Aspirin Plus Clopidogrel Combination Therapy: A New Era in Stroke Prevention?

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September 30th, 2016
Objectives

- Provide an overview of stroke and the AHA/ASA Guidelines on using aspirin plus clopidogrel combination therapy in secondary stroke prevention
- Review stroke prevention and the role of antiplatelet therapy
- Evaluate clinical evidence on the use combination therapy in secondary stroke prevention
- Determine place in therapy of combination therapy in post-stroke patients

Epidemiology

- In the US, there are 795,000 new and recurrent strokes annually - 87% ischemic, 13% hemorrhagic
- There are about 610,000 first occurrences of stroke and 185,000 recurrent strokes per year
- Stroke is considered a leading cause of morbidity and the third leading cause of death in the United States

Ischemic Stroke Subtypes

- Atherosclerosis
  - Occlusion of intra- and extra-cranial arteries
  - Thrombus as common cause
- Stenosis
  - Narrowing of vessel lumen
  - Hypertension, smoking, diabetes as common cause
  - Lacunar infarcts - small artery stenosis
- cardioembolic
  - Commonly caused by atrial fibrillation
  - Thrombi dislodge and occlude blood vessel

Pathophysiology

- Hemorrhagic Stroke
  - Blood leaks into brain tissue
- Ischemic Stroke
  - Blood clots stop the flow of blood to an area of the brain

Transient Ischemic Attack

- Temporary blockage by a clot
- Symptoms occur quickly and resolve within 24 hours
- Usually causes no permanent injury to brain
Role of Antiplatelet Therapy

- Prevention of platelet activation and aggregation
- Acute management of stroke
- Secondary prevention of stroke
  - ASA monotherapy
  - Clopidogrel monotherapy
  - ASA/dipyridamole
  - ASA/clopidogrel?

Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>ASA</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irreversibly inhibit (COX-1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors</td>
<td>Irreversibly blocks P2Y12 component of ADP receptors on platelet surface, reducing platelet aggregation</td>
</tr>
<tr>
<td>Dose</td>
<td>50 - 325 mg daily</td>
<td>Loading dose 300 - 600 mg 75 mg maintenance</td>
</tr>
<tr>
<td>Time to Peak Effect</td>
<td>1 - 2 hours</td>
<td>Loading dose: 24 hours Maintenance dose: 5 - 7 days</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic conjugation with glucuronic acid</td>
<td>CYP2C19 Effectiveness depends on activation of the prodrug to active metabolite</td>
</tr>
<tr>
<td>Adverse Drug Reactions</td>
<td>Increased risk of bleeding Upset stomach</td>
<td>Increased risk of bleeding Epistaxis</td>
</tr>
</tbody>
</table>

2014 AHA/ASA Guidelines

Noncardioembolic Stroke or TIA

- The combination of ASA/clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation of 90 days (Class IIb, LOE B) NEW RECOMMENDATION

Severe Stenosis of Major Artery

- In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70-99%) of major intracranial artery, the addition of clopidogrel 75 mg/d to ASA for 90 days might be reasonable (Class IIb, LOE B) NEW RECOMMENDATION

Clinical Question:

What is the role of ASA/clopidogrel combination in secondary stroke prevention?
Patient Population

Inclusion

- Ischemic stroke or TIA in the previous 3 months
- ≥ 1 risk factors within previous 3 years
  - History of ischemic stroke
  - History of myocardial infarction
  - Angina pectoris
  - Diabetes
  - Symptomatic peripheral arterial disease

Exclusion

- < 40 years old
- Increased risk of bleeding
- Severe comorbidities
- Scheduled for major surgery
- Contraindicated to ASA or clopidogrel
- Ischemic stroke or TIA in the previous 3 months
- ≥ 3 risk factors within previous 3 years
  - History of ischemic stroke
  - History of myocardial infarction
  - Angina pectoris
  - Diabetes
  - Symptomatic peripheral arterial disease

Methods

N = 7599

N = 3797
ASA/clopidogrel

N = 3802
Placebo/clopidogrel

- All patients received clopidogrel 75 mg once daily for 18 months
- ASA 75 mg once daily or placebo
- Mean time to randomization was 26.5 days

No difference between two groups in baseline characteristics*

- 60% of patients → small-vessel stenosis
- 40% of patients → large-artery atherosclerosis

