FLAGLER HOSPITAL PROTOCOL – EARLY MANAGEMENT OF ACUTE ISCHEMIC STROKE

As with any protocol, this protocol serves to provide evidence-based, comprehensive recommendations to guide our multidisciplinary team in patient care, with the expectation that expert practitioners will modify and customize as necessary to meet individual patient needs. This protocol is not intended to replace the practitioner's judgment; it is intended to provide guidance to the physician for the group of patients described in the protocol.

In patients with acute ischemic stroke (AIS) is very important to develop a strategy to prevent, detect and correct secondary insults. When a patient has a transient neurological deficit clinically characteristic of transient ischemic attack (TIA), the patient should be evaluated in the same manner as a patient who has an AIS.

It is important to establish a strategy based on clinical stabilization, evaluation, and establishment of prognosis, avoiding secondary insults and adoption of specific individualized therapies including reperfusion therapy, blood pressure control and surgery when indicated.

Creation of a structured protocol is recommended by the American Heart Association (AHA), American Stroke Association (ASA) and the American College of Chest Physicians (ACCP) guidelines (1-3).

OBJECTIVE:

- To optimize the general care and physiological neuroprotection of patients with *acute ischemic stroke* at Flagler Hospital.
- The goal is to complete an evaluation and begin fibrinolytic treatment, when indicated, within 60 minutes of the patient's arrival to the ED as well as to prevent secondary insults. Same approach is also applicable for patients already hospitalized.

SCREENING:
All patients admitted to the hospital with suspected or confirmed diagnosis of *acute ischemic stroke* will be eligible to be included in the protocol.

MONITORING AND INTERVENTIONS:

- For all patients at Flagler Hospital, if the initial history and brief examination are suggestive of a stroke, the stroke code should be activated – code yellow. The ED. NEUR Stroke Diagnostic order set will be activated including tele stroke consult.
- **Time last known well and/or time of onset** are critical historical elements in decision making for IV thrombolysis therapy (0-4.5hrs from onset) and endovascular therapy (0-24hrs from onset).
- A non–contrast CT of the brain will be obtained within 20 minutes and interpreted within 45 minutes of the patient's arrival in the ED or initiation of symptoms for those already hospitalized.
- STAT tests: CBC with platelets, PT/INR, PTT, CMP, high sensitivity troponin, and EKG will be requested upon admission or symptoms presentation if not already done.
- Upon diagnosis, the severity of AIS will be assessed in all patients using the National Institutes of Health Stroke Scale (NIHSS) (see Appendix 1).

The neurologist should determine if a patient is eligible for acute reperfusion with thrombolysis therapy (tenecteplase or tPA-alteplase (see Appendix 2 for inclusion and exclusion criteria).

- The only test that is mandatory before initiation of intravenous thrombolysis is blood glucose. Do not delay fibrinolytic therapy while awaiting the results of the PT, aPTT, or platelet count unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking anticoagulants, or anticoagulation use is uncertain.
    - If known or suspected that the patient is taking direct thrombin inhibitor or direct factor Xa inhibitor, request of thrombin time, or appropriate direct factor Xa activity assay will be at the discretion of neurology.
- Multimodal CT and MRI, including perfusion imaging, should not delay administration of IV tenecteplase or alteplase.
- *For patients presenting with an unknown time of stroke symptom onset and unknown time last known well including those who* awake with stroke symptoms*,* the first-choice imaging is multimodal MRI with DWI, FLAIR, and high-susceptibility sequence to exclude hemorrhage and identify diffusion-positive FLAIR-negative lesions that can be useful for selecting those who can benefit from IV tenecteplase or tPA-alteplase administration. Ordering the MRI will be at the discretion of the neurologist.

The door-to-needle time to start reperfusion therapy with tenecteplase or tPA should be within 60 minutes from hospital arrival or initiation of symptoms for those already hospitalized:

- Start intravenous tenecteplase bolus dose of 0.25 mg/kg to a maximum of 25 mg or tPA-alteplase infusion 0.9 mg/kg (maximum dose 90 mg) over 60 minutes, with 10% of the dose given as IVPB over 1 minute and consult critical care service for admitting the patient to the intensive care unit. Providers will be aware of potential bleeding complications and angioedema especially if the patient is on concomitant ACE inhibitor home medication.
- Measure and document blood pressure and perform neurological assessments every 15 minutes during and after IV tenecteplase or tPA-alteplase infusion for 2 hours, then every 30 minutes for 6 hours, then hourly until 24 hours after IV tPA treatment.
- Increase the frequency of blood pressure measurements if systolic BP is greater than 180 mm Hg or if diastolic BP is greater than 105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels.
- Delay placement of nasogastric tubes, indwelling bladder catheters, or intraarterial pressure catheters if the patient can be safely managed without them.
- Obtain a follow-up CT or MRI scan at 24 hours after tenecteplase or IV tPA before starting anticoagulants or antiplatelet agents.
- Repeat and document NIHSS 24 hours after tenecteplase or tPA infusion and day of discharge.
- Treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction (see appendix 3, 4, and 5).
    - If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion of tPA is still being administered and obtain emergent CT scan.
    - If the patient develops features of angioedema, discontinue the infusion of tPA if still being administered and maintain airway.

The neurologist should determine if the patient is eligible for endovascular therapy (EVT).

- For patients who present in less than 24 hours from time last known well (including patients with wake-up stroke) to determine if there is a large vessel occlusion and therefore potential candidate for EVT, will obtain a *multimodal CT:*
    - CT of the brain

    - CT angiography (CTA) of the brain and neck
    - CT perfusion imaging (CTP) of the brain
        - In patients with no history of renal impairment it is reasonable to proceed with CTA before obtaining serum creatinine concentration.
    - Additional imaging studies such as MRI or MRA will be at the discretion of neurology.
        - Multimodal MR includes MRI of the brain without contrast, high-susceptibility imaging (to exclude hemorrhage), MRA of the head and neck, DWI, and perfusion-weighted imaging (PWI)
- Patients who meet criteria for EVT (see appendix 6 and 7) should be transferred to an institution with the capability to do it.

Disposition and assessment upon admission.

