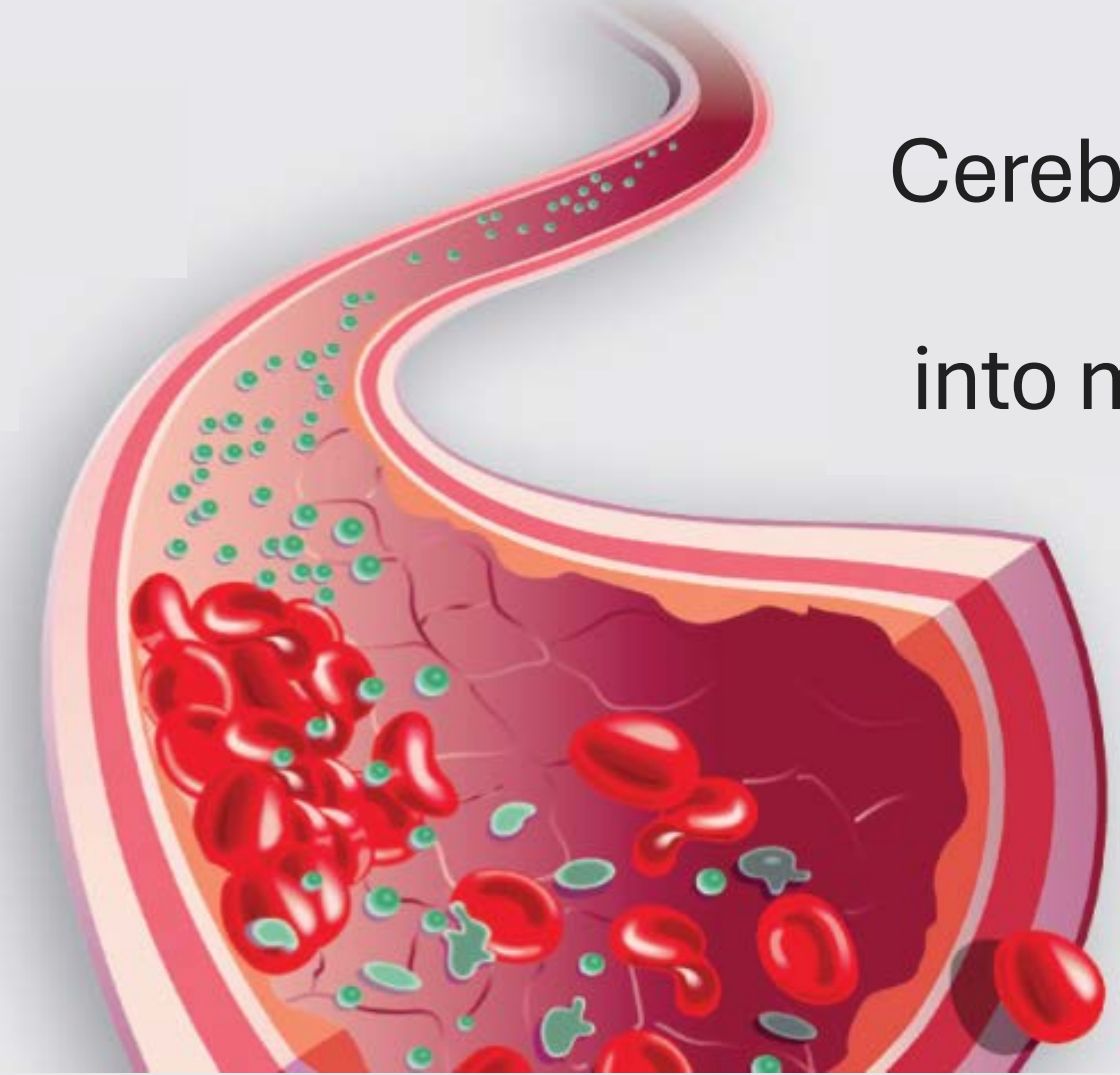
Meet the Hemostasis experts X



Cerebrovascular events revisited: New insights into management and treatment

Vasilis Tentolouris-Piperas, MSc, MAS

Eginitio University Hospital - Stroke Team

Conflicts of Interest Declaration

- Received travel and conference grants from: Pfizer, BIANEΞ, Bayer

Cerebrovascular Events

- Ischemic Events
  - Ischemic Stroke
  - TIA
- Hemorrhagic Events
  - Intracerebral hemorrhage
  - Subarrachnoid hemorrhage

Cerebrovascular Events

- Ischemic Events
  - **Ischemic Stroke**
  - TIA
- Hemorrhagic Events
  - Intracerebral hemorrhage
  - Subarrachnoid hemorrhage

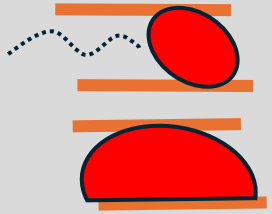
Lecture Structure

- Background – Pathophysiology
- Acute Management
- Secondary Prevention
- Covert Brain Infarcts

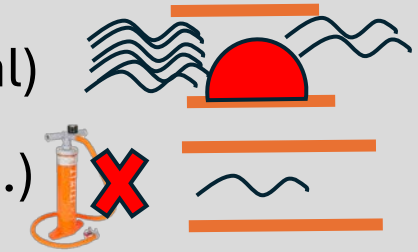
Background - Pathophysiology

Mechanisms of brain ischemia

- **Occlusion of vessel**
  - Embolus (cardiac, artero-arterial, etc.)
  - In-situ artery occlusion: intra/extra-cranial



- **Hypoperfusion**
  - Hemodynamically relevant stenosis (intra/extra-cranial)
  - Systemic (e.g. Cardiac pause, severe hypotension, etc.)
  - Steal syndromes (e.g. subclavia)



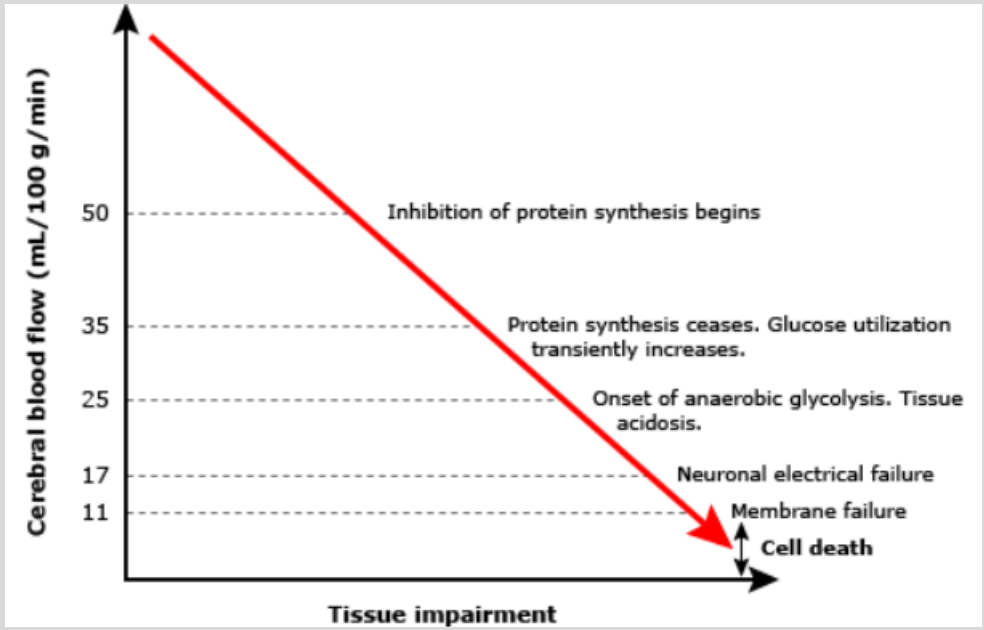


- *Venous drainage insufficiency (venous infarcts)*
- *Metabolic insufficiency (ischemia-like)*
  - *MELAS*
  - *Epileptic activity/seizure – Migrainous infarcts – Cortical Spreading Depression*

Ischemia = drop of Cerebral Blood Flow (CBF)

CBF drop dependent on:

- Area/size of infarct/hypoperfusion
- Duration of infarct/hypoperfusion
- Collateral circulation status



Focal symptoms: arise depending on the brain area where CBF drops enough to cause a significant enough neuronal dysfunction

Ischemic core – Penumbra

Ischemic core -> unsalvageable

Around the core: <u>penumbra!</u>

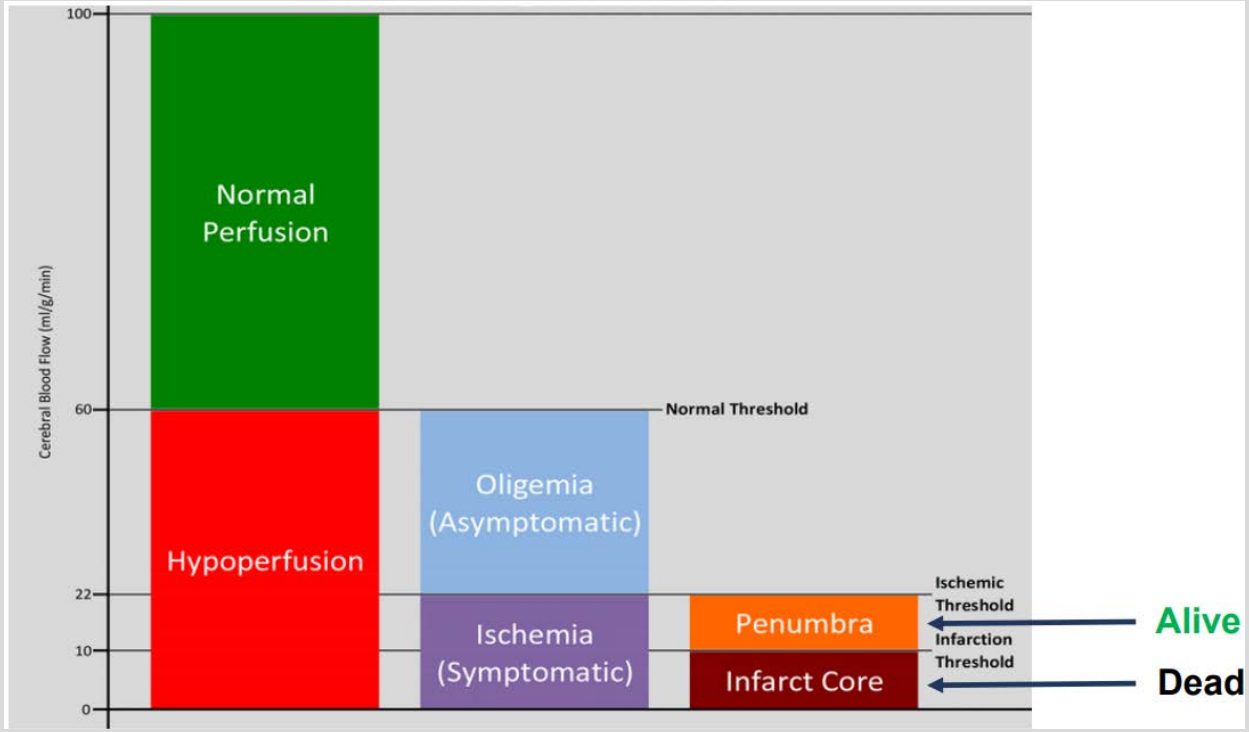
Partial hypoperfusion (> 20-40% CBF)

-> collateral circulation

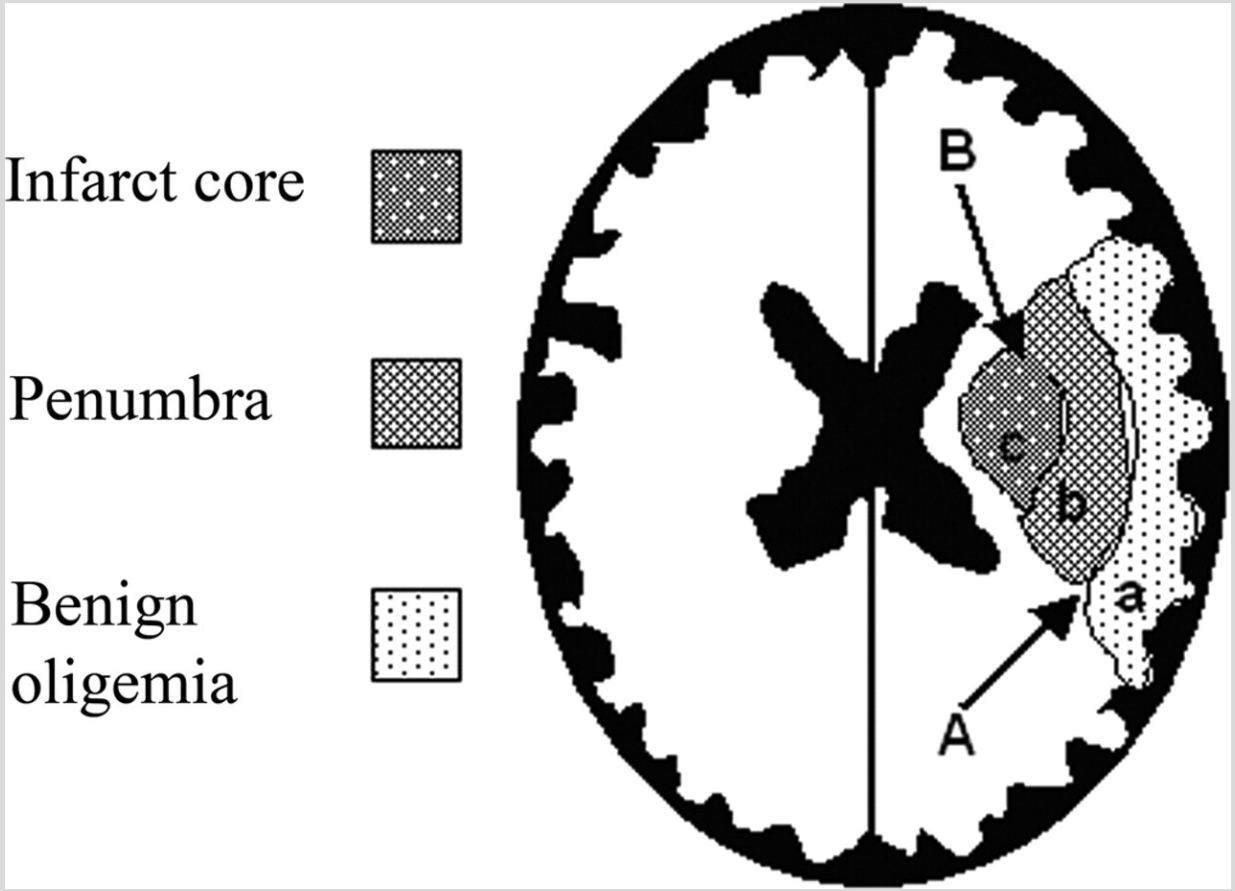
Reversible damage!

