UC San Diego Health

Contemporary Management of Venous Thromboembolic Events (VTEs)

William Pearse, MD

03/06/2024

University of California – San Diego

General Internal Medicine Grand Rounds

UC San Diego Health

Today's Goals

- Accurately define typical venous anatomy, principles of coagulation, and clinical factors that influence thrombogenesis.
- Summarize the clinical evaluations for diagnosing VTEs
- Recognize current anticoagulation medications, dosages, and durations of therapy for patients with various VTEs
- Understand indications for potential involvement with interventional subspecialties
- Discuss the importance of shared decision making in longitudinal VTE management

UC San Diego Health

Disclosures

- I have no personal financial disclosures or consulting interests with third party agencies or proprietary entity producing healthcare goods or services

- I receive research funding from the following:
  - ADC Therapeutics, AstraZeneca, Seattle Genetics: Institutional PI on industry-sponsored trial
  - Epizyme: Collaborating PI on industry-sponsored trial

UC San Diego Health

Venous Thromboembolic Events (VTEs)

- Epidemiology
  - Large burden of disease
    - 600,000 VTEs diagnosed annually in USA
      - 270,000 PEs/year
    - Annual incidence: 80/100,000 person
  - Mortality
    - 100,000 deaths per year
    - Pulmonary embolism
      - “Massive PE”: 30% mortality
      - 4% 30-day mortality; 13% 1-year mortality
      - 5-year cumulative mortality rate is 30%
        - Only 5% will die from recurrent PE
  - Low public awareness

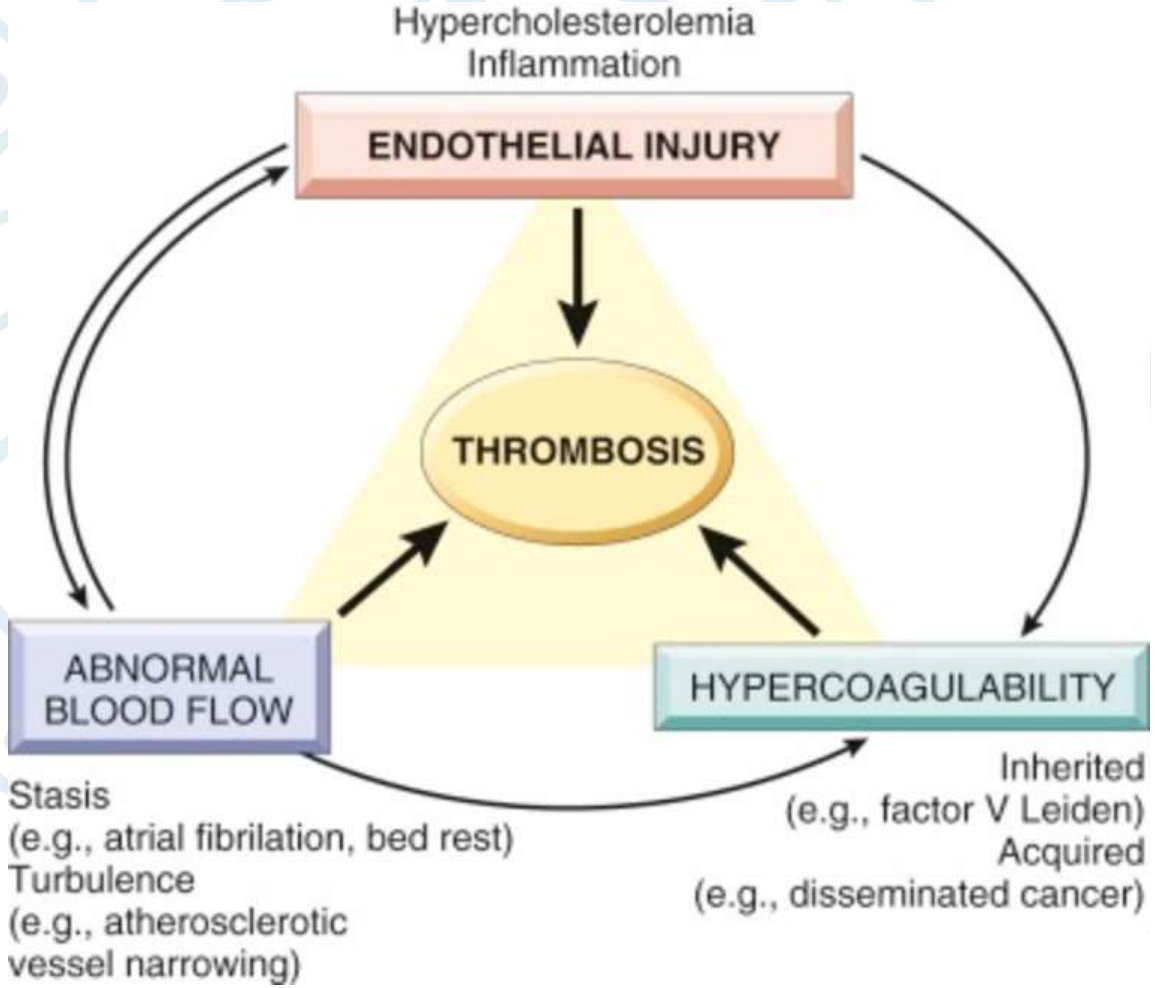
- Types of Venous Clots
  - Proximal Deep Venous Thrombosis
  - Distal Deep Venous Thrombosis
  - Superficial Thrombosis
  - Pulmonary Embolism
  - Splanchnic Vessel Thrombosis
    - Portal Vein Thrombosis
    - Superior Mesenteric Vein Thrombosis
  - Cerebral Venous Sinus Thrombosis

Heit J Thromb Thrombolysis (2016) 41:3–14

UC San Diego Health

Thrombogenesis

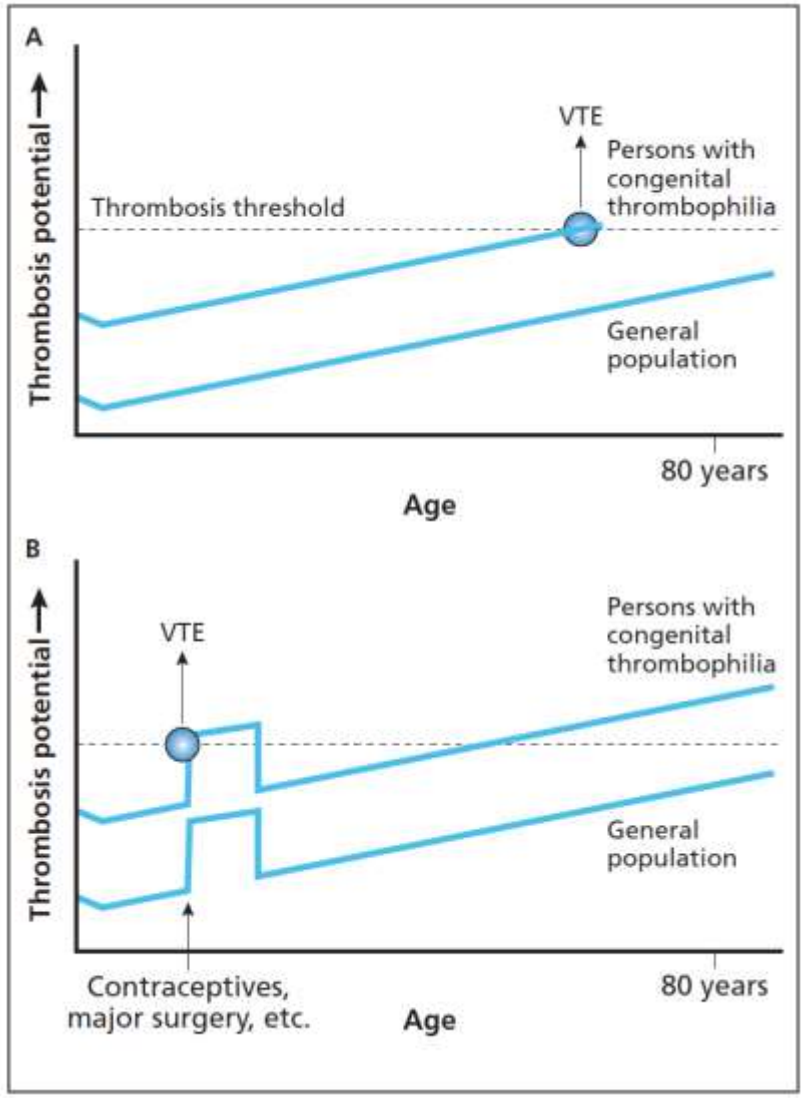
- Virchow's Triade
  - Venous stasis
    - Medical conditions
      - Atrial fibrillation
      - Atherosclerotic disease
      - Functional quadriplegia
    - Surgery
    - Immobility
      - Travel
      - Post-op state
  - Endothelial Injury
    - Surface phenomenon and contact with a procoagulant surface
    - Tissue factor and Factor VIII release
  - Hypercoagulability
    - Inherited
    - Acquired



