Management of Venous Thromboembolism

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October 4, 2021

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  - Research focus: Thrombosis

Disclosures

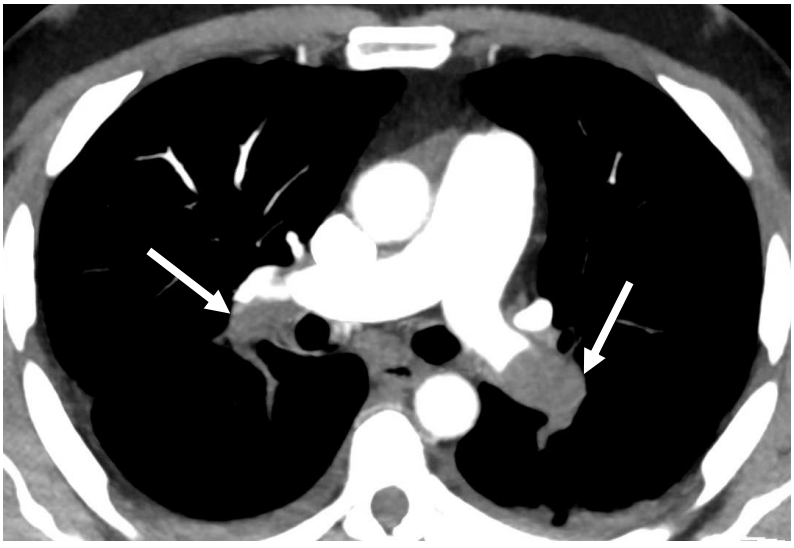
- Research Support:
- Bayer; BMS; Boston Scientific EKOS; Janssen; NHLBI

- Consultant:
- Agile; Bayer

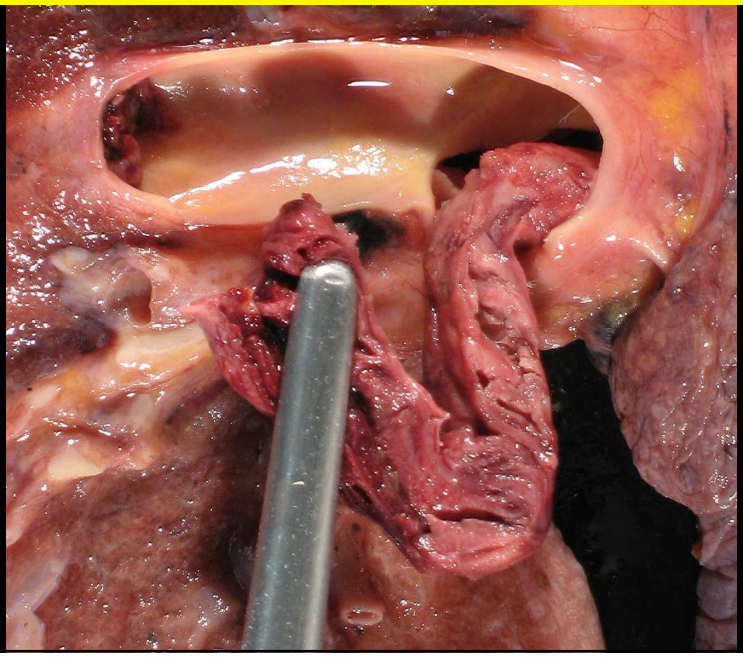
Key Learning Objectives

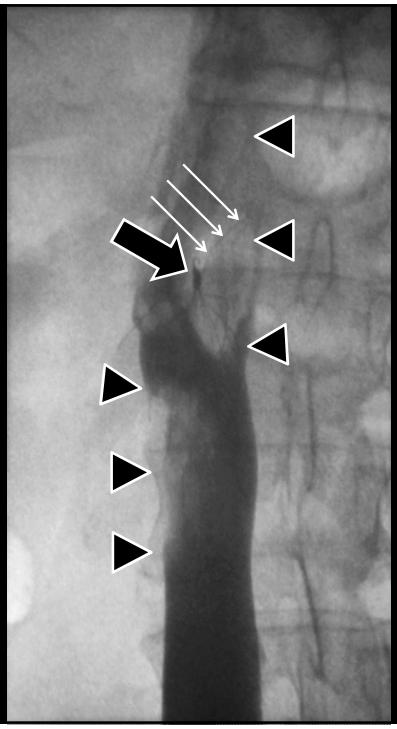
- Epidemiology—mortality rates, inequities
- COVID and VTE
- DOACs for VTE
- Bleeding with DOACs
- Cancer and VTE
- Optimal duration of anticoagulation
- Management beyond anticoagulation: catheter or surgical embolectomy

EPIDEMIOLOGY

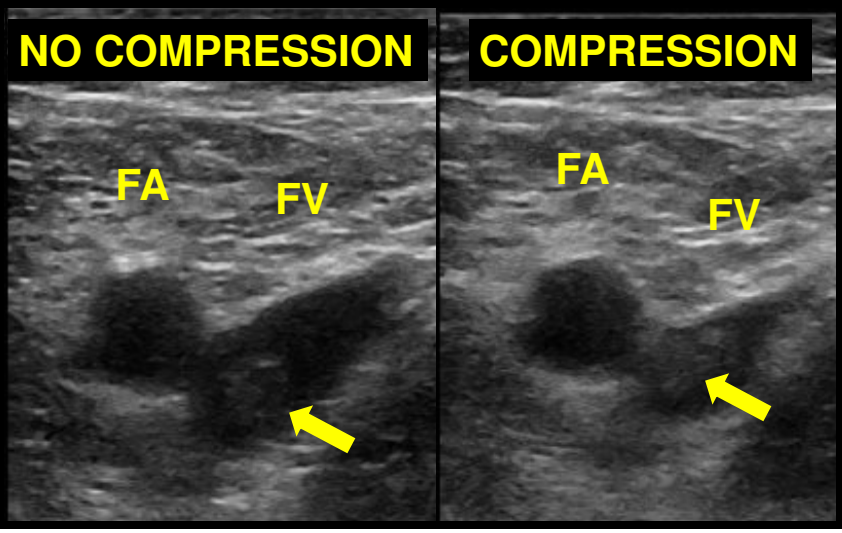


FATAL SADDLE PE: Autopsy





ACUTE DVT in a 29 y.o. man



Post-Mortem Exam in COVID Patient: Right Ventricular Thrombus

Chronic Venous Ulcers: Decrease Quality of Life

POST THROMBOTIC SYNDROME

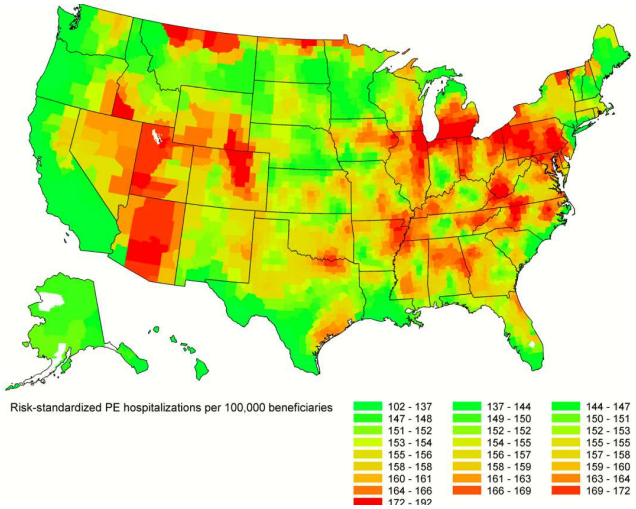
Venous ectasia

Edema

Hyperpigmentation
Venous ulcer

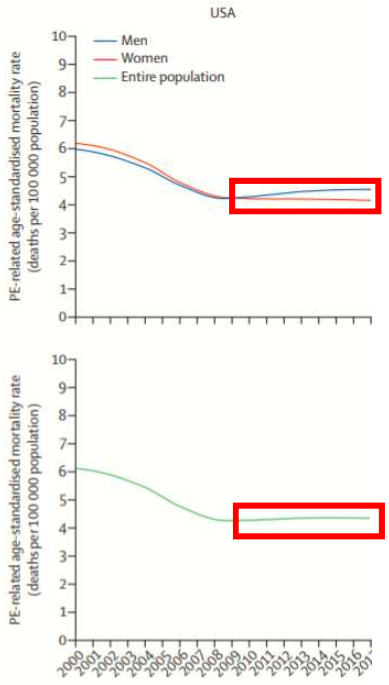
Skin induration
Atrophie Blanche

PE Hospitalizations per 100,000



(Wadhera RK…Goldhaber SZ. JAHA 2021; July 2)

