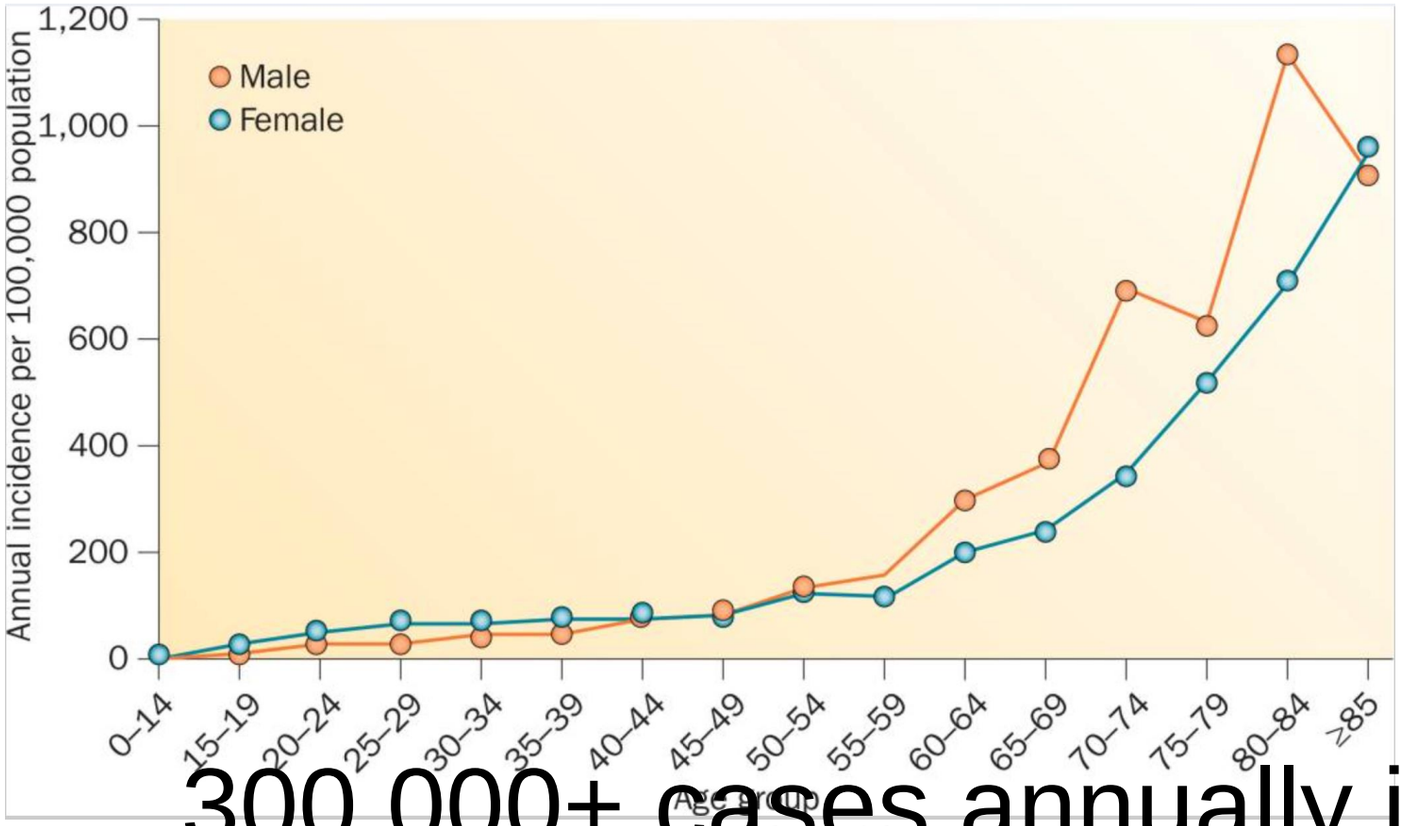
Pulmonary Embolism Literature Review: What is New?

Michael Hooper, M.D., MSc
Associate Professor, Pulmonary and Critical Care Medicine
Eastern Virginia Medical School

- I have no conflicts of interest to report.

VTE Pathogenesis

- Virchow's triad (stasis, endothelial injury, hypercoagulability)
- Acute Death (for PE):
  - 10% sudden death
  - untreated -> 20-30% mortality
  - (DVT) - Clot propogation, Embolization: 15%
  - Recurrence
  - Post-phlebitic syndrome, CTEPH

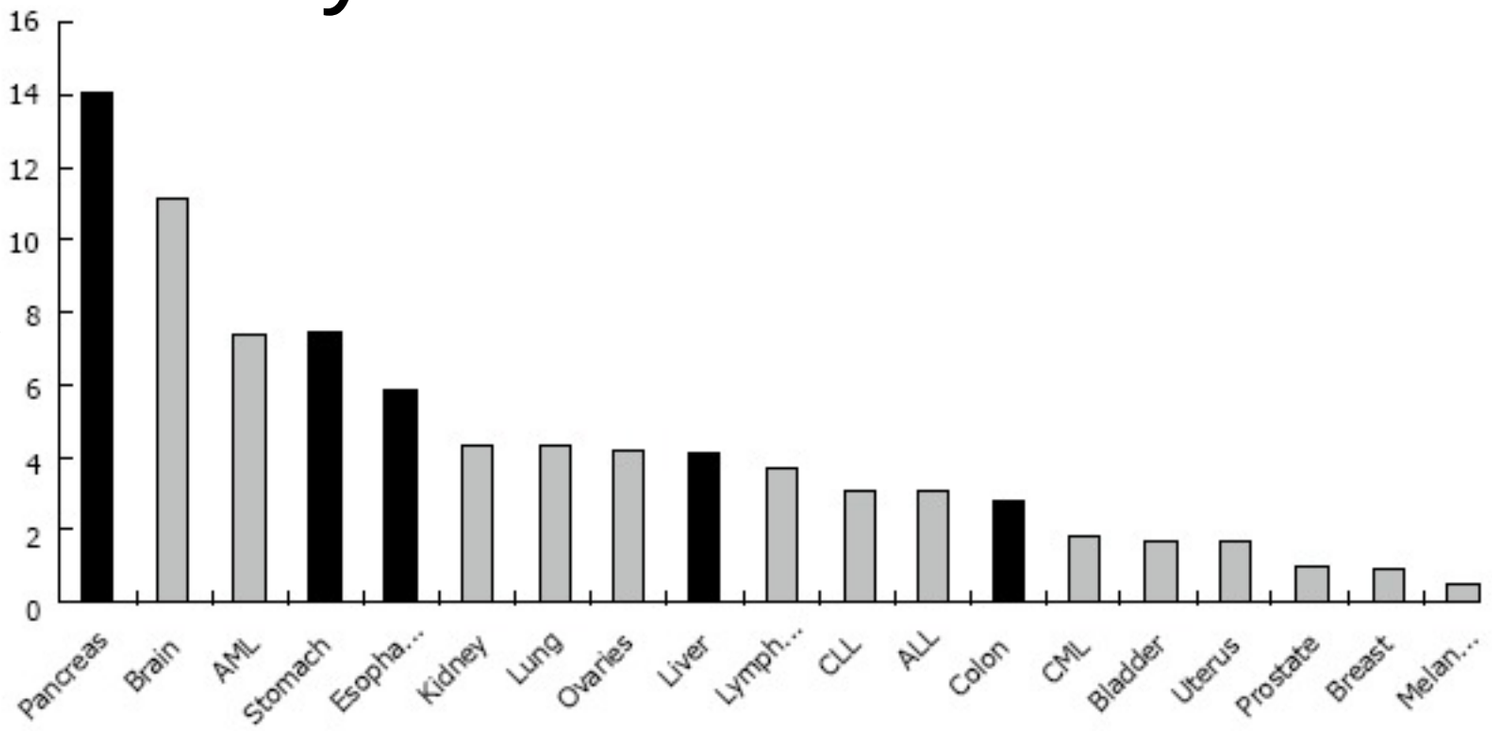


Epidemiology of venous thromboembolism

John A. Heit

Nat Rev Cardiol. 2015 Aug; 12(8): 464–474.

300,000+ cases annually in the United States



World J Gastrointest Oncol. 2016 Mar 15; 8(3): 258–270.
Published online 2016 Mar 15. doi: 10.4251/wjgo.v8.i3.258

PMCID: PMC4789611

Primary prevention and treatment of venous thromboembolic events in patients with gastrointestinal cancers - Review

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US National Library of Medicine
National Institutes of Health

PubMed | "venous thromboembolism" OR "deep vein thrombosis" or "pulmonary embolism" | Search

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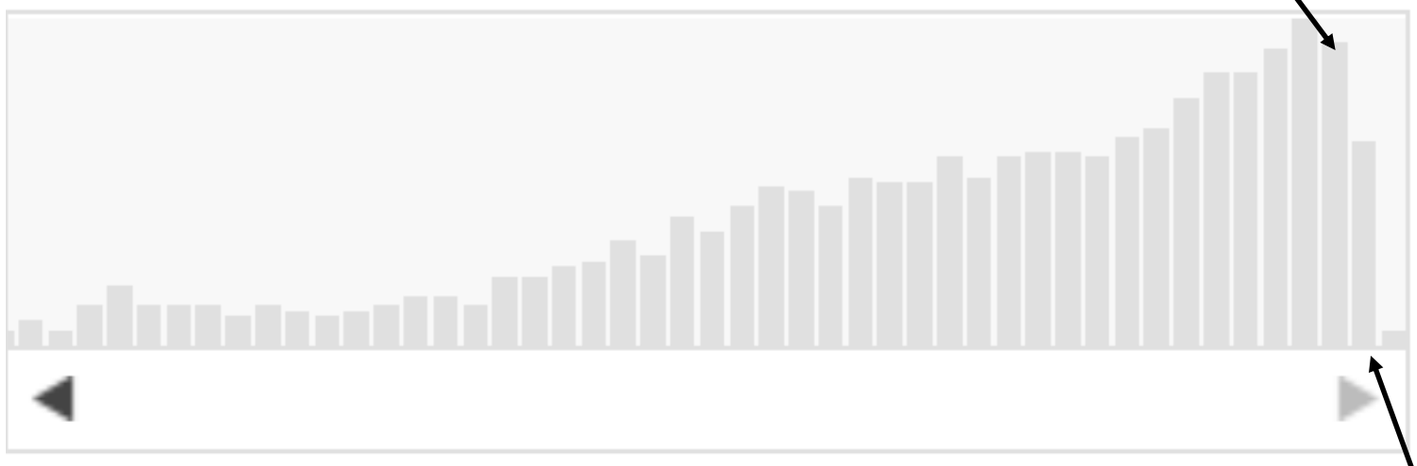
Article types
- ✓ Clinical Trial
- Review
- Customize ...

