How Long Shoud We Treat VTE ?

일시: 2014.5.10(토) 15:30-16:00
장소: 서울아산병원 교육연구관

순천향대학교 구미병원 호흡기내과

황 헌 규

CONTENTS

- History of Clinical trial & What to consider
- Provoked vs unprovoked
- Transient risk factors
- Residual vein occlusion
- Cancer
- Genetic factors
- D-dimer, sex, location
- Model to assess the risk of recurrence.
- Role of NOACs for extended treatment

Timeline for VTE Tx

Timeline for VTE Treatment in ACCP 9th guideline

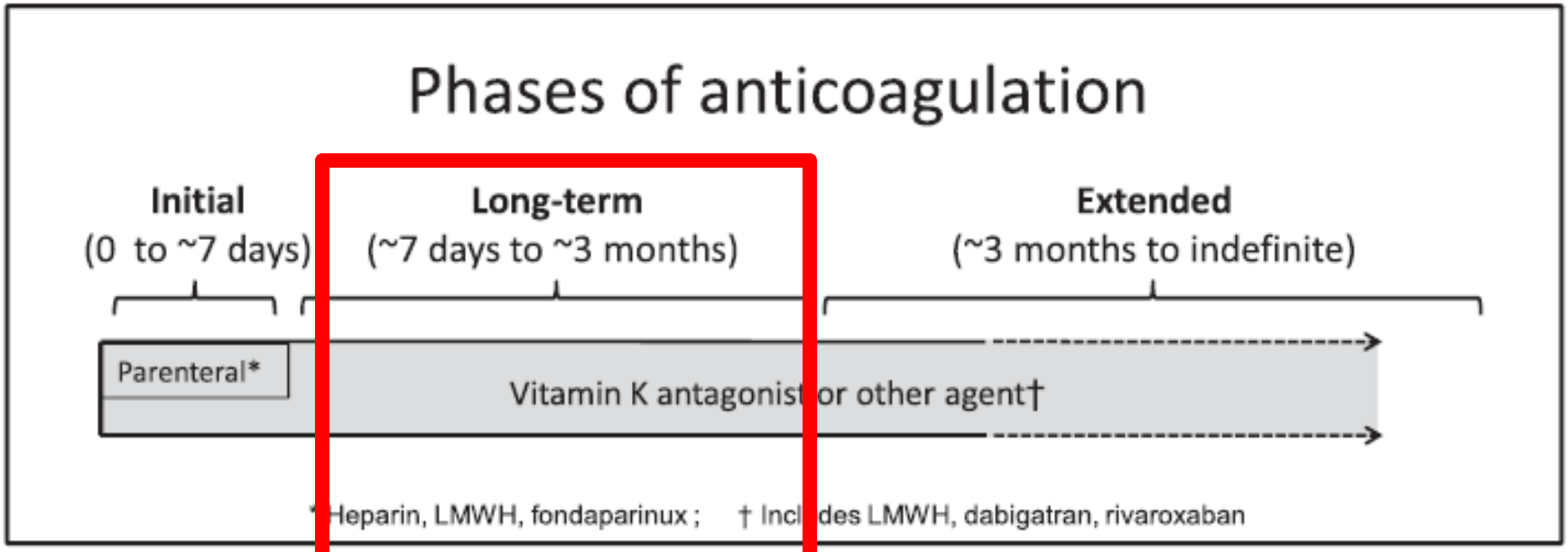


FIGURE 1. Phases of anticoagulation. LMWH = low-molecular-weight heparin.

Kearon et al., ACCP 9th Guideline. Chest 2012;141(2)(Suppl):e419S-3494S

Decision to extend therapy(1)

- Depends on balancing
  - **Increasing risk** of **recurrence** after stopping
  - **AGAINST**
  - Increased risk of **bleeding** with continued Tx

Recurrence vs **Bleeding**

History of Clinical Trials for Comparison of duration

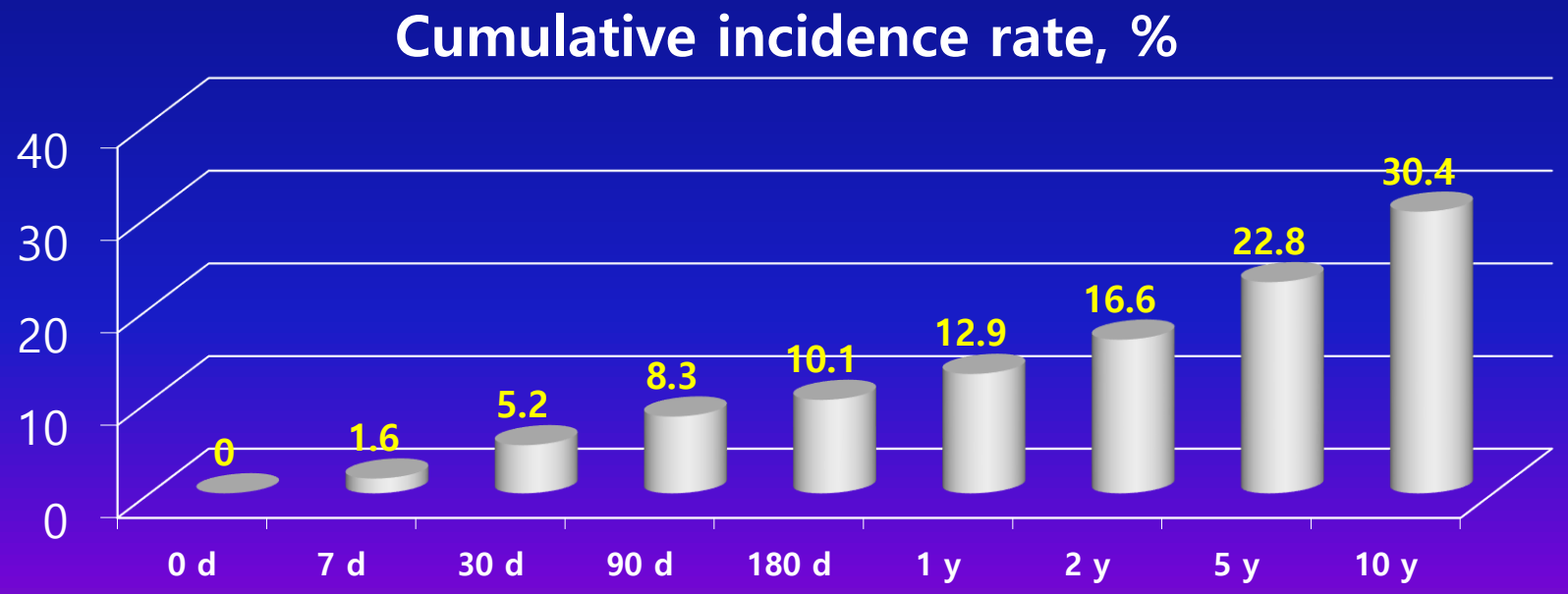
Predictors of recurrence after DVT and PE (1)

- Population-based Cohort Study **(Retrospective)**
- First episode of VTE
- 25-year period from 1966 through 1990
- N=1719, Minnesota
- **Duration: 197.7±559 days (median, 88)**

Heit et al. Arch Intern Med. 2000;160:761-768

Predictors of recurrence after DVT and PE (2)

- Recurred Frequently within **the first 6 to 12 mo**.
- Continues to recur for **at least 10 years.**
- Risk factors: **Neurologic disease or neoplasm**

