Update on Anticoagulation: a selection of topics from the second AT9 focused update from CHEST

Missouri ACP Hospitalist Day

September 15th 2022

Shane Kinard, MD, FACP

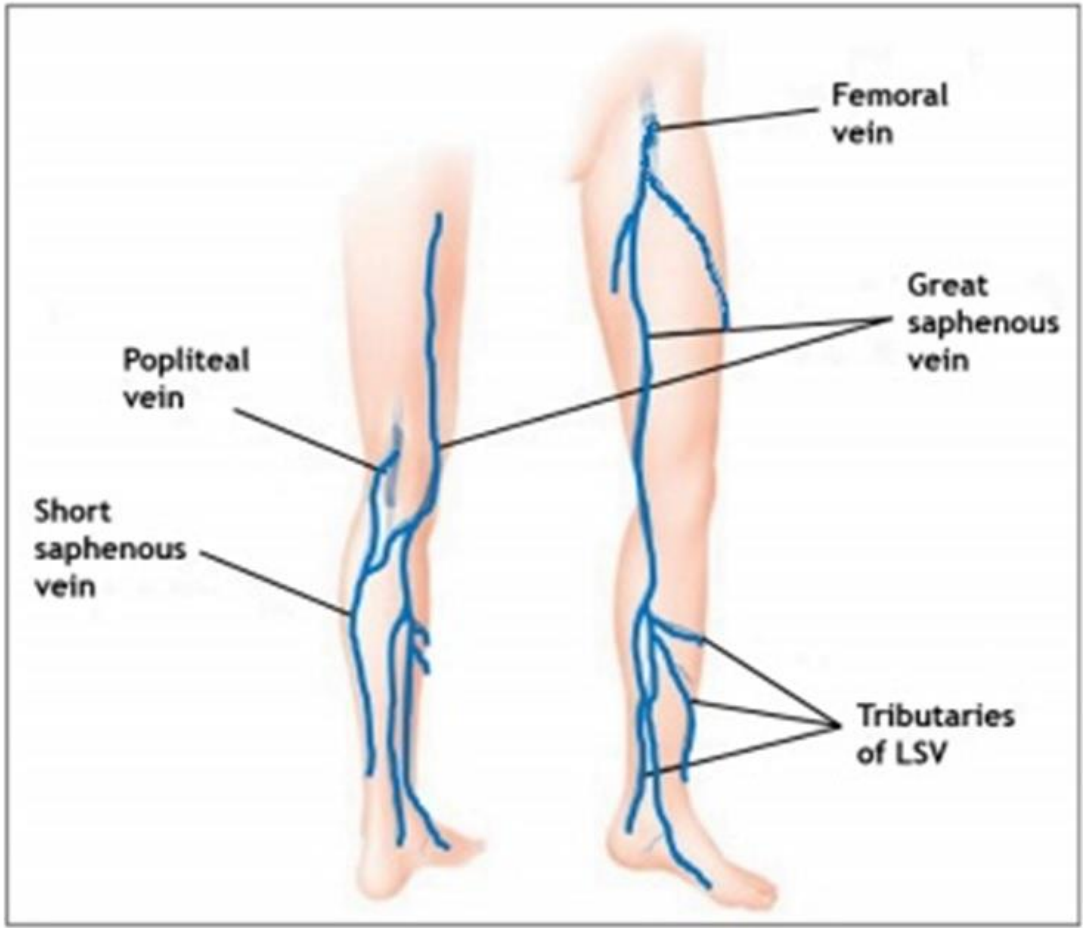
Disclosures

I have no financial or other conflicts of interest to disclose.
However, I am a cat lover… with a quest to persuade…

Objectives

- To review several key elements of the second focused update to the CHEST guidelines for anticoagulation with important applications to practicing internists in the inpatient and outpatient setting.
  - How should I manage *isolated* distal lower extremity DVT?
  - Interventions for post thrombotic syndrome: *should I* recommend them?
  - What are the *first line* therapy recommendations for cancer-associated VTE?
  - Can I, *should I*, manage PE as an outpatient?
  - How long is long enough for anticoagulation in *this* VTE patient?

How should I manage *isolated* distal lower extremity DVT?



Alves et al 2016

Audience Response System – Let's have some fun!

Join the fun: With your camera, scan the QR code and click on the link. Or, type the link into your browser.

https://we.dialog.live/YCW-KH9

Patient Case & Audience Poll

- Mr. W. Warrior is a 45 year old male with a history of obesity and metabolic syndrome who fell and injured his left ankle while hiking on the Appalachian trail. He underwent a LLE duplex after evaluation in an urgent care for calf swelling, which demonstrated an acute gastrocnemius venous thrombosis. He was directed to you for follow up. Would you conclude:
  - A: the swelling is from a high ankle sprain; RICE therapy, no f/u
  - B: the venous thrombosis has a small chance to extend, so order serial LE u/s weekly x2 weeks to f/u for extension, but no AC
  - C: its not really a DVT, but its not normal either, so recommend rivaroxaban 10mg daily or fondaparinux 2.5mg daily x45 days
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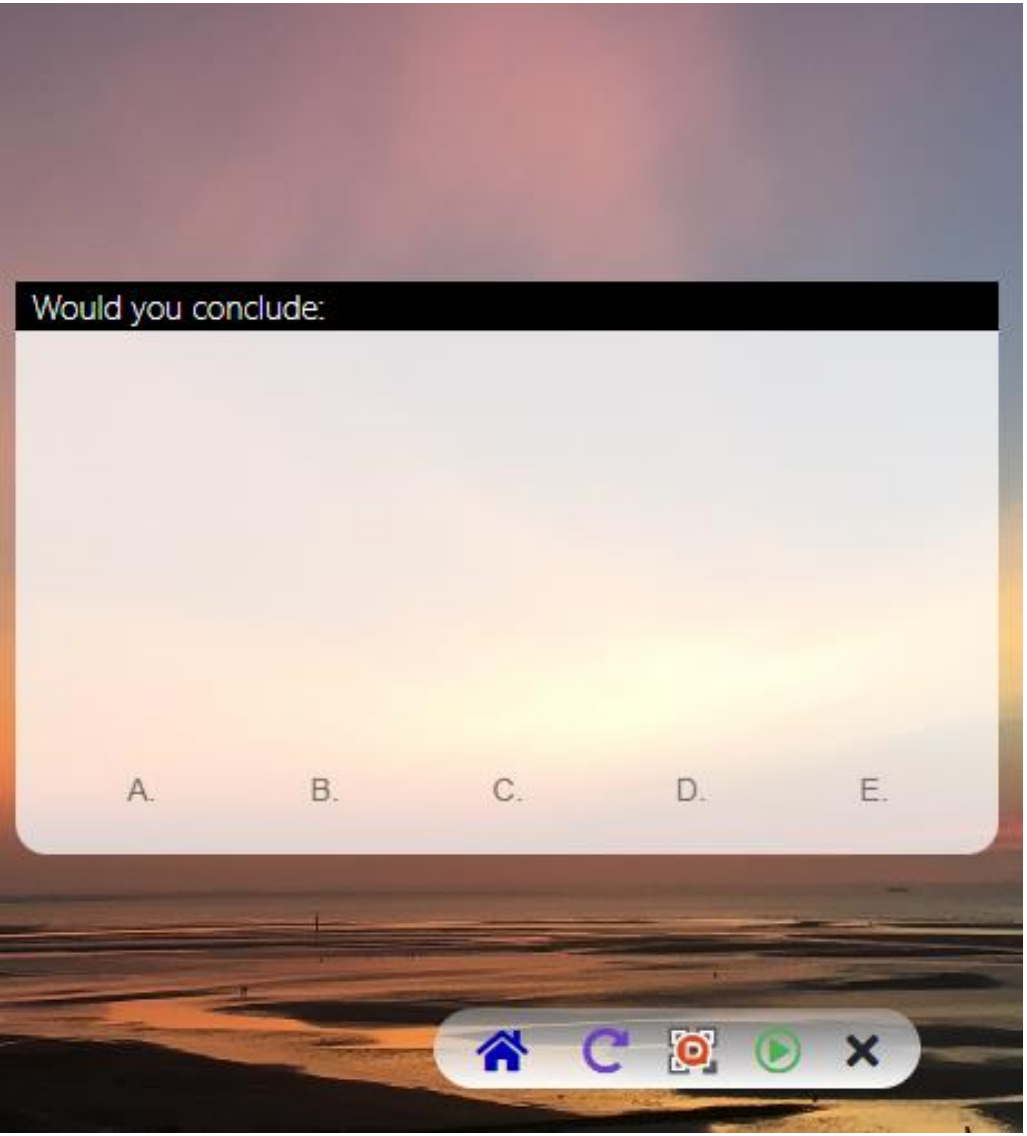

- Would you conclude:
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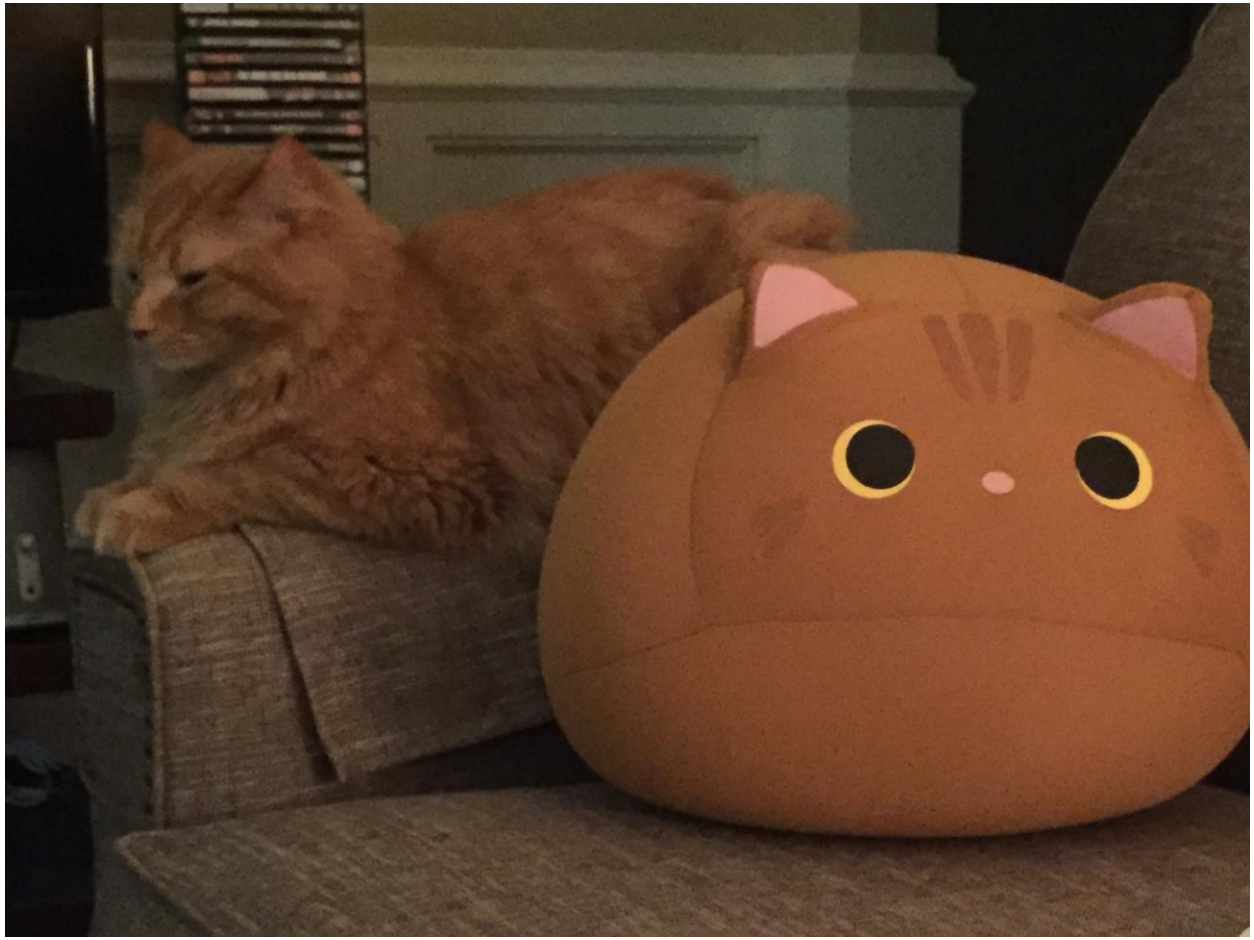
Discussion: is this a real indication for AC?



