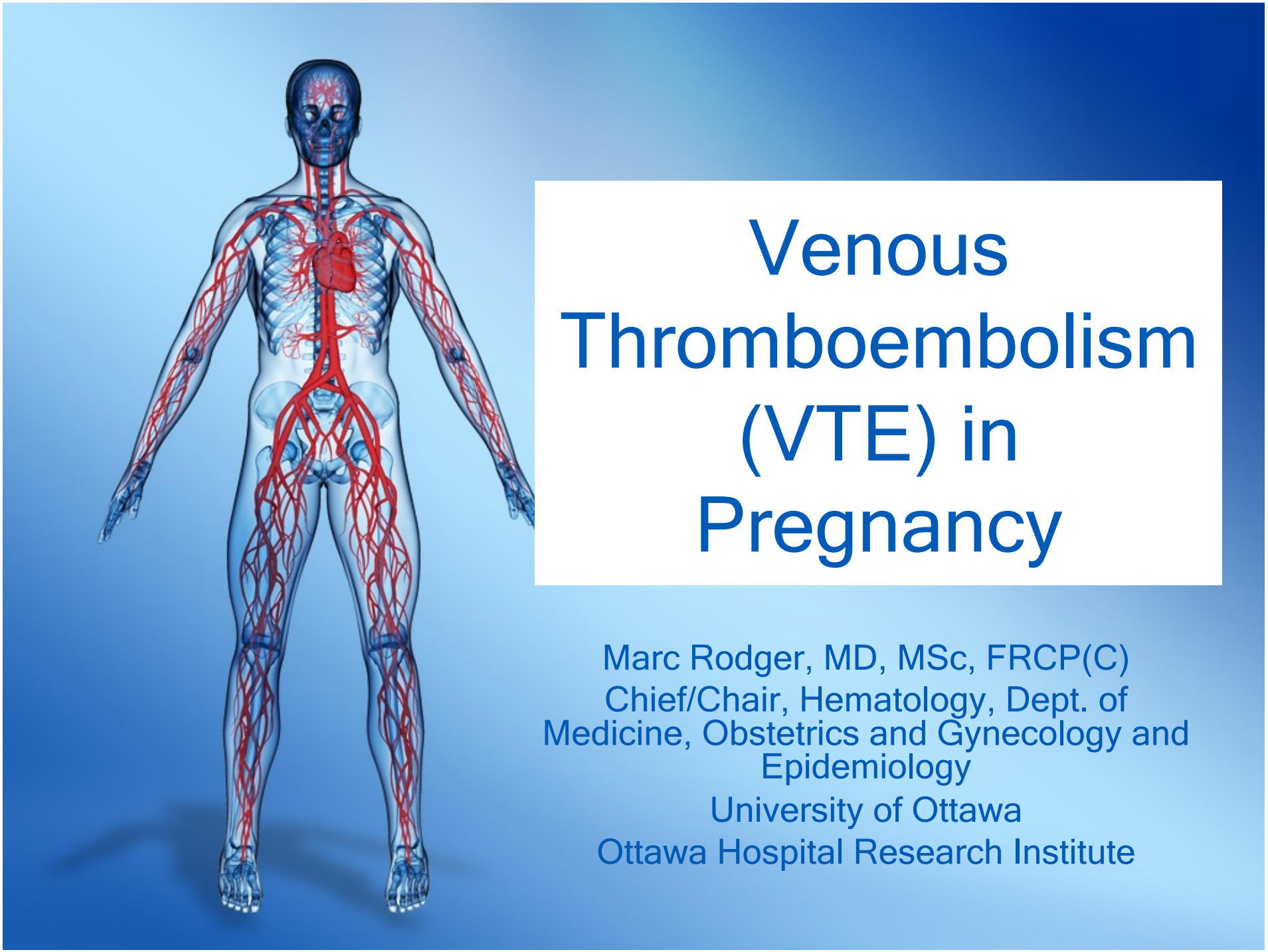
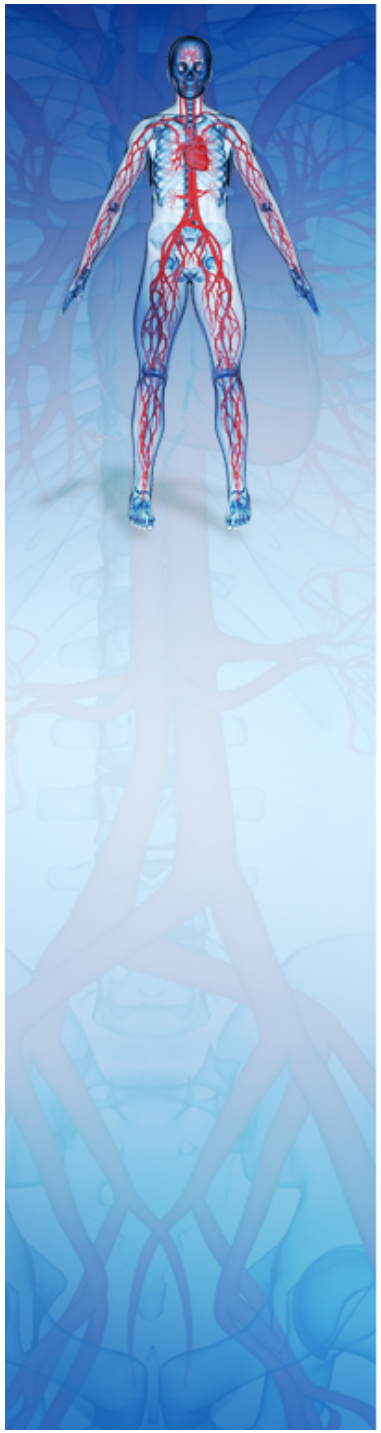


Venous Thromboembolism (VTE) in Pregnancy

Marc Rodger, MD, MSc, FRCP(C)
Chief/Chair, Hematology, Dept. of Medicine, Obstetrics and Gynecology and Epidemiology
University of Ottawa
Ottawa Hospital Research Institute



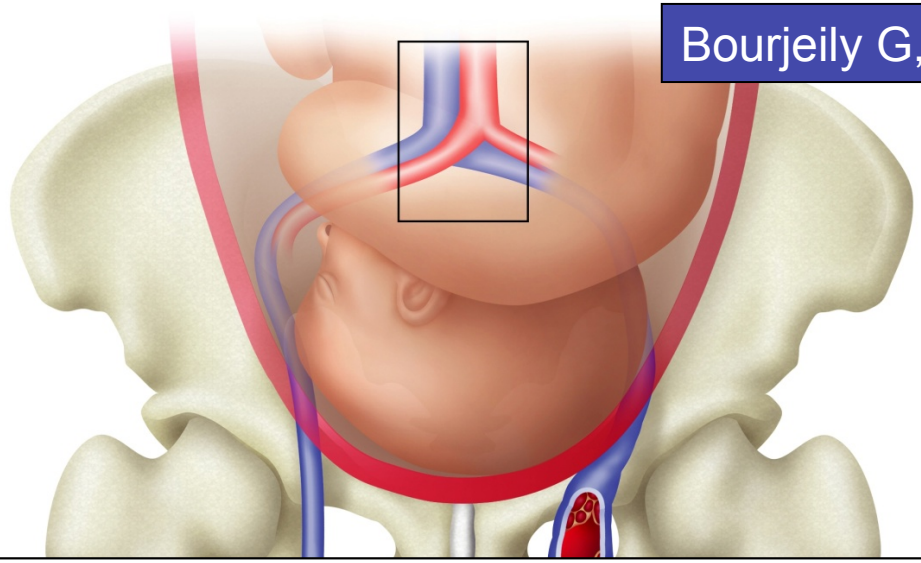
Population Epidemiology

Retrospective cohort studies

- **Suspected VTE** in **~20/1000** pregnancies
- **Antenatal VTE**: **~1/1000** maternities[1-3]
  - Daily antenatal risk **3-7.5x** higher than non-pregnant women[4]
- **Postpartum VTE**: **~0.5/1000** maternities
  - Daily postpartum risk **15-35x** higher than non-pregnant women[4]

1-Andersen BS, Acta Obstet Gynecol Scand,1998; 2-Simpson EL, BJOG 2001; 3-Treffers PE, Int J Gynaecol Obstet 1983; 4-Anderson FA, Arch Intern Med 1991

Bourjeily G, Rodger M, Lancet, 2009



Stasis

Iliac Vein Compression:

Right iliac artery compresses left iliac vein

Gravid Uterus

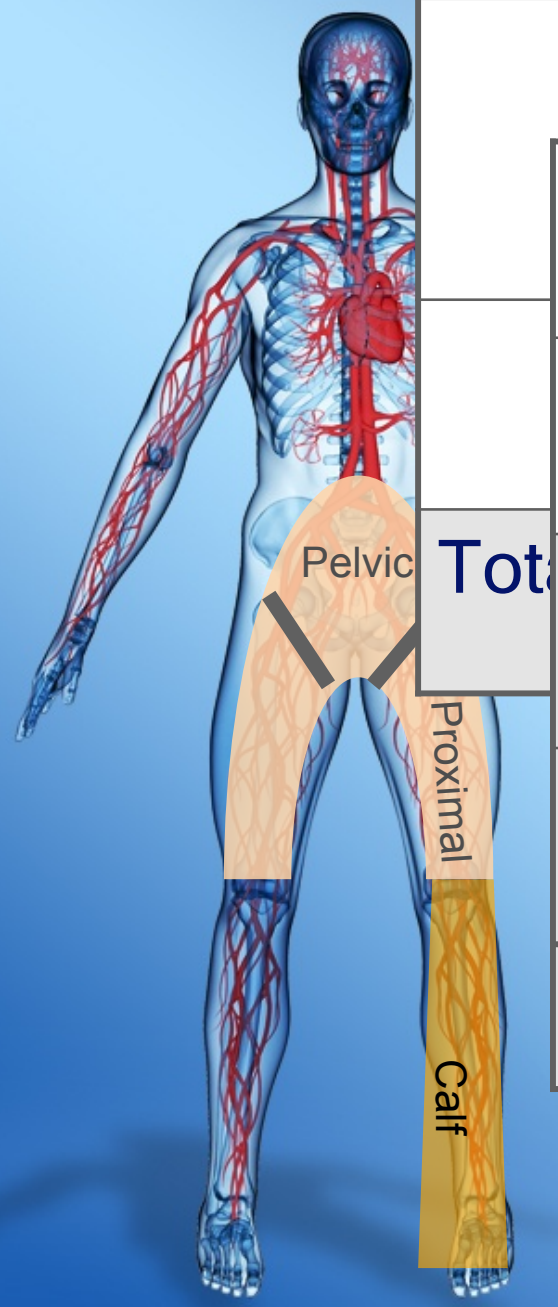
Venodilation: Hormonally Mediated

Bed Rest Immobilization

Vascular Damage
- Vascular compression at delivery
- Assisted or operative delivery

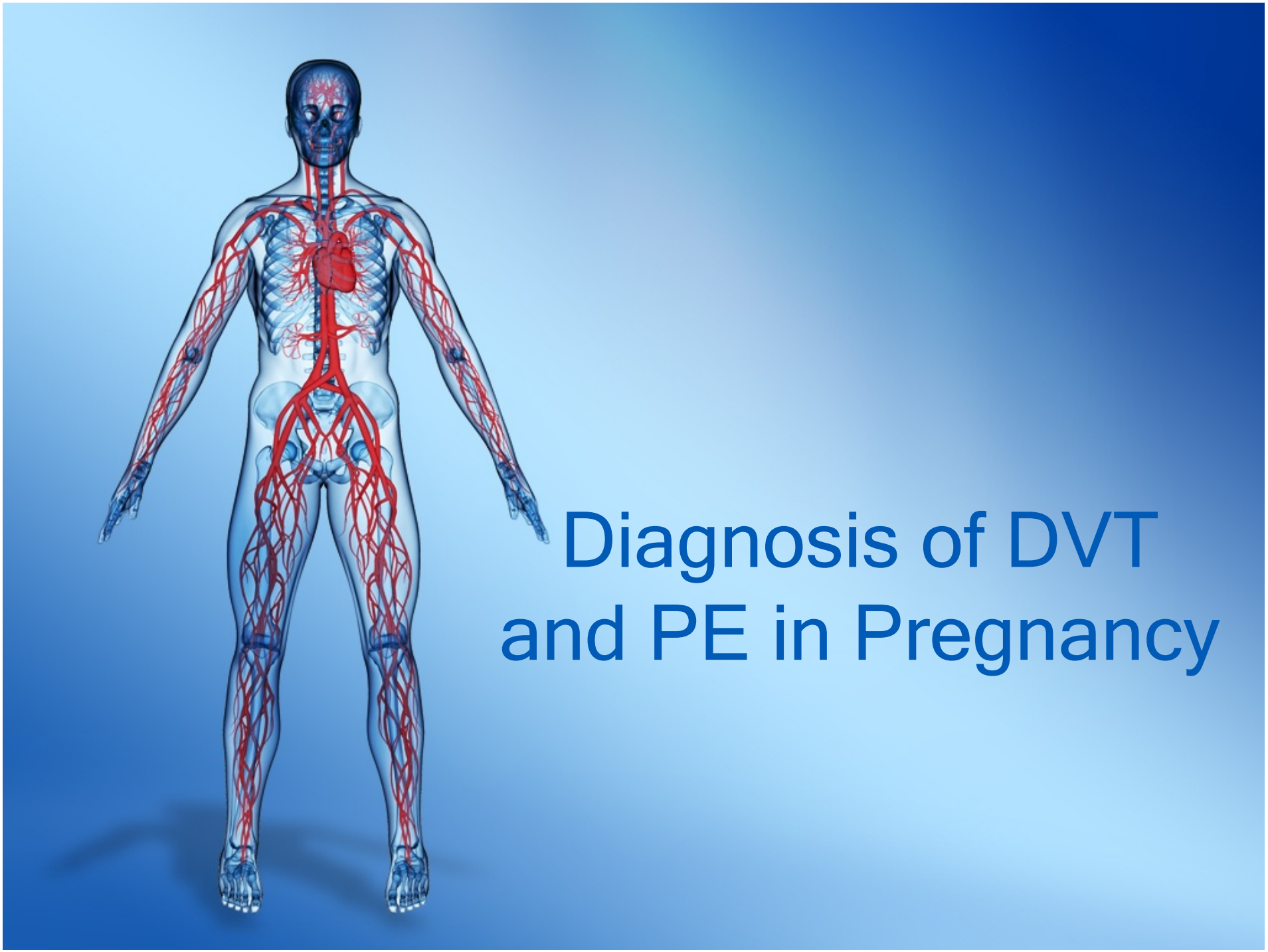
↑fibrinogen, ↑factor V, IX, X XII and VIII levels
- ↓ **Anticoagulant activity:**
  ↓Protein S levels and ↑activated protein C resistance
- ↓ **Fibrinolytic activity:**
  ↑PAI-1 and 2 and ↓t-PA activity

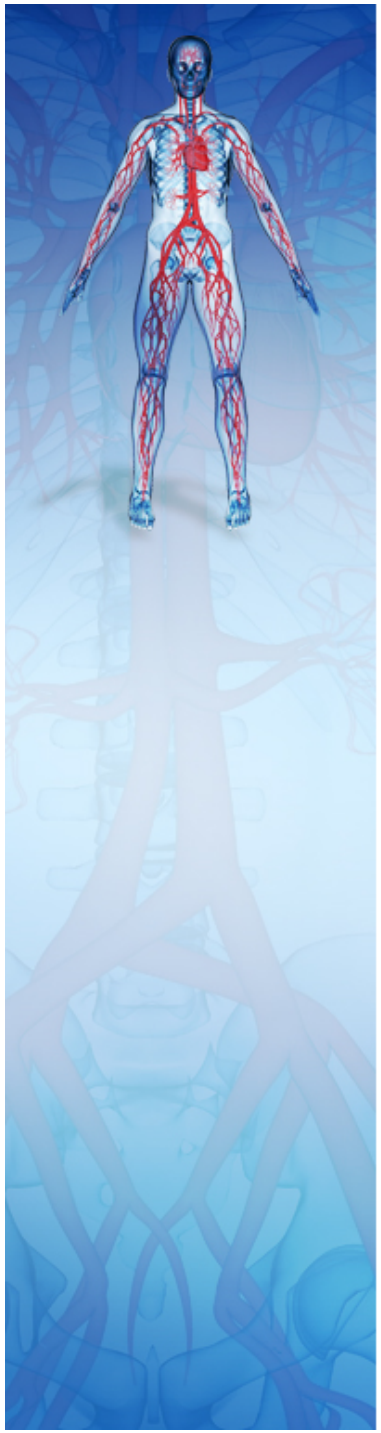
= more thrombin generation + less clot dissolution



	Pregnant[1]	Non-Pregnant[3]
Isolated Pelvic	17%	0%
Proximal Without Calf	71%	1%
Proximal with Calf	29%	99%
Total	100%	100%

1- Chan, CMAJ, 2010
2- Ouriel, J Vasc Surg, 2000
3- Cogo, Arch Int Med, 1993

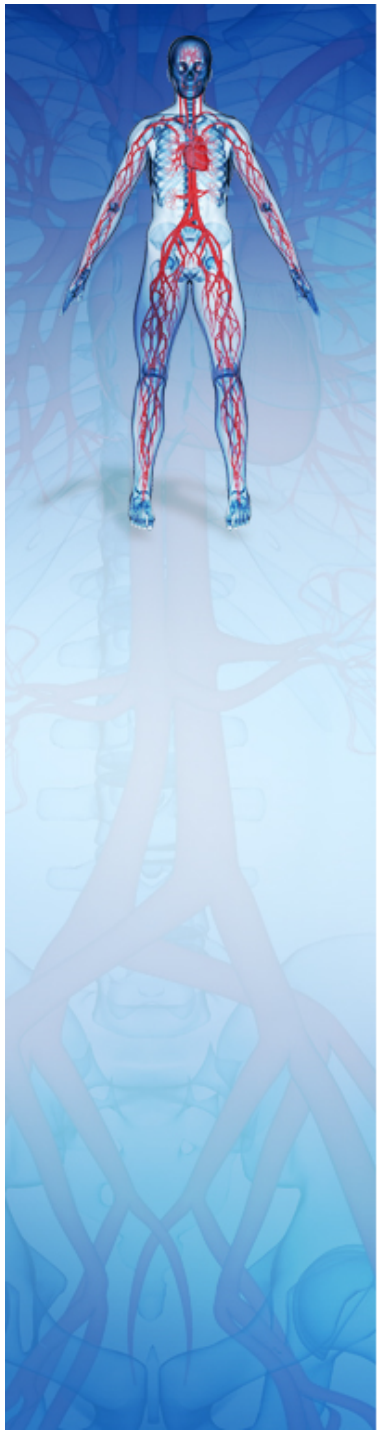

Diagnosis of DVT
and PE in Pregnancy



Case (Fictional)

- 30 yo woman presents at 8 weeks GA with a tender swollen left leg/ buttock

Exam: left thigh/calf are >5 cm bigger than her right leg



Case (fictional)

How would you exclude DVT?

