Fibrinolytická léčba

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Fibrinolytická léčba

- rozdělení fibrinolytik
- FL - STEMI
- FL - ischemický ictus
- FL - plicní embolie

- lokální FL (intraarteriální, nitrožilní)
- FL u srdeční zástavy
- FL u trombózy mechanické chlopně
- intrapleurální FL

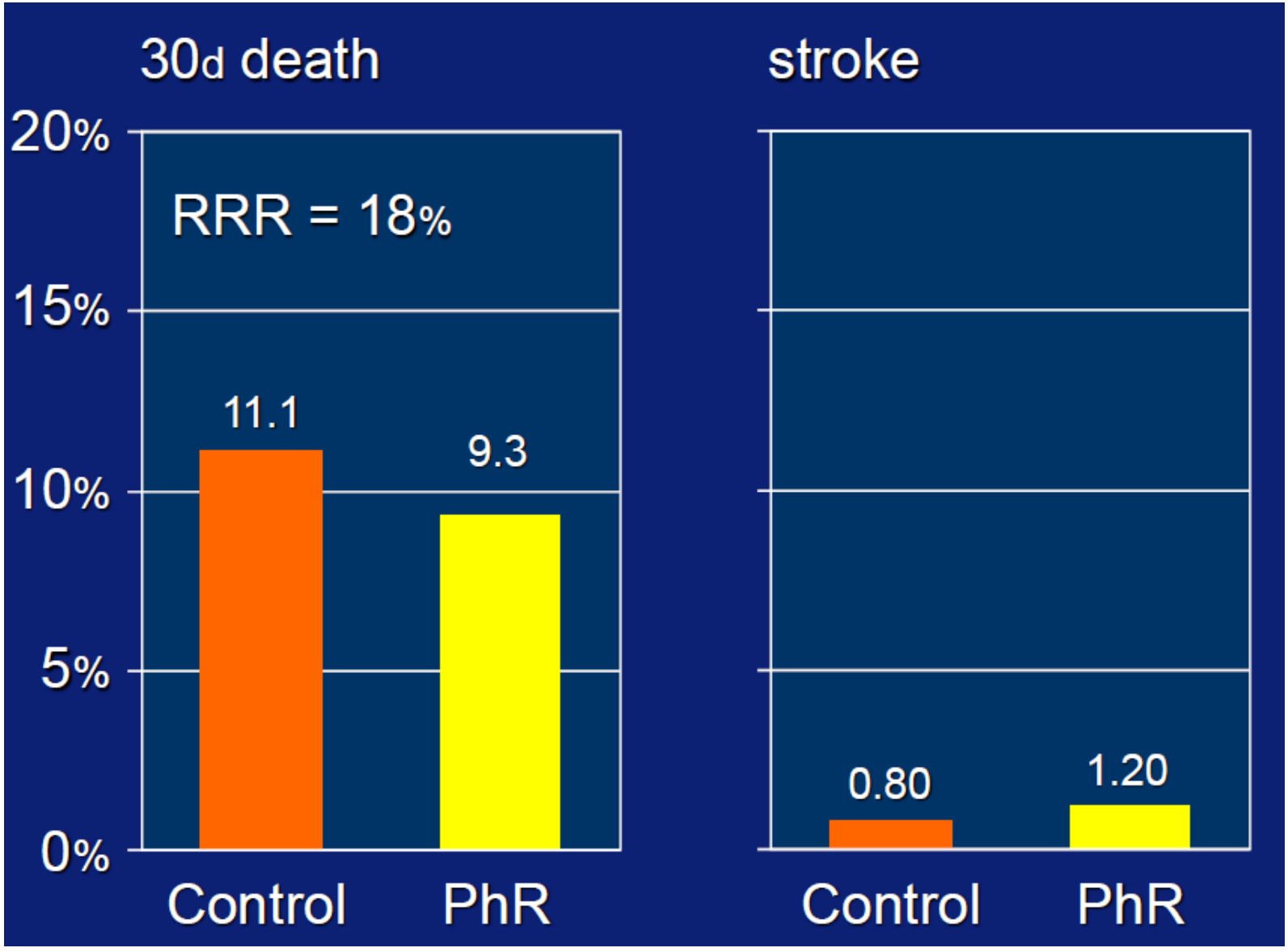
Rozdělení trombolytik dle generací (selektivita k fibrinu)