UC San Diego Health

Threshold Model of Thrombogenesis

- Threshold Model
  - Background risk, increases with age
  - Risks are dynamic and may increase toward a threshold with either inherited or acquired risk factors
- Inherited Thrombophilia
  - Family history in 1st degree relative
- Acquired Risk Factors
  - Advanced age
  - Obesity
  - Cancer
  - Immobility (acute vs chronic considerations)
- Circumstantial Triggers
  - Surgery
  - Pregnancy
  - Hormone therapy
  - Tobacco product use



UC San Diego Health

Clinical Evaluations for Acute Events

UC San Diego Health

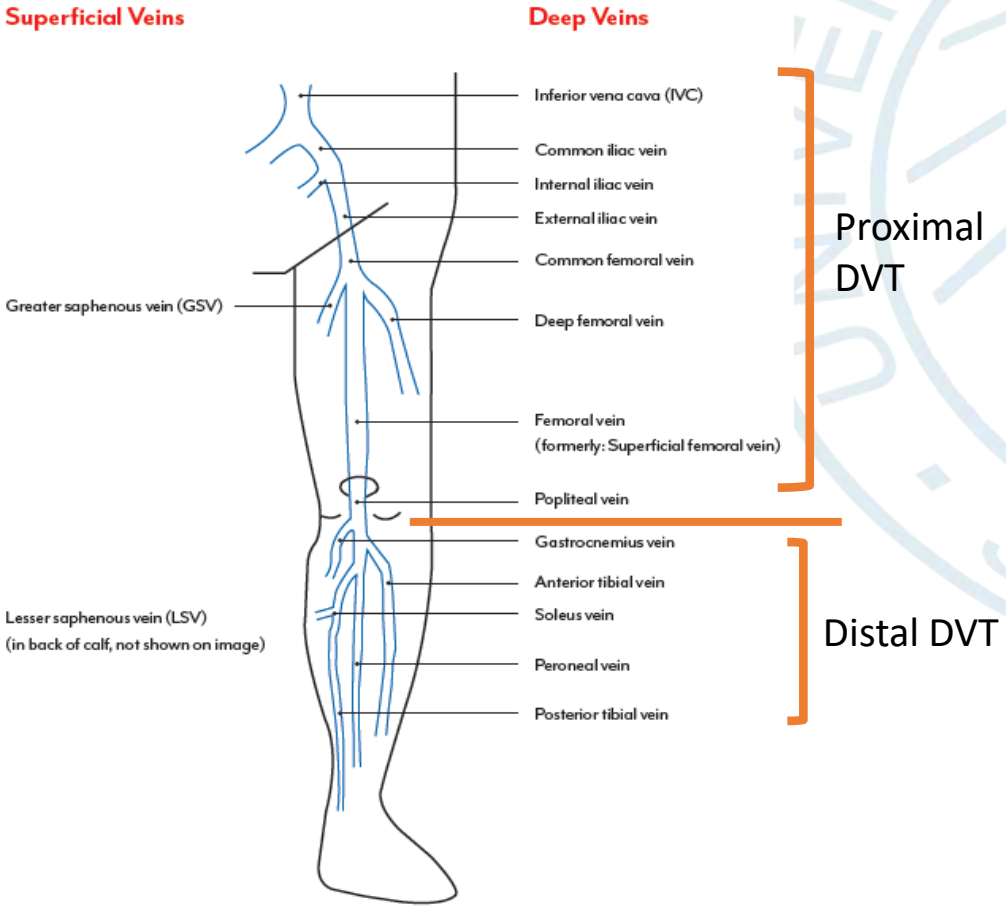
Making a Diagnosis

- Clinical Features
  - Contingent on anatomic location
    - Proximal DVTs are typically more symptomatic
  - Pain in the affected limb
    - 91% sensitive
    - 87% specific
  - Pitting lower extremity edema
    - 97% sensitive
    - 88% specific
  - Skin erythema
  - Pain with passive dorsiflexion of affected limb (Homan's sign)
    - 54% sensitive
    - 89% specific
  - Peripheral cyanosis
- Laboratory Features
  - Elevated D-dimer
  - Coags are recommended
- Imaging Studies
  - Duplex Ultrasound of the affected limb
  - CT angiogram
  - CT venogram
  - V/Q scan (as rule-out)
    - Low-risk
      - NPV 79%
    - Intermediate-risk
      - NPV 67%
    - High-risk
      - PPV only 30%
      - PPV when Wells score is >7 increases to 72%
- Clinical Pre-test Models
  - Wells Criteria for DVT
    - Scores ≥ 2 should prompt imaging
  - Wells Criteria for PE
    - Strong sensitivity and NPV
  - PERC rule for PE
    - Any point warrants diagnostic imaging for PE

