Thrombolysis in Patients with Recent DOAC Use

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NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

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Disclosures

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Important Disclosures

- I am not an expert on this topic
- I am a Vascular Neurologist who deals with this issue on a daily basis
- I may have strong opinions/bias

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

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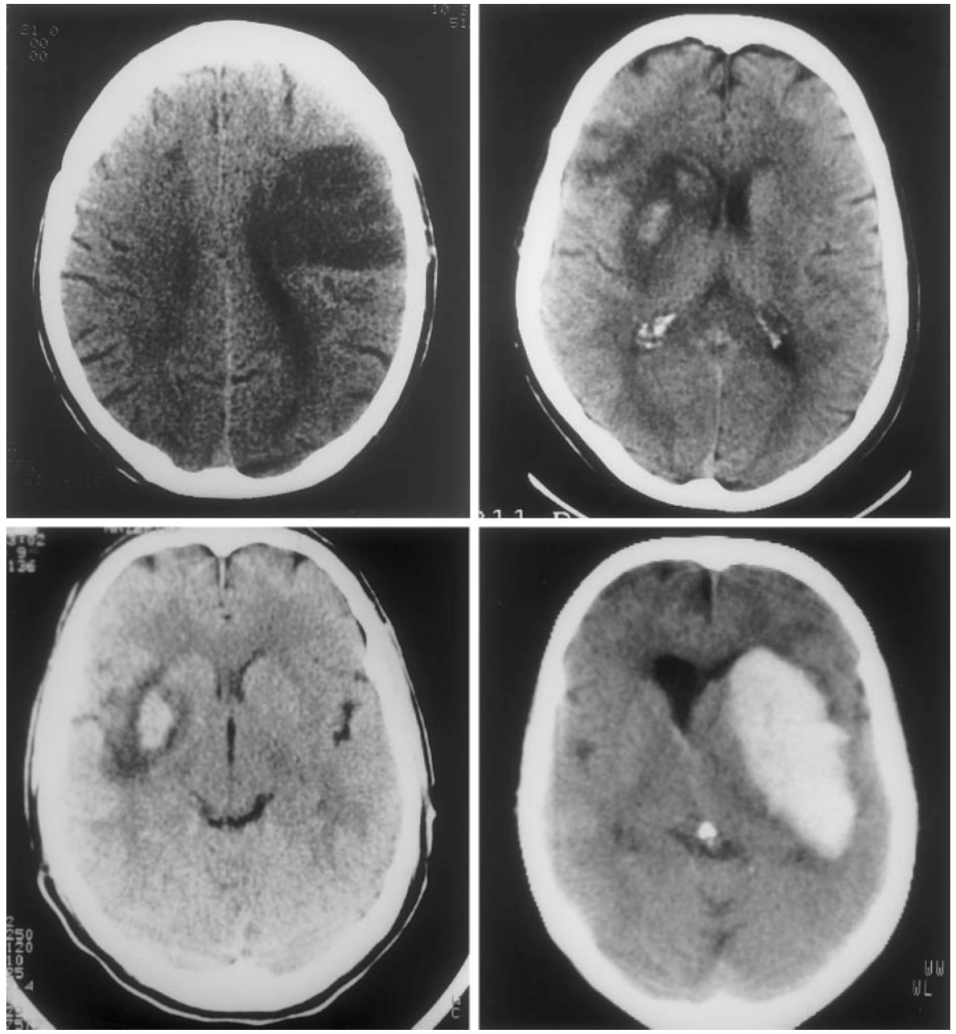
Thrombin inhibitors or factor Xa inhibitors	The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful.† (*COR III: Harm; LOE C-EO*)§‖ IV alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 h (assuming normal renal metabolizing function). (Alteplase could be considered when appropriate laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these ACs for >48 h and renal function is normal.) (Recommendation wording modified to match COR III stratifications.)



(*Stroke*. 1999;30:2280-2284.)

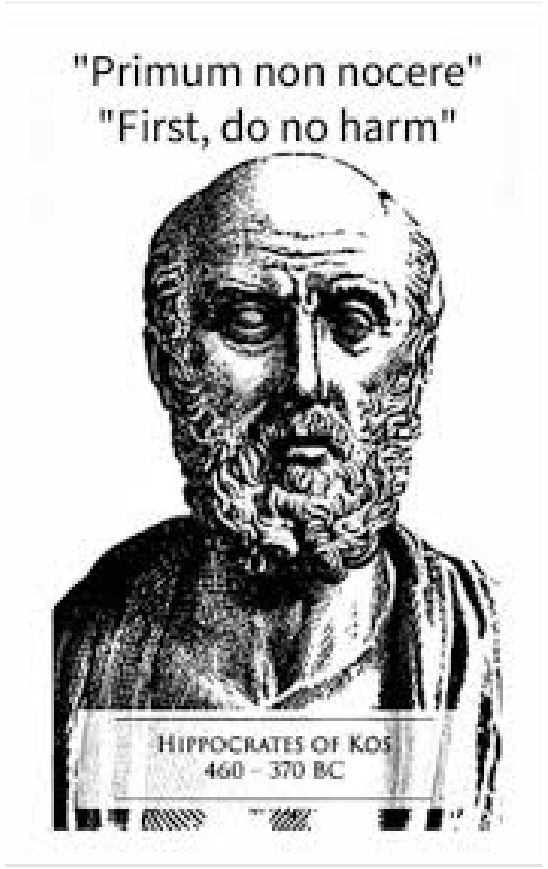
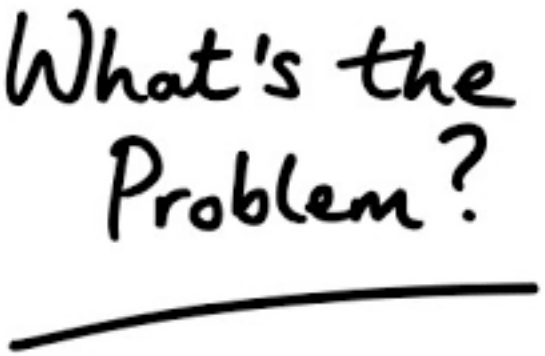
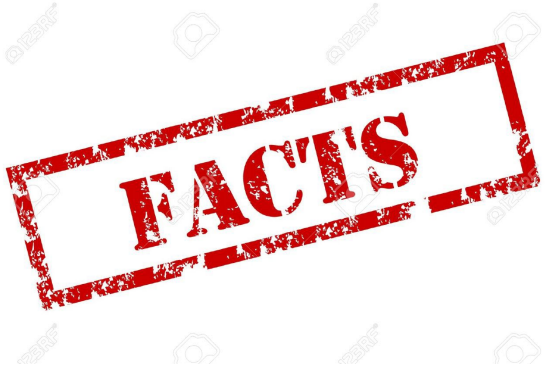


Figure 1. Subtypes of hemorrhagic transformation: HI1 (top left), HI2 (top right), PH1 (bottom left), and PH2 (bottom right).

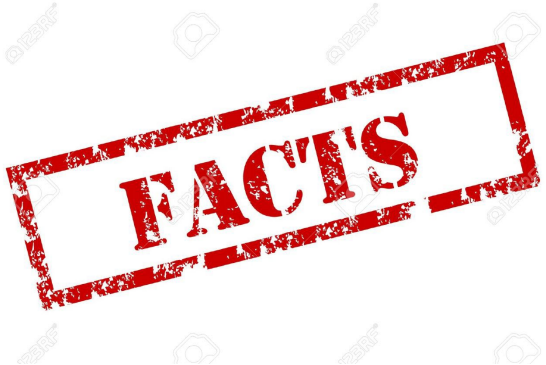


- Readily available coagulation tests (PT, PTT and INR) have poor sensitivity and specificity for determining DOACs' anticoagulation effect
  - High values may help to exclude patients on DOACs
  - Normal results are not helpful

- Plasma levels of DOACs or Anti-Xa assays are better, but processing takes a long time and they are not available in most hospitals in the US



- It is estimated that over 6 million patients in the United States are treated with anticoagulants
- Of Medicare fee-for-service beneficiaries enrolled in parts A, B and D who used oral anticoagulants, DOAC use increased steadily from 4.7% to 47.9%, while warfarin use declined from 52.4% to 17.7% in 2022.
- About 3.5 million Part D enrollees filled prescriptions for apixaban
- Indications for DOACs are increasing and the use of DOACs is rapidly rising



The mainstay treatment for acute ischemic stroke is IVT and EVT

- AFib is the most common type of cardiac arrhythmia. It has a significant global impact, affecting nearly 40 million individuals worldwide and 6 million in the United States alone.
- Incidence and prevalence of atrial fibrillation (AF) have been increasing over time
- AFib is a frequent cause of ischemic stroke particularly in the elderly
- Up to 28% of patients presenting with IS who are “taking” DOACs are potentially eligible for IVT
- In a German study, 6% of patients on DOACs, who are otherwise, eligible for IVT received it. Being on DOACs was the most cited reason for withholding IVT

Patients with AFib & ischemic stroke are at increased risk for recurrent ischemic stroke despite being on OAC

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 1807–1814
https://doi.org/10.1093/eurheartj/ehad200

CLINICAL RESEARCH
Arrhythmias

Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation

Alexander P. Benz [1,2]*, Stefan H. Hohnloser [3], John W. Eikelboom [1], Anthony P. Carnicelli [4,5], Robert P. Giugliano [6], Christopher B. Granger [4], Josephine Harrington [4], Ziad Hijazi [7], David A. Morrow [6], Manesh R. Patel [4], David J. Seiffge [8], Ashkan Shoamanesh [1], Lars Wallentin [7], Qilong Yi[9], and Stuart J. Connolly [1]; on behalf of the COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) Investigators

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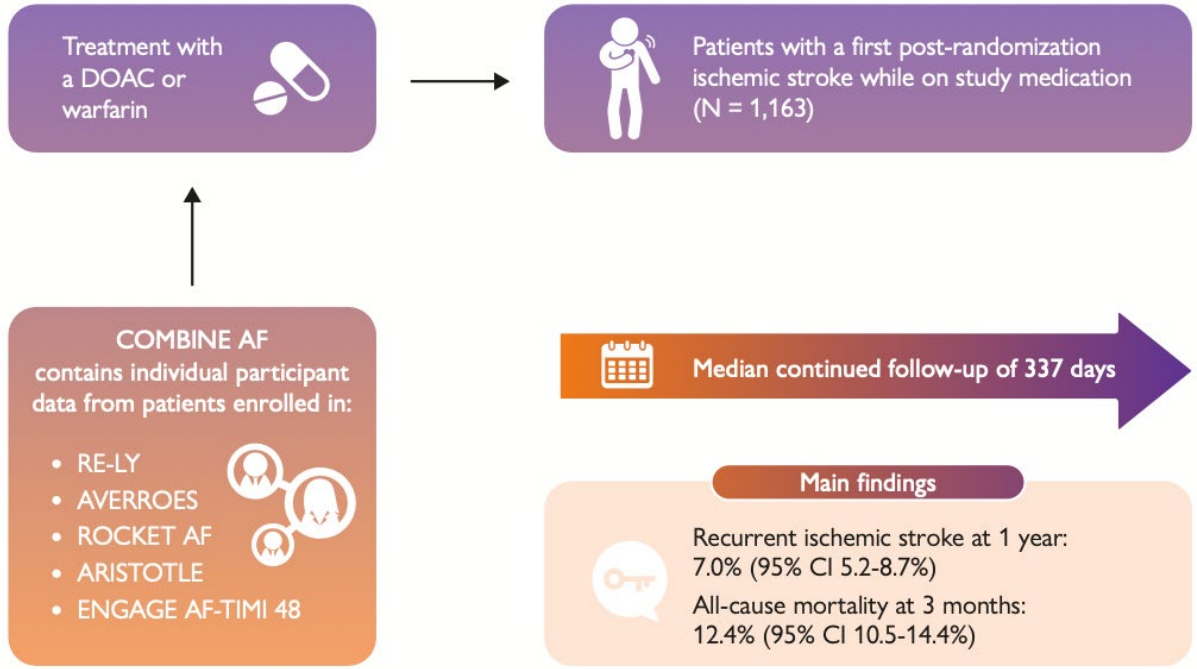
Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation



Acute ischemic stroke on anti-Xa inhibitors: Pharmacokinetics and outcomes

Colin Basso, BS,[a] Eric Goldstein, MD,[a] Xing Dai, MD,[a] Maheen Rana, MD,[a] Liqi Shu, MD,[a] Casandra Chen, MD,[a] Joseph Sweeney, MD,[b] Christoph Stretz, MD,[a] Eric E. Smith, MD,[c] M. Edip Gurol, MD,[d] Adam de Havenon, MD,[e] Tina Burton, MD,[a] David Fussell-Louie, PharmD,[f] Karen Furie, MD,[a] and Shadi Yaghi, MD[a]

Background and Purpose: Direct oral anticoagulant (DOAC) ingestion within 48 h is an exclusion for thrombolysis in acute ischemic stroke (AIS) patients. We aim to shed light on pharmacokinetic correlates and outcomes in patients with AIS excluded from thrombolysis due to DOAC use. *Methods:* This is a single center retrospective study of consecutive patients with AIS within 4.5 h from last known normal and excluded from thrombolytic therapy due to confirmed Xa inhibitor DOAC ($DOAC_{Xa}$) intake within the prior 48 h. We used linear regression to test the correlation between time from last $DOAC_{Xa}$ ingestion and anti-Xa level. *Results:* Over a period of 2.5 years, we identified 44 patients who did not receive thrombolysis because of presumed DOAC intake within 48 h. In adjusted linear regression, there was an association between time from last DOAC ingestion and Xa level (beta = −0.69, $p < 0.001$). Among the 37 patients with known atrial fibrillation not receiving alteplase due to DOAC use, the 90-day mortality was 35.1% (13/37) and 77% (10/13) of deaths were stroke related. *Conclusions:* Patients with AIS on DOAC therapy face a heightened risk of mortality. Studies are needed to investigate the safety and efficacy of thrombolysis in such patients based on time of last DOAC ingestion and/or anti-Xa/drug level.