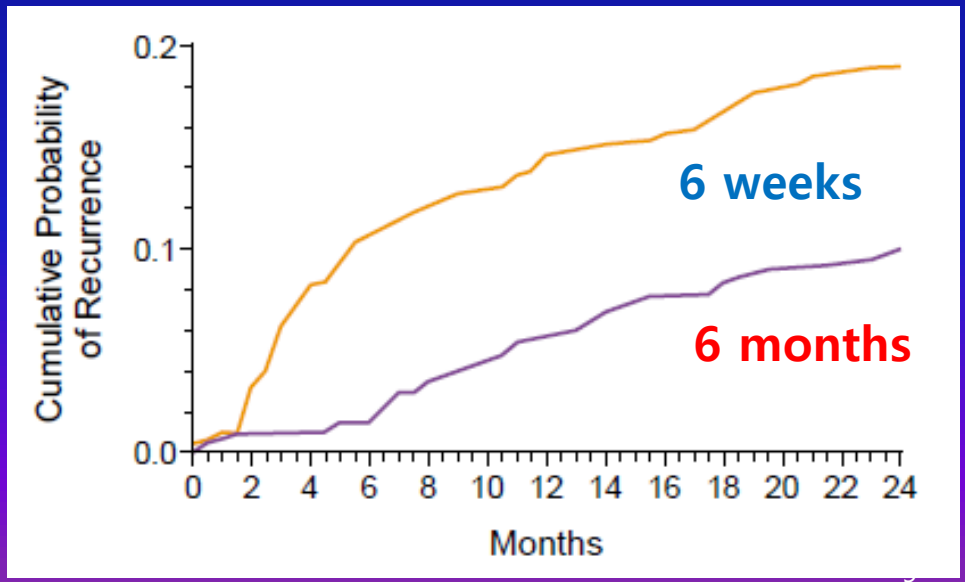


Heit et al. Arch Intern Med. 2000;160:761-768

Six weeks vs six months on Tx after a First Episode of VTE

- **Multicenter trial**
- **Six weeks** vs **six months**
- 902 patients enrolled (443 vs 454)
- Two year follow-up
- 80(18.1%, 95%CI 14.5-21.0) vs 43 (9.5%, 95%CI 6.8-12.2)

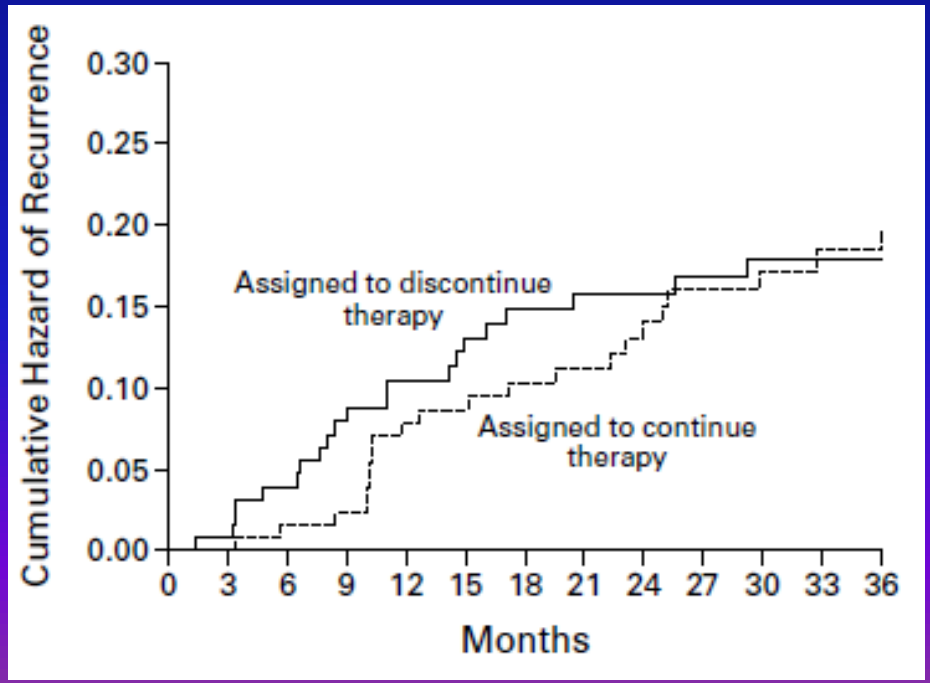
- **No difference** in mortality
- **Parallel** for 1.5 y **thereafter**



Schulman S. NEJM 1995;332:1661-5

3 months vs 1 year on Tx for first Idiopathic proximal DVT (1)

- Patients who **completed three months** of OAT
- Randomly assigned to
  - discontinuation
  - Or continuation for nine additional months
- Two year follow-up



Agnelli NEJM 2001;345(3):165-9

3 months vs 1 year on Tx for first Idiopathic proximal DVT (2)

- Clinical benefit associated with extending duration of OAT to one year is **not maintained after** therapy is discontinued.

Outcome	Discontinuation of OAT (N=133)	Continuation of OAT (N=134)
VTE, No of Pt (%)	21 (15.8)	21 (15.7)
Major bleeding	2 (1.5)	**4 (3.0)**
Death	7 (5.3)	7 (5.2)
At least one adverse event	28 (21.1)	31 (23.1)

Agnelli NEJM 2001;345(3):165-9

Bleeding Risk in Patient on OAT

- Annual incidence of **major bleeding** in patient on warfarin for **longer than 3 months**[1,2]
  - 2-3%
  - Fatality 9.1% (95% CI, 2.5 to 21.7)

- Frequency of recurrence at 2 to 3 years in patient taking 3 mo vs 12 mo of OAT[3]
  - Similar

1) Eikelboom J. et al. BMJ 2007;336:645
2) Linkins et al. Ann Intern Med, 2003;139(11):893-900
3) Agnelli NEJM 2001;345(3):165-9

Decision to extend therapy

- **Recurrence** vs **Bleeding**

- **Strategy for balancing**
  1. Long term OAT, if **highest risk of recurrence**
  2. Stopping OAT, if **low risk of recurrence,** considering **bleeding risk**
  3. **How to decide if risk of recurrence exists between highest and low risk?**

The World until Yesterday

1930's Heparin

1940's Vitamin K antagonists (VKAs)

1980's LMWH

1990's Direct thrombin inhibitors

2004 Oral direct thrombin(IIa) inhibitors

2008 Oral direct factor Xa inhibitors

Provoked vs Unprovoked

Surgical Provoking factor

in sources of meta-analysis

- **Orthopedic, general, urologic, or gynecologic** surgery
- Surgery within **6 weeks to 3 months**
- Surgery with **general anesthesia > 30 minutes within 8 weeks**

Iorio Arch Intern Med 2010;170(19):1710-6

Non-Surgical Provoking factor
in sources of meta-analysis

- Various forms of **immobilization within 3 d vs 7 d before** DVT diagnosis
  - Fracture or plaster casting of lower limb for **3 d within 8w vs 3mo**
- Pregnancy,
- Estrogen use for contraception
- Hormonal therapy
- Postpartum events up to **2 mo vs 3mo** after delivery
- 6 h continuous air flight or road travel within 1 week of onset

Iorio Arch Intern Med 2010;170(19):1710-6

Provoked **vs** **Unprovoked**

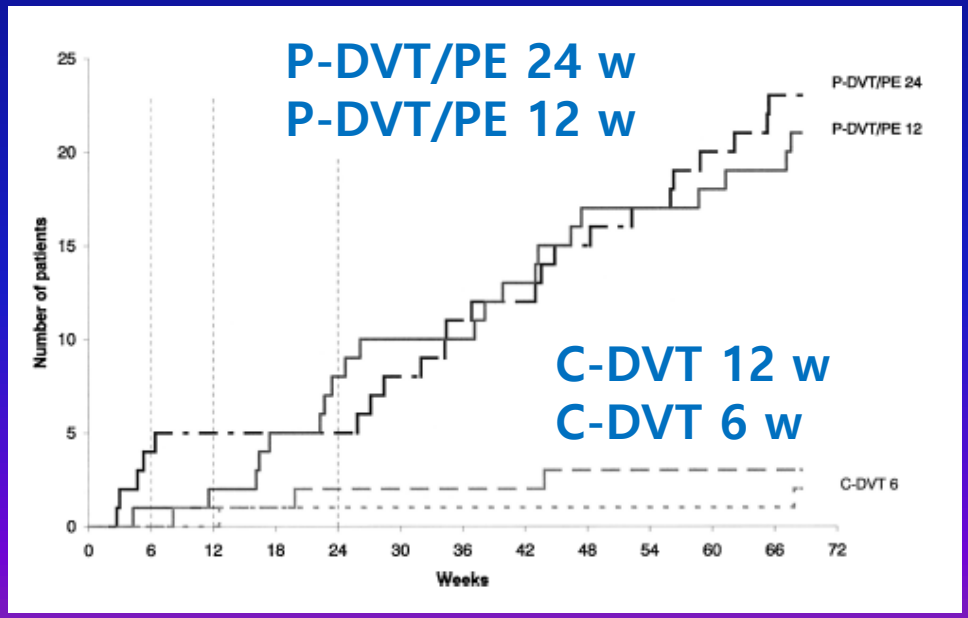
- VTE **without** a convincing provoking factor
- Presence and reversibility of risk factors is a **continuum**.
- Criteria or definition of 'unprovoked' divide this **continuum**.
- Gray zone ?
  - Surgery (3mo, 2mo)
  - Bed rest (3days, <1.5 mo, < 3mo)
  - Estrogen therapy (< 1mo, < 2mo)
  - Cancer (< 2y, < 5y, not specified)

