Medical treatment of acute ischaemic stroke

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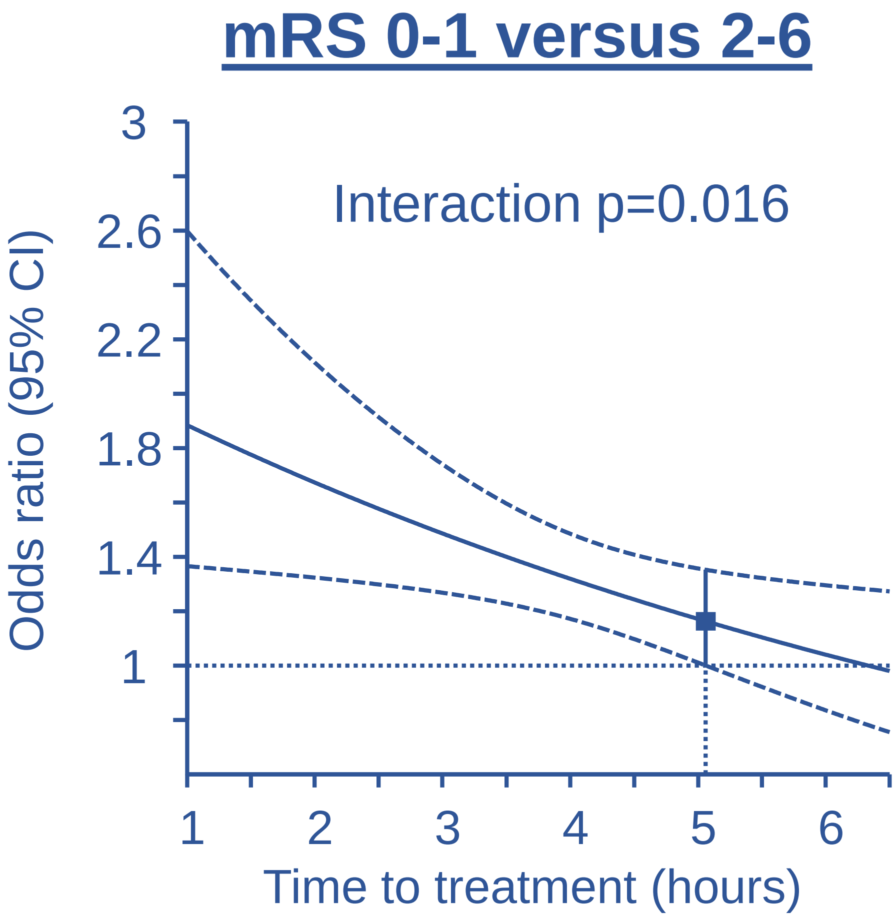
NHS Lothian

- Thrombolysis
  - Alteplase
  - Low versus high dose
  - Tenectoplase
  - Unknown time of onset
  - Mild stroke
- Antiplatelets
- Blood pressure lowering
- Stroke unit

Why is individual participant data meta-analysis important?

- Analysis can be standardised across studies
- Missing data can be accounted for at the individual level
- Prognostic factors adjusted for consistently (e.g. age, time and NIHSS)
- Effect in specific subgroups of participants can be obtained across studies

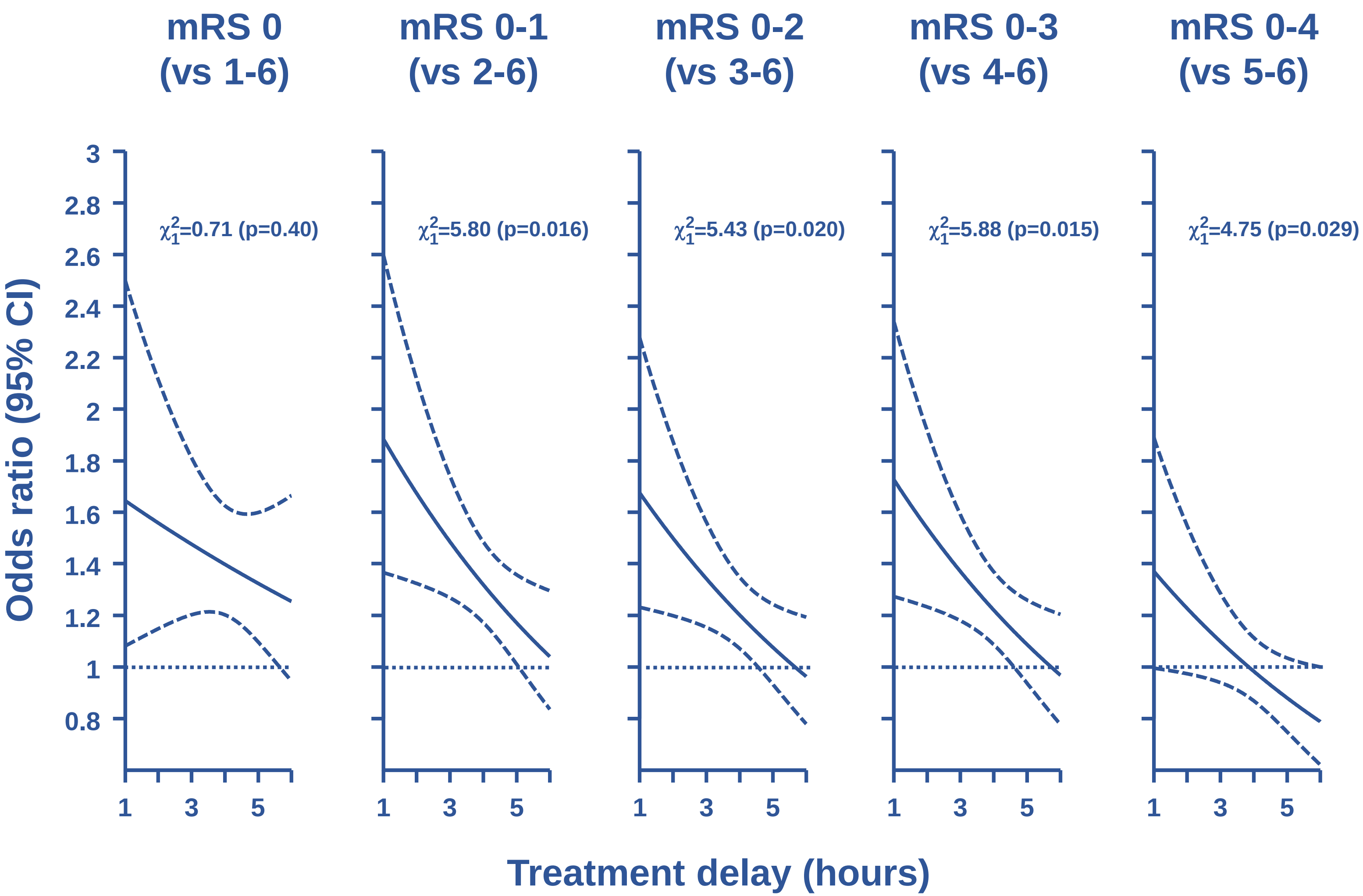
1. The proportional benefits of alteplase increase with earlier treatment (independently of age and severity)



Slope not significantly altered by age or stroke severity

Emberson et al. Lancet (2014)

1. The proportional benefits of alteplase increase with earlier treatment (independently of age and severity)

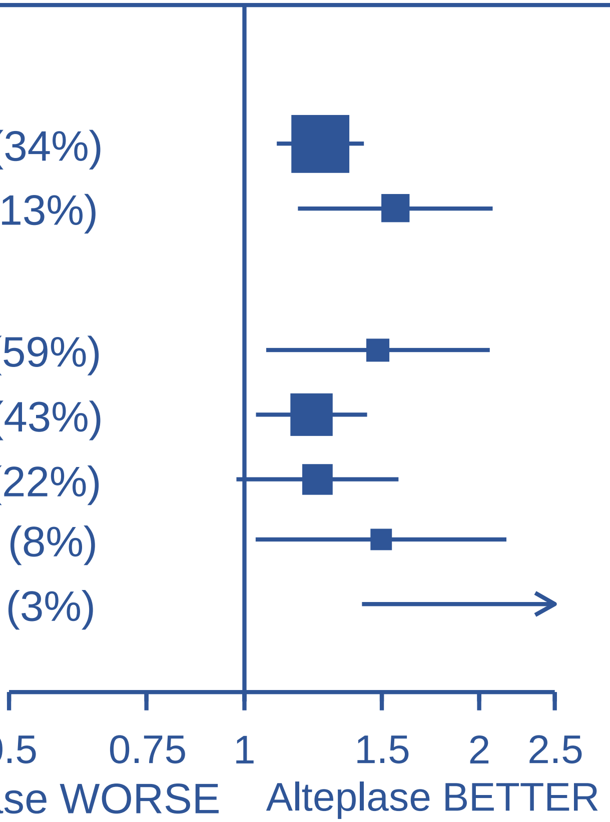


Lees et al. Stroke (2016)

