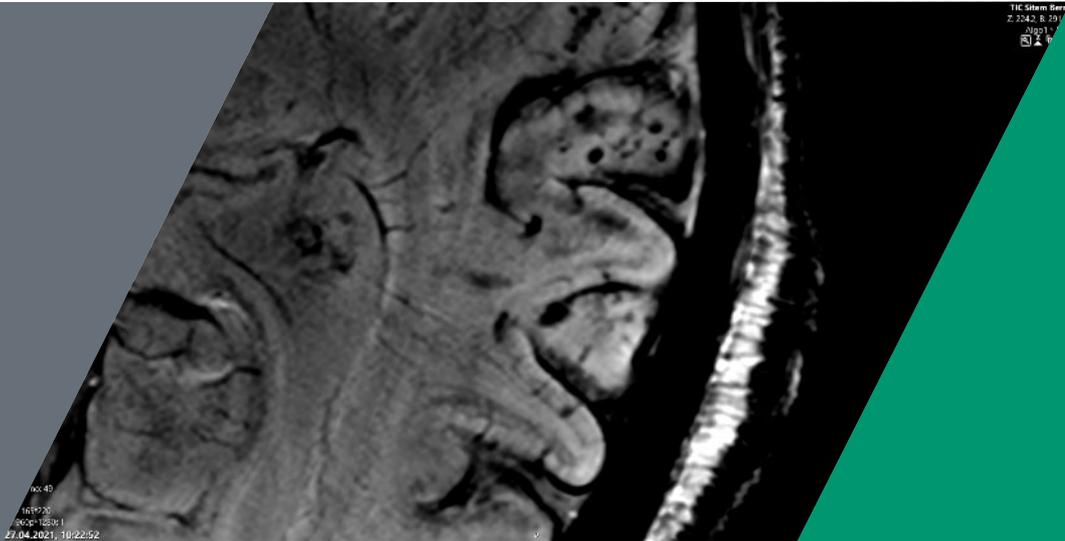


Intracerebral haemorrhage in the young and very old

David Seiffge, Inselspital University Hospital Bern



Disclosures

Employer	Inselspital, University Hospital Bern (Switzerland)
Memberships	ESO, SNG, SSS, SGKN
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Honoraria (all paid to employer)	Bayer, Alexion/Portola

What is young, what is old?



Pediatric patients
(<18 years)

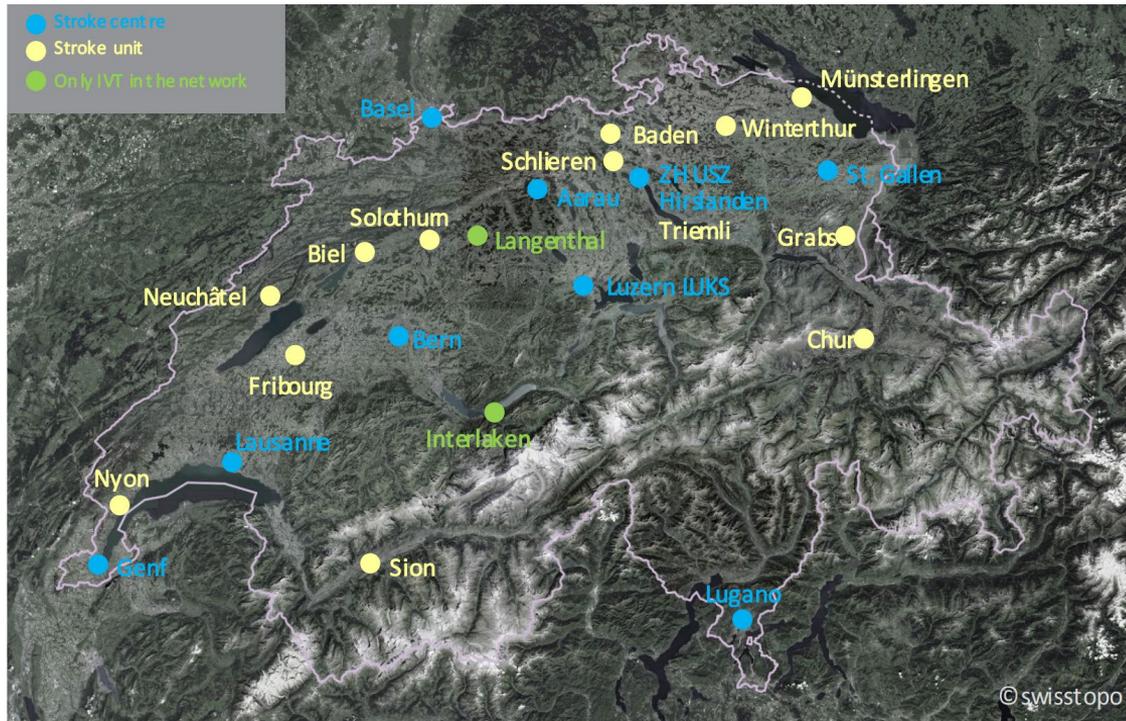


Young adults
(18-45years)



The very old
(>85 years)