Key Words: Direct oral anticoagulants—DOAC—Acute stroke—Alteplase—Outcome

- Are patients on DOACs who present with acute ischemic stroke and receive IVT at increased risk for hemorrhagic transformation?

- Do patients taking DOACs who present with AIS and are treated with IVT have worse outcomes/increased mortality?

Do patients taking DOACs who present with AIS and are treated with IVT benefit from IVT?

Why are these questions being asked?

- Lower risks of ICH with DOACs compared to warfarin
  - DOACs do not affect FVII or FVIIa while warfarin blocks FVII synthesis, which reduces extrinsic coagulation pathways
  - Compared to warfarin, DOACs have little impact on post-ischemic disruption of BBB permeability
  - DOACs lessen the activation of matrix metalloproteinase

- Is it possible the DOACs may enhance the therapeutic benefits from thrombolysis in achieving recanalization without increasing bleeding risk?

Does IVT with rt-PA increase HT in DOAC-treated experimental stroke models?

ORIGINAL ARTICLE

Rivaroxaban does not increase hemorrhage after thrombolysis in experimental ischemic stroke

Robert Ploen[1,5], Li Sun[1,5], Wei Zhou[1], Stefan Heitmeier[2], Markus Zorn[3], Ekkehart Jenetzky[4] and Roland Veltkamp[1]

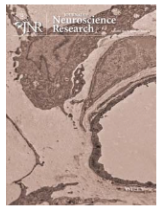
The management of acute ischemic stroke during anticoagulation with a novel oral anticoagulant (NOAC) is challenging because intravenous thrombolysis is contraindicated because of a putative increased risk of intracerebral hemorrhagic complications. We examined the risk of secondary postischemic hemorrhage after thrombolysis in rodents pretreated with rivaroxaban or warfarin. Mice were pretreated with either rivaroxaban (30 mg/kg), warfarin (target international normalized ratio 2 to 3) or vehicle. After 2 or 3 hours, middle cerebral artery occlusion (MCAO), mice received 9 mg/kg recombinant tissue plasminogen activator. Twenty-four hours after MCAO, secondary hemorrhage was quantified using a macroscopic hemorrhage score and hemoglobin spectrophotometry. Blood–brain barrier (BBB) permeability was measured by Evans Blue spectrofluorometry. To increase the validity of our findings, experiments were also performed using a thromboembolic model in anticoagulated rats. Infarct size did not differ among groups. Pretreatment with warfarin led to significantly more secondary hemorrhage compared with rivaroxaban and nonanticoagulated controls after 2- and 3-hour ischemia in mice as well as in rats. Blood–brain barrier permeability was significantly higher in the warfarin group compared with rivaroxaban and control. Thus, rivaroxaban in contrast to warfarin does not increase secondary hemorrhage after thrombolysis in experimental cerebral ischemia. Less effects of rivaroxaban on postischemic BBB permeability may account for this difference.

Journal of Cerebral Blood Flow & Metabolism (2014) **34,** 495–501; doi:10.1038/jcbfm.2013.226; published online 18 December 2013

Keywords: animal models; antithrombotics; blood–brain barrier; brain ischemia; intracerebral hemorrhage; thrombolysis

Journal of Neuroscience Research 95:1818–1828 (2017)

Reduction of Intracerebral Hemorrhage by Rivaroxaban after tPA Thrombolysis Is Associated with Downregulation of PAR-1 and PAR-2



Ryuta Morihara,[1] Toru Yamashita,[1] Syoichiro Kono,[1] Jingwei Shang,[1] Yumiko Nakano,[1] Kota Sato,[1] Nozomi Hishikawa,[1] Yasuyuki Ohta,[1] Stefan Heitmeier,[2] Elisabeth Perzborn,[2] and Koji Abe[1]*

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[2]Bayer Pharma AG, Drug Discovery–Global Therapeutic Research Groups, Cardiovascular Pharmacology, Wuppertal, Germany

This study aimed to assess the risk of intracerebral hemorrhage (ICH) after tissue-type plasminogen activator (tPA) treatment in rivaroxaban compared with warfarin-pretreated male Wistar rat brain after ischemia in relation to activation profiles of protease-activated receptor-1, -2, -3, and -4 (PAR-1, -2, -3, and -4). After pretreatment with warfarin (0.2 mg/kg/day), low-dose rivaroxaban (60 mg/kg/day), high-dose rivaroxaban (120 mg/kg/day), or vehicle for 14 days, transient middle cerebral artery occlusion was induced for 90 min, followed by reperfusion with tPA (10 mg/kg/10 ml). Infarct volume, hemorrhagic volume, immunoglobulin G leakage, and blood parameters were examined. Twenty-four hours after reperfusion, immunohistochemistry for PARs was performed in brain sections. ICH volume was increased in the warfarin-pretreated group compared with the rivaroxaban-treated group. PAR-1, -2, -3, and -4 were widely expressed in the normal brain, and their levels were increased in the ischemic brain, especially in the peri-ischemic lesion. Warfarin pretreatment enhanced the expression of PAR-1 and PAR-2 in the peri-ischemic lesion, whereas rivaroxaban pretreatment did not. The present study shows a lower risk of brain hemorrhage in rivaroxaban-pretreated compared with warfarin-pretreated rats following tPA administration to the ischemic brain. It is suggested that the relative downregulation of PAR-1 and PAR-2 by rivaroxaban compared with warfarin pretreatment might be partly involved in the mechanism of reduced hemorrhagic complications in patients receiving rivaroxaban in clinical trials.

Key words: PAR-3; PAR-4; tissue plasminogen activator; warfarin

INTRODUCTION

Atrial fibrillation increases with age, causing cardiogenic embolic stroke to be the major cause of stroke among the elderly. Warfarin effectively prevents such cardioembolic stroke; however, there are several problems associated with warfarin use, such as its narrow therapeutic range that necessitates frequent blood monitoring, interactions with medications and foods, and increased risk of hemorrhage. The novel oral anticoagulant rivaroxaban is a direct activated factor X (FXa) inhibitor that is noninferior to warfarin for the prevention of stroke and is superior for bleeding side effects without blood monitoring (Patel et al., 2011). However, the mechanism of the

SIGNIFICANCE

Several clinical trials have reported that rivaroxaban, a direct activated factor X (FXa) inhibitor, is superior to warfarin in terms of reducing intracerebral hemorrhage (ICH); however, the mechanism of ICH reduction by rivaroxaban is unclear. Some reports suggest that the effects of FXa are mediated by protease-activated receptors (PARs) and that activation of PARs contributes to neurodegeneration in neurological disorders. In an animal stroke model followed by tPA, we observed that warfarin pretreatment enhanced the expression of PAR-1 and PAR-2 in the brain, whereas rivaroxaban pretreatment did not. This result might be partly involved in the mechanism of reduced ICH in patients receiving rivaroxaban.

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Additional Supporting Information may be found in the online version of this article.

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Hemorrhagic Transformation After Large Cerebral Infarction in Rats Pretreated With Dabigatran or Warfarin

Il Kwon, PhD; Sunho An, MS; Jayoung Kim, MS; Seung-Hee Yang, MS; Joonsang Yoo, MD; Jang-Hyun Baek, MD; Hyo Suk Nam, MD, PhD; Young Dae Kim, MD, PhD; Hye Sun Lee, PhD; Hyun-Jung Choi, PhD; Ji Hoe Heo, MD, PhD

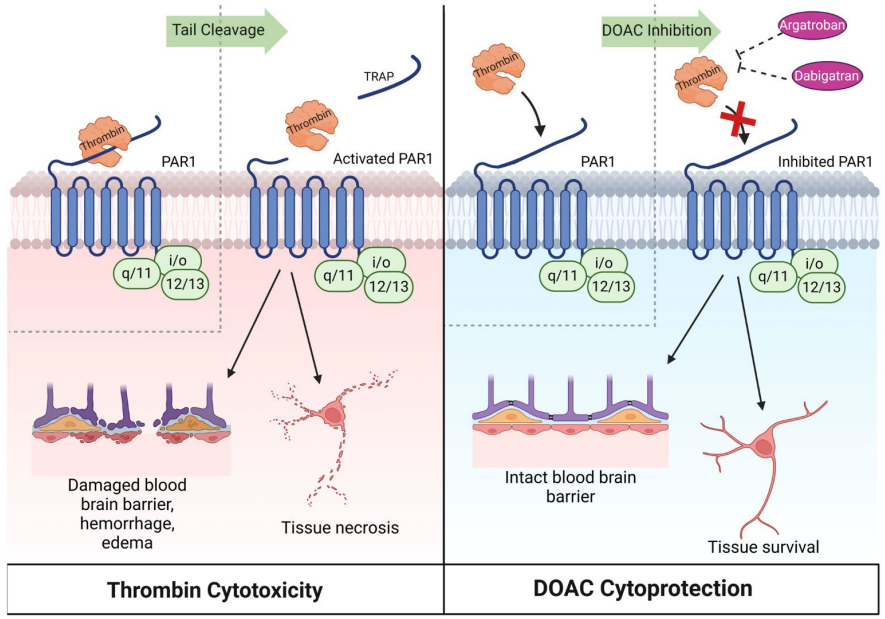
Background and Purpose—It is uncertain whether hemorrhagic transformation (HT) after large cerebral infarction is less frequent in dabigatran users than warfarin users. We compared the occurrence of HT after large cerebral infarction among rats pretreated with dabigatran, warfarin, or placebo.

Methods—This was a triple-blind, randomized, and placebo-controlled experiment. After treatment with warfarin (0.2 mg/kg), dabigatran (20 mg/kg), or saline for 7 days, Wistar rats were subjected to transient middle cerebral artery occlusion. As the primary outcome, HT was determined by gradient-recalled echo imaging. For the secondary outcome, intracranial hemorrhage was assessed via gradient-recalled echo imaging in surviving rats and via autopsy for dead rats.

Results—Of 62 rats, there were 33 deaths (53.2%, 17 technical reasons). Of the intention-to-treat population, 33 rats underwent brain imaging. HT was less frequent in the dabigatran group than the warfarin group (placebo 2/14 [14%], dabigatran 0/10 [0%], and warfarin 9/9 [100%]; dabigatran versus warfarin; $P<0.001$). In all 62 rats, compared with the placebo (2/14 [14.3%]), the incidence of intracranial hemorrhage was significantly higher in the warfarin group (19/29 [65.5%]; $P=0.003$), but not in the dabigatran group (6/19 [31.6%]; $P=0.420$). Mortality was significantly higher in the warfarin group than the dabigatran group (79.3% versus 47.4%; $P=0.022$), but not related to the hemorrhage frequency.

Conclusions—The risk of HT after a large cerebral infarction was significantly increased in rats pretreated with warfarin than those with dabigatran. However, the results here may not have an exact clinical translation.

Visual Overview—An online visual overview is available for this article. **(*Stroke*. 2017;48:2865-2871. DOI: 10.1161/STROKEAHA.117.017751.)**



- Increased thrombin generation during AIS has toxic effects on endothelial cells resulting in BBB leakage and predisposition to HT
- DOACs act as either direct thrombin inhibitors (Dabigatran) or inhibitors of thrombin generation from prothrombin by inhibiting activated Factor Xa
- By inhibiting thrombin (which acts on PAR1 receptor of neurons, astrocytes & endothelial cells resulting in their death), DOACs use may lead to cell and BBB protection and reduced risk of HT
- Warfarin, on the other hand, reduces the amount of Factor VII available for interaction with tissue factor (the key initiator of coagulation) and reduces extrinsic coagulation pathways and fibrin formation

Annals of Neurology, First published: 11 September 2024, DOI: (10.1002/ana.27058)

Direct translation of animal data to patients requires caution!

JAMA Neurology | Original Investigation

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

Thomas R. Meinel, MD; Duncan Wilson, PhD; Henrik Gensicke, MD; Jan F. Scheitz, MD; Peter Ringleb, MD; Ioana Goganau, MD; Johannes Kaesmacher, MD; Hee-Joon Bae, MD; Do Yeon Kim, MD; Pawel Kermer, MD; Kentaro Suzuki, MD; Kazumi Kimura, MD; Kosmas Macha, MD; Masatoshi Koga, MD; Shinichi Wada, MD; Valerian Altersberger, MD; Alexander Salerno, MD; Logesh Palanikumar, MD; Andrea Zini, MD; Stefano Forlivesi, MD; Lars Kellert, MD; Johannes Wischmann, MD; Espen S. Kristoffersen, MD, PhD; James Beharry, MD; P. Alan Barber, PhD; Jae Beom Hong, MD; Carlo Cereda, MD; Eckhard Schlemm, MBBS, PhD; Yusuke Yakushiji, MD; Sven Poli, MD, MSc; Ronen Leker, MD; Michele Romoli, MD; Marialuisa Zedde, MD; Sami Curtze, MD; Benno Ikenberg, MD; Timo Uphaus, MD; David Giannandrea, MD; Pere Cardona Portela, MD; Roland Veltkamp, MD; Annemarei Ranta, PhD; Marcel Arnold, MD; Urs Fischer, MD; Jae-Kwan Cha, MD; Teddy Y. Wu, PhD; Jan C. Purrucker, MD, MSc; David J. Seiffge, MD; and the DOAC-IVT Writing Group; for the International DOAC-IVT, TRISP, and CRCS-K-NIH Collaboration

IMPORTANCE International guidelines recommend avoiding intravenous thrombolysis (IVT) in patients with ischemic stroke who have a recent intake of a direct oral anticoagulant (DOAC).

