THE UNIVERSITY of TENNESSEE
HEALTH SCIENCE CENTER

Advanced Neurosonology: Dx and Rx TCD in Acute Stroke

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Disclosures

Funding: Cerevast Therapeutics, Inc.
Speaker's Bureau: Genentech, Inc
Editorial Board
    Cerebrovasc Dis, Intl J Stroke, JON
Director, Neurosonology Examination 1998-2018
    American Society of Neuroimaging
Former Board Member
    ICAVL, ASN, SVIN
Inventor, US Patent # 6733450
President, ASN

1998

TJC Requirements and Brain Attack Coalition Guidelines for Comprehensive Centers:

- Key Personnel –
  - Neurologists
  - Neurosurgeons
  - Vascular Surgeons
  - Intensivists (Neuro-Critical Care Specialists)
  - Advanced Practice Nurses (Masters or Doctoral degree)
  - Endovascular Specialists
  - Ultrasound Technicians
  - Physical Medicine/Rehabilitation Physicians & Therapists
- Endovascular Treatment –
  - Angioplasty/Stents
  - Coil embolization
  - Intra-arterial lytic and mechanical clot retrieval/disruption
- Expanded Neuroradiology Capabilities –
  - MRI/MRA/DWI
  - CT Angiography
  - Digital Angiography
  - Echocardiography (TTE/TEE)
  - Carotid and Transcranial Doppler
- Stroke Unit & ICU
- Rehabilitation Program
- Formal Patient and Staff Education
- Stroke Registry with Outcomes/Process Tracking

Evaluation of a Stroke Patient

H&P Head CT ECG, blood work-up

↓

TCD, CDUS, CTA, MRA

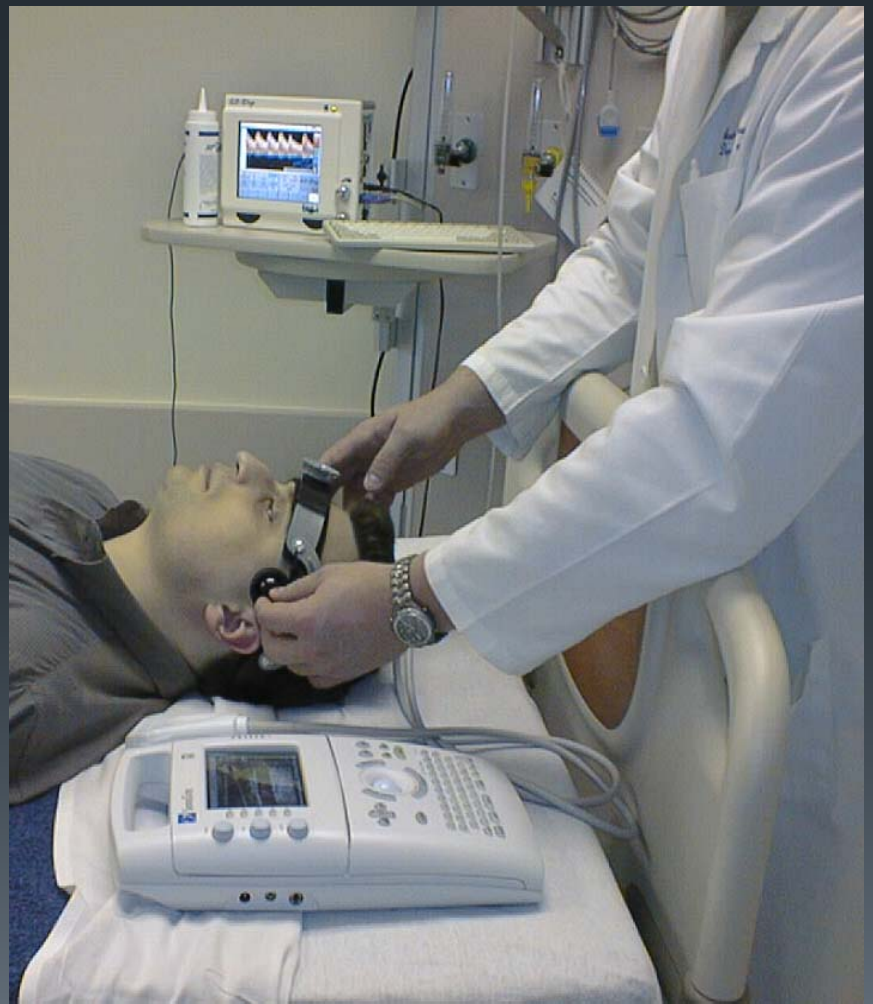
↓

Invasive Angiography

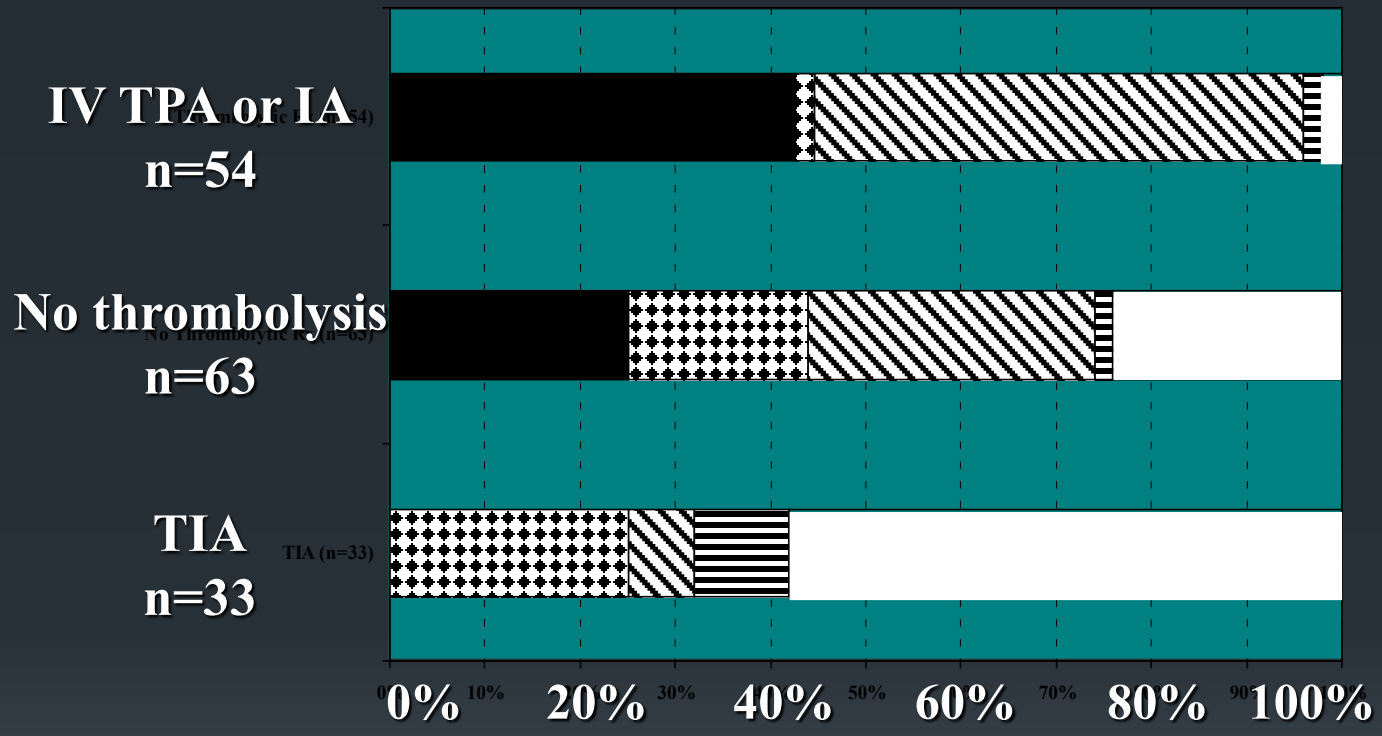
CLOTBUST: Find Thrombus Fast

NIHSS is sensitive to clot presence (≥10 points)

- Portable TCD and duplex
- Fast track protocol
- Use full power
- High PRF, gate ≥ 10 mm
- Occlusion(s) location
- The worst residual flow
- Monitoring set



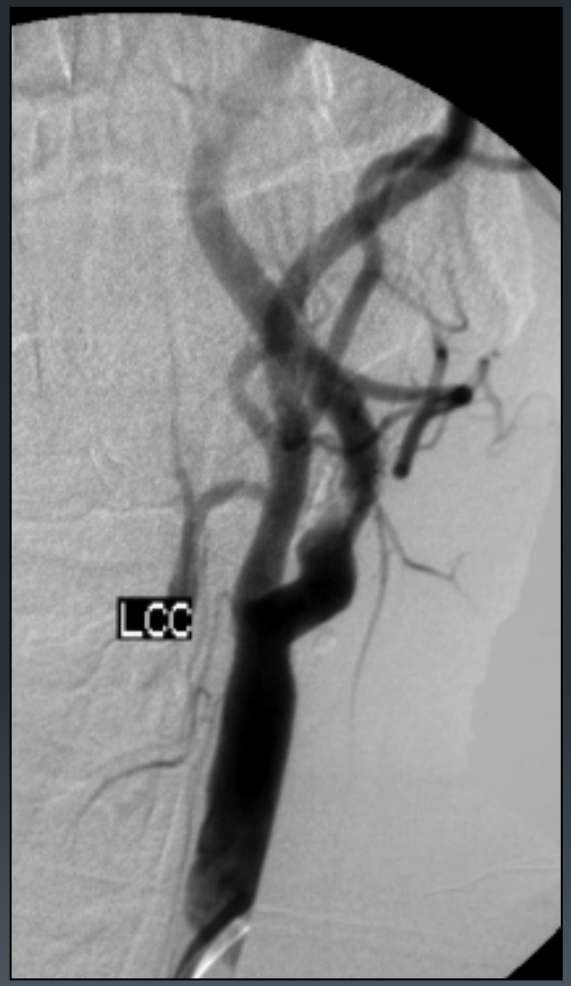
Carotid US + TCD: Lesions Amenable to Intervention

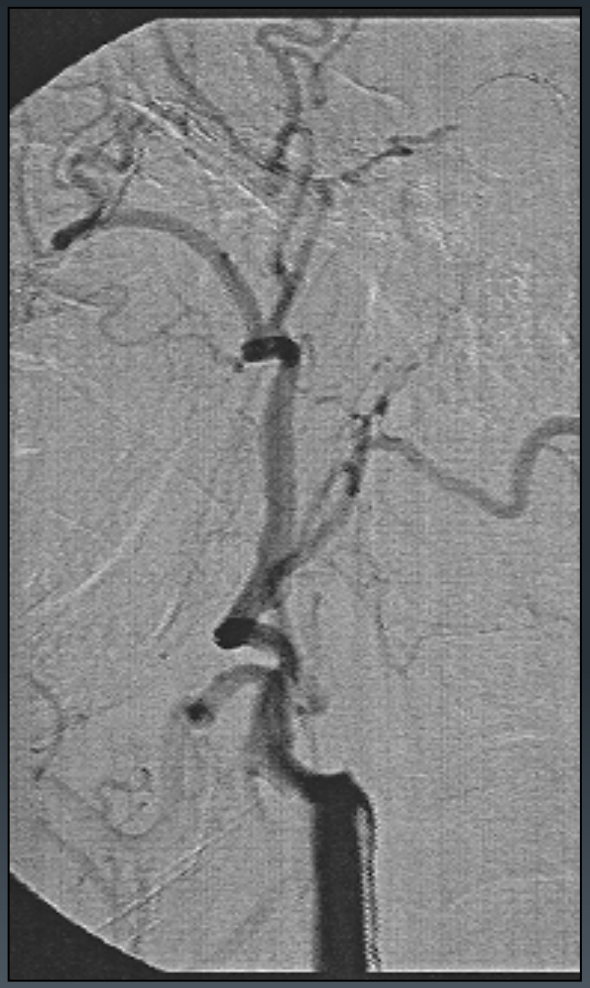


Neurovascular US exam yields excellent agreement with urgent DSA

Chernyshev et al. Stroke 2005:36:32-37.

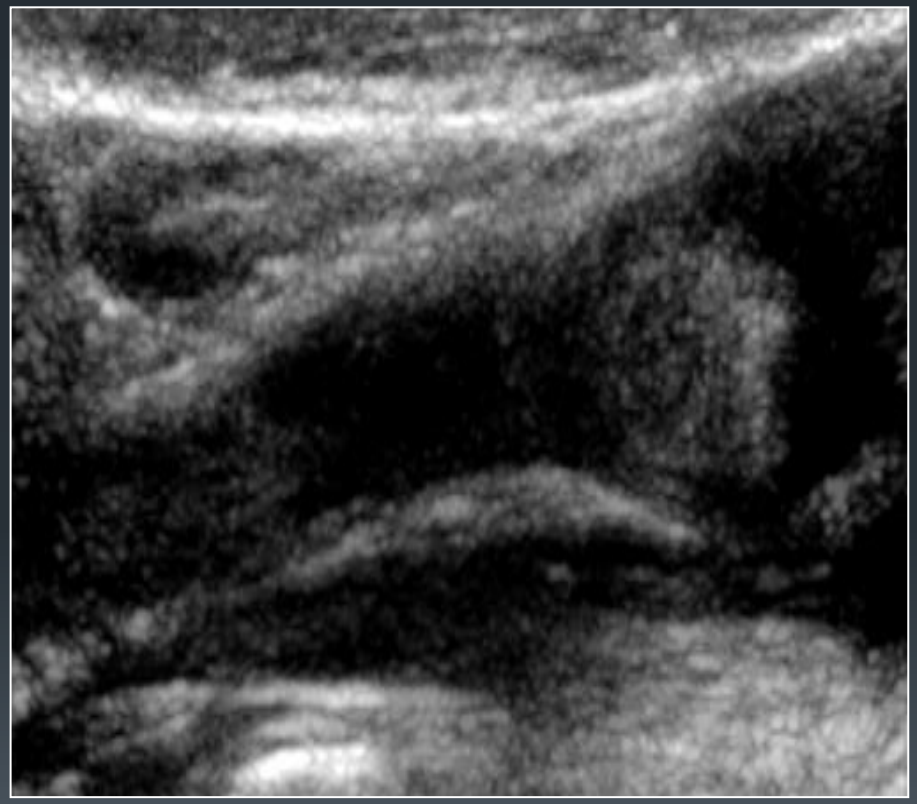
Acute vs Chronic

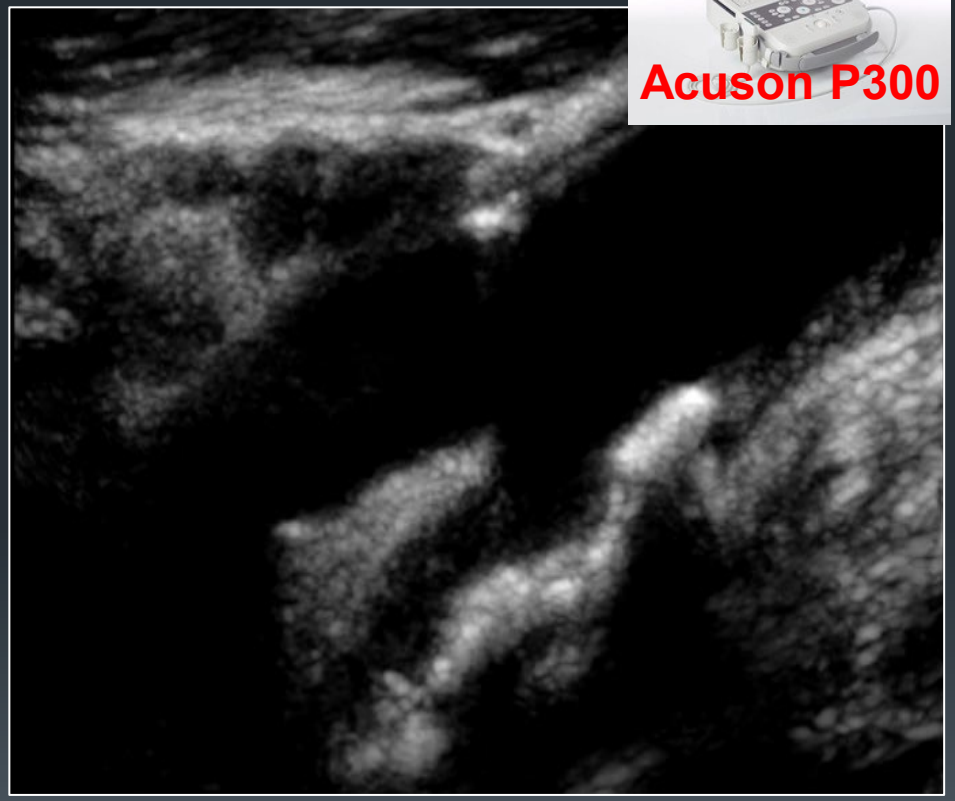




Carotid Occlusion: Acute or Chronic

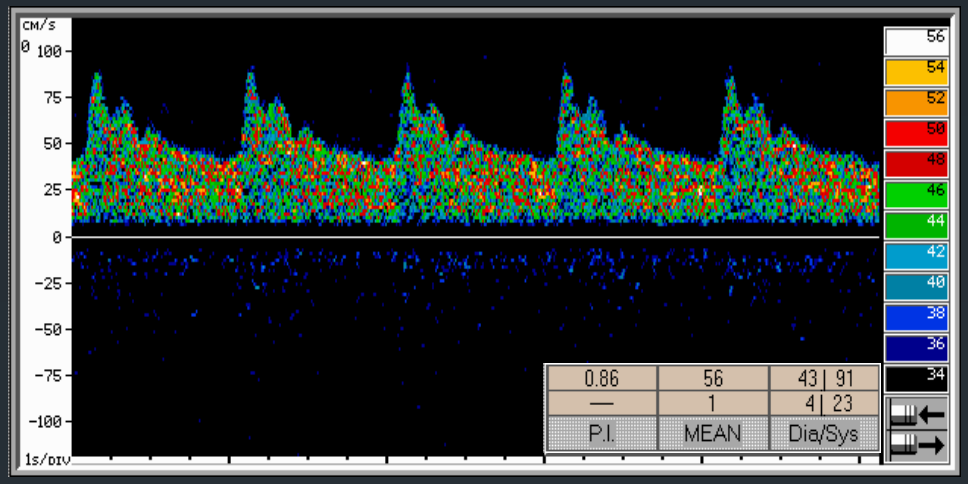
- Acute: normal vessel diameter, preserved intima-media complex, some distensibility
- Chronic: fibrosis, vessel collapse, lack of vessel wall pulsations

