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Transforming patient care.

Stroke Mechanisms, Etiologies, and Updates in Acute Stroke Management
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Disclosures

Lily Ackermann has no relevant financial or advisory relationships with corporate organizations related to this activity.

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Boston, MA

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- *Editor-in-Chief* Journal of Clinical Outcomes Management

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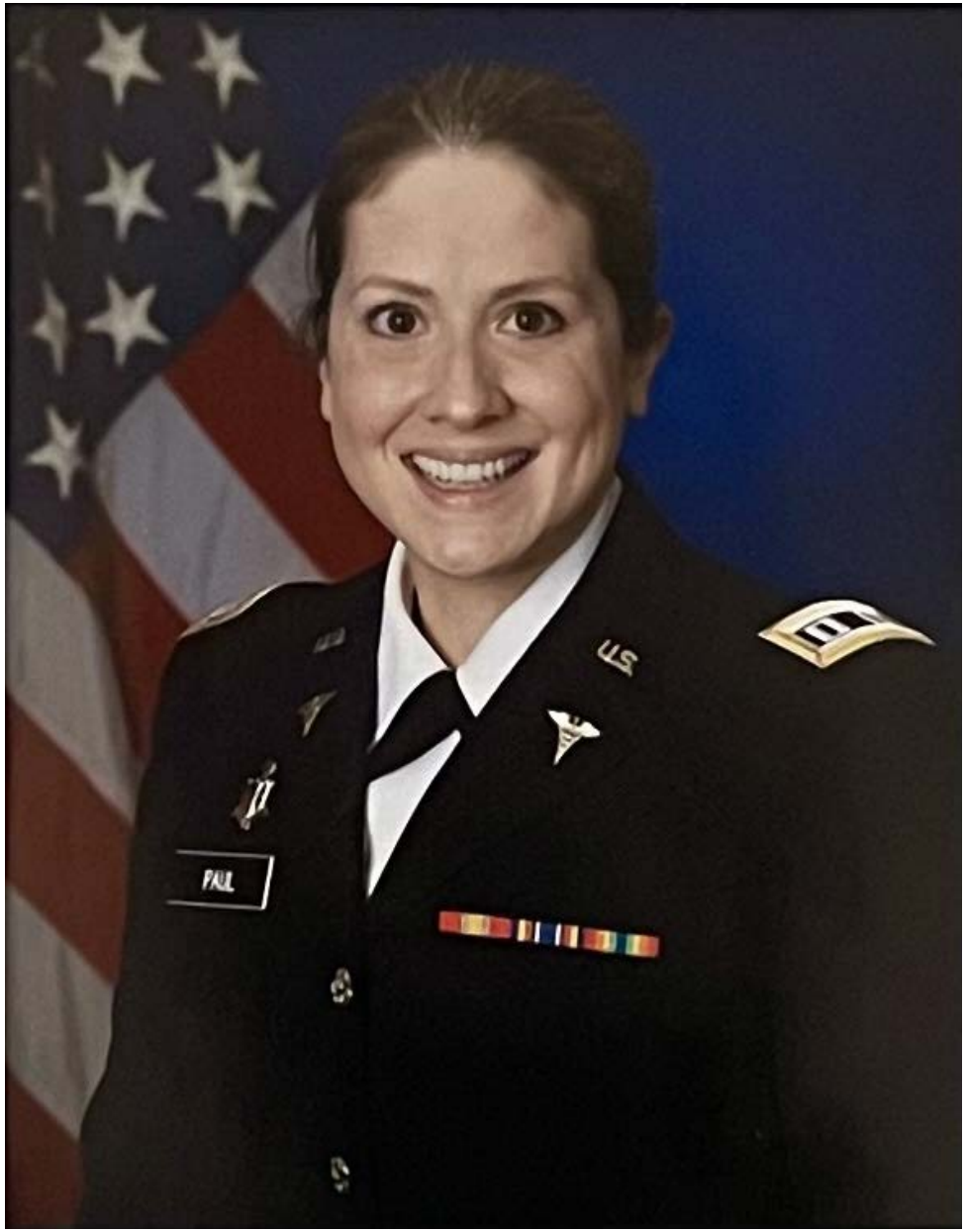

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Disclosures

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QUESTIONS

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Question 1

Intravenous tPA is contraindicated unless you know the exact time of onset of stroke

A. True

B. False

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Question 2

73 y/o male not currently on any medications is admitted with a minor stroke. His initial NIH score is 2. Head CT and CTA head/neck are both unremarkable. An MRI obtained shows multiple small infarcts (embolic pattern). What medication should he be started on?

A. DOAC

B. Aspirin and Clopidogrel for DAPT

C. Aspirin for antiplatelet mono therapy

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Objectives:

What is stroke, TIA, and infarct?

What causes stroke?

How do we treat stroke?

- **-How mild is too mild? (severity of stroke)**
- **-How high is too high? (BP)**
- **-Which IVtPA is better? (tenecteplase vs alteplase)**
- **-How small is too small? (LVO/MVO/SVO)**
- **-How big is too big? (large core infarcts)**
- **-How late is too late? (late presenter IVtPA 4.5-24hrs)**

What is stroke?

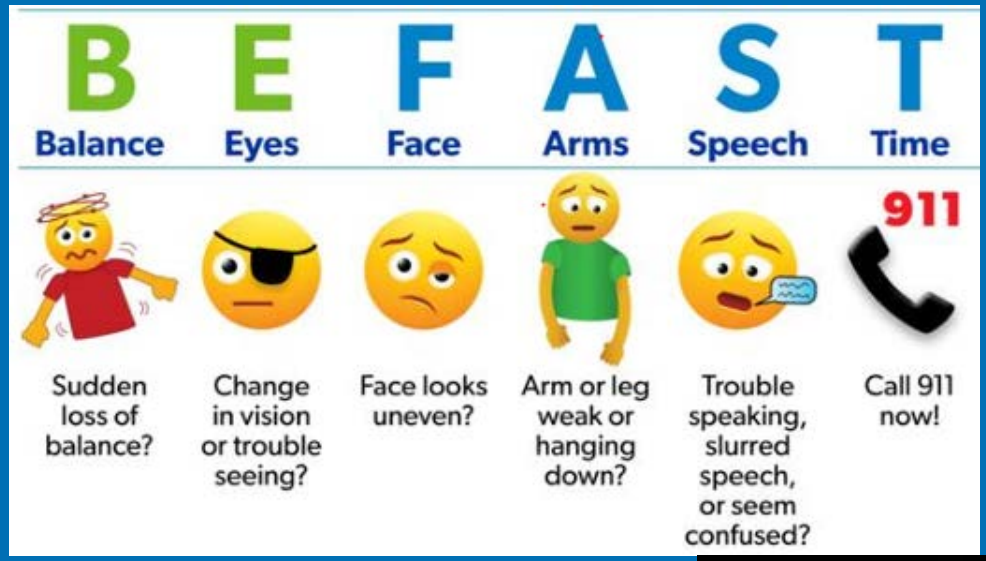
“A neurological deficit in a vascular territory.”

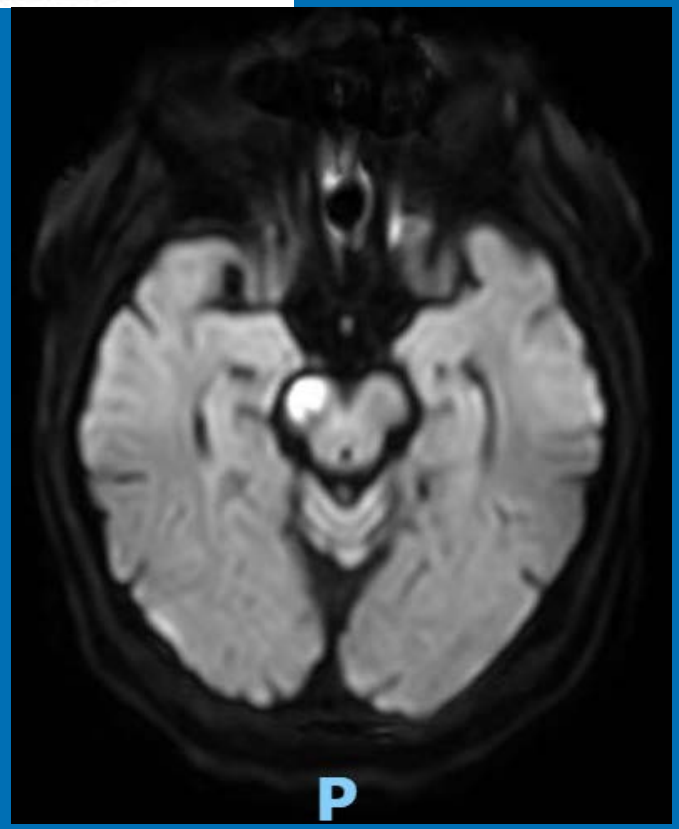
Clinical diagnosis:

Thorough history
Physical Exam

What is infarct?

Radiological diagnosis





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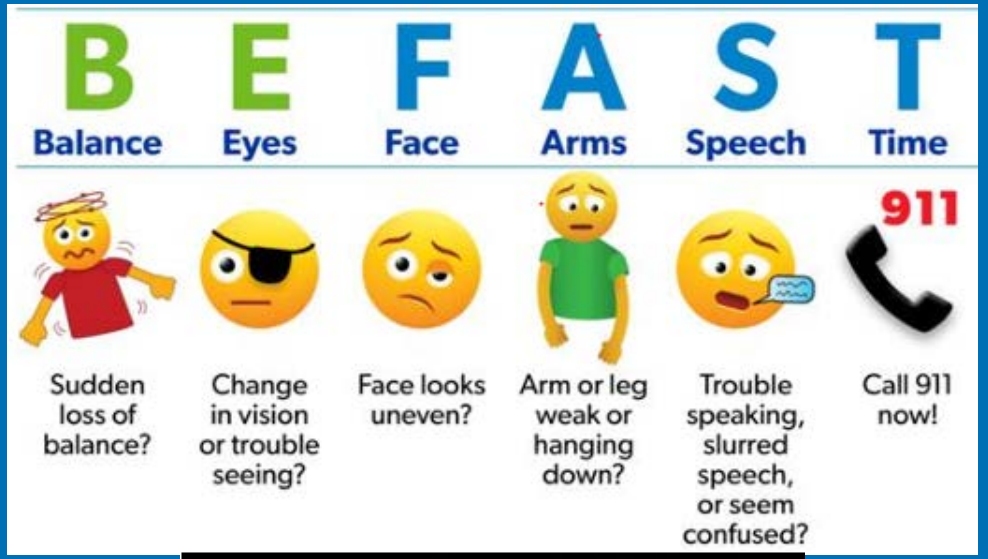
What is TIA?

