Update on Stroke Therapies

Those Darn Randomized Trials

7 Sep 2013
Gary S Gronseth, MD, FAAN
Professor of Neurology
University of Kansas
Therapy/Narrow[filter] AND ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields])) OR "cerebrovascular disorders"[All Fields] OR ("cerebrovascular"[All Fields] AND "disease"[All Fields]) OR "cerebrovascular disease"[All Fields])
Internal Validity

External Validity

Randomize

Active

Control

Good

Poor

Patients

Intervention

Comparator

Outcome
Stroke Prevention

• Primary: Preventing the first stroke
  “Asymptomatic patient”

• Secondary: Preventing recurrence
  “Symptomatic patient”

• Tertiary: Minimizing damage
  “Acute stroke patient”

• Quaternary: Maximizing function
  “Post stroke patient”
• The USPSTF recommends the use of aspirin for men age 45 to 79 years when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage. Go to the Clinical Considerations section for discussion of benefits and harms. Grade: A recommendation.

• The USPSTF recommends the use of aspirin for women age 55 to 79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage. Go to the Clinical Considerations section for discussion of benefits and harms. Grade: A recommendation.

• The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of aspirin for cardiovascular disease prevention in men and women 80 years or older. Grade: I statement.

• The USPSTF recommends against the use of aspirin for stroke prevention in women younger than 55 years and for myocardial infarction prevention in men younger than 45 years. Grade: D recommendation.
Women’s Heath Study

**Randomize**

**Active**
- 19934

**Control**
- 19942

**Ischemic Stoke**

- 0.8%
- 1%

**Follow-up** 97.2%

**RR 0.8 (0.65 to 0.98)**

**P:** US female healthcare professionals

**I:** ASA 100 mg qod

**C:** No ASA

**O:** Stroke TIA
- Stroke severity
- 10 Years
Women’s Health Study

Total Stroke

Aspirin (N=391)

Placebo (N=474)

Legend:
- TIA
- mRS 0-1
- mRS 2-3
- mRS 4-6
Stroke Prevention

- **Primary:** Preventing the first stroke
  “Asymptomatic patient”
- **Secondary:** Preventing recurrence
  “Symptomatic patient”
- **Tertiary:** Minimizing damage
  “Acute stroke patient”
- **Quaternary:** Maximizing function
  “Post stroke patient”
# Selecting an Antithrombotic

**AHA Guideline 2010**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class/Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce risk of recurrent stroke and other cardiovascular events <em>(Class I; Level of Evidence A)</em>.</td>
<td>Class I; Level A</td>
</tr>
<tr>
<td>Aspirin (50 mg/d to 325 mg/d) monotherapy <em>(Class I; Level of Evidence A)</em>, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily <em>(Class I; Level of Evidence B)</em>, and clopidogrel 75 mg monotherapy <em>(Class Ila; Level of Evidence B)</em> are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.</td>
<td>Class I; Level A; Class I; Level B; Class Ila; Level B</td>
</tr>
<tr>
<td>The addition of aspirin to clopidogrel increases risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA <em>(Class III; Level of Evidence A)</em>.</td>
<td>Class III; Level A</td>
</tr>
<tr>
<td>For patients allergic to aspirin, clopidogrel is reasonable <em>(Class Ila; Level of Evidence C)</em>.</td>
<td>Class Ila; Level C</td>
</tr>
<tr>
<td>For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin <em>(Class IIb; Level of Evidence C)</em>.</td>
<td>Class IIb; Level C</td>
</tr>
</tbody>
</table>
Clopidogrel plus ASA

CAPRIE

CHARISMA

MATCH

Plavix

Plavix & ASA
Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*

DOI: 10.1056/NEJMoa1204133
Recent symptomatic lacunar infarct

Clopidogrel 75mg & ASA 325mg

ASA 325 mg

Recurrent Stroke 3.4 years
Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial

James Kennedy, Michael D Hill, Karla J Ryckborst, Michael Eliaziw, Andrew M Demchuk, Alastair M Buchan, for the FASTER Investigators*

<table>
<thead>
<tr>
<th></th>
<th>Risk ratio (95% CI)</th>
<th>Events, treatment</th>
<th>Events, control</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASTER</td>
<td>0.68 (0.44-1.04)</td>
<td>29/198</td>
<td>42/194</td>
<td>93.10</td>
</tr>
</tbody>
</table>

Favours dual antiplatelet therapy  Favours single antiplatelet therapy
Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators*
CHANCE

Randomize

Clopidogrel (75 mg) plus ASA (75 mg)

ASA (75 mg alone)

P: Minor Ischemic stroke/TIA < 24 hours
I: Clopidogrel (75 mg) plus ASA (75 mg)
C: ASA (75 mg alone)
O: Stroke at 90 days

<table>
<thead>
<tr>
<th></th>
<th>Clop &amp; ASA</th>
<th>ASA alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>8.2%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Bleed</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

2584

2586

16

20
CHANCE

Survival Free of Stroke

Days since Randomization

Hazard ratio, 0.68 (95% CI, 0.57–0.81)
P<0.001
Intracranial Artery Stenosis

• RCT Evidence
  – Warfarin no better than ASA
    • WARSS
    • WAISD
  – EC-IC bypass ineffective
    • EC-IC bypass study 1985
    • COSS 2010
Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Colin P. Derdeyn, M.D., Tanya N. Turan, M.D., David Fiorella, M.D., Ph.D., Bethany F. Lane, R.N., L. Scott Janis, Ph.D., Helmi L. Lutsep, M.D., Stanley L. Barnwell, M.D., Ph.D., Michael F. Waters, M.D., Ph.D., Brian L. Hoh, M.D., J. Maurice Hourihane, M.D., Elad I. Levy, M.D., Andrei V. Alexandrov, M.D., Mark R. Harrigan, M.D., David Chiu, M.D., Richard P. Klucznik, M.D., Joni M. Clark, M.D., Cameron G. McDougall, M.D., Mark D. Johnson, M.D., G. Lee Pride, Jr., M.D., Michel T. Torbey, M.D., M.P.H., Osama O. Zaidat, M.D., Zoran Rumboldt, M.D., and Harry J. Cloft, M.D., Ph.D., for the SAMMPRIS Trial Investigators*
**SAMMPRIS**

**Randomize**

- **PTAS**
  - 224
- **Medical**
  - 227

**Stroke & death within 30 days**

<table>
<thead>
<tr>
<th>Hx TIA/Stroke intracranial stenosis ≥ 70%</th>
<th>Wingspan stent</th>
<th>Medical therapy alone</th>
<th>Stroke or death within 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.7%</td>
<td>5.8%</td>
<td>2.2%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

**Dead**

<table>
<thead>
<tr>
<th>Medical therapy alone</th>
<th>Wingspan stent</th>
<th>Hx TIA/Stroke intracranial stenosis ≥ 70%</th>
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<tbody>
<tr>
<td>2.2%</td>
<td>0.4%</td>
<td>14.7%</td>
</tr>
</tbody>
</table>

**P:** Hx TIA/Stroke intracranial stenosis ≥ 70%

**I:** Wingspan stent

**C:** Medical therapy alone

**O:** Stroke or death within 30 days
Randomized Controlled Trial of Symptomatic Middle Cerebral Artery Stenosis
Endovascular Versus Medical Therapy in a Chinese population

Zhongrong Miao, MD, PhD; Lidan Jiang, MD; Hao Wu, MD, PhD; Yuhai Bao, MD, PhD; Liqun Jiao, MD, PhD; Shenmao Li, MD; Jian Wu, MD, PhD; Yang Hua, MD, PhD; Yan Li, MD; Junlei Zhu, MD; Fengshui Zhu, MD; Xuezong Liu, MD; Feng Ling, MD, PhD

Background and Purpose—To investigate the efficacy and safety of percutaneous transluminal angioplasty and stenting (PTAS) for symptomatic middle cerebral artery stenosis compared with standard medical treatment in a low-risk Chinese population.

