Difficult decision making in the management of ICH

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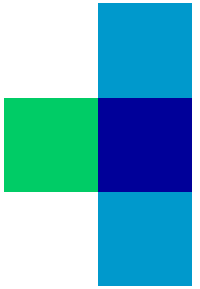
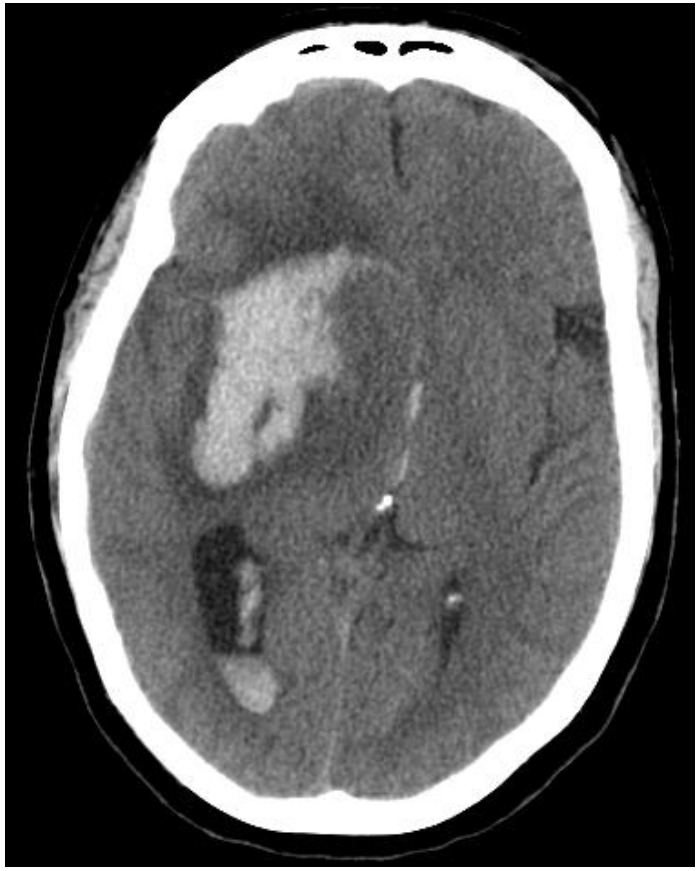
Germany



ICH - Case



55 yo construction exec

- Poorly controlled hypertension
- Slumps over table at board meeting

Arrives at ED 30 min after onset

- GCS 9
- BP 225/110

What do you do?

- Hematoma evacuation?
- Lower BP to systolic < 140 mmHg?
- ICP monitor?
- DNR? This is a bad disease and these folks never do well.

ICH - Management

No treatment (medical or surgical) proven beneficial in improving outcome (mortality or function) in randomized, controlled trial

Is this still true?

Guidelines for ICH management
(US, Europe, Japan)

Primary and Secondary Brain Injury

- 1º: tissue displacement, brain herniation, hydrocephalus
- 2º: perihematoma injury; hematoma expansion; cellular toxicity of blood products

ICH - Prognosis

Mortality

- ?á30-35% within 1 week
- ?á60% within 1 year
- ?á80% after 10 years
- No difference between

  1988 und 1998-2003

Functional Independence

?á10% after 6 months

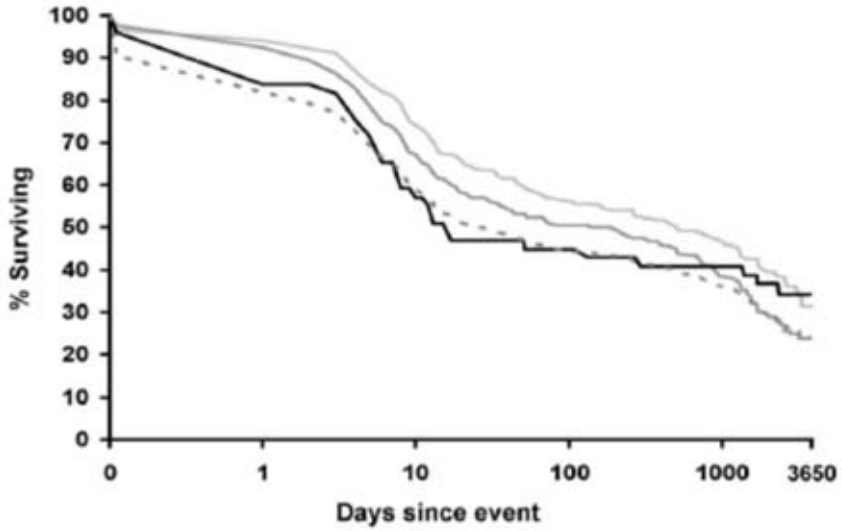


Figure. Kaplan–Meier survival curves over 10 years (logarithmic scale) in patients with deep (light grey line), lobar (dark grey line), or posterior fossa (black line) ICH (P=0.0947; log rank test). Data referring to all hemorrhages (dotted line) are given as reference and include cases of probable ICHs.

Sacco 2009 Stroke

Weimar 2003 Cerebrovasc Dis

Flaherty 2006 Neurology

Fogelholm 2005 JNNP

Broderick 1993 Stroke

Outcome Predictors – The ICH Score

Component		ICH Score Points
GCS Score	3-4	2
	5-12	1
	13-15	0
ICH Volume (cc)	≥ 30	1
	< 30	0
Intraventricular Hemorrhage	Yes	1
	No	0
Infratentorial Origin	Yes	1
	No	0
Age (years)	≥ 80	1
	< 80	0
Total ICH Score		**0 - 6**

Hemphill, *Stroke* 2001

ICH – prognostic factors

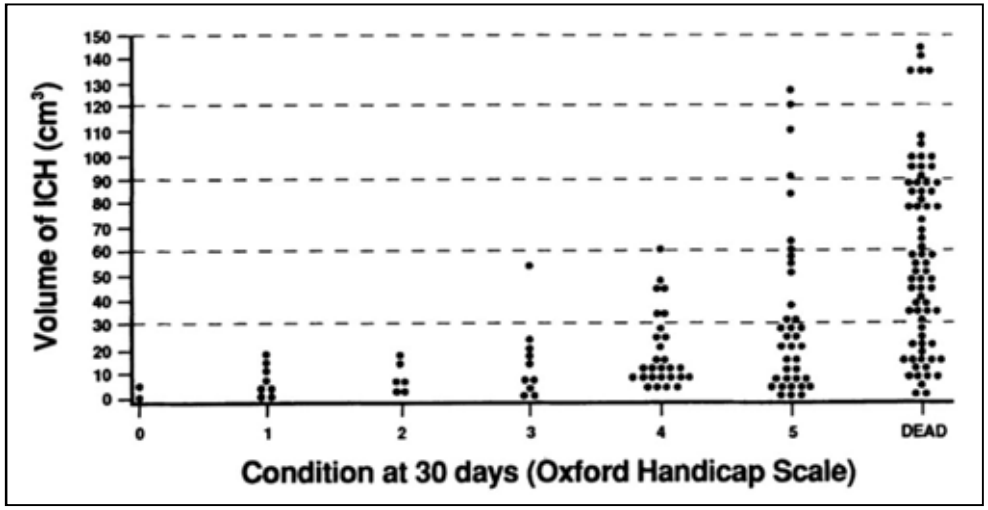
not influencable:

Initial hematoma volume

age

GCS on admission

Location of ICH



influencable:

Basic management

Hemorrhage growth / re-bleeding

Edema formation

Intraventricular clot

Hydrocephalus

Broderick 1993 Stroke

Davis 2006 Neurology

Hemphill 2001 Stroke

Tuhrim 1999 Crit Care Med

Ozdemir 2008 Neurol Res

Shapiro 1994 J Neurosurg

Diringer 1998 Stroke

Becker 2001 Neurology

Zurasky 2005 Neurology

Bhattathiri 2006 Acta Neurochir

Steiner 2006 Neurosurgery

ICH – treatment targets

Basic management

- Tracheostomy
- Prophylaxis DVT
- BP

ICH surgery

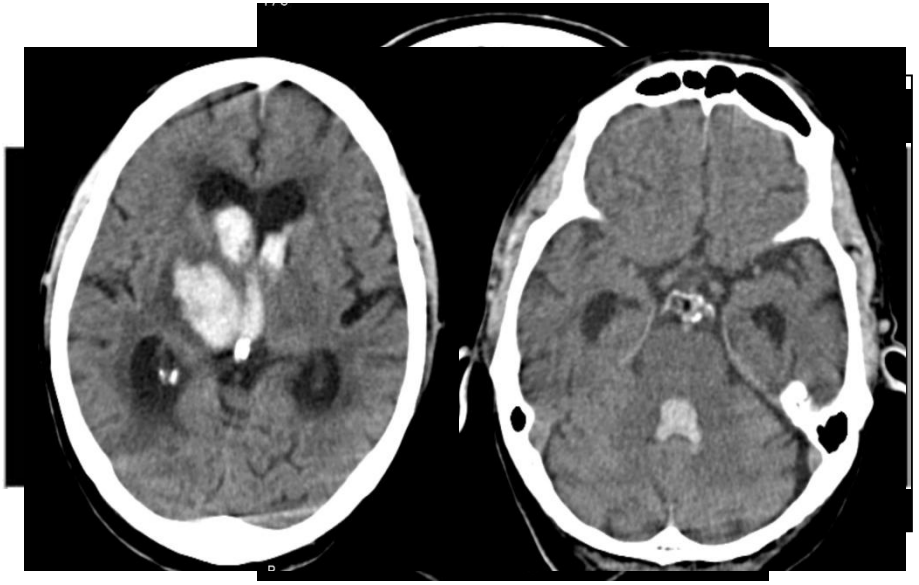
- Hematoma evacuation
- minimal invasive (MISTIE)

ICH growth

- Hemostasis
- OAT-ICH – INR normalization

Edema formation

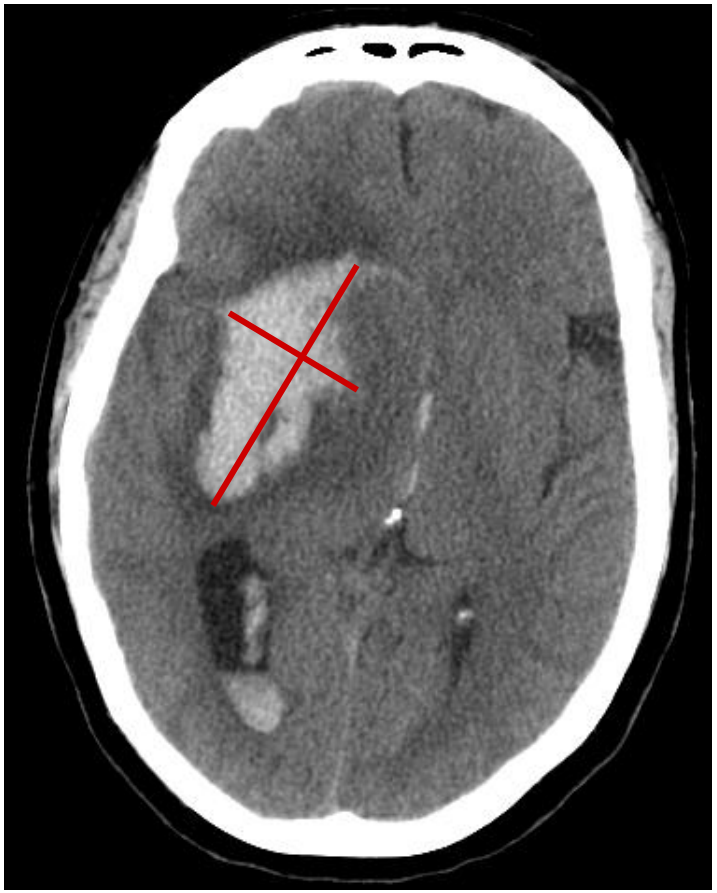
- ICP-monitoring
- Decompressive surgery
- Hypothermia



Intraventricular hemorrhage and hydrocepahlus

- Intraventricular fibrinolysis
- Lumbar drains

ICH Volume



$$\frac{A \times B \times C}{2}$$

Select CT slice with largest ICH
A = longest axis (cm)
B = longest axis perpendicular to A (cm)
C = # of slices x slice thickness (cm)

Estimated volume of spheroid
Correlates well w/ planimetric CT analysis

Clinical routine – „difficult questions“

Basic management (RR, DVT, aso)…?

Prevention of hematoma growth..?

Surgical hemorrhage evacuation…?

Management of brain edema…?

External ventricular drainage…?

Management of intraventricular hemorrhage..?

Subgroup OAC-ICH…?

Withdrawel of therapy..?

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Treatment Target – Basic Management
- blood pressure -

Prospective trials on blood pressure lowering in acute ICH

	INTERACT-2	INTERACT-1	ATACH-1
N	2794	403	60
Blood pressure threshold	BPS < 140 vs. < 180 mmHg	BPS < 140 vs. < 180 mmHg	BPS < 200, < 170, < 140 mmHg
Blood pressure difference at 1 hour after treatment	14 mmHg	13,3 mmHg	-
Primary endpoint	Death or disability at day 90	Proportional change of hematoma volume at 24 hours	Treatment feasibility and safety demonstrated
	p = 0,06	0,04	-
Secondary Endpoint	mRS: ordinal analysis at day 90	Hematoma growth at 24 hours	
	0,04	0,05	
	Mortality: no difference	Mortality: no difference	

*Systolic pressure at 1 hour: Intensive treatment group: 150 mmHg; Standard treatment group: 164 mmHg
** Systolic pressure at 1 hour: Intensive treatment group: 153 mmHg; Standard treatment group: 167 mmHg

Anderson CS et al. *N Engl J Med*. 2013;368:2355-2365
Anderson CS et al. Lancet Neurol. 2008;7:391-399
Qureshi AI at el. *Crit Care Med*. 2010;38:637-648

BP in ICH - Expert Consensus

Guidelines for the Management of Spontaneous ICH

– AHA Stroke Council, 2010

Blood Pressure

- If concern for elevated ICP
  - Maintain SBP < 180 mmHg and MAP < 130 mmHg and keep CPP 60-80 mmHg
- If no concern for elevated ICP
  - Target MAP < 110 mmHg or BP < 160/90
- Lowering systolic BP acutely to < 140 mmHg is probably safe

Arbitrary expert opinion based on recognized paucity of data and less overall concern for perihematoma ischemia

BP Lowering Trials in ICH

INTERACT – Australia/NZ, China

- Randomized open-label study
- Entry criteria - ? 2 SBP measurements (? 150 to ? 220 mm Hg)
- BP-lowering regimen < 6 h of onset
- BP Rx goals – SBP < 180 v. SBP < 140
- "Vanguard" phase completed – 404 patients, 95% in China (Lancet, 2008)
  - Possible modest effect on hematoma expansion in adjusted analysis
  - No clinical efficacy signal
  - ~2500 patient pivotal trial started in late 2008

ATACH – NIH (*CCM* 2010)

- PI – Adnan Qureshi; N=60
- "Dose-escalation" study of safety & feasibility of achieving 3 successive BP goals for 24 hours after acute ICH
- Conclusions -safe

Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

Craig S. Anderson, M.D., Ph.D., Emma Heeley, Ph.D., Yining Huang, M.D., Jiguang Wang, M.D., Christian Stapf, M.D., Candice Delcourt, M.D., Richard Lindley, M.D., Thompson Robinson, M.D., Pablo Lavados, M.D., M.P.H., Bruce Neal, M.D., Ph.D., Jun Hata, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Mark Parsons, M.D., Ph.D., Yuechun Li, M.D., Jinchao Wang, M.D., Stephane Heritier, Ph.D., Qiang Li, B.Sc., Mark Woodward, Ph.D., R. John Simes, M.D., Ph.D., Stephen M. Davis, M.D., and John Chalmers, M.D., Ph.D., for the INTERACT2 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE
Published online May 29, 2013

- Randomized 2839 subjects
- Same protocol as INTERACT
- Outcome at 90 days tested 2 ways
- Rankin scale dichotomized at 2/3
- Proportional odds analysis across entire Rankin scale
- 68% of subjects from China

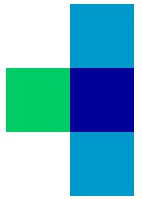


Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.*

Variable	Intensive Blood-Pressure Lowering (N=1399)	Guideline-Recommended Blood-Pressure Lowering (N=1430)	Odds Ratio (95% CI)	P Value
Primary outcome: death or major disability — no./total no. (%)†	719/1382 (52.0)	785/1412 (55.6)	0.87 (0.75–1.01)	0.06
Secondary outcomes				
Score on the modified Rankin scale — no./total no. (%)‡			0.87 (0.77–1.00)	0.04
0: No symptoms at all	112/1382 (8.1)	107/1412 (7.6)		
1: No substantive disability despite symptoms	292/1382 (21.1)	254/1412 (18.0)		
2: Slight disability	259/1382 (18.7)	266/1412 (18.8)		
3: Moderate disability requiring some help	220/1382 (15.9)	234/1412 (16.6)		
4: Moderate–severe disability requiring assistance with daily living	250/1382 (18.1)	268/1412 (19.0)		
5: Severe disability, bed-bound and incontinent	83/1382 (6.0)	113/1412 (8.0)		
6: Death by 90 days	166/1382 (12.0)	170/1412 (12.0)		
Death — no./total no. (%)	166/1394 (11.9)	170/1421 (12.0)	0.99 (0.79–1.25)	0.96

3.6%

No difference in hematoma expansion between groups

1. **So does it work?**
2. **Is it a clinically meaningful effect?**

Treatment Target – Basic Management
- DVT prophylaxis -

NOVO 7 Study: incidence of PE: 1-2%

incidence of DVT: 2% (Mayer 2005 N Engl J Med)

Boeer A, et al. **Early heparin therapy in patients with spontaneous intracerebral haemorrhage.** *J Neurol Neurosurg Psychiatry* 1991:

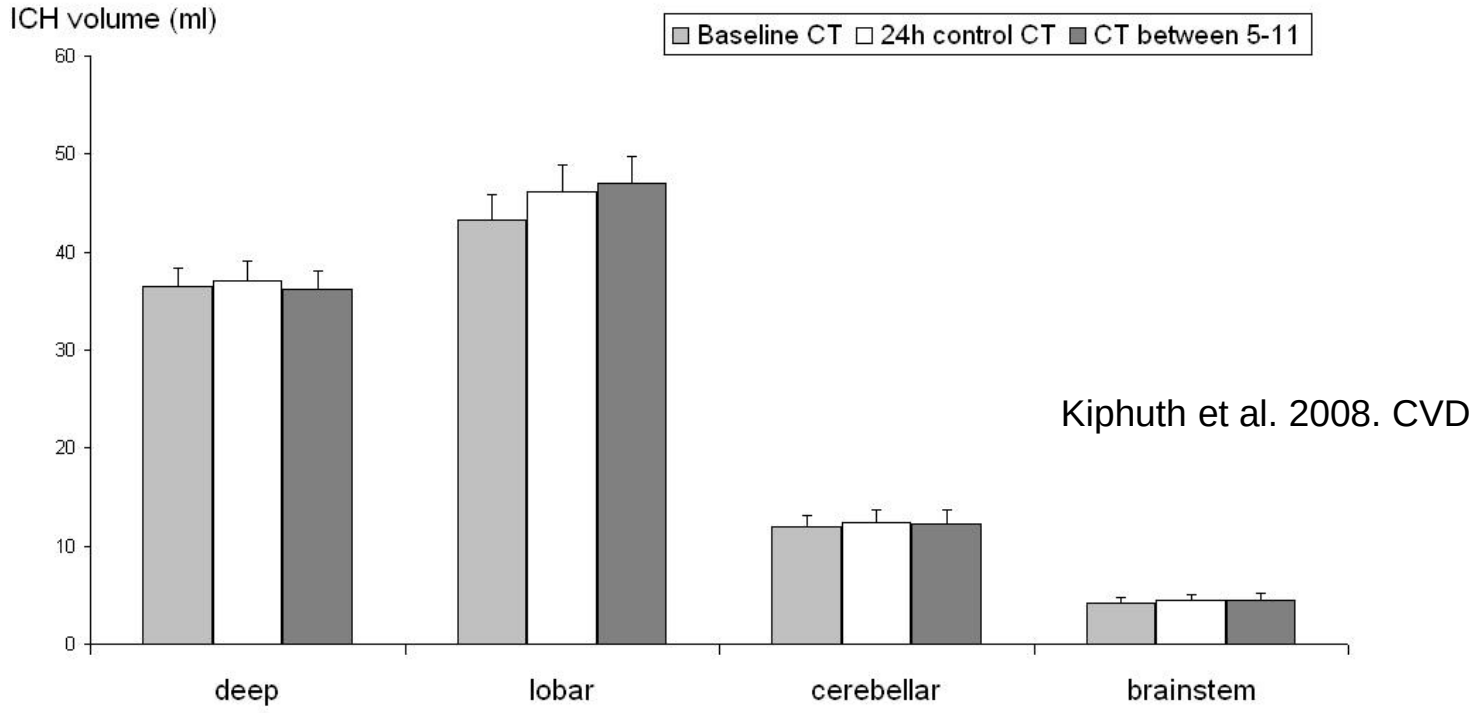
- early unfractionated heparin safe without bleeding complications

However: fear of rebleeding

Treatment Target – Basic Management
- DVT prophylaxis -

„Hemorrhage growth“:

- No „significant“: Volumen >33% in follow-up CT
- 2 „moderate“: Volumen >20% in follow-up CT



Kiphuth et al. 2008. CVD

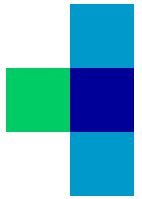
Treatment Target – Basic Management
- DVT prophylaxis -

Anticoagulation vs. alternatives

- Design: Metaanalyse
- Inclusion criteria:
  - Indication: ICH
  - RCT, non-randomized controlled trials with
  - comparison of unfractionated heparin, LWMH or heparinoids with non-anticoagulation measurements (elastic stockings, compression devices, placebo
- Outcomes:
  - Symptomatic and asymptomatic DVT,
  - Symptomatic and asymptomatic PE,
  - Any form of haemtoma* enlargement or
  - Death

any symptomatic or asymptomatic hematoma (ICH) enlargement or rebleeding

Paciaroni M et al. J Thromb Haemost 2011;9:893-898



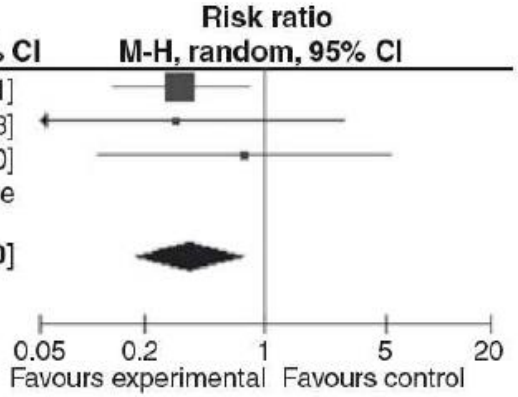
Treatment Target – Basic Management
- DVT prophylaxis -

Anticoagulation vs. alternatives

Outcome:
Symptomatic und asymptomatic pulmonary embolism

Study or subgroup	Heparin Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Boeer	6	47	9	23	72.4%	0.33 [0.13, 0.81]
Orken	1	39	3	36	12.0%	0.31 [0.03, 2.83]
Tetri	2	232	2	175	15.6%	0.75 [0.11, 5.30]
Wasay	0	200	0	248		Not estimable
Total (95% CI)		**518**		**482**	**100.0%**	**0.37 [0.17, 0.80]**
Total events	9		14			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.62$, df = 2 ($P = 0.73$); $I^2 = 0\%$
Test for overall effect: $Z = 2.54$ ($P = 0.01$)



Paciaroni M et al. J Thromb Haemost 2011;9:893-898

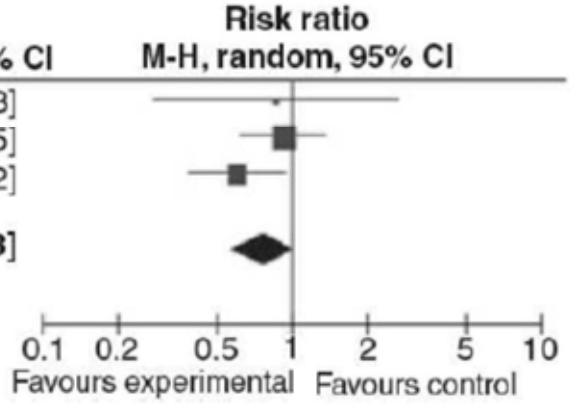
Treatment Target – Basic Management
- DVT prophylaxis -

Anticoagulation vs. alternatives

Outcome: mortality

Study or subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk ratio M-H, random, 95% CI
Boeer	7	47	4	23	6.8%	0.86 [0.28, 2.63]
Tetri	45	232	37	175	51.7%	0.92 [0.62, 1.35]
Wasay	25	200	52	248	41.4%	0.60 [0.38, 0.92]
Total (95% CI)		**479**		**446**	**100.0%**	**0.76 [0.57, 1.03]**
Total events	77		93			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.13$, df = 2 ($P = 0.35$); $I^2 = 6\%$
Test for overall effect: $Z = 1.79$ ($P = 0.07$)



Clinical routine – „difficult questions“

Basic management (RR, DVT, aso)…?

Prevention of hematoma growth..?

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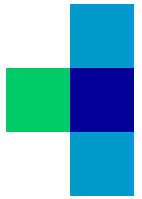
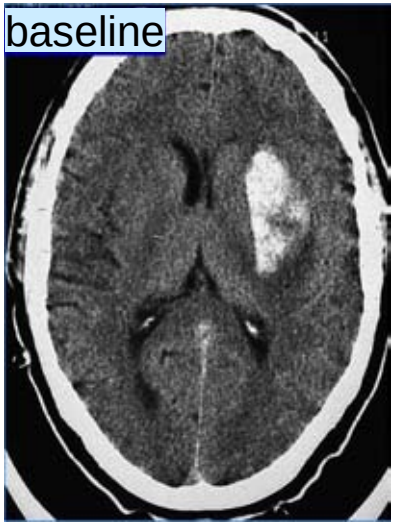
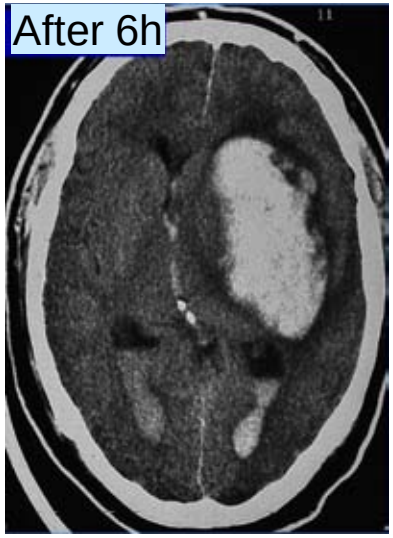


Treatment Target - „hemorrhage growth“





Time window until CT	Brott ´97 n=103	Fujii ´94 n=627	Fujitsu´90 n=107	Kazui ´96 n=204	TOTAL
0-3h	26%	18%	NA	36%	24%
3-6h	NA	8%	NA	16%	11%
0-6h	NA	17%	21%	29%	19%
6-24h	12%	2%	NA	10%	5%

Hematoma Expansion in ICH

Previously suggested as

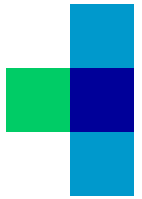
- rare
- suggestive of underlying AVM, coagulopathy

Studies of early serial CT show as common

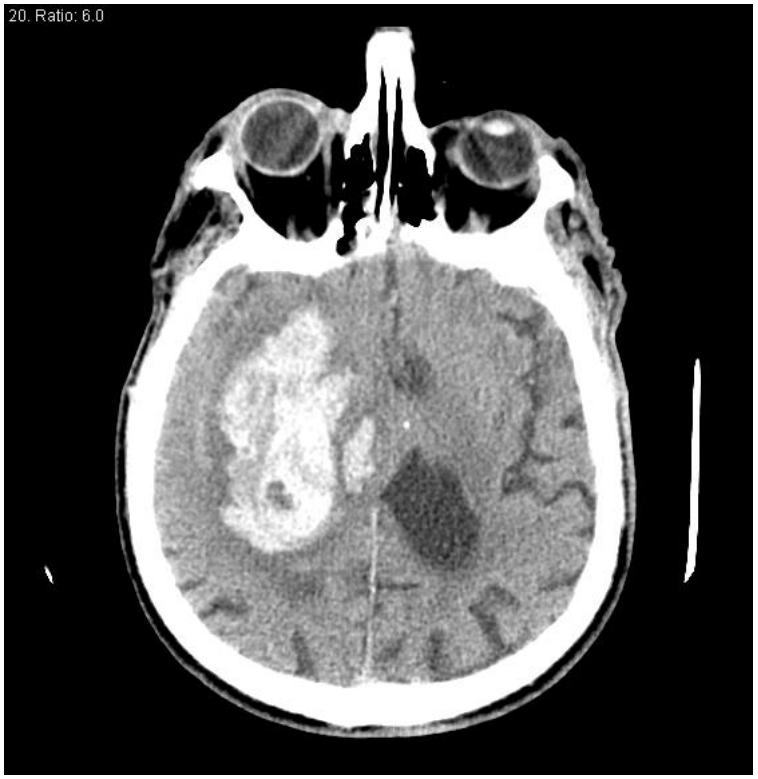
- 72% of patients have some hematoma expansion over initial 24 hrs
- 38% have significant (>33%) expansion over 24 hrs, usually clinically significant
  - w/in 1 hr in 26% of cases

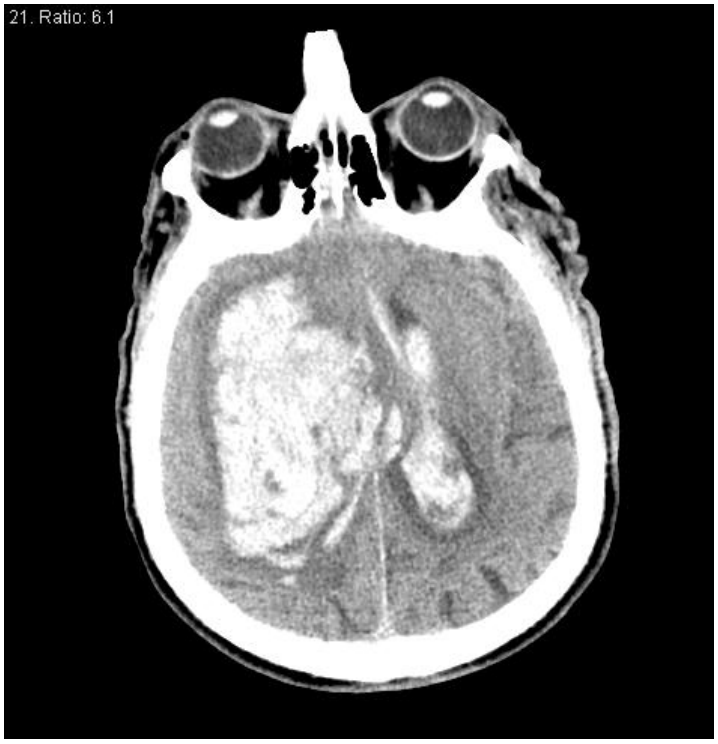
Hematoma expansion worsens outcome

Davis et al. *Neurology* 2006
Brott et al. *Stroke* 1997



Hematoma Expansion in ICH





Hematoma Expansion in ICH

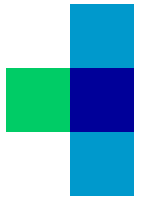
Characteristics

- occurs mostly w/in 24 hours (esp. 6 hours) from onset
- usually associated with clinical deterioration

Mechanism?

