ISCHEMIC AND HEMORRHAGIC UPDATE:
CURRENT PRACTICES AND FUTURE DIRECTIONS

May 17, 2010
at
Boston Omni Parker House Hotel
60 School Street, Boston

COURSE DIRECTORS:
CHRISTOPHER S. OGILVY, MD
DAVID M. GREER, MD
ISCHEMIC AND HEMORRHAGIC UPDATE:

Current Practices and Future Directions

May 17, 2010

Boston Omni Parker House Hotel
60 School St, Boston

Under the Direction of:
The Massachusetts General Hospital Brain Aneurysm/AVM Center and Stroke Service

CME’s provided by:
The Harvard Medical School Department of Continuing Education

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Now, in accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council on Continuing Medical Education, speakers and their spouses/partners, and planners have been asked to disclose any relationship they have to companies producing pharmaceuticals, medical equipment, prosthesis, etc. that might be germane to the content of their lectures. Please note that now in accordance with recent policies from the ACCME, relationships of the person involved in the CME activity must include financial relationships of a spouse or partner.

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   Joshua Goldstein, M.D., PhD  
   Steven Feske, M.D.  
   David Greer, M.D.  
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   David Jho, MD, PhD  
   Christopher S. Ogilvy, M.D  
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   Jonathan Rasand, MD  
   Natalia Rost, M.D.  
   Lee Schwamm, M.D.  
   Aneesh Singhal, M.D.  
   Elizabeth Van Cott, MD

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   Research Funding

   Elad Levy, M.D.  
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   Shareholder

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   Coaxia, Inc.  
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THE MASSACHUSETTS GENERAL HOSPITAL BRAIN ANEURYSM/AVM CENTER AND STROKE SERVICE

GRATEFULLY ACKNOWLEDGES THE CONTRIBUTIONS:

Boston Scientific
Codman Neurovascular
Micrus Endovascular Corporation
Mizuho America, Inc.
Penumbra, Inc

TOWARDS THE SUPPORT OF OUR 2010 COURSE
Ischemic and Hemorrhagic Update: *Current Practices and Future Directions*
Directors: Christopher S. Ogilvy, M.D. and David Greer, M.D.
Rooftop Ballroom
Omni Parker House Hotel
Monday, May 17, 2010

Stroke has occurred: What now? Initial urgent management, evaluation and treatment of stroke patients
Moderator: D. Greer

7:55 - 8:00 Welcome.............................................................................................................................. Ogilvy, Greer
8:00 - 8:20 Emergency evaluation of ischemic stroke........................................................................... J. Goldstein 1
8:20 - 8:45 Neuroimaging for acute ischemic stroke- Rapid neurologic evaluation of the stroke patient, the essentials ................................................................. G.Gonzalez 17
8:45 - 9:05 Thrombolysis for ischemic stroke: intravenous therapy, Current recommendations and standards ............................................................. S. Feske 33
9:05 - 9:25 Intra-arterial ischemic stroke therapies: who should be treated and when............................ E. Levy 41
9:40 - 10:00 Arterial Dissections-Intracranial, extracranial: medical and endovascular management... R. Nogueira 129
10:00 - 10:15 Discussion
10:15 - 10:45 Coffee
10:45 - 11:05 ICU management of acute stroke: medical and surgical care........................................ D. Greer 135
11:05 - 11:25 Intracranial atherosclerotic disease: medical and endovascular management............... E. Levy 157
11:25 - 11:45 Cardiogenic and uncommon causes of stroke, including PFO’s ......................... A. Singhal 209
11:45 - 12:00pm Discussion
12:00 - 1:15 Luncheon session: *Hypercoaguable states and stroke prone patients* E. VanCott 221

**Outpatient Management of Stroke Prone Patients**
Moderator: C.Ogilvy

1:15 - 1:35 Risk factors for stroke- what to look for................................................................. L. Schwamm 239
1:35 - 1:55 Antithrombotic Therapy (Preventative)................................................................. D. Thaler 249
1:55 - 2:15 Office management of stroke prone patients: Who should be screened, what tests should be used and how often?......................................................... M. Jaff 251
2:15 - 2:40 Carotid artery disease- indications for treatment and results of endarterectomy and stenting ............................................................... C. Ogilvy 259
2:40 - 3:00 Subclavian and vertebral artery atherosclerotic disease – intra and extracranial management ................................................................. F. Buonanno 283
3:00 - 3:15 Discussion
3:15 - 3:45 Break

**Hemorrhagic Stroke/Intraparenchymal Hemorrhage**
Moderator: D. Greer

3:45 - 4:05 Emergency management of intraparenchymal and subarachnoid hemorrhage .......... J. Edlow 287
4:05 - 4:25 Imaging for intraparenchymal and subarachoidal hemorrhage- what is needed, what isn’t. J. Rabinov 295
4:25 - 4:45 Intracranial aneurysms- ruptured and unruptured...................................................... C. Ogilvy 301
4:45 - 5:05 Intracranial hemorrhage: Medical treatment and surgical indications. What does data show................................................................. J. Rosand 351
5:05 - 5:25 Intraparenchymal Hemorrhage from causes other than hypertension ..................... D. Jho 365
5:25 - 5:40 Discussion
Emergency Evaluation of Ischemic Stroke

Joshua N. Goldstein, MD, PhD
Department of Emergency Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, MA

Disclosure: Dr. Goldstein has received consulting fees from Genentech and CSL Behring.

Outline

I. Prehospital Management
II. Why Create Stroke Centers?
III. Designation of Stroke Centers
IV. Emergency Evaluation and Diagnosis of Acute Ischemic Stroke
V. General Supportive Care and Treatment of Acute Complications

Prehospital management

• The role played by EMS is critical.
• Patients transported by EMS have shorter time to presentation, more rapid time to physician evaluation, and shorter time to neuroimaging.
EMS evaluation

- ABCs
- Cardiac monitoring
- IV access
- Supplemental oxygen if needed
- Fingerstick glucose
- Alert the receiving ED
- **Rapid transport to a stroke center! (More on this later)**

EMS stroke scales

- LA Prehospital Stroke Scale
  - Last time symptom free
  - Screening: Age, Seizures, Symptoms<24 hours,
    Not previously bedridden, Blood glucose 60-400
  - Exam: Facial, grip strength, arm strength
- Cincinnati Prehospital Stroke Scale
  - Facial droop, arm drift, speech

II. Stroke Centers – the concept

- Current AHA guidelines recommend that EMS transport stroke patients to the closest available “stroke center”.
- Thrombolysis for ischemic stroke will be covered in an upcoming lecture; the question is, can all hospitals safely use this intervention?
The “Average” Emergency Department

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<tr>
<td>40-49k</td>
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<tr>
<td>&gt;50k</td>
<td>375</td>
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“Higher” volume EDs

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Emergency Departments with ≥5,000 visits/year
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“Lower” volume EDs

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Emergency Departments with <5,000 visits/year
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US Emergency Departments

• How many EDs are in the USA?
  • Approximately 4,862
• 75% of EDs see less than <30,000 patients per year.
• This translates into seeing <250 stroke patients/year.
• Approximately <50 patients per year will present within 3 hours.


Thrombolysis in community hospitals

• Some studies have found that tPA delivery in community hospitals is associated with more protocol deviations and higher rates of symptomatic intracranial hemorrhage.
• However, others have shown that community hospitals CAN deliver TPA appropriately, provided the right infrastructure.

ACEP Policy Statement

• “Intravenous tPA may be an efficacious therapy for the management of acute ischemic stroke if properly used incorporating the guidelines established by the NINDS.”
• “There is insufficient evidence at this time to endorse the use of intravenous tPA in clinical practice when systems are not in place to ensure that the inclusion/exclusion criteria established by the NINDS guidelines for tPA use in acute stroke are followed.
• “…therefore, the decision for an ED to use intravenous tPA for acute stroke should begin at the institutional level.”
SAEM Position

- “Currently insufficient data exist to mandate thrombolytic therapy as the standard of care for acute ischemic stroke for all patients across all medical treatment settings.”

- Note that following the ECASS 3 trial, this statement has been officially withdrawn.

AAEM Position

- “…objective evidence regarding the efficacy, safety, and applicability of tPA for acute ischemic stroke is insufficient to warrant its classification as standard of care.”

- “…physicians are advised to use their discretion when considering its use.”

EM position statements

- The decision regarding thrombolysis should be made at the hospital level first.
- Emergency physicians should deliver this therapy within the context of a formal hospital policy.
- Stroke center designation may accomplish this goal.
III. Stroke Centers

• Brain Attack Coalition Stroke Centers
• JCAHO Stroke Centers
• Massachusetts Department of Public Health Stroke Centers

Brain Attack Coalition Stroke Center

• Primary Stroke Centers (PSC)
  • Ability to care for uncomplicated strokes
  • Use acute therapy such as tPA
  • Admits to a stroke unit
• Comprehensive Stroke Centers (CSC)
  • Reserved for centers with a comprehensive array of services

Brain Attack Coalition Primary Stroke Center

• Acute Stroke Team available
• Written care protocols, including use of tPA
• Coordination with EMS
• Neurosurgery available
• Neuroimaging available
• Ongoing QI
• Stroke center director
• Admission to a stroke unit
Brain Attack Coalition
Comprehensive Stroke Center

- Stroke Center director
- Vascular neurologists and neurosurgeons
- Vascular surgeons who can perform CEA
- Radiologists and CT, CTA, MRI, MRA
- Interventional neuroradiologists
- ED and EMS support
- Stroke-trained nurses and APNs
- Stroke unit and ICU with critical or neurointensive care physicians
- Echocardiography, ultrasound, TCDs
- Rehab specialists, case managers, social workers

JCAHO Stroke Center

1. DVT Prophylaxis
2. Discharged on antithrombotics
3. Patients with A. fib. receive anticoagulants
4. TPA use considered
5. Antithrombotic therapy within 48 hours of admission
6. Lipid profile sent
7. Speech and swallow eval. before oral intake
8. Stroke education
9. Smoking cessation
10. Rehabilitation considered.

Mass. DPH Stroke Center

- Written care protocols, both ED and inpatient.
- Acute Stroke Team available
- CT/MRI/Radiology availability
- Neurosurgery available
- QI system in place
- One major goal: Increase the number of stroke patients who receive tPA
- Most hospitals in Massachusetts carry this designation.
AHA Stroke Center recommendations

- The creation of Primary Stroke Centers is strongly recommended.
- Certification by an external body (such as JCAHO) is strongly recommended.
- EMS should bypass hospitals that do not have resources to treat stroke.

IV. Emergency Evaluation of Acute Ischemic Stroke

- History
  - Time of symptom onset is the single most important piece of history.
  - Defined as when they were last known to be symptom free.
- Physical exam
  - ABCs
  - Neurologic exam (enhanced by use of a formal scale such as NIHSS)

Immediate diagnostic studies

- Blood glucose
- CBC, Chem7, coagulation studies
  - Note – AHA states that tPA should NOT be delayed pending these results unless an abnormality is clinically suspected.
- ECG, cardiac enzymes
  - Cardiac arrhythmias are not uncommon
- O2 saturation
- Neuroimaging
Acute neuroimaging

- In most centers, this will be a CT scan
  - CT scanners are available 24/7 in 94% of US EDs.
  - MRI is available 24/7 in 13% of US EDs.
- For emergency providers, the goal is to image as rapidly as possible.
- AHA Goal: Door-CT within 25 minutes.

Early neurologic consultation

- Emergency neurologic consultation is available in some, but not all hospitals.
- This can be performed in person, by telephone, or by video (Telestroke). AHA comments that “Telemedicine can be an effective method to provide expert stroke care”.
- Partners Telestroke provides emergency stroke consultation to many hospitals in Massachusetts.
Brain imaging
• To be covered by the next lecture (Dr. Gonzalez)

Thrombolytics
• To be covered by another lecture (Dr. Feske)

How to ensure rapid imaging and treatment?
• Institutional commitment
  • It is critical to have involvement from Neurology, Emergency Medicine, Radiology, and Pharmacy.
• Formal process in place
• Measure metrics

Nationally, how many patients undergo CT within 25 minutes?

Fig. 7. Percent of eligible patients who had brain imaging completed within 25 minutes from arrival

- The Top Hospitalized Achieved
- The Top 10% of Hospitals Achieved at Least
- The Top 10% of Hospitals Achieved at Most
- The Bottom 10% of Hospitals Achieved at Most
- The Bottom Hospitalized Achieved
- Massachusetts Patient Average Time
Nationally, how many patients receive IV-tPA within 60 minutes?

What is the average door-needle time?

At our hospital (MGH) – effect of an intervention

- In 2008 we implemented a group paging system “ED2CT”.
- The ED MD sends a single page that activates:
  - Stroke fellow
  - Neurology resident
  - Neuroradiology fellow
  - CT technologist
  - ED pharmacist
- We compared the effect on outcomes
Effect of group page “ED2CT” on MGH times:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-ED2CT</th>
<th>Post-ED2CT</th>
<th>p value</th>
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<tbody>
<tr>
<td>Door-CT</td>
<td>29 min</td>
<td>20 min</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Door-TPA</td>
<td>59 min</td>
<td>51 min</td>
<td>0.02</td>
</tr>
<tr>
<td>Door-CT&lt;25min</td>
<td>43%</td>
<td>67%</td>
<td>0.01</td>
</tr>
<tr>
<td>Door-TPA&lt;60min</td>
<td>52%</td>
<td>72%</td>
<td>0.03</td>
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</tbody>
</table>

Reducing the median time by just a few minutes has a big impact on the % of patients that achieve the goal times.

Rapid times to imaging and treatment requires a team effort

- One system (ours at MGH) is shown here:
V. Supportive care

- Airway support if needed
- Deliver oxygen if patient is hypoxic
- Fever
  - Seek a source
  - Treat the fever with antipyretics
- Cardiac monitoring
  - Arrhythmias are common
- Hyperglycemia
  - If serum glucose > 200mg/dl, initiate treatment

Blood pressure control

- Elevated BP is common on arrival but often spontaneously falls in the first hours.
- Management is controversial.
- Two major categories of patient:
  - Non-tPA candidates
  - tPA candidates
Blood pressure — non TPA candidates

• BP<220/120
  • No treatment. Rapid lowering of BP may decrease cerebral perfusion pressure

• BP>220/120
  • Lower by 15-25% over the first day.
    • Labetalol 10-20mg IV, or 2-8mg/minute
    • Nitropaste 1-2 inches
    • Nicardipine 5mg/h, titrate up to 15mg/h
    • Avoid SL nifedipine
  • Note that nitroprusside is currently recommended only as a rescue agent if other options fail.

Blood pressure — TPA candidates

• BP>185/110
  • Labetalol 10-20mg IV, repeat x1
  • Nitropaste 1-2 inches
  • Nicardipine 5-15mg/hr
  • If BP remains >185/110, defer tPA

Blood pressure — After TPA

• BP>180/105
  • Labetalol 10 every 10-20 min up to 300mg
  • Labetalol 2-8mg/min infusion
  • Nicardipine 5-15mg/hr
  • If BP not controlled, consider nitroprusside
Conclusions: Stroke care in the emergency department

- Significant emphasis on EMS involvement.
- The future of stroke likely involves development of stroke systems of care, with emphasis on “stroke centers” with a demonstrated institutional commitment and preferential transport to such centers.
- Focus on eliminating delays to diagnosis and treatment
Evidence Based MRI in Acute Ischemic Stroke

R. Gilberto González, MD, PhD
Neuroradiology Division
Massachusetts General Hospital

Purpose of Advanced Imaging
Stroke Physiology
Determinants of Clinical Outcomes
- Symptom severity
- Site of Occlusion
- Size of core
- Treatment
Can Perfusion CT/MR Enhance Outcomes?
Imaging algorithm

Ischemic Infarction Types

Major
NIHSS >10
Large Art. Occl.
Large Infarct mRS ≥3

Minor
NIHSS ≤10
No L. Art. Occl.
Small Infarct mRS 0-2

Lacunar

~35%
~45%
~20%
Goal of Treatment

- Major
  - NIHSS >10
  - Large Art. Occl.
  - Large Infarct
  - mRS ≥3

- Minor
  - NIHSS ≤10
  - No L. Art. Occl.
  - Small Infarct
  - mRS 0-2

Lacunar

Evidence Based MRI in Acute Ischemic Stroke

- Purpose of Advanced Imaging
- Stroke Physiology
- Determinants of Clinical Outcomes
  - Symptom severity
  - Site of Occlusion
  - Size of core
  - Treatment
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- Imaging algorithm

Collateral Flow
Evidence Based MRI in Acute Ischemic Stroke

- Purpose of Advanced Imaging
- Stroke Physiology
- Determinants of Clinical Outcomes
  - Symptom severity
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  - Size of core
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Core+Penumbra
Neurological Exam

Evidence Based MRI in Acute Ischemic Stroke

- Determinants of Clinical Outcomes
  - Symptom severity
  - Site of Occlusion
  - Size of core
  - Treatment
BASIS
Boston Acute Stroke Imaging Scale

Outcomes of 230 Consecutive Acute Ischemic Stroke Patients

<table>
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<th>Minor (N=173)</th>
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<td>Discharge to Rehabilitation Facility</td>
<td>35 (71%)</td>
<td>29 (17%)</td>
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<td>Discharge to Home</td>
<td>9 (18%)</td>
<td>131 (76%)</td>
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<tr>
<td>Length of Stay, Days (SE)</td>
<td>12.5 (1.3)</td>
<td>3.2 (0.2)</td>
<td>&lt;0.0001</td>
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Evidence Based MRI in Acute Ischemic Stroke

• Determinants of Clinical Outcomes
  – Symptom severity
  – Site of Occlusion
  – Size of Core
  – Treatment

2.6 h post L Hemiplegia

38 yo M L Hemiparesis unknown duration

Prediction of clinical outcome

• DWI best predictor of final infarct volume

• DWI > 70 cc’s is specific for poor outcome
  » Sanak et al, Neuroradiology 2006
  » Schaefer et al, Stroke, in press
Evidence Based MRI in Acute Ischemic Stroke

• Determinants of Clinical Outcomes
  – Symptom severity
  – Site of Occlusion
  – Size of core
  – Treatment

Goal of Treatment

Major
NIHSS >10
Large Art. Occl.
Large Infarct
mRS ≥3

Minor
NIHSS ≤10
No L. Art. Occl.
Small Infarct
mRS 0-2

Lacunar
STOPstroke Study: Effect of tPA

Evidence Based MRI in Acute Ischemic Stroke

- Purpose of Advanced Imaging
- Stroke Physiology
- Determinants of Clinical Outcomes
  - Symptom severity
  - Site of Occlusion
  - Size of core
  - Treatment
- Can Perfusion CT/MR Enhance Outcomes?
- Imaging algorithm

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- **Compensated Low CPP**
- **Benign Oligemia**
- **Core**
“Time to Peak” (TTP)

Time = [Gd]

Baseline (pre-contrast) Transit of contrast bolus

MTTCBV = CBF

Peak of residue function

Area under concentration curve

AIF

Time R2*

(relative concentration) CBV

CBV

CBF

MTT
Lactate

ATP, PCr

CPP (torr)

100

60

80

40

20

0

OEF (%)

100

60

80

40

20

0

Electrical Failure

CMRO₂ (mmol/100g/min)

200

120

80

40

0

CBV (ml/100g)

10

6

8

2

0

MTT (sec)

50

30

40

20

10

CBF (ml/100g/min)

75

45

60

15

0

Examples of ROI Placements

Compensated Condition

Misery Condition

Luxury Condition

Compensated low CPP "core" benign oligemia

Underperfused, Alive

Underperfused, Dead

Reperfused, Alive

Reperfused, Dead

Underperfused, Alive

Underperfused, Dead

Reperfused, Alive

Reperfused, Dead

Examples of ROI Placements

DWI PWI

6x6 pixel placed in center of DWI lesion

6x6 pixel placed in contralateral location
### CBV in the Stroke Core

<table>
<thead>
<tr>
<th>CBV</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>1</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>2</td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>3</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>4</td>
</tr>
</tbody>
</table>

### Compensated Condition

<table>
<thead>
<tr>
<th>CBV</th>
<th>CBF</th>
<th>MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>↑</td>
<td>-</td>
</tr>
</tbody>
</table>

### Misery Condition

<table>
<thead>
<tr>
<th>CBV</th>
<th>CBF</th>
<th>MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underperfused, Alive</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Underperfused, Dead</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### Luxury Condition

<table>
<thead>
<tr>
<th>CBV</th>
<th>CBF</th>
<th>MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfused, Alive</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Reperfused, Dead</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

### Metabolic Parameters

<table>
<thead>
<tr>
<th>Condition</th>
<th>CPP (torr)</th>
<th>CBV (ml/100g)</th>
<th>CBF (ml/100g/min)</th>
<th>MTT (sec)</th>
<th>OEF (%)</th>
<th>CMRO2 (mmol/100g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensated Core</td>
<td>100</td>
<td>10</td>
<td>45</td>
<td>50</td>
<td>0</td>
<td>160</td>
</tr>
<tr>
<td>Benign Oligemia</td>
<td>60</td>
<td>8</td>
<td>30</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

### Other Parameters

- **OEF** (%)
- **CMRO2** (mmol/100g/min)
A very inconvenient truth:

Measurement Error

The three inconvenient truths of MR perfusion post-processing

<table>
<thead>
<tr>
<th>Problem</th>
<th>Artifactual result</th>
<th>Solution(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Truncation of time course</td>
<td>CBV, MTT</td>
<td>1. Scan longer! 2. Curve fitting</td>
</tr>
<tr>
<td>II Bolus arrival delay</td>
<td>CBF, MTT</td>
<td>1. oSVD 2. Local AIF 3. Delay compensation</td>
</tr>
<tr>
<td>III Bolus dispersion</td>
<td>CBF, MTT</td>
<td>1. Local AIF</td>
</tr>
</tbody>
</table>

Absolute CBF measurement with MRP

Hagen T et al., JCAT 1999; 23(2):257-64.
Absolute CBF measurement with CTP


"...on the basis of postprocessing variability alone, if the true CBF value is 20 mL/100g/min, measurements of CBF...can vary by approximately ±7-10 mL/100g/min...."
Evidence Based MRI in Acute Ischemic Stroke

- Purpose of Advanced Imaging
- Stroke Physiology
- Determinants of Clinical Outcomes
  - Symptom severity
  - Site of Occlusion
  - Size of core
  - Treatment
- Can Perfusion CT/MR Enhance Outcomes?
- Imaging algorithm

Acute Ischemic Stroke
Recommended Imaging Algorithm

- NCCT
- CTA
- MR Capable?
- Yes: DWI
- No: CTP
- ICA/MCA/Basilar Occlusion+Small DWI?
- Yes: IA Rx
- No: MRP
- No IA Rx
Evidence Based MRI
in Acute Ischemic Stroke

- Purpose of Advanced Imaging
- Stroke Physiology
- Determinants of Clinical Outcomes
  - Symptom severity
  - Site of Occlusion
  - Size of core
  - Treatment
- Can Perfusion CT/MR Enhance Outcomes?
- Imaging algorithm
Update on Thrombolytic Therapy for Acute Ischemic Stroke (See the Annotated References to identify all study acronyms used here.)

I. Early attempts with streptokinase
In the mid 1990s, following upon successful use of thrombolytic therapy for acute myocardial infarction, several studies tested the thrombolytic agent streptokinase in patients with acute ischemic stroke. These studies, MAST-E, ASK, and MAST-I all failed to show a benefit and rather showed an increased hazard due to cerebral hemorrhage. The ASK study did show a trend of benefit within the tight time window of 3 hours, suggesting that treatment early after onset of stroke symptoms would be an important design element of later studies. These negative studies, therefore, highlighted two important features of the coming experience: that cerebral hemorrhage was a major risk that would limit therapy and that very early therapy would be important.

II. Initial successful use of rtPA
In 1995, the first large-scale study of intravenous tPA (ECASS I) was negative but showed some beneficial trends. In December 1995, the NINDS trial of intravenous tPA was the first study to show a clear benefit. Although, the other large studies, such as ECASS I and II and the ATLANTIS study were negative for their primary endpoints, few patients enrolled in these studies were treated within 3 hours of stroke onset. Yet these studies did show some beneficial trends, and a meta-analysis of the patients treated in all of these studies also suggested that therapy was beneficial. After the publication of the NINDS study, the FDA approved intravenous tPA for use within 3 hours of stroke onset, and practice rapidly changed as many centers began to implement this new policy of treatment.

III. Extension to the community
After the publication of the NINDS study and the FDA approval of tPA for intravenous use, it was still not clear if the use of tPA for ischemic stroke could be safely and effectively implemented in the larger medical community. Using data from 389 patients, the STARS observational study of the performance of community and academic medical centers suggested that, although the protocol violations rate might be great when the intravenous thrombolytic therapy was widely applied, it could be given with safety and efficacy comparable to that achieve in the NINDS study. A subsequent meta-analysis of 15 post-approval studies analyzed the use of intravenous tPA in 2639 with similar results, i.e. comparable efficacy and safety despite a high rate of protocol violations. Use in the community has had similar validation in Canada (CASES) Europe (SITS-MOST). Both of these studies showed rates of excellent clinical outcome comparable to the NINDS study and the pooled data from NINDS, ECASS, and ATLANTIS for patients treated within 3 hours of stroke onset rates of symptomatic hemorrhage that were, in fact, lower than in the randomized controlled trials.

IV. Attempts to extend the window of opportunity
Despite the widespread mobilization of medical systems in the effort to provide acute stroke therapy, only a small percentage of patients with acute stroke get thrombolytic therapy. A major reason for this is the very narrow 3-hour time-window of opportunity.
from the time of onset. Efforts to extend the use of thrombolysis have included efforts to show that a subset of patients might be treated beyond the 3-hour window, either defined temporally or defined by imaging measures of relevant pathophysiology, such as diffusion-perfusion mismatch. Initial studies treating patients beyond 3-hours, such as ECASS I and ATLANTIS (part A) have produced negative results. However, a meta-analysis of patients from the NINDS, ECASS, and ATLANTIS studies suggested a statistically significant benefit for treatment up to 4.5 hours. In 2008, the ECASS III study reported benefit of treatment in the 3-4.5 hour window in a subset of patients. It remains unclear if the findings of this study will be brought into community practice on a large scale. Although preliminary studies using desmoteplase and selecting patients based on diffusion-perfusion mismatch (DIAS, DEDAS) were promising, a larger study with clinical endpoints (DIAS-2) failed to show benefit. The ongoing DIAS-3 and DIAS-4 trials continue to study desmoteplase in the 3-9 hr window with different imaging criteria for patient selection.

V. Attempts to augment effective clot lysis
In 2004, the CLOTBUST II study demonstrated safety and found trends favoring benefit from the addition of therapeutic ultrasound to IV tPA to promote early recanalization. Research on therapeutic ultrasound has continued and included the injection of microspheres to further enhance ultrasound-induced clot lysis. Planning for a large-scale Phase III clinical trial of this therapy is underway.

VI. Current guidelines
Current guidelines published by the American Academy of Neurology and the American Stroke Association/American Heart Association encourage medical centers to establish efficient systems to assess patients rapidly to offer acute therapy to as many as may qualify. These guidelines for implementation closely follow the protocol used in the NINDS trial, using the 3-hour window. In 2009, the American Stroke Association updated its guidelines to recommend therapy of selected patients up to 4.5 hours after stroke onset based on the ECASS III trial. Following the protocol of the ECASS III trial, this guideline excludes patients over age 80 or less than 18, those with NIHSS > 25, those who are taking warfarin or other anticoagulants without regard for the INR, and those who have the combination of history of prior stroke AND diabetes mellitus.
Annotated References for Major Trial of IV Thrombolytics

MAST-E
The Mulicenter Acute Stroke Trial-Europe Study Group. Thrombotic therapy with streptokinase in acute ischemic stroke. N Engl J Med 1996;335(3):145-50. *This phase III trial compared intravenous streptokinase to placebo given within 6 hours of acute stroke affecting causing middle cerebral artery syndrome. There was no difference in the rate of death or severe disability at 6 months between the two groups. The mortality at 10 days was higher in the SK group (34% v 18%; p=0.002). This higher rate of death was due mainly to a higher rate of hemorrhagic transformation.*

ASK
Streptokinase for acute ischemic stroke with relationship to time of administration. Australian Streptokinase (ASK) Trial Study Group. JAMA 1996;276(12):961-6. *This phase III study compared SK to placebo given within 4 hours of stroke onset. Those treated with SK beyond 3 hours had a greater mortality rate. The SK group showed a trend toward more hematomas and higher mortality among all subjects.*

MAST-I
Multicentre Acute Stroke Trial--Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Lancet 1995;346(8989):1509-14. See also: Multicentre Acute Stroke Trial--Italy (MAST-I) Group. Dissent: An alternative interpretation of MAST-I. Lancet 1995;346(8989):1515. *This phase III trial used a 2x2 factorial design to compare the benefit of SK, aspirin 300 mg daily, both, or neither given within 6 hours of onset of acute ischemic stroke. SK was associated with a higher mortality at 10 days.*

ECASS I
The European Cooperative Acute Stroke Study Investigators. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study. JAMA 1995;274(13):1017-25. *This phase III study compared the benefit of intravenous tPA (1.1 mg/kg) to placebo given within 6 hours of stroke onset. The study was negative for its primary endpoint (clinical outcome at 90 days) in the intention-to-treat analysis. However, an efficacy analysis limited to the target population showed a slight benefit of therapy.*

NINDS tPA Stroke Trial
The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. Engl J Med 1995;333:1581-7. *This phase III study compared the benefit of intravenous tPA (0.9 mg/kg) and placebo when given within 90 minutes (half of the patients) or 180 minutes (half of the patients) of stroke onset. The first part of this study looked at the benefit measure by improvement in the NIHSS after 24 hours. This part of the study showed no significant difference between the two groups, but there was a benefit measured after 24 hours in those treated within 90 minutes. At 3 months, treated patients were significantly more likely to have minimal or no neurologic disability (modified Rankin Scale ≤1). Using various measures*
of the neurologic examination, activities of daily living, and disability, the treated patient did better than the placebo group by 11-12% (absolute risk reduction) or about 30% (relative risk reduction). This benefit was achieved without any increase in the rate of severe disability or death. Symptomatic cerebral hemorrhage was more likely after tPA therapy (6.4% vs 0.6%). This was the first unequivocally positive thrombolytic trial for acute stroke therapy. This trial led the FDA to approve tPA for use in acute ischemic stroke in June 1996.

**ECASS II**
Second European-Australasian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352(9136):1245-51. This phase III study compared the benefit of intravenous tPA (dose lowered to the 0.9 mg/kg dose used in the NINDS study) to placebo given within 6 hours of stroke onset. There was no difference in favorable outcome between the two groups whether treated within 3 or from 3-6 hours.

**ATLANTIS part A**
The ATLANTIS Study Investigators. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. JAMA 1999;282(21):2019-26. This phase III study compared the benefit of intravenous tPA (0.9 mg/kg) to placebo given 3-5 hours after stroke onset. There was no difference in NIHSS at 90 days nor in measures of clinical outcome at 30 or 90 days. The rate of symptomatic hemorrhage was greater in the treatment group (1.1 vs 7.0%; p=0.001).

**STARS**
Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. JAMA 2000;283(9):1189-91. This phase IV observational trial reported the clinical outcome and safety of standard IV tPA in 389 patients treated in 57 centers including 33 community hospitals and 24 academic medical centers. Thirty days after treatment, 35% had very good outcomes (MRS ≤1) and 43% were independent (MRS ≤2). Symptomatic ICH occurred in 3.3%. The median time from stroke onset to treatment was 2 hours 44 minutes. Protocol violations were recorded in 32.6%. This study suggested that the benefit found in the NINDS IV tPA study could be replicated in wider use, despite a high rate of protocol violations.

**CLOTBUST II**
Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moyé LA, Hill MD, Wojner AW; CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351(21):2154-5. Patients receiving IV tPA within 3 hours of stroke onset were randomized to receive either continuous 2-MHz transcranial Doppler ultrasound or placebo in this phase II safety trial. 126 patients were randomized (63 to each group) and assessed primarily for hemorrhage and clinical deterioration and for complete recanalization by ultrasound or dramatic clinical recovery. Symptomatic intracerebral hemorrhage occurred in 3 patients in each group. Complete recanalization
occurred in 49% of the treatment group and 19% of the control group. After 24 hours, 44% in the treatment group and 40% in the control group had dramatic clinical recovery. After 3 months, 42% in the treatment group and 29% in the control group had excellent clinical outcomes with mRS score 0-1.

