Supplemental Material

Safety and Feasibility of Argatroban, Recombinant Tissue Plasminogen Activator and Intra-arterial Therapy in Stroke (*ARTSS-IA Study*)

Table I. ARTSS-IA Study Eligibility Criteria

Inclusion Criteria

1. Disabling Ischemic stroke symptoms with onset ≤ 3 hours treated with IV rt-PA by local standards or ≤ 4.5 hours according to local standard of care.
   Symptoms must be distinguished from another ischemic event such as syncope, seizure, migraine, subarachnoid hemorrhage and hypoglycemia. If the patient reports awakening with the event, the time of onset should be considered as the last time the patient (or a witness to the patient's condition) considered herself/himself normal.
2. Patients should meet local, institutional criteria to undergo emergent Endovascular Therapy (Intra-Arterial) to include:
   a. IAT must be able to begin before 6-hours of stroke onset or last seen well.
   b. CT-Angiogram confirmation of intra-arterial occlusion in any of the following locations: terminal ICA, MCA (M1 or M2 territories), PCA, distal vertebral or basilar artery.
   c. ASPECTS score on non-contrast head CT must be ≥6.
   d. IAT must be able to begin within 90 minutes of qualifying CT scan.
   3. Age ≥18.
   4. Females of childbearing potential must have a negative pregnancy test ($_{\beta}$HCG) prior to the administration of trial medication.
   5. Signed (written) informed consent by the patient or the patient's legal representative and/or guardian.

Exclusion Criteria

1. Evidence of intracranial hemorrhage (ICH) on baseline CT scan or diagnosis of a non-vascular cause of neurologic deficit.
2. NIHSS Level of Consciousness score (1a) ≥ 2.
3. Pre-existing disability with mRS >2.
4. Any evidence of clinically significant bleeding, or known coagulopathy.
5. INR >1.5.
6. Patients with an elevated aPTT greater than the upper limit of normal (test can be repeated if investigator suspects a falsely elevated value such as when the collection tube is not completely filled).
7. Patients currently, or within the previous 24 hours, on an oral direct thrombin inhibitor (i.e., dabigatran), a factor 10a inhibitor (i.e., rivaroxaban, apixaban), or any other long-acting anticoagulant.

8. Heparin flush required for an IV line. Line flushes with saline only.
9. Any history of intra-cranial hemorrhage, known ateriovenous-malformation or unsecured cerebral aneurysms.
10. Significant bleeding episode [e.g. gastrointestinal (GI) or urinary tract] within the 3 weeks before study enrollment.
11. Major surgery or serious trauma in last 2 weeks.
12. Patients who have had an arterial puncture at a non-compressible site, biopsy of parenchymal organ, or lumbar puncture within the last 2 weeks.
13. Previous stroke, myocardial infarction (MI), post myocardial infarction pericarditis, intracranial surgery, or significant head trauma within 3 months.
14. Uncontrolled hypertension (SBP > 185 mmHg or DBP >110 mmHg) that does not respond to intravenous anti-hypertensive agents.
15. Surgical intervention (any reason) anticipated within the next 48 hours.
16. Known history of clinically significant hepatic dysfunction or liver disease – including a current history of alcohol abuse.
17. Abnormal blood glucose <50 mg/dL (2.7 mmol/L).
18. History of primary or metastatic brain tumor.
19. Current platelet count < 100,000/mm^3.
20. Life expectancy < 3 months.
21. Patients who, in the judgment of the investigator, needs to be on concomitant (i.e., during the Argatroban infusion) anticoagulants other than Argatroban, including any form of heparin, UFH, LMWH, defibrinogenating agent, dextran, other direct thrombin inhibitors or thrombolytic agents, GPIIb/IIIa inhibitor or warfarin. [*Caveat: However, if in the judgment of the investigator a patient needs to be anticoagulated, **but** this can be deferred for 48 hours, then they could be included.]
22. Currently participating or has participated in any investigational drug or device study within 30 days before the first dose of study medication.
23. Known hypersensitivity to Argatroban or its agents.
24. **Additional exclusion criteria if patient presents between 3-4.5 hours**:
    a) Age >80
    b) Currently taking oral anticoagulants (regardless of INR)
    c) A history of stroke and diabetes
    d) NIHSS > 25

Table II. Argatroban Dosing Algorithm

Suggested Titration Algorithm

The algorithm below is a guideline for assisting investigators in making dosage adjustment to attain the protocol target aPTTs 2.25 times patient baseline value. Please note that due to inter-patient variability these adjustments may not definitely result in the achievement of the specified aPTT ranges and that variations in the dosage amounts may be required.