Text availability
- Abstract
- Free full text
- Full text

Publication dates
- 5 years
- 10 years
- Custom range...

Species
- ✓ Humans
- Other Animals

2016: 272 articles



2017: 185 articles

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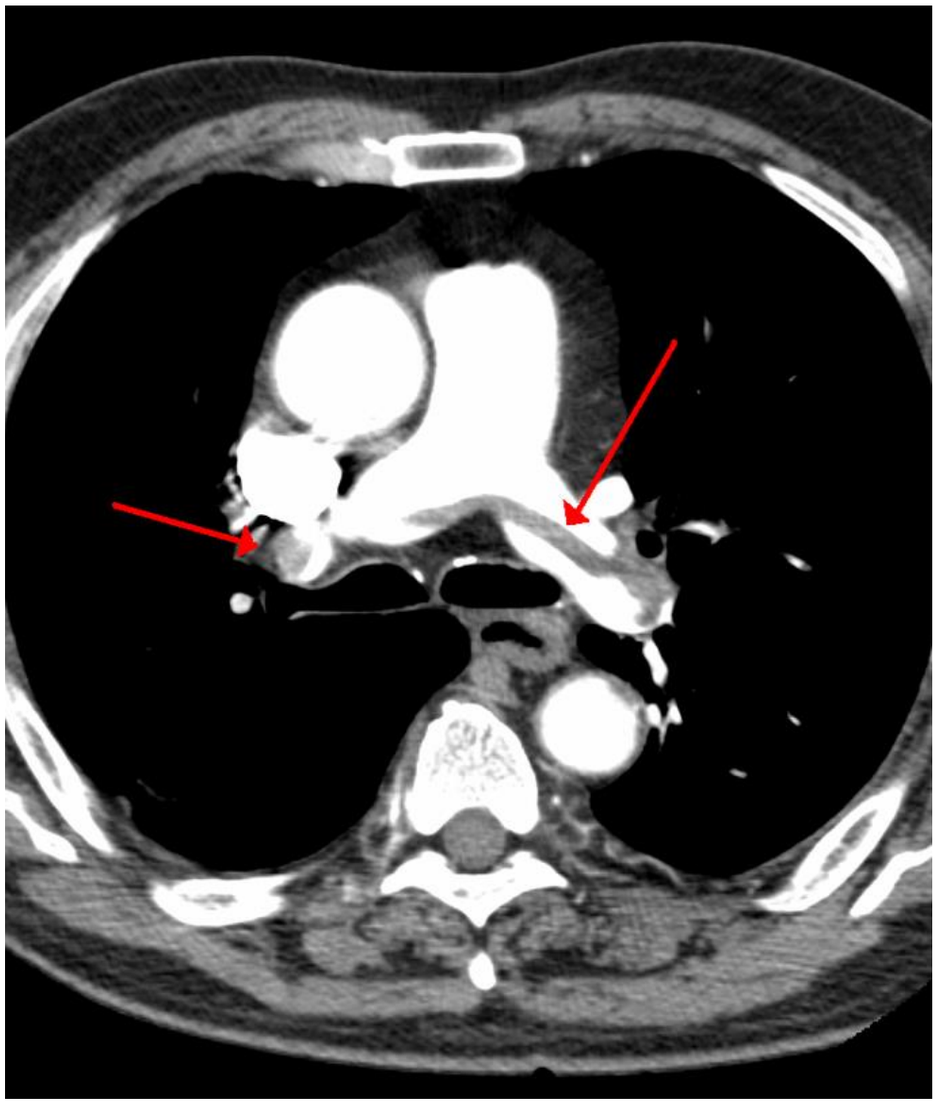
Since 2000: > 3,500 articles

VTE Overview

- Diagnosis
- Classifying Disease
- Treatment
  - Medical +/- Invasive
- Secondary Prevention



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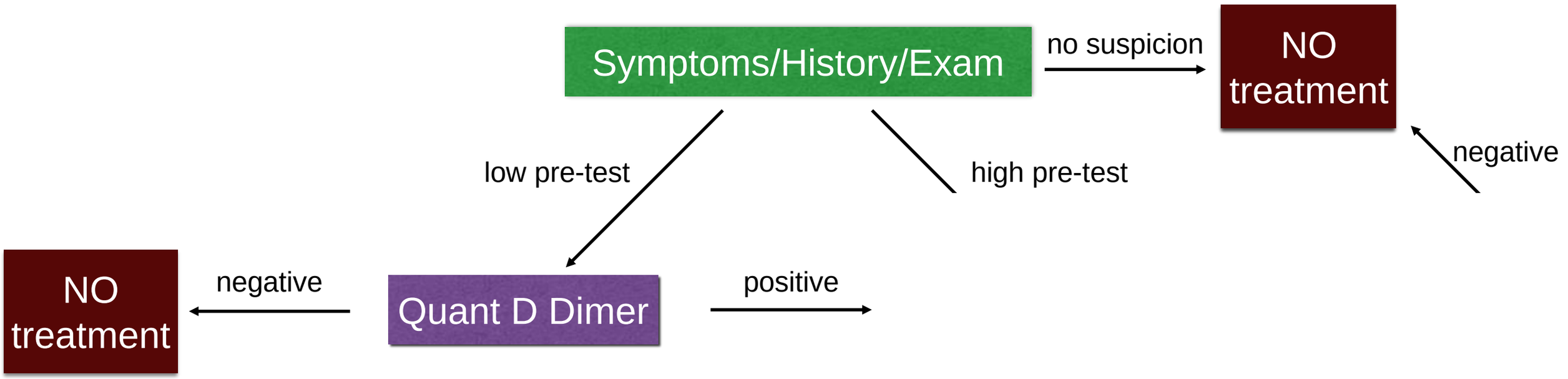
Diagnostic Approach for Suspected PE in a Stable Patient



The concept of “pre-test probability” is not entirely consistent among providers.

Many ongoing efforts to improve our ability to estimate probability of PE or outcome prior to expensive or harmful testing.

- **clinical signs of DVT?**
- **hemoptysis?**
- **PE is the most likely diagnosis?**

Zero items and D-dimer less than 1000 ng/mL
OR
≥1 items and D-dimer less than 500 ng/mL =
PE excluded

Outcome = #VTE in 3 months of follow-up

ry outcome was the number of required CTPA compared with the Wells' diagnostic

Lancet 2017; 390: 289–97

- **clinical signs of DVT?**
- **hemoptysis?**
- **PE is the most likely diagnosis?**

- 13% of patients had PE in this cohort.

- 2946 (85%) ruled out:
  - 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up, with an incidence of 0·61%
  - The incidence of fatal pulmonary embolism was 0·20%

- 14% reduction in CTPA compared to Well's criteria

Lancet 2017; 390: 289–97

PERC: Pulmonary Embolism Rule-Out Criteria

- New onset SOB/chest pain
- Low Risk PE (gestalt < 15%)
- Excluded if obvious alternative DX, shock/resp failure, contraindication to w/u, already anti-coagulated

- O2 Sat: 94%
- Pulse 100
- Age 50
- Unilateral leg swelling
- Hemoptysis
- Recent trauma/surgery
- Prior VTE
- Exogenous Estrogen

Frend et al. JAMA 2018;319 (6): 559-566

Table 3. Main Outcomes in the Study of Pulmonary Embolism Rule-Out Criteria

Characteristics	No. (%) PERC	No. (%) Control	Mean Difference, % (95% CI)	Number Needed to Treat	*P* Value
Intention-to-treat population, No.[a]	962	954			
Thromboembolic event at 3 mo (primary outcome)	32 (3)	29 (3)	0.2 (−∞ to 1.6)[b]		.12
CTPA performed	129 (13)	220 (23)	9.7 (6.1 to 13.2)	10	<.001
Length of ED stay, median (IQR), h:min	4:36 (3:16 to 6:21)	5:14 (3:50 to 7:18)	−00:36 (−1:08 to −0:04)		<.001
Hospital admission	121 (13)	152 (16)	3.3 (0.1 to 6.6)	30	.04
Anticoagulation therapy introduced	21 (2)	33 (3)	1.3 (0.3 to 2.9)	78	.09
Hospital readmission at 3 mo	43 (4)	62 (7)	2.1 (−0.1 to 4.3)	48	.051
All-cause death at 3 mo	3 (0.3)	2 (0.2)	0.1 (−0.5 to 0.7)		>.99
Per-protocol population, No.[a]	847	902			
Thromboembolic event at 3 mo (primary outcome)	1 (0.1)	0	0.1 (−∞ to 0.8)[b]		
CTPA performed	114 (14)	211 (23)	9.9 (6.2 to 13.6)	10	<.001
Length of ED stay, median (IQR), h:min	4:34 (3:12 to 6:14)	5:12 (3:50 to 7:17)	−00:37 (−1:11 to −0:02)		<.001
Hospital admission	101 (12)	139 (15)	3.5 (0.2 to 6.8)	29	.03
Anticoagulation therapy introduced	19 (2)	28 (3)	0.8 (−0.8 to 2.5)	116	.27
Hospital readmission at 3 mo	38 (4)	62 (7)	2.4 (0.1 to 4.7)	42	.03
All-cause death at 3 mo	1 (0.1)	1 (0.1)	0.01 (−0.4 to 0.4)		>.99

Thromb Res. 2017 Apr;152:49-51. doi: 10.1016/j.thromres.2017.02.007. Epub 2017 Feb 13.

Performance of the age-adjusted cut-off for D-dimer in patients with cancer and suspected pulmonary embolism.

RESULTS: Of 3324 patients with suspected PE, 429 (12.9%) patients had cancer. The prevalence of PE was 25.2% in cancer patients and 18% in patients without cancer (p<0.001). Among cancer patients with an unlikely CDR, 9.9% had a DD <500µg/L as compared with 19.7% using the age-adjusted cutoff. In patients without cancer, these rates were 30.1% and 41.9%. The proportion of cancer patients in whom PE could be excluded by CDR and DD doubled from 6.3% to 12.6%. No VTE occurred during three-month follow-up (failure rate 0.0% (95% CI 0.0-6.9%)).

CONCLUSION: Compared with the conventional cutoff, the age-adjusted D-dimer cutoff doubles the proportion of patients with cancer in whom PE can be safely excluded by CDR and DD without imaging.

