AntiThrombotic Therapy after Hemorrhagic Stroke

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ASSISTANT Professor of Neurology, Director, Johns Hopkins Bayview Medical Center Stroke Program, Associate Program Director, Johns Hopkins Neurology Residency; Baltimore, MD

Objectives:
• Identify the most feared complication of re-initiating anticoagulation after hemorrhagic stroke
• Define the most common etiologies of hemorrhagic stroke and how they influence risk of recurrence
• Discuss the other major risk factors thought to lead to increased risk of intracranial hemorrhage
• Describe how the same factors may lead to increased risk of hemorrhagic transformation of ischemic stroke
Antithrombotic Therapy after Hemorrhagic Stroke

Elisabeth B. Marsh MD
Assistant Professor of Neurology
Disclosures

Medical Director, Johns Hopkins Bayview Medical Center Stroke Program

Associate Program Director, Neurology Residency, Johns Hopkins School of Medicine

Site Neurologist
- Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI)
- Stenting for treatment of intracranial aneurysms

SURPASS
FRED
Objectives

• Scope of the problem
• Existing data for anticoagulating after primary intracranial hemorrhage (ICH)
• Clinical application
  – Determining risk versus benefit
    • Etiology of the ICH
    • Indication for anticoagulation
    • Agent
    • Other risk factors for anticoagulation
• What we’ve learned from hemorrhagic transformation
  – HeRS score- a tool for risk stratification
Scope of the Problem

• ICH is relatively uncommon in the United States
  – Overall incidence within the general population: 25/100,000 person years
• Increases significantly with warfarin
  – 2-3/100 person years
• Affects both young and old
• Carries significant morbidity and mortality
  – Deadliest form of stroke
  – Twice as high on coumadin (76% reported in one study)
• Increasing indications for anticoagulation
  – Systemic thrombosis
    • PE, DVT
  – Stroke Prevention
    • Atrial fibrillation, heart failure, mechanical valves
• New agents make it more ‘user friendly’
Prior data

• Small case series
• 2007- American Stroke Council
  – Meta-analysis: restart 7-14 days after ICH
• Mayo Clinic Proceeding
  – Expert panel: consider re-initiating 3-10 days following ICH in high risk individuals
• Large, multicenter, retrospective cohort analysis of 2,869 patients presenting with ICH
• analyzed the hazard of both recurrent ICH and ischemic stroke in relation to the timing of warfarin initiation
• **Population:**
  – 234 warfarin associated- 132 survived the first week
  – 45 restarted on warfarin (mean duration 5.6 weeks after ICH and followed for median of 17 months)
• **Results:**
  – Recurrent ICH (HR 5.6; 95% CI 1.8–17.2)
  – Ischemic stroke (HR 0.11; 95% CI 0.014–0.890)
• **Conclusion:**
  – Optimal time to restart anticoagulation 10-30 weeks post hemorrhage
Majeed, et al.

• Why so different?

• *Bias toward lower risk indications*
  • Fewer prosthetic heart valves (n=28) versus atrial fibrillation (n=101)
    – Which patients were restarted
      • CHADS-2 scores
        – Higher scores (≥2) restarted more frequently
    – When they were restarted
      • Patients with mechanical valves more likely to be:
        – Restarted (79% v 22%)
        – Restarted earlier (med 3.1-4.6wk v 9.2wk)
### Newer data
Claasen et al, 2008

#### Table 3. Follow-up Data in 48 Patients With Warfarin\(^a\)-Associated ICH

<table>
<thead>
<tr>
<th></th>
<th>Restarted Group</th>
<th>Nonrestarted Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up, mo</td>
<td>49.8</td>
<td>36.1</td>
</tr>
<tr>
<td>Mean mRS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At discharge</td>
<td>3.1</td>
<td>2.6</td>
</tr>
<tr>
<td>At latest follow-up</td>
<td>4.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Mean time to death, mo</td>
<td>55.6</td>
<td>21.8</td>
</tr>
</tbody>
</table>

