Белодробен тромбемболизъм с умерен и висок риск

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Jiménez's levels of belief

With apologies to the levels of evidence

Levels of belief

- Class 0: Things I believe
- Class 0a: Things I believe despite the available data
- Class 1: Randomised controlled clinical trials that agree with what I believe
- Class 2: Other prospectively collected data
- Class 3: Expert opinion
- Class 4: Randomised controlled clinical trials that don't agree with what I believe
- Class 5: What you believe that I don't

Проблемът

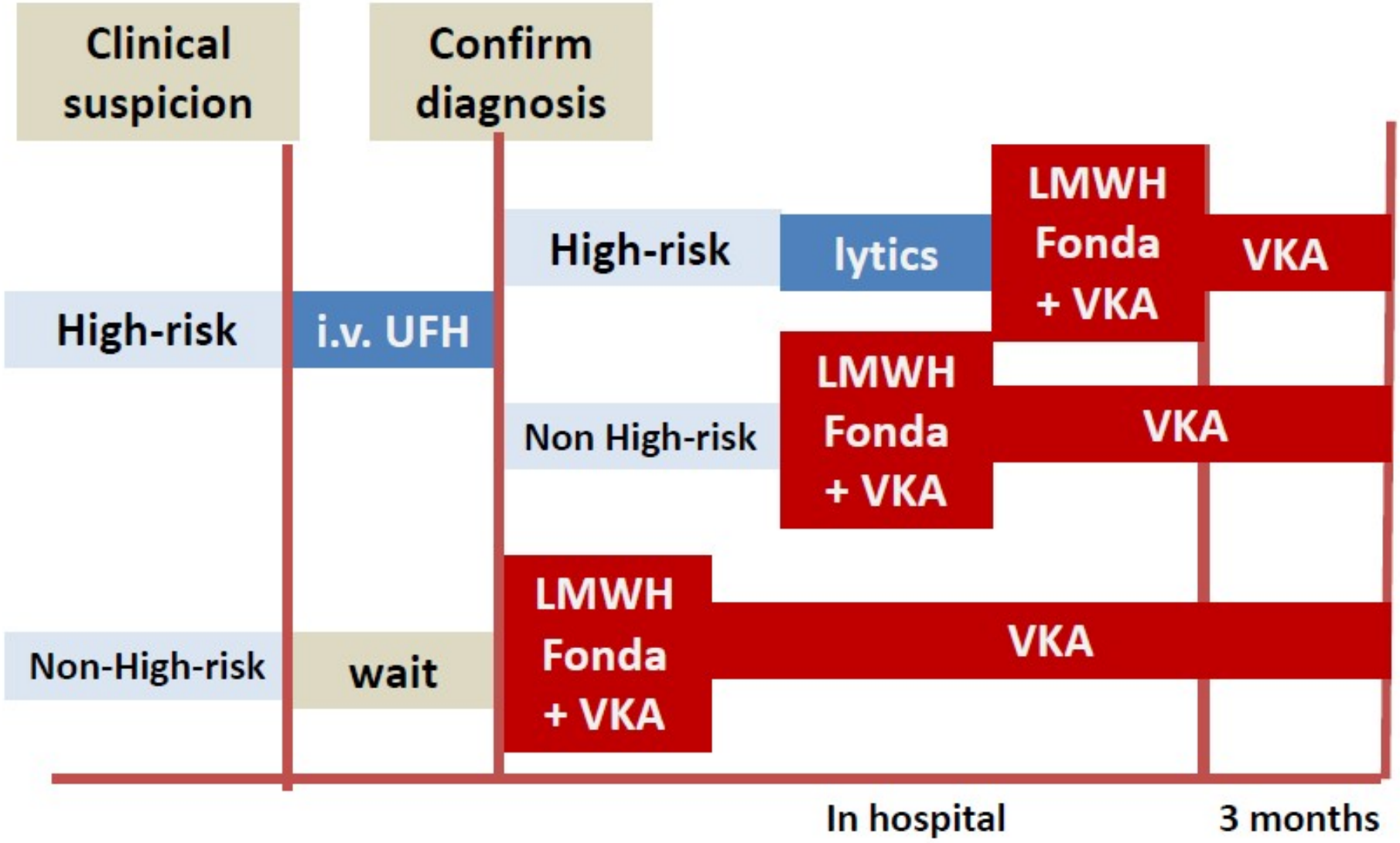
- 46 смъртни случаи – 11 с възможен масивен БТЕ
  - 3 потвърдени с аутопсия
  - 4 неразпознати, диагностицирани постмортем
    - всичките 7- представяне с клиника на шок
  - *6 от 11 с абсолютни контраиндикации за системна фибринолиза*
  - среден болничен престой – 27 часа

* 2005 Смъртност ИКС – Кардиологична клиника, УМБАЛ Света Ана, София, 8 легла и 900 болни годишно

Проблемът

Acute Myocardial Infarction	Pulmonary Embolism
Highly prevalent	Highly prevalent
High mortality %	High mortality %
Pathways are clear	Pathways
10 mins ECG 30 mins lytics 60 mins PCI	?????

Поведение при БТЕ



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

Guidelines on the diagnosis and management of acute pulmonary embolism

PE-related early MORTALITY RISK		RISK MARKERS			Potential treatment implications
		CLINICAL (shock or hypotension)	RV dysfunction	Myocardial injury	
HIGH >15%		+	(+)[a]	(+)[a]	Thrombolysis or embolectomy
NON HIGH	Intermediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

“Saddle PE” - AngioVac

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			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

European Heart Journal (2008) 29, 2276–2315
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Guidelines on the diagnosis and management of acute pulmonary embolism

High-risk PE

Recommendation	Class	Level
Thrombolytic therapy in patients with high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension	I	A
Surgical pulmonary embolectomy if thrombolysis is absolutely contraindicated or has failed	I	C
Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be an alternative to surgical treatment	IIb	C

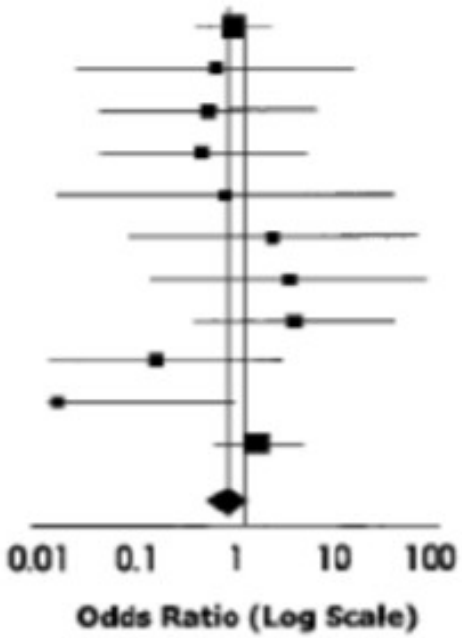
Approved thrombolytic regimens for PE

Streptokinase	250 000 U as a loading dose over 30 min, followed by 100 000 U/h over 12–24 h Accelerated regimen: 1.5 million IU over 2 h
Urokinase	4400 U per kg of body weight as a loading dose over 10 min, followed by 4400 /kg/h over 12–24 h Accelerated regimen: 3 million U over 2 h
Reteplase	100 mg over 2 h Accelerated regimen: 0.6 mg/kg for 15 min
Alteplase	Two bolus injections of 10 U 30 min apart
Tenecteplase	30–50 mg bolus for 5–10 s adjusted for body weight

Pulmonary Embolism Thrombolysis (meta-analysis)

Eleven trials - 748 patients included
No evidence for a benefit of thrombolytic therapy

Study	Thrombolysis	Heparin	OR	95% CI
UPET, 1973	10/82	14/78	0.63	0.26 - 1.53
Tibbutt et al, 1974	0/13	1/17	0.41	0.02 - 10.83
Ly et al, 1978	1/14	2/11	0.35	0.03 - 4.42
Dotter et al, 1979	1/15	3/16	0.31	0.03 - 3.36
Marini et al, 1988	0/20	0/10	0.51	0.01 - 27.68
PIOPED, 1990	1/9	0/4	1.59	0.05 - 47.52
Levine et al, 1990	1/33	0/25	2.35	0.09 - 60.24
Dalla-Volta et al, 1992	3/20	1/16	2.65	0.25 - 28.24
Goldhaber et al, 1993	0/46	4/55	0.12	0.01 - 2.35
Jerjes-Sanchez et al, 1995	0/4	4/4	0.01	0.00 - 0.77
Konstantinides et al, 2002	8/118	7/138	1.36	0.48 - 3.87
Total	**25/374**	**36/374**	**0.67**	**0.40 - 1.12**



1y endpoint
Recurrent pulmonary embolism or death

Wan S et al Circulation. 2004;110:744-749

Тромболиза

TABLE 2. Death or Recurrent PE of Thrombolysis Versus Heparin Alone in Randomized Controlled Trials With Inclusion of Patients With Massive PE

	Death/Recurrent PE			
Trial	Thrombolysis	Heparin	OR	95% CI
UPET,[25] 1973	10/82	14/78	0.63	0.26–1.53
Tibutt et al,[26] 1974	0/13	1/17	0.41	0.02– 0.83
Ly et al,[27] 1978	1/14	2/11	0.35	0.03–4.42
Dotter et al,[28] 1979	1/15	3/16	0.31	0.03–3.36
Jerjes-Sanchez,[29] 1995	0/4	4/4	0.01	0.00–0.77
Overall[11]	12/128	24/126	0.45	0.22–0.92

UPET indicates Urokinase in Pulmonary Embolism Trial.

