Journal Club Summary Handout by Oleg Shulik, MD

Case: 89 y/o African American female was admitted to ACE unit with diagnosis of TIA.
Patient was last seen well 6 hours prior and was brought in by her family member to ER due to sudden onset of facial droop on her left side that slowly resolved over the course of several hours but still was noticeable for her family members thus they brought her to ER.

She is a lovely elderly that lives with her family and is independent in her ADL's and IADLs. Her PMH is only significant for HTN that is well controlled and type II DM that is diet controlled and her last HgA1c was 6.6. Her PSH is unremarkable, and she has been hospitalized only once in her life, 2 month ago, for LGIB, for which she underwent colonoscopy that showed internal hemorrhoids. She takes Lisinopril and Metformin as well as MVI.

In ER her VS: SBP 120/70 HR 75 Physical exam is consistent with mild new onset facial droop.
Rest of the neurological examination is unremarkable.

She was evaluated by an ER resident that recommended to start the patient on Plavix (Clopidogrel) in addition to Aspirin based on a recent article in NEJM that suggest benefit of dual antiplatelet therapy in patients in patients with high risk TIA

INTRODUCTION:
Cerebral ischemia: (TIA/Stroke) w/o imaging changes.
TIA - reversible, risk for stoke in a first 2 days: ABCD2 (0-5)
Stroke – disabling (major)/ non disabling (mild/silent): clinical diagnosis
Stoke severity and prognosis after Stroke : Rankin score (0 asymptomatic – 2 mild – 6 death)
NIHSS < 3 minor stroke.
It's all about platelets….

BACKGROUND:
1.

- IST (Lancet 1997) – ASA in 48 hours of ischemic stroke onset reduces the risk of a 14-days recurrence of stroke. 2013
    - 2011/2013 AHA/ASA guidelines recommend administration of aspirin (325mg) within 24 to 48 hours after stroke onset (Level 1A)
- MATCH (Lancet 2004) – ASA + Clopidogrel in a patients with prior TIA or CVA DID NOT! Reduce rates of recurrent ischemic CVA or TIA, and combo-tx conferred great risk of major and life threatening bleeding.
    - 2011 AHA/ASA stroke guidelines recommend against adding aspirin to clopidogrel (Class III, A)
    - MATCH study design criticism: (lacunar infarcts/ not acute settings)
- **<u>CHANCE</u>**

Patient(P) : Adults with new onset of high risk - TIA or mild Stroke .
Intervention(I): Aspirin(21 days) and Clopidogrel in the first 24 hours for 90 days
Control(C) : Aspirin in the first 24 hours for 90 days
Hypothesis (O) : Combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stoke in the first 90 days and does not! Increase risk of hemorrhage.

Methods: Study Oversight (2) and Design

- Multicenter, randomized, placebo-controlled trial
- N=5,170
  - Aspirin (n=2,586)
  - Aspirin/clopidogrel (n=2,584)
- Setting: 114 centers in China
- Enrollment: 2009-2012
- Follow-up: 90 days
- Analysis: Intention-to-treat
- Primary outcome: Stroke

Population

Inclusion Criteria

- Age ≥40 years
- Either of the following:
  - Minor ischemic stroke (NIHSS score ≤3)
  - High-risk TIA ($ABCD^2$ score ≥4)
- Symptom onset ≤24 hours

Exclusion Criteria (bold – common in geriatric population)

- CT/MRI brain with hemorrhage, vascular malformations, tumor, abscess, or other similar non-ischemic brain disease
- *Isolated sensory symptoms, visual changes, dizziness or vertigo without evidence of acute infarction*
- **Pre-event Rankin score >2**
- Other need for anticoagulation including AF
- History of intracranial hemorrhage
- Need for long-term antiplatelet therapy
- **Anticoagulation therapy in prior 10 days**
- **GI bleeding or major surgery in prior 3 months**
- Likely revascularization surgery in following 3 months
- Planned intervention that would require cessation of study medication
- TIA or minor stroke from surgical intervention
- **Life expectancy <3 months**

- Females with child-bearing capacity not on contraception without a negative pregnancy test
- Other investigational drug use

Baseline Characteristics (Table 1)

From the aspirin group.

