Comparison of **A**nti-coagulation and anti-**P**latelet **T**herapies for **I**ntracranial **V**ascular **A**therostenosis

CAPTIVA

Study Protocol

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CAPTIVA Protocol Signature Page

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to 21 CFR parts 50, 54, 56 and 45 CFR part 46, ICH Good Clinical Practices Guidelines, Health Canada Food and Drug Regulations Division 5 Part C, and Institutional Review Board (IRB) requirements.

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Clinical Site

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Site Principal Investigator Signature Date

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Site Principal Investigator Printed Name

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1 STUDY SUMMARY

OBJECTIVE	CAPTIVA is a two-stage Phase III trial randomizing subjects with stroke attributed to 70-99% intracranial atherosclerotic stenosis (sICAS) to: 1) ticagrelor + aspirin 2) low dose rivaroxaban + aspirin 3) clopidogrel + aspirin The primary goal of the trial is to determine if the experimental arm(s) (rivaroxaban or ticagrelor or both) are superior to the clopidogrel arm for lowering the 1-year rate of the primary endpoint (ischemic stroke, intracerebral hemorrhage (ICH), or vascular death). The first stage of the trial is concluded by an interim safety analysis intended to identify an excess of parenchymal intracerebral hemorrhage (ICH) or non-ICH major hemorrhage with ticagrelor + aspirin or low dose rivaroxaban + aspirin that could lead to an early termination of one or both of those arms. The second stage of the trial will determine if the experimental arm(s) (rivaroxaban or ticagrelor or both) that progress to stage 2 are superior to the clopidogrel arm for lowering the 1-year rate of the primary endpoint (ischemic stroke, intracerebral hemorrhage (ICH), or vascular death). An exploratory aim is to estimate the impact of CYP2C19 loss-of-function (LOF) carrier status on any benefit that the ticagrelor or low dose rivaroxaban arms may have in lowering the primary endpoint compared with the clopidogrel arm.
STUDY DESIGN AND FUNDING SOURCE	The study is an investigator-initiated, multi-center, randomized, prospective double-blinded study. NIH/NINDS is the funding source.
STUDY POPULATION AND TREATMENT ASSIGNMENTS	Subjects with stroke (defined by a symptomatic cerebral infarct) within 30 days prior to randomization that is attributed to 70-99% stenosis of a major intracranial artery. Subjects will be randomized in a double-blind fashion to: 1) ticagrelor 180 mg loading dose*****, then 90 mg twice a day thereafter for 1 year; 2) rivaroxaban 2.5 mg twice daily for 1 year; 3) clopidogrel 600 mg loading dose*****, then 75 mg once a day thereafter for 1 year. *****Refer to Section 10.1 for exceptions to loading dose administration in study subjects

	All subjects will also be treated with aspirin 81 mg daily and intensive risk factor management for 1 year. The original planned sample size is 1683 subjects. Prior to the planned interim futility analysis, a blinded sample size re-estimation will be performed.
CLINICAL SITES	Approximately 150 sites total, including up to 30 sites within Canada
PRIMARY ENDPOINTS	The primary efficacy endpoint is ischemic stroke, ICH, or vascular death within 1 year. Ischemic stroke is defined by acute focal signs or symptoms of cerebral, spinal cord, or retinal involvement of any duration associated with imaging, pathological, or other objective evidence of arterial infarction ***OR*** clinical evidence of cerebral, spinal cord, or retinal focal arterial ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.[1] ICH is defined by symptomatic parenchymal intracerebral hemorrhage. Vascular death is defined by sudden cardiac death without proven MI, or death within 30 days of any of the following: ischemic stroke, ICH, any other non-ICH major hemorrhage, MI, congestive heart failure, cardiac or cerebral vascular procedure, pulmonary embolus, ruptured aortic aneurysm, or acute ischemia of a limb or internal organ.
INVESTIGATIONAL DRUGS	Ticagrelor made by AstraZeneca Rivaroxaban made by Janssen Pharmaceuticals
INTENDED USE	The ticagrelor + aspirin treatment group will take ticagrelor 180 mg loading dose*****, then 90 mg twice a day thereafter and aspirin 81 mg daily for 1 year for the intention of preventing recurrent stroke. *Refer to Section 10.1 for exceptions to loading dose administration in study subjects The rivaroxaban + aspirin treatment groups will take rivaroxaban 2.5 mg twice daily and aspirin 81 mg daily for 1 year for the intention of preventing recurrent stroke.
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2 STUDY RATIONALE

Magnitude of Clinical Problem. Symptomatic intracranial atherosclerotic stenosis (sICAS) is one of the most common causes of stroke worldwide and is associated with a particularly high risk of recurrent stroke compared with other subtypes.[2-4] In the US, approximately 10% of all strokes are due to sICAS,[5] accounting for approximately 80,000 strokes each year.

Limitations of Current Treatment. The SAMMPRIS trial randomized subjects with minor stroke or TIA due to 70-99% sICAS to medical management versus angioplasty and stenting. Both treatment arms received dual antiplatelet therapy with clopidogrel + aspirin and intensive risk factor management. SAMMPRIS found medical management was superior to angioplasty and stenting in preventing the primary endpoint (any stroke or death within 30 days after enrollment or ischemic stroke in the territory of the qualifying artery beyond 30 days after enrollment)[3,4] but the 1-year rate of an ischemic stroke (using the AHA definition of stroke that includes acute focal signs or symptoms of cerebral, spinal cord, or retinal involvement of any duration associated with imaging, pathological, or other objective evidence of arterial infarction OR clinical evidence of cerebral, spinal cord, or retinal focal arterial ischemic injury based on symptoms persisting >24 hours or until death, and other etiologies excluded[1]), ICH or vascular death in the subgroup of patients in the medical arm of SAMMPRIS who qualified with a symptomatic infarct was still very high (27%).[6,7] A recent registry (WEAVE) found a low rate of periprocedural stroke with stenting in highly selected subjects who met the new Humanitarian Device Exemption (HDE) criteria for the Wingspan stent developed after SAMMPRIS.[8] However, subjects who did not meet the HDE criteria (who are the vast majority of patients with sICAS and will comprise most of the subjects in CAPTIVA) had a very high rate of periprocedural stroke in WEAVE.[9] Other potential therapies for sICAS include angioplasty alone[10,11] and bypass surgery[12] but the safety and potential efficacy of these therapies have not been evaluated in large prospective multicenter trials. As such, intensive medical management remains the standard care.[13] However, given the persistently high rate of stroke on the current standard care for high-risk patients with sICAS (clopidogrel + aspirin and intensive risk factor management), more effective therapies are urgently needed.

Rationale for Combining Ticagrelor + Aspirin for sICAS. Ticagrelor is a direct P2Y12 receptor antagonist that provides faster, greater and more consistent inhibition of the P2Y12 platelet receptor than clopidogrel.[14,15] Ticagrelor has a faster onset of action than clopidogrel, achieving maximal platelet reactivity inhibition in 1 hour, compared to clopidogrel (6-12 hours).[16,17] Ticagrelor also achieves greater suppression of platelet reactivity than clopidogrel, both in the first hours and during maintenance therapy.[18] Additionally, ticagrelor has pleiotropic effects such as an increase in plasma adenosine, which has significant vasodilatory properties[19] and exerts further platelet inhibition.[20] Additionally, ticagrelor may be more effective than clopidogrel in CYP2C19 LOF carriers who don't fully metabolize clopidogrel to its active form,[21] however, randomized trials (ONSET/OFFSET and RESPOND) have shown ticagrelor exhibits lower platelet reactivity than clopidogrel by all assays irrespective of *CYP2C19* genotype or metabolizer status (P<0.01).[22] In PLATO, a trial of subjects with acute coronary syndromes, the primary outcome occurred less often in the ticagrelor arm compared with the clopidogrel arm irrespective of *CYP2C19* genotype.[23] Thus, ticagrelor has several pharmacological properties that may offer potential advantages over clopidogrel in patients with sICAS.

Although monotherapy with ticagrelor is an option to consider for treating patients with sICAS, the available data suggests combining ticagrelor with aspirin may be more effective. In SOCRATES, participants with minor stroke or TIA were randomized to ticagrelor versus aspirin and followed for the primary endpoint of stroke, MI, and death.[24] SOCRATES failed to show superiority of

ticagrelor over aspirin for the primary endpoint whereas the recent THALES trial showed that the combination of ticagrelor and aspirin was significantly more effective than aspirin alone for reducing the risk of stroke or death at 30 days in patients presenting with acute TIA or stroke,[25] particularly those subjects with sICAS.[26] However, the combination of ticagrelor and aspirin was associated with higher risk of bleeding.[25] Given that combining either ticagrelor or clopidogrel with aspirin was more effective than aspirin alone for preventing stroke in THALES,[25] POINT,[27] and CHANCE,[28] dual antiplatelet treatment (DAPT) is more effective than aspirin monotherapy for preventing recurrent stroke, especially in patients with sICAS as suggested by subgroup analyses in CHANCE and THALES.[26,29] While the duration of DAPT in these three trials was for 30-90 days, the optimal duration for patients with sICAS is likely longer because their risk of stroke remains very high up to 12 months.

The only stroke prevention trial that has compared ticagrelor + aspirin with clopidogrel + aspirin is the PRINCE trial.[30] PRINCE randomized 675 subjects with high-risk TIA or minor stroke at 26 Chinese centers to ticagrelor + aspirin versus clopidogrel + aspirin.[30] While there was a non-significant reduction in stroke at 90 days with ticagrelor + aspirin (6.3%) versus clopidogrel + aspirin (8.8%) (HR 0.70, 95% CI 0.40-1.22, P=0.20) in the entire study cohort, the 90-day stroke rate in subjects with large artery atherosclerosis (predominantly sICAS in China) was significantly lower in the ticagrelor + aspirin group (6.0%) versus the clopidogrel + aspirin group (13.1%) (HR 0.45, 95% CI 0.20-0.98, P=0.04).[30] There was no significant difference in major bleeding (ticagrelor + aspirin 1.5% versus clopidogrel + aspirin 1.2%, P=0.72) or intracranial hemorrhage (ICH) (ticagrelor + aspirin 0.9% versus clopidogrel + aspirin 0.6%, P=0.72); however ticagrelor was associated with more minimal bleeding (ticagrelor + aspirin 19.0% versus clopidogrel + aspirin 10.6%, P=0.003).[30] Additionally, dyspnea was more common with ticagrelor + aspirin (4.2%) vs clopidogrel + aspirin (0%) (P=0.0001).[30] Dyspnea is a known side-effect of ticagrelor that has been attributed to inhibition of P2Y12 receptors on sensory neurons that increases the sensation of dyspnea without compromising pulmonary or cardiac dysfunction.[31] The superiority of ticagrelor + aspirin over clopidogrel + aspirin in the large artery stenosis subgroup in PRINCE provides a strong basis for evaluating the potential efficacy of ticagrelor + aspirin for sICAS.

