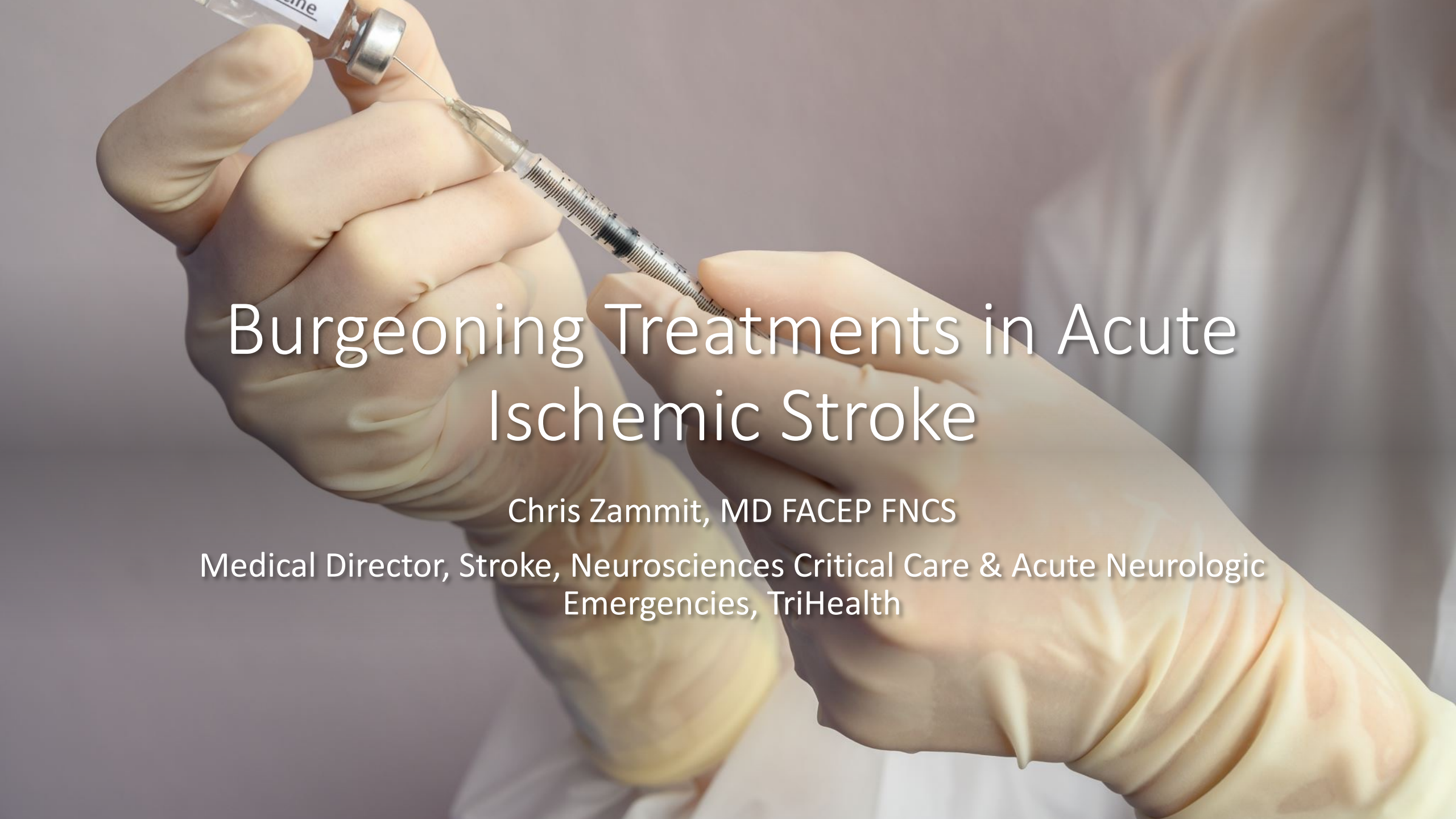
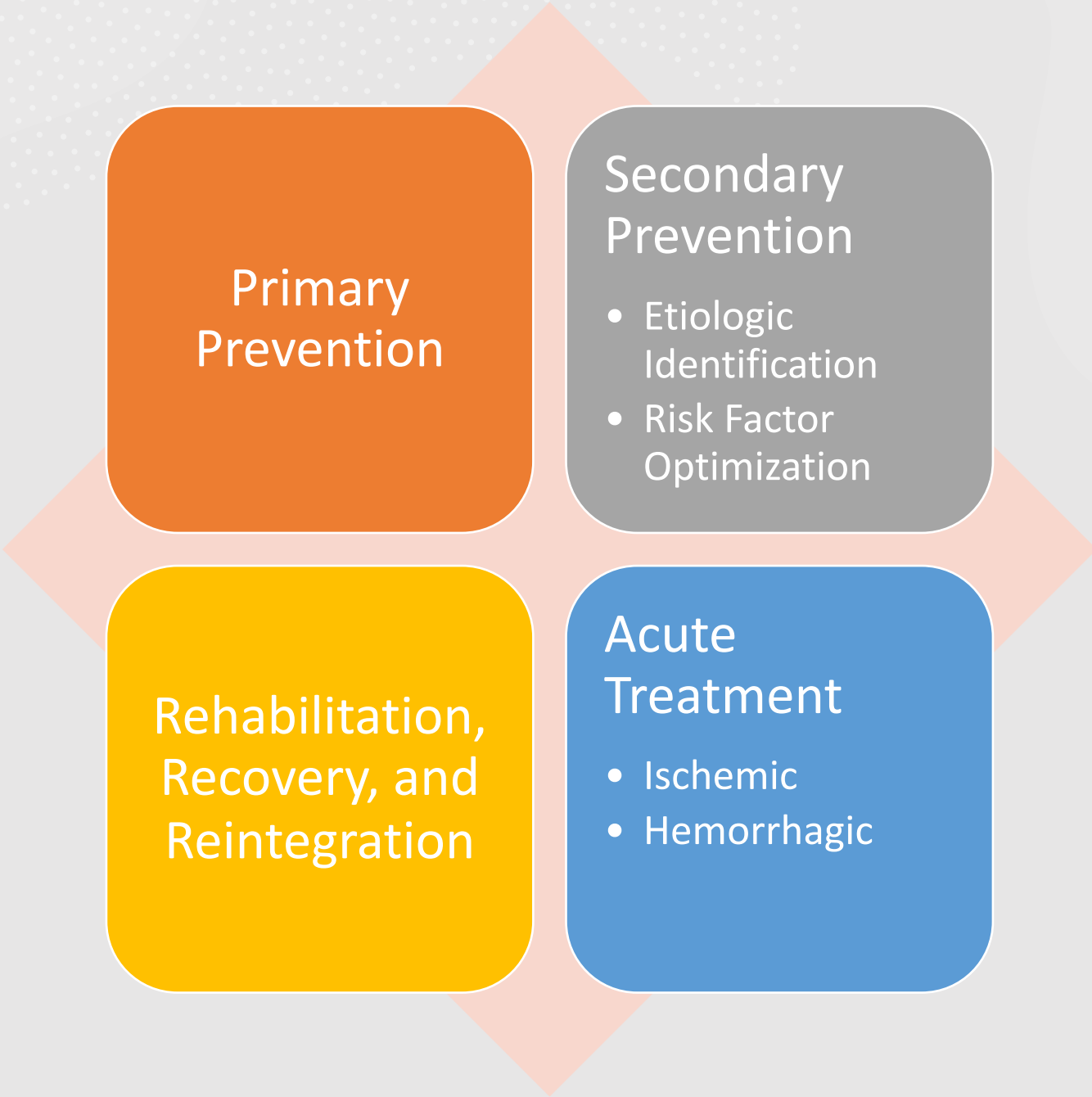


Burgeoning Treatments in Acute Ischemic Stroke

Chris Zammit, MD FACEP FNCS

Medical Director, Stroke, Neurosciences Critical Care & Acute Neurologic Emergencies, TriHealth

Domains of Stroke Care



Acute Ischemic Stroke Treatments Over the Years

Treatment	Published
Alteplase 0 - 3 hours from LKWT	1995
Alteplase 3 - 4.5 hours from LKWT	2011
Thrombectomy for Anterior Circulation Large Vessel Occlusion with Small Core Infarction, NIHSS >/= 6, and 0-6 hours from LKWT	2015
Thrombectomy for Anterior Circulation Large Vessel Occlusion with small core infarction, NIHSS >/= 6, 6-24 Hours from LKWT	2018
Alteplase > 4.5 hours from LKWT, < 4.5 hours from Symptom Discovery by MRI DWI:T2 FLAIR Mismatch	2018
Alteplase 4.5 - 9 hours from LKWT by automated quantitative CT Perfusion	2019

Recent Advances

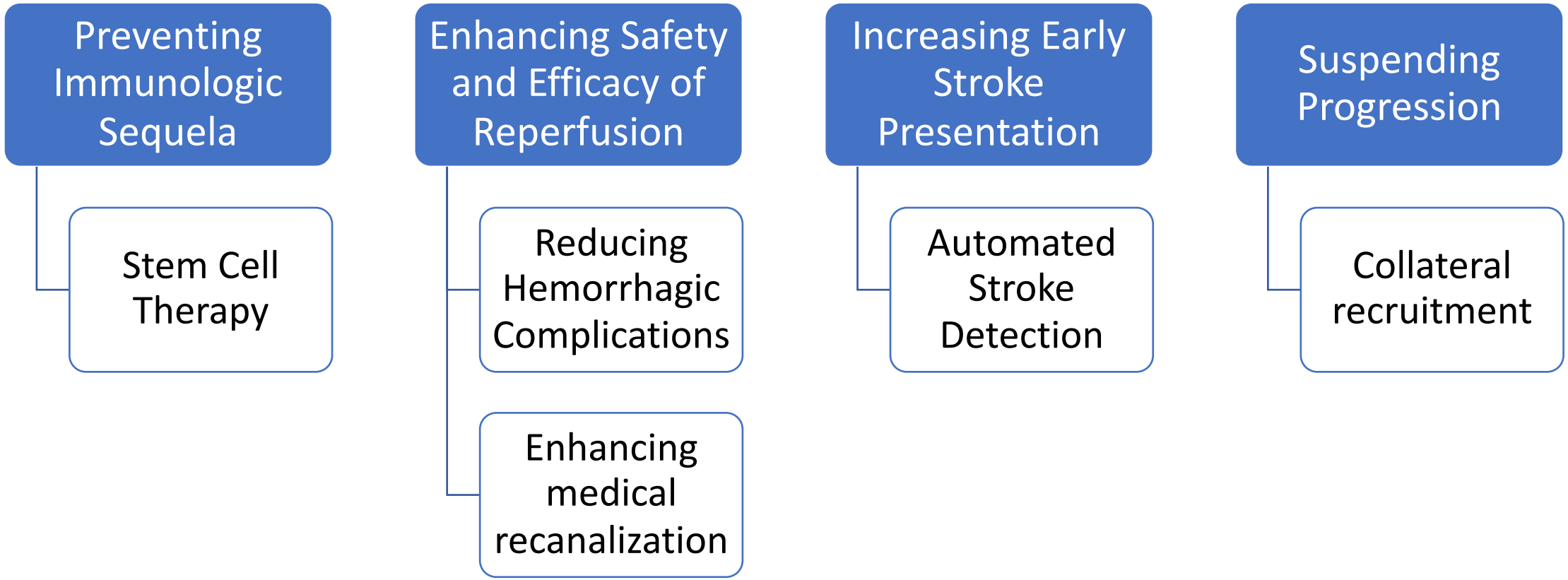
Thrombectomy for Anterior Circulation Large Vessel Occlusion with large core infarction

Thrombectomy for Basilar Artery Occlusion (BAO)

Tenecteplase non-inferior to Alteplase

Tenecteplase superior to Alteplase in Large Vessel Occlusion

Promising Treatments On the Horizon



Immunologic Sequela of Stroke

- Stroke-associated immunosuppression
- Potential induced autoimmunity to CSF antigens
- Immunologic cascade in response to cerebral ischemia
- Immune system’s role in ischemic preconditioning
- Splenic activation with is obviated with reduced infarct size in animal models