- Age Adjusted D-dimer valid in multiple populations
- Safely “rules out” PE and decreases unnecessary testing

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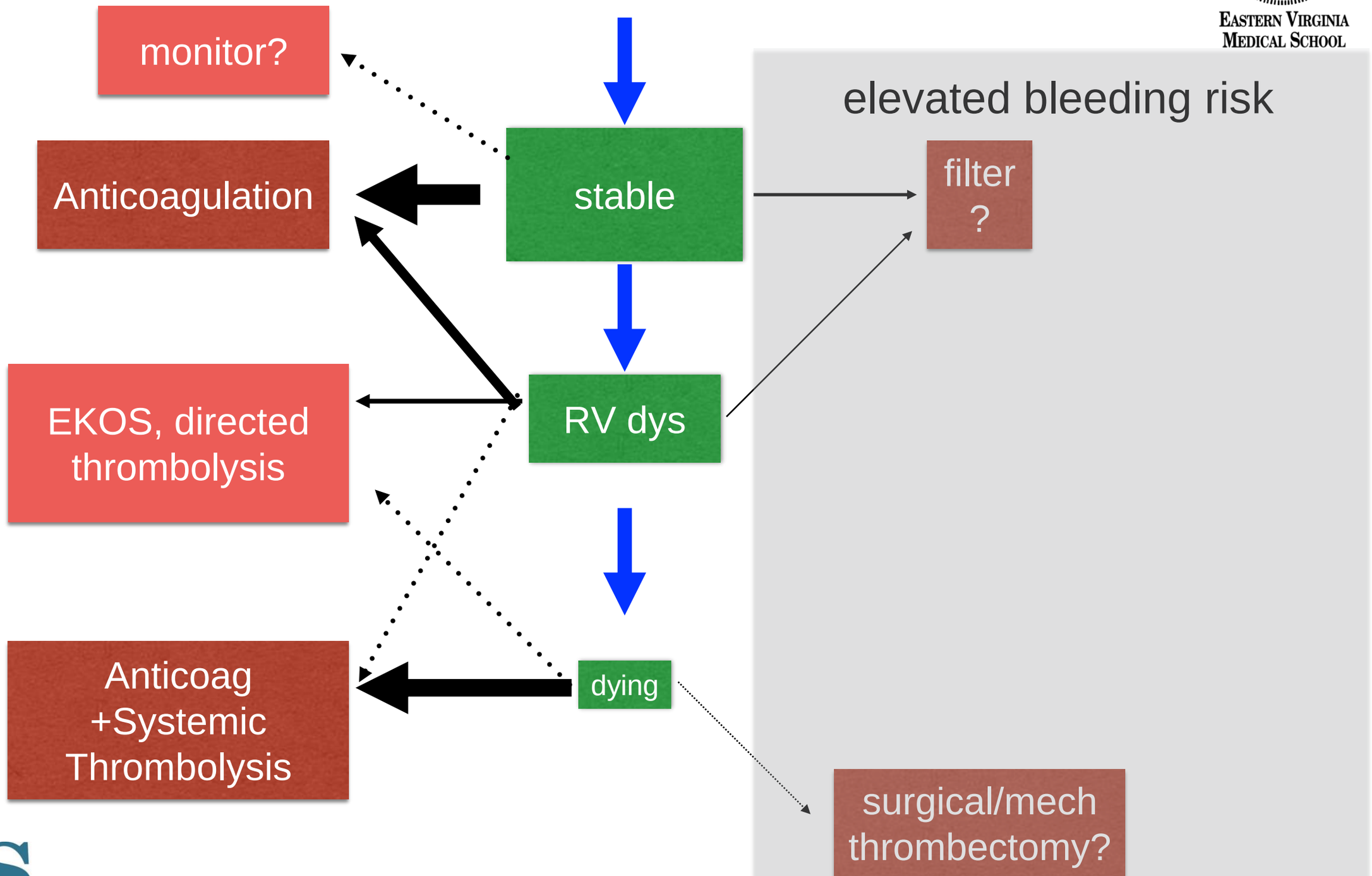
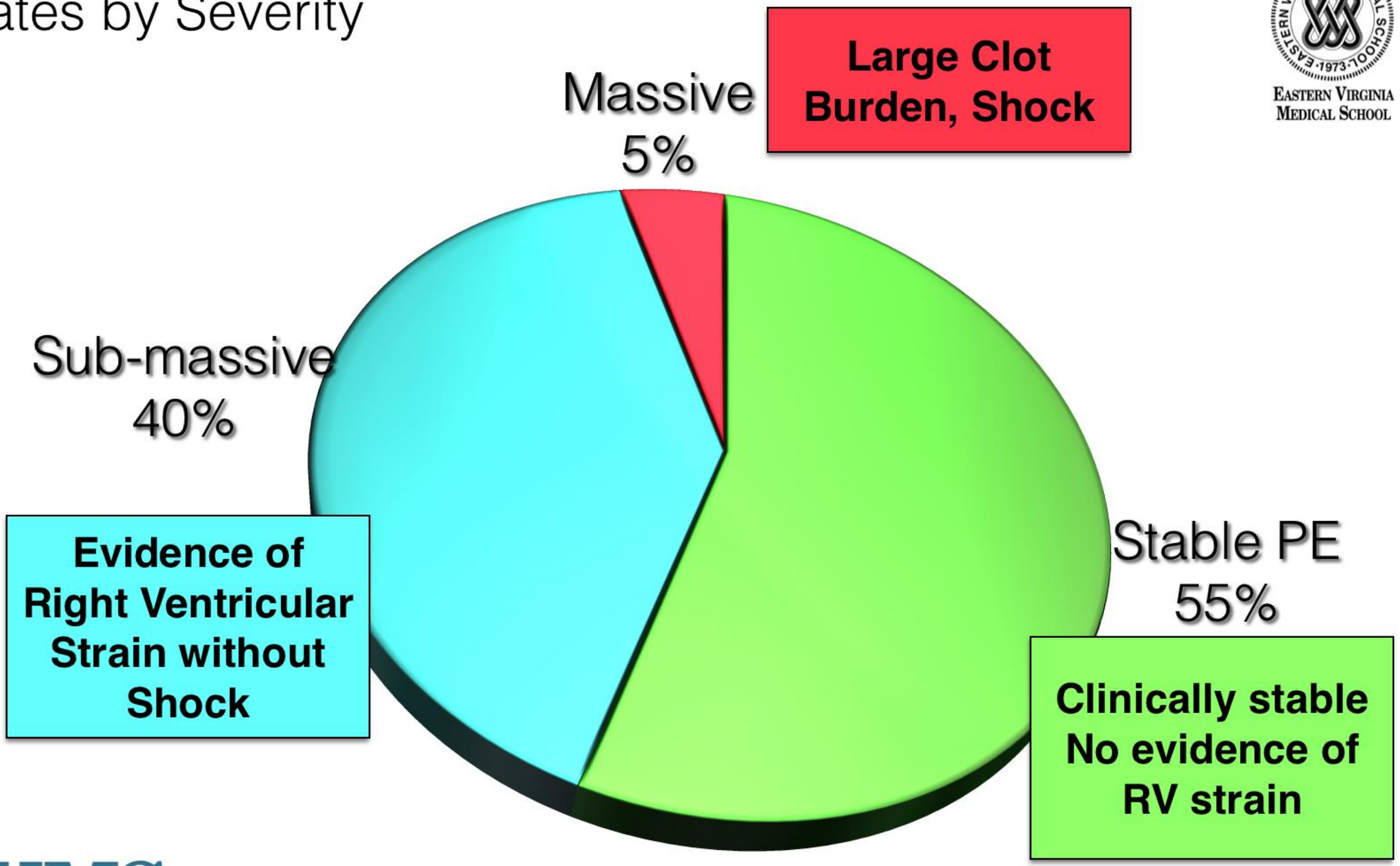
PE Acute Therapeutic Approach



