THE WARREN ALPERT
Medical School
BROWN UNIVERSITY

Rhode Island STROKE SYMPOSIUM

Are there contraindications to Thrombolysis?

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DISCLOSURE

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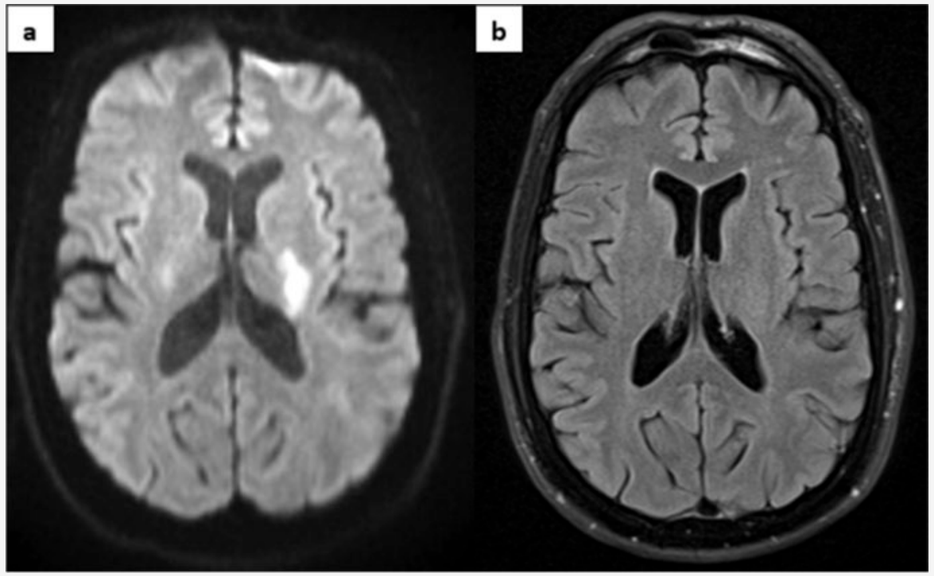
What are **indications** for thrombolysis in acute ischemic stroke?

1) Presentation within 4.5 hours of last known well or stroke onset
   *Wake up stroke or unwitnessed onset beyond 4.5 hours with MRI DWI-FLAIR mismatch and meets WAKE-UP trial criteria

2) Non contrast CT or MRI head to rule of presents of intracranial hemorrhage

3) Clearly disabling deficit, regardless of NIHSS



Powers et al., *Stroke.*, 2019

What are **absolute contraindications** for thrombolysis in acute ischemic stroke?

Class III recommendations:

1. Intracranial hemorrhage on CT/MRI at baseline
2. Non-disabling deficit
3. Ischemic stroke within 3 months
4. Severe head trauma within 3 months
5. Intracranial/intraspinal surgery within 3 months
6. History of ICH
7. Obvious hypoattenuation on CT
8. GI bleeding within 21 days
9. Coagulopathy – Platelet >100000/cumm; INR >1.7
10. Full treatment dose LMWH within 24 hours
11. Thrombin or factor Xa inhibitors within 48 hours
12. Concomitant abciximab or iv aspirin
13. Aortic dissection
14. Intraaxial neoplasm

Powers et al., *Stroke.*, 2019

What are **relative contraindications** for thrombolysis in acute ischemic stroke?

Class IIb recommendations, decision based on stroke severity and on a case-by-case basis:

1) Major surgery within 14 days
2) Blood glucose <50 or >400 mg/dL
3) Dural puncture within 7 days
4) Arterial puncture within 7 days
5) Major extracranial trauma within 14 days
6) Past GI/GU bleeding
7) Intracranial arterial dissection
8) Unruptured intracranial aneurysm
9) Known cerebral microbleed burden >10
10) Acute pericarditis
11) Acute or Recent MI within 3 months
12) Pregnancy
13) Sickle Cell disease
14) Stroke mimics

Powers et al., *Stroke.*, 2019

Non-disabling deficits

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Does intravenous alteplase benefit patients with ischemic stroke presenting with minor neurologic deficits judged not clearly disabling?

CONCLUSION The study did not demonstrate a significant benefit of alteplase for patients with minor nondisabling acute ischemic stroke, but early study termination precludes definitive conclusions.