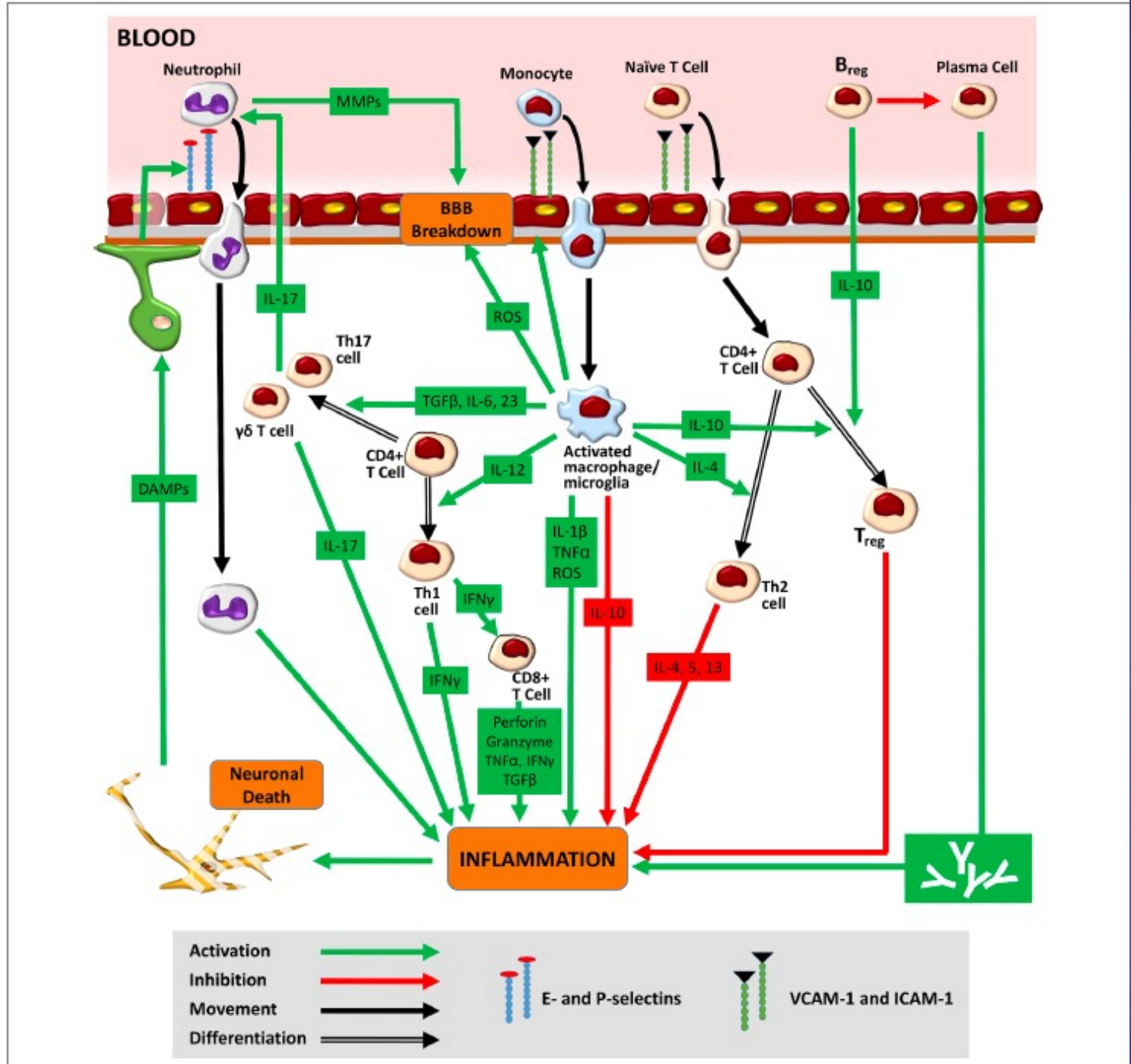
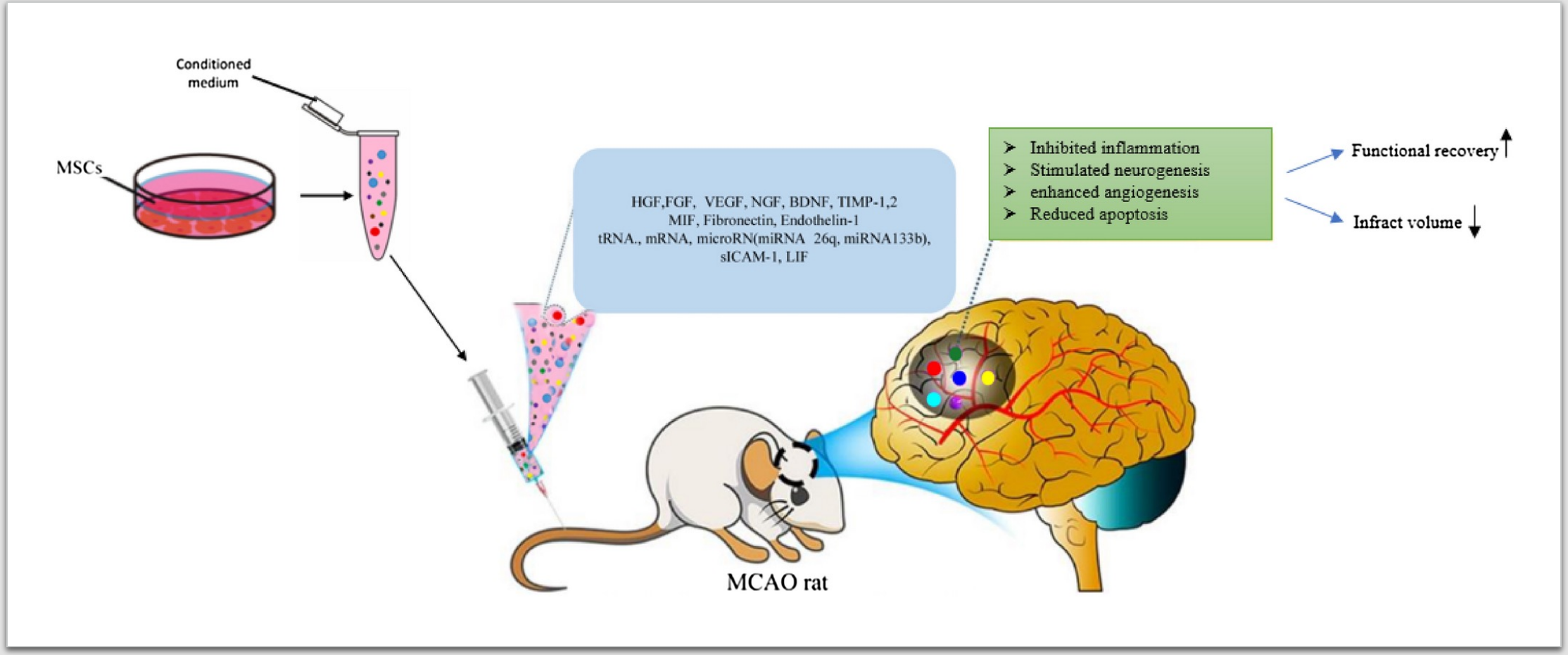


FIGURE 2 | Immune response to stroke. Hypoperfusion causes an immediate deprivation of glucose and oxygen to the brain, leading to widespread neuronal cell

Malone K, Amu S, Moore AC, Waeber C. Immunomodulatory Therapeutic Strategies in Stroke. Front Pharmacol. 2019 Jun 20;10:630. doi: 10.3389/fphar.2019.00630. eCollection 2019.

Effects of conditioned medium derived from Mesenchymal Stem Cells on stroke recovery



Behzadifard M, Aboutaleb N, Dolatshahi M, et al. Neuroprotective Effects of Conditioned Medium of Mesenchymal Stem Cells (MSC-CM) as a Therapy for Ischemic Stroke Recovery: A Systematic Review. Neurochem Res. 2023 May;48(5):1280-1292. doi: 10.1007/s11064-022-03848-x. Epub 2022 Dec 30.

Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial

David C Hess, Lawrence R Wechsler, Wayne M Clark, Sean I Savitz, Gary A Ford, David Chiu, Dileep R Yavagal, Ken Uchino, David S Liebeskind, Alexander P Auchus, Souvik Sen, Cathy A Sila, Jeffrey D Vest, Robert W Mays

	Day 90			1 year		
	Multipotent adult progenitor cell (n=31)	Placebo (n=61)	p value	Multipotent adult progenitor cell (n=31)	Placebo (n=61)	p value
Efficacy						
mRS ≤2 (scale, 0–6)	14 (45%)	22 (36%)	0·38	16 (52%)	27 (44%)	0·50
Improvement in NIHSS of ≥75%	15 (48%)	23 (38%)	0·33	16 (52%)	28 (46%)	0·61
Barthel index ≥95 (scale 1–100)	18 (58%)	27 (44%)	0·18	22 (71%)	29 (48%)	0·0252
NIHSS ≤1 or ≥11 point improvement	14 (45%)	18 (30%)	0·14	..	..	..
mRS shift	..	..	0·13	..	..	0·07
mRS ≤1 (scale 0–6)	5 (16%)	7 (12%)	0·53	10 (32%)	8 (13%)	0·0281
NIHSS ≤1	10 (32%)	10 (16%)	0·08	11 (36%)	12 (20%)	0·09
Excellent outcome*	5 (16%)	4 (7%)	0·14	9 (29%)	5 (8%)	0·0081
Safety						
Life-threatening adverse events or death	..	..	..	3 (10%)	15 (25%)	0·09
Secondary infections	..	..	..	5 (16%)	29 (48%)	0·0033

Table 4: **Post-hoc outcomes for early treatment (<36 h) for groups 2 and 3 combined**

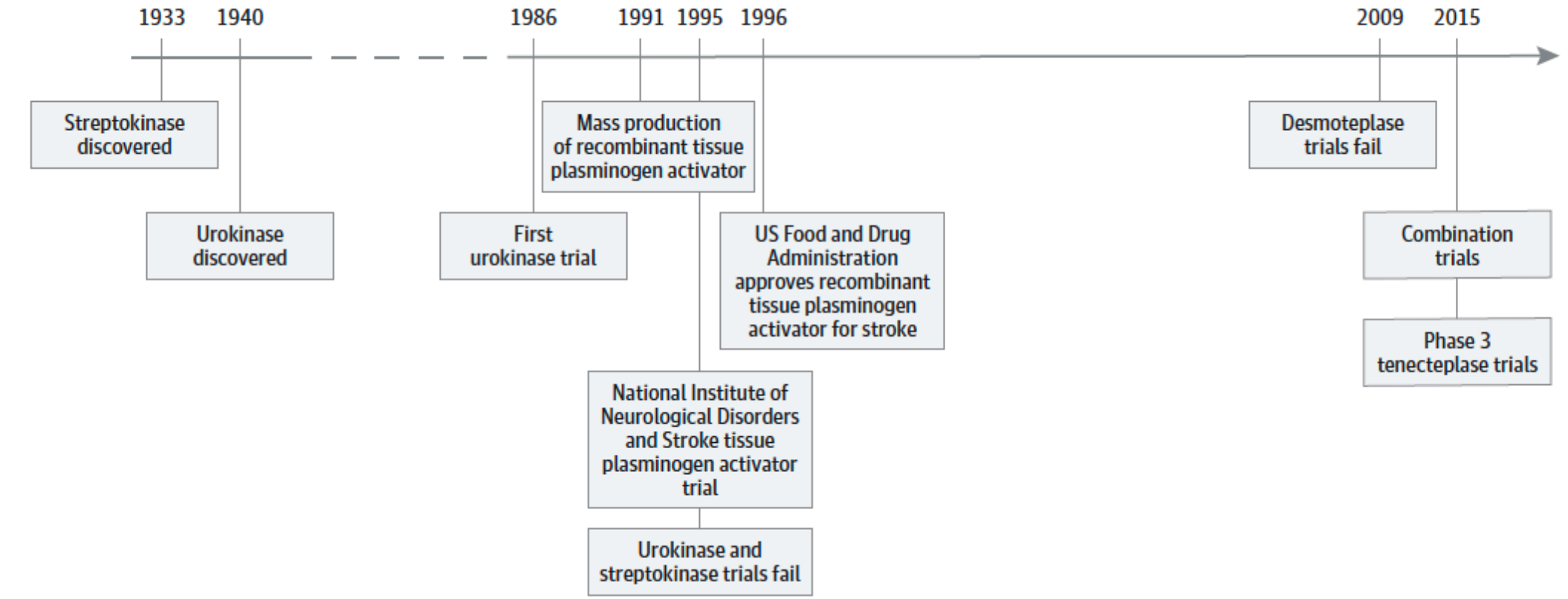
Lancet Neurol 2017; 16: 360–68

Enhancing Efficacy of Medical Recanalization

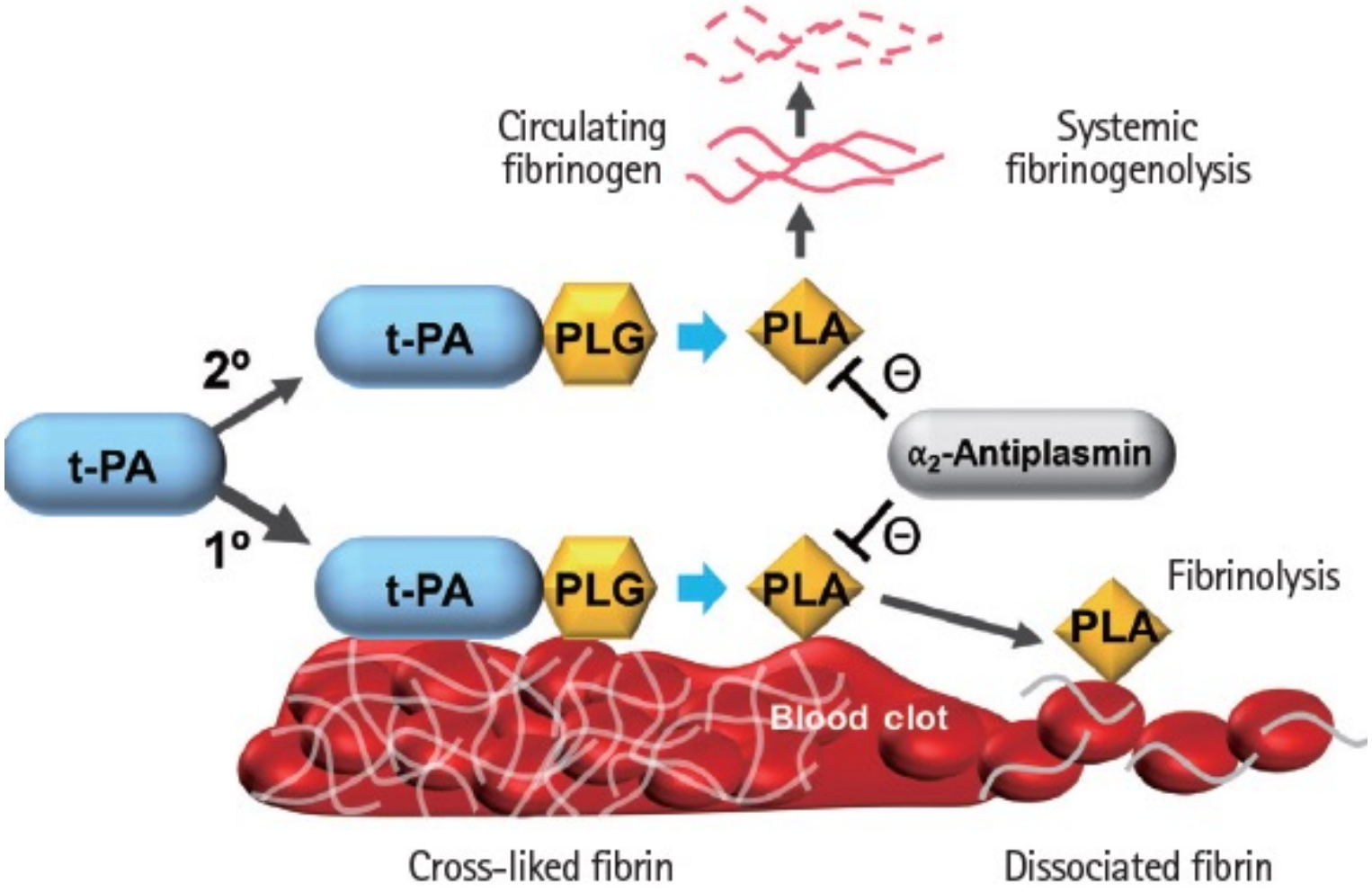
- Novel Thrombolytics
- Mitigating Hemorrhagic Complications
- Thrombolytic adjuncts