1. streptokináza, urokináza , anistrepláza

2. tkáňový aktivátor plasminogenu (altepláza, tPA), prourokináza

3. tenekteplá za (TNK-tPa), retepláza, lanotepláza, desmotepláza

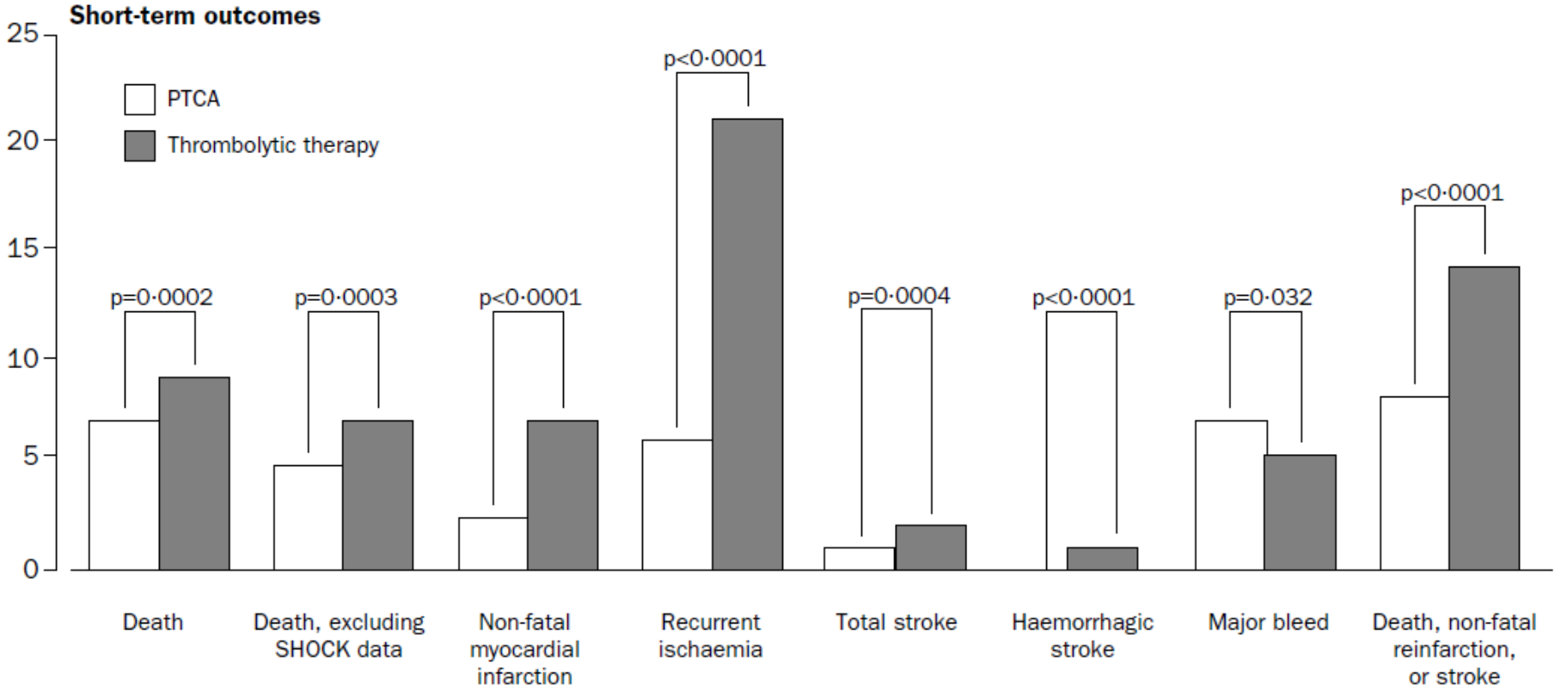
STEMI: 80´s - FTT metaanalysis
lytics vs. control (9 trials, > 56 000 pts)



Reperfusion therapy choices ?

Is lysis an alternative to pPCI in the first place?

Keeley, Lancet 2003;361:13



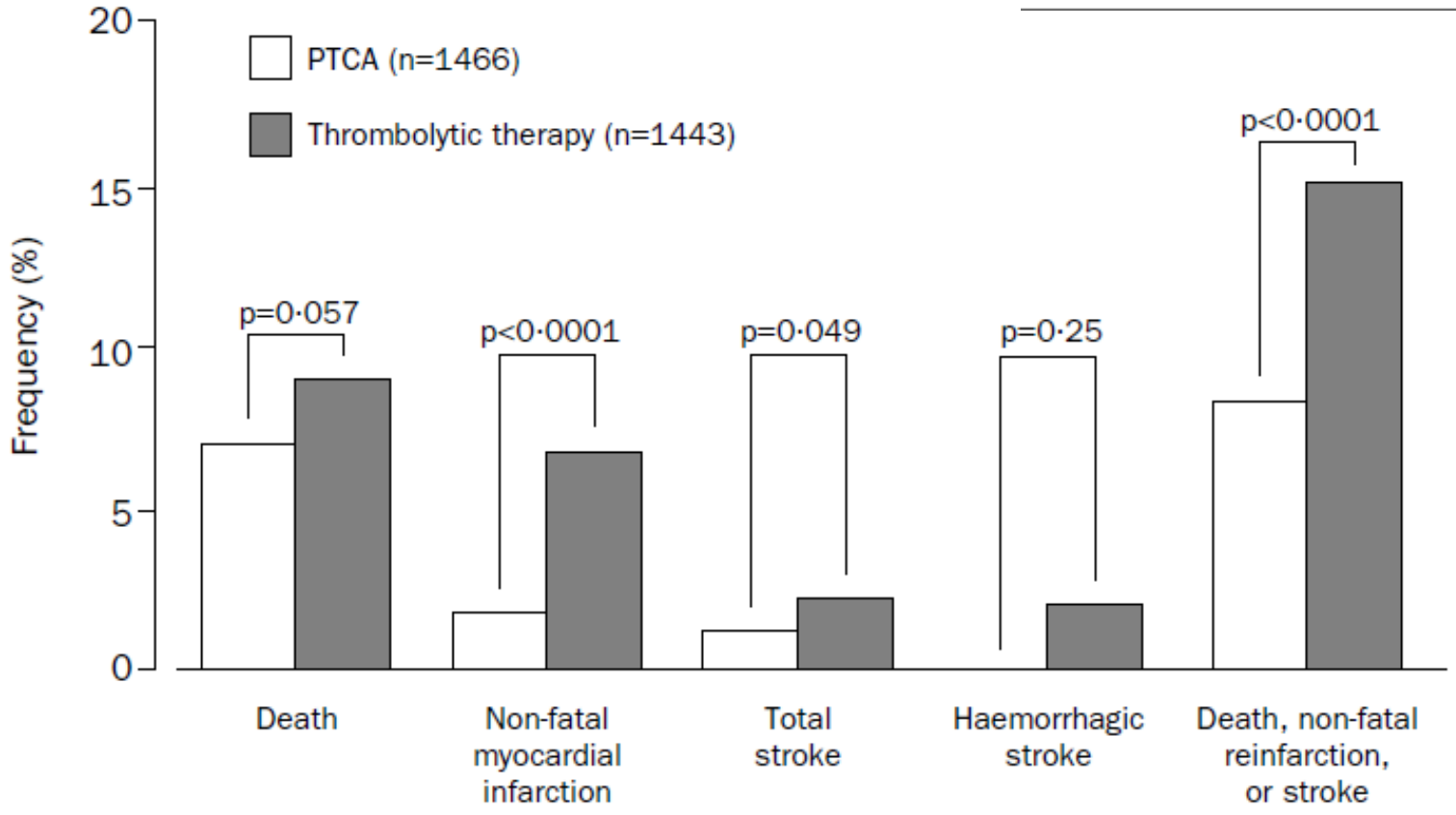
23 studies, 7739 thrombolytic-eligible patients with STEMI to primary PTCA (n=3872) or FL (n=3867).
Streptokinase – 8 trials (n=1837), fibrin-specific agents – 15 trials (n=5902).

