QuICR
Quality Improvement & Clinical Research
Alberta Stroke Program

# Stroke Update and Treatment Improvement

Michael D Hill

# Disclosure Slide

- In the last 5 years:
  - I have been funded by CIHR, HSF Alberta/NWT/Nunavut, CSN, AHFMR, NINDS (NIH)
  - I have received speaker fees/honouraria from Hoffmann-La Roche Canada Ltd., Sanofi Canada, Boehringer-Ingelheim Canada, Novo-Nordisk Canada
  - I have been an advisor to NovoNordisk Canada, Genentech Ltd, Stem Cell Therapeutics, Vernalis Group Ltd., Sanofi Canada; Portola therapeutics
  - I hold no stock or direct investment in any pharmaceutical or device company (except those possibly in mutual funds)
  - I believe you/we should “give the juice” (ie. tPA) far more often that we do

# Outline

- QuICR and SCN Introduction
- Thrombolysis for Acute Stroke
- Imaging for Acute Stroke and for TIA/Minor Stroke
- Endovascular and Red Deer's role

# Context

- APSS
- SAP
- QuICR QI objectives
  - Door-to-needle
    - Endovascular
  - TIA/minor stroke

# Stroke is a clinical syndrome
## defined by imaging

1. Ischemia:  AIS and TIA (85%)

2. Intracerebral hemorrhage (7.5%)

3. Sub-arachnoid hemorrhage (7.5%)

# Stroke Presentation

- Stroke is SUDDEN (seconds to minutes)
- Stroke is usually PAINLESS
- Deficits may not be maximal at onset and may progress
- Stroke is the most common cause of sudden focal neurological deficits IN ALL AGE GROUPS (including you!)

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ORIGINAL CONTRIBUTION

# Comparison of MRI and CT for Detection of Acute Intracerebral Hemorrhage


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**Context** Noncontrast computed tomography (CT) is the standard brain imaging study for the initial evaluation of patients with acute stroke symptoms. Multimodal magnetic resonance imaging (MRI) has been proposed as an alternative to CT in the emergency stroke setting. However, the accuracy of MRI relative to CT for the detection of hyperacute intracerebral hemorrhage has not been demonstrated.

**Objective** To compare the accuracy of MRI and CT for detection of acute intracerebral hemorrhage in patients presenting with acute focal stroke symptoms.

**Design, Setting, and Patients** A prospective, multicenter study was performed at 2 stroke centers (UCLA Medical Center and Suburban Hospital, Bethesda, Md), between October 2000 and February 2003. Patients presenting with focal stroke symptoms within 6 hours of onset underwent brain MRI followed by noncontrast CT.

**Main Outcome Measures** Acute intracerebral hemorrhage and any intracerebral hemorrhage diagnosed on gradient recalled echo (GRE) MRI and CT scans by a consensus of 4 blinded readers.

**Results** The study was stopped early, after 200 patients were enrolled, when it became apparent at the time of an unplanned interim analysis that MRI was detecting cases of hemorrhagic transformation not detected by CT. For the diagnosis of any hemorrhage, MRI was positive in 71 patients with CT positive in 29 ($P<.001$). For the diagnosis of acute hemorrhage, MRI and CT were equivalent (96% concordance). Acute hemorrhage was diagnosed in 25 patients on both MRI and CT. In 4 other patients, acute hemorrhage was present on MRI but not on the corresponding CT—each of these 4 cases was interpreted as hemorrhagic transformation of an ischemic infarct. In 3 patients, regions interpreted as acute hemorrhage on CT were interpreted as chronic hemorrhage on MRI. In 1 patient, subarachnoid hemorrhage was diagnosed on CT but not on MRI. In 49 patients, chronic hemorrhage, most often microbleeds, was visualized on MRI but not on CT.

**Conclusion** MRI may be as accurate as CT for the detection of acute hemorrhage in patients presenting with acute focal stroke symptoms and is more accurate than CT for the detection of chronic intracerebral hemorrhage.



JAMA. 2004;292:1823-1830 www.jama.com



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# AIS Diagnosis

- Clinical
- CT scan
  - Sensitive for severe stroke
  - 20% sensitive for all stroke – ie. Misses small ischemic lesions
  - Takes a trained eye
- MRI (DWI)
  - Highly sensitive for all ischemic stroke

# 1. Principles of Emergency Stroke Treatment

- Speed
- Rapid diagnosis
  - ICH
  - SAH
  - AIS
  - TIA
  - CVST

# Speed

- System issue – process engineering at all levels from pre-hospital, triage, imaging, treatment
- Applies to all stroke types

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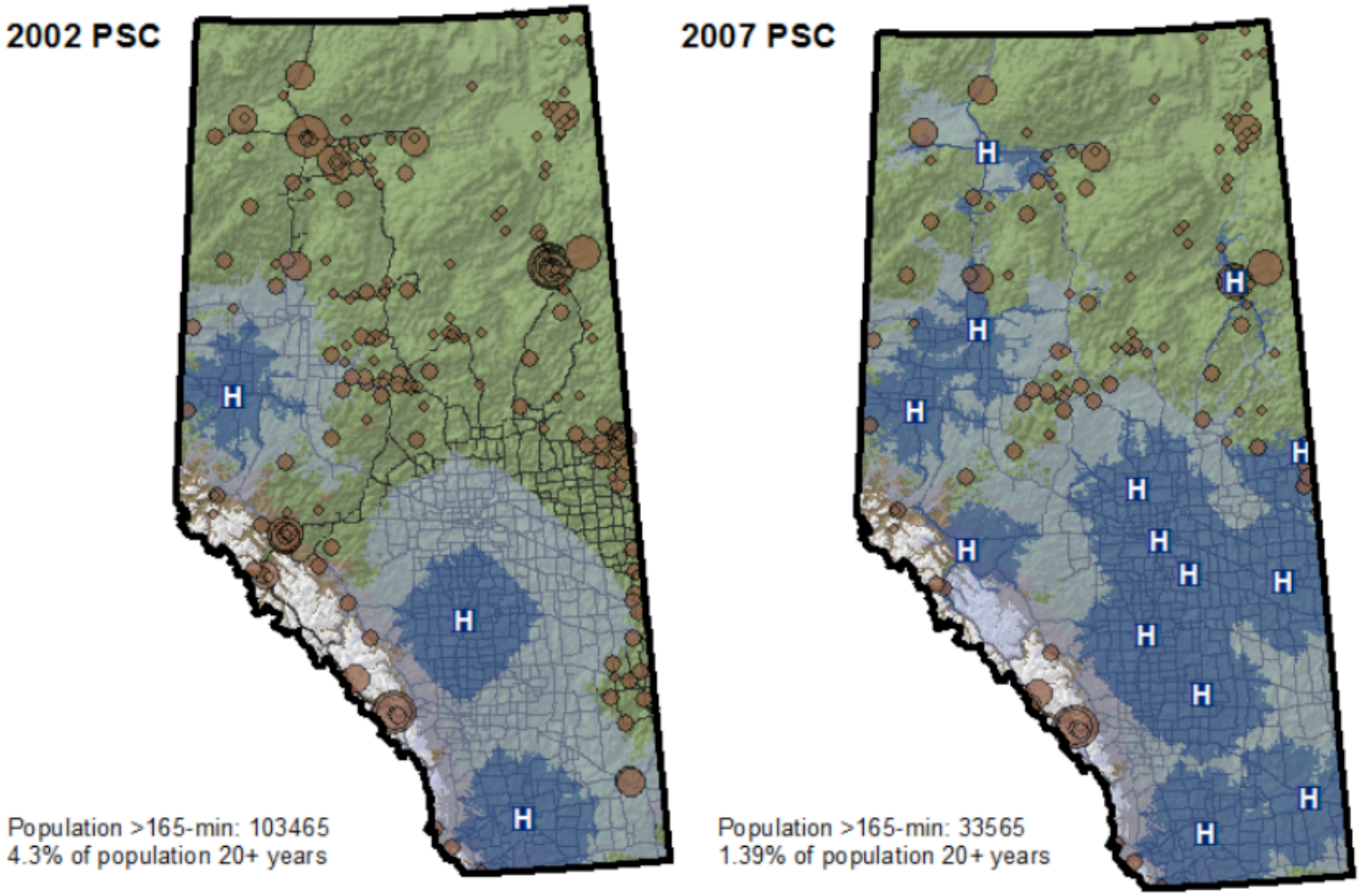
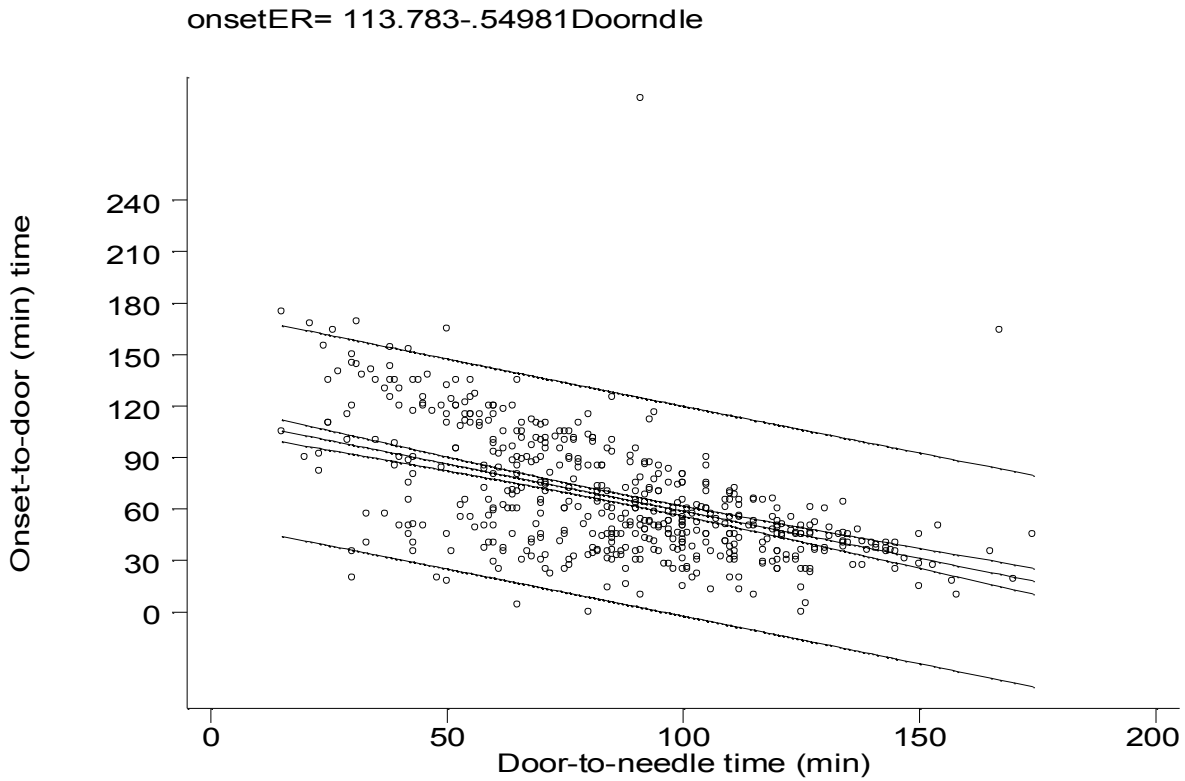
# EMS Bypass to Stroke Centres

**Figure 3. Critical transport time service areas around Primary and Comprehensive Stroke Centres, 2002 and 2007, and population age ≥20-years considered to be without timely geographic access to acute stroke care. Statistics Canada 2006 census data.**



# Human Nature?




**For each 10 minute delay in ER arrival, treatment was 18 minutes faster!**

# Diagnosis

1. If they have a deficit when you see them, no matter how slight, it will be a stroke.
2. Examine language/speech, power, sensation, vision and co-ordination.
   - Sensation, vision, co-ordination commonly missed.
3. Imaging – usually CT
   - Push the patient to CT. You should have a CT within 25 minutes of arrival at triage.