History of Thrombolysis

Figure 1. History of Thrombolysis

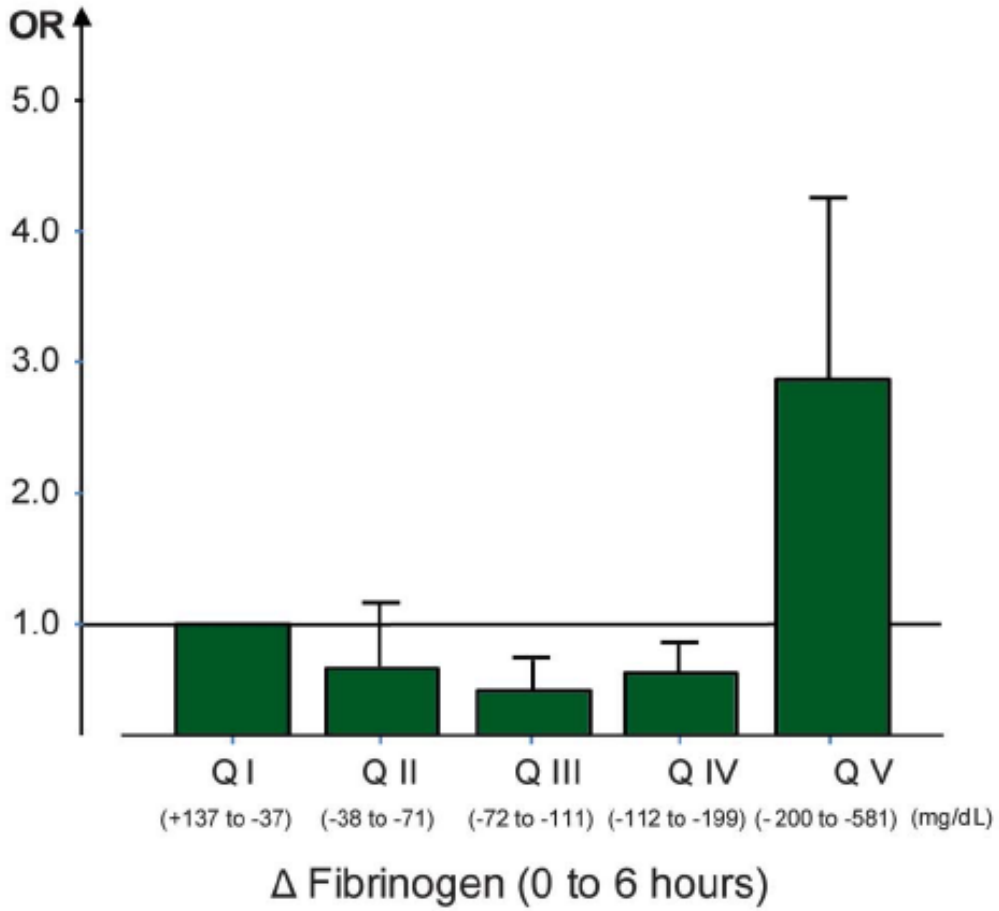


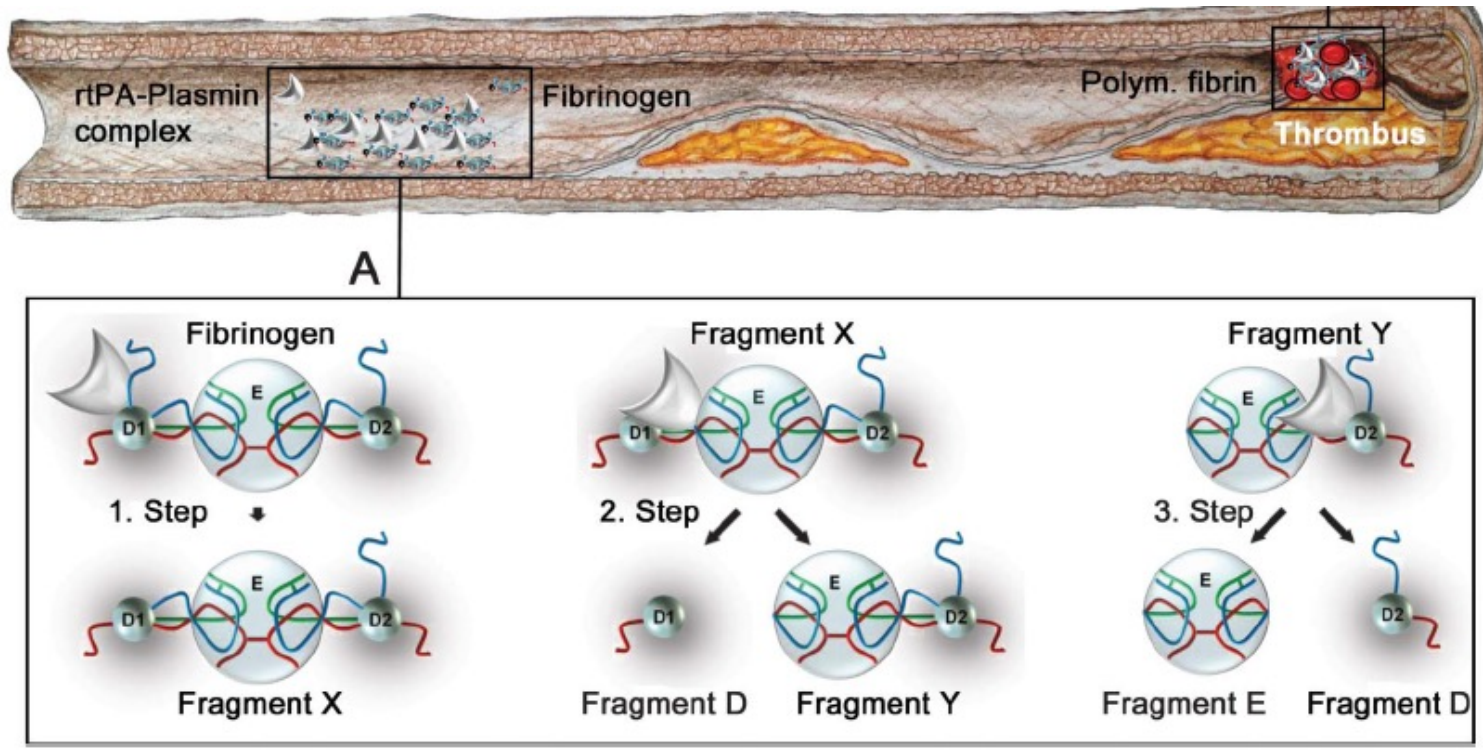
Mechanism of Thrombolysis



Fibrinogen degradation coagulopathy and bleeding complications after stroke thrombolysis

Association between Δfibrinogen$_{0\text{-}6\ hours}$ and bleeding complications across quintile groups



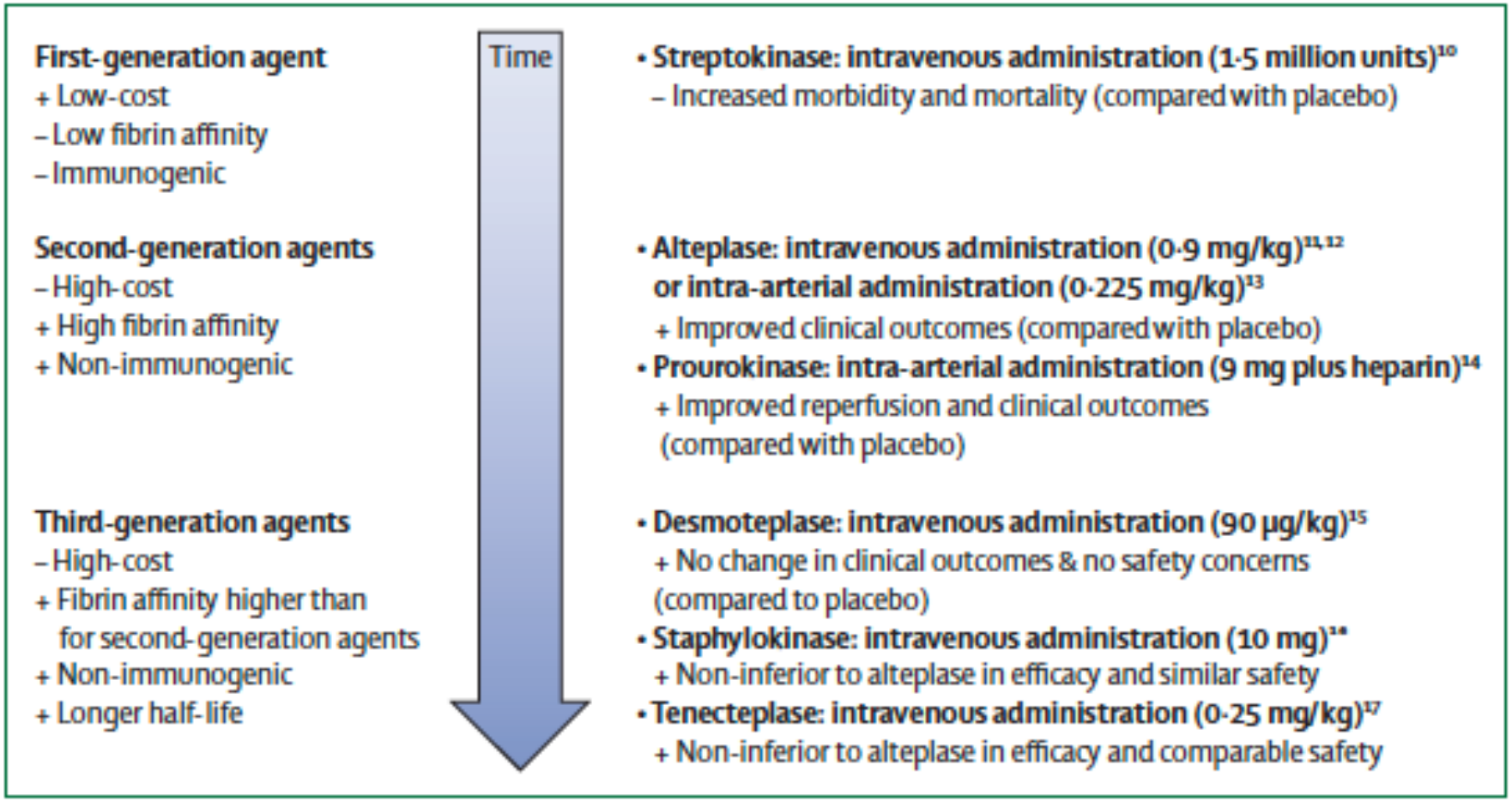


Thrombolytic Characteristics

Table 1. Properties of Thrombolytic Agents

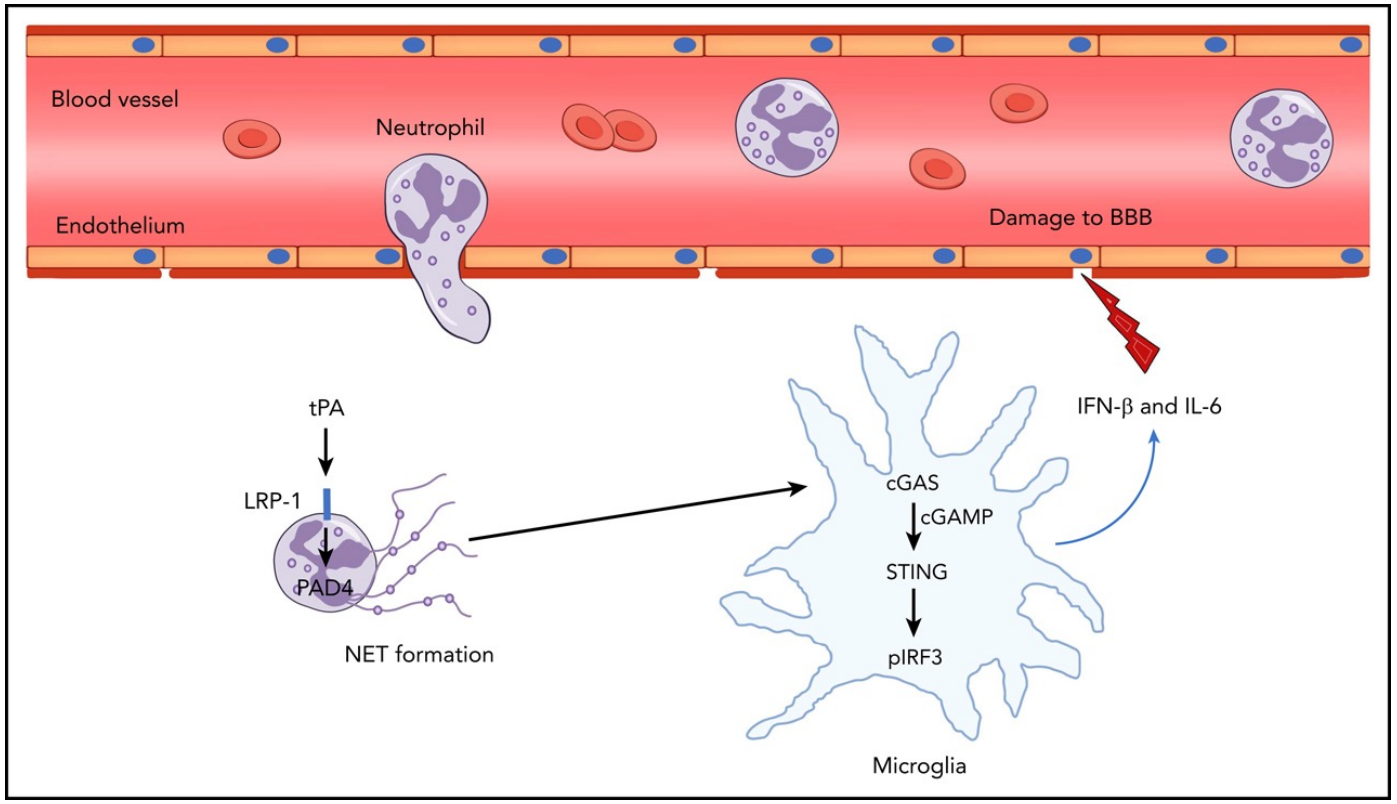
Agent	Fibrin Selectivity	PAI-1 Inhibition	Half-life, min	BBB Opening	HDL-C Level Lowering
Alteplase	Moderate	High	4-8	Moderate	Moderate
Streptokinase	Negligible	Negligible	6	Unknown	Unknown
Urokinase	Negligible	High	15	Unknown	Unknown
Desmoteplase	Very high	Unknown	138	Negligible	Unknown
Tenecteplase	High	Low	11-20	Unknown	Low