OBJECTIVE To determine the risk of symptomatic intracranial hemorrhage (sICH) associated with use of IVT in patients with recent DOAC ingestion.

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.

RESULTS Of 33 207 included patients, 14 458 (43.5%) were female, and the median (IQR) age was 73 (62-80) years. The median (IQR) National Institutes of Health Stroke Scale score was 9 (5-16). Of the 832 patients taking DOAC, 252 (30.3%) received DOAC reversal before IVT (all idarucizumab), 225 (27.0%) had DOAC-level measurements, and 355 (42.7%) received IVT without measuring DOAC plasma levels or reversal treatment. The unadjusted rate of sICH was 2.5% (95% CI, 1.6-3.8) in patients taking DOACs compared with 4.1% (95% CI, 3.9-4.4) in control patients using no anticoagulants. Recent DOAC ingestion was associated with lower odds of sICH after IVT compared with no anticoagulation (adjusted odds ratio, 0.57; 95% CI, 0.36-0.92). This finding was consistent among the different selection strategies and in sensitivity analyses of patients with detectable plasma levels or very recent ingestion.

CONCLUSIONS AND RELEVANCE In this study, there was insufficient evidence of excess harm associated with off-label IVT in selected patients after ischemic stroke with recent DOAC ingestion.

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Table 2. Details on Medication, Laboratory Workup, and Acute Recanalization Therapy According to the Selection Strategy Used

Measure	Total, No.	No. (%) DOAC plasma levels measured (n = 225)	No. (%) Neither known levels nor idarucizumab (n = 355)	No. (%) Idarucizumab (n = 252)	*P* value
Age, median (IQR), y	832	80 (73-87)	79 (72-84)	77 (71-83)	.005
Sex					
Female	832	111 (49.3)	160 (45.1)	84 (33.3)	<.001
Male		114 (50.7)	195 (54.9)	168 (66.7)	
NIHSS score, median (IQR)	828	10 (6-16)	13 (7-18)	10 (6-16)	.006
Type of anticoagulation used					
Dabigatran	832	15 (6.7)	75 (21.1)	252 (100)	<.001
Rivaroxaban		119 (52.9)	139 (39.2)	0	
Apixaban		73 (32.4)	90 (25.4)	0	
Edoxaban		18 (8.0)	50 (14.1)	0	
DOAC agent not specified		0	1 (0.3)	0	
Time from last ingestion to admission					
<12 h	832	39 (17.3)	73 (20.6)	130 (51.6)	<.001
12-24 h		48 (21.3)	78 (22.0)	32 (12.7)	
24-48 h		43 (19.1)	59 (16.6)	1 (0.4)	
Exact time point unknown but <48 h		95 (42.2)	145 (40.8)	89 (35.3)	
Time from last ingestion to admission, median (IQR), h	503	14.4 (9-24)	14 (9.51667-25)	7 (4.75-11)	<.001
International normalized ratio, median (IQR)	674	1.1 (1-1.2)	1.1 (1.02-1.2)	1.13 (1.1-1.2)	.001
Activated partial thrombin time, median (IQR), s	664	29 (26-33)	30 (27-34)	37 (29-46)	<.001
Thrombin time, median (IQR), s	260	16.6 (15.2-18.3)	14.6 (11.4-17.4)	81.4 (43.9-120.0)	<.001
DOAC plasma level, median (IQR), ng/mL	244	21 (4.6-46)	NA	83 (27-134)	NA
Type of intravenous thrombolysis used					
Alteplase	831	223 (99.1)	351 (99.2)	206 (81.7)	<.001
Tenecteplase		2 (0.9)	3 (0.8)	46 (18.3)	
Time from symptom onset to intravenous thrombolysis, median (IQR), h	632	155 (105-230)	145 (97-190)	159 (120-202)	.03
Mechanical thrombectomy	832	79 (35.1)	139 (39.2)	67 (26.6)	.005
Time from symptom onset to groin puncture, median (IQR), h	199	188 (100-274)	182 (148-225)	296 (205-367)	<.001
Symptomatic intracranial hemorrhage within 36 h	832	7 (3.1)	11 (3.1)	3 (1.2)	.27
Any hemorrhagic transformation within 36 h	784	46 (20.5)	79 (22.3)	16 (7.8)	<.001

- Retrospective cohort study
- 33,207 patients
- 832 (2.5) taking DOCAs
  - 30% received idarucizumab before IVT
  - 20% had DOAC-level measured
  - 43% received IVT w/o DOAC reversal or level measurement

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.

eTable 7. Rates of Outcome Categories in the Modified Rankin Scale at 90 Days According to Group

Modified Rankin Scale Category	Patients with recent ingestion of DOACs (n= 664)	Controls (n= 29,026)
0	89 (13.4%)	5,861 (20.2%)
1	106 (16.0%)	5,963 (20.5%)
2	104 (15.7%)	4,642 (16.0%)
3	110 (16.6%)	3,998 (13.8%)
4	82 (12.4%)	3,103 (10.7%)
5	54 (8.1%)	1,623 (5.6%)
6	119 (17.9%)	3,836 (13.2%)

Functional outcome at 90 days was known for 664 DOAC-treated patients (~ 80%) and 29,026 controls (~ 88%)
Unadjusted mRS scores.

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BMC Neurology

RESEARCH Open Access

Meta-analysis of outcomes following intravenous thrombolysis in patients with ischemic stroke on direct oral anticoagulants

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Abstract

Background There has been debate on the use of intravenous thrombolysis (IVT) in patients with ischemic stroke and the recent use of direct oral anticoagulants (DOACs). Studies have compared these patients with non-DOAC groups in terms of outcomes. Herein, we aimed to systematically investigate the association between DOAC use and IVT's efficacy and safety outcomes.

Results A comprehensive systematic search was performed in PubMed, Embase, Scopus, and the Web of Science for the identification of relevant studies. After screening and data extraction, a random-effect meta-analysis was performed to calculate the odds ratio (OR) and 95% confidence interval (CI) for comparison of outcomes between patients on DOAC and controls. Six studies were included in the final review. They investigated a total of 254,742 patients, among which 3,499 had recent use of DOACs. The most commonly used DOACs were rivaroxaban and apixaban. The patients on DOAC had significantly higher rates of atrial fibrillation, hypertension, diabetes, and smoking. Good functional outcome defined by modified Rankin Scale (mRS) 0–2 was significantly lower in patients who received DOACs (OR 0.71, 95% CI 0.62 to 0.81, $P<0.01$). However, in the subgroup analysis of 90-day mRS 0–2, there was no significant difference between groups (OR 0.71, 95% 0.46 to 1.11, $P=0.14$). All-cause mortality was not different between the groups (OR 1.02, 95% CI 0.68 to 1.52, $P=0.93$). Similarly, there was no significant difference in either of the in-hospital and 90-day mortality subgroups. Regarding symptomatic intracranial hemorrhage (sICH), the previous DOAC use was not associated with an increased risk of bleeding (OR 0.98, 95% CI 0.69 to 1.39, $P=0.92$). A similar finding was observed for the meta-analysis of any ICH (OR 1.15, 95% CI 0.94 to 1.40, $P=0.18$).

Conclusions Based on our findings, IVT could be considered as a treatment option in ischemic stroke patients with recent use of DOACs since it was not associated with an increased risk of sICH, as suggested by earlier studies. Further larger studies are needed to confirm these findings and establish the safety of IVT in patients on DOAC.

Keywords Intravenous thrombolysis, Stroke, Factor xa inhibitors, Systematic review, Meta-analysis

- 6 studies - 254,742 patients
  - DOACs (mostly rivaroxaban & apixaban) = 3,499 (1.4%)
  - Controls = 251,243
- Retrospective or prospective cohorts assessing the outcomes following IVT in patients with ischemic stroke and recent use of DOACs and comparing it with non-DOAC user controls.

Table 1 Baseline characteristics of included studies

Study	Year	Design	Country	Population	DOACs type	N total	N DOAC	N Control
Kam et al.	2022	Retrospective Cohort	United States	Patients with acute ischemic stroke undergoing IVT with alteplase, either taking NOACs or not taking anticoagulants	Rivaroxaban, Apixaban, or Edoxaban	163,038	2,207	160,831
Meinel et al.	2023	Retrospective Cohort	Europe, Asia, Australia, and New Zealand	Adult patients with ischemic stroke who underwent IVT, either with or without recent use of DOACs	Rivaroxaban, Dabigatran, Apixaban, or Edoxaban	33,207	832	32,375
Okada et al.	2022	Prospective Cohort	Japan	Acute ischemic stroke patients who underwent IVT with alteplase, patients with or without use of DOACs in latest 48 h	Rivaroxaban, Dabigatran, Apixaban, or Edoxaban	793	40	753
Seiffge et al.	2015	Retrospective Cohort	Europe	Patients with acute ischemic stroke who underwent IVT, IAT, or both	Rivaroxaban, Apixaban, or Dabigatran	9,016	78	8,938
Xian et al.	2017	Retrospective Cohort	United States	Patients with acute ischemic stroke who received thrombolytic therapy, with NOACs or no anticoagulation	Rivaroxaban, Apixaban, or Dabigatran	41,387	251	41,136
Tasi et al.	2023	Retrospective Cohort	Taiwan	Adult patients ≥ 20 years diagnosed with acute ischemic stroke treated with alteplase, with treatment status of NOAC and no oral anticoagulants	Rivaroxaban, Dabigatran, Apixaban, or Edoxaban	7,301	91	7,210

DOAC: direct oral anticoagulant, NOAC: novel oral anticoagulant, IVT: intravenous thrombolysis, IAT: intra-arterial treatment

Outcome	Kam et al, 2022	Meinel et al, 2023	Okada et al, 2022	Seiffge et al, 2015	Xian et al, 2017	Tsai et al, 2023	DOAC		Non-DOAC		Odds Ratio (95% CI)	OR	P-value	I^2 (%)
							Event	Total	Event	Total				
Modified Rankin Scale 0-2	✓	✓	✓	✗	✓	✗	875	2,227	62,100	131,357	0.71 (0.62 to 0.81)		**<0.01**	35.61
Discharge	✓	✗	✗	✗	✓	✗	557	1,531	45,259	101,687	0.74 (0.67 to 0.82)		**<0.01**	0
90-days	✗	✓	✓	✗	✗	✗	318	696	16,841	29,670	0.71 (0.46 to 1.11)		0.14	46.92
Modified Rankin Scale 0-1	✓	✓	✓	✗	✓	✗	614	2,227	46,694	131,357	0.68 (0.61 to 0.76)		**<0.01**	11.34
Discharge	✓	✗	✗	✗	✓	✗	406	1,531	34,586	101,687	0.72 (0.64 to 0.81)		**<0.01**	0
90-days	✗	✓	✓	✗	✗	✗	208	696	12,108	29,670	0.62 (0.52 to 0.73)		**<0.01**	0
All-Cause Mortality	✓	✗	✓	✗	✓	✓	168	2,592	8,026	162,193	1.02 (0.68 to 1.52)		0.93	39.91
In-hospital	✓	✗	✗	✗	✓	✓	166	2,552	7,983	161,440	0.99 (0.61 to 1.61)		0.96	58.11
90-days	✗	✗	✓	✗	✗	✗	2	40	43	753	0.87 (0.20 to 3.72)		0.85	-
Symptomatic ICH	✓	✓	✓	✓	✓	✗	118	3,381	8,428	242,603	0.98 (0.69 to 1.39)		0.92	46.12
Any ICH	✓	✗	✓	✗	✗	✓	104	2,338	5,848	161,948	1.15 (0.94 to 1.40)		0.18	0

