SOCIETÀ MEDICA DI SANTA MARIA NUOVA

XI EDIZIONE

Giornate Mediche di Santa Maria Nuova 2019

PROGETTUALITÀ E INNOVAZIONI A SANTA MARIA NUOVA E NELL'AZIENDA USL TOSCANA CENTRO

Tra scienza, aspetti normativi e sostenibilità

3-4 Ottobre 2019

La RM encefalo in acuto: guida per l'estensione delle indicazioni alla trombolisi nello stroke

A. Giuello
DEA Ospedale Santa Maria Nuova
Firenze

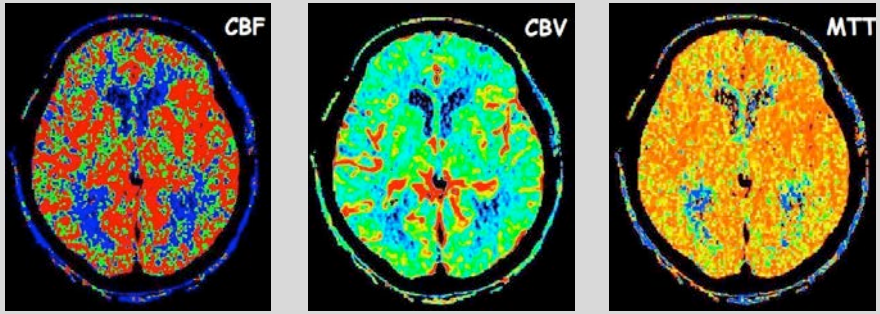
Azienda USL Toscana centro
Servizio Sanitario della Toscana

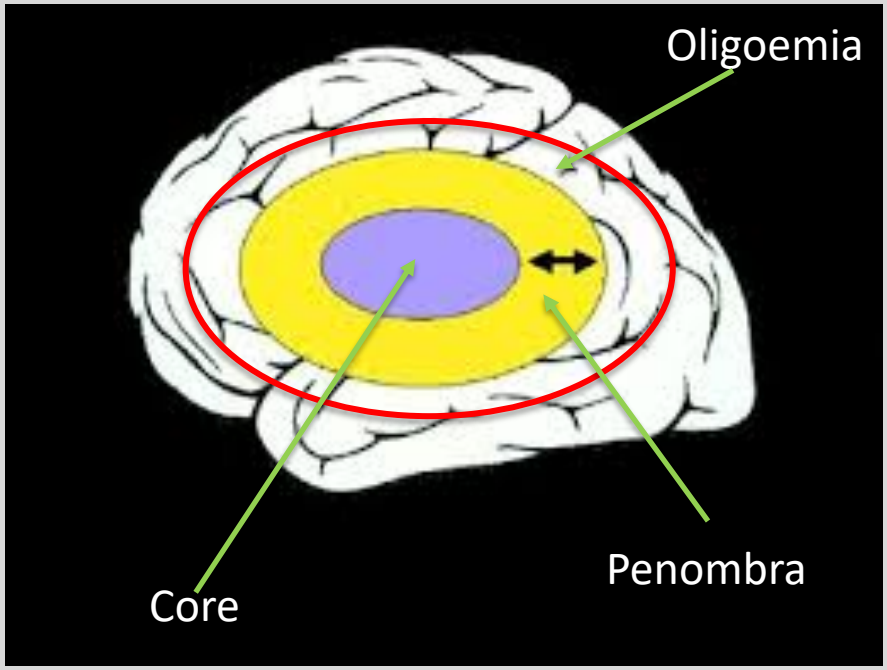
La sottoscritta Alessandra Giuello,
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

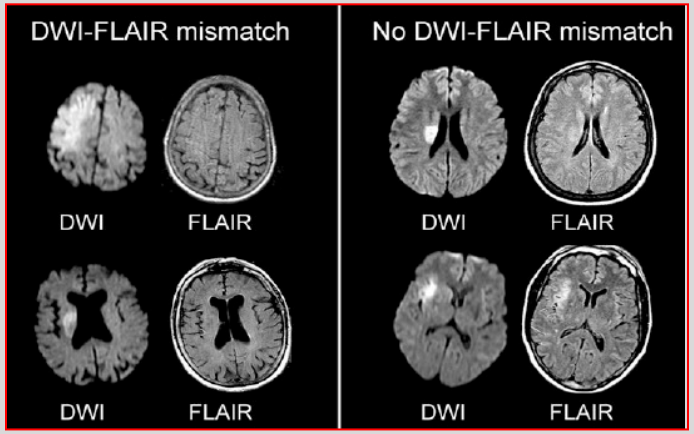
che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

TC perfusion





Mismatch DWI-FLAIR



- **Elevata specificità**
- **Valore predittivo positivo**

DWI–FLAIR-mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study.

Lancet Neurol 2011;10:978–86.

2.2. Brain Imaging	COR	LOE
1. All patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival to hospital. In most cases, noncontrast CT (NCCT) will provide the necessary information to make decisions about acute management.	I	B-NR

Powers et al 2018 Guidelines for Management of Acute Ischemic Stroke

Raccomandazione 5.2.a **Forte a favore**

E' raccomandato eseguire una TC cerebrale o una RM encefalo, in emergenza, per distinguere l'ictus emorragico da quello ischemico; la TC è considerata l'esame di primo livello nella fase acuta.

Raccomandazione 5.2.b **Forte a favore**

Prima di ogni trattamento specifico per l'ictus ischemico è raccomandata l'esecuzione in emergenza dell'imaging cerebrale. Nella maggior parte dei casi, un esame TC eseguito in condizioni basali, senza somministrazione del contrasto, fornirà le informazioni necessarie per prendere decisioni circa la gestione dell'emergenza.

SPREAD Linee guida italiane di prevenzione e trattamento
Raccomandazioni e sintesi -21 luglio 2016

Il trattamento con r-tPA e.v. (0,9 mg/kg, dose massima 90 mg, il 10% della dose in bolo, il rimanente in infusione di 60 minuti) è raccomandato entro 4.5 ore dall'esordio di un ictus ischemico senza limiti superiori di età e di gravità. È comunque indicato che il trattamento sia effettuato il più precocemente possibile (Raccomandazione 9.1)