-> greatest potential for survival

-> <u>therapeutic target</u>



Ischemic core – Penumbra

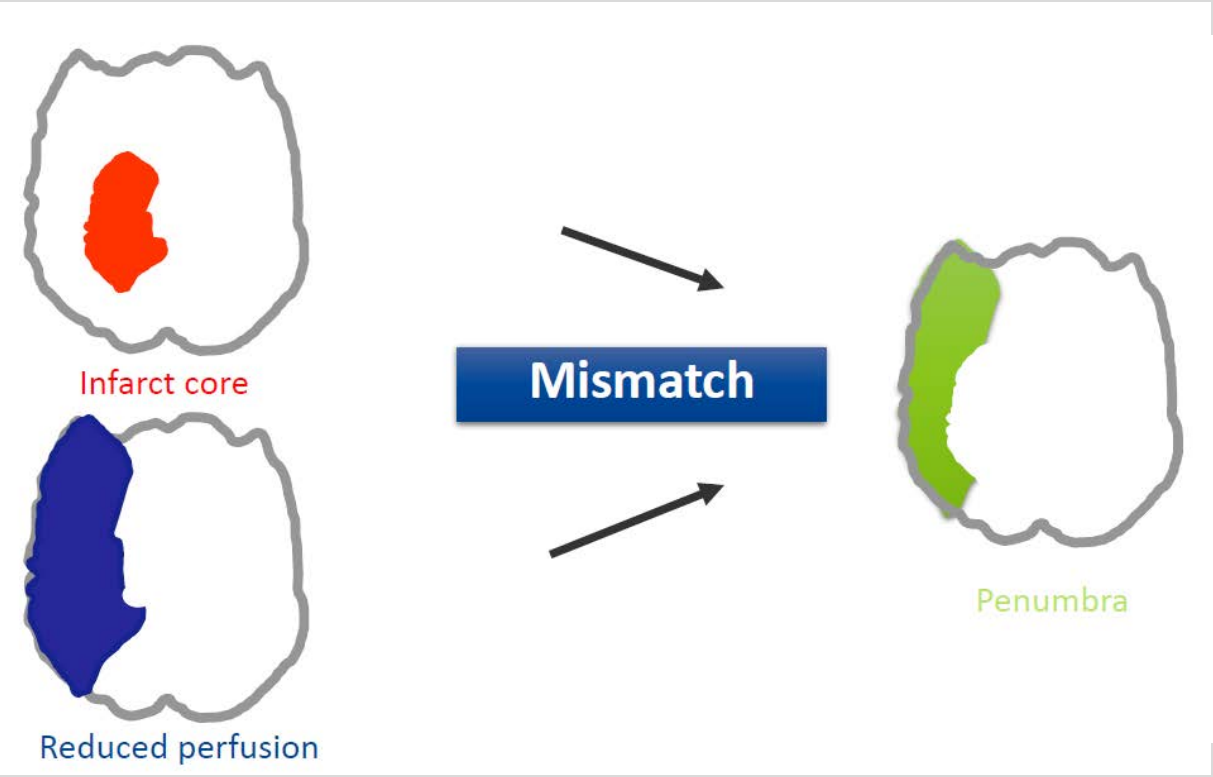


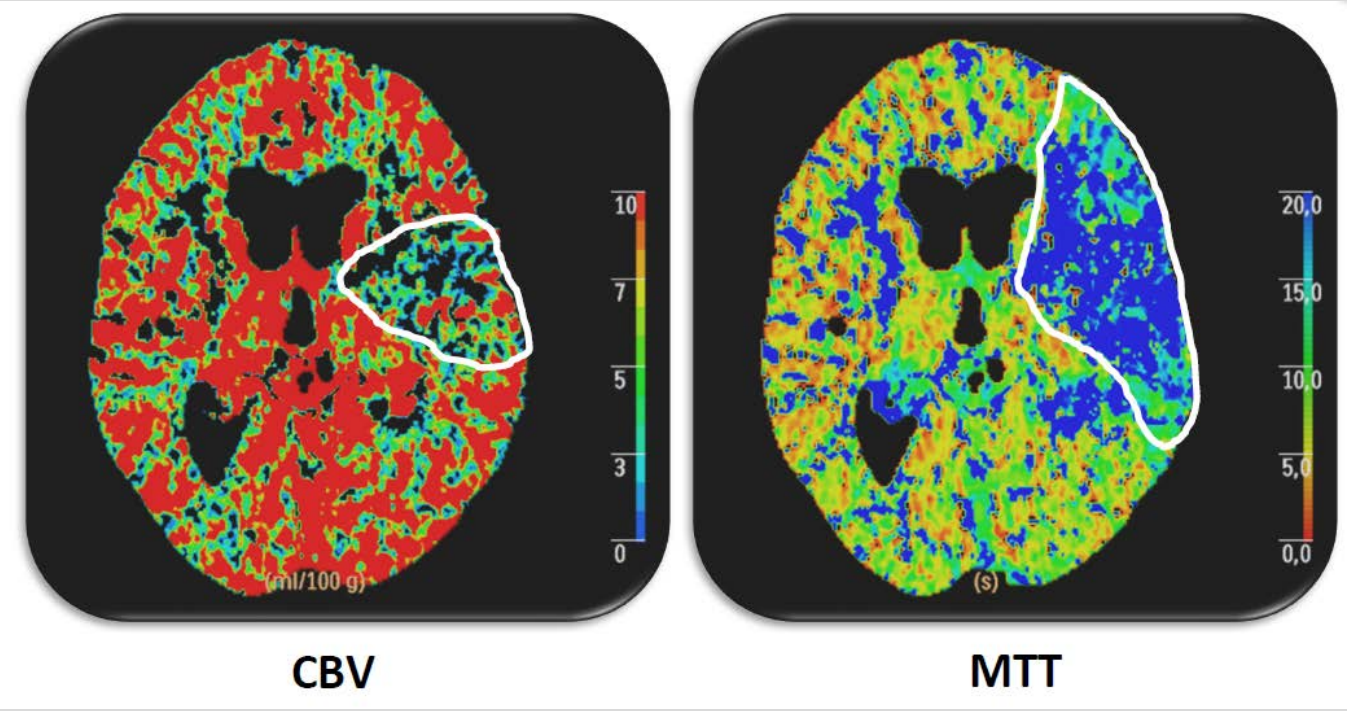
Stroke
A Journal of Cerebral Circulation
NOVEMBER-DECEMBER 1981
VOL. 12 NO. 6

Editorial

Thresholds in Cerebral Ischemia — The Ischemic Penumbra

Penumbral Imaging





Time is brain!

Stroke is a dynamic process evolving over time

Earlier treatment

Better outcomes!

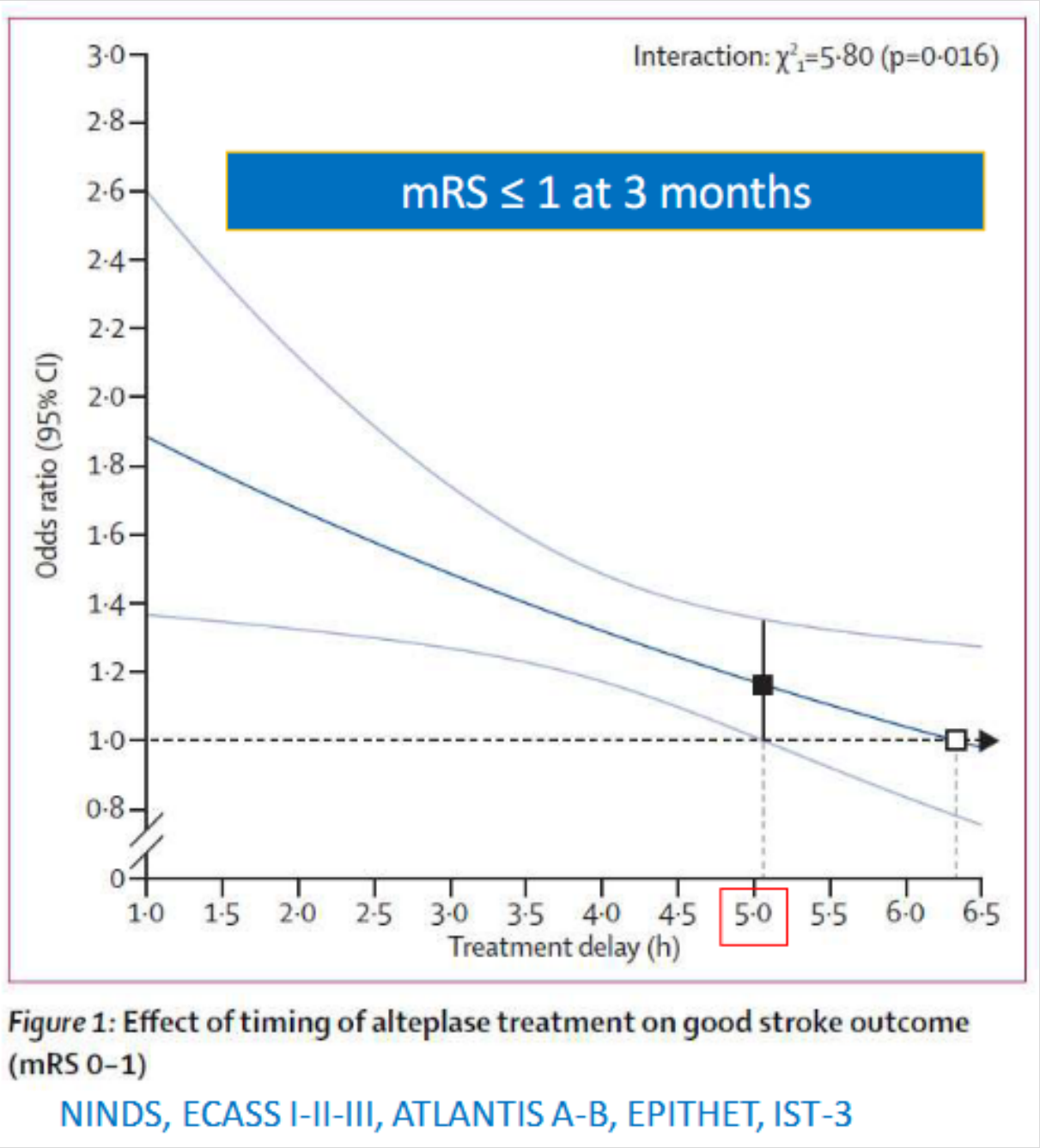


Figure 1: **Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)**

NINDS, ECASS I-II-III, ATLANTIS A-B, EPITHET, IST-3

Emberson J et al, Lancet 2014

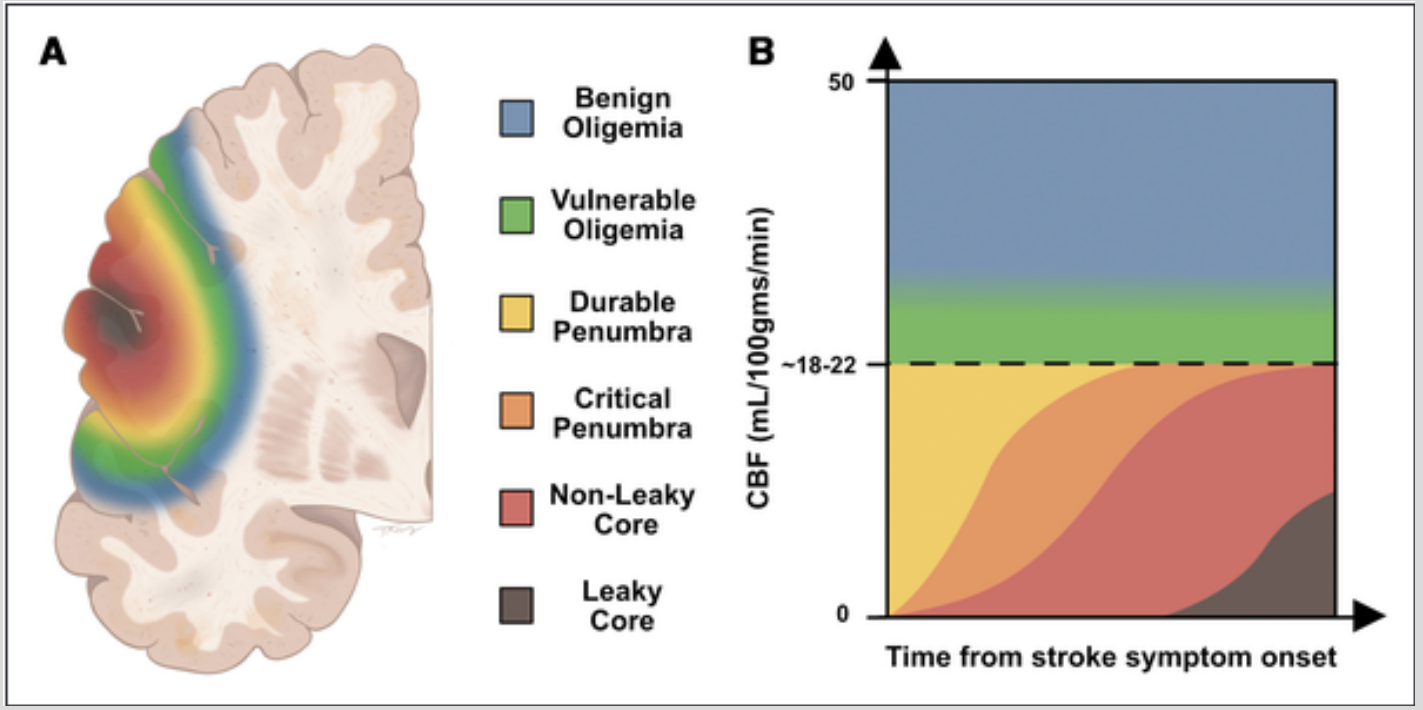
Penumbra 2.0

Stroke
Volume 57, Issue 7, July 2026; Pages 2237-2247
https://doi.org/10.1161/STROKEAHA.126.055331