Circulation. 2005;112:e28-e32

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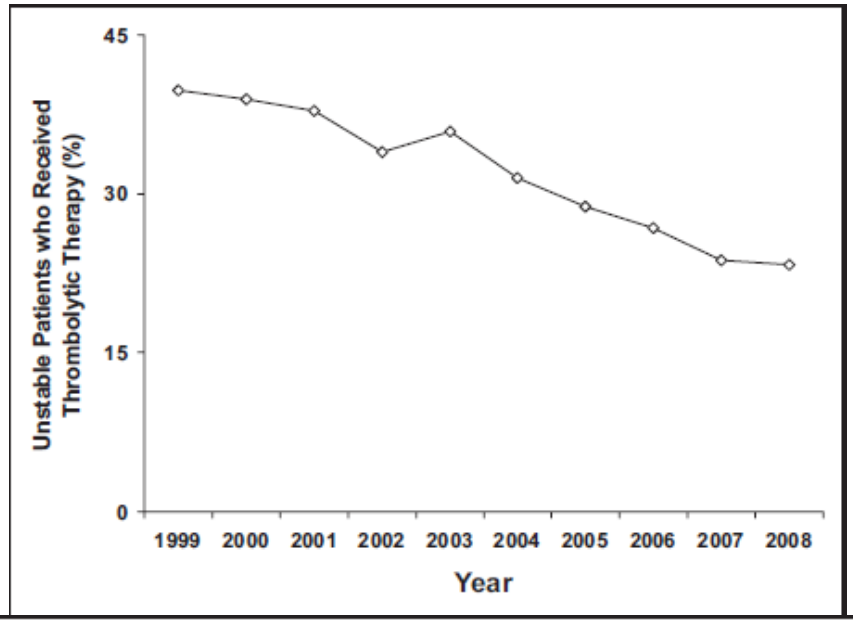
Епидемиологични данни

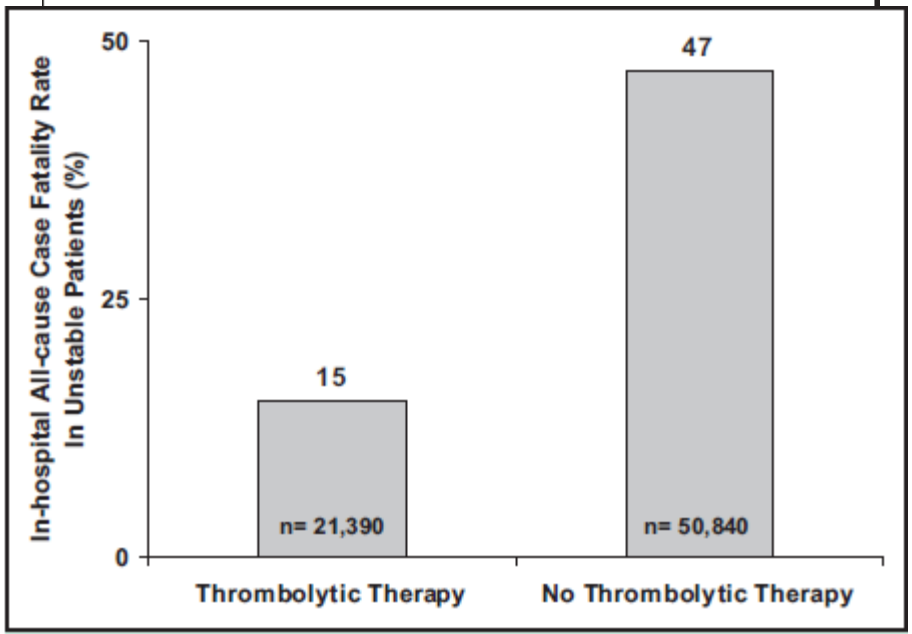
- **USA 1999-2008**

- **2 110 320 дехоспитализирани БТЕ**
- **72 230 (3,4%) нестабилни (шок, апаратна вентилация)**
- **21 390 (30%) фибринолиза**



Фибринолизирани пациенти

- **Обща смъртност RR 0,31 (0,3 – 0,32)**
- *The American Journal of Medicine (2012) 125, 465-470*
- **(0,19-0,22)**

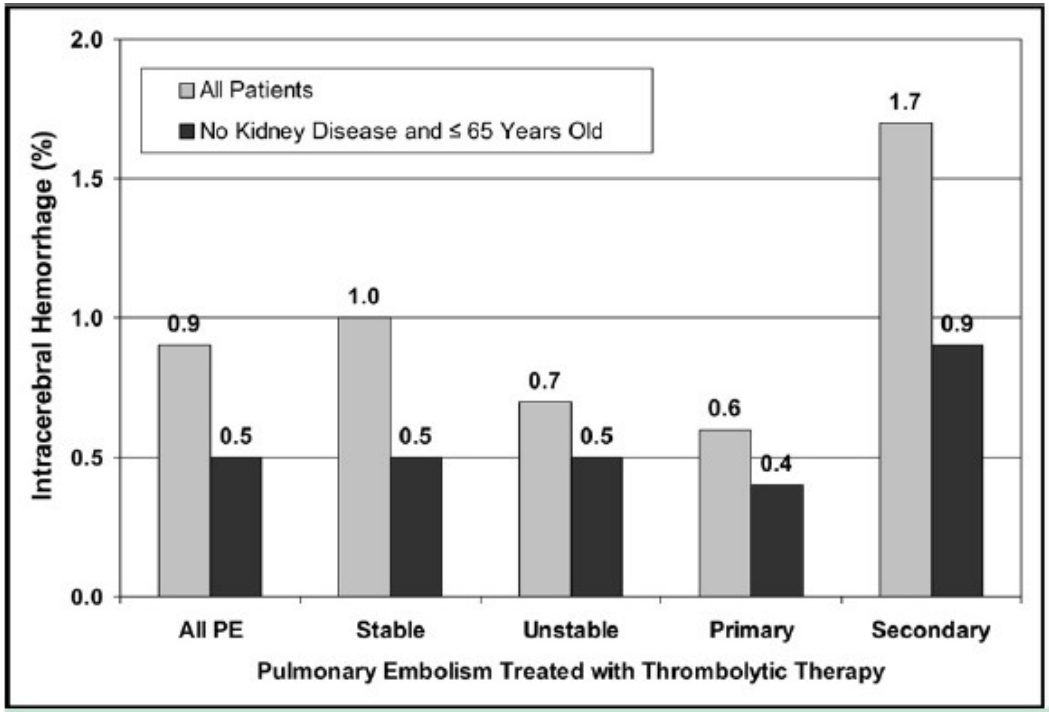


Епидемиологични данни

- **USA 1999-2008**
- **21 390 (30%) фибринолиза**

Фибринолизирани пациенти

- **Интрацеребрална хеморагия при 430 (0,9%)**



The American Journal of Medicine (2012) 125, 465-470

The American Journal of Medicine (2012) 125, 50-56

Риск от кървене
Рандомизирани проучвания

Study	Design	Thrombolytic	Bleeding in thrombolysis group: Major	Bleeding in thrombolysis group: Intracranial / fatal
UPET 1973	P, R	UK (vs. heparin)	37/82	1/82
USPET 1974	P, R	UK vs. SK (no heparin group)	32/113 12/54	0/113 0/54
Levine 1990	P, R	rtPA (vs. heparin)	0/33	0/33
PAIMS-2 1992	P, R	rtPA (vs. heparin)	4/20	2/20
Meyer 1992	P, R	rtPA vs. UK (no heparin group)	7/34 8/29	1/34 1/29
Sors 1994	P, R	2 rtPA regimens (no heparin group)	0/53	0/53
Kanter 1997	meta-analysis (5 studies)	rtPA vs. UK (or vs. heparin)	---	6/312
MAPPET 2002	P, R	rtPA (vs. heparin)	1/118	0/118
Overall			101/536 (19%)	11/536 (2.0%)

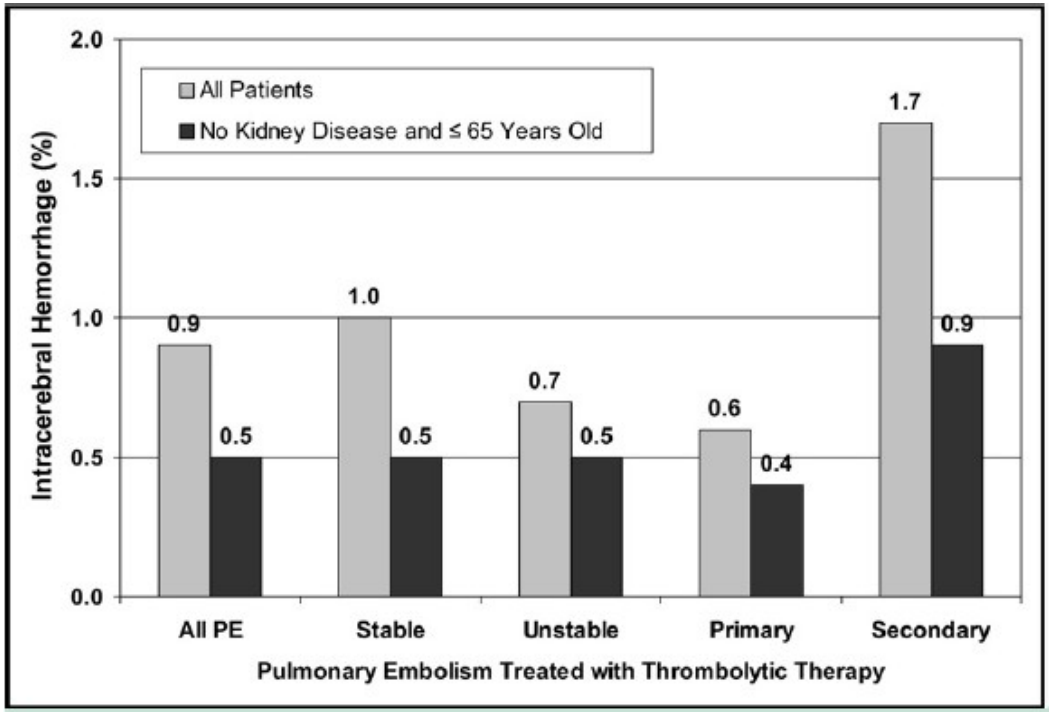
Епидемиологични данни

- **USA 1999-2008**
- **21 390 (30%) фибринолиза**

Фибринолизирани пациенти

- **Интрацеребрална хеморагия при 430 (0,9%)**

Сред нестабилните пациенти неполучили фибринолиза



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емболектомия

Acute pulmonary embolism: a current surgical approach

Antoine Digonnet, Antoine Moya-Plana, Stephane Aubert, Erwan Flecher, Nicolas Bonnet, Pascal Leprince, Alain Pavieand 2007;6:27-29;

