VTE: 2016 ACCP Update with Best Evidence and Best Practices

Steven Deitelzweig, MD, MMM, SFHM

Associate Professor of Medicine – University of Queensland School of Medicine

System Chairman – Hospital Medicine

Medical Director – Regional Business Development

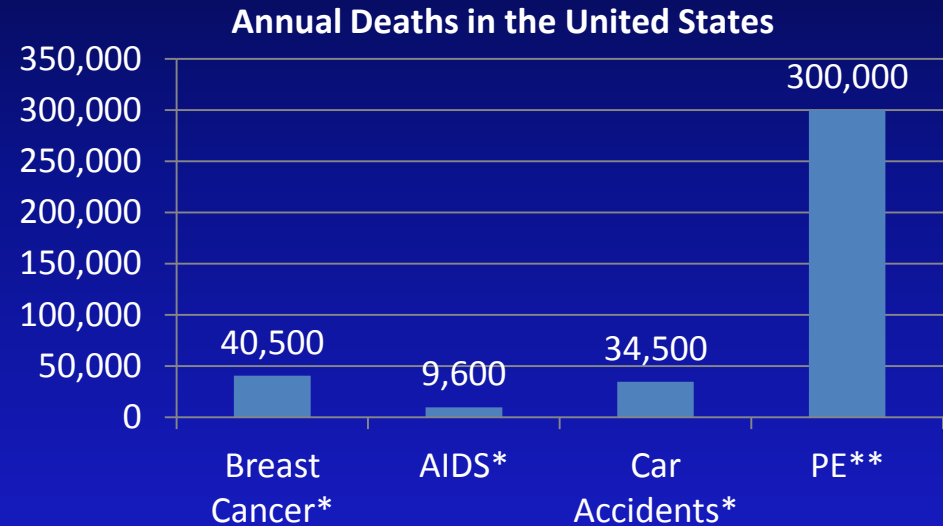Ochsner Health System

sdeitelzweig@ochsner.org

Disclosures

- Research Funding
  - BMS
  - Optum Insight
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  - Janssen

Putting It Into Perspective

PE kills more people each year than HIV, car accidents, and breast cancer...*combined*[1]

- Up to 300,000 people a year die from PE in the US[2]
- It is the third most common cardiovascular illness[3]
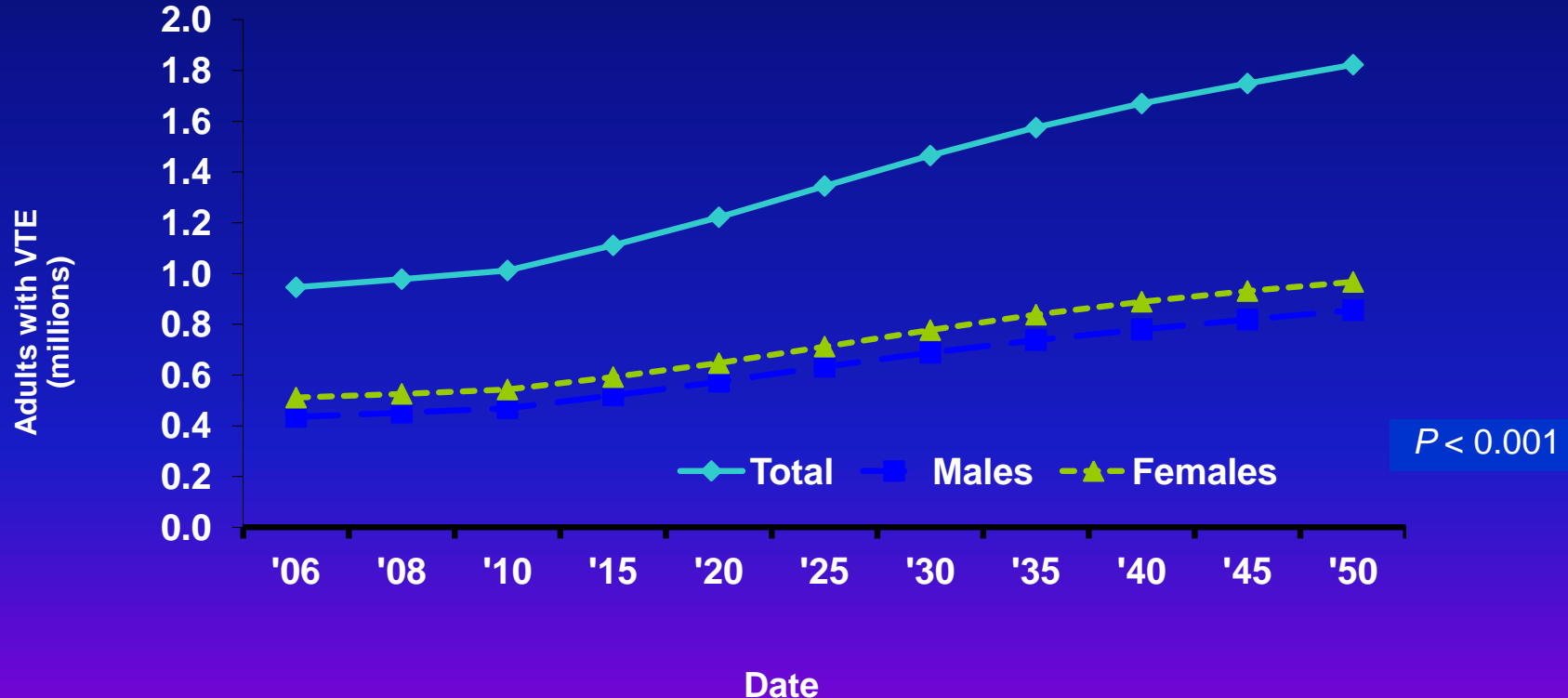- Direct annual payer cost in the US have been estimated at 1.5 billion[4]

Annual Deaths in the United States

Category	Deaths
Breast Cancer*	40,500
AIDS*	9,600
Car Accidents*	34,500
PE**	300,000

* CDC 2008
** Consensus Estimates range from 100,000 to 300,000

1. Rathbun S. *Circulation.* 2009; 119(15) e480-e482. **2.** Tapson VF. *N Engl J Med.* 2008;358: 1037-1052. **3.** Goldhaber SZ. *J Am Coll Cardiol.* 1992, 19: (2): 246-247. **4.** Macdougall DA et al. *Am J Health-Syst Pharm.* 2006;63(20 suppl 6):S5-S15.

Trends in VTE: Prevalence to Double by 2050

Projected VTE Rates (2006-2050)[1]

Deitelzweig SB, et al. American J Hematology. 2011 86:217-220.

2016 Updated VTE Guidelines/ Guidance Statements

AC Forum

- The Anticoagulation Forum is the largest peer organization of anticoagulation service providers in North America.

- The board of directors (composed of members from multiple disciplines) come together to formulate a set of guidelines that is not only based on evidence but also expert opinion and experience.

- The guidelines cover all aspects of treatment and management of DVT and PE.

- Free open access to all manuscripts at: **http://acforum.org/landing/index.html**

Topic	New!	Changed	New evidence but no change
Choice of long term (first 3 mo) and extended anticoagulant therapy	✔		
Whether to treat a subsegmental PE	✔		
Aspirin for extended treatment of VTE	✔		
Management of Recurrent VTE on Anticoagulant Therapy	✔		

Topic	New!	Changed	New evidence but no change
Duration of treatment		✔	
Use of Compression Stockings to Prevent Post-Thrombotic Syndrome		✔	
Whether and How to Prescribe Anticoagulants to Patients with Isolated Distal DVT			✔
Catheter-Directed Thrombolysis for Acute DVT of the Leg			✔
Role of IVC Filters in Addition to Anticoagulation for Acute DVT or PE			✔

Topic	New!	Changed	New evidence but no change
Treatment of Acute Pulmonary Embolism Out of Hospital			✔
Systemic Thrombolytic Therapy for Pulmonary Embolism			✔
Thrombolytic Therapy in Patients with Upper Extremity DVT			✔

TOPICS

- Catheter related thrombosis
- Calf vein thrombosis and extensive DVT
- Risk stratification and Treatment of PE
- Duration of anticoagulation for VTE
- Management of recurrent VTE on AC

DOACs vs NOACs

RECOMMENDATIONS AND GUIDELINES

Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH

G. D. BARNES, * W. AGENO,† J. ANSELL‡ and S. KAATZ,§ FOR THE SUBCOMMITTEE ON THE CONTROL OF ANTICOAGULATION

*Frankel Cardiovascular Center and Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA; †Division of Internal Medicine, University of Insubria, Varese, Italy; ‡Department of Internal Medicine, Lenox Hill Hospital, New York, NY; and §Hurley Medical Center, Michigan State University, Flint, MI, USA

Scope and methodology

Oral anticoagulants are used to prevent and treat a wide range of thromboembolic diseases. Currently available oral anticoagulants include the vitamin K antagonists (VKAs), such as warfarin. VKAs reduce the synthesis of functional vitamin K-dependent factors (factor II, FVII, FIX, FX, as well as protein C and protein S) by interfering with the vitamin K redox cycle. The newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban

not is scientifically unappealing. Perhaps more importantly, there is at least one reported account where the term NOAC written in the medical record was interpreted as meaning 'No AntiCoagulation,' potentially resulting in the patient not receiving the critical therapy that was intended [3].