*Appendix Page 1

Results

<table>
<thead>
<tr>
<th></th>
<th>ASA /Clopidogrel (N = 3797)</th>
<th>Clopidogrel (N = 3802)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome*</td>
<td>586 (16%)</td>
<td>636 (17%)</td>
<td>0.244</td>
</tr>
<tr>
<td>Secondary Outcome</td>
<td>201 (5%)</td>
<td>201 (5%)</td>
<td>0.992</td>
</tr>
<tr>
<td>Safety – N (%)</td>
<td>339 (9%)</td>
<td>347 (9%)</td>
<td>0.790</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>73 (2%)</td>
<td>22 (1%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>120 (3%)</td>
<td>39 (1%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Author’s Conclusion:

- Addition of ASA to clopidogrel in high-risk patients with recent ischemic stroke or TIA did not reduce major vascular events
- Risk of life-threatening or major bleeding is increased by adding ASA

Clinical Question:

What is the role of stroke subtypes in secondary stroke prevention?

Study Critiques

- Well-designed, multicenter, randomized control trial
- Well-balanced baseline characteristics
- Included high-risk patients
- Long follow-up period
- Large sample size
- Majority of patient suffered from small-vessel stenosis
- Excluded patients with increased risk of bleeding
- Did not meet power (N = 7600 for 80% power vs. N = 7599 enrolled)

Effects of Clopidogrel Added to ASA in Recent Lacunar Stroke (SPS3*)

Design: Prospective, multicenter, double-blind, randomized-controlled trial

Methods:

- 3020 patients → clopidogrel 75 mg/d + ASA 325 mg/d vs. ASA 325 mg/d x 3 month
- Primary endpoint: stroke recurrence
- Median time to randomization: 62 days

Results:

- Risk of recurrent stroke was not significantly reduced with ASA/clopidogrel, p = 0.48
- All-cause mortality was increased among ASA/clopidogrel, p = 0.004
- Risk of hemorrhage almost doubled with ASA/clopidogrel, p < 0.001

Conclusion:

- ASA/clopidogrel was not significantly more effective than ASA in reducing rate of MI, stroke, or death from CVD causes and significantly increased bleeding risk

Limitations:

- Limited generalization to general stroke patient population
- Usage of higher ASA dose can result in higher bleeding risk

*Appendix Pages 1, 2, 3
Clinical Question:
What is the role of time of initiation of ASA/clopidogrel therapy in secondary stroke prevention?

[Image of a slide with a blue background and text]

CHANCE Study Overview

Objective
• Assess whether ASA/clopidogrel initiated soon after TIA or minor stroke could reduce early risk of stroke

Design
• Randomized, double-blind, multicenter trial
• Conducted from 2009-2012 at 114 centers in China

Endpoint
• Primary: stroke occurrence during 90 day follow up
• Secondary: new clinical vascular event

Patient Population

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 ≥ 40 years old</td>
<td>Patients with hemorrhage, vascular malformation, tumor, abscess, or other nonischemic brain disease</td>
</tr>
<tr>
<td>Diagnosis of an acute minor stroke</td>
<td>Isolated sensory symptoms</td>
</tr>
<tr>
<td>TIA</td>
<td>Isolated visual changes or isolated dizziness or vertigo without evidence of acute infarction</td>
</tr>
<tr>
<td>Focal brain ischemic with resolution of symptoms within 24 hours after onset</td>
<td>History of intracranial hemorrhage</td>
</tr>
<tr>
<td>Moderate to high risk of stroke ( neuroscience ABCD² ≥ 4)</td>
<td>On long-term therapy affect platelet function</td>
</tr>
<tr>
<td>Ability to start treatment within 24 hours after symptoms onset</td>
<td>GI bleeding or major surgery without previous 3 months</td>
</tr>
</tbody>
</table>

Methods

Total 41561 patients were screened
Randomized 1:1
N = 5170
N = 2584
ASA/clopidogrel
ASA

