Updates in Stroke Management

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Disclosure

- I have no actual or potential conflict of interest in relation to this program presentation

Objectives

1. Discuss the window of opportunity and role of early reperfusion therapy with intravenous fibrinolysis
2. Analyze the role of dual antiplatelet therapy in the acute and chronic treatment of ischemic stroke
3. Determine a safe and appropriate antithrombotic treatment option in the setting of atrial fibrillation
4. Discuss the timing of anticoagulation for secondary stroke prevention in the setting of atrial fibrillation

Ischemic Stroke

- Approximately 795,000 adults experience an ischemic stroke each year
  - High risk for recurrence (185,000)

- Additional 240,000 adults experience a TIA

Circulation. 2018;137:e67–e492.

Acute Ischemic Stroke

- Immediate goal of therapy is to reduce neurologic injury and long-term disability
- Once through the hyperacute period, goal of therapy is to prevent recurrence and ultimately decrease mortality
- Treatment for acute ischemic stroke has a narrow therapeutic window making timely evaluation and diagnosis essential

Stroke. 2018;49:e46-e99.

Acute Treatment Options

- IV tissue plasminogen activator (tPA)
- Aspirin (ASA)
- Aspirin plus clopidogrel
- Ticagrelor

Stroke. 2018;49:e46-e99.

Objective #1

- Discuss the window of opportunity and role of early reperfusion therapy with intravenous fibrinolysis

tPA

- Recommended due to its ability to achieve early reperfusion and improve neurological outcomes
- Initiation of local fibrinolysis
  - Binds directly to fibrin
  - Plasminogen converts to plasmin
  - Results in clot dissolution
- tPA puts patients at risk for major bleeding necessitating extensive inclusion and exclusion criteria for use
- It is estimated that fewer than 2% of patients receive treatment

Timing of Initiation

- Benefit of therapy is time dependent and treatment should be initiated as quickly as possible
- If the time of onset is unknown patients are ineligible to receive tPA
- tPA should be administered within 3 hours of symptom onset
  - The IDEAL door-to-needle time should be within 60 minutes from hospital arrival
- The benefit of tPA up to 4.5 hours after symptom onset has been established in specific patients

Stroke. 2018;49:e46-e99.

The Journey from 3 to 4.5 Hours

- NINDS (1995)
- ECASS I (1995)
- ECASS II (1998)
- ATLANTIS (1999)
- ECASS III (2008)

NINDS

- Assessed the safety and efficacy of tPA when administered within 3 hours of symptom onset
- 624 patients randomized to receive tPA 0.9mg/kg or placebo
- Significant improvement at 90 days in the tPA group
- Occurrence of intracranial hemorrhage higher in tPA group

NEJM. 1995;333:1581-7.

Evidence	Purpose	Treatment	Efficacy	Safety
ECASS I	620 patients within 6 hours	tPA 1.1 mg/kg versus placebo	No difference at 90 days	Increased mortality and intracranial hemorrhage
ECASS II	800 patients within 6 hours	tPA 0.9 mg/kg versus placebo	No difference at 90 days	Increased intracranial hemorrhage
ATLANTIS (A)	142 patients within 6 hours	tPA 0.9 mg/kg versus placebo	No difference at 30 days	Increased mortality and intracranial hemorrhage
ATLANTIS (B)	547 patients within 3-5 hours	tPA 0.9 mg/kg versus placebo	No difference at 90 days	Increased intracranial hemorrhage

JAMA. 1995;274:1017-25. Lancet. 1998;352:1245-51. Stroke. 2000;31:811 JAMA. 1999;282:2019-26.

ECASS III

- Assessed the safety and efficacy of tPA when administered between 3 and 4.5 hours of symptom onset
- 821 patients randomized to receive tPA 0.9mg/kg or placebo
- Several additional exclusion criteria:
  - Age older than 80 years
  - Any use of oral anticoagulants
  - Prior history of stroke and diabetes
  - Baseline NIHSS score greater than 25
- Significant improvement at 90 days in the tPA group
- Increased incidence of intracranial hemorrhage in tPA group

NEJM. 2008;359:1317-29.

AHA/ASA 2009 Update

- Eligibility criteria are similar to the 3 hour window with the addition of the following **exclusion** criteria:
  - Patients > than 80 years
  - Patients taking PO anticoagulants
  - Patients with a history of BOTH stroke and diabetes
  - Patients with a baseline NIHSS > 25

Stroke. 2009;40:2945-2948.

Pooled analysis

- Results of ECASS III study were reinforced in a pooled analysis
  - Supported use of tPA when administered within 4.5 hours of symptom onset
  - Importance of early treatment was reiterated by the investigators as patients treated within the first 90 minutes derived the most benefit

Lancet 2010;375:1695-703.