End point events, No. of patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Restarted Group</th>
<th>Nonrestarted Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic stroke</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Thromboembolism, nonstroke</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nonembolic ischemic stroke</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nontraumatic ICH</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Traumatic ICH</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
- 2015 Danish registry (1997-2013)
- Patients with afib and index ICH
- On anticoagulation on presentation
- HR for ischemia (AC v no tx) = 0.55
- Didn’t report timing of initiation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk of stroke</th>
<th>Recurrent ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>27.3/100 pt yr</td>
<td>5.3</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>25.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>13.6</td>
<td>8</td>
</tr>
</tbody>
</table>
**Should anticoagulation be resumed after intracerebral hemorrhage?**

**JOSHUA N. GOLDSTEIN**, MD, PhD, Assistant Professor and **STEVEN M. GREENBERG**, MD, PhD, Director

<table>
<thead>
<tr>
<th>AUTHORS AND TREATMENT</th>
<th>NO. OF PATIENTS</th>
<th>THROMBOEMBOLIC EVENTS</th>
<th>RECURRENT ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vleeschouwer et al(^74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin restarted</td>
<td>25</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Warfarin not restarted</td>
<td>81</td>
<td>8 (10%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Claassen et al(^73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin restarted</td>
<td>25</td>
<td>6 (24%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Warfarin not restarted</td>
<td>27</td>
<td>13 (48%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Butler et al(^75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin restarted</td>
<td>13(^a)</td>
<td>3 (23%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Bertram et al(^76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin restarted</td>
<td>15(^b)</td>
<td>5 (33%)</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>

\(^a\)All with prosthetic valves
\(^b\)All at high risk
Bottom line

- Weigh need for anticoagulation v. risk
  - Etiology of the ICH
  - Indication for anticoagulation
  - Agent
  - Other risk factors for anticoagulation
Clinical application

- Comes down to 2 questions:
  1. Should anticoagulation be restarted at all?
  2. How long do we wait?
1. Etiology of ICH

• Informs WHETHER to restart at all

• Precipitated?
  – INR
  – Blood pressure control
  – Trauma

• Underlying vasculopathy
Underlying vasculopathy

- Recurrent risk reported as 1% at 3 months
- Long term risk: 2-4% per year
  - Function of the underlying vasculopathy
    - HTN versus cerebral amyloid angiopathy (CAA)
  - Presence and number of microbleeds on GRE imaging
2. Indication for Anticoagulation

- Informs both WHETHER and WHEN to restart

- Clear indications for acute therapy
  - DVT and PE
    - Risk of recurrence 4% per year
  - Mechanical valves
    - Risk of stroke 4% per year
    - MV 5 fold risk of valve thrombosis and 1.5 fold risk of systemic embolus compared to AV
# Atrial Fibrillation- CHADS2 Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S&lt;sub&gt;2&lt;/sub&gt; Prior Stroke or TIA or Thromboembolism</td>
<td>2</td>
</tr>
</tbody>
</table>

**Cumulative risk over time**

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>Stroke Risk %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>1.2–3.0</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>2.0–3.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>3.1–5.1</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>4.6–7.3</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>6.3–11.1</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>8.2–17.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
<td>10.5–27.4</td>
</tr>
</tbody>
</table>

Circulation 2004; 110 (16): 2287–2292

A-fib group: 604 patients
No a-fib: 309 patients

51% vs 36% (p <0.001) had severe stroke for a-fib vs NSR
Primary Prevention

- **AFASAK**: Warfarin (INR 2.8-4.2) vs 75 mg/d aspirin
  - RRR 54% vs placebo or aspirin, ARR 2.6% per year
- **SPAF-1**: Warfarin (INR 1.4-2.8) vs 325 mg/d aspirin
  - RRR 58% by warfarin, ARR 4.7% per year; RRR 32% by aspirin
- **BAATAF**: Warfarin (INR 1.2-1.5) vs “could choose aspirin”
  - RRR 86%, ARR 2.4% per year
- **CAFA**: Warfarin (INR 2-3) vs placebo
  - RRR 37%, ARR 1.2% per year
- **SPINAF**: Warfarin (INR 1.4-2.8) vs placebo
  - RRR 79%, ARR 3.3% per year
- **Combined primary prevention**: RRR 64%, ARR 2.7%
Secondary Prevention