Current recommendation:

- In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (weak recommendation, moderate-certainty evidence) or (ii) with severe symptoms or risk factors for extension (see text), we suggest anticoagulation over serial imaging of the deep veins (weak recommendation, low-certainty evidence).

Stevens et al, 2021 (CHEST AT9.2)

Factors impacting AC decision

- Favors anticoagulation:
- D-dimer is positive (particularly when markedly so without an alternative reason)
- Thrombosis is extensive (e.g., >5 cm in length, involves multiple veins, >7 mm in maximum diameter)
- Thrombosis is close to the proximal veins
- No reversible provoking factor for DVT
- The patient has active cancer
- The patient has a history of VTE
- The patient is admitted (inpatient)
- The patient has COVID-19 infection
- The patient is highly symptomatic
- Patient preference to avoid repeat imaging

- Favor serial imaging:
- Thrombosis confined to the muscular veins of the calf (i.e., soleus, gastrocnemius)
- High or moderate risk for bleeding
- Patient preference to avoid anticoagulation

Stevens et al, 2021

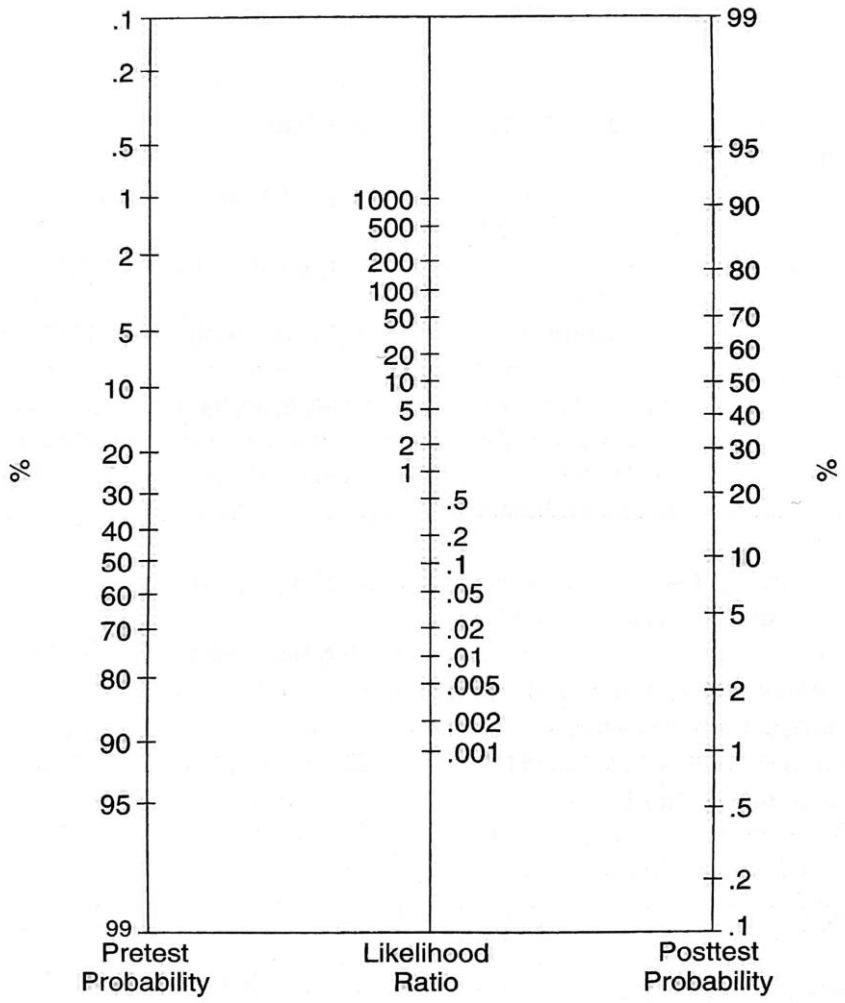


Figure 1-7 A Nomogram for Applying Likelihood Ratios
Adapted from Sackett et al.[1]

Roy et al, 2007

Tools for estimating bleeding risk

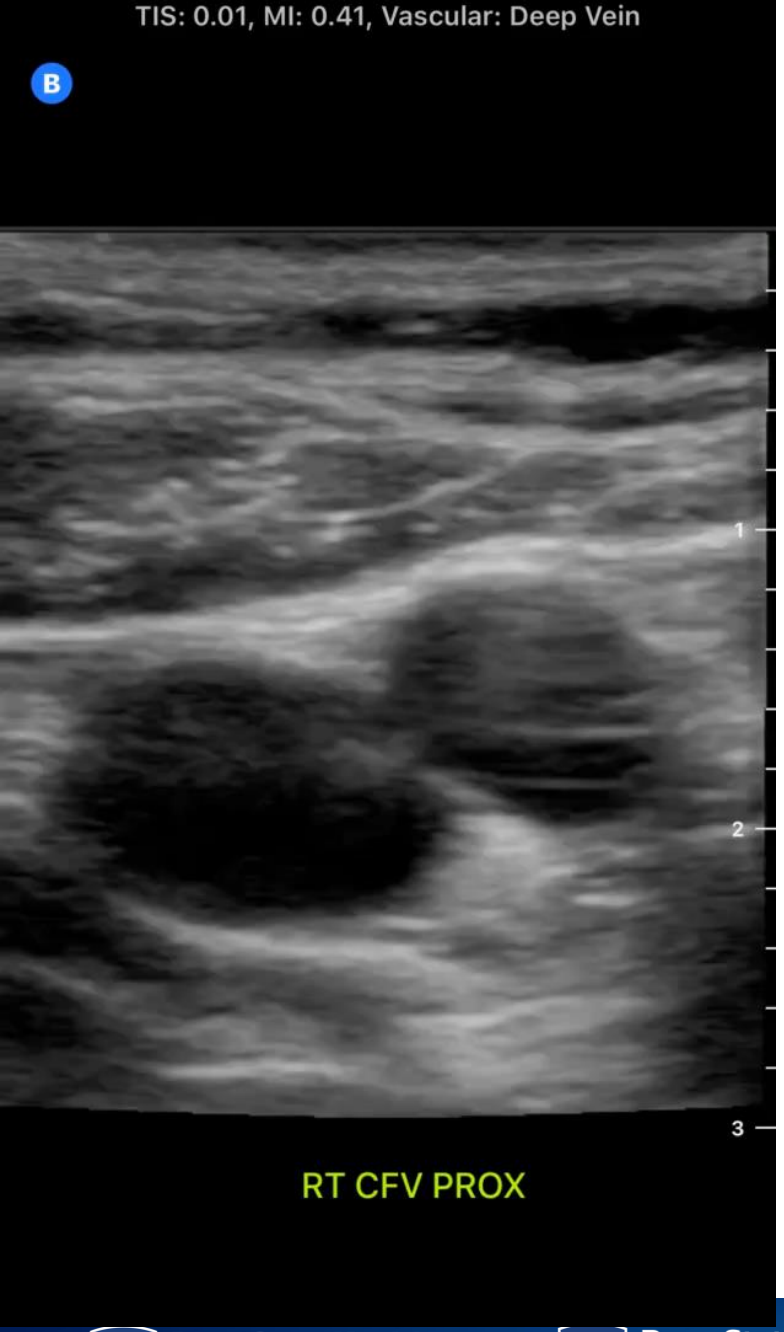
- HAS-BLED
  - Validated for predicting long-term bleeding risk on OAC for A-fib
  - AUC .7-.78; Validation cohorts less accurate in cancer
- VTE-BLEED
  - Derived from RE-LY trial data, subsequent validations in non-trial populations
  - Binary stratification: low vs. high risk
- Tip: Stopping ASA will significantly reduce bleeding risk. Reevaluate indication upon completion of anticoagulation.
- Caution: assess for OTC NSAID use

Brown et al, 2018 & Nishimoto et al, 2019

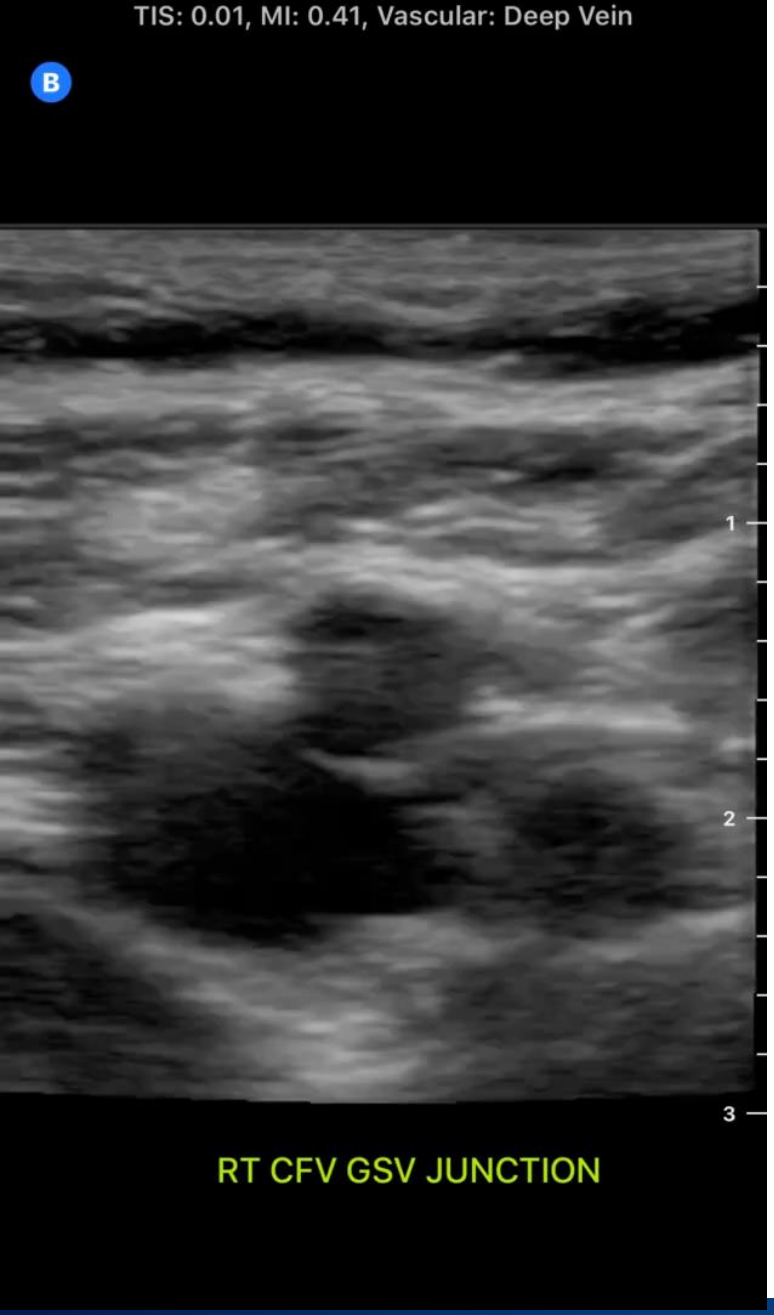
Serial Monitoring, now what?