TOPICAL REVIEWS

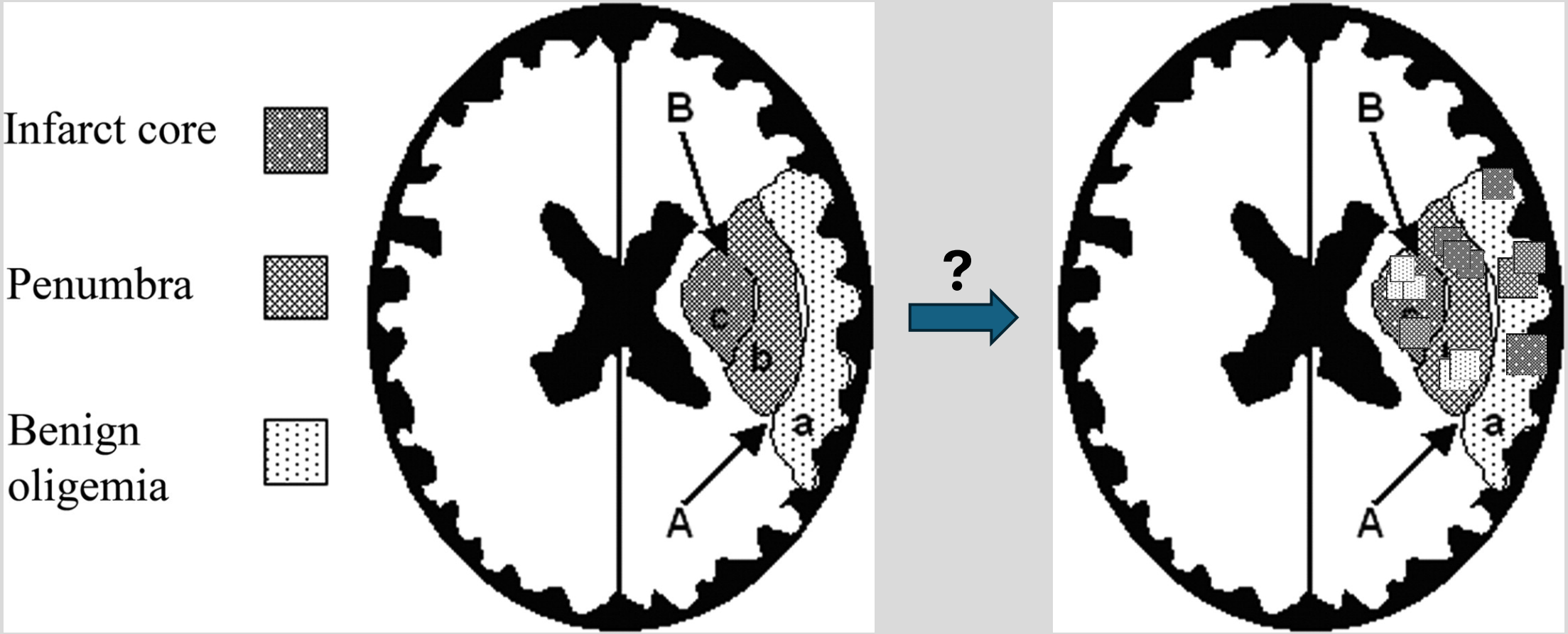
Redefining the Cerebral Ischemic Core-Penumbra-Oligemia Continuum

Umberto Pensato, MD, Johanna M. Ospel, MD, PhD, Aravind Ganesh, MD, Nishita Singh, MD, Mohammed Almekhlafi, MD, Gabriel Broocks, MD, Giorgio Busto, MD, Enrico Fainardi, MD, Diego Gutierrez Vasquez, MD, Tyler Henry, MD, Maarten G. Lansberg, MD, Felix Ng, MD, Thanh N. Nguyen, MD, Jean-Marc Olivot, MD, Mark W. Parsons, MD, Vignan Yogendrakumar, MD, Andrea Zini, MD, Beom Joon Kim, MD, Vivek Yedavalli, MD, Gregory W. Albers, MD, Bruce C.V. Campbell, MD, Michael D. Hill, MD, Bijoy K. Menon, MD, and Andrew M. Demchuk, MD



	Definitions
Benign oligemia	A brain region with very mild hypoperfusion that is not at risk of infarction and will remain viable regardless of reperfusion.
Vulnerable oligemia	A brain region with mild hypoperfusion that is not currently threatened by ischemic injury but may convert to ischemic penumbra if physiological conditions change, such as blood pressure reduction, hypercapnia, or hyperglycemia.
Durable penumbra	A brain region with moderate hypoperfusion that remains viable for an extended period, even without prompt reperfusion. However, if reperfusion is not achieved, the tissue will progress to infarction.
Critical penumbra	A brain region with severe hypoperfusion that is severely compromised by ischemic damage. Although not yet irreversibly injured at the time of assessment, it is highly vulnerable, and its survival depends on urgent restoration of blood flow.
Nonleaky core	A brain region that is irreversibly injured at the time of evaluation and will progress to infarction regardless of reperfusion.
Leaky core	A brain region that is irreversibly injured at the time of evaluation, which also shows early disruption of the blood-brain barrier. If reperfusion occurs, the tissue is at high risk for malignant cerebral edema and parenchymal hemorrhage.

Penumbra 2.0



Pathophysiology - New insights

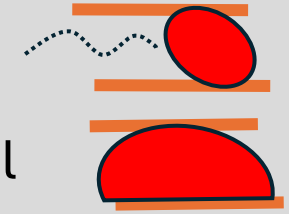


- Ischemic **stroke is a dynamic process** evolving over time
- Imaging is giving us a **snapshot** of this process which could go either way
- Infarct evolution is not the same for everybody! (**fast vs slow progressors**)
- **Penumbra concept may be outdated**, things are more complicated
- May explain some of the phenomena we observe
  - Large-core patients showing favorable outcomes with reperfusion
  - No-reflow phenomenon

Acute Ischemic Stroke Management

Acute treatment of brain ischemia

- **Occlusion of vessel**
  - Embolus (cardiac, artero-arterial, etc.)
  - In-situ artery occlusion: intra/extra-cranial



- **Hypoperfusion**
  - Hemodynamically relevant stenosis (intra/extra-cranial)
  - Systemic (e.g. Cardiac pause, severe hypotension, etc.)
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- *Venous drainage insufficiency (venous infarcts)*
- *Metabolic insufficiency (ischemia-like)*
  - *MELAS*
  - *Epileptic activity/seizure – Migrainous infarcts – Cortical Spreading Depression*

History – The Dark Ages



- Neutral/negative initial trials – (streptokinase, heparin)
- No acute reperfusion therapies
- Aggressive observation…
- 1997-2000! Aspirin

Stroke
Volume 31, Issue 6, June 2000; Pages 1240-1249
https://doi.org/10.1161/01.STR.31.6.1240

ORIGINAL CONTRIBUTIONS

Indications for Early Aspirin Use in Acute Ischemic Stroke

A Combined Analysis of 40 000 Randomized Patients From the Chinese Acute Stroke Trial and the International Stroke Trial

ZhengMing Chen, Peter Sandercock, HongChao Pan, Carl Counsell, Rory Collins, LiSheng Liu, JingXian Xie, Charles Warlow, Richard Peto, and on behalf of the CAST and IST collaborative groups

History – Thrombolysis – rtPA (alteplase)

- Cardiology use for ACS (1987)
- NINDS – first positive rtPA trial (**1995**)
- ECASS, ECASS2, ATLANTIS – neutral for primary outcomes
- Some positive for secondary ourcomes (now common primaries)
- Positive meta-analysis μετα-ανάλυση (Hacke, 2004)
- ECASS 3 positive (3h -> 4.5h)
- Time-based decision making: up to 4.5h
- First extended time-window trials – EXTEND, WAKE-UP

Boysen, G, and ECASS Study Group. “European Cooperative Acute Stroke Study (ECASS): (rt-PA-Thrombolysis in acute stroke) study design and progress report.” *European journal of neurology* vol. 1,3 (1995): 213-9. doi:10.1111/j.1468-1331.1995.tb00074.x
Hacke, W et al. “Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators.” *Lancet (London, England)* vol. 352,9136 (1998): 1245-51. doi:10.1016/s0140-6736(98)08020-9
Albers, Gregory W et al. “ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke.” *Stroke* vol. 33,2 (2002): 493-5. doi:10.1161/hs0202.102599
Hacke, Werner et al. “Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials.” *Lancet (London, England)* vol. 363,9411 (2004): 768-74. doi:10.1016/S0140-6736(04)15692-4
Bluhmki, Erich et al. “Stroke treatment with alteplase given 3.0-4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial.” *The Lancet. Neurology* vol. 8,12 (2009): 1095-102. doi:10.1016/S1474-4422(09)702

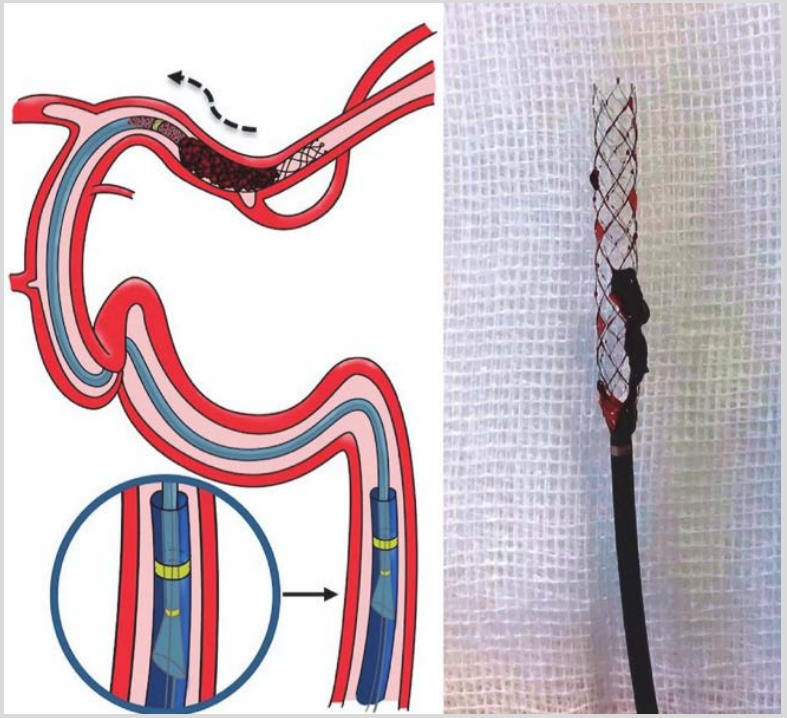
History – Mechanical Thrombectomy

- Early trials 2013 (IMS III, SYNTHESIS, MR RESCUE): neutral/negative!
  - Lacked vascular imaging for all patients pre-intervention
  - Old devices/techniques
  - Selection bias!?
- HERMES collaboration 2015 (MR CLEAN, ESCAPE, EXTENT-IA, SWIFT PRIME, REVASCAT)
- **NNT 2.6** for mRS Shift
- DAWN, DEFUSE-3: extended treatment window to 6h-24h

Acute Management – Age of Enlightenment

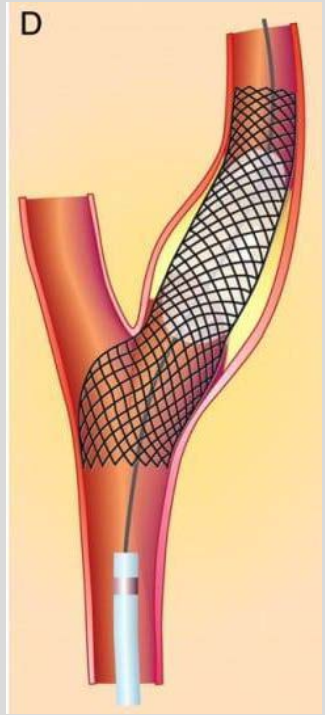


Mechanical Thrombectomy



Remollo S Journal of NeuroInterventional Surgery 2021;13:A134-A135.

