Cor et Vasa

Available online at www.sciencedirect.com

ScienceDirect

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

ELSEVIER

Původní sdělení | Original research article

The importance of time: Time delays in acute stroke

Giuseppe Marchese[a], Bohumír Procházka[b], Petr Widimský[c]

[a] *Department of Cardiology, University Hospital of Verona, Italy*
[b] *Státní zdravotní ústav, Praha, Česká republika*
[c] *Kardiocentrum 3. lékařské fakulty Univerzity Karlovy a Fakultní nemocnice Královské Vinohrady, Praha, Česká republika*

ARTICLE INFO

Article history:
Received: 9. 12. 2015
Received in revised form: 7. 3. 2016
Accepted: 8. 3. 2016
Available online: 28. 3. 2016

Klíčová slova:
Akutní ischemická cévní mozková příhoda
Endovaskulární léčba
Katetrizační léčba
Trombektomie

SOUHRN

Kontext: Endovaskulární léčba (EVL) těžké akutní ischemické cévní mozkové příhody (iCMP) na podkladě uzávěru velkých cév je účinná a bezpečná. Nicméně stále ještě probíhá diskuse o významu časové prodlevy a využívání vyspělých zobrazovacích metod u penumbry na úkor ztráty cenných minut.
Metody: Provedli jsme metaanalýzu zaměřenou na časový aspekt v randomizovaných klinických studiích (RCT), v nichž se metodicky začaly používat stent-retrievery s novými technologiemi. Zvolený časový interval byla doba od nástupu příznaků až do zavedení katétru do třísla (od doby, kdy byl pacient naposled viděn v pořádku, až do doby zavedení zavaděče na katetrizačním sálu). Primárním sledovaným parametrem byl dobrý funkční výsledek (mRS 0–2) po 90 dnech, mezi sekundární sledované parametry patřily mortalita do 90 dnů a symptomatické krvácení do mozku. Kromě toho jsme provedli subanalýzu pacientů s EVL ve snaze zjistit případné korelace mezi kratší dobou do výkonu a výsledným stavem. Stejnou subanalýzu jsme provedli po zařazení údajů z jednoramenných registrů, v nichž byly použity údaje pacientů, u nichž byl výkon proveden pomocí moderních stent-retrieverů.
Výsledky: Celkem byly analyzovány údaje 1 287 pacientů (pět RCT); 634 pacientů s EVL bylo dále rozděleno do dvou skupin podle časového údaje (kratší/delší než 240 min). Mimoto bylo 1 501 pacientů léčených EVL (devět studií) rozděleno do dvou předem specifikovaných skupin (kratší/delší) a jejich údaje analyzovány. Jak v metaanalýze, tak v subanalýze byl u skupiny s kratší dobou do výkonu zjištěn lepší funkční výsledek po 90 dnech (log OR = –2,07; 95% CI [–3,00 až –1,14]) a méně případů úmrtí (log OR = –0,56; 95% CI [–3,66 až –2,55]); to ukazuje, že doba od nástupu příznaků do zavedení katétru do třísla velmi významně ovlivňuje mortalitu. Naopak nitrolebeční krvácení bylo zaznamenáno častěji ve skupině s dlouhým intervalem (log OR = 0,18; 95% CI [–1,36 až –1,71]), což prokazuje, jak časové prodlevy mohou důsledky iCMP dále zhoršit.
Závěry: Tato metaanalýza přináší další důkazy podporující představu, že v léčbě akutních ischemických cévních mozkových příhod platí, že „čas je mozek". Obecně lze konstatovat, že časně zahájená endovaskulární léčba (punkce třísla do < 4 hodin) významně zlepšuje výsledný stav pacienta. Zdravotnické systémy musejí vyvinout maximální úsilí o zkrácení prodlevy mezi samotnou příhodou a zahájením léčby akutní cévní mozkové příhody v nemocnici. Čím dříve je pacient dopraven do nemocnice, tím důležitější je rychlé zahájení jeho léčby s nadějí na jeho plné neurologické zotavení.

ABSTRACT

Background: Endovascular treatment (EVT) of severe acute ischemic stroke (AIS) determined by large vessel occlusion (LVO) is effective and safe. Debate still goes on especially about time importance and utilization of advanced penumbra imaging at the expense of losing valuable minutes.
Methods: We did a meta-analysis focused on time of randomized clinical trials (RCTs) that started to use methodically the new-tech stent retrievers. The chosen time interval was onset-groin time (from last seen well to sheath insertion in the cathlab). Primary outcome was good functional outcome (mRS of 0–2) at 90 days, secondary outcomes were mortality at 90 days and symptomatic intra-cerebral hemorrhage (sICH). Further-

Address: Giuseppe Marchese, MD, Department of Cardiology, University Hospital of Verona, Ospedale di Borgo Trento, Piazzale Stefani 1, 37126 Verona, Italy, e-mail: dr.gmarchese@gmail.com
DOI: 10.1016/j.crvasa.2016.03.002

Please cite this article as: G. Marchese, et al., The importance of time: Time delays in acute stroke, Cor et Vasa 58 (2016) e225–e232 as published in the online version of *Cor et Vasa* available at http://www.sciencedirect.com/science/article/pii/S0010865016300170

more, we did a sub-analysis of the EVT patients to find a correlation between faster times and outcomes. We did the same sub-analysis including also single-arm registries that used modern stent retrievers.

