Reperfusion therapy in acute myocardial infarction and acute ischaemic stroke: similarities and differences

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STEMI Prague 1982

ANOTACE

Čas lék čes 1983; 122: 694-6.

PRVNÍ ZKUŠENOSTI SE SELEKTIVNÍ INTRAKORONÁRNÍ TROMBOLYTICKOU LÉČBOU

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Souhrn

Referováno o případu mladého muže s transmurálním anteroseptolaterálním infarktem myokardu, který byl ošetřen selektivní intrakoronární trombolytickou léčbou. Rekanalizace byla hodnocena opakovanou koronarografií a efekt včasné reperfúze na kinetiku a funkci levé

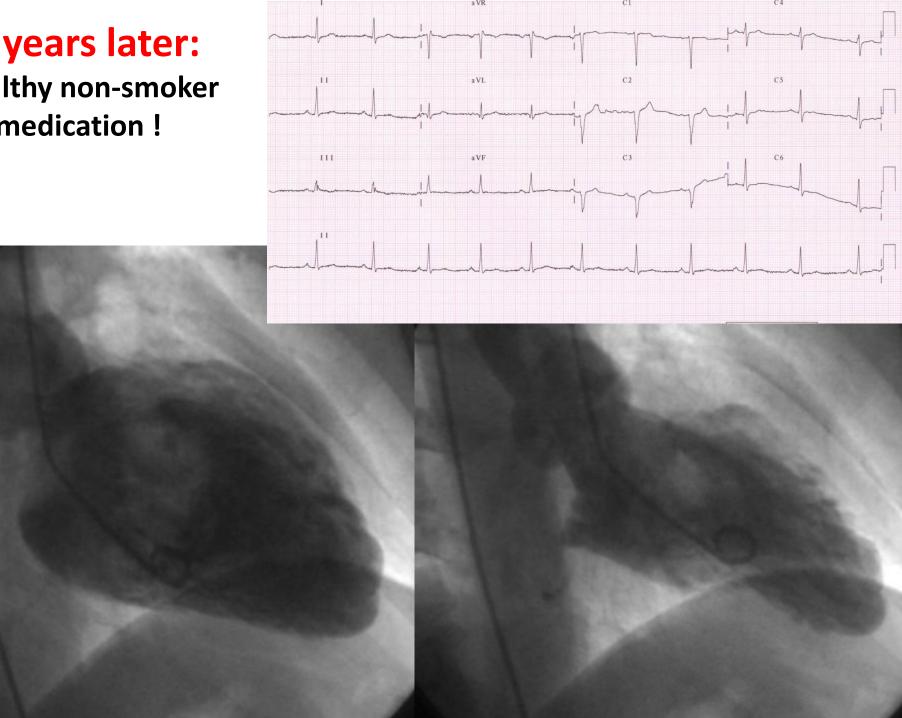
37-years old smoker, acute LAD occlusion (TIMI 0 flow)

Single-vessel disease Intracoronary streptokinase infusion – TIMI 3 flow

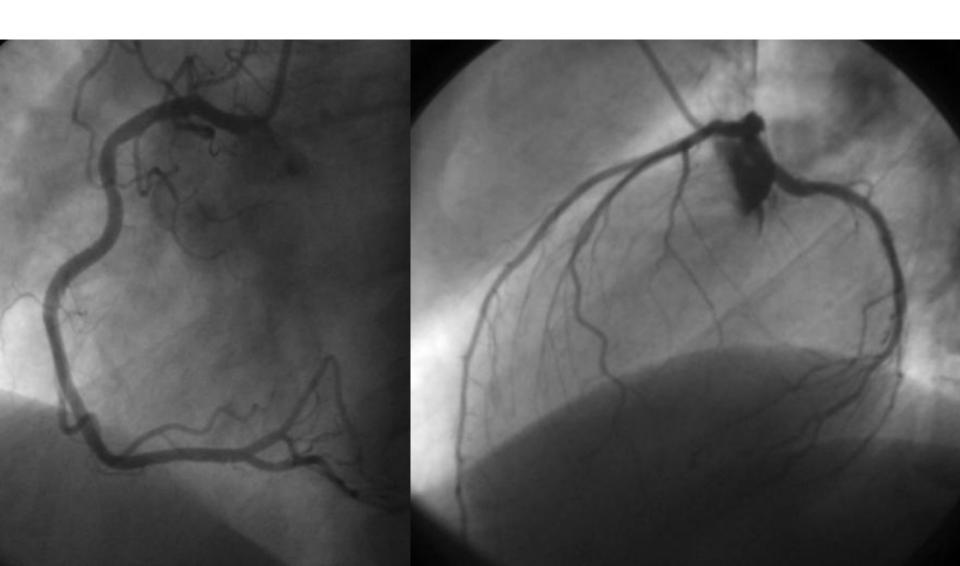
Dec. 20, 1982

24 years later:

Healthy non-smoker No medication!



CAG 24 years after successfull reperfusion therapy



STEMI
Zwolle
1993

A COMPARISON OF IMMEDIATE CORONARY ANGIOPLASTY WITH INTRAVENOUS STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

Felix Zijlstra, M.D., Ph.D., Menko Jan de Boer, M.D., Jan C.A. Hoorntje, M.D., Ph.D., Stoffer Reiffers, Ph.D., Johan H.C. Reiber, Ph.D., and Harry Suryapranata, M.D., Ph.D.

Abstract *Background*. Despite the widespread use of intravenous thrombolytic therapy and of immediate percutaneous transluminal coronary angioplasty for the treatment of acute myocardial infarction, randomized comparisons of the two approaches to reperfusion are lacking. We report the results of a prospective, randomized trial comparing immediate coronary angioplasty (without previous thrombolytic therapy) with intravenous streptokinase treatment.

Methods. A total of 142 patients with acute myocardial infarction were randomly assigned to receive one of the two treatments. The left ventricular ejection fraction was measured by radionuclide scanning before hospital discharge. Quantitative coronary angiography was performed to assess the degree of residual stenosis in the infarct-related arteries.

Results. A total of 72 patients were assigned to receive streptokinase and 70 patients to undergo immediate angioplasty. Angioplasty was technically successful in 64 of the 65 patients who underwent the procedure. Infarction

recurred in nine patients assigned to receive streptokinase, but in none of those assigned to receive angioplasty (P = 0.003). Fourteen patients in the streptokinase group had unstable angina after their infarction, but only four in the angioplasty group (P = 0.02). The mean (\pm SD) left ventricular ejection fraction as measured before discharge was 45 ± 12 percent in the streptokinase group and 51 ± 11 percent in the angioplasty group (P = 0.004). The infarct-related artery was patent in 68 percent of the patients in the streptokinase group and 91 percent of those in the angioplasty group (P = 0.001). Quantitative coronary angiography revealed stenosis of 36 ± 20 percent of the luminal diameter in the angioplasty group, as compared with 76 ± 19 percent in the streptokinase group (P<0.001).

Conclusions. Immediate angioplasty after acute myocardial infarction was associated with a higher rate of patency of the infarct-related artery, a less severe residual stenotic lesion, better left ventricular function, and less recurrent myocardial ischemia and infarction than was intravenous streptokinase. (N Engl J Med 1993;328:680-4.)