Acute Stenting



www.vascularsurgeryassociates.net/contents/treatments/carotid-stenting

Intravenous Thrombolysis (IVT)

Endovascular Treatment (EVT)

IVT: Tenecteplase

- **Longer half-life** compared to rtPA
- Higher **specificity to fibrin**
- Higher **resistance to Plasmin Activator Inhibitor 1**
- **Bolus** administration (instead of bolus+1h infusion)
- Doesn't require refrigeration
- **Superior** to rtPA **for LVO recanalisation**
- **Non-inferior** to rtPA **for other scenarios**
- **Similar safety** profile

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

Evidence-based recommendation
For patients with large vessel occlusion acute ischaemic stroke of <4.5 hr duration who are eligible for intravenous thrombolysis, we recommend tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg. Intravenous thrombolysis should not delay mechanical thrombectomy.
Quality of evidence: Moderate ⊕⊕⊕
Strength of recommendation: Strong ↑↑

ESO 2023

4.6.2. Choice of Thrombolytic Agent

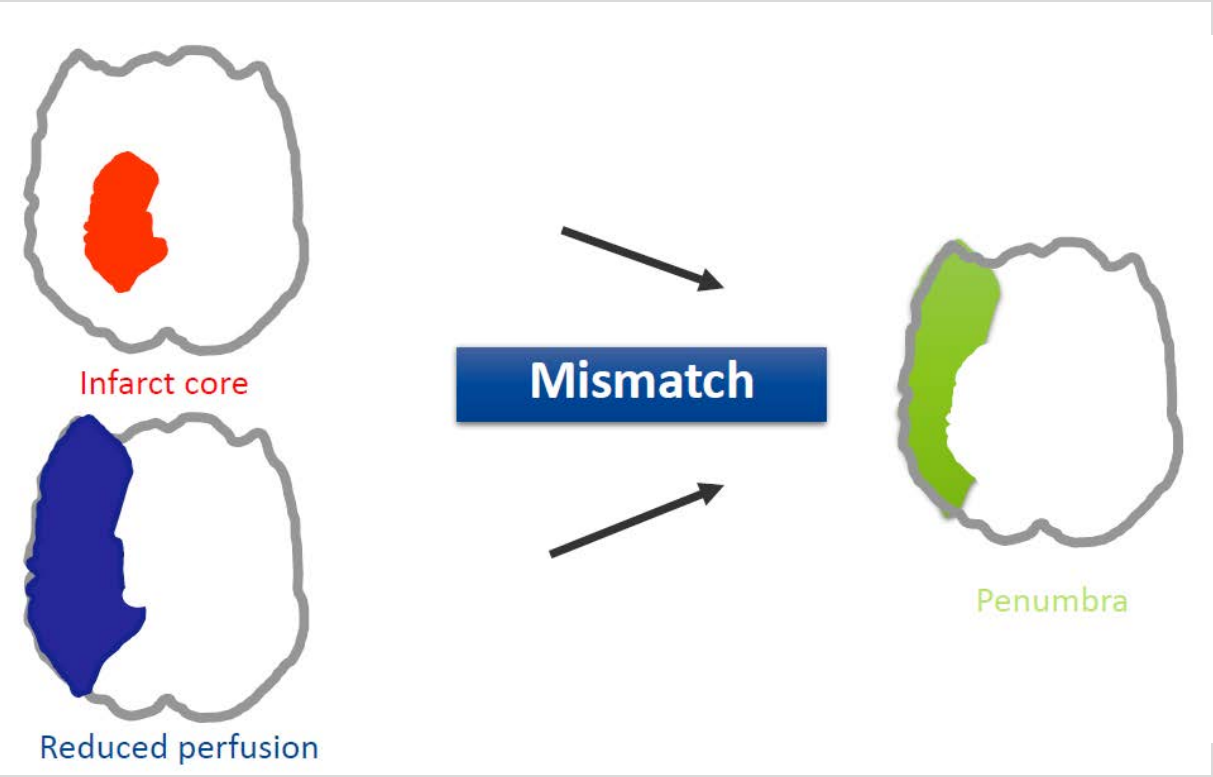
Recommendations for Choice of Thrombolytic Agent
Referenced studies that support the recommendations are summarized in the online data supplement.

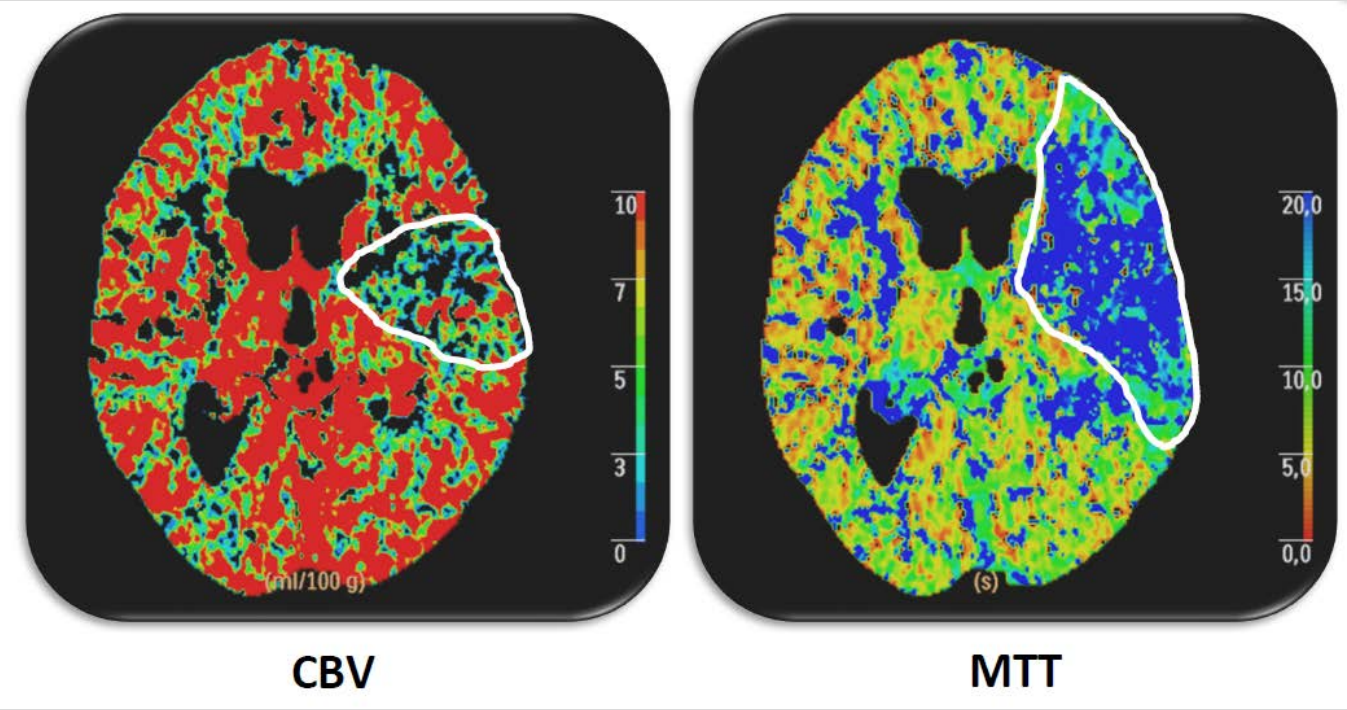
COR	LOE	Recommendations
1	A	1. In adult patients with AIS presenting within 4.5 hours of symptom onset or last known well and eligible for IVT, tenecteplase at a dose of 0.25 mg/kg body weight (max 25 mg) or alteplase at a dose of 0.9 mg/kg body weight (max 90 mg) is recommended to improve functional outcomes.[1–5]

AHA 2026

Berge, Eivind et al. "European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke." *European stroke journal* vol. 6,1 (2021): I-LXII. doi:10.1177/2396987321989865
Prabhakaran, Shyam et al. "2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association." *Stroke* vol. 57,8 (2026): e316-e436. doi:10.1161/STR.0000000000000513

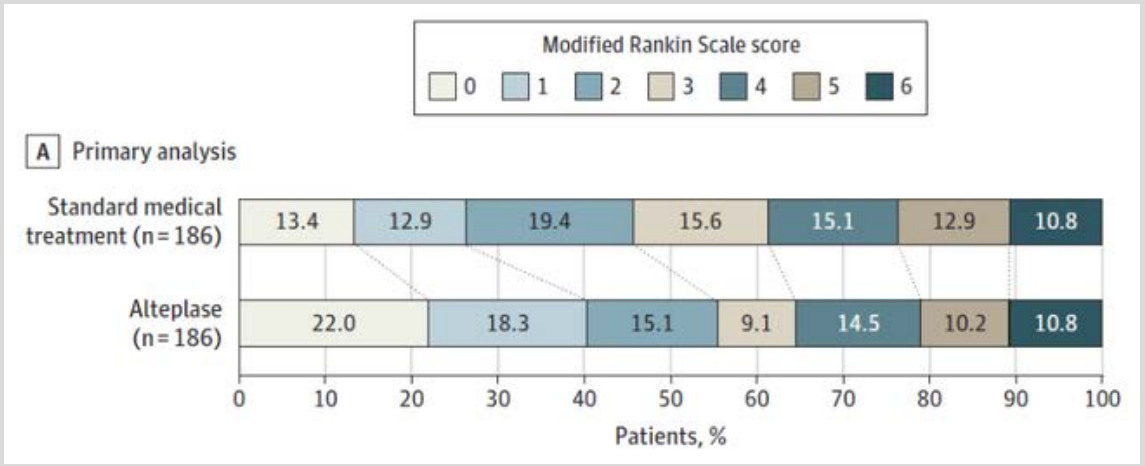
IVT: Tissue-based paradigm

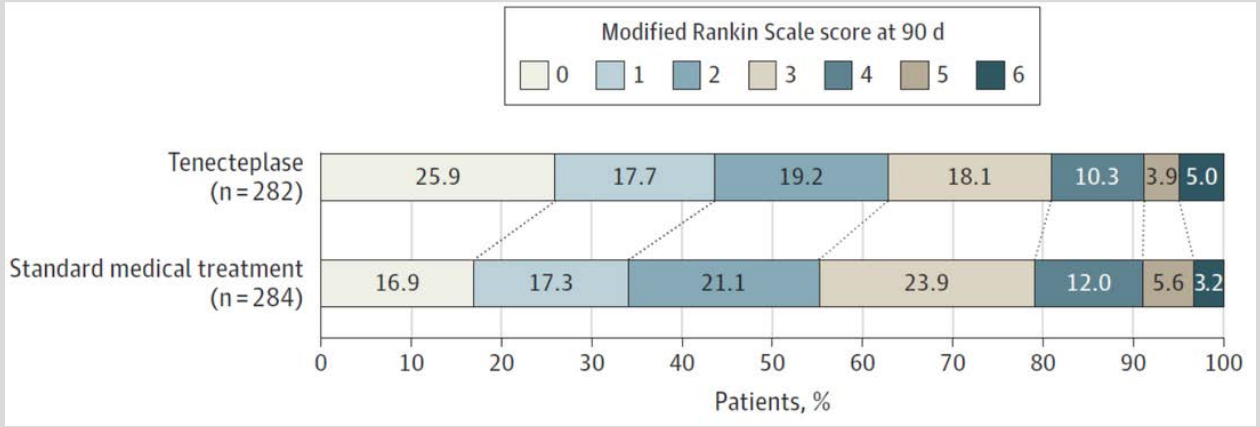




IVT: Tissue-based paradigm

- Advanced imaging enables better patient selection
- **Extending the time-window beyond 9 hours**
- TIMELESS, TRACE-3, HOPE, OPTION, *TENACITY*





Zhou Y, He Y, Campbell BCV, et al; for the HOPE investigators. Alteplase for acute ischemic stroke at 4.5 to 24 hours: the HOPE randomized clinical trial. *JAMA*. Published online August 7, 2025. doi:10.1001/jama.2025.12063

MA G, Mo R, Zuo Y, et al; OPTION Investigators. Tenecteplase for acute non-large vessel occlusion 4.5 to 24 hours after ischemic stroke: the OPTION randomized clinical trial. *JAMA*. Published February 5, 2026. doi:10.1001/jama.2026.0210

IVT: NOAC patients

- OAC patients were excluded from all thrombolysis trials
- Absolute contra-indication in older guidelines

Recommendation

For patients with acute ischaemic stroke of < 4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e. calibrated anti-Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), we suggest no intravenous thrombolysis.

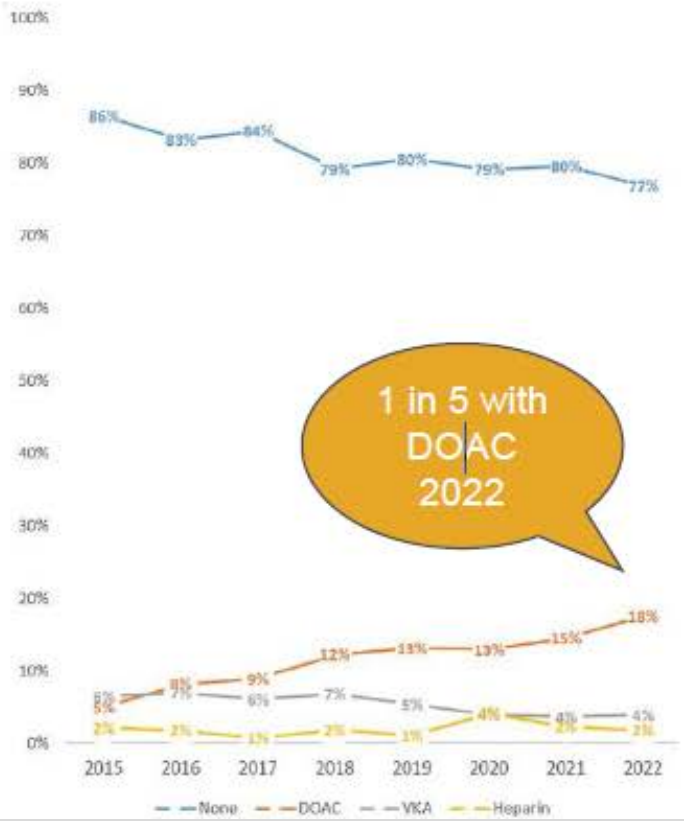
Quality of evidence: **Very Low** ⊕

Strength of recommendation: **Strong** ↓↓

ESO 2021

Berge, Eivind et al. “European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke.” *European stroke journal* vol. 6,1 (2021): I-LXII. doi:10.1177/2396987321989865
Prabhakaran, Shyam et al. “2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association.” *Stroke* vol. 57,8 (2026): e316-e436. doi:10.1161/STR.0000000000000513