- “Recommend no anticoagulation if the thrombus does not extend” (strong recommendation, moderate-certainty evidence)
- “Suggest anticoagulation if the thrombus extends but remains confined to the distal veins” (weak recommendation, very low-certainty evidence)
  - Low-DVT-pretest probability patients receiving only proximal vein ultrasonography have similar outcomes compared to patients undergoing no imaging
  - Estimates of progression highly dependent on population surveyed, but CHEST approximated at 10-15%
- “Recommend anticoagulation if the thrombus extends into the proximal veins”(strong recommendation, moderate-certainty evidence).
  - Use a typical intensity and duration of AC as for proximal

Stevens et al, 2021



- 2D compression ultrasound to exclude proximal DVT using portable handheld device



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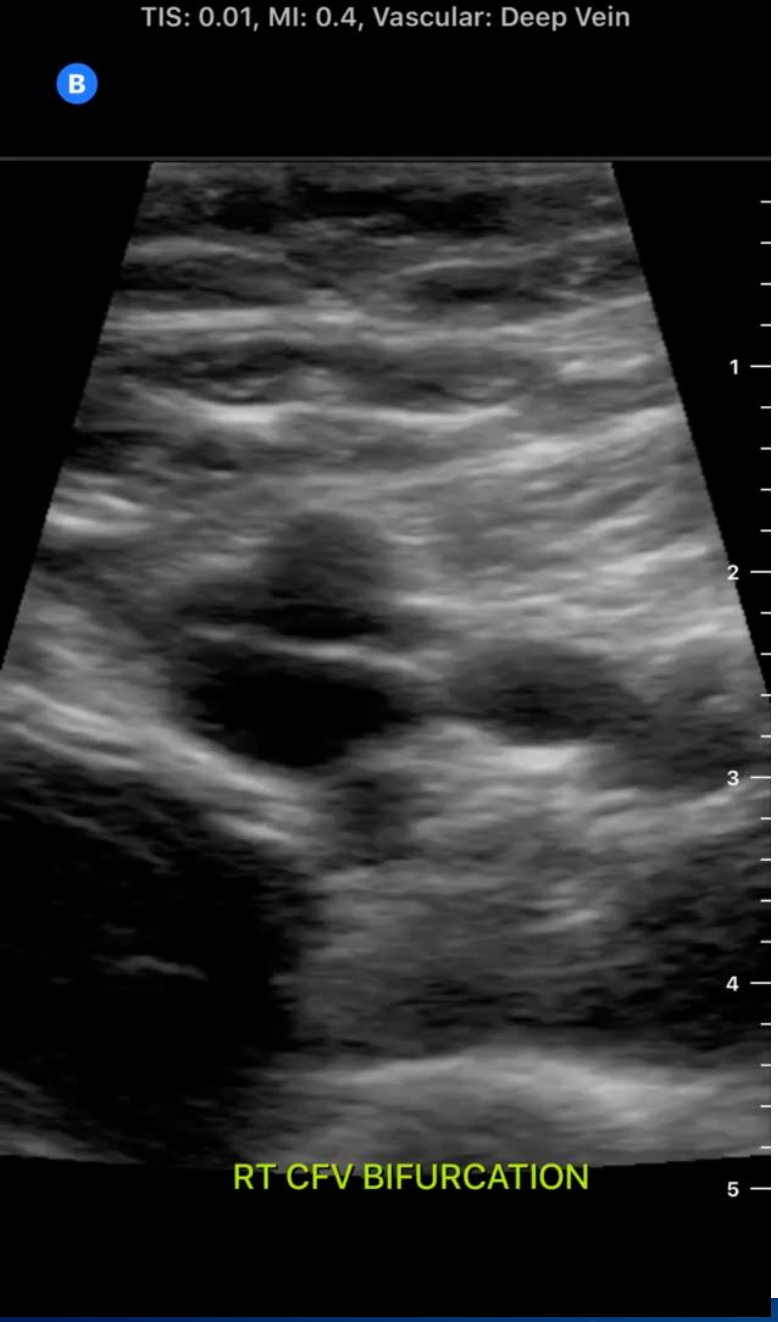

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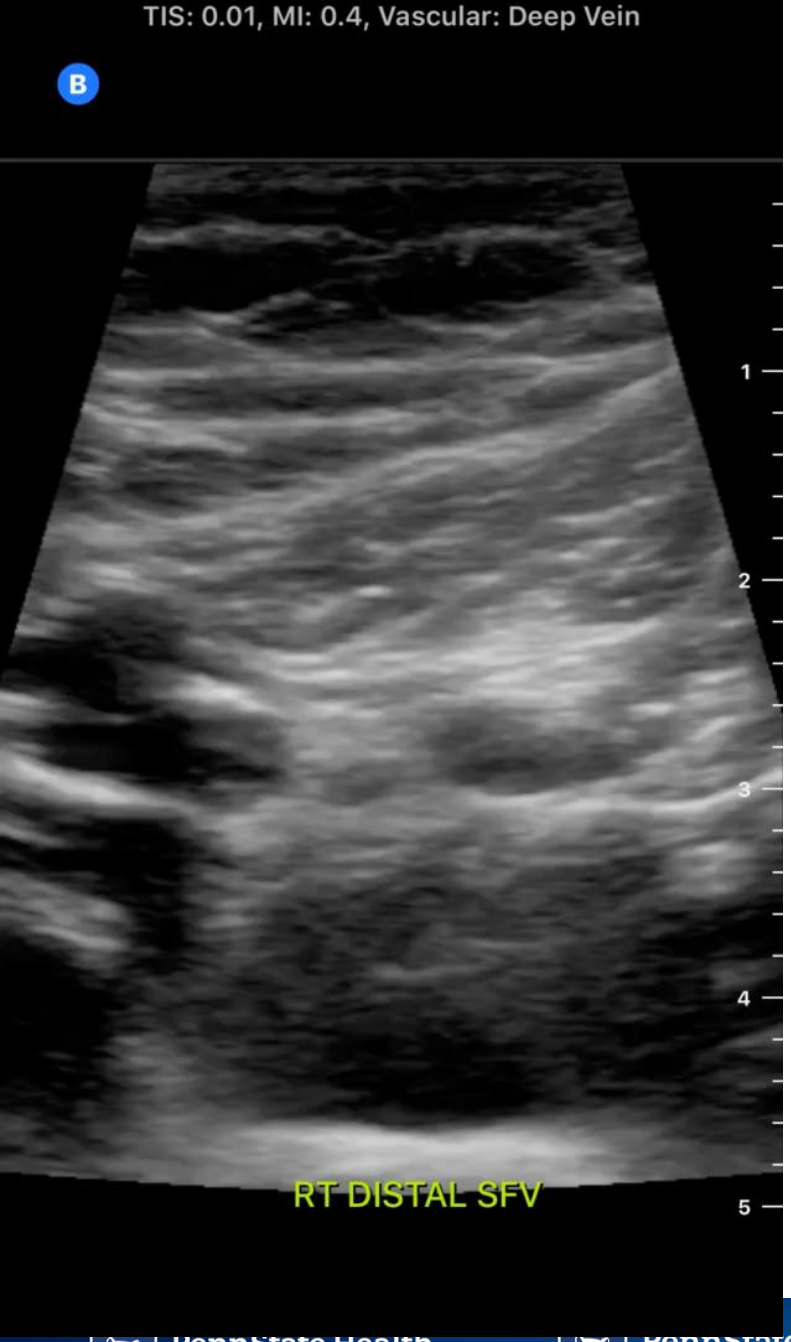

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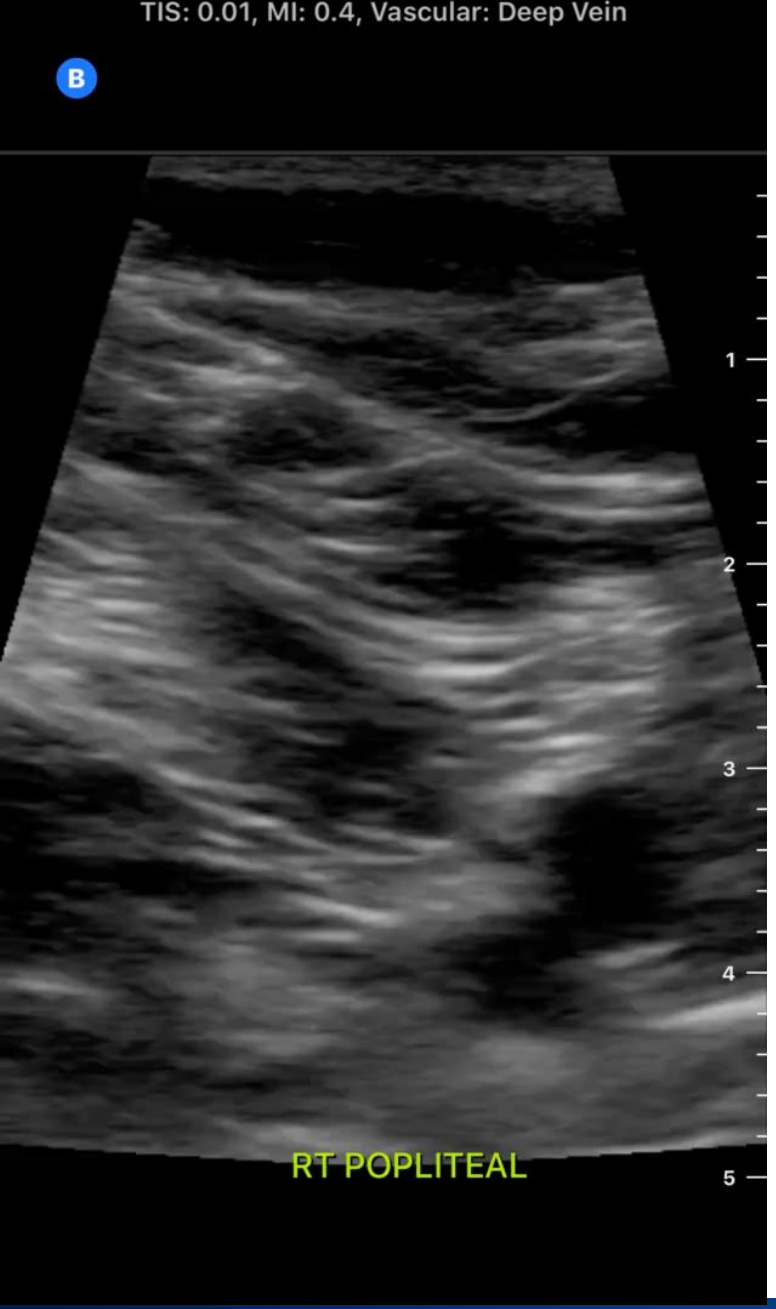

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Just remember…

Patient Case Revisited

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  - E: I'd probably ask my office mates and follow the majority vote

Interventions for post thrombotic syndrome: *should I* recommend them?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

S. Vedantham, S.Z. Goldhaber, J.A. Julian, S.R. Kahn, M.R. Jaff, D.J. Cohen, E. Magnuson, M.K. Razavi, A.J. Comerota, H.L. Gornik, T.P. Murphy, L. Lewis, J.R. Duncan, P. Nieters, M.C. Derfler, M. Filion, C.-S. Gu, S. Kee, J. Schneider, N. Saad, M. Blinder, S. Moll, D. Sacks, J. Lin, J. Rundback, M. Garcia, R. Razdan, E. VanderWoude, V. Marques, and C. Kearon, for the ATTRACT Trial Investigators*

ABSTRACT

BACKGROUND

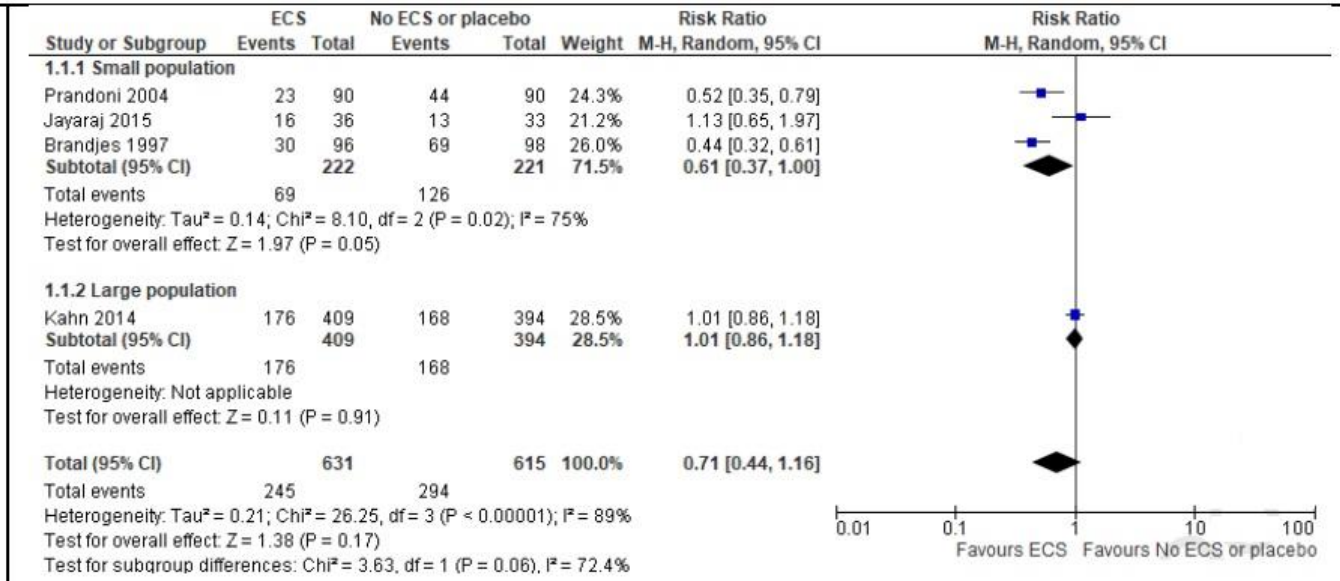
The post-thrombotic syndrome frequently develops in patients with proximal deep-vein thrombosis despite treatment with anticoagulant therapy. Pharmacomechanical catheter-directed thrombolysis (hereafter "pharmacomechanical thrombolysis") rapidly removes thrombus and is hypothesized to reduce the risk of the post-thrombotic syndrome.

