What registry data contributed to intracerebral haemorrhage research

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Disclosures

Research funding

• Swiss National Science Foundation, Swiss Heart Foundation, Bangerter-Rhyner Foundation, AstraZeneca (Externally sponsored research program)

Speaker/Advisory board (used for research funding)

• AstraZeneca, Pfizer, VarmX, Bioxodes, ECMREG
In 2023, 3(!) positive RCTs for treatment of ICH have been published, presented or announced.
History of (mainly unsuccessful) RCTs in ICH management

- 1993: stroke unit
- 2005: surgery (STICH)
- 2008: rFactor VIIa (FAST)
- 2013: surgery (STICH II)
- 2013: intensive BP lowering (Interact2)
- 2016: very intensive BP lowering (ATACH-II)
- 2016: thrombocytes (on antiplatelets. PATCH)
- 2018: tranexamic acid (TICH-2)
- 2019: deferoxamine (i-DEF; phase 2)
- 2019: minimally invasive surgery with rtPA (MISTIE III)

NNT

18

-
History of (mainly unsuccessful) RCTs in ICH management

- **2023:** care bundle* (Interact3)
  - BP lowering, strict glucose control, antipyrexia, rapid reversal of anticoagulation

- **2023:** min. invasive, trans-sulcal, parafasc. surgery (ENRICH) 11?
  - Lobar ICH only

- **2024:** hemicraniectomy (SWITCH)

- **2025:** rFactorVIIa <2hrs (FASTEST)

- **2025:** minimally invasive endoscopy guided surgery (EVACUATE)

- **2026:** minimally invasive endoscopy guided surgery (DIST; MIND)

- **2029:** tranexamic acid (TICH-3)
The Swiss Stroke Registry (29.12.2022 – 83137 patients)

Bernhard Siepen
PhD candidate

Martina Göldlin
PhD candidate
Etiology, 3-Month Functional Outcome and Recurrent Events in Non-Traumatic Intracerebral Hemorrhage

Insel Gruppe – Intracerebral haemorrhage

Goeldlin et al JoS 2022

Figure 1. Mechanistic classification of intracerebral hemorrhage (ICH) etiology: comparison of the original and adapted SWASH-U (structural lesion > systemic disease > medication > amyloid angiopathy > hypertension > unknown) classifications. CAA, cerebral amyloid angiopathy.

