California Pacific Medical Center
A Sutter Health Affiliate

The SMART Approach to Acute Ischemic Stroke Therapy

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October 29, 2010

Sutter Pacific Medical Foundation at CPMC

CPMC Comprehensive Stroke Care Center and Center for Stroke Research

Disclosures

- Speaker at Education/Training Session for Genentech (2010)
- Sutter Pacific Medical Foundation Grant for CTP/IV rt-PA (PERFUSE) Investigator-Initiated Study (2011)

Acute Ischemic Stroke

- Definitions and epidemiology
  - Acute ischemic stroke (AIS)

- Hyperacute (<6-8 hrs) AIS strategies and therapy
  - Approved therapies
  - Emerging therapies
  - The SMART rt-PA inclusion and exclusion criteria
  - Neuroimaging as a selection tool

  - Healthcare infrastructure for stroke patient triage and care
  - Streamlining care
  - Telemedicine

Stroke Epidemiology and Facts

- 3rd leading cause of death and leading cause of disability in US
- Prevalence: ~750,000 strokes/year in US, 70% of patients survive
- Cost: ~$68 billion/year
- RF's: >40 yrs, heart dz, HTN, tob, DM, HL, h/o TIA/stroke, obesity, drug use, recent childbirth, sedentary lifestyle

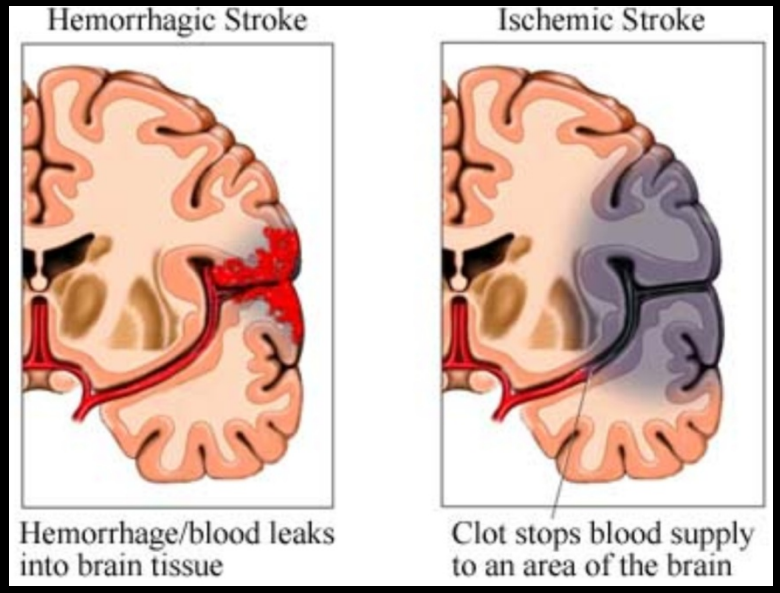
Stroke Epidemiology and Facts

- Sex:
  - ~60,000 more women than men have stroke/year
  - 60% of total stroke deaths are women
- Race:
  - African Americans twice likely to die from stroke, rate of first stroke double of Caucasians
  - AA males 3x likely to have ischemic stroke than same age grp of Caucasians
  - ~50% AA women will die of CV disease (hrt dz or stroke)
  - Asian Americans: increased risk of hemorrhagic stroke and intracranial atherosclerosis, but overall lower risk of death from stroke

Stroke Definitions

- Ischemic and hemorrhagic stroke:
  - Sudden neurologic damage
  - Caused by disturbance of circulation to the brain/spinal cord/retina

- Transient Ischemic Attack (TIA):
  - Temporary, focal neurologic deficit related to ischemia, lasting <24 hrs
  - Tissue-based def'n: transient episode of neuro dysfunction caused by ischemia without acute infarction



Stroke 2009; 40: 2276-2293

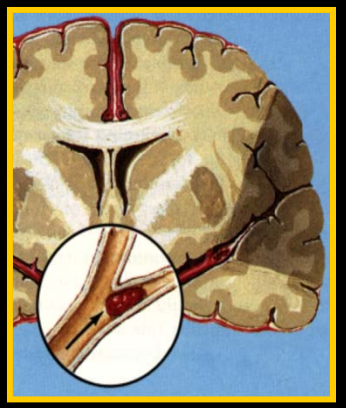
Etiologic Subtypes of Stroke and Frequency

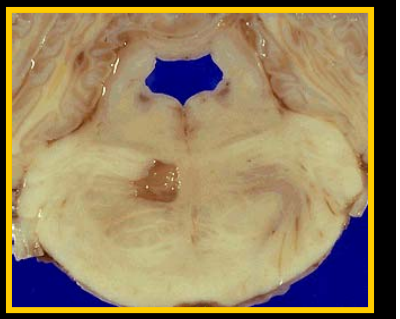
Ischemic (85%)

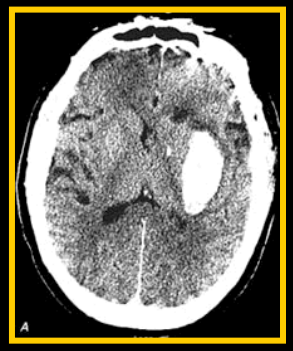
- Unknown (25%)
- Embolism (20%)
- Small Vessel Disease/ Lacunar (20%)
- Thromboembolic (20%)

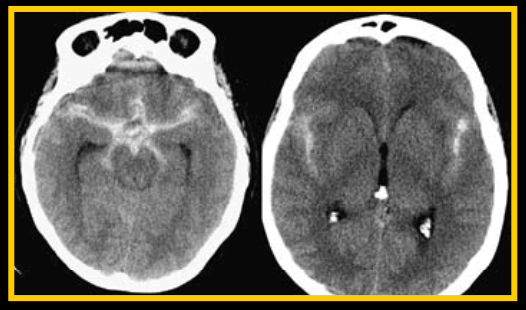
Hemorrhagic (15%)

- Intracerebral hemorrhage (10%)
- SAH: Aneurysm (5%)









Chest. 1998;114:683S-698S; *Stroke*. 1999;30:736-743.

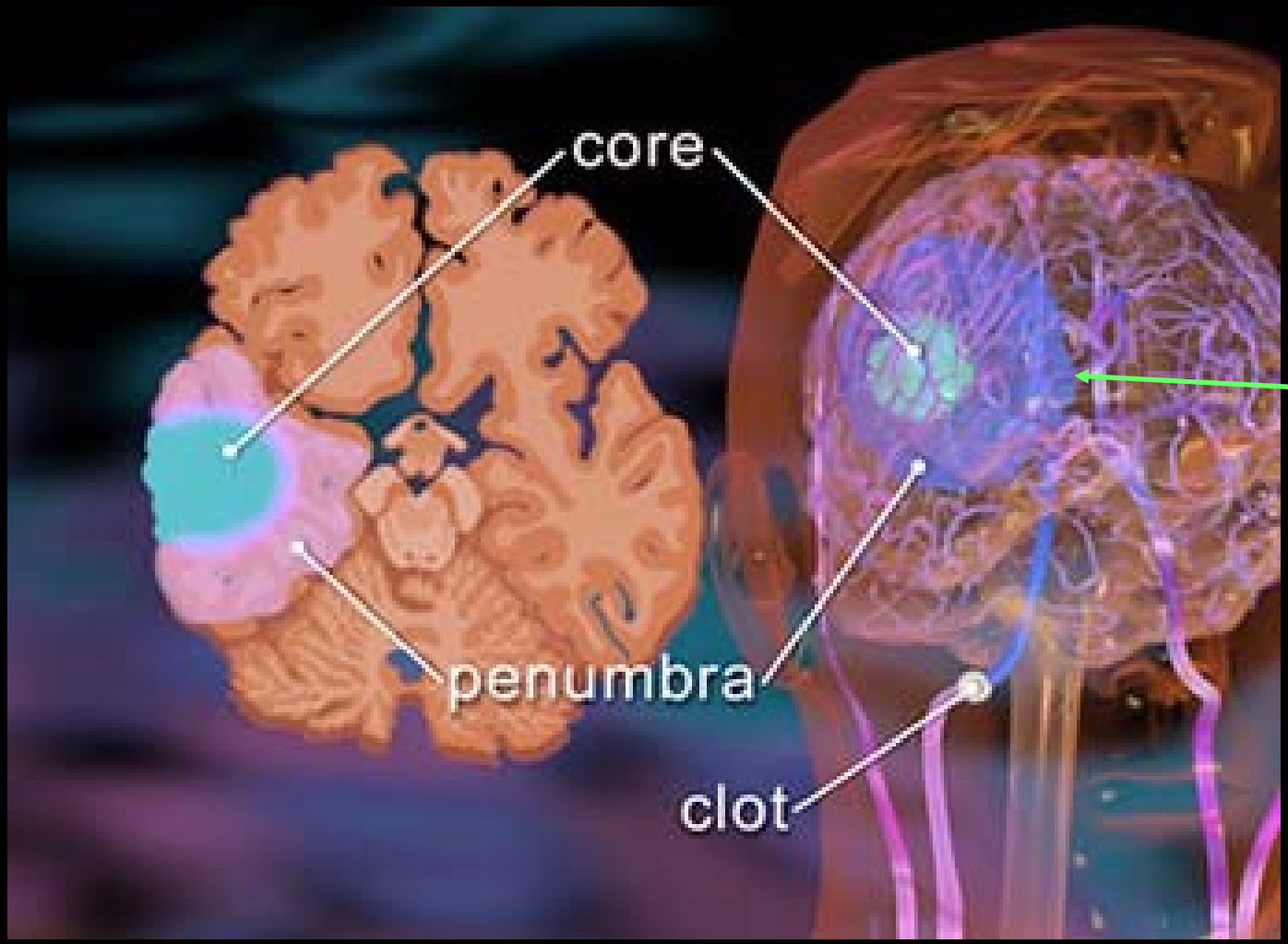
Acute Ischemic Stroke (AIS): Hyperacute

- Strategies
- Approved therapies
- SMART Criteria
- Neuroimaging as a tool to identify best therapeutic option: cases

Acute Ischemic Stroke (AIS): Hyperacute Strategies

- Reperfusion and recanalization:
  - Drug therapy (rt-PA)
  - Devices
- Neuroprotection:
  - Pre-hospital (Mg++ Rx)
  - Post-hospital (hypothermia, hyperoxia?)
- Augmenting collateral flow and saving ischemic penumbra:
  - HTN'ive therapy
  - Devices

AIS Hyperacute Strategies: Saving “Tissue at Risk”