# 2. Thrombolysis

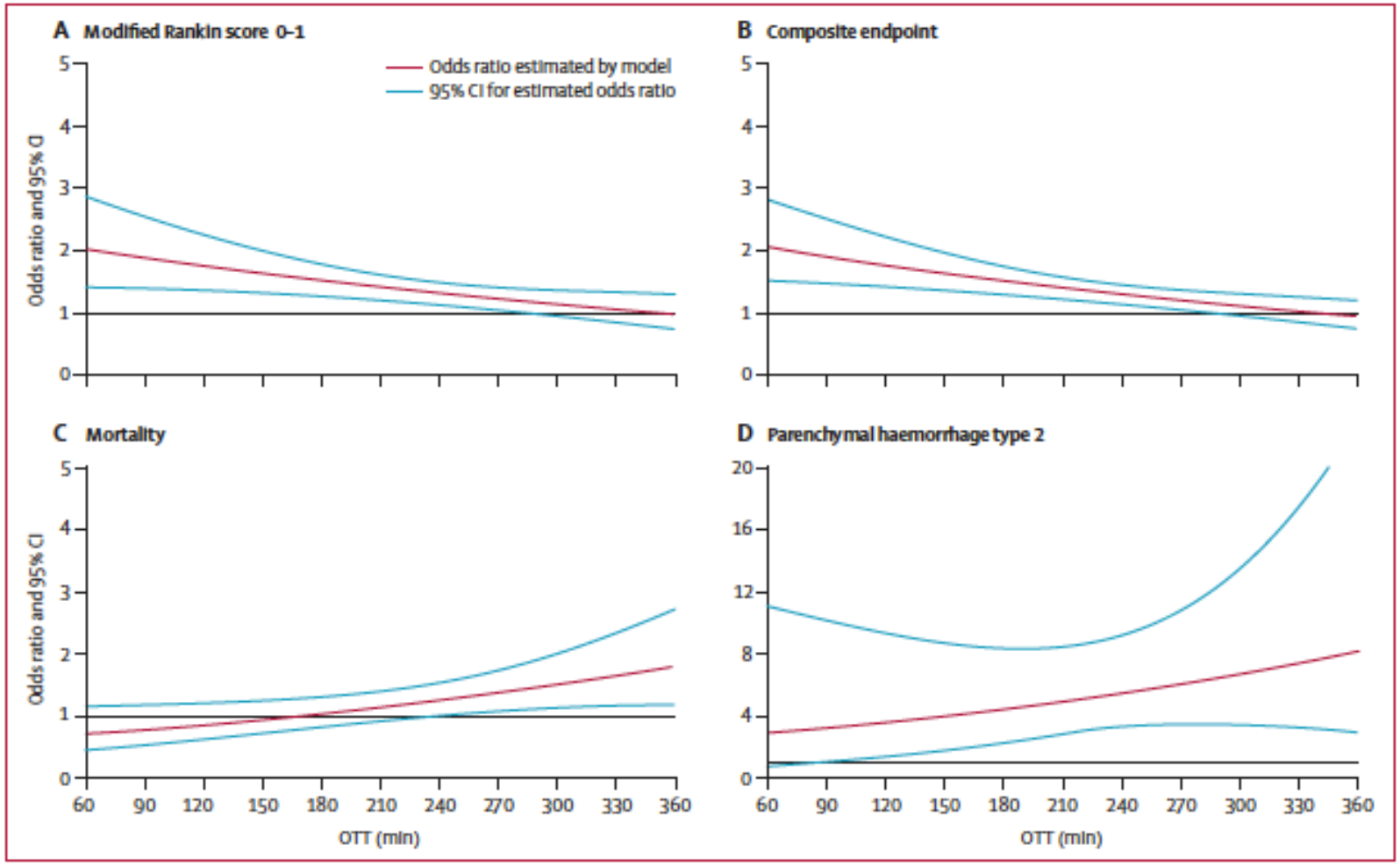
- Offer thrombolysis to disabled patients with acute ischemic stroke
  - No hemorrhage on imaging
  - Not a wipe out stroke on imaging
  - Early in the time window
  - You should treat with a door-to-needle time < 60 minutes and ideally faster than that
  - No general medical thrombolysis contraindications

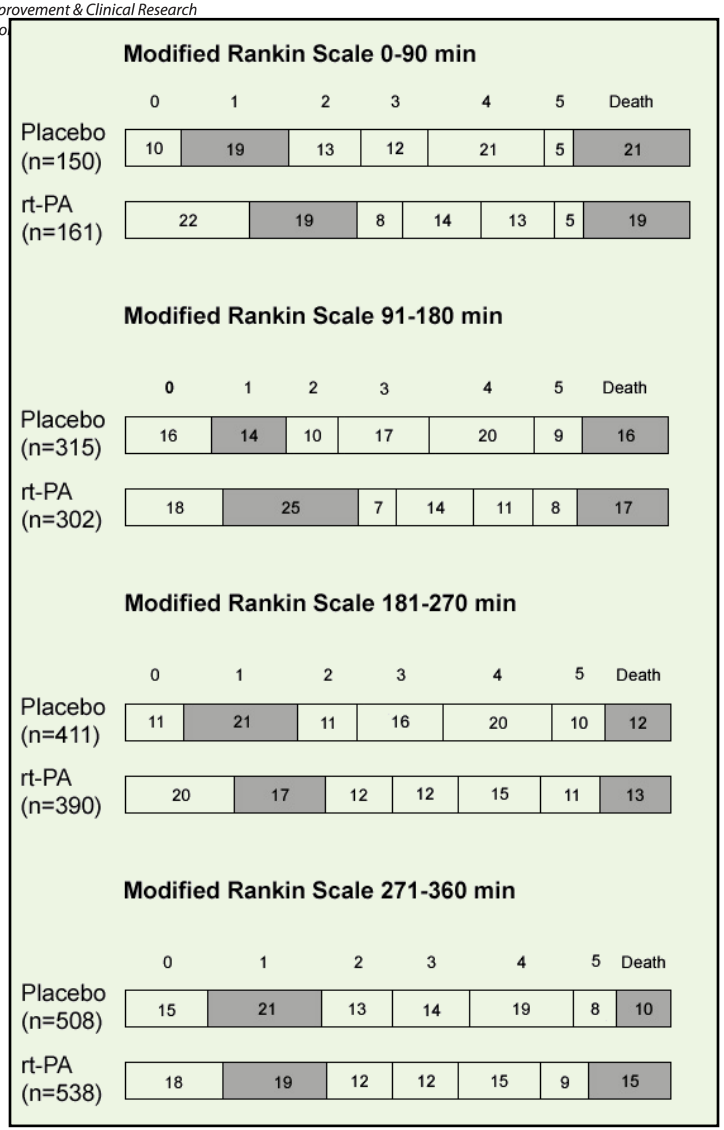
# Stroke Clinical Trials:
## Thrombolysis

- MAST-E, MAST-I, ASK
- ECASS-1
- NINDS tPA Stroke Trial
- ECASS-2
- ATLANTIS
- EPITHET
- DIAS
- ECASS-3
- IST-3

# Time and outcome

[Lees et al. *Lancet* 2010; 375: 1695–1703]

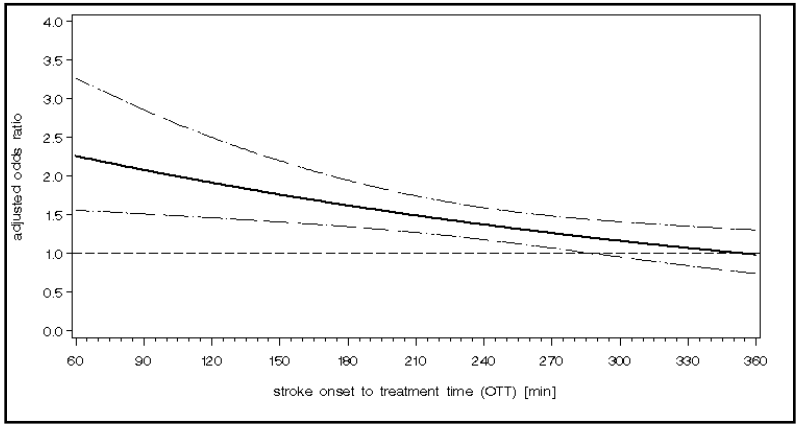





0–90 min, n=311;
91–180 min, n=618;
181–270 min, n=801;
270–360 min, n=1046.

Values do not equal 100% because of rounding.

## Time is an effect modifier




The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. *Lancet* 2004; 363 (9411): 768-774.

