Acilde Pulmoner Emboli Yaklaşımlarında Yenilikler

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Tanım

Pulmoner arterin veya dallarından birinin, vücudun başka bir yerinde çıkan materyal tıkanması

- Trombüs
- Tümör
- Hava
- Yağ

- Genellikle proksimal alt ekstremite venlerinden kaynaklanan bir pıhtının, yerinden kopması sonucu venöz sistem boyunca ilerleyerek pulmoner arterlere yerleşmesi sonucu gelişir.

- Yıllık insidansı 23-269/100.000
- VTE riski yaşla birlikte artar ve 80 yaşından sonra,45-50 yaşındakine göre yaklaşık 10 katına yükselir.
- Hamilelik ve oral kontraseptifler sebebiyle doğurgan yaş grubundaki kadınlarda daha sık görüldüğüne dair bulgular mevcutken, genel olarak her iki cinsiyette eşit görülmektedir.
- Mevsimsel değişiklik gösterebilip, özellikle kış aylarında daha sık görülmektedir.
- VTE saptananların ailelerinde de VTE insidansı yüksek saptanır ve kardeşlerde risk yaklaşık 3 kat fazladır.

Risk faktörleri

Genetik risk faktörleri	Kazanılmış risk faktörleri
Aktive protein C rezistansı: (Faktör V Leiden)	Alt ekstremite kırığı
Protrombin G20210A mutasyonu	Kalça veya diz replasmanı
Protein C eksikliği	Majör cerrahi (Pelvik, abdominal)
Protein S eksikliği	Majör travma
Antitrombin III eksikliği	Miyokard infarktüsü
Hiperhomosisteinemi	Spinal kord yaralanması
Faktör VIII artışı	İmmobilizasyon
Faktör VII eksikliği	Konjestif kalp yetmezliği
Konjenital disfibrinojenemi	Kemoterapi
Plazminojen eksikliği	Antifosfolipid sendromu
Faktör IX artışı	Oral kontraseptif kullanımı
	Östrojen tedavisi
	Kanser
	İnme
	Şişmanlık
	İleri yaş
	Gebelik/Lohusalık
	Santral venöz kateter
	Polisitemia vera
	Uzun süreli seyahat
	Nefrotik sendrom

- Mortalite oranı %15 ,

- Tanı konduktan sonraki ilk 2 haftalık süre içerisindeki mortalite oranı ise %12.4

Goldhaber S, Visani L, De R. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353(9162):1386-1389.

Semptomlar	Bulgular
Açıklanamayan dispne	Takipne (>20/dk)
Batıcı veya atipik göğüs ağrısı	Taşikardi (>100/dk)
Hemoptizi	Raller
Çarpıntı	DVT bulguları
Senkop/presenkop	Ateş
Anksiyete	Üçüncü veya 4. kalp sesi
Öksürük	Pulmoner 2. seste şiddetlenme
Bacakta şişme, kızarıklık, ağrı	Triküspit yetersizliği üfürümü

DVT: Derin ven trombozu

Elektrokardiyografi

- Atriyal aritmiler (örn. Atriyal fibrilasyon)
- Bradikardi (dakikada 50 atış) veya taşikardi (dakikada> 100 vuruş)
- Yeni sağ dal bloğu
- Düşük Q dalgaları (II, III ve aVF)
- ST segment değişiklikleri ve T dalgası inversiyonu
- S1Q3T3 kalıbı

Arterial Kan gazı

- PE'lu hastaların% 18'inde normal olabilir
- Hipoksemi (% 74)
- Alveolar arteriyel gradiyentte genişleme (% 62 ila 86)
- Solunum alkalozu ve hipokapni (% 41)

Stein PD, Goldhaber SZ, Henry JW, Miller AC. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. Chest 1996; 109:78.

- Klinik belirti ve semptomlar non-spesifik olduğu için PE tanısını erken koymak zor olabilir.
- Akla getirmek ve kuşkulanmak!
- Bunun için başlangıçtaki semptom ve bulguların yanında risk faktörlerinin varlığı dikkate alınmalıdır.
- Klinik şüphe varlığında ileri tetkikler düşünülmelidir.

D-dimer

- D-dimer'ın negatif prediktif değeri yüksektir.
- Normal D-dimer seviyeleri PE veya DVT'nin muhtemel olmadığını gösterir.
- ELISA yöntemi ile D-dimer ölçümlerinin tanısal sensitivitesi %95'tir.
- Negatif ELISA D-dimer + Klinik olasılık testleri
- İleri değerlendirmeye gerek kalmadan PE şüpheli hastaların %30'unda PE dışlanabilir.

- Yaşla beraber D-dimer spesivitesi azalır.
- 80 yaş üzeri %10'lara iner.
- Yaşlı hastalarda d-dimer değerlendirmesinde yaşa bağlı cut-off değerlerinin kullanılması önerilmiştir*.
- <50 yaş 500 µg/L
- >50 yaş yaş x 10 µg/L

*Schouten HJ, Geersing GJ, Koek HL, Zuithoff NP, Janssen KJ, Douma RA, van Delden JJ, Moons KG, Reitsma JB. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ 2013;346:f2492.

Klinik Olasılığın Değerlendirilmesi

- Wells
- Revize Geneva
- Years !!!!!! (2017)

Wells

Bulgu	Puan
DVT semptom ve bulguları varlığı	3,0
Alternatif tanı olasılığı düşük	3,0
Taşikardi (>100/dk)	1,5
Son 4 hafta içinde immobilizasyon veya cerrahi öyküsü	1,5
Daha önce DVT veya pulmoner emboli öyküsü	1,5
Hemoptizi	1,0
Kanser varlığı	1,0

DVT: Derin ven trombozu

Toplam puan:

<2,0 puan: Düşük klinik olasılık	*≤4 puan: PTE olası değil*
2,0- 6,0 puan: Orta klinik olasılık	*>4 puan: PTE olası*
>6,0 puan: Yüksek klinik olasılık	

