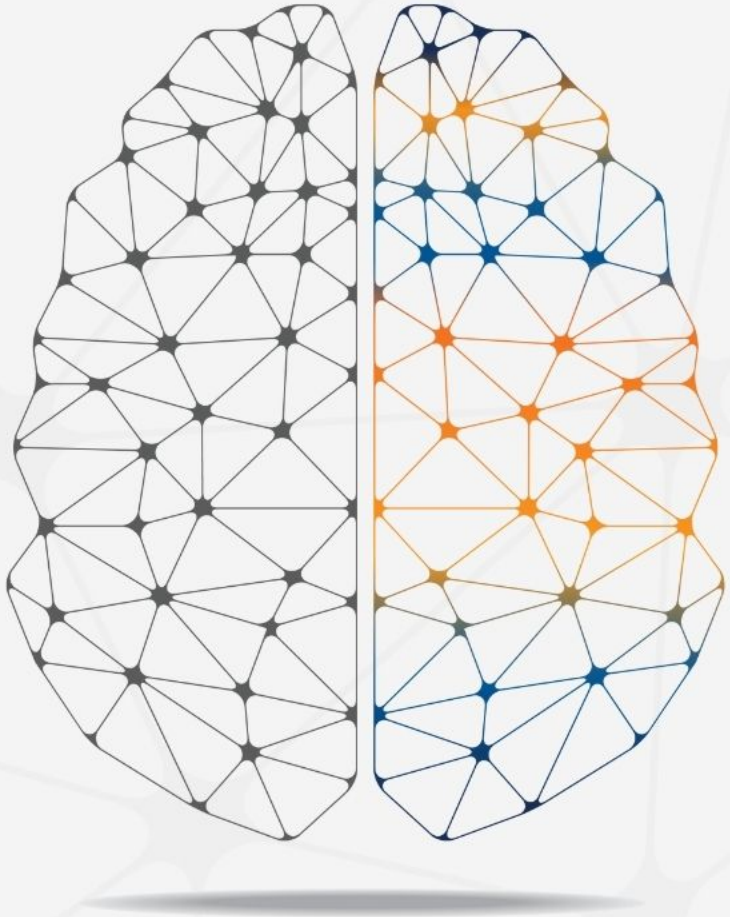


CAPTIVA

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

COLLABORATORS and FUNDING

National Institute of Neurological Disorders and Stroke

Clinical Coordinating Center

National Coordinating Center

National Data &
Risk Factor Management Centers

Rivaroxaban & Placebo Funding

Ticagrelor

Welcome PIs and Coordinators

- Microphones will be muted
- During the presentation, place all questions in chat
- At the conclusion of the presentation, use the “Raise Hand” function for Q&A session
- The webinar is being recorded and will be emailed to all site contacts and posted on the StrokeNet website

AGENDA

I. Welcome & Introductions
II. CAPTIVA Rationale
III. Study Design
IV. Over-encapsulation Design
V. Study Progress
VI. “To Do” List for Sites
VII. Overall Timeline
VIII. CHANCE-2 (NEJM Article)
IX. Questions & Answers

CAPTIVA

UF	MUSC	UC
Brian Hoh	Marc Chimowitz	Joe Broderick
Larisa Cavallari	Renee Martin	Noor Sabagha
Renee Boyette	Sharon Yeatts	Jamey Frasure
Jessica Smith	Tanya Turan	Amy Sulken
	Jessica Griffin	Achala Vagal

Rationale for CAPTIVA

sICAD

- sICAD: one of most common causes of stroke worldwide

  Gorelick et al, Stroke 2008

- 8-10% of stroke in the US (~80,000 per year)

  Sacco et al, Stroke 1997

- 1-year rate of ischemic stroke, ICH, vascular death 27%

  SAMMPRIS medical arm subjects who qualified by symptomatic infarct

Rationale for CAPTIVA

SAMMPRIS *Chimowitz et al, NEJM 2011; Derdeyn et al, Lancet 2014*

	PTAS (n=224)	Medical (n=227)	
Primary Endpoint: stroke or death <30d, ischemic stroke in territory >30d, stroke or death <30d of revascularization procedure	23%	15%	P=0.02
Primary Endpoint beyond 30d	10%	10%	P=NS
Any stroke	26%	19%	P=0.046
Major hemorrhage	13%	4%	P=0.0009

