What is new in venous thrombosis in 2019

Vicky Tagalakis MD FRCP
Division of General Internal Medicine
CETAC
Jewish General Hospital
McGill University

Disclosures

Advisory board

- Pfizer
- Bayer
- Sanofi
- Leo Pharma
- Servier

Research funding

- Pfizer
- Sanofi
- CIHR

Objectives

1. To be familiar with a diagnostic strategy for pulmonary embolism (PE) that avoids chest imaging in up to 40% of pregnant women (ARTEMIS[1])
2. To learn of primary prophylaxis strategies for PE and deep vein thrombosis(DVT) in cancer patients (AVERT[2], CASSINI[3])

1. Van der Pol LM et al, *NEJM* **2019**; 380 (12):1139-49
2. Carrier M, et al. *NEJM* **2019**;380(8):711-719
3. Khorana AA, et al. *NEJM* **2019**;380(8):720-728; 3. Ay C, et al. *Blood* 2010;116:5377–5382

ORIGINAL ARTICLE

Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism

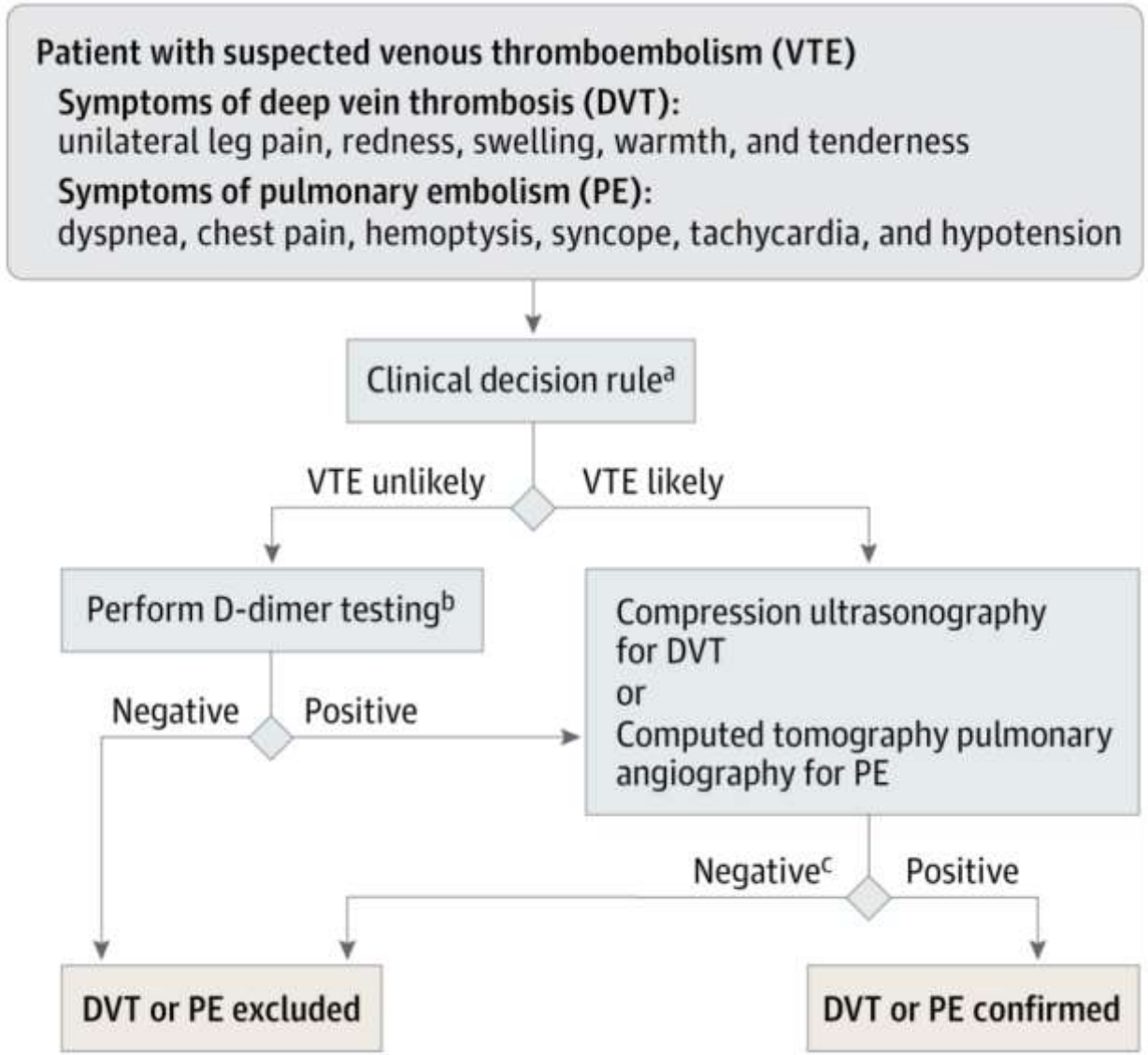
Liselotte M. van der Pol, M.D., Cecile Tromeur, M.D., Ingrid M. Bistervels, M.D., Fionnuala Ni Ainle, M.D., Thomas van Bemmel, M.D., Laurent Bertoletti, M.D., Francis Couturaud, M.D., Yordi P.A. van Dooren, M.D., Antoine Elias, M.D., Laura M. Faber, M.D., Herman M.A. Hofstee, M.D., Tom van der Hulle, M.D., et al., for the Artemis Study Investigators*

