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TEACHING HOSPITAL

New Anticoagulants: What is new in 2020?

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Disclosures

Rachel P. Rosovsky, MD, MPH

- Institutional Research Support: Janssen, BMS
- Advisory/Consultant: Portola, BMS, Janssen, Dova

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Agenda

- Scope of the problem
- Recent advances in venous thromboembolism (VTE)
  - Cancer and clotting
  - Outpatient treatment of VTE
  - Novel approaches to treating pulmonary embolism.

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Pulmonary Embolism: Scope of the Problem

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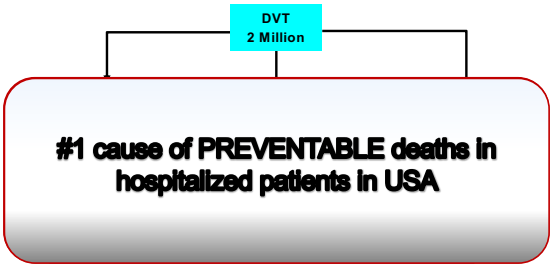
Venous Thromboembolism: The Third Leading Cause of Cardiovascular Death



Hirsh J and Hoak J. *American Heart Association*. 1996.
Heit J et al. *Blood*. 2005;106: Abstract 910.
Anderson FA et al. *Am J Hematol*. 2007;82:777-82.

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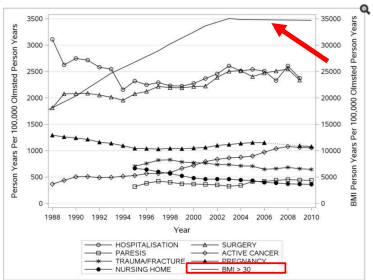
Incidence of Pulmonary Embolism



Am J Hematol. 2011 Feb;86(2):217-20
Heit, Thromb Hemost, 2017

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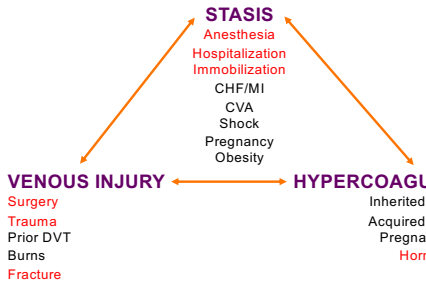
Virchow's Triad



Cleve Clin J Med 1999;66:113-23

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Antipsychotics and Antidepressants

- Systematic Review of antidepressants and VTE
  - 8 observational studies
  - 960,113 participants
  - 9027 VTE cases.
- Results:
  - RR 1.27 (1.06-1.51) for VTE comparing antidepressant use with no antidepressant use
  - Tricyclic antidepressants > Selective serotonin reuptake inhibitors > Other antidepressants

VTE = venous thromboembolism; RR = relative risk
Kunutsoret al. Ann Med. 2018

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Antipsychotics and Antidepressants

- Million Women Study in UK
  - 734,092 women
    - 6.9% reported use of antidepressants
    - 2.7% reported use of other psychotropic drugs
    - 1.8% reported being treated for depression or anxiety but not use of psychotropic drugs.
  - During follow-up, average 7.3 years
    - 3922 women were hospitalized for and/or died from VTE.
    - Women antidepressant had significantly higher risk of VTE than women who reported neither depression nor psychotropic drugs (HR: 1.39; 95% CI, 1.23-1.56).
    - VTE risk was not significantly increased in women who reported being treated for depression or anxiety but no use of antidepressants or other psychotropic drugs

VTE = venous thromboembolism; HR = hazard ratio
Parkin et al. J Am Heart Ass. 2017

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Why worry about Pulmonary Embolus?

- Fatal within 1 h after the onset of symptoms in 10% of cases
- Untreated PE mortality rate ~30%

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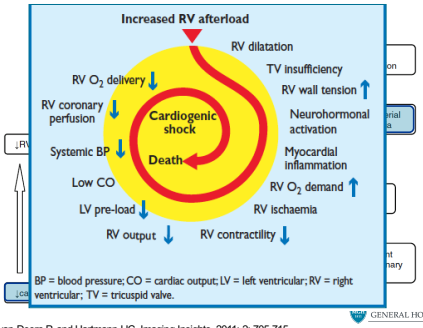
Pathophysiology of Pulmonary Embolism



Abrahams van-Doorn P. and Hartmann IJC. Imaging Insights. 2011; 2: 705-715
Eur Heart J. 2014 Nov 14;35(43):3033-69, 3069a-3069k

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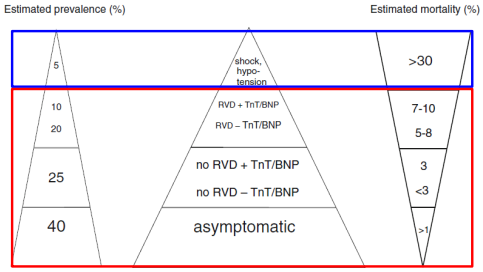
Most Patients with PE do Well, but some do not



Becattini C, Agnelli G. Thromb Haemost. 2008; 100(5): 747–751
Abrahams van-Doorn P. and Hartmann IJC. Imaging Insights. 2011; 2: 705-715
Dalen JE. Chest. 2002; 122: 1801-17

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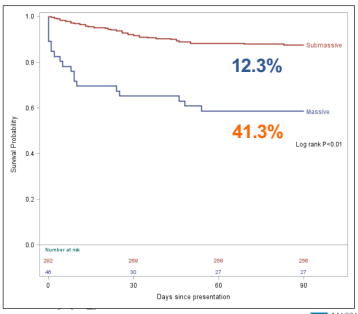
PE Mortality (ICOPER)



Secemsky E, Chang Y, Jain C, Beckman J, Giri J, Jaff M, Rosenfield R, Rosovsky R , Kabrhel C, Weinberg I. *Am J Medicine, 2018*

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Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- Most severe form of PE morbidity
- 2-4%
- No screening
- >50% don't have diagnosis PE prior

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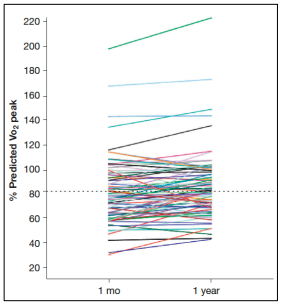
"Post-PE" Syndrome



- Characterized by:
  - Persistent dyspnea
  - Exercise limitation
  - Reduced health-related quality of life

At one year:
46.5% had exercise limitation;
percent predicted $V\dot{O}_2$<80%

Kahn. CHEST 2017; 151(5):1058-1068

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Pulmonary Embolism:

Current Treatment Options

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Lots of Options

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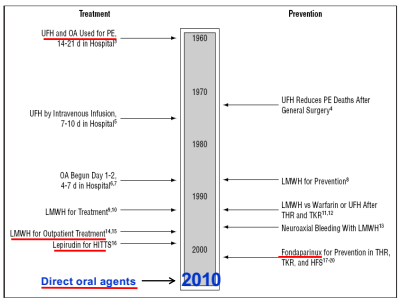
Time Line