IVT: NOAC patients



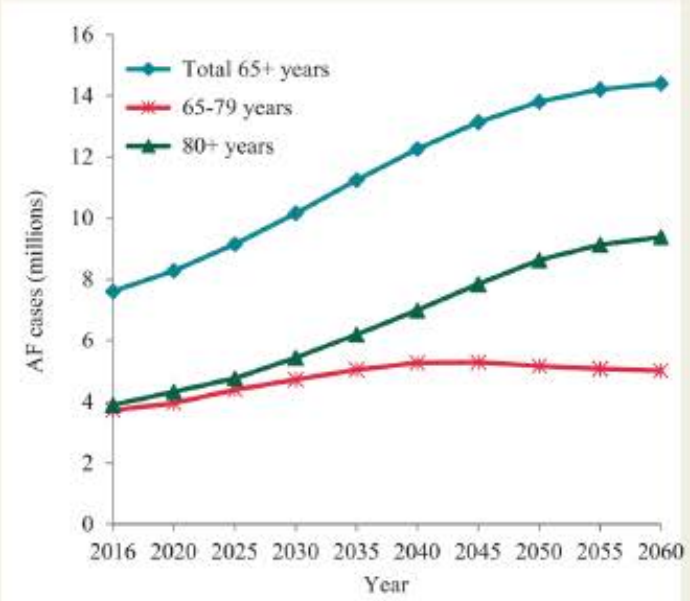
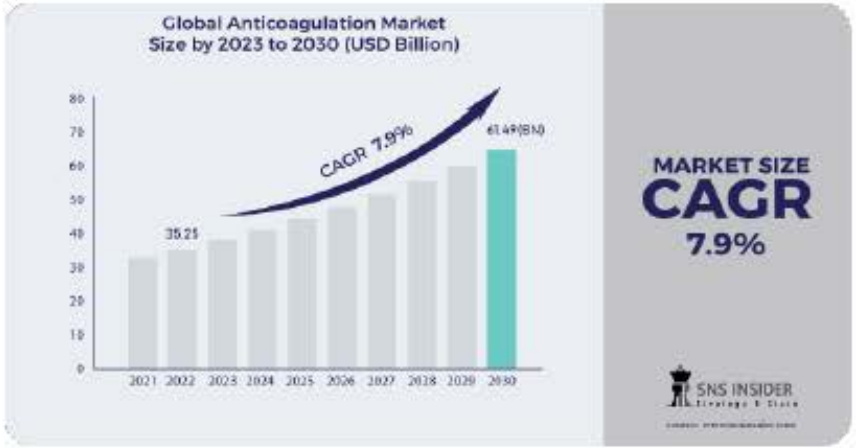


Figure 3 Projections of number of European Union elderly with atrial fibrillation between 2016 and 2060. AF, atrial fibrillation.



Bücke, Philipp et al. "Intravenous thrombolysis in patients with recent intake of direct oral anticoagulants: A target trial analysis after the liberalization of institutional guidelines." *European stroke journal* vol. 9,4 (2024): 959-967. doi:10.1177/23969873241252751

Di Carlo et al. Europace(2019) 21, 1468-1475

https://www.snsinsider.com/reports/anticoagulation-market-2567

IVT: NOAC patients

JAMA Neurology | Original Investigation

Intravenous Thrombolysis in Patients With Ischemic Stroke and Recent Ingestion of Direct Oral Anticoagulants

DESIGN, SETTING, AND PARTICIPANTS This international, multicenter, retrospective cohort study included 64 primary and comprehensive stroke centers across Europe, Asia, Australia, and New Zealand. Consecutive adult patients with ischemic stroke who received IVT (both with and without thrombectomy) were included. Patients whose last known DOAC ingestion was more than 48 hours before stroke onset were excluded. A total of 832 patients with recent DOAC use were compared with 32 375 controls without recent DOAC use. Data were collected from January 2008 to December 2021.

EXPOSURES Prior DOAC therapy (confirmed last ingestion within 48 hours prior to IVT) compared with no prior oral anticoagulation.

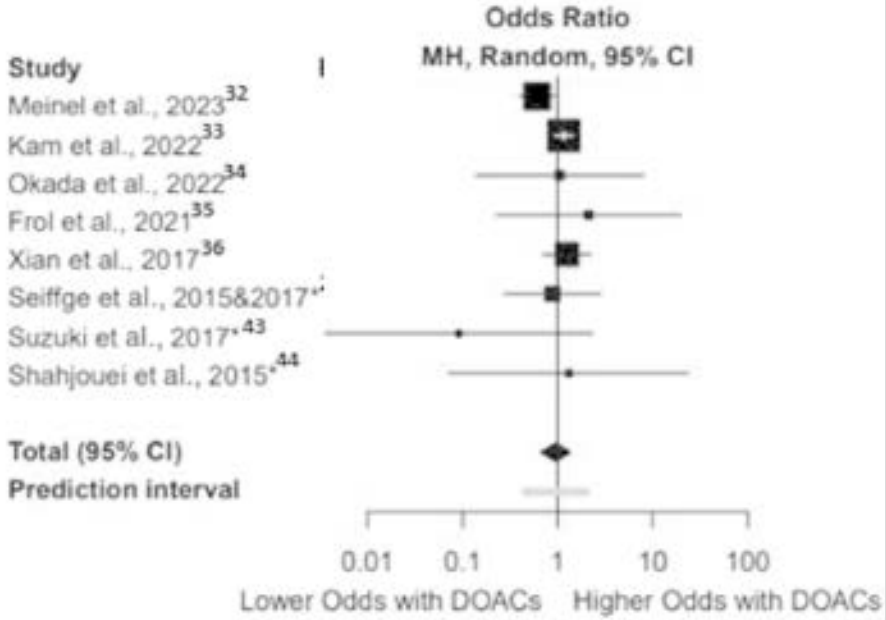
MAIN OUTCOMES AND MEASURES The main outcome was sICH within 36 hours after IVT, defined as worsening of at least 4 points on the National Institutes of Health Stroke Scale and attributed to radiologically evident intracranial hemorrhage. Outcomes were compared according to different selection strategies (DOAC-level measurements, DOAC reversal treatment, IVT with neither DOAC-level measurement nor idarucizumab). The association of sICH with DOAC plasma levels and very recent ingestions was explored in sensitivity analyses.

Table 1. Patient Baseline Characteristics

Characteristic	Total, No.	No. (%) All patients (N = 33 207)	Controls (n = 32 375)	Patients with recent ingestion of DOACs (n = 832)	P value
Age, median (IQR), y	33 198	73 (62-80)	72 (62-80)	79 (71-85)	<.001
Sex					
Female	33 199	14 458 (43.5)	14 103 (43.6)	355 (42.7)	.60
Male		18 741 (56.5)	18 264 (56.4)	477 (57.3)	
Geographical region					
Europe	33 207	21 266 (64.0)	20 792 (64.2)	474 (57.0)	<.001
Asia		6698 (20.2)	6489 (20.0)	209 (25.1)	
Australia and New Zealand		5243 (15.8)	5094 (15.7)	149 (17.9)	
NIHSS score, median (IQR)[a]	32 928	9 (5-16)	9 (5-16)	11 (6-17)	<.001
Prestroke modified Rankin Scale score, median (IQR)[b]	29 059	0 (0-0)	0 (0-0)	0 (0-1)	<.001
Systolic blood pressure, mean (SD), mm Hg	29 178	154 (28)	154 (28)	154 (27)	.67
Time from symptom onset to hospital admission, median (SD), h	12 179	1.3 (0.8-2.3)	1.3 (0.8-2.3)	1.7 (1.0-2.6)	<.001
Blood glucose level, mean (SD), mg/dL	28 711	133 (48)	133 (48)	133 (45)	.77
International normalized ratio, median (IQR)	17 471	1 (1-1.1)	1 (1-1.1)	1.1 (1.02-1.2)	<.001
Risk factors and medication[c]					
Arterial hypertension	33 000	20 637 (62.5)	20 072 (62.2)	565 (75.1)	<.001
Current smoking	30 337	5891 (19.4)	5796 (19.6)	95 (12.8)	<.001
History of hypercholesterolemia	32 941	12 413 (37.7)	12 091 (37.6)	322 (43.2)	.002
Diabetes	32 978	6484 (19.7)	6311 (19.6)	173 (23.2)	.01
Antiplatelet therapy	29 884	10 471 (35.0)	10 383 (35.7)	88 (11.2)	<.001
AF	16 629	4616 (27.8)	4008 (25.1)	608 (90.1)	<.001
If taking anticoagulation, AF as reason for anticoagulation	1248	1171 (93.8)	609 (90.2)	562 (98.1)	
Type of anticoagulation used					
Dabigatran	33 207	0	0	342 (41)	<.001
Rivaroxaban		0	0	258 (31)	
Apixaban		0	0	163 (20)	
Edoxaban		0	0	68 (8)	
DOAC, not specified which agent		0	0	1 (<1)	
Vitamin K antagonists		0	0	689	

Meinel et al. *JAMA Neurology* 2023 Mar 1;80(3):233-243

IVT: NOAC patients



Ghannam et al. *JAHA* 2023 12(24)

Intravenous Thrombolysis in Patients with Recent Intake of Direct Oral Anticoagulants

A Target Trial Analysis and Comparison with Reversal Agent Use

Question

Is off-label intravenous thrombolysis (IVT) after recent intake of direct oral anticoagulants (**DOACs**) **safe and effective**?

Is DOAC reversal safe & effective?

Population

Stroke patients with **disabling deficit (NIHSS ≥2) otherwise eligible for IVT**.

Last DOAC intake within 48 hours
28 stroke centers internationally

Methods

Target trial analysis of observational data **comparing off-label IVT vs no IVT**

Secondary analysis for comparison of DOAC **reversal** (all from Australian stroke registry) **vs. no reversal prior to IVT**

Outcomes

Safety: **sICH** (ECASS 2)
Mortality

Efficacy: **Good outcome**
(mRS 0-2 or return to baseline)

Cohort:

- **1342 patients** (median age 80 (IQR 73-86), NIHSS 11 (6-18), 50% female, 52% endovascular therapy, 88% atrial fibrillation)
- **IVT given in 342**/1342 **(25%)**
- **141 (41%) verified DOAC intake <12 h** and 92 (27%) within 12-24 h.

Results:

sICH (ECASS-2)	10/328 (3.0%)	54/921 (5.9%)
Adjusted difference	**-2.1%** (-5.3% to +1.2%)	
Mortality	16% (12 to 20%)	23% (20 to 26%)
Adjusted difference	**-3.3%** (-9.5% to +2.9%)	
Good outcome	62% (56 to 68%)	44% (41 to 47%)
Adjusted difference	**+14.4%** (+7.1% to +21.8%)	

Comparing 289 patients with reversal to 283 without, there were no significant differences in symptomatic ICH, major bleeding, or efficacy outcomes.

Cite as Meinel T. et al. Stroke 2025

Conclusion

This analysis **confirms** previous observational data regarding **the safety of off-label IVT in patients with recent DOAC intake**. **More data** and dedicated trials **are needed for patients with confirmed high DOAC plasma levels** and regarding the efficacy and safety of DOAC reversal prior to IVT.

IVT: NOAC patients

- OAC patients were excluded from all thrombolysis trials
- **Relative** contra-indication in newer guidelines
- Multiple RCTs are ongoing…

Conditions That are Relative Contraindications	
DOAC exposure	In patients with disabling symptoms and recent DOAC exposure (<48 hours) who are within the window for alteplase/tenecteplase, the safety of IV thrombolysis is unknown. Emerging but limited observational data suggest IV thrombolysis may be considered after a thorough benefit vs risk analysis on an individual basis. Benefit vs risk assessments should include considering the timing of the last DOAC administration, renal function, stroke severity, and availability of endovascular thrombectomy as well as availability of DOAC reversal agents and DOAC-specific anti-factor Xa/thrombin time assays acknowledging the potential for delay in thrombolysis and potential increased thrombotic risk. All aspects of DOAC management (timing, reversal agent use, assay results), should be recorded carefully to facilitate ongoing safety analyses. Definitive clinical trials are needed to establish the safety of IV thrombolysis in DOAC patients.