There is a clear need to reach a consensus on the nomenclature of oral anticoagulants, and several experts have called for consensus around the nomenclature for oral anticoagulants [2,4–7].

We aimed to develop guidance from the Control of Anticoagulation SSC of ISTH on the most appropriate abbreviation for the newer/novel/target-specific/direct-act-

CASE #1

A 55 year old woman being treated for osteomyelitis of the spine develops right upper extremity swelling. U/S reveals a DVT in the subclavian and axillary vein. She has a PICC line in that arm. She needs 4 more weeks of antibiotics. You start anticoagulation. Do you need to pull the line?

a. Yes
b. No

Upper Extremity DVT
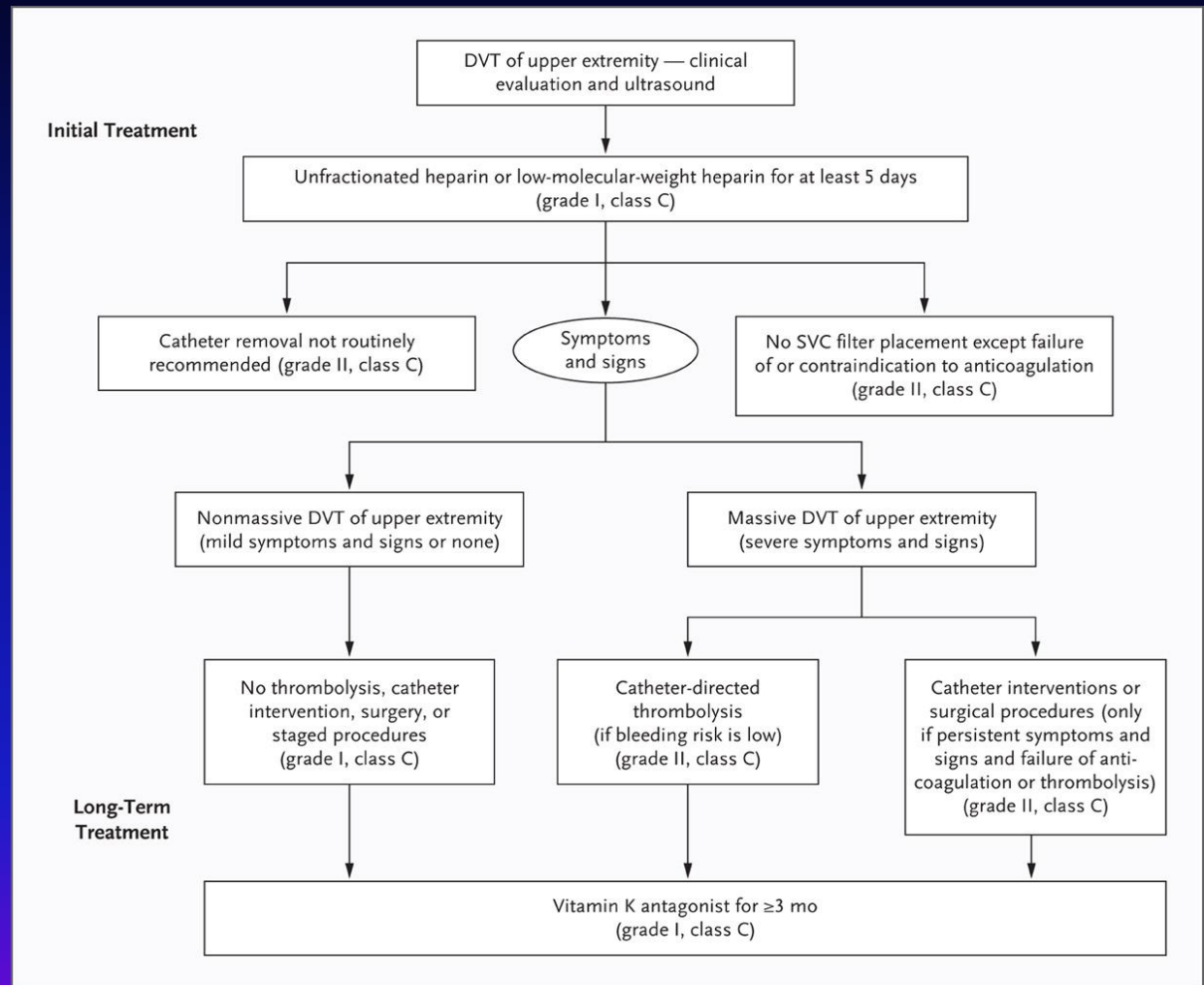
Remove catheter (after 3-5 days of anticoagulation if possible) if:
Infection
Malfunction
AC contraindicated
AC failed
Cath not needed

DVT of upper extremity — clinical evaluation and ultrasound

Initial Treatment

Unfractionated heparin or low-molecular-weight heparin for at least 5 days (grade I, class C)

Catheter removal not routinely recommended (grade II, class C)

Symptoms and signs

No SVC filter placement except failure of or contraindication to anticoagulation (grade II, class C)

Nonmassive DVT of upper extremity (mild symptoms and signs or none)

Massive DVT of upper extremity (severe symptoms and signs)

No thrombolysis, catheter intervention, surgery, or staged procedures (grade I, class C)

Catheter-directed thrombolysis (if bleeding risk is low) (grade II, class C)

Catheter interventions or surgical procedures (only if persistent symptoms and signs and failure of anti-coagulation or thrombolysis) (grade II, class C)

Long-Term Treatment

Vitamin K antagonist for ≥3 mo (grade I, class C)

Upper Extremity DVT

ACCP 2012 UE DVT (Stephan Moll MD, CLOTCONNECT.ORG)

- If DVT that involves the axillary or more proximal veins, anticoagulation therapy alone is suggested, rather than thrombolytic therapy. Length of anticoagulation: at least 3 months.
- In upper extremity DVT not associated with a central venous catheter: 3 months of anticoagulation is recommended.
- In upper extremity DVT associated with a central venous catheter:
  - Suggestion is to not remove the catheter if it is functional and there is an ongoing need for the catheter. Anticoagulation should be given as long as the catheter is in place.
  - If the catheter is removed, anticoagulation should continue for 3 months thereafter.

Thrombolytic Therapy in Patients with Upper Extremity DVT

- Panel suggests the use of thrombolysis will only benefit patients who meet the following criteria:
  - Severe symptoms
  - Symptoms <14 days
  - Good functional status
  - Thrombus involving most of the subclavian and axillary vein
  - Life expectancy ≥ 1 year
  - Low risk for bleeding

Thrombolytic Therapy in Patients with Upper Extremity DVT

2012	2016
In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C)**.	**In patients with acute UEDVT that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis** (Grade 2C).