- Associated with elevated BP?
  - interaction of elevated glucose (or Hgb A_{1C}) and systolic blood pressure on admission $\geq$ 200 mm Hg (Kazui 1998)
  - Lack of association b/t hemodynamic factors and ICH hematoma growth (Jauch, *Stroke* 2006)
- Perihematoma coagulopathy/DIC?

Is this a target for intervention?



Hemostatic Agents

FAST - Phase III Trial of rFVIIa in acute ICH

ICH patients

- Without coagulopathy
- CT scan w/in 3 hours
- Rx w/in 1 hour of CT scan
- 841 patients randomized; 821 patients dosed

F/U of phase IIb trial that showed

- Decreased hematoma expansion
- Lower mortality and better functional outcome
- Modest increase in thrombotic events

First large ICH medical trial ever conducted

Protocol similar to phase IIb trial

rFVIIa 80 µg/kg vs 20 µg/kg vs placebo

FAST: Primary Results

Hematoma Growth at 24 hrs	Placebo	20 ?g/kg	80 ?g/kg	P
Mean % change	26%	18%	11%	<0.001 (80 ?g/kg vs placebo)
Absolute difference	7.8 ± 18.7	4.7 ± 14.8	3.8 ± 15.3	0.009 (80 ?g/kg vs placebo)
Modified Rankin Score ≥ 5 at 90 days	24%	26%	29%	NS
Mortality	19%	18%	21%	NS
Arterial Thrombotic Events	4%	5%	8%	0.04
Cerebral Infarction	1%	1%	3%	0.14

Reduces hematoma expansion

No effect on clinical outcome

Increase in arterial thrombotic events

Treatment Target - „hemorrhage growth“

rFVIIa: is there a chance?

Stroke

Can a Subset of Intracerebral Hemorrhage Patients Benefit From Hemostatic Therapy With Recombinant Activated Factor VII?

Stephan A. Mayer, MD; Stephen M. Davis, MD; Brett E. Skolnick, PhD; Nikolai C. [illegible]
Kamilla Begtrup, MSc; Joseph P. Broderick, MD; Michael N. Diringer, M[illegible]

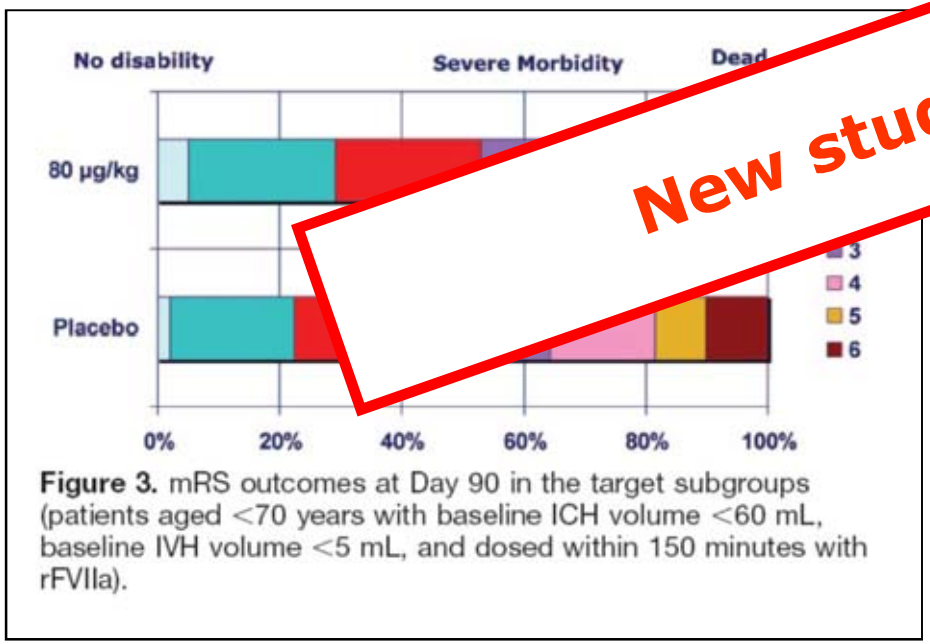


Figure 3. mRS outcomes at Day 90 in the target subgroups (patients aged <70 years with baseline ICH volume <60 mL, baseline IVH volume <5 mL, and dosed within 150 minutes with rFVIIa).

New study upcoming?

- [illegible]noc
- § age <70a
- § ICH volume <60ml
- § IVH volume <5ml
- § Treatment within 150min

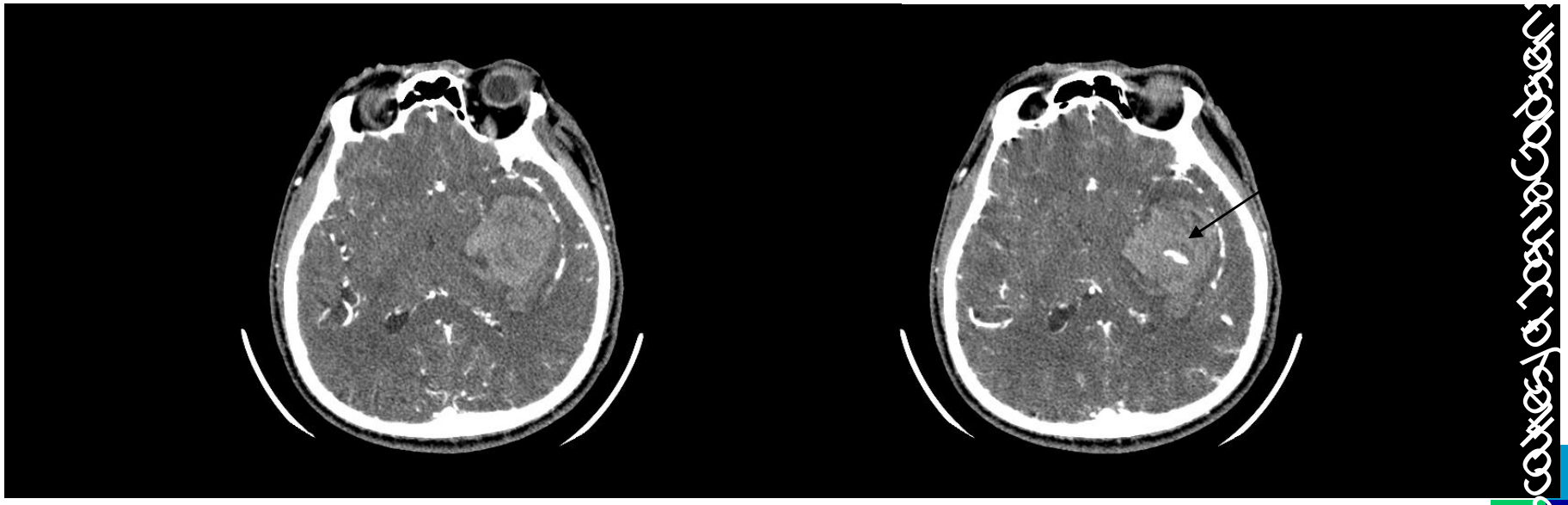
Mayer 2009 Stroke

CT “spot sign”

Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage

J.N. Goldstein, MD, PhD; L.E. Fazen, BA; R. Snider, BA; K. Schwab, BA; S.M. Greenberg, MD, PhD; E.E. Smith, MD; M.H. Lev, MD; and J. Rosand, MD, MS

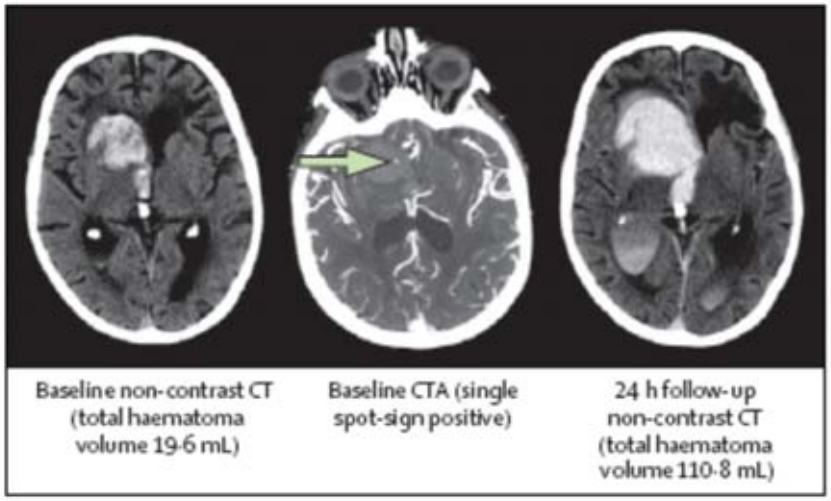
NEUROLOGY 2007;68:889–894



Treatment Target - „hemorrhage growth“

Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study

Andrew M Demchuk, Dar Dowlatshahi, David Rodriguez-Luna, Carlos A Molina, Yolanda Silva Blas, Imanuel Dzialowski, Adam Kobayashi, Jean-Martin Boulanger, Cheemun Lum, Gord Gubitz, Vasantha Padma, Jayanta Roy, Carlos S Kase, Jayme Kosior, Rohit Bhatia, Sarah Tymchuk, Suresh Subramaniam, David J Gladstone, Michael D Hill, Richard I Aviv, for the PREDICT/Sunnybrook ICH CTA study group



Baseline non-contrast CT (total haematoma volume 19·6 mL) | Baseline CTA (single spot-sign positive) | 24 h follow-up non-contrast CT (total haematoma volume 110·8 mL)

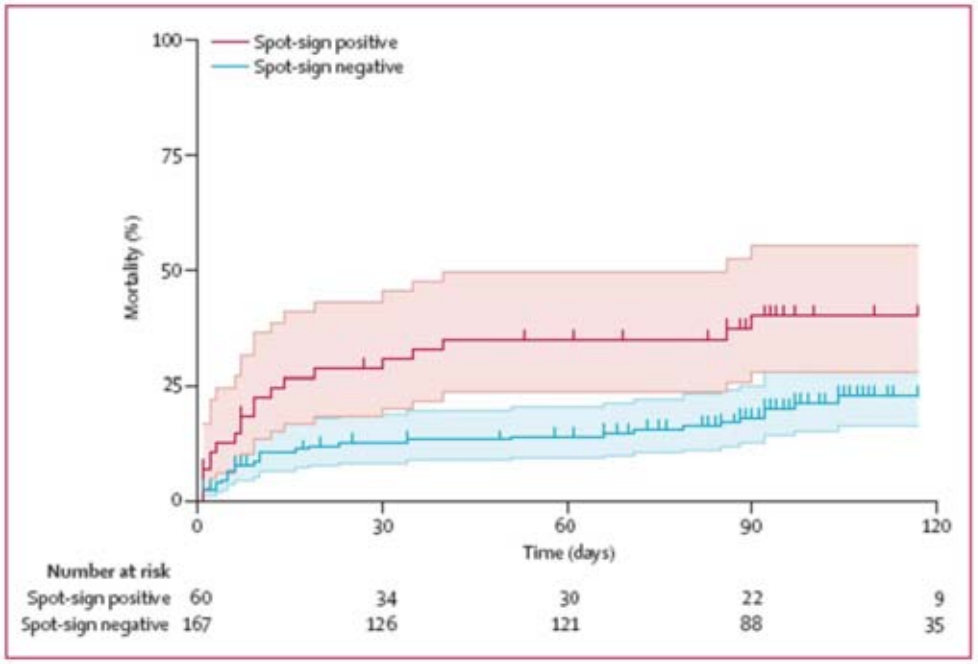


Figure 2: **Risk of death by CTA spot-sign status**
Log-rank test p=0·0006. Shaded areas represent 95% confidence intervals.

Lancet Neurol 2012

Clinical routine – „difficult questions“

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Management of brain edema…?

External ventricular drainage…?

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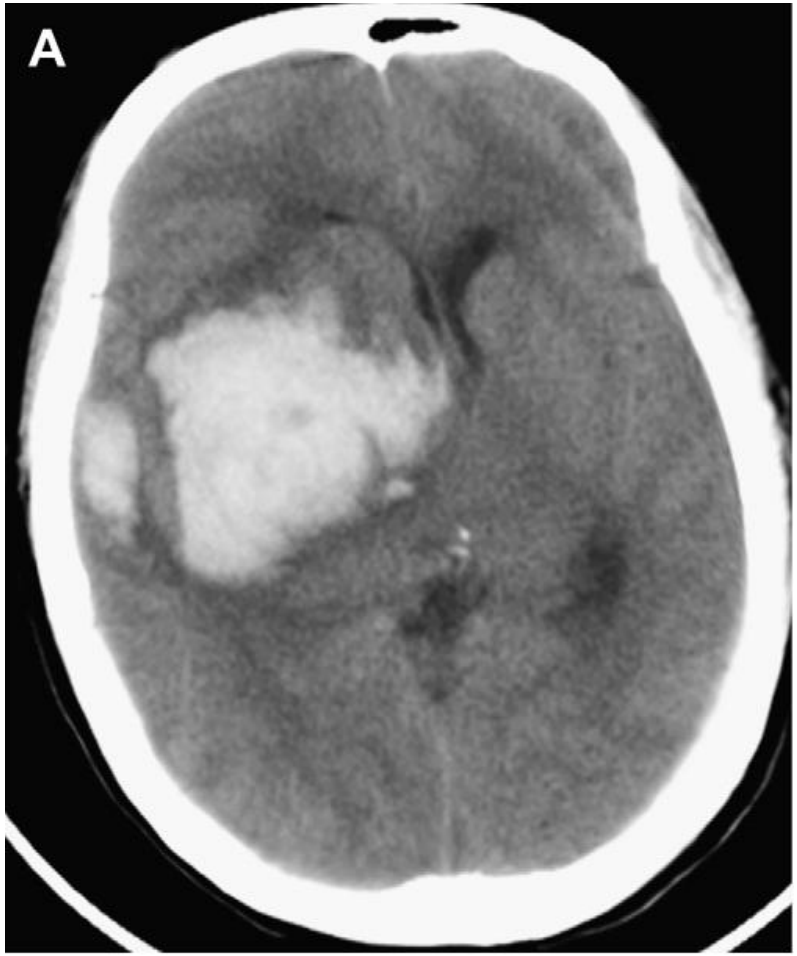
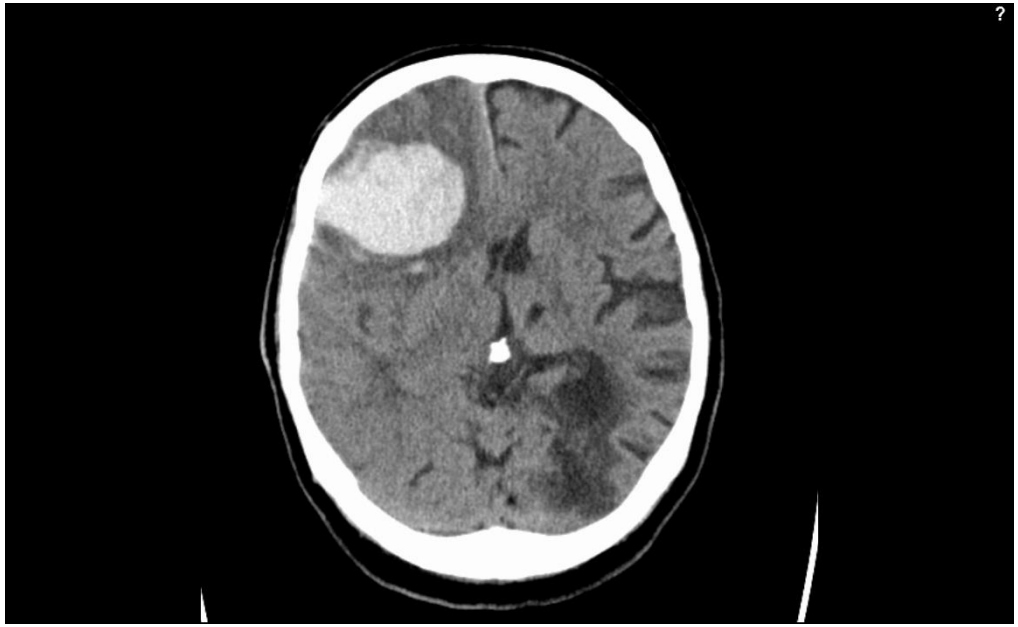
Subgroup OAC-ICH…?

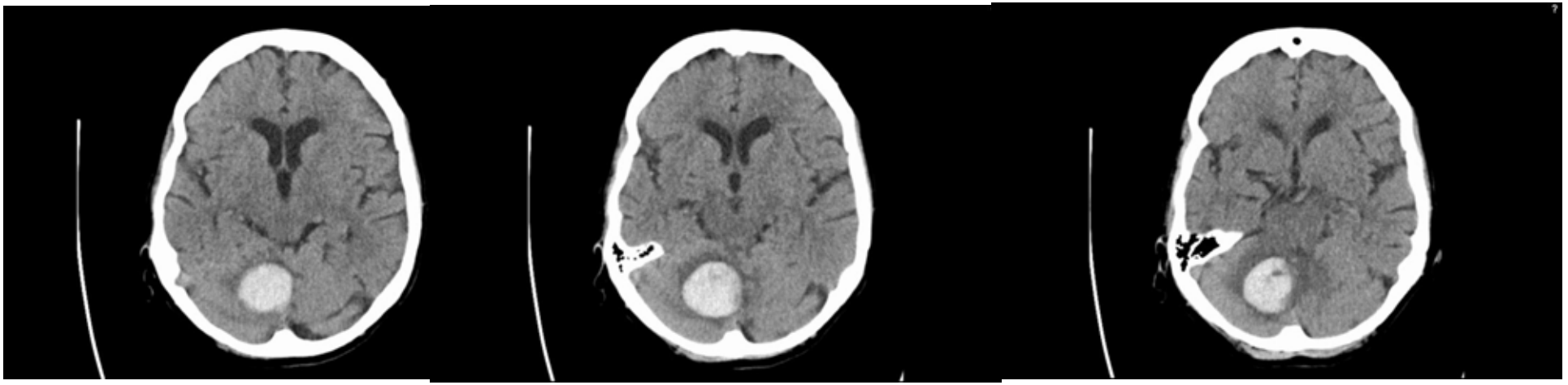
Withdrawel of therapy..?

ICH surgery





ICH surgery



Surgical Trial for ICH (STICH)

Completed in 2003

Largest study of surgery in ICH (>1000 pts)

Does a policy of “Early Surgery” improve outcome in patients with spontaneous supratentorial ICH compared with a policy of “Initial Conservative Treatment”?

- Randomisation within 72 hours of ictus
- Surgery within 24 hours of randomisation
- Selection based on “uncertainty principle”

ICH surgery

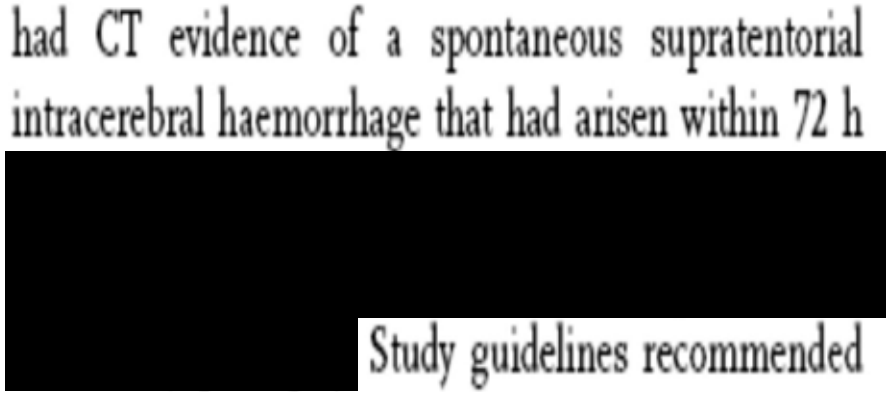
STICH (Surgical Trial in Intracerebral Hemorrhage)

Supratentorial ICH (n=1033)

Therapy within 72h

early Operation vs. konservative

„Uncertainty“ principle


had CT evidence of a spontaneous supratentorial intracerebral haemorrhage that had arisen within 72 h

Study guidelines recommended

Mendelow 2005 Lancet

ICH surgery

STICH (Surgical Trial in Intracerebral Hemorrhage)

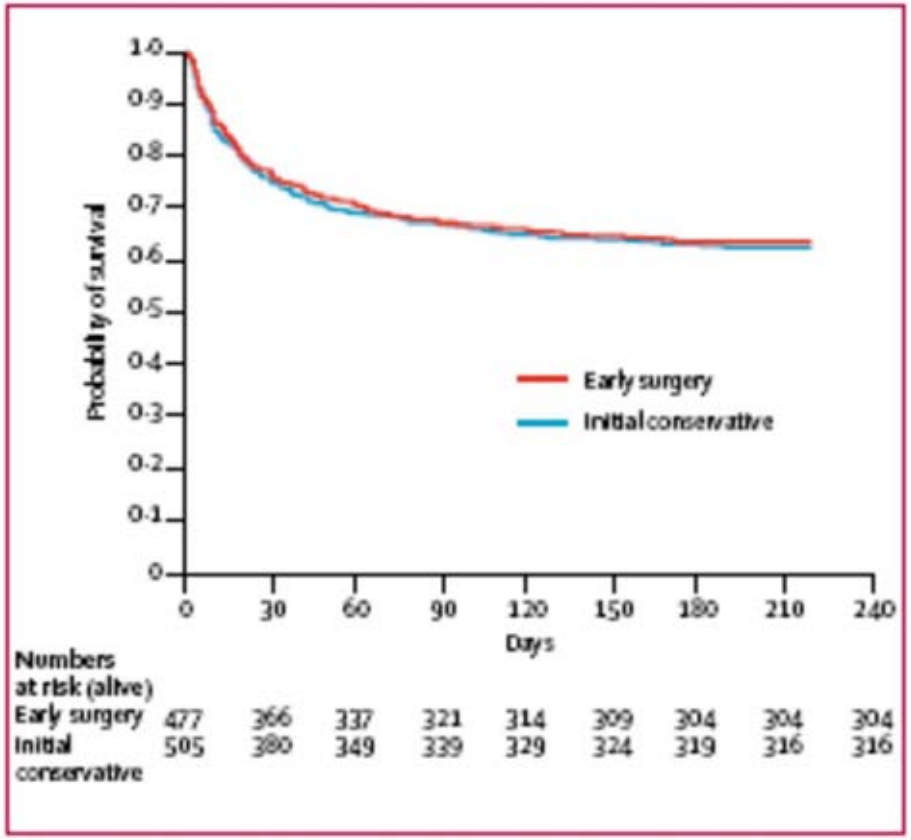


Figure 2: Kaplan-Meier survival curves

Mendelow 2005 Lancet

Surgical Trial for ICH (STICH)

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STICH - Results

Mortality	Early Surgery	Initial Conservative tx
Alive	304 (64%)	316 (63%)
Dead	173 (36%)	189 (37%)

Primary Outcome ("Prognosis based" functional outcome)	Early Surgery	Initial Conservative tx
Favourable	112 (26%)	118 (24%)
Unfavourable	346 (74%)	351 (76%)

- No Difference
- 26% of patients randomised to Initial Conservative Treatment later had surgery
- Early surgery is not harmful
- There is no evidence favoring early surgery in supratentorial ICH

ICH surgery

STICH – **Subgroup-Analysis**

Study or subcategory	Early surgery n/N	Initial conservative treatment n/N	Odds ratio (fixed) 95% CI	Odds ratio (fixed) 95% CI
Age				
<65	182/262	204/284		0·89 (0·62–1·29)
≥65	164/206	174/212		0·85 (0·52–1·39)
GCS				
5–8	80/88	83/99		1·93 (0·78–4·75)
9–12	140/187	158/196		0·72 (0·44–1·16)
13–15	126/193	137/201		0·88 (0·58–1·34)
Side of haematoma				
Left hemisphere	186/246	208/265		0·85 (0·56–1·28)
Right hemisphere	160/222	170/231		0·93 (0·61–1·40)
Site of haematoma				
Lobar	107/181	130/194		0·71 (0·47–1·08)
Basal ganglia/thalamus	236/284	247/300		1·05 (0·69–1·62)
Haematoma volume				
≤50 mL	211/302	238/323		0·83 (0·58–1·17)
>50 mL	135/166	140/173		1·03 (0·60–1·77)
Depth from cortical surface				
≤1 cm	170/257	192/260		0·69 (0·47–1·01)
>1 cm	174/208	184/234		1·39 (0·86–2·25)

Mendelow 2005 Lancet

Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial

A David Mendelow, Barbara A Gregson, Elise N Rowan, Gordon D Murray, Anil Gholkar, Patrick M Mitchell, for the STICH II Investigators

- Lobar ICH within 1 cm of cortical surface
- Hematoma volume 10-100 cc
- Randomized within 48 hours of onset
- Best motor score on GCS of ≥ 5
- Conscious
- No intraventricular hemorrhage

- Randomly assigned to surgery within 12 hours or not
- 6 month GOSE
- "Prognosis-based" outcome
- Enrolled ~5% of patients screened
- 21% of non-surgical group received delayed surgery

ICH surgery

STICH II

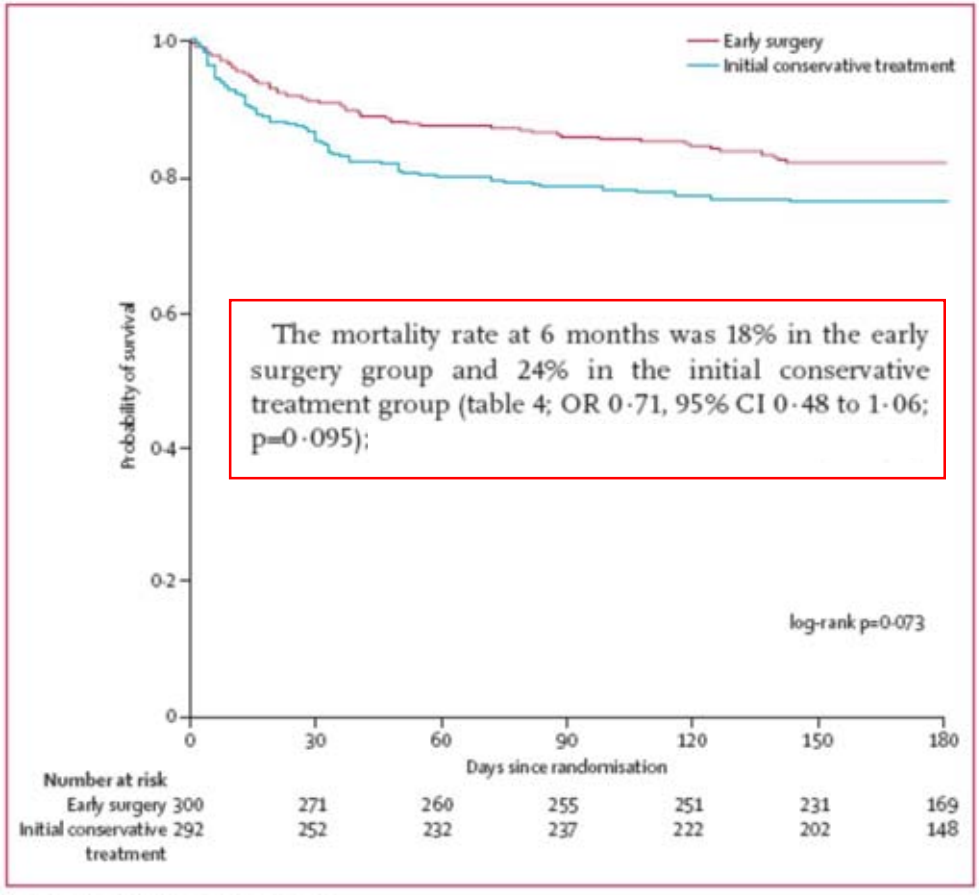


Figure 2: Kaplan–Meier survival curve

1) Overall, no evidence for surgery in lobar ICH without IVH
2) Maybe advantages in survival for those patients with poor prognosis

STICH II versus STICH I...

