Management of Acute Stroke

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Acute Ischaemic Stroke

Evidence based Treatment: Acute Ischemic Stroke

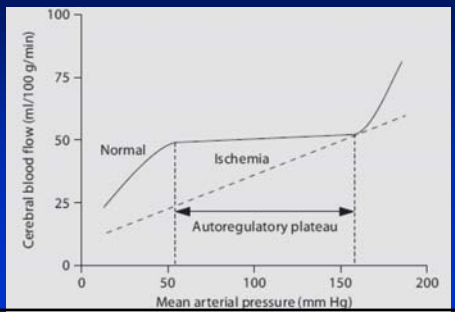
- Aspirin within 48 hours
- Medical care in the Acute Stroke Unit with multidisciplinary collaboration
- Intravenous thrombolytic therapy (by TPA) within 4.5 hours
- Decompressive hemicraniectomy for malignant MCA infarction

BP Management

- Hypertension occurs commonly after stroke. Even in patients without a history of hypertension, blood pressure is often elevated acutely and typically returns to baseline spontaneously over the first week.
- A U-shaped relationship between admission blood pressure and death has been found in some studies: both elevated and low blood pressures are associated with high rates of early and late death
- Theoretical reasons in favor of lowering elevated blood pressure acutely:
  - reduce the formation of edema
  - lessen the risk of hemorrhagic transformation.
  - allowing blood pressure to remain high risks acute myocardial infarction, pulmonary edema, and renal failure in a population already prone to cardiac and renal disease.

BP Management

- The acute treatment of hypertension is controversial
- Impaired autoregulation in the peri-infarct area will result in further reduction of cerebral blood flow (CBF) with lowering of blood pressure



BP Management

- Larger blood pressure reductions have been associated with early neurologic worsening, larger infarct volumes, and higher rates of poor outcome and death
- Current consensus: not to control BP unless:
  - SBP > 210, DBP > 120 or MBP > 150
  - Hypertensive urgency: APO, hypertensive encephalopathy, dissection, renal failure
- Preferred antihypertensive medication: IV and short acting for easy and fine titration:
  - Labetolol
  - Nicardipine
  - Esmolol

American Stroke Society 2009 Guidelines

Table 10. Recommendations for Treatment of Elevated Blood Pressure in Acute Ischemic Stroke

Blood Pressure Level	Treatment
Not eligible for thrombolytic therapy	
Systolic <220 mm Hg or diastolic <120 mm Hg	Observe unless there is other end-organ involvement, eg, aortic dissection, acute myocardial infarction, pulmonary edema, hypertensive encephalopathy. Treat other symptoms of stroke such as headache, pain, agitation, nausea, and vomiting. Treat other acute complications of stroke, including hypoxia, increased ICP, seizures, or hypoglycemia.
Systolic >220 mm Hg or diastolic <121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 min. May repeat or double every 10 min (maximum dose 300 mg) or Nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h. Aim for a 10% to 15% reduction of blood pressure
Diastolic >140 mm Hg	Nitroprusside 0.5 μg/kg per min IV infusion as initial dose with continuous blood pressure monitoring. Aim for a 10% to 15% reduction of blood pressure.

Induced Hypertension

- Rarely needed if head of bed flat, volume is euvolemic, pressure is not too low.
- Patients with fluctuating neurological deficits that were **NOT** treated with tPA
- Ensure intravascular volume is optimal prior to inducing hypertension (HTN)
- Treatment of blood pressure sensitive deficits in ischemic stroke that raises systolic BP by 20 to 30 % in an attempt to increase cerebral blood flow
  - Usually started in the setting of a low MBP (~ 80mm Hg) and targeted at a moderate MAP (~ 110mm Hg)
  - Max systolic BP 200 mm Hg

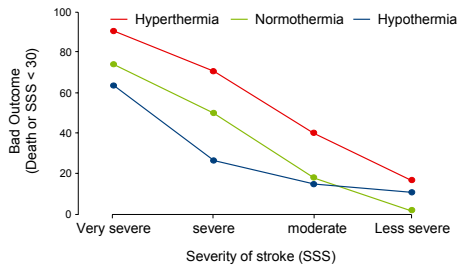
Induced Hypertension

- Phenylephrine
  - Monitor for left ventricular afterload that may not be well compensated for
- Norepinephrine/ Dopamine
  - Monitor for tachycardia
- Abort treatment if no improvement noted
- Risk of induced HTN therapy- reperfusion hemorrhage
- Remains an unproven treatment strategy
- Evidences only from case series: use of induced hypertension in patients who responded with an improvement in neurological exam had improved clinical outcome at discharge

Hyperthermia

- Fever (> 37.5^0 c)
- Correlation was found in a meta-analysis between temperature elevation and cerebral infarct volume
  - Increased body temp is a predictor of poorer patient outcome and is an independent factor in short and long-term mortality rate
  - Rationale: for additional injury may be related to increased metabolic demands and free radical production

Body temperature and acute stroke

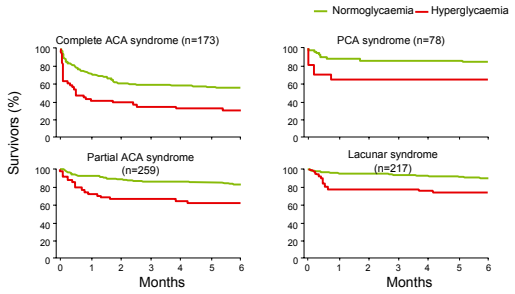


Lancet 1996; 347: 422-25.

Hyperthermia

- Fever (> 37.5^0 c)
  - Common within the first 48 hours (25%)
  - Warrants workup to identify etiology e.g. infection
  - Initiation of treatment specific to etiology
  - Treatment
    - Treatment of underlying pathology if possible
    - Immediate lowering of temperature
    - Acetaminophen by mouth or rectum: 1gm every 6 hours, as needed (not useful in RCT). Study using 6gm per day is ongoing
    - Ice packs & surface cooling

Acute hyperglycaemia (> 6.1 mmol/l) worsens prognosis of ischaemic stroke

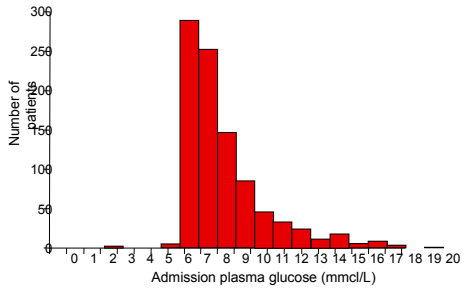


Weir CJ, et al., *BMJ* 1997; 314: 1303.

Hyperglycemia

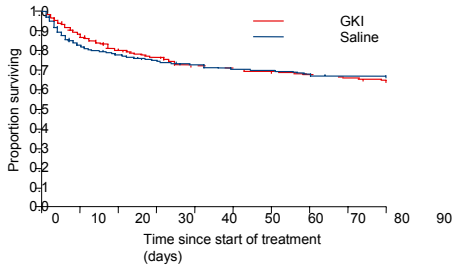
- Hyperglycemia is associated with:
  - Infarct expansion & worsening stroke outcomes
  - NINDS analysis found increased risk of hemorrhagic transformation and worse clinical outcome
- Etiology-unknown
  - Lactic acidosis and free radical production
  - Stress induced vs. undiagnosed diabetes
- Goal blood sugar: < 8mmol/l
- Treatment
  - Regular sc insulin or Insulin infusion

Admission glucose in Glucose Insulin Stroke Trial (GIST-UK)



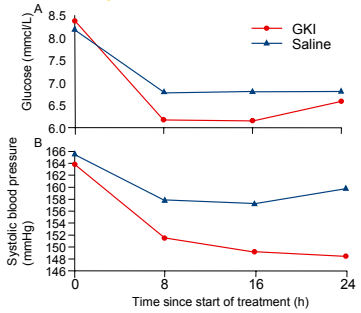
Lancet Neurology 2007; 6: 397-406.

Glucose reduction and outcome in GIST-UK



Lancet Neurology 2007; 6: 397-406.