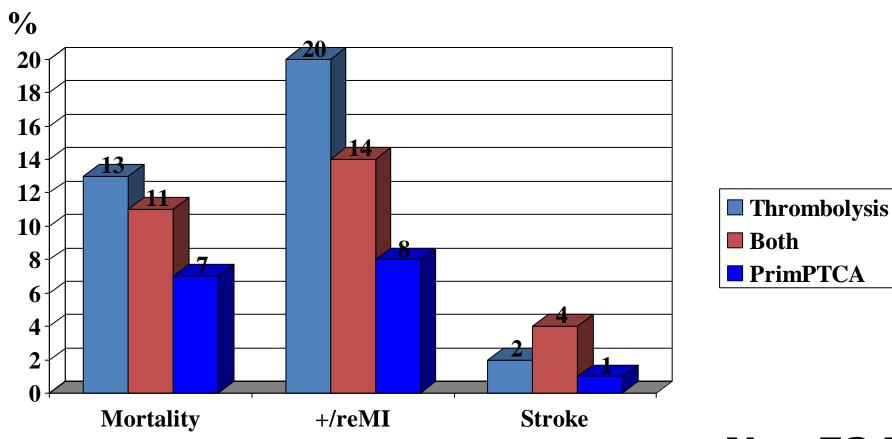


STEMI Czech Republic 1997-2002

PRAGUE-1 (n=300) and LIMI (n=224)

(F. Vermeer, Heart 1999; 82: 426-31;

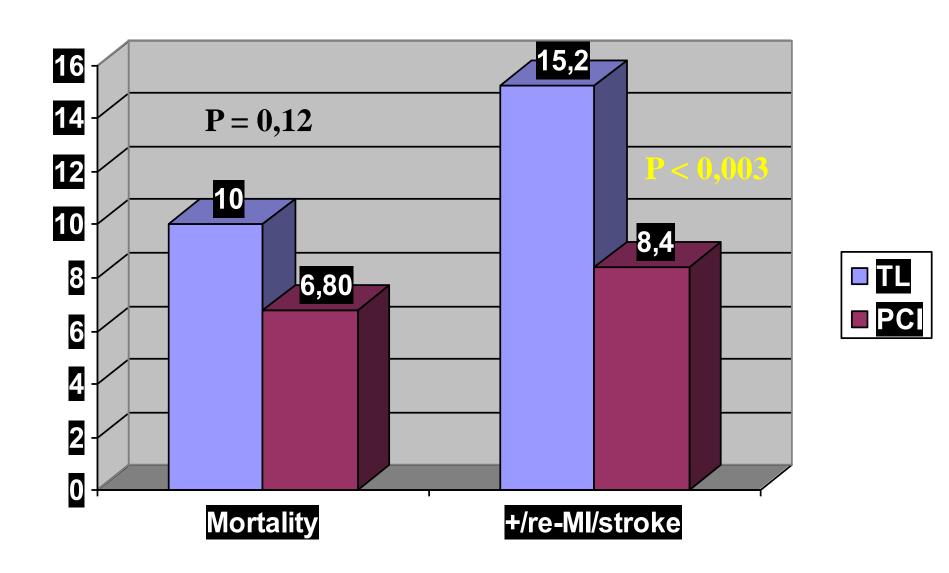
P. Widimský, Eur Heart J 2000; 21: 823-31)