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Direct Oral Anticoagulants

- Direct Thrombin Inhibitor
  - Pradaxa: Dabigatran
- Factor Xa inhibitors
  - Xarelto: Rivaroxaban
  - Eliquis: Apixaban
  - Savaysa: Edoxaban
  - Bevyxxa: Betrixaban *

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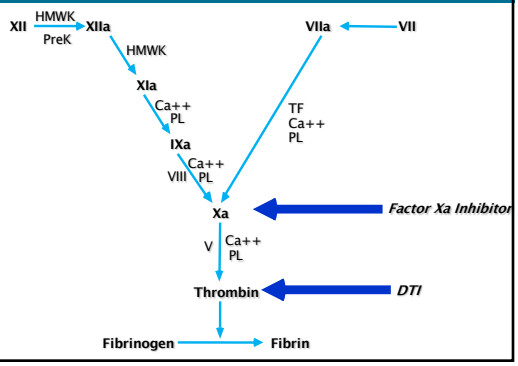
Direct Oral Anticoagulants



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Direct oral anticoagulants

- Effective
- Safe

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Direct oral anticoagulants:

They are effective for PE!

Table 2. Efficacy Outcome of Recurrent VTE with Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute VTE

	Recurrent VTE or VTE-related death	
Anticoagulant	n/N (%)	RR* (95% CI)
Apixaban	59/2691 (2.3)	0.84 (0.60–1.18)
Dabigatran	60/2553 (2.4)	1.09 (0.76–1.57)
Edoxaban	130/4118 (3.2)	0.89 (0.70–1.13)
Rivaroxaban†	86/4150 (2.1)	0.90 (0.68–1.20)

CI indicates confidence interval; RR, relative risk; and VTE, venous thromboembolism.

*RR was recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]).

†Efficacy outcome for EINSTEIN studies was recurrent VTE, and not combined recurrent VTE or VTE-related death.

Bacchus et al. Arterioscler Thromb Vasc Biol. 2015;

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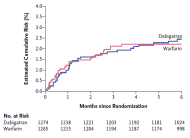
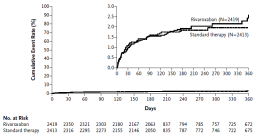
Direct oral anticoagulants: *Efficacy*

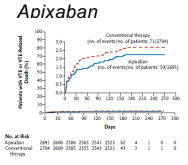
Dabigatran



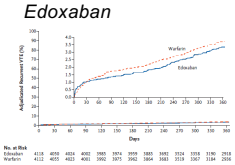
Rivaroxaban



Apixaban



Edoxaban



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Direct oral anticoagulants:

They are safe!

Table 3. Safety Outcomes of Bleeding With Use of Non–Vitamin K Antagonist Oral Anticoagulants in Comparison With Vitamin K Antagonists in the Treatment of Acute Venous Thromboembolism

	Major Bleeding or Clinically Relevant Nonmajor Bleeding		Major Bleeding		ICH	
Anticoagulant	Incidence, n/N (%)	RR* (95% CI)	Incidence, n/N (%)	RR* (95% CI)	Incidence, n/N (%)	RR* (95% CI)
Apixaban	115/2691 (4.3)	0.44 (0.36–0.55)	15/2691 (0.6)	0.31 (0.17–0.55)	3/2691 (0.1)	0.50 (0.13–2.01)
Dabigatran	136/2553 (5.3)	0.63 (0.51–0.77)	37/2553 (1.4)	0.73 (0.48–1.10)	2/2553 (0.1)	0.40 (0.08–2.06)
Edoxaban	349/4118 (8.5)	0.81 (0.71–0.94)	56/4118 (1.4)	0.84 (0.59–1.21)	5/4118 (0.1)	0.28 (0.10–0.75)
Rivaroxaban	388/4150 (9.3)	0.94 (0.82–1.07)	40/4150 (1.0)	0.55 (0.38–0.81)	3/2419 (0.1)	0.25 (0.07–0.88)

CI indicates confidence interval; ICH, intracranial hemorrhage; and RR, relative risk.
*RR recalculated from the hazard ratio for optimal comparison (dabigatran [from RE-COVER II pooled analysis], edoxaban, and rivaroxaban [combined data from EINSTEIN-DVT and EINSTEIN-PE study]). ICH includes both fatal and nonfatal ICH with RR calculated from each study.

Bacchus et al. Arterioscler Thromb Vasc Biol. 2015;

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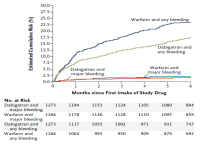
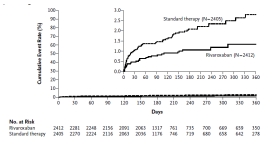
Direct oral anticoagulants: *Safety*

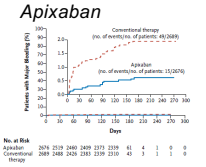
Dabigatran



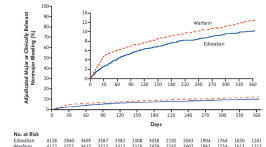
Rivaroxaban



Apixaban



Edoxaban



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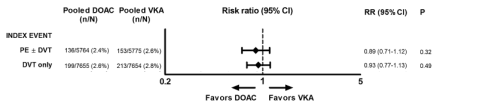
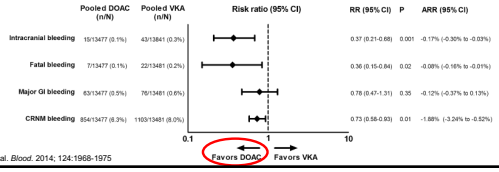
DOACs vs. LMWH/Warfarin for Acute VTE

Meta-analysis; N=27,023

Efficacy: First recurrent VTE or VTE-related death



Safety



van Es N et al. *Blood*. 2014; 124:1968-1975

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DOACs: Advantages

Effective, safe, patient satisfaction, simple and reliable

- Oral
- No need for monitoring
- Predictable absorption and metabolism
- No need for titration or dose adjustments
- Rapid onset of action
- Short half life
- Few drug-drug interactions
- Few dietary restrictions
- Greater convenience

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Direct Oral Anticoagulants

Effective, safe, simple and reliable and patients are satisfied

All approved for the treatment of DVT and PE (guidelines)

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How to Choose Which DOAC?

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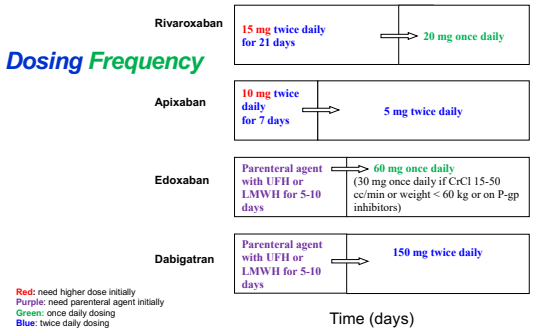
Key differences between DOACs dosing in treatment of acute VTE



Red: need higher dose initially
Purple: need parenteral agent initially
Green: once daily dosing
Blue: twice daily dosing

Rosovsky, Merli. TVIR. 2017

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Are DOACs appropriate for everyone?