# IV tPA time relationship

## time is brain [Emberson et al. Lancet 2014]

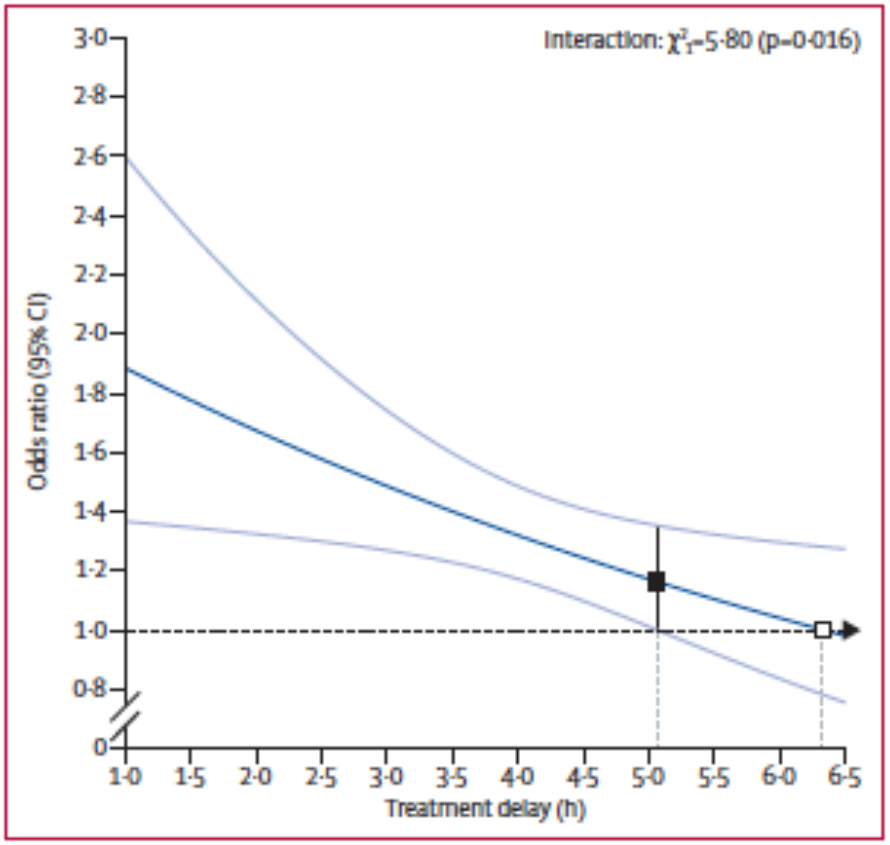



*Figure 1:* **Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)**

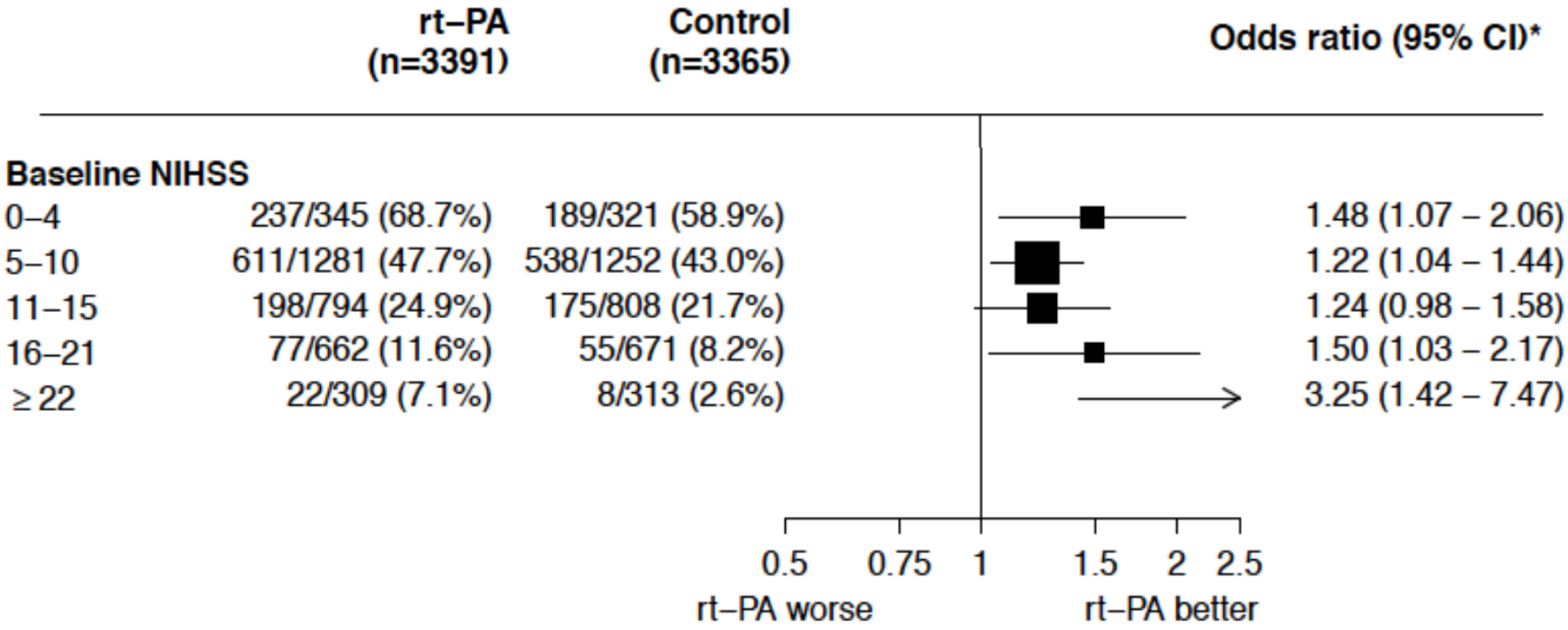
- Early treatment with IV tPA reduced death and disability at 90 days
- The lower bound of the confidence interval cross unity at approximately 5 hours
- Speed is a critical factor in treatment

# Do: Treat improving stroke…

- 30% of patients deemed too mild or rapidly improving are disabled or dead at hospital discharge (Barber et al., Neurology)
  - DO treat if not completely better
  - DO treat if fluctuating
- <u>Rule of thumb</u>
- Disabled = Can't walk OR can't talk OR can't see OR can't hold arm up against gravity

# Treat minor stroke?

Effect of rt−PA on a good stroke outcome (mRS 0−1) by stroke severity



# 3. Ischemic stroke: Blood pressure

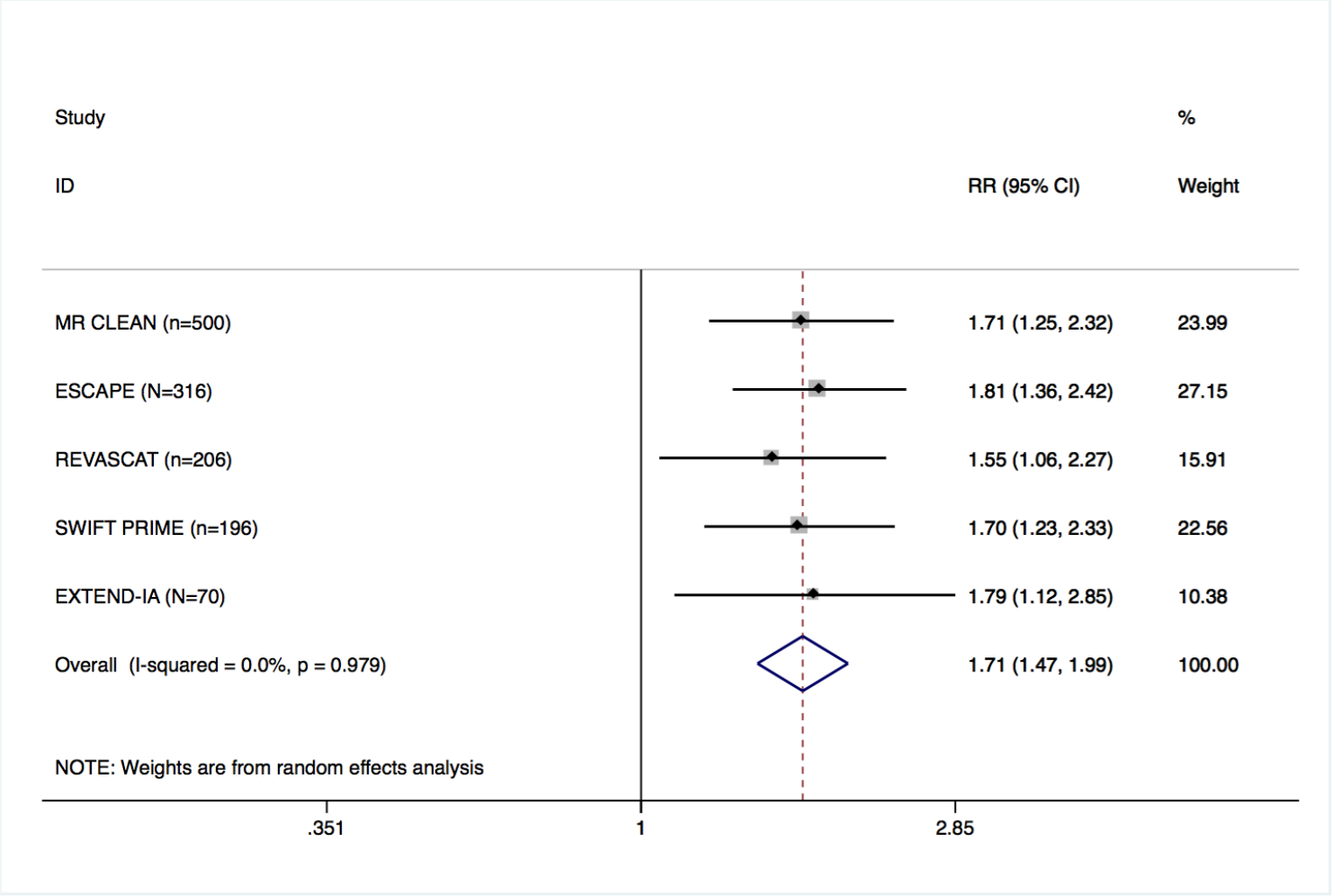
- Treat blood pressure for thrombolysis
  - tPA in one arm
  - Labetalol in the other

- For all other ischemic strokes, leave the BP alone
  - It is elevated because of stroke
  - It comes down normally in the first 48h
  - Rapid treatment in the setting of a blocked artery can worsen ischemia