21 пациента – 14 в шок (50% от тях с контраиндикации за фибринолиза), и 7 хемодинамично стабилни, с ДК дисфункция.

8 починали – всичките от групата с шок

Сред преживелите – 1 пациент е бил 25 дни на апаратна вентилация, 2 са били с пневмония, 1 с ОБН

Катетърни техники: "Фармакомеханична терапия"

- тромбфрагментация, дистална емобилизация, парциална реканализация и когато е възможно тромбаспирация – частично възстановяване на кръвния ток и увеличаване на контактната повърхност на тромба
- логична стъпка – комбиниране с фибринолиза и хепарин

	Clinical success (a)	Studies > 80% lytics	Studies < 80% lytics	Major complications	Minor complications
N = 594	86%	91%	83%	2%	8%

(a) Defined as stabilization of hemodynamic, resolution of hypoxia and survival

Kuo WT et al J Vasc Interv Rad J 2009;20:1431-1440

Heparin vs Lysis (в лечението на масивния БТЕ)

- Фибринолиза >> Heparin
  - Възстановяване на белодробната перфузия @ 24 ч
    - 30-35% ↓ фибринолиза
      - Интервенционни т-ки по-добри? Вероятно, но недоказано все още...
    - 0.05% heparin
    - Но, и при двете 65-70% @ 7 дни
  - Рекурентен БЕ/Смърт
    - 19% heparin
    - 9.4% фибринолиза
  - ??% интервенционални техники
    - *Значима роля*, особено ако докажат по-голяма безопасност

Wan et al. *Circulation.* 2004; 110: 744-749.

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

Guidelines on the diagnosis and management of acute pulmonary embolism

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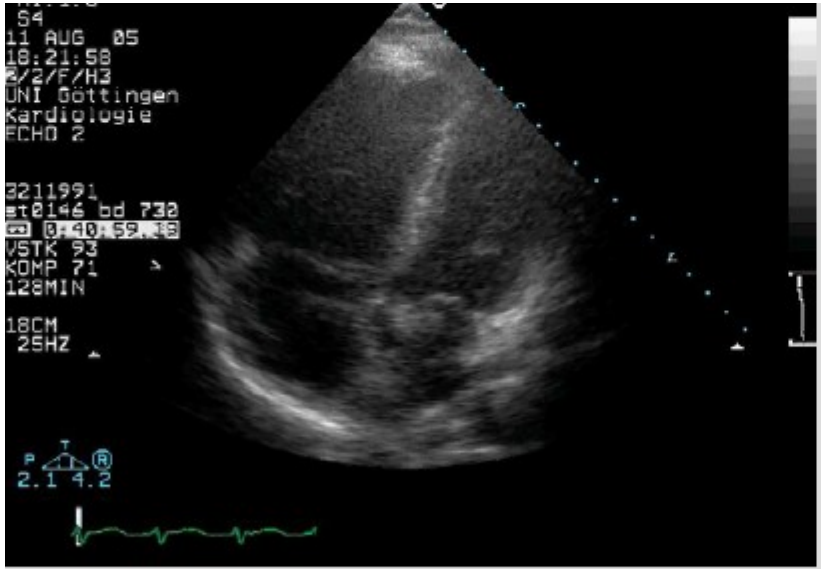
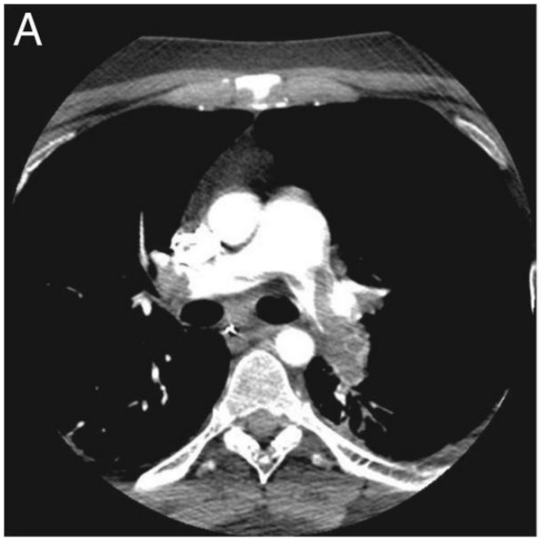
NON HIGH	Intermediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