- *Cancer*
  - LMWH used to be preferred agent
- *Liver disease or coagulopathy*
  - LMWH is the preferred agent
- *Pregnancy*
  - LMWH
- *Renal*
  - VKA, some data with apixaban

LMWH – low molecule weight heparin
VKA = vitamin K antagonist

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The Case of the Swollen Leg

Rosovsky, Harrison's Oncology. 2018

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Cancer and Thrombosis

Association Between Cancer and Thrombosis

- 1865: Armand Trousseau
- Migrans thrombophlebitis as forewarning of occult cancer.

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Epidemiology: Cancer and Thrombosis

- 1.8 M new cancer diagnosis (USA, 2018)
- Thrombosis is common complication of cancer
- 1 in 5 will develop venous thromboembolism

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Epidemiology: Cancer and Thrombosis

VTE is the 2nd leading cause of cancer related deaths after cancer itself.

VTE = venous thromboembolism

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Epidemiology: Cancer and Thrombosis

Cancer patients:

- 2-3 times more likely to have recurrent VTE than non cancer patients.
- 2-6 times more likely to have hemorrhagic complications from anticoagulant therapy than non cancer patients.

VTE= venous thromboembolism

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Epidemiology: Cancer and Thrombosis

- Cancer patients with VTE:
  - more likely to be diagnosed with later stage cancer.

VTE= venous thromboembolism

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Epidemiology: Cancer and Thrombosis

- Cancer patients with VTE:
  - more likely to have decreased survival.

VTE= venous thromboembolism

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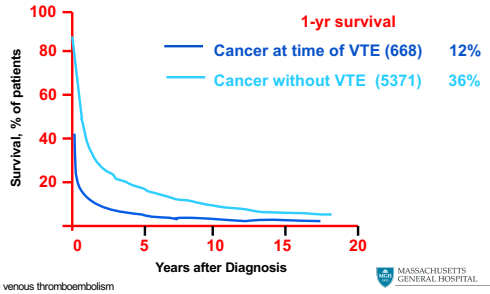
Survival: Cancer and Thrombosis

Danish Cancer Registry (668 VTE 5371 without)



VTE= venous thromboembolism

Sorensen et al. *NEJM* 2000;343:1846-1850.

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The Case of the Swollen Leg

How should he be treated?

Rosovsky, Harrison's Oncology,. 2018

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Lots of options

What do you use to treat a cancer patient with a new DVT?

1. Aspirin
2. Unfractionated heparin (UFH)
3. Low molecular weight heparin (LMWH)
4. Warfarin
5. Fondaparinux
6. Abixaban
7. Rivaroxaban
8. parenteral agent followed by Dabigatran
9. parenteral agent followed by Edoxaban
10. No treatment
11. IVC filter

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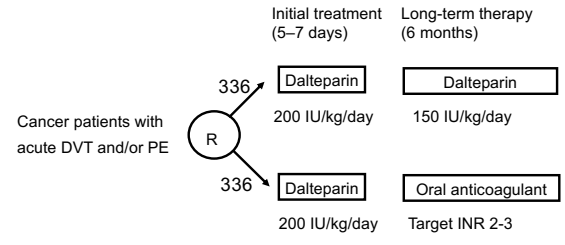
Treatment: CLOT Trial



OAC = oral anticoagulant

Lee AY, et al. *NEJM.* 2003;349:146-53.

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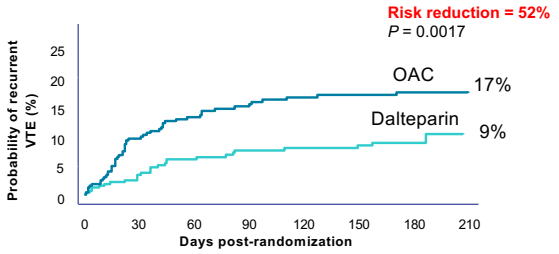
Cancer and VTE: CLOT Trial



OAC = oral anticoagulant

Lee AY, et al. *NEJM.* 2003;349:146-53.

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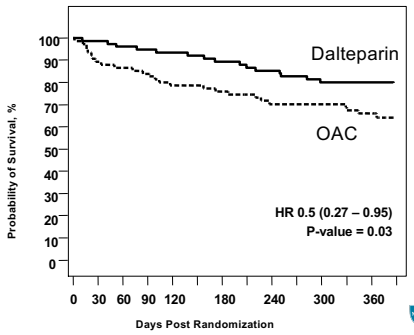
CLOT Trial: Mortality



CLOT Trial:

12 Month Mortality: patients without metastases

Lee AY, et al. *JCO* 2005; 23:2123-2129.

OAC= oral anticoagulant

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The Case of the Swollen Leg

Can cancer patients be treated with a DOAC?

Rosovsky, Harrison's Oncology.. 2018

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Direct Oral Anticoagulants

What is the data with DOACS in cancer patients?

- Each of the trials included 5-10% cancer patients
- Compared to warfarin
- New trials

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ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine

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Cancer and VTE: Hokusai

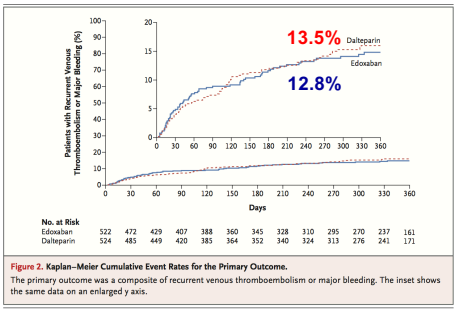

Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.
The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

Raskob, et al. NEJM. 2017

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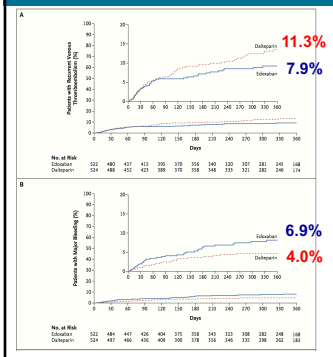
Cancer and VTE: Hokusai



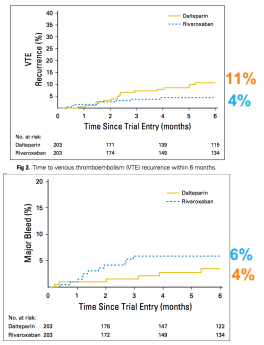
Raskob, et al. NEJM. 2017

50

Cancer and VTE: Hokusai and Select-D

JOURNAL OF CLINICAL ONCOLOGY | RAPID COMMUNICATION

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)



Three-fold relative increase in CRNMB with rivaroxaban compared with dalteparin

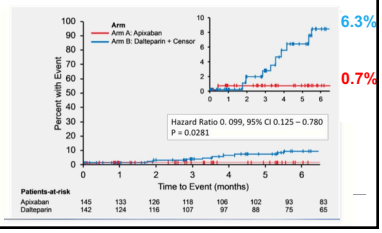
Raskob, et al. NEJM. 2017; Young et al. NEJM. 2018