POPULATION

169 Men

144 Women

Patients with acute ischemic stroke and minor deficits (NIHSS scores 0-5) judged not clearly disabling at presentation by local investigators

Mean age: **62** years

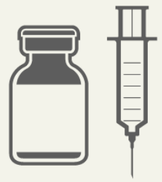
LOCATIONS

53
US Stroke networks

INTERVENTION

313 Patients enrolled

156



Alteplase
0.9 mg/kg within 3 hours of stroke onset

157

Aspirin
325 mg within 24 hours of stroke onset

PRIMARY OUTCOME

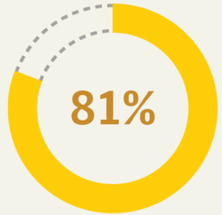
Difference in favorable functional outcome, defined as a modified Rankin Scale (mRS) score of 0 or 1 at 90 days

FINDINGS

Favorable functional outcomes at 90 days

Alteplase

Aspirin



Adjusted absolute risk difference:

-1.10%

(95% CI, -9.44% to 7.25%)

Khatri P, Kleindorfer DO, Devlin T, et al; for the PRISMS Investigators. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial [published July 10, 2018]. *JAMA*. doi:10.1001/jama.2018.8496

Non-disabling deficits

JAMA®

QUESTION Is dual antiplatelet therapy (DAPT) noninferior to intravenous thrombolysis in patients with minor nondisabling acute ischemic stroke?

CONCLUSION Among patients with minor nondisabling acute ischemic stroke presenting within 4.5 hours of symptom onset, DAPT, compared with intravenous alteplase, met the criteria for noninferiority with regard to excellent functional outcome at 90 days.

POPULATION

496 Women
223 Men

Adults with acute minor nondisabling stroke (National Institutes of Health Stroke Scale score ≤5)

Median age: **64** years

LOCATIONS

38
Hospitals
in China

INTERVENTION

760 Patients randomized
719 Patients analyzed

393
DAPT
Loading doses of clopidogrel and aspirin, followed by daily doses, and guideline-based antiplatelet treatment

367
Alteplase
Intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg) followed by guideline-based antiplatelet treatment

PRIMARY OUTCOME

Excellent functional outcome, defined as a modified Rankin scale score (range, 0 [no symptoms] to 6 [death]) of 0 or 1, at 90 days

FINDINGS

Patients with excellent functional outcome at 90 days

DAPT	Alteplase
93.8%	91.4%
(346 of 369 patients)	(320 of 350 patients)

DAPT was noninferior to intravenous alteplase:

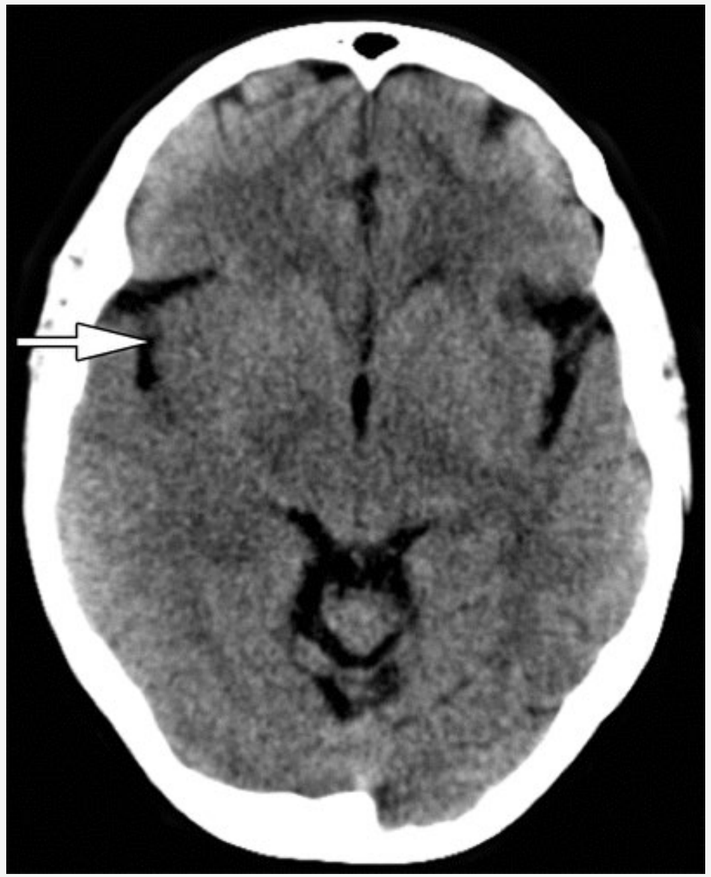
Risk difference of having excellent outcome at 90 days,