Trend for reduced mortality

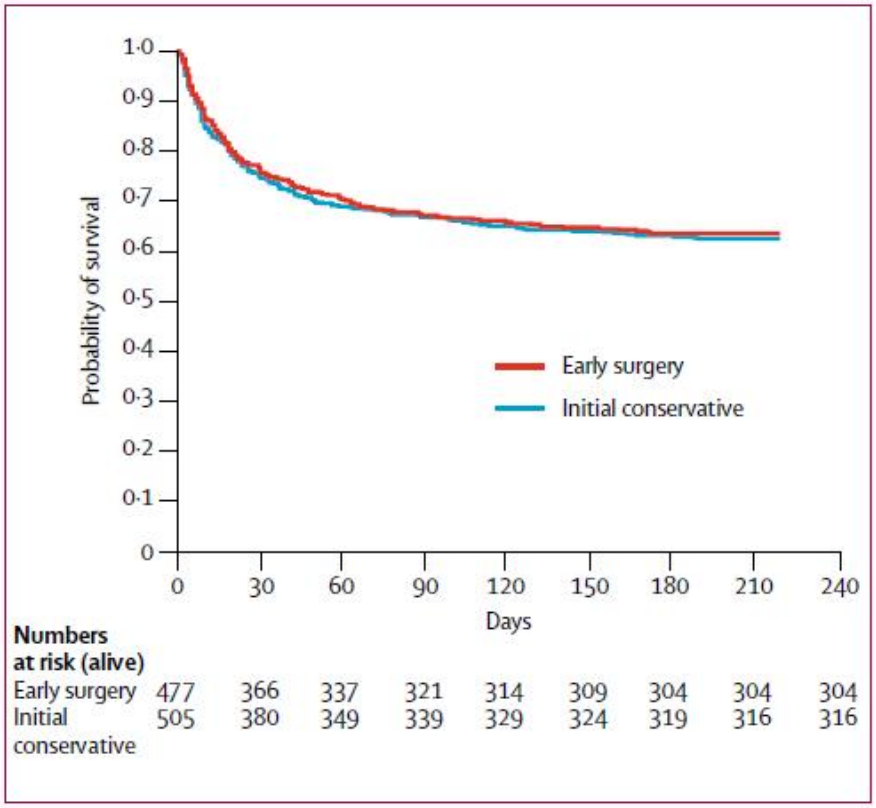


Figure 2: Kaplan-Meier survival curves

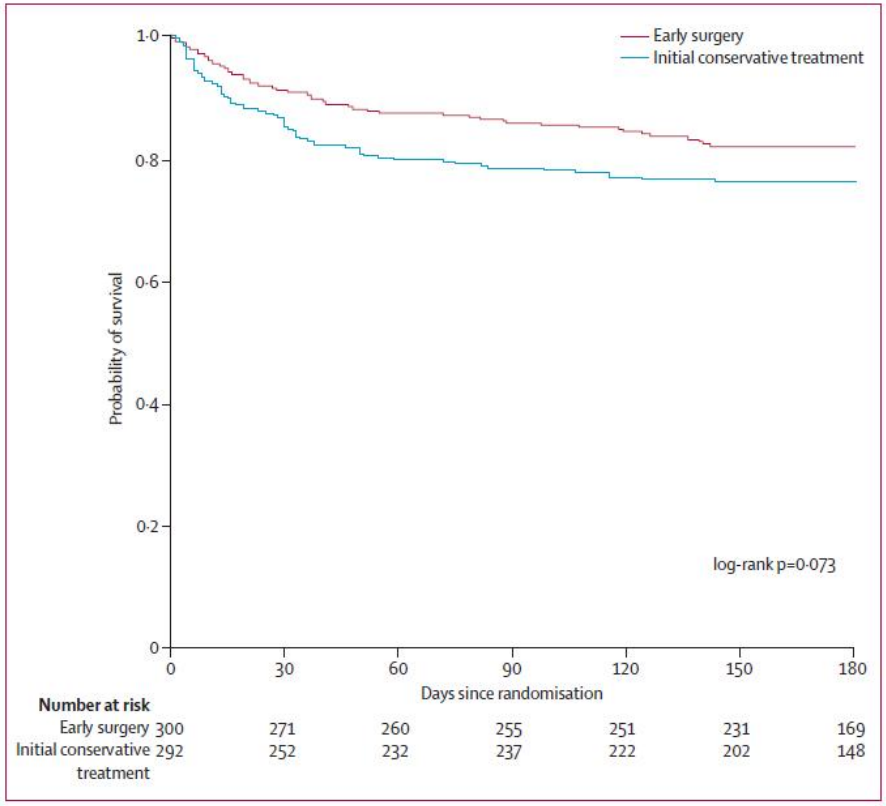


Figure 2: Kaplan–Meier survival curve

ICH surgery

SUPRATENTORIAL

No evidence and no general recommendation for surgery

INFRATENTORIAL

- cerebellar ICH >2-3 cm,
- Clinical worsening or imminent brain stem compression with hydrocephalus
- If surgery, probably the earlier the better

MISTIE

Minimally invasive surgery plus recombinant t-PA for intracerebral hemorrhage evacuation (Mould *Stroke* 2013) (n=118)

Dose-ranging and safety study for image-guided catheter placement with subsequent t-PA instillation and clot aspiration

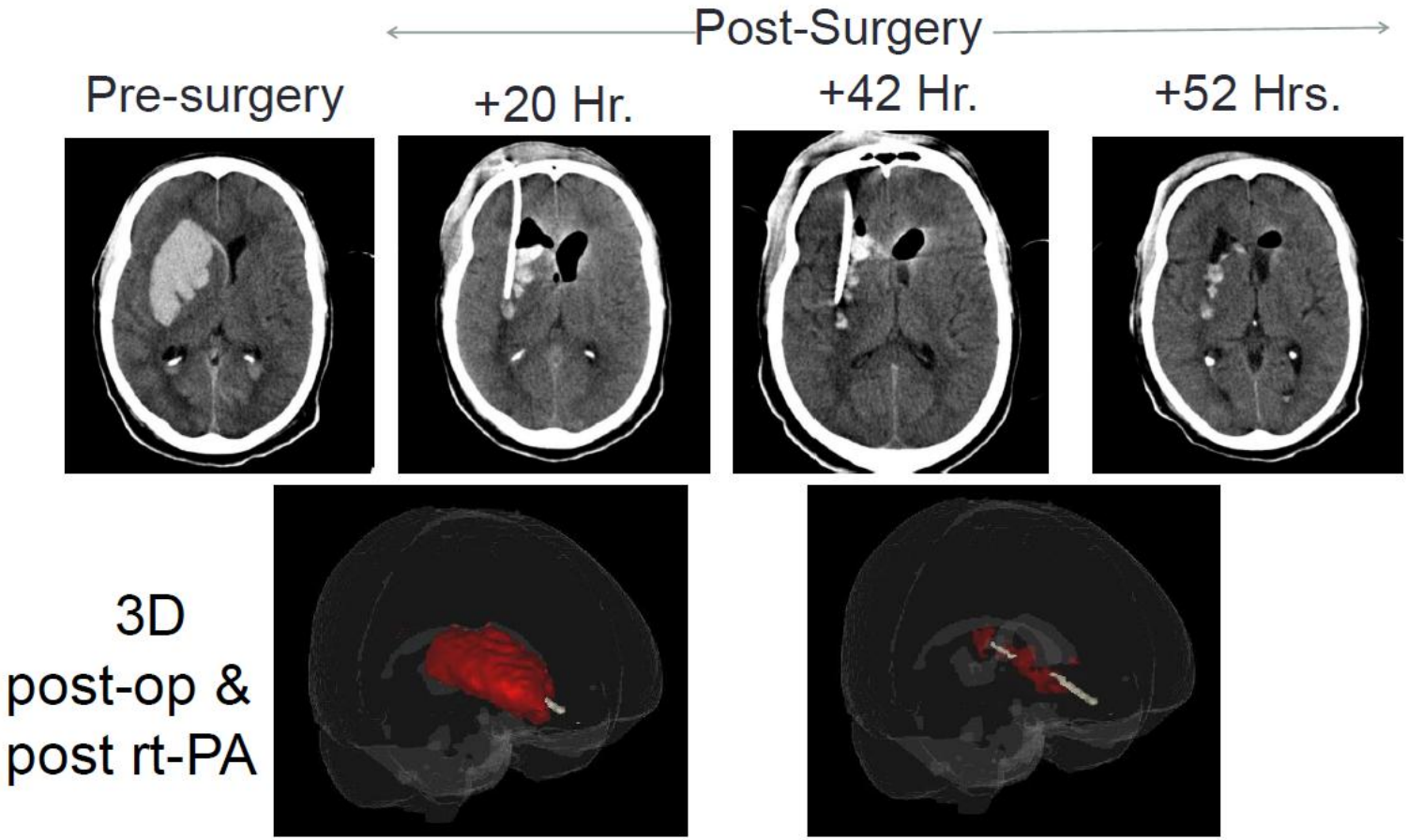
ICES group – endoscopic hematoma removal

Hematoma removal associated with decreased peri-hematomal edema

MISTIE phase 3 trial proposed and under review at NIH

ICH surgery – minimal invasive

Surgical Intervention



ICH surgery – minimal invasive

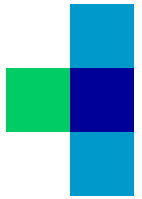
Key I/E Criteria

Exclusion

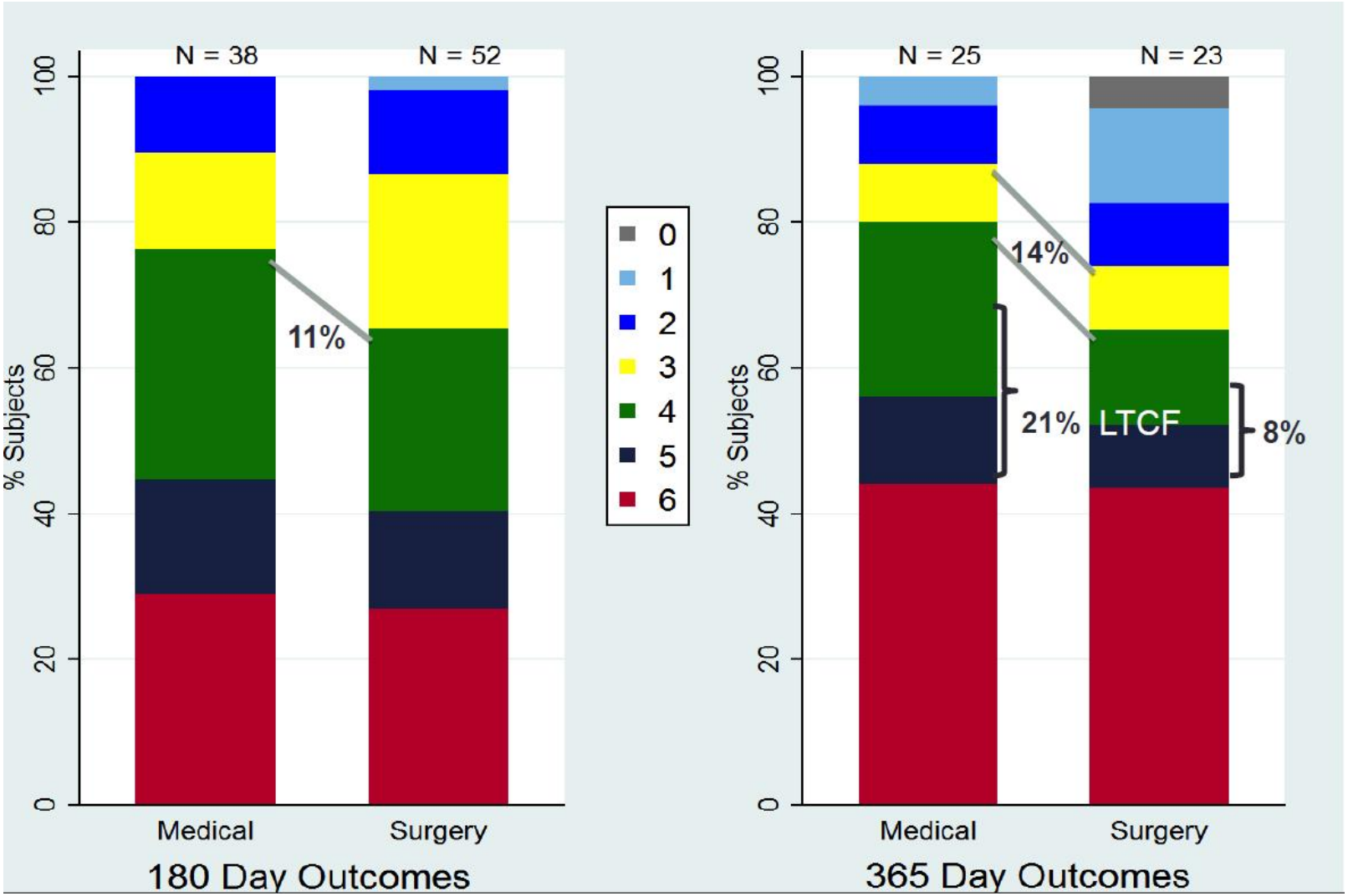
- Infratentorial ICH
- Vascular malformation or brain tumor
- Irreversibly impaired brainstem function

Inclusion

- Age 18-75
- GCS ≤ 13 or NIHSS ≥ 6
- Spontaneous supratentorial ICH ≥ 20cc
- Stable clot at second CT scan performed ≥ 6 hours after diagnosis



ICH surgery – minimal invasive



ICH surgery
- conclusion and recommendations -

For most patients with ICH, the usefulness of surgery is uncertain	Class IIb, Level of Evidence New Recommendation
Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible	Class I, Level of Evidence B Revised recommendation
Initial treatment of these cerebellar hemorrhage patients with ventricular drainage alone rather than surgical evacuation is not recommended	Class III, Level of Evidence C). New Recommendation
For patients presenting with lobar clots >30 cc and within 1 cm of the surface, evacuation of supratentorial ICH by standard craniotomy might be considered	Class IIb, Level of Evidence B Updated recommendation
The effectiveness of minimally invasive clot evacuation utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is uncertain and is considered investigational	Class IIb, Level of Evidence B New Recommendation
While theoretically attractive, no clear evidence at present indicates that ultra-early removal of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding	Class III, Level of Evidence B Revised from the previous guideline

Clinical routine – „difficult questions“

Basic management (RR, DVT, aso)…?

Prevention of hematoma growth..?

Surgical hemorrhage evacuation…?

External ventricular drainage…?

Management of brain edema…?

Management of intraventricular hemorrhage..?

Subgroup OAC-ICH…?

Withdrawel of therapy..?

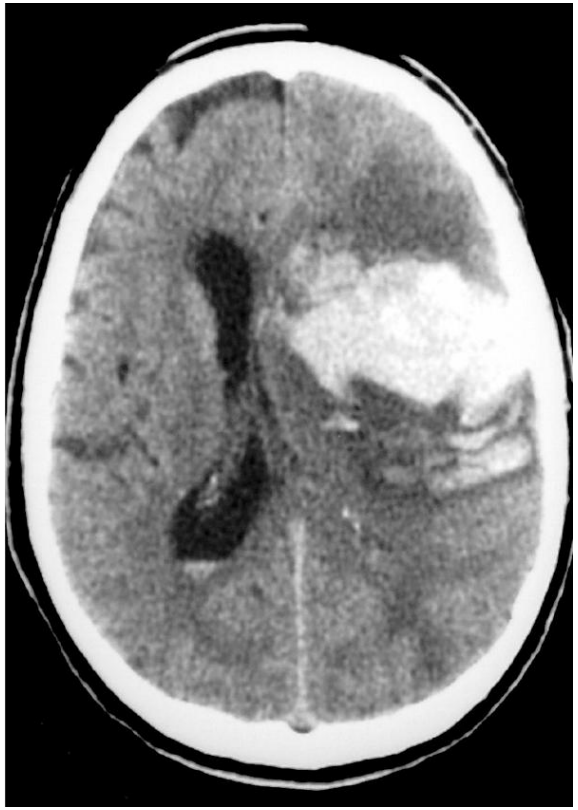
External ventricular drainage..?

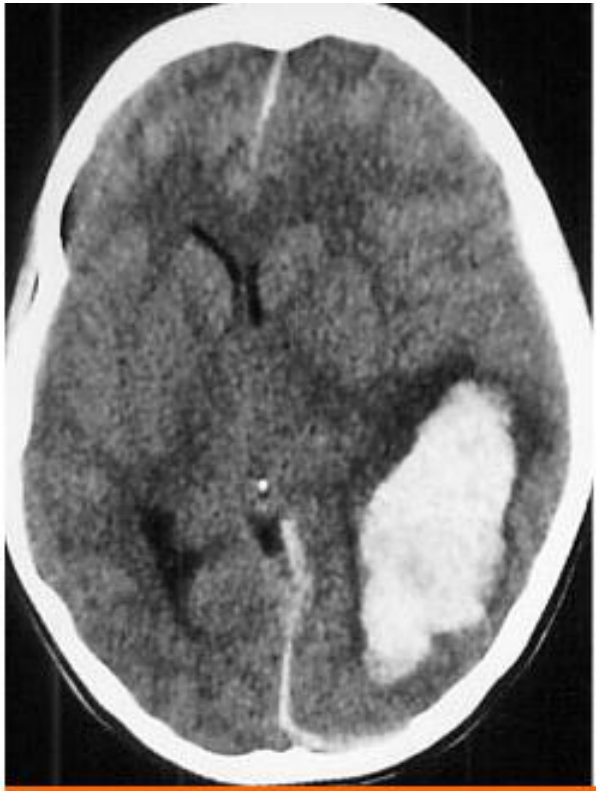
Goal of cerebral monitoring:

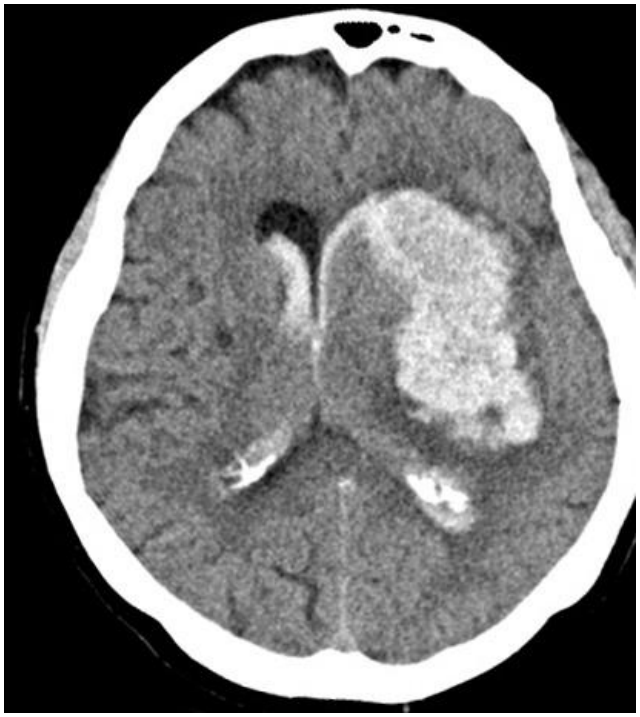
Prevention of secondary brain damage

- early recognition of reversible damage
- monitoring of specific ICP-lowering therapy
- helps establishing prognosis of cclinical course
- may result in improved neurological outcome?

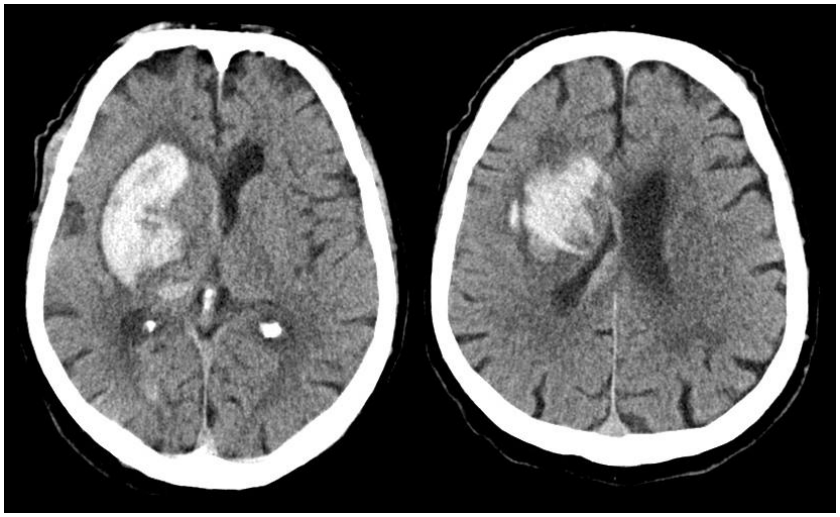
External ventricular drainage..?

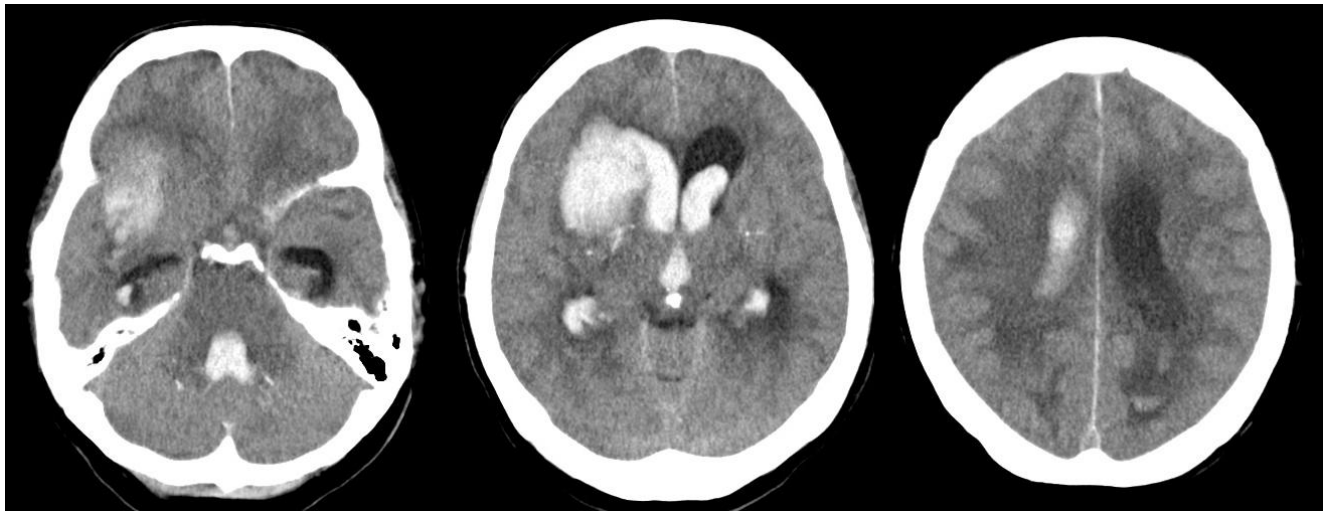






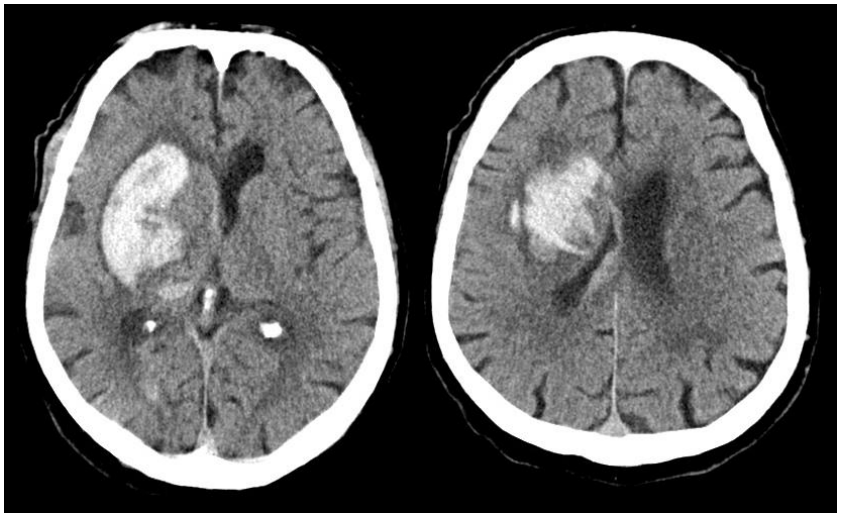
External ventricular drainage..?

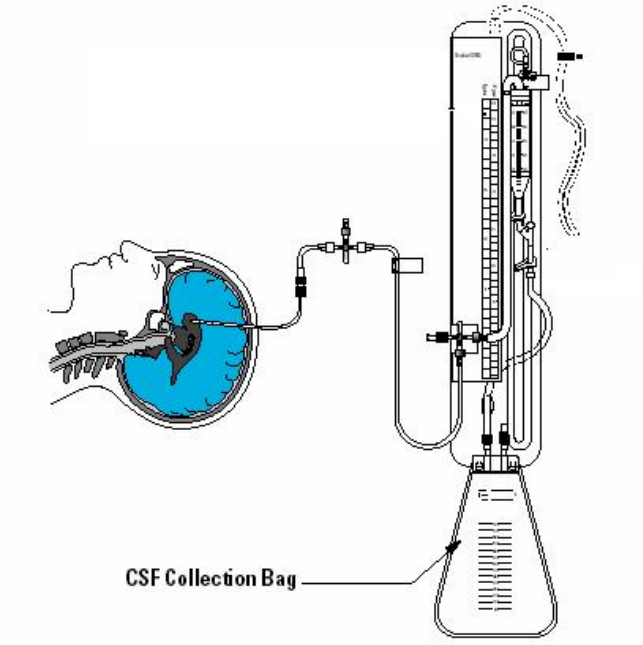




External ventricular drainage..?

Acute life-saving procedure in occlusive hydrocephalus





Enables physician:

- Drainage of CSF
- ICP Monitoring

External ventricular drainage..?