- The patient will be placed on continuous telemetry. Consult neurology for all patients with diagnosis of suspected AIS and consult critical care service, neurosurgery, and cardiology on as needed basis.
- Neuroimaging evaluation
    - If not done as part of determining eligibility for acute reperfusion with thrombolysis therapy or EVT, ordering multimodal CT and or MRI will be at the discretion of Neurology. In general, MRI including DWI is the preferred brain diagnostic imaging within 24 hours of symptom onset.
        - Standard brain MRI protocols can reliably diagnose both acute ischemic stroke and acute hemorrhagic stroke in emergency settings. MRI is equivalent to noncontrast CT for the detection of acute intraparenchymal hemorrhage and is better than noncontrast CT for the detection of chronic hemorrhage.
        - A major advantage of MRI is that DWI is much more sensitive than noncontrast CT for detection of acute ischemic stroke and the exclusion of some stroke mimics. This can be particularly helpful when the diagnosis of stroke is in doubt. For example, the absence of a lesion on DWI can suggest that symptoms are caused by a stroke mimic.
- Echocardiography with bubble adequately detect cardiogenic and aortic sources for cerebral embolism other than atrial fibrillation as well as the presence of PFO. However, its use can be postponed to later in the hospitalization when the patient is in a more stable clinical condition unless there is a moderate or high suspicion of endocarditis.

General Care

The general care and physiological neuroprotection will be characterized by maintaining the following variables:

- Antiplatelets and anticoagulation strategy
- Blood pressure (BP) control
- Maintenance of normothermia - Temperature less than 37.8 ℃ and evaluation and treatment of fever source
- Maintenance of euvolemia
- Maintenance of normoxemia: SaO2 greater than 94%
- Maintenance of normocapnia: PaCO2 35 to 40 mmHg
- Maintenance of normonatremia: sodium 135 to 145 meq/L
- Maintenance of glycemia: glucose 110 to 200 mg/dL

- Venous thromboembolism prevention
- Aspiration precautions
- Feeding must be supplied early
- Management of specific conditions

A. Antiplatelets and Anticoagulation Strategy.

Use of Antiplatelets

- In the absence of contraindications (hemorrhagic transformation or systemic bleeding), antiplatelet therapy with aspirin alone or with dual antiplatelet therapy (DAPT) should be started as soon as possible after the diagnosis of TIA or AIS, even before the evaluation for ischemic mechanism is complete. For those treated with tenecteplase or IV tPA, aspirin administration or other antiplatelet agents will be delayed until 24 hours later.
- For patients already on antiplatelet therapy with either aspirin or clopidogrel at the time of stroke onset, will continue their existing antiplatelet regimen when the NIHSS score is >5.
- Beyond the acute phase of ischemic stroke, long-term antiplatelet therapy for secondary stroke prevention should be continued with aspirin or clopidogrel per neurology and cardiology.
    - ***Aspirin oral monotherapy*** (162 to 325 mg/d).
        - Within 24 hours after TIA or AIS onset for patients with:
            - TIA of low risk, as defined by an $ABCD^2$ (see appendix 8) score <4.
            - AIS of moderate or greater severity, as defined by a NIHSS score >5.
        - After 24 hours if the patient received thrombolysis.
    - ***Short term dual antiplatelet therapy (DAPT) using aspirin plus clopidogrel*.**
        - Within 24 hours after TIA or AIS onset for patients with:
            - High risk TIA, defined as an $ABCD^2$ score of ≥4.
            - Minor AIS, defined by an NIHSS score ≤5.
            - Severe intracranial large artery stenosis, defined by AIS attributed to an intracranial large artery atherosclerotic stenosis of 70 to 99 percent.
        - After 24 hours if the patient received thrombolysis.

Regimen:

- Aspirin 160 to 325 mg loading dose, followed by 80 mg daily plus clopidogrel (300 to 600 mg loading dose, followed by 75 mg daily) for 21 days for patients with high-risk TIA or minor ischemic stroke and extended to 90 days for patients with stroke due to intracranial large artery atherosclerotic stenosis of 70 to 99 percent
- Thereafter, antiplatelet treatment with aspirin alone or clopidogrel alone should be continued indefinitely

Use of Anticoagulation

Patients with AIS or TIA are at increased risk of recurrent ischemic stroke and at risk for hemorrhagic transformation. Anticoagulation reduces the risk of recurrent ischemic stroke but increases the risk of cerebral hemorrhage during the acute poststroke phase.

- Previous evidence suggested that urgent anticoagulation with heparin or oral anticoagulants in patients with AIS, both cardioembolic or thrombotic, is associated with higher risk of bleeding and worse outcomes compared with aspirin treatment (1-5). However, more recent study (6) showed a potential small advantage and no disadvantage using early direct oral anticoagulants (DOACs) in patients with AIS and atrial fibrillation (AF).
    - **Urgent anticoagulation post AIS with heparin is not recommended**.

        - The use of full dose heparin or enoxaparin with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after AIS, in general is not recommended for treatment of patients with AIS including those with new or known AF.
    - **In patients with TIA in the setting of AF, it is reasonable to initiate urgent anticoagulation after the index event to reduce the risk of recurrent stroke.**
    - Based on size of infarct consider early use of anticoagulation with DOACs (Apixaban 5 mg P.O. q12h or Rivaroxaban 20 mg P.O. daily) in patients with AF.
        - Within 48 hours after minor or moderate stroke onset
        - On day 6 or 7 after a major stroke onset.
- The severity of stroke for the purpose of initiation of DOACs will be defined based on brain imaging studies:
    - Minor stroke: an infarct of ≤1.5 cm.
    - Moderate stroke: an infarct in the distribution of a cortical superficial branch of the middle, anterior, or posterior cerebral artery.
    - Major stroke: infarcts >1.5 cm in the distribution of these arteries or a brainstem or cerebellar infarct.

