VENÖZ TROMBOEMBOLİ VE YENİ ORAL ANTİKOAGÜLANLAR

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9 Aralık 2017

İSTANBUL

VENÖZ TROMBOEMBOLİ

- Koroner arter hastalığı ve inmenin ardından kardiyovasküler 3. mortalite nedenidir.
- Batı ülkelerinde halen puerperal ve postoperatif dönemde en sık ölüm nedenidir.
- 6 Büyük Avrupa ülkesinde her yıl 1 milyondan fazla VTE ve buna bağlı ölüm olmaktadır.
- Ölümlerin ¾ ‘ü hastanede gerçekleşmektedir.

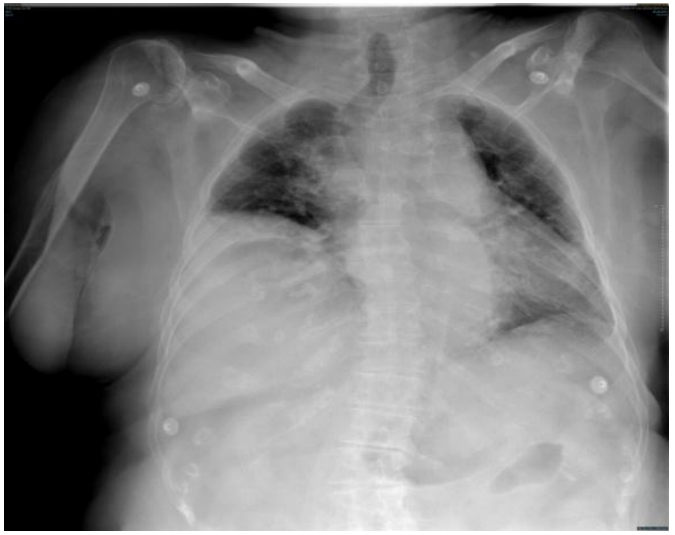
Hiperkoagülabilite	Vasküler hasar
İleri yaş	Cerrahi
Aktif kanser	Travma veya kırıklar
Antifosfolipid sendrom	Santral venöz kateter ve pacemaker
Östrojen tedavisi	
Hamilelik ve puerperium	**Venöz staz veya immobilizasyon**
Kişisel veya ailesel venöz tromboemboli hikayesi	Akut medikal nedenlerle hastaneye yatış/ Postoperatif dönem
Obezite	Bakım evlerinde yaşamak
Otoimmün ve kronik inflamatuar hastalıklar	Dört saatten uzun süren yolculuklar
Heparin kaynaklı trombositopeni	Parezi ve paralizi durumları
Genetik risk faktörleri	
Faktör V Leiden mutasyonu	Protein C yetersizliği
Protrombin 20210G - A mutasyonu	Protein S yetersizliği
Antitrombin yetersizliği	0 Kan grubu dışı kan grupları

VENÖZ TROMBOEMBOLİ

- Pulmoner emboli tanısı klinik şüpheyle başlar.
- Semptom ve bulgular ile beraber risk faktörleri birlikte değerlendirilmelidir.
- Dünya nüfusunun ve bireylerin yaşam sürelerinin artmasıyla bu hastalık ile daha sık karşılaşacağız.

86 yaşında kadın hasta

- 1 ay önce kollarında büllöz lezyonlar, büllöz pemfigoid (biyopsi)
- Yatağa bağımlı yaşıyor,
- Nefes darlığı ile başvuruyor.
- KB:110/60 mmHg
- Nabız: 105/dk

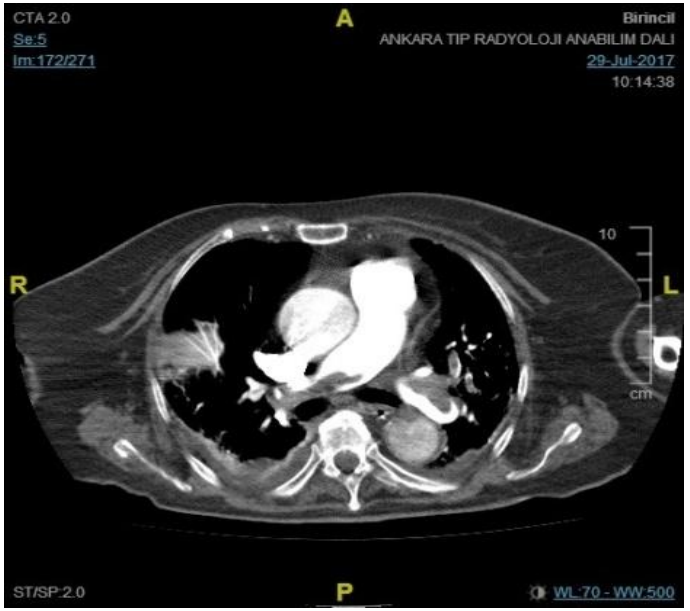


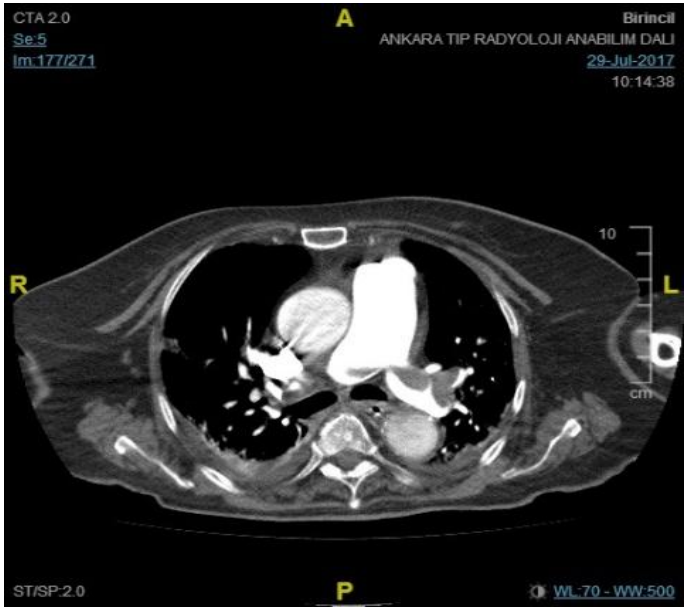
Kriterler	Puan
DVT semptom ve bulguları	3 / 0
PE dışında alternatif tanı olasılığının az olması	3 / 3
Kalb hızının 100/dk üzerinde olması	1.5 / 1.5
Hareketsizlik veya 4 hafta içinde cerrahi	1.5 / 1.5
Önceden DVT ve PE hikayesi	1.5 / 0
Hemoptizi	1 / 0
Aktif kanser	1 / 0

PE olasılığı düşük	4 puan ve altı
PE olasılığı muhtemel	4 puan üstü

- 6 puan / PE muhtemel

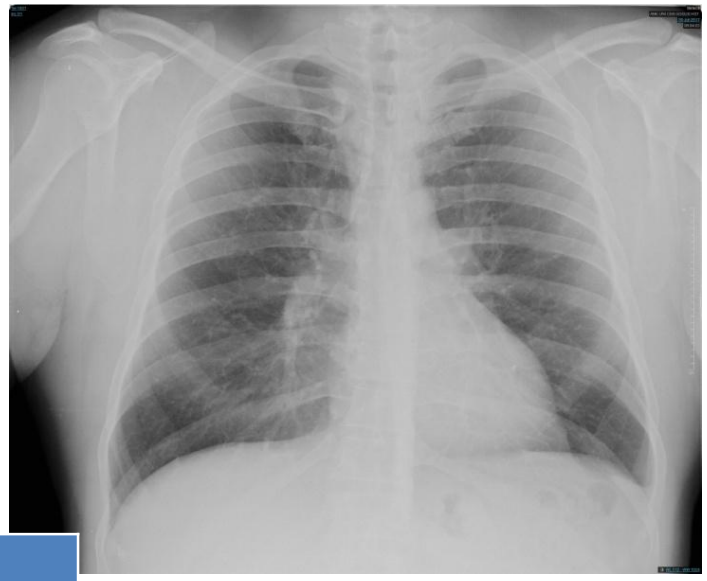
- D-dimer : 2382
- Cre:1.02 , CRP:72
- Eko PAB: 72 mmHg
- Pulmoner BT anjiyografi *pulmoner trunkusdan başlayıp her iki ana dala yayılan trombus*





38 yaşında erkek hasta

- Nefes darlığı nedeniyle başvuruyor.
- 2 ay önce iş kazası, bacakta diz üstünde kırık
- Son 1 haftadır bacakta şişlik , kızarıklık
- KB:130/85 mmHg
- Nabız: 80/dk



Kriterler	Puan
DVT semptom ve bulguları	3 / 3
PE dışında alternatif tanı olasılığının az olması	3 / 3?
Kalb hızının 100/dk üzerinde olması	1.5 / 0
Hareketsizlik/4 hafta içinde cerrahi,travma	1.5 / 1.5
Önceden DVT ve PE hikayesi	1.5 / 0
Hemoptizi	1 / 0
Aktif kanser	1 / 0

PE olasılığı düşük	4 puan ve altı
PE olasılığı muhtemel	4 puan üstü

7.5 puan / PE muhtemel
4.5 puan hala PE muhtemel

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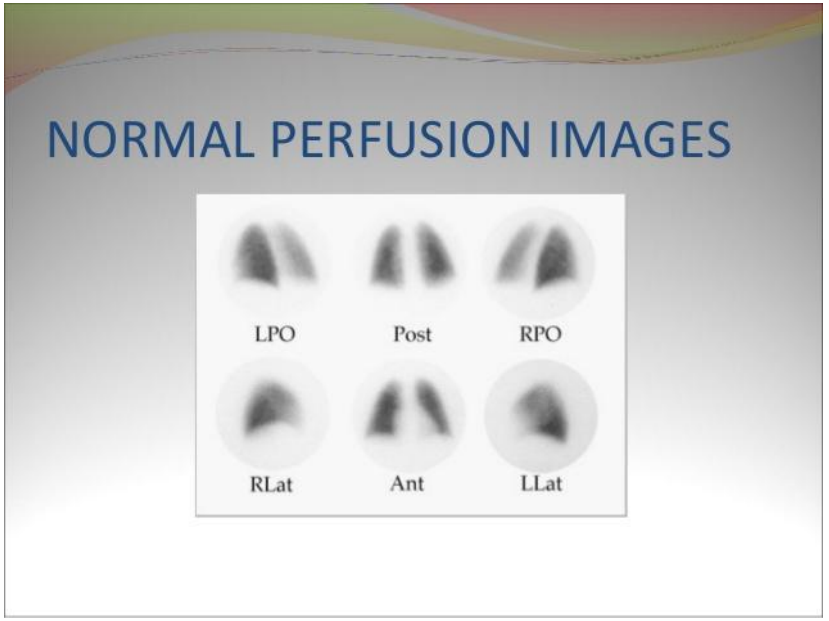
- D-dimer: 580, CRP:5.3
- Sol popliteal ve derin krural venlerde akut süreçte tromboz,
- İlaç allerjisi tanımlıyor,
- Kontrast allerji testi negatif olmasına rağmen, koruyucu steroidle yapılmak isteniyor, ancak hasta steroide reaksiyon veriyor (kaşıntı, psişik reaksiyonlar, maküler döküntü ??)