- **EAFT**: warfarin (INR 2.5-4) vs 300 mg/d ASA vs placebo
  - RRR 66% vs placebo, ARR 8.4% per yr; RRR 40% vs aspirin
- **SPAF II**: Warfarin vs 325 mg/d ASA
  - RRR 27%, ARR 0.6% per yr
  - BUT- no difference/ high stroke rates in pts >75 yo
- **SPAF III**: 2 components:
  - Low-risk: all got ASA, 2.2% stroke rate per year
  - High-risk: warfarin (INR 2-3) vs fixed dose warfarin (1.2-1.5) plus aspirin: stopped early b/c big difference favoring adjusted-dose warfarin: 8% per yr vs 2% per year; ARR 6% per year
- **BAFTA**: warfarin (INR 2-3) vs 75 mg/d ASA in pts <75 yo
  - RRR 52%, ARR 2%/yr. Hemorrhage rates similar
- **Combined secondary prevention ARR 8.4% per year**
Heart Failure- indication less clear


*Risk 1-3% per year
3. Choice of Anticoagulant

- **Heparin**
  - Able to turn off and to reverse
  - Good choice in high risk patients who need to be anticoagulated acutely

- **Coumadin**
  - Able to let the INR drift up
  - Know how it’s going to interact
  - Need for frequent monitoring

- **NOACs**
  - Less interactions
  - Therapeutic immediately
  - Easier to monitor
  - Don’t know about all the side effects yet
  - “no antidote”
## Risk of Intracranial Hemorrhage

### Atrial Fibrillation Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug 1</th>
<th>Drug 2</th>
<th>RR/HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin 0.3%</td>
<td>NOAC</td>
<td>0.40</td>
<td>0.27-0.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Warfarin 0.8%</td>
<td>Apixaban</td>
<td>0.42</td>
<td>0.30-0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Warfarin 0.7%</td>
<td>Rivaroxaban</td>
<td>0.67</td>
<td>0.47-0.93</td>
<td>0.02</td>
</tr>
</tbody>
</table>
A word on antiplatelet agents

- Typically safe to consider much earlier (within 24-28 hours of ICH)
- Increased bleeding risk when added to anticoagulation
  - Except when continued stroke and mechanical valves
  - Occasionally for cardiac benefit
- A reasonable choice in the individual who is felt to be ‘too high risk for anticoagulation’
  - Atrial fibrillation
  - ???Amyloid angiopathy???
4. Other risk factors for ICH

<table>
<thead>
<tr>
<th>Score</th>
<th>N</th>
<th>Type of Bleeding</th>
<th>Time Period</th>
<th>Associated Factors</th>
<th>Hemorrhage Rate</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAS-BLED</td>
<td>3,978 patients with afib</td>
<td>intracranial or hospitalization or Hgb decrease &gt;2g/L and/or transfusion</td>
<td>1 year follow-up period</td>
<td>hypertension, abnormal liver/renal function, stroke, bleeding history, labile INR, &gt;65 years, drugs/alcohol</td>
<td>53 (1.5%)</td>
<td>C statistic = 0.720</td>
</tr>
<tr>
<td>HEMORR2HAGES¹</td>
<td>3,791 Medicare patients with afib</td>
<td>hospitalization for any hemorrhage defined by Medicare claims</td>
<td>up to 1,000 days post-discharge</td>
<td>prior bleed, hepatic or renal disease, ethanol, cancer, &gt;75 years, low platelets, hypertension, anemia, genetics, falls, stroke</td>
<td>162 (4.3%); 25 intracranial (0.7%)</td>
<td>C statistic = 0.670*</td>
</tr>
</tbody>
</table>

