Yeni ESC rehberi eşliğinde Pulmoner Embolide 3 soru 3 öneri

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Giriş

- Klinik olarak DVT veya PE olarak ortaya çıkan venöz tromboembolizm (VTE), global olarak miyokard infarktüsü ve inmenin ardından üçüncü en sık akut kardiyovasküler sendromdur.
- Epidemiyolojik çalışmalarda, PE için yıllık insidans oranları 100.000 popülasyonda 39-115; DVT için insidans oranları 100.000 popülasyonda 53-162 arasındadır.
- Kesitsel veriler, VTE insidansının 80 yaş üzeri bireylerde, yaşamın beşinci dekadında olan bireylere göre neredeyse **sekiz kat** daha yüksek olduğunu göstermektedir.

- Daha etkili tedaviler ve müdahalelerin artan kullanımı ve rehberlere daha iyi uyulması, büyük olasılıkla son yıllarda PE'nin prognozu üzerinde önemli bir olumlu etki yapmıştır.
- Bununla birlikte, modern çağda (subsegmental PE veya hatta PE olamayan vakalar) **PE'nin aşırı teşhisine yönelik bir eğilim de vardır ve bu toplam PE sayısını şişirerek ölüm oranlarında yanlış bir düşüşe yol açabilir.**

2019'da yeni/revize kavramlar
Tanı
Yaş veya klinik olasılık için ayarlanan D-dimer cut-off değerleri sabit cut-off değerlere alternatif olarak kullanılabilir.
BT anjiografi ve akciğer taraması kullanılırken güncel radyasyon dozları hakkında bilgi verilir
Risk Değerlendirmesi
Hemodinamik instabilite ve yüksek riskli PE'nin net bir tanımı sağlandı.
Komorbidite / ağırlaştırıcı koşullar ve genel ölüm yerine PE şiddetinin ve erken PE ile ilişkili riskin değerlendirilmesi tavsiye edilir.
Klinik risk skorlamasına göre 'düşük riskli' hastalarda RV işlev bozukluğunun olabileceğine dair net bir uyarı vardır ve bu erken taburculukları etkiler.
Akut fazda tedavi
Yüksek riskli PE için hemodinamik ve solunum desteği ile ilgili bölüm gözden geçirildi.
Yüksek riskli PE için özel bir yönetim algoritması önerilmiştir
YOAK'lar uygun hastalarda antikoagülasyon için ilk seçenek olarak önerilmektedir; VKA, YOAK'a alternatiftir.
Risk ayarlı yönetim algoritması, klinik PE şiddetini, ağırlaştırıcı koşulları / komorbiditesini ve RV fonksiyon bozukluğunun varlığını göz önünde bulundurarak revize edildi.

İlk 3 aydan sonra Kronik Tedavi
VTE rekürrensi için risk faktörleri yüksek, orta ve düşük rekürrens risk faktörlerine göre sınıflandırıldı
Uzatılmış antikoagülasyon için PE endeksi için küçük bir geçici veya geri dönüşümlü risk faktörü varlığını, herhangi bir kalıcı risk faktörü veya tanımlanabilir bir risk faktörü yokluğunu içeren potansiyel endikasyonlar tartışılmıştır.
Rehberlerin desteklediği 'Provoke' ve 'Unprovoke' terimleri potansiyel olarak yanıltıcı ve antikoagülasyonun süresiyle ilgili karar vermede yardımcı olmadığından artık kullanılmıyor.
VTE rekürrens skorları, antikoagülasyon tedavisi alan hastalar için kanama skorlarına paralel olarak sunuldu ve tartışıldı.
Tedavinin ilk 6 ayından sonra uzatılmış antikoagülasyon için daha düşük bir apixaban veya rivaroksaban dozu düşünülmelidir.
Kanserde PE
Edoxaban veya rivaroksaban, NOAC'larla artan kanama riski nedeniyle gastrointestinal kanserli hastalar hariç LMWH'ye alternatif olarak düşünülmelidir.
Gebelikte PE
Gebelikte şüpheli PE için özel bir tanı algoritması önerilmiştir.
Gebelikte PE tanısında kullanılan prosedürlerle ilgili radyasyon maruziyeti hakkında güncel bilgiler verilmektedir
Uzun süreli sekeller
Hastaneden topluma dönüşü en uygun şekilde sağlamak için PE sonrası entegre bir hasta bakımı modeli önerilmiştir.
Hasta bakımı konusundaki öneriler, sadece CTEPH'ye değil, tüm PE sonrası belirtiler ve fonksiyonel sınırlama spektrumuna genişletilmiştir.

Tanı

- Klinik olasılığın tahmini için Geneva ve Wells skorlarının basitleştirilmiş hali klinik pratikte kullanılır.
- Tanısal testlerin gereksiz kullanımını önlemek için Pulmoner Emboli Dışlama Kriterleri geliştirilmiştir.

Items	Clinical decision rule points	
	Original version[1]	Simplified version[2]
Previous PE or DVT	1.5	1
Heart rate >100 b.p.m.	1.5	1
Surgery or immobilization within the past 4 weeks	1.5	1
Haemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alterative diagnosis less likely than PE	3	1
Clinical probability		
Three-level score		
Low	0–1	N/A
Intermediate	2–6	N/A
High	≥7	N/A
Two-level score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2

Modifiye Geneva skoru	Puan
Bacağın palpasyonu ile ağrı veya tek taraflı ödem	4
Tek taraflı alt extremitede ağrı	3
Nabız 75-94	3
≥95	5
Önceden geçirilmiş DVT veya PE	3
Son 1 ayda cerrahi veya ekstremite fraktürü	2
Hemoptizi	2
Aktif kanser	2
Yaş>65	1
Klinik olasılık (Modifiye Geneva)	
3 basamaklı skor	
Düşük	0-3
Orta	4-10
Yüksek	≥11
2 basamaklı skor	
PE olasılığı düşük	0-5
PE olasılığı yüksek	≥6

Pulmonary Embolism Rule-Out Criteria

Is the patient > 49 years?

Is the pulse rate > 99 beats per minute?

Is pulse oximetry < 95% on room air?

Does the patient have current hemoptysis?

Is the patient taking exogenous estrogen?

Does the patient have a history of venous thromboembolism?

Has the patient had surgery or trauma requiring hospitalization in the past four weeks?

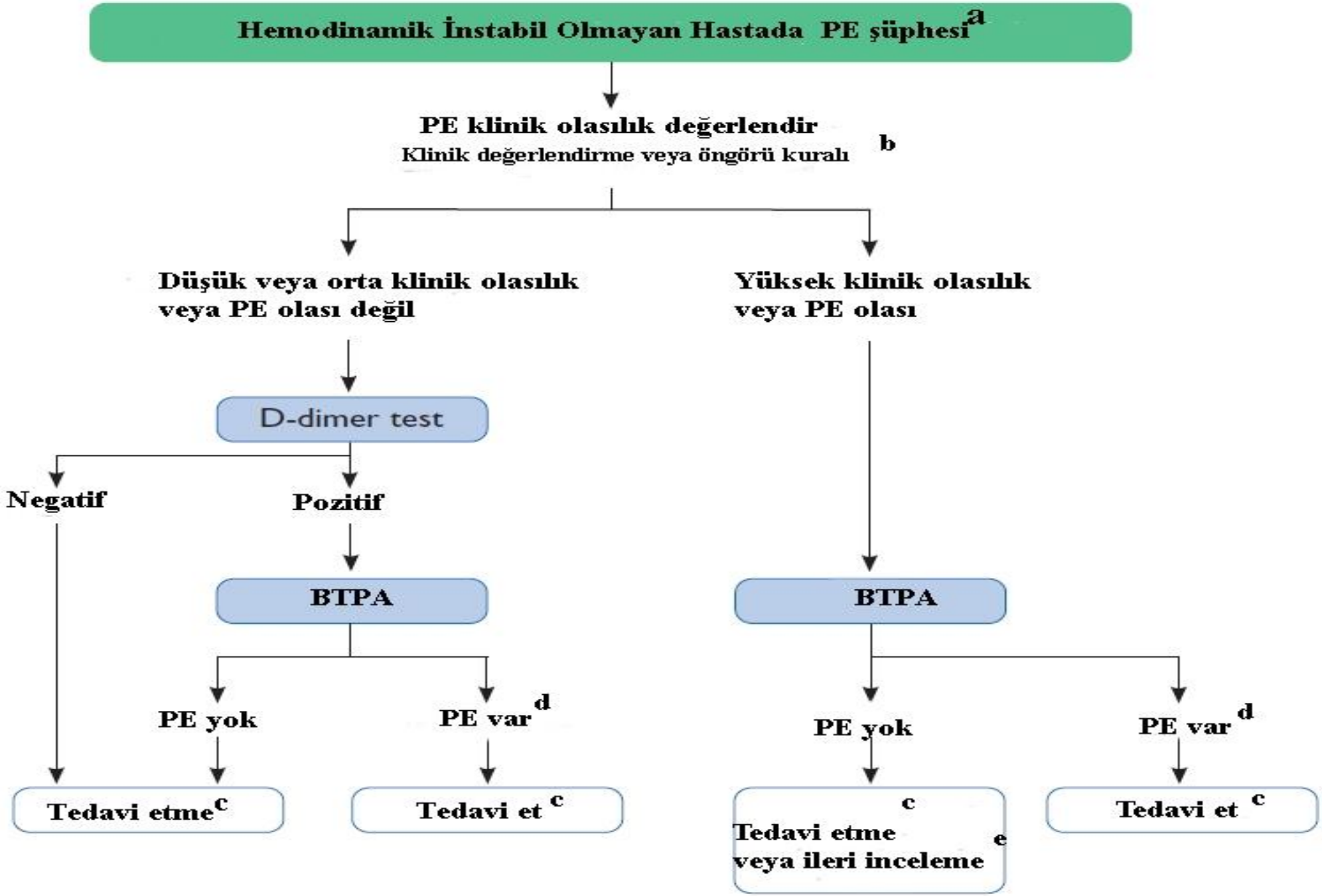
Does the patient have unilateral leg swelling?