Eichinger. Circulation 2010;121(14):1630-6

Transient Risk Factors

Calf, Proximal DVT or PE

- Open-label, randomized trial in 736 patients
- Comparison of 6 and 12 weeks of therapy for calf DVT
  - 6 weeks for calf DVT
- Lower recurrence rate for **C-DVT** than for P-DVT or PE
- Equivalence between **3** and 6 months for P-DVT or PE
  - 3 months for **temporary** risk factors

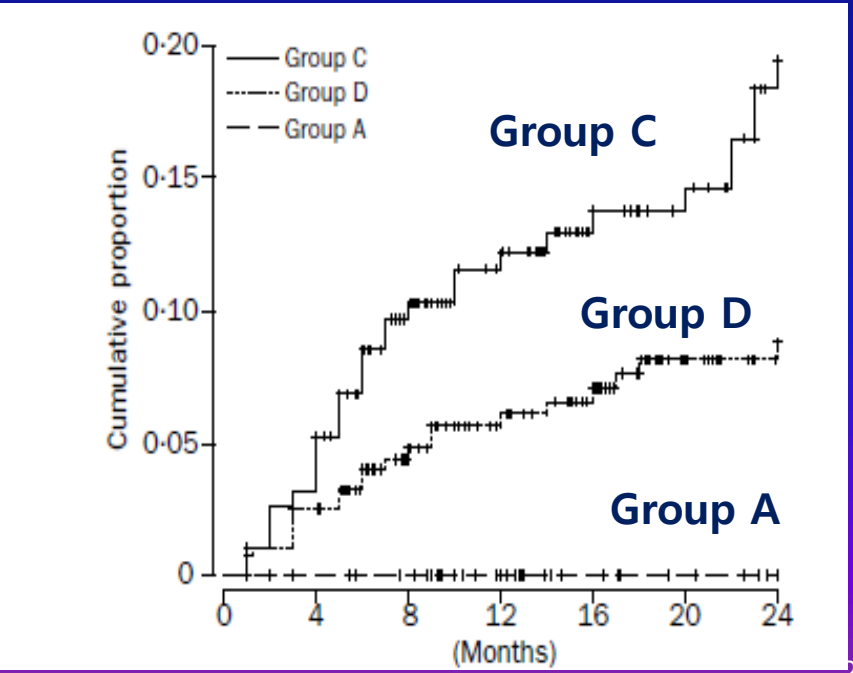


Pinede. Criculation 2001;103:2453-2460

Transient Risk Factors(1)

- Stratification for risk for recurrence after **first episode of VTE**
- Prospectively follow up a cohort
  - **At 2 years**, cumulative recurrence rate in **570 pts** was **11%**
  - Very low rate of recurrence in patients with **postoperative** VTE

  - Group C: Idiopathic (**19.4%**)
  - Group D: Non-surgical risk factor
  - Group A: **Post surgery** (**0%**)

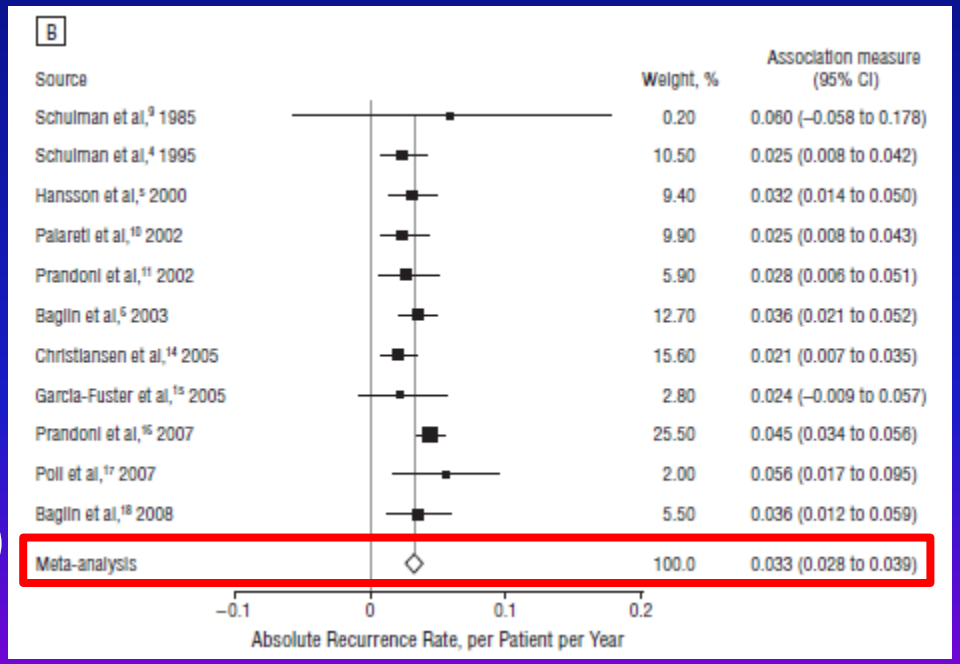


Baglin Lancet 2003 ;362(9383):p.523-6

Transient Risk Factors(2)

Meta-analysis of 11 studies

- Risk of recurrence after a first episode of VTE **in 2yrs**
- In **all patients** with a transient risk factors
  - 3.3%/year
- VTE provoked by **surgery**
  - 0.7%/year(95% CI 0-1.5%)
- By **non-surgical factor**
  - 4.2%/year(95% CI 2.8-5.6)
- **Unprovoked**
  - 7.4%/year (95% CI 6.5-8.2%)



Iorio Arch Intern Med 2010;170(19):1710-6

Duration of Anticoagulation in ACCP 9th Guideline

Diagnosis	Duration if available
Unprovoked PE & DVT of the Leg (Isolated distal or proximal)	At least 3 mo 1B And Reassess
First VTE (unprovoked PE & proximal DVT of leg) with low or moderate bleeding risk	Extended (> 3mo) 2B & reassess at periodic interval
First VTE (unprovoked PE & proximal DVT of leg) with high bleeding risk	3 mo 1B
First VTE (unprovoked distal DVT of leg) with low or moderate bleeding risk	3 mo 2B
First VTE (unprovoked distal DVT of leg) with high bleeding risk	3 mo 1B
Second unprovoked VTE with Low or moderate risk of bleeding	Extended (> 3mo) Low-1B, Moderate-2B
with high risk of bleeding	3 mo 2B