2. No evidence that age or severity modify these proportional benefits

mRS 0-1 versus 2-6

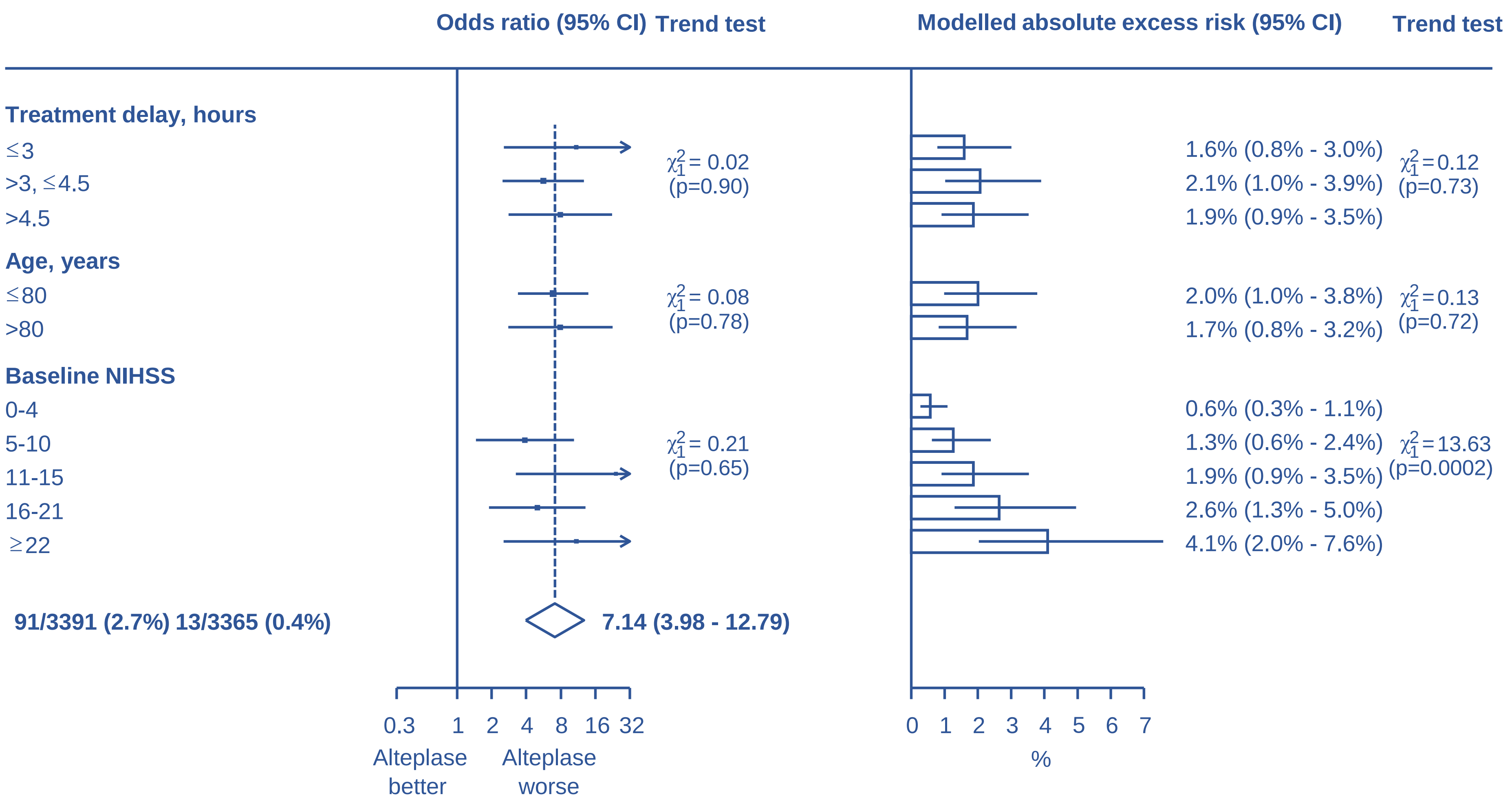
	Alteplase (n=3391)	Control (n=3365)	Odds ratio (95% CI)
Age (years)			
≤80	990/2512 (39%)	853/2515 (34%)	1.25 (1.10 - 1.42)
>80	155/879 (18%)	112/850 (13%)	1.56 (1.17 - 2.08)
Baseline NIHSS			
0-4	237/345 (69%)	189/321 (59%)	1.48 (1.07 - 2.06)
5-10	611/1281 (48%)	538/1252 (43%)	1.22 (1.04 - 1.44)
11-15	198/794 (25%)	175/808 (22%)	1.24 (0.98 - 1.58)
16-21	77/662 (12%)	55/671 (8%)	1.50 (1.03 - 2.17)
≥22	22/309 (7%)	8/313 (3%)	3.25 (1.42 - 7.47)



Emberson et al. Lancet (2014)

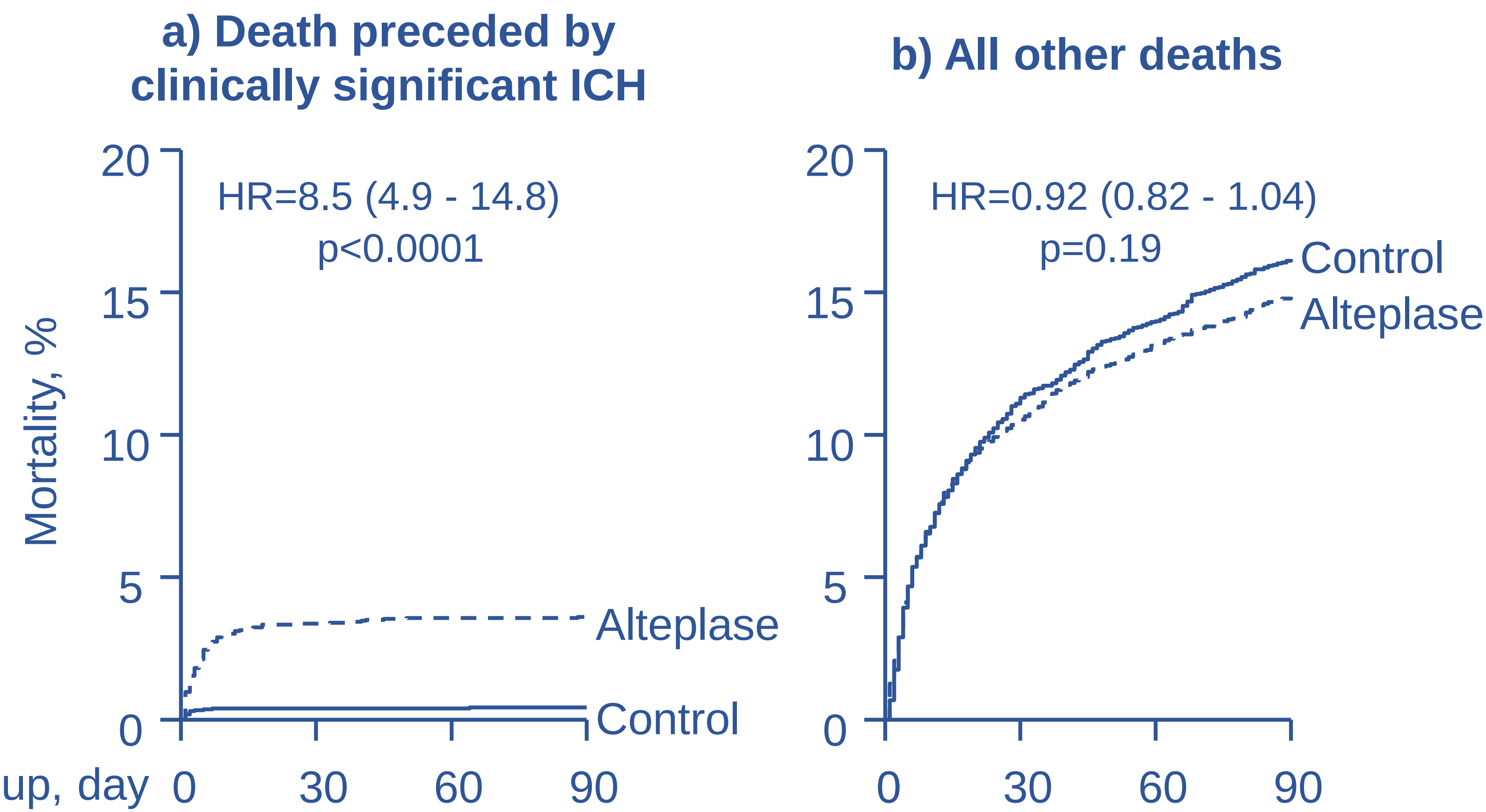
3a. Increased early risk of death from ICH…