Results: Totally data from 1287 patients (5 RCTs) were analyzed, whose 634 EVT patients were divided into two groups based on time (faster/slower than 240 min). Furthermore 1501 EVT-treated patients (9 studies) were divided into two pre-specified groups (fast/slow) and analyzed. In both meta-analysis and sub-analysis, the fast group had better functional outcome at 90 days (log OR = –2.07, 95% CI [–3.00, –1.14]) and less deaths (log OR = –0.56, 95% CI [–3.66, –2.55]), demonstrating that onset-groin time has a strong impact even on mortality. On the other hand, sICH resulted to be more frequent in the slow group (log OR = 0.18, 95% CI [–1.36, –1.71]) emphasizing how delays could even worsen AIS.

Conclusions: This meta-analysis supports the "Time is brain" strategy in treatment of acute ischemic stroke. In general, fast endovascular treatment (groin puncture within < 4 h) significantly improves patients' outcomes. Healthcare systems should develop maximal effort to shorten pre-hospital and in-hospital delays in acute stroke patients. The earlier the patient is presenting, the more important is the fast track, offering chance for full neurologic recovery.

Keywords:
Acute ischemic stroke
Catheter-based therapy
Endovascular therapy
Thrombectomy

Introduction

Ischemic stroke is one of the most important causes of death and severe functional disability around the world nowadays, with a very high human price and a strong impact on healthcare systems.

Intra-venous rtPA (iv rtPA) initiated up to 4.5 h from symptom onset is indicated for acute ischemic stroke (AIS) based on the 2013 American Heart Association (AHA) Guidelines [1]. The latest 2015 update from AHA [2] introduced 1A indication for endovascular therapy (EVT) after five recent randomized controlled trials [3–8] (RCT) strongly supported the use of EVT in specifically selected patients, in particular those with evidence of large clots in the distal internal carotid artery (ICA) or in the middle cerebral artery (segment M1 or M2) and with a severe clinical presentation (high NIHSS). Before these successful RCTs, there were three neutral trials during 2013 [9–11] that were not able to demonstrate benefit from EVT due to suboptimal patient selection and old technology (modern thrombectomy retrievers used only in minority of patients).

Going through the recent RCTs, we can point out some differences in methodology and inclusion criteria that could be underestimated or misinterpreted.

The net benefit in terms of good functional outcome for EVT in comparison with the control iv rtPA-alone groups on the eligible patients is now confirmed by recent meta-analysis and review articles [12–16] and the importance of time to revascularization is highlighted by several studies about iv rtPA [17] or EVT [18–20].

We aimed to investigate the influence of time delays on the major outcomes of AIS treated by EVT in the current stent retrievers' era.

Methods

Data sources

We searched PubMed, Cochrane CENTRAL, Web of Science, and the National Institutes of Health Clinical Trials from 1 January 1995 (year of publication of the NINDS rtPA Stroke trial) through 30 October 2015, for English language, peer-reviewed publications. The following Medical Subject Heading terms and/or keywords were used for database searches: 'acute ischemic stroke', 'intra-arterial therapy', 'endovascular treatment', 'endovascular therapy', 'thrombectomy', and 'catheter-based treatment'. Related reviews, clinical trial databases and the reference lists of all retrieved articles were also searched manually for relevant studies. Any disagreements were resolved by discussion.

Study selection and eligibility criteria

We included trials with at least 12 weeks of follow-up, both double-blind and open-label trial designs were eligible for inclusion. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses of RCTs for our protocol [21].

We decided to analyze manuscripts that started to use mechanical thrombectomy with modern stent-retrievers, excluding the neutral 2013 RCTs for their methodology limits already highlighted in other papers [22,23], in particular for their limited use of these last generation devices.

Choice of times and outcomes

We decided to compare the time from the stroke onset (or last seen well) to the sheath insertion in the cathlab (onset-groin time) because it is the most relevant time interval across the studies and the only one always present in all the EVT arms.

The primary specified outcome was the proportion of patients with a good functional outcome defined with the modified Rankin Scale (mRS of 0–2) at 90 days from stroke onset. Secondary outcomes included mortality at 90 days and symptomatic intra-cerebral hemorrhage (sICH). Asymptomatic ICH was defined in different ways across the RCTs so it was excluded from the analysis.

Statistical analysis

Key statistical analysis was conducted by an external independent statistician (B.P.).