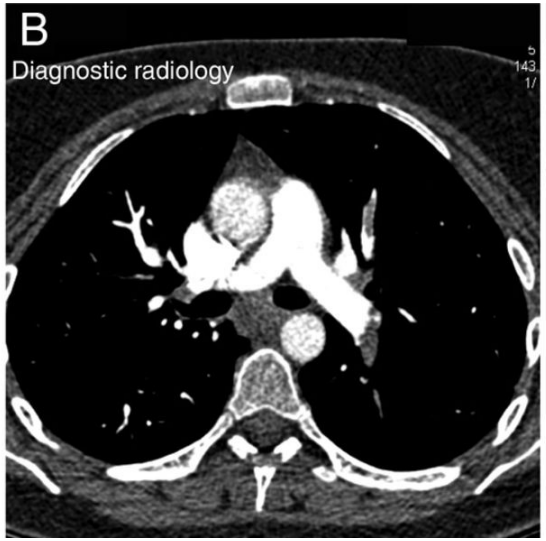
Дилатация на ДК

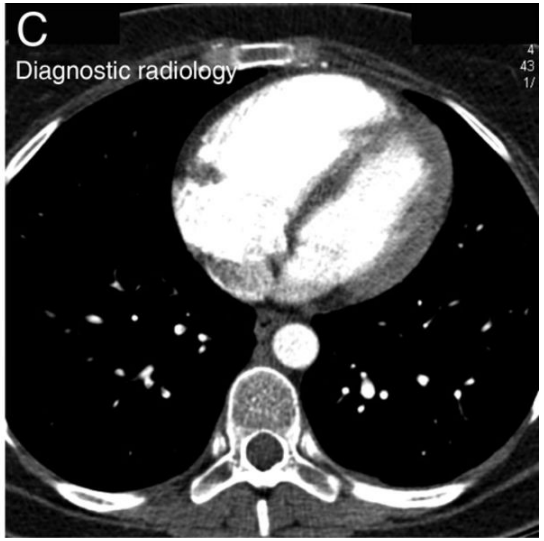


Echo criteria

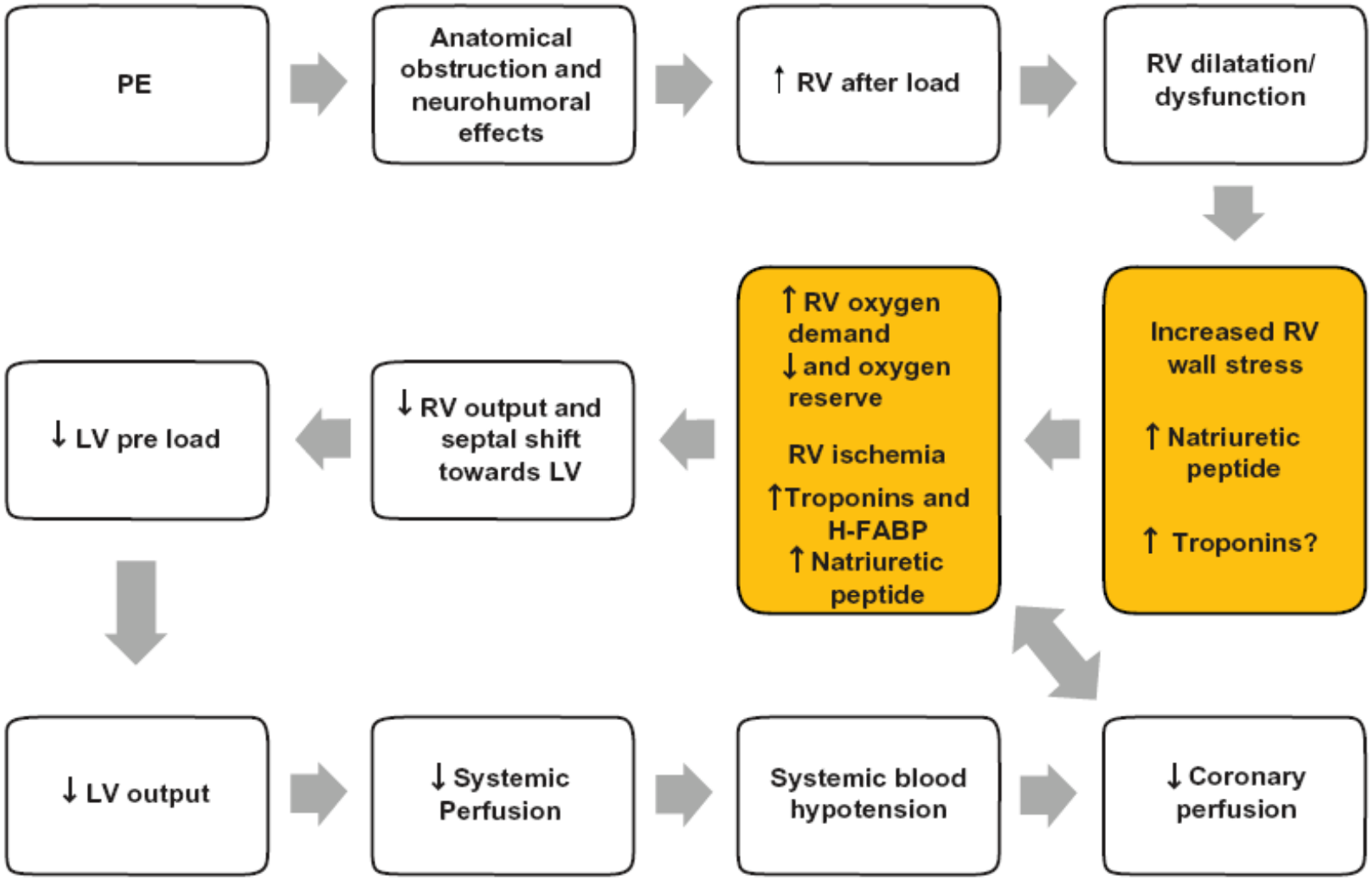
- RV dilatation (RV>LV, or RVEDD >30 mm)
- RV free wall hypokinesia
- Paradoxical septal wall
- Pulmonary hypertension (RV-RA gradient >30 mm Hg, or pulmonary acceleration time <80 ms)







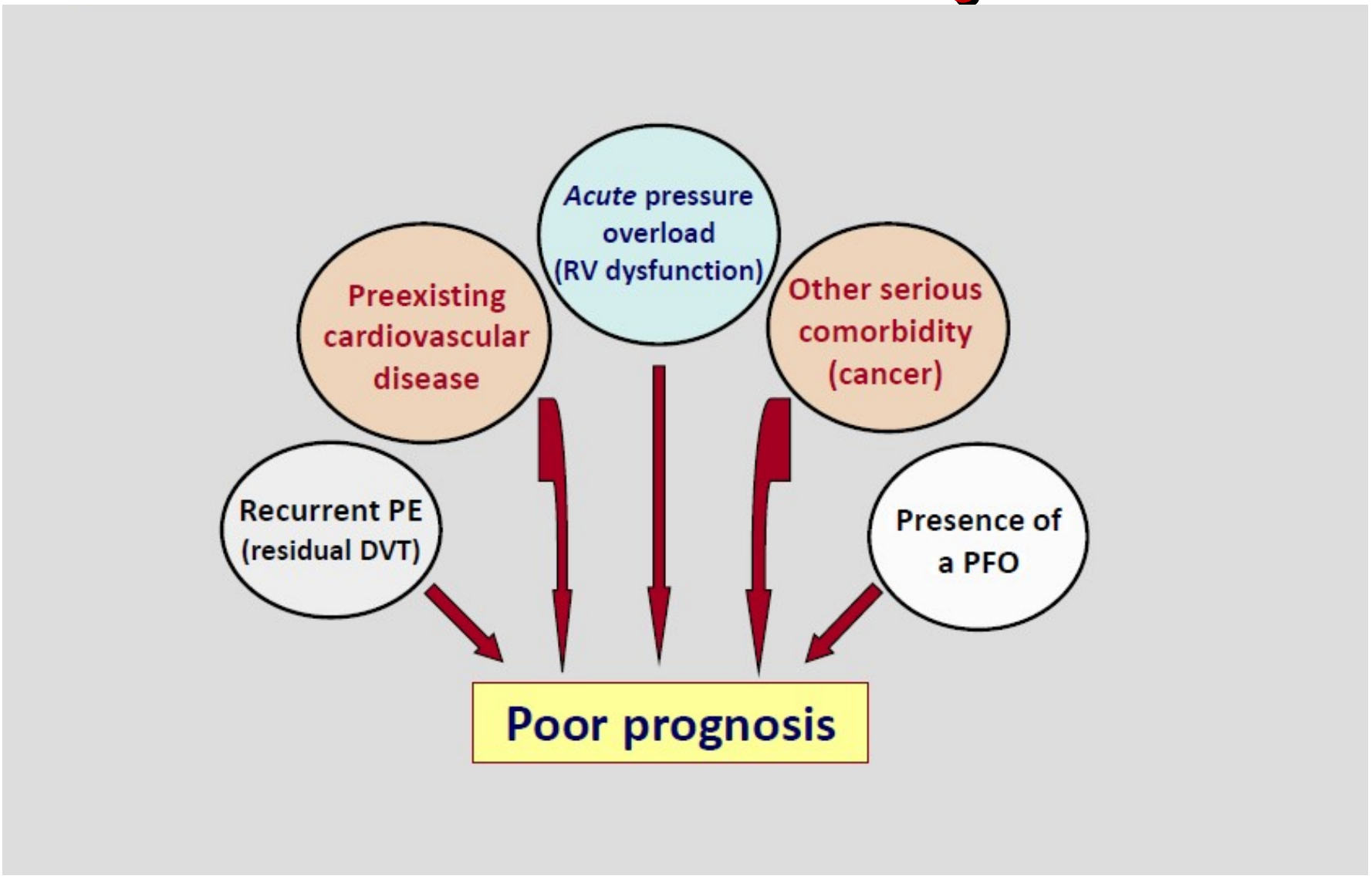
NPV 60%,PPV 58%


PE
Anatomical obstruction and neurohumoral effects
↑ RV after load
RV dilatation/ dysfunction
Increased RV wall stress
↑ Natriuretic peptide
↑ Troponins?
↑ RV oxygen demand
↓ and oxygen reserve
RV ischemia
↑Troponins and H-FABP
↑ Natriuretic peptide
↓ RV output and septal shift towards LV
↓ LV pre load
↓ LV output
↓ Systemic Perfusion
Systemic blood hypotension
↓ Coronary perfusion

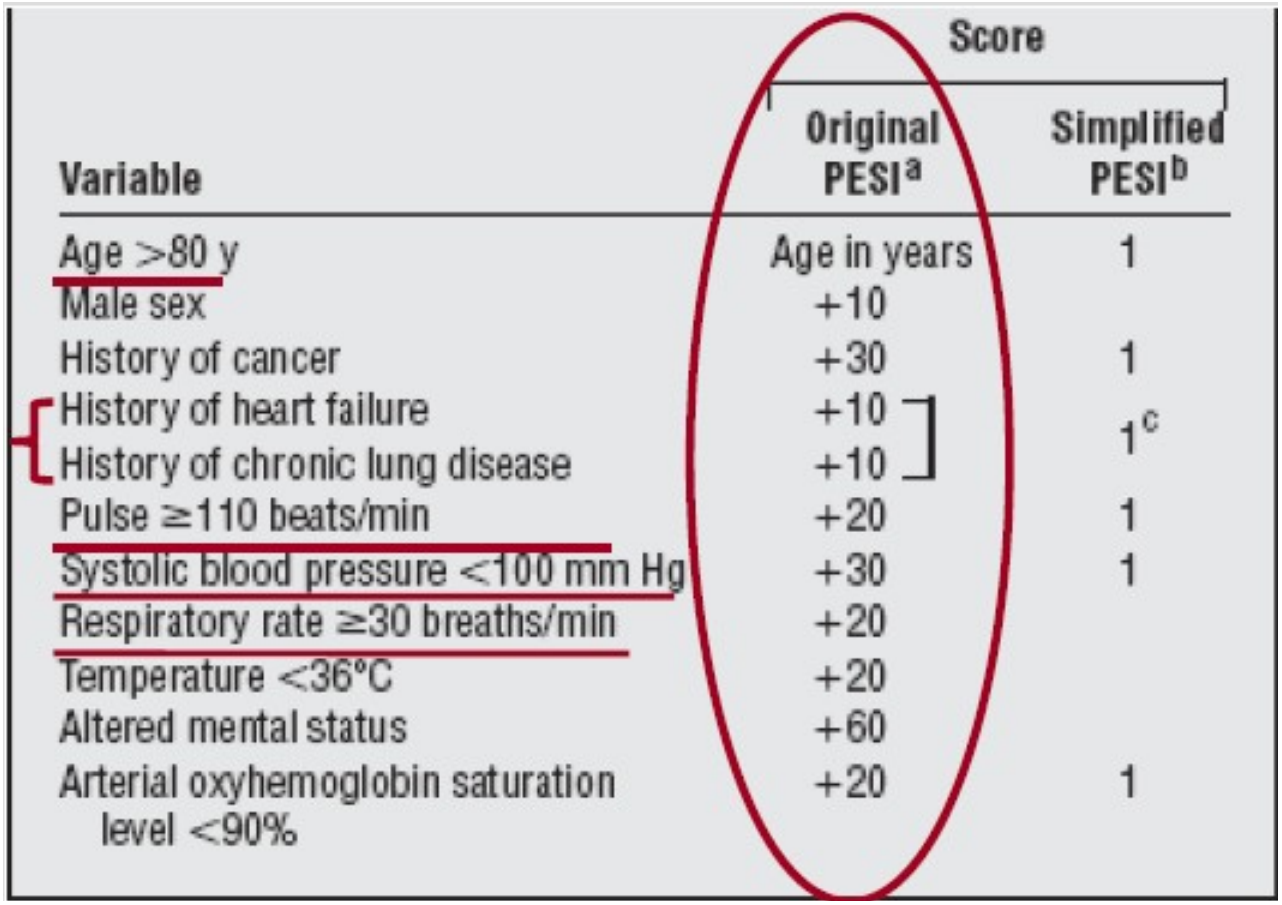
BNP&cTn – ниска позитивна предсказваща стойност