Use of Antiplatelets and Anticoagulation for non-cardioembolic AIS and other specific conditions

a. For patients with non-cardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.
b. The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke or for nonocclusive, extracranial intraluminal (e.g., cervical carotid, vertebrobasilar arteries) thrombus or patients with arterial dissection are not well established and will be at the discretion of neurology and cardiology.
c. The usefulness of urgent anticoagulation with heparin in AIS in patients with intracardiac or intra-arterial thrombus or thrombus associated with prosthetic or native cardiac valves is controversial and will be at the discretion of neurology and cardiology.
d. Urgent anticoagulation other than DOACs for the management of *non-cerebrovascular* conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications.
e. In patients with stroke or TIA in the setting of nonvalvular AF who have contraindications for lifelong anticoagulation but can tolerate at least 45 days, it may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce the chance of recurrent stroke and bleeding.
f. In patients with a mechanical aortic valve, anticoagulation with higher-intensity warfarin to achieve an INR of 3.0 (range, 2.5–3.5) will be administered.
g. For patients with AIS and extracranial carotid or vertebral arterial dissection, treatment with either antiplatelet or anticoagulant therapy for 3 to 6 months may be reasonable and will be at the discretion of neurology and cardiology.
h. In patients with AIS or TIA and left atrial or left ventricular thrombus, anticoagulation with therapeutic warfarin, INR 2 to 3, for at least 3 months rather than DOAC is recommended to reduce the risk of recurrent stroke.
i. In patients with ischemic stroke or TIA in sinus rhythm with ischemic or nonischemic cardiomyopathy and reduced EF without evidence of left atrial or left ventricular thrombus, the

effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized per cardiology and neurology discretion.

B. General acute stroke care

The following steps must be applied in parallel rather than in sequence:

- **Assess vital signs and neurochecks** every 15 min during the initial hour, then every one hour x4, every 2 hours x4, every 4 hours x72 hours and then per unit protocol, or more frequently when clinically indicated. If a patient received reperfusion therapy, follow recommended monitoring stated previously.
- **Keep head elevated** 15 to 30 degrees and in midline position unless otherwise specified by practitioner. Head elevation and midline position are important because they affect the brain venous drainage and consequently the intracranial pressure (ICP). The benefit of flat head positioning early after hospitalization for stroke is uncertain.
- **Keep euvolemia** with isotonic solutions either plasmalyte, LR or NS on average at 30 ml/Kg/d plus unusual losses.
- **Temperature Control.** Maintain temperature less than or equal to 37.8 degrees Celsius using PO/PR acetaminophen 650 mg every 6 hours along with evaluation and treatment of fever source.
- **Monitor continuous O2 Saturation in all patients and end-tidal CO2 when feasible**. Administer oxygen by nasal cannula to hypoxemic patients. Hypoxemia is defined as "O2 sat less than 94% on room air." If supplemental oxygen is required, communicate this to the practitioner. Routine supplemental oxygen is not required acutely in non-hypoxemic patients.
- **Aspiration precautions.** Keep NPO until dysphagia screening and aspiration risk is evaluated and until knows if the patient will undergo procedures. Therefore, IV fluids will be used at a maintenance rate, on average 30 ml/Kg/d plus unusual losses, until dysphagia screening or speech language pathology evaluate the patient.
- **Determine if intubation is required** to assure adequate oxygenation and ventilation, prevent aspiration, and manage increased intracranial pressure. As a rule, all patients in coma should be intubated.
    - Follow a lung and brain protective strategy including use of physiologic tidal volume (4 to 8 ml/Kg IBW), lowest FiO2 possible and level of PEEP to maintain a plateau pressure less than 30 and driving pressure <15. Therapeutic targets will be directed at:
        - Maintain SaO2 greater than 94%. Tissue hypoxia is known to be detrimental but brain hyperoxia is also associated with deleterious effects including arterial vasoconstriction and promoting inflammation through activation of free radicals.
        - Maintain normal levels of CO2 (PaCO2: 35 to 40 mm Hg) since hypercapnia causes cerebral vasodilatation and increase in ICP, whereas hypocapnia causes vasoconstriction triggering cerebral ischemia.
        - Selection of PEEP will be of paramount importance because it can affect the brain venous drainage and consequently the ICP (higher PEEP can decrease cerebral venous drainage).

C. Blood pressure management.

All patients who require treatment with continuous intravenous antihypertensive medications should undergo placement of an intra-arterial catheter for BP monitoring and those who need

vasopressor therapy should have a midline, PICC line or central venous catheter unless contraindicated following the established Flagler Infusion Service Protocol.

Management of hypertension

- In patients with BP <220/120 mm Hg who are not candidate for acute reperfusion therapy - tPA and do not have a concomitant condition that would benefit from lowering the blood pressure such as acute coronary syndrome, aortic dissection, or heart failure, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an AIS is not effective.
- For patients with AIS and markedly elevated BP ≥220/120 mm Hg initiating, or reinitiating treatment of hypertension is indicated. A reasonable goal is to lower blood pressure by 15% within the first 48 to 72 hours after onset of stroke. Specific BP targets will be outlined in the respective order set according to the presenting level of BP
- The BP target and need for antihypertensive treatment for patients with associated cardiovascular conditions such as acute coronary syndrome, aortic dissection or heart failure will be based on clinical judgement and in collaboration with cardiology.
- For patients with arterial hypertension who are candidates for acute reperfusion therapy - tPA, treatment is recommended if BP is greater than 185/110 mm Hg. During acute reperfusion therapy - tPA, the goal is to maintain BP at or below 180/105 mm Hg.
- Consider intensive target of SBP 130–140 mmHg within the first 24 hours based on more recent study.

Antihypertensive treatment:

- Short-acting IV antihypertensive can be used PRNs until drips are available: Labetalol 20 mg IV every 10 minutes or hydralazine 10 mg IV q2-4 hrs as needed to attain target blood pressure (as noted above).
- Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5 to 15 minutes, maximum 15 mg/h; or
- Labetalol 10 mg IV followed by continuous IV infusion 2 to 8mg/min.
- If the BP level is still higher than the target despite infusion of the maximum dose of Nicardipine or Labetalol for 30 minutes, add the second agent Labetalol or Nicardipine IV infusions.
- If the BP level is still higher than the target, despite combination of infusion of the maximum dose of Nicardipine and Labetalol for 30 minutes, consider IV sodium nitroprusside. Start IV infusion at 0.25 mcg/Kg/min and titrate up to max dose of 10 mcg/Kg/min.

Antihypertensive therapy will be started, or restarted in those with preexistent hypertension, after the first 48 to 72 hours of AIS onset in patients with BP >140/90 mm Hg who are neurologically stable.

Management of hypotension

Defined as SBP less than 120 mmHg or MAP less than 70 mmHg

- Establish the etiology
- Volume replenishment with isotonic crystalloids (plasmalyte, LR or normal saline) will be the first approach.
- If hypotension persists after correction of volume deficit, continuous infusions of vasopressors should be considered.
- If SBP is less than 120 mmHg or MAP less than 70 mmHg after IV fluids, start Norepinephrine IV infusion at 1 mg/min and titrate up to 30 mg/min. If patient continues hypotensive, call practitioner.