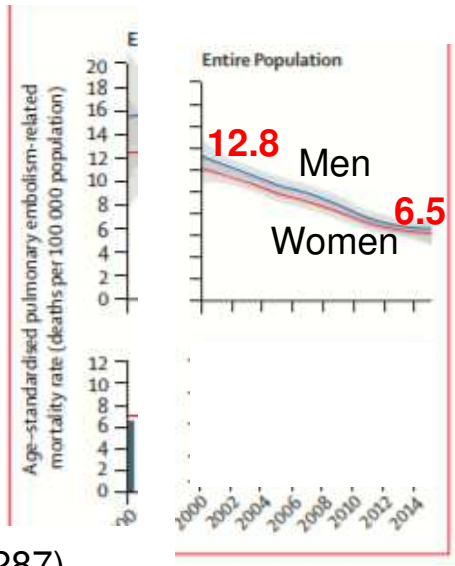
PE-Related Age-Adjusted Mortality in USA



(Barco S. Lancet Respir Med 2021; 9: 33-42)

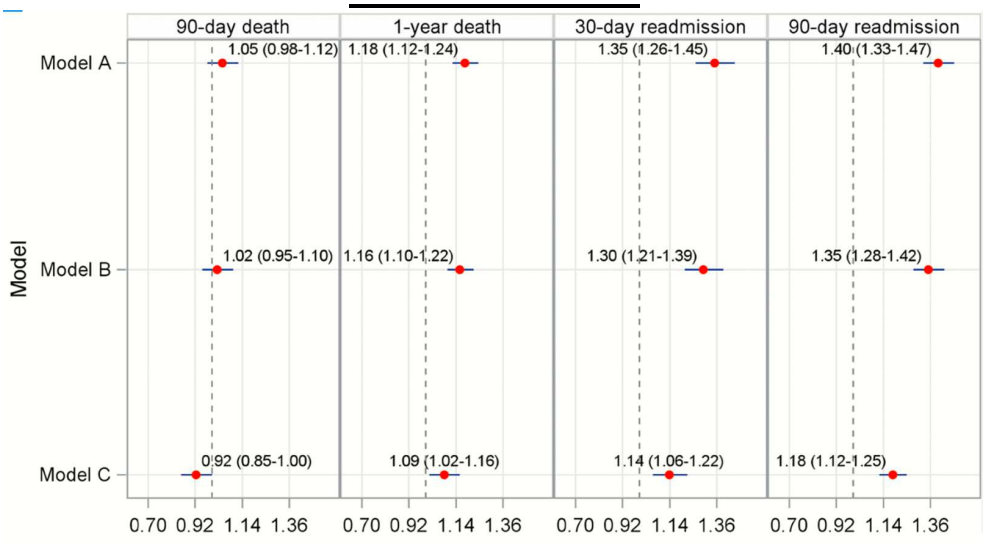
Trends in PE Mortality in Europe and Asia

A continuous decrease in PE mortality from 2000 to 2015



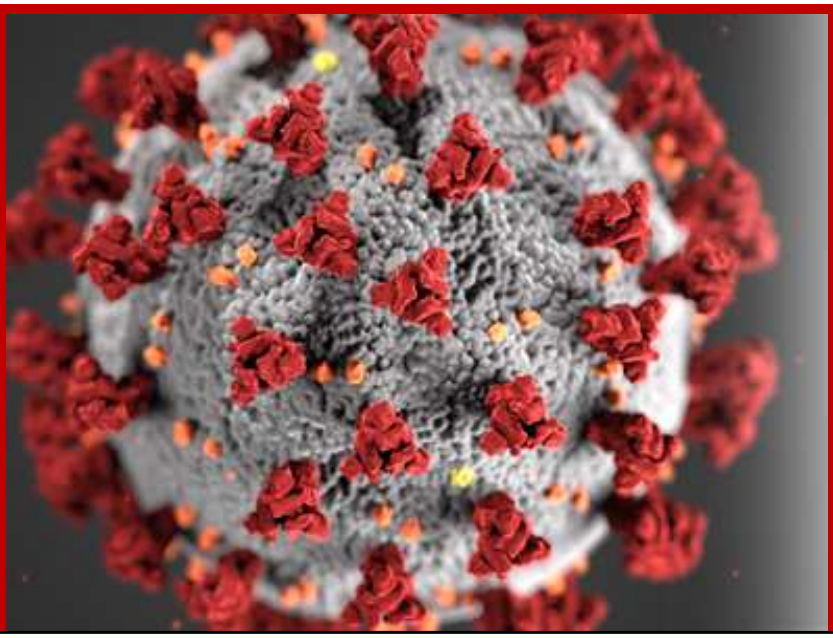
(Barco S. Lancet Respir Med 2020; 8: 277-287)

Mortality and Readmissions among Disadvantaged Older Adults

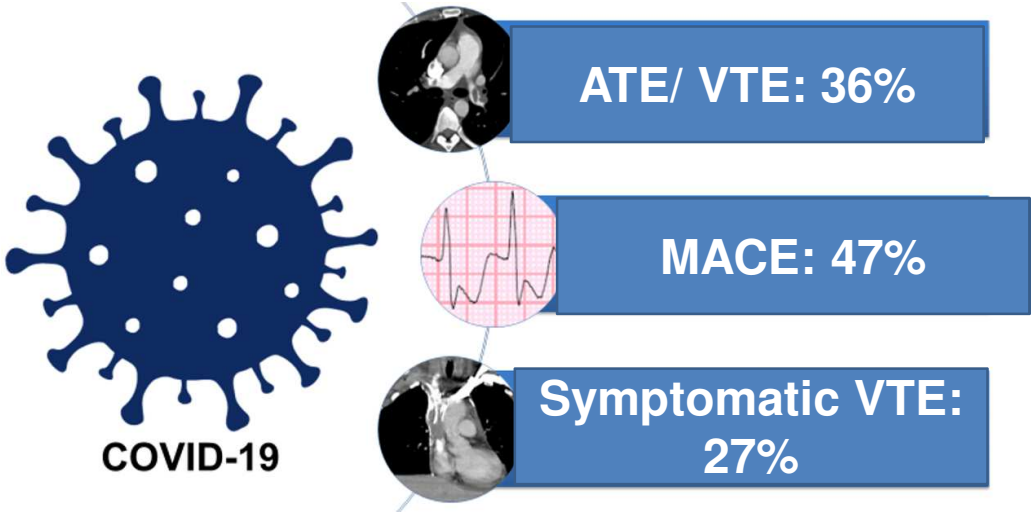


(Wadhera RK…Goldhaber SZ. JAHA 2021; July 2)