Indication:

Ventriculomegaly mit

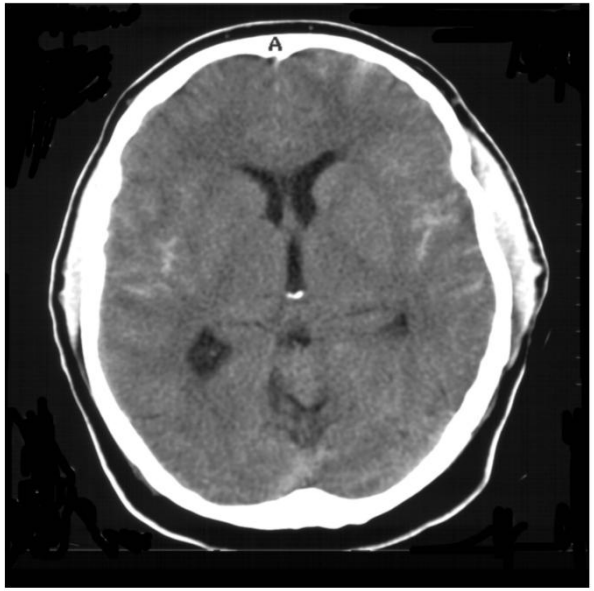
- GCS < 12
- Hunt-Hess-Grad >= 2
- Hunt-Hess-Grad >= 3
- No response to contact

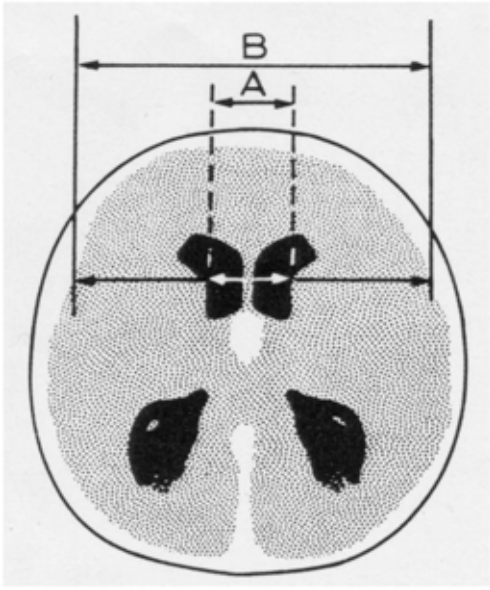
Patients with ongoing clinical worsening

Patients who cannot be monitored clinically

External ventricular drainage..?

Bicaudatus-Index





$$\text{Index} = \frac{A}{B}$$

Der Bicaudatus-Index is age-dependent:

< 36 y: 0,16

...

> 75 y: 0,21

van Gijn, JNS 1985
Hasan, Stroke 1989

Clinical routine – „difficult questions“

Basic management (RR, DVT, aso)…?

Prevention of hematoma growth..?

Surgical hemorrhage evacuation…?

External ventricular drainage…?

Management of brain edema…?

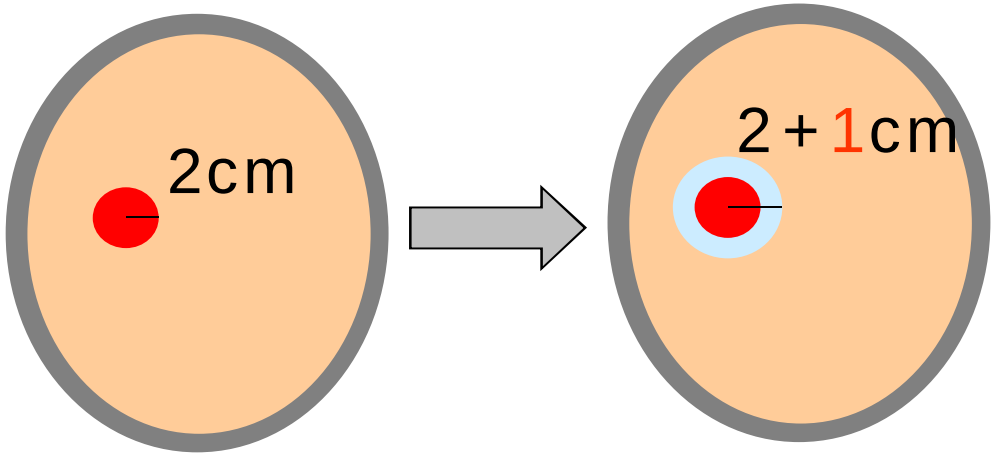
Management of intraventricular hemorrhage..?

Subgroup OAC-ICH…?

Withdrawel of therapy..?

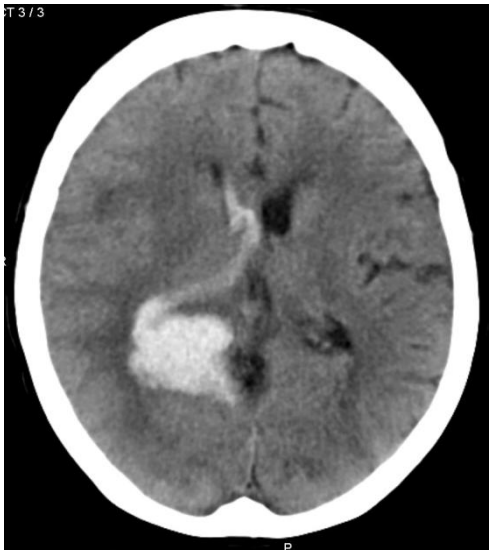
Treatment Target - „edema formation“

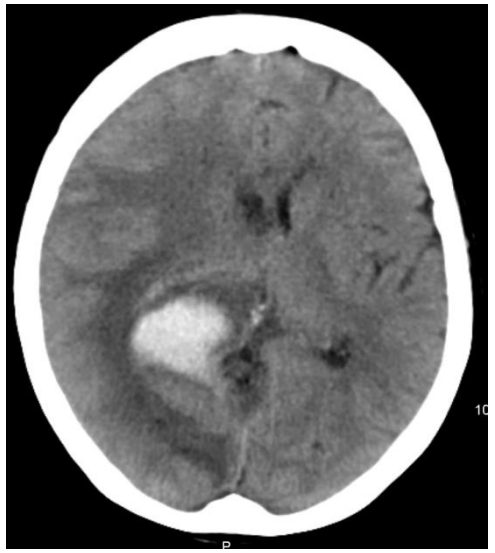
$$V = 4/3 * ?\mu * r^3$$



V_1 = 33.5 ml

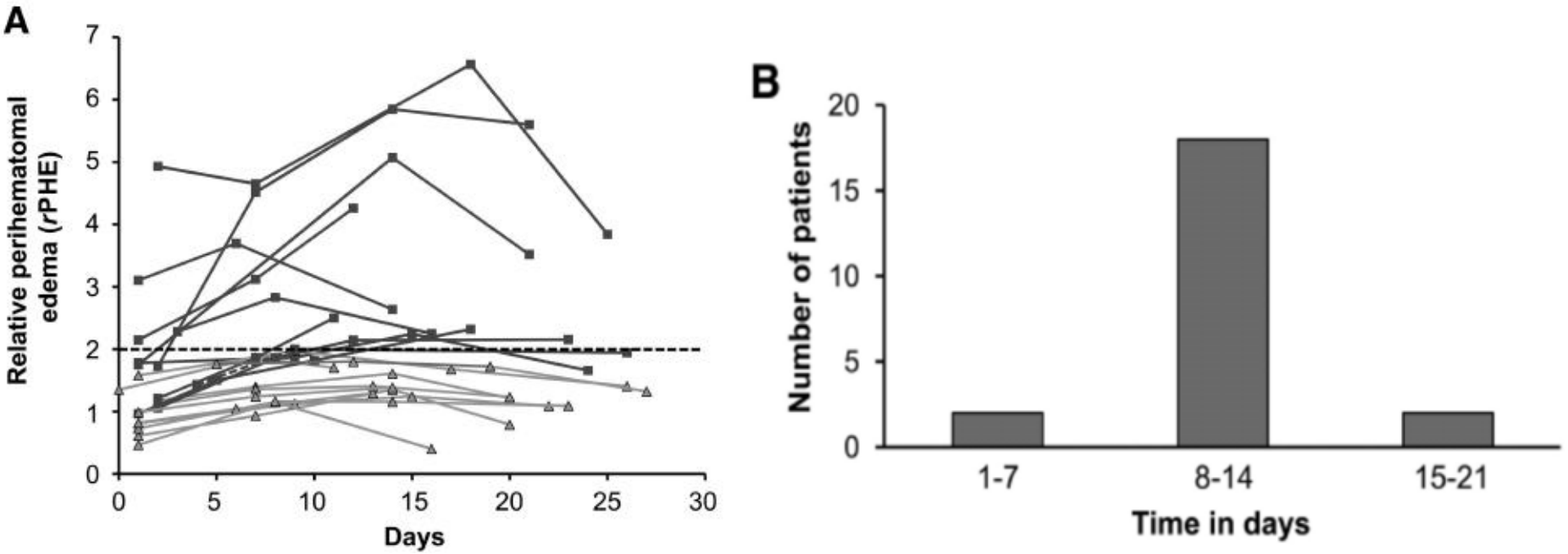
V_2 = 113 ml
(= ~3x V_1)





Treatment Target - „edema formation“

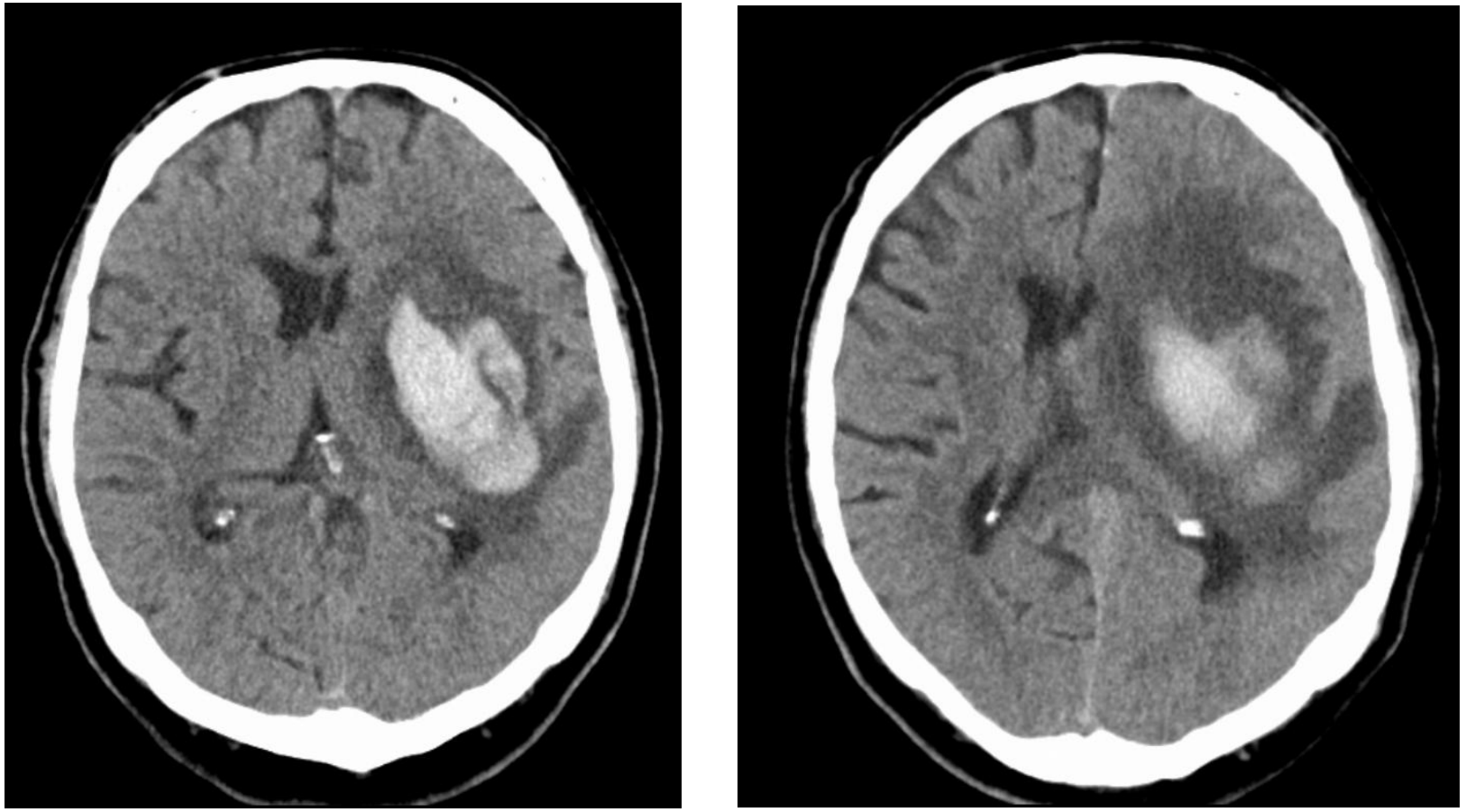
Natural History of Perihematomal Edema After Intracerebral Hemorrhage Measured by Serial Magnetic Resonance Imaging



- à **Ödementwicklung am ausgeprägtesten innerhalb der ersten 2 Tage**
- à **Maximale Ödenausbreitung gegen Ende der zweiten Woche**

Venkatasubramanian et al. 2011 Stroke

Treatment Target - „edema formation“



Treatment? When?

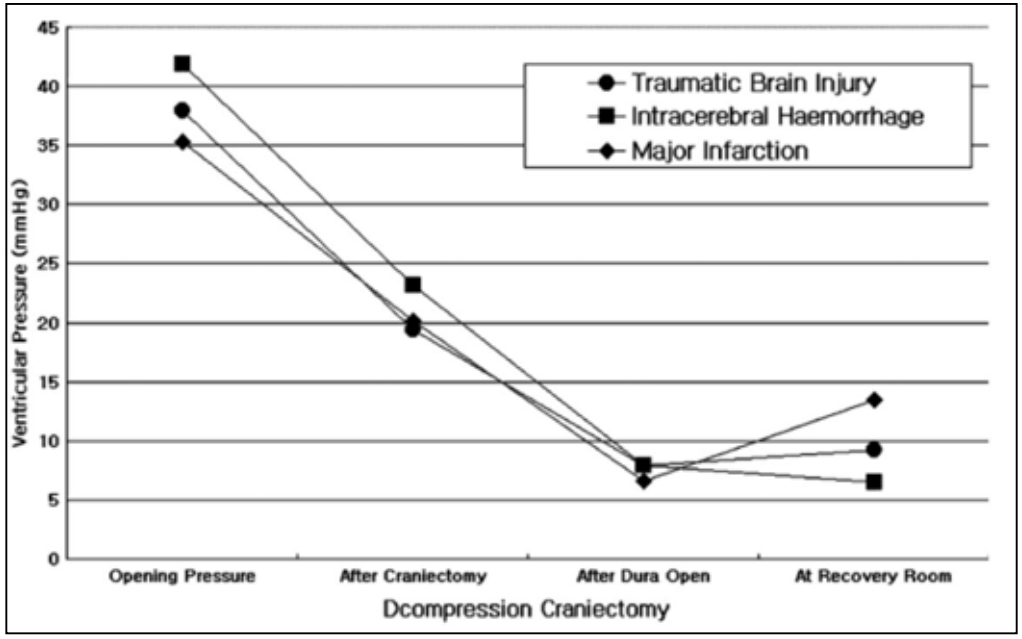
Treatment Target - „edema formation“

Lowering intracranial pressure*

Consider:

- Elevation of body position; if ICP probe consider CPP threshold (e.g.CPP> 60mmHg)
- EVD in case of hydrocephalus or clinical deterioration and neuroradiological evidence of brainstem compression
- Osmotic therapy using
  - Glycerol (500ml 10% per day)
  - Mannitol (100ml 20%; day 1 to 5: 6/day; day 6: 3/day; day 7: 2/day)
  - Hyper-HAES (3%, natrium value target area: 145 to 155 mmol/l or osmolality 310 to 320 mOsmol/kg
- Intermittent hyperventilation (pCO_2 > 28 mmHg)
- Analgosedation
- Hypothermia
- Haematoma evacuation with / without craniectomy

Treatment Target - „edema formation“ - Decompressive Surgery? -



Kim 2009 Acta Neurochir

n=24 (ICB)

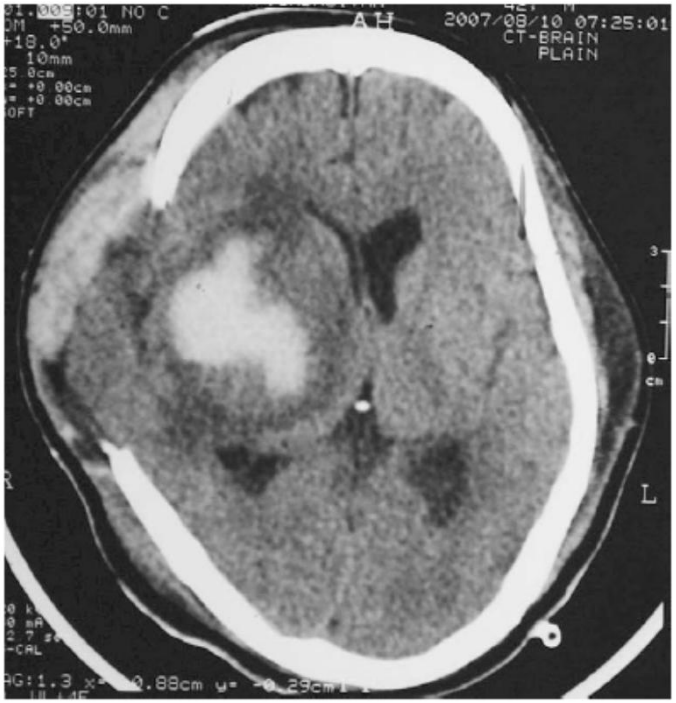


Figure 3. *Third of serial CT scans of one patient showing course of events in right putaminal bleed and hemicraniectomy. On postoperative day 10, there is reduction in hematoma and basal cisterns are opening up.*

Ramnarayan 2009 J Stroke Cerebrovasc Dis

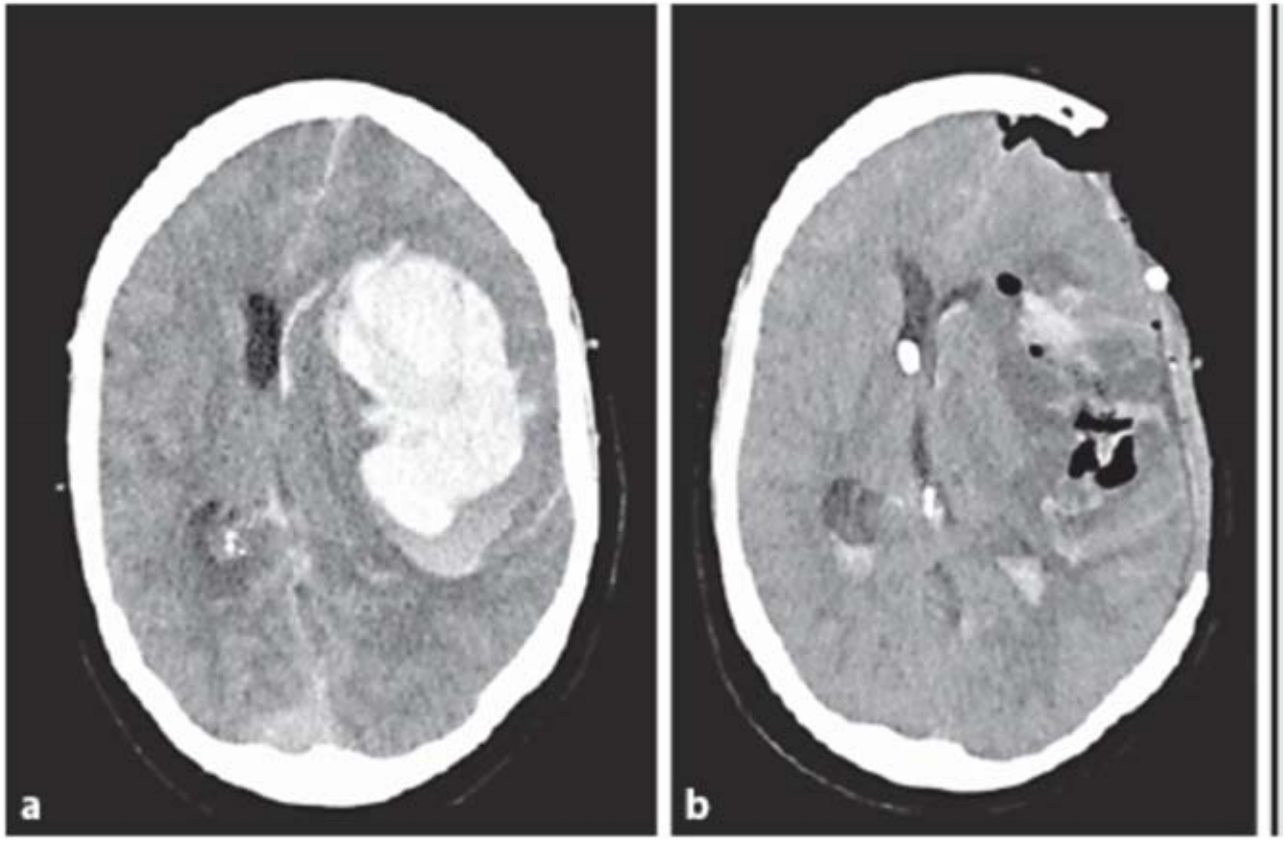
n=23

Neurological Vignette

European Neurology

When Decompressive Craniectomy Does Not Lead to Decompression: Sinking Skin Flap Syndrome after Intracerebral Hemorrhage

Received: October 8, 2010
Accepted: October 12, 2010
Published online: November 6, 2010



Treatment Target - „edema formation“ - Hypothermia? -

Experimental data from animals

- Reduction of edema
- Functional improvement

Stabilizes BBB

Reduction of inflammatory processes

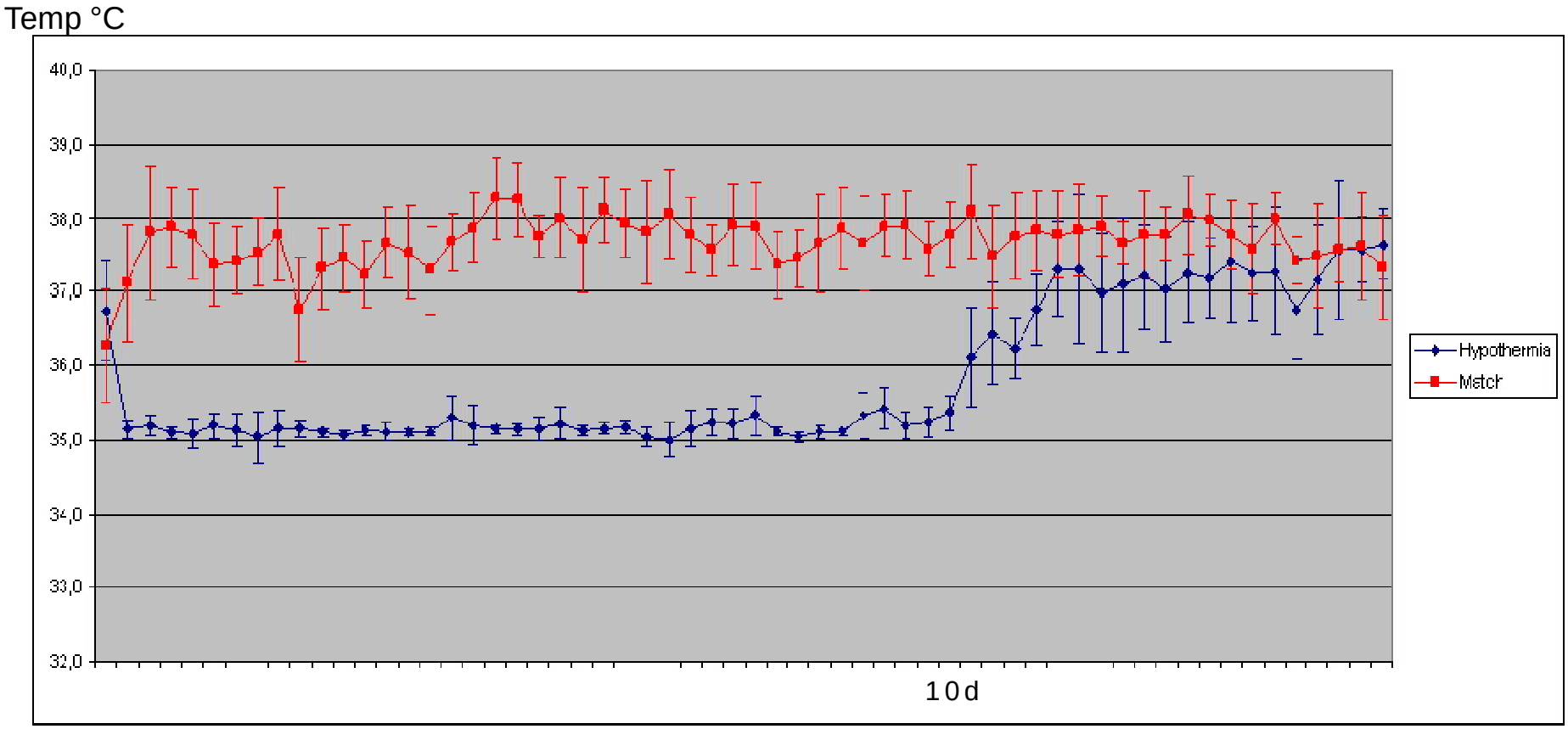
prevents progression of edema formation

à early initiation?!