To compare the results in different studies the forest chart from metaphor package of program R was used (http://cran.r-project.org/). The problem for quantitative data was that for the same variables were used different descriptions in the different studies: mean and SD, or median and quartiles, or median and minimum and maximum. To solve this problem, we supposed normal distribution and estimated mean as median and we estimated SD from normal distribution with appropriate quartiles, respect to maximum and minimum.

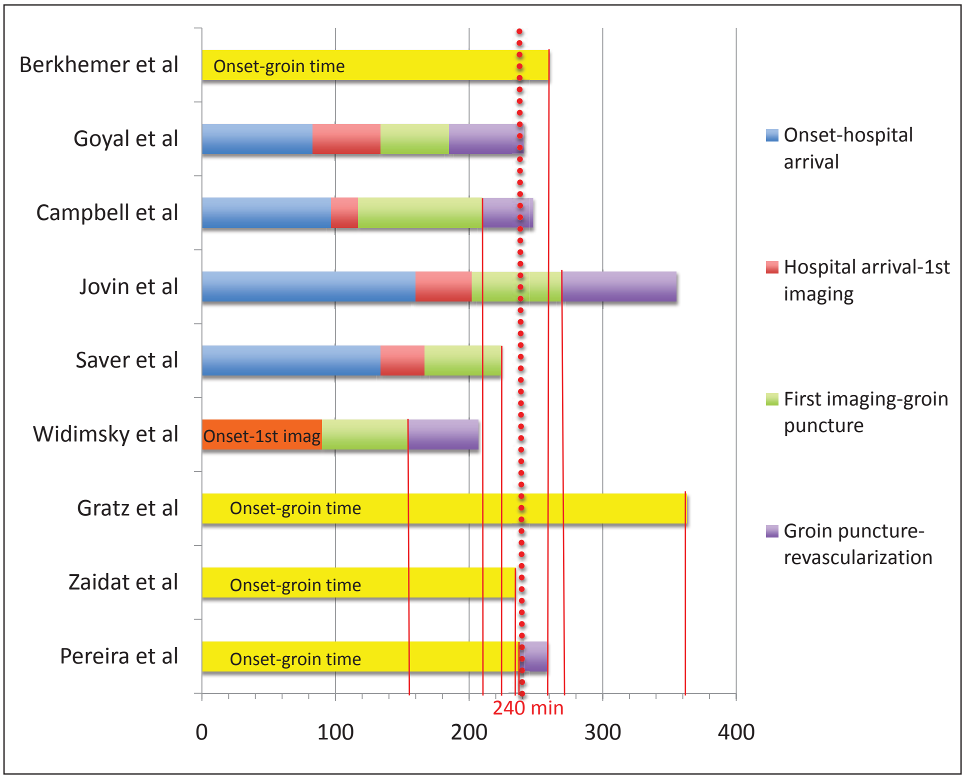

Fig. 1 – Representation of time intervals between the different studies (onset-groin times are compared with vertical red lines).

