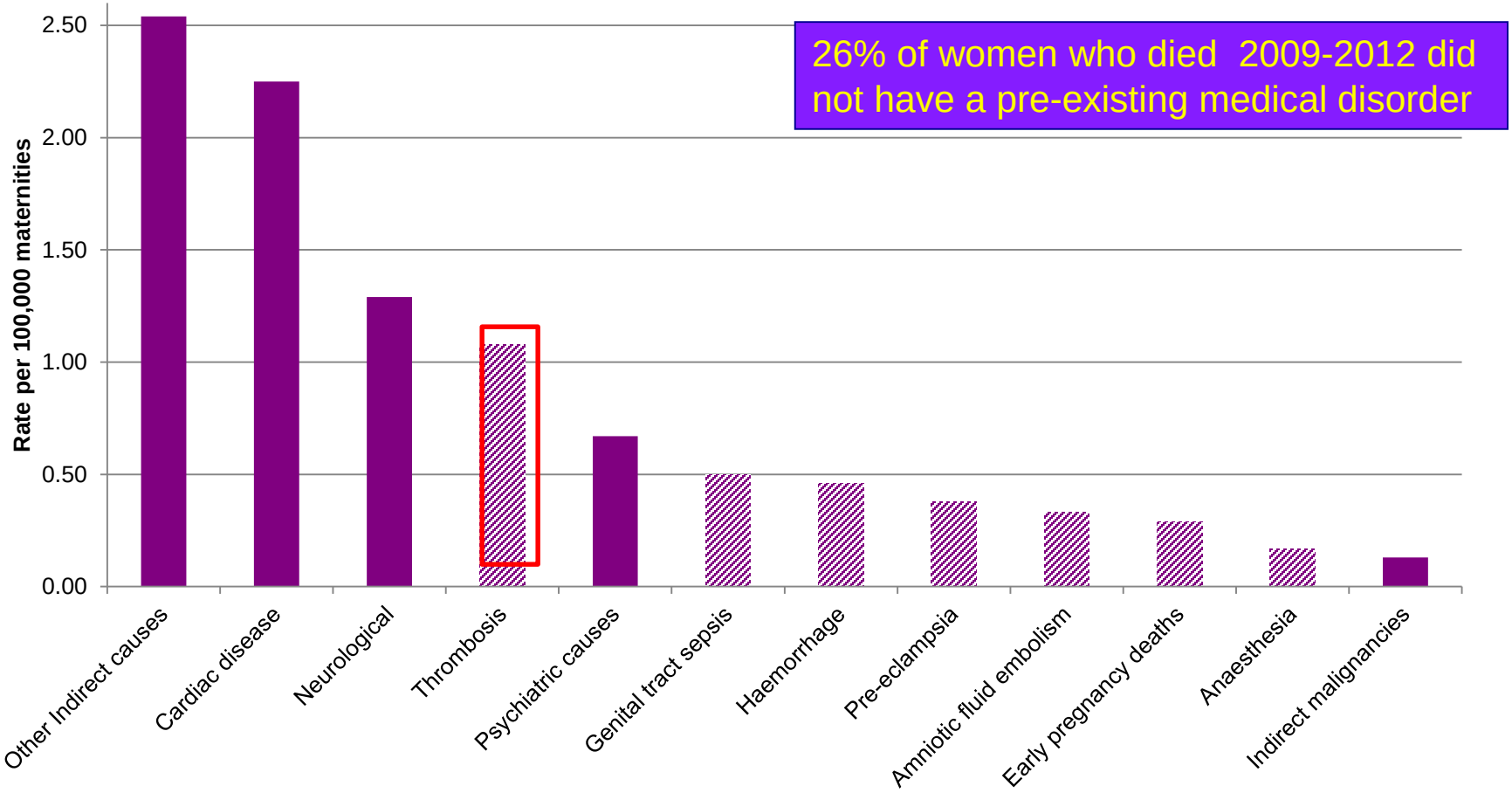
QUẢN LÝ THUYÊN TẮC PHỔI TRONG THAI KỲ

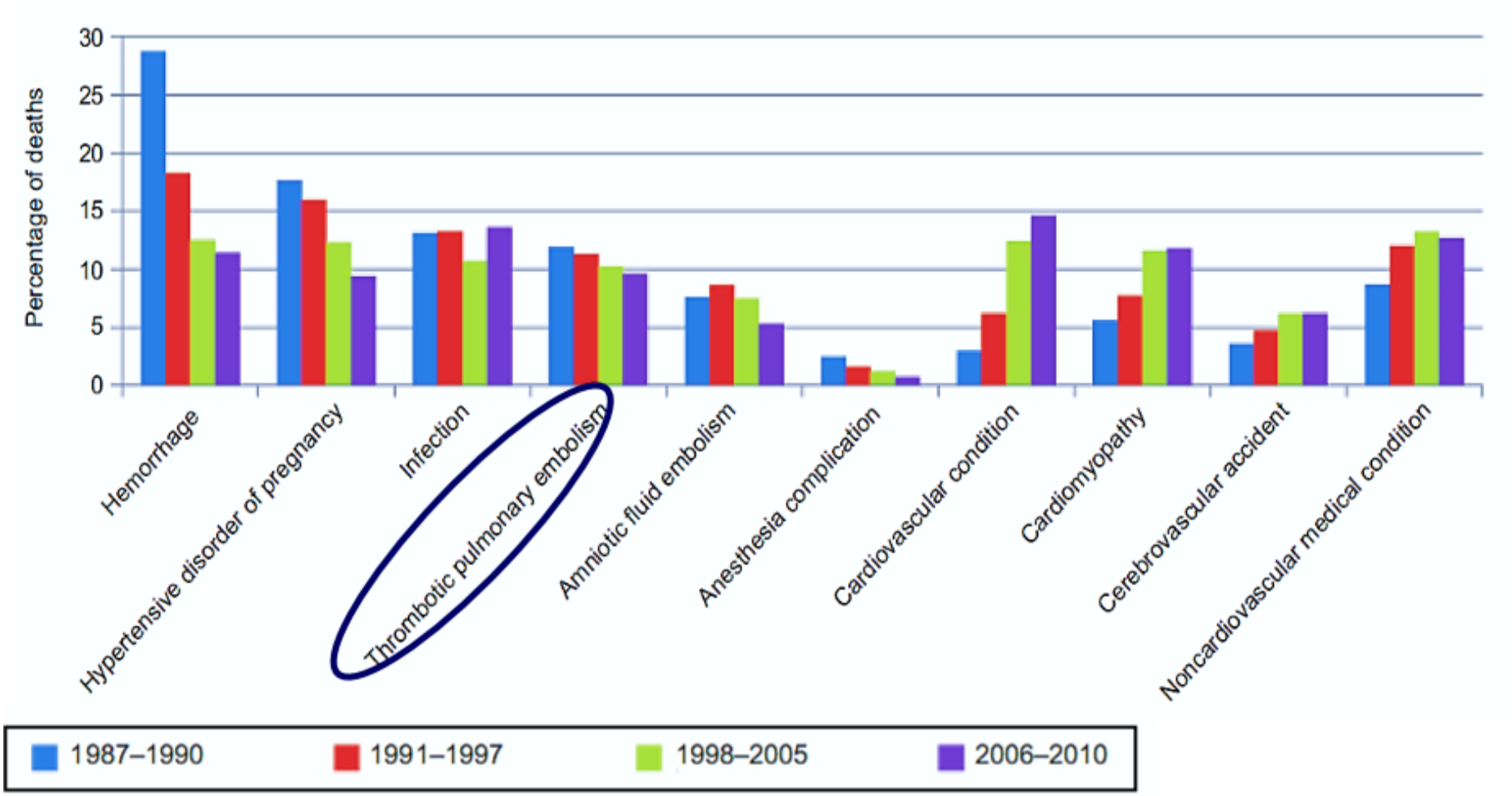
BS BÙI THẾ DŨNG
KHOA NỘI TIM MẠCH
BV ĐẠI HỌC Y DƯỢC

Causes of maternal death



Solid bars show indirect causes, hatched bars show direct causes

PREGNANCY- RELATED MORTALI TY IN THE U.S (1987 – 2010)



Creanga AA, et al. Obstet Gynecol 2015;125:5–12

Columbia University Medical Center

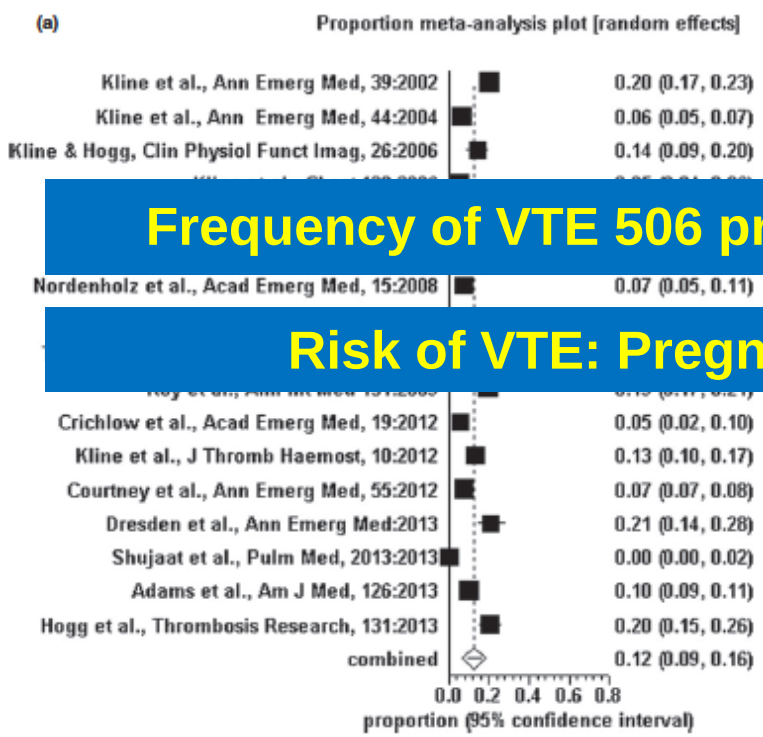
ACOG

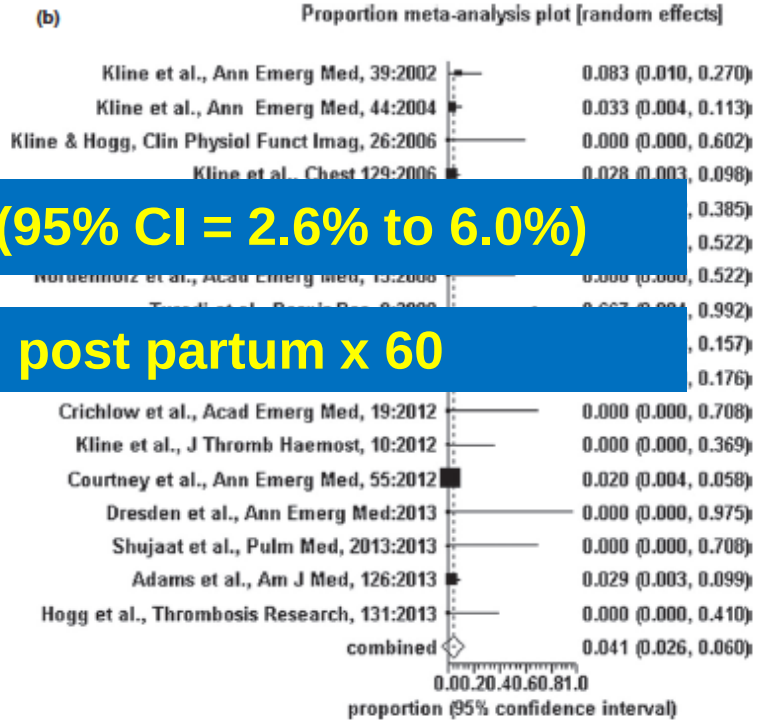
Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

EVIDENCE-BASED DIAGNOSTICS

Systematic Review and Meta-analysis of Pregnant Patients Investigated for Suspected Pulmonary Embolism in the Emergency Department

Jeffrey A. Kline, MD, Danielle M. Richardson, Martin P. Than, MBBS, Andrea Penaloza, MD, PhD, and Pierre-Marie Roy, MD