Blood pressure in UK-GIST



mean difference in glucose 0·57 mmol/L (p<0·001)

mean difference in blood pressure 9·0 mmHg (p<0·0001)

Medical Treatment of Cerebral Edema

- Use of isotonic solution (normal saline) as maintenance instead hypotonic solution
- Intubation and Hyperventilation
  - Target pCO2 25-30mmHg
  - Transient effect
  - Induce secondary ischaemic injury due to vasoconstriction
  - Use as temporal measures
- Osmotic therapy
  - Mannitol
    - 0.25 to 0.5g/kg IV over 20 minutes q4-6h
    - Some use high dose 1.4g/kg in a bolus in case of sudden deterioration
    - Must avoid hypovolemia and hypotension that can accompany the excessive diuresis.
    - Timing and administration of subsequent doses can be guided by clinical response and monitored by the serum osmolality

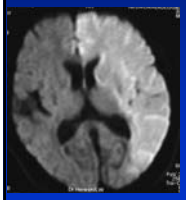
Medical Treatment of Cerebral Edema

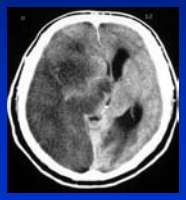
- Osmotic therapy
  - Hypertonic saline
    - Increasing evidence suggests its efficacy may be better than mannitol in acute ischemic stroke without the associated complications of hypovolemia
    - For acute lowering of ICP, 30-60ml of 23.4% saline is infused over 20 min.
    - 3% hypertonic saline infusions can be used to maintain serum Na gradients
- Moderate Hypothermia
  - 33-34°C
  - External cooling or endovascular cooling

Decompressive Hemicraniectomy

Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials

Katayoun Vahedi, Jeannette Hofmeijer, Eric Juettler, Eric Vicaut, Bernard George, Ale Algra, G Johan Amelink, Peter Schmiedeck, Stefan Schwab, Peter M Rothwell, Marie-Germaine Bousser, H Bart van der Worp, Werner Hacke, for the DECIMAL, DESTINY, and HAMLET investigators





DECIMAL (France)
HAMLET (Netherland)
DESTINY (Germany)

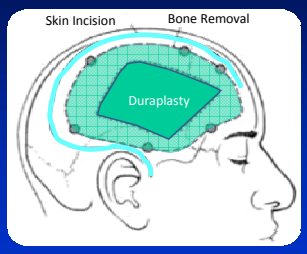
22.06.2010

Inclusion Criteria

Age 18-60
Clinical deficits suggestive of MCA territory infarct
NIHSS > 15
LOC ≥ 1 (not alert, but arousable to minor stimulation)
CT > 50% MCA territory infarct or DWI volume > 145 cm^3
Onset with 45 hours (Surgery within 48 hours of onset)
Written informed consent

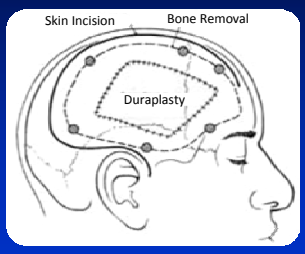
Surgical Procedure

- Large skin incision at the ear
- Bone flap removed
  - Diameter ≥ 12cm
  - Include frontal, temporal and parietal bones
- Dura opened
- Dural patch secured to enlarge the intradural space



Surgical Procedure

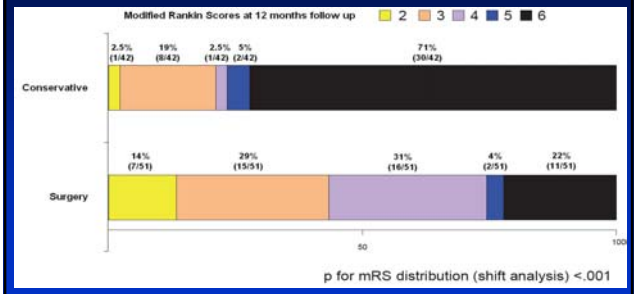
- Temporal muscles and skin flap re-approximated and sutured
- Infracted brain tissue not resected
- Cranioplasty after 6 weeks with stored bone flap or acrylate



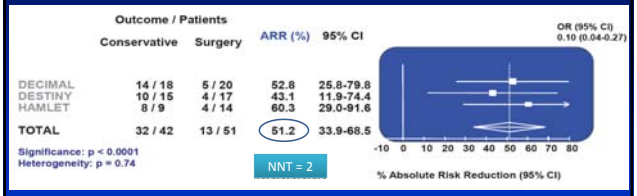
Demographics

	Surgery	Conservative
Age	46 +/- 9	44 +/- 9
History of TIA / Stroke	10%	5%
Aphasia	55%	60%
NIHSS	22 (19-25)	22 (21-27)
Hours to randomization	21.5 (17-29)	20.5 (14-28)

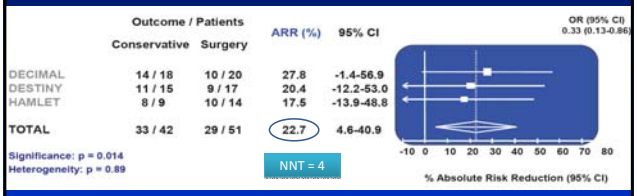
mRS at 12 months FU



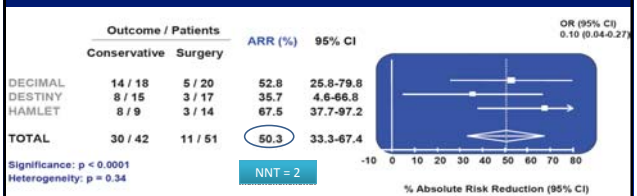
Primary Endpoint
mRS ≥ 5 at 12 months



Secondary Endpoint
mRS ≥ 4 at 12 months



Secondary Endpoint
Death at 12 months



Discussion

- It is a pooled analysis of three RCT
- Decompressive surgery increased survival from 28% to 78% and the probability of survival with mRS≤3 doubles
- The probability of survival in a condition requiring assistance from others (mRS 4) increases > 10 times
- The results can probably not be generalized to patients ≥60 yr old, but RCT is still ongoing for elderly population

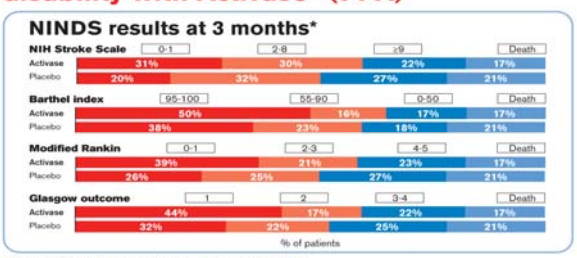
Evidence of IV TPA Treatment within 3hrs

National Institute of Neurological Disorder and Stroke (NINDS) trial

- double blinded randomized control trial
- 624 patients
- tPA - dose : ***0.9 mg/kg***
  window : 3 hrs
- early infarct signs in CT scan is NOT an exclusion criteria
- Target BP control :
  Protocol using IV Labetalol and/or IV Nitroprusside to maintain BP </= 180/105

NEJM 1995;333:1581-1587

More patients recover with minimal or no disability with Activase® (t-PA)



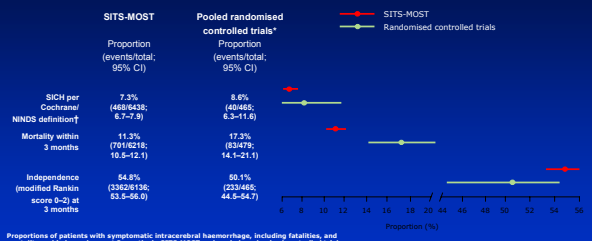
*Values do not total 100% because of rounding.
NIH = National Institutes of Health.
Scores of ≤1 on the NIHSS, 95 to 100 on the Barthel index, ≤1 on the modified Rankin scale, and 1 on the Glasgow outcome scale were considered to indicate a favorable outcome.
Reference: NINDS rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581-1587.