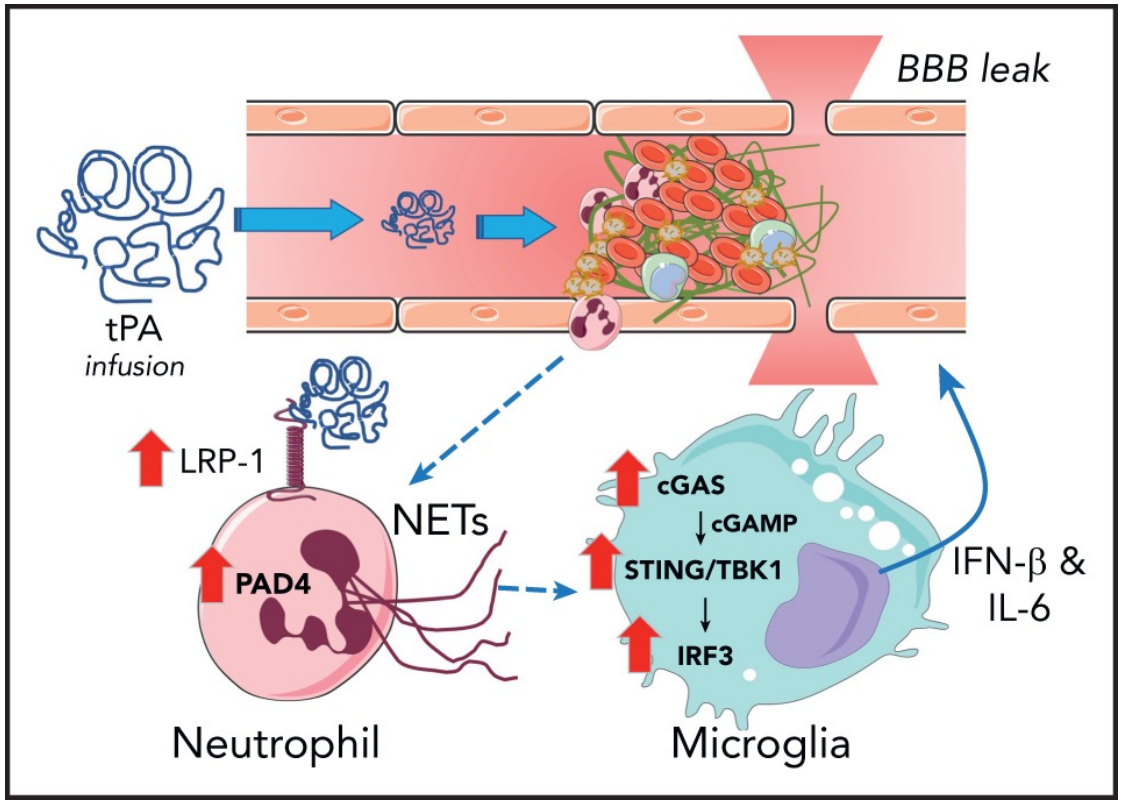
Evolution of Thrombolytic agents for the treatment of acute ischemic stroke



Tsivgoulis G, Katsanos A, Sandset E, et al. Thrombolysis for acute ischaemic stroke: current status and future perspectives. *Lancet Neurol*. 2023 May;22(5):418-429. doi: 10.1016/S1474-4422(22)00519-1. Epub 2023 Mar 9.

Neutrophil extracellular traps (NETs) promote tPA-induced ICH via cGAS





"DNase I treatment (to degrade NETs) or genetically imposed PAD4 deficiency (to prevent NET formation) mitigated reactive changes in the brain after ischemic challenge. Notably, both interventions significantly suppressed tPA driven BBB permeability, mitigated loss of gap junction proteins (ie, zonula occludens-1 [ZO-1], occludin, claudin-5, and vascular endothelial-cadherin [VEcadherin]), reduced ICH, and improved neurologic deficits (as shown by behavioral testing)."

Wang R, Zhu Y, Liu Z, et al. Neutrophil extracellular traps promote tPA-induced brain hemorrhage via cGAS in mice with stroke. *Blood*. 2021 Jul 8;138(1):91-103. doi: 10.1182/blood.2020008913.

Flick M. Mechanism of ICH with tPA thrombolysis. *Blood*. 2021 Jul 8;138(1):8-9. doi: 10.1182/blood.2021011268.

A first-in-human study of the anti-inflammatory profibrinolytic TMS-007, an SMTP family triprenyl phenol

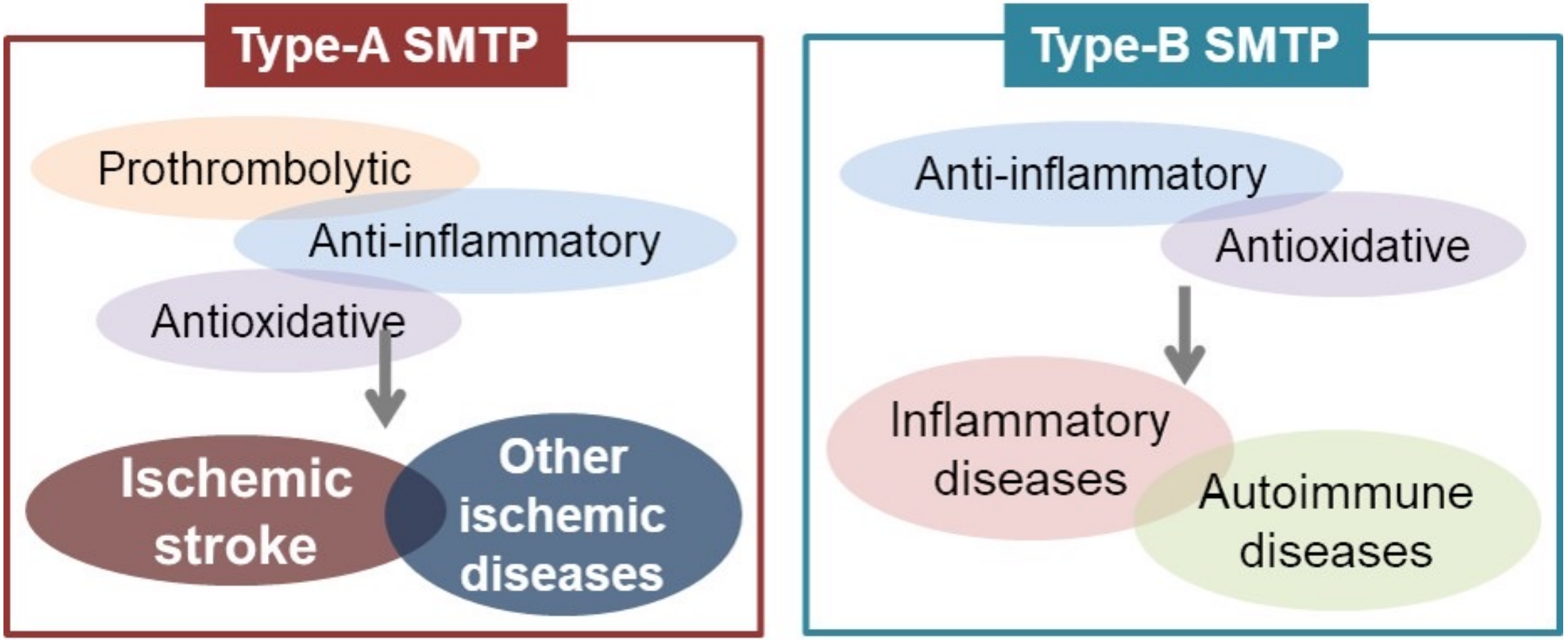


Figure 2. Pharmacological activities of SMTP

SMTP = Stachybotrys microspora triprenyl phenols

https://www.tms-japan.co.jp/en/business/r-and-d/technology.html

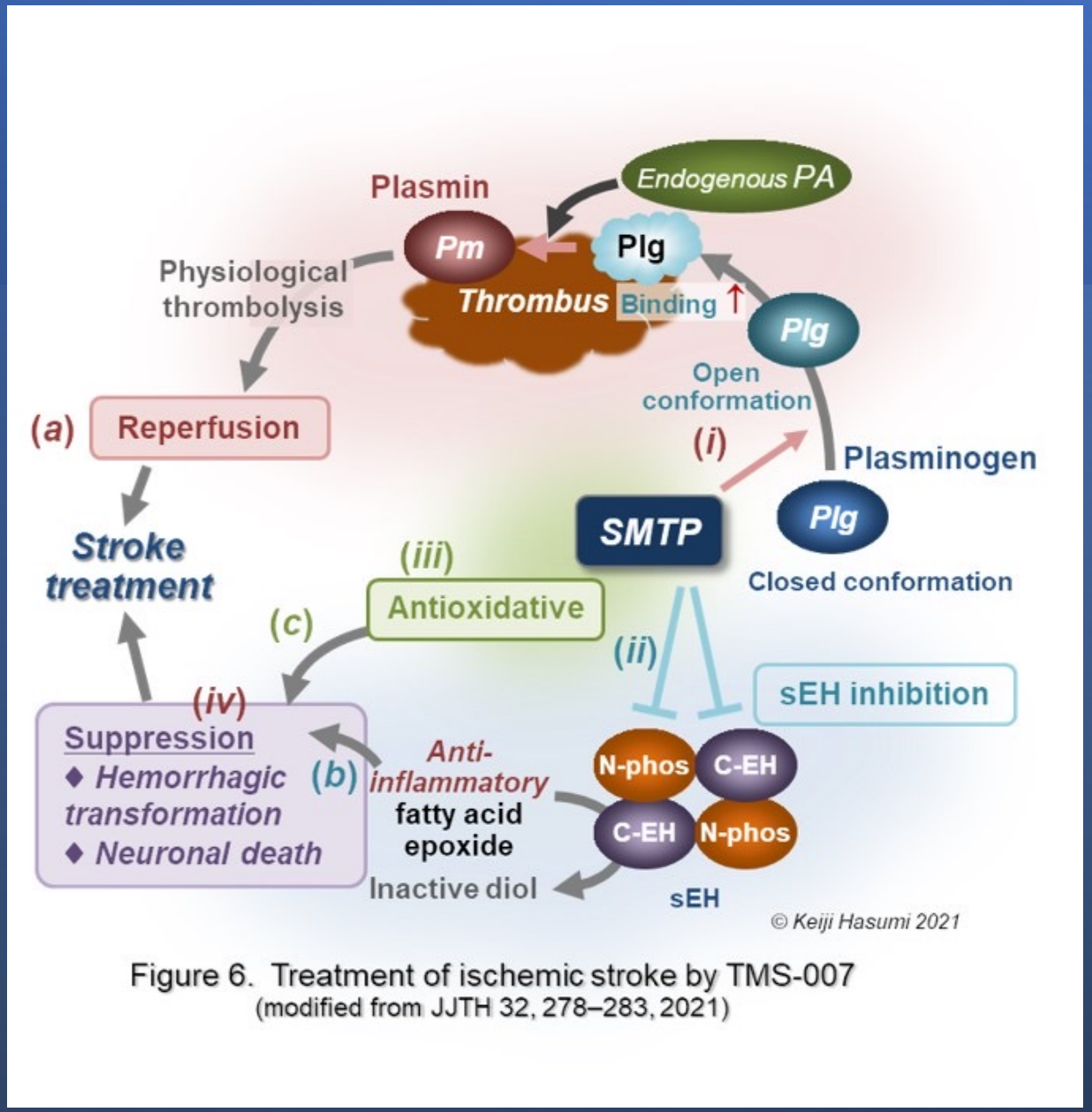


Figure 6. Treatment of ischemic stroke by TMS-007
(modified from JJTH 32, 278–283, 2021)

https://www.tms-japan.co.jp/en/business/r-and-d/technology.html

Abstract WMP1: Results From A Phase 2a Study Of TMS-007, An SMTP Family Anti-inflammatory Prothrombolytic, On Patients With Acute Ischemic Stroke Up To 12 Hours After Onset