Reperfusion therapy

Is lysis an alternative for transfer for pPCI ?

Transfer for primary PCI vs **on-site** lysis meta-analysis

Keeley, Lancet 2003;361:13



*LIMI, Prague I & II, Air PAMI, DANAMI-2

The NEW ENGLAND JOURNAL of MEDICINE

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Facilitated PCI in Patients with ST-Elevation Myocardial Infarction

Stephen G. Ellis, M.D., Michal Tendera, M.D., Mark A. de Belder, M.D., Ad J. van Boven, M.D., Petr Widimsky, M.D., Luc Janssens, M.D., H.R. Andersen, M.D., Amadeo Betriu, M.D., Stefano Savonitto, M.D.,

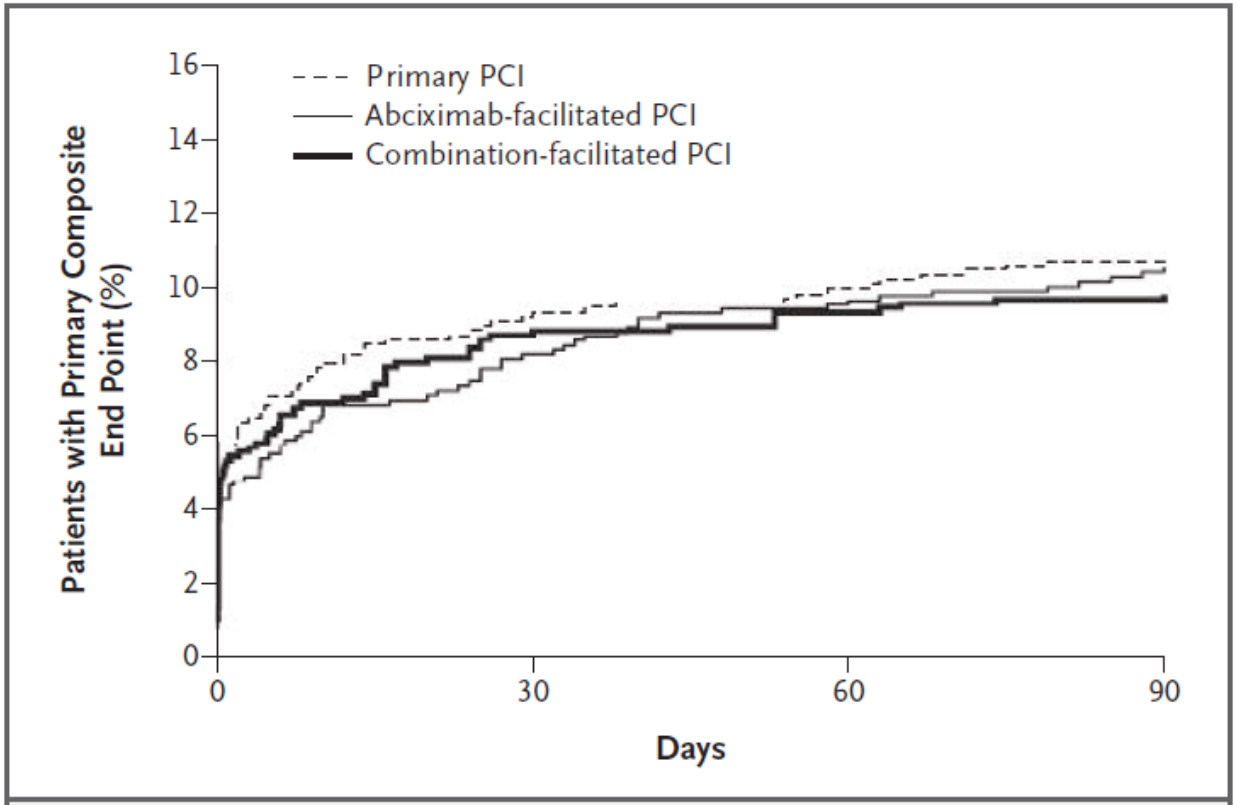
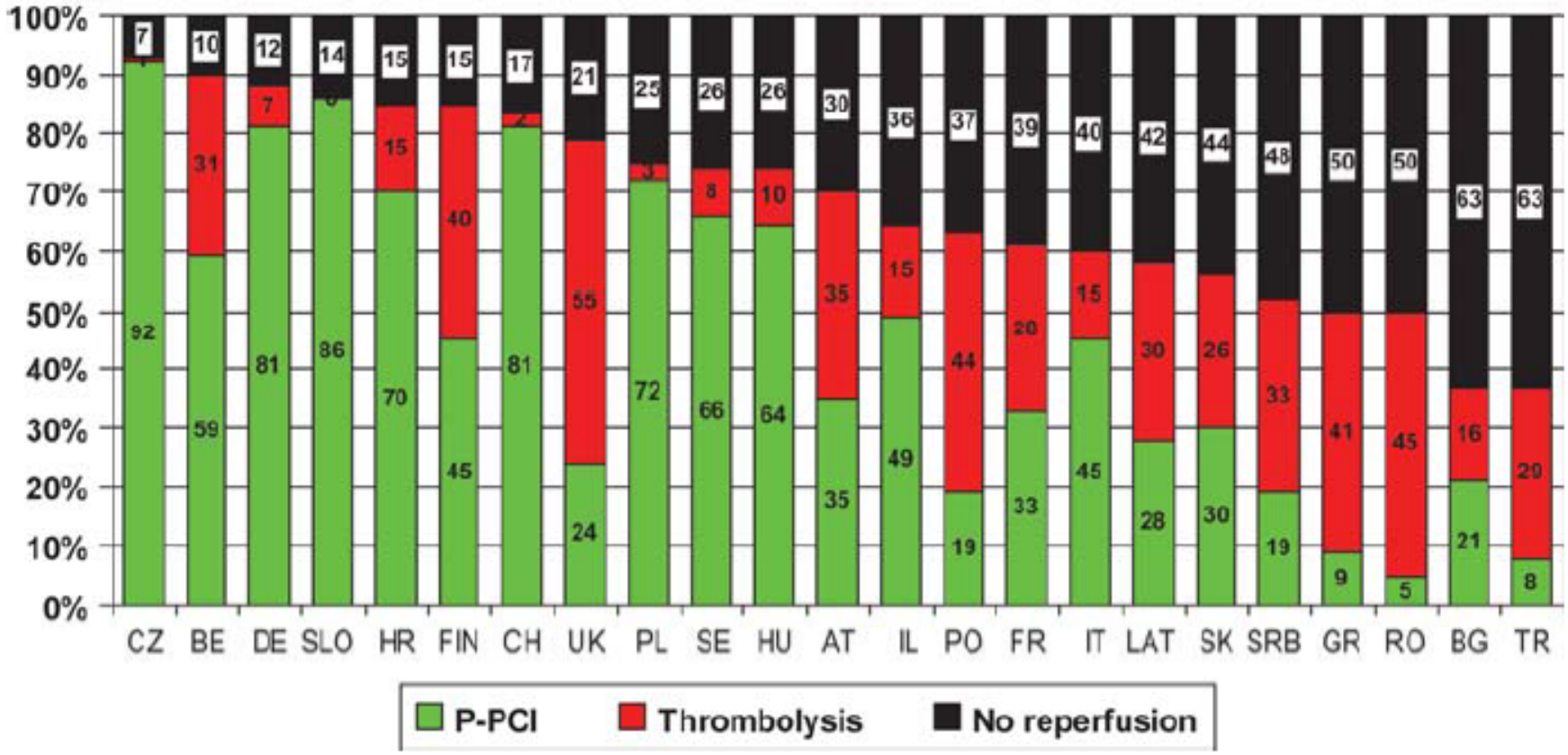