CASES
Hill MD, Buchan AM, the Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigator. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. CMAJ 2005;172(10):1307-12. This post-licensing study was mandated by the Canadian government to assess the effectiveness of alteplase in clinical practice. Over a period of 2.5 years, 1135 patients were enrolled from 60 centers, including all major hospitals across Canada. The data included an estimated 84% of all patients treated with tPA for ischemic stroke during the study interval. Excellent clinical outcome (mRS 0-1) was observed in 37%. Symptomatic hemorrhage occurred in 4.6%. However, 75% of those with sICH died during the hospitalization. 1.3% of patients had hemiorolinguial angioedema. These results are comparable to those reported in controlled clinical trials.

DIAS
The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): A phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005;36:66-73. This phase II trial looked at an extended window and the use of diffusion-perfusion mismatch by MRI was a patient selection criterion. The safety study showed excess symptomatic ICH at the higher doses tested, therefore lower doses were tried. The lower dose portion of the study showed no excess of symptomatic ICH and a dose-dependent trend of increased rate of reperfusion (achieving significance at the higher (125 microg/kg) dose. Clinical outcomes followed a dose-dependent favorable trend.

DEDAS
AJ, Eyding D, Albers GW, et al, DEDAS investigators. Dose escalation of desmoteplase for acute ischemic stroke (DEDAS): evidence of safety and efficacy 6-9 hours after stroke onset. Stroke 2006;37:1227-31. This is the US counterpart of the DIAS trial with the same entry criteria and goals. The small phase II study showed a trend toward benefit in the higher dose (125 microg/kg) group both for 90-day clinical outcome and for reperfusion based on MRI.

DIAS-2
Hacke W, Furlan AJ, A-Rawi Y, et al. Intravenous demoteplase in patients with acute ischaemic stroke selected by MRI perfusion – diffusion-weighted imaging or perfusion CT (DIAS-2): a prospective, randomized, double-blind, placebo-controlled study. Lancet Neurology 2009;8:141-50. This phase III study followed up the DIAS and DEDAS studies investigating the clinical outcome in patients receiving two doses of desmoteplase (90 microg/kg and 125 microg/kg) using the same 3-9 hour window and diffusion-perfusion mismatch criteria (≥ 20%) used in the DIAS trial. The percentage of patients with good clinical outcomes as defined as the study endpoint were less in the higher dose.
treatment group compared to placebo (placebo 46%, 90 microg 47%, 125 microg 36%), and the rate of symptomatic hemorrhage was also greater (placebo 0, 90 microg 3.5%, 125 microg 4.5 %), and more patients in this group died (placebo 6%, 90 microg 5%, 125 microg 21%). The investigators noted that the strokes were mild, and the responder rate in the placebo group was higher than anticipated, and 10 of the 14 deaths were felt to be unrelated to the drug. Follow-up studies of desmoteplase with different imaging selection criteria, DIAS-3 and DIAS-4, are ongoing.

SITS-MOST
Wahlgren N, Ahmed N, Davalos A, et al, for the SITS-MOST investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275-82. To comply with European Union regulations, the SITS-MOST study was organized as an observational study to assess the safety of intravenous tPA in the community when given within 3 hours of stroke onset. The reported the results in 6483 patients treated in hospitals. The data from this study were compared with pooled data from patients treated within 3 hours of onset in the NINDS, ECASS I and II, and ATLANTIS studies. In comparable patients (NIHSS SITS-MOST 12 vs pooled 13), the rate of symptomatic intracranial hemorrhage was less than in the controlled trials (7.3% vs 8.6%). Mortality was also less (11.3% vs 17.3%). Favorable outcome based on modified Rankin Scale scores at 3 months were similar (mRS ≤ 2: 54.8% vs 49.0% and mRS ≤ 1: 38.9% vs 42.3%). Like STARS, this study suggests that intravenous tPA can be extended to the community with safety and effectiveness comparable to that found in the controlled trials.

EPITHET
Davis SM, Donnan GA, Parsons MW, et al, EPITHET investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomized trial. Lancet Neurology 2008;7(4):299-309. This phase II study compared IV tPA to placebo given at 3-6 hours after symptoms onset. Patients were not selected based on diffusion-perfusion mismatch, but 86% of the patients had mismatch allowing the investigators to study that criterion as a potential selector. The study was negative for its primary endpoint, growth of the stroke lesion at 90 days in patients with mismatch, but there was a trend in favor of less growth in the treatment group. There were trends in favor therapy for the secondary endpoints less relative infarct growth, patients with no growth, and percent of patients with reperfusion. In patients who did have reperfusion, there was significantly less infarct growth, and there were better neurologic and functional outcomes.

ECASS III
The European Cooperative Acute Stroke Study Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29. This blinded, placebo-controlled trial compared the benefit of intravenous tPA (0.9 mg/kg) to placebo in patients in the 3 to 4.5 hour window. Otherwise patient selection criteria were similar to those in the NINDS study, with the following exception that restricted eligibility: NIHSS > 25, stroke visible by imaging of more than one third of the
MCA territory, combination of prior stroke and diabetes mellitus, any oral anticoagulation treatment. When assessed for favorable (mRS ≤ 1) vs unfavorable outcome (mRS ≥ 2), treatment favored treatment with an absolute risk reduction of about 7% (favorable outcome 52.4% vs 45.2%). A global analysis comparable to that used in the NINDS trial also favored treatment. Symptomatic intracranial hemorrhage was increased compared to placebo comparable in amount to that in NINDS tPA-treated patients using the NINDS definition, and fatal hemorrhage was less than in the NINDS trial (0.7% vs 2.9%). Mortality did not differ in treated and untreated patients, and was also less than in the NINDS trial. It is too early to know how much this study will affect practice in community and academic hospitals.

Current guidelines from the American Stroke Association and American Academy of Neurology


Intra-arterial Ischemic Stroke Therapy
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Buffalo Disclosure Information
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Major Stockholder: Boston Scientific, Access Closure Inc, Niagara Gorge Medical

UNLABELED/UNAPPROVED USES DISCLOSURE:
CAS and EP Systems, coronary balloon angioplasty

Acute Ischemic Stroke Burden
• Third most common cause of death in industrialized nations
• The single most common reason for permanent adult disability
• Estimated direct and indirect cost of stroke in the US for 2009: $88.9 billion
• 25% die within 1 year of the initial stroke
• Of the survivors
  • 30 to 50% do not regain functional independence
  • 15 to 30% are permanently disabled
• WHO 2002 (Worldwide)
  • 15.3 million strokes per year
  • 8.5 of the 57 million deaths every year
Four Frontiers of Stroke Care

- Pathophysiology Based Imaging to Enhance Patient Selection
- Improved Mechanical Thrombectomy Devices to Improve Technical Revascularization Outcomes
- Tiered system development and Telemedicine to enhance timely patient presentation
- Forging Interdisciplinary and Industry Ties to Bring Bench Work to the Bedside

Clinical Summary

- 61 yo F with acute onset left-sided weakness, neglect 7 hours ago
- On examination- Hemiplegia, Hemisensory loss, dysarthria, aphasia
- Presentation NIHSS: 25

CTA
CTH

CBV  CBF  TTP

Dx angio

TIMI 0

Decision Making

- Young patients
- 6 hours after stroke onset
- NCCT- No early ischemic changes
- CTP
  - Large penumbra
  - 20-30% occluded territory core
  - No basal ganglia region core
- Angiography
  - Distal M1 occlusion
  - Preserved lenticulostriate perforators
Outcome

- NIHSS-12 after 24 hours
- NIHSS- 6 at discharge
- mRS 1 at 3 months

Case Example Blends
Principles that Support the Future of Stroke Care

- CT Perfusion as Imaging Triage
- Novel Application of Intracranial Stent in lieu of mechanical thrombectomy
- Goal: Apply the lessons of every case in a manner beyond the anecdotal
  ~Rational Progression of Inquiry

Where have we come from?
AHA guidelines for AIS 2007

- Urgent anti-coagulation is not recommended
- ASA within 24-48 hrs is recommended (except <24 hrs after rt-PA)
- IV rt-PA in appropriate patients
- IA thrombolysis is a treatment option in major stroke patients <6 hours of occlusion who are not IV rt-PA candidates
- MERCI device is a reasonable intervention in selected patients (other interventions should be used in the setting of clinical trials)

AHA 2009 modification

- Increased time window of IV rt-PA after ECASS III-4.5h
- Narrower patient selection
  - 80 years or younger
  - If taking oral anticoagulants, international normalized ratio <1.7
  - Baseline NIHSS score ≤25
  - No history of both stroke and diabetes

RCT for AIS Revascularization

<table>
<thead>
<tr>
<th>Trial</th>
<th>NINDS</th>
<th>ECASS III</th>
<th>PROCAT II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Type</td>
<td>IV rt-PA vs. Placebo</td>
<td>IV rt-PA vs. Placebo</td>
<td>IA rt-PA + Asp vs. Heparin</td>
</tr>
<tr>
<td>Patients</td>
<td>333 (168 vs. 165)</td>
<td>821 (618 vs. 403)</td>
<td>180 (121 vs. 59)</td>
</tr>
<tr>
<td>Time Window Hours</td>
<td>0.3</td>
<td>3-4.5</td>
<td>0-6</td>
</tr>
<tr>
<td>Presentation NIHSS</td>
<td>14 vs. 15</td>
<td>10.7 vs. 11.6</td>
<td>17 vs. 17</td>
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<tr>
<td>Recanalization</td>
<td>NR</td>
<td>NR</td>
<td>66 vs. 18</td>
</tr>
<tr>
<td>Outcome (%) at 3 months</td>
<td>mRS ≤ 1: 39 vs. 26</td>
<td>mRS ≤ 1: 52.4 vs. 45.2</td>
<td>mRS ≤ 2: 40 vs. 25</td>
</tr>
<tr>
<td>mRS Recanalization Rates (%)</td>
<td>6.4 vs. 0.6</td>
<td>2.4 vs. 0.2</td>
<td>10 vs. 2</td>
</tr>
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</table>
### Prospective Intervention Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>IMS II</th>
<th>MERCI</th>
<th>M2 MERCI</th>
<th>Penumbra</th>
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</thead>
<tbody>
<tr>
<td>Treatment Type</td>
<td>IA MERCI + IA/T</td>
<td>IA Meri + IA/T</td>
<td>IA Merci + IA/T</td>
<td>IA Penumbra + IA/T</td>
</tr>
<tr>
<td>Patients</td>
<td>81</td>
<td>144</td>
<td>164</td>
<td>125</td>
</tr>
<tr>
<td>Time Window</td>
<td>0-3</td>
<td>0-8</td>
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<tr>
<td>Penetration</td>
<td>19</td>
<td>20</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Recanalization (%)</td>
<td>66</td>
<td>66.5 (66 device alone)</td>
<td>66 (66 Merci alone)</td>
<td>66 (66 Device alone)</td>
</tr>
<tr>
<td>Outcome (%) at 3 months mRS ≤ 2</td>
<td><strong>46</strong></td>
<td><strong>36</strong></td>
<td><strong>36</strong></td>
<td><strong>25</strong></td>
</tr>
<tr>
<td>SICH Rates (%)</td>
<td>9.9</td>
<td>7.8</td>
<td>9.8</td>
<td>11.2</td>
</tr>
</tbody>
</table>

### Where are we going?

### THE PARADIGM SHIFT

**The Buffalo Protocol**

- Mechanical Thrombectomy and Thrombolitics are Complementary Modalities
- CT Perfusion to Assess Salvageable Penumbra
  - Physiological Imaging for Patient Selection
  - Expansion of therapeutic window beyond 8 hours
Components of Stroke Patient Assessment

- Radiographic
  - Presence of Large Vessel Occlusion
  - CT angiography
  - Non-Contrast CT
  - CT Perfusion
- Clinical
  - NIH Stroke Scale
  - Time of stroke symptom onset
  - Suspected Etiology of Stroke

Non-Contrast CT

- Rule Out Hemorrhagic Conversion
- Early CT signs of completed infarct
  - Hypodense MCA
  - Loss of Grey-White Differentiation (Insular Ribbon)
  - Sulcal Effacement
  - Hypodensity in vascular distribution

CT Angiogram

- Aortic Arch through Intracranial Vessels
- High fidelity imaging of structural lesions
- Contrast in Arterial and Venous Phase may aid in evaluating the length and extent of an obstructive lesion
- Provides Structural Target and macrovascular access planning for contemplated endovascular option
CTA shows tortuous access

CT Perfusion
• Time To Peak (TTP): sensitive for ischemia
• Mean Transit Time (MTT): reflects capillary phase blood flow
  – Penumbra MTT > 145%
• Cerebral Blood Flow (CBF) and Volume (CBV): tend towards core infarct specificity
  – Infarct Core less than 2 ml/100 gm of tissue

Aquilion
Our CT Perfusion Experience

- Favorable Profiles for intervention
  - Small infarct core
  - Penumbra > 50% of occluded large vessel territory
  - Young patients

Our CT Perfusion Experience

- Unfavorable Profiles for intervention
  - Infarct Core > 30% of occluded vessel territory
  - Basal Ganglia involvement in infarct core
  - Increased risk of sICH

- Not as reliable as early ischemic changes in the initial 1-2 hours after stroke onset
Patient Selection

- Predictors of worse outcome:
  - Age > 80
  - SICH after intervention
  - ICA-T and Tandem EC-IC occlusions
- Higher chances of good outcome:
  - MCA distal M1 and M2 occlusions
  - Within 6 hours of stroke onset
  - Age <80
  - Small core, Large penumbra
  - No basal ganglia core, preserved lenticulostriate perforators

Goal of Physiology-based Imaging:

Rational Approach to Therapeutic Time Thresholds

History of Present Illness

- 26 yo, WF
- NIHSS 9
- R hemiparesis 1/5 RUE; 2/5 RLE
- R Facial droop
- R neglect
- Moderate expressive aphasia
- 3 hours out
Baseline CT

A small "black hole"

After 2 units IA rtapase
History of Present Illness: Ignore Basal Ganglia and CTP at your peril!

- 64 year old
- 7 hour onset
- NIHSS 23
- Hypodensity on Non-contrast CT
- Decreased CBV/CFB in basal ganglia
- Devastating stroke without intervention

Post Procedural Day 7: NIHSS 0
M1 spontaneously recanalized but inferior M2 trunk still TIMI 0
Post-Procedural CT
Hemorrhagic Silhouette of pre-operative infarct
Presentation after 8 hours:
Reaching Patients Previously Beyond Reach

- Higher risk of SICH around 20%
- Strict patient and therapy selection- 20% patients improve to mRS ≤ 2
- Wake-up stroke: 25% of ALL STROKES
  - Time of stroke symptom onset not known
  - Recanalization rates, SICH rates and outcomes comparable to intervention in patients presenting within 8 hours with CT Perfusion selection

Safety and Effectiveness of Endovascular Therapy After 8 Hours of Acute Ischemic Stroke Onset and Wake-up Strokes

Saifullah K. Nizamuddin, MD, MS; Kenneth V. Snyder, MD, PhD; Anurat H. Siddiqui, MD, PhD; Catherine C. Ivaska, MD, L, Nelson Bratton, MD; Emer L. Levy, MD

Background and Purpose—This is a retrospective review of patients who underwent endovascular recanalization with intra-arterial thrombectomy alone, including surgery take from June 2005 and June 2015.

Methods—Thirty patients with a modified modified Rankin score ≤ 2 and NIHSS burn ≤ 13 were included. All had anterior CT, CTA, and CT perfusion scans to evaluate for anatomy from brain. Recanalization effectiveness was assessed by angiograms obtained within 90 hours after intervention. Patient, treatment characteristics, and imaging and treatment outcomes were captured.

Results—Thirty patients were included (97.7% males, 4% with hemorrhagic conversion), with 90% of anterior CT or CTA showing an occlusion of the M1 segment (90% M1, 0% M2, 10% M1 and M2). Nineteen patients (63%) had a regular angiographic follow-up scan and were categorized as being functional (18%) or non-functional (0% M1, 0% M2, 4% M1 and M2). The average NIHSS score was 12.33 (10-16). The average duration of follow-up scan was 24 hours (12-48 hours). Patients had a modified Rankin score of 2 and NIHSS score of 2. The average interval of 8 hours was 12.33 (10-16). The average duration of follow-up scan was 24 hours (12-48 hours).

Conclusions—Our data show that delayed imaging in acute stroke patients can be used to improve clinical outcomes.

Role for Angiography

- Confirm location of occlusion by CTA
- Critical assessment of collateral flow adequacy: vascular compensation
- Screen for basal ganglia involvement in infarct core with concomitant increased SICH risk
- Early venous filling or luxury perfusion from lenticulostriate perforator region
- Intervention Planning (i.e. stent size)
Our policy for IVT

- Only after CT stroke Study
- Only after exclusion of large vessel occlusions and other indications for primary endovascular therapy
- 0-4.5 hour time window
- Secondary endovascular therapy after failed IVT

Primary Endovascular Therapy

- Large vessel or angular artery occlusion
- Dominant hemisphere with speech changes
- Acute vessel dissection
- Contraindication for t-PA

Secondary Endovascular Therapy after failed IVT

- Did not improve after IVT
- Fail to improve by 4 NIHSS points within the first hour
- Reocclusion after IVT
  - Improve and then decline after IVT
  - 34% reocclusion and poor outcome after reocclusion with IVT
Timely Recanalization the Key

An Example from SARIS

65 yo male
Onset 6hrs before presentation
NIHSS = 14
From puncture to recanalization = 24 minutes

4 hours after procedure...
NIHSS = 0

Outcomes increase with Recanalization

- Meta-analysis by Rha and Saver
- 53 studies, 2066 patients
- mRS ≤ 2 at 3 months more frequent, OR 4.43
- Decreased mortality at 3 months, OR 0.24
- Higher recanalization with endovascular therapy
Secondary Endpoint – Modified Rankin Scale (mRS) 90 Day mRS of Revascularized vs. Non-revascularized Patients

<table>
<thead>
<tr>
<th>mRS 0-2</th>
<th>mRS 3-5</th>
<th>Death</th>
<th>Successful Revascularization (n=51)</th>
<th>Unsuccessful Revascularization (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27/51</td>
<td>15/4</td>
<td>7</td>
<td>16/5</td>
<td>1</td>
</tr>
<tr>
<td>p &lt;0.001</td>
<td>‡</td>
<td></td>
<td>29/47</td>
<td></td>
</tr>
</tbody>
</table>

‡ All p values from Fisher's exact test for mRS 0-2 outcome displayed for descriptive purpose

Merci and Penumbra: Conventional Mechanical Revascularization

Current Strategies For the Endovascular Management of Acute Stroke

- Pharmacologic
  - Intra-arterial tPA
- Mechanical
  - Concentric - Meri Device
  - Penumbra
  - EXOS
- Foreign body retrieval devices
  - Alligator, Neuronet, Snare
- Best data demonstrate only 50-80% recanalization rate rate
- Endovascular Bypass
Merci Case Example

Concentric Multi-Merci
- Multi-Merci Recanalization Rates
  - 56% (59/111) Retriever alone
  - 69.4% (77/111) Post Procedure
  - TEL < 2500
  - 33% XG:
    - Included 22 patients who failed IV tPA
  - Multi-Merci Part II includes an additional 52 patients
    - mRRI < 2.9%
    - Mortality: 30%
    - Symptomatic ICH: 7.9%
    - Asymptomatic ICH: 20.9%

History of Present Illness
- 76 year old woman with prior history of multiple brain Aneurysms clipped, coiled and VPS
- Unknown onset over 12 hours ago
- NIHSS 30
- History of Atrial Fibrillation off Coumadin for GI bleed
CT perfusion bilateral PCA ischemia

CTA shows midbasilar artery occlusion

Solution R radial artery access
Initial angiogram confirms mid-basilar occlusion
MERCI retriever deployed in a typical Buffalo patient

Clot retrieved

Post intervention improvement from NIHSS 30 down to 4
- Discharge to rehab.
- Home in 2 weeks
- Pancakes for the grandchildren
Penumbra Data

- NIHSS > 8 and less than 8h from onset
- 81.6% revascularization to TIMI 2 or 3
- SAE 3.2%
- ICH symptomatic 11.2%, asymptomatic 16.8%
- NIHSS improved by >/= 4 57.8%
- mRS < = 2 25%
- Mortality at 30d 26.4%

Penumbra Case Example

History of Present Illness

- 83 yo male
- acute RMCA stroke
- left plegic, R gaze preference, L facial droop, dysarthric
- NIHSS > 10

- onset > 14 hrs
- PMH = paroxysmal atrf (discovered on this admission)
Initial CT: R MCA hyperdense sign

Initial CT perfusion: relative CBV preservation suggests ischemia rather than infarct, ie salvageable!!

$13.9 \times 2.5 = 34.8$

CBF*CBV product suggests tissue remains salvageable.
Combo micro + guide cath run demonstrates clot location/size, distal patency.

After MERCI, integrilin, retavase, MERCI again → TIMI-II inferior division clot still present.

clot still present

clot, no sup. M2
The Buffalo Experience

PROSPECTIVE REGISTRY OF AIS INTERVENTIONS
2006-2008
(in press World Neurosurgery, May)

Methods

• Endovascular AIS interventions from 2006 to 2008 were recorded prospectively
• Admission: Patient demographics; comorbid conditions; smoking status; tix CVA/TIA; API/AC status, and/or statin therapy at presentation; time of stroke onset; presentation NIHSS; location of occlusion; degree of occlusion (TIMI).

Methods

• CT Perfusion Study (Aquilon One – 320 slice scanner or 64 slice scanner)
• All analyzed and processed by Endovascular Fellow
• Preserved Volume Map (>30%)
Demographics

- 193 patients
- Not candidates or contraindication to IV tPA
- Mean age 68.4 ± 17.8 (Median 73)
- Male: 82, Female: 111
- Mean presenting NIHSS 13.9 ± 5.3 (Median 14)

Time to Treatment

- Average time-to-treatment was 345 min (34min–19h)
  - 0–3 hours: 60
  - 3–8 hours: 80
  - >8 hours: 30
- Door to needle time: 194.4 ± 265.4 min (Median 114.5 min)
- Needle to recanalization time: 78.0 ± 40.4 min (Median 72 min)

Location of occlusion

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of patients</th>
<th>Recanalization Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial supra-otic</td>
<td>34</td>
<td>67.6</td>
</tr>
<tr>
<td>Petrous ICA</td>
<td>9</td>
<td>70.7</td>
</tr>
<tr>
<td>ICA-Terminal</td>
<td>29</td>
<td>48.3 vs. 73 (P=0.007)</td>
</tr>
<tr>
<td>MCA</td>
<td>138</td>
<td>71.7</td>
</tr>
<tr>
<td>ACA</td>
<td>16</td>
<td>81.3</td>
</tr>
<tr>
<td>Tandem EC-IC</td>
<td>23</td>
<td>69.6</td>
</tr>
<tr>
<td>Anterior Circulation</td>
<td>165</td>
<td>66</td>
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<tr>
<td>Posterior Circulation</td>
<td>24</td>
<td>79.2</td>
</tr>
<tr>
<td>Total</td>
<td>193</td>
<td>69.4</td>
</tr>
</tbody>
</table>
Etiology

- Arterioembolic: 41
- Cardioembolic: 97
- Dissection: 9
- L-R shunt: 3
- Unknown: 52

Types of Therapy

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>No. patients</th>
<th>Recanalization rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merci retriever</td>
<td>108</td>
<td>67.6</td>
</tr>
<tr>
<td>Penumbra</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Intracranial stent</td>
<td>32</td>
<td>71.2</td>
</tr>
<tr>
<td>Intracranial angioplasty</td>
<td>35</td>
<td>63.8</td>
</tr>
<tr>
<td>Extracranial stent</td>
<td>26</td>
<td>72.2</td>
</tr>
<tr>
<td>Extracranial angioplasty</td>
<td>24</td>
<td>75</td>
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<tr>
<td>GPIIb-IIIa antagonist</td>
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<td></td>
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<tr>
<td>Intravenous</td>
<td>38</td>
<td>76.3</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>54</td>
<td>66.7</td>
</tr>
</tbody>
</table>

Types of Therapies

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Number of Patients</th>
<th>Recanalization (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical only</td>
<td>94</td>
<td>71.2</td>
</tr>
<tr>
<td>Pharmacological only</td>
<td>24</td>
<td>62.5</td>
</tr>
<tr>
<td>Both</td>
<td>75</td>
<td>69.3</td>
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</table>
End Points

- Recanalization Rate
- SICH Rates
- Outcomes at 3 months
- Mortality at 3 months

Summary

<table>
<thead>
<tr>
<th></th>
<th>NINDS</th>
<th>Proact II</th>
<th>IMS II</th>
<th>Burch</th>
<th>Penumbra</th>
<th>Buffalo Exp</th>
<th>&lt; 8 hr</th>
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<td>180</td>
<td>81</td>
<td>104</td>
<td>125</td>
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<td>17</td>
<td>19</td>
<td>19</td>
<td>17</td>
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<tr>
<td>Recan</td>
<td>66%</td>
<td>58%</td>
<td>68%</td>
<td>82%</td>
<td>70%</td>
<td>66%</td>
<td>65%</td>
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<tr>
<td>SICH</td>
<td>6%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>11%</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>mRS (0-2)</td>
<td>39%</td>
<td>41%</td>
<td>44%</td>
<td>36%</td>
<td>25%</td>
<td>39%</td>
<td>44%</td>
</tr>
<tr>
<td>Mortality</td>
<td>17%</td>
<td>25%</td>
<td>18%</td>
<td>26%</td>
<td>32%</td>
<td>28%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Occlusions and Recanalizations

- Occlusions
  - TIMI 1: 32
  - TIMI 0: 161
- Recanalization (69.9%)
  - TIMI 3: 67
  - TIMI 2: 68
Predictors of SICH

- Atrial Fibrillation, OR=2.79, P=0.022 is the only predictor of SICH.
- Atrial fibrillation despite an increase in SICH did not cause any significant difference in outcomes at 3 months.
- In future, patients with AFib should be considered as high risk for SICH during decision making for endovascular therapy.

Time Window

- No difference in endpoints between 0-8 hours and wake-up strokes.
- First study to show efficacy of endovascular therapy in wake-up strokes.
- Time-window is not a predictor of outcome after CT-Perfusion based patient selection.
- Higher SICH rates (20%) and worse outcomes due to SICH if treated after 8 hours.
- But 20% of patients after 8hrs still recover to mRS < 2 if carefully selected.

Octogenarians: Inferior 3-month Outcomes

- mRS≥3
- Age > 80, OR=3.16, P=0.001
- SICH, OR=6.73, P=0.008
- The usefulness of endovascular therapy in this group need to be evaluated carefully in larger multi-center studies.
Strengths

- All comor population
- Careful patient and therapy selection
- Not confined to specific inclusion criteria, therapy type or time window like the other prospective trials

Limitations of Study

- Subgroups not directly comparable due to selection bias
- CT Perfusion trends require further analysis and confirmation (statistical power)
- Prospective Registry for data collection but no a priori hypothesis or ongoing control group

SARIS CASE
History of Present Illness

- HPI: 62 yo LH WF 3 days s/p vaginal hysterectomy presenting with acute onset of left hemiplegia and speech change.
- 4.5 hrs from onset.
- Recently taken off coumadin for surgery.
- PMH/PSH: Altb, RA, gout, HTN, Pacemaker, nephrectomy

Physical Exam

- NIHSS of 15
- Left-sided homonymous hemianopsia, and
  - Right gaze preference
- Flaccid Left-sided hemiparesis,
- Slurred speech,
- Left-sided facial droop
Devices

- 6 fr envoy
- Prowler 14
- Synchro 2 stll
- Transcend exchange
- Wingspan 3.5 x 15 mm stent
Outcome

- Recanalized to TIMI 3
- Time to Recanalization ~ 20 min
- Discharged to rehab with NIHSS 5

Primary Stent for Stroke – a new paradigm
Use of a vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods

Clinical article
J. Martin, M.D., M.S.*; Richardson J. Hosty, M.D., Ph.D.; Janisse Shanski, M.D., M.S.*
Wendy W. Kwon, M.D., Ph.D.; Christopher Krieger, M.D., Ph.D.*
S. Rodriguez R. Brotchi, M.D., M.S.; Neal A. Glassman, M.D.*
Amos S. Revin, M.D., Ph.D.; L. Nelson Squires, M.D.; Alan S. Buls, M.D.*
and E. Paul Levy, M.D.*

- PROOF OF CONCEPT: STENTS WORK IN REFRACTORY CASES
- Twenty patients with Enterprise stent for salvage after other modalities failed for recanalization of AIS
- Presentation NIHSS 17
- TIMI 2/3 recanalization 100%
- Mean NIHSS improvement at discharge 8 points

Clinical summary

- 41 yo truck driver
- Acute R hemiparesis, to nearest ER
- REACH consult, TPA given
- Pt worsened, NIHSS 19, needed intubation
- TX to Gates hospital 9 hrs after onset

CT perfusion normal!

Caveat!
Brainstem not included
Plain CT

CTA

Finding

- Acute vertebro-basilar occlusion with CVA
- Likely a consequence to calcified VA stenosis R
Options?

- Medical therapy? ASA, Plavix, TPA?
- Thrombolysis? Merci? Penumbra?
- Angioplasty?
- Surgical bypass? Suboccipital decompression?
- Ventriculostomy?

Temporary endovascular bypass

- Capitalizes on mechanical advantages of stent for recanalization
- Avoids necessity for dual antiplatelet therapy (problematic in case of future open surgical interventions)
- Avoids device related long-term complications (instent-stenosis)


Angio pre-intervention

L VA ends in PICA, does not contribute to BA
Angio pre-intervention

Intervention, working views, double injection technique

Temporary endovascular bypass
Patient improved immediately -> NIHSS 8, extubated
POD#3 worsening, increased lethargy (brain edema)
Emergent ventriculostomy, SOC
Pt made an excellent recovery, d/c after 15 days (NIHSS 3)

NIHSS score is now a “1”
At this point, tx for remaining stenosis with Xience stent
(Everolimus eluting stent, cardiac)
Pt remains to do well (NIHSS1)
First FDA and Drug Administration-Approved Prospective Trial of Primary Intravenous Stenting for Acute Stroke. SARIS (Stent-Assisted Recanalization in Acute Ischemic Stroke)


- Presentation NIHSS 14
- Recanalization 100%
- SICH 5%
- mRS < 2 at 3 months 45%
- Mortality at 3 months 25%

SARIS outpaces the Buffalo Mechanical Revascularization Experience

<table>
<thead>
<tr>
<th></th>
<th>SARIS 9 hr</th>
<th>0-3 hr Enda</th>
<th>SARIS 9 hr</th>
<th>0-3 hr Enda</th>
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<tr>
<td>Age</td>
<td>14</td>
<td>13</td>
<td>30</td>
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<td>NIHSS</td>
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<td>13</td>
<td>14</td>
<td>15</td>
</tr>
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<td>Recan</td>
<td>70%</td>
<td>69%</td>
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<td>Mortality</td>
<td>28%</td>
<td>26%</td>
<td>25%</td>
<td>26%</td>
</tr>
</tbody>
</table>

SARIS II in progress
Stentriever: An Inspired Platform for Mechanical Thrombectomy

- Flow restoration in manner analogous to stent
  - Use flow to aid thrombectomy
  - Provide the brain with holiday from ischemia even if overall pass ultimately fails
- No permanent hardware. Most of the time
- SWIFT trial for Solitaire FR
  - First 4 US cases performed at Buffalo

FIRST US SOLITAIRE CASE

History of Present Illness

- 55 year old
- H/O coronary artery disease s/p coronary stents and now non-compliant with ASA/Plavix
- Acute onset of Left Hemiparesis, Gaze Deviation and Neglect
- NIHSS 10
- Presents 4 hours post-ictus
Therapy

- Full Dose IV TPA given.
- CT scan at 40 minutes of infusion w/o ICH
- No clinical improvement
- Angio Suite for Mechanical Intervention
- ASA 650 mg NGT given
Solitaire Swift Trial

- 6 Fr Envo
- Heparinized to ACT of
- Gold Tip Microwire
- Prowler Select Plus Microcatheter
- 4 mm x 20 mm Solitaire
- Note: Rebar 18 and Marksmen are microcatheter alternatives
Clinical Outcome

- NIHSS 2 for LLE slight weakness and very mild residual facial
- Discharged home.

