Case studies in Veno-thromboemblic Disease

including a little bit about the “not-so-new” oral anticoagulants

Dr Jason Butler

Senior Staff Haematologist

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Summary

- Cancer-associated Thrombosis
- Thrombophilia screening
- Using d-dimers and ultrasounds to guide treatment cessation
- Impact of hormone therapy on VTE risk

- Reversal guidelines for the Direct Oral Anticoagulants (DOAC’s)

Case 1

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - No PMHx
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 2

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - 2 weeks post knee reconstruction (Netball injury)
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 3

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - K16/40, G_1P_0
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 4

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - No PMHx
  - No personal Hx of VTE
  - Cousin died of massive P.E. 3 years earlier

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 5

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - Undergoing chemotherapy for metastatic Breast Ca
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 6

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - Osler-Weber-Rendu Syndrome (Hereditary Haemorrhagic Telangiectasia)
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 7

- 28 year female
  - Presents with 2/7 Hx of swollen left arm with pain on abduction
  - No risk factors / PMHx
  - No personal or FHx of VTE

  - Duplex USS: occlusive subclavian vein DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Case 8

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - No PMHx
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

  - Current medications: Only combined oral contraceptive pill (OCP)

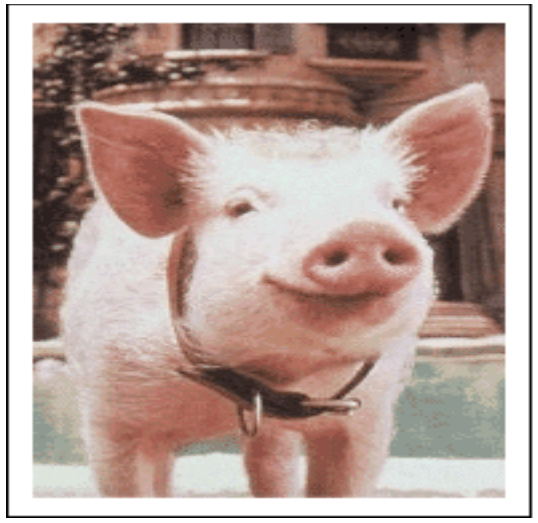
Case 9

- 78 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - PMHx: NIDDM, Hypertension, ?possible TIA, mild chronic renal impairment
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

  - On aspirin, metformin, diamicron, karvezide, lipitor

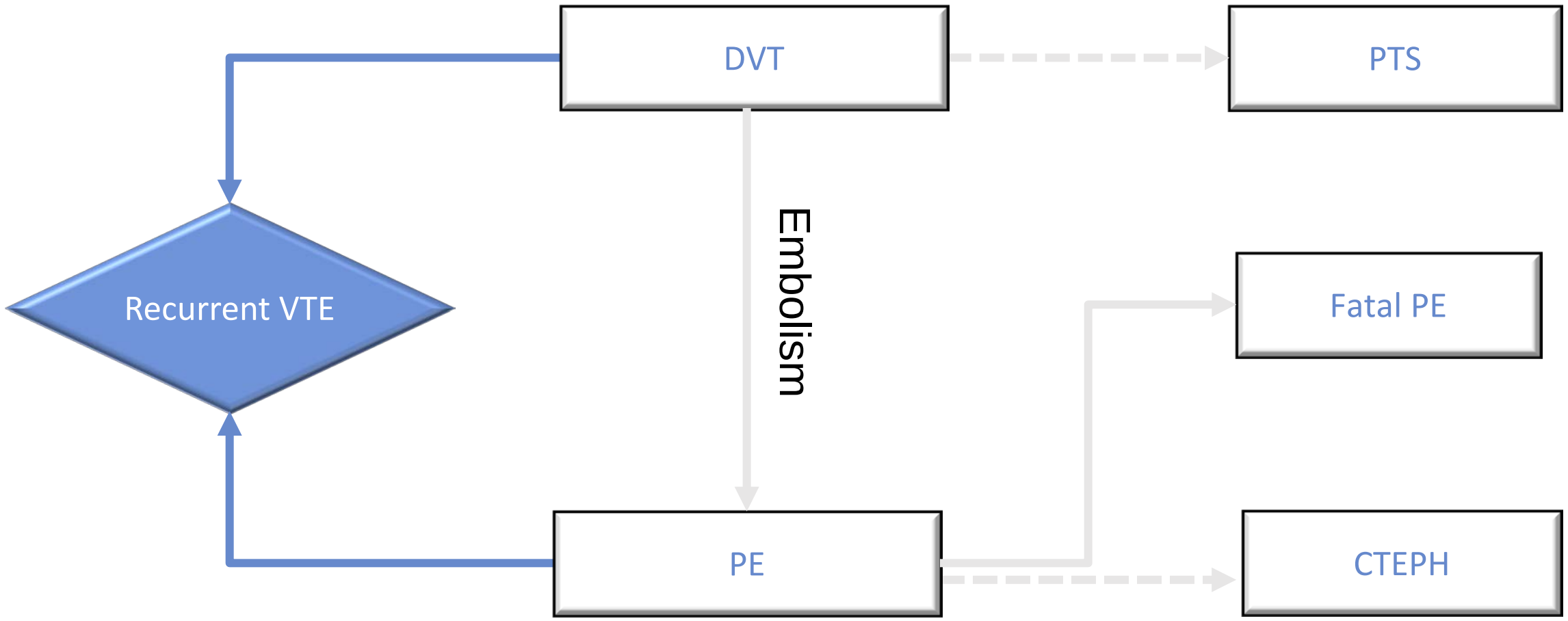
1933-1940 - Karl Paul Link successfully isolated / extracted the anticoagulant factor (dicoumarol)
1941 – coumarin patented
1948 – rodenticide
1954 – regulatory approval




Gordon Fairclough


30 mL Multiple-Dose Vial
HEPARIN
Sodium Injection, USP
1,000 USP Units/mL
FOR IV OR SC USE
FROM PORCINE INTESTINES
NOT for LOCK FLUSH

Effective early anticoagulation may reduce thromboembolic complications following VTE