51

Recently Presented Trial

Adam VTE Trial

- 300 patients
- RCT: apixaban vs dalteparin
- 6 months



DOAC: direct oral anticoagu
SOC: standard of care

McBane et al, JTH. Oct. 20

52

What I do …

- ***GI cancers***
- ***Procedures***
- ***Bleeding***
- ***Targeted Agents***
- ***P-gp, CYP3A4***
- ***Liver and kidney function***
- ***Brain Mets***
- ***Patient preference & Insurance***

- ***Ongoing Trial***

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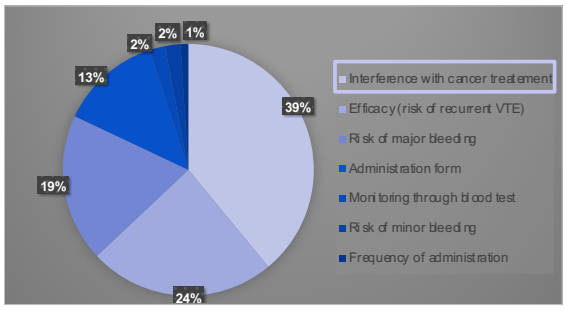
Most Important Factors to Patients When Choosing an Anticoagulant



VTE = venous thromboembolism

Noble, Haematol. 2015

54

Are DOACs appropriate for everyone?

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Should DOACs be used in…?

- Breast feeding
- Cardiac valves
- Insurance/Cost: long term use

NO!

- Pediatrics
- Extreme weights
- Antiphospholipid
- High bleeding risk (lack of reversal agent)
- High risk PE or advanced therapies

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Use of DOACs in pediatrics

- EINSTEIN-Jr
  - Phase 3 randomized, open-label study, evaluating efficacy and safety of rivaroxaban compared to standard anticoagulation
  - 500 children
  - Birth to 17 years
  - Previously diagnosed acute VTE who had started heparin.
  - 107 sites in 28 countries.

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Should DOACs be used in…?

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NO!

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Use of DOACs in extreme weights

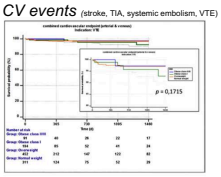
- *Data from Dresden DOAC Registry*
- *3432 patients*
- *1077 with BMI >30*

Table 3
Clinical effectiveness and safety outcomes in patients with BMI ≥ 30 kg/m².

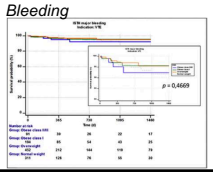
	Events (n)	event/100 pt. years (95% CI)
BMI 30–35 (n = 731)		
Combined effectiveness endpoint	30	1.84 (1.24–2.63)
ISTH major bleeding	34	2.09 (1.44–2.91)
BMI 35–40 (n = 248)		
Combined effectiveness endpoint	9	1.56 (0.71–2.96)
ISTH major bleeding	13	2.23 (1.19–3.81)
BMI > 40 (n = 98)		
Combined effectiveness endpoint	1	0.49 (0.01–2.71)
ISTH major bleeding	7	3.45 (1.39–7.12)

Tittl. Int J Cardiol. 2018.

CV events (stroke, TIA, systemic embolism, VTE)



Bleeding



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Should DOACs be used in…?

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Use of DOACs for treatment of APLS

Table 1
Direct oral anticoagulant (DOAC)-treated APS patients based on 4 case reports and 7 case series published.

N (PAPS/SAPS)	DOAC (Dose)	Mean F/U time (range)	Recurrence
3 (2/1)	Rivaroxaban (20 mg QD): 2 Dabigatran (150 mg QD): 1	5.7 ± 0.6 m (5–6 m)	100% (2 AT, 1 DVT)
3 (NR/NR)	Rivaroxaban (20 mg QD):2 Dabigatran (150 mg BID):1	9 ± 4.2 m (6–12 m)	100% (2 SVT, 1 AT)
1 (1/0)	Rivaroxaban (20 mg QD)	NR	No
12 (8/4)	Rivaroxaban (20 mg QD)	11.4 ± 4.4 m (2–16 m)	16.7% (2 DVT)
1 (1/0)	Rivaroxaban (15 mg QD)	7 m	No
1 (1/0)	Rivaroxaban (NR)	3 m	100% (AT)
1 (1/0)	Dabigatran (NR)	NR	No
35 (NR/NR)	Rivaroxaban (20 mg QD)	10 m[a] (6–24 m)	No
8 (4/4)	Rivaroxaban (20 mg QD): 7 Apixaban (5 mg QD): 1	19 ± 10.7 m (2–36 m)	No
26 (12/14)	Rivaroxaban (15-30 mg QD): 15 Dabigatran (150 mg BID): 11	19.2 ± 11.7 m (1–39 m)	3.8% (AT)
8 (8/0)	Rivaroxaban (20 mg QD)	5–365 days[b]	88% (4 AT, 2VT, 1 TIA)

PAPS: primary antiphospholipid syndrome; **SAPS**: APS associated with other autoimmune diseases; **NR**: no report; **AT**: arterial thrombosis; **VT**: vein thrombosis; **SVT**: superficial vein thrombosis; **TIA:** transient ischemic attack; **m**: months; f/u: follow-up; QD: daily; BID: twice a day.
[a] Median.
[b] Only time to recurrence was reported (median: 90 days).

Systematic review of DOAC use in APS: 4 case reports and 7 case series.
20% recurrent thrombosis risk with mean follow-up of 12 months

Yazici. Throm Research. 2017.

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Should DOACs be used in…?

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NO!

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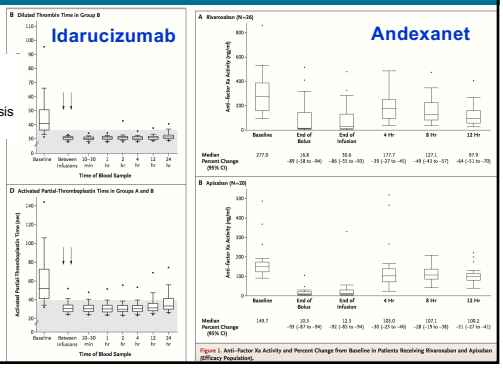
High Bleeding risk and reversal agents

- 67 pt
- Bleed
- 79% hemostasis



Pollack et al. NEJM. 2017
Connolly et al. NEJM. 2016

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Should DOACs be used in…?

- Breast feeding
- Cardiac valves
- Insurance/Cost: long term use

- Pediatrics
- Extreme weights
- Antiphospholipid
- High bleeding risk
- High risk PE or advanced therapies

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High Risk PE

- ***Edoxaban trial***
  - 1/3 patients had right ventricular dysfunction.
  - Reduction in recurrences in edoxaban group.
    - Rate of recurrent VTE in subgroup was 3.3% in edoxaban group and 6.2% in warfarin group (HR, 0.52; 95% CI, 0.28 to 0.98).
- ***Rivaroxaban trial***
  - 12% of patients ICU, suggesting some patients high-risk characteristics, but no specific analysis on them.