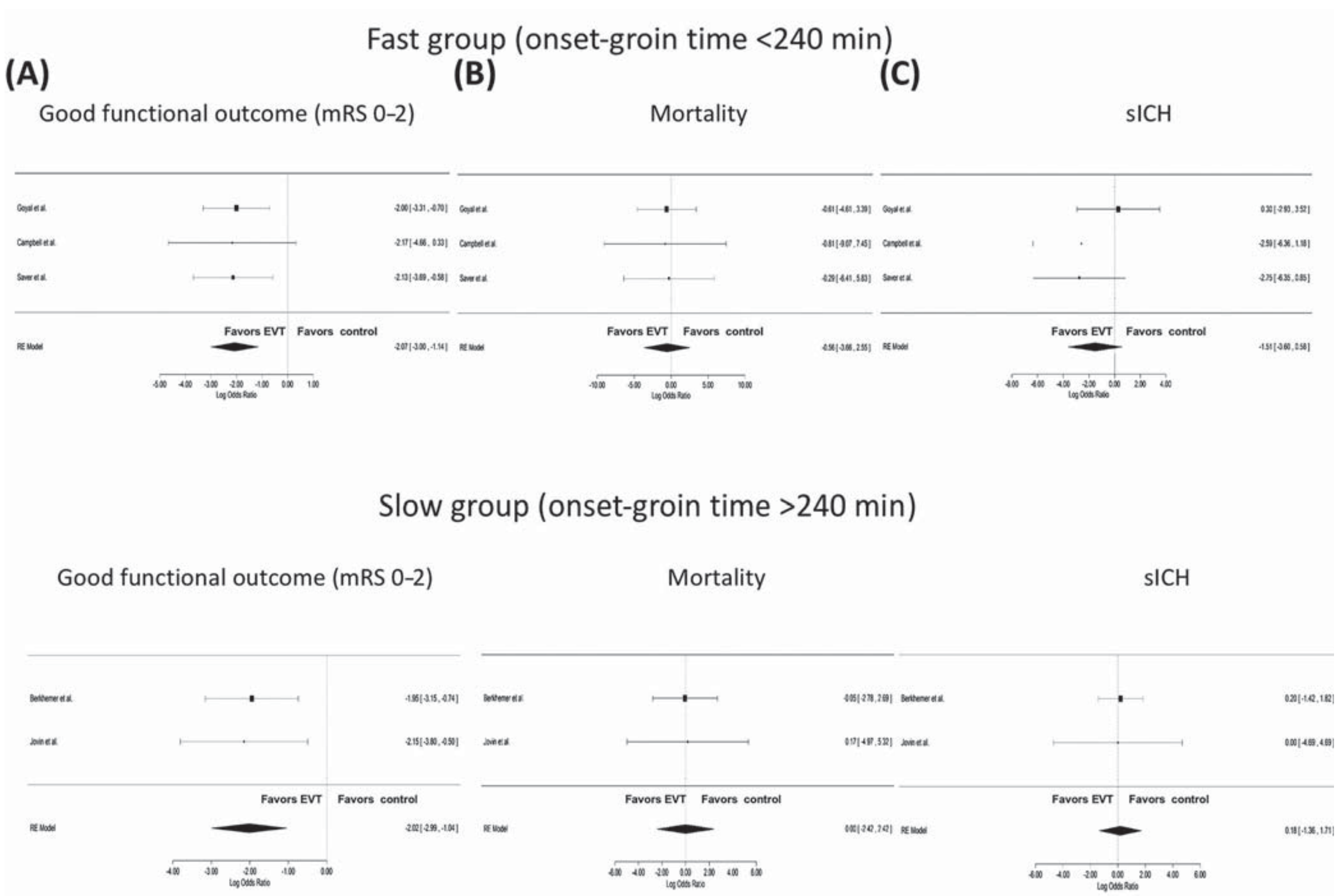

Fig. 2 – Forest plot of the major outcomes in the fast and slow groups. (A) Log OR of good functional outcome (mRS 0–2) in endovascular therapy (EVT) and control arms after 90 days. (B) Log OR of mortality in EVT and control arms after 90 days. (C) Log OR of symptomatic intra-cerebral hemorrhage (sICH) in EVT and control arms.

Table 1 – Study details

Study name	Trial period	Study design	Primary outcome	Secondary outcomes	sICH definition[a]	Stroke imaging	Total patients/ EVT-arm patients (n)	Received iv rtPA in EVT arm	Onset--groin time (min)	Successful reperfusion (TICI 2b–3)
MR CLEAN Berkhemer et al.	2010–2014	RCT	mRS ≤2 at 90 days	NIHSS score after 24 h and other	ECASS II	Non-contrast CT or MRI, CTA/MRA/DSA	500/233	87.1%	260	58.7%
ESCAPE Goyal et al.	2013–2014	RCT	mRS at 90 days	Mortality at 90 day, sICH and other	Any ICH with 2 NIHSS pt. increase	Non-contrast CT, CTA (multiphase)	315/165	72.7%	185	72.4%
EXTEND-IA Campbell et al.	2012–2014	RCT	Reperfusion at 24 h and early neurologic improvement	Mortality at 90 days and sICH	SITS-MOST	Non-contrast CT, CTA/ MRA, perfusion CT or diffusion MRI	70/35	100%	210	86.2%
REVASCAT Jovin et al.	2012–2014	RCT	mRS at 90 days	Mortality at 90 days, sICH and other	Both	Non-contrast CT or MRI, CTA/MRA, angiogram	206/103	68%	269	65.7%
SWIFT-PRIME Saver et al.	2012–2014	RCT	mRS at 90 days	mRS ≤2 and mortality at 90 days, sICH and other	NA	Non-contrast CT or MRI, CTA/MRA	196/93	98%	224	88%
CARDIO-NEURO REGISTRY Widimsky et al.	2012–2014	Single-arm registry	mRS ≤2 at 90 days and successful recanilization	Mortality at 90 days and sICH	ECASS II	Non-contrast CT, CTA	84/84	0%	165	74% TICI 2a–3
BERNESE STROKE REGISTRY Gratz et al.	2010–2012	Single-arm registry	mRS ≤2 at 90 days and successful recanilization	Mortality at 90 days and sICH, device adv. events	ECASS II	Non-contrast CT or MRI, CTA	227/227	NA	363	72.5%
NASA REGISTRY Zaidat et al.	2012–2013	Single-arm registry	Successful recanilization	mRS ≤2 and mortality at 90 days, sICH	ECASS II	Non-contrast CT or MRI, CTA/MRA	354/354	NA	235	70.9%
STAR REGISTRY Pereira et al.	2010–2012	Single-arm registry	mRS ≤2 at 90 days and successful recanilization	Mortality at 90 days and sICH, device adv. events	ECASS II	Non-contrast CT or MRI, CTA	202/202	59%	238	88.1%

