ICAD- Current Management: Who Warrants Intervention and Who Warrants Medical Management

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Disclosures

- Research Funding From the NIH / NINDS for the WASID, SAMMPRIS and CAPTIVA trials, NIH Wingspan Stenting Registry, K24 and CTSA KL2, and StrokeNetwork Grants
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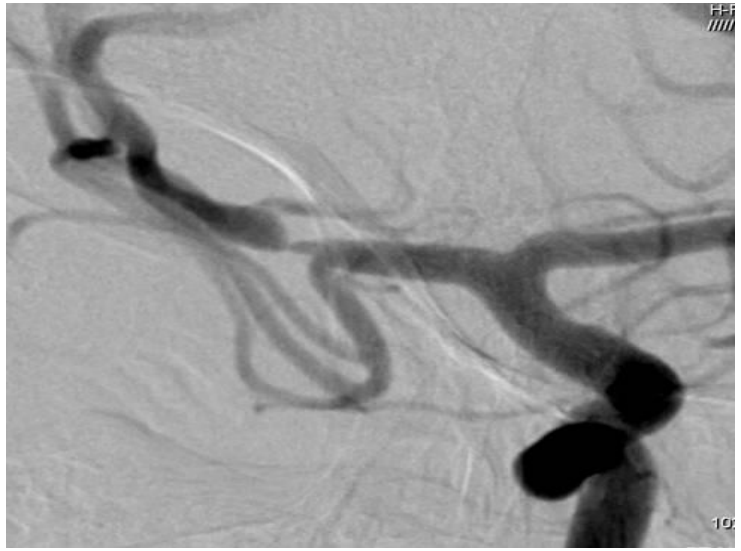
Outline

- Incidence and Risk
- Randomized Trials in Subjects with ICAS
- Alternative Treatments?
- AHA Guidelines on ICAS Rx

World-Wide Burden of Intracranial Atherosclerosis



- USA: Important cause of stroke (8-10%), especially in Blacks (15-29%), Hispanics, and Asians
- China 33–50%, Thailand 47%, S. Korea 56%
- Based on ethnic and racial make-up of world population, one of the most common cause of stroke
- Particularly High Risk of Recurrent Stroke

Recurrent Stroke Rates For Different Causes of Stroke

Clinical group	Study	1-year risk (%)
Afib on eliquis	ARISTOTLE	**1.2**
Sx cervical carotid stenosis_stent	CREST (annnualized)	**2.0**
Small vessel disease	SPS3	**2.5**
Sx cervical carotid stenosis_cea	CREST (annnualized)	**2.5**
Afib, chads =>3	ARISTOTLE	**2.9**
Afib, chads_vasc 3	Friberg 2012	**3.2**
CHF < 15% + hx stroke	WARCEF subgroup	**5.9**
ICAD > 50%	WASID	**8.0**
Afib, chads_vasc 7 (untreated)	Friberg 2012	**11.2**
ICAD > 70%	SAMPRISS	**23.0**

Randomized Treatment Trials in ICAS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