Residual Vein Occlusion

Residual vein occlusion 1-1

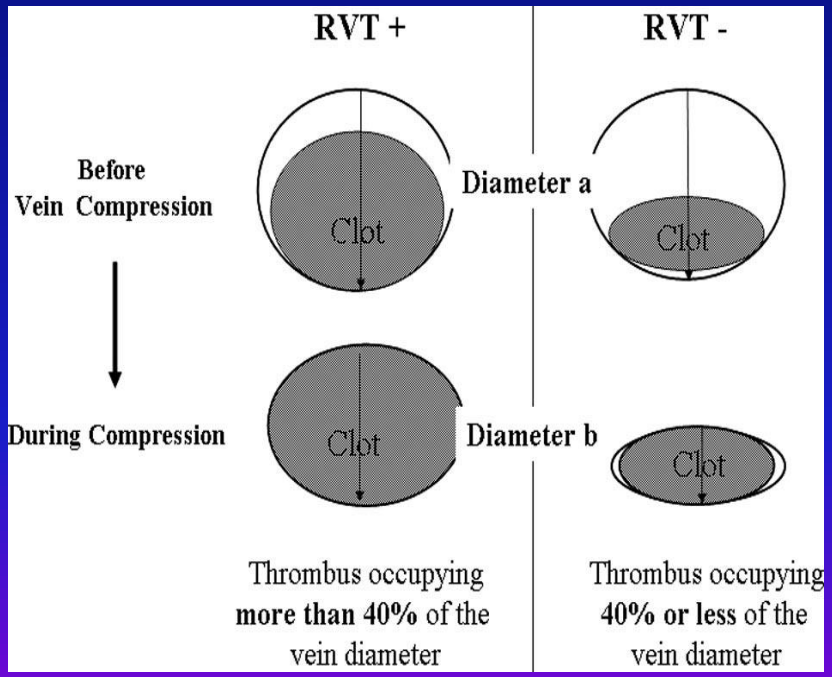
- To establish duration of anticoagulation after a first episode of **idiopathic and provoked** DVT: The duration based on Compression UltraSonography (DACUS) study

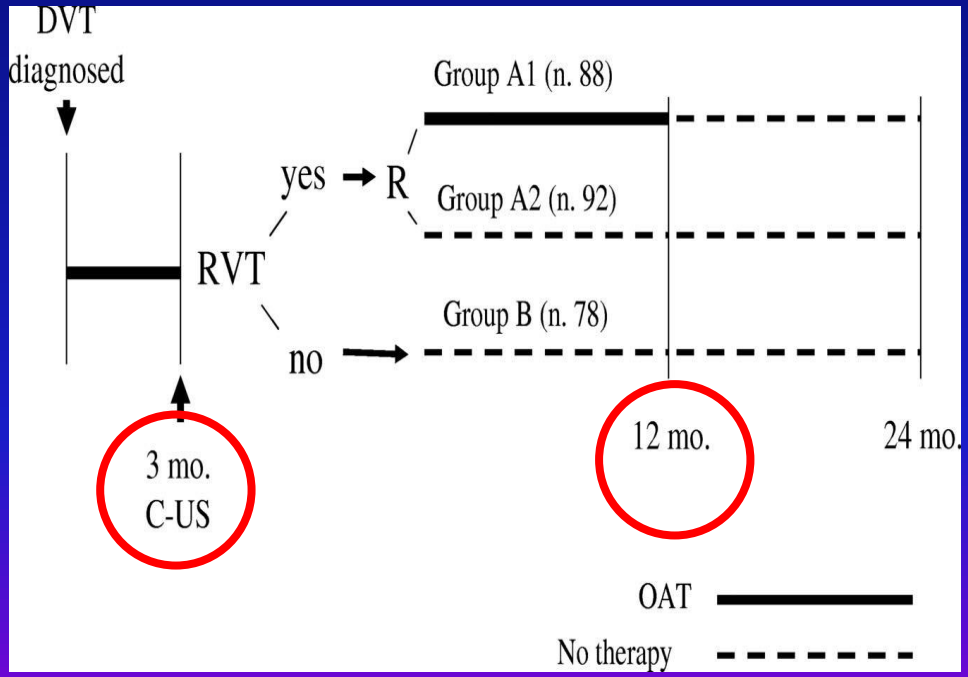
Residual thrombosis was detected
in 180 (69.8%) of 258 patients CUS
after 3 month on oral anticoagulant therapy (OAT)

Siragusa Blood. 2008;112:511-515

Residual vein occlusion 1-2

- Group A1: patients with RVT who continued OAT for 12 months
- Group A2: randomized to stop OAT after 3 months
- Group B: patients **without** RVT after 3





Siragusa Blood. 2008;112:511-515

Residual vein occlusion 1-3

- **RVT(-) on CUS after 3m Tx** , identifies a group of patients at **very low risk** for recurrent thrombosis who can **safely stop OAT**.

Table 2. Study outcomes

Outcomes	Group A1, n = 88	Group A2, n = 92	Group B, n = 78	P
Recurrences, no./total (%)	17/88 (19.3)	25/92 (27.2)	1/78 (1.3)	.213 (A1 vs A2); .001 (A1 vs B);
Recurrences, no. per 100 person-years	10.1	15.2	0.63	.421 (A1 vs A2)*; .021 (A1 vs B)*
Type of recurrent VTE				
DVT	17	25	1	
DVT plus PE	0	0	0	
Isolated PE	0	1†	0	
Contralateral	4	5	0	
Major bleeding, no./total (%)	2/88 (2.3)	1/92 (1.1)	0/78 (0)	.534 (A1 vs A2)‡
Major bleeding, no. per 100 person-years	1.1	0.53	0	.685 (A1 vs A2)*

Siragusa Blood. 2008;112:511-515

Residual vein occlusion 2-1

- REVERSE **Cohort** Study
- 452 patients with a first '**unprovoked**' major VTE
- RVO was determined by CUS after **completion of 5-7 months**
- Association with increased risk of recurrent VTE
- Mean 18 months follow-up

G, L.E.G J Thromb Haemost. 2011;9(6):1126-32

Residual vein occlusion 2-2

Results

- 45 out of 231 patients with abnormal CUS (19.5%)
- 32 out of 220 patients with normal CUS (14.6%)

Conclusion

- **No significant association** between abnormal CUS at inclusion and the risk of recurrent
- Hazard ratio 1.4 (95% CI, 0.9-2.1, p=0.19)
- RVO **not useful** to guide duration of OAT.

G, L.E.G J Thromb Haemost. 2011;9(6):1126-32

Cancer and VTE

Cancer & VTE (1)

- Cumulative incidence of **recurrent** VTE during OAT
- Of the 842 included patients,
- 181 had known cancer at entry.
- 12 month follow-up

Prandoni Blood. 2002;100(10):3484-8

Cancer & VTE (2)

- 12-month cumulative incidence of recurrent VTE
- In cancer patient: 20.7% (95% CI, 15.6%-25.8%)
- In patients without Cancer 6.8% (95% CI 1.9%-5.4%)

Hazard ratio

3.2 (95% CI 1.9-5.4)

