bleed 0.3% vs. 0.1% (p – 0.18)
RECORD 2 Kakkar AK et al. Lancet 2008 Jul 5;372(9632):31-9	Extended duration rivaroxaban against short term enoxaparin 2509 patients THR	Rivaroxaban 10 mg OD 31-39 days Vs. Enoxaparin 40 mg OD 10-14 days	All cause mortality and incidence of VTE 2% vs. 9.3%	
RECORD 3 & 4 Lassen et al. N Engl J Med 2008; 358:2776-2786 Turpie AG. Lancet 2009 May 16;373(9676):1673-80	TKR 2531 and 3148 patients	Rivaroxaban 10 mg OD vs. enoxaparin 40 mg OD And 30 mg BD (RECORD 4)	Non inferior	No significant difference

	Study Design	Intervention	Primary outcome	Safety outcome
EINSTEIN N Engl J Med 363;26 December 23, 2010	1. Acute DVT 3449 patients Randomized Open label Non-inferiority trial	Rivaroxaban 10 mg OD post-op Vs. Enoxaparin 40 mg OD	2.1% vs. 3.0%	Any bleed 8.1% vs. 8.1%
	2. Maintenance rx for 6-12 months in whom 6-12 months anticoagulation completed 602 + 594 patients Randomized Placebo controlled Superiority	15 mg BD 3 weeks f/b 20 mg OD Enoxaparin s.c f/b warfarin/acenocoumarol	1.3% vs. 7.1%	Major bleed 0.7% vs. 0%

	Study Design	Intervention	Primary outcome	Safety outcome
EINSTEIN PE N Engl J Med 366;14 April 5, 2012	1. Acute symptomatic PTE 4832 patients Randomized Open label Non-inferiority trial	Rivaroxaban 15 mg BD 3 weeks f/b 20 mg OD Enoxaparin sc f/b warfarin/acenocoumarol	2.1% vs. 1.8%	Any bleed 10.3% vs. 11.4% Major bleed 1.1% vs. 2.2%

