



Gestione critica del paziente con ictus

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A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

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*A. Serge Bracard, Xavier Ducrocq, Jean Louis Mas, Marc Soudant, Catherine Oppenheim, Thierry Moulin, Francis Guillemin, on behalf of the THRACE investigators**

The NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Endovascular Therapy with Perfusion-Im

B.C.V. Campbell, P.J. Mitchell, T.J. Kleindienst, B. Yan, R.J. Dowling, M.W. Parsons, M.A. Simpson, F. Miteff, C.R. Levi, M. Krause, T.J. Harrington, B.S. Steinfort, M. Priglinger, T. Ang, R. Scroop, P.A. Barber, B.I. T. Wijeratne, T.G. Phan, W. Chong, R.V. Chandra, C.F. Bladin, M. L. de Villiers, H. Ma, P.M. Desmond, G.A. Donnan, and S.M. for the EXTEND-IA Investigators*

Randomized Assessment of Rapid Thrombolytic Treatment of Ischemic Stroke

Demchuk, B.K. Menon, M. Eesa, J.L. Rempel, J. Thornton, D. Roy, L. Willinsky, B.L. Sapkota, D. Dowlatshahi, D.F. Frei, N.R. Kamal, A.Y. Poppe, K.J. Ryckborst, F.L. Silver, A. Shuaib, D. Tamplieri, P.A. Burns, H. Choe, J.-H. Heo, G. Linares, J.L. Mandzia, J. Shankar, J. Coutts, E.E. Smith, W.F. Morrish, J.H. Wong, M.W. Lowerison, ESCAPE Trial Investigators*

Thromboembolic Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

T.G. Jovin, A. Chirillo, L. San Román, J. Saver, E. López-Cancio, H. Quesada, M. R. von Kummer, M. C. Mocco, and the THERAPY Trial Investigators

Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone

J. Mocco, Osama O. Zaidat, Rüdiger von Kummer, Albert J. Yoo, Rishi Gupta, Demetrius Lopes, Don Frei, Harish Shownkeen, Ron Budzik, Zahra A. Ajani, Aaron Grossman, Dorethea Altschul, Cameron McDougall, Lindsey Blake, Brian-Fred Fitzsimmons, Dileep Yavagal, John Terry, Jeffrey Farkas, Seon Kyu Lee, Blaise Baxter, Martin Wiesmann, Michael Knauth, Donald Heck, Syed Hussain, David Chiu, Michael J. Alexander, Timothy Malisch, Jawad Kirmani, Laszlo Miskolczi, Pooja Khatri and for the THERAPY Trial Investigators

Stroke, published online August 2, 2016;



American
Heart
Association



American
Stroke
Association

Baseline characteristics

Clinical trial Control	Trial end	Proven occlusion	Ischemic penumbra	IV rt-PA (%)	OTrt-PA min	OTR min Time w	OTG min	Stent- retriever	Outcome variable
MR CLEAN (n=500) IV rt-PA	Ended	ICA, M1, M2, A1, A2	NA	rt-PA failure 89%	86	204 (6.0h)	260	81%	mRS at 90d (shift)
ESCAPE (n=316) BMT	Halted	ICA, M1	ASPECT 6-10 + good collaterals	Bridging 75%	117	169 (12.0h)	185	86%	mRS at 90d (shift)
EXTEND IA (n= 70) IV rt-PA	Halted	ICA, M1, M2	pCT or MR Tmax 6sec Core <70mL	Bridging 100%	136	157 (4.5h)	210	100%	24h reperfusion 3 days NIHSS
SWIFT PRIME (n=196) IV rt-PA	Halted	ICA, M1	ASPECT 6-10*	Bridging 100%	112	188 (6h)	224	100%	mRS at 90d (shift)
REVASCAT (n=206) BMT	Halted at 1 st interim	ICA, M1	ASPECT 6-10	rt-PA failure (30') 73%	111	223 (8.0h)	269	100%	mRS at 90d (shift)
THRACE (n=404) IV rt-PA	Halted at 1 st interim	ICA, M1 (2 pts. M2, 4 pts. BAO)	NA	Bridging 100%	150	170 (5 h)	NA	100%	mRS 0-2 at 90d
THERAPY (n=108 IV rt-PA	Halted	ICA, M1, M2	Early CT signs >1/2 MCA	Bridging 100%	108	181	123	0% Aspiration	mRS 0-2 at 90d

OTrt-PA: median time from onset to rt-PA (in pts. who received it); OTR: median time from onset to randomisation; OTG: median time from onset to groin puncture; Time w: maximum time window; mRS, modified Rankin scale; BMT: Best medical therapy (includes IV alteplase if eligible); RCT, randomised controlled trial; EVT, endovascular therapy; ICA, internal carotid artery; CTP, computer tomography perfusion
 * MRI or CTP mismatch >1.8 in the first 71 patients

Berkhemer OA et al. *N Engl J Med* 2015;372:11-20.

