Anticoagulation management after a clot

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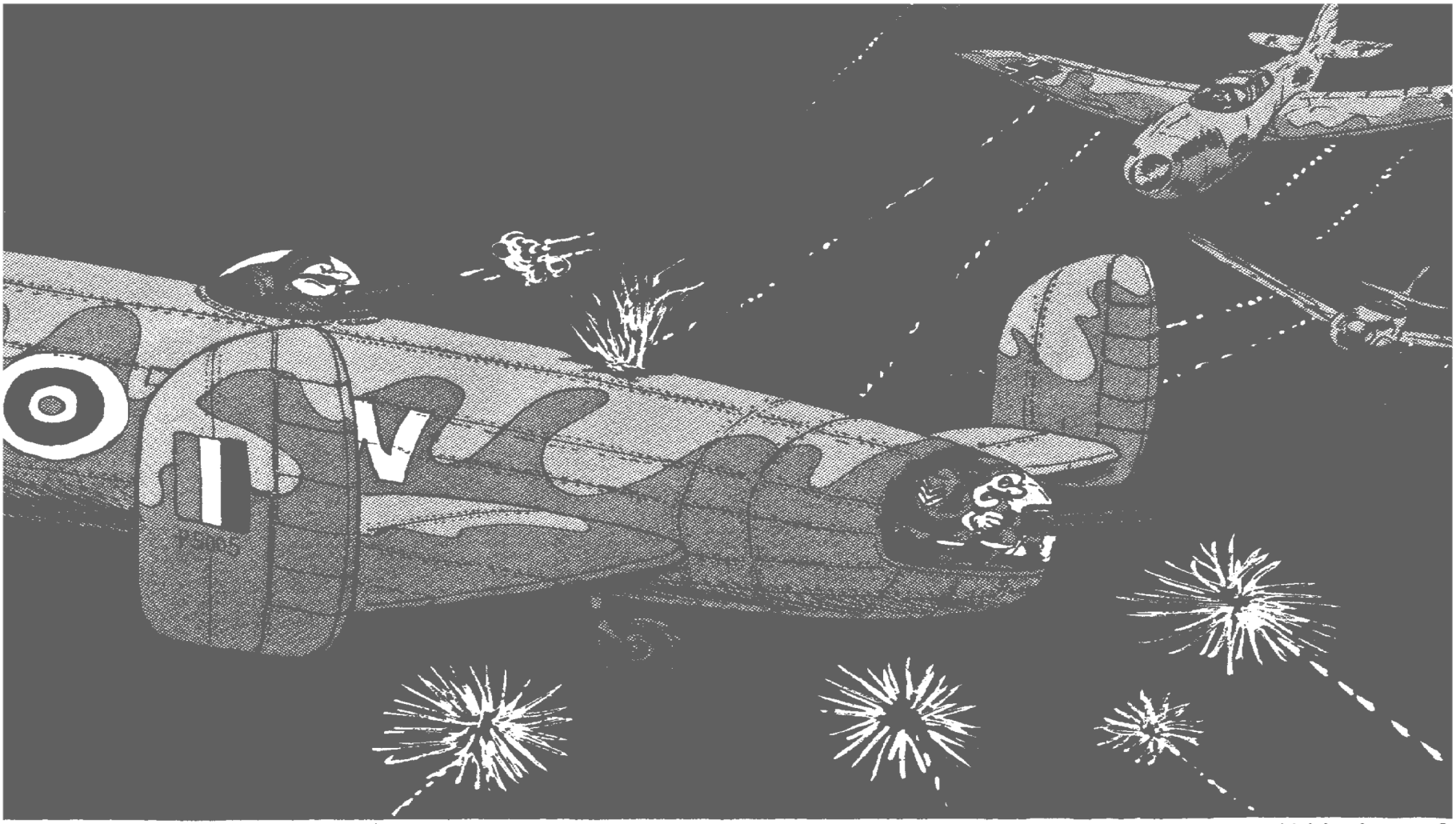
What this presentation covers