Rivaroxaban in VTE prevention in orthopedic surgeries



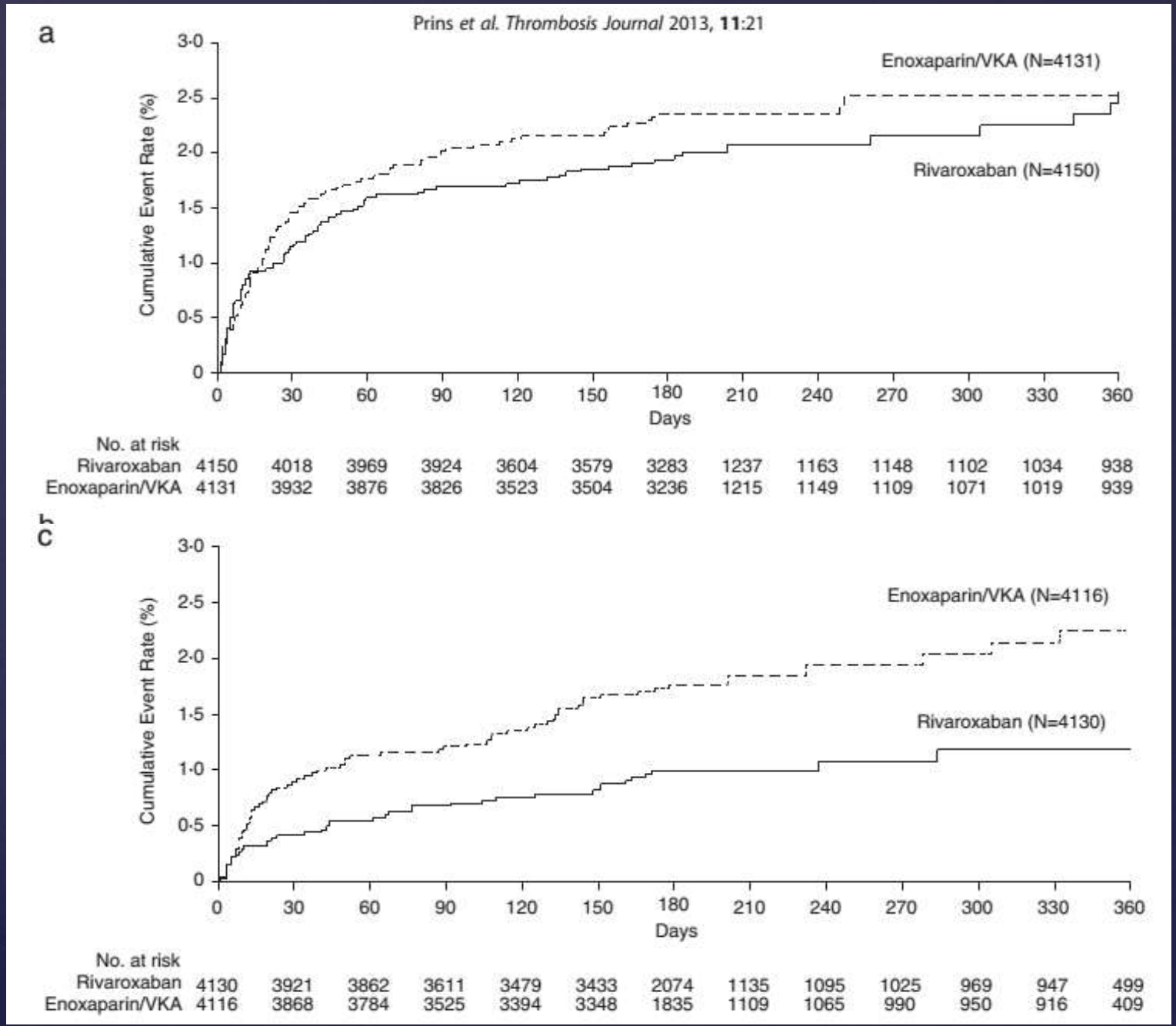
Study or Subgroup	New anticoagulant Events	Total	Enoxaparin Events	Total	Weight	Risk Ratio Mantel-Haenszel, Random, 95% CI
1.1.2 Rivaroxaban						
Record 1	18	1595	58	1558	24.6%	0.30 [0.18, 0.51]
Record 3	79	824	166	878	39.0%	0.51 [0.39, 0.65]
Record 4	67	965	97	959	36.4%	0.69 [0.51, 0.92]
Subtotal (95% CI)		3384		3395	100.0%	0.50 [0.34, 0.73]
Total events	164		321			

Heterogeneity: Tau² = 0.08; Chi² = 7.40, df = 2 (P = 0.02); I² = 73%

Test for overall effect: Z = 3.63 (P = 0.0003)

Yoshida Rde A et al. Ann Vasc Surg. 2013 Apr;27(3):355-69

EINSTEIN DVT- PE pooled analysis



Apixaban

- Selective, direct acting reversible factor Xa inhibitor
- Not affected by food intake
- Fecal excretion (75% of the drug)
- Contraindicated with azoles, macrolides

Apixaban

Key trials

- orthopedic patients ADVANCE 1, 2 ,3
- Medically ill patients ADOPT trial
- AMPLIFY – apixaban for acute VTE
- AVERROES, ARISTOTLE – AF and stroke

	Study Design	Intervention	1 ^{0} outcome	Safety outcome
ADVANCE 1 Lassen MR et al N Engl J Med 2010	TKR 3195 patients Randomised Non-inferiority trial	Apixaban 2.5 mg BD post-op Vs. Enoxaparin 30 mg BD	Non inferiority proven	Bleed 2.9% vs. 4.3% (significant)
ADVANCE 2 Lassen MR et al. Lancet 2010	TKR 3057 patients Non inferiority	Apixaban 2.5 mg BD Vs. Enoxaparin 40 mg OD	15.1% vs. 24% (Event rate)	Similar (non significant reduction)
ADVANCE 3 Lassen MR et al N Engl J Med 2010	THR 5407 patients Superiority Randomized Double blind	Apixaban 2.5 mg BD for five weeks post surgery Vs. Enoxaparin 40 mg OD	Non inferior as well as superior 1.4% vs. 3.9%	No significant difference

	Study Design	Intervention	Primary outcome	Safety outcome
AMPLIFY N Engl J Med. Aug 2013; 369(9)	Acute VTE 5395 patients Randomized Double blind Non-inferiority trial	Apixaban 10 mg BD 7 days f/b 5 mg BD for 6 months Vs. Enoxaparin sc for 7 days f/b warfarin (INR 2-3)	2.3% vs. 2.7%	Any bleed 4.3% vs. 9.7% (Significant reduction)

