Future Cerebral Hemorrhage in anticoagulated patients with Cerebral Microbleeds

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Brain bleeding
**Brain Bleeds**

A patient-centered website on the types, causes, prevention and management of brain bleeds.

- Intracerebral Hemorrhage (ICH)
- Cerebral Amyloid Angiopathy
- Hypertensive ICH
- Microbleeds
- Superficial Siderosis
- Subdural Hemorrhage
- Subarachnoid Hemorrhage

**Intracerebral Hemorrhage (ICH)** is the medical term for bleeding in the brain tissue. This is by far the most common type of brain bleeding and it mostly occurs in older adults with small vessel diseases of the brain but ICH can be seen in all age groups.

**Microbleeds** and **superficial siderosis** are tiny brain bleeds whereas white matter disease originates from chronic low blood flow in deeper brain regions. These pathologies, all related to diseases of brain's small vessels, increase one's risk of brain bleeding.

**Subdural Hemorrhage** (SDH) is bleeding in outer layers around the brain that usually requires surgical intervention. SDH might be related to trauma but they can also occur spontaneously. The latter, called Chronic SDH, is mostly seen in older adults and it is an increasingly common problem.
Figure 2. Prevalence of Antithrombotic Therapies in Patients With Atrial Fibrillation (AF) Across the Spectrum of Stroke Risk by the CHADS\textsubscript{2} Score and the CHA\textsubscript{2}DS\textsubscript{2}-VASc Score

A) Prevalence of treatment strategies across the spectrum of CHADS\textsubscript{2} score

B) Prevalence of treatment strategies across the spectrum of CHA\textsubscript{2}DS\textsubscript{2}-VASc score

Cross-sectional registry study of outpatients with AF enrolled in the American College of Cardiology National Cardiovascular Data Registry's PINNACLE Registry between January 1, 2008, and December 30, 2012.

Hsu JAMA 2016
OACs and ICH

• In patients taking oral anticoagulants (OACs), the annual rate of intracranial hemorrhage is 0.3% to 0.6%.

• Of these bleeds, 46% to 86% are intracerebral; 13% to 45% are subdural, and 1% to 8% are subarachnoid.

• With 30- to 90-day mortality rates of 40% to 65%, intracerebral hemorrhage (ICH) has the worst prognosis.
Two types of ICH

cerebral small vessel disease (SVD)
cerebral amyloid angiopathy (CAA)
large artery occlusion (multiple or strategic)
hypoperfusion

secondary loss of white and grey matter (atrophy)
lobar hemorrhage
multiple infarcts
strategic infarcts
depth hemorrhage
microinfarcts
enlarged perivascular spaces
WML
lacune
microbleeds

CT scans showing different types of hemorrhage.
Hypertensive Deep IPH

- Hypertensive patient with non-traumatic hemorrhage in
  - deep hemispheric regions
    - Basal ganglia
    - Thalamus
  - brainstem
  in the absence of other pathology (vascular, neoplastic, ...)
- Annual recurrence risk about 2%
Cerebral amyloid angiopathy
# Cerebral Amyloid Angiopathy

## Definite CAA

Full postmortem examination demonstrating:
- Lobar, cortical, or corticosubcortical hemorrhage
- Severe CAA with vasculopathy
- Absence of other diagnostic lesion

## Probable CAA with supporting pathology

Clinical data and pathologic tissue demonstrating:
- Lobar, cortical, or corticosubcortical hemorrhage
- Some degree of CAA in specimen
- Absence of other diagnostic lesion

## Probable CAA

Clinical data and MRI or CT demonstrating:
- Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions
- Age more than 55 years
- Absence of other cause of hemorrhage

## Possible CAA

Clinical data and MRI or CT demonstrating:
- Single lobar, cortical, or corticosubcortical hemorrhage
- Age more than 55 years
- Absence of other cause of hemorrhage