CASE #2

A 45 year old man presents with moderate calf pain and swelling for 5 days since he was kicked playing soccer. Ultrasound shows DVT in the posterior tibeal vein. Does he need anticoagulation?

a) Yes
b) No

NEW CHEST GUIDELINES

In patients with acute isolated distal DVT (IDDVT) of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

Kearon et al CHEST 2016

ISOLATED DISTAL DVT
ant/post tibeal, peroneal

TREATMENT

LOW RISK

u/s 1-2 weeks and treat only if extends proximally
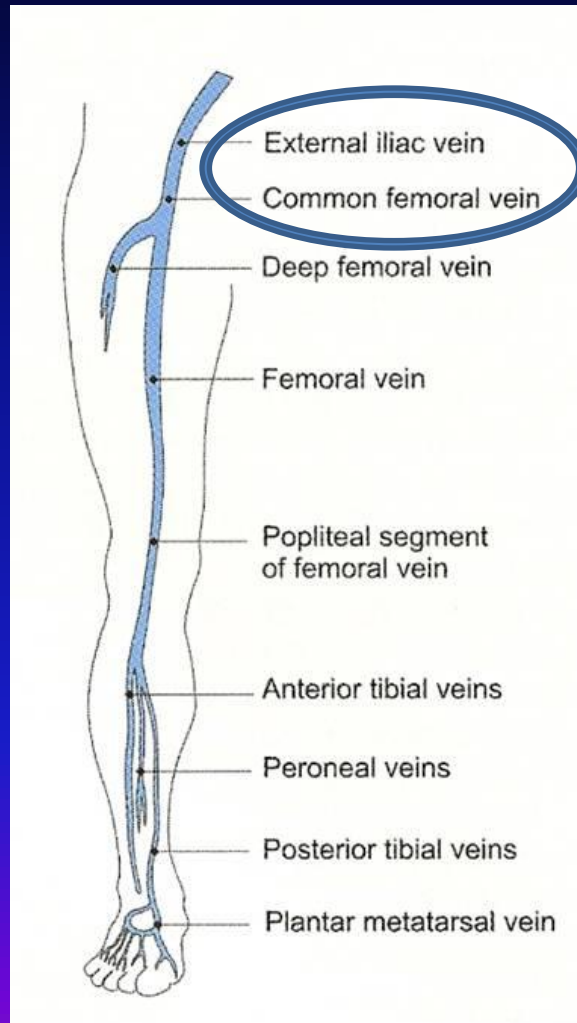
HIGH RISK

treatment same as proximal DVT

HIGH RISK

- + d-dimer
- severe symptoms
- cancer
- VTE history
- no reversible provoking factor
- hospitalized
- near proximal veins
- > 5 cm long, mult veins, > 7 mm

Iliofemoral Venous Thrombosis

- **common femoral ± iliac** veins
- 25% of symptomatic LE DVT
- ↑ PTS
- ↑ recurrent VTE 2.4x

PMID: 21722789, 19017588, 11343664

CaVenT Trial

- Randomized, open label, 209 patients
- DVT above mid-thigh level
  - Stratified for pelvic involvement
- Intervention: CDT with rt-PA (Alteplase)
- Control: LMWH + warfarin
- Outcome:
  - Frequency of PTS (Villalta) 24 months
  - Iliofemoral patency 6 months

PMID: 22172244 (2012)

CaVenT Trial: 5-Year FU

	Adjunctive catheter-directed thrombolysis (n=87)		Standard treatment (n=89)		p value*	Risk difference (absolute risk reduction)
Post-thrombotic syndrome	37	42·5% (32·7–53·0)	63	70·8% (60·6–79·3)	<0·0001	28% (14–42)
Villalta severity category						
Mild (score 5–9)	31/37	83·8% (68·5–92·7)	49/63	77·8% (66·0–86·4)	..	..
Moderate (score 10–14)	2/37	5·4% (0·57–18·6)	13/63	20·6% (12·3–32·3)	..	..
Severe (score >14)	4/37	10·8% (3·7–25·3)	1/63	1·6% (0·0–9·3)	..	..
Iliofemoral patency†	68/86	79·1% (69·2–86·4)	61/86	70·9% (60·6–79·5)	0·218	–8% (–21 to 5)
Femoropopliteal reflux	54/87	62·1% (51·6–71·6)	75/89	84·3% (75·2–90·5)	<0·0004	22% (10–35)

Data are n, n/N, or % (95% CI), unless otherwise stated.*χ² test. †Four patients had inconclusive iliofemoral patency assessments at 5 years.

ACCP Guidelines 2016

- 16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

"...patients who are most likely to benefit from CDT have **iliofemoral** DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year, and a low risk of bleeding."

2012	2016
In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C).	In patients with acute proximal DVT of the leg, recommend anticoagulant therapy alone over catheter-directed thrombolysis (Grade 2C).

CASE #3

A 55 year-old man presents with pleuritic chest pain. His BP is 120/70, HR 105, RR is 18, and his O2 sat is 97%. His physical exam is unremarkable. A chest CT shows multiple pulmonary emboli. ECG is normal.

CASE #3

What is this patient's risk of early mortality related to PE?

A) 1%

B) 10%

C) 20%

Pulmonary Embolism Severity Index
Estimates the risk of 30-day mortality from PE

Table 1 Points assigned to prognostic variables in the prognostic model

Prognostic variables	Points assigned
Demographics	
Age (years)	Age
Male sex	+10
Comorbid conditions	
Cancer	+30
Heart failure	+10
Chronic lung disease	+10
Clinical findings	
Pulse ≥110 per minute	+20
Systolic blood pressure <100 mmHg	+30
Respiratory rate ≥30 per minute	+20
Temperature < 36°C	+20
Altered mental status[a]	+60
Arterial oxygen saturation <90%[b]	+20

Class (Risk)	Score/Points	30-Day Mortality
I (Very Low)	<66	0%
II (Low)	66-85	1%
III (Intermed)	86-105	3.1%
IV (High)	106-125	10.4%
V (Very High)	>125	24.4%

Total point score obtained by summing patients age in years and the points for each applicable characteristic

Aujesky D et al, Eur Heart J 2006; 27:476-481.

Simplification of the Pulmonary Embolism Severity Index for Prognostication in Patients With Acute Symptomatic Pulmonary Embolism

David Jiménez, MD, PhD; Drahomir Aujesky, MD; Lisa Moores, MD; Vicente Gómez, MD;
José Luis Lobo, MD, PhD; Fernando Uresandi, MD, PhD; Remedios Otero, MD, PhD;
Manuel Monreal, MD, PhD; Alfonso Muriel, MSc; Roger D. Yusen, MD; for the RIETE Investigators

Simplified Version
(Score > 1 = high risk)
- age > 80 y
- history of cancer
- COPD
- pulse ≥110 bpm
- BP < 100 mmHg
- art O2 sat < 90%

Patients in Simplified PESI:
Low risk 30-day mortality of 1%
High risk 30-day mortality of 10.9%

*Estimates the risk of
30-day mortality from PE*

Case #3

The patient has no contraindications to anticoagulant therapy and she is willing to follow your recommendations. In fact, she has seen several TV advertisements for DOACs. At this point how would you treat the patient?

a) Administer systemic thrombolytics per protocol

b) Initiate either IV heparin drip or SC LMWH therapy

c) Initiate either inpatient or outpatient po rivaroxaban or apixaban after a period of observation

Case #3

You decide to

a) Admit patient for anticoagulation and monitoring

b) Discharge patient to home with LMWH/warfarin , rivaroxaban, or apixaban and arrange close follow up as outpatient

ACCP 2016:
Choice of Long Term (1st 3 Months) & Extended Anticoagulant Therapy

- **In patients with DVT of the leg or PE (w/o active cancer):**
  - **DOAC's are preferred over warfarin (Grade 2B)**
  - **Warfarin preferred over LMWH (Grade 2C)**

  - No one DOAC is preferred over the other
  - Extended treatment w/ DOACs reduces recurrent VTE and is associated with less bleeding risks

Kearon C, et al. CHEST Guideline, *Chest.* 2016.

ACCP 2016:
Outpatient Treatment of Low Risk PE

Suitable for outpatient treatment:

1. No contraindications (recent bleeding, severe renal/liver disease, or severe thrombocytopenia)

2. Expected to be compliant with treatment

3. Feels well enough to be treated at home

- Clinical prediction rules such as PESI (<85 or simplified score 0) can identify low-risk patients
- Echo and biomarkers not routinely recommended
- If noted, RV dysfunction or increased biomarker levels should discourage home treatment

Kearon C, et al. CHEST Guideline, *Chest.* 2016.

