



*California Pacific
Medical Center*

A Sutter Health Affiliate



Advancing Acute Stroke Treatment Using the S.M.A.R.T. Approach

David C Tong MD

Medical Director

CPMC Comprehensive Stroke Care Center

Director

CPMC Center for Stroke Research

San Francisco, CA

Thrombolysis use very low

- Only ~1.1%-5.0% of ALL ischemic stroke patients receive thrombolysis^{1,2,3}
 - 5-10% at stroke centers (15% highest reported)⁴
- Why?
 - Conservative treatment criteria?

1. Ann Emerg Med May 2007

2. Stroke 32(8); 2001

3. Stroke 2011; Online June 2

4. Arch Neurol 2001;58:2009–2013

Thrombolysis use very low

- Only ~1.1%-5.0% of ALL ischemic stroke patients receive thrombolysis^{1,2,3}
 - 5-10% at stroke centers (15% highest reported)⁴
- Why?
 - Conservative treatment criteria
 - Few vascular neurology specialists available

1. Ann Emerg Med May 2007

2. Stroke 32(8); 2001

3. Stroke 2011; Online June 2

4. Arch Neurol 2001;58:2009–2013

Telemedicine/TeleStroke

- Gets expert to bedside fast
- 2-way HD audio/video
- Remote control
- Inexpensive



Key Concepts

- We can increase thrombolysis treatment rates and improve outcomes
 - At least 25-30% of ischemic stroke patients may be treatable