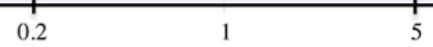
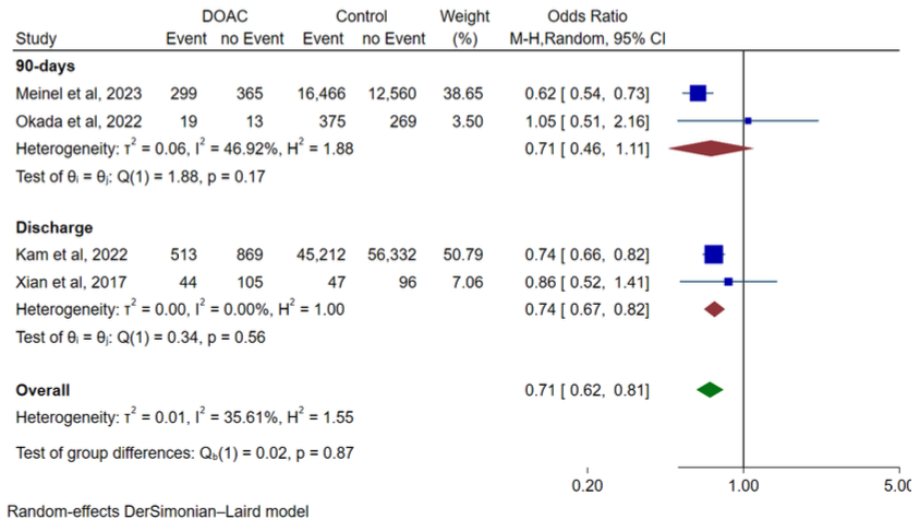
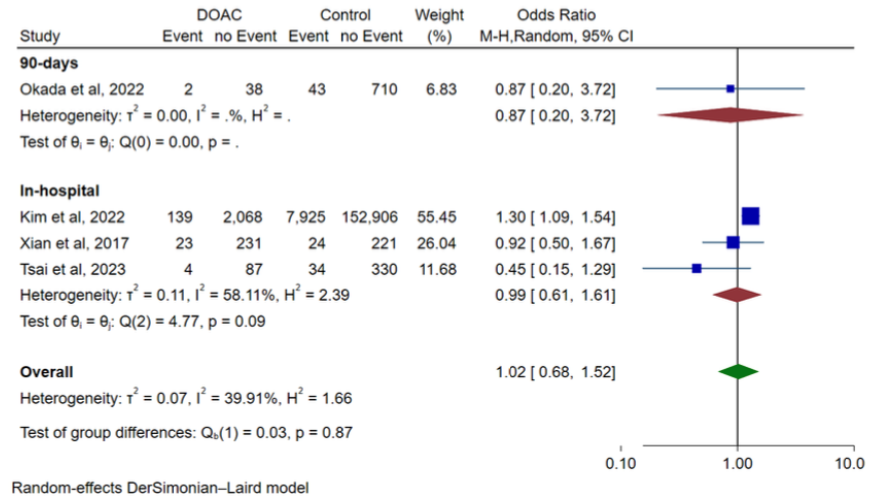


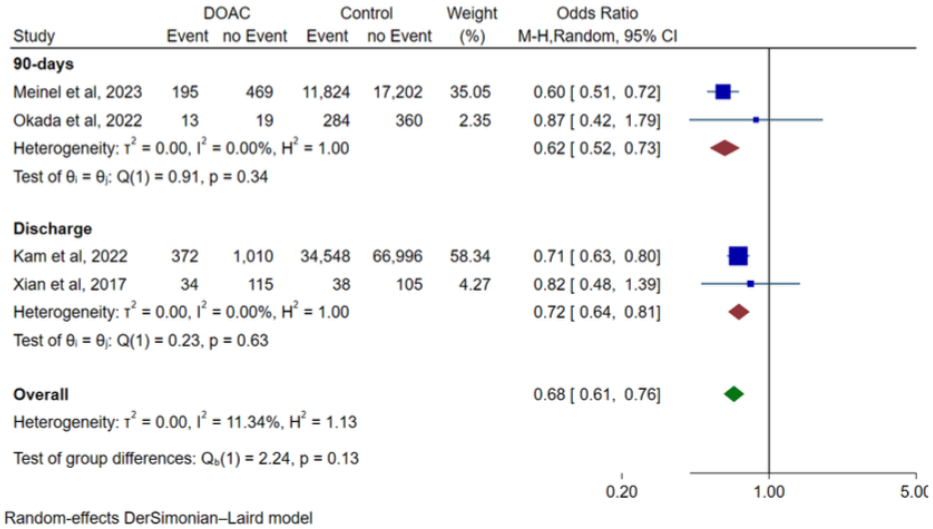
Fig. 3 Summary of all meta-analyses regarding all-cause mortality, modified Rankin Scale 0–2, and symptomatic ICH



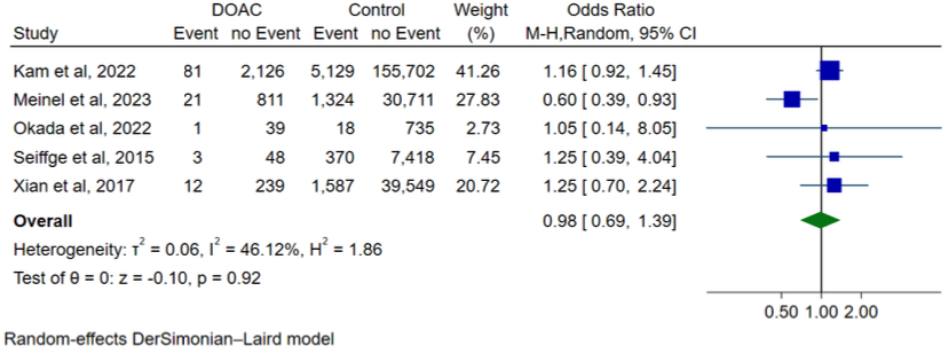
Supplementary Figure 1. *Forest plot for meta-analysis of modified Rankin Score 0-2 in patients on DOACs vs. controls*



Supplementary Figure 5. *Forest plot for meta-analysis of all-cause mortality in patients on DOACs vs. controls*



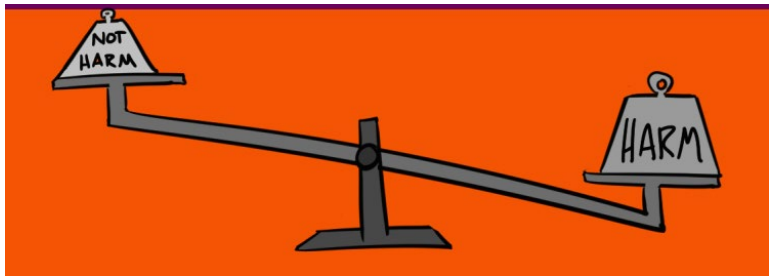
Supplementary Figure 3. *Forest plot for meta-analysis of modified Rankin Score 0-1 in patients on DOACs vs. controls*



Supplementary Figure 7. *Forest plot for meta-analysis of symptomatic ICH in patients on DOACs vs. controls*

Summary

Is safety the only factor?



- Good functional outcome defined as mRS 0–2 was significantly lower in patients who received DOACs
- In subgroup analysis of 90-day mRS 0–2, there was no significant difference between groups
- All-cause mortality was not different between the groups
- Previous DOAC use was not associated with an increased risk of symptomatic ICH or any ICH

IVT could be considered as a treatment option in ischemic stroke patients with recent use of DOACs since it was not associated with an increased risk of sICH

JAMA Internal Medicine | Original Investigation

Risk of Bleeding Following Non–Vitamin K Antagonist Oral Anticoagulant Use in Patients With Acute Ischemic Stroke Treated With Alteplase

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Supplemental content

IMPORTANCE Current guidelines advise against intravenous alteplase therapy for treatment of acute ischemic stroke in patients previously treated with non–vitamin K antagonist oral anticoagulants (NOACs).

OBJECTIVE To evaluate the risk of bleeding and mortality after alteplase treatment for acute ischemic stroke among patients treated with NOACs compared to those not treated with NOACs.

DESIGN, SETTING, AND PARTICIPANTS This nationwide, population-based cohort study was conducted in Taiwan using data from Taiwan's National Health Insurance Research Database from January 2011 through November 2020 and included 7483 patients treated with alteplase for acute ischemic stroke. A meta-analysis incorporating the results of the study with those of previous studies was performed, and the review protocol was prospectively registered with PROSPERO.

EXPOSURES NOAC treatment within 2 days prior to stroke, compared to either no anticoagulant treatment or warfarin treatment.

MAIN OUTCOMES AND MEASURES The primary outcome was intracranial hemorrhage after intravenous alteplase during the index hospitalization (the hospitalization subsequent to alteplase administration). Secondary outcomes were major bleeding events and mortality during the index hospitalization. Propensity score matching was used to control potential confounders. Logistic regression was used to estimate the odds ratio (OR) of outcome events. Meta-analysis was performed using a random-effects model.

RESULTS Of the 7483 included patients (mean [SD] age, 67.4 [12.7] years; 2908 [38.9%] female individuals and 4575 [61.1%] male individuals), 91 (1.2%), 182 (2.4%), and 7210 (96.4%) received NOACs, warfarin, and no anticoagulants prior to their stroke, respectively. Compared to patients who were not treated with anticoagulants, those treated with NOACs did not have significantly higher risks of intracranial hemorrhage (risk difference [RD], 2.47% [95% CI, −4.23% to 9.17%]; OR, 1.37 [95% CI, 0.62-3.03]), major bleeding (RD, 4.95% [95% CI, −2.56% to 12.45%]; OR, 1.69 [95% CI, 0.83-3.45]), or in-hospital mortality (RD, −4.95% [95% CI, −10.11% to 0.22%]; OR, 0.45 [95% CI, 0.15-1.29]) in the propensity score–matched analyses. Furthermore, the risks of bleeding and mortality were not significantly different between patients treated with NOACs and those treated with warfarin. Similar results were obtained in the meta-analysis.

CONCLUSIONS AND RELEVANCE In this cohort study with meta-analysis, compared to no treatment with anticoagulants, treatment with NOACs prior to stroke was not associated with a higher risk of intracranial hemorrhage, major bleeding, or mortality in patients receiving intravenous alteplase for acute ischemic stroke.

- Nationwide Taiwan-based cohort study
- 7483 patients treated with IV alteplase (? dose)
  - DOAC (1.2%) vs. Warfarin (2.4%) or no AC (96.4%)
- + Meta-analysis incorporating this study with previous studies (9 studies including 257389 patients)

Table 2. Comparison of Bleeding and Mortality Risks Between Groups After Propensity Score Matching

	NOAC vs non-OAC[a]				NOAC vs warfarin[b]			
	No. (%)				No. (%)			
Outcome	NOAC	Non-OAC	RD, % (95% CI)[c]	OR (95% CI)[c]	NOAC	Warfarin	RD, % (95% CI)[c]	OR (95% CI)[c]
Primary outcome								
Intracranial hemorrhage	9 (9.9)	27 (7.4)	2.47 (−4.23 to 9.17)	1.37 (0.62 to 3.03)	8 (10.4)	9 (11.7)	−1.30 (−11.2 to 8.60)	0.88 (0.32 to 2.40)
Secondary outcomes								
All major bleeding[d]	12 (13.2)	30 (8.2)	4.95 (−2.56 to 12.45)	1.69 (0.83 to 3.45)	11 (14.3)	13 (16.9)	−2.60 (−14.05 to 8.85)	0.82 (0.34 to 1.97)
Other critical bleeding[e]	3 (3.3)	3 (0.8)	2.47 (−1.31 to 6.26)	4.10 (0.81 to 20.67)	3 (3.9)	4 (5.2)	−1.30 (−7.88 to 5.28)	0.74 (0.16 to 3.42)
30-d Mortality	8 (8.8)	40 (11.0)	−2.2 (−8.84 to 4.45)	0.78 (0.35 to 1.73)	6 (7.8)	9 (11.7)	−3.90 (−13.24 to 5.45)	0.64 (0.22 to 1.89)
In-hospital mortality	4 (4.4)	34 (9.3)	−4.95 (−10.11 to 0.22)	0.45 (0.15 to 1.29)	3 (3.9)	9 (11.7)	−7.79 (−16.17 to 0.59)	0.31 (0.08 to 1.18)

Abbreviations: NOAC, non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; RD, risk difference.

[a] There were 91 patients in the NOAC group and 364 patients in the non-OAC group after propensity score matching.

[b] There were 77 patients each in the NOAC and warfarin groups after propensity score matching.

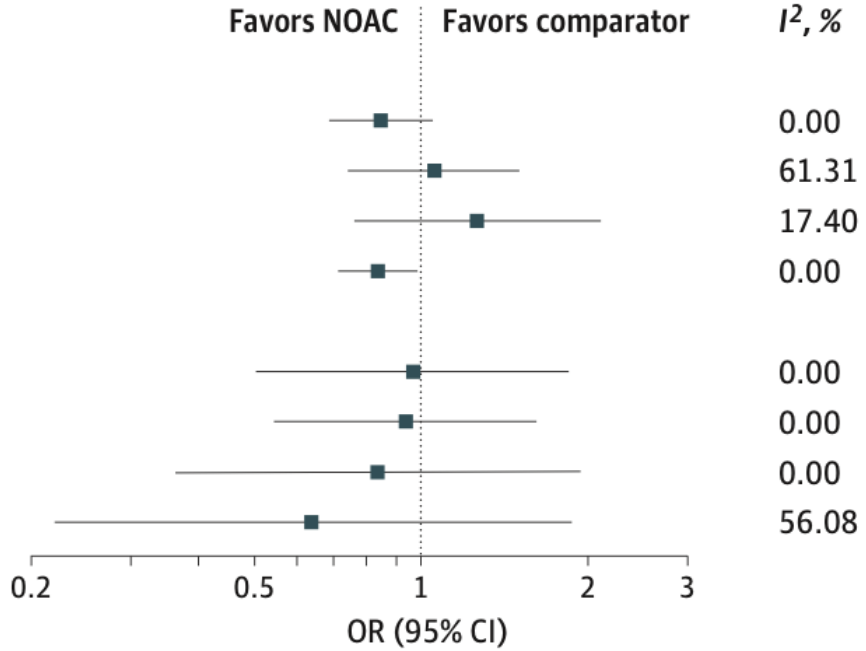
[c] The OR and RD were calculated using the population after propensity score matching.