Outpatient Treatment of Pulmonary Embolism (OPTE)

outcome	Out N=171	In N=168	Difference in %age	p value
Recurrent VTE	1	0	0.6%	0.01
Major bleed*	3	0	1.8%	0.08
Mortality	1	1	0.6%	0.05

- Excluded: O2 sat < 90%, SBP<100, chest pain active or high risk bleeding, recent CVA GIB in past 2 weeks, plt<75K, crcl < 30, wt > 150 kg, anticoagulation failure, poor follow up
- If discharged called every day for one week
- major bleeds-2 IM hematomas day 3/13; 1 DUB day 50

Aujesky D. et al. Lancet. 2011 Jul 2;378
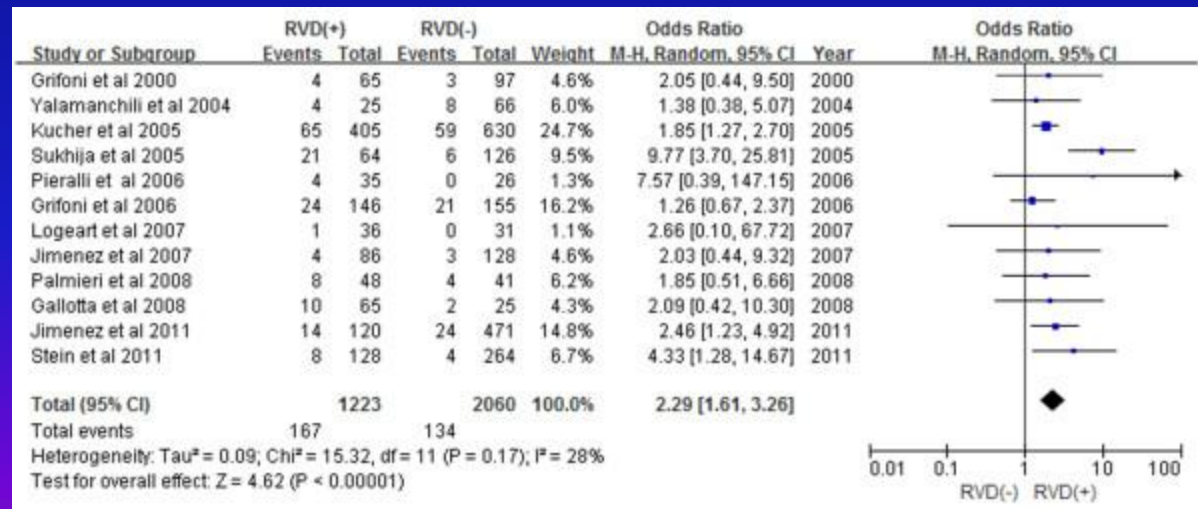
Echocardiogram and PE Prognosis

Meta-analysis - RV dysfunction as a prognostic factor in stable patients with PE

- 12 trials, 3283 hemodynamically stable patients with acute PE
  - 1223 patients (37.3%) RVD+
  - 2060 patients (62.7%) RVD-

MORTALITY

167/1223 (13.7%)

134/2060 (6.5%)

Study or Subgroup	RVD(+) Events	Total	RVD(-) Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Grifoni et al 2000	4	65	3	97	4.6%	2.05 [0.44, 9.50]	2000
Yalamanchili et al 2004	4	25	8	66	6.0%	1.38 [0.38, 5.07]	2004
Kucher et al 2005	65	405	59	630	24.7%	1.85 [1.27, 2.70]	2005
Sukhija et al 2005	21	64	6	126	9.5%	9.77 [3.70, 25.81]	2005
Pieralli et al 2006	4	35	0	26	1.3%	7.57 [0.39, 147.15]	2006
Grifoni et al 2006	24	146	21	155	16.2%	1.26 [0.67, 2.37]	2006
Logeart et al 2007	1	36	0	31	1.1%	2.66 [0.10, 67.72]	2007
Jimenez et al 2007	4	86	3	128	4.6%	2.03 [0.44, 9.32]	2007
Palmieri et al 2008	8	48	4	41	6.2%	1.85 [0.51, 6.66]	2008
Gallotta et al 2008	10	65	2	25	4.3%	2.09 [0.42, 10.30]	2008
Jimenez et al 2011	14	120	24	471	14.8%	2.46 [1.23, 4.92]	2011
Stein et al 2011	8	128	4	264	6.7%	4.33 [1.28, 14.67]	2011
Total (95% CI)		1223		2060	100.0%	2.29 [1.61, 3.26]	
Total events	167		134				

Heterogeneity: Tau² = 0.09; Chi² = 15.32, df = 11 (P = 0.17); I² = 28%
Test for overall effect: Z = 4.62 (P < 0.00001)

Cho JH, et al. *BMC Cardiovascular Disorders.* 2014;14:64.

ACCP Guidelines for Outpatient Treatment of Patients With DVT/PE

Acute DVT

Low-Risk PE

Current guidelines recommend initial treatment at home over treatment in-hospital (Grade 1B)

Current guidelines recommend early discharge over standard discharge (Grade 2B)

These recommendations are contingent on adequate home circumstances, including:

- Well-maintained living conditions
- Strong support network
- Phone access

- Patient feeling well enough for home treatment
- Ability to be promptly rehospitalized

Hospitalizations and Other Healthcare Resource Utilization among Patients with Deep Vein Thrombosis Treated with Rivaroxaban versus Low-Molecular Weight Heparin and Warfarin in the Outpatient Setting

Deitelzweig S, Laliberté F, Crivera C, et al. Hospitalizations and Utilization of Other Healthcare Resources among Patients with Deep Vein Thrombosis Treated with Rivaroxaban versus Low-Molecular-Weight Heparin and Warfarin in the Outpatient Setting. *Clinical Therapeutics.* 2016; [In press]

Study Results
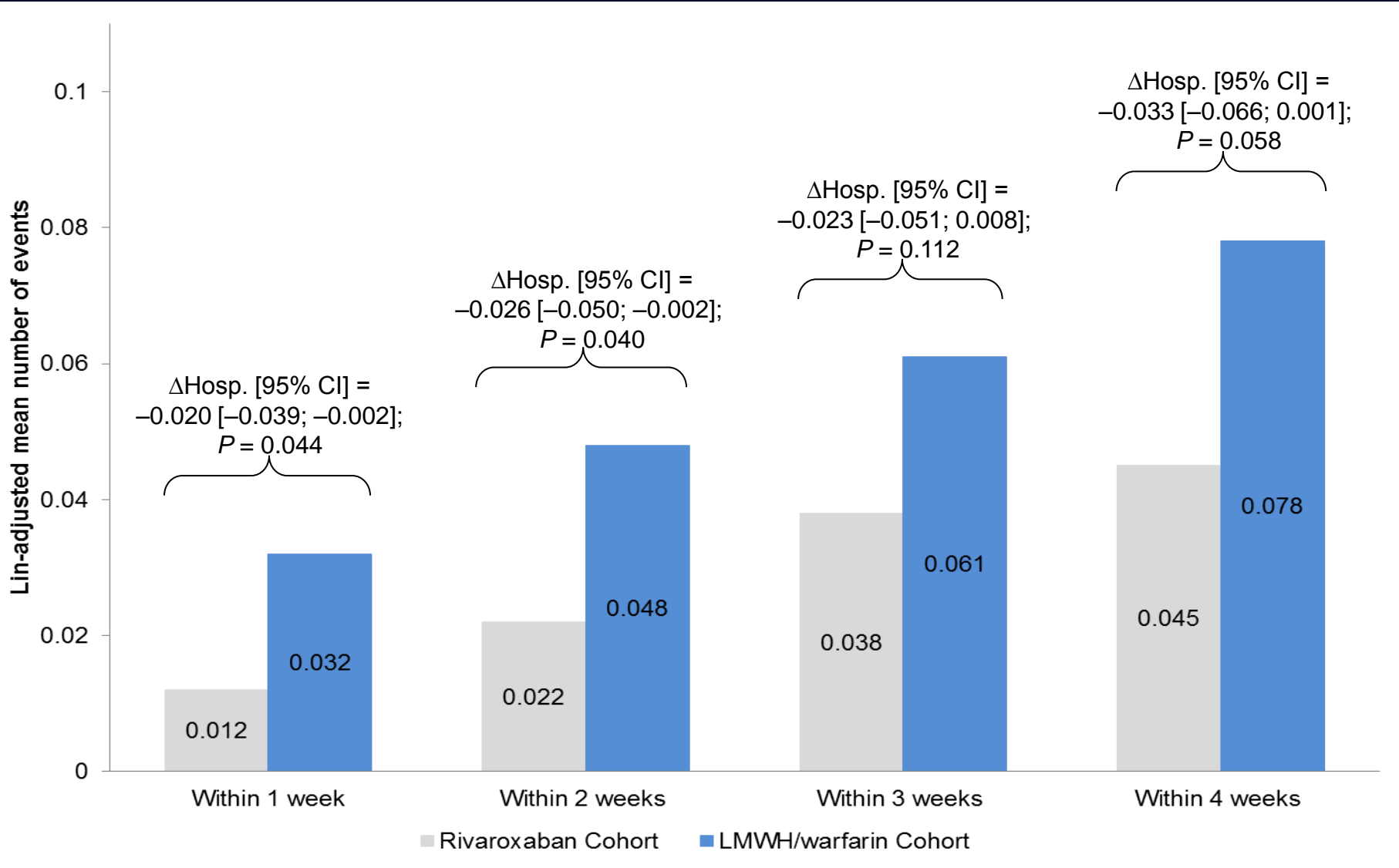
Figure 1. All-Cause Hospitalization – Matched Rivaroxaban and LMWH/Warfarin Users