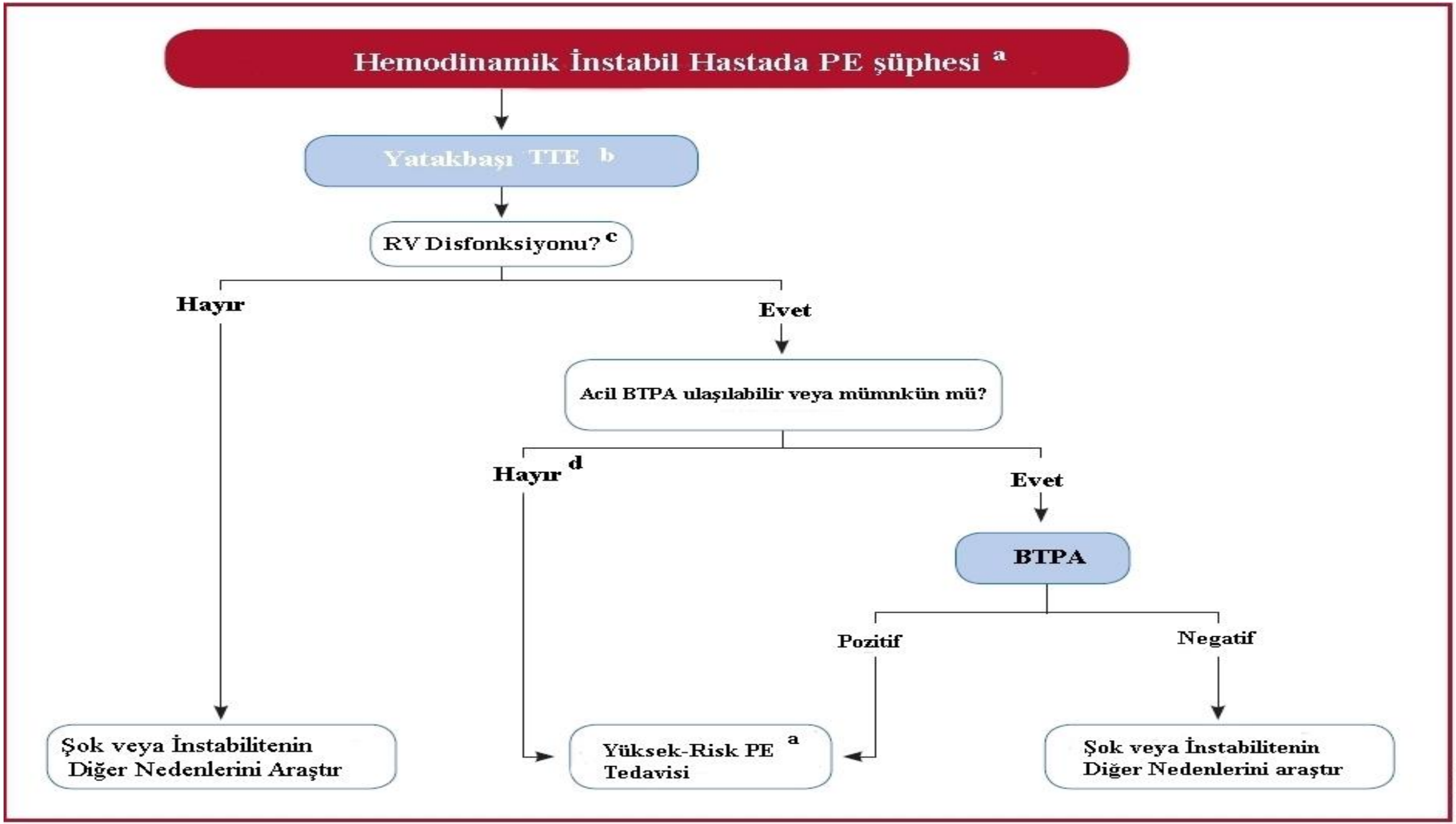
NOTE: *If the patient is considered to be at very low risk of pulmonary embolism (< 15% risk) based on the physician's pretest suspicion, and answers "no" to all eight questions, the criteria results are considered negative.*

Adapted with permission from Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost. *2008;6(5):773.*

- D-dimer'in şüpheli PE'de özgüllüğü, 80 yaşından büyük hastalarda yaşla birlikte ∼% 10'a kadar kararlı bir şekilde azalır. Yeni rehberde yaşa göre ayarlanmış bir D-dimer cut-off değerinin kullanılması veya klinik olasılığa uyarlanmış bir D-dimer testinin kullanılması, sabit cut-off seviyesine bir alternatif olarak önerilmiştir **(>50 yaş hastalarda yaş x10 µg/L)(Kanıt 2A).**
- **Klinik olasılığı yüksek olan hastalarda D-dimer dışlama kriteri olarak kullanılmamalıdır(kanıt 3A).**

- Klinik şüpheli hastada KUS **proksimal venlerde** trombus gösteriyorsa VTE (ve PE) kabul edilir (Kanıt 1A). Şayet distal venlerde trombus gösteriyorsa PE tanısı için ek testlere ihtiyaç vardır (Kanıt 2A).
- MR PE yi dışlama için önerilmiyor (Kanıt 3A)


Hemodinamik İnstabil Olmayan Hastada PE şüphesi[a]
PE klinik olasılık değerlendir
Klinik değerlendirme veya öngörü kuralı [b]
Düşük veya orta klinik olasılık veya PE olası değil
Yüksek klinik olasılık veya PE olası
D-dimer test
Negatif
Pozitif
BTPA
BTPA
PE yok
PE var [d]
PE yok
PE var [d]
Tedavi etme[c]
Tedavi et [c]
Tedavi etme [c] veya ileri inceleme [e]
Tedavi et [c]


Hemodinamik İnstabil Hastada PE şüphesi [a]
Yatakbaşı TTE [b]
RV Disfonksiyonu? [c]
Hayır
Evet
Acil BTPA ulaşılabilir veya mümnkün mü?
Hayır [d]
Evet
BTPA
Pozitif
Negatif
Şok veya İnstabilitenin Diğer Nedenlerini Araştır
Yüksek-Risk PE Tedavisi [a]
Şok veya İnstabilitenin Diğer Nedenlerini araştır
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Prognozu değerlendirmeye göre yapılmış sınıflama 2014

Table 9 Classification of patients with acute PE based on early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI ≥1[a]	Signs of RV dysfunction on an imaging test[b]	Cardiac laboratory biomarkers[c]
High		+	(+)[d]	+	(+)[d]
Intermediate	Intermediate–high	-	+	Both positive	
	Intermediate–low	-	+	Either one (or none) positive[e]	
Low		-	-	Assessment optional; if assessed, both negative[e]	

2019

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate–high	-	+[e]	+	+
	Intermediate–low	-	+[e]	One (or none) positive	
Low		-	-	-	Assesment optional; if assessed, negative

Table 4 Definition of haemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation)

(1) Cardiac arrest	(2) Obstructive shock[68–70]	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis
	And	
	End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	

BP = blood pressure.

Prognostic Model for Pulmonary Embolism: PESI Score

Class 1	Very low risk	≤ 65
Class 2	Low risk	66-85
Class 3	Intermediate risk	86-105
Class 4	High risk	106-125
Class 5	Very high risk	> 125

Predictor	Points	Predictor	Points
Age	Age in yrs	Clinical findings:	
Male	+10	Pulse ≥ 110/min	+20
Comorbid conditions:		SBP < 100 mm Hg	+30
Cancer	+30	Respiratory rate ≥ 30/min	+20
Heart failure	+10	Temperature < 36° C	+20
Chronic lung disease	+10	Altered mental status	+60
		O_2 saturation < 90%	+20

Aujesky D, et al. *Am J Respir Crit Care Med*. 2005;172:1041-1046.

sPESI

- 1- 80 Yaş üstü
- 2- 90 saturasyon altı
- 3- 100 sistolik kan basıncı altı
- 4- 110 nabız üstü
- 5- Kronik kardiyopulmoner hastalık
- 6- Malignite
- HERBİRİ 1 PUAN, HERHANGİ BİRİNİN OLMASI YETERLİ

PESI Class III to V indicates moderate to very high 30-day mortality risk; sPESI ≥1 point(s) indicate high 30-day mortality risk.

Jimenez D, et al. Arch Intern Med 2010;170:1383-9.

Table 3. Thirty-Day Mortality Within Risk Strata Derived From the Original and the Simplified PESI in the Derivation and Validation Cohorts

PESI Risk Categories	Original PESI Derivation Cohort, % (95% CI)		Simplified PESI Derivation Study Cohort, % (95% CI)	
	Patients (n=10 354)	Deaths[a] (n=953)	Patients (n=995)	Deaths (n=78)
Original				
I	19.4 (18.7-20.2)	1.1 (0.7-1.7)	14.3 (12.1-16.4)[b]	2.1 (0.2-4.5)
II	21.5 (20.7-22.3)	3.1 (2.5-4.0)	22.0 (19.4-24.6)	2.7 (0.6-4.9)
III	21.7 (20.9-22.5)	6.5 (5.5-7.6)	27.7 (25.0-30.5)[b]	5.4 (2.8-8.1)
IV	16.4 (15.7-17.1)	10.4 (9.0-11.9)	21.5 (18.9-24.1)[b]	10.3 (6.2-14.3)
V	21.0 (20.3-21.8)	24.5 (22.7-26.9)	14.5 (12.3-16.7)[b]	22.2 (15.4-29.0)
Low[d]	40.9 (40.0-41.8)	2.1 (1.7-2.6)	36.3 (33.3-39.3)[c]	2.5 (0.9-4.1)
High[d]	59.1 (58.1-60.0)	14.0 (13.1-14.9)	63.7 (60.7-66.7)	10.9 (8.5-13.3)
Simplified				
Low			30.7 (27.8-33.5)	1.0 (0.0-2.1)
High			69.3 (66.5-72.2)	10.9 (8.5-13.2)

Akut fazda tedavi

- Oksijen saturasyonu 90’nın altında olan hastalara oksijen desteği verilmesi önerilir.
- Sağ kalp yükünü arttıracağından sıvı yüklenmesinden kaçınılmalıdır. İhtiyaç halinde 500 cc altında sıvı verilebilir.
- Hipotansiyon durumunda norepinefrin veya dobutamine kullanılmalıdır.

- **Orta-yüksek klinik olasılık** olan hastalarda testler sonuçlanmadan DMAH, fondaparinux veya UFH ile tedaviye başlanmalıdır (Kanıt 1C).
- **DMAH ve fondaparinux** başlangıç tedavi için daha az majör kanamayı artırması ve daha az heparin ilişkili trombositopeni yapması nedeniyle UFH'e üstündür (Kanıt 1A).
- **UFH**
  - kreatin klirensi (CrCl) ≤30ml/dk olan hastalarda ve
  - ağır obez olanlarda önerilir.

1. SORU

- Akut PE de ilk seçenek antikoagülan tedavi nedir?
- A-Warfarin
- B-YOAK

- **YOAK'lar** uygun hastalarda antikoagülasyon için **ilk seçenek** olarak önerilmektedir; VKA, YOAK’a alternatiftir **(Kanıt 1A).**
- Dabigatran, rivaroxaban, and apixaban **CrCl 30-60 ml/dk** olanlarda doz ayarlamasına gerek olmadan verilebilir.
- Edoksaban bu hastalarda 30 mg verilmelidir.
- **VKA** 60 yaşından genç hastalarda ilk gün 10 mgr, sonrasında 5 mgr olarak devam edilmeli, başlangıçta yanında UFH, DMAH veya Fondaparinux başlanmalı ve İKİ ARDIŞIK GÜN INR değeri 2-3 aralığında saptandığında diğer tedaviler kesilerek VKA ile tedaviye devam edilmelidir.