Goyal M et al. *N Engl J Med* 2015;372:1019-1030

Campbell BCV et al. *N Engl J Med* 2015;372:1009-1018

Jovin TG et al, *N Engl J Med* 2015 DOI:10.1056/NEJMoa1503780

Saver JL, *N Engl J med* 2015 DOI:10.1056/NEJMoa1415061

Efficacy

Clinical trial	mRS 0-2 T vs C Adj. OR, 95%CI	24h Complete recanalisation T vs C	Infarct volume median (IQR) T vs C
MR CLEAN (n=500) IV rt-PA	33% vs 19% 2.2 (1.4, 3.4)	75% vs 34%	49 (22,96) vs 79 (34-125)
ESCAPE (n=316) BMT	53% vs 29%	NA	NA
EXTEND IA (n= 70) IV rt-PA	71% vs 40% 4.2 (1.4, 12)	94% vs 43%	11 (0, 24) vs 35 (6, 73) †
SWIFT PRIME (n=196) IV rt-PA	60% vs 35% 2.7 (1.5, 4.9)	83% vs 40%*	NA
REVASCAT (n=206) BMT	44% vs 28% 2.1 (1.1, 4.0)	NA	16 (8, 58) vs 39 (12, 87)
THRACE (n=404) IV rt-PA	53% vs 42% 1.55 (1.05-2.30)	NA	NA
THERAPY (n=108) IV rt-PA	38% vs 30%\$ 1.4 (0.60-3.3)	NA	NA

Berkhemer OA et al. *N Engl J Med* 2015;372:11-20.

Goyal M et al. *N Engl J Med* 2015;372:1019-1030

Campbell BCV et al. *N Engl J Med* 2015;372:1009-1018

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Saver JL, *N Engl J med* 2015 DOI:10.1056/NEJMoa1415061

Bracard S, *Lancet Neurol* 2016; 15:1138-47

Mocco J, *Stroke* 2016;47:2331-38

T, thrombectomy; C, control; IQR, interquartile range; mRS, modified Rankin score; BMT, best medical therapy; OR, odds ratio

* Successful reperfusion (>90%) on CTP or MRI

† Infarct growth

‡ Decrease of 8 or more points in NIHSS score or score = 0-2

Safety

Clinical trial Control	Death at 90 days T vs C	SICH (PH2) T vs Control	SAH T vs C
MR CLEAN (n=500) IV rt-PA	21% vs 22%	6% vs 5.2%	0.9% vs 0%
ESCAPE (n=316) BMT	10% vs 19%	3.6% vs 2.7%	0.6% vs 0%
EXTEND IA (n= 70) IV rt-PA	9% vs 20%	0% vs 6%	1% vs 0%
SWIFT PRIME (n=196) IV rt-PA	9% vs 12%	0% vs 3.1%	4% vs 1%
REVASCAT (n=206) BMT	18%/ vs 15%	1.9% vs 1.9%	4.9% vs 1.9%
THRACE (n=404)	12% vs 13%	7% vs 4%	4% vs 1%
THERAPY (n=108)	12% vs 23.9%	9.3% vs 9.7%	NA

Berkhemer OA et al. *N Engl J Med* 2015;372:11-20.

Goyal M et al. *N Engl J Med* 2015;372:1019-1030

Campbell BCV et al. *N Engl J Med* 2015;372:1009-1018

Jovin TG et al, *N Engl J Med* 2015 DOI:10.1056/NEJMoa1503780

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Bracard S, *Lancet Neurol* 2016; 15:1138-47

Mocco J, *Stroke* 2016;47:2331-38

BMT: Best medical therapy (includes IV alteplase if eligible);
SICH, symptomatic intracerebral haemorrhage; SAH,
subarachnoid haemorrhage

Linee guida ISO-SPREAD

Raccomandazione 9.11

Forte contro

In pazienti eleggibili alla trombolisi e.v., trattamenti di riparazione endoarteriosi **non sono raccomandati** in alternativa a questa

Raccomandazione 9.12

Forte a favore

Le tecniche di trombectomia meccanica **sono raccomandate** entro 6 ore dall'esordio dei sintomi in pazienti con occlusione di carotide interna intra-cranica, arteria cerebrale media tratti 1-2, arteria cerebrale anteriore tratto 1, che non rispondono o che non possono essere sottoposti alla trombolisi e.v.