Revize Geneva

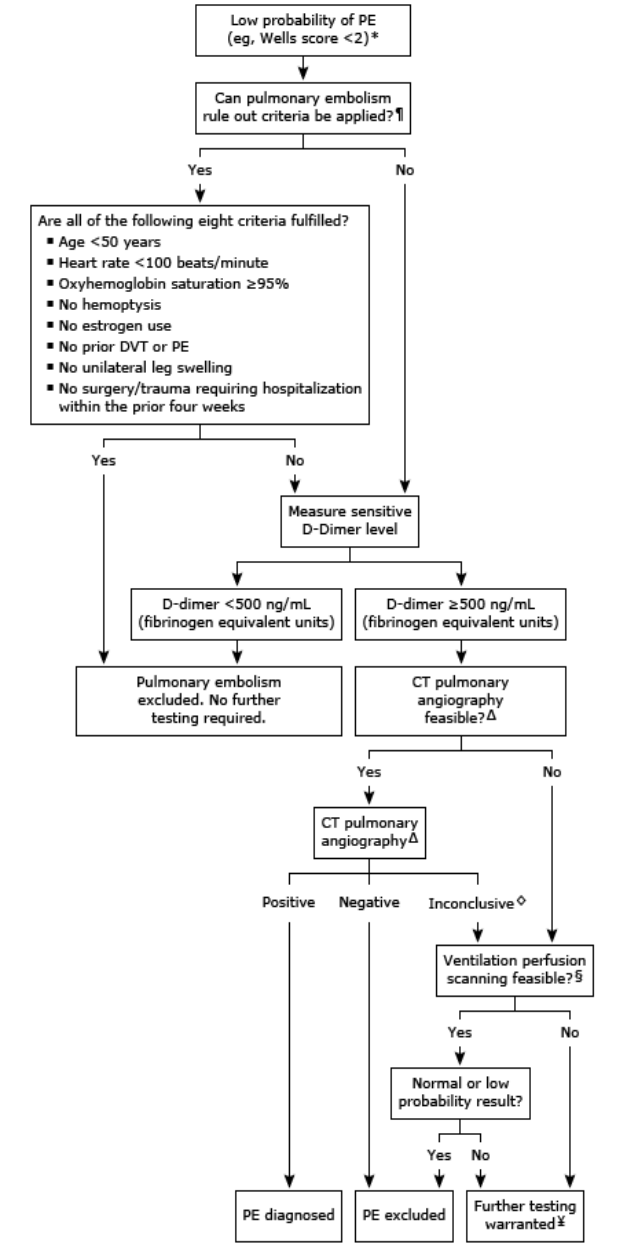
Bulgu	Puan
>65 yaş	1
Daha önce DVT veya PTE öyküsü	3
Bir hafta içinde cerrahi veya ekstremite fraktürü öyküsü	2
Aktif kanser varlığı	2
Tek taraflı alt ekstremitede ağrı	3
Hemoptizi	2
Kalp hızı: 75-94/dakika	3
Kalp hızı: >95/dakika	5
Bacağın palpasyonu ile ağrı veya tek taraflı bacakta ödem-şişlik	4

DVT: Derin ven trombozu; PTE: Pulmoner tromboembolizm

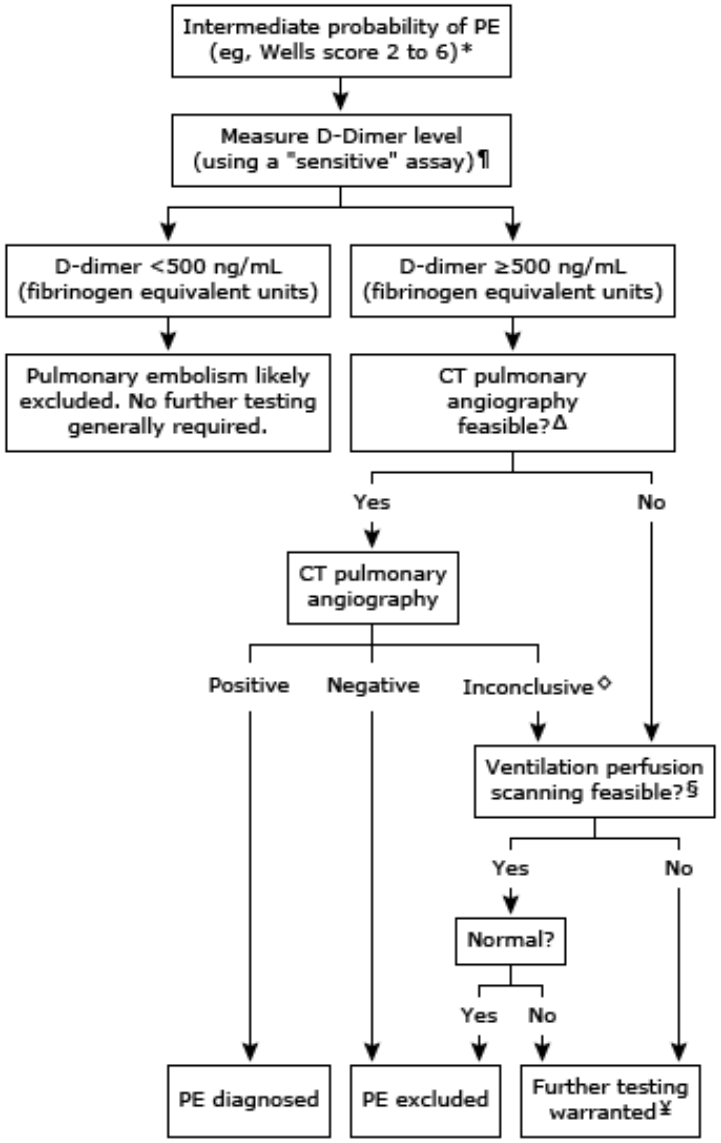
Toplam puan:

0-3 puan: Düşük olasılık	*0-5 puan: PTE olası değil*
4-10 puan: Orta olasılık	*>6 puan: PTE olası*
≥11 puan: Yüksek olasılık	

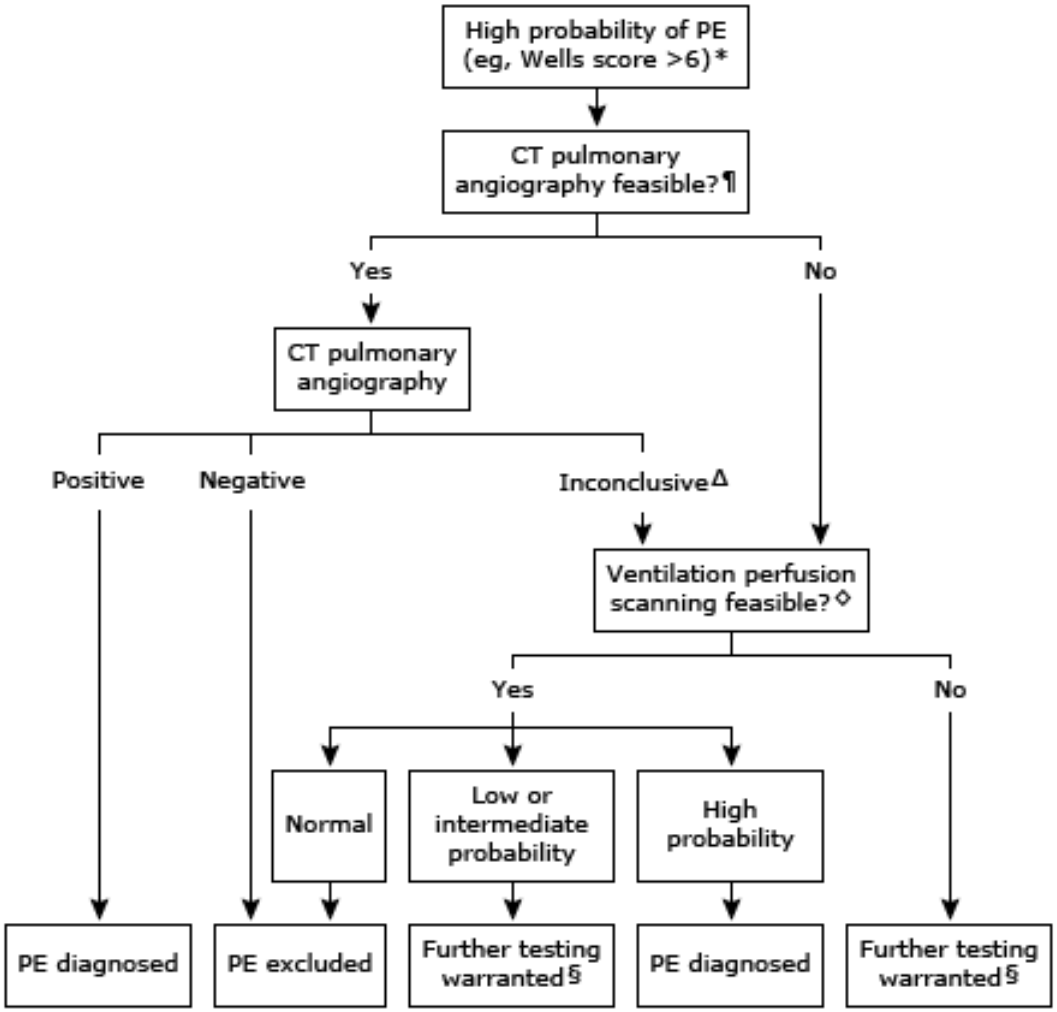
Evaluation of the nonpregnant adult with low probability of pulmonary embolism