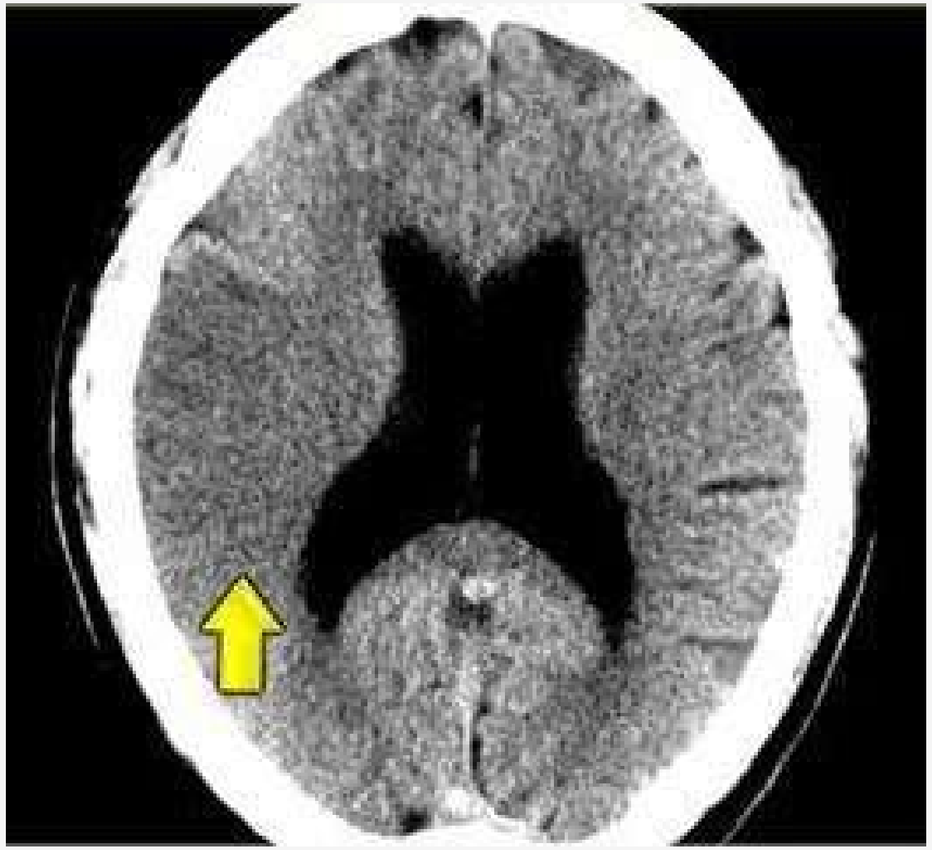
2.3% (unadjusted 95% CI, −1.5% to 6.2%);
P value for noninferiority < .001