Rates by Severity



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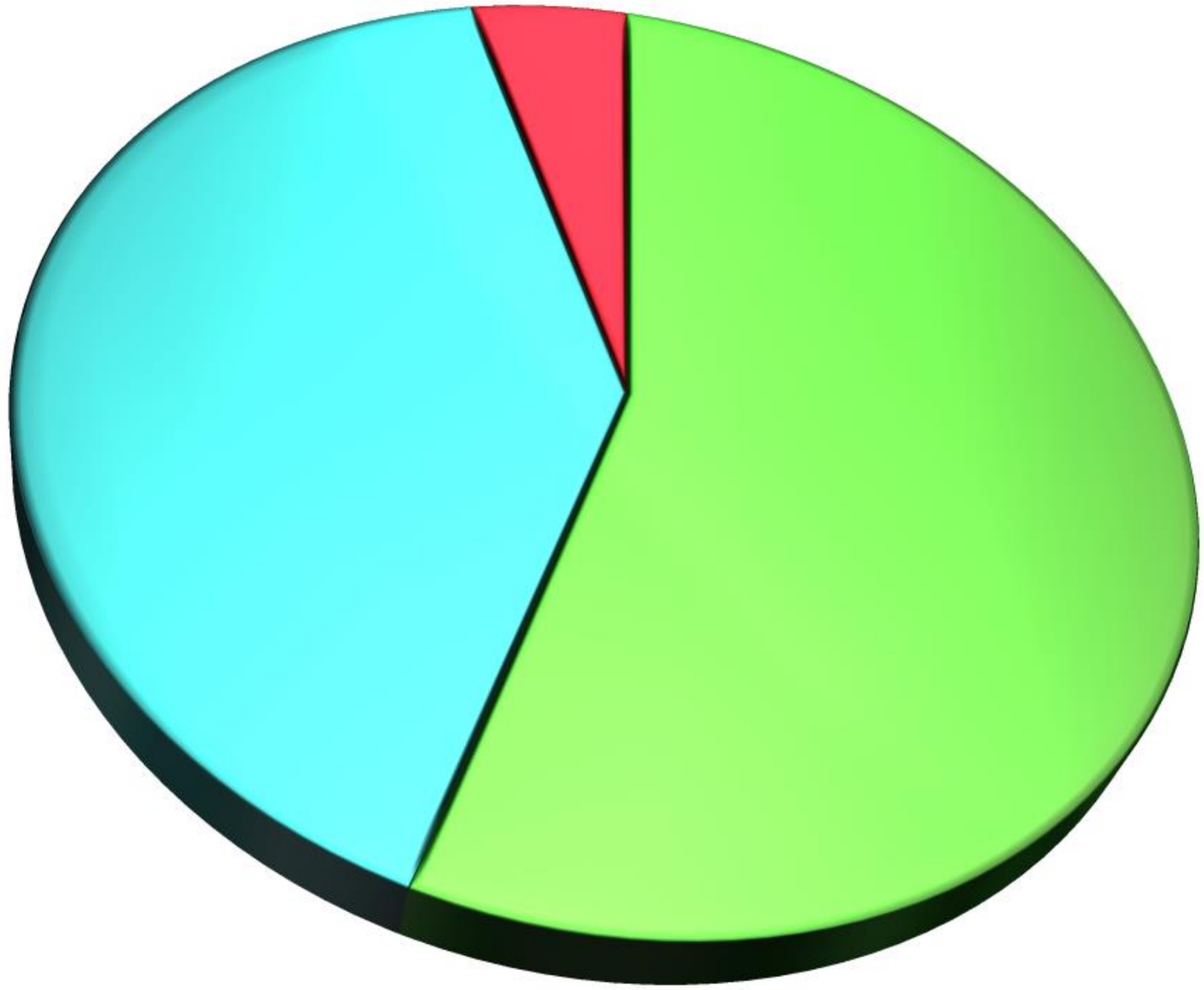
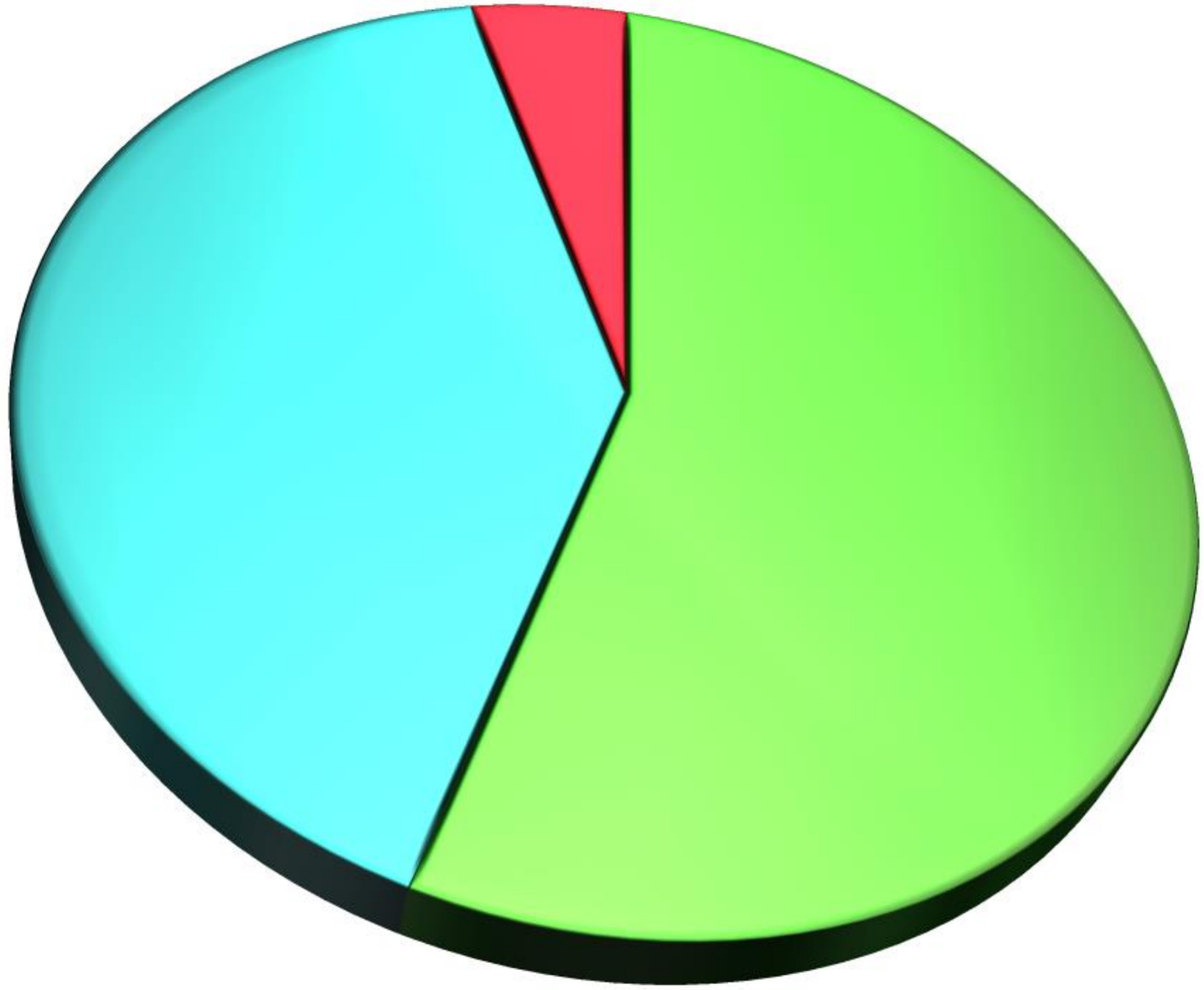
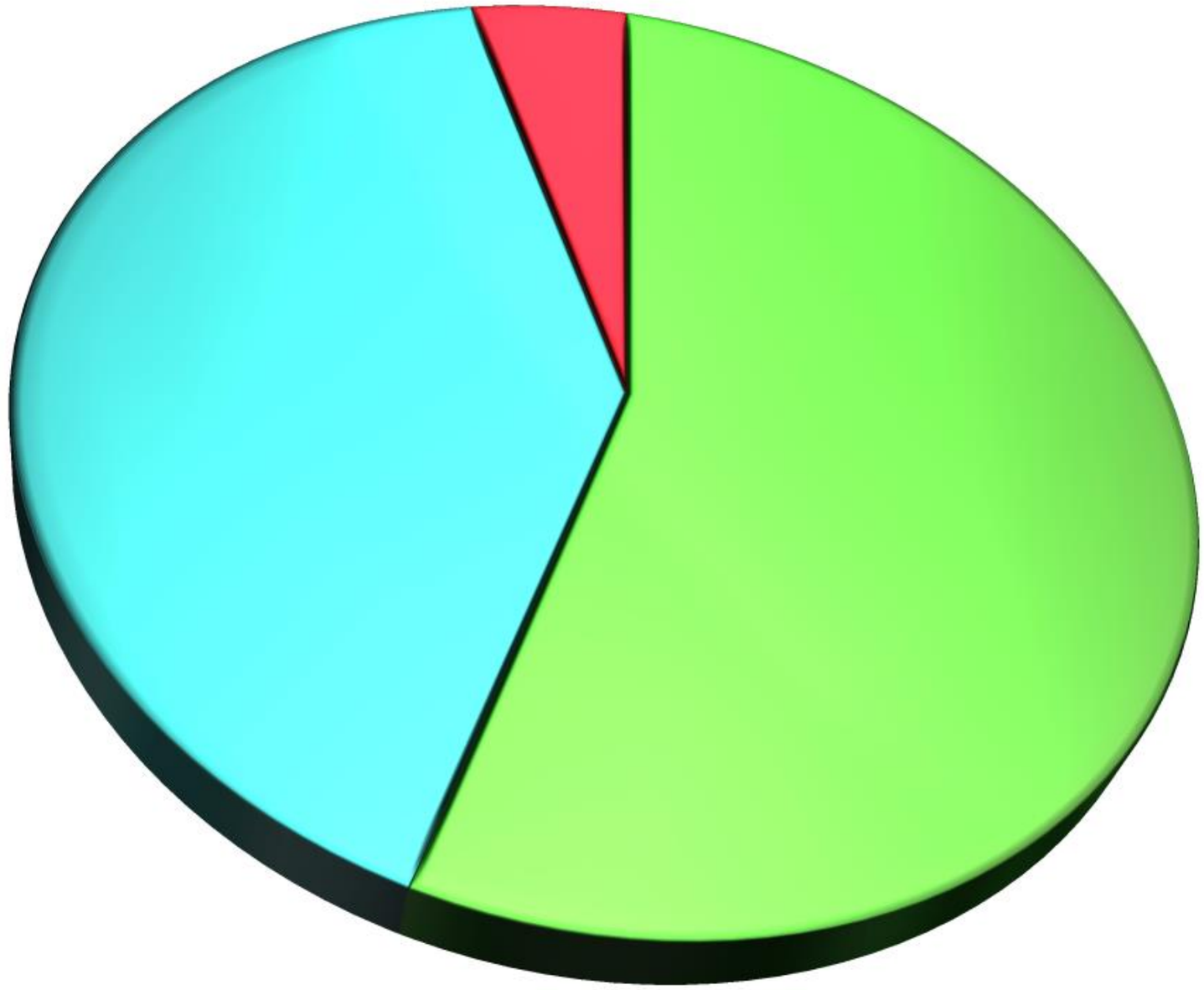
Overall mortality = ~5-20%