SECOND US SWIFT CASE:
The Challenges of Development

History of Present Illness

- 76 year old
- H/O atrial fibrillation with recent embolic stroke complicated by hemorrhagic conversion
- On coumadin; INR 1.6 on presentation.
- Acute onset L hemiplegia, dysarthria at home
- Presents to ED 3 hours from ictus
- NIHSS 13: Left hemiplegia, neglect, sensory deficit
Solitaire FR

- R M1 occlusion with salvageable penumbra
- Neurology team declined to offer TPA due to intracranial hemorrhage within 30 days
- Angio suite for Acute revascularization.
  - 6 Fr Envoy
  - Prowler Plus and Gold Tip
  - 4 x 20 mm Solitaire FR
Lesion Crossed into Superior M2 Trunk

First Solitaire FR Deployment
TIMI 3 result after retrieval but inferior M2 trunk remains occluded
Poor Flow Restoration Due to Immense clot burden. On retrieval, stent detached!

IA Integrillin given to prevent propagation of thrombus in inferior M2 trunk into M1
Angiogram Post-op Day 1:
Stent Patent
CT Post-op Day 3: Not in time for the Inferior Trunk!
Clinical Outcome

- Disposition to Rehab likely
- Awaiting evaluation whether can participate in 3 hours of minimum therapy
- Currently undergoing PT/OT
- NIHSS 10
  - L hemiparesis (arm greater than leg)
  - L sensory disturbance
  - Neglect and Gaze deviation improved

THIRD US SOLITAIRE CASE
History of Present Illness

- 65 year old
- Known Aflib off coumadin (INR 1.3) due to recent ex lap for diverticulitis
- Acute Onset L hemiplegia
- Presents at 4.5 hours after ictus
- NIHSS 13
- Loaded with 650 mg po ASA
Solitaire FR Deployment

TIMI 3 post-Retrieval
Post-Operative Course

- NIHSS 1 due to residual facial
- Will be discharged home
What if he were taken to a “Designated Stroke Center” Without Endovascular Capability?

Engineering Systems of Health Service Delivery
Bringing Patients to the Intervention

Future of Stroke: Requires Engagement of Health System Design
- System needs to get the patient to care
- Stroke and Hub Model
- Designated Stroke Center versus Comprehensive Stroke Center
- The Role of Telemedicine
Network of the Future

Comprehensive Stroke Center
“S I R E N”

- S... Stroke Team (24/7).
- I... Imaging Center (multimodality 24/7).
- R... Rapid Response (door-needle <30min).
- E... Endovascular Team (24/7).
- N... Neuro ICU.

NYSDOH Designated Stroke Center

For Stroke Awareness, the Bar is High

For Stroke treatment, the Bar is Low
FALSE

The best stroke center is the one closest to you.

DOH Directive
EMT to deliver patients to
“nearest designated stroke center”

Designated Stroke Center
Vs
Comprehensive Stroke Center

What makes up a Comprehensive Stroke Center of Excellence

• NYSDOH Stroke Designation
• The Joint Commission Disease Specific Coordination of Care Certification
• American Heart/American Stroke Association GWTG Award for Stroke Care
• Neuro Imaging: Availability of a CT (64 slice or greater) with CT Perfusion and CT Angiogram
• MRI,DWI, Perfusion
• Endovascular team available therefore:
  – Door to catheter at emboli site < 90 minutes
  – Interventional neurosurgeon or radiologist on call 24/7/365
  – Treats many (500-10000) stroke cases per year
What makes up a Comprehensive Stroke Center of Excellence (continued)

• Dedicated Neuro Intensive Care Unit with Credentialed Neurocritical Care Physician
• A minimum number (4-5) catheter based stroke interventions per month
• Peer reviewed published results of Stroke Intervention from the specific facility

Comprehensive Stroke Centers

Important Factors
• Volume—the more you do, the better you get
• Best in class clinical outcomes
• Published results (clinical and research)
• Breadth and depth of clinical services
• Unique technology
• Nationally recognized clinicians
• Medical education, local and national
• Community outreach

GVI: Final Cornerstone in the Future of Stroke Care

• Collaboration with Basic Scientists
  — Materials Science and Engineering
  — Biological, Chemical and Radiologic Science
• Collaboration with other clinicians
  — Neurology, Cardiology, Vascular Surgery
• Partnership with Industry
  — From Bench to Proof-of-Concept
  — Industry Role to Manufacture and Bring to Patients
Conclusions

- Decision-making Algorithm
  - Clinical Exam, Time of Onset, Age to weigh risk of significant ICH versus penumbra preservation
  - Imaging: CTP, non-contrast head CT, CTA and involvement of basal ganglia
- Technical Nuances of Mechanical Revascularization
  - Penumbra, Merci, Intracranial stent (SARIS), Stentrievers (Solitaire and Trevo)
In Buffalo, Four Avenues of Progress Against a Terrible Disease

- Imaging with CT Perfusion
- Mechanical Thrombectomy with Intracranial Stenting and Stentriever
- Health Systems Delivery with a Tiered Stroke System and the use of Telemedicine
- Collaboration with Basic Scientists, Clinicians and Industry with the Global Vascular Institute

Thank you!
Antiplatelets, anticoagulants for TIA and stroke: When to use what?

A. Objectives

- Review and understand the definitions and subtypes of ischemic stroke
- Review and understand the level of evidence and class of current AHA/ASA recommendations for use of antiplatelets and anticoagulants in ischemic stroke
- Review and understand the current guidelines for use of antiplatelets and anticoagulants in acute ischemic stroke
- Review and understand the current guidelines and for use of antiplatelets and anticoagulants in secondary stroke prevention

Major References:

B. Definition and subtypes

Ischemic stroke is a complex syndrome of multiple etiologies resulting from interruption of blood flow to defined areas of the brain. Multiple stroke subtypes are thought to be the result of atherosclerosis of the cerebral arteries, large and small, that supply the brain, as well as the result of embolism to the brain from the aorta (atherogenic brain emboli), heart (cardiogenic emboli, predominantly due to atrial fibrillation), and in up to 25-30% of strokes, an unknown source (cryptogenic infarcts). Large artery atherosclerotic infarct can occur due to disruption of normal cerebral perfusion either due to severe arterial stenosis (“hemodynamic” mechanism) or due to thrombosis and artery-to-artery embolism. In lacunar (small, subcortical) infarcts, lipohyalinosis and other occlusive diseases of the small penetrating brain arteries are thought to be responsible. Despite thorough evaluation, the specific pathogenesis of stroke in individual patients is sometimes difficult to elucidate. Furthermore, treatment of each individual stroke
patient should consider the underlying etiology as well as the timeline of clinical presentation, including the time of onset.

C. Use of antiplatelet and anticoagulants in acute ischemic stroke.

- Patients who are not eligible for IV or intraarterial thrombolysis therapy should be considered for a variety of antithrombotic agents, including those investigated in clinical trials of acute ischemic stroke (aspirin, heparin, low molecular weight heparins, and heparinoids). Other antiplatelet agents proven effective in the long-term reduction of recurrent ischemic events are undergoing evaluation in the acute setting.

- Antithrombotic therapy in acute cerebrovascular ischemia may benefit patients by: (1) reduction of the risk of stroke progression or recurrent cerebral thromboembolism; and (2) prevention of venous thromboembolic complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE).

- Multiple stroke mechanisms complicate the use of antithrombotic agents and impart various risks of the outcomes and risk profile for complications; therefore, few trials have been adequately designed to accurately assess the differential efficacy of antithrombotic therapies by stroke subtype. Early evaluation of the underlying mechanism of stroke may allow guide the therapy based on a presumptive diagnostic subtype.

Recommendations:

1. Anticoagulants for Altering Outcomes Among Acute Stroke in Patients Not Eligible for Thrombolysis

   - For patients with acute ischemic stroke, we recommend against full-dose anticoagulation with IV, SC, or low-molecular-weight heparins or heparinoids (Grade 1B).

   - For patients with acute ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy (initial dose of 150–325 mg) [Grade 1A].

2. Antithrombotic Therapy for Prevention of Deep Vein Thrombosis and Pulmonary Embolism in Acute Ischemic Stroke

   - For acute stroke patients with restricted mobility, we recommend prophylactic low-dose SC heparin or low-molecular-weight heparins (Grade 1A).

   - For patients who have contraindications to anticoagulants, we recommend intermittent pneumatic compression (IPC) devices or elastic stockings (Grade 1B).
D. Use of antiplatelet and anticoagulants in secondary stroke prevention

- Four antiplatelet agents have been shown to reduce the risk of ischemic stroke after a stroke or TIA and are currently approved by the FDA for this indication (aspirin, ticlopidine, clopidogrel, and dipyridamole/aspirin combination). Antiplatelet therapy has been shown to be associated with a 28% relative odds reduction in nonfatal strokes and a 16% reduction in fatal strokes in a meta-analysis of results of 21 randomized trials comparing antiplatelet therapy with placebo in 18,270 patients with prior stroke or TIA.

- Each antiplatelet agent has been shown to be more efficacious than placebo in secondary stroke prevention; however, their safety profile and costs associated with daily use differ. Aspirin showed similar efficacy in preventing vascular events at the higher and lower range doses; however, higher doses of aspirin have been associated with a greater risk of gastrointestinal hemorrhage. Ticlopidine has had limited use given its risk of neutropenia, rash, diarrhea, and thrombotic thrombocytopenic purpura in addition to the bleeding complications. Clopidogrel has safety profile similar to that of aspirin but reports of thrombotic thrombocytopenic purpura have been described. Use of combination of aspirin and extended-release dipyridamole is routinely accompanied by headache at the therapy initiation. In addition, no clinical data suggest that additional aspirin could alter the safety and efficacy of this combination antiplatelet agent.

- Selection of oral antiplatelet therapy may be influenced by each individual patient’s comorbid illnesses, side effects, and costs. Aspirin is less expensive, which may affect long-term adherence. However, even small reductions in vascular events compared with aspirin may make combination dipyridamole and aspirin or clopidogrel cost-effective from a broader societal perspective. For patients intolerant to aspirin because of allergy or gastrointestinal side effects, clopidogrel is an appropriate choice. Dipyridamole is not tolerated by some patients because of persistent headache. The combination of aspirin and clopidogrel may be appropriate for patients with recent presentation with acute coronary syndromes or after vascular stenting. At present, the selection of antiplatelet therapy after stroke and TIA should be individualized.

- The use of oral anticoagulants to prevent recurrent stroke among patients with noncardioembolic stroke, including strokes caused by large-artery EC or IC atherostenosis, small penetrating artery disease, and cryptogenic infarcts have been addressed in several randomized trials including the Stroke Prevention in Reversible Ischemia Trial (SPIRIT), the Warfarin Aspirin Recurrent Stroke Study (WARSS), and the
Warfarin-Aspirin Symptomatic Intracranial Disease (WASID). All demonstrated similar efficacy vs. increased bleeding rate with the use of oral anticoagulation long-term.

**Recommendations:**

- For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (*Class I, Level of Evidence A*).

- Aspirin (50 to 325 mg/d) monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy (*Class I, Level of Evidence A*).

- Compared with aspirin alone, both the combination of aspirin and extended-release dipyridamole and clopidogrel are safe. The combination of aspirin and extended-release dipyridamole is recommended over aspirin alone (*Class I, Level of Evidence B*) and clopidogrel may be considered instead of aspirin alone (*Class IIb, Level of Evidence B*) on the basis of direct-comparison trials. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, tolerance, and other clinical characteristics.

- For patients allergic to aspirin, clopidogrel is reasonable (*Class IIa, Level of Evidence B*).

- The addition of aspirin to clopidogrel increases the risk of hemorrhage (*Class III, Level of Evidence A*). Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (ie, coronary stent or acute coronary syndrome) (*I*).

- 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 for noncardioembolic patients, no single agent or combination has been studied in patients who have had an event while receiving aspirin.

**E. Special considerations: recommendations**

- For patients with ischemic stroke or TIA and extracranial arterial dissection, use of warfarin for 3 to 6 months or use of antiplatelet agents is reasonable (*Class IIa, Level of Evidence B*). Beyond 3 to 6 months, long-term antiplatelet therapy is reasonable for most stroke or TIA patients. Anticoagulant therapy beyond 3 to 6 months may be considered among patients with recurrent ischemic events (*Class IIb, Level of Evidence C*)

- For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event (*Class IIa, Level of Evidence B*). Warfarin is reasonable for
high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis (Class IIa, Level of Evidence C).

• Patients with ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for deep vein thrombosis, which is an indication for short- or long-term anticoagulant therapy, depending on the clinical and hematologic circumstances (Class I, Level of Evidence A). Patients should be fully evaluated for alternative mechanisms of stroke. In the absence of venous thrombosis, long-term anticoagulants or antiplatelet therapy is reasonable (Class IIa, Level of Evidence C). Patients with a history of recurrent thrombotic events may be considered for long-term anticoagulation (Class IIb, Level of Evidence C)

• For cases of cryptogenic ischemic stroke or TIA and positive APL antibodies, antiplatelet therapy is reasonable (Class IIa, Level of Evidence B). For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis, oral anticoagulation with a target INR of 2 to 3 is reasonable (Class IIa, Level of Evidence B)

• For patients with cerebral venous sinus thrombosis, UFH or LMWH is reasonable even in the presence of hemorrhagic infarction (Class IIa, Level of Evidence B). Continuation of anticoagulation with an oral anticoagulant agent is reasonable for 3 to 6 months, followed by antiplatelet therapy (Class IIa, Level of Evidence C)

• In those with a recent acute myocardial infarction, other acute coronary syndrome, or a recently placed coronary stent, we recommend clopidogrel plus aspirin (75–100 mg) [Grade 1A]. The optimal duration of dual antiplatelet therapy depends on the specific cardiac indication (see other articles in this supplement).

• In patients undergoing carotid endarterectomy, we recommend aspirin (50–100 mg/d) prior to and following the procedure (Grade 1A).

• In patients with atrial fibrillation who have suffered a recent stroke or TIA, we recommend long-term oral anticoagulation (target INR, 2.5; range, 2.0-3.0) [Grade 1A].

• For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin at a dose of 75–325 mg/d (Grade 1B).

• In patients with stroke associated with aortic atherosclerotic lesions, we recommend antiplatelet therapy over no therapy (Grade 1A). For patients with cryptogenic stroke associated with mobile aortic arch thrombi, we suggest either oral anticoagulation or antiplatelet agents (Grade 2C).
# "Size of Treatment Effect"

<table>
<thead>
<tr>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
<th>Class III</th>
</tr>
</thead>
</table>
| Multiple (3-5) population risk strata evaluated* | Limited (2-3) population risk strata evaluated* | Very limited (1-2) population risk strata evaluated* | Risk > Benefit  
No additional studies needed |
| General consistency of direction and magnitude of effect | Recommendation that procedure or treatment is useful/effective  
Sufficient evidence from multiple randomized trials or meta-analyses | Recommendation that procedure or treatment is useful/effective  
Limited evidence from single randomized trial or non-randomized studies | Recommendation that procedure or treatment not useful/effective and may be harmful  
Sufficient evidence from multiple randomized trials or meta-analyses |
| Recommendation that procedure or treatment is useful/effective  
Sufficient evidence from multiple randomized trials or meta-analyses | Recommendation in favor of treatment or procedure being useful/effective  
Some conflicting evidence from multiple randomized trials or meta-analyses | Recommendation in favor of treatment or procedure being useful/effective  
Only diverging expert opinion, case studies, or standard-of-care | Recommendation in favor of treatment or procedure being useful/effective  
Only diverging expert opinion, case studies, or standard-of-care |
| Procedure/Treatment SHOULD be performed/administered | Procedure/Treatment MAY BE CONSIDERED | Procedure/Treatment MAY BE CONSIDERED | Procedure/Treatment should NOT be performed/administered  
SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL |

**Suggested phrases for writing recommendations**

- **Should**
  - is recommended
  - is indicated
  - is useful/effective/beneficial
- **Is reasonable**
  - can be useful/effective/beneficial
  - may/might be recommended or indicated
  - may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established
- **Is not recommended**
  - is not indicated
  - should not
  - is not useful/effective/beneficial
  - may/might be harmful

---

*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers’ comprehension of the guidelines and will allow queries at the individual recommendation level.
Significance of ICA dissection (ICAD)

- Accounts for up to 20% of ischemic strokes in young adults
- Annual incidence rate of 2.6 (95% CI, 1.86 to 3.33) per 100,000 inhabitants. Extracranial internal carotid artery dissection (eICAD) can be expected in about 1.7 to 3.0/100,000 per year
- 47% of strokes documented in an ICAD population
- Associated with trauma, although 50% of patients with dissections and stroke have no clear history of antecedent neck trauma
- The risk of recurrent stroke in patients with ICAD is < 1% per year
- Evidence from randomized trials on the best clinical therapy is still missing

Causes of ICAD

- Two major causes: spontaneous and traumatic
  - Spontaneous
    - Incidence is 2.6 to 2.9 per 100,000 inhabitants per year
    - Clinical manifestation include: headache, neck pain, Horner syndrome, stroke/TIA
    - Hereditary connective tissue disorders and/or a family history of stroke
  - Traumatic
    - Commonly associated with severe trauma to the head and/or neck
    - The probable mechanism of injury is rapid deceleration, with resultant hyperextension of the neck, stretching the ICA over the upper cervical vertebrae, producing an intimal tear

Pathology of Dissection

- Subintimal Dissection: stenosis of the arterial lumen
- Subadventitial Dissection: aneurysmal dilatation of the artery ("pseudoaneurysm" is a misnomer in this setting because the walls are composed of blood-vessel elements, e.g. media and adventitia)

Pathogenesis of Dissection

- **Genetic Factors:** exact type of arteriopathy remains elusive in most cases.
  - Ehlers-Danlos syndrome type IV
  - Marfan’s syndrome
  - Autosomal dominant polycystic kidney disease
  - Osteogenesis imperfecta type I
  - Fibromuscular dysplasia
- **Environmental Factors:**
  - Hyperextension or rotation of the neck
  - Chiropractic manipulation of the neck: ~1 in 20,000 spinal manipulations causes a stroke
  - Recent history of a respiratory tract infection

Major patterns of ICAD

- Stenotic (48%)
- Occlusive (35%)
- Dissecting (pseudo) aneurysm (17%)
The significance of vessel patency

- In 40 patients with spontaneous ICAD related stroke, the number, size and pattern of DWI lesions between patients with stenotic ICAD (n=15) and occlusive ICAD (n=25) were compared.
- In stroke attributable to spontaneous ICAD (siCAD), diffusion-weighted imaging characteristics may be influenced by the patency of the carotid artery.

Pathophysiology of ICAD related Strokes

- Artery-to-artery embolism or by causing significant stenosis and occlusion of the proximal vessel.
- A thrombus formation in the dissected artery with secondary distal embolism is the most likely mechanism of cerebral infarction in CAD.
Management of Carotid dissection

- **Medical Treatment:**
  - Because the pathophysiology of the strokes attributed to ICAD is mainly thrombo-embolic, anticoagulation has been recommended to prevent a new event.
  - No randomized trials have studied anticoagulation vs. antiplatelet therapy (CADISP study group, Stroke 2007;38:2605–2611).
  - In the acute phase, rIVtPA has been reported as a safe and effective treatment (Barre L et al. Neurology 2006;54:2159–2161). However, tandem occlusion seems to independently predict poor outcome after rIVtPA (Rubiera M et al. Stroke 2006;37:2301–2305).

- **Endovascular Treatment:**
  - Thrombolysis seems to be safe. More data is needed to prove efficacy (Meta-Analysis by Menon R et al. J Neurol Neurosurg Psych 2008;79:1122–1127).
  - Angioplasty and Stenting are effective and safe with or without pseudoaneurysm (Kadkhodayan Y et al. AJNR Am J Neurorad 2005; 26:2328–35).
  - It has also been performed with success in patients with acute tandem ICA-MCA occlusion with ICAD, using extracranial carotid stents (Lavallee PC et al. Stroke 2007;38:2270–2274).

**Antiplatelets Vs. Anticoagulation in Cervical Artery Dissection - CADISP study group**

- Meta-analysis on the treatment of cervical artery dissection
- Antiplatelet is suggested to be preferable in
  - NIHSS ≥15 in intracranial dissection, local compression syndromes without ischemia, or concomitant diseases with increased bleeding risk
- Anticoagulation seems more adequate in
  - CAD with occlusion of the dissected artery, high intensity transient signals in transcranial ultrasound studies, multiple ischemic events in the same circulation, or with free-floating thrombus

**Medical Treatment**

- Retrospective, two-center study over 16 years
- 48 patients with CAD of whom 32 had ICAD
- **Anticoagulation therapy**
  - Typically IV heparin followed by 3–6 months of oral Coumadin
- **Antiplatelet therapy**
  - Typically with Aspirin

**Meta-Analysis on Medical Treatment for ICAD**

- Systematic review in over 700 patients

**Cervical Artery Dissection in Stroke Study – CADISS trial**

- Randomized multicentre prospective study comparing antiplatelet therapy with anticoagulation for patients with acute (within 7 days of onset) carotid and vertebral dissection – 32 centers in UK
- Intracerebral artery dissection is excluded
- Patients are randomized to antiplatelet therapy (aspirin, dipyridamole or clopidogrel alone or in dual combination) or anticoagulation therapy [heparin followed by warfarin aiming for an INR of 2-3] for at least 3 months

**Endpoints (follow up at 3 months)**

- Primary Endpoint: ipsilateral stroke or death (any cause)
- Secondary Endpoints: ipsilateral TIA, stroke or death (any cause); major bleeding; presence of residual stenosis (>50%)

**It has been estimated that a definite trial on this purpose would require a sample size of the order of 2000**

**Feasibility phase will first enroll 250 subjects**

**Angioplasty and Stenting in Cervical dissection**

- Meta-analysis on the treatment of cervical artery dissection
  - 145 citations of which 6 met the criteria
  - All studies were non-randomized, retrospective and included 97 procedures in 93 patients
  - Stenting was performed for both traumatic and spontaneous dissection

**Angiographic results with good resolution of stenosis, when present, and only 2 re-stenosis**

**Endovascular treatment: Case series**

- Twelve patients with ICAD over 2 years with the following indication for endovascular treatment
  - Recurrent ischemic events despite adequate anticoagulation
  - Contraindication to anticoagulation
  - Significant DWI/PWI mismatch

**Endovascular treatment**

- Combined rt-PA and IA treatment of sICAD with tandem ICA-MCA occlusion
- ICAD with tandem may carry a poor prognosis even following IVr-PA treatment
- Recent reports suggest a better outcome with Stenting when compared to IVr-PA alone (Lavalle PC et al. Stroke 2007;38:2270-2274)
Stenting vs IVr-tPA in ICAD with Tandem

Comparison of clinical outcomes in 10 consecutive patients with ICAD and Tandem ICA-MCA within 3 hours of the onset.
Thank you for your attention!
Intensive Care Management of Ischemic Stroke

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Massachusetts General Hospital
Harvard Medical School

Objectives

- Initial Stabilization/Monitoring
- Fluid and Electrolyte Management
- Blood Pressure Management
- Prevention of Complications
- Cerebral Edema Management
- Decompressive Craniectomy

Initial Stabilization - pulmonary

- Larger strokes often have associated:
  - decreased levels of arousal
  - poor airway protection
- Primary brainstem events may warrant even earlier attention to airway protection
- Ventilation must take into account the level of PEEP - may impair venous return and thus increase ICP
Neurocardiology

- Myocardial infarction is common in the acute stroke setting, as are atrial and ventricular dysrhythmias.
- Ay et al found 50/738 ischemic stroke patients found strong correlation of MI with involvement of the right insula. 1
- A meta-analysis of 65,966 stroke and TIA patients found annual risks of
  - 2.1% for non-stroke vascular death
  - 2.2% for total MI
  - 0.9% for non-fatal MI
  - 1.1% for fatal MI


Cardiac Dysrhythmias with Stroke

- Right brain → sympathetic predominance
- Left brain → parasympathetic predominance?
- Right temporal lobe strokes (particularly insular cortex) often cause a catecholamine surge
  - sinus tachycardia
  - ventricular tachycardia.
- Strokes on either side can cause a parasympathetic deficit
- Also seen in hypothalamic and medullary lesions
- Patients most at risk already have a damaged heart


ICU Monitoring Post-stroke

- All patients should be evaluated for MI, and consideration given to
  - Arterial line monitoring (for strict blood pressure monitoring, oxygenation monitoring, and ease of blood draws)
  - Central venous catheterization (common)
  - Pulmonary arterial catheterization (occasional)
Fluid and Electrolyte Management

- Patients may need to be kept NPO for the first several days after stroke, including withholding of enteral feeding
- In patients at risk of cerebral edema, avoid hypotonic fluids
  - Typical maintenance fluids are D5NS w/ 20 KCl at 50-100 cc/hr
  - Mindful management of electrolytes, particularly Na, K, Ca and Ma

Fluid and Electrolyte Management

- Hyperglycemia has been linked with:
  - Increased volumes of stroke in experimental models and humans
  - Increased cerebral edema for both ischemic and hemorrhagic strokes
  - Worse neurological outcomes in humans
  - Increased rates of hemorrhagic transformation after IV TPA


Fluid and Electrolyte Management - Glucose

- Proposed mechanisms of injury include:
  - Acidosis
  - Increased excitotoxic amino acids
  - Increased cerebral edema
  - BBB breakdown
- Management: tight glucose control, preferably with continuous insulin infusion protocols (unproven)

Prevention of Complications

- DVT prophylaxis
  - Ted hose, pneumatic compression boots
  - LMWH (or unfractionated heparin if renal insuff)
- GI prophylaxis - H2 blockers, PPIs
- Early feeding (when possible)
- Chest PT, positioning
- Stool softeners, bowel motility agents
- Most common infectious complications early include pneumonia > UTI

Stroke Therapies – Hypertension:
BP control with **thrombolysis**

- Labetolol 10-20 mg IV over 1-2 minutes for SBP > 185 or DBP > 110.
- Labetolol or **Nicardipine** infusions for persistently elevated blood pressure, especially within the 1st 24 hours.

Stroke Therapies – Hypertension:
BP control with thrombolysis

- Nitrates may cause cerebral vasodilation, increased ICP, impaired autoregulation
  - May also cause excessive hypotension in elderly or hypovolemic patients
  - May cause rebound hypertension during withdrawal
  - Potential for cyanide and thyocyanate toxicity with prolonged infusion
### Antihypertensive Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetolol</td>
<td>α-1, β-1, β-2</td>
<td>0.5-2.0 mg/min infusion</td>
<td>Bradycardia, bronchospasm</td>
</tr>
<tr>
<td>Esmolol</td>
<td>β-1 antagonist</td>
<td>50-200 mcg/kg/min infusion</td>
<td>Bradycardia, bronchospasm</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>CCB (dihydropyridine)</td>
<td>5-15 mg/hr infusion</td>
<td>Reflex tachycardia, LV failure, AS</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td>DA-1 agonist</td>
<td>0.1-0.3 mg/kg/min infusion</td>
<td>Tachycardia, glaucoma, liver dz</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Vasodilator (arterial and venous)</td>
<td>0.25-10 mg/kg/min infusion</td>
<td>Increased ICP, N/V, pulmonary shunting, toxicity</td>
</tr>
</tbody>
</table>

### Stroke Therapies - Induced Hypertension

- **Theory:** may save penumbral tissue (as well as function) by supporting the collateral circulation.
- **May be particularly effective in patients with known proximal stenoses/occlusions**
- **Prospective trials are underway, but preliminary data suggests relatively safety:**
  - Watch for MI
  - Watch for ICH
  - Length of stay

### Vasopressors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>α-1 agonist</td>
<td>40-180 mcg/min</td>
<td>Bradycardia or tachycardia, MI</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α-1, β-1 agonist</td>
<td>2-40 mcg/min</td>
<td>Tachycardia, infusion site necrosis, MI, sulfasens.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>DA-1 agonist, α-1, DA-1 ag.</td>
<td>1-2.5 mcg/kg/min</td>
<td>Headache, tachycardia, CAD, sulfasens.</td>
</tr>
<tr>
<td></td>
<td>α-1, β-1, DA ag.</td>
<td>2.5-10 mcg/kg/min &gt;10 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>β-1, β-2 agonist</td>
<td>2-20 mcg/kg/min</td>
<td>Tachycardia, MI, cardiac ectopy</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>ADH analog</td>
<td>0.01-0.1 unit/min</td>
<td>Arrhythmias, MI, sedatives, H2O intake</td>
</tr>
</tbody>
</table>

5/11/10
Extracranial-Intracranial Bypass Surgery

A branch of the external carotid artery is used to bypass the occlusion and provide increased blood flow to the brain.

Treatment of Cerebral Edema from Ischemic Stroke

- Two critical situations:
  - Cerebellar hemispheric infarction with mass effect and effacement of the 4th ventricle
  - Massive MCA infarction

Cerebellar Infarction with Mass Effect
Treatment of Cerebral Edema from Cerebellar Stroke

- CEREBELLAR hemispheric strokes with mass effect and/or 4th ventricular compression should be considered for early decompression
- possibility for rapid deterioration with acute hydrocephalus, herniation.
- Ventriculostomy:
  - consider as a bridge to surgery
  - continued post-operatively, given post-operative swelling and continued risk of hydrocephalus
- Serial CT scans every 1-2 days post-operatively to ensure resolving edema and/or hydrocephalus.

Left MCA Infarction with Mass Effect

Cerebral Edema – who is at risk?

- 201 patients with large MCA strokes...
- Multivariate analysis found predictors of fatal brain edema:
  - h/o HTN (OR 3.0)
  - h/o CHF (OR 2.1)
  - ↑ WBC (OR 1.08 per 1000 WBC/mcl)
  - >50% MCA hypodensity (OR 6.3)
  - Involvement of additional vascular territories (ACA, PCA, anterior choroidal; OR 3.3).
- Initial LOC, NIHSS, early nausea/vomiting, and serum glucose also associated

Cerebral Edema – who is at risk?

- Also should factor in patient age – younger patients have less atrophy, less room to swell before developing ICP issues.
- Older patients may have a worse outcome with a tendency toward less aggressive measures of treatment (selection bias).

Timing of deterioration

- Quereshi et al performed a multicenter retrospective chart review of massive MCA infarctions, clinical deterioration at
  - 48 hours in 68%
  - 72 hours in 88%


Cerebral Edema from Cerebral Hemispheric Stroke

- General Measures
- Hyperventilation
- Osmotic Therapy
- Barbiturates
- Steroids
- Hypothermia
- Hemicraniectomy/surgical decompression
Cerebral Edema - general measures

- HOB elevation - 20-30°, head midline to avoid jugular compression
- Careful volume management
  - Avoid hypervolemia, but hypotension may cause a reflex cerebral vasodilation and increased CBF, thereby increasing ICP
- Fever control - fever associated with
  - Increased volumes of stroke¹
  - Increased cerebral edema from stroke²
  - Worse outcome from stroke³


Hyperventilation

- Lowers ICP by inducing vasoconstriction, reducing CBF
- Effect lasts minutes to hours at most
- May be complicated by
  - Vasoconstriction with worsening of cerebral ischemia
  - Rebound vasodilation and increased ICP with reversal
- No recent clinical trials, but trials from the 70's found no significant effect on outcome.

Osmotic Therapy - Mannitol
Osmotic Therapy – Mannitol

- Mannitol – extracellular, non-metabolizable sugar
  - creates a gradient by drawing water into the intravascular component from the intracellular and interstitial spaces.
  - May also increase blood flow in the microcirculation by decreasing serum viscosity

Effect may last several days, with repeated doses.

However, water tends to be extracted from normal brain tissue greater than infarcted tissue, as an intact blood-brain barrier is required – e.g. although ICP may be lowered, tissue shifts may be worsened.¹

Mannitol takes longer to eliminate from the CSF compared to the blood, which may further worsen the rebound effect.

In a non-randomized head-to-head trial of mannitol vs. hypertonic saline, mannitol significantly improved CPP to a greater degree than hypertonic saline.¹

No randomized controlled trial has been performed for mannitol in space-occupying cerebral infarction.