Interpretation The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up. Our findings lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

Rationale for CAPTIVA

Medical Management Post-SAMMPRIS

Turan et al, Cerebrovasc Dis 2014

- Survey of US neurologists and neurointerventionalists 1-year post-SAMMPRIS (n=302/2080)
- 82% SAMMPRIS changed their practice
- Maximal medical therapy
  - 61% DAPT + aggressive medical therapy SBP<140 LDL<70
  - 4% only DAPT

Rationale for CAPTIVA

- Compelling data for clopidogrel + aspirin *(POINT and CHANCE)*
- Ticagrelor + aspirin *(THALES and PRINCE)*
- Low dose rivaroxaban + aspirin *(COMPASS and COMMANDER HF)*
- Efficient: one control arm
- Comparison is to clopidogrel arm not against each other

Study Design

1683 subjects with symptomatic infarct due to 70-99% sICAS

1 year treatment & follow-up

First Stage: Safety Analysis

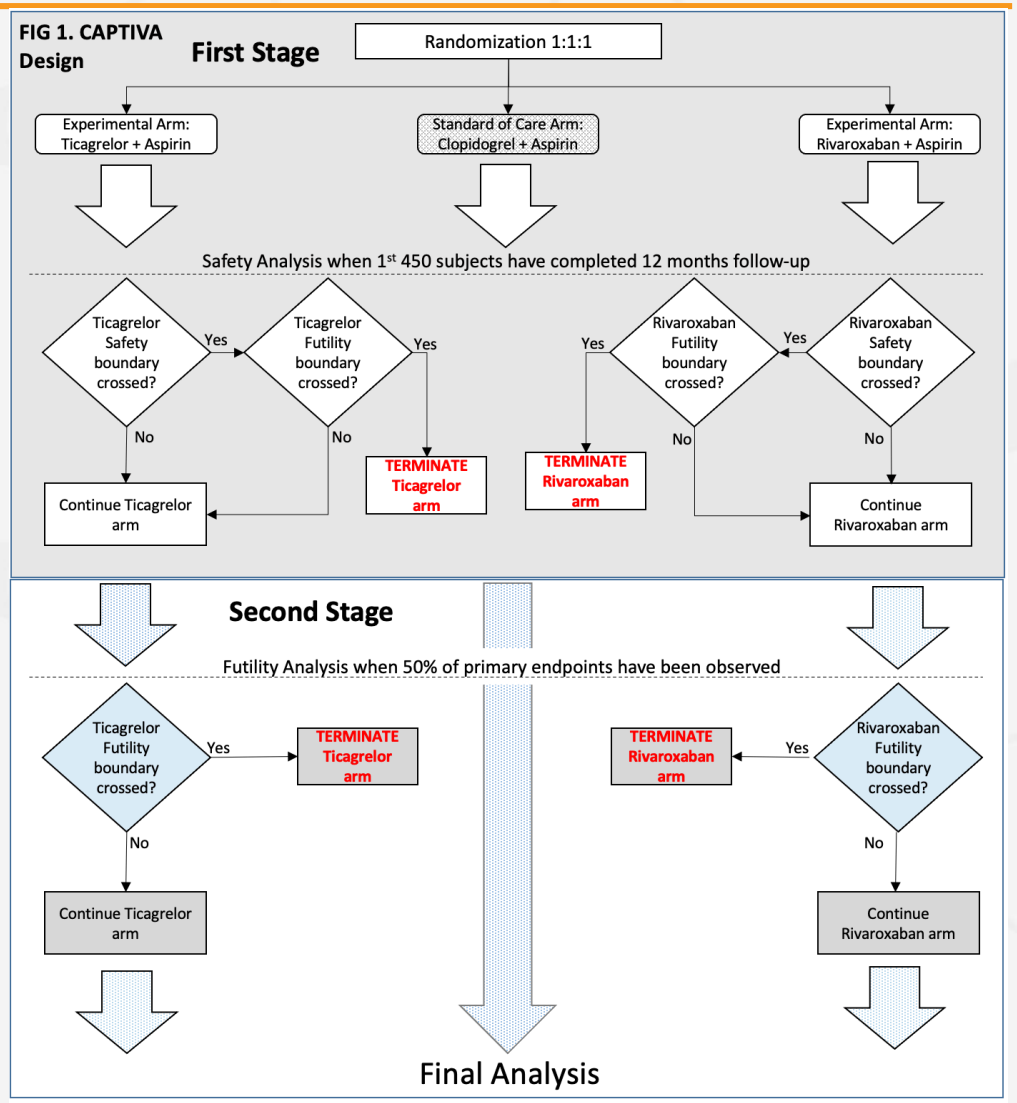
1. Parenchymal brain hemorrhage (ICH)
2. Major non-ICH hemorrhage (ISTH criteria Schulman et al, JTH 2005)