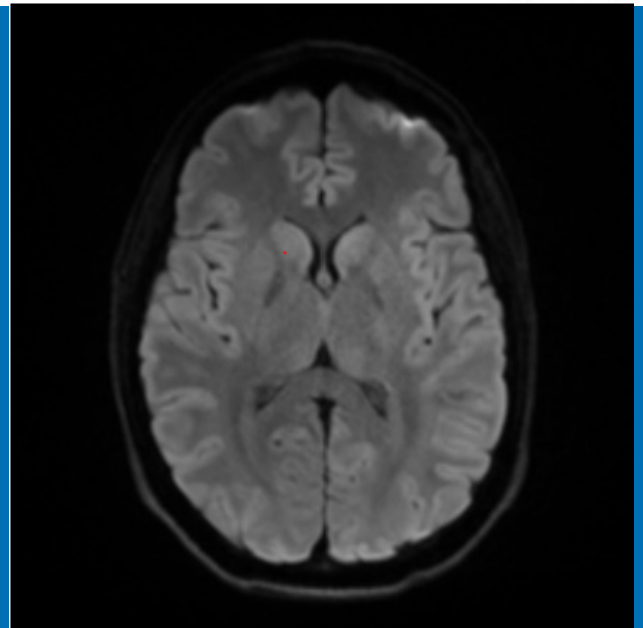
“A neurological deficit in a vascular territory, but it resolves within 24 hours and does not result in MRI brain findings.”

Clinical suspicion +

Radiologic confirmation

A stroke scare that luckily resolves within 24 hours without any trace (clinical nor radiological).





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What is not TIA/stroke?

Non-specific transient dizziness/lightheadedness

Other poorly described/understood spells

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Stroke is a symptom!

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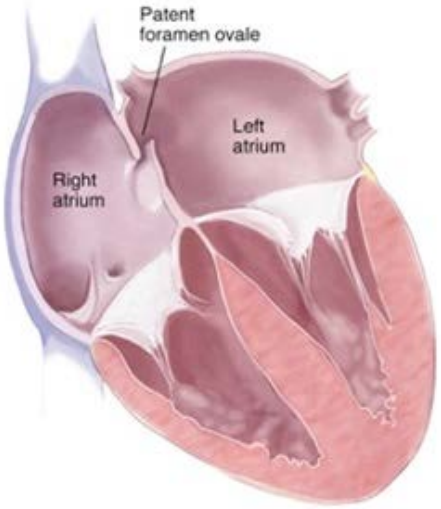
Mechanisms of Stroke

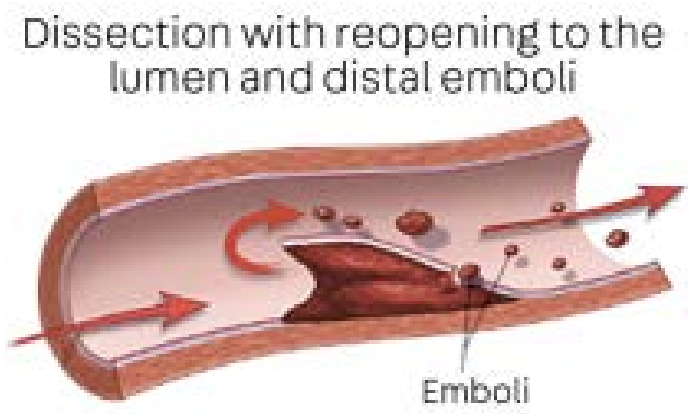
- Embolic
- Hypoperfusion
- Branch atheromatous disease
- In-situ thrombus
- Vasospasm
- Inflammatory stenosis
- Compression
- Small vessel disease

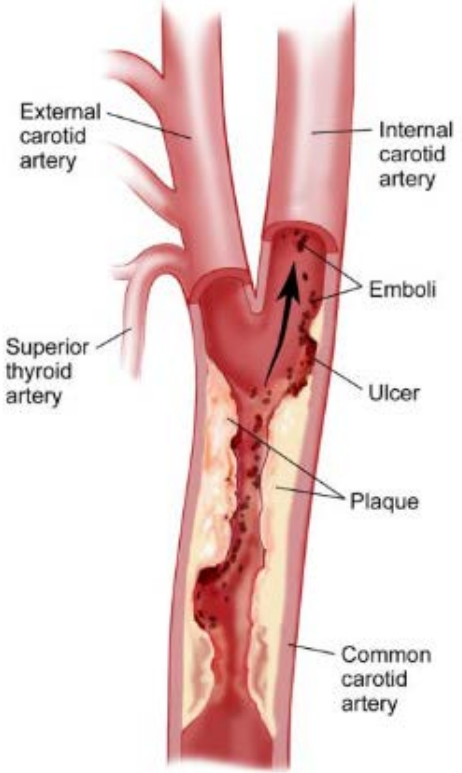
Let’s add some etiologies, part 1/3:



Embolic sources:

- Parodoxical (via a shunt ie. PFO as conduit)
  - DVT, Valve tissue –venous
- Cardioembolic
  - AF, long pauses, low EF, PFO as nidus, endocarditis (infectious and non), valve tissue, myxoma
- Aortic arch
  - Atheroma, dissection
- Artery to artery
  - Large artery atherosclerosis, arterial dissection
- Cardiac assist devices
  - ECMO, Impella





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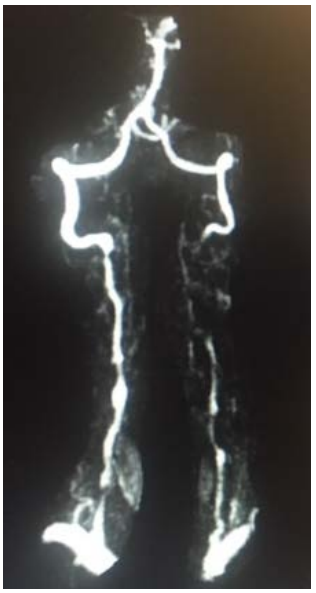
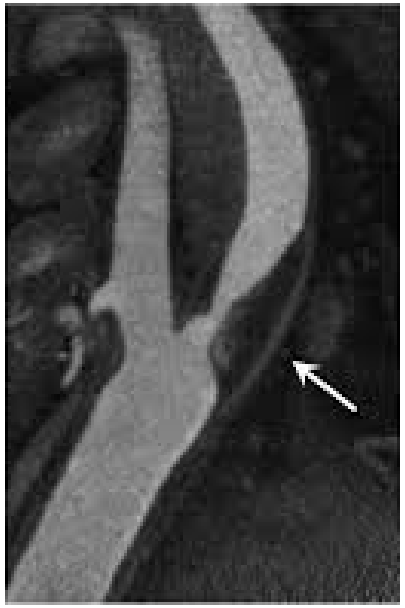
Let’s add some etiologies, part 2/3:

- Hypoperfusion:
  - Through a fixed stenosis
    - Large artery atherosclerosis, intracranial atherosclerotic disease, arterial dissection +/- hypotension/hypovolemia





  - Watershed brain territories
    - Hypotension/hypovolemia

- Branch atheromatous disease:
  - Parent vessel athero occluding daughter vessel
  - Perforators off the basilar artery (BA)
  - Lenticulostriates off the middle cerebral artery (MCA)
    - Intracranial atherosclerotic disease

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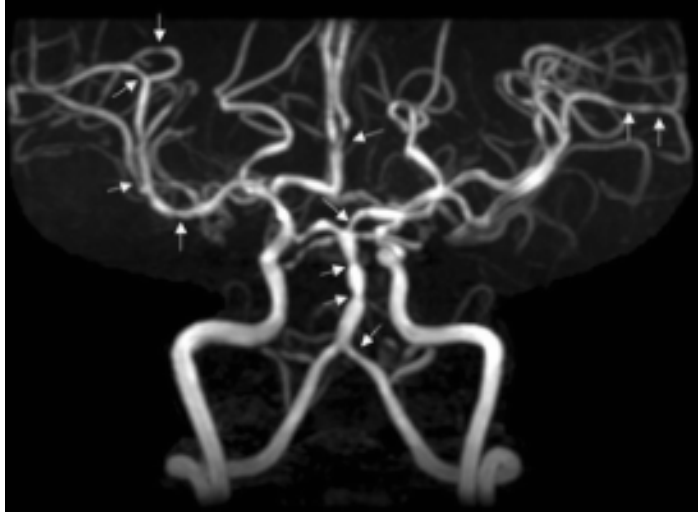
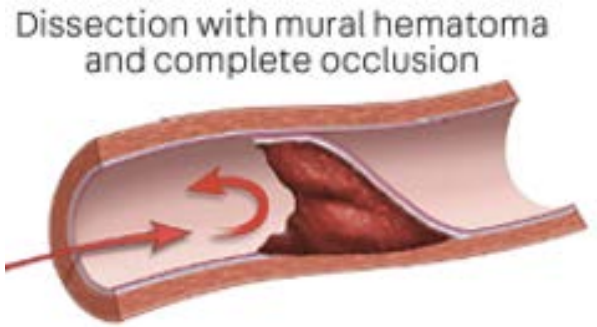
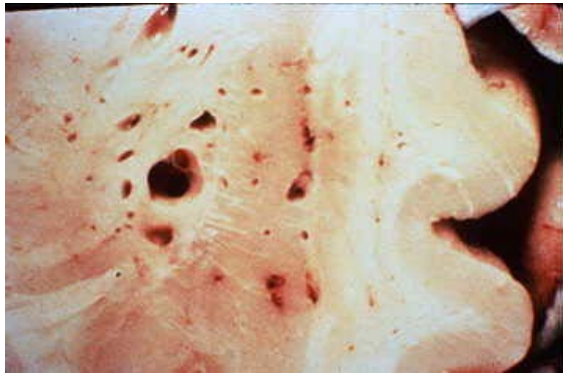
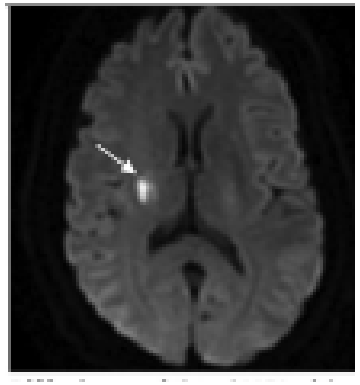
Let's add some etiologies, part 3/3:



- In-situ thrombus:
  - Cerebral arterial thrombi
    - Thrombophilia ie. antiphospholipid syndrome (APLS)
- Vasospasm:
  - Reversible cerebral vasoconstrictive syndrome (RCVS)
- Inflammatory stenosis:
  - Vasculitis
- Compression:
  - Arterial dissection, mass effect from i.e. mass
- Lacune= small vessel disease
  - Hypertension, aging, etc







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ACUTE STROKE CARE

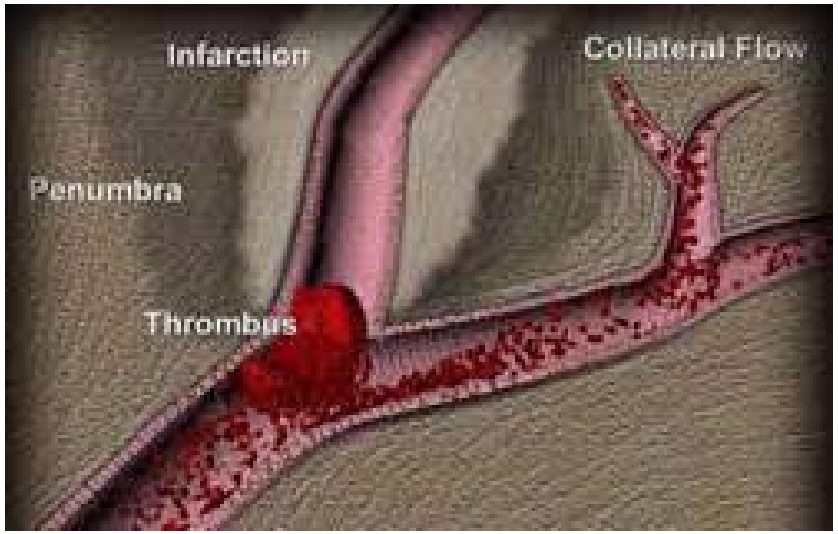
!! PROMPT REPERFUSION !!