- CT pulmoner anjiyografi hasta tarafından reddedilince yapılamadı.
- V/Q sintigrafisi normal.



KRİTERLER WELLS SKORU	PUAN ORİJİNAL	BASİTLEŞTİRİLMİŞ
Önceden PE ve DVT	1.5	1
Son 4 haftada cerrahi veya immobilizasyon	1.5	1
Kanser	1	1
Hemoptizi	1	1
Kalb hızının 100 üzerinde	1.5	1
DVT klinik bulguları	3	1
PE dışında alternatif tanı olasılığının az olması	3	1

Üç düzeyli olasılık skoru		
Düşük	0-1	
Orta	2-6	
Yüksek	7 ve üzeri	
İki düzeyli olasılık skoru		
PE olasılığı yok	0-4	0-1
PE muhtemel	4 üzeri	2 ve üzeri

	Puan	
Gözden geçirilmiş Cenevre skorlaması	**Orijinal hali**	**Basit hali**
65 yaş üzeri	1	1
Önceden DVT ve PE	3	1
Son 1 ayda cerrahi veya kırık	2	1
Aktif malignite	2	1
Tek taraflı ekstremite ağrısı	3	1
Hemoptizi	2	1
Kalb hızı 75-94	3	1
95 /dk üzeri	5	2
Alt ekstremite ağrısı derin venlerde ağrılı palpasyon veya ödem	4	1
Üç düzeyli skorlama		
Düşük	0-3	0-2
Orta	4-10	2-4
Yüksek	11 ve üzeri	5 ve üzeri
İki düzeyli skorlama		
PE olasılığı düşük	0-5	0-2
PE olması muhtemel	6 ve üzeri	3 ve üzeri

VENÖZ TROMBOEMBOLİ

- *50 yaş altı,*
- *nabız 100/dk altındaysa,*
- *SaO2 %94 üstündeyse,*
- *Bacakta şişlik yoksa, hemoptizi yoksa, geçirilmiş travma ve cerrahi işlem yoksa, östrojen kullanımı yoksa,*
- PE tanısından uzaklaşılabilir.

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CLINICAL GUIDELINE

Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians

Ali S. Raja, MD; Jeffrey O. Greenberg, MD; Amir Qaseem, MD, PhD, MHA; Thomas D. Denberg, MD, PhD; Nick Fitterman, MD; and Jeremiah D. Schuur, MD, MHS, for the Clinical Guidelines Committee of the American College of Physicians*

Description: Pulmonary embolism (PE) can be a severe disease and is difficult to diagnose, given its nonspecific signs and symptoms. Because of this, testing patients with suspected acute PE has increased dramatically. However, the overuse of some tests, particularly computed tomography (CT) and plasma D-dimer measurement, may not improve care while potentially leading to patient harm and unnecessary expense.

Methods: The literature search encompassed studies indexed by MEDLINE (1966–2014; English-language only) and included all clinical trials and meta-analyses on diagnostic strategies, decision rules, laboratory tests, and imaging studies for the diagnosis of PE. This document is not based on a formal systematic review, but instead seeks to provide practical advice based on the best available evidence and recent guidelines. The target audience for this paper is all clinicians; the target patient population is all adults, both inpatient and outpatient, suspected of having acute PE.

Best Practice Advice 1: Clinicians should use validated clinical prediction rules to estimate pretest probability in patients in whom acute PE is being considered.

Best Practice Advice 2: Clinicians should not obtain D-dimer measurements or imaging studies in patients with a low pretest probability of PE and who meet all Pulmonary Embolism Rule-Out Criteria.

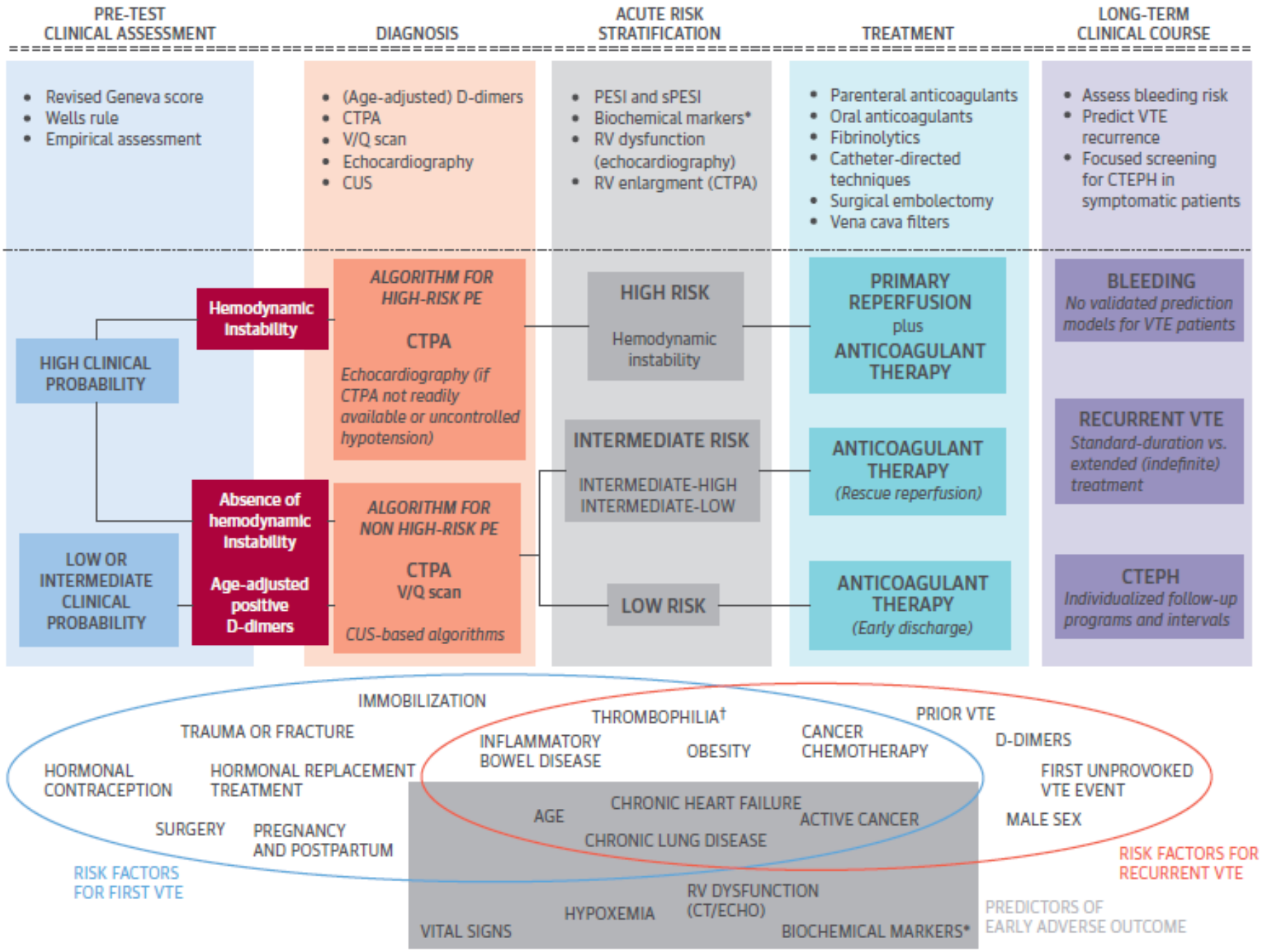
Best Practice Advice 3: Clinicians should obtain a high-sensitivity D-dimer measurement as the initial diagnostic test in patients who have an intermediate pretest probability of PE or in patients with low pretest probability of PE who do not meet all Pulmonary Embolism Rule-Out Criteria. Clinicians should not use imaging studies as the initial test in patients who have a low or intermediate pretest probability of PE.

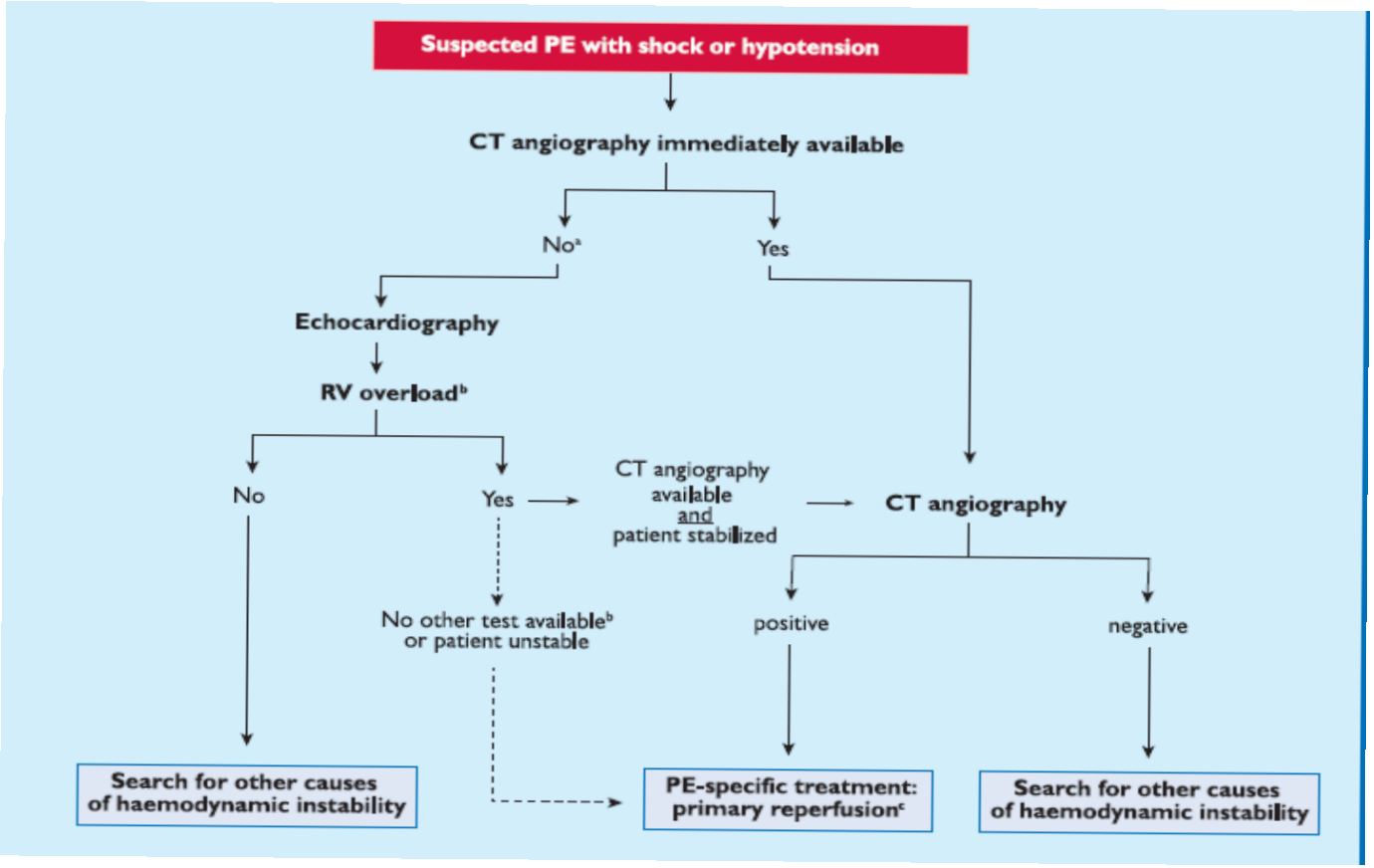
Best Practice Advice 4: Clinicians should use age-adjusted D-dimer thresholds (age × 10 ng/mL rather than a generic 500 ng/mL) in patients older than 50 years to determine whether imaging is warranted.