NINDS - Results

- As compared with patients given placebo, patients treated with tPA were at least 30% more likely to have minimal or no disability at 3 months, as measured by the outcome scale
- Absolute increase in favourable outcome : 11 to 13%
- Number needed to treat (NNT) : 8
- Overall symptomatic hemorrhages 6.4%, compared with 0.6% for placebo

Research result reproduced in clinical setting and community hospitals

Outcomes of SITS-MOST compared to randomised controlled trials

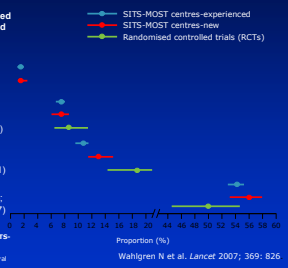


Proportions of patients with symptomatic intracerebral haemorrhage, including fatalities, and mortality and independence at 3 months in SITS-MOST and pooled randomised controlled trials
SICH=symptomatic intracerebral haemorrhage.
*Active arms. †NIHSS≤1 and any haemorrhage.

Wahlgren N et al. *Lancet* 2007; 369: 826

Outcomes for new and experienced centres in SITS-MOST compared with RCTs

	SITS-MOST		Randomised controlled trials*
	Experienced	New	
SICH rates per SITS-MOST†	1.6% (81/4958; 1.3–2.0)	1.7% (26/1486; 1.2–2.6)	NA
SICH rates per NINDS/Cochrane‡	7.3% (359/4947; 6.6–8.0)	7.3% (109/1491; 6.1–8.7)	8.6% (40/465; 6.3–11.6)
Mortality within 3 months	10.6% (505/4742; 9.8–11.6)	13.3% (196/1476; 11.6–15.1)	17.3% (83/479; 14.1–21.1)
Independence (modified Rankin Score, 0–2) at 3 months	54.4% (2544/4675; 53.0–55.8)	56.0% (818/1461; 53.4–58.5)	50.1% (233/465; 44.5–54.7)



Proportions of patients with symptomatic intracerebral haemorrhage, including fatalities, and mortality and independence at 3 months in experienced and new SITS-MOST centres and pooled randomised controlled trials
Data are % (n/N; 95% CI). SICH=symptomatic intracerebral haemorrhage. *Active arms. †NIHSS:4 and primary intracerebral haemorrhage/remote primary intracerebral haemorrhage type 2. ‡NIHSS:≤1 and any haemorrhage.

Wahlgren N et al. *Lancet* 2007; 369: 826

Evidence of IV TPA Treatment by meta-analysis

ARTICLES Lancet 2004; 363: 768–74

Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials

The results *suggest a potential benefit up to 4.5hr*, but this potential might come with some risks

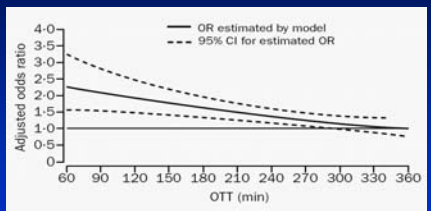


Figure 3: **Model estimating odds ratio for favourable outcome at 3 months in rt-PA-treated patients compared with controls by OTT**
Adjusted for age, baseline glucose concentration, baseline NIHSS measurement, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS measurement.

ARTICLES Lancet 2004; 363: 768–74

Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials

Pooled analysis
N = 2775
Median age = 68 yrs
0.9% Asians
Median baseline NIHSS 11
Median OTT 243 min

Odds of a favourable 3-month outcome increased as OTT decreased (p=0·005)

	Treatment	n	Odds ratio (95% CI)*	
			Adjusted	Unadjusted
Interval (min)				
0–90	rt-PA	161	2·81 (1·75–4·50)	1·96 (1·30–2·95)
	Placebo	150		
91–180	rt-PA	302	1·55 (1·12–2·15)	1·65 (1·23–2·22)
	Placebo	315		
181–270	rt-PA	390	1·40 (1·05–1·85)	1·34 (1·04–1·72)
	Placebo	411		
271–360	rt-PA	538	1·15 (0·90–1·47)	1·04 (0·84–1·29)
	Placebo	508		

3-month favourable outcomes include Rankin (0–1), Barthel (95–100), and NIHSS (0–1). One, eight, nine, and six patients from NINDS part I, ECASS I, ECASS II, and ATLANTIS B, respectively, were excluded from this analysis since they were randomised after 360 min or OTT was not reported. *Odds ratios calculated from global statistical approach[11] by ITT analysis. Adjusted odds ratios were calculated adjusting for age, baseline glucose concentration, baseline NIHSS, baseline diastolic blood pressure, previous hypertension, and interaction between age and baseline NIHSS.

Table 1: **Odds ratio for a favourable outcome at 3 months after stroke**

Evidence of IV TPA Treatment from 3 to 4.5hr

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 25, 2008 VOL. 359 NO. 13

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

Werner Hacke, M.D., Markku Kaste, M.D., Erich Bluhmki, Ph.D., Miroslav Brozman, M.D., Antoni Dávalos, M.D., Donata Guidetti, M.D., Vincent Larrue, M.D., Kennedy R. Lees, M.D., Zakaria Medeghri, M.D., Thomas Machnig, M.D., Dietmar Schneider, M.D., Rüdiger von Kummer, M.D., Nils Wahlgren, M.D., and Danilo Toni, M.D., for the ECASS Investigators*

ECASS-III

Results

An absolute improvement of 7.2%

Table 3. Odds Ratios for Primary End Point and Secondary End Point, Including Components, in the Intention-to-Treat and Per-Protocol Populations at 90 Days.*

End Point	Intention-to-Treat Population				Per-Protocol Population			
	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value	Alteplase Group (N=375)	Placebo Group (N=355)	Odds Ratio (95% CI)	P Value
	no. (%)				no. (%)			
Primary end point								
mRS score of 0 or 1 — unadjusted analysis	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†	206 (54.9)	161 (45.4)	1.47 (1.10–1.97)	0.01†
mRS score of 0 or 1 — adjusted analysis‡	—	—	1.42 (1.02–1.98)	0.04‖				
Secondary end point								
Global outcome¶	—	—	1.28 (1.00–1.65)	0.05	—	—	1.39 (1.07–1.80)	0.02
mRS score of 0 or 1‖	219 (52.4)	182 (45.2)	1.34 (1.02–1.76)	0.04†	206 (54.9)	161 (45.4)	1.47 (1.10–1.97)	0.01†
Barthel Index score ≥95**	265 (63.4)	236 (58.6)	1.23 (0.93–1.62)	0.16†	248 (66.1)	211 (59.4)	1.33 (0.99–1.80)	0.06†
NIHSS score of 0 or 1††	210 (50.2)	174 (43.2)	1.33 (1.01–1.75)	0.04†	197 (52.5)	155 (43.7)	1.43 (1.07–1.91)	0.02†
GOS score of 1‡‡	213 (51.0)	183 (45.4)	1.25 (0.95–1.64)	0.11†	200 (53.3)	165 (46.5)	1.32 (0.98–1.76)	0.06†

The odds The odds for a favorable outcome (the ability to return to an independent lifestyle) after stroke were 28% higher with alteplase than with placebo

Table 5. Prespecified Safety End Points and Other Serious Adverse Events.*

Adverse Events	Alteplase Group (N=418)	Placebo Group (N=403)	Odds Ratio (95% CI)	P Value
	no. (%)			
Prespecified safety end points				
Any ICH	113 (27.0)	71 (17.6)	1.73 (1.24–2.42)	0.001
Symptomatic ICH				
According to ECASS III definition†	10 (2.4)	1 (0.2)	9.85 (1.26–77.32)	0.008
According to ECASS II definition‡	22 (5.3)	9 (2.2)	2.43 (1.11–5.35)	0.02
According to SITS–MOST definition§	8 (1.9)	1 (0.2)	7.84 (0.98–63.00)	0.02
According to NINDS definition¶	33 (7.9)	14 (3.5)	2.38 (1.25–4.52)	0.006
Fatal ICH	3 (0.7)	0	—	—
Symptomatic edema	29 (6.9)	29 (7.2)	0.96 (0.56–1.64)	0.89
Death	32 (7.7)	34 (8.4)	0.90 (0.54–1.49)	0.68