- Background
- Current treatment
- New agents
- Duration of treatment

VTE risk



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"Of course what really scares me is the deep vein thrombosis risk"

VTE risk

Aims of treatment

- To prevent extension
- To prevent embolisation
- To allow stabilisation and recanalisation
- To prevent recurrence
- To prevent long term effects (PTS, PH)

Current Treatment

- Initial treatment with UFH, LMWH, SP
- No placebo controlled trials
- Minimum 5 days (average 7)
- LMWH drug of choice for cancer patients

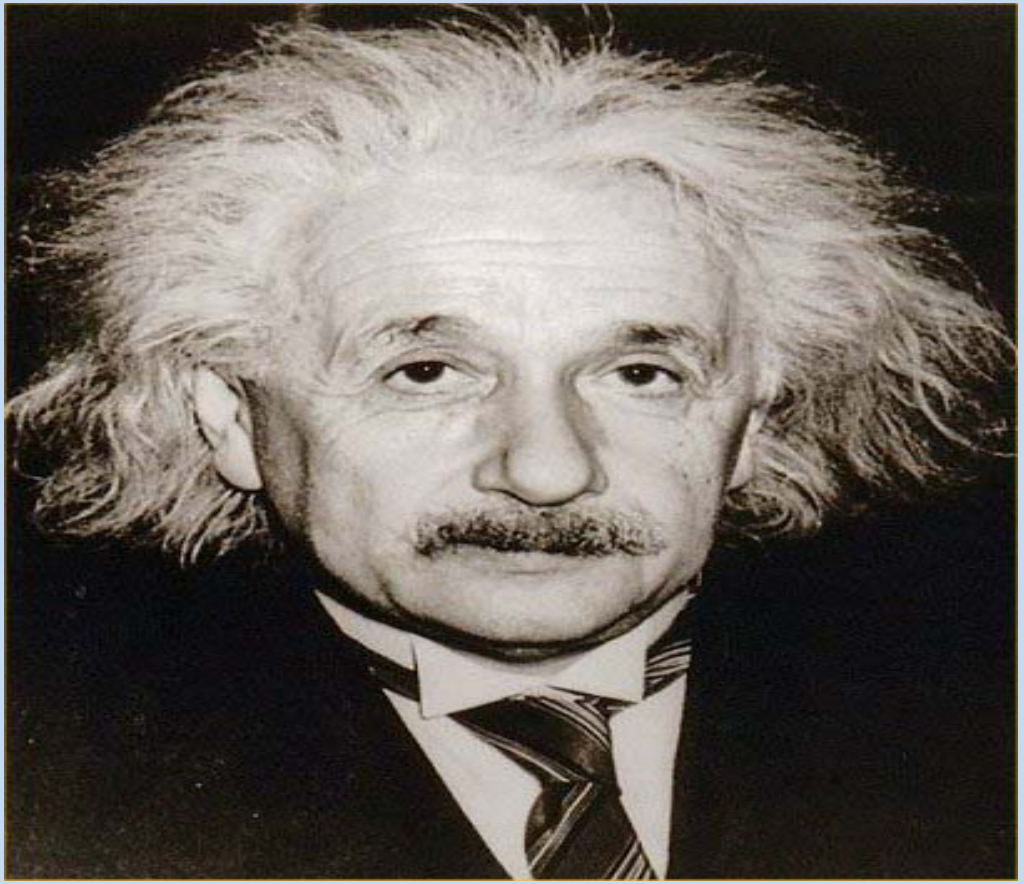
Current Treatment

- Combined with warfarin (VKA)
- Treatment phase 3-12 months
- One placebo controlled trial (PE pts, Barritt and Jordan 1960)
- Duration of therapy?

Current Treatment – What's the problem?