Tissue at risk or ischemic penumbra

AIS Hyperacute: Case 1

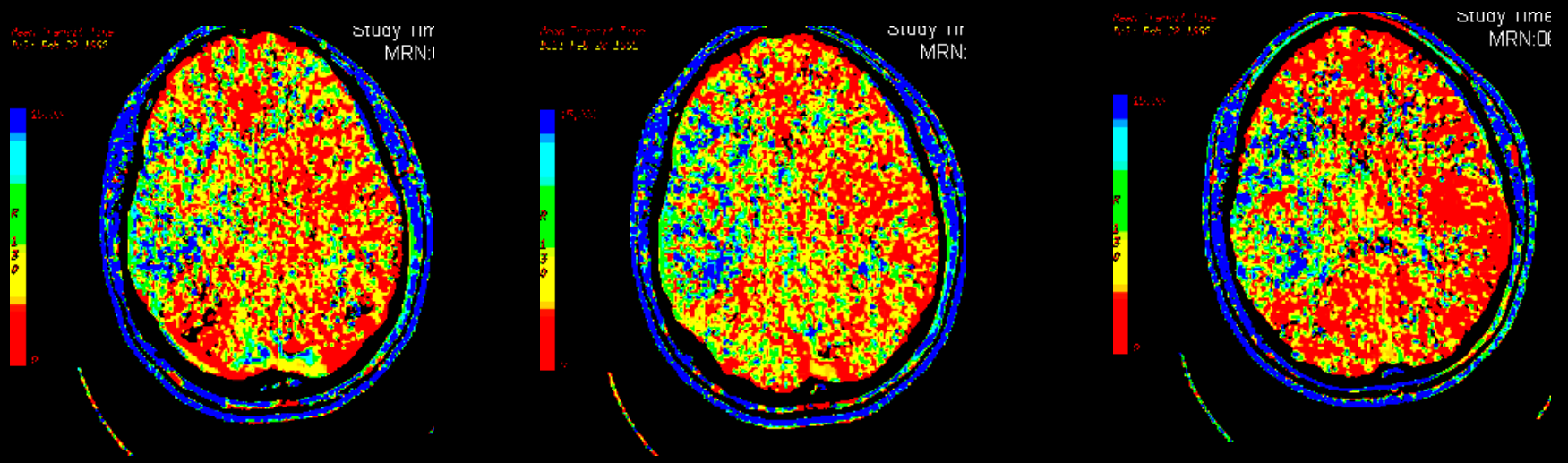
- History
  - 16 yo boy with h/o stroke 2006 (R MCA, no residual), migraine H/A
  - Last seen normal 13:30 noted to have L facial droop, slurred speech, poor balance while walking + severe H/A
  - PMH: neg stroke workup except for ?elevated Factor XIII; migraine H/A but uncomplicated; asthma
  - SH: basketball prodigy, no h/o drugs of abuse
- ED Assessment at 15:13:
  - MS: alert, very mild L neglect, orient x 3, language intact
  - CN: dense L facial droop, dysarthria
  - Motor: slower L FFM/FT; mild L dysmetria on FNF