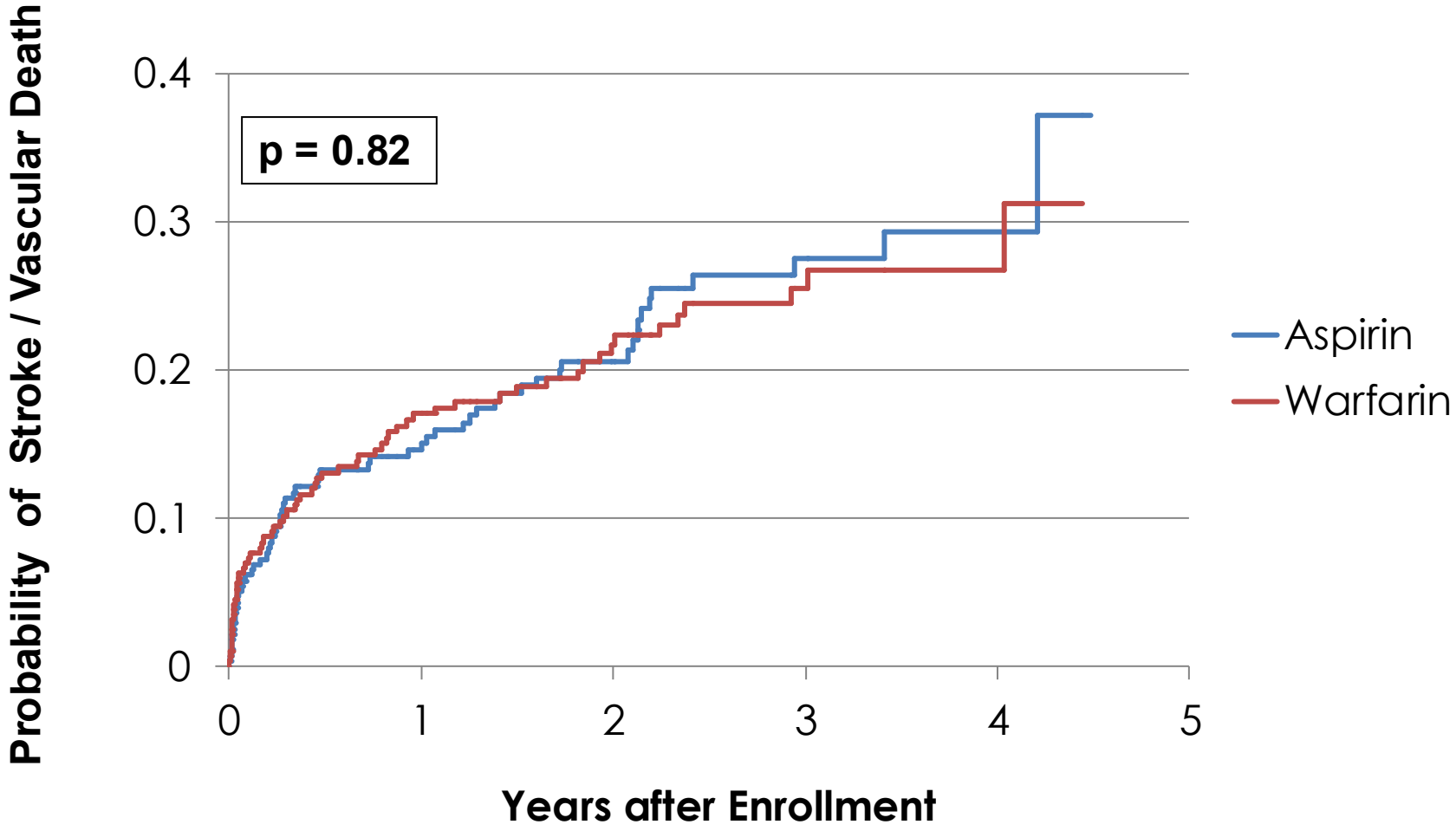
Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Harriet Howlett-Smith, R.N., Barney J. Stern, M.D., Vicki S. Hertzberg, Ph.D., Michael R. Frankel, M.D., Steven R. Levine, M.D., Seemant Chaturvedi, M.D., Scott E. Kasner, M.D., Curtis G. Benesch, M.D., Cathy A. Sila, M.D., Tudor G. Jovin, M.D., and Jose G. Romano, M.D., for the Warfarin–Aspirin Symptomatic Intracranial Disease Trial Investigators*

ABSTRACT

WASID Primary Endpoint:

Stroke and Vascular Death



Stroke in Territory: 70-99% Stenosis and Time from Qualifying Event

	At 1 Year	At 2 Years
≤ 30 days	22.9 % (95% CI 15.4 – 30.4%)	25% (95% CI 17.2% - 32.9%)
> 30 days	9% (95% CI 2.1 – 16.0%)	9% (95% CI 2.1 – 16.0%)

Stenting & Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis

SAMMPRIS

Study Design

Angioplasty and Stenting (Wingspan System) + Aggressive Medical Management

vs.