Rationale for Combining Low Dose Novel Anticoagulant (NOAC) + Aspirin for sICAS. The mechanistic rationale for combining anticoagulation with antiplatelet therapy for preventing vascular events in patients with sICAS is that progression of atherosclerosis from a stable to an unstable state is associated with both increased platelet and procoagulant activity and thrombin generation.[32,33] Combining anticoagulation with antiplatelet therapy would address all these prothrombotic mechanisms. However, this combination could also increase the risk of major hemorrhage, including ICH, particularly if full dose anticoagulation and antiplatelet therapy is used.[34] This led to the rationale for combining a low dose of a NOAC with low dose aspirin for preventing major vascular events in patients with atherosclerosis in the COMPASS trial.

In the COMPASS trial, 27,395 subjects with CAD or peripheral vascular disease (PVD), including subjects with carotid stenosis, were randomized to low dose rivaroxaban (2.5mg twice daily) + aspirin (100mg), moderate dose rivaroxaban (5 mg twice daily) alone, or aspirin alone (100mg).[35] The main results of COMPASS are shown in **Table 1**.

Table 1. Results of COMPASS: Low Dose Rivaroxaban + Aspirin vs Aspirin Alone	
Outcome Measure	
Primary endpoint (cardiovascular death, stroke, MI)	4.1% vs. 5.4% (HR 0.76, 95% CI 0.66-0.86, P<0.001)
Stroke (ischemic and hemorrhagic)	0.9% vs. 1.6% (HR 0.56, 95% CI 0.42 – 0.75, P<0.0001)
Ischemic stroke in 1032 subjects with previous stroke	1.1% vs. 3.4% (HR, 0.33; 95% CI, 0.14–0.77; P =0.01)
Major hemorrhage	3.2% vs. 1.9%, (HR 1.66, 95% CI 1.37–2.03, p<0.0001)
ICH	0.4% vs. 0.3%, (HR 1.17, 95% CI 0.71–1.93, p= 0.54)

Patients in the low dose rivaroxaban + aspirin arm had significantly fewer primary endpoints and stroke alone than aspirin during a mean follow-up of 1.9 years. Strokes that were not attributed to small vessel occlusion, carotid stenosis or cardioembolism (which would include a high percentage of strokes related to sICAS) were particularly reduced with low dose rivaroxaban + aspirin.[35] A subgroup analysis of 1,032 subjects in COMPASS who had a previous stroke showed that low dose rivaroxaban + aspirin was very effective in lowering the rate of ischemic stroke (Table 1).[37]

In contrast, moderate dose rivaroxaban alone was not associated with a lower rate of stroke compared to aspirin alone in the entire COMPASS cohort (1.3% vs 1.6%; HR 0.81, 95% CI 0.62–1.05; p=0.10) or in the subgroup with previous stroke (HR, 0.79; 95% CI, 0.41–1.52; P =0.47).[35,37] Other studies in patients with embolic stroke of uncertain source have also shown that full dose NOACs alone are no more effective than aspirin alone for stroke prevention.[36,37,39] These studies suggest that combining a low dose NOAC with aspirin may be most effective for reducing stroke.

While low dose rivaroxaban + aspirin was associated with a lower rate of stroke in COMPASS subjects, major hemorrhages (mostly gastrointestinal, urinary or skin) were significantly higher in the low dose rivaroxaban + aspirin arm compared to the aspirin arm (Table 1). However, there was no difference in the rate of ICH or fatal bleeding between these two arms (Table 1). In contrast, there was a significant increase in ICH with moderate dose rivaroxaban alone compared to aspirin alone (0.52% vs 0.27%; HR 1.87, 95% CI 1.13–3.11).[38] Subjects with a prior stroke in COMPASS had a higher annualized rate of ICH of 0.3% compared with 0.09% for those without prior stroke (HR, 3.12; 95% CI, 1.22–7.98; P =0.02). However, the total number of ICHs was small in the subjects with prior stroke (rivaroxaban + aspirin 2, rivaroxaban alone 3, aspirin alone 0).[39]

A second trial has also shown that low dose rivaroxaban + antiplatelet therapy is more effective in lowering the risk of stroke or TIA compared with antiplatelet therapy alone. In the COMMANDER HF trial,[40],[41] subjects with heart failure and underlying CAD were randomized to low dose rivaroxaban or placebo, in addition to antiplatelet therapy at the discretion of the treating physician. The low dose rivaroxaban arm had a significantly lower risk of stroke or TIA than the placebo arm (1.29 events vs. 1.90 events per 100 patient-years, hazard ratio 0.68, 95% confidence interval 0.49–0.94) and no increased risk of ICH (0.13 events vs.0.17 events per 100 patient-years) or fatal bleeding or bleeding into a critical space (0.44 events vs.0.55 events per 100 patient-years) even though 90% of subjects were also on aspirin and a third of subjects were on dual antiplatelet therapy at baseline.[41]

Since the endpoint that was lowered the most in COMPASS and COMMANDER HF was ischemic stroke, and the pathophysiology of stroke associated with atherosclerotic intracranial stenosis should be responsive to combining anticoagulation and antiplatelet therapy, a trial evaluating the

safety and efficacy of a low dose NOAC and aspirin for preventing recurrent stroke in patients with sICAS is warranted and needed.[42] Low dose rivaroxaban is currently the only FDA and Health Canada approved NOAC for use in combination with aspirin for secondary prevention.

Rationale and Timeliness for a Two-Stage Phase III 3-Arm Study. CAPTIVA is a two-stage Phase III 3-arm, double-blind trial in which subjects with symptomatic infarct in the territory of 70-99% sICAS will be randomized 1:1:1 to 1-year treatment of ticagrelor + aspirin, low dose rivaroxaban + aspirin, or clopidogrel + aspirin. The proposed 3-arm trial is timely and efficient because there are now compelling data showing that combining clopidogrel and aspirin (POINT[27] and CHANCE[28]), rivaroxaban and aspirin (COMPASS[38]), and ticagrelor and aspirin (THALES[26]) are all superior to aspirin alone in preventing recurrent ischemic stroke. However, these different dual antithrombotic approaches have never been evaluated in a single trial. The CAPTIVA trial provides a unique opportunity to evaluate the safety and efficacy of these therapies in subjects with sICAS, a population at highest risk for stroke recurrence. Comparing the two novel arms against one standard care control arm (rather than in 2 separate simultaneous or consecutive trials) will take advantage of the StrokeNet infrastructure to maximize recruitment, save resources, and accelerate the development of more effective therapies for sICAS.

The main intent of CAPTIVA is to establish that at least one of the two novel therapies being evaluated is more effective than the current standard care for sICAS. CAPTIVA is not designed or powered to answer which of the two novel arms is more effective – that would require a much larger sample size. Nevertheless, CAPTIVA will provide important safety and efficacy data on both novel therapies. If both treatments are superior to clopidogrel + aspirin, that would be similar to the scenario with atrial fibrillation in which several NOACs have been shown to be more effective than warfarin but none of the NOACs have been directly compared with each other in a randomized trial.

Rationale for Studying CYP2C19 Loss-of-Function Allele Carrier Status as an Exploratory Aim. Clopidogrel is a pro-drug that requires a two-step enzymatic process in the liver to form its active metabolite. Carriers of genetic single-nucleotide loss-of-function (LOF) polymorphisms for the cytochrome P450 (CYP) 2C19 enzyme do not adequately metabolize clopidogrel to its active form.[42] However, the stroke literature on the effect of CYP2C19 LOF carrier status on clinical outcome is inconclusive. While the CHANCE trial performed in China showed that clopidogrel + aspirin reduced recurrent stroke compared to aspirin alone in LOF non-carriers but not in carriers,[43] the POINT trial performed mainly in the USA showed no significant interaction with LOF carrier status and stroke events.[44] Multiple stroke trials demonstrate no effect of CYP2C19 LOF carrier status on risk of recurrent stroke on clopidogrel.[44-47] Our previous study showed sICAS LOF carriers inexplicably had *lower* stroke events on-clopidogrel than non-carriers.[48] The cardiology literature also provides conflicting data on the impact of *CYP2C19* genotype on cardiac outcomes,[49-52] with supporting evidence for an association between CYP2C19 LOF carrier status and cardiac events on clopidogrel largely limited to stented patients, and not medically treated patients.

Given the uncertainty about the impact of *CYP2C19* genotype on cerebrocardiovascular outcomes, current guidelines do not recommend genotype testing. Stroke prevention guidelines,[13,53] cardiology guidelines,[54-56] and UpToDate, the most commonly used medical reference for practitioners, do not recommend genotype testing. The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published a statement regarding the FDA boxed warning on CYP2C19 testing and advised clinicians there is not enough scientific evidence to recommend CYP2C19 testing.[57] The current Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines do not make recommendations on who should

undergo CYP2C19 testing but do suggest consideration of alternative treatments to clopidogrel in known CYP2C19 intermediate and poor metabolizers .[58] Given the conflicting data on the role of *CYP2C19* genotyping on outcomes and guidelines recommending against genotype testing, clopidogrel + aspirin without genotype testing remains the standard care in subjects with sICAS. CAPTIVA does provide an opportunity in an exploratory aim to estimate the impact of CYP2C19 LOF carrier status on any identified benefit that the ticagrelor or low dose rivaroxaban arms may have compared with the clopidogrel arm.