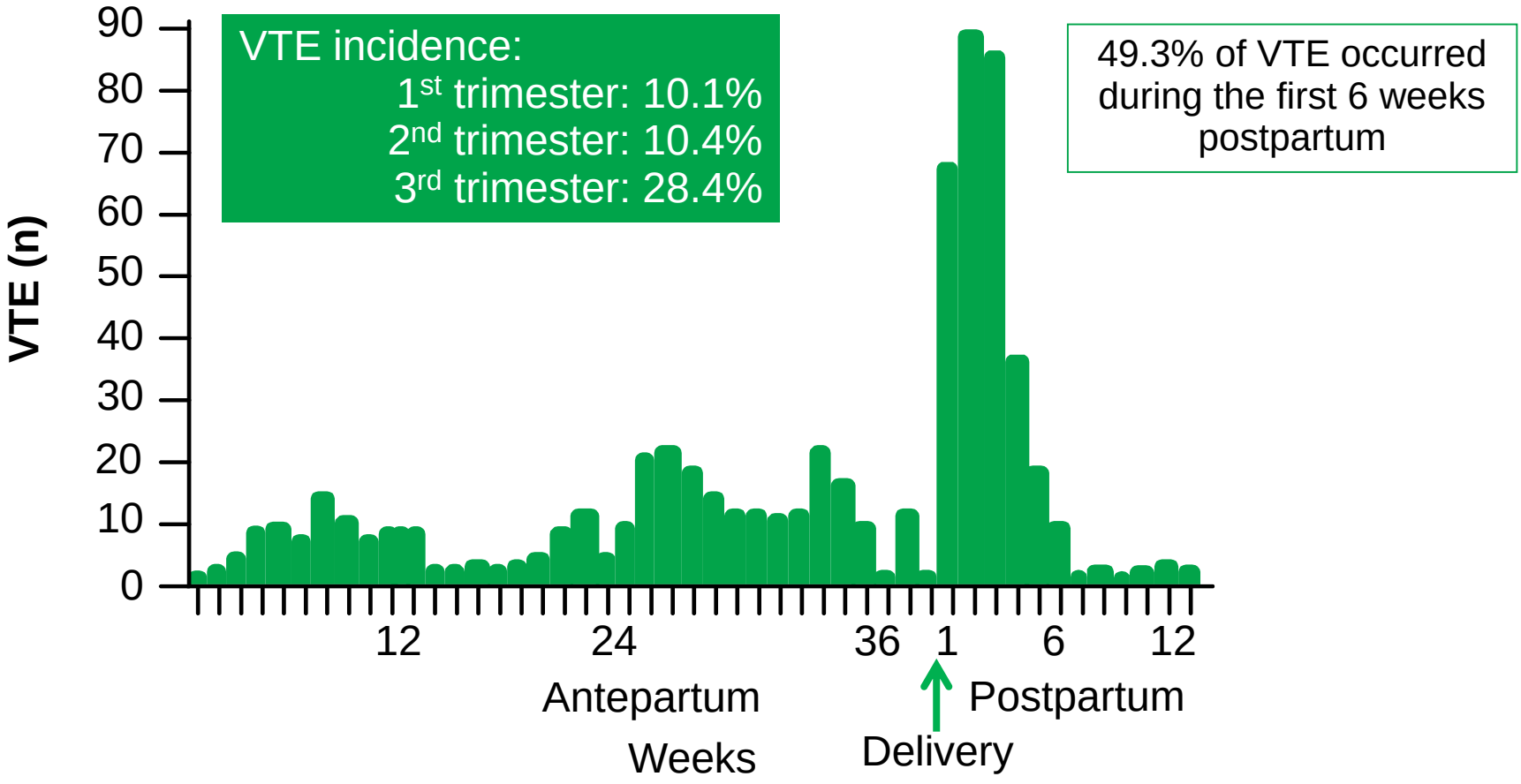




Frequency of VTE 506 preg 4.1% (95% CI = 2.6% to 6.0%)

Risk of VTE: Pregnancy x 5, post partum x 60

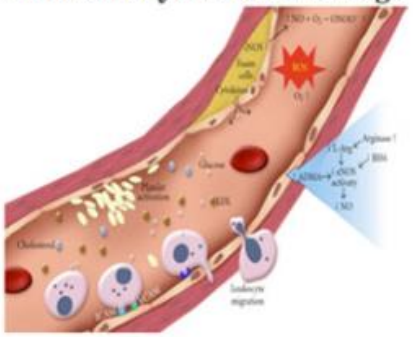
Distribution of VTE in pregnancy and puerperium



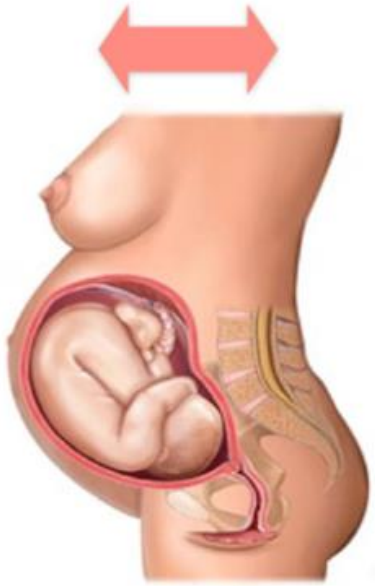
Jacobsen *et al*. *Am J Obstet Gynecol* 2008;198(2):233.e1–7

Virchow’s triad in pregnancy

Endothelial dysfunction/damage

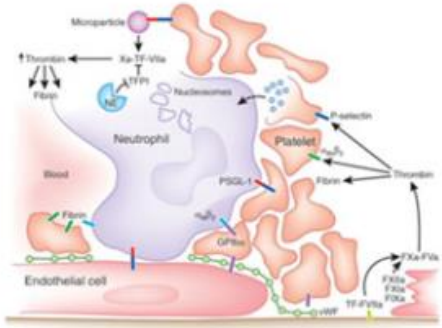


Venous stasis



- Progesterone-mediated increases in venous distensibility and capacity
- Right iliac artery has a compressive effect on the left common iliac vein
- The uterus induced a compressive effect on the common iliac vein

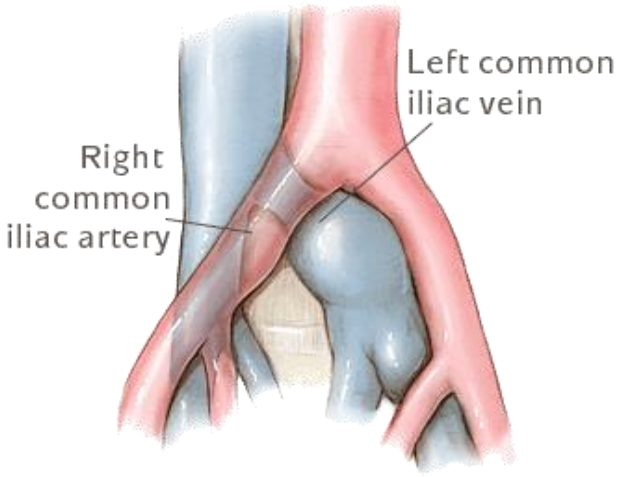
- Increased circulating levels of clotting factors I, II, VII, VIII, IX, and X
- Protein S levels declined
- Platelet activation is increased
- Generation of fibrin increased, and fibrinolytic activity is decreased



Thrombophilic milieu

DVT in Pregnancy

- 88% on left (vs. 55% in non pregnant)
- 71% proximal (vs. 9% in non pregnant)
  - ✓ 64% were restricted to the iliac and/or femoral vein.



PE incidence was higher postnatally (0.22 vs. 0.06/1,000 deliveries)

Chan WS et al. CMAJ 2010; 182:657-600

REDUCING THE RISK OF VTE DURING PREGNANCY AND PUERPERIUM

- VTE risk assessment tools should be applied to every patient

- Risk assessment tools are based on recommendations from major society guidelines:
  - ✓ American College of Obstetricians and Gynecology (ACOG)
  - ✓ American College of Chest Physicians (ACCP)
  - ✓ Royal College of Obstetricians and Gynaecologists (RCOG)

- Pharmacologic prophylaxis may be with unfractionated heparin (UFH) or low-molecular weight heparin (LMWH)

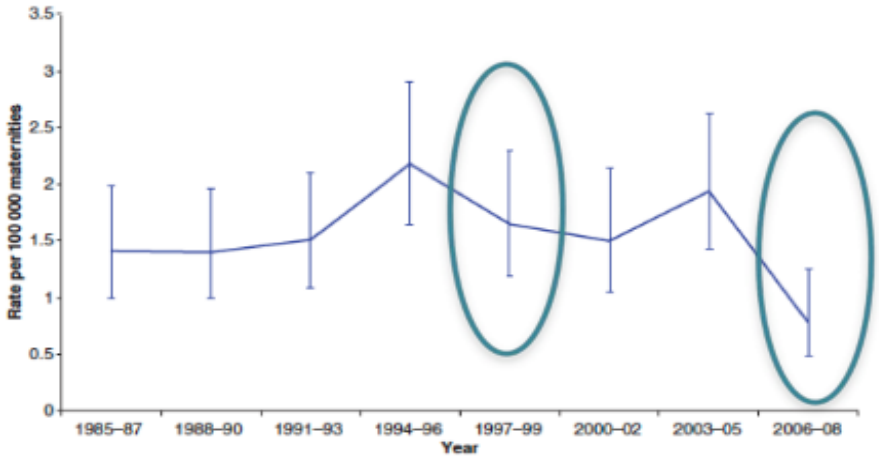
Chest, Feb 2012; 141
ACOG Practice Bulletin No 123, 2011
RCOG, 2015 Green Top 37a

COLUMBIA UNIVERSITY MEDICAL CENTER

ACOG THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

Impact of RCOG guidelines

- RCOG guideline 1995
  - Highlighted risks of C-section and VTE
    - LMWH recommended with additional risk factors
- RCOG guideline 2004
  - Risk assessment following vaginal delivery
  - LMWH recommended with additional risk factors



Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

First Prenatal Visit - ACOG Practice 2011

Clinical history	Anticoagulation
• Multiple VTE episodes • VTE with high-risk (HR) thrombophilia • VTE with acquired thrombophilia	Treatment dose LMWH or UFH
• Idiopathic VTE • VTE with pregnancy or oral contraceptive • VTE with low risk (LR) thrombophilia • Family history of VTE with HR thrombophilia • HR thrombophilia	Prophylactic LMWH or UFH
• 1st VTE provoked • Family history of VTE with LR thrombophilia • LR thrombophilia (no prior event)	No treatment

High-risk thrombophilia:Homozygous Factor V Leiden or prothrombin gene mutation, antithrombin III deficiency, compound heterozygote disorders. Low-risk thrombophilia: Heterozygous Factor V Leiden or prothrombin gene mutation, Protein C or S deficiency. Acquired thrombophilia: Antiphospholipid antibody syndrome.

ACCP RECOMMENDATIONS

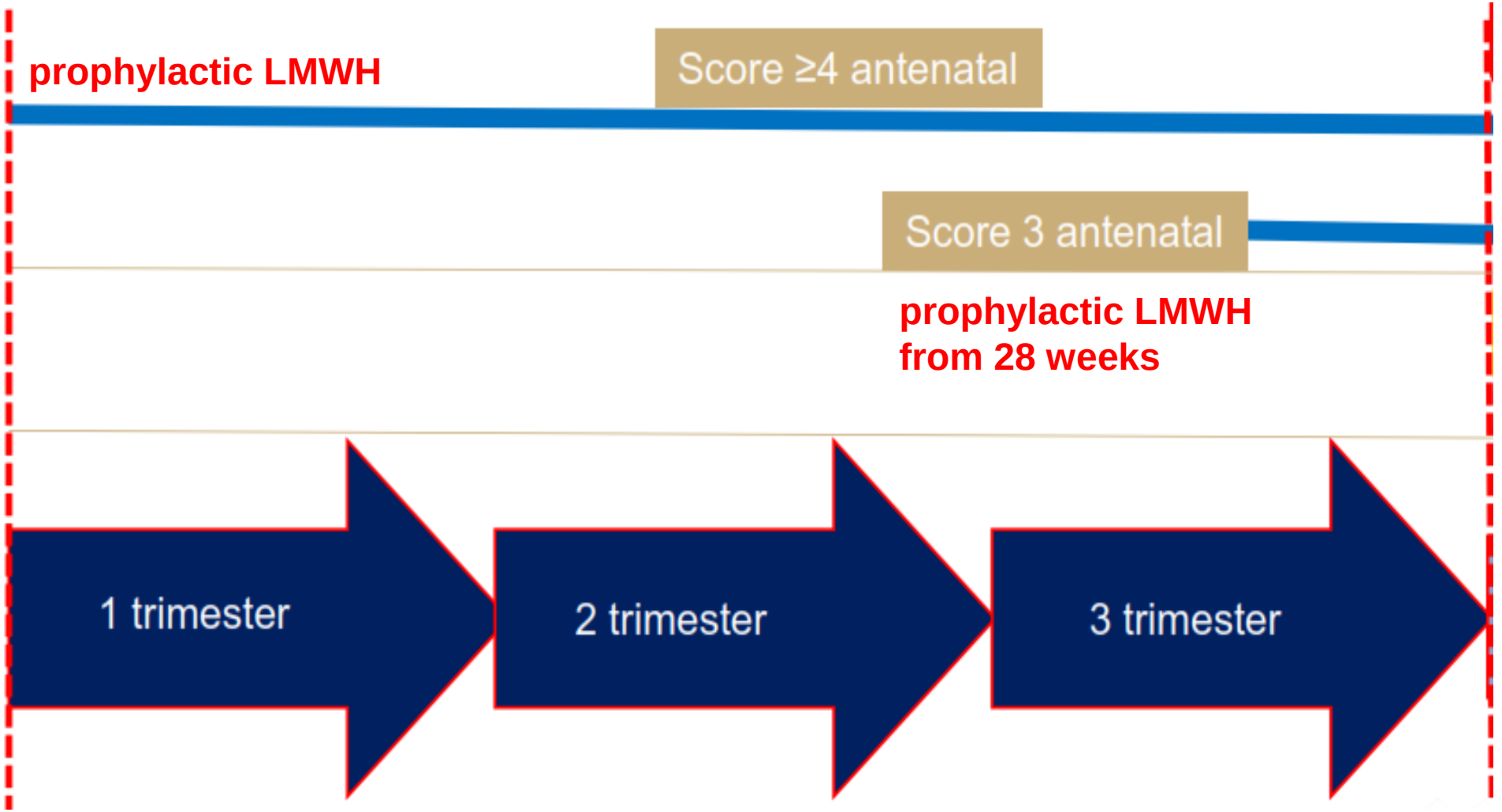
- Pharmacologic prophylaxis (LMWH) recommended → **one major** or **two or more minor** risk factors
- Mechanical prophylaxis recommended → contraindications to pharmacologic prophylaxis