Aggressive Medical Management Alone

Main SAMMPRIS Inclusion Criteria

- 70 - 99% stenosis
- Recent (within 30 days) non-disabling stroke or TIA

Stroke or Death Rates at 30 Days

Period	PTAS	Medical	Absolute RR	P-value
30 Days	14.7%	5.8%	8.9%	0.002

NNH = 11

N Engl J Med 2011; 365:993-1003

Primary Endpoint (Stroke or Death at 30 Days or Stroke in the Territory Beyond 30 Days)

Period	PTAS	Medical	Absolute RR	P-value
30 Days	14.7%	5.8%	8.9%	0.002
Year 1	19.7%	12.6%	7.1%	0.04
Year 2	20.6%	14.1%	6.5%	0.07
Year 3	23.9%	14.9%	9.0%	0.02

Lancet. 2014; 383(9914):333-41

VISSIT Trial

Balloon-expandable Pharos stent
Zaidat et al. JAMA 2015

- Similar entrance criteria to SAMMPRIS
- Similar medical management (except LDLc < 100 mg/dl, no lifestyle intervention)
- Included sites in Europe and China
- Enrollment stopped early (112 patients)
- Peri-procedural (30-day) stroke - 25.8%
  - 17.2% ischemic stroke, 8.6% hemorrhagic stroke
- Any stroke within 30 days or stroke in terr. to 1 yr: **43.1%** in stenting group, **9.4%** in medical group) ----> NNH = 3.

China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS)

- Wingspan stenting vs. medical Rx in subject with TIA or stroke from 70-99% stenosis
- If stroke QE, wait > 3 weeks to enroll
- 8 high-volume Chinese centers
- Perforator strokes excluded

Interv Neuroradiol. 2015;21(2):196-204

CASSISS Trial

JAMA

QUESTION In transient ischemic attack (TIA) or ischemic stroke due to intracranial atherosclerotic stenosis, does angioplasty and stenting ≥3 weeks after the index event along with standard medical therapy reduce the risk of stroke or death vs medical therapy alone?

CONCLUSION This randomized clinical trial's findings did not support the addition of percutaneous transluminal angioplasty and stenting to medical therapy for the treatment of patients with symptomatic severe intracranial atherosclerotic stenosis.

POPULATION

263 Men
95 Women

Adults with TIA or nondisabling ischemic stroke attributed to severe intracranial stenosis

Mean age: 56.3 years

LOCATIONS

8
Centers
in China

INTERVENTION

380 Patients randomized
358 Patients analyzed

176

Stenting plus medical therapy

Percutaneous transluminal angioplasty and stenting plus medical therapy

182

Medical therapy alone

Aspirin and clopidogrel for 90 days (single antiplatelet therapy thereafter) and control of stroke risk factors

PRIMARY OUTCOME

Composite of stroke or death within 30 days or stroke in the qualifying artery territory beyond 30 days through 1 year

FINDINGS

Risk of stroke or death

Stenting plus medical therapy
8.0% (14 of 176 patients)

Medical therapy alone
7.2% (13 of 181 patients)

There was no significant difference between groups:

Between-group difference, 0.4%
(95% CI, −5.0% to 5.9%)

Hazard ratio, 1.10
(95% CI, 0.52 to 2.35)

Gao P, Wang T, Wang D, et al; CASSISS Trial Investigators. Effect of stenting plus medical therapy vs medical therapy alone on risk of stroke and death in patients with symptomatic intracranial stenosis: the CASSISS randomized clinical trial. *JAMA*. Published August 9, 2022. doi:10.1001/jama.2022.12000

Primary Endpoints in Select Subgroups in Medical Group in SAMMPRIS

- Qualifying Event = TIA: 5.6% at 1 yr
- Qualifying Event = Stroke: 16.1% at 1 yr
- Qualifying Event = Borderzone Infarct: 21.1% at 1 yr
- More Effective Treatments Needed for High-Risk Subgroups, Particularly in Patients with Hemodynamic Compromise

Waters, et al. JAMA Neurol, 2016;73(3):308 Wabnitz, et al. Stroke. 2019;50:143-147

Alternative Treatments?

- Drug-eluting stent
- Angioplasty alone
- Alternative antithrombotic agents

JAMA Neurology | Original Investigation

Comparison of Drug-Eluting Stent With Bare-Metal Stent in Patients With Symptomatic High-grade Intracranial Atherosclerotic Stenosis

A Randomized Clinical Trial

Baixue Jia, MD; Xuelei Zhang, MD; Ning Ma, MD; Dapeng Mo, MD; Feng Gao, MD; Xuan Sun, MD; Ligang Song, MD; Lian Liu, MD; Yiming Deng, MD; Xiaotong Xu, MD; Yong Zhang, MD; Zengpin Liu, MD; Sheng Guan, MD; Fan Zhang, MD; Bing Li, MD; Hongbo Zheng, MD; Xinfeng Liu, MD; Yajie Liu, MD; Kangning Chen, MD; Jie Shuai, MD; Jieqing Wan, MD; Jun Wang, MD; Xiangqun Shi, MD; Tianxiao Li, MD; Binge Chang, MD; David S. Liebeskind, MD; Wengui Yu, MD, PhD; Zhongrong Miao, MD; for the NOVA Trial Investigators