N = 524

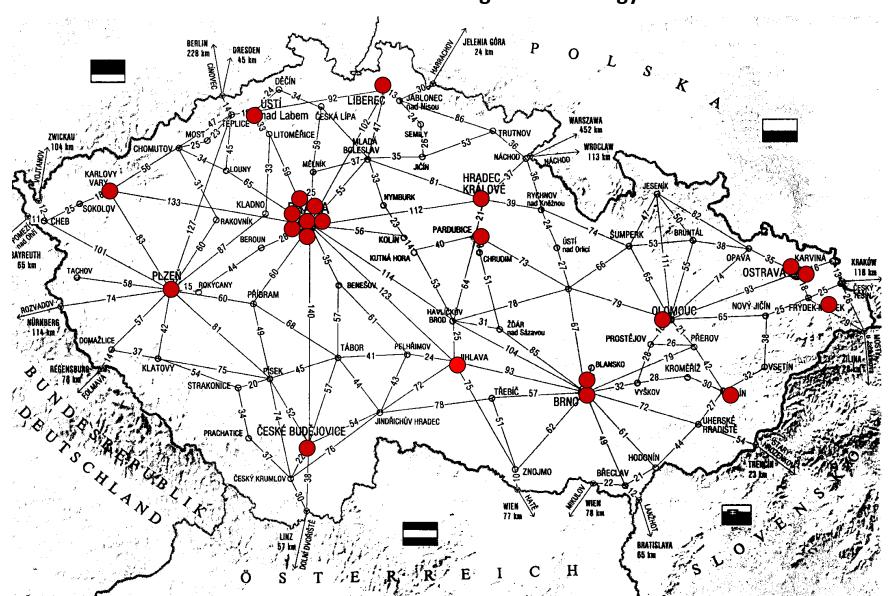
PRAGUE-2: 30. den

Eur Heart J. 2003 Jan;24(1):94-104

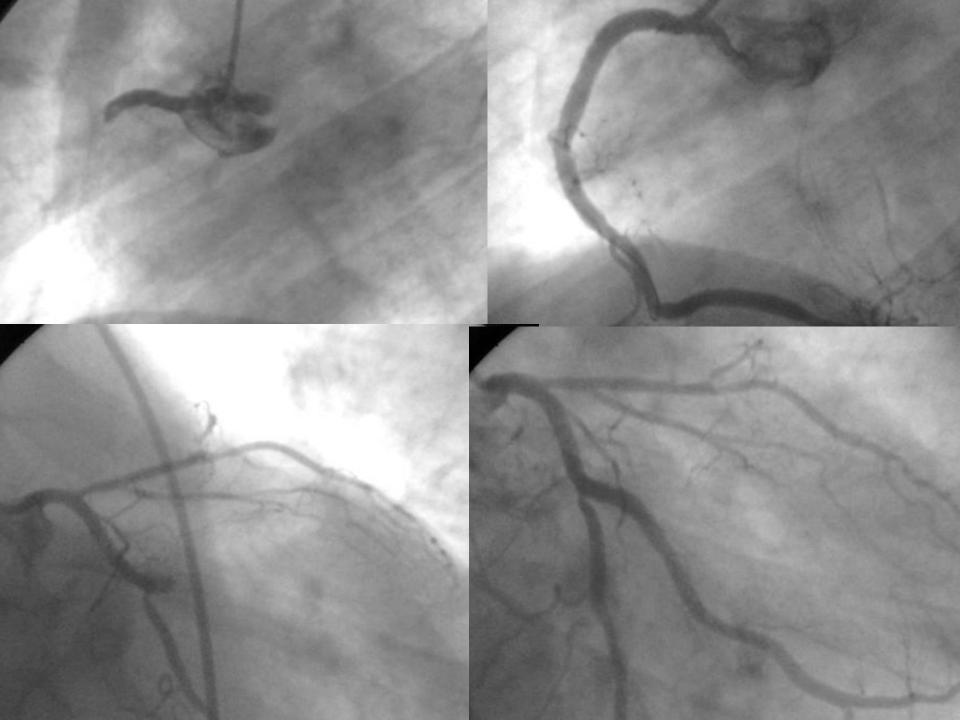


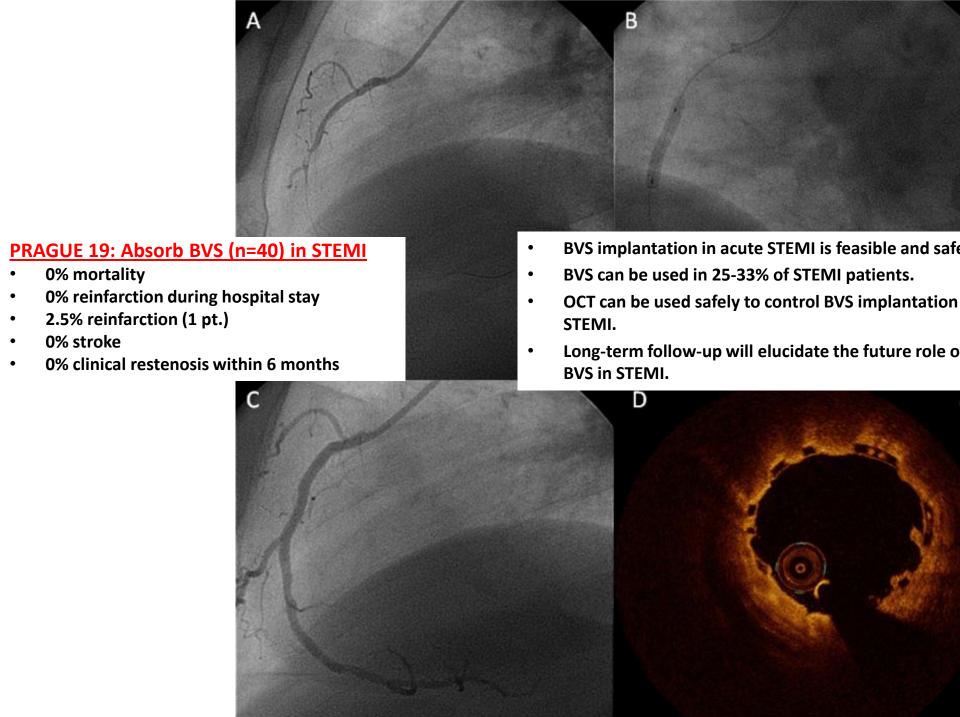
Primary PCI recommended by official guidelines:

2002 Czech Society of Cardiology 2003 European Society of Cardiology 2004 American College of Cardiology



STEMI Prague 2013



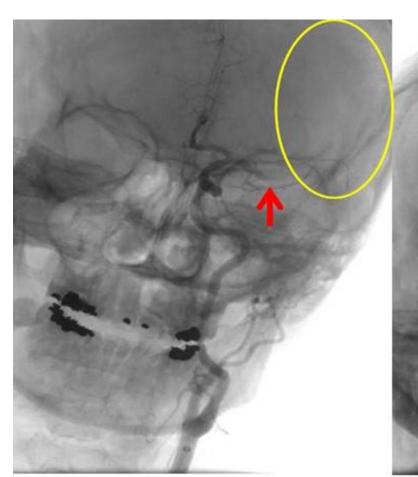


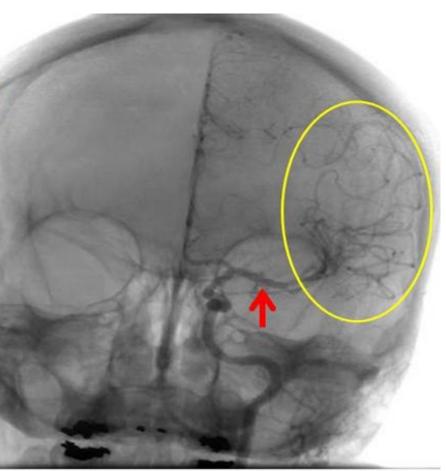
Acute stroke Brno 2010



Václav Chaloupka, president of the Czech Society of Cardiology 2008-11: acute hemispheric stroke not treated by reperfusion

Acute stroke, Prague 2012: Three young females (37-46 years) with acute stroke (NIHSS 12-17) and full neurologic recovery within 48 hours

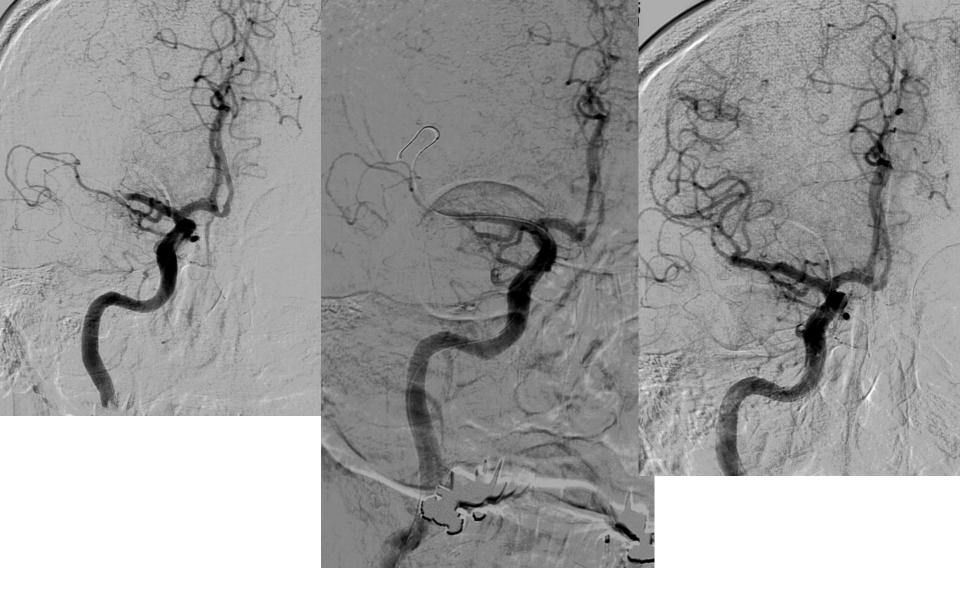




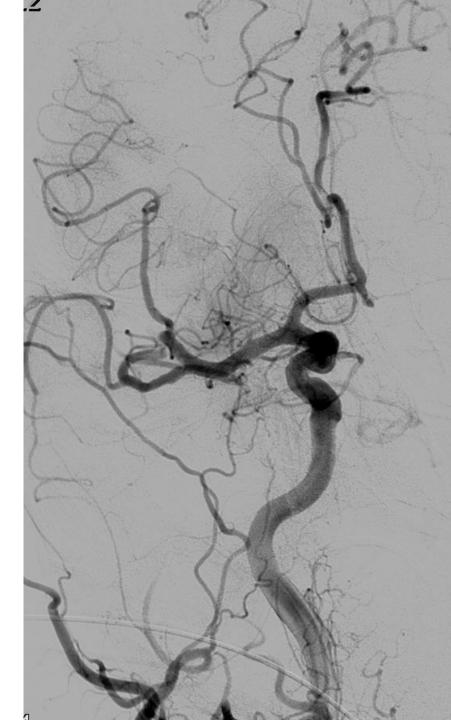












Acute stroke and acute MI: SIMILARITIES

	Acute myocardial infarction	Acute ischemic stroke
Pathophysiology	Arterial occlusion + ischemic	Arterial occlusion + ischemic
	necrosis	necrosis
Clinical picture	Acute onset	Acute onset
Prognosis	High mortality (if untreated)	High mortality (if untreated)
Effective treatment	Reperfusion therapy	Reperfusion therapy
Thrombolytic treatment	Early reperfusion achieved in	Early reperfusion achieved in
	<50% of treated patients	<50% of treated patients
	Bleeding complications may	Bleeding complications may
	be fatal	be fatal
	Early reocclusion is frequent	Early reocclusion is frequent
Pharmaco-invasive	Does not offer superior	Does not offer superior
treatment (thrombolysis +	results to either method if	results to either method if
mechanical intervention)	performed alone	performed alone
Catheter-based	Clearly established as the	Emerging as the most
thrombectomy	most effective therapy.	effective therapy

