Should We Take a **CHANCE** or Is There a **POINT**

Subtitle: A Dive into the use of Clopidogrel and Aspirin for TIA and AIS

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**OBJECTIVES**

1. Evaluate the current guidelines supporting the use of clopidogrel and aspirin
2. Dissect the evidence behind the use of clopidogrel and aspirin for minor AIS and TIA
3. Discuss clinical implications of antiplatelet therapy use in stroke and TIA based on current guidelines and primary literature

**PATIENT CASE**

**CC:** “I have a weird pain in my chest”

**HPI:** DA is a 54-yr male who arrives into ED triage via EMS with mild CP, left facial droop and left sided weakness for the past 9 minutes. He was fine during his morning jog, but then when he sat down to rest his left side became limp with some slurred speech.

**PATIENT CT AND LABS**

<table>
<thead>
<tr>
<th>Transient Ischemic Attack (TIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BP</strong></td>
</tr>
<tr>
<td>134/92</td>
</tr>
<tr>
<td><strong>O2 sat</strong></td>
</tr>
<tr>
<td>96% on RA</td>
</tr>
</tbody>
</table>

ECG is normal sinus rhythm

**MEDICATIONS**

**Home Medications**
- Lisinopril 5mg daily
- Vitamin B12 complex daily

**ER Course**
- ASA 325mg chewed
- NTG SL 0.4mg tablet x 1
- Oxygen to maintain saturation >94%
- Metoprolol 5mg IV
  - Reduced BP 154/84
  - Reduced HR 90

**ABBREVIATIONS**

- DAPT: Dual Antiplatelet Therapy
- AIS: Acute Ischemic Stroke
- TIA: Transient Ischemic Attack
- BMP: Basic Metabolic Panel
- PAD: Peripheral Artery Disease
- CAD: Coronary Artery Disease
- CVF: Cardiovascular Disease
- DLD: Dyslipidemia
- HTN: Hypertension
- ER: Emergency Room
- ED: Emergency Department
- NTG: Nitroglycerin
- RA: Room Air
- BMI: Body Mass Index
- Fx: Function
- PMH: Past Medical History
- PO: By Mouth
- GCS: Glasgow Coma Scale
- SBO: Shortness of Breath
- FH: Family History
- EtOH: Alcohol
- HR: Heart Rate
- NPO: Nothing by Mouth
- PMHx: Past Medical History

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- Metoprolol 5mg IV
  - Reduced BP 154/84
  - Reduced HR 90
NIHSS SCORE FOR STROKE

- A 11 item scoring system that has a maximum score of 42

<table>
<thead>
<tr>
<th>National Institute Health Stroke Scale (NIHSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 60 years</td>
</tr>
<tr>
<td>BP ≥ 140/90 mmHg</td>
</tr>
<tr>
<td>Clinical features of the TIA</td>
</tr>
<tr>
<td>Duration of symptoms</td>
</tr>
<tr>
<td>History of diabetes</td>
</tr>
</tbody>
</table>

0 = No Stroke
1-4 = Minor Stroke
5-15 = Moderate Stroke
16-20 = Moderate-Severe Stroke
21-42 = Severe Stroke

EMS UPON ARRIVAL

**NIHSS:**
- Level of consciousness (0-3+)
- Orientation to month/age (0-2+ ea)
- Responds to commands (0-2+)
- Gaze (0-2+)
- Visual field (0-3+)
- Facial movement (0-3+)
- Motor function for arm & leg (0-4+ ea)

**Score = 4**

WHAT IS A STROKE?

Currently the 5th leading cause of death in the United States
Caused by reduced circulation to the brain resulting in neurological symptoms
- Reduced oxygen to the brain
- Less nutrients
- Cell death

Signs and symptoms recognition, medical history, and time are important

MINOR ISCHEMIC EVENT TYPES

- Ischemic (80%)
  - Blocked artery by thrombus or embolic
  - Usually from atherosclerosis
  - Central thrombosis
  - Central embolism
  - Complications at risk for more hemorrhagic conversion post thrombolysis

- TIA
  - "Mini-stroke" temporary occlusion
  - Clot or block
  - "Warning stroke"
  - deficit lasts <24hrs (usually <30min)

ABCD² SCORE FOR TIA

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 60 years</td>
<td>Y/N</td>
<td>≤ 1</td>
</tr>
<tr>
<td>BP ≥ 140/90 mmHg</td>
<td>Y/N</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Clinical features of the TIA</td>
<td>Motor function for arm &amp; leg</td>
<td>0-4+</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>&lt; 10 minutes</td>
<td>≤ 1</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>Y/N</td>
<td>≤ 1</td>
</tr>
</tbody>
</table>