AHA 2026

Berge, Eivind et al. “European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke.” *European stroke journal* vol. 6,1 (2021): I-LXII. doi:10.1177/2396987321989865
Prabhakaran, Shyam et al. “2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association.” *Stroke* vol. 57,8 (2026): e316-e436. doi:10.1161/STR.0000000000000513

EVT – Large Core



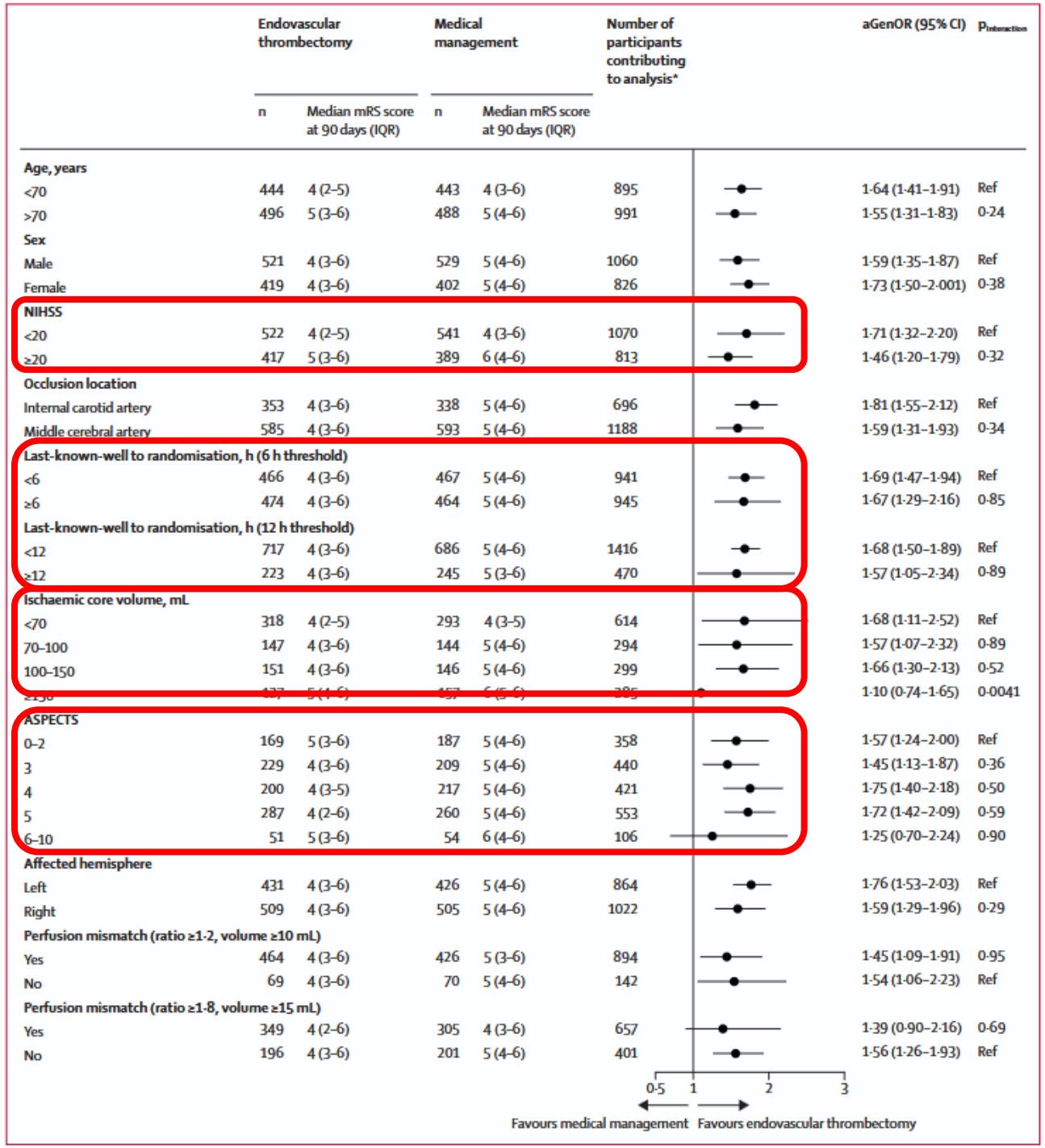


EVT – Large Core

- High NIHSS (severe stroke)
- Low ASPECTS (large lesion)
- Large core (adv. Imaging)
- Late arrival

Endovascular thrombectomy for patients with large-core ischaemic stroke presenting up to 24 h after onset (ATLAS): a systematic review and individual patient data meta-analysis with central imaging adjudication

Amrou Sarraj, Götz Thomalla*, Shinichi Yoshimura*, Xiaochuan Huo*, Vincent Costalat*, Osama O Zaidat*, Caroline Arquizan*, Hannah Johns, Vignan Yogendrakumar, Leonid Churilov, Deep Pujara, Clark W Sitton, David S Liebeskind, Manabu Inoue, Charles Majoie, Ludo Beenen, Mohammad Ammar Abdulrazzak, Aditya Chaturvedi, Sarthak Singh, Mark W Parsons, Angelique Denis, Nobuyuki Sakai, Thanh N Nguyen, Jean François Albucher, Sami Al Kasab, Ameer E Hassan, Michael Abraham, Ansar Rai, Hilde Henon, Dapeng Sun, Hiroshi Yamagami, Fabien Subtil, Susanne Bonekamp, Kazutaka Uchida, Guangxiong Yuan, Benjamin Gory, Wade Smith, Santiago Ortega-Gutierrez, Spiros Blackburn, Sunil A Sheth, Gaultier Marnat, Liping Liu, Manabu Shirakawa, Jens Fiehler, Märit Jensen, Seigo Shindo, Raul G Nogueira, Ramesh Grandhi, Pascal Jabbour, Muhammad Shazam Hussain, Diederik Dippel, Yilong Wang, Yukako Yazawa, Claus Z Simonsen, Yongjun Wang, Michael Chen, Michael D Hill, James C Grotta, Bertrand Laperguet†, Tudor G Jovin†, Albert J Yoo†, Martin Bendszus†, Bruce C V Campbell†, Takeshi Morimoto†, Zhongrong Miao†, for the ATLAS Investigators‡*

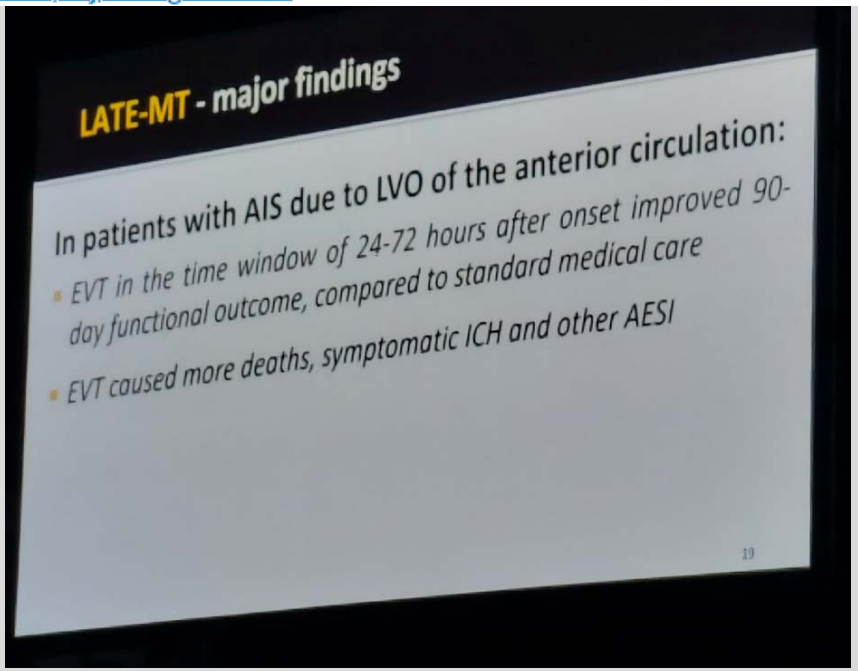


EVT – After (24) hours

ABSTRACT NUMBER: ESOC2026LB121 LB121 - LARGE ARTERY OCCLUSION TREATED IN EXTENDED TIME WITH MECHANICAL THROMBECTOMY (LATE-MT) : A MULTICENTRE, RANDOMISED CONTROLLED TRIAL

Pengfei Yang, Lili Song, Yongwei Zhang, Hongjian Shen, Craig Anderson, Jianmin Liu

European Stroke Journal, Volume 11, Issue Supplement_1, May 2026, Page i989, https://doi.org/10.1093/esj/aakag023.1858



Acute Treatment – New Insights



- Aggressive observation is a thing of the past
- Ischemic stroke is now a **treatable condition in the acute phase**
- Prevention of disability and death is possible w/ **timely intervention**
- **Indications** for acute treatment **are ever expanding**

  (beyond time windows, NOAC, large-core)
- The next frontier is **implementation**

Secondary Prevention

Secondary Prevention

Largely dependent on underlying etiology

TOAST classification

- Large-artery disease (intra/extra-cranial atherosclerosis >50% stenosis)
- Small-Vessel disease
- Cardioembolism
  - Atrial Fibrillation
  - PFO
- Other determined etiology (dissection, paraneoplastic, autoimmune etc.)
- Cryptogenic
  - ESUS – Embolic Stroke of Undetermined Source (despite adequate investigation)

Secondary Prevention

Largely dependent on underlying etiology

TOAST classification

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- Other determined etiology (dissection, paraneoplastic, autoimmune etc.)
- Cryptogenic
  - **ESUS** (embolic source not found)

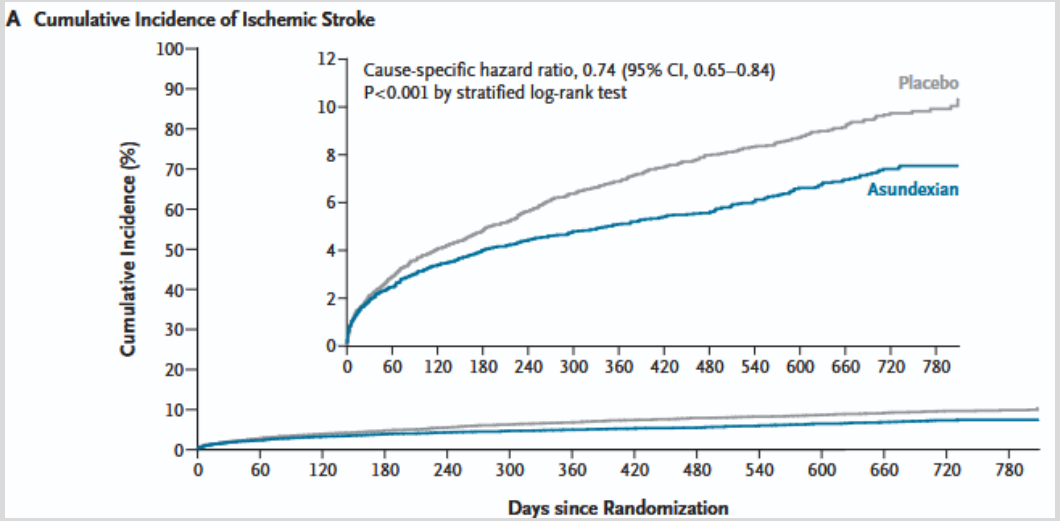
S. Prevention – Factor XIa inhibition

- Significant percentage of **stroke recurrence despite best medical treatment**
- New treatments are needed
- Observation: genetic **lack of XI factor leads to lower stroke-risk**
- Factor XIa inhibition may be an attractive drug target
- Primary coagulation cascade is relatively preserved

  -> no/low bleeding risk?

S. Prevention – Factor XIa inhibition

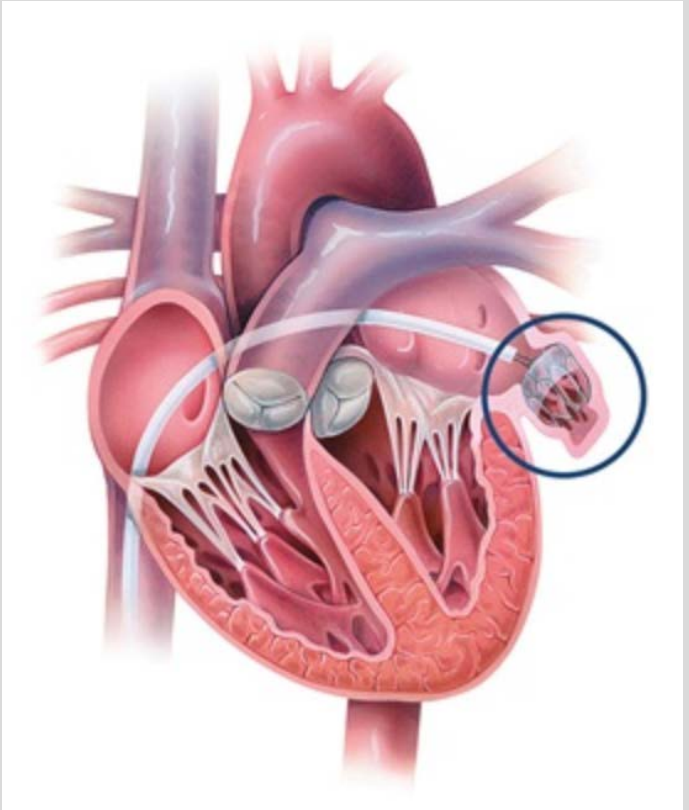
- Factor XIa inhibition **for AF – neutral** (OCEANIC-AF)
- OCEANIC-STROKE was positive w/o safety signal (asundexian)
- LIBREXIA closed recruitment, awaiting results (milvexian)



- Awaiting expedited ESO guidelines
- Developing injectable antibodies/ASO/siRNA for long-term inhibition

Sharma, Mukul et al. “Asundexian for Secondary Stroke Prevention.” *The New England journal of medicine* vol. 394,15 (2026): 1467-1479. doi:10.1056/NEJMoa2513880

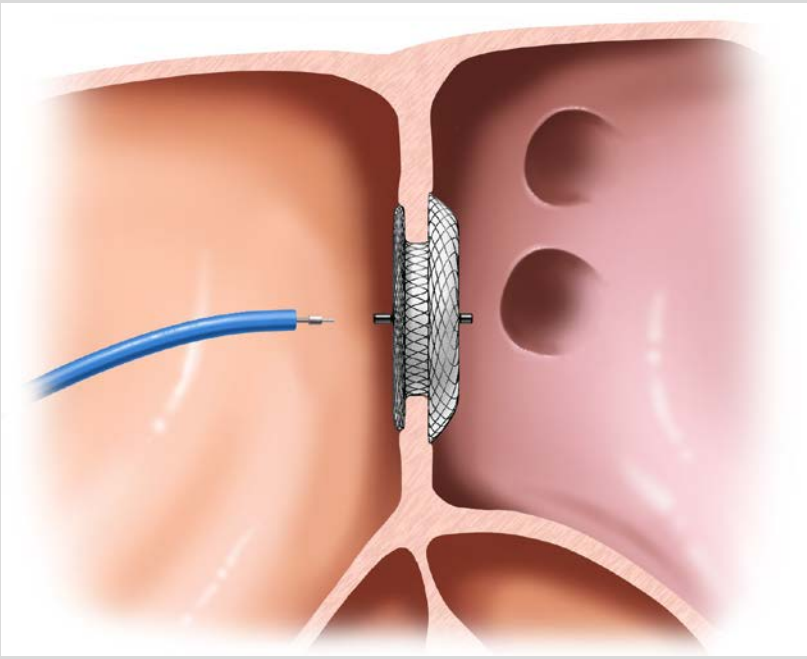
S. Prevention – LAAO



- 90% of thrombi in AF patients are found in the LAA
- **Breakthrough strokes increasingly more common**
- Left atrial appendage occlusion (LAA-O)
- Closure is established option for high bleeding risk patients
- Potential adjuvant therapy for AF patients with high thrombotic risk

https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/left-atrial-appendage-closure-procedures
Seiffge, David J et al. “Left Atrial Appendage Occlusion and Its Role in Stroke Prevention.” *Stroke* vol. 56,7 (2025): 1928-1937. doi:10.1161/STROKEAHA.124.043867