- If SBP less than 120 mmHg or MAP less than 70 mmHg and HR greater than 130 after IV fluids, or patient has atrial fibrillation with rapid ventricular response, start Phenylephrine IV infusion at 30 mcg/min and titrate up to 200 mcg/min. If patient continues hypotensive, call practitioner.

D. Seizure prophylaxis and treatment

There is no data to suggest prophylactic anti-epileptic therapy decreases seizure risk. Anti-epileptic therapy should always be used for treatment of known clinical or electrographic seizures after stroke in a manner similar to other acute neurological conditions.

E. Glycemic Control

Maintenance of normoglycemia: both hyperglycemia and hypoglycemia should be avoided. Blood glucose will be maintained within a range of 110 to 180 mg/dL.

- For glucose less than 70 mg/dl, institute the Flagler Hospital hypoglycemia protocol.
- For glucose between 70 and 149 mg/dl continue monitoring per unit protocol.
- For glucose greater than 149 mg/dl, institute the standard Flagler Hospital sliding scale insulin dose regimen.
- For glucose greater than 215 mg/dl for two consecutive tests institute continuous IV insulin infusion per Flagler hospital protocol (ICU patients only).

F. Serum Na levels

Maintain serum sodium to 135 to 145 mmol/L. Serum Na levels will be checked daily or more frequently if needed x 3 days and then on as needed basis.

G. Follow up Neuro-imaging Studies

In patients suspected of having ischemic stroke or TIA, if the initial CT or MRI does not demonstrate symptomatic cerebral infarct, will request a follow-up CT or MRI of the brain within 24 to 48 hours of the initial presentation to confirm diagnosis.

Patients with acute ischemic stroke are at risk for expansion, bleeding transformation and recurrence. The decision when to repeat brain imaging studies will be at the discretion of Neurology.

H. Intracranial pressure monitoring and management

- Elevate the head of the bed 15 to 30 degrees with head midline, once hypovolemia is excluded and providing it is not stated as a contraindication.
- Analgesia and sedation, particularly in unstable, intubated patients. Sedation should be titrated to control pain and minimize ICP elevation, while still permitting clinical evaluation of the patient's neurologic status targeting RASS 0 to -1 and BPS less than or equal to 3 per Flagler ABCDEF protocol. Consider neuromuscular blockade to reduce ICP only in patients who are not responsive to analgesia and sedation alone.
- Treatment of elevated ICP should be considered for comatose patients with GCS less than 8, those with clinical evidence of transtentorial herniation or those with hydrocephalus. Therapies for reducing elevated ICP include pharmacological treatment with mannitol or hypertonic saline solution, drainage of cerebrospinal fluid (CSF) and hyperventilation.
    - There is no clear evidence of superiority of either mannitol or hypertonic saline at reducing intracranial pressure. Either can be used to achieve plasma hyperosmolality (300 to 320 mOsm/L) and serum sodium to 145 to 155 mmol/L until the limit of serum osmolality of 320 mOsm/L or sodium 155 mmol/L respectively.

- **Hypertonic saline solution:**
  - 3% NaCl (513 mmol/L) 150 mL IV bolus over 10 to 15 min, or
  - 7.5% NaCl (1283 mmol/L) 75 ml over 20 min, or
  - 23.4% NaCl (4008 mmol/L) 30 mL over 2 to 10 min.
    - 7.5% NaCl and 23.4% NaCl will be given preferably through a PICC line or central venous access, but emergent use through a peripheral line can be authorized by the intensivist.
  - If Na levels persist below 145 mEq/L despite boluses administration of hypertonic saline solution, a titratable continuous infusion of 3% NaCl at initial rate of 30 – 50 ml/h targeting serum Na levels of 145-155 mmol/L and serum osmolality 300 – 320 mOsm/L can be used.
- **Mannitol 20%**
  - Initial 1 g/kg IV infusion over 30 min, followed by repeat dosing of 0.25 to 0.5 g/kg IV infusion over 30 min every six hours as needed. Check osmolarity and serum Na in 6 hours before additional doses. Hold for serum osmolality equal or greater than 320 mOsm/L or serum Na equal or greater than 155 mmol/L.

- Repeat hypertonic solution or mannitol dosing can be given as needed
- Check osmolarity and serum Na in 6 hours before additional doses.
  - Hold for serum osmolality equal or greater than 320 mOsm/L or serum Na equal or greater than 155 mmol/L.
- **ICP monitoring** is encouraged in those patients that merit aggressive medical care and are suspected to have increased ICP. Placement of intraventricular catheter (ventriculostomy) will be at the discretion of Neurosurgery.
  - Measuring ICP allows directed treatment of ICP and blood pressure with the goal of keeping ICP less than 20 mmHg and maintaining a cerebral perfusion pressure (CPP= MAP – ICP) of 50 to 70 mmHg.
  - Drainage of cerebrospinal fluid (CSF) is an effective means of lowering ICP; therefore, drainage of CSF will be set to be drained intermittently at not more than 20 mL per hour to maintain the ICP less than 20 mmHg in those patients with intraventricular catheter (ventriculostomy) in place.
  - Use of brief moderate hyperventilation (PaCO2 target, 30–34 mmHg) is a reasonable treatment for patients with acute severe neurological decline from brain swelling as a bridge to more definitive therapy.

I. Surgery

The role of neurosurgical intervention for the treatment of cerebellar infarction and large “malignant” supratentorial infarction will be at the discretion of Neurosurgery.

- Ventriculostomy will be considered in the treatment of obstructive hydrocephalus after cerebellar infarction. Concomitant or subsequent decompressive suboccipital craniectomy with dural expansion will be considered in patients with cerebellar infarction causing neurological deterioration from brainstem compression despite maximal medical therapy.
- In patients <60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion is reasonable.

J. Carotid Revascularization

The usefulness of emergent or urgent CEA in patients with unstable neurological status (e.g., stroke-in evolution) or when clinical indicators or brain imaging suggests a small infarct core with large territory at risk (e.g., penumbra), compromised by inadequate flow from a critical carotid stenosis or occlusion, or in the case of acute neurological deficit after CEA, in which acute thrombosis of the surgical site is suspected, is not well established and will be at the discretion of cardiovascular surgery, cardiology and neurology.