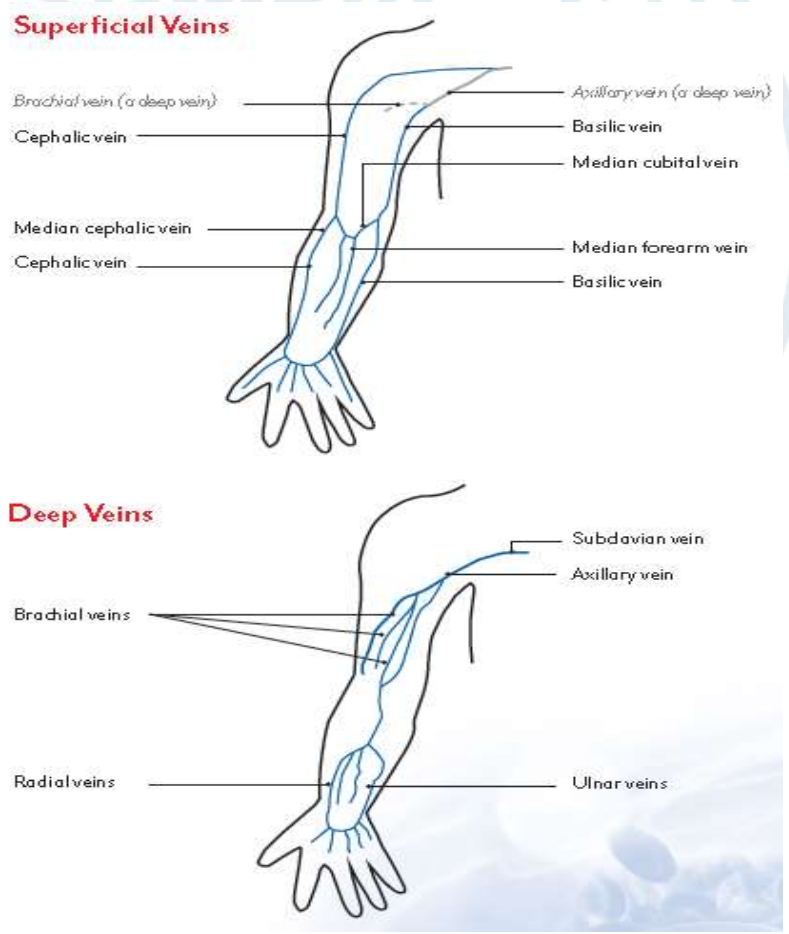
UC San Diego Health

Define the Clot:
Deep Vein Thrombosis

Legs



Arms



UC San Diego Health

Management Strategies:
Deep Vein Thrombosis

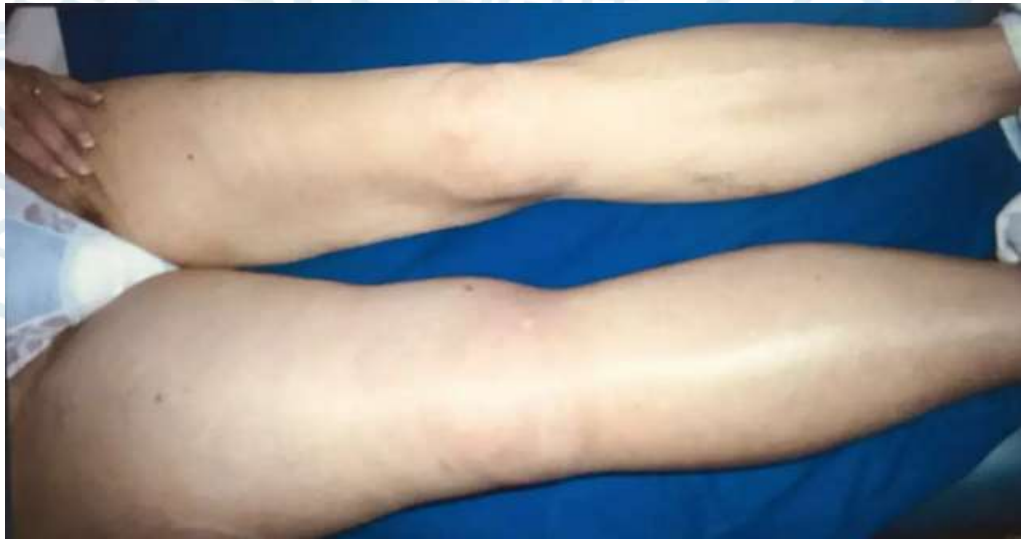
- Initial Anticoagulation
  - DOACs are typical first-line agents in most patients
  - Lovenox 1mg/kg subQ q12hrs
  - Warfarin with parenteral bridging
- Supportive Strategies
  - Analgesics
  - Compression stockings are controversial
- 3 months is sufficient for therapeutic anticoagulation
  - Four randomized trials compared 3 months of anticoagulation with 6 and 12 months of therapy and there is no significant difference in recurrence risk

Feature	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Bioavailability	60-80%	80%	62%	7%
Peak (hours)	2.4-4	3	1-2	2
Half-life (hours)	9	8-15	10-14	14-17
Excretion (%)	Kidney/bile (66/33)	Kidney/bile (25/75)	Kidney (50)	Kidney (80)
Need for IV/SC prior to PO* for acute VTE	no	no	Yes- 5 day lead-in	Yes- 5 day lead-in

UC San Diego Health

Thrombolytics in Venous Thromboses

- In the setting of life- or limb-threatening disease
  - Phlegmasia cerulea dolens
  - Phlegmasia alba dolens
- In the setting of organ-threatening disease
  - Progressive portal vein or IVC thrombosis
- Ileo-femoral DVT
  - ATTRACT trial: no difference in recurrence risk or PTS incidence, higher rate of major bleeding
  - CaVenT trial: reduced 5-year incidence of severe PTS (per Villalta score), no improvement on EQ-5D QoL assessments



N Engl J Med 2017; 377:2240-2252
Lancet Haematology 2016; 3(2):e64-71

UC San Diego Health

Define the Clot:
Pulmonary Embolism

AHA Guidelines*	ESC Guidelines**	ACCP/CHEST Guidelines†
Massive: Acute PE with sustained hypotension SBP <90mmHg for at least 15 min or requiring inotropic support, not due to a cause other than PE (arrythmias, hypovolemia, sepsis, LV dysfunction, pulselessness, profound bradycardia with shock)	**High Risk:** Acute PE with shock or hypotension SBP <90mmHg, or SBP drop by ≥ 40mmHg, for at least 15 min, not due to a cause other than PE	**PE with Hypotension:** Acute PE with sustained hypotension SBP <90mmHg for at least 15 min, not due to a cause other than PE High vs Low Bleeding Risk
Submassive: Acute PE without systemic hypotension (SBP >90mmHG) AND either.. RV dysfunction (RV/LV ratio >0.9, RV dysfunction on echo, RV dilation on CT scan, Elevated BNP (90) or NtproBNP (500), EKG evidence RV strain) Myocardial necrosis (elevated TNI >0.4ng/mL, TNT >0.1ng/mL)	**Intermediate High Risk:** Acute PE without hypotension **and** elevated PESI score with RV dysfunction **AND** serology Pos **Intermediate Low Risk:** Acute PE without hypotension **and** elevated PESI score with or without RV dysfunction **OR** serology Pos	**PE without Hypotension:** Acute PE without systemic hypotension (SBP >90mmHG) and Using clinical judgment and testing (imaging, serology etc..) to determine level of monitoring and support needed
Non-massive Acute PE without clinical markers of adverse prognosis	**Low Risk:** Acute PE with low PESI score	

* Jaff et al; Circulation. 2011; 123: 1788-1830
** Konstantinides et al; EurHeartJ. 2014;
† Kearon et al; CHEST. 2016; 149(2): 315-352

UC San Diego Health

Management Strategies:
Acute Pulmonary Embolism

- Medical Therapies – Low risk
  - Initial Anticoagulation
    - DOACs vs VKA
      - Similar efficacy, decreased risk of major bleeding
    - DOAC vs LMWH
      - No difference in efficacy, incidence of major and non-major bleeding, or all-cause mortality
- Medical Therapies – Int risk
  - UFH bolus with CIV heparin gtt and inpatient management is SoC

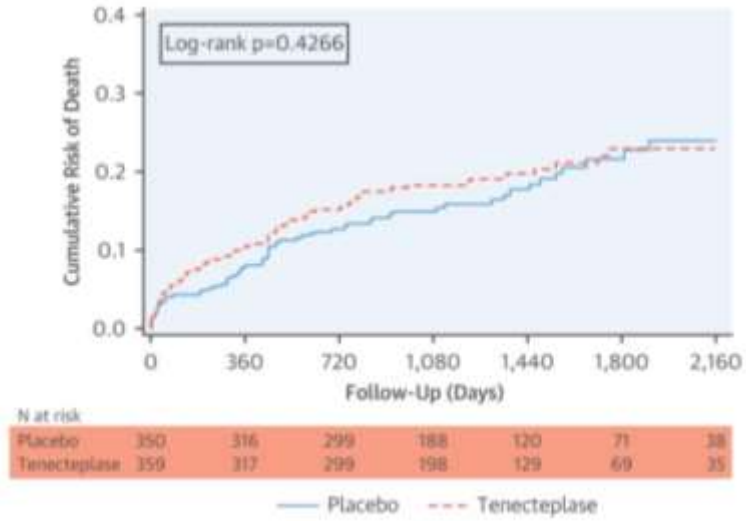
Drug	Dose	Special considerations
UFH 1	80 unit/kg IV bolus, followed by an 18-unit/kg/h infusion [6].	
Enoxaparin	1 mg/kg subQ 2 BID 3 [8, 9].	
Dalteparin	200 IU/kg/day 4 subQ for one month, followed by 150 IU/kg/day subcutaneously for months 2 through 6 [10].	Maximum of 18,000 IU per day.
Fondaparinux	<50 kg:5 mg subQ daily 50–100 mg: 7.5 mg subQ daily >100 kg: 10 mg subQ daily	Initiate warfarin within 72 h and give concomitantly for at least 5 days.
Edoxaban	60 mg po once daily; 30 mg once daily if body weight ≤ 60 kg	Not for use in patients with CrCl >95 mL/min 5. Dose after 5 to 10 days of initial therapy with a parenteral anticoagulant.
Apixaban	10 mg po twice daily for 7 days followed by 5 mg twice daily [11].	
Rivaroxaban	15 mg po twice daily x 3 weeks, then 20 mg once daily x at least 6 months [12].	Take with food to improve absorption [13, 14, 15]
Dabigatran	150 mg po BID [16].; 110 mg BID for patients ≥80 years	Dose after 5 to 10 days of initial therapy with a parenteral anticoagulant. Reduce dose to 110 mg BID for patients ≥80 years or ≥ 75 years with at least one bleeding risk factor.