Naoko Nishimura, Kuniyasu Niizuma, Michael Wald, Keiko Hasegawa, Teiji Tominaga and Keiji Hasumi

Originally published 3 Feb 2022 | https://doi.org/10.1161/str.53.suppl_1.WMP1 | Stroke. 2022;53:AWMP1

pharmacological evidence. We evaluated TMS-007 in a randomized, placebo-controlled, double-blind, dose-escalation phase 2a study. TMS-007 or placebo was administered as a single intravenous infusion at a dose of 1, 3, or 6 mg/kg to AIS patients who were ineligible for t-PA or thrombectomy within 12 h of LKN. The number of patients allocated to placebo and TMS-007 at doses 1, 3, and 6 mg/kg were 38, 6, 18, and 28, respectively. The combined TMS-007 dosing group (Group T; n = 52) was compared with placebo group (Group P; n = 38). The average age was ~72 years old and time since LKN to treatment was ~9 h in both groups (not significantly different). The incidence of symptomatic intracranial hemorrhage (ICH) with worsening NIHSS score of <=4 points per site physician (primary endpoint) was 0% in Group T compared to 3% (n = 1) in Group P. The number of ICH event within 24 h, including symptomatic and asymptomatic, was 6 in Group T and 5 in Group P. Total number of AE was 207 in Group T and 162 in Group P, with gastrointestinal diseases as the most common events in both groups (n = 40 and 32, respectively). TMS-007 was associated with a significant improvement in functional independence at 90 days (secondary endpoint): 40% of patients in Group T achieved a score of 0 or 1 on the mRS, compared to 18% in Group P ($p < 0.05$). Recanalization, defined by any improvement in arterial occlusive lesion score on magnetic resonance angiography in those with visible occlusion at baseline per central neuroradiologist, occurred in 58.3% (14/24) of Group T compared to 26.7% (4/15) of Group P (odds-ratio, 4.23; 95% CI, 0.99 to 18.07). TMS-007 was generally safe and well tolerated up to 6 mg/kg. TMS-007 may expand the treatment time window for the treatment of AIS. Due to the small study size, more data on efficacy is warranted in patients with visible occlusion.

Biogen Announces Exercise of Option to Acquire the Investigational Drug TMS-007 for Acute Ischemic Stroke Based on Positive Phase 2a Data

MAY 12, 2021 • NEWS RELEASE

- *TMS-007 has the potential to be a next generation thrombolytic with an improved benefit-risk profile*
- *Acute ischemic stroke is caused by a blockage of blood supply to the brain, and current thrombolytics are limited in use due in part to increased risks of bleeding*
- *Phase 2a study demonstrated positive impacts on blood vessel reopening and patient functional recovery with no incidence of symptomatic intracranial hemorrhage*
- *Biogen to make a one-time payment of $18 million and may pay potential milestone payments and royalties to TMS Co., Ltd.*

https://investors.biogen.com/news-releases/news-release-details/biogen-announces-exercise-option-acquire-investigational-drug

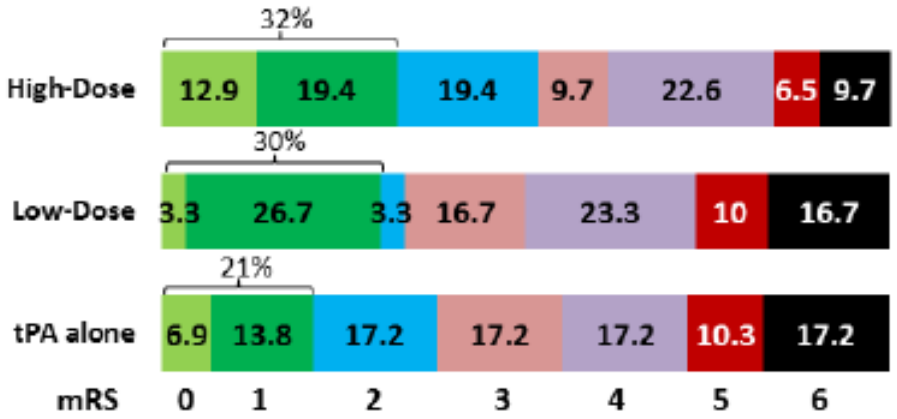
Thrombolytic Adjuncts

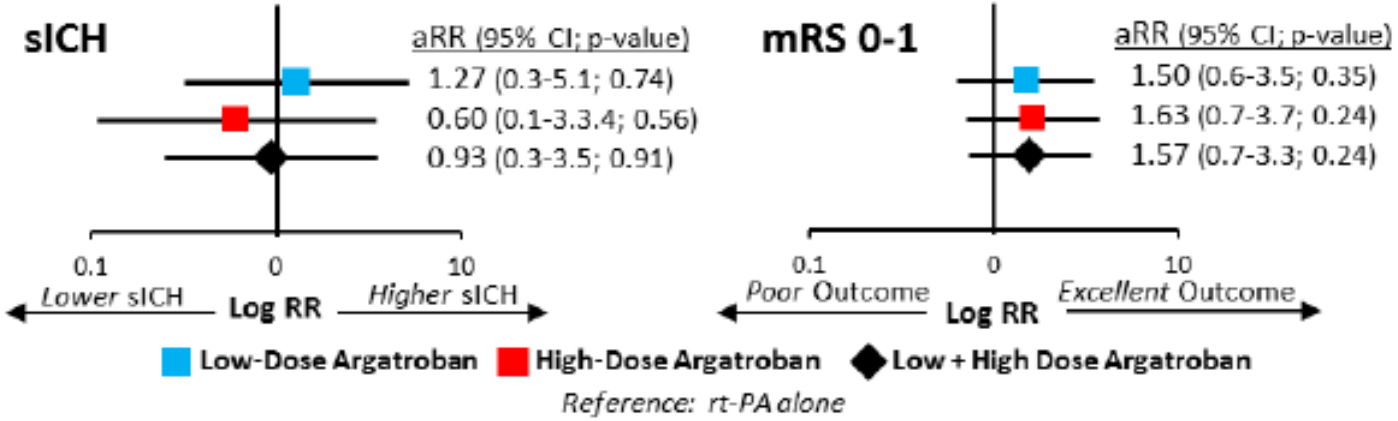
"tPA recanalization occurs in ~50% of occluded arteries one hour after treatment. Arterial re-occlusion occurs in 14-34% of tPA treated patients within two hours and is associated with worse outcome"- MOST Protocol

Could adjunctive anti-thrombotics maintain medical recanalization without increasing hemorrhagic complications??

Agratroban or Eptifibatide??

Table 1 – Design and Sample Size of Six Completed Phase 2 Trials						
	ARTSS	ARTSS-2	ARTSS-IA	CLEAR	CLEAR-ER	CLEAR-FDR
Intervention	0.9mg/kg rt-PA + low dose argatroban	0.9mg/kg rt-PA + low or high dose argatroban	0.9mg/kg rt-PA + high dose argatroban	0.3mg/kg and 0.45mg/kg rt-PA + eptifibatide	0.6mg/kg rt-PA + eptifibatide	0.9mg/kg rt-PA + eptifibatide
Study Size	n=65, single arm	n=90, 3-arms	n=10, single arm	n=94, 69 combination, 25 rt-PA	n=126, 101 combination, 25 rt-PA	n=27, single arm
Randomized	No	Yes	No	Yes	Yes	No





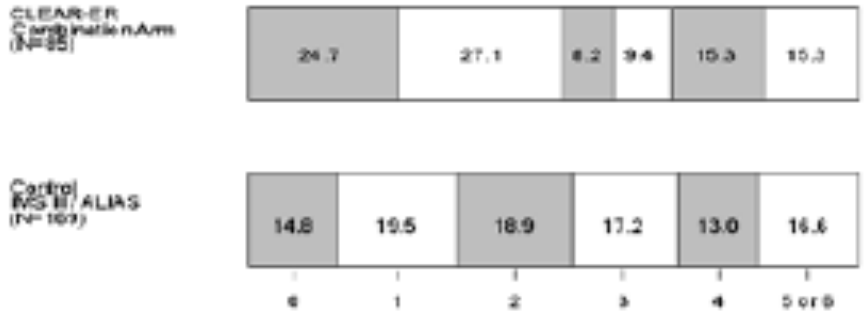
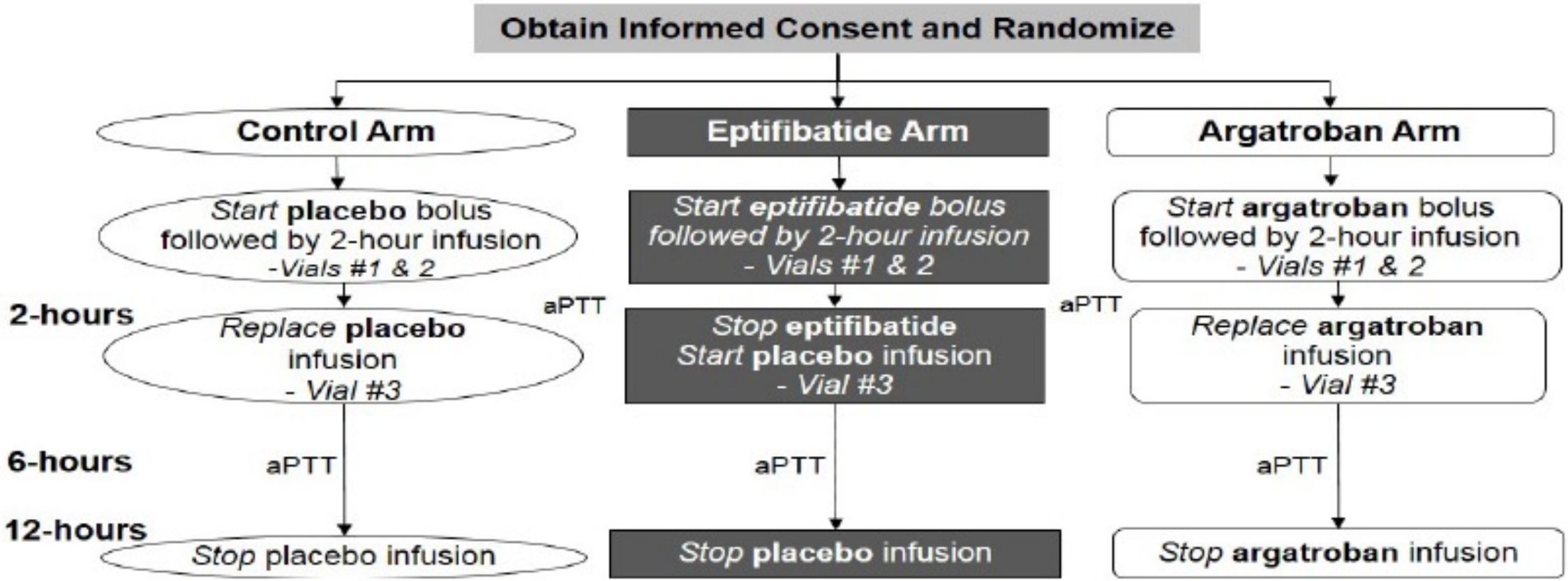