MAJOR RISK FACTORS	MINOR RISK FACTORS

• Immobility (strict bed rest ≥1 week in the antepartum period)
• Postpartum haemorrhage ≥1000 mL with surgery
• Previous VTE
• Preeclampsia with fetal growth restriction
• Thrombophilia
  Antithrombin deficiency
  Factor V Leiden (homozygous or heterozygous)
  Prothrombin G20210A (homozygous or heterozygous)
• Medical conditions
  Systemic Lupus erythematosus
  Heart disease
  Sickle cell disease
• Blood transfusion
• Postpartum infection
	• BMI >30 kg/m2
	• Multiple pregnancy
	• Emergency caesarean
	• Smoking >10 cigarettes/day
	• Fetal growth restriction
	• Thrombophilia
	  Protein C deficiency
	  Protein S deficiency
	• Preeclampsia

Chest, Feb 2012; 141

VTE Risk Score: RCOG (early pregnancy)



VTE Risk Score: RCOG (post-partum)

- any previous VTE
- all pregnant women with antenatal medicinal VTE prophylaxis
- High-risk thrombophilia (hereditary defects, e.g. antithrombin deficiency, combined thrombophilic defects, homozygous factor-
- V Leiden or prothrombin mutation)
- Low-risk thrombophilia + positive family history

→ **VTE risk HIGH**
Postnatal NMH in prophylactic dosage for at least 6 weeks

- secondary section
- BMI ≥ 40 kg/m2
- in case of prolonged (≥ 3 days) or renewed hospital stay
- any surgical intervention (except episiotomy, treatment of injuries to the perineum)
- comorbidity e.g. cancer, heart failure, active lupus erythematosus, nephrotic syndrome, diabetes mellitus type I with nephropathy, inflammatory bowel disease, sickle cell anemia, current intravenous drug dependence

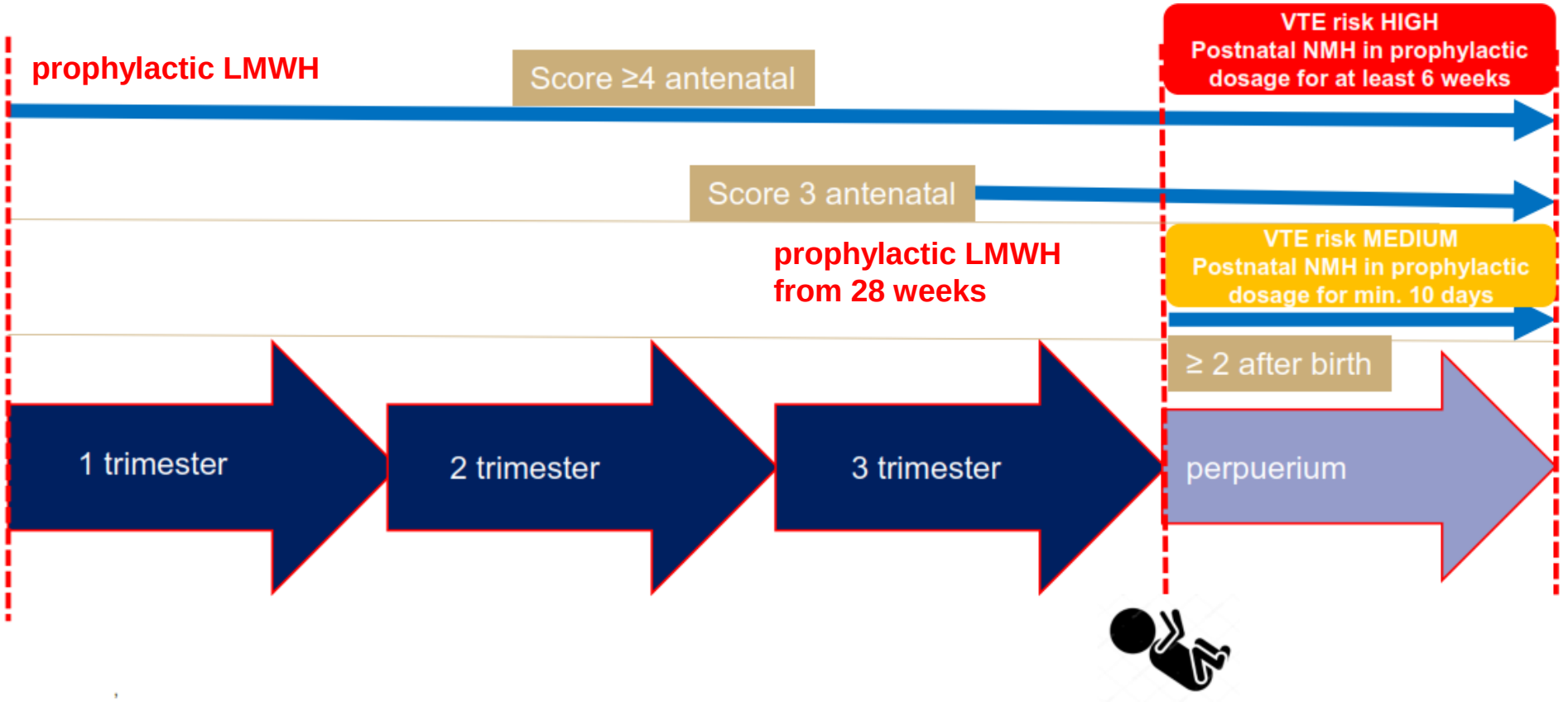
→ **VTE risk MEDIUM**
Postnatal NMH in prophylactic dosage for min. 10 days

- Age > 35 years
- BMI ≥ 30 kg/m2 Parity ≥ 3
- Smoking elective section
- positive family history
- Low-risk thrombophilia (e.g. homozygous factor V Leiden or prothrombin mutation)
- pronounced varicosis
- current systemic infection
- Immobility e.g. paraplegia, long-distance travel
- Preeclampsia in current pregnancy
- multiple pregnancy
- Premature birth < 37. SSW in current pregnancy
- stillbirth in current pregnancy
- vaginal-operative delivery from the middle of the pelvis
- protracted course of birth (> 24 hours)
- postpartum bleeding > 1 liter or blood transfusion

≥2 Risk factors → **VTE risk MEDIUM**
Postnatal NMH in prophylactic dosage for min. 10 days

<2 Risk factors → **VTE risk LOW**
Early mobilisation and prevention Dehydration

RCOG Score, Risk Factors, and prophylactic treatment



Thromboprophylactic Doses of LMWH

Weight (kg)	Enoxaparin	Dalteparin	Tinzaparin (75u/kg/day)
< 50	20 mg daily	2500 units daily	3500 units daily
50–90	40 mg daily	5000 units daily	4500 units daily
91–130	60 mg daily*	7500 units daily*	7000 units daily*
131–170	80 mg daily*	10 000 units daily*	9000 units daily*
> 170	0.6 mg/kg/day*	75 units/kg/day*	75 u/kg/day*
High prophylactic (intermediate) dose for women weighing 50–90 kg	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Treatment dose	1 mg/kg/12 hourly antenatal; 1.5 mg/kg/daily postnatal	100 units/kg/12 hourly or 200 units/kg/daily postnatal	175 u/kg/daily (antenatal and postnatal)

* may be given in two divided doses

RCOG Green-top Guideline No. 37

Chẩn đoán PE trong thai kỳ có gì khác biệt???

Guideline summary on clinical prediction rules and D-Dimer testing for suspected PE in pregnancy

Guideline summary on clinical prediction rules	Recommendation
Working Group in Women's Health the Society of Thrombosis and Haemostasis (GTH 2016)	No recommendation
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"Clinicians should be aware that, at present, there is no evidence to support the use of pretest probability assessment in the management of acute VTE in pregnancy." (Grade A recommendation)
European Society of Cardiology (ESC 2014)	No recommendation
Society of Obstetricians and Gynecologist of Canada (SOGC 2014)	"Neither D-dimer alone nor clinical prediction rules should be used to rule out VTE in pregnant women without objective testing." (Class D recommendation)
Australia and N (2012)	
American Thora	
European Assoc	

Neither D-Dimer alone nor clinical prediction rules should be used to rule out VTE in pregnant women without objective testing

Guideline sur	
Working Group Haemostasis	ormal D-dimer test
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"D-dimer testing should not be performed in the investigation of acute VTE in pregnancy." (Grade D recommendation)
European Society of Cardiology (ESC 2014)	"D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients." (Class IIb recommendation)
Society of Obstetricians and Gynecologist of Canada (SOGC 2014)	"Neither D-dimer alone nor clinical prediction rules should be used to rule out VTE in pregnant women without objective testing." (Class D recommendation)
Australia and New Zealand Guidelines (ANZ), endorsed by ASTH & SOMANZ (2012)	No recommendation
American Thoracic Society/Society of Thoracic Radiology (ATS/STR 2011)	"In pregnant women with suspected PE, we suggest that D-dimer not be used to exclude PE." (Weak recommendation)
European Association of Nuclear Medicine (EANM 2009)	No recommendation

Modified Wells score validation in pregnancy

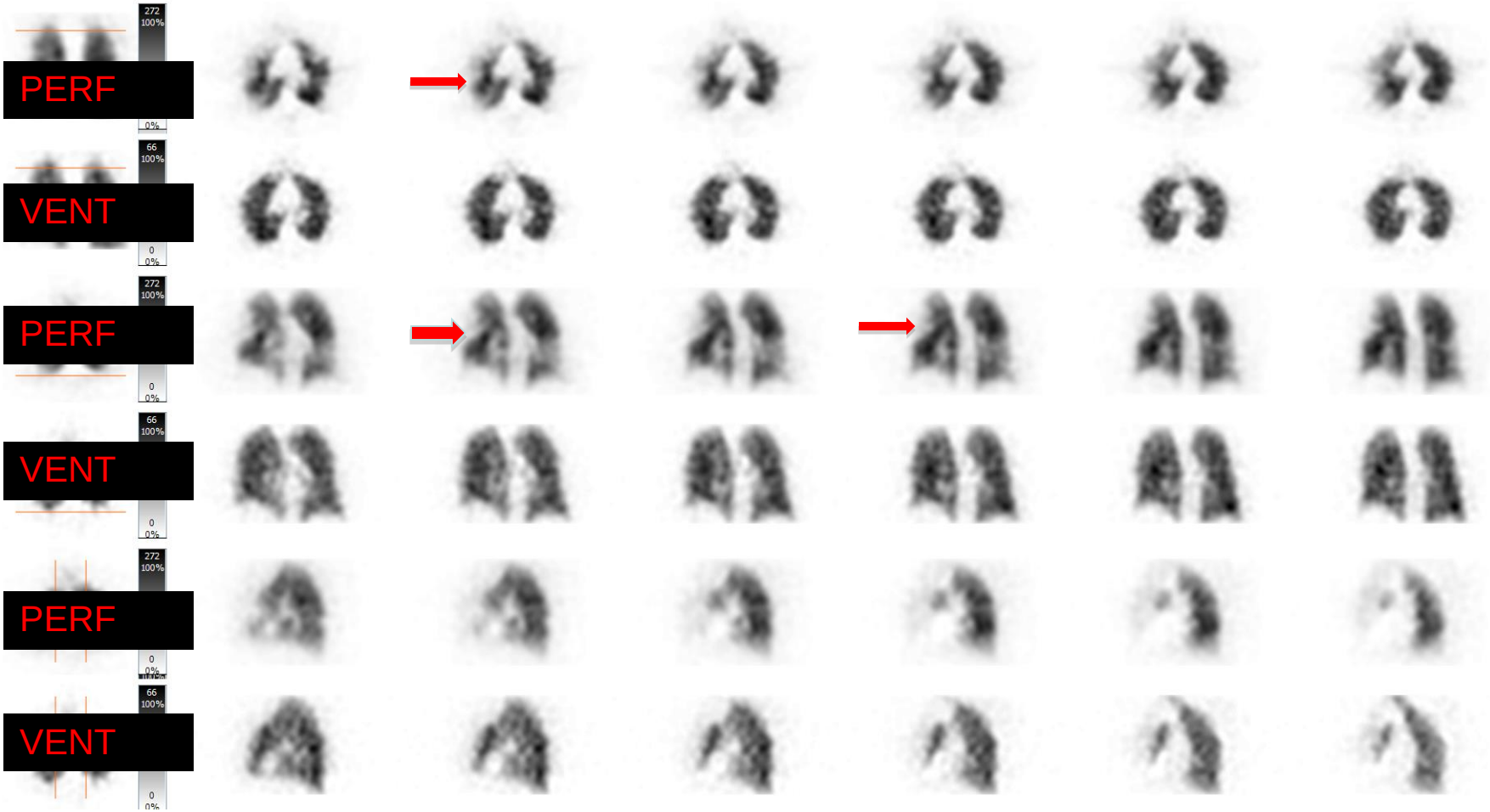
Clinical condition	Score
Clinical evidence of a DVT	3.0
Other diagnosis less likely	3.0
Tachycardia	1.5
Immobilization or surgery in past 4 weeks	1.5
History of DVT or PE	1.5
Haemoptysis	1.0
Malignancy (treatment in past 6 months)	1.0
Modified Wells score >6 = High VTE risk (59 % probability based on pooled data)	

