Trombolitik tedavi, Hangi hastalara, Nasıl?

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Acıbadem Kayseri Hastanesi

Sunum Planı

- 1- Pulmoner Emboli Sınıflaması
- 2- Trombolitik ilaçlar
- 3- Masif embolide sistemik trombolitik
- 4- Trombolitik dozları-yarı doz?
- 5- Kateter ile verilen trombolitik?
- 6- Intermediate risk (submasif) embolide trombolitik
- 7- Komplikasyonlar
- 8- Kontrendikasyonlar
- 9- Gebelerde trombolitik
- 10- Rehber önerileri

Pulmoner Emboli Sınıflaması

- **ATS 1999, ESC 2000, BTS 2003, ACEP 2003, ACCP 2004, ACCP 2008**

1- MASİF (Kardiak arrest, şok, hipotansiyon)

2- SUB-MASİF (normotansif PE + sağ kalp hastalığı VAR)

3-NON-MASİF (normotansif PE - sağ kalp hastalığı YOK)

- **ESC 2008**
- 1- Yüksek risk (kardiak arrest, şok, hipotansiyon)
- 2- Yüksek risk dışı
  - Orta Risk (normotansif PE ile beraber sağ kalp hastalığı ve/veya yüksek BNP ve/veya troponin seviyeleri)
  - Düşük Risk (sağ kalp hastalığı olmadan normotansif PE ve düşük BNP ve troponin seviyesi)

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]	

ESC 2014, European Heart Journal

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)

- Sağ ventrikül disfonksiyonu için EKO da RV dilatasyonu ve /veya diastol sonu RV/LV oranının 0.9 veya 1.0 ın üstünde olması; RV serbest duvar hipokinezisi; veya BT de diastol sonu RV/LV oranının 0.9 veya 1.0 ın üstünde olması olarak tanımlanır.
- Myokard hasarı için troponon I veya T nin artışı veya sağ kalp yetmezliği sonucu olarak natriüretik peptid konsantrasyonunun artması olarak tanımlanır
- Hipotansiyon veya şok varsa ne PESI ne de laboratuar testlerine bakmak gerekli değildir.

- **<u>Hipotansiyon açıklama:</u>**
- **Sistolik** kan basıncının 90 mmHg nin altında olması veya hipovolemi-sepsis-yeni başlayan aritmi olmadan15 dk dan fazla süre **40 mmHg** den daha fazla düşüş yaşaması

PULMONER EMBOLİDE SORUNLAR

- 1- Hemodinamik instabilite ile gelen PE hastalarının %30 veya daha fazlası ilk 30 günde ölmektedir.
- 2- Kalan hastaların %30 hayatı tehdit edici rekürrens yaşarlar
- 3- PE hastalarının %1-9 unda KTEPH gelişir.

Konstantinides VS, Semin Respir Crit Care Med. 2017;38:56-65

NEDEN TROMBOLİTİK TEDAVİ VERMELİYİZ?