- Use **SMART** (**S**implified **M**anagement of **A**cute stroke using **R**evised **T**reatment) criteria
 - Safe, effective
 - Increases patient treatment eligibility

Case

Case: DT

- 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

DT: 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

Thrombolysis Contraindications in this Case

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

What should we do?

SMART

**Simplified Management of Acute
Stroke Using Revised Treatment
Criteria**

The SMART Premise

- Current IV rt-PA treatment criteria are too strict
 - Clinical trial \neq clinical practice
 - Most rt-PA exclusion criteria are *not* evidence based
 - Many centers' exclusion criteria even more strict than guidelines and clinical trials
- Simplified Management of Acute Stroke using Revised Treatment Criteria (SMART)
 - Rethink exclusion criteria
 - Streamline management
 - Increase number of candidates for treatment

SMART: IV rt-PA

Absolute Exclusion Criteria

- Acute hemorrhage that is the cause of the patient's symptoms
- “Significant” Neurological deficit
 - Would disable patient if untreated

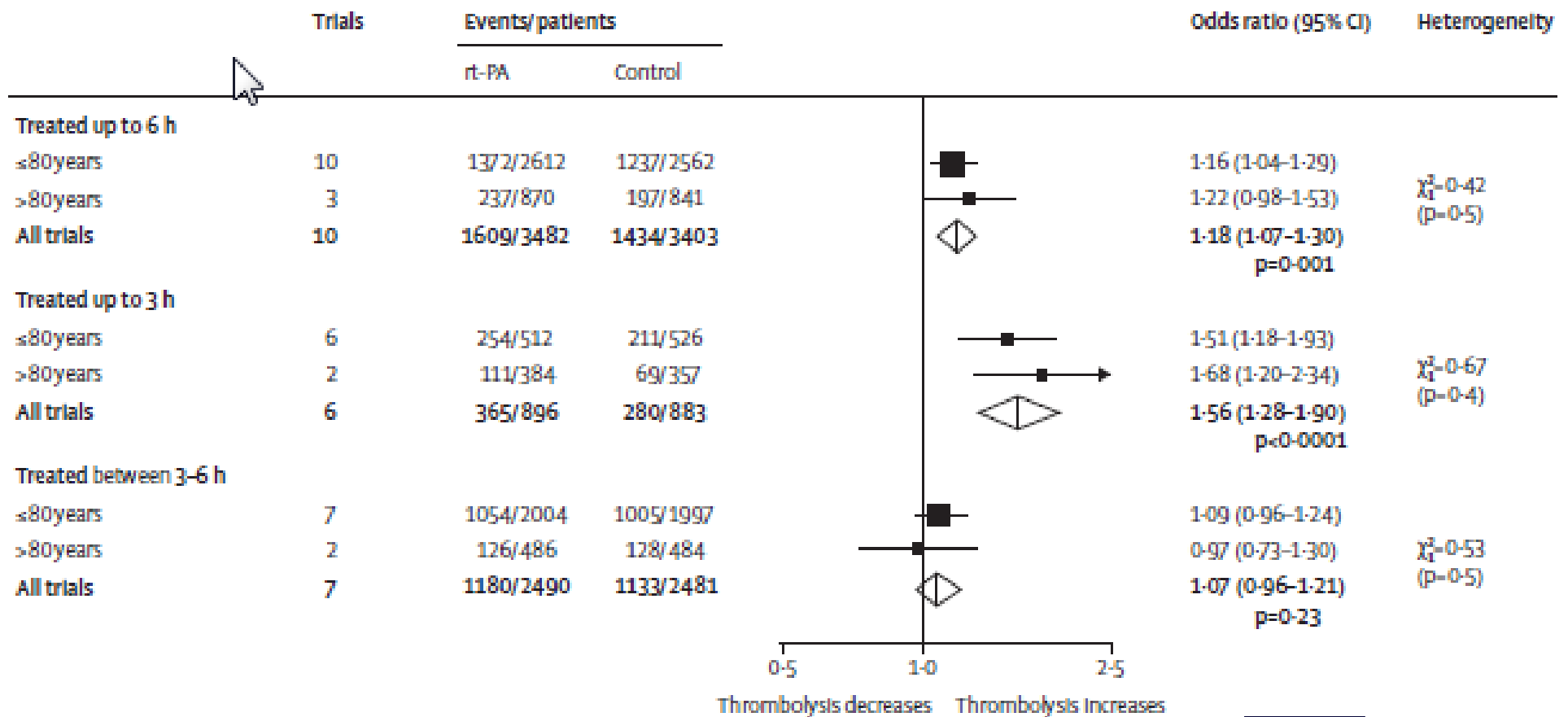
Common IV rt-PA Contraindications That Are NOT SMART Criteria