Acute stroke and acute MI: DIFFERENCES

DITTERENCES			
	Acute myocardial infarction	Acute ischemic stroke	
Etiology	Uniform: plaque rupture +	Multiple: cardioembolic,	
	thrombosis in situ in 90-95%	arterioembolic, thrombosis in	
		situ, lacunar, cryptogenic.	
Arterial occlusive thrombus	Found in 95% of acute coronary	Found only in cca 35% of acute	
feasible for catheter-based	angiograms	CT-angiograms	
thrombectomy			
Time window symptom onset -	24 hours (48 h in some patients)	3 hours (8 hours in some	
intervention start (to offer		patients)	
benefit and not harm)			
Reperfusion damage	Only theoretical, clinically always	Reperfusion damage (bleeding) is	
	reperfusion benefit	a real clinical problem	
Clinical picture	Pain (dyspnoe) alerts the patient	Neurologic dysfunction + no pain	
	to call early for help	= late medical contact	
Diagnostic method before	ECG (fast, simple, cheap, at the	CT (takes more time, expensive,	
reperfusion therapy indication	site of first medical contact)	in-hospital)	
Laboratory diagnostic marker	troponin	None yet available	
Contraindications for catheter-	None	Intracranial bleeding or advanced	
based thrombectomy		ischemia on CT	
% of hospitalized patients who	>90%	<10%	
undergo reperfusion therapy			

CZ: acute stroke vs. acute MI

40 000 hospital admissions for stroke or TIA 30 000 hospital admissions for ACS (20 000 for AMI)

Stroke

- 120 catheter based thrombectomy (CBT)
- 1600 thrombolysis
- Best center: 32 CBT / year
- Other centers 5-15 CBT / year

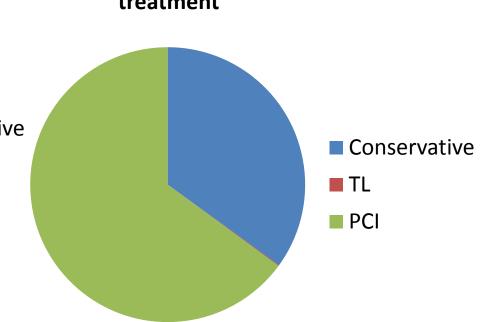
Acute stroke treatment

Conservative TL CBT

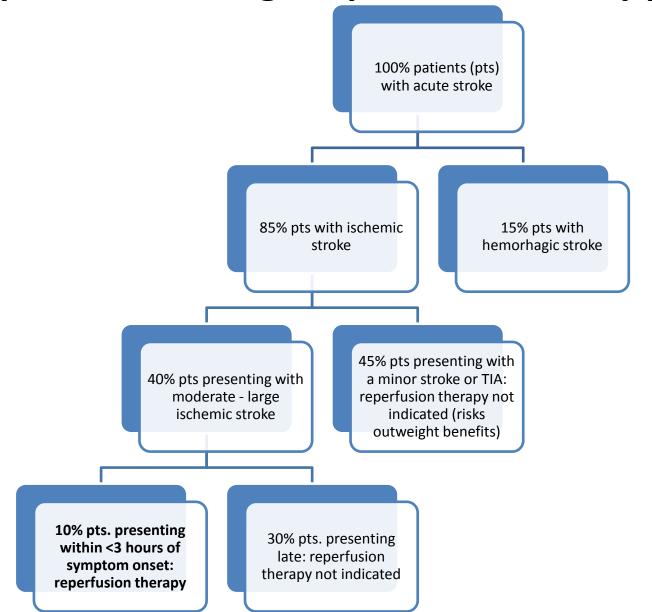
AMI

- 22 000 acute/early CAG
- 0,4% thrombolysis for STEMI
- Best center: >700 PCI for ACS / year
- Other centers: 200 600 PCI for ACS

Acute MI (STEMI + nonSTEMI) treatment



Why only a small minority of acute stroke patients undergo reperfusion therapy?



Possible explanations for low use of reperfusion therapy in acute stroke

Disease related explanations	Health care related explanations
Many acute strokes are not suitable for reperfusion (e.g. hemorhagic strokes)	Risks of reperfusion therapy are currently unacceptably high in pts with small strokes or TIAs
Fast development of necrosis	Many health professionals do not consider acute stroke as "superemergency" (are not aware of benefits of very early reperfusion therapy)
Risk of intracerebral bleeding (hemorhagic conversion of ischemic stroke) Absence of alerting symptoms (e.g. pain)	

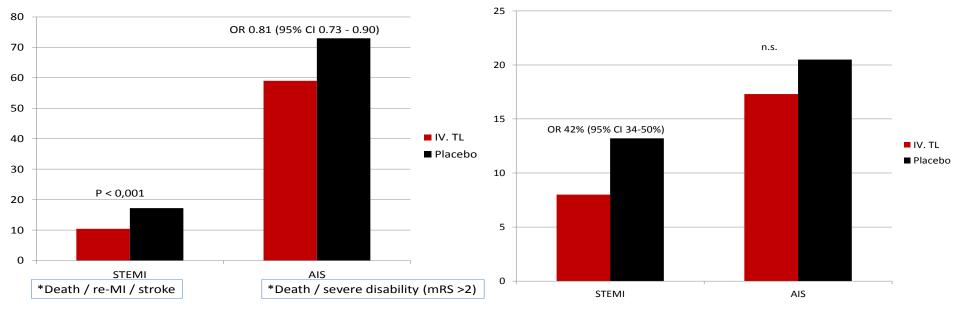
AMI – stroke: similar outcome trends

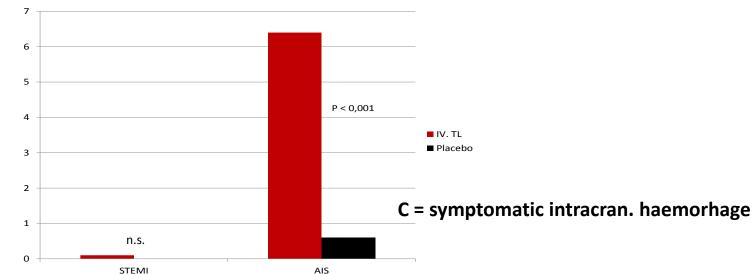
I.V. thrombolysis vs. placebo in AMI and in stroke

A = "hard" clinical endpoints death / reinfarction / stroke for STEMI death / severe disability (mRS >2) for stroke Lancet 1988; 349-60 NEJM 1995; 1581-7

Cochrane Database Syst Rev 2009 Oct 7; (4): CD000213

B = all cause mortality





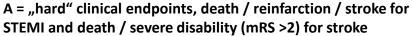
Intraarterial vs. intravenous thrombolysis in AMI and in stroke