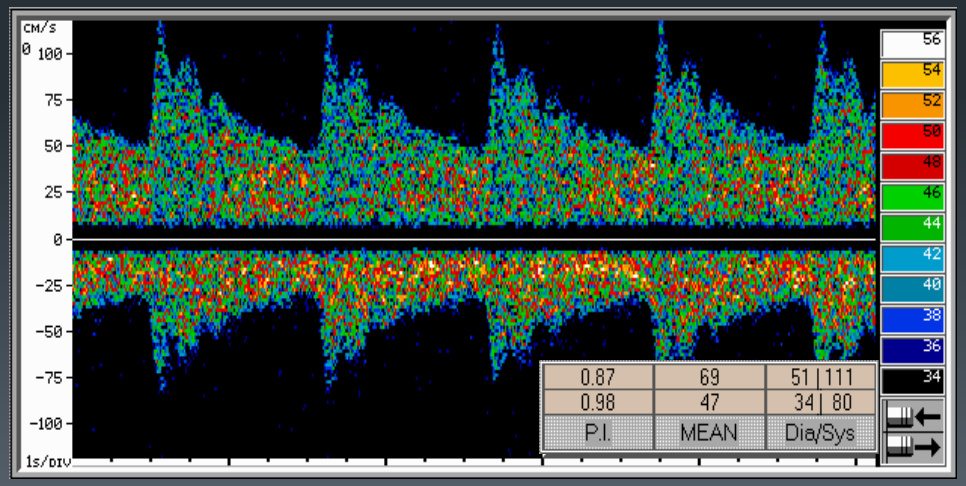




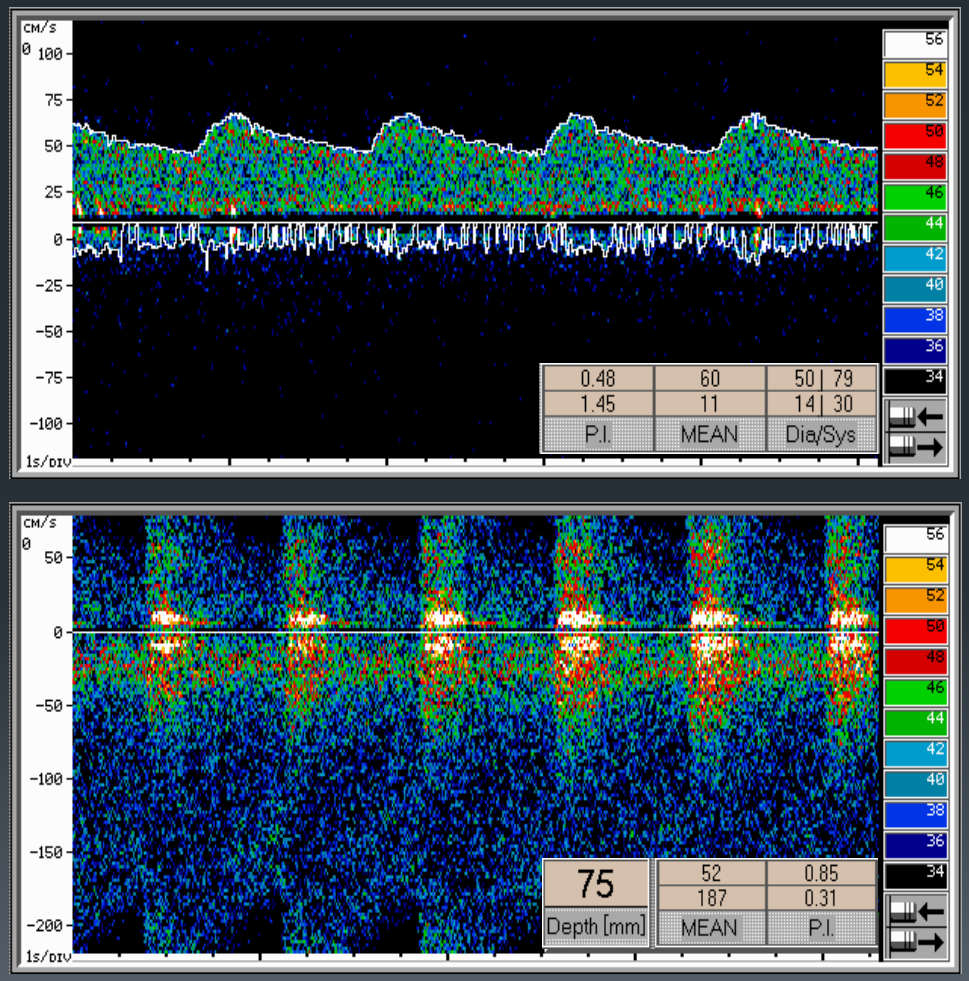
Cerbrovascular Ultrasound in Stroke Prevention and Treatment (2nd Ed)
Oxford: Wiley-Blackwell Publishers. 2011. ISBN 9781405195768

Normal MCA and MCA/ACA Waveforms





Normal MCA and ACA Waveforms with Severe ICA Stenosis



TCD and CTA in Acute Ischemia

Validation of Transcranial Doppler With Computed Tomography Angiography in Acute Cerebral Ischemia

Georgios Tsivgoulis, MD, RVT; Vijay K. Sharma, MD, RVT; Annabelle Y. Lao, MD; Marc D. Malkoff, MD; Andrei V. Alexandrov, MD, RVT

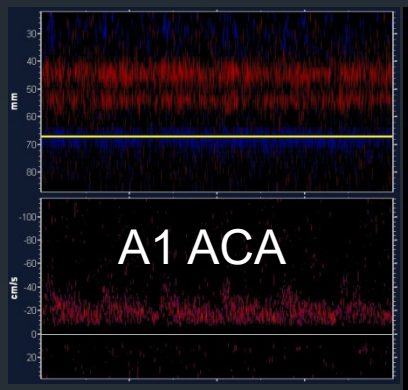
Background and Purpose—Both transcranial Doppler (TCD) and spiral computed tomography angiography (CTA) are used for noninvasive vascular assessment tools in acute stroke. We aimed to evaluate the diagnostic accuracy of TCD against CTA in patients with acute cerebral ischemia.

Methods—Consecutive patients presenting to the Emergency Department with symptoms of acute (<24 hours) cerebral ischemia underwent emergent high-resolution brain CTA with a multidetector helical scanner. TCD was performed at bedside with a standardized, fast-track insonation protocol before or shortly (<2 hours) after completion of the CTA. Previously published diagnostic criteria were prospectively applied for TCD interpretation independent of angiographic findings.

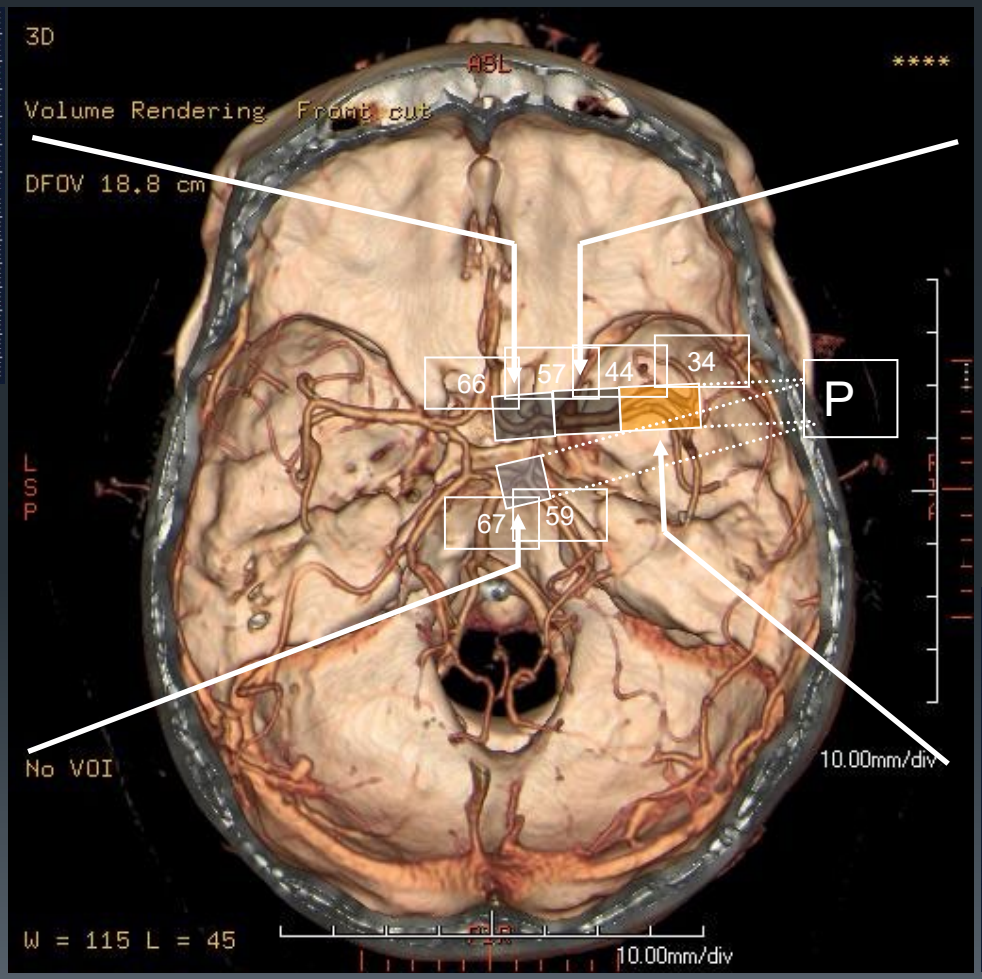
Results—A total of 132 patients (74 men, mean±SD age 63±15 years) underwent emergent neurovascular assessment with brain CTA and TCD. Compared with CTA, TCD showed 34 true-positive, 9 false-negative, 5 false-positive, and 84 true-negative studies (sensitivity 79.1%, specificity 94.3%, positive predictive value 87.2%, negative predictive value 90.3%, and accuracy 89.4%). In 9 cases (7%), TCD showed findings complementary to the CTA (real-time embolization, collateralization of flow with extracranial internal carotid artery disease, alternating flow signals indicative of steal phenomenon).

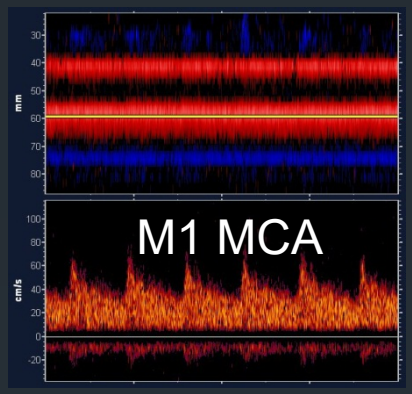
Conclusions—Bedside TCD examination yields satisfactory agreement with urgent brain CTA in the evaluation of patients with acute cerebral ischemia. TCD can provide real-time flow findings that are complementary to information provided by CTA. (***Stroke*. 2007;38:1245-1249.**)