All occurred w/i the first 22-36 hrs after initiation of treatment

Management after IV rTPA given

Monitoring of patient after rTPA Rx

- Close observation is necessary for the first 24 hours
  - Every 15 minutes for 2 hours
  - Every 30 minutes for 4 hours
  - Then hourly observation
- Neurobservation and BP monitoring
  - Sleeping patient must be waken up to confirm the conscious level
- Aim to detect any neurological deterioration and keep BP < 180/105

QEH post TPA BP control Protocol

Blood Pressure Control Protocol

1) Monitor arterial blood pressure during the first 24 hours after starting treatment
   - Every 15 minutes for 2 hours after starting the infusion, then
   - Every 30 minutes for 6 hours, then
   - Every 60 minutes until 24 hours after starting treatment

2) The use of IV anti-hypertensive agents:

Drugs	Dilution	Common Range (50-60kg Adult)	Infusion Range
Labetalol (Trandate)	200mg in 100ml D5	0.5 – 2.5mg/min	15 -75ml/ hr
Nitroprusside (Niprid)	50mg in 50ml D5	0.5 – 10mcg/kg/min	2 – 36ml/hr

For sudden surge of BP, be aware of the development of the intracranial haemorrhage

3) If systolic blood pressure is 180 – 230 mm Hg or if diastolic blood pressure is 105 – 120 mm Hg for two or more readings 5 – 10 minutes apart, the following is recommended

- Give intravenous **labetalol 10 mg** bolus as slow injection. The dose may be repeated or doubled every 10 to 15 minutes up to a total dose of 150 mg.

  OR

  Give initial bolus dose of **labetalol 10mg** and then follow with a continuous labetalol infusion given at a rate of **1mg/min infusion (30ml/hr according to the standard dilution dosage**. Then step up by 0.5mg/min infusion **(15ml/hr each step)** every 15 minutes if BP still above target.
- **Monitor blood pressure every 15 minutes** during treatment and observe for development of hypotension. If BP< 160/90, started to titrate the infusion down by 15ml/hr every 15 minutes.
- Aim to keep BP 160-180/90-105

If systolic blood pressure is greater than 230 mm Hg or if diastolic blood pressure is in the range of 121 – 140 mm Hg for two or more readings 5 to 10 minutes apart, the following is recommended:

- Give intravenous **labetalol 20mg bolus** as slow injection . The dose may be repeated or doubled every 10 minutes up to a total dose of 150 mg.

  OR

  Give initial bolus dose of **labetalol 20mg** and then follow with a continuous labetalol infusion given at a rate of **1mg/min infusion (30ml/hr according to the standard dilution dosage**. Then step up by 0.5mg/min infusion **(15ml/hr each step)** every 15 minutes if BP still above target
- **Monitor blood pressure every 15 minutes** during use of labetalol treatment and observe for development of hypotension. If BP< 160/90, started to titrate the infusion down by 15ml/hr every 15 minutes.
- If no satisfactory response, infuse **sodium nitroprusside** (0.5 to 10 mcg/kg/minute) and started at **0.5 mcg/kg/min (2ml/hr infusion according to the standard infusion and usual body weight of 60kg)** and titrated up/down by 0.5 mcg/kg/min **(2ml/hr steps)** every 5-10 minutes to keep BP 160-180/90-105.
- Suggest ICU consultation if patient managed in ASU with nitroprusside infusion started
- Continue **monitoring of blood pressure every 5 -10 minutes while on nitroprusside.**

If the diastolic blood pressure is greater than 140 mm Hg for two or more readings to 10 minutes apart, the following is recommended:

- Infuse **sodium nitroprusside immediately as stated above**.
- Suggest ICU consultation if patient managed in ASU with nitroprusside infusion started.
- **Monitor blood pressure every 5-10 minutes** during the infusion of sodium, nitroprusside and observe for development of hypotension.

Further Care of Patient

- Minimise physical handling of patient
  - Strict bed rest for the first 24 hours
  - Safety precautions to prevent fall
- Minimise invasive procedures
  - Avoid foley insertion for at least 30 minutes after infusion
  - Avoid Ryle tube insertion for at least 24 hours
  - Leave heparin block in situ for blood taking if possible
  - If venepuncture is required, apply direct pressure to puncture site for 20 minutes

Key Observations

- Neurological deterioration
  - Decreased GCS
  - Increased weakness
- Symptoms suspicious of ICH
  - Sudden headache
  - Sudden vomiting/ nausea
  - Sudden surge of BP
- Systemic bleeding
- Allergic reaction

Perform CT brain as soon as possible if ICH is suspected

Also prepare to give 6 unit of platelet conc and 6 unit of cryoprecipitate/FFP

Symptomatic ICH after IV TPA Treatment

- No anti-dose
- Adequate replacement of Clotting factors and Platelet Concentrate
- Intubation and hyperventilation
- Neurosurgeon assessment

Table 1: Risk of symptomatic intracranial hemorrhage related to administration of tissue plasminogen activator in the NINDS Stroke Study[15]

Pretreatment variable	Risk of symptomatic intracranial hemorrhage, %
NIHSS score	
> 20 (most severe)	17
11–20	4–5
< 10 (least severe)	2–3
Edema or mass effect on CT	
Present	31
Absent	6

Stroke 1997; 28: 2109-18

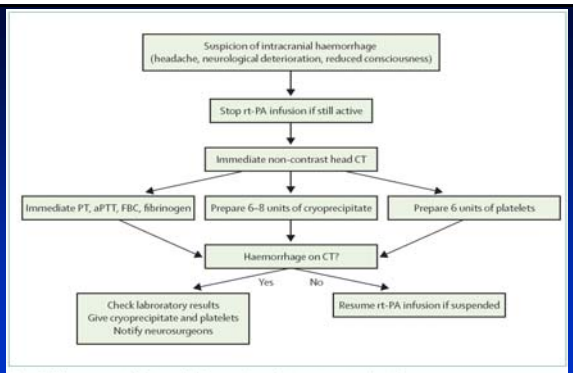


Figure 2: **Management of intracranial haemorrhage after treatment with rt-PA**
PT=prothrombin time. aPTT=activated partial thromboplastin time. FBC=full blood count.

Lancet 2007

Summary

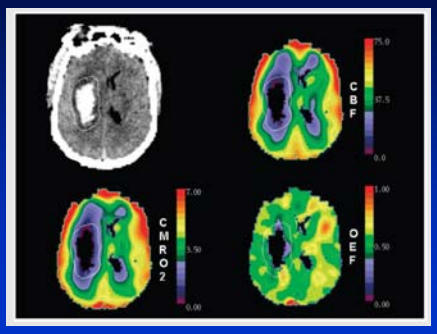
- Time is brain, act fast to deliver the drug.
- Main risk of treatment is ICH
- Tight BP control < 180/105 is important to reduce the complication of ICH
  - if the BP is not high initially, it is not common to have sudden surge up of hypertension. Such occurrence might be suggestive of developing ICH
- Observe for any neurological deterioration to consider repeated CT scan study

Intracerebral Haemorrhage

BP Management

- BP reduction
  - Potential benefits:
    - May ameliorate local edema
    - May limit early haematoma growth
  - Potential risk:
    - Aggravation of perilesional ischeamia

ICH PET Study: no evidence of peri-haematoma ischeamia



INTERACT study

- Randomized, openlabel,active-control, parallel-assignment, safety/efficacy study
- Randomized to aggressive BP management, with a goal of reducing systolic BP to less than 140 mm Hg within 1 hour, or standard management targeting systolic BP less than 180 mm Hg
- Mean time from symptom onset to treatment was around 4 hrs
- At 1 hour the mean systolic BP was 153 mm Hg in the intensive group and 167 mm Hg in the control group
- From 1 to 24 hours, BP was146 mm Hg in the intensive group and 157 mm Hg in the control group
- Mean proportional hematoma growth in the intensive group was 13.7% compared with 36.3% in the control group (difference 22.6%, 95% CI, 0.6-44.5%; P=.04) at 24 hours
- Intensive BP lowering treatment did not alter the risks of neurologic deterioration or secondary clinical outcomes at 90 days

Practical Recommendation

- To maintain a systolic BP < 180mmg Hg and/or mean BP < 130mmg Hg
- Reduction in mean arterial BP by 15% within the first 24 hrs is probably safe
- IV labetalol and nicardipine is the preferred drug for emergency use
- No solid data to support more aggressive BP control to arrive at a better clinical outcome

American Stroke ICH Guideline 2007

TABLE 2. Suggested Recommended Guidelines for Treating Elevated Blood Pressure in Spontaneous ICH

1. If SBP is >200 mm Hg or MAP is >150 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure (eg, MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

SBP indicates systolic blood pressure; MAP, mean arterial pressure.

