AVC Normandie

Actualités et perspectives en neurovasculaire

hors thrombectomie (C Arquizan)

L'AVC en Normandie - 9ème journée régionale médicale

20 juin 2024

Marion Boulanger

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Inserm
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PhIND
PHYSIOPATHOLOGY & IMAGING OF NEUROLOGICAL DISORDERS

Plan

- **Extended time window for tenecteplase in ischaemic stroke**
- IV tenecteplase:
  - ≤ 4.5h: TASTE and ORIGINAL trials
  - Minor stroke and TIA ≤12h: TEMPO-2 trial
  - Anterior circulation LVO 4.5 to 24h: TRACE III and TIMELESS trials
- IA tenecteplase
  - Posterior LVO: ATTENTION-IA trial

- **BP control before IV thrombolysis**: TRUTH study
- **Large Hemispheric Infarction**: CHARM trial
- **Intensive early blood pressure reduction**: INTERACT4 trial
- **Decompressive craniectomy for deep intracerebral haemorrhage**: SWITCH trial
- **Secondary prevention after ischaemic stroke**: CONVINCE trial

Guideline

EUROPEAN STROKE JOURNAL

European Stroke Journal
2023, Vol. 8(1) 8–54

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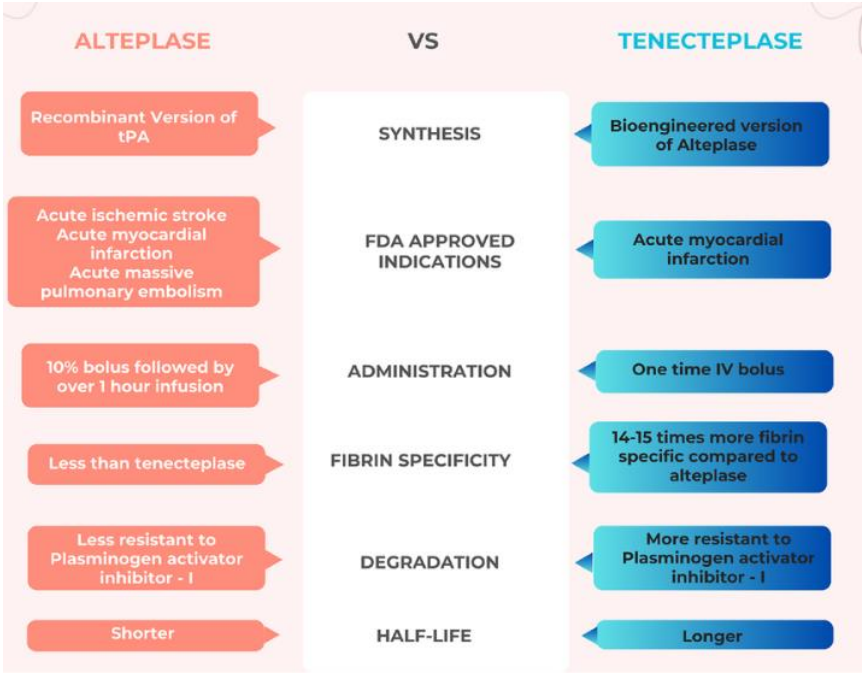
SAGE

European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke

Sonia Alamowitch[1], Guillaume Turc[2,3,4,5], Lina Palaiodimou[6], Andrew Bivard[7], Alan Cameron[8], Gian Marco De Marchis[9,10], Annette Fromm[11], Janika Kõrv[12], Melinda B Roaldsen[13], Aristeidis H Katsanos[14] and Georgios Tsivgoulis[6*]

Evidence-based recommendation
For patients with acute ischaemic stroke of <4.5 hrs duration who are eligible for intravenous thrombolysis, tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg.
Quality of evidence: **Moderate** ⊕⊕⊕
Strength of recommendation: **Strong** ↑↑



Expert consensus statement
All MWG members suggest favouring tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg for patients with acute ischaemic stroke of <4.5 hrs duration in light of safety and efficacy data and because tenecteplase can be administered with a single bolus rather than a 1-hr infusion.
Voting: 9/9 members

Expert consensus statement
All MWG members suggest that tenecteplase 0.25 mg/kg could be a reasonable alternative to alteplase 0.9 mg/kg for patients with acute ischaemic stroke on awakening from sleep or acute ischemic stroke of unknown onset and who are eligible for intravenous thrombolysis after selection with advanced imaging (FLAIR-DWI mismatch or perfusion mismatch as outlined in the 2021 ESO Guidelines on IVT).
Voting: 9/9 members