Reperfüzyon tedavisi

- PE de trombolitik tedavi ile pulmoner obstrüksiyon, pulmoner arter basıncı ve pulmoner vasküler rezisdansta UFH ne göre çok daha hızlı düzelme sağlanır.
- İlk 48 saatte en yüksek etkiyi gösterir ama 6-14 güne kadar etkilidir.
- Metaanalizde **%9.9** ciddi kanama yaptığı ve **%1.7** intrakranial kanama yaptığı gösterilmiştir.
- Yüksek riskli PE hastalarında Kanıt 1B olarak önerilmektedir.

Molecule	Regimen	Contraindications to fibrinolysis
rtPA	100 mg over 2 h	**Absolute**
	0.6 mg/kg over 15 min (maximum dose 50 mg)[a]	History of haemorrhagic stroke or stroke of unknown origin
Streptokinase	250 000 IU as a loading dose over 30 min, followed by 100 000 IU/h over 12–24 h	Ischaemic stroke in previous 6 months
	Accelerated regimen: 1.5 million IU over 2 h	Central nervous system neoplasm
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24 h	Major trauma, surgery, or head injury in previous 3 weeks
	Accelerated regimen: 3 million IU over 2 h	Bleeding diathesis
		Active bleeding
		Relative
		Transient ischaemic attack in previous 6 months
		Oral anticoagulation
		Pregnancy or first post-partum week
		Non-compressible puncture sites
		Traumatic resuscitation
		Refractory hypertension (systolic BP >180 mmHg)
		Advanced liver disease
		Infective endocarditis
		Active peptic ulcer

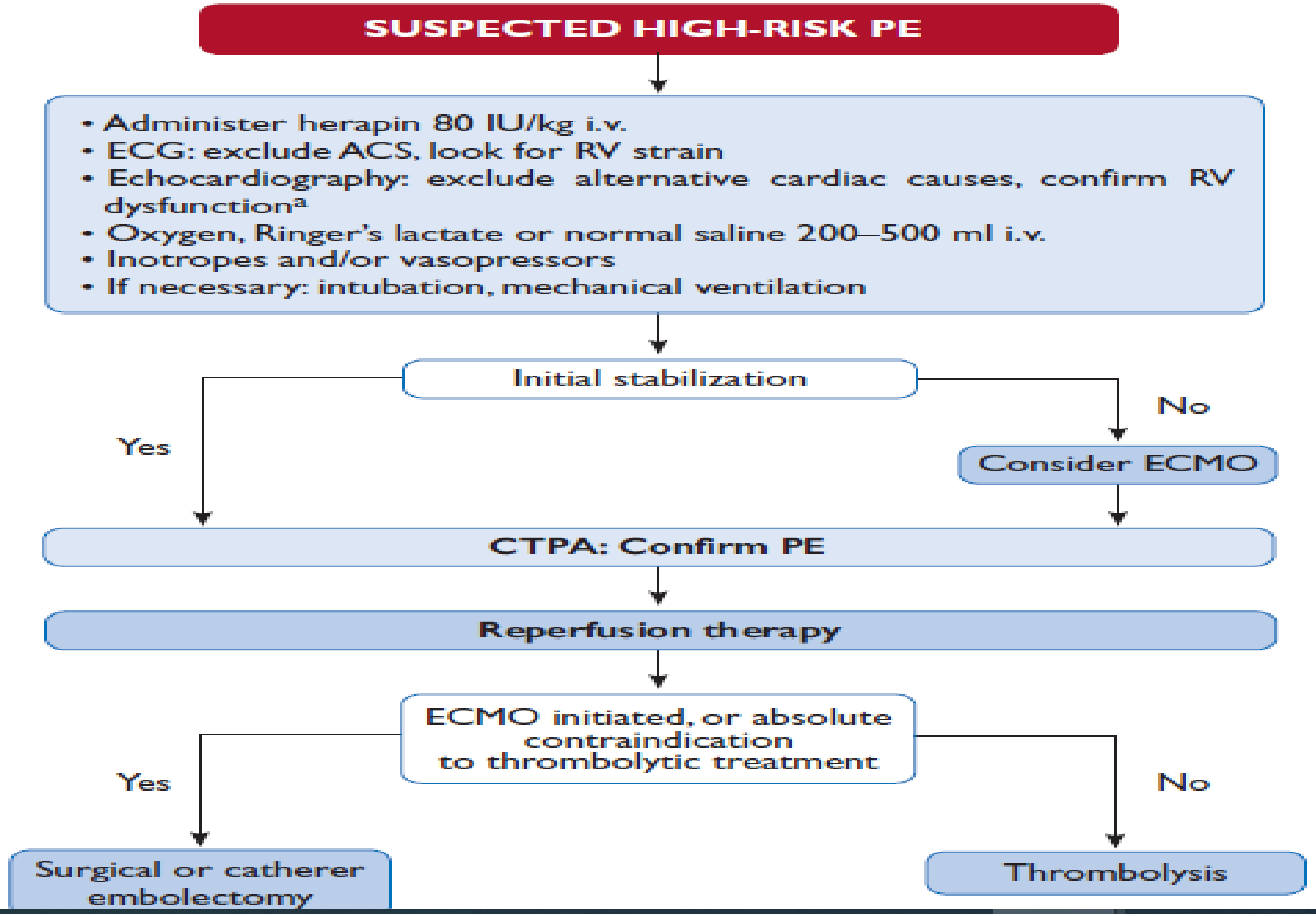
BP = blood pressure; IU = international units; rtPA, recombinant tissue-type plasminogen activator.

[a]This is the accelerated regimen for rtPA in pulmonary embolism; it is not officially approved, but it is sometimes used in extreme haemodynamic instability such as cardiac arrest.

Riske göre tedavi önerileri

- **Yüksek riskli hastalar**
- Yüksek riskli pulmoner embolisi olan hastalarda gecikmeden kiloya göre ***iv bolus UFH*** hemen başlanmalıdır (Kanıt 1C).
- ***Sistemik trombolitik*** tedavi önerilmektedir (Kanıt 1B).
- Sistemik trombolitik tedavi kontrendike olduğu veya başarısız olduğu durumlarda cerrahi trombektomi önerilmektedir (Kanıt 1C).
- Sistemik trombolitik tedavi kontrendike olduğu veya başarısız olduğu durumlarda perkutan kateter aracılıklı tedavi kullanılabilir (Kanıt 2aC).

YÜKSEK RİSK APE'ye ACİL YAKLAŞIM



2. Soru

- Trombolitik tedavi tam doz mu verilmeli yoksa yarı doz mu?
- A- Tam doz
- B- Yarı doz

Hangi trombolitik dozu?

Efficacy and Safety of Low Dose Recombinant Tissue-Type Plasminogen Activator for the Treatment of Acute Pulmonary Thromboembolism

A Randomized, Multicenter, Controlled Trial

Chen Wang, MD, PhD, FCCP; Zhenguo Zhai, MD, PhD; Yuanhua Yang, MD; Qi Wu, MD,

Background: Optimal dosing of the recombinant tissue-type plasminogen activator (rt-PA) is important in treating pulmonary thromboembolism (PTE). The aim of this study was to compare the efficacy and safety of a 50 mg/2 h rt-PA regimen with a 100 mg/2 h rt-PA regimen in patients with acute PTE.

Methods: A prospective, randomized, multicenter trial was conducted in which 118 patients with acute PTE and either hemodynamic instability or massive pulmonary artery obstruction were randomly assigned to receive a treatment regiment of either rt-PA at 50 mg/2 h (n = 65) or 100 mg/2 h (n = 53). The efficacy was determined by observing the improvements of right ventricular dysfunctions (RVDs) on echocardiograms, lung perfusion defects on ventilation perfusion lung scans, and pulmonary artery obstructions on CT angiograms. The adverse events, including death, bleeding, and PTE recurrence, were also evaluated.

Results: Progressive improvements in RVDs, lung perfusion defects, and pulmonary artery obstructions were found to be similarly significant in both treatment groups. This is true for patients with either hemodynamic instability or massive pulmonary artery obstruction. Three (6%) patients in the rt-PA 100 mg/2 h group and one (2%) in the rt-PA 50 mg/2 h group died as the result of either PTE or bleeding. Importantly, the 50 mg/2 h rt-PA regimen resulted in less bleeding tendency than the 100 mg/2 h regimen (3% vs 10%), especially in patients with a body weight < 65 kg (14.8% vs 41.2%, $P = .049$). No fatal recurrent PTE was found in either group.

Conclusions: Compared with the 100 mg/2 h regimen, the 50 mg/2 h rt-PA regimen exhibits similar efficacy and perhaps better safety in patients with acute PTE. These findings support the notion that optimizing rt-PA dosing is worthwhile when treating patients with PTE.

Trial registration: clinicaltrials.gov; Identifier: NCT00781378

Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial)

Mohsen Sharifi, MD[a,b,*], Curt Bay, PhD[b], Laura Skrocki, DO[a], Farnoosh Rahimi, MD[a], and Mahshid Mehdipour, DMD[a,b], "MOPETT" Investigators

The role of low-dose thrombolysis in the reduction of pulmonary artery pressure in moderate pulmonary embolism (PE) has not been investigated. Because the lungs are very sensitive to thrombolysis, we postulated that effective and safe thrombolysis might be achieved by a lower dose of tissue plasminogen activator. The purpose of the present study was to evaluate the role of this "safe dose" thrombolysis in the reduction of pulmonary artery pressure in moderate PE. During a 22-month period, 121 patients with moderate PE were randomized to receive a "safe dose" of tissue plasminogen activator plus anticoagulation (thrombolysis group [TG], n = 61 patients) or anticoagulation alone (control group [CG], n = 60). The primary end points consisted of pulmonary hypertension and the composite end point of pulmonary hypertension and recurrent PE at 28 months. Pulmonary hypertension and the composite end point developed in 9 of 58 patients (16%) in the TG and 32 of 56 patients (57%) in the CG ($p < 0.001$) and 9 of 58 patients (16%) in the TG and 35 of 56 patients (63%) in the CG ($p < 0.001$), respectively. The secondary end points were total mortality, the duration of hospital stay, bleeding at the index hospitalization, recurrent PE, and the combination of mortality and recurrent PE. The duration of hospitalization was 2.2 ± 0.5 days in the TG and 4.9 ± 0.8 days in the CG ($p < 0.001$). The combination of death plus recurrent PE was 1 (1.6%) in TG and 6 (10%) in the CG ($p = 0.0489$). No bleeding occurred in any group, and despite a positive trend in favor of a "safe dose" thrombolysis, no significant difference was noted in the rate of individual outcomes of death and recurrent PE when assessed independently. In conclusion, the results from the present prospective randomized trial suggests that "safe dose" thrombolysis is safe and effective in the treatment of moderate PE, with a significant immediate reduction in the pulmonary artery pressure that was maintained at 28 months. (Am J Cardiol 2013;111:273—277)

Thrombosis Research 133 (2014) 357–363

Contents lists available at ScienceDirect

Thrombosis Research

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Regular Article

Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: A systematic review and meta-analysis

Zhu Zhang [a], Zhen-guo Zhai [a,*], Li-rong Liang [a], Fang-fang Liu [a], Yuan-hua Yang [a], Chen Wang [a,b]

Table 1
Characteristics of the included of randomized controlled trials comparing different dosages and regimens of rt-PA or heparin in the treatment of acute PE.