Second Stage: Primary Endpoint

1. Ischemic stroke (AHA definition Sacco et al, Stroke 2013)
2. ICH
3. Vascular death

Secondary Endpoints

1. Composite of the primary endpoint and MI
2. All stroke (ischemic and ICH)
3. Ischemic Stroke
4. Ischemic stroke in the territory of the qualifying stenotic artery
5. All death



Over-encapsulation Design

	Ticagrelor Arm		Rivaroxaban Arm		Clopidrogrel Arm	
	AM	PM	AM	PM	AM	PM
Day 1	2 ticagrelor 6 placebo	1 placebo	1 rivaroxaban 7 placebo	1 rivaroxaban	8 clopidrogrel	1 placebo
Days 2-365	1 ticagrelor	1 ticagrelor	1 rivaroxaban	1 rivaroxaban	1 clopidrogrel	1 placebo

Initial double-dummy design:
3 different bottles x twice daily dosing=Compliance Challenges

Steering Committee Feedback

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Study Progress

I. Protocol & consent approved by Advarra

II. CRFs near completion & simplified
   - Not requiring sites to complete vascular and brain imaging forms
   - Only requiring reporting of AEs that are possibly or definitely related to study interventions

III. MOP in final draft

IV. Study antithrombotic medications being produced

V. WebDCU™ database being finalized

"To Do" List for Sites

- Contact the NCC if you have not received your Welcome Letter and IRB packet
- Obtain cIRB (Advarra) approval
- Upload DOA's and Regulatory Documents in WebDCU™ beginning in January
- Execute Site Agreement
  - Will begin sending in January if your site has a Reliance Agreement in place with Advarra
  - Contact Amy Sulken (NCC Project Manager) for assistance
- Attend Virtual Investigator Meeting
- Complete Site Readiness Call
- Notify NCC when site contacts change

"To Do" List for Sites (cont.)

- Enroll all eligible subjects

Principal Investigators from the first 8 sites to be "released to enroll" will be invited to join the Year 1 CAPTIVA Steering Committee

Overall Timeline

- Planned for 5-year trial
- 115 sites & 1,683 subjects
- Project 4.6 subjects per site/year

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CHANCE-2 (NEJM)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA

Yongjun Wang, M.D., Xia Meng, M.D., Ph.D., Anxin Wang, Ph.D., Xuewei Xie, M.D., Ph.D., Yuesong Pan, Ph.D., S. Claiborne Johnston, M.D., Ph.D., Hao Li, Ph.D., Philip M. Bath, D.Sc., F.Med.Sci., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jing Jing, M.D., Ph.D., Jinxi Lin, M.D., Ph.D., Siying Niu, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Zixiao Li, M.D., Ph.D., Yong Jiang, Ph.D., Wei Li, M.D., Ph.D., Liping Liu, M.D., Ph.D., Jie Xu, M.D., Ph.D., Liguo Chang, M.D., Lihua Wang, M.D., Ph.D., Xianbo Zhuang, M.D., Ph.D., Jinguo Zhao, M.D., Yefang Feng, M.D., Honghao Man, M.D., Guozhong Li, M.D., Ph.D., and Baojun Wang, M.D., Ph.D., for the CHANCE-2 Investigators*

Table 2. Efficacy and Safety Outcomes.