Mannitol and the Osmolar Gap

- Serum osmolality correlates poorly with serum mannitol concentrations – follow the osmolar gap.
- Concern for renal damage with incomplete mannitol clearance between doses.
- Multiple formulations have been evaluated for calculating OG
  - \(1.86 (Na + K) + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}\)^1


Osmotic Therapy - Glycerol

- Glycerol – sugar; neuroprotective qualities?
- One microdialysis study in stroke patients found ICP reductions for 70 minutes, but rapid accumulation of glycerol in brain tissue\(^1\)
- A Cochrane review suggested a favorable effect for glycerol in short-term survival, but not in long-term outcomes.\(^2\)

Osmotic Therapy – Hypertonic Saline

- Hypertonic saline – high tonicity; actively excluded from an intact blood-brain barrier
- Will decrease edema in the affected and unaffected hemisphere, as shown in rats.¹
- May be given as a bolus, or as a continuous infusion; multiple doses have been evaluated (3.0-23.4%).


Osmotic Therapy – hypertonic saline

- Systemic effects
  - Transient volume expansion
  - Hemodilution
  - Natriuresis
  - Improved pulmonary gas exchange.
- Adverse effects
  - Electrolyte abnormalities
  - CHF
  - Bleeding
  - Phlebitis
Osmotic Therapy – hypertonic saline

- No randomized trials have evaluated hypertonic saline for functional outcome in hemispheric cerebral infarction.
- May be given in cases of persistently elevated ICP refractory to mannitol therapy.

Reflection Coefficient – selectivity of the BBB to a particular substance

Table 1. Reflection coefficients of compounds used for treatment of cerebral edema and intracranial hypertension.

<table>
<thead>
<tr>
<th>Osmotic Compound</th>
<th>Molecular Weight</th>
<th>Reflection Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>78.10</td>
<td>0.09</td>
</tr>
<tr>
<td>Glyceraldehyde</td>
<td>52.09</td>
<td>0.90</td>
</tr>
<tr>
<td>Mannitol</td>
<td>182.17</td>
<td>0.90</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>58.45</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Reflection coefficients are derived from previous studies (81–91).


Osmotic Therapy

- Furosemide – loop diuretic; decreases ICP by lowering total body water content.
- May be used in combination with other agents.
- No randomized controlled clinical trials of Furosemide in cerebral infarction.
Barbiturates

- Decrease ICP by reducing the cerebral metabolic rate, and may be free radical scavengers.
- Also cause hypotension, which may compound ischemia by reducing CPP
- Also increased risk of infection, long elimination time with prolonged use
- No benefit demonstrated yet for cerebral infarction (although no randomized studies have been performed)

Steroids

- Decreases vasogenic edema, not cytotoxic edema.
- No benefit in cerebral infarction (or hemorrhage), as determined in a large meta-analysis\(^1\)

Hypothermia

- Acts by decreasing cerebral metabolic rate, stabilizing cell membranes, preserving the blood-brain barrier, reducing the inflammatory response, and reducing glutamate release.
- Early treatment may decrease infarct volume.

---

### Hypothermia for Stroke?

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Method of cooling</th>
<th>Target temperature (°C)</th>
<th>Time required to reach target (h)</th>
<th>Time from onset of stroke to start of cooling (h)</th>
<th>Duration of cooling (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naritomi</td>
<td>4</td>
<td>Cooling blankets, alcohol compresses</td>
<td>33</td>
<td>0-2</td>
<td>5</td>
<td>0-2 days</td>
</tr>
<tr>
<td>Schwab</td>
<td>25</td>
<td>Cooling blankets, cold infusions, cold washing</td>
<td>33</td>
<td>3-7</td>
<td>14</td>
<td>0-2 days</td>
</tr>
<tr>
<td>Georgiades</td>
<td>6</td>
<td>Intravenous cooling device</td>
<td>33</td>
<td>2-4</td>
<td>28</td>
<td>2-3 days</td>
</tr>
<tr>
<td>COOL AID</td>
<td>10</td>
<td>Cooling blankets, ice water and alcohol rubs</td>
<td>32-33</td>
<td>4-11</td>
<td>6</td>
<td>1-4 days</td>
</tr>
<tr>
<td>Schwab</td>
<td>50</td>
<td>Cooling blankets, alcohol and ice bags</td>
<td>32-33</td>
<td>4-11</td>
<td>22</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Kammersgaard</td>
<td>17</td>
<td>Cooling blankets</td>
<td>35.5</td>
<td>4-6</td>
<td>3</td>
<td>0-3 days</td>
</tr>
</tbody>
</table>


### Hypothermia for Stroke

- Helps by reducing ICP, perhaps mitigating ischemia
- Complications include:
  - Pneumonia
  - Elevated ICP with rewarming (often leading to death)
  - Theoretical concern for hemorrhagic conversion?

### COOL AID

- Randomized study of 40 patients presenting within 12 hours
- 18 hypothermia, 33°C for 24 hours
- 22 standard medical management
- Similar clinical outcomes, lesion growth on MRI
- Appears safe. Is it effective?
- Need further randomized trials

**NOCSS**

- Nordic Cooling Stroke Study
- Multi-center, multi-national trial
- 1000 patients, 25 centers*
- Within 6 hours, moderate to severe hemispheric stroke
- Cool to 35 degrees with surface cooling, meperidine for shivering.

* Terminated after enrolling only 44 patients

---

**CHILI**

- Controlled Hypothermia in Large Infarction
- Large anterior circulation ischemic stroke without herniation, hemorrhage, or thrombolysis; within 72 hours
- Arctic Sun cooling to 35°C for 48 hours
- Controlled rewarming by 0.5 °C every 12 hours until 37 °C

---

**IV TPA & hypothermia**

- **ICTUS-L** (Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (SPOTRIAS))
- IV TPA +/- hypothermia within 3 hours
- IV TPA +/- hypothermia within 6 hours
  - Or just hypothermia
  - Or "best medical care"
- 59 patients enrolled
ICTUS-L

- Preliminary conclusions:
  - Mean NIHSS 14 +/- 5
  - All patients can be cooled safely without side effects
  - Increased risk of pneumonia initially (14 vs. 3 patients, p=0.001), improved with better shivering control protocol (meperidine, buspar, surface warming)
  - Most patients cooled between 33.1°C and 34.5°C (target 33°C, but allowed "permissive cooling")
  - At 3 months, 18% with hypothermia had mRS 0/1, vs. 24% in control group (p=NS)
  - ICTUS 2/3 planned

ICTUS 2/3

- Plan for 400 randomized patients
- Will include ischemic stroke patients treated within 3 hours of symptom onset with IV rt-PA, NIHSS ≥7 and ≤20, age 18-80.
- Primary outcome: favorable neurological outcome at 90 days (mRS 0 or 1)

IV TPA & hypothermia

- TPA +/- hypothermia, and caffeine (8mg/kg) and ethanol (0.4g/kg) within 4 hours of stroke
  - 20 patients treated
  - IV TPA to those eligible
  - Hypothermia (endovascular or surface) within 5 hours, cooled for 24 hours to 33-35°C
  - Meperidine and buspirone to control shivering
  - Concluded feasible and safe, needs further study
Hypothermia

- Side effects:
  - Coagulopathy (elevated PT&PTT, thrombocytopenia)
  - Increased infection risk
  - Cardiac dysrhythmias (bradycardia)
  - Hyperglycemia, hypo/hyperkalemia, pancreatitis, mild acidosis
  - Interference with P450 drugs
  - Rebound elevations in ICP may occur with more rapid re-warming (even if passive).
  - Slow controlled re-warming may reduce this risk
  - No randomized studies have been performed yet for patients with massive cerebral infarction.


Cranial Cooling Cap


Intravascular cooling

(Radiant Catheter System)
Medivance: Arctic Sun

**Four pads are recommended:**
- Two on the abdomen and lower back
- Two on the thighs

Optional fifth pad can be used for larger patients.

Pads connected to a bedside cooling unit that circulates cold, sterile water
40% body surface covered
The chest remains exposed
The Energy Transfer Pads may be removed and placed on the same patient, or left in place for three days (72 hours)

---

**Hemicraniectomy/Surgical Decompression**

- May decrease tissue shifts, decrease ICP, and prevent secondary ischemic injury secondary to decreased CPP.
- Must involve a large hemicraniectomy window and duraplasty.
- Studies have typically included patients with infarction of >50% of the MCA territory.
- Surgical morbidity and mortality is negligible with the procedure; complications typically occur when the hemicraniectomy window is inadequate, necessitating expansion/resection.

---

**Early Hemicraniectomy**

Hemicraniectomy/Surgical Decompression

- Timing of surgery is crucial, as patients with clinical deterioration may already be incurring secondary injury.
- ICP monitor(s) likely unhelpful in predicting failure of medical therapy.

Factors for deterioration after hemicraniectomy

- History of hypertension was associated with poor outcome in decompressed patients
- Associated with chronically impaired autoregulation?


Hemicraniectomy/Surgical Decompression

- Factors to consider are patient age (lower age with improved outcome), timing of surgery, and side of infarct (dominant vs. non-dominant hemisphere).
- Some studies have suggested that quality of life in patients with severe aphasias may not be necessarily worse than in patients with non-dominant hemispheric lesions.¹

Hemicraniectomy Trials

- **HAMLET, DECIMAL and DESTINY** pooled analysis of 93 patients
  - Favorable outcome 75% vs. 24% for mRS≤4 at 1 year (NNT=2)
  - 43% vs. 21% for mRS≤3 (NNT=4)
  - 78% vs. 29% for survival (NNT=2)


HAMLET

- 64 patients randomized to DC vs. best medical therapy within **4 days** of stroke
- NIHSS ≥16 for right, ≥21 for left
- GCS down to 13 or less
- At least 2/3 MCA territory involved, but not whole hemisphere (ACA, MCA and PCA)
- Mortality reduced from 59% to 22%
- mRS 0-3 NOT significantly achieve
- Concluded that earlier surgery better


ICP monitoring

- Clinical exam
- Non-invasive techniques
  - TCD - increased MFV, pulsatility index
  - CT/MRI
  - Optic nerve sheath
  - Acoustic impedance
ICP monitoring

- EVD
  - Most accurate, can drain CSF
  - 2-6% ICH risk
  - Risk for meningitis/ventriculitis
- Camino ICP monitor
  - Fiberoptic transducer placed into brain parenchyma
- Licox
  - Measure temperature, tissue oxygenation
  - Cerebral microdialysis also possible
- Epidural/subarachnoid "bolt" or catheters
  - Least invasive, least accurate

Summary

- Medical complications of massive ischemic stroke are common, including poor airway protection and cardiac dysrhythmias.
- Multiple measure should be taken to prevent secondary complications, such as DVT prophylaxis and gastric ulcer protection.
- Acceptable management options for cerebral edema from infarction may include hyperventilation, osmotic agents, hypothermia, and surgical decompression.
Intracranial Atherosclerotic Disease (ICAD): Medical and Endovascular Management

Elad I. Levy, MD FACS FAHA
David Orion, MD
Alexander A. Khalessi MD MS
Department of Neurological Surgery
University of Buffalo

Acute stroke >700,000
New traumatic brain injuries 600,000
Aneurysmal SAH 30,000
Primary brain tumor 18,000
AVM rupture 17,000

Projected number of strokes in US: 2002 - 2025
STROKE

- Leading Cause of Adult Disability
- Direct cost: $60 Billion

Stroke

- Most prevalent neurologic condition
- Most common discharge diagnosis to nursing homes
- Most common diagnosis treated in rehab

Stroke Survivors

- NIH study of ischemic stroke survivors age 65 and older:
  - 50% had partial paralysis
  - 30% were unable to walk without assistance
  - 19% had cognitive impairment
  - 35% had depressive symptoms
  - 26% were institutionalized in a nursing home
Management of risk factors can reduce stroke incidence by 50%.

Stroke Risk

- Previous stroke
- TIA

10-fold increase

Causes of Stroke

- 85% Infarction
- 15% Hemorrhage
  - Intracranial
  - Subarachnoid

- 25% Large vessel Athero
  - Intracranial
  - Extracranial

- 25% Small vessel occlusive disease (lacunes)

- 25% Cardiembolic

- 20% Others:
  - Cryptogenic
  - Other, unusual

- 15% Hemorrhage
  - Intracranial
  - Subarachnoid
The natural history of Intracranial stenoses remains elusive: may undergo progression, regression, or remain stable.

Intracranial Stenosis

- ~10% of strokes & TIAs due to intracranial arterial stenosis
- Higher rates in Asians, Blacks, Hispanics
- In USA = 70-90,000 of 900,000 stroke/TIA annually

Patients with intracranial arterial stenosis are a high risk group
- ~15% annual recurrent stroke rate (range 10-24%)

Annual Death and Stroke Rates According to the Distribution of Stenosis in Intracranial Atherosclerosis

<table>
<thead>
<tr>
<th>Disease Distribution</th>
<th>Death Rate per Annum, %</th>
<th>Any Stroke per Annum, %</th>
<th>Isotopic Stroke per Annum, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid</td>
<td>9.5–17.2</td>
<td>3.9–11.7</td>
<td>3.1–8.1</td>
</tr>
<tr>
<td>MCA</td>
<td>3.3–7.7</td>
<td>2.8–4.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Vertebralbasilar</td>
<td>6.1–9.7</td>
<td>2.4–13.1</td>
<td>0–8.7</td>
</tr>
</tbody>
</table>
Medical Management

- Aggressive management of risk factors
  - Hypertension, Hypercholesterolemia, Cigarette smoking
- Aspirin and Warfarin
  - Use dates back to 1955
  - Retrospective studies suggested Warfarin may be better than Aspirin
  - Until recently, in USA, Neurologists were split 50:50

WASID Trial

- Warfarin-Aspirin Symptomatic Intracranial Disease
  - Double blind, randomized, multi-center
  - 569 patients with TIA or minor stroke
  - Symptomatic angiographically verified 50-99% intracranial stenosis
  - Warfarin (INR 2-3) vs. aspirin (1300mg/d)
  - Primary endpoint = Ischemic stroke, brain hemorrhage, or death from vascular disease

New England Journal of Medicine (March 31, 2005)

WASID Trial: Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin vs Warfarin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4.3 vs 9.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>MI or sudden death</td>
<td>2.9 vs 7.3%</td>
<td>0.02</td>
</tr>
<tr>
<td>Vascular disease death</td>
<td>3.2 vs 5.9%</td>
<td>0.16 NS</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>1.1 vs 3.8%</td>
<td>0.05</td>
</tr>
<tr>
<td>Major Hemorrhage</td>
<td>3.2 vs 8.3%</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>22.1 vs 21.8%</td>
<td>0.83 NS</td>
</tr>
</tbody>
</table>

- Conclusion: Warfarin has significantly higher adverse events and no benefit over aspirin
WASID Trial: Results

• Recurrent stroke rate – over 2 years

  - Aspirin 19.7%
  - 8-12% when Aspirin used for other high risk groups
  - Warfarin 17.2 %
  - 8-14% when Warfarin used for other high risk groups

Enrollment stopped due to increased adverse events in warfarin group
Conclusion: Warfarin has significantly higher adverse events and no benefit over aspirin

Patients with 70-99% symptomatic stenosis highest risk of stroke (18% at 1 year)

This Highlights the Need for Other Effective Therapies....

Many Lessons from Cardiology...

• However, the cerebrovascular anatomy is unique:
  - Surrounded by CSF
  - Less Adventitia and Elastic Tissue
  - More Smooth Muscle
  - Large deficit from occlusion of small perforators
  - Bony walls within petrous cervical and vertebral arteries
Tough anatomy

Self-Expanding Stents (SES)

- More flexibility
- Less radial force exerted during deployment

Device Characteristics

- Reduce restenosis by reducing:
  - Vessel trauma (balloon-inflation)
  - Metal-artery ratio (thin, self-expanding)
  - Drug coatings?

- Needs to get there:
  - Tortuous
  - Low flow state (stenosis)
  - Friable vessels with disease
  - Easily perforated
  - Need to maintain access at all times

Can not traumatize the vessel
Balloon expansion
MCA Stent with restenosis

Cross section of Stent

Intimal Hyperplasia and Jailed Perforator

Model Anatomy

- Vessel Composition:
  - Cerebral vessels differ from peripheral vessels:
    - exhibit a smaller intima, media, and adventitia
  - Yet contain a greater % of smooth muscle cells
Stent LMCA Inferior Division

- Vision 3x12mm stent placed in inferior division
- Significant improvement in inferior division

Safety profile of the procedure

Meta-analysis of all retrospective and prospective case series published until March 2006

Found:
Peri-interventional rates of 7.9% for stroke, 3.4% for death, 9.5% for stroke or death.

Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)

- First prospective study for stents
- A multicenter, nonrandomized, prospective feasibility study
- Evaluated the Neurolink intracranial stent system (Guidant, Santa Clara, Calif)
- Treatment of extracranial vertebral or intracranial cerebral artery stenosis.
SSYLVIA trial Results
61 patients with symptoms attributed to a single arterial stenosis ≥ 50% stenosis.
70.5% of the patients had an intracranial stenosis.
Post stent -30-day stroke rate was 6.6% and 0% mortality rate.
Successful stent placement – 95%
At 6 months restenosis rate (>50%) was 32.4%, in stented arteries.
39% of these recurred stenoses were symptomatic.
7.3% had strokes between 30 days and 1 year after intervention.
Composite 1-year stroke rate was 13.1%

On the basis of the SSYLVIA trial study, the US FDA granted the company a humanitarian device exemption to use balloon angioplasty and stent placement to treat high-risk patients with significant intracranial and extracranial atherosclerotic disease for which medical therapy had failed.


Chronic Intracranial Stenosis
Clinical summary
HPI: 77 yo M, repetitive episodic L hemiparesis
Meds: ASA 325
CTA
Heavily calcified R M1 stenosis

CTP
Perfusion deficit
R MCA territory (MTT)

Pre-angio
What to do?

- Medical therapy? ASA, Plavix?
- Angioplasty?
- Surgical bypass?

Background

- Natural history of IC stenosis (7% - 11%, WASID)
- Surgery is not favorable (EC/IC trial)
- PTCA results ~ 40% residual stenosis
- Cardiac balloon mounted stent < 10% residual stenosis, stiff, does not maneuver well IC
- Self-expanding intracranial stent with excellent short term results, but 30% recurrence rate
- Pharos: IC flexibility & balloon mounted

Pharos stent, 1st in US

- Significant radial force is needed to open this calcified chronic stenosis -> balloon mounted stent
- Pharos stent as designed for intracranial use -> more flexible than cardiac stents -> better control / navigation
Intervention

- Significant calcification -> Pharos Stent
- Loaded with ASA / Plavix 3 days prior to procedure
- Conscious sedation
- 6 Fr envoy, synchro2, Prowler 14, Transcend floppy exchange wire, Pharos 2.5 mm x 8 mm stent, 7 atmos

Post-angio

Result

- 0% residual stenosis
- No complication- d/c home POD #1
- No clinical symptoms x 2 months post-op
- Dual antiplatelet therapy until 3 months
- F/U angio in 1 months
- d/c Plavix if no restenosis
Tandem L ICA stenosis

Gateway-Wingspan for petrous & supraclinoid ICA

Tandem Lesions

- 59 yo woman presented with dysarthria and right upper extremity weakness (NIHSS 3)
- On aspirin pre-admission

Preoperative Studies
Tandem Left ICA Lesions with Flow Limitation

Collaterals Present but Insufficient

Treatment Options

- Patient had several episodes of worsening dysarthria and RUE weakness related to SBP < 160. Improved each time with hypertension.
- Angioplasty both lesions
- Angioplasty and stent both lesions
- Stent only one lesion and angioplasty the other
Treatment

• Crossed lesion with Synchro-14 and Prowler 14.
• Angioplasty of supraclinoid segment with Sprinter 2 x 12 mm balloon

Treatment

• Angioplasty followed by stenting of petrous segment with Gateway 3.5 x 20 mm balloon and Wingspan 4 x 20 mm

Hospital Course

• Stable neurologically (NIHSS 2)
• Discharged home POD #2
• On aspirin and clopidogrel
Hospital Course

- Returned on POD 18 with transient worsening of RUE weakness and dysarthria associated with SBP 140s (NIHSS 7)
- Improved to NIHSS 3 with hydration

Follow-up Angiography

Plan

- Antihypertensives held
- Patient stable (NIHSS 2)
- Stenting of suprACLINOID segment planned at one month from original procedure
Procedure

- 6F stiff Envoy
- Gateway 2.5x15mm
- Transcend exchange length microwire
- Wingspan 3.5x20mm
- Heparin 3500 for ACT 327
Post-op course

• R U/E involuntary movement lasting for about 1 hour- resolved
  - Focal hyperperfusion @ basal ganglia?

• Head CT: no significant findings

• D/C home on the next day

Illustrative Case

70 yo. Intermittent R hand/arm numbness, L petrous ICA stenosis
Pt underwent stenting with use of concentric balloon catheter for distal protection

Promus 3 x 15 drug eluting stent

Everolimus-Eluting Coronary Stent System
Post-stent

- The patient tolerated the procedure well
- Discharged to home POD #1 neurologically intact

SAMMPRIS trial
(Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis)

- A phase III clinical trial
  - Prospective, randomized multicenter clinical NIH/NINDS trial
    - medical vs endovascular treatment
    - symptomatic patients with 70–99% intracranial stenosis
Wingspan Stent

• Balloon angioplasty

• Stent placement
  – Self-expanding
  – Flexible
  – Microcatheter delivery system

SUNY Buffalo
FDA Sponsored IDE
9/07

Technique

Wingspan technique- a new concept in cerebral artery revascularization.
use of balloon angioplasty followed by placement
of a self-expanding nitinol microstent across the
atherosclerotic lesion in the brain.

Winspan IDE Registry

• Barrow Neurological Institute
  – Felipe C. Albuquerque
  – Cameron G McDougall

• Cleveland Clinic Foundation
  – David Fiorella
  – Thomas J Masaryk
  – Peter A Rasmussen
  – Henry Woo

• SUNY Buffalo
  – L. Nelson Hopkins
  – Elad Levy

• University of Wisconsin
  – Beverly Aagaard-Kienitz
  – David Neiman
  – Aquilla Turk
Inclusion/Exclusion Criteria

**Inclusion Criteria**
- Intracranial atheromatous lesions treated with the Gateway Balloon-Wingspan Stent system

**Exclusion Criteria**
- Treatment in the setting of an acute ischemic stroke intervention
- Re-treatment of a lesion originally treated with PTA and stenting
- Treatment of a non-atheromatous lesion
- Dissection
- Asymptomatic atheromatous lesion with stent used primarily to support the embolization of an aneurysm

Goals of the Registry

**SAFETY:** Peri-procedural complications
- Assess M and M rates and causes
- Learn from any complications

**EFFICACY:** Track event rates after treatment
- Primary Endpoint: Ipsi Stroke and Neurological Death
- Secondary Endpoints: Rates of ISR
  - Symptomatic/Asymptomatic
  - Re-treatment rates

Technique
Updated Results

- 129 patients with 137 lesions treated with Gateway-Wingspan system for intracranial atheromatous disease

Demographic Information

- Age: 35-85 (average 62.3)
- Sex: 75 M; 54 F
- Presenting Symptom – 77/129 (59.7%) presenting with stroke
Results: Lesion Location

- ACA, 1
- Middle Cerebral Artery, 37
- Basilar Artery, 25
- Vertebral Artery, 29
- Internal Carotid Artery, 45

Terminus:
- 3
- Supraclinoid: 15
- Cavernous: 14
- Petrous: 13

Angiographic Results

93/137 Lesions > 70% Stenosis
Procedural Success

• Stent Successfully Placed: 97.8%

• Stent Successfully Placed < 50% Stenosis: 95.0%

• Stent Successfully Placed, < 50% Stenosis, No Morbidity or Mortality: 90.6%

Peri-Procedural Clinical Results

• Immediate Neurological Outcomes
  - 137 Lesions Treated
  - Permanent Neurological Morbidity (5.1%)
    - 4 Death (2.9%)
    - 1 ICH with aphasia and hemiparesis (0.7%)
    - 1 perforator infarct (0.7%)
    - 1 delayed stroke with in stent thrombus (0.7%)

Follow Up Protocol

• Clinical Timepoints
  - 1 Month, 3-6 Months, 9-15 Months

• Angiographic Timepoints
  - 3-6 Months, 9-15 Months
> 3-6 Month Clinical FU

- 81 patients
  - 7 STROKES; 1 STROKE-DEATH: (8/81: 9.9%)
    - In-Stent Restenosis: (2)
    - Discontinuation of ASA/Plavix: (4)
    - Unknown (2)
  - 1 IPH:
    - Symptomatic ISR with minor DWI pos stroke
    - Reperfusion hemorrhage after PTA

Definition of ISR

- 50% Stenosis
  - AND-
  - > 20% Late Luminal Loss

Initial Imaging FU

- 84 lesions with imaging follow up
  - 65 Angio, 17 CTA only, 2 MR only
  - 25 ISR and 4 Thrombosis
    - 34.5% ISR/Thrombosis
      - 19 ASYMPTOMATIC STENOSIS
      - 6 SYMPTOMATIC ISR
        - 2 with Stroke – small ipsi "dots" on diffusion
        - 4 with TIA
      - 2 of 4 SYMPTOMATIC STENT THROMBOSIS
        - Stroke-Death (1)
        - Stroke (1)
In Stent Re-Stenosis

- Symptomatic Status
- Predictors/Risk Factors
  - Patient Characteristics
  - Procedural Details
  - Distribution of the Lesion

Clinical Impact of ISR

3/4 of ISR is Asymptomatic
Symptomatic ISR typically does not shift clinical status

ISR and clinical presentation

Not related to Qualifying Event
Slight trend toward stroke (OR 1.8, 0.63-5.2)
Risk Factors and ISR

Not related to Risk Factors

ISR and Smoking

Trend for tobacco use (OR 2.16, 0.76-6.2)

Stenosis and ISR

Not related to Pre- or Post-Treatment Stenosis
**Technical Details vs. ISR**

Not related to Procedural Details

---

**Anterior versus Posterior Circulation**

Significantly more common in **ANTERIOR CIRCULATION**
(OR 3.98, 1.2 – 13.2)

---

**In-Stent Restenosis or Thrombosis**
In-Stent Restenosis

No difference between ICA and MCA
Not simply related to vessel size

Re-Treatments: Risk Profile

• 15 Re-PTA
  - 4/15 PTA complicated by in-stent dissection requiring a second Wingspan stent in two cases
  - 1 complicated by post-PTA reperfusion hemorrhage

Wingspan ISR Summary

• Anterior Circulation more common than Posterior Circulation (~3x)
• No other obvious predisposing factors
• Onset may be as early as 6 weeks
• May occur after normal study at 3 months
• Lesion progression up to 6 months
Wingspan ISR Summary

• Usually **asymptomatic** (3/4)

• When symptomatic, clinical events are typically **relatively minor**

• **No criteria for the re-treatment of Asymptomatic Lesions**

• **Re-treatment is relatively safe** (1/15; 6.7%)

---

Wingspan ISR Summary

• Remaining Questions:
  - **What is the natural history of bad ISR?**
  - **What medical therapy for untreated ISR?**
  - **What happens after we re-treat these lesions?**
  - **What if a second stent is required?**
  - **Is it worthwhile to survey asymptomatic patients with cerebral angiography or CTA?**

---

Symptomatic basilar stenosis

Wingspan

Ischemic complication
Acute conscious disturbance post stent
IA integrin
Pontine infarcts
70 yo F

- Admitted with several intermittent episodes of lightheadedness, unsteady gait, numbness in the right face and mouth, and episodes of bilateral arm and leg weakness.
- Transferred from an outside hospital
- PMH: HTN, glaucoma (R eye)
- MRI: negative for acute stroke
Post angioplasty/stent

- 30 minutes after the procedure, the patient became drowsy and did not follow commands
- Head CT was negative
- Emergent re-angiography was done
  - No evidence of acute thrombosis or occlusion of the basilar artery
  - Integrilin was injected intra-arterially

Post-op course

- Neurologically recovered gradually after IA thrombolysis
- 2 units of PRBC transfusion for groin hematoma
Post-stent MRI

Complication
60 yo M
Multiple Strokes on ASA and Plavix

M1 Calcified Stenosis
Hemiplegic, Aphasic

Ischemic complication

History

- 71-y/o female
- 5 days prior to admission, L-LE weakness
- Admitted to BGH –had recurrent TIA - intermittent left facial droop 3 episodes.
- PMH: DM, Hypertension, Dyslipidemia, GERD. Possible prior TIAs
- PSH: Splenectomy
Exam

• Cranial nerves - intact.
• Motor - 5/5- except L-LE -4/5
• Sensory - N
• Cerebellar - N

CTA

• severe stenosis of the supraclinoid right ICA
  right M1 segment with diminished flow
  proximal basilar artery- moderate to severe
  stenosis

CT – baseline – old Rt MCA
• DWI - hits in the right MCA distribution
Dx – Angio

- Delayed filling of right MCA and ACA distribution.

High-grade stenosis of the supraclinoid ICA

Measured - 83%

The patient also had mid basilar artery - a moderate stenosis as 60%.
SAMMPRIS Trial

- Pt was randomized for stent as part of Sammpris trial
- Loaded with ASA plavix
- Response test:
  - Aspirin Platelet Inhibition - 427
  - P2Y12 Percent Inhibition – 7%
    - Therapeutic: Higher than 20% P2Y12% inhibition is associated with an anti-platelet effect.

Procedure

- As part of SAMMPRIS trial, procedure was performed under general anesthesia with the neural monitoring using SEP and EEG

DEVICES USED:

- 7 French sheath
- Neuron 6 French
- 0.035 Glidewire.
- Heparin total of 7000 units.
- Synchro-2 with microwire with SL 10, 45 degrees microcatheter.
- Gateway balloon 2.5 x 15,
- Wingspan stent 4 x 20.
3-D rotational view was performed to better outline the degree of stenosis, as well as the extent of the lesion and the exact location.

A Synchro-2 with SL10 were used and were advanced through the Neuron. Roadmap catheter with microwire were advanced through the stenosis into the distal right MCA (M2 or M3).

• Gateway balloon 2.5 x 15 was advanced and angioplasty was performed.
• Significant improvement in the lumen diameter.
SL 10 was removed and Wingspan 4 x 20 stent was advanced and was deployed with proximal and covering the ICA severe narrowing, and distal end into the M1 segment.
Number of insular branches including M2 and M3 segments which were not visualized, with delay filling.

CT scan was performed and started systemic Integriilin to help perfusion of distal branches, the slow washout of distal MCA.

While the patient had been recovering in the intensive care unit and she had a new onset of Atrial Fibrillation.

Started on Heparin

- Pt was found the next morning with worsening of her baseline weakness on the left side.
CTA- occlusion of the right MCA.

CTP –rt MCA - TTP elevation with partially preserved BCV

Patient was taken emergently to the angiography suite for acute stroke intervention
Distal stent occlusion

After a dual run with the microcatheter tip distal to the stent demonstrating the occluded segment balloon angioplasty was performed.

Following run -reperfusion distal to the prior occlusion at the distal aspect of the stent.

Reperfusion of the MCA into a final TIMI 2 from complete occlusion.
1 day after Follow-up angiogram

- Right ICA/MCA stent and shows open stent.
- Filling defect in the distal end of the stent, which is not flow-limiting.
- Pt was on aspirin, Plavix, and IV heparin

- Plavix response was persistently low despite reloading and BID dosage.
- Plavix was hence discontinued. The patient was started on Ticlid.
- Ticlid response measured by ADP test, has shown some response, but it is not optimal. Ticlid dose has been increased.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Date</th>
<th>Time</th>
<th>Results</th>
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<tbody>
<tr>
<td>1</td>
<td>3/8/2010</td>
<td>4:15:00 AM</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>3/11/2010</td>
<td>4:40:00 AM</td>
<td>8</td>
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<td>3</td>
<td>3/18/2010</td>
<td>5:20:00 AM</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>3/19/2010</td>
<td>9:30:00 AM</td>
<td>6</td>
</tr>
</tbody>
</table>

Was sent to Rehabilitation

- Aspirin, ticlopidine, and Coumadin for atrial fibrillation.
- Decreased motor strength on the left side -3/5
  Lt facial droop.