Figure 3. Kaplan–Meier Estimates of the Proportion of Patients with the Composite End Point.

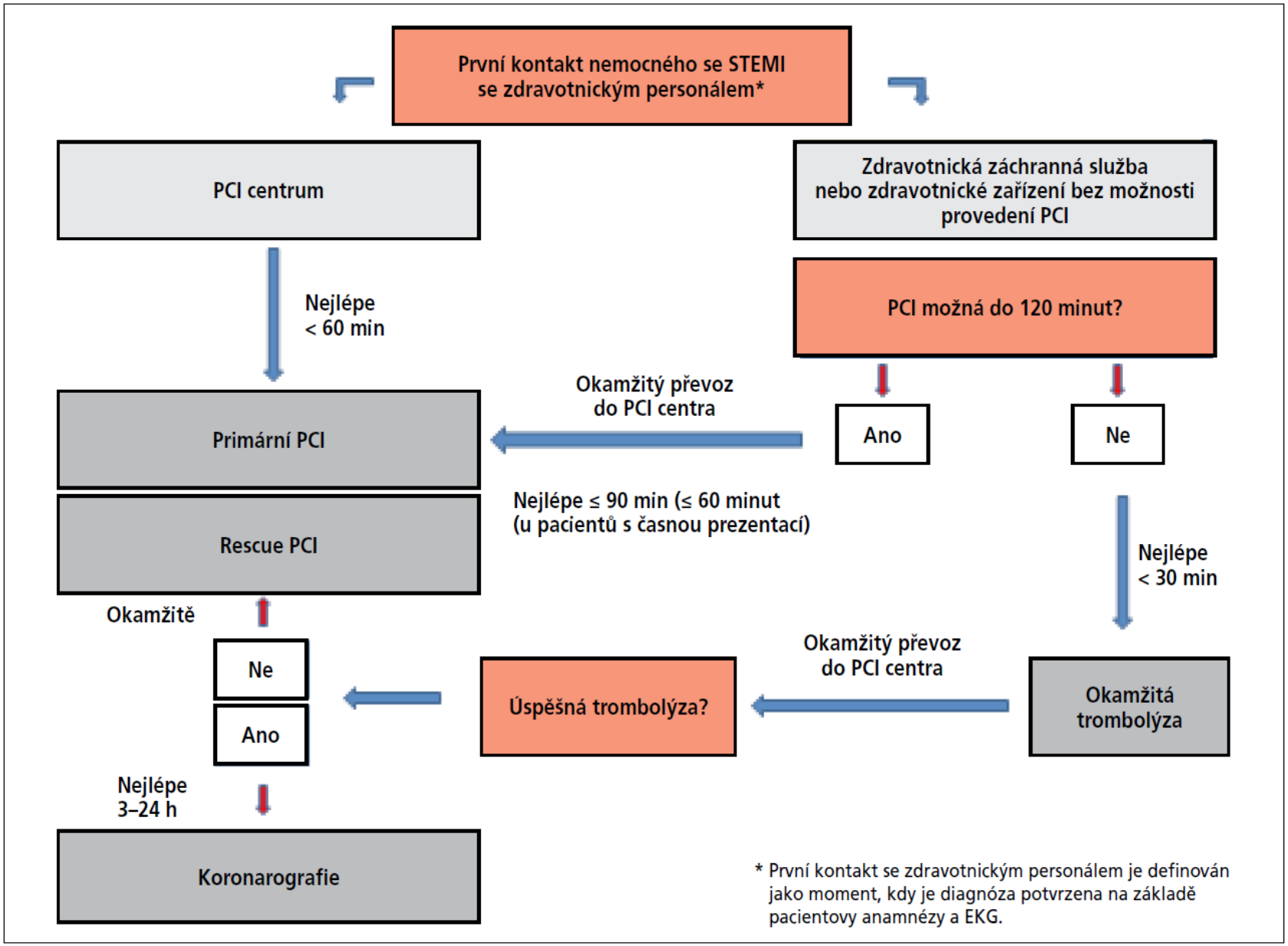
The composite end point included death from all causes and complications of myocardial infarction from randomization through day 90. Data are