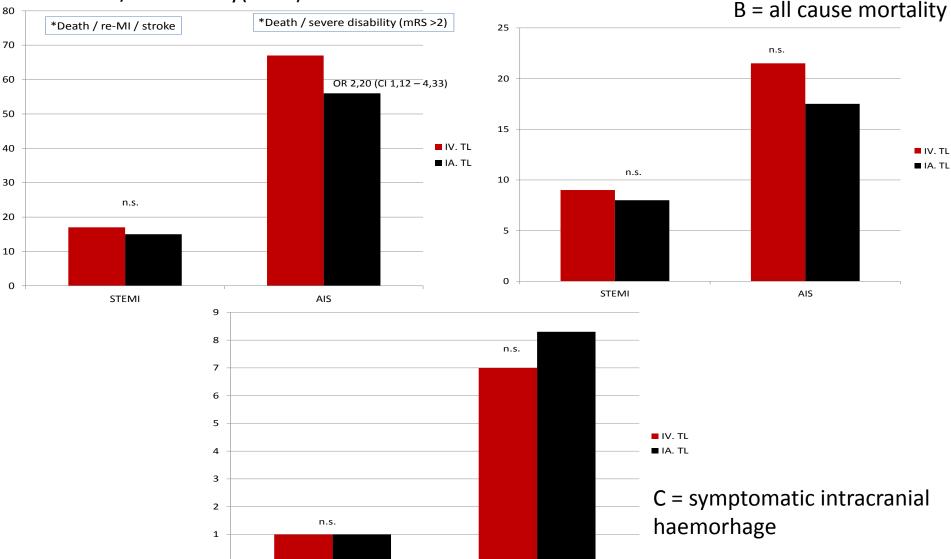
STEMI

Stroke. 2012;43:1302-1308

N Engl J Med 1983; 309: 1477-82. N Engl J Med 1984; 311: 1457-63.

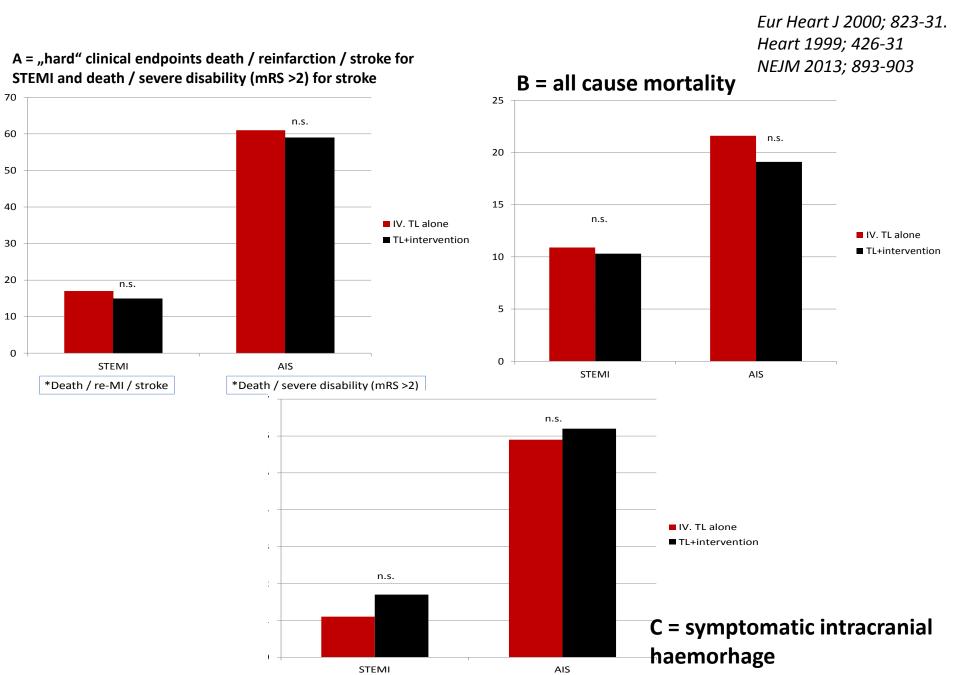
Lancet. 1985; 2: 578-82.



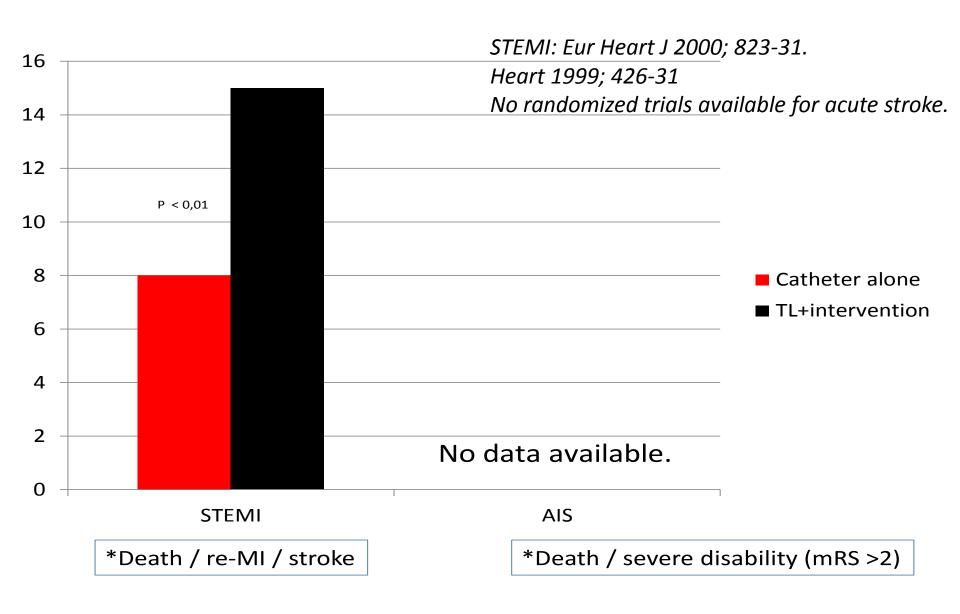


AIS

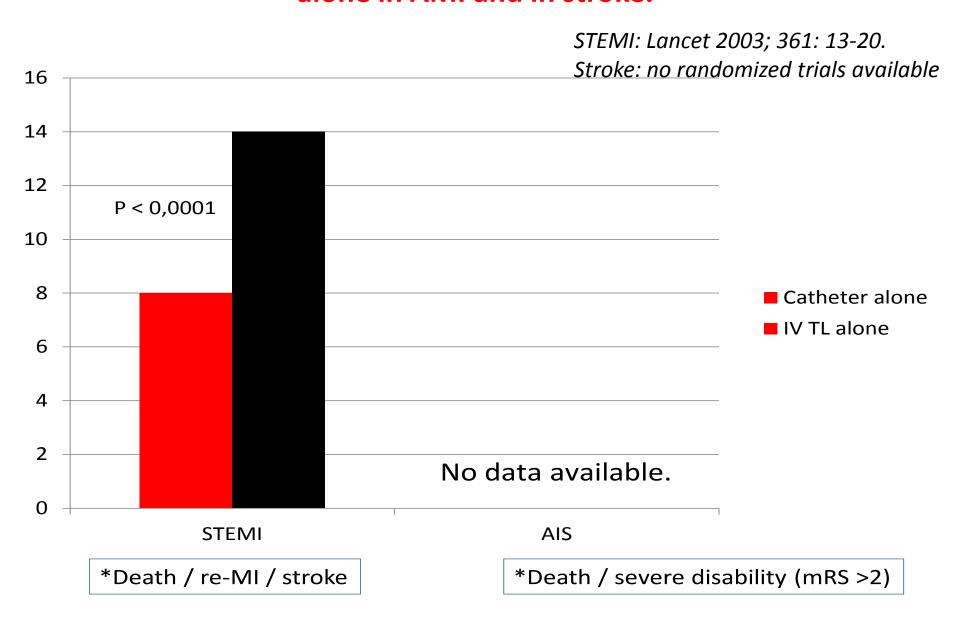
I.V. thrombolysis vs. facilitated intervention in AMI and in stroke