Results

<table>
<thead>
<tr>
<th>ASA / Clopidogrel (N = 2584)</th>
<th>ASA (N = 2586)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome – N, %</td>
<td>212 (8.2)</td>
<td>303 (11.7)</td>
</tr>
<tr>
<td>Secondary Outcome – N, %</td>
<td>216 (8.4)</td>
<td>307 (11.9)</td>
</tr>
<tr>
<td>Stroke, MI, or death from CVD</td>
<td>204 (7.9)</td>
<td>295 (11.4)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>8 (0.3)</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>10 (0.4)</td>
<td>10 (0.4)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>39 (1.5)</td>
<td>47 (1.8)</td>
</tr>
<tr>
<td>Safety – N, %</td>
<td>60 (2.3)</td>
<td>41 (1.6)</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>4 (0.2)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>3 (0.1)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>10 (0.4)</td>
<td>10 (0.4)</td>
</tr>
<tr>
<td>Mild bleeding</td>
<td>30 (1.2)</td>
<td>19 (0.7)</td>
</tr>
</tbody>
</table>

Results – Stroke Free Survival

[Graph showing stroke free survival]
Author’s Conclusion

• In patients with high-risk TIA or minor ischemic stroke, ASA/clopidogrel combination is superior to ASA for reducing recurrent stroke within 90 days
• ASA/clopidogrel did not cause more hemorrhagic events than ASA alone

Study Critiques

- Well-designed, multicenter, randomized control trial
- Well-balanced baseline characteristics
- Included patients at high risk for recurrent stroke
- Sufficiently powered
- Large sample size
- Lack of generalizability
- Conducted in China where rate of stroke is higher
- Higher rate of CYP2C19 polymorphism in China
- Excluded patients with increased risk of bleeding
- Relatively short follow-up

CHANCE: CYP2C19 Subgroup

• Objective: Estimate association between CYP2C19 genetic variants and outcomes
• Method: CYP2C19 alleles were genotyped among 2933 patients enrolled
• Primary outcome: New stroke
• Results:
  – Combination reduced rate of events in non-carriers but not in carriers of genetic polymorphism, \( p = 0.02 \)
  – Bleeding rate did not vary significantly, \( p = 0.78 \)
• Conclusion: Combination reduced risk of new stroke after 90 days in those who were non-carriers of genetic polymorphism

CHANCE: Time to Randomization Subgroup

• Objective: Analyze benefits associated with combination therapy if administered \( \leq 12 \) hours
  – Randomized \( \leq 12 \) hours was independent predictor of ischemic stroke
• Method: Pre-specified group of patients randomized \( \leq 12 \) hours
• Primary outcome: Ischemic stroke during 90-day follow-up
• Results:
  – 12.34% ASA vs. 9.59% combination experienced recurrent ischemic stroke, \( p = 0.02 \)
  – No difference detected in hemorrhagic events, \( p = 0.29 \)
• Conclusion: Among patients treated within 12 hours, combination was more effective in reducing recurrent ischemic stroke risk

Future Direction – POINT Trial

- A prospective, randomized, multicenter, double-blinded, placebo-controlled trial (N = 4150) at 210 centers in US and worldwide
- Inclusion criteria:
  - \( \geq 18 \) years of age
  - High-risk TIA, defined ABCD2 score \( \geq 4 \)
  - Minor ischemic stroke with NIHSS score \( \leq 3 \)
- Primary endpoint: Composite of new ischemic vascular events (ischemic stroke, MI or ischemic vascular death) by 90 days
- Study regimens:
  - Clopidogrel 600 mg load, 75 mg/d vs. matching placebo x 90 days
  - ASA 162 mg/d x 5 days, 81 mg/d x 85 days
  - Randomized within 12 hours after symptom onset
  - Anticipated results by 2017

Impact of the Trial:

- First trial conducted outside of China looking at use of ASA/clopidogrel in patients after TIA or minor ischemic stroke
- Administration of therapy within 12 hours of symptoms onset
- Longer duration of ASA/clopidogrel therapy for 90 days

Trial Summary

- ASA/clopidogrel therapy confers no additional benefit and increases bleeding risk
  - MATCH
  - SPS3
- Benefit is observed when ASA is added to clopidogrel within 24 hours after acute minor stroke or TIA without increased bleeding risk
  - CHANCE
Noncardioembolic Stroke or TIA
• The combination of ASA/clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation of 90 days (Class IIb, LOE B) NEW RECOMMENDATION

Severe Stenosis of Major Artery
• In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70-99%) of major intracranial artery, the addition of clopidogrel 75 mg/d to ASA for 90 days might be reasonable (Class IIb, LOE B) NEW RECOMMENDATION

Clinical Question:
What is the role of ASA/clopidogrel therapy in prevention of severe stroke due to stenosis of major artery?