Stroke or death within 30 days: 10 [7.6%] vs 7 [5.3%]; $P = .46$

Stroke from day 31-1 year (1 [0.8%] vs 9 [6.9%]; $P = .03$

In stent restenosis at 1 year: 10 [9.5%] vs 32 [30.2%]; $P < .001$

JAMA Neurology 2022; 79:176-184

Angioplasty Alone

Potential Advantages

- One Step Procedure (vs. 2 Steps With Stenting) - Decrease the Risk of Distal Wire Perforation (SAH)
- No Residual Metal Left in Artery - Lower Risk of Thrombo-Embolism
- Angioplasty Balloons Are Lower Profile Than Stent Bearing Catheters - Less "Snow Plowing" of Atherosclerotic Plaque into Perforators

Disadvantages

- High risk of dissection
- High rate of restenosis

BASIS - Chinese Angioplasty Trial

- 31 centers across China
- 35 - 80 years
- TIA (within 90 days) or ischemic stroke (within 14-90 days) attributed to 70% to 99% ICAS
- Treatment with at least 1 antithrombotic drug and/or standard risk factor management

BASIS - Chinese Angioplasty Trial

JAMA

QUESTION Is balloon angioplasty plus aggressive medical management superior to aggressive medical management alone for severe symptomatic intracranial atherosclerotic stenosis (sICAS)?

CONCLUSION Balloon angioplasty plus aggressive medical management, compared with aggressive medical management alone, significantly lowered the risk of the composite outcome in patients with sICAS.

POPULATION

343 Men
158 Women

Adults aged 35 to 80 years with sICAS

Mean age: 58 years

LOCATIONS

31
Stroke centers in China

INTERVENTION

Balloon angioplasty
Balloon angioplasty plus risk factor management, including dual antiplatelet therapy for 90 days and aspirin daily thereafter

Aggressive medical management
Risk factor management, including dual antiplatelet therapy for 90 days and aspirin daily thereafter

PRIMARY OUTCOME

Stroke or death within 30 days after enrollment or after balloon angioplasty or ischemic stroke or revascularization of the qualifying artery territory after 30 days to 12 months following enrollment

FINDINGS

Incidence of primary outcome

Balloon angioplasty	Aggressive medical management
4.4% (11 of 249 patients)	13.5% (34 of 252 patients)

Results were statistically significant:
Hazard ratio, 0.32
(95% CI, 0.16 to 0.63); $P < .001$

Sun X, Deng Y, Zhang Y, et al; BASIS Investigators. Balloon angioplasty vs medical management for intracranial artery stenosis: the BASIS randomized clinical trial. *JAMA*. Published online September 5, 2024. doi:10.1001/jama.2024.12829

But.....

- **Eligibility window**: 14 – 90 days. Median time from qualifying event to randomization was 34 days, presumably because of concern about safety of earlier angioplasty (biases trial to angioplasty)

- **Site Impact**

Table S7 Post-hoc analysis of treatment interaction on the primary outcome regarding different sites

Site	No. of patients	Balloon angioplasty group (N=233)	Aggressive medical management group (N =238)	Measure of Effect	Treatment Effect (95% CI)	P for interaction
Beijing Tiantan Hospital	256	4(2.9)	19(16.1)	Hazard ratio	0.17(0.06 to 0.51)	.10
Other centers	245	7(6.3)	15(11.2)	Hazard ratio	0.56(0.23 to 1.36)	

Data are n (%). CI denotes confidence interval. IQR denotes interquartile range.