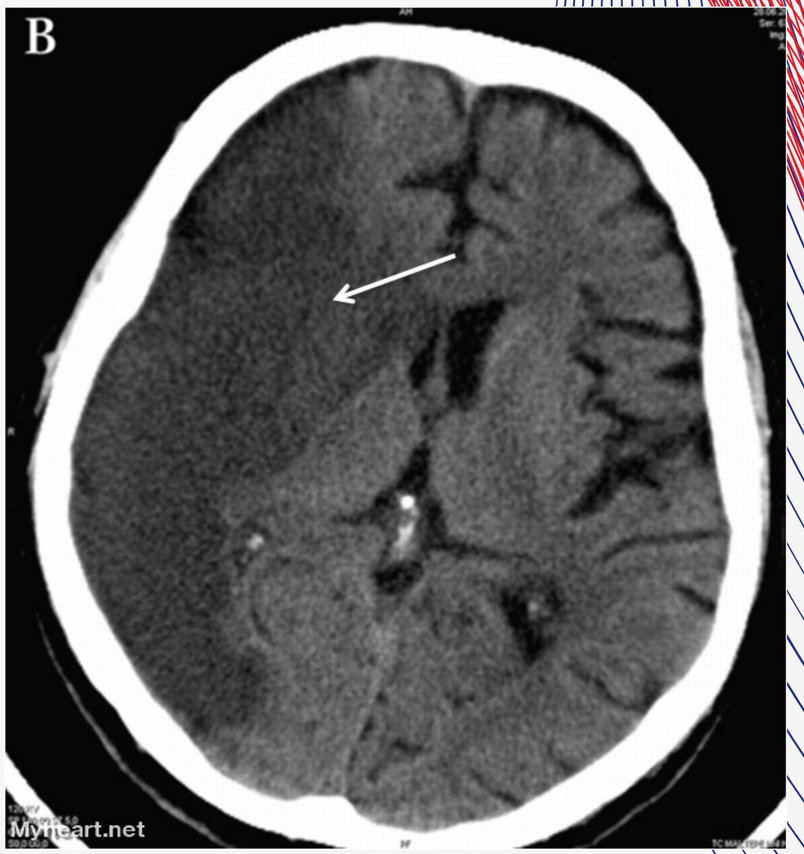
Chen H, Cui Y, Zhou Z, et al; for the ARAMIS Investigators. Dual antiplatelet therapy vs alteplase for patients with minor nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA*. Published June 27, 2023. doi:10.1001/jama.2023.7827

CT Hypodensity

There is no specific data-guided threshold of extent and severity of ischemic changes beyond which thrombolysis is not beneficial