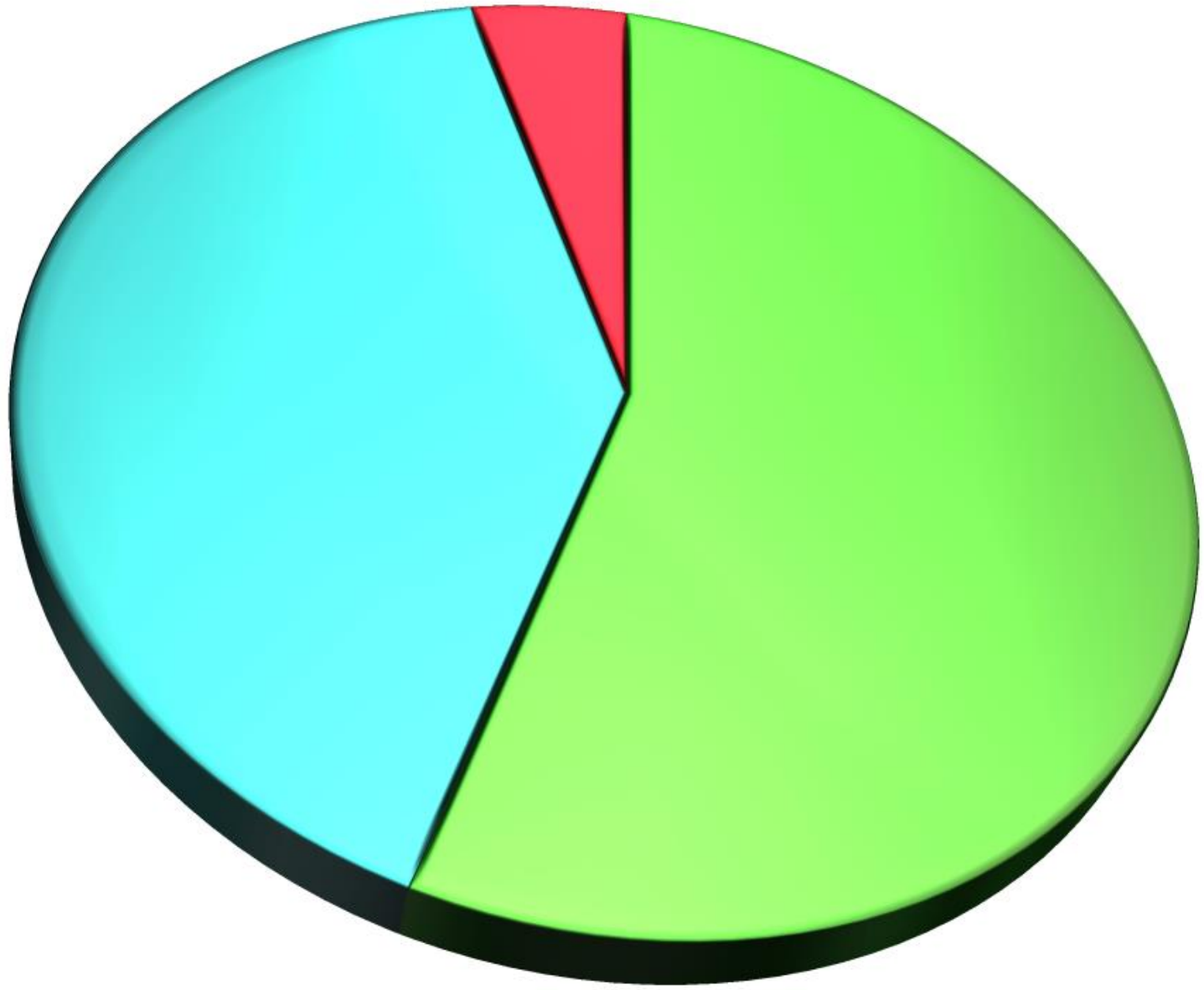
Arrest on Presentation = ~90%

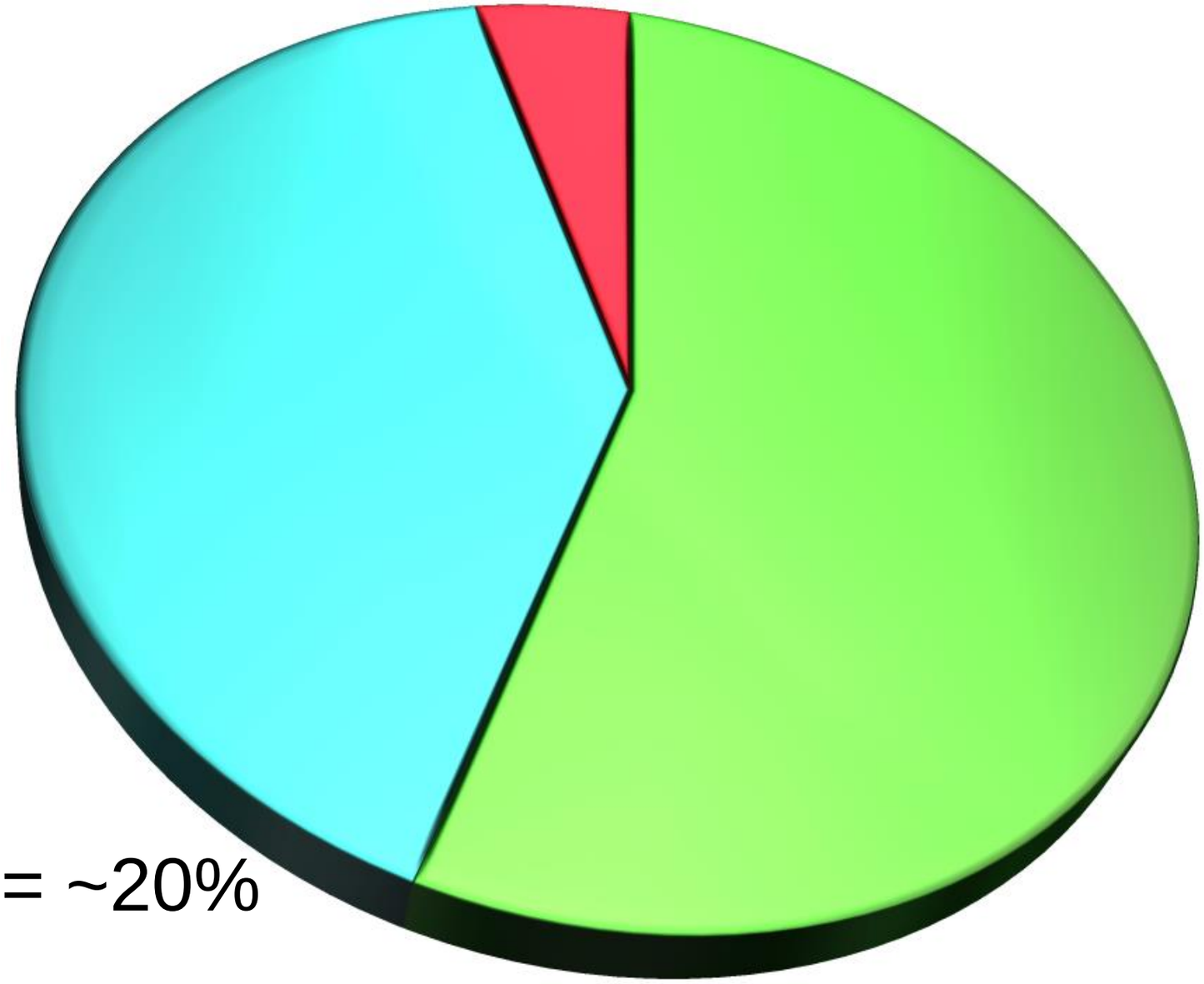


Mech Vent = ~80%

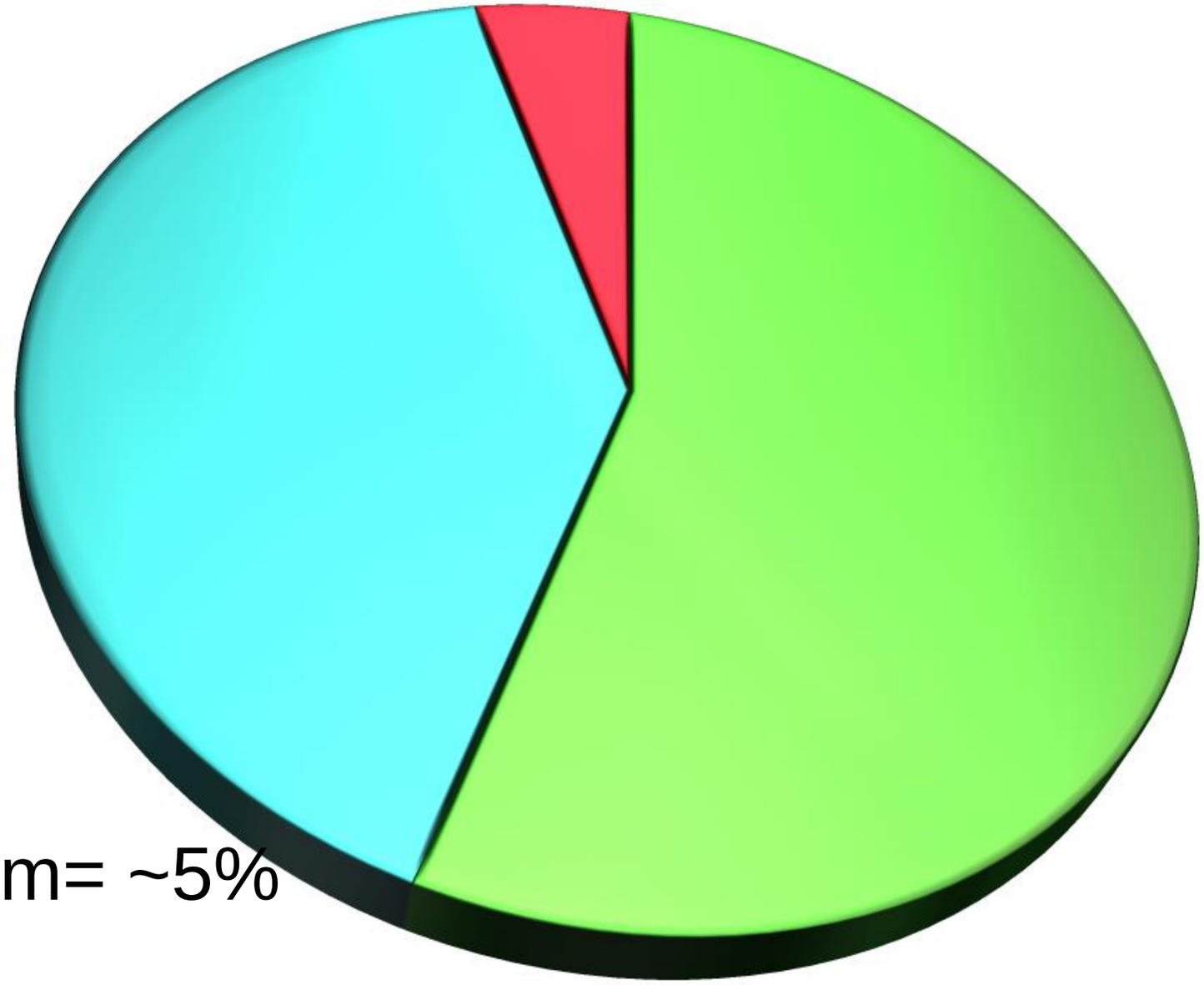


Lytics= ~30%



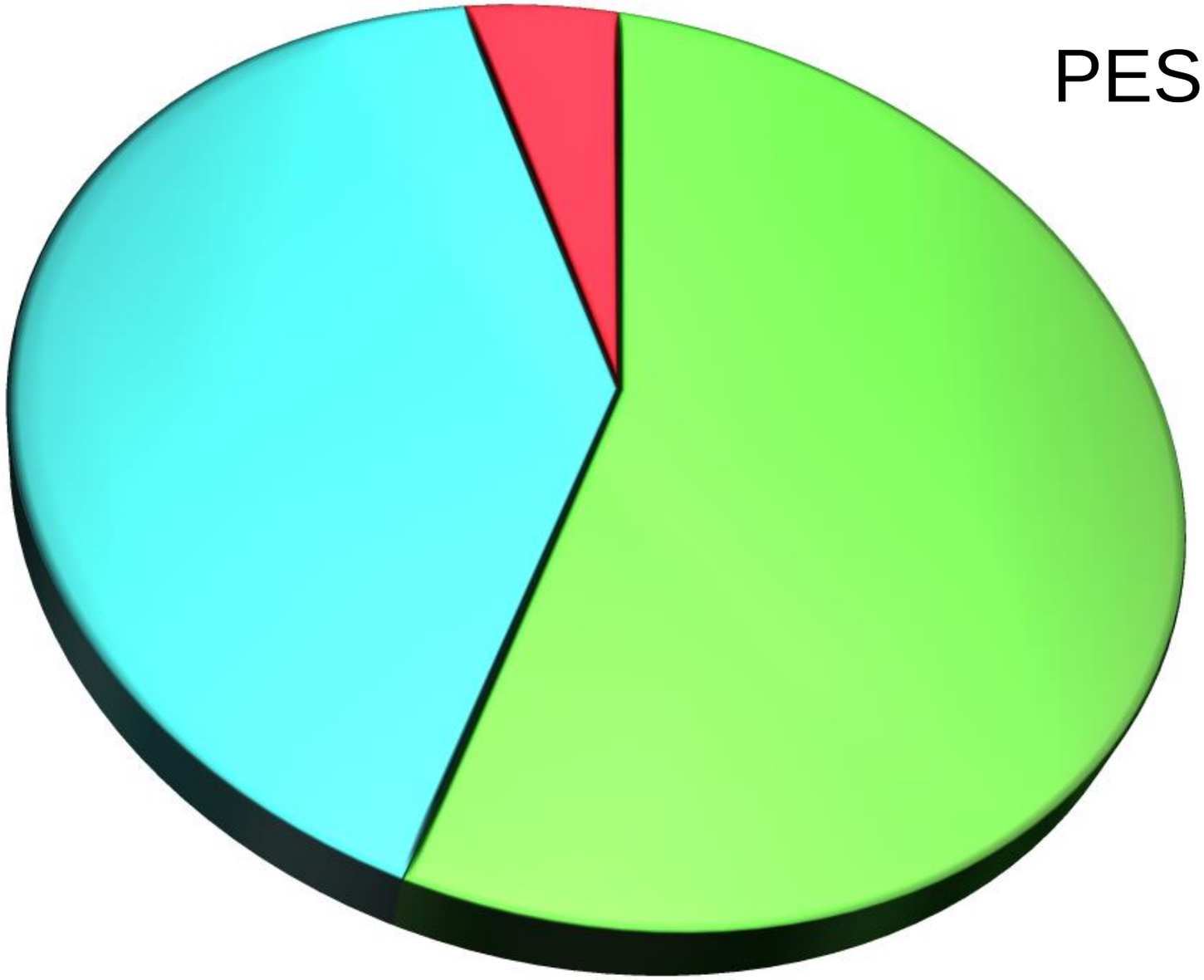