Figure 2. Frequency of intracerebral hemorrhage etiologies. CAA, cerebral amyloid angiopathy.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total [n=2,660]</th>
<th>Hypertension [n=1,238 (46.7%)]</th>
<th>Antithrombotic [n=227 (8.6%)]</th>
<th>CAA [n=217 (8.2%)]</th>
<th>Macrovascular [n=128 (4.9%)]</th>
<th>Other determined etiology [n=274 (10.3%)]</th>
<th>Unknown [n=566 (21.4%)]</th>
<th>P</th>
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<tr>
<td>Demographics</td>
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<tr>
<td>Age (yr)</td>
<td>71.9±14.1</td>
<td>72.8±13.0</td>
<td>78.5±9.8</td>
<td>77.1±8.2</td>
<td>59.3±17.5</td>
<td>66.1±17.6</td>
<td>70.8±14.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Female sex</td>
<td>1,227 (46.5%)</td>
<td>541 (43.9%)</td>
<td>95 (42.0%)</td>
<td>122 (56.2%)</td>
<td>52 (40.6%)</td>
<td>133 (48.5%)</td>
<td>284 (50.3%)</td>
<td>0.002</td>
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<td>Risk factors</td>
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<tr>
<td>Hypertension</td>
<td>2,053 (77.9%)</td>
<td>1,152 (95.0%)</td>
<td>189 (84.0%)</td>
<td>147 (71.0%)</td>
<td>57 (46.7%)</td>
<td>164 (62.4%)</td>
<td>344 (63.4%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Diabetes</td>
<td>864 (31.6%)</td>
<td>196 (16.3%)</td>
<td>43 (19.0%)</td>
<td>27 (12.1%)</td>
<td>14 (11.4%)</td>
<td>40 (14.6%)</td>
<td>62 (11.4%)</td>
<td>0.033</td>
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<td>Hyperlipidemia</td>
<td>1,096 (41.3%)</td>
<td>536 (44.4%)</td>
<td>105 (46.2%)</td>
<td>91 (44.4%)</td>
<td>41 (33.3%)</td>
<td>102 (39.7%)</td>
<td>222 (41.3%)</td>
<td>0.071</td>
</tr>
<tr>
<td>Smoking</td>
<td>306 (11.6%)</td>
<td>142 (11.7%)</td>
<td>26 (11.7%)</td>
<td>15 (7.3%)</td>
<td>17 (13.2%)</td>
<td>40 (15.5%)</td>
<td>66 (12.3%)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>467 (18.2%)</td>
<td>174 (14.4%)</td>
<td>137 (61.4%)</td>
<td>22 (10.6%)</td>
<td>7 (5.7%)</td>
<td>43 (16.7%)</td>
<td>84 (15.5%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Concomitant medication</td>
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<td>Antithrombolytics</td>
<td>729 (28.6%)</td>
<td>368 (31.0%)</td>
<td>46 (20.4%)</td>
<td>71 (33.8%)</td>
<td>28 (22.2%)</td>
<td>66 (25.0%)</td>
<td>150 (27.9%)</td>
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<td>Anticoagulation</td>
<td>568 (22.3%)</td>
<td>193 (16.3%)</td>
<td>212 (93.4%)</td>
<td>24 (11.4%)</td>
<td>8 (6.3%)</td>
<td>51 (19.0%)</td>
<td>80 (14.9%)</td>
<td>&lt;0.001</td>
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<td>DDAAC</td>
<td>241 (42.4%)</td>
<td>99 (55.1%)</td>
<td>74 (34.9%)</td>
<td>12 (50.6%)</td>
<td>3 (37.5%)</td>
<td>18 (35.5%)</td>
<td>35 (43.8%)</td>
<td></td>
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<tr>
<td>VKA</td>
<td>296 (52.1%)</td>
<td>87 (46.1%)</td>
<td>129 (60.3%)</td>
<td>10 (41.6%)</td>
<td>5 (62.5%)</td>
<td>27 (52.9%)</td>
<td>39 (48.6%)</td>
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<tr>
<td>Others</td>
<td>31 (5.4%)</td>
<td>7 (3.6%)</td>
<td>10 (4.7%)</td>
<td>2 (8.3%)</td>
<td>0 (0%)</td>
<td>6 (11.8%)</td>
<td>6 (7.5%)</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>History of ischemic stroke</td>
<td>219 (11.3%)</td>
<td>139 (61.5%)</td>
<td>38 (16.7%)</td>
<td>30 (14.5%)</td>
<td>13 (10.5%)</td>