PMD-TCD – CTA Depth Ranges

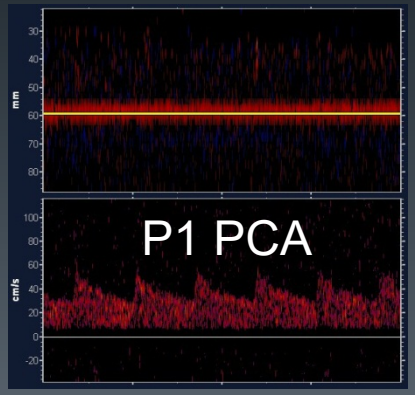


64 – 70mm

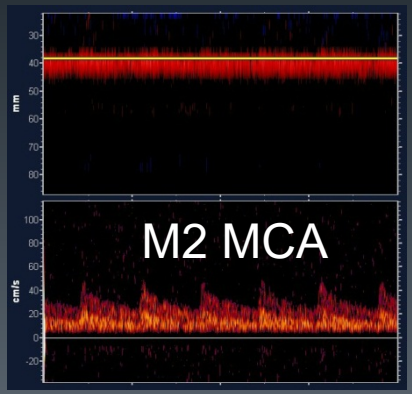




40 – 56mm

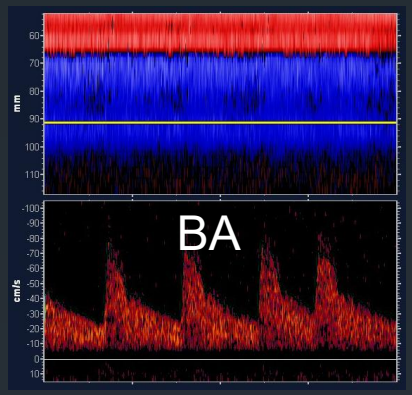


54 – 64mm

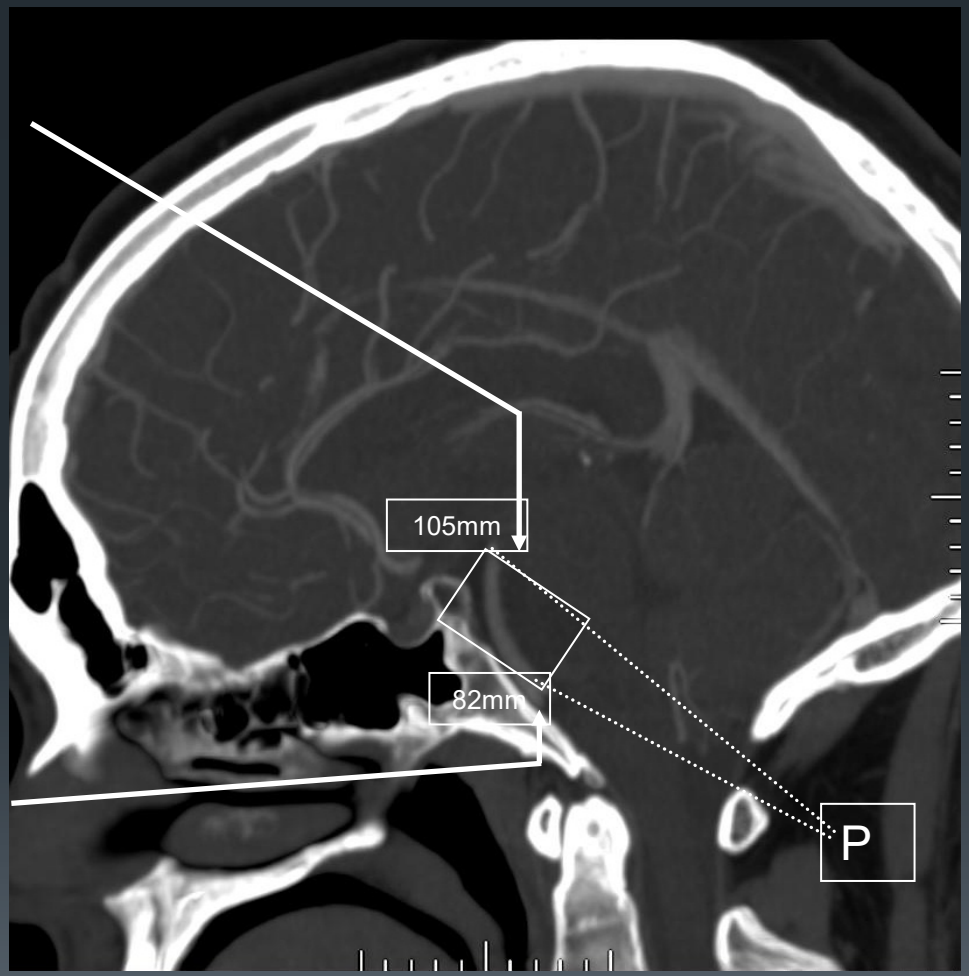


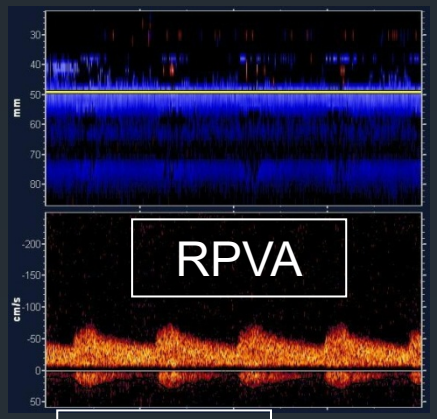
36-46mm

PMD-TCD – CTA Depth Ranges

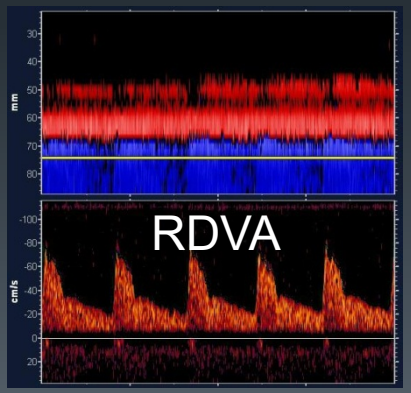


78 - 102mm

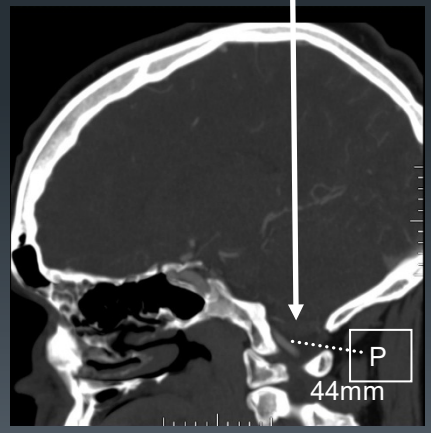




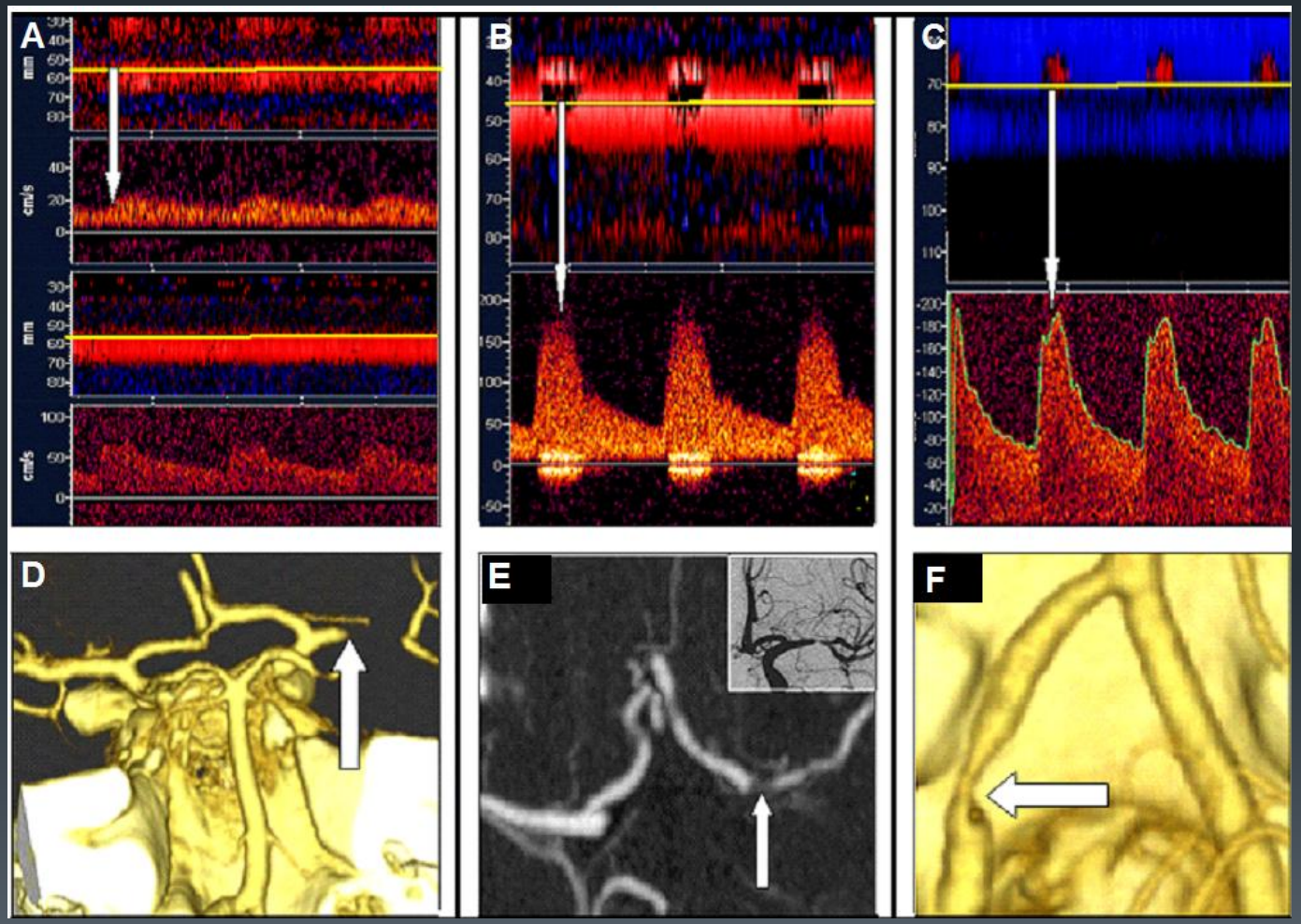
46mm



78mm



TCD and CTA in Acute Ischemia



Tsivgoulis G. et al. Stroke 2007:38:1245-1249.

PMD in Acute Posterior Ischemia

Applications and Advantages of Power Motion-Mode Doppler in Acute Posterior Circulation Cerebral Ischemia

Georgios Tsivgoulis, MD, RVT; Vijay K. Sharma, MD, RVT; Steven L. Hoover, MD;
Annabelle Y. Lao, MD; Agnieszka A. Ardelt, MD, PhD;
Marc D. Malkoff, MD; Andrei V. Alexandrov, MD, RVT

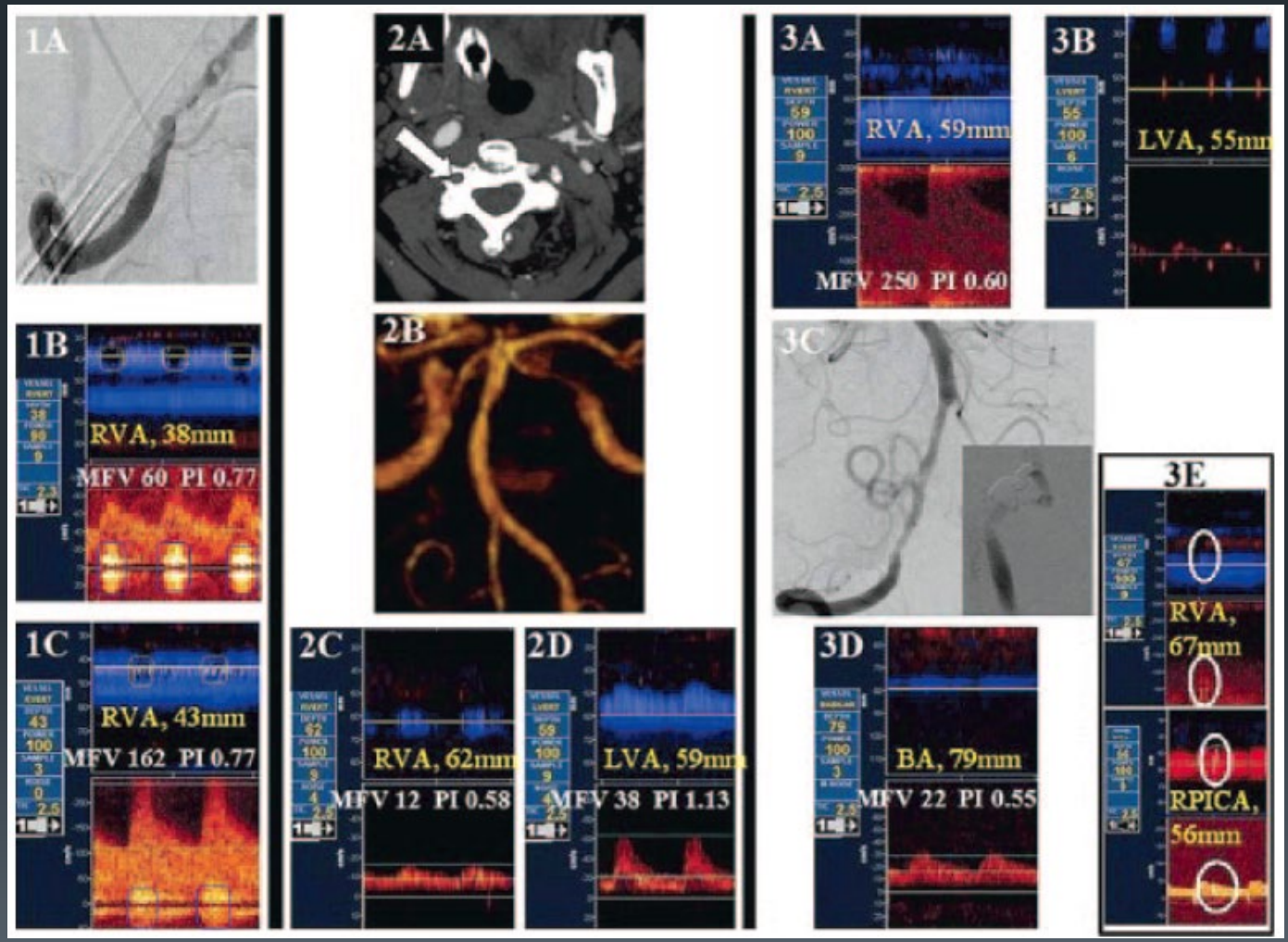
Background and Purpose—Evaluation of posterior circulation with single-gate transcranial Doppler (TCD) is technically challenging and yields lower accuracy parameters in comparison to anterior circulation vessels. Transcranial power motion-mode Doppler (PMD-TCD), in addition to spectral information, simultaneously displays in real-time flow signal intensity and direction over 6 cm of intracranial space. We aimed to evaluate the diagnostic accuracy of PMD-TCD against angiography in detection of acute posterior circulation stenoocclusive disease.

Methods—Consecutive patients presenting to the emergency room with symptoms of acute (<24 hours) cerebral ischemia underwent emergent neurovascular evaluation with PMD-TCD and angiography (computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography). Previously published diagnostic criteria were prospectively applied for PMD-TCD interpretation independent of angiographic findings.

Results—A total of 213 patients (119 men; mean age 65±16 years; ischemic stroke 71%, transient ischemic attack 29%) underwent emergent neurovascular assessment. Compared with angiography, PMD-TCD showed 17 true-positive, 8 false-negative, 6 false-positive, and 182 true-negative studies in posterior circulation vessels (sensitivity 73% [55% to 91%], specificity 96% [93% to 99%], positive predictive value 68% [50% to 86%], negative predictive value 95% [92% to 98%], accuracy 93% [90% to 96%]). In 14 patients (82% of true-positive cases), PMD display showed diagnostic flow signatures complementary to the information provided by the spectral display: reverberating or alternating flow, distal basilar artery flow reversal, high-resistance flow, emboli tracks and, bruit flow signatures.

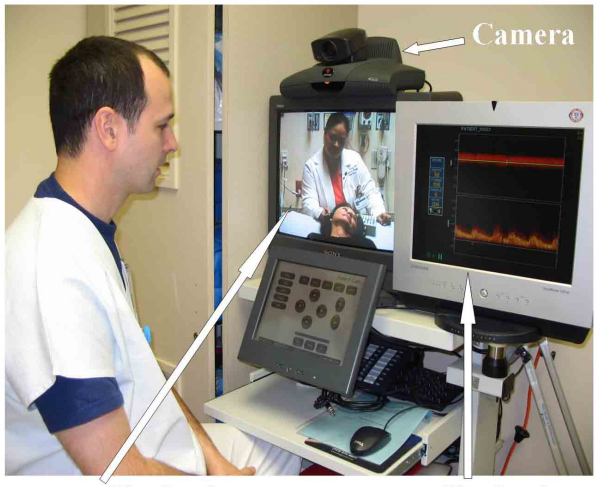
Conclusions—PMD-TCD yields a satisfactory agreement with urgent brain angiography in the evaluation of patients with acute posterior circulation cerebral ischemia. PMD display can depict flow signatures that are complimentary to and can increase confidence in standard single-gate TCD spectral findings. (***Stroke*****. 2008;39:1197-1204.)**

PMD in Acute Posterior Ischemia

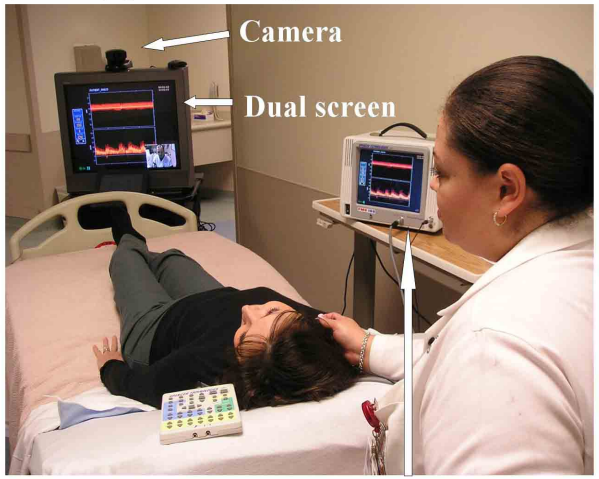


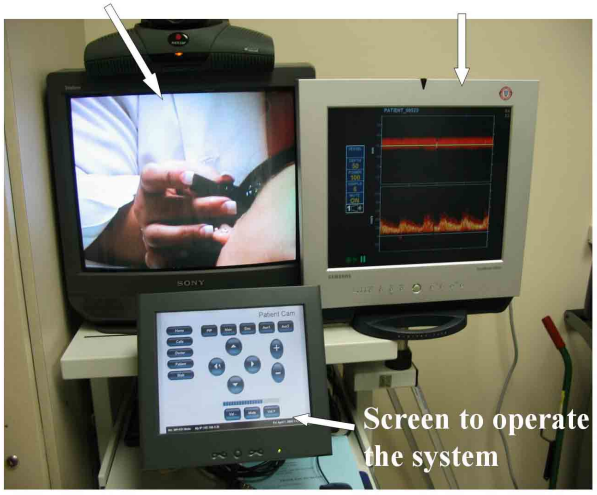
Tsivgoulis G. et al. Stroke 2008:39:1197-1204.

TCD&CDUS via Telemedicine

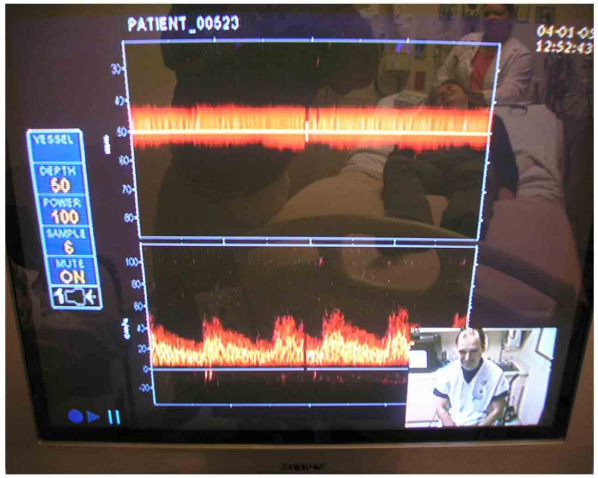


A Phonoscope Health Network® connection between two Polycom® Viewstation FX units





Two video screens, 800 x 600 pixel resolution for two-way, two-image communication



Mikulik R, et al. Stroke 2006;37:229-230.

