Intracerebral haemorrhage in the young and very old

David Seiffge, Inselspital University Hospital Bern
## Disclosures

<table>
<thead>
<tr>
<th>Employer</th>
<th>Inselspital, University Hospital Bern (Switzerland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memberships</td>
<td>ESO, SNG, SSS, SGKN</td>
</tr>
<tr>
<td>Research funds</td>
<td>Swiss National Science Foundation, Swiss Heart Foundation, Bangerter-Rhyner Foundation, Swiss Society of Neurology, Bayer Foundation, Portola/Alexion</td>
</tr>
<tr>
<td>Honoraria (all paid to employer)</td>
<td>Bayer, Alexion/Portola</td>
</tr>
</tbody>
</table>
What is young, what is old?

- Pediatric patients (<18 years)
- Young adults (18-45 years)
- The very old (>85 years)
Data from the Swiss Stroke Registry: The ICH cohort

Study period: 2014-2019

Study population: 2650 patients

23 Swiss Stroke Units and Stroke Centers
Clinical Case

94 year old female patient
Marcoumar therapy atrial fibrillation (INR 1.9)
Left side hemiparesis (NIHSS 3 points)
max-ICH score: 5 points (estimated mortality 50%)

CT on admission

CT at 24 hours

Stroke Unit care
PCC + Vitamin K
Blood pressure control (IA-measurement, <140mmHg)

What is the outcome at 3 months?
Clinical case – 3 months later

- Acute treatment: 3 days Stroke Unit, 14 days geriatric rehabilitation
- Patient back «at home» (retirement home)
- 3 months clinical visit: What are your remaining deficits from the bleeding?

« C’est seulement vraiment beau et fluide lors de la deuxième tentative si je joue la sonate en D-majeur de Haydn*.»

*Patiente était pianiste professionnelle

« Vous devez savoir que la sonate en C-majeur fait partie de ses sonates tardives. Ce sont celles qui sont particulièrement difficiles**.»

** Commentaire du fils, aussi pianiste
Insel Gruppe –

Incidence, frequency and etiology
### Incidence of intracerebral haemorrhage by age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients with intracerebral haemorrhage (n)</th>
<th>Person-years</th>
<th>Incidence per 100 000 person-years (95% CI)</th>
<th>Number of time periods</th>
<th>Incidence ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤44 years</td>
<td>119</td>
<td>5 958 646</td>
<td>1.9 (1.6-2.2)</td>
<td>16</td>
<td>0.10 (0.06-0.14)</td>
</tr>
<tr>
<td>45–54 years</td>
<td>164</td>
<td>725 660</td>
<td>19.1 (13.4-27.4)</td>
<td>15</td>
<td>Reference</td>
</tr>
<tr>
<td>55–64 years</td>
<td>305</td>
<td>865 173</td>
<td>36.5 (28.4-46.7)</td>
<td>16</td>
<td>1.8 (1.3-2.6)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>597</td>
<td>812 077</td>
<td>77.1 (65.0-91.5)</td>
<td>18</td>
<td>3.8 (2.7-5.4)</td>
</tr>
<tr>
<td>75–84 years</td>
<td>665</td>
<td>531 845</td>
<td>136.9 (111.3-168.4)</td>
<td>18</td>
<td>6.8 (4.8-9.6)</td>
</tr>
<tr>
<td>≥85 years</td>
<td>274</td>
<td>170 580</td>
<td>196.0 (148.3-259.1)</td>
<td>17</td>
<td>9.6 (6.6-13.9)</td>
</tr>
</tbody>
</table>

*Because intracerebral haemorrhage is rare in people under age 45 years, the incidence ratios were calculated with the 45–54 years age group as the reference.*

**Table 2: Incidence of intracerebral haemorrhage according to age**
Etiology – what causes intracerebral haemorrhage?

- **Macrovascular causes**
  - Undetermined
  - Cerebral amyloid angiopathy
  - Deep perforator arteriolopathy
  - Other determined cause
  - Undetermined

Data from the Swiss Stroke Registry - unpublished
# Etiology of pediatric ICH

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVM</td>
<td>40%</td>
</tr>
<tr>
<td>Other vascular</td>
<td>7%</td>
</tr>
<tr>
<td>Infection</td>
<td>5%</td>
</tr>
<tr>
<td>Other systemic / local</td>
<td>4%</td>
</tr>
<tr>
<td>Other brain tumor</td>
<td>12%</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>14%</td>
</tr>
<tr>
<td>Hemato</td>
<td>3%</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>4%</td>
</tr>
<tr>
<td>Heart disease complication</td>
<td>0%</td>
</tr>
</tbody>
</table>