Expert consensus statement
For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis and are directly admitted to a thrombectomy-capable center, all MWG members suggest IVT with tenecteplase 0.25 mg/kg or 0.40 mg/kg over skipping IVT.
For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis and are admitted to a center without mechanical thrombectomy capability, all MWG members suggest IVT with tenecteplase 0.25 mg/kg followed by rapid transfer to a thrombectomy-capable center.
Voting: 9/9 members

ORIGINAL non-inferiority trial: Tenecteplase *vs.* alteplase in acute ischaemic stroke

Unpublished data

- Ischaemic stroke ≤4.5 hours
- Tenecteplase 0.25 mg/kg *vs.* Alteplase 0.9 mg/kg
- Non inferiority margin= 0.937

1,489 pts, 30% female
Mean age=65y, mean NIHSS score=7
8% underwent thrombectomy

	Tenecteplase (n=732)	Alteplase (n=723)	
Primary outcome: mRS 0-1 at 90 days	72.7%	70.3%	aRR=1.0278 (0.9678 -1.0915)
Symptomatic ICH	2.6%	3.0%	0.868 (0.460-1.622)
Death at 90 days	4.6%	5.8%	0.795 (0.513-1.232)

TNK noninferior

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Tenecteplase versus alteplase for thrombolysis in patients selected by use of perfusion imaging within 4·5 h of onset of ischaemic stroke (TASTE): a multicentre, randomised, controlled, phase 3 non-inferiority trial

Prof Mark W Parsons, PhD • Vignan Yogendrakumar, PhD • Prof Leonid Churilov, PhD • Carlos Garcia-Esperon, PhD • Prof Bruce C V Campbell, PhD • Michelle L Russell, RN • et al. Show all authors • Show footnotes

Published: June 13, 2024 • DOI: https://doi.org/10.1016/S1474-4422(24)00206-0 • Check for updates

Parsons MW et al. Lancet Neurol 2024

- Ischaemic stroke ≤4.5 hours
- CT perfusion mismatch:
  - Ischemic core <70 mL
  - Penumbra ratio >1.8 or 15ml
- **Not considered for mechanical thrombectomy**
- Tenecteplase 0.25 mg/kg vs. alteplase 0.9mg/kg
- Non inferiority margin of 0.03

Early stopped : 680 pts /800 planned
Median age=74y, 38% female
Median NIHSS score=7, ASPECTS=10
1/3 large-vessel occlusion

Primary outcome	Tenecteplase	Alteplase
mRS 0-1 at 90 days	57%	55%
Standardized risk difference (intention to treat analysis)	0.03 (-0.031 - 0.10)	
Standardized risk difference (per-protocol analysis)	0.05 (-0.02 - 0.12)	

non inferiority (not) met !

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Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial

Prof Shelagh B Coutts, MD • Sandeep Ankolekar, FRCP • Ramana Appireddy, MD • Juan F Arenillas, PhD • Zarina Assis, MD • Peter Bailey, MD • et al. Show all authors • Show footnotes

Published: May 17, 2024 • DOI: https://doi.org/10.1016/S0140-6736(24)00921-8 • Check for updates

Coutts SB et al. Lancet Neurol 2024

- Minor stroke (NIHSS 0-5) or TIA **≤12 hours**
- Visible intracranial occlusion or perfusion deficit
- Tenecteplase 0.25mg/kg vs. non-thrombolytic ttt (aspirin or dual antiplatelet or DOAC)

- Stopped early for futility: 886 pts/1500 planned (42% female)

At 90 days	Tenecteplase (n=432)	Control (=454)	
Primary outcome: Return to baseline neurological functioning	75%	72%	RR=0.96 (0.88-1.04)
Death	5%	1%	aHR=3.8 (1.4-10.2)
Symptomatic intracranial haemorrhages	2%	<1%	RR=4.2 (0.9-19.7)

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ORIGINAL ARTICLE

Tenecteplase for Ischemic Stroke at 4.5 to 24 Hours without Thrombectomy

Yunyun Xiong, M.D., Ph.D., Bruce C.V. Campbell, M.B., B.S., Ph.D., Lee H. Schwamm, M.D., Xia Meng, M.D., Ph.D., Aoming Jin, Ph.D., Mark W. Parsons, M.B., B.S., Ph.D., Marc Fisher, M.D., Yong Jiang, Ph.D., Fengyuan Che, M.D., Lihua Wang, M.D., Ph.D., Li Zhou, M.D., Hongguo Dai, M.D., Xintong Liu, M.D., Yuesong Pan, Ph.D., Chunmiao Duan, M.D., Yuming Xu, M.D., Ph.D., Anding Xu, M.D., Ph.D., Lixia Zong, M.D., Ph.D., Zefeng Tan, M.D., Ph.D., Wanxing Ye, Ph.D., Hao Wang, M.D., Ziran Wang, M.D., Manjun Hao, M.D., Zhixin Cao, M.D., Liyuan Wang, M.D., Shuangzhe Wu, M.D., Hao Li, Ph.D., Zixiao Li, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., and Yongjun Wang, M.D., Ph.D., for the TRACE-III Investigators*