3 SPECIFIC AIMS

Safety Aim: To identify an excess of parenchymal ICH or non-ICH major hemorrhage in the rivaroxaban or ticagrelor arms of the trial that could lead to an early termination of one or both of those arms. This aim will be evaluated in a prespecified safety analysis marking the conclusion of the first stage of the trial.

Efficacy Aim: To determine if the experimental arm(s) (rivaroxaban or ticagrelor or both) that progress to the second stage are superior to the clopidogrel arm for lowering the 1-year rate of the primary efficacy endpoint (ischemic stroke, ICH, or vascular death) in subjects with 70-99% sICAS.

Exploratory Aim: To estimate the impact of CYP2C19 LOF carrier status on any benefit that the ticagrelor or low dose rivaroxaban arms may have in lowering the primary endpoint compared with the clopidogrel arm.

4 SUMMARY OF STUDY DESIGN AND ORGANIZATION

Overview of the CAPTIVA Trial. CAPTIVA is a 3-arm, double-blind Phase III trial. Subjects with a symptomatic infarct attributed to 70-99% stenosis of a major intracranial artery (middle cerebral, intracranial carotid, intracranial vertebral, or basilar) will be randomized to 1-year treatment with:

1) ticagrelor (180 mg loading dose*****, then 90 mg twice daily), or
2) low dose rivaroxaban (2.5 mg twice daily), or
3) clopidogrel (600 mg loading dose*****, then 75 mg daily).

*Refer to Section 10.1 for exceptions to loading dose administration for study subjects

All subjects will also be treated with aspirin (81 mg daily) and receive intensive risk factor management according to the SAMMPRIS protocol.[59] Subjects will be evaluated at 1 month, 4 months, 8 months, and 1 year after randomization. A mouthwash or buccal swab sample will be sent to the University of Florida Center for Pharmacogenomics and Precision Medicine Genotyping Core Laboratory where it will be stored for *CYP2C19* genotype analysis. Since the *CYP2C19* genotype results do not affect randomization or treatment during the study, the genotype analysis will only be performed after randomization and the results will remain blinded to the investigators and subjects until the end of the trial.

The trial is designed to compare the efficacy of the experimental arms to the clopidogrel arm. A prespecified interim safety analysis concludes the first stage of CAPTIVA and will identify an increased risk of the primary safety endpoints of parenchymal ICH or non-ICH major hemorrhage in the low dose rivaroxaban and ticagrelor arms. If a safety concern is identified in an experimental arm at the time of the pre-specified interim safety analysis, an early futility analysis will determine

whether that arm progresses to the second stage of the trial. During the second stage of the trial, a planned interim futility analysis will be performed when 50% of the expected number of primary endpoints have occurred. At the conclusion of the trial, efficacy of the remaining arms will be evaluated. A schematic of the trial design is shown in **Figure 1**.

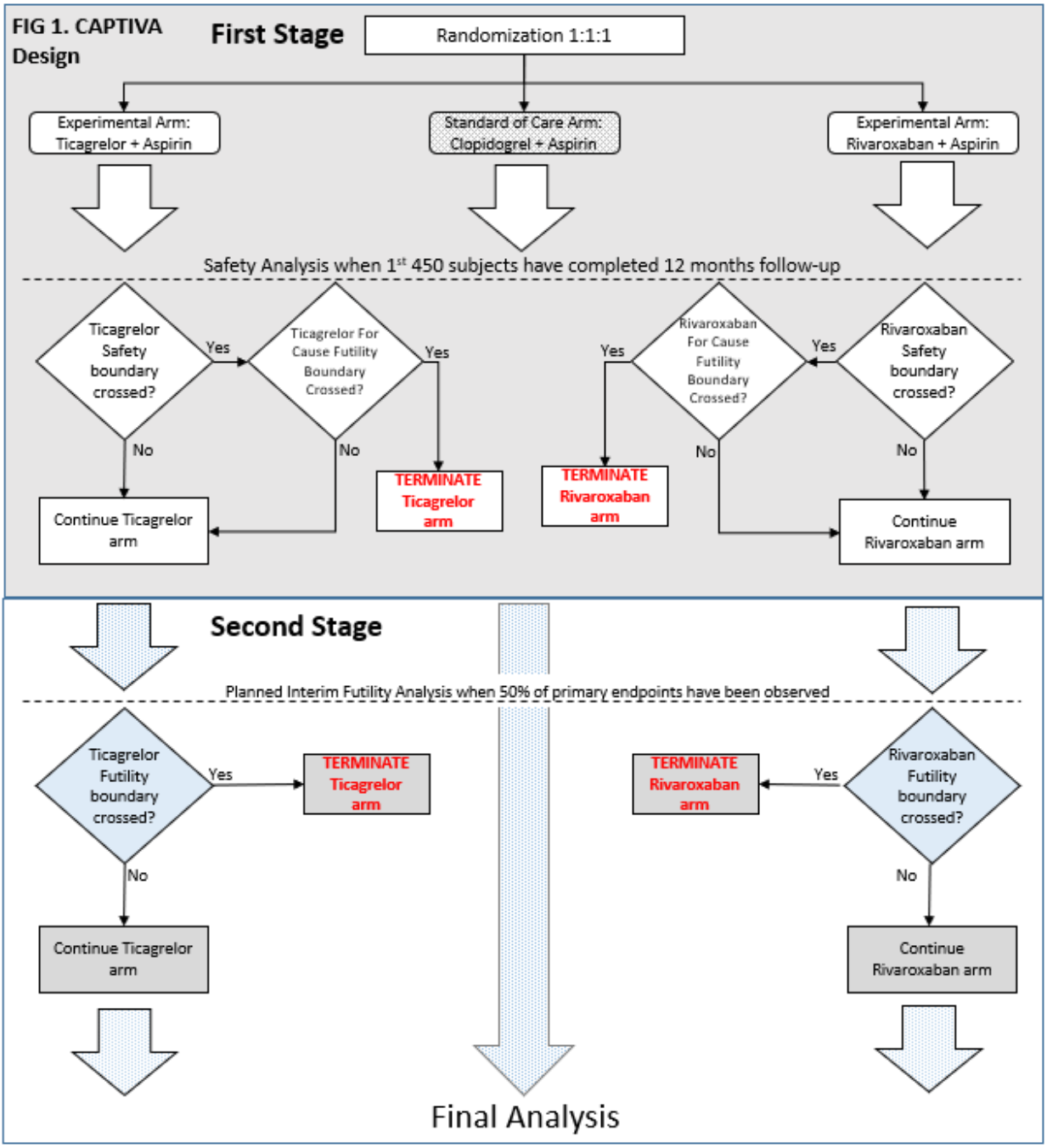

Figure 1: Trial Flow Diagram. Note, the planned interim futility analysis is set to occur in Stage 2 of the design, when 50% of the expected primary endpoints have been observed. For a more detailed explanation, refer to Section 8.4 of the SAP. The sample size re-estimation is intended to occur 3 months prior to the planned interim futility analysis. For a more detailed explanation of this sample size re-estimation, refer to Section 4.3 of the SAP.

4.1 Safety Primary Endpoints

1) Parenchymal intracerebral brain hemorrhage (ICH).

2) Non-ICH major hemorrhage derived from the International Society on Thrombosis and Haemostasis (ISTH) criteria [60] consisting of any of the following:
    a. Fatal bleeding
    b. Symptomatic bleeding in a critical area or organ, such as subarachnoid, intraventricular, subdural, epidural, spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome
    c. Symptomatic bleeding causing a fall in hemoglobin level of 1.24 mmol/L (20g/L or greater) or more, or leading to a transfusion of two units or more of whole blood or red cells.

These safety endpoints will be monitored by the DSMB throughout the trial.

4.2 Efficacy Primary Endpoint

The primary efficacy endpoint is ischemic stroke, ICH, and vascular death.

The definition of ischemic stroke in CAPTIVA is the AHA definition that includes acute focal signs or symptoms of cerebral, spinal cord, or retinal involvement of any duration associated with imaging, pathological, or other objective evidence of arterial infarction OR clinical evidence of cerebral, spinal cord, or retinal focal arterial ischemic injury based on symptoms persisting $\geq$ 24 hours or until death, and other etiologies excluded.[1] ICH is defined by hemorrhage in parenchymal brain tissue detected by CT or MRI that is associated with new neurological symptoms (any of the following: headache, change in level of consciousness, focal neurological symptoms) or seizure. Vascular death is defined by sudden cardiac death without proven MI or death within 30 days of any of the following: ischemic stroke, ICH, non-ICH major hemorrhage, MI, congestive heart failure, cardiac or cerebral vascular procedure, pulmonary embolus, ruptured aortic aneurysm, or acute ischemia of a limb or internal organ.[61]

Secondary Efficacy Endpoints: Secondary endpoints are: 1) Composite of primary endpoint and MI (4th universal definition[62]); 2) All stroke (ischemic and ICH); 3) Ischemic stroke; 4) ischemic stroke in the territory of the qualifying stenotic artery; 5) All death.

Exploratory Outcome Measure: Cognitive outcome at 12 months as measured by the Montreal Cognitive Assessment (MoCA) will be evaluated because there is significant interest in cognitive outcomes in subjects with stroke.[63,64] The MoCA is a validated tool for detecting cognitive impairment.[65]

Blinding. Subjects, investigators, study coordinators, and treating physicians will be blinded to allocation to the three arms. Subjects in all three arms will knowingly receive aspirin and intensive risk factor management through 1 year of follow-up.

Study Organization. The study will be performed through the NIH Stroke Network (StrokeNet). The StrokeNet National Coordinating Center (NCC) is at the University of Cincinnati. The CAPTIVA study Clinical Coordinating Center (CCC) is at the University of Florida. The University of Florida Center for Pharmacogenomics and Precision Medicine Genotyping Core Laboratory will perform *CYP2C19* genotype testing. The Risk Factor Management Center is at the Medical University of South Carolina. The StrokeNet National Data Management Center at the Medical University of South Carolina will serve as the National Data Management Center (NDMC) for CAPTIVA. A web-based system (WebDCU™) will be used for data collection and study management. Approximately 150 sites total, including up to 30 sites within Canada, will participate and enroll subjects in CAPTIVA.