Facilitated intervention vs. catheter intervention alone in AMI and in stroke



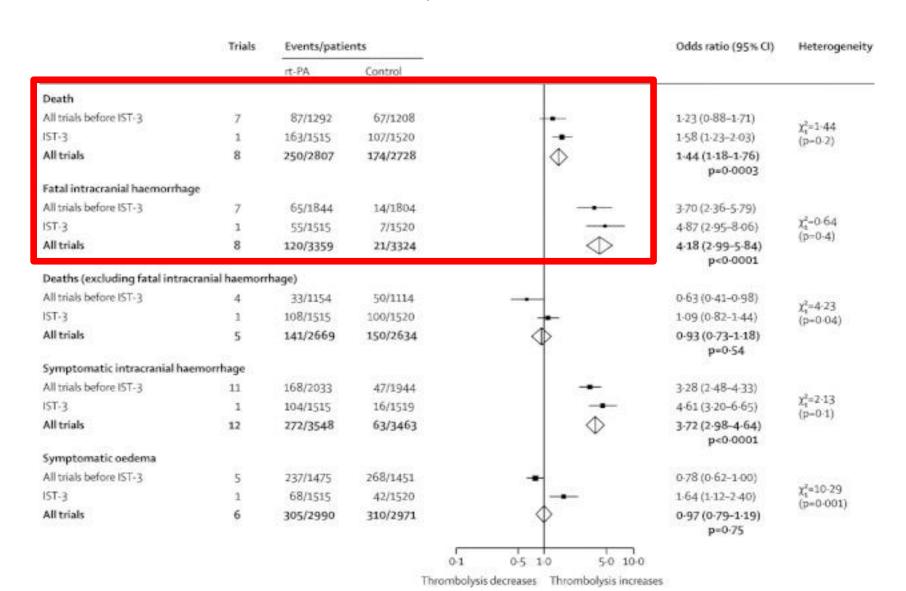
Primary catheter intervention alone versus intravenous thrombolysis alone in AMI and in stroke.



Acute stroke: I.V. thrombolysis vs. placebo

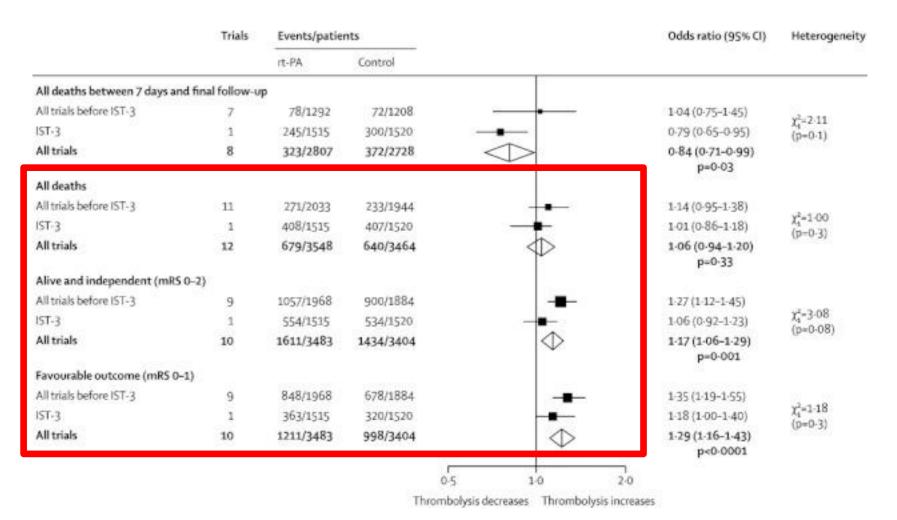
Thrombolysis increases early (7 days) mortality due to 7.7% risk of symptomatic intracranial haemorrhage

Wardlaw JM et al. rt-PA for acute ischaemic stroke: a meta-analysis of 12 trials Lancet 2012; 379: 2364–2372.



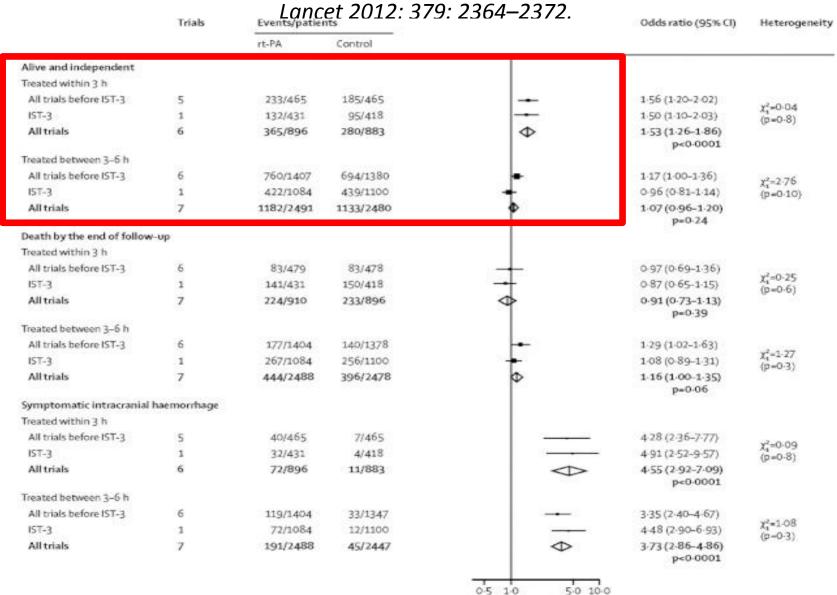
Thrombolysis improves final stroke outcomes due to improved functional recovery of survivors

Wardlaw JM et al. R-tPA for acute ischaemic stroke: a meta-analysis of 12 trials Lancet 2012; 379: 2364–2372.



Thrombolysis is beneficial only when given within <3 hours from stroke onset

Wardlaw JM et al. R-tPA for acute ischaemic stroke: a meta-analysis of 12 trials



Thrombolysis decreases Thrombolysis increases

Acute stroke: Facilitated intervention vs. I.V. thrombolysis

Combined I.V. + I.A. thrombolysis in acute stroke is not superior to simple iv. thrombolysis alone

Mazighi M et al. Stroke 2012;43:1302-1308.

- Metaanalysis of 15 trials with iv. (bridging)
 + ia. TL
- 559 patients, mean NIHSS 17.
- Symptom onset infusion start 135 min.
- Infusion angiography 88 min. (!!!)

Table 3. Pooled Rates of Recanalization and Clinical Outcomes

Outcome	Studies, n	Patients, n	Pooled Rates (95% CI)	₽ Value*	-1^2 , $\%$
Main analysis					
Partial or complete recanalization	15	559	69.6 <u>(</u> 63.9–75.0)	0.011	51.3
Complete recaralization	13	442	35.1 <mark>23.0–48.2)</mark>	<0.001	87.6
Favorable outcome	15	559	48.9 <mark>42.9-54.9)</mark>	0.014	50.2
Mortality	15	585†	17.9 <mark>12.7–23.7)</mark>	<0.001	66.6
aoH	15	627†	8.6 <mark>-</mark> 6.8-10.6)	0.65	0
Sensitivity analysis‡					
Favorable outcome	10	399	44.3 (39.9-48.8)	0.54	0
Mortality	12	474†	18.6 (12.3–25.8)	<0.001	72.2
aOH	11	501†	9.7(7.3-12.4)	0.96	0

Of indicates confidence interval; sICH, symptomatic intracranial hemorrhage.