	Patients No.	Inclusion criteria	Intervention	Length of follow-up
low dose rt-PA vs. heparin				
Levine et al., 1990	58	affirmed by imaging tests, symptoms or signs of PE within 14d, hemodynamically stable, without contraindication of anticoagulation.	rt-PA: 0.6 mg/kg bolus 2 min placebo: NS 0.6 mg/kg bolus 2 min	7d
Sharifi et al., 2013	121	affirmed by imaging tests, symptoms or signs of PE within 10d, Moderate※ PE without contraindication of anticoagulation	rt-PA: 10 mg bolus,≤40 mg/2 h Heparin: 80U/kgbolus + 80U/kg/h or enoxaparin: 1 mg/kg ih bid	28d
low dose rt-PA vs. standard dose rt-PA				
Goldhaber et al., 1994	90	≥18 years, affirmed by imaging tests, symptoms of PE within 14d, without contraindication of anticoagulation	low dose:0.6 mg/kg bolus 15 min max 50 mg standard dose: 100 mg infusion 2 h	20 to 28 h
Sors et al., 1994	53	≥18y, affirmed by imaging tests, symptoms or signs of PE within 14 days mPAP ≥ 20 mmHg and Miller score ≥ 17/34	low dose:0.6 mg/kg.bolus15min max 50 mg standard dose: 100 mg infusion 2 h	20 to 28 h
Wang et al., 2010	118	18 to75y, affirmed by imaging tests, symptoms or signs of PE within 15 days, hemodynamically massive PE§or anatomically massive PE#	low dose: 50 mg infusion 2 h standard dose:100 mg infusion 2 h	14d

PE: pulmonary embolism; PA: pulmonary angiography;rt-PA: recombinant tissue plasminogen activator; Ih = subcutaneously; mPAP = mean pulmonary arterial pressure.

※ Moderate PE was defined as the presence of signs and symptoms of PE plus computed tomographic pulmonary angiographic involvement of >70% involvement of thrombus in >2 lobar or left or right main pulmonary arteries or by a high probability ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥ 2 lobes.

- 5 çalışma, 440 hasta,
- Standart doz ile düşük dozu karşılaştıran 3 çalışma, Hasta sayısı **261**.
- 3 tanesi düşük doz rt-PA (0.6 mg/kg, maximum 50 mg veya **50 mg infüzyon 2 h**) ile standart dozu (**100 mgr, 2 saatte**) karşılaştırıyor.
- Düşük doz tedavi alan 162 hastadan 7 tanesinde majör kanama olurken, tam doz tedavi alan 99 hastanın 11 inde majör kanama gelişiyor (p=0.03).
- PE nüksü açısından iki grup arasında farklılık yok (takip süresi en uzun 14 gün).

Conclusion

This meta-analysis showed that low dose rt-PA was superior to standard dose rt-PA in preventing major bleeding events and remained similar efficacy. In addition, compared with heparin, low dose rt-PA didn't increase the risk of bleeding for eligible PE patients. The results of this meta-analysis were hypothesis-generating. It should be pointed out that larger well-designed multicenter RCTs are needed to confirm the efficacy and safety of low-dose rt-PA regimen in eligible patients with acute PE. Physicians should be cautious in their clinical practice when considering low dose rt-PA therapy to be extended to even broader spectrum of acute PE.

Half-Dose Versus Full-Dose Alteplase for Treatment of Pulmonary Embolism*

Tyree H. Kiser, PharmD[1,2]; Ellen L. Burnham, MD[2,3]; Brendan Clark, MD[2,3]; P. Michael Ho, MD, PhD[2,4]; Richard R. Allen, MS[5]; Marc Moss, MD[2,3]; R. William Vandivier, MD[2,3]

Objectives: Recent evidence suggests that half-dose thrombolysis for pulmonary embolism may provide similar efficacy with reduced bleeding risk compared with full-dose therapy, but comparative studies are lacking. We aimed to evaluate the effectiveness and safety of half-dose versus full-dose alteplase for treatment of pulmonary embolism.

Design: A retrospective cohort study comparing outcomes in patients receiving half-dose (50 mg) versus full-dose (100 mg) alteplase for pulmonary embolism. We used propensity score matching and sensitivity analyses to address confounding and hospital-level clustering.

Setting: Data from 420 hospitals obtained from the Premier Healthcare Database between January 2010 and December 2014.

Subjects: Adult critically ill patients with acute pulmonary embolism treated with IV alteplase therapy.

Interventions: None.

Measurements and Main Results: This study included 3,768 patients: 699 (18.6%) in the half-dose and 3,069 (81.4%) in the full-dose group. At baseline, patients receiving half-dose alteplase required vasopressor therapy (23.3% vs 39.4%; $p < 0.01$) and invasive ventilation (14.3% vs 28.5%; $p < 0.01$) less often, compared with full dose. After propensity matching ($n = 548$ per group), half-dose alteplase was associated with increased treatment escalation (53.8% vs 41.4%; $p < 0.01$), driven mostly by secondary thrombolysis (25.9% vs 7.3%; $p < 0.01$) and catheter thrombus fragmentation (14.2% vs 3.8%; $p < 0.01$). Hospital mortality was similar (13% vs 15%; $p = 0.3$). There was no difference in cerebral hemorrhage (0.5% vs 0.4%; $p = 0.67$), gastrointestinal bleeding (1.6% vs 1.6%; $p = 0.99$), acute blood loss anemia (6.9% vs 4.6%; $p = 0.11$), use of blood products ($p > 0.05$ for all), or documented fibrinolytic adverse events (2.6% vs 2.8%; $p = 0.82$).

Conclusions: Compared with full-dose alteplase, half-dose was associated with similar mortality and rates of major bleeding. Treatment escalation occurred more often in half-dose–treated patients. These results question whether half-dose alteplase provides similar efficacy with improved safety, and highlights the need for further study before use of half-dose alteplase therapy can be routinely recommended in patients with pulmonary embolism. (*Crit Care Med* 2018; 46:1617–1625)

*See also p. 1696.

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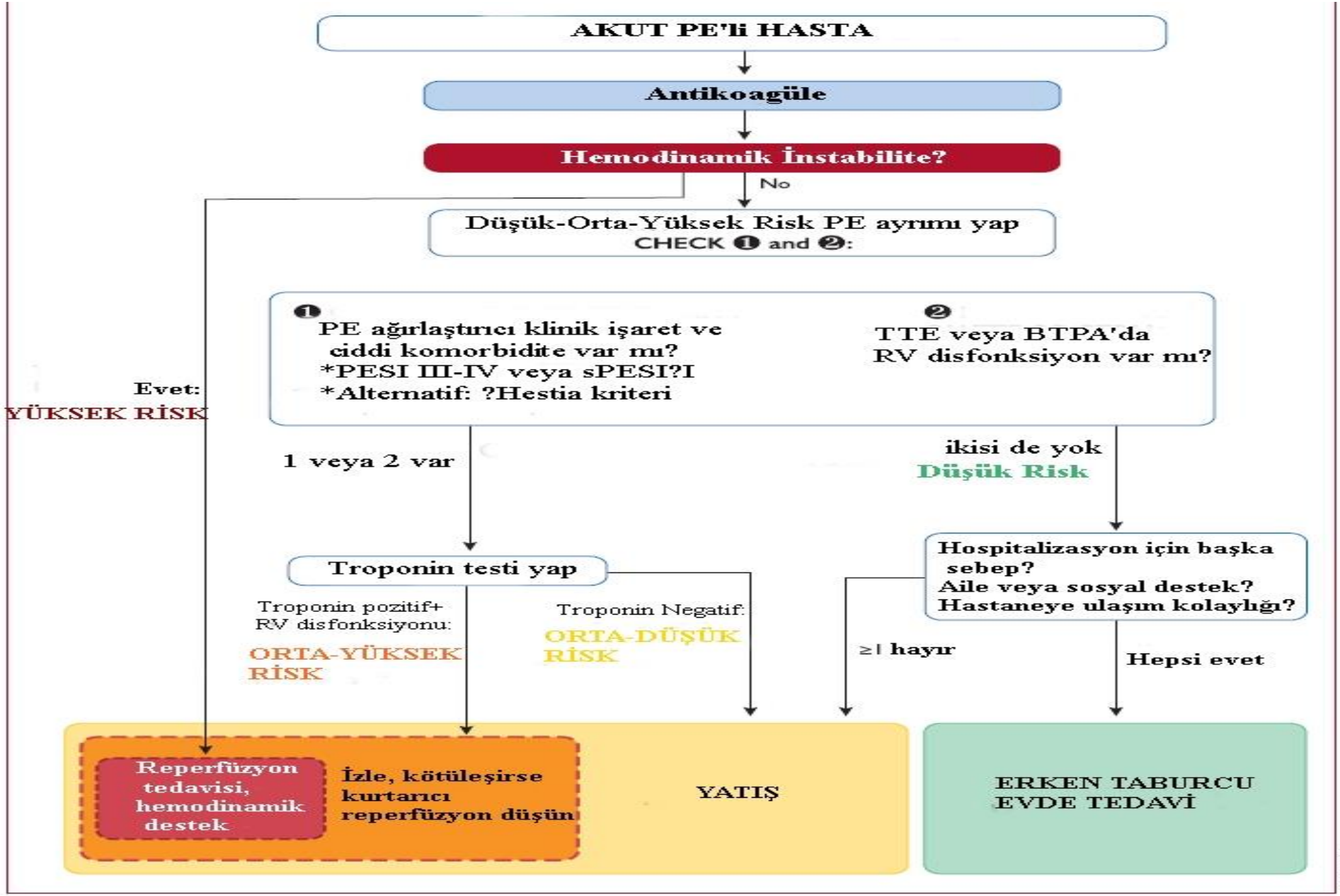
[5]Peak Statistical Services, Evergreen, CO.

- **Orta ve düşük risk hastalar**
- Yüksek veya orta klinik olasılığa sahip hastalarda, tanısal testleri beklerken antikoagülan tedavi başlanmalıdır (Kanıt 1C).
- Eğer parenteral tedavi başlanacaksa UFH yerine **DMAH veya fondaparinux** tercih edilmelidir (Kanıt 1A).
- Eğer oral antikoagülan başlanacaksa ve hasta YOAK kullanmak için uygunsa, warfarin yerine **YOAK** tercih edilmelidir (Kanıt 1A).
- VKA kullanıyor ise hasta, INR 2.5 olana kadar parenteral antikoagülan verilmelidir (Kanıt 1A).
- **Böbrek yetmezliği, gebelik, laktasyon ve antifosfolipid antikor sendromu** olan hastalarda YOAK önerilmiyor (Kanıt 3C).
- Antikoagülan tedavi altında hemodinamik bozukluk gelişenlerde kurtarıcı reperfüzyon tedavisi verilebilir (Kanıt 1B).
- **Rutin reperfüzyon tedavisi önerilmemektedir** (Kanıt 3B).