* anticoagulated group

- What other factors put my patient at risk?
- Data from patients with atrial fibrillation
- Even less data on intracranial bleeding
- No studies dedicated exclusively
Hemorrhagic transformation in patients with acute ischaemic stroke and an indication for anticoagulation

E. B. Marsh, R. H. Llinas, A. E. Hillis and R. F. Gottesman
Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Initial Patients
(143)

26%

Anticoagulated
(117)

23%

Not Anticoagulated
(26)

Bleeding
(30)

No Bleeding
(87)

Bleeding
(6)

No Bleeding
(20)

Hemorrhagic Conversion
(22)

ICH
(8)

4 symptomatic

5 symptomatic

Hemorrhagic Conversion
(6)

ICH
(0)
### Table 1  Patient characteristics: univariate analyses

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 123)</th>
<th>Hemorrhage (n = 30)</th>
<th>No hemorrhage (n = 93)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [years (SD)]</strong></td>
<td>63 (17)</td>
<td>67 (16)</td>
<td>62 (18)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Gender [N (% female)]</strong></td>
<td>66 (54%)</td>
<td>18 (60%)</td>
<td>48 (52%)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Race [N (% African-American)]</strong></td>
<td>54 (44%)</td>
<td>16 (53%)</td>
<td>38 (41%)</td>
<td>0.29</td>
</tr>
<tr>
<td><strong>Stroke type [N (% embolic)]</strong></td>
<td>65 (53%)</td>
<td>16 (53%)</td>
<td>49 (53%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Watershed N = 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-vessel stenosis N = 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacunar N = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic embolization N = 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissection N = 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis N = 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other N = 22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NIHSS [mean (SD)]</strong></td>
<td>9 (7)</td>
<td>11 (6)</td>
<td>8 (7)</td>
<td>0.033</td>
</tr>
<tr>
<td>Antipatelet agent on admission [N (%)]</td>
<td>43 (35%)</td>
<td>13 (45%)</td>
<td>30 (32%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Anticoagulation on admission [N (% coumadin)]</td>
<td>20 (16%)</td>
<td>6 (20%)</td>
<td>14 (15%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Low-density lipoprotein [mean mg/dl (SD)]</td>
<td>86 (30)</td>
<td>79 (42)</td>
<td>88 (38)</td>
<td>0.20</td>
</tr>
<tr>
<td>Renal failure [N (% eGFR &lt; 60 ml/min/1.73 m²)]</td>
<td>42 (34%)</td>
<td>15 (50%)</td>
<td>27 (29%)</td>
<td>0.046</td>
</tr>
<tr>
<td>eGFR [mean (SD)]</td>
<td>50.5 (16)</td>
<td>45.1 (19)</td>
<td>52.0 (15)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Diabetes [N (%)]</strong></td>
<td>37 (30%)</td>
<td>10 (33%)</td>
<td>27 (29%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Peak systolic blood pressure [mean mmHg (SD)]</td>
<td>176 (29)</td>
<td>179 (28)</td>
<td>175 (30)</td>
<td>0.74</td>
</tr>
<tr>
<td>Peak diastolic blood pressure [mean mmHg (SD)]</td>
<td>98 (16)</td>
<td>97 (13)</td>
<td>98 (17)</td>
<td>0.74</td>
</tr>
<tr>
<td>Days systolic blood pressure &gt; 180 mmHg [mean days (SD)]</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>2 (4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Indication for anticoagulation [N (% a fibr)]</td>
<td>46 (37%)</td>
<td>14 (47%)</td>
<td>32 (34%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Anticoagulated [N (%)]</td>
<td>99 (80%)</td>
<td>25 (83%)</td>
<td>74 (80%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Days from stroke to initiation of anticoagulation [mean days (SD)]</td>
<td>8 (12)</td>
<td>8 (7)</td>
<td>8 (13)</td>
<td>0.93</td>
</tr>
<tr>
<td>Peak INR [mean (SD)]</td>
<td>2.5 (2.0)</td>
<td>2.3 (1.8)</td>
<td>2.5 (2.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Peak aPTT [mean (SD)]</td>
<td>3.1 (2.4)</td>
<td>2.8 (1.8)</td>
<td>3.2 (2.6)</td>
<td>0.46</td>
</tr>
<tr>
<td>Days supratherapeutic [mean days (SD)]</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>2 (4)</td>
<td>0.53</td>
</tr>
<tr>
<td>GRE positive [N/80 (%)]</td>
<td>48 (61%)</td>
<td>10 (71%)</td>
<td>38 (58%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Other bleeding [N (%)]</td>
<td>9 (7%)</td>
<td>4 (13%)</td>
<td>5 (5%)</td>
<td>0.22</td>
</tr>
<tr>
<td>tPA [N (%)]</td>
<td>18 (15%)</td>
<td>8 (27%)</td>
<td>10 (11%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*P-values evaluate differences between hemorrhage and no hemorrhage patients. eGFR, estimated glomerular filtration rate; GRE, gradient echo; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time ratio; tPA, tissue plasminogen activator.
Risk of hemorrhage increases 14% for every 10cc increase in volume of infarct.
Renal Impairment is Associated with Higher ICH Risk