Guideline summary on V/Q scan and CTPA for suspected PE in pregnancy

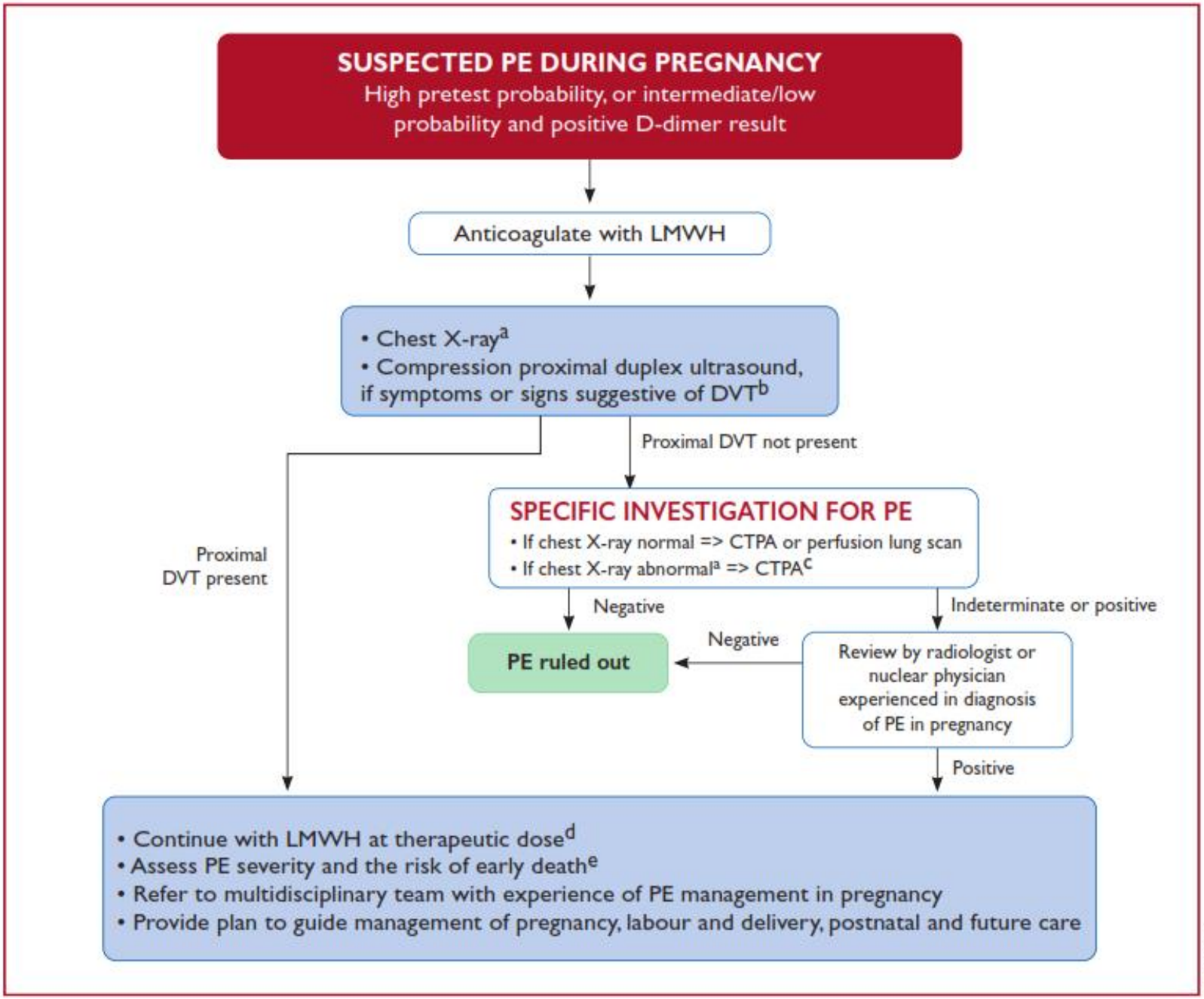
Guideline	Recommendation
Working Group in Women's Health the Society of Thrombosis and Haemostasis (GTH 2016)	"If lung scintigraphy is available, a low-dose perfusion scan is the preferred imaging technique to diagnose or exclude pregnancy-associated PE in women with normal chest X-ray (CXR) because this method exposes maternal breasts to less radiation than CTPA. If an initial CXR is abnormal or if lung scintigraphy is non-conclusive or not available, CTPA should be prioritized."
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"In women with suspected PE without symptoms and signs of DVT, a V/Q lung scan or a CTPA should be performed." (Grade C recommendation) "When the CXR is abnormal and there is clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan." (Grade D recommendation) "Alternative or repeat testing should be carried out where V/Q scan or CTPA is normal
E	n
S	y
Australia and New Zealand Guidelines (ANZ), endorsed by ASTH & SOMANZ (2012)	"V/Q scanning is the preferred investigation in pregnant or postpartum women with suspected PE who have a normal CXR." (Level 1 group consensus) "CTPA should be used in women with an abnormal CXR or where V/Q scanning is inconclusive or not available." (Level 1 group consensus)
American Thoracic Society/Society of Thoracic Radiology (ATS/STR 2011)	"In pregnant women with suspected PE and a normal CXR, we recommend lung scintigraphy as the next imaging test rather than CTPA." (Strong recommendation) "In pregnant women with suspected PE and an abnormal CXR, we suggest CTPA as the next imaging test rather than lung scintigraphy." (Weak recommendation)
European Association of Nuclear Medicine (EANM 2009)	"In pregnancy, particularly during the first trimester, a 2-day protocol starting with a perfusion-only scan followed if necessary by a second day ventilation study." (Grade C recommendation)

normal CXR → V/Q lung scan
abnormal CXR → CTPA

Abnormal V/Q SPECT



** Normal V/Q: 0.8 - 1*


SUSPECTED PE DURING PREGNANCY
High pretest probability, or intermediate/low probability and positive D-dimer result
Anticoagulate with LMWH
• Chest X-ray[a]
• Compression proximal duplex ultrasound, if symptoms or signs suggestive of DVT[b]
Proximal DVT not present
Proximal DVT present
SPECIFIC INVESTIGATION FOR PE
• If chest X-ray normal => CTPA or perfusion lung scan
• If chest X-ray abnormal[a] => CTPA[c]
Negative
Indeterminate or positive
PE ruled out
Negative
Review by radiologist or nuclear physician experienced in diagnosis of PE in pregnancy
Positive
• Continue with LMWH at therapeutic dose[d]
• Assess PE severity and the risk of early death[e]
• Refer to multidisciplinary team with experience of PE management in pregnancy
• Provide plan to guide management of pregnancy, labour and delivery, postnatal and future care
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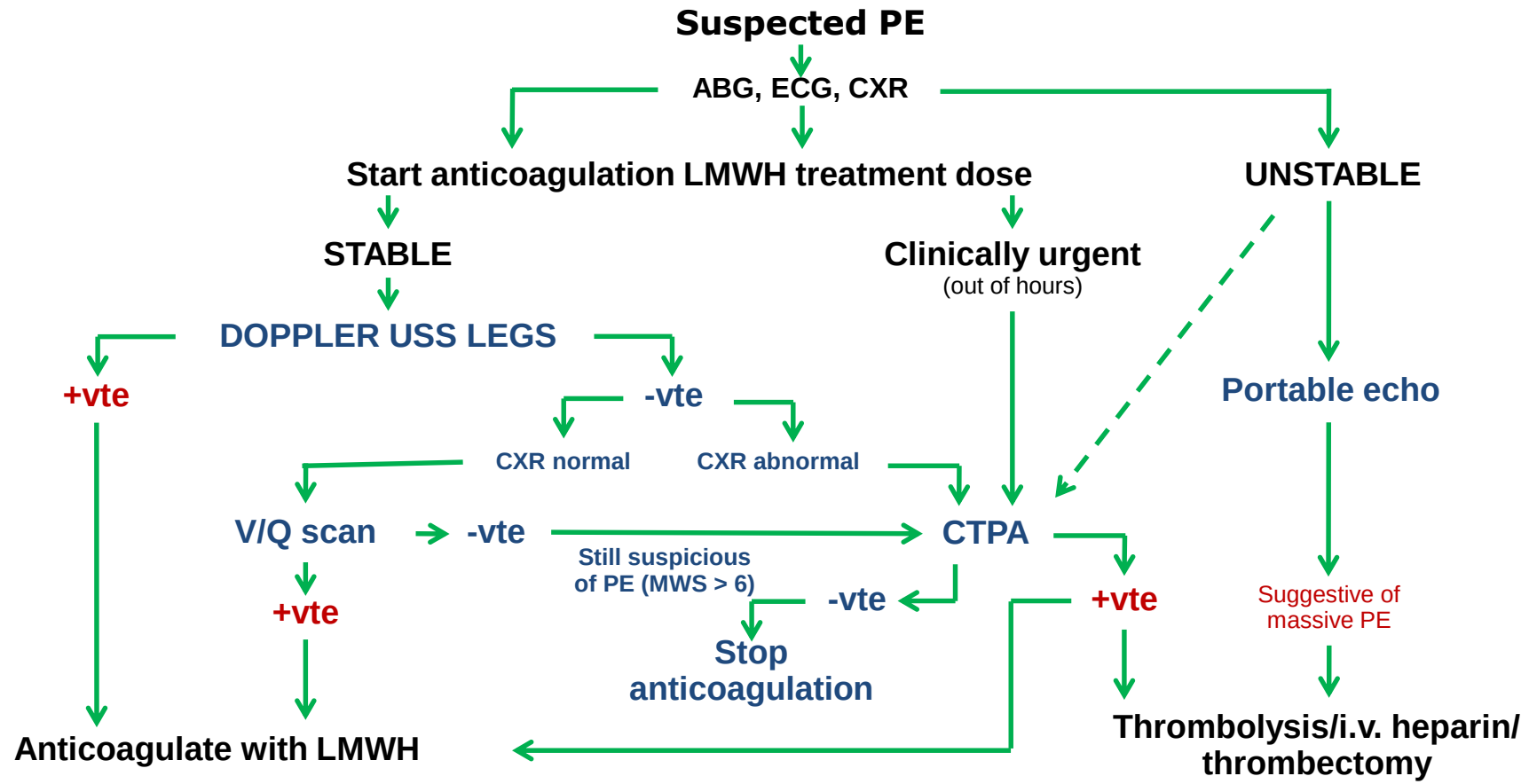
Diagnostic algorithm for PE in pregnancy



ABG, arterial blood gas;
ECG, electrocardiogram;
CXR, Chest X-ray;
USS, ultrasound sonography;
CTPA, computerised tomography pulmonary angiography

Scarsbrook *et al*. *Clin Radiol* 2006;61:1–12

Anticoagulant treatment of VTE in pregnancy

In clinically suspected DVT or PE, treatment with low-molecular-weight heparin (LMWH) should be commenced immediately until the diagnosis is excluded by objective testing, unless treatment is strongly contraindicated.