# Hemorrhage: Blood Pressure

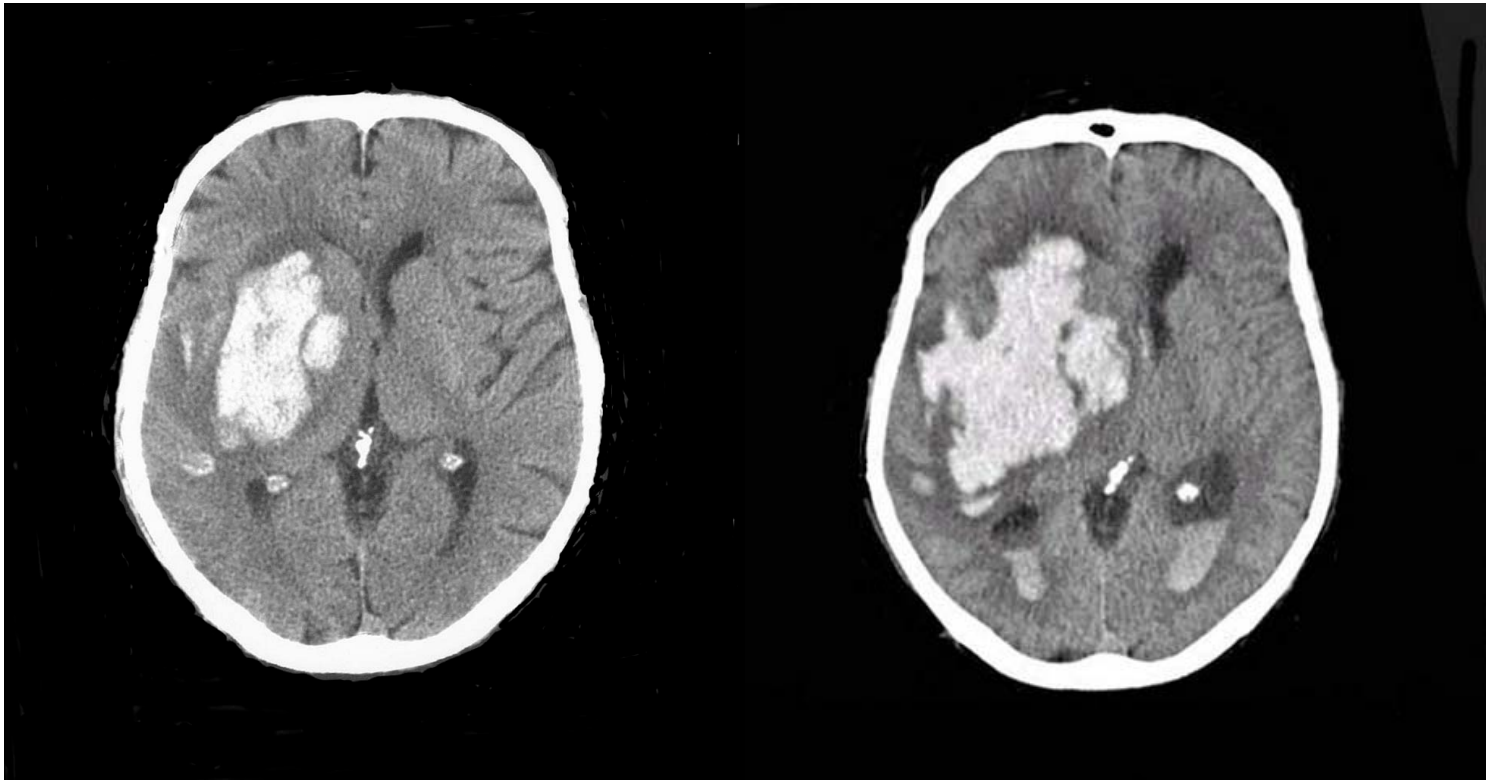
- SAH – treat the blood pressure
  - Reduced risk of early re-bleeding from aneurysm
  - Once aneurysm is secured, let the BP ride high
    - Possible need for induced hypertension later to deal with SAH-associated vasospasm

# Endovascular Trials



# ICH Pathophysiology

*Early hematoma expansion*



**2.0 hours after onset**

**6.5 hours after onset**

- *Continued arterial bleeding*
- *Secondary bleeding into peri-lesional tissue*
- *Peri-lesional edema*

# ICH: Treat the BP?

**Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.***

| Variable | Intensive Blood-Pressure Lowering (N = 1399) | Guideline-Recommended Blood-Pressure Lowering (N = 1430) | Odds Ratio (95% CI) | P Value |
|---|---|---|---|---|
| Primary outcome: death or major disability — no./total no. (%)† | 719/1382 (52.0) | 785/1412 (55.6) | 0.87 (0.75–1.01) | 0.06 |
| Secondary outcomes | | | | |
| Score on the modified Rankin scale — no./total no. (%)‡ | | | 0.87 (0.77–1.00) | 0.04 |
| 0: No symptoms at all | 112/1382 (8.1) | 107/1412 (7.6) | | |
| 1: No substantive disability despite symptoms | 292/1382 (21.1) | 254/1412 (18.0) | | |
| 2: Slight disability | 259/1382 (18.7) | 266/1412 (18.8) | | |
| 3: Moderate disability requiring some help | 220/1382 (15.9) | 234/1412 (16.6) | | |
| 4: Moderate–severe disability requiring assistance with daily living | 250/1382 (18.1) | 268/1412 (19.0) | | |
| 5: Severe disability, bed-bound and incontinent | 83/1382 (6.0) | 113/1412 (8.0) | | |
| 6: Death by 90 days | 166/1382 (12.0) | 170/1412 (12.0) | | |
| Death — no./total no. (%) | 166/1394 (11.9) | 170/1421 (12.0) | 0.99 (0.79–1.25) | 0.96 |

# ICH-ADAPT

[Butcher et al. Stroke. 2013;44:620-626]

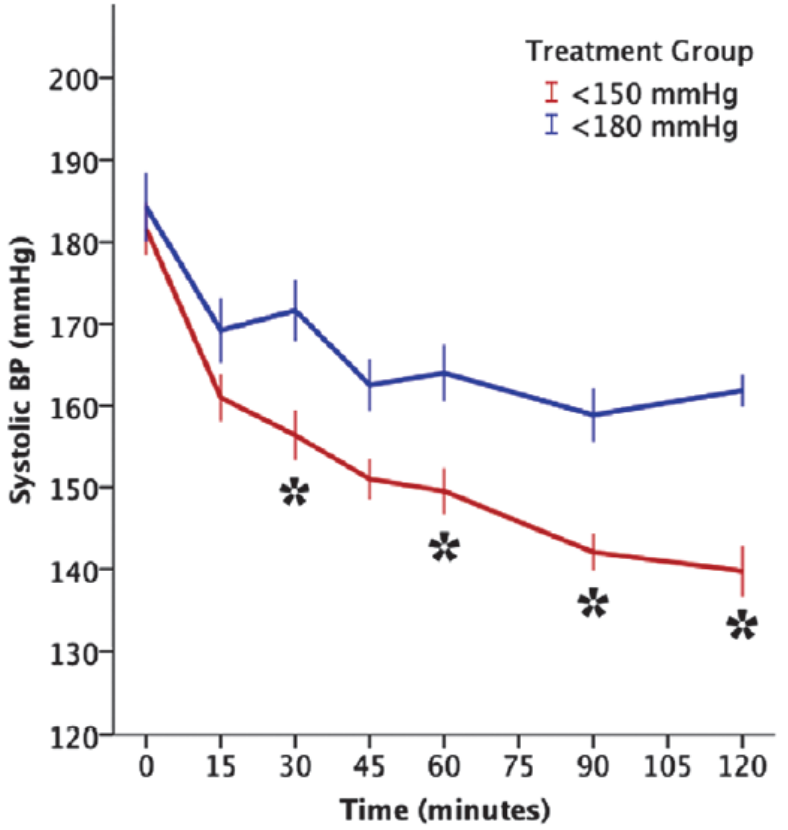



**Figure 2.** Temporal profile of systolic blood pressure (BP) in the <150 mm Hg and <180 mm Hg treatment groups. Error bars are standard error of the mean. Mean systolic BP was considered significantly different at time points, where the 95% confidence intervals did not overlap (*).

# ICH-ADAPT

[Butcher et al. Stroke. 2013;44:620-626]