CTA – CT angiography; DSA – digital subtraction angiography; EVT – endovascular therapy; iv rtPA – intra-venous plasminogen activator; MRA – MR angiography; mRS ≤2 – good functional outcome; NA – not assessed; NIHSS – National Institutes of Health Stroke Scale; RCT – randomized controlled trial; sICH – symptomatic intra-cerebral hemorrhage; TICI – modified Thrombolysis in Cerebral Infarction.
[a] Symptomatic intracranial hemorrhage was defined as parenchymal hemorrhage type 2 on follow-up imaging and neurologic deterioration of at least 4 points on the NIHSS, according to the Safe Implementation of Thrombolysis in Stroke – Monitoring Study (SITS-MOST) criteria, or any symptomatic intracranial hemorrhage and neurologic worsening of at least 4 points on the NIHSS, according to the second European–Australasian Acute Stroke Study (ECASS II) criteria.

The estimated median onset-groin time was 229.9 min for the EVT arm patients so we decided to dichotomize them in two pre-specified groups (fast/slow): faster or slower than 4 h (240 min) to see the impact of time on outcomes.

For representation of the results we use forest plot (for all, iv rtPA/EVT arms, fast/slow groups) of logarithmic odds ratio (log OR) and their 95% confidence interval (95% CI). To compare the impact of iv rtPA/EVT arms or fast/slow groups we used bootstrapping ANOVA model with nuisance categorical parameter [24]. For the qualitative variables we used the forest charts and the Mantel-Haenszel test with nuisance categorical parameter [25].

Moreover, we made crude odds ratio (OR) to directly compare fast/slow groups inside the EVT arms, using analysis of contingency tables (chi-square or Fisher's test) to calculate the association between qualitative variables thus correlating outcomes with the two pre-specified groups [25]. We considered significance level of 5% ($p < 0.05$).

Results

Included studies

Totally 3741 articles were found in the databases and only 27 met eligibility criteria for full text evaluation. Of these, we did a meta-analysis of the five recent trials starting from the end 2014 (MR CLEAN) to have a comparison between time and the different outcomes in all these successful RCTs; we did also a sub-analysis to correlate time and outcomes only in the EVT treated patients (fast/slow groups).

Moreover, we did a sub-analysis (crude OR) including also single arm registries [26–29] to make a direct comparison between time and the different outcomes only between EVT arms of these nine studies.

Study characteristics are shown in Table 1 and the different time intervals of the included studies in Fig. 1.

RCT meta-analysis and sub-analysis

A total of 1287 patients were included from the 5 RCTs, 634 for EVT arms and 653 for control arms (mostly iv rtPA). Dividing the EVT arms in two groups based on time, we have a total of 298 patients in the fast group (mean onset-groin time 207.64 min) and 336 in the slow one (mean onset-groin time 263.83 min).

There were no differences between the two groups in mean age (fast group 68.01 versus slow group 65.74, [CI for difference (–4.25, 8.78), $p = 0.248$]), ASPECT score (9 versus 8, [CI for difference (–1.78, 3.78), $p = 0.24$]) and NIHSS (16.67 versus 17.00, [CI for difference (–4.31, 3.64), $p = 0.434$]).

The pooled log odds ratio for primary and secondary outcomes are shown in Fig. 2 and the crude OR with p-value are shown in Table 2.

Good functional outcome was achieved from 46% of patients treated with EVT against 26% of controls with significant difference (log OR= –2.05, 95% CI [–2.72, –1.37]). The fast group has a higher difference of log OR for good functional outcome than the slow (–2.07 vs –2.02). Comparing fast/slow groups 171 patients (57.6%)

Based on the crude OR, sICHs were significantly lower in the fast group (OR = 3.080 [1.220, 7.776], $p = 0.006$).

EVT studies sub-analysis

A total of 1501 patients from 9 studies were divided in the two pre-specified groups: 811 patients from six studies in the fast group (mean onset-groin time <240 min) and 690 from three studies in the slow group (>240 min).

The crude OR with *p*-value is shown in Table 3.

For the fast group 411 patients (51.1%) had good functional outcome against 253 for the slow group (38.9%) with a statistically significant difference (OR = 1.645 [1.334, 2.029], $p < 0.001$). Looking to mortality, deaths were considerably lower in the fast group than in the slow one (121 patients [15%] versus 163 [25%]: OR = 0.530 [0.408, 0.689], $p < 0.001$). Also sICHs were less for the fasters than for the slowers with statistically significant difference (OR = 0.645 [0.427, 0.975], $p = 0.036$).