Primary PCI in Europe



Widimsky et al. Eur Heart J 2010; 31,943-957

STEMI- ESC guidelines 2012



Obr. 2 – Organizace přednemocniční a nemocniční péče a strategie reperfuze do 24 hodin od prvního kontaktu se zdravotnickým personálem

ESC Guidelines for STEMI

Thrombolysis – Recommendations

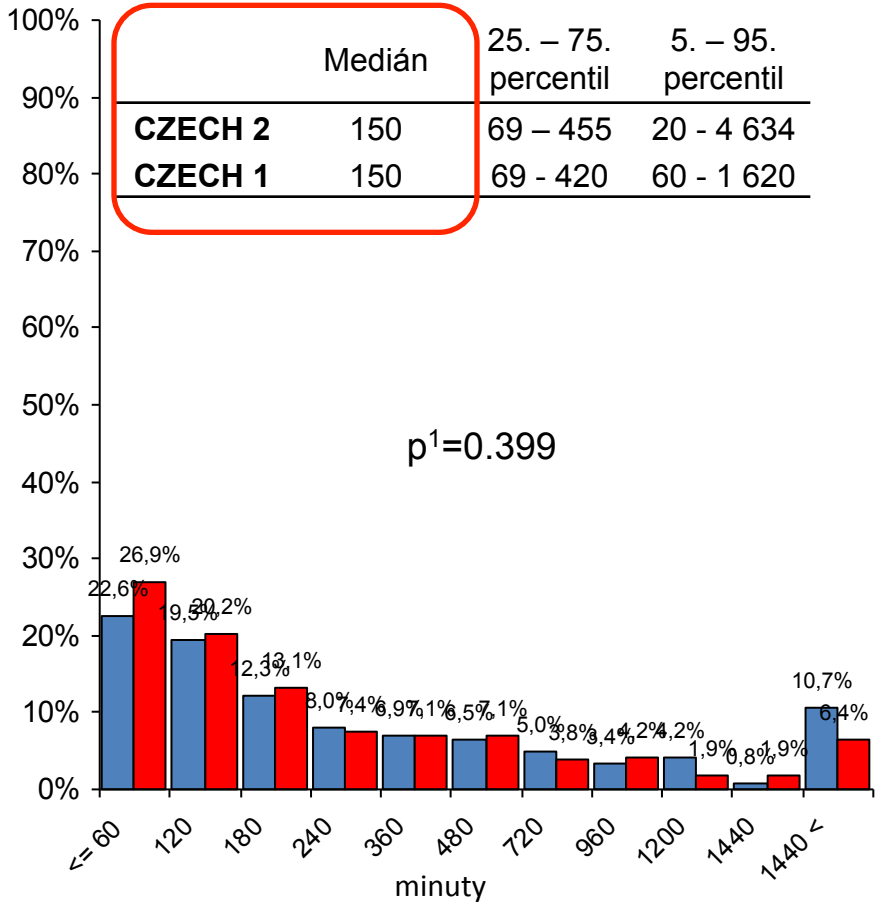
Recommendations	Class[a]	Level[b]
Fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications if primary PCI cannot be performed by an experienced team within 120 min of FMC.	I	A
In patients presenting early (<2 h after symptom onset) with a large infarct and low bleeding risk, fibrinolysis should be considered if time from FMC to balloon inflation is >90 min.	IIa	B
If possible, fibrinolysis should start in the prehospital setting.	IIa	A
A fibrin-specific agent (tenecteplase, alteplase, reteplase) is recommended (over non-fibrin specific agents).	I	B