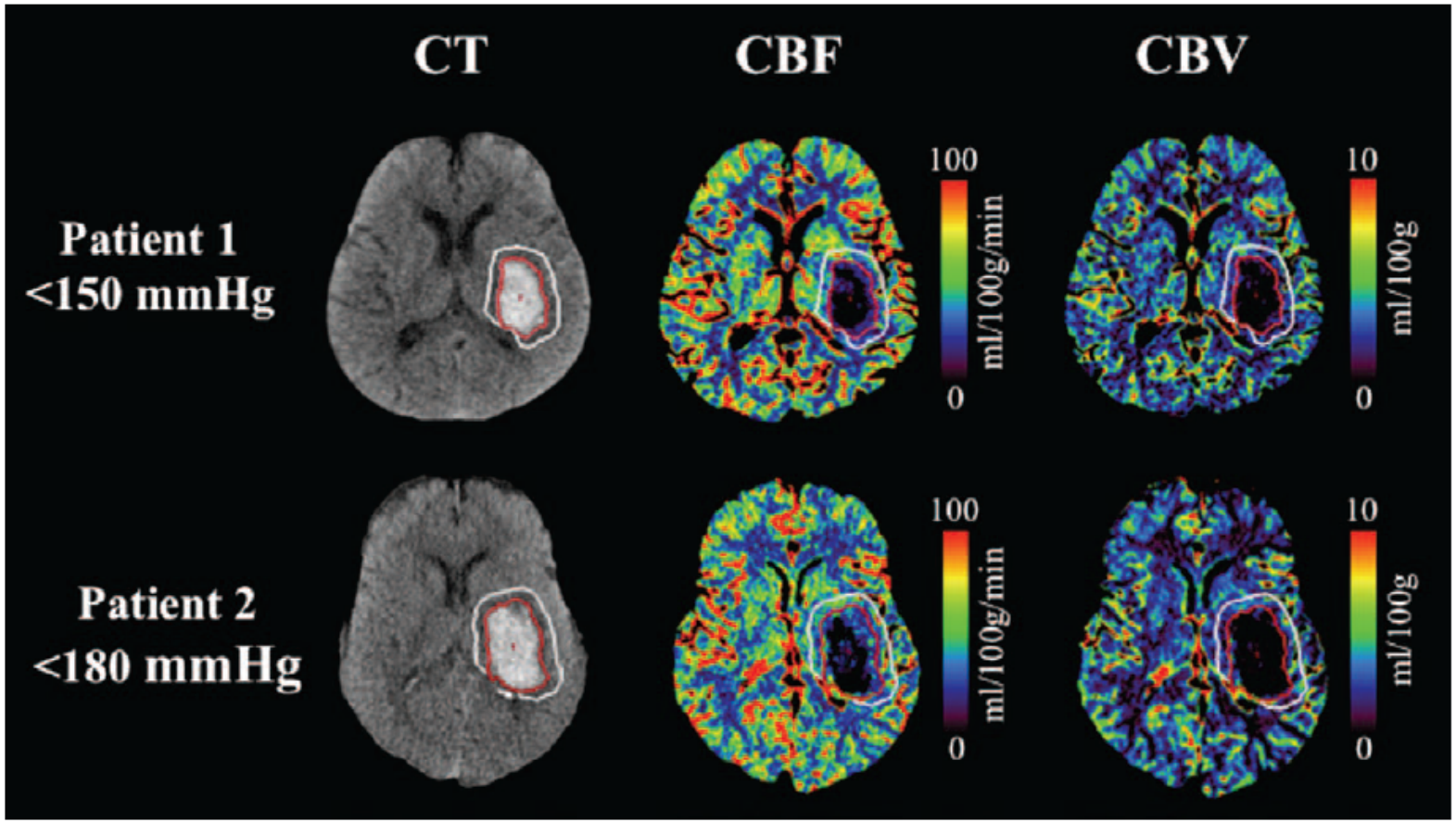



**Figure 3.** Examples of cerebral blood flow (CBF) and cerebral blood volume (CBV) maps and corresponding computed tomography (CT) images in patients after acute blood pressure reduction to <150 mm Hg (top) and <180 mm Hg (bottom). Hematoma (red) and perihematoma (white) regions of interest are demonstrated on all slices. Reductions in CBF are evident in the perihematoma region of both patients.

# Hemorrhage: Blood pressure

- Safe to treat to 140 mmHg systolic
- Benefit is modest or nil
- Unknown if certain sub-groups benefit
- Ongoing trials:
  - ICH-ADAPT-2
  - ATACH

# 4. Antiplatelets

- NO: Thrombolysis patients:
  - No antiplatelets in the first 24h [Danish trial???]
- NO: Hemorrhage patients

- YES: All other ischemia / TIA, give antiplatelets immediately
  - "2 ASA to chew"
  - ASA PR for those who cannot safely swallow

# 5. Disposition

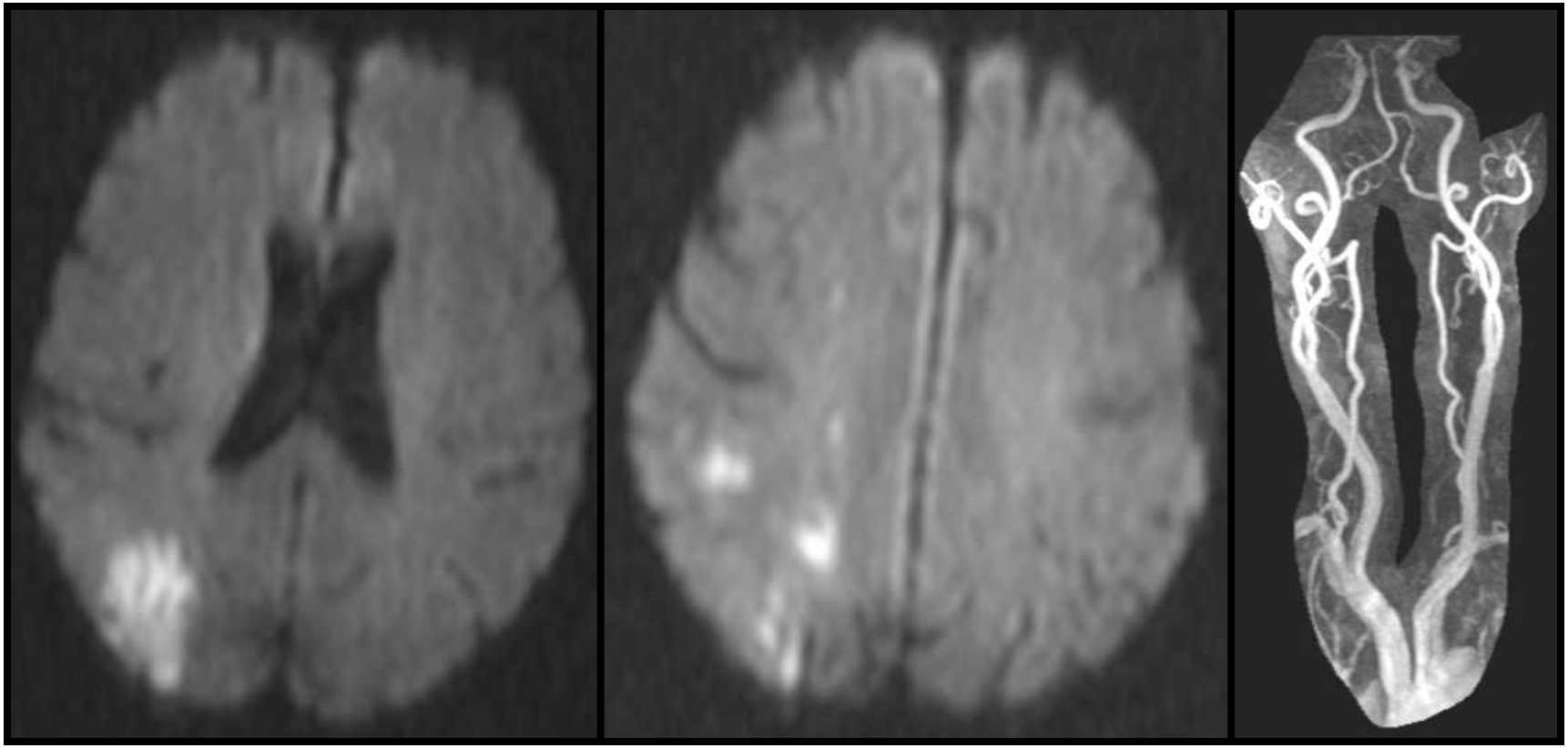
- Thrombolysis patients
  → step-down unit for 12-24h
  → then to a stroke unit
- SAH patients
  → to OR or neuro-angio suite for definitive management of their aneurysm
- ICH patients
  → to a stroke unit. 95% do not require Nsx; they require stroke service admission

# Disposition

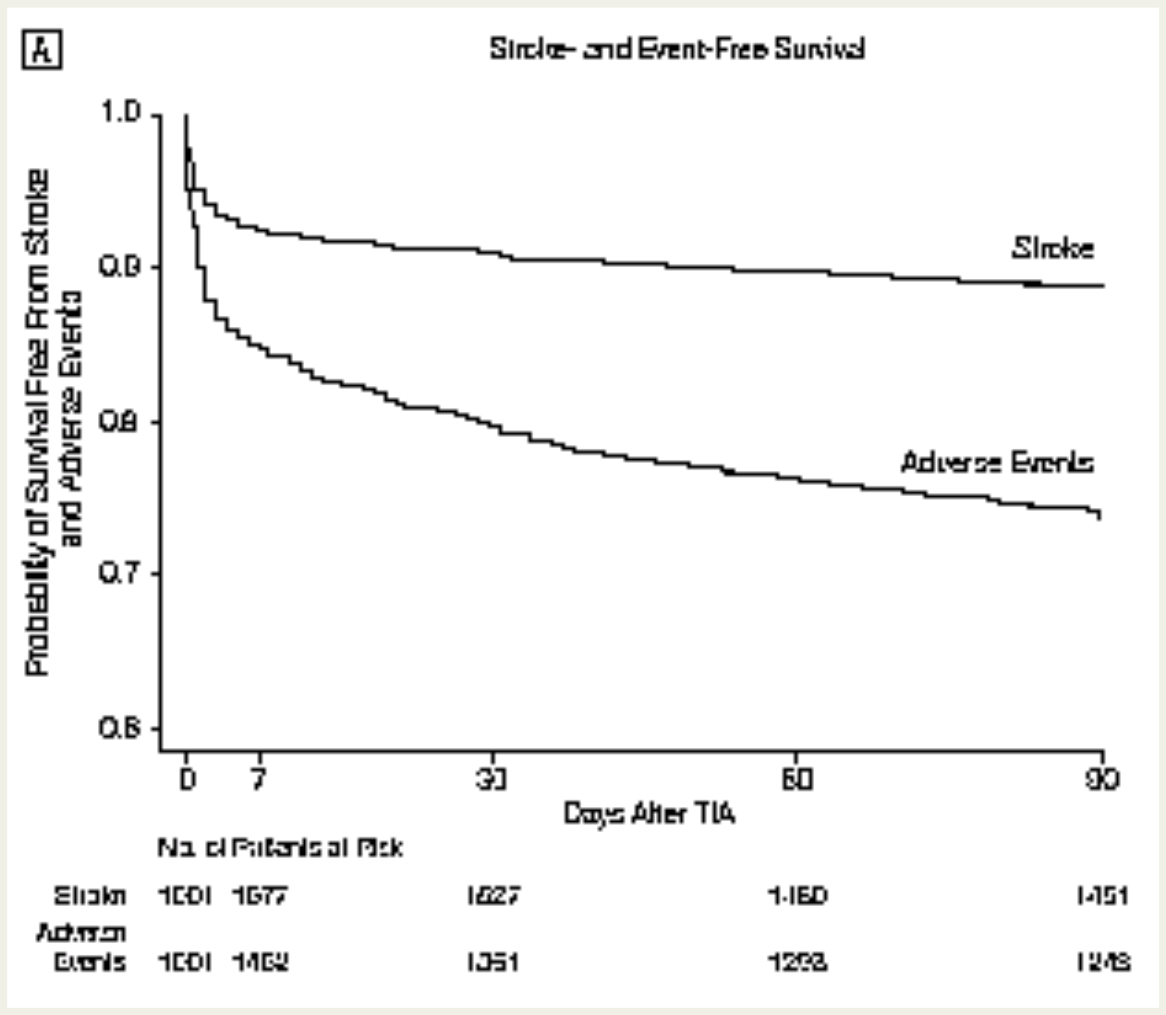
- Ischemic stroke (no thrombolysis)
  - →Stroke unit care
    - →DVT prevention
    - →Swallowing screens and dysphagia management to prevent aspiration pneumonia
    - →Early mobiization and rehabiliation therapy
    - →Diagnostic work-up for stroke mechanism and institution of appropriate secondary prevention