Data from the Swiss Stroke Registry: The ICH cohort



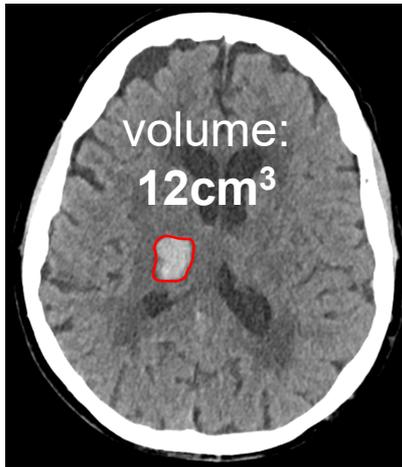
Study period:
2014-2019

Study population:
2650 patients

**23 Swiss Stroke
Units and Stroke
Centers**

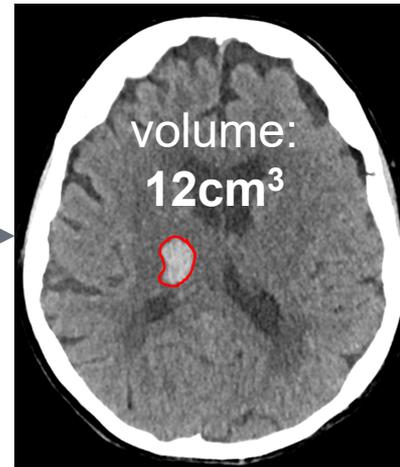
Clinical Case

94 year old femal 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

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



CT at 24 hours

**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

Incidence, frequency and etiology



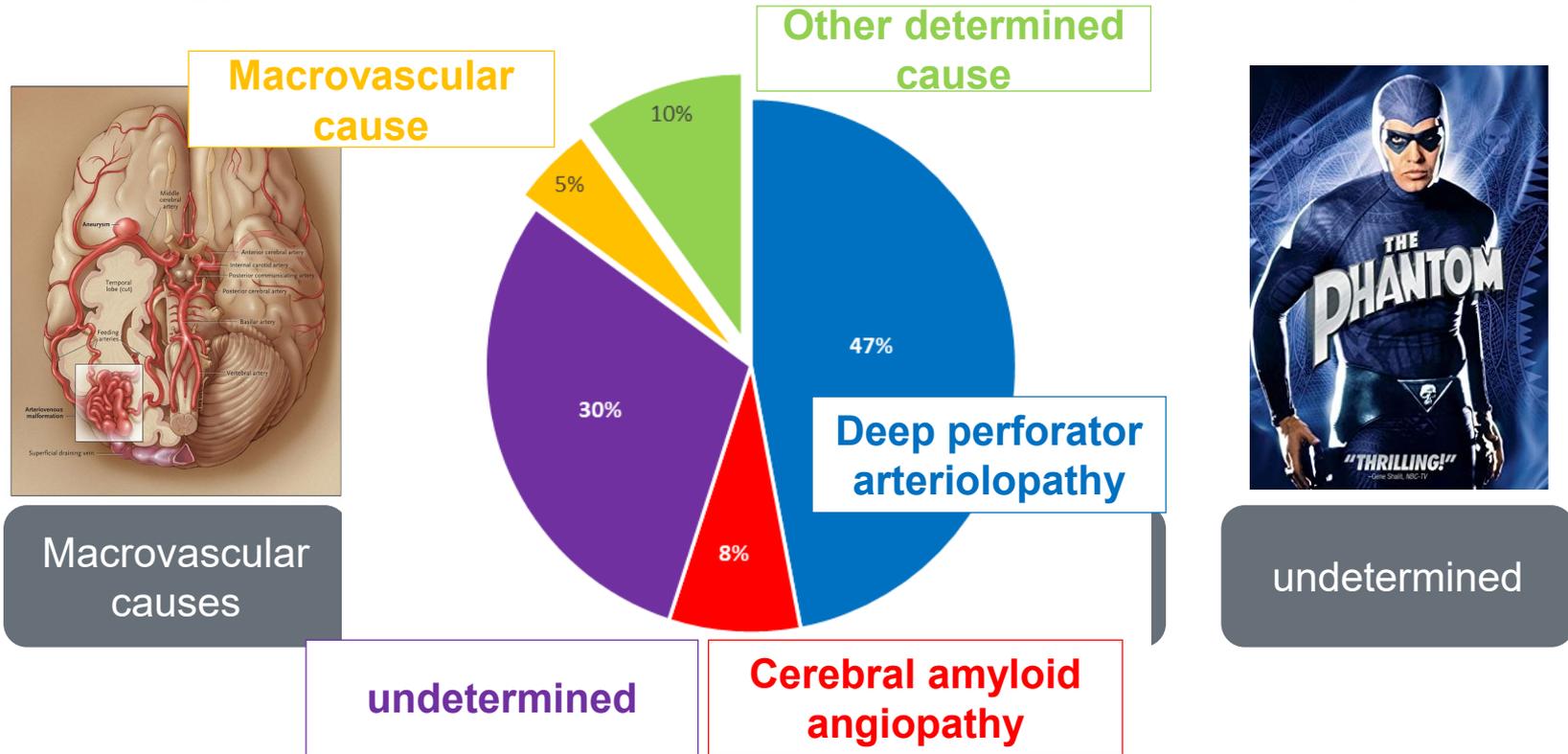
Incidence of intracerebral haemorrhage by age

	Patients with intracerebral haemorrhage (n)	Person-years	Incidence per 100 000 person-years (95% CI)	Number of time periods	Incidence ratio (95% CI)
≤44 years ^{13,19,23,26,27,30,32,33,39-41,43,46-48,52,56}	119	5 958 646	1.9 (1.6-2.2)	16	0.10 (0.06-0.14)
45-54 years ^{19,23,26,27,30,32,33,39-41,43,46-48,52}	164	7 256 660	19.1 (13.4-27.4)	15	Reference
55-64 years ^{19,20,23,26,27,30,32,33,38-40,43,46-48,52}	305	8 651 73	36.5 (28.4-46.7)	16	1.8 (1.3-2.6)
65-74 years ^{19,23,26,27,29,30,32-34,38-41,43,46-48,52}	597	8 120 77	77.1 (65.0-91.5)	18	3.8 (2.7-5.4)
75-84 years ^{19,23,26,27,29,30,32-34,38-41,43,46-48,52}	665	5 318 45	136.9 (111.3-168.4)	18	6.8 (4.8-9.6)
≥85 years ^{19,23,26,27,29,30,32-34,38-41,46-48,52}	274	1 705 80	196.0 (148.3-259.1)	17	9.6 (6.6-13.9)