Časové intervaly STEMI

Doba od začátků potíží do prvního EKG

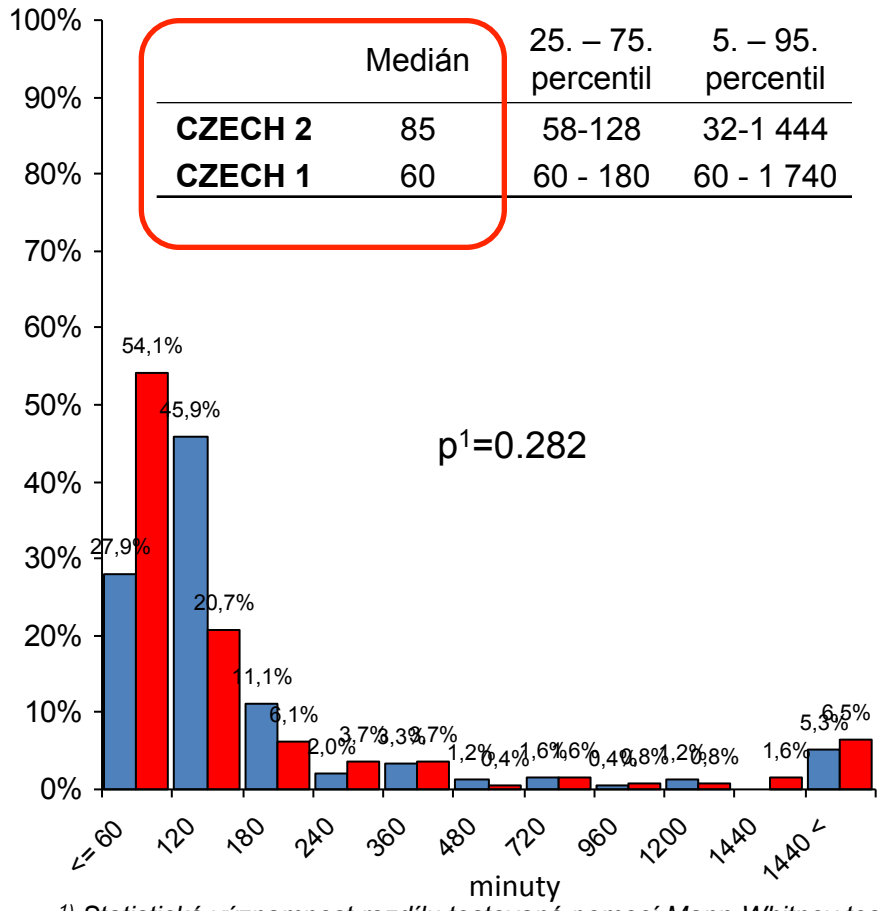
CZECH 2 (N=261)
CZECH 1 (N=442)

	Medián	25. – 75. percentil	5. – 95. percentil
CZECH 2	150	69 – 455	20 - 4 634
CZECH 1	150	69 - 420	60 - 1 620



Doba od prvního EKG do příchodu na sál

	Medián	25. – 75. percentil	5. – 95. percentil
CZECH 2	85	58-128	32-1 444
CZECH 1	60	60 - 180	60 - 1 740



1) *Statistická významnost rozdílu testovaná pomocí Mann-Whitney testu*

Thrombolysis – Agents and doses

	Initial treatment	Specific contraindications
Streptokinase (SK)	1.5 million units over 30–60 min i.v.	Prior SK or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg/kg over 30 min (up to 50 mg) then 0.5 mg/kg over 60 min i.v. (up to 35 mg)	
Reteplase (r-PA)	10 units + 10 units i.v. bolus given 30 min apart	
Tenecteplase (TNK–tPA)	Single i.v. bolus: 30 mg if <60 kg 35 mg if 60 to <70 kg 40 mg if 70 to <80 kg 45 mg if 80 to <90 kg 50 mg if ≥90 kg	

ESC Guidelines for STEMI

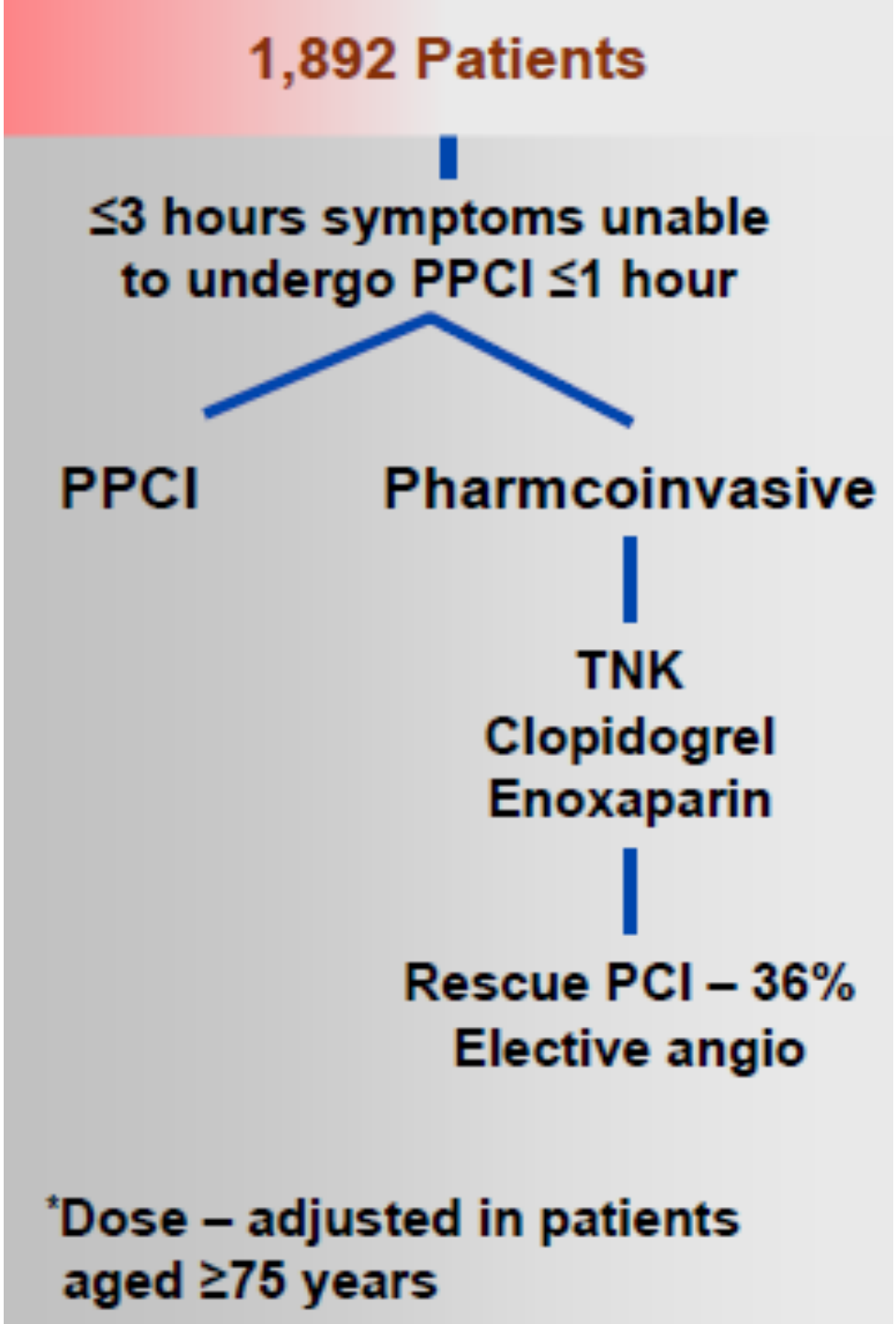
Adjunctive therapy to lysis – Recommendations