Xiong Y et al. NEJM 2024

- Ischaemic stroke **≤4.5-24 hours**
- M1 or M2 occlusion **without mechanical thrombectomy**
- CT/MRI perfusion mismatch:
  - Ischaemic core volume <70 mL
  - Mismatch ratio ≥1.8 and mismatch volume ≥15 mL
- Tenecteplase 0.25 mg/kg vs. antiplatelet therapy (aspirin + clopidogrel, aspirin alone or clopidogrel alone)

516 pts, 32% female
median age=67y, median NIHSS=11

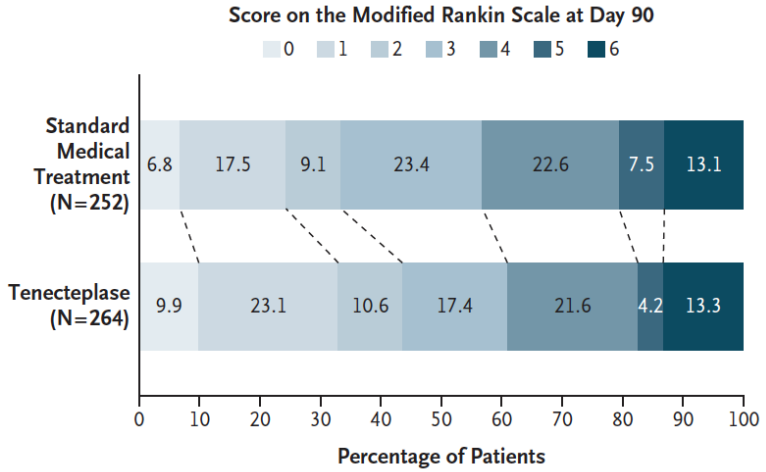

Table 2. Efficacy and Safety Outcomes.

Outcome	Tenecteplase (N=264)	Standard Medical Treatment (N=252)	Effect Size (95% CI)*
Primary outcome			
Score of 0 or 1 on the modified Rankin scale at 90 days — no. (%)†	87 (33.0)	61 (24.2)	1.37 (1.04 to 1.81)
Safety outcomes			
Symptomatic intracranial hemorrhage within 36 hr after randomization — no. (%)¶	8 (3.0)	2 (0.8)	3.82 (0.82 to 17.87)
Death within 90 days — no. (%)	35 (13.3)	33 (13.1)	1.01 (0.65 to 1.58)
Moderate or severe systemic bleeding within 90 days — no. (%)‖	5 (1.9)	2 (0.8)	2.36 (0.46 to 12.09)
Any adverse event — no. (%)	134 (50.8)	129 (51.2)	0.99 (0.84 to 1.17)
Any serious adverse event — no. (%)	53 (20.1)	43 (17.1)	1.18 (0.82 to 1.69)

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ORIGINAL ARTICLE

Tenecteplase for Stroke at 4.5 to 24 Hours with Perfusion-Imaging Selection

G.W. Albers, M. Jumaa, B. Purdon, S.F. Zaidi, C. Streib, A. Shuaib, N. Sangha, M. Kim, M.T. Froehler, N.E. Schwartz, W.M. Clark, C.E. Kircher, M. Yang, L. Massaro, X.-Y. Lu, G.A. Rippon, J.P. Broderick, K. Butcher, M.G. Lansberg, D.S. Liebeskind, A. Nouh, L.H. Schwamm, and B.C.V. Campbell, for the TIMELESS Investigators*