Methods—A prospective, randomized, controlled, single-center clinical trial was conducted comparing PTAS with medical treatment for symptomatic middle cerebral artery stenosis (≥70%). Patients were enrolled according to 1:1 enroll ratio (PTAS: medical). The PTAS group received stenting or balloon angioplasty, whereas the medical treatment group received standard medical treatment (aspirin 100mg plus clopidogrel 75mg/d), and all the patients were under strict control of the risk factors. The end point events were any kind of ipsilateral stroke or transient ischemic attack, or death from any origin during 1-year follow-up.

Results—The enrollment was stopped after 70 patients were enrolled from August 2007 to December 2010, with a 30-day rate of end point events of 8.3% versus 5.9% (P=0.69) for PTAS and medical group, respectively, and 1-year rate of end point events of 19.4% versus 17.6% (P=0.85), respectively. There was no significant difference in baseline characteristics between the 2 groups. The mean follow-up time, which was ongoing, was 9.9±3.9 and 9.7±4.4 months, respectively. Among the risk factors, hypertension was the independent related to the outcome (P=0.015).

Conclusions—This study showed that endovascular treatment is as safe but not better than medical treatment for symptomatic middle cerebral artery stenosis in a low-risk Chinese population. History of hypertension increases the risk of recurrent ischemic events. (*Stroke. 2012;43:3284–3290.*)
Patent Foramen Ovale
Patent Foramen Ovale

Closure I (Starflex device)

RD = -0.1%
(95% CI -2.4% to 2.2%)

<table>
<thead>
<tr>
<th>Stroke</th>
<th>No Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>434</td>
</tr>
<tr>
<td>2.9%</td>
<td>97.1%</td>
</tr>
<tr>
<td>14</td>
<td>448</td>
</tr>
<tr>
<td>3.0%</td>
<td>97.0%</td>
</tr>
</tbody>
</table>

- 909 patients with cryptogenic stroke randomized.
- Followed for 2 years.
- Adjudicated stroke outcome assessment.
Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

John D. Carroll, M.D., Jeffrey L. Saver, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Scott Berry, Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

DOI: 10.1056/NEJMoa1301440
RESPECT

P: Stroke and PFO 18 to 60 years old

I: Amplatzer PFO Occluder

C: Medical Therapy

O: Recurrent Stroke

Randomize

Closure 499

Medical 481

Closure 7%

Medical 0.6%

Stroke

1.8%

3.3%

HR 0.49

95% CI 0.22 to 1.18
A Intention-to-Treat Cohort

Event-free Probability

Years to Event

Hazard ratio, 0.49 (95% CI, 0.22–1.11)
P=0.08 by log-rank test

Closure group (N=9)
Medical-therapy group (N=16)

B As-Treated Cohort

Event-free Probability

Years to Event

Hazard ratio, 0.27 (95% CI, 0.10–0.75)
P=0.007 by log-rank test

Closure group (N=5)
Medical-therapy group (N=16)
Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Jüni, M.D., for the PC Trial Investigators*
PC Trial

P: Cryptogenic stroke and PFO < 60 years old

I: Amplatzer PFO Occluder

C: Medical Therapy

O: Death, Stroke, TIA, embolism 4 years

Diagram:
- Randomize
- Closure: 204
- Medical: 210
- Stroke: 0.5% (2), 2.4% (28)
- HR 0.20, 95% CI 0.02 to 1.72
PC Trial

Hazard ratio, 0.63 (95% CI, 0.24–1.62)
P=0.34
## Three RCTs: ITT HR TIAs and Stroke