Final Head CT
Conclusions

• ICAD remains an important and unforgiving etiology of ischemic stroke
• WASID established the superiority of antiplatelet therapy versus anticoagulation
• Intracranial Stenting has developed from balloon mounted coronary variants to drug-eluting and self-expanding stents
• SAMMPRIS, an ongoing Phase III trial, examines Wingpan SES for symptomatic ICAD
• Angioplasty may ultimately play important
Uncommon Causes of Stroke
Aneesh B. Singhal, M.D.
Associate Professor of Neurology
Massachusetts General Hospital
Harvard Medical School, Boston

Disclosures
Research support: NIH-NINDS R01, P50 awards
Medicolegal expert witness
Honoraria for Lectures Not Funded by Industry

Stroke Etiology
- Large artery athero
- Cardiac embolism
- Lacunar stroke
- Unclassified, Unknown, Undetermined
- Other specified ~5%

‘Other’ [uncommon] causes have a higher frequency in young adults
**Stroke in adults < 45 years**

Accounts for 10% to 13.5% of all stroke

**Incidence:**
- Ischemic stroke = 10 to 23 per 100,000
- Hemorrhagic stroke = 3 to 9 per 100,000

**Race:** African Americans & Hispanics >> Whites

**Spectrum of etiology** is different from that in older individuals..."uncommon causes" more prevalent.

---

**Epidemiology of Stroke, age <45y**

**Baltimore Washington Young Stroke Study**
(Community and Tertiary Care Hospitals)

- Cardiac ~ 15%
- Small vessel disease ~ 10%
- Cryptogenic etiology ~ 32%
- Hematological causes ~ 9%
- Oral contraceptive use ~ 2.5%
- Non-atherosclerotic vasculopathy ~ 6%
- Premature atherosclerosis ~ 2%
- Substance abuse ~ 5%
- Migraine ~ 1%

Kittner et al. Neurology 1998; 50:890-4

---

**Cardiac Causes**

<table>
<thead>
<tr>
<th>Major Risk</th>
<th>Minor Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>1-12%</td>
</tr>
<tr>
<td>LV Thrombus</td>
<td>0-35%</td>
</tr>
<tr>
<td>Atrial Myxoma</td>
<td>30-40%</td>
</tr>
<tr>
<td>Mechanical Valve</td>
<td>1.5-3%</td>
</tr>
<tr>
<td>Infective Endo</td>
<td>12-40%</td>
</tr>
<tr>
<td>Marantic Endo</td>
<td>14-90%</td>
</tr>
<tr>
<td>Dilated CM</td>
<td>?</td>
</tr>
</tbody>
</table>
Hematologic Disorders

Sickle Cell Disease  
Disseminated Intravasc. Coag.  
TTP/HUS  
Hyperhomocysteinemia  
Antiphospholipid antibody  
Protein C, S deficiency  
Anti-thrombin III deficiency  
Factor V Leiden mutation  
Prothrombin G 20210A  
Polycythemia rubra vera  
Essential thrombocytosis  
Paroxysmal nocturnal hemoglobinuria  
Intravascular lymphoma  
Leukemias  
Waldenstrom’s  
Hyperviscosity syndrome  
Nephrotic syndrome

Venous and Arterio-Venous Disorders

Cerebral Venous Sinus Thrombosis  
→ many underlying causes  
→ ischemic stroke, brain hemorrhage  
Arterio-venous malformations  
Cavernous malformations  
AV Fistula  
Venous anomaly

Arterial Causes

1. Large or Medium-Sized Arteries
   a. Carotid and Vertebral artery Dissection
   b. Premature Atherosclerosis
   c. Reversible Cerebral Vasoconstriction Syndromes (e.g. Postpartum angiopathy, TCH, BACNS, Drugs)
   d. Genetic or Inherited: Moyamoya, Sickle, Fabry’s, FMD
   e. Inflammatory: Takayasu, Anti-phospholipid antibody-associated
   f. Infectious: TB, Herpes zoster, syphilis, bacterial, HIV

2. Small Vessel Disease
   a. Inflammatory: PACHS, Giant-cell, Amyloid, PAN, SLE, Behcet’s, Scleroderma, Churg-Strauss, Degos’, Eale’s, Susac, Spatz-Lindenbergh
   b. Infectious: Herpes zoster, cysticercosis
   c. Genetic or Inherited: CADASIL, MERRF, COL4A1 mutation
Genetic and Inherited Disorders

- Cerebral Autosomal Dominant Arteriopathy (CADASIL)
- Mitochondrial disorders (MELAS, KSS)
- Fabry’s Disease, Marfan’s syndrome, Ehlers-Danlos syndrome
- Hereditary endotheliopathy, retinopathy, nephropathy (HERNS)
- Osler-Weber-Rendu syndrome, Osteogenesis imperfecta

Miscellaneous

- Migraine-induced stroke
- OCPs, Epo, ChemoRx agents, illicit drugs, etc

General Comments

Clinical Clues

- Headache
  - Above the eye (carotid artery dissection)
  - Recurrent worst-ever headaches (RCVS)
  - Chronic headache (CADASIL, PACNS, Moyamoya)

- Stereotyped transient ischemic attacks
  - Fixed arterial stenosis e.g. Moyamoya, premature atherosclerosis, focal arteritis

- Clinical setting
  - Infection e.g. TB, HIV, Zoster
  - Exposure to illicit drugs, vasoconstrictive drugs, pregnancy, chemotherapy (RCVS)
  - XRT (radiation associated carotid stenosis)
Clinical Clues

- **Systemic Examination**
  - Arterial pulse: temporal (GCA), radial (Takayasu)
  - Skin lesions e.g. syphilis, Dego's, zoster, neurofibroma
  - Rheumatological conditions e.g. SLE, Wegener's
  - Connective tissue e.g. Marfan’s, EDS

- **Neurological Examination**
  - Multifocal brain and spine deficits (vasculitis)
  - Peripheral nerve involvement (Zoster, HIV)

- **Eye examination**
  - Premature atherosclerosis, Moyamoya, Eale’s disease, HERNs and other genetic conditions

Laboratory and Imaging Clues

- **Blood tests**
  - Abnormal toxicology screen, hypercoag panel
  - Abnormal Rheumatological tests

- **Abnormal cerebrospinal fluid examination results**

- **Brain Imaging: Lesion Patterns**
  - String of pearls (MCA stenosis)
  - Disseminated infarcts (vasculitis)
  - Watershed infarcts with PRES (RCVS)
  - Ext capsule and anterior temporal lobe (CADASIL)
  - Snowball lesions in the corpus callosum (Susac)

Investigations

- Directed towards establishing diagnosis, assessing stroke risk, and progression
  - Blood tests e.g. Lipids, Hypercoag panel, ESR, Lyme, HSV, Toxicology Screen
  - Vascular Imaging e.g. CTA, MRA, DSA
  - Lumbar puncture
  - PET, SPECT and TCD, cerebrovascular ‘reserve’ studies to assess stroke risk
Advanced MRI for Cerebral Arteritis?

Swartz RH et al., Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. Neurology. 2009;72(7):627-34.

Advanced MRI for Cerebral Arteritis?

Diagnosis = Clinical + Imaging + Lab

Recurrent TIAs
- Focal infarcts
- MCA narrow, gado-enhancing

Prior Chickenpox
+ CSF Varicella titer

Chickenpox (varicella) arteritis

Singhal et al., Neurology 2001;56:815-817

Approach to Treatment

- Antiplatelets e.g. aspirin (? risk in vasculitis, moyamoya)
- Anticoagulants (dissection)
- Steroids, immunosuppressive agents (arteritis)
- Statins (premature atherosclerosis)
- Permissive hypertension to boost perfusion ?
- Treatment of infection, malignancy
- Surgical options: intra-arterial stent, balloon angioplasty, EDAS or other synangiosis procedures
The value of experience is not in seeing much, but in seeing wisely

-Osler

PFO and Stroke

PFO prevalence 17-27%, combined with ASA in 70%
High prevalence in individuals with ‘cryptogenic’ stroke
(young adults<55 years, and also those >55 years)

- Paradoxical embolus
  - Source of thrombus
  - ? Prothrombotic state

- Genetic syndrome (migraine, PFO)

- Arrhythmias

PFO Medical Management

Homma et al, WARSS/PICSS study (2002)
- TEE in patients treated with warfarin vs. aspirin
- N=630; 42% with cryptogenic stroke, 34% with PFO
- Large PFO: cryptogenic 20% vs. non-cryptogenic 9.7%
- There was no difference in time to event between warfarin and aspirin groups

Orgera –Meta-analysis (2001)
- coumadin superior to anti-platelet therapy (O.R. 0.37)
- surgical treatment similar to coumadin (O.R. 1.19)
Many PFO Closure Devices…
Clinical Trials ongoing

AAN Recommendations
PFO (alone) is not associated with inc. risk of subsequent stroke or death in medically treated patients with PFO.
PFO and ASA possibly inc. risk of subsequent stroke (not death) in medically treated patients <55 years.
In patients with cryptogenic stroke and PFO or ASA, the evidence is insufficient to determine if warfarin or aspirin is superior in preventing recurrent stroke or death; but bleeding is more frequent with warfarin.
There is insufficient evidence to evaluate the efficacy of surgical or endovascular closure.

Prothrombotic States and Stroke
- Protein C, Protein S, Antithrombin III deficiency
- APCR and Factor V Leiden mutation
- Prothrombin 20210A mutation
- Elevated homocysteine
- Antiphospholipid antibodies
- Heparin Induced Thrombocytopenia (HIT)
- Other: sickle cell, leukocytosis, nephrotic sydrome, hyperviscocity (?), cryoglobulinemia (?)

Triggers: infection, cancer, pregnancy, trauma
Management of prothrombotic state

- Relatively low prevalence even in those with VT
- Even more uncommon in ischemic stroke patients
- Consider in patients with VT and stroke, CVST, setting of stroke and PFO, young adults with 'cryptogenic' embolus
- HIT work-up if platelets low, heparin exposure
- Prothrombin gene, Factor V Leiden
- Ask for risk factors, family history
- Treatment: warfarin, argatroban

Dissection

Carotid and Vertebral Artery Dissection

- 2% of all ischemic strokes
- 25% of stroke in young
- Incidence 2.6 per 100,000 (carotid) and 1.0 per 100,000 (vertebral)
- Peaks in the 5th decade
- Intracranial dissections are rare, occur at younger ages

Intimal tear → sub intimal or sub adventitial hematoma (arterial occlusion, 'pseudo' aneurysm)
Dissection: MRI

- Crescent sign on axial T1 fat sat image

Dissection: management

- Heparin and warfarin (3 months), then Aspirin
  - Cochrane analysis: antiplatelets vs warfarin (26 articles, 327 patients): no difference in outcome
  - Retrospective analysis of 298 consecutive patients (202 anticoagulants, 96 antiplatelets)
    - Rate of ischemic events at 3 months very low and was independent of the type of treatment
- CADISS: international RCT underway
- CADISP: risk factors, genetic susceptibility
- In the acute setting, IV tPA appears safe, effective
- Balloon angioplasty, stents, coils

Reversible Cerebral Vasoconstriction Syndromes (RCVS)
RCVS: overview

- Group of conditions characterized by reversible segmental constriction-dilatation of cerebral arteries
- ~90% have recurrent 'thunderclap' headaches
- Women>men (4:1), age 25-60 yrs, also children
- Brain MRI can be normal or show ischemic stroke, ICH, cSAH, or reversible brain edema (PRES)
- Usually a self-limited condition with benign outcome
- Angiographic reversal occurs within days to weeks
- Pathophysiology: ?altered vasoreactivity

Catabrese et al., Ann Int Med 2007; Ducros et al., Brain 2007

RCVS: Imaging

Cerebral Angiography
• 'beading'
• 'sausage-on-a-string'

RCVS Management

- Simple observation !!
- IV fluids, pain management
- Avoid precipitants e.g. vasoconstrictive drugs
- Ca-Ch Blockers (nimodipine, iv magnesium) do not affect outcome, may reduce headache
- Empiric steroids (given for fear of missing PACNS) are associated with poor outcome!
- Fulminant cases: balloon angioplasty, IA nicardipine (high risk for reperfusion injury)
Distinguishing RCVS from PACNS

<table>
<thead>
<tr>
<th>Feature</th>
<th>RCVS</th>
<th>PACNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Recurrent TCH</td>
<td>Insidious, chronic</td>
</tr>
<tr>
<td>Infarct pattern</td>
<td>&quot;Watershed&quot;</td>
<td>Small, scattered</td>
</tr>
<tr>
<td>Lobar Hemorrhage</td>
<td>Common</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Cortical SAH</td>
<td>Common</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Reversible edema</td>
<td>Common</td>
<td>-</td>
</tr>
<tr>
<td>Angiogram</td>
<td>Sausage on a string (smooth)</td>
<td>Irregular, notched, ectasia</td>
</tr>
</tbody>
</table>

Outcome after Stroke in the Young

296 patients, Iowa Stroke Registry, 1977-92

- 7% died from the acute stroke
- 14% died over a follow-up of 6 yrs (age > 25, large artery)
- 9% had recurrent strokes
- 0.4% had myocardial infarct
- Outcomes good, however only 49% remained completely symptom-free; only 42% resumed work.
- A majority of survivors reported emotional, social, or physical residuals that lessened the quality of life.

Kappelle et al., Stroke 1994

Thank you!
Hypercoagulability and Ischemic Stroke

Elizabeth Van Cott, MD
Director, Coagulation Laboratory
Massachusetts General Hospital
Boston MA

How a Blood Clot Forms

Vessel injury exposes collagen (activates PTT path) and TF (activates PT path)

Natural Ways to Prevent a Blood Clot from Becoming too Large (a Thrombosis)
The typical “Hypercoagulation Panel” is most appropriate for Venous Thromboembolism

- Protein C
- Protein S
- Antithrombin III
- Activated protein C resistance/factor V Leiden
- Prothrombin G20210A

Is this typical (venous) hypercoagulation panel useful for stroke patients?

- Older patient with ischemic stroke – generally no
- Patent foramen ovale – probably
- Young person with unexplained ischemic stroke – maybe, especially protein C
- Positive personal or family history of venous thrombosis – yes
- Cerebral vein thrombosis – yes

Rahemtullah A et al, Arch Pathol Lab Med. 2007;131:890-901

Protein C might be an exception!

- Prospective studies: 3 positive and 1 inconclusive:
  - 2 studies: Low C 6-9 yr follow-up, increased stroke (1 of these was negative for ATIII)
  - 1 study: C deficiency in children with stroke had increased stroke recurrence (not for S or ATIII)
  - 1 inconclusive: only 36 cases of C deficiency, no cases of stroke
- Meta-analysis of retrospective studies: protein C deficiency in children with stroke had higher stroke recurrence (not true for S or ATIII deficiency)
- Retrospective: 226 with C deficiency 7-fold increased risk of stroke before age 55 vs unaffected relatives (5-fold increased for S deficiency; not for ATIII)

Mahmoodi BK et al, Circulation 2008; 118:1659
Rahemtullah A et al, Arch Pathol Lab Med. 2007;131:890-901
Prothrombin G20210A, Factor V Leiden and Ischemic Stroke

- Prospective studies: all negative (4/4 Leiden and 2/2 prothrombin G20210A), adults
- Meta-analyses: 2/3 Leiden negative (OR 1.3 for the positive study), 2/2 prothrombin positive (OR 1.3, 1.4), adults and young adults
- Might be useful in pediatrics, but retrospective studies in pediatrics are conflicting

Rahemtullah A et al, Arch Pathol Lab Med. 2007;131:890-901

Acquired Decreases in Protein C, Protein S, and Antithrombin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Protein C</th>
<th>Protein S</th>
<th>Antithrombin</th>
</tr>
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<tbody>
<tr>
<td>Liver disease</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>↓</td>
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<tr>
<td>Surgery, DIC</td>
<td>↓</td>
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<tr>
<td>Estrogen/</td>
<td>↓</td>
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<tr>
<td>Pregnancy/ OCP</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Acute phase reactions</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Coumadin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>Vitamin K def.</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heparin</td>
<td>↓</td>
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<td>↓</td>
</tr>
</tbody>
</table>

Heterozygous Protein C, Protein S, or Antithrombin Deficiency

- 0.17-0.7% of general population (S, C>A)
- 1-3% of unselected patients with DVT
- 5-9% of patients <70 yo with DVT
- 5-7 fold increased risk for DVT
- Symptomatic families: 50% develop DVT
- Age of onset 10-50 years
Why is Factor V Leiden so common, despite more frequent venous thrombosis and miscarriage?

- Factor V Leiden arose in a single individual 21,000-34,000 years ago, in Europe
- It must have a survival advantage, otherwise it would have become eliminated
Why is Factor V Leiden so common?

Despite more frequent venous thrombosis and miscarriage:

- Less bleeding gives a survival advantage
- What evidence is there that they have less bleeding?

FVL = factor V Leiden

Other, less obvious reasons?

- Embryo implantation (in vitro fertilization) more successful when mother, embryo or both have FVL (Gopel W et al, Lancet 2001; 1238-9)
- Increased sperm count in males with FVL (Cohn DM, J Thromb Haemost 2010; 513-6)
- Shorter time between marriage and first pregnancy for FVL males (but not females): 3.5 fold increased “risk” for pregnancy within first 3 months of marriage (van Denne FM et al, Hum Reprod 2006; 21:967-71)

What other tests are useful? (besides a cholesterol panel)

- Based on prospective studies:
  - C-reactive protein – marker of inflammation
  - Homocysteine – causes atherosclerosis
  - Lipoprotein (a) – causes atherosclerosis
  - Antiphospholipid antibodies – hypercoagulable
    - Lupus anticoagulant
    - Anticardiolipin antibodies

Rahemtullah A et al, Arch Pathol Lab Med. 2007;131:890–901
What do all these “hypercoagulation tests” have in common?

They all are altered during an acute phase reaction

- Plasminogen activator inhibitor-1 (PAI-1) high
- von Willebrand factor (high)
- PTT (shortened)
- Fibrinogen (high)
- Factor VIII (high)
- C-reactive protein (high)
- Protein S (low)
- Plasminogen (low) → Becomes elevated during acute phase reaction

Acute Phase Reactants

- C-reactive protein is the best studied
- My opinion- ordering most of the others (eg PAI-1, vWF) is currently unnecessary, does not provide additional information
- The stroke itself causes these test results to appear hypercoagulable due to an acute phase reaction; can be misleading

C-Reactive Protein (CRP)

- A sensitive marker of inflammation
- Inflammation is associated with atherosclerosis
  - Flu vaccine reduced heart disease and stroke in some studies! (cause-effect not proven)
- Infection may be associated with atherosclerosis? CMV, Herpes, C.pneumoniae, H. pylori, Coxsackie B, periodontal gum disease?
- Elevated CRP predicts a 2 fold increased future risk of MI and stroke (do not test during illness or injury- it becomes temporarily elevated at those times)
C-Reactive Protein (CRP)

- What can be done if its elevated? (when not due to current short-term illness or injury)
  - Aspirin and statins seem to benefit this group of patients
- CRP not known to be causative, rather, predictive
- Basal level stable over time (if not ill or injured)

CRP Prospective Studies

- Healthy subjects at baseline: 4/4 studies were positive
- Stroke or TIA at baseline: 3/3 studies were positive
- Acute stroke at time of testing:
  - CRP 0-12 hours after onset of symptoms was not, but 12-24 hours after was, an independent predictor of poor outcome (increased cerebrovascular and CAD events at 1 year follow-up)
  - CRP tested at various intervals: CRP at discharge (mean 12 days) was strongest independent predictor of new vascular event or death at 1 year follow-up, compared to CRP measured ≤ 3 days after admission
- A number of studies show increased risk of MI

Homocysteine and Stroke: Prospective Studies

- Healthy at baseline: 8 + studies, 2 - studies
- Stroke at baseline: 2/2 + studies
- CAD at baseline: 1/1 + study
- SLE at baseline: 1/1 + study

Rahemtullah A, Van Cott E. Arch Pathol Lab Med 2007; 131:890-901
Homocysteine

- High levels associated with increased risk of
  - Atherosclerosis, leading to MI (similar risk as smoking or cholesterol) and strokes
  - venous thrombosis
- 5-10% of the general population have high levels
- Risk starts to increase with just slight elevations
- Homocysteine = an amino acid

---

Causes of High Homocysteine

- Hereditary: mutation in one of the enzymes in the metabolic pathways
- Acquired:
  - deficiency of B12, folate, or B6
  - renal failure
  - malignancy
  - hypothyroidism
  - medications, eg. methotrexate, theophylline, phenytoin, isoniazid, hydrochlorothiazide

---

![Homocysteine Diagram]

- Folate, vitamin B6, vitamin B12 are needed to metabolize homocysteine
- Deficiencies of these vitamins cause high homocysteine
- These vitamins can be used to treat (reduce) high homocysteine
- Requires MTHFR to regenerate active folate
## MTHFR

- Testing not recommended
- Cytosine to thymine transition at nucleotide 677 in the methylene tetrahydrofolate reductase gene (MTHFR), converting an alanine to a valine
- Heterozygous = asymptomatic
- Homozygous = COMMON among general population; Most studies show NO risk for atherosclerosis or thrombosis, but some do

## Important Lab Issues

- Separate plasma from cells within 1 hour (RBC release homocysteine)
- Keep on ice (slows RBC release of homocysteine)

*Otherwise false elevations can occur*

## Treatment of High Homocysteine

- A unique feature of this hypercoagulable state is that homocysteine levels can be decreased simply by administering vitamins B12 (100 ug), vitamin B6 (3 mg) and folate (400 ug) daily
- Not yet proven that treatment will reduce venous thrombosis, MI or stroke
Folic Acid, Homocysteine and Stroke

- Folic acid for primary prevention reduced stroke, RR 0.75
- Folic acid added to grain in USA and Canada in 1998; decline in stroke mortality accelerated in USA and Canada 1998-2002 but not in UK where grain fortification was not mandatory
  
  *meta-analysis, Wang X et al, Lancet 2007; 369: 1876-82*

---

Hip fracture, Homocysteine and Stroke

- Homocysteine 2-4 fold increased incidence of hip fracture in Framingham Heart Study
- Folate + vitamin B12 given to stroke patients reduced hip fracture rate, RR 0.2
  
  *McLean R et al, NEJM 2004; 350:2042-9*
  *Sato T et al, JAMA 2005; 293:1082-8*

---

Hyperhomocysteinemia

Mechanism

- Endothelial cell injury with increased expression of tissue factor (which activates coagulation)
- Increased platelet adhesion
- Increased small, dense (proatherogenic) LDL
  
  *Mechanism not fully understood*
• Thought to cause atherosclerosis and consequently a 2-3 fold increased risk for stroke or MI
• Consists of LDL with apolipoprotein (a)
• Heterogeneity [180-650 kDa] due to number of kringle 4 repeats in apolipoprotein (a)

Problem with Lipoprotein (a) assays

Lp(a) = lipoprotein (a)

■ Lp(a) with fewer kringle 4 repeats has higher Lp(a) levels and an increased risk for atherosclerosis compared to Lp(a) with many kringle 4 repeats
■ Many assays use antibodies that recognize kringle 4, therefore they OVERESTIMATE “good” Lp(a) with many kringle 4 repeats and UNDERESTIMATE “bad” Lp(a) with fewer kringle 4 repeats
■ This is suspected to be the reason why clinical trials have had conflicting results with Lp(a)

Lipoprotein (a) and Stroke

Prospective studies:

■ Healthy populations: 4+ studies, 1 NS trend, 3- studies
■ Mixed populations: 2+
■ Stroke patients: 1+, 1-

Rahemtullah, Yun Cottr. Arch Pathol Lab Med 2007; 133:1:800-802
Suh Damuk J et al. JAMA 2006, 296:1365-1370
5 year prospective study (n = 826)
- Risk of advanced carotid stenosis >40% (Doppler US) correlated with Lp(a) > 30 mg/dl and < 22 K4 repeats (in 326 subjects with carotid artery disease at baseline)

Apo(a) Isoform Size
(number of Kringle 4)
- 5 year prospective study (n = 826)
- Risk of advanced carotid stenosis >40% (Doppler US) correlated with Lp(a) > 30 mg/dl and < 22 K4 repeats (in 326 subjects with carotid artery disease at baseline)

Examples of Lipoprotein (a) Assays Not Affected by Kringle 4 Repeats
- Polymedco- minimal influence- best test in study:
- ELISA by Sigma – not affected by apo (a) size
- Diasorin II: IS affected
  - Diasorin III is NOT affected, but discontinued by company before they realized this problem
- Mayo: Lp(a) cholesterol by electrophoresis, enzymatic staining of cholesterol in separated Lp(a) particles, densitometry
  McCarron JP... American Heart Association, Orlando, November 2007
  - Mayo also offers a cheaper method that IS affected

Comparison of 2 Assays at MGH 2000
Since small isoforms have higher Lp(a), this data supports that the higher Lp(a) specimens are underestimated by the sendout assay which is based on kringel 4 repeats.
Apolipoprotein (a) gene largely determines the level

- Unaffected by diet, lifestyle, medications (except it is reduced by niacin and estrogen)
- Increased with
  - Acute phase (illness or injury, e.g., stroke)
  - Renal disease, nephrotic syndrome, diabetes with albuminuria
  - Familial hypercholesterolemia
  - African Americans have higher levels
- Decreased in liver disease (made in liver)

Lipoprotein (a) Treatments

Lp (a) is decreased by:
- Estrogen (but is hypercoagulable)
- Niacin

Niacin reduces CAD Events (MI and death)
Due to increased HDL, decreased LDL, decreased small LDL, decreased Lp(a), other?

Lipoprotein (a) HERS Trial:

Estrogen + Progestin vs Placebo
Prospectively followed women with CAD for >4 years:

Relative Hazard for MI

<table>
<thead>
<tr>
<th>Lipoprotein (a) mg/dl</th>
<th>Relative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>1.19</td>
</tr>
<tr>
<td>7-25</td>
<td>1.21</td>
</tr>
<tr>
<td>25-55</td>
<td>1.36</td>
</tr>
<tr>
<td>55-236</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Estrogen was more beneficial if high Lp(a)

*Relative to placebo

JAMA 2000; 283:1845

p = 0.03 for trend
**Lipoprotein (a) in HERS Trial**

Women with greatest reduction in Lp(a) (>8.8 mg/dl) had significantly decreased risk for MI (but not for CHD death) compared to those with < 8.8 mg/dl reductions in Lp(a)

RH = 0.46

Changes in LDL-C, HDL-C, triglycerides

no decrease in risk

_JAMA 2000; 283:1845_

---

**Why might it cause thrombosis?**

- Apo (a) is homologous to plasminogen (kringles 4 and 5 and protease); might compete with plasminogen and thereby inhibit fibrinolysis

  - tPA
  - Plasminogen → plasmin
  - fibrin clot → D-dimers, FDP (fibrin degradation products)

- Inactivates TFPI (tissue factor pathway inhibitor), thereby allowing the PT (extrinsic) pathway of clotting to proceed

_Caplice NM...Blood 2001; 98: 2868-2887_

- Other mechanisms also possible

---

**Antiphospholipid Antibodies**

Acquired (not hereditary) antibodies against phospholipid

- Lupus anticoagulant (LA): detected by clotting tests
- Anticardiolipin antibody (ACA): antibodies against cardiolipin (a phospholipid), detected by ELISA

Can have LA, ACA, Or both:
Antiphospholipid Antibody Syndrome

- Antiphospholipid antibodies are associated with:
  - Arterial thrombosis (mainly stroke)
  - Venous thrombosis
  - Miscarriage
- Diagnosis requires thrombosis or miscarriage plus a positive test (LA and/or ACA) on 2 separate occasions, > 12 weeks apart

Antiphospholipid Antibody Syndrome, cont.

- Anticardiolipin antibody ELISA should be moderate or markedly elevated, that is, > 99th percentile (slight elevations do not "count")
- Anti-β2 glycoprotein ELISA
  - As of 2006, positive results can be used to diagnose the antiphospholipid antibody syndrome (as can lupus anticoagulant or anticardiolipin tests)

What’s the difference between anticardiolipin and anti-β2 glycoprotein I antibody?

- Antigen for anticardiolipin antibody is cardiolipin (a phospholipid) bound to beta-2 glycoprotein I (a protein)
- Anti-β2 glycoprotein ELISA tests for antibody to the protein part of the antigen, does not detect antibodies to just cardiolipin, for example, syphilis patients have antibodies to cardiolipin alone which do not cause thrombosis
- Anti-β2 glycoprotein I are thought to be more specific but less sensitive than anticardiolipin antibody
Experience at MGH over the past one year 2009-2010

- 4500 anti-cardiolipin antibody (ACA) tests performed (4500 IgM and 4500 IgG)
- 500 anti-β2 glycoprotein I (β2GPI) tests performed (IgG)
- 268 patients had both tests requested on the same specimen:
  - 12/268 moderately or markedly positive ACA IgG, negative β2GPI IgG = 4.5% could be false negative if β2GPI done instead of ACA
  - 31/268 ACA IgG+ and only 12/31 were also β2GPI+ (reduced sensitivity)
  - No β2GPI+, ACA- thus β2GPI did not detect any additional cases

Conditions Associated with Antiphospholipid Antibodies

- Primary (no underlying disease or cause)
- Autoimmune disease, especially systemic lupus erythematosisis
- Drug-induced (disappears when drug is stopped)
- Infection (Bacterial, viral, fungal, protozoal)- antibody disappears when infection resolves
- Malignancy (Lymphoproliferative, Hairy cell leukemia)

TIP: How do you monitor anticoagulant therapy for a lupus anticoagulant patient?

- PTT and less often, PT, might be artifactually more prolonged than it should be on heparin or Coumadin
- Can verify heparin anticoagulation with a Heparin assay (anti-factor Xa assay)
- Can verify Coumadin anticoagulation with a chromogenic factor X assay
Monitoring Coumadin with Chromogenic Factor X

<table>
<thead>
<tr>
<th>Chromogenic Factor X</th>
<th>INR &lt; 2 Subtherapeutic</th>
<th>INR 2-3 Therapeutic</th>
<th>INR &gt; 3 Supratherapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<45% predicts therapeutic INR: Argins PA... Pharmacotherapy 2005;25:137

Summary - Hypercoagulability and Strokes

- Typical hypercoagulation panel (protein C, protein S, antithrombin III, factor V Leiden, prothrombin G20210A) might be useful in some cases, such as
  - young persons
  - PFO
  - History of venous thrombosis in self or family
  - Cerebral sinus thrombosis
- Protein C may be the most promising

Summary

- **C-reactive protein** - increased risk of MI & stroke
- **Homocysteine** - increased risk of atherosclerosis, MI, stroke, venous thrombosis
- **Lipoprotein (a)** - increased risk of atherosclerosis, MI & stroke
- **Antiphospholipid antibodies** (lupus anticoagulant or anticardiolipin antibodies) - acquired autoantibodies that cause thrombosis for unclear reasons (mostly strokes and venous thrombosis)
Risk Factors for Stroke: What to look for

Lee H. Schwamm, MD
Professor of Neurology
Harvard Medical School
Director, TeleStroke & Acute Stroke Services
Massachusetts General Hospital

Outline
- Review stroke risk factors
- Review the evidence for secondary prevention interventions for several of these factors

Risk Factors for Stroke

Nonmodifiable
- Age
- Gender
- Race/ethnicity
- Heredity

Modifiable
- Hypertension
- Diabetes
- Cardiac disease
- Atrial fibrillation
- TIA/prior stroke
- Dyslipidemia
- Cigarette smoking
- Alcohol/cocaine abuse
- Physical inactivity
- Carotid stenosis
- Sickle cell disease
- Obesity


Annual rate of first cerebral infarction by age, sex, and race


(GCNKSS: 1999).
Goldstein et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association. 2006

---

**Stroke Risk After Transient Ischemic Attack (TIA)**

1707 patients with TIA identified by emergency department physicians

![Graph showing probability of survival free from stroke](Adapted from Johnston SC, et al. JAMA. 2000;284:2901-2906.)