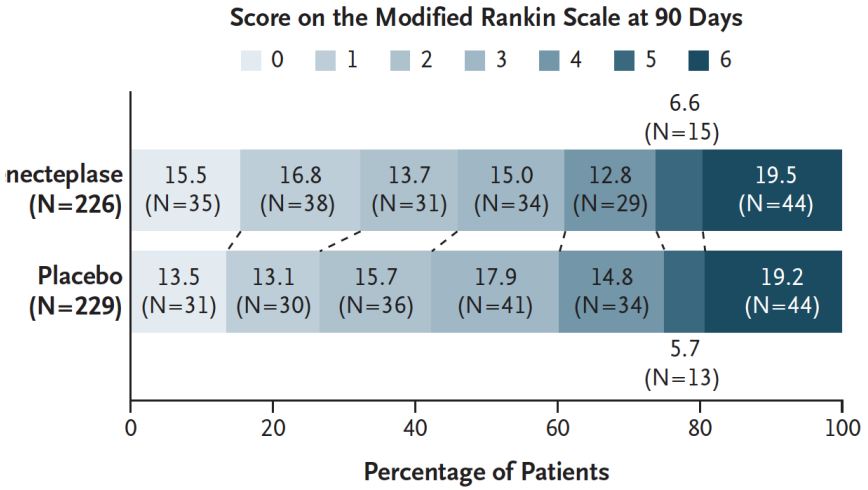
Albers GW et al. NEJM 2024

- Ischaemic stroke **≤4.5-24 hours**
- Anterior circulation LVO
- CT/MRI perfusion mismatch:
  - Ischaemic core volume <70 mL
  - Mismatch ratio ≥1.8 and mismatch volume ≥15 mL
- Tenecteplase 0.25mg/kg vs. placebo

458 pts, 53% female,
median age=72y, median NIHSS=12
77% underwent thrombectomy

Table 2. Clinical, Imaging, and Safety Outcomes.*

Outcome	Tenecteplase (N=228)	Placebo (N=230)	Adjusted Odds Ratio (95% CI)	P Value
Primary efficacy outcome				
Median score on the modified Rankin scale at 90 days (IQR)†	3 (1–5)	3 (1–4)	1.13 (0.82–1.57)	0.45
Secondary efficacy outcomes				
Functional independence at 90 days — no./total no. (%)‡	104/226 (46.0)	97/229 (42.4)	1.18 (0.80–1.74)	
Safety outcomes**				
Death — no./total no. (%)				
Within 30 days	32/218 (14.7)	32/214 (15.0)	—	—
Within 90 days	43/218 (19.7)	39/214 (18.2)††	—	—
Symptomatic intracranial hemorrhage within 36 hr — no./total no. (%)‡‡	7/218 (3.2)	5/214 (2.3)	—	—



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ORIGINAL ARTICLE

Reteplase versus Alteplase for Acute Ischemic Stroke

Shuya Li, M.D., Hong-Qiu Gu, Ph.D., Hao Li, M.D., Ph.D., Xuechun Wang, M.D., Aoming Jin, Ph.D., Shuming Guo, M.D., Guozhi Lu, M.D., Fengyuan Che, M.D., Weiwei Wang, M.D., Yan Wei, M.D., Yilong Wang, M.D., Zixiao Li, M.D., Xia Meng, M.D., Xingquan Zhao, M.D., Liping Liu, M.D., and Yongjun Wang, M.D., for the RAISE Investigators*

Li S et al. NEJM 2024

- Non-inferiority trial
- Ischaemic stroke ≤4.5 hours
- Reteplase 18mg X2 *vs.* Alteplase 0.9 mg/kg
- **Exclusion: intention for mechanical thrombectomy**
- Non-inferiority margin: lower limit of 95%CI of the RR >0.93
- Superiority: lower limit of 95%CI of the RR >1