CAA: Cerebral amyloid angiopathy

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**CAA is a major cause of anticoagulant-related intracerebral hemorrhages**
**TABLE 2. PREDICTORS OF RECURRENCE OF HEMORRHAGE.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NO. of PATIENTS</th>
<th>2-YEAR CUMULATIVE RECURRENCE</th>
<th>RISK RATIO (95% CONFIDENCE INTERVAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>36</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>≥75 yr</td>
<td>35</td>
<td>0.23</td>
<td>1.4 (0.6–3.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
<td>0.15</td>
<td>0.8 (0.3–2.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>33</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>0.21</td>
<td>0.9 (0.4–2.3)</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15</td>
<td>0.25</td>
<td>1.2 (0.4–3.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>0.33</td>
<td>0.7 (0.1–5.2)</td>
</tr>
<tr>
<td>Previous hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>0.61</td>
<td>6.4 (2.2–18.5)*</td>
</tr>
<tr>
<td>Apolipoprotein E genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>32</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>ε2+ ε3</td>
<td>20</td>
<td>0.41</td>
<td>4.7 (1.4–15.9)†</td>
</tr>
<tr>
<td>ε4+ ε3</td>
<td>26</td>
<td>0.27</td>
<td>3.7 (1.1–11.7)†</td>
</tr>
<tr>
<td>Total cohort</td>
<td>71</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 by the log-rank test.
†Eight patients with the ε2/ε4 genotype are included. Comparison is with the ε3/ε3 group.
‡P<0.02 by the log-rank test.
Risk of Future IPH in CAA with or without IPH at Presentation

70 yo p/w acute symptomatic ICH
72 yo p/w cognitive syx and microbleeds BUT NO symptomatic ICH
What is the CMBs?

- Visualized typically by GRE sequence
- **Small round signal loss lesion (< 5 mm)**
- Throughout the whole brain area
- Confused with calcification, small angioma or vessel signal
Related Factors to CMBs

- **Cerebral amyloid angiopathy (CAA)**
  - Greenberg et al., *Neurology* 1996
- **Old age**
  - Roob et al., *Neurology* 1999; Jeerakathil et al., *Stroke* 2004
- **Hypertension**
- **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)**
  - Oberstein et al., *Neurology* 2001; Dichgans et al., *Stroke* 2002
- **White matter hyperintensities**
- **Lacunes**
- **Low serum cholesterol**
  - Lee SH et al. *Stroke* 2002
Clinical Implication of CMBs

- **Risk for hemorrhagic stroke**
  - In patients with lobar hemorrhage
    - 94 patients
    - The 3-year follow-up

<table>
<thead>
<tr>
<th>Number of CMBs</th>
<th>1</th>
<th>2</th>
<th>3-5</th>
<th>≥6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative risk of ICH, %</td>
<td>14</td>
<td>17</td>
<td>38</td>
<td>51</td>
</tr>
</tbody>
</table>

- **In patients with ischemic stroke**
  - 908 patients
  - 26 months follow-up

<table>
<thead>
<tr>
<th>Number of CMBs</th>
<th>0</th>
<th>1</th>
<th>2-4</th>
<th>≥5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative risk of ICH, %</td>
<td>0.6</td>
<td>1.9</td>
<td>4.6</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Clinical Implication of CMBs: Summary

1. CMBs may predict occurrence of subsequent ICH.
   - Greenberg SM. *Stroke* 2004
   - Soo YO. *J Neurology* 2004

2. CMBs were locally related to the sites of ICHs.
   - Lee SH. *Neurology* 2004

3. CMBs may be associated with increased size of ICH.
   - Lee SH. *Neurology* 2006

4. Association with hemorrhagic transformation: Controversial
   - Chelsea S Kidwell. *Stroke* 2002
   - Lee SH, *JNNP* 2008

5. CMBs is related with Warfarin-associated with hemorrhage.
   - Lee SH. *Neurology* 2009

6. Relationship with cognitive dysfunction
   - David J. Werring. *Brain* 2004
Incidence of Symptomatic Hemorrhage in Patients With Lobar Microbleeds