**Major Manifestations of Vascular Disease and Atherothrombotic Events**

- **Cerebral Stroke** (700,000/4.7 M)<sup>1</sup>
- **TIA** (500,000/4.9 M)<sup>2</sup>
- **Cardiac** (2.3 M/14.2 M)<sup>1</sup>
- **MI, Angina pectoris**
- **Peripheral** (8-12 M)<sup>1</sup>

(PAD): Claudication, critical limb ischemia

![Diagram of cerebrovascular disease](Incidence/Prevalence)

**Cerebrovascular Disease: Stroke Types**

<table>
<thead>
<tr>
<th>Ischemic Stroke (80%)</th>
<th>Hemorrhagic Stroke (20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombotic Cerebrovascular Disease (20%)</td>
<td>Cryptogenic (30%)</td>
</tr>
<tr>
<td>Lacunar (25%) (small vessel disease)</td>
<td>Cardioembolic (20%)</td>
</tr>
</tbody>
</table>

**Atherosclerosis accounts for much of the burden**

![Image showing proliferation of smooth muscle cells](Proliferation of Smooth Muscle Cells)

---

**Mortality at 5 Years in Patients who have Presented with Stroke**

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>CV Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18%</td>
<td>39%</td>
</tr>
</tbody>
</table>

*Based on estimated 700,000 annual strokes.*

**Impact of Modifiable Risk Factors on Strokes**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number of Preventable Strokes per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>345,100</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>86,100</td>
</tr>
<tr>
<td>Smoking</td>
<td>65,800</td>
</tr>
<tr>
<td>Afib</td>
<td>32,900</td>
</tr>
<tr>
<td>Heavy EtOH</td>
<td>0</td>
</tr>
</tbody>
</table>

**Case Examples**

**Mr. HONDA**

- 75 yr old obese white male with HTN, DM, hypothyroidism, dyslipidemia, AF, CAD s/p MI, Hx of TIA s/p R CEA complains of recent episode of right arm tingling and clumsiness lasting 15 mins. He noticed trouble opening the beer can, and handling his cigarette.

- Current BP 139/88  P 80 irregular

- What antihypertensive therapy is appropriate? What is the goal BP?

**Blood Pressure Control: Guidelines for Target Levels**

- **Joint National Committee VII (NHLBI)**
  - normal: <120/80
  - pre-hypertension: 120-139/80-89
  - diabetics: <130/80

- **European Society of Hypertension**
  - minimal acceptable: <140/90
  - optimal: <120/80
  - diabetics: <130/80

- **WHO/Int’l Hypertension Society**
  - optimal: <140/90
  - diabetic: <130/80

**PERINDOPRIL Protection Against Recurrent Stroke Study PROGRESS**: Trial Design

<table>
<thead>
<tr>
<th>Study design:</th>
<th>Randomized, double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>History of cerebrovascular disease &lt; 5 years No definite indication for treatment with an ACE inhibitor (e.g. heart failure)</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>definite indication for treatment with an ACE inhibitor (e.g. heart failure) uncontrolled hypertension</td>
</tr>
<tr>
<td>Randomization:</td>
<td>4mg perindopril ± indapamide vs. placebo</td>
</tr>
<tr>
<td>Primary end point:</td>
<td>stroke (fatal or non-fatal)</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>&gt;6000 pts enrolled. 4 years</td>
</tr>
</tbody>
</table>


**Blood Pressure Differences**

*All participants*

![Graph showing blood pressure differences](image)

Mean blood pressure difference 9.0/4.0 mm Hg

**Stroke Subtype**

*All participants*

<table>
<thead>
<tr>
<th>Events</th>
<th>Favors active</th>
<th>Favors placebo</th>
<th>Risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or disabling</td>
<td>123</td>
<td>181</td>
<td>33% (15 to 46)</td>
</tr>
<tr>
<td>Non fatal or disabling</td>
<td>201</td>
<td>262</td>
<td>24% (9 to 37)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>246</td>
<td>319</td>
<td>24% (10 to 35)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>37</td>
<td>74</td>
<td>50% (26 to 67)</td>
</tr>
<tr>
<td>Stroke type unknown</td>
<td>42</td>
<td>51</td>
<td>18% (-24 to 45)</td>
</tr>
</tbody>
</table>

Total stroke (patients) 307/420 (10% 14%) 28% (17 to 38)

**PROGRESS Results: Primary Outcome–Stroke**

28% Risk reduction (95% CI, 17%-38%) P<.0001

Proportion of Patients With First Event (%)

Time (y) 0 6 12 18 24 30 36 42 48

Proportion With Event 0.00 0.05 0.10 0.15 0.20

Placebo Perindopril 4 mg ± Indapamide 2.5 mg (not signif for ACE Inhibitor Rx only)

**Losartan Intervention for Endpoint Reduction (LIFE) Trial Design**

- **Study design:** Randomized, double-blind
- **Inclusion criteria:** age 55-80, high-risk patients with HTN and left ventricular hypertrophy (LVH)
- **Randomization:** Losartan vs. atenolol
- **Primary end point:** Composite of cardiovascular mortality, fatal and non-fatal myocardial infarction, and fatal and non-fatal stroke
- **Follow-up:** >9000 pts enrolled. >4 years


**LIFE Study Blood Pressure During Follow-up**

![Graph showing blood pressure during follow-up](image)

**LIFE Study: Fatal and Nonfatal Stroke**

Intention-to-Treat

Adjusted risk reduction 24.9%; P=.001

Unadjusted risk reduction 25.8%; P=.0006

![Graph showing proportion of patients with first event](image)
**LIFE Study Summary**

- Losartan-based compared with atenolol-based antihypertensive therapy was associated with:
  - reduced cardiovascular morbidity and mortality (-13%)
  - fewer strokes (-25%)
  - similar blood pressure reduction
- Losartan reduced the rate of new-onset diabetes (-25%)
- In the diabetic subgroup, losartan reduced the rate of:
  - combined endpoint of cardiovascular morbidity and mortality (-25%)
  - all-cause mortality (-39%)

---

**Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure**

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP* (mm Hg)</th>
<th>DBP* (mm Hg)</th>
<th>Lifestyle Modification</th>
<th>Without Compelling Indications</th>
<th>With Compelling Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Encourage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
<td>Yes</td>
<td>No antihypertensive drug indicated</td>
<td>Drug(s) for compelling indications*</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>90-99</td>
<td>Yes</td>
<td>Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination</td>
<td>Drug(s) for compelling indications*</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>≥100</td>
<td>Yes</td>
<td>Two-drug combination for most (usually thiazide-type diuretic and ACEI or ARB or BB or CCB)</td>
<td>Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed</td>
</tr>
</tbody>
</table>

* Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

---

**Lipid Control**

**Coronary Heart Disease**

- CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
Table 1. Major Risk Factors (exclusive of LDL cholesterol) that Modify LDL Goals

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

LDL Goal (mg/dL)
- <100: Optimal
- 100-129: Near optimal/above optimal
- 130-159: Borderline high
- ≥160: Very high

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

- **Total Cholesterol**
  - <200: Desirable
  - 200-239: Borderline high
  - ≥240: High

- **LDL Cholesterol**
  - <40: Low
  - ≥60: High

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III (ATP III) Guidelines

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)</th>
<th>LDL Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130 (100–129: drug optional)</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≤20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10–20%: ≥130</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt;160</td>
<td>≥160</td>
<td></td>
</tr>
</tbody>
</table>

Coronary Risk prediction

- CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease
  - peripheral arterial disease
  - abdominal aortic aneurysm
  - symptomatic Carotid Stenosis (>50% obstruction)
- Conditions that increase 10 yr risk > 20%
  - Diabetes mellitus

Established CHD

- multiple major risk factors (especially diabetes)
- severe and poorly controlled risk factors (especially cigarette smoking)
- multiple risk factors of the metabolic syndrome (especially high triglycerides >200 mg/dL plus non-HDL-C >130 mg/dL with low HDL-C <40 mg/dL)

Patients with acute coronary syndromes

Who should have LDL <70 mg/dL?

- Statins (simvastatin, pravastatin, lovastatin)
- Fibrates
- Niacin
- Cholesterol Absorption Inhibitor
- If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug.

New LDL Goal in very high risk pts

- Relative Risk for Coronary Heart Disease (Log Scale)
  - 40
  - 70
  - 100
  - 130
  - 160
  - 190
  - 3.7
  - 2.9
  - 2.2
  - 1.7
  - 1.3
  - 1.0

What drugs?
Heart Protection Study
Impact of Statins on Stroke

<table>
<thead>
<tr>
<th>Stroke etiology</th>
<th>STATIN (10269)</th>
<th>PLACEBO (10267)</th>
<th>Risk ratio and 95% CI</th>
<th>STATIN better</th>
<th>STATIN worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>242</td>
<td>376</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>48</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>68</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjudicated</td>
<td>138</td>
<td>146</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL STROKE</td>
<td>456 (4.4%)</td>
<td>813 (6.0%)</td>
<td>0.4 0.6 0.8 1.0 1.2 1.4</td>
<td>27% SE 5.3 reduction (2P&lt;0.00001)</td>
<td></td>
</tr>
</tbody>
</table>

Patients 40-80 years old, CAD, CVD, PVD, diabetes or HTN. TC > 135 (AHA 2001).


Clinical Impact: Statin Therapy

- Statin therapy reduces the risk of stroke after myocardial infarction1-3
- May be similar reduction following stroke
- FDA approved to reduce the risk of stroke in patients with clinically evident CHD
- Additional data expected from trials restricted to stroke cohorts (e.g. SPARCL)


Undertreatment of Stroke Risk Factors: Low Rate of In-Hospital Lipid Profiling

Percent of eligible patients with lipid profile

<table>
<thead>
<tr>
<th>Percent (%)</th>
<th>Percent of eligible patients with lipid profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.4</td>
<td>GA</td>
</tr>
<tr>
<td>57.4</td>
<td>MA</td>
</tr>
<tr>
<td>45.8</td>
<td>MI</td>
</tr>
<tr>
<td>33.4</td>
<td>OH</td>
</tr>
<tr>
<td>41.5</td>
<td>Total</td>
</tr>
</tbody>
</table>


Impact on Clinical Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>(N=2365)</th>
<th>(N=2366)</th>
<th>P Value</th>
<th>Prespecified Adjusted Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.84 (0.71-0.99)</td>
<td>0.03</td>
<td>0.83 (0.67-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>In-hospital stroke</td>
<td>0.87 (0.73-1.03)</td>
<td>0.11</td>
<td>0.87 (0.71-1.06)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.97 (0.87-1.08)</td>
<td>1.00</td>
<td>0.97 (0.86-1.09)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary event</td>
<td>0.74 (0.60-0.91)</td>
<td>0.04</td>
<td>0.74 (0.59-0.92)</td>
<td>0.03</td>
</tr>
<tr>
<td>Other cardiac events</td>
<td>0.65 (0.49-0.87)</td>
<td>0.004</td>
<td>0.65 (0.50-0.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.00 (0.64-1.50)</td>
<td>1.00</td>
<td>1.00 (0.60-1.60)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.51 (0.35-0.74)</td>
<td>0.001</td>
<td>0.51 (0.35-0.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>0.80 (0.69-0.92)</td>
<td>0.02</td>
<td>0.80 (0.69-0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Coronary event</td>
<td>0.65 (0.50-0.84)</td>
<td>0.001</td>
<td>0.65 (0.49-0.87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.58 (0.46-0.73)</td>
<td>0.001</td>
<td>0.58 (0.46-0.73)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>0.55 (0.43-0.72)</td>
<td>0.001</td>
<td>0.55 (0.43-0.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>0.74 (0.66-0.83)</td>
<td>0.001</td>
<td>0.74 (0.66-0.83)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Blood pressure:
- Systolic: 115-129
- Diastolic: 70-84
- Diabetes: No/Yes
- Cigarette smoking: No/Yes
- Prior AF: No/Yes
- Prior CVD: No/Yes

*Closest ranges vary by gender: women 55-134 and 115-124.
Mr. HONDA

- 75 yr old obese white male with HTN, DM, hypothyroidism, dyslipidemia, AF, CAD s/p MI, Hx of TIA s/p R CEA complains of recent episode of right arm tingling and clumsiness lasting 15 mins. He noticed trouble opening the beer can, and handling his cigarette.

- Should he be on aspirin or warfarin long-term?
- If warfarin, what INR goal?
- What about aspirin plus plavix?

Clinical Impact–Anticoagulation

- Anticoagulation with INR goal of 2.0-3.0 greatly reduces the absolute annual stroke risk of 3-5% in patients with non-valvular atrial fibrillation (NVAF)¹
- Warfarin therapy is dramatically underused in NVAF² with only 40%-60% of patients with A-fib treated
- Warfarin is not more effective than aspirin in unselected patients with non-cardioembolic stroke ³

Inadequate Post-stroke Treatment: Warfarin at Discharge

Risk Reduction in Obesity

Lifestyle Modification

- BMI Categories:
  - Underweight = <18.5
  - Normal weight = 18.5-24.9
  - Overweight = 25-29.9
  - Obesity = BMI of 30 or greater
- Abdominal Girth
  - abdominal obesity is defined by a waist circumference > 102 cm (40 in) in men and > 88 cm (35 in) in women
- Recommendations
  - Weight reduction may be considered for all overweight stroke and TIA patients to maintain the goal of a BMI of 18.5-24.9 kg/m² and a waist circumference of <35 inches for women and <40 inches for men (Class IIb, Level of Evidence C).
AHA Recommendations

- Weight loss to lower elevated blood pressure, elevated blood glucose levels, total cholesterol, LDL-cholesterol, and triglycerides, and to raise low levels of HDL-cholesterol.
- The initial goal should be to reduce body weight by about 10 percent. Weight loss should be about 1 to 2 pounds per week for a period of 6 months.
- Reducing dietary fat alone without reducing calories is not sufficient for weight loss.
- Moderate levels of physical activity for 30 to 45 minutes, 3 to 5 days a week, should be encouraged.

Alcohol Consumption

- Restrict to an average of one to two drinks per day for men and one drink per day for women. (A drink is one 12 oz. beer, 4 oz. of wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits)
- Do not encourage consumption in those who are abstinent

Smoking and Stroke Risk

- Smokers underestimate the risks of CHD CVD
- relative risk of stroke associated with cigarette smoking is 1.5 (95% CI 1.4, 1.6).
- Varies by
  - subtype: IS 1.9, ICH 0.7, and SAH 2.9.
  - age less than 55 years 2.9, 55-74 years 1.8, > 75 years 1.1
  - Amount of cigarettes smoked
  - Gender: W>M

Quit Smoking Makes A Difference

- Current smokers vs. never smokers (RR, 3.7; 95% CI, 2.0 to 6.9).
- Ex-cigarette smokers vs. never smokers (RR, 1.7; 95% CI, 0.9 to 3.3; P = .11);
- Switched to pipe or cigar smoking showed a significantly increased risk (RR, 3.3; 95% CI, 1.6 to 7.1) similar to that of current light smokers.
- Risk drops within 5 years of quitting, dependent on the amount of tobacco smoked.
- Light smokers (< 20 cigarettes/d) = never smoked. Heavy smokers vs. never smoked (RR, 2.2; 95% CI, 1.1 to 4.3).
- The benefit of quitting smoking was observed in both normotensive and hypertensive men, but the absolute benefit was greater in hypertensive subjects.

Smoking Cessation: Insufficient Counseling

- Percentage of eligible patients given counseling or medication pre-discharge:
  - GA: 19.2
  - MA: 36.1
  - MI: 25.5
  - OH: 21.9
  - Total: 23.8

Improvement Over Time in GWTG-Stroke

Outline for Thaler

Antithrombotic management for stroke prevention


Antiplatelet trials

Aspirin

Clopidogrel

Monotherapy: CAPRIE

Combined Rx: CURE, CARESS, CLAIR MATCH, CHARISMA

Aggrenox: ESPS-2, ESPRIT

Aggrenox v. clopidogrel: PROFESS

Warfarin trials

WARSS

WASID

PFO - PICSS

A sobering thought

Michael R. Jaff, DO, RPVI, FAHA
Associate Professor of Medicine
Harvard Medical School
Medical Director, Vascular Center
Massachusetts General Hospital
Boston, Massachusetts

Ischemic and Hemorrhagic Update
May 17, 2010

Common Indications for Carotid Artery Imaging

- Any patient with an audible bruit
- Any patient with a symptom suggestive of cerebral ischemia
  - Amaurosis Fugax/TIA
  - Stroke in patient who is a candidate for revascularization
- Follow-up of a known ICA stenosis >20%
- Follow-up of prior revascularization
  - CEA
  - CAS
- ?Patient with coronary artery disease in need of coronary artery bypass graft surgery

Risk of CV Death Based on Carotid Bruit

Lancet 2008;371:1587-94

Why Would Someone Recommend Screening for Carotid Artery Disease in an Asymptomatic Patient?

- Carotid Artery Disease is Common
- Having an asymptomatic carotid stenosis is bad
- The information would change your clinical management of the patient

Why Would Someone Recommend Screening for Carotid Artery Disease in an Asymptomatic Patient?

- Carotid Artery Disease is Common
- Having an asymptomatic carotid stenosis is bad
- The information would change your clinical management of the patient

Conflicts of Interest

- Consultant
  - Abbott Vascular (non-compensated)
  - Arsenal Medical
  - Atheromed
  - Baxter, Incorporated
  - Becker Venture Services Group
  - Boston Scientific (non-compensated)
  - Covidien (non-compensated)
  - Harvard Clinical Research Institute
  - I.C. Sciences, Incorporated
  - Medtronic (non-compensated)
  - Micell, Incorporated
  - Nexeon Medical Systems
- Equity
  - Access Closure, Inc
  - Hotspur, Inc
  - Icon Interventional, Inc
  - Sadra Medical
  - TMI
  - Vascular Therapies, Inc
- Board Member
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
  - www.vivapvd.com

April, 2010
Prevalence of ≥50% Carotid Stenosis

The Framingham Study

Prevalence of extracranial carotid atherosclerosis assessed by ultrasonography in men aged >65 years.

- Men at 75 yrs
- Women at 75 Yrs
- Age 50

Why Would Someone Recommend Screening for Carotid Artery Disease in an Asymptomatic Patient?

- Carotid Artery Disease is Common
- Having an asymptomatic carotid stenosis is bad
- The information would change your clinical management of the patient

Prevalence of Carotid Artery Disease

Cardiovascular Health Study

Prevalence of extracranial carotid atherosclerosis assessed by ultrasonography in women aged >65 years.

- 50-74%
- 75-99%

Where Do Strokes Come From?

Based on data from NINDS and Framingham

<table>
<thead>
<tr>
<th>TABLE 1. APPROXIMATE DISTRIBUTION OF MAJOR SUBTYPES OF ISCHEMIC STROKE*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Stroke</strong></td>
</tr>
<tr>
<td>Large-vessel atherothrombotic</td>
</tr>
<tr>
<td>Due to internal-carotid-artery stenosis</td>
</tr>
<tr>
<td>Small-vessel (lacunar)</td>
</tr>
<tr>
<td>Embolic</td>
</tr>
<tr>
<td>Due to atrial fibrillation</td>
</tr>
<tr>
<td>Other (due to dissection or other causes)</td>
</tr>
</tbody>
</table>

Kistler, JP. NEJM 2000; 342:1743
Annual Percentage Rate of Vascular Events

696 patients with asymptomatic carotid artery disease followed for a mean of 43 months

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>TIA</th>
<th>Stroke</th>
<th>Cardiac Event</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>1.0</td>
<td>1.3</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>50-75%</td>
<td>3.0</td>
<td>1.3</td>
<td>6.6</td>
<td>3.3</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>7.2</td>
<td>3.3</td>
<td>8.3</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Norris et al., Stroke, 1991

Atherothrombosis & Life Expectancy: Framingham Heart Study

In the FHS, healthy individuals aged 60 years who did not have atherothrombosis were expected to live a further 20 years to the age of 80. Comparatively, patients with a history of MI lived 9.2 fewer years and those with a history of CVA lived 12 fewer years.

Risk of Stroke with ICA Stenosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stenosis</th>
<th>Follow up (y)</th>
<th>N</th>
<th>All CVA + death</th>
<th>Disabling + death</th>
<th>Ipsilateral Disabling</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACST</td>
<td>60-99%</td>
<td>5</td>
<td>3120</td>
<td>11.8%</td>
<td>6.1%</td>
<td>3.7% (.7%)</td>
</tr>
<tr>
<td>U of T</td>
<td>0-99%</td>
<td>10</td>
<td>106</td>
<td>20%</td>
<td>5% (.5%)</td>
<td></td>
</tr>
<tr>
<td>NASCET</td>
<td>50-99%</td>
<td>5</td>
<td>216</td>
<td></td>
<td>5% (.1%)</td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>50-79%</td>
<td>2.1</td>
<td>344</td>
<td>14.8%</td>
<td>9.9%</td>
<td>4% (2%)</td>
</tr>
<tr>
<td>Meta</td>
<td>50-99%</td>
<td>3.1</td>
<td>1225</td>
<td>9.2%</td>
<td>6.2%</td>
<td></td>
</tr>
<tr>
<td>ACBS</td>
<td>50-79%</td>
<td>3.2</td>
<td>207</td>
<td>11%</td>
<td>1.4%</td>
<td>1.4% (5%)</td>
</tr>
<tr>
<td>80-99%</td>
<td>3.2</td>
<td>113</td>
<td></td>
<td>13%</td>
<td>1%</td>
<td>1% (3%)</td>
</tr>
</tbody>
</table>


CAS (n=1262)  CEA (n=1240)

<table>
<thead>
<tr>
<th>Age</th>
<th>69</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female - %</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Asymptomatic - %</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Hypertension - %</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Diabetes - %</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Dyslipidemia - %</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Current smoker - %</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

Presented at the International Stroke Meetings, San Antonio, Texas February 2010

Carotid Artery Intima-Media Thickness and Risk for Myocardial Infarction and Stroke

- Duplex Ultrasonographic measurements of Common and Internal Carotid Artery intima-media thickness
- 4476 patients ≥ 65 years with NO CLINICAL CARDIOVASCULAR DISEASE
- Primary End Points
  - New Myocardial Infarction/Stroke

Cardiovascular disease - %  41   43
Systolic BP, mean mmHg 142 141
% stenosis ≥ 70%  85  87
Days from randomization to treatment 6  7

Presented at the International Stroke Meetings, San Antonio, Texas February 2010
Carotid IMT and Mortality

Why Would Someone Recommend Screening for Carotid Artery Disease in an Asymptomatic Patient?

- Carotid Artery Disease is Common
- Having an asymptomatic carotid stenosis is bad
- The information would change your clinical management of the patient

The World Has NO Idea How to Treat Asymptomatic Carotid Artery Stenosis

ACE Inhibition Prevents Recurrent Stroke

The Progress Trial

6105 subjects with previous stroke randomly assigned to perindopril (n=3051) or placebo (n=3054)

SPARCL: High Dose Atorvastatin vs Placebo
In Patients with Prior CVA/TIA

Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis
A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

- 1007 patients with carotid stenosis (not requiring revascularization) at baseline
  - 3271 patients had no carotid stenosis at baseline
- All patients had stroke/TIA within 6 months of randomization
  - Randomized to Atorvastatin 80 mg/d vs Placebo
    - No known CHD
    - LDL Cholesterol between 100-190 mg/dL
Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis
A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

- Of those patients with carotid artery stenosis at baseline...
  - Atorvastatin lowered any stroke risk by 33%
  - Atorvastatin lowered any CHD event by 43%
  - Later carotid revascularization was reduced by 56%!

Antiplatelet Trialists' Collaboration. BMJ 2002;324:71-86

287 Studies: 135,000 Patients in Comparisons of Antiplatelet Rx vs Control

Effect of Antiplatelet Therapy in Patients with TIA or Stroke

Aspirin & Dipyridamole Decreases Stroke after TIA
European Stroke Prevention Study

Asymptomatic carotid stenosis: what to do
Jessica N. Redgrave and Peter M. Rothwell

Optimal medical treatment is the most important aspect of management of patients with asymptomatic carotid stenosis. On the basis of previous trials, endarterectomy is only of overall benefit in men, and this benefit may now be obviated by improved medical treatment. There is insufficient evidence to advocate the routine use of carotid angioplasty or stenting in patients with asymptomatic stenosis, inaccuracy in the measurement of carotid stenosis

What About Plaque Morphology as a Predictor of Future Events....
The ICAROS Trial

Gray Scale Median: Based on notion that echolucent plaques have higher embolic potential than echodense plaques

Prediction of Stroke with CAS—The ICAROS Trial

Circulation 2004;110:756-62
What Do The “Experts” Say?

**Clinical Guidelines**

Screening for Carotid Artery Stenosis: U.S. Preventive Services Task Force Recommendation Statement

**Annals of Internal Medicine**

U.S. Preventive Services Task Force

**Description**: Update of the 1996 U.S. Preventive Services Task Force statement about screening for asymptomatic carotid artery stenosis (CAS) in the general population.

**Methods**: The U.S. Preventive Services Task Force examined the evidence on the natural history of CAS, systemic review of the sensitivity of screening tests, observational studies of the harms of screening and treatment of asymptomatic CAS, and randomized controlled trials of the benefits of treatment for CAS with carotid endarterectomy. **Recommendation**: Do not screen for asymptomatic CAS in the general adult population. Grade B recommendation.


USPSTF Carotid Screening?

**Screening for Carotid Artery Stenosis**

**Population**

- Adult General Population

**Recommendation**

- Do not screen

**Harms outweigh benefits.**

In the general population, screening with carotid duplex ultrasonography would result in many false-positive results.


**Summaries for Patients**

Screening for Blockages in the Blood Vessels to the Brain: Recommendations from the U.S. Preventive Services Task Force

**What did the authors find?**

The authors found good evidence that the benefits of surgery for people with CAS but no symptoms are minimal. Yet, harms result from both testing and treatment with surgery. Strokes or death happen in about 3 of every 100 people who have carotid artery surgery. The USPSTF was moderately certain that the potential harms of screening for CAS outweigh the potential benefits.

**What does the USPSTF suggest that patients and doctors do?**

Healthy patients should not get routine screening for CAS with ultrasonography.

Duplex Screening for Carotid Artery Disease--CMS

- Screening for occult carotid artery disease not reimbursed by Medicare
- In one study 19.6% denied, but 72.5% of these had abnormal findings!

56 yo Asymptomatic Female Attends an MGH Vascular Center Screening Event

The First Step in Stroke Prevention Will Be To Identify Patients at Risk for Stroke!

**Genomewide Association Studies of Stroke**

- Genomewide study of 4 Caucasian populations
- 19,602 patients
- 1544 strokes over 11 years
- 1164 ischemic


**Forest Plots Showing Associations between Single-Nucleotide Polymorphisms and Total, Ischemic, and Atherothrombotic Strokes**

**Two SNPs located on Chromosome 12p13**

**Associations in the Region Centered on rs11833579 and Containing NINJ2**

---

**Recommended Duplex Follow Up**

<table>
<thead>
<tr>
<th>ICA Stenosis</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19%</td>
<td>Only repeat if new clinical indications are present</td>
</tr>
<tr>
<td>20-39%</td>
<td>Repeat every year</td>
</tr>
<tr>
<td>40-59%</td>
<td>Repeat every year</td>
</tr>
<tr>
<td>60-79%</td>
<td>Repeat every 6 months</td>
</tr>
<tr>
<td>80-99%</td>
<td>Refer for carotid endarterectomy or stent</td>
</tr>
<tr>
<td>Occlusion</td>
<td>Repeat every year</td>
</tr>
</tbody>
</table>

**Post carotid endarterectomy**

Repeat in 6 months and then yearly. If the contralateral side is 80-99%, repeat one week after CE

**Post carotid stent**

Repeat at 24 hours, 3, 6 months and yearly
Carotid artery disease- Indications for treatment and results of endartectomy and stenting

Christopher S. Ogilvy, M.D.
MGH Neurovascular Surgery

The carotid bifurcation

- One of the most studied areas of atherosclerosis in the body
- Procedures for treating disease (endartectomy and stenting) are some of the most closely scrutinized procedures in medicine
- 'Optimal' medical management still not well understood

CAROTID ENDARTECTOMY
CEA-Initial exposure

Exposure of Carotid Bifurcation

Endarterectomy
Plaque and Closure

BACKGROUND

Carotid Endarterectomy

- 50 year history of technique development and refinement
- Up to 200,000 CEAs performed per year in the U.S.¹
- Estimated that 20% of CEAs are performed on “high surgical-risk” patients annually in the U.S.²
- High surgical risk defined:
  - Anatomic - increased procedure risk
  - Medical Co-morbidities - increased risk MI and death

¹. Heart Disease and Stroke Statistics – 2004 Update, American Heart Association

Randomized clinical studies
- Superiority of CEA vs. best medical therapy
  - NASCET¹
    - Symptomatic ≥50% diameter stenosis
  - ACAS²
    - Asymptomatic >60% diameter stenosis
  - ECST³
    - Symptomatic >50% diameter stenosis
  - VA Cooperative Study⁴
    - Symptomatic >50% diameter stenosis

¹. NASCET Trial Collaborators NEJM 325:445-453, 1991
². ACAS Executive Committee JAMA 273:1421-1428, 1995
⁴. Hobson et al., NEJM 328:221-227, 1993
Asymptomatic Carotid Stenosis

• ACAS study-
  – If stenosis is greater than 60%, 5 year risk with natural history=11% (2.2% per year)
  – With surgical intervention, 5 year risk, 5.1% (1% per year)

ACAS: the world's largest vascular surgery trial
Entry 1993 – 2003
3120 patients randomised
Immediate CEA vs Deferral CEA

<table>
<thead>
<tr>
<th>Immediate CEA</th>
<th>Deferral CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CEA: carotid endarterectomy)</td>
<td>(i.e. deferral until CEA seems more clearly needed)</td>
</tr>
</tbody>
</table>

ACST TRIAL
**Symptomatic Carotid Artery Stenosis**

- Nascet Study 1986—For patients with stenosis >70%
  - 26% any stroke risk at 2 years with ASA rx
  - 9% any stroke risk at 2 years with endarterectomy
  - 30-day perioperative stroke risk was 5.8%

**NASCET Trial**

**ECST-European Carotid Surgery Trial**

- Lower stroke rate in medically managed patients than NASCET (16.8% at 3 years vs. 26% in 2 years in ECST)
- Perioperative surgical risk of any stroke or death was 7% vs 5.8% in NASCET
- Conclusion: While benefit observed for stenosis of >80% (70% by Nascet criteria) there was no clear benefit of endarterectomy below 80% stenosis

**ECST Trial-2003**
FOR CAROTID ENDARTECTOMY

- Several large, randomized clinical trials demonstrate benefit of CEA over medical management for carefully selected symptomatic and asymptomatic patients
- ENTER: CAROTID ARTERY ANGIOPLASTY AND STENTING

---

Carotid Angioplasty and Stenting (CAS)

---

Embolic Protection during Stenting
Cerebral Protection Strategies

- Distal ICA Filering
- Distal Flow Blockage by ICA Occlusion
- Flow Reversed by CCA and ECA Occlusion
- Proximal Flow Blockage by CCA and ECA Occlusion

Protect
Epic
Maveric
Empire
Armour

Challenges in comparing strategies
“moving targets”

- Medical Rx evolving - better drugs and increased understanding of pathophysiology
- CEA improving - evolving techniques
- CAS improving - better devices, increased experience, & better case selection

Other Challenges
- Event rates low - large number of patients required to detect difference (or equivalence)
- “noise” from other causes of stroke
- Physicians/patients - pre-conceived notions about best Rx; reluctance to accept change

RCT’s: CAS vs. OMT for stroke prevention

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>High-risk</td>
</tr>
<tr>
<td><strong>None</strong></td>
<td><strong>None</strong></td>
</tr>
</tbody>
</table>

- In absence of “head to head” trials vs. OMT, can only infer ability of CAS to prevent stroke based on:
  a) registry studies of CAS and
  b) RCT’s comparing it to CEA!
Carotid angioplasty and stenting

• As cartoid stenting evolved, 'stand alone' trials were conducted to reach FDA approval for various stents
• Over time, there has been a gradual overall reduction in the morbidity and mortality with stenting for carotid artery disease
• Early on, the concept of trials to compare stenting with carotid endarterectomy were proposed

11 device approval trials: all approved

Trials CEA/CAS
• CAVATAS, Carotid and Vertebral Artery Transluminal Angioplasty Study; CEA, carotid endarterectomy;
• CREST, Carotid Revascularization Endarterectomy versus Stent Trial;
• EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis;
• ICSS, International Carotid Stenting Study;
• SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy;
• SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy.
Promise of Stenting: SAPPHIRE study

- Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE)
  - 1st randomized study comparing CEA with stenting with distal embolic protection.
  - High risk groups studied (Age >80).

- Rate of major adverse events (stroke, MI or death) at 1 yr:
  - 12.2% in stent group
  - 20.1% in CEA group.
- Higher recurrent stenosis in CEA (4.3%) compared to stent group (0.6%).