Seizure Prophylaxis

- Seizure after ICH
  - 10% have generalized tonic-clonic seizures
  - No evidence of prevention of epileptogenesis with anticonvulsant
- Option: prophylactic phenytoin for 7 days for patients with large ICH at risk for increased ICH or patients with intracranial surgery done

Surgical Trial of ICH

Early surgery versus initial conservative treatment

(STICH Trial)

- 1033 primary ICH patients
- ICH onset within 72 hrs
- Favorable outcome at months
  - Early surgery: 26%
  - Initial conservative: 24%

(p=0.414)

Surgical Trial of ICH

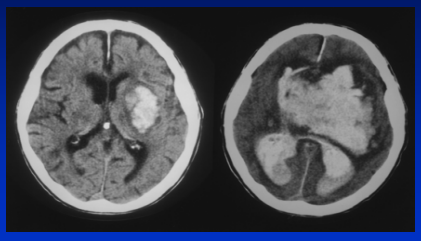
- Patients could be included if the responsible neurosurgeons was uncertain about the benefits of either Rx (the clinical uncertainty principle)
- Early surgery group: time between onset and surgery = 30 hr (median), 16% done within 12 hrs.
- Initial conservative Rx group: 26% underwent surgery after an initial period of observation.

	Early surgery (n=503)	Initial conservative treatment (n=530)
Site of haematoma		
Lobar	196 (39%)	214 (40%)
Basal ganglia/thalamic	210 (42%)	224 (42%)
Both	94 (19%)	90 (17%)
Not assessable	3 (1%)	2
Left side of haematoma	265 (53%)	285 (54%)
Haematoma volume (mL)*	40 (24–63)	37 (23 – 60)
Minimum depth from cortical surface (cm)	1·0 (0·1–2·0)	1·0 (0·0–2·0)

Data are number (%) or median (IQR). *Volume=length×width×height/2.[28]

Table 2: **Haematoma characteristics**

Acute Haemostatic Treatment



On admission 1 hour later

Acute Haemostatic Treatment

FAST Study - Phase II dose-finding study

Recombinant Activated Factor VII (rFVIIa) in Acute ICH study

- 399 primary ICH patients
- Treatment given within 4 hours of ICH onset
- Randomized controlled trial
- Randomized to placebo and three different dosage of rFVIIa
- Primary outcome: % change in ICH volume at 24 hrs
- Clinical outcome: functional score at 90 days

Table 2. Lesion Volumes on CT According to Study Group.*

Variable	Placebo (N=96)	rFVIIa 40 μg/kg (N=108)	rFVIIa 80 μg/kg (N=92)	rFVIIa 160 μg/kg (N=103)	rFVIIa Combined (N=303)
Volume of ICH					
At baseline — ml	24±22	22±22	23±24	26±30	24±26
At 24 hr — ml	32±29	26±29	28±31	28±32	27±30
Estimated mean relative increase from baseline — % (98.3% CI)	29 (16 to 44)	16 (4 to 28)	14 (2 to 27)	11 (0 to 23)	14 (7 to 21)
P value, vs. placebo	—	0.07	0.05	0.02†	0.01†
Estimated mean absolute increase from baseline — ml (98.3% CI)	8.7 (4.9 to 12.4)	5.4 (1.7 to 9.0)	4.2 (0.3 to 8.0)	2.9 (−0.8 to 6.6)	4.2 (2.0 to 6.3)
P value, vs. placebo	—	0.13	0.04	0.008†	0.01†
Volume of ICH plus IVH					
At baseline — ml		29±29	25±24	27±28	30±31	27±28
At 24 hr — ml		38±37	30±34	33±36	33±36	32±36
Estimated mean relative increase from baseline — % (98.3% CI)	31 (18 to 46)	16 (4 to 28)	14 (2 to 27)	13 (2 to 25)	14 (7 to 21)
P value, vs. placebo	—	0.04	0.03	0.01†	0.006†
Estimated mean absolute increase from baseline — ml (98.3% CI)	10.8 (6.0 to 15.6)	7.2 (2.5 to 11.8)	5.1 (0.1 to 10.0)	4.0 (−0.8 to 8.7)	5.4 (2.7 to 8.2)
P value, vs. placebo	—	0.19	0.05	0.02†	0.02
Volume of ICH plus IVH plus edema					
At 72 hr — ml		69±58	56±48	50±43	51±42	53±45
Estimated mean difference from placebo — ml (98.3% CI)	—	−6.5 (−17.1 to 4.0)	−12.2 (−23.2 to 1.3)	−14.4 (−25.1 to −3.7)	−11.0 (−19.7 to −2.1)
P value, vs. placebo	—	0.14	0.008†	0.001†	0.003†

Table 3. Clinical Outcomes and Thromboembolic Severe Adverse Events at 90 Days According to Study Group.*

Variable	Placebo (N=96)	rFVIIa 40 μg/kg (N=108)	rFVIIa 80 μg/kg (N=92)	rFVIIa 160 μg/kg (N=103)	rFVIIa Combined (N=303)
Survival					
Died — no. (%)	28 (29)	19 (18)	17 (18)	20 (19)	56 (18)
Odds ratio for survival (95% CI)	—	1.9 (1.0–3.8)	1.8 (0.9–3.6)	1.7 (0.9–3.3)	1.8 (1.1–3.0)
P value		0.05	0.10	0.11	0.02
Modified Rankin Scale†					
Unfavorable outcome — no. (%)	66 (69)	59 (55)	45 (49)	56 (54)	160 (53)
Odds ratio for improvement (95% CI)	—	2.2 (1.1–4.0)	2.4 (1.3–4.6)	2.1 (1.1–4.1)	2.2 (1.3–3.8)
P value	—	0.02	0.008	0.02	0.004
Extended Glasgow Outcome Scale‡					
Unfavorable outcome — no. (%)	78 (81)	78 (72)	66 (72)	77 (75)	221 (73)
Odds ratio for improvement (95% CI)	—	1.9 (0.9–3.8)	1.5 (0.7–3.2)	1.4 (0.7–3.0)	1.6 (0.9–3.0)
P value	—	0.09	0.28	0.36	0.14
Barthel Index§					
Median score	25.0	55.0	67.5	55.0	60.0
P value	—	0.07	0.01	0.02	0.006
National Institutes of Health Stroke Scale¶					
Median score	12.5	6.0	5.0	7.0	6.0
P value	—	0.03	0.004	0.02	0.008
Thromboembolic serious adverse events — no. (%)					
Total	2 (2)	7 (6)	4 (4)	10 (10)	21 (7)
Arterial	0	6 (6)	2 (2)	8 (8)	16 (5)
Venous	2 (2)	1 (1)	2 (2)	2 (2)	5 (2)

Efficacy and Safety of Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

Stephan A. Mayer, M.D., Nikolai C. Brun, M.D., Ph.D., Kamilla Begtrup, M.Sc., Joseph Broderick, M.D., Stephen Davis, M.D., Michael N. Diringer, M.D., Brett E. Skolnick, Ph.D., Thorsten Steiner, M.D., for the FAST Trial Investigators