Ellis S. van Etten, MD; Eitan Auriel, MD, MSc; Kellen E. Haley, BA; Alison M. Ayres, BA; Anastasia Vashkevich, BA; Kristin M. Schwab, BA; Jonathan Rosand, MD, MSc; Anand Viswanathan, MD, PhD; Steven M. Greenberg, MD, PhD; M. Edip Gurol, MD, MSc

Background and Purpose—Lobar microbleeds suggestive of cerebral amyloid angiopathy (CAA) are often identified on MRI in the absence of lobar intracerebral hemorrhage (ICH). We compared the baseline characteristics and risk of subsequent ICH among such patients to those presenting with CAA-related lobar ICH.

Methods—Clinical data (demographics, risk factors), apolipoprotein E genotype, neuroimaging markers of CAA severity (microbleed counts, leukoaraiosis volume), and clinical outcomes (incidence rates of ICH and death during a mean follow-up of 5.3±3.8 years) were compared between 63 patients enrolled because of incidentally found microbleeds and 316 with CAA-related ICH, in our prospectively enrolled cohort. Predictors of incident ICH were explored in the microbleed-only patients using multivariable Cox regression models.

Results—Microbleed-only patients shared similar demographic, apolipoprotein E, and vascular risk profiles with lobar ICH patients, but had more lobar microbleeds (median, 10 versus 2; P<0.001) and higher leukoaraiosis volumes (median, 31 versus 23 mL; P=0.02). Microbleed-only patients had a nontrivial incidence rate of ICH, not different from patients presenting with ICH (5 versus 8.9 per 100 person-years; adjusted hazard ratio, 0.58; 95% confidence interval, 0.31–1.06; P=0.08). Microbleed-only patients had a higher mortality rate (hazard ratio, 1.67; 95% confidence interval, 1.1–2.6) compared with ICH survivors. Warfarin use and increasing age were independent predictors of future ICH among microbleed-only patients after correction for other covariates.

Conclusions—Patients presenting with isolated lobar microbleeds on MRI have a genetic, neuroimaging, and hemorrhagic risk profile suggestive of severe CAA pathology. They have a substantial risk of incident ICH, potentially affecting decisions regarding anticoagulation in clinical situations. (Stroke. 2014;45:2280-2285.)

Key Words: cerebral amyloid angiopathy ■ cerebral hemorrhage ■ cerebral microbleeds ■ magnetic resonance imaging
<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Lobar Microbleed-Only (n=60)</th>
<th>Lobar ICH (n=240)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event: occurrence of lobar ICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed person-years</td>
<td>241</td>
<td>968</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>No. of occurrence (%)</td>
<td>12 (20)</td>
<td>86 (36)</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Incidence of ICH per 100 person-years (95% CI)</td>
<td>5 (2.6–8.7)</td>
<td>8.9 (7.1–11)</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>0.57 (0.3–1.04)</td>
<td>Ref</td>
<td>0.07</td>
</tr>
<tr>
<td>Adjusted hazard ratio* (95% CI)</td>
<td>0.58 (0.31–1.06)</td>
<td>Ref</td>
<td>0.08</td>
</tr>
<tr>
<td>Event: occurrence of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed person-years</td>
<td>261</td>
<td>1316</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>No. of occurrence (%)</td>
<td>31 (52)</td>
<td>105 (44)</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Incidence of death per 100 person-years (95% CI)</td>
<td>11.9 (8–16.8)</td>
<td>8 (6.5–9.7)</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>1.8 (1.2–2.8)</td>
<td>Ref</td>
<td>0.005</td>
</tr>
<tr>
<td>Adjusted hazard ratio* (95% CI)</td>
<td>1.67 (1.1–2.6)</td>
<td>Ref</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ICH, intracerebral hemorrhage; and ref, reference for hazard ratios.
*Adjusted for age, sex, hypertension, microbleed count, and white matter hyperintensity volume.
Cerebral microbleeds are a risk factor for warfarin-related intracerebral hemorrhage

