TROMBOLİTİK AJANLARIN GENEL ÖZELLİKLERİ

Uzm.Dr. Müge Günalp

AÜTF Acil Tıp AD

Acilde trombolitik kullanımı

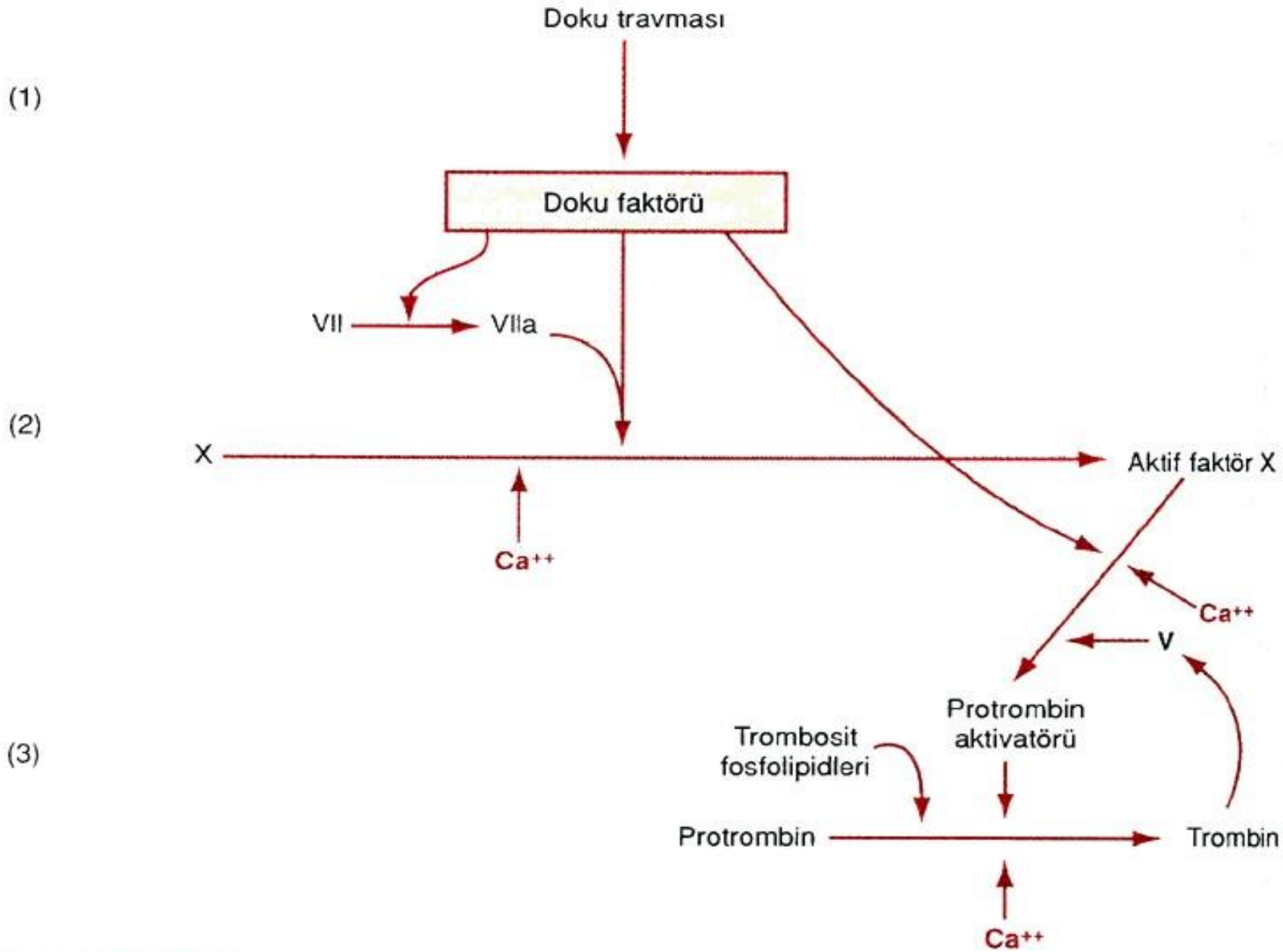
- Miyokard infarktüsü,iskemik inme,periferik arter ve derin ven trombozları ve PE gibi tromboembolik olaylar ile mortalite
- Trombüsün ilerlemesini engellemek ve dolaşımın devamlılığının sağlanması→ endojen fibrinolitik sistem → farmakolojik fibrinolitik madde

Acilde trombolitik kullanımı

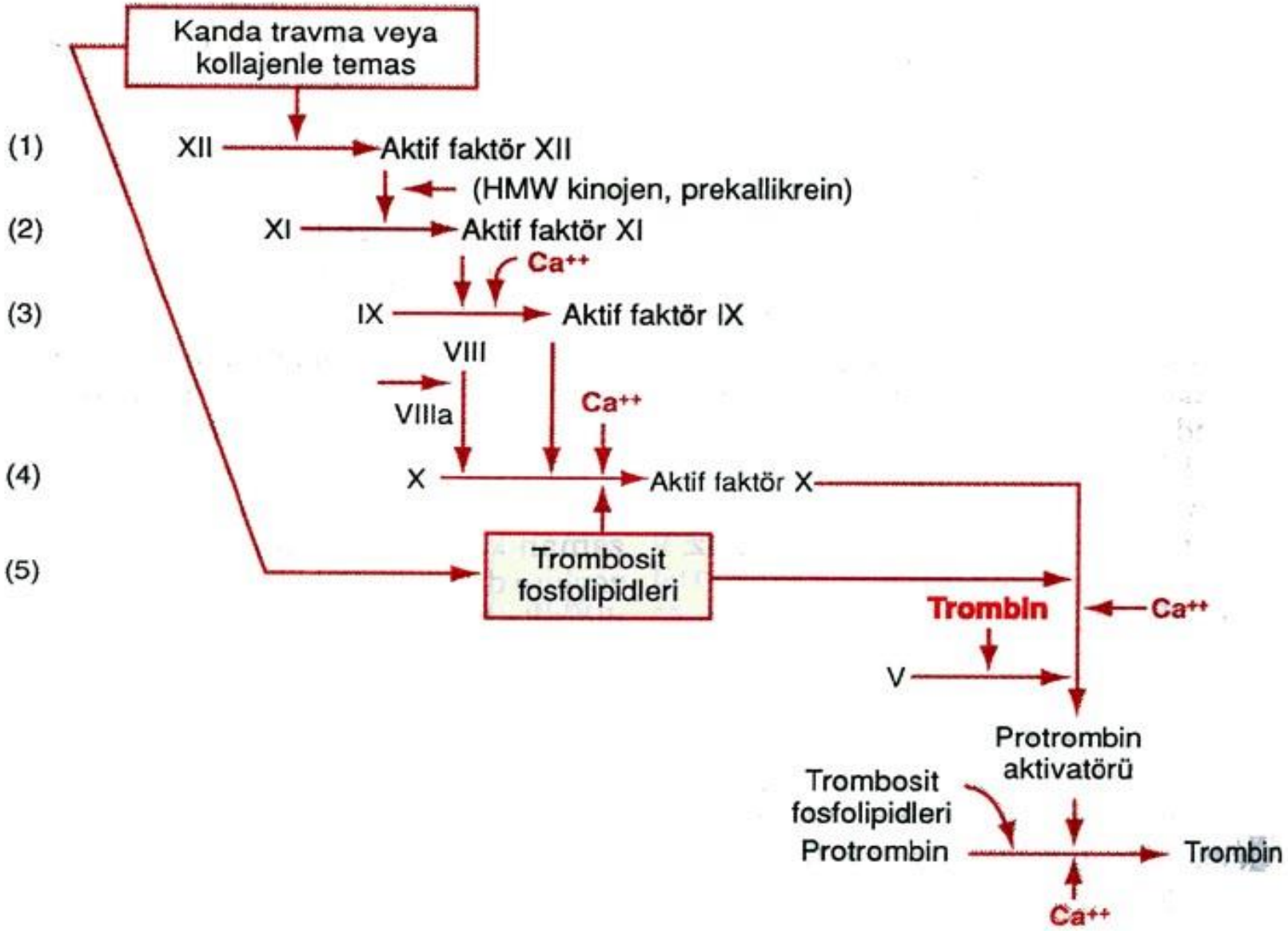
- Uyguladıklarımız
  -Akut STEMI
  -Akut iskemik inme (Sonotromboliz)
  -Massif pulmoner emboli
  -KPR
- Duyduklarımız
  -Periferik arter hastalığı
  -Santral retinal arter tıkanıklığı
  -Kalıcı kateter tıkanıklığı
  -PNH
  -DVT
  -İntraplevral