[d] All major bleeding was defined as any event of intracranial hemorrhage, gastrointestinal tract bleeding, or bleeding at any other critical site.

[e] Other critical bleeding was defined as all major bleeding events excluding instances of intracranial hemorrhage.

Figure 3. Forest Plot of the Risk of Intracranial Hemorrhage (ICH) and Other Events According to Anticoagulation Therapy Before Stroke

Outcome	No. of studies	Events, No./total No.		Pooled OR (95% CI)	I^2, %
		NOAC	Comparator		
NOAC vs non-OAC					
Symptomatic ICH	4	105/2847	6475/193 864	0.85 (0.69-1.04)	0.00
Any ICH	5	186/2938	10 867/194 228	1.06 (0.74-1.50)	61.31
Major bleeding	4	30/2583	937/162 193	1.26 (0.76-2.08)	17.40
In-hospital mortality	3	166/2543	7983/161 440	0.83 (0.70-1.00)	0.00
NOAC vs warfarin					
Symptomatic ICH	5	15/360	49/878	0.97 (0.51-1.83)	0.00
Any ICH	6	23/437	58/955	0.94 (0.55-1.61)	0.00
Major bleeding	2	12/322	14/322	0.84 (0.36-1.92)	0.00
In-hospital mortality	2	26/322	33/322	0.64 (0.22-1.85)	56.08



NOAC indicates non–vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio.

Summary

- Compared to patients who were not treated with AC, those treated with DOACs did not have significantly higher risks of ICH, major bleeding, or mortality during hospitalization.

Treatment with DOACs may be considered safe in Asian patients with acute ischemic stroke receiving intravenous alteplase

Journal of the American Heart Association

ORIGINAL RESEARCH

Intravenous Thrombolysis for Acute Ischemic Stroke in Patients With Recent Direct Oral Anticoagulant Use: A Systematic Review and Meta-Analysis

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BACKGROUND: Intravenous thrombolysis (IVT) is an effective stroke therapy that remains underused. Currently, the use of IVT in patients with recent direct oral anticoagulant (DOAC) intake is not recommended. In this study we aim to investigate the safety and efficacy of IVT in patients with acute ischemic stroke and recent DOAC use.

METHODS AND RESULTS: A systematic review and meta-analysis of proportions evaluating IVT with recent DOAC use was conducted. Outcomes included symptomatic intracranial hemorrhage, any intracranial hemorrhage, serious systemic bleeding, and 90-day functional independence (modified Rankin scale score 0–2). Additionally, rates were compared between patients receiving IVT using DOAC and non-DOAC by a random effect meta-analysis to calculate pooled odds ratios (OR) for each outcome. Finally, sensitivity analysis for idarucizumab, National Institutes of Health Stroke Scale, and timing of DOAC administration was completed. Fourteen studies with 247 079 patients were included (3610 in DOAC and 243 469 in non-DOAC). The rates of IVT complications in the DOAC group were 3% (95% CI, 3–4) symptomatic intracranial hemorrhage, 12% (95% CI, 7–19) any ICH, and 0.7% (95%CI, 0–1) serious systemic bleeding, and 90-day functional independence was achieved in 57% (95% CI, 43–70). The rates of symptomatic intracranial hemorrhage (3.4 versus 3.5%; OR, 0.95 [95% CI, 0.67–1.36]), any intracranial hemorrhage (17.7 versus 17.3%; OR, 1.23 [95% CI, 0.61–2.48]), serious systemic bleeding (0.7 versus 0.6%; OR, 1.27 [95% CI, 0.79–2.02]), and 90-day modified Rankin scale score 0–2 (46.4 versus 56.8%; OR, 1.21 [95% CI, 0.400–3.67]) did not differ between DOAC and non-DOAC groups. There was no difference in symptomatic intracranial hemorrhage rate based on idarucizumab administration.

CONCLUSIONS: Patients with acute ischemic stroke treated with IVT in recent DOAC versus non-DOAC use have similar rates of hemorrhagic complications and functional independence. Further prospective randomized trials are warranted.

- 14 studies – 247079 patients
  - 3610 (1.46%) DOAC
  - 243469 non-DOAC

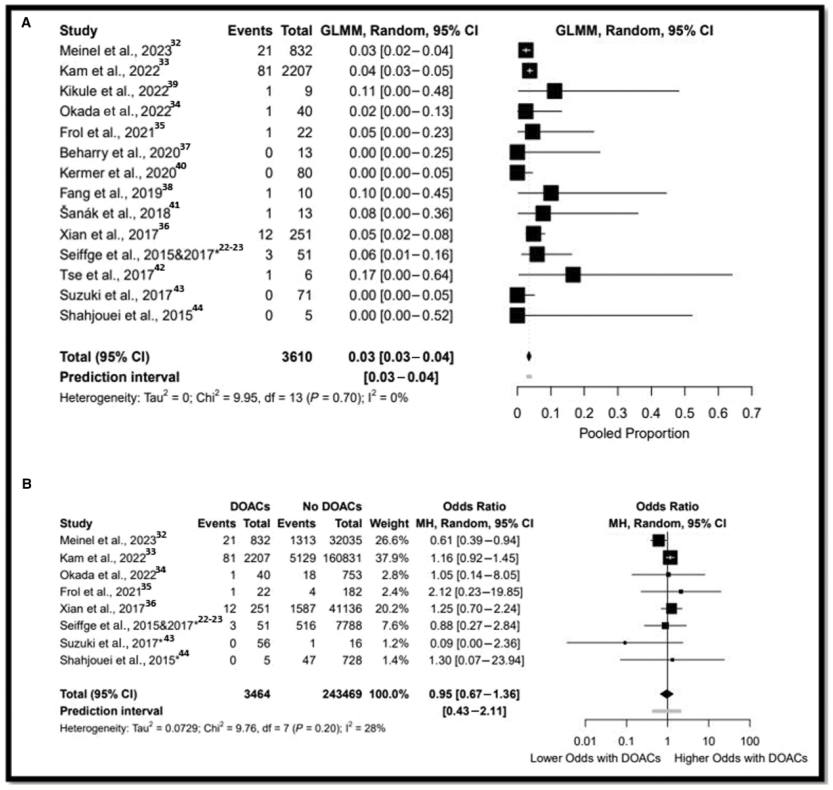


Figure 1. **Forest plot for IVT in patients were taking DOAC for symptomatic intracranial hemorrhage.**
A, Refers to the meta-analysis of proportions. **B**, Refers to the comparative analysis. *: direct communication with the authors. DOAC indicates direct oral anticoagulant; GLMM, generalized linear mixed model; IVT, intravenous thrombolysis; and MH, Mantel–Haenszel.

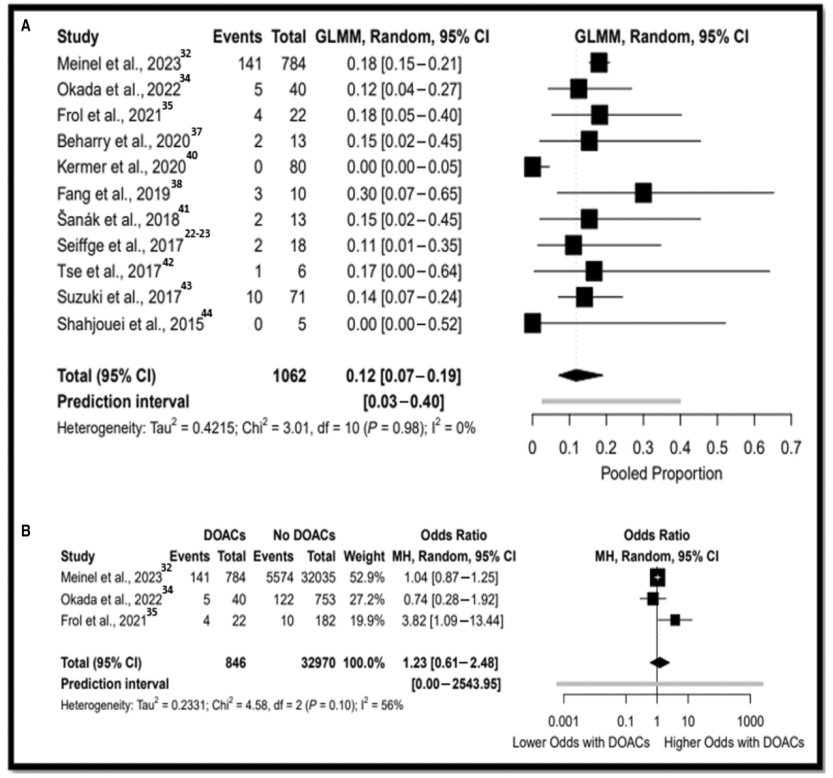


Figure 2. **Forest plot for IVT in patients were taking DOAC for any ICH.**
A, Refers to the meta-analysis of proportions. **B**, Refers to the comparative analysis. DOAC indicates direct oral anticoagulant; GLMM, generalized linear mixed model; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; and MH, Mantel–Haenszel.

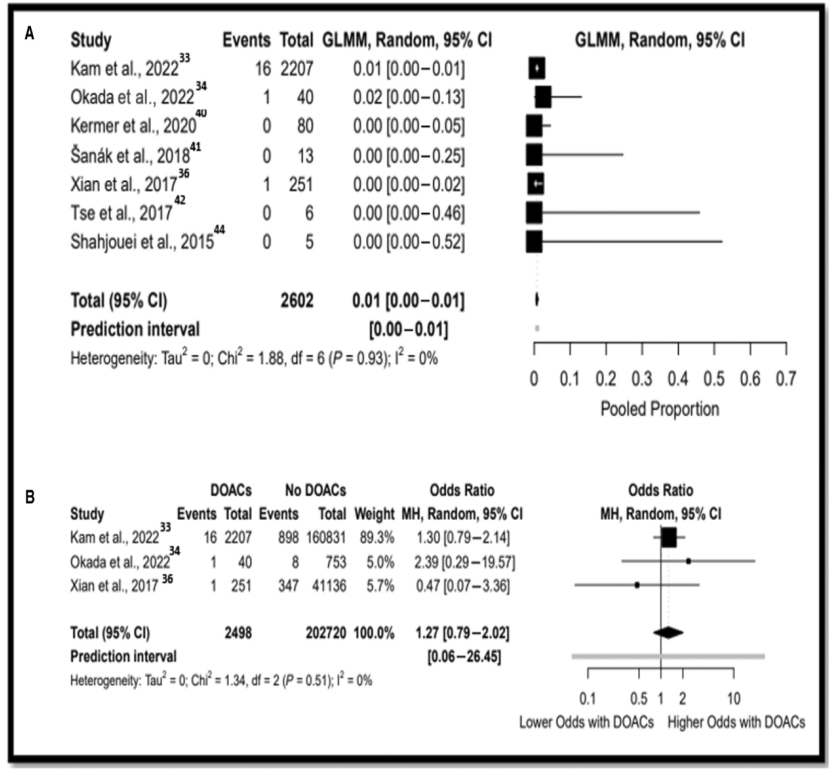


Figure 3. **Forest plot for IVT in patients were taking DOAC for serious systemic bleeding.**
A, Refers to the meta-analysis of proportions. **B**, Refers to the comparative analysis. DOAC indicates direct oral anticoagulant; GLMM, generalized linear mixed model; IVT, intravenous thrombolysis; and MH, Mantel–Haenszel.

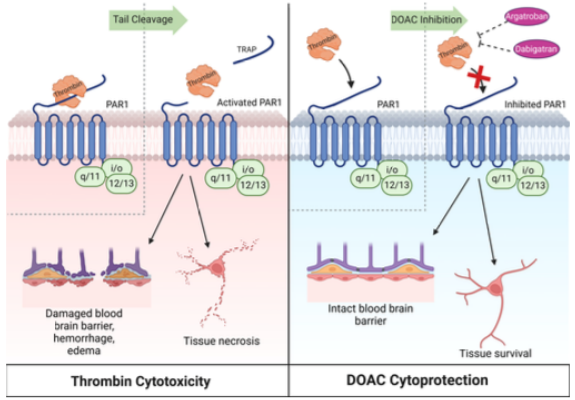
Summary

- No significant difference in rates of sICH, serious systemic bleeding, any ICH, or 90-day mRS 0-2 between patients with recent DOAC use and those not taking DOAC following the administration of IVT.
- No significant difference in sICH rate among those groups based on reception of idarucizumab before IVT (received versus not), as well as NIHSS score (>10 versus ≤10).
- Significantly higher rates of mortality in the DOAC patients who were treated with IVT as compared with the controls. However, this effect was mainly due to one study and the estimated effect became nonsignificant after omitting this study from the analysis!

In the absence of prospective trials to provide a more rigorous assessment of the risk/ benefits in this specific population, the use of IVT may be justified in cases where the recent use of DOAC is unclear.

Before, during, and after: An Argument for Safety and Improved Outcome of Thrombolysis in Acute Ischemic Stroke with Direct Oral Anticoagulant Treatment

Sanaz Monjazeb, MD,[1] Heather V. Chang, BS,[2] and Patrick D. Lyden, MD [1,2]



Clinicians fear thrombolysis after direct oral anticoagulant (DOAC) use due to experience with warfarin. In contrast to vitamin K antagonists such as warfarin, DOACs prevent thrombosis by blocking thrombin. Clinical observational data suggest that thrombolysis may be safe in the setting of DOAC use. Thrombin, a serine protease, acts on the PAR1 receptor of brain cells, resulting in cell killing. Thrombin injury to endothelial cells can lead to blood-brain barrier disruption and hemorrhagic transformation. DOACs such as argatroban and dabigatran, by inhibiting thrombin, prevent PAR1 activation leading to cell protection, blood-brain barrier protection, and reduced risk of hemorrhage. Created with BioRender.com.