Powers et al 2018

Guidelines for Management of Acute Ischemic Stroke

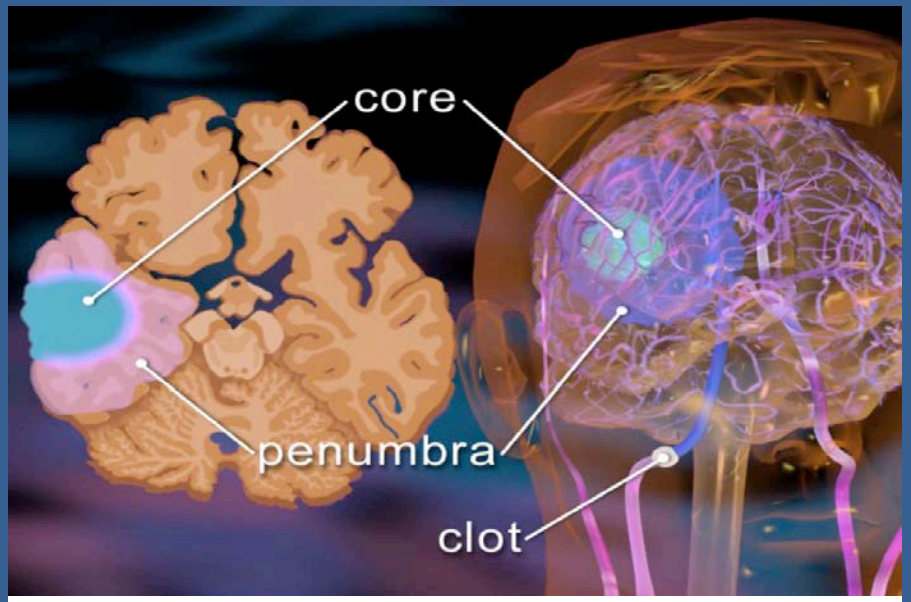
1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 6 to determine patient eligibility.	I	A
IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in Table 6 determine patient eligibility.	I	B-R
16. In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible.	I	A

RICANALIZZAZIONE PRECOCE

OUTCOME MIGLIORE

Penombra ischemica

- severamente ipoperfusa
- danneggiata in modo reversibile
- ancora vitale
- a rischio di infarto se non riperfusa



Le dimensioni dipendono da:

- circoli collaterali
- severità ischemia
- estensione ischemia
- durata ischemia

Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 y
Per Hour	120 million	830 billion	714 km/447 miles	3.6 y
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 wk
Per Second	32 000	230 million	200 meters/218 yards	8.7 h

Ictus ad esordio non determinato

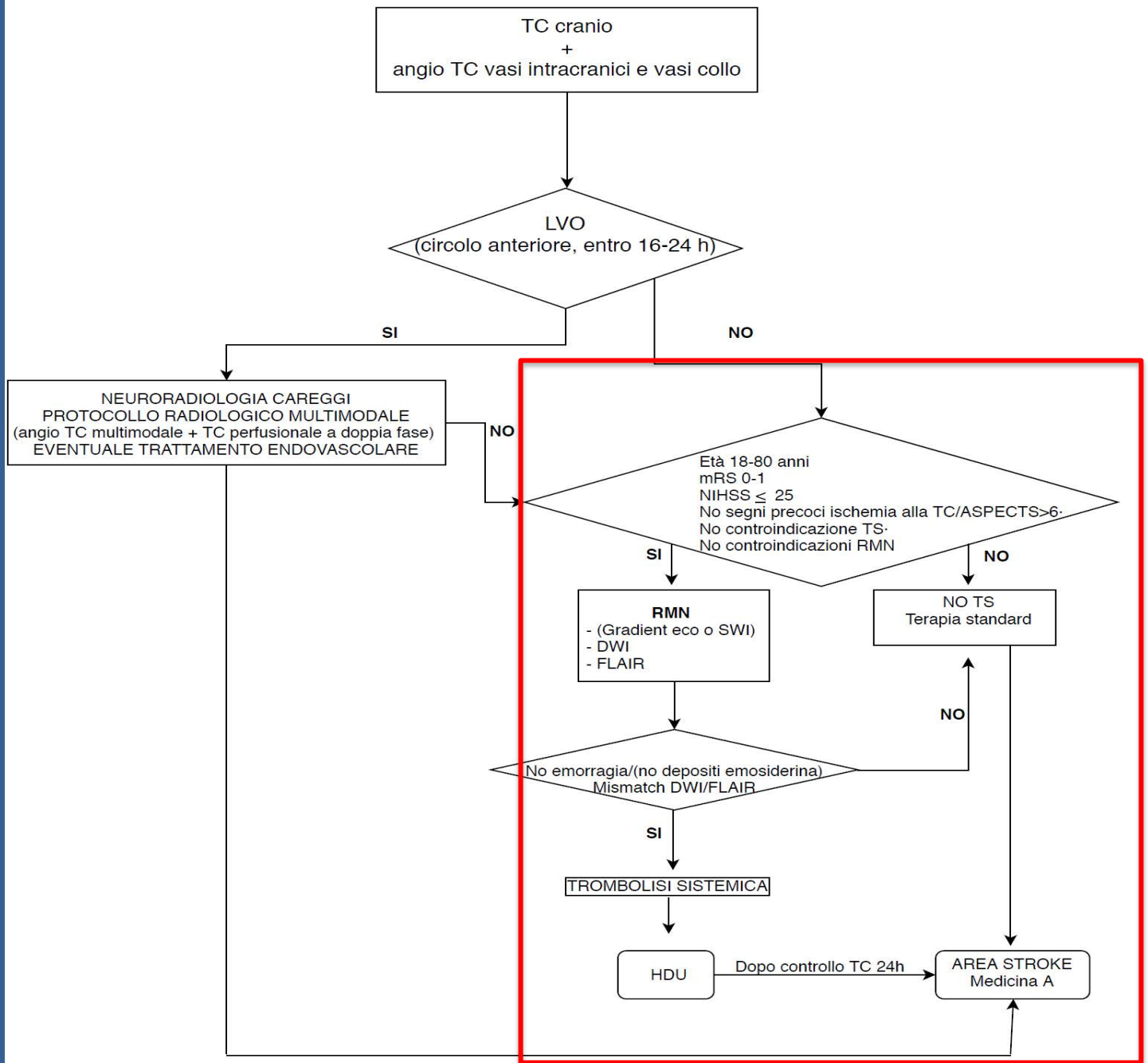
Quanti sono? 20-25%

- Prima causa di invalidità nel mondo
- Seconda causa di demenza nel mondo
- Terza causa di mortalità nei paesi occidentali
- Mortalità a 30 giorni 20%, mortalità a un anno 30%
- 30% sopravvive con una significativa disabilità
- Entro i prossimi 20 anni aumento >30% del numero totale di ictus nell'Unione Europea
- Almeno 100.000 nuovi ricoveri per ictus cerebrale in Italia
- Attualmente in Italia circa 1 milione di persone vive con gli esiti invalidanti di un ictus
- I costi diretti per il SSN ammontano a circa 16 milioni di euro/anno
- 5 milioni di euro/anno in termini di costi indiretti (perdita di produttività)

Si stima che almeno 1/3 dei pazienti con ictus ad esordio indeterminato possa essere candidato a trattamento riperfusivo

Cerebrovasc Dis. 2003;16:128–133
Neurology 2011;76:1662-7
Front Neurol 2014; 5: 35