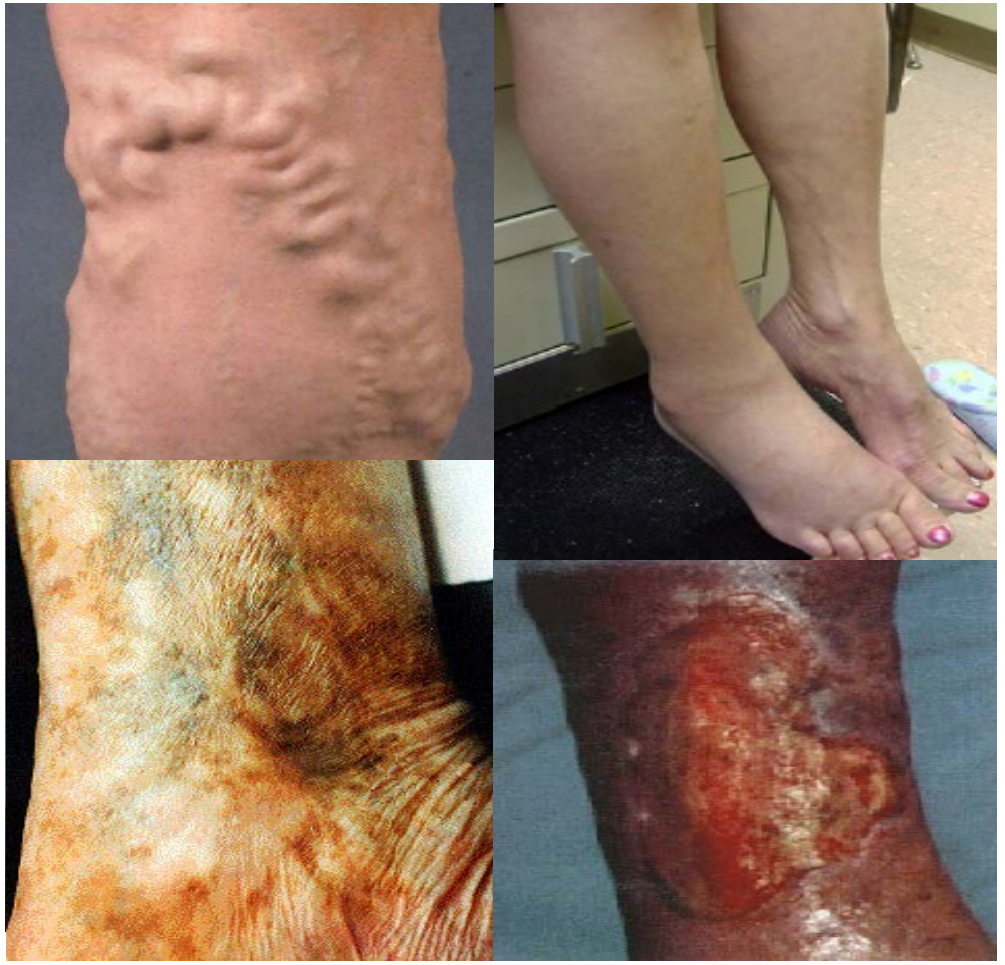
Kearon 2003

Post-thrombotic syndrome

- Occurs in nearly one-third of patients within 5 years after idiopathic DVT[1]
  - It is estimated to affect 600,000 people in the EU each year[2]

- PTS is characterized by:[3]
  - Pain
  - Oedema
  - Hyperpigmentation
  - Eczema
  - Varicose collateral veins
  - Venous ulceration

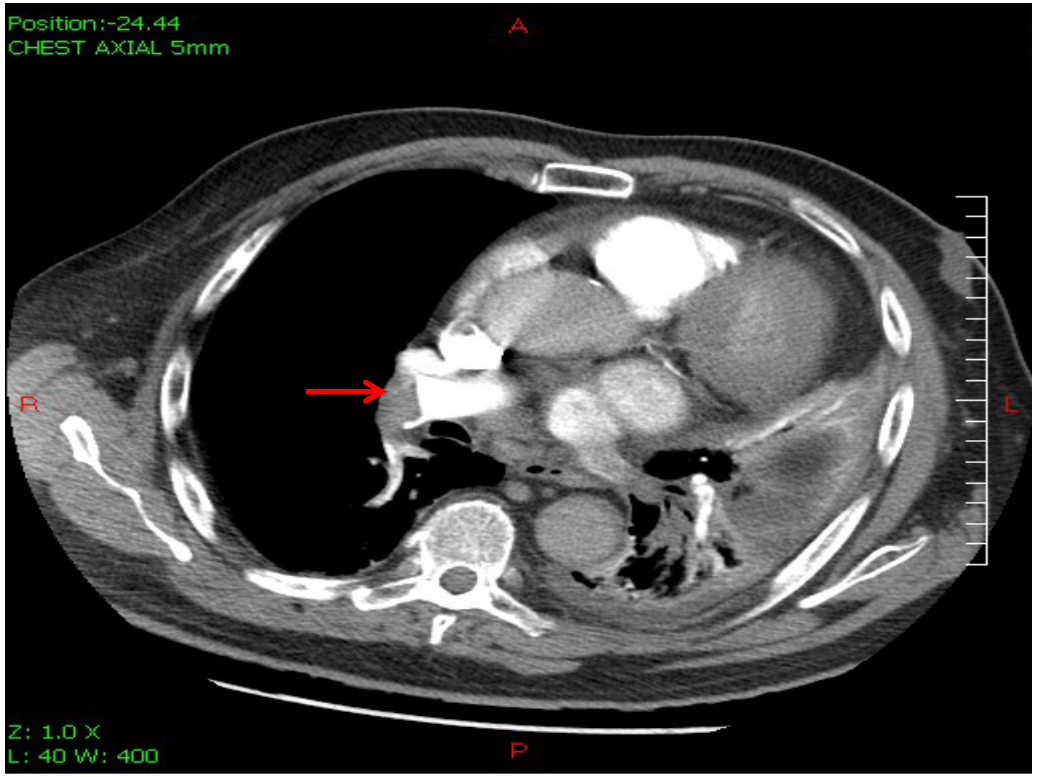
- Associated with significant patient morbidity and reduced QoL



1. Prandoni P *et al*. *Ann Intern Med* 1996;125:1–7; 2. Cohen *et al*, 2007 3. Kahn SR. *J Thromb Thrombolysis* 2006;21:41–48

Chronic thromboembolic pulmonary hypertension

- Serious complication of PE
  - Up to 2-4% of patients with PE are reported to develop CTEPH[1]
  - Progressive condition associated with mortality rates of 4–20%[2]
- Initial phase of disease often asymptomatic or unrecognised
- Symptoms are characterized by:[3]
  - Exertional dyspnoea
  - Weakness
  - Hypoxemia
  - In later stages of the disease, patients may have all the signs of advanced right heart failure

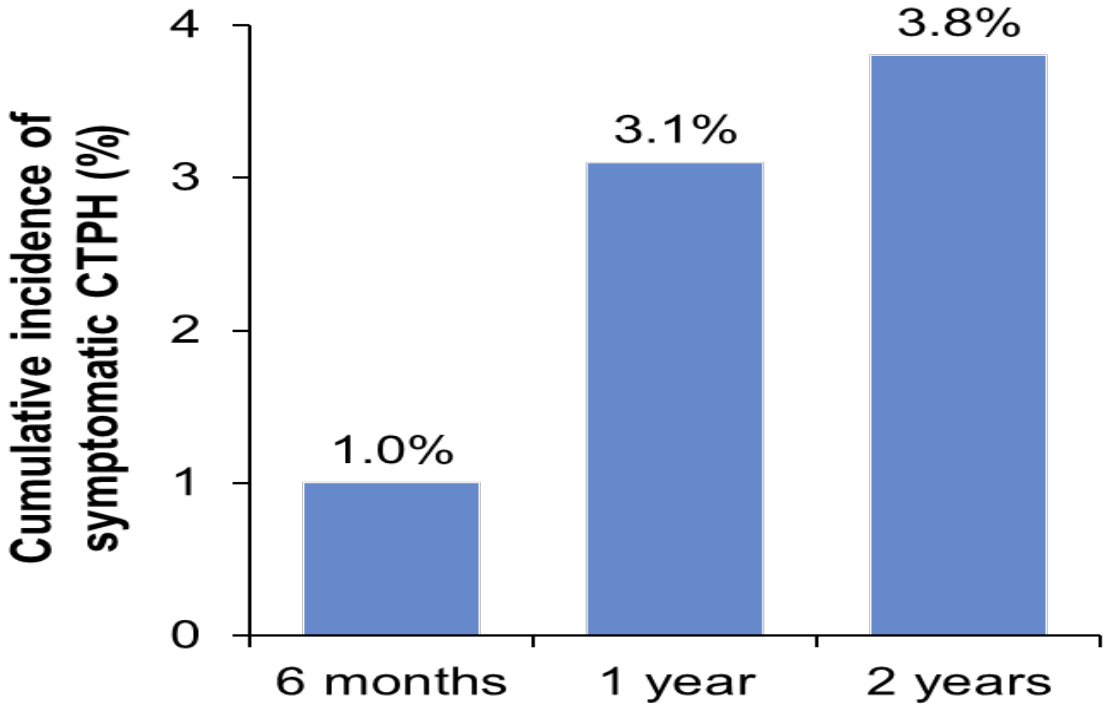


1. Kearon C. *Circulation* 2003;107:I22–I30; 2. Torbicki A *et al*. *Eur Heart J* 2008;29:2276–2315

Chronic thromboembolic pulmonary hypertension

- Pathophysiology
  - The triggering event is related to incomplete resolution of one or more thrombi obstructing the pulmonary vascular bed, resulting in increased vascular resistance[5]
  - Cumulative incidence of symptomatic CTEPH 1.0% at 6 months to 3.8% at 2 years[2]
- Risk factors for CTEPH[2]
  - Previous PE
  - Younger age
  - Larger perfusion defect
  - Idiopathic PE