Protocol Target aPTT Values:

- Target = 2.25 times baseline

A +/- 5% range is permitted when attempting to attain the target aPTT values.

2.25 range = 2.14 – 2.36 (5% of 2.25 = 0.1125)

Suggested algorithm:

If the aPTT value is greater than or equal to +/- 10% of the target value (± 10% of 1.75 = 1.58 – 1.93 and ± 10% of 2.25 = 2.03 – 2.48), begin dosage adjustments at 0.5 μg/kg/min increments. Once the aPTT is within 10% of the target value, decrease dosage adjustments to 0.25 μg/kg/min increments. As the target range is approached, the dosage increments may need to be decreased by 0.125 μg/kg/min amount depending on the patient's sensitivity to the drug. See Figures below for a graphical example of dose titration as well as an example patient titration schedule.

A secure website will allow entering of the patient's weight and baseline PTT. After entering the data, the website will generate a printable (custom to only that individual patient) titration schedule (according to high vs. low dose schedule).

ADDITIONAL SAFETY NOTE:

Instructions for aPTT values from 110 seconds up to greater than 130 seconds:

If the aPTT elevates to **between 110 and 130** seconds, decrease the infusion by 50% (i.e. if 2 μg/kg/min decrease to 1 μg/kg/min), check the aPTT 1 hour following the adjustment. If the follow-up aPTT remains between 110-130, decrease the rate again by 50% and check the PTT 1 hour following the second rate decrease. Continue this process until the aPTT is <110 seconds, then follow the titration protocol generated by the website to maintain the target aPTT.

If the aPTT exceeds **130** seconds, immediately discontinue the infusion and check the aPTT every hour following the discontinuation until the aPTT is **less than 110** seconds. Once the aPTT is below 110 seconds, re-initiate the infusion (without the bolus dose) at the lowest previous dose for that patient that achieved

an acceptable aPTT value. In the event an acceptable previous dose was never reached (i.e., all previous aPTTs were greater than target), restart the infusion at 50% of the previous rate.

Suggested Dosing Algorithm

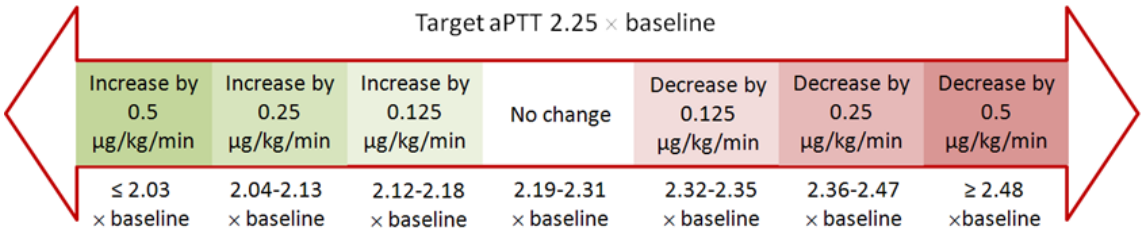

Figure. Example titration schedule for an 80kg patient with a baseline aPTT of 25.0 seconds.