EDOXABAN

- Insignificant effect of food
- One third of the drug is excreted in urine
- Two phase 2 trials: In one Edoxaban was compared with dalteparin and in other with warfarin
- Lower (15 and 30 mg) , higher (60 and 90 mg doses) were evaluated
- Reduction in VTE after THR was noted, with a similar bleeding risk, as compared to the comparator drug

	Study Design	Intervention	Primary outcome	Safety outcome
Hokusai VTE study J Thromb Hemost 2o13 online ; 1 (17)	Acute symptomatic VTE 4921 DVT patients 3319 PTE patients Randomized Double blind Non-inferiority trial 12 months study period	Initial LMWH f/b Edoxaban 60 mg OD (30 mg if creatinine clearance < 30-50 mL/mt) Vs. Warfarin (INR 2-3)	3.2% vs. 3.5% (symptomatic recurrent VTE)	Clinically relevant bleed 8.5% vs. 10.3%

Comparison of NOACs

Review	Drugs	Studies	Main results	Bleeding risk
Huang J Thromb hemos 2011	Apixaban vs. Enoxaparin in TKA	8 RCTs	Apixaban non-inferior	Reduced risk of bleeding in *apixaban*
Yoke et al J clin pharm Ther 2011	Rivaroxaban, dabigatran vs. enoxaparin in orthopedics		1.Rivaroxaban >enoxaparin 2.Dabigatran not superior to enoxaparin 3.Rivaroxaban> dabigatran	R > E D > E R > D
Fox BD et al BMJ 2012	Apixaban , rivaroxaban, dabigatran, ximelagatran, VKA Direct & indirect comparison	9 trials (rivaroxaban - 4 Apixaban – 1 Dabigatran & ximelagatran 2 studies each)	No significant difference in symptomatic recurrent VTE with any of the drugs as compared to VKAs	Bleeding risk is *significantly reduced with rivaroxaban*. Rest are all similar

Review	Drugs	Studies	Main results	Bleeding risk
Nieto JA et al Thromb Res. 2012 Aug;130	Dabigatran, apixaban and rivaroxaban vs. enoxaparin 40 mg OD (in THR, TKR patients)	10 RCTs	Rivaroxaban > enoxaparin (RR for VTE/DVT 0.50) Apixaban > enoxaparin (RR for VTE/DVT 0.69) Dabigatran > enoxaparin (RR for VTE/DVT 1.02)	Similar in enoxaparin and NOAC. *Trend towards more bleeding in rivaroxaban* Apixaban least clinically relevant bleed
Yoshida Rde et al Ann Vasc surg 2013	Rivaroxaban, dabigatran, apixaban vs. enoxaparin (orthopedic sutgeries)	15 clinical trials	1. Rivaroxaban > enoxaparin 2. Dabigatran 220 mg, Apixaban = enoxaparin 3. Dabigatran 150 mg < enoxaparin	All had similar bleeding risk as compared to enoxaparin. Except- Apixaban significantly reduced bleeding risk

Review	Drugs	Studies	Main results	Bleeding risk
Van Der Hulle et al J Thrombos Hemost 2013 Dec 13.	Rivaroxaban, apixaban, Edoxaban, Dabigatran vs. VKAs in acute VTE	5 RCTs (24455)	RR for recurrent VTE as compared with VKAs 0.88	RR for bleeding was 0.60 Less bleeding risk with NOACs as compared to VKAs