  NIHSS ~5
- CT/CTA/CTP…

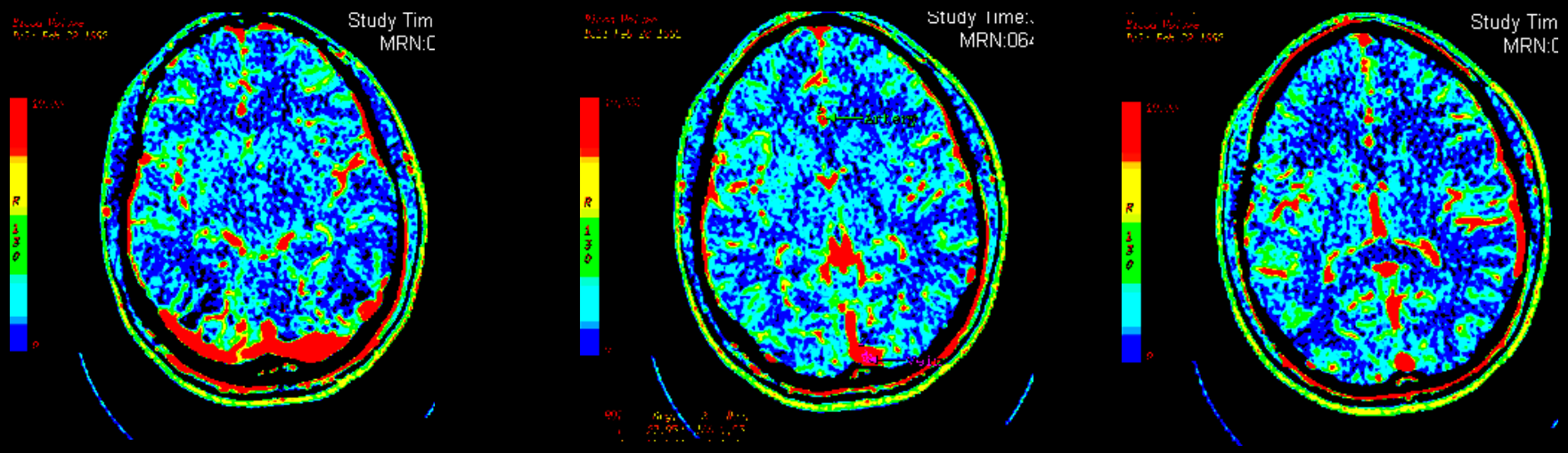
AIS Hyperacute: Case 1
CT

AIS Hyperacute: Case 1
CTP

MTT

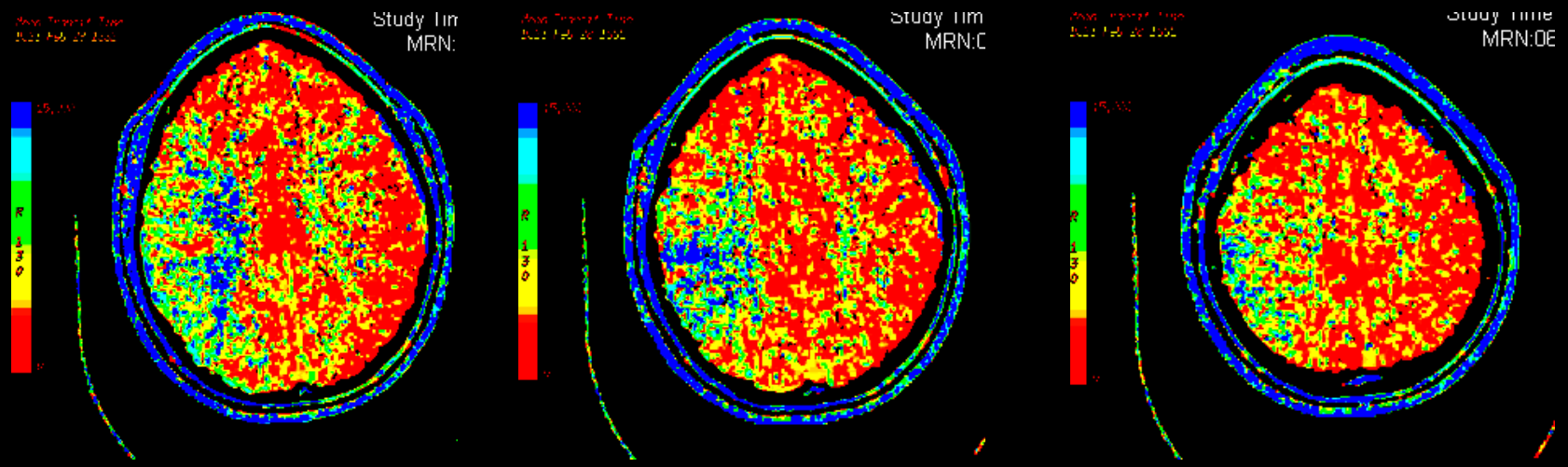


CBV

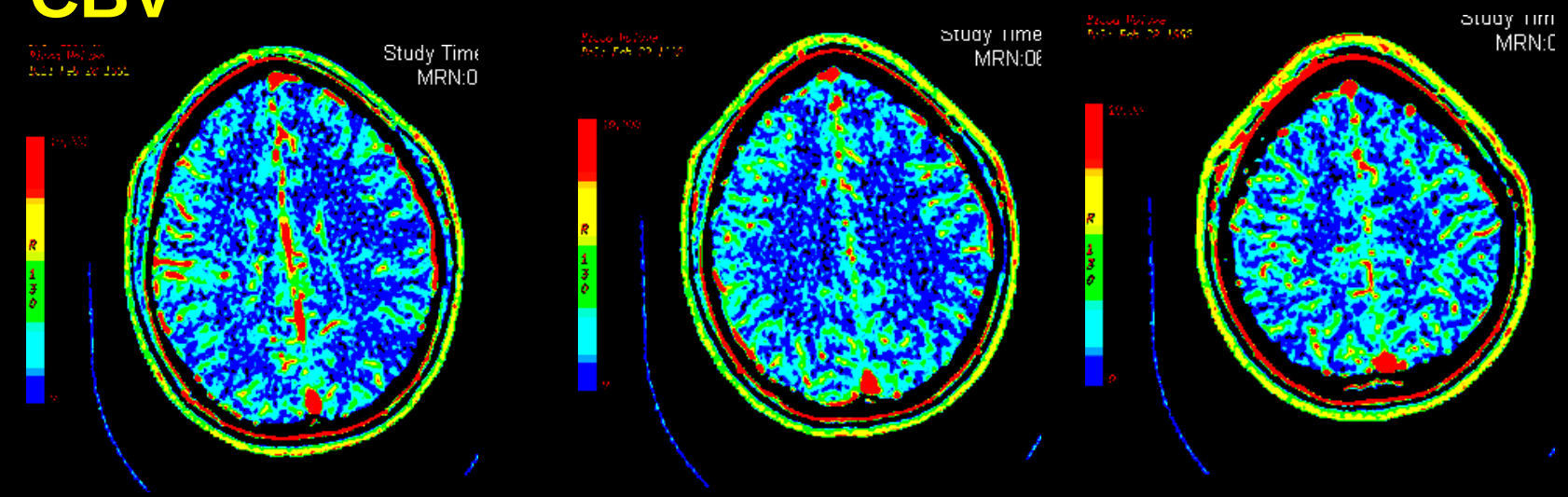


AIS Hyperacute: Case 1
CTP

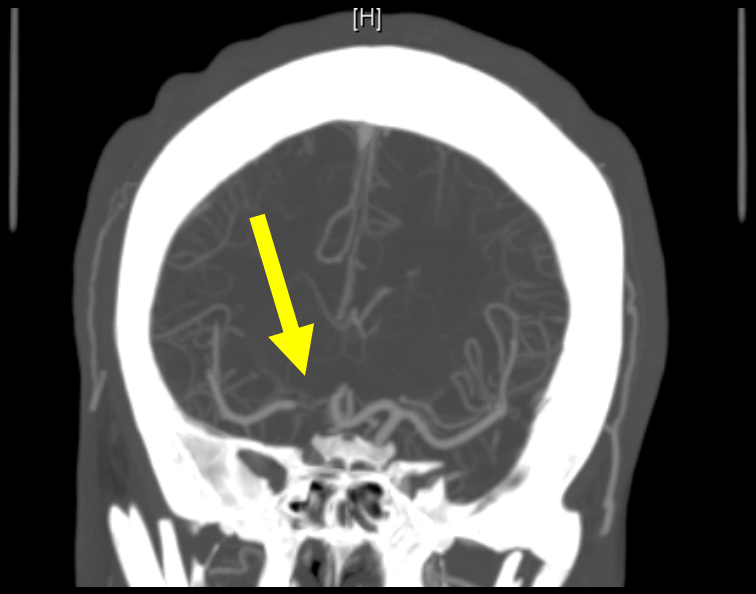
MTT

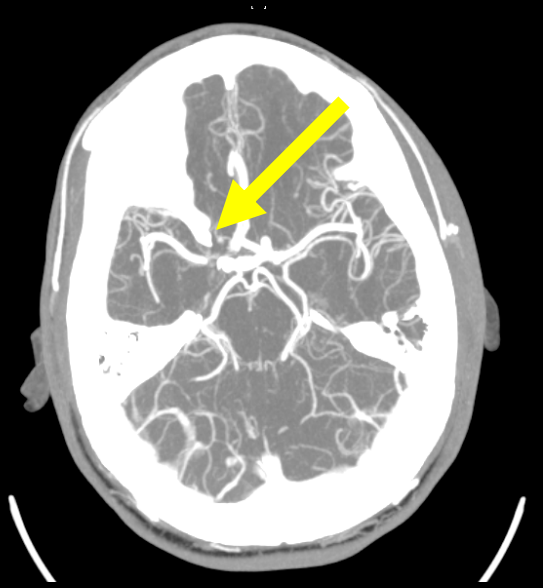


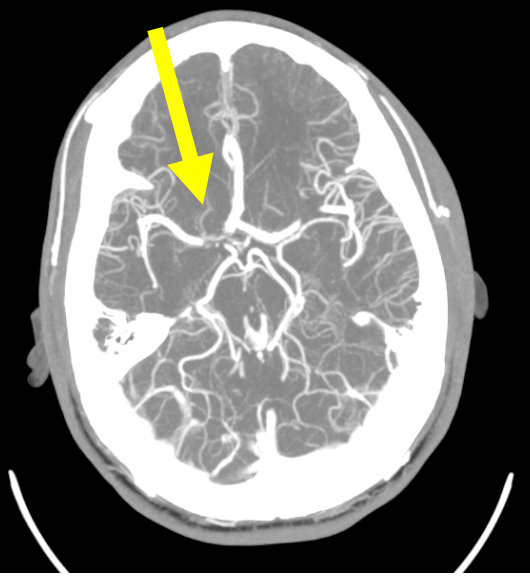
CBV



AIS Hyperacute: Case 1
CTA







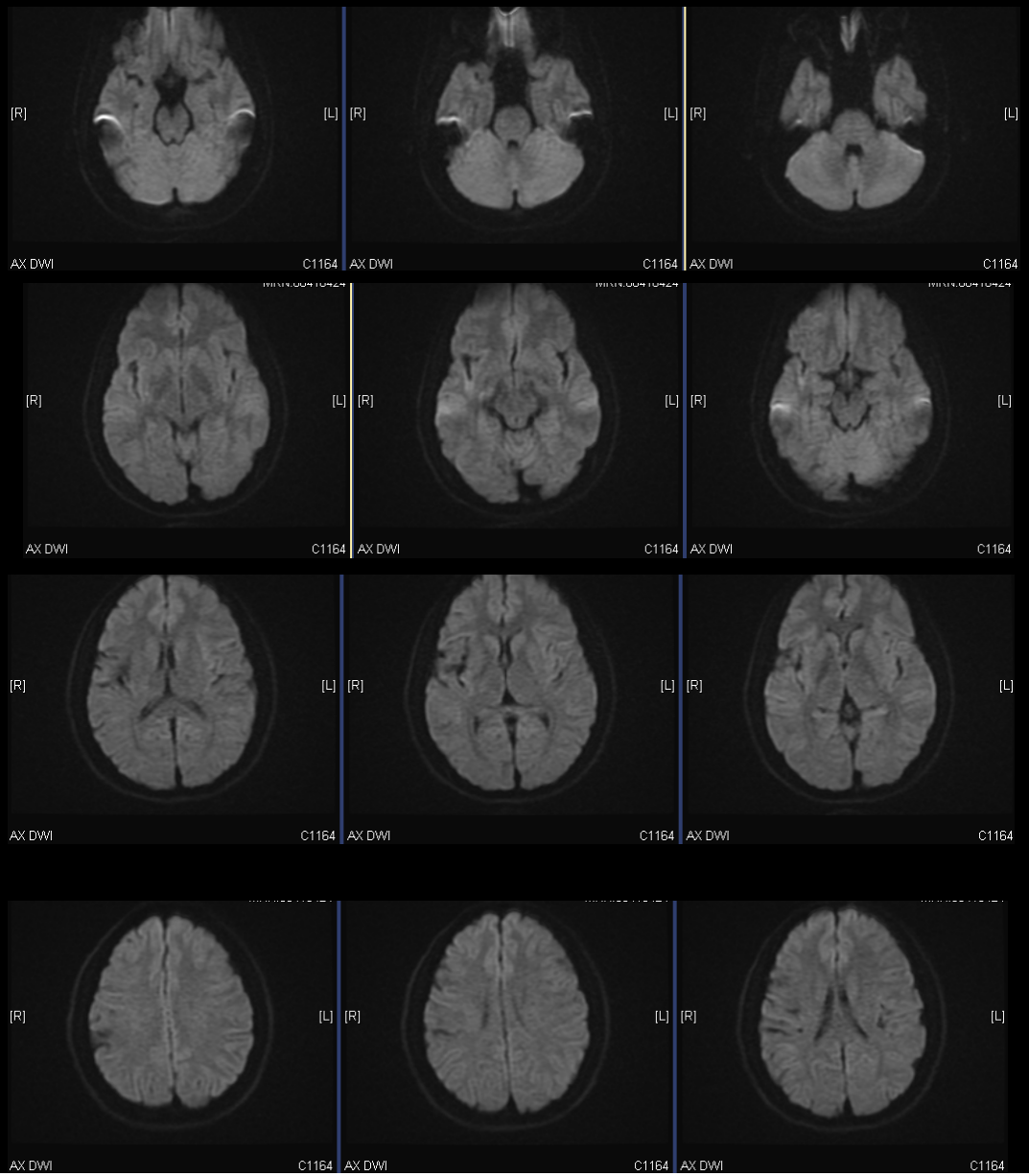
What should we do?

AIS Hyperacute: Case 1

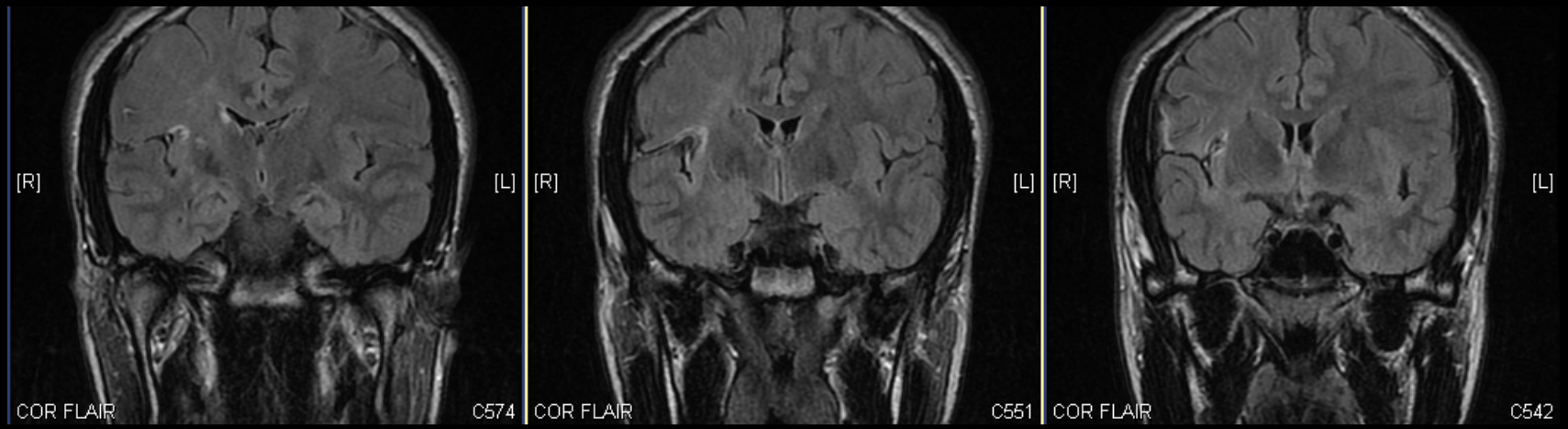
- Hospital Course:
  - -After appropriate consent from mother…
  - -Full dose IV tPA (0.9mg/kg) given at 16:00 (2.5hrs)
  - - Follow-up exam in ICU: H/A persisted, but L facial droop and L wx/ataxia improved
- Follow-up:
  - -Pt continued to improve neurologically
  - -MRI and TTE performed following day…