Fingas 2007 Exp Neurol
Kawanishi 2008 J Stroke Cerebrovasc Dis

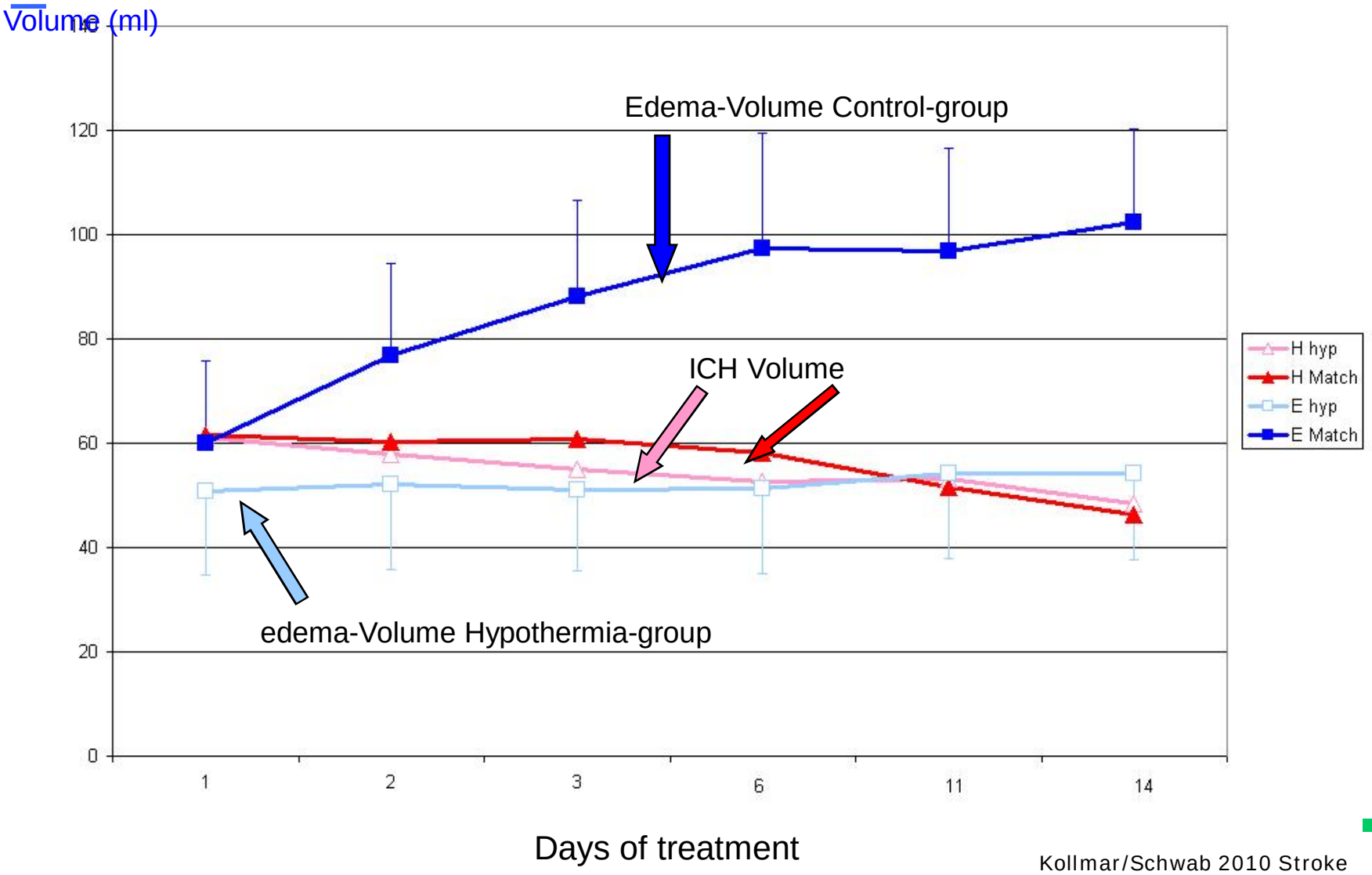
Treatment Target - „edema formation“ - Hypothermia? -

initial data from Erlangen, Germany (n=21)



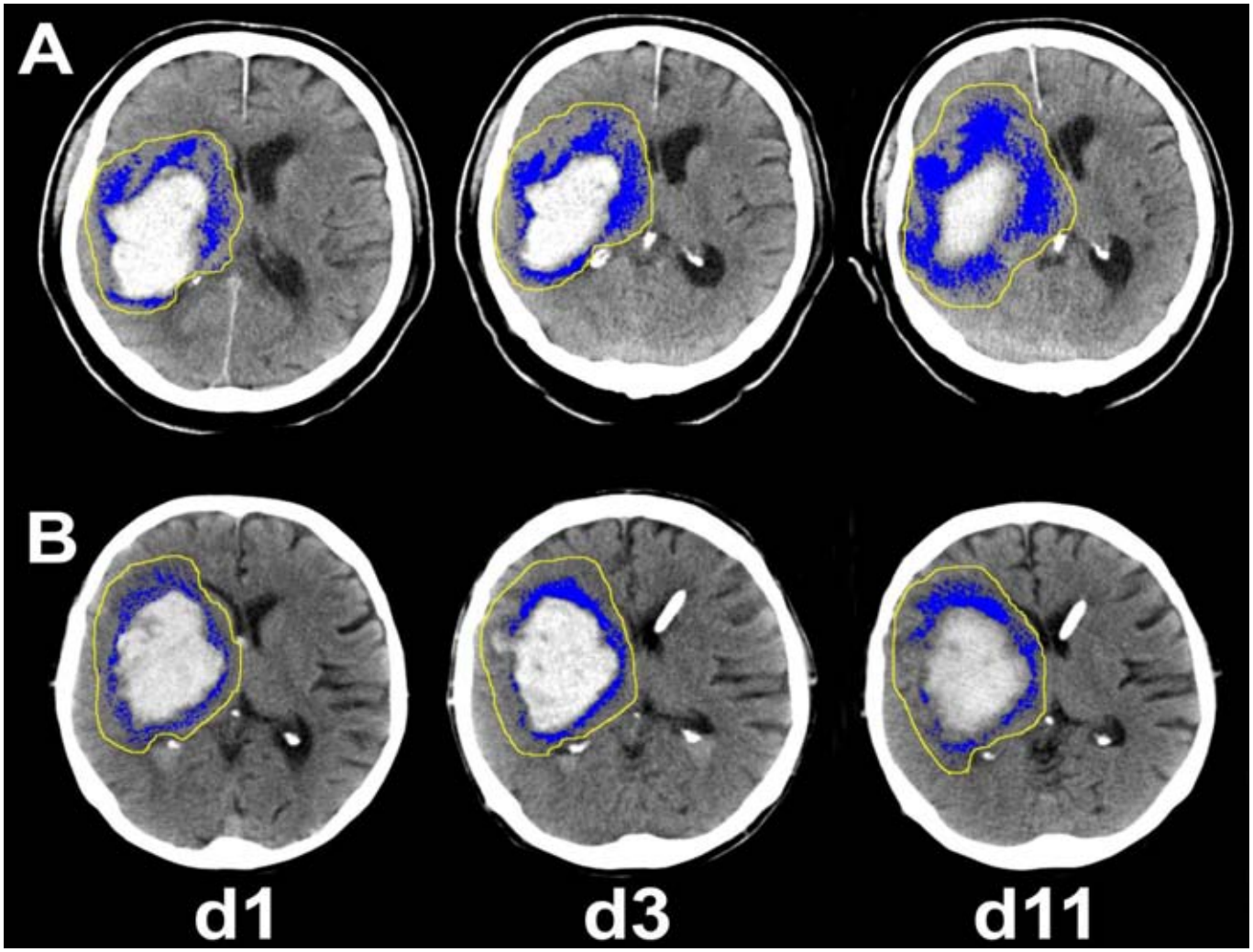
Kollmar/Schwab 2010 Stroke

Treatment Target - „edema formation“ - Hypothermia? -



Kollmar/Schwab 2010 Stroke

Treatment Target - „edema formation“ - Hypothermia? -



Kollmar/Schwab 2010 Stroke

Clinical routine – „difficult questions“

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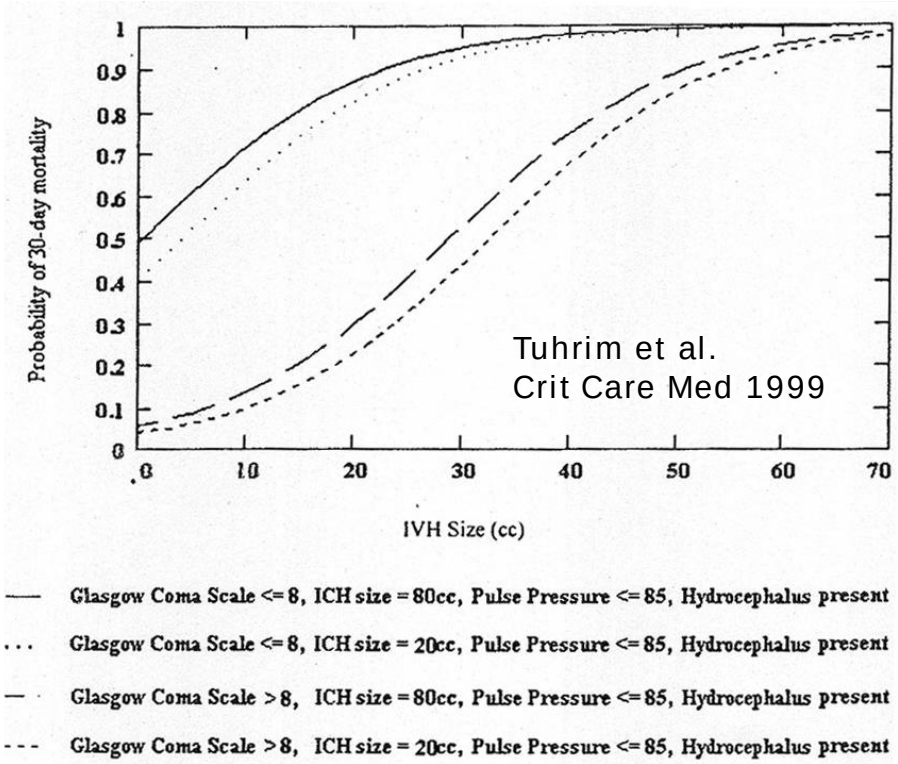
Treatment Target - intraventricular hemorrhage



IVH ?±25–45% after primary ICH

IVH + hydrocephalus ?Œ15–30%

Independent prognostic parameter

Morbidity and mortality increased

Lethality within 30 days:

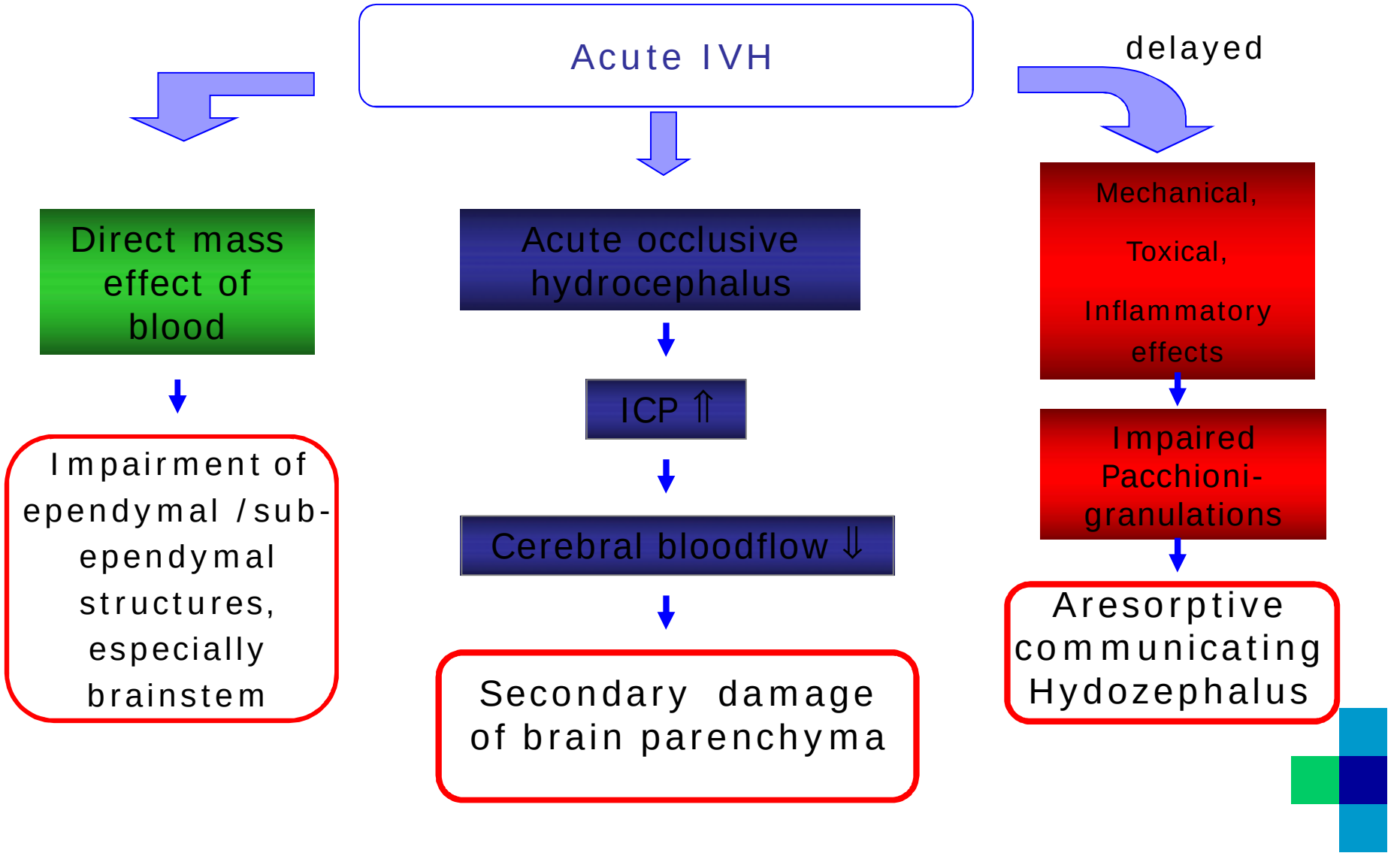
43-59% (vs. 9% without IVH)

STICH, NOVO 7, FAST:

poor Outcome in 70-90 %

Optimal treatment so far unknown

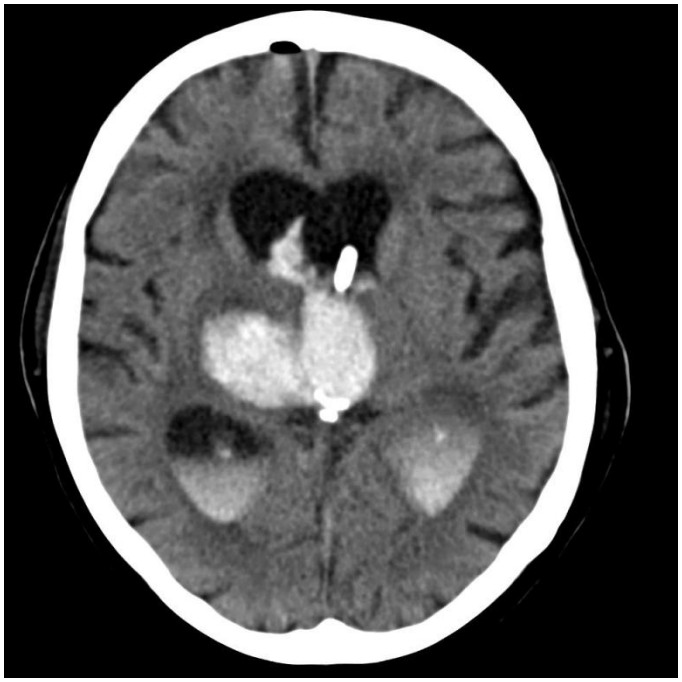
Treatment Target - intraventricular hemorrhage

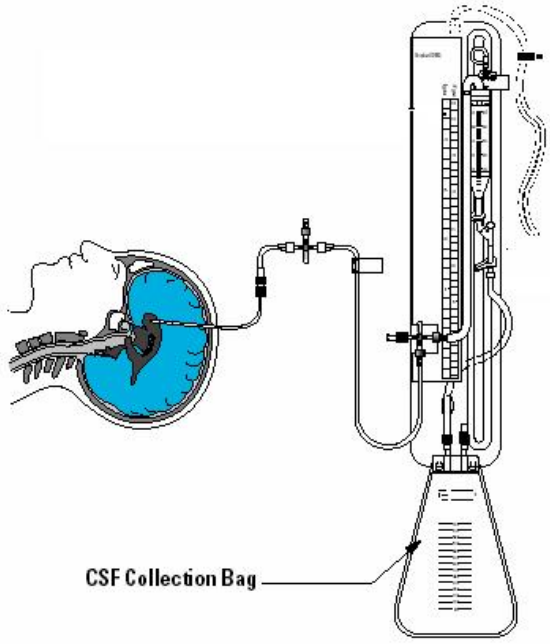


Treatment Target - intraventricular hemorrhage

Insertion of external ventricular drains (EVD)

Acute life-saving procedure in occlusive hydrocephalus



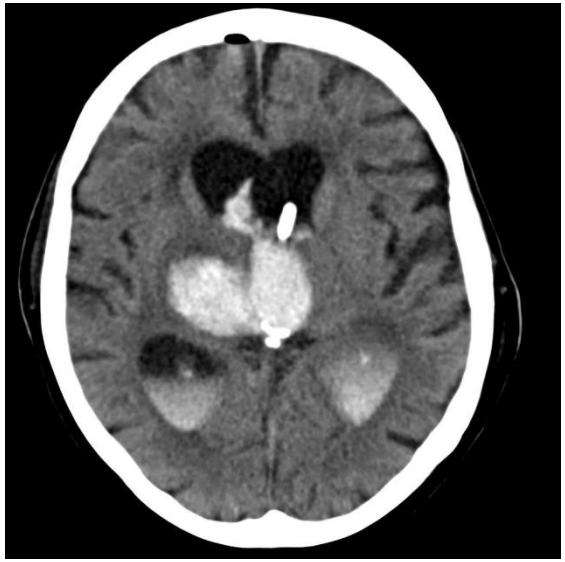


Enables physician:

- § Drainage of CSF
- § Drainage of IVH
- § ICP Monitoring

Treatment Target - intraventricular hemorrhage

Problems during course of the disease



EVD-“occlusion“

Risk of infections

à repeated EVD-exchanges

after 2-3 EVD-exchanges

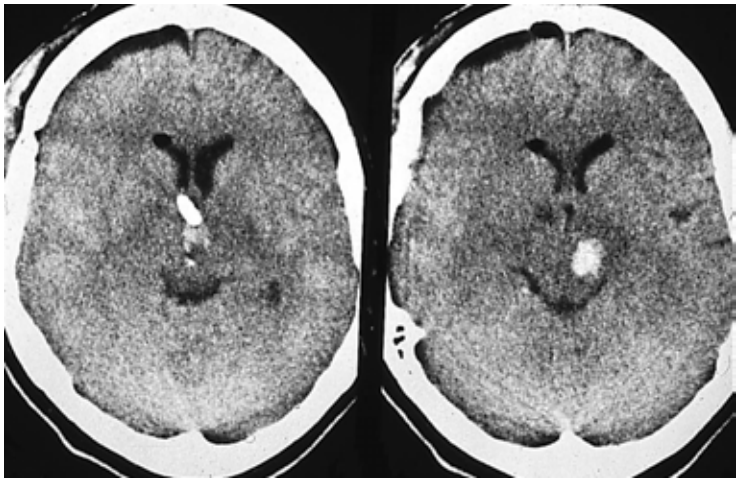
à permanent VP-Shunt

Catheter track bleeds

Parenchymal bleeds

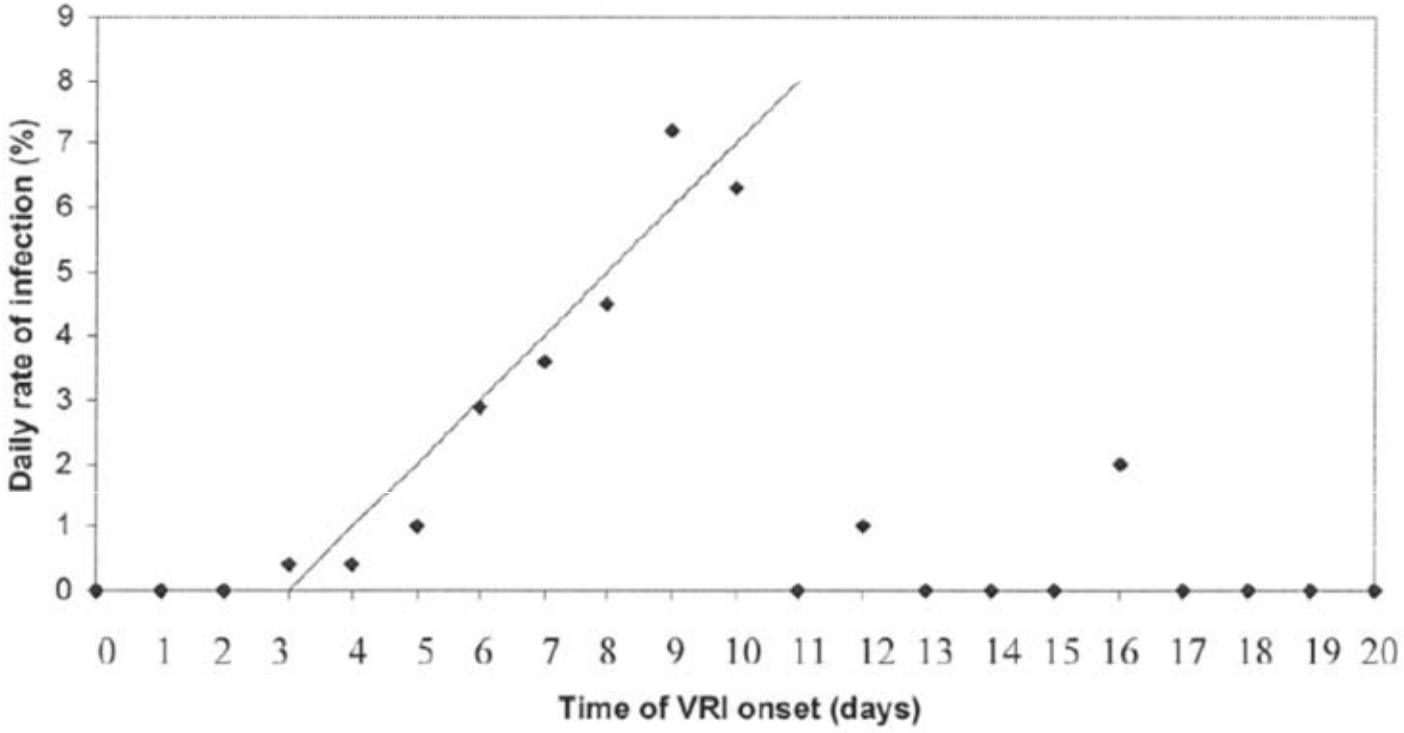
Addional trauma

dislocation



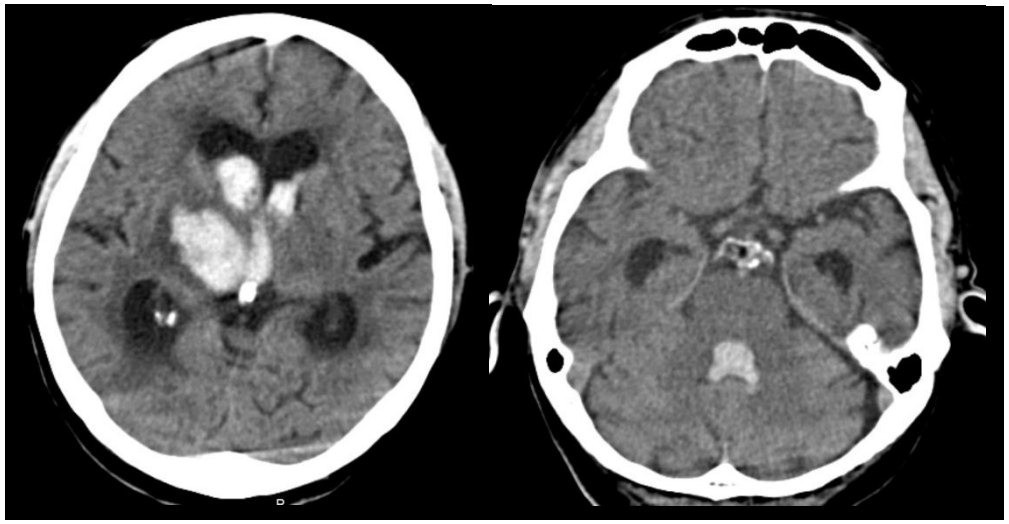
Treatment Target - intraventricular hemorrhage

Time and probability of infection after EVD placement



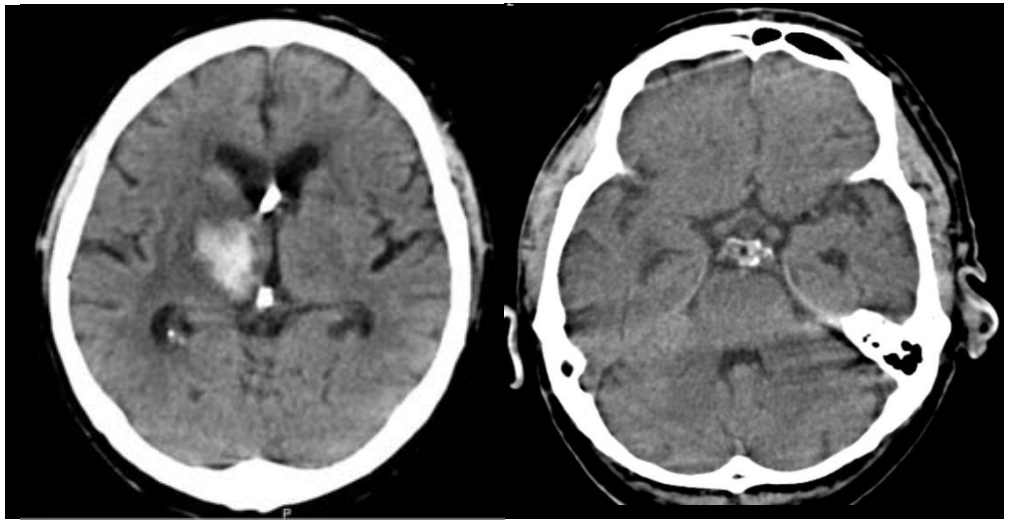
Bota DP at al. J Neurosurg 2005;103:468-472

Intraventricular fibrinolysis



admission

3x4mg rtPA



Day 3

Intraventricular fibrinolysis

Rationale

Ensures functionality of EVD

Hastened IVH clot lysis

Reduction of increased ICP

Treatment of occlusive hydrocephalus

Avoidance of VP-shunts

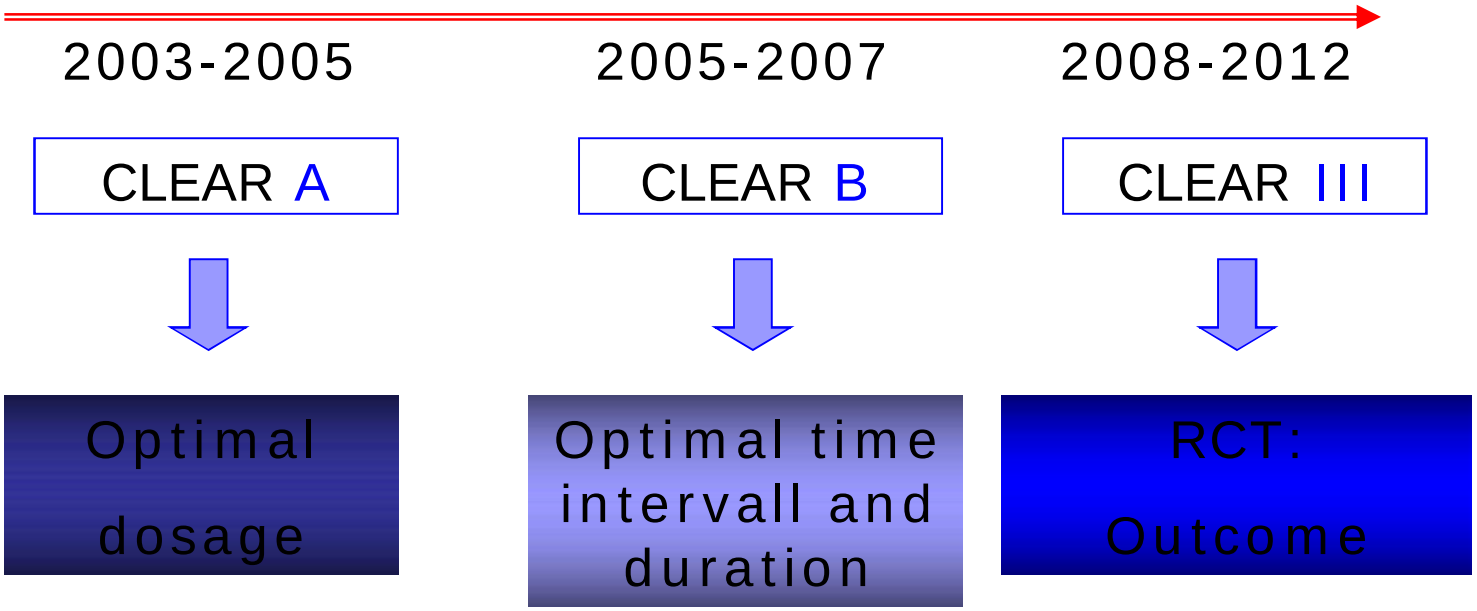
Shortening of neurocritical care duration

Intraventricular fibrinolysis

CLEAR IVH

Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage rt-PA Treatment of Brain Hemorrhage