- Demographics: Age 62 years, female 34.7%
- **Baseline health data: SBP 150 mmHg, DBP 90 mmHg, BMI 25**
- PMH: HTN 65.1%, DM 21.0%, HLD 10.9%, PE <0.1%, ischemic stroke 20.0%, TIA 3.1%, MI 2.0%, angina 3.4%, HF 1.5%, AF/AFL 1.9%, valvular heart disease 0.4%, ever smoker 42.7%
- Symptom onset <12h: 49.5%
- Qualifying event:
    - TIA 28.2%
    - Minor stroke 71.8%
- Mean $ABCD^2$ score (for TIAs only): 4

Interventions

- Randomization to one of two groups:
    - Aspirin group received aspirin **75-300mg (based on MD discretion)** on day one followed by 75mg daily plus placebo clopidogrel
    - Aspirin/clopidogrel group received clopidogrel 300mg and aspirin 75-300mg on day one, followed by clopidogrel 75mg daily; aspirin was continued at 75mg daily through day 21 and placebo aspirin was given thereafter
- All patients had a CT and/or MRI performed as part of routine workup
- Thrombolytics were disallowed

Outcomes(Table 2)

Comparisons are aspirin vs. aspirin/clopidogrel. All outcomes are at 90 days.

3. Efficacy outcomes and Safety outcomes – definition

Primary Outcome – Results of efficacy outcomes (Table 2)

Stroke

11.7% vs. 8.2% (HR 0.68; 95% CI 0.57-0.81; P<0.001; NNT=29) / 6.8% vs 5.2% in disabling Stroke

Secondary Outcomes – Results of efficacy outcomes

Stroke, MI, CV mortality

11.9% vs. 8.4% (HR 0.69; 95% CI 0.58-0.82; P<0.001)

Ischemic stroke: 11.4% vs. 7.9% (HR 0.67; 95% CI 0.56-0.81; P<0.001)

Hemorrhagic stroke: 0.3% vs. 0.3% (HR 1.01; 95% CI 0.38-2.70; P=0.98)

MI: 0.1% vs. 0.1% (HR 1.44; 95% CI 0.24-8.63; P=0.68)

CV mortality: 0.2% vs. 0.2% (HR 1.16; 95% CI 0.35-3.79; P=0.81)

All-cause mortality

0.4% vs. 0.4% (HR 0.97; 0.40-2.33; P=0.94)

TIA

1.8% vs. 1.5% (HR 0.82; 0.53-1.26; P=0.36)

Adverse Events – Results of Safety outcomes (Table 2)
Bleeding
1.6% vs. 2.3% (HR 1.41; 95% CI 0.95-2.10; P=0.09)
Mild: 0.7% vs. 1.2% (HR 1.57; 95% CI 0.88-2.79; P=0.12)
Moderate: 0.2% vs. 0.1% (HR 0.73; 95% CI 0.16-3.26; P=0.68)
Severe: 0.2% vs. 0.2% (HR 0.94; 95% CI 0.24-3.79; P=0.94)

Subgroup Analysis (Fig 2)
There was no interaction for the primary endpoint for age, sex, stroke vs. TIA, $ABCD^2$ score, history of stroke or TIA, HTN, DM, BP on presentation, or recent aspirin use.

Discussion (Fig 1)

Pros:
Criticisms

- Chinese only patients, a population with a much higher rate of stroke (and more large-vessel strokes) than in the US
- Low treatment of comorbid diseases increasing risk for stroke in the trial population (eg, HTN, DM)
- Low rate of screened patients included as participants
- Polymorphisms affecting clopidogrel metabolism are more common in Chinese patients
- Unknown benefit after 90 days

Applicability and Geriatric Patient! Back to our case – open forum.

SEE ARTICLE FOR TABLES AND FIGURES