B

Booking or early pregnancy weight	Initial dose of enoxaparin
< 50 kg	40 mg twice daily or 60 mg once daily
50–69 kg	60 mg twice daily or 90 mg once daily
70–89 kg	80 mg twice daily or 120 mg once daily
90–109 kg	100 mg twice daily or 150 mg once daily
110–125 kg	120 mg twice daily or 180 mg once daily
> 125 kg	Discuss with haematologist

(booking weight :body weight at the first antenatal appointment with the gynaecologist, e.g. 8–10 weeks of pregnancy)

RCOG Green-top guideline 37b 2015

Thrombectomy

- Fetal death 20 – 40%
- Mother risk is low

Thrombolytic therapy

- rtPA, streptokinase, tenecteplase: do not cross the placenta
- Maternal bleeding: 1 – 6%, maternal death: 1%
- Fetal loss: 1 – 2%

Martillotti. Treatment options for severe pulmonary embolism during pregnancy and the postpartum period: a systematic review. *Journal of Thrombosis and Haemostasis*, 15:1942–1950

Maintenance treatment of PE

Treatment with therapeutic doses of subcutaneous LMWH should be employed during the remainder of the pregnancy and for at least 6 weeks postnatally and until at least 3 months of treatment has been given in total. **B**

Women should be taught to self-inject LMWH and arrangements made to allow safe disposal of needles and syringes. Outpatient follow-up should include clinical assessment and advice with monitoring of blood platelets and peak anti-Xa levels if appropriate (see sections 5 and 6.3). **C**

Because of their adverse effects on the fetus, vitamin K antagonists, such as warfarin, should not be used for antenatal VTE treatment. **C**

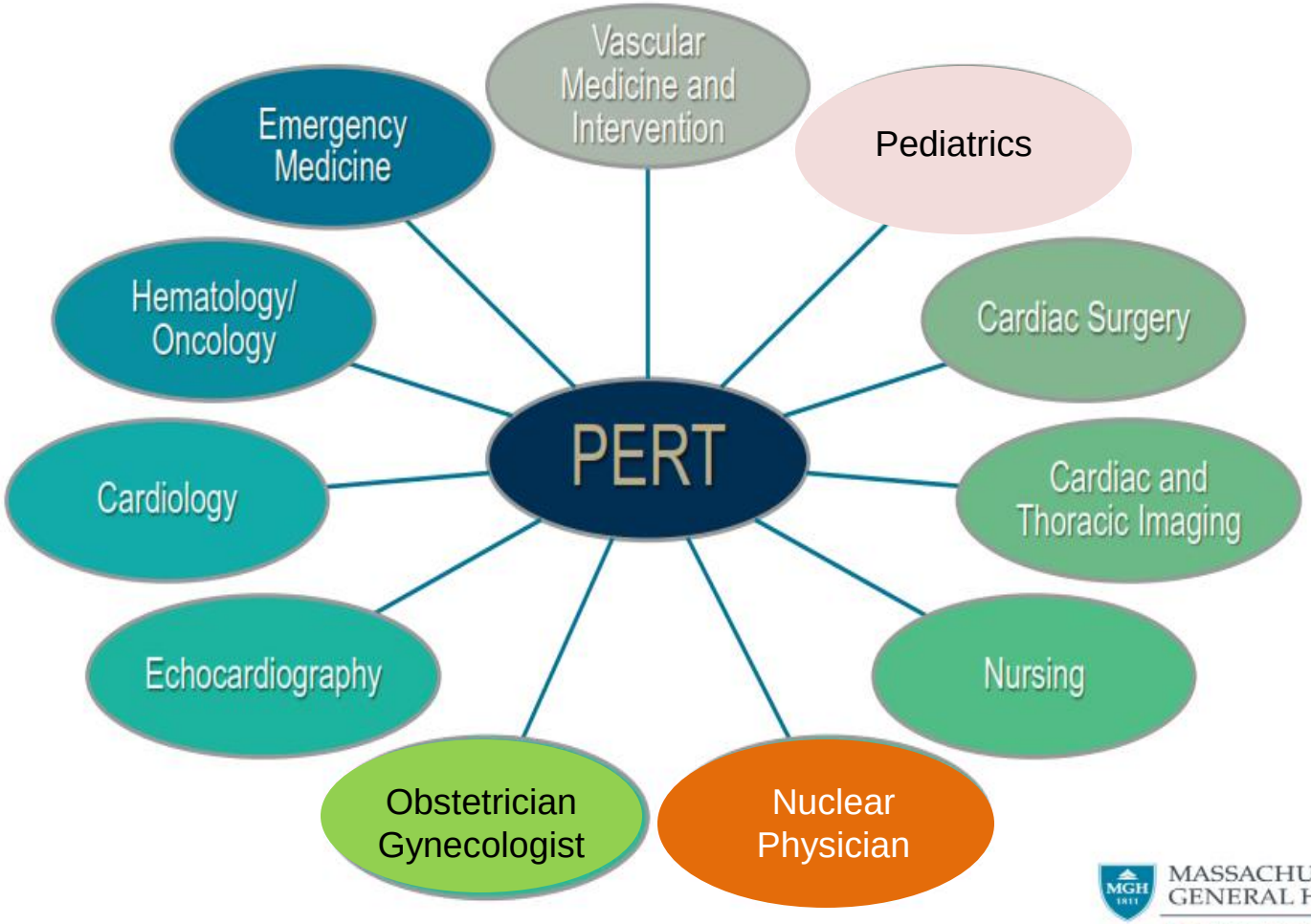
Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding. **D**

RCOG Green-top guideline 37b 2015

Recommendations for the prevention and treatment of VTE

Recommendations	Class	level
A documented assessment of risk factors for VTE before or in early pregnancy is recommended in all women	I	C
For high-risk women, it is recommended to give a weight-related prophylactic dose of LMWH	I	B
Thrombolytics to manage patients with pulmonary embolism is only recommended in patients with severe hypotension or shock	I	C
In women on therapeutic LMWH, planned delivery should be considered at around 39 weeks	IIa	C
NOACs are not recommended during pregnancy or lactation	III	C

Role of PERT (PE Responde Teams)



MASSACHUSETTS GENERAL HOSPITAL
INSTITUTE FOR HEART, VASCULAR AND STROKE CARE

Modified from MGH

DIỄN TIẾN MUỘN CỦA THUYÊN TẮC PHỔI

Diễn tiến PE với kháng đông

- Cục máu đông tiêu dần sau 3 tháng trong đa số các TH → không cần chụp CT kiểm tra thường quy
- Cục máu đông tổ chức hóa → CTEPH* (< 10%)
- Khó thở + giảm gắng sức kéo dài sau PE:

  Không phải CTEPH (20 – 75% PE)

→ Chăm sóc BN sau PE:

1. Phục hồi chức năng, điều trị bệnh đồng mắc và nguy cơ tim mạch, giáo dục hành vi…
2. Phát hiện sớm CTEPH

ESC guidelines. *European Heart Journal* (2019) 00,161

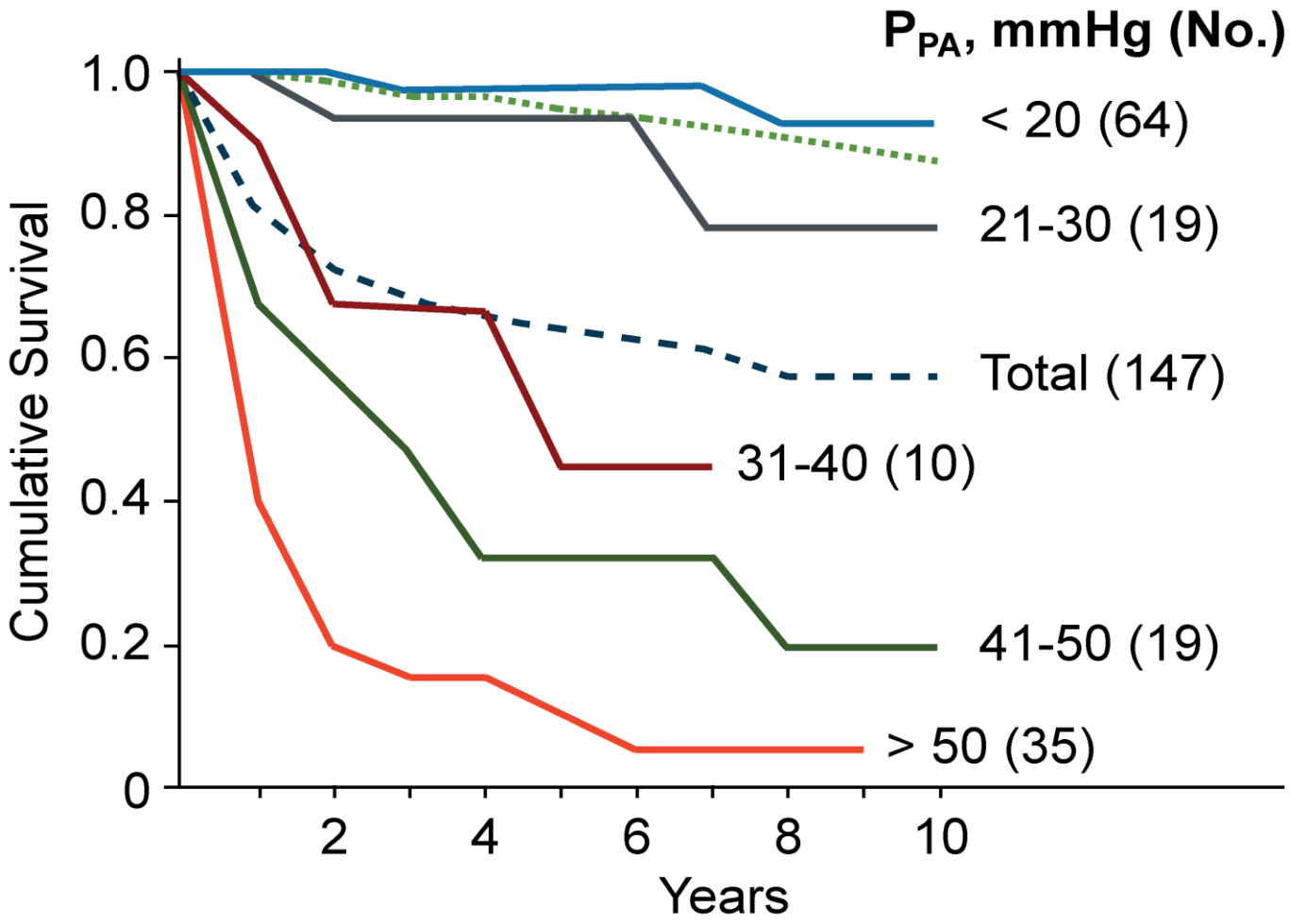
Triệu chứng kéo dài “cơ năng” sau PE

- Kéo dài 6 tháng – 3 năm sau PE
- Thăm dò CN phổi, siêu âm tim: bình thường
- Yếu tố dự đoán: cao tuổi, bệnh tim phổi đồng mắc, béo phì, hút thuốc, tăng áp ĐMP và suy thất phải khi PE
- Không liên quan với “tiêu sợi huyết” trong giai đoạn cấp

ESC guidelines. *European Heart Journal* (2019) 00,161

Patients With Untreated CTEPH

Survival and mean P_{PA}



Riedel M et al.

Green dotted line represents predicted survival among men 40-50 years old.