Figure 2 – mRS Ranken Distribution

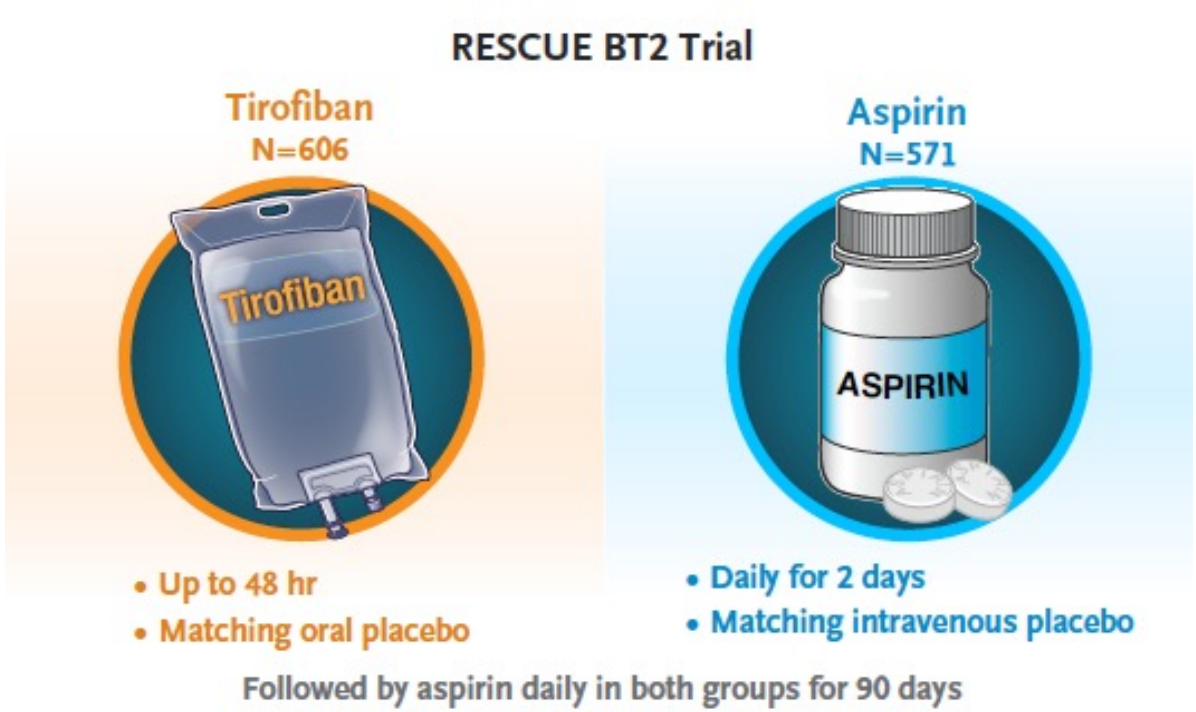
MOST

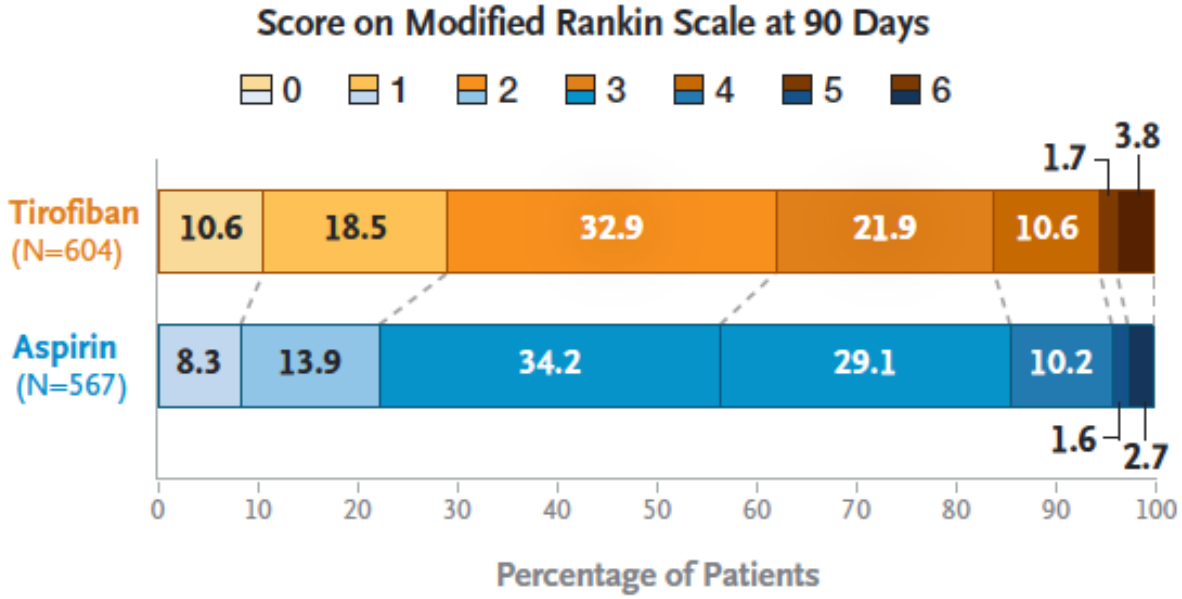
Multi-arm Optimization of Stroke Thrombolysis (MOST): a blinded, randomized controlled adaptive, multi-arm, adjunctive-thrombolysis efficacy trial in ischemic stroke.



Tirofiban for Stroke without Large or Medium-Sized Vessel Occlusion

W. Zi, J. Song, W. Kong, J. Huang, C. Guo, W. He, Y. Yu, B. Zhang, W. Geng, X. Tan, Yaoyu Tian, Z. Liu, M. Cao, D. Cheng, B. Li, W. Huang, J. Liu, P. Wang, Z. Yu, H. Liang, S. Yang, M. Tang, W. Liu, X. Huang, S. Liu, Y. Tang, Y. Wu, L. Yao, Z. Shi, P. He, H. Zhao, Z. Chen, J. Luo, Y. Wan, Q. Shi, M. Wang, De Yang, X. Chen, F. Huang, J. Mu, H. Li, Z. Li, J. Zheng, S. Xie, T. Cai, Y. Peng, W. Xie, Z. Qiu, C. Liu, C. Yue, L. Li, Yan Tian, Dahong Yang, J. Miao, J. Yang, J. Hu, R.G. Nogueira, D. Wang, J.L. Saver, F. Li, and Q. Yang, for the RESCUE BT2 Investigators*





"excellent outcome was significantly higher in the tirofiban group than in the aspirin group (29.1% vs. 22.2%; P = 0.02)."

N Engl J Med 2023;388:2025-36.

Glenzocimab: Antibody to platelet glycoprotein VI

ACTMIS- 1b/2a
ACTISAVE- Add to to tPA +/- thrombectomy
GREEN- Add on to thrombectomy only

https://www.acticor-biotech.com/our-product/glenzocimab-in-acute-ischemic-stroke

Automated Stroke Detection

Emerging “Wearables”

Neuralert Technologies Stroke Detection Wristband Named to TIME's List of the Best Inventions of 2022

Neuralert Technologies has announced that its lightweight, non-invasive wristband device that automates stroke detection and alerting, has been selected for TIME's List of the Best Inventions of 2022. TIME revealed its annual list of the Best Inventions November 10, featuring 200 extraordinary innovations changing our lives today.

PHILADELPHIA (PRWEB) NOVEMBER 14, 2022

Neuralert Technologies has announced that its lightweight, non-invasive wristband device that automates stroke detection and alerting, has been selected for TIME's List of the Best Inventions of 2022. TIME revealed its annual list of the Best Inventions November 10, featuring 200 extraordinary innovations changing our lives today.

One of the hallmark indications of stroke is asymmetrical arm movement (e.g., weakness, neglect or less movement on one side). Neuralert's stroke detection device can identify the onset of asymmetric movement in as little as fifteen minutes, even if the wearer is asleep. The device requires no time-wasting baseline development, significantly speeding stroke detection, assessment, and treatment; which can saves lives, improve outcomes, and help patients to continue to live full and independent lives.

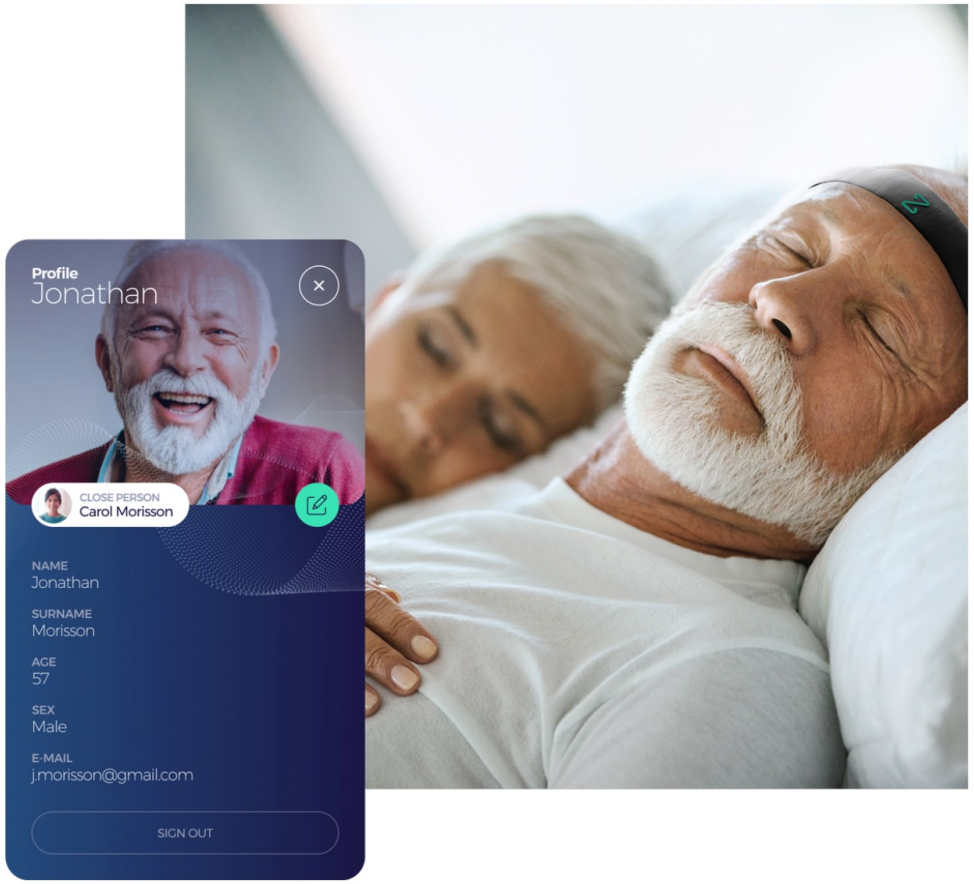
Neuralert Technologies Stroke Detection Wristband Named to TIME's List of the Best Inventions of 2022

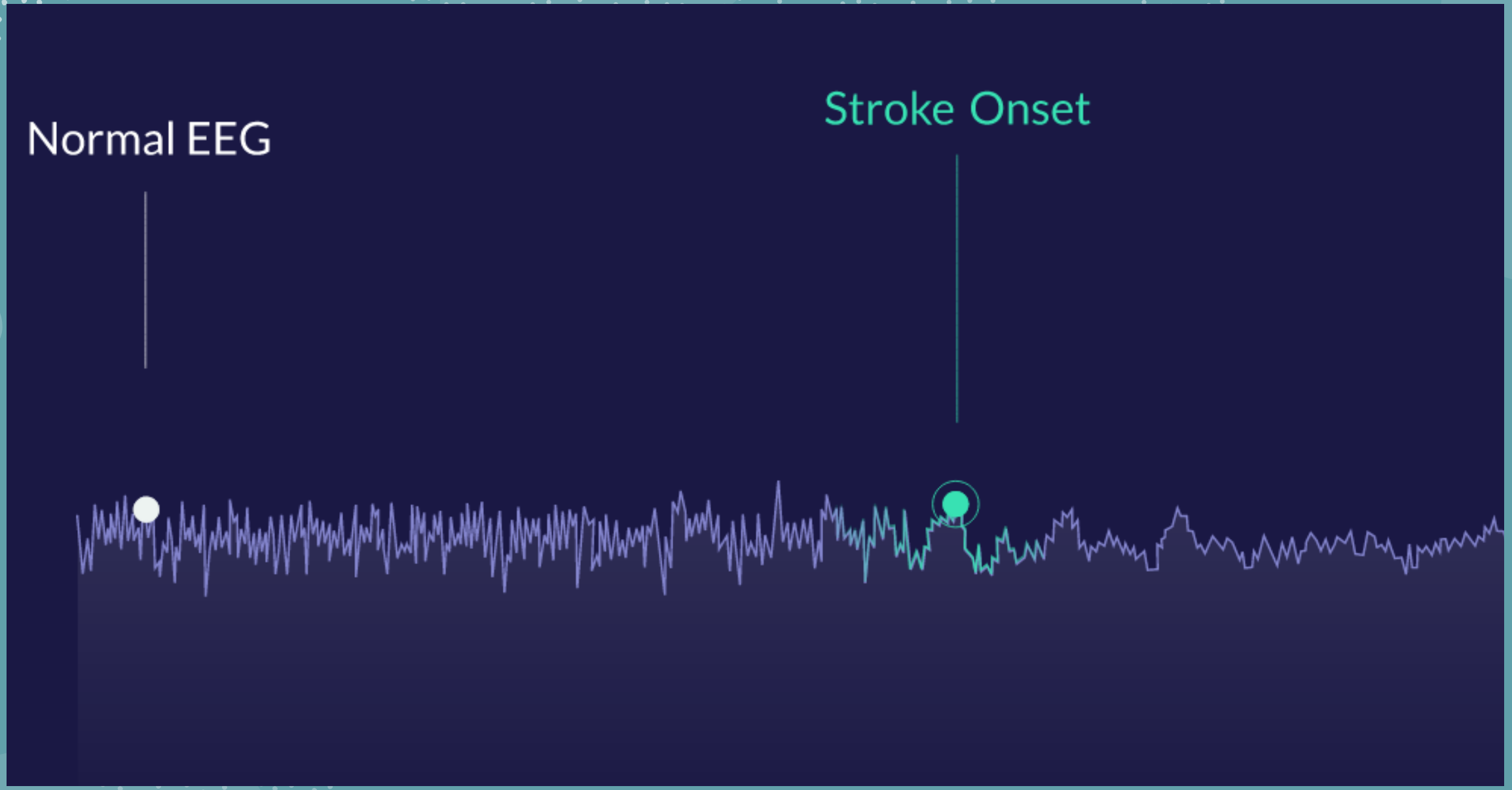
zeit medical

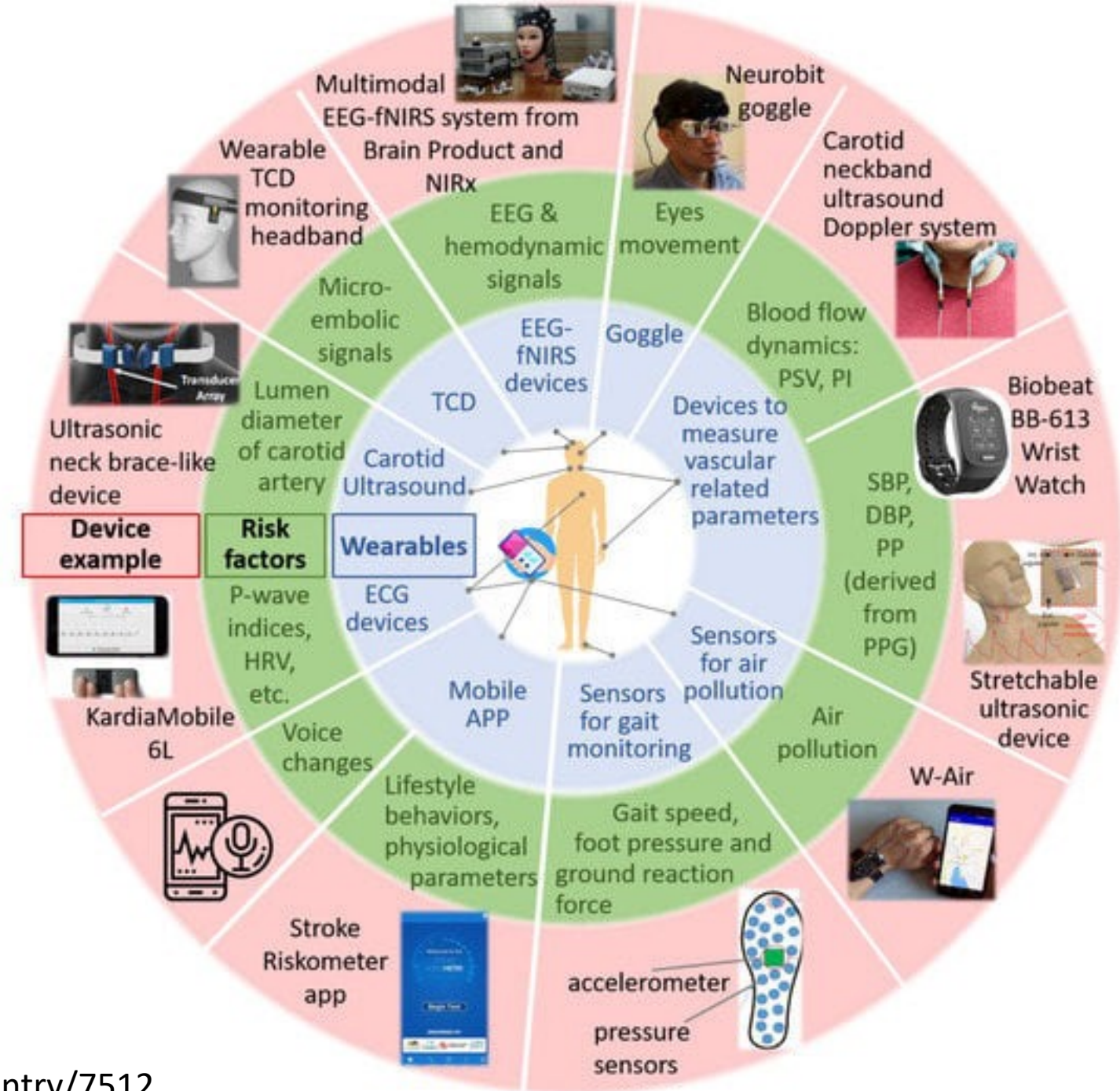
Sleep **without worrying** about stroke

Our smart headband constantly monitors the electrical activity of your brain and gets help immediately, should you need it.