Author	Pts (n)	Marker	Ref. value*	Positive (%)	NPV (%)	PPV (%)
Giannitsis, 2000	56	Trop T	**0.10**	32	**97**	44
Konstantinides, 2002	106	Trop I	**0.07**	41	**98**	14
Konstantinides, 2002	106	Trop T	**0.04**	37	**97**	12
Janata, 2003	106	Trop T	**0.09**	11	**99**	34
Pruszczyk, 2003	64	Trop T	**0.01**	50	**100**	25

Други индикатори за неблагоприятна прогноза в



Pulmonary Embolism Severity Index



Variable	Score: Original PESI[a]	Score: Simplified PESI[b]
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation level <90%	+20	1

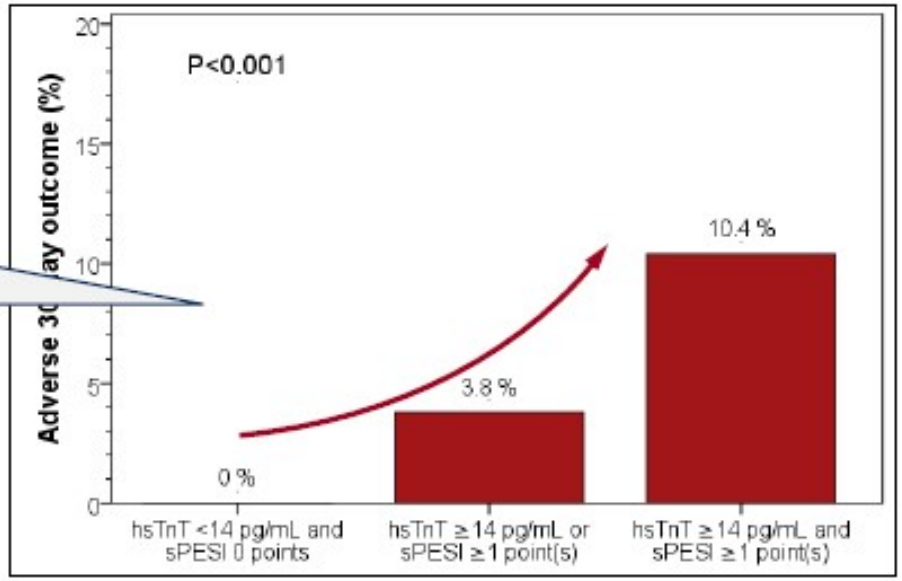
Нисък риск – 0 (30-32%)

Висок риск ≥1

sPESI and hsTnT

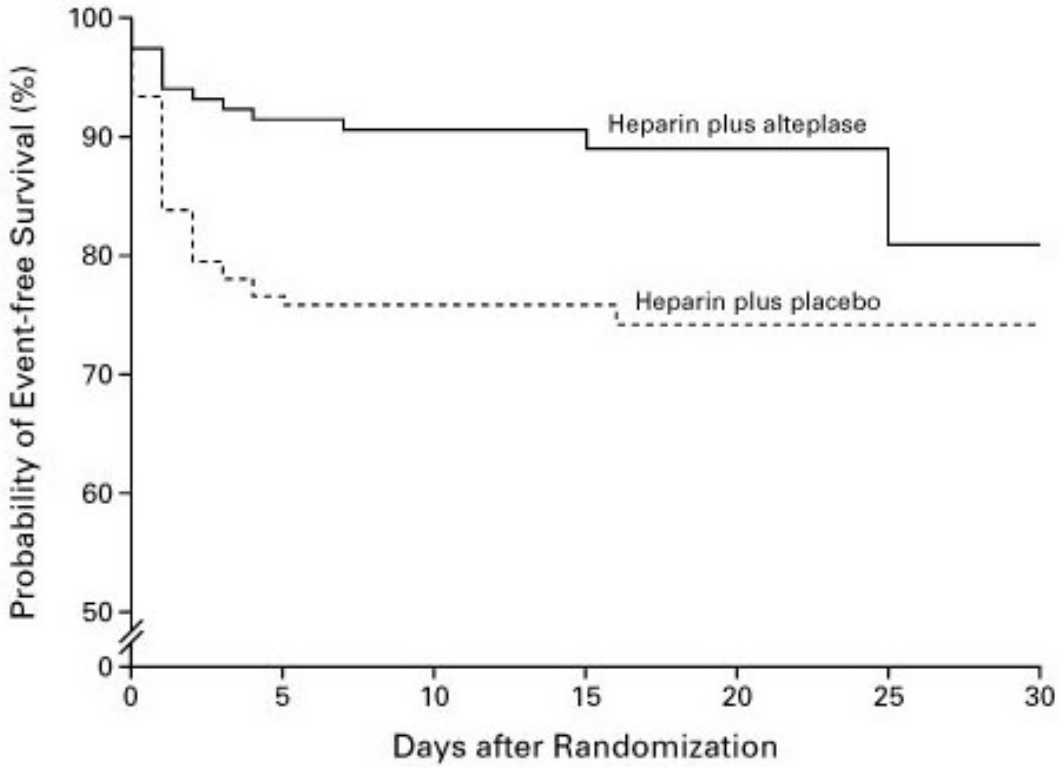
	AUC	95% CI	Sens.	Spec.	PPV	NPV
hsTnT ≥14 pg/ml	0.73	0.65-0.82	0.87	0.42	0.09	0.98
sPESI ≥1 point(s)	0.67	0.59-0.75	0.94	0.40	0.09	0.99
hsTnT ≥14 pg/ml *and* sPESI ≥1 point(s)	0.69	0.60-0.77	1.00	0.26	0.08	1.00

None of the 127 patients (24%) with sPESI of 0 points *and* hsTnT <14 pg/ml had an adverse 30-day outcome.



Lankeit M, Circulation 2011

Pulmonary Embolism-3 Trial: Heparin plus Alteplase Compared with Heparin Alone in Patients with Submassive Pulmonary Embolism



No. at Risk							
Heparin plus alteplase	118	107	96	57	26	11	6
Heparin plus placebo	137	105	87	53	24	3	2

Konstantinides et al. N Engl J Med 2002; 347:1143-115

Heparin vs Lysis (субмасивен БТЕ)

- Смъртност
  - 3.0% Heparin
  - <1.0% IV lysis
    - Много трудно за интервенционалните т-ки да докажат предимство
- По-добре @ *<u>дългосрочно проследяване</u>*
  - Персистираща RV дисфункция
  - Хронична тромбемболична ПХ
  - Качество на живот

ORIGINAL INVESTIGATION

Association of Persistent Right Ventricular Dysfunction at Hospital Discharge After Acute Pulmonary Embolism With Recurrent Thromboembolic Events

Stefano Grifoni, MD; Simone Vanni, MD; Simone Magazzini, MD; Iacopo Olivotto, MD; Alberto Conti, MD; Maurizio Zanobetti, MD; Gianluca Polidori, MD; Filippo Pieralli, MD; Nazerian Peiman, MD; Cecilia Becattini, MD; Giancarlo Agnelli, MD

Background: In patients with acute pulmonary embolism, right ventricular dysfunction (RVD) on hospital admission is a predictor of adverse short-term clinical outcome. The aim of this study was to evaluate the prognostic

M

ence of 1 or more of the following: right ventricular dilation (without hypertrophy), paradoxical septal systolic motion, and Doppler evidence of pulmonary hypertension. Patients were followed up at 2, 6, and 12 months and yearly thereafter. The primary end point was symptomatic, recurrent fatal or nonfatal VTE.

Results: Patients were categorized as those (1) without RVD (155 patients [51.5%]), (2) with RVD regression (RVD on admission but not at discharge; 87 patients [28.9%]), and (3) with persistent RVD (RVD on admission and at

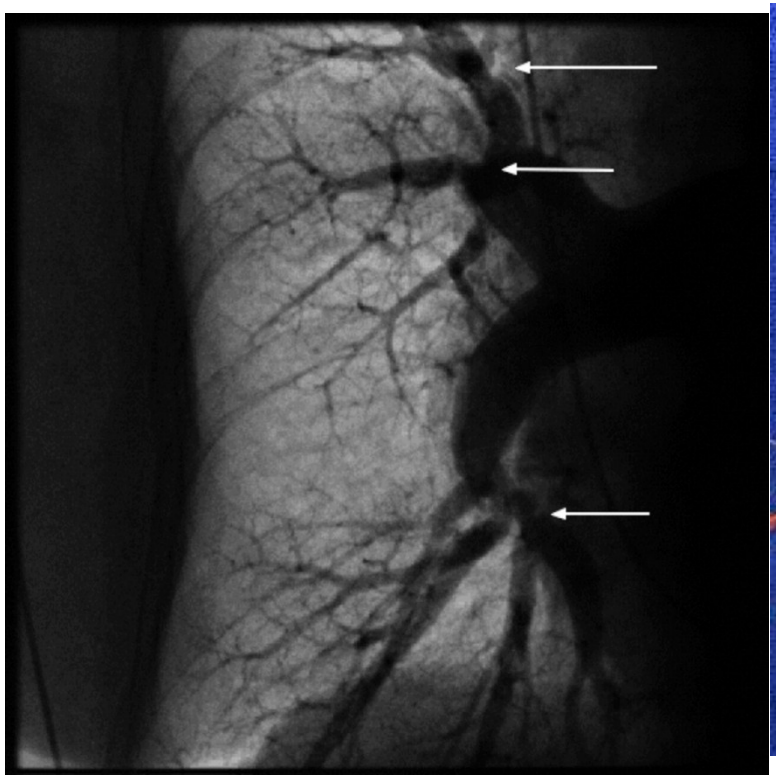
Conclusion: Persistent RVD at hospital discharge after an acute pulmonary embolism is associated with recurrent VTE.