Fatal ICH within 7 days



Whiteley et al. Lancet Neurology (2016)

3b. BUT, no significant effect on other early causes of death, or on later deaths

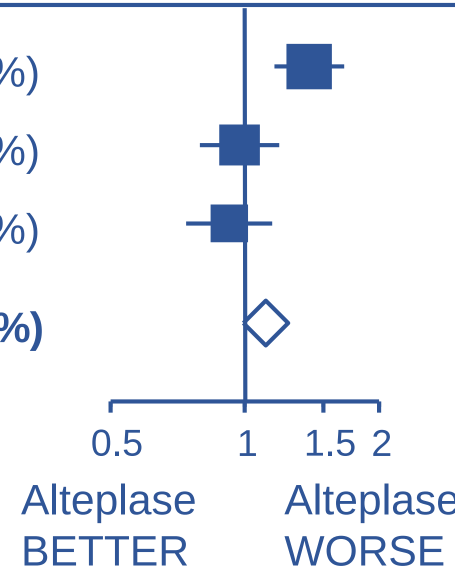


Number dead								
Alteplase	0	111	117	118	0	349	436	490
Control	0	13	13	14	0	379	469	542

Whiteley et al. Lancet Neurology (2016)

3b. BUT, no significant effect on other early causes of death, or on later deaths

Risk period	Alteplase (n=3391)	Control (n=3365)	HR (95% CI)
	No. (%) dead within 90 days		
Days 1-7 *	282 (8.3%)	204 (6.1%)	1.39 (1.16-1.67)
Days 8-30	178 (5.2%)	188 (5.6%)	0.97 (0.79-1.20)
Days 31-90	148 (4.4%)	164 (4.9%)	0.92 (0.74-1.15)
Subtotal: 90-day mortality	**608 (17.9%)**	**556 (16.5%)**	**1.11 (0.99-1.25)**



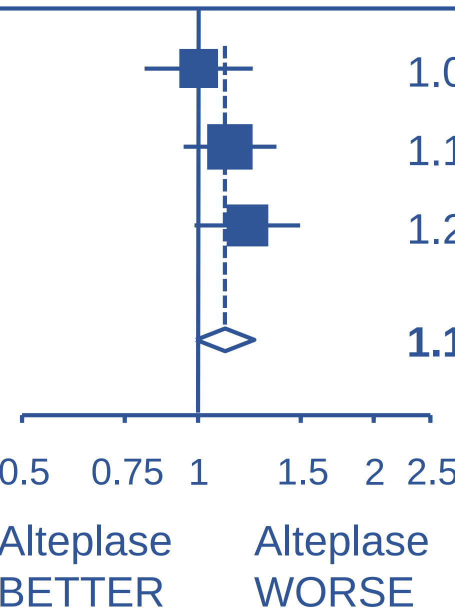
* Includes 91 vs 13 deaths from ICH and 191 vs 191 deaths from other causes

P-value for non-proportionality <0.0001

Emberson et al. Lancet (2014)

4. Among those treated <u>earlier</u>, *suggestion* that early hazard may be followed by later benefit

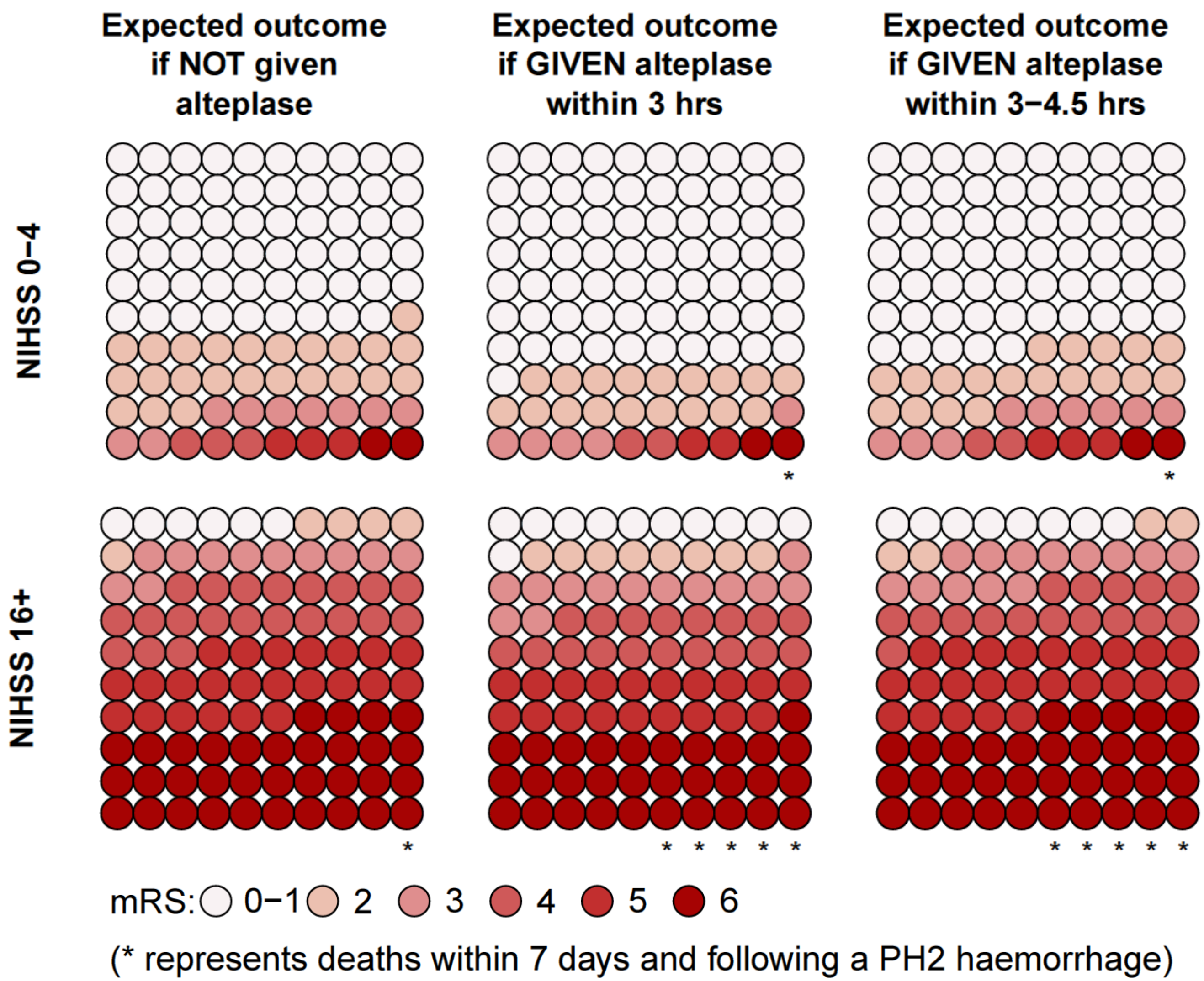
Treatment delay (hours)	No. (%) dead within 90 days: Alteplase (n=3391)	No. (%) dead within 90 days: Control (n=3365)	HR (95% CI)
≤3	175 (22.2%)	166 (21.8%)	1.00 (0.81-1.24)
>3, ≤4.5	232 (16.9%)	229 (15.9%)	1.14 (0.95-1.36)
>4.5	201 (16.4%)	161 (13.8%)	1.22 (0.99-1.50)
All patients	**608 (17.9%)**	**556 (16.5%)**	**1.11 (0.99-1.25)**