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hazard ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio Lower limit Upper limit Z-Value p-Value</td>
<td>Hazard ratio and 95% CI</td>
</tr>
<tr>
<td>Closure I</td>
<td>0.780 0.450</td>
<td>1.351 -0.887 0.375</td>
</tr>
<tr>
<td>PC Trial</td>
<td>0.630 0.242</td>
<td>1.637 -0.948 0.343</td>
</tr>
<tr>
<td>RESPECT</td>
<td>0.490 0.216</td>
<td>1.110 -1.709 0.087</td>
</tr>
<tr>
<td></td>
<td>0.666 0.442</td>
<td>1.006 -1.933 0.053</td>
</tr>
</tbody>
</table>

### Meta Analysis

- **Favors Closure**
- **Favors No Closure**
Atrial Fibrillation
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug</th>
<th>Relative Risk Reduction and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
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<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>Intracranial Bleeding</td>
<td>Dabigatran 150</td>
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<tr>
<td></td>
<td>Rivaroxaban</td>
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<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
<tr>
<td>Gastrointestinal Bleeding</td>
<td>Dabigatran 150</td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td></td>
<td>Rivaroxaban</td>
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</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td><img src="image" alt="Graph" /></td>
</tr>
</tbody>
</table>

Relative risk reductions of new antithrombotic regimens compared to dose-adjusted warfarin for various outcomes.
WATCHMAN Device

PROTECT AF
Rate Ratio
Intervention/Control
0.71 (95% CrI 0.44, 1.30)
Quality of Life Assessment in the Randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) Trial of Patients at Risk for Stroke With Nonvalvular Atrial Fibrillation
PREVAIL

**P:** Patients with NVAF

**I:** Watchman device

**C:** Warfarin (INR 2-3)

**O:** Complications
   Stroke, embolism
   18 months

RR 1.07 (95% CI 0.57 to 1.88)
Equivalence criterion UL 95% CI < 1.75
Stroke Prevention

• Primary: Preventing the first stroke
  “Asymptomatic patient”
• Secondary: Preventing recurrence
  “Symptomatic patient”
• Tertiary: Minimizing damage
  “Acute stroke patient”
• Quaternary: Maximizing function
  “Post stroke patient”
### NINDS tPA Study

#### Key outcomes

<table>
<thead>
<tr>
<th>Good Outcome</th>
<th>tPA</th>
<th>Placebo</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Barthel 95-100</td>
<td>50%</td>
<td>38%</td>
<td>12%*</td>
</tr>
<tr>
<td>• Rankin 0-1</td>
<td>39%</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td>Death</td>
<td>17%</td>
<td>21%</td>
<td>-4%</td>
</tr>
<tr>
<td>Brain hem.</td>
<td>6%</td>
<td>1%</td>
<td>+5%</td>
</tr>
</tbody>
</table>

*12 extra patients/100 given tPA regained normal function*
Risk of ICH by Deviation from NINDS Protocol

Stroke 1998,50:A155

%ICH 36 hrs.

All ICH

Within Protocol

8%

Protocol Deviations

10%

Symptomatic ICH

3%

10%
ECASS 3

- RCT of IV tPA vs placebo for patients last known normal 3 – 4.5 hours prior to treatment
- Patients who received tPA were more likely to achieve mRS 0-1: OR 1.42 (1.02 – 1.98)
- Mortality not changed: 7.7% vs 8.4%
IST-3

The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial

The IST-3 collaborative group*

Summary

Background Thrombolysis is of net benefit in patients with acute ischaemic stroke, who are younger than 80 years of age and are treated within 4·5 h of onset. The third International Stroke Trial (IST-3) sought to determine whether a wider range of patients might benefit up to 6 h from stroke onset.