The main finding of our randomized trial is that carotid-artery stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy in the prevention of stroke, death, or myocardial infarction among patients for whom surgery poses an increased risk. In the secondary analysis, the cumulative incidence of stroke, death, and myocardial infarction, as well as the cumulative incidence of cranial-nerve palsy and revascularization and the length of the hospital stay, were lower among patients who received a stent than among those who underwent surgery. The results of our study are not generalizable to patients at low surgical risk, and studies are under way to assess the appropriateness of stenting in such patients.
SAPPHIRE Study Notes

- 55% of patients were excluded as poor surgical candidates.
- >20% of patients already had recurrent stenosis following CEA at study enrollment (potentially bad candidates for CEA at the start).
- MI, stroke, and death was included as endpoints, while prior CEA studies did not include MI.

“HIGH SURGICAL-RISK” PATIENTS-CONSIDERATION FOR CAS

- CAS may be an option for consideration in patient at high risk for CEA.
Do these findings apply to low risk surgical patients?

EVA-3S

- 527 patients with 60-99% stenosis and TIA or non disabling stroke within 120 days before treatment
- 30 day risk of stroke death 3.9% CEA vs 9.65 CAS
- 6 month risk 6.1% CEA vs 11.7% CAS
- Cranial n. injury 7.7% CEA vs 1.1% CAS
- Trial stopped early

EVA-3S

- No change in CAS stroke rate based on operator experience
- Not all patients had distal protection.
- Improved rate in distal protection patients did not make up the difference in outcomes between CEA/CAS
- Hospital stay was shorter in the stenting group vs endarterectomy group (3 days vs 4 days p. 0.01)
- 30 day incidence of stroke or death in the stent group did not depend on whether patients were on antiplatelet therapy or not.
EVA-3S 4 Year Data

- 4 year Lancet Update October 2008
- 262 patients were randomly assigned to endarterectomy and 265 to stenting. The cumulative probability of periprocedural stroke or death and non-procedural ipsilateral stroke after 4 years of follow-up was higher with stenting than with endarterectomy (11.1% vs 6.2%, hazard ratio [HR] 1.97, 95% CI 1.06-3.67; p=0.03). The HR for periprocedural disabling stroke or death and non-procedural fatal or disabling ipsilateral stroke was 2.00 (0.75-5.33; p=0.17).

SPACE trial

- 1183 patients randomized to CAS or Stenting after presenting with TIA or stroke within 180 days.
- 30 day ipsilateral stroke or death
  - 6.8% Stenting
  - 6.1% CEA

<table>
<thead>
<tr>
<th>Study name or location</th>
<th>CAS n</th>
<th>CEA n</th>
<th>Peto odds ratio</th>
<th>Peto odds ratio</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leicester 1998</td>
<td>9/11</td>
<td>6/12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WALLSTENT 2001</td>
<td>13/197</td>
<td>5/112</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CASSAG 2001</td>
<td>20/311</td>
<td>29/343</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louisville 2001</td>
<td>0/10</td>
<td>1/10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURFIRME 2001</td>
<td>8/167</td>
<td>9/167</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVA-3S 2006</td>
<td>25/290</td>
<td>18/259</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Space 2006</td>
<td>95/599</td>
<td>36/564</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>122/1499</td>
<td>89/1458</td>
<td></td>
<td>1.41 (1.03-1.93)</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure 1 Summary of randomized trials comparing carotid artery stenting (CAS) and carotid endarterectomy (CEA) for the treatment of severe carotid artery stenosis. The combined end point was “any stroke or death within 30 days.” This meta-analysis revealed a significant difference between risks, with CAS showing a disadvantage (OR 1.41, 95% CI 1.07-1.87; P = 0.016). Significant heterogeneity was found for this analysis (Cochran Q = 13.8; P = 0.003).
Meta-analysis of randomized trials comparing carotid artery stenting (CAS) and carotid endarterectomy (CEA) for the treatment of severe carotid artery stenosis. The combined end point was "disabling stroke or death within 30 days" (data were available from five trials only). The risks were similar in the two groups (OR 1.33, 95% CI 0.89–1.98; \( P = 0.17 \)), and no significant heterogeneity was found for this analysis (Cochran \( Q = 5.2; \) \( P = 0.26 \)).

An updated meta-analysis of seven randomized trials that compared the effectiveness of carotid endarterectomy and stenting, mostly in symptomatic patients, reveals a disadvantage of endovascular treatment for the end point "any stroke and death within 30 days after treatment", but the risk of the end point "disabling stroke and death" was similar in the two groups.

Carotid artery stenting

- As with good results with carotid endarterectomy, there are patient specific factors and lesion specific factors that favor good outcome with stenting
- This translates into GOOD JUDGEMENT
CREST Study Design

- Prospective, multicenter, randomized, controlled trial with blinded endpoint adjudication
- Comparing CEA and CAS in participants with symptomatic and asymptomatic stenosis
- 108 US and 9 Canadian sites
- Team included neurologist, interventionalist, surgeon, and research coordinator at each center
Primary Endpoint

Composite:
• Peri-procedural
  • any Clinical Stroke
  • Myocardial infarction
  • Death
• Post-procedural
  • Ipsilateral stroke up to 4 years

Stroke

• An acute neurological ischemic event of at least 24 hours duration with focal signs and symptoms.
• Adjudicated by at least two neurologists blinded to treatment
**Myocardial Infarction (MI)**

- Combination of:
  - Elevation of cardiac enzymes
  - Symptoms of myocardial ischemia or ECG evidence
- Not enzyme-only
- Adjudicated by two cardiologists blinded to treatment

**Secondary Aims**

- Differential efficacy by symptomatic status, sex, and age
- Differential restenosis
- Quality of Life and cost effectiveness

**Major Eligibility Criteria**

*Conventional-risk (not low risk) patients*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sx</th>
<th>Asx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography</td>
<td>≥50%</td>
<td>≥60%</td>
</tr>
<tr>
<td>DUS</td>
<td>≥70%</td>
<td>≥70%</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTA/MRA</td>
<td>&gt;70%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

(if DUS 50-69%)
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>CAS (n=1262)</th>
<th>CEA (n=1240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-%</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Female - %</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Asymptomatic - %</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Hypertension - %</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>Diabetes - %</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Dyslipidemia - %</td>
<td>82</td>
<td>85</td>
</tr>
<tr>
<td>Current smoker - %</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>CAS (n=1262)</th>
<th>CEA (n=1240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease - %</td>
<td>41</td>
<td>43</td>
</tr>
<tr>
<td>Systolic BP, mean mmHg</td>
<td>142</td>
<td>141</td>
</tr>
<tr>
<td>% stenosis ≥ 70%</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>Days from randomization to treatment</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
Primary endpoint ≤ 4 years (mean 2.5)

Peri-procedural outcomes (Stroke, MI)

- MACE (%)
  - CAS
  - CEA

HR = 1.18 95% CI: 0.82-1.68
HR = 1.11 95% CI: 0.81-1.51

P = 0.38

90% of subjects

---

Primary Endpoint

Follow-up Time (years)

% Event (%)

---

Primary outcome — 4 year

- 90% of subjects
- P_{interaction} = 0.020

---

48

79

---
### Peri-procedural Stroke and MI

<table>
<thead>
<tr>
<th></th>
<th>CAS vs. CEA</th>
<th>Hazard Ratio 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke All</td>
<td>4.1 vs. 2.3%</td>
<td>HR = 1.79; 95% CI: 1.14-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.9 vs. 0.6%</td>
<td>HR = 1.35; 95% CI: 0.54-3.36</td>
<td>0.52</td>
</tr>
<tr>
<td>MI</td>
<td>1.1 vs. 2.3%</td>
<td>HR = 0.50; 95% CI: 0.26-0.94</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### Peri-procedural Stroke

<table>
<thead>
<tr>
<th></th>
<th>CAS vs. CEA</th>
<th>Hazard Ratio 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Stroke</td>
<td>4.1 vs. 2.3%</td>
<td>HR = 1.79; 95% CI: 1.14-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0.9 vs. 0.6%</td>
<td>HR = 1.35; 95% CI: 0.54-3.36</td>
<td>0.52</td>
</tr>
</tbody>
</table>

### Cranial Nerve Palsies

<table>
<thead>
<tr>
<th></th>
<th>CAS vs. CEA</th>
<th>Hazard Ratio, 95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 vs. 4.7%</td>
<td>HR = 0.07; 95% CI: 0.02-0.18</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Ipsilateral Stroke after Peri-procedural Period ≤ 4 years

CAS vs. CEA Hazard Ratio, 95% CI P-Value
2.0 vs. 2.4% HR = 0.94; 95% CI: 0.50-1.76 0.85

Summary

• Similarity in the Primary Endpoint driven by differences in perioperative minor stroke and MI
• More MIs after CEA
• More minor strokes after CAS
• Overall VERY LOW morbidity and mortality for both treatment modalities

Impact of periprocedural events (stroke/MI) on SF-36 at 1 year adjusting age, sex, symptomatic cerebrovascular disease and baseline SF-36 measures – Growth Curve Modeling.
Conclusions

- CEA and CAS have similar net outcomes though the individual risks vary, lower stroke with CEA and lower MI with CAS
- Younger patients may have improved efficacy with CAS and older patients have improved efficacy with CEA

CEA and CAS for carotid disease- Current issues

- As CREST data is digested, debated and scrutinized, practice will be influenced
  - Local, regional, national
- A large component to what will drive the treatment of carotid disease will be economic:
  - Government
  - Insurance companies
Lecture #15

Subclavian and vertebral artery atherosclerotic disease- intracranial and extracranial management

Ferdinando Buonanno, MD
Intraparenchymal & Subarachnoid Hemorrhage: ED Management

Jonathan A. Edlow, MD
Department of Emergency Medicine
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School

Subarachnoid hemorrhage

Mid-diagnosis rate
20-25% in older studies
12% in one large US study
5% related to ED (Canadian)

SAH – misdiagnosis

• Least ill patients are most commonly misdiagnosed
• Correctly diagnosed, they have the best outcomes
• Misdiagnosed patients have worse outcomes from early complications (mostly re-bleeding)

So who do you work up?

• History
  • Headache: onset, severity, quality, associated symptoms
  • Risk factor assessment and epidemiological context
• Physical exam
  • Careful cranial nerve exam, visual fields
  • Optic - sub-hyaloid hemorrhage
• Decision-making
  • Is there a plausible alternative explanation for symptoms? (first or worst)

What is the work up for SAH?

• Non-contrast CT scan
• Lumbar puncture (if CT is negative, equivocal or technically inadequate)
• In exceptional cases where both CT and LP are normal, cerebrovascular imaging
  • MRA
  • CT angiography
  • Conventional catheter cerebral angiography
Symptoms suggestive of SAH

- Non-contrast head CT Scan
- Positive for SAH
- Neuro/surgical consultation
- Vascular Imaging
- Management Issues

Lumbar Puncture

- If ambiguity in CT/LP, or
- First presentation > 2 weeks, or
- Very high pre-test risk, or
- Inability/refusal to do LP

Consider CTA

- No aneurysm
- Aneurysm

Symptomatic care

Follow-up

Limitations of the CT scan

- **Timing** - sensitivity decays with time
- **Spectrum bias** - small volume bleeds (“warning bleeds”)
- **Errors in interpretation** (stroke data)
- **Technical factors** - thick cuts, quality of scanner
- **Hematocrit** (< 30) can lead to negative scan

Limitations of LP

Failure to distinguish traumatic tap from true SAH

- Incidence is 10% (400 RBCs) to 15% (1000 RBCs)
- Is visual inspection for xanthochromia is less sensitive than spectrophotometry?
  - Yes, but real-world data suggest that visual inspection clinically performs very well (Linn, 05)
  - The price: spectrophotometry lacks specificity
  - The reality: > 99% of US hospital labs use visual inspection anyway
- Failure to recognize that xanthochromia may be absent in the early hours following SAH

The CT/LP are normal; do I need to do a CTA?

- Patients with severe HA and negative CT and LP **very rarely** have symptomatic aneurysms
  - 7 studies, 813 patients, ≥ 6m f/u: 0 SAH/deaths
  - ACEP clinical policy
- Measure the opening pressure when doing the LP (BIH, CVST, and to distinguish traumatic tap from true hemorrhage or spontaneous IC hypotension if low - < 6cm)

Hypothesis: modern CT is sufficient to exclude SAH without the need for LP

- Retrospective study of 149 patients with SAH 2001-2004 in an academic center (4-slice, 4-detector CT)

Of the total, 139 had + CT and 10 had + LP (overall s-CT: 93%)

Of these 139, 117 had an aneurysm or AVM found; in this group, s-CT was 94%

Of these 117, 67 had only HA with normal mental status; of this group, s-CT was 91%

Bynn; Ann Emerg Med; 2008

Incidence is 10% (400 RBCs) to 15% (1000 RBCs)

Is visual inspection for xanthochromia is less sensitive than spectrophotometry?

Yes, but real-world data suggest that visual inspection clinically performs very well (Linn, 05)

The price: spectrophotometry lacks specificity

The reality: > 99% of US hospital labs use visual inspection anyway

Failure to recognize that xanthochromia may be absent in the early hours following SAH
SAH – when to pursue the work-up beyond CT and LP?

• Consider vascular imaging and/or specialist consultation in patients with:
  • Very high pre-test risk
  • 1st presentation > 2 weeks after onset of symptoms
  • Significant ambiguity in CT or CSF results
  • CSF unobtainable (patient refusal or technical issues)
• Other diagnostic issues
  • LP first strategy
  • Primary MR
  • Primary CTA

Intraparenchymal ICH

• Neurological deficit (focal or generalized)
• With or without headache
• Abrupt onset of vomiting
• Suggestive symptoms of ICH v AIS
  • BP > 180/110
  • Vomiting
  • Confusion
  • Anticoagulant use

What about CTA only?

Computed Tomographic Angiography for the Evaluation of Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>CT Results</th>
<th>LP Results</th>
<th>CTA Results</th>
<th>Angiography Results</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>Male</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>5 mm MCA aneurysm</td>
<td>Dissection</td>
</tr>
<tr>
<td>56</td>
<td>Male</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>5 mm MCA aneurysm</td>
<td>Dissection</td>
</tr>
<tr>
<td>57</td>
<td>Male</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>5 mm MCA aneurysm</td>
<td>Dissection</td>
</tr>
<tr>
<td>58</td>
<td>Male</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>5 mm MCA aneurysm</td>
<td>Dissection</td>
</tr>
<tr>
<td>59</td>
<td>Male</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>5 mm MCA aneurysm</td>
<td>Dissection</td>
</tr>
</tbody>
</table>

All patients awake, none had headache

What is the work up for ICH?

• Non-contrast CT scan
• MRI (can help time the bleed)

• Vascular imaging to define underlying lesion
  • MRA
  • CT angiography
  • Conventional catheter cerebral angiography

Causes of non-traumatic ICH

• Primary
  • Hypertension
  • Amyloid angiopathy
• Secondary
  • OAT (oral anti-coagulation treatment)
  • AVM & aneurysm
  • CVST
  • Cavernous malformation & venous angiomas
  • Dural AV fistula
  • Vasculopathy (Moya-moya, vasculitis, PRES & RCVS, cocaine)
  • Tumor
  • Hemorrhagic conversion of an infarct
Management Issues

- Airway
- Neurosurgical/intervention consultation and transfer
- Angiography
- Blood pressure control
- Anti-fibrinolytics
- Analgesia (pain and anxiety)
- Reverse coagulopathy
- Vasospasm prevention
- Seizure prophylaxis
- Volume and hydration issues
- ICP: hydrocephalus and extra-axial or intra-cerebral hematoma
- Arrhythmia monitoring
- General issues (fever, glucose)
Over-arching considerations:
1. What is the patient’s baseline BP?
2. Is the ICP elevated?
3. Is acute hydrocephalus present?

CPP = MAP – ICP
MAP = Diast + 1/3 (Syst – Diast)

AHA guidelines

- If SBP > 200 (or MAP > 150)
  - Consider “aggressive” BP reduction with continuous IV infusion and BP monitoring q5’
- If SBP > 180 (or MAP > 130),
  - Plus evidence of ↑ ICP, consider monitoring ICP and reduce BP to keep CPP > 60 – 80
  - No evidence of ↑ ICP, consider modest BP reduction (MAP of 110 or ~ 160/90) with frequent clinical re-exams q15’

Primary outcomes: Hematoma expansion & edema increase at 72h

<table>
<thead>
<tr>
<th>180 (guidelines)</th>
<th>140 (intensive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>172 pts</td>
<td>174 pts</td>
</tr>
<tr>
<td>BP achieved @ 1h</td>
<td>167 mm Hg</td>
</tr>
<tr>
<td>Hematoma growth (absolute - ml)</td>
<td>2.7</td>
</tr>
<tr>
<td>Hematoma growth (proportional - %)</td>
<td>36.3%</td>
</tr>
<tr>
<td>Death/dependency</td>
<td>49%</td>
</tr>
<tr>
<td>Early neurological deterioration</td>
<td>15%</td>
</tr>
</tbody>
</table>

* Intensive treatment group drugs: furosemide (35%), urapidil (central α-1 antagonist) (47%), labetalol (6%) and nicardipine (5%)

Excluded patients with GCS of 3-5
IV nicardipine with target BP:
- 170-200: 18 pts
- 140-170: 20 pts
- 110-140: 22 pts

**Primary outcomes:**
1. Feasibility – maintain target BP 24h
2. Neurological deterioration at 24h
3. Serious adverse event < 72h

- 9/60 treatment failures, all in 3rd “intense” group
- 7/60 w/ early deterioration, 1 (6%), 2 (10%), 4 (18%)
- 4/60 w/ SAE, 0, 1 (5%) and 3 (14%)

3 month mortality: 3 (17%), 2 (10%) and 5 (23%)

**ICP management**

- **Causes of elevated ICP in 1st hours**
  - Hydrocephalus
  - Rebleeding
  - Hematoma
- **Treatment**
  - Head/neck position (elevation, C-collar, bandages)
  - Does the patient need an EVD?
  - Osmotic agents (hypertonic saline v mannitol)?
  - Hyperventilation?
  - Surgical decompression?

**Seizures**
- If seizing (~ 8-15% SAH & ICH), treat
- For SAH – “may be considered post-SAHS” (? Other agents over phenytoins)
- For ICH – “may reduce seizures for lobar bleeds”

**Vasospasm (SAH)**
- PO nimodipine improves outcomes ? why

**Rebleeding/hematoma exp**
- SAH & ICH: BP & coagulopathy control
- For SAH – short course of anti-fibrinolytics (Amicar or tranexamic acid)
- ICH - ? rFVIIa in particular sub-groups

**Reverse coagulopathy**
- OAT-associated (to INR < 1.4)
- Heparinized (to PTT < 34 seconds)
- Platelet disorder

**Antihypertensives**

- IV meds that are short-acting, continuous infusion, with a reliable dose-response
- “In” drugs
  - Nicardipine
  - Labetolol
  - Esmolol
- “Out” drugs
  - Nitroprusside (effect on ICP)

**Reverse coagulopathy**

- OAT-associated
  - Standard treatment is FFP & vitamin K
  - Prothrombin complex concentrates
  - r-FVIIa (in OAT patients)
- Heparinized patients
  - Protamine for heparinized patients
  - Platelet dysfunction – transfuse platelets if < 20,000

**Preventing Complications**
1. Seizures
2. Vasospasm
3. Rebleeding & hematoma expansion
4. Reverse coagulopathy

**Table of antifibrinolytics**

<table>
<thead>
<tr>
<th>FFP</th>
<th>Vitamin K</th>
<th>PCC *</th>
<th>r-FVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Rapid ^</td>
<td>4-6 hours (IV)</td>
<td>Very rapid</td>
</tr>
<tr>
<td>Half-life</td>
<td>Short</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Prep time</td>
<td>Compatibility testing &amp; thawing</td>
<td>None</td>
<td>Time to calculate dose *</td>
</tr>
<tr>
<td>Dosing</td>
<td>20-40 cc/kg</td>
<td>5-10mg IV</td>
<td>Varies by lot, INR &amp; weight</td>
</tr>
<tr>
<td>Side-effects</td>
<td>Blood-borne pathogens</td>
<td>Volume issues TRALI</td>
<td>Allergic reaction</td>
</tr>
<tr>
<td>other issues</td>
<td></td>
<td></td>
<td>Need to follow with FFP &amp; Vit K</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombosis</td>
</tr>
</tbody>
</table>

* Generic term for many products with different formulations & ^ “Rapid” once the infusion starts; “real-life” use studies show that it takes many hours
**r-FVIIa in ICH (non-OAT)**

- 2005 – phase 2b PC-RCT < 4h (399 pts)
  - Showed ↓ hematoma growth, mortality at 3 months
- 2008 – phase 3 PC-RCT (841 pts)
  - Did not confirm ↑ in death/disability
  - ↑ in thromboembolic complications
- Hypothesis from sub-group analysis
  - Age < 70 years
  - Hematoma volume < 60ml
  - Treatment < 2.5 hours
  - “Spot” sign + patients

**SAH – Vascular imaging**

- Conventional
  - Gold standard
  - Essential for endovascular treatment
- CT
  - Rapidly improving
  - Becoming standard single pre-operative test
- MR
  - Very sensitive but can miss small aneurysms (< 5mm)
  - May establish alternative diagnoses

**IPH – Vascular imaging ?**

Traditional indications (Zhu; 1996 – 206 pts with DSA)
- Age < 46
- Normotensive
- Location of bleed is lobar (non-typical hypertensive)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Positive Angiography</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤ 45, normotensive 25</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>Age &gt; 45, normotensive 27</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Age ≤ 45, hypertensive 10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age &gt; 45, hypertensive 29</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**CTA in 623 IPH patients**

* 92 (15%) had a vascular lesion
* 531 (85%) no vascular lesion found

**Repeat CT scan**
**Review BP trends**
**Consider EEG**
**Review other management steps in check-list**

**Differential diagnosis of acute, early clinical decompensation**

- Brain ischemia or infarction
- Rebleeding
- Seizure – post-ictal or non-convulsive status
- Hematoma – extra-axial, intra-parenchymal, intra-ventricular
- Hydrocephalus
- Hypo-perfusion (CPP)
Airway

BP control

Treat pain

Preventing Complications
1. Seizures
2. Vasospasm
3. Rebleeding & hematoma expansion
4. Reverse coagulopathy

Differential diagnosis of acute, early clinical decompensation

General Dx/Rx issues
1. Telemetry, ECG, troponin
2. Pre-op labs, & coags
3. Fever, glucose control

Conversation with neuro-vascular specialist

? a specific therapy for a special case

Ongoing Trials

• ATACH-2 – recruit 1280 pts target BP 140 v 180 systolic “standard” (nicardipine) with clinical outcome 30d death/disability
• INTERACT-2 – recruit 2800 pts target BP 140 v “conservative” with clinical outcomes of death/dependency
• CLEAR 3 – tPA intra-ventricular for IVH
• MISTIE – MIS w/tPA for deep ICH (w/o IVH) v best medical management
• STICH 2 – confirm hypothesis from STICH 1 that lobar ICH (without IVH/hydrocephalus) benefit from early surgery v conservative management
• SPOT sign r-FVIIa – Spot sign for predicting FVII response

? a specific therapy for a special case
Angiography, CTA and MRA for Intracranial Hemorrhage

James D. Rabinov, M.D.
Interventional Neuroradiology
Massachusetts General Hospital
Boston, Massachusetts

Intracranial Hemorrhage

IPH-CAVM, AVM, DAVF, SSThrombosis, Tumor, Trauma, Moya, Amyloid, stroke transformation, hyperperfusion post revascularization, HTN, coagulopathy, septic emboli, vasculitis
SAH-Aneurysm, DAVF, Trauma, Benign perimesencephalic hemorrhage, vasculitis, vasoconstriction syndrome, cocaine
SDH-Trauma, PCOM or ACOM, Low pressure CSF, anticoagulation, Coagulopathy,

Algorithms for work up

Medical stabilization if acute presentation
Non-invasive imaging:
CTA with dynamic 4D imaging
MRI with MRA/MRV with gado MRA or TRICKS
Cerebrospinal angiography (1% risk)
Negative work up-Repeat after interval (7-14 days for SAH. 1-2 months for siderosis)
Variable for age and co-morbidity
CT Angiography

Multidetector CT scanner for rapid acquisition of thin slice axial images
Rapid IV bolus injection of contrast 4 cc/sec for 120 cc total
Commercial work station (GE, Vitrea) to reconstruct the data into 2D MIP, slab or 3D surface rendered models
Sensitivity 87-100% for ruptured aneurysm Villablanca, AJNR, 2002

CT Angiography

GE Lightspeed scanner
Injection: Rate 4cc/sec for 120 cc; 25 sec delay; 18 ga IV
Coverage: C1 to vertex
Parameters: Standard algorithm, slice 1.25 mm, image spacing 0.6 mm, table feed 3.75 mm, pitch 3:1, mode HQ, 140 kV, 170 mA, rotation time 0.8 sec, FOV 22 cm

Diagnostic Angiography

Biplane DSA is the gold standard for evaluation of intracranial hemorrhage
Overall risk of <.5-4% (stroke, blood vessel injury, bleeding, infection, renal failure, contrast reaction, death) Johnston, Neurology, 2001
1.2% risk of stroke in ACAS study
Diagnostic Angiography

Sensitivity and specificity 99% due to image quality, incorrect view, tiny aneurysm, partial filling of COW
Contrast reaction: Premedicate with corticosteroids, benedryl, cimetidine
Renal failure: Hydration, sodium bicarbonate, mucomyst, dialysis

Angiogram Negative SAH

Benign perimesencephalic hemorrhage is a diagnosis of exclusion with small amounts of blood around the brain stem, suprasellar cistern and proximal sylvian fissures. van Gijn, Neurology, 1985
Patients should undergo a second diagnostic angiogram 2-4 weeks after initial study

AVM Evaluation

Spetzler Martin classification:
Size of nidus: 0-3 cm, 3-6 cm, >6 cm (1, 2, 3 points)
Eloquent vs. non-eloquent tissue (language, motor) (0, 1 points)
Venous drainage: superficial vs. deep (0, 1 points)
AVM Evaluation

Venous outflow stenosis, varix or occlusion
Direct end vessel arterial supply vs. feeders of passage
Feeding pedicle (11.2%) or intranidal aneurysm (5.5%) Redekop, JNS, 1998
Sub-selective amytal testing through microcatheter
fMRI for language dominance and motor location

TRICKS MRA

Time Resolved Imaging of Contrast Kinetics
Dynamic gadolinium bolus
3D gradient echo sequence
Elliptical concentric K-space acquisition

Dural Arteriovenous Fistula

Classification by Cognard, Radiology, (1995)
I. AVF to venous sinus - antegrade
IIa. AVF with reversal of venous sinus
IIb. AVF with reversal of venous sinus into cortical veins
III. AVF directly into retrograde cortical vein
IV. AVF type III with venous varix/stenosis
V. AVF into cortical vein > spinal vein
What did we forget?
Narrow thinking vs. broad DDx
Missed important medical history-Meds-OCP, antidepressant, cocaine
Incomplete or suboptimal CTA, MRI or angiogram
Misinterpreted CTA, MRI or angiogram
Did not repeat exam during follow up

Specific Errors
SDH: Rare from PCOM or ACOM aneurysm
SAH: De novo aneurysm/pseudoaneurysm, Missed aneurysm on angiographic projection -Rotational angiography and early re-study-IPH: Compressed or thrombosed AVM/AVF Missed vasculitis or cortical vein thrombosis -MRI DWI and susceptibility sequences

Cavernous Malformation
Focal collection of endothelial lined sinusoids which undergo hemorrhage as they enlarge Mixed signal lesion on MRI often with hemosiderin pseudocapsule MRI susceptibility sequence helpful Mixed density on CT +/- calcification 10-30% have associated developmental venous anomaly
Venous Sinus Thrombosis

Predisposing health issues-smoking, OCP, meningitis, sinusitis, iatrogenic
Variable presentation with progressive HA, confusion, focal neurologic/CN deficit
Imaging shows edema, stroke, hemorrhage
CTV or MRV/gadolinium shows absent venous sinus

Vasculopathies

Adult Moya Moya
Vasoconstriction/Call Fleming Syndrome
Eclampsia
Vasculitis-viral (varicella, HIV), Tb, septic emboli, SLE, giant cell arteritis, Behcet’s disease
Sickle cell
Intracranial Aneurysms—Ruptured and Unruptured

Christopher S. Ogilvy, M.D.
Director of Endovascular and Operative Neurovascular Surgery
Professor of Surgery
Harvard Medical School
Massachusetts General Hospital

Headaches and Neurologic Deficits: Level of worry for physicians

• Headache
  – “Worst headache of life”
  – Patient who have never had headaches
  – Headache patients with significant change in headaches

• Neurologic deficits
  – Transient significant weakness or numbness
  – New fixed neurologic deficit
  – Transient or new cranial neuropathy
Intracranial Vascular Lesions of Worry

• Aneurysms

• Vascular Malformations

FORMATION OF INTRACRANIAL ANEURYSMS

• Usually occur at the bifurcation of vessels
• There is most likely a predisposition for aneurysm formation (20-25% familial)
• Local hemodynamics contribute to formation
• Other factors (smoking, hypertension, connective tissue disorders) seem additive to formation of aneurysms

Aneurysms
CIRCLE OF WILLIS
SUBARACHNOID HEMORRHAGE
Histology
Elastin Stain

Normal Vessel

Aneurysm

Ruptured Aneurysm
Elastin Stain

Point of rupture

20X
CAUSES OF SUBARACHNOID HEMORRHAGE

• TRAUMA
• INTRACRANIAL ANEURYSMS
• ARTERIOVENOUS MALFORMATIONS
  – INTRACRANIAL
  – INTRASPINAL
• NEOPLASMS
• HYPERTENSION

PRESENTATION
SEVERITY OF SUBARACHNOID HEMORRHAGE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neurologic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2</td>
<td>Severe headache, stiff neck, no neurologic deficit,</td>
</tr>
<tr>
<td></td>
<td>except cranial nerve palsy</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy, minimal neurologic deficit</td>
</tr>
<tr>
<td>4</td>
<td>Stuporous, moderate or severe hemiparesis</td>
</tr>
<tr>
<td>5</td>
<td>Deep coma, decerebrate posturing</td>
</tr>
</tbody>
</table>

© American Heart Association, Inc

ANEURYSMAL SAH

Presentation

Grade 1-2, 41%
Grade 3, 17%
Grade 4, 27%
DOA, 15%

n = 78 out of 1.46 million for 1983
ref: Ljunggren et al 1984

ANEURYSMS

Small: less than 15 mm
Large: 15-25 mm
Giant: 25-50 mm
Supergiant: greater than 50 mm
INTRACRANIAL ANEURYSMS

• Prevalence at autopsy: 2-5%
• 2-5 million Americans have unruptured cerebral aneurysm

NATURAL HISTORY

Ruptured aneurysm; morbidity and mortality results from:

• Initial hemorrhage
• Rehemorrhage
• Vasospasm
• Hydrocephalus

STUDIES

• CT
• CTA
• LP
• ANGIOGRAPHY
• OTHER- MRI
LUMBAR PUNCTURE

If intact -- safe if after CT

If deficit -- CT first

Centrifuge -- xanthochromia

PRESENT PROBLEMS IN MANAGEMENT OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

• Errors and delays in diagnosis
• Treatment of acute effects
• Prevention of recurrent hemorrhage
• Prevention or treatment of vasospasm or cerebral ischemia

DELAYS IN DIAGNOSIS OF SUBARACHNOID HEMORRHAGE

• Occurs in 20% or 25% of patients
• Most likely to occur among the alert patients who have only a headache
• These patients usually do not have disturbed consciousness or focal neurologic signs
• These cases may represent a "warning leak"
• 1% of ER visits are for headache and 1% of these will be an aneurysmal SAH
MISDIAGNOSIS OF SUBARACHNOID HEMORRHAGE

- Migraine
- Viral illness/flu
- Sinusitis
- Trauma
- Alcohol intoxication
- Hypertensive crisis

- Viral meningitis
- Tension headache
- Cervical disk
- TIA/ischemic stroke
- Drug intoxication

DELAYS IN DIAGNOSIS OF SUBARACHNOID HEMORRHAGE

<table>
<thead>
<tr>
<th>Length of Delays</th>
<th>1-4 Days</th>
<th>&gt;5 Days</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n(%)</td>
<td></td>
</tr>
<tr>
<td>Fail to see physician</td>
<td>3</td>
<td>1</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Delays in transfer</td>
<td>8</td>
<td>5</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Diagnostic error</td>
<td>26</td>
<td>20</td>
<td>46 (73)</td>
</tr>
</tbody>
</table>

Factors indicating a high risk of aneurysmal subarachnoid hemorrhage

**Epidemiologic factors**
- Cigarette smoking
- Hypertension
- Alcohol consumption
- Personal or family history of subarachnoid hemorrhage
- Polycystic kidney disease
- Heritable connective tissue diseases
  - Ehlers-Danlos syndrome (type IV)
  - Pseudoxanthoma elasticum
  - Fibromuscular dysplasia
- Other
  - Sickle cell anemia
  - Alpha1-antitrypsin deficiency
Factors indicating high risk of aneurysmal subarachnoid hemorrhage

Physical findings
• Retinal or subhyaloid hemorrhage
• Nuchal rigidity
• Any unequivocal neurologic finding (local or generalized)

TIMING

ANEURYSMAL SUBARACHNOID HEMORRHAGE

• Rebleed rate (Kassell et al, 1984)
  -4% in the first 24 hours
  1.5%/day from day 2-14
  By 2 weeks: 26.5% rehemorrhage

If untreated:
• 1/3 of patients who recover, die as a result of rehemorrhage by 6 months
• After 6 months, 3%/year chance of another major hemorrhage
PRINCIPLES OF SURGICAL MANAGEMENT
66 Y.O. with 3 intracranial aneurysms
CTA reconstruction

Left MCA and Acomm aneurysms
ENDOVASCULAR TREATMENT OF ANEURYSMS
Endovascular Coiling

Stent-Assisted Coiling

www.bostonscientific.com
Aneurysm-stent and coiled

International Subarachnoid Hemorrhage Trial (ISAT)
Lancet 366; 809-817, 2005

Looking back…

ISAT
Lancet:360, 1267-1274, 2002

- Neurosurgical clipping versus endovascular coiling in 2143 patients
- Prospective, randomized trial
- Treating centers treated 60-200 cases of patients with SAH annually
- Centers entered between 1%-44% of patients available for the study
ISAT – Lancet 2002
Summary of significant results

• 190/801 (23.7%) patients treated with coiling were dead or dependent at 1 year compared to 243/793 (30.6%) of patients treated with clipping (p=0.0019)
• This yielded an absolute risk reduction of 6.9% (95% C.I., 2.5-11.3) and relative risk reduction of 22.6% (95% C.I., 8.9-34.2)

ISAT- Rankin outcome- 1 year

• No statistical difference between individual Rankin groups 3,4,5,6
• Only pooled results of Rankin 3-6 reached an absolute difference of 6% comparing endovascular treatment compared to surgical treatment

ISAT-1 year follow up
**ISAT- Rehemorrhage data**
- Endovascular - 26/801 bled after Rx-1 Yr (3.2%)
- Surgical- 10/793 bled after Rx-1 Yr. (1.26%)

**BIOLOGIC OBSERVATION** - Coils prevent majority of acute rehemorrhages from aneurysms

**STATISTICAL OVERSTATEMENT** - Surgery reduces rebleeding by over 50% compared to endovascular coiling (should, therefore all lesions be clipped???)