4.3 Unblinding

Unblinding (i.e., release of randomization assignment) will be performed if a compelling clinical reason arises. Requests for unblinding will typically originate from a treating physician because of an adverse event.

To preserve study integrity, every effort will be made to minimize unblinding of treatment assignments. Unblinding will only be allowed in the setting of a CAPTIVA subject's acute ischemic stroke, major hemorrhage, or other serious condition when planned acute treatment (other than stopping study antithrombotic medications) requires knowledge of the assigned antithrombotic treatment.

Refer to the Manual of Operation and Procedures (MOP) for detailed unblinding information.

5 SUBJECT SELECTION CRITERIA

5.1 Inclusion Criteria

1. Acute focal symptoms or signs of any duration associated with imaging, pathological, or other objective evidence of arterial infarction **OR** clinical evidence of cerebral, spinal cord, or retinal focal arterial ischemic injury based on symptoms persisting ≥24 hours that occurred within 30 days prior to randomization
2. Index stroke in 1 above is attributed to 70-99% stenosis (or flow gap on MRA) of a major intracranial artery (carotid artery, middle cerebral artery (M1 or M2), vertebral artery (V4), basilar artery, posterior cerebral artery (P1), or anterior cerebral artery (A1)) documented by CTA, MRA, or catheter angiography.

   The method for determining percent stenosis will be by WASID criteria:[66,67]

   Percent stenosis = (1 – [Ds / Dn]) x 100% with Ds (diameter of stenosis) and Dn (diameter of normal vessel).

   These measurements will be made using CTA, MRA, and catheter angiographic systems software.

3. Modified Rankin Scale score of ≤ 4, at time of consent
4. Ability to swallow pills
5. At least 30 years of age, inclusive, at time of consent

Subjects 30-49 years are required to meet at least one of the following additional criteria (1-6) below to qualify for the study. This additional requirement is to increase the likelihood that the symptomatic intracranial stenosis in subjects 30-49 years is atherosclerotic.

1. diabetes treated with insulin for at least 15 years
2. at least 2 of the following atherosclerotic risk factors: hypertension (BP > 140/90 or on antihypertensive therapy); dyslipidemia (LDL > 130 mg /dl or HDL < 40 mg/dl or fasting triglycerides > 150 mg/dl or on lipid lowering therapy); smoking; non-insulin dependent diabetes or insulin dependent diabetes of less than 15 years duration; any of the following vascular events occurring in a parent or sibling who was < 55 years of age for men or < 65 for women at the time of the event: myocardial infarction, coronary artery bypass, coronary

angioplasty or stenting, stroke, carotid endarterectomy or stenting, peripheral vascular surgery for atherosclerotic disease
3. personal history of any of the following: myocardial infarction, coronary artery bypass, coronary angioplasty or stenting, carotid endarterectomy or stenting, or peripheral vascular surgery for atherosclerotic disease
4. any stenosis of an extracranial carotid or vertebral artery, another intracranial artery, subclavian artery, coronary artery, iliac or femoral artery, other lower or upper extremity artery, mesenteric artery, or renal artery that was documented by non-invasive vascular imaging or catheter angiography and is considered atherosclerotic
5. aortic arch atheroma documented by non-invasive vascular imaging or catheter angiography
6. any aortic aneurysm documented by non-invasive vascular imaging or catheter angiography that is considered atherosclerotic

6. Negative pregnancy test in a female who has had any menses in the last 18 months and has not had surgery that would make her unable to become pregnant
7. Subject is willing and able to attend all follow-up evaluations required by the protocol
8. Subject is available by phone
9. Subject understands the purpose and requirements of the study and can make him/herself understood
10. Subject has provided informed consent (use of a LAR is not permitted)

5.2 Exclusion Criteria

1. Previous treatment of target lesion with a stent, angioplasty, or other mechanical device, including mechanical thrombectomy for the qualifying stroke, or plan to perform one of these procedures
2. Plan to perform concomitant endarterectomy, angioplasty or stenting of an extracranial vessel tandem to the symptomatic intracranial stenosis
3. Intracranial tumor (except meningioma) or any intracranial vascular malformation
4. Thrombolytic therapy within 24 hours prior to randomization
5. Progressive neurological signs within 24 hours prior to randomization
6. History of any intracranial hemorrhage (parenchymal, subarachnoid, subdural, epidural)

   asymptomatic radiographic microhemorrhages or hemorrhagic conversion of infarction are not exclusions but the latter requires delaying randomization for 2 weeks from onset of qualifying stroke

7. Intracranial arterial stenosis due to: arterial dissection; MoyaMoya disease; any known vasculitic disease; herpes zoster, varicella zoster or other viral vasculopathy; neurosyphilis; any other intracranial infection; any intracranial stenosis associated with CSF pleocytosis; radiation induced vasculopathy; fibromuscular dysplasia; sickle cell disease; neurofibromatosis; benign angiopathy of central nervous system; postpartum angiopathy; suspected vasospastic process; reversible cerebral vasoconstriction syndrome (RCVS); suspected recanalized embolus
8. Presence of any of the following unequivocal cardiac sources of embolism: chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, left atrial spontaneous echo contrast
9. Known allergy or contraindication to aspirin, rivaroxaban, clopidogrel, or ticagrelor
10. Uncontrolled severe hypertension **(systolic pressure > 180 mm Hg or diastolic pressure > 115 mm Hg)**, active peptic ulcer disease, major systemic hemorrhage within 30 days prior to randomization, active bleed or bleeding diathesis, platelets < 100,000, hematocrit < 30, INR

> 1.5, clotting factor abnormality that increases the risk of bleeding, current alcohol or substance abuse, severe liver impairment (AST or ALT > 3 x normal, cirrhosis), or CrCl < 15 mL/min or on dialysis
11. Major surgery (including stenting of any vessel; open femoral, aortic, or carotid surgery; or cardiac surgery) within 30 days prior to randomization or planned within 90 days after randomization
12. Any condition other than intracranial arterial stenosis that requires the subject to take any antithrombotic medication other than aspirin (NOTE: exceptions allowed for subcutaneous heparin for deep vein thrombosis (DVT) prophylaxis)
13. Dementia or psychiatric problem that prevents the subject from following an outpatient program reliably
14. Co-morbid conditions that may limit survival to less than 12 months
15. Pregnancy or of childbearing potential and unwilling to use contraception for the duration of this study, or currently breastfeeding. If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately
16. Current or anticipated concomitant oral or intravenous therapy with strong CYP3A4 inhibitors or CYP3A4 substrates that cannot be stopped for the course of this study (Refer to **MOP Appendix 1**)
17. Enrollment in another study that would conflict with the current study

Subjects who are known CYP2C19 LOF carriers are not automatically excluded because of the conflicting data on outcomes in previous studies. Study investigators will be required to inform these subjects of these studies and, if these subjects still wish to participate, they may do so understanding that they may get randomized to the clopidogrel arm.

6 INFORMED CONSENT

The principles of Informed Consent, according to FDA Regulations, Health Canada and ICH guidelines on GCP, will be followed. The study consent form, together with the study protocol, will be submitted to the Health Canada and the applicable ethics boards (REBs) for approval. All subjects must provide informed consent to participate and only the subject can provide informed consent.

When a subject is confirmed eligible for CAPTIVA, they will be approached for Informed Consent. The informed consent will be obtained by either the clinical site PI or other members of the study team who are qualified and delegated to perform this task on the Delegation of Authority Log. Initial consent must be obtained in person. This can be done using a REB-approved paper version of the form or, where permitted, an approved method for e-consent (e.g., REDCap).

Reconsenting Process

If there are significant changes in the CAPTIVA protocol during the course of the trial, the REB(s) may require that all active subjects be re-consented. Ideally, re-consenting should be done in person and mirror the initial consenting process; however, situations may occur that make this impractical. Therefore, where approved, re-consent may be obtained remotely using REDCap e-consent, fax, or mail (postal service) in accordance with REB policies. Prior to re-consent, subjects should be presented with a revised consent that includes the new study information and have all questions answered to their satisfaction. Subjects must sign the revised consent to continue to participate in CAPTIVA.

In an effort to review informed consent forms in a timely manner, enrolling sites will upload a PDF of the signed informed consent form into the password protected clinical trial management system, WebDCU™. The PDF file will be linked to the Subject ID but will be stored on a secure server separate from the study's CRF data. The secure server on which these files are stored is not backed up to prevent copies of files containing individually identifiable health information from being copied and stored on non-NDMC back up servers. The files on these servers can only be accessed by designated NDMC study personnel. NDMC staff will remotely monitor the informed consent forms and issues identified will be relayed to the clinical site for corrective and preventative action. After remote monitoring is complete, the PDF file containing the informed consent form will be permanently deleted from the secure server. If a subject must be re-consented, the process will repeat itself.

7 RANDOMIZATION

Once it is determined that a subject meets the eligibility criteria and informed consent is obtained, individuals with the delegated responsibility to perform randomization will log on to the secure, study-dedicated clinical trial management system (WebDCU™) to complete brief Enrollment, Eligibility, and Randomization Case Report Forms, including pertinent demographics and randomization data. The site investigator must confirm that eligibility criteria have been met prior to submitting the CRFs.

The database will assign the subject a study ID number and immediately randomize the subject to a treatment arm. The randomization scheme targets a 1:1:1 treatment allocation while adjusting for imbalance both within a site and overall to the following three arms: 1) ticagrelor + aspirin, 2) low dose rivaroxaban + aspirin, 3) clopidogrel + aspirin. The site study team member will submit a study drug request via WebDCU™ to obtain the Study Drug Kit ID(s) corresponding to a labeled drug kit(s) in the site's inventory.