FAST II Study – Phase III Study

N Engl J Med
Volume 358(20):2127-2137
May 15, 2008

Table 1. Baseline Characteristics and Timing of Treatment.*

Variable	rFVIIa, 20 μg/kg (N=276)	rFVIIa, 80 μg/kg (N=297)	Placebo (N=268)
Age (yr)	65±14	65±13	65±14
Male sex (%)	61	61	63
Race or ethnic group (%)†			
White	72	69	67
Black	9	9	9
Asian	16	18	21
Unknown or other	3	3	3
Location of hemorrhage (%)‡			
Deep gray matter	77	80	78
Lobar regions	23	20	20
Cerebellum	2	2	4
Brain stem	3	2	3
Intraventricular hemorrhage (%)	35	41	29
Glasgow Coma Scale score§			
Median	14	14	15
Range	6–15	6–15	6–15
Glasgow Coma Scale score of 6–8 (%)	6	6	3
NIHSS score¶	13±7	13±7	13±6
Systolic blood pressure at treatment (mm Hg)	179±30	182±32	180±28
Left ventricular hypertrophy on baseline ECG (%)	31	30	23
Time from onset of symptoms to treatment (min)	161±37	160±36	160±38
Treated ≤3 hr after onset of symptoms (%)	72	74	72

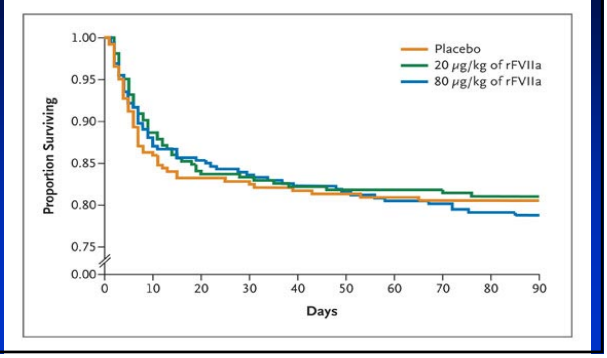
* Plus–minus values are means ±SD. Percentages may not add to 100 because of rounding. ECG denotes electrocardiogram, NIHSS National Institutes of Health Stroke Scale, and rFVIIa recombinant activated factor VII.
† Race or ethnic group was reported by the patient or a family member.
‡ More than one region could be involved in a given patient.
§ Scores range from 15 (normal) to 3 (deep coma).
¶ Scores range from 0 (normal) to 42 (coma with quadriplegia).

Table 2. Hemorrhage Volumes at Baseline and Follow-up.*

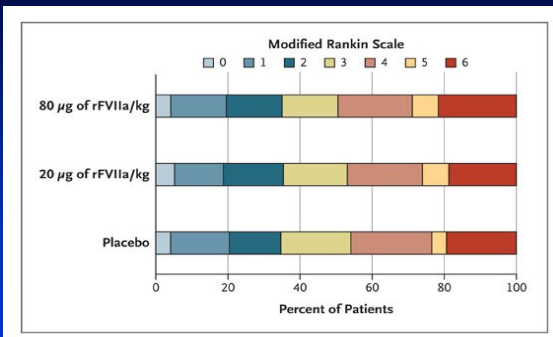
Variable	rFVIIa, 20 μg/kg (N=276)	rFVIIa, 80 μg/kg (N=297)	Placebo (N=268)
Volume of intracerebral hemorrhage			
At baseline — ml	24±26	23±26	22±24
At 24 hr — ml	28±30	25±28	28±31
Estimated percent increase from baseline — mean (95% CI)	18 (13 to 24)	11 (6 to 17)	26 (20 to 32)
P value vs. placebo	0.09	<0.001	—
Estimated milliliters of increase from baseline — mean (95% CI)	4.9 (2.9 to 7.0)	3.7 (1.7 to 5.7)	7.5 (5.4 to 9.6)
P value vs. placebo	0.08	0.009	—
Volume of intraventricular hemorrhage			
At baseline — ml	3.6±8.0	5.3±11.7	2.7±7.5
At 24 hr — ml	5.8±17.2	5.4±10.8	4.6±10.3
Estimated milliliters of increase from baseline — mean (95% CI)	2.0 (0.6 to 3.3)	1.0 (−0.2 to 2.3)	1.6 (0.3 to 3.0)
P value vs. placebo	0.74	0.51	—
Volume of intracerebral hemorrhage plus intraventricular hemorrhage plus edema			
At baseline — ml	46±45	46±49	42±47
At 72 hr — ml	71±69	65±66	68±67
Estimated milliliters of increase from baseline — mean (95% CI)	26 (21 to 31)	22 (17 to 27)	29 (23 to 34)
P value vs. placebo	0.53	0.06	—

* Plus–minus values are means ±SD. For estimated mean increases, 95% confidence intervals (CIs) are derived from a linear mixed model with the patient and the center as random effects and baseline volume of the hemorrhage, time from onset of symptoms to baseline CT scan, and time from baseline CT scan to treatment as fixed effects. CT scans at 24 hours were missing for 12 patients receiving placebo, 17 receiving 20 μg of rFVIIa (recombined activated factor VII) per kilogram, and 12 receiving 80 μg of rFVIIa per kilogram.

Kaplan-Meier Survival Curves



Clinical Outcome at 90 Days According to the Modified Rankin Scale



Conclusion of FAST II Study

Hemostatic therapy with rFVIIa reduced growth of the hematoma but did not improve survival or functional outcome after intracerebral hemorrhage

Management of Warfarin related ICH

Hematoma Growth in Oral Anticoagulant Related Intracerebral Hemorrhage

Brett Cucchiara, MD; Steven Messe, MD; Lauren Sansing, MD; Scott Kasner, MD; Patrick Lyden, MD; for the CHANT Investigators

	SICH (n=267)	OAT ICH (n=18)	*P* Value
ICH volume change, median (IQR)	0.9 mL (0–5.4)	9.6 mL (0–19.4)	0.03
>33% ICH expansion	26%	56%	0.006
Any ICH expansion	65%	78%	0.27
	SICH (n=282)	OAT ICH (n=21)	*P* Value
Mortality	17%	62%	<0.001
mRS 4–6	50%	90%	0.001

(*Stroke*. 2008;39:2993-2996.)

Vitamin K

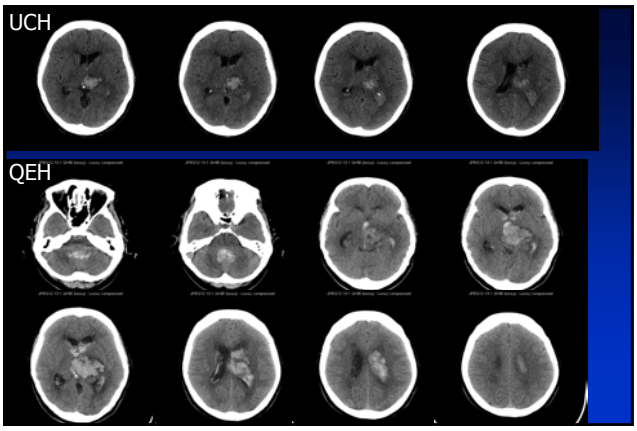
- Usually 10mg iv, Take 6-24 h to correct the INR
- Replacement of factors IX and X might take >24 hours
- To sustain the reversal of the warfarin effect. Replacement of clotting factors by FFP alone is not long lasting
- Risk of anaphylaxis with intravenous injection (very rare)
- Warfarin resistance in higher doses up to 1 wk

FFP Infusion

- Replacement of all clotting factors
- Requires checking for ABO blood compatibility
  - With prior type & screen, take 0.5 hr for unfrozen procedure in blood bank, 1 hr for infusion (Total: 1.5 hr)
  - Without prior type & screen, take 2 hr for cross match, 0.5 hr for unfrozen procedure in blood bank, 1 hr for infusion (Total: 3.5 hr)
- Usual dosage: 15 ml/kg infusion
- 1 to 2 hr for infusion, typical 12-32 h for reversal
- Rapid infusion of large volume of FFP might cause fluid overload

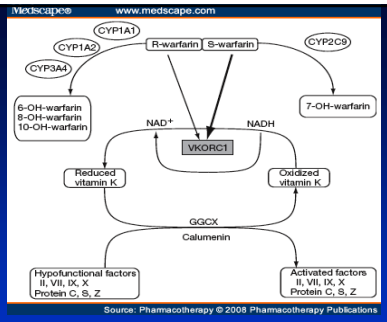
Case example

- F/57
- Transferred from UCH with warfarin related ICH to NS unit
- On arrival GCS 14
- Vit K not given, 6 unit FFP ordered
- Deteriorated to GCS 11 (40 minutes later)
- Deteriorated to GCS 7 (60 minutes later)
- FFP still not yet started. FFP started 2.5 hr later
- Patient died