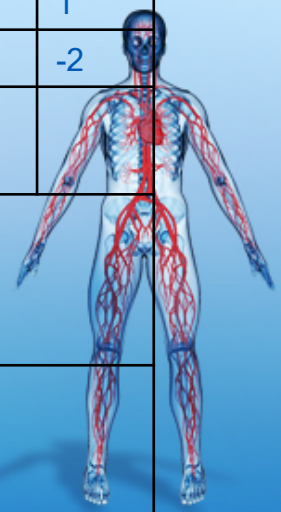
1. Negative D-dimer alone
2. Low Wells model and negative D-Dimer
3. Single negative compression US (CUS)
4. Negative serial compression US (CUS) on Day 1, 3 and day 7
5. Negative compression ultrasound (CUS) and negative MRV Day 1

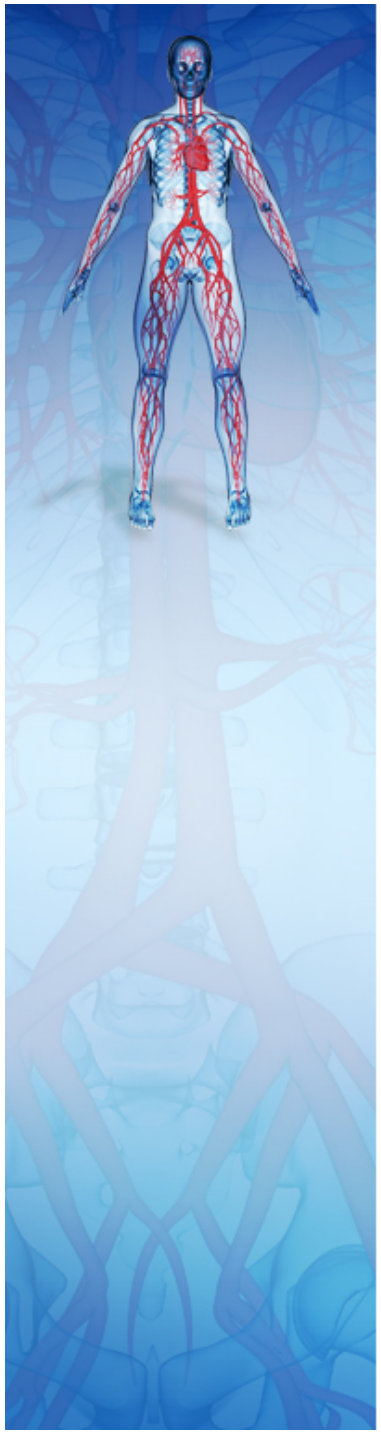
Wells Clinical Model for DVT

Wells P, et al. Value of Assessment of Pre-test Probability of Deep-Vein Thrombosis in Clinical Management. Lancet Vol. 350, Dec 1997, 1795-1798.

Active cancer (treatment ongoing or within past 6 months or palliative)	1
Recent paresis, paralysis or cast immobilization of lower limb (within past 4 weeks)	1
Recently bedridden for more than 3 days or major surgery within the past four weeks	1
Localized tenderness of the deep venous system	1
Oedema of entire leg	1
Calf swelling > 3 cm when compared with contralateral calf (measured 10 cm under the tibial tuberosity)	1
Pitting oedema more marked on suspected side	1
Collateral vein network (non-varicose) (replaced by previous VTE in recent versions)	1
Another diagnosis as likely or more likely than DVT	-2
Total Score:	

Probability is: **High** **Intermediate** **Low**	 **if total is equal to or greater than 3** **if total is 1 or 2** **if total is 0**
Probability is: **Likely** **Unlikely**	 **if total is >1** **if total is ≤1**





LEFt Clinical Decision Rule looks good …but needs validation

- Multi-center cohort
- 194 pregnant women with ?DVT
  - Collect potential predictors

- Gold standard: Serial CUS and 90d F/U
  - 17 (8.8%) had DVT

	Points
Left Leg	+1
Extremity Swelling (calf ≥ 2cm)	+1
First **t**rimester	+1
Total:	

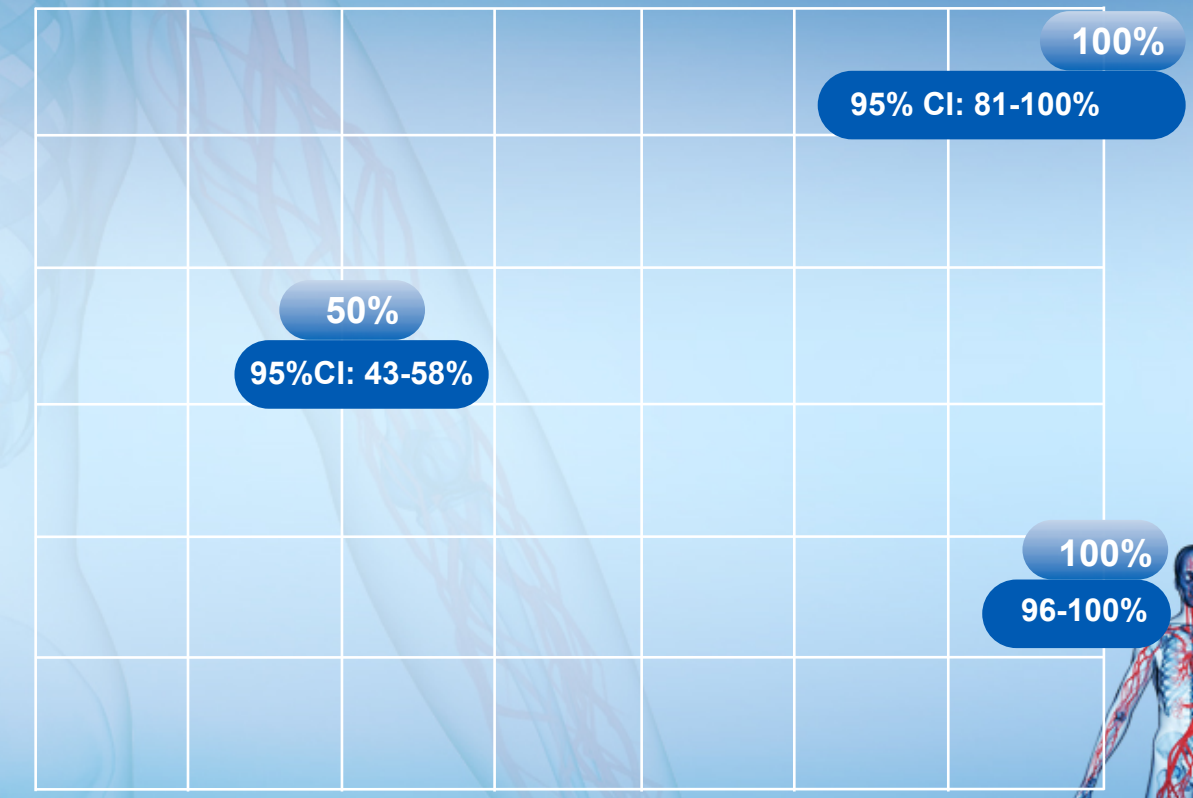
1- Chan, Ann Int Med, 2009

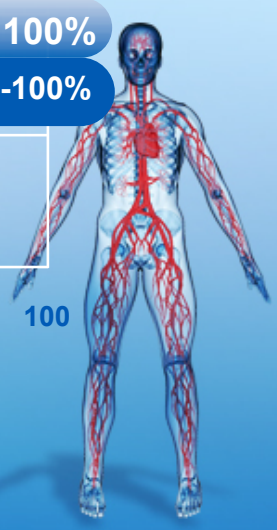
LEFt Score= 0 to exclude DVT in pregnancy

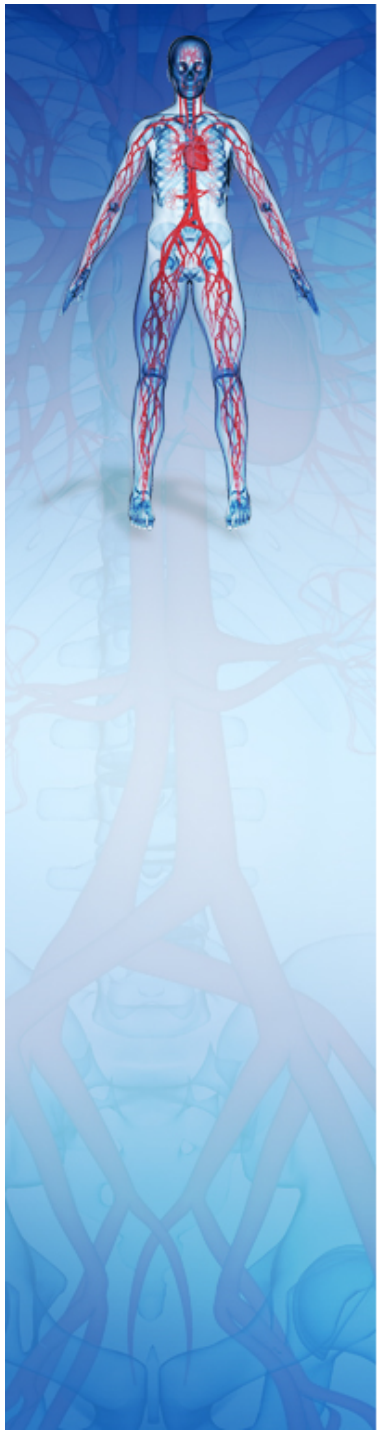
Sensitivity

Specificity

Negative predictive value







Meta- analysis of retrospetcive cohort studies (n= 439 ?DVT)

LEFT =0 points (164 patients)

- Negative Predictive Value: 99% (163/164) (95% CI: 96.6-99.9%)

LEFT = 0,1 points (362)

- Negative Predictive Value: 97.2% (352/362) (95% CI: 95.0-98.5%)

1- Le Moigne, Thrombosis Research, 2014

Hierarchy of Evidence for Clinical Prediction Rules

- Level IV: Rules that need further evaluation before they can be applied clinically
  - Rules have been derived but not validated or have only been validated in split samples, large retrospective databases, or by statistical techniques.

Center for Health Evidence:http://www.cche.net/usersguides/prediction.asp

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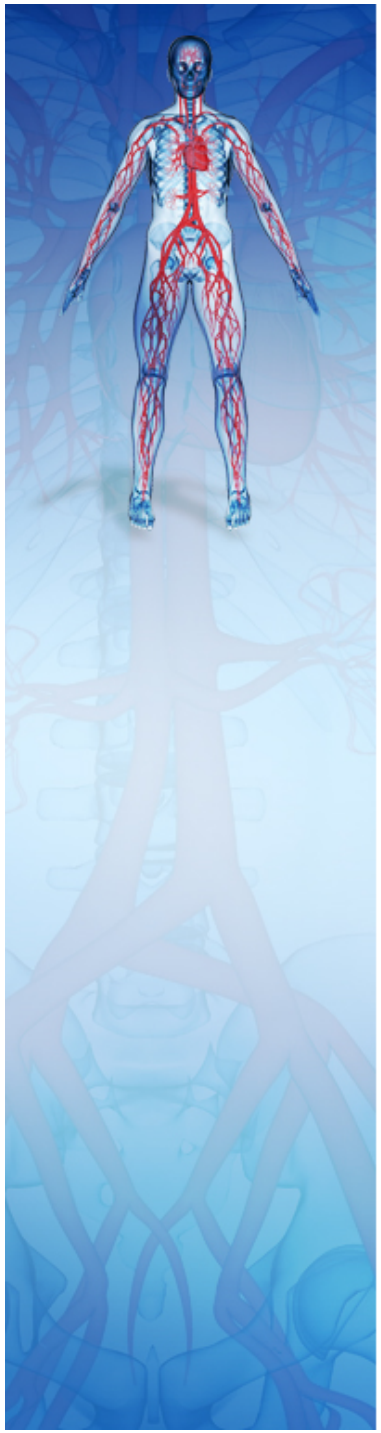


D-Dimer alone to exclude DVT in pregnancy looks good …but needs validation

- Multi-center cohort
- 149 pregnant women with ?DVT
  - SimpliRED D-Dimer
- Gold standard: Serial CUS and 90d F/U
  - 13 (8.7%) had DVT

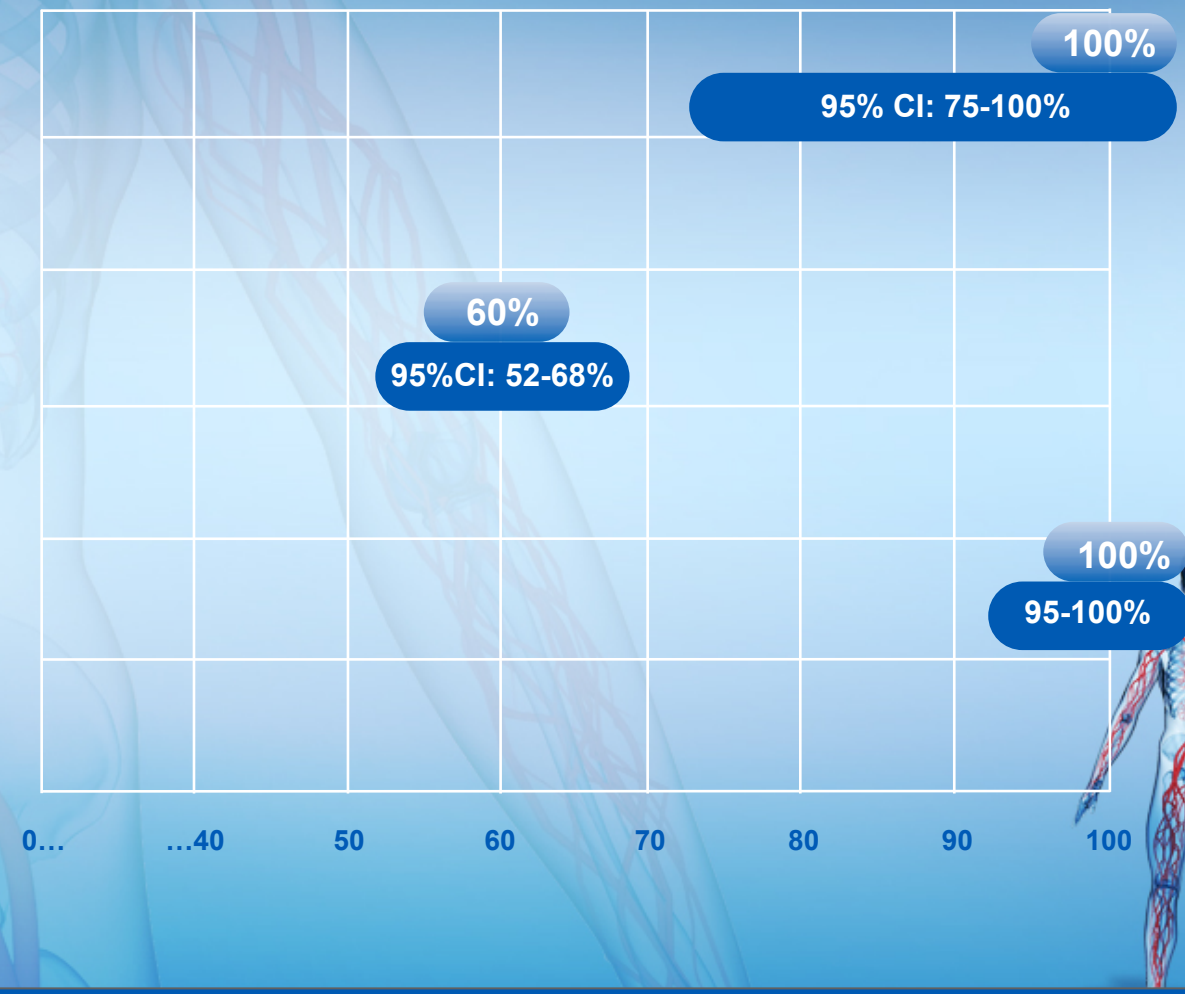
WS Chan, S Chunilal, A Lee, M. Rodger and JS Ginsberg. Annals Int Med 2007

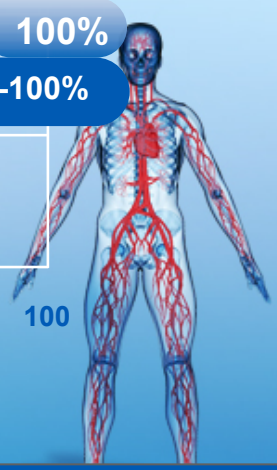
Normal D-Dimer to exclude DVT in pregnancy