- 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
- Dementia
- Renal failure, recent MI (unless <1 wk), other co morbidity
- Early infarct signs on CT
- Clear cut onset time

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-PA⁶
- No age cut off
 - Older patients generally do worse, but still benefit from treatment⁶⁻⁹
 - IST 3/SITS/VISTA registries support this approach^{10,11}

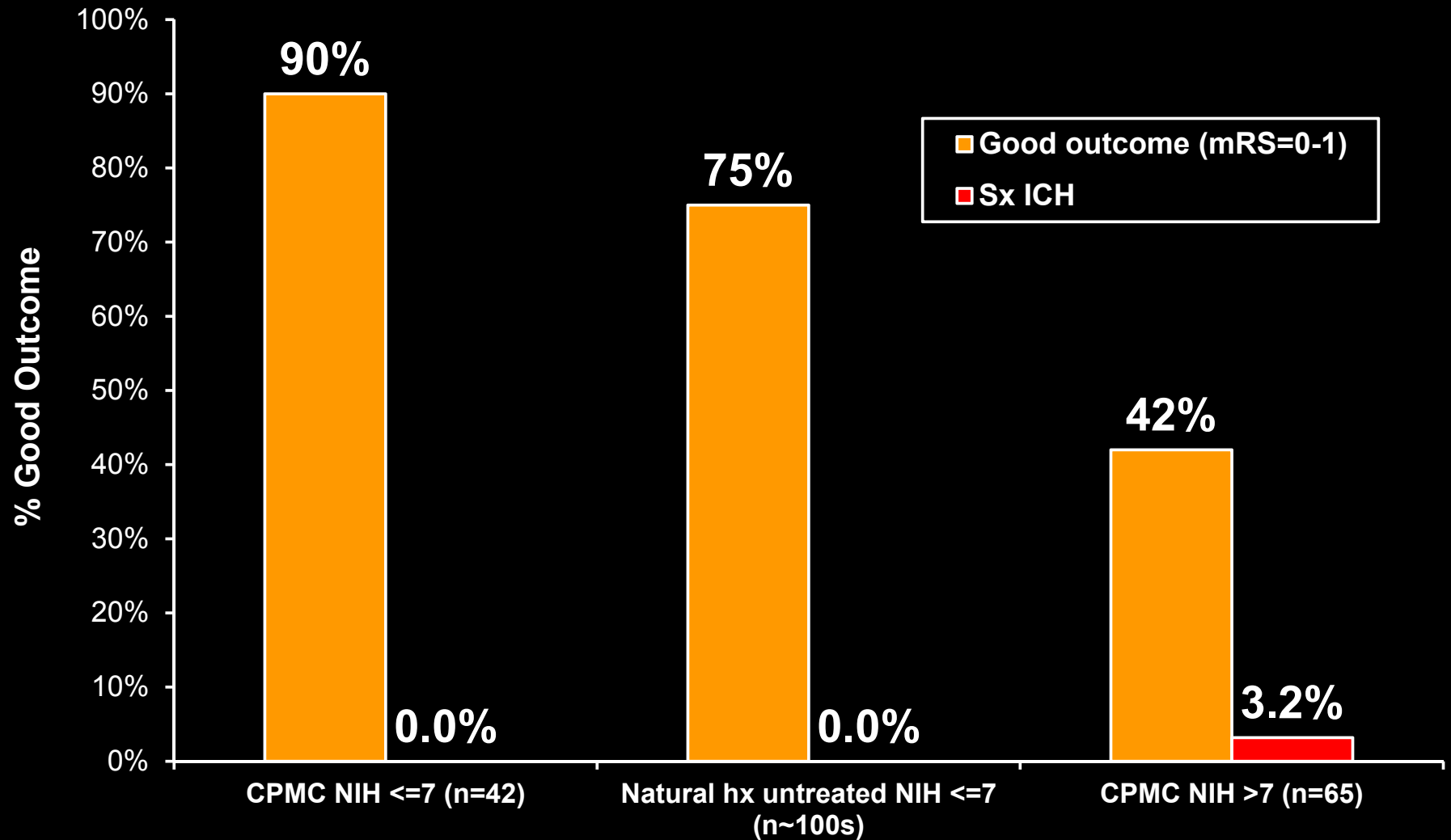
1. Smith, Stroke. 2005 Nov;36(11):2497-9
2. Nedeltchev Stroke. 2007;38:2531-2535
3. Barber, Neurology 2001;56:1015-1020
4. Ann Emerg Med. 2005; 46: 243-252
5. De Kayser, Stroke. 2007;38:2612-2618
6. Stroke 28; 1997: 2119-2125
7. Eur Neurol. 2005;54(3):140-4
8. BMJ 2010;341:bmj.c6046
9. Stroke. 2010;41:2840
10. Mishra N K et al. BMJ 2010;341:bmj.c6046
11. Lancet. 2012 Jun 23: 379 (9834) 2352-63



n=7012

Lancet. 2012 Jun 23 379(9834): 2364 -72

rt-PA in Mild Strokes (NIHSS ≤ 7): SMART Vs Natural History



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 additional doses of rt-PA causes more bleeding, especially if delayed
 - Data supporting IA thrombolysis is lower quality than that supporting IV

IV vs. IA therapy myths^{1,2}

- **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 analysis²
- **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

¹Stroke. 2007;38:2191-2195

²Stroke. 2006; 37: 922–928.

IV Rt-PA in Anticoagulated Patients

- No reports of increased harm in anticoagulated patients
 - In fact, some old IV rt-PA studies routinely used heparin after treatment
 - IA therapy often includes full anticoagulation
- Increased risk in anticoagulated patients is purely theoretical
 - Are anticoagulated stroke patients less likely to bleed?
 - Why do these patients experience clot formation despite anticoagulation?