^{*} $^{\circ}$? associated with χ° test for heterogeneity.

througing patients eligible for bridging therapy not treated by intra-arterial therapy from Interventional Management of Stroke trials.

 $[\]sharp$ Restricted to studies with clinical outcome closest to the Interventional Management of Stroke III definition. 6

ORIGINAL ARTICLE

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

Joseph P. Broderick, M.D., Yuko Y. Palesch, Ph.D., Andrew M. Demchuk, M.D.,
Sharon D. Yeatts, Ph.D., Pooja Khatri, M.D., Michael D. Hill, M.D.,
Edward C. Jauch, M.D., Tudor G. Jovin, M.D., Bernard Yan, M.D.,
Frank L. Silver, M.D., Rüdiger von Kummer, M.D., Carlos A. Molina, M.D.,
Bart M. Demaerschalk, M.D., Ronald Budzik, M.D., Wayne M. Clark, M.D.,
Osama O. Zaidat, M.D., Tim W. Malisch, M.D., Mayank Goyal, M.D.,
Wouter J. Schonewille, M.D., Mikael Mazighi, M.D., Ph.D., Stefan T. Engelter, M.D.,
Craig Anderson, M.D., Ph.D., Judith Spiller, R.N., B.S.N.,
Janice Carrozzella, R.N., B.A., R.T. (R.), Karla J. Ryckborst, R.N., B.N., L. Scott Janis, Ph.D.,
Renée H. Martin, Ph.D., Lydia D. Foster, M.S., and Thomas A. Tomsick, M.D.,
for the Interventional Management of Stroke (IMS) III Investigators

- All 656 participants received intravenous t-PA (0.9 mg per kilogram), with 10% as a bolus and the remainder infused over a 1-hour period (maximum dose, 90 mg).
- Randomization within 40 minutes after the initiation of the infusion.
- Mean enrollment rate: 2 patients / center / year (2006-12)!
- Only 47% patients underwent CT-angiography at baseline
- Group A (intravenous t-PA, n = 222, median NIHSS = 16)
- Group B (endovascular- therapy, n = 434, median NIHSS = 17): angiography as soon as possible (interhospital transfer allowed). No angiographic evidence of a treatable occlusion = no additional treatment. Treatable vascular occlusion = endovascular intervention with an approach chosen by the site neurointerventionalist (thrombectomy with the Merci, Penumbra or Solitaire, or endovascular t-PA infusion). Angiographic procedure had to begin within 5 hours and be completed within 7 hours after the onset of stroke. Heparin 2000 U bolus, followed by an infusion of 450 U /hour during endovascular therapy, discontinued at the end of the procedure.
- Death / disability (mRS >2): 59,2% (endovascular) vs. 61,3% (iv. tPA), n.s.

IMS-III outcomes

Broderick JP et al. NEJM 2013

Table 2. Primary and Secondary Safety End Points.≅						
End Point	Endovascular Therapy (N = 434)	Intravenous t-PA Alone (N= 222)	P Value			
Death — no. (%)						
Within 7 days	52 (12.0)	24 (10.8)	0.57			
Within 90 days	83 (19.1)	48 (21.6)	0.52			
Intracerebral hemorrhage within 30 hr — no. (%)						
Symptomatic	27 (6.2)	13 (5.9)	0.83			
Asymptomatic	119 (27.4)	42 (18.9)	0.01			
Parenchymal hematoma identified within 30 hr — no./total no. (%)†						
Type 2	25/417 (6.0)	13/207 (6.3)	0.90			
Type 1	15/417 (3.6)	3/207 (1.4)	0.12			
Hemorrhage — no./total no. (%)						
Subarachnoid	48/417 (11.5)	12/207 (5.8)	0.02			
Intraventricular	27/417 (6.5)	10/207 (4.8)	0.40			
Major complication due to nonintracerebral bleeding within 5 days — no. (%)\$	13 (3.0)	5 (2.3)	0.55			
Recurrent stroke within 90 days — no. (%)	22 (5.1)	14 (6.3)	0.54			
Device or procedural complication — no. (%):	70 (16.1)	_				

ORIGINAL ARTICLE

A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H.,
Jeffry R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D.,
Brett C. Meyer, M.D., Scott Olson, M.D., Lee H. Schwamm, M.D., Albert J. Yoo, M.D.,
Randolph S. Marshall, M.D., Philip M. Meyers, M.D., Dileep R. Yavagal, M.D.,
Max Wintermark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D.,
and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators*

- 118 patients within 8 hours (mean 5.5 h) after the onset of anteriorcirculation strokes randomized to undergo mechanical embolectomy (Merci or Penumbra) or standard care.
- Mean enrollment rate: <1 patient / center / year ! (2004-11)
- Randomization was stratified according to whether the patient had a favorable penumbral pattern (58% pts.) or a nonpenumbral pattern (42% pts.).
- Revascularization in the embolectomy group achieved in 67%.
- 3-months mortality 21%, symptomatic intracranial hemorrhage 4% (both groups)
- Mean mRS 3.9 vs. 3.9 (p = 0.99).
- Embolectomy was not superior to standard care even among patients with a favorable penumbral pattern (mean score, 3.9 vs. 3.4; P = 0.23)

ORIGINAL ARTICLE

Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Nichelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D., for the SYNTHESIS Expansion Investigators*

- 362 patients with acute stroke (median NIHSS = 13) within 4.5 hours randomized to endovascular therapy
- i.a. t-PA + mechanical clot disruption with a micro-guidewire (n = 109) or clot retrieval device in a small proportion only (Solitaire n = 18, Penumbra n = 9, Trevo n = 5, Merci n = 5)
- median time from stroke onset to the start of treatment was 3.75 hours for endovascular therapy and 2.75 hours for intravenous t-PA (P<0.001).
- Death or disability (mRS >1) at 3 months: 69,6% (endovascular) vs. 65,2% (i.v., p=0.16).
- symptomatic intracranial hemorrhage within 7 days occurred in 6% of the patients in each group

"Endovascular therapy" of acute stroke: senseless, misleading term mixing apples with oranges! Term should be abandoned.

If there is any future, it lies in true primary CBT!!!

- i.a. thrombolysis (useless!)
- facilitated intervention (not superior to iv. thrombolysis alone)
- rescue intervention after failed thrombolysis (value not known, possibly low due to delays)
- intracerebral balloon angioplasty or stenting (value questionable, possibly none)
- true primary (timely, without thrombolysis)
 catheter-based thrombectomy (minority of patients
 in all trials, outdated devices)

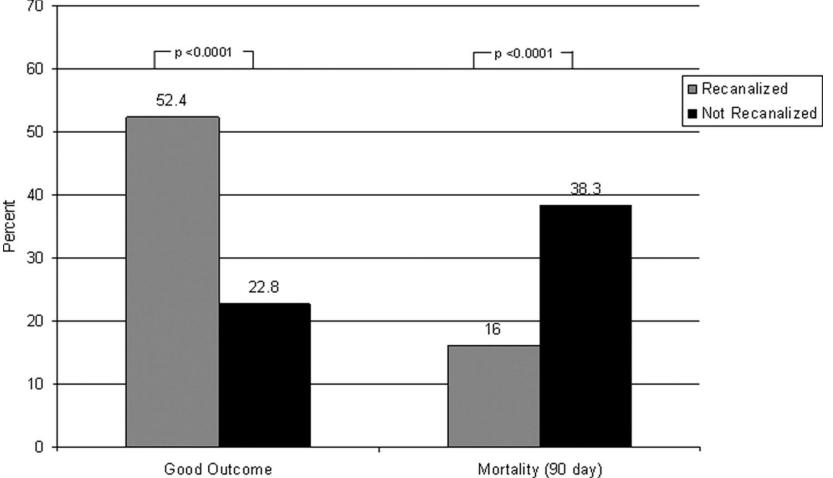
Acute stroke: Primary (direct) catheter-based thrombectomy

Dorn F et al. Endovascular Treatment of Acute Intracerebral Artery Occlusions with the Solitaire Stent: Single-Centre Experience with 108 Recanalization Procedures. Cerebrovasc Dis 2012;34:70–77.