Direct oral anticoagulants are the primary stroke prevention option in patients with atrial fibrillation. Anticoagulant use before stroke, however, might inhibit clinician comfort with thrombolysis if a stroke does occur. Resuming anticoagulants after ischemic stroke is also problematic for fear of hemorrhage. We describe extensive literature showing that thrombolysis is safe after stroke with direct anticoagulant use. Early reinstitution of direct anticoagulant treatment is associated with lower risk of embolic recurrence and lower hemorrhage risk. The use of direct anticoagulants before, during, and after thrombolysis appears to be safe and is likely to promote improved outcomes after ischemic stroke.

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- Limitations of available literature:
  - Retrospective
  - Case reports/series subject to publication bias
  - Non-randomized and prone to selection bias
  - Small number of DOACs-treated patients
  - Differences in characteristics, comorbidities, stroke subtype and severity between studied groups and heterogeneity between studies
  - Most studies use rt-PA. Nowadays, the use of TNK is rapidly rising
  - The doses of alteplase and TNK varied depending or regional guidelines/practice.
  - Some studies lumped all non-DOAC-treated patients, i.e. warfarin + no AC, together. Thus, potentially decreasing risk difference in HT between groups
  - The DOAC and control groups were non-concurrent, i.e. enrolled at different time periods
  - What is the appropriate control group?
  - The studies are likely underpowered to analyze subgroups including selection strategies and IVT + EVT use

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Magic of Randomization versus the Myth of Real-World Evidence

Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P., and Richard Peto, F.R.S.

Nonrandomized observational analyses of large electronic patient databases are being promoted as an alternative to randomized clinical trials as a source of "real-world evidence" about the efficacy and safety of new and existing treatments.[1-3] For drugs or procedures that are already being used widely, such observational studies may involve exposure of large numbers of patients. Consequently, they have the potential to detect rare adverse effects that cannot plausibly be attributed to bias, generally because the relative risk is large (e.g., Reye's syndrome associated with the use of aspirin, or rhabdomyolysis associated with the use of statin therapy).[4] Nonrandomized clinical observation may also suffice to detect large beneficial effects when good outcomes would not otherwise be expected (e.g., control of diabetic ketoacidosis with insulin treatment, or the rapid shrinking of tumors with chemotherapy).

However, because of the potential biases inherent in observational studies, such studies cannot generally be trusted when — as is often the case — the effects of the treatment of interest are actually null or only moderate (i.e., less than a twofold difference in the incidence of the health outcome between using and not using the treatment).[4-6] In those circumstances, large observational studies may yield misleading associations of a treatment with health outcomes that are statistically significant but noncausal, or that are mistakenly null when the treatment really does have clinically important effects. Instead, randomized, controlled trials of adequate size are generally required to ensure that any moderate benefits or moderate harms of a treatment are assessed reliably enough to guide patient care appropriately (Box 1).[5-7]

Reliance on nonrandomized observational studies risks inadequate assessments of both safety and efficacy because the potential biases with respect to both can be appreciable. For example, the treatment that is being assessed may well have been provided more or less often to patients who had an increased or decreased risk of various health outcomes. Indeed, that is what would be expected in medical practice, since both the severity of the disease being treated and the presence of other conditions may well affect the choice of treatment (often in ways that cannot be reliably quantified). Even when associations of various health outcomes with a particular treatment remain statistically significant after adjustment for all the known differences between patients who received it and those who did not receive it, these adjusted associations may still reflect residual confounding because of differences in factors that were assessed only incompletely or not at all (and therefore could not be taken fully into account in adjusted analyses). Modeling studies indicate that potential biases in observational studies may well be large enough to lead to the false conclusion that a treatment produces benefit or harm, with none of a range of statistical strategies capable of adjusting with certainty for bias. Those findings are consistent with findings from reviews that compared estimates of treatment effects from observational studies with estimates from randomized trials, with examples in which results for the same intervention were similar but also many in which the results were importantly different.[8-12]

Such discrepancies are illustrated by a database analysis involving the entire Danish population that found that the relative risk of death from cancer was 15% lower (95% confidence interval, 13 to 18) among patients who had taken statin therapy for only a few years than among those who had not taken statin therapy, even after statistical adjustment for what was

Example: Statins increase cardiovascular mortality!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

Sune F. Nielsen, Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc.
and Stig E. Bojesen, M.D., Ph.D., D.M.Sc.

ABSTRACT

BACKGROUND

A reduction in the availability of cholesterol may limit the cellular proliferation required for cancer growth and metastasis. We tested the hypothesis that statin use begun before a cancer diagnosis is associated with reduced cancer-related mortality.

METHODS

We assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, with follow-up until December 31, 2009. Among patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins.

RESULTS

Multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, were 0.85 (95% confidence interval [CI], 0.83 to 0.87) for death from any cause and 0.85 (95% CI, 0.82 to 0.87) for death from cancer. Adjusted hazard ratios for death from any cause according to the defined daily statin dose (the assumed average maintenance dose per day) were 0.82 (95% CI, 0.81 to 0.85) for a dose of 0.01 to 0.75 defined daily dose per day, 0.87 (95% CI, 0.83 to 0.89) for 0.76 to 1.50 defined daily dose per day, and 0.87 (95% CI, 0.81 to 0.91) for higher than 1.50 defined daily dose per day; the corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81 to 0.86), 0.87 (95% CI, 0.83 to 0.91), and 0.87 (95% CI, 0.81 to 0.92). The reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types.

CONCLUSIONS

Statin use in patients with cancer is associated with reduced cancer-related mortality. This suggests a need for trials of statins in patients with cancer.

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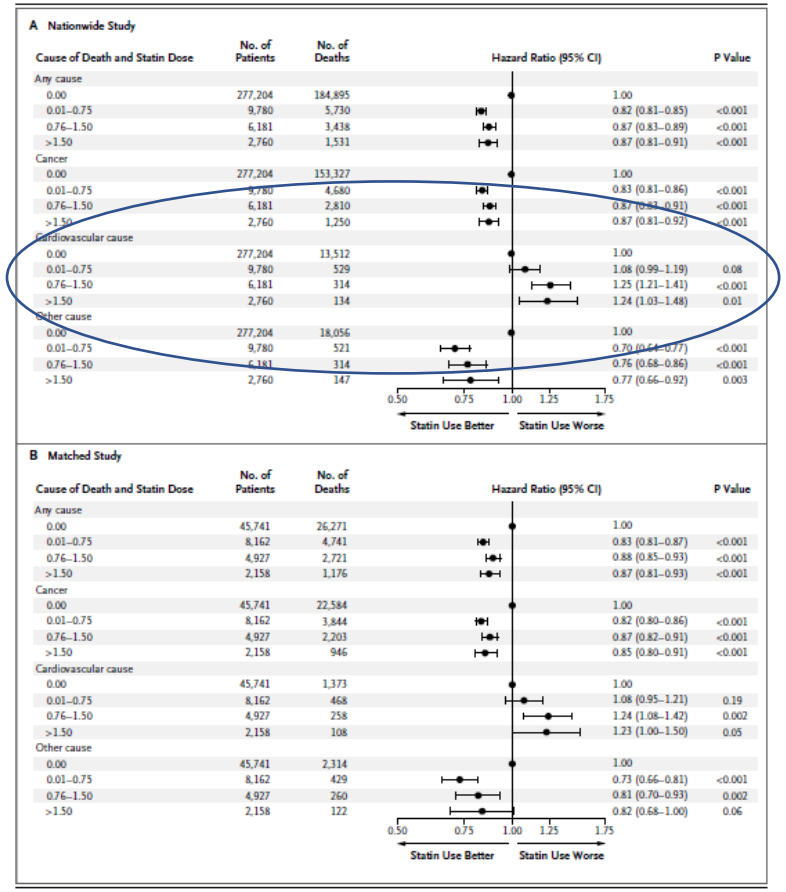

American Heart/Stroke Association[65]	The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful. Intravenous alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 hours (assuming normal renal metabolising function).
Japanese consensus statement[38]	For dabigatran IVT is not recommended if aPTT >1.5 times or last dose is <4 hours. In this case, IVT can be considered after intravenous administration of idarucizumab. For factor Xa inhibitors IVT is not recommended if INR exceeds at least 1.7. IVT is not recommended if the time of the last dose is <4 hours IVT can be considered if the time of the last dose is ≥4 hours and the level of INR is ≤1.7). IVT after emergent reversal of prolonged INR using antidotes for other anticoagulants is not recommended.
ESO Karolinska Stroke Update 2018[66]	Patients with acute ischaemic stroke under VKA or DOAC treatment with proven large vessel occlusion should be offered IVT (if feasible) and endovascular treatment (thrombectomy). Thrombolysis allowed if DOAC plasma levels <30 ng/mL If no DOAC plasma levels available, INR measurement using Hemochron Signature Elite is possible under specific circumstances
French Society of Vascular Neurology[40]	IVT if no intake >48 hours or DOAC level <50 ng/mL. Conventional testing with TT, aPTT, PT and anti-Xa levels may be used (DOAC dependant). In the case of Dabigatran, reversal with Idaracizumab may also be considered.
Australian guidelines (https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management)	Comparable to French Society of Vascular Neurology

Seiffge DJ, *et al*. *J Neurol Neurosurg Psychiatry* 2021;**92**:534–541. doi:10.1136/jnnp-2020-325456

Selection based on time

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half-life	13 hours	5–13 hours	12 hours	12 hours
Time to peak	1.5–3 hours	2–3 hours	3–4 hours	1–2 hours
Oral bio-availability	3%–7%	80%–100%	50%	60%
Renal clearance	80%	70%	45%	50%
Conventional tests	Normal thrombin time=no dabigatran circulating. Other tests not useful.	Not useful	Not useful	Not useful
Suggested assays	Dilute thrombin time or ecarin-based clotting assays	Calibrated anti-Xa assays	Calibrated anti-Xa assays	Calibrated anti-Xa assays

Time since last dose >48h

- Time since last intake may not always correlate with DOAC level/activity
- Age, kidney function, drug interactions, and/or genetic polymorphism may all lead to inter-person variability

Reversal of coagulopathy

	Idarucizumab	Andexanet alfa
Brand name	Praxbind	Ondexxya Andexxa
Target	Dabigatran	Rivaroxaban Apixaban Edoxaban[a]
Mode of action	Non-competitive inhibitor	Decoy protein sequestering FXa inhibitors
Administration	Intravenous	Intravenous
Dosing	5 g in 2 separate vials (infusion within 15 min)	Low dose: 400 mg bolus, 2-h infusion 4 mg/min High dose: 800 mg bolus, 2-h infusion 8 mg/min
Specific dosing recommendations	NA	Last DOAC intake >8 h ago: low dose Last DOAC intake <8 h ago: high dose (rivaroxaban >10 mg, apixaban >5 mg), low dose (rivaroxaban <10 mg, apixaban <5 mg)
Onset	10–30 min	Within minutes
Half-life	45 min	5–7 h

Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

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ABSTRACT

BACKGROUND

Patients with acute intracerebral hemorrhage who are receiving factor Xa inhibitors have a risk of hematoma expansion. The effect of andexanet alfa, an agent that reverses the effects of factor Xa inhibitors, on hematoma volume expansion has not been well studied.

METHODS

We randomly assigned, in a 1:1 ratio, patients who had taken factor Xa inhibitors within 15 hours before having an acute intracerebral hemorrhage to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined by expansion of the hematoma volume by 35% or less at 12 hours after baseline, an increase in the score on the National Institutes of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety end points were thrombotic events and death.

RESULTS

A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti–factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.

CONCLUSIONS

Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion AstraZeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Connolly can be contacted at stuart.connolly@phri.ca or at the Population Health Research Institute, Hamilton Health Sciences, McMaster University, 30 Birge St., Room C3-204, Hamilton ON L8L 0A6, Canada.

*A list of the ANNEXA-I investigators is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2313040

CME

Table 2. Efficacy End Points.

End Point	Andexanet (N=224)	Usual Care (N=228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤35%†	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	
NIHSS score change <7 points	188/214 (87.9)	181/218 (83.0)	4.6 (–2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (0.0 to 7.6)	
Hematoma volume increase ≥12.5 ml‡	24/216 (11.1)	36/214 (16.8)	–5.6 (–12.0 to 0.8)	
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	

Table 3. Thrombotic Events and Deaths at 30 Days.*

Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

Selection based on DOAC plasma level

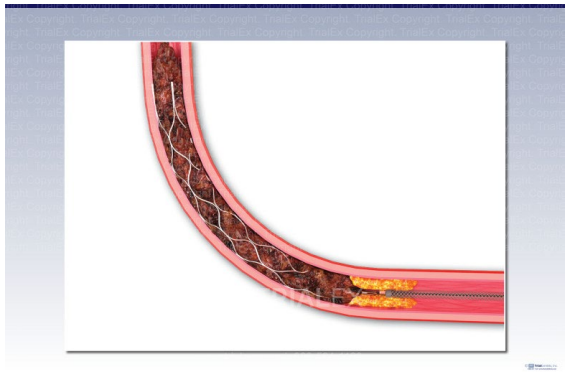
Or

Calibrated anti-Xa level <30 ng/ml

- Would be ideal
- BUT, lack of availability and/or delayed reporting (sent-out) are problematic in the vast majority of US hospitals
- ? TEG (under investigations)
- Perhaps, we should advocate for point-of-care testing as a requirement for CSC certification process!