National Stroke Association; 2018

RISK FACTORS

- **Modifiable**
  - HTN (>120/80)
  - Tobacco/Alcohol
  - O/D
  - DM
  - Obstructive Sleep Apnea
  - CVD (HF, defects, IE or AFib)
  - Oral estrogen and/or progesterone

- **Non-modifiable**
  - > 55yo
  - African American
  - Men
  - FH of stroke, CVA or TIA

National Stroke Association; 2018
PAST TRIAL - MATCH

- **Aim:** Does clopidogrel/ASA reduce recurrent events compared to clopidogrel alone in TIA & AIS

- **Demographics**
  - >40yo (66yrs), 37% female, 21% TIA, 79% AIS, 53% lacunar stroke (small vessel)
  - PMH:
    - Previous ischemic stroke 27%, previous TIA 19%, previous MI 5%, angina pectoris 13%, symptomatic PAD 10%, hypertension 78%, diabetes mellitus 68%, hyperlipidemia 56%, past or current smoker 38%
  - 19% randomized in <7days, 49% in 7-31days, 32% >31days

- **Inclusion**
  - Ischemic stroke/TIA in prior 3 months
  - ≥1 risk factors in past 3 years:
    - Ischemic stroke
    - MI
    - Angina pectoris
    - Diabetes mellitus
    - Symptomatic PAD

- **End Point**
  - First occurrence of ischemic stroke, MI, CV death or hospitalisation for acute ischemic event
  - Secondary prevention
  - Interventions
    - ASA 75mg + Clopidogrel 75mg
    - Clopidogrel 75mg

- **Results (干预 vs control)**
  - UA, worse PAD or TIA 16% vs 17%
  - MI 2% each (ea)
  - Ischemic stroke 8% vs 9%
  - Life-threatening bleed 3% vs 1% (p < 0.0001)
  - No difference; increase risk of major bleed w/o significantly reducing risk of recurrent stroke
  - NNH: Bleed – 50
  - 17% relative risk reduction in those treated within 7 days

- **Secondary Prevention**
  - S = statin
  - A = ACEI/ARB
  - A = ASA/Antiplatelet
  - B = Beta-blocker

- **CLOPIDOGREL WITH ASPIRIN IN ACUTE MINOR STROKE OR TRANSIENT ISCHEMIC ATTACK [CHANCE]**

  **Objective**
  - For acute minor ischemic stroke or TIA, does early administration of ASA/clopidogrel reduce the rates of stroke compared to ASA monotherapy.

  **Methods**
  - Multicenter, randomized, placebo-controlled trial
  - N = 5170 (ASA = 2586; ASA/Plavix = 2584)
  - Setting: China in 114 centers
  - Enrollment: 2009-2012

  **GUSTO Criteria**
  - Minor – spontaneous gross hematuria, hematemesis, observed bleeding associated with fall in Hgb ≥3g/dl, Hct drop ≤15%
  - Moderate – Bleeding requiring transfusion
  - Severe – Fatal or ICH, or bleeding resulting in substantial hemodynamic compromise requiring treatment

**AT DISCHARGE**

- **Secondary Prevention**
  - Continue lisinopril 5mg
  - Add:
    - Metoprolol XL 50mg
    - Atorvastatin 40mg
    - ASA 81mg

  **What antiplatelet regimen should be started?**
  - A) ASA alone
  - B) ASA + Plavix 75mg
  - C) ASA/dipyridamole alone

**CHANCE - DESIGNS**


CHANCE - DESIGNS

Inclusion:
>40yo, NIHSS ≤3, ABCD2 ≥4, symptom onset ≤24hrs

Exclusion:
Evidence of/hx of hemorrhage, neuro changes w/o evidence of acute infarct, Rankin >2, other need for anticoagulation, GI bleed w/in 3 months, revascularization w/in 3 months, stroke caused by surgery, pregnancy, other investigational drug

Interventions:
Aspirin group - 75-300mg on day 1, then 75mg daily plus placebo clopidogrel
Aspirin/clopidogrel group - clopidogrel 300mg and aspirin 75-300mg on day 1, then clopidogrel 75mg daily, aspirin 75mg daily through day 21 and placebo aspirin was given thereafter


CHANCE - RESULTS

Outcomes:
Primary: Stroke at 90 days.
Secondary: MI, CV mortality, All-cause mortality, TIA