Weighted mean

- Porcar et al. (2018)
- Piastra et al. (2017)
- Giudici et al. (2017)
- Abbas et al. (2016)
- Deng et al. (2015)
- Liu et al. (2015)
- Lo et al. (2013)
- Beslow et al. (2014)
- Beslow et al. (2013)
- Christenson et al. (2010)
- Beslow et al. (2010)
- Jordan et al. (2009)
- Lo et al. (2008)
- de Ribaupierre et al. (2008)
- Strouse et al. (2000)
- Liu et al. (2006)
- Zahrane et al. (2005)
- Chung et al. (2004)
- Meyer-Heim et al. (2003)
- Blom et al. (2003)
- Larthier et al. (2000)
- Al-Jeraileh et al. (2000)
- Lin et al. (1999)
- Beran-Koehn et al. (1999)
- Earley et al. (1998)
- Giroud et al. (1997)
- Visuthiphan et al. (1996)
- Giroud et al. (1995)
- Broderick et al. (1993)

Insel Gruppe – ICH in the young and very old

Boulouis et al STROKE 2019
Etiology of pediatric ICH

- AVM
- Cavernoma
- Aneurysm
- Clotting deficiency

Insel Gruppe – ICH in the young and very old

Boulouis et al JNS 2021, Sporns et al JCM 2020
Frequency and comorbidities – data from the SSR

Percentage of patients with ICH by age group

- Young (18-45): 18.10%
- Middle aged (46-84): 5.40%
- Very old (>85): 76.50%

Frequency of comorbidities and prior antithrombotic medication by age group

- Hypertension
  - Young (18-45)
  - Middle aged (46-84)
  - Very old (>85)
- Diabetes
  - Young (18-45)
  - Middle aged (46-84)
  - Very old (>85)
- Prior anticoagulation
  - Young (18-45)
  - Middle aged (46-84)
  - Very old (>85)
- Prior antiplatelets
  - Young (18-45)
  - Middle aged (46-84)
  - Very old (>85)

Insel Gruppe – ICH in the young and very old

Data from the Swiss Stroke Registry - unpublished
Etiology – data from the SSR

Data from the Swiss Stroke Registry - unpublished
Case fatality, functional outcome and event rate
### Case fatality of intracerebral haemorrhage by age

<table>
<thead>
<tr>
<th>Mid-year of study</th>
<th>Patients with intracerebral haemorrhage (n)</th>
<th>Case fatality</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td>&lt;65 years</td>
<td>65-74 years</td>
<td>75-84 years</td>
<td>&gt;85 years</td>
</tr>
<tr>
<td>Oxford, UK¹⁹</td>
<td>1983</td>
<td>66</td>
<td>..</td>
<td>..</td>
<td>42.0 (20.3-66.5)</td>
<td>44.4 (21.5-69.2)</td>
<td>58.0 (36.6-77.9)</td>
</tr>
<tr>
<td>Okinawa, Japan⁵⁵</td>
<td>1989</td>
<td>1412</td>
<td>18.8 (16.1-21.5)</td>
<td>16.2 (13.3-19.1)</td>
<td>17.3 (14.6-19.9)</td>
<td>14.5 (10.4-18.7)</td>
<td>18.8 (13.8-23.7)</td>
</tr>
<tr>
<td>Arcadia, Greece⁴⁸</td>
<td>1994</td>
<td>77</td>
<td>44.0 (30.0-58.7)</td>
<td>51.8 (32.0-71.3)</td>
<td>33.3 (14.6-57.0)</td>
<td>31.8 (13.9-54.9)</td>
<td>63.2 (38.4-83.7)</td>
</tr>
<tr>
<td>Malmö, Sweden¹⁸</td>
<td>1995</td>
<td>699</td>
<td>23.9 (19.4-28.3)</td>
<td>22.7 (18.2-27.1)</td>
<td>14.3 (8.9-19.6)</td>
<td>18.9 (13.4-24.5)</td>
<td>29.8 (24.0-35.5)</td>
</tr>
<tr>
<td>China²⁹†</td>
<td>1998</td>
<td>2275</td>
<td>48.4 (45.7-51.1)</td>
<td>50.7 (47.5-53.9)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Melbourne, Australia⁵⁷</td>
<td>1998</td>
<td>151</td>
<td>29.2 (19.0-41.1)</td>
<td>50.6 (39.1-62.1)</td>
<td>..</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Örebro, Sweden⁹⁹</td>
<td>1999</td>
<td>44</td>
<td>..</td>
<td>..</td>
<td>25.0 (3.2-65.1)</td>
<td>21.4 (4.7-50.8)</td>
<td>12.5 (1.6-38.3)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>35.4 (33.6-37.1)</td>
<td>35.3 (33.2-37.4)</td>
<td>17.6 (15.3-20.0)</td>
<td>18.1 (14.8-21.4)</td>
<td>26.8 (23.1-30.5)</td>
<td>30.9 (25.1-36.7)</td>
</tr>
</tbody>
</table>