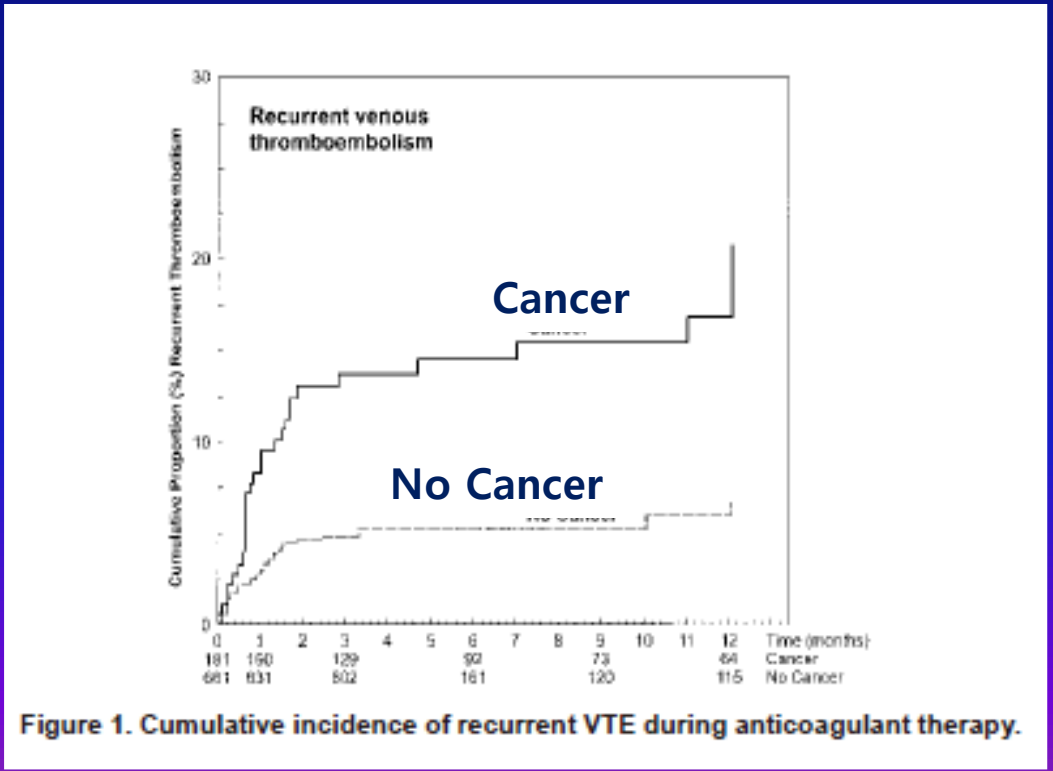


Figure 1. Cumulative incidence of recurrent VTE during anticoagulant therapy.

Prandoni Blood. 2002;100(10):3484-8

Cancer & VTE (3)

- 12-month cumulative incidence of major bleeding
- In cancer patient: 12.4% (95% CI, 6.5%-18.2%)
- In patients without Cancer 4.9% (95% CI 2.5%-7.4%)

Hazard ratio of
2.2 (95% CI, 1.2-4.1)

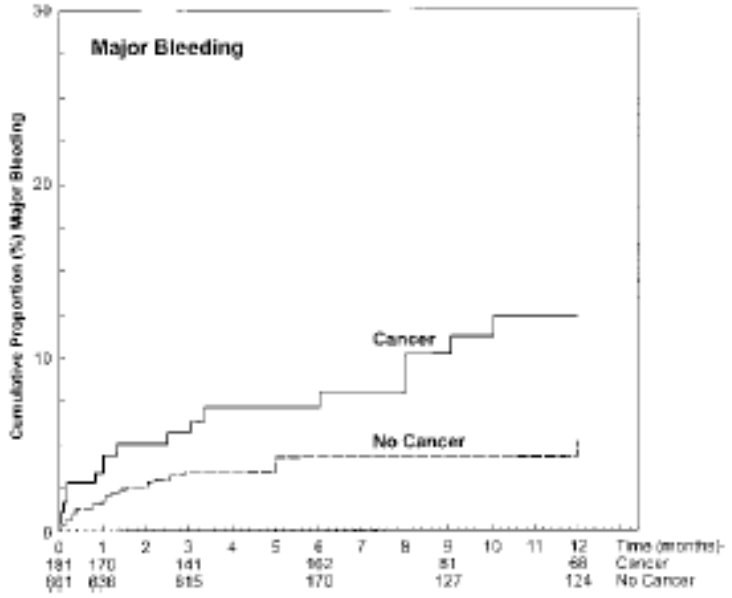


Figure 2. Cumulative incidence of clinically important bleeding during anticoagulant therapy in DVT patients with and without cancer.

Prandoni Blood. 2002;100(10):3484-8

Cancer & Recurrence (4)

- Most patients with active cancer should receive **extended therapy** because of a **high** risk of recurrence.
  (ACCP 9th Guideline)

Kearon et al., ACCP 9th Guideline. Chest 2012;141(2)(Suppl):e419S-3494S

Thrombophilic Genetic Factors

Thrombophilia

Factor V Leiden and Prothrombin G20210A

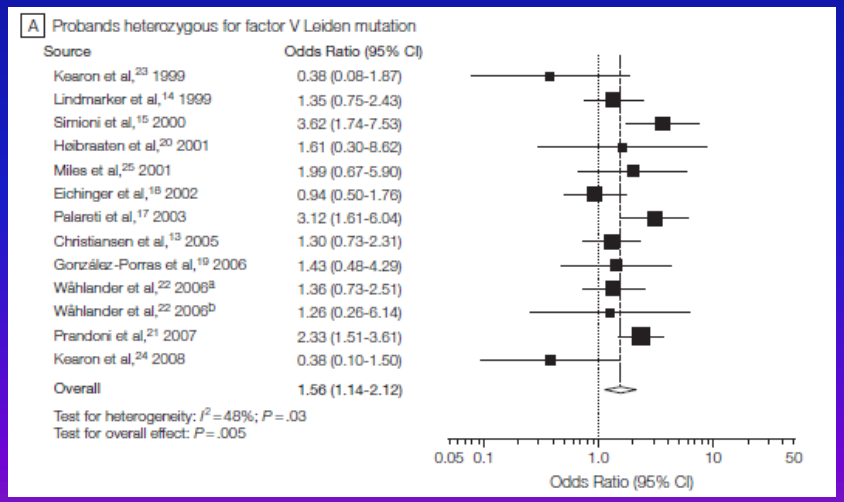
- **Question**: Utility of Testing for **genetic risks** for VTE ?
- **Rates of recurrent VTE** in adults with VTE with **factor V Leiden (FVL)** or **prothrombin G20210A mutation**.
- Systematic review

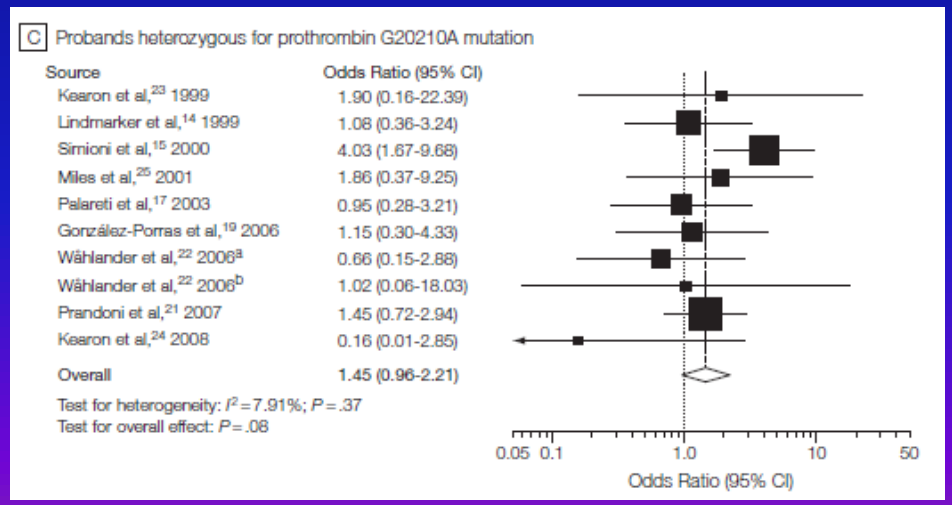
Segal JB, et al. JAMA. 2009;301(23):2472-2485

Thrombophilia

Factor V Leiden and Prothrombin G20210A

- Patients with **FVL** is at increased risk of recurrent VTE.
  - Overall Odd ratio 1.56(95% CI, 1.14-2.12)
- Patients with **Prothrombin G20210A**:
  - Overall Odd ratio 1.45(95% CI, 0.96-2.21)
- It is unknown whether testing for genetic factor improves in adults with VTE or in family members of those with a mutation





Segal JB, et al. JAMA. 2009;301(23):2472-2485

Clinical guideline for testing for heritable thrombophilia

- **Initiation and intensity** of anticoagulant therapy following a diagnosis of acute venous thrombosis should be the same in patients with and without heritable thrombophilia (1B).

- **Indiscriminate testing** for heritable thrombophilias in unselected patients presenting with a first episode of venous thrombosis is **not indicated** (1B).

- Testing for heritable thrombophilias in selected patients, such as those with a **strong family history of unprovoked recurrent thrombosis**, may influence decisions regarding duration of anticoagulation (C). It **is not possible to give a validated recommendation** as to how such patients should be selected.