8 *CYP2C19* GENOTYPE AND ANTITHROMBOTIC THERAPY TESTING

After enrollment, a mouthwash or buccal swab sample will be collected and shipped to the University of Florida Center for Pharmacogenomics and Precision Medicine Genotyping Core Laboratory for *CYP2C19* genotype testing. Genomic DNA will be isolated and genotyped for both loss-of-function and increased function (gain-of-function) alleles, including **2* (c.681G>A; rs4244285), **3* (c.636G>A; rs4986893), and **17* (c.-806C>T; rs12248560, as our group has previously described.[48,68]

For subjects who have provided consent, any remaining samples after completion of *CYP2C19* genotype testing will be stored at the University of Florida and banked for future research. Otherwise, samples will be destroyed.

Any laboratory or point of care testing of the antithrombotic therapy used in the trial in study subjects once they are enrolled in the trial is a protocol violation. This testing includes VerifyNow (P2Y12 Plavix assay) or platelet mapping thromboelastography (TEG) or *CYP2C19* genotype testing performed other than by the University of Florida Center for Pharmacogenomics and Precision Medicine Genotyping Core Laboratory.

9 CENTRAL IMAGING REVIEW

All baseline imaging (CT/CTA, MRI/MRA, or DSA) which confirmed subject eligibility and imaging during follow-up (e.g. imaging conducted in the evaluation and management of stroke) will be uploaded to Ambra Health through the Imaging Management Center in the Department of Radiology at the University of Cincinnati. Ambra Health is a web-based medical imaging infrastructure software platform with HIPAA and 21CFR Part 11 complaint technology and robust infrastructure to allow secure medical image upload, storage and transfer.

All neuroimaging will be reviewed and adjudicated by the central neuroradiologist based at the University of Florida. The neuroradiologist, who is blinded to the site readings, will measure percent diameter stenosis using the WASID technique. These central readings will be the final readings in the trial.

Based on the intent- to-treat principle, subjects whose central qualifying imaging readings indicate < 70% intracranial arterial stenosis will still be included in the intention-to-treat analysis. Sites that have an excessive rate of local readings with ≥ 70% stenosis and central readings with < 70% stenosis will undergo reeducation on the WASID measurement technique.

10 MEDICAL MANAGEMENT: ANTITHROMBOTIC THERAPY AND RISK FACTOR MANAGEMENT

10.1 Antithrombotic Therapy

Subjects will be randomized to 1-year of treatment with:

1) Ticagrelor 180 mg loading dose (see exception below) and then 90 mg twice a day thereafter and aspirin 81 mg per day, or
2) Rivaroxaban 2.5 mg twice daily and aspirin 81 mg per day, or
3) Clopidogrel 600 mg loading dose (see exception below) and then 75 mg per day thereafter and aspirin 81 mg per day.

Exception: Subjects who have been on clopidogrel or ticagrelor for at least 5 consecutive days prior to randomization *OR* received a greater than or equal to 300 mg loading dose of clopidogrel or a greater than or equal to 180 mg loading dose of ticagrelor within 5 days before randomization followed by daily clopidogrel or ticagrelor will not receive the loading dose of study antithrombotic medications on day of randomization. Instead, they will start the maintenance dose of the study antithrombotic medications on the day they are randomized.

Immediately after randomization, subjects should take their loading dose in the presence of study staff. Subjects who are exempt from the loading dose should start their maintenance dose when randomized. Subsequent maintenance doses should be administered with an 6 to 12-hour interval (preferably close to 12) between doses, with the timing adjusted such that the maintenance doses can be taken in the morning and the evening for the remainder of the one-year treatment period.

Aspirin can be taken at any time on the day of randomization and for the remainder of the one-year treatment period.

IP will be shipped to Canada, and will be packaged, labelled and supplied locally. Sites will be supplied with unblinded aspirin bottles, blinded antithrombotic loading dose bottles, and blinded 4-month antithrombotic maintenance dose kits. Refer to the Pharmacy MOP for specific details regarding the antithrombotic medications provided at enrollment and 4-month and 8-month refill evaluations.

The blinded tamper-evident sealed kits **SHOULD NOT** be opened before dispensing to the subject.

The labels on the maintenance dose bottles will be color coded and clearly labeled “A.M.” or “P.M.” to promote compliance. Subjects will also be provided with a medication diary and pill trays to assist them with medication compliance.

An IND exemption has been granted by the FDA to study ticagrelor and rivaroxaban in CAPTIVA.

Rationale for 1 Year of Antithrombotic Therapy and Follow-Up. There are compelling reasons for 1 year of antithrombotic therapy. In subjects who qualified for SAMMPRIS with a symptomatic infarct, the rates of recurrent ischemic stroke (using the AHA definition) in the territory of the stenotic artery more than doubled from 3 months to 12 months – these rates were 7.8% at 3 months, 13.3% at 6 months, 19.7% at 12 months, and 20.9% at 24 months.[6] On the basis of the SAMMPRIS data, almost half of stroke neurologists in the US already use clopidogrel + aspirin for longer than the 3 months duration used in most SAMMPRIS patients.[69] There is some preliminary data from SAMMPRIS that using clopidogrel for longer than 3 months may lower the risk of stroke but could also increase the risk of major hemorrhage: In 50 subjects in the medical arm of SAMMPRIS who continued clopidogrel beyond 3 months for cardiac reasons, 3 (6.0%) had a primary endpoint and 2 (4.0%) had a major hemorrhage beyond 3 months whereas in 158 subjects who stopped clopidogrel at 3 months, 17 (10.8%) had a primary endpoint and 4 (2.5%) had a major hemorrhage beyond 3 months.[70] While these differences were not statistically significant (likely because of very low power) this analysis does provide some data supporting the use of clopidogrel for longer than 3 months to lower the high risk of stroke from 3 months to 1 year. The duration of follow-up is limited to 1 year because the stroke and vascular death rate beyond 1 year was very low in SAMMPRIS [4] and WASID.[71]

Rationale for Aspirin Dose. We are using aspirin 81mg daily in CAPTIVA for several reasons: 1) the safety data on combining aspirin and low dose rivaroxaban comes from the COMPASS trial, which used low dose aspirin (100mg daily); 2) PRINCE also used low dose aspirin (100mg daily) in the ticagrelor and clopidogrel arms. While there was no significant difference between the two arms in major bleeding or ICH, the ticagrelor arm did have significantly more minimal bleeding;[30] 3) 81 mg falls within the recommended aspirin dose range for secondary prevention (50 – 325mg);[13] 4) There is some concern about higher dose aspirin decreasing the efficacy of ticagrelor[72] (there is an FDA black box warning on this). We are using 81mg rather than the 100mg used in COMPASS and PRINCE because 81mg is the commercially available low dose of aspirin in the USA. While a recent meta-analysis suggested that aspirin dose should be adjusted according to bodyweight,[73] the analysis only assessed aspirin for primary prevention and did not evaluate doses of aspirin when used in combination with other antithrombotic agents. Importantly, all three arms of CAPTIVA will receive the same dose of aspirin so any impact that bodyweight has on aspirin efficacy should be similar in all three arms.

Rationale for Ticagrelor Dose. The ticagrelor dose in CAPTIVA is based on the PRINCE trial in which subjects who were randomized to ticagrelor received 90mg twice daily.[30] The PEGASUS-TIMI 54 trial of subjects with coronary disease suggested that ticagrelor 60mg twice daily is as effective as the 90mg twice daily dose, but differences in safety were not statistically significant.[74]

While the results of PEGASUS-TIMI 54 motivated the investigators of the THEMIS trial of subjects with diabetes to lower the dose of ticagrelor partway through the study,[74] the rationale for using the ticagrelor 90mg twice daily dose in CAPTIVA is that PRINCE more closely resembles the target population of CAPTIVA and there wasn't a significant difference in safety between the 90mg twice daily or the 60mg twice daily ticagrelor dose in PEGASUS-TIMI 54.

10.2 Proton-pump Inhibitors (PPIs)

The most common adverse event from all the antithrombotic medications used in CAPTIVA is gastrointestinal bleeding. In order to decrease the risk of gastrointestinal bleeding in CAPTIVA, study investigators will be encouraged, but not required, to prescribe a proton-pump inhibitor for the 1-year duration of dual antithrombotic therapy in the trial. Pantoprazole was associated with a lower risk of bleeding from gastroduodenal lesions in the COMPASS trial and was not associated with any safety adverse events with the exception of a small increase in the risk of enteric infections.[75,76] Additionally, pantoprazole does not reduce the antiplatelet effect of clopidogrel or ticagrelor.[77,78] Clopidogrel prescribing information recommends avoiding concurrent use with omeprazole and esomeprazole due to the possibility that combined use may result in decreased clopidogrel effectiveness. Pantoprazole or rabeprazole are better alternatives. If those PPIs are limited due to cost, consider lansoprazole (Prevacid), which can be obtained over-the-counter.

10.3 Risk Factor Management

Risk factor management at each site will be similar to that in the SAMMPRIS trial.[59] Each subject's risk factors will be managed by the study team. In addition, a health coach from the lifestyle modification program, INTERVENT (also used in SAMMPRIS) will be assigned to each subject. The study team will be required to follow the protocols established for the trial for the primary risk factors (LDL and blood pressure). The study team will also be responsible for the management of other risk factors (non-HDL cholesterol, diabetes targeting a hemoglobin A1c of < 7%, smoking, sedentary lifestyle, high body mass index) using national guidelines provided to each site. Assistance to the study team in achieving primary and secondary risk factor goals will be provided by the INTERVENT health coach and the subject's primary care physician (especially for management of diabetic medications). INTERVENT will call the subject by phone within the first week after randomization to complete enrollment in INTERVENT and schedule the first health coach call. Coaching calls will occur approximately every 2 weeks for the first 3 months, then once a month throughout follow-up. These calls typically last 15-20 minutes. At scheduled intervals, the INTERVENT health coach will generate a subject-specific Goals and Action Plan report that summarizes the recommendations for risk factor management, which is provided to the subject and the study site personnel. The INTERVENT counseling schedule will be staggered with the site study evaluation schedule in order to ensure that the most recent INTERVENT report is available to the study team for required follow-up evaluations.