Use this table for dosage adjustment based on latest aPTT result vs. target of 2.25 x baseline.		
aPTT multiplier Range	if latest aPTT Level is:	Adjust Rate (mcg/kg/min)
<= 2.03 x Baseline	<= 50.9	Increase by 0.5
2.04 - 2.13 x Baseline	51.0 - 52.9	Increase by 0.25
2.12 - 2.18 x Baseline	53.0 - 54.7	Increase by 0.125
2.19 - 2.31 x Baseline	54.8 - 57.8	No Change
2.32 - 2.35 x Baseline	57.9 - 58.8	Decrease by 0.125 *or by 50% of current dose if reduction would result in a rate of zero.
2.36 - 2.47 x Baseline	58.9 - 61.8	Decrease by 0.25 *or by 50% of current dose if reduction would result in a rate of zero.
>= 2.48 x Baseline	>= 61.9	Decrease by 0.5 *or by 50% of current dose if reduction would result in a rate of zero.
	110 - 130	**Decrease infusion by 50% of the current dose.** Check aPTT 1 hour after reducing the rate. If the follow-up aPTT still 110 - 130, decrease the rate again by 50% and check the PTT 1 hour later. Continue this process until the aPTT is < 110 seconds, then follow the titration protocol above.
	> 130	**Immediately hold the infusion.** Check the aPTT every hour following the discontinuation until the aPTT is less than 110 seconds. Once the aPTT is below 110 seconds, re-initiate the infusion (without the bolus dose) at the lowest previous dose for that patient that achieved an acceptable aPTT value. In the event an acceptable previous dose was never reached (i.e., all previous aPTTs were greater than target), restart the infusion at 50% of the previous rate.

Table III. Guidance for Intra-Arterial Therapy in the ARTSS-IA Study

This document provides guidance regarding intra-arterial (IA) therapy for patients treated in the ARTSS-IA study. It also includes a case-report form for collecting IA-specific data. Recent publication of five randomized clinical trials (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT and SWIFT-PRIME) demonstrated efficacy of IA in selected patients with large, proximal vessel occlusions. EXTEND-IA, the only trial to collect a prospective screening log, found <10% of IV-tPA treated patients could be randomized predominantly because of lack of proximal occlusion or availability of ET procedural teams.

Although trial eligibility varied to some degree, the common inclusion criteria were:

- Presence of a small core (infarcted tissue already noticeable on parenchymal imaging);
- Occlusion of a proximal intracranial artery in the anterior circulation (carotid terminus, M1 MCA or two proximal M2 MCA which function as a distal M1);
- Ability to start ET <6-hours from stroke onset;
    - Fast times to ET groin-puncture and first recanalization attempt (60-90 minutes from non-contrast head CT)
    - Avoidance of general anesthesia during ET
    - Stentreivers as first-line thrombectomy device

Although each ARTSS-IA study center may have developed their own IA-protocol, below we provide guidance for patients who are eligible for ARTSS-IA. Since time delays are correlated with lower odds of good clinical outcome, IA candidates should not be delayed from reaching the angio-suite due to ARTSS-IA study procedures including obtaining informed-consent. Safety and potential efficacy of combination systemic anticoagulation and IA has been described. A post-hoc analysis of stroke embolectomy (Multi-MERCI trial) compared cases that received IV-heparin (n=24 with median dose of 3000 units) to those that did not (n=27).[4] There was no increased risk of intracerebral hemorrhage or death. In a multivariable analysis, procedural heparin use was independently associated with <u>good clinical outcome</u> (mRS 0-2) at months (OR 5.89; 95%CI: 1.34-25.92, p=0.0189).

<u>IA patient selection:</u>

1) IA therapy team is able to start procedure before 6-hours from stroke onset.
2) Able to puncture the groin within 60min and first recanalization attempt within 90min of qualifying CT scan.
3) ASPECTS score of ≥6
    i. ASPECTS certification of investigators is strongly recommended.
4) CT-Angiogram confirmation of intra-arterial occlusion in anterior circulation (terminal ICA, M1 or M2 branches) or proximal posterior-circulation occlusion (PCA, vertebral and basilar arteries).

<u>IA procedure:</u>

1) General anesthesia should be avoided and the use of local/conscious sedation is strongly preferred.
2) IA revascularization may be undertaken with any currently available and approved device or paradigm and used according to the manufacturer's specifications for use. However, first-line preference remains stentrievers.
3) We recommend avoiding additional intra-arterial alteplase or other thrombolytic as these drugs are not approved for this indication and risk of intracranial hemorrhage most likely outweighs potential benefit.
4) We recommend not treating distal embolization (distal M2, M3, etc) in the setting of adequate proximal recanalization.