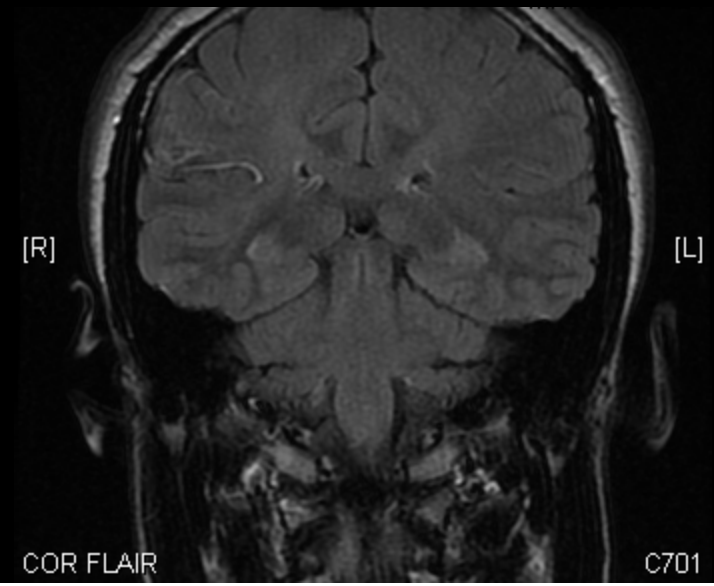
AIS Hyperacute: Case 1
MRI

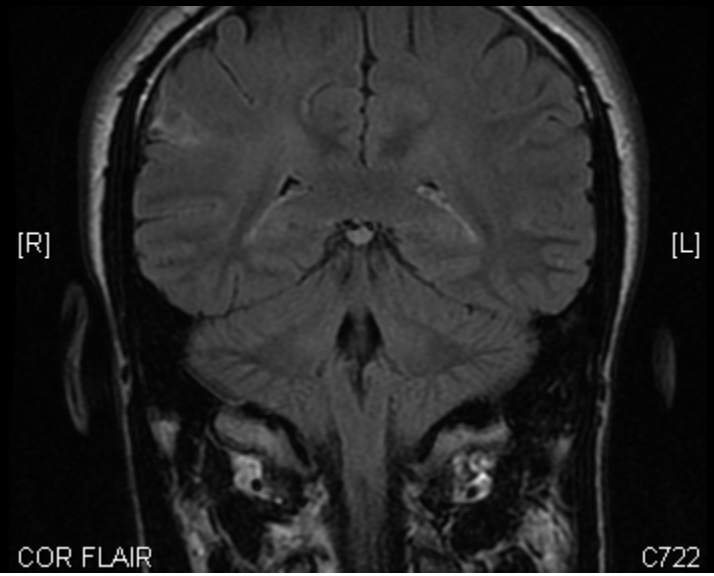
DWI



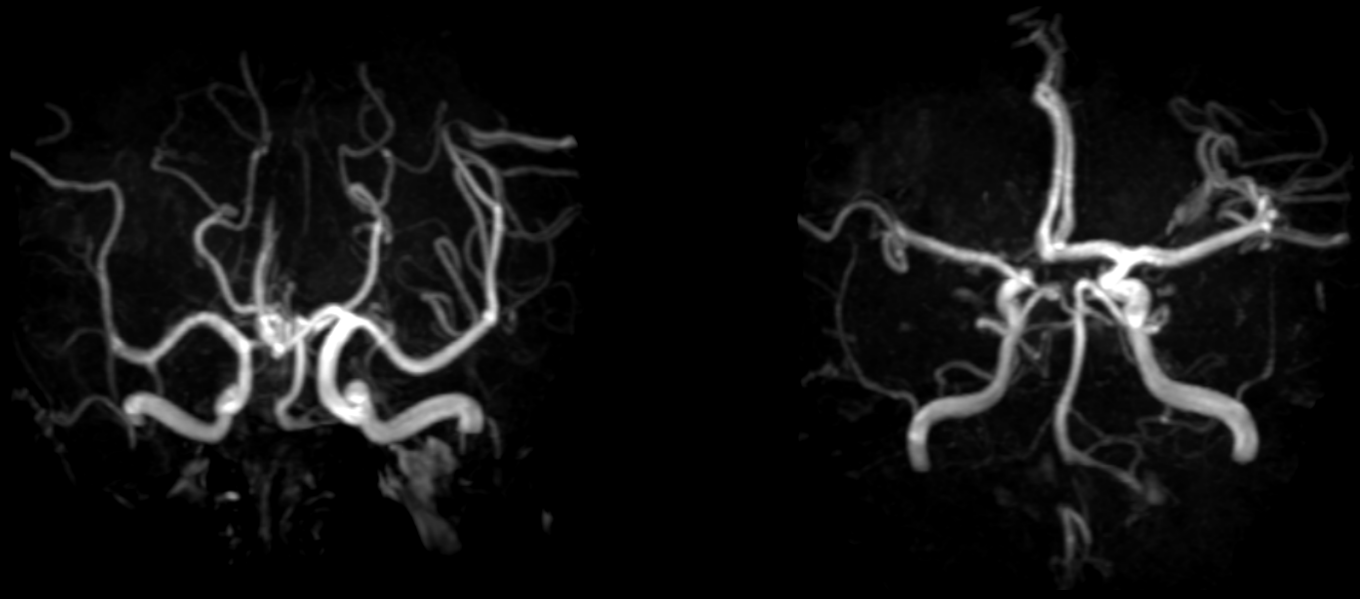
AIS Hyperacute: Case 1
MRI
FLAIR







AIS Hyperacute: Case 1
MRA



AIS Hyperacute: Case 1

- Hospital Course:
  - -TTE and TEE: mitral valve mass (atrial side); mass consistent with vegetation or papillary fibroelastoma; valve itself is normal
  - -Pt underwent CT surgery to remove mass…
- Follow-up:
  - -Pathology of mass: thrombus
  - -Hypercoag w/up performed, Heme/Onc consulted
  - -Pt started on coumadin
  - -Pt back to normal as outpt

AIS Hyperacute: Therapies

- Approved therapies
  - Thrombolysis: IV rt-PA
  - Mechanical embolectomy (approved devices but not proven therapy)
- Emerging therapies
  - Thrombolysis: IA rt-PA, combined IV and IA rt-PA, new fibrinolytics
  - New devices: U/S augmentation
  - Neuroprotection: hypothermia, neuroprotective drugs
  - Augmentation of collateral flow

Thrombolysis

Thrombolytic Therapy: Background

- Recombinant Tissue Plasminogen Activator (rt-PA, Alteplase, tPA)
  - Clot dissolving medication
  - Originally used in pt's with MI
  - IV tPA approved by FDA for stroke use 6/96
  - Initially approved for use ***less than 3 hours*** after symptom onset, now safe to use up to ***4.5 hrs***

Thrombolysis with IV rt-PA: Clinical Outcomes

- 30-40% increase in chance of good outcome at 3 mth (39% rt-PA vs 26% placebo mRS 0-1 at 3 mth)
- Number needed to treat: 8 pt's for one without significant disability
- 6.4% chance of symptomatic ICH (vs. 0.6%)
  - *Overall mortality similar in both groups*
  - *ICH mostly in people with severe stroke*
- Outcome depends upon:
  - *Benefit seen in all subgroups*
  - *Severity of symptoms*
  - *Time to treatment*
  - *Other medical factors (i.e. blood pressure, general medical condition, brain imaging findings, recent bleeding/surgery etc)*

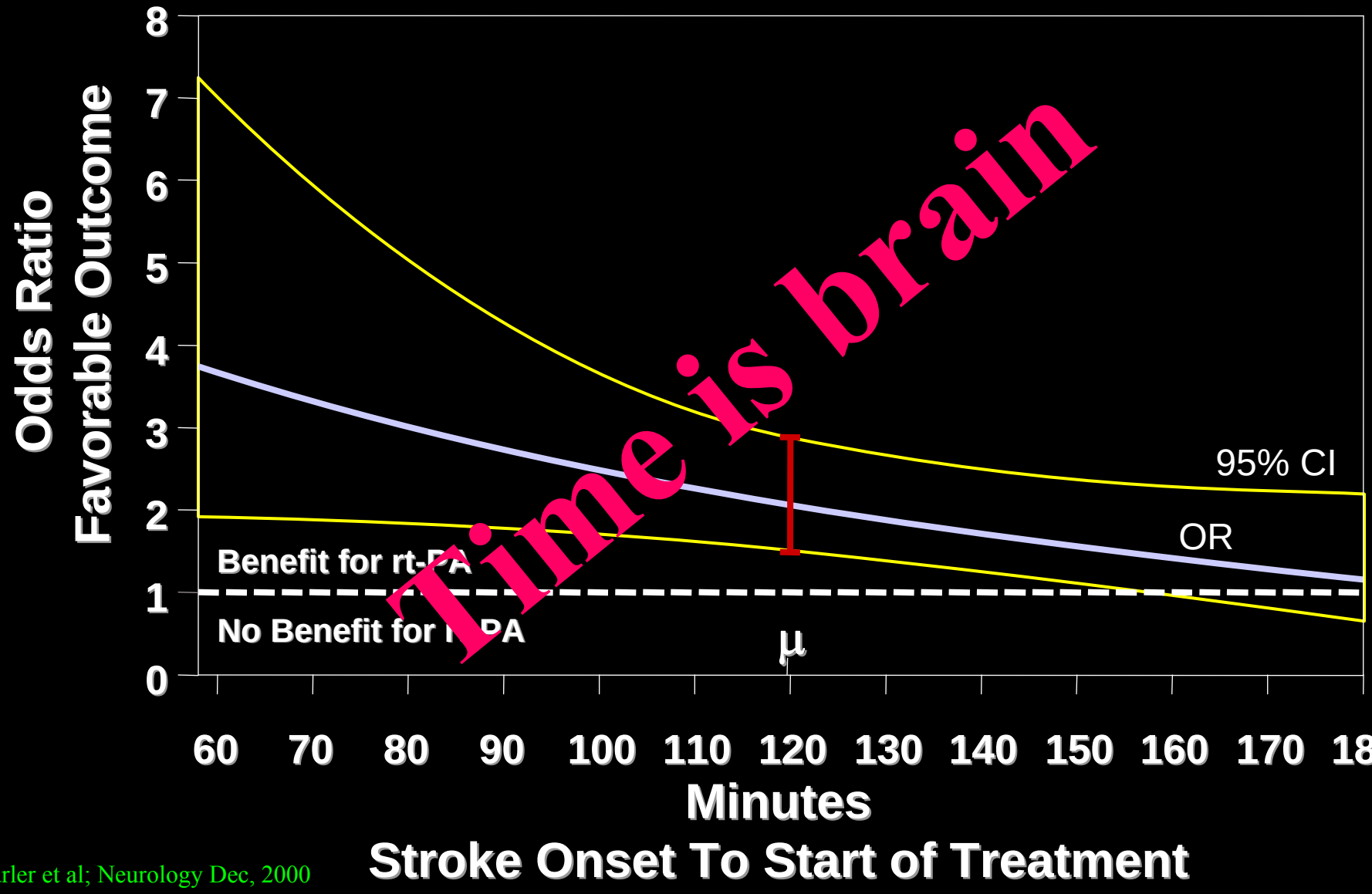
NEJM 1995; 333: 1581-7

Time Window for IV rt-PA Extended: ECASS III

- Time of onset ≤ 3-4.5 hrs
  - More pts had favorable outcome at 90 days (52% vs. 45%; OR 1.34) with rt-PA
  - Similar to original rt-PA study (OR 1.7)
  - Different exclusion criteria: >80 yo, NIHSS>25, DM and prior stroke
- Safety:
  - Any ICH 27% vs. 17.6%, symptomatic ICH 2.4% vs. 0.2% in placebo (less than original study)
  - No change in mortality
- CPMC, AHA/ASA Guidelines: IV rt-PA window extended to 0-4.5 hrs

NEJM 2008; 359: 1318-1329
Stroke 2009; 40: 2945-48

NINDS rt-PA Stroke Study:
Time to Treatment and Odds Ratio of Favorable Outcome



Marler et al; Neurology Dec, 2000

* Lancet 2004 (363): pooled analysis

Relative **Contraindications to rt-PA**

- Conditions that increases bleeding risk:
  - Anticoagulation (INR > 1.7), recent (< 30d) surgery/ head trauma or stroke, low platelets, other bleeding disorder, acute transmural MI
- Seizures at stroke onset
  - To avoid stroke mimics due to seizure (Todd's paralysis)
- Uncontrolled BP >185/110
  - May tx with 1-2 doses IV BP meds within 10-15'
- Significant metabolic abnormality
  - To avoid stroke mimics due to metabolic derangement
- Rapidly resolving symptoms
  - Mild to moderate fluctuations common
- Major CT scan abnormality
  - Commonly over interpreted
- Significant dementia, short life expectancy

NEJM 1995; 333: 1581-7

Broadening Indications for rt-PA in Acute Stroke?

- Time of onset – up to 4.5 h and beyond?
  - Neuroimaging as a tool to select patients beyond 4.5hr ?
- Defining “significant” neurological deficit
  - Simple rule: If you feel the deficit will impair the patient’s quality of life, then it is “significant”
    - Usually, NIHSS $\geq$ 4 (NIHSS maximum = 42) but will do NIHSS 0!!
- There many clinical situations showing benefit of IV rt-PA beyond guidelines (children, post-op, etc..) - requires further study!
- Recent data showing no significant risk in treating stroke mimics with rt-PA

Stroke 2007: 38: 2612-18

AIS Hyperacute: Case 2

- 91 year old female at remote hospital
- Acute aphasia, right sided weakness
- Symptom onset time: 15:15
- Past Medical History:
  - congestive heart failure
  - atrial fibrillation
  - active bleeding hemorrhoids
- Receiving warfarin: INR 2.5

Case 2: Examination

- Telemedicine consultation using remote video equipment: 16:15 (60 minutes)
- Exam: NIHSS=27 (right hemiplegia, aphasia, neglect, visual field cut)
- Non-Contrast Head CT: negative

What should we do?