Mechanical Devices vs. IV rt-PA

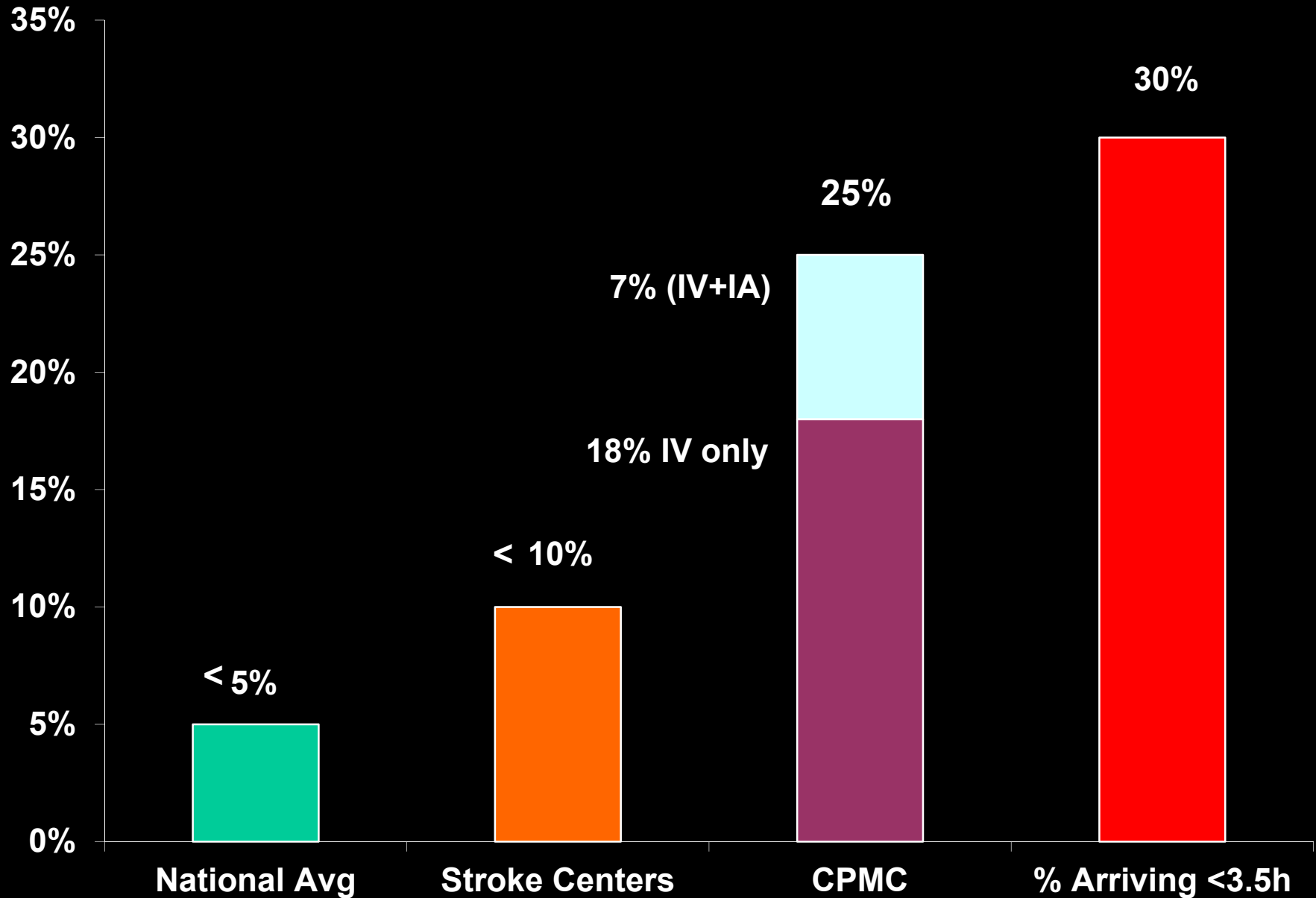
- Not an either/or question
- No reason why mechanical treatment cannot be used with IV rt-PA
- ~50% of patients in recent mechanical thrombectomy trials had IV rt-PA before device use
- No difference in ICH rate in these patients

SMART RESULTS: CPMC

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
- 135 patients (76%) treated with IV rt-PA alone using **SMART** criteria

