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Faculty Disclosure

Dr. Britt lists honoraria for Boehringer-Ingelheim and TEVA Neuroscience. He has indicated no other commercial affiliations. He plans to discuss off-label use of Alteplase (tPA).

2010 STROKE UPDATE

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Intravenous Alteplase (tPA) in Acute Ischemic Stroke (< 3 hours)

- Goal: Door-to-Drip 60 minutes
- Candidates:
  - Arrival in ED within 2 hours of onset
  - No exclusion for treatment
  - PHFH: Include those with mild symptoms (NIHSS < 7) unless purely sensory or isolated hemianopsia

Intravenous Alteplase (tPA) in Acute Ischemic Stroke (< 3 hours)

- Blood pressure:
  - To begin infusion, systolic < 185 AND diastolic < 110
  - During infusion and for 24 hours after completion, systolic < 180 AND diastolic < 105

Intravenous Alteplase (tPA) in Acute Ischemic Stroke (< 3 hours)

- Suspect ICH if: neurologic worsening, HA, vomiting, elevated BP
  - Stop infusion
  - STAT CT head w/o contrast
  - STAT autoheme with platelets, PT, PTT, fibrinogen, and T&C 2 U PRBCs
  - Order prepared for infusion: 8-10 U cryoprecipitate, 4 U FFP, 6-8 U single donor platelets

Intravenous Alteplase (tPA) for Acute Ischemic Stroke (< 3 hours)

- Hemorrhage present on CT:
  - STAT Neurosurgery consultation
  - STAT Hematology consultation for guidance in infusion of the blood products
  - Repeat STAT autoheme with platelets, PT, PTT, and fibrinogen 15 minutes after infusions complete.
  - NOTE: May occur in patients receiving Alteplase (tPA) for non-neurologic causes!

Intravenous Alteplase (tPA) for Acute Ischemic Stroke (< 3 hours)

- Angioedema: 1-2% of patients
  - Sudden swelling of lips, tongue, or oropharynx
  - Increased risk in patients receiving an ACEI
  - Swelling more pronounced on the paretic side
  - Several deaths reported from traumatic intubation.

Intravenous Alteplase (tPA) for Acute Ischemic Stroke (< 3 hours)

- Angioedema treatment:
  - Discontinue infusion
  - Administer STAT all drugs below:
    - Diphenhydramine 50 mg IV push
    - Dexamethasone 10 mg IV push
    - Famotidine 20 mg IV push
  - If edema worsens or laryngospasm develops, administer STAT: Epinephrine 0.3 mg SQ; may repeat in 15 minutes

Intravenous Alteplase (tPA) for Acute Ischemic Stroke (3-4.5 hours)

- ATLANTIS (USA): Negative
- ECASS 3 (EU): Modestly Positive, but:
  - Additional exclusion criteria (<80 years, diabetic with prior stroke, any anticoagulant therapy)
  - Randomization favored treatment arm (NIHSS 9/10)
  - Meta-analysis all 3-6 hour IV thrombolysis trials: slightly positive outcome for treatment

Intravenous Alteplase (tPA) for Acute Ischemic Stroke (3-4.5 hours)

- NNT for rescue to no or minimal deficit
- 0-1.5 hours: 4
- 1.5-3 hours: 8
- 0-3 hours: 7
- 3-4.5 hours: 14
- NNH (w/o protocol violation)
- 0-3 hours: 16
- 3-4.5 hours: 14

Intravenous Alteplase (tPA) for Acute Ischemic Stroke (3-4.5 hours)

- No regulatory approval in US (approved in EU)
- Biomarker research for case selection:

MRI: DWI/MRP imaging validated in EPITHIT, being used in EXTEND to identify infarct core and the ischemic penumbra for selection of patients for IV thrombolysis 3-4.5 hrs after symptom onset; some limitations

Intra-arterial Clot Lysis or Retrieval (for large Vessel Occlusion)

- Posterior Circulation: Basilar or bilateral vertebral artery occlusion
  - IA intervention results better; IV tPA only of endovascular treatment unavailable
  - Time window of efficacy: up to 12 hours after symptom onset

Intra-arterial Clot Lysis or Retrieval

- Anterior circulation: (Treat with IV tPA if < 3 hours)
- PROACT II: IA prourokinase < 6 hours, more good outcomes (MRS ≤2) with treatment- 40%/25%, but ICH rate 10%/2%; death rate equal: FDA approval denied
- IA thrombolysis with tPA
- Embolectomy: faster than thrombolysis when successful
  - Merci Retriever (mechanical)
  - Penumbra device (mechanical + vacuum aspiration) Trial: 125 pts, 82% recanalization rate (TIMI 2 or 3), 25% good outcomes (MRS ≤2)
  - Both approved for clot removal in patients with stroke