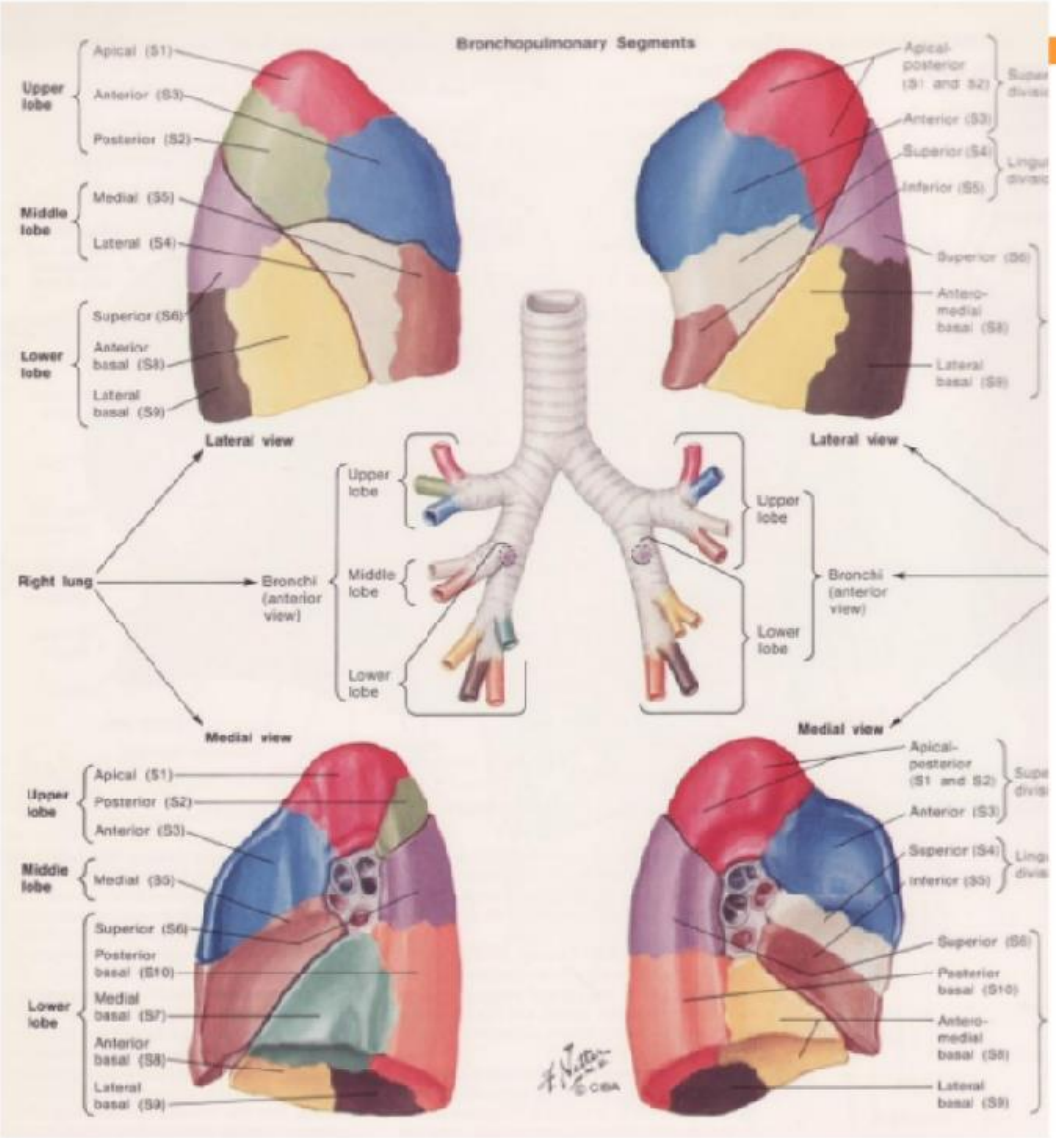
Risk factors for CTEPH

Findings related to the acute PE event (obtained at PE diagnosis)	Concomitant chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3–6 month follow-up)
Previous episodes of PE or DVT	Ventriculo-atrial shunts
Large pulmonary arterial thrombi on CTPA	Infected chronic i.v. lines or pacemakers
Echocardiographic signs of PH/RV dysfunction	History of splenectomy
CTPA findings suggestive of pre-existing chronic thromboembolic disease	Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels
	Non-O blood group
	Hypothyroidism treated with thyroid hormones
	History of cancer
	Myeloproliferative disorders
	Inflammatory bowel disease
	Chronic osteomyelitis

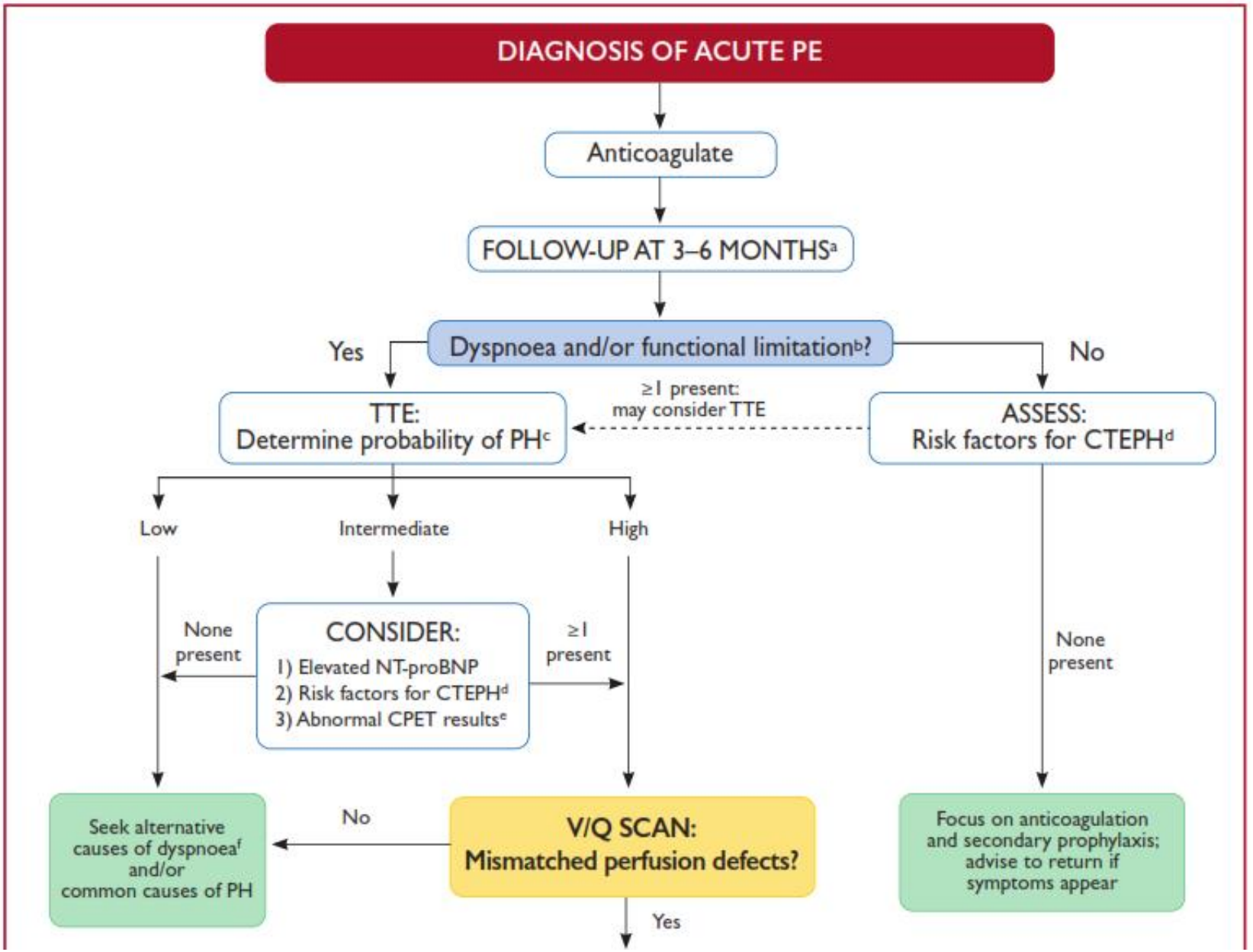
Bonderman D et al. Risk factors for chronic thromboembolic pulmonary hypertension *Eur Respir J* 2003:325–331

Methods: Qanadli index

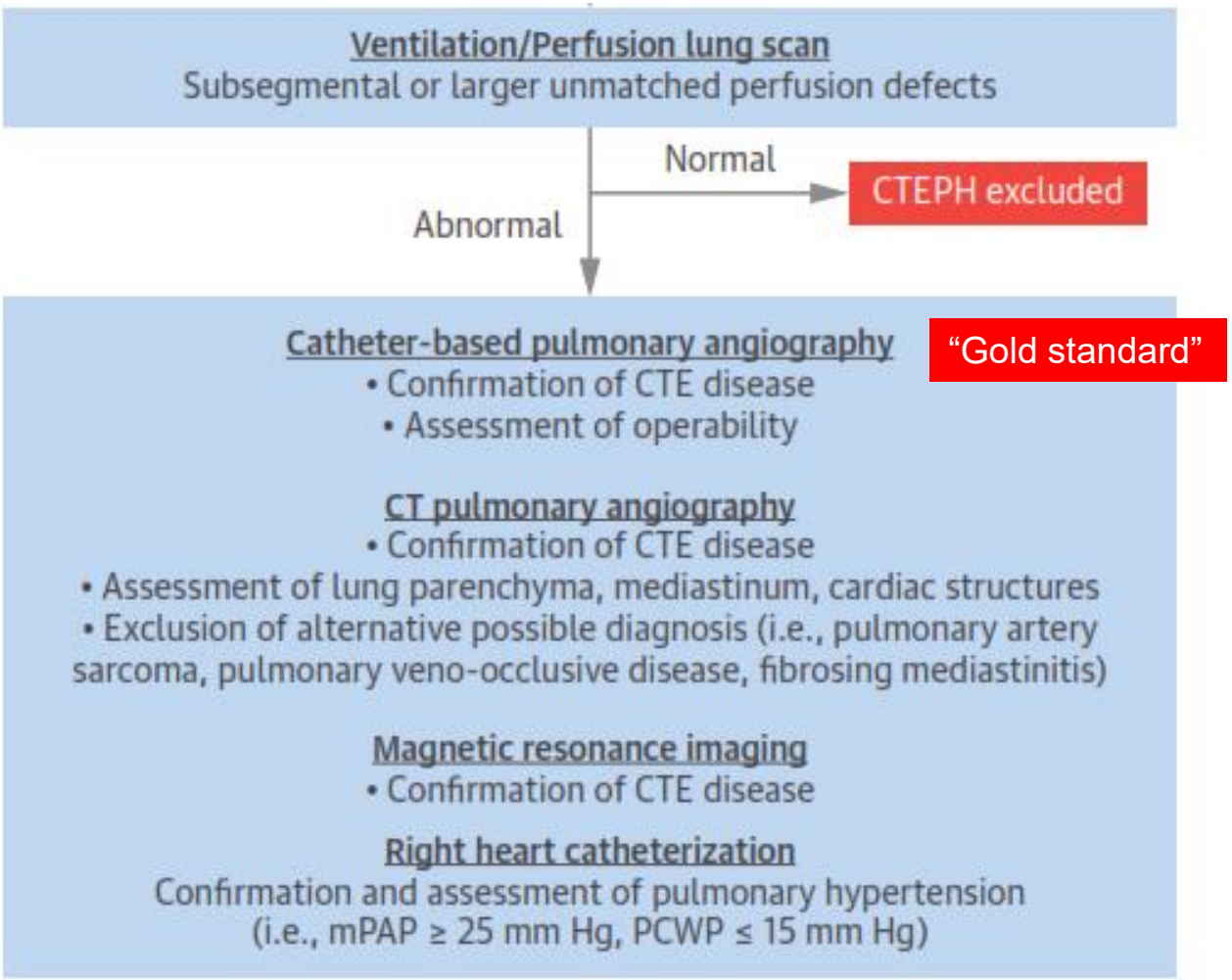
- Severity of pulmonary embolism
- Computation depends on artery occlusion level
  - +0: no occlusion
  - +1: partial
  - +2 : complete occlusion



10 đoạn động mạch ở mỗi phổi
Tắc nghẽn nặng khi thang điểm Qanadli (QS) > 18/40 điểm.



ESC guidelines. *European Heart Journal* (2019) 00,161



Mahmud et al. Chronic Thromboembolic Pulmonary Hypertension. *JACC* vol. 71, NO. 21, 2018

Comparing V/Q and CTPA: Which is the Preferred Strategy in Clinical Practice?