% All Ischemic Stroke Patients Treated with Thrombolysis



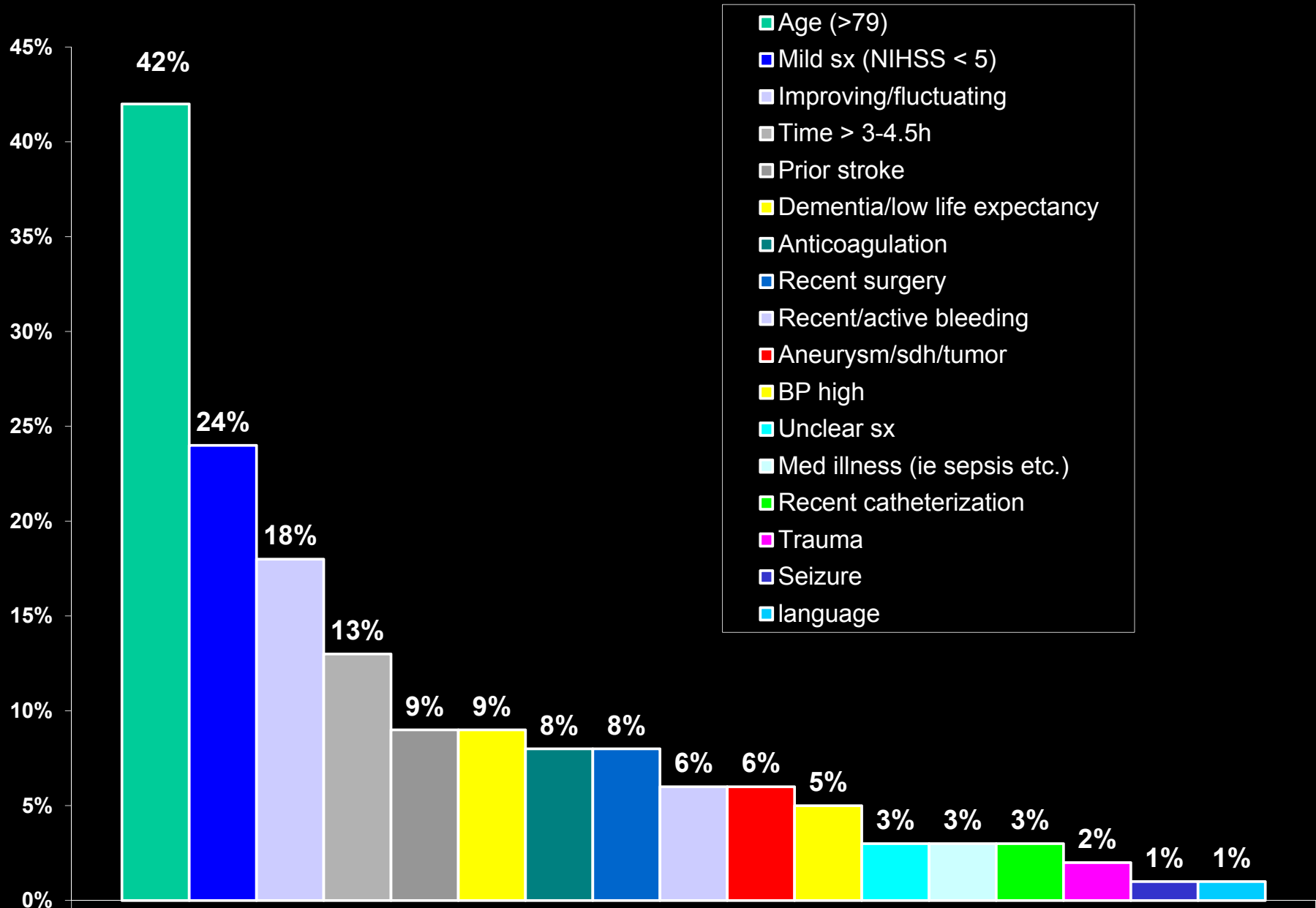
SMART IV rt-PA Stroke Patient Characteristics