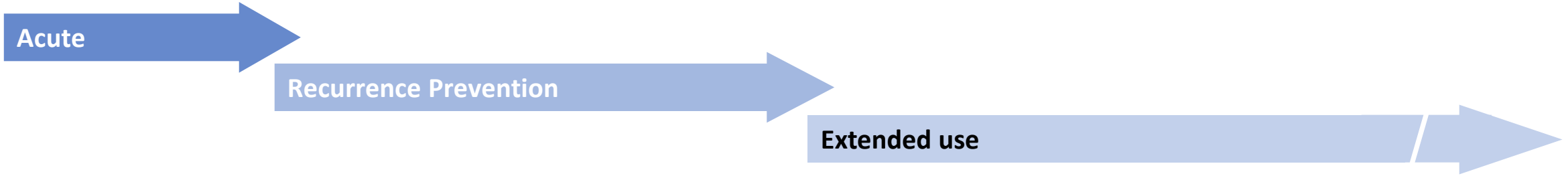
Prospective long-term study of 223 patients with acute PE and no previous VTE[2]



1. Benotti *et al*, 1983; 2. Pengo *et al*, 2004; 3. Marti D *et al*, 2010; 4. Guerin *et al*, 2014; 5. Lang, 2009

VTE: disease phases and conventional anticoagulation treatment strategies

Treatment phases



Types and intensity of conventional anticoagulation treatment

UFH, LMWH, fondaparinux

Initial, parenteral therapeutic dose

At least 5 days

VKA INR 2.0–3.0

Early maintenance/secondary prevention

At least 3 months

VKA INR 2.0–3.0 or 1.5–1.9

Long-term maintenance anticoagulation/ secondary prevention

>3 months/years/indefinite*

*With re-assessment of the individual benefit–risk at periodic intervals

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Cancer-associated Thrombosis (CAT)

- Risk for VTE increased up to 4-7 fold in patients with cancer[1,2]
  - 10-20% patients with cancer develop symptomatic VTE
  - 20% of all patients diagnosed with VTE have active cancer
- Patients with cancer and VTE have a shorter life expectancy
  - VTE is second leading cause of death after cancer itself (independent predictor)
  - More likely advanced/disseminated malignancy at diagnosis than in patients without VTE
  - 3-fold lower survival than in cancer patients without VTE
- "Idiopathic" VTE
  - 2-4 fold increased risk of cancer diagnosis within next 12 months

1. Vedovati MC *et al. CHEST.* 2015; 147(2):475-83; 2. Barsam SJ *et al. B J Haem.*2013; 161:786-77;

3. Laporte S *et al*. *Circulation.* 2008; 117:1171-16.

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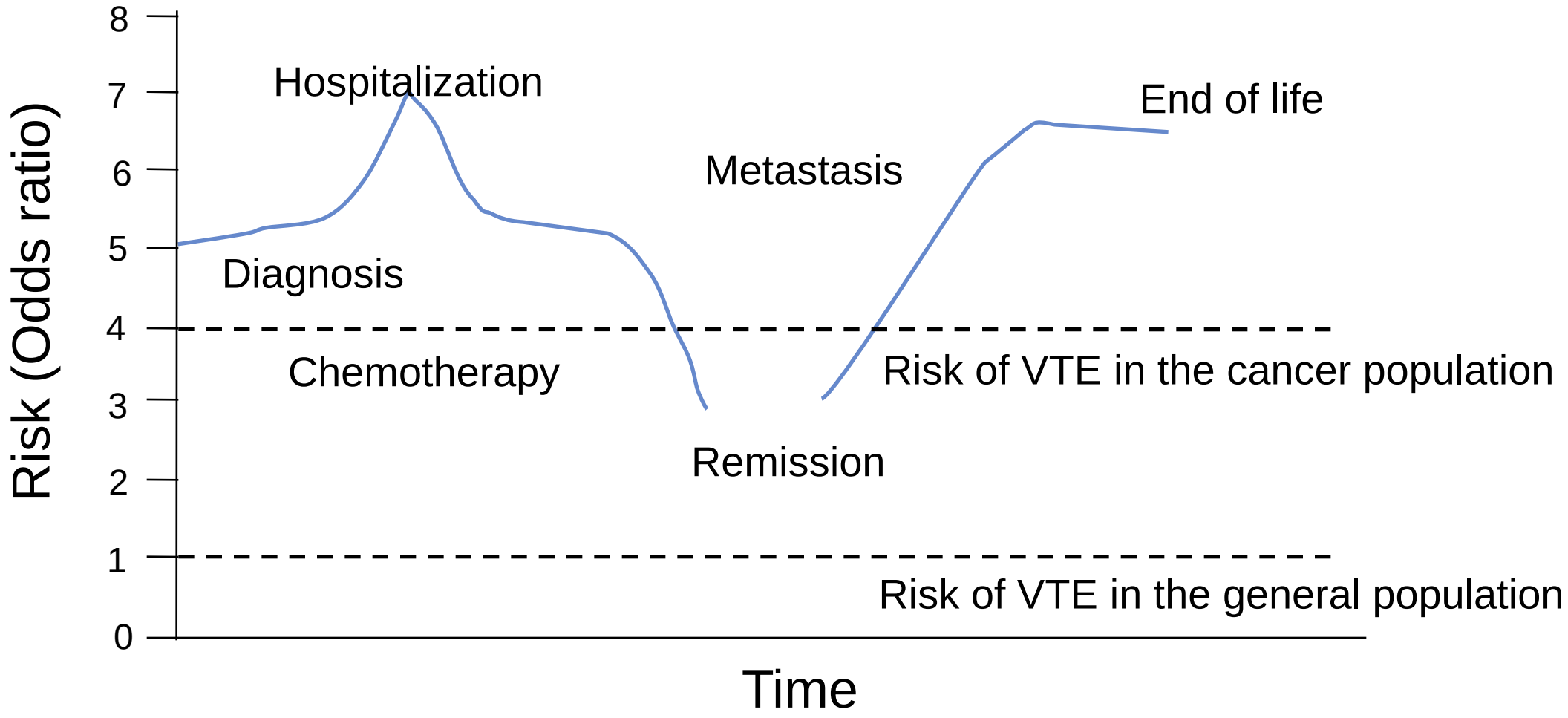
Risk factors for CAT

Category	Risk Factor	Increased Risk
Tumour-related	Site	Brain, pancreas, gastric, ovarian, lung, myeloma, lymphoma, renal
	Duration of cancer	<3 months since diagnosis
	Grade	High
	Stage	Advanced
	Biomarker	Tissue factor, soluble P-selectin, D-dimer, C-reactive protein
Patient-related	Non-specific-cancer	Age > 40 years, female, co-morbidities, infection, obesity, anaemia, dehydration, past history of VTE, family history of VTE, inherited hypercoagulable states, concurrent acute illness, pulmonary disease, renal disease, prolonged immobility, smoking
	Cancer-specific	Thrombocytosis, leucocytosis, anaemia, hospitalization, acquired protein C resistance
Treatment-related	Surgical	Major laparotomy or laparoscopy lasting more than 30min; major abdominal or pelvic operation
	Pharmacological	Aggressive chemotherapy, anti-angiogenic medication, growth factors, blood product
	Indwelling venous catheter-related	Central venous catheter, femoral venous catheter, peripheral venous catheter

Adapted from Barsam SJ *et al. B J Haem.* 2013;161:764-77.

Risk of PE/DVT varies during the natural history of Cancer care



Rao et al., in Cancer-Associated Thrombosis. (Khorana and Francis, Eds) 2007

Unique challenges to anticoagulant therapies in cancer patients

- Interactions
- Thrombocytopenia
- Coagulopathies e.g. DIC
- Hepatic Impairment
- Renal Impairment
- In-dwelling devices
  - Central Venous Access Devices
  - Drains

Role of Cancer Screening

- How extensive should search for “occult” maligancy be?
  - Data ranges from clinical history, examination, basic bloods, CXR thru to CT abdomen / pelvis and tumour markers
  - Across prospective and epidemiological studies

- No convincing role for screening in absence of “target” symptoms

Cornuz J Ann Intern Med 1996; 125: 785-93
Nordstrom M, BMJ 1994; 308: 891-4.
Piccioli A J Thromb Haemost 2004; 2: 884-9.
Monreal M. J Thromb Haemost 2004; 2: 876-81.