Van der Pol LM et al, *NEJM* 2019; 380 (12):1139-49

Diagnosing deep vein thrombosis and pulmonary embolism in pregnancy

- PE –> leading cause of maternal death in Western countries
- Incidence of PE 1.72 cases per 1000 deliveries[1]
- Accounts of 1 death in every 100,000 deliveries[2]
- Wide overlap between VTE clinical Sxs and Sxs due to physiological changes in pregnancy (eg. ⇧HR, leg swelling, and SOB)
- Low threshold to test for PE during pregnancy
- Clinical dilemma →3-5% prevalence of PE among pregnant women with suspected PE, as compared to 15 to 20% among non-pregnant women[3]

Diagnostic management of patients with suspected DVT or PE in non-pregnant population



JAMA. 2018;320(15):1583-1594. doi:10.1001/jama.2018.14346

Diagnosing DVT and PE

- Overall, VTE can be excluded in **29% (95% CI 20-40%)** of patients with suspected DVT and in **28% (95% CI 20-37%)** of patients with suspected PE[1,2] with the use of diagnostic algorithm including pretest probability and d-dimer testing (clinical decision rule – CDR)

- Almost 30% of suspected VTE cases can be ruled out safely without imaging

1. Geersing GJ *BMJ* 2014
2. van ES N *Ann Intern Med* 2016

Diagnostic PE algorithm in pregnancy?

- Studies validating use of CDRs to rule out PE without imaging tests during pregnancy are scarce
- PE can be ruled out without chest CT pulmonary angiography (CTPA) in only 16% of pregnant women on the basis of a decision rule, d-dimer, & compression ultrasonography of both legs [1]
- Diagnostic workup of pregnant women with suspected PE relies mainly on imaging chest i (i.e. CTPA or ventilation–perfusion scanning)
  - Potential harm to mother and fetus through exposure to intravenous contrast and ionizing radiation[2,3,4]

YEARS algorithm

- YEARS algorithm developed to r/o PE using a two tiered d-dimer threshold in an effort to reduce # of patients getting CTPA[1]

1) Are there signs of DVT?
2) Does the patient have hemoptysis?
3) Is PE the most likely diagnosis?

