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. Symptoms or signs of any duration associated with an infarct on brain imaging that occurred within 30 days prior to randomization
2. Index infarct in 1 above is attributed to 70-99% stenosis (or flow gap on MRA) of a major intracranial artery (carotid artery, MCA stem (M1), vertebral artery, or basilar artery) 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
4. Ability to swallow pills
5. Age 30-80 years, inclusive, at time of consent

Subjects 30-49 years are required to meet <u>at least one</u> 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 return for all follow-up visits 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 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. 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, uncontrolled severe hypertension (systolic pressure > 180 mm Hg or diastolic pressure > 115 mm Hg), severe liver impairment (AST or ALT > 3 x normal, cirrhosis), or CrCl < 15 mL/min or on dialysis
11. Major surgery (including open femoral, aortic, or carotid surgery, cardiac) 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 while hospitalized)
13. Severe neurological deficit that renders the subject incapable of living independently
14. Dementia or psychiatric problem that prevents the subject from following an outpatient program reliably
15. Co-morbid conditions that may limit survival to less than 12 months

16. 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
17. 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 **Appendix 3**)
18. 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 and ICH guidelines on GCP, will be followed. The study consent form, together with the study protocol, will be submitted to the central IRB 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 CIRB approved paper version of the form or a StrokeNet approved HIPAA-compliant 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 CIRB 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, re-consent may be obtained remotely using REDCap e-consent, fax, or mail (postal service) in accordance with CIRB 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.