Balgin British Journal of Haematology 2010;149;209-220

How to Assess the Risk

Model to assess the Risk of Recurrence

- MEN continue and HERDOO2 model
- Vienna guideline (Updated in 2014)
- DASH Prediction Model
- D-dimer in PROLONG I & II study

MEN continue and HERDOO2 (1)

- Multicenter prospective cohort study
- 646 patients with a **first unprovoked** major VTE
- Mean 18-month follow-up
- 69 potential predictor of recurrent VTE
- Patient were taking OAT (5-7 months after initiation).

- HER, Sex, ethnic, age, wt, ht, BMI, D-dimer, Hb, FVL, HRT, Homocysteine, FVIII
- Mutivariate analysis using logistic regression

Rodger et al. CMAJ. 2008;179(5):417-26
Le Gal. et al. Thromb Haemost. 2010;104(3)498-503

MEN continue and **HERDOO2** (2)

- Annual risk of recurrent VTE: 9.3% (95% CI, 7.7-11.3)
- Man had a 13.7% (95% CI, 10.8-17.0)
- High risk women**(>=2 risks**): 14.1% (95% CI, 10.9-17.3)
- Low risk women (0 or 1 risk): 1.6% (95% CI, 0.3-4.6)

- **H**yperpigmentation, **E**dema or **R**edness
- **D**-dimer > 250 mcg/l **while taking OAT**
- **O**besity (BMI >= 30)
- **O**lder age (>=65)

Rodger et al. CMAJ. 2008;179(5):417-26
Le Gal. et al. Thromb Haemost. 2010;104(3)498-503

MEN continue and HERDOO2 (3)

- Low risk women (0 or 1 risk): 1.6% (95% CI, 0.3-4.6)
- Women with 0 or 1 risk factor **may safely discontinue** OAT after 6 months of therapy following a first unprovoked VTE.

Rodger et al. CMAJ. 2008;179(5):417-26
Le Gal. et al. Thromb Haemost. 2010;104(3)498-503

Vienna Prediction Model (1)

- Prospective cohort
- 929 patients with a **first unprovoked VTE**
- Followed of 43.3 months after discontinuation of OAT

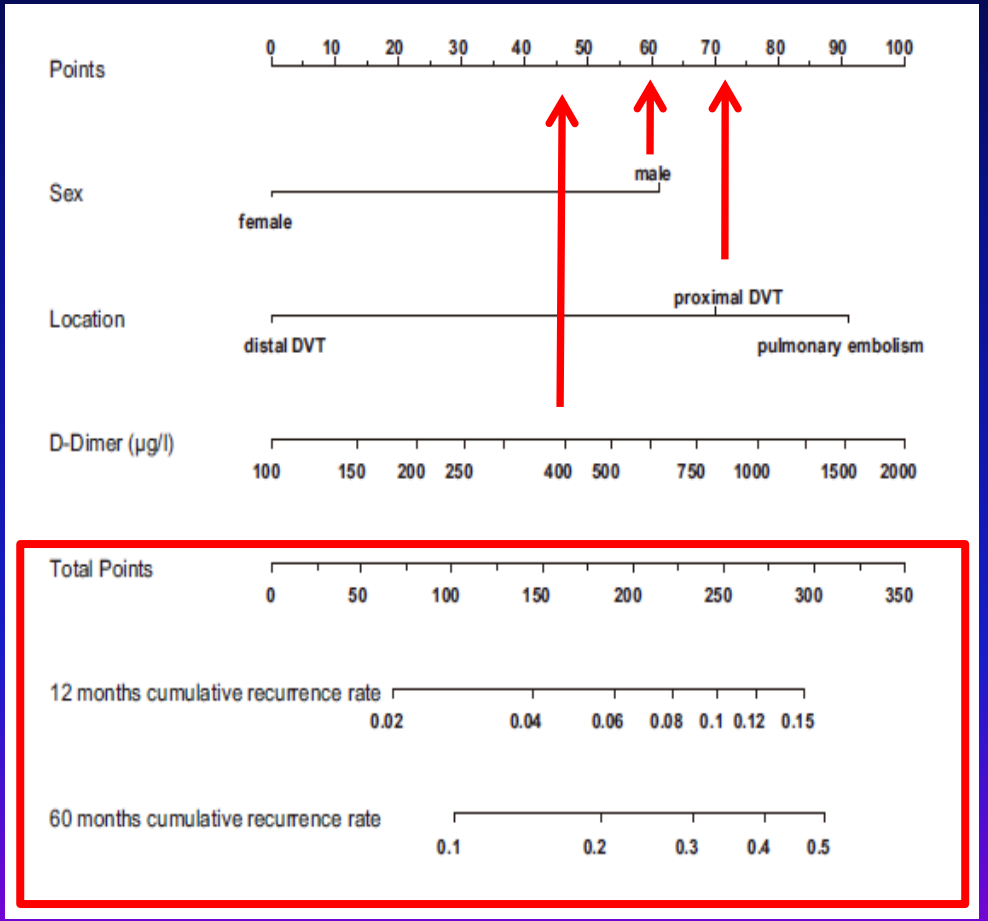
- Quantitative D-dimer **a month after** stopping therapy
- Sex (higher risk for men)
- Location of thrombosis (distal, proximal DVT, or PE)

Eichinger Circulation. 2010;121(14):1630-6
Eichinger J Am Heart Assoc. 2014;3:

Vienna Prediction Model (2)

Table 3. Multivariable Cox Regression Models Including D-Dimer (A) and Peak Thrombin Levels (B)

Variable	Hazard Ratio	95% CI	*P*
Model A			
Male vs female sex	1.90	1.31–2.75	<0.001
Pulmonary embolism vs distal thrombosis	2.60	1.49–4.53	<0.001
Proximal vs distal thrombosis	2.08	1.16–3.74	0.01
D-dimer (per doubling)	1.27	1.08–1.51	0.005
Model B			
Variable			
Male vs female sex	2.05	1.36–3.09	<0.001
Pulmonary embolism vs distal thrombosis	2.32	1.32–4.09	0.004
Proximal vs distal thrombosis	1.88	1.03–3.44	0.04
Peak thrombin (per 100 nmol/L)	1.38	1.17–1.63	<0.001



Eichinger Circulation. 2010;121(14):1630-6

Eichinger J Am Heart Assoc. 2014;3:

Dynamic Vienna Prediction Model (1)

- D-Dimer levels **over time** and the risk of recurrent VTE
- Patients with unprovoked VTE can be stratified according to their recurrence risk based on