KOAGÜLASYON
KASKADI
Factor XI
Factor IX
Factor VII
Factor X
FXIIa
FXIa
FVIIa
Tissue Factor Pathway Inhibitor
Anti-thrombin (Antithrombin III)
FXIa-AT
FXa-AT
FVai
Protein S
Activated Protein C
Protein C receptor
Protein C
Plasmogen
Fibrin-TPA
Plasmin
Plasminogen activator inhibitor-1
α2-Antiplasmin
Plasmin-α2-AP
TPA-PAI-1
FDPs
Fibrogen degradation products
Legend
Positive feedback
Not essential
Negative feedback
Cell membrane
Activation cleavage site
GLA domain
Processing cleavage site
Krinkle domain
Fibronectin(Type I) domain
EGF domain
Fibronectin(Type II) domain


DON'T PANIC

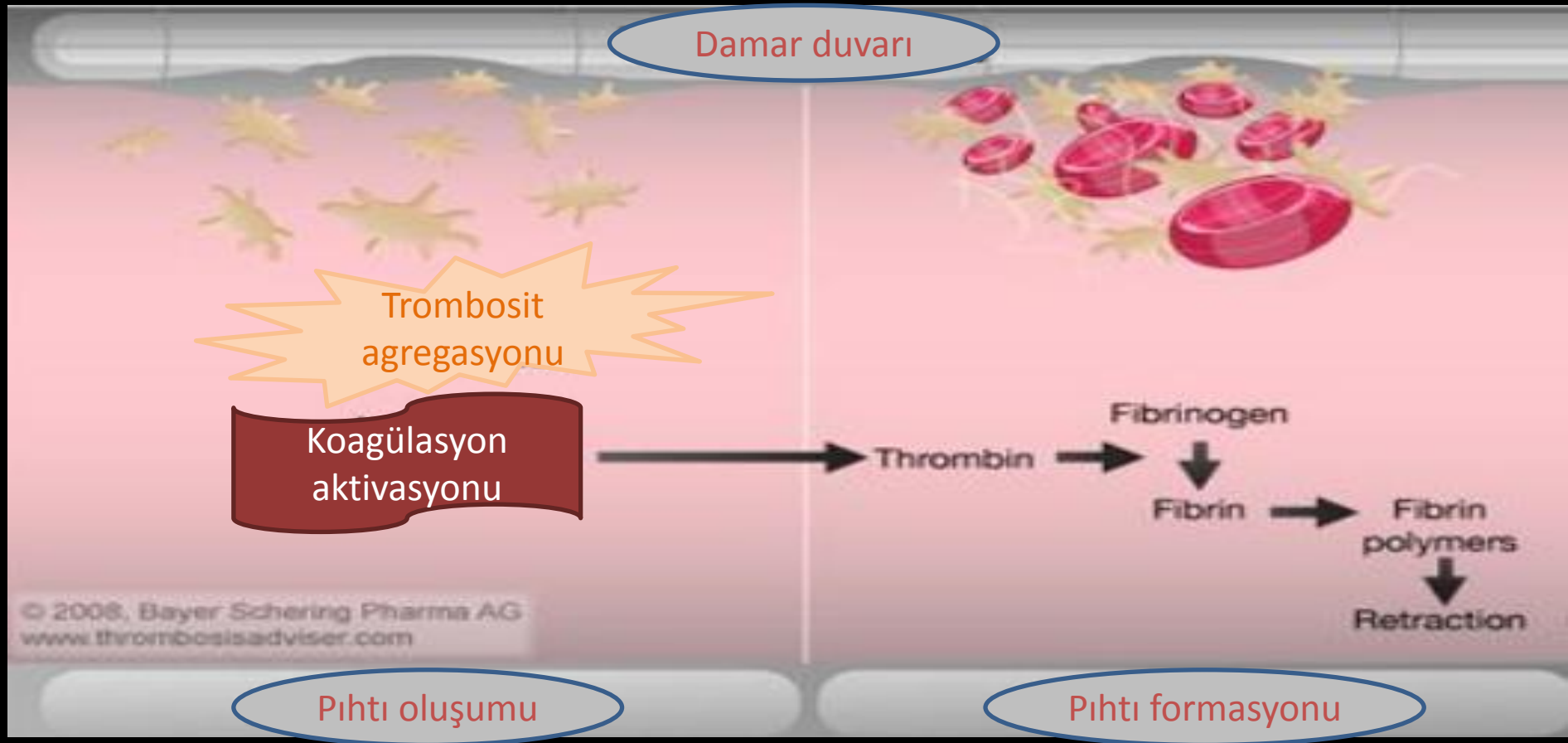


Pıhtılaşma mekanizmasını başlatan ekstrensek yol



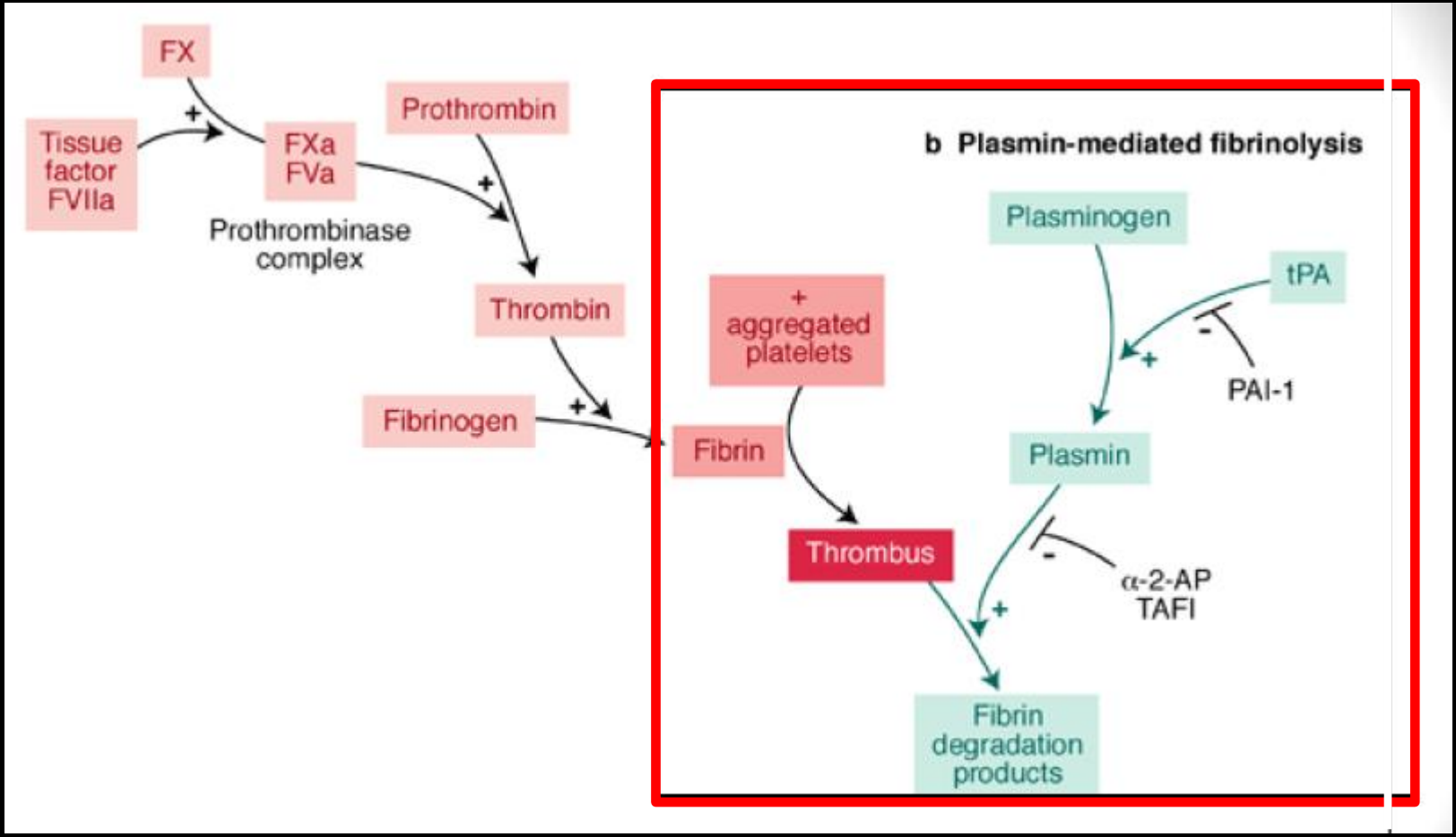
Pıhtılaşma mekanizmasını başlatan intrensek yol