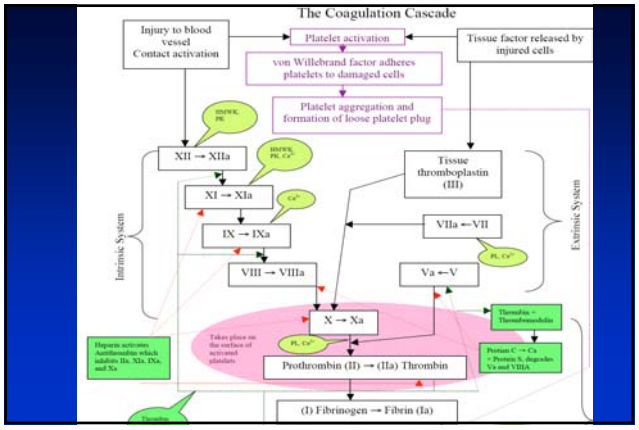


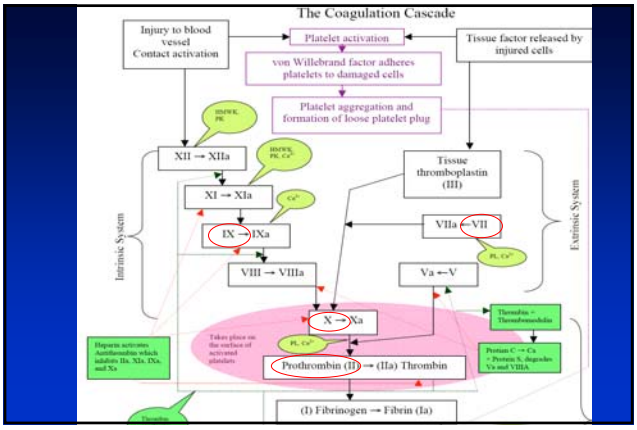
Implication

- Half of the patients with warfarin related ICH will deteriorate, most within 6 hrs, due to ICH expansion
- FFP was not fast enough to reverse the bleeding tendency
- Any other treatment?



Warfarin inhibit the vitamin K action to produce Factor II, VII, IX and X





Prothrombin Complex Concentrate (PCC)

- It contains factor II, IX, X +/- VII
- Previously widely used in the treatment of hemophilia B prior to the availability of high-purity plasma-derived and recombinant Factor IX concentrates
- Have been commonly used to treat warfarin-associated ICH in Europe
- Commercial products in powder for reconstitution (not a blood product from Blood Bank)

Prothrombin Complex Concentrate (PCC)

- Use of PCCs normalizes the INR more rapidly (within 15 minutes) than FFP infusion, although its effect on clinical outcomes is unproved
- No ABO blood group needed
- Optimal dosage not well defined. 25 to 50U/kg infusion in 10 minutes
- Limited availability, cost, variable cofactor content based on manufacturer
- Potentially prothrombotic

Studies comparing PCCs with FFP

- Fredriksson et al: retrospective review
  - comparing PCC (average dose 25.8 U/kg) with FFP (average 600ml) in 17 patients with ICH
  - PCC was associated with a significantly shorter time to INR correction ($P < 0.001$)
  - PCC significantly reduced the progression of ICH signs and symptoms compared with FFP ($P < 0.05$)
- Makris et al: retrospective review
  - comparing the efficacy of PCC injection or FFP infusion in 41 patients with major bleeding or who required urgent reversal of warfarin therapy
  - Complete correction of the INR occurred within 15 min in 28 of 29 patients treated with PCC (50 U/kg) versus none of 12 patients given FFP (800ml)

Am. J. Hematol. 83:137–143, 2008.

Studies comparing PCCs with FFP

- Boulis et al: randomized controlled study
  - The rate of INR correction was significantly greater ($P < 0.01$) and the time to correction significantly shorter ($P < 0.01$) in patients with ICH treated with FFP plus PCC (40– 50 U/kg; n=5) versus FFP alone (n=8).
  - Although no difference in neurologic outcomes was noted between the 2 treatment groups, 5 of 8 patients who received FFP monotherapy had higher complication rates related to fluid overload
- Cartmill et al: case-controlled study
  - In 12 patients with ICH, PCC (50 U/kg) achieved a significantly more rapid and complete INR reversal and correction than FFP (800ml) ($P < 0.001$)

Am. J. Hematol. 83:137–143, 2008.

Role of prothrombin complex concentrates in reversing warfarin anticoagulation: A review of the literature

Cindy A. Leissinger,[1]* Philip M. Blatt,[2] W. Keith Hoots,[3] and Bruce Ewenstein[4]

Conclusion of the Review

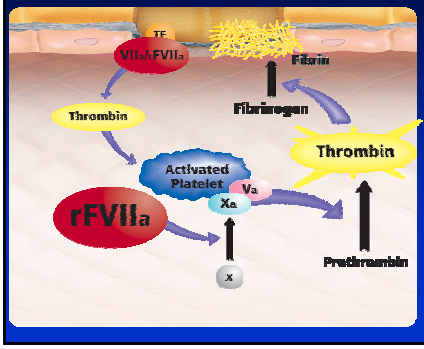
- While PCCs offer rapid and specific replacement of the depleted vitamin K-dependent factors, there is a pressing need for further evidence-based treatment guidelines to optimize therapy
- Until such trials are accomplished, accumulating experience demonstrates that PCCs are superior to FFP for the urgent reversal of warfarin in patients with life-threatening hemorrhage, especially in patients with profound suppression of vitamin K-dependent factors

Am. J. Hematol. 83:137–143, 2008.

Recombinant FVIIa (Novoseven)

- At pharmacologic doses, recombinant activated factor VII (rFVIIa) directly activates factor X on the surface of activated platelets, resulting in a thrombin burst and acceleration of coagulation
- Bolus injection, reversal of INR within 15 minutes
- Short half-life, very expensive
- Potentially prothrombotic,
- Uncertain safety?

NovoSeven® Mode of Action



Tissue factor (TF)/FVIIa, or TF/rFVIIa interaction, is necessary to initiatiate haemostasis

At pharmacological concentrations rFVIIa directly activates FX on the surface of locally activated platelets. This activation will initiate the "thrombin burst" independently of FVIII and FIX. This step is independent of TF.

The *thrombin burst* leads to the formation of a stable clot

Recombinant Factor VIIa for Rapid Reversal of Warfarin Anticoagulation in Acute Intracranial Hemorrhage

William D. Freeman, MD; Thomas G. Brott, MD; Kevin M. Barrett, MD; Pablo R. Castillo, MD; H. Gordon Deen, Jr, MD; Leo F. Czervionke, MD; and James F. Meschia, MD

- A consecutive series of 7 patients (median age, 87 years; 5 women) with symptomatic, nontraumatic warfarin-related ICH treated with intravenous rFVIIa
- Mean INR decreased from 2.7 to 1.08 after administration of rFVIIa
- The median Glasgow Coma Scale was 14 (range, 4-15).
- The mean time from onset to treatment was 6.2 hours.
- The mean initial dose of rFVIIa was 62.1 µg/kg.
- Five of the 7 patients survived and were dismissed from the hospital with significant disability (Glasgow Outcome Scale, 3)
- 2 patients died during hospitalization