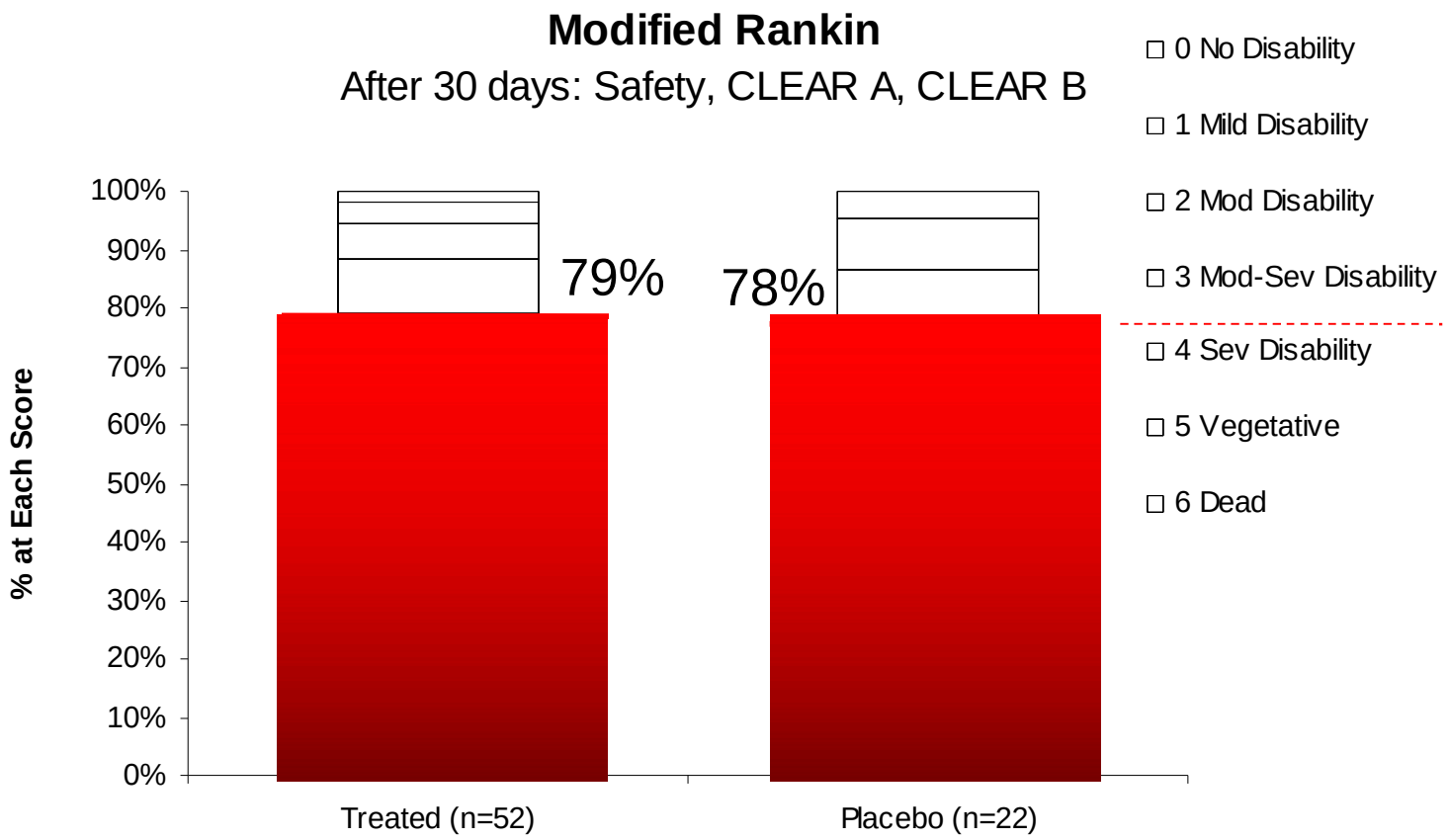
A multicenter, randomized, double-blind, placebo-controlled trial



Intraventricular fibrinolysis

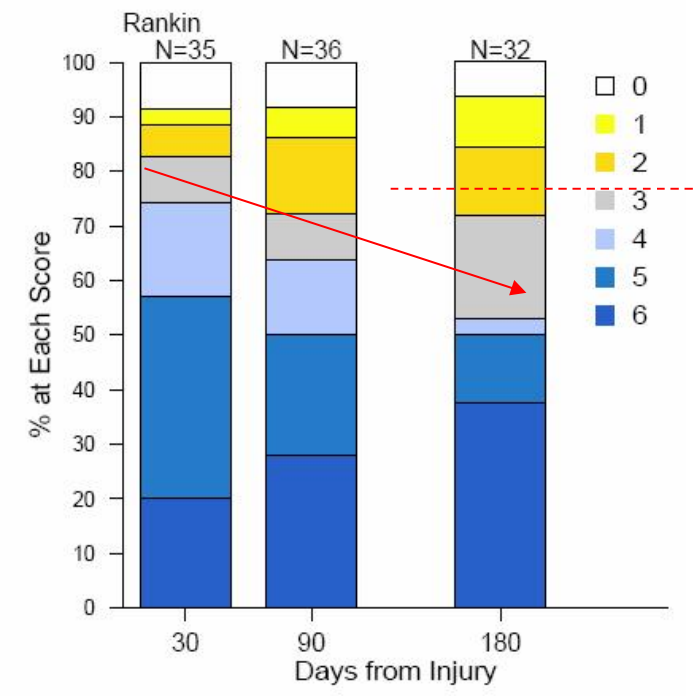
CLEAR-IVH

- clinical Outcome of patients of CLEAR A & B -



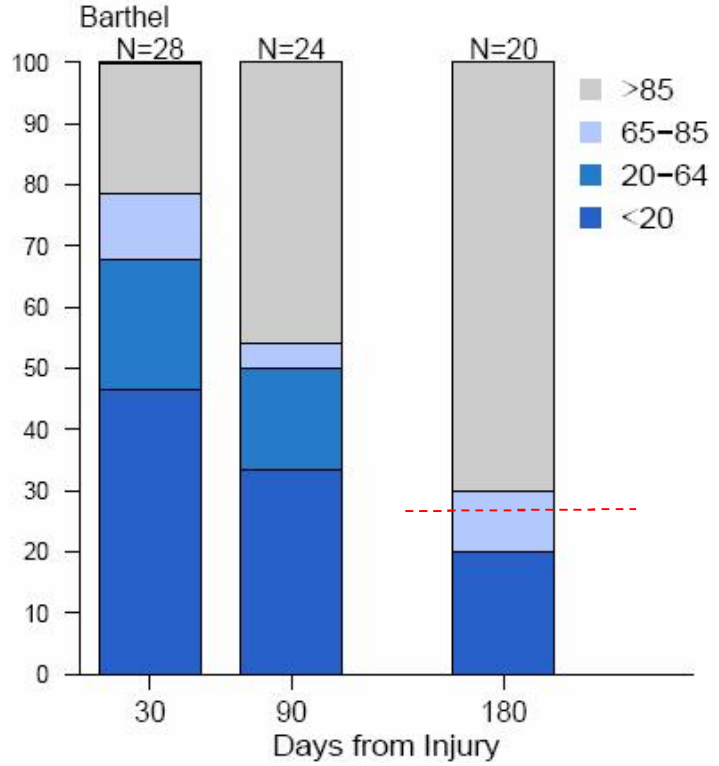
Intraventricular fibrinolysis

...however, after 90 and 180 days



mRS 4-6:

52%



BI>85:

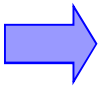
70%

Intraventricular fibrinolysis

CLEAR-IVH
- Phase III -

2009-2012?

CLEAR III



Placebo-controlled

Double blinded

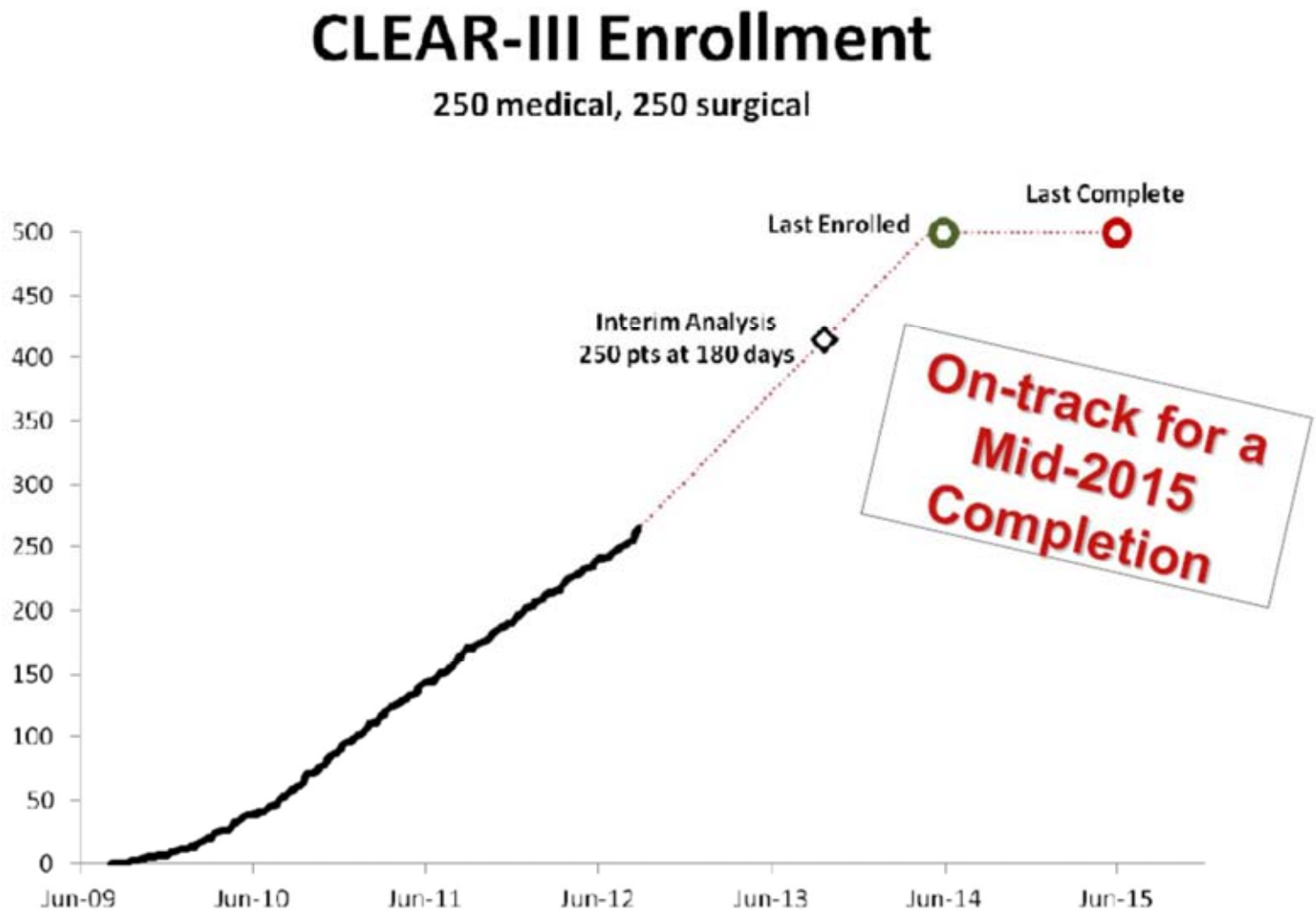
Randomized

Planned patients: 500 (currently ? 87)

Primary endpoint: mRS after 6 months

Power-assumption: 15 % „Shift“ in Outcome mRS 0-3

Intraventricular fibrinolysis



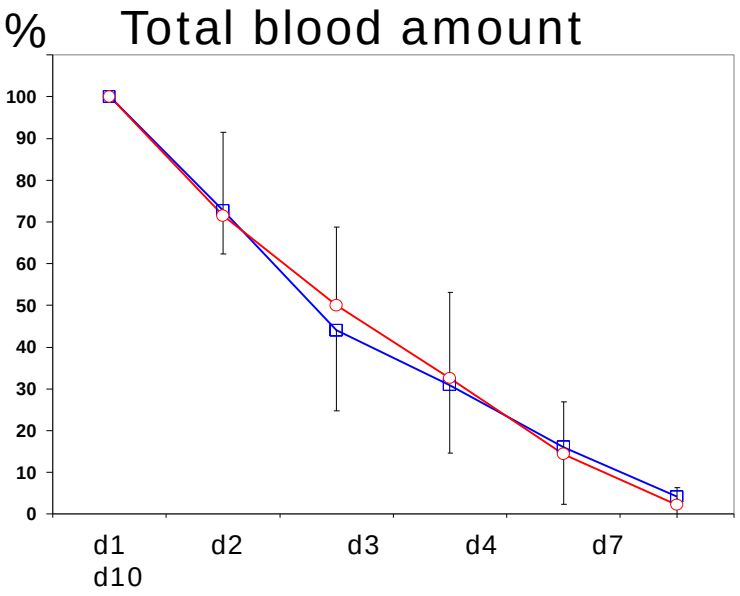
Hanley D, WSC 2012

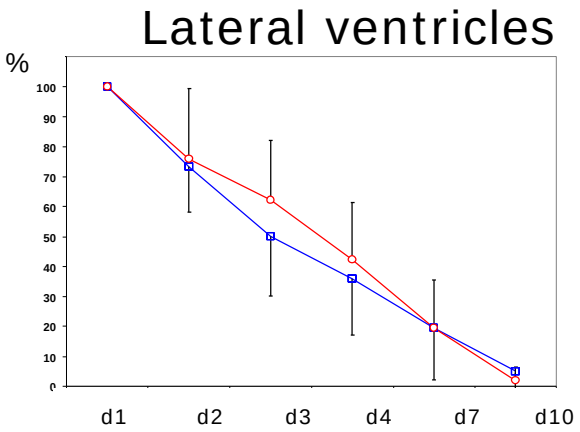
Intraventricular fibrinolysis

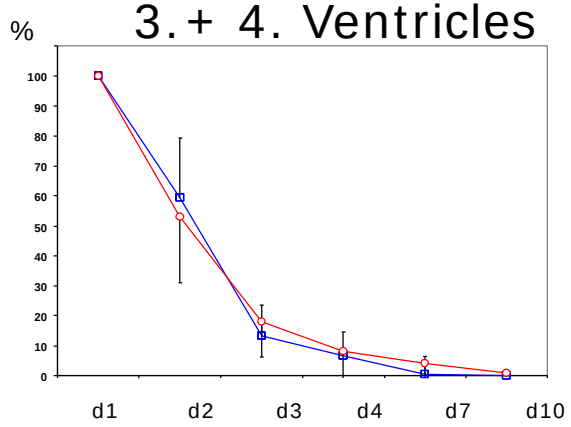
1 *versus* 2 EVD:
Reduction of ventricular clot volume

1 EVD (n=13)

2 EVDs (n=14)







Staykov 2009 JNNP

Intraventricular fibrinolysis

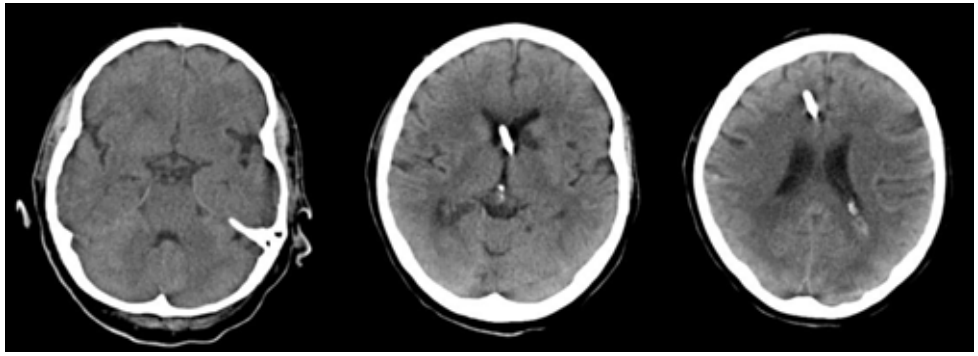
Lokalisation der EVD und IVH-Clearance

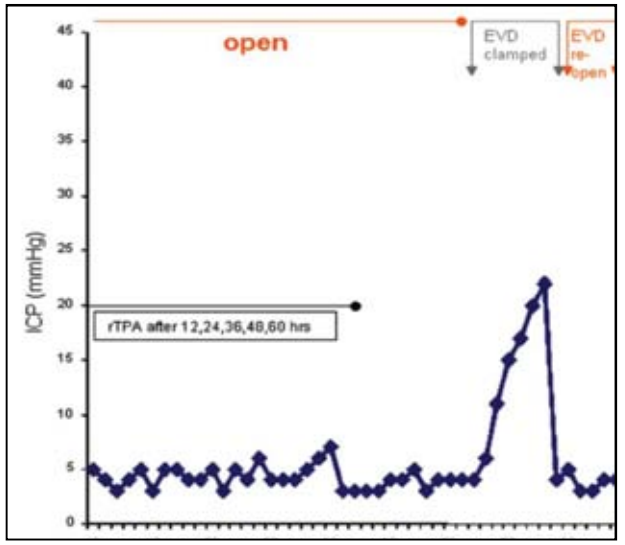
- Design: N=100 (CLEAR IVH)
- Inclusion-criteria: SICH + IVH
- Ergebnisse:
  1. Clearance within 3 days: after rt-PA faster than placebo (p<0,005)
  2. Clearancs and location of EVD:
     1. Lysis-group: faster when placed ipsilateral (p=0,09, 95% CI: 29,62 to 0,69)
     2. Placebo: no signal
     3. ICH in III und IV. ventricle: EVD location (I or II ventricle) plays no role

Jaffe J et al. Neurosurgery. 2012;70:1258-1263; discussion 1263-1254

Post-hemorrhagic hydrocephalus

3d after admission: ventricles free from blood





…..however, **ICP increase** after clamping of EVD

in **>80%** of all patients in acute phase

Post-hemorrhagic hydrocephalus

Problems of communicating hydrocephalus:

continuous EVD-drainage necessary

- Dislocation
- Infection
- Obstruction

Permanent VP-Shunt – when?

- decision on VP-Shunts usually after 2-3 weeks

?? 15%-33% of patients with EVD and aresorptive hydrocephalus need VP-shunting (if not received IVF)

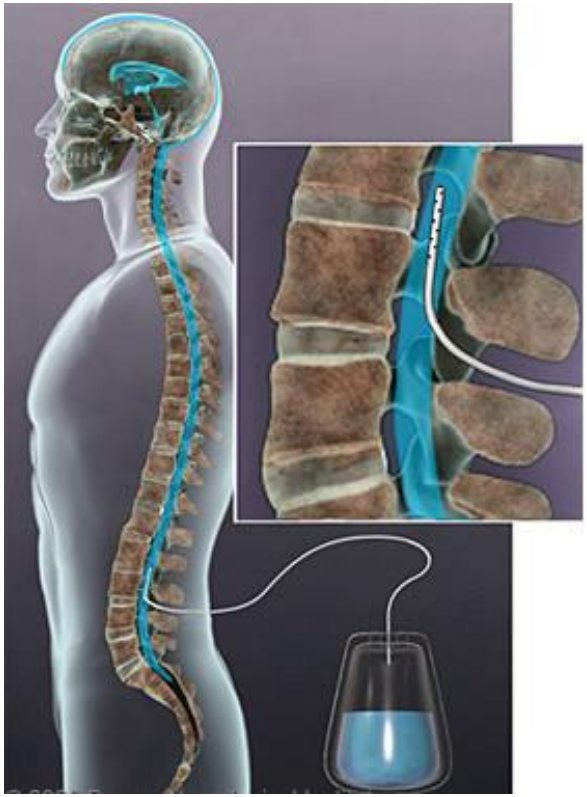
VP-Shunt - Malfunction

- In 1. year up to **40%** (even experienced neurosurgeons)
- **70-80%** of pateints with VP-Shunt need revision
- Causes both on proximal and distal end
- Infection up to **8-10%**

Engelhard 2004 Surg Neurol

Post-hemorrhagic hydrocephalus
- Lumbar drains -

Concept of lumbar drains



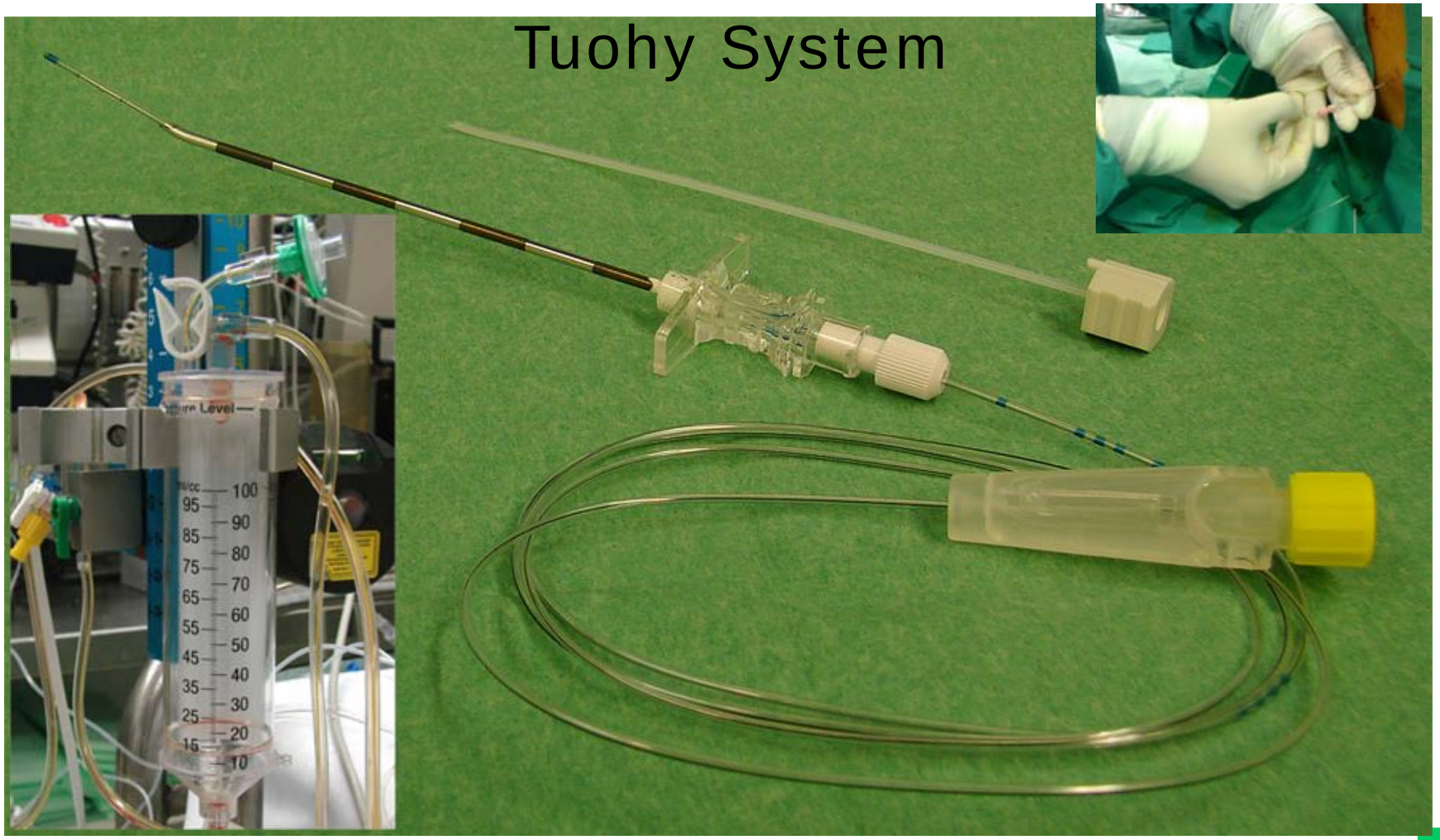
1) As soon as IVH is resorbed and „cleared“#
   3. and 4. ventricles (CT-based) and

2) EVD-clamping fails à

3) Diagnosis of aresorptive hydrocephalus
   with communicating inner and outer CSF spaces

Placement of Lumbar drain should sufficiently drain CSF spaces – thereby replacing the EVD

Post-hemorrhagic hydrocephalus
- Lumbar drains -

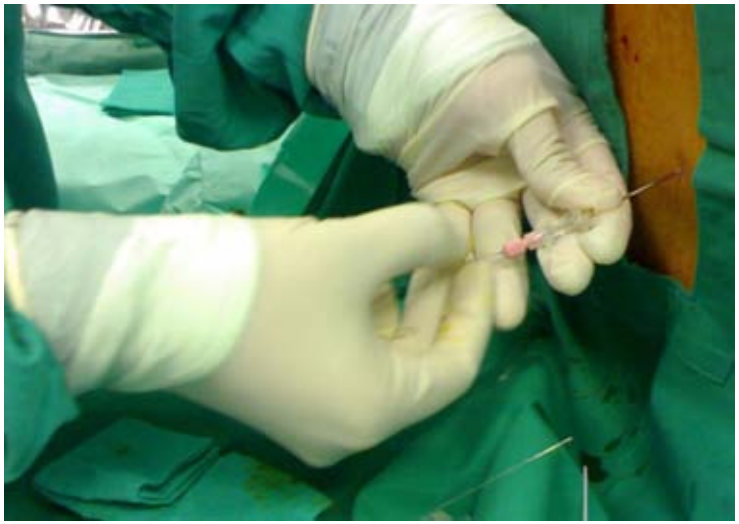


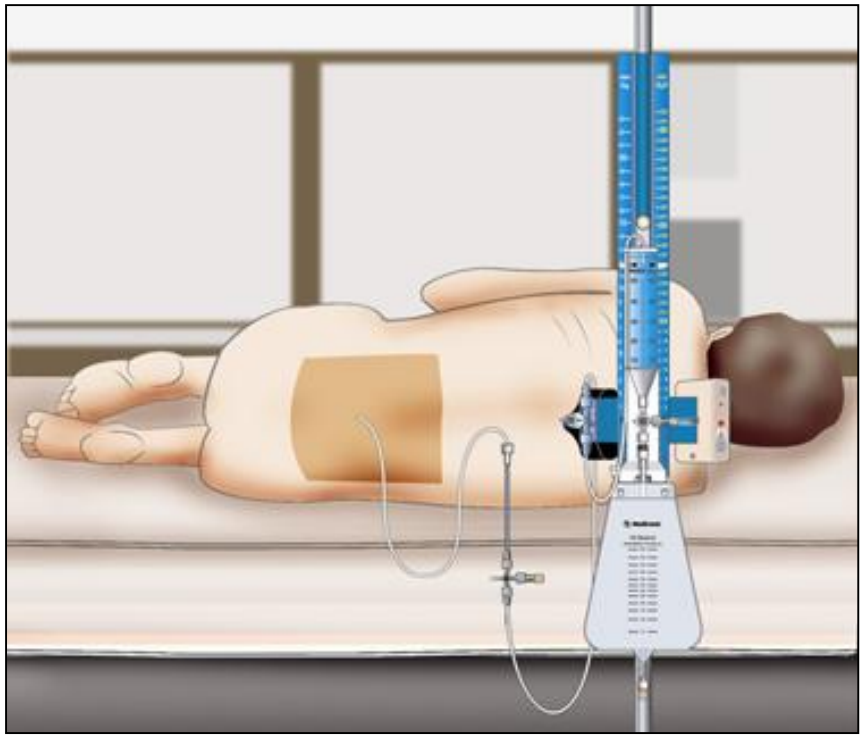
Post-hemorrhagic hydrocephalus
- Lumbar drains -

Benefits of Lumbar drains compared to EVD

less invasive (à less complications such as catheter tract bleeds, symptomatic seizures)

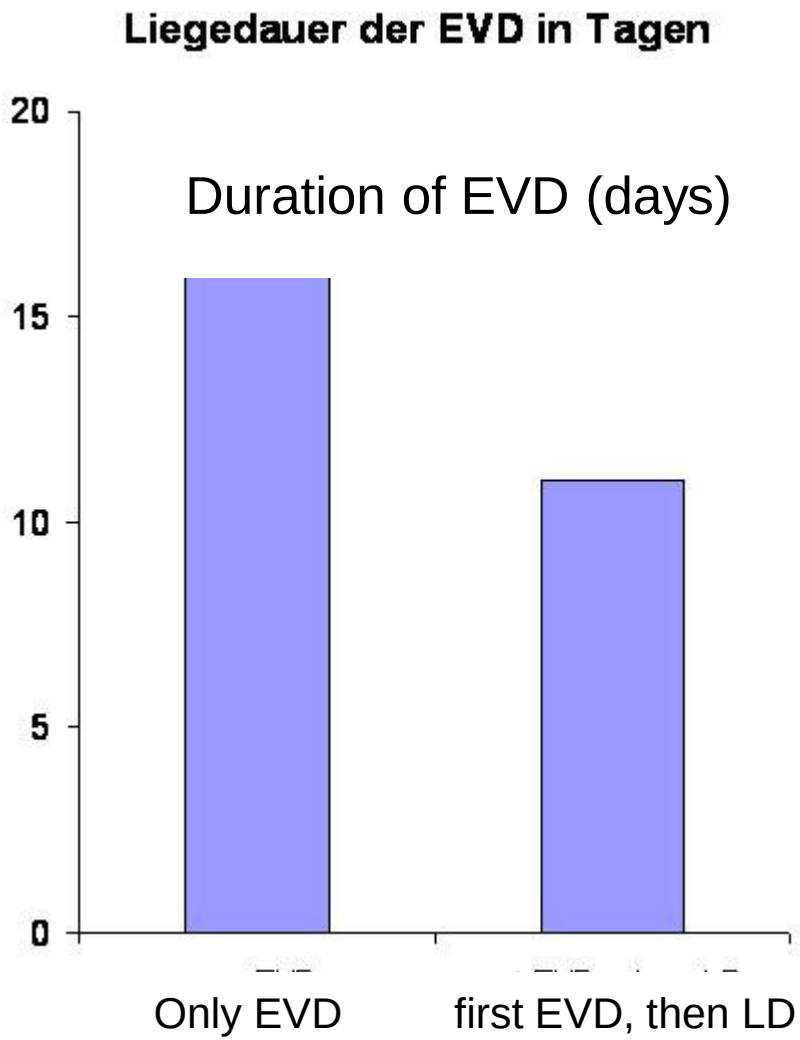
Quick exchange (bed-side technique)

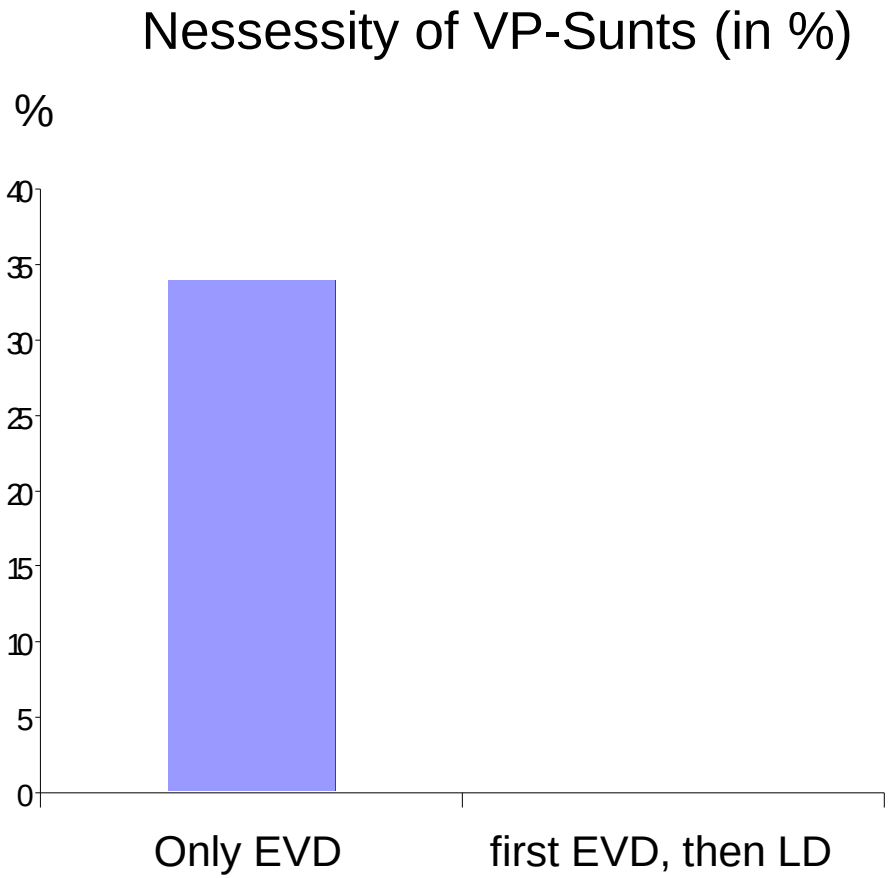




à duration of CSF drainage may be increased
à Pacchioni Granulations have more time for reconstitution
à Reduction of nessessity of VP-Shunts?