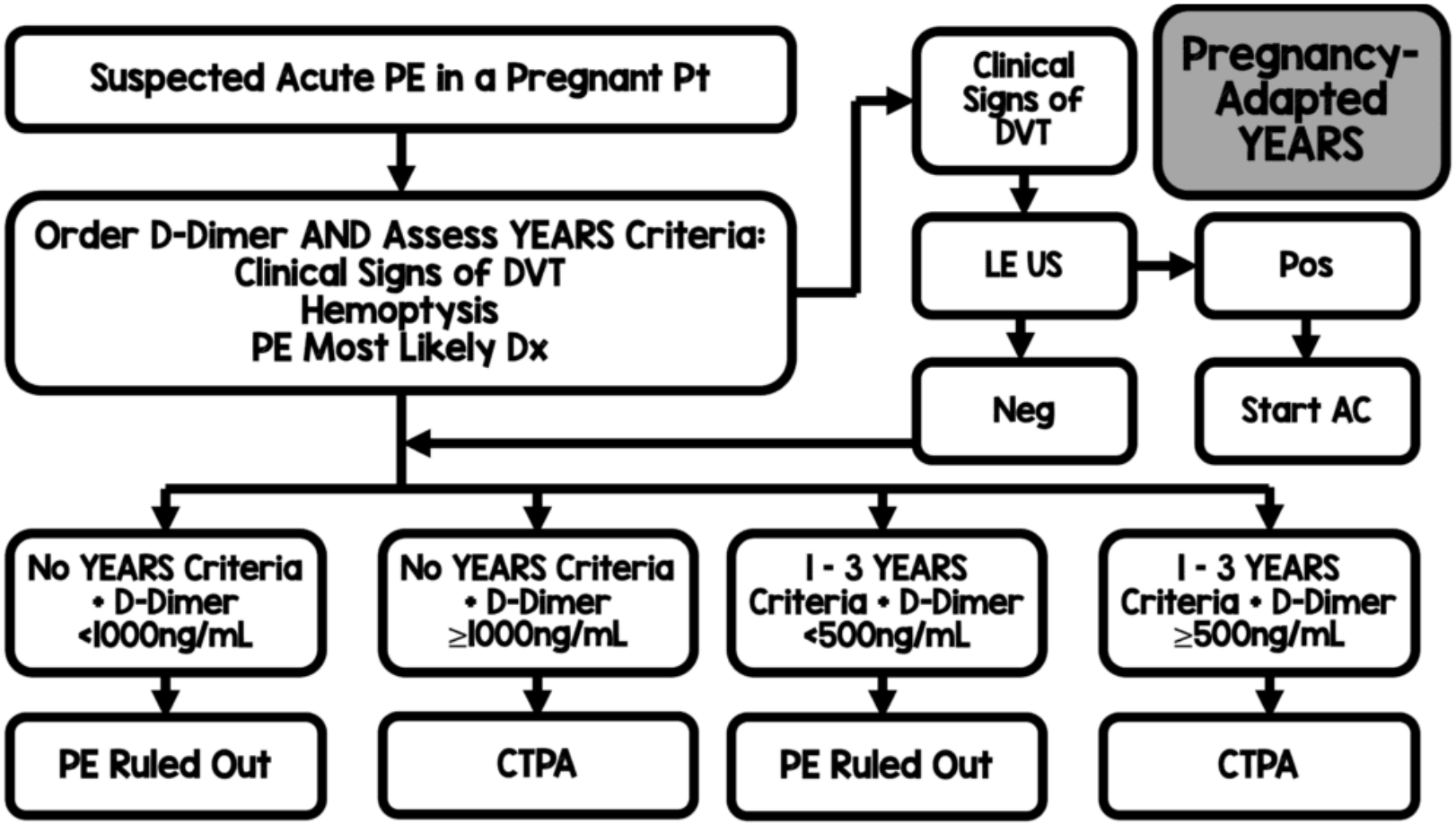
If **NO** to all 3 questions, d-dimer threshold set at 1000 ng/ml FEU
If **YES** to any of the 3 questions, d-dimer threshold set at 500ng/ml FEU

1. Van der Hulle et, Lancet 2017;390:289-97

ARTEMIS: Methods

- Prospective, multicenter at 11 academic and 7 nonacademic H
- Pregnant and over 18 yo referred to ED or obstetrical ward for suspected PE (new or worsening CP or SOB +/- hemoptysis or tachycardia)
- **1^0 outcome** = cumulative incidence of symptomatic VTE during a 3 – month f/u in a subgroup of women in whom AC was withheld due to a negative YEARS algorithm
- **2^0 outcome** = proportion of patients being evaluated for PE who did not require a CTPA base on the algorithm

YEARS Rule: Pregnant women with suspected PE



van der Pol LM et al. Pregnancy-Adapted YEARS Algorithm for diagnosis of Suspected Pulmonary Embolism. NEJM 2019; 380(12): 1139-49. PMID: 30893534

Demographic and Baseline Characteristics of Pregnant Patients with Suspected Pulmonary Embolism.*

Table 1. Demographic and Baseline Characteristics of Pregnant Patients with Suspected Pulmonary Embolism.*

