Hemostasis Update

Tom DeLoughery, MD MACP FAWM

Oregon Health and Sciences University

OHSU GENERAL HEMATOLOGY

DISCLOSURE

Relevant Financial Relationship(s)

Speaker Bureau - None

Consultant/Research – none

What I am Talking About

- Therapy of VTE
- Duration of anticoagulation
- Thrombophilia work-ups

Don’t Use Standard Heparin!

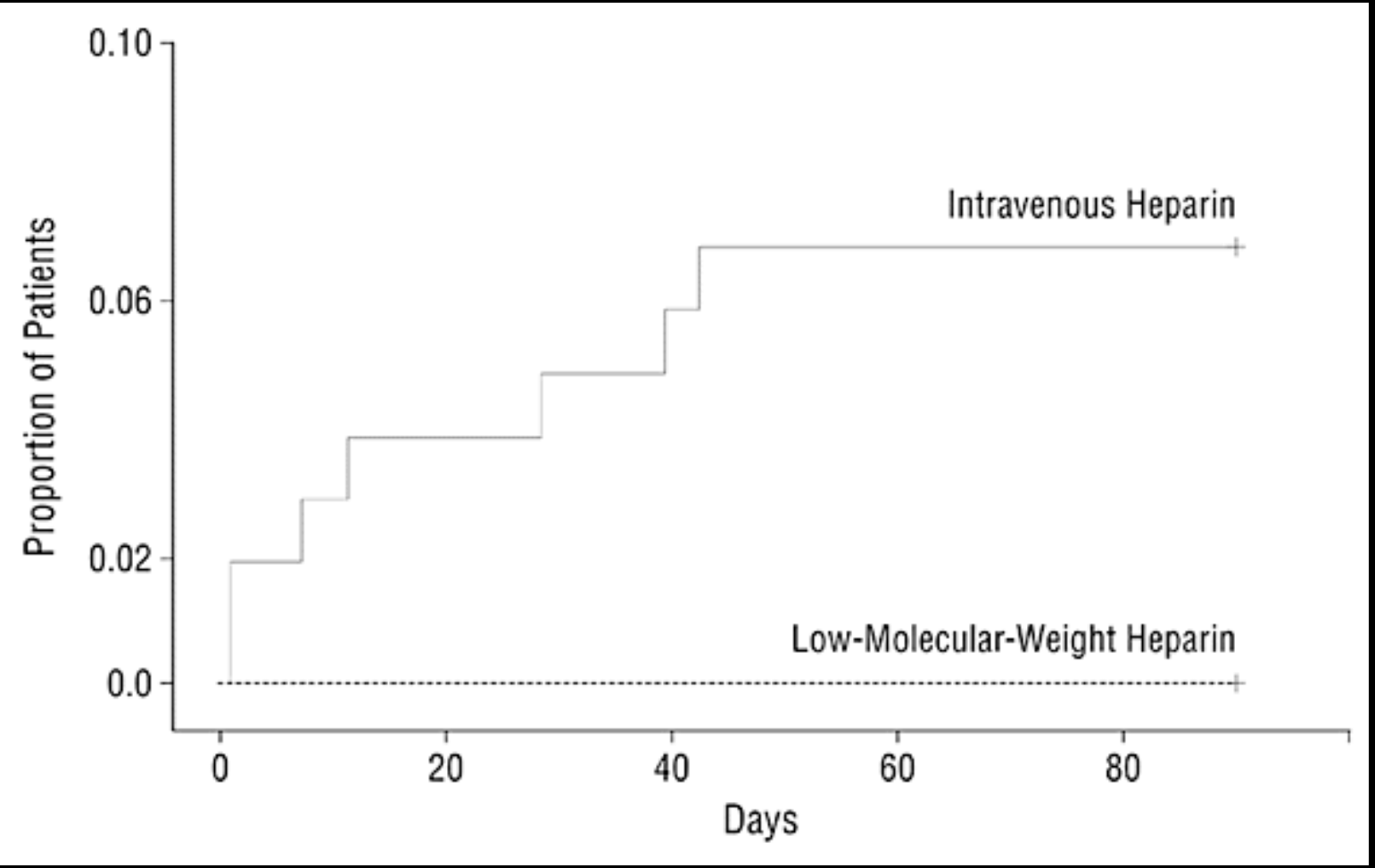
Heparin

- LMWH was shown in the 90's to be superior to standard heparin
  - Better outcomes
  - Instantly therapeutic
    - > 50% UFH not at goal at 24 hrs
  - No need for the inaccurate PTT
  - Much less HIT
  - Much easier
  - Cheap ~ $20/day
  - Reversible with protamine

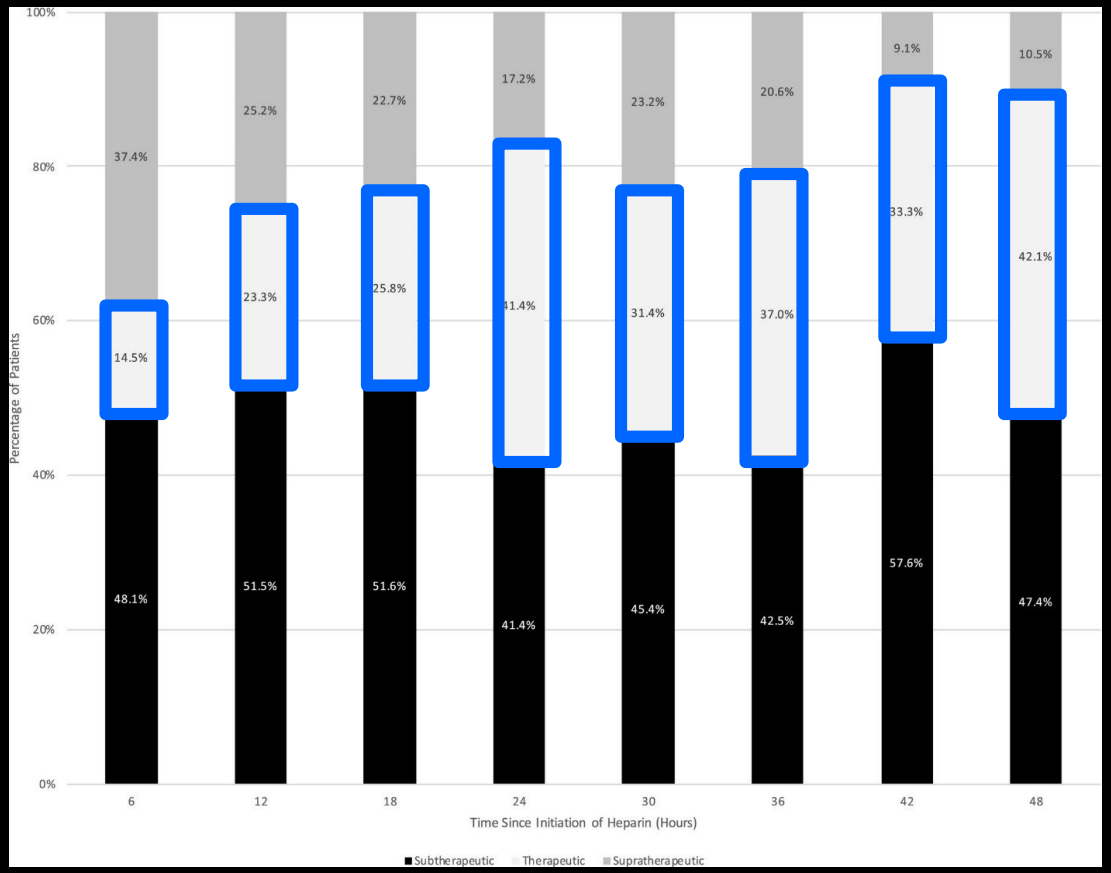
Meta-analysis of LMWH inpatient therapy

Recurrent DVT day 1-15		
LMWH	SH	
3/365 (0.8)	12/371 (3.2%)	RR 76%
Recurrent DVT day 16 -90		
LMWH	SH	
7/365 (1.9%)	12/371 (3.2%)	RR 61%
Bleeding		
LMWH	SH	
12/394 (3.0%)	27/402 (6.7%)	RR 58%

LMWH vs UFH: Therapy of Pulmonary Embolism



Analysis of PTT in Patients With PE First 48 Hours of Anticoagulation With UFH



Academic Emergency Medicine, 27: 117-127, 2020

Renal Disease

- Enoxaparin adjustment FDA approved
  - Decreased clearance of drug with decreased creatinine clearances
- Renal dosing (< 30ml/min)
  - Therapy: 1 mg/kg q 24 hrs
  - Prophylaxis: 20-30 mg/day
- For therapy check level after third dose
- No difference in major bleeding compared to UFH

Procedures

- No issues with IR procedures for PE
- Not that much difference in half-life

Safety of Therapeutic Anticoagulation with Low-Molecular-Weight Heparin or Unfractionated Heparin Infusion during Catheter-Directed Thrombolysis for Acute Pulmonary Embolism

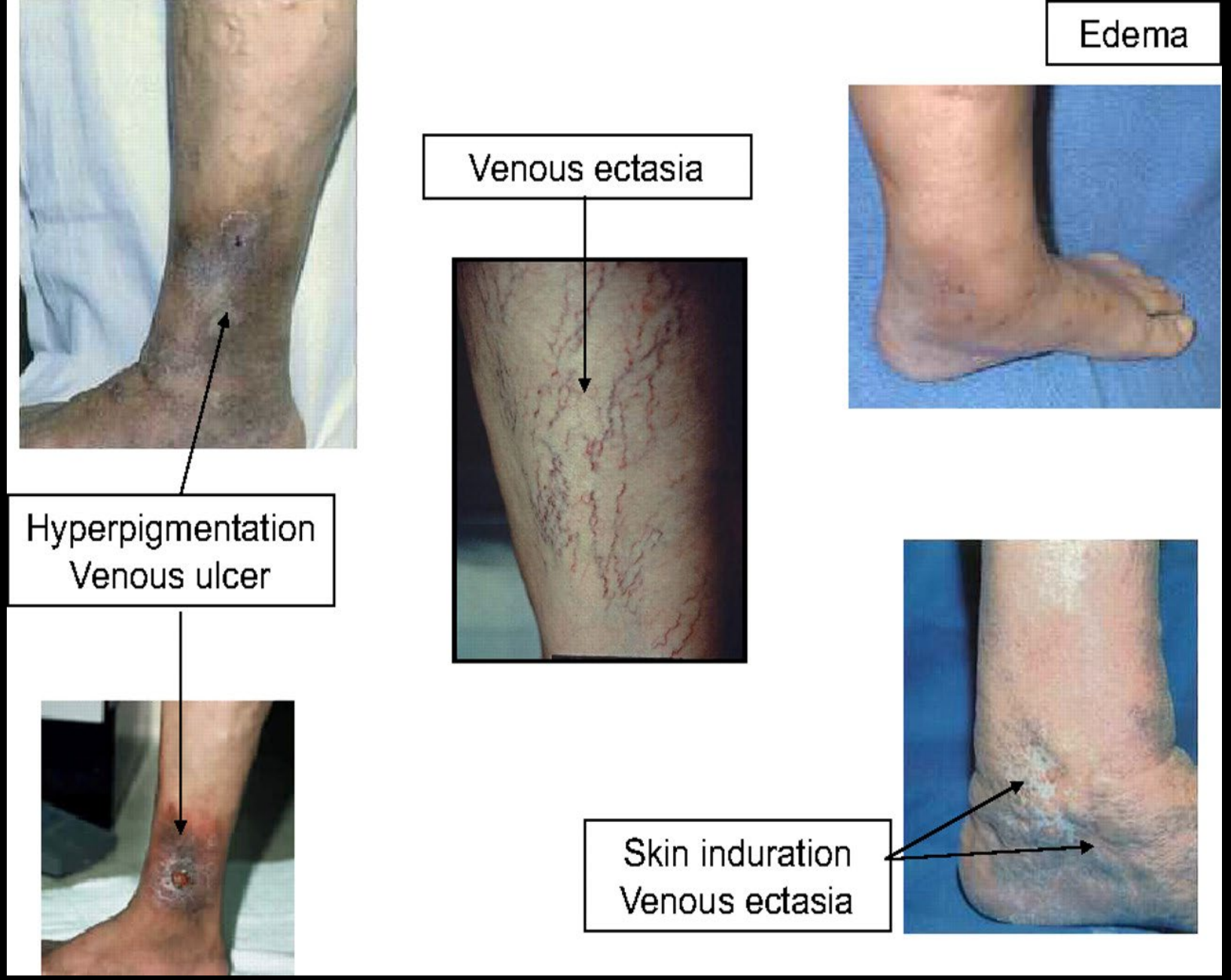
J Vasc Interv Radiol . 2020 Apr;31(4):537-543