1412 pts, 29.5% female
Median age=63y, median NIHSS=6

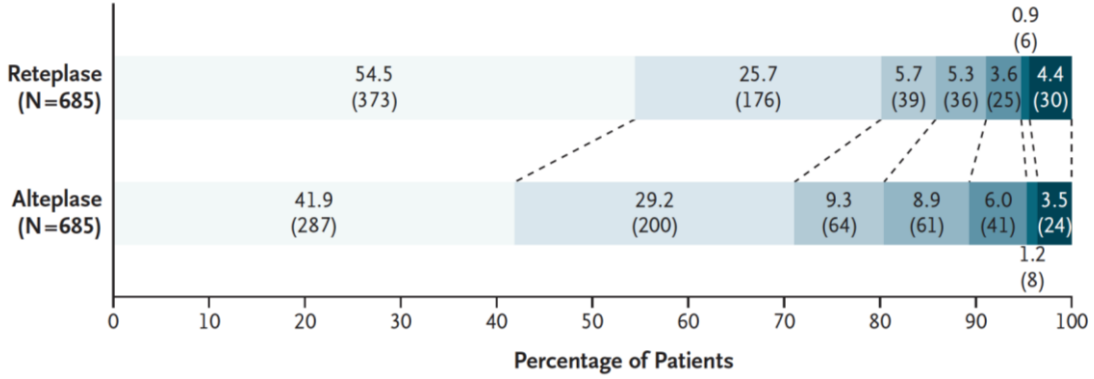

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Reteplase (N=707)	Alteplase (N=705)	Risk Ratio or Common Odds Ratio (95% CI)	Risk Difference (95% CI)
				percentage points
Primary outcome				
Modified Rankin scale score of 0 or 1 at 90 days — no. (%)	562 (79.5)	496 (70.4)	1.13 (1.05–1.21)	9.4 (3.3–15.4)
Secondary outcomes				
Modified Rankin scale score of 0–2 at 90 days — no. (%)	603 (85.3)	563 (79.8)	1.07 (1.02–1.12)	5.8 (1.8–9.8)
Median modified Rankin scale score at 90 days (IQR)	0 (0–1)	1 (0–2)	0.61 (0.27–0.95)†	

Table 3. Safety Outcomes.*

Outcome	Reteplase (N=700)	Alteplase (N=699)	Risk Ratio (95% CI)
	no. of patients (%)		
Primary safety outcome			
Symptomatic intracranial hemorrhage within 36 hr†	17 (2.4)	14 (2.0)	1.21 (0.54–2.75)
Secondary safety outcomes			
Symptomatic intracranial hemorrhage within 7 days†	17 (2.4)	15 (2.1)	1.13 (0.52–2.44)
Parenchymal hemorrhage type 2 within 36 hr‡	12 (1.7)	10 (1.4)	1.20 (0.36–4.03)
Any intracranial hemorrhage within 90 days§	54 (7.7)	34 (4.9)	1.59 (1.00–2.51)
Major hemorrhage within 90 days§	23 (3.3)	21 (3.0)	1.09 (0.65–1.85)
Clinically relevant nonmassive hemorrhage within 90 days§	38 (5.4)	17 (2.4)	2.23 (1.03–4.84)
Death within 90 days	30 (4.3)	24 (3.4)	1.25 (0.66–2.35)
Death within 7 days	11 (1.6)	11 (1.6)	1.00 (0.35–2.83)
Any adverse event	641 (91.6)	576 (82.4)	1.11 (1.03–1.20)
Serious adverse event	105 (15.0)	83 (11.9)	1.26 (0.99–1.61)

ATTENTION IA trial: Intra-arterial Tenecteplase After Endovascular Thrombectomy in Acute Posterior Circulation Arterial Occlusion

Unpublished data

- Ischaemic stroke + occlusion of V4, basilar, or P1 ≤24 hours
- NIHSS ≥6 + PC ASPECTS ≥6
- Successful recanalization (eTICI≥2b/3) after thrombectomy
- Intra-arterial tenecteplase *vs*. standard of care

	Thrombectomy + IA tenecteplase	**Thrombectomy alone**	**Difference**
Primary outcome: mRS 0-1 at 90 days	34%	26%	NS
mRS 0-2 at 90 days	-	-	NS
mRS 0-3 at 90 days	-	-	NS
Symptomatic intracranial haemorrhage	8%	3%	NS
Death at 90 days	-	-	NS

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Safety and efficacy of active blood-pressure reduction to the recommended thresholds for intravenous thrombolysis in patients with acute ischaemic stroke in the Netherlands (TRUTH): a prospective, observational, cluster-based, parallel-group study

Thomas P Zonneveld, MD • Sarah E Vermeer, MD PhD • Erik W van Zwet, MD PhD • Adrien E D Groot, MD PhD • Prof Ale Algra, MD PhD • Leo A M Aerden, MD PhD • et al. Show all authors • Show footnotes

Published: May 16, 2024 • DOI: https://doi.org/10.1016/S1474-4422(24)00177-7 • Check for updates

Zonneveld TP et al. Lancet Neurol. 2024

- Observational study
- Ischaemic stroke + BP >185/110mmHg
- Otherwise eligible for IV thrombolysis (alteplase)
- Centres with active BP-lowering strategy *vs*. centres with non-lowering strategy

Primary outcome:
Ordinal mRS: aOR=1.27 (0.96-1.68)