2018 AHA/ASA Update

- "Careful analysis of available published data indicates that these exclusion criteria may not be justified in practice" (IB)
  - **Patients >80**
    - tPA is safe and can be as effective as in younger patients (*Class IIa; B-NR*)
  - **Patients taking warfarin and INR ≤1.7**
    - tPA appears safe and may be beneficial(*Class IIb; B-NR*)
  - **Patients with prior stroke and diabetes**
    - tPA may be as effective as treatment in the 3 hour window (*Class IIb; B-NR*)
  - **Patients with very severe stroke (NIHSS > 25)**
    - Benefit is uncertain (*Class IIb; C-LD*)

Stroke. 2016;47:581–641.
Stroke. 2018;49:e46-e99.

Key Takeaways

- Patients should be treated with tPA as early as possible to maximize the benefit
- Opportunity to expand treatment within 4.5 hours
- “Having more time does not mean we should be allowed to take more time.”

NEJM. 2008;359:1317-29.

Objective #2

- Analyze the role of dual antiplatelet therapy in the acute and chronic treatment of ischemic stroke

Recurrence

- Annual risk for a repeat event is approximately 3% to 4%
- Highest risk within the first days to weeks post initial event
- Antiplatelet therapy is the mainstay of secondary prevention

Stroke. 2014;45:2160-2236.

Secondary Prevention

Antiplatelet Therapy	Recommendation	
Aspirin 50 - 325 mg PO daily	Acceptable initial therapy	I A
ER dipyridamole 200 mg + aspirin 25 mg PO BID	Acceptable initial therapy	I B
Clopidogrel 75 mg PO daily	Reasonable option instead of ASA or ASA/DP	IIa B
	Alternative to aspirin-allergic patients	IIa B

- What about the combination of aspirin and clopidogrel?

Stroke. 2014;45:2160-2236.

Aspirin plus Clopidogrel

Evidence	Purpose	Treatment	Efficacy	Safety
MATCH	7599 patients with stroke or TIA within 3 months	ASA/clopidogrel versus clopidogrel	No difference	Increased risk of bleeding
CHARISMA	15,603 patients (35% with stroke or TIA) within 5 years	ASA/clopidogrel versus ASA	No difference	Increased risk of bleeding
SPS3	3026 patients with lacunar stroke within 6 months	ASA/clopidogrel versus ASA	No difference	Increased risk of bleeding

Lancet. 2004;364:331-337.
N Engl J Med. 2006; 354:1706-1716.
N Engl J Med. 2012; 367:817-825.

Implications of MATCH, CHARISMA, and SPS3

- Combination of aspirin and clopidogrel
  - Not recommended for routine long-term secondary prevention after ischemic stroke or TIA
  - When initiated days to years after a ischemic stroke or TIA
  - And continued for 2 to 3 years
- Class III; Level of Evidence A

Stroke. 2014;45:2160-2236.

Acute treatment options

- IV tissue plasminogen activator (tPA)
- Aspirin (ASA)
  - Treatment within 24-48 hours of symptom onset
- **Aspirin plus clopidogrel**

- Ticagrelor
  - SOCRATES (N Engl J Med. 2016; 375:35-43)
  - 180 mg PO x 1 then 90mg PO BID x 90 days
  - Alternative in minor stroke or TIA in patients with a contraindication to ASA

Stroke. 2018;49:e46-e99.

CHANCE

- 5170 patients in China with acute, minor ischemic stroke or TIA
  - Acute: Randomized within 24 hours
  - Minor: NIHSS score of 3 or less
- **Day 1**
  - Clopidogrel 300 mg x 1 PLUS aspirin 75 to 300 mg x 1
  - Aspirin 75 to 300 mg x 1
- **Days 2-21**
  - Clopidogrel 75 mg daily PLUS Aspirin 75 mg daily
  - Aspirin 75 mg daily
- **Days 22-90**
  - Clopidogrel 75 mg daily
  - Aspirin 75 mg daily

N Engl J Med. 2013; 369:11-19.

CHANCE

Endpoint at 90 days	ASA/Clopidogrel x 21 days, then clopidogrel	Aspirin	P Value
Stroke	8.2%	11.7%	<0.001
Severe Bleeding	0.2%	0.2%	0.94
Mild Bleeding	1.2%	0.7%	0.12
Any bleeding	2.3%	1.6%	0.09

N Engl J Med. 2013; 369:11-19.

POINT

- 4881 patients from 269 international sites with acute, minor ischemic stroke or high-risk TIA
  - Acute: Randomized within 12 hours
  - Minor: NIHSS score of 3 or less
- 90 Days of Treatment
  - Clopidogrel 600mg then 75mg daily **PLUS** ASA 50-325mg daily
  - ASA 50-325mg daily **PLUS** placebo

N Engl J Med. 2018;379:215-225.

