Medical Treatment of PE
When, Why, For How Long, Can I Remember

Geno J. Merli, MD, MACP, FSVM, FHM
Professor Medicine & Surgery
Co-Director Jefferson Vascular Center
Sidney Kimmel Medical College
Thomas Jefferson University Hospitals

Disclosures

- Co-Investigator: PAUSE VIRTUAL Study, Research Grant Canadian Gov.

Classification of Pulmonary Embolism
Risk of Early In-Hospital or 30-day Death

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

Medical Management
Pharmacologic Therapies

Standard PE Treatment

Agent	Treatment Dose	Half Life	Renal Clearance
UFH	Intravenous 80 u/kg Bolus 18 u/kg/hr Infusion Adjust to lab therapeutic range Uncommon Dosing Schedule Subcutaneous UFH 333 u/kg, SC first dose 250 u/kg, SC, Q12hrs No adjustment bridge to warfarin	1.5 hrs	30%
Dalteparin	100 IU/kg, Q12hrs 200 IU/kg, Qday	3-4 hrs	80%
Enoxaparin	1 mg/kg/ Q12hrs 1.5 mg/kg/ Qday	3-4 hrs	80%
Fondaparinx	< 50 kg – 5 mg Qday 50-100 kg – 7.5 mg Qday > 100 kg – 10 mg	17-21 hrs	100%

Adjustment Unfractionated Heparin

Activated PTT	Change in Dosage
< 35 sec (< 12 x control)	80 U/kg bolus, increase infusion rate by 4 U/kg/hr
35 – 45 sec (1.2 – 1.5 x control)	40 U/kg bolus, increase infusion rate by 2 U/kg/hr
46 – 70 sec (1.5 – 2.3 x control)	No Change
71 – 90 sec (2.3 – 3.0 x control)	Reduce infusion rate by 2 U/kg/hr
> 90 sec (> 3.0 x control)	Stop infusion for 1 hr, the reduce infusion rate by 3U/kg/hr

Raschke et al. Ann Intern Med 1993;119:874

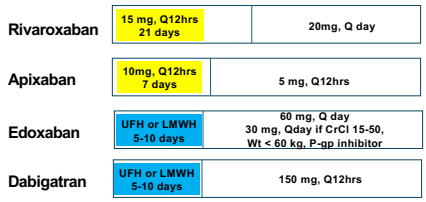
Why Use Weight-Based Heparin

Outcomes	Standard UFH	Weight-Based UFH	P Value
1st aPTT > 1.5*	32%	86%	< 0.001
aPTT > 1.5 in 24 hrs	77%	97%	0.002
aPTT therapeutic in 24hrs	75%	89%	0.08
Minor Bleeding	2/52	2/63	1
Major Bleeding	1/52	0	0.45
RVTE	8/32 (25%)	2/41 (5%)	0.02

* aPTT > 1.5 times control

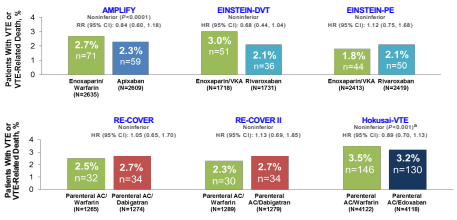
Raschke et al. Ann Intern Med 1993;119:874

Acute Treatment VTE
Direct Oral Anticoagulants



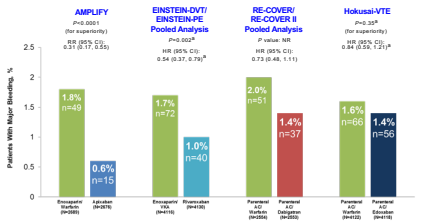
Rosovsky & Merli, Tech Vasc Interven Rad. 2017;20:141

Primary Efficacy Outcomes in DOAC
VTE Treatment Trials



Agnelli G, et al NEJM 2013;369:799
Einstein Investigators NEJM 2010;363:2499
Einstein Investigators NEJM 2012;366:1287
Schulman S, et al NEJM 2009;361:2342
The Hokusai-VTE Investigators, NEJM 2013;369:1406

Major Bleeding Outcomes in DOAC
VTE Treatment Trials



Agnelli G, et al NEJM 2013;369:799
Einstein Investigators NEJM 2010;363:2499
Einstein Investigators NEJM 2012;366:1287
Schulman S, et al NEJM 2009;361:2342
The Hokusai-VTE Investigators, NEJM 2013;369:1406