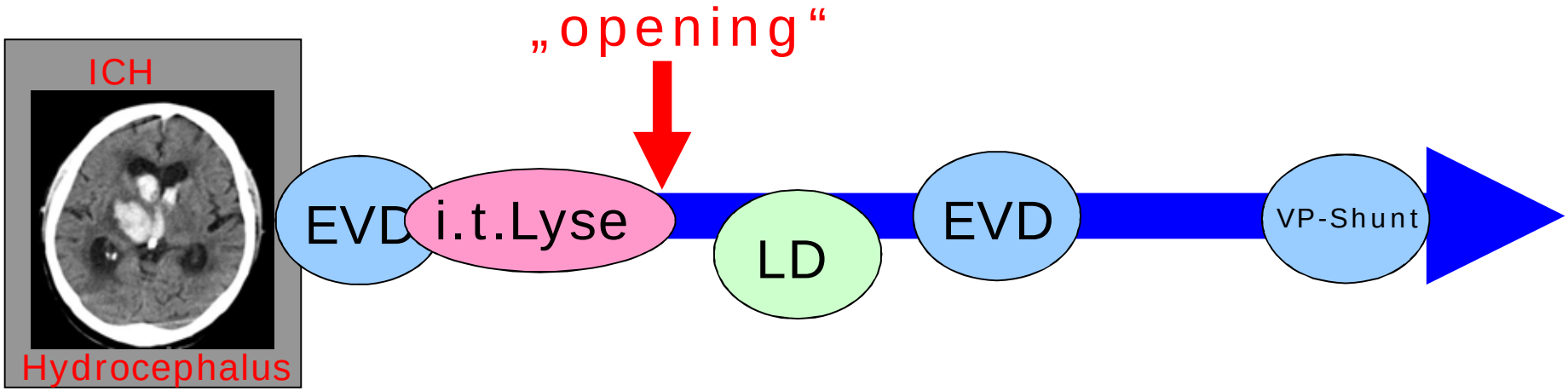
Post-hemorrhagic hydrocephalus
ar drains -





Huttner 2007 Stroke

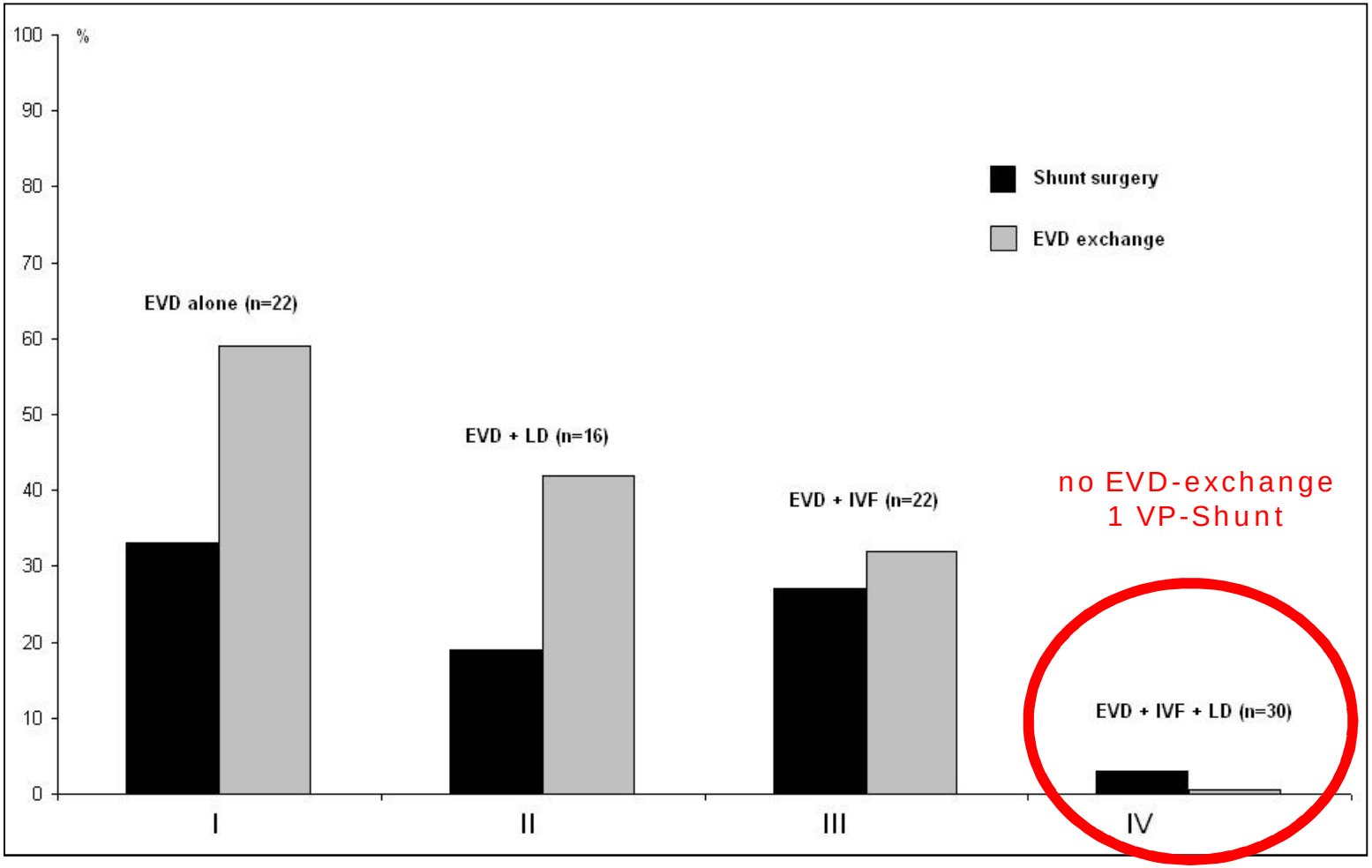
Combination of IVF and Lumbar drains



Avoidance of EVD-exchange and VP-Shunts by combination of intraventricular fibrinolysis and lumbar drains

Huttner&Staykov 2010

Combination of IVF and Lumbar drains



Staykov et al. 2009 STROKE

Conclusion – Treatment of IVH

EVD placement in occlusive hydrocephalus

Intraventricular fibrinolysis speeds-up clot resolution

Intraventricular fibrinolysis leads to

- less EVD-exchanges
- less VP-shunts
- Influenes outcome? (CLEAR-IVH)

As soon as aresorptive hydrocephalus is diagnosed à place LD

Lumbar drainage leads to

- Less EVD-exchanges
- Less VP-shunts

Combination of IVF and LD leads to

- No EVD-exchanges
- Almost no VP-shunts

Clinical routine – „difficult questions“

Basic management (RR, DVT, aso)…?

Prevention of hematoma growth..?

Surgical hemorrhage evacuation…?

External ventricular drainage…?

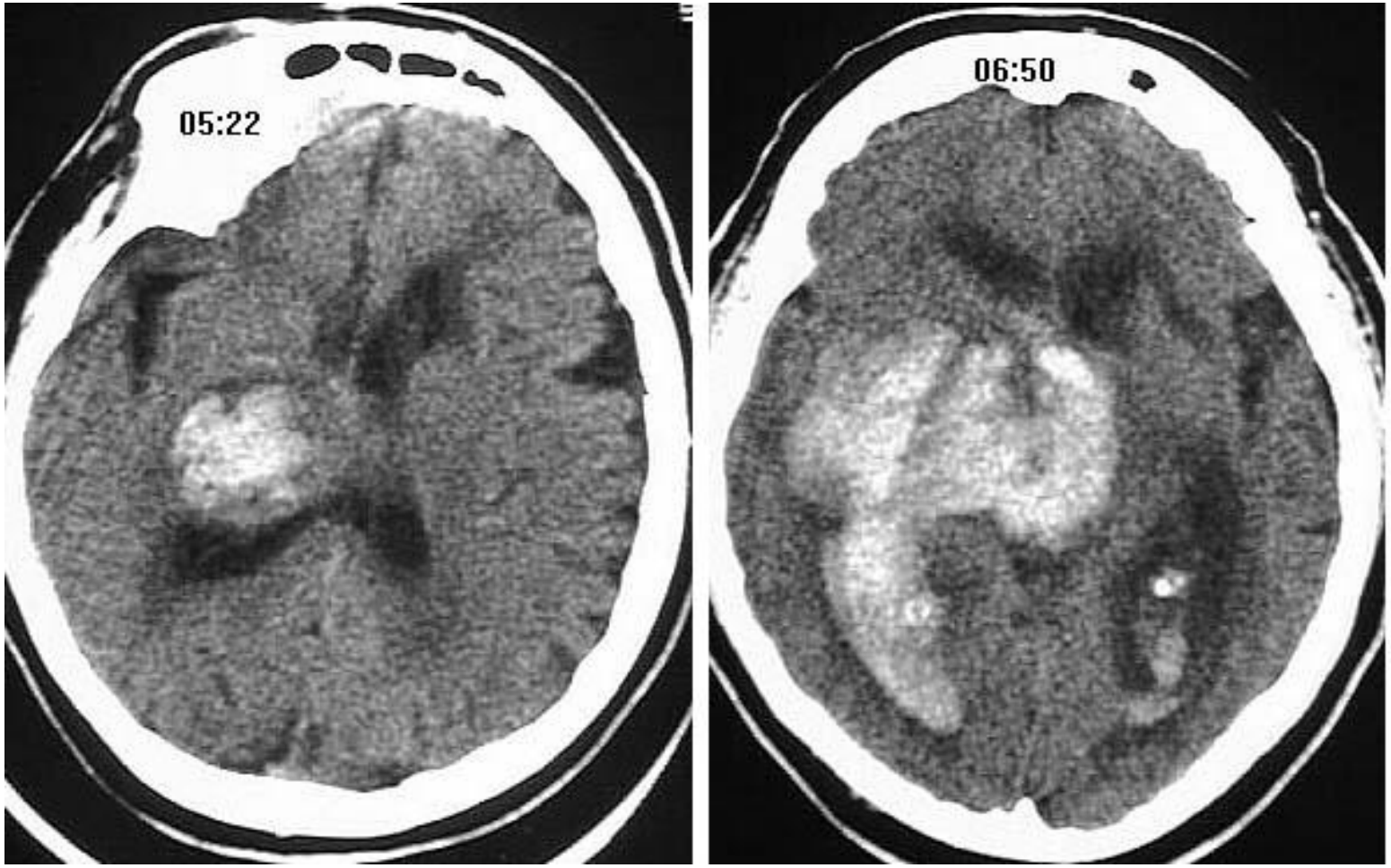
Management of brain edema…?

Management of intraventricular hemorrhage..?

Subgroup OAC-ICH…?

Withdrawel of therapy..?

Treatment Target - „hemorrhage growth“ - ICH related to oral anticoagulants -



Treatment Target - „hemorrhage growth“ - ICH related to oral anticoagulants -

ICH volume larger the higher the INR (>3) (Flaherty ML, et al. Neurology 2008)

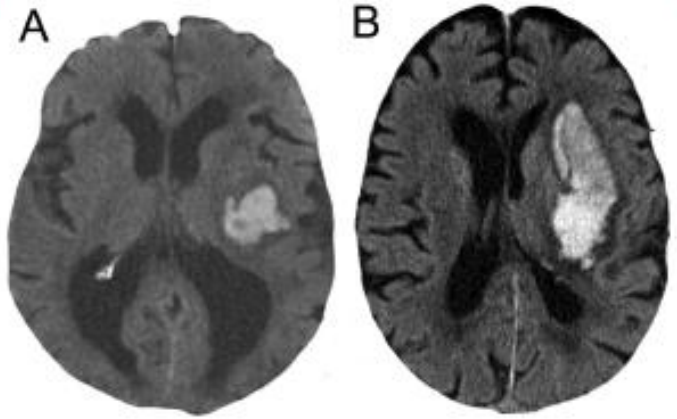
Outcome OAT-ICH worse than primary ICH

Mortality up to 67% after 1y (Rosand J, et al. Arch Intern Med)

Predictors for hematoma growth:

- initial systolic BP (Zubkov AY, et al. Arch Neurol. 2008)
- Incompletely reversed INR after 2h (Huttner HB, et al. Stroke 2006)

Figure Comparison of 15- and 40-mL intracerebral hematomas



CT scans from 15-mL (A) and 40-mL (B) deep cerebral intracerebral hemorrhages (ICHs). This approximates the difference between an ICH with an international normalized ratio (INR) <1.2 and an ICH with an INR >3.0 as seen in the multivariable generalized linear model.

Treatment Target - „hemorrhage growth“ - ICH related to oral anticoagulants -

Treatment options for INR reversal:

Vitamin K

Fresh Frozen Plasma (FFP)

Prothrombin Complex Concentrate (PCC)

rFaktor VIIa

Treatment Target - „hemorrhage growth“ - ICH related to oral anticoagulants -

INR < 1.5	PCC / + (N=31)	FFP / + (N=18)	VAK (N=6)
Growth	19.3% P<0.01	33.3%	50%

INR < 1.5 within 2 hours	26 (83%) P<0.01	7 (38.8%)	0
Growth	19.2% n.s.	28.5%	0

Huttner et al. Stroke 2006;47:404-408

Conclusions

ESO recommendation

Conclusion

1. Acute hypertension: Lowering blood pressure seems to be safe
2. Hematoma expansion
   - No hemostatic therapy outside of trials
   - Consider individually: evacuation in lobar ICH without IV
3. Intraventricular hemorrhage and hydrocephalus
   - EVD if hydrocephalus apparent
4. Elevated ICP: Consider intervention at ICP 20mmHg
5. Seizures: treat only if clinically / electrophysiologically detectable
6. Fever: normothermia
7. Thromboprophylaxis: LMWH / stockings+compression devices

Clinical routine – „difficult questions“

Basic management (RR, DVT, aso)…?

Prevention of hematoma growth..?

Surgical hemorrhage evacuation…?

External ventricular drainage…?

Management of brain edema…?

Management of intraventricular hemorrhage..?

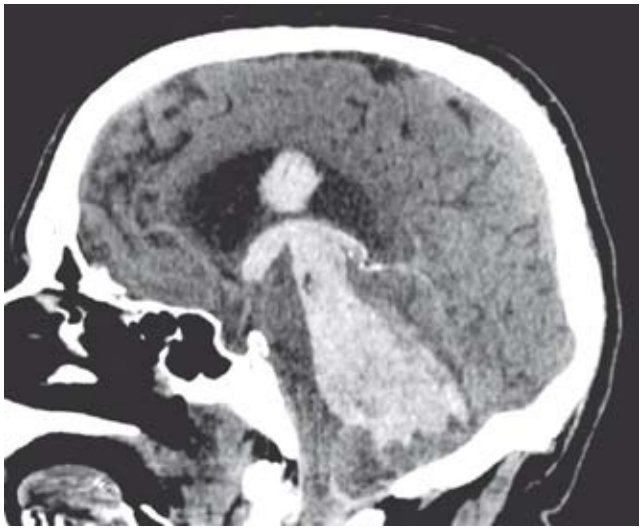
Subgroup OAC-ICH…?

Withdrawel of therapy..?

Termination of therapy: when and how?

IMAGES IN CLINICAL MEDICINE

Central Nervous System Hemorrhage



- **68 J., Warfarin (INR = 2,2); comatose, GCS = 3; areactive pupil; CT**
- **The only discussion of palliative therapy was in the last sentence:**

After discussions with the patient's family, the goals of care were shifted toward comfort measures. He was extubated and died.

PALLIMED

A HOSPICE & PALLIATIVE MEDICINE BLOG

Home | About | Contribute | Disclaimer | Privacy

All | Contributors | Post Type | Symptoms | Setting

Never Extubate a Dying Patient?

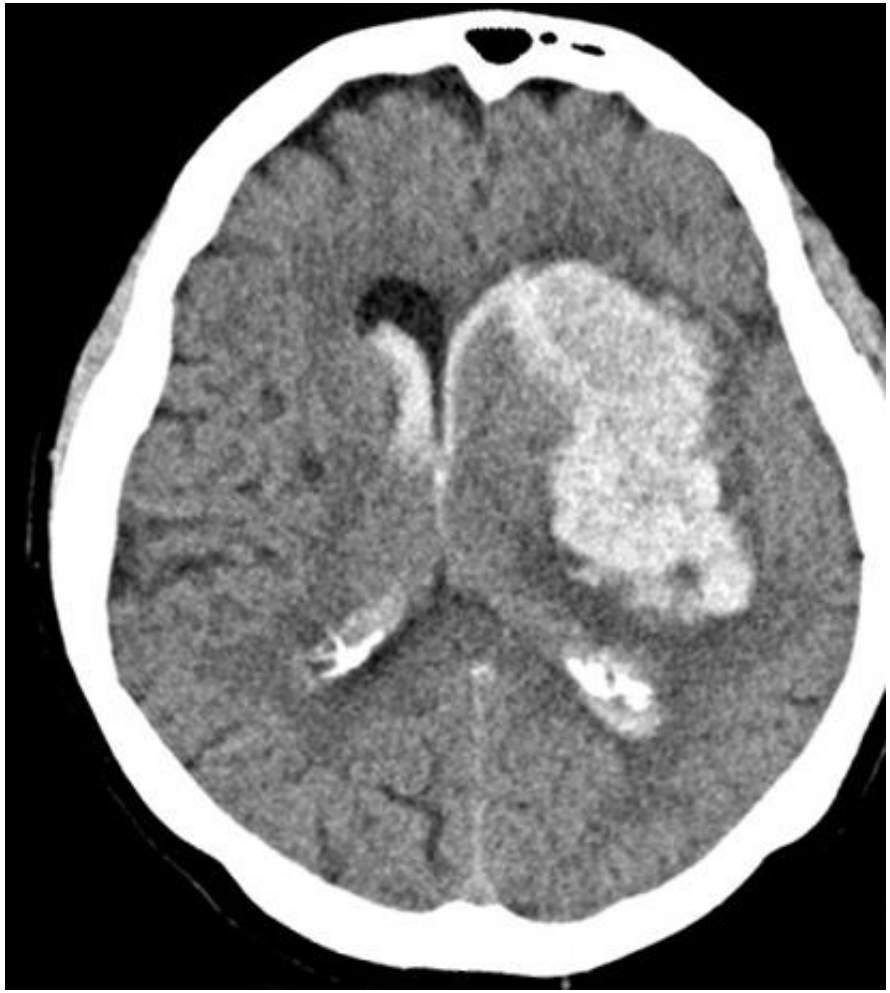
Being familiar with other medical blogs is a great way to keep up on how other doctors and nurses approach care for the dying. In fact, many of the most popular posts always seem to involve frustrations of medical futility, or the emotional impact of caring for dying patients. The range in tone for these p
demeaning of patients and families to eloquent and demonstrative of the c

A recent post by the anonymous blogger, the Buckeye Surgeon, highlighte
came across the post from Kevin MD, a popular medical blog aggregator.

Docs identify „significant“ brain activity

28.01.2013, 10:33 Uhr | AFP

fMRI durch Martin Monti



47-y male, 2h ago headache,
Hemiparese right, aphasia, Somnolent.

20%	10%
80%	90%
80%	90%
80%	90%
50%	70%
50%	70%
50%	70%
80%	90%
50%	50%
30%	50%
60%	90%
20%	60%

admission

- Normal (Morphin)
- Stroke (Mittelweg)
- Intensiv

EVD?

Intraventrikular lysis?

If sepsis then full therapy?

Dialysis if renal failure?

ARDS-treatment >72h?

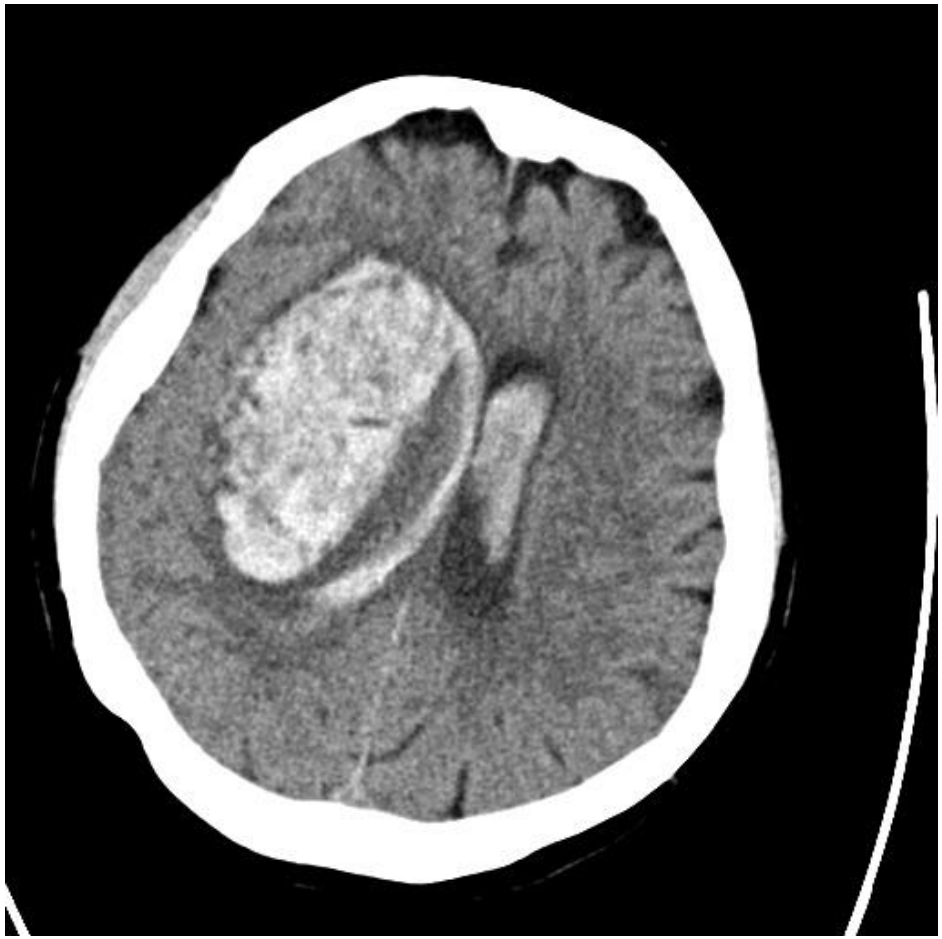
ICP Therapy:

- Mannitol
- Hypothermia?
- Barbiturates?

Reanimation:

- pharmacological?
- defibrillation?

If there was a standard advance directive



78-y woman, previous healthy,
3h ago acute hemiparesis left, dysarthria, Somnolenz.

90%	50%
10%	50%
10%	50%
10%	50%
10%	40%
0%	30%
0%	30%
10%	50%
0%	40%
0%	20%
10%	50%
0%	20%

admission

- Normal (Morphin)
- Stroke (Mittelweg)
- Intensiv

EVD?

Intraventrikular lysis?

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- Hypothermia?
- Barbiturates?

Reanimation:

- pharmacological?
- defibrillation?