ORIGINAL ARTICLE

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

R.G. Nogueira, A.P. Jadhav, D.C. Haussen, A. Bonafe, R.F. Budzik, P. Bhuva,
D.R. Yavagal, M. Ribo, C. Cognard, R.A. Hanel, C.A. Sila, A.E. Hassan, M. Millan,
E.I. Levy, P. Mitchell, M. Chen, J.D. English, Q.A. Shah, F.L. Silver, V.M. Pereira,
B.P. Mehta, B.W. Baxter, M.G. Abraham, P. Cardona, E. Veznedaroglu,
F.R. Hellinger, L. Feng, J.F. Kirmani, D.K. Lopes, B.T. Jankowitz, M.R. Frankel,
V. Costalat, N.A. Vora, A.J. Yoo, A.M. Malik, A.J. Furlan, M. Rubiera, A. Aghaebrahim,
J.-M. Olivot, W.G. Tekle, R. Shields, T. Graves, R.J. Lewis, W.S. Smith,
D.S. Liebeskind, J.L. Saver, and T.G. Jovin, for the DAWN Trial Investigators*

ORIGINAL ARTICLE

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging

G.W. Albers, M.P. Marks, S. Kemp, S. Christensen, J.P. Tsai, S. Ortega-Gutierrez,
R.A. McTaggart, M.T. Torbey, M. Kim-Tenser, T. Leslie-Mazwi, A. Sarraj,
S.E. Kasner, S.A. Ansari, S.D. Yeatts, S. Hamilton, M. Mlynash, J.J. Heit,
G. Zaharchuk, S. Kim, J. Carrozzella, Y.Y. Palesch, A.M. Demchuk, R. Bammer,
P.W. Lavori, J.P. Broderick, and M.G. Lansberg, for the DEFUSE 3 Investigators*

Baseline characteristics

Clinical trial Control	Trial end	Proven occlusion	Enrollement criteria	Imaging	OTR hrs Time w	Device	Outcome variable
DAWN (n=206) BMT	Ended	ICA, M1, M2	A: age ≥ 80 y + NIHSS ≥ 10 + Ivol < 21 ml B: age < 80 y + NIHSS ≥ 10 + Ivol < 31 ml C: age < 80 y + NIHSS ≥ 20 + Ivol 31 – 51 ml	DW MR or pCT (RAPID)	10.53 (IQR 8:09-11:40)	Trevo	mRS at 90d
DEFUSE-3 (n=182) BMT	Halted	ICA, M1	Ischemic core < 70 ml + hP/core ≥ 1.8 + hP ≥ 15 ml	DW/PW MR or pCT (RAPID)	12.2 (IQR 10.2-16.3)	Any	mRS at 90d

OTR: median time from onset to randomisation; Time w: maximum time window; mRS, modified Rankin scale; ICA, internal carotid artery; M1, M2, Middle cerebral artery tracts 1 or 2; pCT, computer tomography perfusion; DW/PW MR, diffusion/perfusion magnetic resonance; Ivol, Infarct volume; hP, hypoperfusion

Efficacy

Clinical trial	mRS 0-2 T vs C	24h Complete recanalisation T vs C	Infarct volume ml, median (IQR) T vs C
DAWN (n=206)	49% vs 13%	77% vs 39%	8 (0-48) vs 22 (8-68)
DEFUSE-3 (n=182)	45% vs 17% OR 2.67 (95% I.C. 1.60-4.48)	78% vs 18%	35 (18-82) vs 41 (25-106)

Safety

Clinical trial Control	mRS 5-6 at 90 days T vs C	SICH (PH2) T vs Control	SAH T vs C
DAWN (n=206)	19% vs 18%	6% vs 3%	0%
DEFUSE-3 (n=182)	14% vs 26%	7% vs 4%	1.1%

T, thrombectomy; C, control; IQR, interquartile range; mRS, modified Rankin score; OR, odds ratio;
SICH, symptomatic intracerebral haemorrhage; SAH, subarachnoid haemorrhage