WASID
Objective
• Compare ASA versus warfarin in patients with intracranial stenosis for stroke prevention

Method
• TIA or stroke caused by 50 - 99% stenosis of major artery
• 569 patients → warfarin (INR 2 - 3) vs. ASA 1300 mg/d
• Primary endpoint: ischemic stroke, hemorrhage, death

Results
• Primary endpoint: 22.1% ASA vs. 21.8% warfarin, p = 0.83
• Warfarin associated with higher rates of death
• 9.7% warfarin vs. 4.3% ASA, p = 0.02

Conclusion
• ASA should be used in preference to warfarin for intracranial stenosis of major artery patients

Aggressive Medical Treatment with or without Stenting in High-Risk Patients with Intracranial Artery Stenosis (SAMMPRIS*)

Design: A prospective, randomized, multicenter, superiority trial

Methods:
• 451 patients → medical treatment (N = 227) vs. PTAS + medical treatment (N = 224)
• Medical treatment → ASA 325 mg/d x 3 yrs + Clopidogrel 75 mg/d x 90 days
• Primary endpoint: composite endpoint of stroke or death during follow-up*

Results:
• 15% in medical group vs. 23% in stenting had primary endpoint event, p = 0.0252
• Occurrence of major hemorrhage was higher in PTAS/medical treatment, p = 0.0009

Conclusion:
• Aggressive medical treatment is superior to PTAS for high-risk patients with intracranial stenosis of major artery over extended follow-up

Limitations:
• Trial cannot be double-blinded
• Usage of higher ASA dose can result in higher bleeding risk

Trial Summary
• ASA is preferred for intracranial stenosis of major artery
  • WASID
• Medical treatment (ASA/clopidogrel) is preferred over medical treatment plus PTAS
  • SAMMPRIS

Both WASID and SAMMPRIS had similar inclusion criteria
• WASID: 30-day stroke rate and death of 10.7%
• SAMMPRIS: 30-day stroke rate and death of 5.8%
• Substantially lower stroke and death rate in SAMMPRIS suggests benefit of ASA/clopidogrel

Clinical Application
Bring It Back to the Guidelines

<table>
<thead>
<tr>
<th>Guideline Recommendation</th>
<th>Supporting Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>The combination of ASA/clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation of 90 days</td>
<td>• CHANCE</td>
</tr>
<tr>
<td>In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70-99%) of major intracranial artery, the addition of clopidogrel 75 mg/d to ASA for 90 days might be reasonable</td>
<td>• WASID</td>
</tr>
<tr>
<td>• SAMMPRIS</td>
<td>• Not a head-to-head trial comparing medical treatment</td>
</tr>
</tbody>
</table>

Place in Therapy

- Conflicting results and limitations among various trials
- Consider individual patient characteristics
  - Important to weigh benefit vs. risk
  - Types of stroke
  - Timing of initiation
- Consider duration of combination therapy
  - Unclear of appropriate duration for minor stroke or TIA
  - 90-day duration for severe stenosis of major artery
- Future studies are warranted

Conclusion

ASA/clopidogrel therapy can be considered if patient meets the following:

- Minor stroke or TIA
  - Within 24 hours after symptom onset
  - Low bleeding risk
  - Continue ASA/clopidogrel for 21 days
- Severe stroke due to 70-99% stenosis of major artery
  - Within past 30 days
  - Low bleeding risk
  - Continue ASA/clopidogrel for 90 days

Final Thoughts

- As one of the most detrimental diseases, risk of recurrent stroke is highest after an acute ischemic stroke or TIA
- Use of antiplatelet therapy is crucial for secondary prevention of stroke
- The 2014 ASA/AHA Guidelines state ASA/clopidogrel therapy can be considered for acute minor stroke, TIA or severe stroke due to stenosis of major artery
- Current trials have shown conflicting evidence on effectiveness of ASA/clopidogrel therapy
- Important to consider patients individually and weigh benefit versus risks when considering ASA/clopidogrel therapy

Acknowledgement

- Tamara Knight, PharmD, BCPS
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- Lydia Chen, PharmD, BCPS
- Fellow Co-Residents

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Appendices – Aspirin Plus Clopidogrel Combination Therapy: A New Era in Stroke Prevention?