Conclusion

- Standard heparin should be used only on rare occasions

Post-Thrombotic Syndrome

- Common complication of DVT
- 20-50% of all patients
- 5-10% severe
- Can be disabling



Blood, 19 November 2009, Vol. 114:4624-4631.

PTS: Risk Factors

- Common femoral or iliac vein thrombosis
- Previous DVT
- High BMI
- Older age
- Inadequate initial anticoagulation

Prevention

- Prevent thrombosis!
- Knee-high compression stockings – controversial but…
  - Apply within 24 hours
  - 20-30mmHg
  - At least 6 months
- Keep the patient active
- DOACs
  - 4 studies show less PTS

Post-PE Syndrome?

- 50% of patients with PE report dyspnea 6 months later
- 20-70% state health status worse
- Seemingly not related to clot residual or scarring
- Chest pain/discomfort very common
- Warn/reassure patients
- “Cardiac” rehab

Duration of Therapy

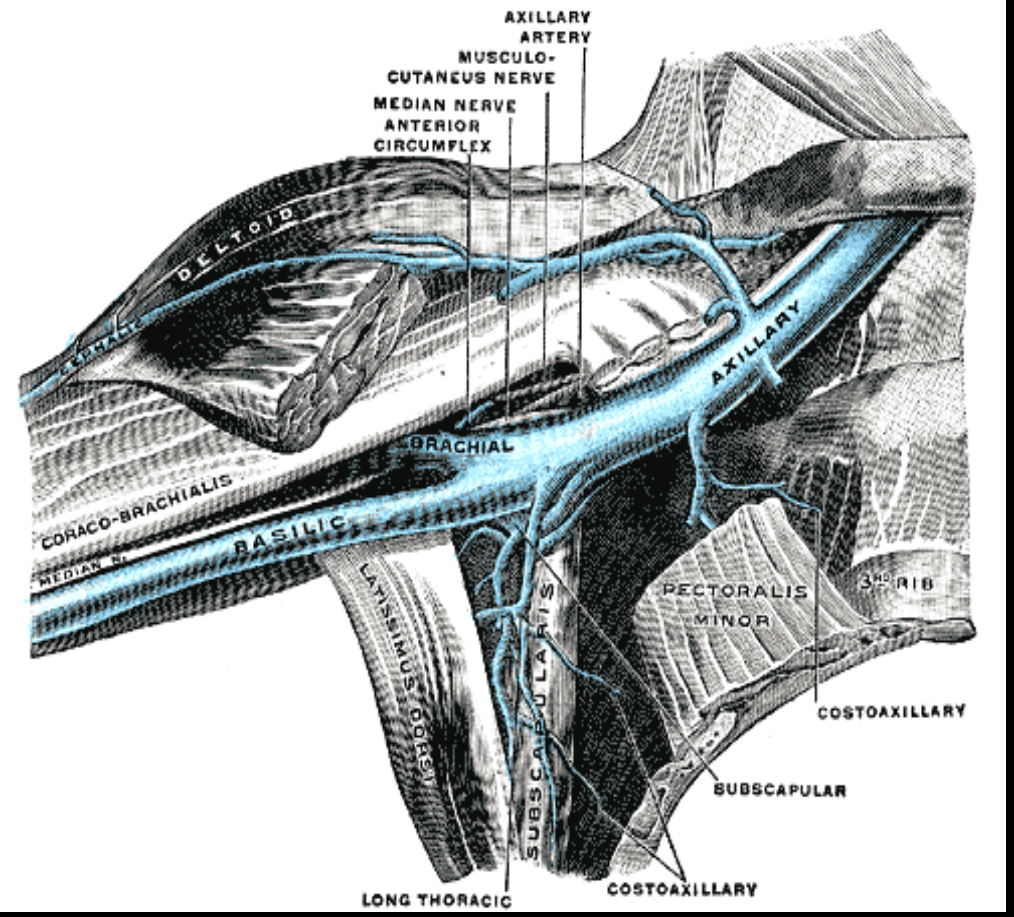
Idiopathic versus provoked thrombosis is **the biggest** determinant of risk of recurrent thrombosis

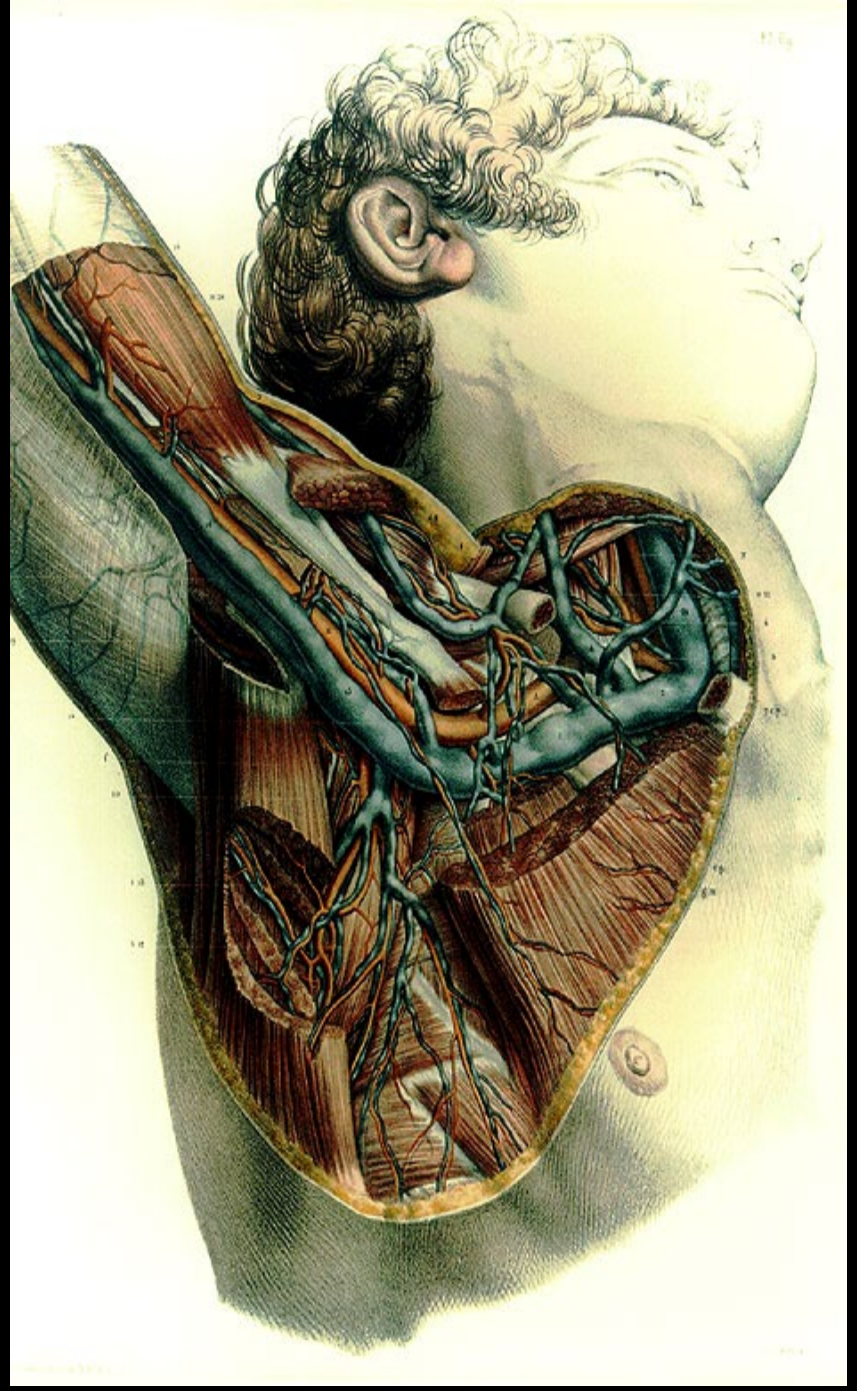
Duration of Therapy

- Not all thrombosis are the same
- Can stratify patients by:
  - Site of thrombosis
  - Circumstances of thrombosis
    - Most important!

Upper Extremity Thrombosis

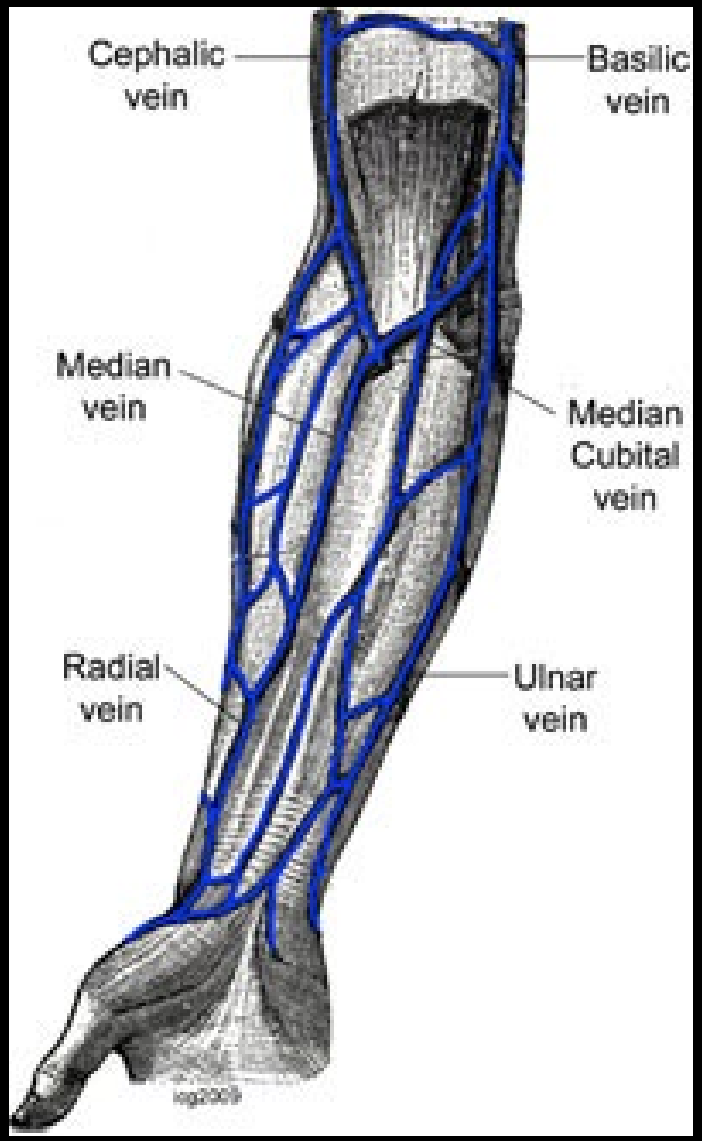
- Mechanical defects
  - Catheter
    - PICC 3-5%
  - Local venous trauma
- Prophylaxis ineffective
- Low risk of serious sequela