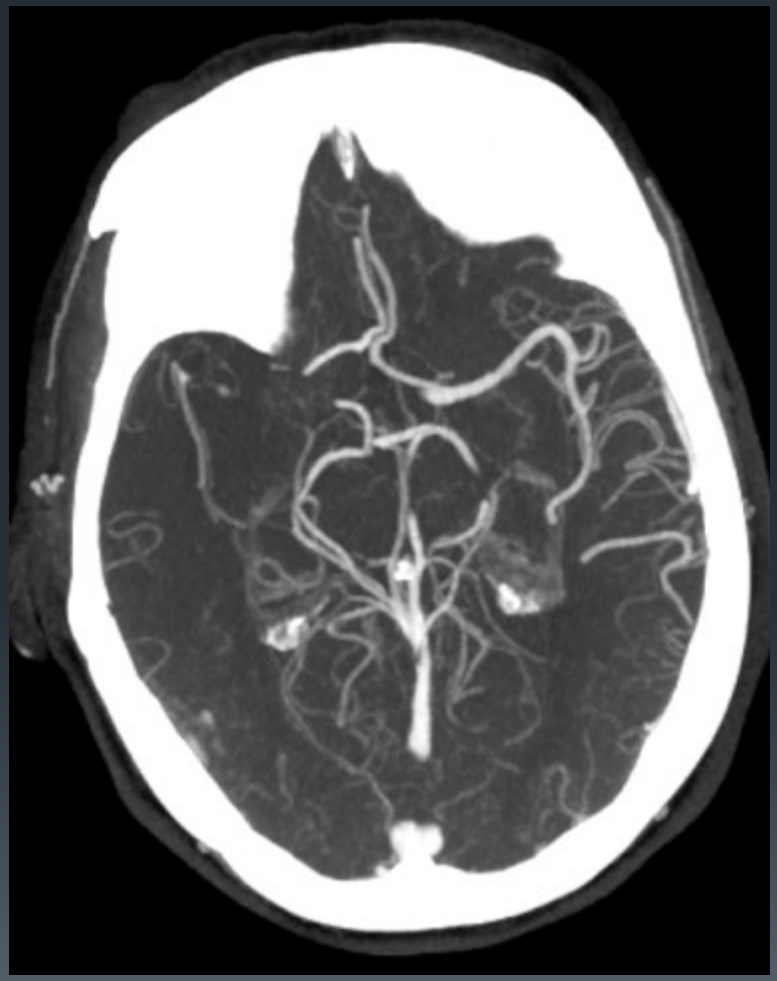
Evaluation of a Stroke Patient

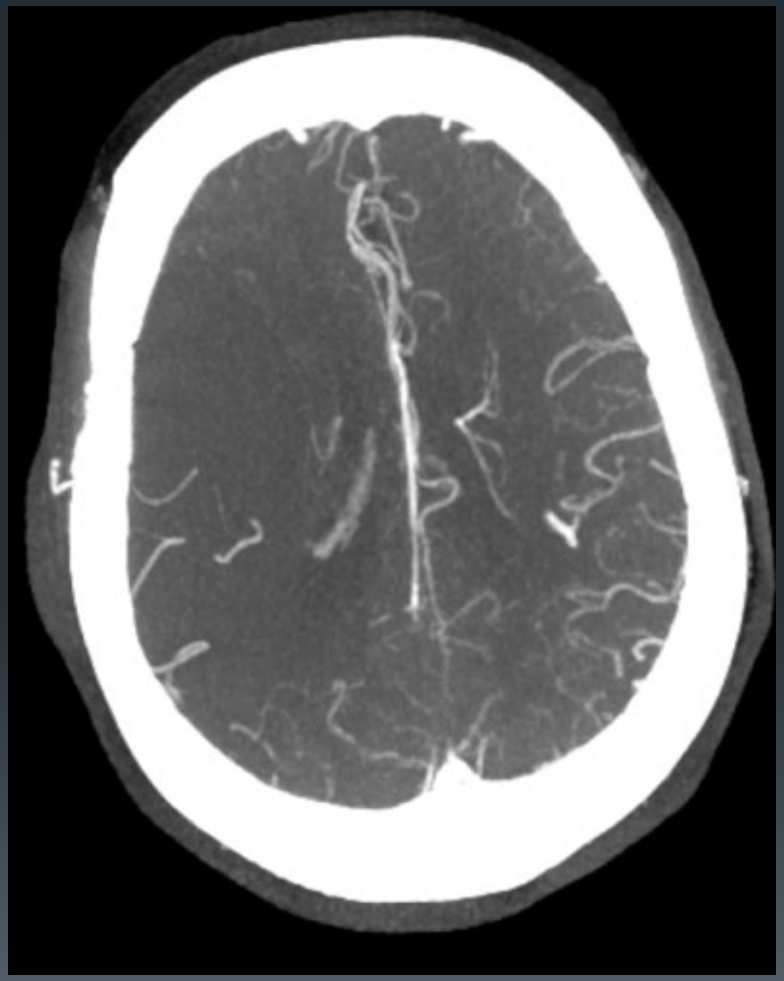
H&P Head CT ECG, blood work-up

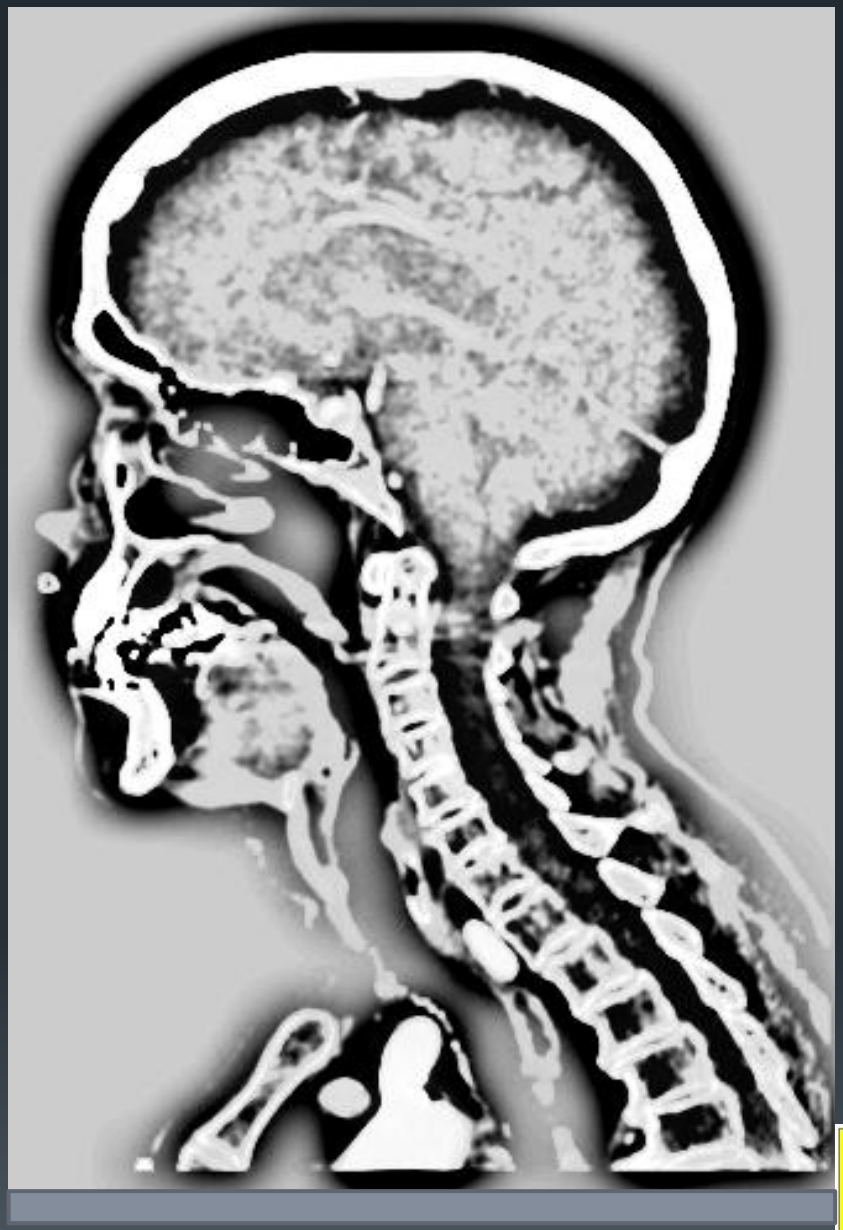
CTA

Invasive Angiography

Good or Bad Collaterals?



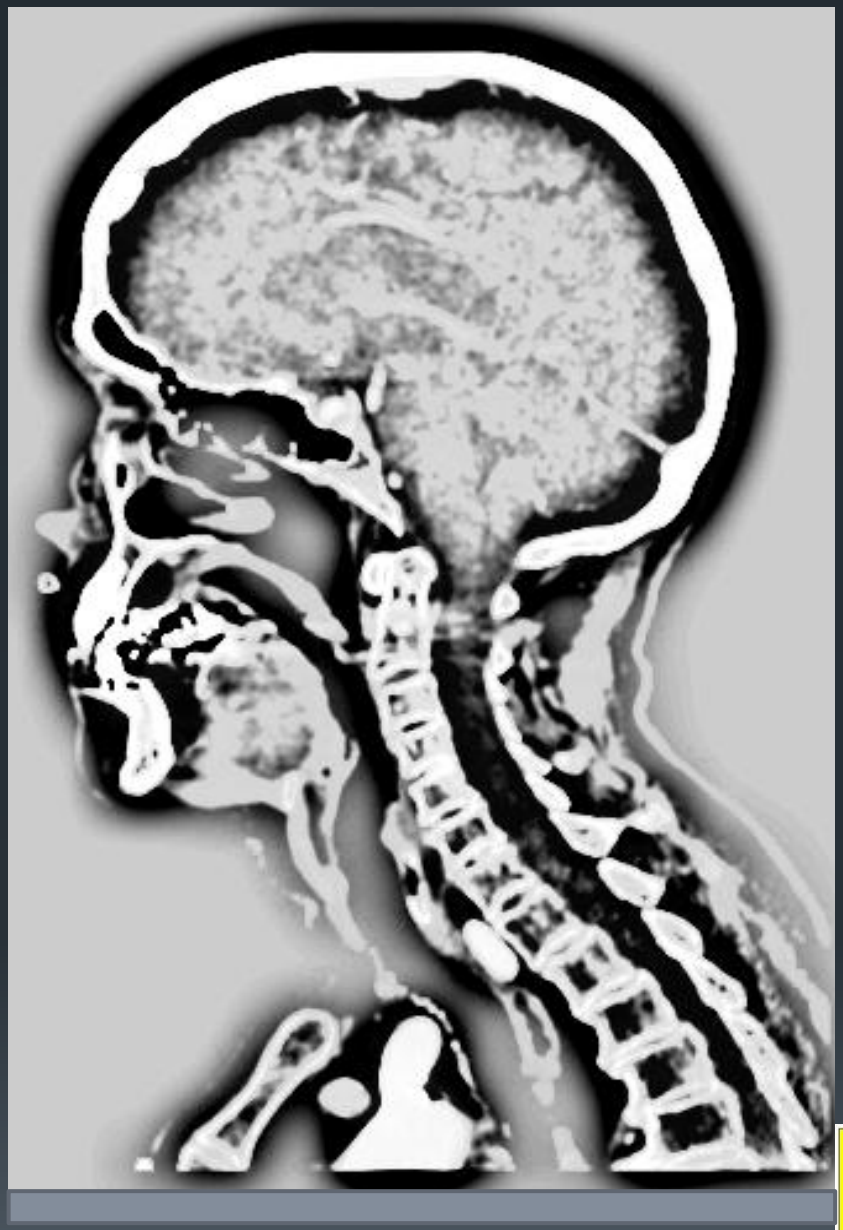




Multiphase CTA

- Refine CTA
- 3 phases
- One injection
- Relatively easy to standardize and train
- Minimal post processing time

mgoyal@ucalgary.ca



Multiphase CTA

Collateral Scoring on mCTA

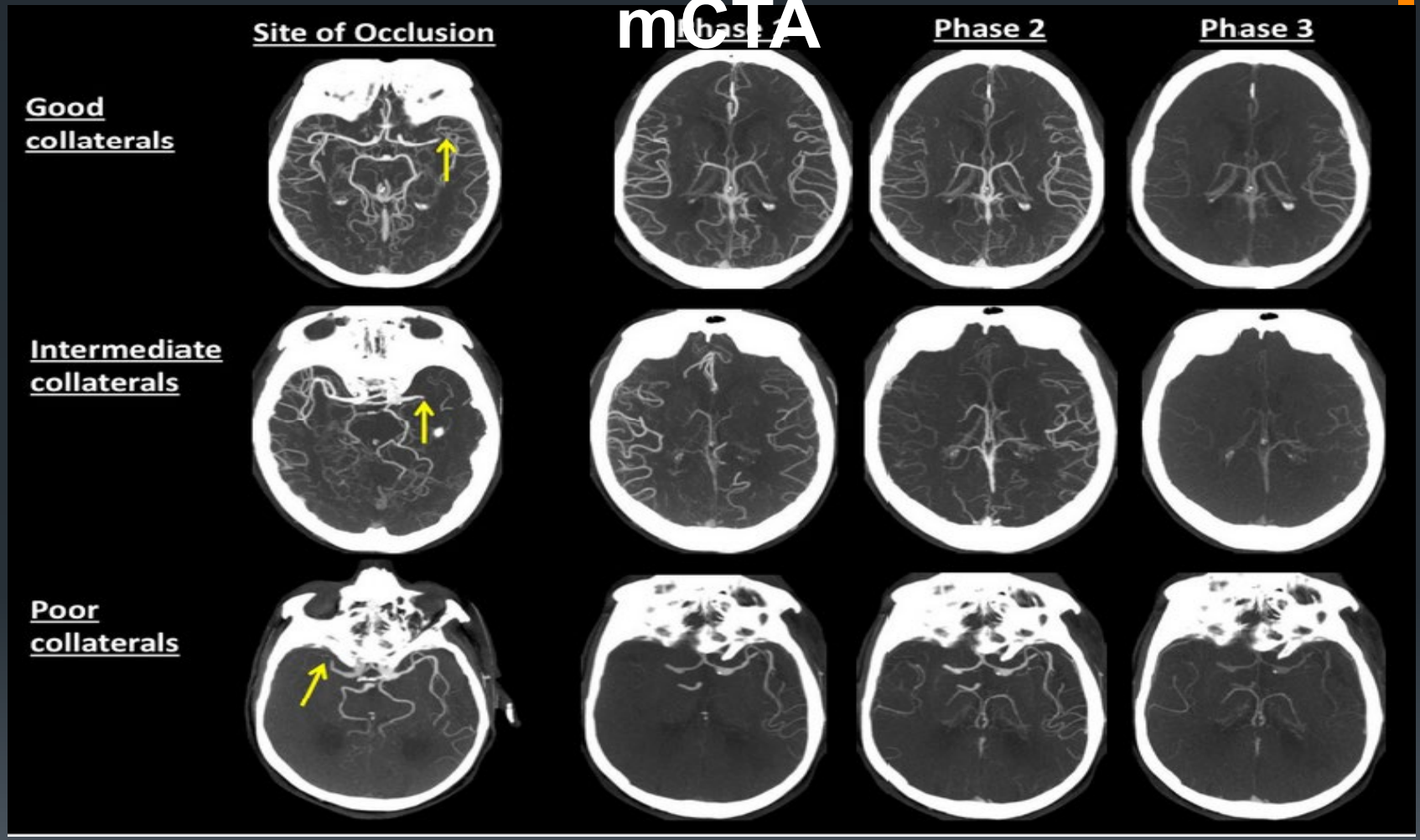


Figure. Upper panel shows a patient with a left M1 MCA occlusion (arrow) and good collaterals (backfilling arteries) on multi-phase CTA. Middle Panel shows a patient with a left M1 MCA occlusion (arrow) and intermediate collaterals. Lower panel shows a patient with a right M1 MCA occlsion (arrow) and poor collaterals (minimal backfilling arteries) on multi-phase CTA.

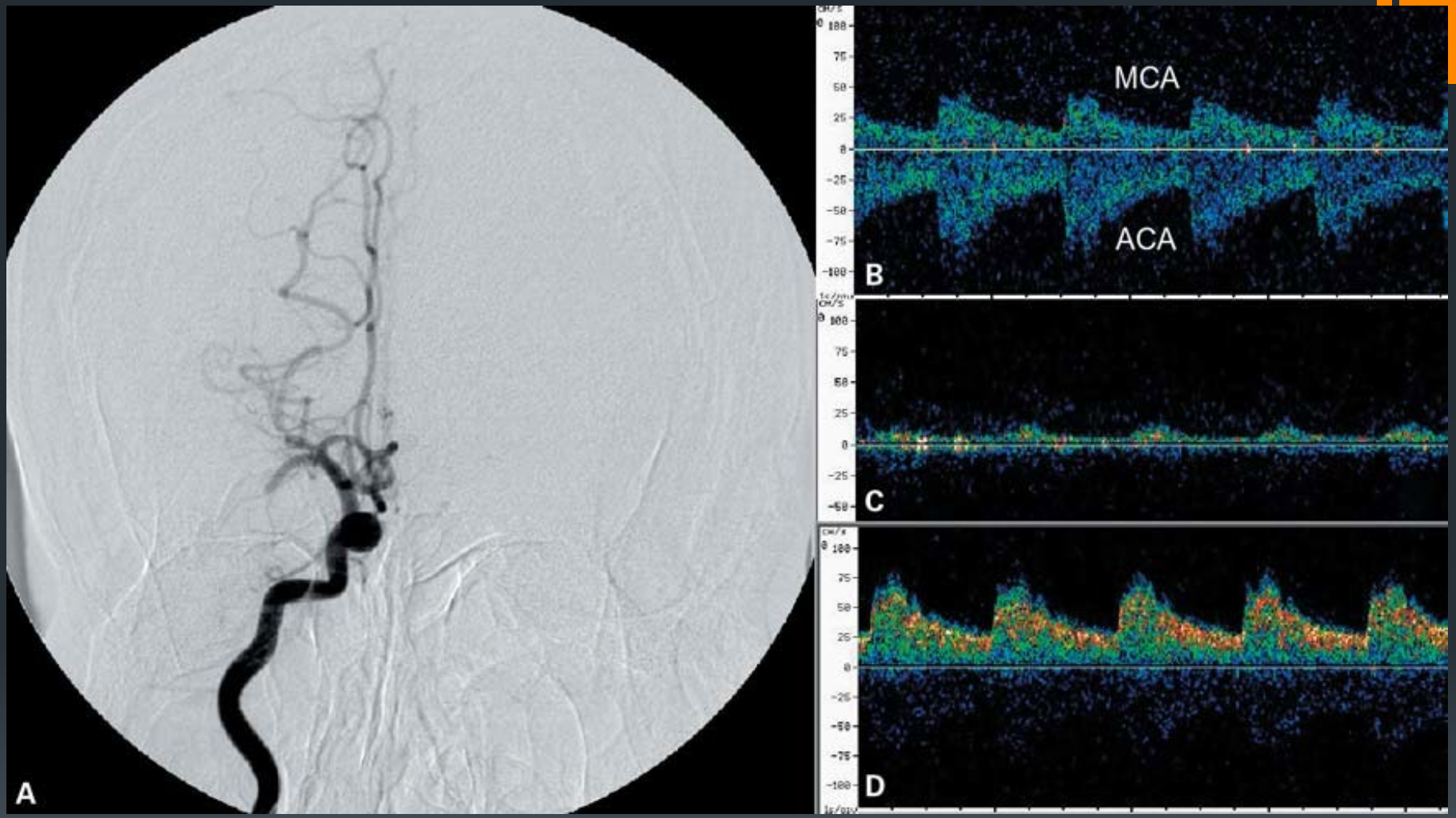
Collaterals in Stroke Research

18 Meyer JS, Denny-Brown D: The cerebral collateral circulation. I. Factors influencing collateral blood flow. Neurology 1957;7:447–458.

Flow Diversion in Transcranial Doppler Ultrasound Is Associated with Better Improvement in Patients with Acute Middle Cerebral Artery Occlusion

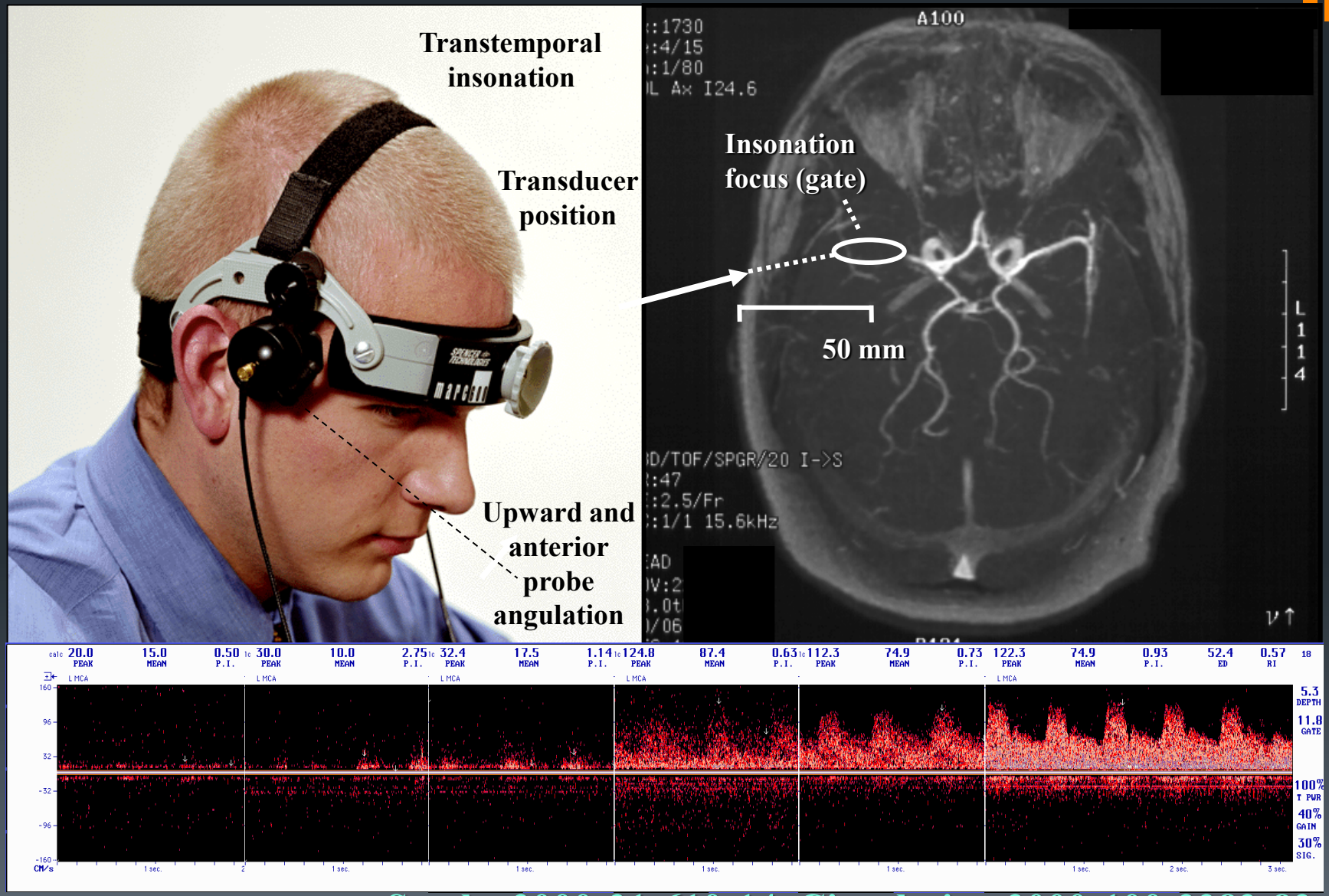
Yo Sik Kim[a] John Stirling Meyer[b] Zsolt Garami[c] Carlos A. Molina[e]
Aleksandra M. Pavlovic[f, g] Andrei V. Alexandrov[d]

Cerebrovascular Dis 2006;21:74-78.