Recommendations	Class[a]	Level[b]
Oral or i.v. aspirin must be administered.	I	B
Clopidogrel is indicated in addition to aspirin.	I	A
Antithrombin co-therapy with fibrinolysis		
Anticoagulation is recommended in STEMI patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
• Enoxaparin i.v followed by s.c. (using the regimen described below) (preferred over UFH).	I	A
• UFH given as a weight-adjusted i.v. bolus and infusion.	I	C
In patients treated with streptokinase, fondaparinux i.v. bolus followed by s.c. dose 24 h later.	IIa	B

Fibrinolytic therapy - contraindications

ABSOLUTE	RELATIVE
• Previous ICH or stroke of unknown origin at any time	• TIA in less than 3 months 6M
• Ischemic stroke in the preceding 6 months	• Oral anticoagulants
• Central nervous system damage, neoplasms or atrioventrcular malformations	• Pregnancy or within 1 week post partum
• Recent major trauma/surgery/head injury 3M	• Refractory hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm HG)
• Gastrointestinal bleeding within the past month	• Advanced liver disease
• Known bleeding disorder	• Infective endocarditis
• Aortic dissection	• Active peptic ulcer
• Non-compressible punctures in the past 24 hours relative…	• Prolonged or traumatic resuscitation

- **Absolutní kontraindikace dle ČKS 2007 – dop. plicní embolie**
  - aktivní vnitřní krvácení
  - nedávné spontánní intrakraniální krvácení



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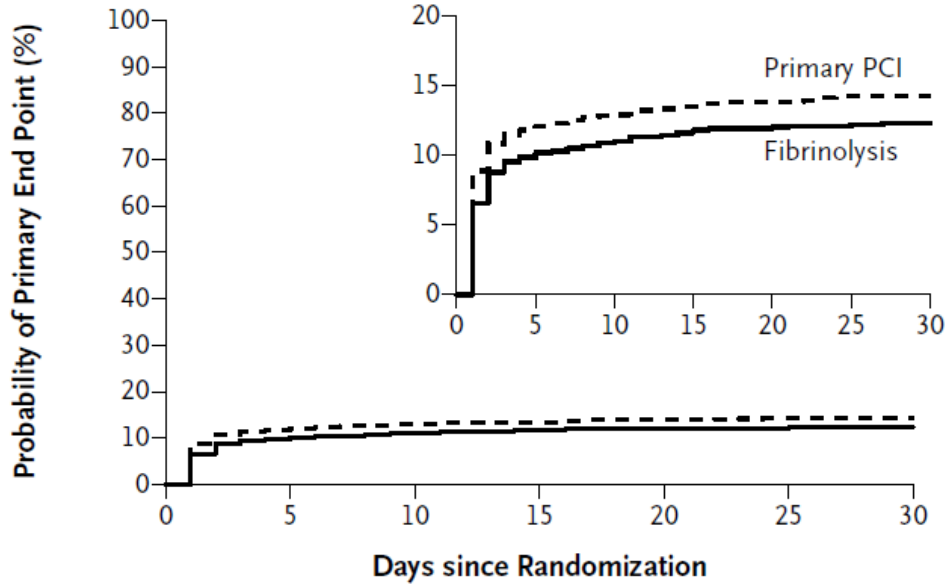
Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

Paul W. Armstrong, M.D., Anthony H. Gershlick, M.D., Patrick Goldstein, M.D., Robert Wilcox, M.D.,

Po zařazení 20 % pacientů byla dávka TNK u pacientů > 75 let redukována na polovinu (clopidogrel jen 75 mg enoxaparine bez i.v. bolusu)



No. at Risk

Fibrinolysis	943	848	837	829	827	825	823
Primary PCI	948	836	824	818	815	811	811

Figure 1. Kaplan–Meier Curves for the Primary End Point.

The primary end point was a composite of death from any cause, shock, congestive heart failure, or reinfarction within 30 days (P=0.21 by the log-rank test). PCI denotes percutaneous coronary intervention. The inset shows the same data on an enlarged y axis.