### Table 2: Radiologic findings

<table>
<thead>
<tr>
<th>Variables</th>
<th>ICH cases (n = 24)</th>
<th>Controls (n = 48)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of microbleeds</td>
<td>19 (79.2%)</td>
<td>11 (22.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of microbleeds</td>
<td>9.0 ± 26.8</td>
<td>0.5 ± 1.03</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Location of microbleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar area</td>
<td>14 (58.3%; 73.7%†)</td>
<td>5 (10.4%; 45.5%†)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>10 (41.7%; 52.6%†)</td>
<td>2 (4.2%; 18.2%†)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Thalamus</td>
<td>7 (29.2%; 36.8%†)</td>
<td>6 (12.5%; 54.5%†)</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Brainstem</td>
<td>5 (20.8%; 26.3%†)</td>
<td>0 (0%; 0%†)</td>
<td>0.005§</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>7 (29.2%; 36.8%†)</td>
<td>2 (4.2%; 18.2%†)</td>
<td>0.008§</td>
</tr>
<tr>
<td>WMH</td>
<td>12 (50.0%)</td>
<td>12 (25.0%)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

### Table 3: Conditional logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT-INR</td>
<td>4.13</td>
<td>1.40-12.77</td>
<td>0.011</td>
</tr>
<tr>
<td>Presence of microbleeds</td>
<td>83.12</td>
<td>5.96-1,159.10</td>
<td>0.001</td>
</tr>
<tr>
<td>WMH</td>
<td>3.60</td>
<td>0.70-113.64</td>
<td>0.093</td>
</tr>
<tr>
<td>Variables</td>
<td>B</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------</td>
<td>------</td>
<td>--------------</td>
</tr>
<tr>
<td>PT-INR</td>
<td>1.42</td>
<td>4.13</td>
<td>1.58-10.81</td>
</tr>
<tr>
<td>Presence of microbleeds</td>
<td><strong>2.48</strong></td>
<td><strong>11.99</strong></td>
<td><strong>2.86-50.33</strong></td>
</tr>
<tr>
<td>White matter hyperintensity</td>
<td>1.28</td>
<td>3.60</td>
<td>0.83-15.48</td>
</tr>
</tbody>
</table>
Cortical superficial siderosis multifocality in cerebral amyloid angiopathy

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Marco Pasi, MD
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<table>
<thead>
<tr>
<th>cSS multifocality score</th>
<th>Recurrence rate (95% CI) (per 100 patient-years of follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.97 (3.38-7.30)</td>
</tr>
<tr>
<td>1</td>
<td>6.49 (3.09-13.61)</td>
</tr>
<tr>
<td>2</td>
<td>13.51 (7.03-25.96)</td>
</tr>
<tr>
<td>3</td>
<td>16.20 (7.72-33.96)</td>
</tr>
<tr>
<td>4</td>
<td>26.90 (14-51.71)</td>
</tr>
<tr>
<td>Total</td>
<td>7.49 (5.79-9.69)</td>
</tr>
</tbody>
</table>

Multifocality (presence and spread) was the significantly higher with cSS multifocality (P < 0.001). The median ICH risk (hazard ratio 3.19; 95% confidence interval 2.0-5.1) per 100 patient-years of follow-up.}

Flair fluid-attenuated inversion recovery; ICH intracerebral hemorrhage; MGH Massachusetts General Hospital; T2*GRE T2*weighted gradient-recalled echo; TFNE transient focal neurological episodes; WMH white matter hyperintensity.