COVID-19 and VTE: A Perilous Combination

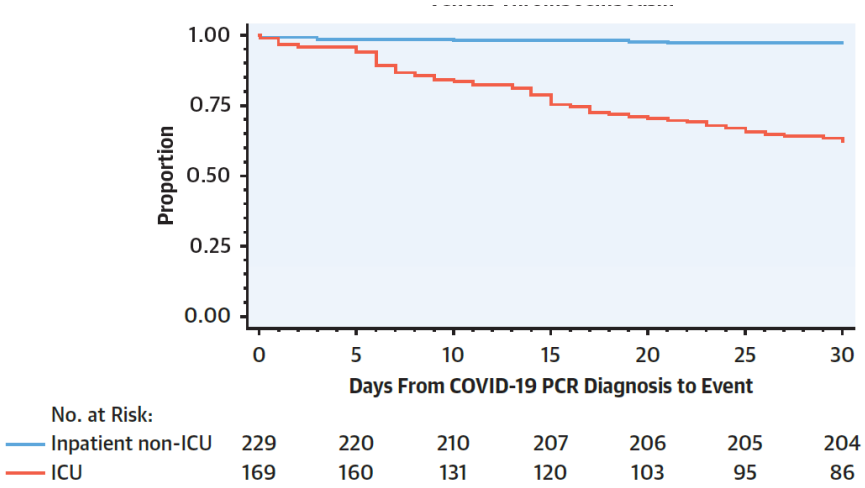


Corona-VTE Cohort (N=1,114): ICU Subset



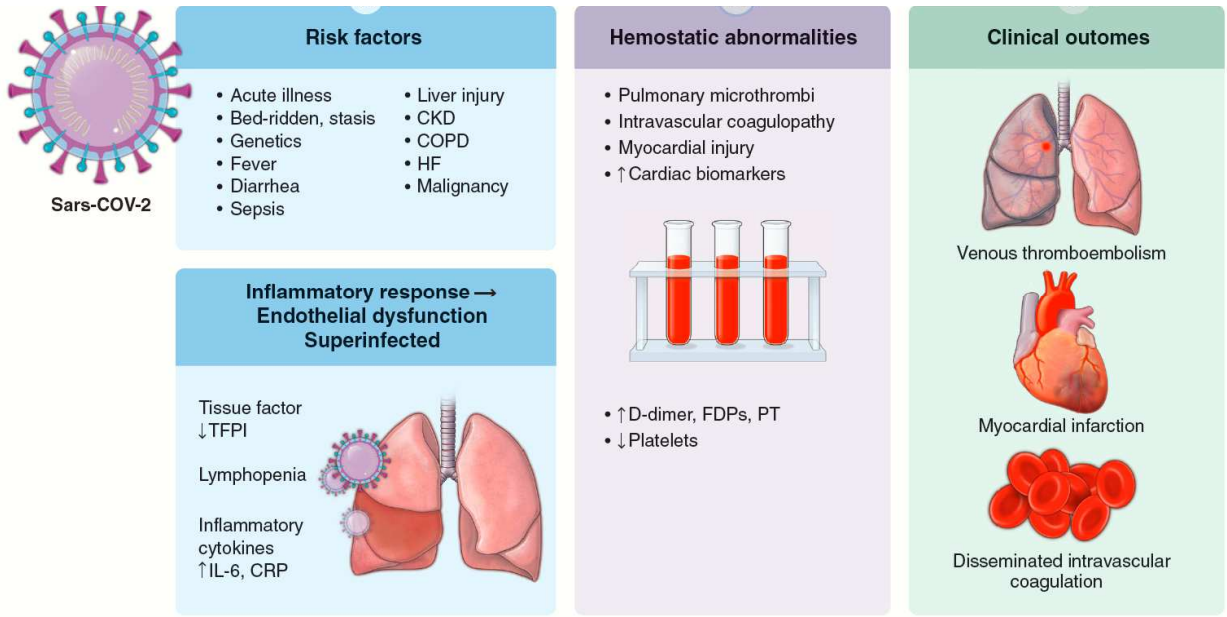
(Piazza G…Goldhaber SZ. JACC 2020; November 3)

Proportion without Major ATE or VTE



(Piazza G…Goldhaber SZ. JACC 2020; November 3)

Hemostatic Abnormalities and Adverse Clinical Outcomes



(Bikdeli B, et al. JACC 2020; 75: 2950-2973)

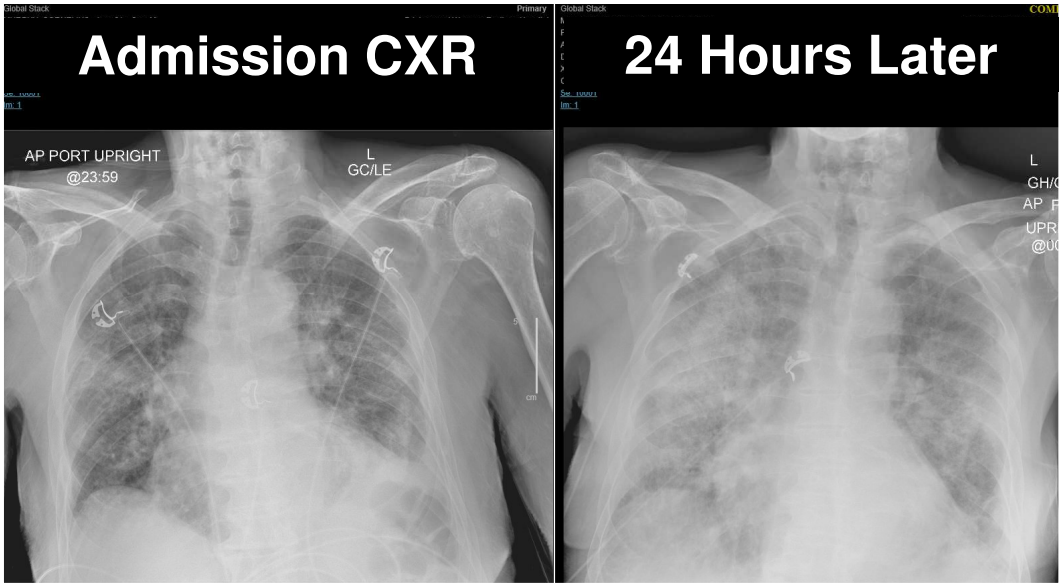
COVID Autopsy Findings

(Fox SE. Lancet Respir Med 2020; 8: 681-686)

Case #1: COVID in the ICU

- An 81 y.o. with COVID pneumonia: Admitted to ICU
- Requires 45 L/min oxygen + dopa 10 mcg/kg/min
- To prevent VTE, you order

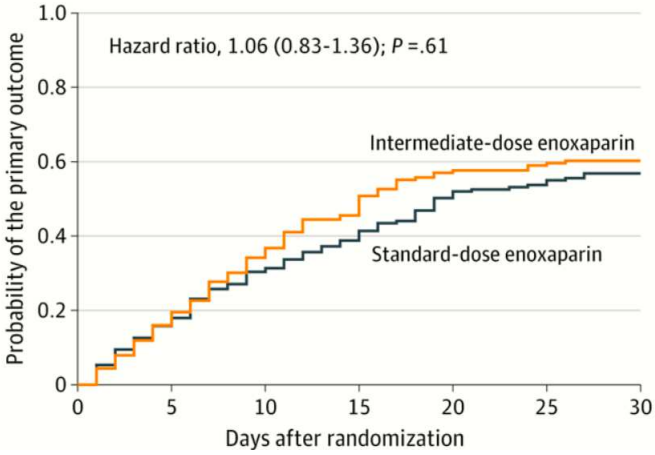
A) Compression stockings, pneumatic compression
B) Prophylactic dose heparin or LMWH
C) Intermediate dose heparin
D) Full dose heparin



Intermediate (Half-Dose) vs. **Prophylactic Dose**

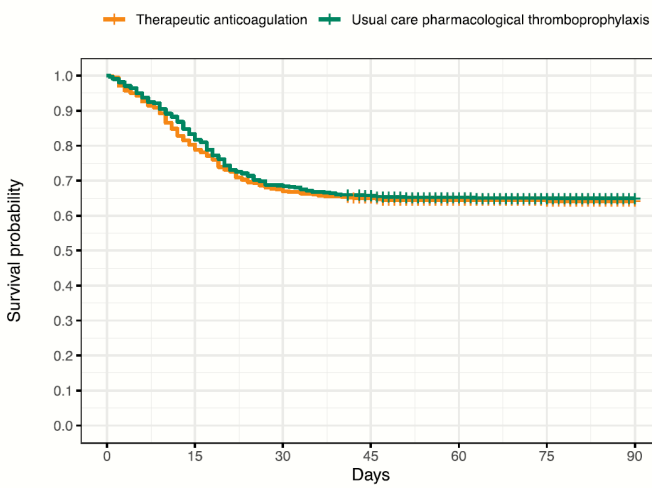
Heparin To Prevent VTE:COVID ICU (N=562)

[Primary Endpoint: Arterial or venous thrombosis, ECMO, death]



(INSPIRATION Investigators. JAMA 2021; March 18)

Survival: **Full Therapeutic** Dose vs. VTE **Prophylaxis Dose** in COVID ICU Patients (N=1,074)



(REMAP-CAP, ACTIV-4a, ATTACC Investigators. NEJM 2021; 385: 777-789)

Case #1: COVID in the ICU

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A) Compression stockings, pneumatic compression

B) Prophylactic dose heparin or LMWH

C) Intermediate dose heparin

D) Full dose heparin

Case #2: COVID in the Step-Down Unit

- A 61 y.o. with COVID pneumonia: Step-Down Unit
- Needs 12 L/min O_2 + remdesivir + dexamethasone
- To prevent VTE, you order:

A) Compression stockings, pneumatic compression
B) Prophylactic dose heparin or LMWH
C) Intermediate dose heparin
D) Full dose heparin anticoagulation

Full Therapeutic Dose vs. VTE **Prophylaxis Dose** in COVID Step-Down Unit Patients (N=2,219)