Linee guida ISO-SPREAD

Rapid recommendation

Raccomandazione

Debole a favore

Le tecniche di trombectomia meccanica **sono indicate** in pazienti con ictus ischemico da occlusione della carotide interna intracranica o del tratto prossimale dell'arteria cerebrale media, visti in condizione di normalità nelle ultime 6 -24 ore e con una delle seguenti condizioni:

- età \geq 80 anni, punteggio NIHSS \geq 10 e volume infartuale $<$ 21 ml
- età $<$ 80 anni, punteggio NIHSS \geq 10 e volume infartuale $<$ 31 ml
- età $<$ 80 anni, punteggio NIHSS \geq 20 e volume infartuale fra 31 e 51 ml

Il volume infartuale deve essere valutato con risonanza magnetica con sequenze in diffusione (RM DW) o con TC di perfusione (pTC) e calcolato con un software automatico

Linee guida ISO-SPREAD

Rapid recommendation

Raccomandazione

Debole a favore

Le tecniche di trombectomia meccanica **sono indicate** in pazienti con ictus ischemico da occlusione della carotide interna intracranica o del tratto prossimale dell'arteria cerebrale media, visti in condizione di normalità nelle ultime 6 -16 ore e con una delle seguenti condizioni:

- volume basale dell'infarto inferiore a 70 ml
- rapporto volumetrico fra area di ipoperfusione e area infartuale uguale o superiore a 1.8

Volume infartuale basale e volume dell'area ipoperfusa debbono essere valutati con risonanza magnetica con sequenze in diffusione e perfusione (RM DW/PW) o con TC di perfusione (pTC) e calcolati con un software automatico

Number Needed to Treat

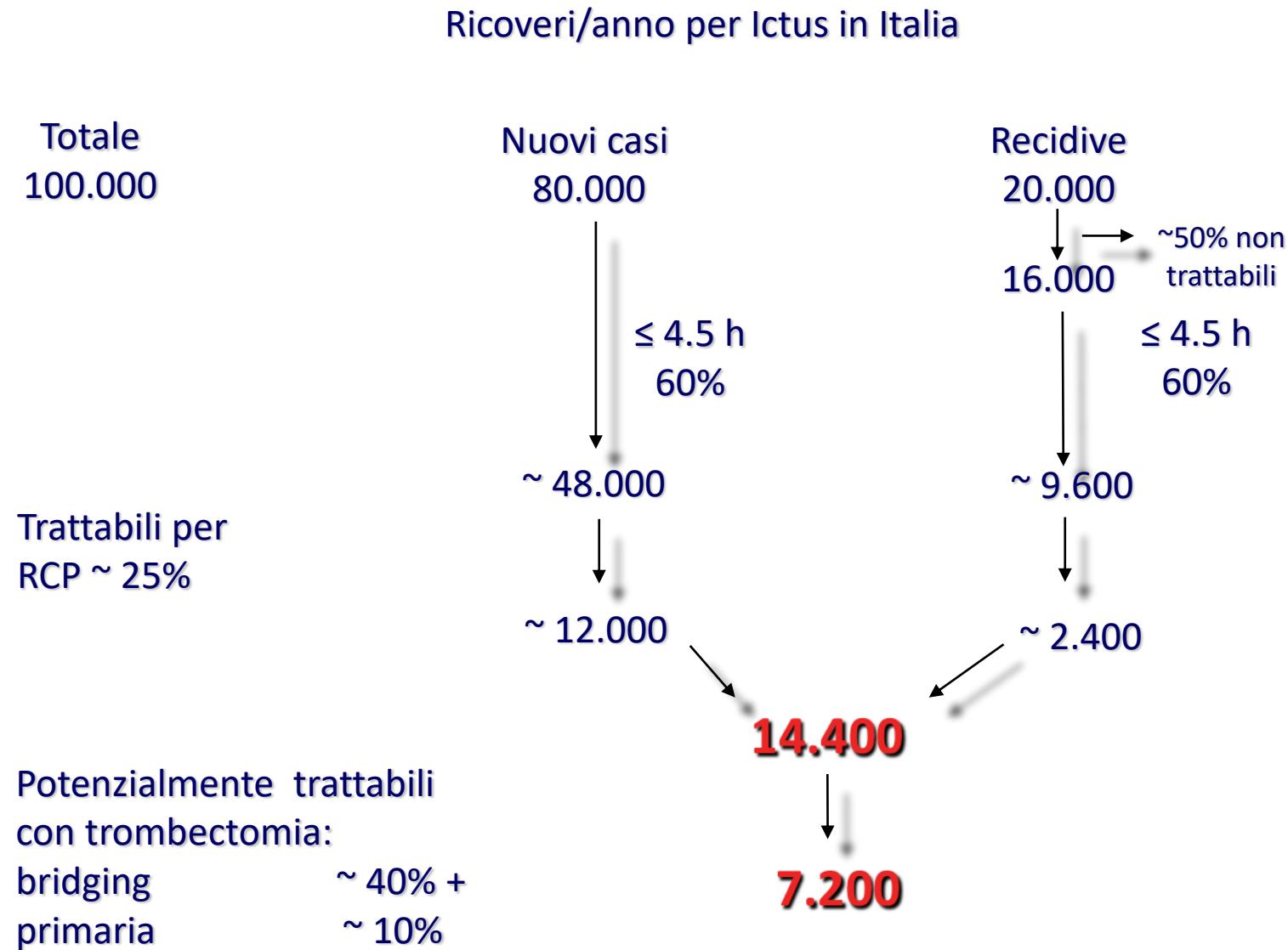
Treatment	NNT
Stroke Unit	20
Aspirin	83
t-PA < 6 hrs	18
t-PA 3 - 4.5 hrs	14
t-PA < 3 hrs	7
Thrombectomy < 6 hrs	2.6
Thrombectomy 6-24 hrs	2.7
Thrombectomy 6-16 ore	3.6