Discussion

In this study we highlighted the importance of time delays in managing the hyperacute phase of ischemic stroke and our results confirmed that all the outcomes are improved when the onset-groin time is shortened. In both meta-analysis and sub-analysis, the fast group has better functional outcome at 90 days and less deaths, demonstrating that onset-groin time has a strong impact even on mortality. On the other hand, it is impressive how sICH results to be more frequent in the slow group emphasizing how time could play a role in the development of the major complication of AIS.

From our interventional cardiology background, time runs faster for brain than for muscle in the heart: it was estimated that each minute 1.9 million neurons, 14 billion synapses and 12 km of myelinated fibers are destroyed [30].

From a recent meta-analysis [20] it seems that for every thousand patients treated, every 15-min acceleration is associated with a 34 more patients having reduced final disability by one or more levels on the mRS and that for every 5-min delay in endovascular reperfusion, 1 out of every 100 patients treated has a worse disability outcome.

We want to focus on the logistic organization of the out-of-hospital and in-hospital stroke network, trying to find some critical points that could improve the onset-reperfusion time.

We strongly believe that the stroke care community needs the more simplified clinical-diagnostic algorithm to discriminate the acute stroke patients that could benefit from EVT, especially for those with onset-groin time < 4 h (*early comers*).

As for the STEMI guidelines development during the last 20 years, in which we assisted how ECG played a paramount role in discriminating patients that need a primary PCI versus the others that can wait for a belated interventional approach, we need a "black&white" criterion able to direct to the cathlab this group of patients that could benefit from prompt EVT. The pivotal role of CT angiography is now clear and it is considered mandatory to define large vessel occlusion (LVO) strokes while there is still big debate on the use of additional advanced penumbra imaging (API) to assess perfusion or collateral circulation, over the basic CT to exclude ICH and define the infarct area. In hyperacute stroke management, there is the need of a super-fast imaging protocol to minimize the onset-1st imaging-groin time intervals, avoiding any useless loss of time.

Even if the trials that used API had the highest proportion of patients with mRS 0–2 at 90 days, the knowledge of the number of patients who were excluded by various imaging approaches is incomplete. EXTEND-IA is the only trial that reported reasons for exclusion based on screening log data: of patients treated with rtPA, 495 of 1044 (47%) were excluded because of an absence of evidence for LVO on CT angiography and only a little proportion of patients (4% overall) were excluded by perfusion imaging criteria [31].

A group of studies [32–34] support the idea that time is less important than demonstrating salvageable brain tissue with a perfusion–diffusion mismatch: Lansberg et al. [32] state that "because time is an imprecise surrogate for the presence of salvageable brain tissue, it is also an imperfect criterion for selecting patients who are likely to benefit from reperfusion". This opinion could keep the community in the wrong direction, we cannot focus our attention on this percentage of patients that for different reasons have a stable penumbra as time goes on (di-

Table 2 – Crude OR and *p*-value for the 5 studies sub-analysis

	Fast group	Slow group	OR (95% CI)	*p*-value
mRS ≤2	171/297 (57.6%)	121/336 (36%)	0.415 (0.301, 0.571)	<0.0001
Mortality	29/298 (9.7%)	68/336 (20.2%)	2.354 (1.476, 3.752)	<0.0001
sICH	6/298 (2%)	20/336 (5.9%)	3.080 (1.220, 7.776)	0.006

mRS ≤2 – good functional outcome; sICH – symptomatic intra-cerebral hemorrhage.

Table 3 – Crude OR and *p*-value for the 9 studies sub-analysis

	Fast group	Slow group	OR (95% CI)	*p*-value
mRS ≤2	411/804 (51.1%)	253/651 (38.9%)	1.645 (1.334, 2.029)	<0.0001
Death	121/806 (15%)	163/651 (25%)	0.530 (0.408, 0.689)	<0.0001
sICH	43/810 (5.3%)	55/688 (8%)	0.645 (0.427, 0.975)	0.018

mRS ≤2 – good functional outcome; sICH – symptomatic intra-cerebral hemorrhage.

fferent stroke pathophysiology, very good collateral circulation) but we all need to accelerate the triage system to allow that the number of *early-comers* will grow and all the initiatives to shorten the intra-hospital logistics, comprising the fastest imaging protocol to keep in the cathlab patients with LVO.

For this purpose, it could be useful to develop a score system to identify severe strokes (NIHHS > 15) with LVO at the time of stroke onset, especially in the out-of-hospital setting [35]. Moreover, there are some studies that tested the usage of ambulances working as mobile stroke unit with the possibility to perform 1st-imaging and start iv rtPA, to direct properly AIS patients to Primary Stroke Centers and to further shorten the onset-groin time thus annulling the door-1st imaging time [36,37].