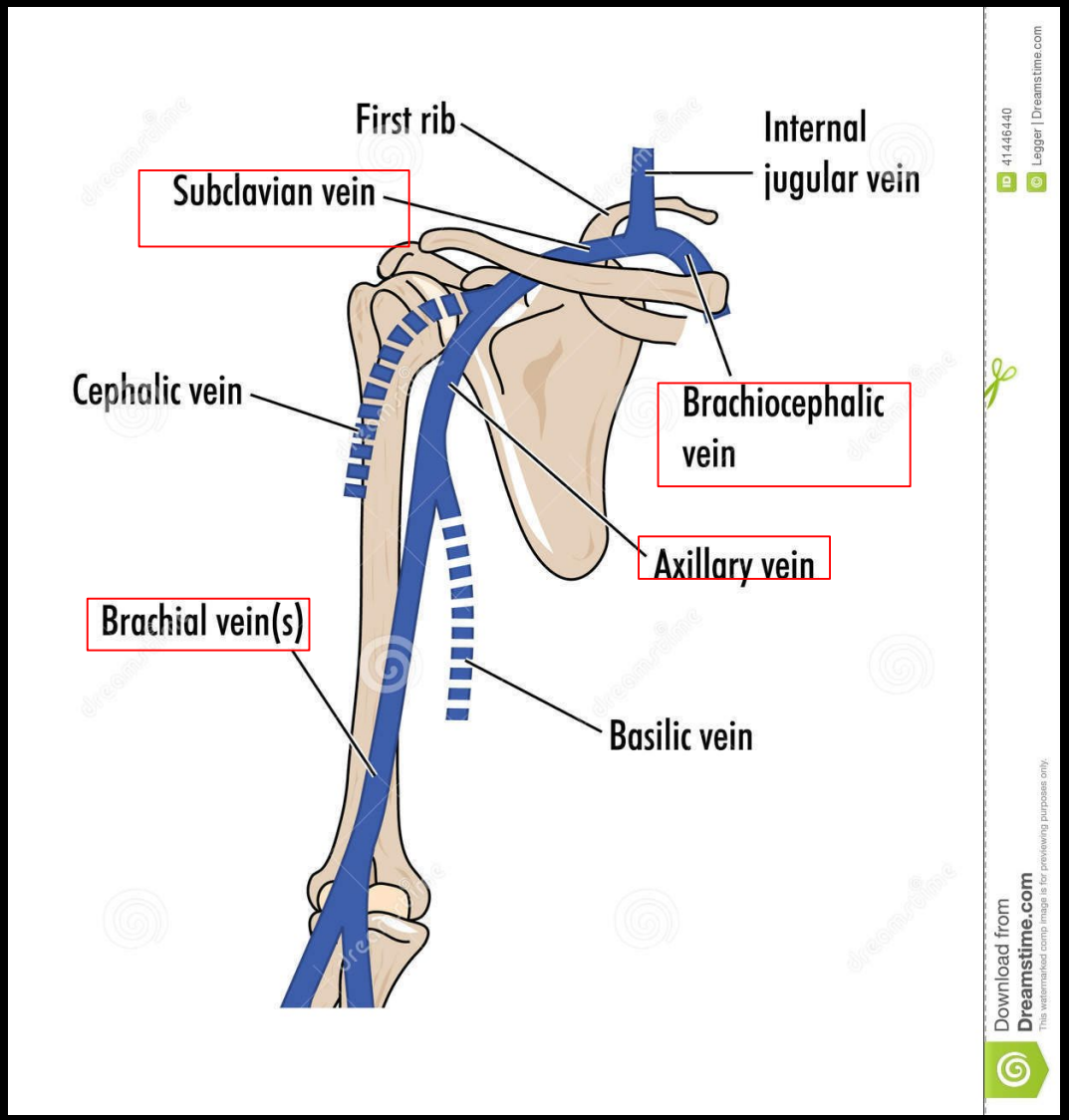

AXILLARY ARTERY
MUSCULO-CUTANEUS NERVE
MEDIAN NERVE
ANTERIOR CIRCUMFLEX
DELTOID
CEPHALIC
AXILLARY
BRACHIAL
CORACO-BRACHIALIS
BASILIC
MEDIAN N.
LATISSIMUS DORSI
SUBSCAPULARIS
PECTORALIS MINOR
3RD RIB
COSTOAXILLARY
SUBSCAPULAR
LONG THORACIC
COSTOAXILLARY



Upper Extremity Thrombosis

- Therapy: PICC Catheter
  - Key is removing catheter
  - No new one for at least 10 days
  - Benefit of anticoagulation uncertain
    - 25% rate of bleeding
  - Remember many are superficial thrombosis





Upper Extremity Thrombosis

- Therapy: Non-PICC Catheter
  - Line can be removed
    - –Assess need for anticoagulation
    - –Substantial rate of bleeding
      - » 5% major bleeding
  - Line cannot be removed
    - –3 months anticoagulation
    - –High rates of serious bleeding

Upper Extremity Thrombosis

- "Spontaneous"
  - 3 months anticoagulation
  - Look for underlying vascular defects
  - Consider thrombolytic therapy
    - ~75% with underlying lesions

Portland Portal Vein Protocol

Portal Vein: Cirrhosis

- Incidental
  - SMV negative – no treat
  - SMV involved - treat
- Symptomatic – treat

Noncirrhotics: Symptomatic

- Provoked
  - Surgery
  - Infection, etc.
    - Treatment: 3 months
    - Work-up: not recommended
- Unprovoked
  - PNH, MPS, APLA
  - Indefinite anticoagulation

2017 Meta-Analysis

- 8 studies with 353 patients
- Recanalization
  - 71% vs 42%
- Complete recanalization
  - 53% vs 33%
- PVT progression
  - 9% vs 33%
- Bleeding
  - 11% vs 11%
- Gastro 153:480, 2017

2021 Update: DOAC & PVT

- DOAC vs Warfarin
  - Increased PVT recanalization – RR = 1.67
  - Decreased progression – RR = 0.14
- Anticoagulation in PVT
  - Increased PVT recanalization – OR 4.29
  - Decreased progression – OR 0.26
  - Bleeding slightly up – OR 1.16

Dig Liver Dis 2022 Jan;54(1):56-62
Hepatol Int 2021 Dec;15(6):1356-1375

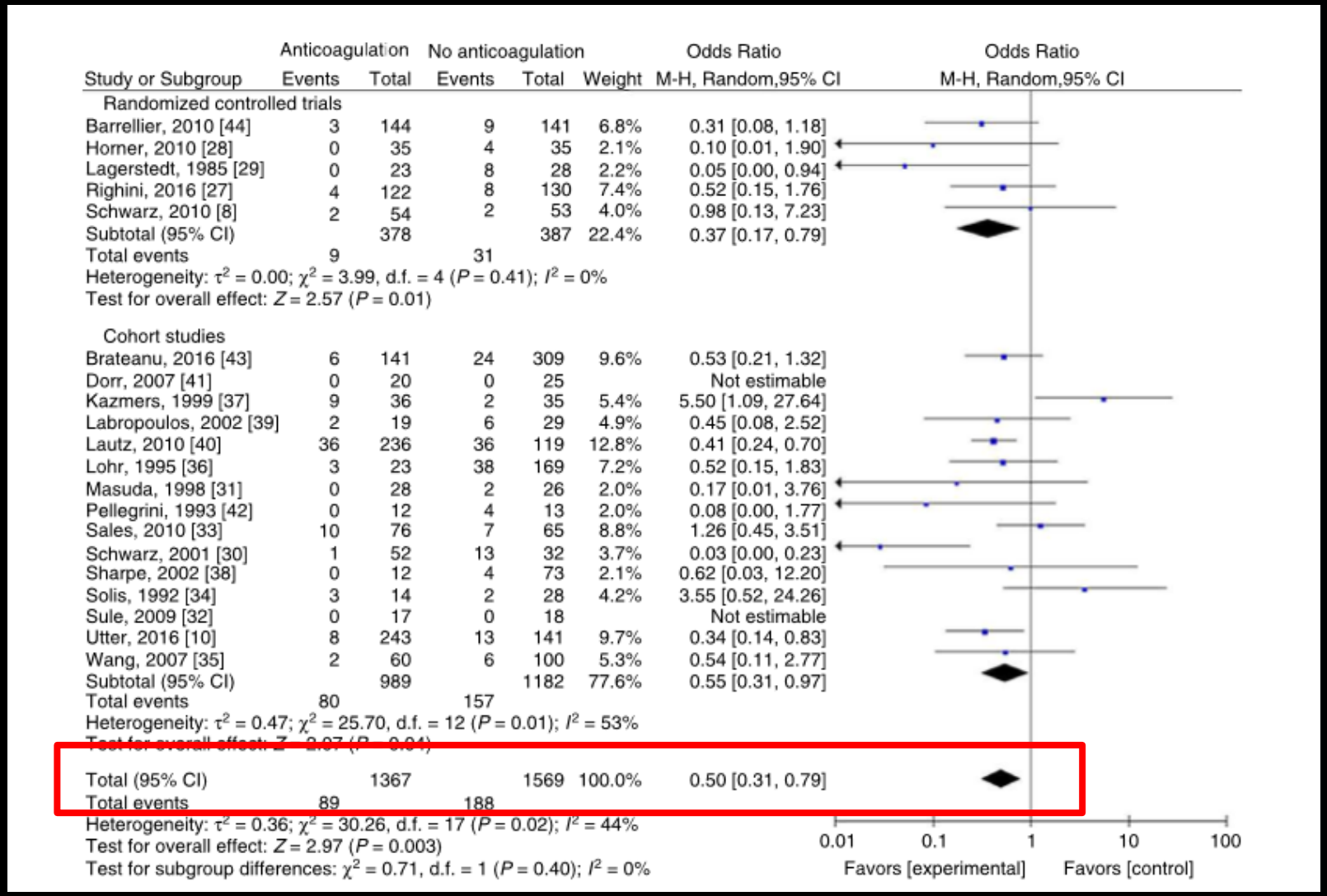
DOAC in PVT

- Increasing data on safety in liver disease
  - Easier to use
  - Less bleeding
- Drug of choice: apixaban
- Exception Child C
  - Case by case basis