Other Issues with BASIS *

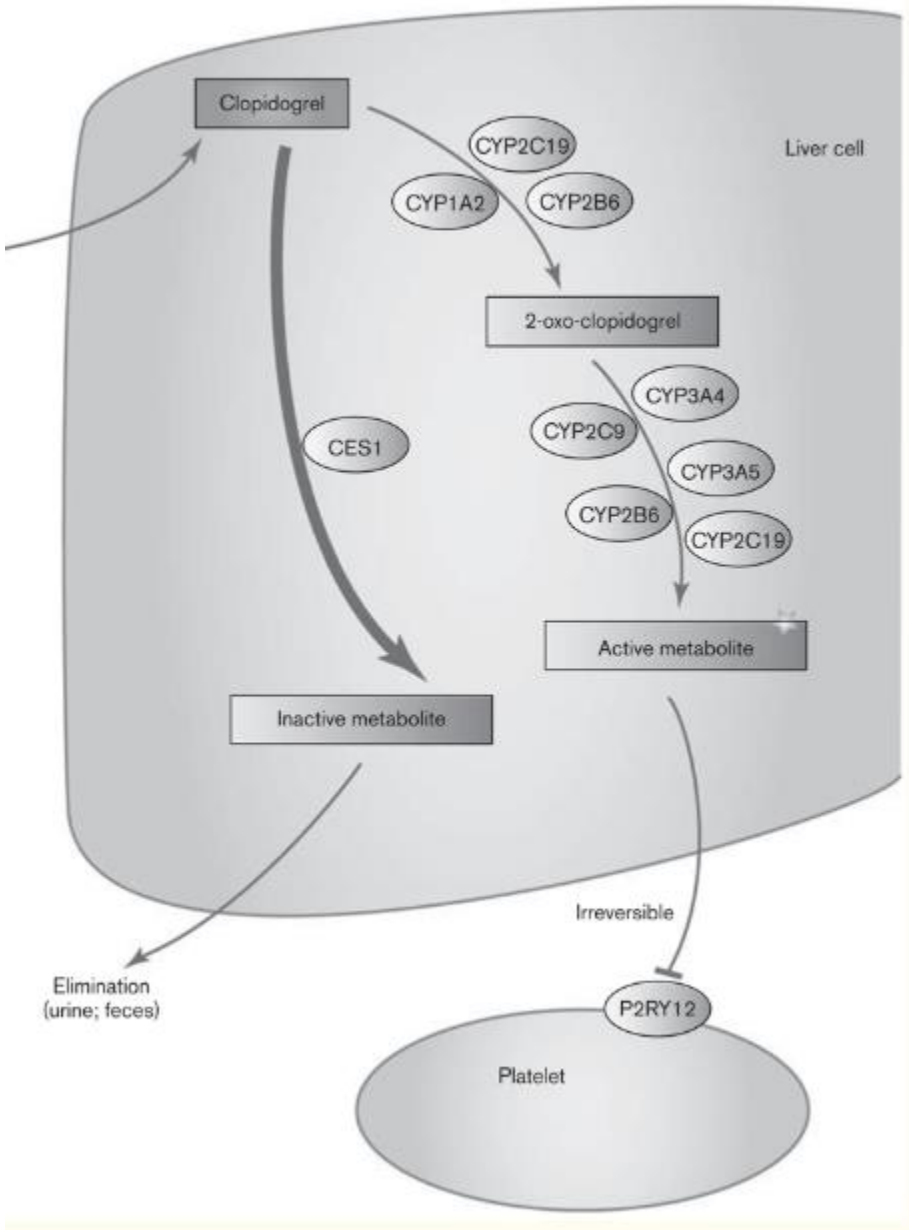
- **High rate of periprocedural dissection** after angioplasty (14.5%) requiring rescue stenting
- **BASIS performed entirely in China** - needs to be validated in a Western population
- **2 previous meta-analyses** of angioplasty for ICAS from other regions of the world showed stroke or death rates of 5% at 30 days and 9% at 1 year [1,2]

* Turan TN, Derdeyn CP. Is Balloon Angioplasty the Future for Intracranial Stenosis? JAMA. 2024 Sep 5. doi: 10.1001/jama.2024.13547

1. Stapleton CJ, et al. Neurosurgery. 2020;86(6):755-762.
2. Seyedsaadat SM, et al. J Neurointerv Surg. 2020;12(4):380-385.