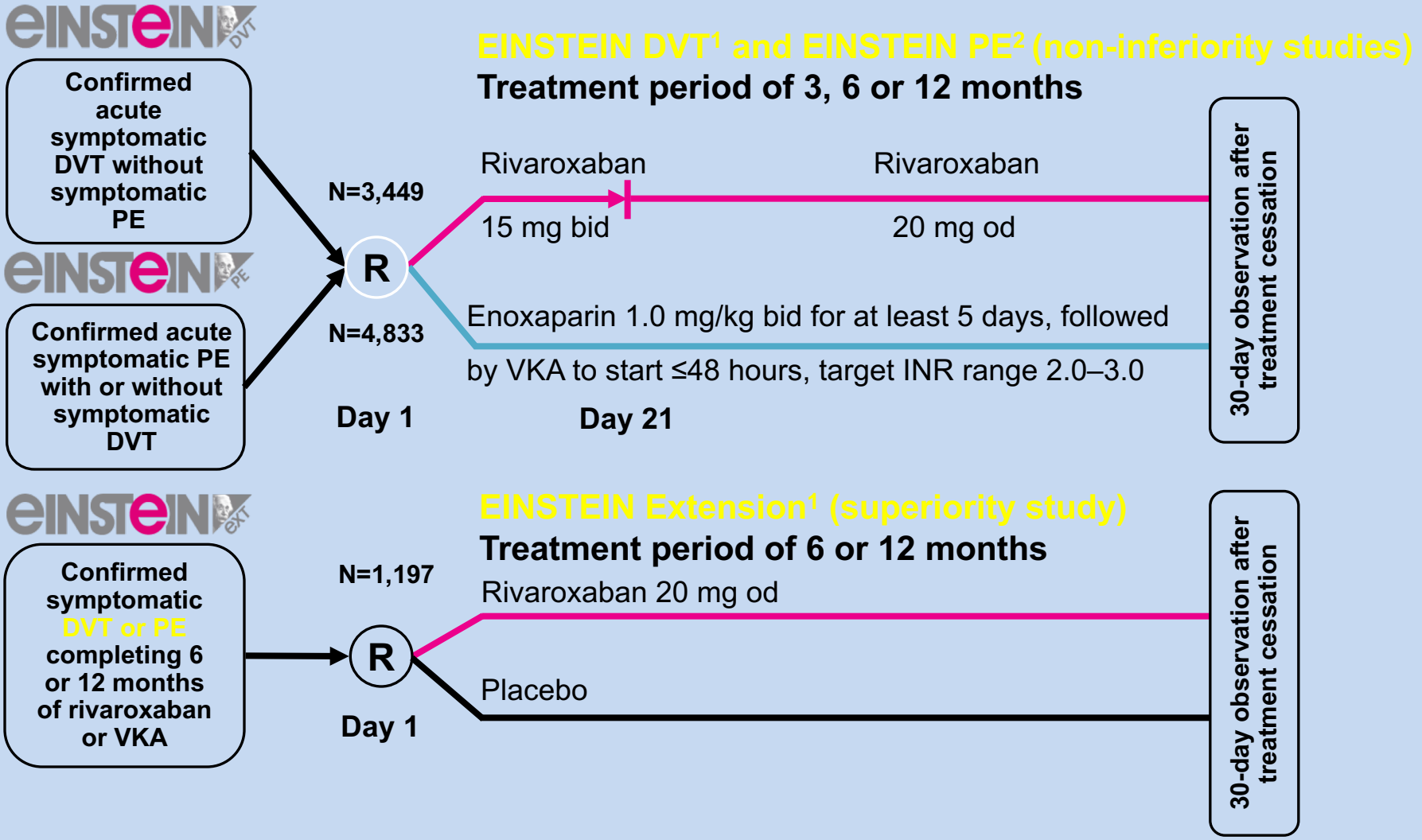
- INR monitoring
- Which LMWH – HIT??
- Bleeding versus recurrence
- Duration of therapy

Einstein



....not him

Rivaroxaban EINSTEIN phase III: study designs



The EINSTEIN investigators, **1.** N Eng J Med 2010;363:2499-2510 & **2.** N Eng J Med 2012;366:1287-1297