Evaluation of the nonpregnant adult with intermediate probability of pulmonary embolism



Evaluation of the nonpregnant adult with high probability of pulmonary embolism



Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study

*Tom van der Hulle, Whitney Y Cheung, Stephanie Kooij, Ludo F M Beenen, Thomas van Bemmel, Josien van Es, Laura M Faber, Germa M Hazelaar, Christian Heringhaus, Herman Hofstee, Marcel M C Hovens, Karin A H Kaasjager, Rick C J van Klink, Marieke J H A Kruip, Rinske F Loeffen, Albert T A Mairuhu, Saskia Middeldorp, Mathilde Nijkeuter, Liselotte M van der Pol, Suzanne Schol-Gelok, Marije ten Wolde, Frederikus A Klok, Menno V Huisman, for the YEARS study group**

Summary

Background Validated diagnostic algorithms in patients with suspected pulmonary embolism are often not used correctly or only benefit subgroups of patients, leading to overuse of computed tomography pulmonary angiography (CTPA). The YEARS clinical decision rule that incorporates differential D-dimer cutoff values at presentation, has been developed to be fast, to be compatible with clinical practice, and to reduce the number of CTPA investigations in all age groups. We aimed to prospectively evaluate this novel and simplified diagnostic algorithm for suspected acute pulmonary embolism.

Methods We did a prospective, multicentre, cohort study in 12 hospitals in the Netherlands, including consecutive patients with suspected pulmonary embolism between Oct 5, 2013, to July 9, 2015. Patients were managed by simultaneous assessment of the YEARS clinical decision rule, consisting of three items (clinical signs of deep vein thrombosis, haemoptysis, and whether pulmonary embolism is the most likely diagnosis), and D-dimer concentrations. In patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL, pulmonary embolism was considered excluded. All other patients had CTPA. The primary outcome was the number of independently adjudicated events of venous thromboembolism during 3 months of follow-up after pulmonary embolism was excluded, and the secondary outcome was the number of required CTPA compared with the Wells' diagnostic algorithm. For the primary outcome regarding the safety of the diagnostic strategy, we used a per-protocol approach. For the secondary outcome regarding the efficiency of the diagnostic strategy, we used an intention-to-diagnose approach. This trial is registered with the Netherlands Trial Registry, number NTR4193.

Findings 3616 consecutive patients with clinically suspected pulmonary embolism were screened, of whom 151 (4%) were excluded. The remaining 3465 patients were assessed of whom 456 (13%) were diagnosed with pulmonary embolism at baseline. Of the 2946 patients (85%) in whom pulmonary embolism was ruled out at baseline and remained untreated, 18 patients were diagnosed with symptomatic venous thromboembolism during 3-month follow-up (0·61%, 95% CI 0·36–0·96) of whom six had fatal pulmonary embolism (0·20%, 0·07–0·44). CTPA was not indicated in 1651 (48%) patients with the YEARS algorithm compared with 1174 (34%) patients, if Wells' rule and fixed D-dimer threshold of less than 500 ng/mL would have been applied, a difference of 14% (95% CI 12–16).

Interpretation In our study pulmonary embolism was safely excluded by the YEARS diagnostic algorithm in patients with suspected pulmonary embolism. The main advantage of the YEARS algorithm in our patients is the absolute 14% decrease of CTPA examinations in all ages and across several relevant subgroups.

Funding This study was supported by unrestricted grants from the participating hospitals.