Even mild renal impairment significantly increases hemorrhage risk.

Multivariable model

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yr)</td>
<td>1.31</td>
<td>0.98-1.74</td>
</tr>
<tr>
<td>GFR Category</td>
<td>1.81</td>
<td>1.01-3.26</td>
</tr>
<tr>
<td>Infarct Volume (per 10 cc)</td>
<td>1.13</td>
<td>1.05-1.21</td>
</tr>
</tbody>
</table>
Hemorrhagic Risk Stratification score (HeRS)

- Score to determine risk of hemorrhagic transformation of ischemic stroke during hospitalization
- Patients with stroke plus indication for anticoagulation
- Uses stroke size, degree of renal failure, and age as continuous variables

This research was supported by:
NIH/NINDS Research Education Program for Residents and Fellows in Neurology and Neurosurgery (5 R25 NS065729-04) and by The Johns Hopkins Clinician Scientist Award, both held by Elisabeth Marsh, MD

Elisabeth B. Marsh, MD, Rafael H. Llinas, MD, Peter H. Dziedzic, MS, Rebecca F. Gottesman, MD PhD

Probability of hemorrhagic transformation:

- This includes Symptomatic and Asymptomatic hemorrhage during hospitalization
- **17.34%**

Details:
- GFR: Mild
- Age: 72
  - A: 4.5
  - B: 2.3
  - C: 11
- Thickness: 0.5
- Volume: 28.46 - Entered

Home  About App
HeRS score has been validated in a unique inpatient cohort
Renal Impairment: an Interesting Observation

Within our population

- IV tPA
  - 18 treated $\rightarrow$ 8 bled (44%)
  - 3 with Renal Failure $\rightarrow$ 2 bled (67%)
Retrospective analysis

224 patients presenting with symptoms concerning for an acute stroke who met NINDS criteria and were administered IV tPA

Variables of Interest:
- Age
- Race
- Sex
- NIHSS
- Comorbidities (HTN, HLD, afib, DM)
- Anterior/posterior circulation
- LDL
- Blood glucose
- Renal function
Results

- 57 (25%) patients had evidence of ICH on neuroimaging
- Majority asymptomatic
  - 43/57 (75%)
  - 6.3% sICH rate overall
- Renal impairment NOT associated with combined symptomatic and asymptomatic ICH (p=0.359); however, adjusted 5.5-fold increased odds of sICH when Cr >1.0 mg/dL (95% CI 1.08-28.39)
Patients with Cr >1.0mg/dL have a 10.6% risk of sICH after IV tPA versus a 1.8% risk in those with normal renal function.
Renal impairment also may influence severity of hemorrhage

- 17/21 (81%) parenchymal hemorrhages had renal impairment

- Patients with Cr >1.0 are 4.7 times more likely to have a severe bleed
Decreased GFR was associated with a 4 fold increase in the rate of hemorrhagic but not ischemic strokes.
Evidence for high risk of cerebral hemorrhage in chronic dialysis patients.