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2. MATCH Baseline Characteristics
3. MATCH Results – Primary Outcome
4. SPS3 Trial Enlargement
5. SPS3 Patient Population
6. SPS3 Baseline Characteristics
7. CHANCE Exclusion Criteria
8. CHANCE Exclusion Criteria
9. CHANCE Baseline Characteristics
10. National Institute of Health Stroke Scale
11. Modified Rankin Scale
12. ABCD² Score
13. SAMMPRIS Trial Enlargement
14. SAMMPRIS Patient Population
15. SAMMPRIS Baseline Characteristics
16. SAMMPRIS Primary Endpoint
17. Abbreviations
**Guideline Recommendation**

<table>
<thead>
<tr>
<th>Level of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong>: treatment should be performed</td>
<td><strong>A</strong>: multiple randomized clinical trials or meta-analyses</td>
</tr>
<tr>
<td><strong>Class IIa</strong>: it is reasonable to perform treatment</td>
<td><strong>B</strong>: single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td><strong>Class IIb</strong>: treatment may be considered</td>
<td><strong>C</strong>: expert opinions</td>
</tr>
<tr>
<td><strong>Class III</strong>: treatment is not effective and may be harmful</td>
<td></td>
</tr>
</tbody>
</table>

Kernan WN, et al. *Stroke* 2014;45:1-77
<table>
<thead>
<tr>
<th></th>
<th>ASA/Clopidogrel (N = 3797)</th>
<th>Clopidogrel (N = 3802)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) age (years)</strong></td>
<td>66.5 (9.9)</td>
<td>66.1 (9.9)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>1415 (37%)</td>
<td>1406 (37%)</td>
</tr>
<tr>
<td><strong>Transient ischemic attack (TIA)</strong></td>
<td>797 (21%)</td>
<td>808 (21%)</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong></td>
<td>3000 (79%)</td>
<td>2994 (79%)</td>
</tr>
<tr>
<td><strong>Stroke Subtypes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>1019 (34%)</td>
<td>1020 (34%)</td>
</tr>
<tr>
<td>Small-vessel occlusion</td>
<td>1590 (53%)</td>
<td>1558 (52%)</td>
</tr>
<tr>
<td><strong>Modified Rankin Scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None to slight disability (0-2)</td>
<td>2197 (73%)</td>
<td>2201 (74%)</td>
</tr>
<tr>
<td>Moderate disability (3)</td>
<td>455 (15%)</td>
<td>426 (14%)</td>
</tr>
<tr>
<td><strong>Risks Factors and Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>14 (24%)</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>39 (66%)</td>
<td>40 (68%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>36 (61%)</td>
<td>33 (56%)</td>
</tr>
</tbody>
</table>

MATCH Results – Primary Outcome

Number of patients with Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin + Clopidogrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>59</td>
<td>62</td>
</tr>
<tr>
<td>Stroke</td>
<td>299</td>
<td>319</td>
</tr>
<tr>
<td>Other Vascular Death</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>169</td>
<td>181</td>
</tr>
</tbody>
</table>

## Effects of Clopidogrel Added to ASA in Recent Lacunar Stroke (SPS3*)

**Design:** Prospective, randomized, multicenter, double-blind, placebo-controlled trial

**Methods:**
- 3020 patients → clopidogrel 75 mg/d + ASA 325 mg/d vs. ASA 325 mg/d × 3 month
- **Primary endpoint:** stroke recurrence
- Median time to randomization: 62 days

**Results:**
- Risk of recurrent stroke was not significantly reduced with ASA/clopidogrel, \( p = 0.48 \)
- All-cause mortality was increased among ASA/clopidogrel, \( p = 0.004 \)
- Risk of hemorrhage almost doubled with ASA/clopidogrel, \( p < 0.001 \)

**Conclusion:**
- ASA/clopidogrel was not significantly more effective than ASA in reducing rate of MI, stroke, or death from CVD causes and significantly increased bleeding risk

**Limitations:**
- Limited generalization to general stroke patient population
- Usage of higher ASA dose can result in higher bleeding risk