- 104 patients treated with the Solitaire® stent retriever
- 75% of them received also thrombolysis.
- recanalization rate 78%.
- mean NIHSS decreased from 15,3 (before) to 7,8 (after treatment).
- Mortality was 16% (anterior circulation) and 47,8% (posterior circulation).
- Intracranial bleeding occured in 8%.

Imaging-based endovascular therapy for acute anterior circulation stroke treated >8 hours from time last seen well (n=237)

Rates of good outcomes and mortality at 90 days according to revascularization status.



Jovin T G et al. Stroke 2011;42:2206-2211



Jovin TG et al. Stroke 2011 Aug;42(8):2206-11.

67-years old female with tandem occlusion (ICA + MCA), NIHSS=20, presenting 11 h after stroke onset!

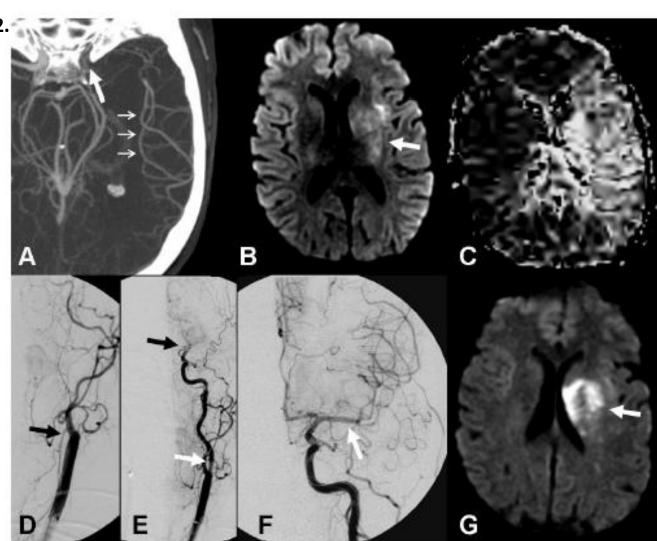
A: CTA shows distal MCA branches (small arrows) = collateral flow.

B: MRI small ischemia, but C: large penumbra.

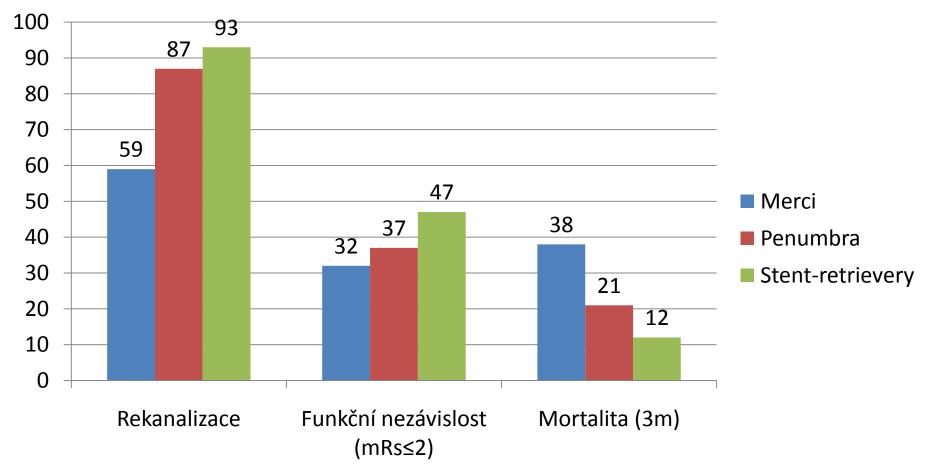
D-F: This CT+MR finding led to catheter-based intervention on both occlusion sites

G: MRI after 24 h: infarct, but nearly entire penumbra saved

3 months later: NIHSS=4, mRS=2.



Almekhlafi MA et al. A Meta-Analysis of Observational Intra-Arterial Stroke Therapy Studies Using the Merci Device, Penumbra System, and Retrievable Stents. AJNR Am J Neuroradiol. 2012 Jul 26. [Epub ahead of print]



• Metaanalýza 16 registrů katetrizačních trombektomií: 4x Merci (n=357), 8x Penumbra (n=455), 4x moderní stent-retrievery Solitaire[®] či Trevo[®] (n=113)

Protocols of the Cardiocenter Vinohrady for the use of catheter-based thrombectomy versus iv. thrombolysis

- 1. Catheter-based thrombectomy (CBT) is the primary treatment strategy and should be done without lytics. Thrombolysis will not be combined with CBT.
- 2. Intravenous thrombolysis (TL) is the secondary treatment strategy whenever CBT cannot be initiated timely (see table). Decision to use thrombolysis means automatically, that the intervention team will not be alerted.

This strategy is based on the following facts from many trials and metaanalyses:

- Thrombolysis increase the risk of intracranial bleeding 3-fold to 10-fold
- The only subgroup of patients deriving mortality benefit from thrombolysis are patients treated within < 90 minutes from stroke onset
- Intraarterial thrombolysis was never shown to be superior to intravenous TL
- Catheter intervention after TL or simultaneously with TL is not superior to TL alone
- The best outcomes seem to be achieved with direct CBT alone (without TL) whenever the intervention can be initiated timely

Catheter-based thrombectomy vs. Thrombolysis in acute stroke

	('RI ctart		CT - CBT >60 min.
Stroke onset – CT scan <90 min.	CBT	TL	TL
Stroke onset - CT 90 - 180 min.	CBT	CBT	TL
Stroke onset - CT 180 - 360 min.	СВТ	CBT	CBT

Thrombolysis, catheter intervention or both?

- Thrombolysis decreases the risk of severe disability but at the price of increased mortality in all subgroups except very early treatment (<90 minutes).
- Intraarterial thrombolysis has no added value over intravenous
- Direct catheter based thrombectomy (CBT) may be the best treatment option if performed without delay.
- This may be implemented by close cooperation between neurologists and cardiologists (STEMI 24/7 networks used for acute stroke).

Summary

- The latest generation of stent retrievers is able to recanalize >70% of occluded intracranial arteries (approximately twice more compared to thrombolysis).
- However, it is not yet known whether this translates to better clinical outcomes.
- The sufficient data on outcomes after primary CBT (without thrombolysis) are still missing and trials comparing iv. thrombolysis versus primary CBT are urgently needed.

Cave! Acute stroke intervention is much more difficult task compared to primary PCI:

- Extremely complex logistics
- Few suitable patients = lack of proper staff training, delays in therapy
- Difficult pharmacotherapy (high risk for i.c. bleed)
- Very short time window (when therapy can help)
- Procedural technique

Future?

- The only approach to be compared with simple i.v. thrombolysis in future trials should be catheter-based thrombectomy with modern stent-retrievers
- Time delay between diagnosis (CT or MR) and invasive angiography should be <45 minutes.
- To organize this in acute stroke setting is a real challenge!