Cerebrovascular Dis 2006;21:74-78.

TCD Monitors the Residual Flow Signals



Stroke 2000;31:610-14. Circulation 2000;100:2282-83.


EXAM #84 : :
01-10-0
08:58:0
VESSEL
DEPTH
50
POWER
100
SAMPLE
9
M NOISE
-12
1
30
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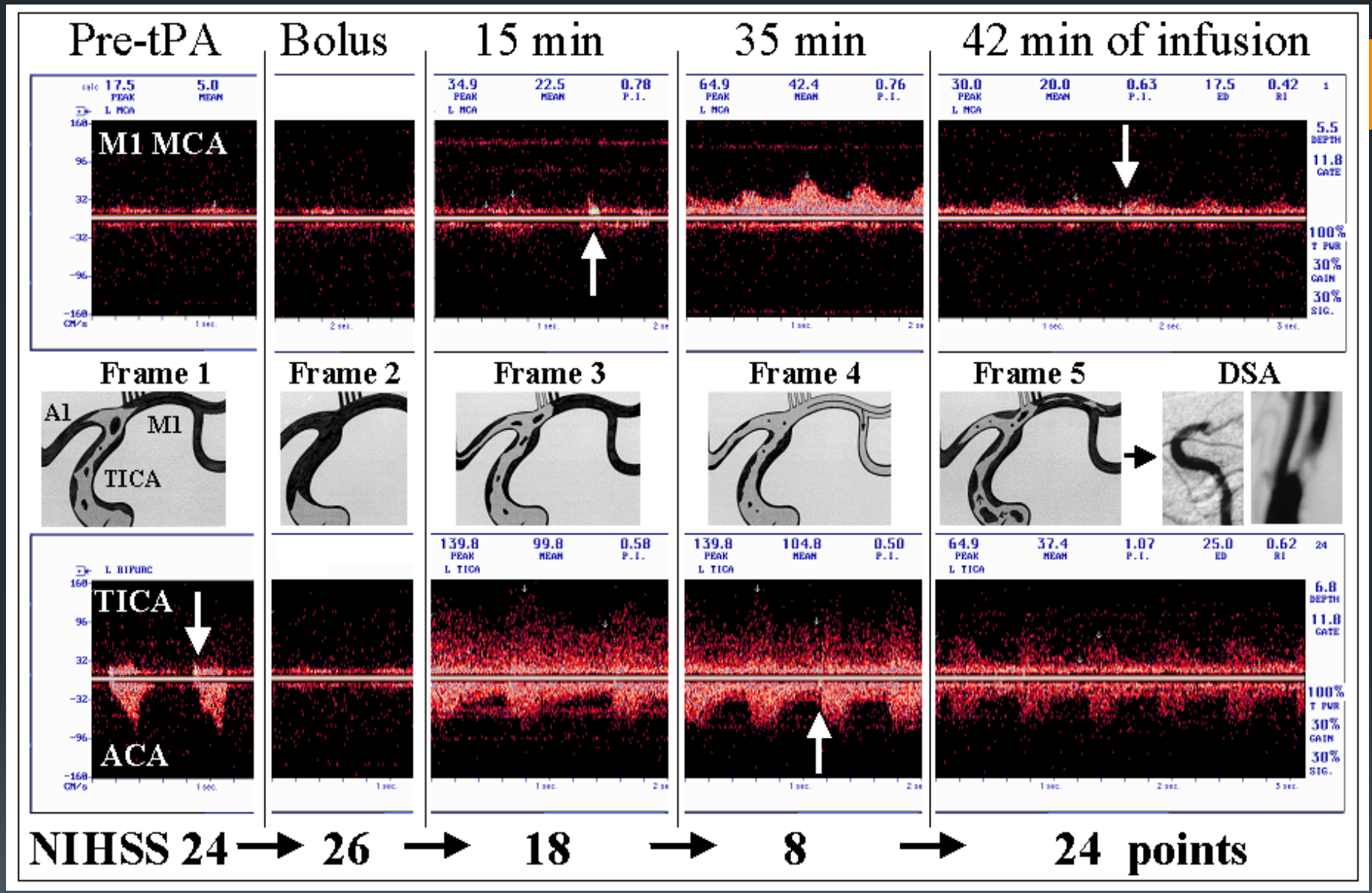
+2
+1
0
-1
kHz
+80
+40
0
cm/s



Neurology 2001;56:568-570.

CME

Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator

Andrei V. Alexandrov, MD; and James C. Grotta, MD

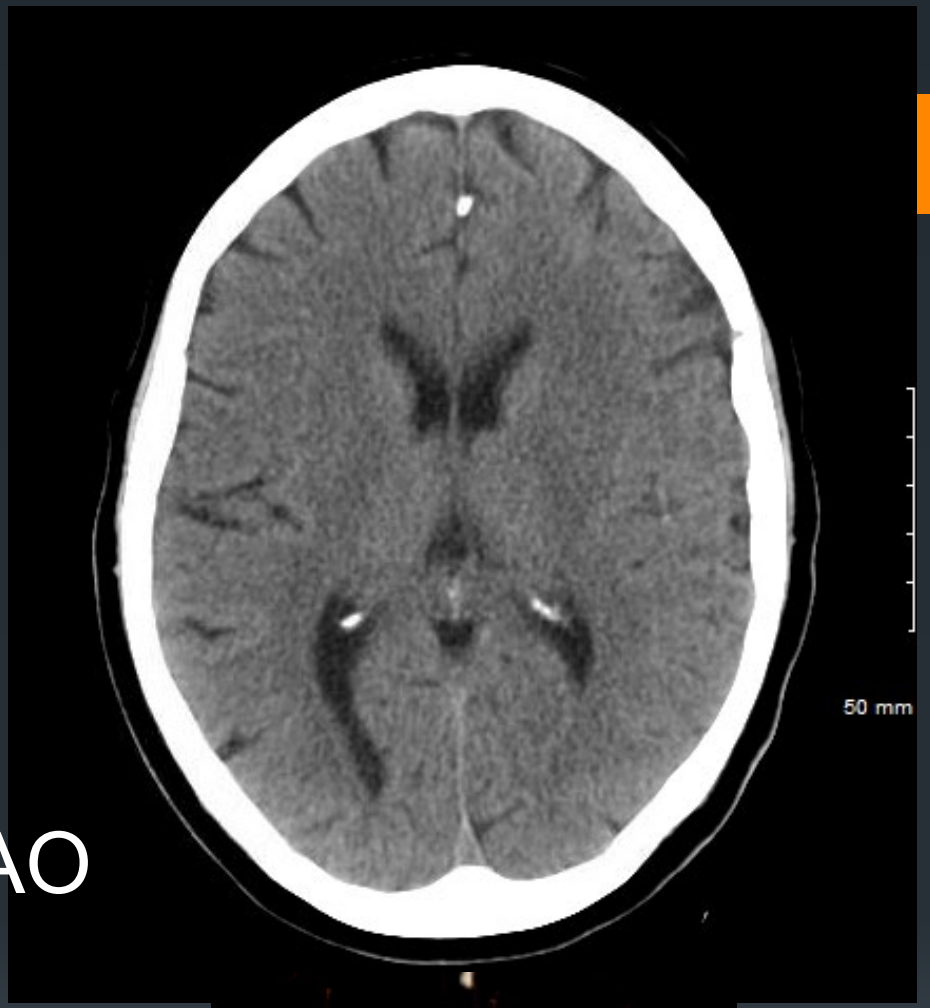
-Reocclusion occurs in up to 27% of TPA treated patients with MCA occlusions

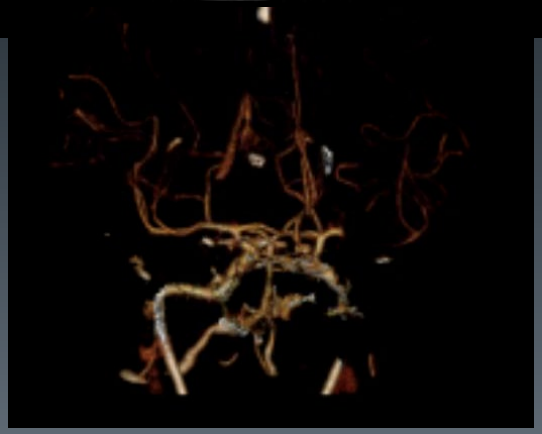
-Reocclusion accounts for 2/3 of early clinical deterioration following improvement

NEUROLOGY 2002;59:862–867

Case illustration

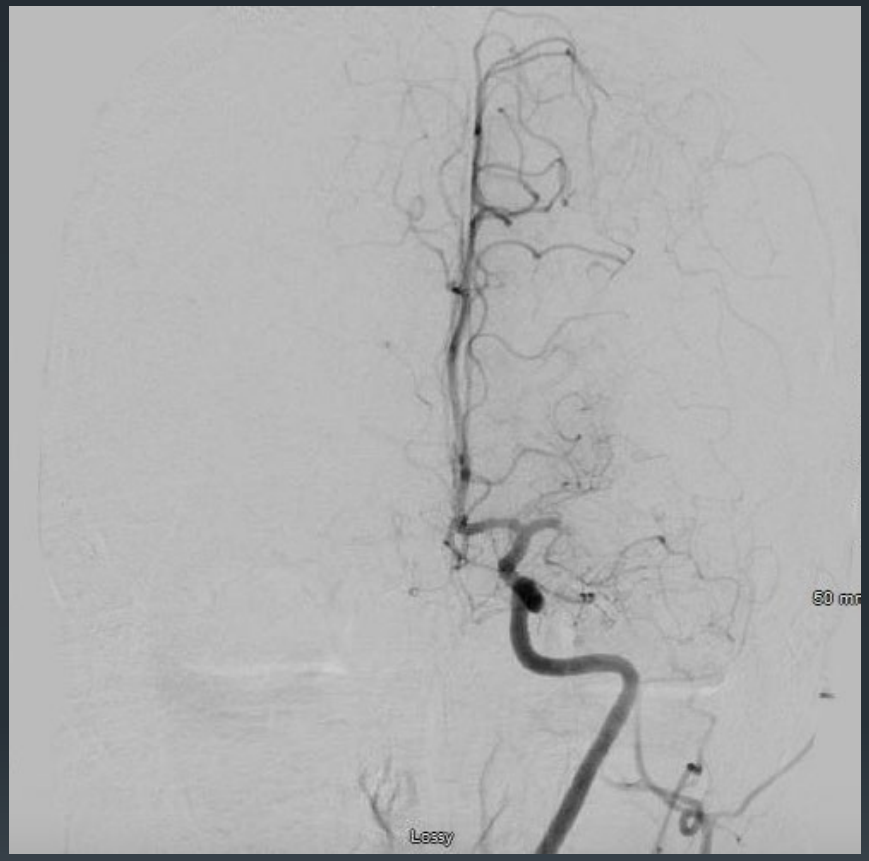
- 60 y.o. AA man
- NIHSS 17
- ASPECTS 9
- iv tPA at 3 hrs
- CTA persisting LMCAO after transfer

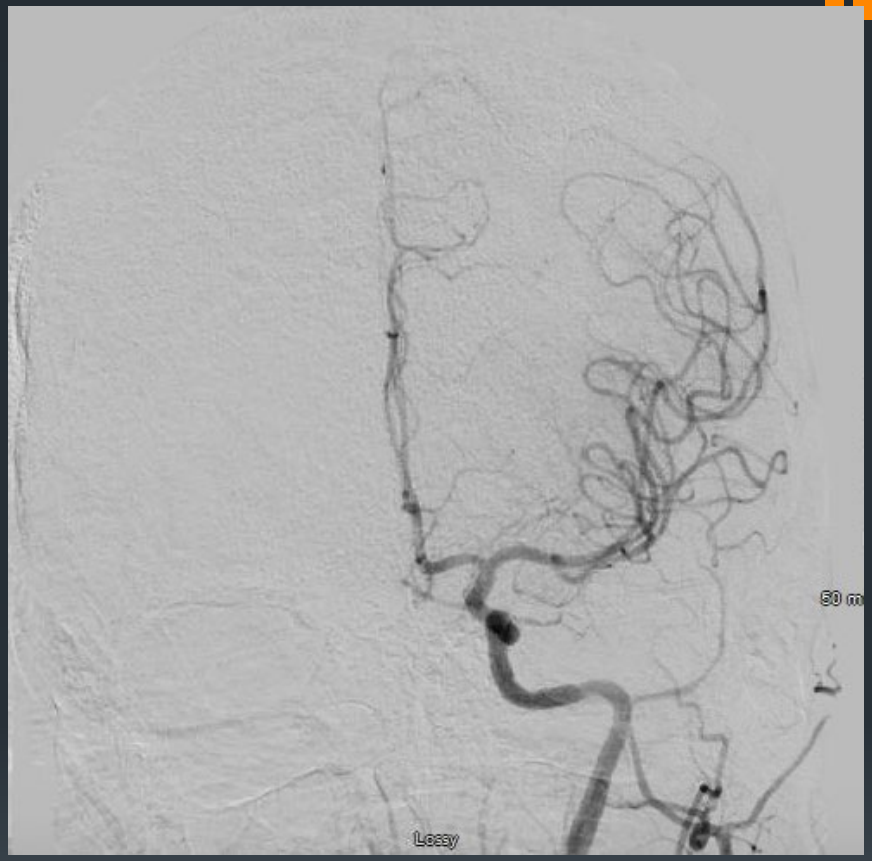




Images courtesy of Dr Nitin Goyal

Case illustration

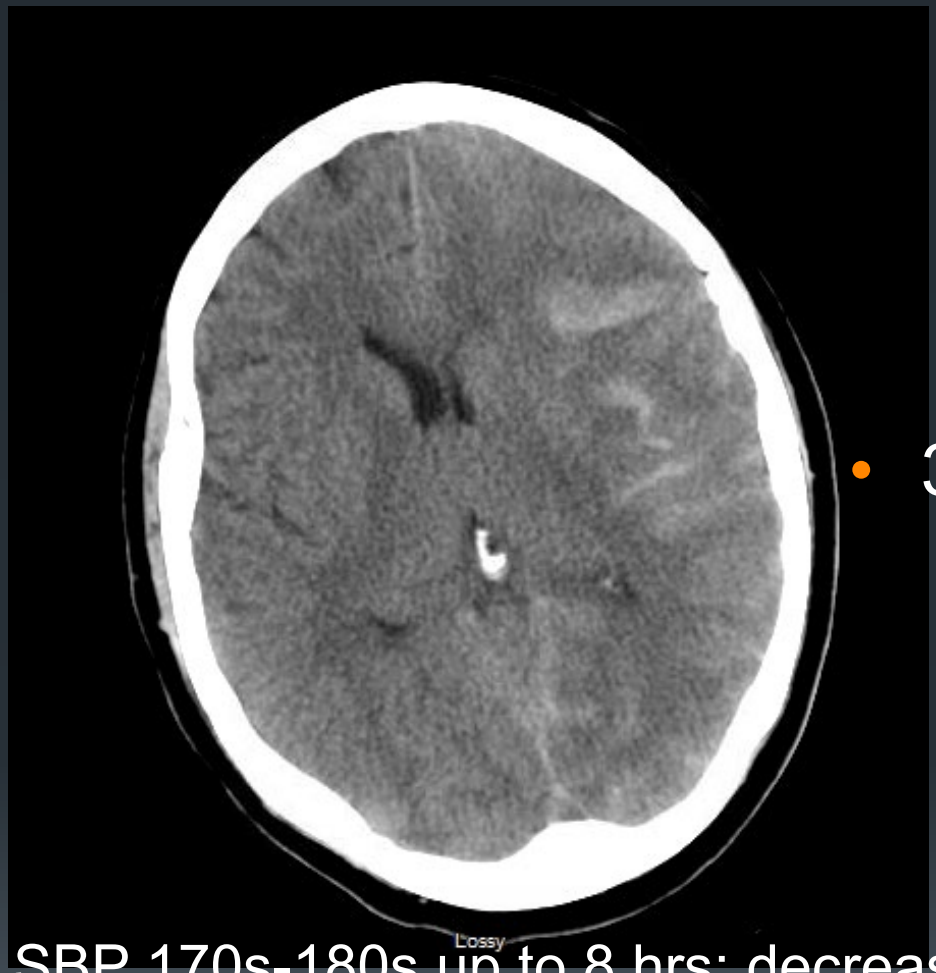




- Symptom onset to TICI 3 246 min

Images courtesy of Dr Nitin Goyal

Case illustration



- 3 month mRS 4

- Post MT SBP 170s-180s up to 8 hrs; decreasing LOC

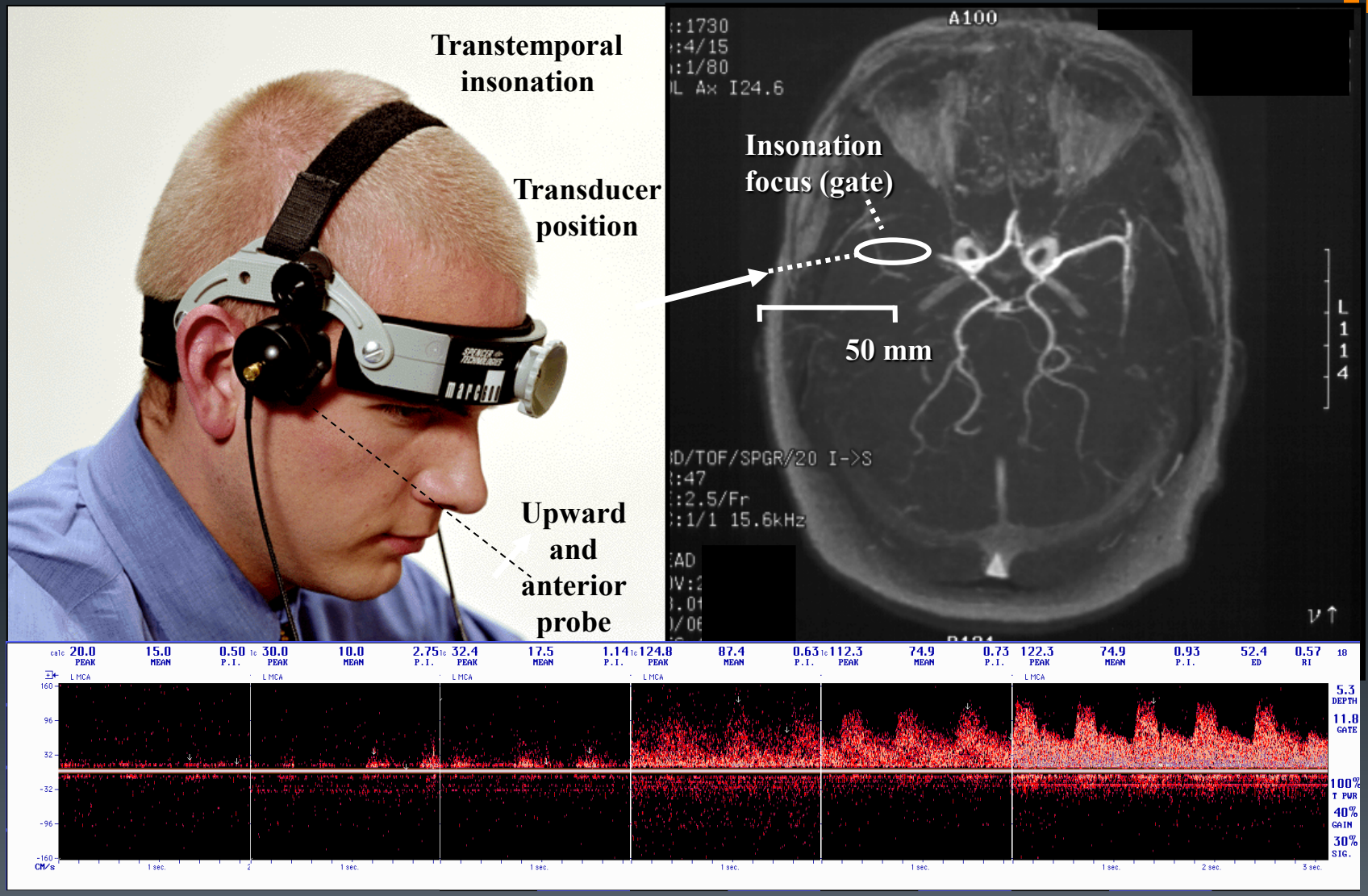
Images courtesy of Dr Nitin Goyal

Knowns from bp mgmt for iv tPa

- BP goals before bolus below<185/110 mm Hg and <180/105 for 24 hrs post treatment were set by NINDS-rt-PA Stroke Study. Violations increase sICH risk OR 2.59; 95% CI, 1.07 to 6.25; P=0.034
- Pre-bolus SBP inversely associated with recanalization: OR per 10-mm Hg increase 0.85; 95% CI: 0.74 to 0.98, P=0.022