Mayo Clin Proc. 2004;79(12):1495-1500

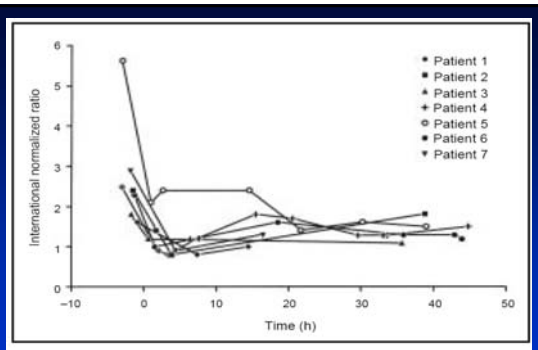
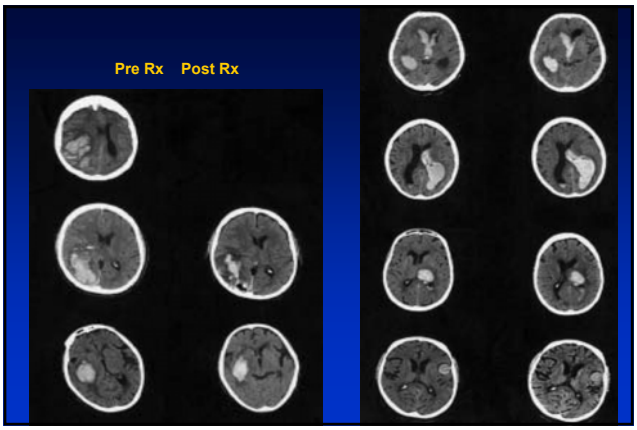


FIGURE 2. International normalized ratios before and as long as 48 hours after administration of recombinant factor VIIa. Time zero is defined as the time of administration of recombinant factor VIIa. Patients also received fresh frozen plasma, vitamin K, or both.



What Is the Evidence for the Off-label Use of Recombinant Factor VIIa (rFVIIa) in the Acute Reversal of Warfarin?

ASH Evidence-based Review 2008

Rachel P. Rosovsky[1] and Mark A. Crowther[2]

[1]Massachusetts General Hospital and Harvard Medical School, Boston, MA; [2]St. Joseph's Hospital and McMaster University, Hamilton, Ontario, Canada

- 13 publications with 1–16 patients included in each
- All publications were retrospective, nonrandomised and consisted largely of case series or case reports without adequate controls
- Most patients also received FFP as well as vitamin K in addition to the rFVIIa.
- Authors' conclusion: although the rFVIIa rapidly corrects the INR, its clinical impact on stopping bleeding was unclear

Hematology Am Soc Hematol Educ Program 2008:36–38

Adverse Effect of PCC and rFVIIa- Prothrombotic Effect

- The main adverse effect of concern with both PCC and rFVIIa is the risk of thrombosis when given to reverse the anticoagulation of individuals at high pro-thrombotic risk in the first place
- Leissinger et al:
  - systematic review of 14 clinical trials on the role of PCC in warfarin reversal
  - 7 (1.5%) thrombotic events (3 thrombotic strokes, 2DVTs and 2 non-Q-wave MIs) reported in a total of 460 patients

J Thromb Thrombolysis (2010) 29:171–181

Adverse Effect of PCC and rFVIIa- Prothrombotic Effect

- Insufficient patients on warfarin treated with rFVIIa to be able to evaluate the thrombotic risk in this specific situation.
- Hsia et al:
  - recent meta-analysis of 22 randomised controlled trials of rFVIIa in non-hemophilic patients
  - the thrombotic risk was higher for arterial events in the rFVIIa-treated patients at 4.5% compared to the placebo group 2.0%

J Thromb Thrombolysis (2010) 29:171–18

What is the standard Rx for acute reversal of warfarin effect?

- Vit K 10mg IV is a must
- Together with FFP or PCC or rFVIIa or any combination of them?
- No high level clinical outcome based evidence to support

What did the guidelines mention?

bjh guideline

Guidelines on oral anticoagulation (warfarin): third edition – 2005 update

T. P. Baglin,[1] D. M. Keeling,[2] and H. G. Watson[3] for the British Committee for Standards in Haematology

Recommendation

- Reversal of anticoagulation in patients with major bleeding requires administration of a factor concentrate (50U/kg) in preference to FFP (15ml/kg) , when this is available (grade B, level III)
- administration of intravenous (5 or 10mg) rather than oral vitamin K (grade B, level IIa)

 132, 277–285

Pharmacology and Management of the Vitamin K Antagonists*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Jack Ansell, MD; Jack Hirsh, MD; Elaine Hylek, MD, MPH; Alan Jacobson, MD; Mark Crowther, MD; and Gualtiero Palareti, MD

In patients with life-threatening bleeding (*eg*, intracranial hemorrhage) and elevated INR, regardless of the magnitude of the elevation,
We recommend holding warfarin therapy and administering fresh frozen plasma, PCC, or recombinant factor VIIa supplemented with vitamin K (10mg) by slow IV infusion, repeated, if necessary, depending on the INR (Grade 1C)

(CHEST 2008; 133;160S–198S)

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Joseph Broderick, Sander Connolly, Edward Feldmann, Daniel Hanley, Carlos Kase, Derk Krieger, Marc Mayberg, Lewis Morgenstern, Christopher S. Ogilvy, Paul Vespa and Mario Zuccarello

Stroke 2007;38;2001-2023; originally published online May 3, 2007;
DOI: 10.1161/STROKEAHA.107.183689

- Patients with warfarin-associated ICH should be treated with intravenous vitamin K to reverse the effects of warfarin and with treatment to replace clotting factors *(Class I, Level of Evidence B)*
- Prothrombin complex concentrate, factor IX complex concentrate, and rFVIIa normalize the laboratory elevation of the INR very rapidly and with lower volumes of fluid than FFP but with greater potential of thromboembolism. FFP is another potential choice but is associated with greater volumes and much longer infusion times *(Class IIb, Level of Evidence B)*

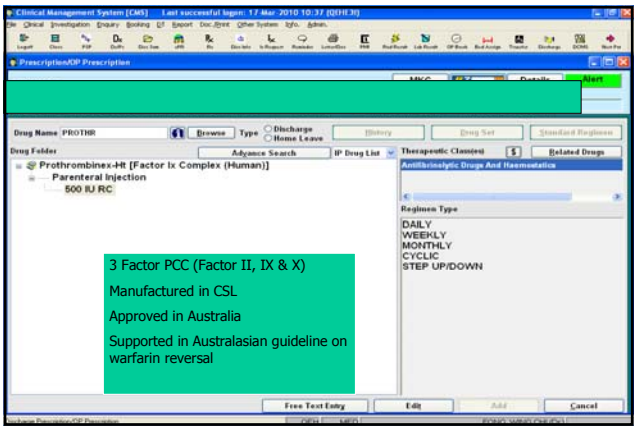
POSITION STATEMENT

Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis

Ross I Baker, Paul B Coughlin, Alex S Gallus, Paul L Harper, Hatem H Salem and Erica M Wood; the Warfarin Reversal Consensus Group

- To reverse the effects of warfarin, vitamin K1 can be given. Immediate reversal is achieved with a prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP). Vitamin K1 is essential for sustaining the reversal achieved by PCC and FFP.
- Prothrombinex-HT is the only PCC approved in Australia and New Zealand for warfarin reversal. (25-50 U/kg) It contains factors II, IX and X, and low levels of factor VII. FFP (150-300ml) should be added to Prothrombinex-HT as a source of factor VII when used for warfarin reversal

MJA • Volume 181 Number 9 • 1 November 2004



Conclusion: Warfarin Related ICH

- Warfarin related ICH is a life threatening disease.
- Immediate reversal of warfarin effect is essential
- Vit K 10mg is a must to sustain the effect of warfarin reversal
- FFP + Vit K is not effective to prevent the deterioration
- PCC seems faster than FFP. But the optimal dosage is not yet well defined
- The thrombotic risk is low (1 to 2%) as compared with the ICH expansion risk (50%)
- rFVIIa seems to be a promising treatment option to arrest the ongoing bleeding
- In view of the prothrombotic effect of PCC, it is only used for acute reverse of warfarin effect in situation of life threatening bleeding only

Neurocritical Care Unit can improve ICH outcome

Neurologic Critical Care

Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage

Michael N. Diringer, MD, FCCM; Dorothy F. Edwards, PhD

Impact of a Neuroscience Intensive Care Unit on Neurosurgical Patient Outcomes and Cost of Care

Evidence-Based Support for an Intensivist-Directed Specialty ICU Model of Care

*†Marek A. Mirski, †Cheryl ee W. J. Chang, and †Robert Cowan

Thank You