VTE Prevention

- No convincing data for role of prophylaxis outside conventional risk periods i.e. perioperative, prolonged hospitalisation[1]
  - BUT: High risk diseases e.g. pancreatic Ca
- Role for extended prophylaxis in high-risk procedures e.g. orthopaedic
- Prophylaxis for CVAD's
  - No benefit to VKA's or LMWH[2,3,4]

1. ENOXACAN Study Group Br J Surg. (1997); 84: 1099-103.
2. Couban S JCO (2005); 23:4063-9.
3. Verso M, JCO (2005); 23:4057-62.
4. Karthaus Ann Oncol (2006); 17:289-96.

Treatment options for CAT

- Long-term low-molecular weight therapy (LMWH)
- LMWH followed by long-term Vitamin K antagonist (VKA)
- Direct Oral Anticoagulants (DOAC)
  - AntiXa inhibitors e.g. rivaroxaban, apixaban
  - Direct thrombin inhibitors e.g. dabigatran

1. The EINSTEIN Investigators. *N Engl J Med.* 2010;363:2499–2510;
2. The EINSTEIN-PE Investigators. *N Engl J Med.* 2012;366:1287–97.

LMWH v UFH for initial therapy

- Cochrane review - 16 randomised trials
- Reduction in mortality at 3 months
    - RR 0.71 (0.52 – 0.98)
- Non-significant trend to VTE recurrence reduction
    - RR 0.78 (0.29 – 2.08)
- ? Due to direct anti-cancer effect in some diseases

Akl E Cochrane Database Syst Rev (2011);6:CD0066-49

LMWH v VKA for intermediate / extended Rx

- Cochrane review - 3 RCT's (all open label) (n=1022)
- Significant reduction in VTE recurrence w/ LMWH
    - HR 0.47 (0.32-0.71)
- Safety and survival no different

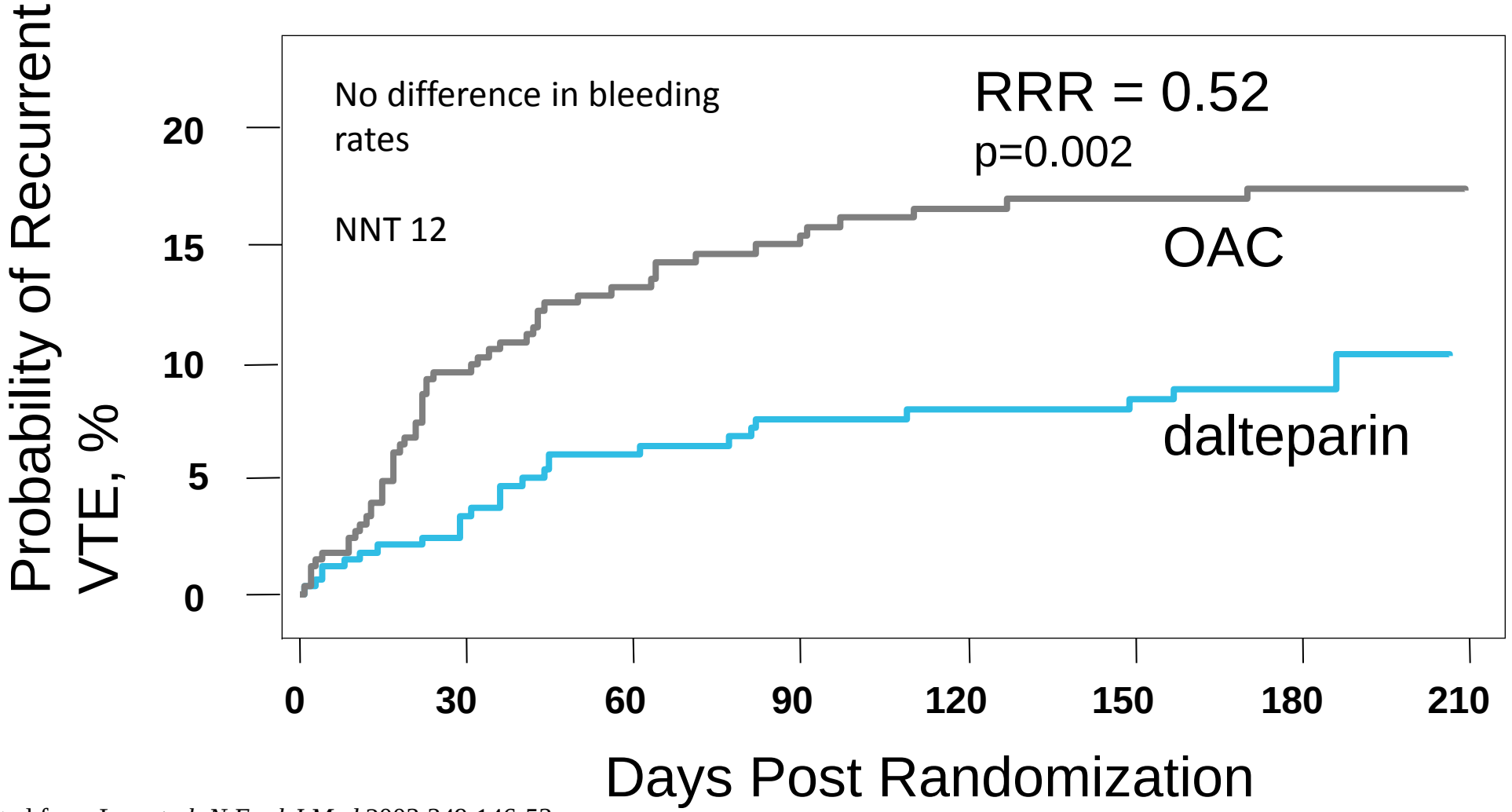
1. Akl, E Coch Database Sys Rev (2011); CD006650

Which LMWH?

- Only dalteparin (fragmin) has demonstrated clear benefit in efficacy in individual randomised control trial (CLOT study)[1]
  - Only formulation FDA licensed
- LITE & CANTHANOX studies showed NS trends[2,3]
- Most consensus guidelines do not discriminate
- Used interchangably in clinical practice