Features of stroke units studied in randomised trials

Assessment and monitoring	Medical	Systematic clinical history and examination
		Routine investigations: serum biochemistry, haematology, EKG, CT
		Investigations in selected patients: carotid doppler, echocg, MRI
	Nursing	General care needs, vital signs, swallow assessment, fluid balance, pressure-area risks, neurological monitoring
	Therapy	Assessment of impairments and function
Early management	<p>Il successo dei trial, sia di trombolisi intravenosa che di trombectomia meccanica, è strettamente correlato con la gestione post-trattamento: effetto Stroke Unit</p>	
Multidisciplinary team rehabilitation	Rehabilitation process	Formal multidisciplinary meetings once a week (plus informal meetings) Early rehabilitation, goal-setting, and involvement of carers Close linking of nursing with other multidisciplinary care Provision of information on stroke, recovery, and services
Discharge planning		Early assessment of discharge needs Discharge plan involving patient and carers

REGIONE	Popolazione	Centri TIV	1/200.000	Centri TEV	1/1.000.000
Valle d' Aosta	128.298 mila	1	166.6%	1	n.a.
Umbria	894.762 mila	5	111.1%	2	224.7%
Piemonte	4,424 milioni	24	108.5%	4 (+1)	90.9% (113.6%)
Abruzzo	1,328 milioni	7	105.4%	5	376.5%
Liguria	1,575 milioni	8	102.5%	2	133.3%
Toscana	3,753 milioni	19(+3)	101.6%(117.6%)	3	81.1%
Veneto	4,925 milioni	22	89.4%	6	122.4%
Lombardia	10 milioni	35(+3)	70.0%(76.0%)	8	80%
Molise	314.725 mila	1	66.7%	0	0%
Marche	1,551 milioni	5(+2)	64.9% (90.9%)	1	66.7%
Emilia Romagna	4,451 milioni	14	63%	5	113.6%
Calabria	1,973 milioni	5	50.6%	3	30.6%
Friuli VG	1,223 milioni	3(+1)	49%(65.4%)	2	166.7%
Sicilia	5,082 milioni	12(+6)	47.2%(70.8%)	2	40%
Lazio	5,882 milioni	12 (+6)	40.8%(61.2%)	4(+3)	68%(119%)
Alto Adige	511.750 mila	1	40.0%	1	200%
Trentino	534.405 mila	1	38.4%	0	0%
Sardegna	1,663 milioni	3	36.1%	3	187.5%
Basilicata	574.782 mila	1(+1)	34.8%(69.6%)	0	0%
Puglia	4,087 milioni	7	34.3%	2	49.0%
Campania	5.869 milioni	4(+1)	13.6%(17%)	1	17,2%
Totale	60.744.722	190 (+23)	62.6 % (70.1%)	55 (+4)	90.5% (97.1%)

Quanti pazienti dovremmo trattare?