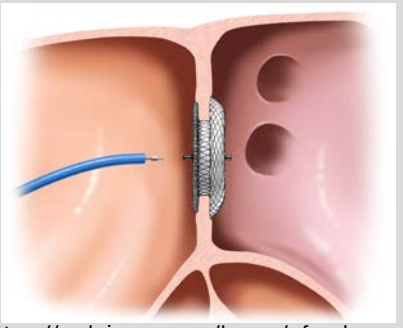
S. Prevention – PFO closure



https://rodnieoro.com/home/pfo-closure

- PFO is a recognized cause of ischemic stroke (paradoxical embolism, in-situ thrombosis
- Closure is established measure for young patients
- Prevents stroke recurrence over a long period of time
- Based on PASCAL classification
- **Exploring closure for older patients**

S. Prevention – PFO closure



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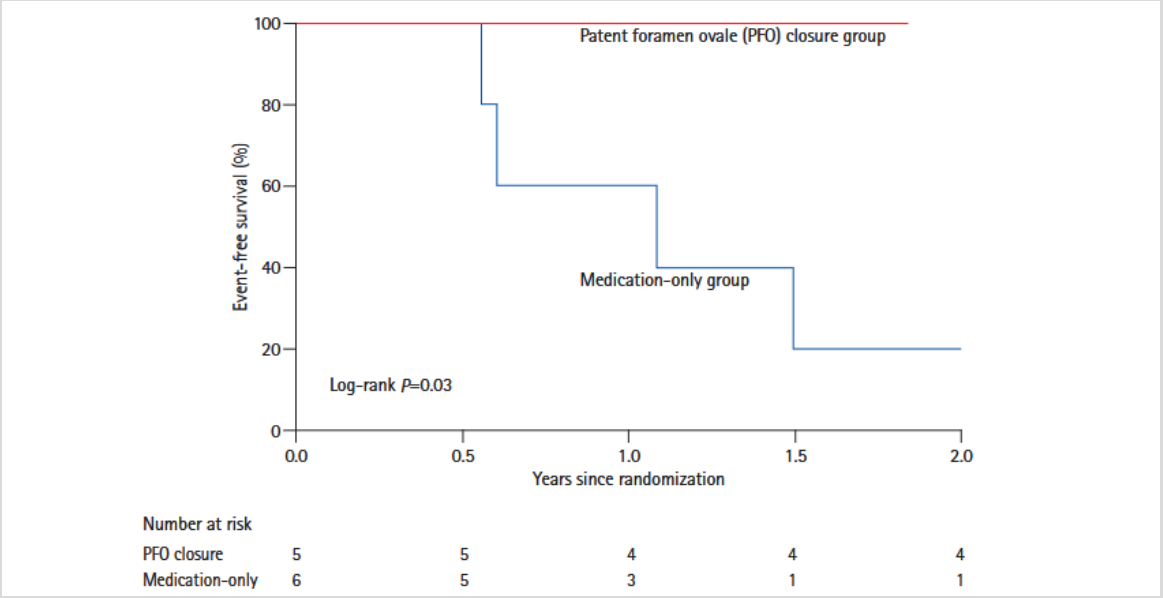
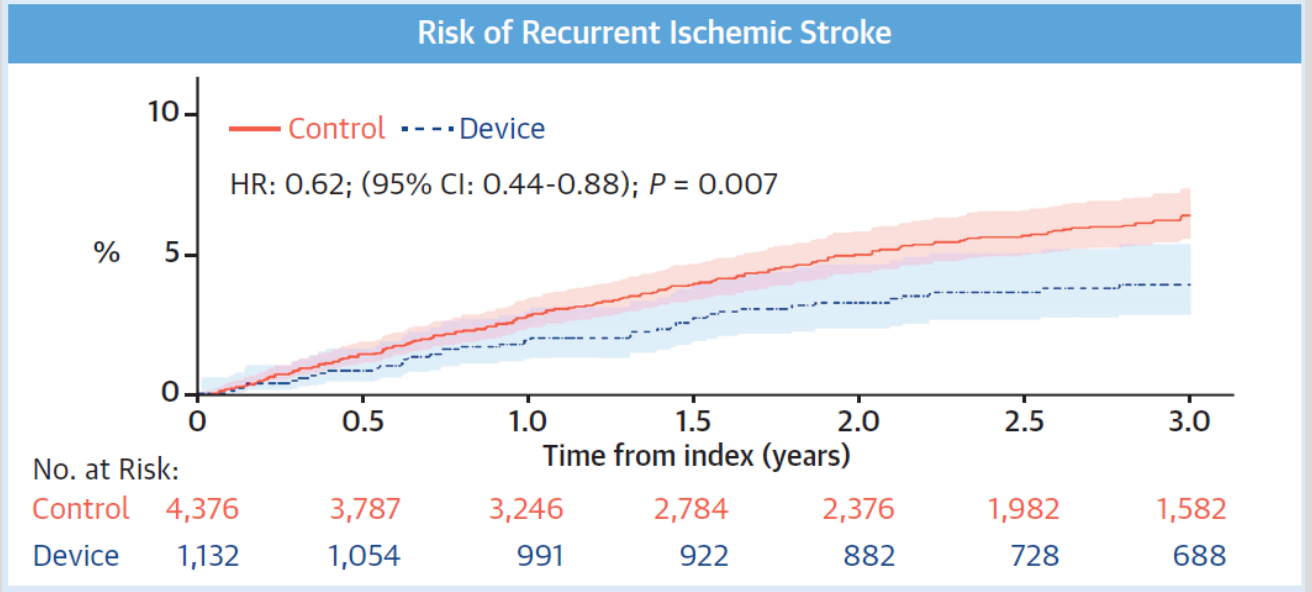


Post-hoc analysis of RCT



Large-scale retrospective study

Kwon H, Lee PH, Song JK, Kwon SU, Kang DW, Kim JS. Patent Foramen Ovale Closure in Old Stroke Patients: A Subgroup Analysis of the DEFENSE-PFO Trial. *J Stroke*. 2021;23(2):289-292. doi:10.5853/jos.2021.00647

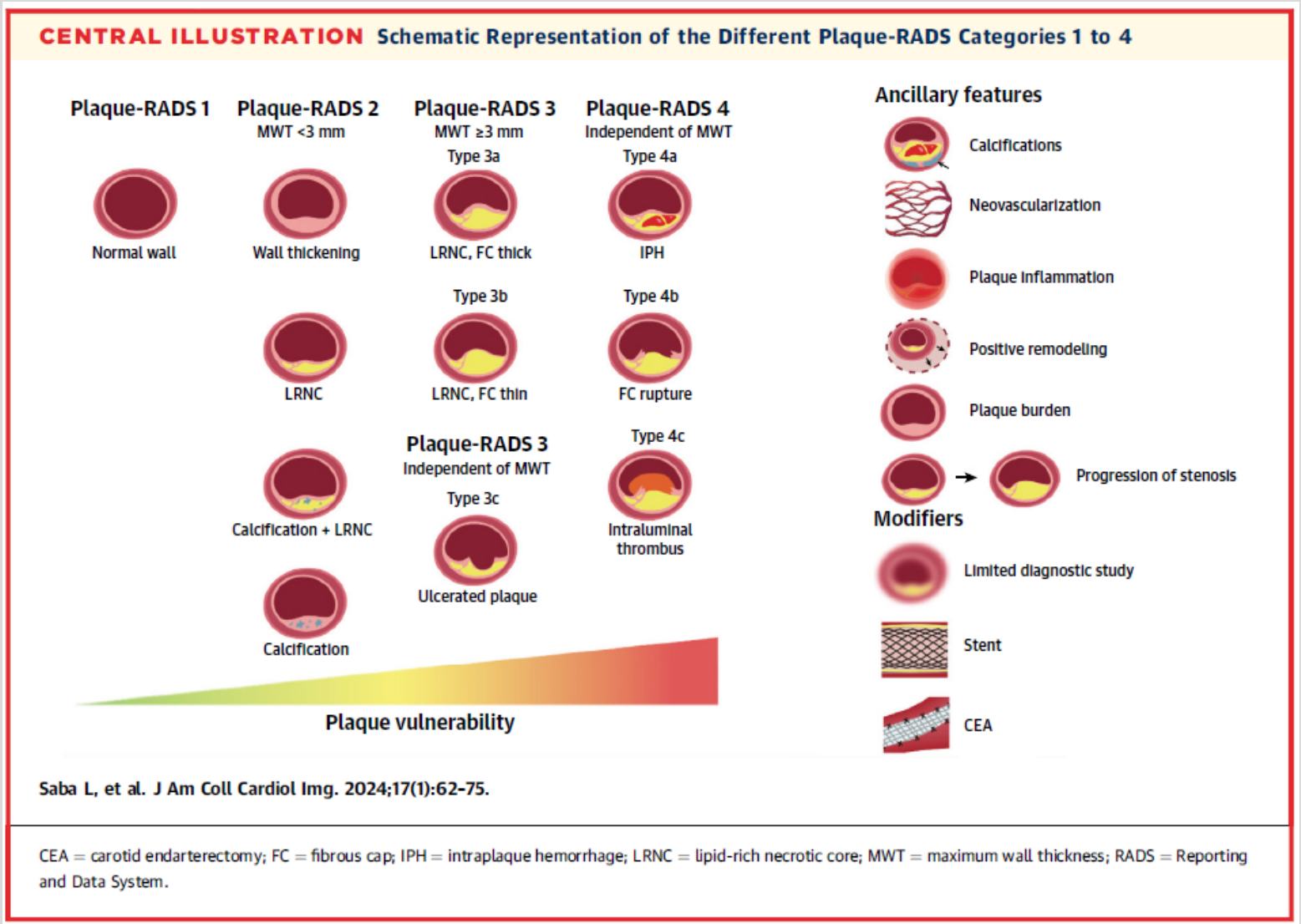
Satpathy, Ruby et al. "PFO Device Closure in Patients >60 Years of Age With Ischemic Stroke: Results From U.S. Medicare Beneficiaries." *JACC. Cardiovascular interventions* vol. 18,10 (2025): 1303-1314. doi:10.1016/j.jcin.2025.03.034

S. Prevention – Vulnerable plaques

- Atherotic plaques are more than stenosis grade!
- Low-grade stenoses may exhibit dangerous characteristics
  - Thin/ruptured fibrous cap
  - Ulcers
  - Intra-luminal thrombus
  - In-plaque hemorrhage
- A percentage of ESUS-classified stroke may be so explained
- Aggressive management of vulnerable plaques may be required

Saba, Luca et al. “Carotid Plaque-RADS: A Novel Stroke Risk Classification System.” *JACC. Cardiovascular imaging* vol. 17,1 (2024): 62-75. doi:10.1016/j.jcmg.2023.09.005

S. Prevention – Vulnerable plaques



Saba, Luca et al. “Carotid Plaque-RADS: A Novel Stroke Risk Classification System.” *JACC. Cardiovascular imaging* vol. 17,1 (2024): 62-75. doi:10.1016/j.jcmg.2023.09.005

S. Prevention – Modifiable RF Management

- Important for all stroke types
- BP management
  - Low-dose, multiple categories, poly-pill
  - Lower targets (130/80)
- Lipid management –
  - Lower targets (even <40mg/dl for very high risk patients
  - Lpa to better characterize patient risk
  - PCSK9i
- Diabetes
  - GLP1a revolution - better profile for AIS prevention

Secondary Prevention – New insights

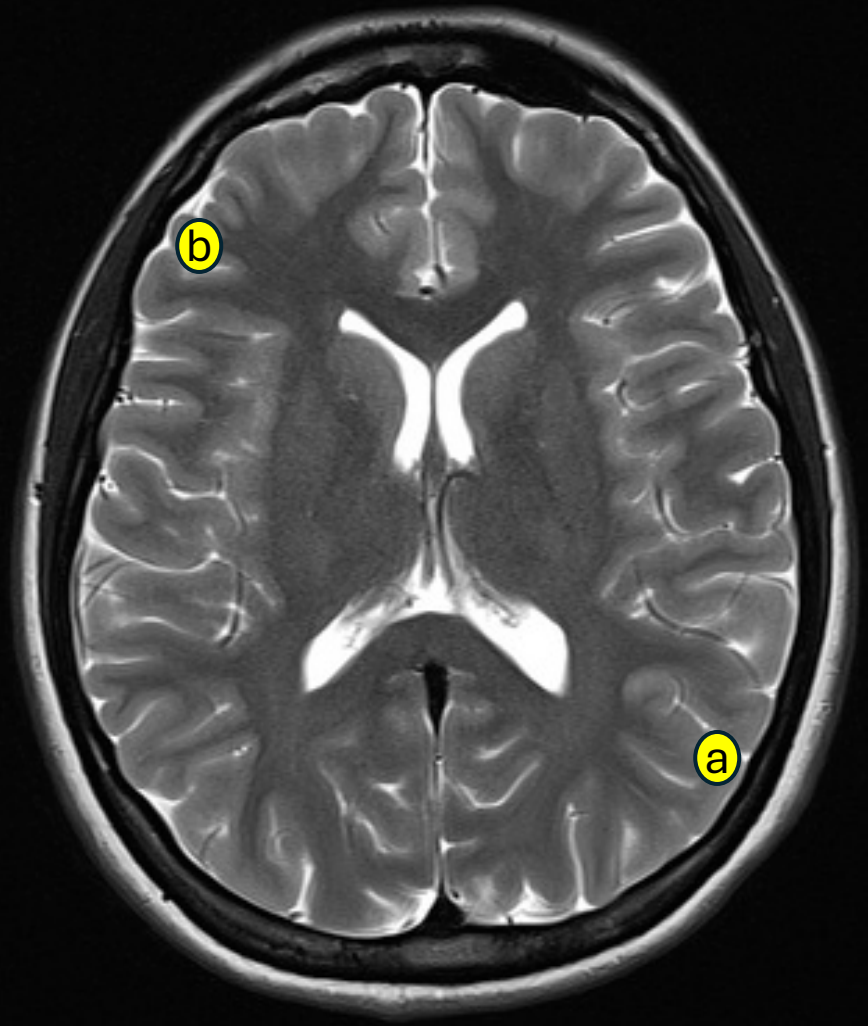


- **Significant residual stroke risk** despite best medical treatment
- **New antithrombotic treatments** provide better prevention
- **New interventions** reduce embolic risk of cardiac disease
- Recognizing **previously hidden/underestimated** embolic **causes**
- Modifiable **risk factor control is becoming more aggressive**