Arch Intern Med. 2006;166:2151-2156

Смъртност дължаща се на БЕ – 3 год проследяване:

- 13.3% персистираща ДК дисфункция
- 4.4% без ДК дисфункция

ДСК (2009 г.) - налягания в артерия пулмоналис 77/22/42 mmHg, сърдечен индекс 2.6 l/min/m^2, БСС 580 dyn/s/cm-5 (1169 dyn/s/cm-5/m2).



Контролна ДСК 3 месеца след операцията - налягане в артерия пулмоналис 54/12/31 mmHg, минутен обем 6,4 l/min, БСС 179 dyn/s/cm-5

Контролна ДСК 3 години след операцията - налягане в артерия пулмоналис 42/12/25 mmHg,

Пулмоналнa хипертония и субмасивен БТЕ

- N = 200
  - 118 лекувани с heparin
  - 21 влошена хемодинамика - фибринолиза
  - F/U = 180 преживели

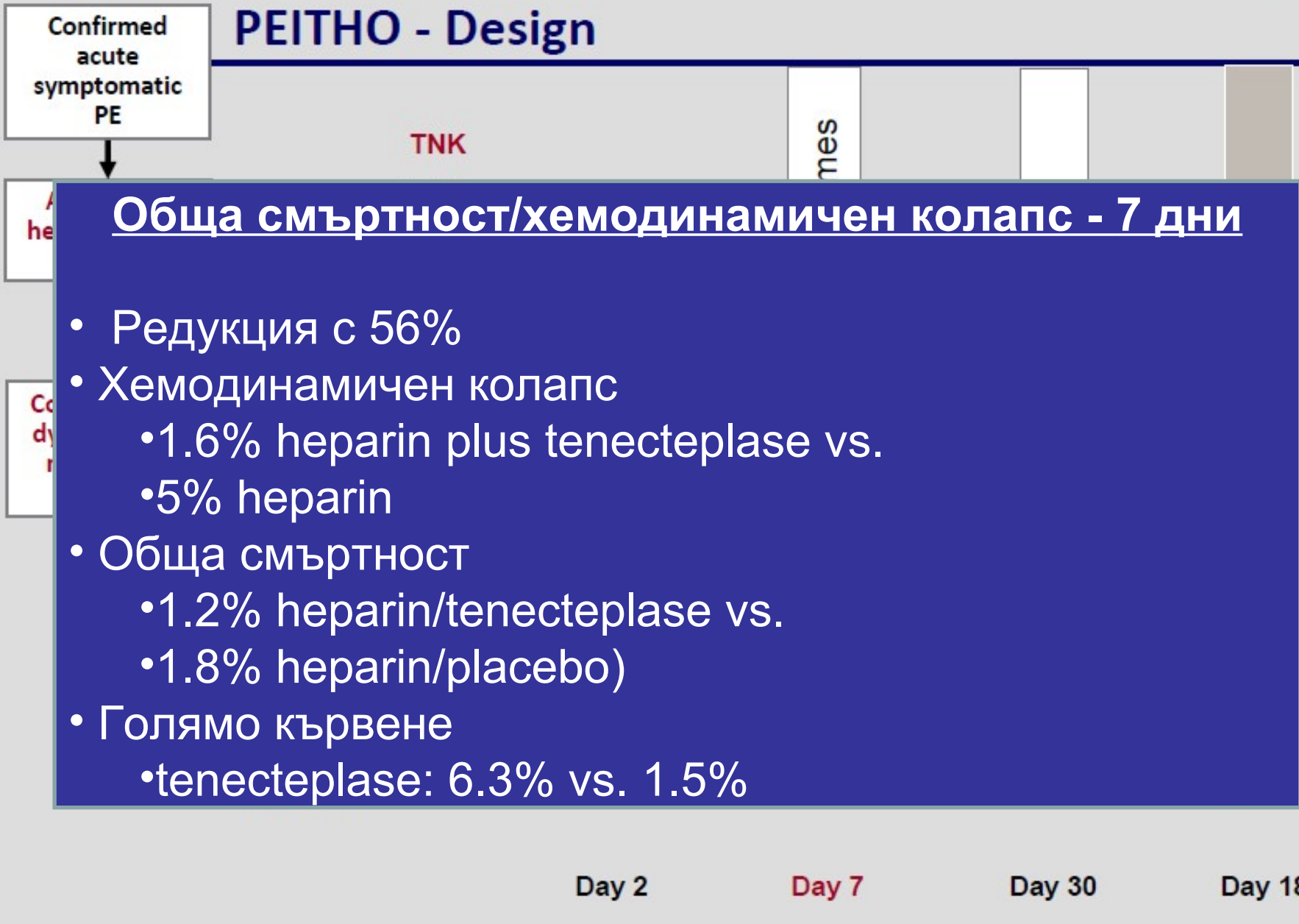
	Heparin	Лиза
• RVSP > 40 mmHg диагноза	35%	61%
• 6 mo RVSP > изходна	27%	0%
• 6 mo NYHA class > 3	46%	


Circulation

Препоръки за катетърна емболектомия и фрагментация при остър БЕ

Recommendations	Level of Evidence
Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis	**Class IIa; Level of Evidence C**
Catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain unstable after receiving fibrinolysis	**Class IIa; Level of Evidence C**
For patients with massive PE who cannot receive fibrinolysis or who remain unstable after fibrinolysis, it is reasonable to consider transfer to an institution experienced in either catheter embolectomy or surgical embolectomy if these procedures are not available locally and safe transfer can be	**Class IIa; Level of Evidence C**
Either catheter embolectomy or surgical embolectomy may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory failure, severe RV dysfunction,	**Class IIb; Level of Evidence C**
Catheter embolectomy and surgical thrombectomy are not	**Class III;**

PEITHO - Design

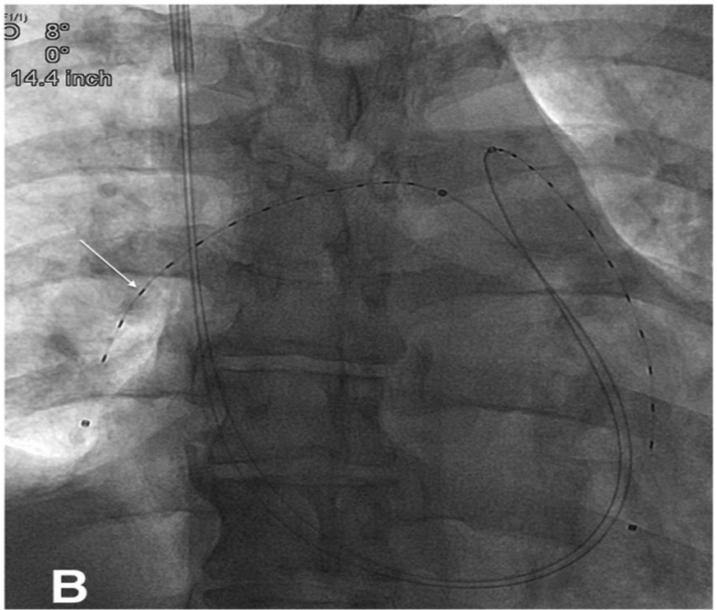


Обща смъртност/хемодинамичен колапс - 7 дни

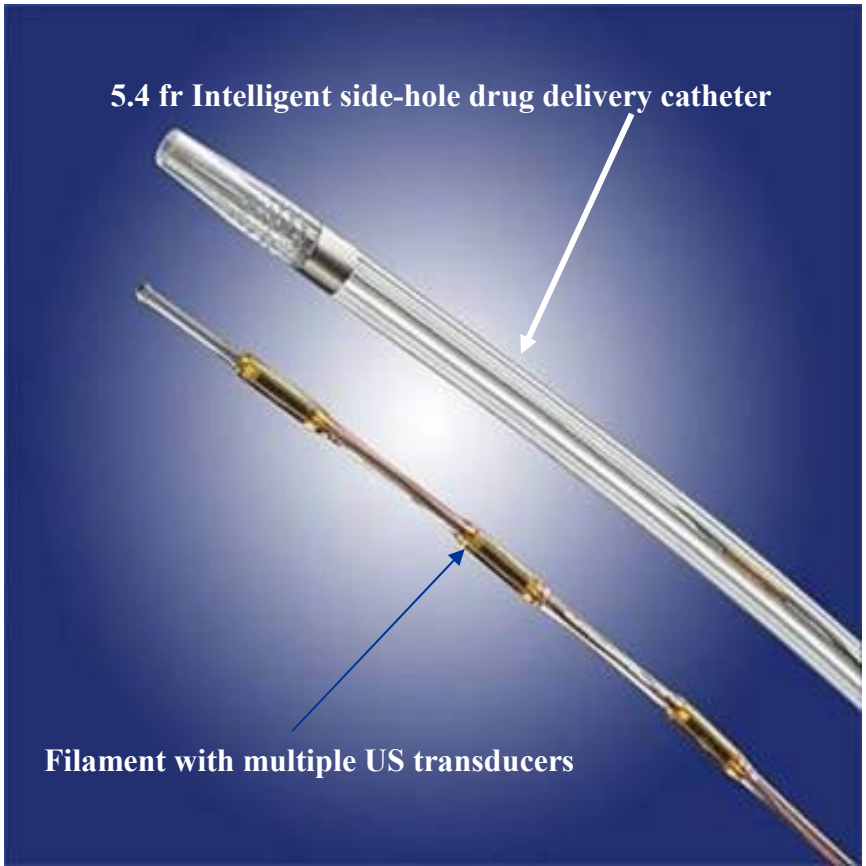
- Редукция с 56%
- Хемодинамичен колапс
  - 1.6% heparin plus tenecteplase vs.
  - 5% heparin
- Обща смъртност
  - 1.2% heparin/tenecteplase vs.
  - 1.8% heparin/placebo)
- Голямо кървене
  - tenecteplase: 6.3% vs. 1.5%