Study Results

Associated Healthcare Costs:

- All-cause total healthcare costs were significantly lower for rivaroxaban users compared to LMWH/warfarin users over 1 week ($2,332 vs $3,428; P <0.001) and 2 weeks ($3,108 vs $4,524; P <0.001) and were numerically (but not statistically significantly) lower over 3 and 4 weeks

- All-cause hospitalization costs were significantly lower for rivaroxaban users compared to LMWH/warfarin users over 1 week ($171 vs $873; P = 0.014) and 2 weeks ($466 vs $1,342; P = 0.036) and were numerically (but not statistically significantly) lower over 3 and 4 weeks

- The pharmacy costs were significantly lower for patients treated with rivaroxaban over 1, 2, 3, and 4 weeks (P <0.001), with rivaroxaban users incurring about half the cost of the LMWH/warfarin users over the first 2 weeks

ACCP 2016 *VTE Treatment*

Subsegmental PE
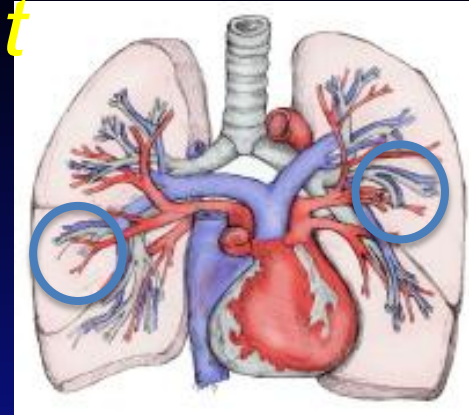
- Subsegmental PE: confined to the subsegmental pulmonary artery

  – A true subsegmental PE is thought to be likely to have arisen from a small DVT.

- Unclear how clinically relevant these events are, and thus unclear whether or not to treat these events with anticoagulants as risk may be > benefit

- Diagnosis is more likely to be a false positive finding compared to a diagnosis of PE in the segmental or more proximal pulmonary arteries

Subsegmental PE

- With new advancements in imaging, diagnosis of these events has increased.

- **In patients diagnosed with a subsegmental PE and confirmed to have no proximal DVT and have a low risk for a recurrent clotting event, surveillance is recommended over anticoagulation (Grade 2C)**

- **But if patient has a high risk for recurrent VTE, anticoagulation is recommended over surveillance (Grade 2C).**

Comparison of NOAC Trials in DVT/PE Treatment: Study Designs

	XARELTO® (rivaroxaban)	ELIQUIS® (apixaban)	PRADAXA® (dabigatran)	LIXIANA® (edoxaban)
Trials	EINSTEIN DVT & PE	AMPLIFY	RECOVER I & II	HOKUSAI VTE
Sample size, n (%)	N=8282	N=5395	N=5107	N=8240
PE patients, n (%)	4832 (58)	1836 (34)	~31%	3319 (40)
Active cancer, n (%)**	430 (5.3)	143 (2.7)	~4.7%	208 (2.5)‡
Unprovoked, n (%)	5255 (63)	4845 (90)	N/A	5410 (66)
Regimen	Single oral agent concept	Single oral agent concept	Initial Heparin Bridge Required	Initial Heparin Bridge Required
Dosing	**15mg bid** x **21 d**, then **20 mg qd** [3, 6, or 12 mo]	**10 mg bid** x **7 d**, then **5 mg bid** [6 mo]	**LMWH/UFH** x **5-10 d**, then **150 mg bid** [6 mo]	**LMWH/UFH** x **5-12 d**, then **60 mg qd** [3, 6, or 12 mo]

*Postrandomization.

**At baseline.

†Double-dummy period – oral drug only, dabigatran vs warfarin.

‡HOKUSAI enrolled 771(9.3%) patients with cancer listed as the cause of DVT or PE.

For Presentation Only – Not intended for data comparison.

DVT/PE Labels: Treatment

|	XARELTO® (rivaroxaban)	ELIQUIS® (apixaban)	PRADAXA® (dabigatran)	LIXIANA® (edoxaban)
Dosing	**15mg bid** x **21 d**, then **20 mg qd** [3, 6, or 12 mo]	**10 mg bid** x **7 d**, then **5 mg bid** [6 mo]	**LMWH/UFH** x **5-10 d**, then **150 mg bid** [6 mo]	**LMWH/UFH** x **5-12 d**, then **60 mg qd** [3, 6, or 12 mo]
Efficacy	Noninferior	Noninferior	Noninferior	Noninferior
Major Bleeding	↓ 46%	↓ 69%	Noninferior * ↓ 40%†	Noninferior
MB/CRNMB	Noninferior	↓ 56%	↓ 38%* ↓ 44%†	↓ 19%
Renal Adjustment	Avoid if CrCL<30 mL/min	PK/PD	Avoid if CrCL<30 mL/min	30 mg qd if CrCL 30-50 mL/min; Avoid if <30 mL/min

*Postrandomization.

†Double dummy period – oral drug only, dabigatran vs warfarin.

For Presentation Only – Not intended for data comparison.

Relative Comparison of DOACs

VTE recurrence and rates of major or CRNM bleeding in VTE studies that compared DOACs with either LMWH and VKAs or VKAs
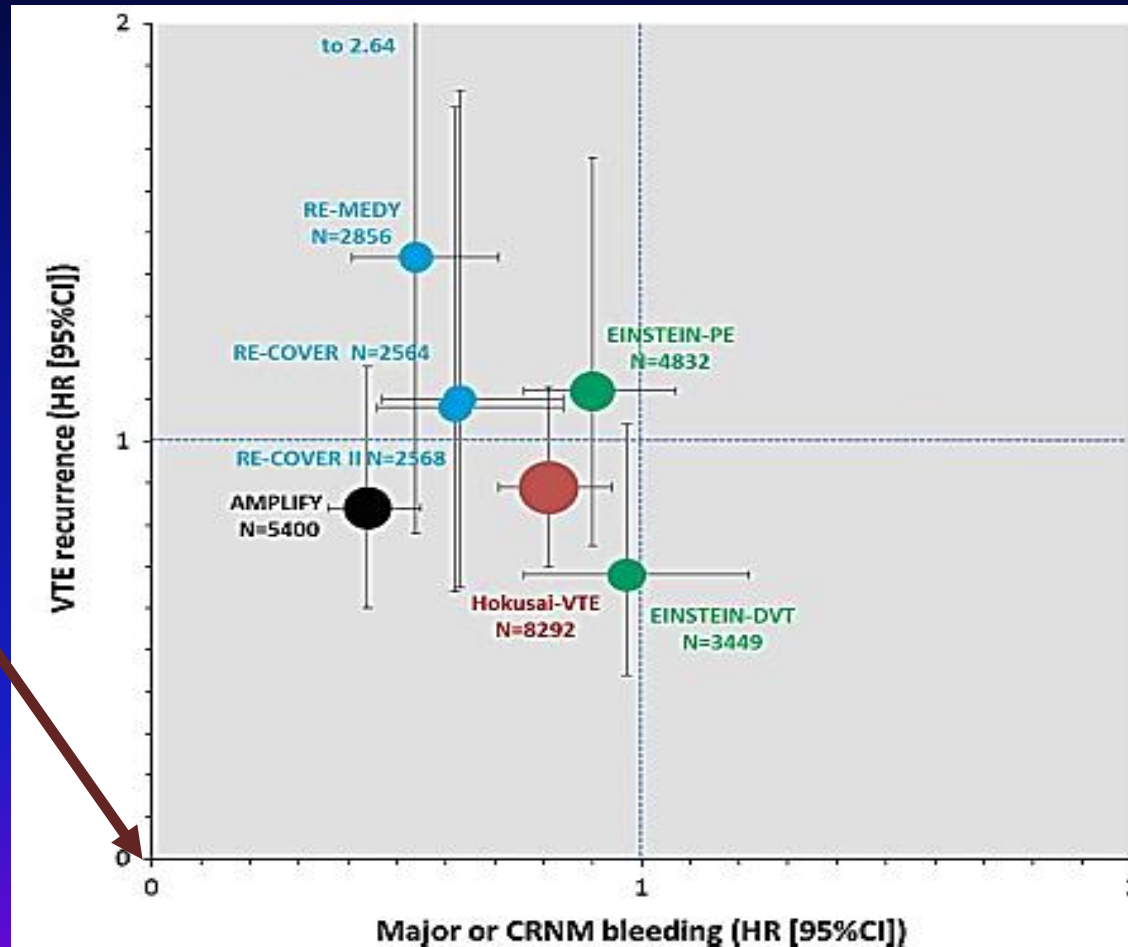
Perfect Outcome