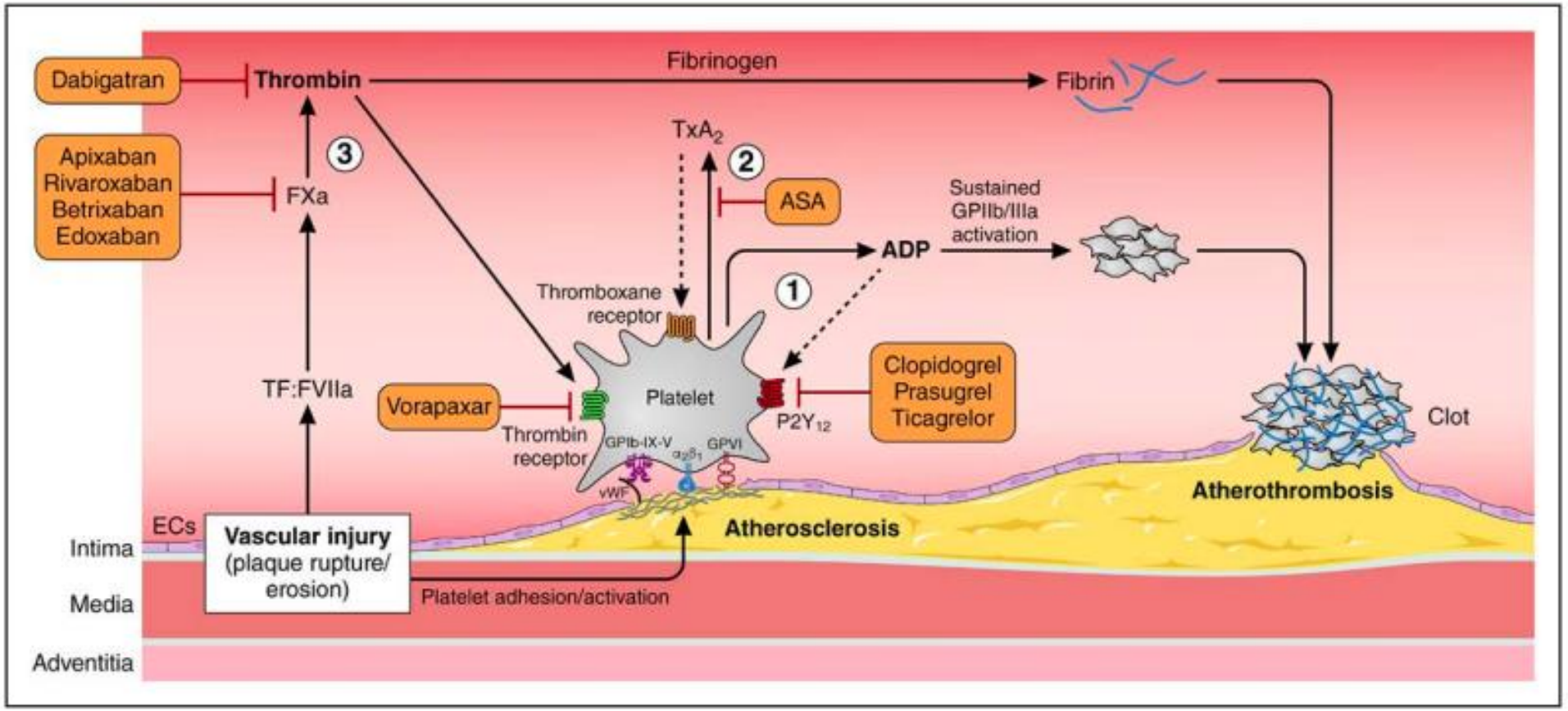
Alternative Antithrombotic Regimens

Clopidogrel Activation



Pharmacogenet Genomics. 2010 Jul; 20(7): 463–465.

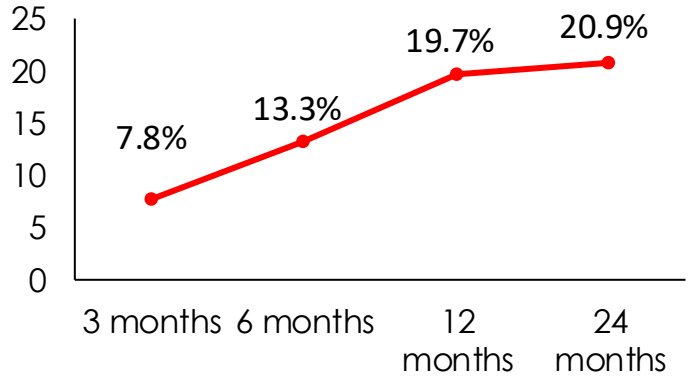
Mechanisms of Atherothrombosis and Potential Therapeutic Targets



From Circulation. 2019;139:2170–2185.