Long-term VTE Prevention

Group	Recurrent VTE	Hazard Ratio	Major Bleed
Dabigatran 150mg,Q12	0.4%	0.08 (0.02-0.25)	0.3%
Placebo	5.6%		0.0%
Apix 5 mg Q12h	1.7%	0.2 (0.11-0.34)	0.1%
Apix 2.5 mg Q12h	1.7%	0.19 (0.11-0.33)	0.2%
Placebo	8.8%		0.5%
Riva 20mg Qday	1.3%	0.18 (0.09-0.39)	0.7%
Placebo	7.1%		0.0%
Riva 20mg, Qday	1.5%	0.34 (0.20-0.59)	0.5%
Riva 10mg, Qday	1.2%	0.26 (0.14-0.47)	0.4%
ASA 100mg, Qday	4.4%		0.3%

Schulman S, et al NEJM 2013;368:709-71
Agnelli G, et al NEJM 2012;1-10
Einstein Investigators NEJM 2010;363:2499-2510
Weitz J, et al. NEJM 2017;376:1211

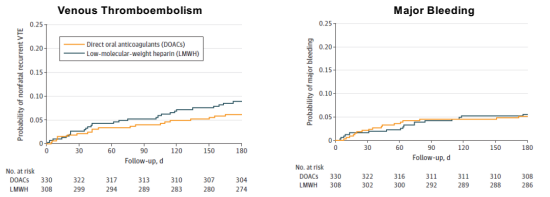
DOAC vs LMWH Cancer VTE Treatment

Outcome	Houksai Cancer (1) Edoxaban	SELECT (2) Rivaroxaban	ADAM (3) Apixaban	CARAVAGGIO (4) Apixaban
VTE DOAC	7.9% (41/522)	4% (8/203)	0.7% (1/145)	5.6% (32/576)
VTE LMWH	11.3% (59/524)	11% (18/203)	6.3% (9/124)	7.9% (46/579)
	HR 0.71(95%CI 0.48-1.06)	HR 0.43(95%CI 0.48-1.06)	HR 0.099(95%CI 0.013-0.78)	HR 0.63(95%CI 0.37-1.07)
Major Bld DOAC	6.9% (36/522)	6% (11/203)	0% (0/145)	3.8% (22/576)
Major Bld LMWH	4% (21/524)	4% (6/203)	1.4% (2/142)	4% (23/579)
	HR 1.77 (95% CI 1.03-3.04)	HR 1.83 (95%CI 0.68-4.96)	HR 0	HR 0.82(95% CI 0.4-1.69)

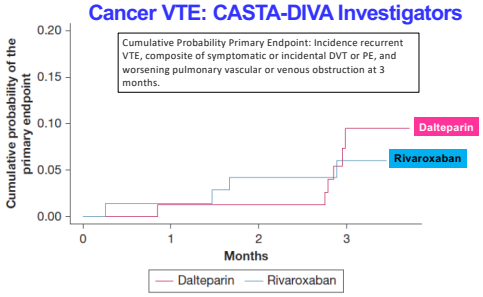
1. Raskob G, et al NEJM 2018;378:615
2. Young A, et al J Clin Oncol 2018;36:2017
3. McBane R, et al J Thromb Haemost 2020;18:411
4. Agnelli G, et al NEJM 2020;382:1599

CANVAS Study
VTE & Major Bleeding

- Schrag D et al. JAMA. 2023;329(22):1924-1933.

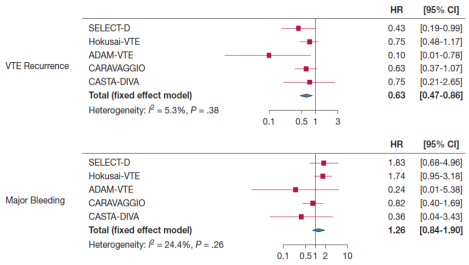


Cancer VTE: CASTA-DIVA Investigators



Planquette B et al. Chest 2022;161:781-790

Meta-Analysis VTE & Cancer Trials



Planquette B et al. Chest 2022;161:781-790

15

When, Why, How Long, Can I Remember

16

Classification of Pulmonary Embolism
Risk of Early In-Hospital or 30-day Death

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

High Risk Early Mortality

WHEN
- UFH is largely restricted to patients with overt hemodynamic instability or imminent hemodynamic decompensation in whom primary reperfusion treatment will be necessary.
- UFH is also recommended for patients with serious renal impairment [creatinine clearance (CrCl) ≤ 30 mL/min] or morbid obesity.