When should you use a new oral anticoagulant?

- Your patient is adherent
- Your patient has a poor INR control (TTR < 60%)
- Your patient has good renal function (creatinine clearance 50 ml/min or better)
- Your patient has good hepatic function (AST/ALT and bilirubin normal or < 2x ULN)

When should you avoid a new oral anticoagulant?

- Your patient is poorly adherent
- Your patient has poor renal or hepatic function
- Your patient is on strong p-glycoprotein or CYP 3A4 inhibitors/inducers
- Your patient is pregnant
- Your patient is on dual anti-platelet therapy
- Your patient has cancer – probably changing

Catheter-Based Thrombus Removal for the Initial Treatment of PE

- Evidence for the use of CDT compared with anticoagulation alone, CDT compared to systemic thrombolytic therapy, and catheter-based treatment without thrombolytic therapy is low quality and recommendations made are weak.
- CDT may be more effective than systemic thrombolysis:
  - Achieves a higher local concentration of thrombolytic drug by infusing the drug directly into the PE itself.
  - Fragmentation of the thrombus due to the placement of the catheter may enhance pharmacologic or endogenous thrombolysis

Catheter-Based Thrombus Removal for the Initial Treatment of PE

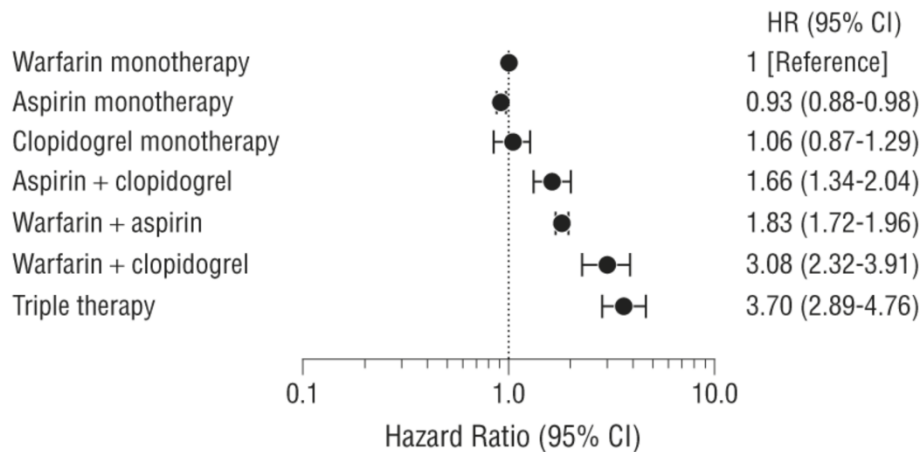| 2012	2016
In patients with acute PE associated with hypotension and who have (i) contraindications to thrombolysis, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are avail-able, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C)**.**	**In patients with acute PE associated with hypotension and who have (i) high bleeding risk, (ii) failed thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are avail-able, we suggest catheter-assisted thrombus removal over no such intervention** (Grade 2C)**.**
In patients with acute PE, when a thrombolytic agent is used, we suggest administration through a peripheral vein over a pulmonary artery catheter (Grade 2C)**.**	**In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter directed thrombolysis (CDT) (Grade 2C).**

Case #4

A 65 year old man with history of HTN and hyerlipidemia is admitted with a new PE. He is on ASA and statin. He is started on LMWH and bridged to warfarin. You:

A) stop his aspirin now that he is on warfarin due to concerns of increased risk of bleeding

B) continue ASA for primary prophylaxis

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

	HR (95% CI)
Warfarin monotherapy	1 [Reference]
Aspirin monotherapy	0.93 (0.88-0.98)
Clopidogrel monotherapy	1.06 (0.87-1.29)
Aspirin + clopidogrel	1.66 (1.34-2.04)
Warfarin + aspirin	1.83 (1.72-1.96)
Warfarin + clopidogrel	3.08 (2.32-3.91)
Triple therapy	3.70 (2.89-4.76)

Hazard Ratio (95% CI)

warfarin + asa= 2x
warfarin + asa + clopidigrel=3x

Hansen M et al. Arch Intern Med. 2010

CHEST GUIDELINES

"For patients taking warfarin we suggest AVOIDING concomitant antiplatelet therapy except where benefit is likely to be greater than harm: valves, ACS, stents, CABG" (2C)

Holbrook A et al. CHEST 2012 (Suppl);Anand S et al JAMA 1999l

Case #5a:How long will you recommend this patient stay on anticoagulation?

55 yo man with unprovoked PE?