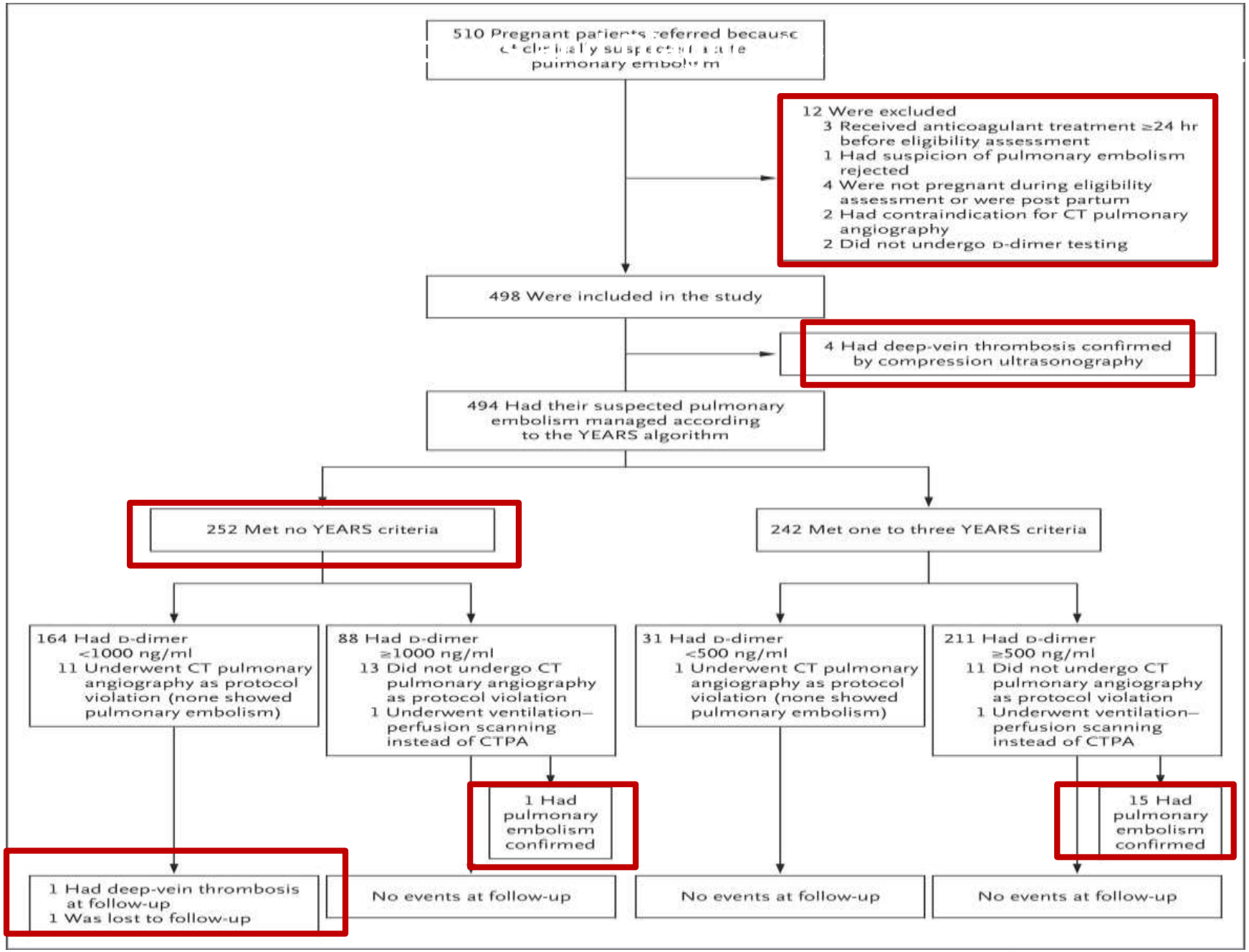
Characteristic	Patients (N=498)
Mean age (±SD) — yr	30±5.8
Median duration of pregnancy (IQR) — wk	25 (17–31)
Trimester of pregnancy — no. (%)	
First: 0 to 12 wk 6 days of gestation	74 (15)
Second: 13 wk 0 days to 26 wk 6 days of gestation	193 (39)
Third: 27 wk 0 days to 42 wk of gestation	231 (46)
YEARS criteria — no. (%)	
Patients who met no criteria	252 (51)
Patients who met one to three criteria	246 (49)
Clinical signs of deep-vein thrombosis	47 (19)
Hemoptysis	19 (7.7)
Pulmonary embolism as the most likely diagnosis	218 (89)
First pregnancy — no. (%)	133 (27)
Median duration of reported symptoms (IQR) — days	2 (1–6)
Air travel in the previous 4 wk — no. (%)	12 (2.4)
Surgery in the previous 4 wk — no. (%)	5 (1.0)
Immobilization for >3 days in the previous 4 wk — no. (%)	31 (6.2)
Current smoker — no. (%)	37 (7.4)
Known asthma — no. (%)	62 (12)
Previous VTE — no. (%)	30 (6.0)
Known thrombophilia — no. (%)	14 (2.8)
Outpatient — no. (%)	419 (84)

* IQR denotes interquartile range, and VTE venous thromboembolism.

LM van der Pol et al. N Engl J Med 2019;

ARTEMIS STUDIES: RESULTS

Variable	N	Comment
Women screened	510	N=12 (2.4%) excluded
Included in the study	498 46% in 3rd trimester	
Total # of VTE at baseline	20 (4%, 95% CI 2.6-6.1)	
YEARS -ve	252 (51%)	
YEARS +ve	24 (49%)	
Primary outcome (cumulative incidence of Sx VTE at 3 months)	1 (0.21%, 95% CI 0.4-1.2)	N=477 (96%) PE ruled out at baseline N=476 no symptomatic VTE at 3 months
Secondary outcome (% of patients who did not require a CTPA based on algorithm)	39% (95% CI 35-44)	N=195 of 498 did not require a CTPA N=12 (6.2%) underwent CTPA (protocol violation)



LM van der Pol et al. N Engl J Med 2019;380:1139-1149.