ICTUS AD ESORDIO NON DETERMINATO



Overview of Reports of Reperfusion Treatment in Stroke With Unknown Onset

References	Sample Size*	Treatment	Imaging Concept	Exclusion of Large Infarct Lesions	Exclusion by Estimation of Lesion Age	Median NIHSS o.a.	mRS 0–2 at Day 90	Mortality at Day 90	SICH
IV tPA only									
Aoki et al[26]	10	IV tPA	DWI–FLAIR mismatch	Yes	Yes	14	40%	0%	0%
Bai et al[27]	48	IV tPA	DWI–FLAIR mismatch	Yes	Yes	11†	‡	‡	‡
Breuer et al[24]	10	IV tPA	Penumbral: MRI	Yes	Yes	10.5	50%	n.a.	0%
Ebinger et al[25]	17	IV tPA	n.s. (MRI was used in all patients)	n.a.	n.a.	13	35.3%	0%	0%
Manawadu et al[15]	68	IV tPA	NCCT	Yes	No	11.5	36.8%	14.7%	2.9%
Michel et al[30]	6	IV tPA	Penumbral: CTP	Yes	No	17	66.7%	0%	0%
IV tPA+endovascular treatment									
Barreto et al[31]	46	IV tPA/endovascular	Individual decision, mainly NCCT	Yes	No	16	28%	15%	4.3%
Cho et al[28]	32	IV tPA/endovascular	Penumbral: MRI	Yes	Yes	14.5	50%	n.a.	6.3%
Kang et al[29]	83	IV tPA/endovascular	Penumbral: MRI	Yes	Yes	14	44.6%	n.a.	3.6%
Kim et al[14]	29	IV tPA/endovascular	NCCT	Yes	No	13	44.8%	10.3%	10.3%
Endovascular treatment									
Aghaebrahim et al[32]	78	Endovascular (several)	Penumbral: MRI or CTP	Individual decision	No	15†	43%	21%	n.a.
Jung et al[33]	55	Endovascular (several)	Individual decision (penumbral: MRI in 58%)	Yes	Yes	15	37%	25.9%	3.7%
Mokin et al[34]	52	Endovascular (MT+aspiration)	Penumbral: CTP	Yes	No	…	48.1%	23.8%	13.5%
Natarajan et al[35]	21	Endovascular (several)	Penumbral: CTP	Individual decision	No	14†	42.9%	n.a.	14.3%
Stampfl et al[36]	19	Endovascular (MT only)	Penumbral: MRI or CTP	Yes	No	17	10.5%	36.8%	21.1%

Stroke. 2015;46:2707-2713. DOI: 10.1161/STROKEAHA.115.009701

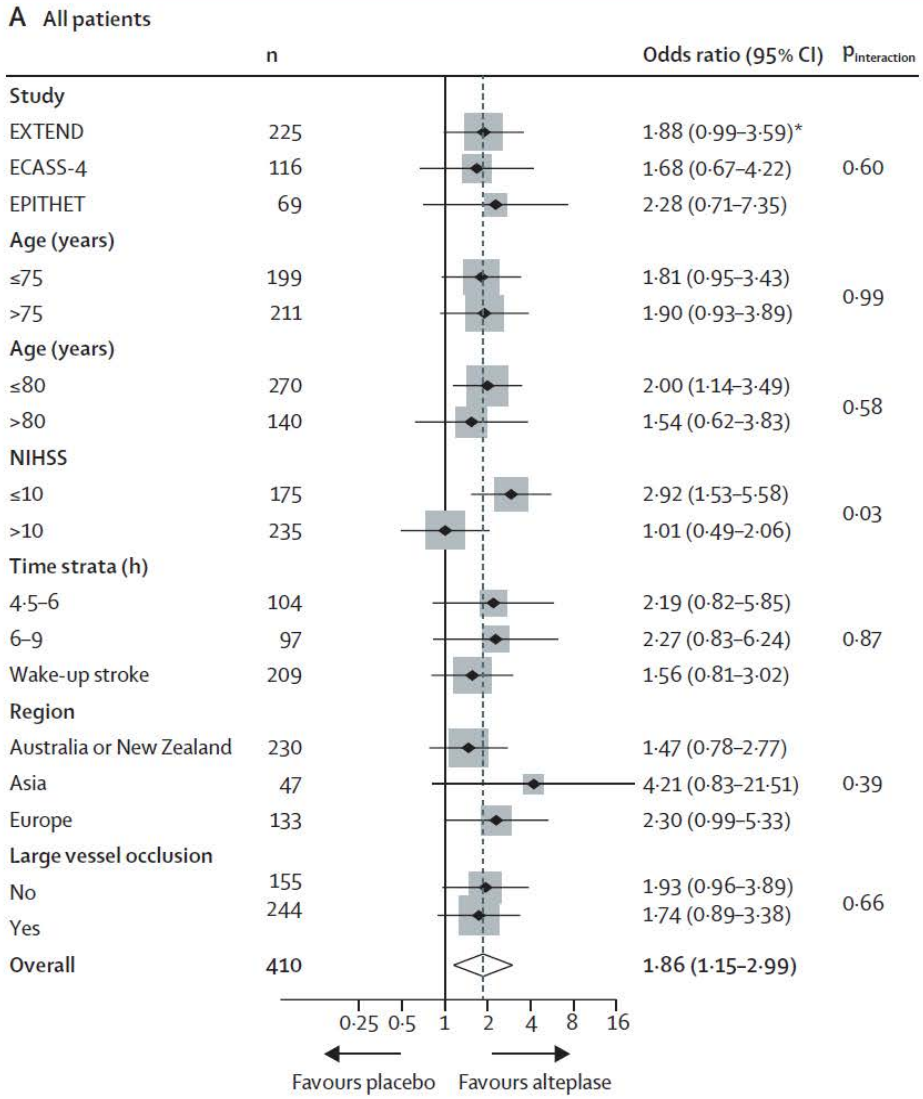
Trials Enrolling Stroke Patients With Unknown Onset