POINT

Endpoint at 90 days	ASA + Clopidogrel	Aspirin	P Value
Composite*	5%	6.5%	0.02
Ischemic stroke	4.6%	6.3%	0.01
Major hemorrhage	0.9%	0.4%	0.02
Minor hemorrhage	1.6%	0.5%	<0.001

* Ischemic stroke, myocardial infarction, or death form ischemic vascular causes

N Engl J Med. 2018;379:215-225.

Implications of CHANCE & POINT

- Combination of aspirin and clopidogrel
  - Minor ischemic stroke (NIHSS <3) or TIA
  - Initiate within 12-24 hours
  - Continued for 21 days

- *Class IIb; Level of Evidence B*

N Engl J Med. 2018;379:215-225.
N Engl J Med. 2013; 369:11-19.

Key Takeaways

- Timing does matter
- Duration of therapy matters
- Ischemic stroke severity (or TIA)

Objective #3

- Determine a safe and appropriate antithrombotic treatment option in the setting of atrial fibrillation

Guidelines

- **American Heart Association (AHA), American College of Cardiology (ACC), Heart Rhythm Society (HRS)**
  - Guideline for the Management of Patients With Atrial Fibrillation.
    - J Am Coll Cardiol. 2014;64(21):e1-e76.

- **American College of Chest Physicians (ACCP)**
  - Antithrombotic Therapy for Atrial Fibrillation.
    - Chest. 2018; *in press.*

Atrial Fibrillation and Stroke

- Atrial fibrillation affects approximately 2.7 million Americans
  - Accounts for 15% of all strokes
  - Without thromboprophylaxis, the risk of stroke is approximately 5% per year
- Oral anticoagulation (OAC) therapy reduces the risk of stroke but increases the risk of bleeding
- Risk of stroke varies across different groups of patients

Arch Intern Med. 1994;154(13):1449-1457.
Circulation. 2015;131(4):e29-e322.

Risk Based Approach

- Risk based approach accepted by AHA, ACC, HRS, and ACCP

- Atrial Fibrillation Investigators (AFI)
- Stroke Prevention in Atrial Fibrillation Investigators (SPAF)

- Commonly used schematics
  - $CHADS_2$ (2001)
  - CHA_2DS_2-VASc (2010)

- Available schema have only modest ability to predict stroke
  - C statistics between 0.55-0.7

$CHADS_2$

- C = Recent **C**HF exacerbation (1 point)
- H = History of **H**ypertension (1 point)
- A = **A**ge > 75 (1 point)
- D = **D**iabetes mellitus (1 point)
- S = Prior history of **S**troke or TIA (2 points)

JAMA 2001;285(22):2864–2870.

CHA_2DS_2-VASc

- C = **C**ongestive Heart Failure/Left Ventricular Dysfunction (1 point)
- H = **H**ypertension (1 point)
- A = **A**ge > 75 (2 points)
- D = **D**iabetes mellitus (1 point)
- S = **S**troke/TIA/thromboembolism (2 points)
- V= **V**ascular disease (prior MI, PAD, or aortic plaque) (1 point)
- A = **A**ge 65-74 (1 point)
- Sc = **S**ex category (female) (1 point)

CHEST. 2010;137(2):263-272.

Antithrombotic Treatment Options

- OAC Therapy
  - Vitamin K Antagonist
    - Warfarin
  - Non-vitamin K antagonist oral anticoagulant (NOAC)
    - Apixaban
    - Dabigatran
    - Edoxaban
    - Rivaroxaban
- Aspirin
- Aspirin plus clopidogrel
- Omit therapy

AHA/ACC/HRS

- CHA_2DS_2-VASc score recommended to assess stroke risk (IB)
- CHA_2DS_2-VASc has a broader score range and more risk factors
  - More clearly defines anticoagulation recommendations
- $CHADS_2$
  - Those at lowest risk are not well identified

J Am Coll Cardiol. 2014;64(21):e1-e76.

AHA/ACC/HRS

CHA2DS2-VASc Score	Antithrombotic Recommendation
CHA_2DS_2-VASc = 0	Reasonable to omit therapy (IIaB)
CHA_2DS_2-VASc = 1	No therapy OR Aspirin OR Oral anticoagulant (IIbC)
CHA_2DS_2-VASc ≥ 2	Warfarin (IA) OR Dabigatran, Rivaroxaban, or Apixaban (IB)
Patients with mechanical valves	Warfarin (IB)
CHA_2DS_2-VASc ≥ 2 with ESRD	Warfarin (IIaB)

J Am Coll Cardiol. 2014;64(21):e1-e76.