Outcome	Full-Dose Heparin	Prophylactic-Dose Heparin
Survival to Discharge	92.7%	91.8%
No Need for Organ Support	79.3%	75.4%
Major Thrombosis/ Death	8.0%	9.9%
Major Bleeding	1.9%	0.9%

(REMAP-CAP, ACTIV-4a, ATTACC Investigators. NEJM 2021; 385: 790-802)

Case #2: COVID in the Step-Down Unit

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- Needs 12 L/min O_2 + remdesivir + dexamethasone
- To prevent VTE, you order:

A) Compression stockings, pneumatic compression
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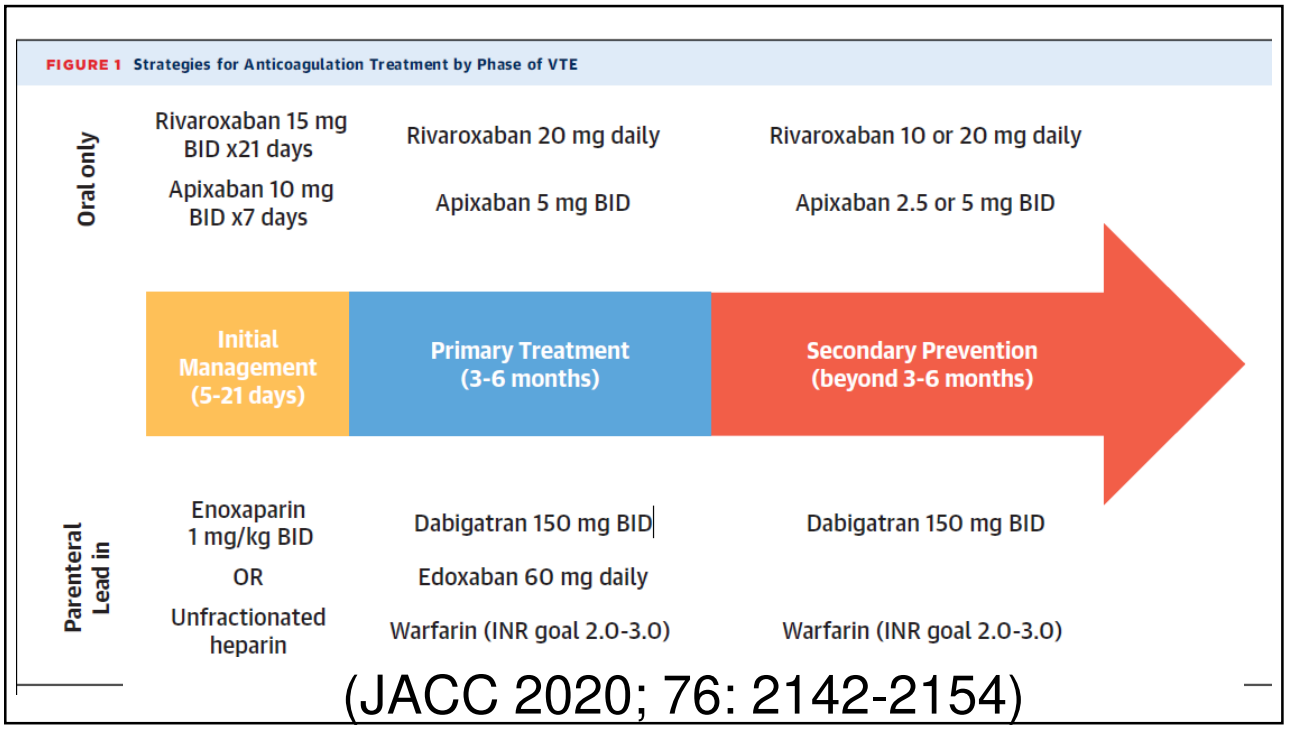
DOAC Paradigm To Treat

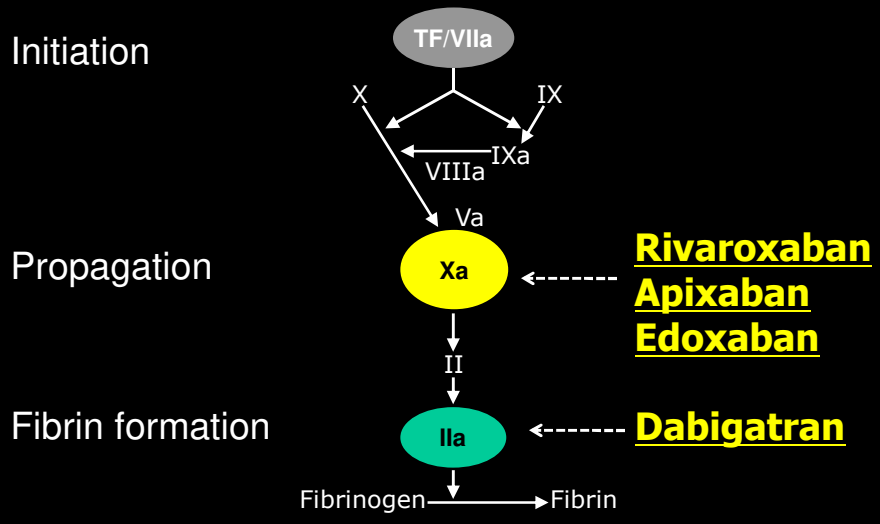
Pulmonary Embolism and DVT

(Renner E, Barnes G. JACC 2020; 76: 2142-2154)



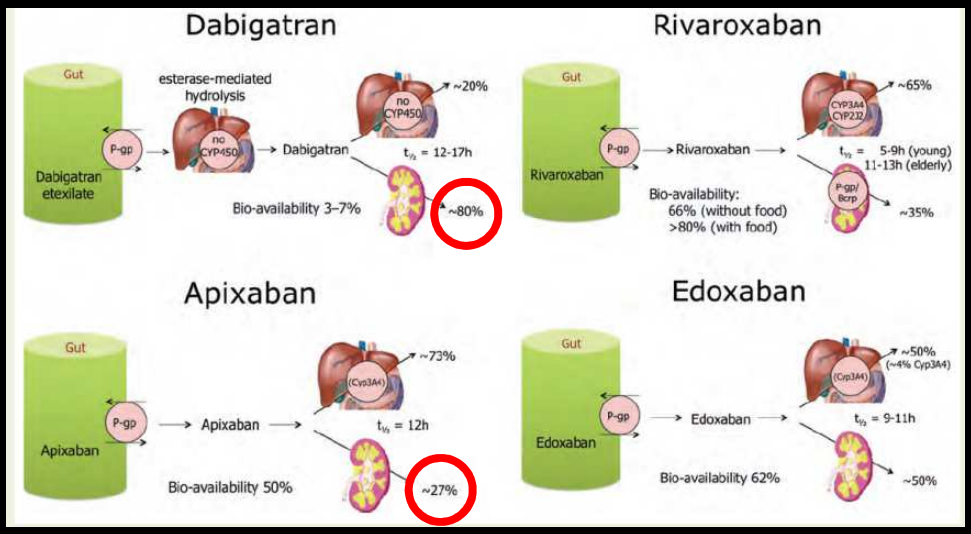
(JACC 2020; 76: 2142-2154)

DOACS: Sites of Action



(Circulation 2011;123:1436-1450)

DOACS Differ in Liver/ Kidney Metabolism



(Europace 2013; 15: 625-651)

Plasma DOAC Levels:

Apixaban and Rivaroxaban

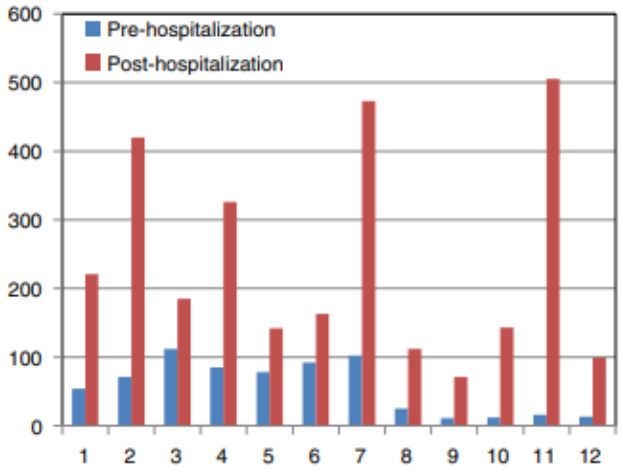
Plasma DOAC Levels Arrive at BWH

- **In September 2020**, the BWH Hematology laboratory began offering Apixaban and Rivaroxaban testing.
- Testing: available 24/7. Turn-around-time: 50 minutes.
- **Reportable Range**: 23 ng/mL – 500 ng/mL