Einstein-PE Investigators. N Engl J Med 2012;366:1287-1297
Hokusai-VTE Investigators. N Engl J Med. 2013;369:1406-15.

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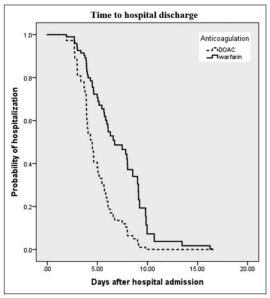
DOACS and Catheter Directed Thrombolysis?

Apixaban or Rivaroxaban Versus Warfarin for Treatment of Submassive Pulmonary Embolism After Catheter-Directed Thrombolysis

Use of DOAC after CDT associated with significant decrease hospital LOS compared to warfarin



Groetzinger et al. Clin & Appl Thromb/Hemost. 2018.

66

Direct oral anticoagulants: Are they for everyone?

- Yes, for majority of VTE patients
- Selection criteria:
  - Need for invasive procedures
  - Contraindications
  - Adequate organ function
  - Drug interactions
  - Cost

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Cautions with Direct Oral Anticoagulants

- No monitoring for effect
  - Compliance
- Renal and hepatic failure
- Reimbursement issues
  - COST (warfarin $5/mo vs $250-350/mo)
- Clinician familiarity
- Lack of guidelines
  - bleeding complications

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Direct oral anticoagulants: Other important questions

- Duration of anticoagulation
- Can VTE patients be treated as an outpatient
- Management of bleeding with DOAC
- Peri-operative/procedure management: how long to hold medication
- How to switch from one agent to another

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The Case of the Swollen Leg

How long should patients with VTE be treated?

Rosovsky, Harrison's Oncology,. 2018

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Risk of recurrent VTE

Type of VTE	1 year risk	5 year risk
Provoked by surgery	1%	3%
Provoked by non surgical reversible risk	5%	15%
Unprovoked VTE	10%	30%
Cancer associated	15%	*

* Not predicted due to high mortality rate from cancer
VTE = venous thromboembolism

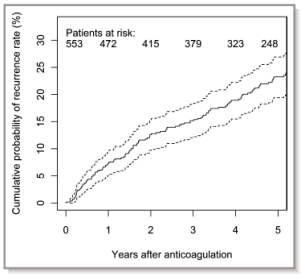
71 Kearon et al. CHEST. 2012.

71

VIENNA Prediction Model

Cumulative rate of recurrence in patients with first unprovoked VTE who stopped anticoagulation

Key points:
1. *At 5 years, risk is 25%*
2. *Increases with time*



VTE = venous thromboembolism

72 Eichenger. J Am Heart Assoc. 2014.

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Who warrants long term anticoagulation?

- Most likely to benefit
  - Idiopathic VTE
  - Active cancer
  - Antiphospholipid syndrome
  - Recurrent VTE
  - "high risk" thrombophilia
- Possible benefit
  - Provoked VTE with persistent risk factors

VTE = venous thromboembolism

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Extended Anticoagulation

Antithrombotic Therapy for VTE Disease
CHEST Guideline and Expert Panel Report

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy.

Kearaon. CHEST 2016;149(2):315-352

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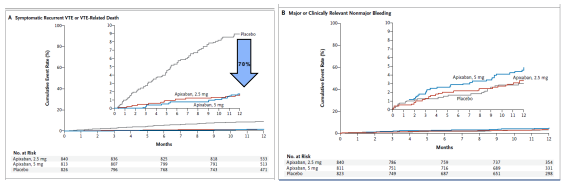
AMPLIFY EXTENSION

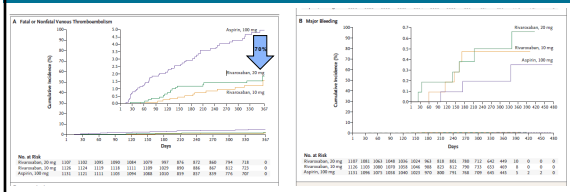


Apixaban reduced the risk of recurrent VTE without increasing the rate of major bleeding

Agnelli et al. NEJM. 2013.

75

EINSTEIN CHOICE



Rivaroxaban reduced the risk of recurrent VTE compared to aspirin without increasing rate of major bleeding

AC = anticoagulation

Weitz et al. NEJM. 3017.

76

How do I apply these results to my patients?

- Unprovoked
- Provoked with ongoing risk factors
- Reassess

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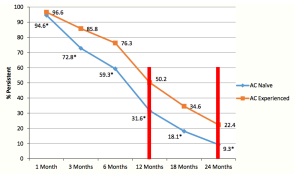
Reassess Frequently

Medical Adherence and Persistence with DOACs



AC Naïve (N)	29,148	22,432	18,268	9,743	5,591	2,870
AC Experienced (N)	34,064	30,269	26,891	17,707	12,203	7,885

Figure 1. Persistence with initial DOAC treatment, overall (all DOACs).
*Denotes a statistically significant difference between AC-naïve and AC-experienced users (p<0.05).

Manzoor. Pharmacotherapy. 2017

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The Case of the Swollen Leg

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Direct oral anticoagulants: Other important questions

- Duration of anticoagulation
- Can VTE patients be treated as an outpatient
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- Peri-operative/procedure management: how long to hold medication
- How to switch from one agent to another

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The Case of the Swollen Leg

Can he be treated as an outpatient?

Rosovsky, Harrison's Oncology.. 2018

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Other Important Topics

Do all patients with DVT or PE need to be admitted: Data behind outpatient treatment

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Outpatient Treatment for VTE

*20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).

- Clinically stable with good cardiopulmonary reserve.
- No contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (ie, <70,000/mm3).
- Expected to be compliant with treatment
- Patient feels well enough to be treated at home and has support.
- No presence of right ventricular dysfunction or increased cardiac biomarker levels.

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Kearon et al. CHEST 2016; 149(2):315-352.
10th Edition (Jan 2016) of *CHEST* guidelines for Antithrombotic Therapy for VTE Disease.