Data are % (95% CI). *Patients older than age 18 years. †Patients older than age 25 years.

**Table 4: Intracerebral haemorrhage case fatality at 1 month according to sex and age**
**Functional outcome – data from the SSR**

**Functionally independent (mRS 0-2)**
- VERY OLD >85y:
  - 17.9%
- AGED 46-84y:
  - 41.6%
- YOUNG 18-45y:
  - 67.0%

**Severely disabled (mRS 4-5)**
- VERY OLD >85y:
  - 15.0%
- AGED 46-84y:
  - 18.5%
- YOUNG 18-45y:
  - 11.6%

Data from the Swiss Stroke Registry - unpublished
Remember the old lady from the case scenario?
Intracerebral haemorrhage – acute event, chronic disease

**Complications and long term disability:**

- Epileptic seizures (10% after 10 years)
- Cognitive impairment (14% after 1 year, 28% after 4 years)
- Functional disability
- Hydrocephalus/Shunt

**Vascular events:**

- Recurrent ICH (1.3-7.4% per year)
- Ischaemic stroke (1.4-6.8% per year)
- Arterial-ischaemic events (?)

Recurrent ICH and ischaemic stroke at 3 months

Data from the Swiss Stroke Registry - unpublished
Intracerebral haemorrhage – a novel marker of vascular risk

Figure 2. Kaplan-Meier Analysis of the Risk of an Arterial Ischemic Event After Intracerebral Hemorrhage (ICH)

Increased risk for:

- Arterial-ischaemic events (HR 2.3; 95% CI, 1.7-3.1)
- Ischaemic stroke (HR 3.1; 95% CI, 2.1-4.5)
- Myocardial infarction (HR 1.9; 95% CI, 1.2-2.9)

Pooled analysis of large population-based cohort studies (n=47 866)
Recurrent ICH and ischaemic stroke

Risk by haematoma location:
- **Recurrence of ICH:**
  - Lobar (5.1%) vs Non-lobar (1.8%)
  - HR 3.2, 95% CI 1.6–6.3

Risk by atrial fibrillation:
- **Recurrence of ICH:** No difference
- **Ischaemic stroke:**
  - AF (6.3%) vs No AF (0.7%)
  - HR 8.2, 95% CI 3.3–20.3
MRI guided risk assessment

A) DWI lesion

B) Recurrent intracerebral hemorrhage

C) Ischemic stroke

Rezidiv-ICH

ICH due to CAA 10.4%
ICH due to DPA 1.6%
ICH with mixed microbleeds 5.1%

Cerebral microbleeds

deep lobar
Blood pressure control:
- target <130/90mmHg

Which medication? Target level?

Antiplatelet agents:
- (Re-)start after ICH if valid indication (e.g. coronary heart disease, ischaemic stroke)
- Timing: after 4 weeks

Atrial fibrillation:
- Optimal treatment unclear
- RCTs ongoing

RESTART trial, LANCET 2019
Left atrial appendage occlusions

<table>
<thead>
<tr>
<th>Trial</th>
<th>Notable inclusion criteria</th>
<th>Post-closure antithrombotic regimen</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT AF</td>
<td>No contraindication to warfarin</td>
<td>- Warfarin to 45 days, then</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Aspirin/clopidogrel to 6 months</td>
<td></td>
</tr>
<tr>
<td>PREVAIL</td>
<td>No contraindication to warfarin</td>
<td>- Warfarin/aspirin to 45 days, then</td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Aspirin/clopidogrel to 6 months, then</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Aspirin 325 mg/day indefinitely</td>
<td></td>
</tr>
<tr>
<td>PRAGUE-17</td>
<td>Bleeding history or predisposition (~50%), cardioembolic stroke while on anticoagulation (~33%), or high CHA₂DS₂-VASc or HAS-BLED score</td>
<td>- Aspirin/clopidogrel to 3 months, then</td>
<td>NOAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Aspirin 100 mg/day indefinitely</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients enrolled