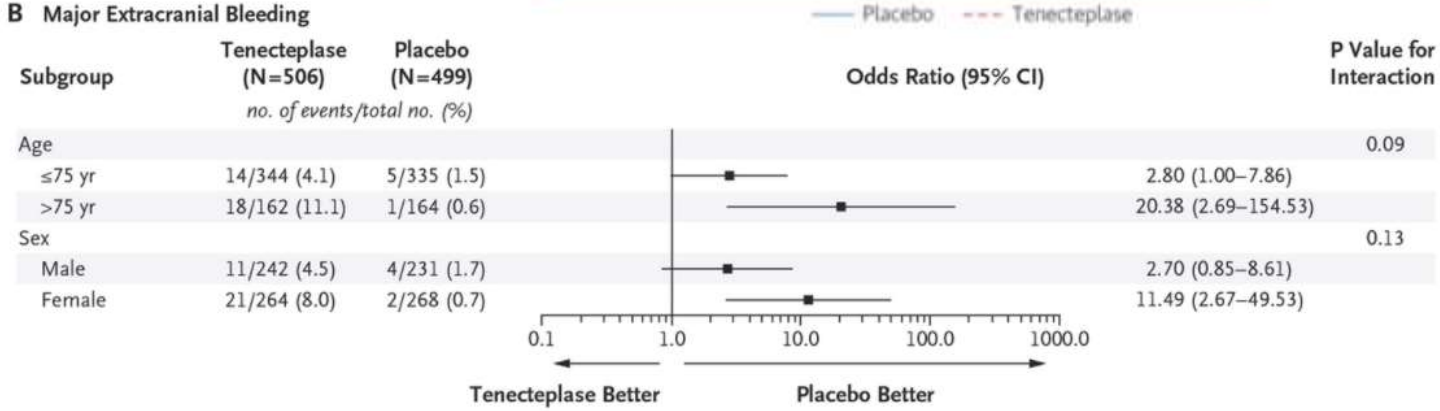
Chest. 2016;149:315-352

UC San Diego Health

Management Strategies:
Acute Pulmonary Embolism

- Systemic Thrombolytic Therapy
  - Indicated: Massive PE (sustained shock)
  - Not Indicated: Submassive PE
    - PEITHO trial showed no benefit to mortality at any follow-up timepoint
    - High rate of hemorrhagic stroke and major bleeding
    - No difference in residual dyspnea, RV dysfunction, or incidence of CTEPH among both arms



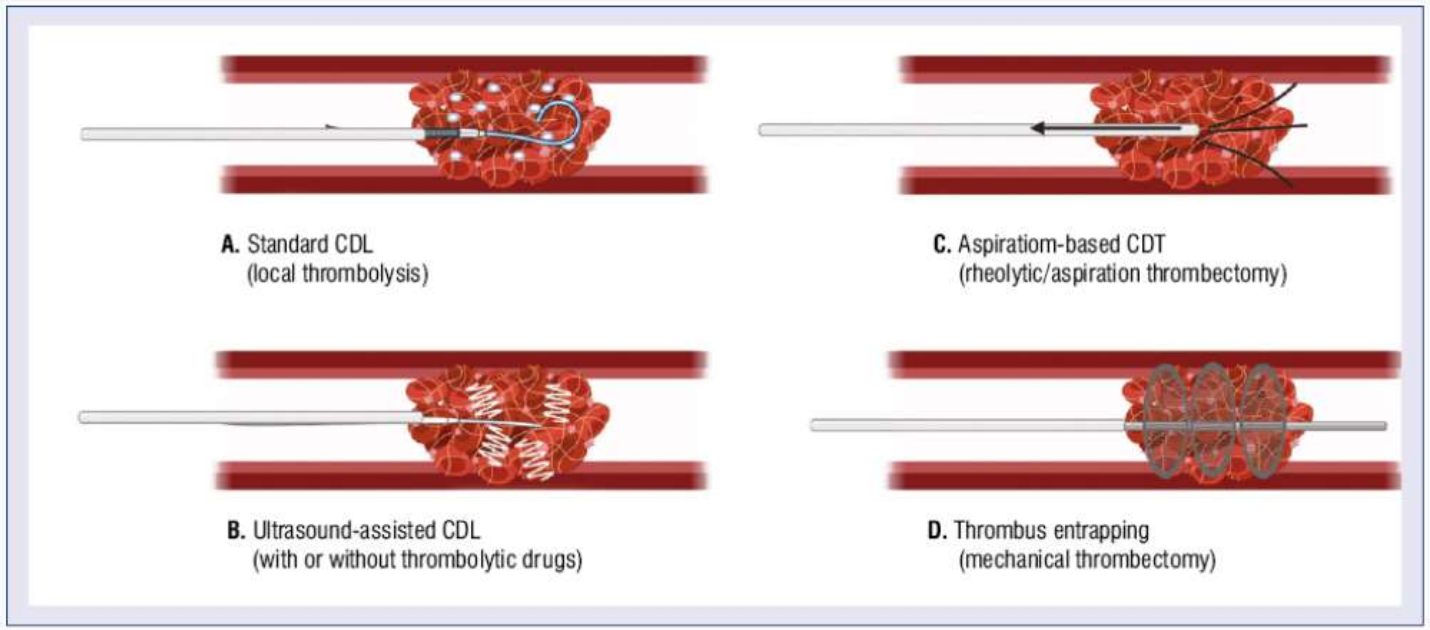


Meyer 2014 N Engl J Med 370:1402–1411
J Am Coll Cardiol. 2017;69(12):1536

UC San Diego Health

Management Strategies:
Acute Pulmonary Embolism

- Catheter Directed Therapies
  - Mechanical thrombectomy or infused thrombolytic directly at PA (rather than systemically)
  - Per CHEST guidelines, should be considered in:
    - Persistent hemodynamic instability despite systemic thrombolytic therapy
    - High risk of death before systemic thrombolytics are expected to manifest effectiveness
    - Submassive PE with hemodynamic deterioration despite therapeutic AC
    - High risk of major systemic bleeding
  - Significant debate over timing, what endpoints are clinically meaningful, operator expertise



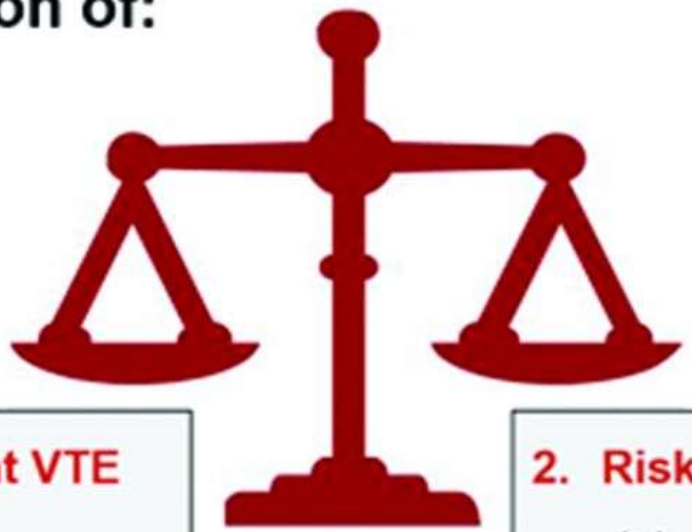
UC San Diego Health

Determining Duration of Anticoagulation

Risk of VTE recurrence vs risk of bleeding

No "one size fits all" answer

Conglomerate decision of:



1. **Risk factors for recurrent VTE**
   (a)…., (b)…., (c) …..