JOIN TO GET IT FIRST

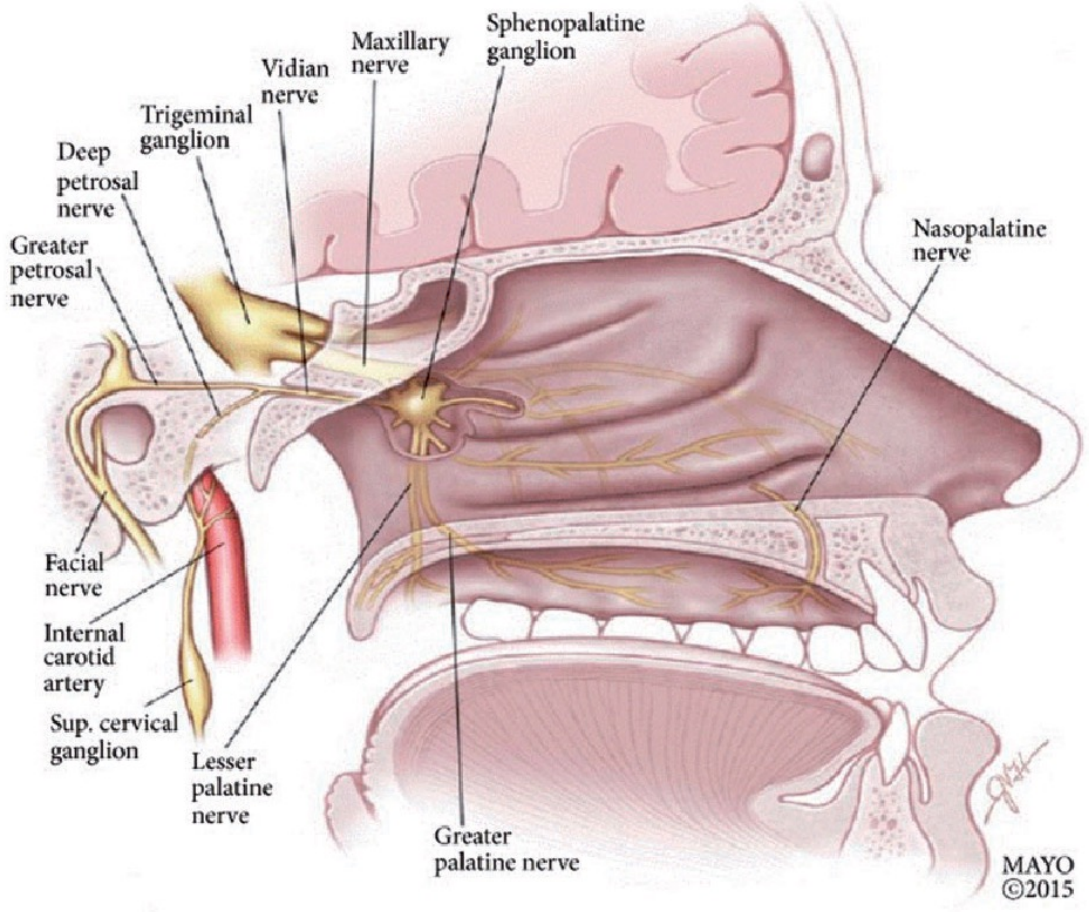


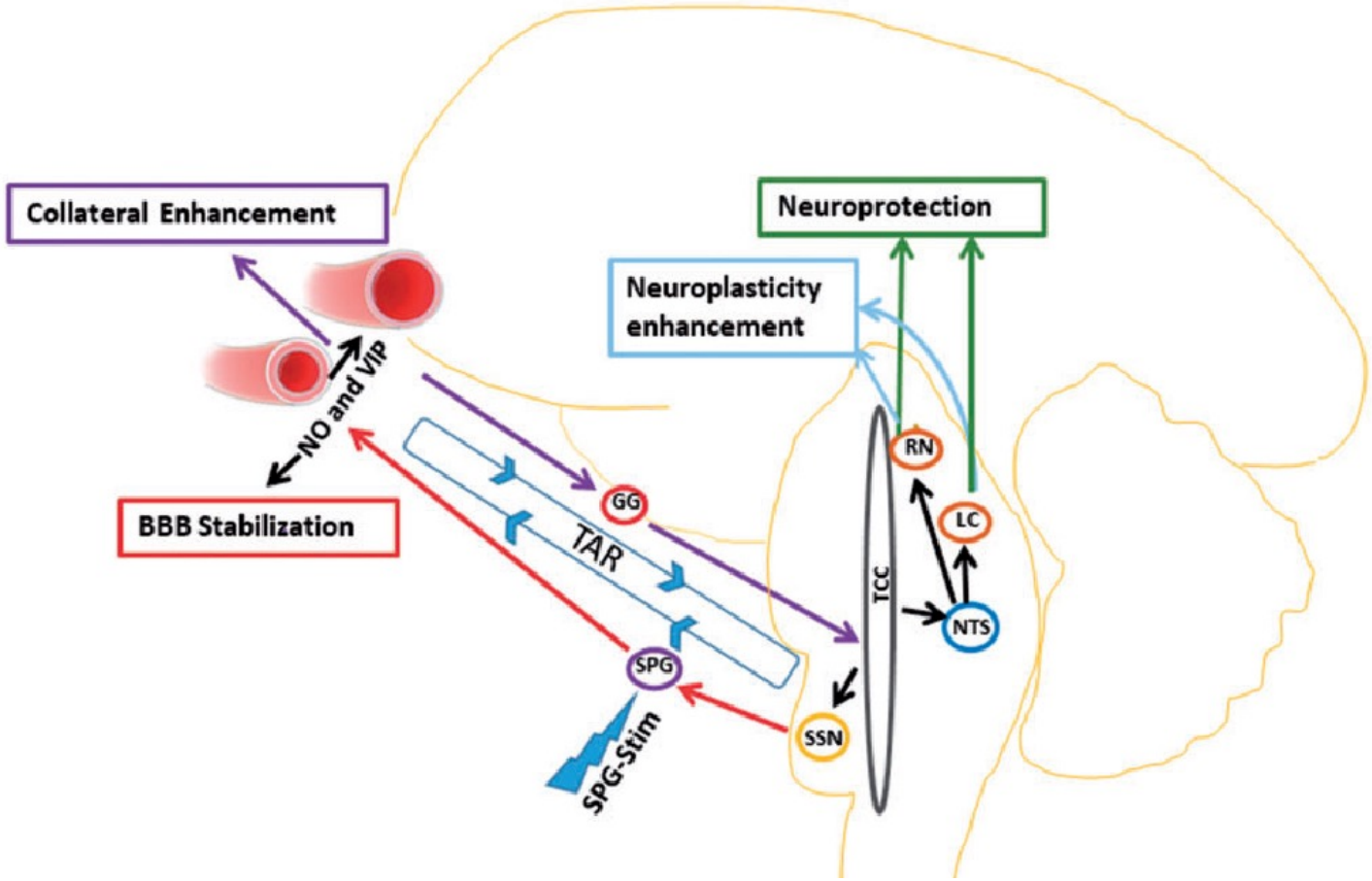

Normal EEG
Stroke Onset



https://encyclopedia.pub/entry/7512

Collateral Recruitment
Sphenopalatine Ganglion Stimulation





https://www.semanticscholar.org/paper/Mechanisms-of-action-of-acute-and-subacute-ganglion-Hosseini Saver/59d81ebe5619608ee9668399fd883122f0fe0243

Sphenopalatine Ganglion Stimulation to Augment Cerebral Blood Flow

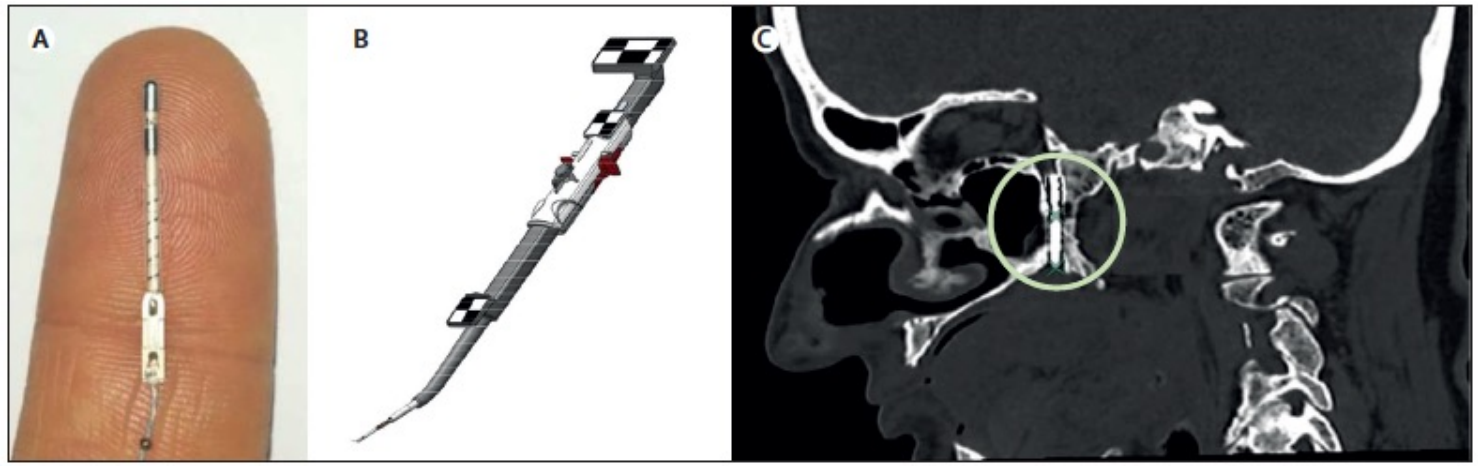
A Randomized, Sham-Controlled Trial

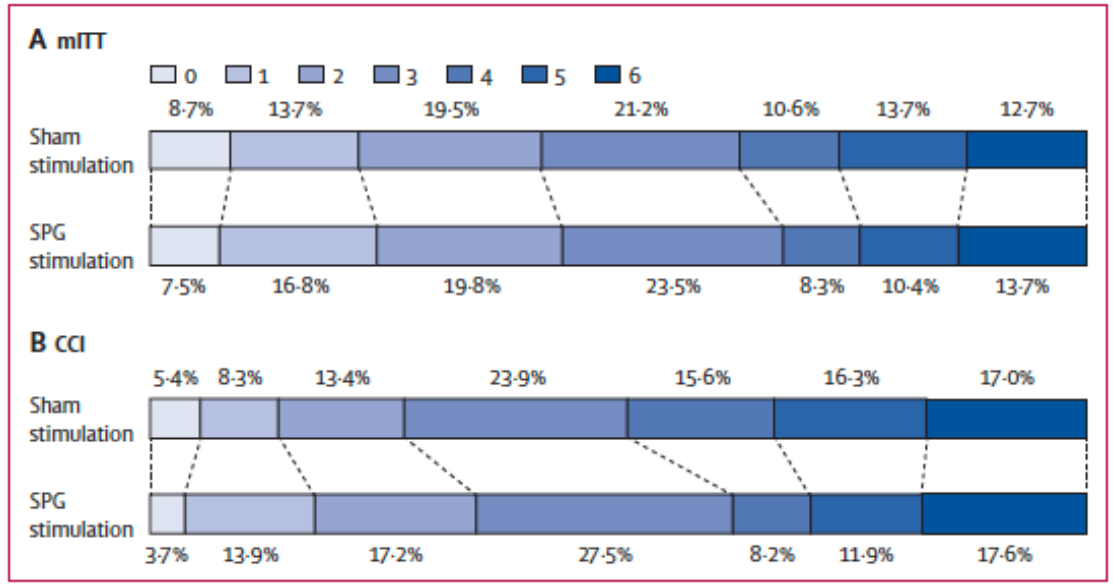
Natan M. Bornstein, MD*; Jeffrey L. Saver, MD*; Hans-Christoph Diener, MD; Philip B. Gorelick, MD; Ashfaq Shuaib, MD; Yoram Solberg, MD; Thomas Devlin, MD, PhD; Thomas Leung, MD; Carlos A. Molina, MD; for the ImpACT-24A Investigators†

(*Stroke*.2019;50:2108-2117.