WHY
- Immediate anticoagulation with UFH: short half life, flexible dosing, monitoring (aPTT or ACT)

HOW LONG
- Continue UFH until the next step in anticoagulant management
- Convert to DOAC or Vitamin K Antagonist depending on etiology PE and/or DVT
- In special cases weigh-based LMWH many be indicated

Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT)

Initial Results From a Prospective Multicenter Registry

William T. Kuo, MD, FCCP; Arjun Banerjee, BS; Paul S. Kim, MD; Frank J. DeMarco Jr, MD, FCCP; Jason R. Levy, MD,

- During all thrombolytic infusions, full therapeutic anticoagulation was suspended, and only a small dose of heparin (300-500 units/h) was continued to minimize the risk of peri-sheath clot formation per established protocol.
- After completion of CDT, all patients resumed therapeutic parenteral anticoagulation bridging to warfarin, an injectable anticoagulant as monotherapy, or rivaroxaban

Kuo W, et al Chest 2015;148(3):667

A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism

The SEATTLE II Study

- During the procedure, intravenous unfractionated heparin was continued at intermediate intensity with a target aPTT of 40 to 60 s.
- After removal of the drug delivery device(s), the access site was manually compressed for at least 5 min. Fifteen minutes after achieving hemostasis, full therapeutic anticoagulation was restarted.

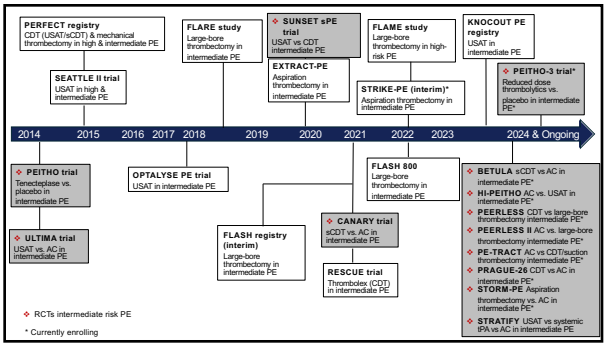
Piazza G et al. JACC: Cardiovasc Interven 2015;8:10

Intermediate Risk Early High Mortality

WHEN
- UFH is largely restricted to patients with overt hemodynamic instability or imminent hemodynamic decompensation in whom primary re-perfusion treatment will be necessary.
- Weight-Based Dosing LMWH
- UFH recommended Renal Dysfunction (CrCl < 30 ml/min) or Morbid Obesity

WHY
- Immediate anticoagulation UFH: short half life, flexible dosing, monitoring (aPTT or ACT)
- LMWH achieves Immediate anticoagulation, no monitoring, must consider renal impairment (CrCl < 30 ml/min)

HOW LONG
- Continue UFH or LMWH until the next step in anticoagulant management
- Convert to DOAC or Vitamin K Antagonist depending on etiology PE and/or DVT
- In special cases weigh-based LMWH many be indicated



Intermediate Risk Early Low Mortality

WHEN
- Weight-Based Dosing LMWH
- UFH weight-based dosing for patient with renal dysfunction (CrCl < 30 ml/min) or Morbid Obesity
- Direct Oral Anticoagulants when patient is stable and progressing to the next level of care

WHY
- LMWH achieves Immediate anticoagulation, no monitoring, must consider renal impairment (CrCl < 30 ml/min)
- Renal Dysfunction UFH: short half life, flexible dosing, monitoring (aPTT or ACT)

HOW LONG
- Continue LMWH until the next step in anticoagulant management
- Convert to DOAC or Vitamin K Antagonist depending on etiology PE and/or DVT
- In special cases weigh-based LMWH many be indicated

Low Risk Mortality

WHEN
- Direct Oral Anticoagulants initial therapy at recommended dosing

WHY
- Direct Oral Anticoagulants: fixed dose, do not require monitoring, less drug interactions

HOW LONG
- Duration of therapy depends on etiology PE and/or DVT

Antithrombotic Therapy for VTE Disease

Second Update of the CHEST Guideline and Expert Panel Report

Scott M. Stevens, MD; Scott C. Woller, MD; Lisa Baumann Kreuziger, MD; Henri Bounameaux, MD;

- In patients with low-risk PE we recommend outpatient treatment over hospitalization provided access to medications, ability to access outpatient care, and home circumstances are adequate (strong recommendation, low-certainty evidence).

Stevens S, et al Chest 2021;160(6):e545

Recommendations Early Discharge Low-Risk Pulmonary Embolism

Recommendation	Class[a]	Level[b]
Carefully selected patients with low-risk PE should be considered for early discharge and continuation of treatment at home, if proper outpatient care and anticoagulant treatment can be provided.[c] 178,206,317–319	IIa	A

Konstantinides S et al Eur Heart J 2020;41:543

Can I remember

- **If you are like me, repetition works best !**
- **Email me and I will send you this slide deck!**

Geno.Merli@Jefferson.Edu