Best Practice Advice 5: Clinicians should not obtain any imaging studies in patients with a D-dimer level below the age-adjusted cutoff.

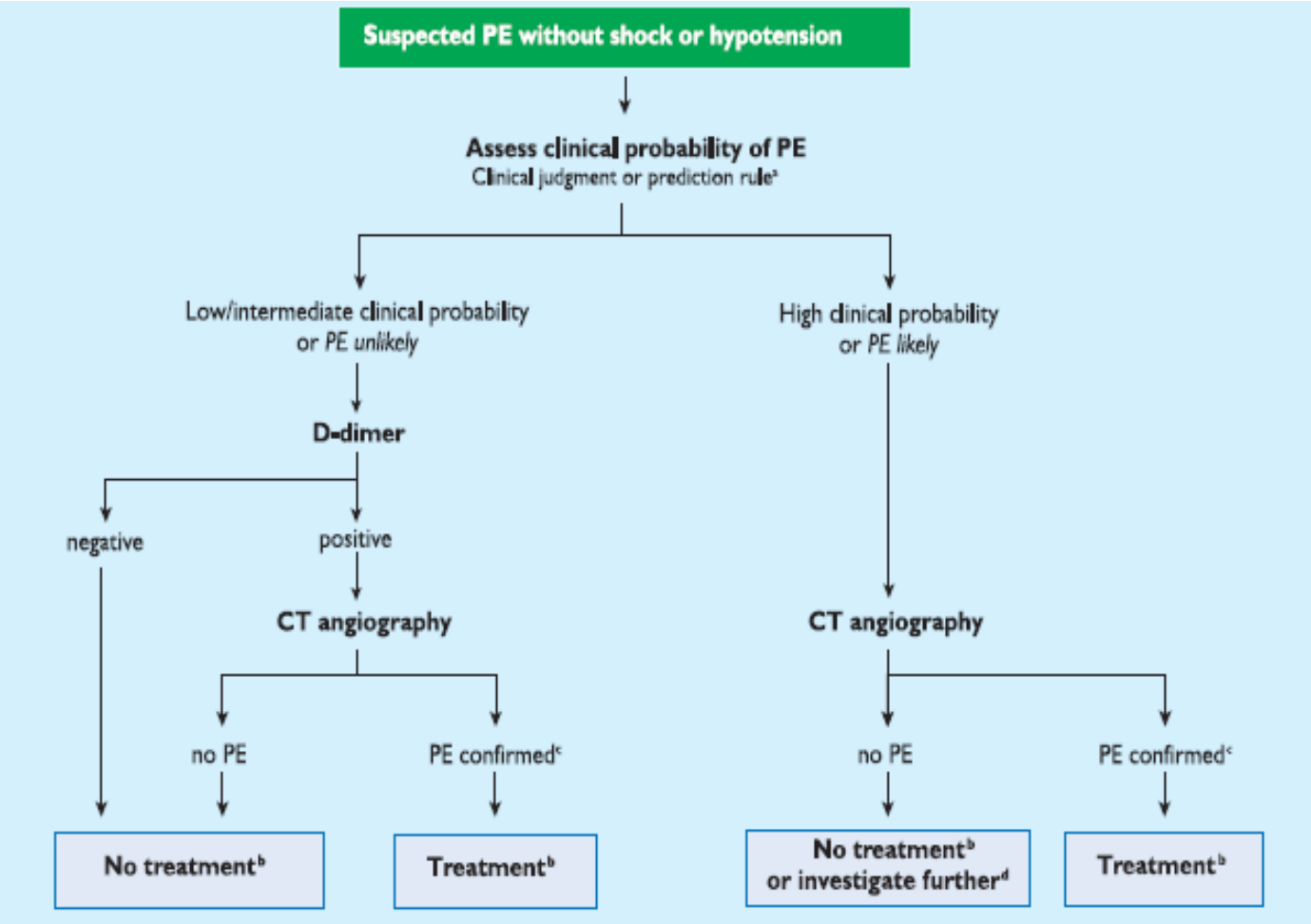
Best Practice Advice 6: Clinicians should obtain imaging with CT pulmonary angiography (CTPA) in patients with high pretest probability of PE. Clinicians should reserve ventilation–perfusion scans for patients who have a contraindication to CTPA or if CTPA is not available. Clinicians should not obtain a D-dimer measurement in patients with a high pretest probability of PE.

Ann Intern Med. 2015;163:701-711. doi:10.7326/M14-1772 **www.annals.org**
For author affiliations, see end of text.
This article was published online first at www.annals.org on 29 September 2015.


PRE-TEST CLINICAL ASSESSMENT
DIAGNOSIS
ACUTE RISK STRATIFICATION
TREATMENT
LONG-TERM CLINICAL COURSE
Revised Geneva score
Wells rule
Empirical assessment
(Age-adjusted) D-dimers
CTPA
V/Q scan
Echocardiography
CUS
PESI and sPESI
Biochemical markers*
RV dysfunction (echocardiography)
RV enlargment (CTPA)
Parenteral anticoagulants
Oral anticoagulants
Fibrinolytics
Catheter-directed techniques
Surgical embolectomy
Vena cava filters
Assess bleeding risk
Predict VTE recurrence
Focused screening for CTEPH in symptomatic patients
HIGH CLINICAL PROBABILITY
Hemodynamic Instability
ALGORITHM FOR HIGH-RISK PE
CTPA
Echocardiography (if CTPA not readily available or uncontrolled hypotension)
HIGH RISK
Hemodynamic instability
PRIMARY REPERFUSION
plus
ANTICOAGULANT THERAPY
LOW OR INTERMEDIATE CLINICAL PROBABILITY
Absence of hemodynamic Instability
Age-adjusted positive D-dimers
ALGORITHM FOR NON HIGH-RISK PE
CTPA
V/Q scan
CUS-based algorithms
INTERMEDIATE RISK
INTERMEDIATE-HIGH
INTERMEDIATE-LOW
ANTICOAGULANT THERAPY
(Rescue reperfusion)
LOW RISK
ANTICOAGULANT THERAPY
(Early discharge)
BLEEDING
No validated prediction models for VTE patients
RECURRENT VTE
Standard-duration vs. extended (indefinite) treatment
CTEPH
Individualized follow-up programs and intervals
IMMOBILIZATION
TRAUMA OR FRACTURE
HORMONAL CONTRACEPTION
HORMONAL REPLACEMENT TREATMENT
SURGERY
PREGNANCY AND POSTPARTUM
RISK FACTORS FOR FIRST VTE
THROMBOPHILIA†
INFLAMMATORY BOWEL DISEASE
OBESITY
CANCER CHEMOTHERAPY
PRIOR VTE
D-DIMERS
FIRST UNPROVOKED VTE EVENT
MALE SEX
RISK FACTORS FOR RECURRENT VTE
AGE
CHRONIC HEART FAILURE
ACTIVE CANCER
CHRONIC LUNG DISEASE
RV DYSFUNCTION (CT/ECHO)
HYPOXEMIA
VITAL SIGNS
BIOCHEMICAL MARKERS*
PREDICTORS OF EARLY ADVERSE OUTCOME



- Akut pulmoner embolili hastaların prognozlarının öngörüsü için klinik risk değerlendirmesi gereklidir.
- Hemodinamik olarak stabil olmayan şok ve hipotansiyonlu hastalar yüksek riskli hastalardır.