5) For patients with tandem extracranial/intracranial occlusions or high-grade stenosis, we do not recommend emergent stent placement during the initial IA procedure. Instead, the primary goal of IA is treating the intracranial occlusion followed by re-evaluating the ICA lesion which might now be improved due to forward flow. The operator can consider mild angioplasty of the extracranial lesion with plans to reassess in the following 1-2 days for carotid revascularization (endarterectomy versus stent).
6) Once the intracranial target lesion is reached, we recommend that the procedure duration should be no longer than 90 minutes since the procedure duration, number of utilized devices/passes and IA microcatheter contrast injections have all been associated with increased risk of bleeding or arterial damage/dissection. In the ESCAPE trial, the median (IQR) from groin puncture to first ET reperfusion was only 33 (26-47) minutes.[3]
7) Immediately after recanalization, systolic blood pressure should be reduced and strictly maintained between 120-140 mmHg with short-acting intravenous medications.
8) Additional anticoagulants (other than heparinized flushes -see #9 below) and antiplatelet medications (aspirin, clopidogrel, 2b/3a inhibitors, etc) should be avoided as part of IA therapy.
    - We recommend no intravenous (IV) Heparin before or during ET since Argatroban will provide anticoagulation.
    - Intra-arterial (IA) [unfractionated] heparinized pressure-bag flushes are allowed (access sheath; guide catheter and microcatheter). Operators also have the option of running normal saline only through the arterial access sheath. We recommend a lower concentration (1unit/1mL = 1,000units in 1 liter bag) to avoid higher levels of anticoagulation. No more than 2.5units/1mL (2,500units in 1-liter bag) should be used.
        - To avoid large volumes of infused heparinized flush, we recommend the use of an in-line pressure transducer which maintains ≤30 mL/hour flow.
        - At the conclusion of the IA procedure, the estimated total units of infused IA-heparin should be recorded.
9) ACT and STAT aPTT labs should be drawn immediately after IA completion or at 2-hours post-Argatroban bolus, whichever comes first. Due to the immediate availability of the ACT and for safety of supratherapeutic anticoagulation, the Argatroban infusion will be held (until the aPTT results are available) if the ACT is >250 (aPTT ≈80-83sec).[5,6] Once the aPTT is available, Argatroban medication titration will proceed according to the patient-specific protocol.
10) Femoral Access Sheath
    - We recommend a delayed removal of the groin sheath due to the concurrent medications. However, the choice of closure-device, manual pressure or delayed removal is left to the discretion of the local operator/institutional policies.

REFERENCES

1. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.
2. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009-18.
3. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019-30.
4. Nahab F, Walker GA, Dion JE, Smith WS. Safety of periprocedural heparin in acute ischemic stroke endovascular therapy: the multi MERCI trial. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2012;21:790-3.
5. Argatroban Investigators Brochure. Texas Biotechnology Corportation. Revised 28 June 2001.
6. Swan SK, Hursting MJ. The pharmacokinetics and pharmacodynamics of argatroban: effects of age, gender, and hepatic or renal dysfunction. Pharmacotherapy 2000;20:318-29.

Table IV. Safety Stopping Rule

The investigators have proposed that the risk of sICH will not exceed 10% by adding Argatroban to IV-rt-PA and IAT. Therefore, we consider the minimum number of ICH cases required to yield a risk that has the lower limit of the confidence interval greater than 10% as the stopping rule.

Safety stopping rules have been created in order to identify a high rate of symptomatic intracranial hemorrhage. If the actual sICH rate exceeds the lower limit of 95% CI for a 10% sICH rate, the study will be stopped (see Table below).

Table. Halting rules for 95% Confidence Interval (CI) using Group Sequential Interval Estimation Technique.

Sample Size (N)	Number of sICH (X)	Percent P=X/N	Lower limit of 95% CI	Upper limit of 95% CI
10	4	0.40	0.122	0.738

References

1. Alan Agresti and Brent A. Coull. Approximate Is Better than "Exact" for Interval Estimation of Binomial Proportions. *The American Statistician, 52(2), 119-126.*

2. Lawrence D. Brown, T. Tony Cai, Anirban DasGupta. Interval Estimation for a Binomial Proportion. *Statistical Science, 16(2),101-117.*