Intra-arterial Clot Lysis or Retrieval

- IA interventions have a "Recanalization/Outcome Mismatch."
  - Average two hours trigger to groin puncture, longer to recanalization when successful
  - AHA/ASA 2007 evidence-based guideline for Early Stroke Management: "(Endovascular therapies) cannot be recommended outside the setting of clinical trials"
  - Remain experimental for compassionate use with rare exceptions (i.e., MCA clot from AF after CABG, abnormal hemostasis)

Intra-arterial Clot Lysis or Retrieval

- Clinical Research ongoing:
  - IMS III: large artery occlusion, < 3 hours from onset; 2/3 calculated dose IV tPA, then IA therapy if large vessel occlusion persists. But: recruiting slowly.
  - Penumbra Clinical trial: large vessel occlusion, ± IV tPA, randomized to IA treatment (retrieval only) or best medical care.

Spontaneous Intracerebral Hemorrhage

- Blood Pressure: MAP 100-120 mmHg in first 48 hours, < 100 mmHg thereafter
- ICP monitoring: If GCS < 9, to keep cerebral perfusion pressure (CPP = MAP minus the ICP) > 70 mm Hg

Correction of Coagulopathy in Patients with Oral Anticoagulant-Related Intracranial Hemorrhage

- STAT Vitamin K 10 mg IV
- STAT Prothrombin Complex Concentrate (CHEST suppl: 2005)
- INR 1.4 – 2.0: Profilnine 25 IU/kg IV bolus
- INR > 2.0: Profilnine 40 IU/kg IV bolus
- Repeat INR ½ and 12 hours after bolus given; if > 1.4: FFP 2-4 units

Statin Therapy for Acute Ischemic Stroke

- Resume by Day 2 in patients receiving a statin PTA
- SPARCL: "high intensity lipid lowering" strategy tested with Atorvastatin (Lipitor) 80 mg/day in patients without known coronary disease; target LDL 70. Result: 2% absolute risk reduction of recurrent stroke. (Increased ICH rate, no increased death rate)
- SPARCL subgroup analysis: LDL, HDL, triglycerides and blood pressure targets have linear cumulative ARR (60% if all four achieved)

Antiplatelet Therapy for Secondary Stroke Prevention

- AHA/ASA Guidelines:
  - Noncardioembolic stroke – antiplatelet therapy:
  - ASA, dipyridamole ER/ASA (Aggrenox), clopridogrel (Plavix) acceptable options
  - Aggrenox recommended over ASA alone; Plavix over ASA (from heart disease studies)
  - Plavix plus ASA: For acute coronary syndrome or recent stent only; no adjunctive benefit in stroke patients but increased hemorrhage risk.

Antiplatelet Therapy for Secondary Stroke Prevention

- PROFESS
  - 20,000 patients: Plavix/Aggrenox equal randomization
  - F/U 2 ½ years
  - Recurrent stroke: Plavix 8.8%/Aggrenox 9.0 (NSS)
  - AMI, vascular deaths equal
  - Recurrent stroke an ICH: Plavix 4%, Aggrenox 9% (SS), BUT number of events small
  - AHA/ASA guidelines for secondary stroke prevention have not been modified on basis of PROFESS

Antiplatelet Therapy

- ASA and Plavix resistance: Significant percentage of patients
- Testing efficacy on platelet aggregation:
  - ASA: Platelet Function Screen (PFS 100)
  - Plavix: Verify Now (P2Y12)
  - Plavix: prodrug activated by CYP 2C19, which is inhibited by PPIs, especially omeprazole

Stenting for Secondary Stroke Prevention

- Stenting of ICA at bifurcation indicated if:
  - Prior endarterectomy
  - Contralateral ICA occlusion
  - Poor neck tissue (XRT, radical neck dissection)
  - ? Poor surgical candidate
  - High Bifurcation
  - O/W: Carotid endarterectomy

Stenting for Secondary Stroke Prevention

- Intracranial
  - Feasible: ICA-MCA junction: ICA terminus, proximal MCA, proximal ACA, BA, distal VA.
  - "Wingspan" Stent (Boston Scientific)
  - BUT: Restenosis or occlusion frequent, although outcomes not always adverse.
  - SAMMPRIS: trial of intensive medical therapy with and without stenting; PSHMC a site

Patent Foramen Ovale

- 25 % of population
- 1-2% absolute increased lifetime risk of acute ischemic stroke
- No benefit of closure for secondary stroke prevention has been demonstrated.
- Only potential proof of benefit: outcome of ongoing closure plus ASA vs ASA trial; recruiting slowly.

Percutaneous Left Atrial Appendage Closure for Nonvalvular Atrial Fibrillation

- PROTECT AF trial of Watchman Device
  - Not inferior to Warfarin (stroke, death, thromboembolism)
  - Some procedural complications, especially pericardial effusion.
  - Increased hemorrhagic events with Warfarin
  - FDA advisory panel recommended approval (2009); other devices being tested