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See Comment page 210

*YEARS study group is listed at the end of this paper

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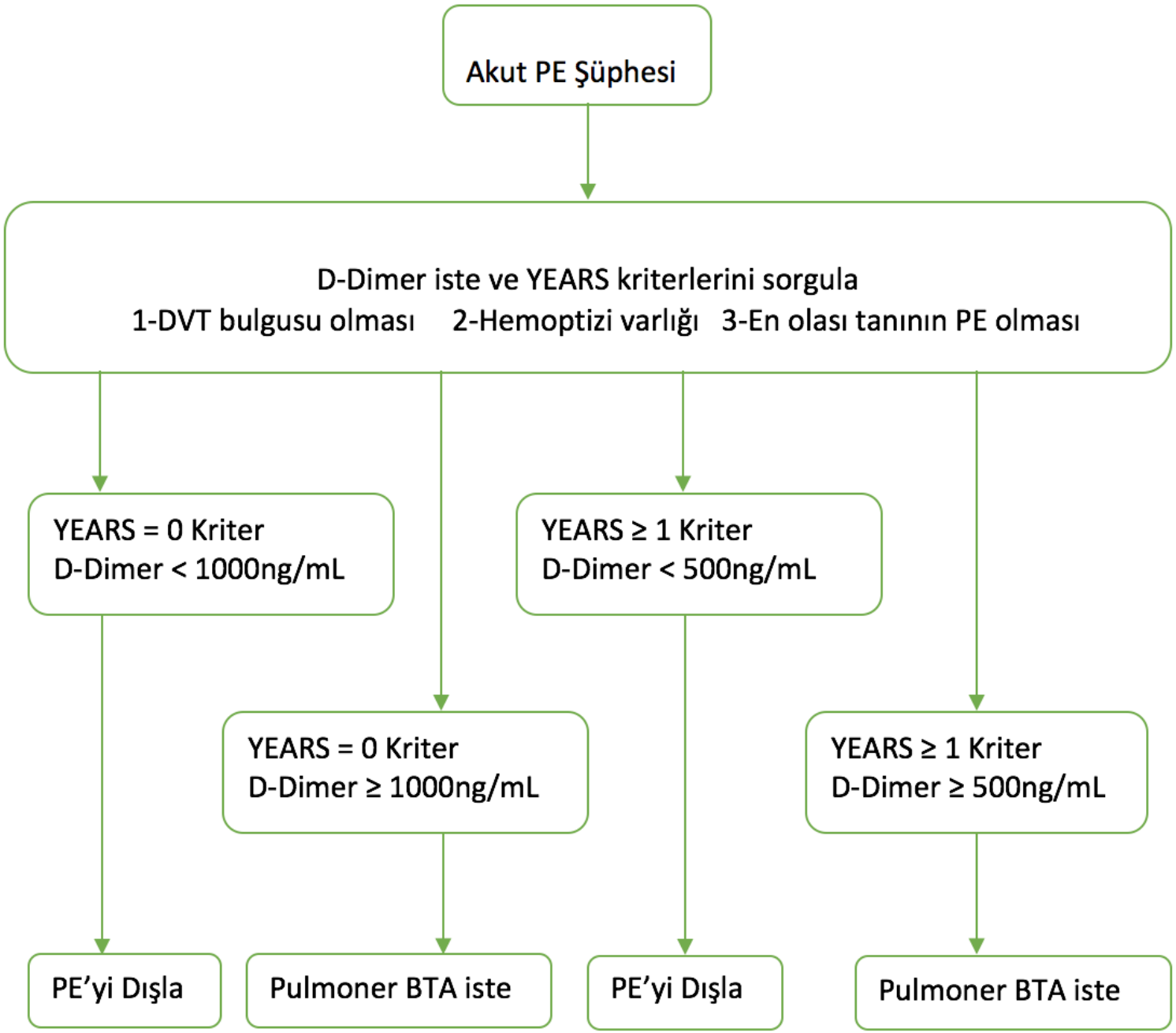
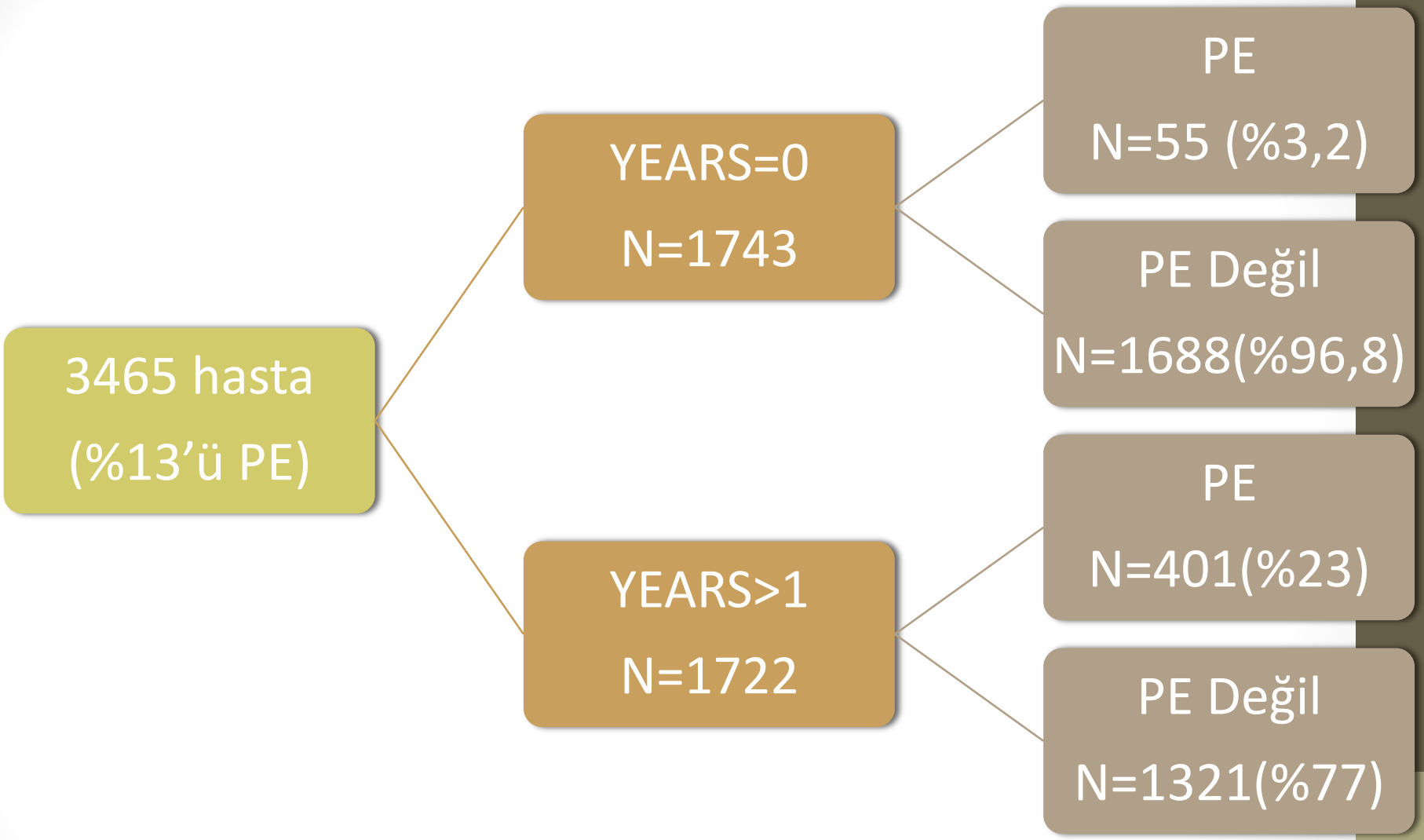
NEDEN ?

- Tanısal değerliliğinin yüksek olması ve kolay erişimi sebebiyle pulmoner BT anjio kullandığımız bir tanı yöntemidir.
- klinik olarak anlamsız subsegmental PE tanılarını arttırmakta
- maliyeti yükseltmekte
- hastaların gereksiz radyasyona maruziyetine sebep
- kontrast nefropatisi gibi istenmeyen durumlara yol açabilmektedir


Akut PE Şüphesi
D-Dimer iste ve YEARS kriterlerini sorgula
1-DVT bulgusu olması 2-Hemoptizi varlığı 3-En olası tanının PE olması
YEARS = 0 Kriter
D-Dimer < 1000ng/mL
YEARS ≥ 1 Kriter
D-Dimer < 500ng/mL
YEARS = 0 Kriter
D-Dimer ≥ 1000ng/mL
YEARS ≥ 1 Kriter
D-Dimer ≥ 500ng/mL
PE'yi Dışla
Pulmoner BTA iste
PE'yi Dışla
Pulmoner BTA iste


3465 hasta
(%13'ü PE)
YEARS=0
N=1743
YEARS>1
N=1722
PE
N=55 (%3,2)
PE Değil
N=1688(%96,8)
PE
N=401(%23)
PE Değil
N=1321(%77)

- 3616 ardışık hasta değerlendirilmiş. Bu hastalardan 151'i dışlama kriterleri gereğince dışlanmış.
- 3465 hastanın 456'sı (%13) PE tanısı almış
- Hiçbir YEARS kriteri mevcut olmayan hasta sayısı 1743 olarak bulunmuş ve bu hastaların 55'i (%3.2) PE tanısı almış.
- Bir veya daha fazla YEARS kriteri mevcut olan hasta sayısı 1722 olarak bulunmuş ve bu hastaların 401'i (%23) PE tanısı almış.