Calf Vein Thrombosis

- High risk of progression
  - Up to 10% progression
  - PE rate 2-3%
- **12 weeks** therapy for most patients

Calf Vein Thrombosis Therapy



Study or Subgroup	Anticoagulation Events	Total	No anticoagulation Events	Total	Weight	Odds Ratio M-H, Random,95% CI
Randomized controlled trials						
Barrellier, 2010 [44]	3	144	9	141	6.8%	0.31 [0.08, 1.18]
Horner, 2010 [28]	0	35	4	35	2.1%	0.10 [0.01, 1.90]
Lagerstedt, 1985 [29]	0	23	8	28	2.2%	0.05 [0.00, 0.94]
Righini, 2016 [27]	4	122	8	130	7.4%	0.52 [0.15, 1.76]
Schwarz, 2010 [8]	2	54	2	53	4.0%	0.98 [0.13, 7.23]
Subtotal (95% CI)		378		387	22.4%	0.37 [0.17, 0.79]
Total events	9		31			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.99$, d.f. = 4 ($P = 0.41$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.57$ ($P = 0.01$)						
Cohort studies						
Brateanu, 2016 [43]	6	141	24	309	9.6%	0.53 [0.21, 1.32]
Dorr, 2007 [41]	0	20	0	25		Not estimable
Kazmers, 1999 [37]	9	36	2	35	5.4%	5.50 [1.09, 27.64]
Labropoulos, 2002 [39]	2	19	6	29	4.9%	0.45 [0.08, 2.52]
Lautz, 2010 [40]	36	236	36	119	12.8%	0.41 [0.24, 0.70]
Lohr, 1995 [36]	3	23	38	169	7.2%	0.52 [0.15, 1.83]
Masuda, 1998 [31]	0	28	2	26	2.0%	0.17 [0.01, 3.76]
Pellegrini, 1993 [42]	0	12	4	13	2.0%	0.08 [0.00, 1.77]
Sales, 2010 [33]	10	76	7	65	8.8%	1.26 [0.45, 3.51]
Schwarz, 2001 [30]	1	52	13	32	3.7%	0.03 [0.00, 0.23]
Sharpe, 2002 [38]	0	12	4	73	2.1%	0.62 [0.03, 12.20]
Solis, 1992 [34]	3	14	2	28	4.2%	3.55 [0.52, 24.26]
Sule, 2009 [32]	0	17	0	18		Not estimable
Utter, 2016 [10]	8	243	13	141	9.7%	0.34 [0.14, 0.83]
Wang, 2007 [35]	2	60	6	100	5.3%	0.54 [0.11, 2.77]
Subtotal (95% CI)		989		1182	77.6%	0.55 [0.31, 0.97]
Total events	80		157			
Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 25.70$, d.f. = 12 ($P = 0.01$); $I^2 = 53\%$						
Test for overall effect: Z = 2.07 (P = 0.04)						
Total (95% CI)		1367		1569	100.0%	0.50 [0.31, 0.79]
Total events	89		188			
Heterogeneity: $\tau^2 = 0.36$; $\chi^2 = 30.26$, d.f. = 17 ($P = 0.02$); $I^2 = 44\%$						
Test for overall effect: $Z = 2.97$ ($P = 0.003$)						
Test for subgroup differences: $\chi^2 = 0.71$, d.f. = 1 ($P = 0.40$); $I^2 = 0\%$						

Journal of Thrombosis and Haemostasis, **15**: 1142–1154

Calf Vein Thrombosis Therapy

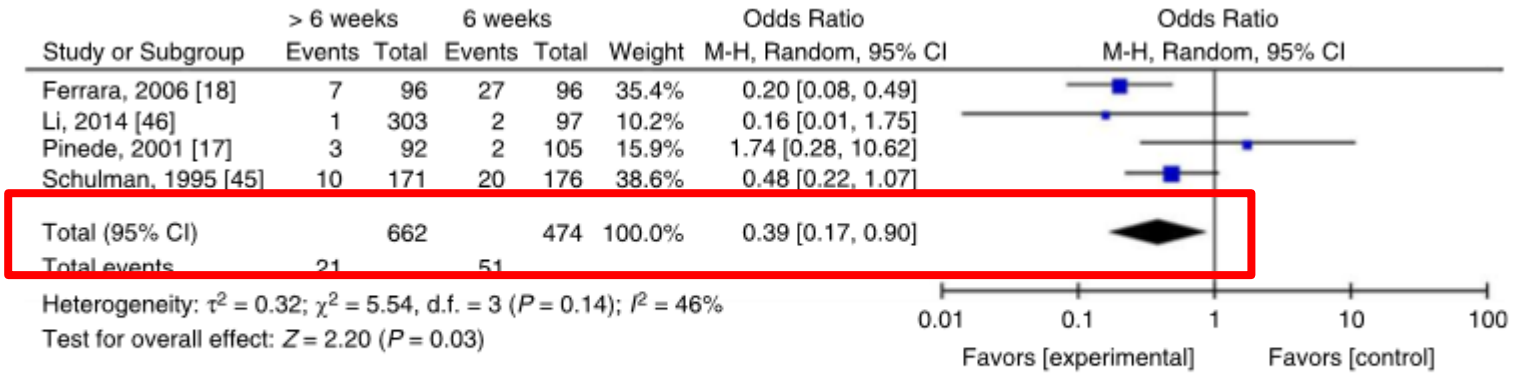


Fig. 6. Recurrent venous thromboembolism in patients receiving anticoagulant treatment for > 6 weeks versus 6 weeks. CI, confidence interval; d.f, degrees of freedom; M-H, Mantel-Haenszel. [Color figure can be viewed at wileyonlinelibrary.com]

Journal of Thrombosis and Haemostasis, **15**: 1142–1154

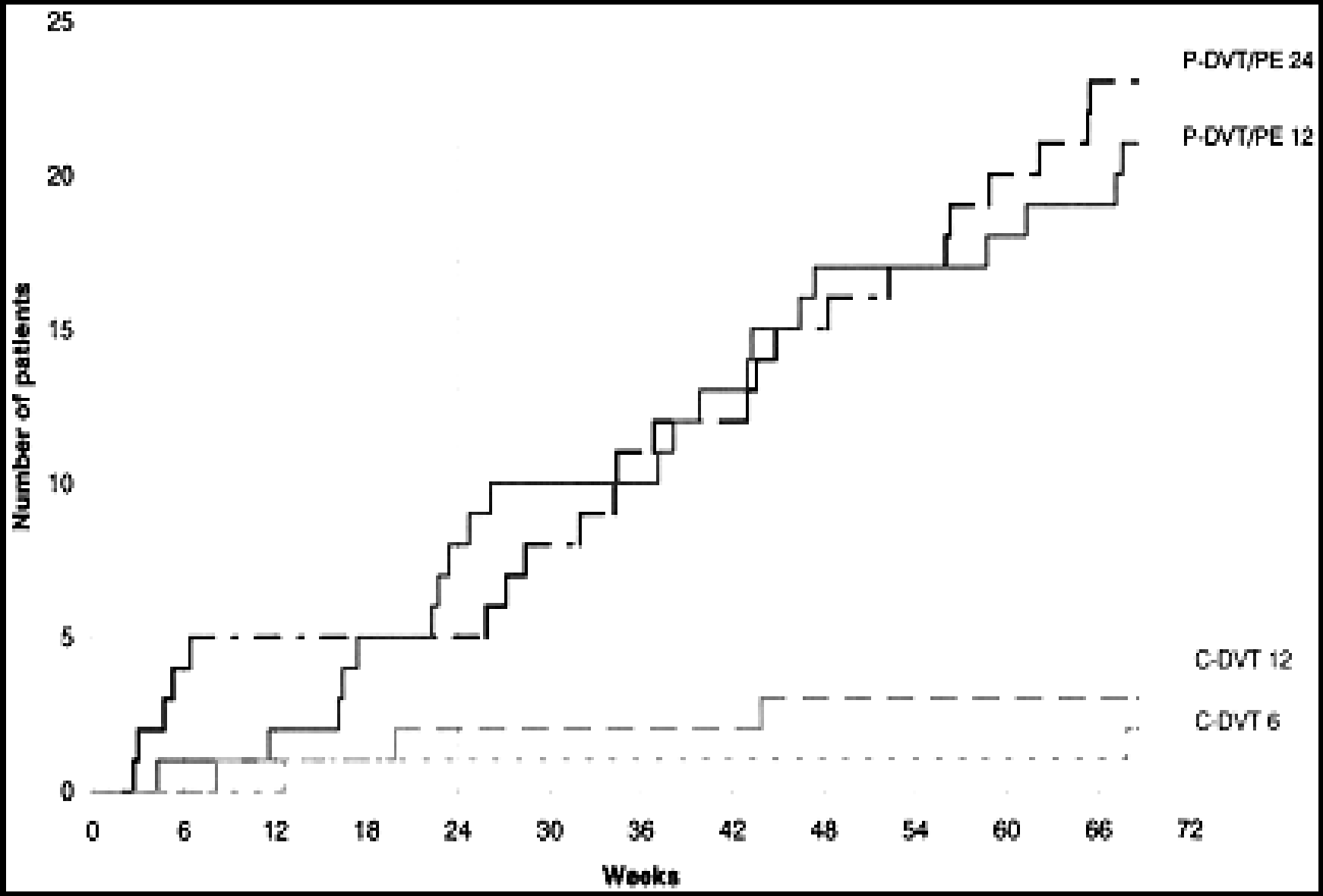
Distal DVT Trial

- Rivaroxaban 6 vs 12 weeks
- N = 400
- rDVT 6: 15% 12:8%
- No major bleeding
- BMJ. 2022 11 23; 379:e072623

Duration of Therapy: Proximal DVT

- 3 months
  - Provoked DVT
    - Especially estrogen related
- No benefit with 6 months except more bleeding
- Obtain scan at end of therapy for new baseline
  - J Thromb Haemost. 2011 Dec;9(12):2406-10

Proximal DVT



Circulation, May 2001; 103: 2453 - 2460.