YEARS Study: Primary and Secondary Outcomes.*

Table 2. Primary and Secondary Outcomes.*

Variable	All Patients (N=498)	Patients Who Did Not Have Deep-Vein Thrombosis at Baseline (N=494)	
		CT Pulmonary Angiography Not Indicated	CT Pulmonary Angiography Indicated†
Pulmonary embolism confirmed at baseline			
No./total no.	20/498‡	0/195	16/299
% (95% CI)	4.0 (2.6–6.1)	0 (0.0–2.0)	5.4 (3.3–8.5)
Diagnosis of VTE during follow-up in patients who did not have VTE at baseline			
No./total no.	1/477§	1/195	0/283
% (95% CI)	0.21 (0.04–1.2)¶	0.51 (0.09–2.9)‖	0 (0.00–1.4)

* CT denotes computed tomography.
† Ventilation–perfusion scanning was performed instead of CT pulmonary angiography in 2 patients.
‡ Four of the 498 patients had deep-vein thrombosis, which was confirmed by compression ultrasonography.
§ The denominator of 477 comprises all patients who did not have VTE at baseline and who were not lost to follow up.
¶ These results represent the primary outcome.
‖ These results represent the secondary outcome.

LM van der Pol et al. N Engl J Med 2019;380:1139-1149.

YEARS Study: Limitations

- External validity is questioned (France and Netherlands)
- Protocol violations: 24 patients who should have had CTPA did not (24 of 299); 12 patients underwent CTPA who should not have had imaging (12 of 195)
- Parallel timing of assessment of YEARS criteria and d-dimer, physicians may have been aware of the d-dimer level which may have biased the evaluation of patients

YEARS Study: Take Home Message

- Pragmatic as pregnant women with DVT do not require CTPA
- YEARS criteria are simple
- Not all patients had a CTPA and so some PEs may have been missed
  - Clinical significance of missed PE? Probably irrelevant
- Prevalence of PE of 4% is consistent with prior published reports
- Efficiency of algorithm highest during 1st trimester: CTPA avoided in 65% of women who began study in 1st trimester vs. 32% in women who entered study in 3rd trimester; trimester adjusted d-dimer?
- “PE as most likely diagnosis”
  - Subjective criterion
  - MD gestalt in real life vs. study?

ORIGINAL ARTICLE

Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

Alok A. Khorana, M.D., Gerald A. Soff, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Saroj Vadhan-Raj, M.D., M.H.C.M., C.M.Q., Hanno Riess, M.D., Ph.D., Ted Wun, M.D., Michael B. Streiff, M.D., David A. Garcia, M.D., Howard A. Liebman, M.D., Chandra P. Belani, M.D., Eileen M. O'Reilly, M.D., Jai N. Patel, Pharm.D., et al., for the CASSINI Investigators*

Khorana AA, et al. *NEJM*. 2019;380(8):720-728

ORIGINAL ARTICLE

Apixaban to Prevent Venous Thromboembolism in Patients with Cancer

Marc Carrier, M.D., Karim Abou-Nassar, M.D., Ranjeeta Mallick, Ph.D., Vicky Tagalakis, M.D., Sudeep Shivakumar, M.D., Ariah Schattner, M.D., Philip Kuruvilla, M.D., Danny Hill, M.D., Silvana Spadafora, M.D., Katerine Marquis, M.D., Mateya Trinkaus, M.D., Anna Tomiak, M.D., et al., for the AVERT Investigators*

Carrier M, et al. *NEJM*. 2019;380(8):711-719

Khorana risk score: predictive model for cancer associated thrombosis

Patient characteristic	Risk score*
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $\geq$350 x 10^9/L	1
Hemoglobin level <100g/L or use of red cell growth factor	1
Prechemotherapy leukocyte count >11 x 10^9/L	1
BMI $\geq$35 kg/m^2	1

*Scores
≥3 = high risk
1 or 2 = intermediate risk
0 = low risk

BMI, body mass index; CAT, cancer-associated thrombosis; VTE, venous thromboembolism

Khorana AA, et al. *Blood*. 2008;111(10):4902-4907

Prevention of VTE in patients with cancer

- Cancer patients are at increased risk of VTE;
  - Chemotherapy further increases this risk;
  - Anticoagulation can prevent VTE but is associated with costs and complications (mainly bleeding)
- What if only those with highest VTE risk were exposed to anticoagulation?
  - Maximize the benefit-to-risk balance
- Can we use low dose DOACs as prevention of VTE in patients with cancer?
  - AVERT and CASSINI trials enrolled patients at high risk for VTE to low dose DOAC vs placebo

CAT, cancer-associated thrombosis; DOAC, direct oral anticoagulant; VTE, venous thromboembolism

AVERT and CASSINI: baseline study characteristics

- Placebo controlled 1:1 randomized trials; treatment period = 180 days
- Target population: ambulatory cancer patients undergoing chemotherapy