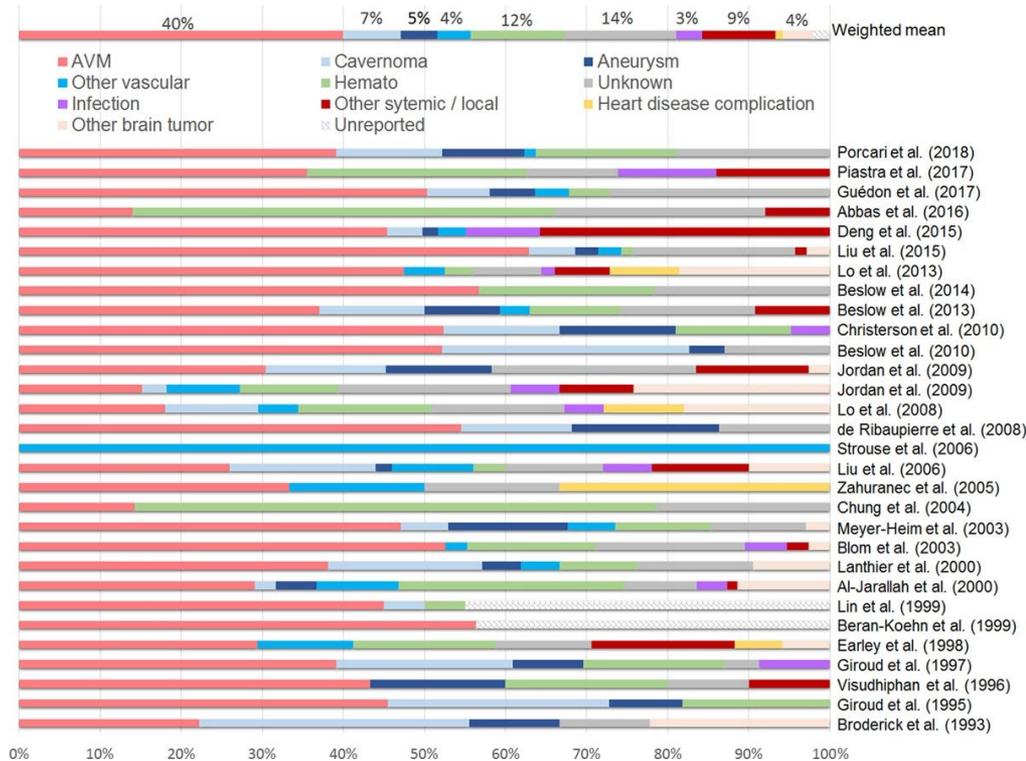
Because intracerebral haemorrhage is rare in people under age 45 years, the incidence ratios were calculated with the 45-54 years age group as the reference.

Table 2: Incidence of intracerebral haemorrhage according to age

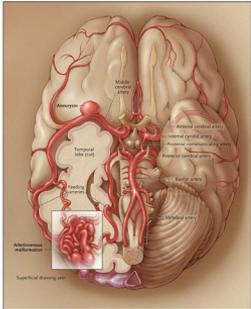
Etiology – what causes intracerebral haemorrhage?