Third Department of Internal Medicine, School of Medicine, University of The Ryukyus, Okinawa, Japan.

1600 Japanese patients on HD, RR of ICH compared to ‘normals’ = 10.7

doi: 10.1093/ndt/gfp694
Advance Access publication 27 December 2009

Cerebral microbleeds in predialysis patients with chronic kidney disease

Hideaki Shima¹, Eiji Ishimura², Toshihide Naganuma³, Takeshi Yamazaki³, Ikue Kobayashi¹, Kaori Shidara¹, Katsuhito Mon¹, Yoshiaki Takemoto³, Tetsuo Shoji¹, Masaaki Inaba¹, Mikio Okamura⁴, Tatsuya Nakatani³ and Yoshiki Nishizawa¹

Group with microbleeds was more likely to have worse GFR (stage 5 CKD) than controls and the patients with renal failure who didn’t bleed.
Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis

Giovanni Di Minno, M.D., Jose Martinez, M.D., Mar-Lee McKean, Ph.D., Jose De La Rosa, M.D., James F. Burke, M.D., Scott Murphy, M.D.

Division of Nephrology, Cardesza Foundation for Hematologic Research, and the Department of Medicine, Jefferson Medical College of the Thomas Jefferson University, Philadelphia, Pennsylvania USA

- Decreased activity of vWF
- Increased levels of cyclic glutamine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) reduce the production of Thromboxane A2 and ADP
Blood-brain barrier breakdown in acute and chronic cerebrovascular disease.

Yang Y, Rosenberg GA.
Department of Neurology, University of New Mexico, Albuquerque, NM 87107, USA.
Renal Failure and other risk factors for Primary ICH?

- Rates of systemic hypertension exceed 90% in industrialized nations.

- **Hypothesis:** In patients with longstanding hypertension, the risk factors for presenting with a small vessel lacunar infarct are different than those for hypertensive ICH.
Factors predictive of small vessel lacune versus hypertensive ICH

- **Age ≥ 65 years**
  - (OR 1.76, CI 0.81-3.80)

- **Race: African American**
  - (OR 1.70, CI 0.78-3.72)

- **Gender: Female**
  - (OR 1.56, CI 0.72-3.33)

- **Serum Creatinine > 1.0**

- **Presence of Cerebral Microbleeds**
  - (OR 1.35, CI 0.49-3.75)

- **PWWM Grade ≥ 6**
  - trended toward predicting ICH
In patients who present with an acute ischemic stroke who also have an indication for anticoagulation:

- Age, stroke volume, and renal impairment are predictors of hemorrhagic conversion.

- Those patients placed on anticoagulation following stroke are no more likely to bleed, but may have more severe bleeding.

Hemorrhagic Transformation: Our Conclusions- Who Bleeds?
ICH after IV tPA: Our Conclusions- Who Bleeds?

In patients administered IV tPA for treatment of acute ischemic stroke:

- A serum Cr $>1.0$ mg/dL is associated with increased risk of symptomatic ICH, while a normal Cr is associated with relatively low risk.
In patients with longstanding systemic hypertension:

- Age, African American race, male gender, and microbleeds predict hypertensive ICH.

- The role of renal failure in hypertensive ICH is unclear.
Applying to primary ICH: the bottom line

- The patient is an individual
- Weigh need for anticoagulation v. risk
  - Etiology of the ICH
  - Indication for anticoagulation
  - Agent
  - Other risk factors for anticoagulation
Case 1

- 68 year old man with history of hypertension and a mechanical MVR who presented yesterday with a 30cc ICH and an INR of 5.