- In patients with TIA or nondisabling stroke, when revascularization is indicated, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery to increase the likelihood of stroke free outcome.

K. Patent foramen ovale (PFO) management

- Treatment with antiplatelet therapy is recommended for patients with AIS and PFO who have no indication for anticoagulation therapy otherwise consistent with the recommendations for cryptogenic stroke.
- It is now considered reasonable to percutaneously close PFO in patients who meet each of the following criteria:
    - Age 18–60 years
    - Nonlacunar stroke
    - No other evident source of stroke despite a comprehensive evaluation
    - High risk PFO features (right-to-left interatrial shunt or septal atrial aneurysm)

L. Nutrition

- All patients will be placed on a strict nothing-by-mouth order until an assessment of the ability to swallow is completed - dysphagia screen as below.
- The Post Extubation Swallow Screen will be administered in all patients by nursing prior to the initiation of eating, drinking, or receiving oral medications unless there are exclusion criteria (see Appendix 9). If the patient meets exclusion criteria for the swallow screen, or does not pass the screening, an order will be submitted in the electronic record for further assessment and dysphagia management by a speech therapist.
- Enteral diet should be started within 7 days of admission after an acute stroke. Will follow Nutrition Flagler Hospital protocol.

M. Venous thromboembolism prevention

- Patients will have intermittent pneumatic compression for prevention of venous thromboembolism beginning the day of hospital admission unless contraindicated.
- The benefit of prophylactic-dose subcutaneous unfractionated heparin or LMWH in immobile patients with AIS is not well established. It is generally avoided within 24hrs of tPA and if there is any CT evidence of intracranial hemorrhage.
    - Will use prophylactic-dose subcutaneous unfractionated heparin or LMWH 24 to 48hrs after AIS.
    - For patients who receive tPA it can be used if cleared by neurology 24hrs after tPA.
    - Once the patient is initiated on pharmacological prophylaxis there will be no indication for intermittent pneumatic compression.

N. Mobilization

Mobilization will begin as soon as the patient's condition is considered stable following Flagler protocol. All patients will have Physical Therapy, Occupational Therapy evaluation and regular skin assessments.

O. Other:

Routine placement of indwelling bladder catheters should not be performed.

CONSENT:

Explicit informed patient consent for fibrinolytic therapy and a provider's note documenting explicit discussion in a consent conversation will be required. For the incompetent patient, consent may be provided by a legally authorized representative who can provide proxy consent.

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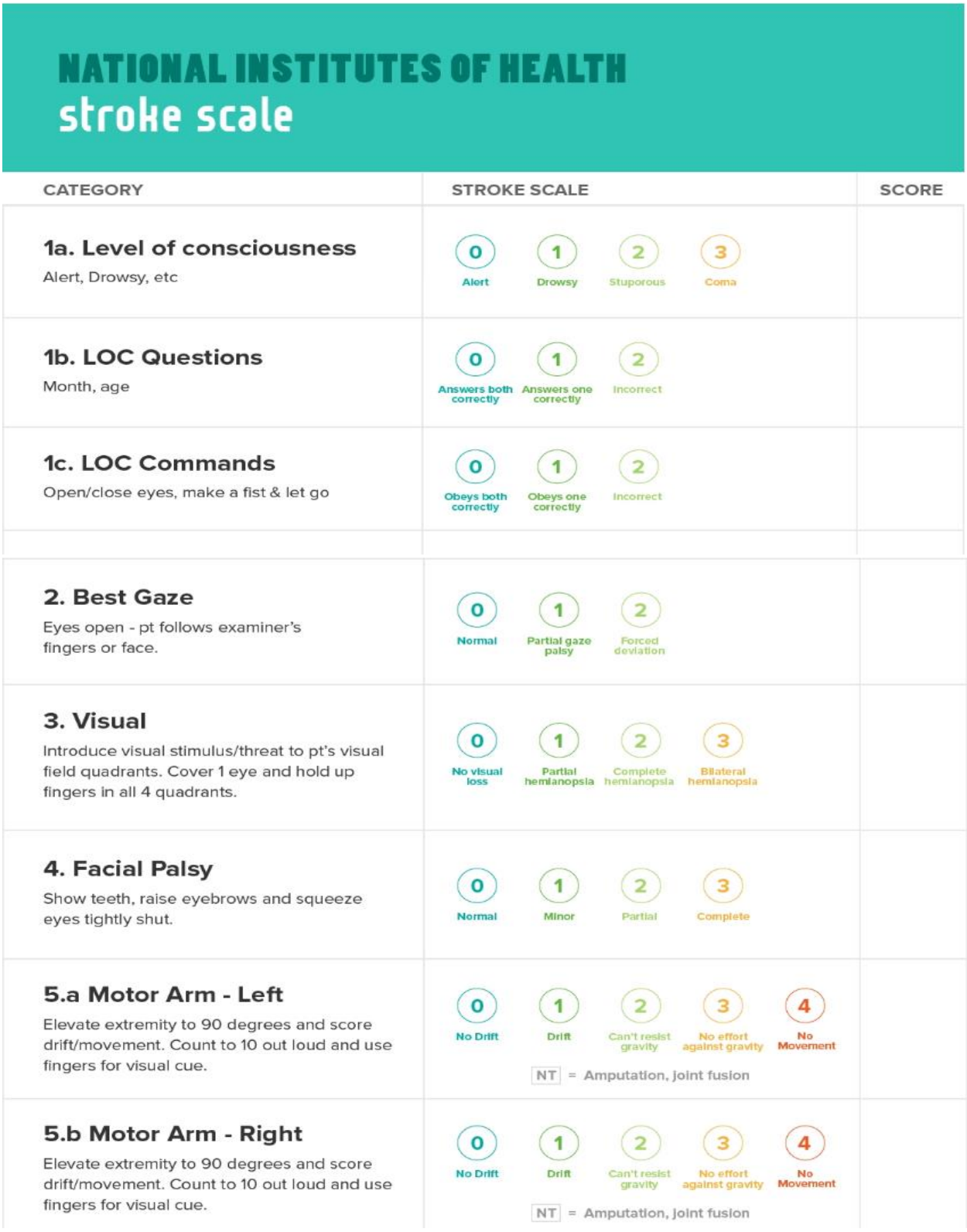
Appendix 1. National Institutes of Health Stroke Scale (NIHSS)