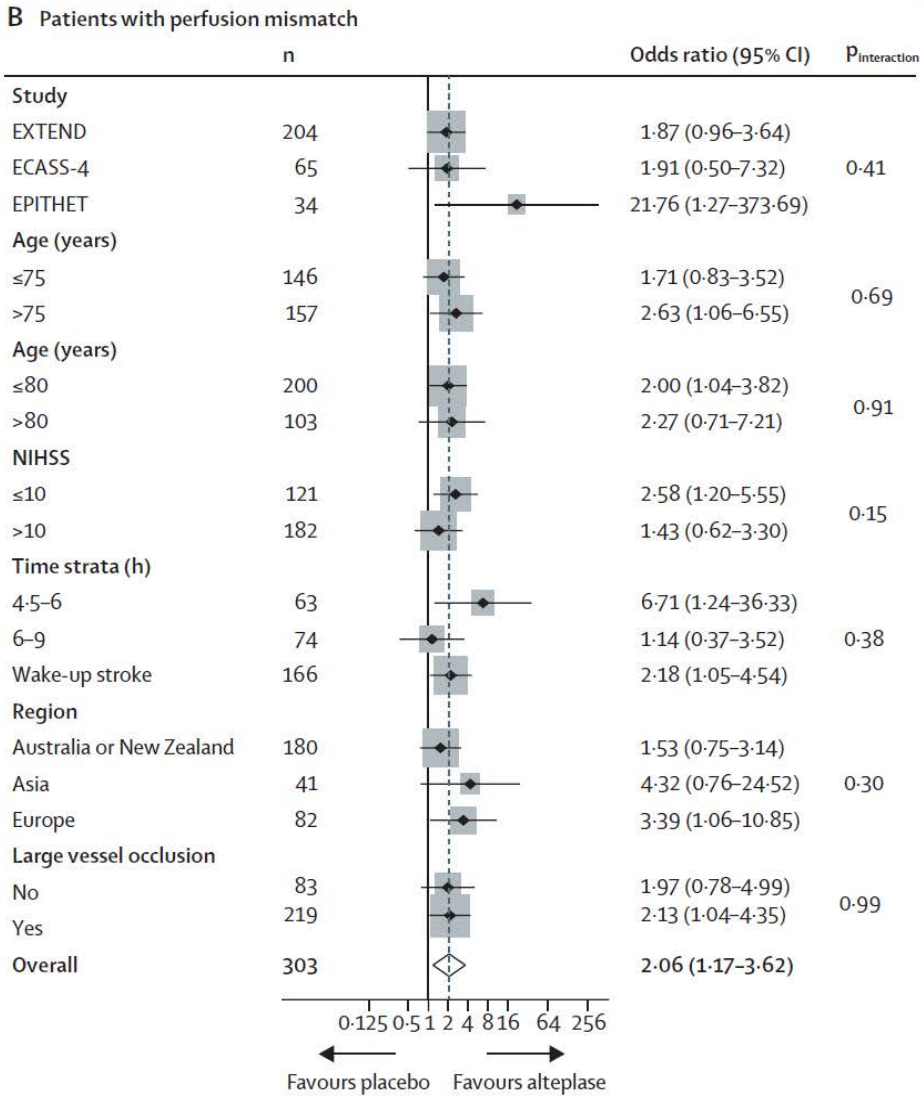
Acronym	Study Population	Investigational Treatment	Comparator	Imaging Concept	Further Imaging Exclusion Criteria	Planned Sample Size	Trial Identifier
DAWN	Late onset stroke incl. unknown time of symptom onset	Endovascular (Trevo thrombectomy procedure)±IV tPA	Standard of care	Proximal occlusion; clinical-imaging mismatch: high NIHSS score with small DWI/ CTP-rCBF lesion	Large ischemic lesion >1/3 MCA	500	NCT02142283
ECASS-4:EXTEND	Stroke onset 4.5–9 h incl. unknown time of symptom onset	IV tPA (Alteplase 0.9 mg/kg)	Placebo	Penumbral: MRI	DWI lesion >1/3 MCA/ >100 mL	264	EudraCT no. 2012-003609-80
EXTEND[38]	Stroke onset 4.5–9 h incl. unknown time of symptom onset	IV tPA (Alteplase 0.9 or 0.6 mg/kg)	Placebo	Penumbral: MRI or CTP	Infarct core >1/3 MCA/ >70 mL	400	NCT00887328
MR WITNESS	Unknown time of symptom onset	IV tPA (Alteplase 0.9 mg/kg)	n.a.	Estimation of lesion age: DWI–FLAIR mismatch	>10 microbleeds	80	NCT01282242
NORTEST[39]	Eligible for IV tPA+subgroup <4.5 h after symptom recognition	Intravenous TNK 0.4 mg/kg	IV tPA (Alteplase 0.9 mg/kg)	For wake-up stroke: estimation of lesion age: DWI–FLAIR mismatch	n.a.	954	NCT01949948 EudraCT No 2011-005793-33
POSITIVE	Stroke onset <12 h incl. unknown time of symptom onset	Endovascular (aspiration, stent retriever)	Standard of care	Proximal occlusion; penumbral: MRI or CTP (by local practice)	Infarct on CT >1/3 MCA or ASPECTS <7	750	NCT01852201
THAWS[40]	Unknown time of symptom onset	IV tPA (Alteplase 0.6 mg/kg)	Placebo	Estimation of lesion age: DWI–FLAIR mismatch	DWI ASPECTS <5	300	NCT02002325
WAKE-UP[41]	Unknown time of symptom onset	IV tPA (Alteplase 0.9 mg/kg)	Placebo	Estimation of lesion age: DWI–FLAIR mismatch	DWI lesion >1/3 MCA/ >100 mL	800	NCT01525290 EudraCT No. 2011-005906-32

Stroke. 2015;46:2707-2713. DOI: 10.1161/STROKEAHA.115.009701

Extending thrombolysis to 4·5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data

Subgroup analyses





Lancet 2019; 394: 139–47

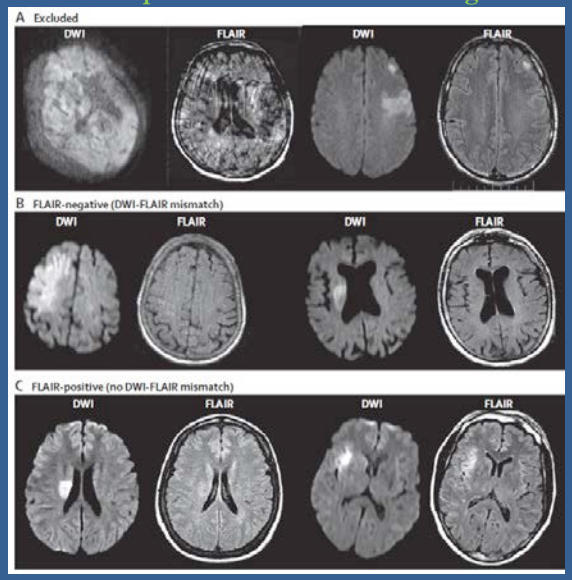
DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study

	Included in final analysis (n=543)	Excluded from final analysis (n=100)
Age (years, mean [95% CI])	66·0 (64·7–67·3)	69·0 (66·4–71·5)
Female	251 (46%)	47 (47%)
NIHSS score on admission	8 (4–15)*	11 (5–17)
Time to MRI (min)	201 (110–321)*	152 (96–271)
Field strength 3 T	86 (16%)	12 (12%)