Duration of Therapy

- What is an Idiopathic Thrombosis?
  - No trauma, surgery or hospital stay for 1-3 months
  - No estrogens
  - No long travel (> 4 hours)
  - No cancer or major risk factors
  - Exact definition controversial

1st Idiopathic VTE

- High rates (30-40%) of recurrence off anticoagulation
- Multiple RCTs show benefit of long term anticoagulation
  - Marked increase in recurrence when stopping anticoagulation

BMJ 2019 Meta-analysis

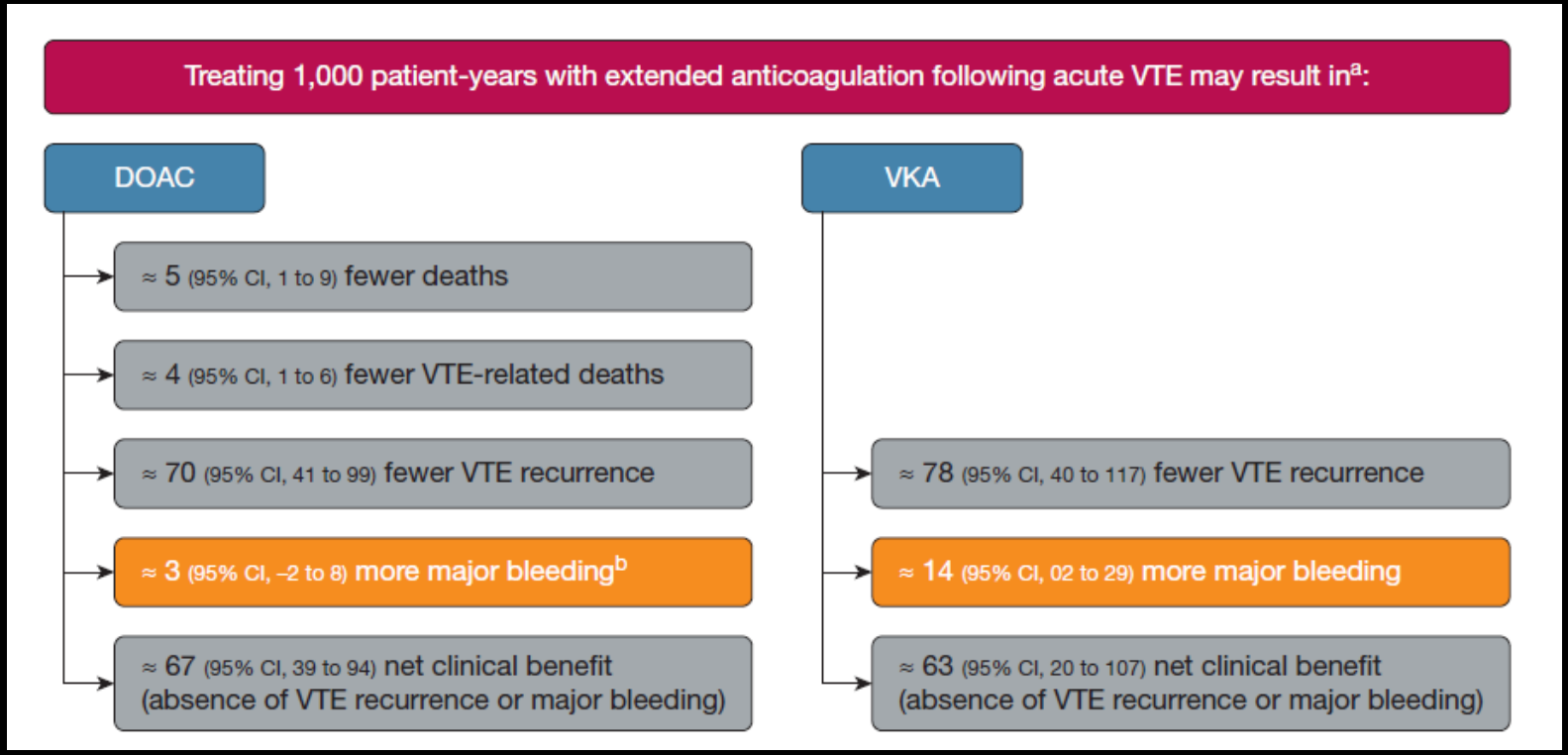
Year	Risk	Cumulative Incidence
1 Year	10.3%	-
2 year	6.3%	16%
3-5 years	3.8%/year	25% 5 years
6-10 years	3.1/year	36% 10 years

Case fatality rate for recurrence 4%

Distal thrombosis 1/10th of risk

BMJ 2019: 366:4364

Extended Therapy



Chest 155:1199-1216, 2019

Two Phases of VTE Therapy

- Active phase (3 months)
  - Prevents reactivation of initial thrombosis
- Secondary prevention (> 3 months)
  - Prevents new thrombosis
  - Need to identify patients who will benefit

- J Thromb Haemo 2012: 10: 507–5

D-Dimers

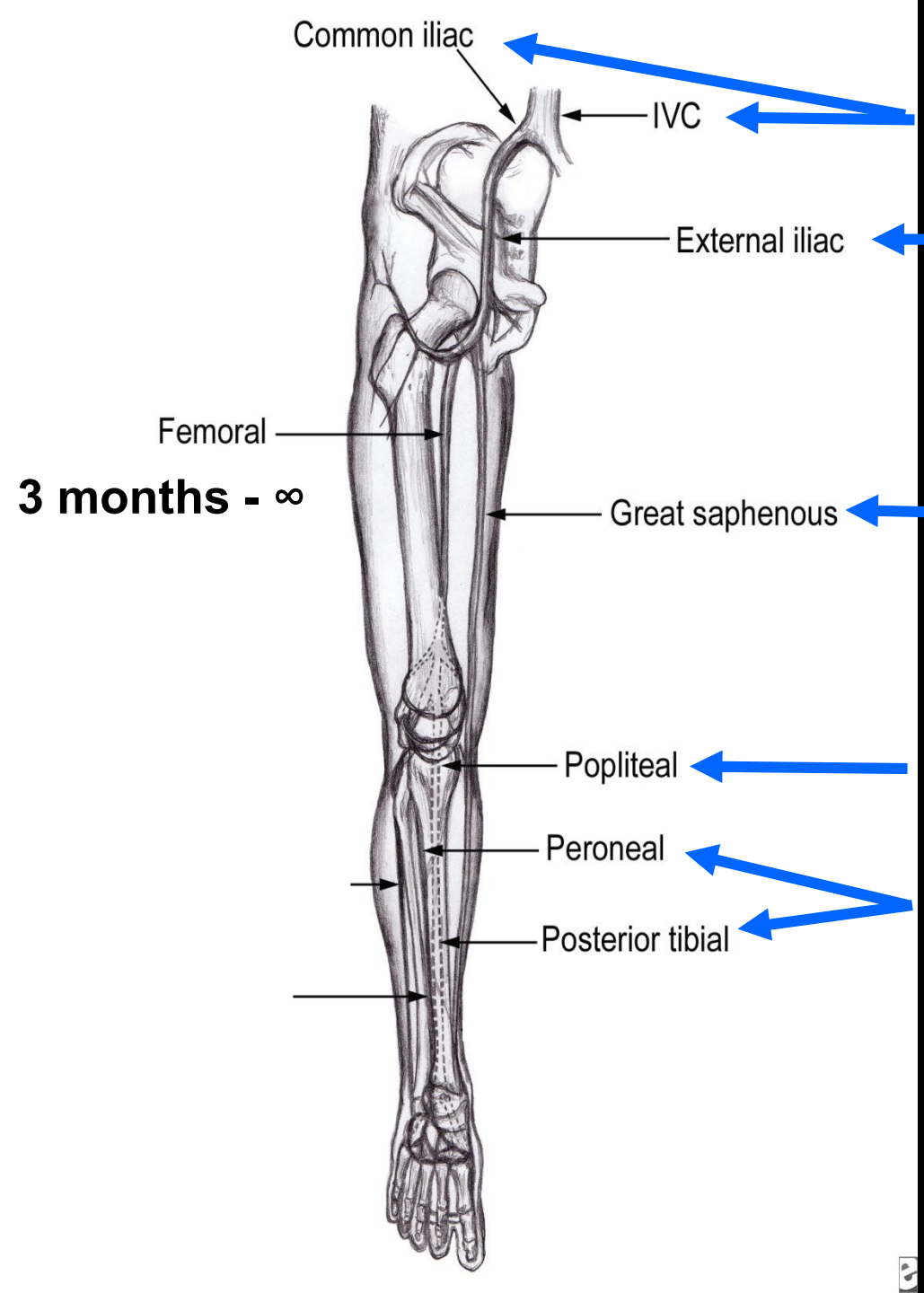
- D-dimers checked off therapy to predict risk
- Meta-analysis
  - 7 studies
  - Positive D-Dimer: 10%/yr
  - Negative D-Dimer: 2.9 - 4.0%/yr
- Unclear if repeat testing helps
- Most recent study showed high rates of recurrence with negative D-dimer 5%/yr

Idiopathic VTE

- No good prediction rules
  - Negative D-dimer - NOT predictive
  - Thrombus resolution – NOT predictive
- Still need better prediction rules!
- Safer anticoagulants is shifting balance toward longer treatment

Duration of Therapy

- Indefinite
  - >1 DVT (except upper ext)
  - Acquired hypercoagulable states
  - Idiopathic unusual site
  - Idiopathic severe pulmonary embolism
- 3 months
  - Provoked pulmonary embolism


Common iliac
IVC
External iliac
Femoral
3 months - ∞
Great saphenous
Popliteal
Peroneal
Posterior tibial
3 months - ∞
3 months - ∞
14 days
(prophylactic dose)
3 months - ∞
3 months

What about Hypercoagulable States?

- Testing not recommend
  - Provoked thrombosis
  - Arterial thrombosis (inherited thrombophilia)
  - Upper extremity
  - Distal thrombosis
  - Superfical thrombosis

DOACs

- Robust randomized trial data for all new anticoagulants
- Now recommend by ACCP/ASH first line over warfarin
- Irreversibility = Myth
  - Less need to reverse
  - No difference in bleeding outcomes in multiple studies

DOAC in VTE

- Recurrent VTE: 0.90 (0.77-1.06)
- Major bleeding: 0.74 (0.59-0.85)
- ICH: 0.37 (0.21-0.68)
- Fatal bleeding: 0.36 (0.15-0.84)