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Einstein DVT- results

- 3449 pts (1731 Rivaroxaban)
- Rivaroxaban 36 (2.1%) vs 51 (3%) recurrent events
- Major bleeding 8.1% in both

Einstein PE

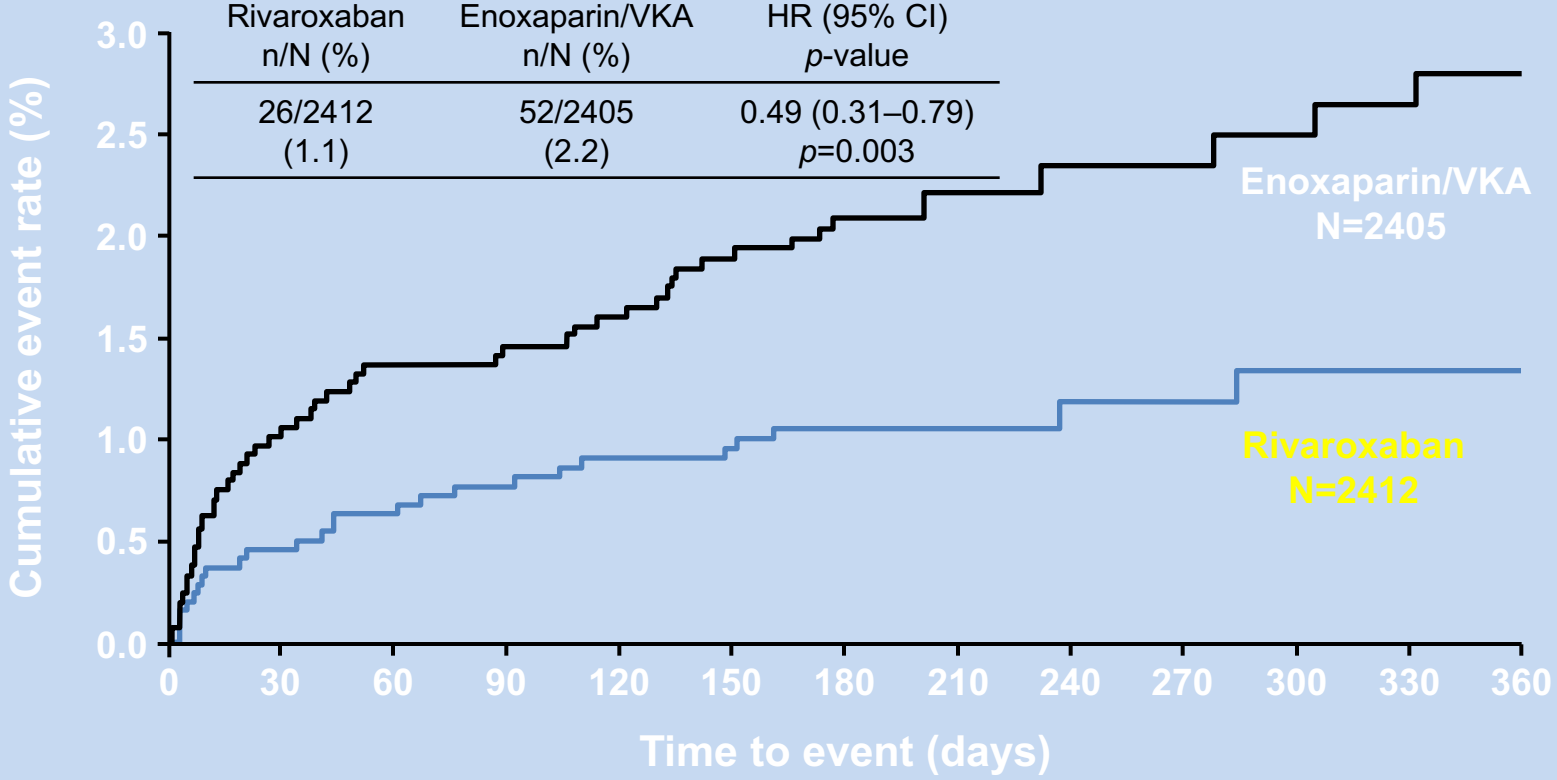
As per DVT study

4,833 pts

Non-inferior

EINSTEIN PE: Major bleeding

Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	HR (95% CI) *p*-value
26/2412 (1.1)	52/2405 (2.2)	0.49 (0.31–0.79) *p*=0.003