Please refer to the Risk Factor Management Manual of Operations for more details of risk factor management.

10.3.1 Primary Risk Factors

Achieving Target LDL

The LDL management algorithm is described in detail in the Risk Factor Management Manual of Operations. In brief, baseline local laboratory values within 90 days prior or on the day of enrollment will qualify as the initial LDL levels for the determination of treatment. All subjects in

this trial with a baseline LDL ≥1.8 mmol/L who are not already on a statin will be started on atorvastatin 40 mg per day. For subjects with a LDL ≥1.8 mmol/L who are already on a statin, the dose will be increased to a dose equivalent to 40mg of atorvastatin (See **Table 2** for the equivalent doses of statins). For subjects on statins (e.g. pravastatin, lovastatin) whose maximum dose provides less LDL lowering effect than atorvastatin 40 mg per day, it is recommended that those subjects should be switched to atorvastatin 40 mg per day. For subjects with a baseline LDL ≥1.8 mmol/L who are already on atorvastatin 40 mg, the dose will be increased to atorvastatin 80 mg.

All subjects with a baseline LDL ≥1.8 mmol/L will have a repeat LDL measurement at the 30-day evaluation and if the 30-day LDL level is still ≥ 1.8 mmol/L, their statin therapy will be increased (if not on a maximal dose) or ezetimibe or a PCSK9 inhibitor may be added (if already on a maximum tolerated dose of statin). A repeat LDL level should be measured 4-6 weeks after starting or changing the dose of any lipid-lowering medication. Additional titration of lipid lowering medications (including adding ezetimibe or a PCSK9 inhibitor if needed) should be continued until the subject's LDL is < 1.8 mmol/L. LDL levels will also be checked at the 1-year close-out evaluation in all subjects.

Table 2: Relative LDL-lowering Efficacy of Statin and Statin-based Therapies*

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin**	Simva	% ↓ LDL-C
--	40 mg	1 mg	20 mg	20 mg	--	--	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	--	--	20 mg	38%
20 mg	--	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	--			--	10 mg	10/20 mg	80 mg	47%
80 mg	--			--	20 mg	10/40 mg	--	55%
	--			--	40 mg	10/80 mg	--	63%

Atorva = Atorvastatin; Fluva = Fluvastatin; Pitava = Pitavastatin; Lova = Lovastatin;
Prava = Pravstatin; Rosuva = Rosuvastatin; Simva = Simvastatin

*Based on individual statin efficacy data, not head-to-head comparisons between statins.

**No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.
http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm

The study team will have access to lipid experts on the Risk Factor Management Committee about problems with individual subjects by contacting the Risk Factor Management Center.

Liver enzyme (AST and ALT) testing and creatine phosphokinase level (CPK) performed within 90 days prior to randomization (typically at the time of the qualifying stroke) will be considered the baseline values. Repeat testing will only be performed during the trial if clinically indicated. If repeat ALT or AST levels exceed 3x normal, the subject will return in 1 week for repeat testing. If the ALT or AST levels still exceed 3x normal, atorvastatin (or whatever statin the subject is on) will be stopped. Creatine phosphokinase level (CPK) should be repeated if the subject develops muscular symptoms during follow-up. If the CPK levels exceed 10x normal, depending on the associated clinical syndrome, the CPK level may be checked again within 1 week (e.g., if there is a history of recent trauma or strenuous exercise) or the atorvastatin (or whatever statin the subject is on) will be stopped (clinical evidence of myopathy).

Blood Pressure Management

The blood pressure management protocol is similar to that used in the SAMMPRIS trial.[59] See the Risk Factor Management Manual of Operations for the blood pressure management algorithm.

The study team at each clinical site will supervise hypertension management for CAPTIVA subjects. Study personnel are encouraged to use the CAPTIVA algorithm for managing blood pressure in the trial and adjust it, if necessary, based on individual subject characteristics, co-morbidities, and side-effects. The CAPTIVA Risk Factor Management Center will review blood pressure management at each clinical site on an ongoing basis. Study personnel will have access to blood pressure experts on the Risk Factor Management Committee about problems with individual subjects by contacting the Risk Factor Management Center.

Blood pressure will be checked at each scheduled evaluation and subjects will be considered "in target" if the systolic blood pressure is <140 mmHg. For subjects above target, the blood pressure medications will be adjusted and a repeat BP check will be performed in approximately 30 days. Once the BP is in target, the subject resumes the next protocol scheduled evaluation (i.e., at 4, 8 or 12 months after randomization).

Selection of antihypertensives will be based on individual subject factors with emphasis on guideline-based regimens.

As part of routine care, all subjects will have serum creatinine, potassium, and sodium level checked prior to randomization, 30 days after starting or changing the dose of an ACE inhibitor, ARB, or diuretic and at 1 year to assess for alterations in renal function and electrolytes that could influence antihypertensive agent choice. Additionally, all subjects taking spironolactone (or other potassium-sparing diuretics) will have serum creatinine, potassium and sodium checked 7-14 days after starting or changing the dose as part of routine care.

10.3.2 Secondary Risk Factors

Non-HDL Cholesterol

Non-HDL cholesterol <2.6 mmol/L is considered an important secondary target. Non-HDL cholesterol consists of LDL plus the additional cholesterol carried by triglyceride rich lipoproteins - very low-density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). Therefore, once LDL has been maximally treated, if non-HDL cholesterol ≥ 2.6 mmol/L and fasting triglycerides are ≥ 1.6 mmol/L mg/dl, refer to the Risk Factor Management Manual of Operations for management options or contact the Risk Factor Management Center.

Diabetes Management

Diabetes management will be performed by study personnel and the subject's outside physicians (primary care or diabetologist) to achieve a target HgA1c < 7.0% as per current standard of care. (unless there is a compelling reason for a less-stringent target, such as a subject with a history of severe hypoglycemia) based on the recommendations of the American Diabetes Association.[77]

Smoking Cessation

Current smoking status will be assessed by the PACE Smoking Score at every evaluation. Smoking cessation will be strongly encouraged by the study team.

Targeted Weight Management

Weight will be assessed at each follow-up evaluation and BMI charts will be provided to each study team. The standard formula for calculating BMI is:

BMI = (Weight in Pounds / (Height in inches) x (Height in inches)) x 703

An online BMI Calculator can be found at:

http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm

The target goals for BMI in study subjects are as follows:

If the initial BMI is 25-27 kg/m^2, the target BMI is < 25 kg/m^2.
If the initial BMI is > 27 kg/m^2, the target is a 10% weight loss.

Physical Activity

Physical activity status will be assessed by the PACE Current Physical Activity Status Score at every evaluation. Study personnel are encouraged to emphasize the importance of physical activity to the subject. Moderate intensity activities will be recommended at least 3 times per week (optimally five times per week) for 30 minutes per session in subjects able to participate.

Moderation of Alcohol

Subjects will be told to limit daily alcohol intake to 1 oz. of ethanol (2 oz. of 100-proof whiskey, 8 oz. of wine, 24 oz. of beer).

Schedule of Recommended Laboratory Tests to Monitor Risk Factors

The schedule of recommended standard of care tests to monitor risk factors and medications used for risk factor management are provided in **Appendix 2**.

11 SCHEDULE FOR FOLLOW-UP

All subjects in CAPTIVA will be evaluated at 1 month, 4 months, 8 months, and 1 year when they will have their blood pressure checked, risk factors optimized, and will be assessed for study endpoints. At these evaluations, pill counts of the study antithrombotic medications and aspirin tablets will be obtained. At each of these evaluations, subjects will also be asked about adverse events and changes in medications since the last evaluation. For subjects whose systolic blood pressure is greater than or equal to >140/90 mmHg at any evaluation, an adjustment in the blood pressure medications should be made and the subject's blood pressure level should be checked again 30 days later. The following definitions and windows will be used for follow-up evaluations:

Assessment	**Window**	**Definition**
Baseline		Randomization Day

1 month	±7 days	Day 23-37, inclusive
4 months	±7 days	Day 113-127, inclusive
8 months	±7 days	Day 233-247, inclusive
1 year	±7 days	Day 358-372, inclusive

12 EVALUATION OF ENDPOINTS AND ADVERSE EVENTS

The primary endpoint is ischemic stroke (using the AHA/ASA definition of stroke[1]), ICH, or vascular death during 1 year of follow-up. Subjects will be carefully instructed to contact the study team immediately if they develop new neurological symptoms (or other adverse events), and site personnel must evaluate subjects as soon as possible after symptom onset. If the site personnel suspects that the symptoms are ischemic or hemorrhagic in nature, a brain MRI must be obtained as soon as possible and no later than 2 weeks after onset (head CT is permissible only if subject cannot tolerate or has contraindication to MRI). If MRI is not considered necessary as standard care, the study will pay for the MRI. All neuroimaging will be reviewed and adjudicated by the central neuroradiologist who is based at the University of Florida.

All reported neurological events and bleeding episodes will be adjudicated centrally by blinded stroke neurologists with extensive experience adjudicating such endpoints in other stroke trials. All myocardial infarctions and deaths will be adjudicated blinded to treatment assignment by cardiologist adjudicators who are experienced adjudicators in cardiology trials.

All subjects who are adjudicated as having a stroke during the study will continue on their assigned treatment that will remain blinded unless their treating physicians choose open-label antithrombotic therapy. These subjects will continue to be followed to one year after randomization.

13 ASSESSMENT OF SAFETY

13.1 Adverse Events and Serious Adverse Events

13.1.1 Definition of Adverse Events (AE)

An adverse event is the development of any untoward medical occurrence or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, even if no study treatment has been administered.