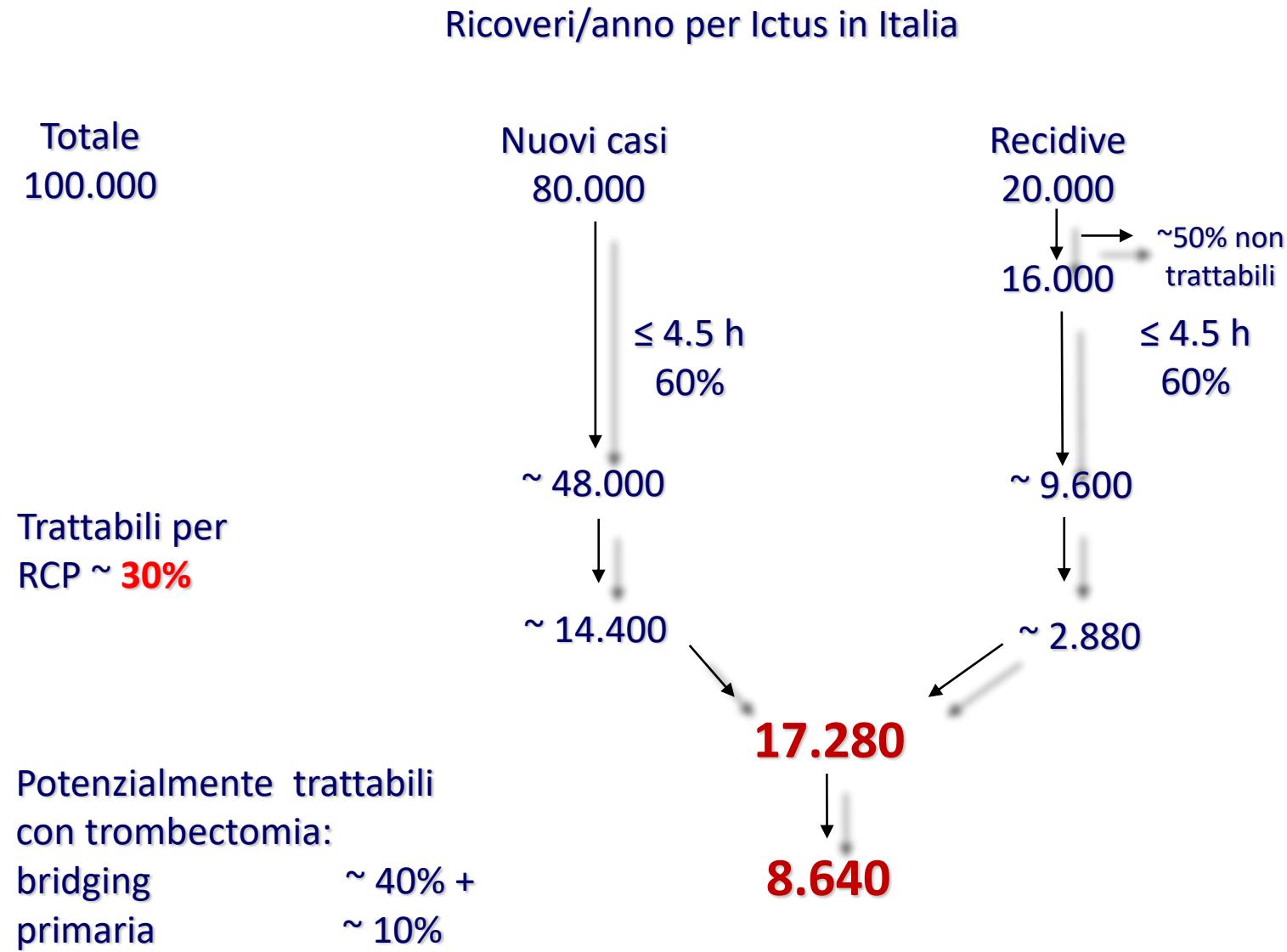
REGIONE	Popolazione	Centri TIV	1/200.000	TOTALE 2017 (%)
Liguria	1,575 milioni	8	102.5%	546/374
Friuli VG	1,223 milioni	3(+1)	49% (65.4%)	394/290
Alto Adige	511.750 mila	1	40.0%	157/120
Veneto	4,925 milioni	22	89.4%	1521/1168
Abruzzo	1,328 milioni	7	105.4%	373/314
Valle d' Aosta	128.298 mila	1	166.6%	31/30
Marche	1,551 milioni	5(+2)	64.9% (90.9%)	330/330
Toscana	3,753 milioni	19(+3)	101.6%(117.6%)	860/890
Piemonte	4,424 milioni	24	108.5%	960/1048
Sardegna	1,663 milioni	3	36.1%	359/394
Umbria	894.762 mila	5	111.1%	193/212
Trentino	534.405 mila	1	38.4%	101/126
Emilia Romagna	4,451 milioni	14	63%	815/1054
Lombardia	10 milioni	35(+3)	70.0%(76.0%)	1648/2370
Lazio	5,882 milioni	12(+6)	40.4%(61.2%)	867/1384
Calabria	1,973 milioni	5	50.6%	274/468
Puglia	4,087 milioni	7	34.3%	429/968
Sicilia	5,082 milioni	12(+6)	47.2(70.8%)	472/1204
Basilicata	574.782 mila	1(+1)	34.8%(69.6%)	30/138
Campania	5.869 milioni	4(+1)	13.6%(17%)	140/1390
Molise	314.725 mila	1	66.7%	0/74
Totale	60.744.722	190 (+23)	62.6 % (70.1%)	10500/14400
				72.9%