Number of patients at risk

Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Enoxaparin/VKA	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Safety population

The EINSTEIN investigators, N Eng J Med 2012;366:1287-1297

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Einstein - Conclusion

Rivaroxaban

- **Non-inferior acutely compared with standard therapy**
- **Superior in terms of secondary prevention compared with placebo but some excess bleeding**
- **Pre-specified joint analysis suggest superiority of rivaroxaban**

Einstein

A new era?

NOAC VTE trials

DRUG	TRIAL	INITIATION	MAINTAINANCE*
DABIGATRAN	RE-COVER	LMWH ≥ 5 days	150mg bd
RIVAROXABAN	EINSTEIN	15mg bd 21 days	20mg od
APIXABAN	AMPLIFY	10mg bd 7 days	5mg bd
EDOXABAN	Hokusai-VTE	LMWH ≥ 5 days	60mg od

* GFR>50 ml/min

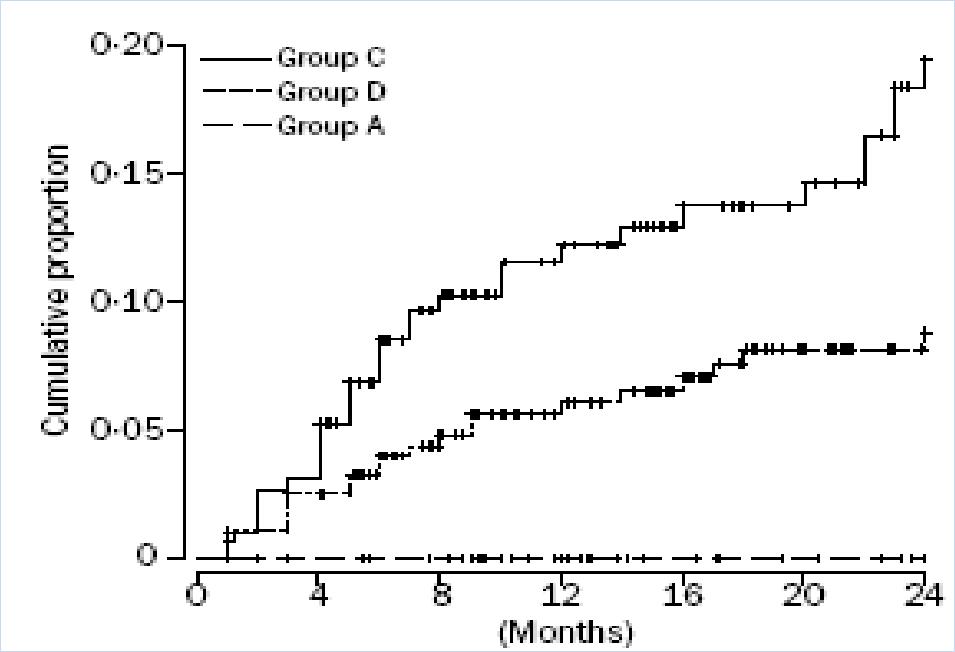
Length of Treatment

- 1st episode of idiopathic VTE should be treated with warfarin at an INR of 2.0 to 3.0 at least three months
- the optimal length of time and optimal degree of anticoagulation are not known

- Baglin T et al. JTH 2012 Duration of anticoagulant therapy after a first episode of unprovoked pulmonary embolus or deep vein thrombosis: guidance from the scientific and standardization committee of the international society on thrombosis and haemostasis.
- Boutitie F et al. BMJ 2011; 342:d3036 Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials.