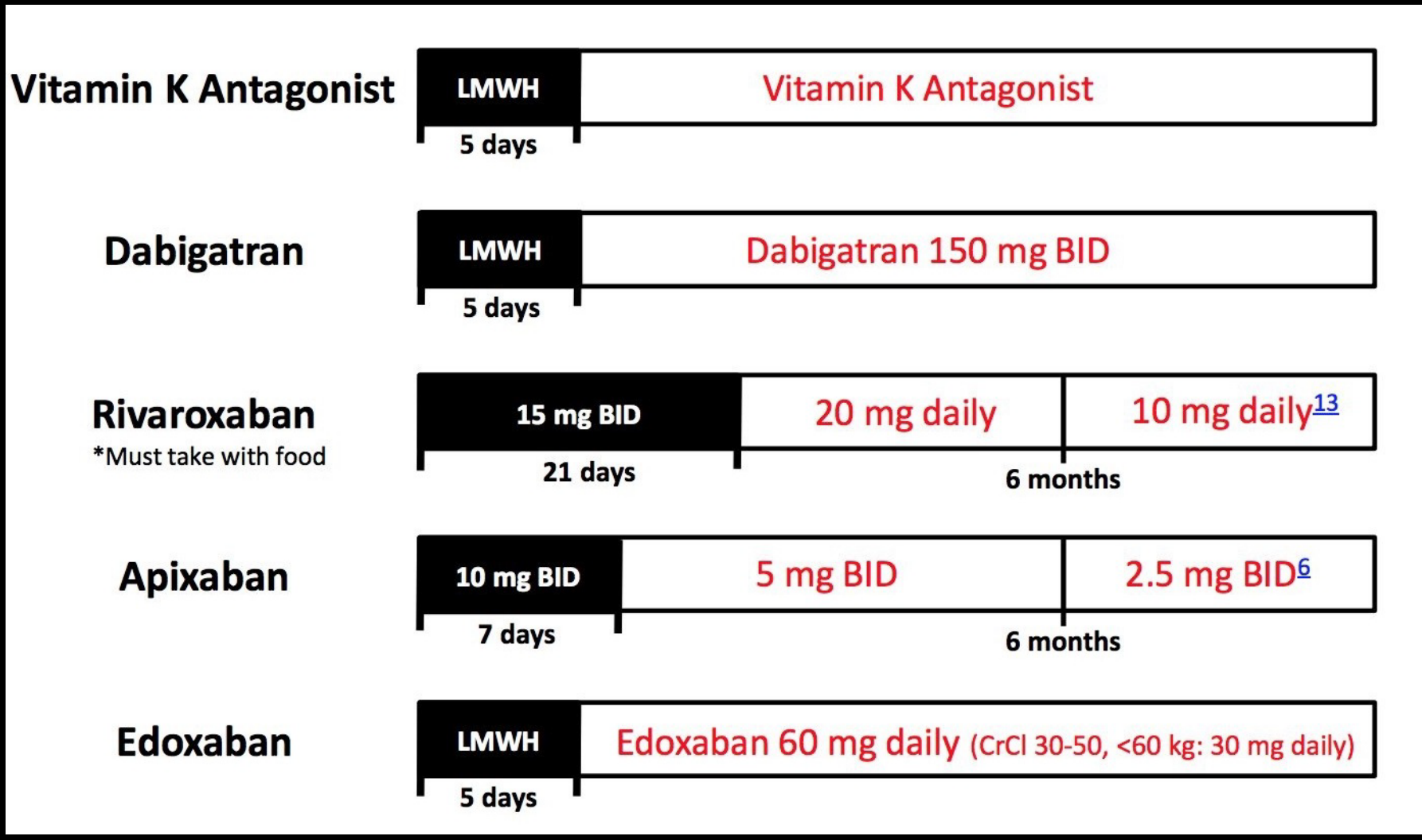
Blood 2014;124(12):1968-1975

Eur J Vasc Endovasc Surg. 2014 Nov;48(5):565-575.

Venous Thrombosis

Drug	Heparin First?	Thrombosis	Bleeding
Apixaban	No*	Equal	Safer
Dabigatran	Yes	Equal	Equal
Edoxaban	Yes	Equal	Safer
Rivaroxaban	No*	Equal	Safer

*Apixaban 10mg bid x 7 days then 5mg BID
*Rivaroxaban 15mg bid x 21 days then 20mg daily


Vitamin K Antagonist
LMWH
5 days
Vitamin K Antagonist
Dabigatran
LMWH
5 days
Dabigatran 150 mg BID
Rivaroxaban
*Must take with food
15 mg BID
21 days
20 mg daily
6 months
10 mg daily[13]
Apixaban
10 mg BID
7 days
5 mg BID
6 months
2.5 mg BID[6]
Edoxaban
LMWH
5 days
Edoxaban 60 mg daily (CrCl 30-50, <60 kg: 30 mg daily)

Lower Dose DOACs?

- Older data for lower doses in chronic therapy of VTE
  - LMWH
  - Ximelagatran
  - Did not work for warfarin

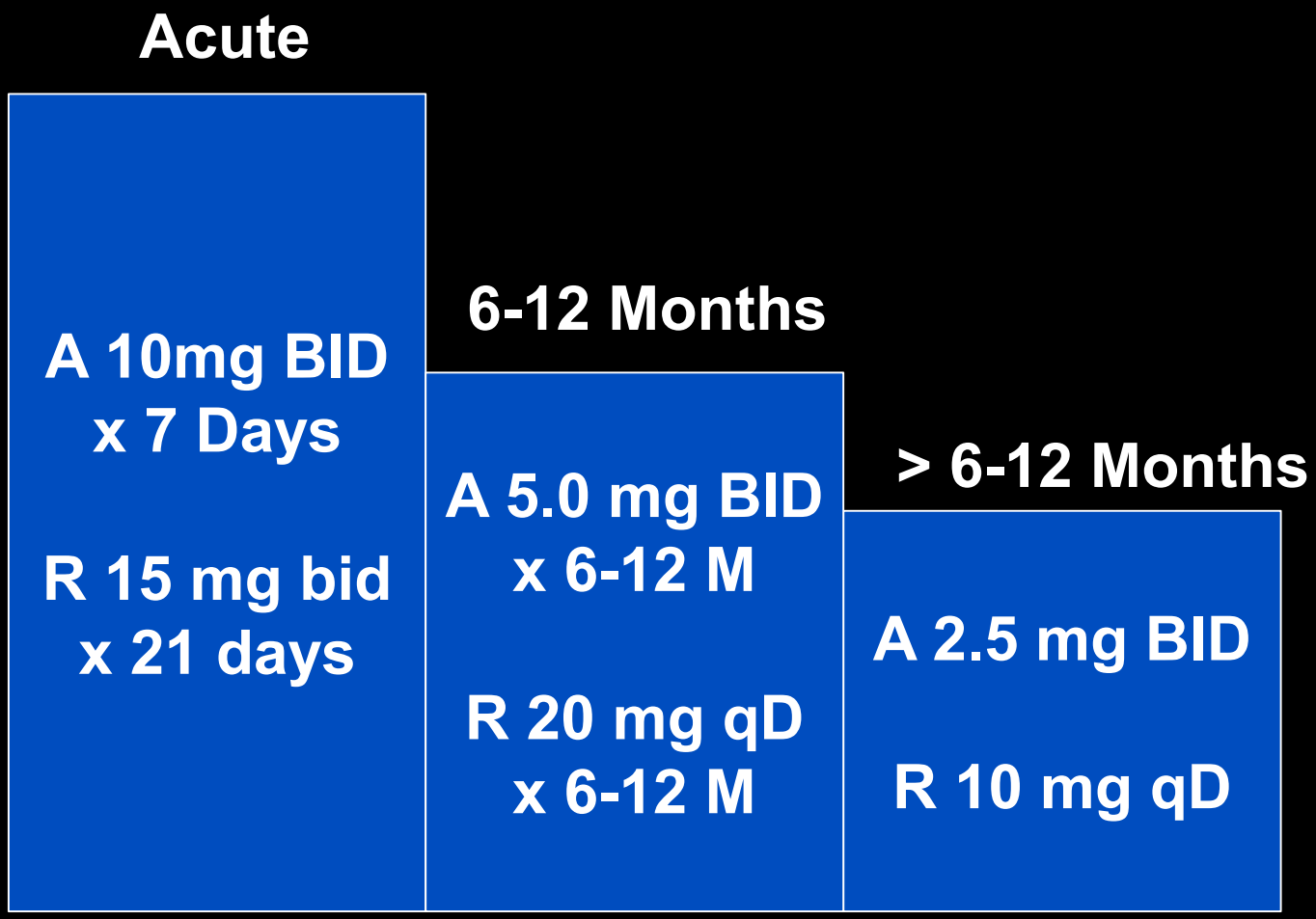
Low Dose DOAC

- Two trials
  - Rivaroxaban 20mg vs 10mg
  - Apixaban 5mg vs 2.5 mg
- Start 6-12 months after VTE
- No difference in VTE or bleeding
  - Trend toward reduce major bleeding

Lower Dose Therapy

- Only for chronic venous thrombosis!!
- NOT
  - Atrial fibrillation
  - Cancer
  - Bad thrombophilia
  - Visceral vein thrombosis

DOAC VTE Stepped Care



DOACs in Cancer

- Advantages
  - Few drug no food interactions
  - Short half-life
  - Not a shot
- Warfarin inferior to LMWH
  - Increase thrombosis
- Less than 33% of cancer patients on LMWH

Cancer

- 4 RCT: DOAC vs LMWH
- Recurrence: HR 0.62 (sig)
- Major Bleeding: HR 1.33 (NS)
- Relevant bleeding: HR 1.58 (sig)

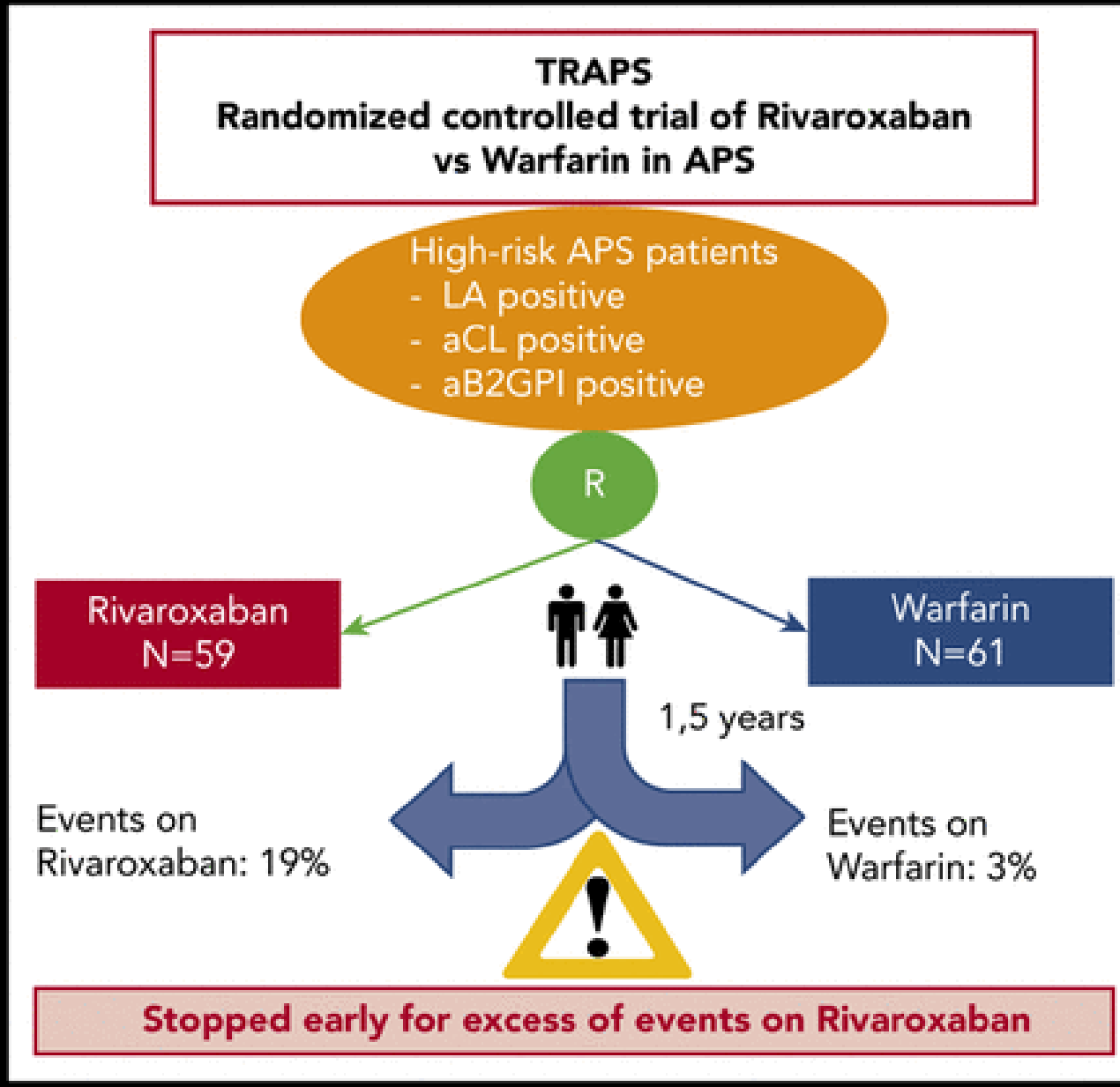
- Tao DL, Eur J Haem 2020

Cancer

- DOACs now front line
- Reserve LMWH for break through thrombosis
- GI bleeding issue
  - Less with apixaban