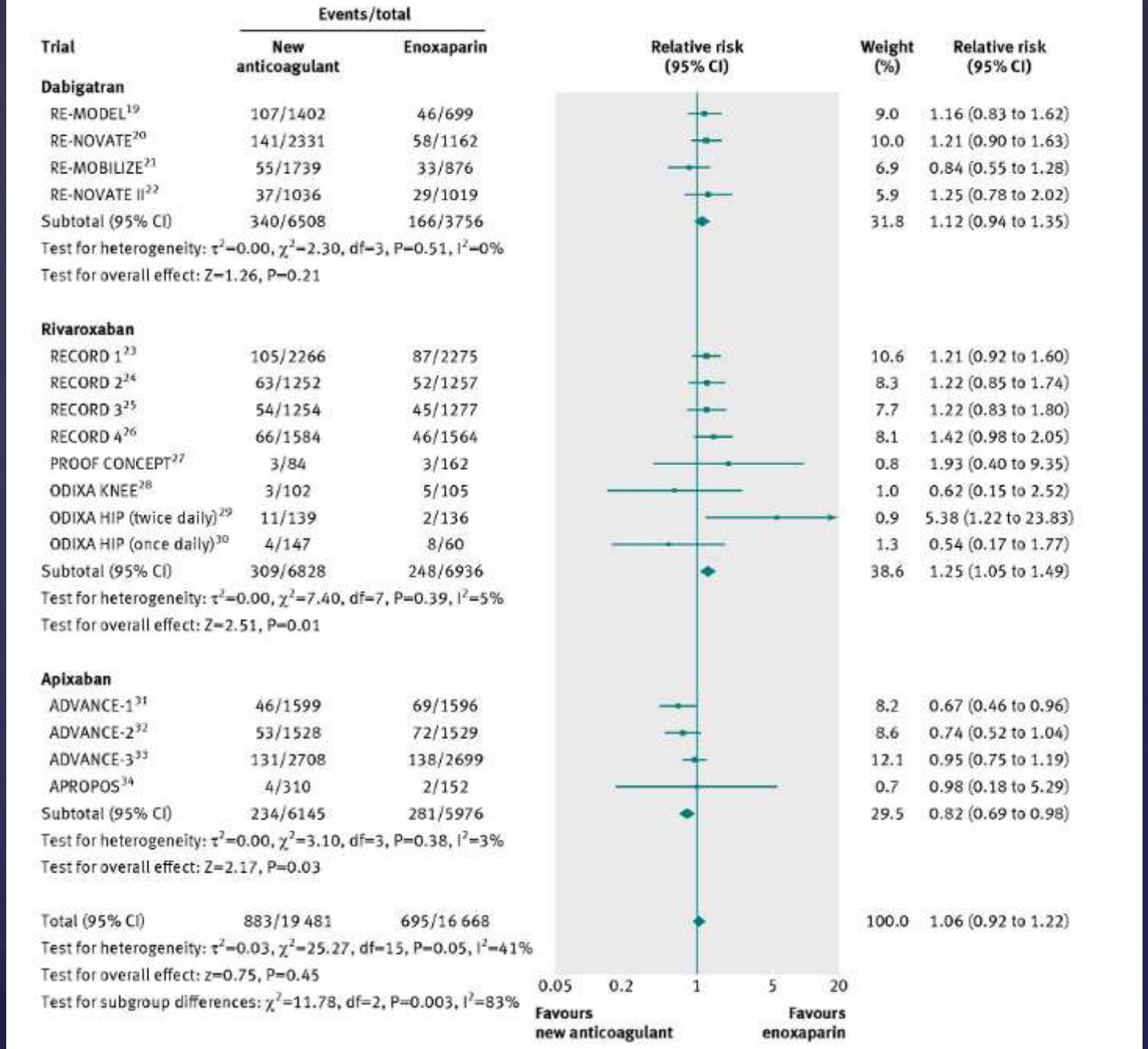
Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons

Antonio Gómez-Outes *clinical assessor*[1], Ana Isabel Terleira-Fernández *associate professor*[2], M Luisa Suárez-Gea *clinical assessor*[1], Emilio Vargas-Castrillón *professor*[2]

Outcomes	Relative risk (95% CI)		
	Rivaroxaban *v* dabigatran	Rivaroxaban *v* apixaban	Apixaban *v* dabigatran
Symptomatic venous thromboembolism	0.68 (0.21 to 2.23)	0.59 (0.26 to 1.33)	1.16 (0.31 to 4.28)
Clinically relevant bleeding	1.12 (0.87 to 1.44)	1.52 (1.19 to 1.95)	0.73 (0.57 to 0.94)
Major bleeding	1.37 (0.79 to 2.39)	1.59 (0.84 to 3.02)	0.86 (0.41 to 1.83)
Net clinical endpoint	0.95 (0.61 to 1.48)	0.96 (0.66 to 1.40)	0.99 (0.61 to 1.61)

*Random effects model, events while receiving treatment.

Gomez-Outes A et al.BMJ. 2012 Jun 14;344:e3675



Gomez-Outes A et al.BMJ. 2012 Jun 14;344:e3675

Direct head-head comparison?