     a) 3 months

     b) 6 months

     c) 12 months

     d) Indefinitely

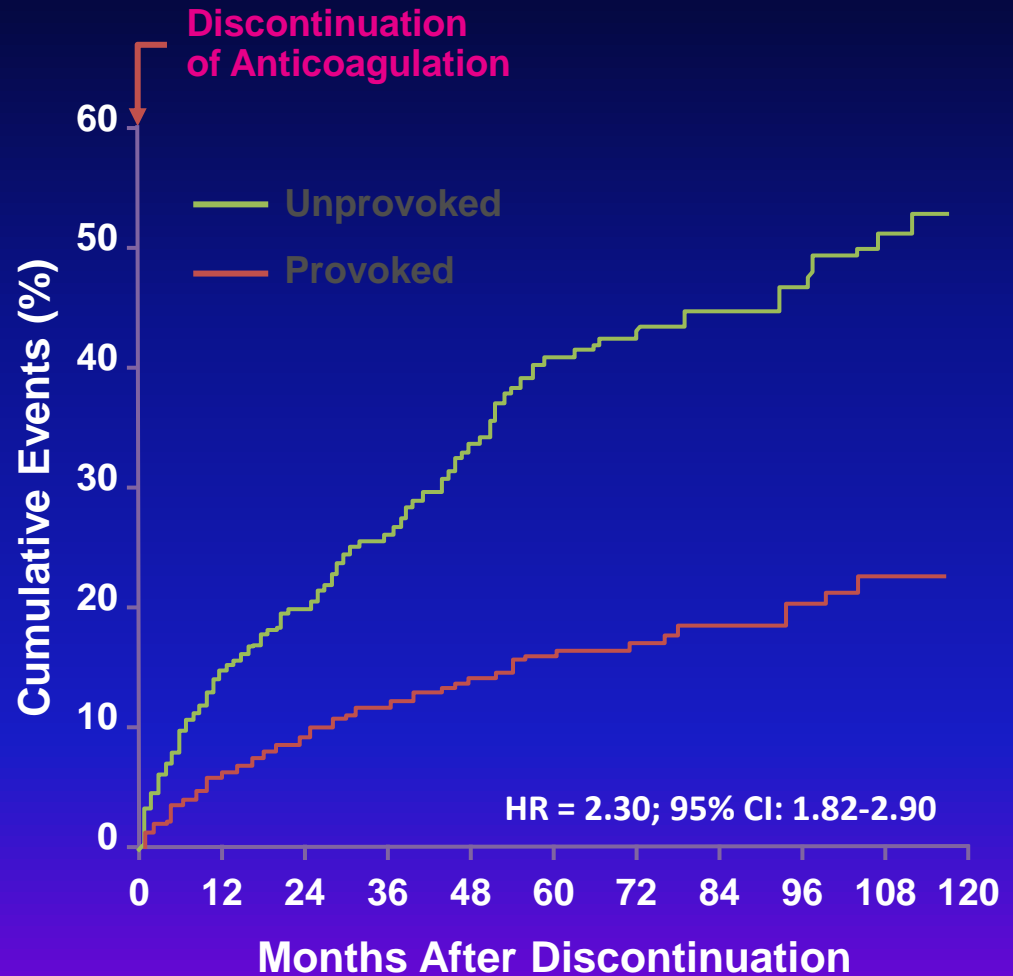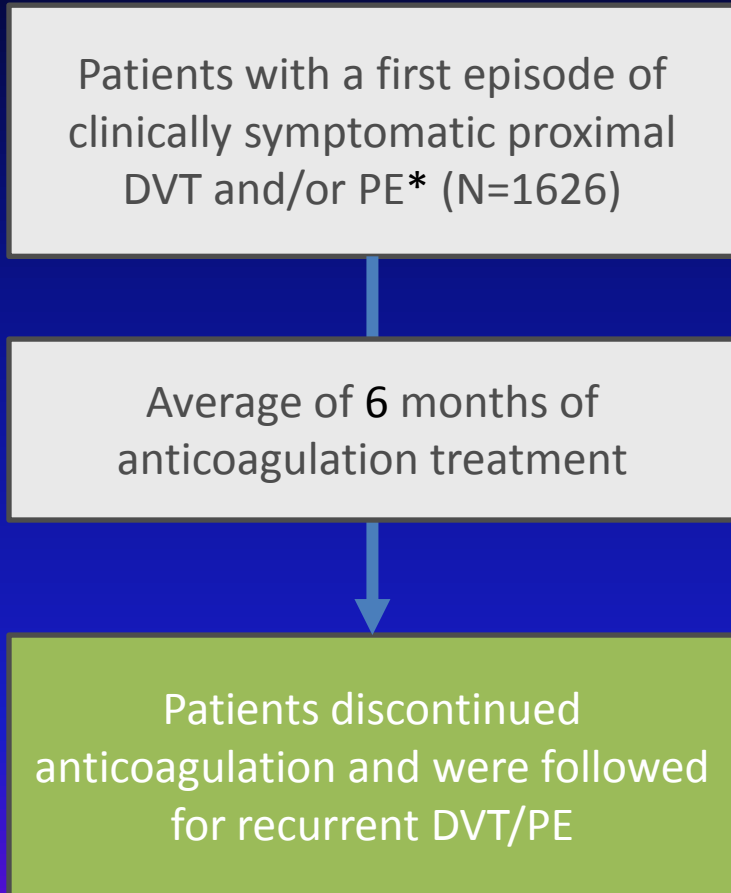# Case #5b: How long will you recommend this patient stay on anticoagulation?

*68 yo woman with
provoked PE ?*

      a) 3 months

      b) 6 months

      c) 12 months

      d) Indefinitely

Risk of VTE Recurrence After Cessation of VTE

Risk factor	1st yr	Next 5 yrs
Distal DVT	3% (6%)	<10%
Major-transient	3%	10%
Minor-transient	5-6%	15%
Unprovoked	At least 10%	30%
Recurrent	> 10%	> 30%

Kearon, Blood 2005

The Risk of Recurrence Is Higher With Unprovoked VTE After Discontinuation of Anticoagulation[91]

Patients with a first episode of clinically symptomatic proximal DVT and/or PE* (N=1626)

Average of 6 months of anticoagulation treatment

Patients discontinued anticoagulation and were followed for recurrent DVT/PE

Discontinuation of Anticoagulation

Cumulative Events (%)

— **Unprovoked**
— **Provoked**

HR = 2.30; 95% CI: 1.82-2.90

Months After Discontinuation

*Excluded patients with active cancer, prior VTE, an indication for indefinite anticoagulation, geographic inaccessibility to follow-up, or poor life expectancy.

Clinical presentation predicts likelihood and type of recurrence

- Distal (calf vein thrombosis)
  - Low risk of recurrence/PE
- Proximal- nearly 5 fold increased recurrence risk over distal
- PE vs. DVT
  - Patients presenting with PE are 3x more likely to suffer recurrent PE than those presenting with DVT

Baglin T et al J Thromb Haemost. 2010

Clinical Scores to Predict Recurrence

	Men continue and HER DOO2	Vienna Prediction Model	DASH-Score
Author (reference)	Rodger et al. (24)	Eichinger et al. (25)	Tosetto et al. (26)
Number of patients	646	929	1818
Design	Prospective cohort	Prospective cohort	Patient level meta-analysis
Predictive variables	Men: none Women: Age ≥ 60 years Signs of PTS BMI ≥ 30 kg/m^2 D-dimer ≥ 250 μg/l during anticoagulation	Sex Location of first VTE D-Dimer after anticoagulation	Abnormal D-Dimer after anticoagulation Age < 50 years Male sex Hormonal therapy
Recurrence risk Low risk	≤ 1 point 1.6% (95% CI 0.3%–4.6%)	≤ 180 points (according to nomogram) 4.4% (95% CI 2.7%-6.2%)	≤ 1 point 3.1% (95% CI 2.3 – 3.9)

D-dimer and Recurrent VTE

		D-dmer +	D-dimer -
Prolong (18 months)	D-dimer @ 1 month after AC stopped	15%	6.2%
Annals 2008 (one year)	Systematic review	8.9	3.5%
Prolong II (one year)	d-dimer q 2 months after 1st negative d-dimer	27%	2.9%
Cosmi et al (18 months)	d-dimer & RVO	9-12%	0-5%

Verhovsek et al Ann Intern Med 2008;Cosmi et al Blood 2010;Palareti NEJM 2006;Cosmi Thromb Haemost 2011

Duration of AC Treatment Based on Type of VTE

Type of VTE	Recommended Duration of Treatment 2012	Recommended Duration of Treatment 2016
Proximal DVT of the leg or PE provoked by surgery	3 months	3 months
DVT of the leg or PE provoked by a nonsurgical transient risk factor	3 months	3 months
Isolated distal DVT of the leg provoked by surgery or nonsurgical transient risk factor	3 months	3 months
Unprovoked PE or DVT of the leg	At least 3 months	At least 3 months
Pt's first DVT that is an unprovoked proximal DVT of the leg or PE	At least 3 months	Extended therapy (no scheduled stop date)
In patients with a second unprovoked VTE with a low bleeding risk	Recommend extended therapy	Extended therapy (no scheduled stop date)
In patients with a second unprovoked VTE with a moderate bleeding risk	Suggest extended therapy	At least 3 months
In patients with a second unprovoked VTE with a high bleeding risk	Suggest 3 months	3 months
Patients with DVT of the leg and active cancer w/ or w/o high risk of bleeding	Extended therapy	Extended therapy (no scheduled stop date)

ACCP Guidelines Regarding Extended Therapy Are Stratified by Bleeding Risk

- Currently, there is a lack of well-validated tools to stratify the risk of major bleeding during extended anticoagulant therapy in patients with VTE
- However, the risk of bleeding in patients receiving anticoagulant therapy may increase with the prevalence of certain factors, including:

- Advanced age
- Cancer
- Kidney or liver failure
- Comorbidity and reduced functional capacity

- Antiplatelet therapy
- Previous stroke
- Anemia
- Alcohol abuse

- Thrombocytopenia

- Previous bleeding
- Diabetes
- Frequent falls
- Poor anticoagulant control
- Recent surgery

ACCP Guidelines Regarding Extended Therapy Are Stratified by Bleeding Risk

	Estimated Absolute Risk of Major Bleeding After 3 Months of Anticoagulation, % per year		
	Low Risk (0 Risk Factors)	Moderate Risk (1 Risk Factor)	High Risk (≥2 Risk Factors)
Baseline risk of bleeding with no anticoagulation	0.3	0.6	≥2.5
Increased risk with anticoagulation	0.5	1.0	≥4.0
Total risk of bleeding on therapy	0.8	1.6	≥6.5

- Current guidelines recommend extended anticoagulation for most patients with unprovoked DVT/PE and a low to moderate bleeding risk

Aspirin for Extended Treatment of VTE

- **In patients with an unprovoked proximal DVT or PE who are stopping AC treatment and have no contraindication to aspirin, recommend aspirin over no aspirin to prevent recurrent VTE (Grade 2C).**

  - Two randomized trials have compared aspirin to placebo for the prevention of VTE in patients with a first unprovoked PE or VTE who have completed 3-18 months of AC treatment [3,4]

3. Brighton TA, et al. *The New England Journal of Medicine*. 2012. 367(21):1979-1987
4. Becattini C, et al. *The New England Journal of Medicine*. 2012. 366(21):1959-1967.