December 21, 1970

Urokinase Pulmonary Embolism Trial
Phase 1 Results

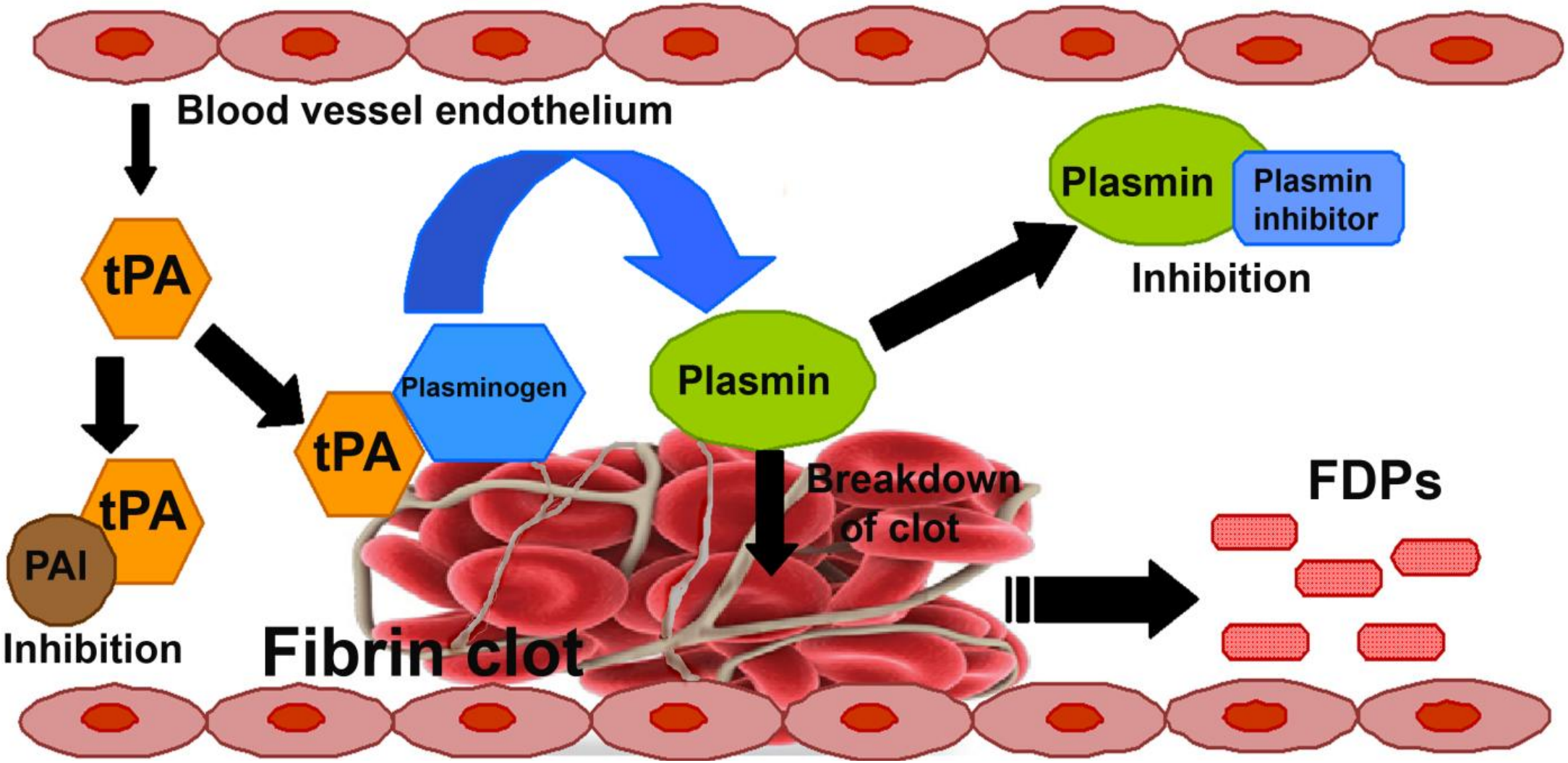
» Author Affiliations

JAMA. 1970;214(12):2163-2172. doi:10.1001/jama.1970.03180120035007

Abstract

In a randomized, national cooperative trial, urokinase and subsequent heparin sodium therapy, when compared to heparin therapy alone, significantly accelerated the resolution rate of pulmonary thromboemboli at 24 hours as shown by pulmonary arteriograms, lung scans, and right-sided pressure measurements. No significant differences in recurrence rate of pulmonary embolism or in the two-week mortality were observed. Bleeding, which occurred in 45% of patients receiving urokinase as contrasted to 27% in the heparin group, was the only complication of urokinase therapy. This increase in bleeding seen with urokinase was closely associated with the invasive procedures necessary to obtain the arteriographic and hemodynamic information. Because the urokinase regimen did not usually achieve complete or nearly complete thrombolysis, and because of its hemorrhagic property, further studies with urokinase in pulmonary thromboembolism are indicated before specific therapeutic recommendations can be made.