# SPS3 Patient Population

<table>
<thead>
<tr>
<th><strong>Inclusion</strong></th>
<th><strong>Exclusion</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- ≥ 30 years old with symptomatic lacunar stroke in preceding 180 days</td>
<td>- Patients with MRI evident of large subcortical infarct</td>
</tr>
<tr>
<td>- ≥ 1 lacunar stroke clinical syndromes lasting &gt; 24 hrs or subcortical TIA</td>
<td>- Surgically amendable ipsilateral carotid artery disease</td>
</tr>
<tr>
<td>- MRI evidence of small subcortical stroke</td>
<td>- History of intracerebral hemorrhage</td>
</tr>
<tr>
<td>- Did not have major risk factors for cardioembolic source of stroke</td>
<td>- Disabling stroke (modified Rankin Score ≥ 4)</td>
</tr>
<tr>
<td></td>
<td>- Contraindicated to receive ASA or clopidogrel</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy or women of child-bearing potential</td>
</tr>
<tr>
<td></td>
<td>- Concurrent participation in another investigational study</td>
</tr>
<tr>
<td></td>
<td>- Other likely cause of stroke</td>
</tr>
<tr>
<td></td>
<td>- Ipsilateral cervical carotid stenosis ≥ 50%</td>
</tr>
</tbody>
</table>

## SPS3 - Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASA/Clopidogrel (N = 1517)</th>
<th>ASA (N = 1503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>62</td>
<td>64</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Mean BP at screening visit (mm Hg)</td>
<td>143/78</td>
<td>143/78</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Use of statin at follow-up visit (%)</td>
<td>84</td>
<td>85</td>
</tr>
<tr>
<td><strong>Qualifying event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke (%)</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Type of lacunar syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure motor hemiparesis (%)</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Pure sensory stroke (%)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sensorimotor stroke (%)</td>
<td>32</td>
<td>30</td>
</tr>
</tbody>
</table>
CHANCE – Exclusion Criteria

- Patients with hemorrhage, vascular malformation, tumor, abscess, or other nonischemic brain disease
- Isolated sensory symptoms
- Isolated visual changes or isolated dizziness or vertigo without evidence of acute infarction
- Modified Rankin scale $\geq 2$ or NIHSS $\geq 4$
- Clear indication for anticoagulation or contraindication to clopidogrel or ASA
- History of intracranial hemorrhage
- On long-term therapy affect platelet function
- Heparin or oral anticoagulant therapy within 10 days before randomization
- GI bleeding or major surgery without previous 3 months
- TIA or minor stroke caused by surgery

CHANCE – Exclusion Criteria

- Planned or probable revascularization within 3 months after screening
- Anticipated requirement for long-term non-study antiplatelet drugs or for nonsteroidal anti-inflammatory drugs affecting platelet function
- Planned surgery or intervention treatment requiring cessation of the study drug
- TIA or minor stroke caused by angiography or surgery
- Severe non-cardiovascular coexisting condition with a life expectancy of less than 3 months
- Women of childbearing age who were not practicing reliable contraception and did not have documented negative pregnancy test
- Patient receiving other investigational drugs or devices

## CHANCE - Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ASA/Clopidogrel (N = 2584)</th>
<th>Clopidogrel (N = 2586)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>33</td>
<td>34.7</td>
</tr>
<tr>
<td>Time to randomization (hr)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>66.4</td>
<td>65.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>21.3</td>
<td>21</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Qualifying event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor stroke (%)</td>
<td>72.3</td>
<td>71.8</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>27.7</td>
<td>28.2</td>
</tr>
<tr>
<td>Median ABCD² score</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Median systolic BP (mm Hg)</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Median diastolic BP (mm Hg)</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

National Institute of Health Stroke Scale

• Assessment of stroke severity
  – Scale (0 to 42)
  – Can be used to assess neurologic deficits

• Score is based on:
  – Level of consciousness
  – Motor function
  – Sensory function
  – Language ability

Modified Rankin Scale

- Measure severity of disability or to perform daily activities in post-stroke patients
- Used for clinical outcome measure
  - Score 0 – 2: no or slight disability
  - Score 3: moderate disability
  - Score 4: moderately severe disability
  - Score 5: severe disability
  - Score 6: death

ABCD$^2$ Score

- Risk assessment designed to predict short-term stroke risk after TIA
  - Score optimized to within 2 days after TIA and stroke risk within 90 days
- Calculated based on 5 independent factors (scale 0 – 7)
  - Age, ≥ 60 years old
  - Blood pressure, SBP ≥ 140 mm Hg OR DBP ≥ 90 mm Hg
  - Clinical features of TIA, unilateral weakness OR speech impairment
  - Duration, TIA ≥ 60 min OR 10-59 min
  - Diabetes