Correspondence to Dr. Gurol: edip@mail.harvard.edu
Patients with Mixed location ICH/Microbleeds

Out of 391 consecutive primary ICH patients enrolled in a prospective registry, 75 (19%) had Mixed-ICH

Table 3. Incidences rates and hazard ratios for the occurrence of ICH and Death in Mixed ICH CAA, and HTN ICH patients

<table>
<thead>
<tr>
<th>Event rate</th>
<th>Number of patients who survived the first 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mixed ICH (N=59)</td>
</tr>
<tr>
<td>Occurrence of lobar ICH</td>
<td></td>
</tr>
<tr>
<td>Observed person-years</td>
<td>195</td>
</tr>
<tr>
<td>Occurrence, n (%)</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>Incidence of ICH per 100 person-years</td>
<td>5.1 (2.5-9.4)</td>
</tr>
<tr>
<td>Crude hazard ratio (95% CI)</td>
<td>Ref</td>
</tr>
<tr>
<td>Adjusted hazard ratio (95% CI)</td>
<td>Ref</td>
</tr>
</tbody>
</table>
Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA
A meta-analysis

5,068 patients from 15 studies
overall pooled prevalence of CMBs in IS/TIA = 25.3%

Duncan Wilson, MD
Andreas Charidimou, PhD
Gareth Ambler, PhD

ABSTRACT

Objective: To determine associations between cerebral microbleed (CMB) burden with recurrent ischemic stroke (IS) and intracerebral hemorrhage (ICH) risk after IS or TIA.

Table 1: Pooled relative risk for recurrent ischemic stroke and intracerebral hemorrhage for different cerebral microbleed (CMB) burden and distribution (all risk ratios are compared to the reference category of no CMBs)

<table>
<thead>
<tr>
<th>CMB distribution, n</th>
<th>Ischemic stroke</th>
<th>Intracerebral hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled absolute event rates, n/N (%)</td>
<td>Pooled absolute risk increase, %</td>
</tr>
<tr>
<td>CMB presence</td>
<td>115/1,284 (9%)</td>
<td>3.4</td>
</tr>
<tr>
<td>1 CMB</td>
<td>31/433 (7.2%)</td>
<td>1.8</td>
</tr>
<tr>
<td>2-4 CMBs</td>
<td>44/433 (10.2%)</td>
<td>4.8</td>
</tr>
<tr>
<td>≥5 CMBs</td>
<td>34/342 (10.5%)</td>
<td>5.1</td>
</tr>
<tr>
<td>Strictly lobar</td>
<td>31/332 (9.3%)</td>
<td>3.9</td>
</tr>
<tr>
<td>Strictly deep</td>
<td>29/437 (6.6%)</td>
<td>1.2</td>
</tr>
<tr>
<td>Mixed</td>
<td>44/411 (10.7%)</td>
<td>5.3</td>
</tr>
</tbody>
</table>

FRCR
David J. Werring, PhD

*Neurology* 2016;87:1501-1510
Probable CAA presenting with ICH
~10% annual ICH recurrence risk

Increased risk when Superficial Siderosis (+)

Deep Hypertensive ICH
~2% annual ICH recurrence risk

Lobar MB only CAA
Annual ICH risk ~5%

Annual ICH risk in patients with bleeding-prone cerebral pathologies
Might be related to trauma OR chronic/spontaneous

The annual estimated incidence of chronic SDH may reach up to 58.1 per 100,000 persons for patients 65 years of age or older.

Estimated chronic SDH patients in 2016 in the US: ~ 38,000

~ 21% of chronic SDH occur on Warfarin, 42.5x ↑ risk then people not on Warfarin

2 years recurrence risk of chronic SDH ~11%
Life-long anticoagulation increases the risk of ICH even in AFib populations without past ICH history. The outcomes of OAC-related ICH (~50% mortality) are worse than non-OAC ICH (~25% mortality). Current guidelines recommend against life-long warfarin use in patients with NVAF and history of CAA-related lobar ICH.