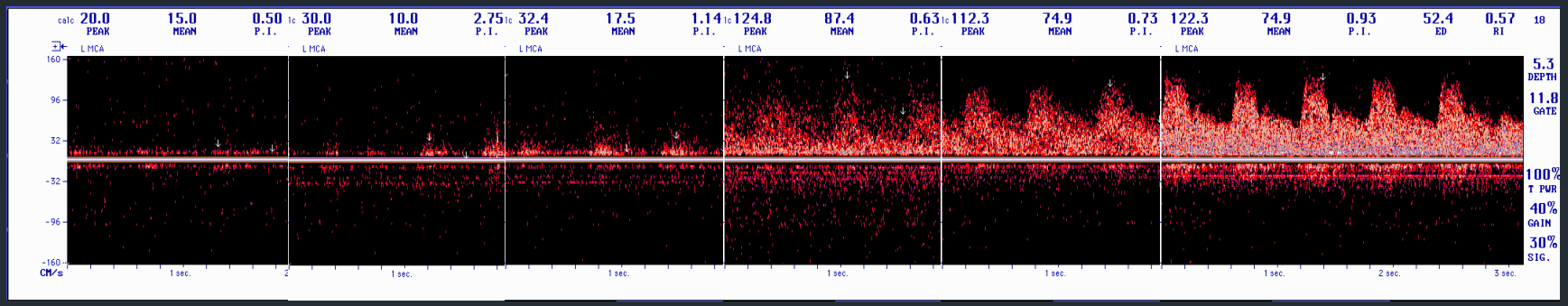
vgoulis G, et al. Stroke 2009;40:3631-3634. TUCSON Trial. Ann Neurol 2009;66:28-38.
Tsivgoulis G, et al. Stroke 2007;38:961-966.

Lessons learned with monitoring



Demchuk AM, et al. Circulation 2000;100:2282-83.

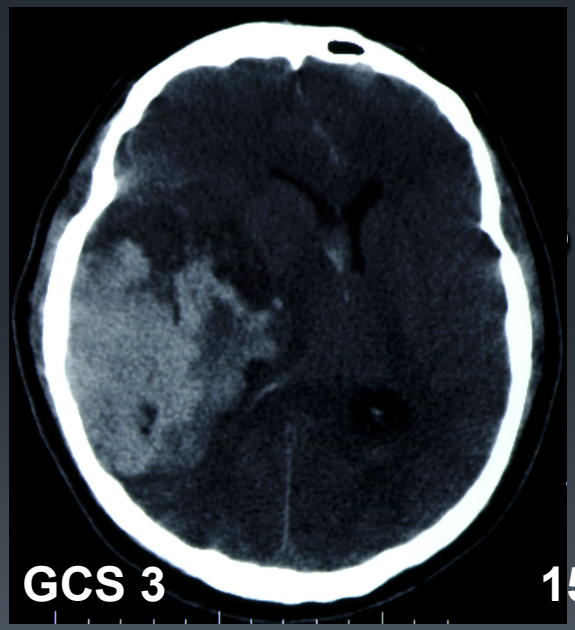
Lessons learned with monitoring



13:02

TPA bolus

NIHSS 15



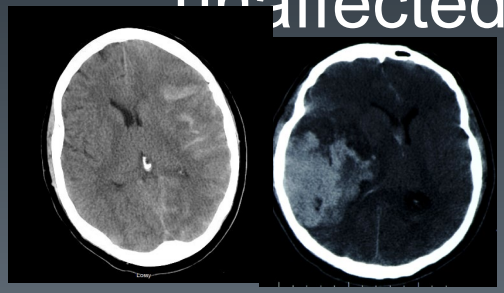
:38

15:25 NIHSS 15

Demchuk AM, et al. Circulation 2000;100:2282-83.

Hyperemic reperfusion after mt

- Analogous to cerebral hyperperfusion syndrome after carotid endarterectomy leading to headache, seizures and SAH/blood extravasation
- Contributes to hemorrhagic transformations, sICH, edema, neurological decline and seizures after stroke
- Directly detectable by TCD during or after MT: normal or elevated MFVs with abnormally low resistance flow pattern (PI decrease >30% vs unaffected side) in the previously occluded vessel[1]



[1]Rubiera M, et al. Stroke 2010;41:695-699.

Until RCT(s) become available…

- TICI 3 + Dramatic neurological recovery < 140/80
- TICI 3, no Neurological improvement <160/90
- TICI 2 ± Neurological improvement <160/90
- No recanalization <160/90 or permissive hypertension <180/90
- Strict BP control to avoid variability in all groups

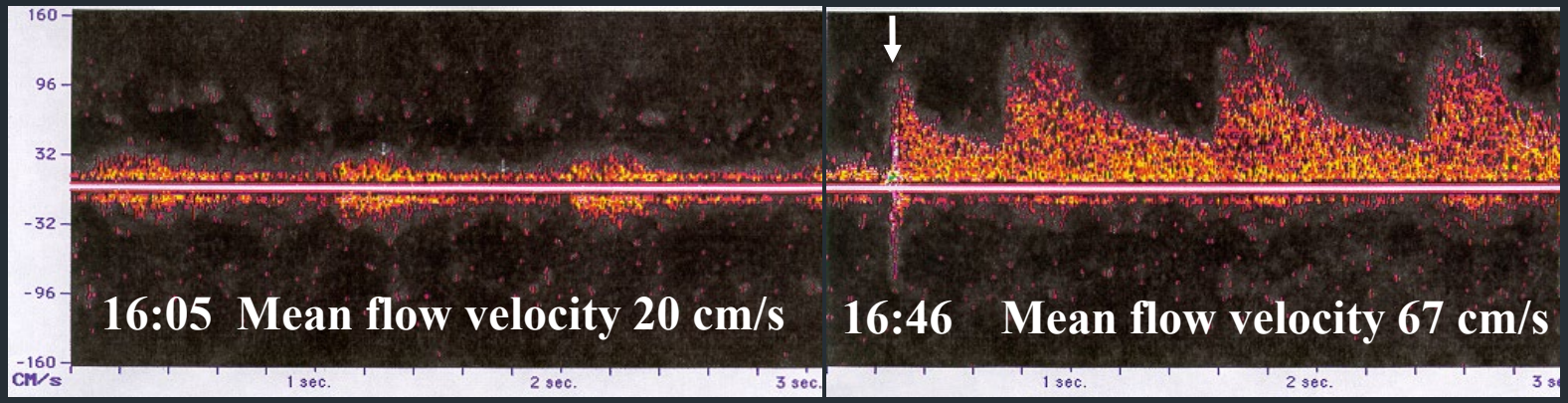
Personal opinion.

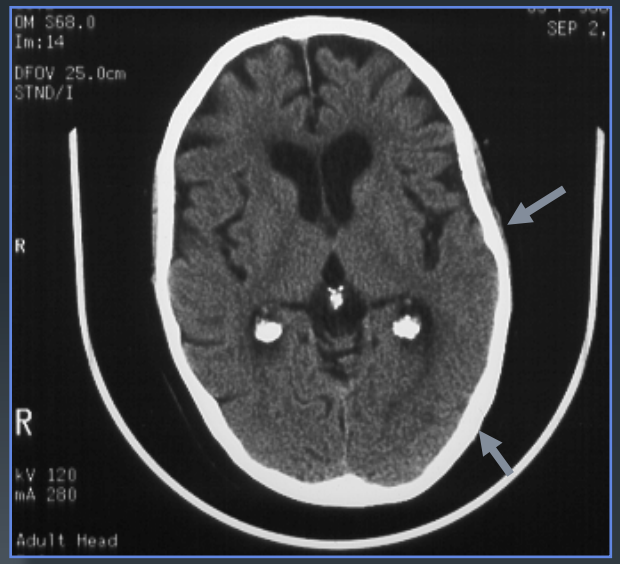
An 85 year old woman with Hx of HTN had a sudden onset of right sided weakness and speech arrest.

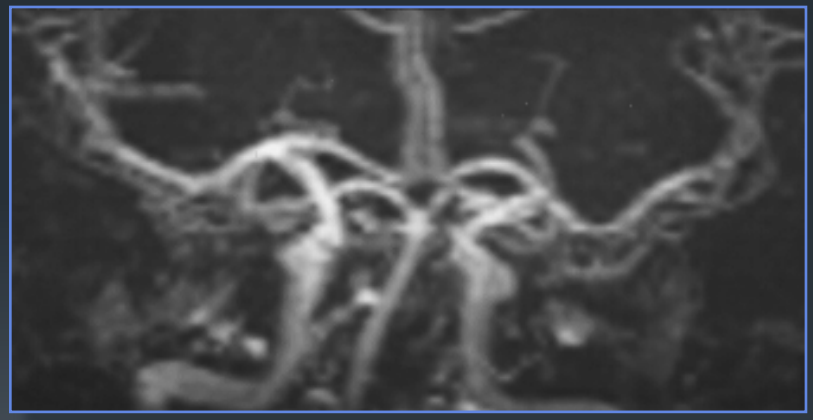
Normal CT scan at 1 hr.
TPA given at 82 minutes from Sx onset.

TCD monitoring initiated prior to TPA bolus.

N Engl J Med 1999;340:894-895.







N Engl J Med 1999;340:894-895.

14:50 – sudden onset right sided weakness/speech arrest.
15:32 – arrival to the hospital, NIHSS 12.
15:50 – normal CT scan.
16:12 – TPA bolus iv.
16:46 – sudden MCA recanalization on TCD.
16:51 – began to regain anti-gravity strength in R arm.
17:00 – began to smile, laugh, and use single words.
17:10 – able to speak in full sentences and had no residual motor weakness.
17:26 – mild comprehension and repetition difficulties.
By the next morning she had no residual deficit and
MRA showed normal intracranial vessels
with no ischemic abnormalities on DWI or T2 sequences.

N Engl J Med 1999;340:894-895.

Dramatic Recovery

Resolution of neurological deficit to the total NIHSS score ≤3 points within 2 hr after TPA bolus

Stroke 2000;31:610-14.

Early Recovery

Reduction of neurological deficit by ≥10 NIHSS points within 24 hr after TPA bolus

NEJM 1995;333:1581-1587.

High Rate of Complete Recanalization and Dramatic Clinical Recovery During tPA Infusion When Continuously Monitored With 2-MHz Transcranial Doppler Monitoring

Andrei V. Alexandrov, MD; Andrew M. Demchuk, MD, FRCPC; Robert A. Felberg, MD; Ioannis Christou, MD; Philip A. Barber, MRCP(UK); W. Scott Burgin, MD; Marc Malkoff, MD; Anne W. Wojner, MSN, CCRN; James C. Grotta, MD

Background and Purpose—Clot dissolution with tissue plasminogen activator (tPA) can lead to early clinical recovery after stroke. Transcranial Doppler (TCD) with low MHz frequency can determine arterial occlusion and monitor recanalization and may potentiate thrombolysis.

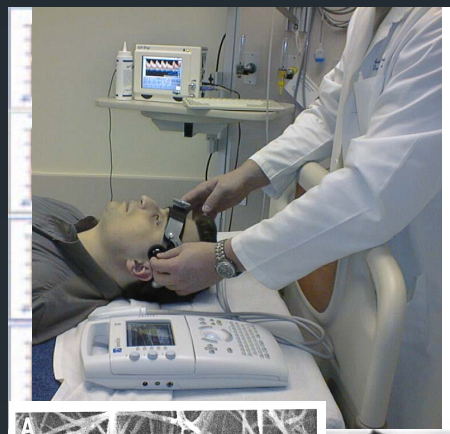
Methods—Stroke patients receiving intravenous tPA were monitored during infusion with portable TCD (Multigon 500M; DWL MultiDop-T) and headframe (Marc series; Spencer Technologies). Residual flow signals were obtained from the clot location identified by TCD. National Institutes of Health Stroke Scale (NIHSS) scores were obtained before and after tPA infusion.

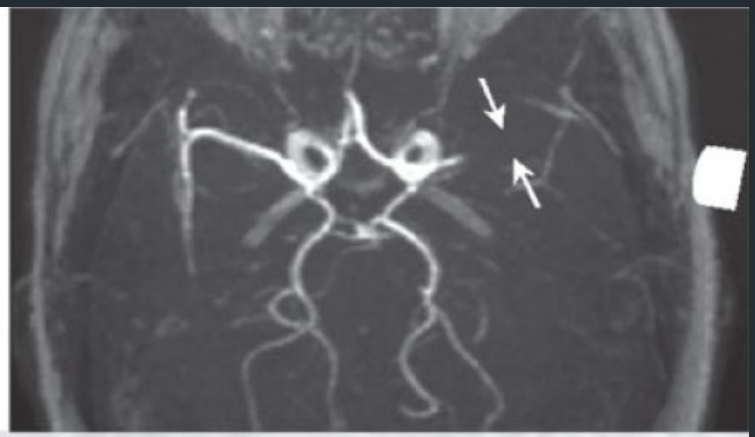
Results—Forty patients were studied (mean age 70±16 years, baseline NIHSS score 18.6±6.2, tPA bolus at 132±54 minutes from symptom onset). TCD monitoring started at 125±52 minutes and continued for the duration of tPA infusion. The middle cerebral artery was occluded in 30 patients, the internal carotid artery was occluded in 11 patients, the basilar artery was occluded in 3 patients, and occlusions were multiple in 7 patients; 4 patients had no windows; and 1 patient had a normal TCD. Recanalization on TCD was found at 45±20 minutes after tPA bolus: recanalization was complete in 12 (30%) and partial in 16 (40%) patients. Dramatic recovery during tPA infusion (total NIHSS score <3) occurred in 8 (20%) of all patients (baseline NIHSS range 6 to 22; all 8 had complete recanalization). Lack of improvement or worsening was associated with no recanalization, late recanalization, or reocclusion on TCD ($C=0.811$, $P \leq 0.01$). Improvement by ≥10 NIHSS points or complete recovery was found in 30% of all patients at the end of tPA infusion and in 40% at 24 hours. Improvement by ≥4 NIHSS points was found in 62.5% of patients at 24 hours.

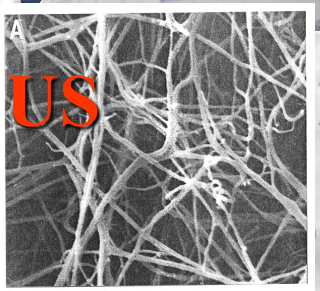
Conclusions—Dramatic recovery during tPA therapy occurred in 20% of all patients when infusion was continuously monitored with TCD. Recovery was associated with recanalization on TCD, whereas no early improvement indicated persistent occlusion or reocclusion. At 24 hours, 40% of all patients improved by ≥10 NIHSS points or recovered completely. Ultrasonic energy transmission by TCD monitoring may expose more clot surface to tPA and facilitate thrombolysis and deserves a controlled trial as a way to potentiate the effect of tPA therapy. **(*Stroke*. 2000;31:610-614.)**

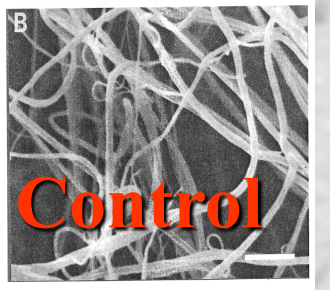
Dx US Enhances Thrombolysis

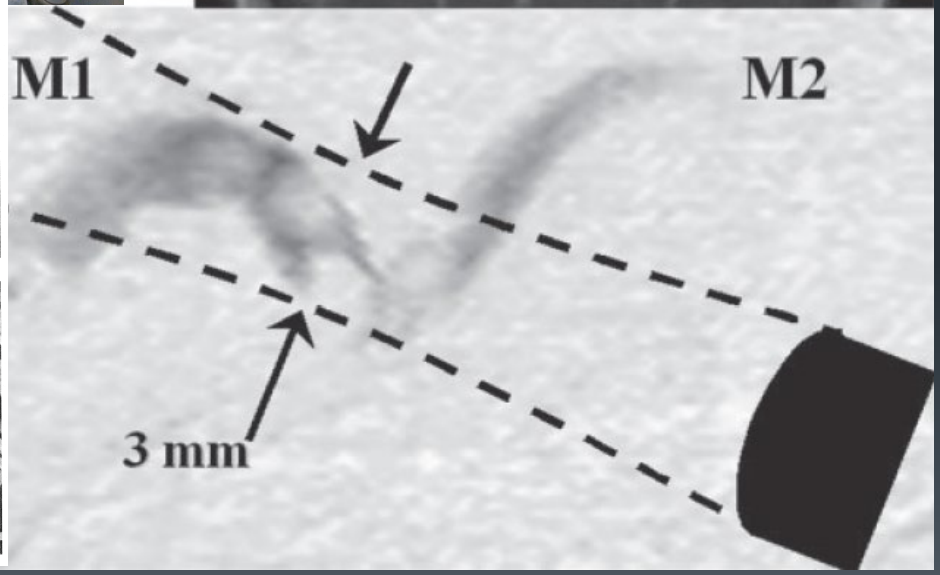
Portable
2 MHz TCD











Possible Mechanisms:

- Reversible changes in fibrin structure
- Plasma streaming through thrombus
- ↑TPA delivered to binding sites

Stroke 2004;35:2722-25.

Houston Barcelona Edmonton Calgary

UT
STAT
Stroke Treatment Team

Vall d'Hebron
Hospital

UNIVERSITY OF ALBERTA
QUAECUMQUE VERA

MO·SFORZE·TOGAM·SUAS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ultrasound-Enhanced Systemic Thrombolysis for Acute Ischemic Stroke

Andrei V. Alexandrov, M.D., Carlos A. Molina, M.D., James C. Grotta, M.D., Zsolt Garami, M.D., Shiela R. Ford, R.N., Jose Alvarez-Sabin, M.D., Joan Montaner, M.D., Maher Saqqur, M.D., Andrew M. Demchuk, M.D., Lemuel A. Moyé, M.D., Ph.D., Michael D. Hill, M.D., and Anne W. Wojner, Ph.D., for the CLOTBUST Investigators*

New Engl J Med 2004;351;2170-2178.

CLOTBUSTER: Results

Safety and efficacy of sonothrombolysis for acute ischaemic stroke: a multicentre, double-blind, phase 3, randomised controlled trial

*Andrei V Alexandrov, Martin Köhrmann, Lauri Soinne, Georgios Tsivgoulis, Andrew D Barreto, Andrew M Demchuk, Vijay K Sharma, Robert Mikulik, Keith W Muir, Gordon Brandt, John Alleman, James C Grotta, Christopher R Levi, Carlos A Molina, Maher Saqqur, Dimitris Mavridis, Theodora Psaltopoulou, Milan Vosko, Jochen B Fiebach, Pitchaiah Mandava, Thomas A Kent, Anne W Alexandrov, Peter D Schellinger, for the CLOTBUST-ER Trial Investigators**

Lancet Neurol 2019; 18: 338–47

NCT#01098981

CLOTBUSTER: Results

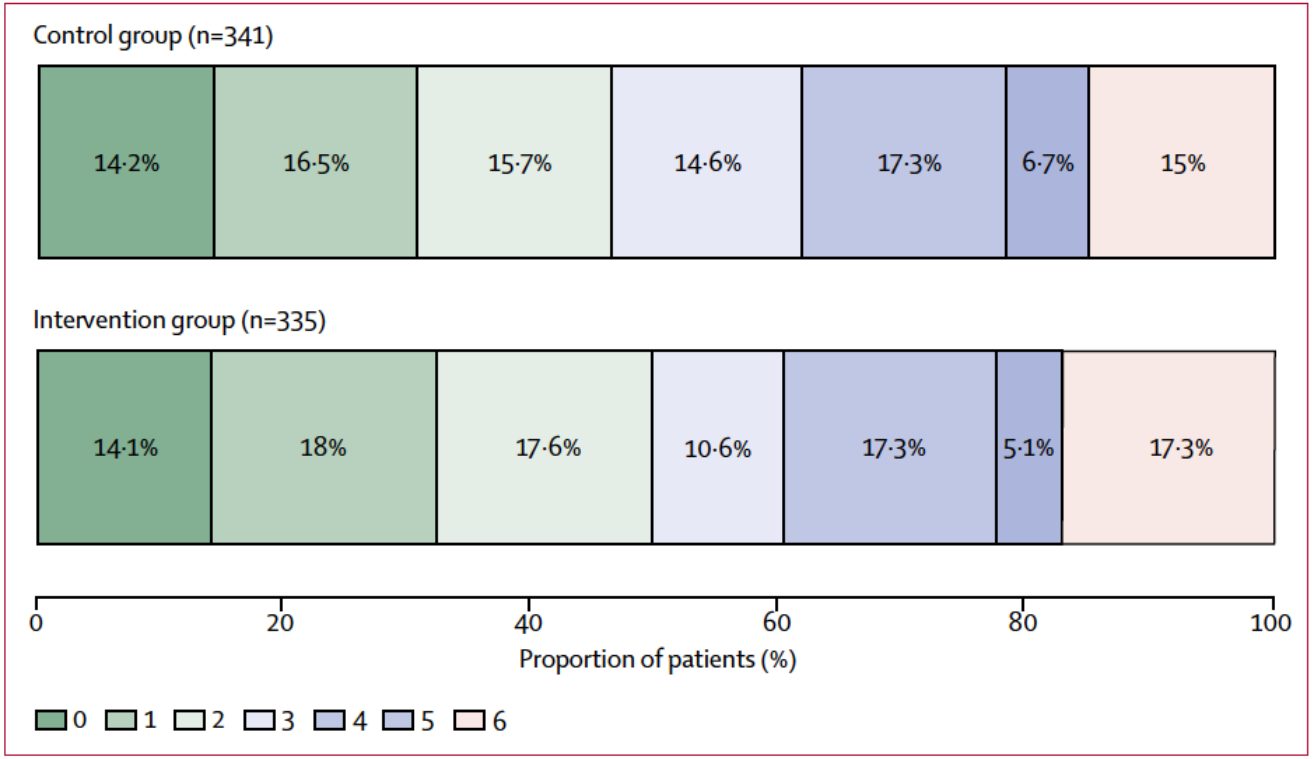


Figure 2: **Modified Rankin Scale scores at 90 days in patients treated with intravenous thrombolysis within 3 h (intention-to-treat population)**

	Intervention group	Control group	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Primary outcome*						
Modified Rankin Scale score at 90 days in patients enrolled within 3 h of symptom onset	3·0 (1·0–4·0)	3·0 (1·0–4·0)	1·03 (0·76–1·40)†	0·84	1·05 (0·77–1·45)†	0·74

Lancet Neurol 2019; 18: 338–47

CLOTBUSTER: Subgroup Analysis

Endovascular equipoise shift in a phase III randomized clinical trial of sonothrombolysis for acute ischemic stroke

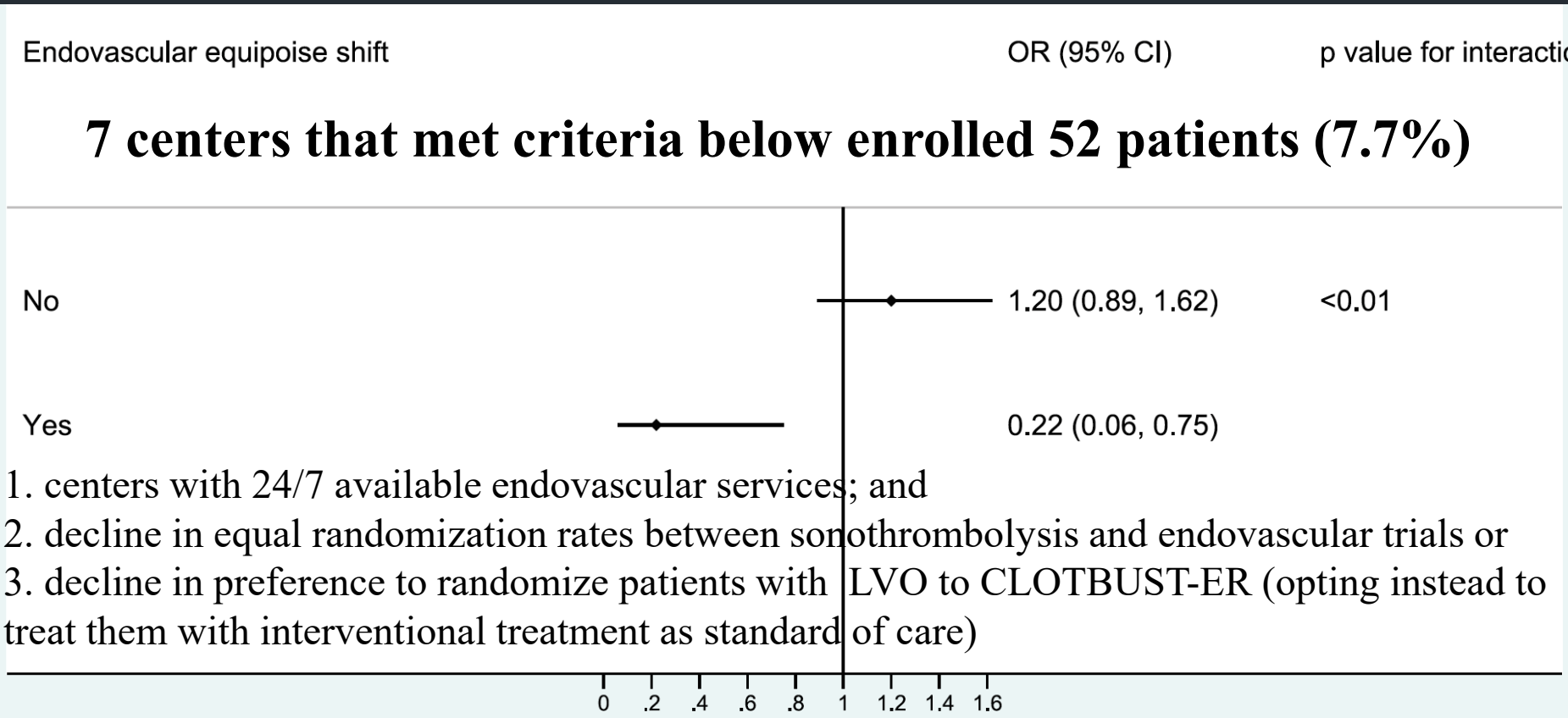
Andrei V. Alexandrov, Georgios Tsivgoulis, Martin Köhrmann, Aristeidis H. Katsanos, Lauri Soinne, Andrew D. Barreto, Travis Rothlisberger, Vijay K. Sharma, Robert Mikulik, Keith W. Muir, Christopher R. Levi, Carlos A. Molina, Maher Saqqur, Dimitris Mavridis, Theodora Psaltopoulou, Milan R. Vosko, Jochen B. Fiebach, Pitchaiah Mandava, Thomas A. Kent, Anne W. Alexandrov and Peter D. Schellinger, for the CLOTBUST-ER Trial Investigators

Ther Adv Neurol Disord

2019, Vol. 12: 1–12

NCT#01098981

CLOTBUSTER: Subgroup Analysis



7 centers that met criteria below enrolled 52 patients (7.7%)

1. centers with 24/7 available endovascular services; and
2. decline in equal randomization rates between sonothrombolysis and endovascular trials or
3. decline in preference to randomize patients with LVO to CLOTBUST-ER (opting instead to treat them with interventional treatment as standard of care)

Ther Adv Neurol Disord 2019;12:1-12.

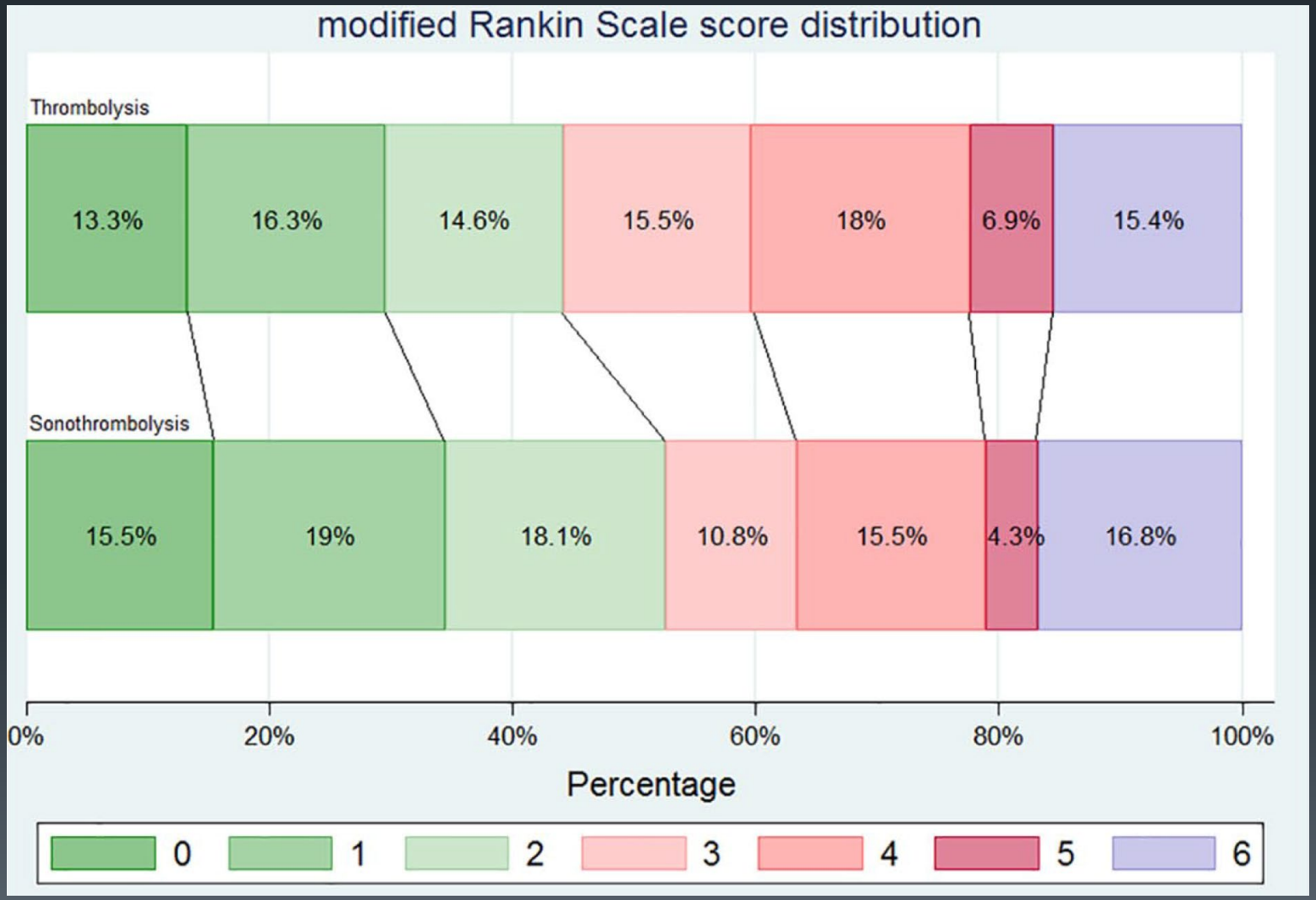
CLOTBUSTER: Subgroup Analysis

Table 1. Baseline characteristics of the study population after removing centers with perceived endovascular equipoise shift.

Variables	Intervention ($n=310$)	Control ($n=314$)	p
Mean age ± SD, years	67.1 ± 10.3	67.0 ± 10.6	0.86
Male sex, *n* (%)	175 (56.4)	187 (59.5)	0.47
Median NIHSS score (IQR), points	15 (11–18)	14 (11–18)	0.81
Hypertension, *n* (%)	178 (57.4)	194 (61.8)	0.29
Diabetes mellitus, *n* (%)	68 (21.9)	75 (23.9)	0.57
Atrial fibrillation, *n* (%)	56 (18.1)	53 (16.9)	0.75
Prestroke modified Rankin scale score 0–1, *n* (%)	309 (99.7)	312 (99.4)	>0.99
Mean systolic blood pressure before tPA bolus ± SD, mmHg[a]	150.0 ± 20.2	150.4 ± 20.1	0.81
Mean diastolic blood pressure before tPA bolus ± SD, mmHg[b]	81.4 ± 13.4	81.8 ± 13.0	0.71
Mean serum glucose before tPA bolus ± SD, mg/dl	139.4 ± 50.5	138.0 ± 53.5	0.74
Median time from symptom onset to tPA bolus (IQR), min	117.5 (95.0–161.5)	128.0 (97.2–165.8)	0.12
Time from symptom onset to tPA bolus within 3 h, *n* (%)	255 (82.3)	262 (83.4)	0.74
Median time from symptom onset to headframe activation (IQR), min	136 (118–182)	150 (116–188)	0.38

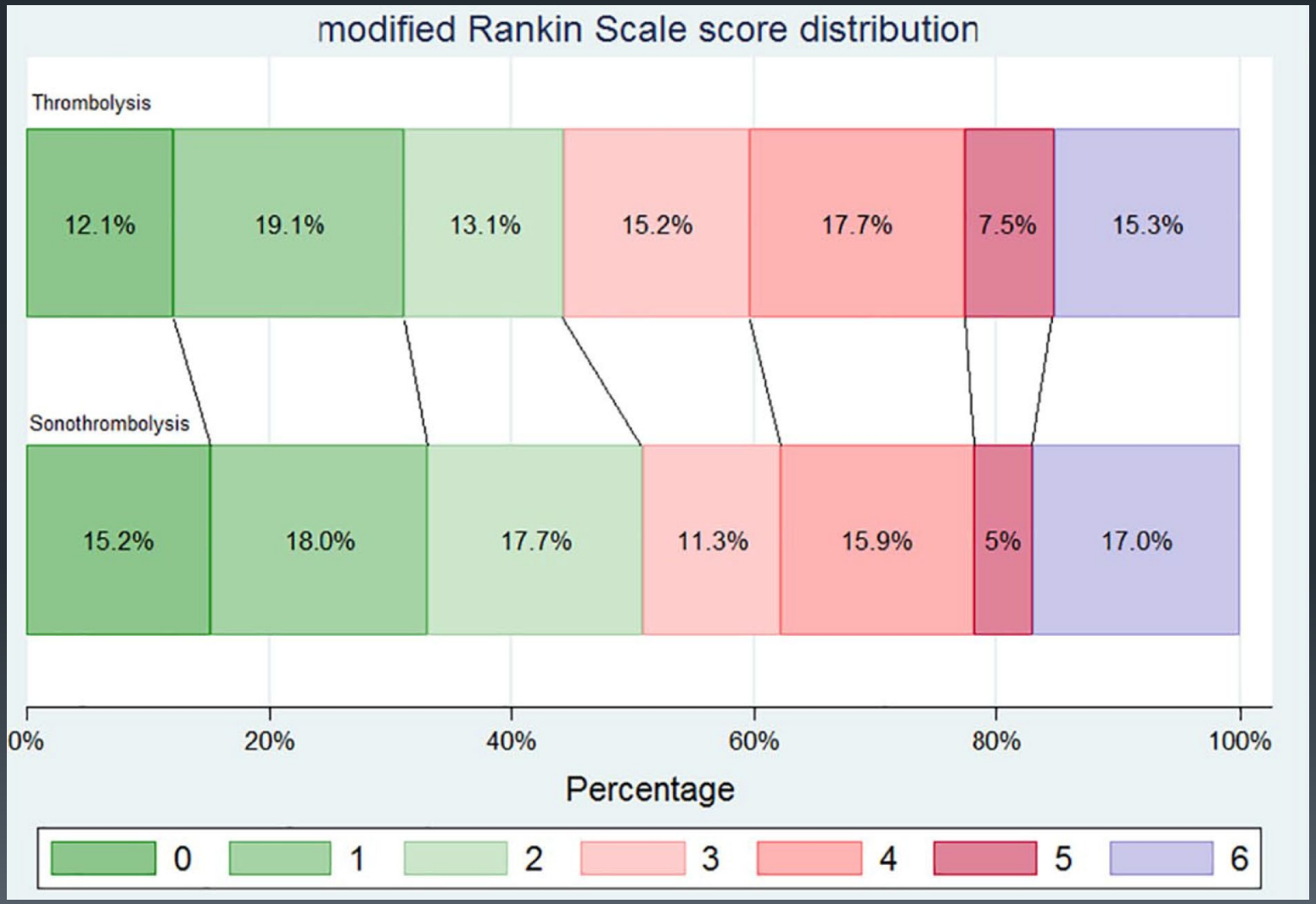
Ther Adv Neurol Disord 2019;12:1-12.