Aspirin for Extended Treatment of VTE

Table 13: Summary of Findings - Aspirin vs Placebo for extended treatment of VTE

Bibliography: Simes et al. (INSPIRE)[70]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Aspirin (95% CI)
All Cause Mortality	1224 (2 studies) up to 4 years	⊕⊕⊖⊖ **LOW**[3,4,5] due to imprecision	**HR 0.82** (0.45 to 1.52)[2]	Moderate risk population[1]	
				5 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Recurrent VTE	1224 (2 studies) up to 4 years	⊕⊕⊕⊖ **MODERATE**[3,5] due to imprecision	**HR 0.65** (0.49 to 0.86)[2]	184 per 1000	60 fewer per 1000 (from 24 fewer to 89 fewer)
Major Bleeding	1224 (2 studies) up to 4 years	⊕⊕⊕⊖ **MODERATE**[3,4] due to imprecision	**HR 1.31** (0.48 to 3.53)[2]	12 per 1000	4 more per 1000 (from 6 fewer to 29 more)

Duration of Anticoagulation Unprovoked VTE

**After 3 months of tx
Assess bleeding risk
Consider indefinite tx
(esp PE, male,
thrombophilia)
patient preference**

IF DVT get u/s. measure d-dimer . If d-dimer + continue AC

**Female:
Clinical prediction rule:<1 and wants to stop anticoagulation-ok**

**Male:
Stop AC and Measure D-dimer at 30days,if low ok If elevated consider Restarting tx**

**High bleed risk
Elderly
Bleed on AC
STOP AC**

Case #5a/b: How long will you recommend these patients stay on anticoagulation?

55 yo man with unprovoked PE?

a) 3 months

b) 6 months

c) 12 months

d) Indefinitely

68 yo woman with provoked PE ?

a) 3 months

b) 6 months

c) 12 months

d) Indefinitely

Use of Compression Stockings to Prevent Post-Thrombotic Syndrome

- Since the 2012 update, a larger multicenter, placebo-controlled trial found that routine use of compression stockings did not reduce the incidence of PTS or have other important benefits[7]

- This study also found that the use of compression stockings did not reduce leg pain 3 months after DVT diagnosis

7. Kahn et al. Lancet. 2014;383(9920):880-888.

2012	2016
In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**.**	**In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS** (Grade 2B).

CASE # 6

A 33 year old woman diagnosed with left lower extremity DVT 3 months ago maintained on warfarin present with complaints of pleuritic chest and shortness of breath. A CT angio of the chest reveals new bilateral subsegmental pulmonary emboli.

CASE #6

She reports compliance with her warfarin therapy and has an INR of 2.5 at the time of admission. She is admitted to your service for recurrent VTE. How do you manage this?

Management of Recurrent VTE on Anticoagulant Therapy

- Currently there are no randomized trials or prospective cohort studies that have evaluated the management of patients with recurrent VTE while on anticoagulant therapy

- Management is based on low quality of evidence and an assessment of the probable risk of recurrence

VTE Despite Anticoagulation

- Medication adherence
- Antiphospholipid antibody syndrome
- Cancer
- DIC/Trousseaus
- Heparin-induced thrombocytopenia
- Myeloproliferative disorder
- Antithrombin deficiency
- Structural defect

# VTE Despite Anticoagulation

- LMWH failure
  - Change to BID dosing
  - Increase dosing by 25-33% (Grade 2C)
  - Follow anti-Xa levels

- Warfarin failure
  - Transition to LMWH then transition to warfarin with higher target OR continue LMWH

Management of Recurrent VTE on Anticoagulant Therapy

- **In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C)**

# Management Algorithm of Recurrent VTE in Cancer
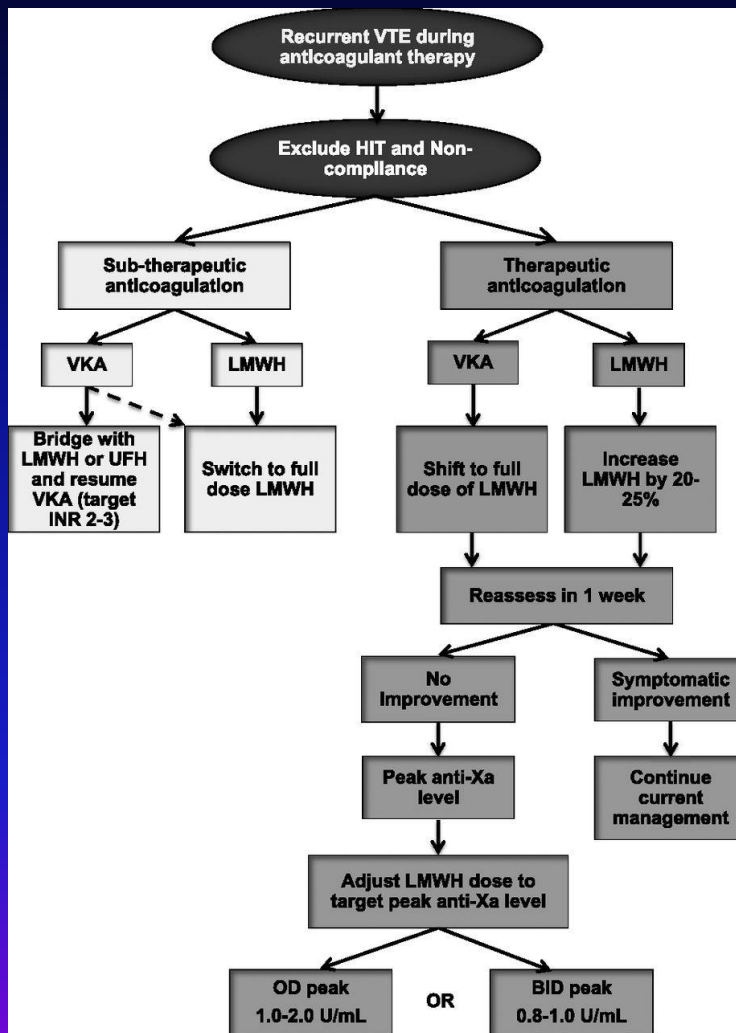
Lee A Y Y et al Blood 2013;122:2310-2317

Role of IVC Filters in Addition to Anticoagulation for Acute DVT or PE

- **In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B).**

- Recommendation from 2012 remains the same, but the quality of evidence has improved

- The PREPIC 2 trial found that IVC filters that are placed for 3 months **did not** reduce recurrent PE in anticoagulated patients

Inferior vena cava (IVC) filter

Inferior vena cava

Filter

Blood clot
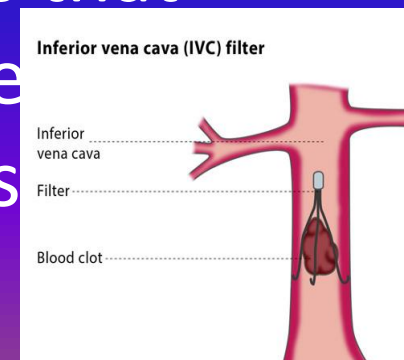
SUMMARY

- Catheter-associated VTE does not mandate catheter removal and requires 3 months of anticoagulation once catheter is removed

- Risk stratify each patient to determine IF calf vein thrombosis needs treatment

- Risk stratify all patients presenting with PE to determine appropriate disposition

SUMMARY

- Minimum effective duration of therapy for VTE is 3 months. If event is unprovoked consider indefinite anticoagulation if bleeding risk is low

- Add DOACS as strong evidence based options for VTE treatment

- Consider assessing individual risk benefit of extended therapy using d-dimer and clinical risk scores

SUMMARY

- Risk benefit of concomitant use of ASA plus warfarin should be assessed in each patient

- Recurrent VTE despite anticoagulation should prompt a work up for HIT, DIC, cancer, APLS MDS and requires intensification of therapy

Questions ?