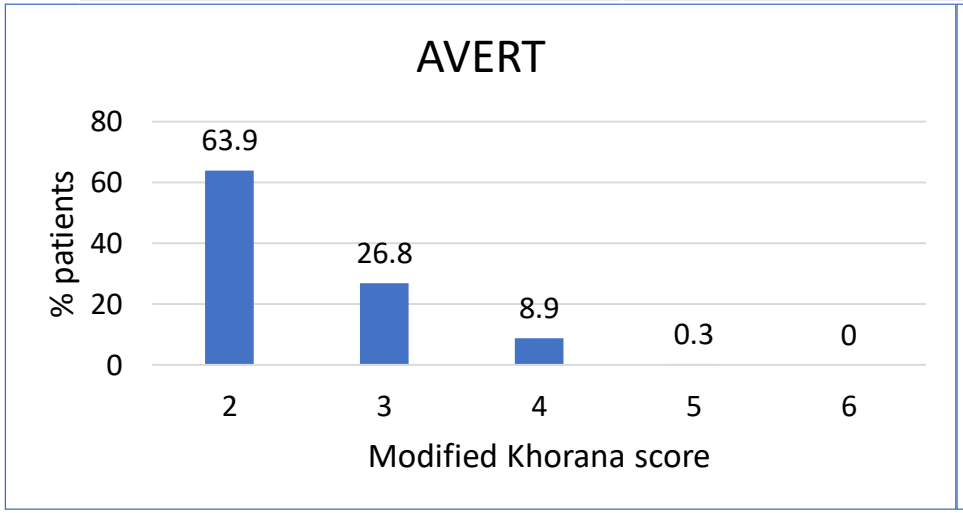
Study characteristics	AVERT[1]	CASSINI[2]
# patients	574	841
Treatment arms	Apixaban 2.5 mg BID vs placebo	Rivaroxaban 10 mg daily vs placebo
Inclusion	Modified Khorana*[3] ≥2	Khorana ≥2 AND **negative screening US at enrollment****
Primary outcome	Objectively confirmed VTE, symptomatic proximal DVT or PE or found on cancer restaging, or fatal PE	Objectively confirmed VTE, symptomatic proximal DVT or if found on screening US that was done every 8 weeks, symptomatic distal DVT, symptomatic upper extremity DVT, symptomatic or incidental PE, death from VTE
Safety outcome	Major bleeding***	Major bleeding***

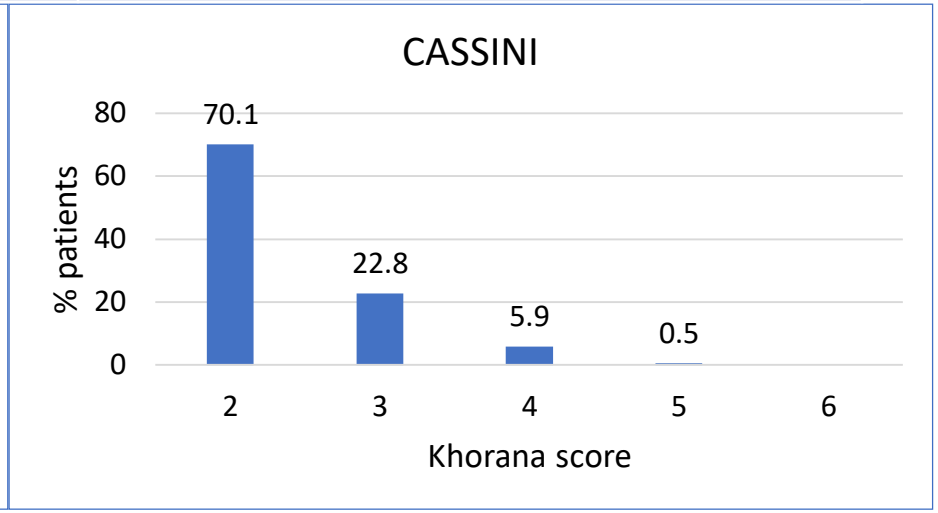
* Modified Khorana risk score included gliomas in "Very High Risk" and multiple myeloma in "High Risk; **4.5% of patients were positive for DVT on enrollment US; note that screening US is not typical in primary care; ***defined per ISTH criteria; BID, twice daily; DVT, deep vein thrombosis; PE, pulmonary embolism; US, ultrasound; VTE, venous thromboembolism

1. Carrier M, et al. *NEJM*. 2019;380(8):711-719; 2. Khorana AA, et al. *NEJM*. 2019;380(8):720-728; 3. Ay C, et al. *Blood* 2010;116:5377–5382.