ACCP 2018

- CHA_2DS_2-VASc
  - Identify patients with LOW stroke risk
  - Patients who should **NOT** be offered antithrombotic therapy
    - **Male:** CHA_2DS_2-VASc = 0
    - **Female:** CHA_2DS_2-VASc = 1
  - Candidates for antithrombotic therapy
    - **Male:** CHA_2DS_2-VASc ≥ 1
    - **Female:** CHA_2DS_2-VASc ≥ 2

Chest. 2018; *in press.*

ACCP 2018

- Bleeding risk assessment should be performed at every patient contact

- HAS-BLED
  - **H**TN (1 point)
  - **A**bnormal renal or liver Disease (1 or 2 points)
  - **S**troke history (1 point)
  - **B**leeding history or predisposition (1 point)
  - **L**abile INR (1 point)
  - **E**lderly (> 65) (1 point)
  - **D**rugs (predispose to bleeding, alcohol) (1 OR 2 points)

Chest. 2018; *in press.*

ACCP 2018

- Address modifiable bleeding risk factors
- Potentially high risk (score ≥ 3) should have more frequent follow-up
- High bleeding risk score is NOT a reason to withhold OAC

Chest. 2018; *in press.*

ACCP 2018

- NOAC over warfarin
  - Consider patient preference, cost, formulary considerations, adherence, and/or compliance with INR testing
- Antiplatelet therapy should be avoided
  - Aspirin monotherapy
  - Aspirin plus clopidogrel

Chest. 2018; *in press.*

Key Takeaways

- Identify patients who are at sufficiently low risk
  - CHA_2DS_2-VASc
  - Can be treated with no antithrombotic therapy
- All other patients can be evaluated for NOAC therapy

Objective #4

- Discuss the timing of anticoagulation for secondary stroke prevention in the setting of atrial fibrillation

Atrial Fibrillation and Stroke Recurrence

- Annual risk for a repeat event is approximately 7 to 10%
  - Highest risk within the first 14 days after the initial event

- $CHADS_2$ and CHA_2DS_2-VASc
  - May underestimate the risk for recurrence in patients with a recent event

- When should OAC be initiated?

Stroke. 2014;45:2160-2236.
Chest. 2018;*in press*

Hemorrhagic Transformation

- Risk ranges between 1.5 to 5% within the first 14 days after the initial event

- Risk factors
  - Large infarct
  - Uncontrolled hypertension
  - Previous hemorrhagic stroke

- How do you balance the benefit versus risk of early use of anticoagulation?

Stroke. 2014;45:2160-2236.
Chest. 2018;*in press*

Heparin Use within 48 Hours

HAEST (2000)	• LWMH vs ASA within 30 hours • No difference
IST Subgroup (2001)	• UFH vs no UFH within 48 hours • Reduced recurrence • Increased intracranial bleeding
Paciaroni, et al (2007)	• Heparin vs control • Trend towards reduced recurrence • Increased intracranial bleeding

Lancet. 2000; 355: 1205-10
Stroke. 2001;32:2333-2337.
Stroke. 2007;38:423-430

Effect of Anticoagulation and Its Timing: The RAF Study

Anticoagulation Intervention	Patients	Mean Day of Initiation
VKA	37.1%	12
LMWH + VKA	36%	7
LMWH	14.7%	7
NOAC	12.1%	9

- Anticoagulation initiated between days 4-14
  - Significantly reduced recurrent events
  - No increased risk of bleeding
- Patients treated with oral agents alone had better outcomes

Stroke. 2015;46:2175-282.

NOAC Use in Acute Cardioembolic Stroke

Dabigatran (RE-LY 2009)	• Excluded: Stroke within 7 days
Rivaroxaban (ROCKET AF 2011)	• Excluded: Stroke within 14 days
Apixaban (ARISTOTLE 2011)	• Excluded: Stroke within 14 days
Edoxaban (ENGAGE 2013)	• Excluded: Stroke within 30 days

Key Takeaways

- Wait to initiate oral anticoagulation for 7 to 14 days
- Hold treatment with first 48 hours
  - Discourage use of heparin products
- Earlier use (< 7 days) - Low risk of bleeding
- Delayed use (>14 days) - High risk of hemorrhagic complications
- Aspirin can be used in the acute setting until full dose anticoagulation is on board

Stroke. 2014;45:2160-2236.
Chest. 2018;*in press*

True or False?

tPA is safe and effective if administered within 6 hours of stroke symptom onset.

✅ True

❌ False

True or False?

Select patients should receive aspirin and clopidogrel for 90 days status post ischemic stroke.

✅ True

❌ False

True or False?

The CHA_2DS_2-VASc scoring system should be used to identify low risk patients who do not need antithrombic therapy for stroke prevention in atrial fibrillation.

✅ True

❌ False

True or False?

All patients should wait at least two weeks before oral anticoagulation therapy is started status post acute cardioembolic stroke.

✅ True

❌ False

Updates in Stroke Management

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