Sensitivity

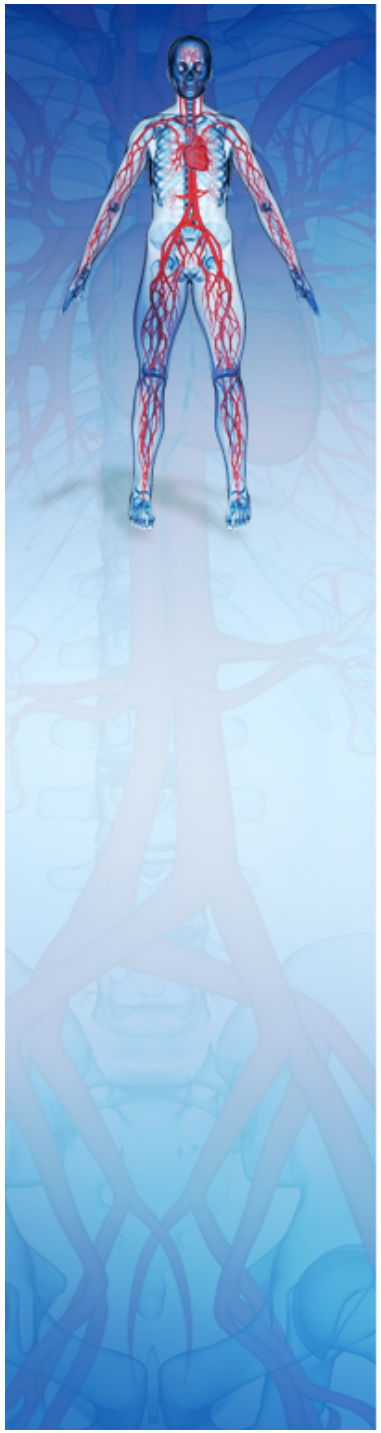
Specificity

Negative predictive value





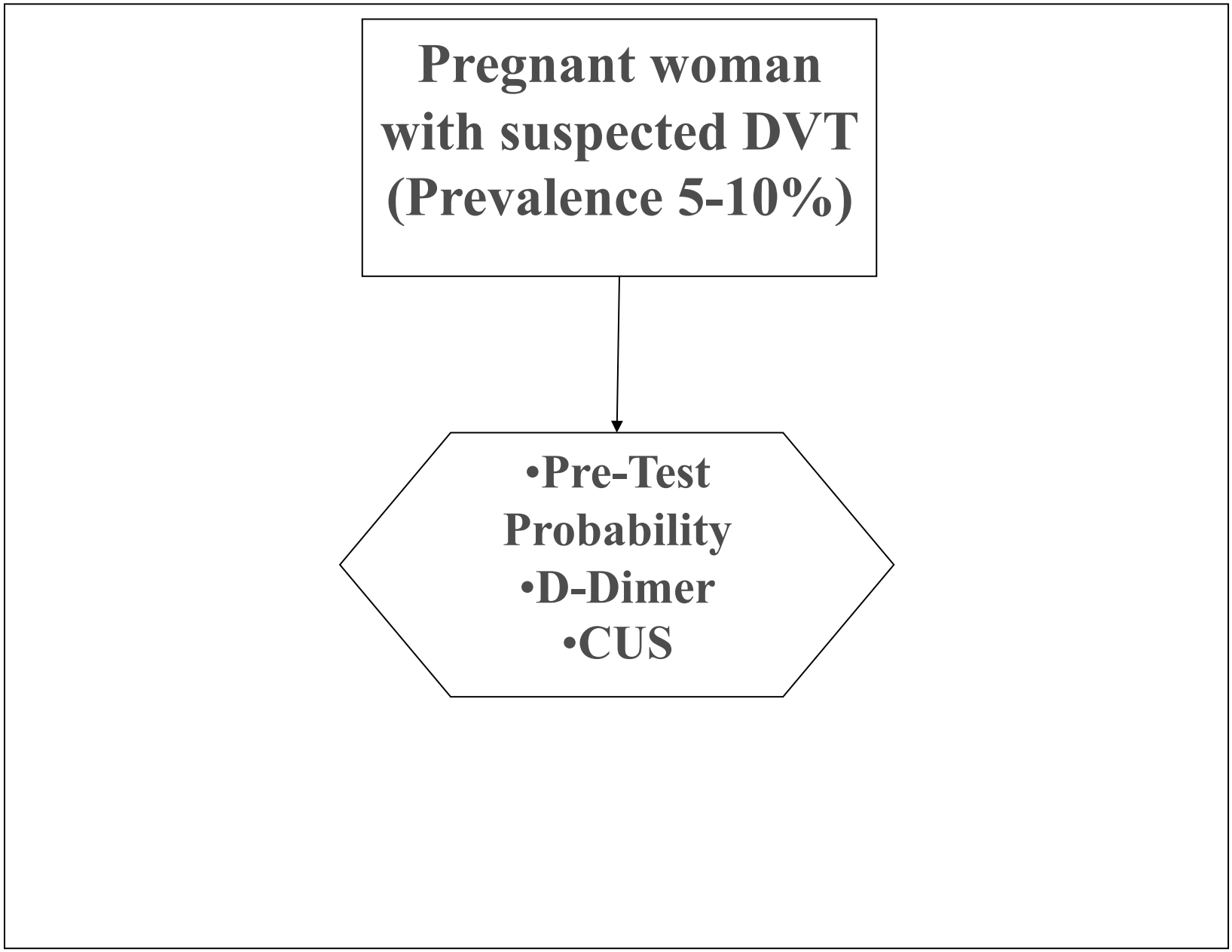
WS Chan, S Chunilal, A Lee, M. Rodger and JS Ginsberg. Annals Int Med 2007



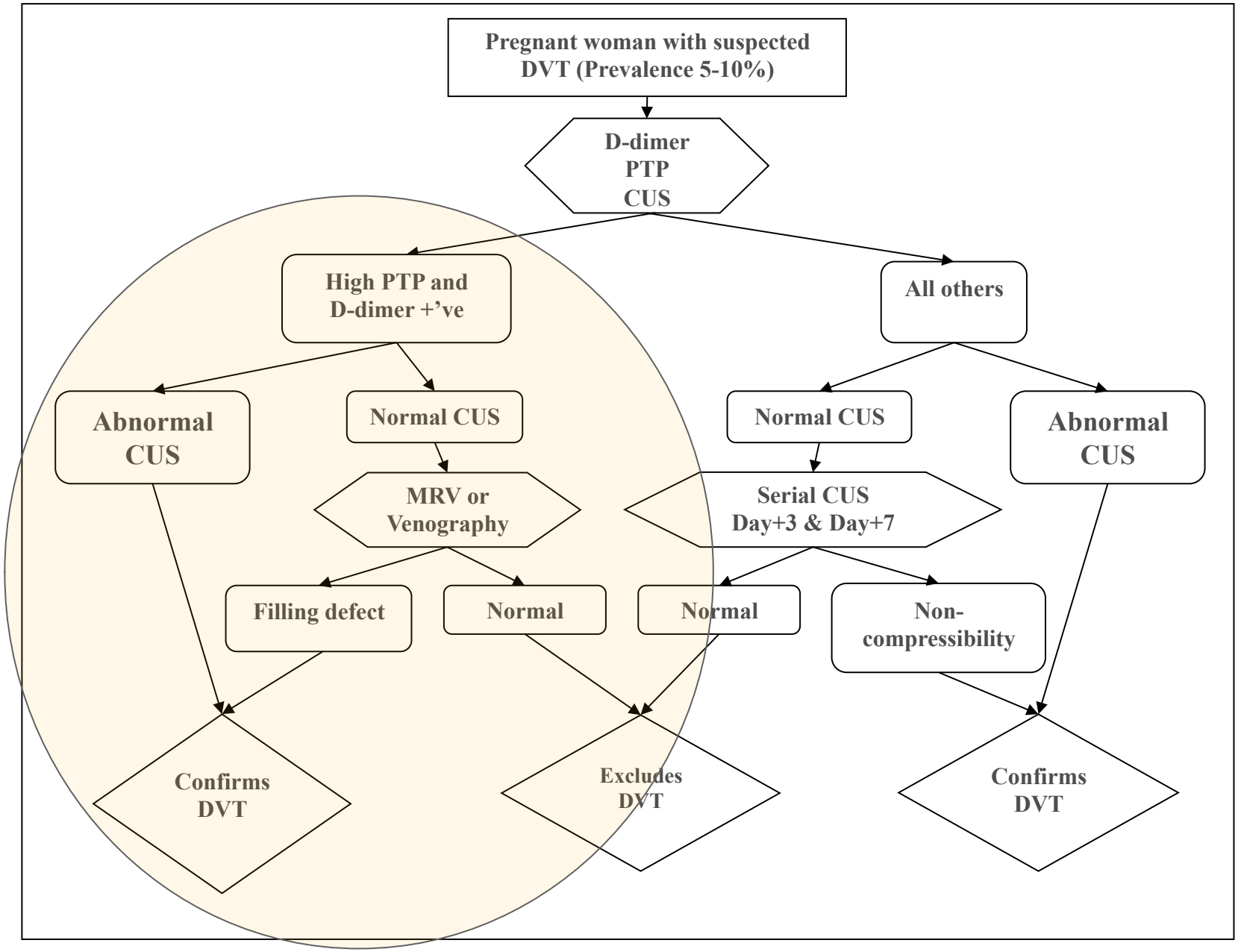
Serial Compression US **Validated** to exclude DVT in Pregnancy: Prospective Cohort Studies

- Chan (2007):
  - 1/178 negative serial US developed DVT during 3-month follow-up period
  - Diagnostic failure rate = 0.6% (95% CI: 0.01% to 3.1%).
- Chan (2013):
  - 1/221 negative serial US developed DVT
  - Diagnostic failure rate= 0.5% (95% CI: 0.1-2.7%).
- **Only validated test!**

WS Chan. Annals Int Med 2007; Chan CMAJ, 2013



PTP: pre-test probability; CUS- Bilateral leg vein compression ultrasound



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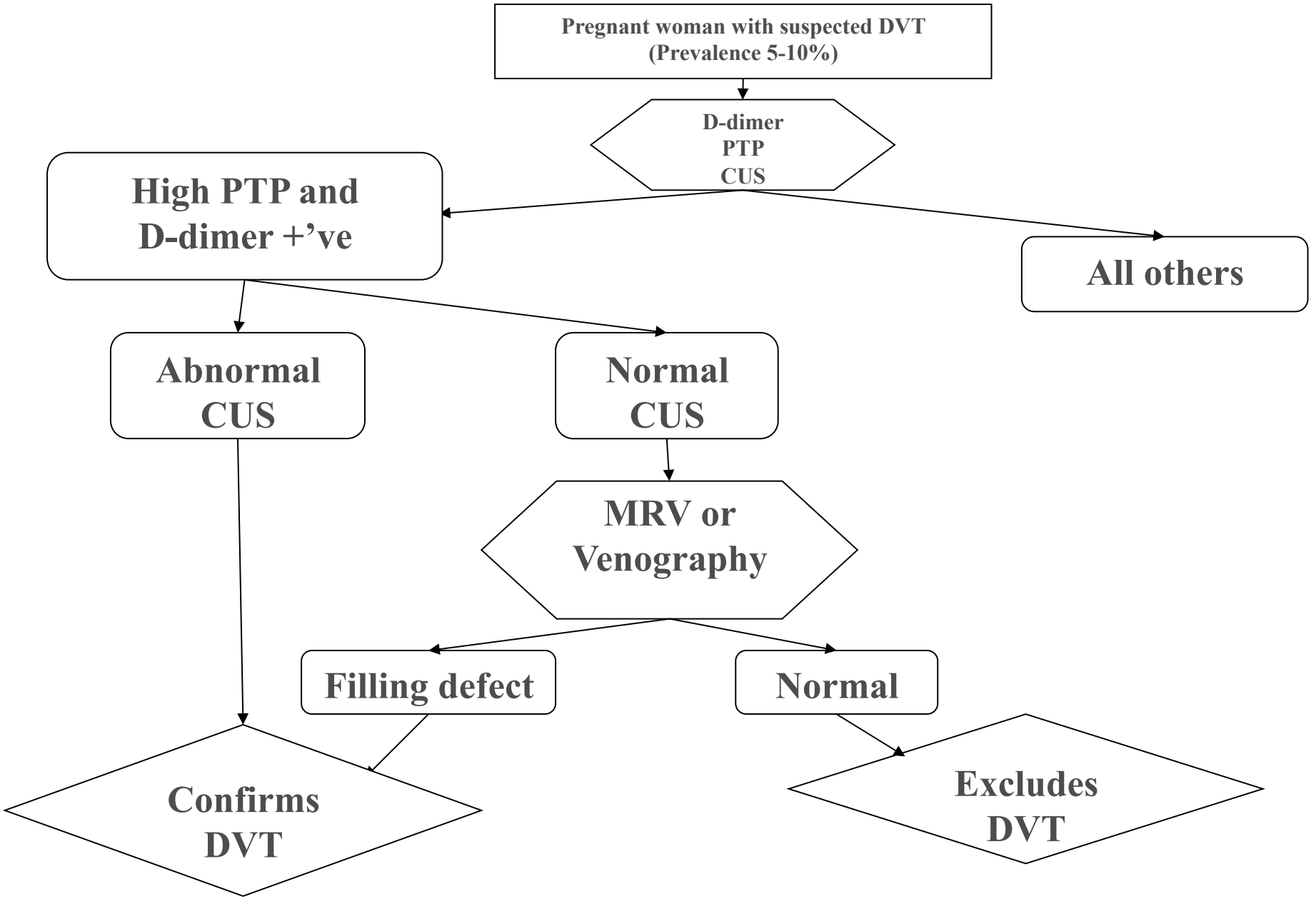

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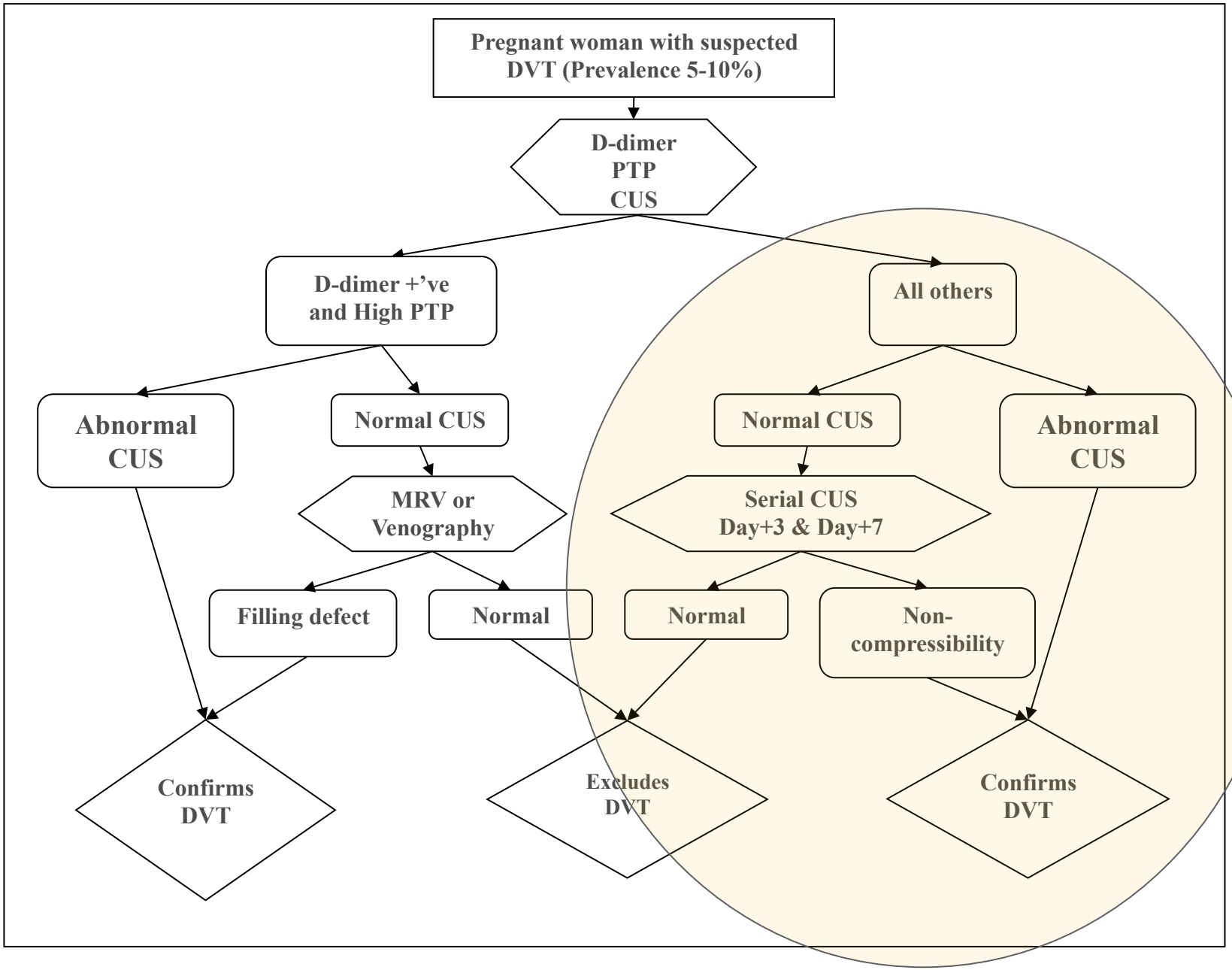

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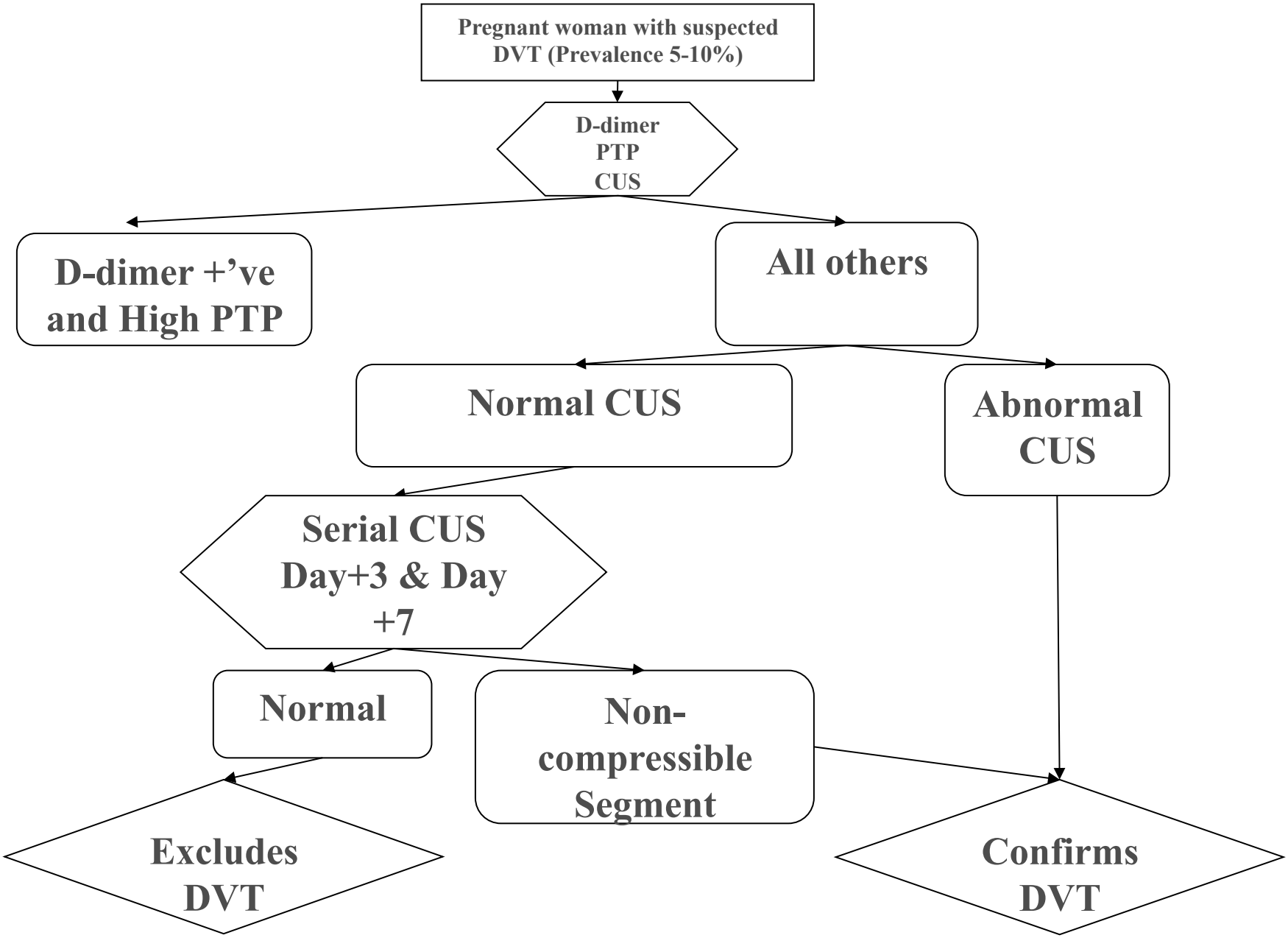