NATIONAL INSTITUTES OF HEALTH
stroke scale

CATEGORY	STROKE SCALE	SCORE
1a. Level of consciousness Alert, Drowsy, etc	0 Alert; 1 Drowsy; 2 Stuporous; 3 Coma	
1b. LOC Questions Month, age	0 Answers both correctly; 1 Answers one correctly; 2 Incorrect	
1c. LOC Commands Open/close eyes, make a fist & let go	0 Obeys both correctly; 1 Obeys one correctly; 2 Incorrect	
2. Best Gaze Eyes open - pt follows examiner's fingers or face.	0 Normal; 1 Partial gaze palsy; 2 Forced deviation	
3. Visual Introduce visual stimulus/threat to pt's visual field quadrants. Cover 1 eye and hold up fingers in all 4 quadrants.	0 No visual loss; 1 Partial hemianopsia; 2 Complete hemianopsia; 3 Bilateral hemianopsia	
4. Facial Palsy Show teeth, raise eyebrows and squeeze eyes tightly shut.	0 Normal; 1 Minor; 2 Partial; 3 Complete	
5.a Motor Arm - Left Elevate extremity to 90 degrees and score drift/movement. Count to 10 out loud and use fingers for visual cue.	0 No Drift; 1 Drift; 2 Can't resist gravity; 3 No effort against gravity; 4 No Movement NT = Amputation, joint fusion	
5.b Motor Arm - Right Elevate extremity to 90 degrees and score drift/movement. Count to 10 out loud and use fingers for visual cue.	0 No Drift; 1 Drift; 2 Can't resist gravity; 3 No effort against gravity; 4 No Movement NT = Amputation, joint fusion	

6.a Motor Leg - Left

Elevate extremity to 30 degrees and score drift/movement. Count to 5 out loud and use fingers for visual cue.

0 No Drift | 1 Drift | 2 Can't resist gravity | 3 No effort against gravity | 4 No Movement

NT = Amputation, joint fusion

6.b Motor Leg - Right

Elevate extremity to 30 degrees and score drift/movement. Count to 5 out loud and use fingers for visual cue.

0 No Drift | 1 Drift | 2 Can't resist gravity | 3 No effort against gravity | 4 No Movement

NT = Amputation, joint fusion

7. Limb Ataxia

Finger to nose, heal down shin

0 Absent | 1 Present in one limb | 2 Present in two limbs

8. Sensory

Pin prick to face, arms, trunk, and legs - compare sharpness side to side

0 Normal | 1 Partial loss | 2 Severe Loss

9. Best Language

Name items, describe picture, and read sentences. Don't forget glasses if they normally wear them.

0 No aphasia | 1 Mild to moderate aphasia | 2 Severe aphasia | 3 Mute

10. Dysarthria

Evaluate speech clarity by pt reading or repeating words on list.

0 Normal articulation | 1 Mild to moderate dysarthria | 2 Near to unintelligible or worse

NT = Intubated or other physical barrier

11. Extinction and Inattention

Use information from prior testing or double simultaneous stimuli testing to identify neglect. Face, arms, legs, and visual fields.

0 No neglect | 1 Partial neglect | 2 Complete neglect

NT = Not Testable acceptable as noted above

Score	Stroke Severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

TOTAL =

Saebo

Appendix 2. Inclusion and Exclusion Characteristics of Patients with Ischemic Stroke Who Could Be Treated with IV tenecteplase or tPA within 3 - 4.5 Hours from Symptom Onset

INDICATIONS FOR THROMBOLYSIS:

Indications to treat with tenecteplase or *IV tPA- alteplase as soon as possible* ***within 3 h.***

- Patients greater than or equal to 18 years of age, includes <80 and >80 y of age.
- Severe stroke symptoms or with mild but disabling stroke symptoms.

Indications to treat with tenecteplase or *IV tPA-alteplase as soon as possible* **in the 3 to 4.5 h *time window.***

- Patients ≤80 y of age
- No history of both diabetes mellitus and prior stroke
- NIHSS score ≤25
- Not taking any OACs
- No imaging evidence of ischemic injury involving more than one third of the MCA territory

The only test that must be measured in all patients before thrombolysis if blood glucose. IV alteplase treatment should not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.

Baseline ECG and troponin assessment is recommended in patients presenting with AIS but should not delay initiation of IV tenecteplase or alteplase.

Usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac, or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of IV alteplase.

Multimodal CT and MRI, including perfusion imaging, should not delay administration of IV tenecteplase or alteplase.

- The use of tenecteplase or tPA-alteplase requires the BP to be <185 mmHg systolic and <110 mmHg diastolic before treatment and <180/105 mmHg for the first 24 hours after treatment.
- Administering IV tenecteplase or t-PA alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV tPA- alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury.
- The use of tenecteplase or tPA-alteplase requires the BP to be <185 mmHg systolic and <110 mmHg diastolic before treatment and <180/105 mmHg for the first 24 hours after treatment.

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CONTRAINDICATIONS FOR THROMBOLYSIS:

- Ischemic stroke patients who have an unclear time and/ or unwitnessed symptom onset and in whom the time last known to be at baseline state is >3 or 4.5 h.
- Patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation. These patients have a poor prognosis despite tenecteplase or IV alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury.
- Prior ischemic stroke within 3 mo.
- Recent severe head trauma (within 3 months).
- History of intracranial/spinal surgery within the prior 3 mo.
- History of intracranial hemorrhage or patients presenting with symptoms and signs most consistent with an SAH.
- Patients with a structural GI malignancy or recent bleeding event within 21 d of their stroke.
- Platelets <100 000, INR >1.7, aPTT >40 s, or PT >15 s.
- Patients taking DOAC unless the patient has not received a dose of these agents for >48.
- Patients who have received a treatment dose of low-molecular-weight heparin (LMWH) within the previous 24 hours. The recommendation refers to full treatment doses and not to prophylactic doses.
- Patients with symptoms consistent with infective endocarditis or patients with known or suspected aortic arch dissection.
- Patients who harbor an intra-axial intracranial neoplasm.

Additional recommendations – relative indications and contraindications

Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV tPA administration carefully if any of these relative contraindications are present:

- The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV tenecteplase or alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies.
- IV tenecteplase or alteplase may be considered for patients who have undergone a lumbar dural puncture in the preceding 7 d.