- 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**

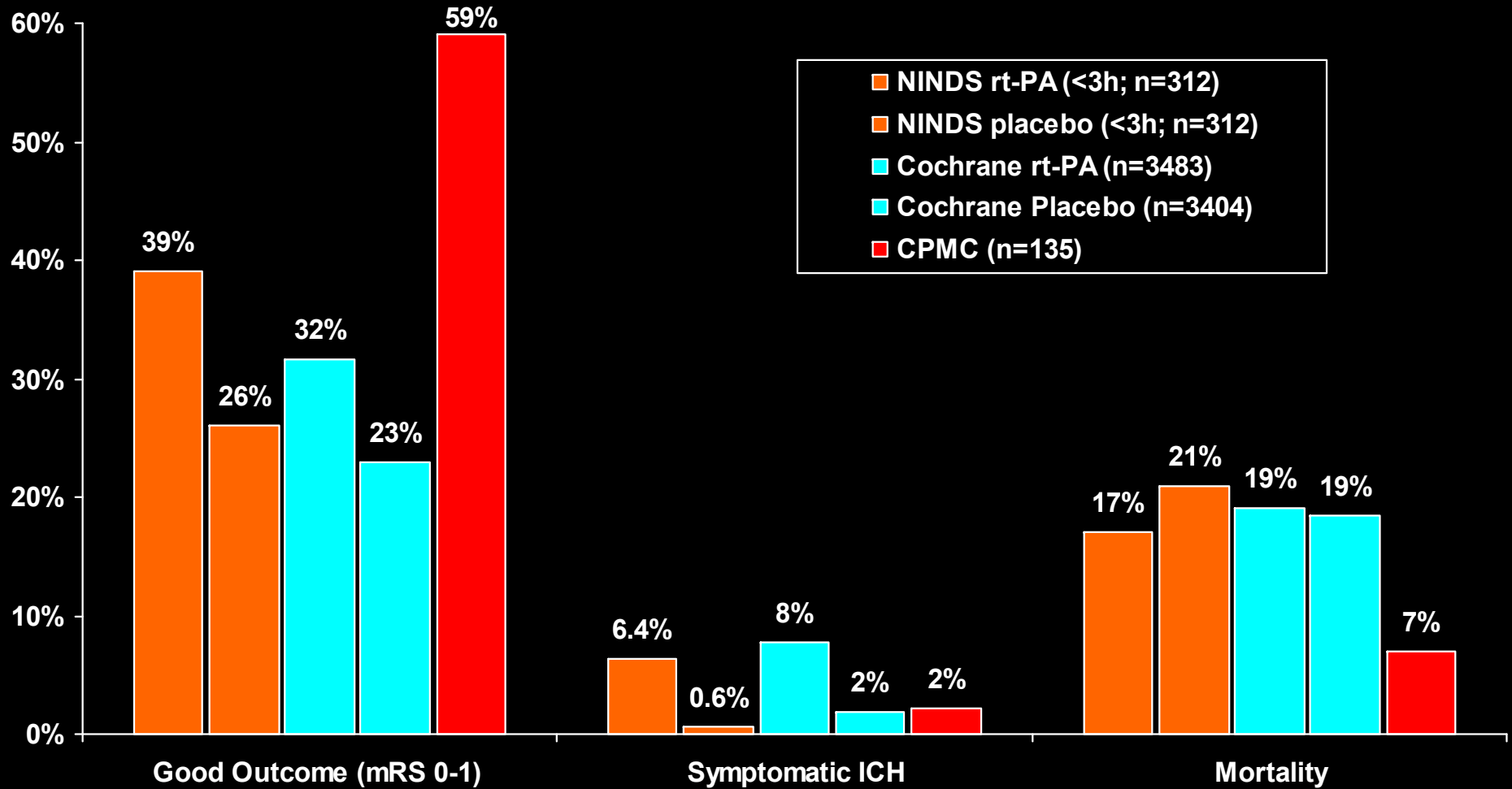
SMART: High Number of Relative Treatment Contraindications

- 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

SMART: Frequency of Common Relative Contraindications



CPMC Versus Major IV rt-PA Studies



NEJM 1995;333:1581-1587

Lancet. 2012 Jun 23 379(9834): 2364 -72

2008-12: IV rt-PA Data

- 427 patients received IV rt-PA
- 213 were transfer patients (50%)
- Symptomatic hemorrhage rate =1%
- Transfers had significantly more severe strokes (NIHSS= 8.2 vs. 6.7)
- Degree of improvement similar between transfers and locally treated patients

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 centers²
 - Bleeding rate = 0%
 - 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. *Neurology* 2010; 74: 1340–1345
3. *Stroke*. 2006; 37: 769–775
4. *Neurology*. 1999; 52: 1784–1792

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

SMART: Streamlining the ED rt-PA Evaluation Process

- No labs required prior to initiation of therapy if clinically appropriate ¹⁻³
- Stroke code alerts CT technologist to clear scanner
- No written consent required
- CT read by treating neurologist

1. Neurology 2006;67:1665-1667.

2. Stroke, Dec 2006; 37: 2935 – 2939.

3.. Acad Emerg Med. 2007 May ;14 (5 Suppl 1):S33.

SMART: Conclusions

- A substantial proportion of stroke patients may be treated safely and effectively with IV rt-PA using **SMART** criteria
- Requires commitment of treating institution and staff
- We should strongly consider revising stroke protocols to reflect changing knowledge about stroke practice

What should we do?

SMART Conclusions

- We can increase thrombolysis treatment rates and improve outcomes
 - 25-30% of ischemic stroke patients treatable
 - Use **SMART** criteria to increase treatment rates
- Neuroimaging:
 - CT perfusion / CT Angiography
- Telemedicine
 - Increases treatment availability and accuracy

Can't All IV rt-PA Subgroups Be Studied With Formal Clinical Trials?