CLOTBUSTER subgroup: 0-3 hrs



Ther Adv Neurol Disord 2019;12:1-12.

CLOTBUSTER subgroup: 0-4.5 hrs



Ther Adv Neurol Disord 2019;12:1-12.

CLOTBUSTER: Subgroup Analysis

Table 2. Primary and secondary efficacy outcomes in the intention-to-treat population after removing centers with perceived endovascular equipoise shift.

Variables	Intervention (*n* = 310)	Control (*n* = 314)	Unadjusted OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*
Primary outcome: ordinal analysis of mRS score at 90 days (median, IQR)						
US[b]	2.0 (1.0–4.0)	3.0 (1.0–4.0)	1.22 (0.88–1.68)	0.22	1.20 (0.87–1.68)	0.27
Global[c]	2.0 (1.0–4.0)	3.0 (1.0–4.0)	1.16 (0.86–1.54)	0.33	1.20 (0.89–1.62)	0.24
Secondary outcomes						
mRS score at 7 days or discharge[d] US	3.0 (1.0–4.0)	4.0 (1.0–5.0)	1.18 (0.86–1.63)	0.30	1.20 (0.86–1.67)	0.27
mRS score at 7 days or discharge[d] Global	3.0 (1.0–4.0)	4.0 (1.0–5.0)	1.12 (0.84–1.50)	0.43	1.22 (0.90–1.64)	0.20
mRS score at 90 days 0–1; US[b], *n* (%)	80 (34.5%)	69 (29.6%)	1.25 (0.85–1.85)	0.27	1.30 (0.85–2.00)	0.22
mRS score at 90 days 0–2; US[b], *n* (%)	122 (52.6%)	103 (44.2%)	1.40 (0.97–2.02)	0.08	1.53 (1.01–2.31)	0.04
mRS score at 90 days 0–2; Global[c], *n* (%)	144 (50.9%)	125 (44.3%)	1.30 (0.93–1.81)	0.13	1.47 (1.02–2.13)	0.04
90 days[e]; US[b], *n* (%)						
Independent functional outcome at 90 days[e]; Global[c], *n* (%)	109 (38.5%)	102 (36.2%)	1.10 (0.79–1.55)	0.60	1.18 (0.83–1.69)	0.36
Dramatic clinical recovery at 2 h[f]; US, *n* (%)	54 (22.0%)	52 (20.5%)	1.10 (0.71–1.69)	0.74	1.12 (0.72–1.74)	0.63
Dramatic clinical recovery at 2 h[f]; Global, *n* (%)	56 (18.8%)	57 (18.7%)	1.00 (0.67–1.51)	1.00	1.05 (0.68–1.61)	0.84
Clinical recovery at 24 h[g]; US, *n* (%)	78 (32.6%)	90 (36.1%)	0.86 (0.59–1.24)	0.45	0.85 (0.58–1.25)	0.42
Clinical recovery at 24 h[g]; Global, *n* (%)	95 (32.8%)	102 (34.3%)	0.93 (0.66–1.31)	0.73	0.96 (0.68–1.37)	0.84
Neurological improvement at 24 h[h]; US, *n* (%)	141 (59.0%)	139 (55.8%)	1.14 (0.79–1.63)	0.52	1.16 (0.80–1.69)	0.43
Neurological improvement at 24 h[h]; Global, *n* (%)	169 (58.3%)	163 (54.9%)	1.15 (0.83–1.59)	0.45	1.20 (0.86–1.69)	0.29
Neurological deterioration at 24 h[i]; US, *n* (%)	20 (8.4%)	17 (6.8%)	1.25 (0.63–2.44)	0.61	1.17 (0.58–2.37)	0.66
Neurological deterioration at 24 h[i]; Global, *n* (%)	26 (9.0%)	19 (6.4%)	1.44 (0.78–2.67)	0.28	1.29 (0.69–2.44)	0.43

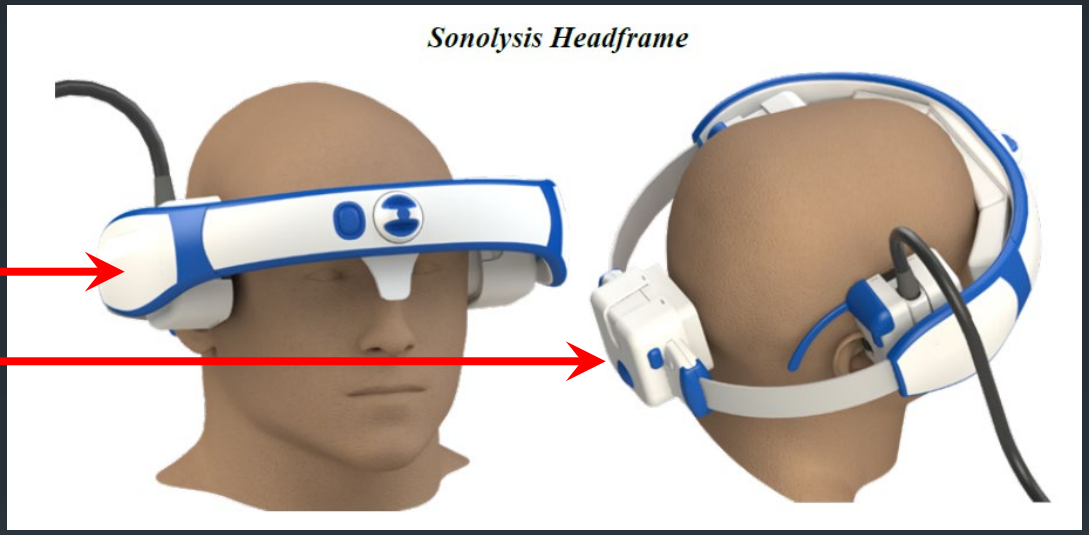
Ther Adv Neurol Disord 2019;12:1-12.

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of the Aureva Transcranial Ultrasound Device with Tissue Plasminogen Activator in Patients with Acute Ischemic Stroke (TRUST)

Andrei Alexandrov, MD
Global principal investigator
Joyce su, sr. Director, clinical affairs
Sponsor: Cerevast Medical, Inc

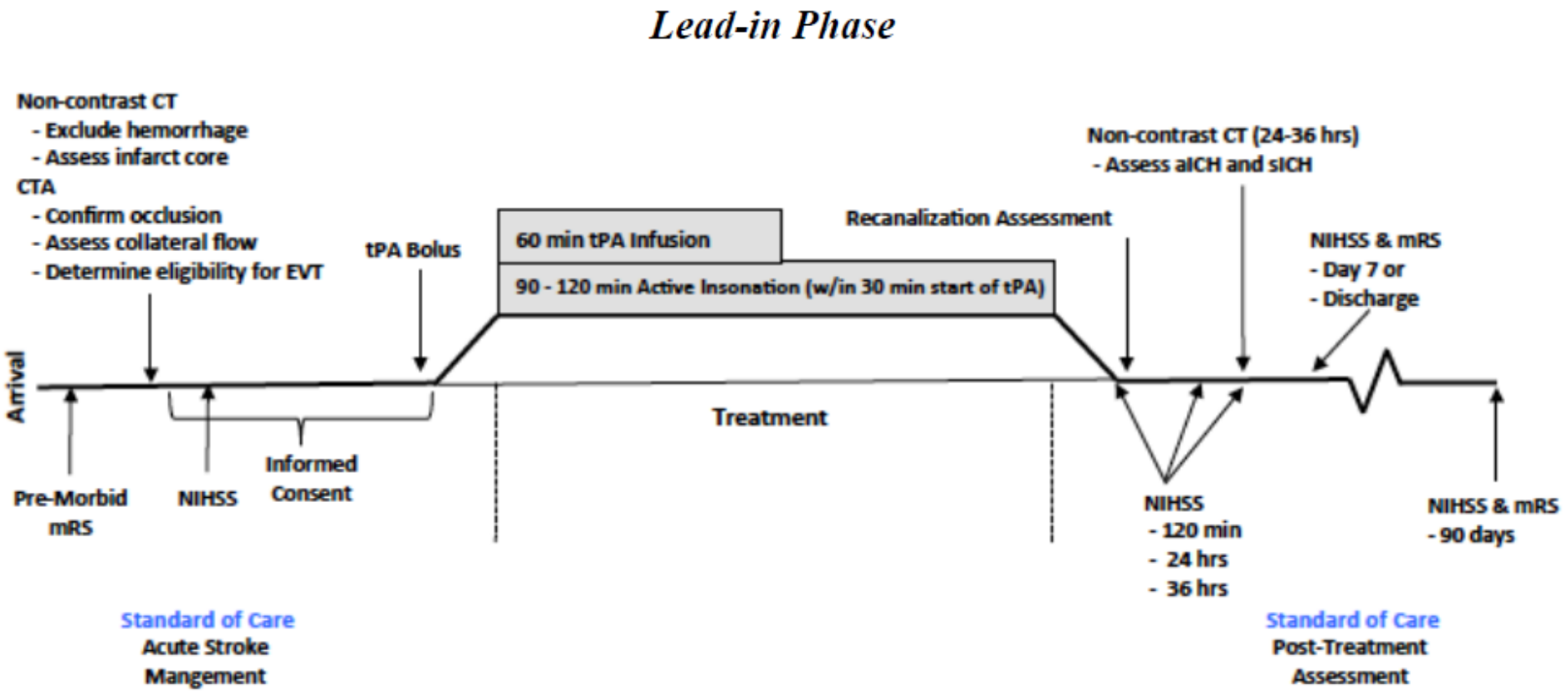
Aureva Transcranial Ultrasound Therapeutic Device

- 3 TRANSDUCERS
  - RIGHT TEMPORAL
  - LEFT TEMPORAL
  - SUBOCCIPITAL



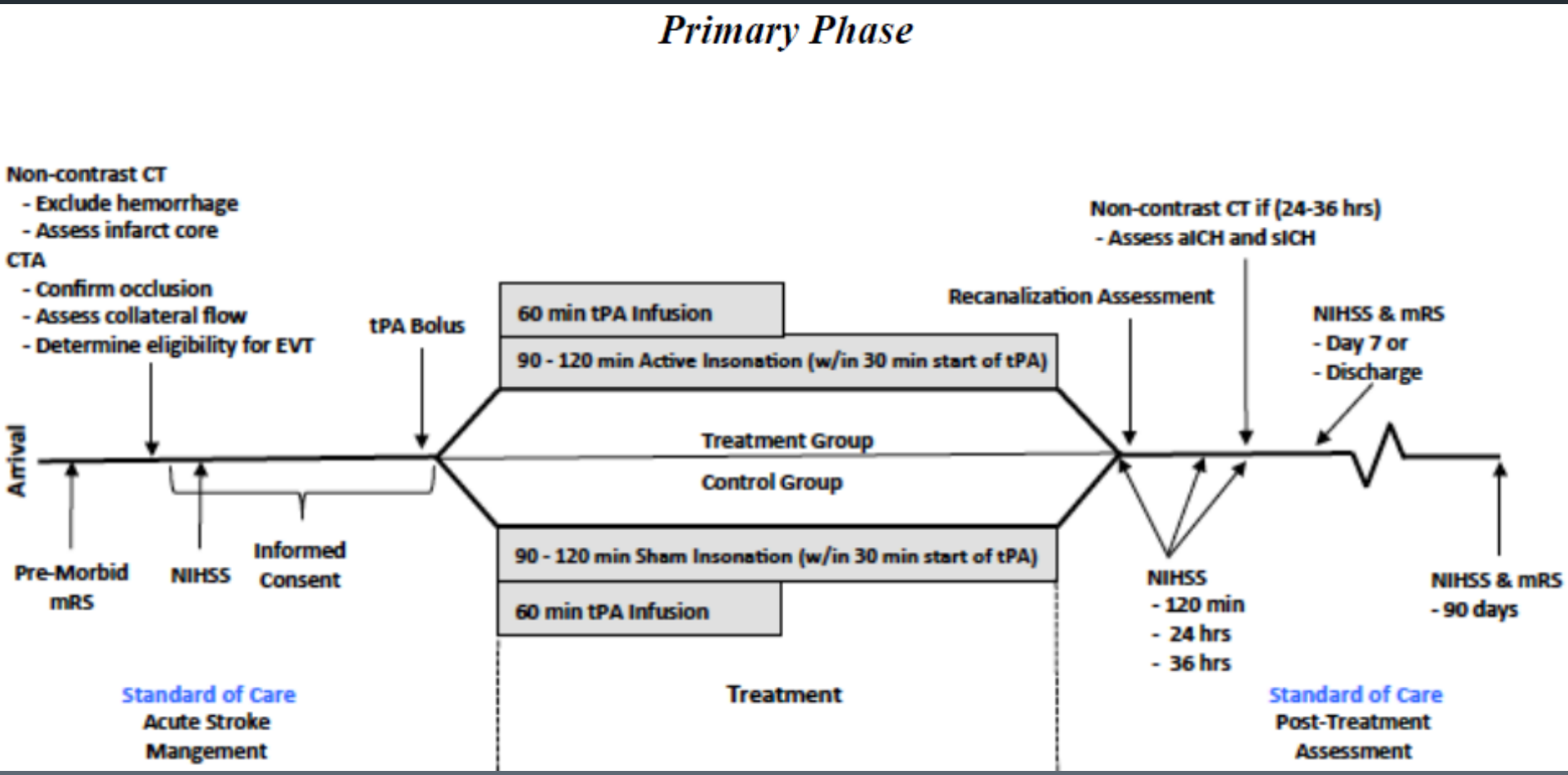
TRUST Trial Design

- Pilot Study: Lead-in Phase
- 40 subjects to be enrolled @ 4 stroke/telemed-networks in US



TRUST Trial Design

- N = 556
- MULTI-CENTER GLOBAL RANDOMIZED (SHAM CONTROL) BLINDED TRIAL



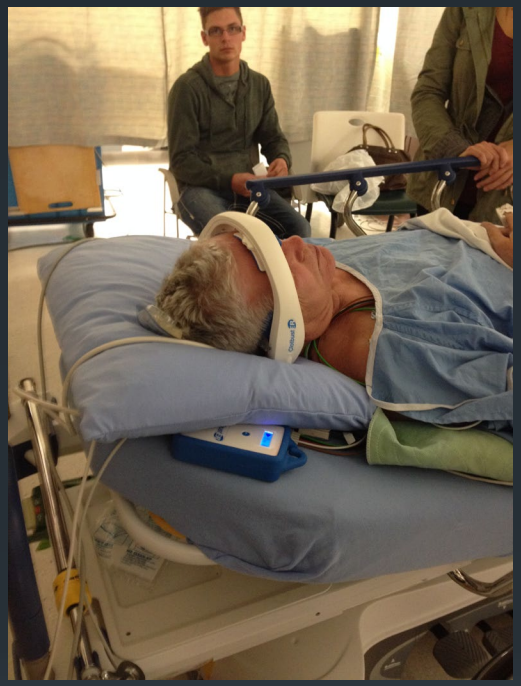
Sonothrombolysis: Current Status

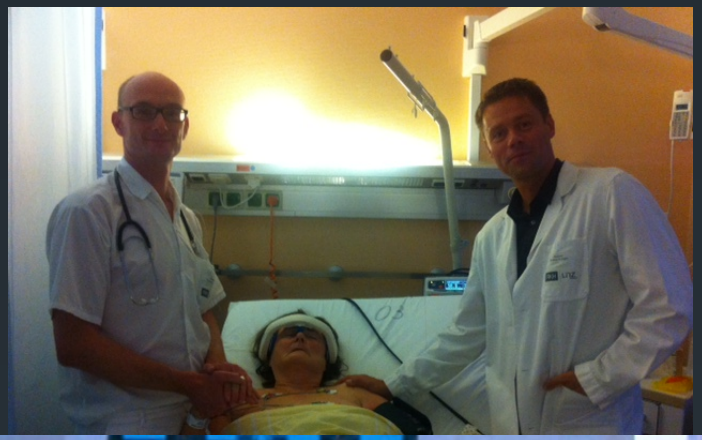
- Feasible, safe
- Has to be delivered to patients with occlusions
- Publication of the only phase III trial pending
- New trial being launched (TRUST)

In the mean time:

- TCD monitoring can be used safely
- Real time information is complimentary to CTA
- Ultrasound aids decisions beyond reperfusion

CLOTBUSTER





Stroke Patient Evaluation with US

- Extension of neurological examination
- Bedside testing
- Real time assessment of hemodynamics
- Ascertaining stroke pathogenesis
- Continuous monitoring
- Aid therapies

Any questions?