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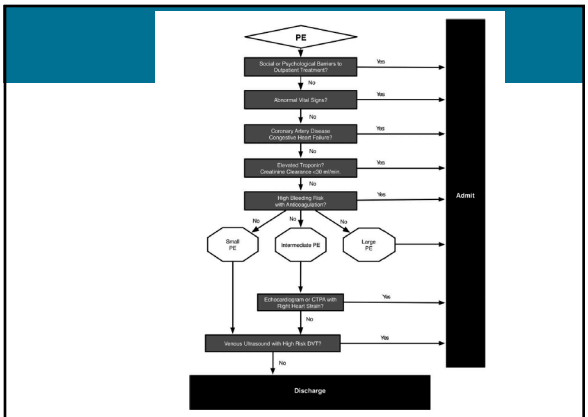

Kabrhel, Rosovsky, Baugh et al. Hospital Practice. 2017
Kabrhel, Rosovsky, Baugh et al. Acad Emerg Med. 2018

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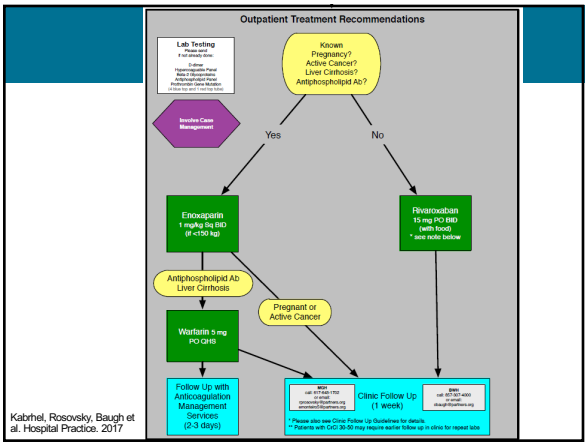

Kabrhel, Rosovsky, Baugh et al. Hospital Practice. 2017

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Outpatient treatment of DVT/PE

Timely follow up is most important component

- 2,212 patients

Table 2
Outpatient VTE Treatment

	Before Protocol	After Protocol	Absolute Difference (95% CI)	Risk Ratio (95% CI)
Total				
PE (with or without identified DVT)	12% 79/661	18% 120/663	6% (2% to 10%)	1.51 (1.16 to 1.97)
Low-risk PE*	18% 65/360	28% 101/355	11% (5% to 17%)	1.60 (1.21 to 2.10)
DVT (without identified PE)	49% 207/420	60% 279/468	10% (4% to 17%)	1.21 (1.07 to 1.37)
All VTE	26% 286/1,081	35% 399/1131	9% (5% to 13%)	1.33 (1.17 to 1.51)
MGH				
PE (with or without identified DVT)	15% (51/344)	24% 78/325	9% (3% to 15%)	1.62 (1.18 to 2.23)
Low-risk PE*	22% (45/202)	37% 70/190	15% (6% to 24%)	1.65 (1.2 to 2.27)
DVT (without identified PE)	53% (135/255)	62% 183/293	10% (1% to 18%)	1.18 (1.02 to 1.37)
All VTE	31% 186/599	42% 261/618	11% (6% to 17%)	1.36 (1.17 to 1.58)
BWH				
PE (with or without identified DVT)	9% 28/317	12% 42/338	4% (-1% to 8%)	1.41 (0.89 to 2.21)
Low-risk PE*	12% 20/163	19% 31/165	7% (-1% to 14%)	1.53 (0.91 to 2.57)
DVT (without identified PE)	44% 72/165	55% 96/175	11% (1% to 22%)	1.26 (1.01 to 1.57)
All VTE	21% 100/482	27% 138/513	6% (1% to 11%)	1.30 (1.04 to 1.62)

Low-risk PE is defined as PE distal to main pulmonary arteries, no right ventricular dilatation, hypokinesis or septal bowing on echocardiogram, no evidence of right heart strain on computed tomography, troponin T negative. If echocardiographic data were unavailable or not performed, they were assumed to be negative.
BWH = Brigham and Women's Hospital; DVT = deep vein thrombosis; MGH = Massachusetts General Hospital; PE = pulmonary embolism; VTE = venous thromboembolism.

Kabrhel, Rosovsky, Baugh et al. Acad Emerg Med. 2018

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Outpatient treatment of DVT/PE

Timely follow up is the most important component

- Mortality, bleeding, and returns to ED were rare and did not increase after protocol.
- Treatment protocol combining risk-stratification, DOAC and defined follow-up increase in PE and DVT patients treated as outpatients, with no increase in adverse outcomes

Kabrhel, Rosovsky, Baugh et al. Acad Emerg Med. 2018

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The Case of the Swollen Leg

How should he be treated if he bleeds?

Rosovsky, Harrison's Oncology.. 2018

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Management of Bleeding on a DOAC

Initial Questions

Is the patient actively bleeding?
Where is the location and what is the severity of the bleed?
Can local hemostatic measures be applied or is a surgical invention or procedure required?
What DOAC is the patient taking and when was the last dose?
Does the patient have renal failure or liver disease which may affect metabolism or clearance of DOAC?
Is the patient on an antiplatelet or alternative medication that may further increase risk of bleeding?
Does the patient have comorbidities that may increase the risk of bleeding?
Is the patient hemodynamically stable?

Initial Testing

Complete Blood Count
Comprehensive Metabolic Panel to assess kidney and liver function
Coagulation tests: PT, PTT, INR
dTT (if on dabigatran) or anti-factor Xa (if on apixaban, rivaroxaban edoxaban)

Intervention: based on severity of bleed ‡

Rosovsky, Merli. 2017 TVIR

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Management of Bleeding on a DOAC

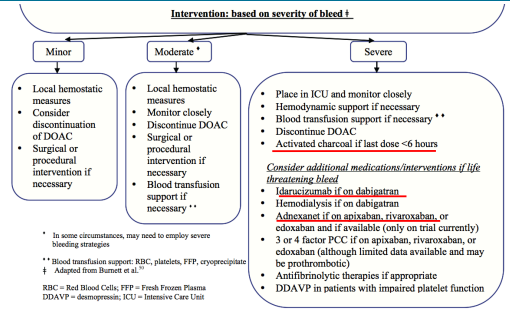

Figure 2 Management of bleeding on a DOAC.

Rosovsky, Merli. 2017 TVIR

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Ideally, we want to prevent bleeding.

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Direct oral anticoagulants: Important questions

- Peri-operative/procedure management? How long to hold medication?
  - What drug patient taking
  - ½ life of the drug
  - Bleeding risk of procedure
  - Bleeding and thrombotic risk of patient
  - Renal function

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How long to hold novel oral agents for procedures:

Look at package inserts

Table 11 Cessation and resumption of DOAC for TI[a] [46, 47, 126, 127]