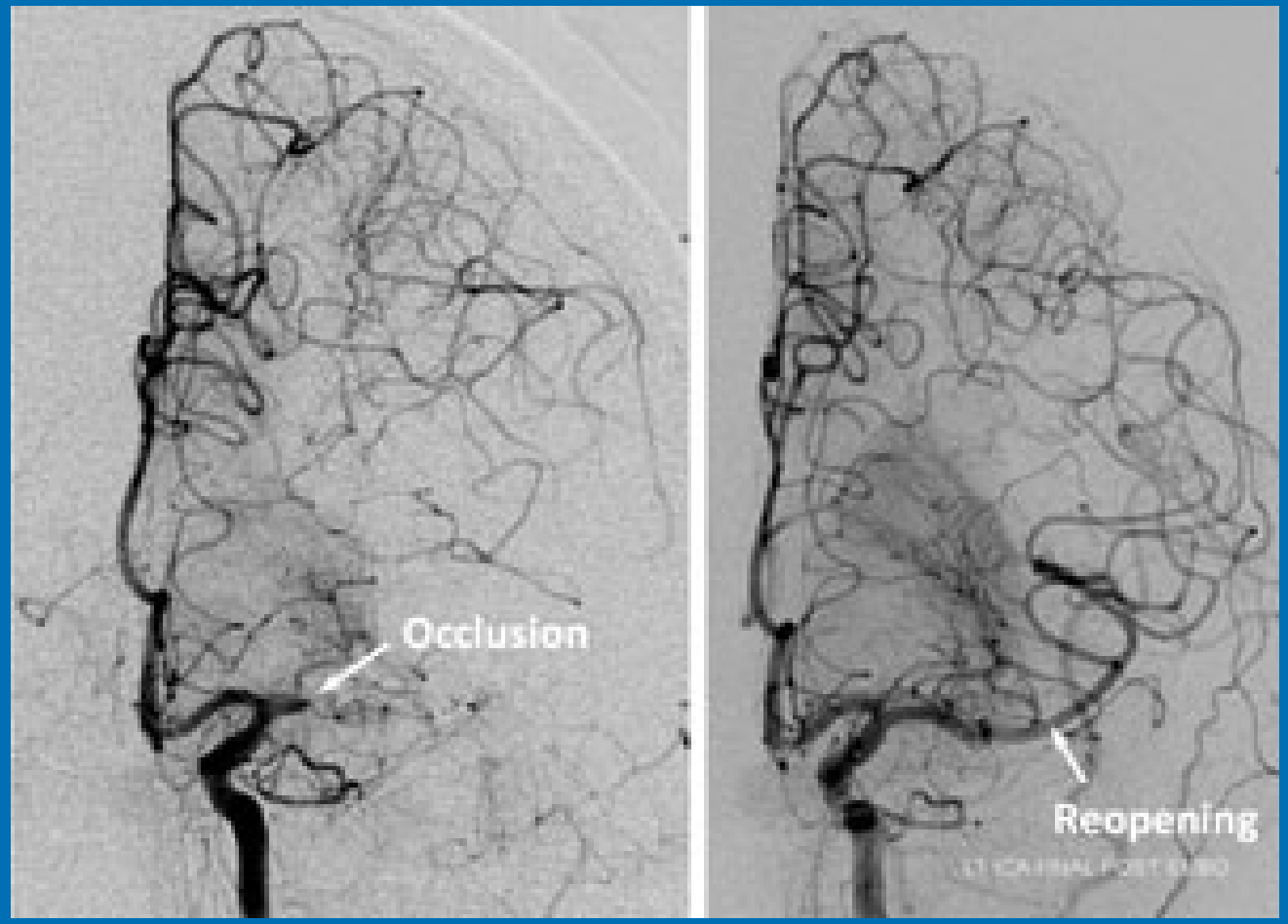
Recanalization of the occluded vessel

Optimize collateral flow

Temporary preservation of the ischemic penumbra

Avoid secondary brain injury





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Case #1

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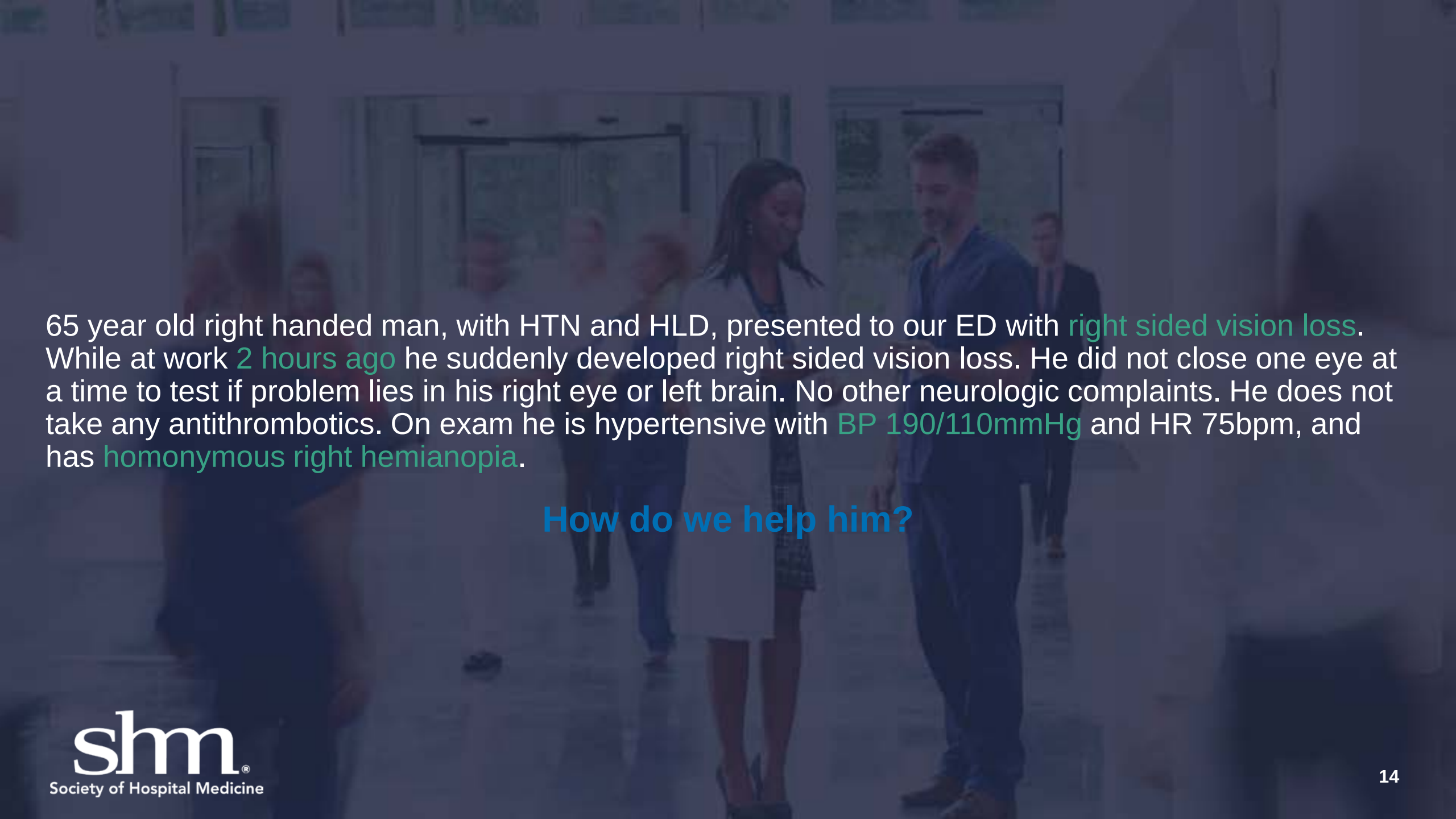

65 year old right handed man, with HTN and HLD, presented to our ED with right sided vision loss. While at work 2 hours ago he suddenly developed right sided vision loss. He did not close one eye at a time to test if problem lies in his right eye or left brain. No other neurologic complaints. He does not take any antithrombotics. On exam he is hypertensive with BP 190/110mmHg and HR 75bpm, and has homonymous right hemianopia.

How do we help him?