- The safety and efficacy of administering IV tenecteplase or alteplase to patients who have had an arterial puncture of a noncompressible blood vessel in the 7 d preceding stroke symptoms are uncertain.
- Preexisting disability does not seem to independently increase the risk of sICH after IV tenecteplase or alteplase, but it may be associated with less neurological improvement and higher mortality. Thrombolytic therapy with IV alteplase for acute stroke patients with preexisting disability (mRS score ≥2) may be reasonable, but decisions should consider relevant factors, including quality of life, social support, place of residence, need for a caregiver, patients' and families' preferences, and goals of care.
- IV tenecteplase or tPA is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon.
- The safety and efficacy of IV tenecteplase or tPA for patients with a clinical history of potential bleeding diathesis or coagulopathy are unknown. IV alteplase may be considered on a case-by-case basis.
- In AIS patients with recent major trauma (within 14 d) not involving the head, IV tenecteplase or alteplase may be carefully considered, with the risks of bleeding from injuries related to the trauma weighed against the severity and potential disability from the ischemic stroke.
- Use of IV tenecteplase or tPA in carefully selected patients presenting with AIS who have undergone a major surgery in the preceding 14 d may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits.
- Reported literature details a low bleeding risk with IV tenecteplase or alteplase administration in the setting of past GI/genitourinary bleeding. Administration of IV alteplase in this patient population may be reasonable.
- IV tenecteplase or tPA in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 h and probably recommended.
- IV tenecteplase or tPA usefulness and hemorrhagic risk in AIS known or suspected to be associated with intracranial arterial dissection remain unknown, uncertain, and not well established.
- For patients known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of IV tenecteplase or alteplase is reasonable and probably recommended.
- For patients presenting known to harbor an unruptured and untreated intracranial vascular malformation the usefulness and risks of administration of IV tenecteplase or alteplase are not well established.
- In otherwise eligible patients who have previously had a small number (1–10) of cerebral microbleed s demonstrated on MRI, administration of IV tenecteplase or alteplase is reasonable.
- IV tenecteplase or alteplase treatment is probably recommended for patients with AIS who harbor an extra-axial intracranial neoplasm.

- The safety and efficacy of alteplase in patients with current malignancy are not well established. Patients with systemic malignancy and reasonable (>6 mo) life expectancy may benefit from IV tenecteplase or alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist.
- For patients presenting with concurrent AIS and acute MI, treatment with IV tenecteplase or alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated, is reasonable.
- For patients with major AIS likely to produce severe disability and acute pericarditis, treatment with IV tenecteplase or alteplase may be reasonable.
- IV tenecteplase or tPA administration may be considered in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding.
- The safety and efficacy of IV tenecteplase or alteplase in the early postpartum period (<14 d after delivery) have not been well established.
- Use of IV tenecteplase or tPA in patients presenting with AIS who have a history of diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions is reasonable to recommend, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurological deficits.
- IV tenecteplase or alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial.

Appendix 3. Management of Intracranial Bleeding Occurring Within 24 Hours After Administration of IV tenecteplase or Alteplase for Treatment of AIS

Symptomatic intracranial hemorrhage (sICH) after thrombolytic therapy is typically based on 2 main factors: the radiographic appearance of the hemorrhage and the presence of associated neurological deterioration. sICH attributed to tenecteplase or tPA occurs within 36 hours from the infusion, with only half of the events being diagnosed by 5 to 10 hours.

- Will classify the appearance of hemorrhagic transformation according to radiographic criteria: hemorrhagic infarction (HI), parenchymal hematoma (PH), or remote ICH (see appendix 4). Most hemorrhages after tPA occur in already infarcted brain tissue
- Will assess the degree of neurological worsening by NIHSS point change
- Will provide an attribution of causality for the worsening.
- Will keep close monitoring during and for at least 24 hours after the infusion in the ICU.

The general principles of treating patients with post-thrombolytic hemorrhage in the setting of ischemic stroke are similar to those used in treating spontaneous intracerebral hemorrhage (see spontaneous ICH Flagler protocol).

Indications for Reversal of tenecteplase or Alteplase-Induced Coagulopathy

- Overall, currently available literature suggests that sICH within 24 hours of tenecteplase or tPA therapy might be a reasonable indication for treatment.

Although very limited data are available to support treatment of asymptomatic bleeding, the use of reversal agents for any asymptomatic parenchymal hematoma occurring within 24 h of tenecteplase or tPA infusion may be considered, particularly in the setting of an ongoing coagulopathy.

- Stop tPA IV infusion if still being administered.
- Obtain immediately fibrinogen level along with CBC, PT/INR, aPTT, and type and crossmatch. Repeat fibrinogen level in 2, 6, and 12 hours.
- Empirically transfuse cryoprecipitate 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h). Anticipate giving more cryoprecipitate as needed to achieve a normal fibrinogen level of ≥150 mg/dL (10 U cryoprecipitate increases fibrinogen by nearly 50 mg/dL). Administer additional cryoprecipitate 10 U as needed for fibrinogen level of <150 mg/dL to achieve a normal fibrinogen level of ≥150 mg/dL.
- Tranexamic acid 1000 mg IV infused over 10 min. Potential for benefit in all patients, but particularly when blood products are contraindicated or declined.
- If platelets <100.000 transfuse 1 donor unit platelet.
- Request hematology and neurosurgery consultations

Appendix 4. Heidelberg Classification Scheme

- Hemorrhagic infarction (HI)
    - Type 1: Scattered small petechiae, no mass effect
    - Type 2: Confluent petechiae, no mass effect
- Parenchymal hematoma (PH)
    - Type 1: Hematoma within infarcted tissue, occupying <30%, no mass effect
    - Type 2: Hematoma occupying ≥30% of the infarcted tissue with obvious mass effect
    - Type 3a: Hematoma remote from infarcted brain tissue
    - Type 3b: Intraventricular hemorrhage
    - Type 3c: Subarachnoid hemorrhage
    - Type 3d: Subdural hemorrhage

Appendix 5. Management of Orolingual Angioedema Associated with IV tenecteplase or tPA Administration for AIS

- Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation. Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.
- Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after tenecteplase or IV tPA. Cricothyroidotomy is rarely needed and also problematic after IV tPA.
- Discontinue IV tPA infusion and hold ACE inhibitors.
- Administer IV methylprednisolone 125 mg.