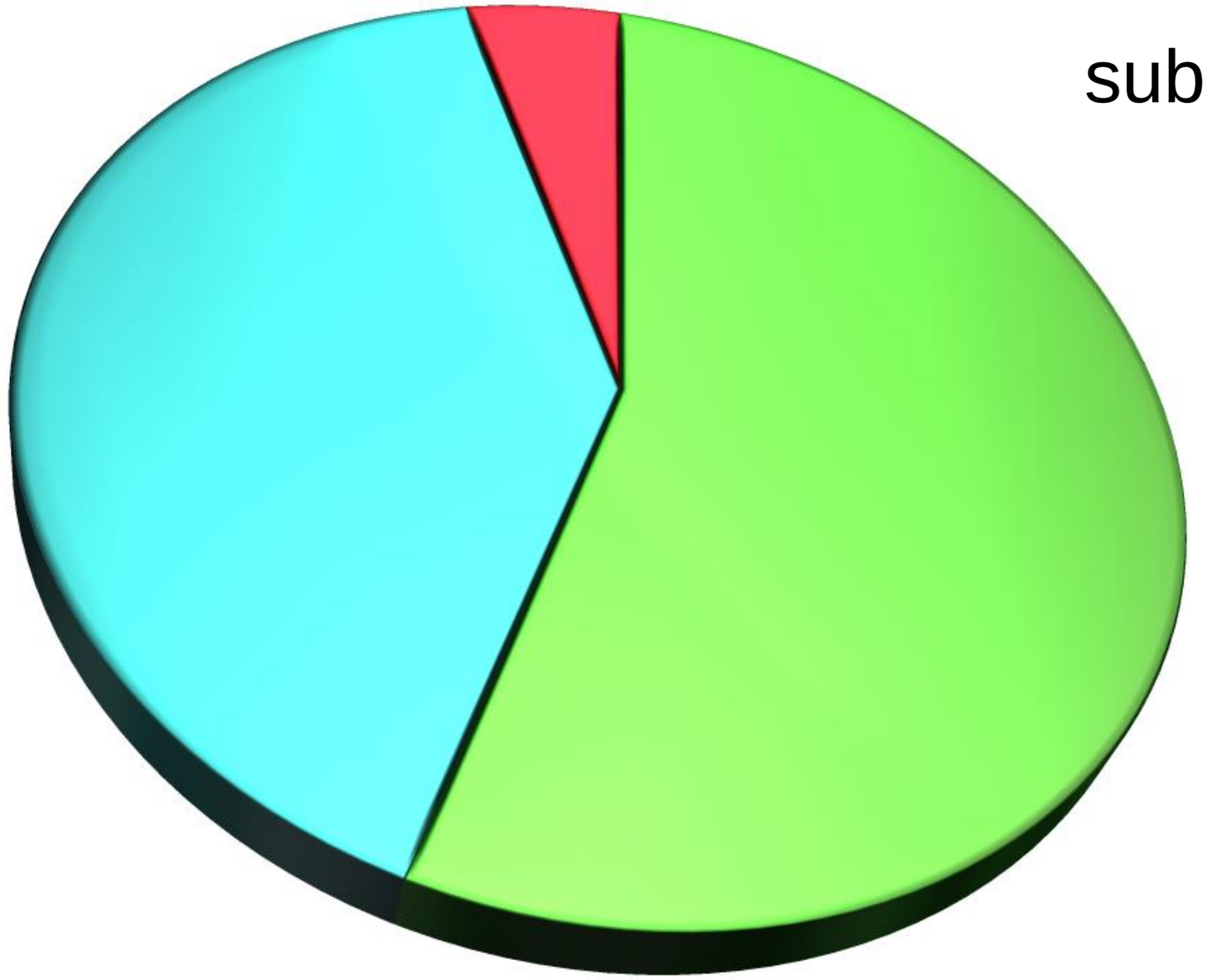
PESI very high= ~20%



PESI medium= ~5%

PESI low= ~1%

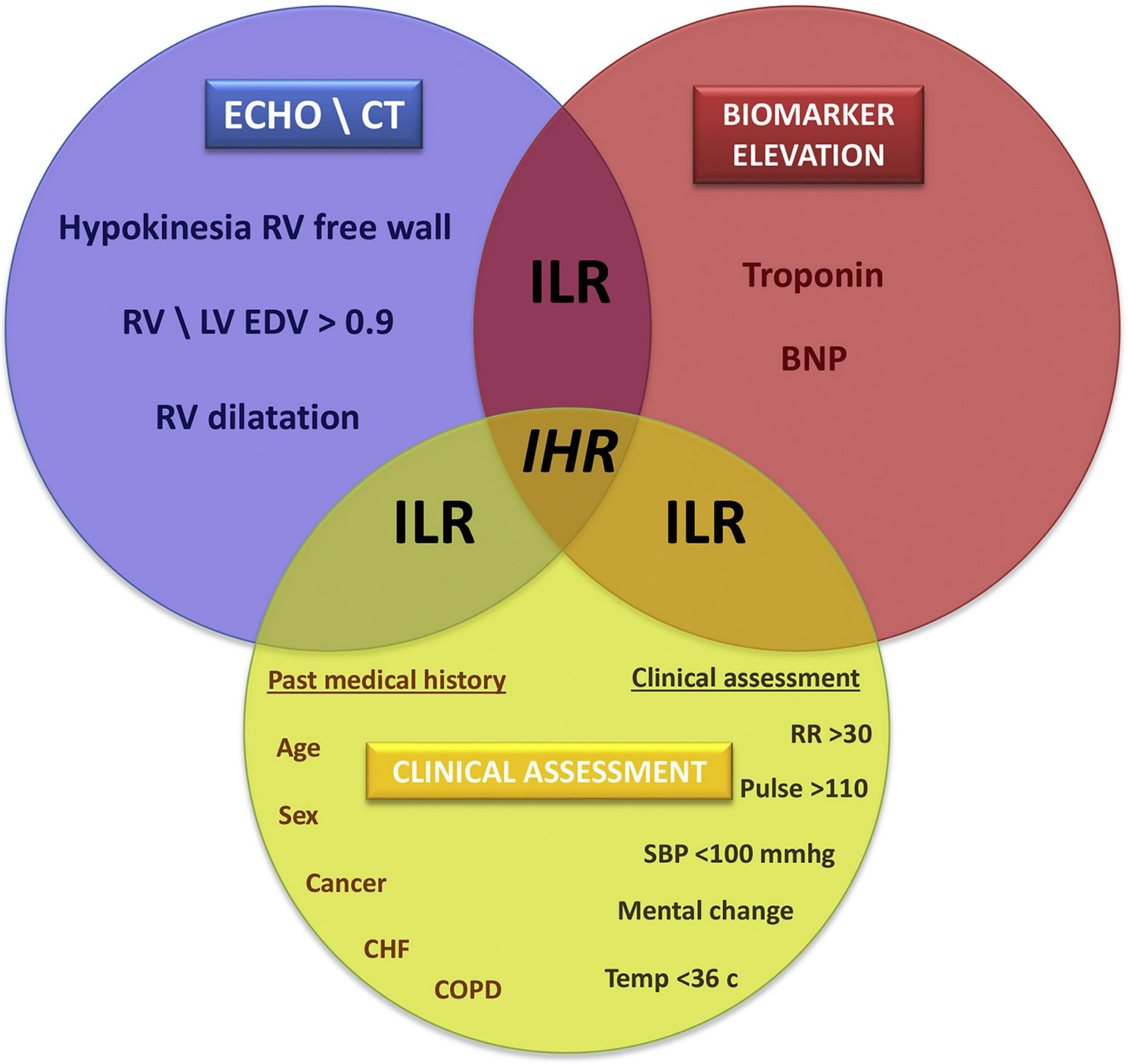




subseg= ~0%

Pulmonary Embolism: Care Standards in 2018

Ariel Borohovitz [a], Mitchell D. Weinberg [b, c], Ido Weinberg [d]