Trend p-value across 3 groups = 0.21

Emberson et al. Lancet (2014)

5. Absolute balance of benefit vs risk depends chiefly on treatment delay and stroke severity



Whiteley et al. Lancet Neurology (2016)

1. Alteplase within 4.5 hours improves the odds of surviving with no significant disability, with earlier treatment resulting in bigger proportional benefits

2. No evidence that age or severity alter these proportional benefits

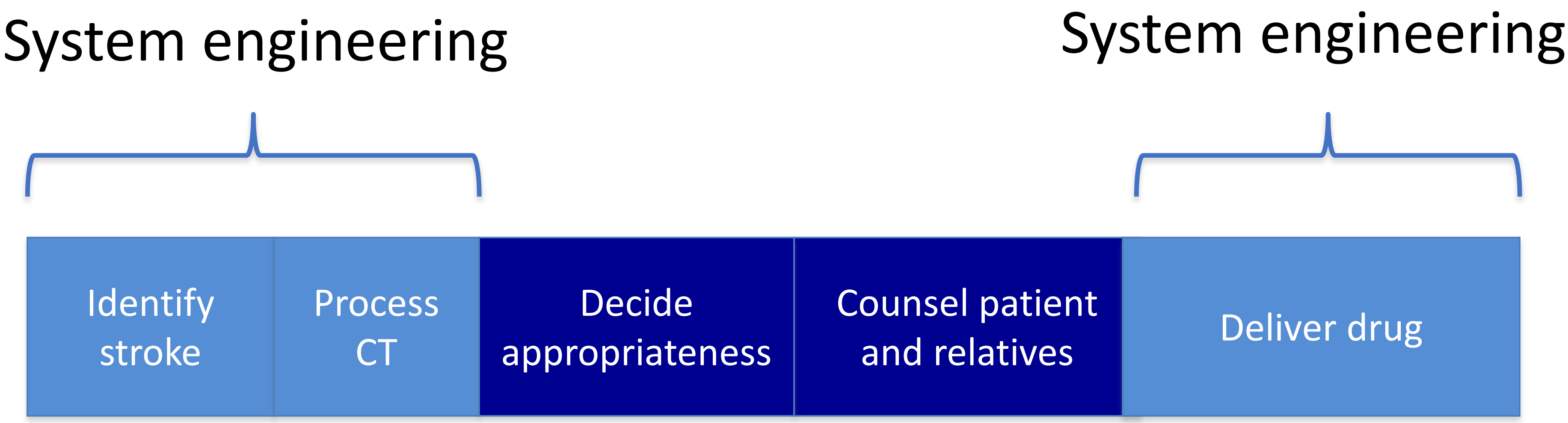
3. Increased early risk of death from ICH, but no significant effect on other causes of early death, or on later deaths

4. Among those treated <u>earlier</u>, *suggestion* that this early hazard may be followed by later mortality benefits

5. Absolute balance of benefit vs risk depends chiefly on treatment delay (which determines benefit) and stroke severity (which determines absolute hazard)

→Treatm patients with alteplase as soon as possible at all ages and stroke severities

In hospital delays



Absolute contraindications

- CT brain imaging reveals acute intracranial haemorrhage
- Active or recent bleeding at a non-compressible site

Relative contraindications

- Presentation more than 4·5 h from time last seen well
- Known coagulopathy
- Blood pressure more than 185/110 mm Hg
- Current treatment with an anticoagulant unless laboratory tests results are normal
- Prior intracranial haemorrhage within 3 months
- Prior ischaemic stroke within 3 months
- Systemic malignancy
- Intracranial malignant neoplasm
- Intracranial arterial dissection
- Blood glucose less than 2 mM or greater than 22 mmol/L
- Suspected or diagnosed aortic dissection
- Large (greater than 10 mm) unruptured and unsecured intracranial aneurysm
- Previous high burden of cerebral microbleeds (more than 10)
- Pregnancy

Absolute contraindications

- CT brain imaging reveals acute intracranial haemorrhage
- Active or recent bleeding at a non-compressible site

Relative contraindications

- Presentation more than 4·5 h from time last seen well *with no imaging selection*
- Known coagulopathy *but do not measure this*
- Blood pressure more than 185/110 mm Hg *but evidence is weak*
- Current treatment with an anticoagulant unless laboratory tests results are normal
- Prior intracranial haemorrhage within 3 months *sICH is increased*
- Prior ischaemic stroke within 3 months
- Systemic malignancy *common and haemorrhage is rare*
- Intracranial malignant neoplasm *are the symptoms really due to stroke?*
- Intracranial arterial dissection *but do not look for this specifically*
- Blood glucose less than 2 mM or greater than 22 mmol/L *treat hypoglycaemia*
- Suspected or diagnosed aortic dissection
- Large (greater than 10 mm) unruptured and unsecured intracranial aneurysm
- Previous high burden of cerebral microbleeds (more than 10) *no indication here*
- Pregnancy *several successfully treated women*

Dose of alteplase

Low does alteplase (0.6mg/kg) versus high dose alteplase (0.9mg/kg) leads to:

lower risk of fatal haemorrhage -1.9%
lower proportion with good outcome -2.1%

→***No advantage in using lower dose alteplase, unless there are particular concerns about early death from haemorrhage***

Anderson, ENCHANTED trial NEJM 2016

Selection of patients for later treatment

WAKE-UP

stroke of unknown symptom onset was of overall benefit if MRI DWI +ve and no FLAIR lesion was present

OR for mRS 0 –1: 1.61; 95% CI, 1.09 to 2.36.

EXTEND

4.5 to 9 hrs with CT or MRI perfusion lesion–ischemic core mismatch of

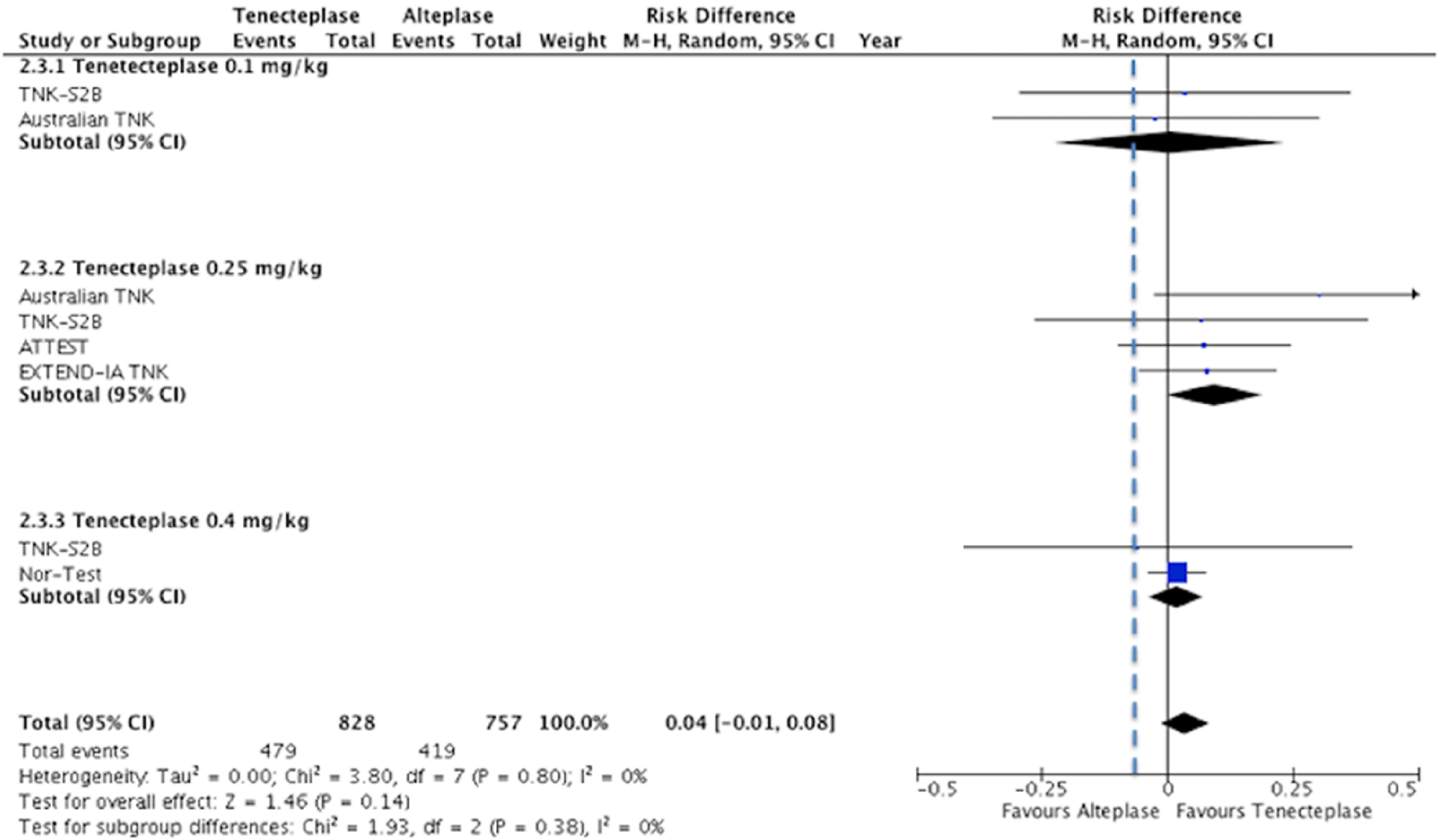
- >1.2 (hypoperfusion) /(ischemic core
- absolute difference in volume greater than 10 ml, and an ischemic-core volume of less than 70 ml