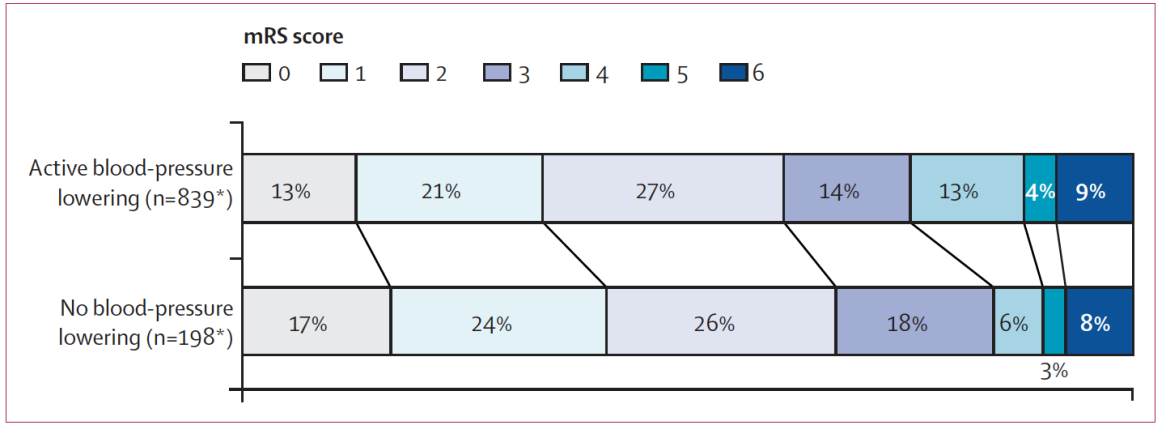

Figure 2: mRS scores at 90 days by blood-pressure-lowering strategy

	Active BP lowering (n=853)	No BP lowering (n=199)	aOR (95%CI)
Received IVT	94%	52%	
Received EVT	8%	4%	
mRS 2-6 at 90 days	66%	59%	1.34 (0.91-1.97)
Symptomatic intracranial haemorrhage	5%	3%	1.28 (0.62-2.62)

CHARM superiority trial: Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Oedema Following Large Hemispheric Infarction

Unpublished data

- Large hemispheric infarction (vol: 80-300cm^3 on DWI, CTP or ASPECTS 1-5)
- Early (<10 hours) IV Glibenclamide *vs*. placebo
- Early stopped (sponsor decision)

- 535 pts (39% IVT, 17% EVT)
- No difference in the primary outcome: ordinal analysis of the mRS at 90 days
- No difference in rates of death, mRS 0-4 at 90 days
- Glibenclamide: transient hypoglycaemia, no major other adverse side effects

- **Post hoc** analyses: in vol <125ml, Glibenclamide: better outcomes
  - mRS 0-3: 36% vs 19%
  - Mortality: 14% vs 22%

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ORIGINAL ARTICLE

Intensive Ambulance-Delivered Blood-Pressure Reduction in Hyperacute Stroke

G. Li, Y. Lin, J. Yang, C.S. Anderson, C. Chen, F. Liu, L. Billot, Q. Li, X. Chen, X. Liu, X. Ren, C. Zhang, P. Xu, L. Wu, F. Wang, D. Qiu, M. Jiang, Y. Peng, C. Li, Y. Huang, X. Zhao, J. Liang, Y. Wang, X. Wu, Xiaoyun Xu, G. Chen, D. Huang, Y. Zhang, L. Zuo, G. Ma, Y. Yang, J. Hao, Xiahong Xu, X. Xiong, Y. Tang, Y. Guo, J. Yu, S. Li, S. He, F. Mao, Q. Tan, S. Tan, N. Yu, R. Xu, M. Sun, B. Li, J. Guo, L. Liu, H. Liu, M. Ouyang, L. Si, H. Arima, P.M. Bath, G.A. Ford, T. Robinson, E.C. Sandset, J.L. Saver, N. Sprigg, H.B. van der Worp, and L. Song, for the INTERACT4 investigators*