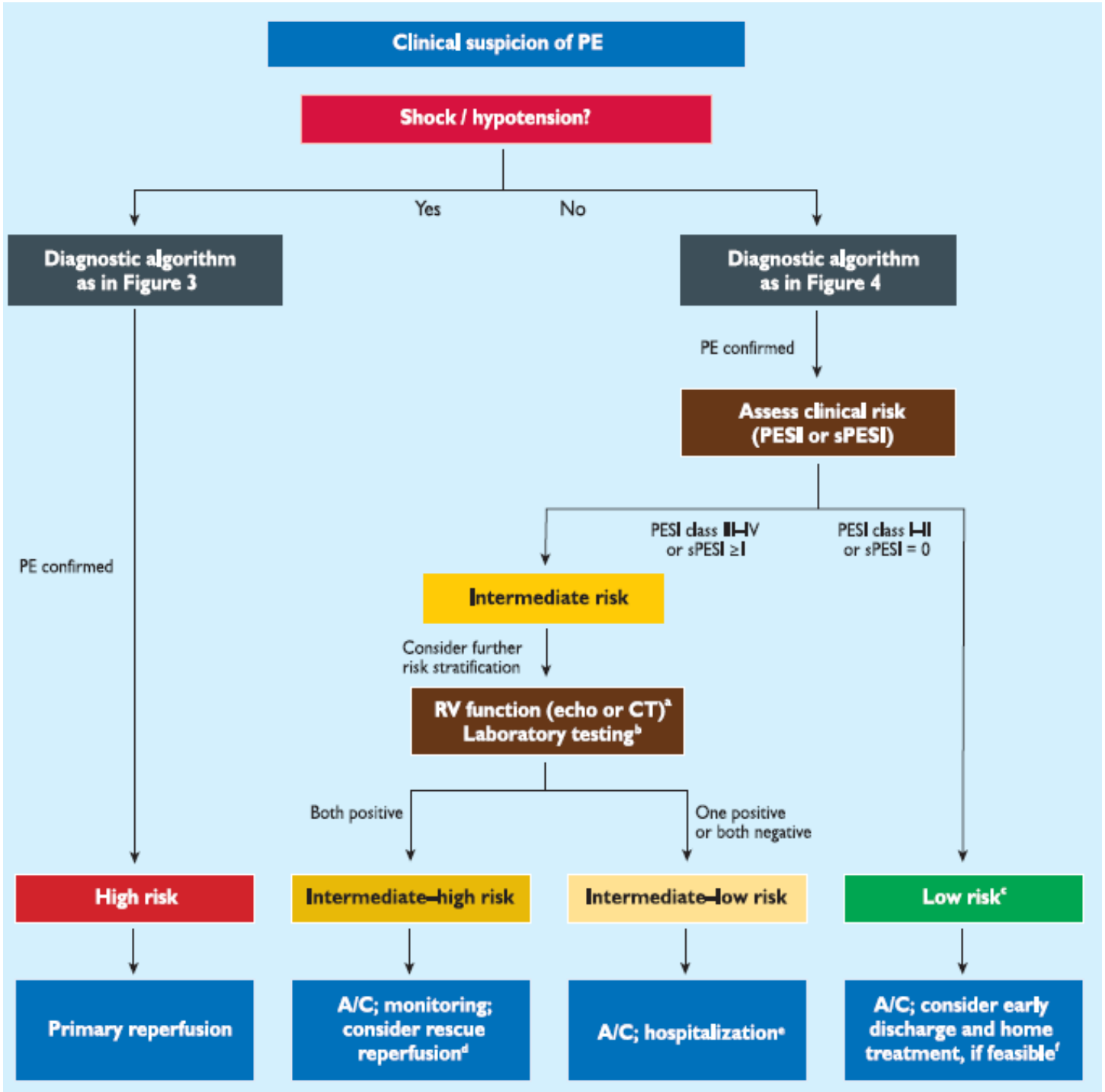


- Şok ve hipotansiyonu olmayan hastalar erken dönemde yüksek riskli olmayan hastalardır.
- Bu hastalarda PESI ve sPESI ile risk değerlendirmesi yapılabilir.

Table 7 Original and simplified PESI

Parameter	Original version[2,14]	Simplified version[2,18]
Age	Age in years	1 point (if age >80 years)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 b.p.m.	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths per minute	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhaemoglobin saturation <90%	+20 points	1 point
	Risk strata[a]	
	Class I:≤65 points very low 30-day mortality risk (0–1.6%) **Class II: 66–85 points** low mortality risk (1.7–3.5%) **Class III: 86–105 points** moderate mortality risk (3.2–7.1%) **Class IV: 106–125 points** high mortality risk (4.0–11.4%) **Class V: >125 points** very high mortality risk (10.0–24.5%)	**0 points**= 30-day mortality risk 1.0% (95% CI 0.0%–2.1%) **≥1 point(s)**= 30-day mortality risk 10.9% (95% CI 8.5%–13.2%)

b.p.m. = beats per minute; PESI = Pulmonary embolism severity index.
[a]based on the sum of points.


Clinical suspicion of PE
Shock / hypotension?
Yes
No
Diagnostic algorithm as in Figure 3
Diagnostic algorithm as in Figure 4
PE confirmed
Assess clinical risk (PESI or sPESI)
PESI class III–V or sPESI ≥1
PESI class I–II or sPESI = 0
PE confirmed
Intermediate risk
Consider further risk stratification
RV function (echo or CT)[a] Laboratory testing[b]
Both positive
One positive or both negative
High risk
Intermediate–high risk
Intermediate–low risk
Low risk[c]
Primary reperfusion
A/C; monitoring; consider rescue reperfusion[d]
A/C; hospitalization[e]
A/C; consider early discharge and home treatment, if feasible[f]

Hastaların erken mortalite riskine göre sınıflandırılması

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]	

- Pulmoner embolili hastaların 1/3'ü düşük risklidir (PESI I-II veya sPESI 0)
- PESI III-IV veya sPESI 1'den fazla olan hastalar orta gruptur.
- Bu grupta Sağ ventrikül fonksiyonlarına ve kardiyak belirteçlere bakılmalıdır.
- Buna göre orta yüksek veya orta düşük risk belirlenir.

ESC Recommendations: Reperfusion

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Reperfusion treatment		
Routine use of primary systemic thrombolysis is not recommended in patients without shock or hypotension.	III	B
Close monitoring is recommended in patients with intermediate-high risk PE to permit early detection of haemodynamic decompensation and timely initiation of rescue reperfusion therapy.	I	B
Thrombolytic therapy should be considered for patients with intermediate-high-risk PE and clinical signs of haemodynamic decompensation.	IIa	B

European Heart Journal (2014):doi:10.1093/eurheartj/ehu283

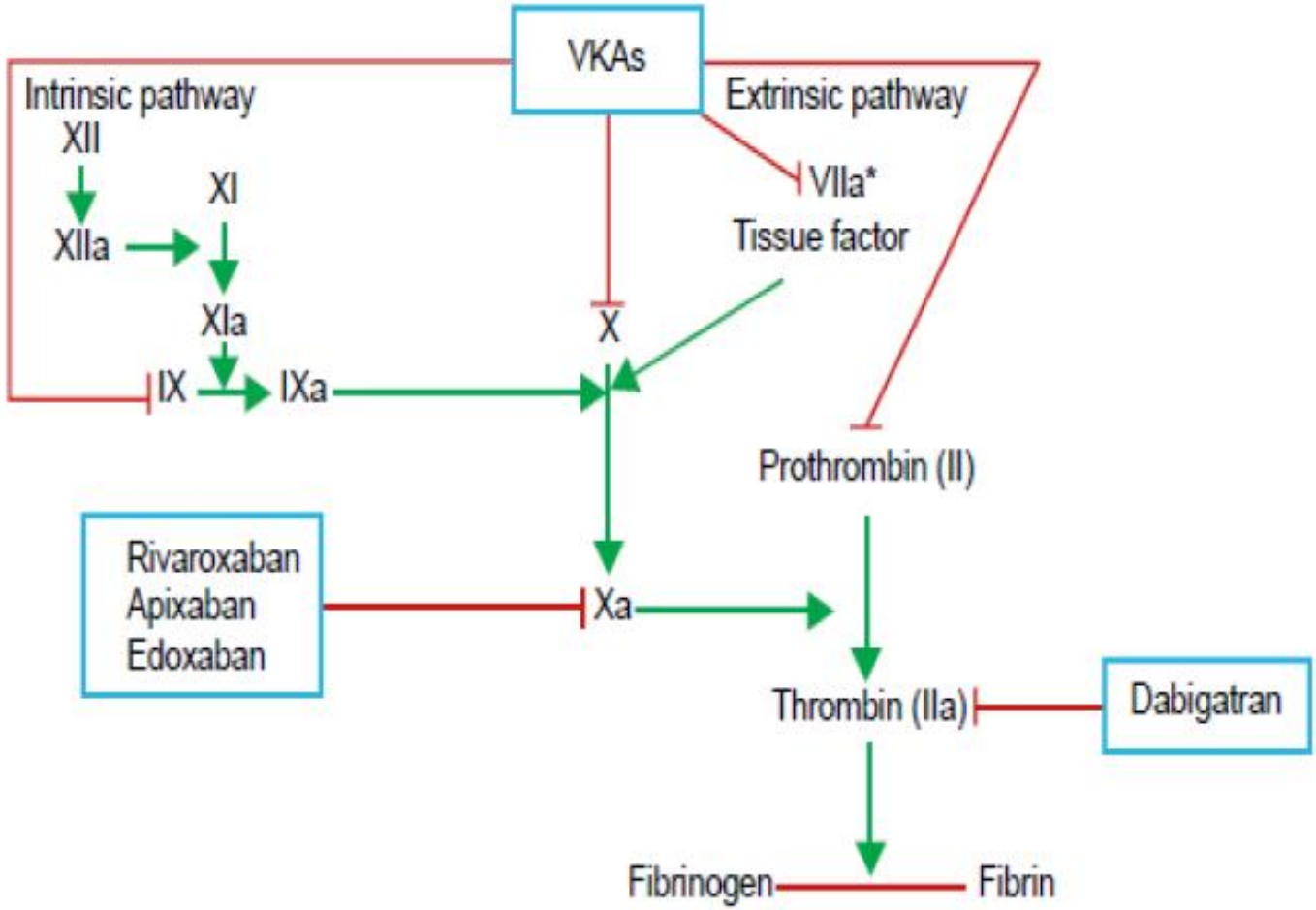
ESC recommendations: Anticoagulation

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Anticoagulation - combination of parenteral treatment with VKA		
Initiation of parenteral anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE while diagnostic work-up is ongoing.	I	C
LMWH or fondaparinux is the recommended form of acute phase parenteral anticoagulation for most patients.	I	A
In parallel to parenteral anticoagulation, treatment with a VKA is recommended, targeting an INR of 2.5 (range 2.0-3.0).	I	B

- Bir çok çalışmada varfarin tedavisi alanların %80'inin INR seviyesi tedavi sınırlarında bulunmamaktadır. *Ryan F: J Clin Pharm Therapy 2008:33(6):581-90*
- INR<2 olmasıyla tromboemboli riski artarken, INR>4.5 olunca kanama oranı artmaktadır. *Heneghan C: Lancet 2006:367:404-411*
- Türkiyede VKA kullanan hastaların ancak %48'i kılavuzların önerdiği INR değerlerine ulaşabilmektedir. *Ertaş F: Türk Kard Der Arşiv 2009:37:161-7*