- Currently not available

- DARINA trial comparing dabigatran vs rivaroxaban vs nadraparin (clinicaltrials.gov NCT01431456)

NOAC in cancer patients

	EINSTEIN DVT [29]	EINSTEIN PE [30]	RE-COVER [36]
Intervention	Rivaroxaban vs. VKA	Rivaroxaban vs. VKA	Dabigatran vs. VKA
No. of patients	3449	4832	2564
Study design	Open label	Open label	Double-blind
Treatment duration	3, 6 or 12 months	3, 6 or 12 months	6 months
Recurrent VTE	2.1% vs. 3.0%	2.1% vs. 1.8%	2.4% vs. 2.1%
Major bleeding	0.8% vs. 1.2%	1.1% vs. 2.2%	1.6% vs. 1.9%
No. of patients with active cancer	207 (6.0%)	223 (4.6%)	121 (4.7%)
Recurrent VTE among cancer patients	3.4% vs. 5.6%	1.8% vs. 2.8%	3.1% vs. 5.3%
Bleeding events among cancer patients	14.4% vs. 15.9%	12.3% vs. 9.3%	NR

	EINSTEIN-EXTENSION [29]	RE-MEDY [37]	AMPLIFY-EXT [34]
Intervention	Rivaroxaban vs. placebo	Dabigatran vs. warfarin	Apixaban 2.5 mg vs. Apixaban 5 mg vs. placebo
No. of patients	1196	2866	2486
Study design	Double-blind	Double-blind	Double-blind
Treatment duration	6 or 12 months	18 months	12 months
Recurrent VTE	1.3% vs. 7.1%	1.8% vs. 1.3%	3.8% vs. 4.2% vs. 11.6%
Major bleeding	0.7% vs. 0	0.9% vs. 1.8%	0.2% vs. 0.1% vs. 0.5%
No. of patients with active cancer	54 (4.5%)	119 (4.1%)	42 (1.7%)
Recurrent VTE among cancer patients	NR	3.3% vs. 1.7%	NR
Bleeding events among cancer patients	NR	NR	NR

den Exter PL et al. **Best Pract Res Clin Haematol. 2013** Jun;26(2):163-9

NOACs in cancer patients

- More chances of bleed than non cancer patients. Sub therapeutic anticoagulation on the other hand increases risk of thrombosis
- May not tolerate orally, due to nausea and vomiting
- Renal dysfunction may be present in these patients
- Data insufficient

VTE in medically ill

- Medically ill includes – CCF NYHA III or IV
- COPD acute exacerbation
- Acute infectious illnesses
- Rheumatological disorders
- Inflammatory bowel diseases
- Mobility of patients in hospital is also taken into account

Thromboprophylaxis in medically ill

- Medically ill patients do benefit from these measures, though the maximum benefit is seen in surgical patients
- Duration of VTE risk extends to few weeks after discharge
- Evaluation of short term (6-10 days) as well as long term thromboprophylaxis (35-40 days) have been undertaken
- EXCLAIM study – Enoxaparin in extended thromboprophylaxis reduced VTE, but significant increase in bleeding was noted

Cohen AA, Rider T. Best Pract Res Clin Haematol. 2013 Jun;26(2):183-90

NOAC in medically ill

- Few trials have been done on this specific subset of patients
- MAGELLAN – Rivaroxaban (10 mg OD) vs enoxaparin f/b placebo
- ADOPT – Apixaban (2.5 mg BD) vs enoxaparin f/b placebo
- Significant increase in bleeding was noted in these patients