2. **Risk factors for bleeding**
   (a)…., (b)…., (c) …..

3. **Patient preference**
   "Warfarin hate factor" or
   "NOAC dislike factor"

Stephan Moll Hematology 2014;2014:297-305

UC San Diego Health

VTE as Chronic Disease

- Recurrence is common in unprovoked VTEs
  - 30% of patients will have a recurrent event over 10 years
- Highest risk of recurrence is closest to the index event
  - Highest in 1st year, however risk will never fall to 0%
- Goal of therapy: reduce risk of recurrence without increasing risk of bleeding

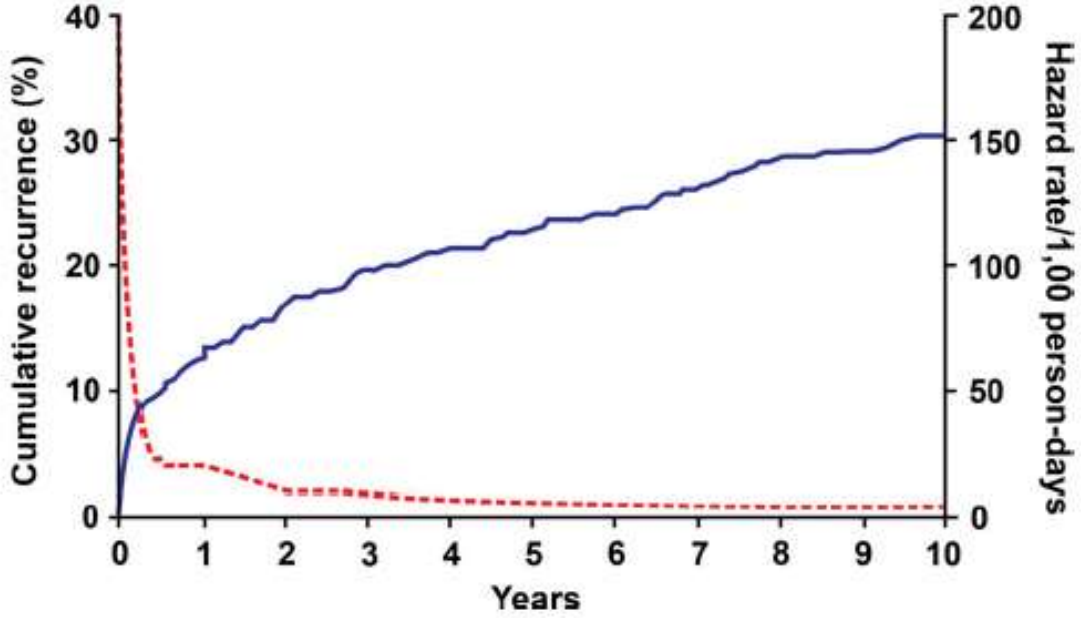


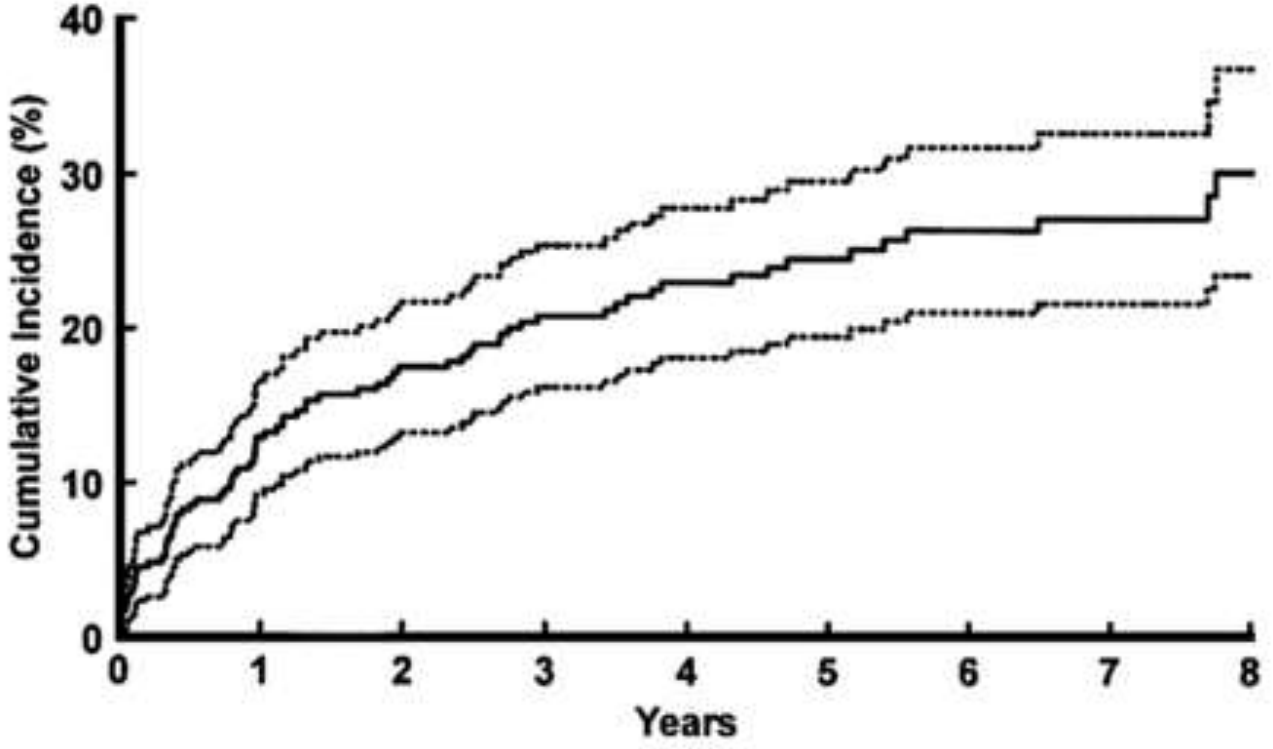
Fig. 4 Cumulative incidence of first venous thromboembolism recurrence (*continuous line*), and the hazard of first recurrence per 1000 person-days (*dotted line*) [32]

Heit J Thromb Thrombolysis (2016) 41:3–14

UC San Diego Health

PE as Chronic Disease

- Very low risk (<3%) of recurrent PE during anticoagulation[1,2]
  - ENSTEIN-PE[3]: symptomatic recurrent VTE – 2.1% in rivaroxaban vs 1.8% in VKA
- Cumulative risk after completing anticoagulation for 1st episode of PE is >30% by 10 years[4]
  - Lowest risk: major transient risk factor (3% per year)
  - Intermediate risk: idiopathic (7% per year)
  - High risk: persistent risk factors (25% per year)
- If the first VTE is a PE, recurrent events are more likely to be PE[5]



1. N Engl J Med 2012; 366:1287–1297
2. N Engl J Med 2013; 369:799–808
3. N Engl J Med 2012; 366:1287-1297
4. Ann Intern Med. 1996;125(1):1-7.
5. Arch internal Med. 2000 Mar 27;160(6):761-

UC San Diego Health

Recurrence Prediction Models

- Clinical scores that may help further risk-stratify in patients with unprovoked VTE
  - DASH Score: scores greater than 2 warrant indefinite therapy
    - Ddimer elevated after 1 month of completion of anticoagulation (2 points)
    - Patient age >50 (1 point)
    - Male vs Female (males = 1 point, female = 0 points)
    - VTE associated with hormone therapy (1 point)
  - HERDOO2 score: used only in women > 18 years (“men get clots and ‘her do too’”)
    - High risk vs not high risk (≥ 2 points warrants indefinite anticoagulation)
    - Post-phlebitis syndrome (eg, skin hyperpigmentation, edema, erythema, etc.)
    - “very specific ddimer”, aka VIDAS Ddimer > 250 ng/dL while on warfarin therapy (1 point)
    - BMI > 30 (1 point)
    - Age > 65 years (1 point)

UC San Diego Health

Is the D-dimer Clinically Meaningful?