AVERT and CASSINI: baseline patient characteristics

Patient characteristics	AVERT[1]	CASSINI[2]
Age (years)	61	63
Men (%)	42	51
Top 5 tumor types (%)	Gynecologic (25.8) Lymphoma (25.3) Pancreatic (13.6) Lung (10.3) Stomach (7.7)	Pancreatic (32.6) Gastric/gastroesophageal junction (20.9) Lung (15.9) Lymphoma (7.0) Ovarian (6.4)





1. Carrier M, et al. *NEJM*. 2019;380(8):711-719; 2. Khorana AA, et al. *NEJM*. 2019;380(8):720-728.

AVERT Outcomes: Modified intent-to-treat* analysis

Outcome	Apixaban (288)	Placebo (275)	Hazard Ratio	*p* value	NNT/NNH
Primary Outcome†	4.2%	10.2%	0.41 (0.26-0.65)	$p<0.001$	17
Major bleeding‡	3.5%	1.8%	2.00 (1.01-3.95)		59
CRNMB	7.3%	5.5%	1.28 (0.89-1.84)		
Death	12.2%	9.8%	1.29 (0.98-1.71)		

*Modified intention-to-treat population included all the patients who had undergone randomization and received at least one dose of apixaban or placebo on or before day 180 (+/- 3 days)

†Approximately 25% were incidental VTE

‡ Most common sites of bleeding were gastrointestinal, hematuria and gynecologic

CRNMB, clinically relevant non-major bleeding; NNH, number needed to harm; NNT, number needed to treat; VTE, venous thromboembolism

Carrier M, et al. *New England Journal of Medicine*. 2019;380(8):711-719.

AVERT Outcomes: On-treatment analysis

Outcome	Apixaban (288)	Placebo (275)	Hazard Ratio	NNT/NNH
VTE	1.0%	7.3%	0.14 (0.05-0.42)	16
Major bleeding	2.1%	1.1%	1.89 (0.39-9.24)	100

NNH, number needed to harm; NNT, number needed to treat; VTE, venous thromboembolism

Carrier M, et al. *New England Journal of Medicine*. 2019;380(8):711-719.

CASSINI Outcomes: Intent-to-treat analysis

Outcome	Rivaroxaban (420)	Placebo (421)	Hazard Ratio	*p* value	NNT/NNH
Primary Outcome*	6.0%	8.8%	0.66 (0.4-1.09)	*p*=0.10	35
Death	20.0%	23.8%	0.83 (0.62-1.11)		
VTE and Death	23.1%	29.5%	0.75 (0.57-0.97)		17

Note that major bleeding was assessed in the on-treatment group only.

*Among VTE events, 25% were incidental PE and 25% were DVT found on screening

NNH, number needed to harm; NNT, number needed to treat; VTE, venous thromboembolism

Khorana AA, et al. *New England Journal of Medicine*. 2019;380(8):720-728.

CASSINI: On-treatment analysis

Outcome	Rivaroxaban (n=420)	Placebo (n=421)	Hazard Ratio	NNT/NNH
VTE	2.6%	6.4%	0.4 (0.20-0.80)	26
	(n=405)	(n=404)		
Major Bleeding	2.0%	1.0%	1.96 (0.59-6.49)	100
CRNMB	2.7%	2.0%	1.34 (0.54-3.32)	

CRNMB, clinically relevant non-major bleeding; NNH, number needed to harm; NNT, number needed to treat; VTE, venous thromboembolism

Khorana AA, et al. *New England Journal of Medicine*. 2019;380(8):720-728.

Summary of thromboprophylaxis trials in ambulatory chemotherapy patients

- Thromboprophylaxis with low dose DOACs appears to be safe in ambulatory cancer patients and may be more tolerable and affordable than LMWH