Indications for Ordering DOAC Levels

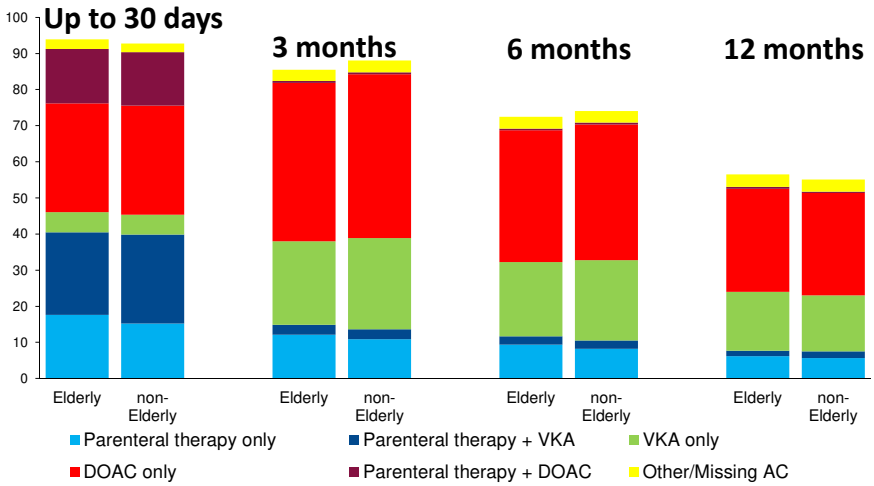
- Obesity or bariatric surgery
- Small, frail
- Unexpected clotting or bleeding
- Preop for emergency surgery
- CKD
- Disorder of GI absorption
- Concomitant meds affecting metabolism

DOAC Levels Skyrocket with Antiviral Therapy for COVID-19: Lopinavir, Ritonavir, Darunavir



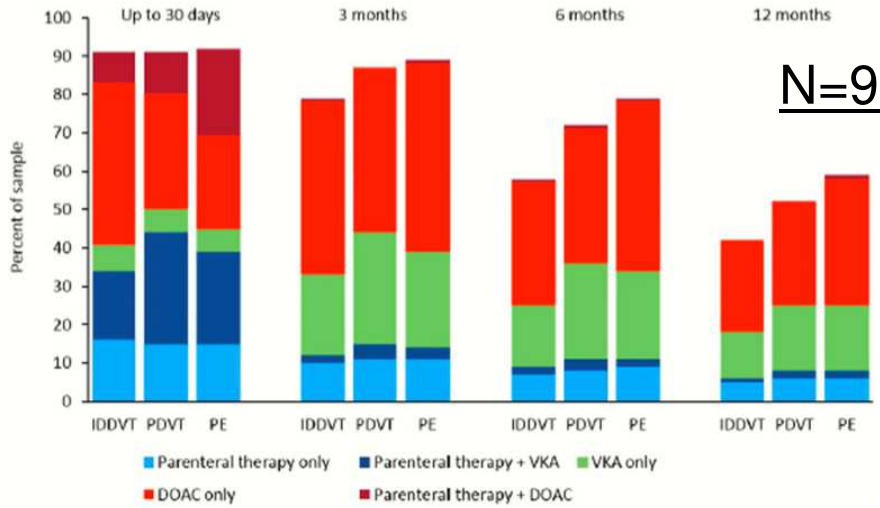
(Testa S, et al. J Thromb Haemost 2020; 18: 1320-1323)

VTE ANTICOAGULATION in Elderly: Long duration, No Agism



(GARFIELD-VTE 2019; unpublished)

Anticoagulation of Idiopathic Distal DVT: GARFIELD-VTE



N=9,728

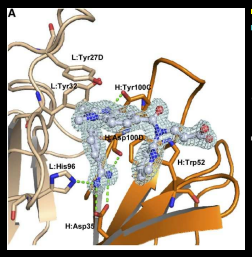
(Schellong SM, Goldhaber SZ, Weitz JI. Thromb Haemost 2019; 119: 1675-1685)

Case #3: Home Treatment of Proximal DVT

- A 78 y.o. woman presented to the ED with marked R calf swelling which had evolved over 24h.
- She weighed 64 kg; creatinine=1.3 mg/dl
- Started on apixaban 10 mg twice daily for one week (loading dose)
- She returns via ambulance 3 days later with lightheadedness, low BP, and tarry stools

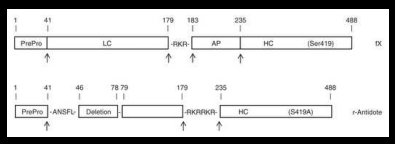
ANTIDOTES TO NOACS

Idarucizumab



Target: Dabigatran

Structure: Humanized antibody fragment (FAb) to dabigatran; FDA approved in October 2015 (NEJM 2015; 373: 511-520)



(NEJM 2015; 373: 2413-2424)

Andexanet alpha

Target: FXa inhibitors

Structure: FXa lacking catalytic & binding activity; This decoy looks like FXa. Antidote for rivaroxaban, apixaban, edoxaban

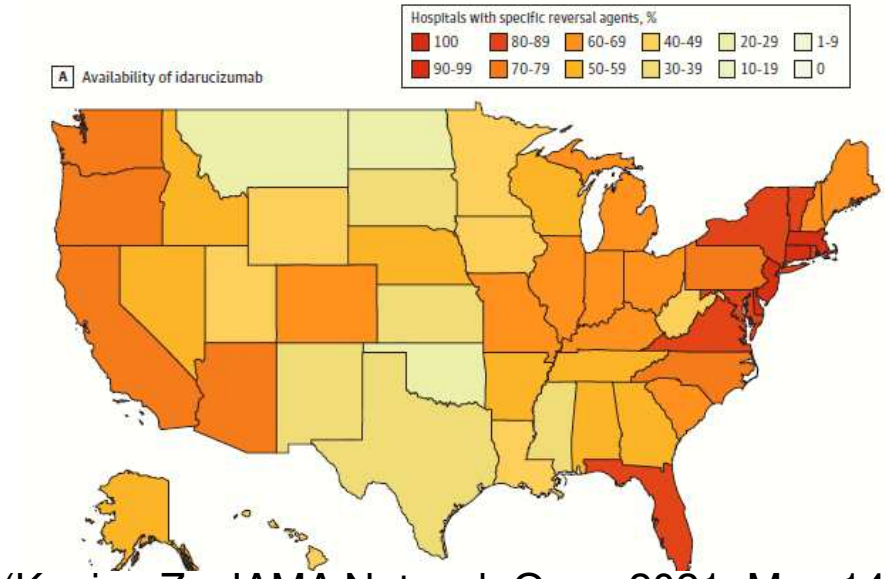
Hospitals with Idarucizumab and Andexanet

Table. Hospitals With Idarucizumab and Andexanet Alfa

Characteristic	Hospitals, No. (%)			
	Idarucizumab available		Andexanet alfa available	
	Yes	No	Yes	No
All hospitals (N = 4276)	2562 (59.9)	1714 (40.1)	499 (11.7)	3777 (88.3)
Hospital type				
Acute care (n = 2950)	2195 (74.4)	755 (25.6)	459 (15.6)	2491 (84.4)
Critical access (n = 1326)	367 (27.7)	959 (72.3)	40 (3.0)	1286 (97.0)
Trauma level status				
Not a trauma center (n = 3748)	2059 (54.9)	1689 (45.1)	348 (9.3)	3400 (90.7)
Trauma center				
Trauma level 1 or 2 (n = 528)	503 (95.3)	25 (4.7)	151 (28.6)	377 (71.4)
Trauma level 1 (n = 217)	204 (94.0)	13 (6.0)	79 (36.4)	138 (63.6)
Trauma level 2 (n = 311)	299 (96.1)	12 (3.9)	72 (23.2)	239 (76.8)