- Administer IV diphenhydramine 50 mg and ranitidine 50 mg IV or famotidine 20 mg IV
- If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL.
- Icatibant, a selective bradykinin B2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed a total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema.

Appendix 6. Indications for endovascular therapy (EVT)

- Prestroke mRS Score 0 to 1 (see Appendix 6). To be performed by practitioner
- Causative occlusion of the internal carotid artery (ICA) or proximal medial cerebral artery (MCA) - segment M1
- Age 18 years and over
- NIHSS score of 6 or greater
- ASPECT CT score of 6 or greater
- Treatment can be initiated within 6 hours (groin puncture) of symptoms onset
- Although the benefits are uncertain, EVT may be reasonable for carefully selected patients with causative occlusion of the MCA M2 or M3 segments, anterior, vertebral, basilar, or posterior cerebral arteries.
- Although the benefits are uncertain, EVT may be reasonable for patients who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the ICA or proximal MCA (M1).
- In selected patients who meet DAWN and DEFUSE-3 eligibility criteria, treatment initiated within 6-16 hours of symptoms onset.
- In selected patients who meet other DAWN eligibility criteria, treatment initiated within 16-24 hours of symptoms onset.
- In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable, and therefore, transfer to an institution with the capability to do endovascular interventions should be considered.

Appendix 7. The Modified Rankin Score (mRS)

The scale runs from 0 to 6, running from perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

Appendix 8. ABCD^2 Score for TIA

ABCD² Score for TIA

Estimates the risk of stroke after a suspected transient ischemic attack (TIA).

Age ≥ 60 years

No
0

Yes
+1

BP ≥ 140/90 mmHg
Initial BP. Either SBP ≥ 140 or DBP ≥ 90.

No
0

Yes
+1

Clinical features of the TIA

Unilateral weakness
+2

Speech disturbance without weakness
+1

Other symptoms
0

Duration of symptoms

<10 minutes
0

10-59 minutes
+1

≥ 60 minutes
+2

History of diabetes

No
0

Yes
+1

0 points

Per the validation study, 0-3 points: Low Risk
2-Day Stroke Risk: 1.0%
7-Day Stroke Risk: 1.2%
90-Day Stroke Risk: 3.1%

Appendix 9. Exclusion Criteria for the Swallow Screen:

Any YES answer to the following risk factors will <u>defer administration</u> of the Swallow Screen:

- Patient is unable to remain alert for testing
- Patient was eating a modified diet due to pre-existing dysphagia prior to intubation
- Patient has a head-of–bed restriction less than 30 degrees
- Tracheostomy tube is present
- Patient is nil per os (npo) for medical/surgical reason

- Patient unable to follow simple commands
- Presence of respiratory distress

Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN)

N Engl J Med 2023; 388:2411-21

Background:

- Early initiation of anticoagulation may increase the risk of intracranial hemorrhage, whereas later initiation may increase the risk of early stroke recurrence.
- Based on early randomized trials focused on rapid anticoagulation with the use of heparin or low-molecular-weight heparin that were associated with a risk of hemorrhage, current guidelines by the AHA and ASA recommend:
    - Delaying anticoagulation in pts with AIS and Afib beyond 14 days if there is a high risk of hemorrhagic transformation of an ischemic brain infarct and beginning anticoagulation between day 2 and day 14 if the risk of this complication is low.
- The timing of anticoagulation with DOAC initiation regarding the risks of stroke recurrence and bleeding after AIS and Afib is unclear.

Methods:

- Open label, multicenter, randomized trial comparing early with later initiation of DOACs in participants with AIS and Afib.
- The timing of initiation of DOAC was based according to the size of the infarct:
    - Minor stroke: infarct of 1.5 cm or smaller.
    - Moderate: an infarct in the distribution of a cortical superficial branch of the middle, anterior, or posterior cerebral artery
    - Large: infarcts in the distribution of these arteries or a brain-stem or cerebellar infarct larger than 1.5 cm.
- Comparison of early vs late DOACs initiation
    - Early:
        - Minor or moderate stroke: within 48 hours after stroke onset
        - Major stroke: day 6 or 7 after stroke onset
    - Late:
        - Minor stroke: day 3 after stroke onset
        - Moderate stroke: day 6 after stroke onset
        - Major stroke: day 12

Results:

- 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke)
- 1006 were assigned to early anticoagulation and 1007 to later anticoagulation.
- A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group (risk difference, −1.18 percentage points by 30 days.

- Recurrent ischemic stroke occurred in:
  - 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group by 30 days.
  - 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days.
- Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days.

CONCLUSIONS:

- No major differences between the early-treatment group and the later-treatment group with respect to the outcome expressed as the potential for a 2.8-percentage-point advantage and a 0.5-percentage-point disadvantage of early initiation.
  - Outcome: composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 and 90 days.
  - The composite results were driven by recurrences of ischemic stroke, which constituted more than half of the 70 primary-outcome events within 30 days.
- At a minimum, we learn from the trial that:
  - The rate of recurrent ischemic stroke with later use of DOACs was low — 2.5% by 30 days.
  - Very few symptomatic intracranial hemorrhages occurred with the early-treatment or the later-treatment strategy — only 0.2% in each group
  - In patients with major stroke, there was no of excess hemorrhagic risk associated with anticoagulation administered at 6 or 7 days.
- Taken as a whole:
  - There is a low likelihood that early anticoagulation, according to the trial definition, causes harm in terms of excess risk of hemorrhage.
  - The estimated between-group difference of 1.1 percentage points in the incidence of recurrent ischemic stroke at 30 days favored early initiation of anticoagulation, if the stroke is small.

Associations of Early Systolic Blood Pressure Control and Outcome After Thrombolysis Eligible Acute Ischemic Stroke: Results from the ENCHANTED Study

Stroke 2022; 53:779–787

- Post hoc secondary analyzes of SBP data from 4511 thrombolyzed AIS participants of the ENCHANTED trial.
  - Intensive target SBP 130–140 mmHg versus guideline-recommended target SBP <180
  - Early and consistent low levels in SBP <140 even as low as 110 to 120 mmHg, over 24 hours is associated with better outcomes in thrombolyzed acute ischemic stroke patients.