<td>25 (9.6%)</td>
<td>45 (8.3%)</td>
<td>0.009</td>
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<tr>
<td>History of transient ischemic attack</td>
<td>116 (4.5%)</td>
<td>56 (4.1%)</td>
<td>13 (6.3%)</td>
<td>14 (6.8%)</td>
<td>1 (0.8%)</td>
<td>0 (0.1%)</td>
<td>30 (5.5%)</td>
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<tr>
<td>History of intracerebral hemorrhage</td>
<td>280 (10.8%)</td>
<td>97 (8.0%)</td>
<td>28 (12.6%)</td>
<td>65 (31.4%)</td>
<td>8 (6.5%)</td>
<td>23 (8.8%)</td>
<td>59 (10.9%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Clinical presentation of admission</td>
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<tr>
<td>NIHSS on admission</td>
<td>8 (3–15)</td>
<td>9 (4–16)</td>
<td>10 (3–17)</td>
<td>5 (2–12)</td>
<td>7 (1–15)</td>
<td>4 (1–11)</td>
<td>6 (2–16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure on admission [mm Hg]</td>
<td>166±31.6</td>
<td>170±31.0</td>
<td>161±32.9</td>
<td>157±26.5</td>
<td>155±33.6</td>
<td>154±28.7</td>
<td>158±29.8</td>
<td>0.013</td>
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<tr>
<td>Diastolic blood pressure on admission [mm Hg]</td>
<td>90±26.3</td>
<td>96±31.1</td>
<td>86±18.2</td>
<td>84±14.9</td>
<td>86±20.5</td>
<td>85±17.2</td>
<td>86±16.9</td>
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<tr>
<td>Management</td>
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<tr>
<td>Treatment at stroke center</td>
<td>2,052 (77.4%)</td>
<td>1,000 (80.8%)</td>
<td>174 (76.7%)</td>
<td>167 (71.0%)</td>
<td>92 (71.9%)</td>
<td>182 (66.4%)</td>
<td>437 (77.2%)</td>
<td>&lt;0.001</td>
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<tr>
<td>MRI performed</td>
<td>969 (42.5%)</td>
<td>347 (32.3%)</td>
<td>55 (20.7%)</td>
<td>106 (52.1)</td>
<td>65 (57.0%)</td>
<td>137 (59.0%)</td>
<td>260 (52.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset-to-admission time [hr]</td>
<td>3.8 (1.4–12.3)</td>
<td>2.8 (1.2–10.0)</td>
<td>4.0 (1.3–13.3)</td>
<td>7.5 (2.1–23.6)</td>
<td>4.7 (1.1–16.2)</td>
<td>5.6 (1.6–24.0)</td>
<td>5.2 (1.6–14.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>Discharge destination</td>
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<tr>
<td>Home</td>
<td>460 (21.8%)</td>
<td>187 (18.4%)</td>
<td>18 (11.3%)</td>
<td>40 (22.7%)</td>
<td>25 (24.5%)</td>
<td>74 (32.7%)</td>
<td>116 (26.0%)</td>
<td>0.001</td>
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<tr>
<td>Nursing home or palliative care</td>
<td>143 (6.2%)</td>
<td>65 (6.4%)</td>
<td>19 (11.9%)</td>
<td>21 (11.8%)</td>
<td>5 (4.9%)</td>
<td>7 (3.1%)</td>
<td>26 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>Other acute care hospital</td>
<td>380 (18.0%)</td>
<td>175 (17.2%)</td>
<td>29 (18.2%)</td>
<td>22 (12.5%)</td>
<td>23 (22.5%)</td>
<td>46 (20.4%)</td>
<td>85 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation hospital</td>
<td>1,129 (53.1%)</td>
<td>590 (56.0%)</td>
<td>93 (56.8%)</td>
<td>93 (52.8%)</td>
<td>46 (48.0%)</td>
<td>99 (43.8%)</td>
<td>305 (47.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation, number (%) or median (interquartile range).
CIA, cranial amyloid angiopathy; DDAAC, direct oral anticoagulation; VKA, vitamin K antagonist; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow coma scale; MRI, magnetic resonance imaging.
*Perimetal anticoagulation.
Intracerebral haemorrhage