Thrombolysis Contraindications in this Case

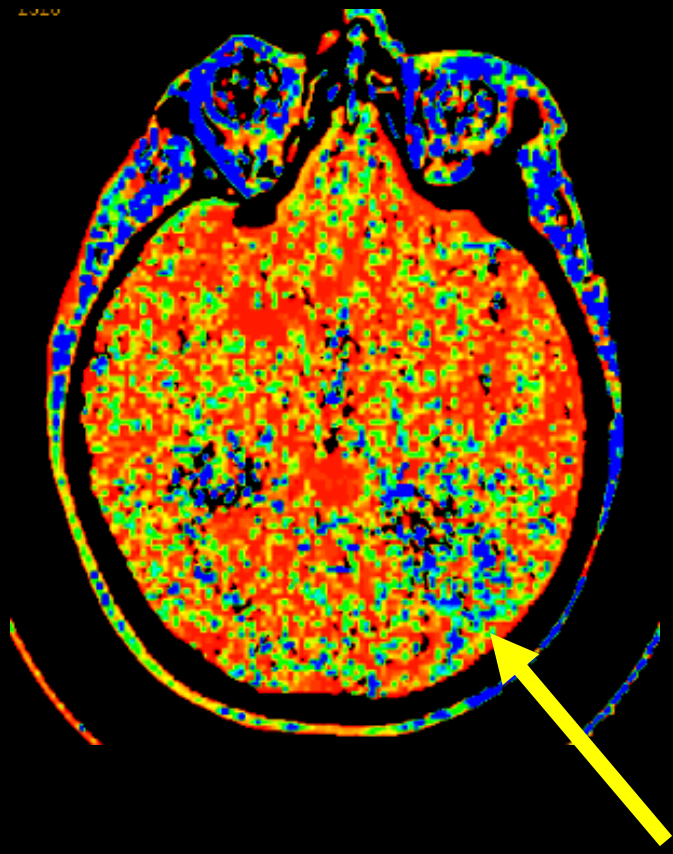
- Older Age (≥80)
- Large stroke (NIHSS >20)
- Anticoagulation (INR 2.5)
- Active Bleeding (hemorrhoids)

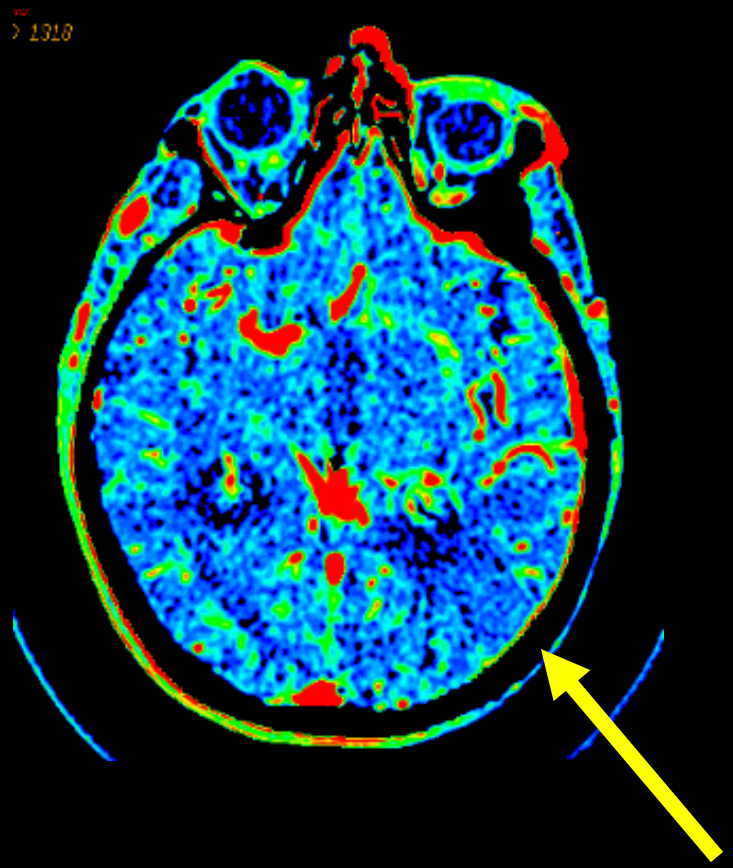
What should we do?

Case 2: Management

- Half dose IV rt-PA (0.45 mg/kg) administered at 17:30 (2h:15m)
- Transferred
- Upon arrival (3 hours later): Aphasia improved, right side strength is better (3/5)
- CTA/CTP performed

CT Perfusion (CTP)





•rMTT (tissue at risk)

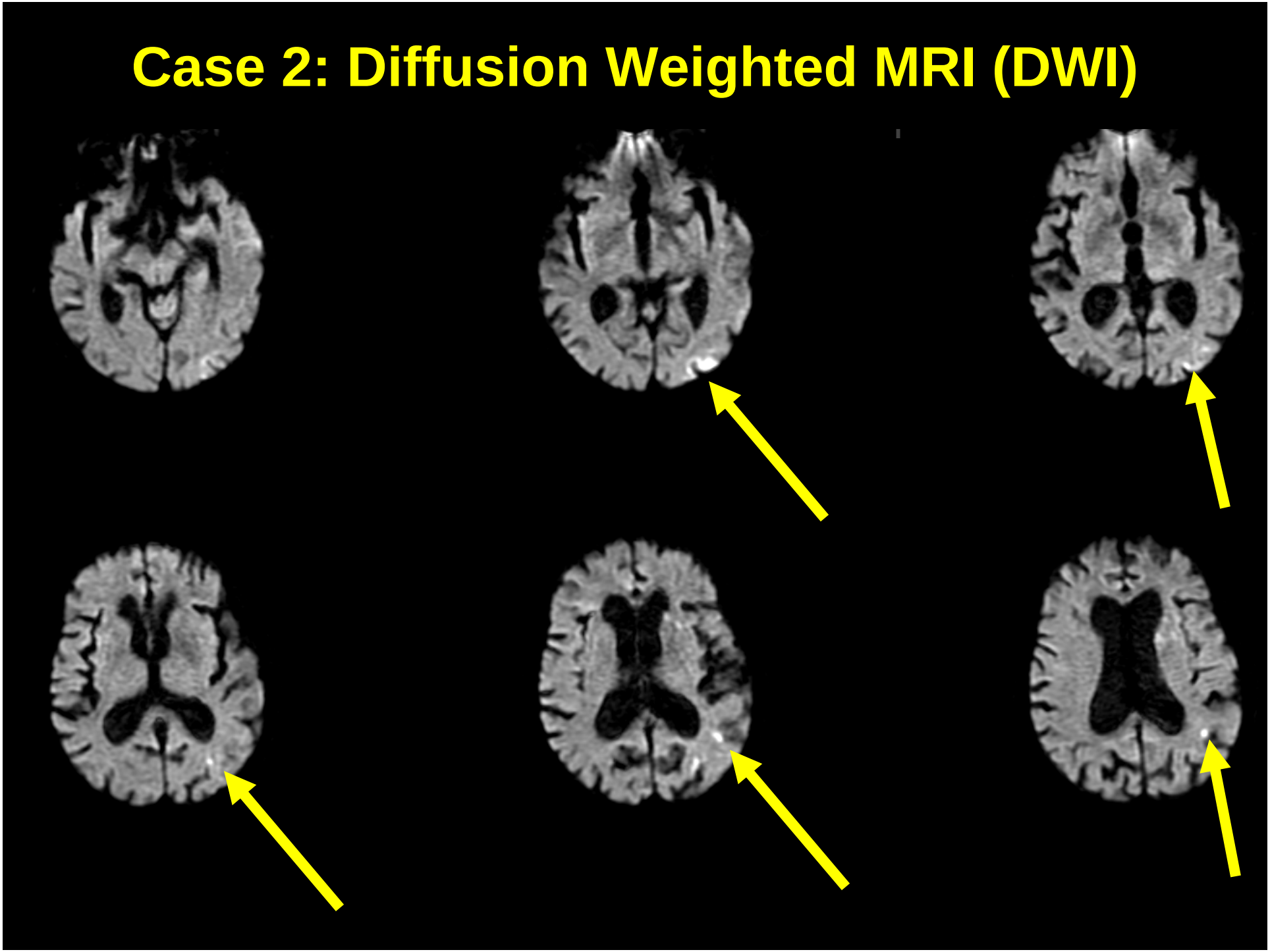
rCBV (damaged tissue)

CT Angiogram (CTA)

Case 2: Management and Outcome

- No further treatment
  - CTP: no tissue at risk
  - CTA: no large artery occlusion
- Patient experienced **full recovery**
- No bleeding
- MRI

Case 2: Diffusion Weighted MRI (DWI)



Conclusions

- IV rt-PA **is <u>not</u>** contraindicated in many patients who are frequently excluded from treatment including:
  - Age >80 (or >90)
  - Large strokes (NIHSS > 20)
  - Anticoagulated (INR >1.7)
  - Active bleeding (mild)
- CTP/CTA useful in management
- Criteria for IV rt-PA need revision
  - Many more patients can be treated safely and effectively
  - **Use SMART criteria!!**

SMART
Simplified Management of Acute Stroke Using Revised Treatment Criteria

Courtesy of Dr. David Tong

Background

- Use of IV rt-PA for ischemic stroke is very low
  - 1.1-3% of all ischemic stroke patients[1,2]
  - ~5-10% of stroke patients at stroke centers
  - Highest published sustained treatment rate:
    - 15% at UT Houston stroke program[3]

1. Ann Emerg Med May 2007
2. Reed, Stroke 32(8); 2001
3. Arch Neurol 2001;58:2009–2013

The SMART Premise

- Current IV rt-PA treatment criteria are too strict
  - Clinical trial ≠ clinical practice
  - Exclusion criteria are ***not*** evidence based
  - Many centers' exclusion criteria even more strict than guidelines

- Simplified Management of Acute Stroke using Revised Treatment Criteria (SMART)
  - Rethink exclusion criteria
  - Increase number of candidates for treatment
  - Streamline management
  - Use new technology to further increase treatment
    - CT perfusion (CTP)/CT angiography (CTA)
    - Telemedicine: inexpensive, accurate