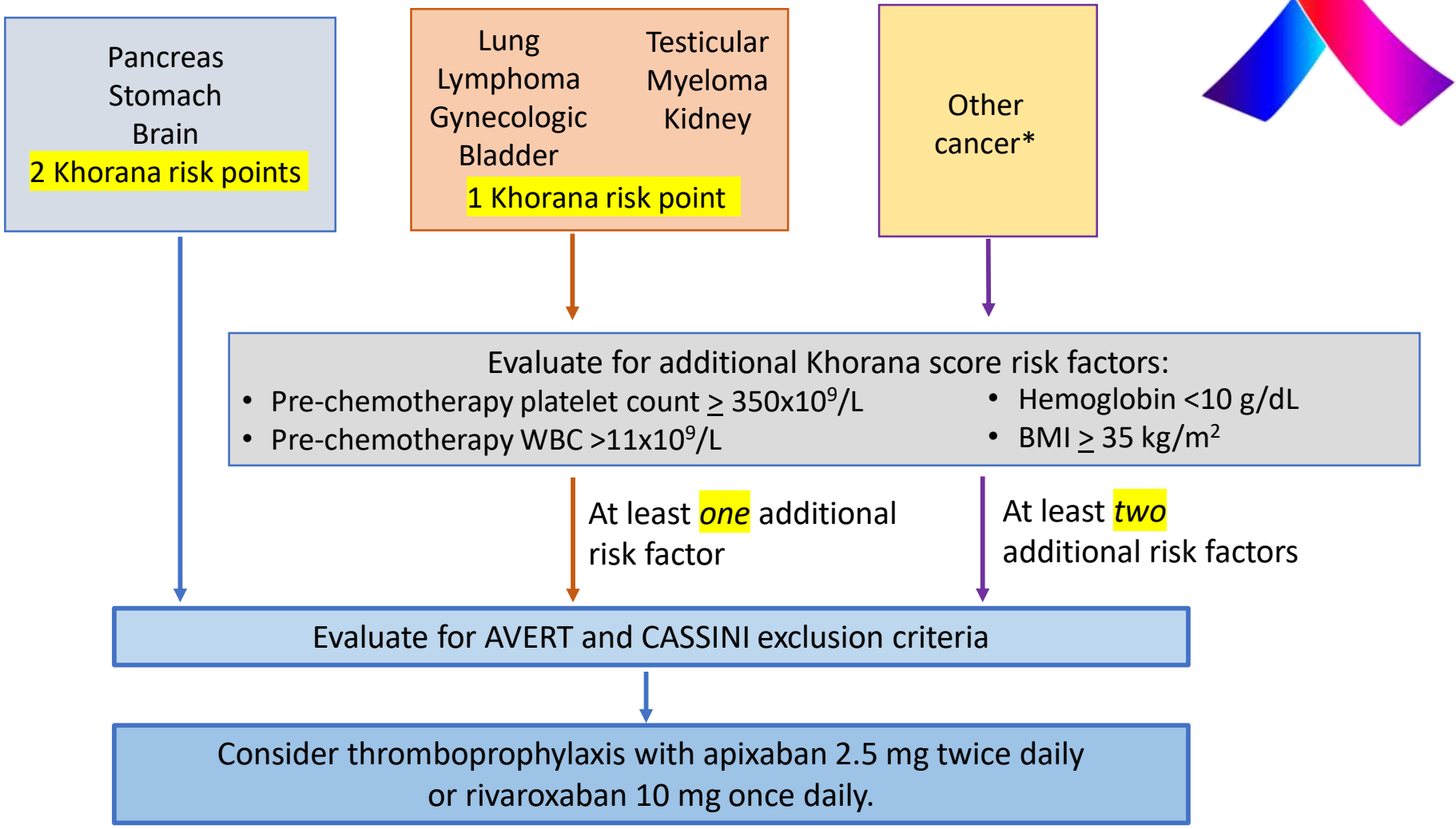
Characteristic	AVERT[1] (Apixaban)	CASSINI[2] (Rivaroxaban)
Primary outcome (VTE) during follow-up period	Statistically significant reduction in VTE	Non-statistically significant reduction in VTE
Anticoagulant regimen	BID	Daily
Cancer subtypes	More gynecologic malignancies	More pancreatic and gastric malignancies
Baseline ultrasound (US) screening	Not done	Patients with baseline US positive for DVT were excluded
Trial events	Did not include DVT diagnosed on surveillance US	Included DVT diagnosed on surveillance US

BID, twice daily; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; US, ultrasound; VTE, venous thromboembolism

1. Carrier M, et al. *New England Journal of Medicine*. 2019;380(8):711-719; 2. Khorana AA, et al. *New England Journal of Medicine*. 2019;380(8):720-728.

Guidance for clinical practice: one potential algorithm based on AVERT and CASSINI

Algorithm to determine candidacy for thromboprophylaxis in ambulatory cancer patients, incorporating the Khorana score ≥2 and AVERT and CASSINI exclusion criteria



*Excluding acute leukemia, myeloproliferative neoplasm, basal cell or squamous cell carcinoma only, and planned stem cell transplant; BMI, body mass index; WBC, white blood cells

Adapted from May J, Moll S. /Thehematologist/Diffusion/9438.aspx. Published February 25, 2019. Accessed May 22, 2019.

Insurance coverage: CAT prophylaxis not covered

- Currently, use of DOACs for thromboprophylaxis is not covered under any public plans
- Gap exists between guidelines recommendation and funding approval
- Limited use coverage may deny patients who are eligible based on guidelines

DOAC, direct oral anticoagulant

Wan D, et al. *Canadian Journal of Cardiology*. 2018;34(11):1412-1425.

Conclusion

- Use of the **YEARS** diagnostic algorithm in conjunction with a two-tiered d-dimer possibly obviates the need for CT chest imaging in 39% of pregnant women presenting with suspected PE
  - External validity?
  - Can this algorithm apply to your clinical environment?
- **Thromboprophylaxis** with low dose DOACs appears to be safe in ambulatory **cancer** patients and may be more tolerable and affordable than LMWH
  - Targeted prophylaxis makes sense
  - Drug coverage?

Thank you

McGill UNIVERSITY

Hôpital général juif
Jewish General Hospital

CETAC
Centre of Excellence in Thrombosis and Anticoagulation Care
Centre d'excellence en thrombose et anticoagulation

Canadian Venous Thromboembolism
Clinical Trials and Outcomes Research Network