>1/3 good outcome

~30% mortality

<4% «bad» outcome

Figure 4. Functional outcomes at 3 months according to intracerebral hemorrhage (ICH) etiology. CAA, cerebral amyloid angiopathy; mRS, modified Rankin Scale.

Goeldlin et al JoS 2022
3 – months outcome: too short after ICH?

Figure 2. Ordinal Distribution of Modified Rankin Scale Score (mRS) at Serial Time Points in Patients With Poor Outcomes at Day 30 in the CLEAR-III and MISTIE-III cohorts

A Distribution of mRS scores in patients with poor outcome (mRS score of 4-5) at day 30 in the CLEAR-III trial

B Distribution of mRS scores in patients with poor outcome (mRS score of 4-5) at day 30 in the MISTIE-III trial
Frequency of CAA-related ICH – autopsy data

- Neither moderate or severe CAA nor other small vessel disease
- Moderate or severe other small vessel disease alone
- Moderate or severe CAA and other small vessel disease together
- Moderate or severe CAA alone

- Non-lobar intracerebral haemorrhage (n=48)
- Lobar intracerebral haemorrhage (n=62)

- CAA
- Mixed CAA/DPA
- DPA

Rodrigues et al Lancet Neurology 2018
MRI-based classification: CADMUS

First step: exclude secondary cause and cryptogenic ICH

Second step: ICH location

Deep ICH (basal ganglia, thalamus, brainstem)

Lobar ICH (supratentorial cerebral lobes)

Undetermined (cerebellar)

Third step: SVD MRI markers

Haemorrhagic MRI markers

Non-haemorrhagic MRI markers

Cerebral amyloid Angiopathy (CAA)

Mixed CAA-DPA (Boston criteria + signs of DPA or deep ICH with SVD features of CAA)

Deep perforator arteriolopathy (DPA) (deep ICH + CAA/MRI/MRA)

Undetermined SVD (signs of SVD on MRI but no fulfilling criteria for DVA, CAA or mixed)

Secondary cause of ICH (i.e. macrovascular, structural, systemic disease)

Cryptogenic ICH (absence of signs of small vessel disease or primary cause of ICH)

17% undetermined

6% DPA

63% mixed CAA-DPA

13% CAA

Goedlin et al accepted
MRI-based classification: CADMUS

Cumulative hazard function for ischaemic stroke

Cumulative hazard function for recurrent ICH

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>CAA</th>
<th>DPA</th>
<th>Mixed CAA-DPA</th>
<th>Undetermined</th>
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<td>a</td>
<td>154</td>
<td>62</td>
<td>751</td>
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<td>b</td>
<td>148</td>
<td>64</td>
<td>720</td>
<td>181</td>
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<td>662</td>
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</table>

Goeldlin et al accepted

Insel Gruppe – Intracerebral haemorrhage

29.09.2023
Intracerebral haemorrhage in patients taking different types of oral anticoagulants – a pooled individual patient data analysis from two national stroke registries

Swiss Stroke Registry (SSR)
- 25 Centers
- 3,750 Patients with ICH
- 01/2014 – 12/2019

Norwegian Stroke Registry (NSR)
- 51 Centers
- 7,984 Patients with ICH
- 01/2013 – 12/2019

Patients excluded (n=385)
- 385 Anticoagulation status missing

Combined data
- 76 Centers
- 11,734 Patients with ICH

11,349 Final study population

8,653 (76.3%)
- No prior use of OACs

1,491 (13.1%)
- Prior use of VKAs

1,205 (10.6%)
- Prior use of DOACs
Frequency of different types of anticoagulants in patients with ICH

B Switzerland

C Norway

Insel Gruppe – Intracerebral haemorrhage

Siepen et al under review
3-months outcomes in patients with OAC-associated ICH

Siepen et al under review
Small vessel disease burden and risk of recurrent cerebrovascular events in patients with lacunar stroke and intracerebral haemorrhage attributable to deep perforator arteriolopathy

Martina B Goedlin¹,²*, Jan Vynckier¹,³*, Madlaine Mueller¹,², Boudewijn Drop¹ ID, Basel Maamari¹, Noah Vonlanthen¹, Bernhard M Siepen¹,², Arsany Hakim¹ ID, Johannes Kaesmacher⁴, Christopher Marvin Jesse⁵, Mandy D Mueller⁵, Thomas R Meinel¹ ID, Morin Beyeler¹,² ID, Leander Clénin¹, Jan Gralla⁴, Werner Z’Graggen¹,⁵ ID, David Bervini⁵, Marcel Arnold¹, Urs Fischer¹,⁶ ID and David J Seiffge¹ ID
Small vessel disease burden and risk of recurrent cerebrovascular events in patients with lacunar stroke and intracerebral hemorrhage attributable to deep perforator arteriolopathy

Do disease burden on MRI, functional outcome and recurrence rate differ between intracerebral hemorrhage (ICH) versus lacunar stroke, if associated with deep perforator arteriolopathy?