Or normal TT, if Dabigatran

Mechanical thrombectomy



Endovascular Stroke Treatment and Risk of Intracranial Hemorrhage in Anticoagulated Patients

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Background and Purpose—We aimed to determine the safety and mortality after mechanical thrombectomy in patients taking vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).

Methods—In a multicenter observational cohort study, we used multiple logistic regression analysis to evaluate associations of symptomatic intracranial hemorrhage (sICH) with VKA or DOAC prescription before thrombectomy as compared with no anticoagulation. The primary outcomes were the rate of sICH and all-cause mortality at 90 days, incorporating sensitivity analysis regarding confirmed therapeutic anticoagulation. Additionally, we performed a systematic review and meta-analysis of literature on this topic.

Results—Altogether, 1932 patients were included (VKA, n=222; DOAC, n=98; no anticoagulation, n=1612); median age, 74 years (interquartile range, 62–82); 49.6% women. VKA prescription was associated with increased odds for sICH and mortality (adjusted odds ratio [aOR], 2.55 [95% CI, 1.35–4.84] and 1.64 [95% CI, 1.09–2.47]) as compared with the control group, whereas no association with DOAC intake was observed (aOR, 0.98 [95% CI, 0.29–3.35] and 1.35 [95% CI, 0.72–2.53]). Sensitivity analyses considering only patients within the confirmed therapeutic anticoagulation range did not alter the findings. A study-level meta-analysis incorporating data from 7462 patients (855 VKAs, 318 DOACs, and 6289 controls) from 15 observational cohorts corroborated these observations, yielding an increased rate of sICH in VKA patients (aOR, 1.62 [95% CI, 1.22–2.17]) but not in DOAC patients (aOR, 1.03 [95% CI, 0.60–1.80]).

Conclusions—Patients taking VKA have an increased risk of sICH and mortality after mechanical thrombectomy. The lower risk of sICH associated with DOAC may also be noticeable in the acute setting. Improved selection might be advisable in VKA-treated patients.

Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT03496064. Systematic Review and Meta-Analysis: CRD42019127464. **(*Stroke*. 2020;51:892-898. DOI: 10.1161/STROKEAHA.119.026606.)**

Table. Outcome Data Comparing Patients According to Status of Oral Anticoagulation on Univariable χ^2 Analysis

Outcome	DOAC (n=98)	VKA (n=222)	Other (n=1622)	*P* Value	*P* for All DOACs vs All VKAs	Warranted Therapeutic DOAC (n=49)	Warranted Therapeutic VKA (n=69)	*P* for Therapeutic DOAC vs Therapeutic VKA
sICH ECASS II	5 (5.2%)	21 (9.5%)	84 (5.2%)	0.033	0.267	2 (4.2%)	5 (7.4%)	0.698
Mortality at 3 mo	21 (31.8%)	64 (34.6%)	347 (23.9%)	0.004	0.763	15 (42.9%)	21 (35.0%)	0.513
Systemic bleeding	0 (0%)	6 (6.5%)	22 (3.4%)	0.287	0.408	0 (0%)	2 (5.3%)	1.000
mRS 0–2 at 3 mo	29 (43.9%)	61 (33%)	648 (44.7%)	0.010	0.135	16 (45.7%)	21 (35.0%)	0.384

DOAC-treated patients also had increased 90-day mortality compared to controls, reflecting the overall worse prognostic profile of patients on AC!

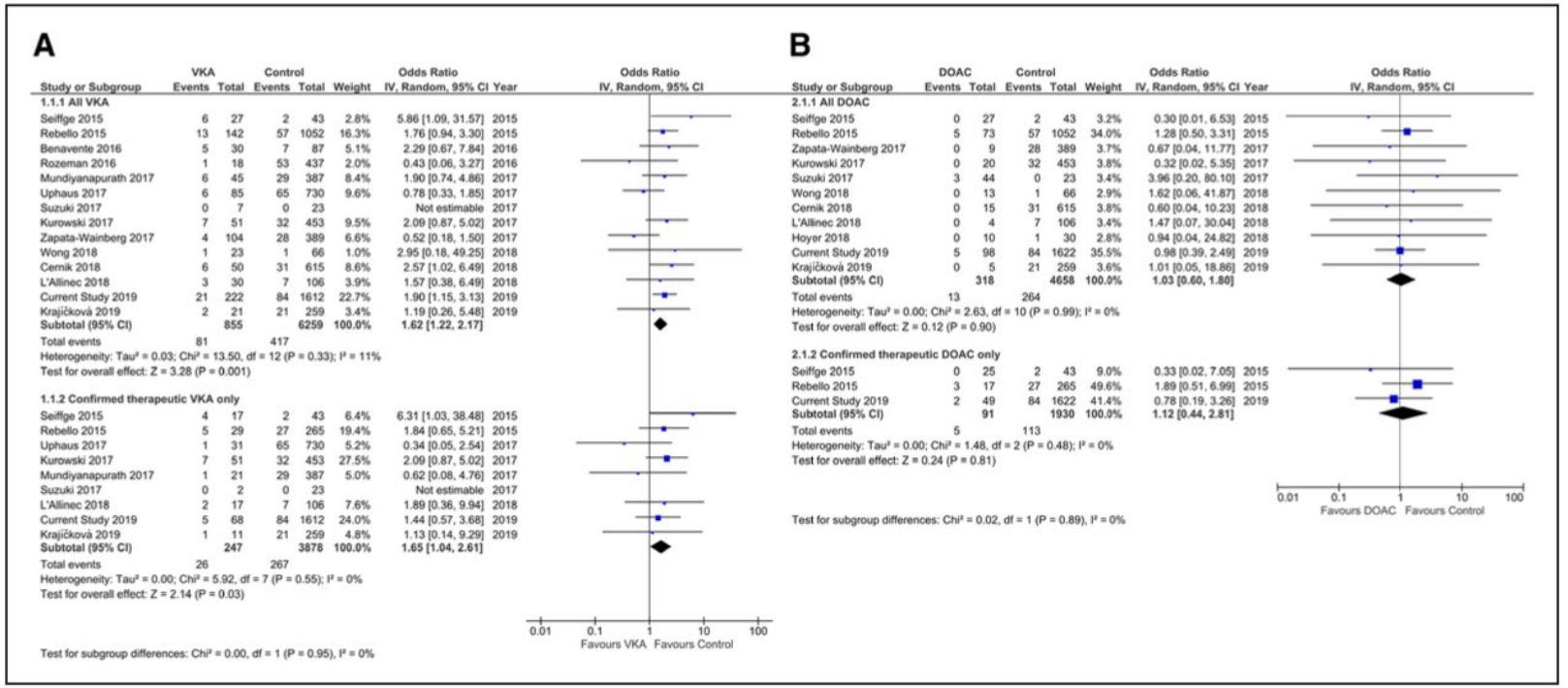

Figure. Meta-analysis of risk of symptomatic intracranial hemorrhage of patients with anticoagulation as compared to controls.[38–43] Forest plot of unadjusted odds ratios for symptomatic intracranial hemorrhage in patients on vitamin K antagonist (VKA; **A**) and direct oral anticoagulant (DOAC; **B**) as compared with patients not on anticoagulation. IV indicates inverse variance.

ORIGINAL RESEARCH

Impact of Direct Oral Anticoagulant Levels on Functional Independence Following Endovascular Thrombectomy in Patients With Atrial Fibrillation

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BACKGROUND: In direct oral anticoagulant (DOAC) users with stroke due to large artery occlusion, endovascular thrombectomy is an effective treatment when intravenous thrombolytic therapy is unsuitable. The purpose of this study is to investigate the association between emergent DOAC levels and endovascular thrombectomy outcomes.

METHODS: Participants with atrial fibrillation, who had a premorbid modified Rankin Scale score of ≤3 and had undergone endovascular thrombectomy for acute stroke, were enrolled. Drug levels upon hospital arrival were measured in the prestroke DOAC users. Head noncontrast computed tomography and computed tomographic angiography images were used to quantify thrombus permeability. The primary outcome was functional independence at 3 months (modified Rankin Scale 0–2 or a return to premorbid status for patients with a premorbid modified Rankin Scale of 3).

RESULTS: The study included 250 patients (antithrombotic agent nonusers, 42.0%; oral anticoagulant users, 34.0%; and antiplatelet users, 24.0%). The primary outcomes did not differ among the 3 groups. Among oral anticoagulant users, 78.8% were DOAC users. Of the 59 DOAC users with available drug level measurements, 62.7% had low levels (<50 ng/mL). Low-level patients were less likely to achieve functional independence than high-level patients (adjusted odds ratio, 0.26 [0.08–0.87]). Compared with antithrombotic nonusers, oral anticoagulant users with therapeutic anticoagulation were more likely to achieve functional independence (adjusted odds ratio, 2.83 [1.18–6.78]), whereas those with inadequate anticoagulation did not. Symptomatic intracerebral hemorrhage occurred in 3 DOAC users in the low-level group (8.1%), 1 DOAC user in the high-level group (4.5%), and 4 antithrombotic nonusers (3.8%). Thrombus permeability was similar between antithrombotic nonusers and low- or high-level DOAC users.

CONCLUSION: Among patients who underwent DOAC therapy and endovascular thrombectomy, those with low DOAC levels were less likely to achieve functional independence. Furthermore, oral anticoagulant users with therapeutic anticoagulation displayed better functional outcomes than antithrombotic nonusers.

Table 2. Stroke Presentation, Management, and Outcomes Among Patients With Atrial Fibrillation Receiving Different Prestroke Antithrombotic Treatments

Prestroke antithrombotic therapy	No Antithrombotic therapy before stroke	OAC*	Antiplatelet therapy before stroke	*P* value
	(N = 105)	(N = 85)	(N = 60)	
Prestroke mRS score†	0 (0–0)	0 (0–1)	0 (0–2)	0.04‡
Initial presentation				
GCS score†	12 (10–15)	11 (9–15)	11 (9–15)	0.90
NIHSS score upon hospital presentation†	18 (14–22)	18 (14–23)	18 (13–23)	0.96
SBP (mmHg)	157.1 ± 28.2	148.9 ± 26.7	156.6 ± 28.9	0.11
DBP (mmHg)	84.3 ± 17.6	83.2 ± 17.1	81.5 ± 16.6	0.62
Characteristics of EVT				
rtPA before EVT	42 (40.0)	13 (15.3)	21 (35.0)	<0.01‡
ASPECT score	8 (7–10)	8 (7–10)	9 (7–10)	0.73
Onset to EVT puncture (hours)	4.4 ± 3.5	3.9 ± 2.6	4.6 ± 3.1	0.40
Within 6 h	21 (20.0)	14 (16.5)	14 (23.3)	0.59
Type of EVT procedure				0.06
Suction thrombectomy	91 (86.7)	70 (82.4)	42 (70.0)	
Stent retriever	1 (1.0)	3 (3.5)	2 (3.3)	
Both	10 (9.5)	11 (12.9)	12 (20.0)	
Intra-arterial rtPA	2 (1.9)	0 (0)	0 (0)	
None‡	1 (1.0)	1 (1.2)	4 (6.7)	
Outcomes				
Functional independence at 3 mo¶	44 (41.9)	42 (49.4)	23 (38.3)	0.37
mRS score at 3 mo	3 (1–4)	3 (2–4)	3 (2–4)	0.49
Symptomatic ICH	4 (3.8)	5 (5.9)	4 (6.7)	0.69
Puncture to recanalization (min)	27.6 ± 21.8	26.3 ± 17.3	25.0 ± 19.0	0.72
Successful reperfusion (TICI 2b-3)	98 (93.3)	76 (89.4)	55 (91.7)	0.63
Early neurological improvement	38 (36.2)	37 (43.5)	21 (35.0)	0.48
Any ICH	37 (35.2)	32 (37.6)	17 (28.3)	0.50
mRS score at discharge	3 (2–4)	3 (2–4)	3 (3–5)	0.31
Poor functional outcome at discharge¶	42 (40.0)	30 (35.3)	27 (45.0)	0.50
Death at discharge	6 (5.7)	4 (6.7)	5 (5.9)	0.97
Death at 3 mo	7 (6.7)	6 (10.0)	5 (5.9)	0.62

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RESEARCH Open Access

Safety and efficacy of endovascular thrombectomy in acute ischemic stroke treated with anticoagulants: a systematic review and meta-analysis

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Abstract

Background: Endovascular thrombectomy (EVT) is an effective therapy in acute ischemic stroke (AIS) with large vessel occlusion, especially for those who are unsuitable for intravenous thrombolysis. However, the safety and efficacy of EVT in AIS patients who receiving oral anticoagulants (OACs) is unclear, especially for the risk of symptomatic intracranial hemorrhage (sICH).

Methods: Database of PubMed, Embase, and Cochrane Library were searched from Jan 1, 2000, through the final search date of Jun 2, 2021. Eligible studies for enrollment required outcomes reported for events of sICH, mortality, functional status, and successful reperfusion. Meta-analysis was conducted to compare the outcomes difference after EVT between AIS patients with or without OACs use. The primary safety outcome was sICH after EVT, and the primary efficacy outcome was functional status at 3 months.