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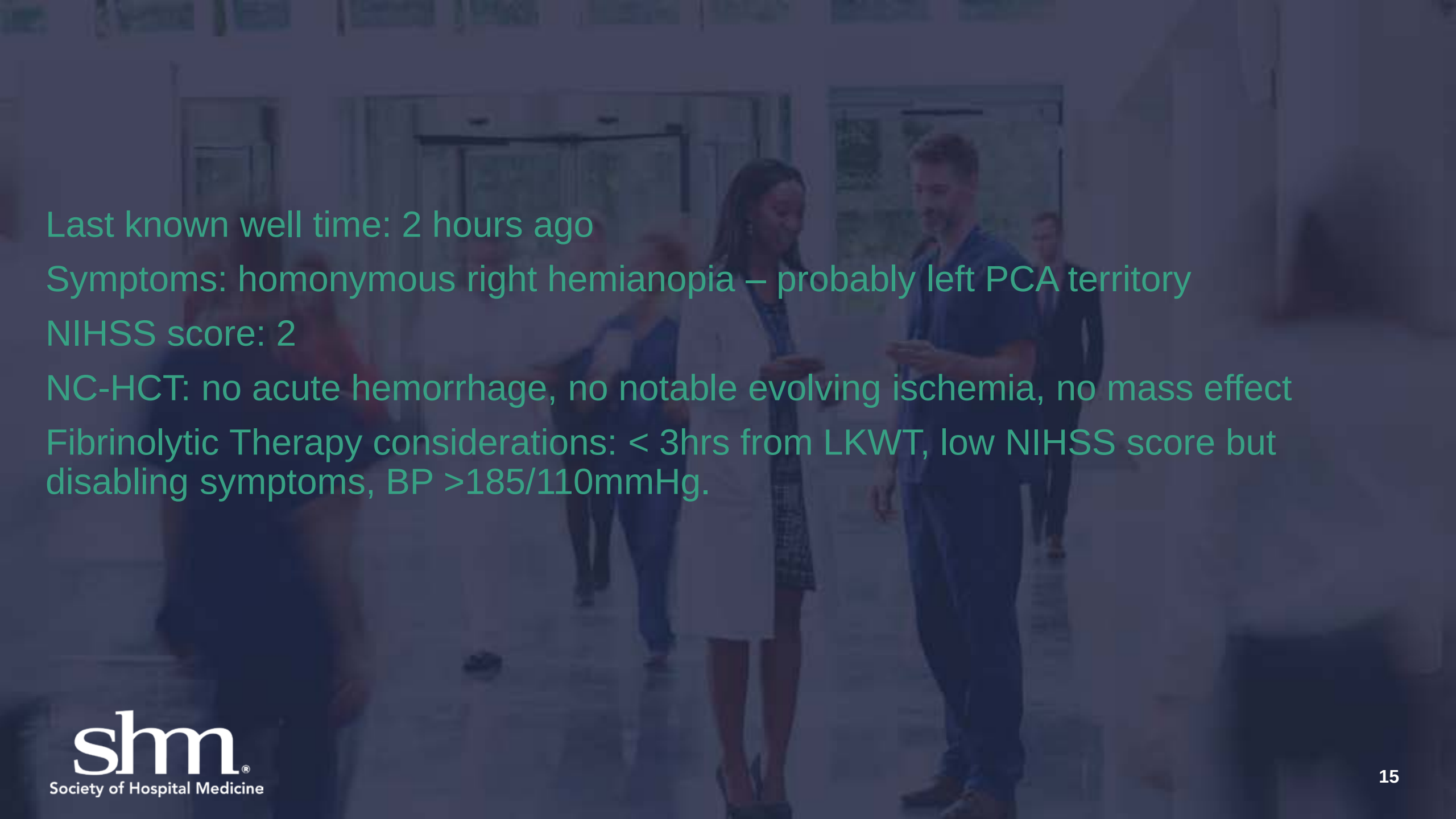

Last known well time: 2 hours ago

Symptoms: homonymous right hemianopia – probably left PCA territory

NIHSS score: 2

NC-HCT: no acute hemorrhage, no notable evolving ischemia, no mass effect

Fibrinolytic Therapy considerations: < 3hrs from LKWT, low NIHSS score but disabling symptoms, BP >185/110mmHg.

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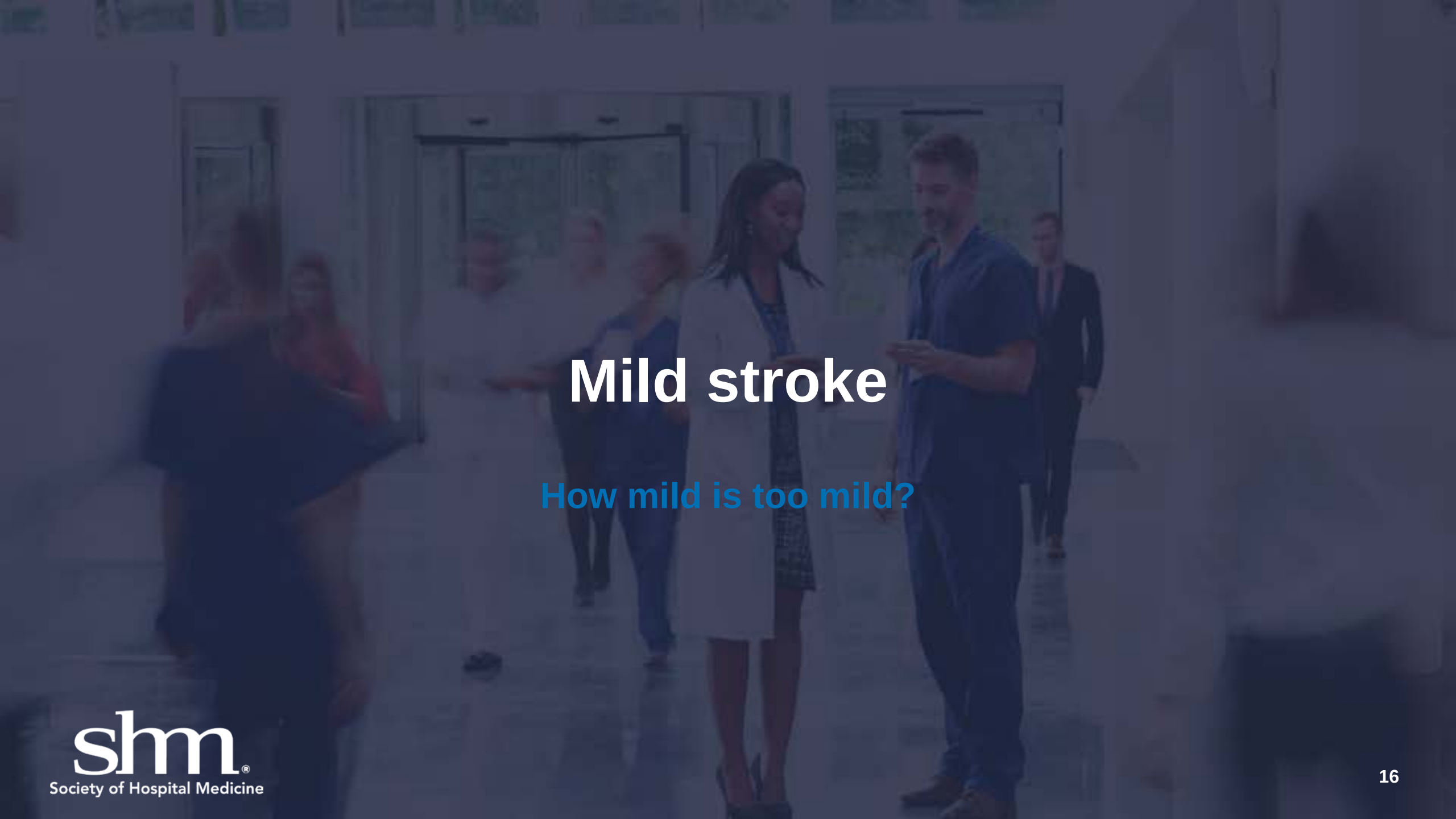

Mild stroke

How mild is too mild?

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3.5.3. Mild Stroke

1. For otherwise eligible patients with mi
alteplase is recommended for patients
of ischemic stroke symptom onset or
state.

2. For otherwise eligible patients with mi
alteplase may be reasonable for patie
4.5 hours of ischemic stroke symptom
baseline state.

3. For otherwise eligible patients with mi
(NIHSS score 0–5), IV alteplase is not
be treated within 3 hours of ischemic
known well or at baseline state.

4. For otherwise eligible patients with mi
(NIHSS 0–5), IV alteplase is not recom
treated within 3 and 4.5 hours of ische
last known well or at baseline state.

Intravenous Alteplase Versus Best Medical Therapy for Patients With Minor Stroke: A Systematic Review and Meta-Analysis

Yang Zhang [#1], Tian Lv [#2], Thanh N Nguyen [3], Simiao Wu [4], Zhi Li [5], Xue Bai [1], Dan Chen [1], Chuansheng Zhao [6], Wanyi Lin [7], Shiqin Chen [8], Yi Sui [1,9]

Affiliations + expand

PMID: 38465591 DOI: 10.1161/STROKEAHA.123.045495

Abstract

Background: The efficacy of thrombolysis (IVT) in minor stroke (National Institutes of Health Stroke Scale score, 0-5) remains inconclusive. The aim of this study is to compare the effectiveness and safety of IVT with best medical therapy (BMT) by means of a systematic review and meta-analysis of randomized controlled trials and observational studies.

Methods: We searched the PubMed, Embase, Cochrane Library, and Web of Science databases to obtain articles related to IVT in minor stroke from inception until August 10, 2023. The primary outcome was an excellent functional outcome, defined as a modified Rankin Scale score of 0 or 1 at 90 days. The associations were calculated for the overall and preformulated subgroups by using the odds ratios (ORs). This study was registered with PROSPERO (CRD42023445856).

Results: A total of 20 high-quality studies, comprised of 13 397 patients with acute minor ischemic stroke, were included. There were no significant differences observed in the modified Rankin Scale scores of 0 to 1 (OR, 1.10 [95% CI, 0.89-1.37]) and 0 to 2 (OR, 1.16 [95% CI, 0.95-1.43]), mortality rates (OR, 0.67 [95% CI, 0.39-1.15]), recurrent stroke (OR, 0.89 [95% CI, 0.57-1.38]), and recurrent ischemic stroke (OR, 1.09 [95% CI, 0.68-1.73]) between the IVT and BMT group. There were differences between the IVT group and the BMT group in terms of early neurological deterioration (OR, 1.81 [95% CI, 1.17-2.80]), symptomatic intracranial hemorrhage (OR, 7.48 [95% CI, 3.55-15.76]), and hemorrhagic transformation (OR, 4.73 [95% CI, 2.40-9.34]). Comparison of modified Rankin Scale score of 0 to 1 remained unchanged in subgroup patients with nondisabling deficits or compared with those using antiplatelets.

Conclusions: These findings indicate that IVT does not yield significant improvement in the functional prognosis of patients with acute minor ischemic stroke. Additionally, it is associated with an increased risk of symptomatic intracranial hemorrhage when compared with the BMT. Moreover, IVT may not have superiority over BMT in patients with nondisabling deficits or those using antiplatelets.

in patients who do not receive sue plasminogen activator because of ing ischemic stroke

llah, Iva Petkovska, Eric Rosenthal, Walter J Koroshetz, Lee H Schwamm

61/01.STR.0000185798.78817.f3

ome patients with mild or improving ischemic stroke symptoms do not sminogen activator (tPA) because they look "too good to treat" (TGT); tcomes.

analyzed data from a prospective single-center study between 2002 and e arriving within 3 hours of symptom onset and not treated with se of mild or improving symptoms.

enting within 3 hours, 41 (34%) were not given tPA because of mild or patients, 11 of 41 (27%) died or were not discharged home because of or persistent "mild" neurological deficit (n=5). No single variable at with death or lack of home discharge. There were 10 of 41 TGT patients improvement in National Institutes of Health Stroke Scale score before ere more likely to have subsequent neurological worsening (relative risk, 5).

inority of patients deemed too good for intravenous tPA were unable to aluation of the stroke severity criteria for tPA eligibility may be indicated.