OR for mRS 0-1: 1.44 95% CI, 1.01 to 2.06;

N Engl J Med 2019; 380:1795-1803

N Engl J Med 2018; 379:611-622

Tenecteplase has superior fibrinolytic activity and ↑ reperfusion rate



For outcome mRS 0-1

Ongoing trials: TEMPO-2: NCT02398656; TASTE: ACTRN12613000243718; TWIST: NCT03181360

Stroke. 2019;50:2156–2162

What is a mild stroke?

Stroke symptoms that would not be very disabling if they were persistent

But 'disabling' depends on the person
A mild **impairment** *may lead to a limited* **activity** *that may reduce* **participation**
e.g. mild non-dominant hand clumsiness for a musician

But prediction of recovery or worsening is imperfect

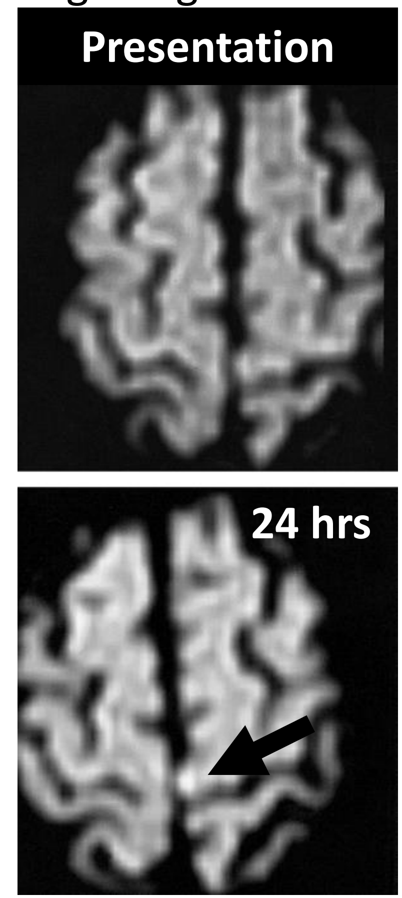
Diagnostic difficulty in mild stroke

- Mild stroke is harder to diagnosis, to rule in or to rule out
- Urgent MR imaging not easily available in most UK centres, not always ‘positive’ in acute ischaemic stroke

In clinical trials of mild stroke, a substantial proportion of randomised patients had a ‘stroke mimic’:

- PRISMS ≤5 NIHSS 13%
- NORTEST median NIHSS 4 17%

Right leg weakness



Predicting disability after mild stroke

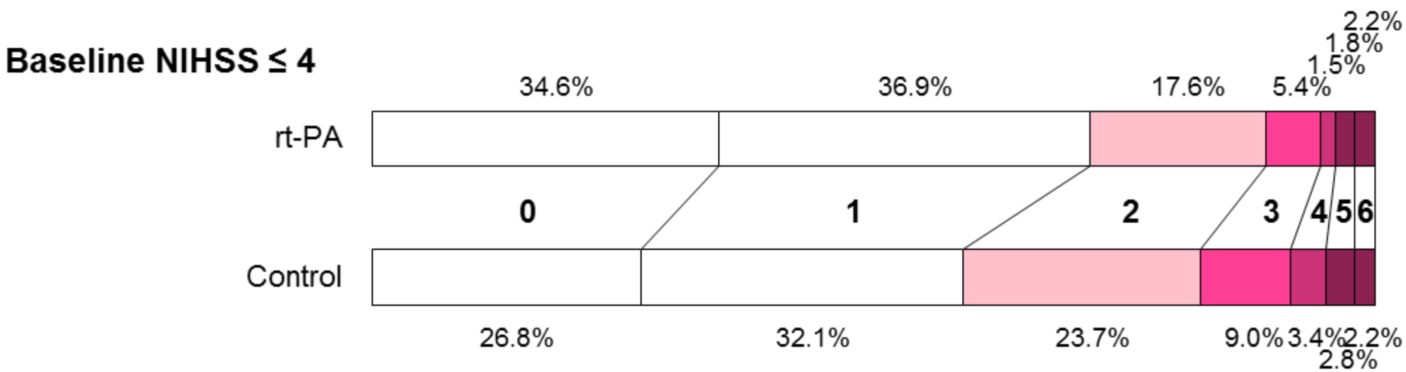
In large and small hospital based cohorts, a 25-30% of mild stroke patients at least changed their daily activities.

mRS is insensitive to cognitive and other more minor poor outcomes

Validated clinical prediction scores	AUC ~0.82
Large artery occlusion + minor symptoms	OR 2.4 (1.4-4) for mRS>2
‘Head up test’ + “ “ “	yet to be validated

→ *Some important impairments and reduced participation not measured by mRS*
→ *No perfect test to differentiate future disability from good recovery*