13.1.2 Definition of Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following outcomes:

- results in death;

- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or causes prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed above

13.1.3 Classification of an Adverse Event

13.1.3.1 SEVERITY OF EVENT

The severity of AEs and SAEs will be reported using the grading system outlined in the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE). The CTCAE provides a grading (severity) scale for each AE term and AEs are listed alphabetically within categories based on anatomy or pathophysiology. The CTCAE (v5.0) displays Grades 1-5 with unique clinical descriptions of severity for each AE based on this general guidance:

CTCAE Severity Grading Summary	
Grade 1:	Mild AE
Grade 2:	Moderate AE
Grade 3:	Severe or Disabling AE
Grade 4:	Life-Threatening AE
Grade 5:	Death related to AE

The complete definitions of these grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

13.1.3.2 RELATIONSHIP TO STUDY AGENT

The relationship of each reported event to the study agent will be assessed and documented by a study investigator. An algorithm to help determine relatedness can be found in the Manual of Operations and Procedures (MOP).

13.1.3.3 EXPECTEDNESS

The Independent Medical Monitor (IMM) will be responsible for determining whether an SAE is **expected** or **unexpected**. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

13.1.4 Time Period and Frequency for Event Assessment and Follow-up

Site personnel will regularly assess and report all reportable events occurring from the time a subject has signed and dated the informed consent form until the subject has completed their final evaluation. All events will be captured on the appropriate CRF and entered into WebDCU™. Information to be collected includes event description, time of onset, PI's assessment of severity, seriousness, relationship to study agent (assessed only by those with the training and authority to make a diagnosis), time of resolution/stabilization of the event, a description of the event, relevant history, and concomitant medications/procedures. All reportable events will be followed for outcome information until resolution or until the last day of study participation. The information in WebDCU™ will be updated as more information becomes available.

13.1.5 Adverse Event Reporting

Site investigators or their designees must report adverse events meeting the following criteria in WebDCU™.

1) Any serious adverse event
2) Any non-serious adverse event that is possibly or definitely related to occurring with the study antithrombotic medications, risk factor management, or any brain or vascular imaging study
3) Primary or secondary endpoints (parenchymal intracerebral brain hemorrhage (ICH), ischemic stroke, vascular death, myocardial infarction, or any non-ICH major hemorrhage)
4) Adverse events of special interest (asymptomatic or incidental cerebral infarct, TIA, ruptured aortic aneurysm, pulmonary embolus, acute ischemia of a limb or internal organ, overdose of study drug, and study drug exposure during pregnancy (occurring in subject or female partner of a male subject))

Non-serious adverse events meeting these criteria must be reported within 5 working days of site awareness and serious adverse events meeting these criteria within 24 hours, excluding weekends/holidays, of site awareness.

13.2 Other Reportable Events

Follow-up information regarding the course of pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported in WebDCU™ on Form 104: Adverse Event. Any pregnancy that occurs in a female partner of a male subject must also be reported. In order for the study team to collect any pregnancy information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Any study antithrombotic product quality complaints must be reported (via telephone or email) within 5 working days of site awareness to the CCC Project Manager or CCC Administrator. Examples include, but are not limited to:

- Mislabeling or misbranding
- Information concerning microbial contamination, including a suspected transmission of any infectious agent by a product

- Any significant chemical, physical, or other changes that indicate deterioration in the distributed product
- Any foreign matter reported to be in the product
- Physical defect (e.g., abnormal product odor, broken or crushed tablets, etc.)

This study is being conducted as an investigator-initiated, NINDS-funded protocol. The FDA has granted a waiver for an investigational new drug (IND) application. Thus, no formal safety reporting to the FDA will be done.

13.3 Unanticipated Problems and Unanticipated Events

13.3.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers *unanticipated problems* (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the REB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Examples of UPs include:

- Suspected abuse/misuse of study drug
- Inadvertent or accidental exposure to study drug
- More frequent or severe side effects than were anticipated as described in the protocol and consent form
- Malfunctioning of research equipment that results or could result in risk to subjects or others
- Interim findings (data analysis and/or safety reports) and/or data safety monitoring reports that indicate an unexpected change to the risks or potential benefits of the research, in terms of severity or frequency
- Publications in the literature that indicate new risks
- Changes in product labeling indicating new risks
- Incorrect labeling, dosing, or dispensing of study drug even if there is no indication of harm (e.g. randomization error)

Unanticipated events include UPs, but may also include other events that do not rise to the level of UPs as outlined above. These include protocol deviations or other unexpected problems that do not necessarily pose a safety concern.

13.3.2 Unanticipated Event Reporting

Clinical sites will report unanticipated events, including UPs and protocol deviations, in accordance with the guidelines listed in the MOP.

13.4 Study Oversight

Safety oversight will be under the direction of the NIH StrokeNet DSMB, which is composed of individuals with the appropriate expertise in overseeing stroke clinical trials. The DSMB will meet at least semiannually to assess safety data on each arm of the study. The DSMB will review data quality and completeness, monitor fidelity to the study protocol, review the adequacy of participant recruitment and retention, review SAEs, and AEs of special interest and make recommendations to the NINDS and the study co-PIs concerning trial continuation, modification, or conclusion.

Additionally, the DSMB may recommend modifications to the protocol if a reversible safety issue is identified. After each meeting, the liaison to the DSMB will prepare a letter to the study principal investigators, which will summarize the DSMB recommendations following the safety review. This letter will be provided to the CIRB and local REBs, where appliable, and site investigators.

The Independent Medical Monitor (IMM) will conduct a review of each SAE to determine expectedness. If the IMM adjudicates the event to be serious, unexpected, and study related, the event will be reported to the cIRB and other IRB/REBs with study oversight according to cIRB and local regulations via a Safety Report generated in WebDCU™.

13.5 Study Halting Rules

The IMM is responsible for ongoing monitoring of reports of SAEs by the clinical centers within 72 hours to ensure Good Clinical Practices (GCP) and to identify safety concerns quickly. The IMM may suggest protocol modifications to the DSMB to prevent the occurrence of particular SAEs, such as modifying the protocol to require frequent measurement of laboratory values predictive of the event or to improve expeditious identification of SAEs. The NDMC will prepare regular reports concerning SAEs and submit them to the DSMB. In the event of unexpected SAEs or an unduly high rate of SAEs, the IMM will promptly contact the NINDS DSMB liaison, who will notify the DSMB Chair. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for continuing or halting the study to the NIH and the study co-PIs.

14 SAMPLE SIZE AND STATISTICAL ANALYSIS

Sample Size Determination for the Primary Safety Outcome

The safety analysis is prespecified to occur when the first 450 randomized subjects have completed the 1-year follow-up period, resulting in approximately 150 patient-years of follow-up in each arm. While the 450th subject is completing the 1-year follow-up period, enrollment projections (15 subjects per arm per month) suggest that an additional 180 subjects per arm will have been randomized. The follow-up time available for these additional subjects will vary but is expected to be approximately 6 months on average, for an additional 90 patient-years of follow-up (180*6/12) per arm. The safety analysis will use available data on all enrolled subjects and is therefore expected to include approximately 240 patient-years of follow-up per arm.

Within each treatment arm, an analysis will be conducted to evaluate an excess risk of ICH as well as non-ICH major hemorrhage. In SAMMPRIS, the ICH rate was 0.5 (exact 80% CI 0.05 – 1.9), and the non-ICH major hemorrhage rate was 2.4 (exact 80% CI 1.2 - 4.5), per 100 patient-years on clopidogrel + aspirin. Even though clopidogrel was only used for 90 days in SAMMPRIS

and will be used for 1 year in CAPTIVA, we are using the 80% CI of the SAMMPRIS rates to be conservative and not overestimate the hemorrhage rates on clopidogrel + aspirin. In each experimental arm, the hypothesis for the safety analysis is that the rate is greater than these upper 80% confidence limits derived from SAMMPRIS. This hypothesis will be tested with a one-sided 0.05 level of significance because we are only interested in identifying an increase in risk (not a decrease). If an experimental arm crosses this safety boundary, this will initiate an unplanned, for cause, futility analysis in order to weigh the risk:benefit ratio of the corresponding experimental arm. With 240 patient-years of follow-up, the safety analysis has 80% power to reject the stated null hypothesis for the true event rates shown in **Table 3**.

Table 3. Safety Analysis	
Safety Event	**Null Hypothesis (per 100 patient-years)**
ICH	Rate ≤1.9
Non-ICH major hemorrhage	Rate ≤4.5

Sample Size Determination for the Primary Efficacy Outcome

All subjects will be followed for one year for the primary outcome. The sample size was calculated based on a two-sample survival analysis comparing the time-to-event of a single experimental arm to clopidogrel + aspirin in EAST v6. The assumed event rate in CAPTIVA is based on high-risk subjects in the medical arm of SAMMPRIS who presented with a symptomatic infarct. The 1-year rate of ischemic stroke, ICH or vascular death was 27%.[6,7] On the other hand, combining clopidogrel and aspirin for 1 year is likely to lower the rate of the primary endpoint so we have assumed a 24% primary event rate in the clopidogrel + aspirin arm. We are seeking a hazard ratio (HR) of 0.66 in CAPTIVA as the reduction in the rate of primary endpoint that would be required to overcome the anticipated higher risk of bleeding in the rivaroxaban and ticagrelor arms and the higher cost of these medications. The PRINCE trial demonstrated a HR of 0.45 for stroke in the ticagrelor + aspirin arm compared with the clopidogrel + arm in participants with large artery atherosclerosis,[30] and the COMPASS trial demonstrated a HR of 0.33 for ischemic stroke in the low dose rivaroxaban + aspirin arm compared to aspirin alone in subjects with a previous ischemic stroke.[38] Thus a HR of 0.66 also seems like an achievable target in CAPTIVA from ticagrelor + aspirin or low dose rivaroxaban + aspirin versus clopidogrel + aspirin.