# Disposition:  Management of Minor Stroke and TIA

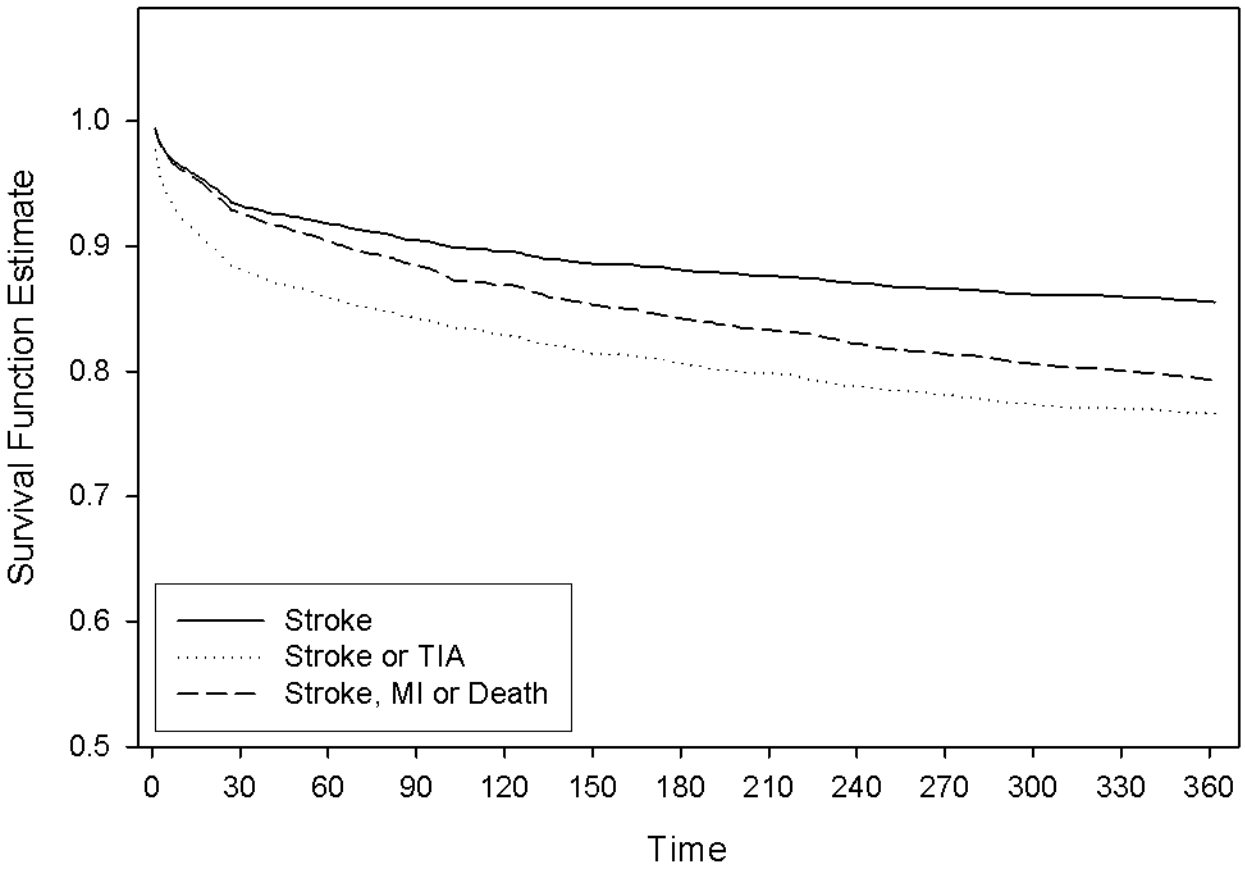
## “TIA”



# Kaplan-Meier Life-Table Analysis of Survival Free from Stroke and All Adverse Events after index TIA (JAMA 2000; 284: 2901-6)

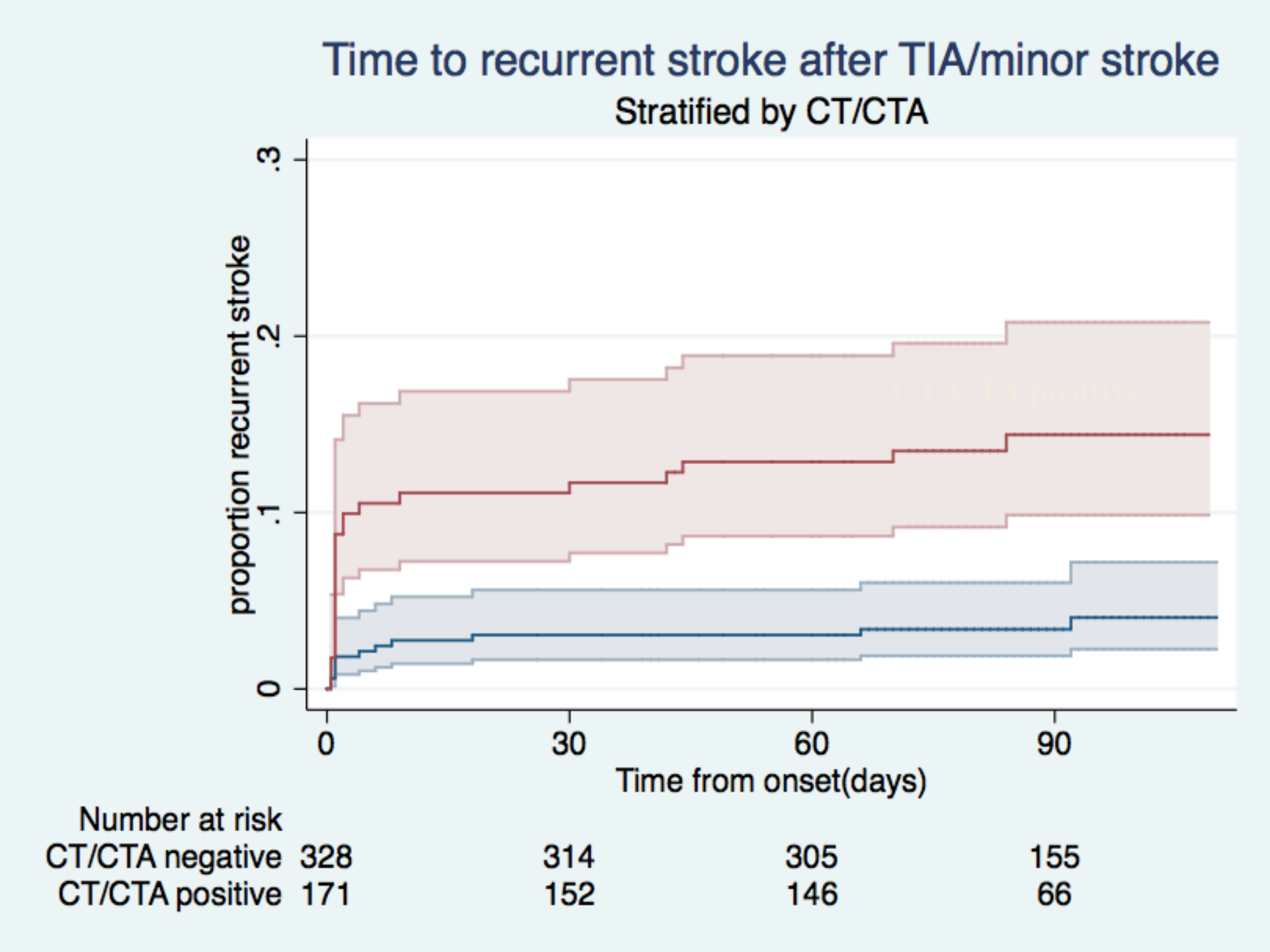


# Risk of Stroke, MI, Death after TIA – **21.8%** at one year



# Disposition: Management of Minor Stroke and TIA

1. Make the correct diagnosis.
2. Use imaging tools to help you.
3. Risk stratify your patient
   - ABCD2 does not work (Perry CMAJ)
   - Risk depends on mechanism
     - Large artery – carotids and verts
     - Atrial fibrillation
     - Lacunar or small vessel


Time to recurrent stroke after TIA/minor stroke
Stratified by CT/CTA
proportion recurrent stroke
0
.1
.2
.3
CT/CTA positive
0
30
60
90
Time from onset(days)
Number at risk
CT/CTA negative 328 314 305 155
CT/CTA positive 171 152 146 66

# Antiplatelets: FASTER

- 2 x 2 factorial design
- ASA, ASA + clopidogrel, ASA + simvastatin, ASA + clopidogrel + simvastatin
- 7500 patients
- **randomise within 12 hours of symptom onset**

# FASTER study

[Kennedy et al. Lancet Neurology 2008]

| | Risk Difference ($CI_{95}$) | Risk Ratio ($CI_{95}$) |
|---|---|---|
| Clopidogrel v Placebo | -3.8% (-9.4 to 1.9) | 0.7 (0.3 to 1.2) |
| Simvastatin v Placebo | 3.3% (-2.3 to 8.9) | 1.5 (0.8 to 2.8) |

# FASTER study

[Kennedy et al. Lancet Neurology 2008]