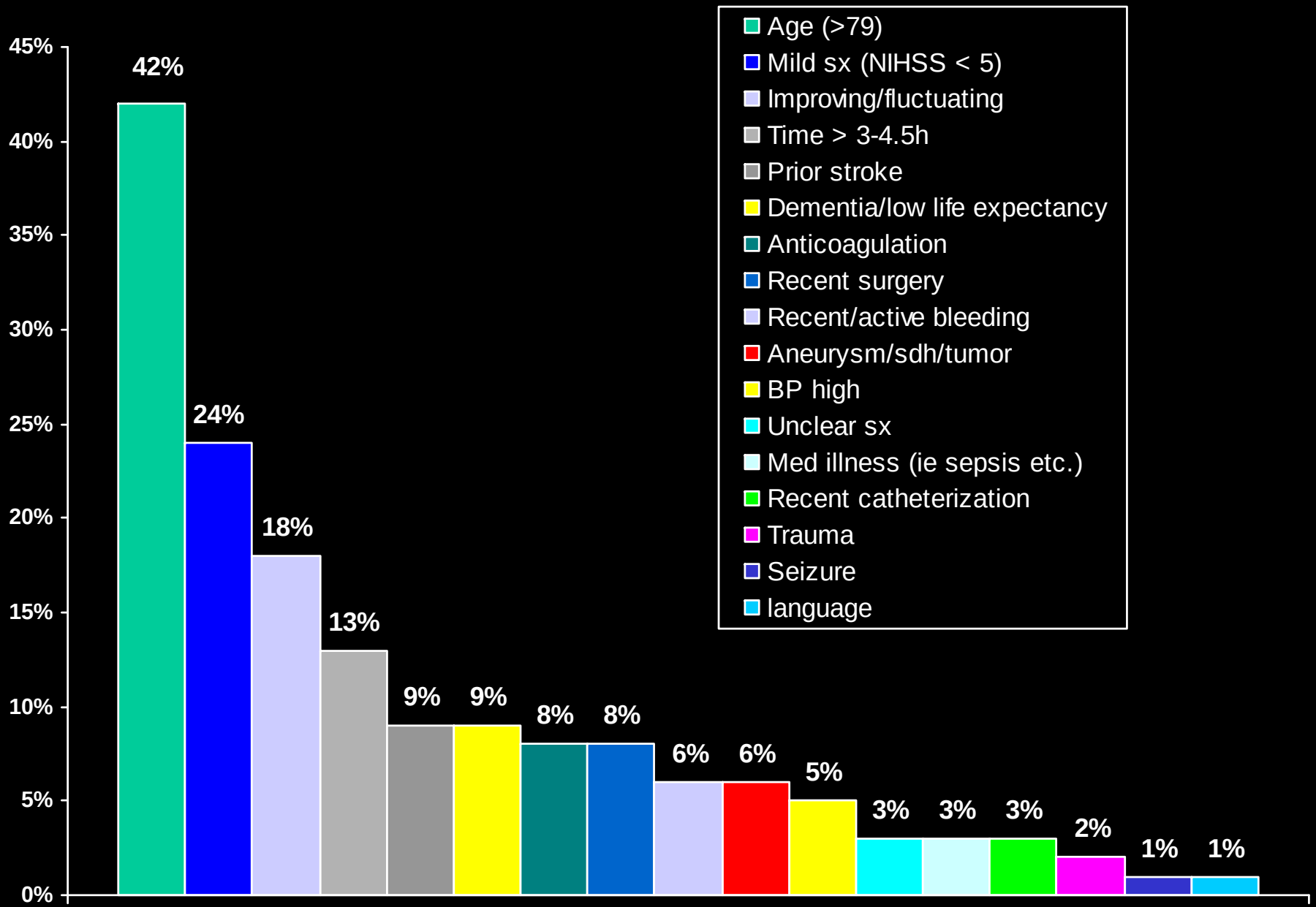
Common IV rt-PA Contraindications That Are NOT SMART Criteria

- Stroke severity (mild or severe)
- Older Age (≥ 80)
- Presence of other asymptomatic brain lesions (e.g. tumor, aneurysm, subdural hematoma etc.)
- Improving symptoms (if still disabling)
- Stroke, head trauma, surgery, other bleeding or arterial puncture < 3 months
- Seizure
- Blood sugar (low or high)
- Elevated PTT/INR (on warfarin, heparin, LMWH)
- Pregnancy/children
- Dementia
- Renal failure, MI, other co morbidity
- Early infarct signs on CT

SMART: IV rt-PA Absolute Exclusion Criterion

- Acute intracranial hemorrhage that is the cause of the patient's symptoms

SMART: Frequency of Common Relative Contraindications



SMART: Reduction of rt-PA Exclusions

- No NIHSS (stroke severity) cut offs
  - symptoms must be “disabling”
  - “mild strokes” cause significant morbidity/mortality
    - ~20-30% of “mild strokes” are disabling, especially if large artery occlusion present [1-3]
    - Represent ~20-30% of acute stroke patients [1-3]
    - Higher risk of subsequent deterioration [1-3]
    - rt-PA effective in these patients [4]
  - Severe strokes also benefit from IV rt-PA[6]
- No age cut off
  - Older patients generally do worse, but still benefit from treatment[6,7]

1. Smith, Stroke. 2005 Nov;36(11):2497-9
2. Nedeltchev Stroke. 2007;38:2531-2535
3. *Barber, Neurology* 2001;56:1015-1020
4. *Ann Emerg Med.* 2005; 46: 243–252
5. De Kayser, Stroke. 2007;38:2612-2618
6. Stroke 28; 1997: 2119-2125
7. Eur Neurol. 2005;54(3):140-4

SMART: Dealing with Stroke MIMICS

- If unclear it is a stroke, should you treat?
  - Risk of hemorrhage is very small (<1%)[1-4]
  - Repercussion of missing treatment may be high
  - Mimics may constitute 10-23% of acute stroke rt-PA cases at high volume centers[1]
    - Risk of bleeding is 0% in these cases
  - If you have not treated a stroke mimic with rt-PA, you are likely under treating

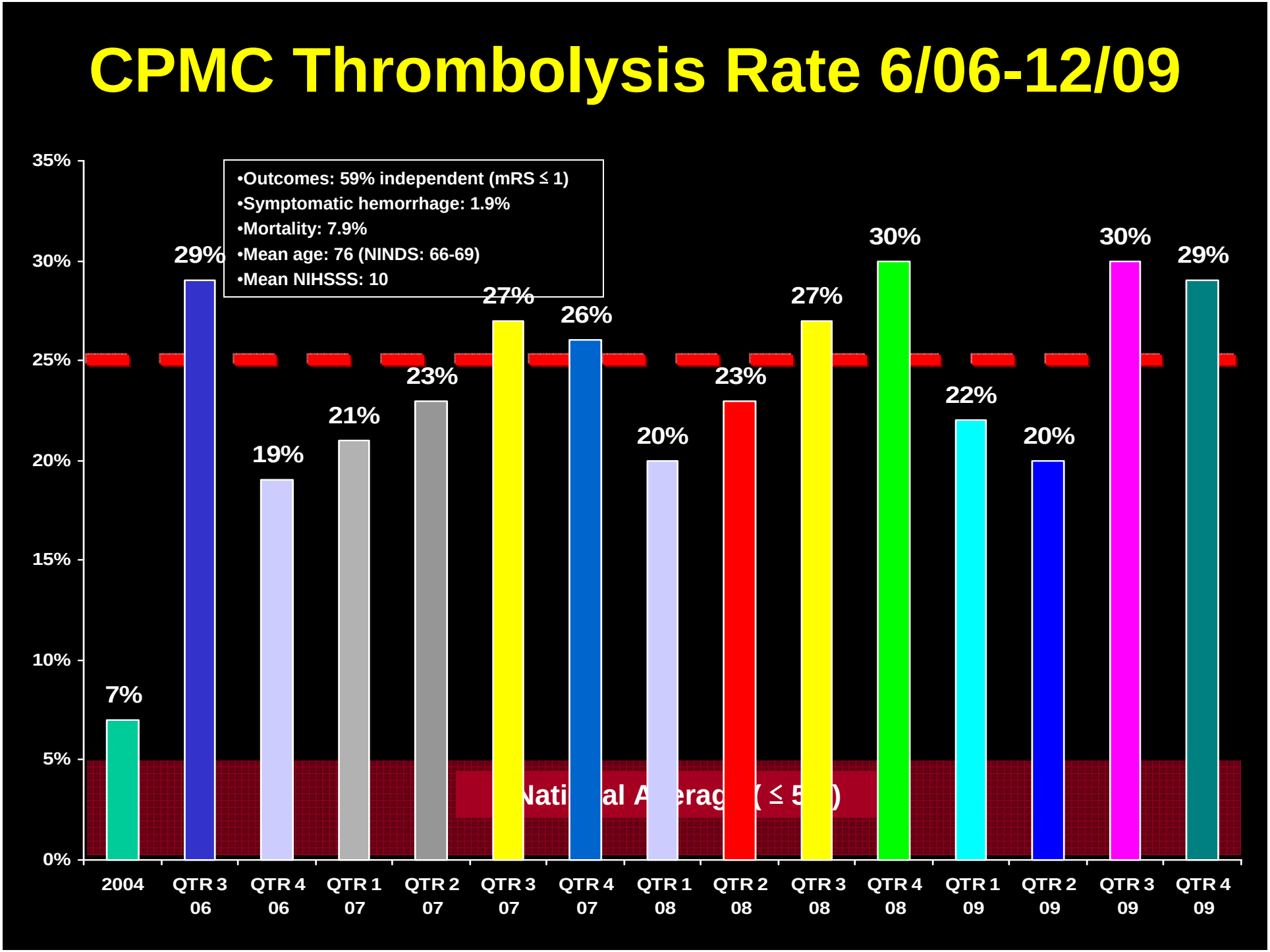
1.Stroke. 2009 Apr;40(4):1522-5

2.Chernyshev, International Stroke Conference 2009

3. Stroke. 2006; 37: 769–775

4. Neurology. 1999; 52: 1784–1792

CPMC Thrombolysis Rate 6/06-12/09



Using SMART Criteria: Our Hospital's Results

- Between 7/06 and 12/09, 178 patients received thrombolysis
  - Represents 25-30% of ***ALL*** acute ischemic stroke patients at our hospital during this time
  - >95% of patients eligible for rt-PA RECEIVE it
- 135 patients (76%) treated with IV rt-PA alone using **SMART** criteria

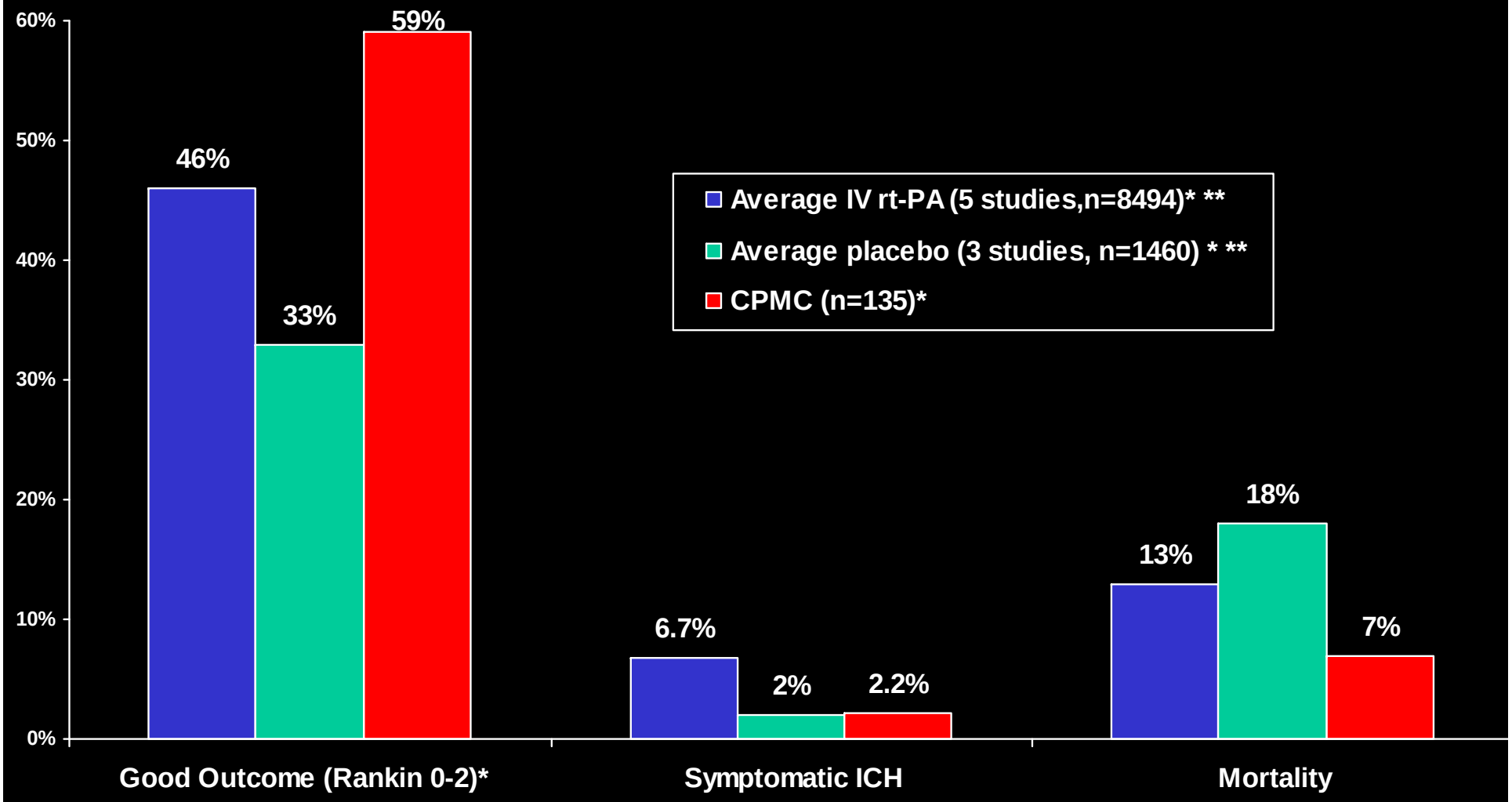
SMART IV rt-PA Stroke Patient Characteristics