Outcome	Ticagrelor–Aspirin (N=3205)		Clopidogrel–Aspirin (N=3207)		Hazard Ratio or Odds Ratio (95% CI)*	P Value
	Patients with Event	Incidence†	Patients with Event	Incidence†		
	no.	%	*no.*	%		
Primary outcome						
Stroke	191	6.0	243	7.6	0.77 (0.64–0.94)	0.008
Secondary outcome‡						
Stroke within 30 days	156	4.9	205	6.4	0.75 (0.61–0.93)	
Vascular event§	229	7.2	293	9.2	0.77 (0.65–0.92)	
Ischemic stroke	189	5.9	238	7.4	0.78 (0.65–0.95)	
Stroke with any disability¶	97	3.1	92	2.9	1.02 (0.77–1.36)	
Ordinal stroke or TIA‖					0.79 (0.66–0.94)	
Fatal stroke: score of 6 on modified Rankin scale	4	0.1	8	0.2		
Severe stroke: score of 4 or 5 on modified Rankin scale	30	0.9	21	0.7		
Moderate stroke: score of 2 or 3 on modified Rankin scale	63	2.0	63	2.0		
Mild stroke: score of 0 or 1 on modified Rankin scale	94	2.9	151	4.7		
TIA	34	1.1	40	1.2		
No stroke or TIA	2980	93.0	2924	91.2		
Primary safety outcome						
Severe or moderate bleeding**	9	0.3	11	0.3	0.82 (0.34–1.98)	0.66
Fatal bleeding	3	0.1	3	0.1	0.97 (0.20–4.81)	
Intracranial hemorrhage	3	0.1	6	0.2	0.49 (0.12–1.96)	
Secondary safety outcome						
Any bleeding	170	5.3	80	2.5	2.18 (1.66–2.85)	
Mild bleeding**	161	5.0	69	2.2	2.41 (1.81–3.20)	
Death	9	0.3	18	0.6	0.50 (0.22–1.11)	

CYP2C19 Equipoise: Ticagrelor Onset of Action

- Difference in KM curves is within the first few days
- Likely due to faster onset of action of ticagrelor