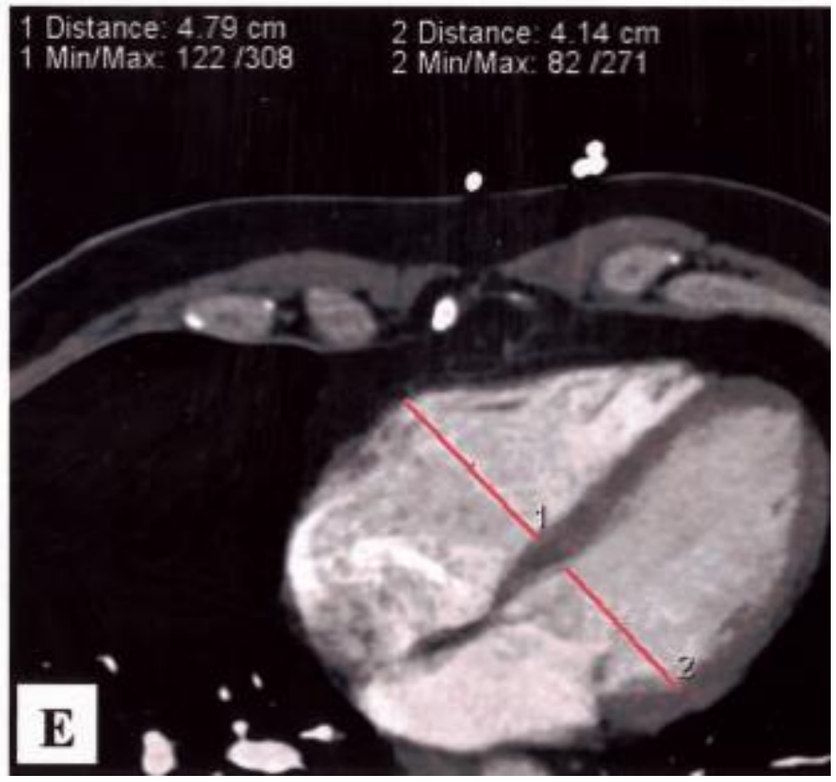


Many variables inform Risk from the disease:

Informs risk tolerance of treatment

Should we treat Submassive PE differently?

- RV/LV ratio > 0.9 is an independent risk factor for mortality
- Persistent RV dysfunction at d/c:
  - 8 fold risk of recurrent, symptomatic PE
  - 4 fold risk of mortality



Quiroz, Circ 2004; 109:2401-2404
Frémont, Chest 2008; 133;558-362
Schoef, Circ 2004; 110:3276-3280
Kucher, Arch Intern Med 2005; 165:1777-1781
Grifoni, Arch Intern Med. 2006 Oct 23;166(19):2151-6.

Systemic Thrombolysis

- Obstructive Shock is a widely accepted indication for systemic thrombolysis. (ACCP Guidelines)

- Has been proposed for:

  - RV dysfunction

  - Respiratory Failure

  - Extensive Clot Burden

  - RA or RV thrombus

  - Patent Foramen Ovale

***22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy** (Grade 1B).

***23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy** (Grade 2C).

Catheter Directed Thrombolysis

- Superior hemodynamic response versus anticoagulation alone
- Significantly lower dose of TPA (15mg to 40mg versus 50mg-100mg) over a longer period of time (12 hours versus 2 hours)
- Potential for lower risk of adverse events and improved efficacy.

Catheter Directed Thrombolysis

- Literature often combines techniques: masseration, angioplasty, wire agitation, rheolytic: all with or without local thrombolytic delivery.

- RCT data proves a **lower risk of long-term pulmonary HTN**, but the NNT for this is very high.

- RCT data (PEITHO) has also shown that lysis in sub-massive PE prevents hemodynamic compromise, but at a risk of bleeding. Can CDT provide the hemodynamic benefit without the bleeding risk?

  - CDT Registry data and RCTs have suggests major bleeding rates of 5-10%: not substantially different than anticoagulation alone.

- Based on safety data and emerging data on benefit, will see this performed more frequently in **select patients** at capable centers

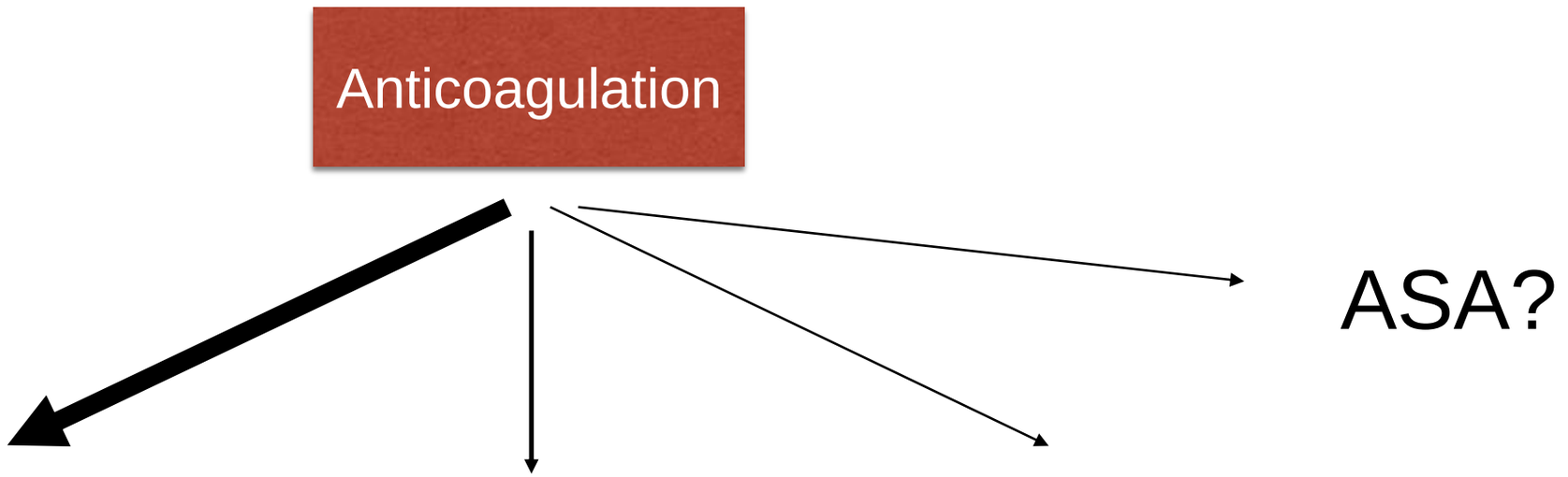
Anticoagulation

- If high suspicion of PE in a sick patient, anticoagulate while figuring it out.

- **For lobar or > PEs, all patients who can be anti-coagulated should be.**

- If hemodynamically stable (no RV strain) and no clot in transition, then anticoagulation alone is sufficient.

PE (unprovoked) Chronic Therapeutic Approach



For at least 3 months. Stop if reversible cause.
Consider indefinite if low bleeding risk.

For VTE without an associated cancer diagnosis, all direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended over vitamin K antagonist (VKA) therapy (all Grade 2B) and VKA therapy is recommended over low molecular weight heparin (LMWH; Grade 2C).

Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report

Clive Kearon MD, PhD [a], Elie A. Akl MD, MPH, PhD [a, b] ✉, Joseph Ornelas PhD [c], Allen Blaivas DO, FCCP [d], David Jimenez MD, PhD, FCCP [e], Henri Bounameaux MD [f], Menno Huisman MD, PhD [g], Christopher S. King MD, FCCP [h], Timothy A. Morris MD, FCCP [i], Namita Sood MD, FCCP [j], Scott M. Stevens MD [k], Janine R.E. Vintch MD, FCCP [l], Philip Wells MD [m], Scott C. Woller MD [k], COL Lisa Moores MD, FCCP [n]

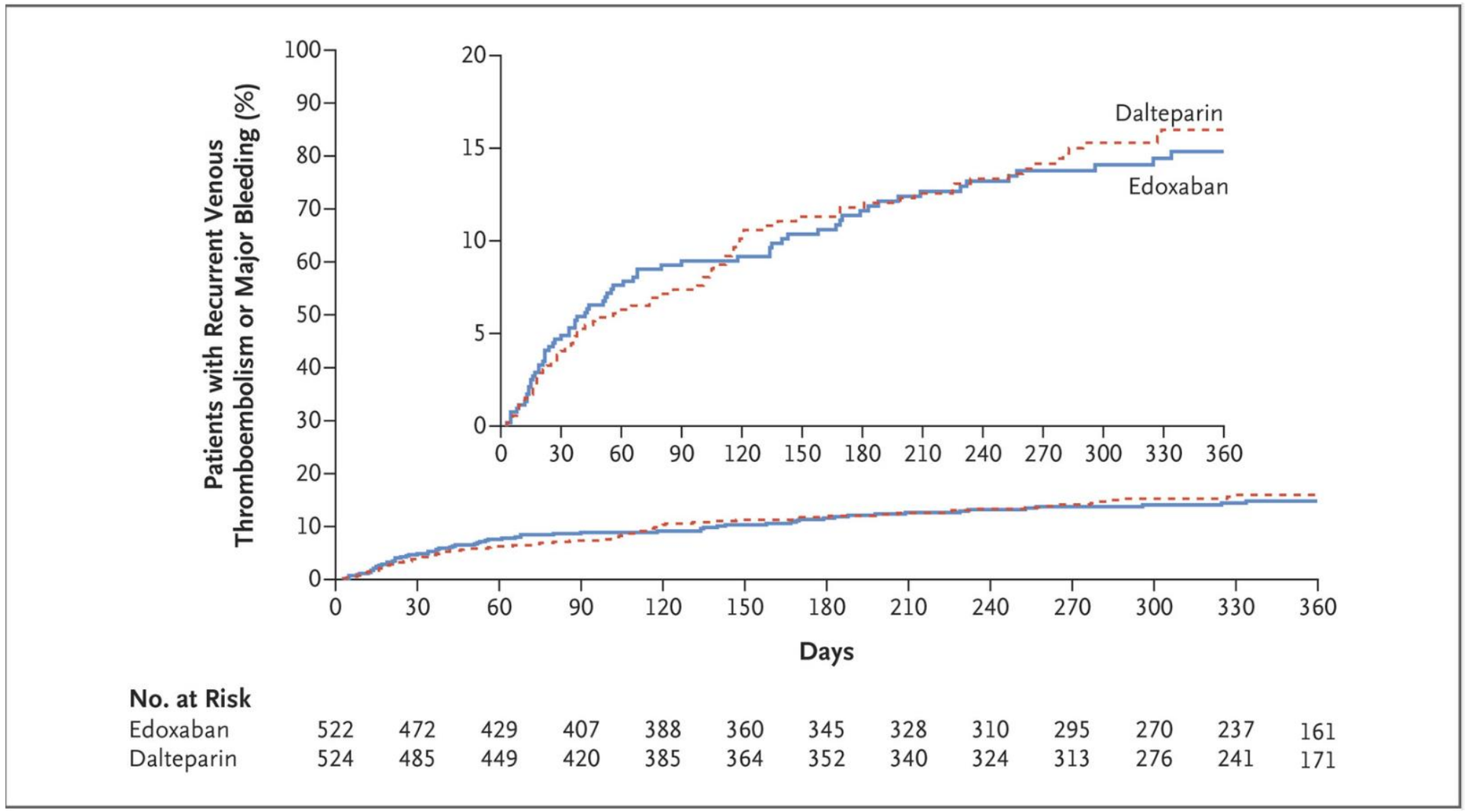
Secondary Prevention of VTE in Malignancy