Statistical Analysis:
• 90% power to detect relative risk reduction of 22% with a two-sided alpha of 0.05
• Assuming an event rate of 14% in the aspirin group and a 5% overall rate of withdrawal
• Difference in stroke rate during 90 days assessed with Cox proportional-hazards model (95% confidence interval)


CHANCE - DISCUSSION

Strengths:
• Relatively large population size
• First trial to look at less severe stroke patients and DAPT use with in first few hours after index event
• Prevention of stroke efficacy was shown

Limitations:
• Chinese population only (CYP2C19)
• Bleding risk can’t be extrapolated due to polymorphisms
• Low percentage of patients with co-morbid conditions

2018 AHA/ASA GUIDELINES FOR EARLY MANAGEMENT OF PATIENTS WITH ACUTE ISCHEMIC STROKE

POWERS WJ, RABINSTEIN AA, ACKERSON T, ET AL.

STANCE ON ANTIPLATELET THERAPY

Focus on AIS:
- ASA within 24-48 hours after onset
  - Therapeutic benefit is similar across dosing range
  - If already on ASA at time of event?
    - Choose alternative antiplatelet?
      - Not well established
      - May reduce risk of CV events and recurrence

STANCE ON ANTIPLATELET THERAPY

Back to patients on ASA and what is recommended:
- Increasing the dose of aspirin?
  - Not well established
  - Risk vs Benefit

What if there is a history of ischemic stroke, atrial fibrillation, and/or coronary artery disease?
- Adding antiplatelet therapy?
  - Unstable angina and coronary artery stenting
  - May warrant dual antiplatelet.

STANCE ON ANTIPLATELET THERAPY

Minor stroke treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel)?
- Can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.
  - Generalizability?

STANCE ON ANTIPLATELET THERAPY

What happened to Aggrenox (ASA/dipyridamole)?
- No longer mentioned in the guidelines or recommended
  - High incidence of bleeding
  - Major adverse effect of headache
  - >50% discontinuation rate in patients taking Aggrenox

CLOPIDOGREL AND ASPIRIN IN ACUTE ISCHEMIC STROKE AND HIGH-RISK TIA [POINT]

JOHNSTON SC, EASTON JD, FARRANT M, ET AL. N ENGL J MED. 2018
**Objective**
Determine whether clopidogrel is effective in improving survival free from major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days when initiated within 12 hours of TIA or minor ischemic stroke onset in patients receiving aspirin.

**Methods**
Prospective, multicenter, randomized, double-blind, placebo-controlled trial

N = 4150 (ASA = 2432; ASA/Plavix = 2449) to 5860

Setting: North America, Europe, Australia, New Zealand (269 sites)
Enrollment: 2010-2017 (was supposed to run until Dec. 2018)

Interventions
- Aspirin group - 50-325mg daily
- Aspirin/clopidogrel group - clopidogrel 600mg and aspirin 50-325mg daily, then clopidogrel 75mg daily

Inclusion
- ≥18yrs, NIHSS ≤2, ABCD2 ≤4, randomize within 12 hours, head CT or MRI to r/o hemorrhage or other causes (vascular malformation, tumor or abscess)

Exclusion
- Candidate for thrombolysis or endovascular intervention, received thrombolysis with in 1 week prior, GI bleed within 3 months

**Outcomes**
- Primary: Composite endpoint of new ischemic vascular event (ischemic stroke, MI or ischemic vascular death) at 90 days.
- Secondary: As treated analysis of primary composite endpoint & major hemorrhage

**Statistical Analysis**
- 90% power to detect a relative risk reduction of 23% with a two-sided alpha of 0.05
- Two analysis were provided as an ITT and as-treated
- Secondary analysis compared treatment effect at 0-7 days, 8-90 days, 0-30 days and 31-90 days.

**Patient Population**
- 82.8% of the patients were in the U.S.
- Race: White 75.2%, Black 20%, Asian 3.3%, others 1.5%; Hispanic ethnic group 6.2%

**Baseline Characteristics**
- Age 65;
- Female 45%;
- PMH: HTN ~70%, DM 28%, ischemic heart disease 10.6%; Smoker 20%
- Mean time to randomization 7.4hrs
- TIA 43.4% (ABCD2 5);
- Minor stroke 56.6% (NIHSS 2)

**Results**
- 82.8% of the patients were in the U.S.
- Race: White 75.2%, Black 20%, Asian 3.3%, others 1.5%; Hispanic ethnic group 6.2%

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- TIA 43.4% (ABCD2 5);
- Minor stroke 56.6% (NIHSS 2)
**POINT – RESULTS**