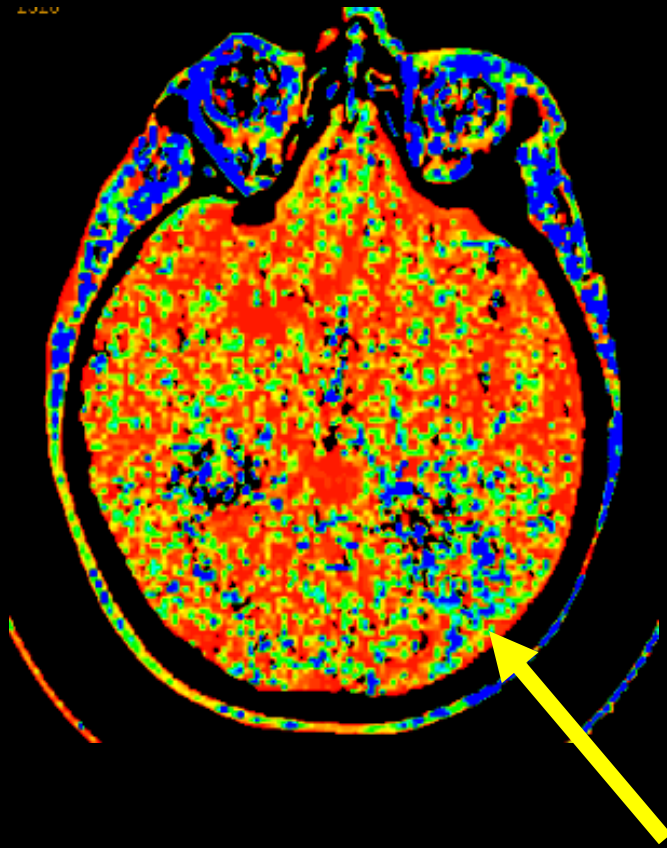
- Impractical: insufficient patients in most subgroups
 - IST-3 took >10 years and got 1/2 planned enrollment
- Expensive
- No subgroup has been identified where rt-PA is ineffective
 - ? Very large complete infarct on MRI > 3h?

Case

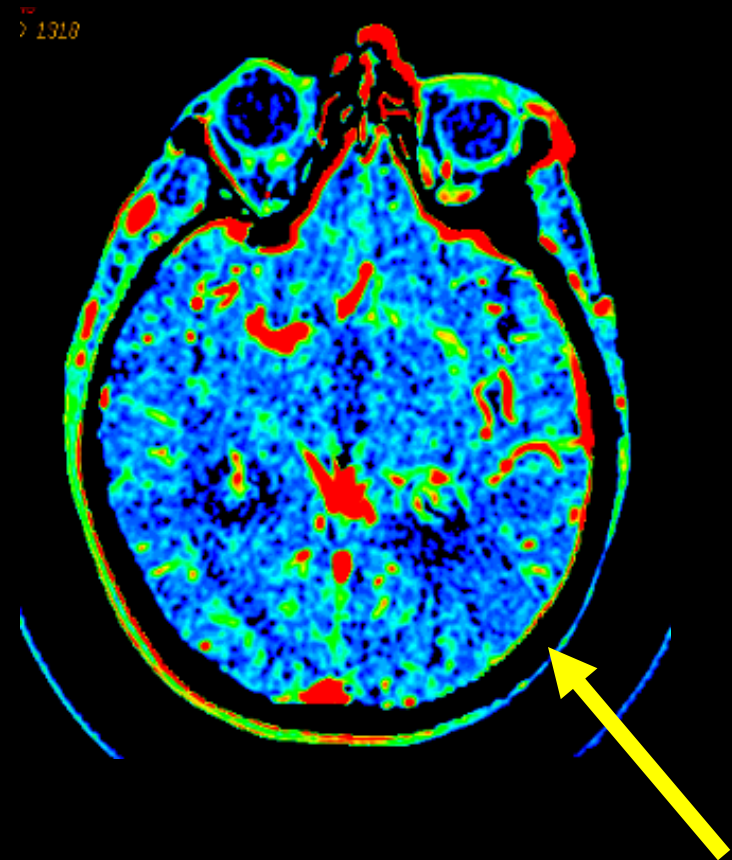
Case Management

- 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)