- Recurrent VTE 11% with warfarin and 7% with low-molecular-weight heparin.
- Subgroup analyses of DOAC studies showed that DOACs at least as effective and safe as warfarin therapy among patients with cancer who have venous thromboembolism

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., et al., for the Hokusai VTE Cancer Investigators*



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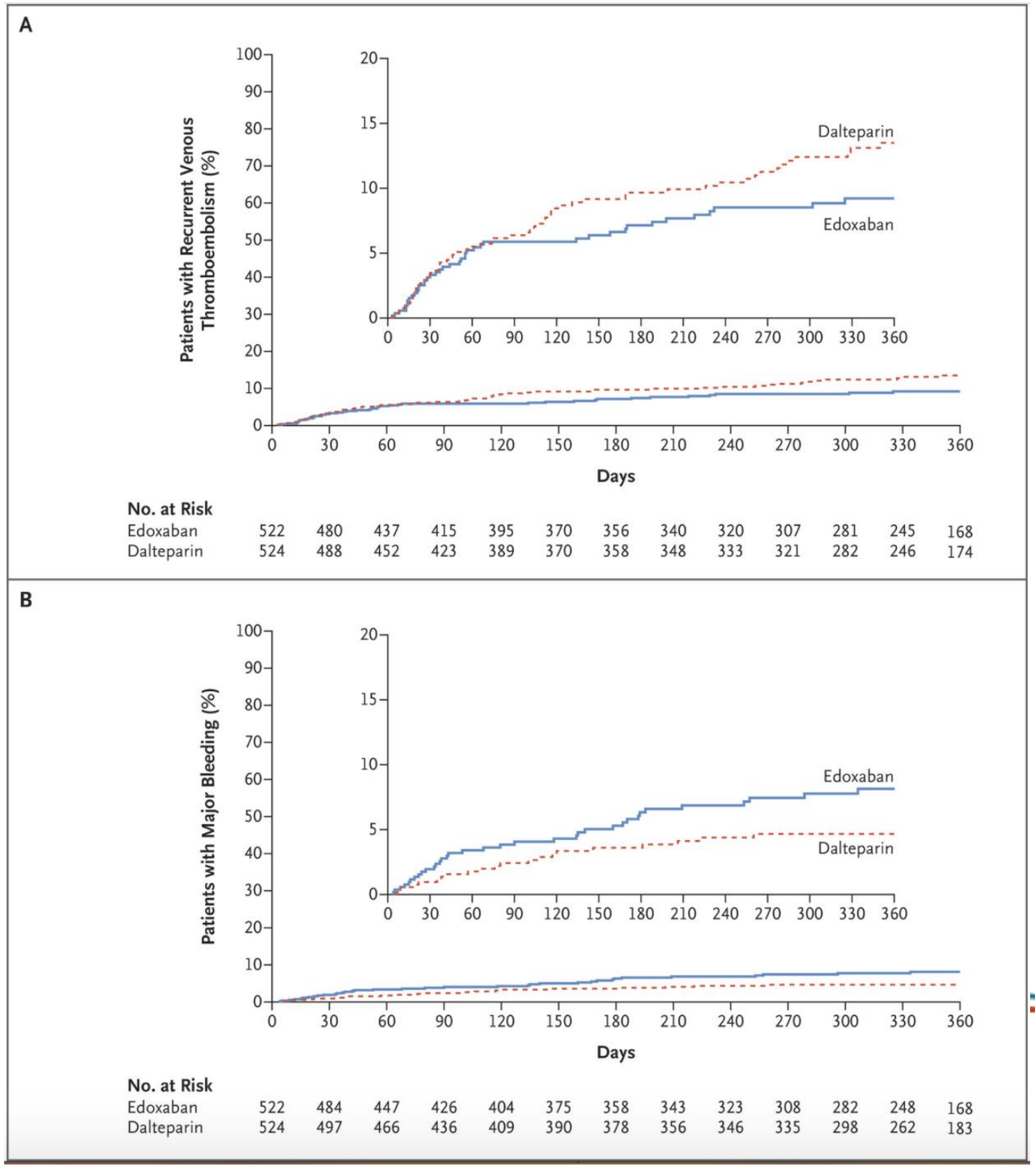


Compliance (12 month) in edoxaban group vs. dalteparin group (38.3% vs. 29.4%).

Secondary Prevention of VTE in Malignancy

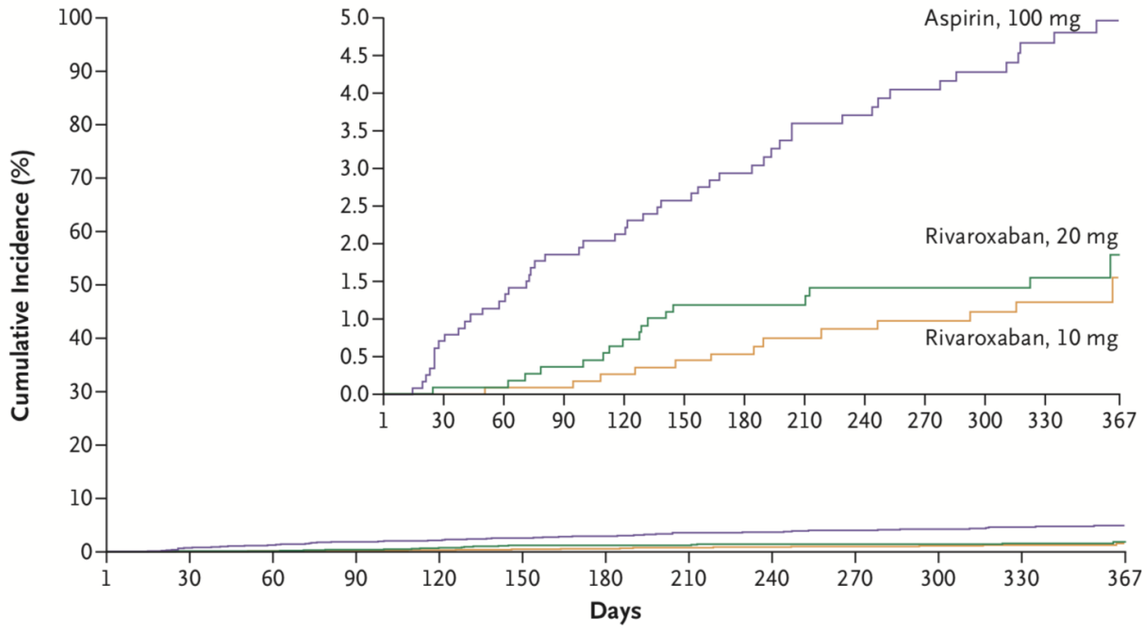
- SELECT-D Trial with similar preliminary results. (Rivaroxaban vs. Dalteparin)
- Consider in patients without a high bleeding risk.
- Avoided if Cr clearance of less than 30 ml/min

ORIGINAL ARTICLE

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

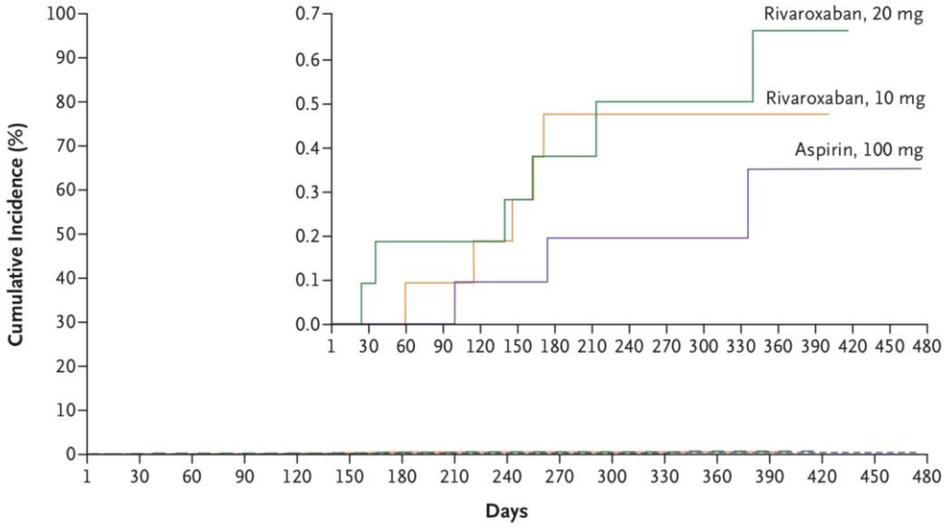
Jeffrey I. Weitz, M.D., Anthonie W.A. Lensing, M.D., Ph.D., Martin H. Prins, M.D., Ph.D., Rupert Bauersachs, M.D., Jan Beyer-Westendorf, M.D., Henri Bounameaux, M.D., Timothy A. Brighton, M.D., Alexander T. Cohen, M.D., Bruce L. Davidson, M.D., M.P.H., Hervé Decousus, M.D., Maria C.S. Freitas, M.D., Ph.D., Gerlind Holberg, V.D., Ph.D., et al., for the EINSTEIN CHOICE Investigators*

A Fatal or Nonfatal Venous Thromboembolism



No. at Risk													
Rivaroxaban, 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban, 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin, 100 mg	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

B Major Bleeding



No. at Risk																	
Rivaroxaban, 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Summary

- For any severity of PE: Disease risk, treatment efficacy, and treatment risk inform treatment.

- For most PEs, anticoagulation alone is sufficient.

- Lytics appear to have a role in submassive/massive PE

- CDT has a role. *Patient selection is critical*.