Expected mRS at 3-6 months, with or without rt-PA within 3 hours



My opinion

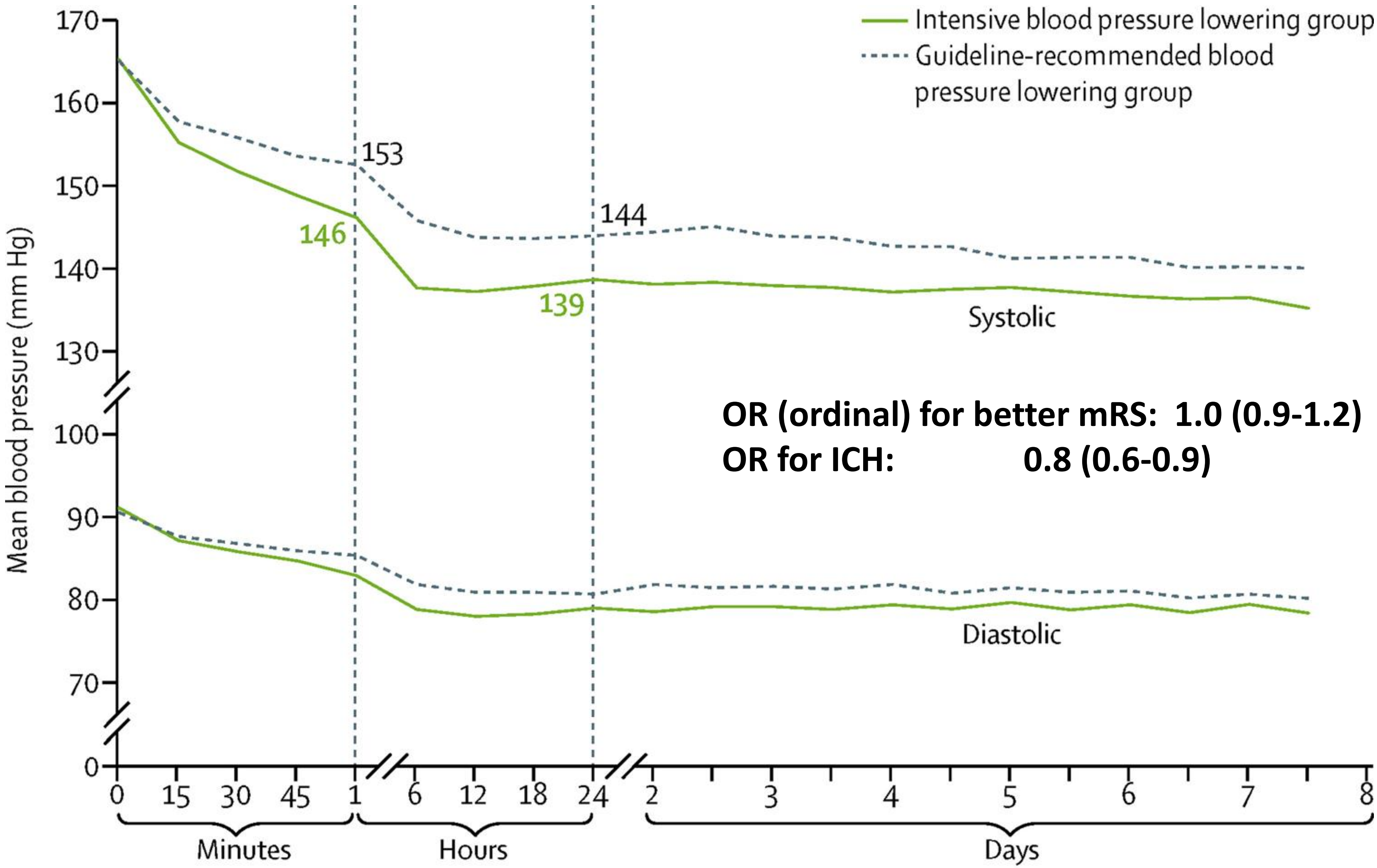
Proceed with alteplase if I am:

- Sure of ischaemic stroke diagnosis
- Deficit is disabling *to this patient* at assessment
- Small risk of intracranial haemorrhage is acceptable *to this patient*

"For patients with minor stroke considered disabling at assessment, intravenous alteplase is recommended. (KSU Grade A)"

BP management in ENCHANTED

Non-invasive using *automated* devices



OR (ordinal) for better mRS: 1.0 (0.9-1.2)

OR for ICH: 0.8 (0.6-0.9)

No evidence of benefit of acute blood pressure lowering on death or disability in the short term after acute ischaemic stroke:

- Different agents
- Degree of BP lowering
- Whether very early or later after stroke

→where BP can be lowered <185mmHg systolic rapidly, then reasonable to do so but prioritise speedy treatment over blood pressure control

Aspirin 300mg by mouth or rectum

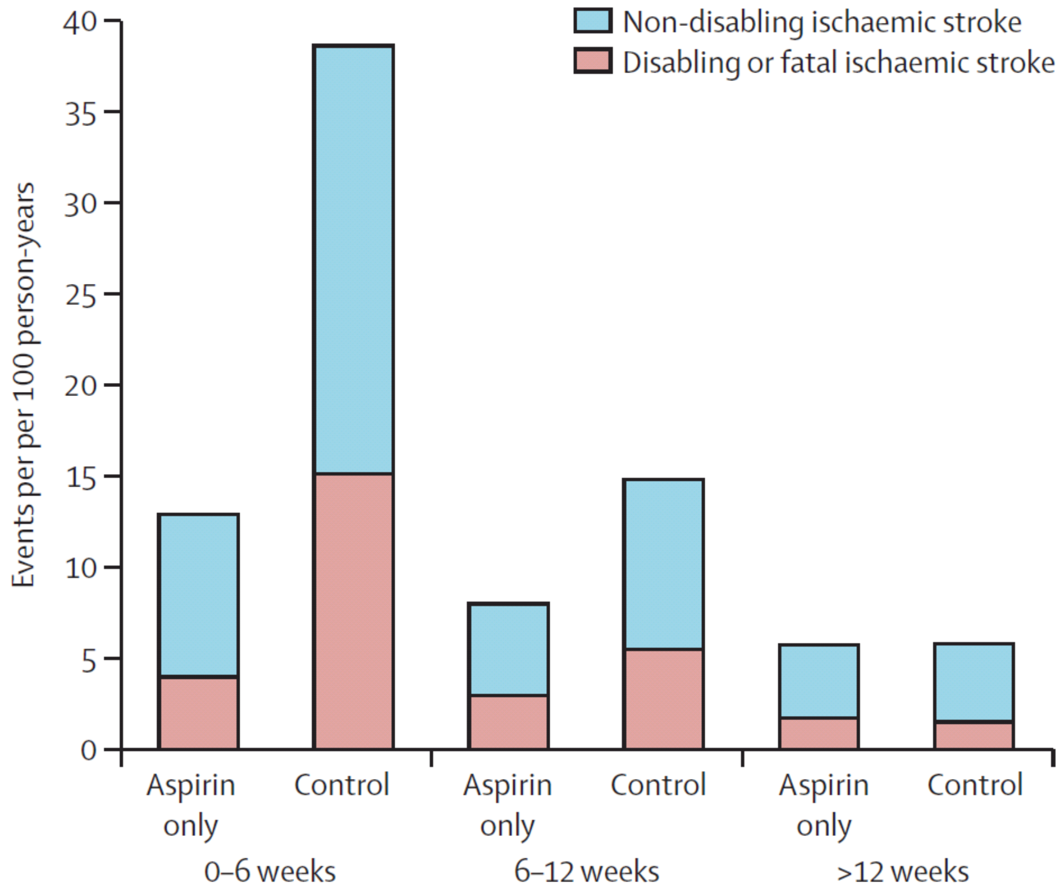
- For every 1000 patients treated,
  - 12 avoid death or dependency,
  - an extra 10 make a complete recovery
  - risk of haemorrhage is low (1-2 per 1000) and is outweighed by the benefits
- Is of net benefit for a wide range of patients

Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke

Pooled data from all trials of aspirin in acute or chronic prevention after stroke or TIA (n=15,778)

Most effect of aspirin <3 months.

Highest stroke risk is <3 months

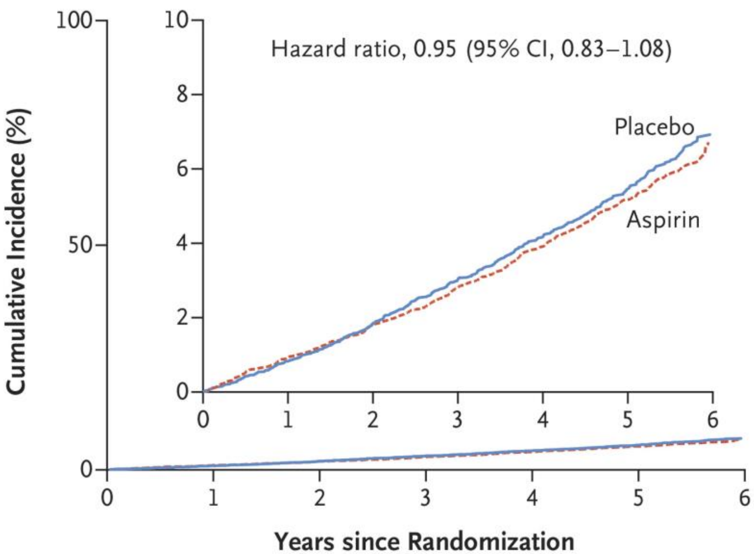


→ ***Give aspirin or clopidogrel soon after symptom onset***

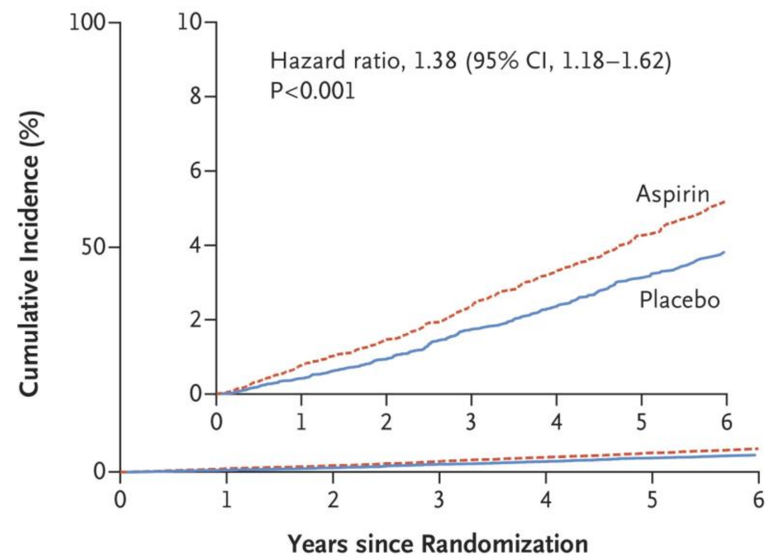
https://doi.org/10.1016/S0140-6736(16)30468-8