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High BP

How high is too high?

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2. Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their SBP is <185 mm Hg and their diastolic BP is <110 mm Hg before IV fibrinolytic therapy is initiated.	I	B-NR

Table 5. Options to Treat Arterial Hypertension in Patients With AIS Who Are Candidates for Emergency Reperfusion Therapy*

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
Other agents (eg, hydralazine, enalaprilat) may also be considered	

IV tPA

tenecteplase vs alteplase

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IV push over 5 seconds (compared to 60-second bolus + 60-minute alteplase infusion)

Less prone to dosing errors = 0.25 mg/kg IV (max 25 mg)

More specific mechanism of action and longer half-life

Potential to reduce key system metrics (DTN time)

Lower average wholesale price (~$2000 less per dose)

THE L

his journal Journ

ARTICLES · Volume 4

Intravenous in
Canada (AcT
randomised

Prof Bijoy K Menon,
Mohammed A Alme

» Author Affiliations | Article Information

JAMA. 2020;323(13):1257-1265. doi:10.1001/jama.2020.1511

om-effects

What if his CTA head/neck also shows left PCA occlusion?

Articles

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Dieder
Aad van der Lugt, Maria A de Miquel, Geoffrey A Donnan,
Lucie A van den Berg, Elad I Levy, Olvert A Berkhemer, Vit
Luis San Román, Marc Ribó, Debbie Beumer, Bruce Stouc
Michael D Hill, Tudor G Jovin, for the HERMES collaborat

5. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.

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Case #2

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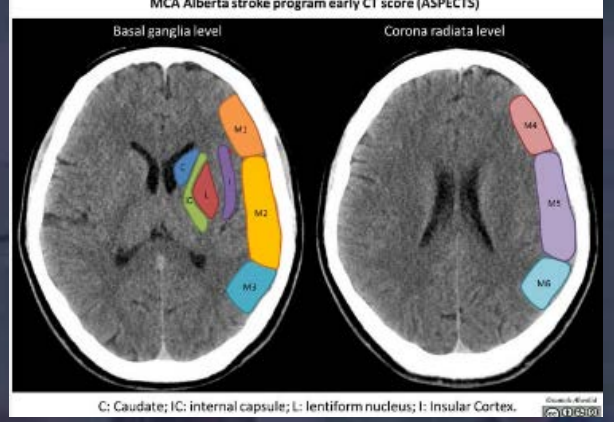
65 year old right handed man, with HTN and HLD, presented to our ED with multiple neurologic symptoms. While at work 5 hours ago he suddenly developed right sided vision loss, right sided weakness, unable to speak, unable to follow instructions, and looking to the left with both eye. He does not take any antithrombotics. On exam he is hypertensive with BP 190/110mmHg and HR 75bpm, and has global aphasia, right facial dense weakness, left gaze preference but can overcome with oculocephalic reflex, homonymous right hemianopia, right upper extremity hemiplegia, right lower extremity hemiparesis, right hemihypoesthesia, and Babinski reflex on the right.

What do we do here?



Last known well time: 5 hours ago

Symptoms: left MCA syndrome

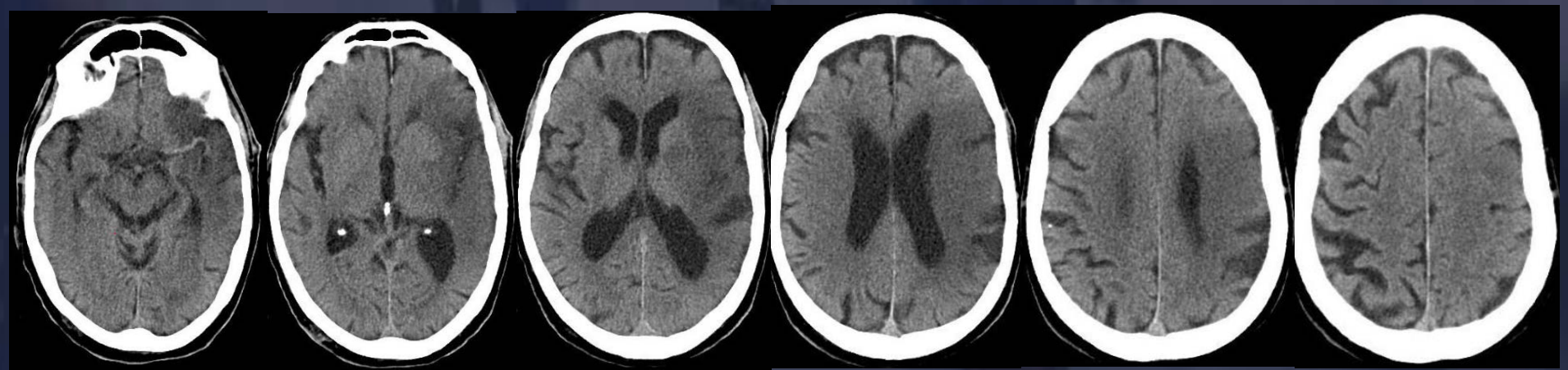
NIHSS score: 19

NC-HCT: large evolving acute ischemic changes in the left MCA territory, approx. 90cc

ASPECTS: 4

CTA head/neck: left MCA M1 occlusion

Fibrinolytic Therapy considerations: >4.5hrs from LKWT, high NIHSS score, BP >185/110mmHg, low ASPECTS, large evolving core infarct >70cc



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Wake-up and unknown time of onset	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) administered within 4.5 h of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 h from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (*COR IIa; LOE B-R*)‡

Suggestions for using neuroimaging to aid selection of patients for thrombolysis and thrombectomy in later time windows

CTP	CTP core < 70 mL	CTP core 70-100 mL	CTP core > 100 mL
Late presenter tPA (ALT or TNK) - Wake up - LKW > 4.5 hours - Unknown LKW < 24 hours	Use for non-LVOs. Consider for LVOs. Do not administer if it will delay EVT.	Avoid	Avoid
Endovascular therapy (EVT) - LKW > 6 hours	Yes	Strongly consider	May consider

4 moderately severe disability, 5 severe disability, and 6 death.

Christopher R. Levi, M.B., B.S., Chung Hsu, Ph.D., Timothy J. Kleinig, Ph.D., +38, for the EXTEND Investigators* Author Info & Affiliations

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ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Suggestions for using neuroimaging to aid selection of patients for thrombolysis and thrombectomy in later time windows

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Endovascular therapy (EVT) - LKW > 6 hours	Yes	Strongly consider	May consider

randomised trial

Martin Bendszus, Jens Fiehler, Fabien Subtil, Susanne Bonekamp, Anne
Antonin Krajina, Laurent Pierot, Claus Z Simonsen, Kamil Zeleňák, Rolf
Franziska Dorn, Fabian Flottmann, Susanne Gellißen, Johannes C Gerbe
Vi Tuan Hua, Märit Jensen, Andreas Kastrup, Christiane Fee Keil, Andrej
Stefan Müller-Hülsbeck, Nico Münnich, Paolo Pagano, Panagiotis Papa
Gernot Reimann, Peter Arthur Ringleb, Maximilian Schell, Eckhard Schl
Eva Vítková, Dominik F Vollherbst, Wolfgang Wick, Götz Thomalla, on b

Better functional status (mRS score shift)	4.7	3.7 to 6.6
Independent walking (mRS score 0–3)	7.1	5.6 to 9.6
Functional independence (mRS score 0–2)	10.6	8.2 to 14.8

Take Home Points:

What is stroke, TIA, and infarct?

Stroke is a symptom and is a clinical diagnosis. TIA is a stroke scare with COMPLETE clinical resolution and no imaging findings.

What causes stroke?

Understanding the mechanism will point you in the correct direction for investigations/etiology/acute and secondary stroke prevention.

How do we treat stroke?

-How mild is too mild? (severity of stroke)

No stroke is too 'mild' to treat if disabling.

-How high is too high? (BP)

Just treat it with a drip if not responding to IVP.

-Which IVtPA is better? (tenecteplase vs alteplase)

Tenecteplase is as safe and effective, and may be a little better in LVO pts, but is also cheaper and is easier to administer.

-How small is too small? (LVO/MVO/SVO)

Can reach fairly distant branches with new endovascular toys.

-How big is too big? (large core infarcts)

IVtPA- <70cc; EVT- no volume is too large

-How late is too late? (late presenter IVtPA 4.5-24hrs)

IVtPA- 4.5-24hrs (CTP/MRI); EVT- 6-24hrs (+/- CTP/MRI)

Thank you

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Mr. Tanner Ian Andrews

70y/o M with a history of HTN and Diabetes

30 min right hand weakness - resolved

BP on presentation 140/85

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TIA

Occurs when there is ischemia WITHOUT acute infarction of brain, spinal cord, or retina causing transient neurologic deficits

Negative imaging

Previous definition involved timing of symptoms (<24 hours) no longer used

MINOR STROKE

No unified definition, but involves infarction of brain, spinal cord or retina with a low NIHSS