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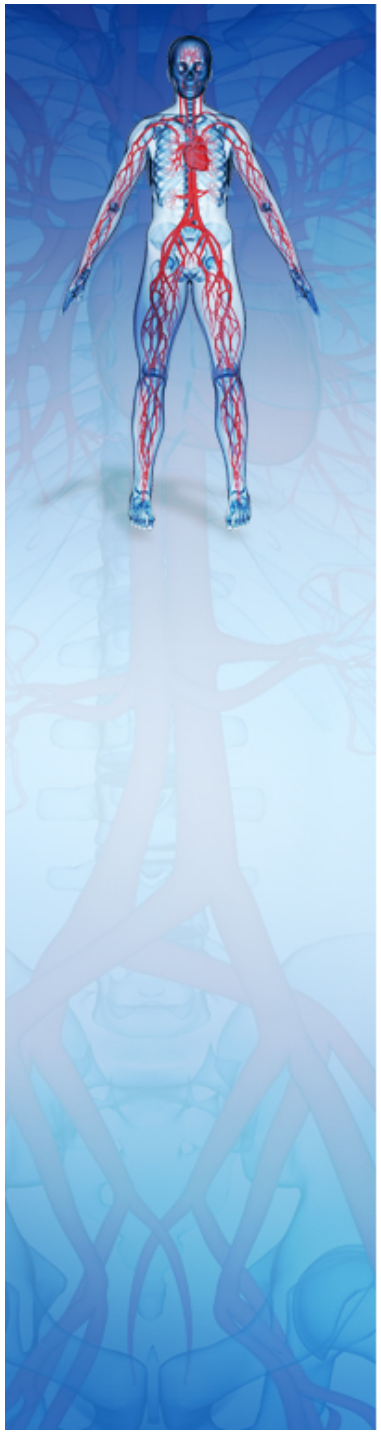

Case (fictional)

How would you exclude DVT?

1. **DDimer positive**
2. Single negative compression US
3. Low Wells model and negative D-Dimer
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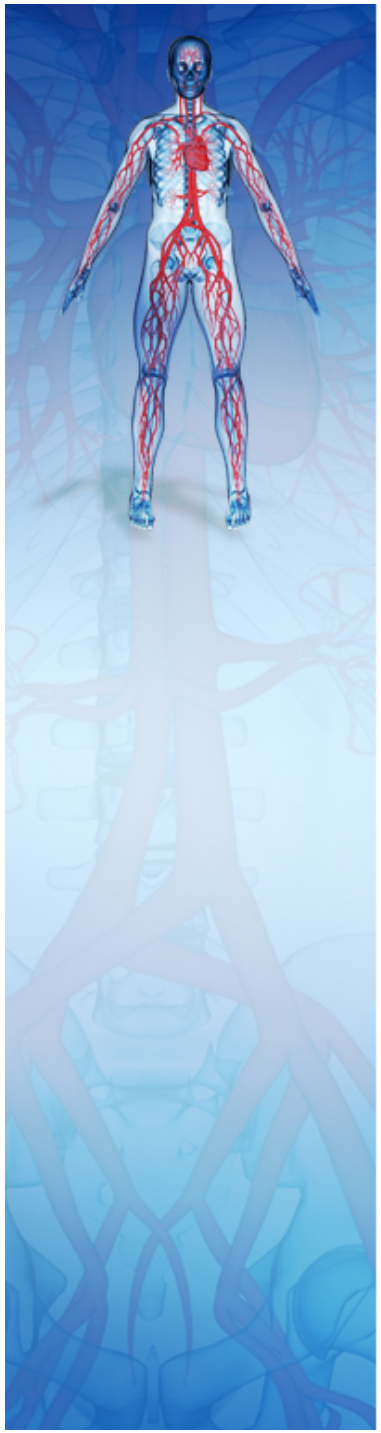

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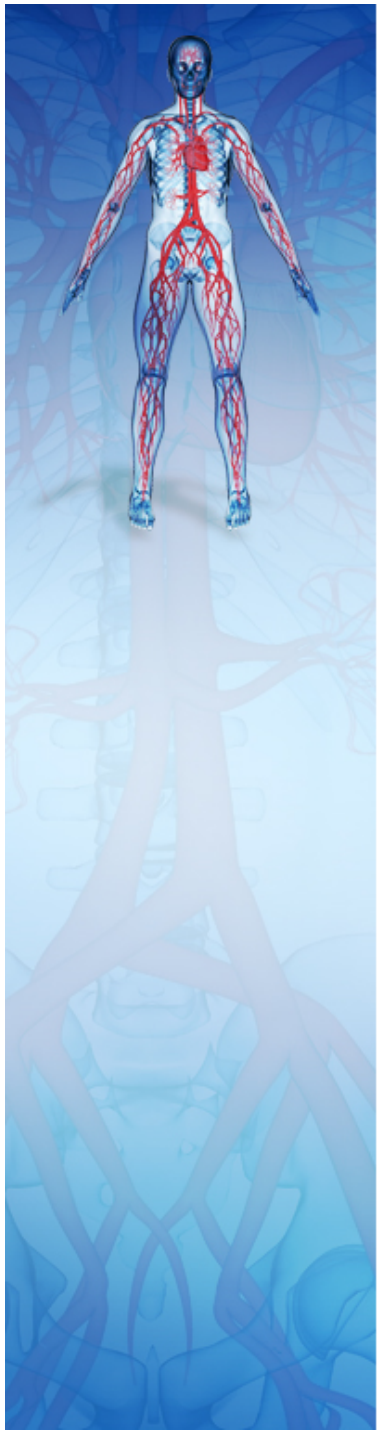


Case (fictional)

30 yo women 30 wks GA presents with pleuritic CP and SOB and positive D-Dimer.

How would you exclude PE?

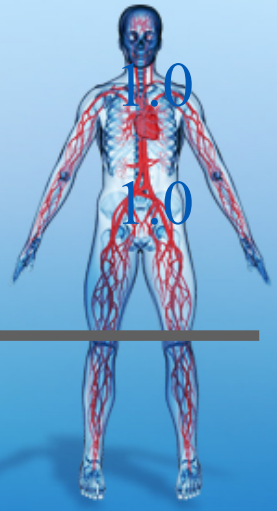
1. Low Wells model
2. Compression US first then if normal do a V/Q; normal V/Q excludes PE
3. V/Q: normal V/Q excludes PE
4. CT pulmonary angiogram: Normal excludes PE

Return to Question 5

Wells Clinical Model for PE

	Points
• Clinical symptoms of DVT	3
• No alternative diagnosis more likely than PE	3
• Heart rate over 100	1.5
• History of immobilization or surgery in previous 4 weeks	1.5
• Previous DVT/PE	1.5
• Hemoptysis	1.0
• Cancer	1.0

Total Score ≤4 = negative, >4 = positive



D-Dimer looks good …but needs validation

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  - 13 (8.7%) had DVT

WS Chan, S Chunilal, A Lee, M. Rodger and JS Ginsberg. Annals Int Med 2007

Table 3. **Patient Outcomes at 3 Months after Exclusion of Pulmonary Embolism***

70% of pregnant women had incomplete work-up for ?PE!!

	(*n* = 418)	(*n* = 506)	alue
Total thromboembolic events, *n* (%)	5 (1.2)	39 (7.7)	<0.001
Nonfatal thromboembolic event, *n*	2	10	0.045
Unexplained sudden death, *n*	3	29	<0.001

* Patients who received anticoagulation for reasons other than thromboembolic disease were excluded from follow-up analysis.

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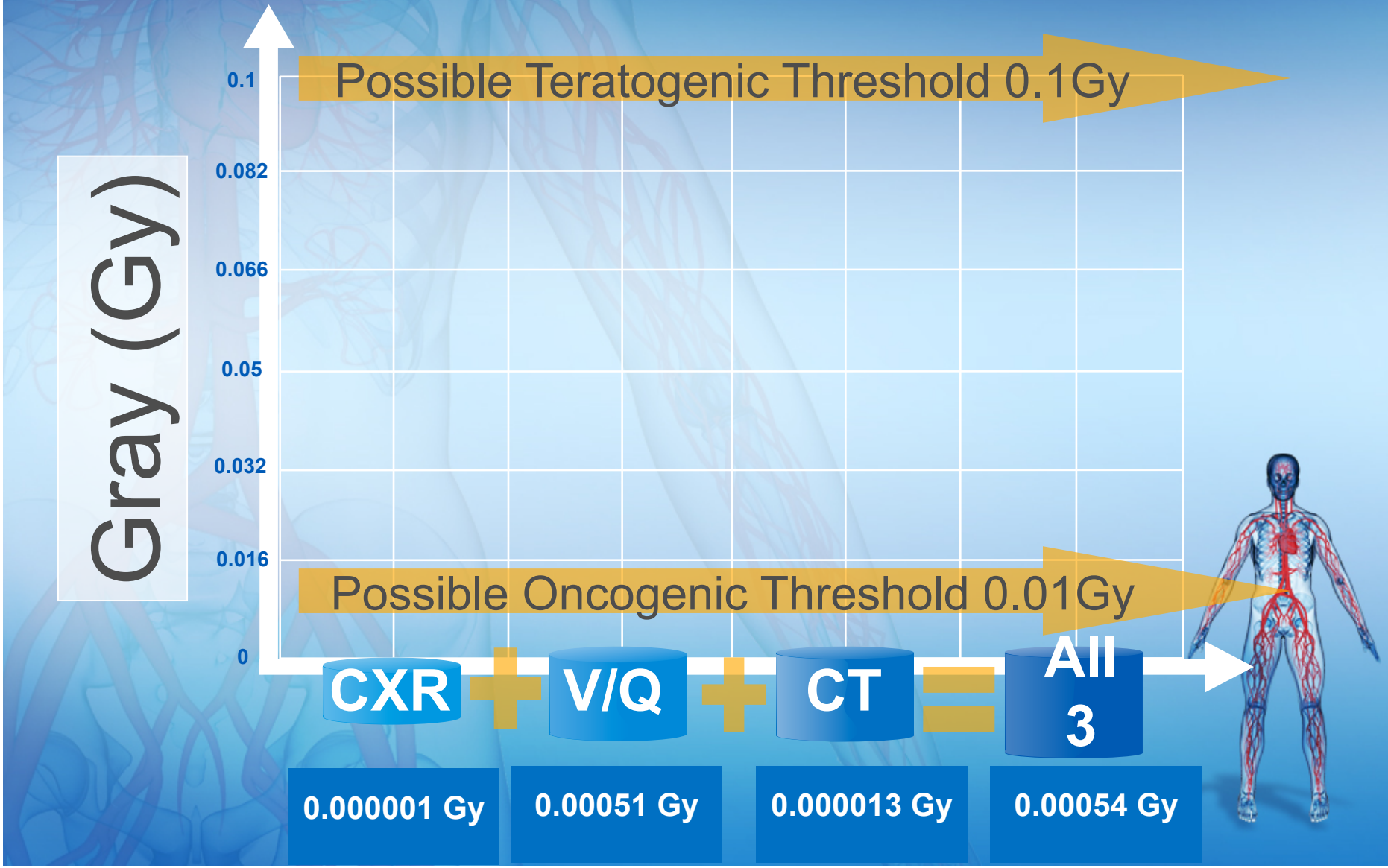
Roy P et al. Ann Intern Med 2006;144:157-164

Annals of Internal Medicine

Radiation Exposure to Fetus



V/Q Test of Choice in Pregnancy: Disadvantages of CT over V/Q

- Proportion non-diagnostic V/Q and CT ***same*** in meta-analysis (2391pts with ?PE in pregnancy)
  - Non-diagnostic CT- 12.5% (95% CI 7.5-18.4%)
  - Non-diagnostic V/Q- 11.5% (95% CI 5.3- 19.6%)

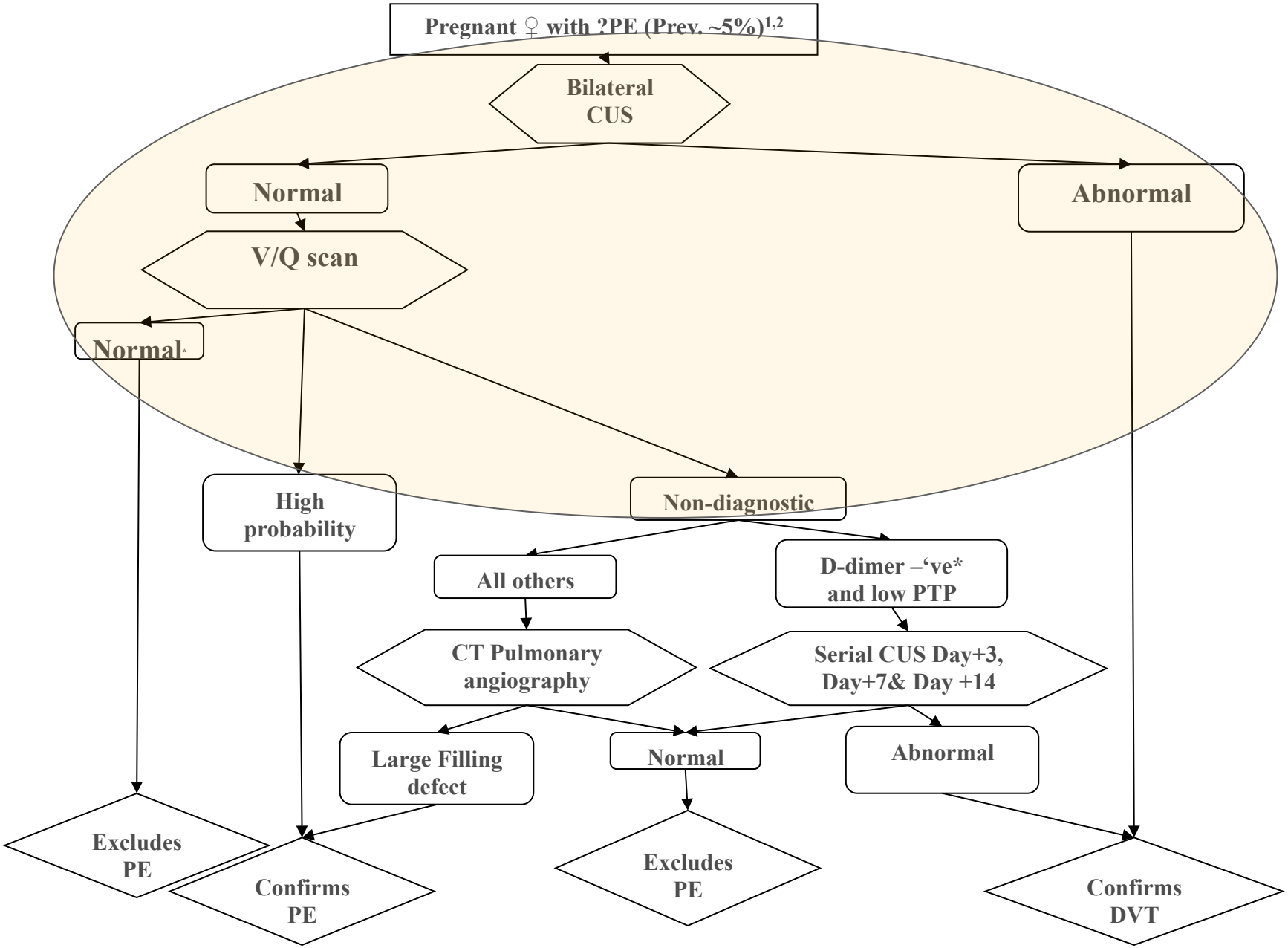
- V/Q normal in >70% of patients in pregnancy with ?PE[2,3]