- 49% male
- Mean NIHSS= 10
- Median age 76 years (NINDS age: 66-69)
  - **42% ≥ 80 years old**
  - **13% ≥ 90 years old**
- Median door to needle time: 58 minutes
- Median symptom onset time to treatment time:
  - **135 minutes (95% CI 65-195 minutes)**
  - **21% >3h after symptom onset**

SMART: High Number of Relative Treatment Contraindications

- On the basis of common IV rt-PA exclusion criteria 89% of these patients would NOT have qualified for thrombolysis
  - 42% age ≥ 80 (13% ≥ 90)
  - 24% NIHSS ≤ 5 (41% NIHSS ≤ 7)
  - Average # contraindications: 1.4, (range 0-4)
  - 45% had more than one relative contraindication

CPMC Versus Major IV rt-PA Studies



*Good outcome = Rankin 0-1 for NINDS/ECASS3 trial/CPMC data
** SITS-MOST/ECASS 3 excluded patients > 80 y, stroke > 1/3 MCA, or "severe", NIHSS > 25, ECASS 3 also excluded DM + prior stroke

- *Lancet. 2007 Jan 27;369(9558):275-82*
- *N Engl J Med 2008;359:1317-29*
- *Lancet. 2004;363:768-774*
- *JAMA. 1999;282:2003-2011*
- *NEJM 1995;333:1581-1587*

AIS: Healthcare Infrastructure

- Streamlining stroke patient triage and care
- Telemedicine

SMART: Streamlining the ED rt-PA Evaluation Process

Evaluation Elements Recommended by AHA/ASA[1]

- Patient history
- Noncontrast CT scan of the brain
- Physical examination
- Neurological examination using a formal stroke scale (eg, NIHSS)
- Diagnostic tests include, but are not limited to:
  - Electrocardiogram (ECG)
  - Blood glucose
  - Serum electrolytes/renal function tests
  - Prothrombin time (PT)/international normalized ratio (INR)
  - Activated partial thromboplastin time (aPTT)
  - Oxygen saturation, complete blood count, including platelet count

Possible Expedited Protocol to Further Reduce Time to Treatment: CPMC Experience[2-4]*

- 1-hour time of arrival to IV rt-PA administration
- Stroke code alerts CT technologist to clear scanner
- 25 minutes to CT completion; 45 minutes for results; Stroke MD reads scans
- 45 minutes to lab results
- Stroke MD available 24/7, telemedicine evaluation possible if not in-house
- Do not wait for lab results for CTP/CTA, or for IV rt-PA if patient is not anticoagulated
- rt-PA ordered the minute CT negative for ICH; estimated weight used (and safe) for IV rt-PA
- No written consent required

***Based on study of 103 patients. CTP = computerized tomography perfusion , CTA = computed tomographic angiography**

1. Adams HP, et al. *Stroke.* 2007;38:1655-1711. 2. Sattin JA, et al. *Stroke.* 2006;37:2935-2939.
3. Gottessman RF, et al. *Neurology.* 2006;67:1665-1667. 4. Mishra S, et al. *Acad Emerg Med.* 2007;14(5 Suppl 1):S33.

CPMC SMART: Rapid ED evaluation

- Door to CT completion: 15 minutes
- Door to needle: 62 minutes
- Symptom onset to needle: 135 minutes

- Requires strong commitment from hospital and staff
- Increases options for treatment

AIS Hyperacute: Case 4

- Male (79 years), chronic atrial fibrillation, on warfarin (INR 2.2)
  - History of prior stroke with residual, mild right visual field cut
- Acute onset left hemiparesis, right gaze preference
- Last considered well: 11:00 pm
  - Possibly okay at 12:00 midnight
- Collapsed going to bathroom: 1:30 am
- Arrival at local ED: 2:30 am; telestroke consult: 3:00 am

AIS: Case 4

- Examination
  - 0/5 left side, right gaze, left visual field, left facial, dysarthria, NIHSS=16
- CT hyperdense MCA dot sign
- Old left occipital stroke

•AIS: Case 4

Case 4: CT

Case 4: Contraindications?

- Anticoagulation?
- Uncertain time of onset?
- Age?

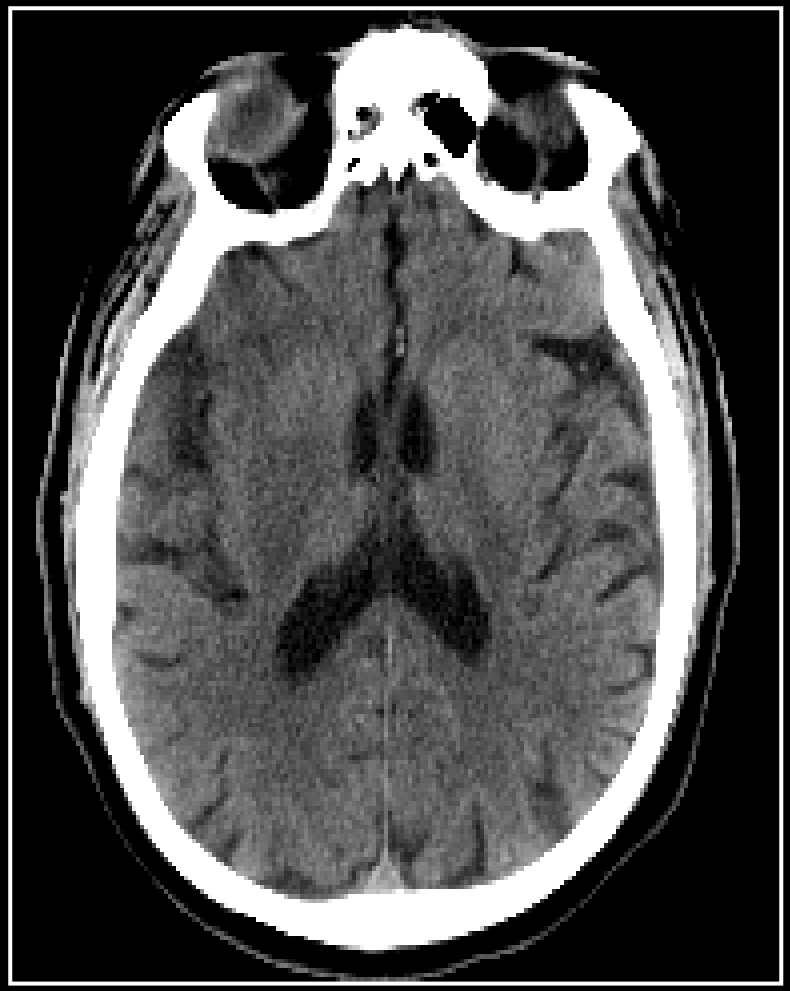
Case 4: Management

- Discussed treatment approach with patient and wife
- Patient treated: 4:00 AM
- Rationale
  - Stroke was severe and unlikely to improve spontaneously
  - Far from IA treatment (at least 2 hours)
  - There is no evidence that IA is better than IV
  - There is no evidence anticoagulation increases bleeding risk significantly
    - IA generally always uses heparin!