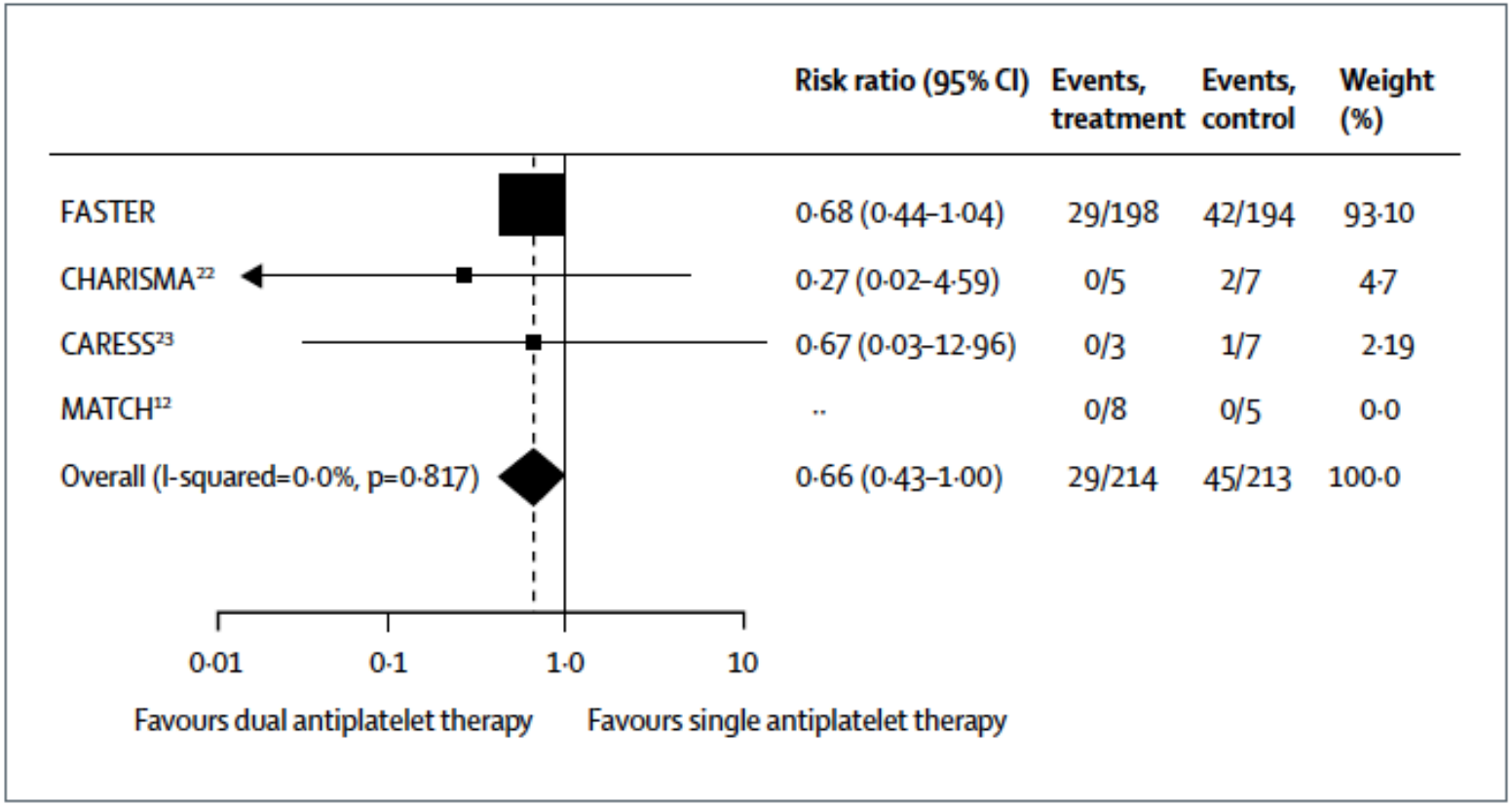



***Figure 2:*** **Fixed-effects meta-analysis of 90-day risk of tertiary efficacy outcome**

Tertiary outcome was combined outcome of stroke, transient ischaemic attack, acute coronary syndrome, and all-cause death in patients enrolled within 24 h of onset of stroke or transient ischaemic attack. Note that x-axis is a logarithmic scale.

# CHANCE

**Clopidogrel plus aspirin vs aspirin alone in acute high-risk transient ischemic attack or minor ischemic stroke‡**

| Outcomes | Clopidogrel plus aspirin | Aspirin alone | At 90 d | |
|---|---|---|---|---|
| | | | RRR (95% CI) | NNT (CI) |
| Stroke | 8.2% | 12% | 30% (17 to 41)§ | 29 (20 to 54)§ |
| Vascular composite‖ | 8.4% | 12% | 30% (17 to 40)§ | 29 (20 to 54)§ |
| Ischemic stroke | 7.9% | 11% | 31% (18 to 42)§ | 29 (20 to 53)§ |
| | | | RRI (CI) | NNH (CI) |
| Moderate-to-severe bleeding | 0.31% | 0.27% | 12% (–132 to 67) | NS |
| Hemorrhagic stroke | 0.3% | 0.3% | 0.1% (–62 to 166)§ | NS§ |

Wang Y, Wang Y, Zhao X, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369:11-9.

# Anticoagulate A.fib Immediately?

IST trial

- fixed dose sc heparin 15000 U
- reduced recurrent stroke slightly in those with afib

HAEST trial

- LMWH
- ~7% risk of early stroke in both groups

# Quality Improvement

- Early referral to a TIA clinic
- Wu C et al
  - Reduction in stroke risk at 90d of 50%

- Probably sensible but evidence is lacking?
- What interventions exactly?

# Speed of Revascularization

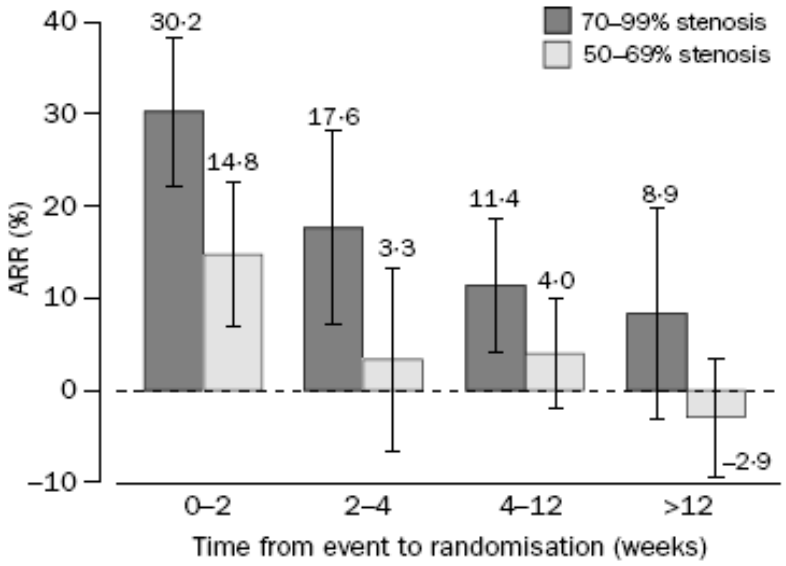
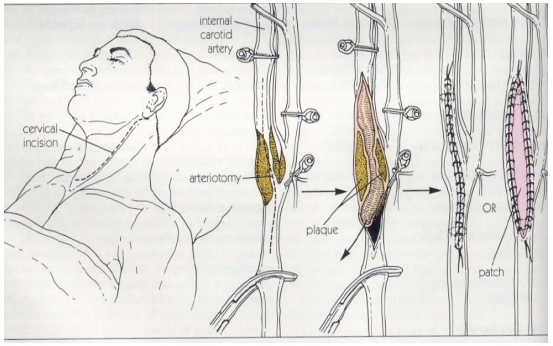



Figure 5: **Absolute reduction with surgery in the 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery in patients with 50–69% stenosis and ⩾70% stenosis without near-occlusion stratified by the time from last symptomatic event to randomisation**

Numbers above bars indicate actual absolute risk reduction. Vertical bars are 95% CIs.




Stromberg et al. Stroke May 2012

- 11.5% 0-2d
- 3.6% 3-7d

# Calgary Model

- Diagnose
- Image everyone – CT and CTA
- Clean CT and CTA
  - →HOME with outpatient clinic follow-up
  - →ASA + clopidogrel
  - →If a.fib then start anticoagulation immediately (coumadin, NOACs)

- Abnormal CTA
  - →Intracranial occlusion → TEMPO trial to thrombolyse
  - →Carotid atherosclerotic disease – admit for endarterectomy or medical mgmt of carotid disease
  - →Other occlusion – admit and observe

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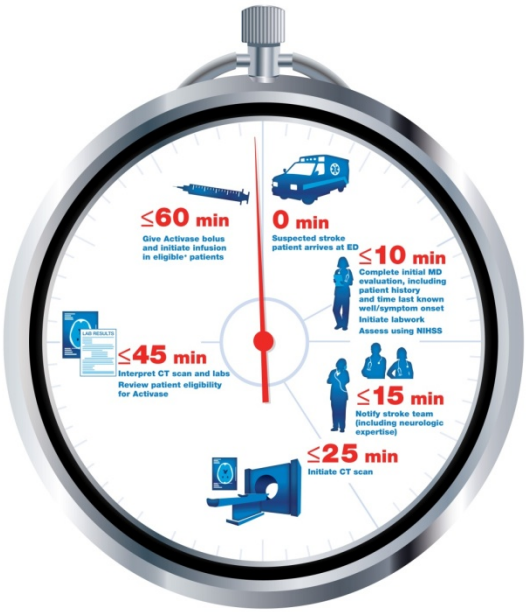
# DOOR-TO-NEEDLE IMPROVEMENT PROJECT

# Time lost is Brain lost !

## 1.9 million neurons lost per minute


Stroke. 2006 Jan;37(1):263-6

# Speed matters

ORIGINAL CONTRIBUTION

## Time to Treatment With Intravenous Tissue Plasminogen Activator and Outcome From Acute Ischemic Stroke

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**Importance** Randomized clinical trials suggest the benefit of intravenous tissue-type plasminogen activator (tPA) in acute ischemic stroke is time dependent. However, modest sample sizes have limited characterization of the extent to which onset to treatment (OTT) time influences outcome; and the generalizability of findings to clinical practice is uncertain.

**Objective** To evaluate the degree to which OTT time is associated with outcome among patients with acute ischemic stroke treated with intraveneous tPA.

**Design, Setting, and Patients** Data were analyzed from 58 353 patients with acute ischemic stroke treated with tPA within 4.5 hours of symptom onset in 1395 hospitals participating in the Get With The Guidelines-Stroke Program, April 2003 to March 2012.

**Main Outcomes and Measures** Relationship between OTT time and in-hospital mortality, symptomatic intracranial hemorrhage, ambulatory status at discharge, and discharge destination.