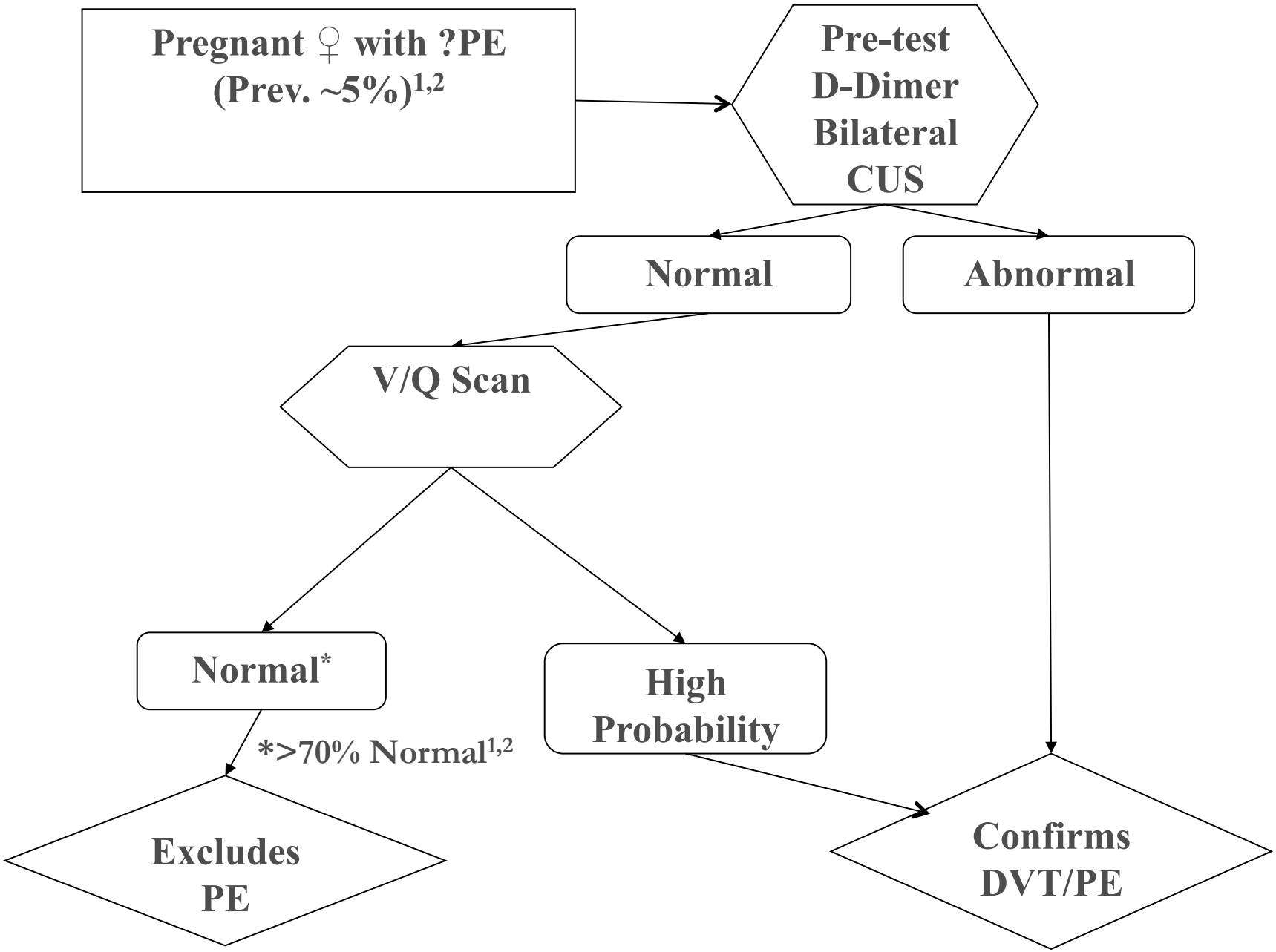
1- Parker, ISTH oral presentation 2015; 2- Chan et al, Arch Int Med, 2002; 3-Cahill, Obstet Gynecol, 2009;

V/Q Test of Choice in Pregnancy: Disadvantages of CT over V/Q

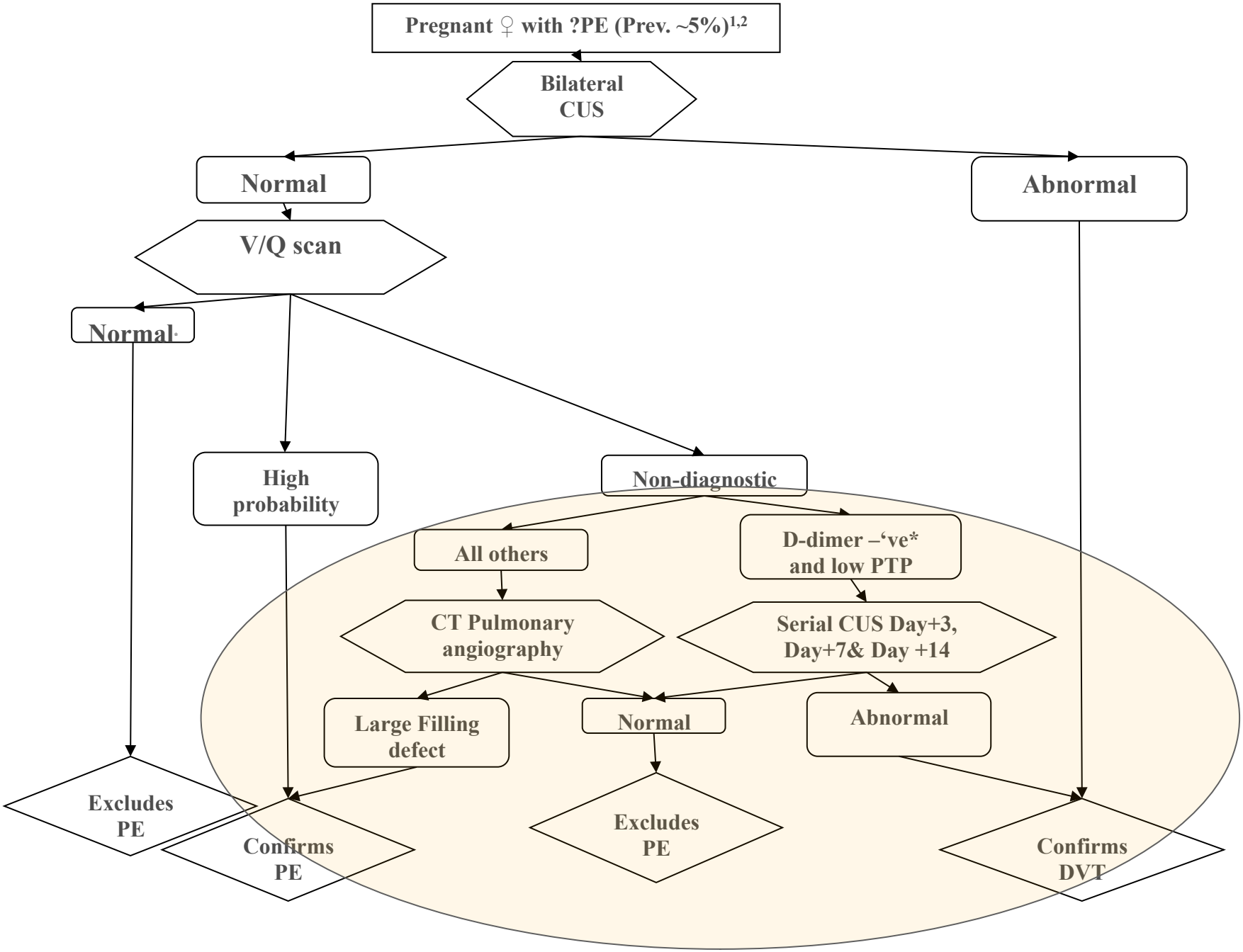
- Increase lifetime risk of malignancy from radiation exposure
  - 150X ↑ breast radiation than V/Q
  - 1 in 143 in 20 y.o. non-pregnant ♀[1]
- SOGC 2014: favor V/Q over CT

1-Einstein, JAMA 2007


Pregnant ♀ with ?PE (Prev. ~5%)[1,2]
Bilateral CUS
Normal
Abnormal
V/Q scan
Normal*
High probability
Non-diagnostic
All others
D-dimer –'ve* and low PTP
CT Pulmonary angiography
Serial CUS Day+3, Day+7& Day +14
Large Filling defect
Normal
Abnormal
Excludes PE
Confirms PE
Excludes PE
Confirms DVT



1-Chan et al, Arch Int Med, 2002; 2-Cahill, Obstet Gynecol, 2009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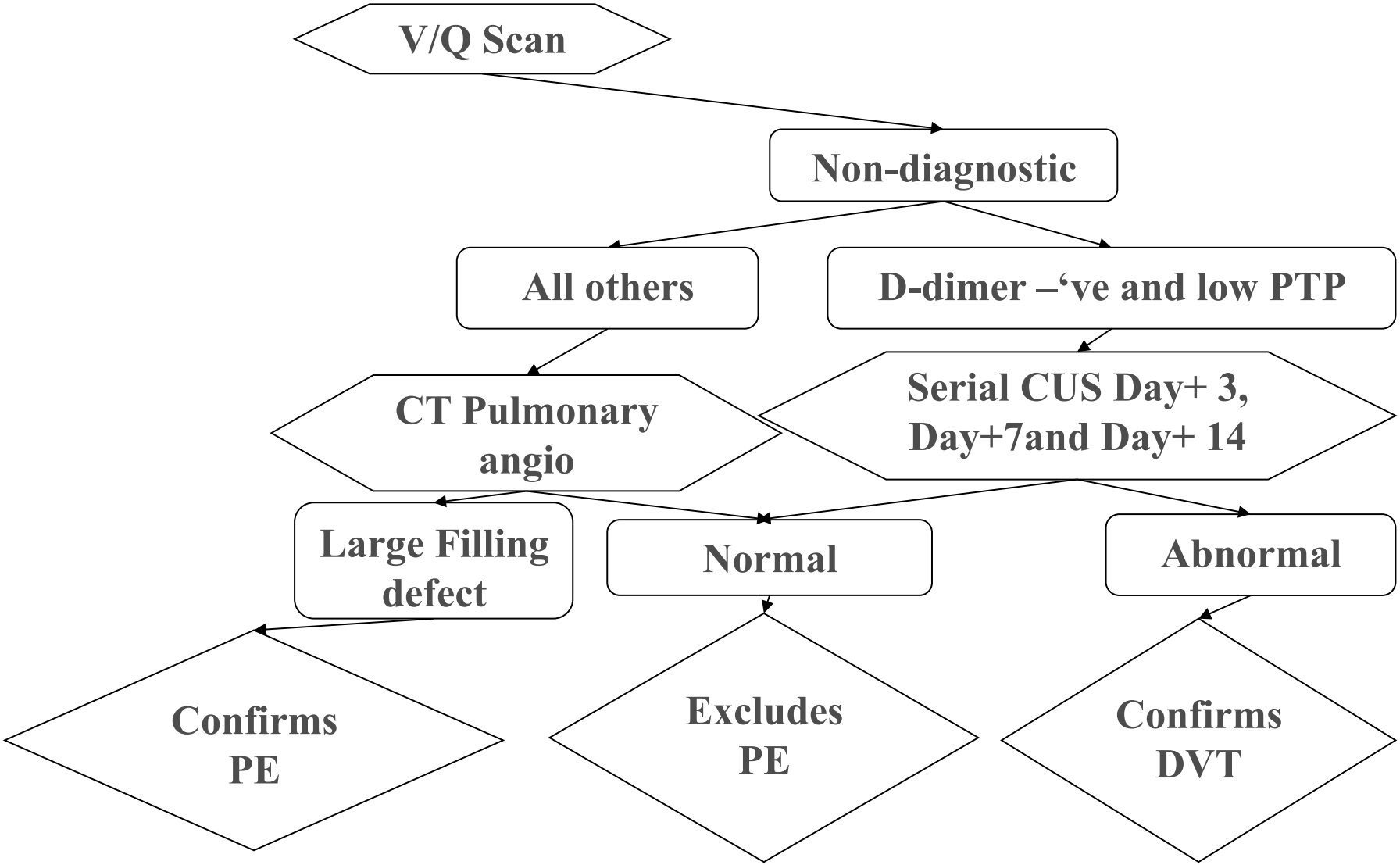
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Serial CUS Day+ 3, Day+7and Day+ 14
Large Filling defect
Normal
Abnormal
Confirms PE
Excludes PE
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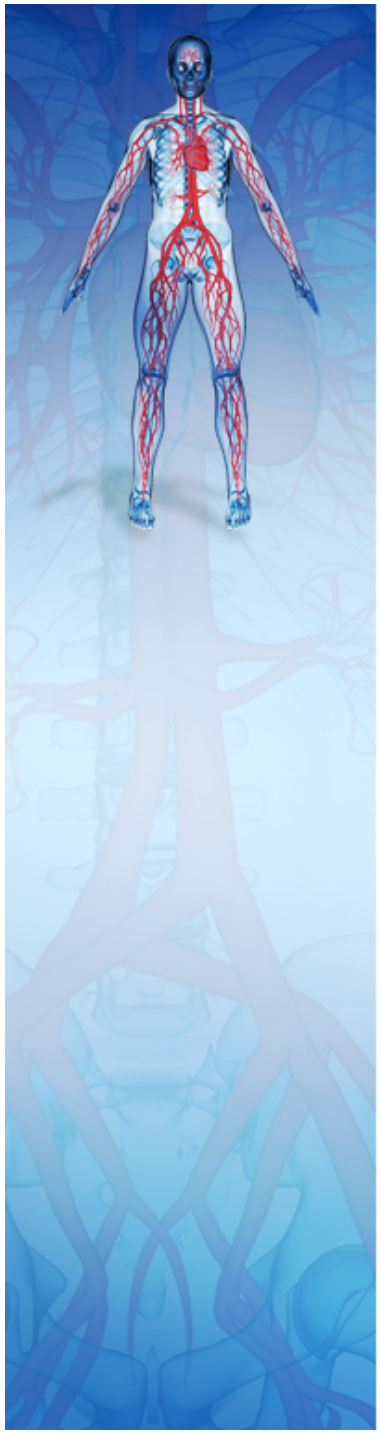

Case (fictional)

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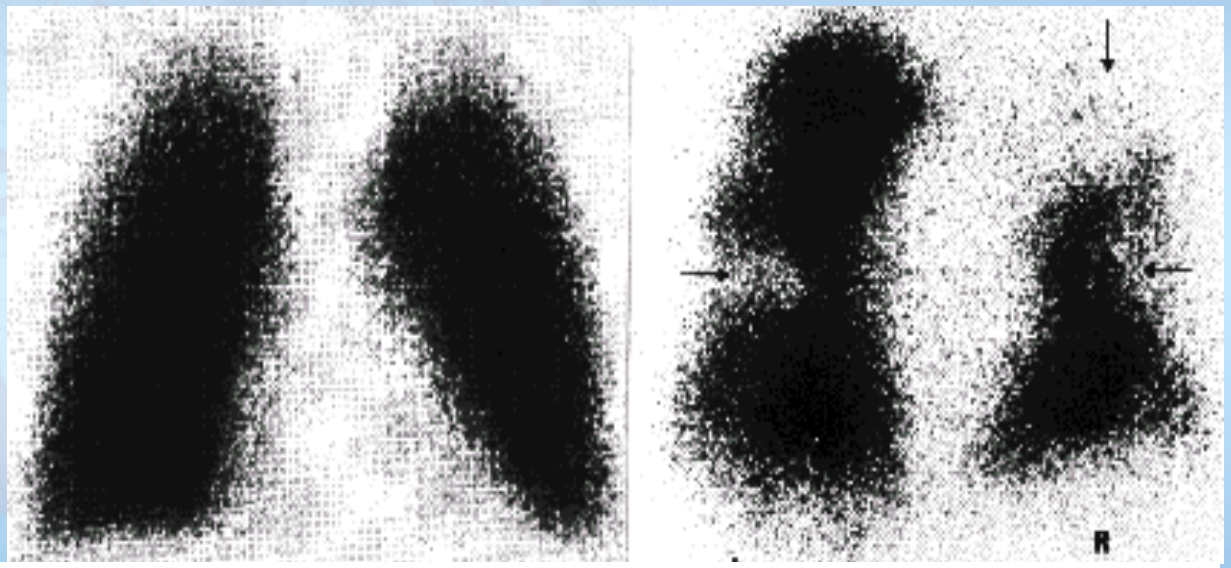
How would you exclude PE?

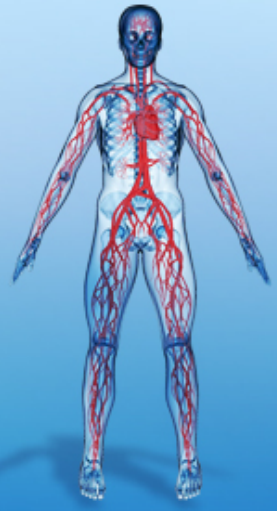
1. Low Wells model
2. **Compression US first then if normal do a V/Q; normal V/Q excludes PE**
3. *V/Q: normal V/Q excludes PE*
4. CT pulmonary angiogram: Normal excludes PE

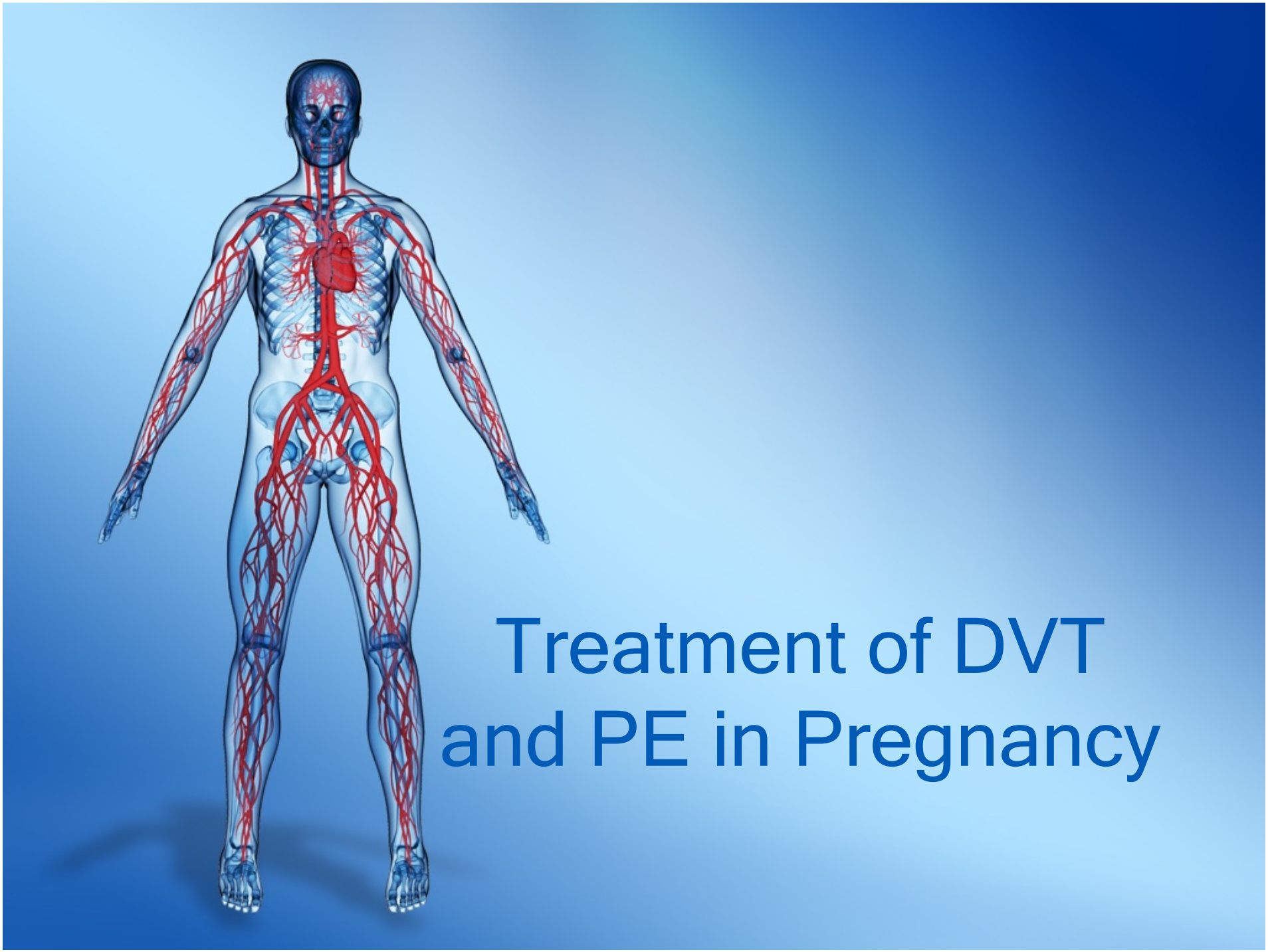
Case (fictional): V/Q Scan- High Probability