**Methods**
- Prospective Stroke Registry 2014-2019
- Deep ICH: 117 patients
- Lacunar stroke: 599 patients

**Results**
- ICH compared to lacunar stroke:
  - SVD burden score: aOR_{shift} 3.19
  - mRS: aOR_{shift} 2.16
  - Similar 3-month recurrence rates

**Conclusion**
- More severe deep perforator arteriolopathy manifesting as ICH compared to lacunar stroke
- Poorer functional outcome in deep ICH compared to lacunar stroke
- No difference in recurrence rates

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doi.org/10.1177_23969873231193237
The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial

Lu Ma*, Xin Hu*, Lili Song*, Xiaoying Chen*, Menglu OuYang, Laurent Billet, Qiang Li, Alejandra Malavera, Xi Li, Paula Munoz-Venturelli, Asitade Silva, Nguyen Huy Thang, Kolawole W Wahab, Jeyaraj D Pandan, Mohammad Wasay, Octavio M Pintes-Neco, Carlos Abanto, Antonio Arauza, Heiping Shi, Guanghai Tang, Sheng Zhu, Xiaochun She, Leiko Liu, Yuki Sakamoto, Shujiang You, Qiao Han, Remard Cretzen, Emily Cheung, Yunze Li, Xia Wang, Chen Chen, Feifeng Liu, Yang Zhao, Hao Li, Yi Liu, Yan Jiang, Lei Chen, Bo Wu, Ming Liu, Jiangyu Xu, Chao You, Craig S Anderson, for the INTERACT3 Investigators
Care bundle delivery at Inselspital Bern

Eligibility and uptake of treatments

- 66% of eligible patients received IV antihypertensive treatment
- 88% of eligible patients had admission RR > 150mmHg
- PCC treatment
- Therapeutic anticoagulation
- Any neurosurgical intervention (<3 hours of admission)
Insel Gruppe – Intracerebral haemorrhage

Care bundle metrics at Inselspital Bern

![Flowchart showing care bundle metrics for patients with intracerebral haemorrhage.](chart.png)

**Admission** → **Imaging** → **IV antihypertensive** → **PCC** → **ED discharge**

- **All patients**:
  - Admission to Imaging: 27 min (IQR 18-52)
  - Imaging to IV antihypertensive: 38 min (IQR 18-72)
  - IV antihypertensive to PCC: 59 min (IQR 37-111)
  - PCC to ED discharge: 139 min (IQR 85-220)

- **Stroke code**:
  - Admission to Imaging: 23 min (IQR 18-35)
  - Imaging to IV antihypertensive: 61 min (IQR 34-84)
  - IV antihypertensive to PCC: 63 min (IQR 45-85)
  - PCC to ED discharge: 157 min (IQR 111-220)

- **Transfer**:
  - Admission to Imaging: 18 min (IQR 9-38)
  - Imaging to IV antihypertensive: 37 min (IQR 17-85)
  - IV antihypertensive to PCC: 103 min (IQR 59-173)

- **Other**:
  - Admission to Imaging: 33 min (IQR 18-86)
  - Imaging to IV antihypertensive: 50 min (IQR 26-136)
  - IV antihypertensive to PCC: 70 min (IQR 41-240)
  - PCC to ED discharge: 203 min (IQR 98-317)

[Insel Gruppe – Intracerebral haemorrhage](chart.png)

Bettschen, Siepen et al under revision

29.09.2023 22
Summary

- After years of failure, in 2023 3 RCTs in ICH have been positive
- Observational studies contributed to our current knowledge about clinical characteristics, prognosis and management of ICH patients
- Swiss Stroke Registry is a useful tool to investigate ICH in Switzerland
- Swiss Stroke Registry data collection for ICH needs to be revised reflecting recent developments and specific aspects of ICH
  - Delivery and metrics of acute treatment (DNT for BP control and anticoagulation reversal!)
  - Aetiology
  - Long-term outcomes (>3 months)