Koagülasyon kaskadı

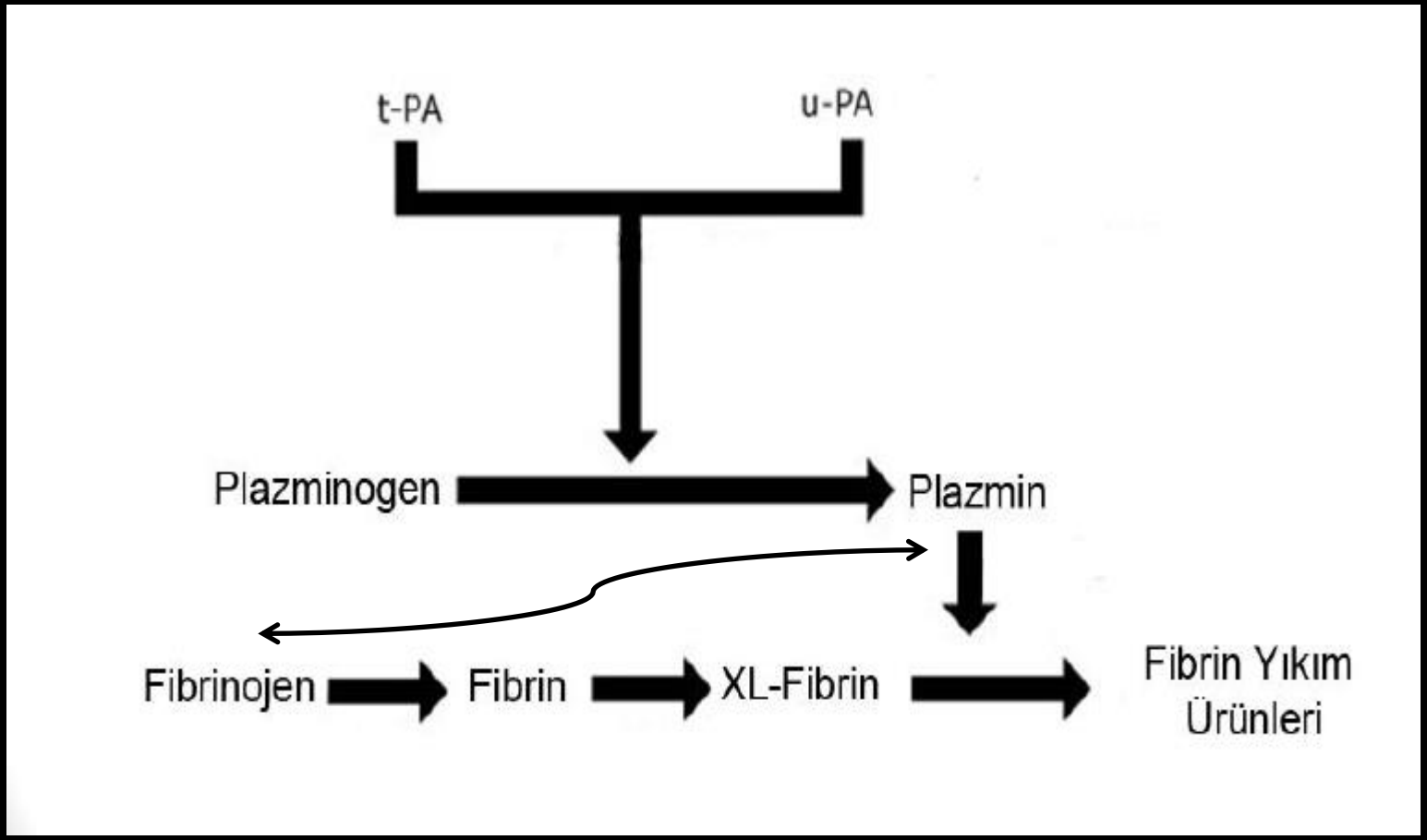


Trombin →Ortak yol

Koagülasyon kaskadı



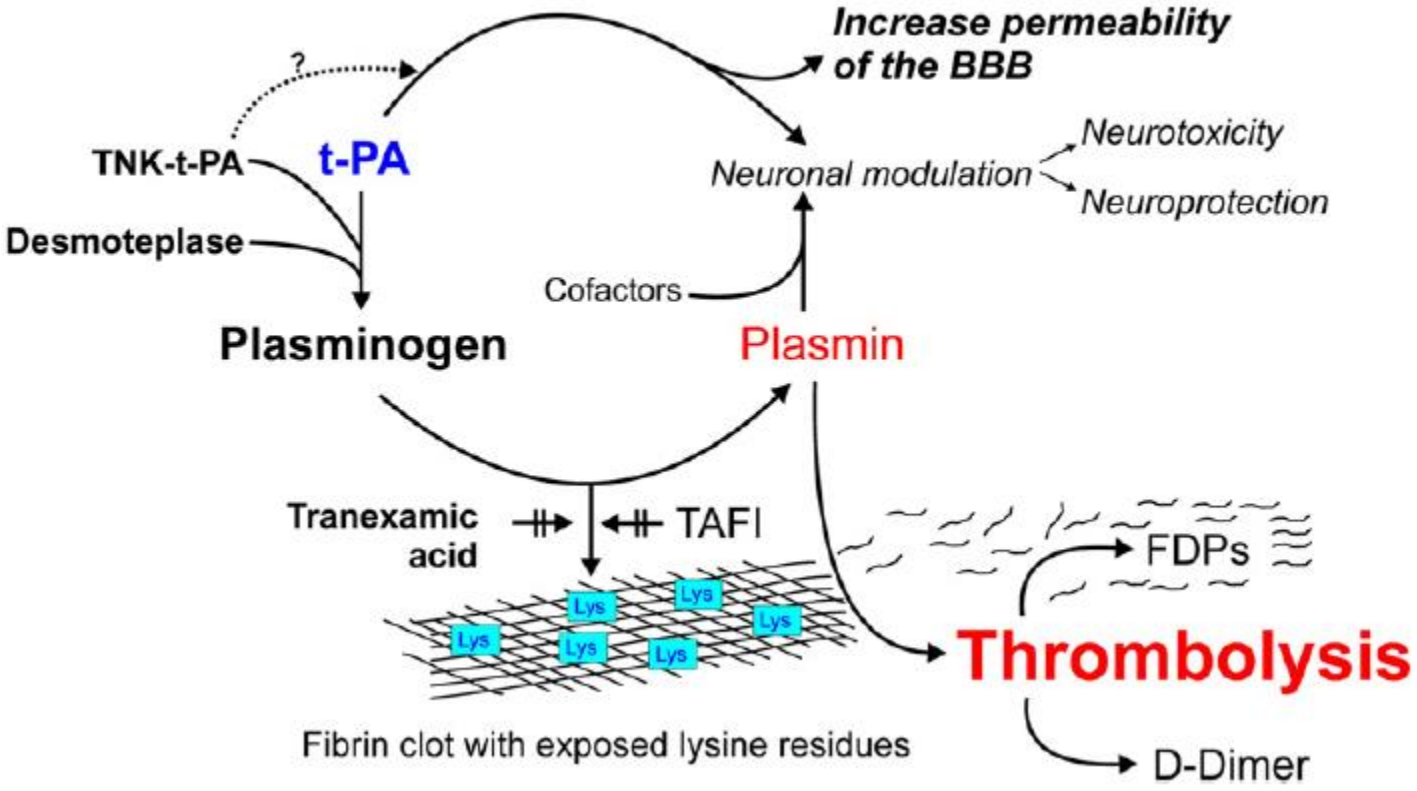
Fibrinolitik Sistem



Trombolitikler

- Amaç plazminojen aktivatörü olan ilaçlar geliştirmek
- Ortak etki mekanizmaları inaktif plazminojeni aktif plazmine çevirmek
- Plazmin substrat spesifitesi ↓
- Plazmin hem fibrini hem de fibrinojeni eritir.
- Amaç fibrine bağlanan trombolitik ajanlar…

Fibrinolitik Sistem



1. Kuşak Trombolitikler

- Klasik trombolitik ajanlar:

  Fibrinojen düzeyi↓,plazma viskozitesi ve trombosit agregasyonunu ↓

  - Bakteri kökenli **Streptokinaz**

  -Plazminojen-streptokinaz kompleksi **Anistreplaz**

  -**Ürokinaz**

1. Kuşak Trombolitikler

- Streptokinaz

  -C grubu ß hemolitik streptokok

  -SK+plazminojen→Plazmin

  -Bakteri ürünü olduğu için immün yanıt ve alerjik reaksiyon

  -Ateş,hipotansiyon,ürtiker,bronkospazm

1. Kuşak Trombolitikler

- Anistreplaz

  -İzole edilmemiş plazminojen SK aktivatör (APSAC)