<table>
<thead>
<tr>
<th>ABCD$^2$ Score</th>
<th>2-day Stroke Risk</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>1.0%</td>
<td>Hospital observation may be unnecessary without another indication (e.g., new atrial fibrillation)</td>
</tr>
<tr>
<td>4-5</td>
<td>4.1%</td>
<td>Hospital observation justified in most situations</td>
</tr>
<tr>
<td>6-7</td>
<td>8.1%</td>
<td>Hospital observation worthwhile</td>
</tr>
</tbody>
</table>

**Aggressive Medical Treatment with or without Stenting in High-Risk Patients with Intracranial Artery Stenosis (SAMMPRIS*)**

**Design:** A prospective, randomized, multicenter, superiority trial

**Methods:**
- 451 patients → medical treatment (N = 227) vs. PTAS + medical treatment (N = 224)
- Medical treatment → ASA 325 mg/d x 3 yrs + Clopidogrel 75 mg/d x 90 days
- **Primary endpoint:** composite endpoint of stroke or death during follow-up*

**Results:**
- 15% in medical group vs. 23% in stenting had primary endpoint event, \( p = 0.0252 \)
- Occurrence of major hemorrhage was higher in PTAS/medical treatment, \( p = 0.0009 \)

**Conclusion:**
- Aggressive medical treatment is **superior** to PTAS for high-risk patients with intracranial stenosis of major artery over extended follow-up

**Limitations:**
- Trial cannot be double-blinded
- Usage of higher ASA dose can result in higher bleeding risk

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SAMMPRIS Patient Population

**Inclusion**

- 30 – 80 years old
- Had non-disabling stroke or TIA within 30 days before enrollment that attributed to 70-99\% atherosclerotic stenosis of major intracranial artery

**Exclusion**

- Tandem extracranial or intracranial stenosis proximal or distal to the target intracranial stenosis
- Intraluminal thrombus proximal to or at the target lesion
- Progressive neurologic signs within 24 hours before enrollment
- Any hemorrhagic infarct within 14 days before enrollment
- Non-atherosclerotic causes of intracranial stenosis
- Presence of cardiac source of embolus

## SAMMPRIS - Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Medical (N = 227)</th>
<th>Medical + PTAS (N = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>59.5</td>
<td>61</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>89</td>
<td>89</td>
</tr>
<tr>
<td>History of lipid disorder (%)</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Mean systolic BP (mm Hg)</td>
<td>146.8</td>
<td>143.9</td>
</tr>
<tr>
<td>Median time from qualifying event to randomization (days)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Stenosis of symptomatic qualifying event (%)</td>
<td>81</td>
<td>80</td>
</tr>
</tbody>
</table>

**Qualifying event**

- Stroke (%) 67 63
- TIA (%) 33 37

SAMMPRIS Primary Endpoint

- Stroke or death within 30 days after enrollment
- Ischemic stroke in territory of qualifying artery ≥ 30 days of enrollment
- Stroke or death within 30 days after revascularization procedure

Abbreviations (Arranged Alphabetically):

- **ABCD²**: Age, Blood Pressure, Clinical Features, Duration of TIA, and Presence of Diabetes
- **ADP**: adenosine diphosphate
- **AHA/ASA**: American Heart Association/American Stroke Association
- **ASA**: aspirin
- **BP**: blood pressure
- **CHANCE**: Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack
- **COX**: cyclooxygenase
- **CV**: cardiovascular
- **CVD**: cardiovascular disease
- **CYP2C19**: cytochrome P450 2C19
- **GI**: gastrointestinal
- **LOE**: level of evidence
- **MATCH**: Aspirin and Clopidogrel Compared with Clopidogrel Alone After Recent Ischemic Stroke or Transient Ischemic Attack in High-risk Patients
- **MI**: myocardial infarction
- **NIHSS**: National Institute of Health Stroke Scale
- **P2Y12**: platelet P2Y12 receptor
- **POINT**: Plate-oriented Inhibition in New TIA and Minor Ischemic Stroke
- **PTAS**: percutaneous transluminal angioplasty and stent
- **SD**: standard deviation
- **TIA**: transient ischemic attack
- **WASID**: Comparison of Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis