

Maximizing benefit from stroke thrombolysis by limiting treatment delay and harnessing information from widely available vascular imaging tools

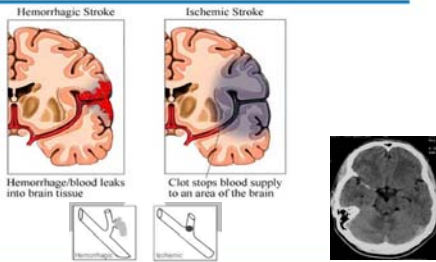
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University of Calgary



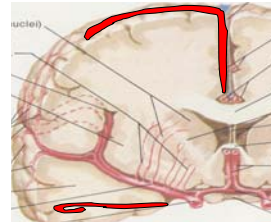
Disclosure Slide

- I have not received an honorarium from Hoffman LaRoche (licensure of tPA) or any endovascular device companies. I did receive a research grant from NovoNordisk Canada.
- I am a member of the Executive Committee of IMS-3.
- I have no stocks or direct investments with pharmaceutical or device companies involved in stroke

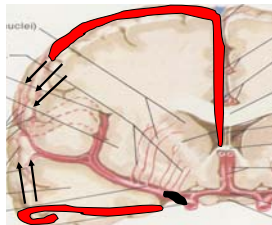
All Stroke Types Can Be Treated



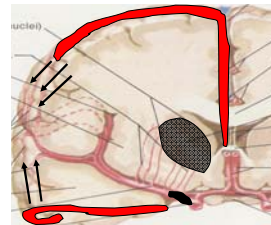
Ischemic Brain Can Be Saved



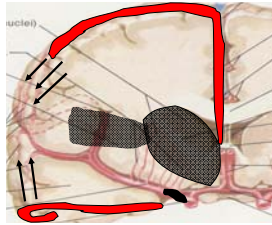
Ischemic Brain Can Be Saved



Ischemic Brain Can Be Saved



Ischemic Brain Can Be Saved



Every Minute Counts: Time is Brain

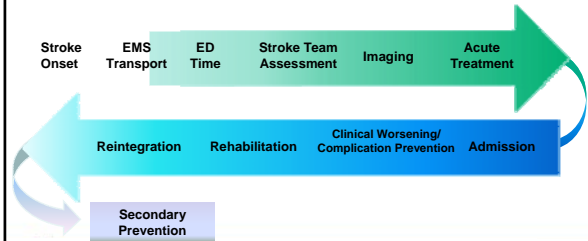
Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

	Neurons Lost	Synapses Lost	Myelinated Fibers Lost	Accelerated Aging
Per Stroke	1.2 billion	8.3 trillion	7140 km/4470 miles	36 yrs
Per Hour	120 billion	830 billion	714/447 miles	3.6 yrs
Per Minute	1.9 million	14 billion	12 km/7.5 miles	3.1 weeks
Per Second	32,000	250 million	200 meters/218 yards	8.7 hours

Stroke Care Continuum



Stroke Care Continuum

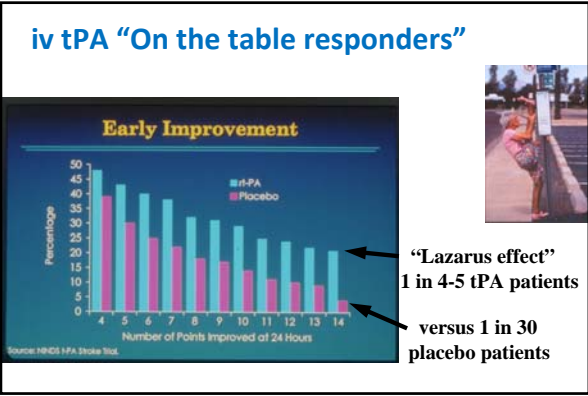
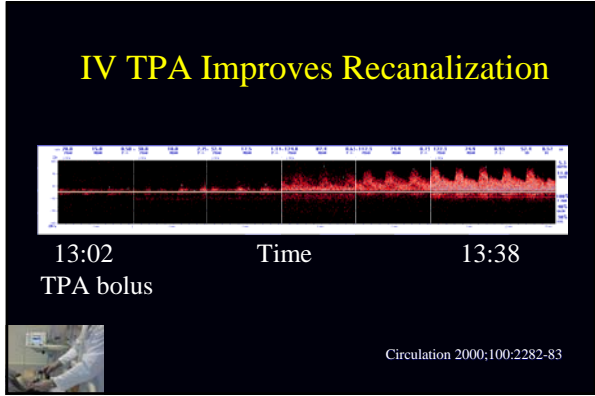


Annual Financial Costs (Cdn)

Acute Treatment reduces degree of disability



Costs	No disability	Mild disability	Moderate disability	Severe disability
	~\$10,000	\$30,000	\$70,000	>\$200,000



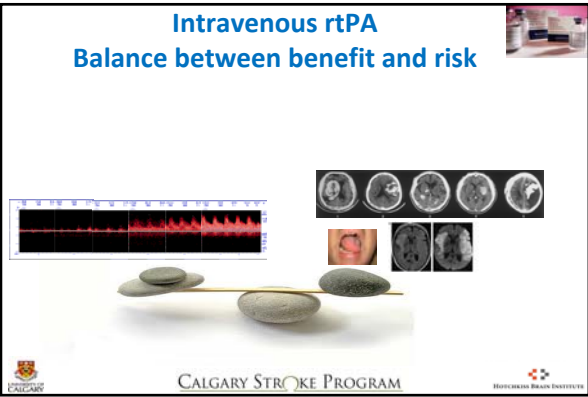
tPA and ICH risk in SITS-MOST Registry

Lancet 2007;369:275-282

	Haemorrhages at 22-36 h imaging scans	Haemorrhages on any post-treatment imaging scans
Local haemorrhages	n=6283	n=6352
None	5369 (85.5%)	5267 (82.9%)
Haemorrhagic infarct type 1	338 (5.4%)	402 (6.3%)
Haemorrhagic infarct type 2	250 (4.0%)	297 (4.7%)
Primary intracerebral haemorrhage type 1	166 (2.6%)	202 (3.2%)
Primary intracerebral haemorrhage type 2	150 (2.5%)	184 (2.9%)
Known remote haemorrhages	n=6282	n=6350
No remote haemorrhage	6111 (97.3%)	6155 (96.9%)
Remote primary intracerebral haemorrhage type 1	105 (1.7%)	113 (1.8%)
Remote primary intracerebral haemorrhage type 2	66 (1.1%)	82 (1.3%)

Data are n (%). Haemorrhagic infarct type 1=small petechiae along the margins of the infarct. Haemorrhagic infarct type 2=more confluent petechiae within the infarct area but without space-occupying effect. Primary intracerebral haemorrhage type 1=blood clots not exceeding 30% of the infarct area with some mild space-occupying effect. Primary intracerebral haemorrhage type 2=blood clots exceeding 30% of the infarct area with substantial space-occupying effect. Remote primary intracerebral haemorrhage type 1=small or medium sized blood clots located remote from the actual infarct, a mild space-occupying effect could be present. Remote primary intracerebral haemorrhage type 2=large confluent dense blood clots in an area remote from the actual infarct; substantial space-occupying effect might be present.

Table 2: Intracerebral haemorrhages detected by CT or MRI study at 22-36 h after treatment and any post-treatment imaging scans

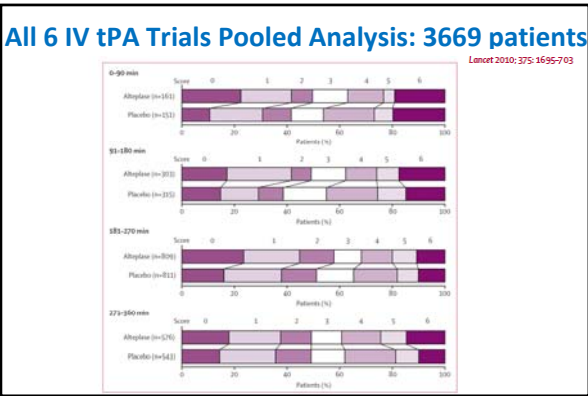


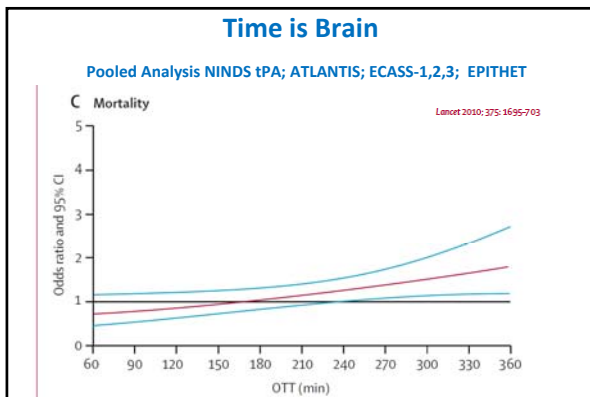
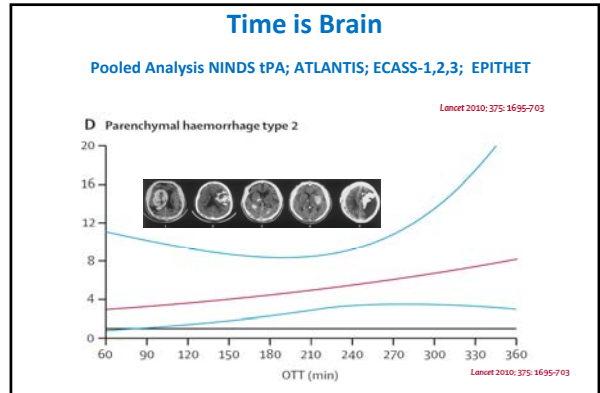
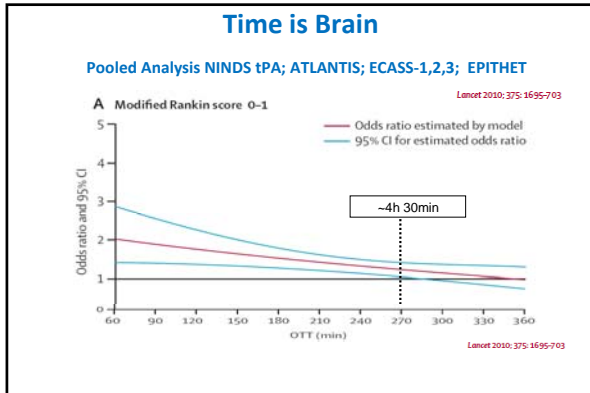
Stroke thrombolysis: Maximizing benefit

Time from onset	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA

CALGARY STROKE PROGRAM

HITCHCOCK BRAIN INSTITUTE





	Number of patients	Mortality, n/N (%)		Odds ratio* (95% CI)	p value
		Placebo	Alteplase		
0-90 min	312	31/151 (20.5%)	30/161 (18.6%)	0.78 (0.41-1.48)	0.4400
91-180 min	618	49/315 (15.6%)	51/303 (16.8%)	1.13 (0.70-1.82)	0.6080
181-270 min	1620	82/811 (10.1%)	89/809 (11.0%)	1.22 (0.87-1.71)	0.2517
181-270 min (excluding EPITHET data)	1589	79/794 (10.0%)	84/795 (10.6%)	1.20 (0.85-1.70)	0.3071
271-360 min	1117	55/542 (10.2%)	86/575 (15.0%)	1.49 (1.00-2.21)	0.0501
271-360 min (excluding EPITHET data)	1051	53/512 (10.0%)	79/539 (14.7%)	1.46 (0.96-2.21)	0.0780
0-360 min	3669	217/1820 (11.9%)	257/1849 (13.9%)	1.19 (0.96-1.47)	0.1080
0-360 min (excluding EPITHET data)	3570	210/1772 (11.8%)	244/1798 (13.6%)	1.17 (0.94-1.45)	0.1578

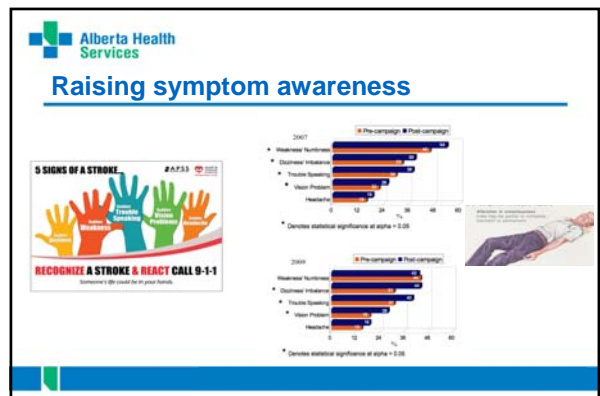
OTT=onset to start of treatment. *Odds ratio adjusted for National Institutes of Health Stroke Scale at baseline (0-2, 8-14, 15-18, >18), age, and diastolic blood pressure (<70, 71-90, >90 mm Hg).

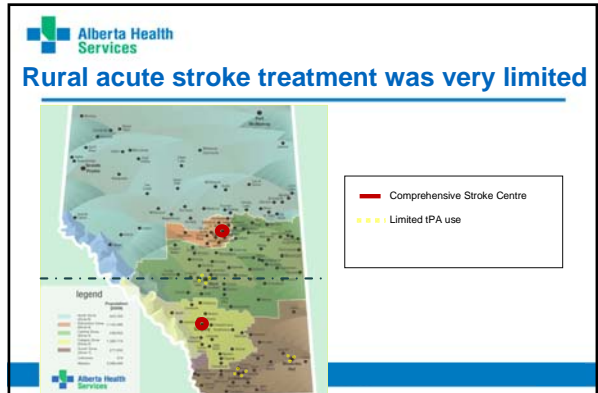
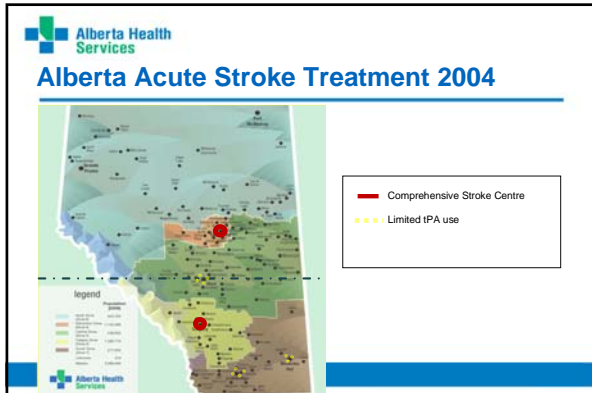
Table 3: Mortality by OTT interval

Stroke thrombolysis: Maximizing benefit

	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA
Time from onset	< 90 min	90-180 min	180-270 min
			>270 min

CALGARY STROKE PROGRAM





Alberta Health Services

APSS

Stroke Centre Designation Criteria

Primary Stroke Centre (PSC) Criteria:




- CT scan availability
- Door to CT time less than 20 minutes with pre-alert
- Stroke expertise on-site or available by Telestroke link
- rtPA treatment availability
- Serves all surrounding communities in which it is the nearest PSC

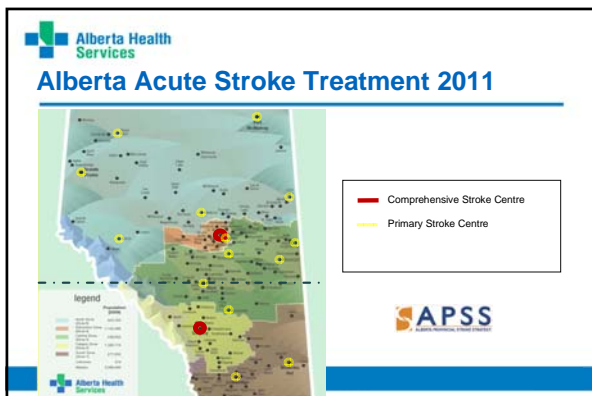
Comprehensive Stroke Centre (CSC) Criteria:

- CT scan availability
- Door to CT time less than 20 minutes with pre-alert
- Stroke team on-site
- Neurosurgical expertise on-site
- Neuro-interventionist expertise on-site
- Central hub of stroke neurologist expertise in a telestroke network

Alberta Health Services

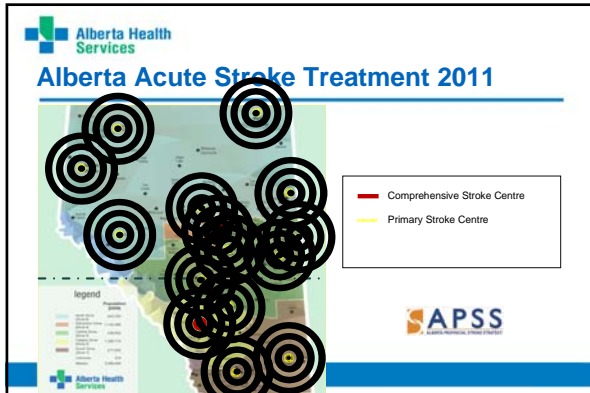
Primary Stroke Centres

- Assessment 
- Basic CT imaging 
- iv tPA delivery 



Alberta Health Services

EMS Hospital Redirect to PSC



Alberta Health Services
EMS Stroke Screening Form

Sample

Alberta Health Services
EMS Stroke Screening Form

Physical Examination Findings	<input type="checkbox"/> Yes → Continue screening process	Is one or more red Physical Examination Findings checked? <input type="checkbox"/> No → Transport to closest medical facility <input type="checkbox"/> Yes → Continue screening process
Level of Consciousness <input type="checkbox"/> Alert <input type="checkbox"/> responds to Verbal <input type="checkbox"/> responds to Pain <input type="checkbox"/> Unresponsive	Speech <input type="checkbox"/> Normal <input type="checkbox"/> Slurred <input type="checkbox"/> Incomprehensible or mute	
Arm Strength <input type="checkbox"/> Normal <input type="checkbox"/> Right-Drills down <input type="checkbox"/> Left-Drills down <input type="checkbox"/> Right-Falls rapidly <input type="checkbox"/> Left-Falls rapidly	Leg Strength <input type="checkbox"/> Normal <input type="checkbox"/> Right-Drills down <input type="checkbox"/> Left-Drills down <input type="checkbox"/> Right-Falls rapidly <input type="checkbox"/> Left-Falls rapidly	Hand Grips <input type="checkbox"/> Normal <input type="checkbox"/> Right-Weak grip <input type="checkbox"/> Left-Weak grip <input type="checkbox"/> Right-No grip <input type="checkbox"/> Left-No grip

Last seen normal to arrive at Primary or Comprehensive Stroke Centre less than 4.5 hours?
 No → Continue screening process
 Yes → screening process - EMS Stroke Screen is positive. En route, provide early pre-notification to closest Primary or Comprehensive Stroke Centre and notify the triage nurse of an "Acute Disabling Stroke"

Stroke Screen

Alberta Health Services
EMS Stroke Screening Form

Physical Examination Findings	<input type="checkbox"/> Yes → Continue screening process	Is one or more red Physical Examination Findings checked? <input type="checkbox"/> No → Transport to closest medical facility <input type="checkbox"/> Yes → Continue screening process
Level of Consciousness <input type="checkbox"/> Alert <input type="checkbox"/> responds to Verbal <input type="checkbox"/> responds to Pain <input type="checkbox"/> Unresponsive	Speech <input type="checkbox"/> Normal <input type="checkbox"/> Slurred <input type="checkbox"/> Incomprehensible or mute	
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Last seen normal to arrive at Primary or Comprehensive Stroke Centre less than 4.5 hours?
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Stroke Screen

Alberta Health Services
EMS Directed Neurological Examination

Is the patient **awake**?

Can patient **communicate**? Is speech slurred?

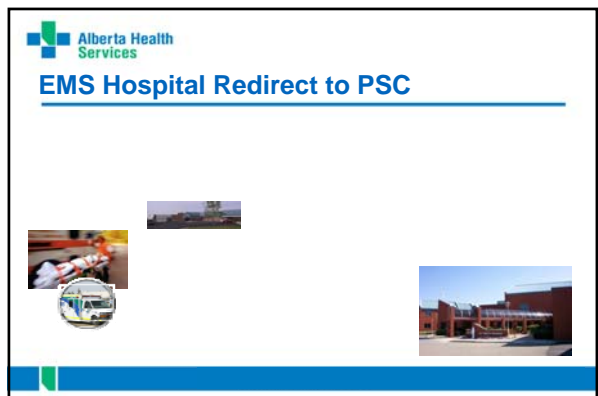
Is there **arm weakness**?

- arm kept 90 degrees against gravity bilaterally?
- hand grips symmetric?

Is there **leg weakness**?

- leg kept 45 degrees against gravity bilaterally?

IS THIS DEFICIT DISABLING ?



EMS Protocol-Transport



Contact Primary Stroke Centre to prewarn of patients' impending arrival.

Transport patient at 30° or less

Nasal cannula O₂ at 2 l/min.
Titrate to O₂ sats in mid 90's

Perform a fingerstick glucose



EMS Protocol-Transport



Start 2 IV lines each arm (at least one antecubital)

18 or 20 gauge is sufficient
Start Normal Saline iv

Tag one IV "For TPA only"

Do not treat hypertension

Do not give ASA

Across the province increases in TPA tx

Center Type Included	Zone Code	Percentage		
		Pre-APSS	On-APSS	Difference
Primary Comprehensive and Others	1	1.9%	10.0%	8.1%
	2	10.6%	15.9%	5.4%
	3	2.0%	5.6%	3.6%
	4	11.2%	10.8%	-0.4%
	5	3.2%	6.2%	2.9%

Some remarkable successes

Institution Code (zone)	Institution Name (zone)	Ischemic Stroke Fiscal Year	
		2008-2009	2009-2010
021 (3)	St Mary's Camrose	12.24%	26.67%
042 (4)	Grey Nuns	7.35%	12.26%
044 (4)	UAH	13.29%	15.85%
061 (5)	Hinton	14.29%	25.00%
079 (1)	Medicine Hat	1.15%	20.00%
085 (5)	Peace River	8.70%	11.11%
092 (3)	Red Deer	5.56%	9.33%
112 (3)	Wainwright	21.43%	29.41%
117 (5)	Fort McMurray	7.14%	16.67%

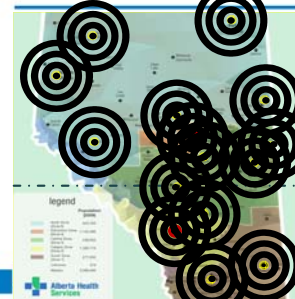
What can we do better after arrival at PSC?



Target is: <60 minute door to needle time



Future Primary Stroke Centres?



Legend

- Comprehensive Stroke Centre
- Primary Stroke Centre

Estimated cost savings if iv tPA tx

- Length of stay 1.5 days shorter¹
- Out of 100 patients¹
 - 12 more are discharged home
 - 8 fewer require rehab
 - 6 fewer require nursing home
- Estimated cost saving per tPA treatment \$20,000 over 30 years²

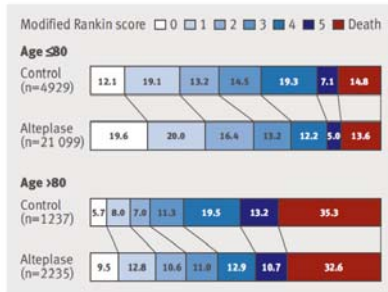
¹ Campbell et al. NINDS tPA Stroke Study Group. Neurology 1998;50:883-891.
² Campbell et al. National use of intravenous alteplase for acute ischemic stroke: an international, descriptive, a cohort of emergency, rapid and cost effectiveness. CNS Drugs 2009;23:15-21.

Stroke thrombolysis: Maximizing benefit

	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA
Time from onset	< 90 min	90-180 min	180-270 min >270 min
Age			
BP/glucose			
NIHSS			

Elderly likely benefit less but still benefit...

BMJ 2010;341:c6046

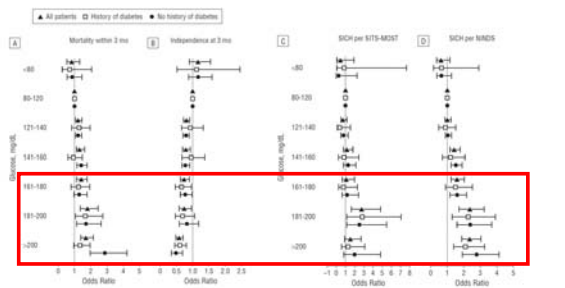


Systolic BP and tPA outcomes –SITS-MOST

Stroke 2009;40:2442-2449



Hyperglycemia and tPA outcomes- SITS-MOST



Arch Neurol 2010;67:1123-30

Sweet Spot for tPA; bNIHSS 6-10 ideal; 11-20 not bad




Table 1: Three-month stroke outcomes in the NINDS tPA stroke trial by baseline stroke severity

NIHSS score	Baseline		90-day NIHSS score of 0-1		90-day mRS score of 0-1		Unadjusted odds ratio for favourable outcome (95% CI)			
	% of placebo patients (n = 312)	% of tPA patients (n = 312)	% of placebo patients	% of tPA patients	% of placebo patients	% of tPA patients				
0-5	5.1	13.5	62.5	69.1	6.6 (-20.9 to 34.1)	15	81.3	78.6	-2.7 (-36 to 3.49)	1.12 (0.36 to 3.49)
6-10	26.6	21.8	34.9	51.5	16.6 (0.9 to 32.2)	6	45.8	67.7	21.9 (6.5 to 37.3)	5 (1.32 to 4.09)
11-20	43.6	44.6	16.9	27.3	10.4 (0.7 to 20.1)	10	21.3	34.5	13.2 (2.7 to 23.7)	8 (1.05 to 2.67)
>20*	24.7	20.2	2.6	6.4	3.8 (-3.2 to 10.8)	26	3.9	9.5	5.6 (-2.8 to 14.0)	1.45 (0.64 to 3.33)

Note: NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin scale, CI = confidence interval, tPA = tissue plasminogen activator, NNT = number needed to treat. *The 95% CI derived using the normal approximation to the binomial distribution, for this group may not be valid owing to small number for each treatment group.

Stroke thrombolysis: Maximizing benefit

	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA	
Time from onset	< 90 min	90-180 min	180-270 min	>270 min
Age	<60 yrs	60-80 yrs	>80 yrs	
BP/glucose	normal	high	very high	
NIHSS	6-10	11-20	>20	≤5



2889 randomized, read-out autumn 2011

Over half of subjects randomized with age>80

>500 subjects randomized with NIHSS <6

Some other tangibles to consider when treating

- Prior meds: ASA + clopidogrel
- Atrial fibrillation: early recurrent stroke
- Cervical artery dissection

ASA+Clopidogrel prior meds and high sICH risk

Table 2. Univariate Analysis of Outcome Parameters

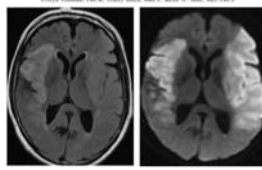
	ASA	CLP	ASA + DP	ASA + CLP	Other AP	Any AP	No AP
sICH per STS-MOST*							
n (%)	73 (2.5)	4 (1.7)	4 (2.3)	6 (4.1)	7 (3.7)	94 (2.5)	85 (1.1)
OR (95% CI)	2.30 (1.67-3.15)	1.55 (0.56-4.26)	2.17 (0.79-5.97)	3.83 (1.65-8.91)	3.41 (1.56-7.47)	2.36 (1.76-3.17)	
sICH per NINDS†							
n (%)	255 (8.6)	16 (6.7)	12 (6.5)	22 (15.2)	20 (10.5)	325 (8.8)	507 (6.5)
OR (95% CI)	1.20 (1.02-1.41)	1.04 (0.62-1.73)	1.08 (0.60-1.96)	2.51 (1.58-3.97)	1.66 (1.04-2.66)	1.38 (1.19-1.60)	
sICH per ECASS ‡§							
n (%)	171 (5.9)	10 (4.2)	10 (5.9)	19 (13.4)	16 (8.5)	228 (6.2)	317 (4.1)
OR (95% CI)	1.42 (1.20-1.70)	1.02 (0.54-1.91)	1.46 (0.78-2.79)	3.47 (2.12-5.68)	2.13 (1.29-3.59)	1.51 (1.29-1.82)	
Excellent recovery§							
n (%)	998 (37.5)	79 (37.6)	63 (41.2)	39 (29.9)	60 (34.1)	1259 (37.2)	2813 (41.4)
OR (95% CI)	0.90 (0.83-0.99)	0.88 (0.67-1.16)	1.03 (0.75-1.40)	0.64 (0.44-0.92)	0.80 (0.59-1.09)	0.89 (0.82-0.97)	
Functional independence¶							
n (%)	1425 (53.6)	107 (51.0)	102 (66.7)	61 (45.2)	88 (50.0)	1783 (53.5)	3922 (57.8)
OR (95% CI)	0.92 (0.85-1.00)	0.81 (0.63-1.05)	1.44 (1.06-1.95)	0.70 (0.50-0.97)	0.83 (0.62-1.10)	0.92 (0.85-1.00)	
Mortality at 3m							
n (%)	402 (15.0)	25 (16.1)	13 (8.5)	31 (22.8)	34 (19.3)	515 (15.3)	727 (10.6)
OR (95% CI)	1.53 (1.34-1.76)	1.07 (0.56-2.01)	0.80 (0.45-1.41)	2.37 (1.72-3.26)	2.07 (1.42-3.02)	1.57 (1.39-1.77)	

*Lacal or remote parenchymal hemorrhage type 2 on the 22- to 36-hour post-treatment imaging scan, combined with a neurological deterioration of ≥ 4 points compared with baseline NIHSS or the lowest NIHSS value between baseline and 24 hours.

Stroke 2010;41:288-294

Atrial fibrillation causes early recurrent ischemic stroke

	Patients With AF	Patients Without AF
n (%)	74 (32.4%)	154 (67.6%)
Age, mean \pm SD, y	76 \pm 10	66.4 \pm 13.4
Male, no. (%)	30 (40%)	91 (59%)
Medical history, no. (%)		
Hypertension	52 (70%)	99 (64%)
Diabetes mellitus	12 (16.2%)	12 (7.8%)
Hyperlipidemia	14 (19%)	34 (22%)
Cigarette smoking	11 (15%)	45 (29%)
Previous TIA or stroke	13 (17.5%)	32 (20.8%)
Aspirin use	44 (59.5%)	61 (39.6%)
Other antiplatelet agent	6 (8%)	16 (10%)
Anticoagulants	5 (6.7%)	2 (1.3%)
Stroke characteristics		
NIHSS, median (IQR)	14 (8-19)	14.5 (7-20)
Time to treatment, mean \pm SD, min	162.7 \pm 32	173.3 \pm 40
END due to		
Incident stroke	12 (16.2%)	22 (14.3%)
Incident stroke	4 (5.4%)	14 (9%)
sICH	3 (4%)	7 (4.5%)
ERS	5 (6.8%)	1 (0.6%)



Stroke 2010;41:1990-1995

Cervical artery dissection and tPA okay

Table 2. Unadjusted Outcome 3 Months After IVT in Patients With Stroke Due to CAD Versus Non-CAD Stroke Cause

Outcome Variables After 3 Months	CAD (n=50)	Non-CAD (n=1007)	P Value	OR	95% CI
Death (all causes), % (n)	3.5% (6)	10.9% (109)	0.22	0.47	0.15-1.55
Favorable outcome,* % (n)	36.4% (20)	44.4% (447)	0.25	0.72	0.41-1.26
Intracranial hemorrhage,† % (n)	14.5% (8)	14.2% (143)	0.99	1.0	0.46-2.20
Asymptomatic	7% (4)	9% (90)			
Symptomatic	7% (4)	5% (53)			
Fatal‡	2% (1)	2% (16)			
Recurrent ischemic stroke	1.8% (1/50)	3.7% (2/4825)	0.71	0.48	0.06-3.83

*Favorable outcome was defined as mRS ≤ 1 .

†Data about ICH were missing in 27 patients (2.5%); all were non-CAD patients.




‡Symptomatic intracranial hemorrhage was defined as any CT/MRI-documented hemorrhage that was temporally related to any deterioration in the patient's clinical condition.

§Fatal hemorrhage was defined as any symptomatic intracranial hemorrhage leading to death.

Reichart M et al. Stroke 2009;40:3772-3776




Stroke thrombolysis: Who should get what?

	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA	
Time from onset	< 90 min	90-180 min	180-270 min	>270 min
Age		<80 yrs	>80 yrs	
BP/glucose	normal		high	very high
NIHSS	6-10	11-20	>20	≤5
Prior meds			ASA+clopidogrel	

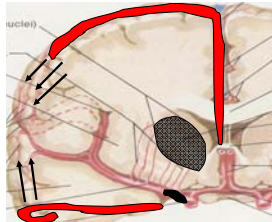
Stroke thrombolysis: What about imaging?

	iv tPA "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA
NCCT EIC/DWI			
Occlusion location			
Thrombus characteristics			

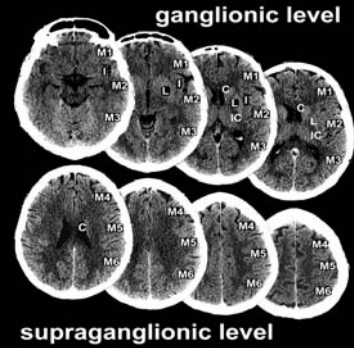




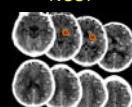
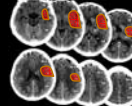
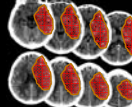


Ischemic Brain Can Be Saved

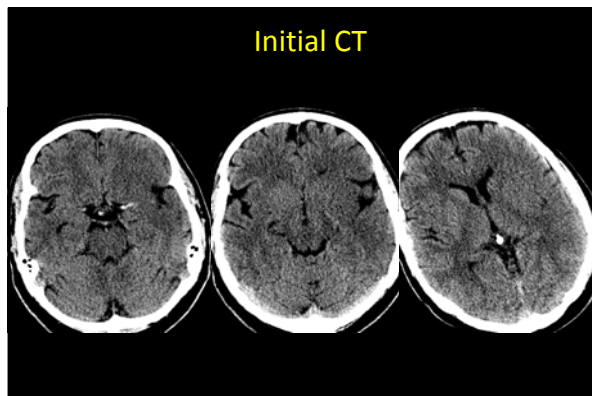


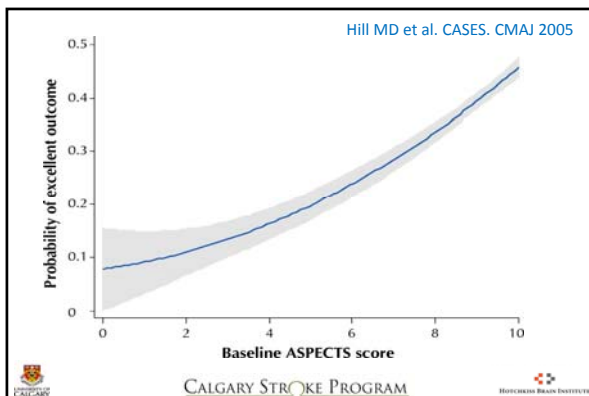
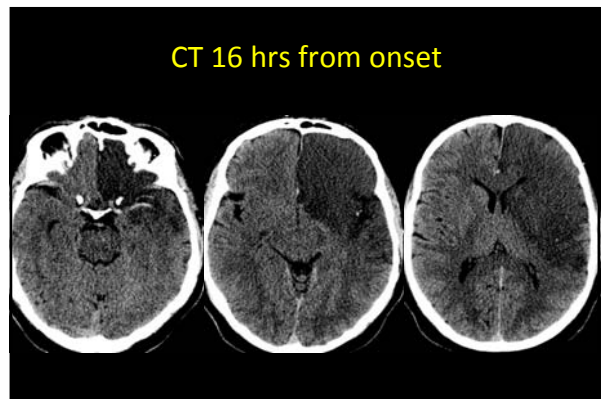
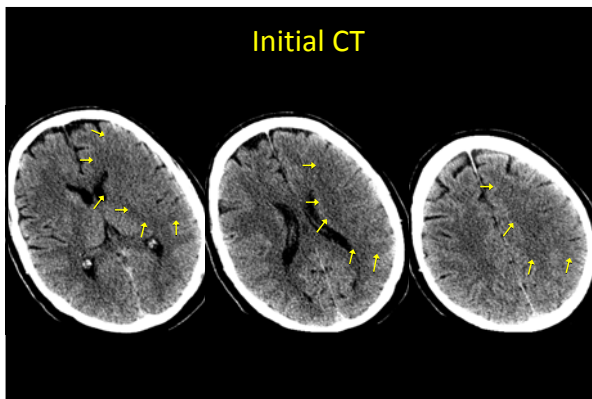
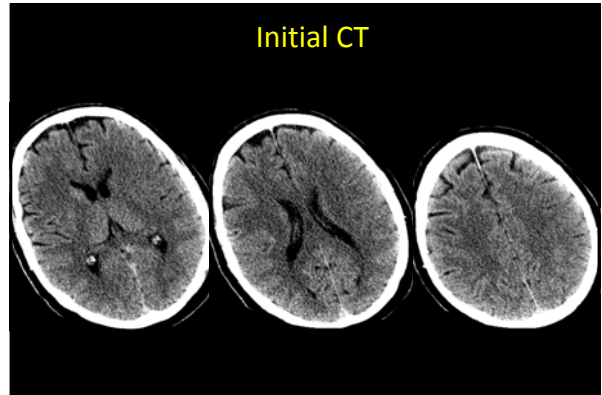
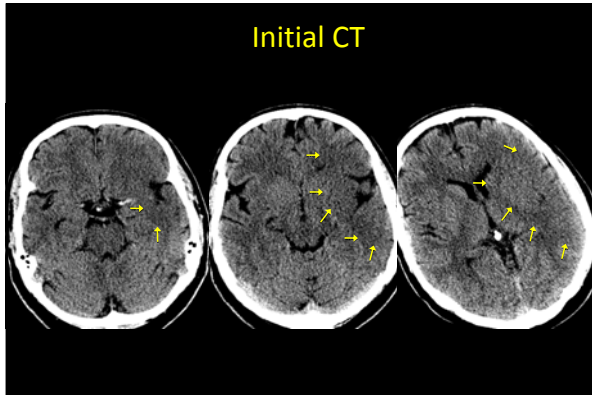
ASPECTS methodology



	NCCT	ASPECTS score
Good scan		8-10
Fair scan		5-7
Poor scan		0-4

Initial CT





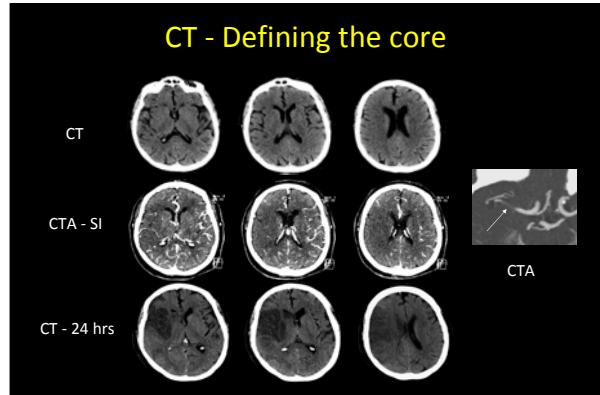
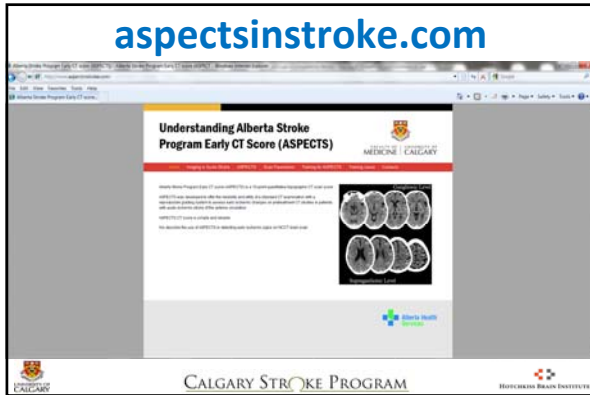
Importance of Early Ischemic Computed Tomography Changes Using ASPECTS in NINDS rtPA Stroke Study

Andrew M. Demchuk, MD, FRCPC; Michael D. Hill, MD, FRCPC; Philip A. Barber, MBChB, FRCPC; Brian Silver, MD, FRCPC; Suresh C. Patel, MD; Steven R. Levine, MD, for the NINDS rtPA Stroke Study Group, NIH

ASPECTS	No.	Placebo Final Infarct Volume (interquartile range)	No.	rtPA Final Infarct Volume (interquartile range)
8-10	203	15.2 mL (1.55-65.9)	199	7.8 mL (0.9-51.8)
3-7	97	66.0 mL (13-136.6)	88	51.1 mL (6.4-130.8)
<3	6	205.3 mL (111.4-228.3)	10	226.3 mL (92.8-290.8)

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HISTORICAL BRAIN INSTITUTE



NCCT/CTASI ASPECTS reliability by time

CT scan performed from symptom onset	NCCT ASPECTS (ICC)	CTASI ASPECTS (ICC)
<90 minutes	0.48 (0.28-0.71)	0.96 (0.93-0.98)
91-180 minutes	0.80 (0.66-0.90)	0.94 (0.89-0.97)
181-360 minutes	0.81 (0.69-0.91)	0.87 (0.78-0.94)
>360 minutes	0.89 (0.81-0.95)	0.89 (0.80-0.95)
Overall	0.78 (0.69-0.84)	0.93 (0.90-0.95)

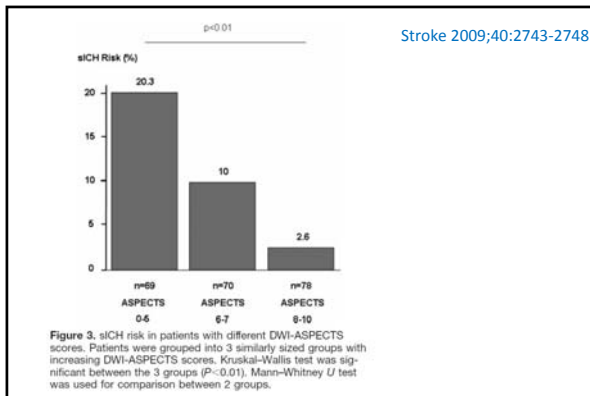
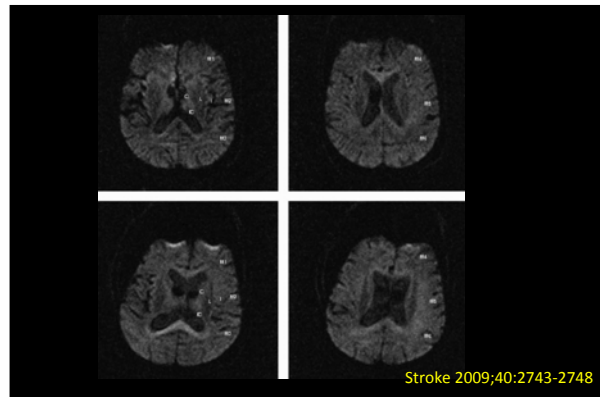
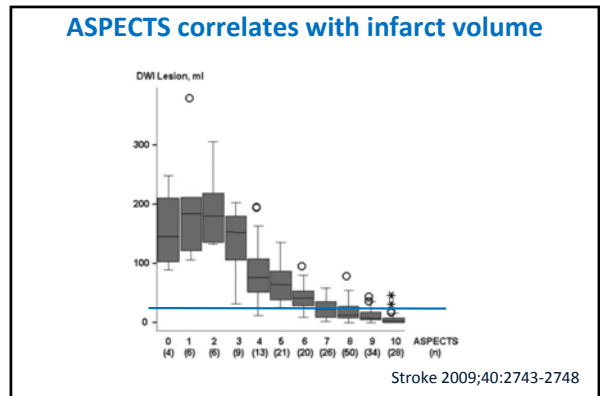


Figure 3. sICH risk in patients with different DWI-ASPECTS scores. Patients were grouped into 3 similarly sized groups with increasing DWI-ASPECTS scores. Kruskal-Wallis test was significant between the 3 groups ($P<0.01$). Mann-Whitney U test was used for comparison between 2 groups.



ASPECTS correlates with infarct volume

Pretreatment diffusion- and perfusion-MR lesion volumes have a crucial influence on clinical response to stroke thrombolysis

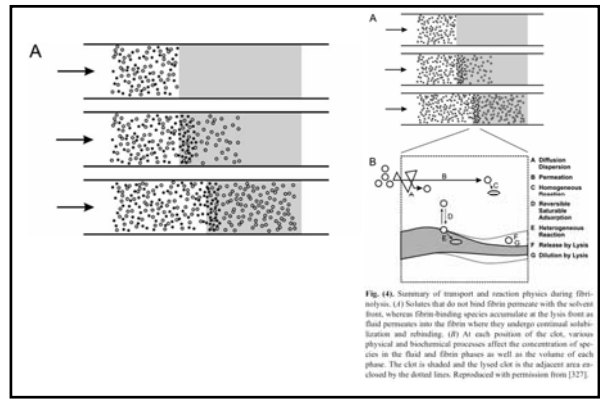
Mark W Parsons*, Scott Chaturvedi*, Patrick McElduff†, Christopher R Levi†, Ken S Bhattacharj, Debra A De Silva, Maria Bohmer, †Alisa Barber, Christopher Shiller†, Geoffrey A Durrant† and Stephen M Davis*, For the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) Investigators

We hypothesized that pretreatment magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) lesion volumes may have influenced clinical response to thrombolysis in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). In 98 patients randomized to intravenous (IV) tissue plasminogen activator (tPA) or placebo 3 to 6 h after stroke onset, we examined increasing acute DWI and PWI lesion volumes (Tmax+2-sec delay increments), and increasing PWI/DWI mismatch ratios, on the odds of both excellent (modified Rankin Scale (mRS): 0 to 1) and poor (mRS: 5 to 6) clinical outcome. Patients with very large PWI lesions (most had internal carotid artery occlusion) had increased odds ratio (OR) of poor outcome with IV-tPA (58% versus 25% placebo; OR=4.13, $P=0.002$ for Tmax+2-sec volume >190 mL). Excellent outcome from tPA treatment was substantially increased in patients with DWI lesions <18 mL (77% versus 18% placebo; OR=15.0, $P<0.001$). Benefit from tPA was also seen with DWI lesions up to 25 mL (59% versus 29% placebo; OR=5.5, $P=0.03$), but not for DWI lesions >25 mL. In contrast, increasing mismatch ratios did not influence the odds of excellent outcome with tPA. Clinical responsiveness to IV-tPA, and stroke outcome, depends more on baseline DWI and PWI lesion volumes than the extent of perfusion-diffusion mismatch.

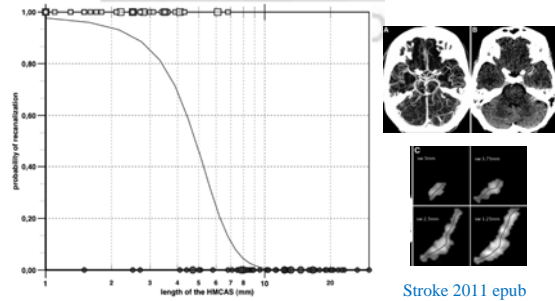
Keywords: Ischemic stroke; diffusion MRI; perfusion MRI; thrombolysis

Stroke thrombolysis: What about imaging?

	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA
NCCT EIC/DWI	ASPECTS 8-10 / DWI <25 ml	ASPECTS 3-7	ASPECTS 0-2 / DWI >100 ml
Occlusion location			
Thrombus characteristics			



Hyperdense Thrombus Length and recanalization



HDMCAS Length Predicts Disappearance at FU with iv tPA

ISC 2011 platform

HDMCAS cases confirmed by CTA involving M1 MCAO
Evaluated cases receiving iv tPA alone

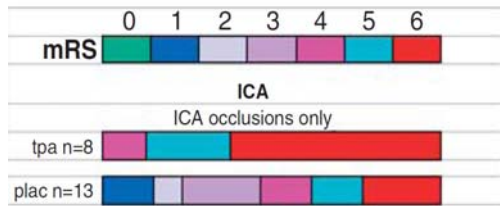
HDMCAS length	Rate of disappearance	
0-1 cm	6/7	85.7%
1-2 cm	9/24	37.5%
>2 cm	0/10	0%

CT-angiography now of superb quality 2-D Reformats critical especially sagittals



TPA Recanalization Rates	1h	2h	24h
	delZoppo et al 1992	Saqqur et al 2007	Zangerle et al 2007
	8%	6%	46%
	26%	30%	53%
	35%	44%	68%

EPITHET Showed No iv tPA benefit in ICA occlusions



Journal of Cerebral Blood Flow & Metabolism advance online publication, 20 January 2010; doi:10.1038/jcbfm.2010.3

Table 2. Treatment Effect Based on Arterial Obstruction Site

	rtPA	Placebo	P
MCA obstruction n=22, n	18	18	
Reperfusion, n	11	15	
Median reperfusion, % (SD)	94.3 (7.7-100)	86.3 (20.8-97.2)	0.281
Recanalization n=10	n=15		
Any recanalization	80% (8)	80% (12)	0.626
Infarct growth, n	11	15	
Geometric mean growth	0.60	1.87	0.037
Clinical outcomes, n	12	15	
Good neurological outcome	67% (8)	40% (6)	0.252
Good functional outcome	67% (8)	47% (7)	0.441
ICA obstruction n=22, n	12	9	
Reperfusion, n	7	12	
Reperfusion, % (SD)	58.3 (29-22)	16.7 (2.5-33.3)	0.037
Recanalization, n	8	12	
Any recanalization	30% (3)	25% (3)	0.642
Infarct growth, n	8	12	
Geometric mean growth	5.12	3.49	0.028
Clinical outcomes, n	8	13	
Good neurological outcome	62% (5)	23% (3)	0.257
Good functional outcome	62% (5)	23% (3)	0.257

Stroke 2010;41:295-299;

Stroke thrombolysis: What about imaging?

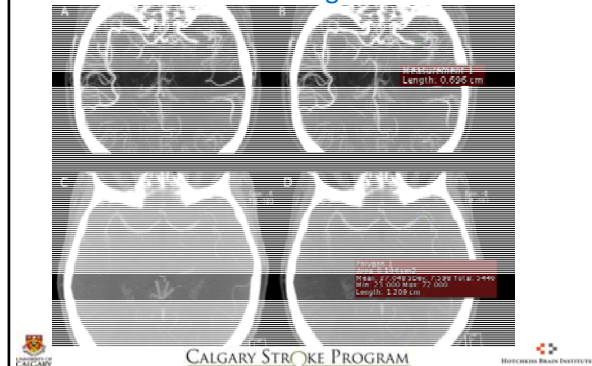
	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA
NCCT EIC/DWI	ASPECTS 8-10 / DWI <25 ml	ASPECTS 3-7	ASPECTS 0-2 / DWI >100 ml
Occlusion location	M2 MCA/distal arteries	M1 MCA	distal ICA
Thrombus characteristics			



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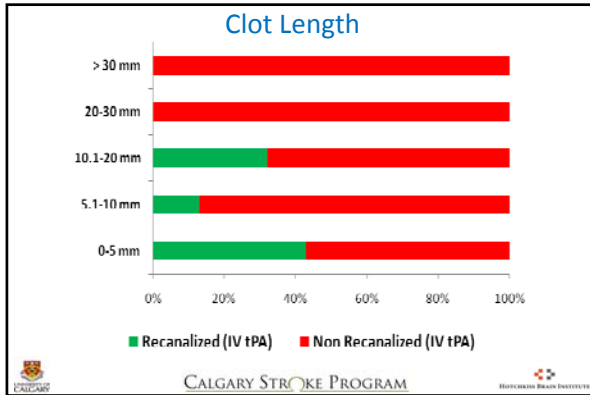


Clot Length



CALGARY STROKE PROGRAM





INTERSeCT multicentre prospective study

Baseline CTA and repeat 4h CTA

- What thrombus characteristics predict 4h recanalization with iv tPA?
- When is recanalization futile?

If interested in participating:
Email- ademchuk@ucalgary.ca

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Stroke thrombolysis: What about imaging?

	iv tPA ideal "sweet spot"	iv tPA modest net benefit	Conservative tx avoid tPA
NCCT EIC/DWI	ASPECTS 8-10 / DWI <25 ml	ASPECTS 3-7	ASPECTS 0-2 / DWI >100 ml
Occlusion location	M2 MCA/distal arteries	M1 MCA distal ICA	
Thrombus characteristics	short length/upstream flow		long length/upstream flow diverted

CALGARY STROKE PROGRAM HOCHSCHELE BRAIN INSTITUTE

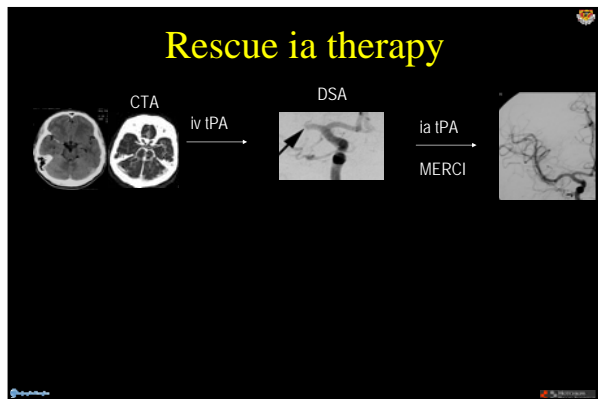
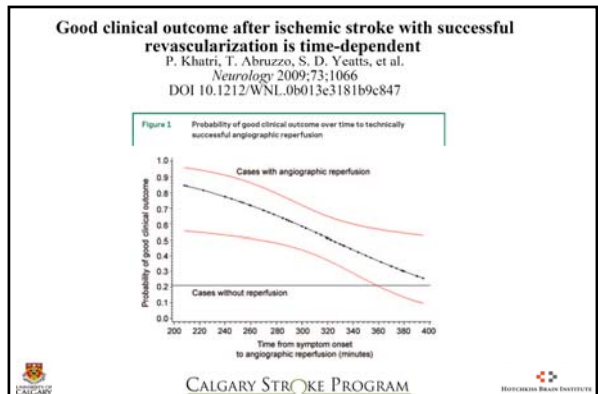


Table 2 Adverse events from intra-arterial procedures


Adverse event	%	References
Unable to access		
Parent vessel by guide catheter*	1.3-2	19, 20, 23, 26
Occluded vessel by microcatheter*	0.7-4.8	19, 20, 23, 26
Occluded vessel by device*	1.3-8.6	23, 26
Dissection parent vessel, with stenosis/occlusion	0-2.4	19, 20, 23, 26, 29
Subarachnoid hemorrhage, vessel perforation	0-3.5	18, 19, 20, 23, 26, 27, 29
Angiographic contrast extravasation, parenchymal hematoma	3.4	20, 23
Symptomatic parenchymal hematoma (no angio contrast extravasation reported)	1.5-10	19, 20, 21, 26, 27, 29, 30
Emboli previously patent middle cerebral artery, anterior cerebral artery, posterior cerebral artery	0-15	19, 23, 26, 27, 29, 30
Puncture site (hematoma, pseudoaneurysm)	2.1-2.5	20, 21, 26, 29

*Operator began with device per instructions for use but was unable to access occluded vessel.


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Mechanical endovascular treatment Recanalization Frequent, Fast and Complete




Merci Retriever Devices




Stentriever






Solitaire™ FR

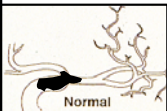


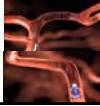


TREVO



Penumbra extraction

Recanalization Rates	MERICI	PENUMBRA	Stentriever
	53-63%	83%	
	46-60%		~90%
	71-82%	83%	

Stentriever may be game changing

INDUSTRY NEWS
Covidien's stroke device moves SWIFTly to FDA queue for approval

After a recommendation from the Data Safety Monitoring Board (DSMB) following promising results, Covidien has moved enrollment into its SWIFT trial, which is investigating the use of the Solitaire FR recanalization device. The company said it will take the trial data directly to FDA in hopes of approval.

The Dublin, Ireland-based company said that it is hoping for approval from the FDA to use the device to help reduce blood flow in acute ischemic stroke patients within eight hours of symptom onset. Covidien's Solitaire received CE mark in 2009 and the SWIFT (Solitaire FR With Intervention For Thrombotic) trial enrollment began in March 2010 in the U.S.

The company said that it will continue to conduct follow-up in the patients already enrolled in the trial, and in the meantime will collaborate with the FDA for the next steps to obtain a PMA clearance.

The aim of the randomized SWIFT trial was to evaluate the safety and efficacy of the Solitaire device compared with the Merci Retriever System (Genentech, Medical) in 200 patients with acute ischemic stroke. The primary endpoint was arterial recanalization of occluded target vessel measured by a TIM score of 2 or 3 following the use of either device without symptomatic intracerebral hemorrhage.

The Solitaire device became part of Covidien's device portfolio after a merger agreement in July where Covidien acquired endovascular and endovascular platforms.

Source: www.covidien.com
Last updated on January 17, 2011 at 1:08 PM EST






IMS-3 Trial

GRANT SUPPORT:
NIH/NINDS U01-NS052220




PRINCIPAL INVESTIGATORS:
Joseph P. Broderick, MD
Thomas Tomsick, MD

FDA IND: #5785
Study Drug: Genentech, Inc.
Microcatheters: EKOS Corp., Concentric Inc., Cordis Neurovascular, Inc.

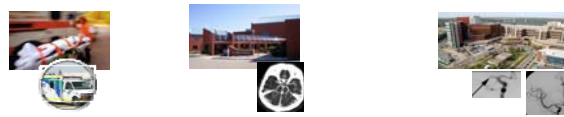


Stroke thrombolysis: Who should get what?

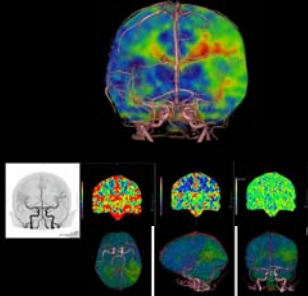
	iv tPA + endovascular "Full court press"	iv tPA alone
Time from onset	60-180 min	180-270 min
Age	<80 yrs	>80 yrs
BP/glucose	normal	high very high
NIHSS	>20 11-20	6-10 ≤5
NCCT EIC/DWI	ASPECTS 8-10 / DWI <20 ml	ASPECTS 3-7
Occlusion location	distal ICA M1 MCA	M2 MCA/distal arteries
Thrombus characteristics	long length/upstream flow diverted	short length/upstream flow

Future: PSC initial tx then CSC

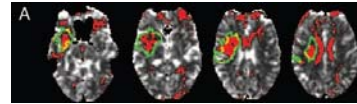


Volume CT (CTA/CTP) Game Changing
 what is already infarcted and how severely?



Regional Very Low Cerebral Blood Volume Predicts Hemorrhagic Transformation Better Than Diffusion-Weighted Imaging Volume and Thresholded Apparent Diffusion Coefficient in Acute Ischemic Stroke
 Bruce C.V. Campbell, Soren Christensen, Kenneth S. Burcher, Ian Gordon, Mark W. Parsons, Patricia M. Desmond, P. Alan Barber, Christopher R. Levi, Christopher F. Bladin, Deidre A. De Silva, Geoffrey A. Donnan, Stephen M. Davis and for the EPITHET Investigators
 Stroke 2010;41:82-88; originally published online Dec 3, 2009;

vICBV > 2 ml



	PH	90d mRS (0-1)
vICBV >2 ml (all subjects)	28%	11%
vICBV >2 ml (tPA only)	43%	

Combination systemic thrombolysis treatment
 Recanalization More Frequently, Faster and Completely



2009 CALGARY STROKE PROGRAM

Thank You for your attention