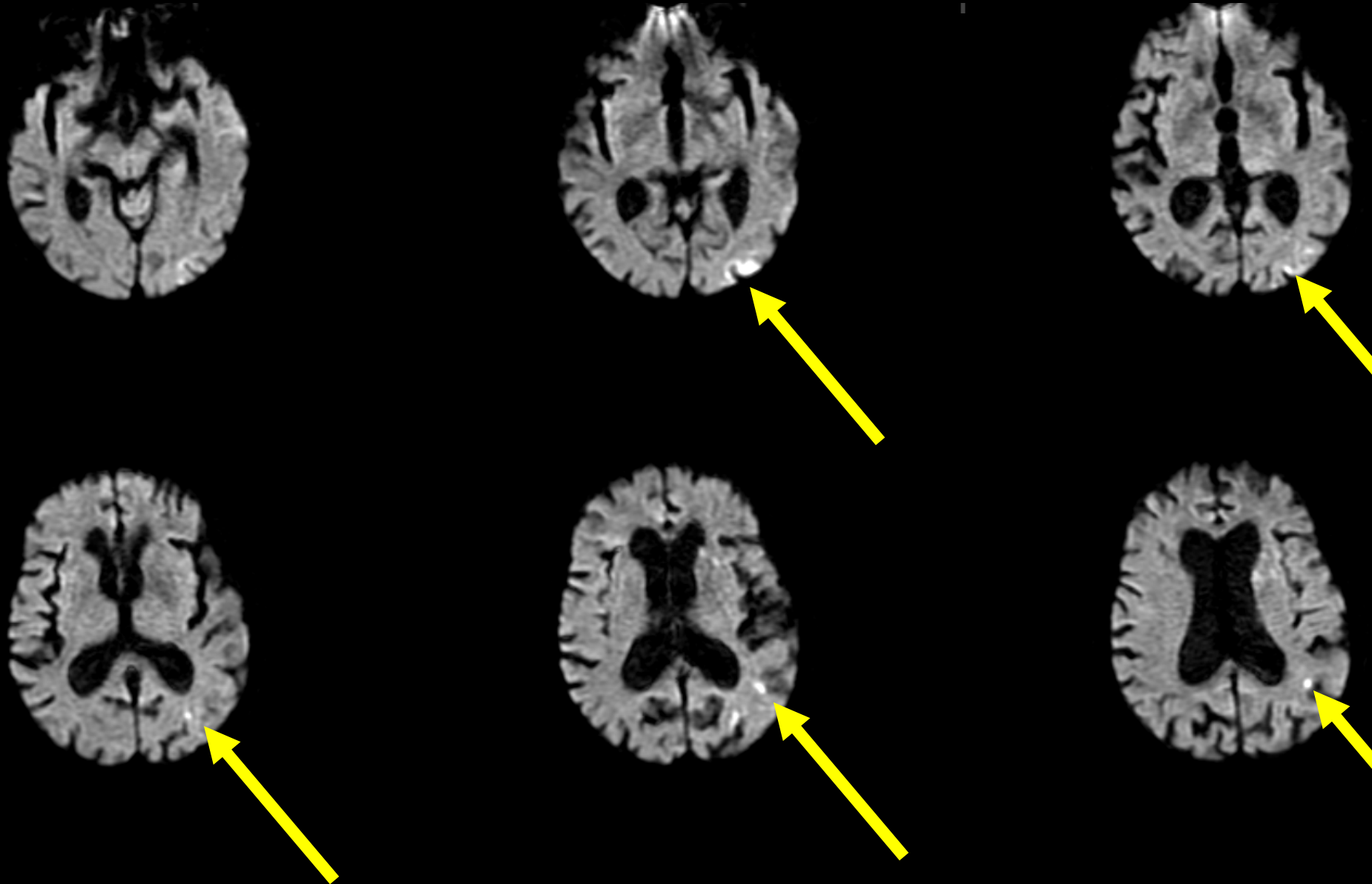
CT Angiogram (CTA)



Management and Outcome

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

DT: Diffusion Weighted MRI (DWI)



IV rt-PA and Anticoagulation: CPMC Experience

- 28 patients (INR > 1.7 or full dose LMWH)
- Received either full dose or half dose IV rt-PA
- No symptomatic intracranial hemorrhage
- Mean NIHSS reduced from 12 to 2

Conclusions

- IV rt-PA is not 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!!**

New Neuroprotection Trial: 18h Time Window

- Phase II study
- Acute ischemic stroke patients
- Eligible even if treated with IV rt-PA or IA intervention
- NIHSS 9-20 (moderate to severe stroke)
- Middle cerebral artery stroke only
- Patients must be transferred to participating center (CPMC)

Comments/Questions