12-Month Dual Antithrombotic Rx: Rationale

- SAMMPRIS subjects who qualified with a symptomatic infarct: rate of recurrent symptomatic infarct in territory of stenotic artery more than doubled from 3 to 12 months[1]
- Half of US stroke neurologists already use clopidogrel + aspirin for longer than 3 months[2]



1. Al Kasab, JSCVD 2017, Lynn, personal communication
2. Turan et al, Cerebrov Dis 2014

CAPTIVA
Comparison of Anti-coagulation and anti-Platelet Therapies for Intracranial Vascular Atherostenosis

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

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MUSC Medical University of South Carolina

Duration of Antithrombotic Therapy

- In SAMMPRIS, 50 medical arm subjects took clopidogrel + ASA longer than 3 months for cardiac reasons *Abdul Rahman L, et al. JSCVD 2020*

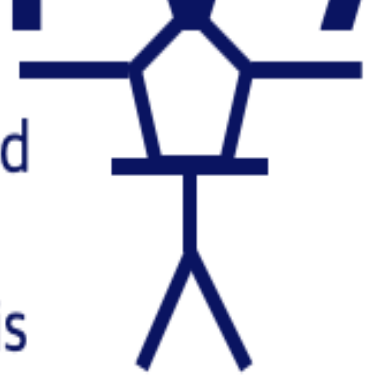
	No clopidogrel beyond 3 months N=158 medical subjects	**Clopidogrel + ASA >3 months N=50 medical subjects**
Stroke >3 months	10.8%	6.0%
Major Hemorrhage >3 months	2.5%	4.0%

CAPTIVA

UF UNIVERSITY of FLORIDA

CAPTIVA

Comparison of Anti-coagulation and
anti-Platelet Therapies for
Intracranial Vascular Atherostenosis



CAPTIVA

- 1683 subjects with non-disabling symptomatic infarct <30 days due to 70-99% stenosis of ICA, M1 or M2, A1, P1, basilar, or intracranial VA enrolled at 115 StrokeNet sites
- Randomize 1:1:1, double-blinded

  - Ticagrelor (180mg load, 90mg BID) + Aspirin (81mg QD)
  - Rivaroxaban (2.5mg BID) + Aspirin (81mg QD)
  - Clopidogrel (600mg load, 75mg QD) + Aspirin (81mg QD)
- Intensive Risk Factor Management (same as SAMMPRIS)
- Sample for CYP2C19 genotype test, blinded
- Follow-up visits 1 month, 4 months, 8 months, 12 months

CAPTIVA
Comparison of Anti-coagulation and anti-Platelet Therapies for Intracranial Vascular Atherostenosis

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

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CAPTIVA Updates

Feb 10, 2026

Tuesday, February 10, 2026

NIH halts arm of clinical trial evaluating a potential stroke treatment

Study found low-dose rivaroxaban to be unsafe and ineffective compared to standard of care.

March 23, 2026

Dear Site PIs and Coordinators,

The DSMB met on March 23 to evaluate the pre-planned futility and safety analysis, and sample size re-estimation. While they indicated there were no safety concerns for the remaining two arms (ticagrelor+aspirin and clopidogrel+aspirin), the sample size re-estimation showed that the required sample size to potentially demonstrate a difference between the two remaining arms was not feasible to achieve. **Therefore, the NINDS instructed us to stop further enrollment.**

ICAD- Current Management: Who Warrants Intervention and Who Warrants Medical Management

AHA/ ASA Guidelines Stroke Prevention 2021

		Angioplasty and Stenting
3: Harm	A	In patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, angioplasty and stenting should not be performed as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA.[353–359]
2b	C-LD	In patients with severe stenosis (70%-99%) of a major intracranial artery and actively progressing symptoms or recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of SBP <140 mm Hg, and high- intensity statin therapy (so-called medical failures), the usefulness of angioplasty alone or stent placement to prevent ischemic stroke in the territory of the stenotic artery is unknown.[350–352]

WASID

Stenting & Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis

SAMMPRIS

CAPTIVA

Comparison of Anti-coagulation and anti-Platelet Therapies for Intracranial Vascular Atherostenosis