Methods In this international, multicentre, randomised, open-treatment trial, patients were allocated to 0·9 mg/kg intravenous recombinant tissue plasminogen activator (rt-PA) or to control. The primary analysis was of the proportion of patients alive and independent, as defined by an Oxford Handicap Score (OHS) of 0–2 at 6 months. The study is registered, ISRCTN25765518.
IST-3

P: Ischemic stroke < 6 hours
Uncertainty regarding use of tPA

I: tPA

C: No tPA

O: Oxford Handicap Score 6 months.
**Figure 2: Outcome at 6 months: Oxford Handicap Scale (OHS) by treatment group**

For the ordinal analysis, which was adjusted for age, National Institutes of Health Stroke Scale (NIHSS), delay (all linear), and presence or absence of visible acute ischaemic change on baseline scan as judged by the expert reader, the statistical analysis plan prespecified that OHS levels 4, 5, and 6 were grouped and 0, 1, 2, 3 remained discrete. In that analysis, the common odds ratio was 1.27 (95% CI 1.10–1.47; p=0.001). An ordinal analysis with OHS levels 0, 1, 2, 3, 4, 5, and 6 all discrete, adjusted in the same way, gave an odds ratio of 1.17 (95% CI 1.03–1.33; p=0.016). rt-PA = recombinant tissue plasminogen activator.
Recent TPA Guidelines

Clinical Policy: Use of Intravenous TPA for the Management of Acute Ischemic Stroke in the Emergency Department

This clinical policy is the result of a collaborative project of the American College of Emergency Physicians and the American Academy of Neurology.

Development Panel
Jonathan A. Edlow, MD (Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA)
Eric E. Smith, MD, MPH (Department of Clinical Neurosciences, Hotchkiss Brain Institute [E.E.S.], University of Calgary, Foothills Medical Centre, Calgary, Canada)
Latha Ganti Stead, MD, MS, MBA (Professor of Emergency Medicine and Neurological Surgery; Director, Center for Brain Injury Research and Education, University of Florida, Gainesville, FL)
Gary Grossmith, MD (Department of Neurology, University of Kansas Medical Center, Kansas City, KS)
Steven R. Messé, MD (Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA)
Andy S. Jagoda, MD (Professor and Chair, Department of Emergency Medicine Mount Sinai School of Medicine; Medical Director, Emergency Department, Mount Sinai Hospital, New York, NY)

Robert L. Wears, MD, MS (Methodologist; Department of Emergency Medicine, University of Florida, Jacksonville, FL)
Wyatt W. Decker, MD (Vice President and Trustee Mayo Clinic, CEO Mayo Clinic Arizona, Scottsdale, AZ)

Providing Project Support:
Rhonda R. Whitson, RPH, Clinical Practice Manager, American College of Emergency Physicians
Thomas S. D. Getchius, Associate Director, Clinical Practice, American Academy of Neurology

Approved by the ACEP Board of Directors, June 13, 2012
Endorsed by the American Academy of Neurology, December 6, 2012
Endorsed by the American Heart Association Stroke Council, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Stroke. 2013;44:870-947; originally published online January 31, 2013; doi: 10.1161/STR.0b013e318284056a
Endovascular Therapies
Pro-urokinase in Acute Cerebral Thromboembolism (PROACT II)

- n=180 (2:1 randomization)
- Angiographically confirmed M1, M2 occlusion
- Intra-arterial thrombolysis within 6 hours
- Heparin 2000 u bolus, then 500 u over 4 hrs
- Benefit of treatment, (p=.04)

Is Intra-Arterial Thrombolysis Beneficial for M2 Occlusions? Subgroup Analysis of the PROACT-II Trial

Ralph Rahme, MD; Todd A. Abruzzo, MD; Renee’ Hebert Martin, PhD; Thomas A. Tomsick, MD; Andrew J. Ringer, MD; Anthony J. Furlan, MD; Janice A. Carrozzella, RN; Pooja Khatri, MD, MSc

Background and Purpose—The role of endovascular therapy for acute M2 trunk occlusions is debatable. Through a subgroup analysis of Prolyse in Acute Cerebral Thromboembolism-II trial, we compared outcomes of M2 occlusions in treatment and control arms.