  -Human plazminojen+bakteriyel SK

  -Sistemik dolaşımda potent bir proteolitik

  -Fibrinojen ↓ plazminojen ↓ Faktör V↓

  Faktör VIII ↓ α_2 antiplazmin ↓

1. Kuşak Trombolitikler

- Ürokinaz

  -Tek zincirli bir serin proteazı

  -İdrarla atılan böbreklerden salınan bir enzim

  -Etkisi SK'a benzer fakat antijenik ve pirojenik değildir

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy in Peripheral Artery Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Pablo Alonso-Coello, MD, PhD; Sergi Bellmunt, MD; Catherine McGorrian, MBBCh, BAO; Sonia S. Anand, MD, PhD; Randolph Cuzman, MD, RVT; Michael H. Criqui, MD, MPH; [illegible]D; Maarten G. Lansberg, MD, PhD; [illegible]cer, MD

Recommendation

6.1-6.3. In patients with acute limb ischemia due to arterial emboli or thrombosis, we suggest immediate systemic anticoagulation with unfractionated heparin over no anticoagulation (Grade 2C); we suggest reperfusion therapy (surgery or intraarterial thrombolysis) over no reperfusion therapy (Grade 2C); and we recommend surgery over intraarterial thrombolysis (Grade 1B). In patients undergoing intraarterial thrombolysis, we suggest rt-PA or urokinase over streptokinase (Grade 2C).

CHEST 2012; 141(2)(Suppl):e669S–e690S

Thrombolytic therapy is effective in paroxysmal nocturnal hemoglobinuria: a series of nine patients and a review of the literature

David J. Araten,[1] Rosario Notaro,[2] Howard T Thaler,[3] Nancy Kernan,[4] Farid Boulad,[4] Hugo Castro-Malaspina,[5] Trudy Small,[4] Andromachi Scaradavou,[4] Heather Magnan,[4] Susan Prockop,[4] Sara Chaffee,[6] Jason Gonsky,[7] Raymond Thertulien,[8] Roberto Tarquini,[9] and Lucio Luzzatto[10]

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ABSTRACT

Background
Thrombosis is the major risk factor for death in patients with paroxysmal nocturnal hemoglobinuria. Previous case reports indicate that venous thrombosis in patients with paroxysmal nocturnal hemoglobinuria is amenable to thrombolysis.

Design and Methods
We reviewed the outcome of thrombolytic therapy for patients with paroxysmal nocturnal hemoglobinuria who had thromboses refractory to anticoagulation at our institutions.

Results
In this study of 41 patients who had at least one thrombotic event, we confirmed a very high incidence of recurrence despite anticoagulation. Nine patients with thrombosis were regarded as eligible for administration of intravenous tissue plasminogen activator, which was effective in reversing thrombi in all of 15 occasions in which it was given. Serious hemorrhagic complications developed in three cases. At last follow-up visit, of the nine patients treated, three had died, and six were in very good to excellent condition in terms of clinical outcome and radiological findings. The only patient in whom thrombolysis may have contributed to a fatal outcome also had complications of "heparin induced thrombocytopenia with thrombosis", which we diagnosed in three additional patients. In our review of the literature, nine out of 15 patients treated with thrombolysis have had a good outcome.

Conclusions
Although it is associated with a significant but manageable risk of bleeding, systemic thrombolysis is a highly effective treatment for reversing venous thromboses in patients with paroxysmal nocturnal hemoglobinuria.

Key words: thrombolysis, paroxysmal nocturnal hemoglobinuria, treatment, outcome.

Citation: Araten DJ, Notaro R, Thaler HT, Kernan N, Boulad F, Castro-Malaspina H, Small T, Scaradavou A, Magnan H, Prockop S, Chaffee S, Gonsky J, Thertulien R, Tarquini R, and Luzzatto L. Thrombolytic therapy is effective in paroxysmal nocturnal hemoglobinuria: a series of nine patients and a review of the literature. Haematologica 2012;97(3):344-352. doi:10.3324/haematol.2011.049767

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The online version of this article has a Supplementary Appendix.

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- Klasik triad:Trombozis,intravasküler hemoliz ve sitopeni
- % 40 hastada tromboz
- Tedavi:kumadin,anti kompleman,trombolitik
- 1985-2009 15 hasta
- 3 hasta streptokinaz , 6 hasta ürokinaz ve 6 hasta tPA

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Table 2. Summary of the literature on thrombolytic therapy in patients with PNH.

Pt	Year	Author	Age	M/F	Sites of thrombosis	Regimen	Radiologic outcome	Clinical outcome
1	1985	Sholar	33	F	HV, IVC	Streptokinase 7500 U/h then 5000 U/h (total of 72 h); second course 2 months later: urokinase 250,000 U bolus then 250,000 U over 12 h	Complete resolution	Good, 2 years follow-up
2	1985	Sholar	33	M	HV, IVC	Streptokinase 250,000 U loading dose then 100,00 units/hour (48 h infusion) route not specified	Complete resolution	Good outcome, 2 years follow-up
3	1992	Kwan	47	F	Budd Chiari Syndrome	tPA iv, 100 mg over 3 h	Not determined	Marked clinical improvement, then bleeding complications, ultimately died
4	1992	Ishiguchi	42	F	IVC, Hepatic veins	Urokinase, catheter-directed, 360,000 U over 35 min, then 240,000 U/day	Partial response	Marked clinical improvement, doing well at 14 month follow-up
5	1993	Prawley	50	M	IVC, HV, SMV	Streptokinase 40,000 U/h catheter-directed into IVC then tPA 5mg x 3 then 7 mg/h via hepatic veins	Partial response	Died after CHOP chemotherapy
6	1994	McMullin	33	F	HV, IVC	Systemic iv tPA 0.25 mg/kg for 2 days	Restored flow	Good outcome, follow-up 6 years post-treatment
7	1994	McMullin	22	F	HV	0.25 mg/kg tPA iv over 3 h, then tPA catheter-directed into hepatic artery (12 mg over 24 h), then 12 mg over 24 h iv, then 50 mg over 24 h	Normal flow in hepatic veins	Good outcome, 2 year follow-up
8	2003	D'Amico	32	M	HV, IVC	Intravenous tPA dose not specified	No	Complicated by HITT
9	2003	Hauser	38	F	HV, IVC	Systemic iv infusion: 25 mg tPA over 3 h, then 25 mg over 21 h x 2 infusions	PR then CR after 2nd infusion	Death from mesenteric thrombosis 4 months later
10	2003	Tsatalas	35	M	HV	tPA, route and dose not specificied	Stable disease	Clinically well after 14 month follow-up
11	2006	Kuo	27	M	RHV, MHV	Urokinase catheter-directed into hepatic veins 125,000 U/h per vein (5 million U/36 h)	Complete	Good outcome after BMT
12	2006	Kuo	34	M	IVC, HV	Urokinase 7.45 million units/47 h catheter-directed localized infusion	Complete	Alive
13	2006	Kuo	14	F	Middle HV	Urokinase, catheter-directed, into hepatic vein: 2.9 million U/24 h	Near CR	Death from complications of subsequent BMT
14	2007	Shindo	39	F	IVC	Urokinase 1000 U/h for 1 week, route not specified	Complete resolution	Subsequent death from complications of aplastic anemia
15	2009	Yin	52	F	SMV, portal vein	500,000 U urokinase, catheter-directed	Some improvement	Clinical improvement

<u>Radyolojik olarak;</u>

8 hasta tam iyileşme

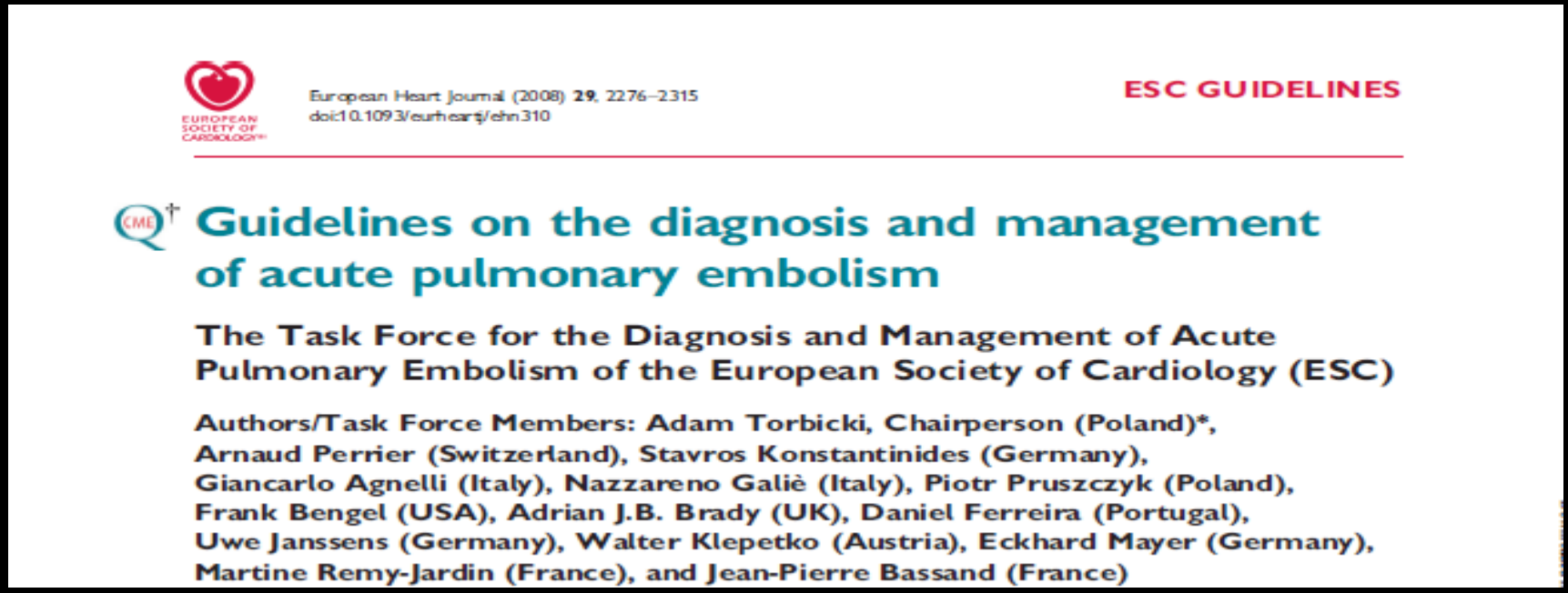
3 hasta parsiyel iyileşme

2 hasta cevapsız

1 hasta belirtilmemiş

9 hasta klinik düzelme

1 hasta hemorajik komplikasyon



European Heart Journal (2008) 29, 2276–2315
doi:10.1093/eurheartj/ehn310

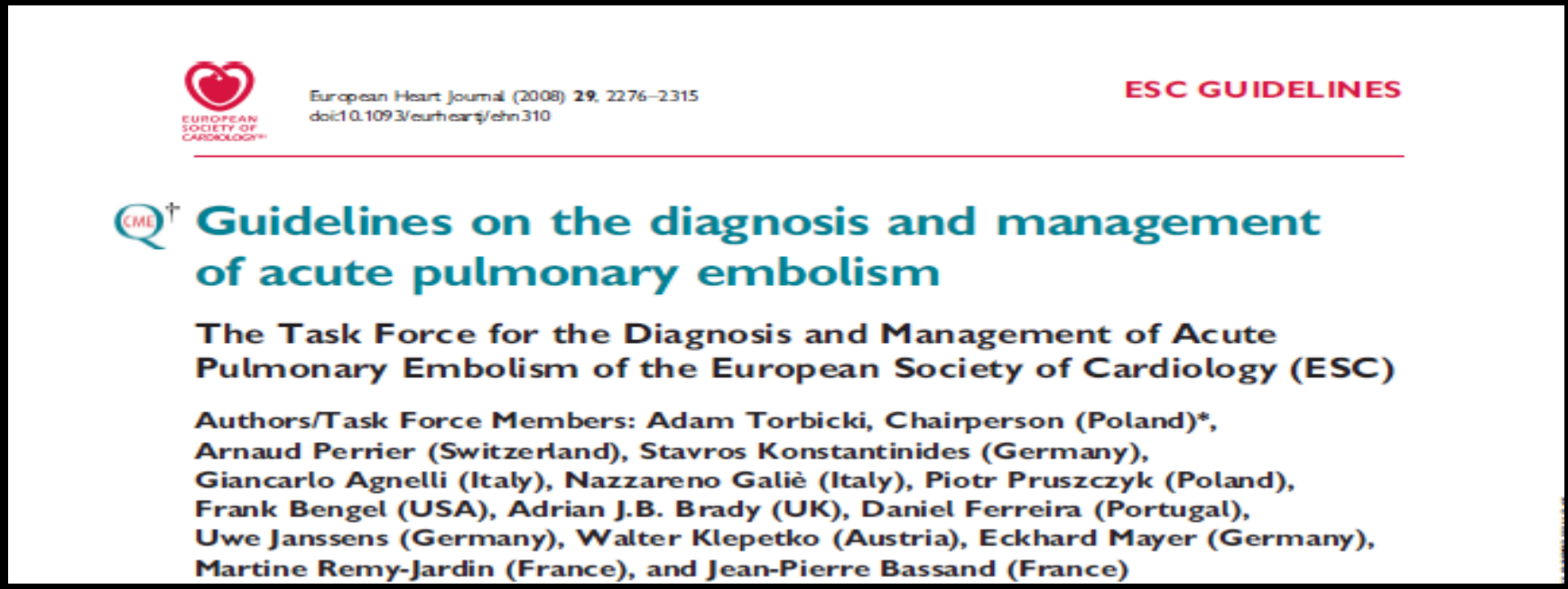
ESC GUIDELINES

Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Authors/Task Force Members: Adam Torbicki, Chairperson (Poland)*, Arnaud Perrier (Switzerland), Stavros Konstantinides (Germany), Giancarlo Agnelli (Italy), Nazzareno Galiè (Italy), Piotr Pruszczyk (Poland), Frank Bengel (USA), Adrian J.B. Brady (UK), Daniel Ferreira (Portugal), Uwe Janssens (Germany), Walter Klepetko (Austria), Eckhard Mayer (Germany), Martine Remy-Jardin (France), and Jean-Pierre Bassand (France)

- Kardiyojenik şok ve/veya persistan arteriyel hipotansiyon tablosuyla gelen, yüksek riskli PE hastaları trombolitik ajanlarla tedavi edilir.
- Yüksek riskli olmayan hastalarda trombolizin rutin kullanımı tavsiye edilmiyor. (Bazı orta riskli PE grubundaki hastalara tromboliz uygulanabilir)
- Trombolitik tedavi, düşük riskli PE hastalarında kullanılmamalıdır.



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- Hastaların %92'sinde, ilk 36 saat içinde klinik ve ekokardiyografik düzelme
- En büyük yarar, belirtilerin başlamasından sonra 48 saat içinde tedaviye başlandığında gözlenir
- 6-14 günden beri belirtileri olan hastalarda da tromboliz yarar sağlayabilir
- **Streptokinaz,ürokinaz** ve tPA onaylanmış trombolitikler

THE COCHRANE LIBRARY
Independent high-quality evidence for health care decision making

Robert J Cameron , Huw Richard H R Davies
Intra-pleural fibrinolytic therapy versus conservative management in the treatment of adult parapneumonic effusions and empyema
2008 Apr 16;(2):CD002312

THORAX
An International Journal Of Respiratory Medicine

Davies HE,Davies RJ, BTS Pleural Disease Guideline G.
Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010.
2010 Aug;65 Suppl 2:ii41-53.

The NEW ENGLAND JOURNAL of MEDICINE

Rahman NM
Intrapleural use of tPA and DNase in pleural infection (Multicenter Intrapleural Sepsis Trial 2)
2011 Aug; 11;365(6):518-26

Surinder Janda, MD; John Swiston, MD, FCCP
Intrapleural Fibrinolytic Therapy for Treatment of Adult Parapneumonic Effusions and Empyemas:A Systematic Review and Meta-analysis
Chest. 2012; 142(2):401-411.

CHEST

Original Research

PULMONARY PROCEDURES

Intrapleural Fibrinolytic Therapy for Treatment of Adult Parapneumonic Effusions and Empyemas

A Systematic Review and Meta-analysis

Study/Year	Country	Study Size (N)	Study Population	Imaging	Chest Tube Size (F)	Intervention
Davies et al[10]/1997	UK	24	CPE or E	CXR, CT scan, U/S	14	Streptokinase, 250,000 International Units OD × 3 d
Bouros et al[9]/1999	Greece	31	CPE or E	CT scan, U/S	28-32	Urokinase, 100,000 International Units OD × 3 d
Tuncozgur et al[27]/2001	Turkey	49	E stage II[a]	CXR, CT scan, U/S	24-36	Urokinase, 100,000 International Units OD × 3 d
Diacon et al[11]/2004	South Africa	53	CPE or E	CXR, U/S	24 or 28	Streptokinase, 250,000 International Units OD × 7 d[b]
Misthos et al[28]/2005	Greece	127	E	CXR, U/S	28-32	Streptokinase, 250,000 International Units OD × 3 d
MIST1[7]/2005	UK	454	CPE or E	CXR	12 (12-20)[c]	Streptokinase, 250,000 International Units bid × 3 d
MIST2[29]/2011	UK	210	CPE or E	CXR	< 15[d]	Alteplase, 10 mg bid × 3 d; DNase, 5 mg bid × 3 d; combination of alteplase and DNase

- 7 adet randomize kontrollü çalışma
- 801 hasta

CHEST

Original Research

PULMONARY PROCEDURES

Intrapleural Fibrinolytic Therapy for Treatment of Adult Parapneumonic Effusions and Empyemas

A Systematic Review and Meta-analysis

Conclusions: This meta-analysis does reveal that fibrinolytic therapy is potentially beneficial in the management of parapneumonic effusions and empyemas in the adult population. Although there is insufficient evidence to support the routine use of this therapy for all parapneumonic effusions/empyemas, fibrinolytic therapy may be considered in patients with loculated pleural effusions, because it may prevent the need for surgical intervention. Further randomized controlled trials with adequate power are needed to definitively address the effect of fibrinolytics and the combination of fibrinolytics and deoxyribonuclease on the clinical outcomes outlined in this analysis in patients with parapneumonic effusions/empyemas.

CHEST 2012; 142(2):401–411


BİR MASAL YAZDIM, "ALİ BABA VE BİR HARAMİ..."
BENCE SEN BUNU GELİŞTİR BİRAZ..!..

2. Kuşak Trombolitikler

- Yapı ve etki bakımından 1. kuşaklara benzer
- Etki süreleri daha uzun
- Fibrin selektif
- Plazminojen aktivatör inhibitörlerine (PAI-1) dayanıklı
- Dolaşımdaki fibrinojen ve plazminojen azalması daha az görülür.

2. Kuşak Trombolitikler

- Doku Plazminojen Aktivatörü (t-PA) (Alteplase)

  -Endotel hücrelerinde üretilir.

  -Rekombinant biyoteknoloji ile insan melanom hücre dizisinden oluşturulur.

  -Plazminojen→Plazmin

  -Fibrin selektivitesi SK ve ürokinaza göre daha güçlüdür.

2. Kuşak Trombolitikler

- Doku Plazminojen Aktivatörü (t-PA) (Alteplase)

  -Nörovasküler permeabilite artışına ve intrakraniyal ödem ve hemorajik tranformasyona yol açabilir.

  Yepes M, Roussel BD, Ali C, et al. Tissue-type Plasminogen activator in the ischemic brain; more than a thrombolytic.Trends Neurosci 2009 Jan; 32 (1): 48-55

  -Nörotoksik (NO salınımı)

  Parathath SR, Parathath S, Tsirka SE. Nitric oxide mediates neurodegeneration and breakdown of the blood-brain barrier in tPA-dependent excitotoxic injury in mice. J Cell Sei 2006 Jan 15; 119 (2): 339-49

  Zhang X, Polavarapu R, She H, et al. Tissue-type plasminogen activator and the low-density lipoprotein receptor related protein mediate cerebral ischemia-induced nuclear factor-kappaB pathway activation. Am J Pathol 2007 Oct;171 (4): 1281-90

ADIS DRUG EVALUATION

CNS Drugs 2012; 26 (10): 899-926
1172-7047/12/0010-0899/$49.95/0

Alteplase

A Review of Its Use in the Management of Acute Ischaemic Stroke

Sohita Dhillon

Adis, Auckland, New Zealand

Various sections of the manuscript reviewed by:

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Data Selection

Sources: Medical literature (including published and unpublished data) on 'alteplase' was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were (('alteplase' or 'recombinant tissue plasminogen activator' or 'rTPA') and ('acute ischaemic stroke' or 'acute ischaemic stroke' or 'stroke')). Searches were last updated 17 August 2012.

Selection: Studies in patients with acute ischaemic stroke who received alteplase. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Alteplase, recombinant tissue plasminogen activator, acute ischaemic stroke, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Acronym/abbreviation	Definition
ATLANTIS	Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischaemic Stroke
CASES	Canadian Alteplase for Stroke Effectiveness Study
ECASS	European Cooperative Acute Stroke Study
EPITHET	Echoplanar Imaging Thrombolytic Evaluation Trial
IST-3	Third International Stroke Trial
NINDS	National Institute of Neurologic Disorders and Stroke
SITS-ISTR	Safe Implementation of Thrombolysis in Stroke-International Stroke Treatment Registry
SITS-MOST	Safe Implementation of Thrombolysis in Stroke MOnitoring STudy

Drugs of Today 2011, 47(7): 559-570

CCC: 1699-3993/2011
DOI: 10.1358/dot.2011.47.7.1600191

THOMSON REUTERS

REVIEW

RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATORS: "TIME MATTERS"

V. Kunadian[1] and C.M. Gibson[2]

[1]Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, U.K. and [2]Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

- TIMI 1 ve 2A(Thrombolysis in Myocardial Infarction)
- GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries)
- GISSI-2 (Italian group for the study of the survival of MI)
- ISIS 3 (The International Studies of Infarct Survival)
- COBALT (Continous infusion versus Double Bolus Administration of Alteplase)

Case Report

Acute Central Retinal Artery Occlusion Treated with Intravenous Recombinant Tissue Plasminogen Activator

Richard J. Nowak, MD, MS, Hardik Amin, MD, Kimberly Robeson, MD, and Joseph L. Schindler, MD

Journal of Stroke and Cerebrovascular Diseases, Vol. 21, No. 8 (November), 2012: pp 913.e5-913.e8

- Gözün iskemik inmesi
- Ağrısız akut monoküler görme kaybı
- Spontan rekanalizasyon % 15 fakat düzelme % 10 altında
- CRAO için rt-PA etkinliği ve güvenirliği ???

Case Report

Acute Central Retinal Artery Occlusion Treated with Intravenous Recombinant Tissue Plasminogen Activator

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- 52 hastanın 28'inde rt-PA ile klinik düzelme
- Tedavi aralığı 2-72 saat
- Düzelme ilk 24 saatte
- Komplikasyonlar belirtilmemiş
- İskemik inme gibi ilk 4.5 saatte ???

Authors, y (country)	Study type	No. of patients (age range)	Treatment window	Diagnostic imaging	Dose of IV rt-PA	Other administered treatments	Study results	Complications
Bertram et al., 1991 (Germany)	Case reports	2 (29, 59)	6.5 and 7 h, respectively	Fluorescein angiography, carotid Doppler	100 mg	Heparin for 3 days; pentoxifylline, acetylsalicylic acid, and hydroxyethyl starch	1 of 2 patients had improved VA >8 Snellen lines	None reported
Mames et al., 1995 (US)	Case series	2 (61, 74)	2.75 and 4 h, respectively	Not specified	Not specified	Paracentesis, ocular massage, sublingual nitroglycerin, IV heparin, and warfarin	Subjective improvement; post-treatment VA of 20/400 and 20/25 (pretreatment VA was not specified)	None reported
Puche et al., 2000 (Spain)	Case reports	2 (58, 62)	24 and 72 h, respectively	None	70 mg	Ocular massage and carbonic anhydrase inhibitor (1 patient)	1 of 2 patients improved from no perception of light to 5/10; the other patient had no improvement	None reported
Kattah et al., 2002 (US)	Prospective	12 (53-89)	2-18 h	Head CT	0.9 mg/kg with 10% given as bolus	Paracentesis, IV heparin, and warfarin × 1 month	10 of 12 had improved VA (4 had 8 Snellen lines of improvement; 6 had 2-4 lines of improvement)	2 patients died within 6 months of an acute cardiac event
Diaconu et al., 2004 (Romania)	Case report	1 (70)	6 h	Fluorescein angiography, echocardiogram, and carotid Doppler	100 mg	Pentoxifyllin, betamethasone, intraocular atropine plus lidocaine, and dalteparin	No improvement	None reported
Mach and Rochazka, 2008 (Czechoslovakia)	Case series	5 (58-72)	5-31 h	Head CT	0.9 mg/kg with 10% given as bolus	None	5 of 5 had improved VA; in 1 patient who received rt-PA in 31 hours, VA decreased shortly after it improved	None reported
Hattenback et al., 2008 (Germany)	Case series	28 (30-85)	<12 h	None	50 mg	IV heparin × 5 days and aspirin	9 of 28 had improved VA of ≥3 Snellen lines; 18 of 28 had stable VA and 1 of 28 had poorer VA	None

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Original

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Alteplase for blood flow restoration in hemodialysis catheters: a multicenter, randomized, prospective study comparing "dwell" versus "push" administration