Cohen AA, Rider T. Best Pract Res Clin Haematol. 2013 Jun;26(2):183-90

MAGELLAN & ADOPT

		MAGELLAN	ADOPT
Indications		VTE prophylaxis when hospitalised with acute medical illness	VTE prophylaxis when hospitalised with acute medical illness
Drug		10 mg rivaroxaban once daily	2.5 mg apixaban twice daily
Comparator		Initially enoxaparin, then placebo during extended phase	Initially enoxaparin, then placebo during extended phase
Design		Multicentre randomised double-blinded trial, non-inferiority during initial phase and superiority during extension phase	Multicentre randomised double-blinded trial, non-inferiority during initial phase and superiority during extension phase
Duration		10 ± 4 days initial phase then 35 ± 4 days extended phase	Initial phase 6–14 days then 30 days extended phase
Inclusion criteria		≥40 years of age with reduced mobility[a] and an acute medical illness requiring hospitalisation	≥40 years of age, an acute medical illness requiring hospitalisation with one additional VTE risk factor (except heart failure or respiratory failure patients) and reduced mobility[b]
Exclusion criteria		Conditions that contraindicate use of enoxaparin or rivaroxaban, recent surgery or head injury, history of haemorrhagic stroke, high bleeding risk, sustained uncontrolled hypertension, alcohol or drug abuse, pregnant or breastfeeding, co-administration of cytochrome P450 3A4 inhibitors and severe renal impairment	Confirmed VTE on admission, co-morbities requiring on-going anti-coagulation, active liver disease, severe renal impairment, anaemia or thrombocytopenia, contra-indication to enoxaparin, co-administration of two or more antiplatelet agents, recent surgery, pregnancy or breastfeeding
Study population	*N*	8101	6528
	Age	Median 71 days for both arms	Median 67 for both arms
	Length of hospitalisation	Median 11 days for both arms	Unknown
Acute medical condition	Infectious disease	46% rivaroxaban arm, 45% enoxaparin arm	22% apixaban arm, 23% placebo arm
	Heart failure (NYHA class III or IV)	32% rivaroxaban arm, 32% enoxaparin arm	38% for both arms
	Respiratory insufficiency	27% rivaroxaban arm, 29% enoxaparin arm	37% for both arms
	Ischaemic stroke	17% rivaroxaban arm, 17% enoxaparin arm	Unknown
	Active cancer	7% rivaroxaban arm, 7% enoxaparin arm	4% apixaban arm, 3% placebo arm
	Inflammatory or rheumatic disease	4% rivaroxaban arm, 4% enoxaparin arm	2% for both arms
Outcomes	Primary efficacy outcome	Rivaroxaban group 4.4% at day 35, enoxaparin then placebo 5.7% at day 35 (RR 0.77, 95% CI 0.0.62–0.96, $P = 0.02$)	Apixaban group 2.7% at day 30, enoxaparin then placebo 3.1% (RR with apixaban 0.87, 95% CI 0.62–1.23, $P = 0.44$)
	Major bleeding and clinically relevant non-major bleeding	2.8% with rivaroxaban and 1.2% with enoxaparin at day 10 ($P < 0.001$). 4.1% with rivaroxaban and 1.7% with enoxaparin then placebo at day 35 ($P < 0.001$)	2.67% with apixaban at day 30 and 2.08% with enoxaparin then placebo (RR 1.28, 95% CI 0.93–1.76, $P = 0.12$)
	Fatal bleeding	7 in the extended rivaroxaban group and 1 in the enoxaparin then placebo group	0 in the apixaban group and 2 in the enoxaparin then placebo group

[a] Defined as at least one day of complete immobility followed by at least 4 days of decreased mobility. Complete immobilisation defined as being totally confined to bed or chair but allowing use a bedside commode or assistance to the bathroom. Decreased mobility causing >50% to be spent in bed or chair.

[b] Defined as moderate or severe restriction in mobility. Moderately restricted allowed for walking within hospital room or to the bathroom, severely restricted mobility defined as confined to bed or to a bedside chair.