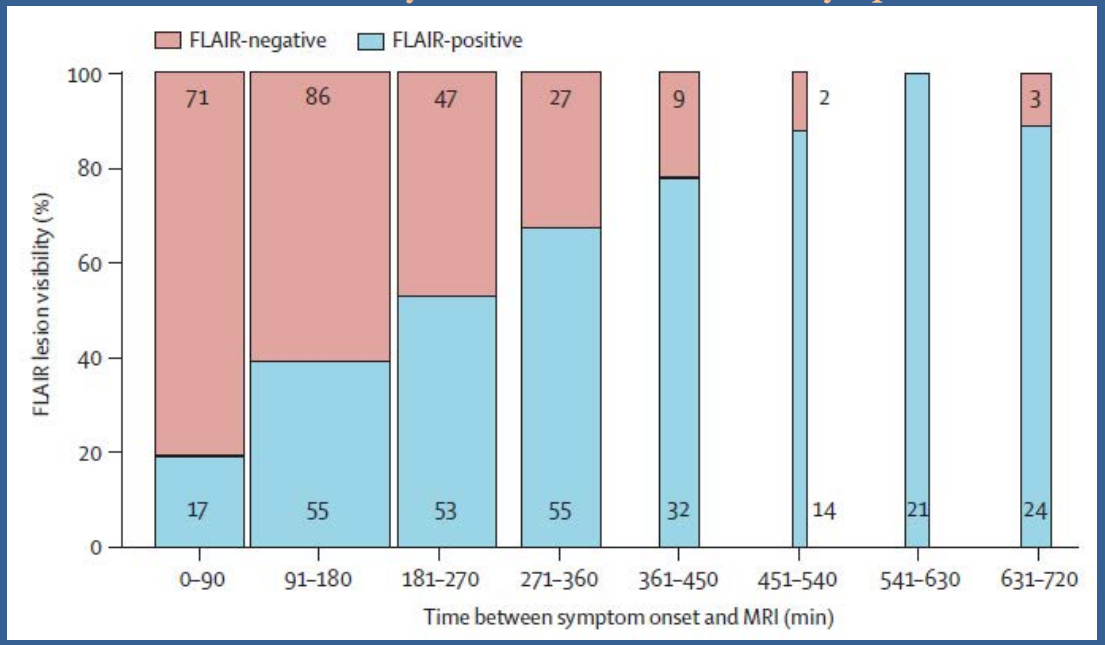
Data are number (%) or median (IQR) unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale.
*Data missing for five patients.

Table 1: Baseline characteristics

Examples of DWI and FLAIR images



FLAIR lesion visibility in relation to time from symptom onset



Lancet Neurol 2011; 10: 978–86

DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4·5 h of symptom onset (PRE-FLAIR): a multicentre observational study

- This study overcomes the limitations of previous smaller, single-centre studies reporting in part contradictory results.
- In four retrospective single-centre studies, predictive values were reported for symptom onset within either 3 h, 4·5 h, or 6 h, and specificity values of a negative FLAIR scan for time from symptom onset within 3 h varied between 71% and 97%.
- Sensitivity of DWI-FLAIR mismatch was low (<50%) in two studies but high (83–95%) in two other studies.
- Our study provides conclusive evidence for the use of DWI-FLAIR mismatch as a surrogate marker to identify patients with unknown time of symptom onset in a large multicentre set of real-life data. Thus, the findings from this study provide the basis for the use of DWI and FLAIR MRI to be tested in a future randomised trial of intravenous thrombolysis in patients with unknown time of symptom onset.

Lancet Neurol 2011; 10: 978–86

DWI – FLAIR Mismatch in Nocturnal Strokes Patients with Unknown Time of Onset

The DWI–FLAIR mismatch was different among groups (unknown 43.7%, control A 63.6%, control B 10.5%; FFH p=0.001). There were significant differences in FLAIR/DWI ratio among the 3 groups (unknown: 0.05±0.12, control A: 0.17±0.15, control B: 0.04±0.06; KW p<0.0001). Post-hoc pair wise comparisons showed that FLAIR/DWI ratio from the unknown group was significantly different from control B (p=0.0045), but not different from control A. DWI volumes were not different among the 3 groups.

Conclusion

A large proportion of nocturnal IS patients with unknown time of stroke initiation have a DWI-FLAIR mismatch suggesting a recent stroke onset.

J Stroke Cerebrovasc Dis. 2013 October ; 22(7): 972–977

Trials Enrolling Stroke Patients With Unknown Onset

Acronym	Study Population	Investigational Treatment	Comparator	Imaging Concept	Further Imaging Exclusion Criteria	Planned Sample Size	Trial Identifier
DAWN	Late onset stroke incl. unknown time of symptom onset	Endovascular (Trevo thrombectomy procedure)±IV tPA	Standard of care	Proximal occlusion; clinical-imaging mismatch: high NIHSS score with small DWI/ CTP-rCBF lesion	Large ischemic lesion >1/3 MCA	500	NCT02142283
ECASS-4:EXTEND	Stroke onset 4.5–9 h incl. unknown time of symptom onset	IV tPA (Alteplase 0.9 mg/kg)	Placebo	Penumbral: MRI	DWI lesion >1/3 MCA/ >100 mL	264	EudraCT no. 2012-003609-80
EXTEND[38]	Stroke onset 4.5–9 h incl. unknown time of symptom onset	IV tPA (Alteplase 0.9 or 0.6 mg/kg)	Placebo	Penumbral: MRI or CTP	Infarct core >1/3 MCA/ >70 mL	400	NCT00887328
MR WITNESS	Unknown time of symptom onset	IV tPA (Alteplase 0.9 mg/kg)	n.a.	Estimation of lesion age: DWI–FLAIR mismatch	>10 microbleeds	80	NCT01282242
NORTEST[39]	Eligible for IV tPA+subgroup <4.5 h after symptom recognition	Intravenous TNK 0.4 mg/kg	IV tPA (Alteplase 0.9 mg/kg)	For wake-up stroke: estimation of lesion age: DWI–FLAIR mismatch	n.a.	954	NCT01949948 EudraCT No 2011-005793-33
POSITIVE	Stroke onset <12 h incl. unknown time of symptom onset	Endovascular (aspiration, stent retriever)	Standard of care	Proximal occlusion; penumbral: MRI or CTP (by local practice)	Infarct on CT >1/3 MCA or ASPECTS <7	750	NCT01852201
THAWS[40]	Unknown time of symptom onset	IV tPA (Alteplase 0.6 mg/kg)	Placebo	Estimation of lesion age: DWI–FLAIR mismatch	DWI ASPECTS <5	300	NCT02002325
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Stroke. 2015;46:2707-2713. DOI: 10.1161/STROKEAHA.115.009701

Intravenous Thrombolysis in Unwitnessed Stroke Onset: MR WITNESS Trial Results

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Objective: Most acute ischemic stroke (AIS) patients with unwitnessed symptom onset are ineligible for intravenous thrombolysis due to timing alone. Lesion evolution on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) correlates with stroke duration, and quantitative mismatch of diffusion-weighted MRI with FLAIR (qDFM) might indicate stroke duration within guideline-recommended thrombolysis. We tested whether intravenous thrombolysis ≤4.5 hours from the time of symptom discovery is safe in patients with qDFM in an open-label, phase 2a, prospective study (NCT01282242).