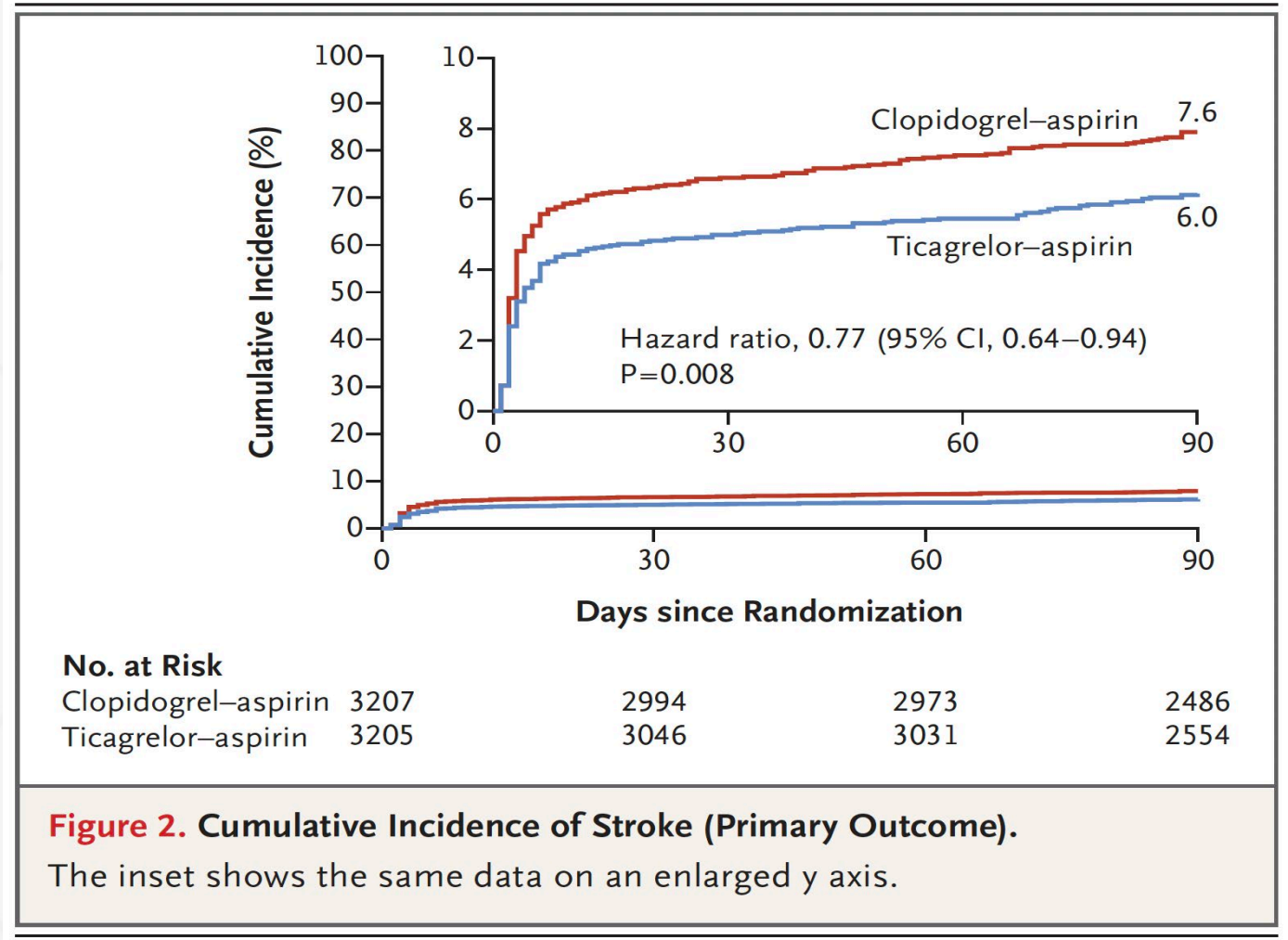

Figure 2. Cumulative Incidence of Stroke (Primary Outcome).
The inset shows the same data on an enlarged y axis.

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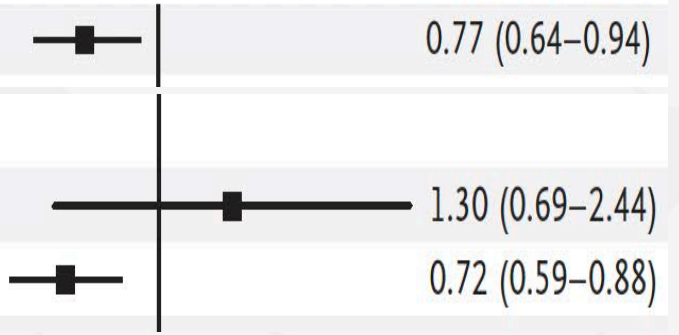
CYP2C19 Equipoise: Ticagrelor Onset of Action

Subgroup	No. of Patients	Ticagrelor–Aspirin	Clopidogrel–Aspirin	Hazard Ratio (95% CI)
		no. of events (%)		
Overall	6412	191 (6.0)	243 (7.6)	0.77 (0.64–0.94)
Previous antiplatelet therapy				
Yes	748	30 (7.8)	23 (6.3)	1.30 (0.69–2.44)
No	5664	161 (5.7)	220 (7.7)	0.72 (0.59–0.88)



- Study participants already on antiplatelet therapy did not appear to benefit from ticagrelor suggesting that the benefit is due to ticagrelor's faster onset of action
- CAPTIVA loading dose
  - Clopidogrel 600mg
  - Ticagrelor 180mg

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CYP2C19 Equipoise after CHANCE-2

- Total bleeding, other adverse events, and withdrawal of therapy all higher in the ticagrelor arm

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CYP2C19 Equipoise after CHANCE-2

- CHANCE-2 was 98% Han Chinese
- CHANCE showed clopidogrel + aspirin was effective in reducing stroke in CYP2C19 LOF noncarriers but not in LOF carriers Wang et al, JAMA 2016
- HOWEVER, POINT: no interaction of CYP2C19 LOF carrier status with stroke outcomes Meschia et al, Stroke 2020
- MAESTRO: randomized trial clopidogrel vs triflusal, no interaction of CYP2C19 LOF carrier status with stroke outcomes Han et al, J Stroke 2017
- Prospective Japanese stroke registry: no interaction of CYP2C19 LOF carrier status with cerebrocardiovascular events Tanaka et al, Circ J 2019
- ACS Trials: PHARMCLO vs POPular Genetics and TAILOR-PCI

Q&A

- Please use the “Raise Hand” function