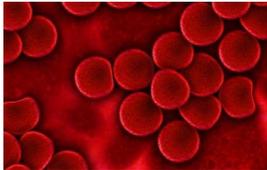
Etiology of pediatric ICH



56%



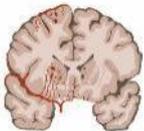
28%



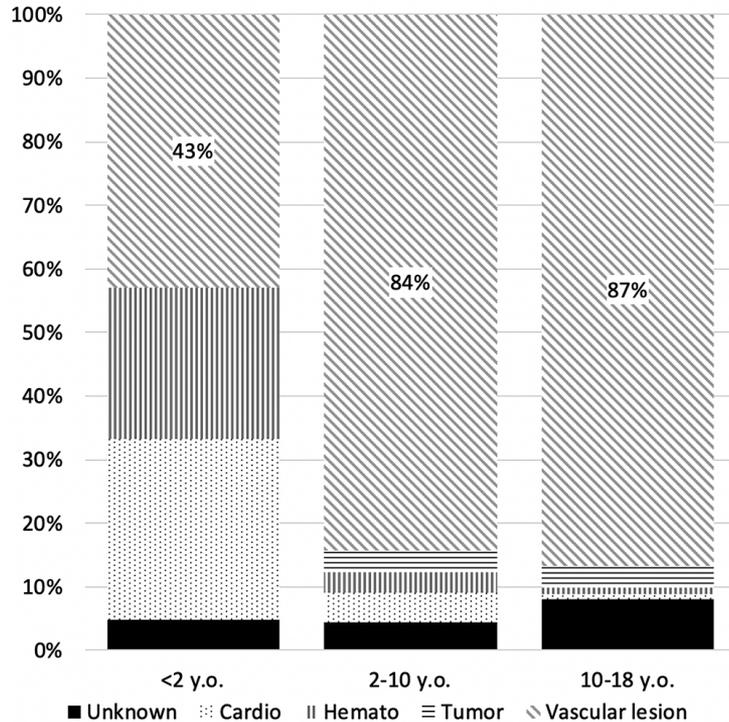
16%



0%



Etiology of pediatric ICH

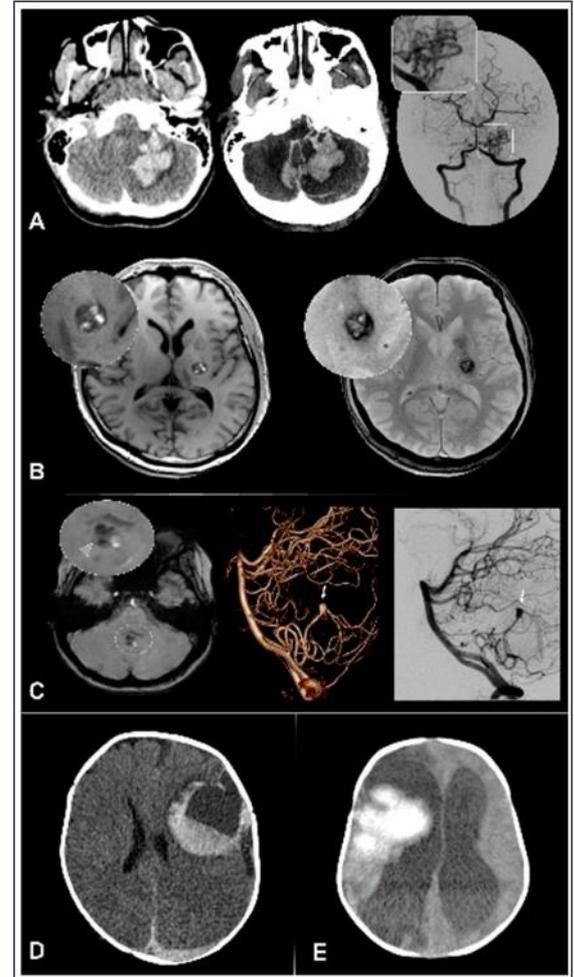


AVM

Cavernoma

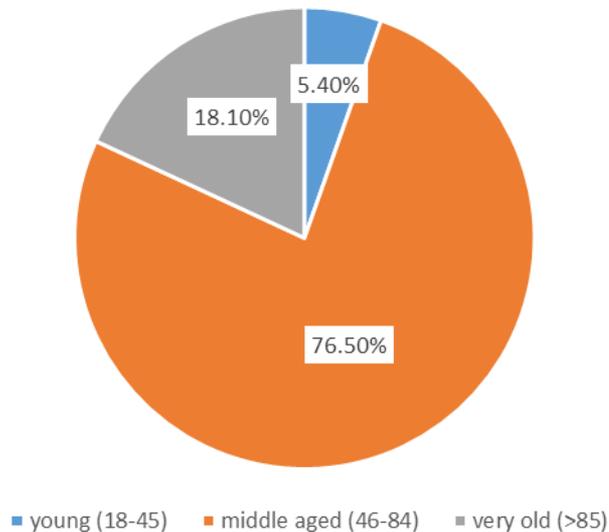
Aneurysm

Clotting deficiency

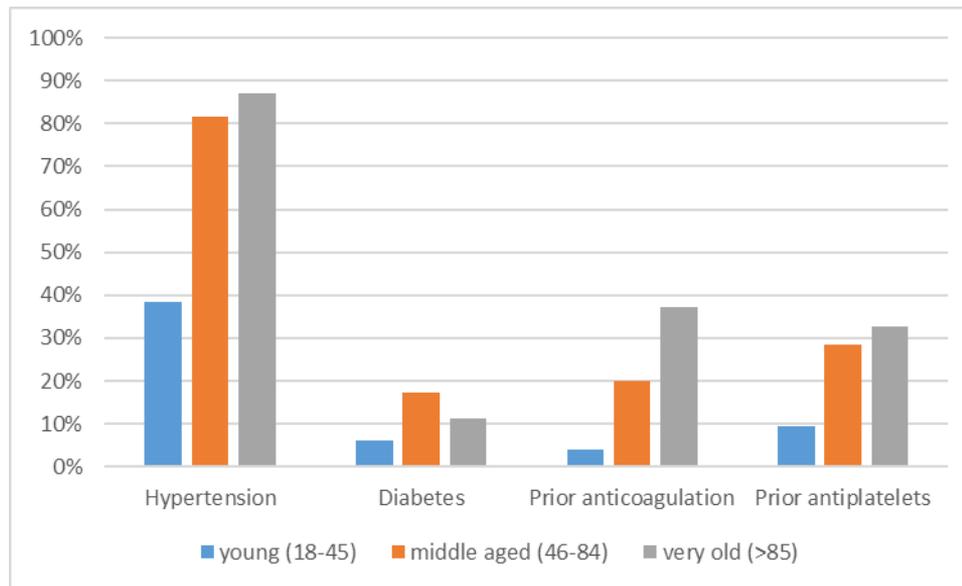


Frequency and comorbidities – data from the SSR

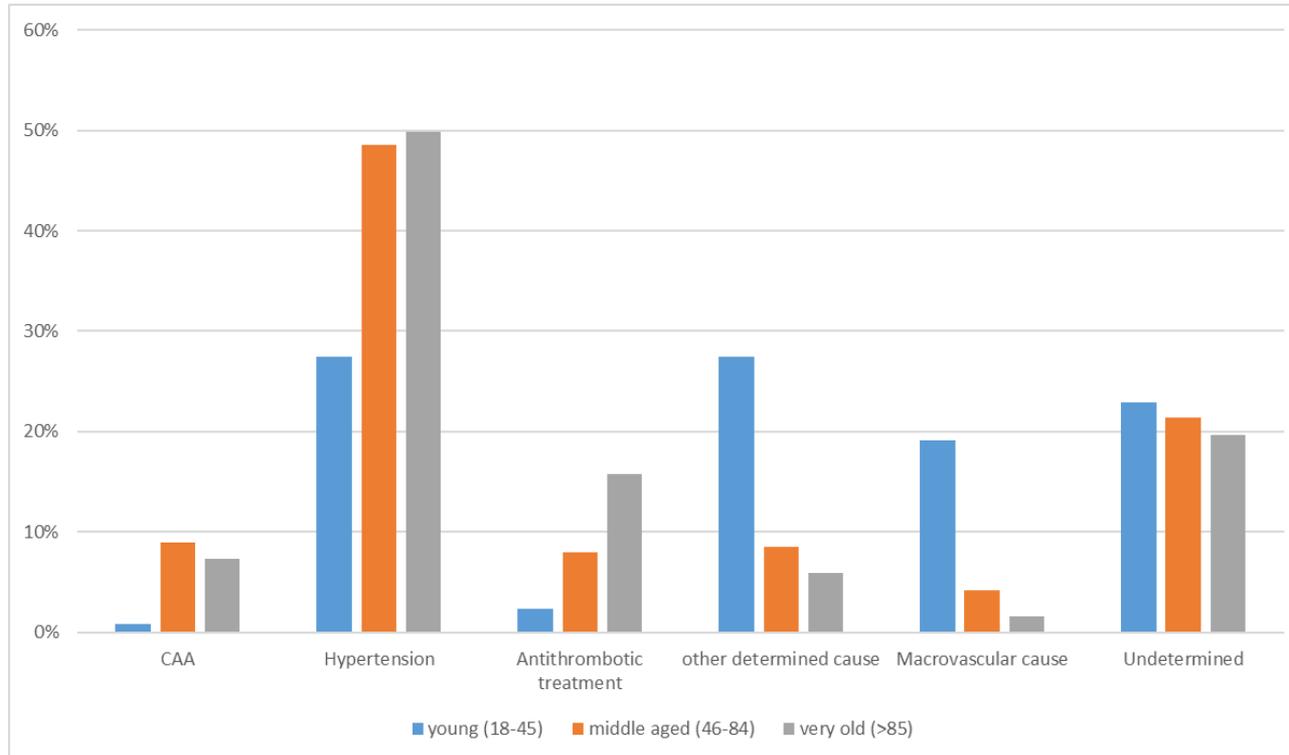
Percentage of patients with ICH by age group