- 707 patients (no patient with history of ICH)
- 407 patients (no patient with history of ICH)
- 404 patients (1 patient with history of ICH)

**LAAO:** level of evidence is LOW.
We should apply the same high standards for devices as for drugs!
Atrial fibrillation and ICH – ongoing RCT

**ENRICH-AF**
- 1200 Patienten, Follow-up 2 Jahre, Edoxaban vs. Aspirin

**APACHE-AF**
- 100 Patienten, Follow-up 2.5 Jahre, Apixaban vs. Aspirin

**PRESTIGE-AF**
- 654 Patienten, Follow-up 3 Jahre, alle DOAC vs. Aspirin

**A3ICH**
- 300 Patienten, Follow-up 2 Jahre, Apixaban vs. Vorhofsohrverschluss vs Aspirin

**STROKE CLOSE**
- 203 Patienten, Follow-up 1 Jahr, alle Antikoagulantien vs. Aspirin
- 700 Patienten, Follow-up 2 Jahre, alle Antikoagulantien vs. Vorhofsohrverschluss

**STROKE**
- 700 Patienten, Follow-up 2 Jahre, alle Antikoagulantien vs. Vorhofsohrverschluss

**CLOSE**
- 700 Patienten, Follow-up 2 Jahre, alle Antikoagulantien vs. Vorhofsohrverschluss

**SOON**
- Start or Stop Antikoagulants Randomised Trial

**INSELGRUPPE**
- Insel Gruppe – ICH in the young and very old
Breacking news ESOC 2021: APACHE-AF

101 patient enrolled
Median follow-up: 1.9 years
OAC: Apixaban

<table>
<thead>
<tr>
<th>Event</th>
<th>On anticoagulation</th>
<th>Not on anticoagulation</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke or vascular death</td>
<td>12</td>
<td>13</td>
<td>0.87 (0.39 to 1.94)</td>
</tr>
<tr>
<td>Intracerebral haemorrhage</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>All major haemorrhagic events</td>
<td>8</td>
<td>1</td>
<td>6.51 (0.80 to 53.13)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>5</td>
<td>8</td>
<td>0.57 (0.18 to 1.79)</td>
</tr>
<tr>
<td>All major occlusive events</td>
<td>4</td>
<td>14</td>
<td>0.29 (0.09 to 0.91)</td>
</tr>
<tr>
<td>All major vascular events</td>
<td>11</td>
<td>19</td>
<td>0.66 (0.31 to 1.39)</td>
</tr>
<tr>
<td>All major vascular events</td>
<td>12</td>
<td>14</td>
<td>0.85 (0.39 to 1.86)</td>
</tr>
</tbody>
</table>

Adjusted for a propensity score including age and ICH location.
Breacking news ESOC 2021: SoSTART

**Secondary outcome: any symptomatic major vascular event**

Start vs. avoid OAC
Adjusted HR 0.51 (0.26–1.03): p=0.060

- **203 patient enrolled**
- **Median follow-up: 1.2 years**
- **OAC: any OAC**

Avoid: n=24/102 (24%)
Start: n=12/101 (12%)
Breacking news ESOC 2021: SoSTART

Results: primary & secondary outcomes
Clinical case – follow up

- **SWI:** No microbleeds
- **FLAIR:** Severe leukencephalopathy with lacunes
- **DWI:** no lesion

**Etiology:** Deep perforator microangiopathy

- **Risik for ischemia:** High (atrial fibrillation and lacunar ischaemia in past!)
- **Risi for ICH-recurrence:** low (no microbleeds, no DWI lesions)

**Therapy:** Apixaban 2x2.5mg + intensive control of BP (<130/90mmHg)
Summary

- Pediatric ICH is rare but serious and mostly due to macrovascular causes, cancer or systemic disease
- In the young (18-45 years), incidence of ICH is low and outcome favourable
- In the very old (>85 years), incidence of ICH is high and outcome is unfavourable
- Data from Switzerland mirror findings from the literature
- Survivors of ICH are vascular high-risk patients
- In many survivors, the risk of arterial-ischaemic events is higher than that of recurrent ICH!
Thank you for your attention!

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