V: Normal

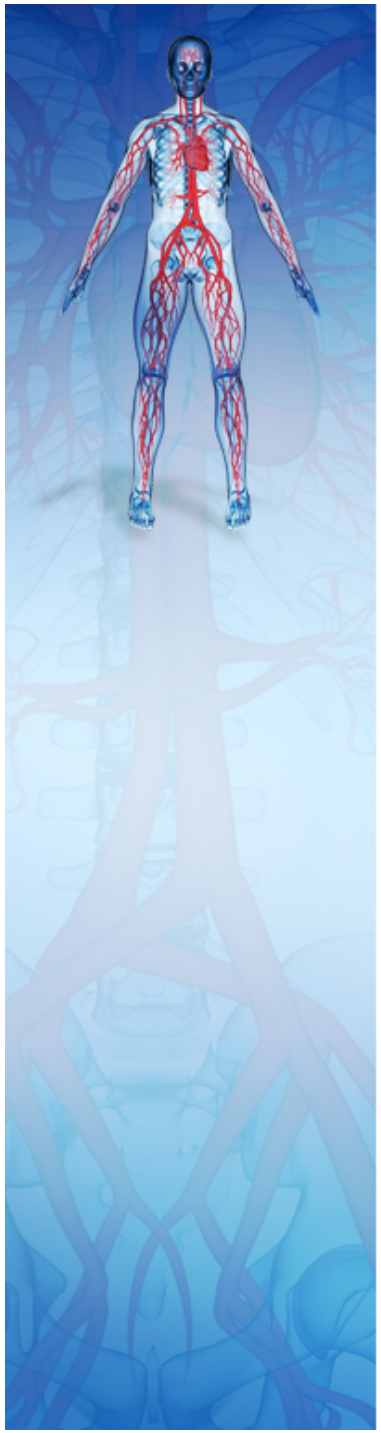
Q: Multiple Large Mismatches




Treatment of DVT
and PE in Pregnancy

Pharmacotherapeutics the options…

- Low Molecular Weight Heparin (LMWH) is the preferred choice in pregnancy (ACCP 2012)
  - Unfractionated heparin
    - BID with at least weekly mid-interval PTTs, 10x ↑ risk of HIT and >10x ↑ risk of osteoporotic fracture
  - Warfarin
    - Teratogenic ante-partum and inconvenient post-partum
  - Direct Oral AntiCoagulants
    - Cross placenta and enter breast milk



Case (fictional)

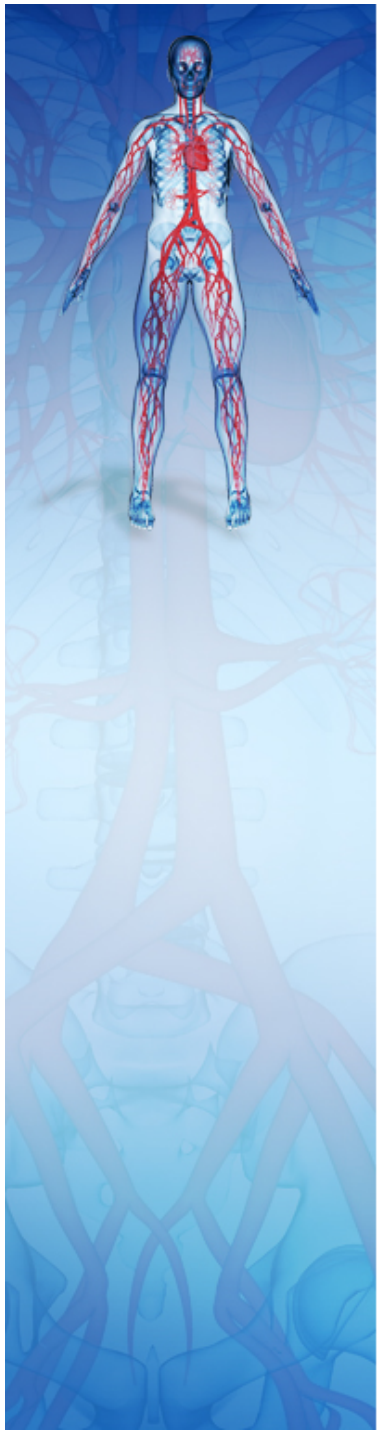
PE is diagnosed at 30 weeks!

Treatment in first 3-4 weeks?

ACCP 2012: No specific recommendations but implied that all of these would be considered reasonable options
SOGC 2014: Text suggests current weight OD or BID with monitoring during first month

monitoring

3. Full *daily* dose LMWH based on current weight; no monitoring
4. Full *daily* dose LMWH based on current weight with weekly anti-Xa monitoring

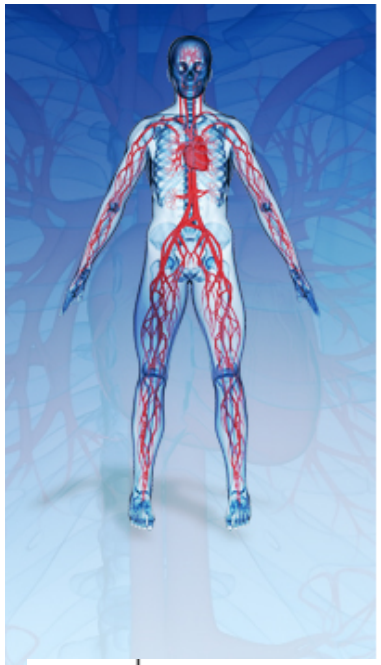


Case (fictional)

PE is diagnosed at 30 weeks!

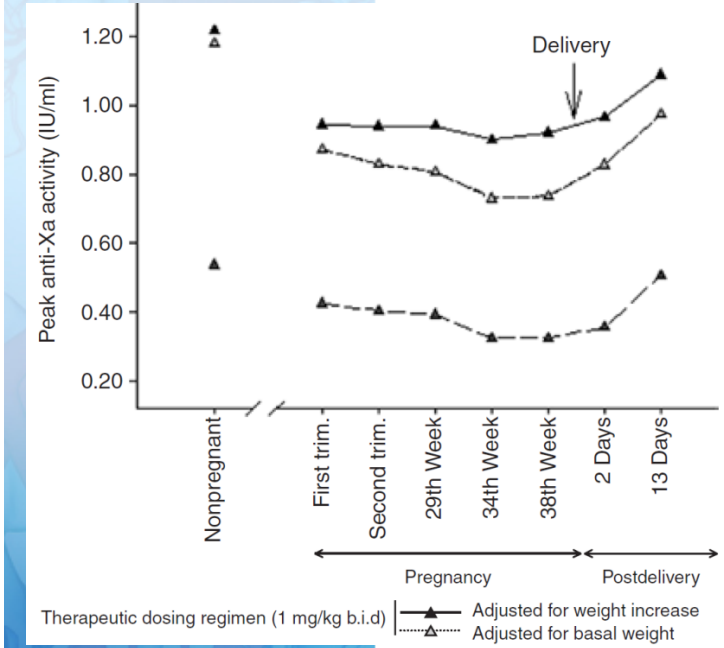
Treatment in first 3-4 weeks?

1. Full *q12h* dose LMWH based on current weight; no monitoring
2. **Full *q12h* dose LMWH based on current weight with weekly anti-Xa monitoring**
3. Full *daily* dose LMWH based on current weight; no monitoring
4. Full *daily* dose LMWH based on current weight with weekly anti-Xa monitoring

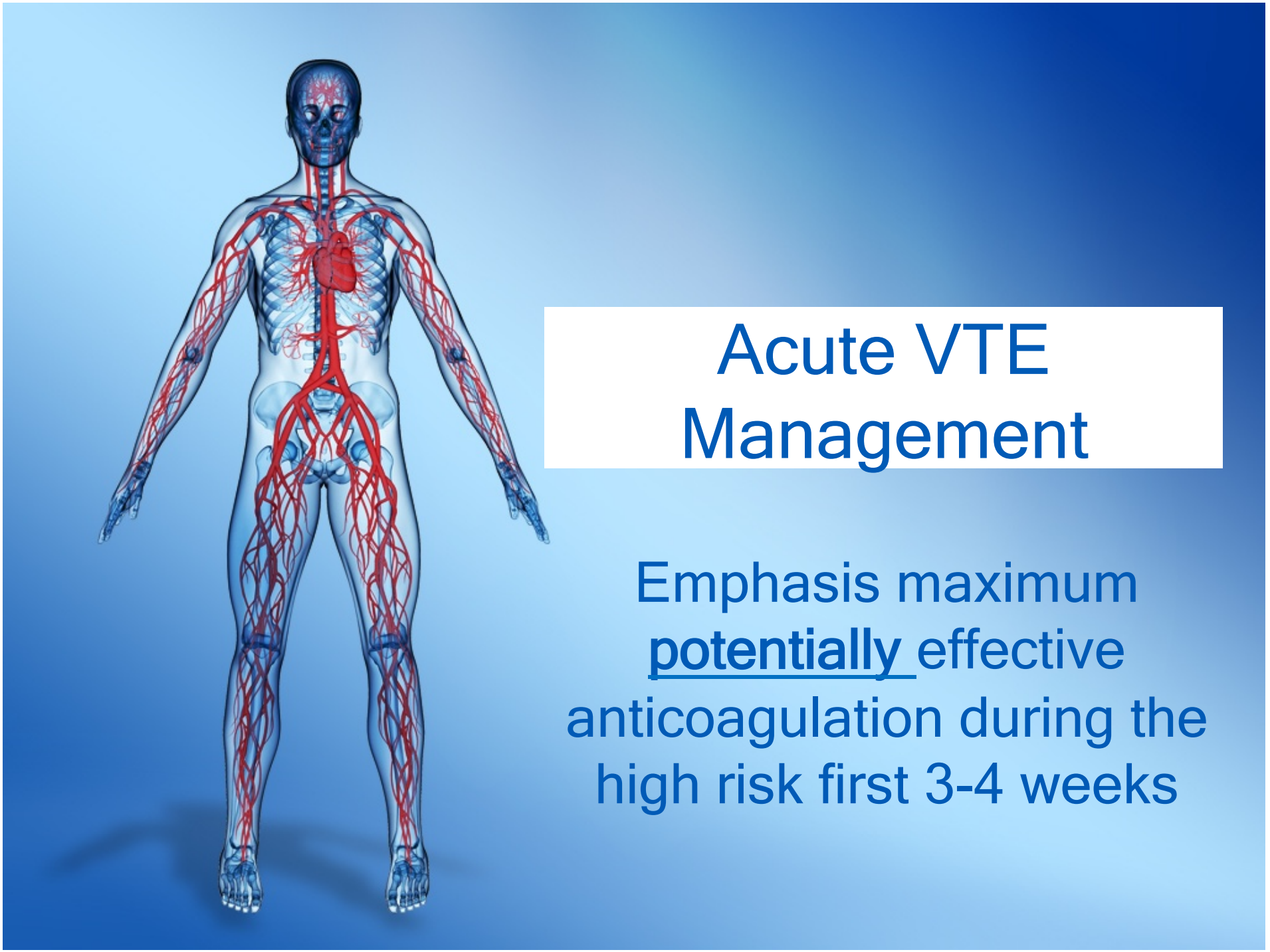


LMWH Pharmacokinetics in pregnancy suggest use **current** body weight

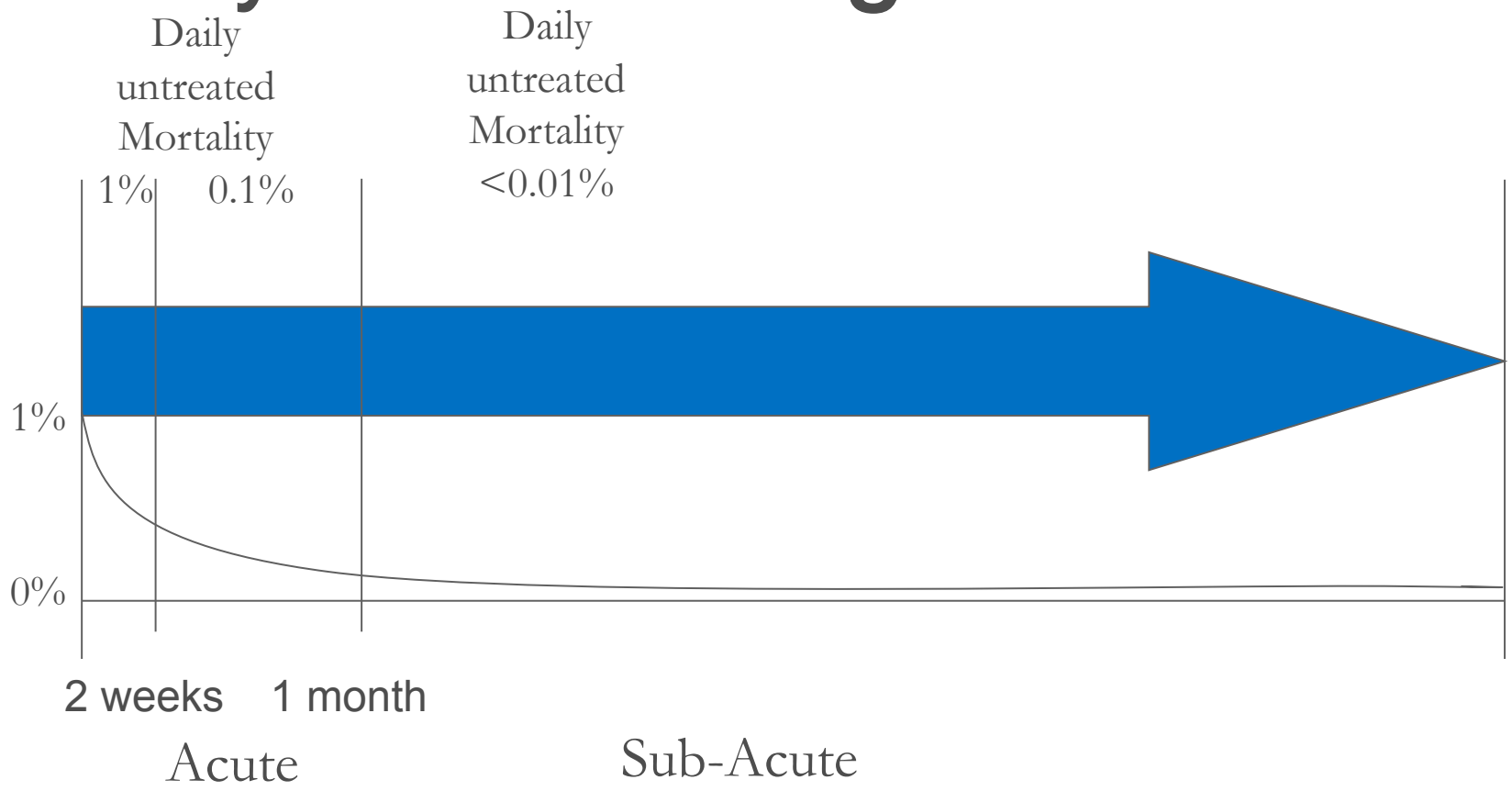
- Population pharmacokinetic study of 75 pregnant ♀ and 38 non-pregnant ♀[1]
  - Clearance higher in pregnant ♀ (0.78 +/-0.03 vs 0.52+/-0.03 l/hr) (parallels 50%↑ GFR 1st trim.)
  - Volume distribution higher in pregnant ♀ (parallels weight gain of pregnancy and additional 40% ↑ last 8 weeks)

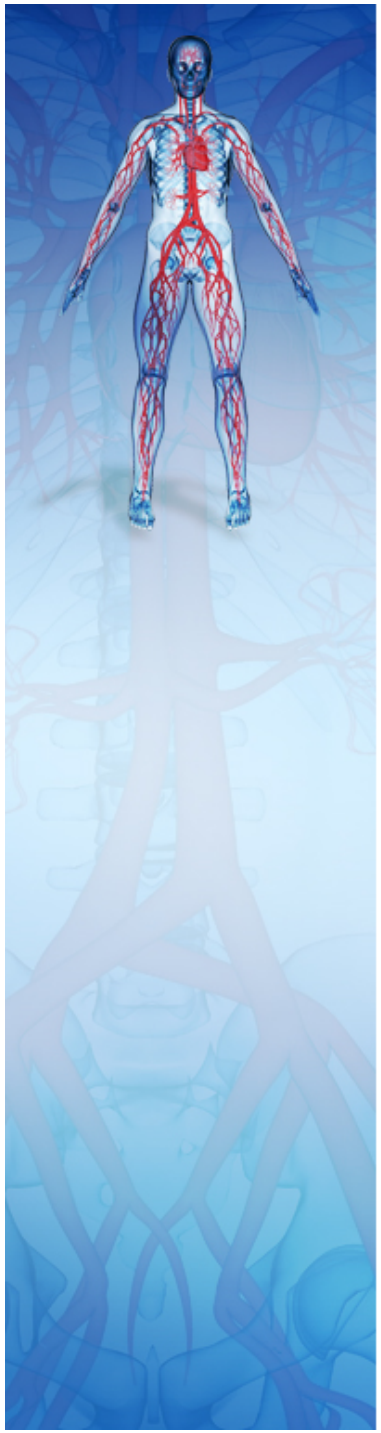


1- Lebaudy, Clin Pharm Therapeutics 2008


Acute VTE Management
Emphasis maximum potentially effective anticoagulation during the high risk first 3-4 weeks