- 6 hasta ölmüş ve bu hastaların ölüm sebebi olarak PE dışlanamamış (0.20%, 95% CI 0.07-0.44).
- Bu hastaların 2 ‘sine PBTA çekilmemiş, diğer 4’üne çekilmiş.
- 3 aylık takiplerde 18 hastaya semptomatik VTE tanısı konmuş (0.61%, 95% CI 0.36-0.96).
- Bu hastaların 7 ‘sine PBTA çekilmemiş, diğer 11’ine ise çekilmiş.

- **YEARS algoritması kullanılması, Well's algoritması** (D-Dimer sınır değeri <500 ng/mL) kullanılması ile **karşılaştırıldığında PBTA ihtiyacındaki azalma %14** (95% CI 12-16) olarak tanımlanmış.
- Aynı karşılaştırma yaş modifiye D-Dimer değerleri kullanılan Well's algoritması ile yapıldığında PBTA ihtiyacındaki azalma %8.7 olarak saptanmış.

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Original Contribution | Full Access

Multicenter Evaluation of the YEARS Criteria in Emergency Department Patients Evaluated for Pulmonary Embolism

Christopher Kabrhel MD,MPH, Astrid Van Hylckama Vlieg PhD, Alona Muzikanski MS, Adam Singer MD, Gregory J. Fermann MD, Samuel Francis MD, Alex Lim kakeng MD, ... See all authors

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This article has been accepted for publication and undergone full peer review but has not been ... More

	Imaging Recommended	Imaging Not Recommended	PE Diagnosed	"Missed" PE**
Wells score </=6 and D-dimer >500*	849 (47%, 95% CI, 45%,50%)	940 (53%, 95% CI, 50%,55%)	82 (5% [95% CI, 4%,6%] of total) (98% [95% CI, 92%,99%] of PE+)	2 (0.2% [95% CI, 0.02%,0.6%] of subjects with no imaging recommended, (2% [95% CI, 0.3%, 8%] of PE+)
YEARS Criteria and variable D-dimer	585 (33%, 95% CI, 31%,35%)	1204 (67%, 95% CI, 65%,70%)	78 (4% [95% CI, 3%,5%] of total) (93%, 95% CI [85%,97%] of PE+)	6 (0.5% [95% CI, 0.2%,1.1%] of subjects with no imaging recommended (7% [95% CI, 3%,15%] of PE+)
Alternative Diagnosis less likely than PE and variable D-dimer	552 (31%, 95% CI, 29%,33%)	1237 (69%, 95% CI 67%,71%)	78 (4% [95% CI, 3%,5%] of total) (93% [95% CI 85%,97% of PE+)	6 (0.5% [95% CI, 0.2%,1.1%] of subjects with no imaging recommended) (7% [95% CI, 3%,15%] of PE+)

Table 3: Test Characteristics of the D-dimer using the YEARS Criteria, Standard Threshold and "Alternative Diagnosis Less Likely than PE" (N=1789)

	Sensitivity (95%CI)	Specificity (95%CI)	NPV (95%CI)	PPV (95%CI)	Negative Likelihood Ratio (95% CI)
Wells score </=6 and D-dimer >500*	97.6% (91.7%-99.7%)	55.0% (52.6%-57.4%)	99.8% (99.2%-100%)	9.7% (7.8%-11.8%)	0.04 (0.01-0.17)
YEARS Criteria and variable D-dimer	92.9% (85.1%-97.3%)	70.3% (68.0%-72.4%)	99.5% (98.9%-99.8%)	13.3% (10.7%-16.4%)	0.10 (0.05-0.22)
Alternative Diagnosis less likely than PE and variable D-dimer	92.9% (85.1%-97.3%)	72.2% (70.0%-74.3%)	99.5% (98.9%-99.8%)	14.1% (11.3%-17.3%)	0.10 (0.05-.21)

Sonuç

- YEARS, Pulmoner emboliyi değerlendirmede bazı vakaları kaçırsada PE ile birlikte NPV'de azalma olmaması ile görüntüleme ihtiyacının azalmasına neden olabilir.

Tanısal Stratejiler

- Şok ve Hipotansiyonun Eşlik Ettiği PE Şüphesi
- Şok ve Hipotansiyonun Eşlik Etmediği PE Şüphesi

Masif emboli de "hipotansiyon" tanımı :

Hipotansiyon;

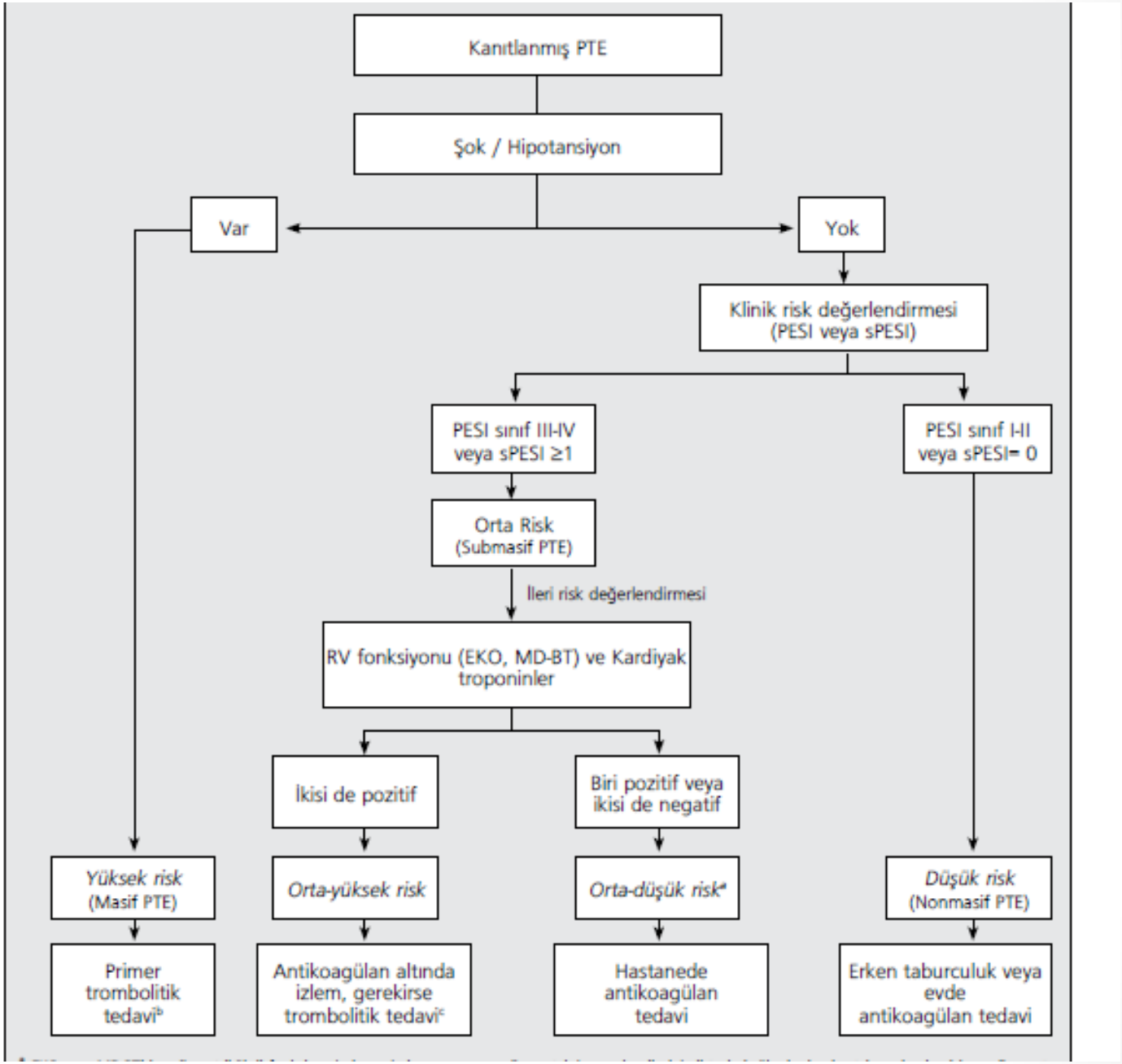
- Sistolik kan basıncının "≤90 mmHg olması,
- Basal sistolik kan basıncının ≥40 mmHg ve daha fazla düşüş olması
- 15 dakika sürmesi
- Vazopresör tedavi gerektiren hipotansiyon
- Aritmi, hipovolemi, sepsis gibi nedenlere bağlı olmaması