Direct Oral Anticoagulants (DOAC)

Advantages:
1) non-inferiority for overall stroke prevention (superiority for Dabigatran and Apixaban)
2) decreased risk of ICH
3) ease of use, once or twice daily intake without the need for blood draws
4) lower risk of drug and food interactions

Concerns in a high ICH Risk population
- All phase 3 DOAC studies excluded patients who had prior ICH, so we do not know how safe these meds are in post-ICH patients
- Mortality of DOAC-ICH 35-48% and similar to Warfarin-ICH in all phase 3 DOAC studies

Other concerns
- Medication compliance
- Safety in older adults with reduced renal function
- Efficacy of reversal strategies
- Cost
VKAs vs DOACs

- The annual rate of ICH ranges from 0.3% to 0.6% in patients taking VKAs 0.1% to 0.2% in those taking DOACs
- DOACs are associated with an overall 50% reduction in the rate of ICH
Hematoma expansion

• In patients not on OAC, hematoma expansion occurs in 30% to 40% of patients within 3 to 6 hours after symptom onset

• Anticoagulation leads to more hematoma growth and higher mortality

• Rates of hematoma expansion are higher in patients taking VKAs
  • Prospective: 54%, Retrospective: 36%

• DOACs: maybe 38% (in small prospective study)
  ➔ Should be reversed promptly and aggressively
Outcome of intracerebral hemorrhage associated with different oral anticoagulants

ABSTRACT

Objective: In an international collaborative multicenter pooled analysis, we compared mortality, functional outcome, intracerebral hemorrhage (ICH) volume, and hematoma expansion (HE) between non-vitamin K antagonist oral anticoagulant-related ICH (NOAC-ICH) and vitamin K antagonist-associated ICH (VKA-ICH).

Methods: We compared all-cause mortality within 90 days for NOAC-ICH and VKA-ICH using a Cox proportional hazards model adjusted for age; sex; baseline Glasgow Coma Scale score, ICH location, and log volume; intraventricular hemorrhage volume; and intracranial surgery. We addressed heterogeneity using a shared frailty term. Good functional outcome was defined as discharge modified Rankin Scale score ≤2 and investigated in multivariable logistic regression. ICH volume was measured by ABC/2 or a semiautomated planimetric method. HE was defined as an ICH volume increase ≥33% or ≥6 mL from baseline within 72 hours.

Results: We included 500 patients (97 NOAC-ICH and 403 VKA-ICH). Median baseline ICH volume was 1.44 mL (interquartile range [IQR] 0.62–3.84) for NOAC-ICH vs 1.05 mL (IQR 0.40–2.27) for VKA-ICH (p = 0.78). We did not find any difference between NOAC-ICH and VKA-ICH for all-cause mortality within 90 days (33% for NOAC-ICH vs 33% for VKA-ICH [p = 0.64], adjusted Cox hazard ratio for NOAC-ICH vs VKA-ICH 0.93 [95% confidence interval CI 0.52–1.64] and for NOAC-ICH vs VKA-ICH [p = 0.90], the rate of HE NOAC-ICH n = 294 (40%) vs VKA-ICH n = 992 (40%) p = 0.84), or functional outcome at hospital discharge (NOAC-ICH vs VKA-ICH odds ratio 0.47, 95% CI 0.18–1.19 [p = 0.11]).

Conclusion: In our international collaborative multicenter pooled analysis, baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome were similar following NOAC-ICH and VKA-ICH. Neurology 2017;88:1-8

GLOSSARY

AF = atrial fibrillation, CI = confidence interval, GCS = Glasgow Coma Scale, HE = hematoma expansion, HR = hazard ratio, ICH = intracerebral hemorrhage, INR = international normalized ratio, IQR = interquartile range, IVH = intraventricular hemorrhage, mRS = modified Rankin Scale, NOAC = non-vitamin K antagonist oral anticoagulant, OAG = oral anticoagulant, PCC = prothrombin complex concentrates, VKA = vitamin K antagonist.

Randomized trials in patients with atrial fibrillation (AF) show that direct (non-vitamin K antagonist [VKA]) oral anticoagulants (NOACs) have about half the incidence of intracerebral hemorrhage (ICH) compared to VKA but with a similar efficacy in preventing ischemic stroke. Nevertheless, there is concern that without specific reversal agents at
Enrolled centers

- Apixaban (n=13), Dabigatran (n=13), Rivaroxaban (n=69)
Figure 1  Flowchart of study design and patient selection

Patients with OAC-ICH identified from 13 centers (N=540)

- NOAC-ICH (n=100)
  - Excluded (n=3): Unknown baseline GCS (3)
  - Included in study (n=97)

- VKA-ICH (n=440)
  - Excluded (n=37):
    - Unknown baseline GCS (15)
    - Unknown baseline INR (12)
    - Baseline INR <1.3 (10)
  - Included in study (n=403)
Figure 2: Survival curve comparing non-vitamin K oral antagonist anticoagulant (NOAC)-associated intracerebral hemorrhage (ICH) and vitamin K antagonist anticoagulant (VKA)-associated ICH 90-day mortality.