Cessation[b]				Resumption	
Renal function[c] (mL/min)	Estimated half-life[d] (hours)	Low bleeding risk surgery[e] (allow 2–3 $t_{1/2}$ between last dose and surgery)	High bleeding risk surgery[f] (allow 4–5 $t_{1/2}$ between last dose and surgery)	Low bleed risk	High bleed risk
Dabigatran (BID dosing)				1 day after procedure (~24 h post-op)	2–3 days after procedure[g] (~48–72 h post-op)
CrCl > 80	$t_{1/2}$ ~ 14	Hold time: 28–42 h # doses to hold: 2	Hold time: 56–70 h # doses to hold: 5–6		
CrCl > 50–79	$t_{1/2}$ ~ 17	Hold time: 34–51 h # doses to hold: 3–4	Hold time: 68–85 h # doses to hold: 6–7		
CrCl 30–49	$t_{1/2}$ ~ 19	Hold time: 38–57 h # doses to hold: 4–5	Hold time: 76–95 h # doses to hold: 7–8		
CrCl 15–29	$t_{1/2}$ ~ 28	Hold time: 56–84 h # doses to hold: 5–7	Hold time: 112–140 h # doses to hold: 9–12		
CrCl < 15[h]	Unknown	Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH			
Rivaroxaban (Once daily dosing)					
CrCl > 80	$t_{1/2}$ ~ 8	Hold time: 16–24 h # doses to hold: 1	Hold time: 32–40 h # doses to hold: 2		
CrCl > 30–79	$t_{1/2}$ ~ 9	Hold time: 18–27 h # doses to hold: 1	Hold time: 36–45 h # doses to hold: 2		
CrCl 15–29	$t_{1/2}$ ~ 10	Hold time: 20–30 h # doses to hold: 1–2	Hold time: 40–50 h # doses to hold: 2–3		
CrCl < 15[h]	Unknown	Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH			
Apixaban (BID dosing)					
CrCl > 50	$t_{1/2}$ ~ 7–8	Hold time: 14–24 h # doses to hold: 2	Hold time: 28–40 h # doses to hold: 4		
CrCl 15–49	$t_{1/2}$ ~ 17–18	Hold time: 34–54 h # doses to hold: 3–4	Hold time: 68–90 h # doses to hold: 6–7		
CrCl < 15[h]	Unknown	Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH			
Edoxaban (Once daily dosing)					
CrCl > 50	$t_{1/2}$ ~ 8–9	Hold time: 16–27 h # doses to hold: 1	Hold time: 32–45 h # doses to hold: 2		
CrCl 30–49	$t_{1/2}$ ~ 9–10	Hold time: 18–30 h # doses to hold: 1	Hold time: 36–50 h # doses to hold: 2		
CrCl 15–29	$t_{1/2}$ ~ 17	Hold time: 34–51 h # doses to hold: 2	Hold time: 68–85 h # doses to hold: 3–4		
CrCl < 15[h]	Unknown	Hold until resolved (e.g. if acute kidney injury) or consider transition to warfarin or UFH			

Burnett et al. *J Thromb Thrombolysis*. 2016

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The Case of the Swollen Leg

What if we need to change his anticoagulation?

Rosovsky, Harrison's Oncology.. 2018

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Switching to/from direct oral anticoagulant: Review package insert

Table 16 Switching to warfarin

DOAC to warfarin	
Dabigatran[a]	Start warfarin and overlap with dabigatran; CrCl ≥50 mL/min, overlap 3 days CrCl 30–50 mL/min, overlap 2 days CrCl 15–30 mL/min, overlap 1 day
Rivaroxaban[a] Apixaban[a]	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Edoxaban[a]	For 60 mg dose, reduce dose to 30 mg and start warfarin concomitantly For 30 mg dose reduce dose to 15 mg and start warfarin concomitantly Stop edoxaban when INR ≥ 2.0

Table 15 Switching to DOACs

Warfarin to DOAC	
Dabigatran[a]	Start when INR < 2.0
Rivaroxaban[a]	Start when INR < 3.0
Apixaban[a]	Start when INR < 2.0
Edoxaban[a]	Start when INR ≤ 2.5
LMWH to DOAC	
Dabigatran Rivaroxaban Apixaban Edoxaban	Start DOAC within 0–2 h of the time of next scheduled dose of LMWH
(iv) UFH to DOAC	
Dabigatran[a] Rivaroxaban[a] Apixaban[a] Edoxaban[a]	Start DOAC immediately after stopping iv UFH Start edoxaban 4 h after stopping iv UFH
As a general rule, we suggest that as INR drops below 2.5, a DOAC can be started	
As a general rule, we suggest that each DOAC can be started within 30 min after stopping (iv) UFH	

[a] Recommendations adapted from company's package insert

Burnett et al. J Thromb Thrombolysis. 2016

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Other Important Topics

Novel approaches to treatment of severe pulmonary embolism

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Case 1

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Importance of expeditiously treating Pulmonary Embolism

- Fatal within 1 hour after the onset of symptoms in 10% of cases
- Untreated PE mortality rate ~30%

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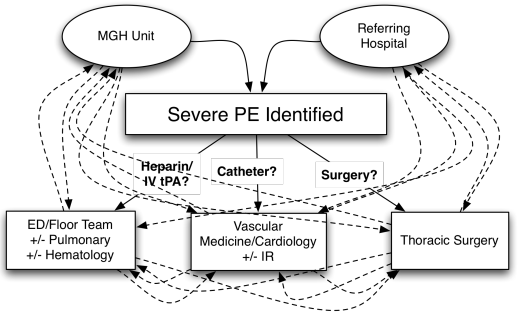
Pulmonary Embolism Response Team (PERT)



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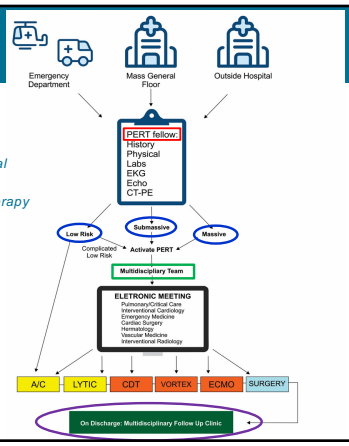
PERT Program Flow Map

Expeditious input & clinical judgment from multiple specialties to optimize therapy



A/C Anticoagulation only
CDT Catheter-direct thrombolysis

Rosovsky et al. Clinics in Chest. 2018

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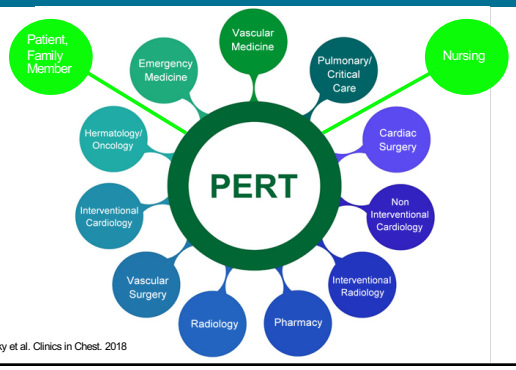
Multidisciplinary Collaboration



Rosovsky et al. Clinics in Chest. 2018

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PERT Team at MGH

A Multidisciplinary Pulmonary Embolism Response Team

Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism

Christopher Kabrhel, MD, MPH; Rachel Rosovsky, MD, MPH; Richard Channick, MD; Michael R. Jaff, DO; Ido Weinberg, MD; Thoralf Sundt, MD; David M. Dudzinski, MD, JD; Josanna Rodriguez-Lopez, MD; Blair A. Parry, CCRC, BA; Savanah Harshbarger, BS; Yuchiao Chang, PhD; and Kenneth Rosenfield, MD

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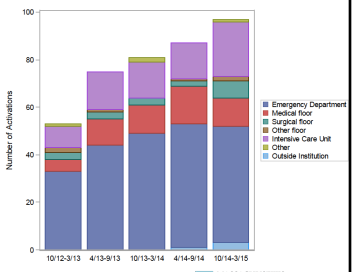
PERT Data: Activations

- As soon as PERT launched
  - Immediate response



Kabrhel, Rosovsky et al. Chest. 2016

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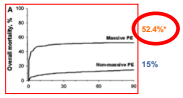
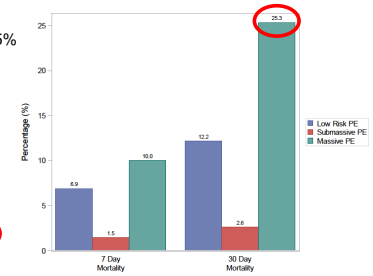
PERT Outcomes: MGH Mortality

- Massive PE mortality 25%
- **Lower than National average of 52%**
- Does our approach improve outcomes?