NIHSS ≤ 3 for DAPT

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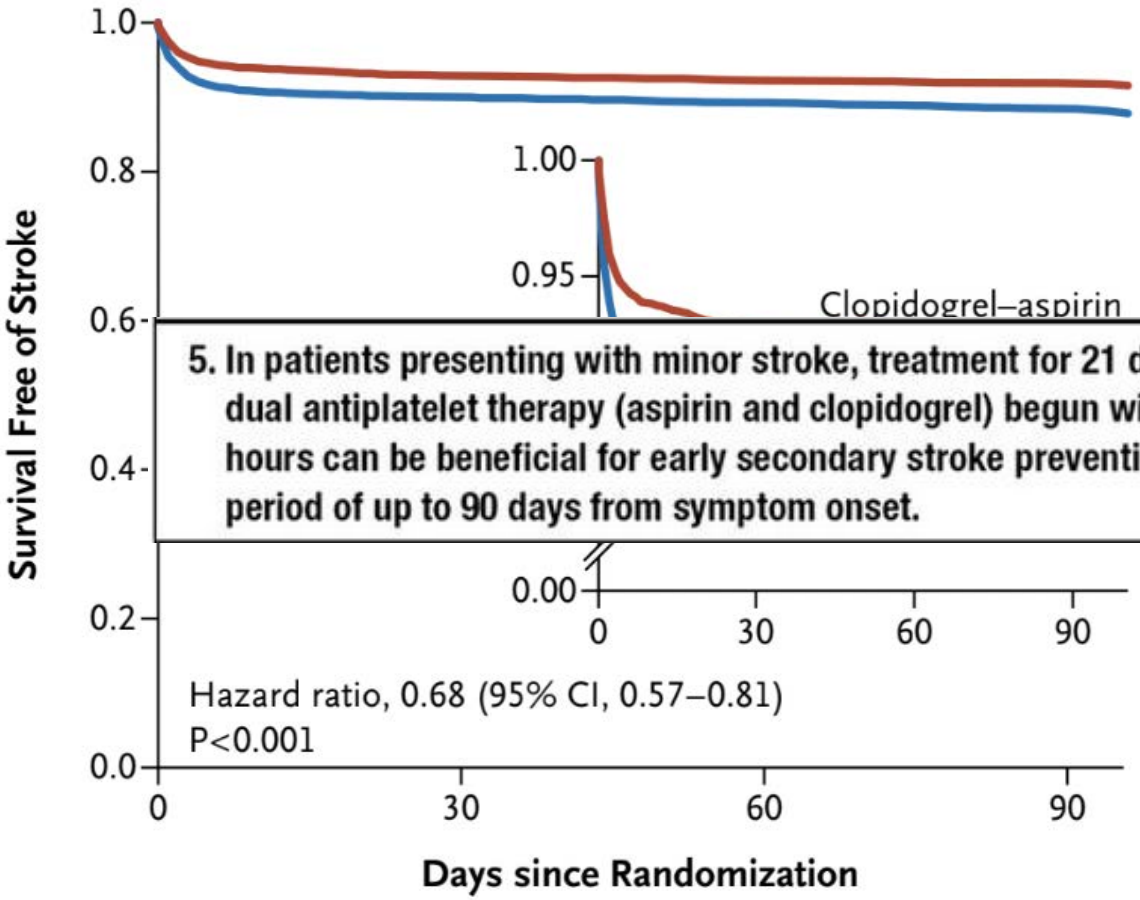
CHANCE, 2013 NEJM



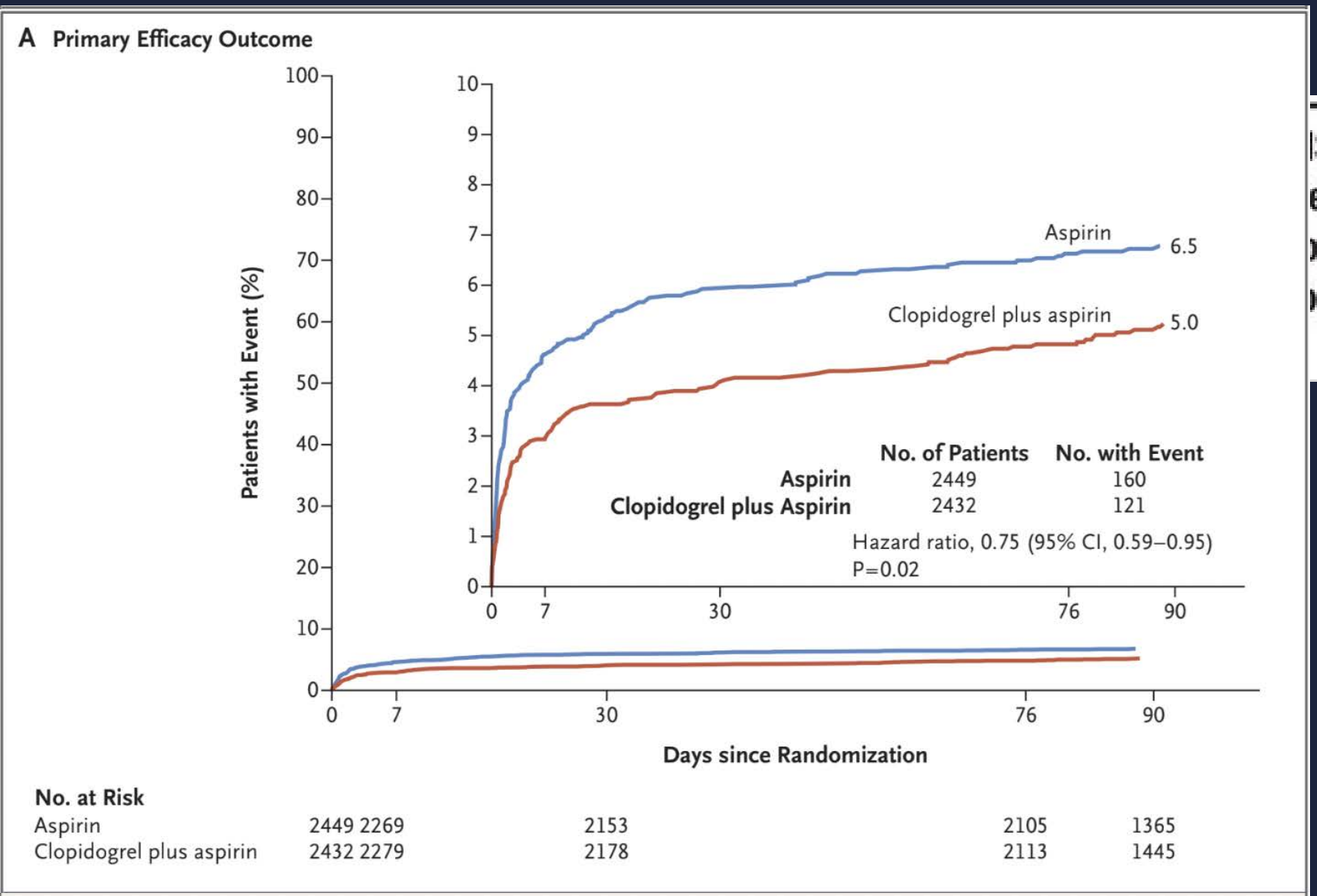
No. at Risk

Aspirin	2586	2307	2287	1906
Clopidogrel–aspirin	2584	2376	2361	1989

5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.

IIa	B-R

POINT, 2018 NEJM



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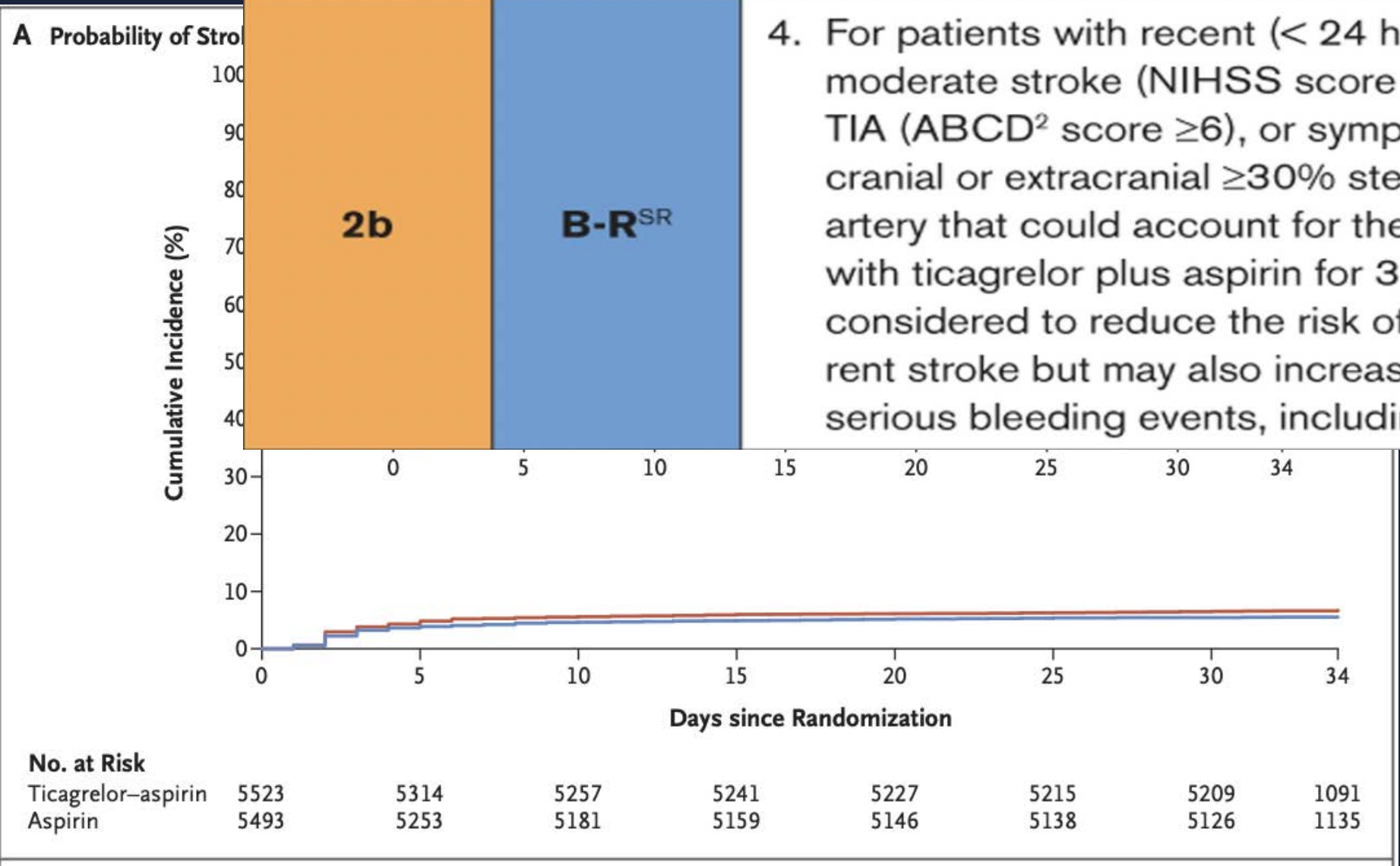
THALES, 2020 NEJM