REGIONE	Popolazione	Centri TEV	1/1.000.000	TIV+TEV	TEV	TOTALE 2017 (%)	
Valle d' Aosta	128.298 mila	1	n.a.	14	8	22/14	157.1%
Toscana	3.753 milioni	3	81.1%	176	149	325/444	73.1%
Emilia Romagna	4.451 milioni	5	113.6%	45	46	367/526	69.7%
Liguria	1.575 milioni	2	133.3%	78	38	116/186	62.4%
Abruzzo	1.328 milioni	4	307%	47	66	90/156	57.7%
Sardegna	1.663 milioni	1 (+2)	62.5%	58	40	98/196	50%
Piemonte	4.424 milioni	4 (+1)	90.9% (113.6%)	161	87	248/524	47.3%
Lazio	5.882 milioni	4(+3)	68%(119%)	189	120	309/696	44.3%
Friuli VG	1.223 milioni	2	166.7%	40	23	63/144	43.7%
Alto Adige	511.750 mila	1	200%	45	3	26+22/60	43.3% (+35.45)
Veneto	4.925 milioni	6	122.4%	148	95	243/584	41.6%
Marche	1.551 milioni	1	66.7%	53	10	63/184	34.2%
Lombardia	10 milioni	8	80%	255	158	484/1184	40.8%
Umbria	894.762 mila	2	224.7%	12	12	24/106	22.6%
Sicilia	5.082 milioni	2	40%	39	90	129/602	21.4%
Puglia	4.087 milioni	2	49%	5	4	78/484	16.1%
Calabria	1.973 milioni	1	52.6%	11	10	21/234	8.9%
Campania	5.869 milioni	1	17.2%	6	17	23/694	3.3%
Trentino	534.405 mila	0	0	9	/	0/62	0%
Molise	314.725 mila	0	0	/	/	0/26	0%
Basilicata	574.782 mila	0	0	/	/	0/68	0%
Totale	60.744.722	55 (+4)	90.5% (97.1%)	1391	976	2675/7200	37.1%