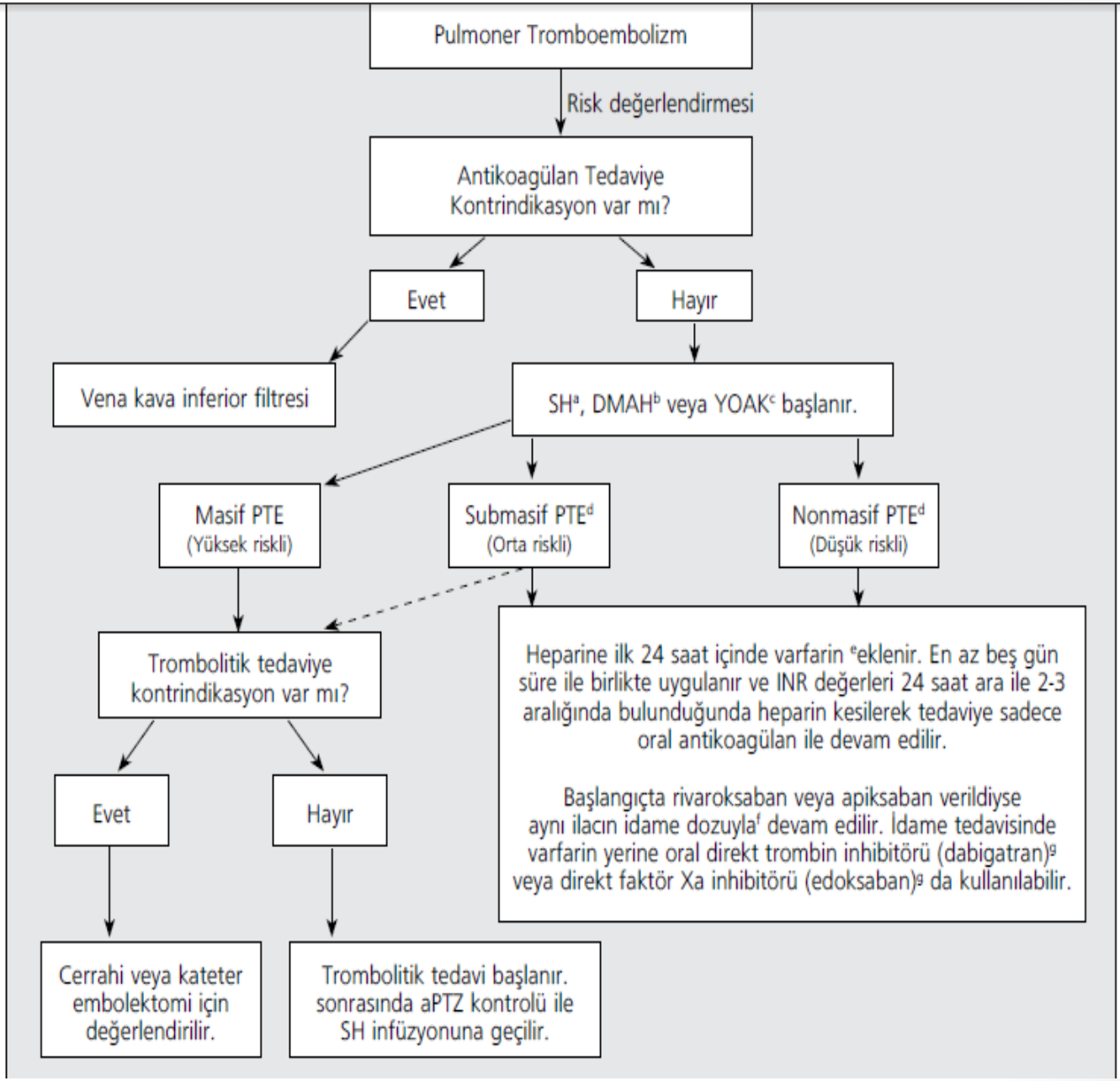
PSEI

Değişken	Skor: Orijinal PESI	Skor: Basitleştirilmiş PESI
Yaş > 80y	Yaş/yıl	1
Erkek cinsiyet	+10	
Kanser öyküsü	+30	
Kalp yetersizliği öyküsü	+10	1*
Kr. Akciğer hastalığı öyküsü	+10	
Nabız ≥ 110/dakika	+20	
Sistolik kan basıncı < 100mm Hg	+30	1
Solunum hızı ≥30/dakika	+20	1
Vücut ısısı < 36^0 C	+20	
Mental durum değişikliği	+60	
Arteriyel O_2 satürasyonu < %90	+20	1

* Kronik kardiyopulmoner hastalık (birinin varlığında 1 puan alır)

PESI		s PESI
Düşük risk	Yüksek risk	
Sınıf I : ≤ 65	Sınıf III : 86-105	Düşük risk : 0
Sınıf II : 66-85	Sınıf IV : 106-125	Yüksek risk : ≥1
	Sınıf V : > 125	


Kanıtlanmış PTE
Şok / Hipotansiyon
Var
Yok
Klinik risk değerlendirmesi (PESI veya sPESI)
PESI sınıf III-IV veya sPESI ≥1
PESI sınıf I-II veya sPESI= 0
Orta Risk (Submasif PTE)
İleri risk değerlendirmesi
RV fonksiyonu (EKO, MD-BT) ve Kardiyak troponinler
İkisi de pozitif
Biri pozitif veya ikisi de negatif
Yüksek risk (Masif PTE)
Orta-yüksek risk
Orta-düşük risk[a]
Düşük risk (Nonmasif PTE)
Primer trombolitik tedavi[b]
Antikoagülan altında izlem, gerekirse trombolitik tedavi[c]
Hastanede antikoagülan tedavi
Erken taburculuk veya evde antikoagülan tedavi


Pulmoner Tromboembolizm
Risk değerlendirmesi
Antikoagülan Tedaviye Kontrindikasyon var mı?
Evet
Hayır
Vena kava inferior filtresi
SH[a], DMAH[b] veya YOAK[c] başlanır.
Masif PTE (Yüksek riskli)
Submasif PTE[d] (Orta riskli)
Nonmasif PTE[d] (Düşük riskli)
Trombolitik tedaviye kontrindikasyon var mı?
Heparine ilk 24 saat içinde varfarin [e]eklenir. En az beş gün süre ile birlikte uygulanır ve INR değerleri 24 saat ara ile 2-3 aralığında bulunduğunda heparin kesilerek tedaviye sadece oral antikoagülan ile devam edilir.
Başlangıçta rivaroksaban veya apiksaban verildiyse aynı ilacın idame dozuyla[f] devam edilir. İdame tedavisinde varfarin yerine oral direkt trombin inhibitörü (dabigatran)[g] veya direkt faktör Xa inhibitörü (edoksaban)[g] da kullanılabilir.
Evet
Hayır
Cerrahi veya kateter embolektomi için değerlendirilir.
Trombolitik tedavi başlanır. sonrasında aPTZ kontrolü ile SH infüzyonuna geçilir.

Tedavi

- Yeni oral antikoagülanlar
- Dabigatran (trombin inhibitörü)
- Edoxaban (Faktör Xa inhibitörü)
- Rivaroxaban (Faktör Xa inhibitörü)
- Apixaban (Faktör Xa inhibitörü)

Format: Abstract Send to

N Engl J Med. 2012 Apr 5;366(14):1287-97. doi: 10.1056/NEJMoa1113572. Epub 2012 Mar 26.

Oral rivaroxaban for the treatment of symptomatic pulmonary embolism.

EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A.

Collaborators (422)

Abstract

BACKGROUND: A fixed-dose regimen of rivaroxaban, an oral factor Xa inhibitor, has been shown to be as effective as standard anticoagulant therapy for the treatment of deep-vein thrombosis, without the need for laboratory monitoring. This approach may also simplify the treatment of pulmonary embolism.

METHODS: In a randomized, open-label, event-driven, noninferiority trial involving 4832 patients who had acute symptomatic pulmonary embolism with or without deep-vein thrombosis, we compared rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist for 3, 6, or 12 months. The primary efficacy outcome was symptomatic recurrent venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS: Rivaroxaban was noninferior to standard therapy (noninferiority margin, 2.0; P=0.003) for the primary efficacy outcome, with 50 events in the rivaroxaban group (2.1%) versus 44 events in the standard-therapy group (1.8%) (hazard ratio, 1.12; 95% confidence interval [CI], 0.75 to 1.68). The principal safety outcome occurred in 10.3% of patients in the rivaroxaban group and 11.4% of those in the standard-therapy group (hazard ratio, 0.90; 95% CI, 0.76 to 1.07; P=0.23). Major bleeding was observed in 26 patients (1.1%) in the rivaroxaban group and 52 patients (2.2%) in the standard-therapy group (hazard ratio, 0.49; 95% CI, 0.31 to 0.79; P=0.003). Rates of other adverse events were similar in the two groups.

CONCLUSIONS: A fixed-dose regimen of rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of pulmonary embolism and had a potentially improved benefit-risk profile. (Funded by Bayer HealthCare and Janssen Pharmaceuticals; EINSTEIN-PE ClinicalTrials.gov number, NCT00439777.).

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Treatment of pulmonary embolism with rivaroxaban: outcomes by simplified Pulmonary Embolism Severity Index score from a post hoc analysis of the EINSTEIN PE study.

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⊕ Author information

Abstract

OBJECTIVES: The objective was to assess adverse outcomes in relation to the simplified Pulmonary Embolism Severity Index (PESI) score in patients treated with rivaroxaban or standard therapy in the phase III EINSTEIN PE study and to evaluate the utility of the simplified PESI score to identify low-risk pulmonary embolism (PE) patients.

METHODS: A post hoc analysis of EINSTEIN PE data was performed to assess the efficacy and safety of rivaroxaban in patients with a range of simplified PESI scores. Recurrent venous thromboembolism, fatal PE, all-cause mortality, and major bleeding were stratified by simplified PESI scores of 0, 1, or ≥2 and according to treatment period at 7, 14, 30, and 90 days and at the end of the full intended treatment period.

RESULTS: Simplified PESI scores could be calculated in 4,831 of the 4,832 randomized patients; of those, 53.6, 36.7, and 9.7% had PESI scores of 0, 1, and ≥2, respectively. Among patients with simplified PESI scores of 0 or 1, fatal PE, all-cause mortality, and other adverse outcomes were uncommon within the first 7, 14, and 30 days. Patients with simplified PESI scores of ≥2 had more frequent adverse outcomes. Major bleeding was lower in the rivaroxaban group, particularly in those with simplified PESI scores of 1 or ≥2.

CONCLUSIONS: The findings support using risk stratification with the simplified PESI score to identify low-risk patients with PE.

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Apixaban for extended treatment of venous thromboembolism.

Agnelli G[1], Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators.

Collaborators (397)

Author information

Abstract

BACKGROUND: Apixaban, an oral factor Xa inhibitor that can be administered in a simple, fixed-dose regimen, may be an option for the extended treatment of venous thromboembolism.

METHODS: In this randomized, double-blind study, we compared two doses of apixaban (2.5 mg and 5 mg, twice daily) with placebo in patients with venous thromboembolism who had completed 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy. The study drugs were administered for 12 months.

RESULTS: A total of 2486 patients underwent randomization, of whom 2482 were included in the intention-to-treat analyses. Symptomatic recurrent venous thromboembolism or death from venous thromboembolism occurred in 73 of the 829 patients (8.8%) who were receiving placebo, as compared with 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban (a difference of 7.2 percentage points; 95% confidence interval [CI], 5.0 to 9.3) and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (a difference of 7.0 percentage points; 95% CI, 4.9 to 9.1) (P<0.001 for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5-mg apixaban group, and 0.1% in the 5-mg apixaban group. The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5-mg apixaban group, and 4.2% in the 5-mg apixaban group. The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group.

CONCLUSIONS: Extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent venous thromboembolism without increasing the rate of major bleeding. (Funded by Bristol-Myers Squibb and Pfizer; AMPLIFY-EXT ClinicalTrials.gov number, NCT00633893.).