Frequency of comorbidities and prior antithrombotic medication by age group



Etiology – data from the SSR



Case fatality, functional outcome and event rate



Case fatality of intracerebral haemorrhage by age

	Mid-year of study	Patients with intracerebral haemorrhage (n)	Case fatality					
			Men	Women	<65 years	65-74 years	75-84 years	>85 years
Oxford, UK ¹⁹	1983	66	42.0 (20.3-66.5)	44.4 (21.5-69.2)	58.0 (36.6-77.9)	80.0 (28.4-99.5)
Okinawa, Japan ⁵⁵	1989	1412	18.8 (16.1-21.5)	16.2 (13.3-19.1)	17.3 (14.6-19.9)	14.5 (10.4-18.7)	18.8 (13.8-23.7)	24.8 (17.1-32.5)
Arcadia, Greece ^{48*}	1994	77	44.0 (30.0-58.7)	51.8 (32.0-71.3)	33.3 (14.6-57.0)	31.8 (13.9-54.9)	63.2 (38.4-83.7)	60.0 (32.3-83.7)
Malmö, Sweden ³⁸	1995	699	23.9 (19.4-28.3)	22.7 (18.2-27.1)	14.3 (8.9-19.6)	18.9 (13.4-24.5)	29.8 (24.0-35.5)	31.3 (22.4-41.4)
China ^{50†}	1998	2275	48.4 (45.7-51.1)	50.7 (47.5-53.9)
Melbourne, Australia ²⁷	1998	151	29.2 (19.0-41.1)	50.6 (39.1-62.1)
Örebro, Sweden ²⁹	1999	44	25.0 (3.2-65.1)	21.4 (4.7-50.8)	12.5 (1.6-38.3)	33.3 (4.3-77.7)
Overall	35.4 (33.6-37.1)	35.3 (33.2-37.4)	17.6 (15.3-20.0)	18.1 (14.8-21.4)	26.8 (23.1-30.5)	30.9 (25.1-36.7)

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)

Severely disabled (mRS 4-5)