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<thead>
<tr>
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<th>Control (ASA)</th>
<th>Intervention (ASA/Clopidogrel)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite Stroke</td>
<td>6.5% N=303</td>
<td>5% N=212</td>
<td>(HR 0.75; 95% CI 0.59-0.95; P=0.02) NNT = 67</td>
</tr>
<tr>
<td>Secondary Stroke</td>
<td>6.3% N=295</td>
<td>4.6% N=204</td>
<td>(HR 0.72; 95% CI 0.56-0.92; P=0.01)</td>
</tr>
<tr>
<td>Ischemic or hemorrhagic</td>
<td>6.4% N=307</td>
<td>4.8% N=216</td>
<td>(HR 0.74; 95% CI 0.58-0.94; P=0.01)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.4%</td>
<td>0.9%</td>
<td>Major—(HR 2.32; 95% CI 1.00-4.97; P=0.04) NNT=200</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>0.7%</td>
<td>Major other than ICH—(HR 2.45; 95% CI 1.20-4.59; P=0.04)</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>1.6%</td>
<td>Minor—(HR 3.12; 95% CI 1.67-5.83; P&lt;0.001)</td>
</tr>
</tbody>
</table>

Common reasons for discontinuation were provider decision due to patient being a candidate for prohibited medications, possible adverse effect or plan decision.

**POINT – SECONDARY RESULTS**

**Strengths**
- Similar inclusion and exclusion to CHANCE
- Similar discontinuation rate in both groups (~29%)
- As treated analysis helped, since the statistics were changed due to the event rate not meeting the required cut off for the population size

**Limitations**
- Long duration of DAPT may have contributed to the increased amount of bleeds.
- Reserve for appropriate population

**TRIAL COMPARISON**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MATCH</th>
<th>CHANCE</th>
<th>POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from index event</td>
<td>≤ 3 months (19% within 7 days)</td>
<td>≤ 24 hours (mean 13 hours)</td>
<td>≤ 12 hours (mean 7.4 hours)</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>66</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>Previous AIS (%)</td>
<td>27</td>
<td>20</td>
<td>excluded</td>
</tr>
<tr>
<td>Previous TIA (%)</td>
<td>19</td>
<td>3</td>
<td>excluded</td>
</tr>
<tr>
<td>Excluded thrombolysis or clot extraction candidates?</td>
<td>No mention (included high risk patients)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>21</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td>AIS (%)</td>
<td>79</td>
<td>72</td>
<td>57</td>
</tr>
</tbody>
</table>
TRIAL COMPARISON

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>CHANCE</th>
<th>POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average ABCD</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Average NIHSS</td>
<td>0.2 (7%)</td>
<td>3 (15%)</td>
<td>4.5 (12%)</td>
</tr>
<tr>
<td>Rankin &gt;2</td>
<td>None</td>
<td>None</td>
<td>2</td>
</tr>
</tbody>
</table>

Intervention
- Clopidogrel/ASA vs. clopidogrel
- Clopidogrel/ASA vs. ASA
- Clopidogrel/ASA vs. ASA

% of new event(s)
- 16 vs. 17

% of severe bleed(s)
- 0.2 vs. 0.2
- 0.9 vs. 0.4

REVISIT PATIENT DA

54 yo male presented with CP, left facial droop, left sided weakness, and mild slurred speech after his morning jog.

Treated appropriately in the hospital and did not receive t-PA.

For home she continued and received:
- S = statin → atorvastatin 40mg
- A = ACEI/ARB → lisinopril 5mg
- A = ASA/Antiplatelet → ASA 81mg
- B = Beta-Blocker → Metoprolol 50mg XL

WHAT IS THE POINT?

- Time and duration of DAPT with clopidogrel + ASA may improve outcomes in preventing recurrent stroke.
- MATCH vs CHANCE vs POINT
- Sub-populations may benefit from DAPT
- Weigh risk and benefit of ischemia and thrombosis/bleeding

UPCOMING TRIALS

- Articulate TMP16: Efficacy and Safety of Ticagrelor in Relation to Time to Loading Dose in the SOCRATES Trial. —> pre-specified exploratory analysis, ticagrelor showed a greater treatment effect over aspirin in patients with TLD <12 h
- THALES Trial: Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death
  - To demonstrate superior efficacy of ticagrelor and ASA compared with placebo and ASA in AIS/TIA patients in the prevention of the composite of stroke and death at 30 days

REFERENCES


Should We Take a CHANCE or Is There a POINT

Subtitle: A Dive into the use of Clopidogrel and Aspirin for TIA and AIS.