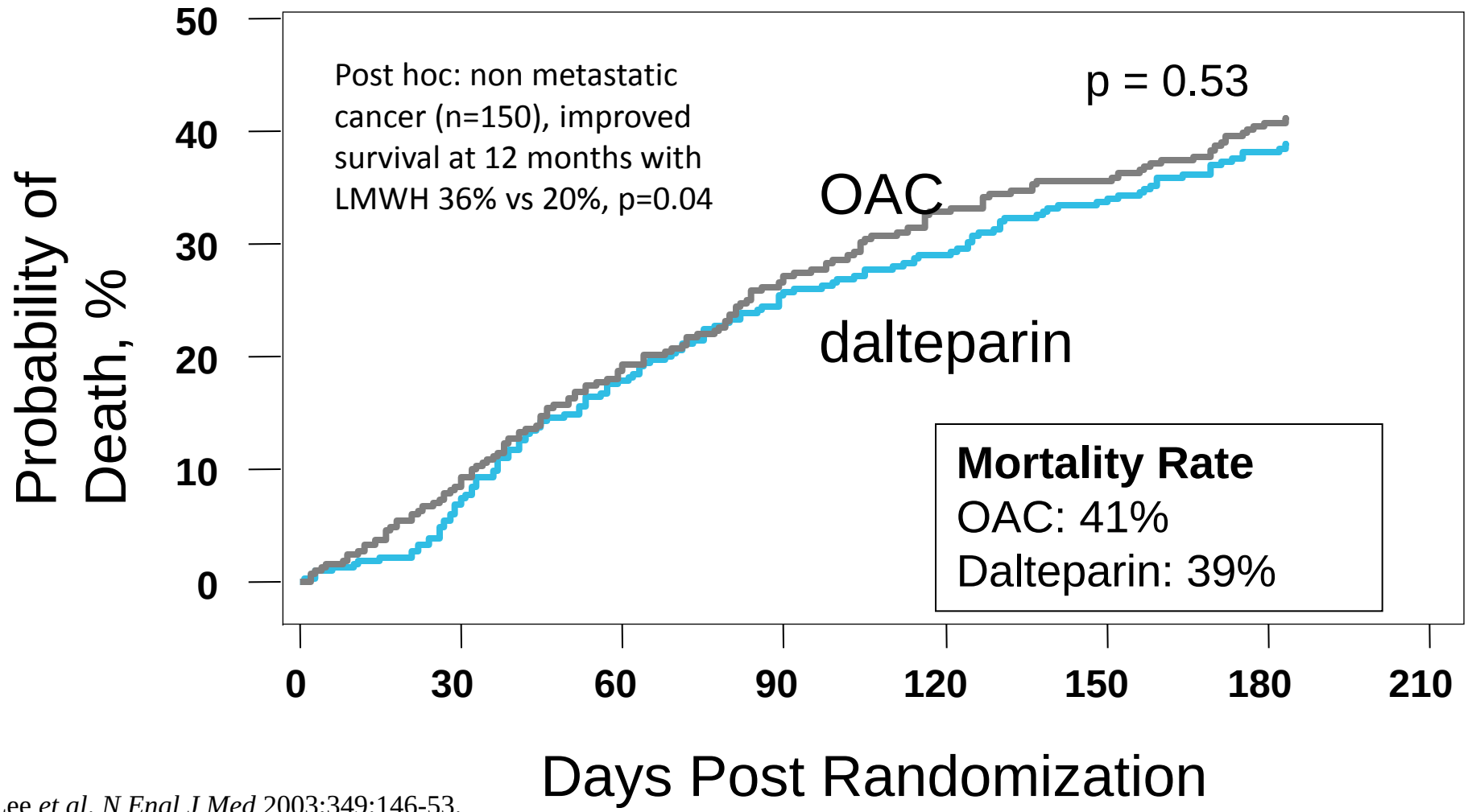
1 Lee NEJM (2003); 349: 146-153
2 Hull RD Am J Med (2006); 119(12): 1062-1072
3 Meyer G Arch Intern Med (2002); 162(15): 1729-1735

CLOT Study- Recurrent VTE



Adapted from Lee *et al*. *N Engl J Med* 2003;349:146-53.

CLOT Study- Overall Mortality



Adapted from Lee *et al*. *N Engl J Med* 2003;349:146-53.

Consensus Guidelines

	ACCP 2012[1]	NCCN 2011[2]	ASCO 2013[3]
Initial/acute treatment	Not addressed in cancer patients.	LMWH Dalteparin 200 U/kg OD Enoxaparin 1 mg/kg BID Tinzaparin 175 U/kg OD Fondaparinux 5 mg (<50 kg), 7.5 mg (50-100 kg), or 10 mg (>100 kg) OD APTT-adjusted UFH infusion	LMWH is preferred for initial 5-10 d of treatment in patients with a CrCl >30 mL/min.
Long-term treatment	LMWH preferred to VKA [2B].*	LMWH is preferred for first 6 mo as monotherapy without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer.	LMWH is preferred for long-term therapy.
	In patients not treated with LMWH, VKA therapy is preferred to dabigatran or rivaroxaban [2C].* Patients receiving extended therapy should continue with the same agent used for the first 3 mo of treatment [2C].*	Warfarin 2.5-5 mg every day initially with subsequent dosing based on INR value targeted at 2-3.	VKAs (target INR, 2-3) are acceptable for long-term therapy if LMWH is not available.
Duration of treatment	Extended anticoagulant therapy is preferred to 3 mo of treatment [2B].*	Minimum 3 mo. Indefinite anticoagulant if active cancer or persistent risk factors.	At least 6 mo duration. Extended anticoagulation with LMWH or VKA may be considered beyond 6 mo for patients with metastatic disease or patients who are receiving chemotherapy.

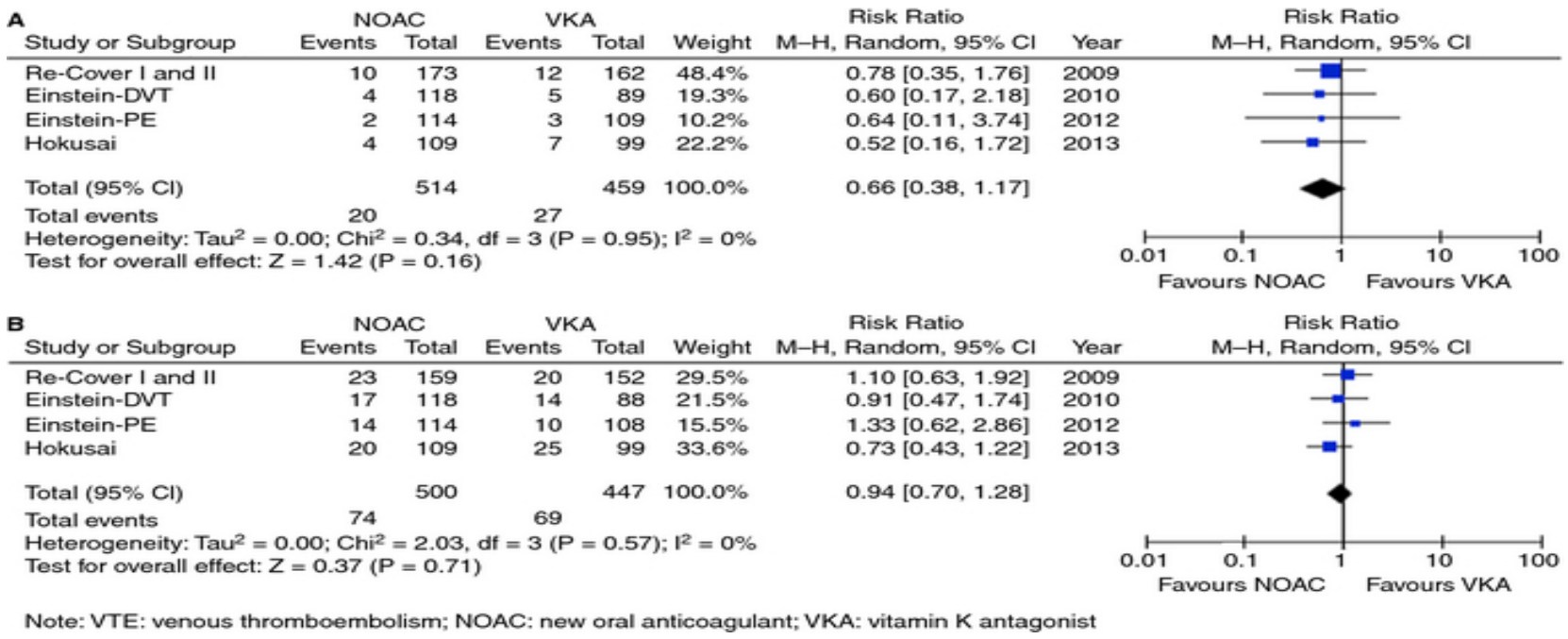
1 Kearon et al Chest (2012) 141(2) Supp e419s
2 Streiff et al JNCCN (2011) 9(7): 714-777
3 Lyman JCO (2013);31:2189-2204

Guidelines for the Duration of Treatment of CAT

Organisation	Duration of LMWH treatment of DVT	Duration of LMWH treatment of PE
British Committee for Standards in Haematology[1]	At least 6 months	
European Society for Medical Oncology[2]	At least 6 months	
American Society of Clinical Oncology[3]	At least 6 months	
American College of Chest Physicians[4]	Extended (unless high bleeding risk)	Extended (unless high bleeding risk)

1. Keeling D *et al. Brit J Haem.* 2011;154(3):311-24; 2. Mandala M *et al. Annals Oncology.* 2011;22:85-92 (on behalf of ESMO guidelines);
3. Lyman GH *et al. J Clin Oncol.* 2015;31:2189-204; 4. Kearon C *et al. CHEST*. 2016;149(2):315-52.