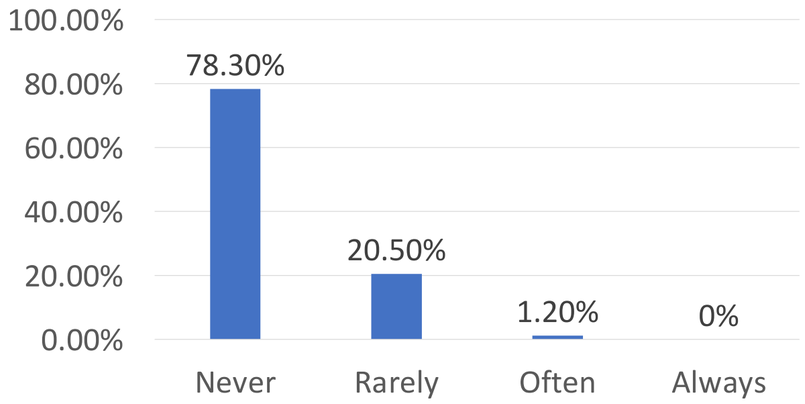




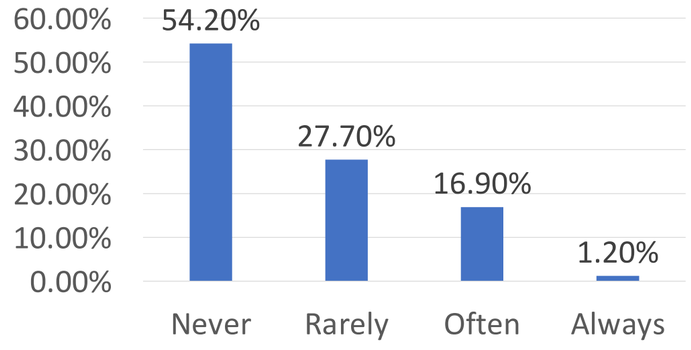


Thrombin or factor Xa inhibitors within 48 hours

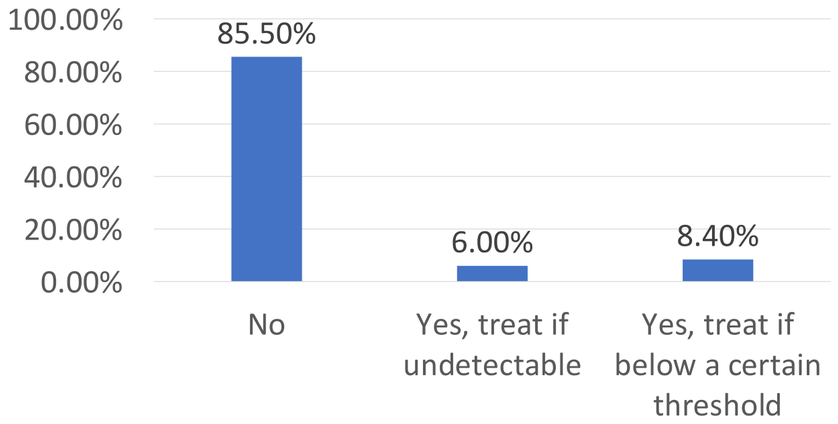
How often do you give intravenous thrombolysis in otherwise eligible patients with suspected acute ischemic stroke but with a known oral ingestion of a direct oral anticoagulation within 12-24 hours prior to presentation?



How often do you give intravenous thrombolysis in otherwise eligible patients with suspected acute ischemic stroke but with a known oral ingestion of a direct oral anticoagulation within 24-48 hours prior to presentation?



Do you use an anti-Xa assay level or drug level to make thrombolysis treatment decisions in patients with suspected acute ischemic stroke but who ingested a direct oral anticoagulant within 48 hours?



Yaghi et al., *Unpublished*

Thrombin or factor Xa inhibitors within 48 hours

No randomized clinical trials; only retrospective, observational data available

Most of the studies have evaluated NOAC use within 7 days preceding the stroke
Only few studies evaluate thrombolysis within 48 hours of NOAC use

Table 3. Outcomes of Patients With Acute Ischemic Stroke Treated With Intravenous Thrombolysis by Selection Strategy

Outcome	Controls (n = 32 035)	All patients with recent ingestion of DOACs (n = 832)	DOAC plasma levels measured (n = 225)	Idarucizumab (n = 252)	Neither known levels nor idarucizumab (n = 355)
Primary outcome					
Symptomatic intracranial hemorrhage within 36 h, % (95% CI)	4.1 (3.9-4.4)	2.5 (1.6-3.8)	3.1 (1.3-6.3)	1.2 (0.2-3.4)	3.1 (1.6-5.5)
Unadjusted OR (95% CI)	NA	0.62 (0.40-0.96)	0.66 (0.31-1.40)	0.30 (0.09-0.92)	0.84 (0.46-1.53)
P value	NA	.03	.28	.04	.56
Adjusted OR (95% CI)	NA	0.57 (0.36-0.92)	0.56 (0.26-1.21)	0.36 (0.09-1.48)	0.66 (0.35-1.25)
P value	NA	.02	.14	.16	.20
Secondary outcomes					
Any hemorrhagic transformation on follow-up imaging within 36 h, % (95% CI)	17.4 (16.9-18.0)	18.0 (15.4-20.9)	20.5 (15.4-26.4)	7.8 (4.5-12.4)	22.2 (18.0-26.9)
Unadjusted OR (95% CI)	NA	1.03 (0.85-1.24)	1.23 (0.89-1.71)	0.38 (0.23-0.63)	1.40 (1.07-1.83)
P value	NA	.78	.21	<.001	.02
Adjusted OR (95% CI)	NA	1.18 (0.95-1.45)	1.13 (0.80-1.59)	0.57 (0.32-1.01)	1.58 (1.16-2.14)
P value	NA	.14	.49	.06	.003
Functional independence at 90 d, % (95% CI)	57 (56-57)	45 (41-49)	40 (33-47)	54 (46-62)	44 (38-50)
Unadjusted OR (95% CI)	NA	0.62 (0.53-0.73)	0.50 (0.37-0.67)	0.91 (0.66-1.25)	0.60 (0.48-0.74)
P value	NA	<.001	<.001	.55	<.001
Adjusted OR (95% CI)	NA	1.13 (0.94-1.36)	0.85 (0.61-1.19)	1.27 (0.84-1.91)	1.29 (0.99-1.68)
P value	NA	.20	.34	.26	.06