Table 3: Cox proportional hazards models: univariable and multivariable analyses for the primary outcome of 90-day mortality.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Units</th>
<th>Univariable model</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.08 (0.77-1.51)</td>
<td>0.65</td>
<td>0.92 (0.69-1.23)</td>
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<tr>
<td>Age</td>
<td></td>
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<tr>
<td>Per year</td>
<td>1.04 (1.02-1.06)</td>
<td>0.001</td>
<td>1.04 (1.01-1.08)</td>
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<tr>
<td>GCS</td>
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<tr>
<td>Par point</td>
<td>0.81 (0.78-0.85)</td>
<td>0.001</td>
<td>0.85 (0.80-0.90)</td>
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<tr>
<td>ICH volume</td>
<td></td>
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<tr>
<td>Per (log mL)</td>
<td>1.58 (1.36-1.82)</td>
<td>0.001</td>
<td>1.38 (1.17-1.64)</td>
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<tr>
<td>IVH volume</td>
<td></td>
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<tr>
<td>Per (log mL)</td>
<td>1.525 (1.37-1.70)</td>
<td>0.001</td>
<td>1.18 (0.98-1.44)</td>
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<td>ICH location</td>
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<td></td>
<td></td>
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<tr>
<td>Lobar area</td>
<td>1.00 (reference)</td>
<td></td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Superficial deep areas</td>
<td>0.64 (0.67-1.22)</td>
<td>0.74</td>
<td>1.26 (0.83-1.96)</td>
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<tr>
<td>Cerebellum</td>
<td>0.73 (0.36-1.45)</td>
<td>0.39</td>
<td>1.31 (0.59-2.93)</td>
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<tr>
<td>Brainstem</td>
<td>0.94 (0.42-2.14)</td>
<td>0.69</td>
<td>3.36 (1.30-8.70)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>vs no neurosurgery</td>
<td>0.84 (0.41-1.71)</td>
<td>0.63</td>
<td>0.45 (0.20-1.00)</td>
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<tr>
<td>Anticoagulant type</td>
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<tr>
<td>VKA</td>
<td>1.00 (reference)</td>
<td></td>
<td>1 (reference)</td>
</tr>
<tr>
<td>NOAC</td>
<td>1.10 (0.73-1.67)</td>
<td>0.65</td>
<td>0.63 (0.52-1.64)</td>
</tr>
</tbody>
</table>

Adjusted for age; sex; baseline Glasgow Coma Scale score; ICH location; and log volume; intraventricular hemorrhage volume; and intracranial surgery.

Abbreviations: CI = confidence interval; GCS = Glasgow Coma Scale; HR = hazard ratio; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.
Case

- M/78
- Known atrial fibrillation (on warfarin 4mg / poor TTR)
- Known CKD stage 3 and hypertension
- Left side weakness (1 DA)
- Initial NIHSS: 2
Progress

- EKG: persistent atrial fibrillation
- Initial PT INR: 1.04
- BP: 140/80
- BUN: 36.1 mg/dL, creatinine: 2.00 mg/dL
- eGFR: 35 ml/min/1.73m²
- CCR: 32ml/min (75 kg)

- Start Eliquis 2.5 mg bid
OPD f/u for 5 months

• 3-mo mRS: 3
• Clinic SBP: 120 - 140
5 months after ischemic stroke
Progress after intracerebral hemorrhage (ICH)