Meta-analysis of the efficacy and safety of new oral anticoagulants in patients with cancer-associated acute venous thromboembolism



Note: VTE: venous thromboembolism; NOAC: new oral anticoagulant; VKA: vitamin K antagonist

Journal of Thrombosis and Haemostasis
Volume 12, Issue 7, pages 1116-1120, 19 JUN 2014 DOI: 10.1111/jth.12605
http://onlinelibrary.wiley.com/doi/10.1111/jth.12605/full#jth12605-fig-0001

Case 1

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - No PMHx
  - No personal or FHx of VTE

  - Duplex USS: proximal occlusive DVT

- What would be your preferred first-line therapy?
- What would be your duration of therapy?

Further Testing

- Has a prothrombotic screen performed
  - Factor V Leiden - **heterozygote for G1691A mutation**
  - Prothrombin – both wild-type

  - Anti-thrombin III levels NORMAL
  - Protein C level NORMAL
  - Protein S level MILDLY REDUCED

  - Anticardiolipin Ab – NOT DETECTED
  - Lupus Anticoagulant – NOT DETECTED

Questions

- Who would have performed the thrombophilia screen?
- Who would do a repeat duplex USS at end of planned Rx?
- Would you use a d-dimer to guide risk?

Role of thrombophilia screen in influencing decisions

- Testing does not predict for likelihood of recurrence in unselected patients
  - FVL risk 1.4 fold versus wild-type; Prothrombin G20210A 1.2-1.7x wild-type[1,2]
  - ATIII, Protein C, Protein S deficiencies < 2.0 fold risk if NO Hx of thrombosis prone family[3,4,5]
- Testing does not reduce incidence of recurrence in cohort studies[6]
- Does not routinely influence duration or intensity of anticoagulation[7]

1. Ho W et al 2006 Arch Int Med; 166: 729-36
2. Marchiori A et al 2007 Haematologica; 92: 1107-1114
3. Baglin T et al 2003 Lancet; 362: 523-26
4. Christiansen S et al 2005 JAMA; 293: 2352
5. De Stefano et al 2006a Haematologica; 91:695-698
6. Schulam S & Tengborn L. 1992 Thromb Haemo; 68: 634-636
7. Kearon, C 2008b Chest; 133: 454S-545S

Role of post-cessation d-dimer in unprovoked VTE

- In patients with ≥ 3 months of anticoagulation, a negative post-cessation D-dimer was associated with 3.5% annual risk for recurrence, versus 8.9% risk of recurrence if positive.[1]

- The timing of the level, patient age, and assay cut-off point did not appear to effect discriminatory capability.[2]

- However, level that is normal at 1 month, but persistently abnormal 2 months later, is associated with increased risk.[3]

1. Verhovsek M et al 2008 Ann Intern Med; 149(7): 481-90
2. Douketis J et al 2010 Ann Intern Med; 153(8): 523-31
3. Cosmi B et al 2010 Blood; 115: 481-88

Role of repeat Duplex USS

- Residual Vein Thrombosis (RVT) has been shown to correlate with increased risk of recurrent VTE.[1]
- Studies difficult to compare due to heterogeneity (study populations, timing / methods of measurement).
- Questionable benefit if used in conjunction with D-dimer.[2]

1. Tan M et al 2011 BJH; 153: 168-78
2. Cosmi et al 2005 Thromb Haemost; 94: 969-74

Case 8

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - No PMHx
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  - Duplex USS: proximal occlusive DVT

  - Current medications: Only combined oral contraceptive pill (OCP)

Case 8

- 28 year female
  - Presents with 2/7 Hx of swollen left leg with pain on mobilisation
  - No PMHx
  - No personal or FHx of VTE
  - Duplex USS: proximal occlusive DVT
  - Current medications: Only combined oral contraceptive pill (OCP)
  - **Who would stop the OCP?**

Role of OCP in causing VTE

- Different formulations have different risks
  - Combined OCP is associated with increased risk
    - Magnitude is dependent upon type of progesterone and dose of ethynlestradiol used[1]
  - Oral progestin-only formulations do not have clear signal for increased risk (small number of studies)[2]
  - Injectable progestins do appear to increase risk[2,3]
  - Mirena (and similar formulations) appear to be safe.[2,3]

1. Stegeman et al 2013 BMJ; 347: f5298
2. Mantha et al 2012 BMJ; 345: e4944
3. Vlieg et al 2010 ATVBl; 30: 2297-2300

ACCP Recommendations for duration of Rx in non-cancer associated thrombosis

- Transient (reversible) risk factor -> 3 months

- Unprovoked -> at least 3 months
  - Consider indefinite anticaogulation in low-risk bleeding
  - Almost all patients with 2nd unprovoked DVT should have indefinite therapy

Special Circumstances

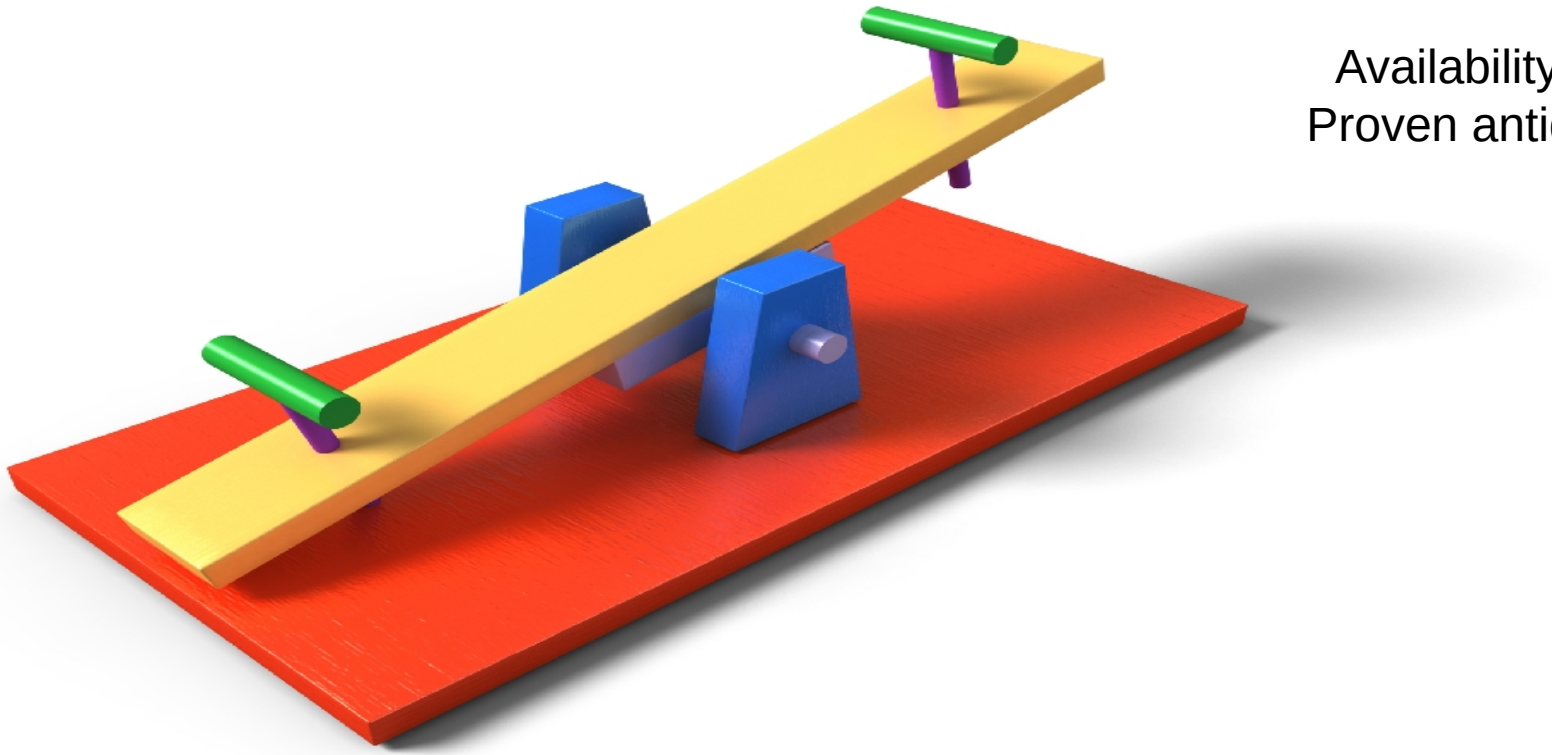
- Recurrent VTE ON-TREATMENT
  - Evaluate haemostatic effect
    - E.g. INR, AntiXa levels