Risk of recurrent VTE based on history of index event

Risk of recurrence after unprovoked VTE 30-40% after 5-10 years



Unprovoked

Non-surgical risk factor

Post-surgery

Cambridge cohort

Baglin et al *Lancet* 2003; 362: 523–26

Length of Treatment – balance of risks Thrombosis vs bleeding

- Risk benefit analysis
- Patients values and preferences in regard to such risks and benefits
- The potential benefit of extending anticoagulation to six (or more) months may be offset by a higher risk of bleeding and the greater cost and inconvenience of the longer duration of treatment

2012 ACCP Guidelines

Recommendations based upon the perceived balance between

- the number of deaths from recurrent VTE prevented by continued anticoagulation

versus

- the number of fatal bleeding episodes associated with continued anticoagulation

Risk of rVTE after discontinuation of anticoagulation

Risk or rVTE	1st year	Thereafter
1st VTE provoked by surgery	1%	0.5%
1st VTE provoked by a nonsurgical factor	5%	2.5%
1st unprovoked VTE	10%	5%
2nd episode unprovoked VTE	15%	7.5%

Risk of major bleeding if anticoagulation is continued

Risk factors	Risk category	During 1st 3 months	Thereafter/yr
None	LOW	1.9%	0.9%
1	INTERMEDIATE	3.2%	1.6%
➢2	HIGH	12.8%	≥ 6.5%

BLEEDING

- Warfarin in top 10 drugs largest number of serious adverse event reports submitted to the United FDA
- Anticoagulants also ranked first in 2003 and 2004 in the number of total mentions of death for drugs "causing adverse effects in therapeutic use"
- a common cause of emergency department visits
- "black box" warning re warfarin's bleeding risk
- Related to the degree of anticoagulation as well as the presence in the patient of pre-existing risk factors for bleeding.

Thrombotic recurrence risk group	LOW bleeding risk group	INTERMEDIATE bleeding risk group	HIGH bleeding risk group
1st VTE provoked by surgery	Discontinue (strong)	Discontinue (strong)	Discontinue (strong)
1st VTE provoked by a nonsurgical factor or 1st unprovoked distal DVT	Discontinue (weak)	Discontinue (weak)	Discontinue (strong)
1st unprovoked proximal DVT or PE	Continue (weak)	Continue (weak)	Discontinue (strong)
2nd episode unprovoked VTE	Continue (strong)	Continue (weak)	Discontinue (weak)

ISTH guidance 2012 – unprovoked VTE

- **In favour of long term a/c (>3-6 months)**
  - Male
  - Moderate to severe PTS
  - Ongoing dyspnoea
  - Satisfactory a/c control
  - Elevated D-dimer 3-4 weeks after stopping (using study validated assay)