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Event	Fibrinolysis (N=944)	Primary PCI (N=948)	P Value
	no./total no. (%)		
Total strokes	15/939 (1.6)	5/946 (0.5)	0.03
Intracranial hemorrhage			
Any	9/939 (1.0)	2/946 (0.2)	0.04
After protocol amendment*	4/747 (0.5)	2/758 (0.3)	0.45

Thrombolysis for acute ischemic stroke - 2013

1. I.v. rtPA (0.9 mg/kg, maximum dose 90 mg, over 60 minutes, 10 % dose in 1 minute) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke *(I,A)*.

2. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival *(I,A)*

3. The use of i.v. rtPa in patients taking NOAC may be harmful and is not recommended unless sensitive lab. tests are normal or the patient has not received a dose of these agents for > 2 days (assuming normal renal metabolizing function)

4. Exclusion – platelets < 100 000/mm3
   - heparin v posledních 48 hod s prodlouženým APTT
   - warfarinizace s aktuálním INR > 1,7

Thrombolysis for acute ischemic stroke - 2013

4. I.v. rtPA is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset *(I,B), but additional exclusion criteria should be respected:*
- patients >80 years old,
- those taking oral anticoagulants regardless of INR,
- baseline NIHSS score >25
- imaging evidence of ischemic injury involving more than 1/3 of the MCA territory,
- history of both stroke and diabetes mellitus.

5. I.v. rtPA is reasonable in patients whose BP can be lowered safely (to below 185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous rtPA *(I, B)*

Pulmonary embolism

Acute phase treatment

Recommendations	Class	Level
PE with shock or hypotension (high risk)		
It is recommended to initiate intravenous anticoagulation with UFH without delay in patients with high-risk PE.	I	C
Thrombolytic therapy is recommended.	I	B
Surgical pulmonary embolectomy is recommended for patients in whom thrombolysis is contraindicated or has failed.	I	C
Percutaneous catheter-directed treatment should be considered as an alternative to surgical pulmonary embolectomy for patients in whom full-dose systemic thrombolysis is contraindicated or has failed.	IIa	C

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

Thrombolytic treatment of PE

Approved thrombolytic regimens for pulmonary embolism	
Streptokinase	250 000 IU as a loading dose over 30 minutes, followed by 100 000 IU/h over 12-24 hours.
	Accelerated regimen: 1.5 million IU over 2 hours.
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12-24 hours.
	Accelerated regimen: 3 million IU over 2 hours.
rtPA	100 mg over 2 hours; or
	0.6 mg/kg over 15 minutes (maximum dose 50 mg).

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

Děkuji za pozornost !

Table 10. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

NINDS and ECASS III inclusion and exclusion criteria for intravenous tPA for acute ischemic stroke.

NINDS Criteria[3]

Inclusion:

Acute ischemic stroke with clearly defined time of onset (who could be treated <3 hours of symptom onset)
Measurable deficit on the NIH stroke scale
Baseline brain CT scan that showed no evidence of hemorrhage.

Exclusion:*

Another stroke or serious head injury within the preceding 3 months
Major surgery within prior 14 days
History of intracranial hemorrhage
Systolic BP >185 mm Hg or diastolic BP >100 mm Hg
Rapidly improving or minor symptoms
Symptoms suggestive of subarachnoid hemorrhage
Gastrointestinal or genitourinary hemorrhage within the previous 21 days
Arterial puncture at a noncompressible site within the previous 7 days
Seizure at onset of stroke
Use of anticoagulation:
patients receiving heparin within the 48 hours preceding the onset of stroke who have an elevated PTT,
patients with a PT >15 seconds (or INR >1.6),
patients with a platelet count <100,000
Glucose level of <50 mg/dL or >400 mg/dL.

ECASS III Criteria[19]

Inclusion:

Acute ischemic stroke with a clearly defined time of onset (who could be treated between 3-4.5 hours from symptom onset)
Age 18-80 years
Stroke symptoms present for at least 30 minutes without significant improvement prior to treatment.
Baseline brain imaging that showed no evidence of hemorrhage.

Exclusion:*

Same as NINDS plus the following additional criteria:
Age >80 years
Severe stroke (NIHSS >25) or by appropriate imaging techniques (defined as >1/3 of the middle cerebral artery territory)
Combination of previous stroke and diabetes mellitus
Any oral anticoagulant use (regardless of INR or PT).

***Exclusions (or cautions) to tPA use that were not specifically mentioned in either study but are generally used**:

Myocardial infarction within previous 3 months (AHA 2007 guidelines)
Pregnancy and early postpartum period
Known bleeding diathesis, recent pericarditis, recent lumbar puncture (Brain Attack Coalition http://www.stroke-site.org/guidelines/tpa_guidelines.html, accessed March 1, 2012).

1. **Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients *(Class I; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
2. **The usefulness of clopidogrel for the treatment of acute ischemic stroke is not well established *(Class IIb; Level of Evidence C)*. Further research testing the usefulness of the emergency administration of clopidogrel in the treatment of patients with acute stroke is required.** (Revised from the previous guideline[13])
3. **The efficacy of intravenous tirofiban and eptifibatide is not well established, and these agents should be used only in the setting of clinical trials *(Class IIb; Level of Evidence C)*.** (New recommendation)
4. **Aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including intravenous rtPA *(Class III; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
5. **The administration of other intravenous antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended *(Class III; Level of Evidence B)*.** (Revised from the previous guideline[13]) **Further research testing the usefulness of emergency administration of these medications as a treatment option in patients with acute ischemic stroke is required.**
6. **The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of intravenous fibrinolysis is not recommended *(Class III; Level of Evidence C)*.** (Revised from the previous guideline[13])