Lavern M. Vercaigne[1], James Zacharias[2], Keevin N. Bernstein[2] and the PUSH Protocol Investigators

[1]Faculty of Pharmacy, and [2]Department of Internal Medicine, Section of Nephrology, University of Manitoba and the Manitoba Renal Program, Winnipeg, Manitoba, Canada

- Hemodiyaliz hastalarında SVK disfonksiyonu sık
- İntraluminal veya periluminal trombozis
- 2mg alteplase 30 dak kateterde tutulur başarısız ise 120 dak→"dwell"
- "push" katetere düzenli aralıklar ile alteplase verilmesi ve diyaliz sırasında ve durdurulduğunda infüzyon

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- 82 hasta;43 dwell 39 push
- Tedaviler arasında farklılık yok
- "push" daha pratik ve "dwell" kadar güvenli

Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial

Tone Enden, Ylva Haig, Nils-Einar Kløw, Carl-Erik Slagsvold, Leiv Sandvik, Waleed Ghanima, Geir Hafsahl, Pål Andre Holme, Lars Olaf Holmen, Anne Mette Njaastad, Gunnar Sandbæk, Per Morten Sandset, on behalf of the CaVenT Study Group

Summary

Background Conventional anticoagulant treatment for acute deep vein thrombosis (DVT) effectively prevents thrombus extension and recurrence, but does not dissolve the clot, and many patients develop post-thrombotic syndrome (PTS). We aimed to examine whether additional treatment with catheter-directed thrombolysis (CDT) using alteplase reduced development of PTS.

Methods Participants in this open-label, randomised controlled trial were recruited from 20 hospitals in the Norwegian southeastern health region. Patients aged 18–75 years with a first-time iliofemoral DVT were included within 21 days from symptom onset. Patients were randomly assigned (1:1) by picking lowest number of sealed envelopes to conventional treatment alone or additional CDT. Randomisation was stratified for involvement of the pelvic veins with blocks of six. We assessed two co-primary outcomes: frequency of PTS as assessed by Villalta score at 24 months, and iliofemoral patency after 6 months. Analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00251771.

Findings 209 patients were randomly assigned to treatment groups (108 control, 101 CDT). At completion of 24 months' follow-up, data for clinical status were available for 189 patients (90%; 99 control, 90 CDT). At 24 months, 37 (41·1%, 95% CI 31·5–51·4) patients allocated additional CDT presented with PTS compared with 55 (55·6%, 95% CI 45·7–65·0) in the control group (p=0·047). The difference in PTS corresponds to an absolute risk reduction of 14·4% (95% CI 0·2–27·9), and the number needed to treat was 7 (95% CI 4–502). Iliofemoral patency after 6 months was reported in 58 patients (65·9%, 95% CI 55·5–75·0) on CDT versus 45 (47·4%, 37·6–57·3) on control (p=0·012). 20 bleeding complications related to CDT included three major and five clinically relevant bleeds.

Interpretation Additional CDT should be considered in patients with a high proximal DVT and low risk of bleeding.

Lancet 2012; 379: 31–38

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See Editorial page 1

See Comment page 3

Department of Haematology (T Enden M.D, Prof P.M. Sandset MD, P.A Holme M.D), **Department of Radiology and Nuclear Medicine** (T Enden, Y Haig M.D, Prof N-E Kløw M.D, G Hafsahl M.D, G Sandbæk M.D), **Oslo Vascular Centre** (C-E Slagsvold M.D), **Department of Clinical Research** (Prof L Sandvik PhD), **and Department of Medicine** (A.M. Njaastad M.D), **Oslo University Hospital, Oslo, Norway; Institute of Clinical Medicine, University of Oslo, Oslo, Norway** (Y Haig, Prof N E Kløw, Prof L Sandvik, G Sandbæk, Prof P M Sandset); and Department of Medicine

CaVenT study

- DVT tedavisi antitrombotik
- PE,ölüm,rekürrens ve post trombotik sendrom
- Ağrı, şişlik,ödem,pigmentasyon,venöz ülserler
- Sistemik tromboliz→ artmış kanama riski
- Kateter yolu ile azaltılmış doz trombolitik
- İliofemoral ven trombozu
- 20 hastane, 18-75 yaş, 21 günlük hikaye,iliofemoral-ortak iliak ven trombozu
- 209 hasta→90 trombolitik,99 standard

CaVenT study

	Additional catheter-directed thrombolysis (n=90)		Standard treatment only (n=99)		p value*
	n	% (95% CI)	n	% (95% CI)	
Post-thrombotic syndrome at 24 months†	37			55·6% (45·7–65·0)	0·047
Iliofemoral patency at 6 months†‡				4% (37·6–57·3)	0·012
Post-thrombotic syndrome at 6 months§				32·2% (23·9–42·1)	0·77

%14 risk azalması

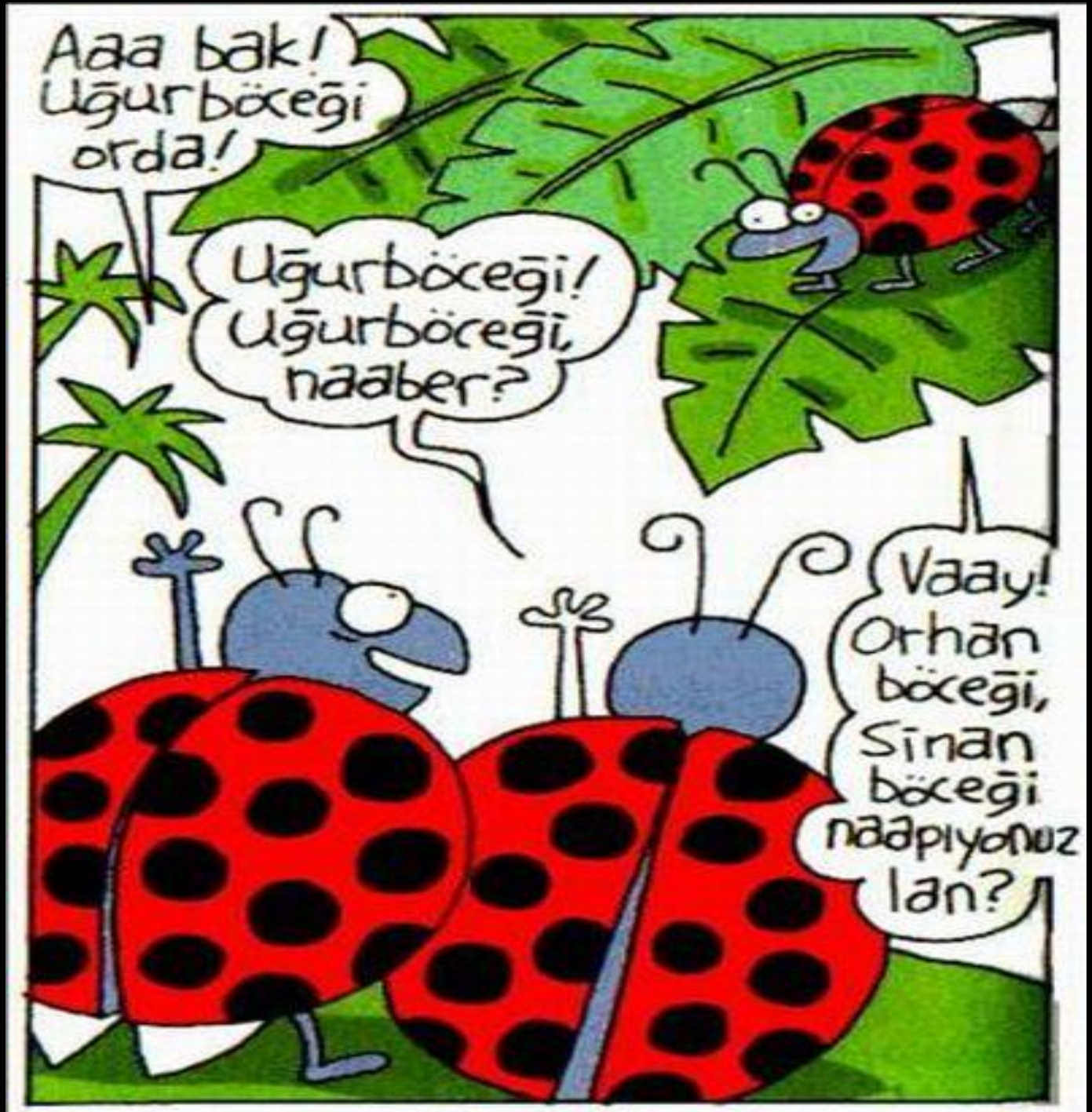
Post-thrombotic syndrome defined as Villalta score of 5 points or higher. *χ^2 test. †Co-primary outcomes. ‡Five patients had inconclusive patency assessments and one was lost to follow-up at 6 months. §Secondary outcome.