17.9%

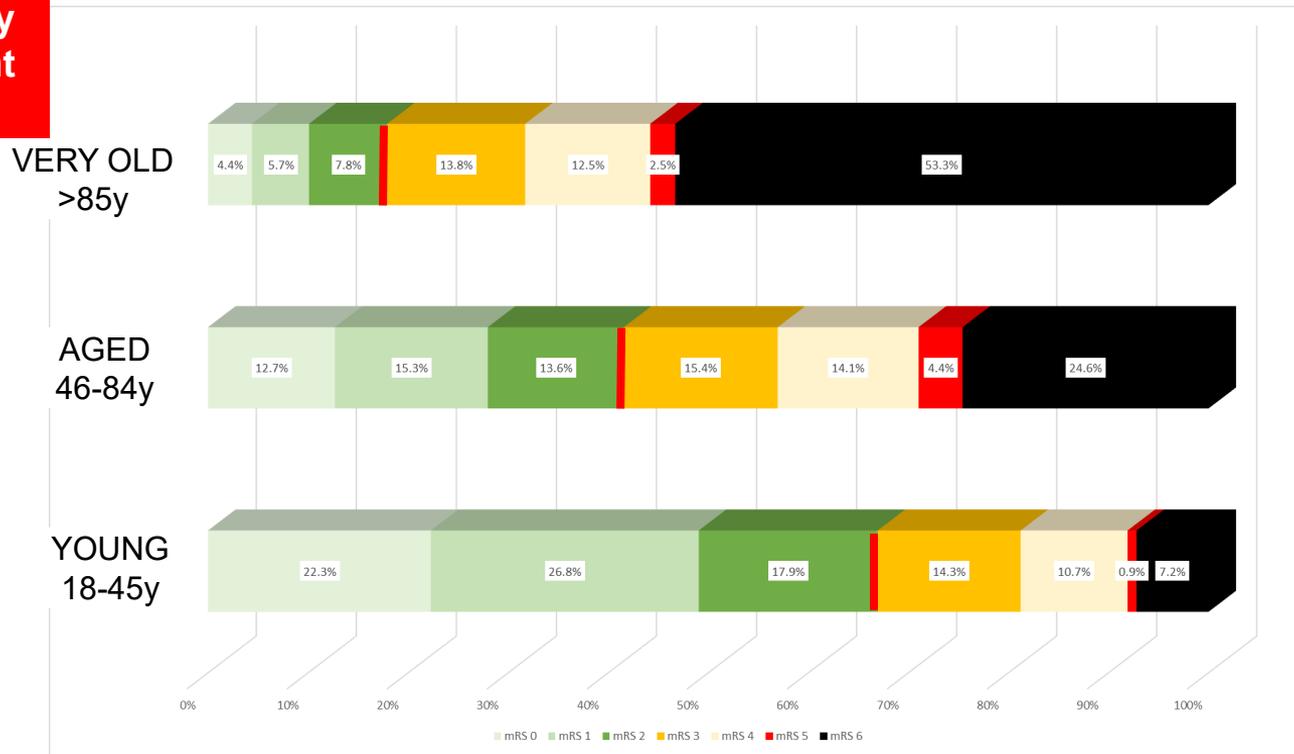
15.0%

41.6%

18.5%

67.0%

11.6%





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

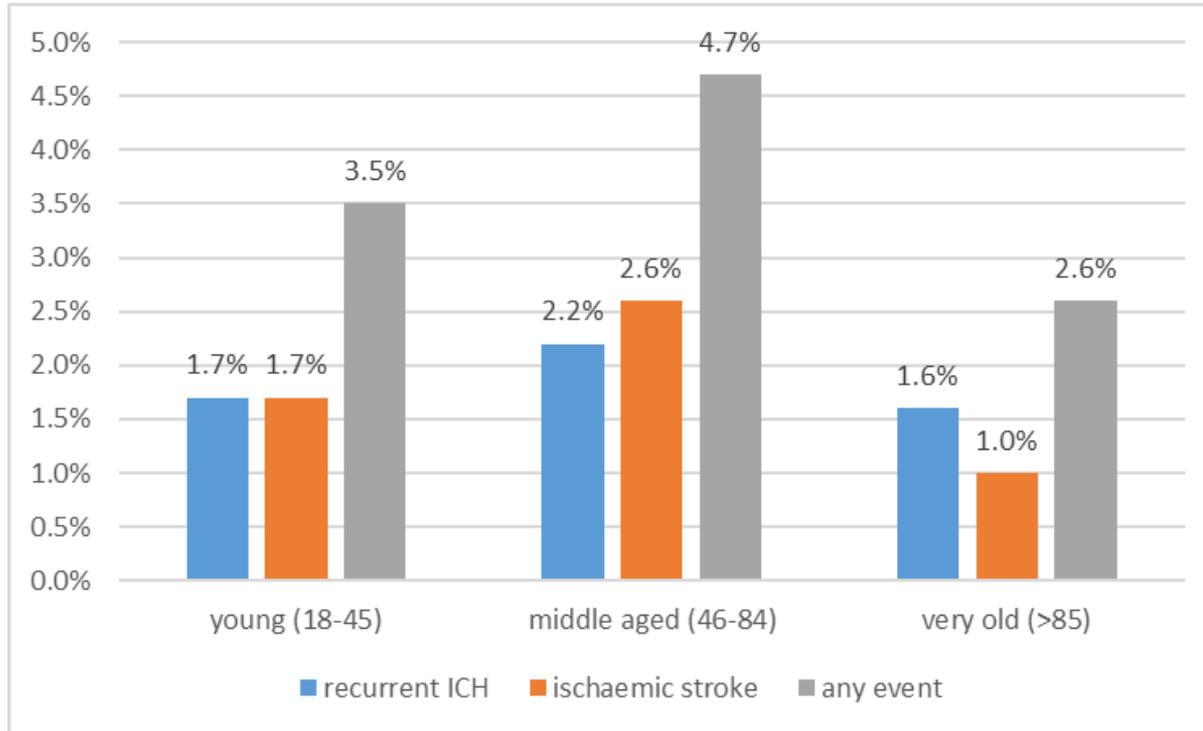
Vascular events:

Recurrent ICH
(1.3-7.4% per year)

Ischaemic stroke
(1.4-6.8% per year)

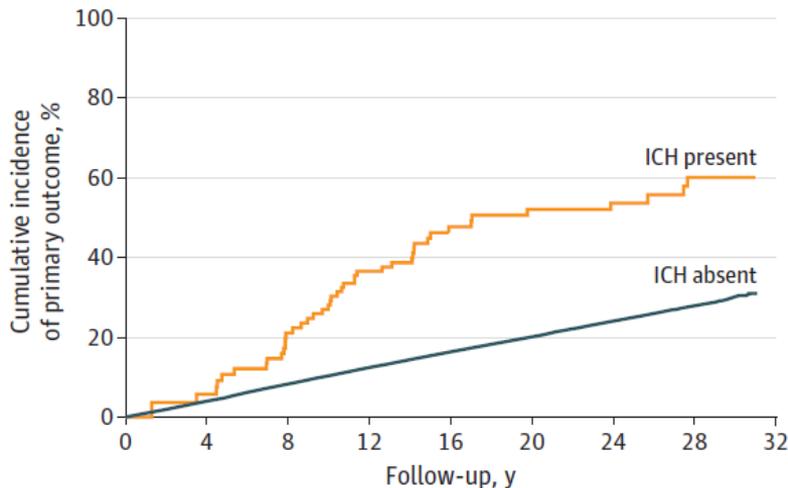
Arterial-ischaemic events
(?)

Recurrent ICH and ischaemic stroke at 3 months



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)



No. at risk	0	4	8	12	16	20	24	28	32
ICH absent	47 866	(3601)	35 407	(2353)	14 367	(1133)	8 874	(513)	0
ICH present	0	(13)	63	(23)	32	(4)	28	(3)	0

Pooled analysis of large population-based cohort studies (n=47 866)

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)

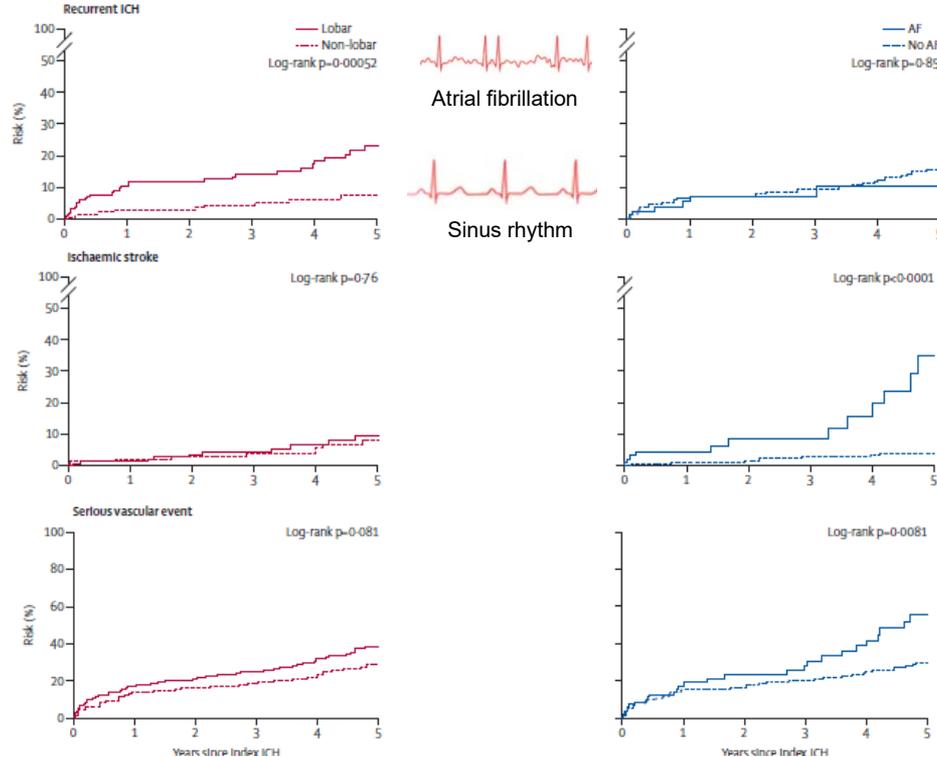
Recurrent ICH and ischaemic stroke



lobar



Non-lobar (=deep)



Risk by to haematoma location:

recurrent ICH
 (lobar 5.1% vs non-lobar 1.8 %
 HR 3.2, 95% CI 1.6–6.3)