AKUT PE'li HASTA
Antikoagüle
Hemodinamik İnstabilite?
No
Düşük-Orta-Yüksek Risk PE ayrımı yap
CHECK ❶ and ❷:
❶
PE ağırlaştırıcı klinik işaret ve ciddi komorbidite var mı?
*PESI III-IV veya sPESI?I
*Alternatif: ?Hestia kriteri
❷
TTE veya BTPA'da RV disfonksiyon var mı?
Evet:
YÜKSEK RİSK
1 veya 2 var
ikisi de yok
Düşük Risk
Troponin testi yap
Troponin pozitif+ RV disfonksiyonu:
ORTA-YÜKSEK RİSK
Troponin Negatif:
ORTA-DÜŞÜK RİSK
Hospitalizasyon için başka sebep?
Aile veya sosyal destek?
Hastaneye ulaşım kolaylığı?
≥I hayır
Hepsi evet
Reperfüzyon tedavisi, hemodinamik destek
İzle, kötüleşirse kurtarıcı reperfüzyon düşün
YATIŞ
ERKEN TABURCU
EVDE TEDAVİ
©ESC 2019

- Soru 3- Intermediate high risk hastalarda trombolitik verelim mi?
- Evet
- Hayır

INTERMEDIATE RİSKTE (SUBMASİF) TROMBOLİTİK

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D.,

N Engl J Med 2014;370:1402-11.

- Randomize, çift kör, hipotansiyonu olmayan intermediate yüksek risk hastalarda **tenekteplaz+ heparin** ile **plasebo + heparin** tedavisi karşılaştırılıyor.
- 1. haftada ölüm, hemodinamik bozukluk ve kanama oranları karşılaştırılıyor.
- 1005 hasta

Table 3. Efficacy Outcomes.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
Primary outcome — no. (%)	13 (2.6)	28 (5.6)	0.44 (0.23–0.87)	0.02
Death from any cause	6 (1.2)	9 (1.8)	0.65 (0.23–1.85)	0.42
Hemodynamic decompensation	8 (1.6)	25 (5.0)	0.30 (0.14–0.68)	0.002
Time between randomization and primary efficacy outcome — days	1.54±1.71	1.79±1.60		
Recurrent pulmonary embolism between randomization and day 7 — no. (%)	1 (0.2)	5 (1.0)	0.20 (0.02–1.68)	0.12
Fatal	0	3 (0.6)		
Nonfatal	1 (0.2)	2 (0.4)		

Table 4. Safety Outcomes in the Intention-to-Treat Population.*

Outcome	Tenecteplase (N=506)	Placebo (N=499)	Odds Ratio (95% CI)	P Value
	no. (%)			
Bleeding between randomization and day 7				
Major extracranial bleeding	32 (6.3)	6 (1.2)	5.55 (2.3–13.39)	<0.001
Minor bleeding	165 (32.6)	43 (8.6)		
Major bleeding†	58 (11.5)	12 (2.4)		
Stroke between randomization and day 7	12 (2.4)	1 (0.2)	12.10 (1.57–93.39)	0.003
Ischemic stroke	2 (0.4)	0		
Hemorrhagic stroke‡	10 (2.0)	1 (0.2)		

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 69, NO. 12, 2017

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.12.039

Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism

Stavros V. Konstantinides, MD, PhD,[a,b] Eric Vicaut, MD, PhD,[c] Thierry Danays, MD,[d] Cecilia Becattini, MD,[e]

- 709 hasta
- 1 ay ve 24 aylık sonuçlar karşılaştırılıyor

TABLE 3 Overall and Cause-Specific 30-Day and Long-Term Mortality

	Tenecteplase (N = 359)	Placebo (N = 350)	p Value
Death from any cause between randomization and day 30	8 (2.2)	10 (2.9)	0.595
Hemodynamic collapse	1 (0.3)	1 (0.3)	
Stroke (ischemic or hemorrhagic)	4 (1.1)	0 (0.0)	
Recurrent pulmonary embolism	0 (0.0)	2 (0.6)	
Respiratory failure	0 (0.0)	2 (0.6)	
Extracranial bleeding	1 (0.3)	0 (0.0)	
Sudden unexplained death	0 (0.0)	2 (0.6)	
Other	2 (0.6)	3 (0.9)	
Death from any cause between day 30 and long-term follow-up	65 (18.1)	53 (15.1)	
Stroke	1 (0.3)	2 (0.6)	
Acute myocardial infarction	0 (0.0)	1 (0.3)	
Respiratory failure	2 (0.6)	1 (0.3)	
Sudden unexplained death	2 (0.6)	0 (0.0)	
Cancer	8 (2.2)	9 (2.6)	
Bleeding	0 (0.0)	1 (0.3)	
Chronic heart failure	1 (0.3)	0 (0.0)	
Other	19 (5.3)	4 (1.1)	
Unknown cause	32 (8.9)	35 (10.0)	
Death from any cause between randomization and long-term follow-up	73 (20.3)	63 (18.0)	0.430

TABLE 4 Findings in Patients With Echocardiographic Long-Term Follow-Up

	Tenecteplase (N = 144)	Placebo (N = 146)	p Value
Right ventricular end-diastolic diameter >30 mm	34 (23.6)	22 (15.1)	0.058
Missing data	12 (8.3)	11 (7.5)	
Right/left ventricular end-diastolic diameter >0.9	34 (23.6)	22 (15.1)	0.834
Missing data	12 (8.3)	11 (7.5)	
Hypokinesia of the right ventricular free wall (any view)	6 (4.2)	5 (3.4)	0.740
Missing data	4 (2.8)	4 (2.7)	
Tricuspid annulus plane systolic excursion reduced	14 (9.7)	7 (4.8)	0.107
Mean, mm Hg	23.6 ± 4.8	23.9 ± 3.6	
Median, mm Hg	24.0 (20.0–27.0)	24.0 (21.0–26.0)	0.551
Missing data,	19 (13.2)	18 (12.3)	
Tricuspid systolic velocity >2.6 m/s	22 (15.3)	27 (18.5)	0.412
Missing data	11 (7.6)	14 (9.6)	
Systolic pulmonary artery pressure, mm Hg			
Mean	31.6 ± 12.3	30.7 ± 10.2	0.527
Median	30.0 (24.0–35.0)	30.0 (25.0–35.0)	
Missing data	33 (22.9)	39 (26.7)	

CONCLUSIONS

In a large, prospective randomized controlled trial of patients with intermediate- to high-risk PE, thrombolytic treatment with tenecteplase did not affect long-term mortality rates, and it did not appear to reduce residual dyspnea, functional limitation, or persisting RV dysfunction, which were mostly mild in both treatment arms. These results suggest that

Kronik tedavi ve nüksün önlenmesi

- Sekonder VTE önlenmesine odaklanan son 15 yıldaki randomize antikoagülasyon çalışmaları, antikoagülan tedavinin kesilmesinden sonra hastaları VTE nüks riskine göre farklı gruplara ayırmıştır.
- Artık provoked-unprovoked yerine bu sınıflama kullanılıyor.

Table 11 Categorization of risk factors for venous thromboembolism based on the risk of recurrence over the long-term

Estimated risk for long-term recurrence[a]	Risk factor category for index PE[b]	Examples[b]
Low (<3% per year)	Major transient or reversible factors associated with >10-fold increased risk for the index VTE event (compared to patients without the risk factor)	• Surgery with general anaesthesia for >30 min • Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness • Trauma with fractures
Intermediate (3–8% per year)	Transient or reversible factors associated with ≤10-fold increased risk for first (index) VTE	• Minor surgery (general anaesthesia for <30 min) • Admission to hospital for <3 days with an acute illness • Oestrogen therapy/contraception • Pregnancy or puerperium • Confined to bed out of hospital for ≥3 days with an acute illness • Leg injury (without fracture) associated with reduced mobility for ≥3 days • Long-haul flight
	Non-malignant persistent risk factors	• Inflammatory bowel disease • Active autoimmune disease
	No identifiable risk factor	
High (>8% per year)		• Active cancer • One or more previous episodes of VTE in the absence of a major transient or reversible factor • Antiphospholipid antibody syndrome

Bunlar önerilir (recommended)

- Nüks açısından düşük riskli, emboli açısından major risk içeren durumlarda (30 dakikadan uzun anestezi, hastalık nedeniyle 3 günden fazla yatağa bağımlı yaşamak veya kırıklar gelişen travmalarda) **3 aylık** tedavinin yeterli olacağı öneriliyor (Kanıt düzeyi **IB**).
- Major veya geri döndürülebilir bir risk faktörü olmadan geçirilen **iki VTE atağında sınırsız süre** (indefinite) antikoagülan öneriliyor (Kanıt düzeyi **IB**).
- Antifosfolipit sendromu olanlarda **WARFARİN ile sınırsız süre** antikoagülan öneriyor (Kanıt düzeyi **IB**).

Bunlar düşünülür (considered)

- **Sınırsız süreli antikoagülasyon**
  - Nedeni saptanmayan ilk atakta düşünülebilir (Kanıt düzeyi **IIaA**).
  - Antifosfolipid antikor sendromu dışında kalıcı risk faktörü varsa ilk atakta düşünülebilir (Kanıt düzeyi **IIaC**).

bjh research paper

A randomised controlled trial of extended anticoagulation treatment *versus* standard treatment for the prevention of recurrent venous thromboembolism (VTE) and post-thrombotic syndrome in patients being treated for a first episode of unprovoked VTE (the ExACT study)

Br J Haematol. 2019 Nov 12.

Charlotte Bradbury,[1] Kate Fletcher,[2]

Summary

- İlk unprovoke pulmoner emboli veya proximal DVT geçiren hastalar
- 281 hasta
- 3 aylık tedavi sonrası ikiye ayrılıyor, 1. grup tedavisi kesiliyor, 2. grup 24 ay tedaviye devam ediyor (warfarin), 24 ayın sonunda rekürrens, kanama oranı, .. karşılaştırılıyor.

Table II. Primary and secondary outcomes.

Outcome	Discontinued AT $n = 134$	Extended AT $n = 139$	Adjusted hazard ratio (95% CI)‡	*P*-value
Primary outcome				
Recurrent VTE				
No of participants with ≥ 1 event – *n* (%)	31 (23·1)	7 (5·0)	0·20 (0·09, 0·46)	<0·001
No. of events§	32	7		
No./100 person-years¶	13·54	2·75		
Secondary outcomes				
Major bleeding events			2·99 (0·81, 11·05)	0·100
No of participants with ≥ 1 event – *n* (%)	3 (2·2)	9 (6·5)		
No. of events	3	9		
No./100 person-years¶	1·18	3·54		
Clinically relevant non-major bleeding events				
No of participants with ≥ 1 event and non-missing event dates† – *n* (%)	19 (14·2)	28 (20·1)	1·51 (0·84, 2·71)	0·165
No of participants with ≥ 1 event† – *n* (%)	21 (15·7)	32 (23·0)		
No. of events†	25	43		
No./100 person-years¶	8·13	12·50		

4. soru

- 6-12 aylık tedaviden sonra APE tedavisine YOAK ile devam edilecekse tam doz mu yoksa yarı doz mu YOAK kullanılmalı?
- A- Tam doz
- B- Yarı doz

Bunlar düşünülür (considered)

- Eğer kanser hastası dışında bir hastada uzun süreli antikoagülasyon öneriliyor ise, 6 aylık tedaviden sonra azaltılmış dozda **apixaban 2x2.5** mgr veya **rivaroxaban 1x10 mgr** düşünülebilir (Kanıt düzeyi IIaA).