Effect of Aspirin on Cardiovascular Events & Bleeding in Healthy Elderly

Cumulative incidence of MI and stroke



Cumulative incidence severe bleeding



Also significant ↑ in mortality by 6 years in aspirin group (HR 1.14; 95% CI, 1.01- 1.29)

→ avoid long-term aspirin to prevent stroke in patients without a definite stroke or TIA

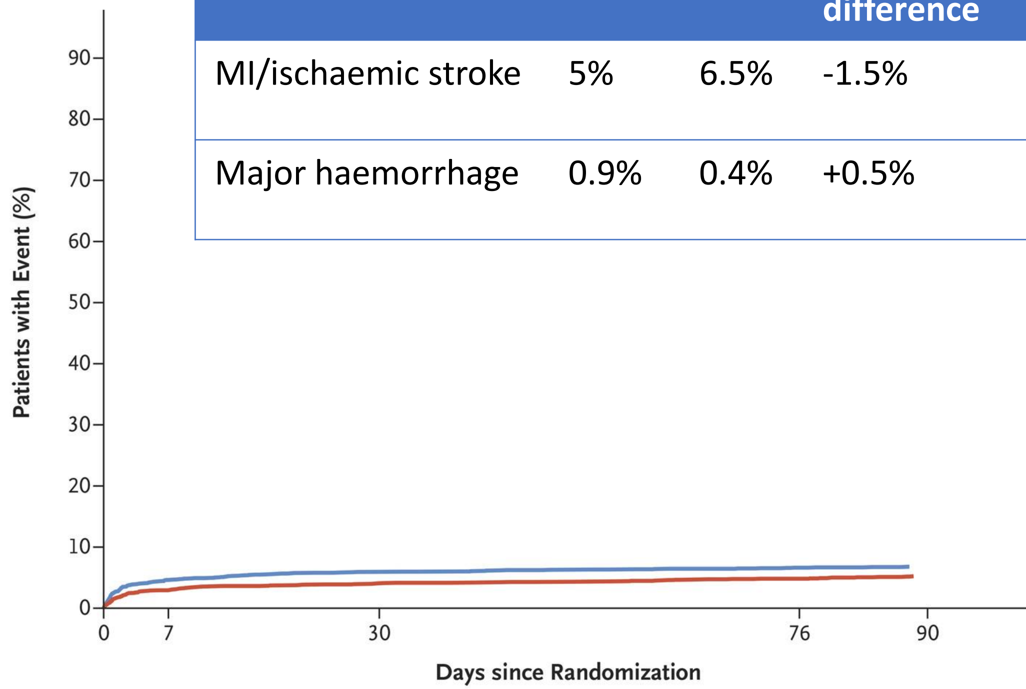
Clopidogrel and aspirin versus aspirin alone in acute ischemic stroke and high-risk TIA

'high risk': minor ischaemic stroke or TIA with ABCD^2 score of >3 (age>60, BP>140/90,clinical features, duration, diabetes)

Loading dose of clopidogrel then aspirin 75-300mg plus clopidogrel 75 mg od.

Most benefit < 1 month

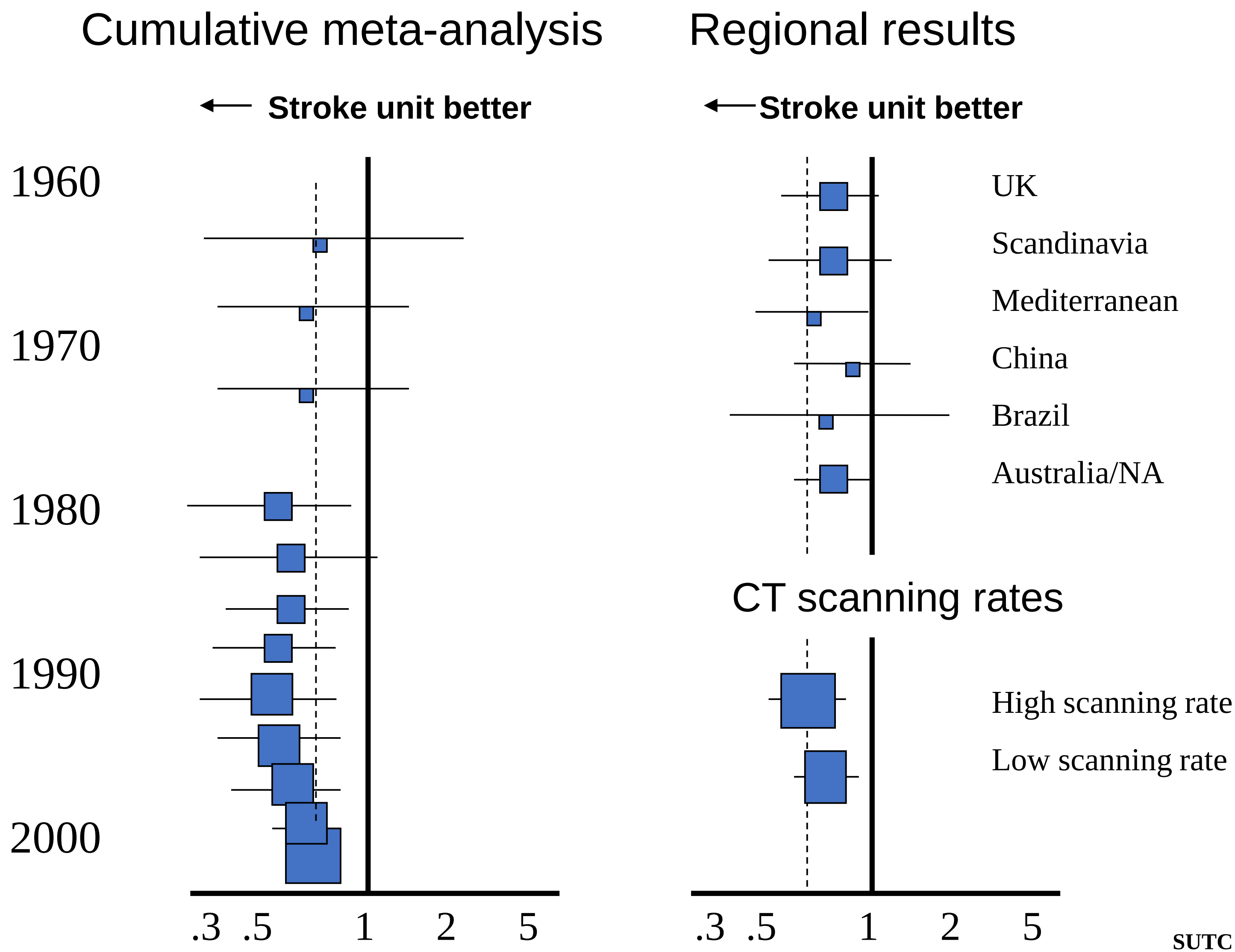
	2AP	1AP	90 day risk difference
MI/ischaemic stroke	5%	6.5%	-1.5%
Major haemorrhage	0.9%	0.4%	+0.5%



→ consider dual antiplatelets for 1 month for those with definite TIA or minor stroke with high risk features

DOI: 10.1056/NEJMoa1800410

Stroke unit - death or institutional care



SUTC (unpublished)