2b

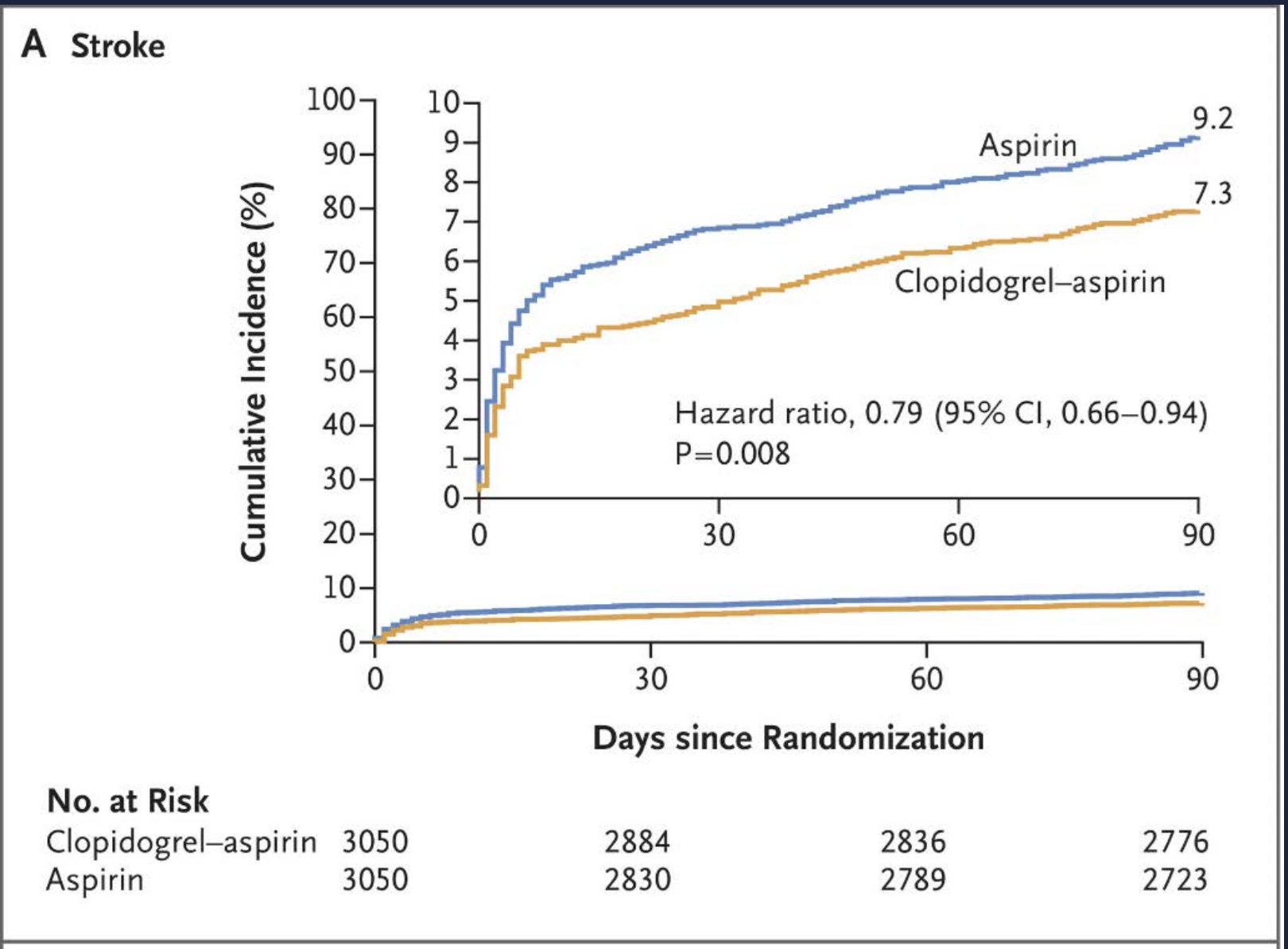
B-R^{SR}

4. For patients with recent (< 24 hours) minor to moderate stroke (NIHSS score ≤5), high-risk TIA (ABCD^2 score ≥6), or symptomatic intracranial or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including ICH.[797]



1	A[SR]	3. For patients with recent minor (NIHSS score ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD^2 score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12–24 hours of symptom onset and at least within 7 days of onset) and continued for 21 to 90 days, followed by SAPT, to reduce the risk of recurrent ischemic stroke.[382,384,410,795,796]

INSPIRES, 2023 NEJM



Dual Antiplatelet Therapy (DAPT)

ABCD2 ≥ 4 OR NIHSS ≤ 3 (non-embolic AIS)

Aspirin/Clopidogrel

Initiate within 72 hours of symptom onset
- **LOAD: 324mg/300mg, Cont 81mg/75mg**
- **Per Guidelines: May be started within 7 days**

Stop after 21-90(?) days of treatment

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Mrs. Andrea Fibiloli

83 y/o F with known history of A. Fib and previous stroke on DOAC.

Presents to the ER with symptoms of new acute stroke

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CARDIOEMBOLIC STROKE

DOAC for NVAF, even in obese patients

No DOAC for ESUS

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ATRIAL FIBRILLATION AND RECURRENT STROKE

Oral AC reduces risk of AIS by 60 - 70%

Residual Risk 1.4% - 8.9% per year

No indication to switch agents or add antiplatelets with repeat stroke

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SEIFFGE ET AL, 2020 ANNALS OF NEUROLOGY

TABLE 3. Observed and Annualized Rates of Outcome Events in Patients with $OAC_{changed}$ and $OAC_{unchanged}$ and Univariate and Multivariate Analysis

	$OAC_{changed}$, n = 307		$OAC_{unchanged}$, n = 585		Univariate		Multivariate[a]	
	Events, n[b]	Annualized Rate (95% CI)	Events, n[b]	Annualized Rate (95% CI)	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
AIS	28	8.8 (5.9–12.4)	47	8.2 (6.1–10.7)	1.1 (0.7–1.7)	0.749	1.2 (0.7–2.1)	0.415
ICH	4	1.3 (0.3–3.2)	13	2.3 (1.2–3.8)	0.6 (0.2–1.8)	0.346	0.8 (0.2–3.2)	0.793
Mortality	19	5.9 (3.6–9.1)	66	11.5 (9.0–14.4)	0.5 (0.3–0.9)	0.012	0.7 (0.4–1.2)	0.177

shm
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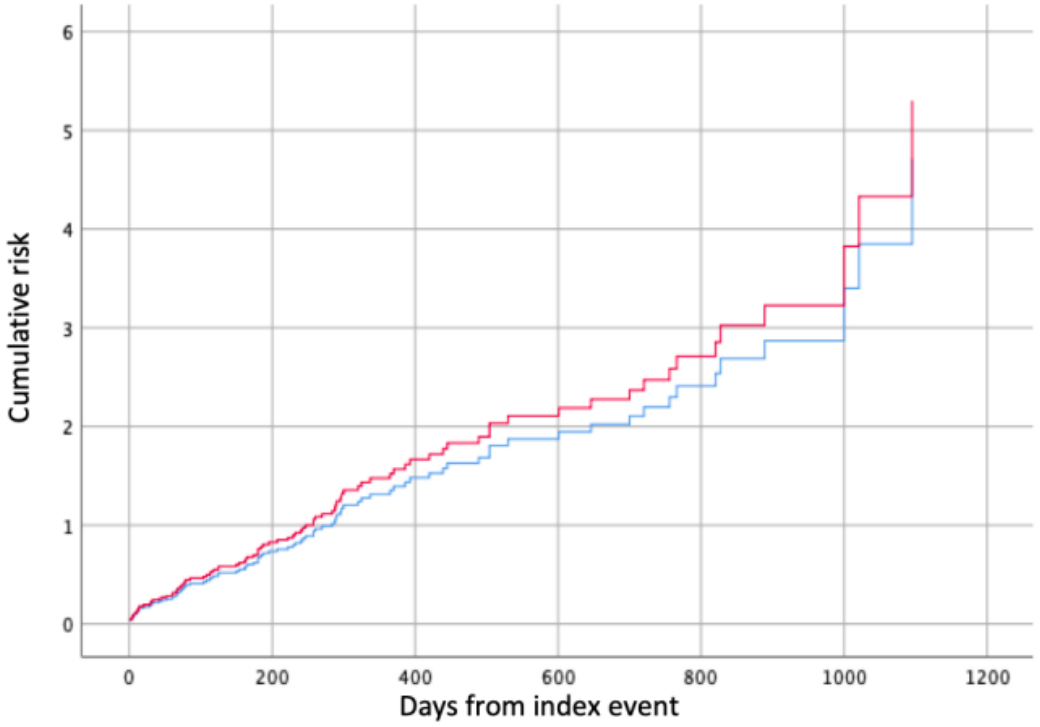
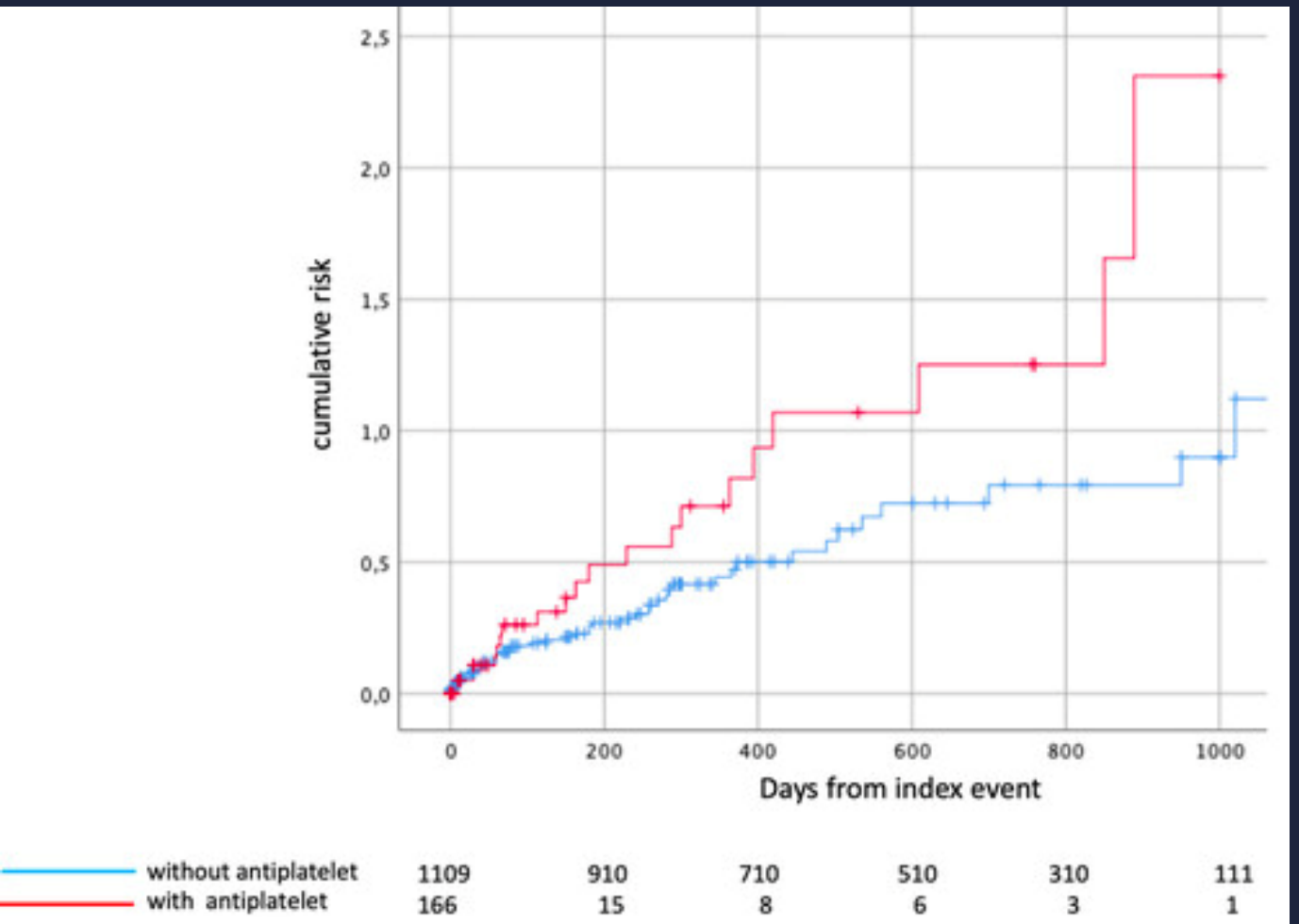
RENO-EXTEND, 2022 STROKE