Table 2: **Short-term and long-term outcomes**

Lancet 2012; 379: 31–38

3. Kuşak Trombolitikler

- 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……..


Aaa bak! Uğurböceği orda!
Uğurböceği! Uğurböceği, naaber?
Vaay! Orhan böceği, Sinan böceği naapıyonuz lan?

3. Kuşak Trombolitikler

- Bakteriyel (rekombinant stafilokinaz)
- Hayvan plazminojen aktivatörleri (vampir yarasa plazminojen aktivatörü)

	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

Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial

The Steering Committee [a]

Background In acute pulmonary embolism (PE), overt right ventricular (RV) failure with cardiogenic shock indicates a poor prognosis. However, normotensive patients with acute RV dysfunction on echocardiography or computed tomography and with myocardial troponin elevation may also have an adverse outcome. Thrombolysis rapidly reverses RV pressure overload in PE, but it remains unclear whether it may improve the early and long-term clinical outcome of selected normotensive patients.

Design The *P*ulmonary *E*mbol*I*sm *THr*O*m*bolysis (PEITHO) trial is a prospective, multicenter, international, randomized (1:1), double-blind comparison of thrombolysis with tenecteplase vs placebo in normotensive patients with confirmed PE, an abnormal right ventricle on echocardiography or computed tomography, and a positive troponin I or T test result. Both treatment groups receive standard anticoagulation. The primary efficacy outcome is the composite of death from any cause or hemodynamic collapse within 7 days of randomization. Safety outcomes include ischemic/hemorrhagic strokes and other major bleeding episodes. In addition, 180-day clinical and echocardiographic follow-up will be performed. The study is expected to enroll approximately 1,000 patients.

Conclusions By determining the benefits vs risks of thrombolysis in submassive or intermediate-risk PE, this trial is expected to answer a long-standing query on the management of this patient population. (Am Heart J 2012;163:33-38.e1.)

PE'ye bağlı erken MORTALİTE RİSKİ		RİSK BELİRTEÇLERİ			Tedavinin potansiyel etkileri
		KLİNİK (şok ya da hipotansiyon)	RV işlev bozukluğu	Miyokart hasarı	
YÜKSEK >%15		+	(+)[a]	(+)[a]	Tromboliz ya da embolektomi
YÜKSEK DEĞİL	Orta %3-15	–	+	+	Hastaneye başvuru
			+	–	
			–	+	
	Düşük >%1	–	–	–	Erken taburcu olma ya da evde tedavi

İntermediate riski olan hastalarda eko/CT'de sağ ventrikül genişlemesi ve/veya yetmezliği saptandığında ve myokardiyal hasarın biyobelirteçlerle kanıtlanması durumunda rekanalizasyon düşünülmelidir.

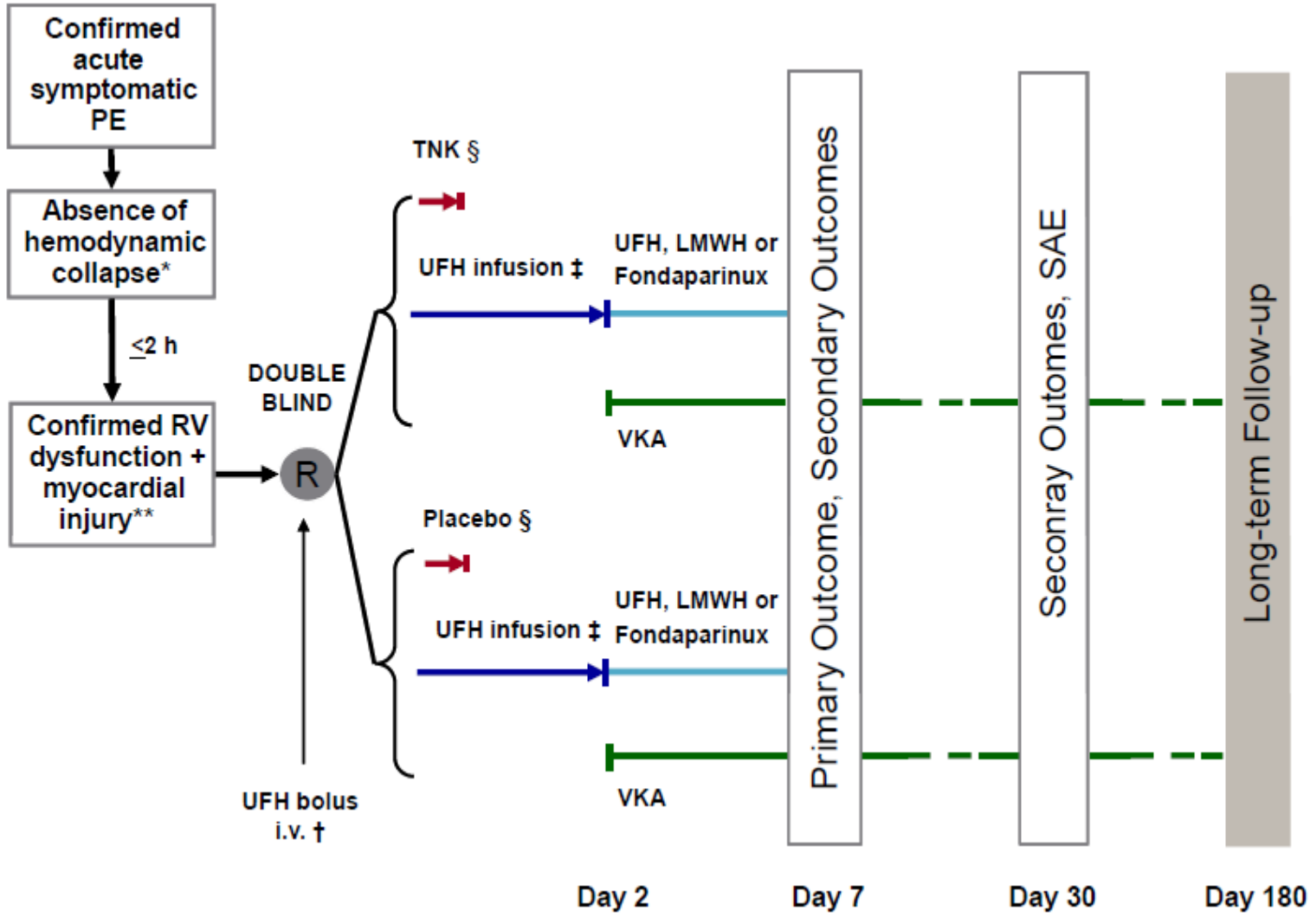
Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial

- Çalışmanın amacı, sağ ventrikül yetm olan ve kardiyak biyobelirteçleri pozitif olan normotensif hastalarda tenectoplase ile trombolizin plaseboya üstünlüğünü kanıtlamak
- Tenektoplase güvenilirliğini değerlendirmek
- Uzun dönem (180 gün) pulmoner HT gelişimi

Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: Rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial

- 1000 kişi planlandı,793 kişi katıldı
- İlk sonlanım 7 gün içinde hemodinamik kollaps
- İkinci sonlanım noktası 7 gün içinde ölüm, PE rekürrensi,30 gün içinde ölüm
- Güvenilirlik sonlanımı ilk 7 günde iskemik yada hemorajik inme,kanama veya ciddi yan etkiler

PEİTHO çalışması




TELEFONUM KAPALI... İŞE GİTMEDİM... EVDE DE YOKUM... AMAN ALLAHIM SAKIN BAŞIMA BİŞEY GELMİŞ OLMASIN?!...
UMARIM Bİ DELİLİK YAPMAM...

Trombolitik tedavinin kontrendikasyonları

Mutlak

- Bilinen kanama
- Hemorajik veya nedeni bilinmeyen inme
- Son 1 ay içinde geçirilen GİS kanama
- Son 3 hafta içinde geçirilmiş travma/cerrahi girişim/kafa travması
- SSS hasarı yada tümörleri
- Son 6 ay içinde gelişen iskemik inme

Görece

- Son 6 ay içinde TİA
- Oral antikoagülan tedavi
- Gebelik yada gebelik sonrası 1. hafta
- Kompresyon yapılamayan kateter girişleri
- Travmatik resüsitasyon
- Tedaviye dirençli HT,sistolik kan basıncı >180 mmHg
- İlerlemiş KC hastalığı
- İnfektif endokardit
- Aktif peptik ülser

Teşekkürler…….