If there was a standard advance directive

End-of-Life Practices in European Intensive Care Units

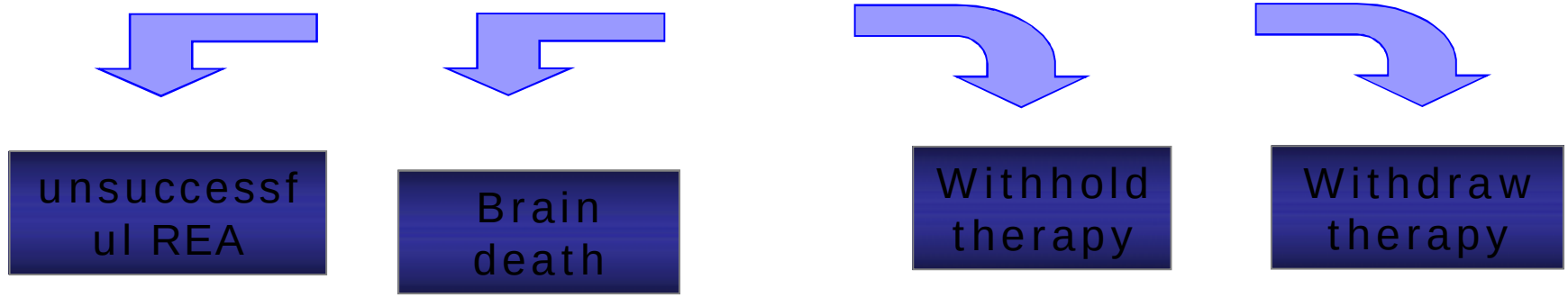
The Ethicus Study

JAMA, August 13, 2003—Vol 290,

Total (N = 4248)

Reasons for death

(mutually exclusive)

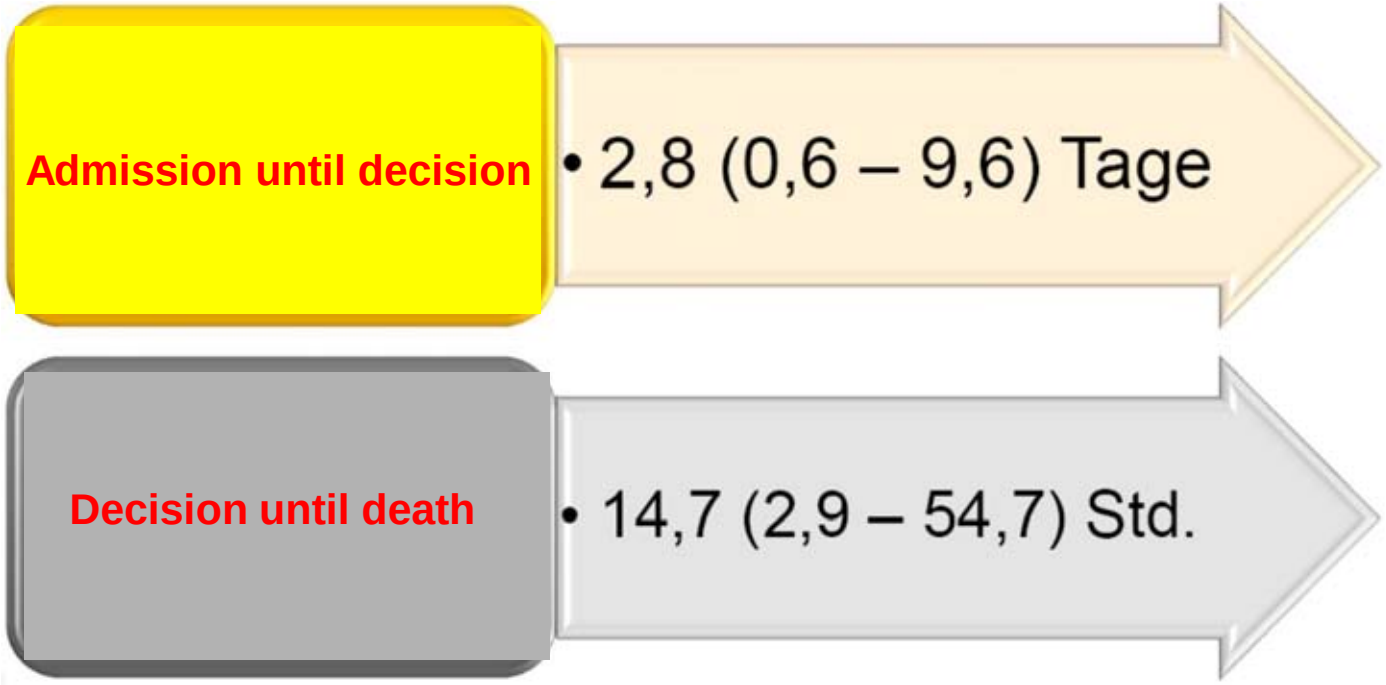


19.6% **7.8%** **37.5%** **35.1%**

End-of-Life Practices in European Intensive Care Units

The Ethicus Study

JAMA, August 13, 2003—Vol 290,

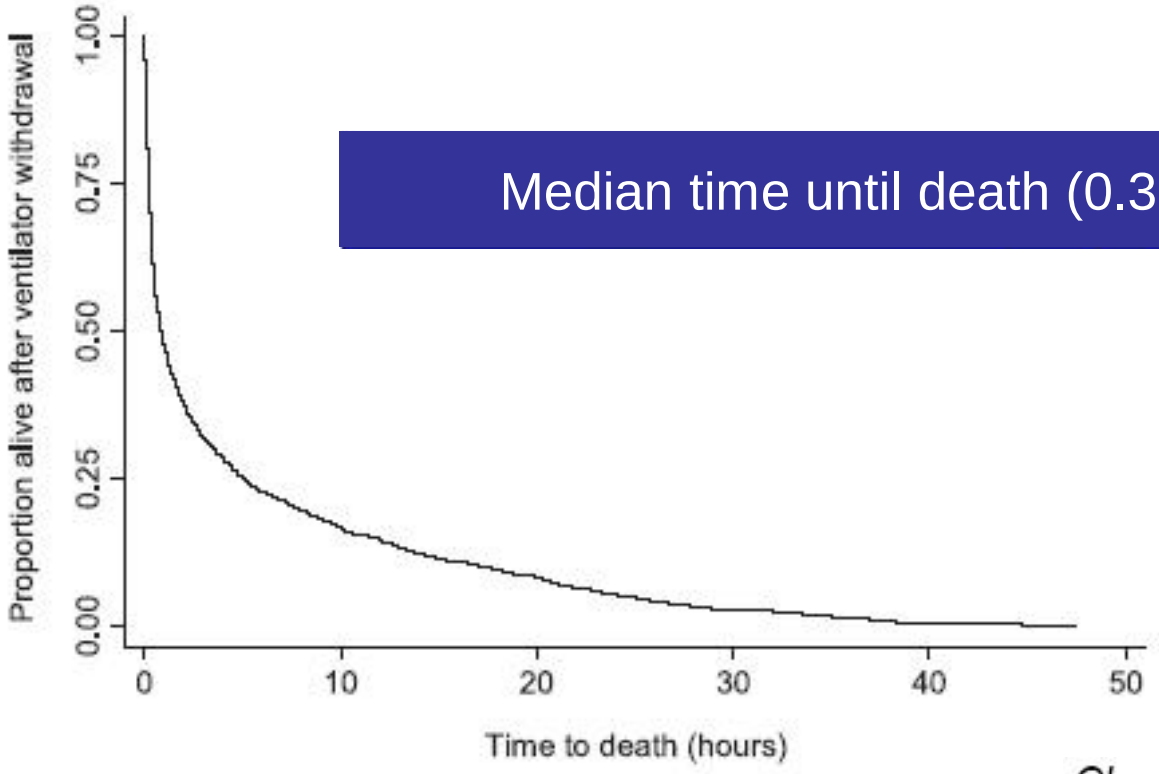


Withdrawel of therapy?

CHEST Original Research
CRITICAL CARE MEDICINE

Predictors of Time to Death After Terminal Withdrawal of Mechanical Ventilation in the ICU

Colin R. Cooke, MD; David L. Hotchkin, MD; Ruth A. Engelberg, PhD; Lewis Rubinson, MD, PhD, FCCP; and J. Randall Curtis, MD, FCCP

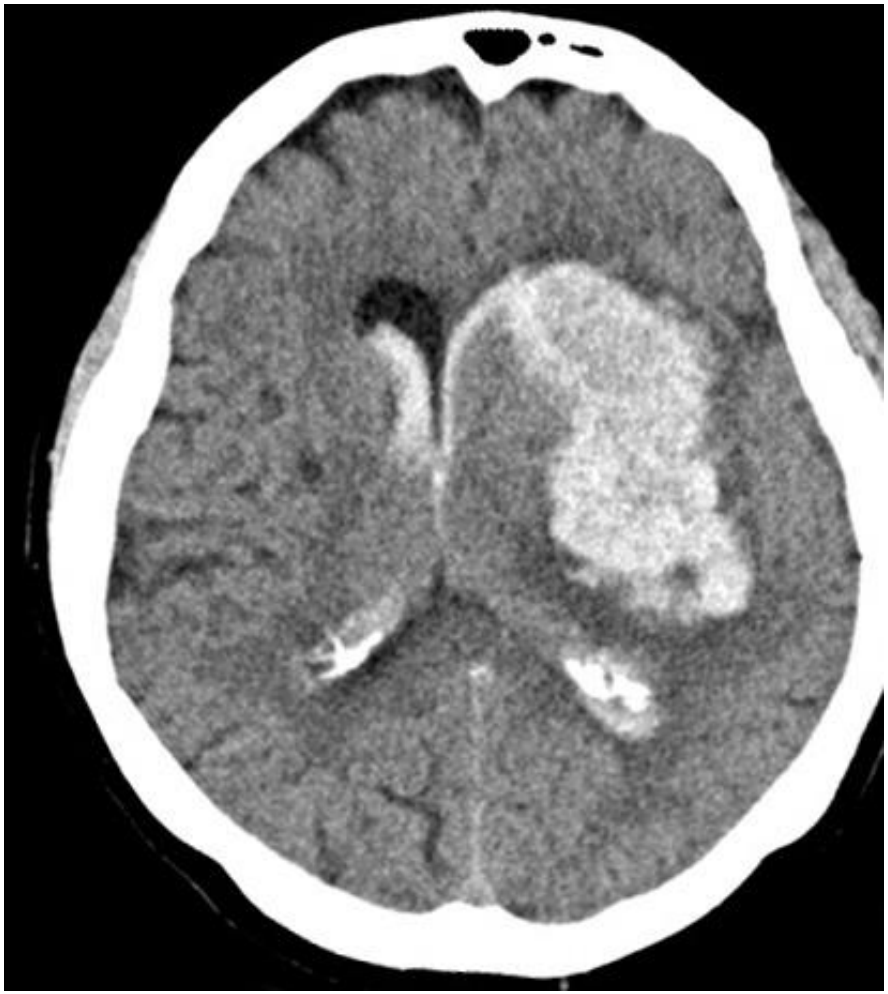


Median time until death (0.35-5.5 hours)

Chest 2010;138;289-297

Withdrawel of therapy?

Problem, if age is most important parameter for decision



Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies

K.J. Becker, MD; A.B. Baxter, MD; W.A. Cohen, MD; H.M. Bybee, BSN; D.L. Tirschwell, MD, MSc; D.W. Newell, MD; H.R. Winn, MD; and W.T. Longstreth, Jr., MD

NEUROLOGY 2001;56:766–772

Self fulfilling prophecy with withdrawal of life support

Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies

K.J. Becker, MD; A.B. Baxter, MD; W.A. Cohen, MD; H.M. Bybee, BSN; D.L. Tirschwell, MD, MSc; D.W. Newell, MD; H.R. Winn, MD; and W.T. Longstreth,

Neurology 2001

ARTICLES

Early care limitations independently predict mortality after intracerebral hemorrhage

D.B. Zahuranec, MD
D.L. Brown, MD
L.D. Lisabeth, PhD
N.R. Gonzales, MD

ABSTRACT Objective: Intracerebral hemorrhage (ICH) is associated with a high early mortality rate. We examined the impact of early do not resuscitate (DNR) orders and other limitations in aggressive care on mortality after ICH in a community-based study. Methods: C… 2000 to 2003 were identified from the Brain Attack Surveillance in…

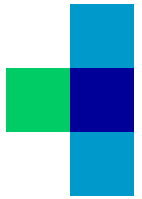
Neurology 2007

Neurologic Critical Care

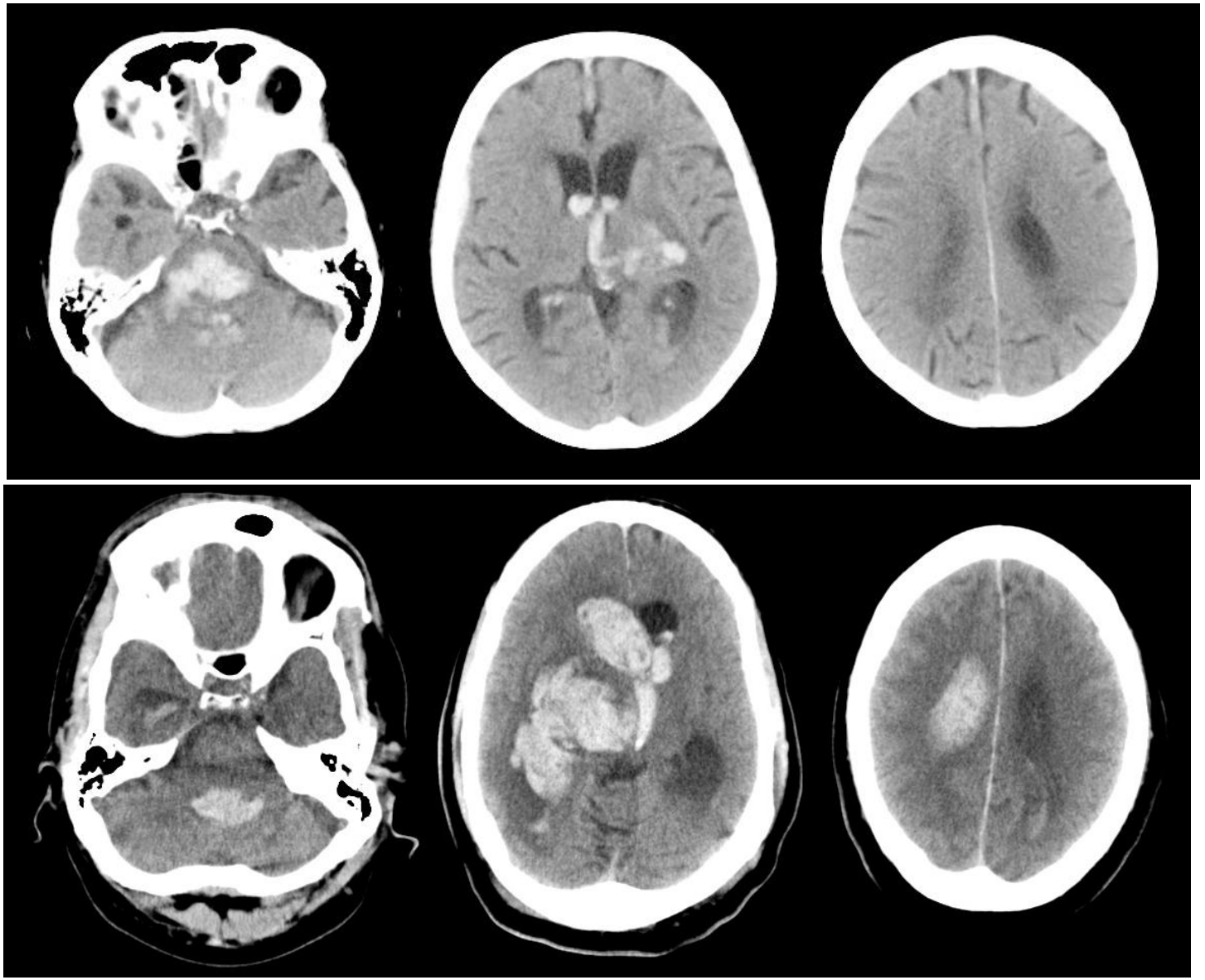
Do-not-attempt-resuscitation orders and prognostic models for intraparenchymal hemorrhage*

Claire J. Creutzfeldt, MD; Kyra J. Becker, MD; Jonathan R. Weinstein, MD, PhD; Sandeep P. Khot, MD; Thomas O. McPharlin, RPh; Thanh G. Ton, PhD; W. T. Longstreth, Jr., MD; David

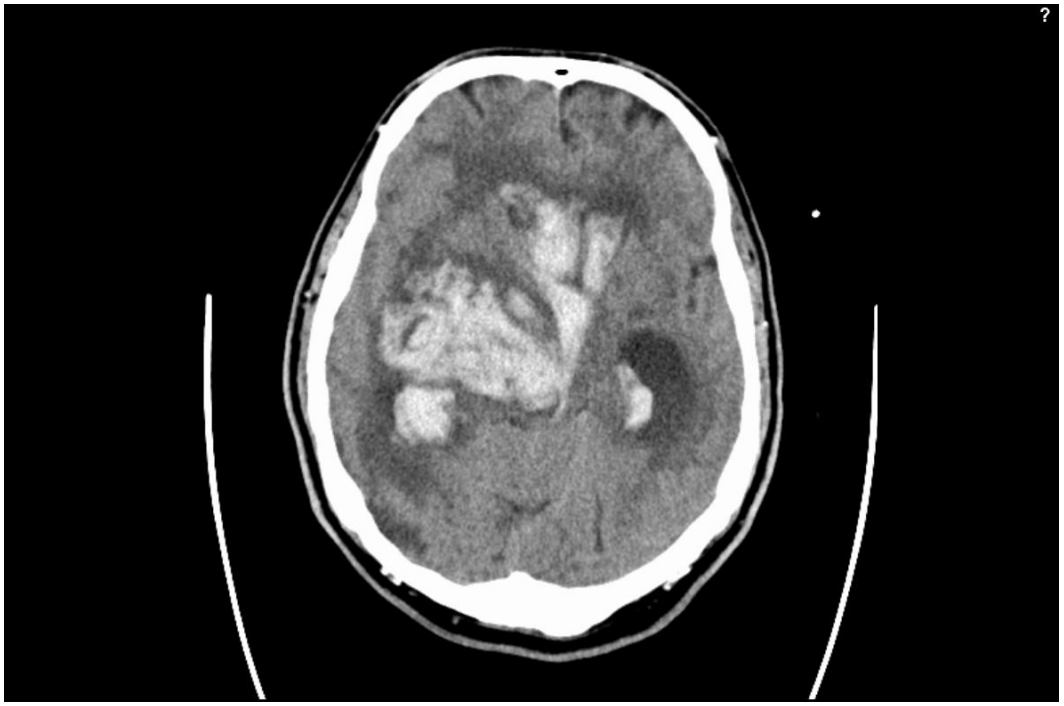
Crit Care Med 2011

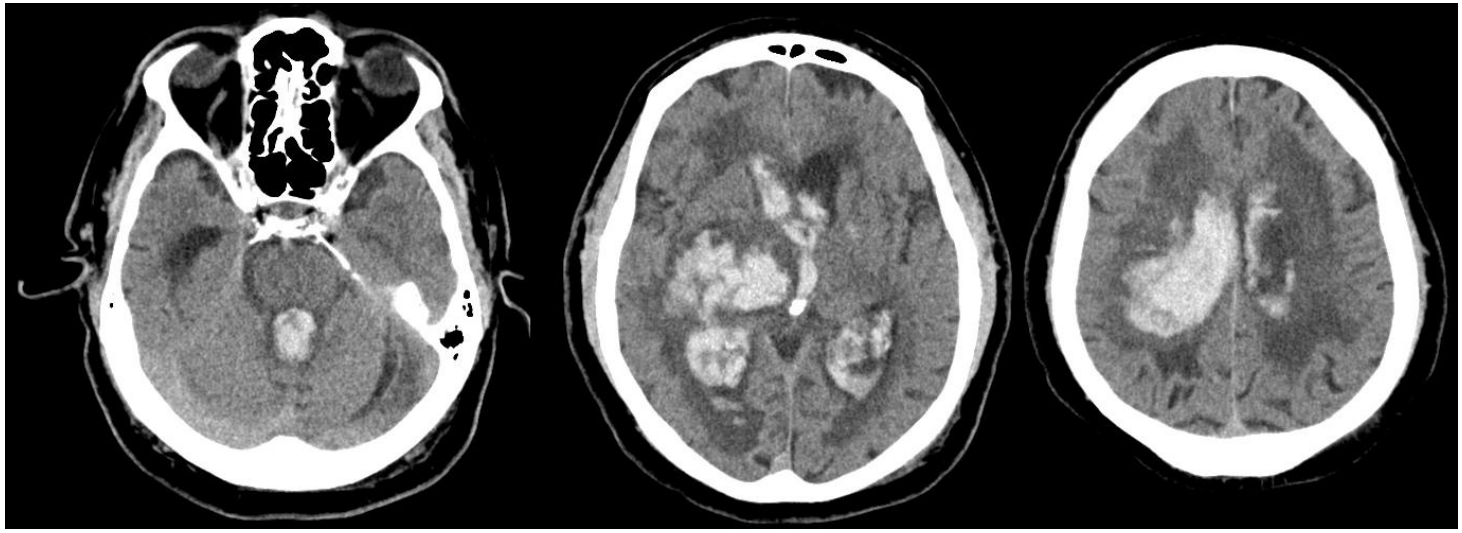


Withdrawel of therapy?



Withdrawel of therapy?





Withdrawel of therapy?

Clinician predictions of intensive care unit mortality*

Graeme Rocker, DM; Deborah Cook, MD; Peter Sjokvist, MD†; Bruce Weaver, MSc; Simon Finfer, MD; Ellen McDonald, RN; John Marshall, MD; Anne Kirby, MD; Mitchell Levy, MD; Peter Dodek, MD; Daren Heyland, MD; Gordon Guyatt, MD; for the Level of Care Study Investigators and the Canadian Critical Care Trials Group

Table 2. Factors predicting intensive care unit (ICU) mortality for 851mechanically ventilated patients

Independent Predictors of Mortality	HR (95% CI)	*p* Value
Admission illness severity		
APACHE II score (5-unit increments)	1.16 (1.08–1.24)	<.001
Daily factors		
MODS (5-unit increments)	2.50 (2.06–3.04)	<.001
Inotropic agents or vasopressors	2.14 (1.66–2.77)	<.001
Dialysis	0.51 (0.35–0.75)	.001

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Withdrawel of therapy?

~~Salus aegroti suprema lex~~

~~the welfare of the patient is to be the highest law~~

Voluntas aegroti suprema lex

the will of the patient is to be the highest law

We do know the will of the patient in ICH

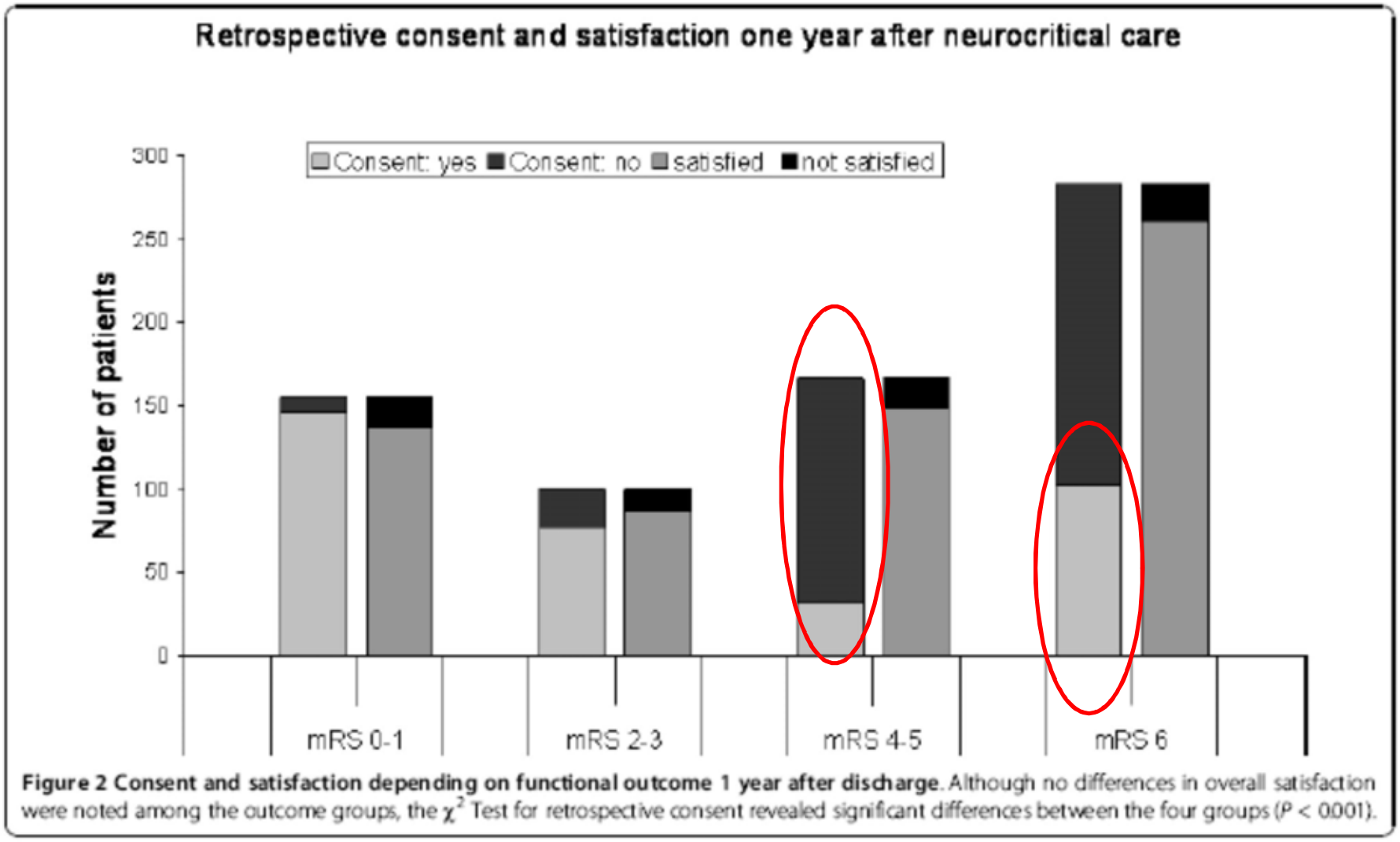

Figure 2 Consent and satisfaction depending on functional outcome 1 year after discharge. Although no differences in overall satisfaction were noted among the outcome groups, the χ^2 Test for retrospective consent revealed significant differences between the four groups ($P < 0.001$).

Kiphuth et al. 2010. Crit Care 14:R144

Table 4 Parameters predicting retrospective consent

	Consent to treatment OR (95% CI)	*P* value
Multivariate analysis		
Ischemia	**0.294 (0.169-0.509)**	**<0.0001**
ICH	**0.306 (0.173-0.541)**	**<0.0001**
Meningoencephalitis	1.076 (0.426-2.721)	0.8764
Epilepsy	0.568 (0.274-1.179)	0.1289
GBS/MG	0.698 (0.218-2.230)	0.5426
Neurodeg./Encephalopathy	0.821 (0.691-1.368)	0.2574
Cerebral neoplasm	**0.572 (0.378-0.911)**	**0.0097**
mRS	**0.610 (0.555-0.671)**	**<0.0001**

Kiphuth et al. 2010. Crit Care 14:R144

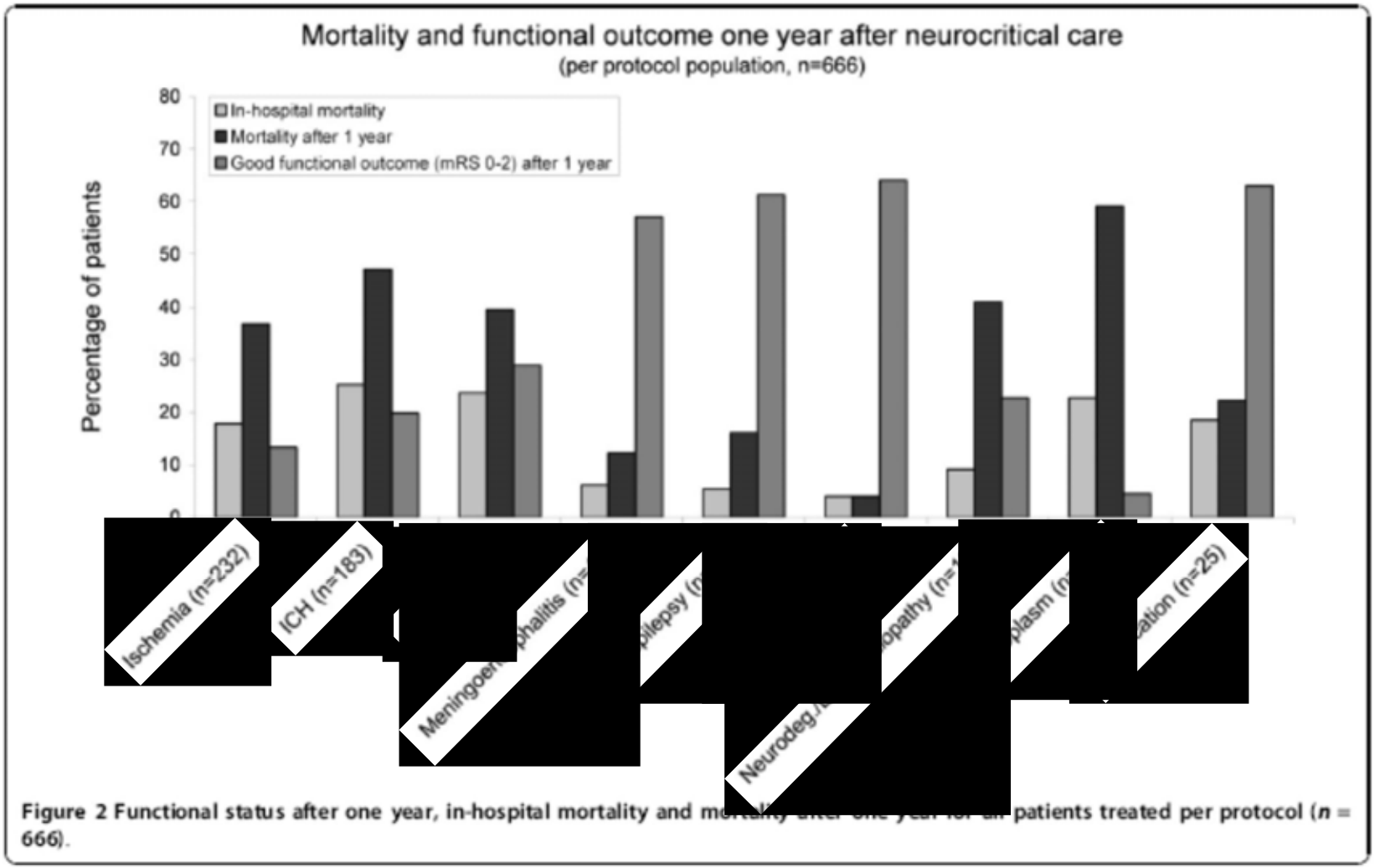

Figure 2 Functional status after one year, in-hospital mortality and mortality after one year for all patients treated per protocol (n = 666).

Kiphuth et al. 2010. Crit Care 14:R136