For the comparison of a single experimental arm to clopidogrel + aspirin, the sample size was calculated for a two-sample survival analysis using EAST v6. In order to detect a HR of 0.66 (decrease in events from 24% to 16.56%) with 80% power, using a two-sided 0.05 level of significance, the required sample size per comparison is 948 (474 per arm). This calculation includes inflation for an interim futility analysis, conducted according to an O'Brien-Fleming error spending function after 50% of events have occurred. The calculation also includes inflation to account for approximately 5% dropout, assuming that dropout is a competing risk. In SAMMPRIS, 3% in the medical arm were lost over the first year of follow-up, so our 5% drop out estimate at 12 months is reasonable. An additional inflation factor of ~1.18 is then applied to account for dilution of the treatment effect associated with approximately 8% non-compliance with antithrombotic therapy, yielding a sample size per comparison of 1122 subjects (561 per arm). The inflation factor is derived via $1/(1-R^2)$, where R represents the non-compliance rate, as suggested in Friedman, Furberg, and DeMets.[78] We expect the non-compliance will largely result from adverse events from the antithrombotic medications (major hemorrhages in all 3 arms and dyspnea in the ticagrelor arm) but we do not expect these rates will exceed 8% in 1 year of follow-up in any arm of the trial. We expect treatment crossover to be very low because it is unlikely that subjects who do not have a primary endpoint will be switched from their blinded treatment arm to

open label treatment with one of the antithrombotic treatments being evaluated in CAPTIVA (note that rivaroxaban and ticagrelor are currently not approved for sICAS). We also expect that it will be very uncommon that subjects will undergo stenting or angioplasty or surgical bypass for their sICAS without having a stroke, which would be a primary endpoint. If a participant does undergo one of these procedures without having a primary endpoint, he/she will continue to be followed in the trial according to intention to treat. Because the same clopidogrel + aspirin arm is used as the control in both comparisons, an additional 561 subjects are required. This results in a total sample size of 1683 subjects. The main intent of CAPTIVA is to establish whether either of the two novel therapies is more effective than the current standard of care for sICAS. These experimental arms are evaluated in a single trial only to improve efficiency. The hypotheses do not constitute a family of hypotheses which must be interpreted together to support a single efficacy declaration; instead, the comparison of each experimental arm to the standard of care arm can be interpreted independently of the other. i.e., the chance of a false positive outcome for either claim of effectiveness is not increased by the presence of the other hypothesis. As such, a multiplicity adjustment is not required.[79-81]

Sample Size Re-Estimation

To reduce the likelihood of an underpowered study due to incorrect assumptions, we propose to conduct a blinded sample size re-estimation in stage 2 prior to the planned interim futility analysis. This sample size re-estimation will occur approximately three months prior to the planned interim futility analysis. Refer to the separate Statistical Analysis Plan for more details on the sample size re-estimation.

The results of the sample size re-estimation will only be shared with the DSMB in closed session. This is done in order to maintain the study blind and avoid potential investigator bias. Ultimately it is the DSMB's decision to recommend an increase in the total sample size, and this decision should take into account the study conduct as well as the safety profile. Administratively, the unblinded statistician will provide the information to the DSMB. This will include the impact on estimated sample size if the power were to be maintained at 80% or reduced. This notification will include a brief report of the safety data (adverse event information by treatment arm) and data quality (protocol deviations by treatment arm). If the inclusion of additional subjects is recommended to maintain adequate power, the DSMB may recommend postponing the planned interim futility analysis (scheduled to occur 3 months after the sample size re-estimation) until a decision about an increase in sample size has been made by NINDS.

Planned Interim Analysis for Futility

One planned Interim analysis for overwhelming futility, conducted according to the beta-spending approach using O'Brien-Fleming type stopping boundaries, is pre-specified to occur when 50% of primary endpoints have been reported. The threshold to reject the null hypotheses for overwhelming futility of a given comparison are provided in the table below.

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Analysis	Look #	Approximate Number of Events	p-value to Stop Experimental Arm
Interim	1	94	p>0.719
Final	2	187	p≥0.05

The approximate number of events detailed in the table above represents the expected number of events for comparing either experimental arm (ticagrelor + aspirin; rivaroxaban + aspirin) to standard care (clopidogrel + aspirin). The comparison for each experimental arm to standard of care will only occur once the desired number of events has been achieved for that comparison. That is, for example, if the number of events combined between the ticagrelor + aspirin arm and clopidogrel + aspirin arms reaches 94 and the number of events combined between the rivaroxaban + aspirin arm and clopidogrel + aspirin arms is only 70, only the futility analysis comparing ticagrelor + aspirin arm to clopidogrel + aspirin will be conducted. Once the number of events between the comparing ticagrelor + aspirin arm to clopidogrel + aspirin reaches 94, the futility analysis comparing these arms will be conducted.

The beta-spending approach gives flexibility in the timing of the interim futility analysis while preserving the power of the trial.

Randomized controlled trials stopped early for benefit have been shown to result in an overestimate of the treatment effect for the primary outcome.[82] The reduced sample size resulting from early termination reduces the precision of the treatment effect estimates; it may also impact our ability to comprehensively evaluate safety profiles and to draw conclusions about important secondary endpoints, a point that Mueller et al[83] argues compromise scientific validity and overlooks societal obligations. Therefore, in order to provide an unbiased and precise estimate of the treatment effect and a thorough evaluation of all relevant endpoints, we have opted not to include an interim analysis for overwhelming efficacy.

15 DATA MANAGEMENT AND QUALITY ASSURANCE

Data management and all statistical analyses in the trial will be performed by the National Data Management Center (NDMC) at the Medical University of South Carolina. This unit has extensive experience managing large multicenter trials and is the data management center for 2 large national clinical trials networks funded by NIH – the Stroke Trials Network (StrokeNet) and the Strategies to Innovate Emergency Care Clinical Trials Network (SIREN). The Data Coordinating Unit (DCU) at the NDMC conducts central monitoring, whereby pre-specified metrics on data quality are monitored centrally. For example, trends within and across sites and over time will be checked periodically by the statistical programmer; and critical data items, such as informed consent documents and primary outcome source documents will be uploaded into the WebDCU™ for verification by the central monitor/data manager. Furthermore, if a site's electronic medical record can be accessed, remote monitoring by the central monitor can occur for pre-specified data items. From these central monitoring activities, if a site is identified as having problems (such as no AEs recorded in spite of enrolling several subjects), for-cause on-site monitoring may be conducted. This will help ensure that all aspects of the current, approved protocol with any amendment(s) are followed. At these visits, original source documents will be reviewed for verification of data in the electronic database. The Investigator/institution guarantees direct access to original source documents by sponsor personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review. The study may also be subject to a quality assurance audit by the sponsor or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during the monitoring visits and possible audits, and that sufficient time is devoted to the process.

16 STUDY DRUG SUPPLY AND ACCOUNTABILITY

The study will provide ticagrelor, rivaroxaban, clopidogrel and aspirin through the pharmacy coordinating center at no cost to the subjects.

Risk factor medications will be prescribed as needed by the study physician based on usual care in accordance with the recommended CAPTIVA LDL and SBP protocols.

17 REGULATORY REQUIREMENTS

The study will be conducted in accordance with the U.S. Food and Drug Administration's (FDA) Code of Federal Regulations (CFR 21), HHS Regulations (45 CFR 46), Health Canada Food and Drug Regulations Division 5 Part C, and Good Clinical Practice (GCP) guidelines.

19 APPENDICES

Appendix 1: Schedule of Evaluations and Assessments

Assessment	Baseline	Month 1 (30 +/- 7 days)	Month 4 (120 +/- 7 days)	Month 8 (240 +/- 7 days)	Month 12 (365 +/- 7 days)
Inclusion & Exclusion Criteria	X				
Informed Consent	X				
Randomization	X				
Medical History	X				
History of Qualifying Stroke	X				
Review Risk Factor Data	X	X	X	X	X
Vital Signs (BP & Weight)	X	X	X	X	X
Neurological Exam[1]	X	X	X	X	X
Modified Rankin[1]	X	X	X	X	X
NIH Stroke Scale[1, 3]	X				
MoCA Test	X				X
Review Medications	X	X	X	X	X
Witness Loading Dose administration, if applicable	X				
Ship Mouthwash or Buccal Swab Sample to UF for Genotyping	X	X[2]			
Upload imaging to Ambra Health	X	PRN	PRN	PRN	PRN
Assess Adverse Events		X	X	X	X
Count All Study Antithrombotic Medications			X	X	X
Prescribe Risk Factor Medications	X	X	X	X	
Order Study Antithrombotic Medications	X		X	X	
Submit eCRFs	X	X	X	X	X

[1]Also required at the time of any neurologic endpoint.

[2]Only required if first sample was inadequate for testing.

[3]NIHSS required at baseline and at the time of any neurologic endpoint; optional at other timepoints in stable subjects

Appendix 2: Schedule of Laboratory Tests

Schedule of Laboratory Tests for Intensive Medical Management		
Laboratory Test*	**Scheduled**	**PRN**
Creatinine (Cr) Potassium (K+) Sodium (Na)	• Baseline**	If on diuretic, ACE inhibitor, or ARB: Periodic determination of serum Cr and serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals, particularly in the elderly and those with significant renal or hepatic impairments. Recommended frequency: • If on diuretic, ACE inhibitor or ARB: 30 days after starting or changing dose • If on spironolactone (or other K+ sparing diuretics): 7-14 days after starting or changing dose
Local Lipid	• Baseline** • 12-month evaluation	- If not in target at baseline repeat at 1 -month evaluation - 4-6 weeks after changing a dose of lipid-lowering medication
AST/ALT	• Baseline**	• If > 3x normal, repeat in 1 wk • As clinically indicated
CK	• Baseline**	• If subject develops symptoms of myalgia
HgA1c†	• Baseline** (all subjects) • 12-month evaluation (if diabetic)	• If subject not meeting treatment goals or if change in therapy, it is recommended that the HgA1c be checked at least quarterly. However, because of the exceptional variability among diabetics, the frequency of HgA1c testing cannot be mandated.

*All tests may be performed at any qualified laboratory. With the exception of the hemoglobin A1c, all tests should be ordered by study personnel managing the subject's blood pressure and statin medications.

**Values within 90 days before randomization are acceptable.

†Study personnel should ensure that subject's primary care physician or diabetologist are following these ADA recommendations for evaluating the HgA1c.

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21 VERSION HISTORY

Changes in Version 4.0 dated December 8, 2023
Not Applicable; New Document. The Canadian version of the protocol will begin with version 4.0 for consistency with US main protocol numbering.