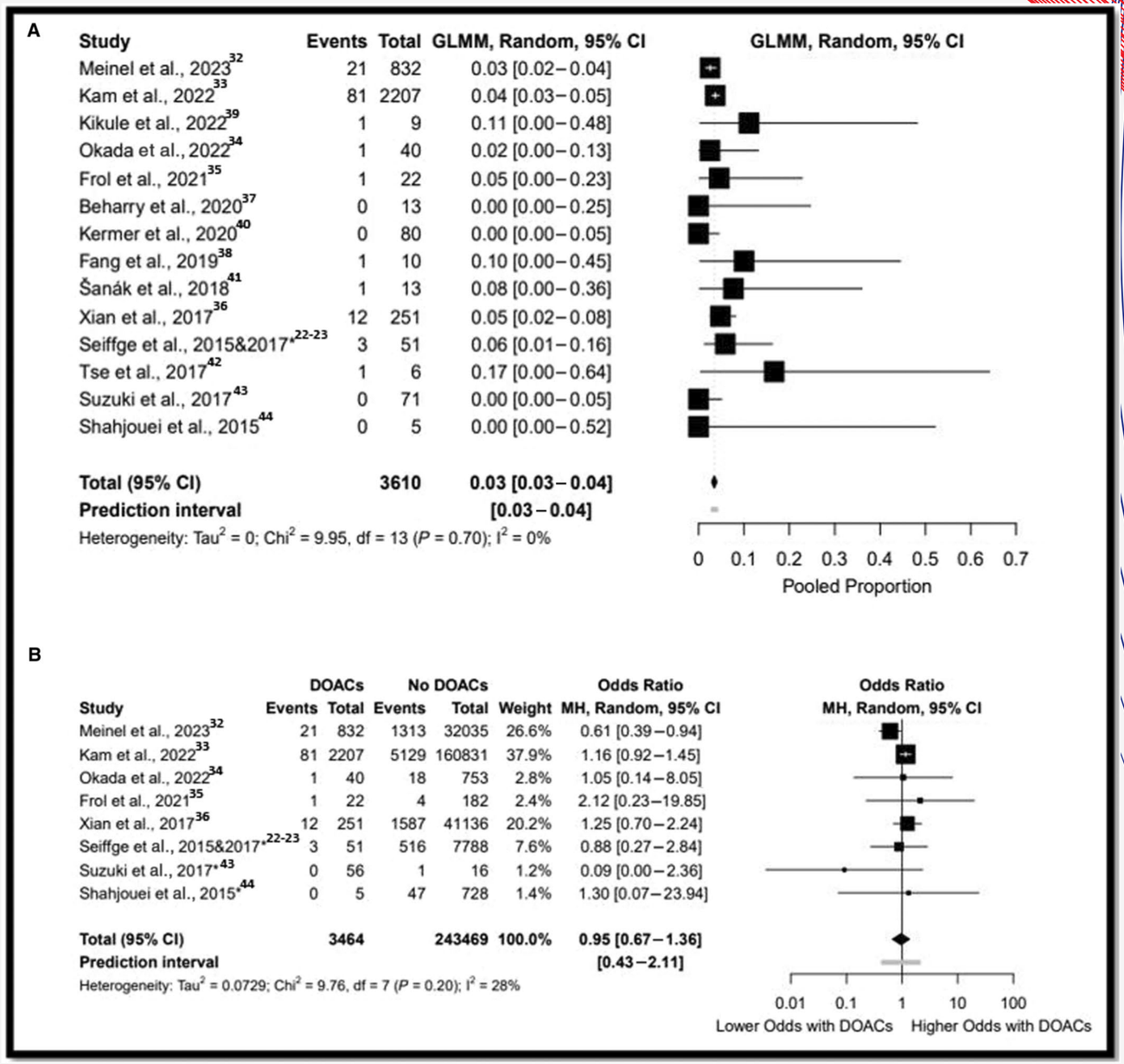
Abbreviations: DOAC, direct oral anticoagulant; NA, not applicable; OR, odds ratio.