- Elevated d-dimer is predictive of recurrence
  - PROLONG study: unprovoked VTE, d-dimer 1 month after stopping anticoagulation.
    - If abnormal d-dimer, randomized to a/c or no a/c
    - 2% and 10.2% recurrences at 18 mo follow-up
  - Those with abnormal d-dimer should be treated indefinitely

- Negative d-dimer is not enough to stop anticoagulation
  - DODS study: high rate of recurrence after unprovoked VTE with a negative qualitative D-dimer test at end of anticoagulation
    - Men: 9.7 % per patient year; 95 % CI 6.7–13.7 %
    - Women: 5.4 % per patient year; 95 % CI 2.5–10.2 %
    - Women with estrogen-associated: low risk for recurrence (0 %,95 % CI 0.0–3.0 %)

Cosmi Blood 2010 115(3):481-488
Kearon Ann. Intern. Med 2015. 162 (1):27–34

A Word on Thrombophilias

- They do not strongly or consistently enough predict VTE recurrence to influence recommendations on duration of anticoagulant therapy (some exceptions)
- ASH Choosing Wisely Campaign: Don’t send in the presence of a major transient risk factor
- Send when testing will impact management (ie, intermediate risk for recurrence)

Hicks et al. *ASH Educational Program 2013:9–14*

UC San Diego Health

Heritable Risk Factors for Recurrence

Table 1.
Prevalence of inherited thrombophilia and relative risk estimates for various clinical manifestations

	Antithrombin deficiency	Protein C deficiency	Protein S deficiency	Factor V Leiden	Prothrombin 20210A mutation
Prevalence in the general population*	0.02%	0.2%	0.03%–0.13%	3%–7%	0.7%–4%
Prevalence in consecutive patients with VTE*	1%	3%	2%	20%	5%
Relative risk for a first VTE†	5–10	4–6.5	1–10	3–5	2–3
Relative risk for recurrent VTE	1.9–2.6	1.4–1.8	1.0–1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3–3.6	1.3–3.6	1.3–3.6	1.0–2.6	0.9–1.3

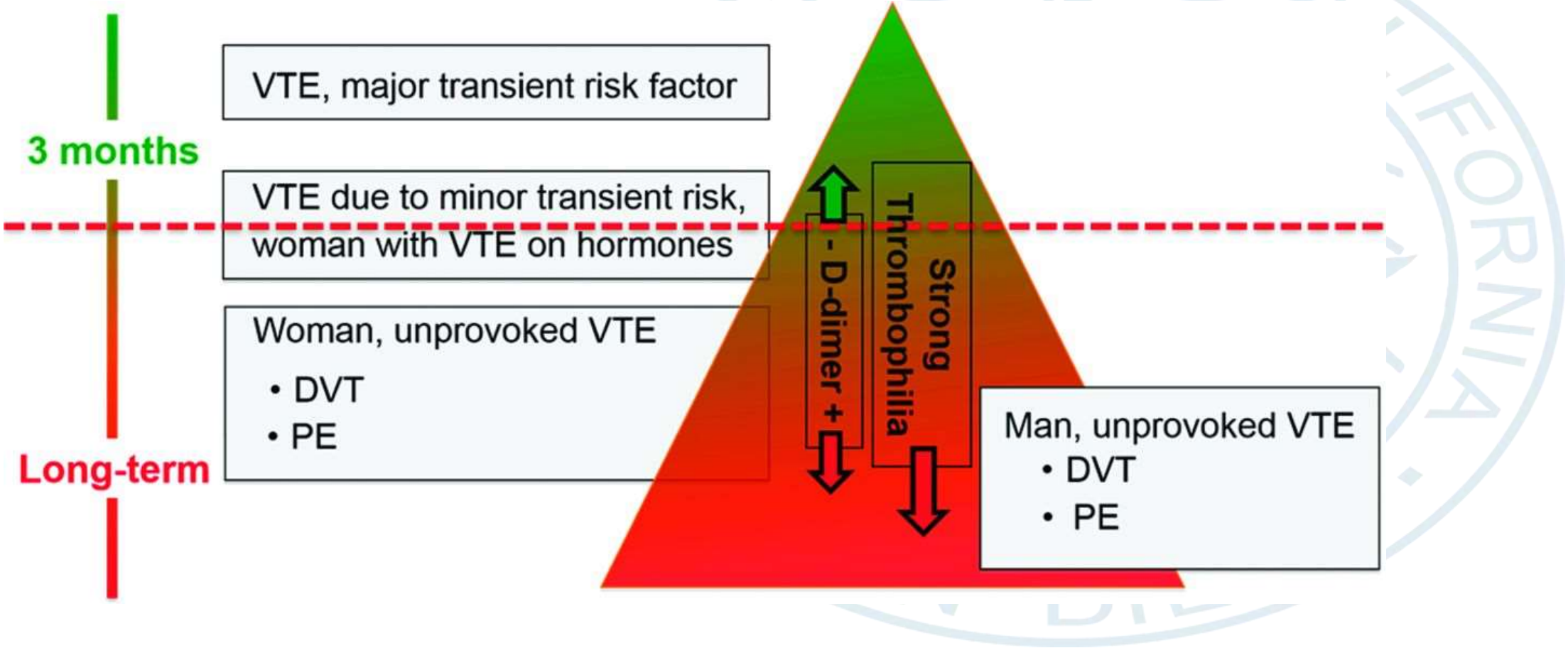
Middeldorp, Hematology ASH Educ Program. 2016 Dec 2;2016(1):1-9.

Estimate Bleeding Risk

- Benefit of a/c when the case fatality from recurrent VTE is lower than the one from bleeding on anticoagulation (~3% for major bleeding)
- No well-validated predictive bleeding score exists for VTE
  - HAS-BLED clinical score-- developed in Afib population
- Individual factors
  - HTN
  - Renal/liver function
  - Stroke
  - Labile INR
  - Age >65
  - Aspirin/NSAIDs or EtOH use
  - Past bleeding

UC San Diego Health

Risk of Recurrence Triangle



Stephan Moll Hematology 2014;2014:297-305

UC San Diego Health

Special Populations

UC San Diego Health

Oral and Parenteral Contraceptives

- Hormone-based contraception increases relative risk of first VTE by 2-4 fold, however absolute risk is still very low (BL risk is 0.19-0.37 per 1000 woman-years)
- For 2nd/3rd generation combined OCPs, those with levonorgestrel as the progestin component will have the lowest risk relative risk
- Progestin-only contraceptive options
  - Progestin-only oral contraceptive and VTE (RR 0.90, CI 0.57-1.45)
  - Progestin IUD and VTE (RR 0.61, CI 0.24-1.53)
  - Depo progestin and VTE (RR 2.67, CI 1.29-5.53)

BMJ 2012, 7(345). e4944

Oral and Parenteral Contraceptives

Contraceptive	Odds ratio	95% CI
COC 30 mcg, desogestrel	7.3	3.30-10.00
COC 30 mcg, levonorgestrel	3.6	1.75-4.60
Depo-Provera	3.6	0.70-1.50
Transdermal patch	2.2	0.70-3.80
Vaginal ring	1.6	1.02-2.37
Progestin-only pills	0.6	0.33-3.41
Levonorgestrel IUD	0.3	0.10-1.26