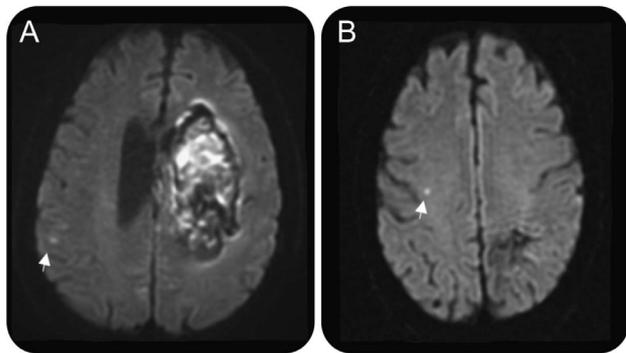
Ischaemic stroke
 No difference

Risk by atrial fibrillation:

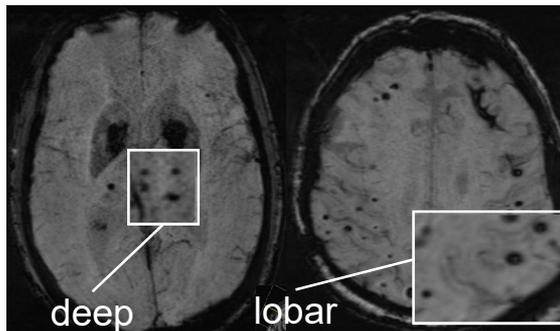
Recurrent ICH
 No difference

Ischaemic stroke:
 (AF 6.3% vs no AF 0.7%
 HR 8.2, 95% CI 3.3–20.3)

MRI guided risk assessment

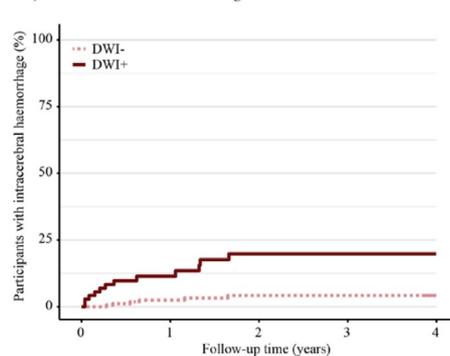


DWI lesion

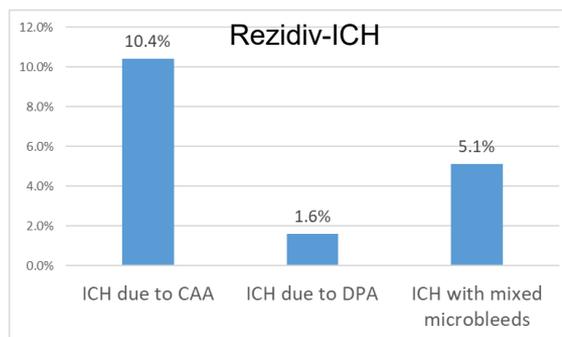
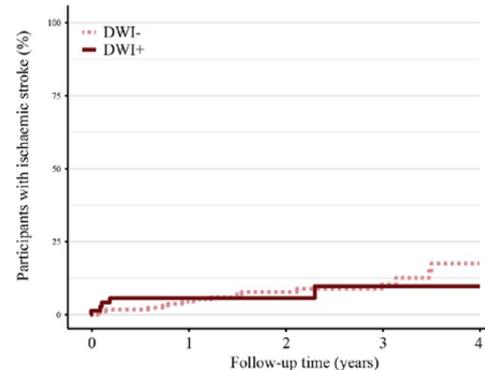


Cerebral microbleeds

B) Recurrent intracerebral haemorrhage



C) Ischaemic stroke



Long-term treatments



Blood pressure control:

target <130/90mmHg

Which medication? Target level?

Antiplatelet agents:

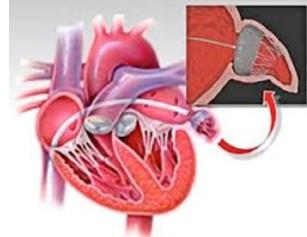
(Re-)start after ICH if valid indication (e.g. coronary heart disease, ischaemic stroke)

Timing: after 4 weeks

Atrial fibrillation:

Optimal treatment unclear

RCTs ongoing



Left atrial appendage occlusions

Trial	Notable inclusion criteria	Post-closure antithrombotic regimen	Control arm	Number of patients enrolled
PROTECT AF	No contraindication to warfarin	<ul style="list-style-type: none"> Warfarin to 45 days, then Aspirin/clopidogrel to 6 months 	Warfarin	707 patients (no patient with history of ICH)
PREVAIL	No contraindication to warfarin	<ul style="list-style-type: none"> Warfarin/aspirin to 45 days, then Aspirin/clopidogrel to 6 months, then Aspirin 325 mg/day indefinitely 	Warfarin	407 patients (no patient with history of ICH)
PRAGUE-17	Bleeding history or predisposition (~50%), cardioembolic stroke while on anticoagulation (~33%), or high CHA ₂ DS ₂ -VASc or HAS-BLED score	<ul style="list-style-type: none"> Aspirin/clopidogrel to 3 months, then Aspirin 100 mg/day indefinitely 	NOAC	404 patients (1 patient with history of ICH)