Performance Indicators for V/Q Scintigraphy and CTPA[a]

Indicator	Scintigraphy		CTPA
	V/Q (1)[b]	V/Q (2)[c]	
Sensitivity, %	97.4	96.2	51.3
Specificity, %	90	94.6	99.3

The sensitivity of the V/Q scan is almost 50 percent greater than that of CTPA (>96 vs ~51 percent, respectively)

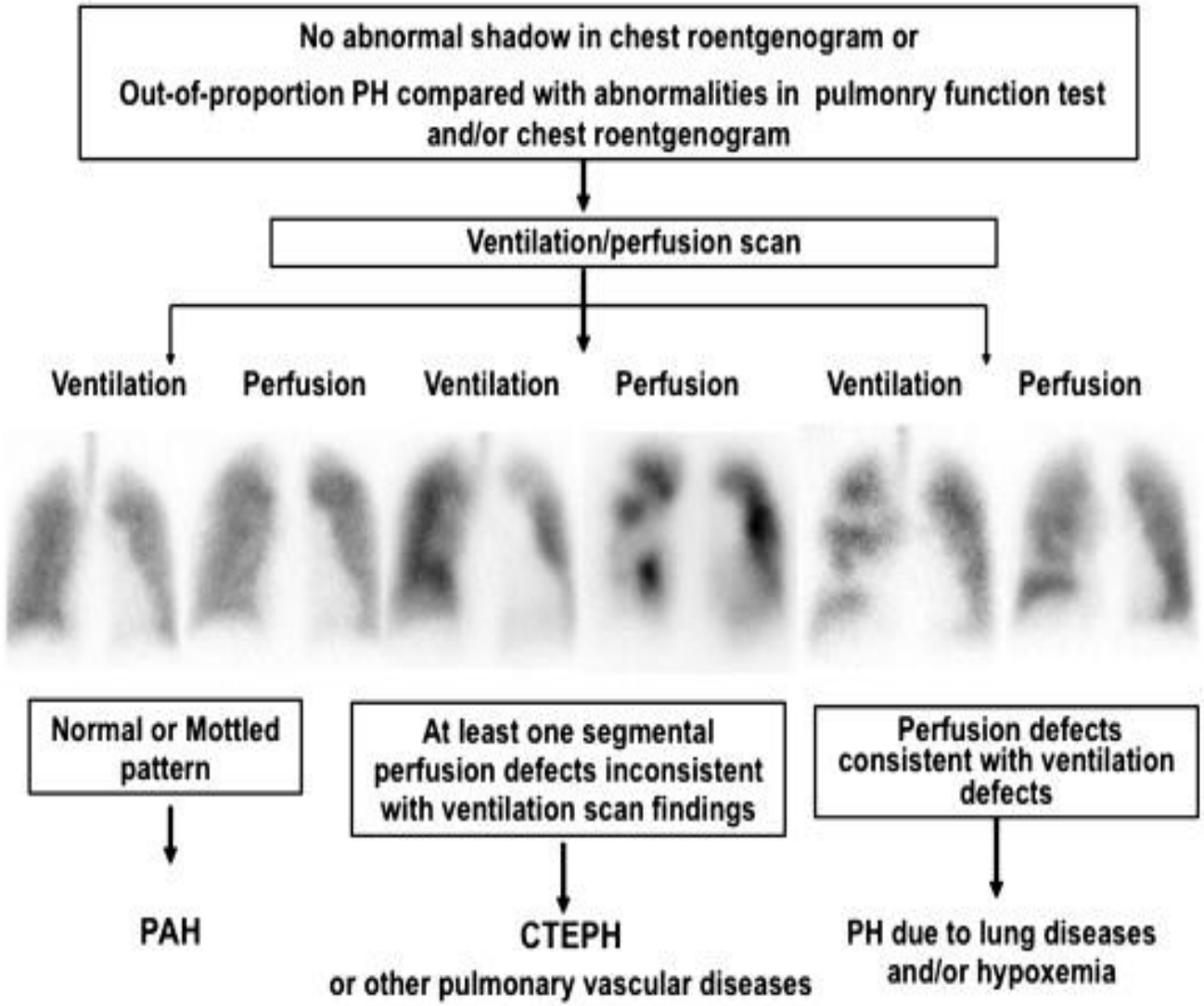
Other indicators favoring V/Q over CTPA:

- Lower radiation exposure
- Fewer IV contrast complications
- Less training for data interpretation
- Low cost[d]

[a] A retrospective analysis of 227 patients.
[b] Intermediate with high-probability scans as indicative of CTEPH.
[c] Only high-probability scans as indicative of CTEPH.
[d] When perfusion is omitted.

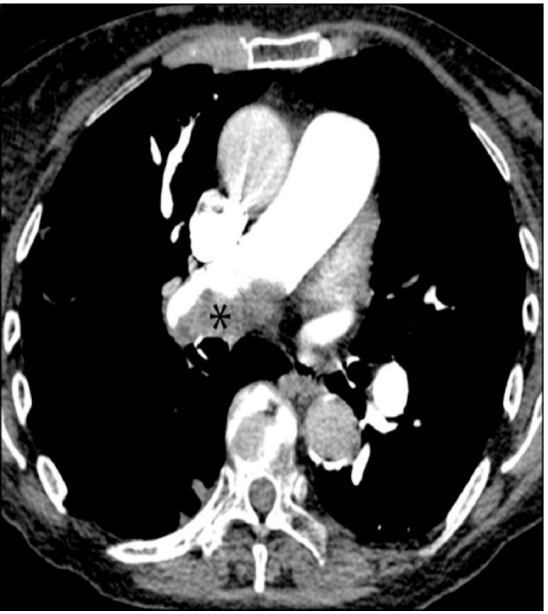
Tunariu N et al. *J Nucl Med*. 2007;48:680-684.

PH Imaging Modalities V/Q scan

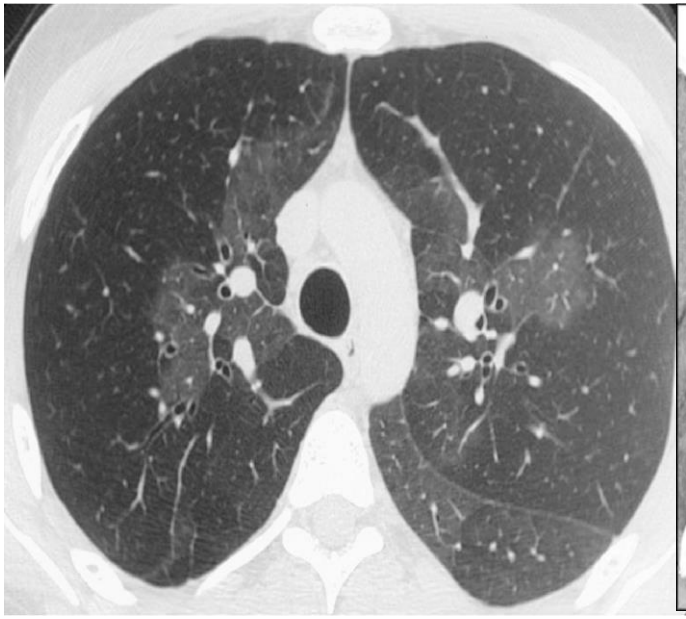


Tanabe . Recent progress in the diagnosis and management of chronic thromboembolic pulmonary hypertension

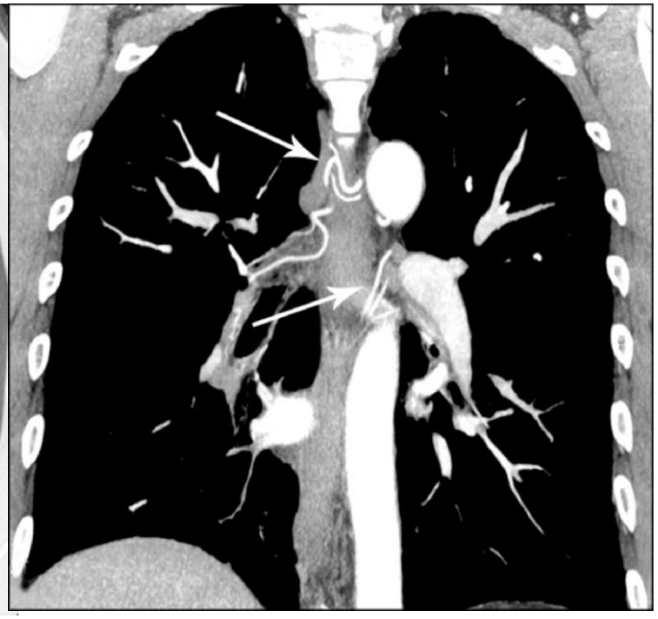
PH Imaging Modalities
CT Pulmonary Angiography



CT pulmonary angiogram demonstrating central pulmonary artery thrombus (asterisk)



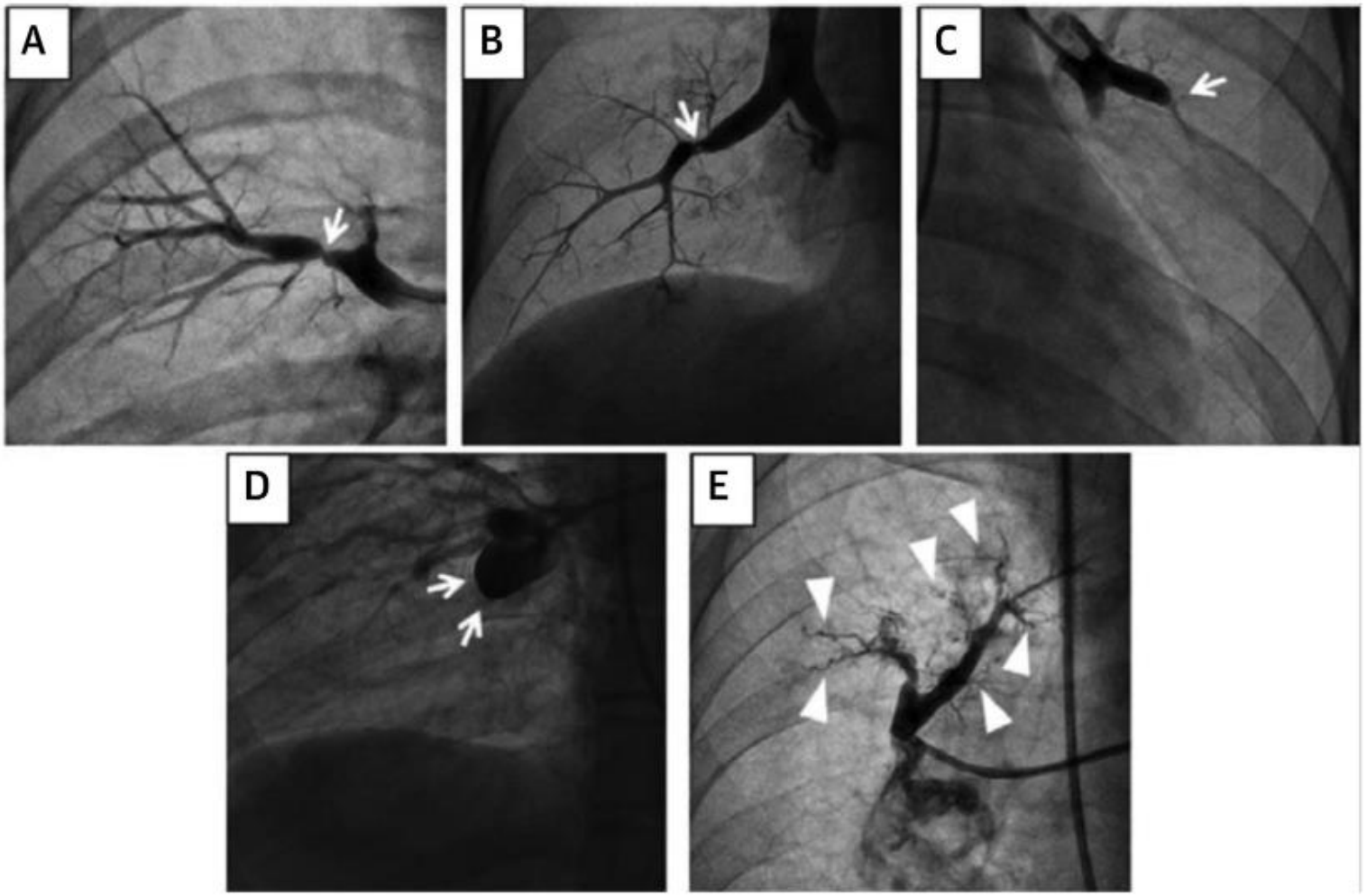
Mosaicism and enlargement of the segmental pulmonary arteries relative to their accompanying bronchi



Bronchial artery hypertrophy (arrows)