Methods: Patients aged 18 to 85 years with AIS of unwitnessed onset at 4.5 to 24 hours since they were last known to be well, treatable within 4.5 hours of symptom discovery with intravenous alteplase (0.9mg/kg), and presenting with qDFM were screened across 14 hospitals. The primary outcome was the risk of symptomatic intracranial hemorrhage (sICH) with preplanned stopping rules. Secondary outcomes included symptomatic brain edema risk, and functional outcomes of 90-day modified Rankin Scale (mRS).

Results: Eighty subjects were enrolled between January 31, 2011 and October 4, 2015 and treated with alteplase at median 11.2 hours (IQR = 9.5–13.3) from when they were last known to be well. There was 1 sICH (1.3%) and 3 cases of symptomatic edema (3.8%). At 90 days, 39% of subjects achieved mRS = 0–1, as did 48% of subjects who had vessel imaging and were without large vessel occlusions.

Interpretation: Intravenous thrombolysis within 4.5 hours of symptom discovery in patients with unwitnessed stroke selected by qDFM, who are beyond the recommended time windows, is safe. A randomized trial testing efficacy using qDFM appears feasible and is warranted in patients without large vessel occlusions.

ANN NEUROL 2018;00:000–000

Trials Enrolling Stroke Patients With Unknown Onset

Acronym	Study Population	Investigational Treatment	Comparator	Imaging Concept	Further Imaging Exclusion Criteria	Planned Sample Size	Trial Identifier
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Stroke. 2015;46:2707-2713. DOI: 10.1161/STROKEAHA.115.009701

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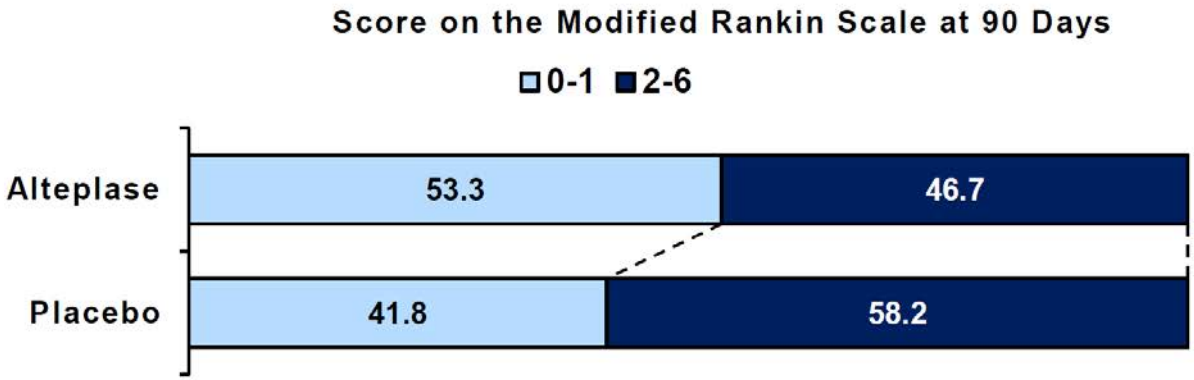
MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

G. Thomalla, C.Z. Simonsen, F. Boutitie, G. Andersen, Y. Berthezene, B. Cheng, B. Cheripelli, T.-H. Cho, F. Fazekas, J. Fiehler, I. Ford, I. Galinovic, S. Gellissen, A. Golsari, J. Gregori, M. Günther, J. Guibernau, K.G. Häusler, M. Hennerici, A. Kemmling, J. Marstrand, B. Modrau, L. Neeb, N. Perez de la Ossa, J. Puig, P. Ringleb, P. Roy, E. Scheel, W. Schonewille, J. Serena, S. Sunaert, K. Villringer, A. Wouters, V. Thijs, M. Ebinger, M. Endres, J.B. Fiebach, R. Lemmens, K.W. Muir, N. Nighoghossian, S. Pedraza, and C. Gerloff, for the WAKE-UP Investigators*

Primary Efficacy Outcomes



Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Favorable outcome (mRS 0-1) at 90 days	131/246 (53.3%)	102/244 (41.8%)	Odds ratio	**1.61 (1.09-2.36)**	**0.02**

** Adjusted for age and NIHSS at baseline*

In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome

- Secondary efficacy endpoint: mRS "shift analysis"

Endpoint	Alteplase (n=254)	Placebo (n=249)	Effect Variable	Adjusted Value (95% CI) *	P-Value
Median mRS score at 90 days („shift analysis")	1 (1-3)	2 (1-3)	Common odds ratio	**1.62 (1.17-2.23)**	**0.003**

- Safety endpoints:

Endpoint	Alteplase	Placebo	Adjusted Odds Ratio (95% CI) *	P-Value
Death at 90 days	4.1%	1.2%	3.38 (0.92-12.52)	0.07
Symptomatic intracranial hemorrhage as defined in SITS-MOST	2.0%	0.4%	4.95 (0.57-42.87)	0.15
Parenchymal hemorrhage type 2 (PH-2)	4.0%	0.4%	**10.46 (1.32-82.77)**	**0.03**
Any serious adverse event (SAE)	22.3%	21.3%		0.83

** Adjusted for age and NIHSS at baseline*

In patients with acute stroke with an unknown time of onset, intravenous alteplase guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia resulted in a significantly better functional outcome and numerically more intracranial hemorrhages than placebo at 90 days

Wake-Up Trial
Key Messages

- In patients with unknown symptom onset stroke with MRI pattern of DWI-FLAIR-mismatch, treatment with alteplase resulted in better functional outcome than placebo.
- Consistent benefit across all categories of outcome and major clinical secondary endpoints.
- Effect size of MRI-guided thrombolysis in unknown symptom onset stroke is comparable to effect size of thrombolysis <4.5 hours.
- Numerically higher rates of symptomatic intracranial hemorrhage and trend towards higher mortality with alteplase, which might have become significant with larger sample size.
- Paradigm change: first positive trial of intravenous thrombolysis relying on patients selection by advanced brain imaging without information on time of symptom onset.
- MRI-guided intravenous thrombolysis represents an effective treatment option for stroke patients with unknown symptom onset, especially for those with minor or moderate stroke who are not eligible for mechanical thrombectomy.