---

**International Subarachnoid Hemorrhage Trial (ISAT)**
*Lancet 366; 809-817, 2005*

---

**ISAT – Lancet 2005**
**Summary of significant results**
- 250/1063 (23.5%) patients treated with coiling were dead or dependent at 1 year compared to 326/1055 (30.9%) of patients treated with clipping (p=0.0001)
- This yielded an absolute risk reduction of 7.4% (95% C.I., 3.6-11.2) and relative risk reduction of 23.9% (95% C.I., 12.4-33.9)
Could late rebleeding overturn the superiority of cranial aneurysm coil embolization over clip ligation seen in the International Subarachnoid Aneurysm Trial


- Compares life years gained when clipping rather than coiling after SAH
- Used estimates of excess rebleed rate for coiling over clipping to trace life year curves
  - e.g. 0% curve = coiling has same annual rebleed rate as clipping (0.063%/year)
  - 0.0152% curve = assumes coiling rebleed rate of 0.0782%, as observed in ISAT

SUBARACHNOID HEMORRHAGE

- Endovascular and surgical treatment considered for every patient
- Recent data (ISAT) has changed the management of ruptured aneurysms
Hydrocephalus from SAH

Occurs in one of 3 major patterns

Acute
- With obtundation or decerebration
- Usually seen with large intraventricular hemorrhage (Acomm and basilar tip)
- Treat with emergency ventriculostomy

Subacute
- Usually communicating type within a few days of hemorrhage
- Treat with ventriculostomy or shunt

Delayed
- Weeks to months after hemorrhage
- Responds well to VP shunt

The Unruptured Cerebral Aneurysm

• Diagnosed with increased frequency due to
  – Availability of less invasive intracranial scanning (MR/CT)
  – Improved sensitivity of scanning
Once an aneurysm is detected or 'read' on a scan – the immediate question for the physician and the patient is what to do?

Once an aneurysm is detected:

• Prove that it is really an aneurysm
• Decide what constitutes an aneurysm
  – "outpouching"
  – "fullness"

Decision Making in Unruptured Aneurysm Treatment?

• Rupture Risk
• Treatment risk
• ISUIA Data
THE PSYCHOLOGY OF UNRUPTURED ANEURYSMS

Natural History

- International Study of Unruptured Intracranial Aneurysms (ISUIA)
  - The Lancet 2003;362:103-10

ISUIA 2003 Retrospective Component

<table>
<thead>
<tr>
<th></th>
<th>GROUP 1 (n = 1077)</th>
<th>GROUP 2 (n = 615)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No history of SAH</td>
<td>History of SAH</td>
</tr>
<tr>
<td></td>
<td>from another aneurysm</td>
<td>from a different aneurysm repaired successfully</td>
</tr>
</tbody>
</table>

5-year Cumulative Rupture Rate

<table>
<thead>
<tr>
<th>Size</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mm</td>
<td>0</td>
<td>1.5%</td>
</tr>
<tr>
<td>7-12 mm</td>
<td>1.5%</td>
<td>2.6%</td>
</tr>
<tr>
<td>13-24 mm</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>≥25 mm</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
</tbody>
</table>

- Predictors of rupture:
  - Size: 7-12 mm, RR 3.3;
  - Location (Tip of basilir, RR 2.3; P-comm, RR 2.1)
Risk of Rupture of Unruptured Intracranial Aneurysms in Relation to Patient and Aneurysm Characteristics: an Updated Meta-Analysis

<table>
<thead>
<tr>
<th>Site</th>
<th>No. Studies</th>
<th>Mean Follow-up</th>
<th>Patient Years</th>
<th>No. of SAH</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>14</td>
<td>5.1 yrs</td>
<td>1083</td>
<td>19</td>
<td>1.4 (0.8-2.3)</td>
</tr>
<tr>
<td>ACA and Pcom</td>
<td>14</td>
<td>5.1 yrs</td>
<td>3558</td>
<td>46</td>
<td>Ref. subgroup</td>
</tr>
<tr>
<td>Pcom</td>
<td>5</td>
<td>5.3 yrs</td>
<td>317</td>
<td>7</td>
<td>1.7 (0.8-3.8)</td>
</tr>
<tr>
<td>MCA</td>
<td>14</td>
<td>5.1 yrs</td>
<td>2734</td>
<td>33</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>Post. Circulation (VA, BA, PCA)</td>
<td>11</td>
<td>4.9 yrs</td>
<td>791</td>
<td>26</td>
<td>2.5 (1.6-4.1)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>10</td>
<td>3.9 yrs</td>
<td>1939</td>
<td>10</td>
<td>Ref. subgroup</td>
</tr>
<tr>
<td>S-10</td>
<td>9</td>
<td>6.1 yrs</td>
<td>1187</td>
<td>14</td>
<td>2.3 (1.0-5.2)</td>
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<tr>
<td>5-10</td>
<td>9</td>
<td>6.3 yrs</td>
<td>3670</td>
<td>55</td>
<td>2.9 (1.6-5.5)</td>
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<tr>
<td>Giant (&gt;15)</td>
<td>8</td>
<td>5.0 yrs</td>
<td>293</td>
<td>18</td>
<td>11.9 (5.5-25.8)</td>
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<tr>
<td>% Incidental</td>
<td>12</td>
<td>5.5 yrs</td>
<td>3315</td>
<td>50</td>
<td>Ref. subgroup</td>
</tr>
<tr>
<td>% Symptomatic</td>
<td>8</td>
<td>5.9 yrs</td>
<td>472</td>
<td>31</td>
<td>4.4 (2.8-6.8)</td>
</tr>
</tbody>
</table>

Natural history/size of aneurysm: Issues to consider

• Every ruptured aneurysm was, at one point, an unruptured aneurysm
• In patients with SAH, 70-80% of aneurysms are smaller than 10 mm (many 4-8 mm)
• In patients with a rupture from a known aneurysm
  – appearance of lesion remains the same radiographically
  – high mortality/morbidity

Treatment Risks: Surgical and Endovascular

• Lesion specific factors
  – Size, location, calcification, thrombus, etc
• Patient specific factors
  – Age, medical condition, anxiety
WHAT IS TRUE SURGICAL RISK OF TREATMENT FOR AN UNRUPTURED INTRACRANIAL ANEURYSM?

MGH Brain AVM/Aneurysm Center
Patients
• 604 Aneurysms
• 481 Patients
• No. of Aneurysms:
  – 5: one patient
  – 4: 8 patients
  – 3: 17 patients
  – 2: 61 patients
  – 1: 394 patients

Distribution of Aneurysm Locations
• Carotid artery N=259, 43%
• MCA N=174, 28%
• Vertbasilar N=67, 11%
• Anterior Cerebral Artery N=99, 17%
Methods:

• Stepwise Logistic Regression Modeling Outcome with Covariates of Age, Size of Aneurysm, and Location Grouped as Anterior or Posterior

• Posterior location defined as any aneurysm of the vertebral or basilar segment

Final Model

<table>
<thead>
<tr>
<th>Factor O.R.</th>
<th>95% C.I.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post.</td>
<td>2.9</td>
<td>1.2-6.9</td>
</tr>
<tr>
<td>Size</td>
<td>1.13</td>
<td>1.1-1.7</td>
</tr>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.0-1.1</td>
</tr>
</tbody>
</table>

Analysis

Based on the final model, predicted probability curves for outcome were generated.
40 y.o., anterior communicating aneurysm, 5 mm in size

What are the risks of surgery?

1.8 % risk (95% C.I. 0.8 %-3%) risk of not living independently after surgery

Risk of Poor Outcome for 5 mm Unruptured Aneurysm-Anterior Circulation
55 y.o. with 10 mm anterior communicating - increase risk to 4%

15 mm and greater -- upper 10% of aneurysms in size
30 y.o. (3.8% treatment risk) vs. 60 y.o. (8% treatment risk)

50 y.o., basilar apex aneurysm, 5 mm in size
5% risk (95% C.I. 2.5-12%) risk of not living independently after surgery

• 60 y.o., basilar apex aneurysm, 10 mm in size

• 12% risk of not living independently after surgery
2. Materials/engineering
   - Embolization glue agents
   - Clot retrieval
   - Coils
     - Complex shape
     - Coated coils

Advances in neurovascular disease over the past 20 years: MATERIALS/ENGINEERING

2. Materials/engineering
   - Stents
     - Pipeline stent (mesh)
Advances in neurovascular disease over the past 20 years: MATERIALS/ENGINEERING

2. Materials/engineering
   – Endovascular clip device

Flow diversion for aneurysmal treatment/thrombosis

Flow Alteration by Porous Stents

Both stents
   • Deflect and dampen impinging flow
   • Decrease inflow rate
   • Increase flow stasis
   • Flow characteristics are different for each stent design
Patient-Specific Stent Design

Design Criteria
- Block the strong impinging flow at proximal neck
- Allow the flow to peripheral vessels

Effect of a Patient-Specific Stent

• Aneurysmal flow velocity was reduced by 93%
• Stasis was increased about 480%
• Direct flow impingement was blocked
• Possibly promote aneurysm thrombosis

Pipeline endovascular device (not called a 'stent')
Pipeline endovascular device

Pipeline endovascular device

2 Pipeline endovascular devices deployed
Third pipeline device deployed

Fourth pipeline device deployed

Four pipeline endovascular devices
Clinical Summary

- 50 Y/O F
- Incidental aneurysm discovered after MVA
- Large Rt Ophthalmic aneurysm [13mm]
- Vision intact
- No neurological deficit

PRE-TREATMENT – AP/Lateral

PRE-TREATMENT - 3D Reconstruction
Devices

• 6 Fr sheath
• 6 Fr Envoy
• 4000 U hep -> ACT 299
• Marksman microcatheter
• Goldtipped microwire
• PED 3.75 x 16, 4.0 x 16, 4.25 x 16
• 6 Fr angio-seal

Magnified views after 1st PED

3.75 x 16 PED

Magnified views after 2nd PED

4.0 x 16 PED
Case #2
Left ophthalmic segment aneurysm [19 mm]

MR # 1000089718
Clinical Presentation

- 65 yo opera singer
- Allergic to iodine dye
- Polycystic kidney disease
- HTN
- Underwent screening
- Incidental aneurysm
- Presents now with residual

Left ophthalmic segment aneurysm
Partial coiling [19 mm]

3D - reconstruction
PRE-TREATMENT – AP/Lateral

*Note significant tortuosity*

Devices

- 6 Fr sheath
- 6 Fr Envoy
- 4000 U hep -> aCT 246 + 500 U hep
- Marksman microcatheter
- Goldtipped microwire
- V18 Budy wire
- PED 3.75 x 16, 4.0 x 18, 4.0 x 12
- 6 Fr angio-seal

POST-TREATMENT – AP
Case #3
Right ophthalmic segment aneurysm [11mm]
MR 1002726229
**Clinical Presentation**

- 61 yo woman with H/A
- No significant medical history
- No neurological deficit
- Full visual fields
- Incidental R ophthalmic aneurysm

**Screening MRA**

![Screening MRA Image]

**PRE-TREATMENT – AP/Lateral DSA**

![PRE-TREATMENT – AP/Lateral DSA Image]
Devices

- 6 Fr sheath
- 6 Fr Envoy
- 4500 hep -> ACT 343
- Marksman microcatheter
- Goldtippped microwire
- PED 3.75 x 14 (x 3)
- 6 Fr angio-seal

POST-TREATMENT – Lateral

POST-TREATMENT – Lateral
Decision Making in Unruptured Aneurysm Treatment

- Surgery and Endovascular options considered for every patient
- Risks and efficacy of different treatments are weighed against the natural history of rupture

Conclusions

- For patients with unruptured aneurysms, both patient specific factors (age, medical co-morbidities) and aneurysm specific factors (size, location, shape) need to be carefully considered
- Endovascular and surgical options should be considered for each patient facing treatment – (age, efficacy, risk)
Other factors to consider for unruptured aneurysm patients

• If an aneurysm is not treated—should it be “followed” with annual or every 5 year radiographic studies?
• What activity level is appropriate for the patient with the small, untreated unruptured aneurysm?

FAMILY SCREENING: ANEURYSMS

• 20-25% of aneurysm patients have a blood relative with an aneurysm
• Recommendation:
  – If there are 2 or more blood relatives with aneurysm, screen family (MRA or CTA)
  – Start screening at age 20 and every 10 yrs

Thank You
Intracerebral Hemorrhage: Medical Treatment and Surgical Indications

Jonathan Rosand MD MSc
Chief, Division of Neurocritical Care and Emergency Neurology, MGH
Director, MGH Neuroscience Intensive Care Unit
Investigator, MGH Center for Human Genetic Research

Disclosures

- National Institutes of Health
  - Research support
- American Heart Association
  - Research support
- Wellcome Trust
  - Research support
- Deane Institute for Integrative Research in Atrial Fibrillation and Stroke
  - Research support

What is ICH?
Acute Manifestation of a Chronic Disease

- Hypertensive vasculopathy
- Cerebral amyloid angiopathy
- Vascular Malformations
- Saccular Aneurysms
**Location:** A clue to the underlying vasculopathy

**White matter disease:** Non-acute manifestation

**ICH:** The most deadly form of stroke
Bleeding and outcome

Continued bleeding and hematoma expansion

Hematoma expansion

- Observed in ~40% of individuals in whom the baseline CT scan is obtained within 3 hours of symptom-onset.
- The longer the delay between symptom-onset and baseline CT scan, the lower the likelihood of observing expansion.
- Sole known predictor of expansion risk: anticoagulation

Davis et al. Neurology. 2006;66:1175-1181
Hematoma expansion: 
Not just an early phenomenon

Pathophysiology of Acute ICH

- Vascular susceptibility due to chronic disease (e.g., hypertension, cerebral amyloid angiopathy)
- Second hit—unknown
- Small artery ruptures, blood extravasates into brain to form hematoma
- Expansion may occur from
  - Continued bleeding from originally injured vessel or vessels
  - Secondary bleeding into ischemic/injured tissue around the original hematoma

Hemostatic Therapy for ICH

- Arrest ongoing bleeding and ICH expansion
- Give as counterpart to rt-PA for stroke
- Recombinant activated factor VII
  - Approved to treat bleeding in hemophiliacs with inhibitors to factors VIII or IX
  - Enhances thrombin generation after vascular damage
  - Reported to reduce bleeding in noncoagulopathic patients
Hemostatic therapy: Whom to target?

The estimated number of patients who will suffer clinically significant hematoma expansion and are thus most likely to benefit from hemostatic therapy (per 1,000 ICH patients):

<table>
<thead>
<tr>
<th>Time of Presentation</th>
<th>Total</th>
<th>Significant Expansion</th>
<th>Included in clinical trials of rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 hours onset</td>
<td>~200</td>
<td>~80</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;3 hours onset</td>
<td>~800</td>
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Flaherty et al. Stroke. 2005;36:2660-2664

rFVIIa for Acute ICH

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<td>&lt;3 hours onset</td>
<td>560 mins</td>
<td>24 hours</td>
<td>90 days</td>
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Mayer et al. NEJM 2008;358:2127-2137

Phase 3 trial: Efficacy in 800 subjects

<table>
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<th>Placebo</th>
<th>20 µg/kg</th>
<th>80 µg/kg</th>
<th>P Value</th>
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<td>Hematoma Growth at 24 Hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change, %</td>
<td>26</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Absolute increase, mL</td>
<td>7.8 ± 18.7</td>
<td>4.7 ± 14.8</td>
<td>3.8 ± 15.3</td>
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<td>Clinical Outcome at 90 Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Rankin Score ≥5, %</td>
<td>24</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>19</td>
<td>18</td>
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Flaherty et al. Stroke. 2005;36:2660-2664

Contrast extravasation on CT Angiography

Multivariable analysis (113 patients) for mortality:
OR 5.24 (1.60–17.1) p=0.006

Is this the next step?

The estimated number of patients who will suffer clinically significant hematoma expansion and are thus most likely to benefit from hemostatic therapy (per 1,000 ICH patients):

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Flaherty et al. Stroke. 2005;36:2660-2664

Spot Sign for Predicting and Treating ICH Growth (STOP-IT)

ICH within 6 hours CT/CTA

+ Spot sign
- Spot sign

rFVIIa (80 mcg/kg) placebo

U. Cincinnati SPOTRIAS Center

ED Management:
Preventing Hematoma Expansion

- Warfarin reversal
  - FFP/prothrombin concentrates/rFVIIa
  - Vitamin K
- Blood pressure control
  - Current guidelines: systolic BP <180
- Clinical Trials
  - Hemostatic therapy
  - Aggressive blood pressure control
Reversing Warfarin Effect:
Time Counts!

- 69 consecutive patients with warfarin-related ICH
- All patients had repeated INR measures and were treated aggressively for ICH in the MGH ED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (N=12)</th>
<th>Yes (N=57)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Door to CT (min)</td>
<td>65 (30-90)</td>
<td>40 (25-85)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>(Median)</td>
<td>(25-75%)</td>
<td></td>
</tr>
<tr>
<td>CT to FFP (min)</td>
<td>210 (150-375)</td>
<td>90 (60-200)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(1-5)</td>
<td>(2-6)</td>
<td></td>
</tr>
<tr>
<td>FFP dose (units)</td>
<td>2</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>CT to Vitamin K (min)</td>
<td>245 (37-361)</td>
<td>87 (25-210)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>(1-5)</td>
<td>(2-6)</td>
<td></td>
</tr>
</tbody>
</table>

ED Management:
Should All Patients Be Reversed?

Because of the high mortality of OAT-ICH and high risk of hematoma expansion, ALL OAT-ICH patients should receive rapid and complete reversal of anticoagulant effect in the Emergency Department.

www.acutestroke.com
Reversing Warfarin Effect in the Emergency Department

Current MGH Guidelines for ICH patients
- Vitamin K 10 mg IV over 10 minutes STAT
- FFP 10 ml/kg over 90 minutes (Prothrombin Concentrate may be substituted for FFP.)
- Team must designate a single physician to take personal responsibility for ensuring that these therapies are administered as fast as possible.
- As soon as FFP ordered, “runner” dispatched to blood bank to collect FFP.

ED Management: The Blood Pressure Question
- Blood Pressure is often elevated in acute ICH.
- Blood pressure is easily manipulated.
  - Does BP reduction reduce risk of expansion?
  - Does BP reduction reduce CBF?

CBF Reduction in ICH

Rosand et al. Cerebrovasc Dis 2002;14:214-20
**INTERACT Trial**

- **N = 404 patients randomized**
- **Baseline CT scan**
- **Percent Change in ICH volume at 24 hours**

**Efficacy**
- Mortality
- mRS
- Barthel Index
- NIHSS

**Safety**
- Adverse events until discharge
- Serious adverse events until day 90

---

**INTERACT**

Preliminary efficacy in 404 subjects

<table>
<thead>
<tr>
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<th>Standard (N=172)</th>
<th>Intensive (N=174)</th>
<th>P Value</th>
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<td></td>
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<tr>
<td>Mean change, %</td>
<td>36 (16-57)</td>
<td>14 (6-22)</td>
<td>.04</td>
</tr>
<tr>
<td>Mean absolute increase, mL (95%CI)</td>
<td>2.7 (1.4-4.0)</td>
<td>0.9 (-0.9-2.7)</td>
<td>.06</td>
</tr>
<tr>
<td>Clinical Outcome at 90 Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median mRS</td>
<td>2(1-4)</td>
<td>2(1-4)</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>13</td>
<td>10</td>
<td>NS</td>
</tr>
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**ED Therapy of ICH:**

Current State of the Art at MGH

- **Medical**
  - **Page stroke beeper**
  - **BP management according to guidelines.**
    - SBP<180 or MAP<110
  - Critical care management (ABC), euglycemia, euvoolemia, euthermia, eunatremia
  - Critical trials
- **Surgery can be life-saving and deficit-sparing in cerebellar ICH**

[www.acutestroke.com](http://www.acutestroke.com)
Intraparenchymal Hemorrhage
(Non-Hypertensive IPH)

David Jho, MD PhD
Massachusetts General Hospital
May 2010

Overview
• Intraparenchymal Hemorrhage (IPH)
  – NOT focusing on SAH or extra-axial hemorrhage (SDH, EDH)
• Etiology
  – Location / Configuration & Age / PMH / Meds
• Work-Up
  – CTA, MRI, angiography, surgical exploration
• CASES (booby traps for medical or surgical mgmt)
Initial Steps

- Reverse any significant Coagulopathy
  - Plavix, Coumadin, Heparin, ASA/NSAIDs
    - Platelet dysfunction without thrombocytopenia
      (uremia - renal failure, EtOH liver dz)
- Control BP
- What is suspected Etiology?
  - Location / Configuration & Age / PtH / Meds
- Two Acute Questions
  - Do I need to evacuate the hematoma tonight?
    - Etiology, Size / Location, Clinical Picture
  - Do I need to place an EVD tonight? (which side or bilateral)
    - IVH with communicating or non-communicating hydrocephalus

Location / Etiology

- Putamen
- Thalamus
- Cerebellum
- Pons
- Lobar

CT

1. Hypertensive
2. Coagulopathy
3. Mass Lesion
   a. Cavernous Hemangioma
   b. Hemorrhagic Tumor
4. Vascular Lesion
   a. AVM / AVF
   b. Aneurysms
5. Hemorrhagic Infarction
6. Thrombosis (Dural Sinus or Cortical)
7. Cerebral Amyloid Angiopathy
8. Vasculopathy (Vasculitis, RCVS)
9. Idiopathic
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<td>Pons</td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td></td>
</tr>
<tr>
<td>Angio, Surgery, MRI</td>
<td>Low threshold for supplemental angiography (and/or MRI)</td>
</tr>
</tbody>
</table>

Low threshold for supplemental angiography (and/or MRI)
**Lobar IPH**

- Ruptured AVM
- Cavernous Malformation
- Hemorrhagic Tumor
- Coagulopathy
- Amyloid Angiopathy
- Vasculitis
- Idiopathic

**Etiology**

1. Coagulopathy
   a. Extrinsic cause (meds, trauma)
   b. Intrinsic cause (platelets, liver dysfxn, bleeding dis)
2. Mass Lesion
   a. Cavernous Hemangioma
   b. Hemorrhagic Tumor
3. Vascular Lesion
   a. Arteriovenous Malformation or Fistula
   b. Aneurysms (SAH-IPH, inf frontal - ACOM, ant temporal - MCA)
4. Hemorrhagic Infarction
   (MCA, cerebellar)
5. Venous Thrombosis
   (Dural Sinus or Cortical) – parasagittal/temporal
6. Cerebral Amyloid Angiopathy
   (CAA, age>60)
7. Vasculopathy
   (Vasculitis, RCVS)
8. Idiopathic

---

1. Coagulopathy
Coagulopathy

- Coagulopathy (+/- trauma) is most commonly associated with SDH (rather than ICH)

- Coagulation Factors (meds or production problem)
  - Anticoagulation
  - Liver disease
  - Chronic malnutrition

- Platelets (problems with production, function, and/or destruction)
  - Thrombocytopenia (chemo, myelodysplasia, ITP, HIT)
  - Dysfunctional platelets (uremia – renal failure, anti-platelet agents)

Coagulopathy Case #1

41M alcoholic (AST 75 : ALT 21) fell out of car window with INR 1.8 and Plt 126

Coagulopathy Case #2

46F on chemotx for NSCLC (Plt 74) with HA, n/v, & LUE/LLE weakness on anticoagulation with Lovenox for PE → Rt parietal craniotomy
Coagulopathy Case #2
46F on chemotx for NSCLC (P/I 74) with HA, n/v, & LUE/LLE weakness on anticoagulation with Lovenox for PE → Rt parietal craniotomy

No tumor in path specimen → 10mo had peritoneal carcinomatosis (hospice)

2. Mass Lesions
[Tumors & Cavernous Malformations]

Hemorrhagic Tumors
- <15% brain tumors bleed overall (metastatic > primary)
  - necrosis, neovascularization, vascular invasion, plasminogen activators
- Lung, breast, choriocarcinoma, melanoma, RCC, thyroid
- high-grade glioma, oligodendroglioma, hemangioblastoma
- rarely lymphoma or sarcoma
- IVH rather than IPH (choroid plexus papilloma, central neurocytoma)
Hemorrhagic Tumor Case #1
66M with back melanoma excised 2yrs prior having HA & n/v (Labs n/r)
T1+ T1+ Susc FLAIR
Resection

Liver & chest/abdominal wall metastases 1mo later

Hemorrhagic Tumor Case #2
56RHM with Lt face melanoma excised ~5yrs prior found on screening MRI for clinical trial to have ~2cm hemorrhagic cystic met → Lt parietal craniotomy
T1+ T1+ Susc FLAIR
Resection

Cav-Mal Case #1
40RHM (no meds & labs n/r) having occipital HA, n/v, & listing to the RI x2wks
MRI
Cav-Mal Case #2
39M roofer developed acute-onset HA & n/v with slurred speech, RUE/RLE weakness, & partial Lt CN3 palsy having ~2cm IPH from Lt thalamus to Lt midbrain

CT
CTA

EVD

MRI
T1+ Susc FLAIR

MRI
Susc Angio

VPS
3. Vascular Lesions

[AVM / AVF > aneurysms]

Aneurysm Case #1
48F with PMH of untreated HTN having sudden-onset severe HA w/ SBP 220s (exam E4VTM6) having Lt gyrus rectus IPIH & extensive SAH w/ 5mm ACOM aneurysm pointed left

Aneurysm Case #2
44F Spanish-speaking only w/ h/o migraines came to OSH ED 3x within past 4d having acute exacerbation of HA but o/w neuro intact, transferred to MGH ED as Lt anterior temporal IPIH
Pial AVM vs Dural AVF

- **Pial AVM**
  - Arterial feeder or intranidal aneurysms
  - Small size
  - Deep venous drainage
  - Normal perfusion pressure breakthrough
  - Spetzler-Martin grade (I - V)
  - IPH Locations: nearly anywhere

- **Dural AVF**
  - Retrograde cortical venous drainage
  - Cognard or Borden classifications
  - IPH Locations: temporal > frontal > cerebellar

---

**AVM / AVF Case #1**

68M with DM / HTN / HL presented with sudden-onset HA, scanning speech, & ataxia having OSH head CT showing large bilateral IPH in cerebellar hemispheres measuring 5.5 x 3.5 x 3.3 cm
AVM / AVF Case #1
Clinically stable so obtained CTA which showed numerous dilated cerebellar veins suspicious for AVM

AVM / AVF Case #1
Angiography showed 1cm cerebellar pial AVM at the superior cerebellar surface with arterial feeders from the left SCA & bilateral PCAs from codominant vertebral arteries (with venous drainage into the left transverse sinus & possibly vein of Galen)

AVM / AVF Case #1
AVM / AVF Case #2

52yo Portugese lady with sudden onset WHOL & transient mild RUE/RLE weakness while cooking having focal 3x2cm IPH in the left inferior-medial frontal lobe with diffuse SAH in the interhemispheric & suprasellar cisterns plus bilateral Sylvian fissures.

CTA showed frontal (anterior cranial fossa) DAVF supplied by bilateral anterior ethmoidal arteries & drainage via large tortuous frontopolar & subfrontal veins into SSS with multiple venous aneurysmal dilatations ranging 3-10mm in size.

Preop angio confirmed frontal (anterior cranial fossa) DAVF with bilateral ethmoidal artery feeders & frontopolar venous drainage with multiple venous aneurysmal dilatations (L fetal PCA noted).
AVM / AVF Case #2
Postop Angio confirmed obliteration of frontal DAVF

AVM / AVF Case #3
60RHM with acute-onset severe HA & receptive aphasia (word salad) having Cognard Type IV left transverse-sigmoid sinus DAVF fed by Lt MMA, Lt occipital artery & Lt post auricular artery with retrograde cortical venous drainage with varices & aneurysmal dilatations

4. Hemorrhagic Infarction
Hemorrhagic Infarction Case #1

86M with Afib on Coumadin held without bridge for ESI tx of lumbar stenosis (INR 1.0) then restarted having Lt MCA superior division hemorrhagic stroke with exam E1VTM4 & FUNC score 3

Venous Thrombosis Case #1

42RHF with his migraines having moderate HA after sneezing with "popping" sound in her left ear having exam E4V3M5 & dense Rt hemiparesis and Lt temporal hemorrhagic infarct with Lt transverse sinus thrombosis

5. Venous Thrombosis

[Dural Sinus or Cortical]
Venous Thrombosis Case #2

24F known anti-thrombin III deficiency (previously failed on Coumadin & Lovenox – then placed on fondaparinux but stopped dx job loss dx) with sudden onset HA having exam E4V4M6 (AOx2) with posterior superior sagittal sinus thrombosis extending to RI transverse sinus underwent transvenous IR tx with Penumbra & Angiojet.

6. Cerebral Amyloid Angiopathy

CAA

- Proteinaceous material deposited in BV walls → weaken BV
- Brain tissue histopath
- Recurrent IPH
- Association with apolipoprotein (Apo) E2 & E4 alleles
Cases

59F with large Rt frontal IPH (amyloid - CAA)

7. Vasculopathy

[Vasculitis, RCVS]

VASCULOPATHY

• HA & change in mental status (inflammatory or infectious)
• String of beads, weakened muscularis layer with BV dilatation
• Fibrotic or inflammatory thickening with BV narrowing
• Toxins (amphetamines / methamphetamines d/t sympathomimetic effects)
• Inflammatory or collagen vascular dz
• Infectious
• Primary angitis of CNS
• Post-partum vasculopathy (really like PRES & can have lobar hemorrhages like PRES)
• Strokes or IPH
8. Idiopathic

END