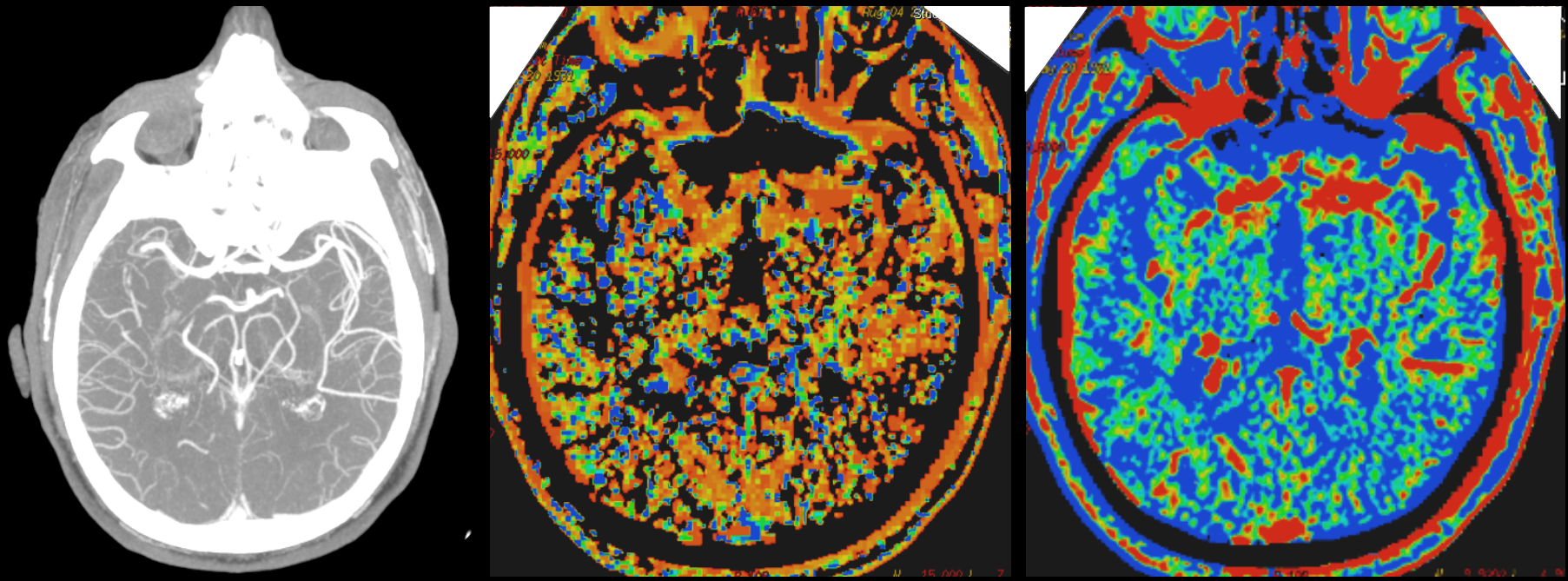
AIS: Case 4

- Upon arrival at CPMC: 6:00 AM
  - Major improvement: NIHSS=2
  - CT/CTA/CTP

FS: CTA/CTP



AIS: Case 4 CTA/CTP

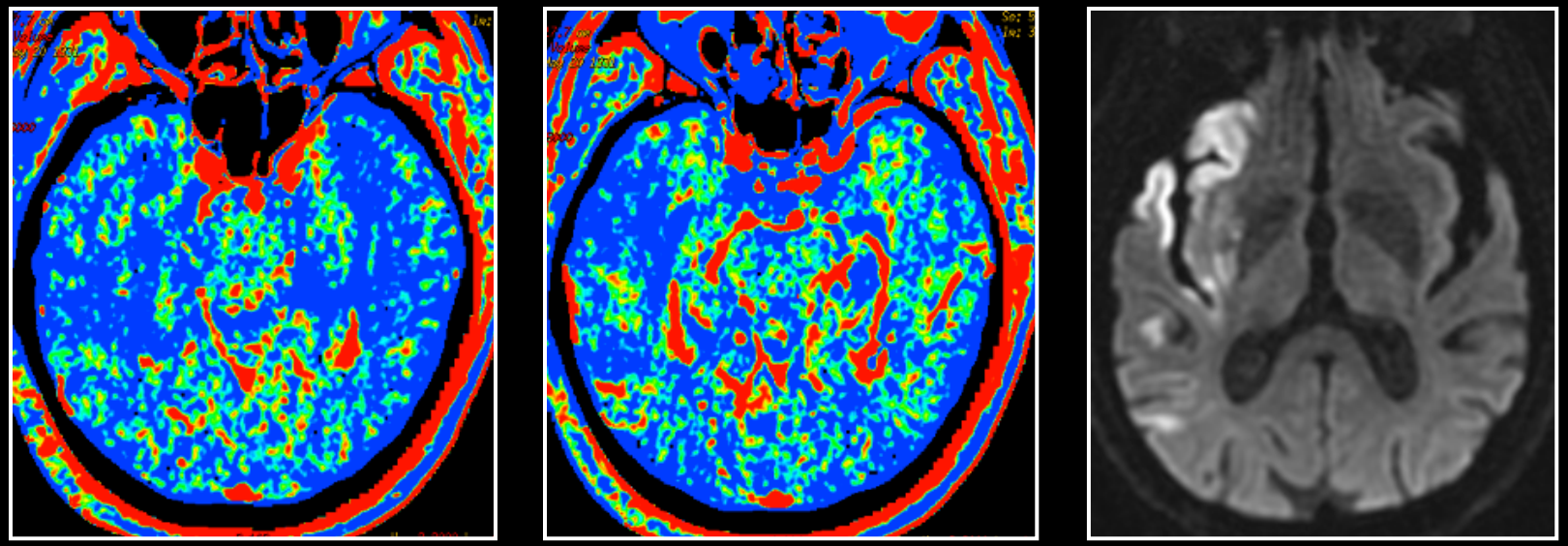


AIS: Case 4

- Despite M2 occlusion, no treatment
- Rationale:
  - CTP shows minimal if any hypoperfusion
  - Clinically, patient is near normal
  - If CTP had been abnormal, one would probably have proceeded (misery perfusion)

•M2 = second division middle cerebral artery.

AIS: Case 4 MRI



- Case 4: Assessment Post-IV tPA

Case 4: Conclusions

- Rethink your exclusions to IV rt-PA
- CTP can aid substantially in treatment decisions and management (if only to reassure you of things)

SMART-TEL: Optimizing Stroke Care Through Telemedicine

Stroke centers provide quality stroke care but have limited reach

Telemedicine

- Well-established mechanism of providing specialized care beyond a hospital's physical confines
- Uses technology to connect patient and physician with a remote specialist:
  - Telephone
  - Teleradiology
  - Videoconferencing
- The use of telemedicine for stroke care, termed 'Telestroke', now typically involves videoconferencing
- Results from the STRokE DOC study demonstrate video conferencing to be superior to telephone consultation in the treatment and management of stroke patients (98% vs 82%, *P* = 0.0009)
- Potential benefits of Telestroke include improved outcomes, reduced morbidity, and mortality

STRokE DOC = Stroke Team Remote Evaluation Using a Digital Observation Camera.

Levine SR, McConnochie KM. *Neurology.* 2007;69:819-820. Meyer BC, et al. *Neurology*. 2005;64:1058-1060.
LaMonte MP, et al. *Stroke.* 2003;34:725-728. Meyer BC, et al. *Lancet Neurol.* 2008;7:787-795.
Stroke 2009;40;2635-2660

Conclusions

- Hyperacute stroke therapy still time-sensitive, several emerging therapies to expand treatment eligibility
- SMART Criteria may increase eligibility and benefit from IV rt-PA
- Stroke centers with 24/7 care and interventional services effective, telemedicine effective
- Neuroimaging is an important focus of research for acute stroke therapy
- Prevention and early detection are still essential first steps

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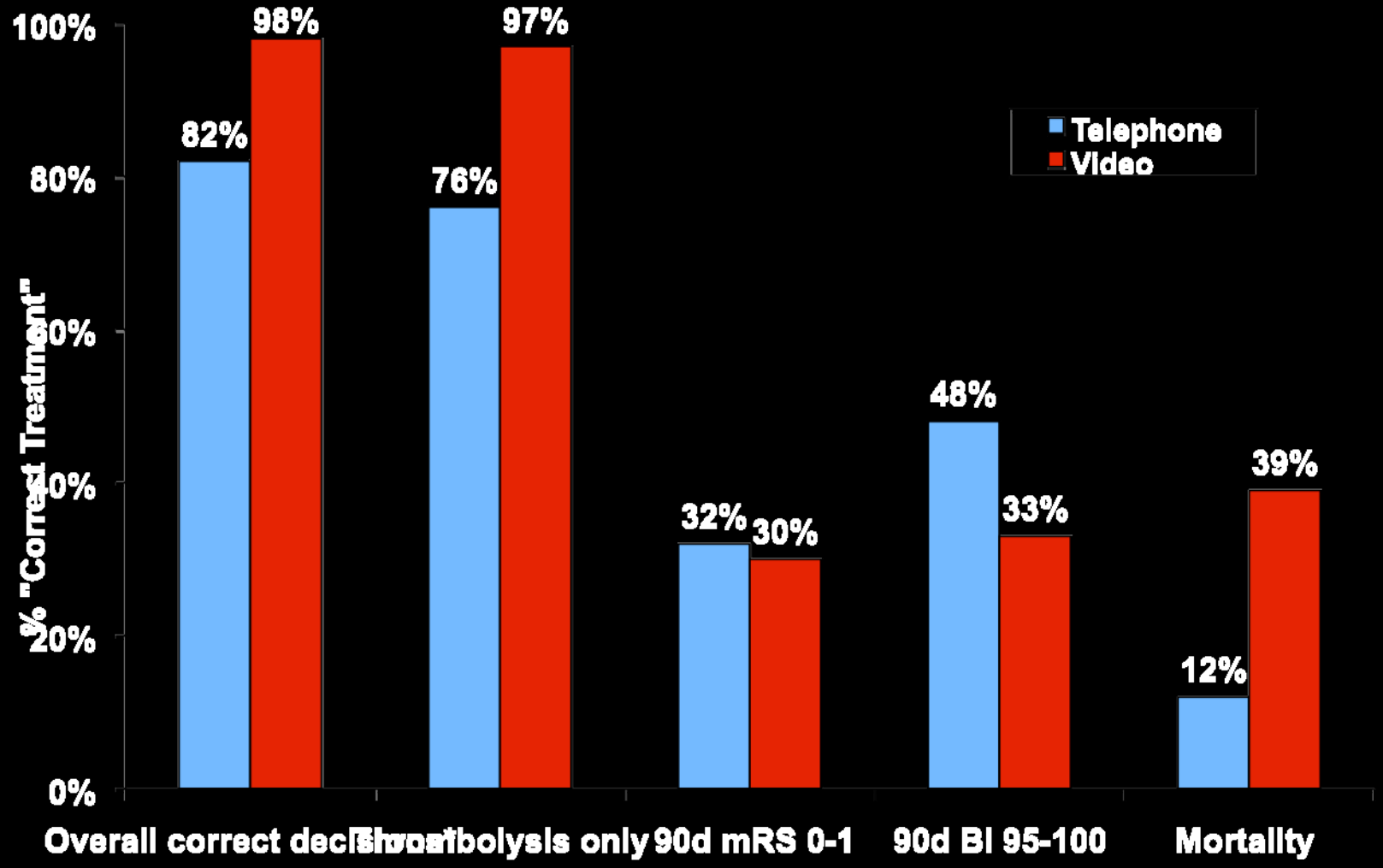
Additional Slides

STROKE DOC Results

NIHSS Mean 9.5 vs. 7.7 (video vs. telephone)



*Odds ratio [OR] 10.9, 95% CI 2.7–44.6; p=0·0009

Lancet Neurol 2008; 7: 787–95

SMART: IV *not* IA Is Preferred Initial Treatment

- Rationale:
  - Time to reperfusion is likely more important than modality of reperfusion
    - IA treatment requires much more time to initiate compared with IV and is generally less available
  - No compelling data that IA is superior to IV, including in large artery occlusion or basilar occlusion
  - IA can always be added to IV (bridging/full dose)
  - IV first may “soften” clot, and make IA more effective
  - No good evidence that higher dose rt-PA causes more bleeding, especially if delayed
  - Data supporting IA thrombolysis is lower quality than that supporting IV

IV vs. IA therapy myths

- IA better than IV due to higher recanalization rate
  - Not been conclusively shown
  - Difficult to make a fair comparison (timing/severity/location)
  - Clinical outcomes may not be significantly different
- IA better >3h
  - ECASS 3 refutes this
- IA better in VB stroke
  - Similar outcomes in meta analysis[2]
- IA superior if occlusion seen on CTA/MRA/CUS
  - See above, limited evidence
- DWI/PWI identifies good IA candidates
  - DEFUSE/EPITHET show IV rt-PA works in these patients

[1]*Stroke*. 2007;38:2191-2195

[2]*Stroke.* 2006; 37: 922–928.

SUPER SMART

(SUpplementing Perfusion To Enhance Recanalization)

- CPMC Protocol: Full Dose IV+IA rt-PA
- 7/07-6/10: 21 patients received full dose IV+IA
- All patients receive pre treatment CTP/CTA
- Median age 63 (43-94)
- Median NIHSS=15
- Revascularization: 95%
- Mean time to IA: 512 minutes (8.5 hours)
- Discharge mRS $\leq$ 2: 29%
- Symptomatic ICH: 5% (n=1)