Covert Brain Infarcts (CBIs) or

“Silent Stroke”

Covert Infarcts or “Silent Strokes”



= imaging-proven brain infarcts with **no clinical episode**

a: “eloquent” area -> more likely overt

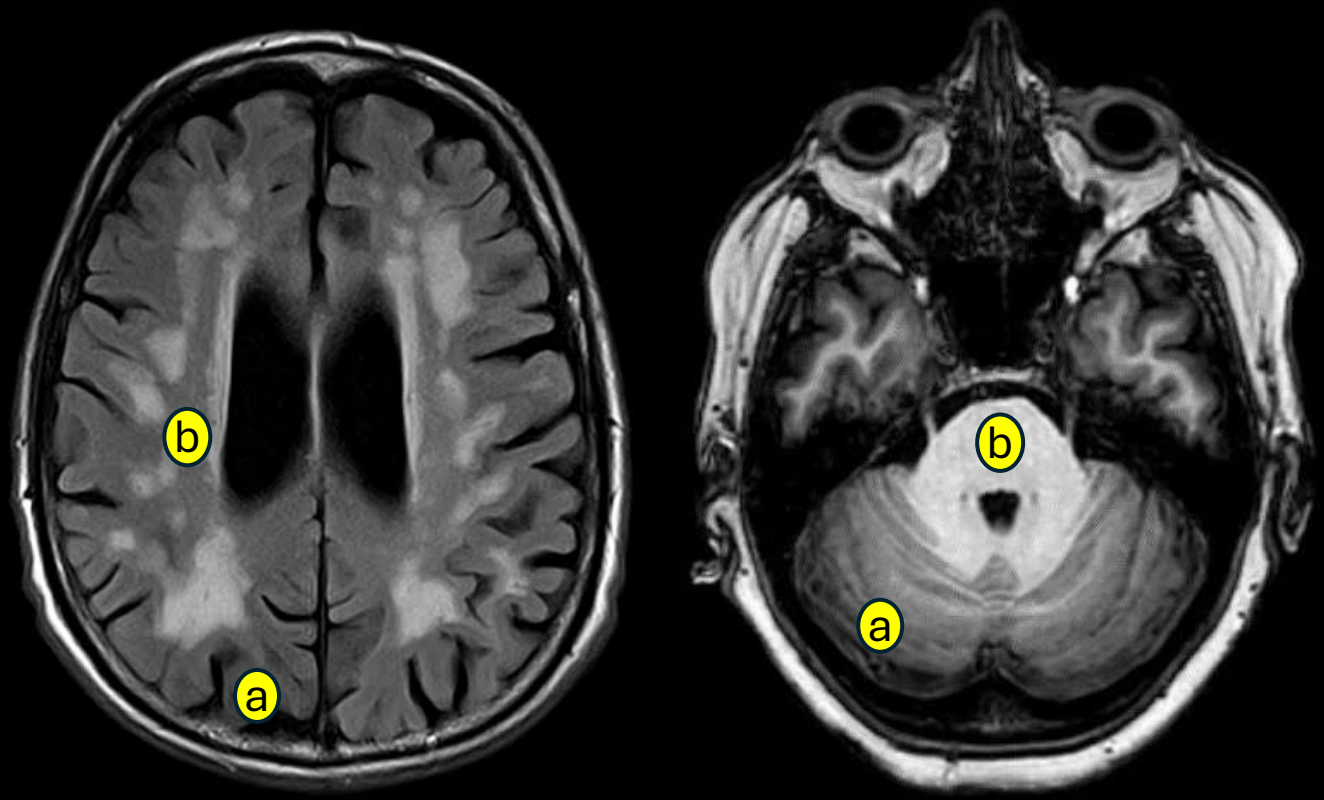
b: “non-eloquent” area -> more likely covert

Covert Brain Infarctions (CBIs)

- Use of MRI scanners globally increasing
- Incidental findings in up to 52% of brain scans
- CBIs are among the most common incidental findings
- Prevalence of at least of 5% in >50yo, up to 30% in >70yo
- Definition difficulties, now included in ICD11 as cerebrovascular events

Wangaryattawanich P, Rutman AM, Petcharunpaisan S, Mossa-Basha M. Incidental findings on brain magnetic resonance imaging (MRI) in adults: a review of imaging spectrum, clinical significance, and management. *Br J Radiol*. 2023;96(1142):20220108. doi:10.1259/bjr.20220108
de Vautibault, Alice et al. “Cardiovascular risk factor control in patients with covert brain infarcts in the prospective SILENT cohort study.” *European stroke journal* vol. 11,1 (2026): aakaf006. doi:10.1093/esj/aakaf006
Giannakakis, Michail Panagiotis et al. “Covert brain infarctions: an illustrative teaching series.” *BMJ case reports* vol. 18,12 e266326. 3 Dec. 2025, doi:10.1136/bcr-2025-266326

Covert Infarcts or “Silent Strokes”

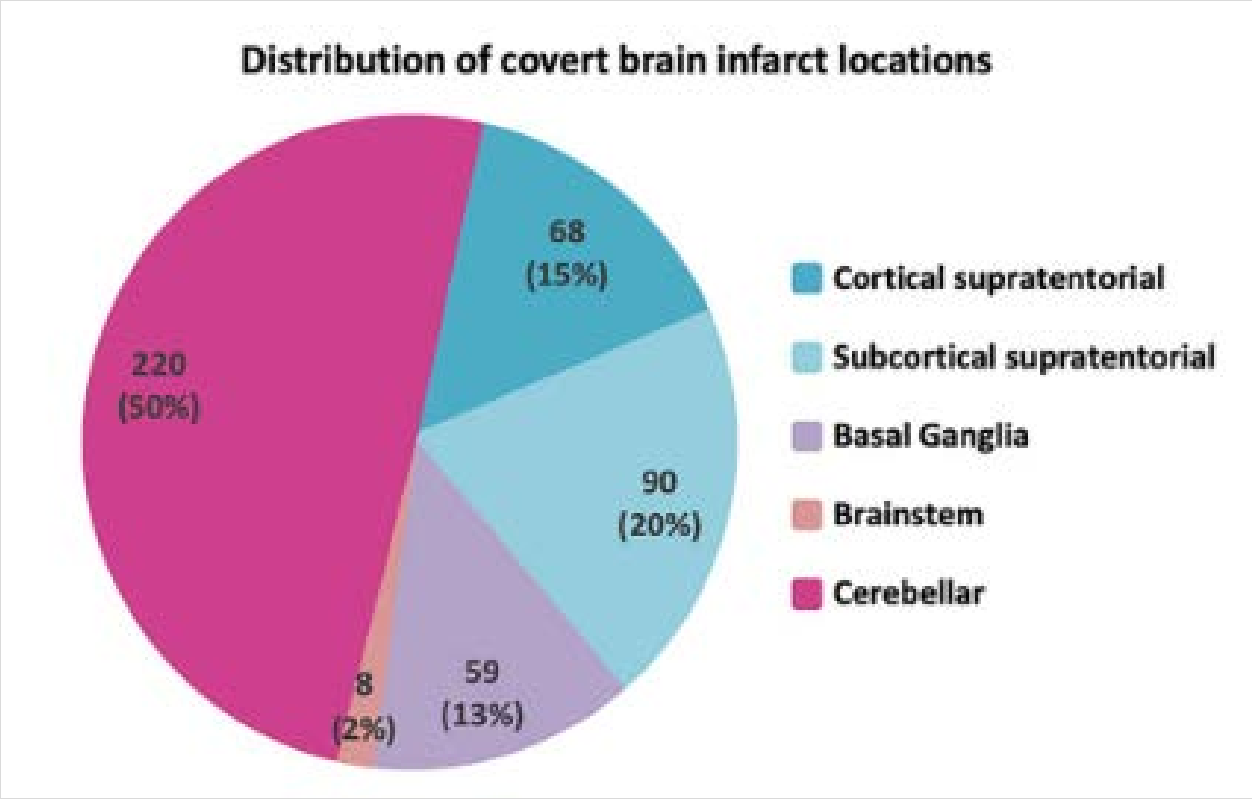


Localization is important!

a: cortical
(likely embolic)

b: subcortical
(likely small-vessel disease)

Covert Brain Infarctions (CBIs)



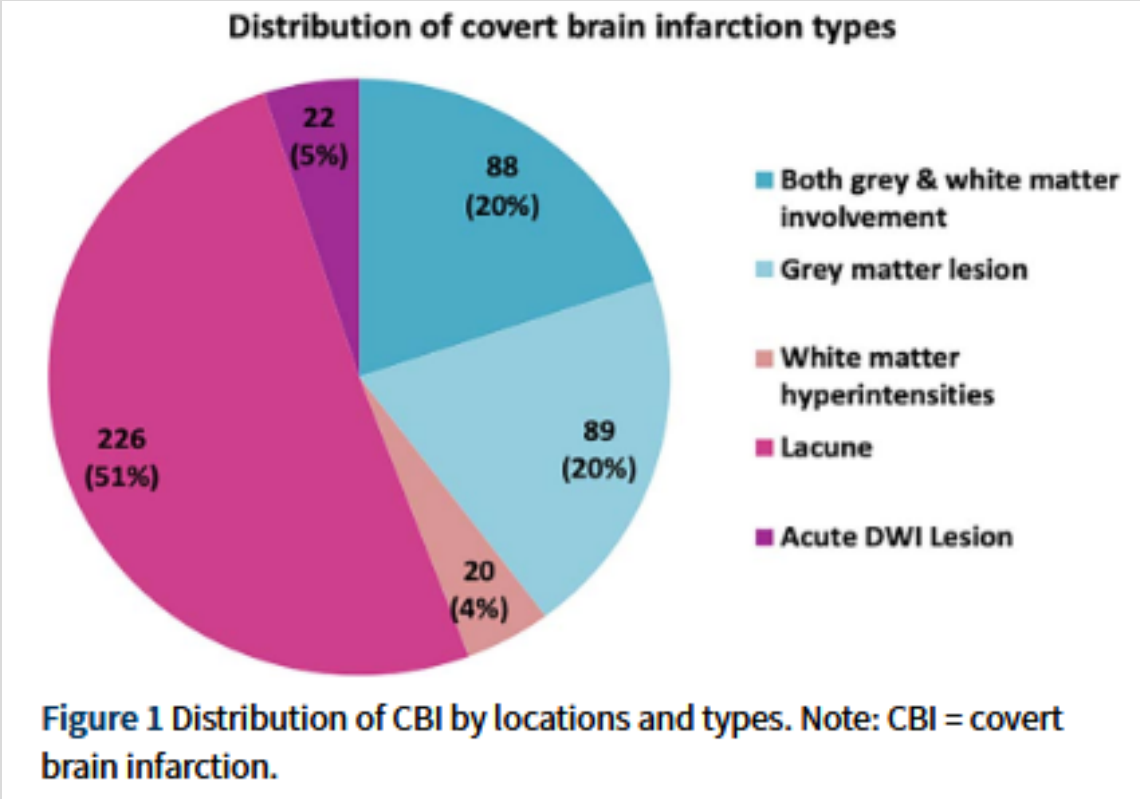


Figure 1 Distribution of CBI by locations and types. Note: CBI = covert brain infarction.

de Vautibault, Alice et al. “Cardiovascular risk factor control in patients with covert brain infarcts in the prospective SILENT cohort study.” *European stroke journal* vol. 11,1 (2026): aakaf006. doi:10.1093/esj/aakaf006

Covert Brain Infarcts (CBIs)

- Likely increase cognitive burden over time
- Increased probability of finding modifiable risk factors

Management?

- Re-take extensive history (maybe not covert?)
- Work-up as if overt (AF? Carotid disease? PFO???)
- Risk factor management
- Secondary prophylaxis?

de Vautibault, Alice et al. “Cardiovascular risk factor control in patients with covert brain infarcts in the prospective SILENT cohort study.” *European stroke journal* vol. 11,1 (2026): aakaf006. doi:10.1093/esj/aakaf006
Giannakakis, Michail Panagiotis et al. “Covert brain infarctions: an illustrative teaching series.” *BMJ case reports* vol. 18,12 e266326. 3 Dec. 2025, doi:10.1136/bcr-2025-266326

Take-home ~~messages~~ new insights



- **Field of stroke** medicine is past the dark ages and **into enlightenment**
- Revolutionary **acute treatments now exist, indications broadening**
- Implementation and ensuring **healthcare equity is the next frontier**
- We are getting better in **recognizing underlying etiologies**
- **Secondary prevention** in all etiology classifications **is ever-evolving**
- **Pre-symptomatic management may be possible** for some

Thank you for your attention! Questions?