Meinel et al., *JAMA, 2023*

Thrombin or factor Xa inhibitors within 48 hours

Meta-analysis of all published studies

sICH outcome

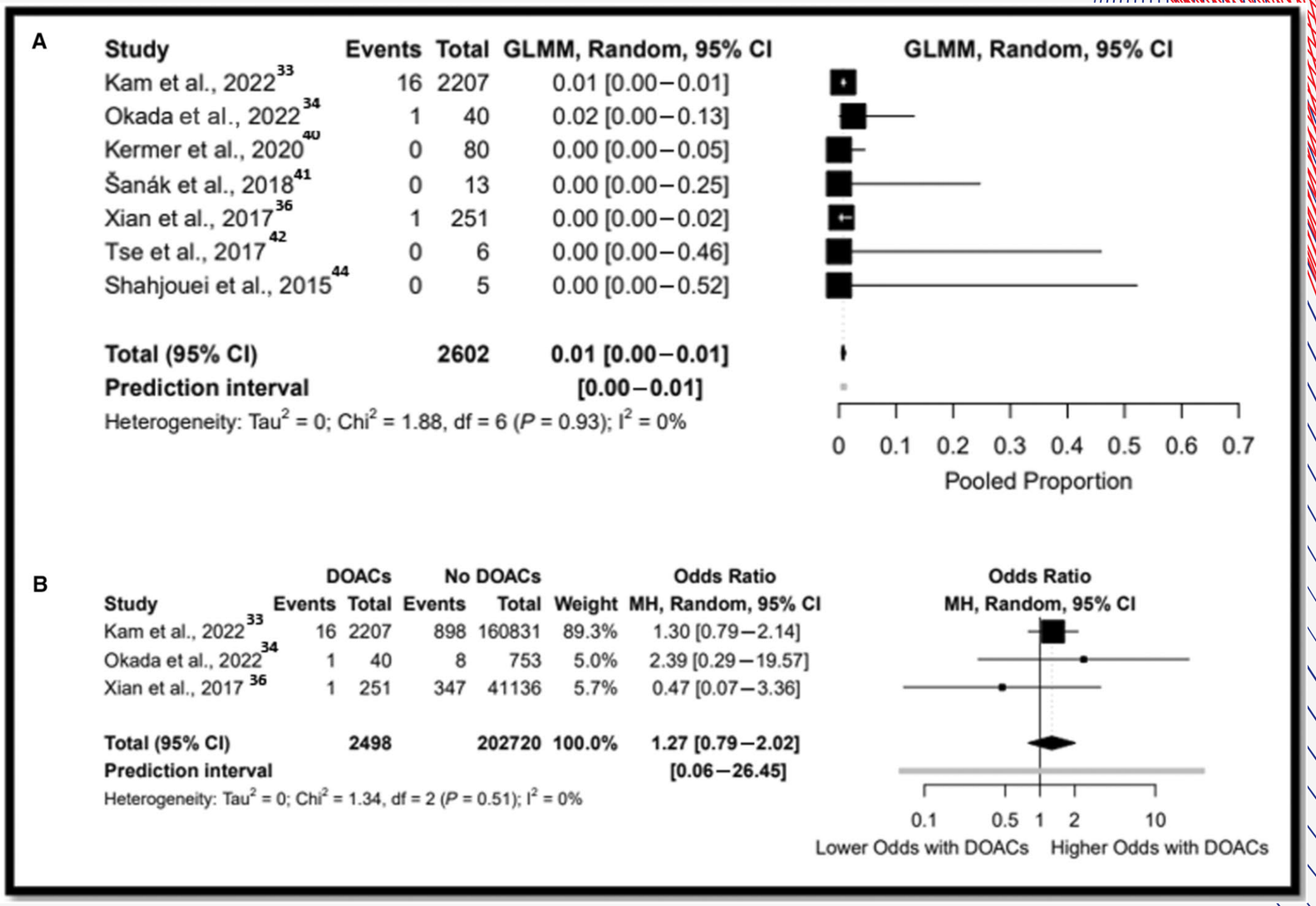


Ghannam et al., *JAHA, 2023*

Thrombin or factor Xa inhibitors within 48 hours

Meta-analysis of all published studies

Serious systemic hemorrhage outcome



Ghannam et al., *JAHA, 2023*

Pregnancy

Only case reports available

Risk of maternal complications including severe systemic hemorrhage seem comparable to non-pregnant patients receiving IVT

1.4% rate of fetal death and 6% rate of miscarriage

IVT should be considered in pregnant patients within 4.5 hours of onset or LKW if other IVT criteria are met

Multidisciplinary decision making

Ghannam et al., *JAHA, 2023*

Thank you!

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