Treatment of VTE: Untreated Mortality in **Non -Pregnant** Patients

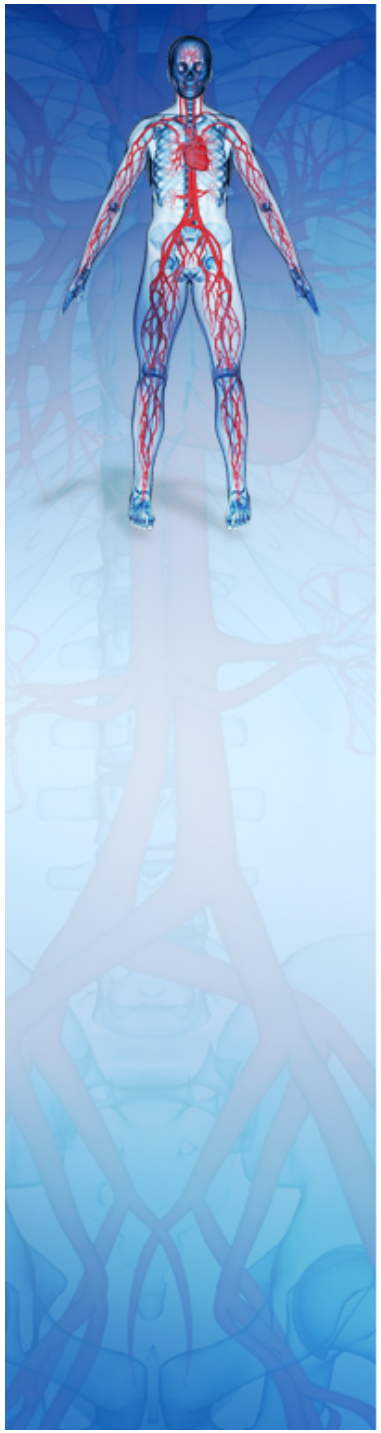




How I treat pregnancy associated VTE in first 3-4 weeks…

- Twice daily (q12h) full dose LMWH based on current pregnancy weight
- Once weekly peak Anti-Xa levels to confirm not sub-“therapeutic”

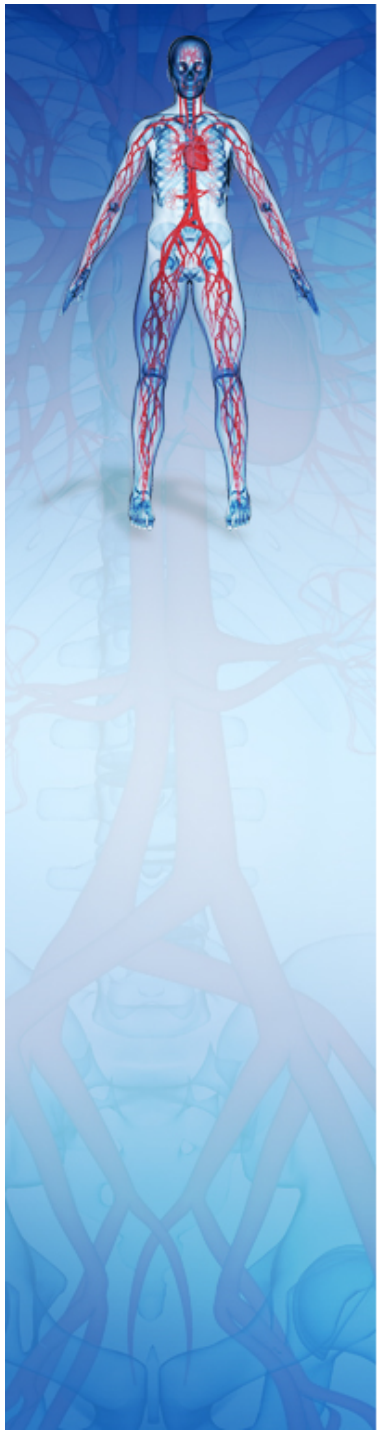
1- van Dongen CJ, Cochrane Database Syst Rev, 2005



How I treat pregnancy associated VTE in first 3-4 weeks…

- Twice daily (q12h) full dose LMWH based on current pregnancy weight
  - Non-pregnant: trend of better efficacy with q12h[1]
  - Pharmacokinetic data suggests earlier trough in pregnancy
- Once weekly peak Anti-Xa levels to confirm not sub-“therapeutic”

1- van Dongen CJ, Cochrane Database Syst Rev, 2005

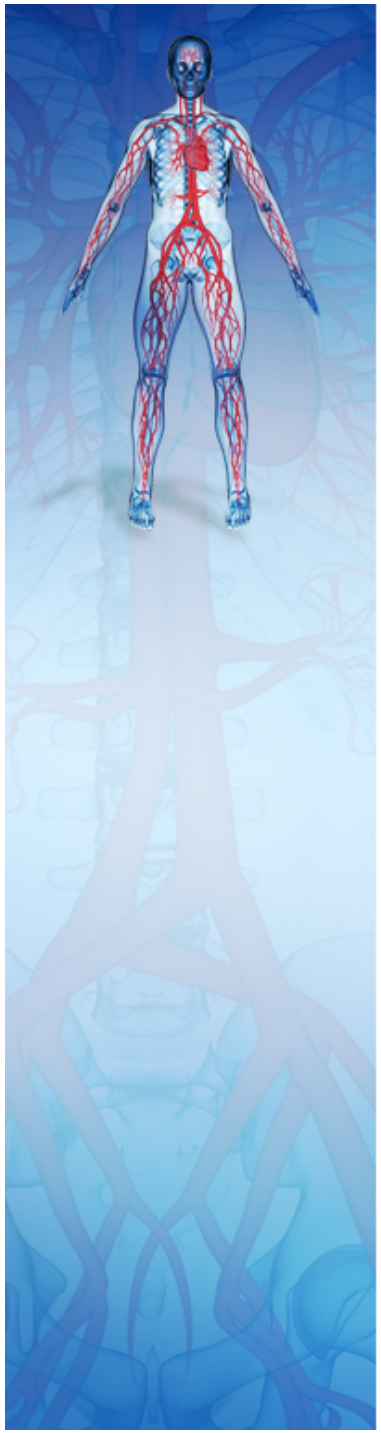


Case (fictional)

Treatment *after* the first month?

ACCP and SOGC: Implied that all of these would be considered reasonable options

2. Full *daily* dose LMWH with anti-Xa monitoring
3. Full *daily* dose LMWH without anti-Xa monitoring
4. 3/4 *daily* dose LMWH without anti-Xa monitoring



Case (fictional)

Treatment *after* the first month?

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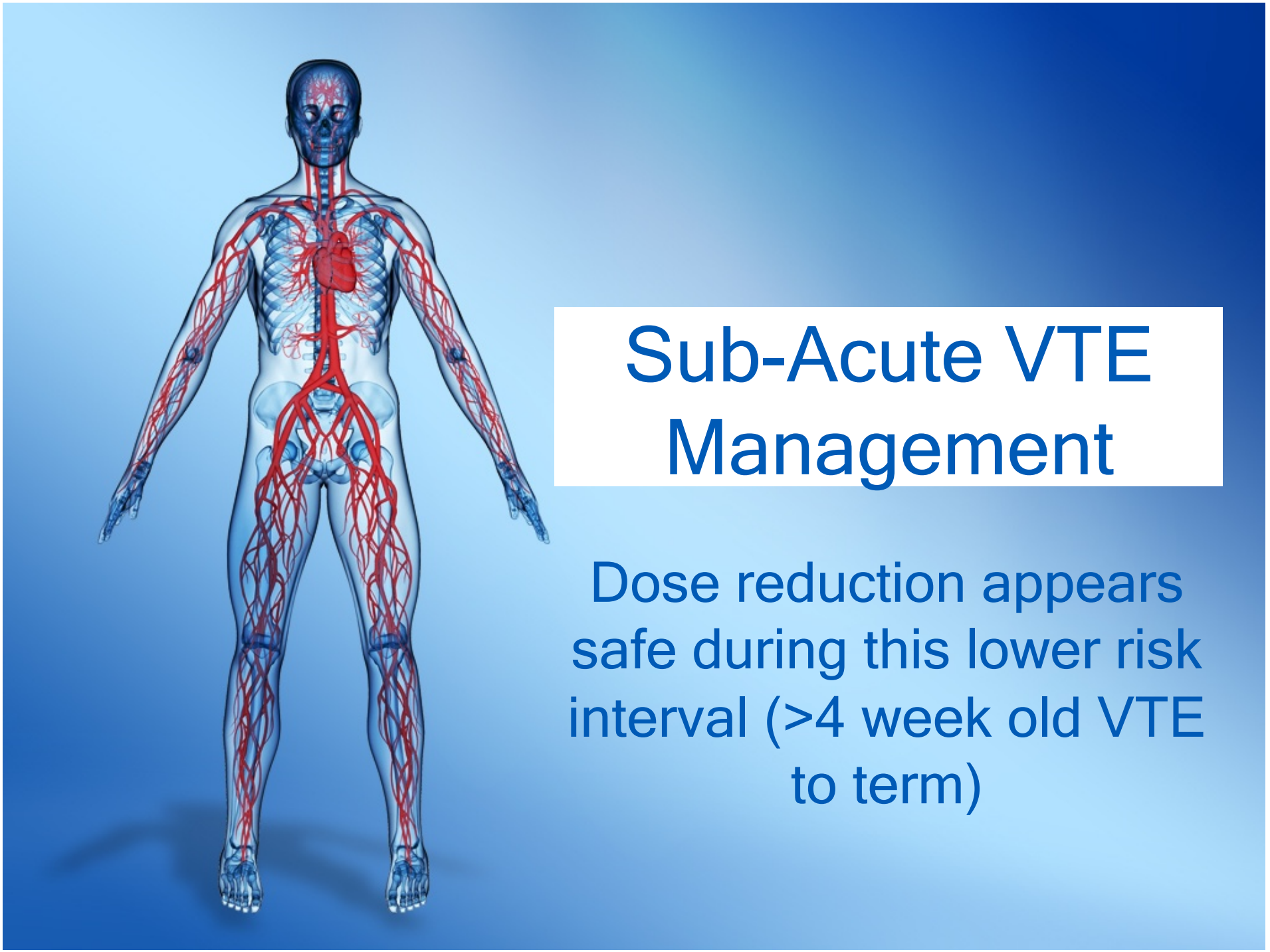
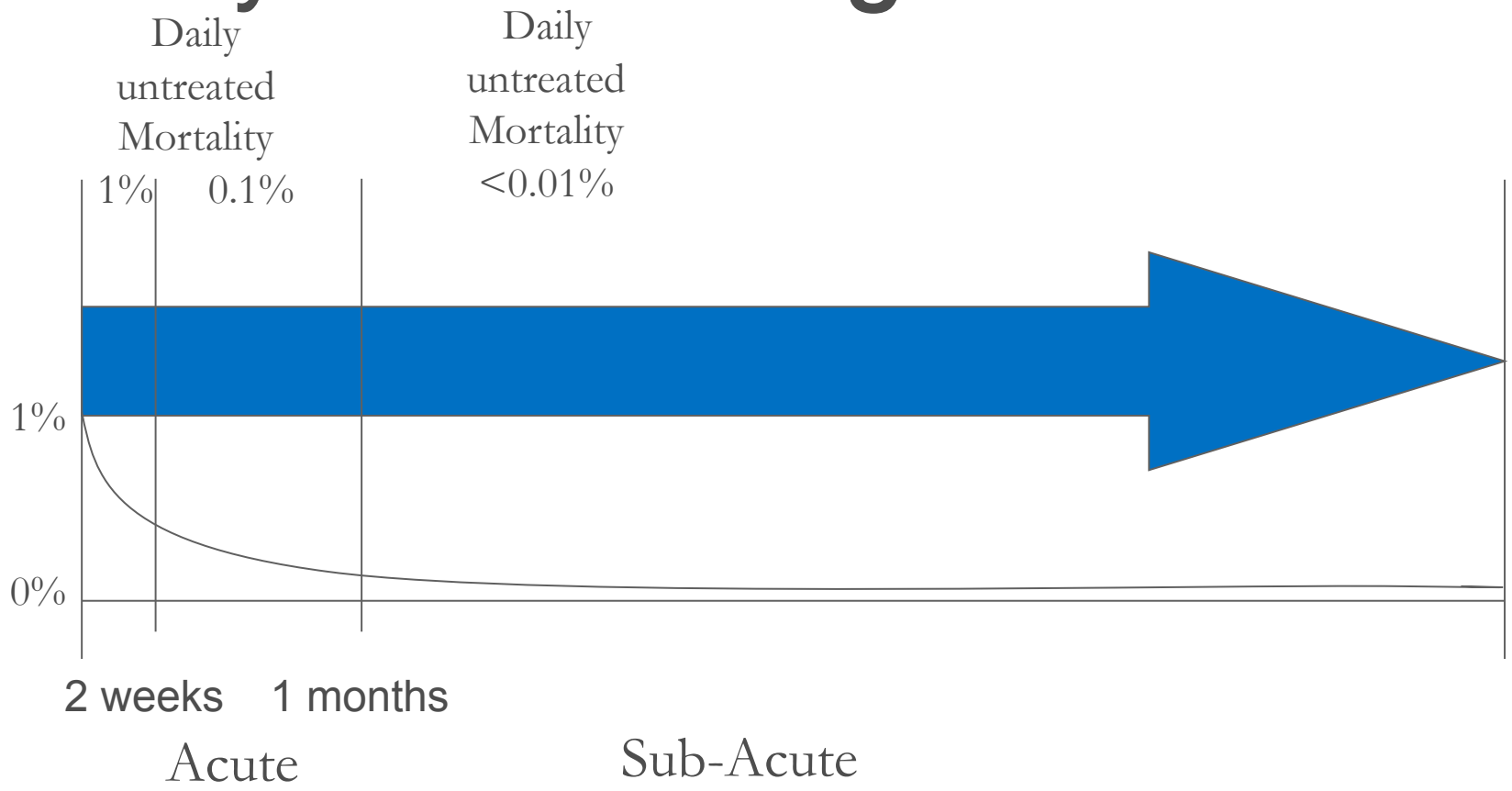
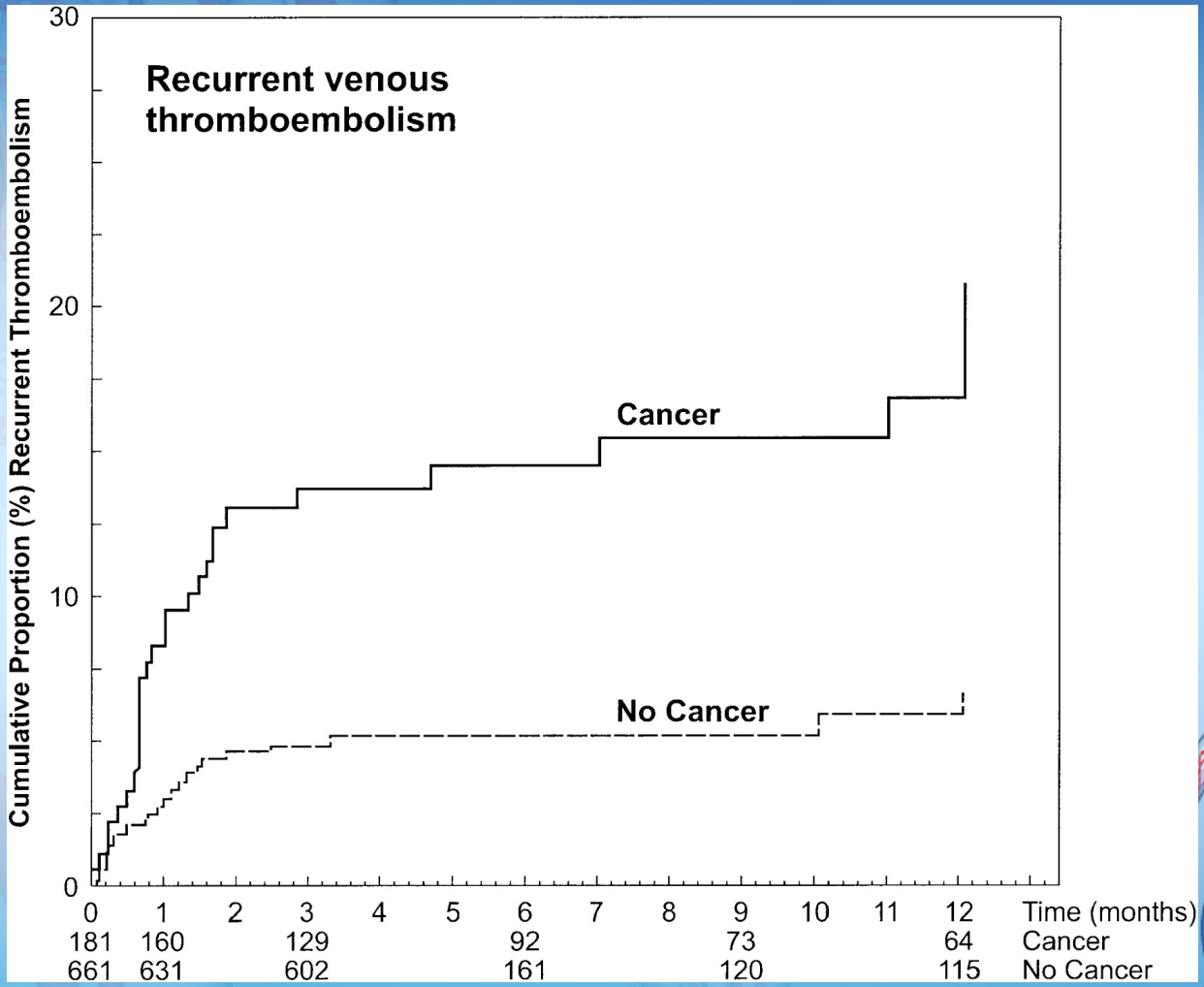
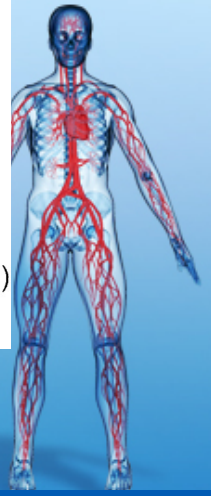

Sub-Acute VTE Management
Dose reduction appears safe during this lower risk interval (>4 week old VTE to term)