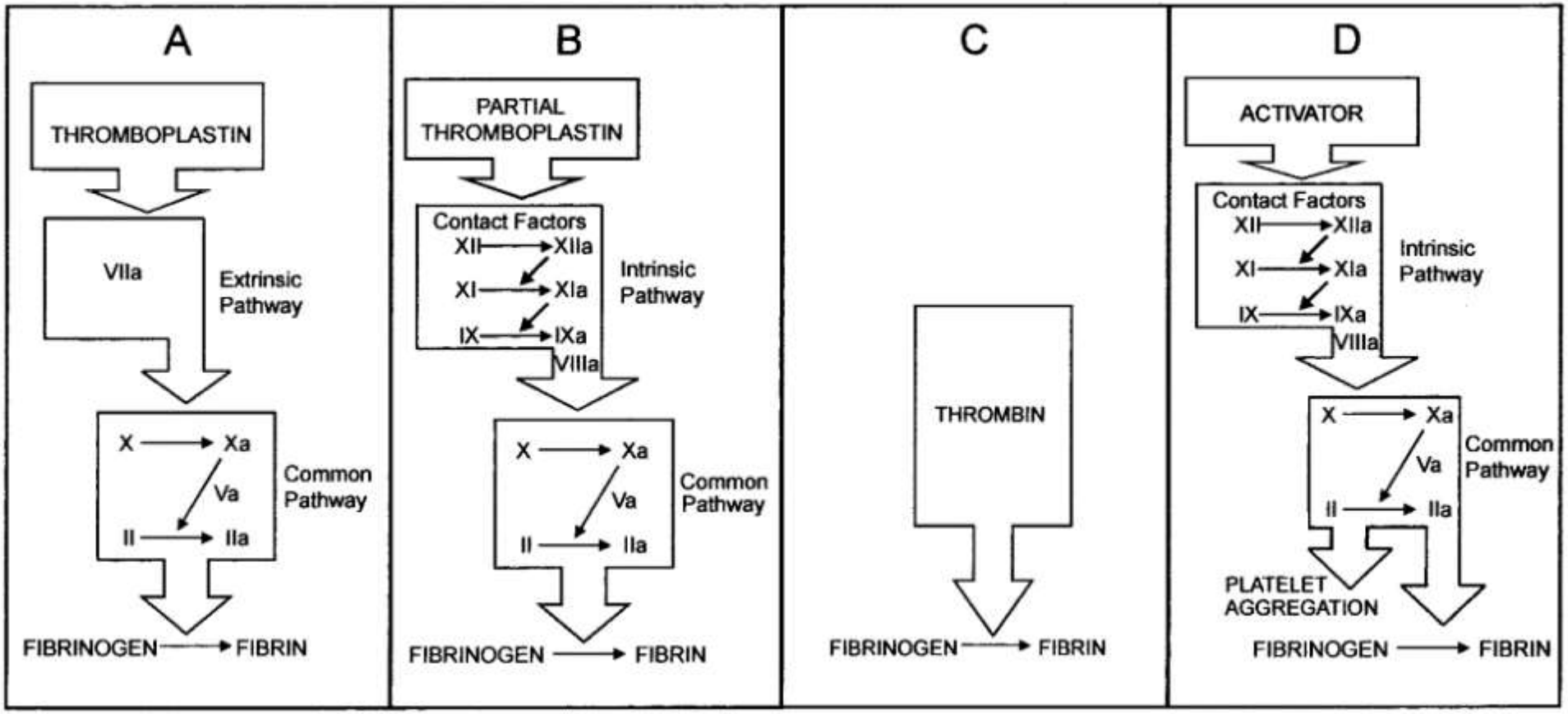
Cohen AA, Rider T. Best Pract Res Clin Haematol. 2013 Jun;26(2):183-90

- Prolonged therapy with apixaban or rivaroxaban reduces the risk of VTE as compared to enoxaparin f/b placebo (RR 0.79)
- Major bleeding – RR of 2.69 for patients on factor Xa inhibitors when compared to enoxaparin

Albertsen IE et al. Drugs. 2012 Sep 10.

Newer anticoagulants & monitoring

- Generally do not require monitoring
- Need may arise
- When reversal is needed for surgery
- May be required when toxicity or overdose is suspected



PT	aPTT	TCT	ACT
Abnormality in extrinsic and common pathway	Intrinsic & common pathway	Detects fibrinogen abnormalities	Whole blood assay, detests platelet aggregation as well 70-180 s normal
	Less sensitive alternative to detect DTI effects	DIC, heparin, DTIs prolong TCT	CABG and intraop monitoring

Ecarin clotting time

- Echis carinatum snake venom converts prothrombin to meizothrombin, a prothrombin intermediate that is sensitive to inhibiton by direct thrombin inhibitors
- Not useful to detect coagulation disorders
- Useful for therapeutic monitoring only
- In a bleeding patient normal ECT precludes Direct thrombin inhibitor as a cause

Risk factors predisposing to major bleed

- Certain factors have been noted uniformly in all trials
- Elderly (>75 years)
- Renal dysfunction
- Pre existing lesions in GI tract
- Use of antiplatelets with anticoagulants