Courtesy of Ewen Robertson, Michael Sproule

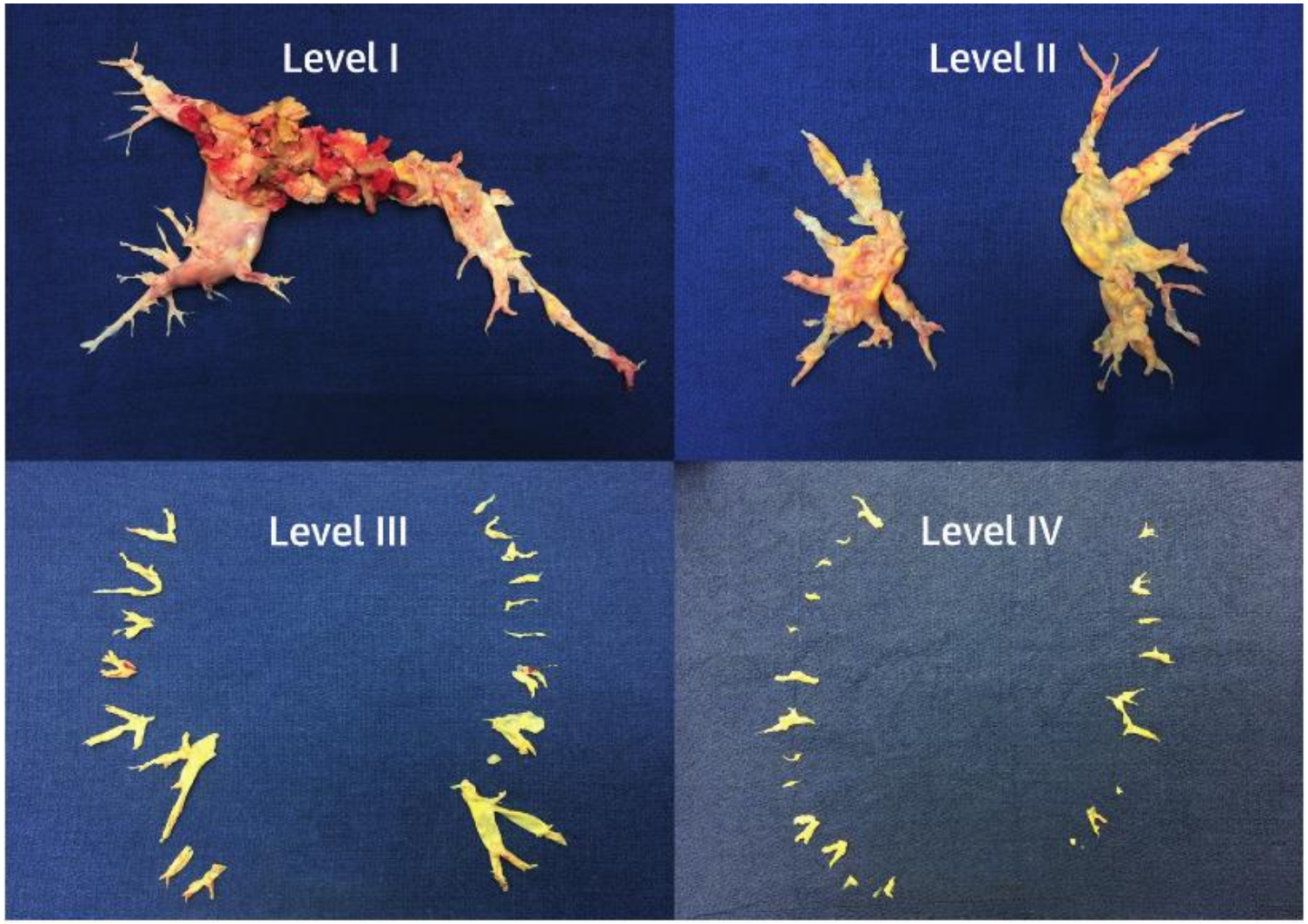
Angiographic Classification of CTEPH Lesions



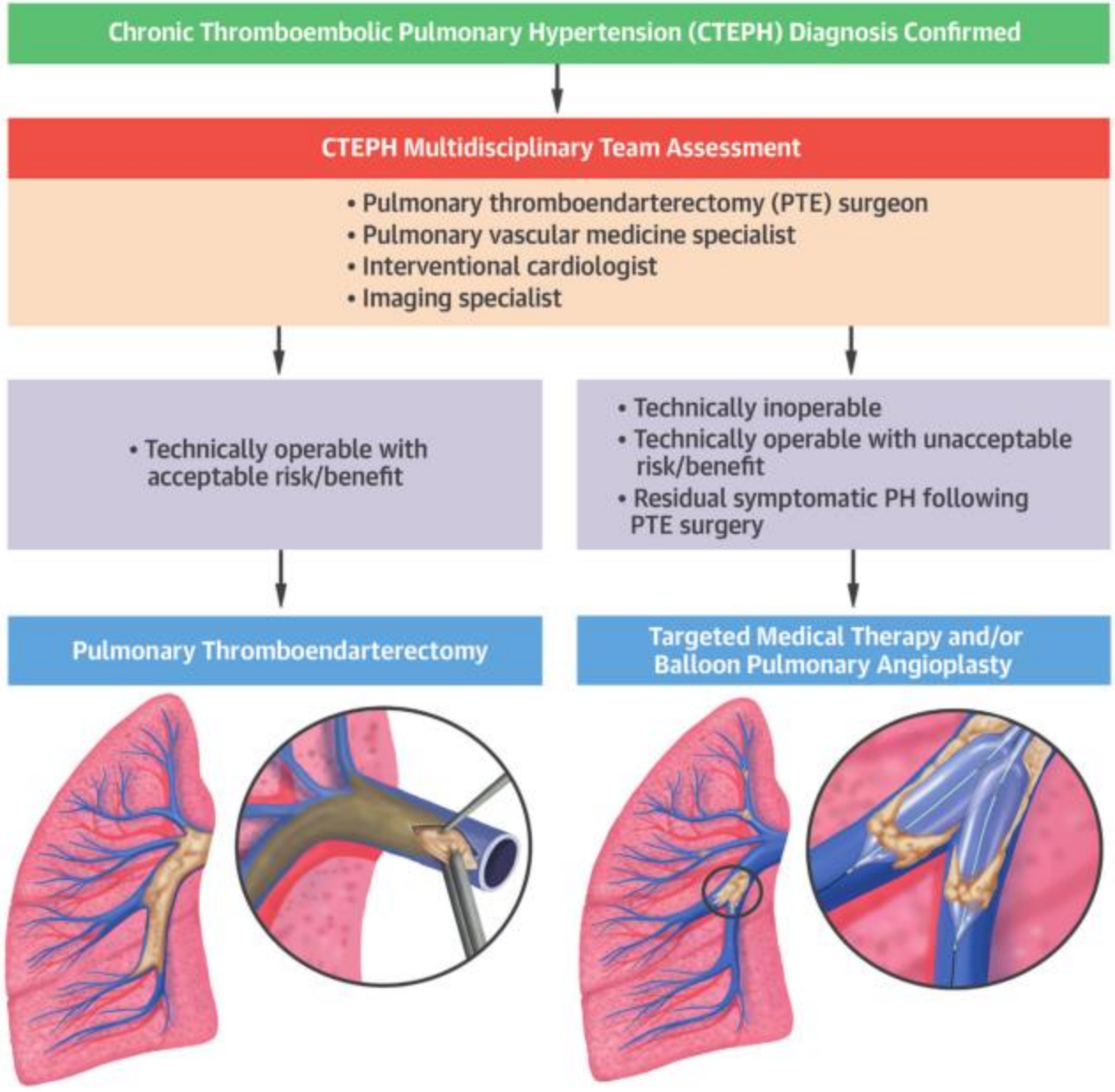
(A) Type A: ring-like stenosis lesion. **(B)** Type B: web lesion. **(C)** Type C: subtotal lesion. **(D)** Type D: total occlusion lesion. **(E)** Type E: tortuous lesion. Type A–D lesions **(arrows)** are located proximal to the subsegmental pulmonary artery, namely, the segmental and subsegmental arteries. Type E lesions **(arrowheads)** are located distal to the subsegmental artery. CTEPH = chronic thromboembolic pulmonary hyper-

Kawakami et al. *Circ Cardiovasc Interv* 2016;9:e003318

Surgical Classification for CTEPH - UC San Diego group

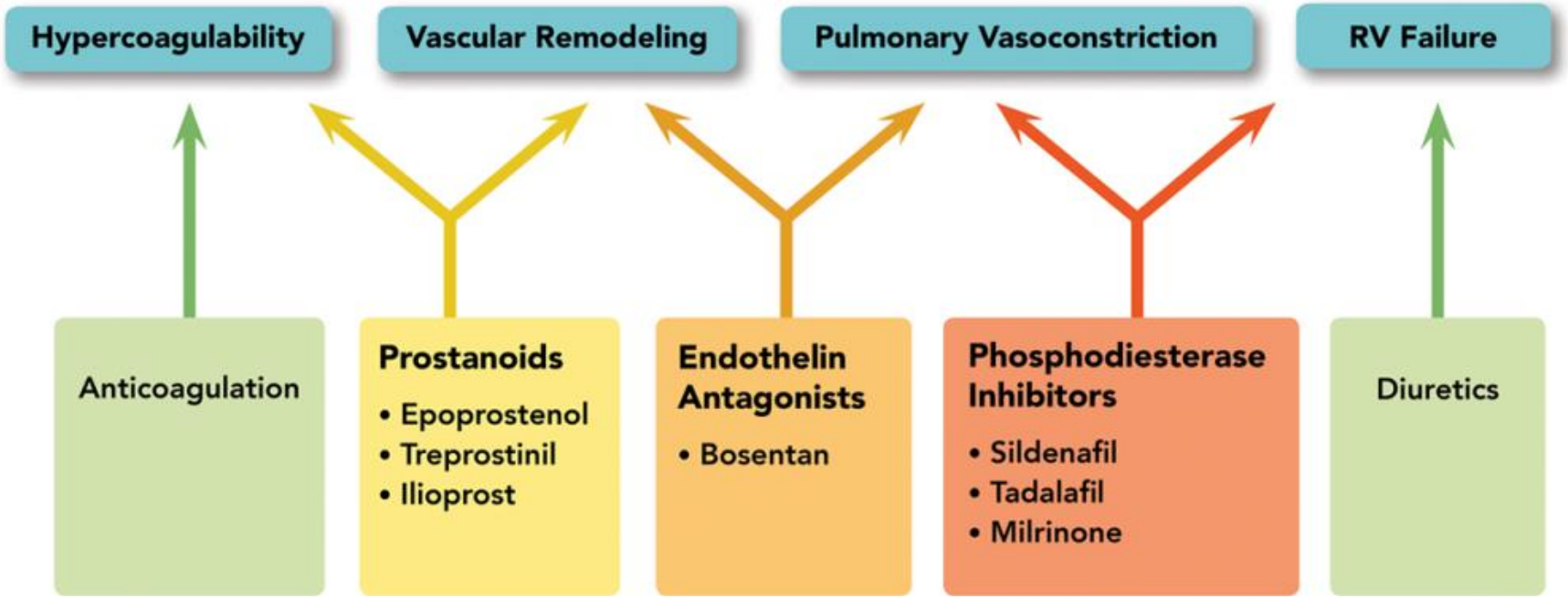


CENTRAL ILLUSTRATION CTEPH Treatment Algorithm by the Multidisciplinary UC San Diego CTEPH Team



Mahmud, E. et al. J Am Coll Cardiol. 2018;71(21):2468-86.

Medical Therapy for the Treatment of CTEPH



Pulmonary Thromboendarterectomy for CTEPH. *Anesthes.* 2014;120(5):1255-1261

Medical Therapy for the Treatment of CTEPH

Drug Class	Evidence and Effects
Soluble guanylate cyclase stimulants (riociguat)	• CHEST-1 trial (randomized, double-blind, placebo-controlled study) (74); Improved pulmonary vascular resistance and 6-min walk distance after 16 weeks • CHEST-2 trial (follow-up extension study) (75); Persistent efficacy for up to 1 yr
Endothelin receptor antagonists (macitentan and bosentan)	Macitentan • MERIT-1 trial (randomized, double-blind, placebo-controlled study) (76); Improved pulmonary vascular resistance after 16 weeks Bosentan • BENEFiT trial (randomized, double blind, placebo-controlled study) (77); Improved pulmonary vascular resistance and cardiac index after 16 weeks • Systematic review of BENEFiT and 10 observational studies (78); Similar results were reported
Phosphodiesterase 5 inhibitors (sildenafil)	• Randomized, double blind, placebo-controlled pilot study (79); Improvement in World Health Organization functional class and pulmonary vascular resistance after 12 weeks
Prostanoids (epoprostenol and treprostinil)	Epoprostenol • Retrospective cohort study in severe inoperable CTEPH (80); Improvement in pulmonary vascular resistance, pulmonary artery pressure, and exercise capacity after 3 months Iloporost • AIR study (randomized, double-blind, placebo-controlled study) (81); Improvement in New York Heart Association functional class and 6-min walk distance at 12 weeks

Mahmud et al. Chronic Thromboembolic Pulmonary Hypertension. *JACC* vol. 71, NO. 21, 2018

Theo dõi sau PE

Recommendations	Class
Lượng giá triệu chứng của bệnh nhân sau khi bị PE 3 – 6 tháng	I B
Phối hợp “đa mô thức” chăm sóc BN sau PE: BS tim mạch, điều dưỡng, BS gia đình, BS – KTV Phục hồi chức năng	I C
BN có bất tương hợp trên V/Q scan sau PE trên 3 tháng cần được chuyển đến chuyên gia CTEPH	I C
BN PE có triệu chứng khó thở/giảm gắng sức kéo dài hoặc mới khởi phát cần được làm các test chẩn đoán chuyên sâu	IIa C
BN PE không có triệu chứng nhưng có nhiều YTNC CTEPH cần được làm các test chẩn đoán chuyên sâu	IIb C

ESC guidelines. *European Heart Journal* (2019) 00,161