Trattamenti TIV e/o TEV in Italia 2017 vs 2016

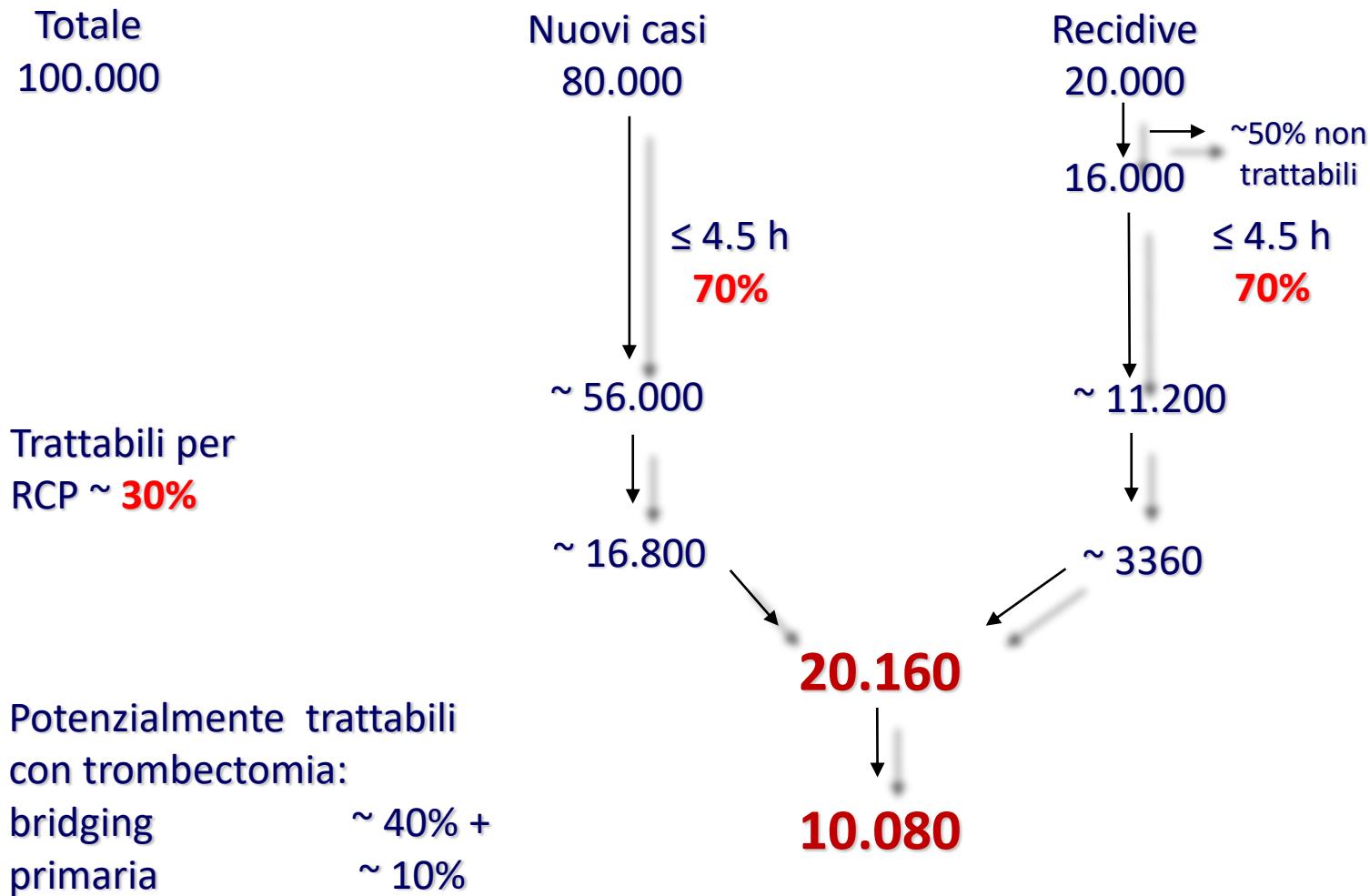
	Totale TIV	Totale TEV
Totale 2016	8342/14400 (57.9%)	2042/7200 (28.4%)
Totale 2017	10500/14400 (72.9%)	2675/7200 (37.1%)
Incremento relativo	+25.9%	+30.6%

Quanti pazienti dovremmo trattare?



Quanti pazienti dovremmo trattare?

Ricoveri/anno per Ictus in Italia



Conclusioni - 1

- Trombolisi intravenosa:
- Stiamo lavorando bene, ma dobbiamo migliorare (Centro-Sud)
- Sei Regioni hanno superato il 100% dei pazienti trattabili secondo le stime attuali: necessario aggiornare le stime (% pz. che arrivano entro 4 ore? % pz. trattabili secondo le nuove LG?)
- Opportuno definire le stime Regione per Regione, basandoci sui dati S.I.O. (compito dei coordinatori regionali)

Conclusioni - 2

- Trattamenti endovascolari:
- Il numero dei centri attivi è vicino a quello previsto dalla Legge Lorenzin ma la distribuzione sul territorio nazionale è disomogenea
- Il numero dei trattamenti effettuati è ancora molto basso rispetto alla stima dei trattamenti da effettuare: l'attività h24 è per ora assicurata solo in 10-12 centri: necessario implementare i team di operatori (formazione; superamento dei vincoli di turn over nelle diverse Regioni)

**Nessuna terapia specifica per l'ictus cerebrale può funzionare senza la gestione competente del paziente in unità neurovascolari:
effetto Stroke Unit**