UC San Diego Health

Oral and Parenteral Contraceptives

- Contraception in patients with prior VTE
  - Progesterone IUD – Mirena or Skyla
  - Copper IUD
  - Progestin-only oral pill
  - Depo injections are controversial, there is likely a risk here
  - Provide VTE prophylaxis with all future pregnancies
    - LMWH 40mg subq daily or UFH 5000u BID if renal disease

UC San Diego Health

Splanchnic Vein Thromboses

- Portal Vein Thrombosis
  - Local risk factors: cirrhosis/portal hypertension, infection, inflammation
  - Systemic risk factors: MPNs (e.g., Polycythemia Vera, Essential Thrombocythemia, or Myelofibrosis), thrombophilia, malignancy
- Superior Mesenteric Vein Thrombosis
  - Inpatient management recommended, can cause ischemia which is a surgical emergency
- Treat for 6 months, consider indefinite anticoagulation if unprovoked
- DOACs are OK if there are no contraindications
- Patients with cirrhosis: anticoagulate if the benefits outweigh the risks
  - Make sure EGD is up to date, ensure plts > 50k/uL
  - Consider long-term anticoagulation in patients without coagulopathy

UC San Diego Health

Cerebral Venous Sinus Thrombosis

- 5% mortality risk from intracranial hemorrhage
- Life-time risk of recurrence is ~4%, systemic VTE risk is ~7%
- Pursue thrombophilia evaluation regardless of presumed etiology
- LMWH/UFH is treatment of choice for initial anticoagulation
  - Goal is recanalization and prevention of clot propagation
- Provide anticoagulation *even when there is hemorrhage*
  - Co-management with neurosurgery is essential
- Treatment duration:
  - 6 months if provoked/transient risk factors
  - 12 months if unprovoked

Cancer-Associated VTE

- Provide therapeutic-dose anticoagulation for minimum 6 months and ideally indefinitely so long as cancer is present and/or receiving cancer-directed therapy
- Excess of UGI bleeding occurs mostly in patients with GI cancers
  - Exception is Apixaban – no increased risk in major GIB when compared with LMWH (HR 1.05, CI 0.44-2.50) from Caravaggio trial
- Watch for drug-drug interactions with cytochrome CYP3A4 chemo
- Use LMWH in patients with thrombocytopenia or those receiving targeted therapies with mAb's or checkpoint inhibitors