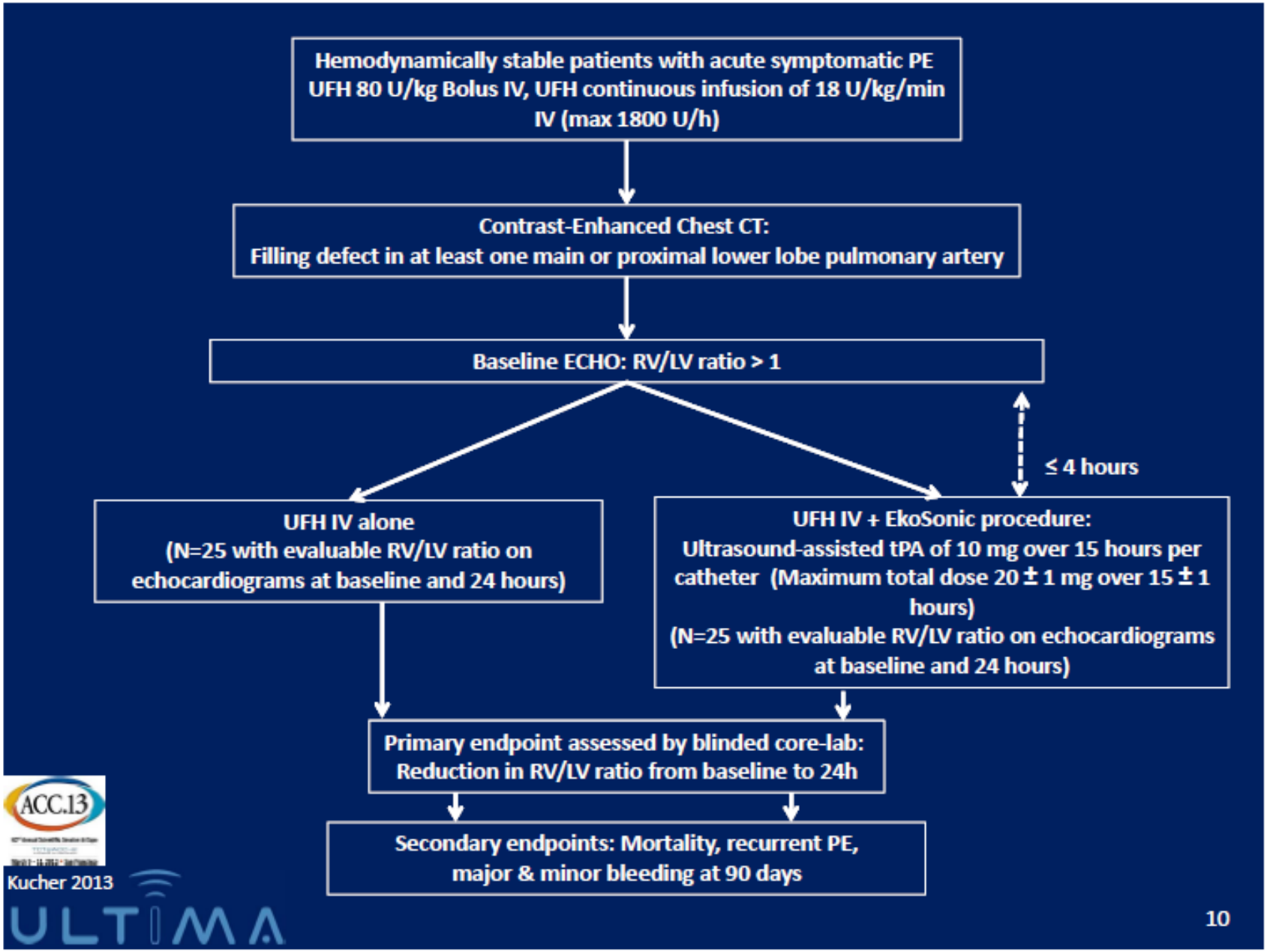
S Konstantinides for the PEITHO Steering Committee. Am Heart J 2012;163:33-38.e1

The Ekosonic Endovascular System

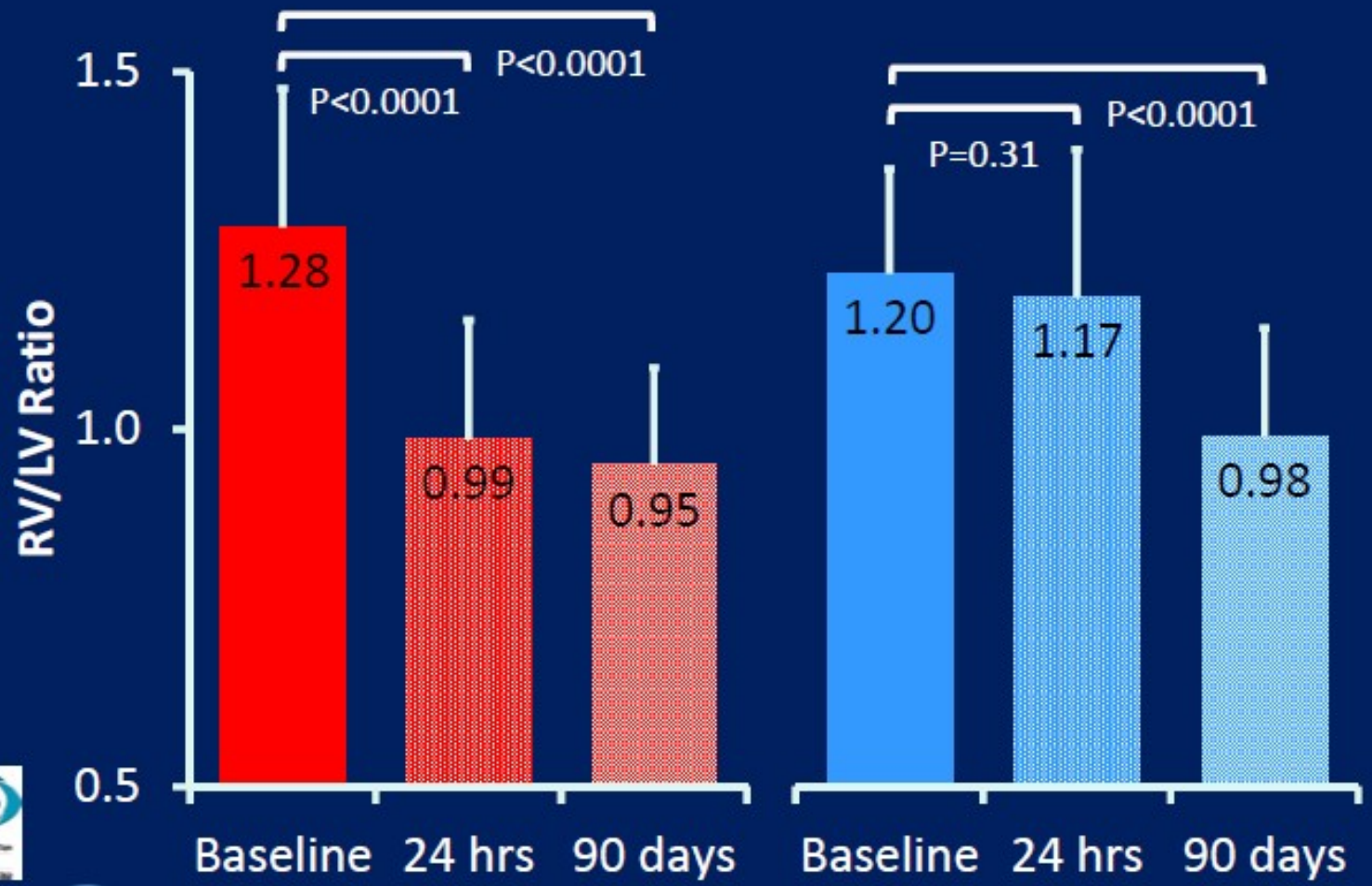


Подаденият нискоенергиен УЗ дисоциира фибриновите нишки и позволява по-ефективна тромболиза с по-ниска доза