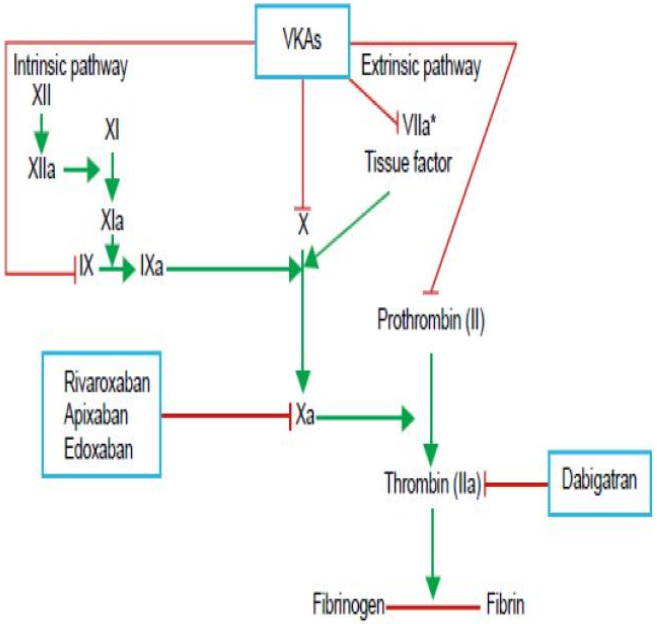
Drug	Target	Oral bioavailability	Time to peak effect	Half-life	Renal clearance	Acute VTE dosing	Drug interactions
Warfarin	VKORC1	100 %	4–5 d	40 h	<1 %	Adjusted dose	CYPP2C9, CYP3A4, CYP1A2, drugs binding human serum albumin
Apixaban	Factor Xa	>50 %	1–2 h	8–15 h	27 %	10 BID/ 5 BID	CYP3A4, P-glycoprotein
Dabigatran	Thrombin	~8 %	2 h	14–17 h	80 %	150 BID	P-glycoprotein
Edoxaban	Factor Xa	~62 %	1–2 h	10–14 h	33 %	60 OD	P-glycoprotein
Rivaroxaban	Factor Xa	>80 %	2–3 h	5–9 h	35 %	15 BID/ 20 OD	CYP3A4, P-glycoprotein

Drug Study name	Recurrent VTE or VTE-related death[a]			Major or clinically relevant nonmajor bleeding		
	DOAC	VKA	HR	DOAC	VKA	HR
Apixaban AMPLIFY	2.3	2.7	0.84 (0.60–1.18)	4.3	9.7	0.44 (0.36–0.55)
Dabigatran RE-COVER I and II	2.4	2.2	1.08 (0.76–1.57)	5.3	8.5	0.62 (0.50–0.76)
Edoxaban[b] Hokusai-VTE	3.2	3.5	0.82 (0.60–1.14)	8.5	10.3	0.81 (0.71–0.94)
Rivaroxaban[b] EINSTEIN-DVT	2.1	3.0	0.68 (0.44–1.04)	8.1	8.1	
Rivaroxaban[b] EINSTEIN-PE	2.1	1.8	1.12 (0.75–1.68)	10.3	11.4	0.90 (0.76–1.07)


VKAs
Intrinsic pathway
XII
XIIa
XI
XIa
IX
IXa
X
Extrinsic pathway
VIIa*
Tissue factor
Prothrombin (II)
Rivaroxaban
Apixaban
Edoxaban
Xa
Thrombin (IIa)
Dabigatran
Fibrinogen
Fibrin

DABİGATRAN - PRADAXA

İlk onay alan YOAK ilaç olup 2008 yılında Avrupa ve 2010 yılında Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) çalışmasında dabigatran ile warfarinin karşılaştırıldığı çalışma sonucunda FDA tarafından onay aldı.



Serbest ve bağlı trombini (FIIa) inhibe ederek fibrinojenin fibrine dönüşünü engeller.

Yarılanma ömrü 14-17 saat,
plazma pik konsantrasyonu 1.5-2 saat

RECOVER ve RECOVER II çalışmalarında DABİGATRAN WARFARİN KADAR ETKİLİ BULUNMUŞTUR

Dabigatran-doz-endikasyon

- Dabigatran dozu klinik durum, endikasyonlar ve böbrek fonksiyonuna göre değişir;
- Ortopedik cerahi vakalarında VTE profilaksisi için
  - Kalça cerahisinden 4 saat sonra 110 mg 1x1 diğer günler 220 mg 1x1 28-35 gün
  - Diz cerahilerinde 10 gün verilir
- VTE tedavisi ve /veya rekurensin önlenmesi için;

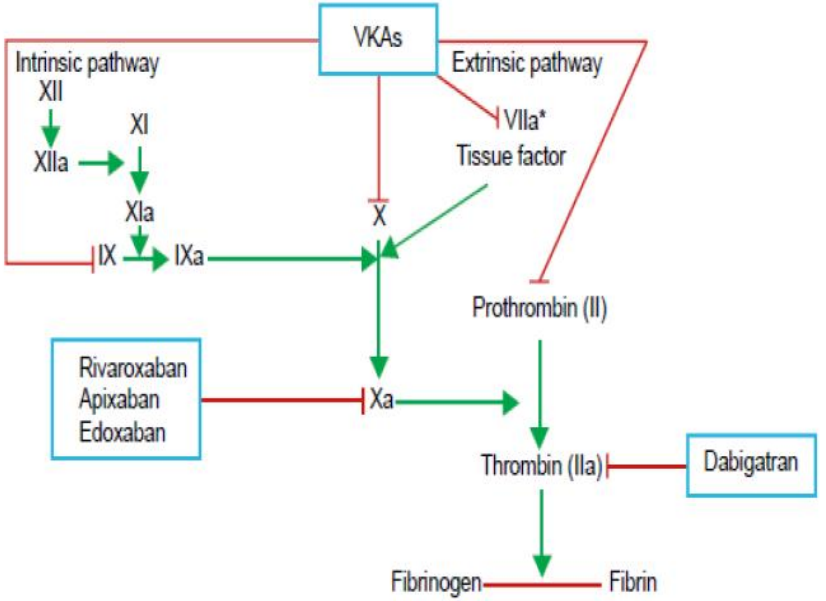
  150 mg 2x1 (CrCl >30 mL/dk).
- NVAF'li hastalarda stroke ve sistemik tromboemboli önlenmesi için;
  - 110 mg veya150 mg oral günde iki kez (CrCl >30 mL/dk).
  - Ayrıca 75 yaşın > hastalarda 150 mg tek doz veya günde 110mg 2 kez verilir

RİVAROKSABAN-XARELTO

Geri dönüşümlü faktör Xa inhibitörüdür.

EMA ve FDA tarafından 2008 yılında onay verilmiştir.

Yarılanma ömrü 7-13 saat,



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

The EINSTEIN–PE Investigators*

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.

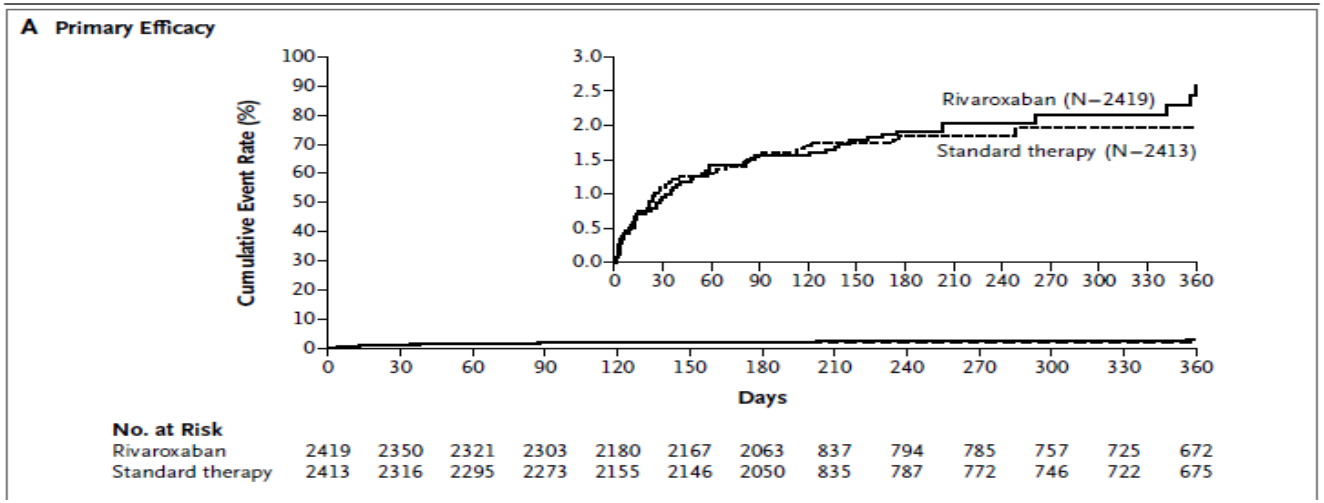
METHODS

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.

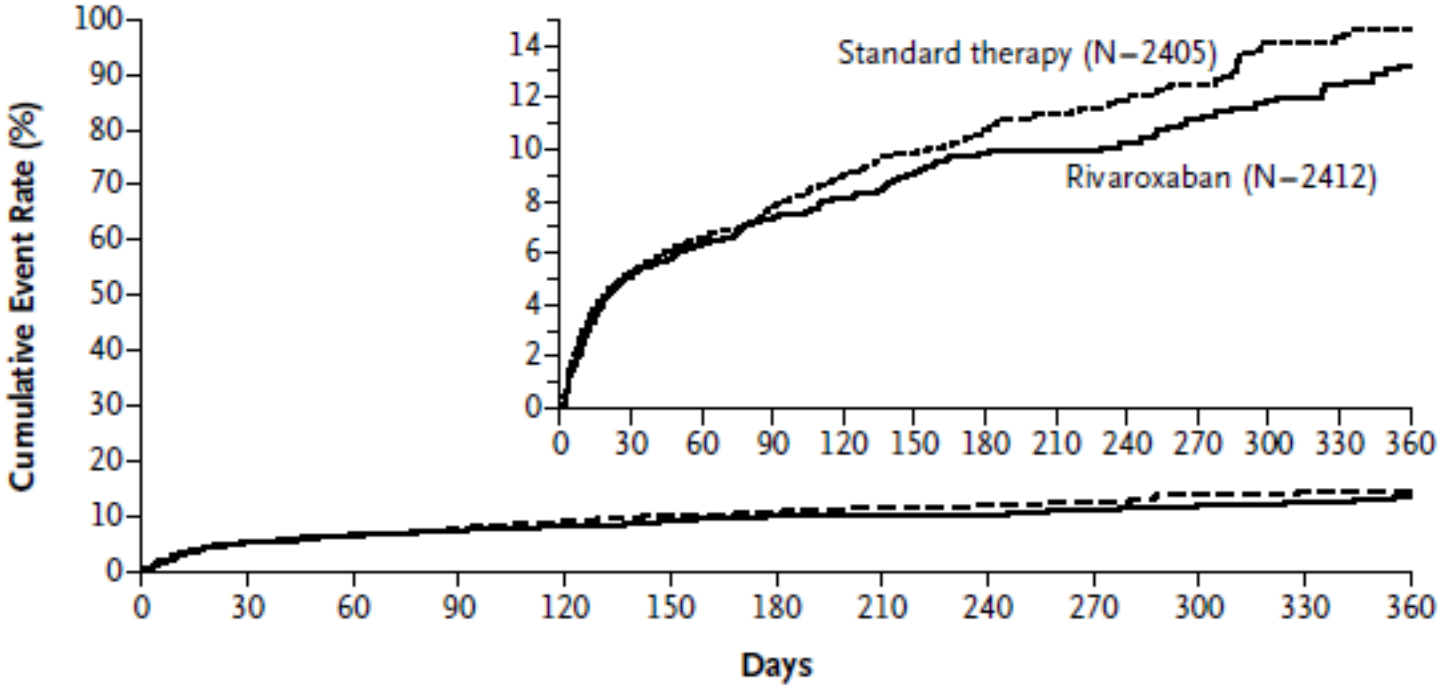
The members of the writing committee (Harry R. Büller, M.D., Martin H. Prins, M.D., Anthonie W.A. Lensing, M.D., Hervé Decousus, M.D., Barry F. Jacobson, M.D., Erich Minar, M.D., Jaromir Chlumsky, M.D., Peter Verhamme, M.D., Phil Wells, M.D., Giancarlo Agnelli, M.D., Alexander Cohen, M.D., Scott D. Berkowitz, M.D., Henri Bounameaux, M.D., Bruce L. Davidson, M.D., Frank Misselwitz, M.D., Alex S. Gallus, M.D., Gary E. Raskob, Ph.D., Sebastian Schellong, M.D., and Annelise Segers, M.D.) take responsibility for the content and integrity of this article. Address reprint requests to Dr. Büller at the Department of Vascular Medicine, Academic Medical Center, F4-275, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at h.r.buller@amc.uva.nl.