Coming back to both DEFUSE-2 [32] and Prabhakaran's multi-center registry [33], onset-groin times were longer than 4 h so it is not possible to have a direct comparison between those who had API with a group of real *early-comers* that could benefit of a fast-track approach. Furthermore, API techniques are paramount for evaluation of the *late-arrivals*, intended as patients with onset-groin time longer than 6 h, and it is reasonable to extend the EVT window to 12–24 h for this group of patients with still a high amount of salvageable tissue demonstrated by API, looking forward for the results of the ongoing DAWN and POSITIVE trials.

But the major purpose of AIS community should be to speed up all the healthcare systems to avoid these delays to still happen; there are some centers that experimented successfully a collaborative cardio-neurologic cooperation [29], exploiting a tested and effective system for out-of-hospital care as the STEMI networks and a 24/7 emergency service (maybe with the double alert system), bypassing emergency room and intensive care unit, thus going directly to CT suite and after to the cathlab or better with a fast-track single-stop approach [38], without useless in-hospital transfers [39].

The helping hand of the interventional cardiologist is now offered, the stroke community should be interested in shaking it.

Conclusion

This meta-analysis supports the "Time is brain" strategy in treatment of acute ischemic stroke. In general, fast endovascular treatment (groin puncture within <4 h) significantly improves patients' outcomes. Healthcare systems should develop maximal effort to shorten pre-hospital and in-hospital delays in acute stroke patients. The earlier the patient is presenting, the more important fast track is offering chance for full neurologic recovery.

Conflict of interest
No conflict of interest.

Funding body
None.

Ethical statement
I declare, on behalf of all authors, that the research was conducted according to Declaration of Helsinki.

Informed consent
I declare that informed consent requirements do not apply to this manuscript.

References

[1] E.C. Jauch, J.L. Saver, H.P. Adams Jr., et al., Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 44 (2013) 870–947.
[2] W.J. Powers, C.P. Derdeyn, J. Biller, et al., 2015 AHA/ASA Q4 Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association, Stroke 46 (2015) 3020–3035.
[3] O.A. Berkhemer, P.S. Fransen, D. Beumer, et al., MR CLEAN Investigators, A randomized trial of intraarterial treatment for acute ischemic stroke, New England Journal of Medicine 372 (2015) 11–20.
[4] B.C. Campbell, P.J. Mitchell, T.J. Kleinig, et al., The EXTEND-IA Investigators, Endovascular therapy for ischemic stroke with perfusion-imaging selection, New England Journal of Medicine 372 (2015) 1009–1018.
[5] M. Goyal, A.M. Demchuk, B.K. Menon, et al., The ESCAPE Trial Investigators, Randomized assessment of rapid endovascular treatment of ischemic stroke, New England Journal of Medicine 372 (2015) 1019–1030.
[6] J.L. Saver, M. Goyal, A. Bonafe, et al., Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke, New England Journal of Medicine 372 (2015) 2285–2295.
[7] T.G. Jovin, A. Chamorro, E. Cobo, et al., REVASCAT Trial Investigators, Thrombectomy within 8 hours after symptom onset in ischemic stroke, New England Journal of Medicine 372 (2015) 2296–2306.
[8] J. Mocco, O. Zaidat, R. Von Kummer, et al. THERAPY TRIAL, for the Penumbra Therapy Trial Investigators, Presented at the European Stroke Organisation Conference (ESOC 2015), Glasgow, 2015, http://www.eso-stroke.org/eso-stroke/esoactivities/eso-meetings-2015.html (20. 4. 2015).
[9] J.P. Broderick, Y.Y. Palesch, A.M. Demchuk, et al., Interventional Management of Stroke (IMS) III Investigators, Endovascular therapy after intravenous t-PA versus t-PA alone for stroke, New England Journal of Medicine 368 (2013) 893–903.
[10] A. Ciccone, L. Valvassori, M. Nichelatti, et al., SYNTHESIS Expansion Investigators, Endovascular treatment for acute ischemic stroke, New England Journal of Medicine 368 (2013) 904–913.
[11] C.S. Kidwell, R. Jahan, J. Gornbein, et al., MR RESCUE Investigators, A trial of imaging selection and endovascular treatment for ischemic stroke, New England Journal of Medicine 368 (2013) 914–923.
[12] K.M. Fargen, D. Neal, D.J. Fiorella, et al., A meta-analysis of prospective randomized controlled trials evaluating endovascular therapy for acute ischemic stroke, Journal of Neurointerventional Surgery 7 (2015) 85–90.
[13] P. Sardar, S. Chatterjee, J. Giri, et al., Endovascular therapy for acute ischaemic stroke: a systematic review and metaanalysis of randomized trials, European Heart Journal 36 (2015) 2373–2380.
[14] A. Falk-Delgado, Å. Kuntze Söderqvist, J. Fransén, A. Falk-Delgado, Improved clinical outcome 3 months after endovascular treatment, including thrombectomy, in patients with acute ischemic stroke: a meta-analysis, Journal of Neurointerventional Surgery (2015) 1–7.
[15] C. Yarbrough, C. Ong, A. Beyer, et al., Endovascular thrombectomy for anterior circulation stroke – systematic review and meta-analysis, Stroke 46 (2015) 3177–3183.
[16] S. Prabhakaran, I. Ruff, R.A. Bernstein, Acute stroke intervention: a systematic review, Journal of the American Medical Association 13 (2015) 1451–1462.