Combined endpoint: ischemic stroke, systemic embolism, intracranial bleeding and major extracranial bleeding (change versus no change)
Cox regression: HR 1.1 (95% CI 0.8-1.7)

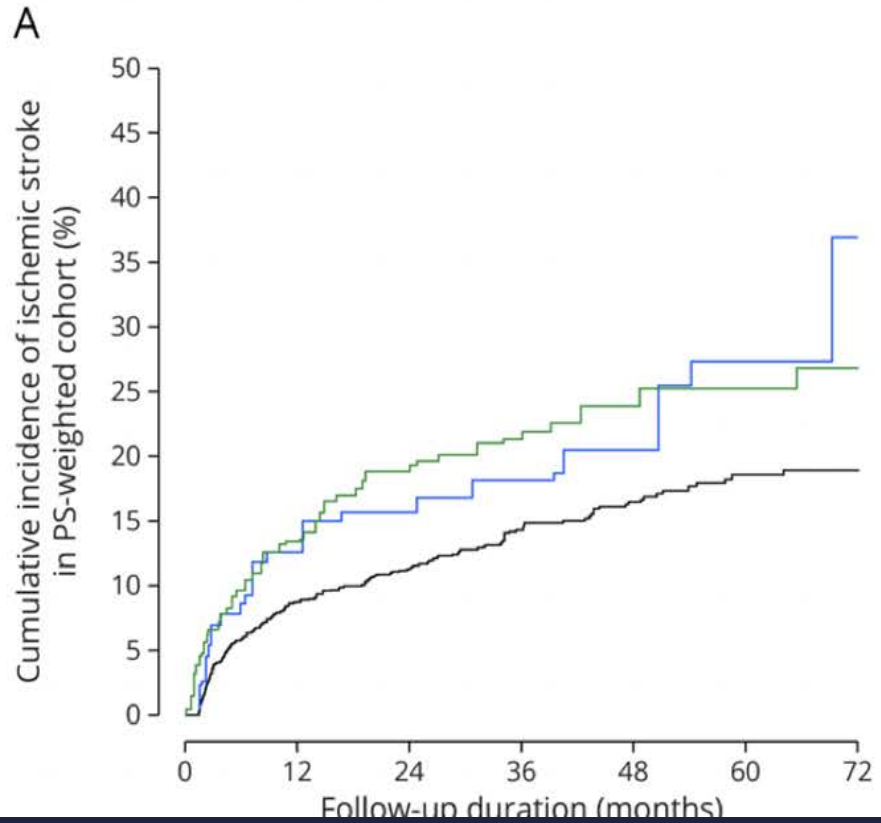
no change
change

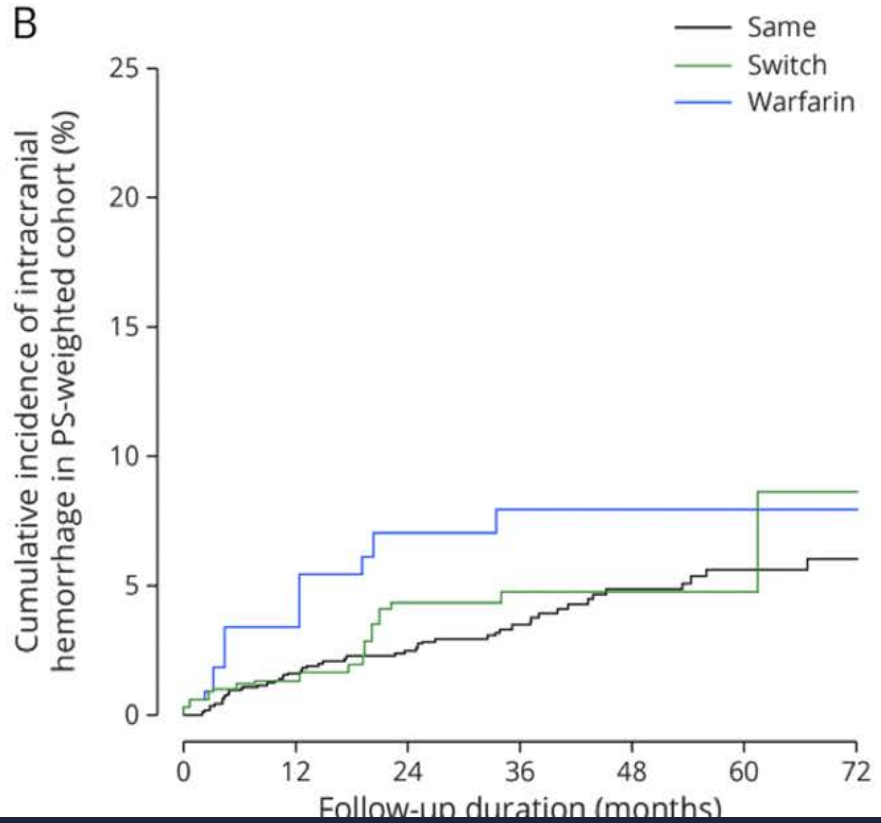
RENO-EXTEND, 2022 STROKE



Hemorrhagic endpoint: intracranial bleeding and major extracranial bleeding (NOAC with or without antiplatelet therapy)
OR 2.8 (95% 1.4-5.5)
Log Rank (Mantel – Cox): p=0.04

IP ET AL, 2023 NEUROLOGY





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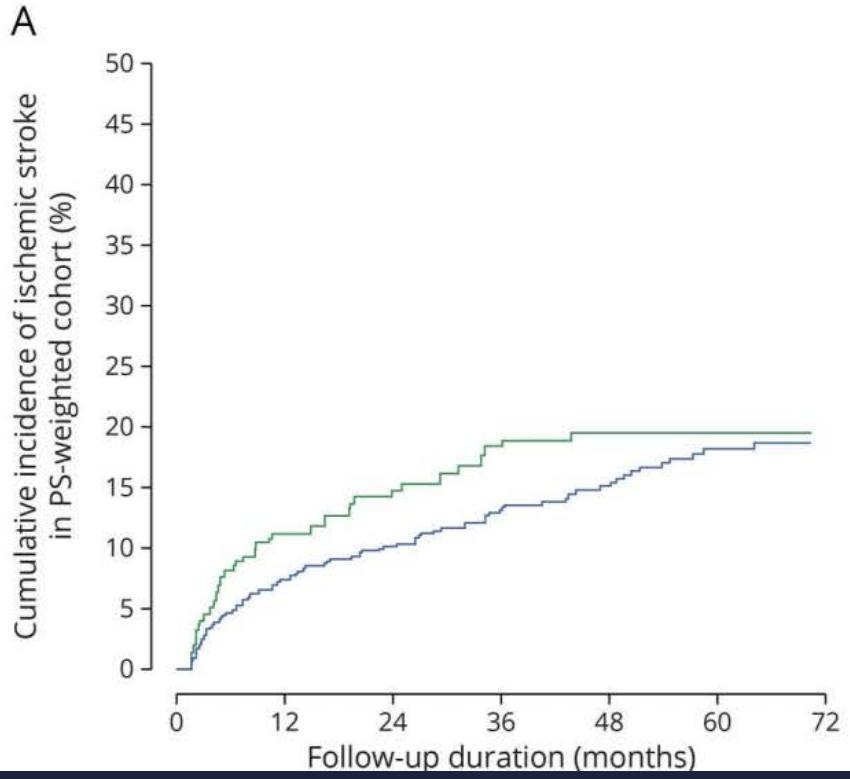
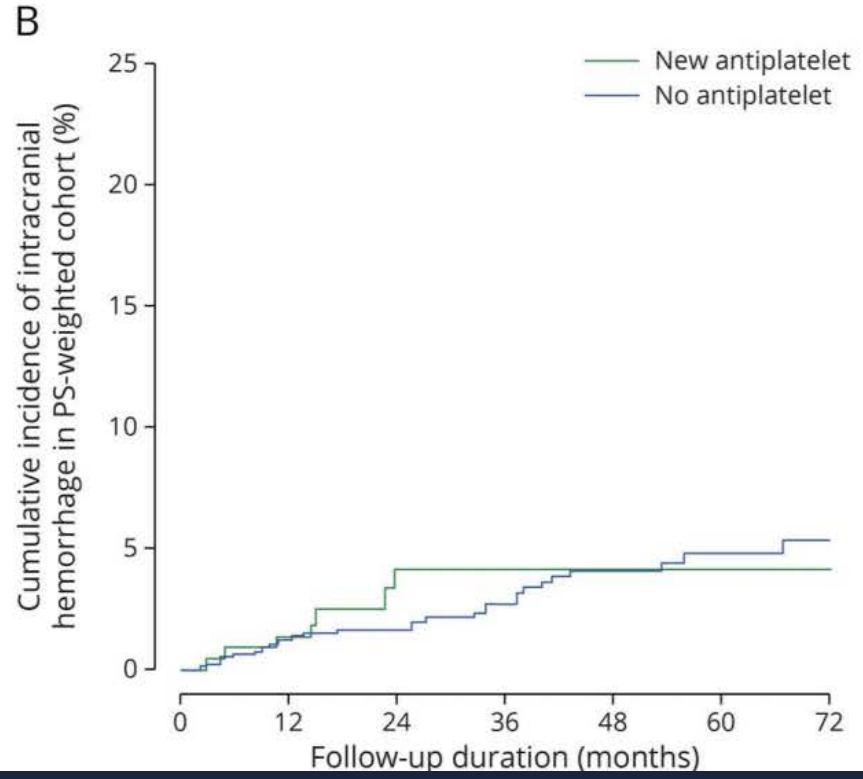
IP ET AL, 2023 NEUROLOGY





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Thank you

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