Chest Recommendation:

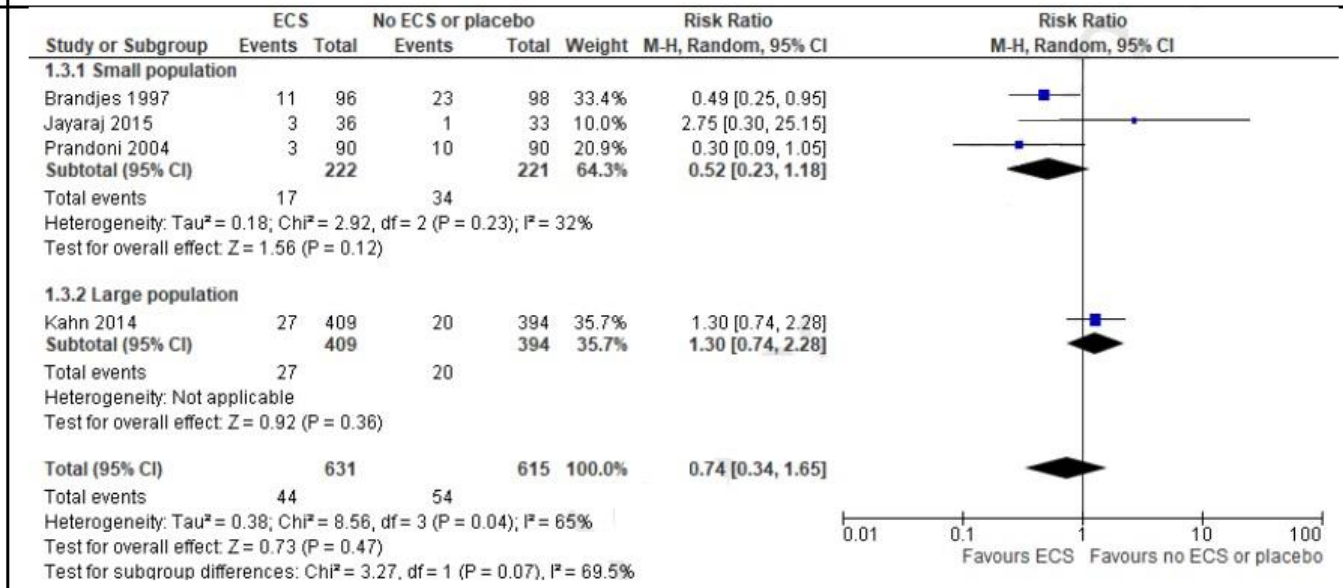
- “In patients with acute DVT of the leg, we suggest against using compression stockings routinely to prevent PTS” (weak recommendation, low certainty evidence).

Stevens et al, 2021

Any PTS



Severe PTS



Graduated Compression Stockings: Treatment

- No evidence for effective treatment PTS sx in acute DVT
  - SOX trial subgroup analysis (included stratification by adherence)

	Mean (SD)*		Difference in means (95% CI)	P-value
	Active ECS N=272	Placebo ECS N=291		
Visit				
Baseline	5.08 (3.33)	5.27 (3.33)	0.19 (-0.36, 0.74)	0.50
14-day	2.20 (2.54)	2.40 (2.63)	0.21 (-0.22, 0.64)	0.35
1-month	1.73 (2.50)	1.71 (2.36)	-0.02 (-0.42, 0.38)	0.93
60-day	1.35 (2.24)	1.10 (1.88)	-0.25 (-0.59, 0.10)	0.16

[#] numbers who attended the one-month follow-up visit were 388, active ECS, and 378, placebo ECS.
* mean (standard deviation) numerical pain rating score, based on a scale of 10 (0, no pain; 10, worst possible pain).

Kahn et al 2014

Catheter-directed thrombolysis for ileo-femoral DVT to prevent PTS

- Ms. M. Thurner is a 50 year old female with a history of obesity, tobacco use, and dyslipidemia who initially presented to your clinic one week ago with acute onset leg and thigh swelling. She was placed on a DOAC and advised to elevate the limb. On reevaluation, she has been compliant with pharmacotherapy, pulses are intact, the limb compartments are soft, and the limb is swollen and tender similar to prior exam. She asks if anything more can be done. Would you:
- A: refer to vascular surgery for lysis evaluation
- B: arrange direct admission for bridging and stat vascular c/s
- C: recommend graduated compression stockings
- D: provide reassurance and expectant guidance

Discussion: why go after the DVT?

What RCT evidence is there for the “patent vein” hypothesis?

Participants	Any lysis	AC alone	Relative (95 CI)	Absolute (CI)
PTS 6mo-5 years				
1393 (6 studies)	383/77[illegible] (52.9)	329/62[illegible]2 (52.9)	RR .78 ([illegible]66-.93)	116 fewer/1000
PTS 5+ years				
211 (2 studies)	41/104 (39.4)	75/107 (70.1)	RR .56 (.43-.73)	308 fewer/1000
Major bleeding (excluding ICS and minor bleeds)				
1943 (19)	72/1073 (6.7)	20/870 (2.3)	2.45 (1.58-3.78)	33 more/1000
Early stroke/ICH				
1943 (19)	3/1073	0/870	RR 1.92 (.34-10.86)	0 fewer/1000

Broderick et al, 2021

Analysis 1.5. Comparison 1: Thrombolysis versus standard anticoagulation, Outcome 5: PTS (intermediate, subgrouped by thrombolysis strategy)

Study or Subgroup	Thrombolysis Events	Thrombolysis Total	Standard anticoagulation Events	Standard anticoagulation Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Systemic						
Elliot 1979	8	24	18	21	6.5%	0.39 [0.22 , 0.70]
Schweizer 2000	55	100	21	25	16.8%	0.65 [0.51 , 0.84]
Subtotal (95% CI)		**124**		**46**	**23.3%**	**0.54 [0.31 , 0.92]**
Total events:	63		39			
Heterogeneity: Tau² = 0.11; Chi² = 3.04, df = 1 (P = 0.08); I² = 67%						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.5.2 Loco-regional						
Schweizer 1998	28	44	18	22	14.6%	0.78 [0.58 , 1.05]
Schweizer 2000	76	100	20	25	17.8%	0.95 [0.76 , 1.19]
Subtotal (95% CI)		**144**		**47**	**32.4%**	**0.88 [0.73 , 1.07]**
Total events:	104		38			
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 1.30 (P = 0.19)						
1.5.3 CDT						
ATTRACT	157	336	171	35	21.0%	0.97 [0.83 , 1.14]
CAVA 2020	22	77	26	75	8.9%	0.82 [0.51 , 1.32]
CAVENT	37	90	55	9	14.3%	0.74 [0.55 , 1.00]
Subtotal (95% CI)		**503**		**529**	**44.3%**	**0.89 [0.74 , 1.05]**
Total events:	216		252			
Heterogeneity: Tau² = 0.01; Chi² = 2.59, df = 2 (P = 0.27); I² = 23%						
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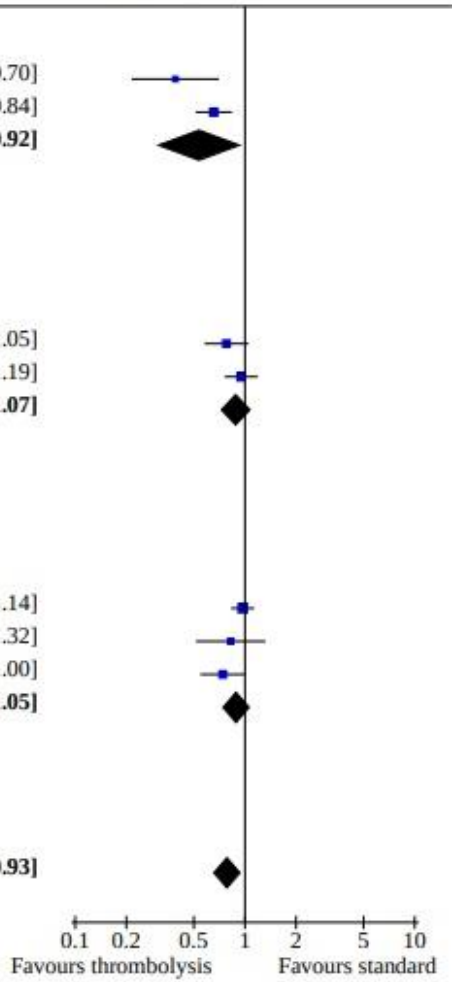
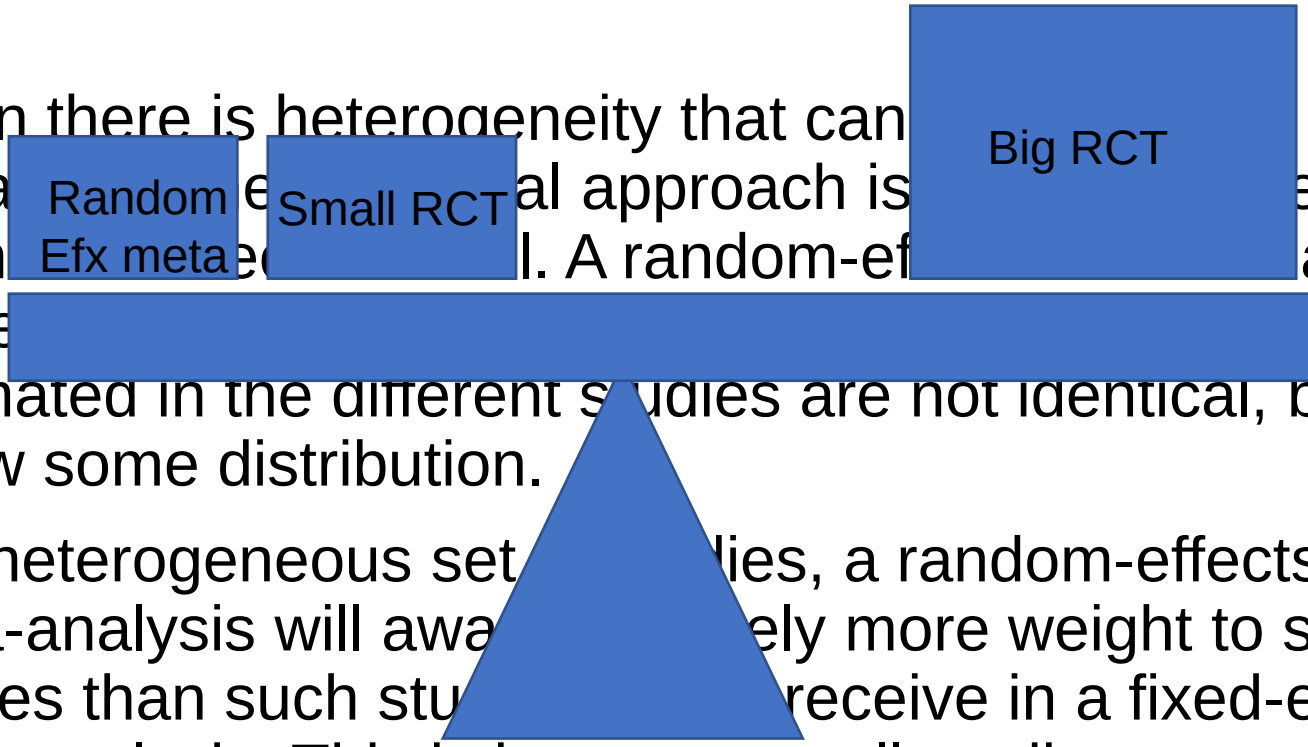
Total (95% CI)		**771**		**622**	**100.0%**	**0.78 [0.66 , 0.93]**
Total events:	383		329			
Heterogeneity: Tau² = 0.03; Chi² = 15.81, df = 6 (P = 0.01); I² = 62%						
Test for overall effect: Z = 2.75 (P = 0.006)						
Test for subgroup differences: Chi² = 3.07, df = 2 (P = 0.22), I² = 34.9%						