Issues to consider

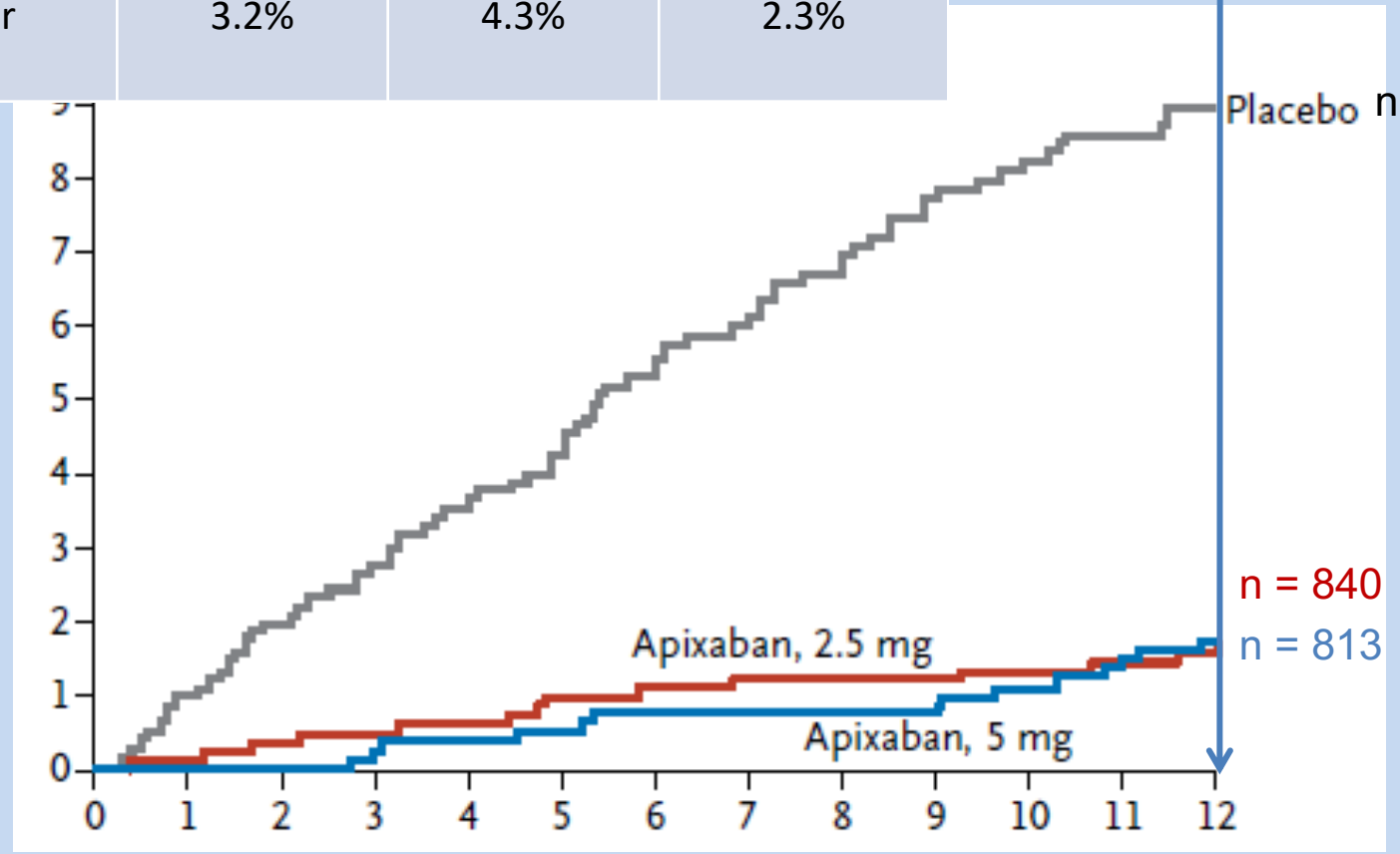
- Patient information and counselling
  - Estimated risk of recurrence
  - Bleeding risk
  - Patient values and preferences

  Age, comorbidities, quality of life issues

Amplify-Ext: Apixaban for VTE

	Apixaban 2.5mg bd	Apixaban 5mg bd	Placebo
Recurrent VTE	1.7%	1.7%	8.8%
Major bleeding	0.2%	0.1%	0.5%
Non-major bleeding	3.2%	4.3%	2.3%