N Engl J Med 2018;379:611-22

Studio WAKE-UP

Centri arruolatori con esperienza nell'uso dell'alteplase nell'ictus ischemico e con la possibilità di eseguire la RM encefalo in urgenza

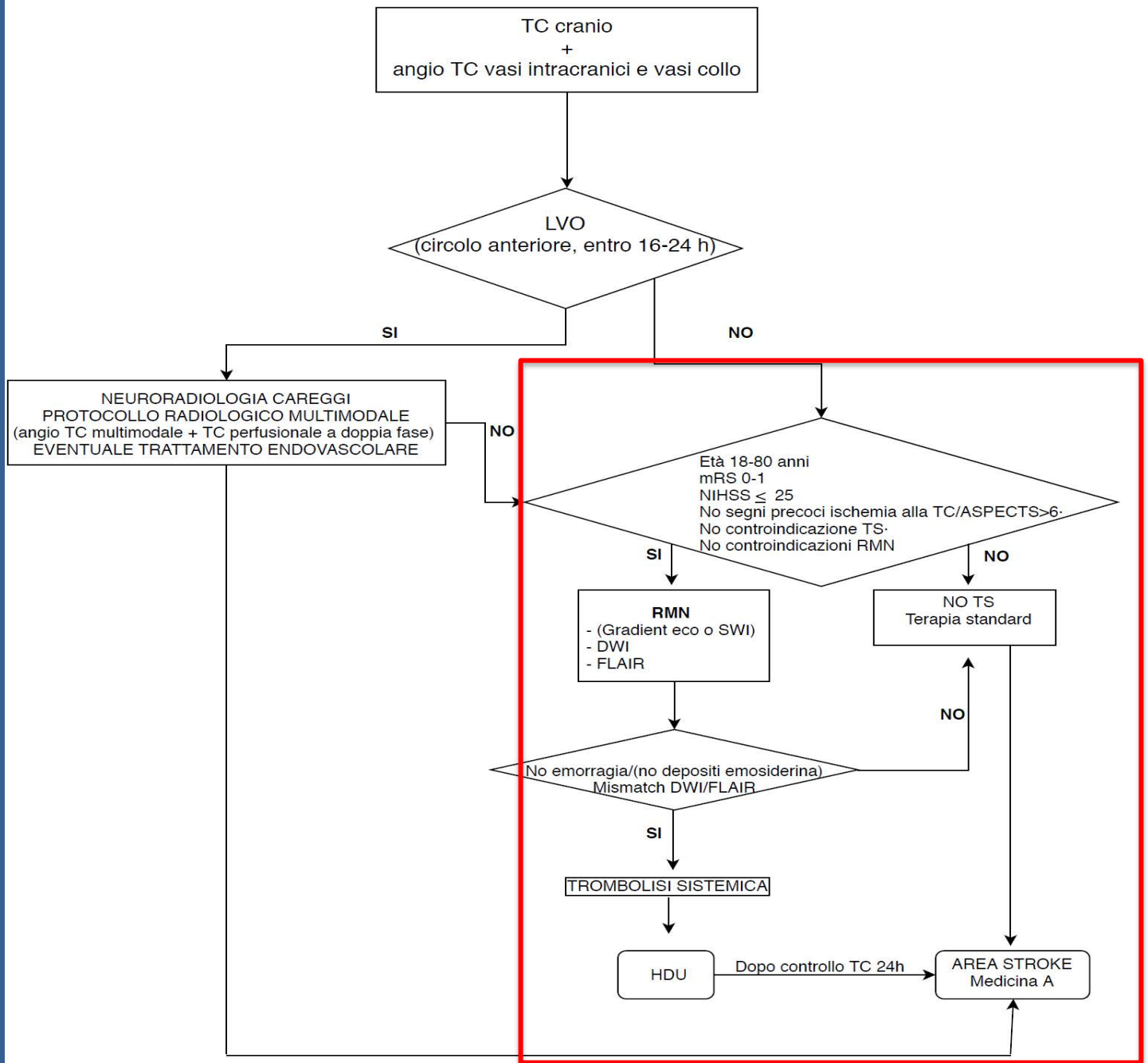
Criteri inclusione

- Segni clinici di ictus acuto
- Età 18-80aa
- Indipendenza nelle attività della vita quotidiana prima dell'ictus
- Ictus al risveglio o non databile per afasia o confusione
- Ultima volta visti sani > 4,5 ore (senza limiti superiori)
- Non fattori di esclusione alla esecuzione della RM encefalo