- No additional weakness after ICH
- F/U brain CT after 5 month from ICH

*Next plan?*
Summary

• Considering lobar microbleeds
• Burden of microbleeds (numbers)
• Other related factors
  • Other lobar hemorrhage, ApoE2 /E4, cortical superficial siderosis
• 2 – 5 – 10 rule
• Many question do not have evidence-based answers so an honest and comprehensive discussion with patient/family is very important
  • Shared-decision making approaches needed in very encounter that involves A-fib pts with high embolic & hemorrhagic risk
Prevention of cardiovascular events in Asian patients with ischaemic stroke at high risk of cerebral haemorrhage (PICASSO): a multicentre, randomised controlled trial

Ruon-Joon Eun, Eun-Jae Lee, Sun-Kwon Jeong, Jin-Ho Park, Young-Jin Lee, Eun-Soo Hong, Eunsook Park, Sung-Boo Yu, Yong-Jae Rho, Ji-Seung Lee, Jun-Young Lee, Dong-Jin Lee, Jong-Suk Oh, Song-Bok Oh, Song-Hoon Ahn, Won-Kwon Lee, Jong-Min Park, Jin-Ho Eun, Sung-Hyuk Seo, Jin-Man Jung, Jeou-Cheol Nam, Dong-Woo Kang, on behalf of the PICASSO investigators

Summary
Background The optimal treatment for patients with ischaemic stroke with a high risk of cerebral haemorrhage is unclear. We assessed the efficacy and safety of cilostazol versus aspirin, with and without placebo, in these patients.

Methods In this randomised, controlled, 2 × 2 factorial trial, we enrolled patients with ischaemic stroke with a history of or imaging findings of intracerebral haemorrhage or two or more microbleeds from 65 centres in three Asian countries. Patients were randomly assigned (1:1:1) to receive oral cilostazol (100 mg twice a day), aspirin (600 mg once a day), cilostazol plus placebo (100 mg twice a day), or aspirin plus placebo with centralised blocks assigned by centre. Cilostazol versus aspirin was investigated double-blinded; placebo treatment was open-label, but the outcome assessor was masked to assignment. The co-primary outcomes were incidence of the composite of stroke, myocardial infarction, or vascular death (efficacy) and incidence of haemorrhagic stroke (safety), which were assessed in intention-to-treat and modified intention-to-treat populations. Efficacy was analysed with a non-inferiority test and a superiority test if non-inferiority was satisfied. Safety was assessed with a superiority test only. This trial is registered with ClinicalTrials.gov, NCT01531532.

Findings Between Aug 1, 2009, and Aug 31, 2013, we randomly assigned 1534 patients to one of the four study groups, of whom 1512 were assessed for the co-primary endpoints. During a median follow-up of 1·9 years (IQR 1·4–3·0), the incidence of composite vascular events was 4·27 per 100 person-years in patients who received cilostazol and 5·33 per 100 person-years in patients who received aspirin (HR 0·80, 95% CI 0·75–0·96; non-inferiority p<0·0017; superiority p=0·10). Incidence of cerebral haemorrhage was 0·61 per 100 person-years in patients who received cilostazol and 1·20 per 100 person-years in those who received aspirin (HR 0·51, 95% CI 0·36–0·68; superiority p=0·002). The incidence of haemorrhagic stroke was 2·24 per 100 person-years in the cilostazol group compared with 4·95 per 100 person-years in the placebo group (HR 0·46, 95% CI 0·32–0·69; superiority p=0·031). The incidence of cardiovascular events was 6·72 per 100 person-years in the placebo group and 6·11 per 100 person-years in the non-placebo group (HRs 1·05, 95% CI 0·98–1·13; p=0·12). Adverse events were similar across the four study groups; the most common events were dizziness, headache, diarrhoea, and constipation.

Interpretation In patients with ischaemic stroke at high risk of cerebral haemorrhage, cilostazol was non-inferior to aspirin for the prevention of cardiovascular events, but did not reduce the risk of haemorrhagic stroke. Addition of placebo to aspirin or cilostazol could be beneficial for reducing the incidence of cardiovascular events.

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