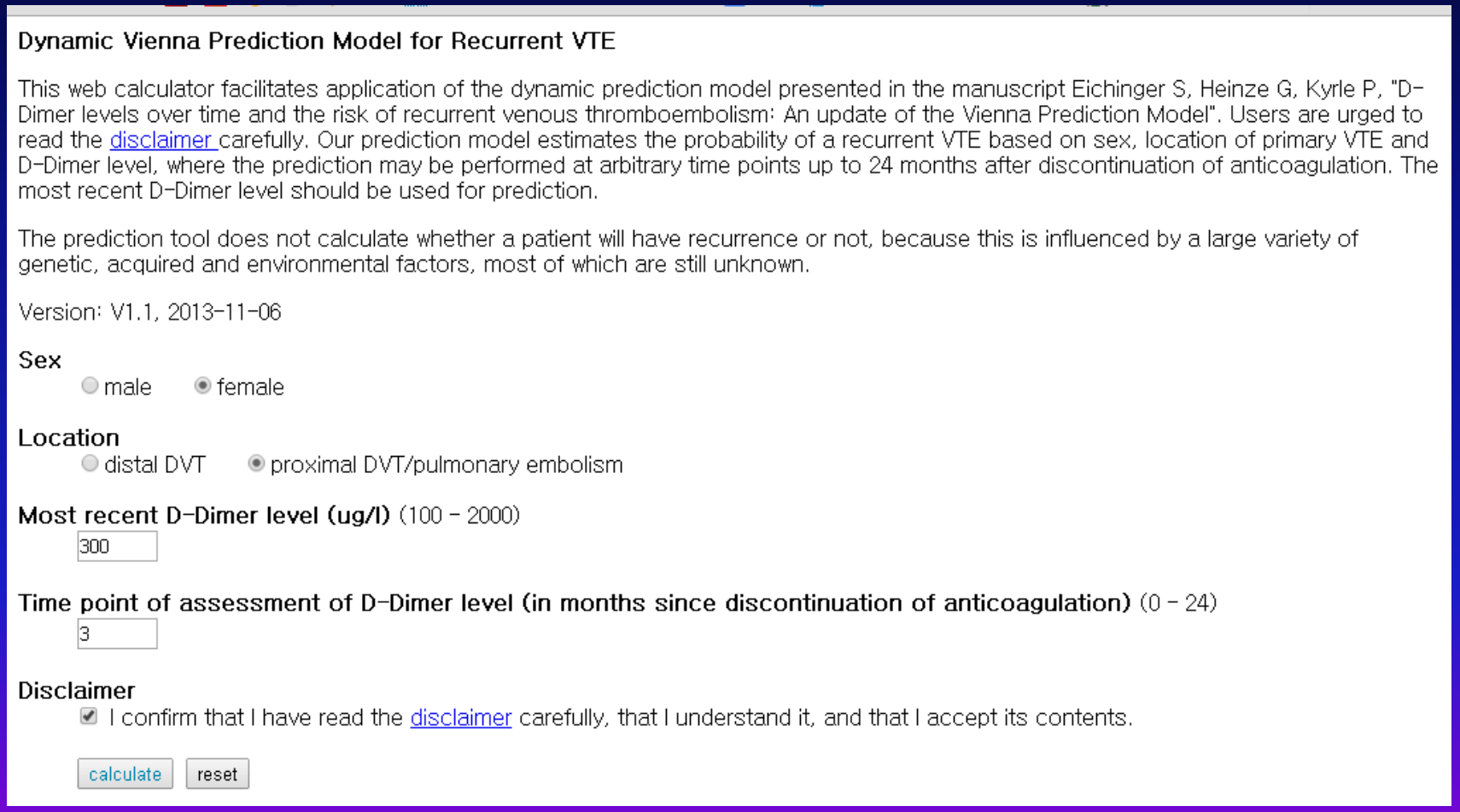
- Sex
- The VTE location
- D-dimer measured **3 weeks(baseline) and 3, 9, 15 and 24 months** after discontinuation of OAT

- **Expand model** to assess recurrence risk from later points on

- 553 patients with a first VTE were followed for a median of 68 months

Eichinger J Am Heart Assoc. 2014;3:

Dynamic Vienna Prediction Model (3)



Dynamic Vienna Prediction Model for Recurrent VTE

This web calculator facilitates application of the dynamic prediction model presented in the manuscript Eichinger S, Heinze G, Kyrle P, "D-Dimer levels over time and the risk of recurrent venous thromboembolism: An update of the Vienna Prediction Model". Users are urged to read the disclaimer carefully. Our prediction model estimates the probability of a recurrent VTE based on sex, location of primary VTE and D-Dimer level, where the prediction may be performed at arbitrary time points up to 24 months after discontinuation of anticoagulation. The most recent D-Dimer level should be used for prediction.

The prediction tool does not calculate whether a patient will have recurrence or not, because this is influenced by a large variety of genetic, acquired and environmental factors, most of which are still unknown.

Version: V1.1, 2013-11-06

Sex

○ male ◉ female

Location

○ distal DVT ◉ proximal DVT/pulmonary embolism

Most recent D-Dimer level (ug/l) (100 - 2000)

300

Time point of assessment of D-Dimer level (in months since discontinuation of anticoagulation) (0 - 24)

3

Disclaimer

☑ I confirm that I have read the disclaimer carefully, that I understand it, and that I accept its contents.

calculate reset

Eichinger J Am Heart Assoc. 2014;3:

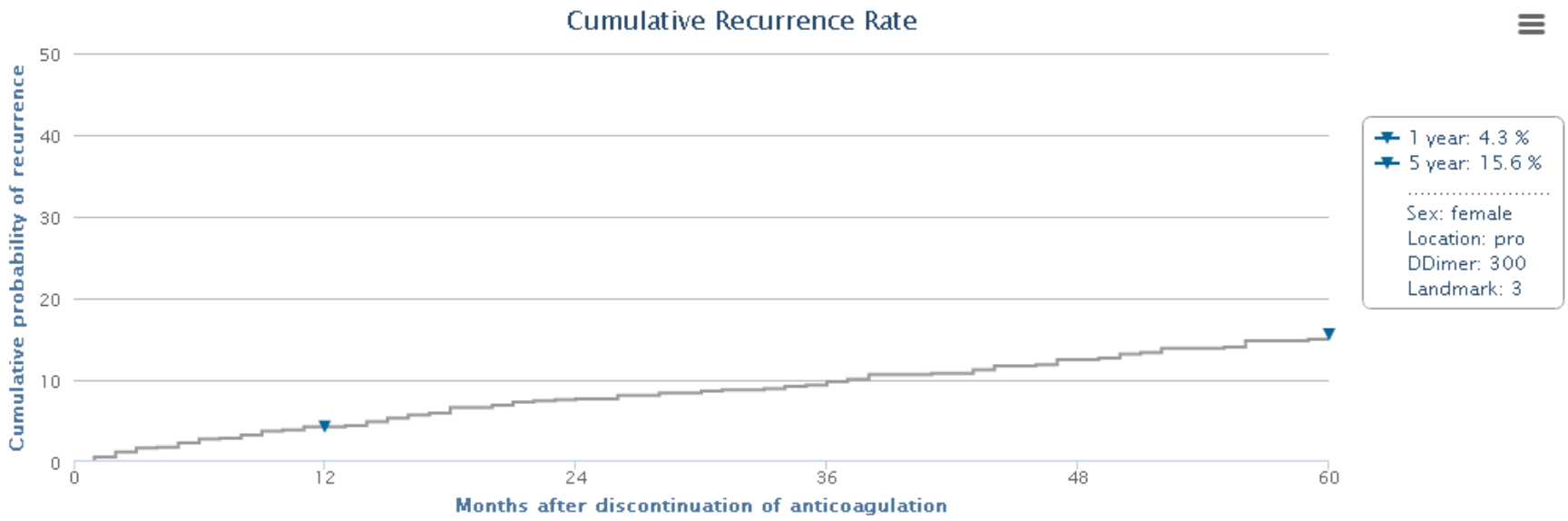
Updated Vienna Prediction Model (4)

Predicted probability of recurrence within 12 months from assessment of D-Dimer level (%):

4.28

Predicted probability of recurrence within 60 months from assessment of D-Dimer level (%):

15.57



Eichinger J Am Heart Assoc. 2014;3:

Role of NOACs in Extended Therapy

Phase III Clinical Trials with NOACs

Anticoagulant	Treatment of VTE Secondary Prevention, publish year	Prevention of stroke in patient with AF
Dabigatran etexilate vs VKA or **placebo**	RE-COVER I (2564) 2009년	RE-LY (18,113)
	RE-COVER II (2500)	RELY-ABLE (6000)
	RE-MEDY (2400) on Feb 2013	
	RE-SONATE (1800) on Feb 2013	
Rivaroxaban vs VKA or placebo	EINSTEIN-DVT (3449) in 2010	Japanese AF (1280)
	EINSTEIN-PE (4500) in 2012	ROCKET-AF (14 000)
	EINSTEIN-Extension(1197) in 2010	