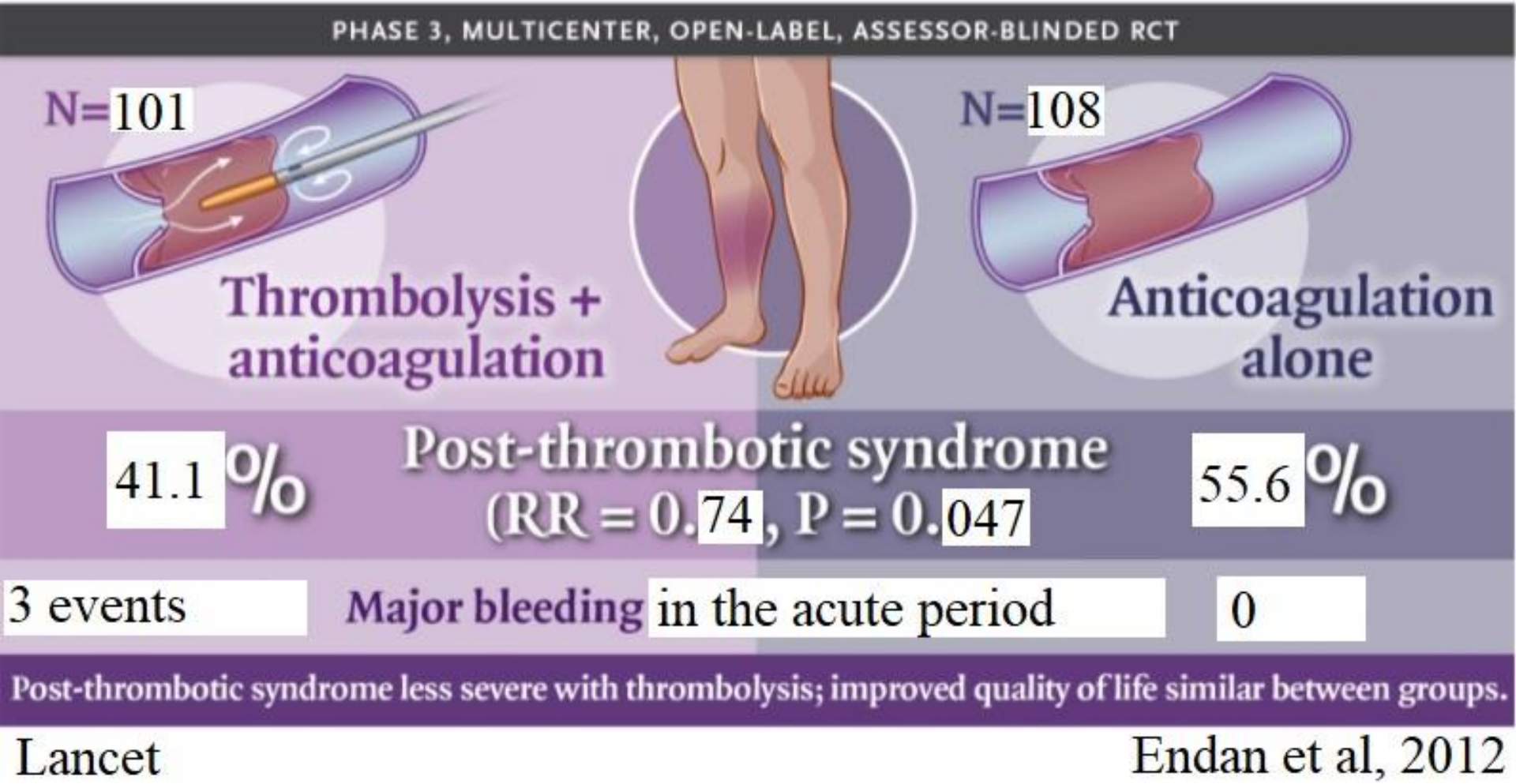
Meta-analysis: more than P < .05



- When there is heterogeneity that can
  expla e al approach is e it into
  a ran l. A random-ef alysis
  mode g
  estimated in the different studies are not identical, but follow some distribution.
- In a heterogeneous set dies, a random-effects meta-analysis will awa ely more weight to smaller studies than such stu receive in a fixed-effect meta-analysis. This is because small studies are more informative for learning about the distribution of effects across studies than for learning about an assumed common intervention effect

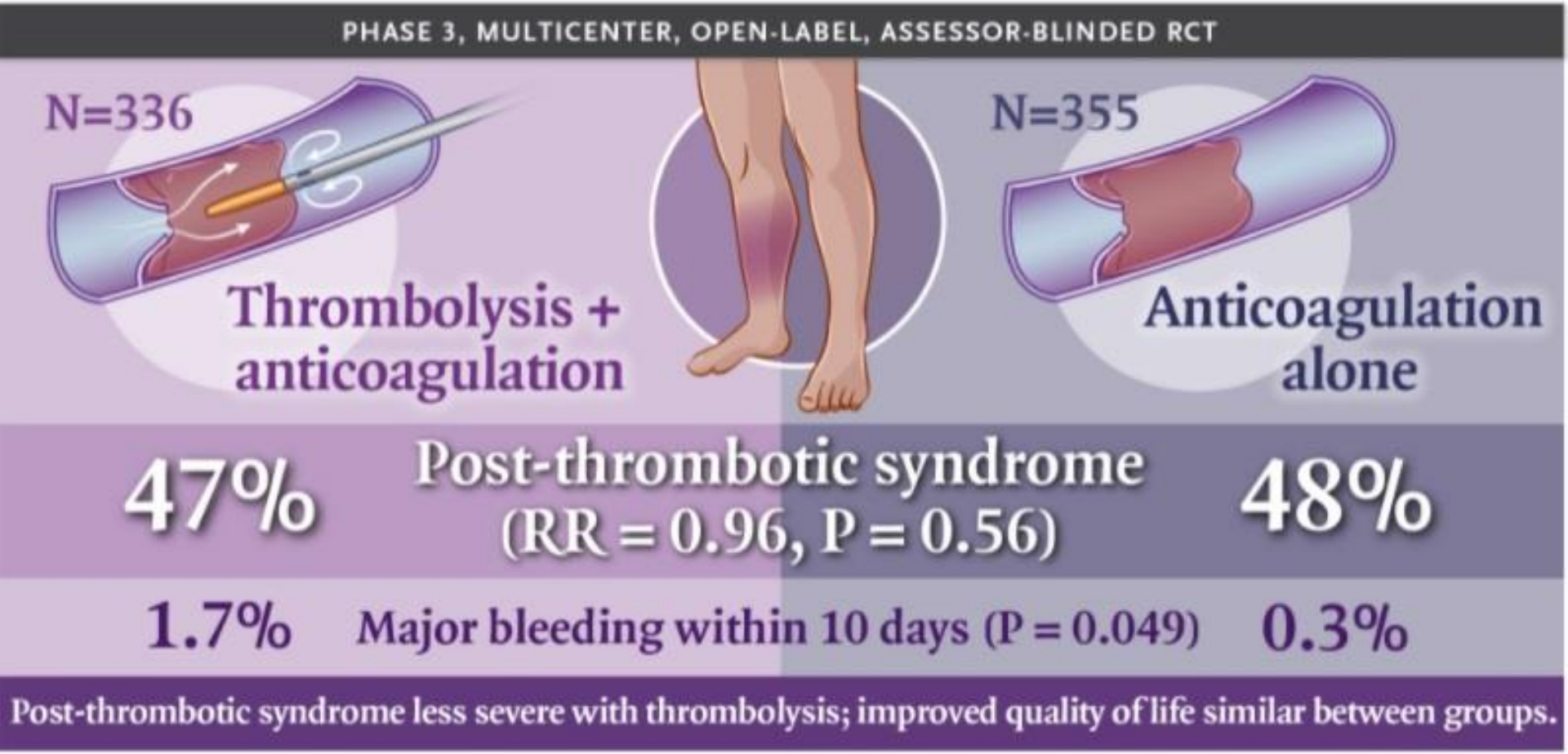
Cochrane Handbook for Systematic Reviews of Interventions

Deeper Dive: CaVenT (2012) PICO



Graphic modified from original format from NEJM 2017

Deeper Dive: ATTRACT (2017) PICO



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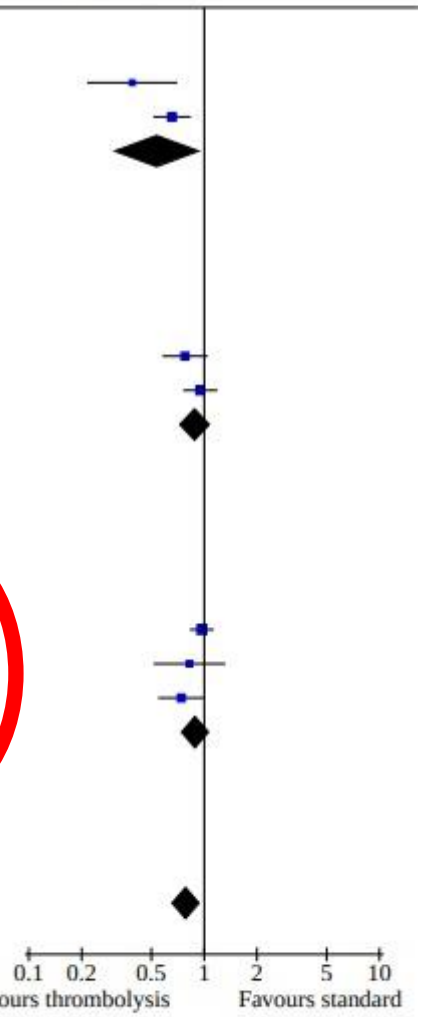

Current Recommendation

- “In patients with acute DVT of the leg we suggest anticoagulant therapy alone over interventional (thrombolytic, mechanical, or pharmacomechanical) therapy” (weak recommendation, moderate-certainty evidence).
- Exceptions:
  - massive (i.e. IVC or iliofemoral) with limb ischemia or vascular compromise (i.e. phlegmasia cerulea dolens)
  - RCT (according to clincaltrials.gov, one use trial based at UKMC)

Stevens et al, 2021

Suggested cost/value reading

- Poston, Jacqueline and Garcia, David “The case against catheter-directed thrombolysis in patients with proximal deep vein thrombosis” Blood Adv. 2018 Jul 24; 2(14): 1803–1805.
- Magnusun et al, ”Cost-Effectiveness of Pharmaco-mechanical Catheter-Directed Thrombolysis vs. Standard Anticoagulation in Patients with Proximal Deep-Vein Thrombosis: Results from the ATTRACT Trial” Circ Cardiovasc Qual Outcomes. 2019 Oct; 12(10): e005659.