LAO: 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



Start or Stop Anticoagulants Randomised Trial



203 Patienten, Follow-up 1 Jahr, alle Antikoagulantien vs. Aspirin



PRESTIGE-AF
PREVENTION OF STROKE IN INTRACEREBRAL HAEMORRHAGE SURVIVORS WITH ATRIAL FIBRILLATION



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

A3ICH

300 Patienten, Follow-up 2 Jahre, Apixaban vs. Vorhoffloherverschluss vs Aspirin



STROKE CLOSE

700 Patienten, Follow-up 2 Jahre, alle Antikoagulantien vs. Vorhoffloherverschluss

Breacking news ESOC 2021: APACHE-AF



APACHE-AF

101 patient
enrolled

Median follow-
up: 1.9years

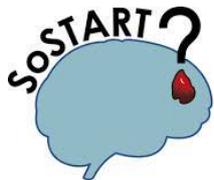
OAC: Apixaban

On-treatment analysis

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

Adjusted for a propensity score including age and ICH location

Breacking news ESOC 2021: SoSTART



Start or Stop Anticoagulants Randomised Trial

203 patient enrolled

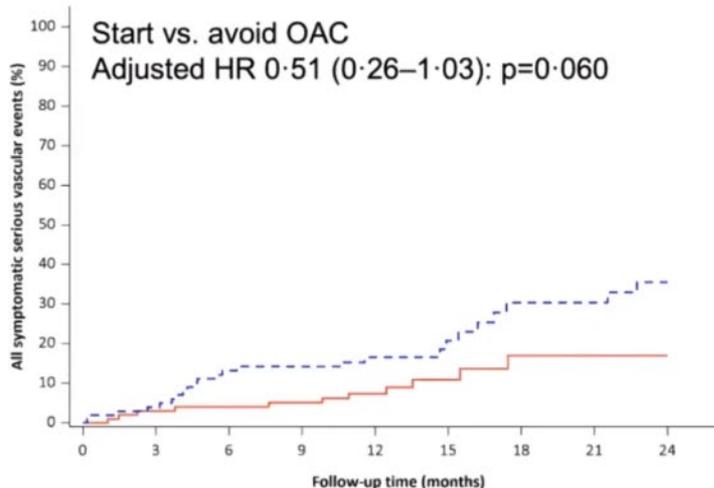
Median follow-up: 1.2years

OAC: any OAC

Secondary outcome: any symptomatic major vascular event



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



Avoid: n=24/102 (24%)

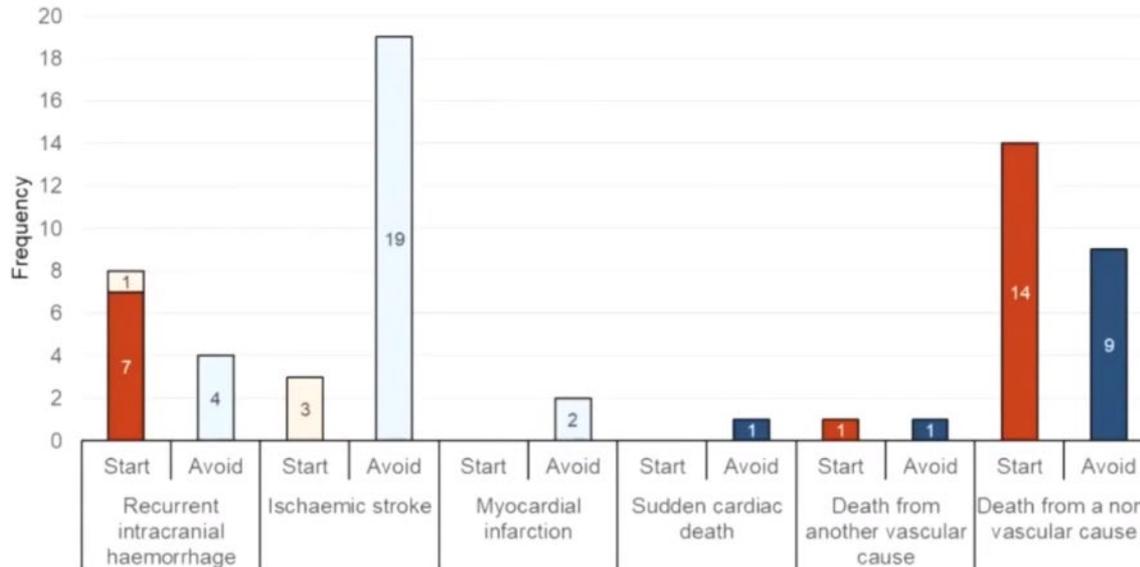
Start: n=12/101 (12%)

Patients-at-Risk (No. Cumulative Events)

	0	3	6	9	12	15	18	21	24
Start	101 (0)	94 (3)	89 (4)	87 (5)	65 (7)	34 (9)	25 (11)	24 (11)	14 (11)
Avoid	102 (0)	94 (4)	85 (13)	84 (14)	59 (16)	36 (18)	27 (22)	27 (22)	16 (24)

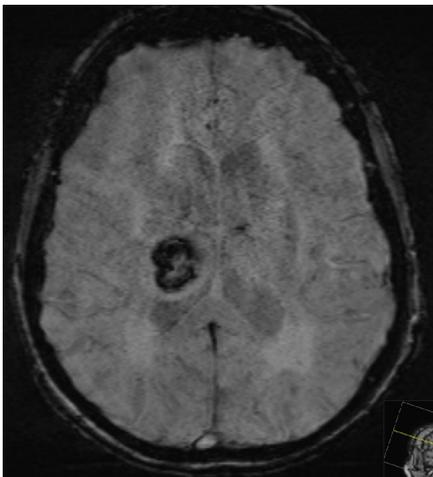
Breaking news ESOC 2021: SoSTART

Results: primary & secondary outcomes

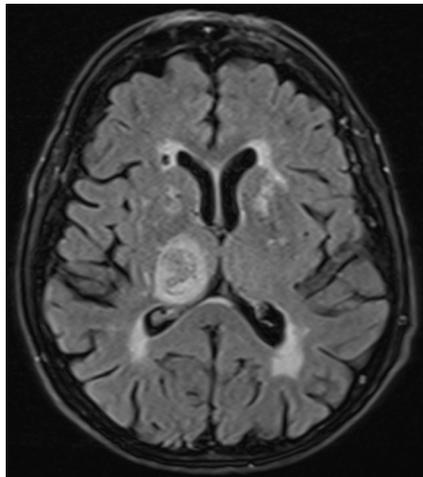




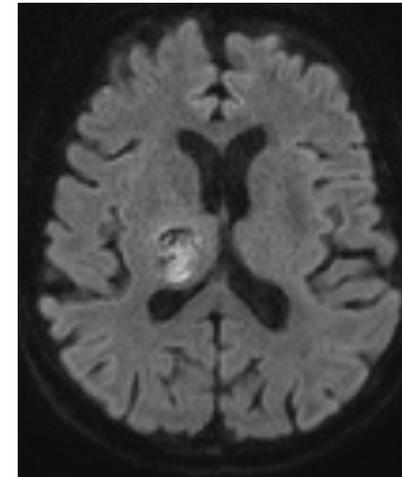
Clinical case – follow up



SWI:
No microbleeds



FLAIR:
Severe leukoencephalopathy 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!

david.seiffge@insel.ch