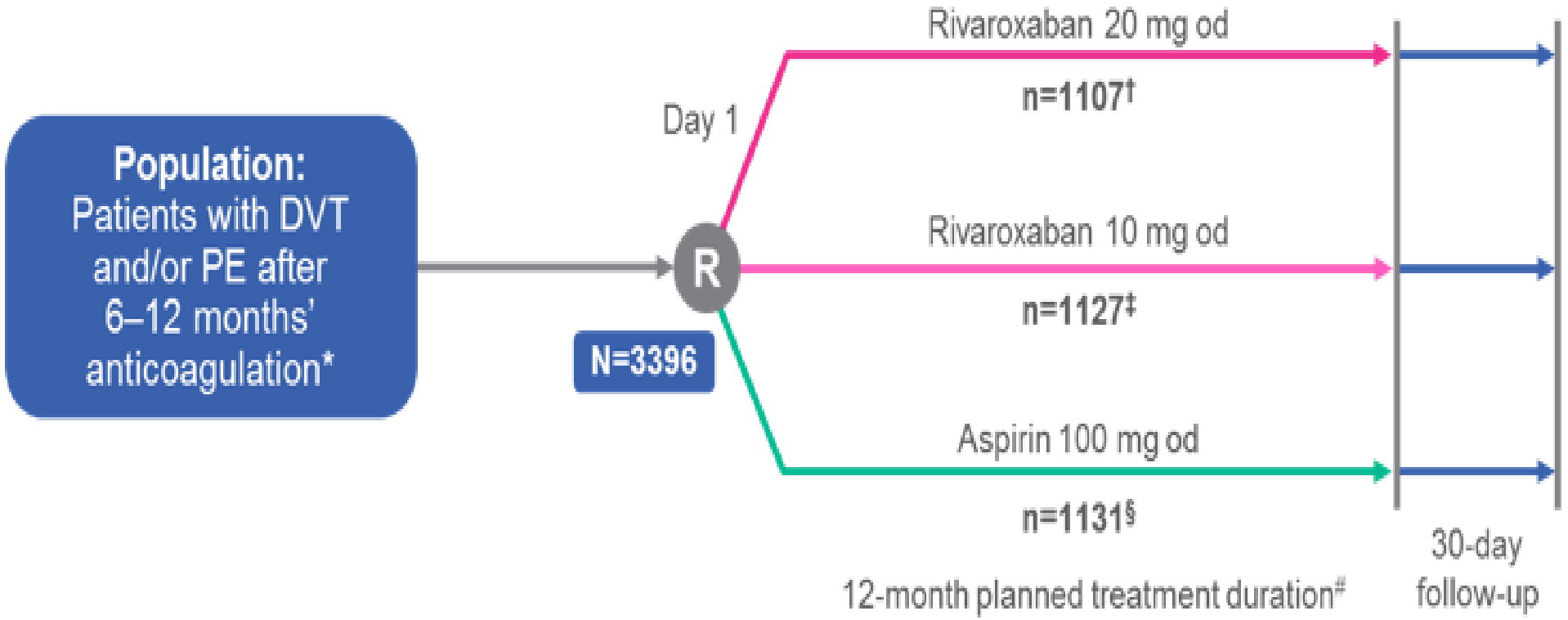
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mart 2017

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf,



Supplemental Table S2. Annualized incidence rates of all pre-specified study outcomes.

Outcome	Rivaroxaban 20 mg (N=1107)		Rivaroxaban 10 mg (N=1127)		Aspirin 100 mg (N=1131)	
	Events (n)	% per person year	Events (n)	% per person year	Events (n)	% per person year
Primary efficacy outcome	17	1.8	13	1.4	50	5.3
Other efficacy outcomes						
Primary efficacy outcome, myocardial infarction, ischemic stroke, or systemic embolism	19	2.0	18	1.9	56	6.0
All-cause mortality	8	0.8	2	0.2	7	0.7
Primary efficacy outcome or all-cause mortality	23	2.4	15	1.6	55	5.8
Primary efficacy outcome or venous thrombosis in other locations	20	2.1	16	1.7	57	6.1
Primary efficacy outcome, myocardial infarction, ischemic stroke, systemic embolism or venous thrombosis in other locations	22	2.3	21	2.2	63	6.7
Principal safety outcome						
Major bleeding (ISTH)	6	0.7	5	0.5	3	0.3

Dec
22
2017

FDA approves low-dose rivaroxaban for long-term PE/DVT prevention

Pulmonary Embolism / DVT / VTE

Add a Comment

The long-term management of recurrent venous thromboembolism continues to evolve with the FDA's approval of once-daily low-dose rivaroxaban, now indicated for patients with recurrent deep venous thrombosis or pulmonary embolism who have completed at least six months of anticoagulation.

FDA approved low-dose rivaroxaban based on data from 3,395 patients in the EINSTEIN-CHOICE study. Both 20 mg and 10 mg daily doses of rivaroxaban appeared equivalent (and better than aspirin) at reducing the risk of recurrent DVT or PE (66% and 74% relative risk reductions, respectively). There was no excess bleeding risk observed.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 21, 2013 VOL. 368 NO. 8

Apixaban for Extended Treatment of Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

AMPLIFY-EXT[1]

- Phase III, randomised, double-blind trial
- 2,482 patients with DVT or PE who completed 6 to 12 months of anticoagulation therapy
- Duration: 12 months

ELIQUIS® prophylactic dose arm
2.5mg BD
N=840

ELIQUIS® treatment dose arm
5mg* BD
N=813

Placebo arm
N=829

Only ELIQUIS® 2.5mg BD* is licensed for extended treatment

Table 2. Clinical Outcomes in the Intention-to-Treat Population during the Intended Active Study Period.*

Outcome	Apixaban, 2.5 mg (N=840)	Apixaban, 5 mg (N=813)	Placebo (N=829)	Relative Risk (95% CI)		
				Apixaban, 2.5 mg, vs. Placebo	Apixaban, 5 mg, vs. Placebo	Apixaban, 2.5 mg vs. 5 mg
	number (percent)					
Recurrent VTE or death from any cause — primary efficacy outcome†	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22–0.48)	0.36 (0.25–0.53)	NA
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11–0.33)	0.20 (0.11–0.34)	0.97 (0.46–2.02)
Non–VTE-related cardiovascular death, myocardial infarction, or stroke	4 (0.5)	5 (0.6)	11 (1.3)	0.36 (0.11–1.12)	0.47(0.16–1.33)	0.77 (0.21–2.88)
Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease–related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13–0.35)	0.23 (0.14–0.38)	0.92 (0.48–1.74)
Major bleeding	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09–2.64)	0.25 (0.03–2.24)	1.93 (0.18–21.25)
Clinically relevant nonmajor bleeding	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72–2.33)	1.82 (1.05–3.18)	0.71 (0.43–1.18)
Major or clinically relevant nonmajor bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69–2.10)	1.62 (0.96–2.73)	0.74 (0.46–1.22)

Does low-dose NOAC therapy increase indications for indefinite anticoagulation ? No

ESC 2019

Recommendations	Class[a]	Level[b]
If extended oral anticoagulation is decided after PE in a patient without cancer, a reduced dose of the NOACs apixaban (2.5 mg b.i.d.) or rivaroxaban (10 mg o.d.) should be considered after 6 months of therapeutic anticoagulation.[352,353]	IIa	A

French 2019

Risk of recurrence	Definition	Duration	Molecule, Dose
Moderate	- Men with 1st VTE not provoked by major risk factor and no persistent risk factors - Women with 1st VTE not provoked by major risk factor and no persistent risk factors and HERDOO2 ≥ 2	6 months or Indefinite (Grade 1+)	*After 6th months* VKA (INR 2-3) or DOAC full-dose or DOAC or low-dose (Grade 1+)
High	APL	Indefinite (Grade 1+)	VKA (INR (2-3) (Grade 1+)
	- Recurrent VTE not provoked by major risk factor - 1st VTE not provoked by major risk factor and major thrombophilia (AT deficiency)	Indefinite (Grade 1+)	VKA (INR 2-3) (Grade 1+) DOAC full-dose (Grade 1+)
	1st episode of high-risk PE not provoked by major risk factor	Indefinite (Grade 2+)	

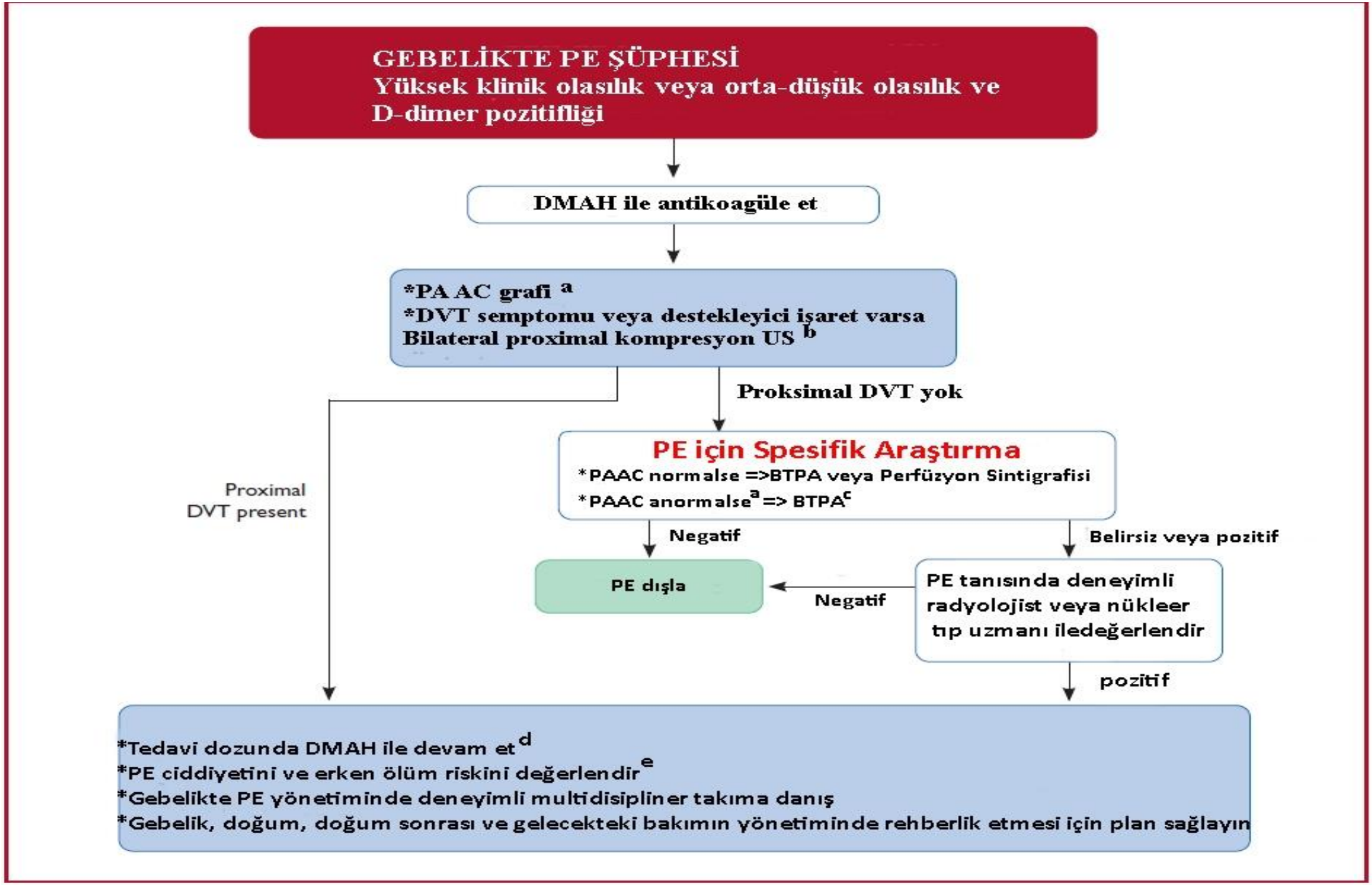
- Antitombin eksikliği, protein C veya S eksikliği, homozigot faktör V leiden mutasyonu veya homozigot protrombin G20210A mutasyonu olan hastalarda **ilk atakta da sınırsız süreli antikoagülasyona adaydırlar.**
- Heterozigot faktör V leiden mutasyonu veya heterozigot protrombin G20210A mutasyonu olan hastalarda uzun süreli tedavi için herhangi bir kanıt **bulunmamaktadır.**