Who NOT to use New Anticoagulants

- Triple positive APLA
- Mechanical Valves
- Rheumatic Valvular disease
- < 50 or > ??? kg

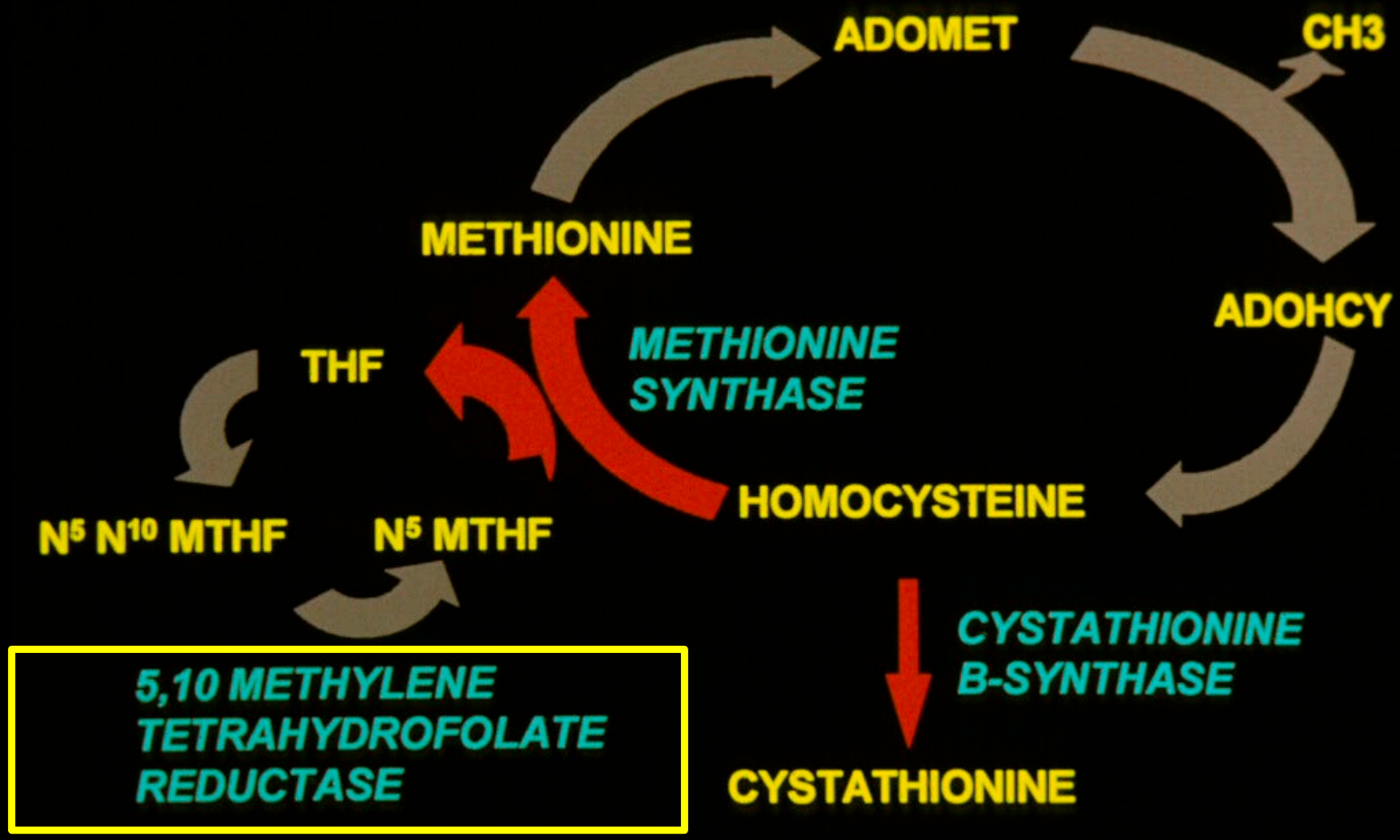

TRAPS
Randomized controlled trial of Rivaroxaban vs Warfarin in APS
High-risk APS patients
- LA positive
- aCL positive
- aB2GPI positive
R
Rivaroxaban N=59
Warfarin N=61
1,5 years
Events on Rivaroxaban: 19%
Events on Warfarin: 3%
Stopped early for excess of events on Rivaroxaban

Direct Oral Anticoagulants

- First line therapy for VTE
- Simplified management
- But
  - Patients still need close follow-up
  - Still need to manage anticoagulants
  - Expense an issue

Thrombophilia

- MTHFR
- APLA


ADOMET
CH3
METHIONINE
ADOHCY
THF
METHIONINE SYNTHASE
HOMOCYSTEINE
N5 N10 MTHF
N5 MTHF
CYSTATHIONINE B-SYNTHASE
5,10 METHYLENE TETRAHYDROFOLATE REDUCTASE
CYSTATHIONINE

MTHFR C667T

Genotype	- Hcy (nmol/ml)
-/-	11.04
+/-	11.03
+/+	13.28*

*P<0.01

Table 1. Prevalence of the MTHFR 677 C-to-T Mutation (Table view)

		MTHFR Genotype*†			
Study Group†	n	Ala/Ala, %	Ala/Val, %	Val/Val, %	Val Allele, %†
Peripheral vascular disease	247	114 (46)	111 (45)	22 (9)	31
Healthy blood donors	170	65 (38)	77 (45)	28 (17)	39
Canadian neonates	293	125 (43)	122 (42)	46 (15)	36
Hospital/laboratory control subjects	133	50 (38)	63 (47)	20 (15)	39

DeLoughery, Circulation. 1996;94:3074–3078

But……

- RCT of lower homocysteine uniformly negative
- Good studies show no relationship between MTHFR and thrombosis
- Hcy more of reflection of inflammation and endothelial damage

MTHFR not Associated with VTE

OR for 1st VTE for CT and TT vs nl MTHFR genotype

MTHFR genotype	Homocysteine; geometric mean* (±SE) (mmol/l)	Cases $n = 507$	Controls $n = 1430$	OR†	95% CI
CC (wild type)	13·69 (±1·01)	255 (50)	726 (51)	1	reference
CT (heterozygote)	14·34 (±1·01)	208 (41)	582 (41)	1·01	0·81–1·25
TT (homozygote)	16·35 (±1·04)	44 (9)	122 (8)	1·02	0·70–1·49

*Calculated in the controls.
†Adjusted for age (5-year age bands) and sex.

"polymorphisms" not "mutations"

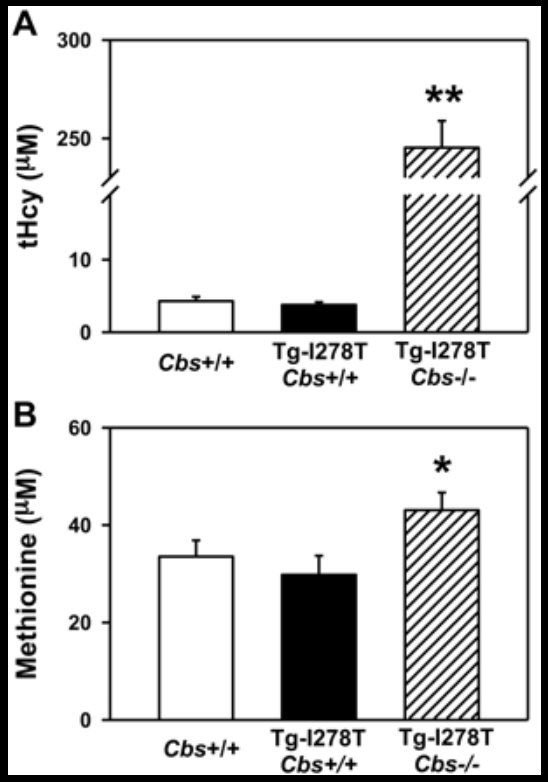
HUNT2: prospective case control of 66,140 Norwegians
505 VTE cases identified, 1458 matched controls
Serum homocysteine level and MTHFR C677T genotype not associated with VTE **Also: Bezemer, Arch Int Med 2007**

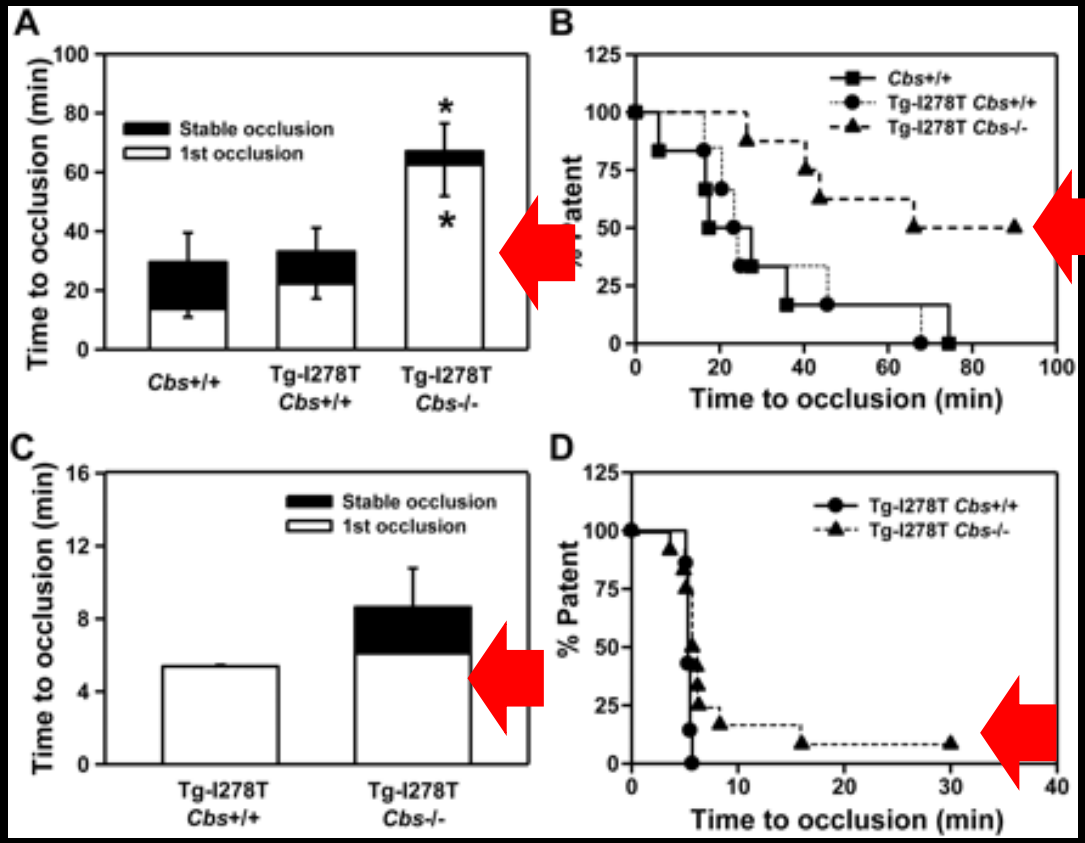
Naess, BJH 2008

A call to action: MTHFR polymorphisms should not be a part of inherited thrombophilia testing

Thomas G. Deloughery MD, MACP, FAWM[1] | Beverley J. Hunt OBE[2] | Geoffrey D. Barnes MD, MSc[3] | Jean M. Connors MD[4] | The WTD Steering Committee

Res Pract Thromb Haemost. 2022 May; 6(4): e12739.