Treatment of VTE: Untreated Mortality in **Non -Pregnant** Patients



blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY





Prandoni, P. et al. Blood 2002;100:3484-3488

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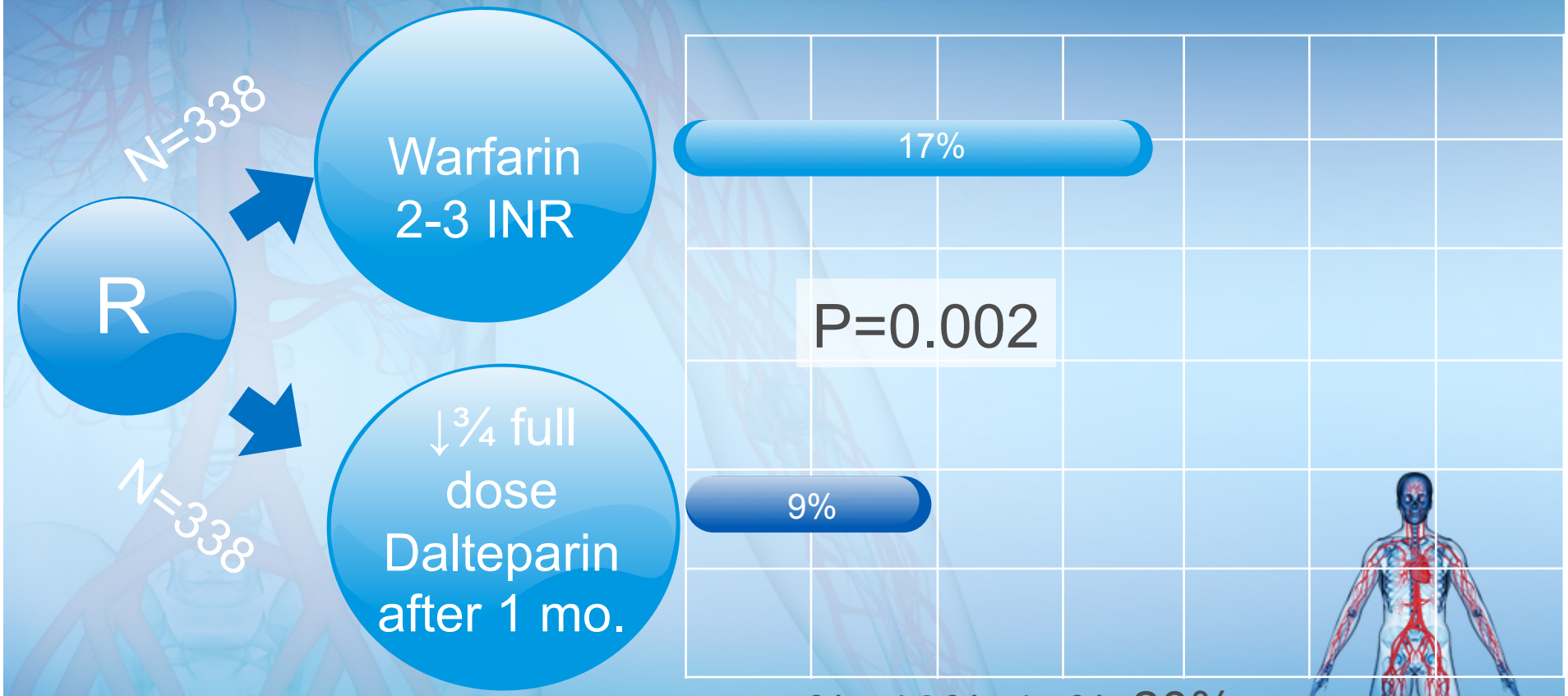
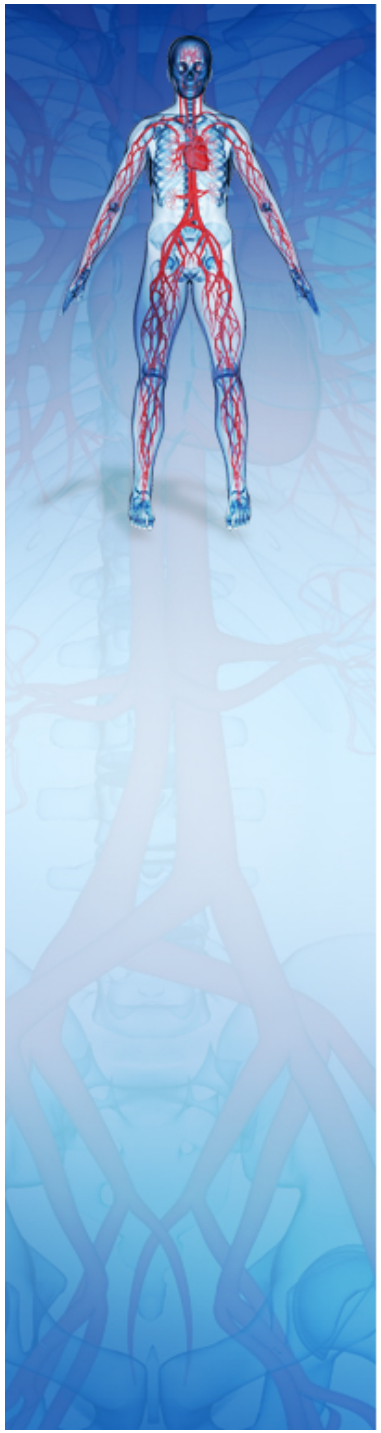
RCT in Cancer Associated Thrombosis



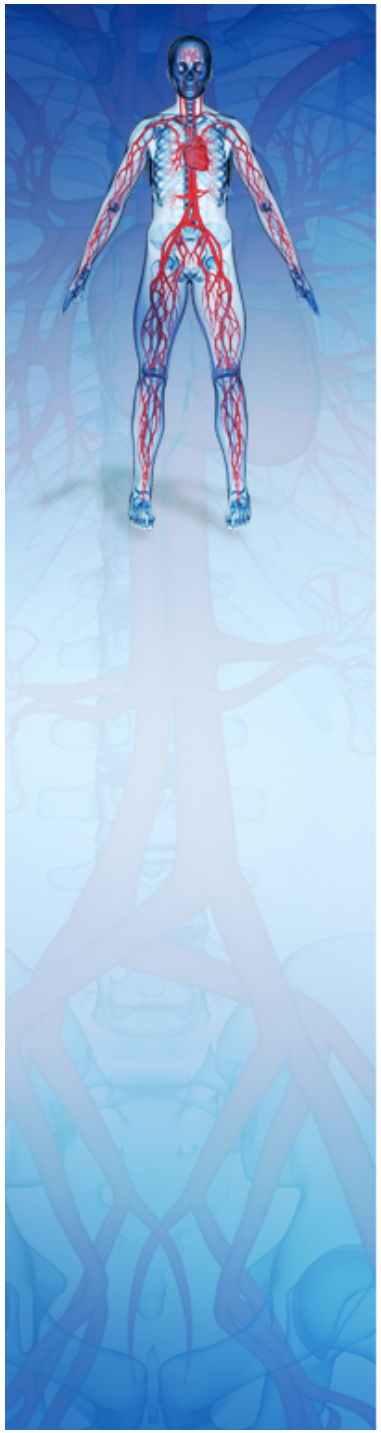
Lee et al. NEJM 2003



How I treat pregnancy associated VTE after 3-4 weeks…

- Once daily 3/4 dose LMWH based on current pregnancy weight with no monitoring
  - Non-pregnant: safe in cancer patients
  - Pregnant: small studies suggest safe[1-3]

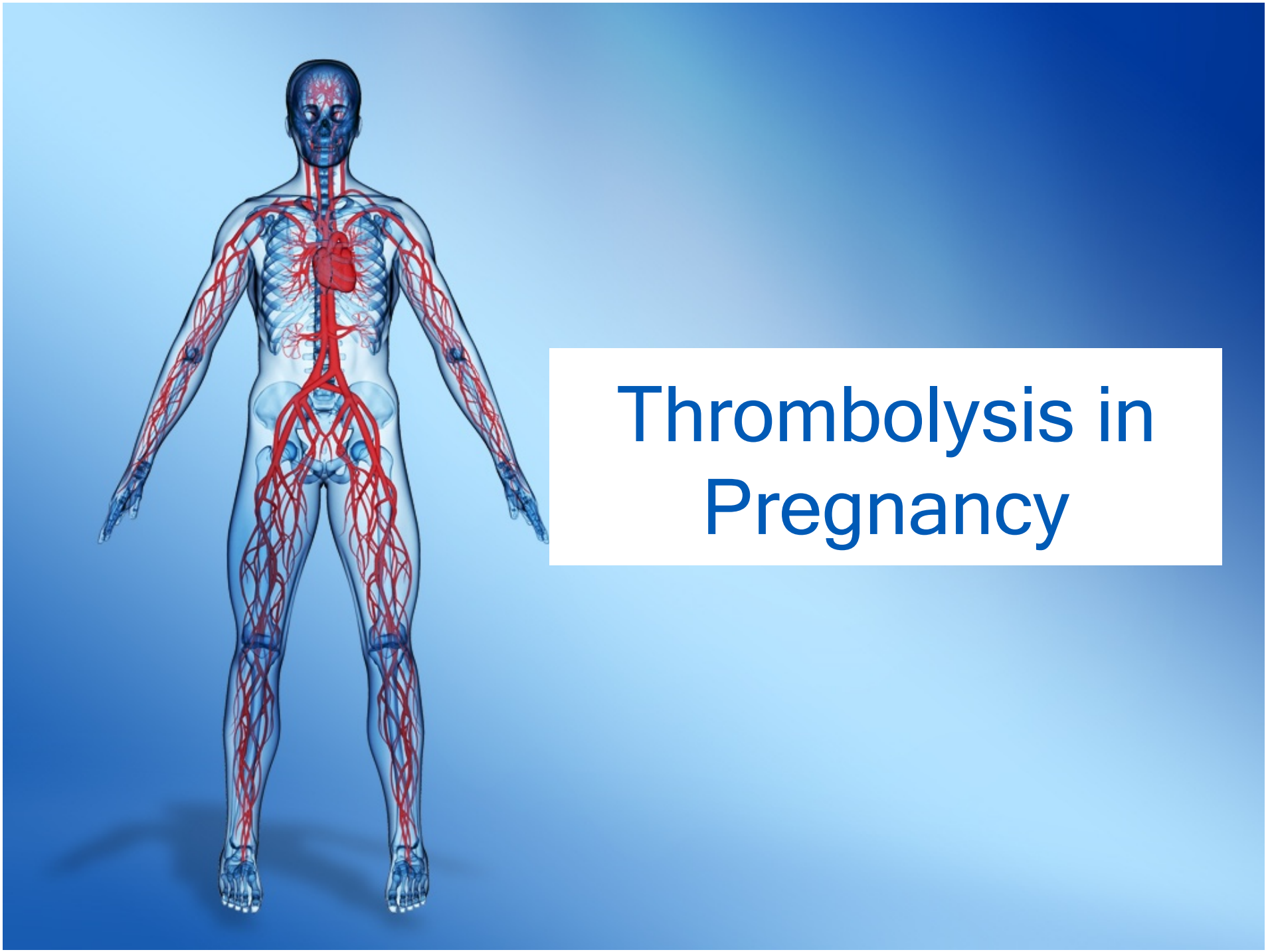
1- Pettila, Kaaja TH, 2002;87:182-186
2-Van Roojen, Acta Obstet Gynecol Scand 2005 84:1018-1023
3-Le Templier, Thrombosis Research, 2009 (abstract)

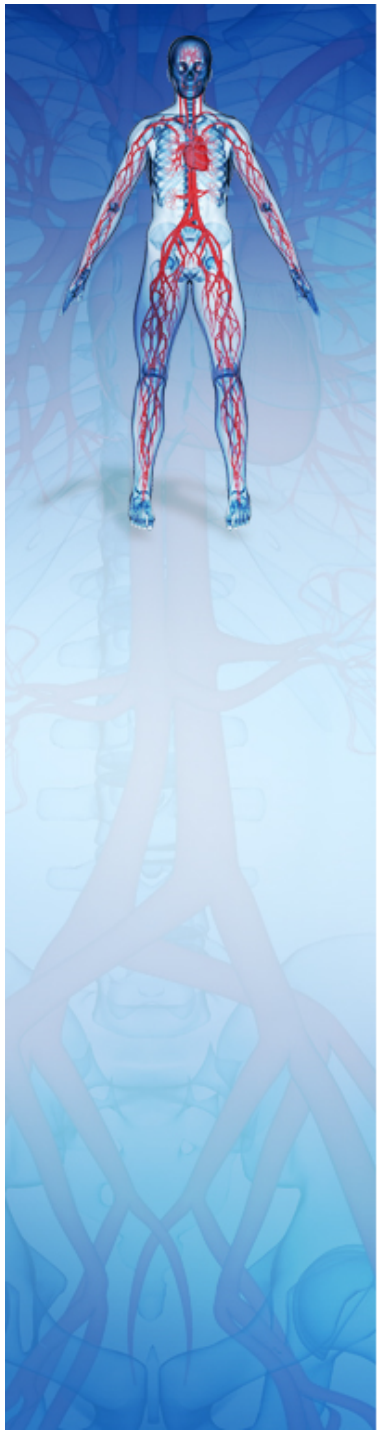


What do your colleagues say they do?…

- ISOM/TIGC survey[1]
  - Initial Acute therapy:
  - -42/69 (61%) LMWH BID over OD
  - -32/69 (46%) monitor Xa
  - Longer-term sub-Acute therapy (>1-3mos)
  - -25/69 (36%) LMWH BID over OD
  - -53/69 (76%) continue full dose
  - -22/69 (32%) monitor Xa[1]

1- Gandara, Thrombosis Journal, 2014;12:12


Thrombolysis in Pregnancy

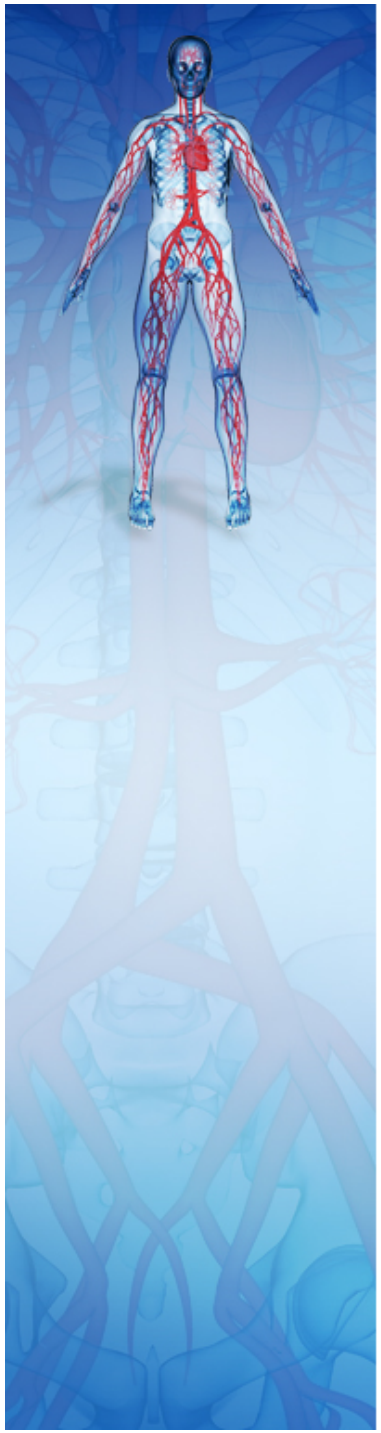


Case 2 (alternate ending)

Massive PE is diagnosed at 30 weeks! (BP 80/pulse on inotropes, SaO2 80% on 100% O2)

Options?

1. Tpa 100mg IV over 2 hrs
2. IV full dose unfractionated heparin



Case 2 (alternate ending)

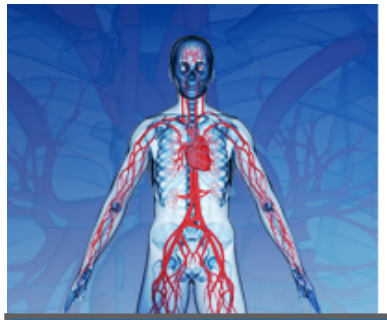
Massive PE is diagnosed at 30 weeks! (BP 80/pulse on inotropes, SaO2 80% on 100% O2)

Options?

1. **Tpa 100mg IV over 2 hrs**
2. IV full dose unfractionated heparin

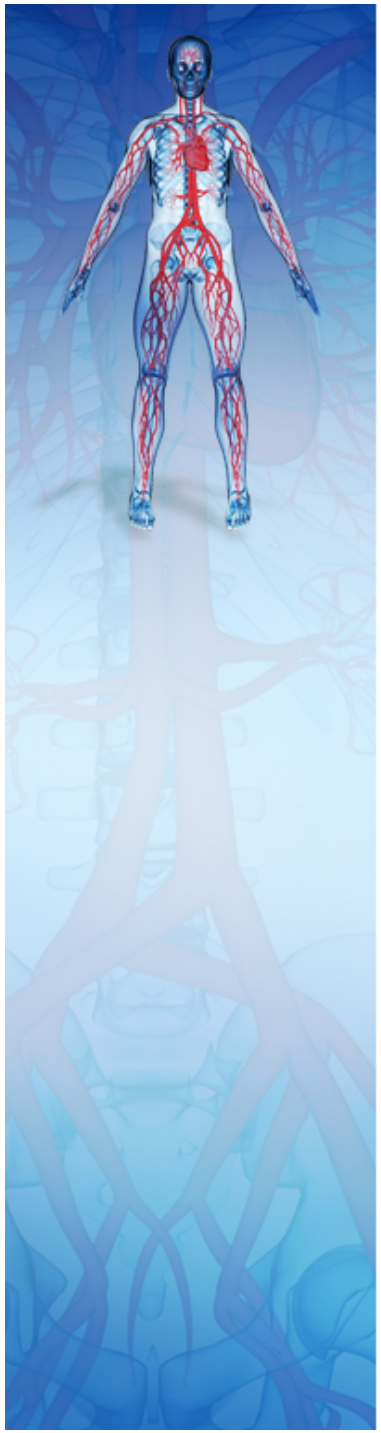
- Case reports support the safety and efficacy of thrombolysis in pregnancy; What choice do we have?
- ACCP/SOGC: Do not use in **non- immediately** life threatening PE

Peri-Partum Management for VTE in this Pregnancy



Peri-Partum Management

Age of VTE	Untreated Daily Fatal PE risk	Peri-Partum Management Post-Partum (PP)
1-14 days	~1%	Retrievable IVC filter LMWH PP D1
2-4 weeks	~0.1%	IV heparin until cervix 3cm Re-start 6 hrs PP
> 4 weeks	~0.01%	Stop split dose LMWH 24hrs prior; re-start PP >6 hours



Take Home Messages

- DVT in pregnancy is likely a north (proximal) to south (distal) disease
- Serial ultrasounds are required to exclude DVT in pregnancy
- V/Q scan remains test of choice for ?PE
- Why *not* dose reduce in sub-acute period for VTE in pregnancy?