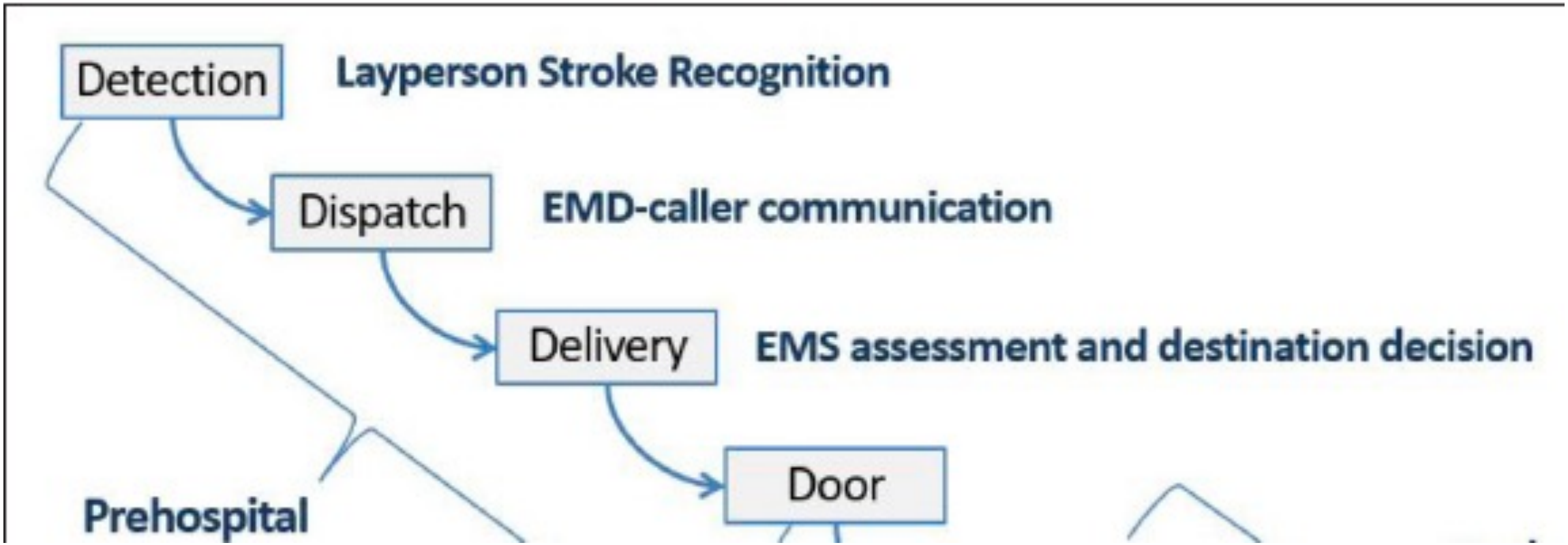
An injectable implant to stimulate the sphenopalatine ganglion for treatment of acute ischaemic stroke up to 24 h from onset (ImpACT-24B): an international, randomised, double-blind, sham-controlled, pivotal trial

Natan M Bornstein, Jeffrey L Saver*, Hans Christoph Diener, Philip B Gorelick, Ashfaq Shuaib, Yoram Solberg, Lisa Thackeray, Milan Savic, Tamar Janelidze, Natia Zarqua, David Yarnitsky, Carlos A Molina, for the ImpACT-24B investigators*

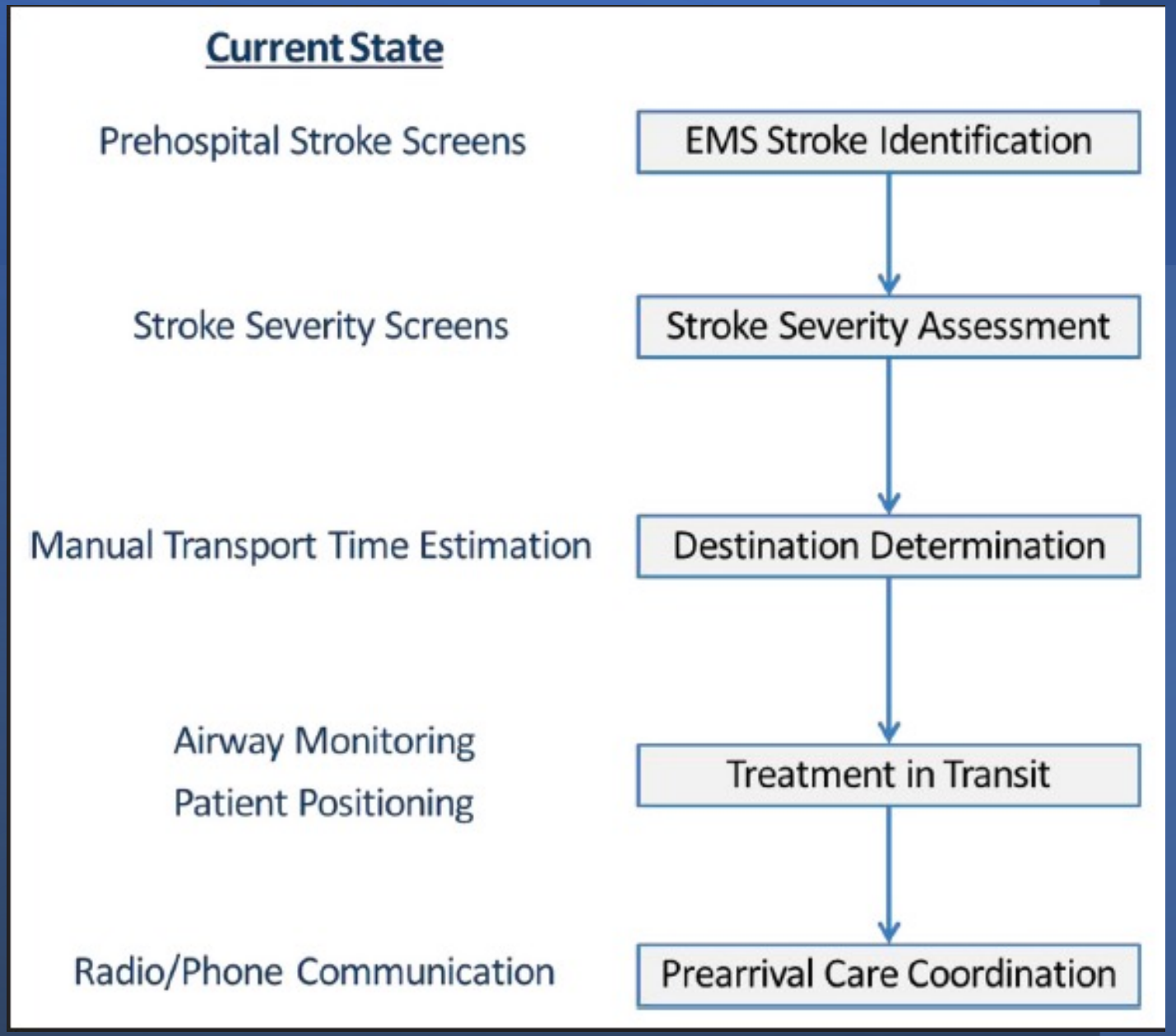





Realizing Opportunities



Stroke. 2023;54:1138–1147. DOI: 10.1161/STROKEAHA.122.039586



Stroke. 2023;54:1416–1425. DOI: 10.1161/STROKEAHA.123.039792

Telestroke Consultation in the Emergency Medical Services Unit: A Novel Approach to Improve Thrombolysis Times

Sami Al Kasab, MD,*†[1] Eyad Almallouhi, MD,*[1] Cheryl Grant, BA,*
Dale Hewitt, EMT,‡ Jessica Hewitt, RN,§ Morgan Baki, DO,*
Perette Sabatino, RN,* David Jones, RN,* and Christine A. Holmstedt, DO*

"Compared to tPA patients treated through STS consultation, TEMS patients had shorter door to needle (DTN) time (21 vs. 38 min, $p < 0.001$). In addition, patients who received MT after bypassing the NSC had shorter onset to groin time compared to those transferred from NSC (216 vs. 293 min, $P = 0.04$)."

Journal of Stroke and Cerebrovascular Diseases, Vol. 30, No. 5 (May), 2021: 105710

Prehospital Telestroke vs Paramedic Scores to Accurately Identify Stroke Reperfusion Candidates

A Cluster Randomized Controlled Trial

Imogene Mary Scott, MBChB, Csilla Manoczki, MBChB, Andrew Herbert Swain, MBChB, PhD, Abhishek Ranjan, MS, Michael Garth McGovern, Alicia Lucy Shyrell Tyson, BNurs PGDip, Melissa Claire Hyslop, BHSc, Martin Michael Punter, MBBS, PhD, and Annemarei Ranta, MD, PhD, FRACP

"Telestroke was 100% (95% CI 90%–100%) and PASTA 70.7% (54.5%–83.9%) accurate in predicting reperfusion candidates compared with preimaging emergency department neurologist assessment ($p < 0.001$)."

Neurology® 2022;99:e2125-e2136. doi:10.1212/WNL.0000000000201104

Hyperacute Ischemic Stroke Care in 2030??

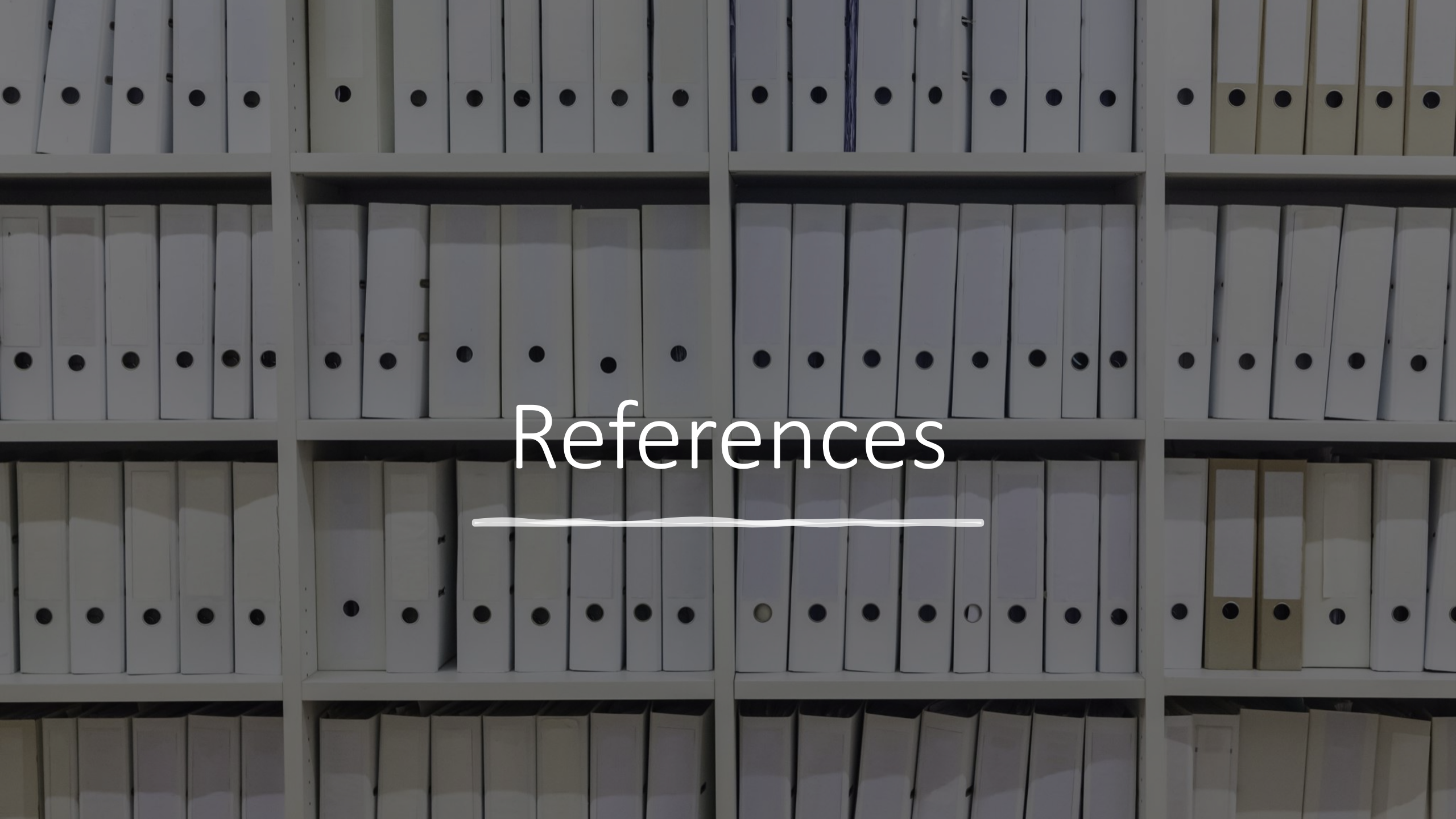
72 yo awakens to EMS arriving at their home after their “wearable” alerted 911 that they were having a stroke

EMS contacts the receiving stroke center and tele-stroke consultation is initiated while in route

Evaluation and Imaging in the ED are rapidly completed and are consistent with a left M1 occlusion and SPG stimulation is initiated

”TriBust” therapy is initiated (3 drug combination of SMTP, low dose TNK, and multipotent adult progenitor stem cells) immediately in the ED and proceed to mechanical thrombectomy

Four hours post “TriBust”, labs are completed to exclude thrombolytic-associated coagulopathy, and if not present, an IV anti-thrombotic infusion is initiated to maintain re-canalization



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