Hemodynamically stable patients with acute symptomatic PE
UFH 80 U/kg Bolus IV, UFH continuous infusion of 18 U/kg/min IV (max 1800 U/h)
Contrast-Enhanced Chest CT:
Filling defect in at least one main or proximal lower lobe pulmonary artery
Baseline ECHO: RV/LV ratio > 1
≤ 4 hours
UFH IV alone
(N=25 with evaluable RV/LV ratio on echocardiograms at baseline and 24 hours)
UFH IV + EkoSonic procedure:
Ultrasound-assisted tPA of 10 mg over 15 hours per catheter (Maximum total dose 20 ± 1 mg over 15 ± 1 hours)
(N=25 with evaluable RV/LV ratio on echocardiograms at baseline and 24 hours)
Primary endpoint assessed by blinded core-lab:
Reduction in RV/LV ratio from baseline to 24h
Secondary endpoints: Mortality, recurrent PE, major & minor bleeding at 90 days
ACC.13
Kucher 2013
ULTIMA
10

RV/LV ratio (echo)

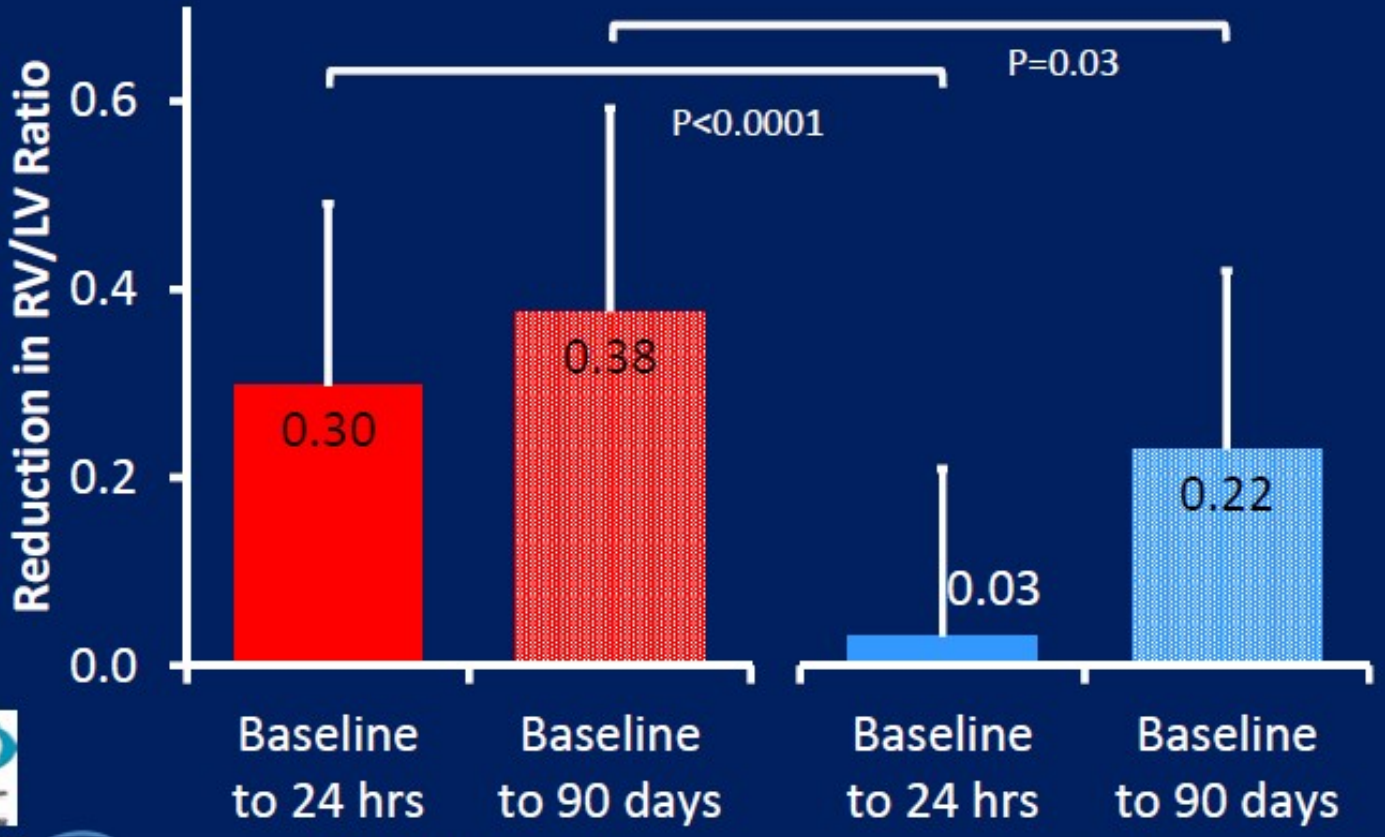


ACC.13

Kucher 2013

ULTIMA

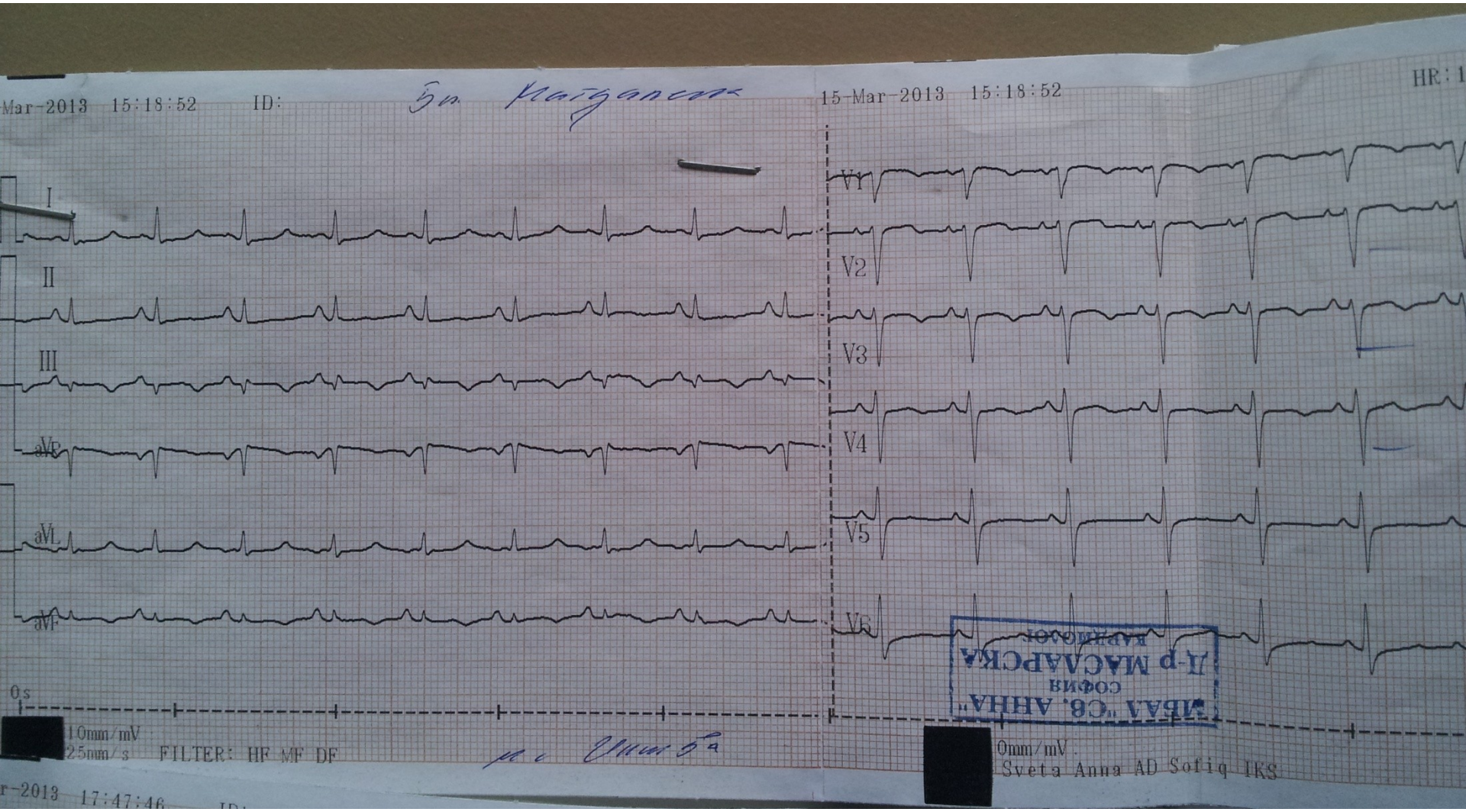
Primary endpoint: Reduction in RV/LV ratio (echo)



ACC.13

Kucher 2013

ULTIMA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I
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HR:
V1
V2
V3
V4
V5
V6
0mm/mV
Sveta Anna AD Sofiq IKS

	Изходни	Крайни
Сърдечна честота	110	84
O2 сатурация	76	91
Налягане в АР	73/38/49	55/21/32
Системно АН	102/62	122/76

Ако при съмнение за масивен или субмасивен БТЕ възприемем подход като при ОМИ диагнозата ще се постави по-рано и преживяемостта ще се увеличи?

Acute Myocardial Infarction	Pulmonary Embolism
Highly prevalent	Highly prevalent
High mortality %	High mortality %
Pathways are clear	Pathways
10 mins ECG 30 mins lytics 60 mins PCI	?????

Получените резултати подкрепят агресивната интервенционална терапия на острия масивен и при определена пропорция пациенти със субмасивен белодробен емболизъм

Сърдечната катетеризационна лаболатория разполага с всичко което е необходимо за провеждане на интервенцията

Цена и време – подобни на тези за провеждане на PTCA при ACS