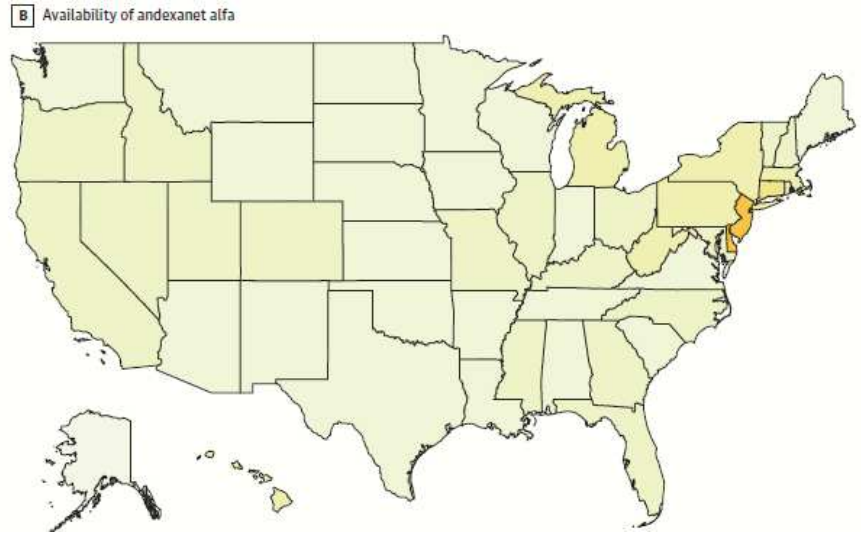
(Kanjee Z. JAMA Network Open 2021; May 14)

Idarucizumab Availability by State



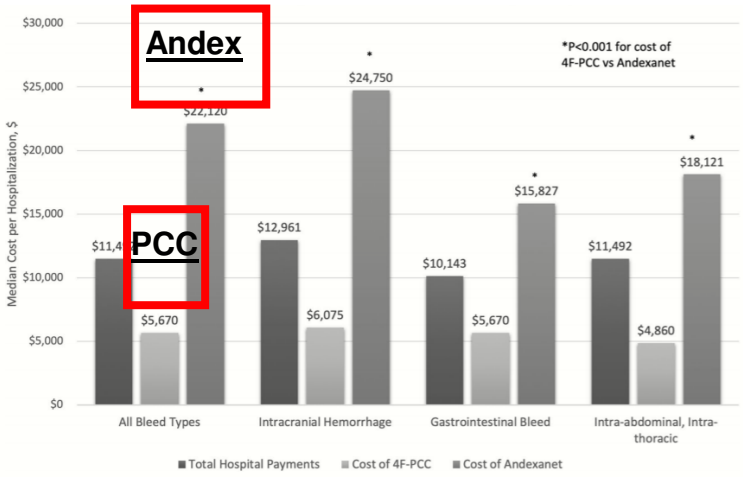
(Kanjee Z. JAMA Network Open 2021; May 14)

Andexanet Availability by State



(Kanjee Z. JAMA Network Open 2021; May 14)

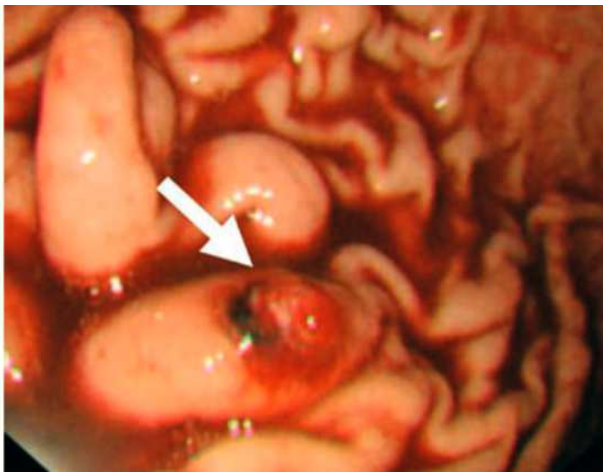
Cost of 4F-PCC versus Andexanet to Reverse Bleeding from DOACs



(Frontera A. JTT 2020; 49: 121-131)

Upshot of Case #3

- She underwent emergency endoscopy.
- The bleeding gastric ulcer was clipped.
- She received 2 units of PRBCs.
- A reversal agent was not needed.



CAN DOACS REPLACE LMWH MONOTHERAPY IN CANCER PATIENTS WITH VTE?

CHALLENGES: ANTICOAGULATING CANCER PATIENTS WITH VTE

- Cancer is thrombogenic: High rates of recurrent thrombosis despite anticoagulation
- Cancer chemotherapy: thrombogenic/ thrombocytopenic
- Occult metastases are bleeding sources
- Interactions among anticoagulants and novel chemotherapeutic agents—uncharted territory
- Frailty

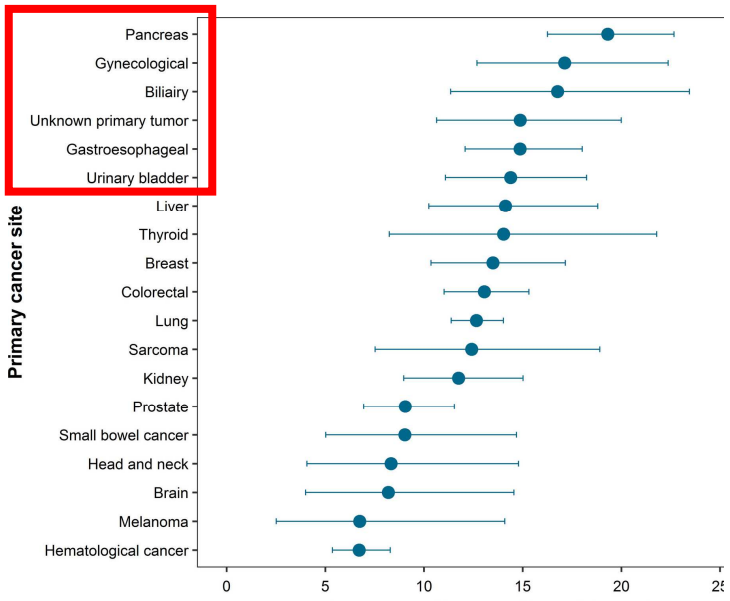
Case #4: 60 y.o. Man with Stage IV Bladder Cancer