[17] J. Emberson, K.R. Lees, P. Lyden, et al., Effect of treatment delay, age and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomized trials, Lancet 384 (2014) 1929–1935.
[18] M. Mazighi, S.A. Chaudhry, M. Ribo, et al., Impact of onset-to-reperfusion time on stroke mortality: a collaborative pooled analysis, Circulation 127 (2013) 1980–1985.
[19] P. Khatri, S.D. Yeatts, M. Mazighi, et al., IMS III Trialists, Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial, Lancet Neurology 13 (2014) 567–574.
[20] S.A. Sheth, R. Jahan, J. Gralla, et al., Time to endovascular reperfusion and degree of disability in acute stroke, Annals of Neurology 78 (2015) 584–593.
[21] A. Liberati, D.G. Altman, J. Tetzlaff, et al., The PRISMA statement for reporting systematic reviews and metaanalyses of studies that evaluate health care interventions: explanation and elaboration, Annals of Internal Medicine 151 (2009) W65–W94.
[22] F.C. Albuquerque, D. Fiorella, J.A. Hirsch, et al., The tribulations of stroke trials, Journal of Neurointerventional Surgery 5 (2013) 181–183.
[23] J. Mocco, D. Fiorella, K.M. Fargen, et al., Endovascular therapy for acute ischemic stroke is indicated and evidence based: a position statement, Journal of Neurointerventional Surgery 7 (2015) 79–81.
[24] P. Armitage, T. Colton, Encyclopedia of Biostatistics, Wiley, Chichester, 1998.
[25] M.H. Gail, J. Benichou, Encyclopedia of Epidemiologic Methods, Wiley, Chichester, 2000.
[26] V.M. Pereira, J. Gralla, A. Davalos, et al., Prospective, multicenter, single-arm study of mechanical thrombectomy using Solitaire Flow Restoration in acute ischemic stroke, Stroke 44 (2013) 2802–2807.
[27] P.P. Gratz, S. Jung, G. Schroth, et al., Outcome of standard and high-risk patients with acute anterior circulation stroke after stent retriever thrombectomy, Stroke 45 (2014) 152–158.
[28] O.O. Zaidat, A.C. Castonguay, R. Gupta, et al., North American Solitaire Stent Retriever Acute Stroke registry: postmarketing revascularization and clinical outcome results, Journal of Neurointerventional Surgery 6 (2014) 584–588.
[29] P. Widimsky, T. Asil, M. Abelson, et al., Direct catheter-based thrombectomy for acute ischemic stroke: outcomes of consecutive patients treated in interventional cardiology centers in close cooperation with neurologists, Journal of the American College of Cardiology 66 (2015) 487–488.
[30] J.L. Saver, Time is brain – quantified, Stroke 37 (2006) 263–266.
[31] B.C. Campbell, G.A. Donnan, K.R. Lees, et al., Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke, Lancet Neurology 14 (2015) 846–854.
[32] M.G. Lansberg, C.W. Cereda, M. Mlynash, et al., Response to endovascular reperfusion is not time-dependent in patients with salvageable tissue, Neurology 85 (2015) 708–714.
[33] S. Prabhakaran, M. Soltanolkotabi, A.R. Honarmand, et al., Perfusion-based selection for endovascular reperfusion therapy in anterior circulation acute ischemic stroke, American Journal of Neuroradiology 35 (2014) 1303–1308.
[34] A.P. Tansy, J.D. Hinman, K.L. Ng, et al., Image more to save more, Frontiers in Neurology 6 (2015) 156.
[35] B.S. Katz, J.T. McMullan, H. Sucharew, et al., Design and validation of a prehospital scale to predict stroke severity: Cincinnati Prehospital Stroke Severity Scale, Stroke 46 (2015) 1508–1512.
[36] M. Ebinger, A. Kunz, M. Wendt, et al., Effects of golden hour thrombolysis. A Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) Substudy, JAMA Neurology 72 (2015) 25–30.
[37] R. Cerejo, S. John, A.B. Buletko, et al., A mobile stroke treatment unit for field triage of patients for intraarterial revascularization therapy, Journal of Neuroimaging 25 (2015) 940–945.
[38] P. Lanzer, P. Widimský, Ischaemic stroke and ST-segment elevation myocardial infarction: fast-track single-stop approach, European Heart Journal 36 (2015) 2348–2355.
[39] P. Widimsky, L.N. Hopkins, Catheter-based interventions for acute ischaemic stroke, European Heart Journal (2015) (Epub ahead of print).