Results: One thousand nine hundred forty studies were screened for eligibility and 15 of them were included in the meta-analysis. Compared the OACs group to control arm, vitamin K antagonists (VKAs) was associated with higher risk of sICH (OR 1.49, 95% CI 1.10–2.02) and mortality (OR 1.67, 95% CI 1.35–2.06). Poor functional outcomes were noted both in the VKAs and direct oral anticoagulants (DOACs) groups (OR 0.62, 95% CI 0.54–0.71 and OR 0.61, 95% CI 0.53–0.71, respectively). No differences in successful reperfusion were observed.

Conclusions: Comparing with DOACs, VKAs use was associated with a higher risk of sICH and mortality after EVT. Patients who did not receive OACs exhibited more favorable outcomes. The successful reperfusion did not differ between groups. However, results for mortality and functional outcomes have to be interpreted with caution since they are based on non-randomized data and unadjusted proportions.

Keywords: Endovascular thrombectomy, Anticoagulants, Symptomatic intracranial hemorrhage

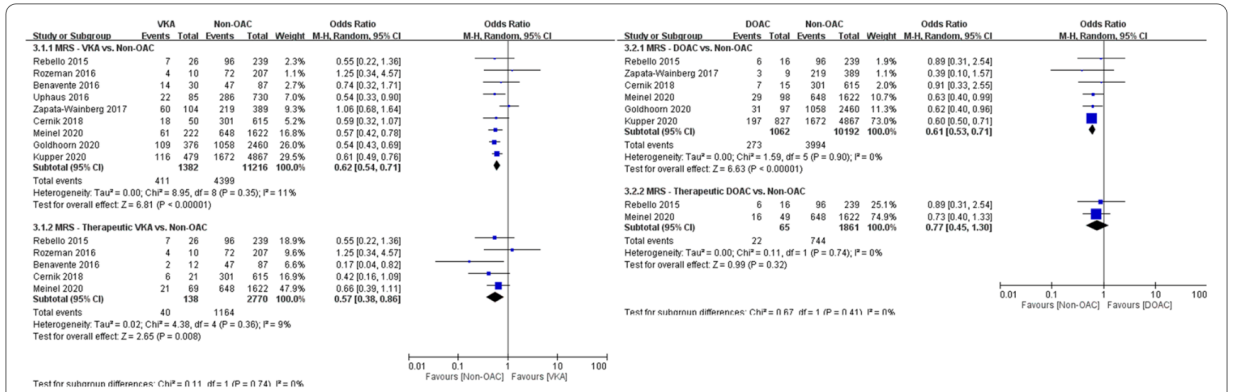


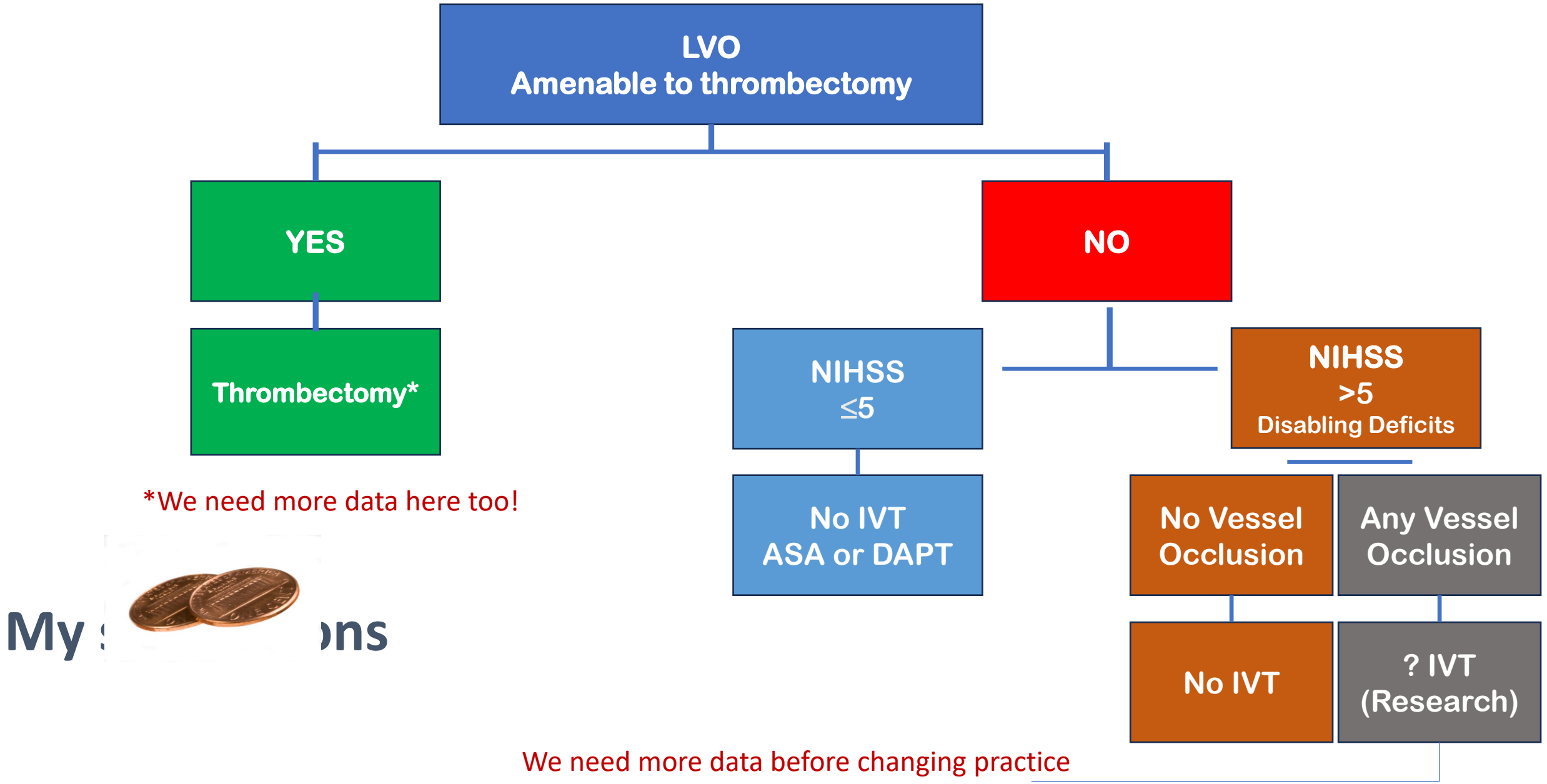
Fig. 4 **A** Forest plot for VKA vs. non-OAC regarding functional outcome. **B** Forest plot for DOAC vs. non-OAC regarding functional outcome

Enrollment in clinical trials

- **The DOAC – International Thrombolysis (DO-IT) randomized controlled trial and registry**
  - Swiss National Science Foundation
  - Thomas Meinel, Luciana Catanese, David Seiffge
  - 800 patients (IVT rt-PA or TNK vs SOC)
  - PROBE design
  - The randomized trial is accompanied by a prospective, international, multi-center, observational cohort study using a target trial design, where patients with recent DOAC intake not receiving thrombolysis as well as patients receiving IVT but without recent DOAC intake, meeting all inclusion and exclusion criteria will be prospectively enrolled and serve as controls.

- **ESTER-DOAC**
  - StrokeNet
  - Shadi Yaghi, Eva Mistry, Ope Adeoye
  - In planning

- **ACT-GLOBAL Thrombolysis Platform**
  - **Bijoy Mundak**
  - **Lower dose TNK (0.12.5 mg/kg) vs. normal dose (0.25 mg/kg) vs. no TNK**



*We need more data here too!

My s ons

JAMA | Original Investigation

Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits

The PRISMS Randomized Clinical Trial

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IMPORTANCE More than half of patients with acute ischemic stroke have minor neurologic deficits (National Institutes of Health Stroke Scale [NIHSS] score of 0-5) at presentation. Although prior major trials of alteplase included patients with low NIHSS scores, few without clearly disabling deficits were enrolled.

OBJECTIVE To evaluate the efficacy and safety of alteplase in patients with NIHSS scores of 0 to 5 whose deficits are not clearly disabling.

DESIGN, SETTING, AND PARTICIPANTS The PRISMS trial was designed as a 948-patient, phase 3b, double-blind, double-placebo, multicenter randomized clinical trial of alteplase compared with aspirin for emergent stroke at 75 stroke hospital networks in the United States. Patients with acute ischemic stroke whose deficits were scored as 0 to 5 on the NIHSS and judged not clearly disabling and in whom study treatment could be initiated within 3 hours of onset were eligible and enrolled from May 30, 2014, to December 20, 2016, with final follow-up on March 22, 2017.

INTERVENTIONS Participants were randomized to receive intravenous alteplase at the standard dose (0.9 mg/kg) with oral placebo (n = 156) or oral aspirin, 325 mg, with intravenous placebo (n = 157).

MAIN OUTCOMES AND MEASURES The primary outcome was the difference in favorable functional outcome, defined as a modified Rankin Scale score of 0 or 1 at 90 days via Cochran-Mantel-Haenszel test stratified by pretreatment NIHSS score, age, and time from onset to treatment. Because of early termination of the trial, prior to unblinding or interim analyses, the plan was revised to examine the risk difference of the primary outcome by a linear model adjusted for the same factors. The primary safety end point was symptomatic intracranial hemorrhage (sICH) within 36 hours of intravenous study treatment.

RESULTS Among 313 patients enrolled at 53 stroke networks (mean age, 62 [SD, 13] years; 144 [46%] women; median NIHSS score, 2 [interquartile range {IQR}, 1-3]; median time to treatment, 2.7 hours [IQR, 2.1-2.9]), 281 (89.8%) completed the trial. At 90 days, 122 patients (78.2%) in the alteplase group vs 128 (81.5%) in the aspirin group achieved a favorable outcome (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%). Five alteplase-treated patients (3.2%) vs 0 aspirin-treated patients had sICH (risk difference, 3.3%; 95% CI, 0.8%-7.4%).

CONCLUSIONS AND RELEVANCE Among patients with minor nondisabling acute ischemic stroke, treatment with alteplase vs aspirin did not increase the likelihood of favorable functional outcome at 90 days. However, the very early study termination precludes any definitive conclusions, and additional research may be warranted.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02072226

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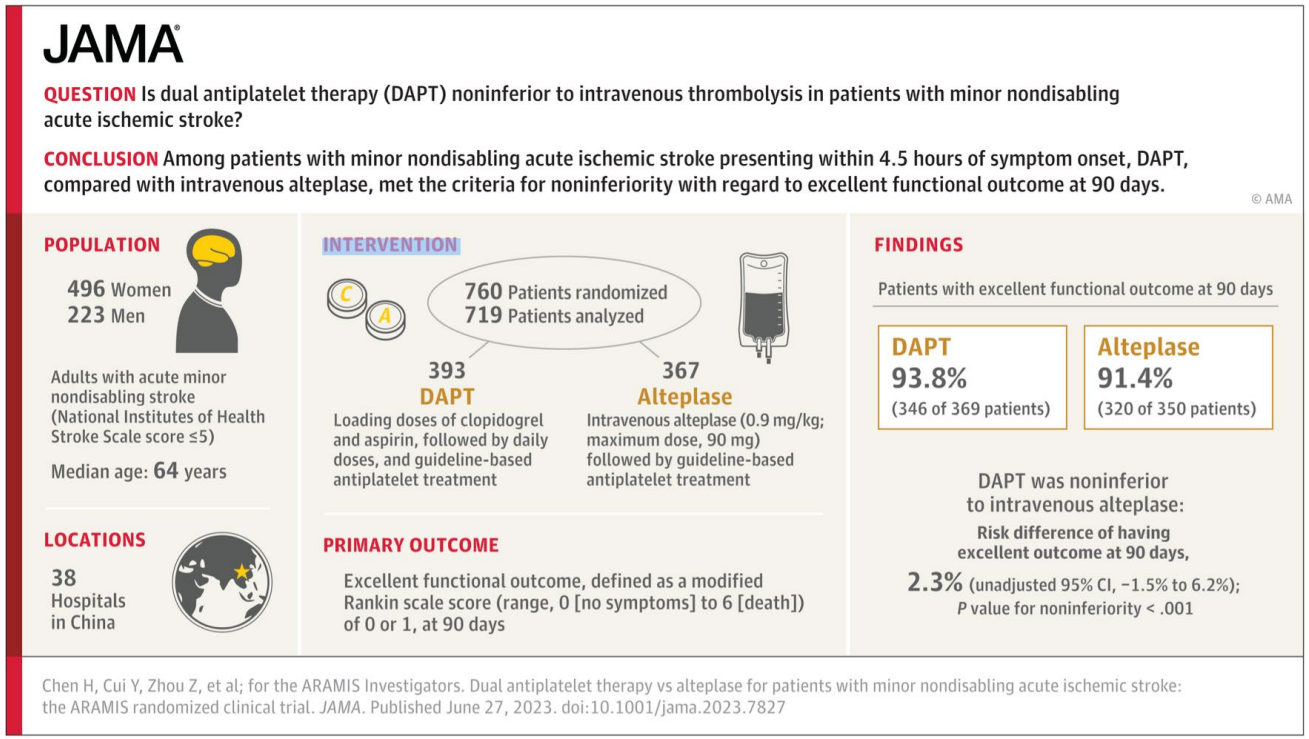

Thank You

For Your Attention!

Any Questions

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