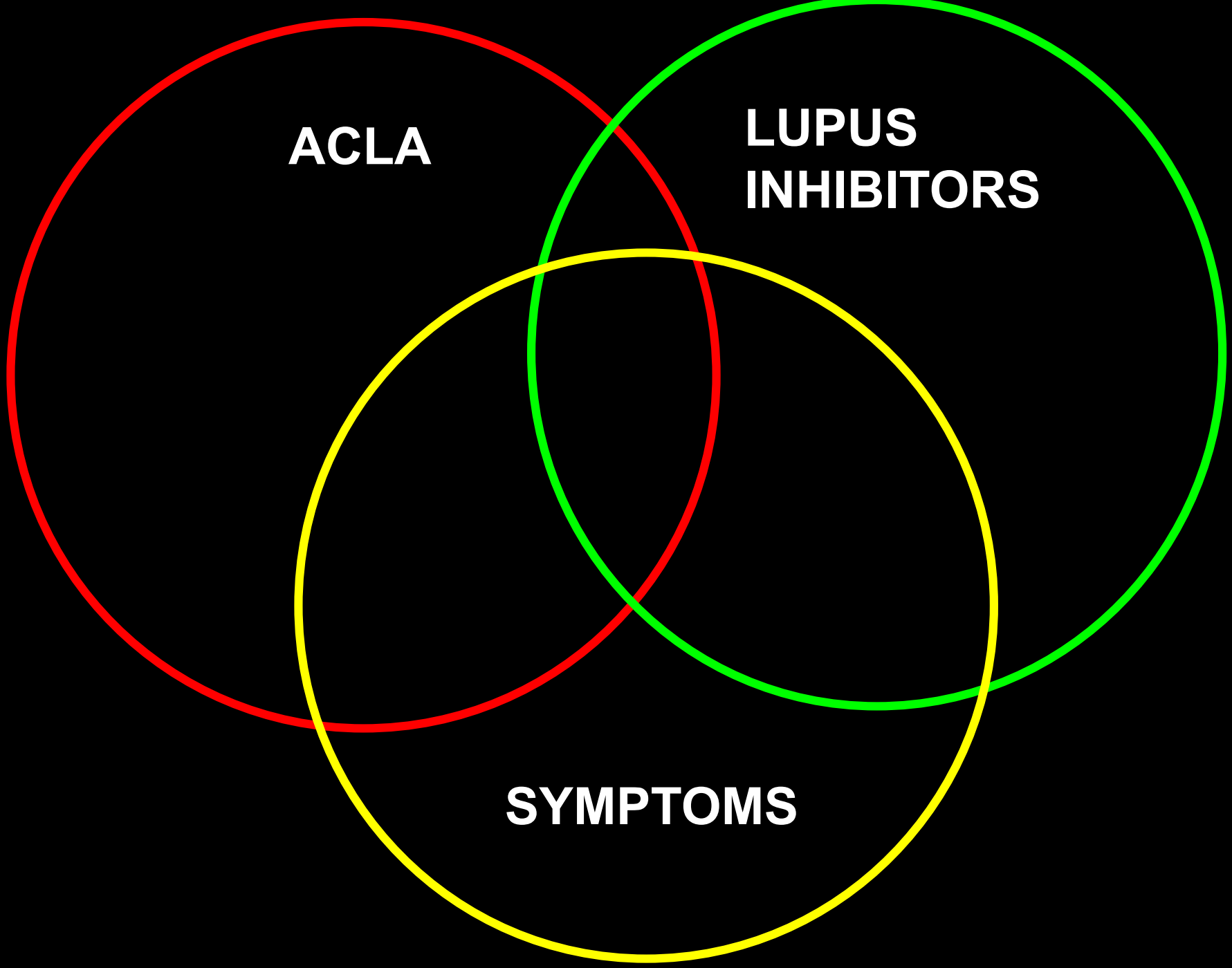
Blood. 2012 Mar 29;119(13):3176-83

Bottom Line

- Hcy not a part of thrombophilia work-ups
- NEVER check MTHFR

How do We Test for APLA?

- Screening aPTT inadequate
- Different APLA behave differently in tests
- Only 60% of ACLA and lupus inhibitors overlap


ACLA
LUPUS
INHIBITORS
SYMPTOMS

Testing for APLA

- Anticardiolipin antibodies
  - ELISA assay
- Antiβ2glycoprotien antibodies
  - ELISA
- Coagulation based test:
  - All based on demonstrating phospholipid dependent antibodies

Anticardiolipin Antibodies

- Based on observation of false positive VDRL
- Laboratory dependent
- Common in older patients
- Low titer ACLA very common (~20-30%)
- High titers predictive of recurrent events
  - How high > **40 units (>99th percentile)**
- Anti-β2 glycoprotein antibodies more predictive??

Testing Strategy

- Get total set
  - dRVVT
    - Ratio is key number
  - Hexagonal
  - Anticardiolipin antibody
  - Antiβ2glycoprotien

Need to Repeat Test

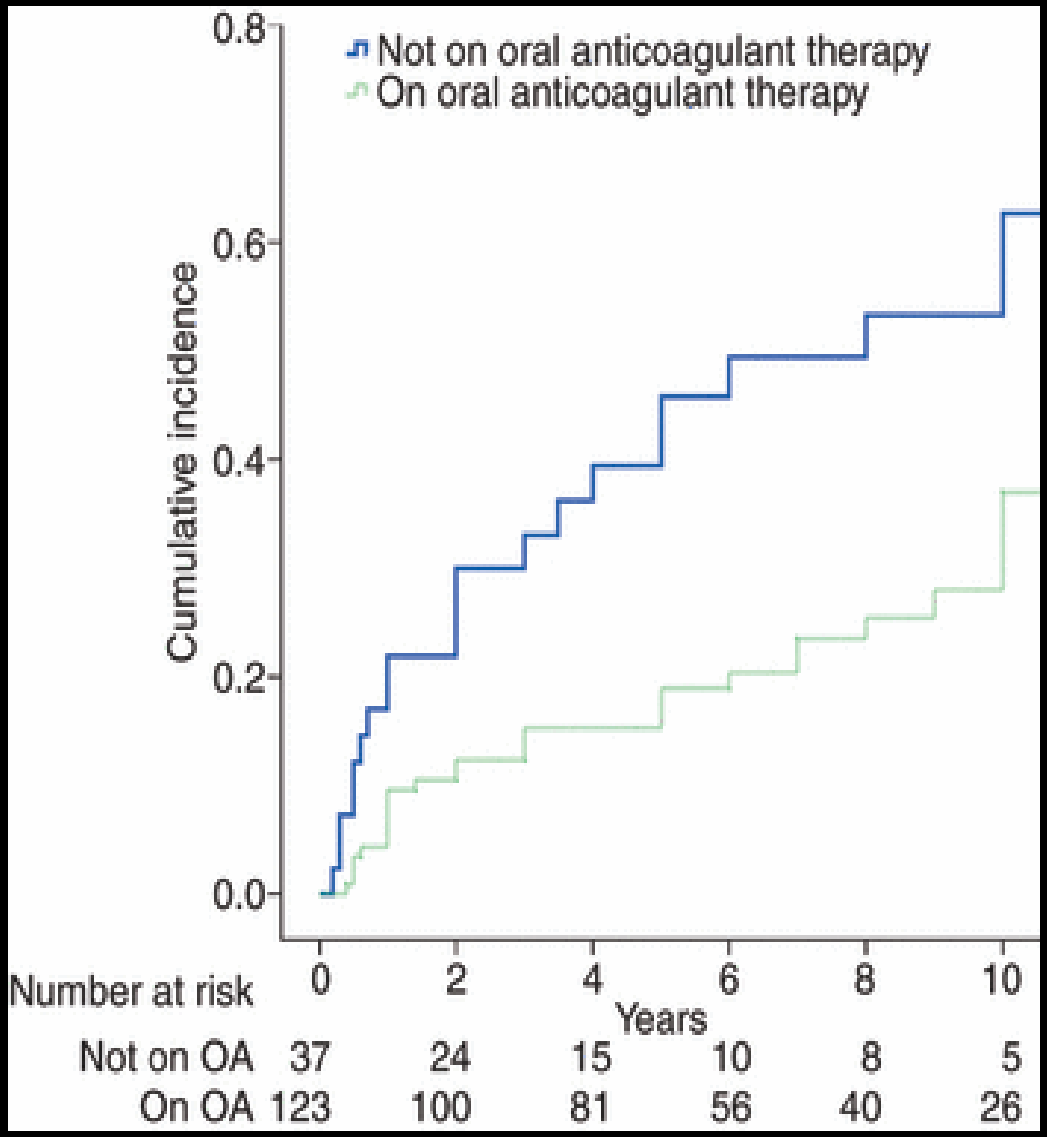
- Triple positive – 98% confirmed
- Double positive – 84% confirmed
- Single positive – 40% confirmed
- Note
  - No LA only confirmed
    - Can be falsely high due to CRP
  - ACLA and Aβ2GP same isotype

Is The APLA Significant?

- More significant if:
  - Good history
  - Younger patient
  - Lupus inhibitor
  - High titer ACLA
  - Positive dRVVT
  - Multiple tests positive

Triple Postive

- LA, ACLA and Aβ2GP positive
  - Same isotype (IgG, etc)
- High risk of recurrance
- High risk of first event
- Higher risk of warfarin refractoriness



Journal of Thrombosis and Haemostasis 8:237-242, 2010

Burn Point #1

- Diagnosis is based on 99th percentile and not lab listed as “abnormal”
- Labs have wildly different 99th percentile and reference ranges
- Know you lab!

ACLA

Cardiolipin IgA Antibody:
0 - 19 CU Negative
>=20 CU Positive
Cardiolipin IgG Antibody:
0 - 19 CU Negative
20 - 94 CU Low Positive
>= 95 CU Moderately to High Positive
Cardiolipin IgM Antibody:
0 - 19 CU Negative
20 - 30 CU Low Positive
>= 31 CU Moderately to High Positive

REFERENCE VALUES

Negative < or =30.0 U
Borderline 30.1-40.0 U
Positive > or =40.1 U

Cardiolipin Antibody, IgG

Effective November 15, 2021

<=14 GPL	Negative
15-19 GPL	Indeterminate
20-80 GPL	Low to Moderately Positive
81 GPL or above	High Positive

AB2GP

Negative <20 CU

Positive >=20 CU

<15.0 U/mL (negative)
15.0-39.9 U/mL (weakly positive)
40.0-79.9 U/mL (positive)
> or =80.0 U/mL (strongly positive)
Results are expressed in arbitrary units.
Reference values apply to all ages.

Burn Point #2

- Persistent
  - Need to demonstrate APLA persists over time (same test)

Burn Point #3

- Direct Oral Anticoagulants
  - All will mess up lupus inhibitors!
  - Many labs do not screen for!
  - Increasing cause of false positive APLA

What I Talked About

- Therapy of VTE
- Duration of anticoagulation
- Thrombophilia work-ups