Catheter-directed thrombolysis for ileo-femoral DVT to prevent PTS

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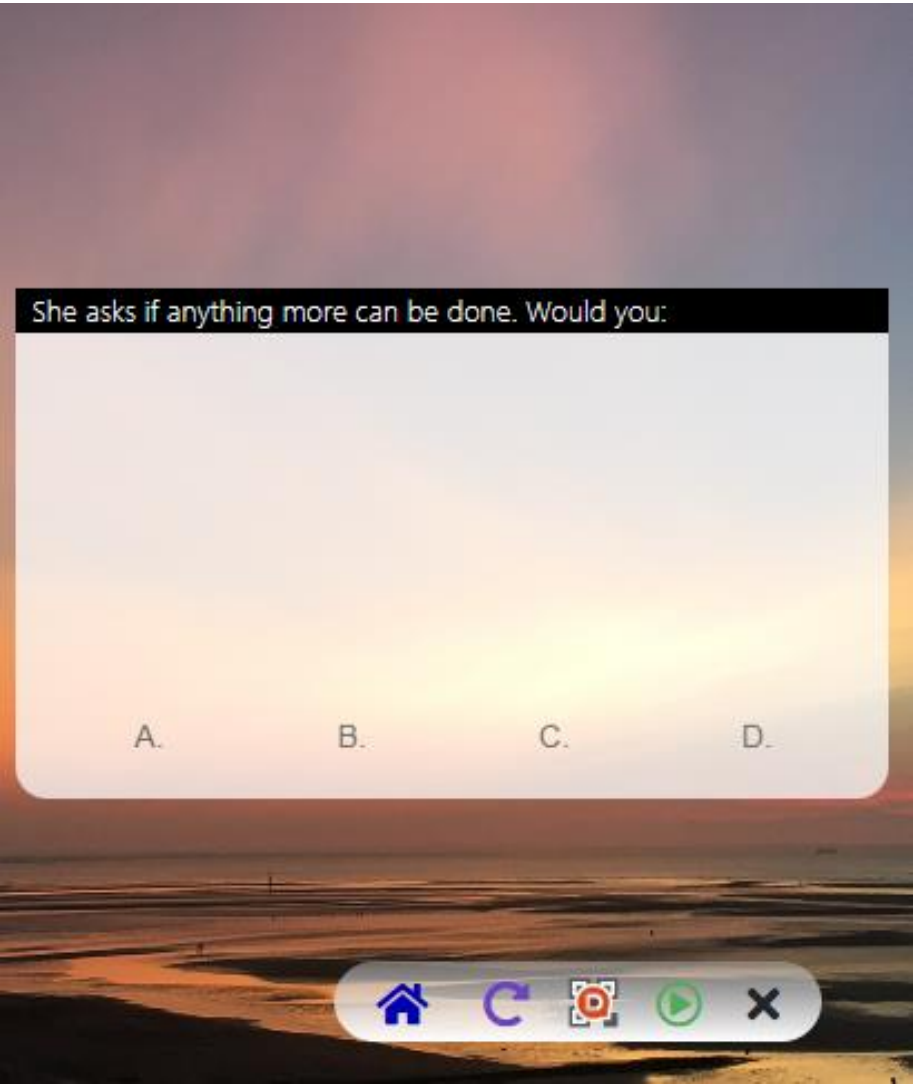

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A: refer to vascular surgery for lysis evaluation

B: arrange direct admission for bridging and stat vascular c/s

C: recommend graduated compression stockings

- D: provide reassurance and expectant guidance

What are the *first line* therapy recommendations for cancer-associated VTE?

…first line therapy recommendations for cancer-associated VTE?

- Mr. T. Delarue is a 72 year-old male with stage III (T3N1) colorectal carcinoma, T2DM, trigeminal neuralgia, and obesity who was recently discharged on enoxaparin after being diagnosed with a non-massive, malignancy-associated segmental pulmonary embolism. He has already grown tired of the expense and discomfort of the injections, and asks you if there is an alternative. He is scheduled to undergo 2 months of FOLFOX neoadjuvant therapy, restaging, and resection if all goes well. Additional medications include metformin and carbamazepine, both of which have been at stable doses. His exam is unremarkable with an oximetry of 94% on room air. His latest labs show a creatinine of .9mg/dL, an A1C of 6.9, and mild AST/ALT elevation <2x ULN.

What therapy would you adjust?

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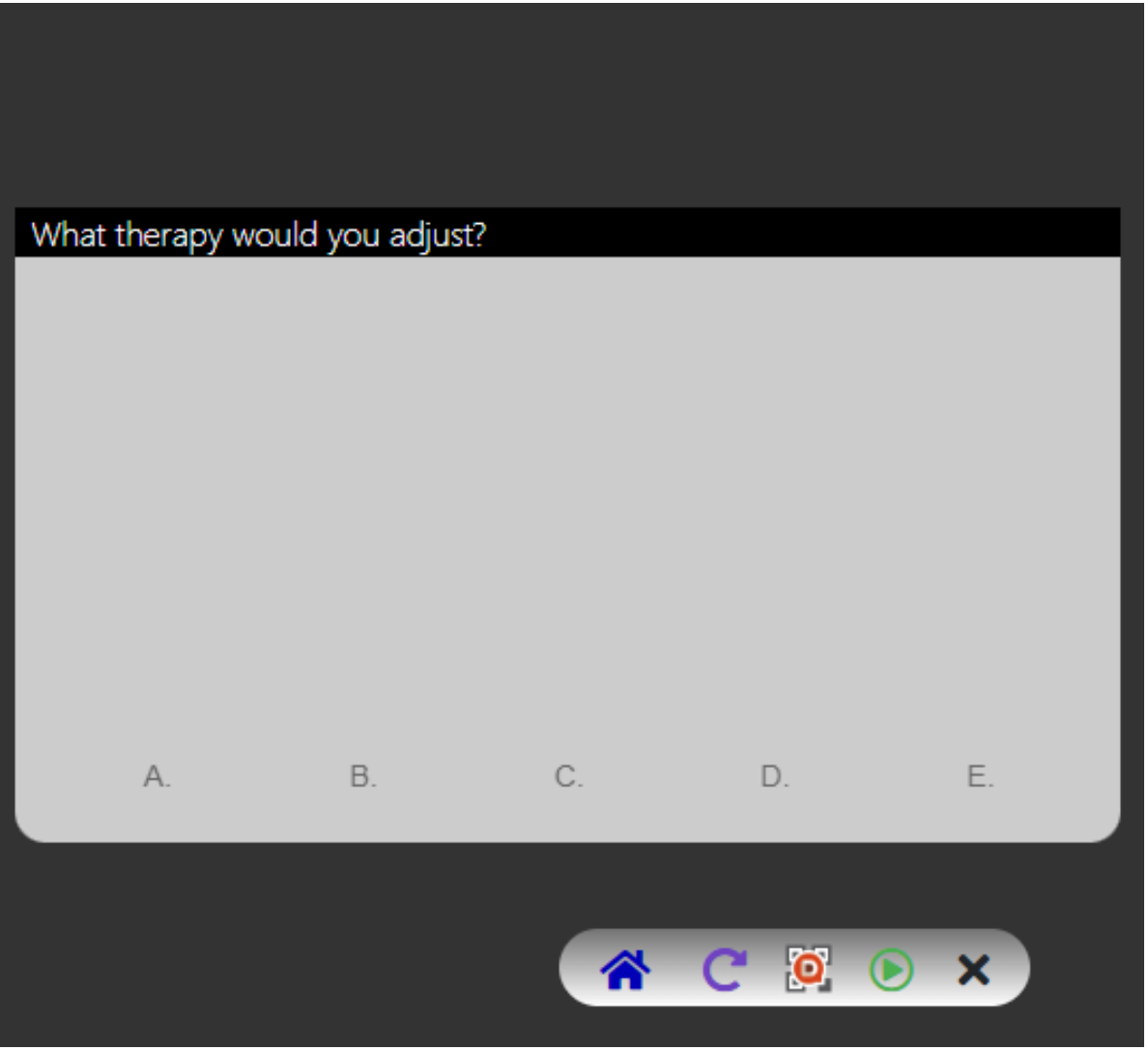
- A: No change in therapy, haven't you read the CLOT trial?
- B: Offer warfarin with serial INR monitoring
- C: Begin edoxaban, rivaroxaban, or apixaban and stop LMWH
- D: Send e-messages to hematology, oncology, and neurology and hope to sort everything out before his current fill runs out
- E: Something else, just give me time to check my phone!

What therapy would you adjust?



- A: No change in therapy, haven't you read the CLOT trial?
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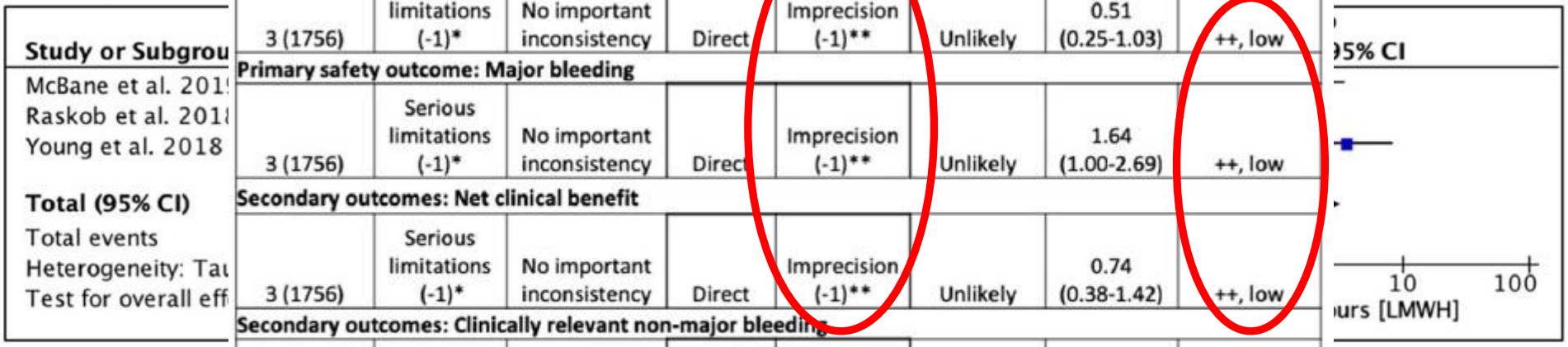
Discussion: which way to go in Cancer Associated Thrombosis (CAT)?

What is the overall evidence for DOACs in Cancer Associated Thrombosis (CAT)?

Number of studies (number of participants)	Quality assessment					Summary of findings	
	Study limitations	Consistency	Directness	Precision	Publication bias	Relative effect (95%CI)	Quality
Primary efficacy outcome: Venous thromboembolism recurrence							
3 (1756)	Serious limitations (-1)*	No important inconsistency	Direct	Imprecision (-1)**	Unlikely	0.51 (0.25-1.03)	++, low
Primary safety outcome: Major bleeding							
3 (1756)	Serious limitations (-1)*	No important inconsistency	Direct	Imprecision (-1)**	Unlikely	1.64 (1.00-2.69)	++, low
Secondary outcomes: Net clinical benefit							
3 (1756)	Serious limitations (-1)*	No important inconsistency	Direct	Imprecision (-1)**	Unlikely	0.74 (0.38-1.42)	++, low
Secondary outcomes: Clinically relevant non-major bleeding							
3 (1756)	Serious limitations (-1)*	No important inconsistency	Direct	No important imprecision	Unlikely	1.83 (1.04-3.20)	+++, moderate
Secondary outcomes: All-cause mortality							
3 (1756)	Serious limitations (-1)*	No important inconsistency	Direct	Imprecision (-1)**	Unlikely	1.06 (0.83-1.35)	++, low

*Open-label, lack of blinding of personnel and participants; **Large confidence interval.