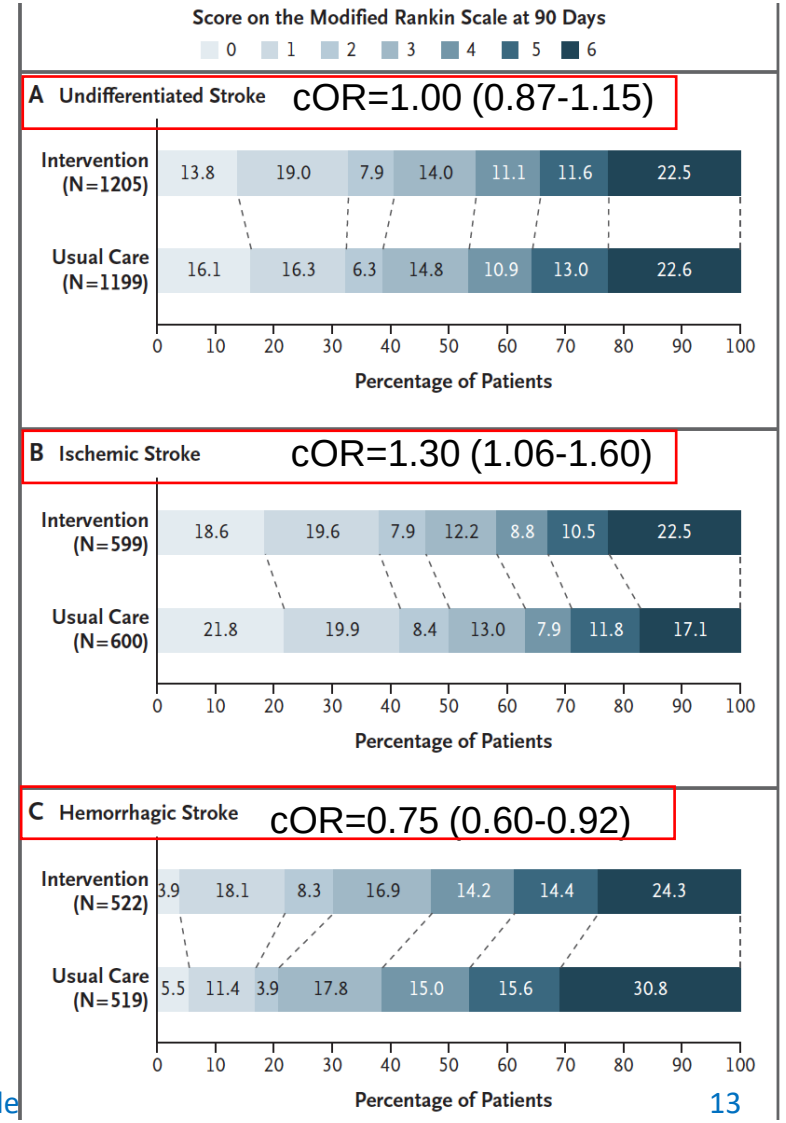
Li G et al. NEJM 2024

- Suspected stroke assessed in the ambulance ≤2 hours
- Systolic BP≥ 150mmHg
- Hyper-early intensive BP reduction (IV urapidil, target: 130-140)

vs. usual BP management (standard in-hospital care)

- 2404 pts (53.5% IS and 46.5% ICH)

- Median time from symptoms onset:
- -to randomisation= 61min !
- -to hospital arrival=78min !



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Decompressive craniectomy plus best medical treatment versus best medical treatment alone for spontaneous severe deep supratentorial intracerebral haemorrhage: a randomised controlled clinical trial

Jürgen Beck, Christian Fung, Daniel Strbian, Lukas Bütikofer, Werner J Z'Graggen, Matthias F Lang, Seraina Beyeler, Jan Gralla, Florian Ringel, Karl Schaller, Nikolaus Plesnila, Marcel Arnold, Werner Hacke, Peter Jüni, Alexander David Mendelow, Christian Stapf, Rustam Al-Shahi Salman, Jenny Bressan, Stefanie Lerch, Arsany Hakim, Nicolas Martinez-Majander, Anna Piippo-Karjalainen, Peter Vajkoczy, Stefan Wolf, Gerrit A Schubert, Anke Höllig, Michael Veldeman, Roland Roelz, Andreas Gruber, Philip Rauch, Dorothee Mielke, Veit Rohde, Thomas Kerz, Eberhard Uhl, Enea Thanasi, Hagen B Huttner, Bernd Kallmünzer, L Jaap Kappelle, Wolfgang Deinsberger, Christian Roth, Robin Lemmens, Jan Leppert, Jose L Sanmillan, Jonathan M Coutinho, Katharina A M Hackenberg, Gernot Reimann, Mikael Mazighi, Claudio L A Bassetti, Heinrich P Mattle, Andreas Raabe, Urs Fischer, on behalf of the SWITCH study investigators*

Beck J et al. Lancet 2024

- Severe deep supratentorial ICH
- Exclusion: cerebellar or brainstem expansion
- Decompressive craniectomy without hematoma evacuation + BMT *vs*. BMT

- Early stopped (insufficient funding)
- 190 pts /300 planned, 32% female, median age: 61y

	Decompressive craniectomy + BMT (n=96)	BMT alone (n=101)	aRR
Primary outcome: mRS 5-6 at 180 days	44%	58%	0.77 (0.59-1.01)
Median mRS at 180days	4	5	cOR=0.57 (0.34-0.97)
Death at 180 days	16%	27%	0.61 (0.36-1.01)
mRS 4-6 at 180 days	86%	86%	0.99 (0.89-1.11)
mRS 5-6 at 365 days	43%	51%	0.81 (0.60-1.08)
Death at 365 days	21%	30%	0.70 (0.45-1.08)