Methods—Solitary M2 occlusions were identified from the Prolyse in Acute Cerebral Thromboembolism-II database. Primary endpoints were successful angiographic reperfusion (TICI 2–3) at 120 minutes and functional independence (mRS 0–2) at 90 days.

Results—Forty-four patients with solitary M2 occlusions, 30 in the treatment arm and 14 in the control arm, were identified. Successful reperfusion (TICI 2–3) was achieved in 53.6% and 16.7% of patients in the treatment and control arms, respectively (P=0.04). A favorable clinical outcome (mRS 0–2) was observed in 53.3% and 28.6%, respectively (P=0.19). Baseline characteristics were similar between the 2 groups.

Conclusions—Intra-arterial thrombolysis may lead to a 3-fold increase in the rate of early reperfusion of solitary M2 occlusions and could potentially double the chance of a favorable functional outcome at 90 days.

Clinical Trial Registration—This trial was not registered because enrollment began before July 1, 2005. (Stroke. 2013;44:240-242.)
Mechanical Thrombolysis

Safety and Efficacy of Mechanical Embolectomy in Acute Ischemic Stroke
Results of the MERCI Trial

Wade S. Smith, MD, PhD; Gene Sung, MD; Sidney Starkman, MD; Jeffrey L. Saver, MD; Chelsea S. Kidwell, MD; Y. Pierre Gobin, MD; Helmi L. Lutsep, MD; Gary M. Nesbit, MD; Thomas Grobelny, MD; Marilyn M. Rymer, MD; Isaac E. Silverman, MD; Randall T. Higashida, MD; Ronald F. Budzik, MD; Michael P. Marks, MD; for the MERCI Trial Investigators

Background and Purpose—The only Food and Drug Administration (FDA)-approved treatment for acute ischemic stroke is tissue plasminogen activator (tPA) given intravenously within 3 hours of symptom onset. An alternative strategy for opening intracranial vessels during stroke is mechanical embolectomy, especially for patients ineligible for intravenous tPA.

Methods—We investigated the safety and efficacy of a novel embolectomy device (Merci Retriever) to open occluded intracranial large vessels within 8 hours of the onset of stroke symptoms in a prospective, nonrandomized, multicenter trial. All patients were ineligible for intravenous tPA. Primary outcomes were recanalization and safety, and secondary outcomes were neurological outcome at 90 days in recanalized versus nonrecanalized patients.
Endovascular Treatment for Acute Ischemic Stroke

Alfonso Ciccone, M.D., Luca Valvassori, M.D., Michele Michelatti, Ph.D., Annalisa Sgoifo, Psy.D., Michela Ponzio, Ph.D., Roberto Sterzi, M.D., and Edoardo Boccardi, M.D., for the SYNTHESIS Expansion Investigators*
SYNTHESIS