B Quality of evidence using GRADE methodology



Mai et al, 2000

CHEST high quality RCT dataset including CARAVAGGIO

Participants	Certainty	DOACs	LMWH	Relative	Absolute/1k
Recurrent VTE					
2894 (4 studies)	High	75/1446 (5.2%)	119/1448 (8.2%)	RR .62 (.43-.91)	31 fewer (47 to 7 fewer)
Major Bleeding at 6mo					
2894 (4 studies)	Moderate	62/1446 (4.3%)	48/1448 (3.3%)	RR 1.31 (.83-2.08)	10 more (6 less-36 more)

Table 11 modified from Stevens et al, 2021

RCT deeper dive: Rivaroxaban and Apixaban bleeding risks

	Rivaroxaban (Young) SELECT-D	Apixaban (McBane) ADAM-VTE	Apixaban (Agnelli) CARAVAGGIO
Patient	203/406, excluded "clinically significant liver dz" and ASA >75mg (i.e. low dose; UK)	150/300, Plt ≤ 50,000/mcL, ALT/AST > 3x ULN, INR ≤ 1.6, Child Pugh B/C, ?ASA	585/1170, Plt ≤ 75,000/mcL, ALT/AST > 3x ULN, INR ≤ 1.6, Child Pugh B/C, ASA >165mg/day, DAPT
Intervention	Randomized, open label, 15mg PO BID x21d, then 20 QPM vs. LMWH	Randomized, open label, 10mg PO BID x7d, then 5mg BID vs. LMWH	Randomized, open label, 10mg PO BID x7d, then 5mg BID vs. LMWH
Comparison (Dalteparin)	200 IU/kg for one month followed by150 IU/kg Qday	200 IU/kg for one month followed by150 IU/kg Qday	200 IU/kg for one month followed by150 IU/kg Qday
Outcome	1° Superior VTE prevention, 2° worse CRNMB	1° Non-inferior bleeding risk, 2° superior VTE prevention	Co-1° Non-inferior efficacy, no difference in major bleeding

Rivaroxaban (SELECT-D)

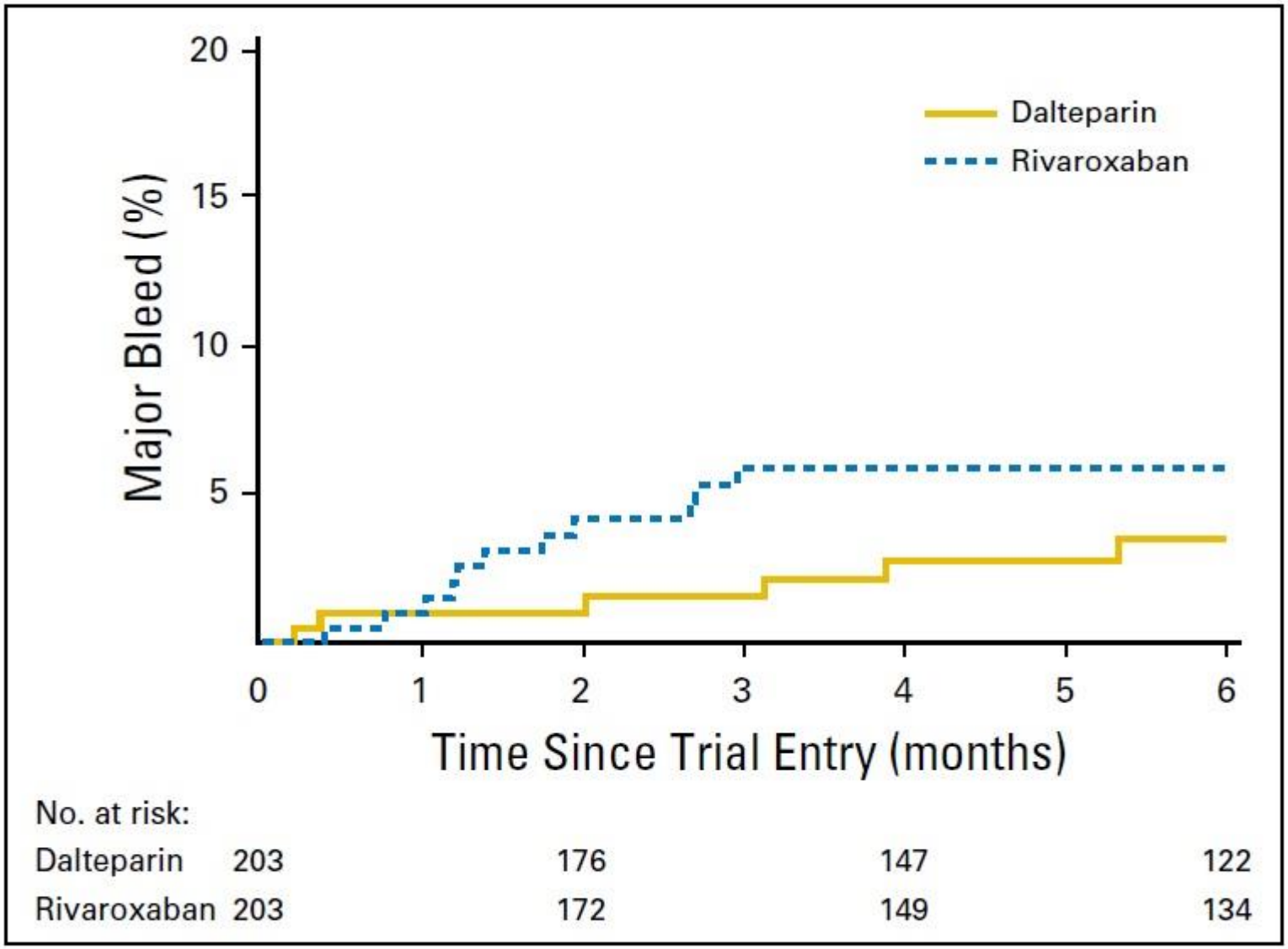
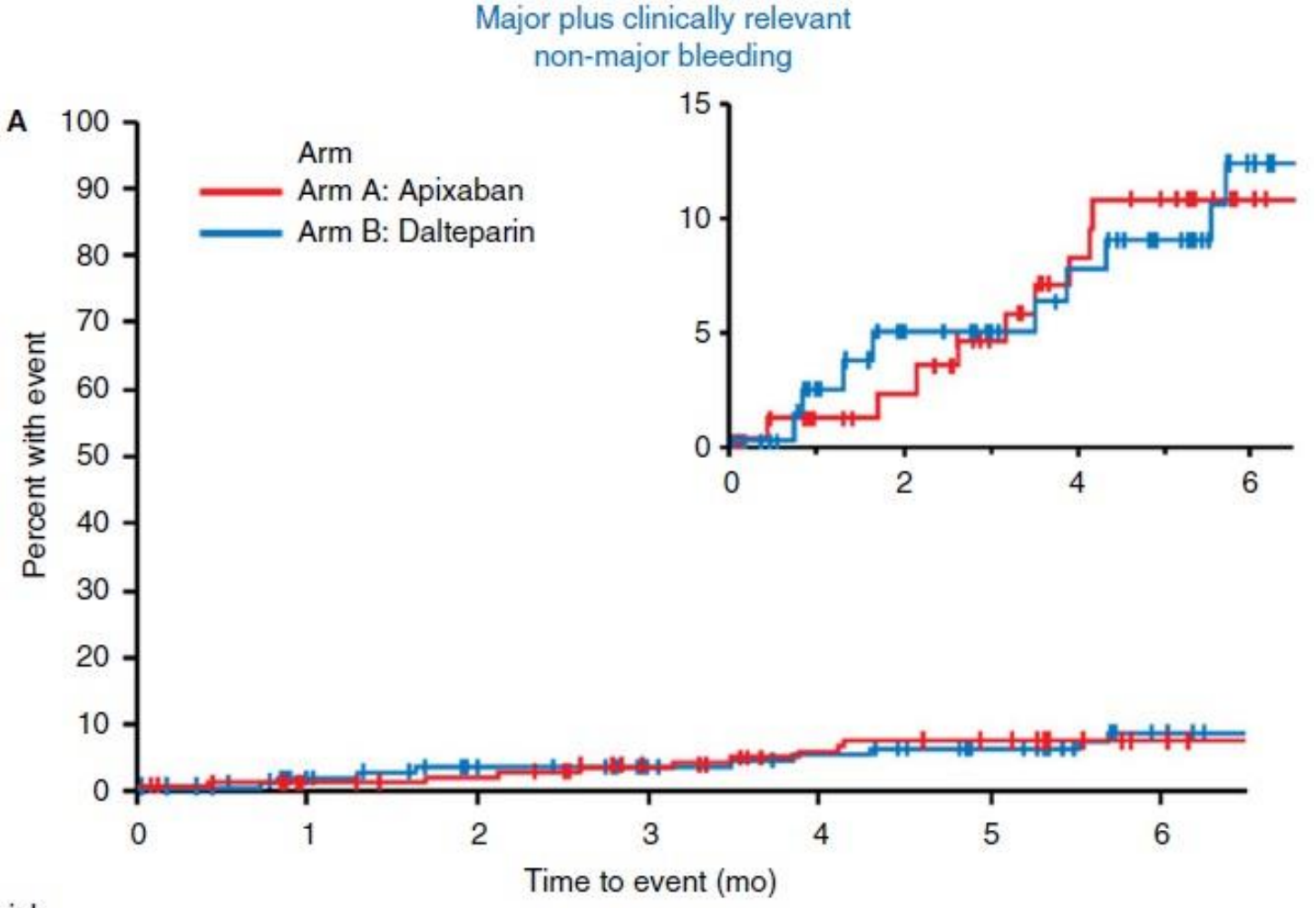


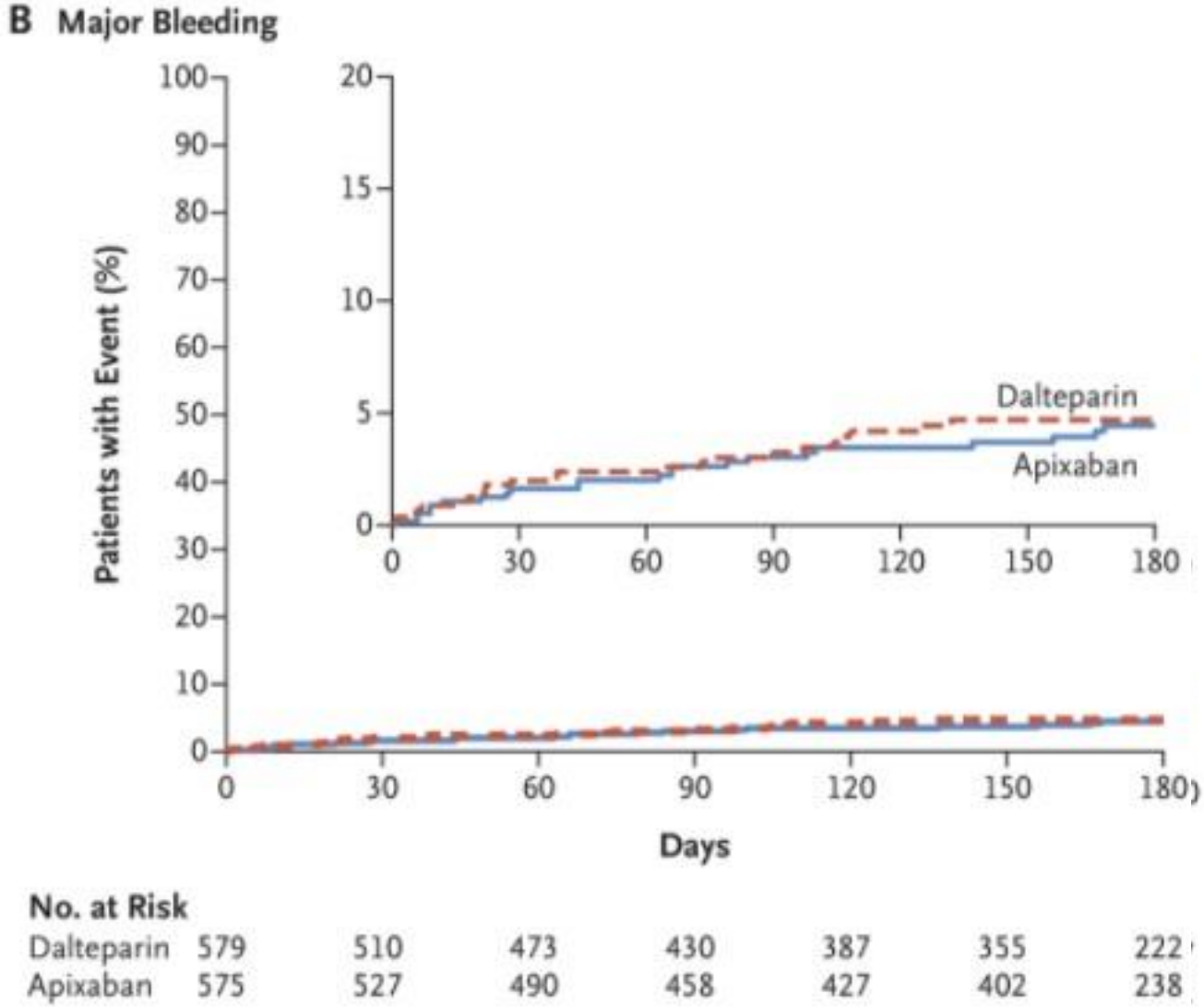
Fig 3. Time to major bleed within 6 months.