Kanser ve Emboli

- 1- **İlk 6 ay**, warfarin yerine **DMAH** önerilir. (Kanıt 2aA)
- 2- GIS kanseri **olmayan** hastalarda DMAH yerine EDOXABAN kullanılabilir (Kanıt 2aB)
- 3- GIS kanseri **olmayan** hastalarda DMAH yerine RİVAROKSABAN kullanılabilir (Kanıt 2aC)
- 4- Kanser hastalarında **malignitede kür saptanana kadar ya da süresiz** antikoagülasyon önerilir (Kanıt 2aB)
- 5- Kanser hastasında rastgele asemptomatik emboli saptanırsa ve bu emboli segmental veya daha proximalde ise, multiple subsegmental ise, DVT+ tek subsegmental ise o zaman aynı semptomatik PTE gibi tedavi edilmelidir (Kanıt 2aB)

Gebelik ve Emboli

- VTE riski hamile kadınlarda benzer yaştaki hamile olmayan kadınlara göre daha yüksektir; Hamilelikte artar, doğum sonrası dönemde zirveye ulaşır.
- Gebelik sırasındaki PE tanısı, belirtiler sıklıkla normal hamilelik belirtileriyle çakıştığı için zor olabilir.
- D-dimer düzeyleri hamilelik sırasında sürekli artar ve üçüncü trimesterde hamile kadınların neredeyse dörtte birinde VTE "ekarte etme" eşiğinin üzerindedir.


GEBELİKTE PE ŞÜPHESİ
Yüksek klinik olasılık veya orta-düşük olasılık ve D-dimer pozitifliği
DMAH ile antikoagüle et
*PA AC grafi a
*DVT semptomu veya destekleyici işaret varsa
Bilateral proximal kompresyon US b
Proksimal DVT yok
Proximal DVT present
PE için Spesifik Araştırma
*PAAC normalse =>BTPA veya Perfüzyon Sintigrafisi
*PAAC anormalse a => BTPA c
Negatif
Belirsiz veya pozitif
PE dışla
Negatif
PE tanısında deneyimli radyolojist veya nükleer tıp uzmanı iledeğerlendir
pozitif
*Tedavi dozunda DMAH ile devam et d
*PE ciddiyetini ve erken ölüm riskini değerlendir e
*Gebelikte PE yönetiminde deneyimli multidisipliner takıma danış
*Gebelik, doğum, doğum sonrası ve gelecekteki bakımın yönetiminde rehberlik etmesi için plan sağlayın
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- Gebelikte PE’de **DMAH** tercih edilmelidir çünkü VKA ve YOAK’ların aksine plasentayı geçmez, fötal hemoraji ve teratojenik etkisi yoktur.
- Her ne kadar minör transplasental geçiş bildirilip yeterli veri mevcut değilse de eğer bir allerji veya advers reaksiyon gelişirse **fondaparinux** tercih edilebilir.
- Tedavi alan gebede **epidural veya spinal anesteziden 24 saat önce** DMAH kesilmelidir.
- Yüksek riskli durumlarda, örneğin yakın zamanda PE'li hastalarda, DMAH'nin doğumdan> 36 saate önce UFH dönüştürülmesi önerilir.
- Antikoagülan tedavi **doğumdan sonra > 6 hafta** ve **en az 3 ay tedavi** süresinde uygulanmalıdır. **Emziren annelere DMAH ve warfarin verilebilir;** YOAK kullanımı tavsiye edilmez.

Akut PE sonrası takip ve KTEPH

- Akut PE olayından 3-6 ay sonra hastaların rutin klinik değerlendirmeleri önerilir.
- Üç aylık tedavi sonrasında akut PE'li hastalar **semptomatikse** ve **V/Q defektleri uyumsuzluğu** mevcutsa, TTE, natriüretik peptid düzeyleri ve / veya kardiyopulmoner egzersiz testleri sonuçları dikkate alındıktan sonra PH/KTEPH(kronik tromboembolik pulmoner hipertansiyon) merkezine yönlendirilmelidir.

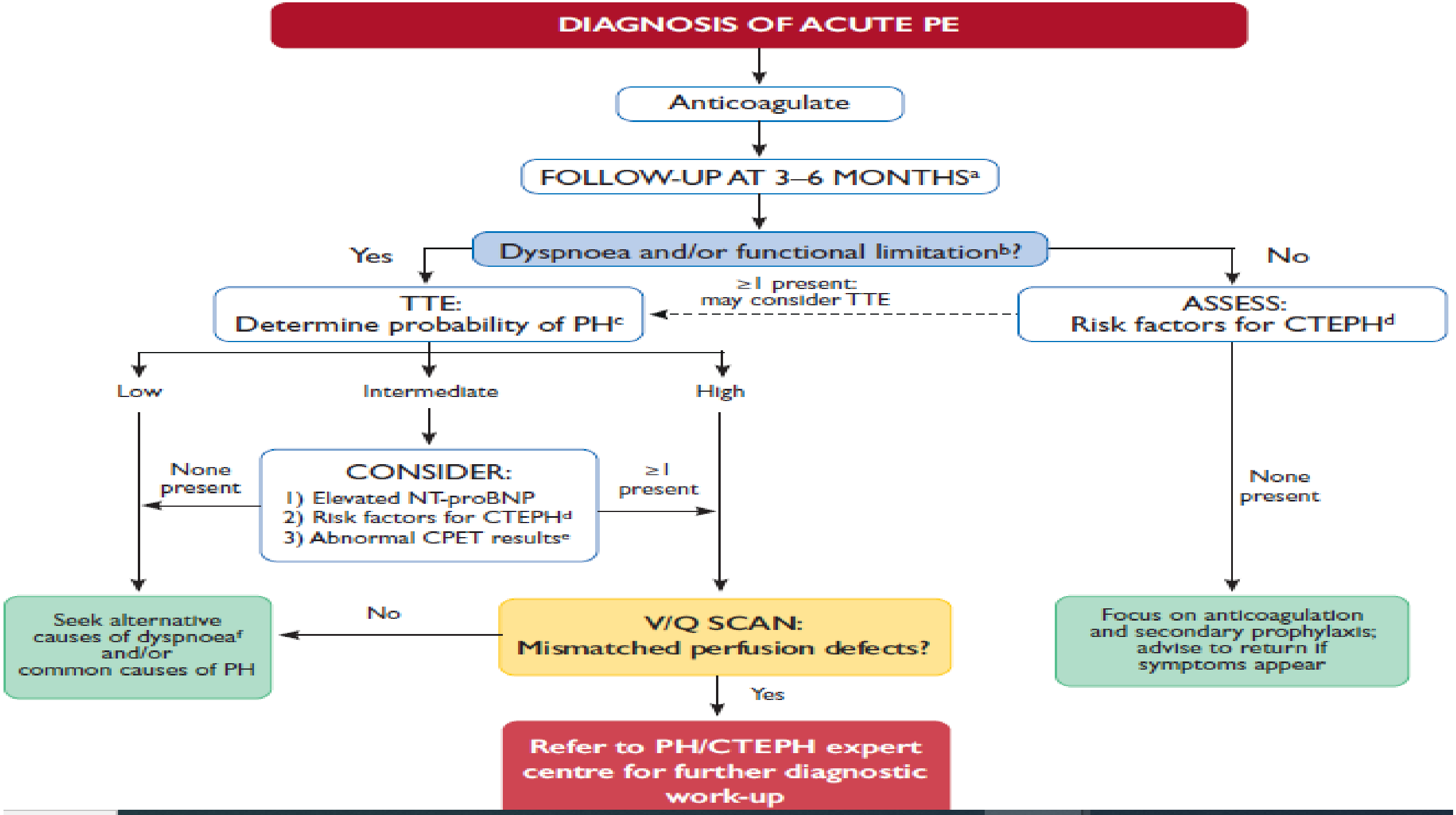
DIAGNOSIS OF ACUTE PE
Anticoagulate
FOLLOW-UP AT 3–6 MONTHS[a]
Dyspnoea and/or functional limitation[b]?
Yes
No
≥1 present: may consider TTE
TTE: Determine probability of PH[c]
ASSESS: Risk factors for CTEPH[d]
Low
Intermediate
High
None present
CONSIDER:
1) Elevated NT-proBNP
2) Risk factors for CTEPH[d]
3) Abnormal CPET results[e]
≥1 present
None present
Seek alternative causes of dyspnoea[f] and/or common causes of PH
No
V/Q SCAN: Mismatched perfusion defects?
Yes
Focus on anticoagulation and secondary prophylaxis; advise to return if symptoms appear
Refer to PH/CTEPH expert centre for further diagnostic work-up

Table 13 Risk factors and predisposing conditions for chronic thromboembolic pulmonary hypertension[447–449]

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[a]	History of splenectomy
CTPA findings suggestive of pre-existing chronic thromboembolic disease[b]	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

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Supplementary Table 9 **Management of pulmonary embolism in specific clinical situations**

Clinical setting	Suggested management[a]	Comments
Subsegmental PE	Single subsegmental PE in an outpatient without cancer and without proximal DVT: • Clinical surveillance. Single subsegmental PE in a hospitalized patient, a patient with cancer, or if associated with confirmed proximal DVT: • Anticoagulant treatment. Multiple subsegmental PE: • Anticoagulant treatment.	• Poor interobserver agreement for the diagnosis of subsegmental PE; diagnosis to be confirmed by an experienced thoracic radiologist. • Suggestion based on indirect evidence, only limited data available.
Incidental PE	If single subsegmental PE: • Proceed as above. In all other cases: • Anticoagulant treatment.	• Suggestion based on retrospective cohort data.
Management of acute PE in a patient with active bleeding	• Insert inferior vena cava filter (preferably retrievable). • Reassess the possibility of anticoagulation as soon as the bleeding has ceased and the patient is stabilized, and remove the filter as soon as anticoagulant treatment is resumed.	