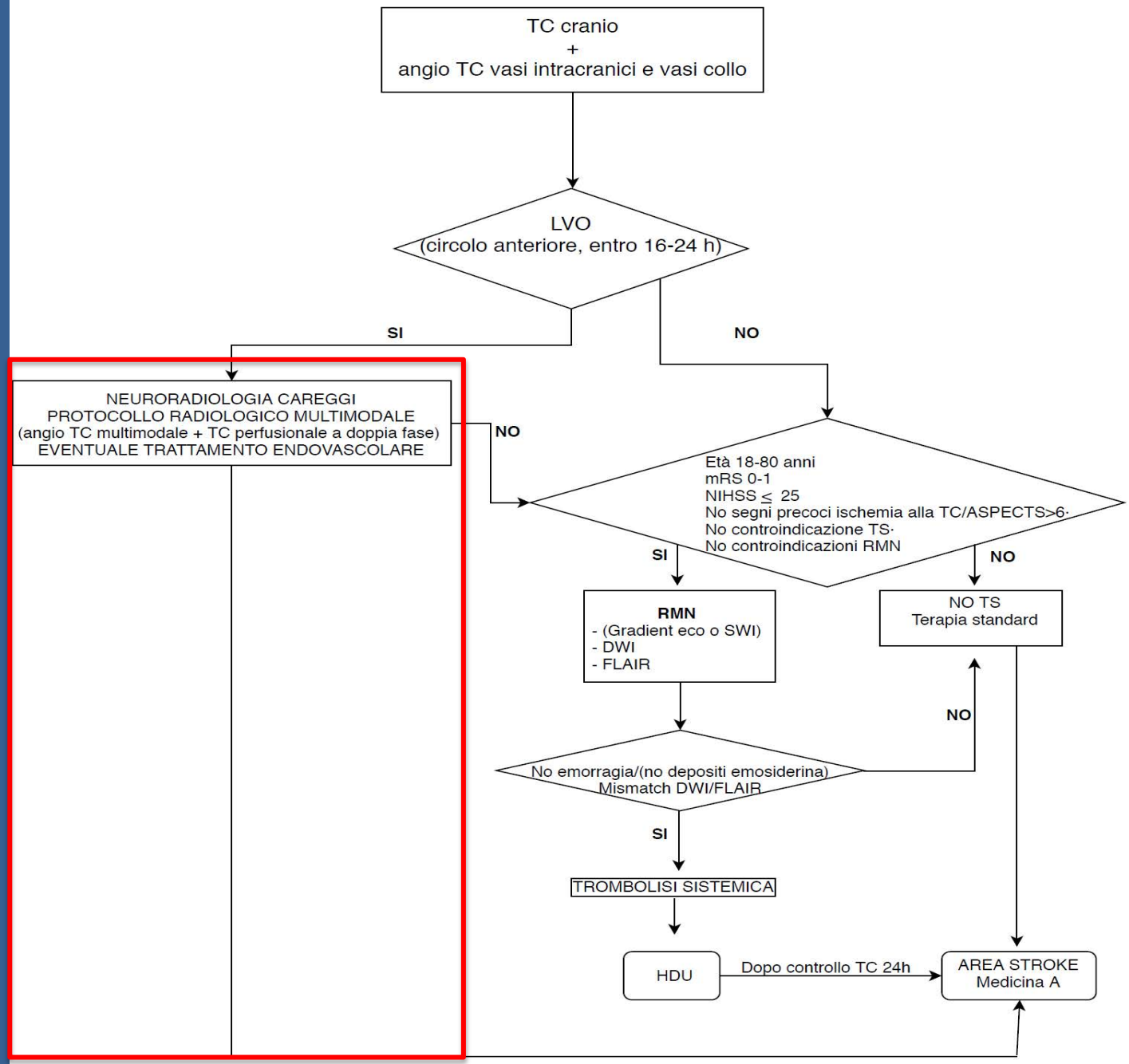
Criteri di esclusione

- Emorragia intracranica alla RM encefalo
- Lesione ischemica maggiore di un terzo del territorio dell'arteria cerebrale media
- Indicazione alla trombectomia meccanica
- NIHSS >25

ICTUS AD ESORDIO NON DETERMINATO



ICTUS AD ESORDIO NON DETERMINATO



Recommendations	COR	LOE
Patients eligible for IV alteplase should receive it even if endovascular treatments being considered	I	A
In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed.	III (Harm)	B-R

Checklist dei criteri di inclusione all'intervento endovascolare per neuroradiologo interventista di guardia (3486527779)

CRITERI

- mRS pre-stroke 0-2
- NIHSS ≥ 6 o clinica suggestiva di ischemia in territorio vertebro-basilare
- Tempo di insorgenza ≤ 6 h (≤ 12 h se occlusione del circolo posteriore)
- TC cranio senza mdc: esclusione di emorragie cerebrali o di infarto in atto > 1/3 del territorio ACM
- angioTC monofasica: occlusione di arteria intrcranica maggiore (ACA, ACM M1 o M2, ACP, arteria basilare, sifone carotideo), occlusione carotide extracranica ± occlusione intracranica
- angioTC multifasica: presenza di circoli collaterali

TERAPIA COMBINATA, NON RESCUE

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3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A	New recommendation.
8. In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	IIa	B-R	New recommendation.
The DAWN trial used clinical imaging mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in function outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33%; 95% CI, 21–44; posterior probability of superiority >0.999).[108] In DAWN, there were few strokes with witnessed onset (12%).The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67; 95% CI, 1.60–4.48; $P<0.0001$).[109] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE-3 eligibility should be strictly adhered to in clinical practice.			See Table XXIII in online Data Supplement 1.

CRITERI DI INCLUSIONE

DEFUSE 3 Trial

- Segni e sintomi compatibili con ictus del circolo anteriore
- Età 18-90 anni
- NIHSS maggiore o uguale a 6
- Tra le 6-16 ore dall'ultima volta visto sano
- mRS pre-stroke < 2
- Acquisizione del consenso informato da parte del paziente o da chi è legalmente autorizzato

DAWN Trial

- Età > 18 anni
- Tra le 6-24 ore dall'ultima volta visto sano
- mRS pre-stroke 0-1
- Esclusione di emorragia intracranica
- Estensione della lesione ischemica < 1/3 territorio ACM

PAZIENTE CON DEFICIT NEUROLOGICO ACUTO CON ESORDIO INDETERMINATO

PROTOCOLLO MULTIMODALE

Metodica	Finalità
TC cerebrale senza mdc:	• *esclusione di emorragie cerebrali (emorragia subaracnoidea o ematoma intraparenchimale)* • *calcolo del punteggio ASPECTS = estensione dell'infarto*
angio-TC multifasica:	• *verifica della presenza e riconoscimento della sede di occlusione* • *valutazione dello stato dei circoli collaterali*
TC Perfusionale a doppia fase:	• *identificazione e analisi volumetrica di core infartuale e penombra ischemica*

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Key Imaging-Based Inclusion Criterial for DEFUSE 3 and DAWN

	DEFUSE 3	DAWN
Ischemic core volume	≤70 mL	≤20 mL if age >80
		≤30 mL if age <80 and NIHSS 10–20
		≤50 mL if age <80 and NIHSS >20
Mismatch volume	≥15 mL and a mismatch ratio of ≥1.8	Not required
Vessel occlusion	M1 or ICA (cervical and intracranial)	M1 or ICA (intracranial and cervical if stent not anticipated to be required)

Stroke. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021011.

Proposta di collaborazione UTC-AOUC per deficit neurologico acuto ad esordio indeterminato

Tenendo conto delle recenti evidenze cliniche nell'ictus al risveglio e ad esordio indeterminato è indicata l'esecuzione di una TC cranio e angioTC dei vasi intracranici

In caso di occlusione di grosso vaso intracranico del circolo anteriore o occlusione dell'arteria basilare , NIHSS ≥ 6, mRS 0-1, ASPECTS ≥6 (entro 6-24 ore dall'ultima volta visto sano) è indicato l'invio del paziente presso la Neuroradiologia di Careggi per l'esecuzione del protocollo radiologico multimodale e della trombectomia meccanica se lo studio neuroradiologico conferma i criteri di inclusione degli studi DAWN e DEFUSE 3

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Proposta per deficit neurologico acuto ad esordio indeterminato senza indicazione alla trombectomia meccanica

Alla luce dei risultati del WAKE UP Trial, nei pazienti con ictus ischemico ad esordio indeterminato o con ictus al risveglio, con una NIHSS < 25, esclusi dalla trombectomia meccanica per assenza di occlusione di grosso vaso, in assenza di controindicazioni alla somministrazione di alteplase può essere indicata l'esecuzione di una RMN encefalo per selezionare i pazientti con mismatch DWI-FLAIR e estensione dell'area ischemica inferiore a 1/3 del territorio dell'arteria cerebrale media suscettibili di trattamento trombolitico sistemico

Le sequenze RM encefalo necessarie nello studio dell'ictus ischemico ad esordio indeterminato (specificando nella richiesta che l'esame viene eseguito per la ricerca di mismatch DWI-FLAIR nel sospetto di insorgenza indeterminata) sono:

- **DWI**
- **FLAIR**
- **Gradient eco o SWI**

Se all'esame TC sono già presenti evidenti segni precoci di ischemia (ASPECT <6) NON è indicato eseguire l'esame RM perché è molto probabile che l'area ischemica sarà già visibile in FLAIR

GRAZIE PER L'ATTENZIONE