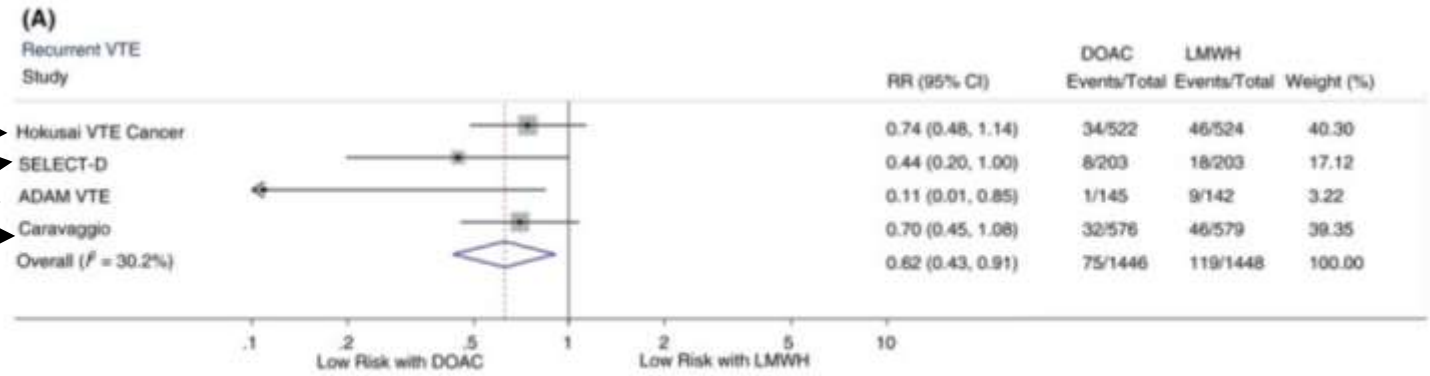
UC San Diego Health

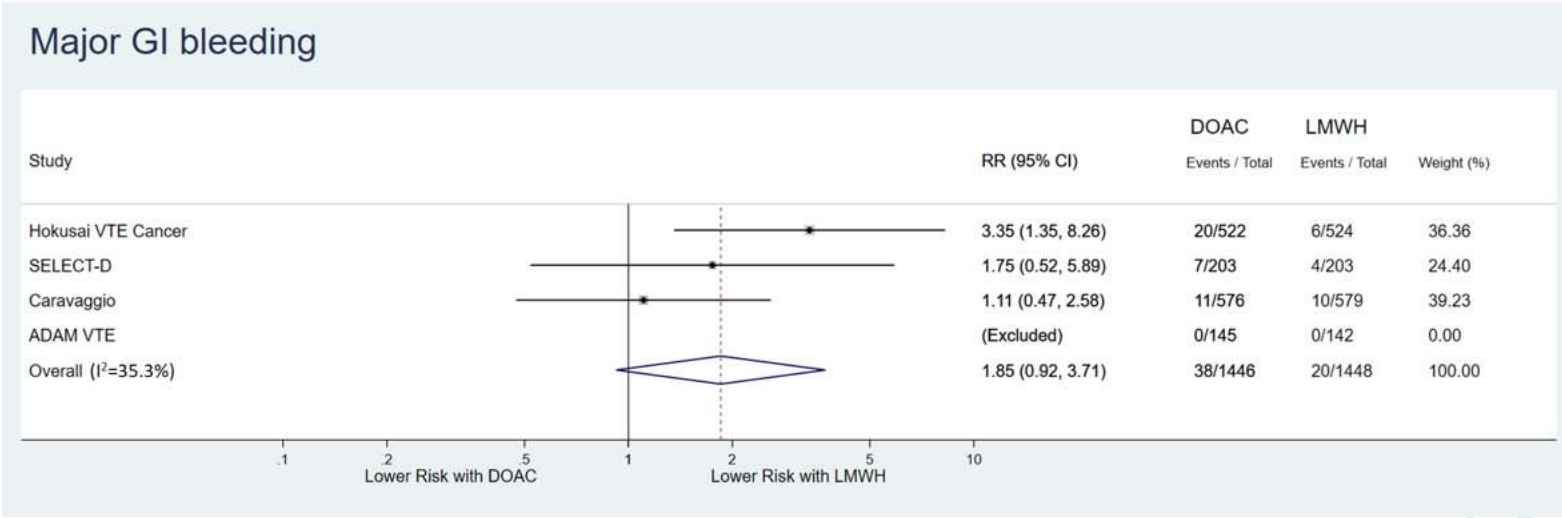
Cancer-Associated VTE

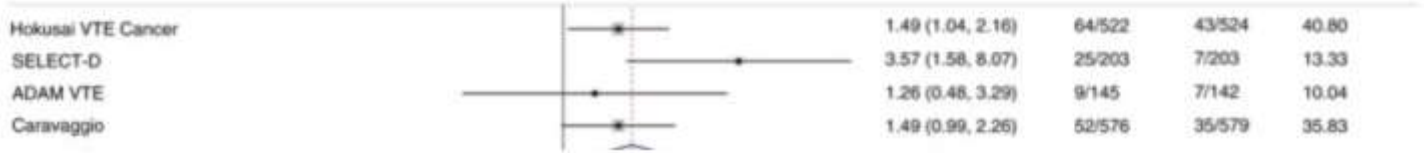
edoxaban → Hokusai VTE Cancer

rivaroxaban → SELECT-D

apixaban → ADAM VTE, Caravaggio





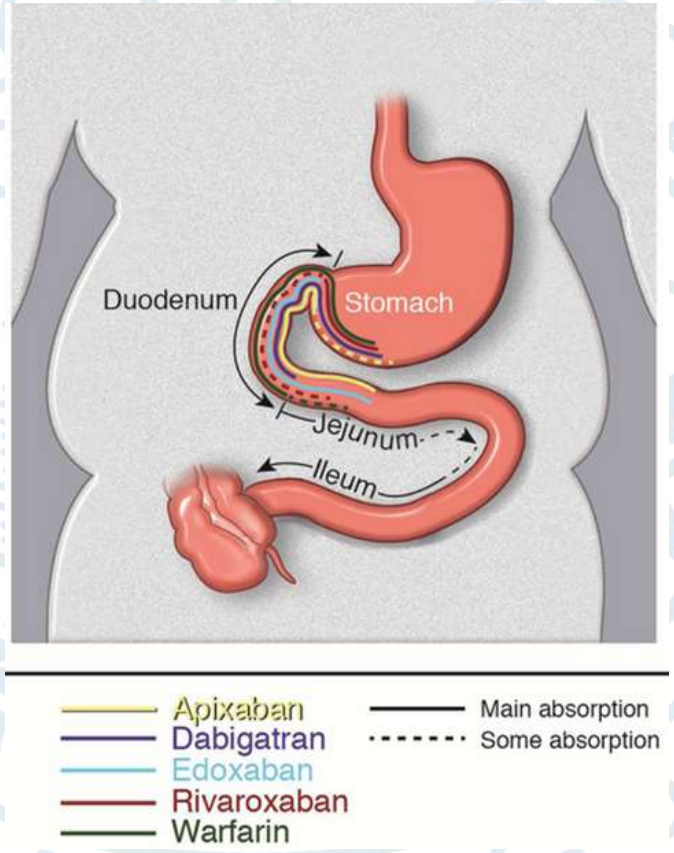


Carrier Blood. 2020 Aug 06;136(6):669-673.
Moik Res Pract Thromb Haemost. 2020 May; 4(4): 550–561.

UC San Diego Health

DOACs: Caution advised

- Patients at the “extremes of weight”
  - (>120 kg, BMI >40, or <60kg
- Liver disease
- Pregnancy and breast feeding
- Bariatric surgery
- Antiphospholipid antibody syndrome
- Concurrent use of CYP3A4



DOAC	Childs Pugh A	Childs Pugh B	Childs Pugh C
Apixaban	✓	-–	×
Rivaroxaban	✓	×	×

UC San Diego Health

DOACs in Renal Disease

- Patients with eGFR < 25-30 were excluded from DOAC trials
- Apixaban
  - Lowest renal clearance (~27%)
  - Hemodialysis: FDA label for use in HD patients, but based on single-dose PK study in 18 patients
  - Retrospective “real world” studies show both safety and efficacy; signal toward reduced incidence of major bleeding vs warfarin
  - Dose-reduce to 2.5mg BID if 2 of the following: age > 80, weight < 60kg, SCr > 1.5
- Rivaroxiban
  - No dose-reduction for treatment of VTE (unlike AF)
  - Do not use if eGFR < 30
- Edoxaban
  - No dose-reduction for treatment of VTE

UC San Diego Health

Isolated Distal DVT

- Embolization potential is far lower than bleeding risk from AC
  - Routine AC not indicated for all patients
- Severe symptoms (pain, swelling, redness): anticoagulated for 3 months
- Mild symptoms with or without risk factors: anticoagulated for 1 month
- Asymptomatic and without risk factors: repeat ultrasound in 14 days to monitor for extension, if >5cm away from saphenofemoral junction, OK to omit AC
- Risk factors:
  - Immobility, cancer, BMI > 40, active tobacco use, <5cm from saphenophemoral junction

Isolated Subsegmental PE

- Better imaging has led to increased detection
- Typically treat for 3 months, even if found incidentally
- If risk factors are present, treat as typical PE

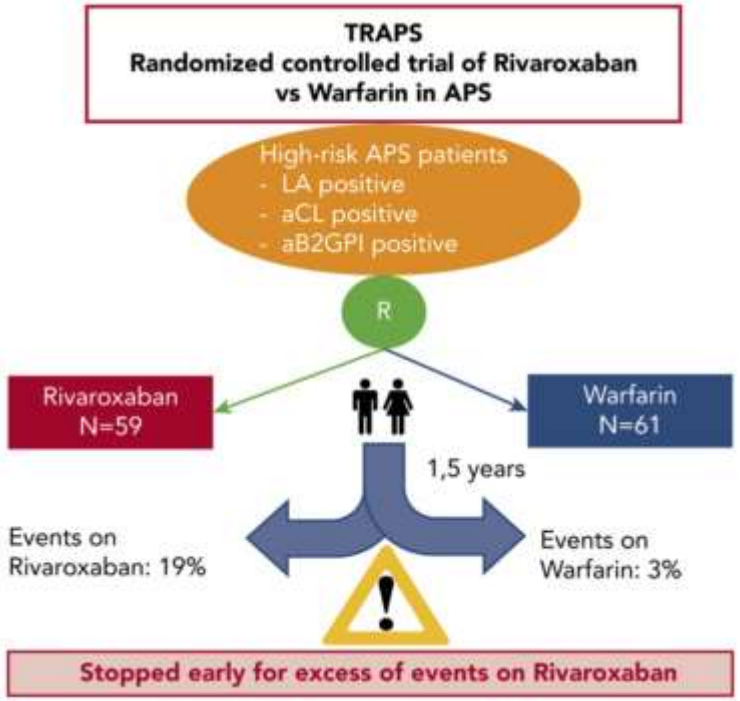
UC San Diego Health

Travel-associated VTE

- Risk is only within 4 weeks
- Immobility associated with travel for 4-12 hours: 2x increased risk
- Travel times ranging 12-16 hours and >16 hours are associated with incidence ratios of 5.3 (CI 2.3-12.4) and 5.7 (CI 2.0-16.5), respectively
- Data is lacking to recommend routine use of AC, low-dose aspirin, or compression stockings for primary ppx
- Patents should be advised to ambulate every 2-4 hours for 15 minute

UC San Diego Health

Antiphospholipid Antibody Syndrome



Adjudicated efficacy and safety outcomes

Outcome, n	"As treated" analysis				ITT analysis			
	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95%	P	Rivaroxaban (n = 59)	Warfarin (n = 61)	HR (95% CI)	P
Thromboembolic events, major bleeding, and vascular death	11 (19)	2 (3)	6.7 (1.5-30.5)	.01	13 (22)	2 (3)	7.4 (1.7-32.9)	.008
Arterial thrombosis	7 (12)	0	—	—	7 (12)	0	—	—
Ischemic stroke	4 (7)	0			4 (7)	0		
Myocardial infarction	3 (5)	0			3 (5)	0		
Venous thromboembolism	0	0			1 (2)	0		
Major bleeding	4 (7)	2 (3)	2.5 (0.5-13.6)	.3	4 (7)	2 (3)	2.3 (0.4-12.5)	.3
Death	0	0	—	—	1 (2)	0	—	—

Blood 2018 132:1365-1371

Anticoagulant	Target	Route	T ½ normal	Monitoring?	Reversal available?
Warfarin	Factors II, VII, IX, X	Oral	36-42h	INR	Yes- Vitamin K and 4-factor PCC
Unfractionated Heparin	Potentiates antithrombin inhibition of thrombin (and Xa)	IV or subcutaneous	Dose-dep; 30 min after 25u/kg bolus	PTT	Yes- protamine
Low molecular weight heparin	Potentiates antithrombin inhibition of Xa (and thrombin)	Subcutaneous	4.5- 7h (Lovenox)	Not routine	Partial- protamine
Fondaparinux	Potentiates antithrombin inhibition of Xa	Subcutaneous	17h	Not routine	No specific agent
Apixaban, rivaroxaban, edoxaban	Factor Xa	Oral	~ 8h	Not routine	No specific agent
Dabigatran	Thormbin	Oral	~14h	Not routine	Idarucizumab
Argatroban	Thrombin	IV	~40 min	PTT	No specific agent

UC San Diego Health

Questions