**P:** Acute ischemic stroke within 4.5 hours

**I:** Endovascular therapy (3.75 hours)

**C:** IV tPA (2.75 hours)

**O:** Rankin score 0 or 1 3 months
Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

**P:** Ischemic stroke < 3 hours
large vessel occlusion suspected

**I:** IV tPA (dose changed) plus
endovascular Rx (several
devices) within 5 hours

**C:** IV tPA alone

**O:** Modified Rankin at 90
days.

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### IMS III

<table>
<thead>
<tr>
<th></th>
<th>Active 434</th>
<th>Control 222</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRs ≤2</td>
<td>40.8%</td>
<td>38.7%</td>
</tr>
<tr>
<td>Dead</td>
<td>19.1%</td>
<td>21.6%</td>
</tr>
</tbody>
</table>
The percentages of patients are shown in or above each cell, according to score on the modified Rankin scale. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Persons with a score of 0, 1, or 2 are considered to be functionally independent. Prespecified secondary analyses showed no significant differences between the two treatment groups across the entire distribution of the modified Rankin score overall (P=0.25); among patients with an NIHSS score of 8 to 19, indicating moderately severe stroke (P=0.83); or among those with an NIHSS score of 20 or more, indicating severe stroke (P=0.06). The abbreviation t-PA denotes tissue plasminogen activator.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–19</td>
<td>452</td>
<td>1.01 (0.78–1.31)</td>
</tr>
<tr>
<td>≥20</td>
<td>204</td>
<td>1.37 (0.63–2.99)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–65 yr</td>
<td>270</td>
<td>1.07 (0.78–1.48)</td>
</tr>
<tr>
<td>≥66 yr</td>
<td>386</td>
<td>1.01 (0.69–1.50)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>316</td>
<td>0.90 (0.62–1.30)</td>
</tr>
<tr>
<td>Male</td>
<td>340</td>
<td>1.18 (0.85–1.65)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or unknown</td>
<td>433</td>
<td>1.13 (0.84–1.52)</td>
</tr>
<tr>
<td>Yes</td>
<td>223</td>
<td>0.89 (0.56–1.39)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤120 min</td>
<td>345</td>
<td>1.24 (0.88–1.74)</td>
</tr>
<tr>
<td>&gt;120 min</td>
<td>310</td>
<td>0.88 (0.62–1.24)</td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–7</td>
<td>271</td>
<td>1.12 (0.67–1.87)</td>
</tr>
<tr>
<td>8–10</td>
<td>378</td>
<td>1.03 (0.79–1.34)</td>
</tr>
<tr>
<td>ICA, M1, or basilar occlusion</td>
<td>220</td>
<td>1.05 (0.67–1.64)</td>
</tr>
<tr>
<td>NIHSS score 8–19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>231</td>
<td>1.16 (0.81–1.68)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA &gt;120 min</td>
<td>221</td>
<td>0.88 (0.61–1.26)</td>
</tr>
<tr>
<td>NIHSS score ≥20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>114</td>
<td>1.77 (0.60–5.21)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA &gt;120 min</td>
<td>89</td>
<td>0.98 (0.28–3.39)</td>
</tr>
<tr>
<td>ICA, M1, or basilar occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA ≤120 min</td>
<td>124</td>
<td>1.18 (0.66–2.10)</td>
</tr>
<tr>
<td>Stroke onset to intravenous t-PA &gt;120 min</td>
<td>96</td>
<td>0.86 (0.42–1.74)</td>
</tr>
</tbody>
</table>
A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H., Jeffry R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D., Brett C. Meyer, M.D., Scott Olson, M.D., Lee H. Schwamm, M.D., Albert J. Yoo, M.D., Randolph S. Marshall, M.D., Philip M. Meyers, M.D., Dileep R. Yavagal, M.D., Max Wintermark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D., and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators*
MR Rescue