Trombolitik Tedavi: Plazminojenin plazmine dönüşümünü sağlayarak trombüs erimesinin sağlanması



European Heart Journal (2015) **36**, 605–614
doi:10.1093/eurheartj/ehu218

CLINICAL RESEARCH
Pulmonary circulation

Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

Christophe Marti[1]*, Gregor John[1], Stavros Konstantinides[2], Christophe Combescure[3], Olivier Sanchez[4], Mareike Lankeit[2], Guy Meyer[4], and Arnaud Perrier[1]

We systematically reviewed randomized controlled studies comparing systemic thrombolytic therapy plus anticoagulation with anticoagulation alone in patients with acute PE. Fifteen trials involving 2057 patients were included in our meta-analysis. Compared with heparin, thrombolytic therapy was associated with a significant reduction of overall mortality (OR; 0.59, 95% CI: 0.36–0.96). This reduction was not statistically significant after exclusion of studies including high-risk PE (OR; 0.64, 95% CI: 0.35–1.17). Thrombolytic therapy was associated with a significant reduction in the combined endpoint of death or treatment escalation (OR: 0.34, 95% CI: 0.22–0.53), PE-related mortality (OR: 0.29; 95% CI: 0.14–0.60) and PE recurrence (OR: 0.50; 95% CI: 0.27–0.94). Major haemorrhage (OR; 2.91, 95% CI: 1.95–4.36) and fatal or intracranial bleeding (OR: 3.18, 95% CI: 1.25–8.11) were significantly more frequent among patients receiving thrombolysis.

Thrombolytic therapy reduces total mortality, PE recurrence, and PE-related mortality in patients with acute PE. The decrease in overall mortality is, however, not significant in haemodynamically stable patients with acute PE. Thrombolytic therapy is associated with an increase of major and fatal or intracranial haemorrhage.

Tedavi seçenekleri

PULMONER TROMBOEMBOLİZM TANI VE TEDAVİ UZLAŞI RAPORU - 2015

Tablo 1. Masif PTE'de trombolitik tedavi[a]

İlaç	Elde edilme şekli	Plazma yarılanma süresi (dk)	Yükleme dozu	İnfüzyon dozu	Önerilen tedavi süresi
SK	C grubu β hemolitik streptokok	18-25	250000 IU, 30 dk	100000 IU/saat	24 saat
UK	İnsan idrarı, insan embriyonu, böbrek hücre kültürü	13-20	4400 IU, 10 dk	4400 IU/kg/saat	12 saat
rt-PA	Rekombinan DNA teknolojisi	2-6	Gerekmiyor[b]	50 mg/saat[c]	2 saat

[a] Tüm ilaçlar periferik damardan intravenöz yolla verilirler. SK: Streptokinaz; UK: Ürokinaz; rt-TPA: Rekombinan doku plazminojen aktivatörü

[b] rt-PA bazı gruplar tarafından alternatif olarak 1-2 dakikada 10 mg yükleme dozu ve takiben 90 mg/iki saatlik infüzyon olarak uygulanmaktadır.

[c] 65 kilogramın altındaki hastalarda iki saatlik toplam doz: 1,5 mg/kg olarak hesaplanır.

Hangi trombolitik ajanı tercih etmeliyim?

- **Fibrin spesifik olmayanalar:** Streptokinaz, Ürokinaz
- **Fibrin spesifik olanlar:** Tpa (Alteplaz, Tenekteplaz, Retaplaz, Desmoteplaz, Lanoteplaz…)
- **1- Streptokinaz:**
- Antijenik olması, ve hipotansiyon, bulanık görme, konfüzyon, halsizlik ve güçsüzlük yapması gibi sık görülen yan etkiler kullanımını sınırlandırmaktadır.
- Antijenik olması nedeniyle ilk kullanımından sonra 6 ay içinde tekrar kullanılamıyor.
- 24 saatte veriliyor
- Fakat ucuz olması nedeniyle hala kullanılabiliyor.
- 1. kuşak trombolitik

https://www.drugs.com/sfx/streptokinase-side-effects.html

JACC Vol. 31, No. 5
April 1998:1057–63

Comparative Efficacy of a Two-Hour Regimen of Streptokinase Versus Alteplase in Acute Massive Pulmonary Embolism: Immediate Clinical and Hemodynamic Outcome and One-Year Follow-Up

NICOLAS MENEVEAU, MD, FRANÇOIS SCHIELE, MD, DAMIEN METZ, MD,*

66 akut masif emboli hastası, 23 tanesi alteplaz, 43 tanesi streptokinaz alıyor; 12, 36-48 saat ve 1 yıllık takip yapılıyor

Alteplaz grubunda pulmoner rezistans 1. saate, streptokinaz grubuna göre daha hızlı düşüyor, fakat 2. saatte hemodinamik stabilite benzer
36-48 saatte pulmoner vasküler obstrukisyon açısından farklılık yok
Kanama açısından farklılık yok
1 yıllık mortalite açısından farklılık yok

- **2- Urokinaz:**
- İlk ajan (1970 de RKÇ sı var)
- 12 saatte veriliyor
- İdrarla atılan böbreklerden salınan bir enzim
- Etkisi SK'a benzer fakat antijenik ve pirojenik değildir.
- 1. kuşak trombolitik

Lancet. 1988 Aug 6;2(8606):293-8.

Randomised controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism.

Goldhaber SZ[1], Kessler CM, Heit J, Markis J, Sharma GV, Dawley D, Nagel JS, Meyerovitz M, Kim D, Vaughan DE, et al.

Author information

Abstract

The effect of intravenous recombinant human tissue-type plasminogen activator (rt-PA) was compared with that of urokinase in 45 patients with angiographically documented pulmonary embolism (PE) in a randomised controlled trial. The two principal end-points were clot lysis at 2 h, as assessed by angiography, and pulmonary reperfusion at 24 h, as assessed by perfusion lung scanning. All patients received the full dose of rt-PA but urokinase infusions were terminated prematurely (on average after 18 h) in 9 patients because of allergy in 1 and uncontrollable bleeding in 8. By 2 h, 82% of rt-PA-treated patients showed clot lysis, compared with 48% of urokinase-treated patients ($p = 0.008$; 95% CI for the difference = 10-58%). Improvement in lung scan reperfusion at 24 h was identical in the two treatment groups. The reduction in fibrinogen did not differ significantly between the rt-PA and urokinase groups (45% vs 39% at 2 h and 34% vs 40% at 24 h). The results indicate that in the dose regimens employed, rt-PA acts more rapidly and is safer than urokinase in the treatment of acute PE.

- **3- tPA:**
- *Alteplaz;*
- -Endotel hücrelerinde üretilir.
- -Rekombinant biyoteknoloji ile insan melanom hücre dizisinden oluşturulur.
- -Plazminojen→Plazmin
- -Fibrin selektivitesi SK ve ürokinaza göre daha güçlüdür.
- 2. Kuşak Trombolitik

- 3. kuşak trombolitik olarak kullanılan tPA lar: Tenekteplaz, Retaplaz, Desmoteplaz,Lanoteplaz…

- Yarılanma ömürlerinin uzatılması
- Enzimatik etkinliğin arttırılması
- Plazma proteaz inhibitörlerine karşı rezistansın geliştirilmesi
- Fibrine bağlanma selektivitesinin artması
- Bu grupta rekombinant doku tipi plazminojen aktivatör mutantları
- Reteplaz,tenekteplaz,lanoteplaz,monteplaz, pamiteplaz……..

Tablo 1. Üçüncü kuşak trombolitik ajanların özellikleri

	Reteplaz	Tenekteplaz	Lanoteplaz	Monteplaz	Pamiteplaz	Stafilokinaz
Moleküler ağırlık, D	39.000	70.000	53.500	68.000	-	16.500
Yarılanma ömrü, dk	14-18	11-20	23-37	23	30-47	6
Fibrin spesifisite	+	+++	+	++	++	++++
PAİ ile inhibisyonu	Evet	Hayır	Hayır	Evet	Evet	Hayır

D=Dalton, dk= dakika, PAİ=Plazminojen aktivatör inhibitör

Türk Kardiyol Der Arş 2004; 32 : 564-570

Hangi trombolitik dozu?

Thrombosis Research 133 (2014) 357–363

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

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 saatte**) 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 ve mortalite 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.

Kateter ile verilen trombolitik tedavi

- Sistemik trombolitik tedavideki majör problem KANAMA
- Özellikle de intrakranial kanama
- Kateter ile verilen trombolitik tedavinin yüksek lokal konsantrasyona ulaşması ve intrakranial kanamanın çok nadir görülmesi 2 önemli avantaj oluşturmaktadır.

Catheterization and Cardiovascular Interventions 89:754–760 (2017)

Safety of Catheter-Directed Thrombolysis for Massive and Submassive Pulmonary Embolism: Results of a Multicenter Registry and Meta-Analysis

Tyler L. Bloomer,[1,2] MD, Georges E. El-Hayek,[3] MD, Michael C. McDaniel,[3] MD,

TABLE II. Meta-Analysis Characteristics and Outcomes

Study	Sample size	Massive PE *n* (%)	Total dose of tPA (mg)	Catheter type	Mortality with sub-massive PE	Mortality with massive PE	ICH	Major bleeding or vascular injury[a]
Current Cohort	137	16 (12)	17[b]	USAT (84%), S-CDT (16%)	0	5	2	13
Chamsuddin et al. [10]	10	10 (100)	21.8	USAT	0	0	0	0
Lin et al. group 1 [11]	11	11 (100)	17.2	USAT	0	1	0	0
Lin et al. group 2 [11]	14	14 (100)	25.4	S-CDT	0	2	0	3
Engelhardt et al. [12]	24	5 (20.8)	33.5	USAT	0	0	0	4
Kennedy et al. [13]	60	12 (20)	35.1	USAT	0	3	0	0
Dumantepe et al. [14]	22	8 (36.4)	21[b]	USAT	0	1	0	0
ULTIMA [5]	30	0 (0)	20.8	USAT	0	0	0	0
Quintana et al. [15]	10	2 (20)	18[b]	USAT	0	0	0	0
Bagla et al. [16]	45	0 (0)	24	USAT	0	0	0	1
Engelberger et al. [17]	52	14 (26.9)	21	USAT	0	2	0	1
Mccabe et al. [18]	53	0 (0)	24.6	USAT	0	0	1	2
Nykamp et al. [19]	45	13 (28.9)	30.5	USAT	0	0	0	0
PERFECT [6]	100	28 (28)	28	USAT (36%), S-CDT (64%)	2	4	0	0
SEATTLE II [7]	150	31 (20.7)	23.7	USAT	2	1	0	13
Liang et al. [20]	69	10 (14.5)	NA	USAT (52%), S-CDT (39%)	1	1	0	2
Yoo et al. [21]	28	12 (42.9)	NA	USAT	0	4	0	1
Total	860	186 (21.6)	24.2		5 (0.74%)	24 (12.9%)	3 (0.35%)	40 (4.65%)

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

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CHEST 2016; 149(2):315-352

- Akut embolisi olup trombolitik tedavi gerektiren hastalarda kateter aracılı trombolitik yerine sistemik trombolitik tedavi önerilmektedir (2C).
- Ama hipotansiyonu olup yüksek kanama riski olan, sistemik tromboliik tedavinin başarısız olduğu veya saatler içinde exitus olacağını düşündüğümüz hastalarada eğer imkanlar hazır ise kateter ile trombolitik tedavi verilebilir (2C).

Trombolitik tedavi sonrası heparin?

- Streptokinaz ve ürokinaz verilirken heparin infüzyonunun durdurulması gerekmektedir.
- Rt-PA verirken heparini durdurmamıza gerek yok.
- Trombolitik tedavi başlanacağı zaman DMAH alan hastalar bir sonraki dozunu 12 veya 24 saat sonra almalıdır (ilacın günde 1 veya 2 kere kullanımına göre).
- Heparinin hızlı geri döndürülebilen etkisinden dolayı trombolitik sonrası ilk başta DMAH yerine heparin verilmesi önerilmektedir.

ESC 2014, European Heart Journal

- Eğer trombolitik tedavi esnasında heparin kesilmiş ise, bolus doz kullanmadan heparine tekrar başlayın ve aPTT kontrolü yaparak heparin infüzyonunu en az 4 saat sürdürmek öneriliyor.
- Birçok yazar kliniklerinde heparin infüzyonuna **1 gün daha** devam ettikten sonra DMAH a geçtiğini belirtiyor (aPTT<140 ise direk DMAH başlanabiliyor, aPTT>140 ise 2 saat sonra başlanması öneriliyor).

Shahidul islam, 2016, advances in Internal Medicine

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 risk hastalarda tenekteplaz+ heparin ile tenekteplaz+plasebo 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)		

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

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- 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

KOMPLİKASYONLAR

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CLINICAL RESEARCH
Pulmonary circulation

Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

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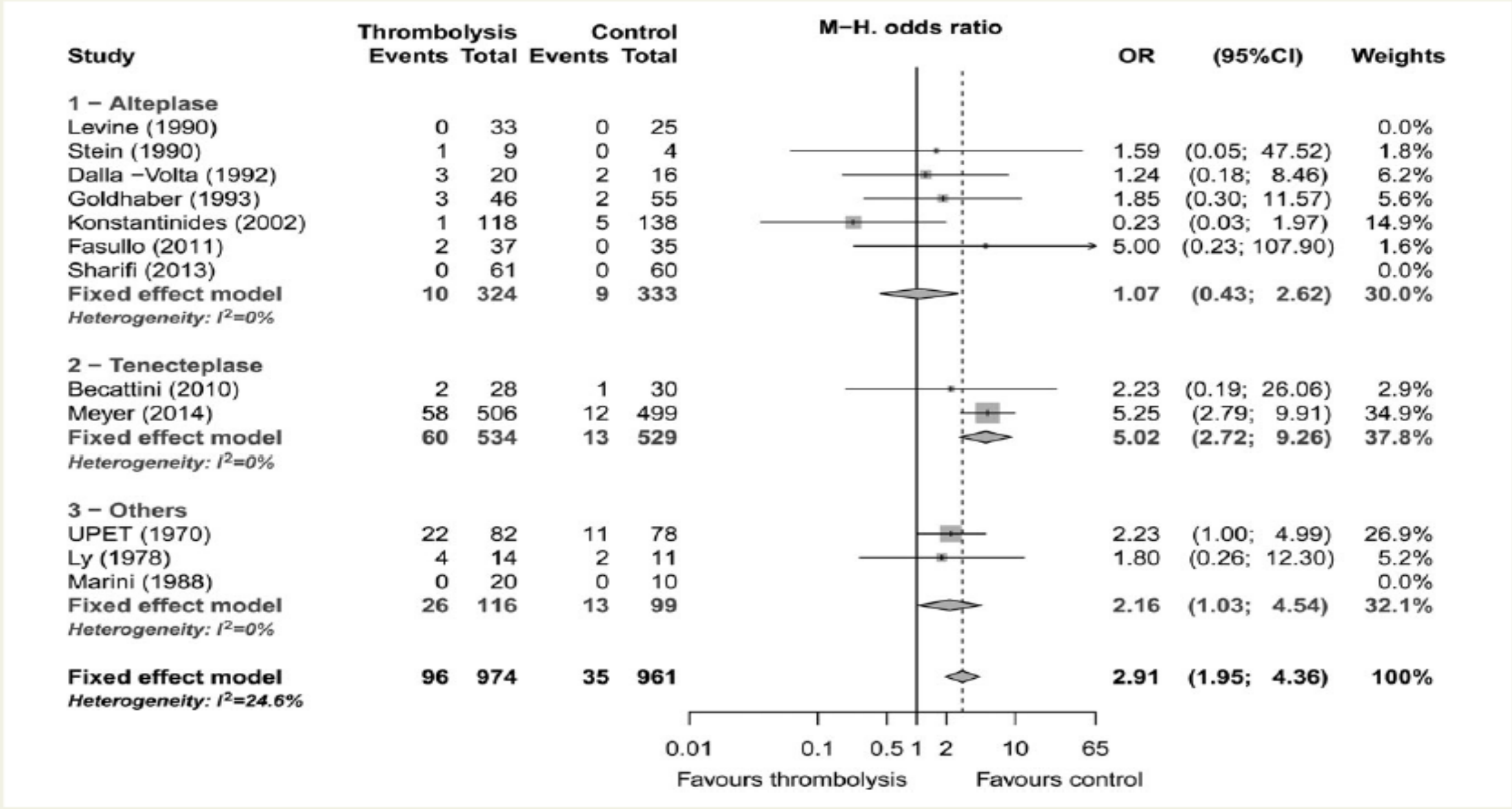

Figure 3 Major bleeding by drug, Forest plot

- **Major bleeding** was reported in 12 studies (**1935** patients) and was present in **9.9%** (**96/974**) of patients allocated to thrombolytic therapy and **3.6%** (**35/961**) of the control group. Thrombolytic treatment was associated with a significantly increased risk of major bleeding (OR: 2.91; 95% CI: 1.95–4.36, **P , 0.0001**).
- The reported incidence of **fatal or intracranial haemorrhage** was **1.7%** (n = **16/933**) in the thrombolysis group and **0.3%** (n = 3/931) in the control group. Thrombolytic treatment was associated with a significantly increased risk of fatal or intracranial haemorrhage (OR: 3.18; 95% CI: 1.25–8.11, **P = 0.008**).

- Finally, the association between thrombolytic therapy and the risk of **major bleeding** was lower in studies using an upper age limit (OR: 1.13; 95%CI: 0.47–2.71) than in studies including **older patients** (OR: 3.71; 95% CI: 2.32–5.92) (**P = 0.02**).
- The risk of **fatal or intracranial haemorrhage** was lower in studies with an upper age limit (OR: 1.82; 95% CI: 0.37–8.93) than those without (OR: 4.11; 95% CI: 1.25–13.5), but this difference was not statistically significant (**P = 0.42**).

Trombolitikler arası kanama farklılıkları

Table 3 Safety outcomes, subgroup analyses

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

KONTRENDİKASYONLAR

Web Table 4 **Contraindications to thrombolytic therapy (adapted from ref. 312)**

Absolute contraindications[a]

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury in the preceding 3 weeks
- Gastrointestinal bleeding within the last month
- Known bleeding risk

Relative contraindications

- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within one week postpartum
- Non-compressible puncture site
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

ESC 2014, European Heart Journal

Absolute contraindications:[a]

[a]Absolute contraindications to thrombolysis might become relative in a patient with immediately life-threatening high-risk PE.

Gebelerde trombolitik?

- Gebelik relatif kontrendike
- rtPA plasentayı geçmez.
- Komplikasyon oranları gebe olmayanlar ile benzer
- 172 gebe hastayı içeren çoğunluğu streptokinaz ile tedavi edilen gebe hastalarda anne ölümü olmamış.
- Ölümcül olmayan kanama oranı %2.9, fetal ölüm %1.7.
- Trombolitik sonrası heparin ve ardından DMAH ile tedaviye devam edilebilir.
- Vit. K antagonistleri ve YOAK gebelikte kontrendike.

Shahidul islam, 2016, advances in Internal Medicine

Son rehberlerin önerileri

Guidelines	Populations	Recommendations	Strength/class	Level of evidence
ESC 2014[7]	High-risk PE	Intravenous anticoagulation with UFH to be initiated without delay	I	C
		Thrombolytic therapy	I	B
		Surgical embolectomy for patients in whom thrombolysis is contraindicated or has failed	I	C
		Percutaneous CDT as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed	IIa	C
	Intermediate-high risk PE	Routine primary systemic thrombolysis not recommended	III	B
		Close monitoring to permit early detection of hemodynamic decompensation	I	B
		Thrombolytic therapy in presence of clinical signs of hemodynamic decompensation	IIa	B
		Surgical embolectomy or percutaneous CDT may be considered if the anticipated risk of bleeding under thrombolytic treatment is high	IIb	C

ACCP 2016[47]	With hypotension	In the absence of high bleeding risk: systemic thrombolysis	2	B
		In the presence of high bleeding risk or if systemic thrombolysis failed: surgical embolectomy	2	C
	Without hypotension	Recommendation against systemically administered thrombolysis	1	B
	Acutely deteriorating during anticoagulation	Systemic thrombolysis	2	C
	Candidates for thrombolysis	Systemic thrombolysis via a peripheral vein or as CDT	2	C

Özet-Sonuç

- 1- Yüksek risk (masif) embolide trombolitik verilmeli.
- 2- Trombolitik yarı doz çalışmaları başarılı görünse de daha çok RKÇ ya ihtiyaç var.
- 3- Kateter ile verilen trombolitik tedavi de başarılı ve kanama oranı daha düşük görünüyor, fakat hala ilk tercih standart trombolitik tedavi.
- 4- Submasif embolide kısa sürede hemodinamik stabilite trombolitik ile daha etkin düzelse de uzun dönemde ve mortalite de belirgin farklılık yok.
- 5- Major problem kanama ve özellikle de intrakranial kanama.
- 6- Gebelerde de ihtiyaç halinde trombolitik verilmelidir.
- 7- Kesin kontrendikasyonlar acil durumda relatif hale gelebilir.

UMARIM FAYDALI OLMUŞTUR

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