- Additional questions?
## Decision Tree

<table>
<thead>
<tr>
<th></th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology of ICH</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Indication for anticoagulation</td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Other risk factors</td>
<td>✔️</td>
<td></td>
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</tbody>
</table>

- **Agent:** heparin
- **Timing:** 4-5 days
Case 2

- 78 year old woman with atrial fibrillation, on coumadin, who presents with a 50cc ICH with ventricular component following a mechanical fall. Her INR is 2.5 with a normal blood pressure.
# Decision Tree

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<th>Pro</th>
<th>Con</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>✓</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Agent: Coumadin or NOAC  
Timing: >2 weeks
Case 3

- 88 year old man with an EF of 25% who presents with a left MCA syndrome.
## Decision Tree

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</tr>
</thead>
<tbody>
<tr>
<td>Etiology of ICH</td>
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<td></td>
</tr>
<tr>
<td>Indication for anticoagulation</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Agent: aspirin

Timing: N/A

HeRS score: 58.2%
Summary

• Weigh need for anticoagulation v. risk
  – Should anticoagulation be restarted?
  – When should it be restarted?
  • Etiology of the ICH
    – Precipitated and/or modifiable risk
  • Indication for anticoagulation
    – emergent or not
• Agent
• Other risk factors for anticoagulation
  – eg., numerous microbleeds, renal impairment
Thank you for your attention

ebmarsh@jhmi.edu

Questions?
Heparin

- Heparin: glycosaminoglycan
  - acts as endogenous inhibitor of factors IIa, IXa, and Xa
  - Metabolized in liver, poor GI absorption
  - Binds to platelets and plasma proteins

- LMW heparins: mostly inhibit Xa
  - less binding to plasma proteins and platelets, longer half-life, dose-independent clearance
  - Primarily excreted by kidneys

* Able to stop and reverse in the high risk patient who really needs it
Warfarin

• Interferes with conversion of Vitamin K
  – Needed to activate factors II, VII, IX and X, also needed for Protein C and S
  – Rapid GI absorption, half-life 36-42 hrs
  – Metabolized in liver, mostly excreted in urine

• PROs
  – Extensive data on behavior; can reverse, can monitor (INR)

• CONs
  – Interacts with many foods and medications, need for frequent monitoring
New Oral Agents
Apixaban  
Rivaroxaban

**Common Pathway**

**Mechanism of Action**

Apixaban  
Rivaroxaban

**Xa Blocker**

Prothrombin

**Dabigatran**

Fibrinogen  
Thrombin  
Fibrin

**Clot**
Direct Thrombin Inhibitors

Dabigatran: FDA approved fall 2010; prodrug

• **PROs:**
  - Directly acts on thrombin, including fibrin-bound thrombin
  - Doesn’t bind to plasma proteins, so more predictable than heparin
  - Shorter half-life (14-17 hours) relative to warfarin
  - No need for monitoring
  - Rapid onset of action (2 hours)

• **CONs:**
  - 80% renally excreted; not recommended if creatinine clearance < 30 ml/hr
  - No known antidote
  - First target: Ximelagatran: although promising in SPORTIF trials, did not get FDA approval due to hepatotoxicity
Factor Xa Inhibitors

Rivaroxaban: FDA approved July 2011
Apixaban: FDA approved December 2012
Edoxaban: noninferior to warfarin in DVT with less bleeding (NEJM, 2013)

• PROS:
  – Available orally
  – Not a prodrug
  – Predictable onset of effect and plasma concentration
  – Not affected by age, renal, or hepatic disease
  – Does not require monitoring
  – Shorter half-life (~5-15 hrs depending on drug/population)

• CONS:
  – Impaired elimination if given with strong CYP3A4 inhibitors (ketonazole)
  – No known antidote
  – Enhanced rebound hypercoaguability??