April 2019: Sudden onset of pain in R groin and leg, with purplish discoloration

Leg is warm with good distal pulses

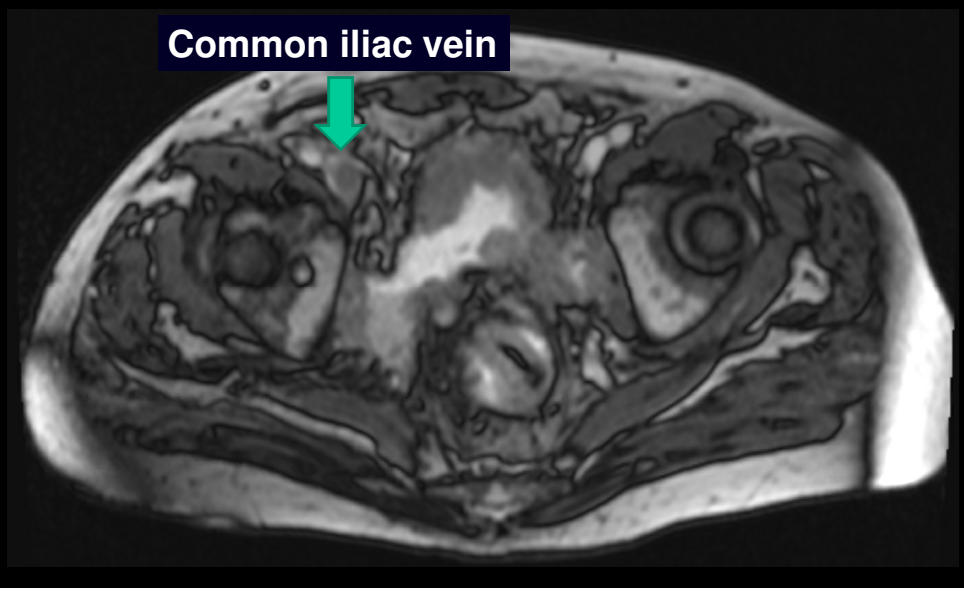
BWH ED—imaging of R leg obtained

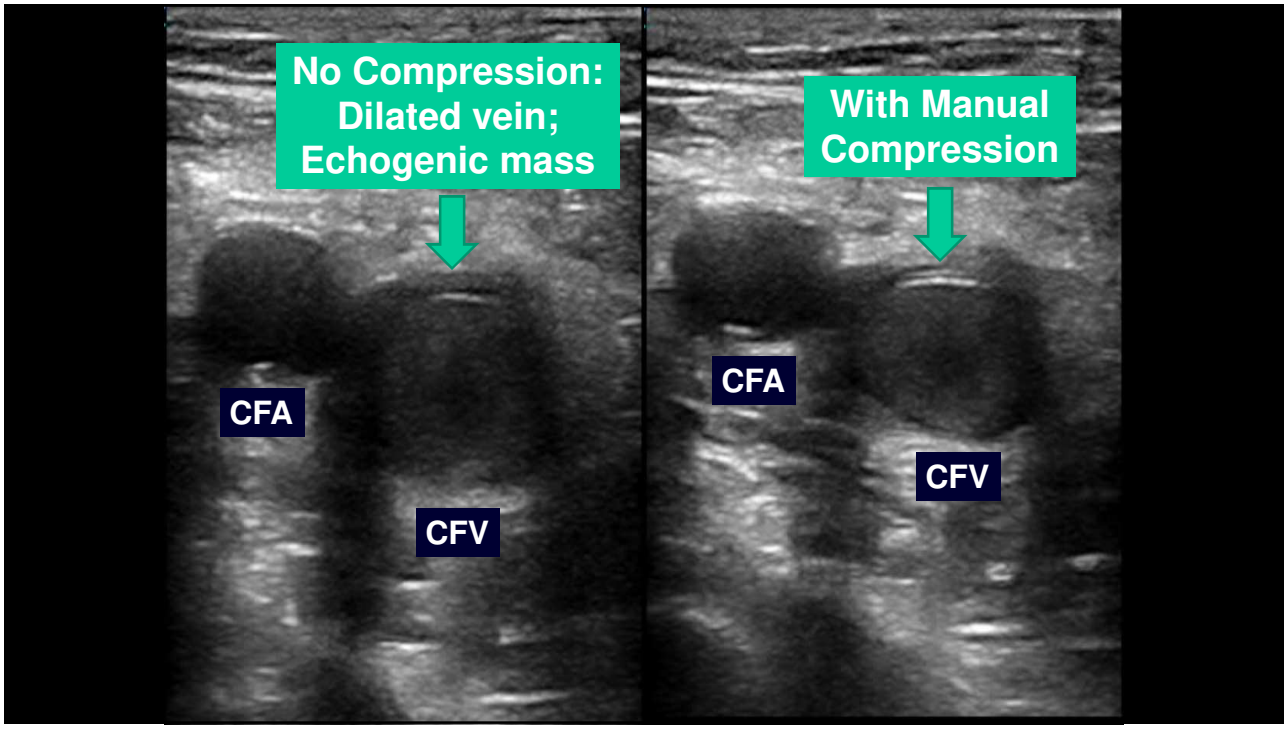
Cancer Sites in PE Patients



(Gimbel IA. JTH 2021; 19: 1228-1235)

60 y.o. Man with Stage IV Bladder Cancer





CANCER / ACUTE VTE: DOAC vs. Dalteparin

DOAC	Trial Result
Edoxaban (Hokusai)	Better efficacy; Less GI safety; (NEJM 2018)
Rivaroxaban (SELECT-D)	Better efficacy; Less GI safety (J Clin Oncol 2018)
Apixaban* (Caravaggio)	Same efficacy; Same safety (NEJM 2020)

Optimal Duration of Anticoagulation: Requiem for the Concepts of "Provoked" and "Unprovoked" VTE

2019 ESC PE Guidelines

"**Terminology such as 'provoked' vs. 'unprovoked' PE/ VTE is no longer supported by the Guidelines**, as it is **potentially misleading** and **not helpful for decision-making** regarding the duration of anticoagulation."

(European Heart Journal 2020; 21: 543-603)

Duration of Anticoagulation

"Extended oral anticoagulation of indefinite duration should be considered for patients with a first episode of PE and:

1) No identifiable risk factor
2) A persistent risk factor (other than antiphospholipid syndrome)
3) A minor transient or reversible risk factor"

(European Heart Journal 2020; 21: 543-603)

2019 ESC PE Guidelines: Risk of Recurrent VTE

Risk of Recurrence	Examples
Low (<3%/ year)	Major surgery or major trauma
Intermediate (3% to 8%/ year)	Minor surgery Hospitalized with acute medical illness Pregnancy/ estrogens Long-haul flight
	Ulcerative colitis or Crohn's disease
	No identifiable risk factor (formerly called "unprovoked")
High (>8%/ year)	Active cancer Antiphospholipid syndrome

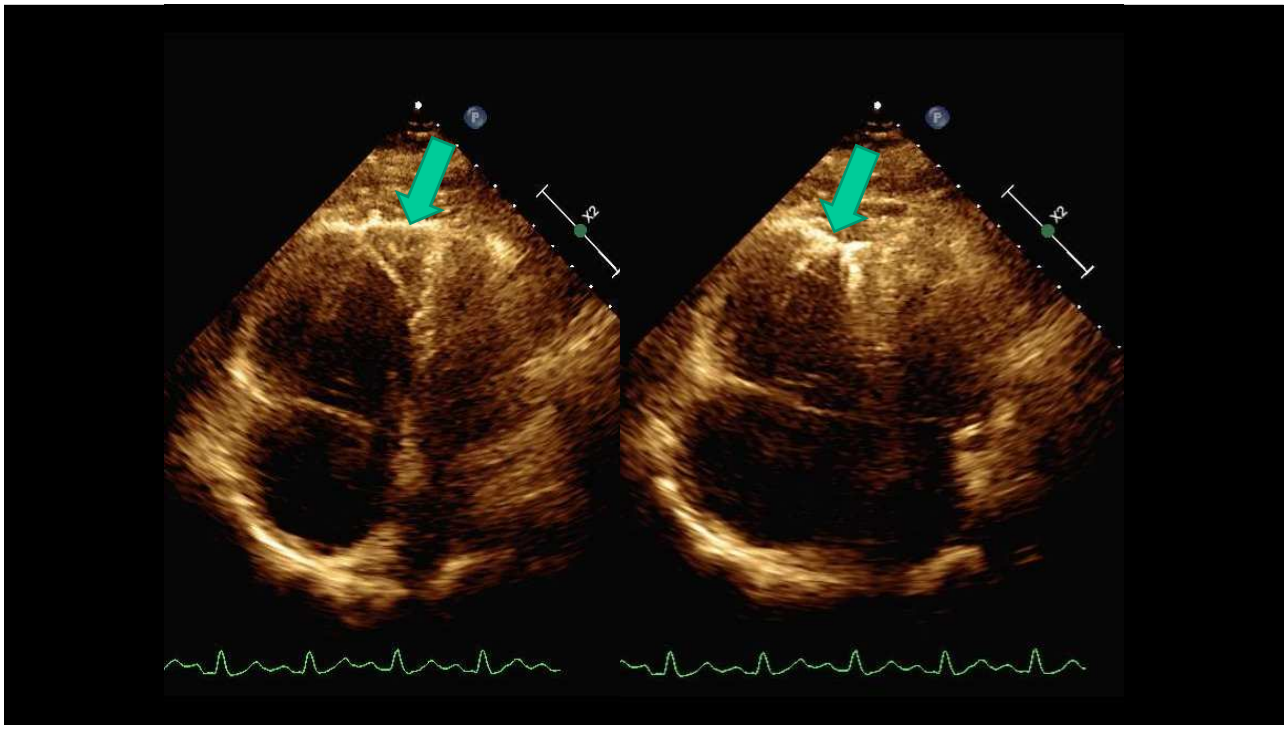
ADVANCED THERAPY BEYOND ANTICOAGULATON

Case #5: CODE PE IN ED; "MASSIVE PE ON 10 OF LEVOPHED"

- 62 y.o. woman awakened and became dizzy, cold, sweaty, SOB, and faint while sitting on the toilet
- RN daughter called 911