Supplementary Table 6 **Non-vitamin K antagonist oral anticoagulants**

Characteristics[a]	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Time to peak effect	1–2 h	1–3 h	1–2 h	2–4 h
Half-life	8–14 h	14–17 h	5–11 h	7–11 h
Renal elimination	27%	80%	50%	33%
Caveats due to interactions with concomitant medication[b]	Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (azole antimycotics, HIV protease inhibitors). Concomitant use with strong CYP3A4 and P-gp inducers (rifampicin, phenytoin, carbamazepine, phenobarbital, or St John's Wort) may lead to an ~50% reduction in apixaban exposure.	Strong P-gp inhibitors (systemic ketoconazole, cyclosporine, itraconazole, and dronedarone) are contraindicated. Concomitant treatment with tacrolimus is not recommended. Concomitant administration of P-gp inducers (rifampicin, St John's wort, carbamazepine, and phenytoin) is expected to result in decreased dabigatran plasma concentrations and should be avoided.	In patients concomitantly taking edoxaban and the P-gp inhibitors cyclosporine, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg edoxaban o.d.	Not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (azole antimycotics, HIV protease inhibitors)
Further conditions in which NOACs are contraindicated or not recommended[c]	CrCl <15 mL/min. Severe hepatic impairment (Child–Pugh C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min. Concomitant treatment with P-gp inhibitors in patients with CrCl <50 mL/min.	CrCl <15 mL/min. Moderate or severe hepatic impairment. (Child–Pugh B and C) or hepatic disease associated with coagulopathy.	CrCl <30 mL/min (FDA); CrCl <15 mL/min (EMA). Moderate or severe hepatic impairment. (Child–Pugh B and C) or hepatic disease associated with coagulopathy.
Reversal agent	Andexanet	Idarucizumab	Andexanet	Andexanet

Dtsch Arztebl Int. 2018;115(17): 287–294.

Pharmacokinetic characteristics and dosage adjustments according to renal function_as recommended in the guidelines of the European Society of Cardiology

Characteristics	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Elimination half life	12–17 hours	12 hours	10–14 hours	5–9 hours (young age) 11–13 hours (older age)
Licensed for CrCl	≥ 30 mL/min	≥ 15 mL/min	≥ 15 mL/min*[4]	≥ 15 mL/min
Dosage if renal function = normal	2 × 150 mg*[5]	2 × 5 mg	1 × 60 mg*[2]	1 × 20 mg
Dosage in patients with chronic kidney disease	2 × 110 mg*[3] (CrCl: 30–49 mL/min)	2 × 2.5 mg (CrCl: 15–29 mL/min) 2 × 2.5 mg in the presence of two or three risk factors: – Creatinine ≥ 1.5 mg/dL – Age ≥ 80 years – Weight ≤ 60 kg	1 × 30 mg (CrCl: 15–49 mL/min)	1 × 15 mg (CrCl: 15–49 mL/min)
Antidote	Idarucizumab (licensed)	Currently under investigation	Currently under investigation	Currently under investigation

CrCl: creatinine clearance; H2B: H2 blocker; NOAC: non–vitamin-K dependent oral anticoagulants; PPI: proton pump inhibitor; P-gp: P-glycoprotein

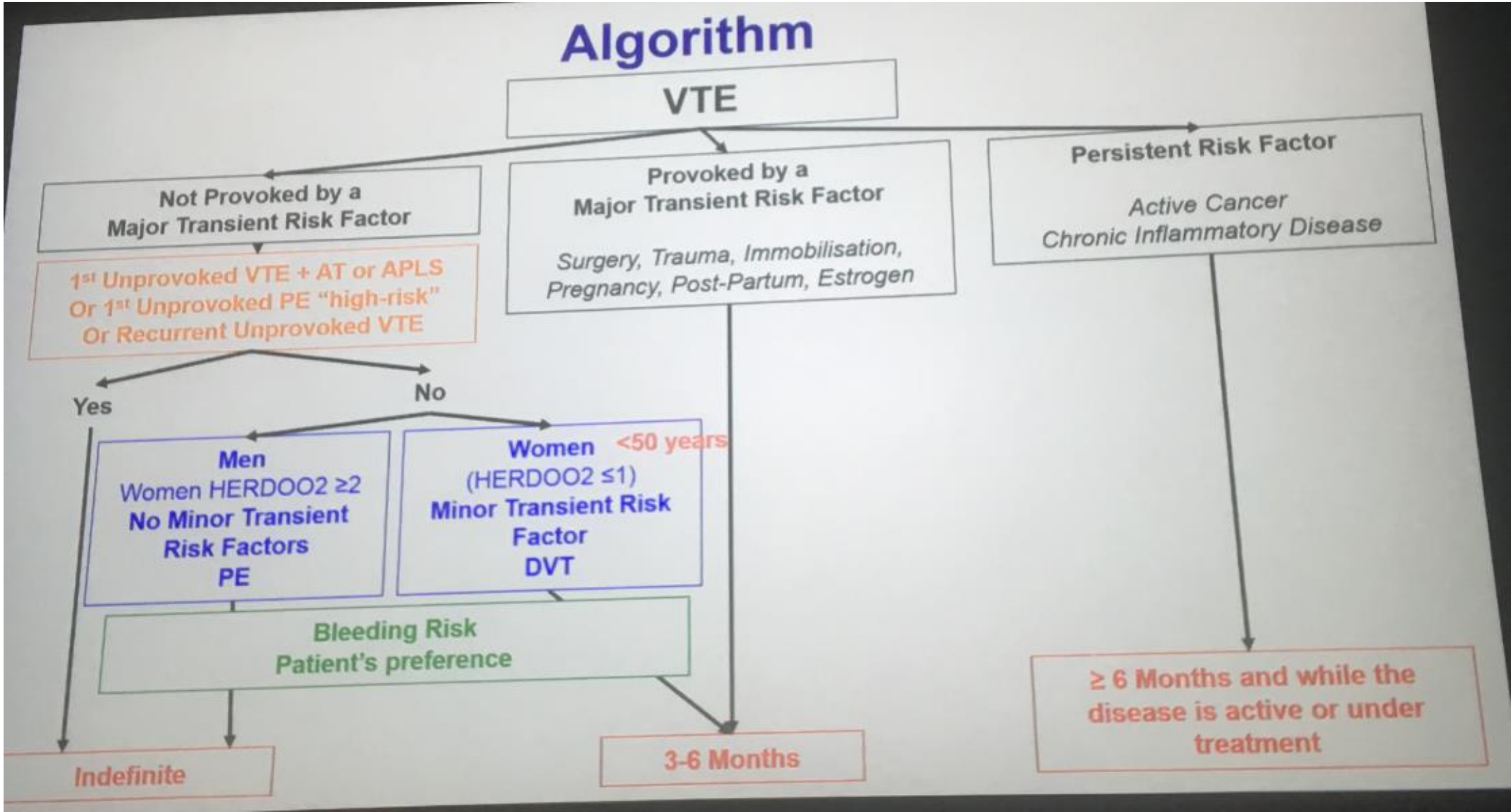
*[1] Reported as individual value that represents the medians of the ranges of different studies

*[2] Because of tendentially lowered effectiveness of edoxaban in higher creatinine clearance. the European licensing authority recommends the use of edoxaban in patients?_with a high creatinine

*[3] Reduction from 2 × 150 mg to 2 × 110 mg in patients = 80 years

*[4] Reduction to 1 × 30 mg if body weight = 60 kg or patient is taking (P-gp) inhibitors (ciclosporin. dronedarone. erythromycin. ketoconazole)

*[5] Reduction from 2 × 150 mg to 2 × 110 mg according to licensed use not obilgatory. but should be considered in patients with a high risk for hemorrhage. Reduction to 2 × 110 mg if patients als


Algorithm
VTE
Not Provoked by a Major Transient Risk Factor
Provoked by a Major Transient Risk Factor
Surgery, Trauma, Immobilisation, Pregnancy, Post-Partum, Estrogen
Persistent Risk Factor
Active Cancer
Chronic Inflammatory Disease
1st Unprovoked VTE + AT or APLS
Or 1st Unprovoked PE "high-risk"
Or Recurrent Unprovoked VTE
Yes
No
Men
Women HERDOO2 ≥2
No Minor Transient Risk Factors
PE
Women <50 years
(HERDOO2 ≤1)
Minor Transient Risk Factor
DVT
Bleeding Risk
Patient's preference
Indefinite
3-6 Months
≥ 6 Months and while the disease is active or under treatment

HERDOO2 Rule

	Predictor	Scoring
H	Hyperpigmentation	1 point total, if any one of these criteria is present
E	Edema	
R	Redness of either leg	
D	D-dimer ≥ 250 µg/L while anticoagulated	1
O	Obesity with BMI ≥ 30 kg/m^2	1
O	Older age, ie, ≥ 65 years	1

Decision Making:		
Women:	0-1	Discontinue anticoagulation
	≥2	Continue anticoagulation
All men		Continue long-term anticoagulation

Rodger MA, et al. *BMJ*. 2017;356:j1065.

VTE BLEED SCORE

Table 1. The VTE-BLEED score.

Factor	Score
Active cancer[a]	2
Male with uncontrolled arterial hypertension[b]	1
Anaemia[c]	1.5
History of bleeding[d]	1.5
Age ≥60 years old	1.5
Renal dysfunction[e]	1.5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

[a]Cancer diagnosed within six months before diagnosis of VTE (excluding basal-cell or squamous-cell carcinoma of the skin), recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within six months before the VTE was diagnosed. [b]Males with uncontrolled arterial hypertension were defined by values of systolic blood pressure ≥140 mmHg at baseline. [c]Haemoglobin <13 g/dl in men or <12 g/dl in women. [d]Including prior major or non-major clinically relevant bleeding event, rectal bleeding, frequent nose bleeding, or haematuria. [e]The estimated glomerular filtration rate (eGRF) <60 ml/min defined the presence of renal dysfunction: eGRF was calculated at baseline with the Cockcroft-Gault formulas, which include serum creatinine, age, and body weight.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