Kabrhel et al. Chest. 2016

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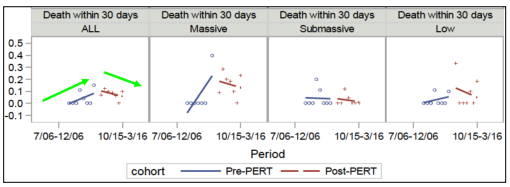
Time Trend in Death Pre-PERT and Post-PERT



Rosovsky et al, JTT. 2018

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Received: 2 December 2018 | Accepted: 9 April 2019
DOI: 10.1002/rth2.12216

REVIEW ARTICLE

rpth

Pulmonary embolism response teams: Purpose, evidence for efficacy, and future research directions

Rachel Rosovsky MD, MPH[1] | Ken Zhao MD[2] | Akhilesh Sista MD, FSIR[2] | Belinda Rivera-Lebron MD, MS, FCCP[3] | Christopher Kabrhel MD, MPH[4]

- 32 published descriptions or reviews of how various PERTs establish, organize, operate, and/or manage their programs
- 12 prospective and retrospective studies involving PERT.
- Preliminary results from early adopters suggest that PERT facilitates access to advanced therapies

PERT = pulmonary embolism response team

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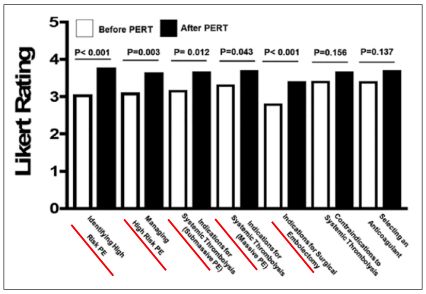
Impact of PERT on Trainee Physicians



Trainee physicians perceptions before and after PERT implementation

Elbadawi et al. Vasc Med. 2018

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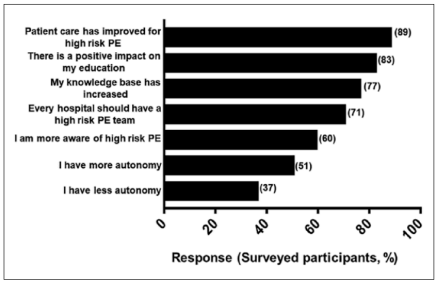
Impact of PERT on Trainee Physicians



Trainee perception of PERT and the effects on their autonomy, quality of care, medical education, hospital effectiveness in managing high risk PE.

Elbadawi et al. Vasc Med. 2018

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6.4 Multidisciplinary pulmonary embolism teams

The concept of multidisciplinary rapid-response teams for the management of 'severe' (high-risk and selected cases of intermediate-risk) PE emerged in the USA, with increasing acceptance by the medical community and implementation in hospitals in Europe and worldwide. Set-up of PE response teams (PERT) is encouraged, as they address the needs of modern systems-based healthcare.[301] A PERT brings together a team of specialists from different disciplines including, for example, cardiology, pulmonology, haematology, vascular medicine, anaesthesiology/intensi (interventional) radiology. The te face or via web conference) to er allows the formulation of a treatr ate implementation.[301] The exac of a PERT are not fixed, depend available in each hospital for the r

6.8 Recommendations for multidisciplinary pulmonary embolism teams

Recommendation	Class[a]	Level[b]
Set-up of a multidisciplinary team and a programme for the management of high- and (in selected cases) intermediate-risk PE should be considered, depending on the resources and expertise available in each hospital.	IIa	C

PE = pulmonary embolism.
[a]Class of recommendation.
[b]Level of evidence.

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Expanding PERT Nationally and Internationally…

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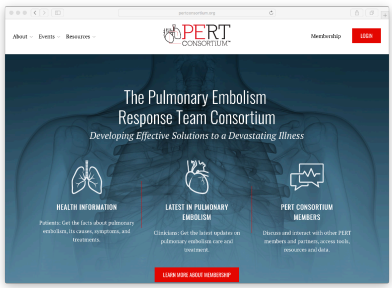
Creation of PERT Consortium



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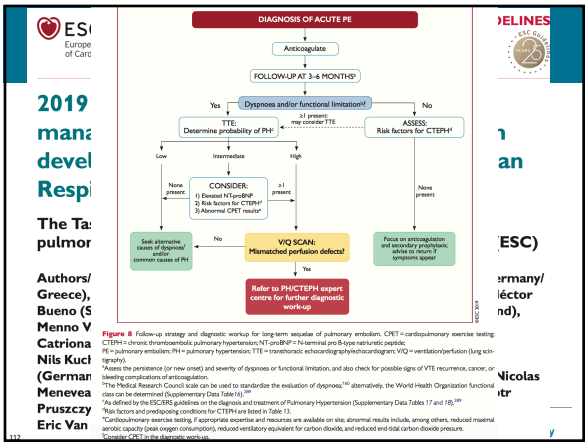

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How can you get involved?

March
VTE Awareness Month

October 13
World Thrombosis Day

Educate patients and providers!

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How can you get involved?

- Join or start your PERT team!!!!
- 6th Annual PERT Consortium Meeting and Scientific Symposium:

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Case 1: Multi-disciplinary Collaborative Decision-Making

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Closing Reflections

- VTE is a major cause of morbidity and mortality
- DOACs: exciting addition to VTE treatment. **1st line**
  - Similar efficacy/mortality as warfarin, better bleeding
- Novel agents may be attractive alternative in cancer patients; efficacy and safety is currently under investigation..
- Consider treating low risk VTE as outpatient
- Treatment for life threatening pulmonary embolism may be best served via multidisciplinary approach. PERT National Consortium has been created and will study this approach.

VTE – venous thromboembolism
PERT = Pulmonary Embolism Response Team

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Key Points and Next Steps

Key Points

- The direct oral anticoagulants (DOACs) have similar efficacy as warfarin, but better bleeding profiles and are now used as first line in many patients.
- Selecting which DOAC to use will depend on patient factors and preferences and drug characteristics.
- There are still some populations in whom DOACs should not be used (ie: pregnancy, cardiac valves, liver failure)

Next Steps

- When prescribing a DOAC, know that each one has a different dosing pattern and administration - some require a higher dose initially and others require a heparin lead in and one requires to be taken with food. Educate your patients about how to take their DOAC.

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Thank you

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