PRESENTATION TO ED

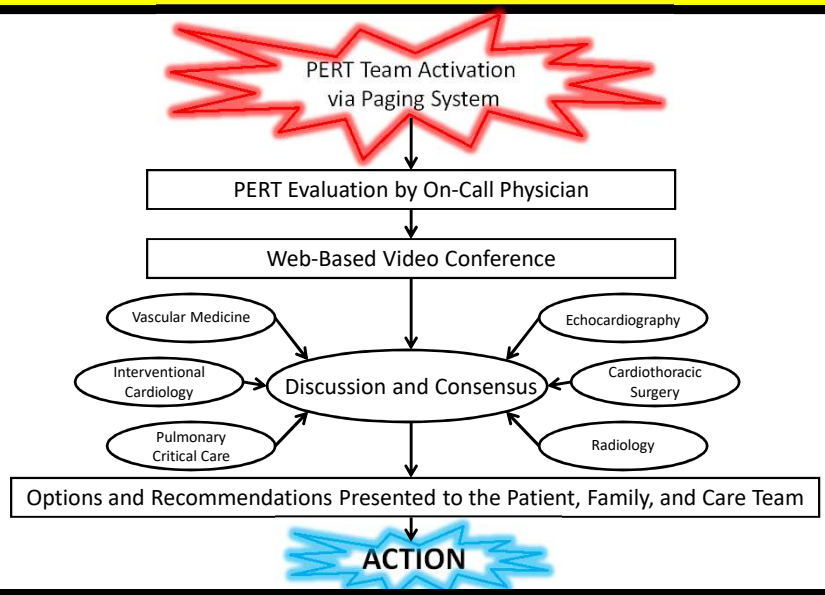
- Markedly SOB; gasping, pale, diaphoretic; RR=30/min; BP=70/ to 82/56 mm Hg; HR=134/min; O_2 sat=89% RA; 98 kg (obese)
- TnT=0.06 U; WBC=15.4K; Gluc=233; Creat=1.0; GFR=55; AST=137; Lactic Acid=4.5
- Levophed titrated up to 10 mcg/min;
- Bedside ECHO: Marked RV dilatation/ HK; septum bows to LA; positive McConnell's sign



OPTIONS THAT WERE DISCUSSED (BRIEFLY)

1) Begin heparin continuous IV infusion at 18 U/kg/h
2) Chest CT scan, with contrast
3) EKOS with TPA 24 mg total dose
4) TPA 100 mg/ 2h via peripheral IV
5) Surgical pulmonary embolectomy
6) Something else (none of the above)

PE RESPONSE TEAM (PERT)

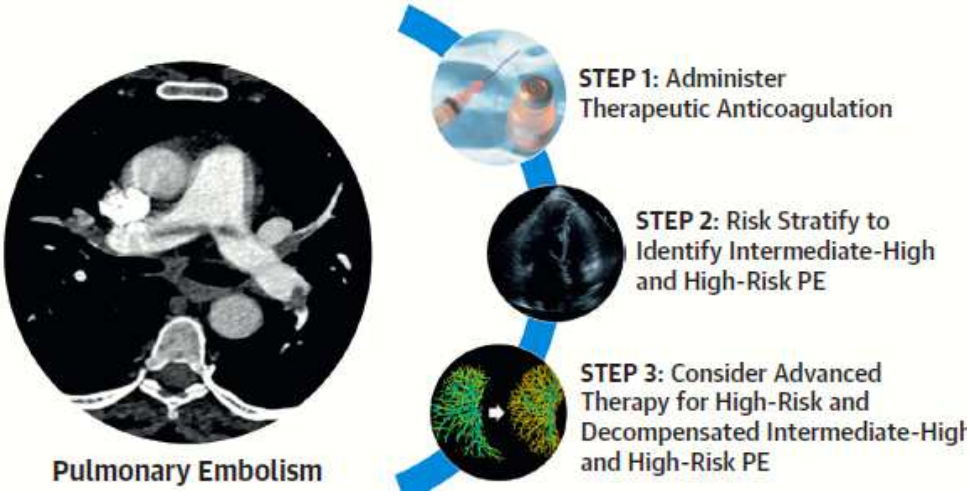


(Dudzinski D, Piazza G. Circulation 2016; 133: 98-103)

WHAT WE DID

1) Decided on systemic lysis with “half-dose TPA”
2) TPA 10 mg/ 1 min via peripheral IV
3) TPA 40 mg/2h
4) Levophed was weaned.
5) She felt “90% back to normal” in < 2h later
6) No bleeding, not even slight oozing, at IV or phlebotomy puncture sites

Advanced Management: Intermediate and High-Risk PE



(Piazza G. JACC 2021; 76: 2117-2127)

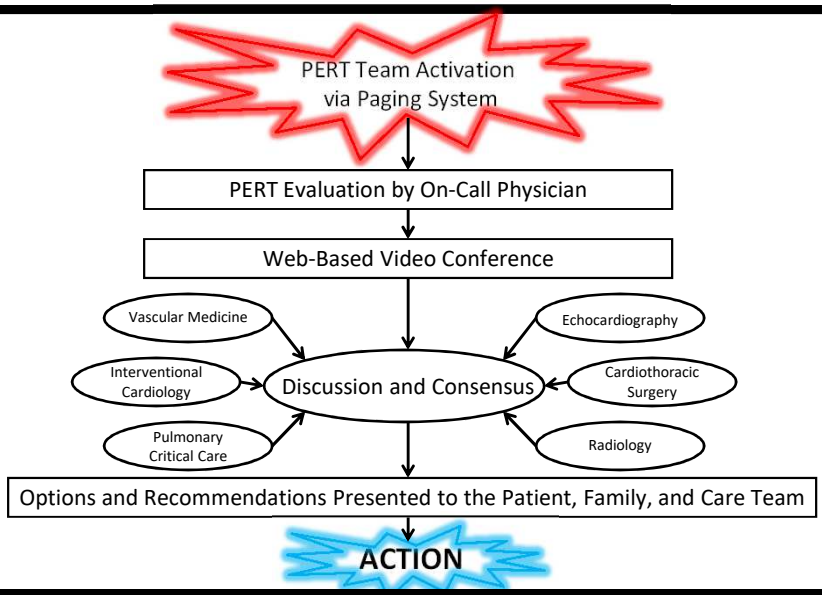
Options for Advanced Therapy in Acute PE

TABLE 1 Options for Advanced Therapy in Acute PE

Option	Indications	Advantages	Disadvantages
Systemic fibrinolysis	High- and intermediate-high-risk PE	• Rapid administration • Decreases mortality • Prevents hemodynamic collapse • Expedites RV recovery and symptom relief	• 2%–5% risk of ICH
Catheter-directed therapy	High- and intermediate-high-risk PE	• Expedites RV recovery and symptom relief • Reduced risk of ICH • Option for mechanical embolectomy with some devices	• Limited long-term and comparative data • May take time to mobilize
Surgical embolectomy	High- and intermediate-high-risk PE	• Expedites RV recovery and symptom relief • Reduced risk of ICH • Avoids need for fibrinolysis	• Limited long-term and comparative data • May take time to mobilize • Limited to more centrally located PE
ECMO	Refractory cardiogenic shock	• Supports hemodynamics and oxygenation in patients with refractory shock or hypoxemia	• Limited long-term and comparative data • May take time to mobilize

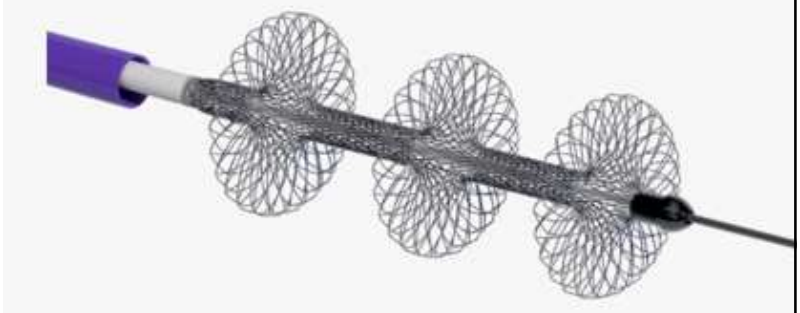
(Piazza G. JACC 2021; 76: 2117-2127)

PE RESPONSE TEAM (PERT)



(Dudzinski D, Piazza G. Circulation 2016; 133: 98-103)

FlowTriever: 20F—No TPA



BRIGHAM HEALTH
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HARVA TEACH

BWH FlowTriever Pulmonary Embolectomy #1—Drs. Bergmark and Shah

SURGICAL EMBOLECTOMY AT BWH: SURGEON'S CELL PHONE

Summary/ Take Home Points

1. The poorest among us have the worst PE outcomes
2. COVID patients in the ICU have high rates of PE/ DVT
3. When prescribing a DOAC, assess the bleeding risk, liver function, and kidney function
4. Patients with cancer and VTE can often be treated safely and effectively with a DOAC rather than LMWH
5. Consider extended duration AC in most VTE patients rather than a fixed “stop date.”
6. Advanced therapy: thrombolysis, catheter or surgical embolectomy

References

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- Piazza G. Registry of Thromboembolic Complications in patients with COVID-19. JACC 2020; 76: 2060-2072
- Chopard R. Lower Extremity VTE. JAMA 2020; 324: 1765-1776
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