Apixaban (ADAM-VTE)

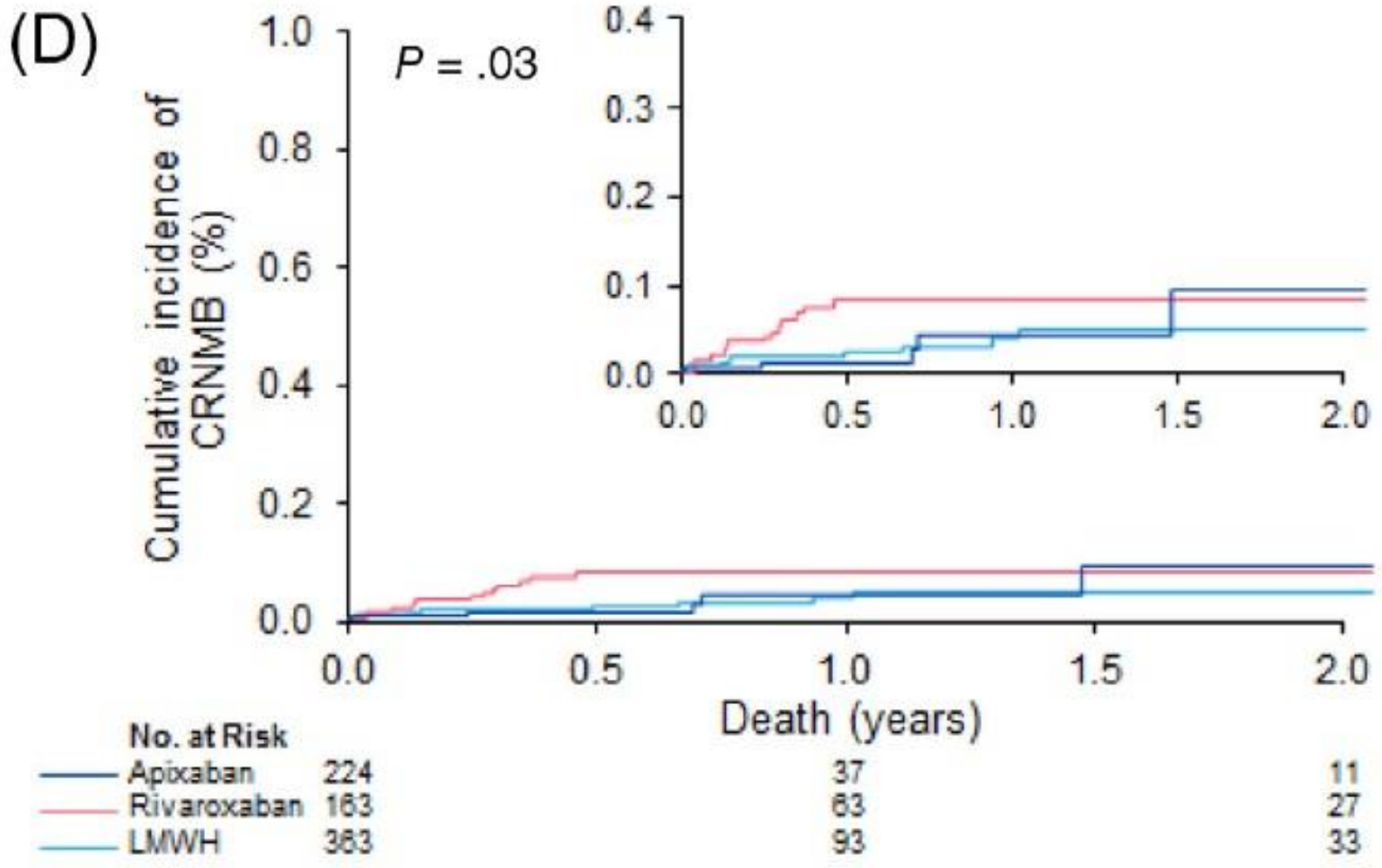


Patients-at-risk									
Apixaban	145	133	125	115	102	96	88	78	74
Dalteparin	142	123	114	107	100	90	76	64	62

Apixaban (CARAVAGGIO)



Is there *any* head to head data?



CHEST 2021 Recommendation

- **In patients with acute VTE in the setting of cancer ("cancer-associated thrombosis") we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence).**

ASH 2021 Recommendation

- For the short-term treatment of VTE (first 3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⨁⨁◯◯). DOAC is also *suggested* over VKA (conditional recommendation, very low certainty in the evidence of effects ⨁◯◯◯). If a DOAC is not used, the ASH guideline panel *suggests* LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⨁⨁⨁◯).

Ortel et al, 2020

Stevens et al, 2021

DOAC do's and don'ts w/ malignancy

- Don't Rx w/ untreated upper GI malignancy (caution w/ untreated pulmonary or renal malignancy), significant cytopenias (common w/ leukemias & MM which were underrepresented or excluded in trials), intracranial primary or metastasis due to bleeding risk
- Beware tolerability for patients on emetogenic chemotherapy w/ h/o significant N/V (provide alternative Rx and if/then instructions)
- Avoid coadministration w/ additional antithrombotic therapies unless strongly indicated (CHEST AT9 recommended AC alone for stable CAD w/ VKA; DOAC?)
- Avoid w/ strong CYP3A4 and p-gp inducers/inhibitors and advanced liver disease
- Preemptive education to patients re: bleeding risk, r/b/a (i.e. shared decision making)

What therapy would you adjust?

- Mr. T. Delarue is a 72 year-old male with stage III (T3N1) colorectal carcinoma, T2DM, trigeminal neuralgia, and obesity who was recently discharged on enoxaparin after being diagnosed with a non-massive, malignancy-associated segmental pulmonary embolism. He has already grown tired of the expense and discomfort of the injections, and asks you if there is an alternative. He is scheduled to undergo 2 months of FOLFOX neoadjuvant therapy, restaging, and resection if all goes well. Additional medications include metformin and carbamazepine, both of which have been at stable doses. His exam is unremarkable with an oximetry of 94% on room air. His latest labs show a creatinine of .9mg/dL, an A1C of 6.9, and mild AST/ALT elevation <2x ULN.

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- E: Something else, just give me time to check my phone!

Can I, *should I*, manage PE as an outpatient?

- **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).**
- *Remark: While the formal [evidence to decision] assessment warrants a weak recommendation in favor of anticoagulation ("suggest") the panelists upgraded the guidance to a strong recommendation, placing a very high value on avoiding the potential increase in risk of harm (including much greater cost) related to hospitalization even though the magnitude of benefit is similar.*

Stevens et al, 2021

How long is long enough for anticoagulation in *this* VTE patient?

- Major or minor provoking factor w/o persistent risk:
  - 3 months
- Do I need to continue for “3-6 months”?
  - No (3mo or indefinite)
- Who should be offered/recommended indefinite tx?
  - Unprovoked DVT or PE, persistent provoking factors
- What is the preferred tx for prolonged 2° prevention?
  - Reduced dose DOAC starting at 6 months
- When should “indefinite” anticoagulation be reevaluated?
  - Annually, or after a clinical bleeding event

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- Roy et al, *JAMA*, The Rationale Clinical Exam, April 25, 2007—Vol 297, No. 16 (Reprinted)
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- Nishimoto et al, “Validation of the VTE-BLEED score’s long-term performance for major bleeding in patients with venous thromboembolisms: From the COMMAND VTE registry” 26 Nov 2019*, JTH*

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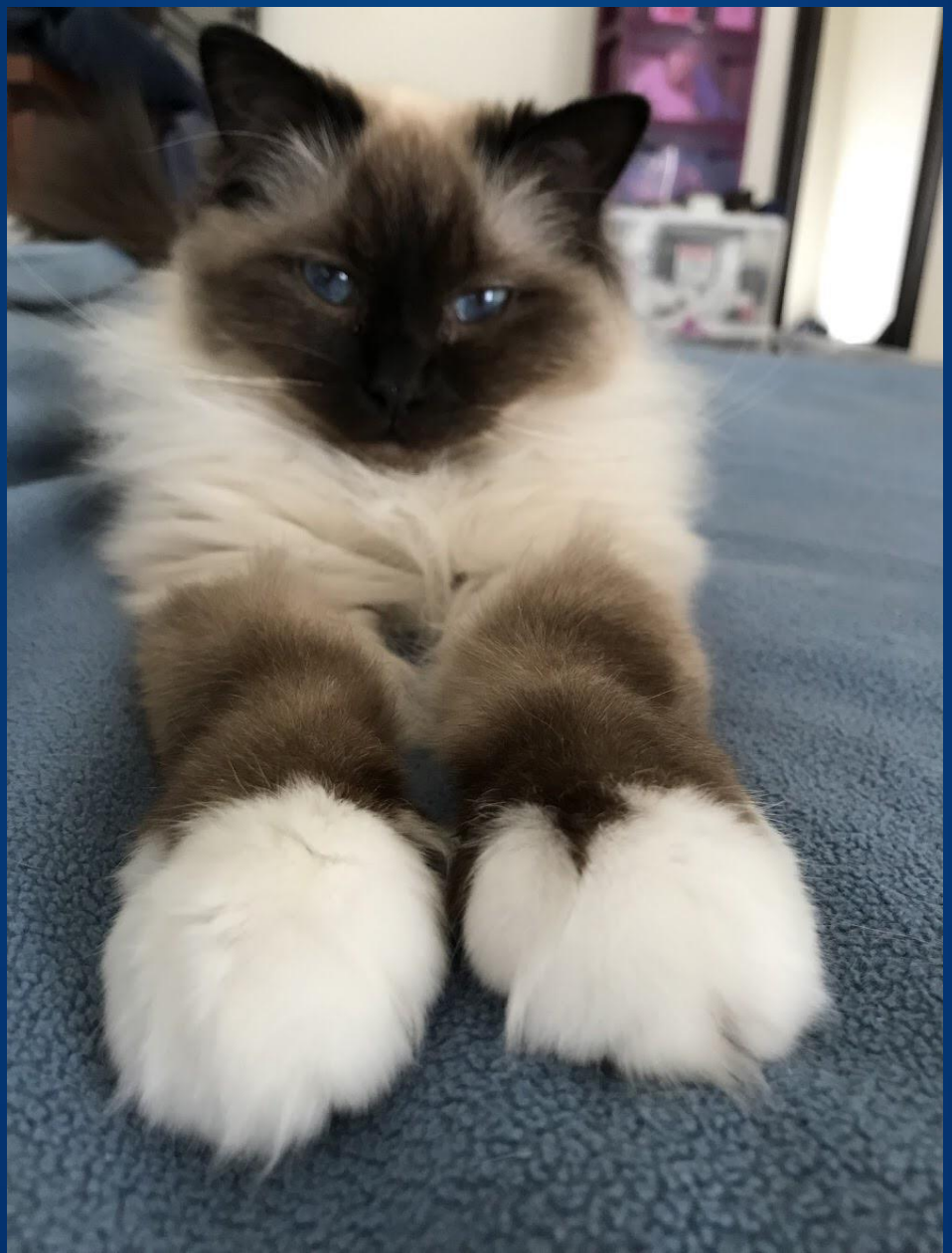
End Presentation



Dedicated in loving memory of “Fluffy”, 2017-2021