    - If suboptimal: optimise dosing (increase dose)
    - If optimal: change class, consider IVC filters

- Do incidental findings need to be treated?
  - Small volume of evidence favours “YES”

Menapace L Thromb Haemostas (2011); 106(2): 371-378
Sun J Lung Cancer (2010); 69(3): 330-336

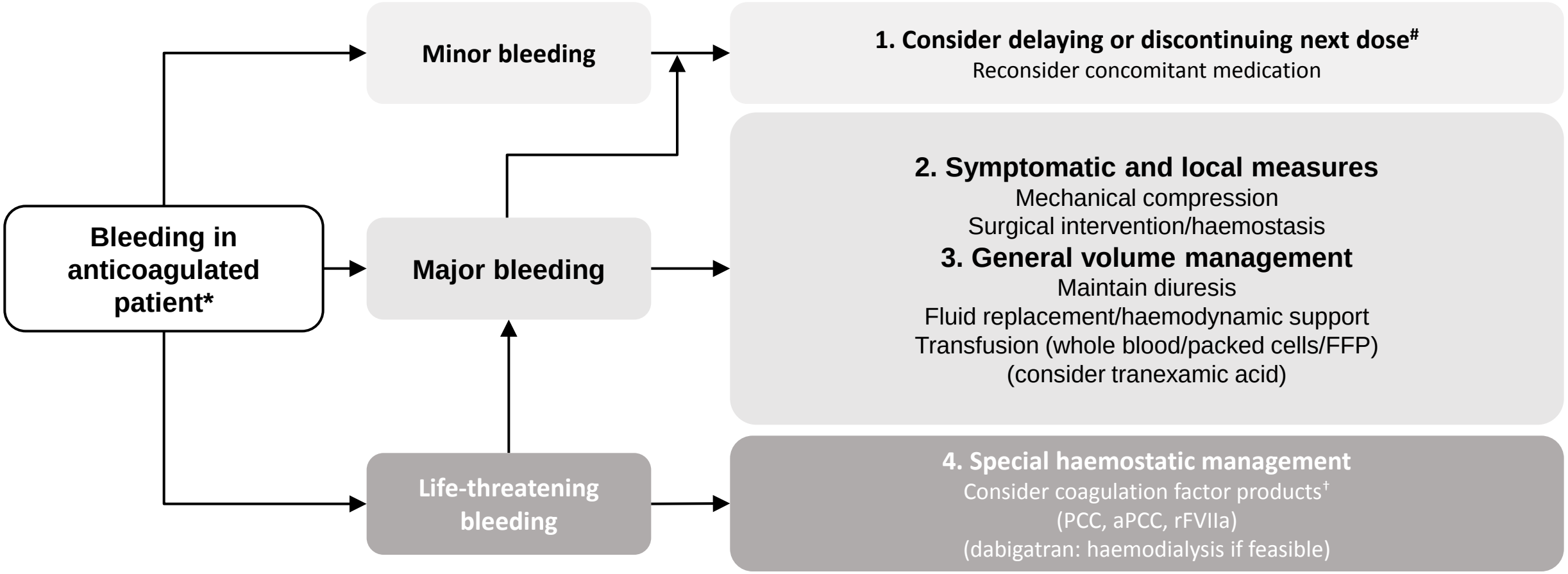
The Risk See-Saw in choice of anti-coagulant



Availability of
Proven antidote

Lower bleeding
Risk

Bleeding management protocols are currently in place



*Assessment of bleeding should also include location; #temporary or permanent discontinuation should always balance the risk of bleeding against the increased risk of thromboembolic events occasioned by the discontinuation

†The clinical efficacy of coagulation factor products in active bleeding has not been established for novel oral anticoagulant agents

Heidbuchel *et al,* 2013; Makris *et al,* 2012; Peacock *et al,* 2012

Outcome of bleeding – post-hoc analysis of ROCKET-AF

Table 6 Outcomes post-major bleed

Outcome[a]	Rivaroxaban (n = 431)	Warfarin (n = 409)	HR (95% CI)[b]	Treatment × major bleed interaction, P-value[c]
Stroke or systemic embolism[d]	20 (4.7%)	22 (5.4%)		
Time to stroke or SE, median (range), days	64 (16–249)	15 (1–71)		
Post-major bleed			0.888 (0.420, 1.876)	0.5135
Pre/no major bleed			1.102 (0.715, 1698)	
Composite of all stroke, non-CNS embolism, MI/UA, and all-cause death	104 (24.8%)	120 (29.9%)		
Time to composite of all stroke, non-CNS embolism, MI/UA, and all-cause death, median (range), days	58 (8–248)	11 (2–82)		
Post-major bleed			0.758 (0.530, 1.082)	0.0975
Pre/no major bleed			0.970 (0.768, 1.225)	
All-cause death	86 (20.4%)	105 (26.1%)		
Time to all-cause death, median (range), days	60 (8–246)	7 (2–88)		
Post-major bleed			0.688 (0.455, 1.042)	0.1098
Pre-/no major bleed			0.905 (0.686, 1.194)	
MI/UA	11 (2.6%)	7 (1.7%)		
Time to MI/UA, median (range), days	282 (9–485)	14 (3–26)		
Post-major bleed			1.848 (0.572, 5.971)	0.5597
Pre/no major bleed			1.374 (0.707, 2.670)	

Piccini et al (2014) European Heart Journal 35(28): 1873-1880

Idarucizumab

- Monoclonal antibody fragment that binds ***DABIGATRAN***
- Binds in high-affinity 1:1 molar ratio
- Binds to dabigatran 350 times more avidly than thrombin
- Given as 2 x 2.5g 50mL boluses, no greater than 15 mins apart
- Most larger hospitals are developing protocols

Idarucizumab

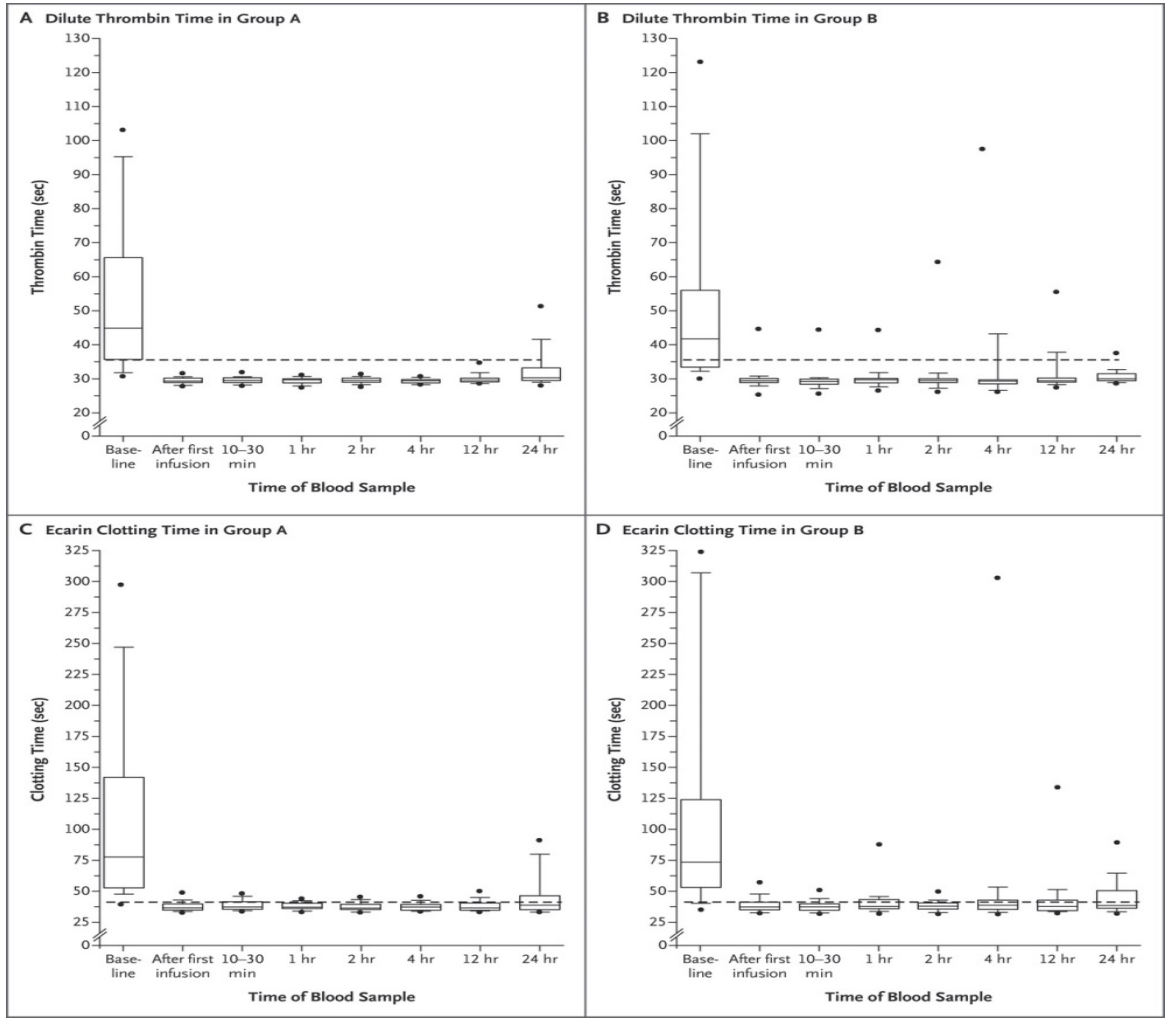
Table 1. Clinical Characteristics of the Patients.*

Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — kg			
Median	70.5	73.0	71.9
Range	42.4–127.5	49.5–116.0	42.4–127.5
Creatinine clearance‡			
Value — ml/min			
Mean	59±33	65±36	62±35
Median	54	60	58
Range	16–187	11–171	11–187
Distribution — no. (%)			
<30 ml/min	5 (10)	7 (18)	12 (13)
30 to <50 ml/min	14 (27)	6 (15)	20 (22)
50 to <80 ml/min	16 (31)	11 (28)	27 (30)
≥80 ml/min	6 (12)	9 (23)	15 (17)
Missing data	10 (20)	6 (15)	16 (18)
Dose of dabigatran — no. (%)			
150 mg twice daily	14 (27)	15 (38)	29 (32)
110 mg twice daily	34 (67)	24 (62)	58 (64)
75 mg twice daily	1 (2)	0	1 (1)
Other	2 (4)	0	2 (2)
Indication for dabigatran — no. (%)			
Atrial fibrillation	47 (92)	39 (100)	86 (96)
Venous thromboembolism	1 (2)	0	1 (1)
Other	3 (6)	0	3 (3)
Time since last intake of dabigatran			
Median — hr	15.2	16.6	15.4
Distribution — no. (%)			
<12 hr	17 (33)	15 (38)	32 (36)
12 to <24 hr	21 (41)	10 (26)	31 (34)
24 to <48 hr	12 (24)	10 (26)	22 (24)
≥48 hr	1 (2)	4 (10)	5 (6)
Elevated dilute thrombin time at baseline — no. (%)	40 (78)	28 (72)	68 (76)
Elevated ecarin clotting time at baseline — no. (%)	47 (92)	34 (87)	81 (90)
Type of bleeding — no. (%)§			
Intracranial	18 (35)	—	18 (20)
Trauma-related	9 (18)	—	9 (10)
Gastrointestinal	20 (39)	—	20 (22)
Other	11 (22)	—	11 (12)

* Plus–minus values are means ±SD. Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.
† Race or ethnic group was self-reported.
‡ Creatinine clearance was estimated by the Cockroft–Gault equation.
§ Patients may have had more than one type of bleeding.

Pollack CV Jr et al. N Engl J Med 2015;373:511-520.

Idarucizumab

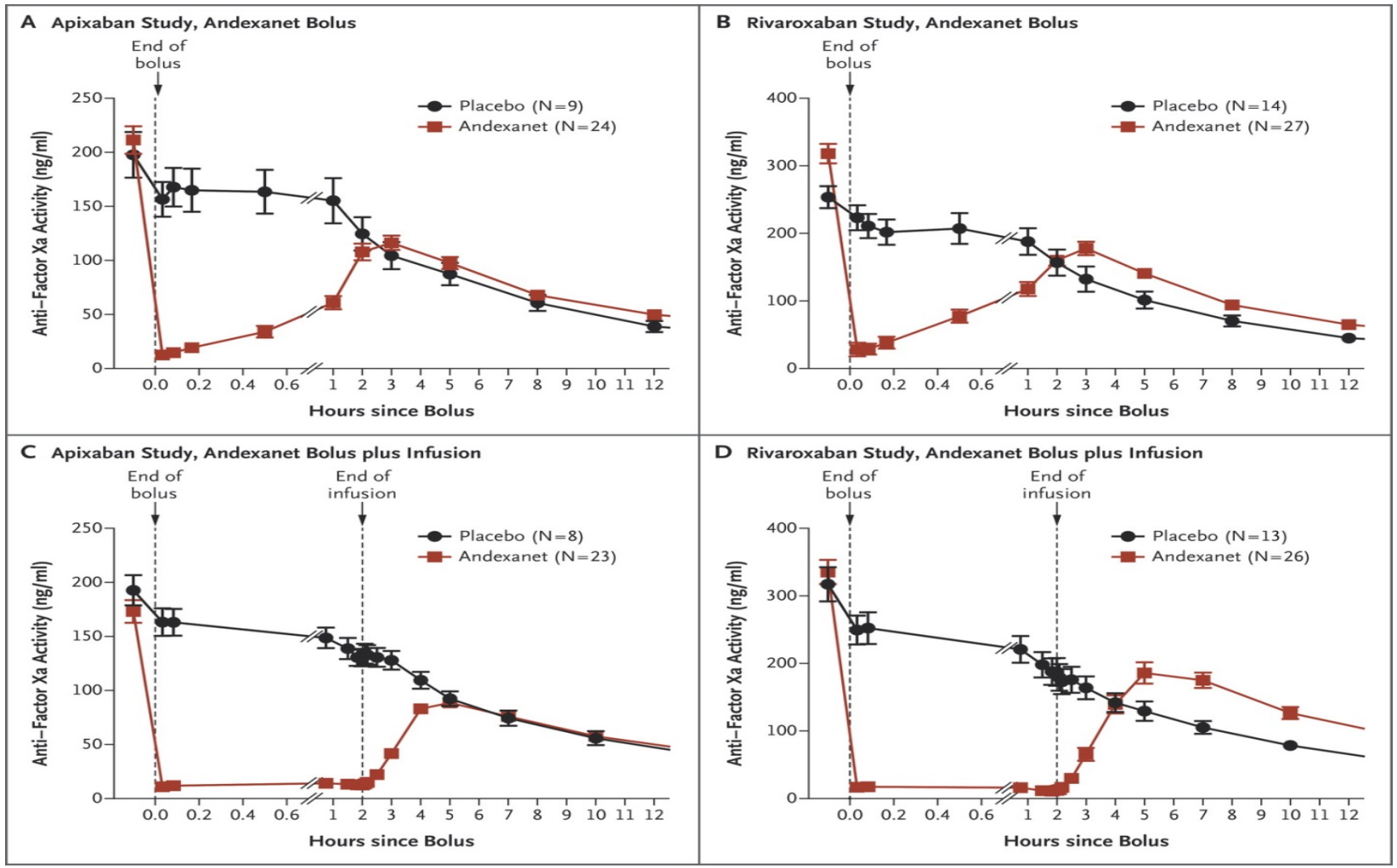


Pollack CV Jr et al. N Engl J Med 2015;373:511-520.

Andexanet Alpha

- Recombinant modified human factor Xa decoy protein
- Binds in high-affinity 1:1 molar ratio
- Catalytically inactive
- Now FDA approved

Andexanet Alpha



Siegal DM et al. N Engl J Med 2015;373:2413-2424.

The End