**Results** Among the 58 353 tPA-treated patients, median age was 72 years, 50.3% were women, median OTT time was 144 minutes (interquartile range, 115-170), 9.3% (5404) had OTT time of 0 to 90 minutes, 77.2% (45 029) had OTT time of 91 to 180 minutes, and 13.6% (7920) had OTT time of 181 to 270 minutes. Median pretreatment National Institutes of Health Stroke Scale documented in 87.7% of patients was 11 (interquartile range, 6-17). Patient factors most strongly associated with shorter OTT included greater stroke severity (odds ratio [OR], 2.8; 95% CI, 2.5-3.1 per 5-point increase), arrival by ambulance (OR, 5.9; 95% CI, 4.5-7.3), and arrival during regular hours (OR, 4.6; 95% CI, 3.8-5.4). Overall, there were 5142 (8.8%) in-hospital deaths, 2873 (4.9%) patients had intracranial hemorrhage, 19 491 (33.4%) patients achieved independent ambulation at hospital discharge, and 22 541 (38.6%) patients were discharged to home. Faster OTT, in 15-minute increments, was associated with reduced in-hospital mortality (OR, 0.96; 95% CI, 0.95-0.98; $P < .001$), reduced symptomatic

INTRAVENOUS (IV) TISSUE-TYPE PLASminogen activator (tPA) is a treatment of proven benefit for select patients with acute ischemic stroke as long as 4.5 hours after onset.[1,2] Available evidence suggests a strong influence of time to therapy on the magnitude of treatment benefit. In stroke animal models, time to reperfusion is a dominant determinant of final infarct volume.[3] In human patients, imaging studies show the volume of ir-

JAMA. 2013;309(23):2480-2488

*For 1000 treated patients, every 15-minutes of faster treatment resulted in:*

- 18 more patients with improved ambulation at discharge
- 8 more with fully independent ambulation
- 7 more discharged home


# Reducing in-hospital delay to 20 minutes in stroke thrombolysis

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## ABSTRACT

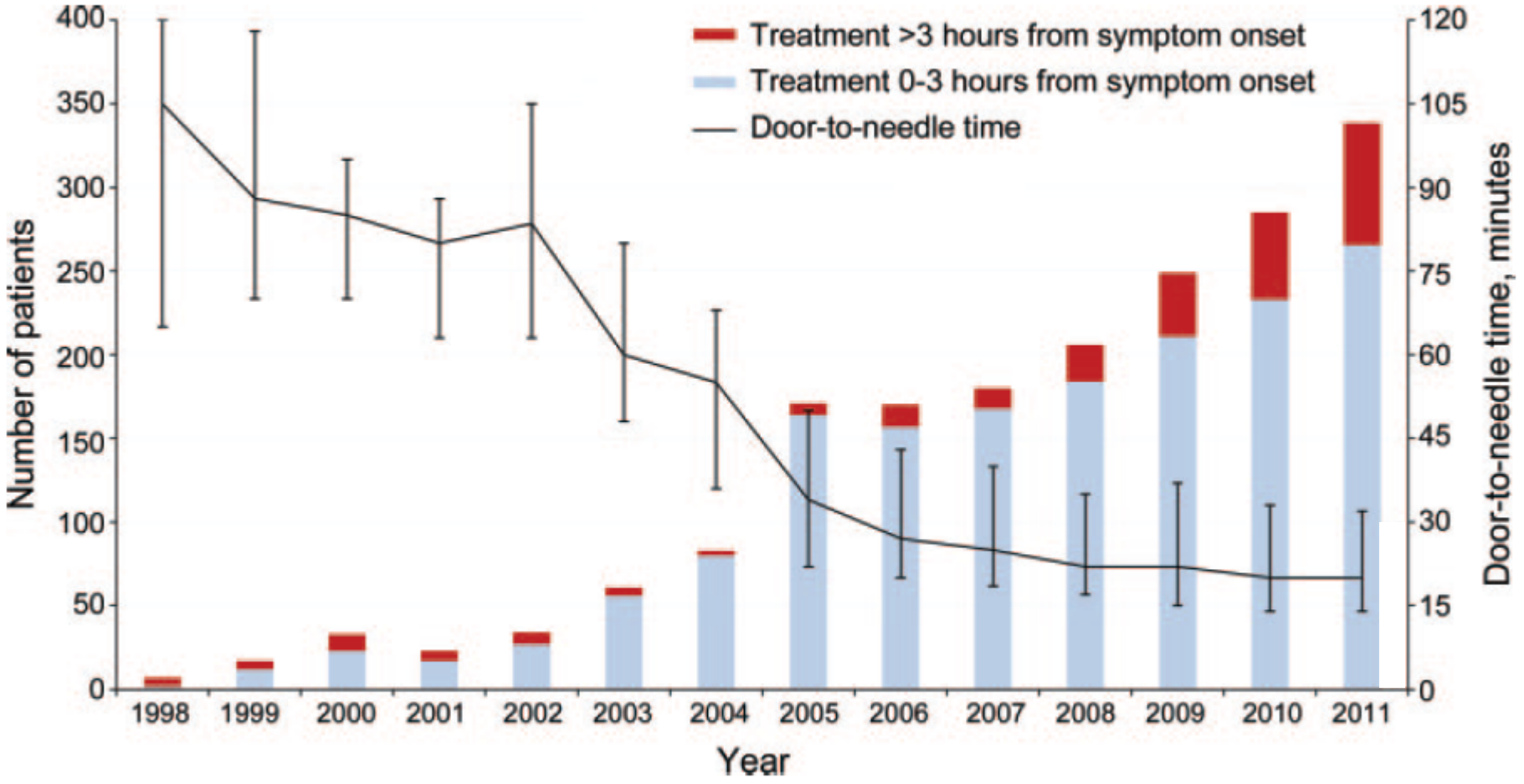
**Objectives:** Efficacy of thrombolytic therapy for ischemic stroke decreases with time elapsed from symptom onset. We analyzed the effect of interventions aimed to reduce treatment delays in our single-center observational series.

**Methods:** All consecutive ischemic stroke patients treated with IV alteplase (tissue plasminogen activator [tPA]) were prospectively registered in the Helsinki Stroke Thrombolysis Registry. A series of interventions to reduce treatment delays were implemented over the years 1998 to 2011. In-hospital delays were analyzed as annual median door-to-needle time (DNT) in minutes, with interquartile range.

**Results:** A total of 1,860 patients were treated between June 1995 and June 2011, which included 174 patients with basilar artery occlusion (BAO) treated mostly beyond 4.5 hours from symptom onset. In the non-BAO patients, the DNT was reduced annually, from median 105 minutes (65–120) in 1998, to 60 minutes (48–80) in 2003, further on to 20 minutes (14–32) in 2011. In 2011, we treated with tPA 31% of ischemic stroke patients admitted to our hospital. Of these, 94% were treated within 60 minutes from arrival. Performing angiography or perfusion imaging doubled the in-hospital delays. Patients with in-hospital stroke or arriving very soon from symptom onset had longer delays because there was no time to prepare for their arrival.

**Conclusions:** With multiple concurrent strategies it is possible to cut the median in-hospital delay to 20 minutes. The key is to do as little as possible after the patient has arrived at the emergency room and as much as possible before that, while the patient is being transported. *Neurology*® 2012;79:306–313

Figure 1 Number of annually treated patients and median door-to-needle times




Annual patients, with those treated beyond 3 hours in red (bars, left axis) and median door-to-needle time in minutes with interquartile range (line, right axis). Total n = 1,686. The projected number of patients for 2011 is based on the observed numbers of the first 6 months.

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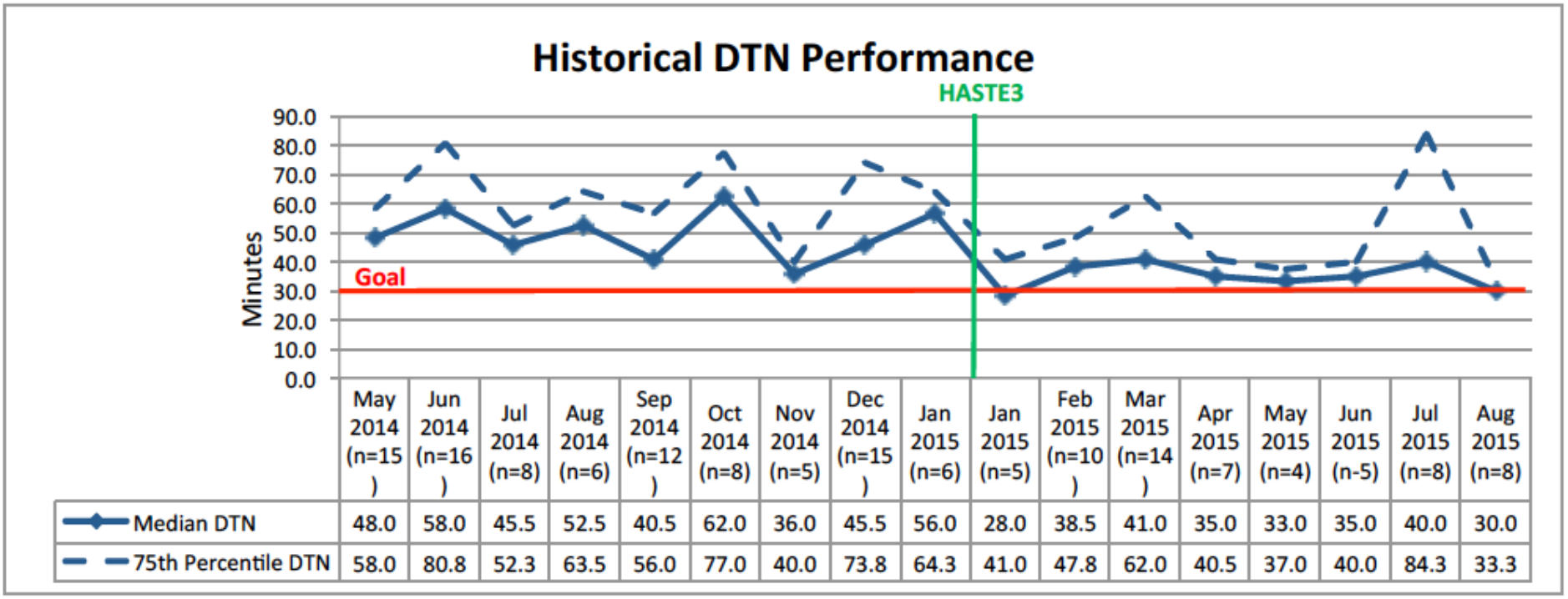
# Calgary DNT




| | May 2014 (n=15) | Jun 2014 (n=16) | Jul 2014 (n=8) | Aug 2014 (n=6) | Sep 2014 (n=12) | Oct 2014 (n=8) | Nov 2014 (n=5) | Dec 2014 (n=15) | Jan 2015 (n=6) | Jan 2015 (n=5) | Feb 2015 (n=10) | Mar 2015 (n=14) | Apr 2015 (n=7) | May 2015 (n=4) | Jun 2015 (n-5) | Jul 2015 (n=8) | Aug 2015 (n=8) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Median DTN | 48.0 | 58.0 | 45.5 | 52.5 | 40.5 | 62.0 | 36.0 | 45.5 | 56.0 | 28.0 | 38.5 | 41.0 | 35.0 | 33.0 | 35.0 | 40.0 | 30.0 |
| 75th Percentile DTN | 58.0 | 80.8 | 52.3 | 63.5 | 56.0 | 77.0 | 40.0 | 73.8 | 64.3 | 41.0 | 47.8 | 62.0 | 40.5 | 37.0 | 40.0 | 84.3 | 33.3 |