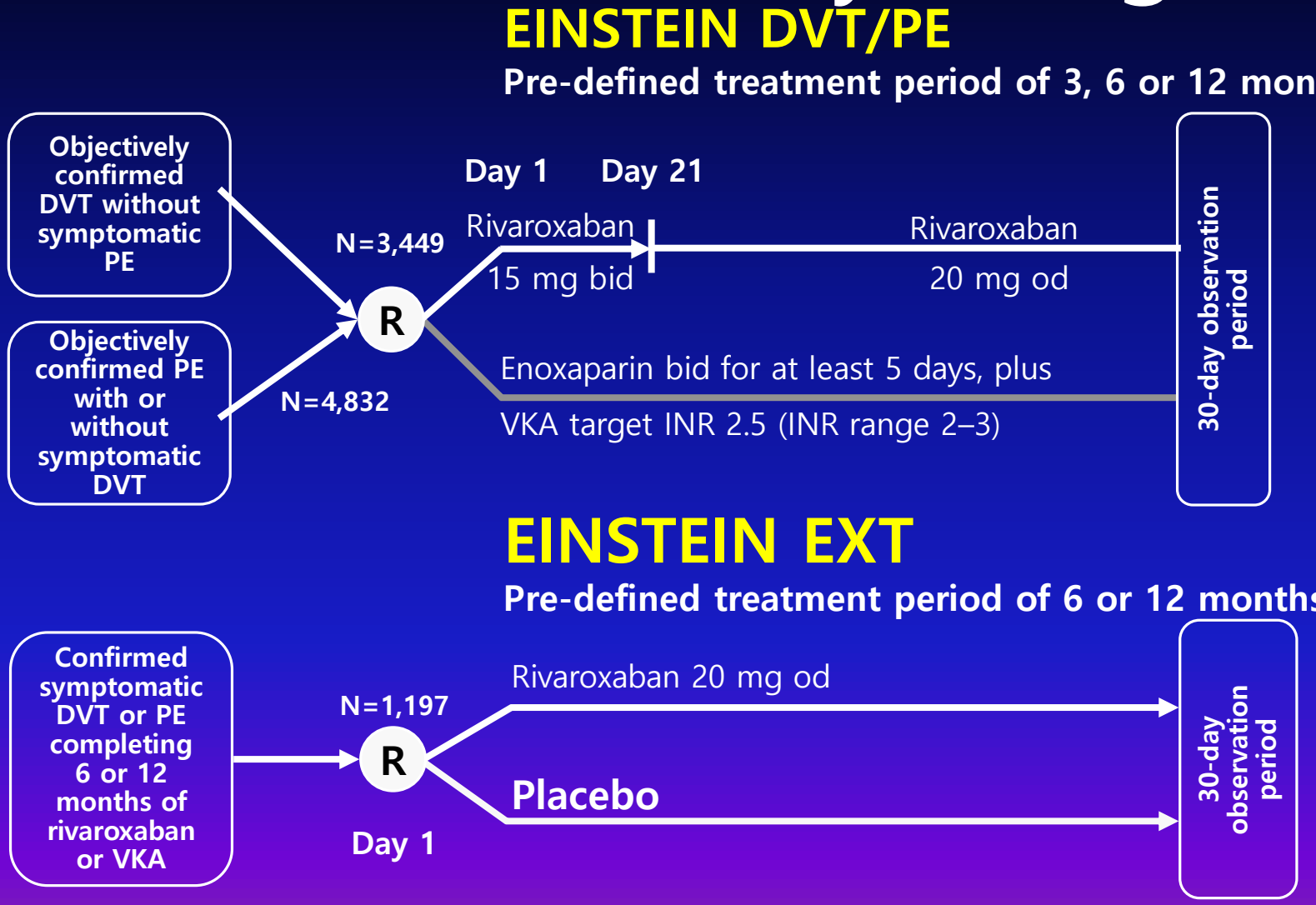
Eikelboom, *Circulation*. 2010;121:1523-1532

Phase III Clinical Trials with NOACs

Anticoagulant	Treatment of VTE Secondary Prevention, Publish year	Prevention of stroke in patient with AF
Apixaban Xa inhibitor VS warfarin or placebo	AMPLIFY VTE/PE (5400) in 2013	AVERROES (5600)
	AMPLIFY Ext (2486) in 2013	ARISTOTLE (15 000)
Edoxaban Xa inhibitor	Hokusai VTE/PE in 2013	ENGAGE AF TIMI 48

Eikelboom, *Circulation*. 2010;121:1523-1532

EINSTEIN: study designs



1. Bauersachs NEJM 2010;363(26):2499-510 2. Buller NEJM 2012;366(14)1287-97

Primary efficacy and Safety in the trials for extended treatment of VTE

Agents (Trial name)	Risk estimate (95% CI)		
	Recurrent VTE, %	Major bleeding, %	Major + CRNMB, %
Rivaroxaban (EINSTEIN-EXT)*	**HR 0.18 (0.09-0.39)**	Not estimable (4 vs 0)	**5.19 (2.3-11.7)**
Dabigatran (RESONATE)*	**HR 0.08 (0.02-0.25)**	Not estimable (2 vs 0)	**2.92 (1.52-5.60)**
Apixaban 2.5mg (AMPLIFY-EXT)*	**HR 0.33 (0.22-0.48)**	HR 0.49 (0.09-2.64)	1.20 (0.69-2.10)
Apixaban 5mg (AMPLIFY-EXT)*	**HR 0.36 (0.25-0.53)**	HR 0.25 (0.03-2.24)	1.62 (0.96-2.73)
	Recurrent VTE, %	Major bleeding, %	Major + CRNMB, %
Dabigatran (REMEDY)**	HR 1.44 (0.78-2.64)	HR 0.52 (0.27-1.02)	**0.54 (0.41-0.71)**

CRNMB : clinically relevant non-major bleeding, HR : hazard ratio, VTE : venous thromboembolism, PE : pulmonary embolism, DVT : deep vein thrombosis, CI : confidence interval
*Compared with placebo, **Compared with warfarin

SchulmanThromb Haemost 2014;111(4):575-582

Approval in KFDA and FDA

- **Rivaroxaban** : KFDA Approval in 2013
- **Dabigatran**: FDA Apprvoal on April 7th, 2014 for Tx of VTE and secondary prevention
- **Apixaban**: not yet approved for use in DVT and PE
- **Edoxaban**: not approved in the US, applied the European Medicines Agency(EMA) for VTE indication.

Summary (1)

- Optimal duration of OAT depends on balancing recurrence against bleeding.
- Clinical benefit associated with extending duration of OAT **to one year** is **not maintained after** therapy is discontinued.
- Try to find out **transient and high risk factor**.

Summary (2)

- At least 3 month-OAT in patient with a first episode of VTE
- Six week-OAT in patients with isolated distal DVT.
- No RVO in provoked DVT

- High risk
  - Cancer
  - Thrombosis
  - Severe post-thrombotic syndrome
  - More than on episode of unprovoked thrombosis

Summary (3)

- In patient **at intermediate(?) risk of recurrence**
- MEN continue HERDOO2 with 0 or 1 vs >=2
- Dynamic Vienna prediction model: Web-based
  - Sex, VTE location, D-dimer
- DASH (D-dimer, Age, Sex, Hormone)
  - Score <=1 low risk
- **NOACs** for extended therapy, as needed

Take Home Message

- Stop OAT, if low risk
- Continue OAT, if high risk
- If intermediate risk,
  - Reassess risk, on the basis of risk model

경청해 주셔서 감사합니다

Distal DVT – a benign disease?

- What is distal?
  - Knee joint – DURAC trialCalf vs popliteal – Palareti Semi Thromb Hemost 2006;32:659-72
- Contemporary discussion
  - CACTUS-PTS trial with 600 patients with isolated distal DVT
  - Randomised to 6 weeks of LMWH vs placebo (ClinicalTrials.gov NCT00421538)
  - Outcome recurrence at 6 weeks and PTS at 1 year

Distal DVT – a benign disease?

Risk factors for extension of distal DVT

- Positive D-dimer
- Thrombus > 5cm or close to proximal veins
- Thrombosis in multiple distal veins
- No reversible provoking factors
- Active cancer
- History of venous thromboembolism
- Thrombosis in hospitalized patient

Schulman 2014 Thrombosis Research