Risk factors predisposing to major bleed

- Retrospective observation of data from New Zealand had shown that prescriber error contributes to 25% cases of bleeding, which includes :
- Starting dabigatran before INR had fallen to 2 or less
- Inappropriately high dosage in elderly (>80) and in those with renal dysfunction

John W et al. N Engl J Med 2012: 366; 864

Management of bleed with NOACs

- Supportive measures
- For direct thrombin inhibitors –

  Activated charcoal

  Desmopressin and vWF concentrates

  Activated factor VIIa

  Prothrombin complex concentrates

  Hemodialysis and hemoperfusion

  Monoclonal antibodies against Dabigatran

Majeed A, Schulman S. Best Pract Res Clin Haematol. 2013 Jun;26(2):191-202

Management of bleed with NOACs

- Supportive measures
- For Factor Xa inhibitors –

  Activated charcoal

  Activated factor VIIa

  Prothrombin complex concentrates

  Universal factor X a reversal agent (PRT4445)

  Universal NOACs reversal agent (PER977)

Majeed A, Schulman S. Best Pract Res Clin Haematol. 2013 Jun;26(2):191-202

Do the trials answer all our questions?

- All have similar study design, primary and safety outcomes
- Funded by pharmaceutical giants
- Though multi center trials. Almost up to 75% of the trial participants are from Europe and North America
- Average BMI of participants in most of these trials 28 kg/m^2 (approximately)
- Data are based on VTE prevention in TKA and THA. Data on medically ill patients sparse

Asian scenario

- VTE was considered an uncommon disease in Asia – probably under recognized and under reported (Sing Med J 1968, Br Med J 1964)
- Recent data reveal an increased incidence (though still less than western literature) Cohen et al. Thrombosis research. Sept 2012
- Low rates of thromboprophylaxis in Asian countries (≤20% surgical patients in china, India and Pakistan)

Cohen et al. Thrombosis research. Sept 2012

Challenges in India

- Do we have the data?
- Are the side effects or effects of these drugs similar to what is seen worldwide?
- A very large market and an unregulated pharma industry (potential for exploitation)
- Cost factor

Trial population vs. Average Indian

Parameters	Trial data	Reference Indian
Weight in kg	80 – 85 kg	60 kg (men) 55 kg (women)
BMI kg/m^2	28	20 (average)
Diet	Consistent	Inconsistent
Most of the studies included "Asian" population between 2 – 8% of the total study group. RE-COVER II (2013) had the highest proportion (20%) Asians		

Generic name	Brand name	Strength	Cost (30 days)	Monitoring
Warfarin	Sofarin Warf Unifarin	1, 2, 5 ,10 mg Cost for 5 mg tablets	Rs 60/- Rs 123/- Rs 74/-	INR Rs 120/- Rs 600(5 times a month)
Acenocoumarol	Nistrom 2 mg 10 tab Rs 39 4 mg 10 tab Rs 57	2 mg 4 mg	Rs 117/- Rs 171/-	INR Rs 120/- Rs 600(5 times a month)
Dabigatran	Pradaxa	110 mg (Rs 718 for 10) 150 mg (Rs 720 for 10)	Rs 4200/- (150 mg BD)	None
Rivaroxaban	Xarelto	10 mg (Rs 725 for 5 tab)	Rs 4350/- (10 mg OD) Rs 6000/- (15 mg OD)	None
Apixaban	Eliquis	2.5 mg (Rs 725 for 10 tab)	Rs 4350 (2.5 mg BD)	None

Adapted from CIMS India

	Ideal agent	VKAs	Rivaroxaban	Apixiban	Edoxaban	Dabigatran
Administration	Oral	P.O	P.O	P.O	P.O	P.O
Onset	Rapid onset	Late	Rapid	Rapid	Rapid	Rapid
Effect of food	None					
Dosing	Fixed	Varies	Fixed	Fixed	Fixed	Fixed
Monitoring	None	INR	None	None	None	None
Therapeutic window	Wide	Narrow	Wide	Wide	Wide	Wide
Drug interaction	None	Significant				
Antidote	Yes	Yes	No	No	No	No

Summary

- Newer oral anticoagulants appear to be as effective as the existing agents. They have certain definite advantages over current standard therapy
- Long term safety is yet to be ascertained
- Better and more feasible tests to assess bleeding risk are required
- Cost may be a limiting factor in India as of today
- Data regarding the performance of these drugs in India are to be collected