Randomize

Mechanical  Usual care

70  57

Good

Revasc

12  11

40  39

P: Large vessel stroke within 8 hours

I: Merci or Penumbra

C: Usual care

O: Modified Rankin scale 90 days
Shown are 90-day modified Rankin scores in patients undergoing embolectomy or receiving standard medical care for the treatment of acute ischemic stroke with a favorable penumbral pattern (substantial salvageable tissue and small infarct core) or a nonpenumbral pattern (large core or small or absent penumbra), after adjustment for age. The percentages of patients are shown in or above each cell. The modified Rankin scale ranges from 0 to 6, with higher scores indicating increased disability. Among all patients, mean modified Rankin scores did not differ between embolectomy and standard medical care (3.9 vs. 3.9, P=0.99). Embolectomy was not superior to standard medical care in patients with either a favorable penumbral pattern (mean score, 3.9 vs. 3.4; P=0.23) or a nonpenumbral pattern (mean score, 4.0 vs. 4.4, P=0.32).
Endovascular Treatment for Acute Ischemic Stroke — Still Unproven
Marc I. Chimowitz, M.B., Ch.B.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients and Sites</th>
<th>Enrollment Period</th>
<th>Key Patient Characteristics</th>
<th>Test Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMS III7</td>
<td>656 Patients enrolled (target, 900) at 58 sites</td>
<td>2006–2012</td>
<td>NIHSS score, ≥10; anterior or posterior circulation; 92% of 306 patients who underwent baseline CT angiography had large-artery occlusions</td>
<td>IV t-PA followed by endovascular therapy</td>
</tr>
<tr>
<td>SYNTHESIS Expansion8</td>
<td>362 Patients enrolled at 24 sites</td>
<td>2008–2012</td>
<td>No limit on NIHSS score; anterior or posterior circulation; no data on percentage of patients with large-artery occlusions</td>
<td>Endovascular therapy</td>
</tr>
<tr>
<td>MR RESCUE9</td>
<td>127 Patients enrolled at 22 sites but analysis restricted to 118 patients</td>
<td>2004–2011</td>
<td>NIHSS score, 6–29; large-vessel occlusion involving anterior circulation (ICA, M1, M2) required; 58% had favorable penumbral pattern</td>
<td>Endovascular therapy; 43.8% of patients in this group also initially received IV t-PA</td>
</tr>
</tbody>
</table>
Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial

Jeffrey L Saver, Reza Jahan, Elad I Levy, Tudor G Jovin, Blaise Baxter, Raul G Nogueira, Wayne Clark, Ronald Budzik, Osama O Zaidat, for the SWIFT Trialists

Lancet 2012; 380: 1241–49
**P:** Acute stroke, treatable with thrombectomy, within 8 hours

**I:** Solitaire

**C:** Merci

**O:** Restoration of flow

3 month neurologic outcome
SWIFT

<table>
<thead>
<tr>
<th></th>
<th>Merci</th>
<th>Solitaire</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>No substantial disability despite symptoms</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>Slight disability</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Severe disability</td>
<td>2%</td>
<td>22%</td>
</tr>
<tr>
<td>Death</td>
<td>44%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>
Stroke Prevention

- **Primary:** Preventing the first stroke
  “Asymptomatic patient”
- **Secondary:** Preventing recurrence
  “Symptomatic patient”
- **Tertiary:** Minimizing damage
  “Acute stroke patient”
- **Quaternary:** Maximizing function
  “Post stroke patient”
Effect of High- and Low-Frequency Repetitive Transcranial Magnetic Stimulation on Visuospatial Neglect in Patients With Acute Stroke: A Double-Blind, Sham-Controlled Trial

Bo Ryun Kim, MD, a Min Ho Chun, MD, PhD, b Dae-Yul Kim, MD, PhD, b Sook Joung Lee, MD b

From the aDepartment of Rehabilitation Medicine, Regional Cardiacerebrovascular Center, Jeju National University Hospital, University of Jeju School of Medicine, Jeju; and bDepartment of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.
**rTMS**

- **P:** Right hemispheric stroke with neglect
- **I:** 10 sessions tMS
- **C:** 10 sessions sham tMS
- **O:** Motor free visual perception test

**Randomize**

<table>
<thead>
<tr>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>9</td>
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</table>

**ΔMVPT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>6.6 ± 1.8</td>
<td>3.3 ± 2.3</td>
</tr>
</tbody>
</table>
Summary of Update re: Stroke “Prevention”

• Primary
  – ASA mildly effective for primary stroke prevention in women
• Secondary
  – ASA/Clopidogrel might be effective for stroke prevention in early post-stroke period
  – PFO closure remains investigational
  – There are many new options for stroke prevention in atrial fib. Watchman device is not one of them yet.
  – Intracranial stenting is dangerous in the short term.
• Tertiary
  – IV tPA remains our best therapy for treating acute ischemic stroke
  – Endovascular therapy for acute stroke remains investigational. Some hope in Solitaire device.
• Quatenary
  – Transcranial magnetic stimulation may speed stroke recovery