Rivaroksaban grubu ilk 3 hafta 2x15 mg ve daha sonra 1x20 mg ile tedaviye devam ediliyor.

Standart tedavi kolunda enoxaparin 2x1 mg/kg ve INR 2 üzerine çıkınca enoxaparin kesiliyor ve Vit K antagonisti ile tedavi devam ediyor.



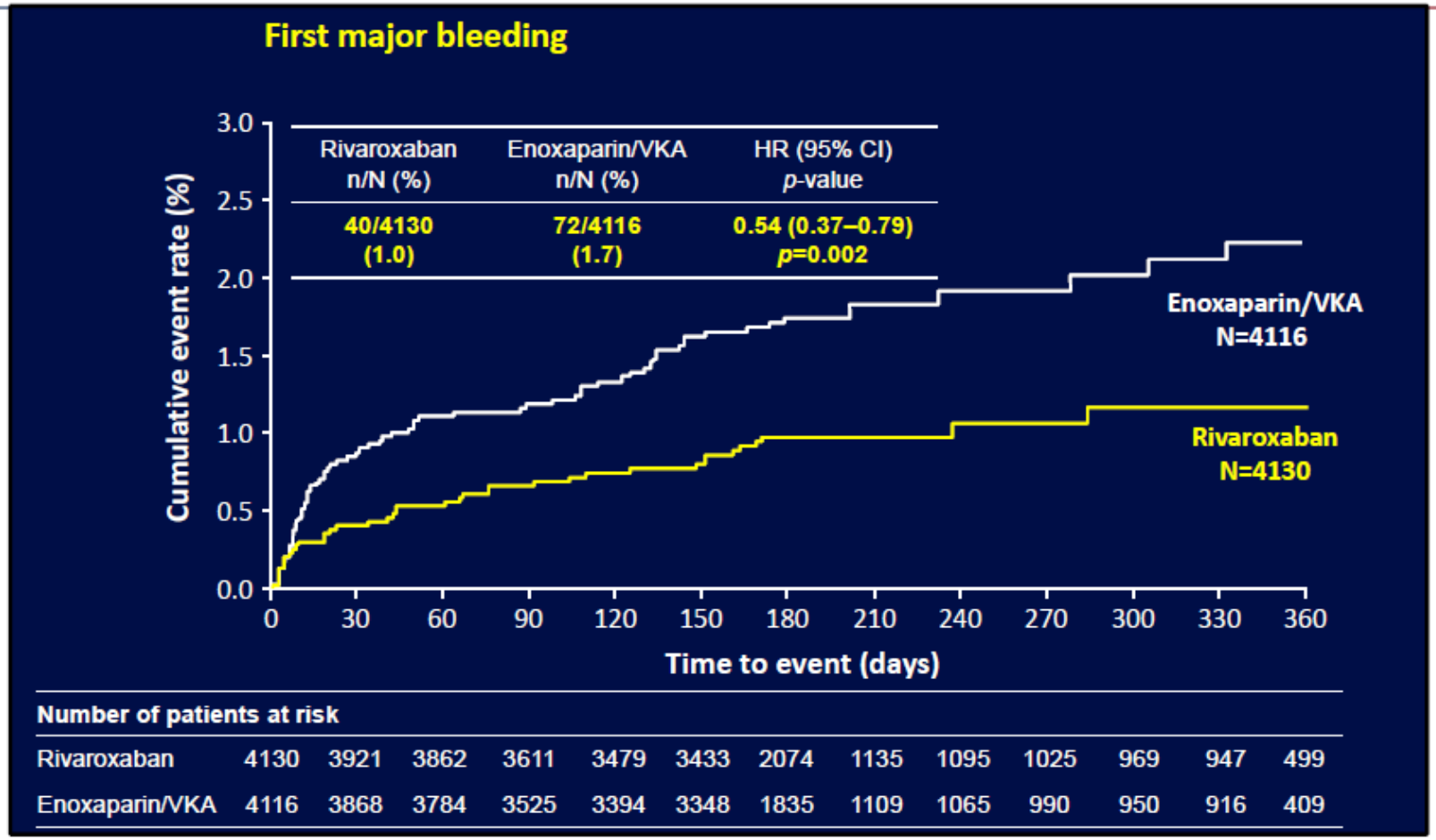
B **Clinically Significant Bleeding**



No. at Risk

Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Standard therapy	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

EINSTEIN DVT and EINSTEIN PE pooled analysis: major bleeding



Safety population

HR Büller for the EINSTEIN Investigators. Presented at ASH 2012

Analysis of major bleeding

	Rivaroxaban (n=2412)		Enoxaparin/VKA (n=2405)		HR (95% CI) *P* Value
	n	(%)	n	(%)	
Major bleeding*	**26**	**(1.1)**	**52**	**(2.2)**	0.49 (0.31–0.79) *p*=0.003
Fatal	**2**	**(<0.1)**	**3**	**(0.1)**	
Retroperitoneal	0		1	(<0.1)	
Intracranial	2	(<0.1)	2	(<0.1)	
Bleeding into a critical organ	**7**	**(0.3)**	**26**	**(1.1)**	
Intracranial	**1**	**(<0.1)**	**10**	**(0.4)**	
Retroperitoneal	**1**	**(<0.1)**	**7**	**(0.3)**	
Intraocular	2	(<0.1)	2	(<0.1)	
Pericardial	0		2	(<0.1)	
Intraarticular	0		3	(0.1)	
Adrenals	1	(<0.1)	0		
Hemothorax	1	(<0.1)	1	(<0.1)	
Intraabdominal (instability)	1	(<0.1)	2	(<0.1)	
Hb↓ ≥2 g/dl, ≥2 Transfusions	**17**	**(0.7)**	**26**	**(1.1)**	

*some patients had >1 event; safety population

The EINSTEIN–PE Investigators N Engl J Med 2012; 366:1287 - 1297

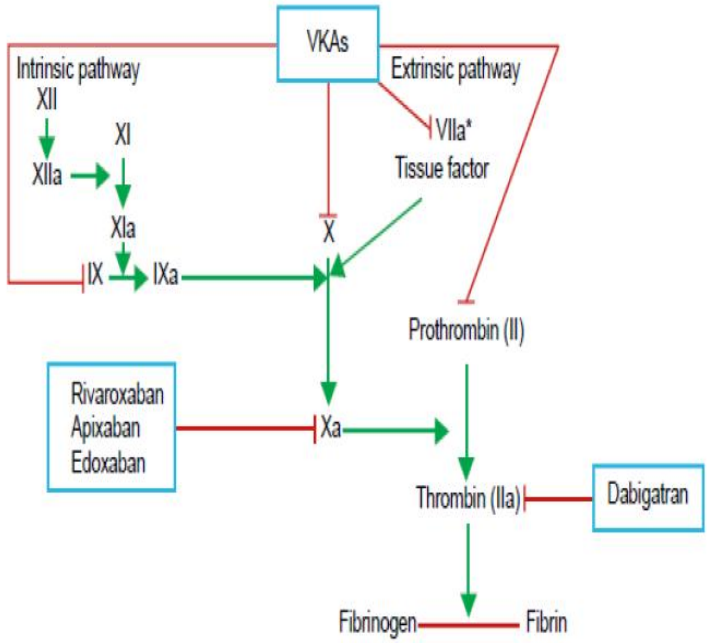
Rivaroksaban-doz-endikasyon

- Rivaroksaban'ın 15 mg ve 20mg tb formları olup. Tedavi dozu klinik endikasyon ve böbrek fonksiyonlarına göre değişmektedir.

- Ortopedik cerahi vakalarında VTE profilaksisi için;
  Kalça op.'da 10mg 35 gün, diz op.'da 12 gün verilir.
- VTE tedavisi ve /veya rekurensin önlenmesi için;
  - İlk 21 gün günde iki kez 15 mg'takiben 20 mg günde bir kez verilir
- NVAF'li hastalarda stroke ve sistemik tromboemboli önlenmesi için;
  - CrCL>50ml/dk ise 20 mg günde tek doz; CrCl 15-50 ml/dk arasında ise 15 mg günde tek doz verilir

APİXABAN-ELIQUIS

- Oral yolla alınan direkt ve kompetetif faktör Xa inhibitörüdür.
- Oral biyoyararlanımı iyidir.
- Yiyeceklerden etkilenmez
- Yarılanma ömrü 12 saattir.
- 2011 yılında FDA ve EMA onayı almıştır.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 29, 2013 VOL. 369 NO. 9

Oral Apixaban for the Treatment of Acute 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., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY Investigators*

ABSTRACT

BACKGROUND

Apixaban, an oral factor Xa inhibitor administered in fixed doses, may simplify the treatment of venous thromboembolism.

METHODS

In this randomized, double-blind study, we compared apixaban (at a dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) with conventional therapy (subcutaneous enoxaparin, followed by warfarin) in 5395 patients with acute venous thromboembolism. The primary efficacy outcome was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism. The principal safety outcomes were major bleeding alone and major bleeding plus clin-

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Apixaban-doz-endikasyon

- Apixaban'ın dozu klinik endikasyon,yaş, kg ve hastanın böbrek fonksiyonlarına göre değişmektedir.
- Ortopedik cerahi vakalarında VTE profilaksisi için;
  - Kalça op'da 2.5 mg günde iki kez 35 gün ve diz op'da ise 12 gün verilir
- VTE tedavisi ve /veya rekurensin önlenmesi için;
  - 10 gün 2x10 mg/gün sonraki günler 2x5 mg/gün
- NVAF'li hastalarda stroke ve sistemik tromboemboli önlenmesi için;
  - CrCl>50mL/dk olan hastalarda 2x5mg ve şu kriterlerden ikisi var ise eğer;yaş>80, vücut kg<60 veya serum kreatinin>1.5 mg/dL ise eğer 2x 2.5 mg/gün verilir.

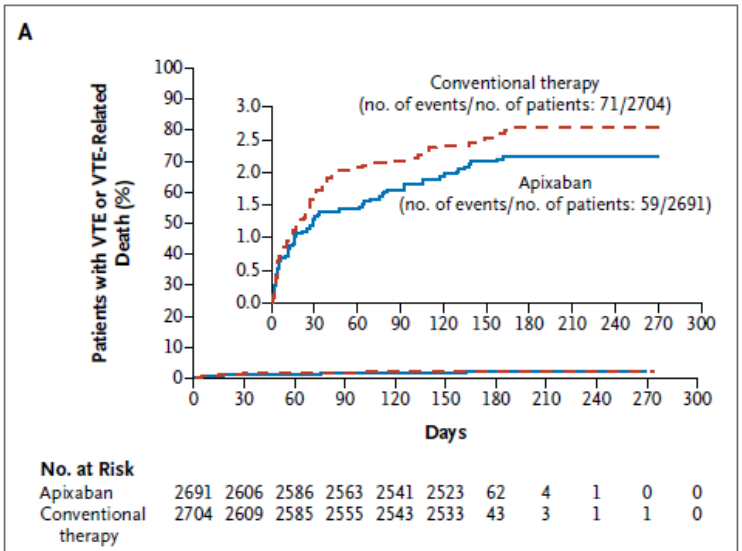


Figure 2. Kaplan–Meier Cumulative Event Rates.

Kaplan–Meier curves are shown for the first event of recurrent venous thromboembolism (VTE) or VTE-related death (Panel A) and for the first episode of major bleeding (Panel B). In each panel, the inset shows the same data on an enlarged y axis.

EDOXABAN-LIXIANA

Oral yolla alınan direkt ve spesifik faktör Xa inhibitörüdür.

%50'si böbrekle atılır.

1-2 saat içinde maks. konsantrasyona ulaşır

Yarılanma ömrü 9-11 saattir.

The NEW ENGLAND JOURNAL of MEDICINE

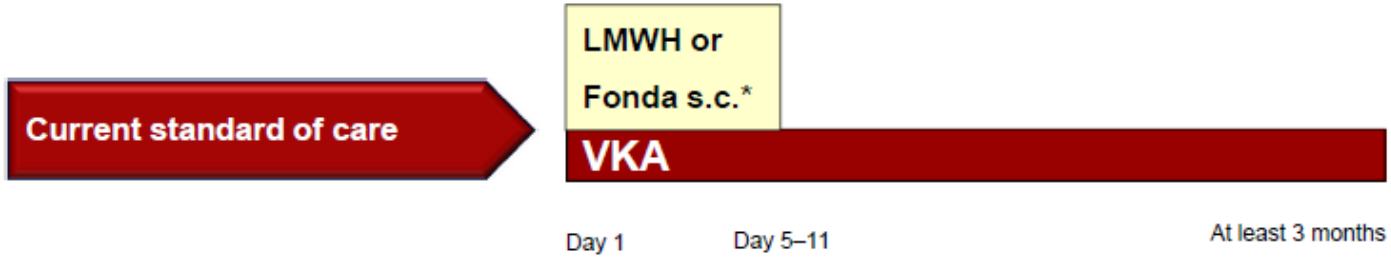
ORIGINAL ARTICLE

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

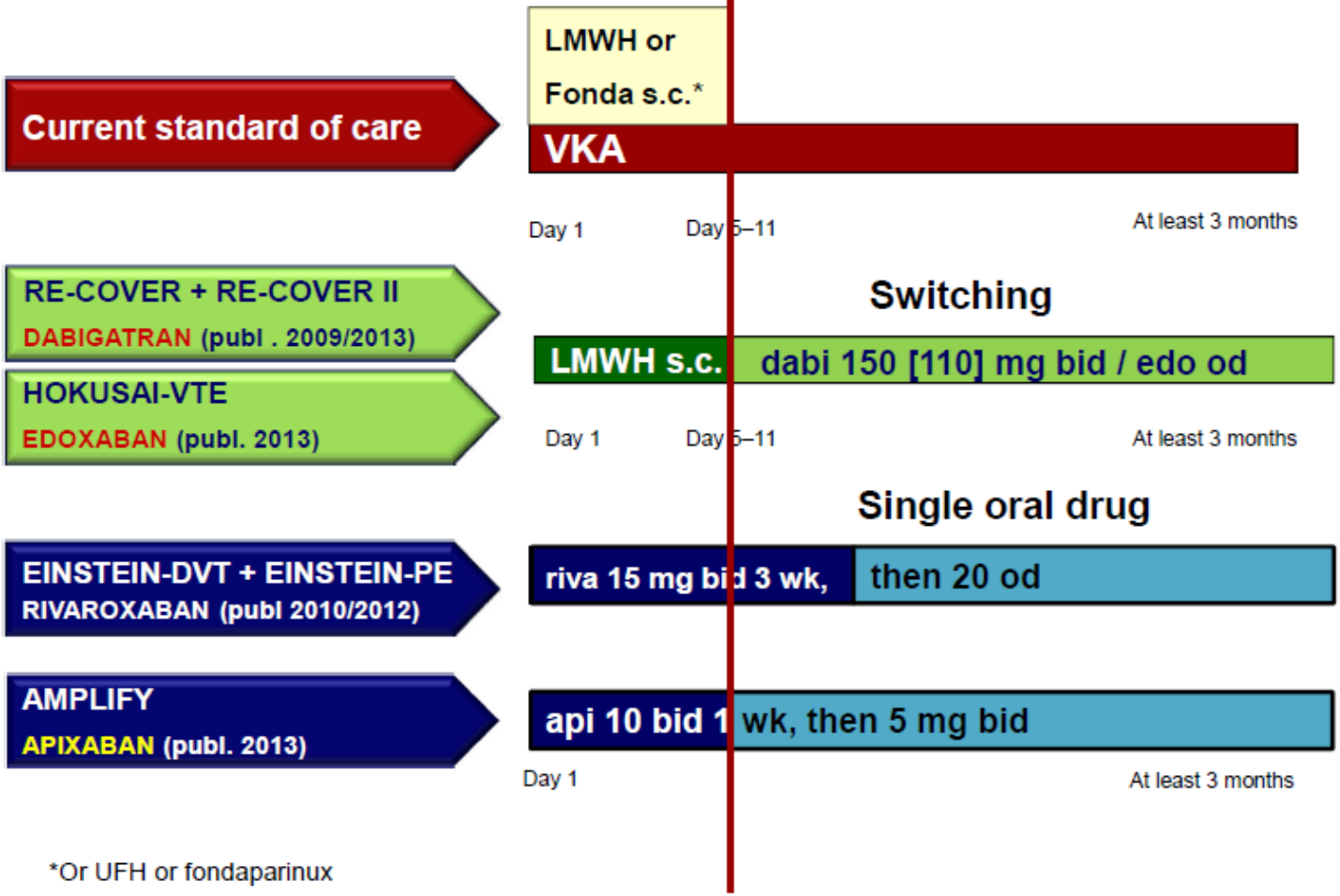
The Hokusai-VTE Investigators*

- HOKUASİ-VTE çalışması diye bilinen bu çalışmada Edoxaban 60 mg, edoxaban 30mg ile varfarin karşılaştırlmış. Her iki grup ta da ilk 5 gün LMWH(enoxaparin)verilmiş çalışmanın sonucunda ;
- Edoxaban varfarin kadar etkili bulunmuş, kanama edoxaban grubunda daha az bulunmuştur.

Anticoagulation for pulmonary embolism



New regimens for anticoagulation in VTE



*Or UFH or fondaparinux

ESC recommendations: NOACs

Recommendations	Class	Level
PE without shock or hypotension (intermediate or low risk)		
Anticoagulation - new oral anticoagulants		
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) is recommended.	I	B
As an alternative to the combination of parenteral anticoagulation with a VKA, anticoagulation with apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) is recommended.	I	B
As an alternative to VKA treatment, administration of dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) is recommended following acute-phase parenteral anticoagulation.	I	B
As an alternative to VKA treatment, administration of edoxaban is recommended following acute-phase parenteral anticoagulation.	I	B
New oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment.	III	A

Which strategy for which patient?

NOACs an *alternative* to standard treatment (NMH/VKA):

- In **high-risk PE** (unstable) → start UFH

  → after stabilization switch to NOAC possible.

- In **intermediate-high-risk** PE → start UFH/LMWH

  → after reversal of RV dysfunction (48-72 hrs) switch to NOAC possible.

- In **intermediate-low-risk PE**, or DVT treated **in hospital**: *equipoise*

  → LMWH and switch to NOAC, or *single oral drug* regimen with Rivaroxaban/Apixaban.

- In **low-risk PE and ambulatory DVT** treatment

  → *single oral drug* strategy with Rivaroxaban/Apixaban more attractive

Table 11 Overview of phase III clinical trials with non-vitamin K-dependent new oral anticoagulants (NOACs) for the acute-phase treatment and standard duration of anticoagulation after VTE

Drug	Trial	Design	Treatments and dosage	Duration	Patients	Efficacy outcome (results)	Safety outcome (results)
Dabigatran	RE-COVER[293]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs. 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs. 1.9% under warfarin
	RE-COVER II[294]	Double-blind, double-dummy	Enoxaparin/dabigatran (150 mg b.i.d.)[a] vs. enoxaparin/warfarin	6 months	2589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs. 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs. 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT[295]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	3449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs. 8.1% under warfarin
	EINSTEIN-PE[296]	Open-label	Rivaroxaban (15 mg b.i.d. for 3 weeks, then 20 mg o.d.) vs. enoxaparin/warfarin	3, 6, or 12 months	4832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs. 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs. 11.4% under warfarin
Apixaban	AMPLIFY[297]	Double-blind, double-dummy	Apixaban (10 mg b.i.d. for 7 days, then 5 mg b.i.d.) vs. enoxaparin/warfarin	6 months	5395 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 2.3% under apixaban vs. 2.7% under warfarin	Major bleeding: 0.6% under apixaban vs. 1.8% under warfarin
Edoxaban	Hokusai-VTE[298]	Double-blind, double-dummy	LMWH/edoxaban (60 mg o.d.; 30 mg o.d. if creatinine clearance 30–50 ml/min or body weight <60 kg) vs. UFH or LMWH/warfarin	Variable, 3–12 months	8240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs. 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs. 10.3% under warfarin

b.i.d. = bis in die (twice daily); CRNM = clinically relevant non-major; DVT = deep vein thrombosis; o.d. = omni die (once daily); PE = pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism.