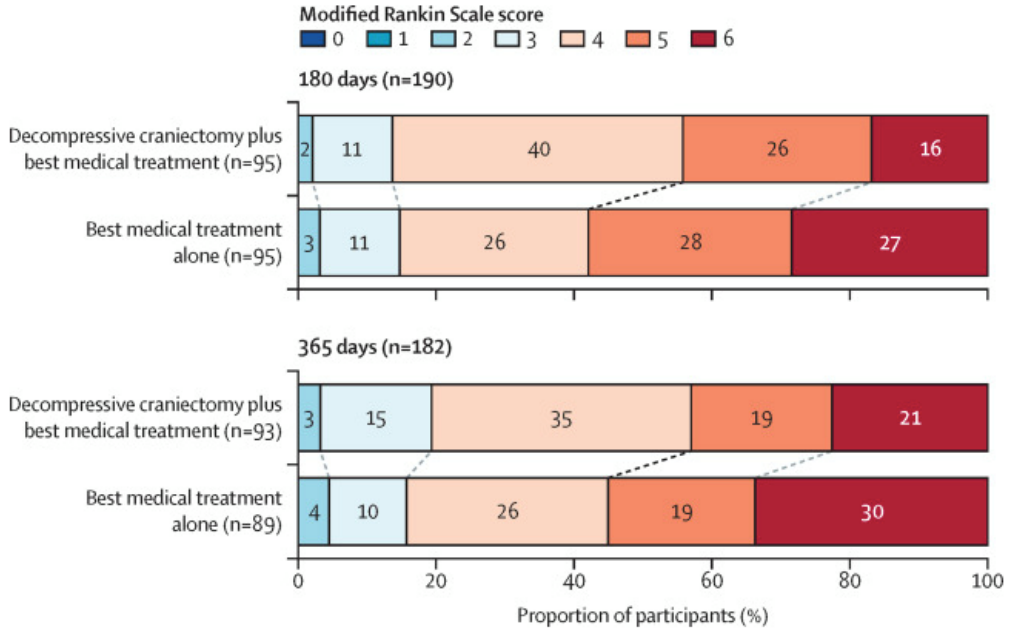

Figure 2 mRS score at day 180 and day 365

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Long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE): a randomised controlled trial

Prof Peter Kelly, MD • Prof Robin Lemmens, MD • Prof Christian Weimar, MD • Prof Cathal Walsh, PhD • Prof Francisco Purroy, MD • Prof Mark Barber, MD • et al. Show all authors

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Kelly PJ et al. Lancet 2024

- Non-cardioembolic ischaemic stroke or high-risk TIA ≤72 hours - 28days
- Colchicine 0.5mg/d + usual care (antiplatelet, lipid-lowering, antihypertensive ttt, and appropriate lifestyle advice) *vs*. usual care alone

- Early stopped 92% of planned outcomes (insufficient funding)
- 3154 pts, 30% female, mean age=66y
- Median follow-up: 34months

Subgroup analysis:
Prior CAD: Greater risk reduction

	Colchicine (n=1569)	Placebo (n=1575)	aHR
Primary outcome: recurrent IS, MI, vascular death (244 IS, 94 MI)	9.8% (3.32/100 person-years)	11.8% (3.92/100 person-years)	0.84 (0.68-1.05)

8% fewer outcomes > probably underpowered

Similar % of serious side effects
Colchicine:
-Non adherence =20%
-Diarrhea (12.1%), nausea (3.4%), resolved quickly
-1/5 permanently discontinued colchicine

Conclusion

- IV thrombolysis in ischaemic stroke ≤4.5 hours:
  - Tenecteplase: effective and safe
  - Reteplase: efficacy and safety of to be confirmed in other trials
  - No clear benefit of early active blood-pressure-lowering strategy
- Ischaemic stroke and intracranial occlusion ≤4.5-24 hours :
  - Tenecteplase may be effective with a trend towards higher sICH
- Minor stroke and intracranial occlusion ≤12 hours:
  - Do NOT routinely use IV thrombolysis
- Suspected stroke before brain imaging:
  - Do NOT early reduce blood-pressure
- Deep severe supratentorial intracerebral haemorrhage
  - No benefit of decompressive craniectomy
- Secondary prevention of non-cardioembolic ischaemic stroke:
  - No clear benefit of colchicine
  - Colchicine might be useful in subgroup atherosclerosis stroke or prior CAD
  - Do include in the ongoing RIISC THETIS trial