Symptomatic VTE or death



N Eng J Med 2013;368:699-708

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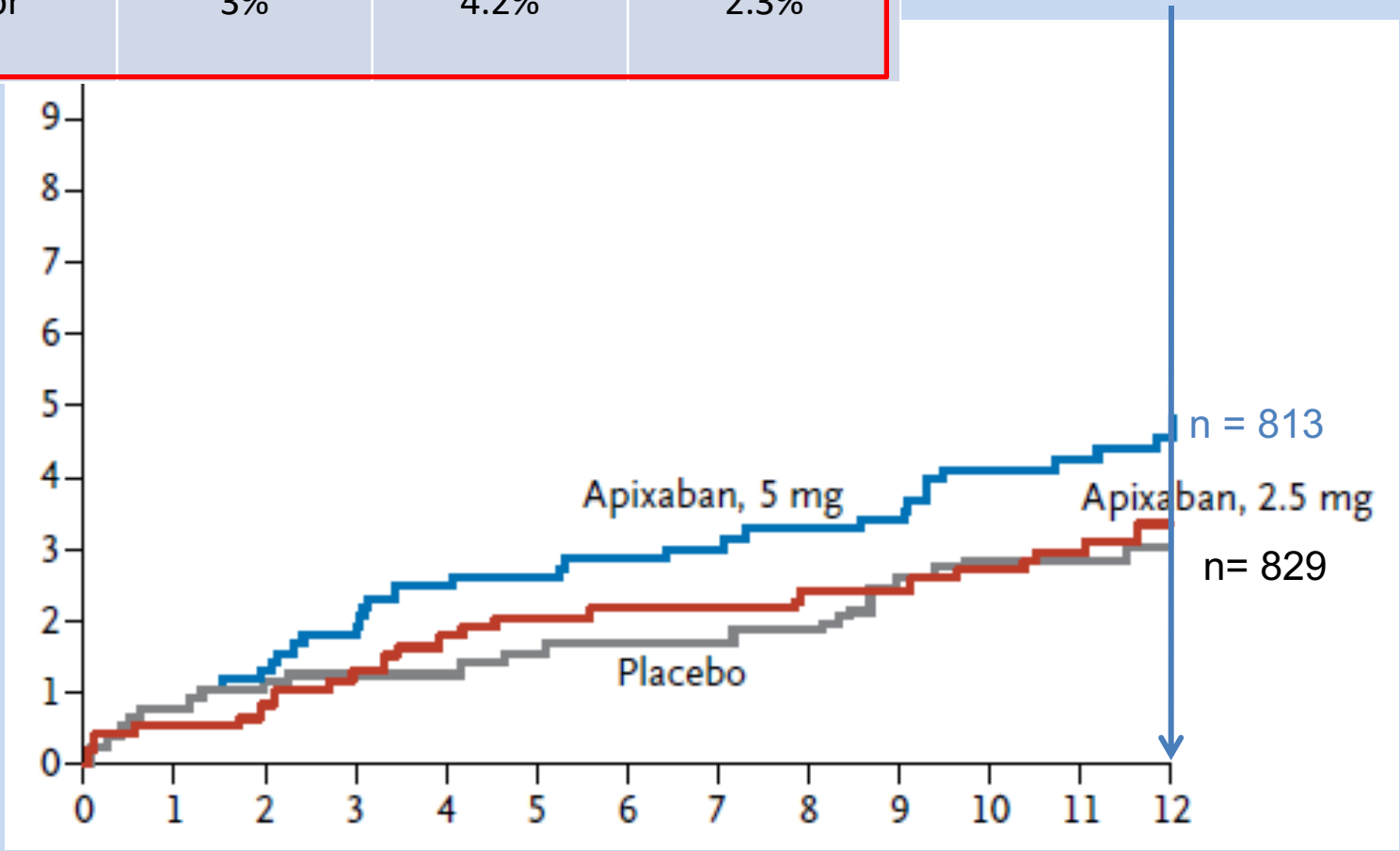
Recurrent VTE	1.7%	1.7%	8.8%
Major bleeding	0.2%	0.1%	0.5%
Non-major bleeding	3%	4.2%	2.3%

Major or Clinically Releva
Non-major Bleeding



N Eng J Med 2013;368:699-708

Length of Treatment

Who is truly low risk of recurrence?

Who is truly high risk of bleeding?

Other issues

- Stockings
- HRT/OCP
- Aspirin
- Travel
- Hospital Admission

Conclusion

- New agents now available
- Optimal length of time of anticoagulation are not known (low risk of recurrence)
- Cost?
- New care pathways
- Warfarin here for a while yet