[a] Approved doses of dabigatran are 150 mg b.i.d. and 110 mg b.i.d.

- VTE geçiren olgularda antikoagülasyon etkinliği ortaya konmuş olmakla birlikte tedavi kesilmesini izleyen dönemde VTE nüksü riski geçen süre içinde birikimsel olarak artmaktadır.

VTE recurrence: early versus late

Cohort data 1980's -1990's

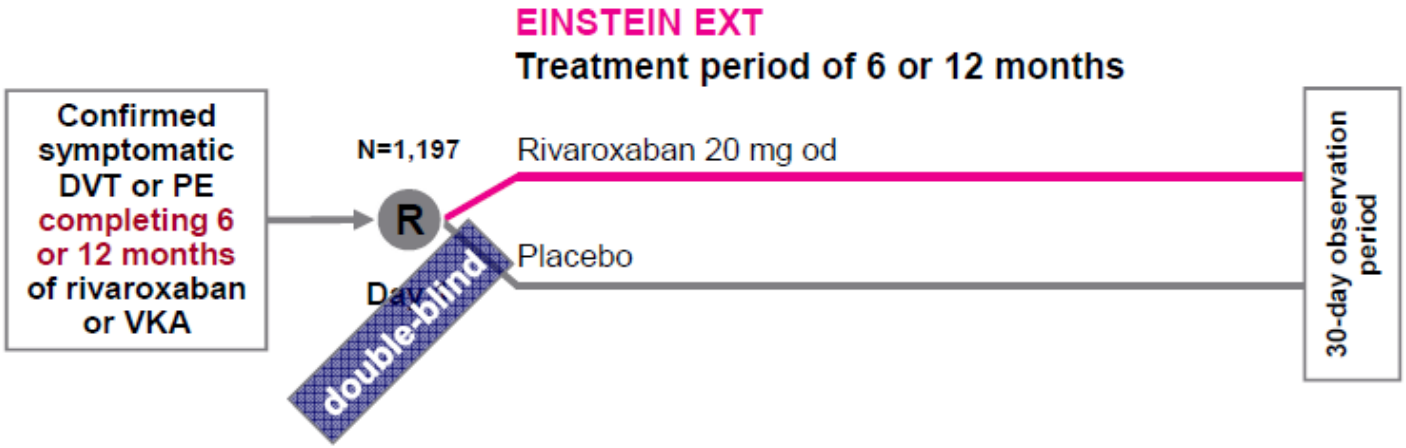
	Cumulative incidence	*Projected annual* incidence rate
2 weeks	2%	55%
3 months	6,4%	30%
6 months	8%	18%
2 years	17%	8,5%
5 years	24%	4,8%
8 years	30%	3,8%

17

P Prandoni. *Ann Intern Med* 1996;125:1-7
P Prandoni. *Haematologica* 1997; 82: 423-428

- Metaanalizlerde (8 çalışma/ 2994 hasta) kısa süreli varfarin tedavisine kıyasla uzun süreli tedavi ile VTE nüksünde ileri derecede azalma,
- Dört çalışmada (808 olgu) kısa süreli varfarin tedavisine kıyasla uzun süreli tedavi ile majör kanama riskinde anlamlı artış ortaya konmuştur.

EINSTEIN-EXT: extended treatment with rivaroxaban



EINSTEIN DVT, PE, Extension Evaluation Study Information available at: http://clinicaltrials.gov

EINSTEIN-EXT: primary efficacy outcome

	Rivaroxaban (n=602)		Placebo (n=594)	
	n	(%)	n	(%)
Symptomatic recurrent VTE*	**8**	**(1.3)#**	**42**	**(7.1)**
Recurrent DVT	5	(0.8)	31	(5.2)
Non-fatal PE	2	(0.3)	13	(2.2)
Fatal PE	0	(0)	1	(0.2)
Death of unknown cause (PE could not be excluded)	1	(0.2)	0	(0)

ITT population; *some patients had more then one event; #$p<0.001$

The EINSTEIN Investigators *N Engl J Med* 2010;363:2499–2510

EINSTEIN-EXT: major bleeding

	Placebo (n=590)	Rivaroxaban (n=598)	
Major bleeding	**0**	**4**	**(0.7%)***
Bleeding contributing to death	0	0	
Bleeding in a critical site	0	0	
Associated with fall in haemoglobin ≥2 g/dl and/or transfusion			
Gastrointestinal bleeding	0	3	(0.5%)
Menorrhagia	0	1	(0.2%)

*p=0.11

- Number needed to harm: approximately 139

Safety population

R Bauersachs for the EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

EINSTEIN-EXT: non-major bleeding events

	Rivaroxaban (n=598)		Placebo (n=590)	
	n	(%)	n	(%)
Clinically relevant non-major bleeds	**32**	**(5.4)**	**7**	**(1.2)**
Hematuria/uterine bleeding	12	(2.0)	2	(0.3)
Nasal	8	(1.3)	1	(0.2)
Rectal	7	(1.0)	2	(0.3)
Cutaneous	4	(0.7)	2	(0.3)
Ear	1	(0.2)	0	(0)
Gastrointestinal	1	(0.2)	0	(0)
Dental extraction	1	(0.2)	0	(0)

Safety population; some patients had more than one event.

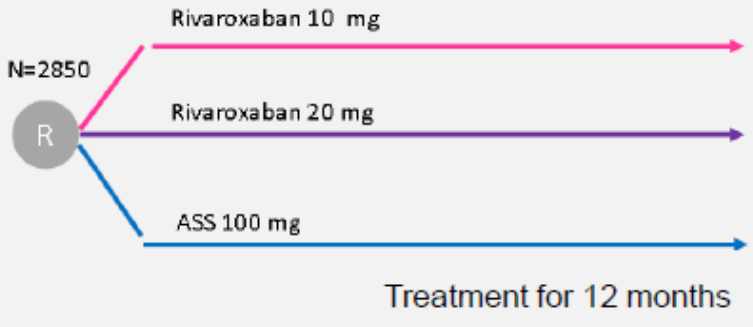
R Bauersachs for the EINSTEIN Investigators. N Engl J Med. 2010;363:2499-510

Extended prophylaxis: further progress

$\text{Einstein}_{\text{Choice}}$ – Extended systemic thromboembolism prevention

Randomized, double-blind controlled, phase-3 trial

Pts with confirmed symptomatic PE or DVT, treated for 6-12 months



L.DE.GM.03.2014.1437

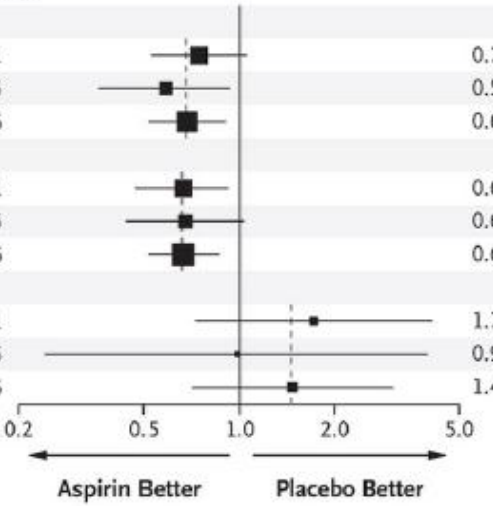
Timelines : FPFP: Q1 2014
LPLV: Q3 2016

Länder: Deutschland
30 weitere Länder

www.clinicaltrials.gov/ct2/show/NCT02064439

Aspirin for secondary VTE prevention?

Outcome and Study	Placebo	Aspirin	Hazard Ratio (95% CI)	P Value	P Value for Heterogeneity
	no. of events/total no. of patients				
Venous thromboembolism					0.42
ASPIRE	73/411	57/411	0.74 (0.52–1.05)	0.09	
WARFASA	43/197	28/205	0.58 (0.36–0.93)	0.02	
Pooled	116/608	85/616	0.68 (0.51–0.90)	0.007	
Major vascular events					0.96
ASPIRE	88/411	62/411	0.66 (0.48–0.92)	0.01	
WARFASA	48/197	36/205	0.67 (0.43–1.03)	0.06	
Pooled	136/608	98/616	0.66 (0.51–0.86)	0.002	
Clinically relevant bleeding					0.50
ASPIRE	8/411	14/411	1.72 (0.72–4.11)	0.22	
WARFASA	4/197	4/205	0.98 (0.24–3.96)	0.97	
Pooled	12/608	18/616	1.47 (0.70–3.08)	0.31	



Brighton TA et al. N Engl J Med 2012;367:1979-1987.

Study	Active[a]	Comparator	Design	Expected reduction	Treatment duration	No. Patients enrolled	VTE rate in control group	Risk reduction for recurrent VTE	Major or CRNM bleeding in active[a] group
RE-SONATE[370]	Dabigatran 150 mg b.i.d.[c]	Placebo	Superiority	70%	6 months	1343	5.6%	92%	5.3%
RE-MEDY[370]	Dabigatran 150 mg b.i.d.[c]	Warfarin (INR 2–3)	Non-inferiority	Absolute increase, <2.8	18–36 months	2856	1.3%	Risk difference, 0.38% vs. VKA	5.6% (vs. 10.2% in warfarin arm)
EINSTEIN Ext[235]	Rivaroxaban 20 mg daily	Placebo	Superiority	70%	6–12 months	1196	7.1%	82%	6.0%
AMPLIFY Ext[371]	Apixaban 5.0 mg b.i.d.	Placebo	Superiority	41%	12 months	2486	8.8%	80%	4.2%
	Apixaban 2.5 mg b.i.d.[d]							81%	3.0%
WARFASA[368]	Aspirin	Placebo	Superiority	40%	≥24 months	402	11.2%[b]	40%	1.0%[b]
ASPIRE[369]	Aspirin	Placebo	Superiority	30%	4 years (actual, 27 months)	822	6.5%[b]	26%	1.7%[b]

Teşekkürler