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Multicenter Trial of Rivaroxaban for Early Discharge of Pulmonary Embolism From the Emergency Department (MERCURY PE): Rationale and Design.

Singer AJ[1], Xiang J[2], Kabrhel C[3], Merli GJ[4], Pollack C[5], Tapson VF[6], Wildgoose P[2], Peacock WF[7].

Author information

Abstract

OBJECTIVES: Traditionally, patients with pulmonary embolism (PE) are admitted from the emergency department and treated with low-molecular-weight heparin followed by warfarin. Several studies now demonstrate that it is possible to identify low-risk PE patients that can safely be treated as outpatients. The advent of the direct-acting oral anticoagulants such as rivaroxaban has made it easier than ever to manage patients outside of the hospital. This article describes the design of a randomized controlled trial aimed at testing the hypothesis that low-risk PE patients can be safely and effectively managed at home using rivaroxaban, resulting in fewer days of hospitalization than standard-of-care treatment.

METHODS: We have initiated a multicenter, open-label, randomized clinical trial in which low-risk adult PE patients (identified by the Hestia criteria) are randomized to outpatient management with oral rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily for 90 days versus standard care, determined by the treating physician and based on local practices. The primary clinical endpoint will be the total number of inpatient hospital days (including the index admission) for venous thromboembolic or bleeding-related events during the first 30 days after randomization. A total of 150 subjects per group will provide 82% power to detect a difference of 1 day or greater in the primary outcome.

RESULTS: Patient enrollment is ongoing at present in 45 of 60 planned sites. No interim analysis is planned and the study is being monitored by a data safety management board.

CONCLUSIONS: The MERCURY PE study is designed to test the hypothesis that outpatient management of low-risk PE patients with rivaroxaban reduces the number of hospitalization days from venous thromboembolism and bleeding compared with standard care. This article describes the rationale and methodology for this study.

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Efficacy and safety of outpatient treatment with direct oral anticoagulation in pulmonary embolism

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Abstract

Anticoagulant treatment of acute pulmonary embolism (PE) has traditionally been hospital-based. The lesser need for monitoring with the increasingly used direct acting oral anticoagulants (DOAC) in comparison to warfarin potentially facilitates outpatient treatment of PE with these drugs. This study aimed to evaluate efficacy and safety of outpatient treatment of PE with DOAC. We extracted data from the Swedish quality registry for patients on oral anticoagulation (AuriculA) for all 245 patients in the southernmost hospital region in Sweden (1.3 million inhabitants) selected for outpatient treatment with of PE with DOAC during 2013–2015. Comorbidites, risk factors, and simplified pulmonary embolism severity index were evaluated at baseline, and death, recurrent venous thromboembolism (VTE), and bleeding was recorded during 6 months of follow-up. Outpatient treatment was defined as discharge from the emergency department within 24 h. During 6 months of follow-up, one patient died during DOAC therapy, the cause of death was unrelated to VTE. No VTE recurrences occured, whereas, one patient experienced major bleeding, and five patients experienced minor bleedings. Outpatient treatment of PE with DOAC is efficient and safe in selected patients.

Table 2 Treatment data in 245 patients in the Skåne region treated with direct DOAC because of PE during 2013–2015, *n* (%)

	Total
Treatment for 6 months	238 (97)
<6 months	7 (3)
Dabigatran[a]	2 (1)
Rivaroxaban[a]	225 (92)
Apixaban[a]	23 (9)
Risk stratification, sPESI score	
0	127 (52)
1	98 (40)
2	18 (7)
3	1 (0.4)
4	1 (0.4)

[a] Three patients changed from rivaroxaban to apixaban and one patient from rivaroxaban to dabigatran

Table 3 6 months follow-up of 245 patients in the Skåne region treated with direct DOAC because of PE during 2013–2015, *n* (%)

At 6 months	Total, *n*=245
Death	1 (0,4)
Major bleeding	1 (0.4)
Minor bleeding	5 (2)
Objective imaging for recurrent PE	9 (4)
Recurrent VTE	0 (0)
Newly detected malignancy	3 (1)

DVT Deep venous thromboembolism, *ED* emergency department

Yeni oral antikoagülanlar

avantajları

- oral olmaları
- hızlı etkileri
- yarı ömürlerinin kısa olması
- laboratuvar takip gerektirmemeleri
- seyrek intrakraniyal kanama yapmaları
- yiyecek ve ilaçlarla etkileşimlerinin az olması

dezavantajları

- antidotlarının bulunmaması
- kısa yarı ömürleri nedeniyle bir-iki doz atlandığında etkilerinin kaybolması
- geçerliliği ispatlanmış izlem metodlarının bulunmaması
- obezite, yaşlılık, renal yetersizlik, kanser gibi özel durumlarda doz ayarlaması ve yönetim algoritmalarına sahip olmamaları

Rivaroxaban

- Faktör Xa inhibitörü
- oral yolla alındıktan 2-4 saat sonra maksimum konsantrasyona ulaşır
- Hem karaciğer, hem de böbrek yoluyla atılır.
- DVT ve nonmasif PTE için akut dönemde 3 hafta süre ile 2 x 15 mg/gün dozunda kullanılır
- Ardından 20 mg/gün tek doz olarak uzun süreli idame tedavisine (sekonder proflaksi) geçilir

Dabigatran

- direkt trombin inhibitörüdür
- Alındıktan 1-2 saat sonra maksimum konsantrasyona ulaşır.
- Yarılanma ömrü 12-17 saattir.
- Renal yolla atılır.
- Nonmasif PTE'nin uzun süreli idame tedavisinde 2x150 mg/gün dozunda kullanılabilir.
- Seksen yaşın üzerinde, gastrit, özofajit ve gastroözofageal reflü varlığında 2x110 mg/gün önerilmektedir

.Schulman S, Kearon C, Kakkar AK, et al. RE–MEDY trial investigators. RE–SONATE trial investigators. Extended use of dabigatran, varfarin or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.

Apiksaban

- faktör Xa inhibitörüdür
- maksimum konsantrasyona 3 ila 4 saat içinde ulaşır
- yarılanma ömrü yaklaşık 12 saattir.
- Nonmasif VTE tedavisinde akut dönemde 7 gün 2x10 mg
- uzun süreli idame tedavisinde 2x5 mg/gün olarak önerilmektedir.

Agnelli G, Buller HR, Cohen A, et al. AMPLIFY-EXT investigators. Oral apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708

Edoksaban

- direkt faktör Xa inhibitörüdür
- Eliminasyon yarı ömrü 8-10 saattir
- Yapılan faz III çalışmada akut VTE'li hastalarda en az beş günlük heparin tedavisini takiben 60 mg/gün tek doz verilen edoksabanın varfarin kadar etkin olduğu gösterilmiştir.

- Schulman S, Kearon C, Kakkar AK, et al. RE–MEDY trial investigators. RE–SONATE trial investigators. Extended use of dabigatran, varfarin or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.

TEŞEKKÜRLER