Preventing stroke:

1. Antiplatelet
2. Blood pressure lowering
3. LDL-cholesterol lowering
4. Look for AF
5. Look for carotid stenosis
6. Stopping smoking advice
7. Diet advice
8. Look for PFO

Carotid stenosis

	Absolute risk reduction in stroke			
	Delay to endarterectomy			
Stenosis	<2 wks	2-4 wks	4-12 wks	>12 wks
70-99%	-30%	-17%	-11%	-9% (NS)
50-69%	-15%	-3%	-4%	0

But since these trials:

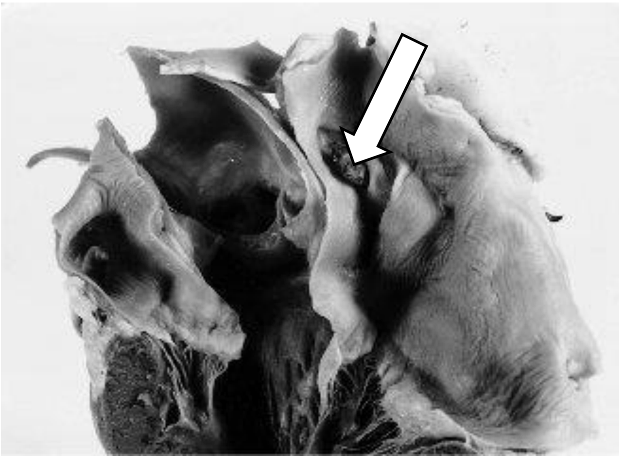
- Medical treatment has improved
- Risks of surgery ~ 3-4%
- Shared decision making has taken off

→ explicitly discuss with candidates for endarterectomy

→ avoid endarterectomy in those who don't want surgery or are unable to discuss risks

Patent foramen ovale

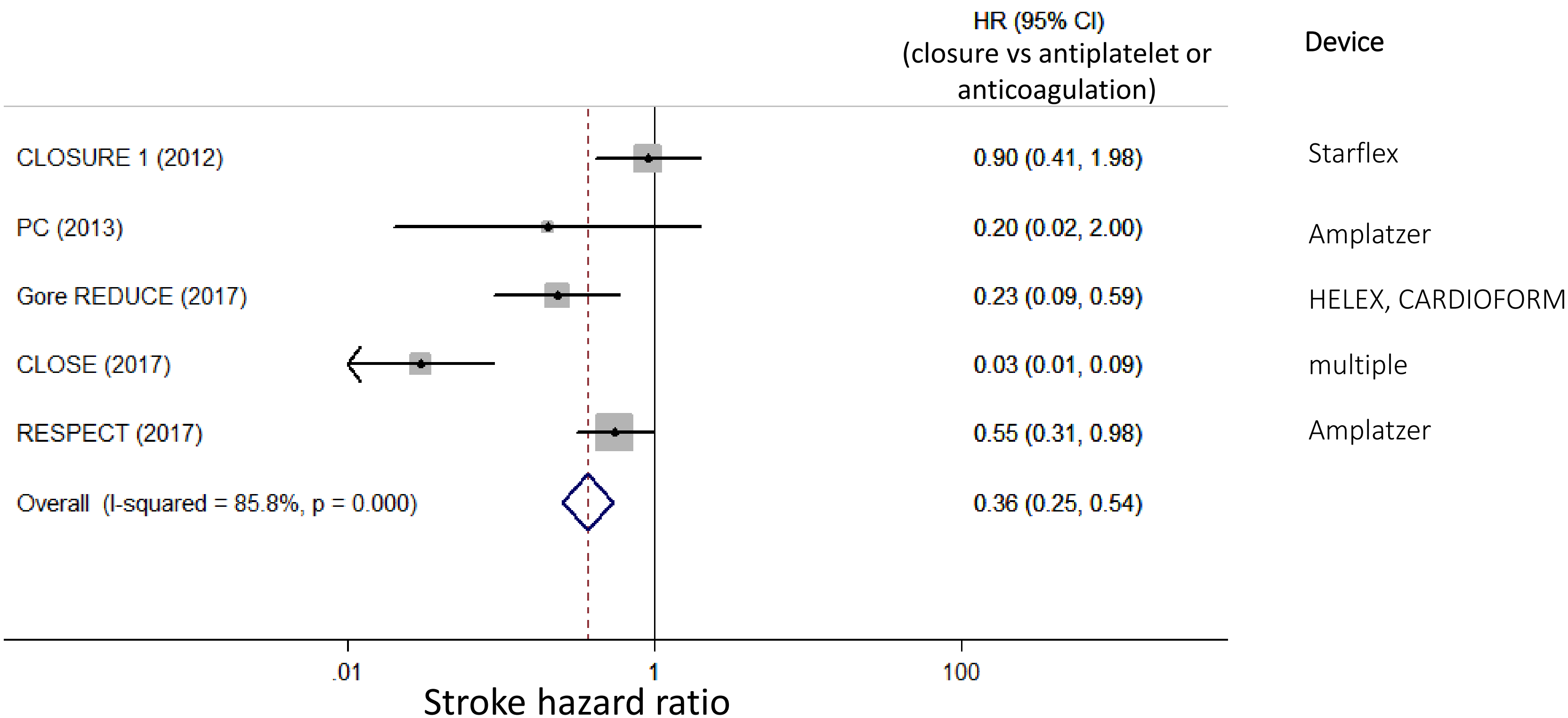
Clot through a PFO



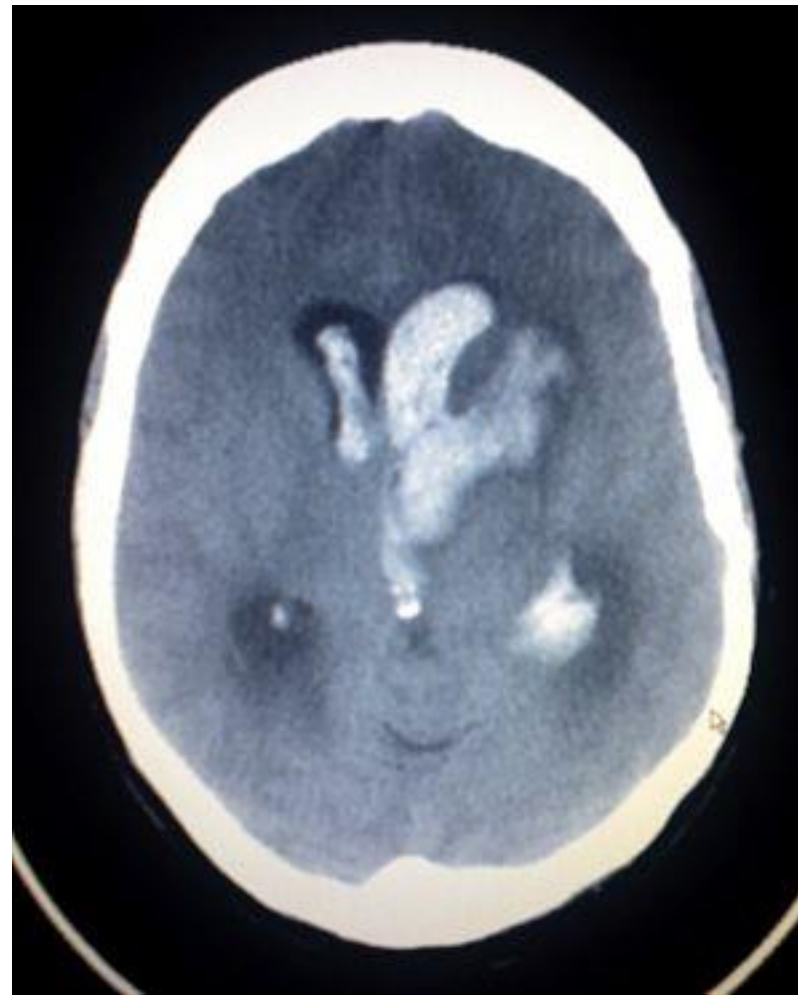
- Patent foramen ovale: ~25% prevalence

Closure ↓ stroke risk for patients with PFO:

- after stroke, <60 years, large interatrial shunt or atrioseptal aneurysm, no other stroke mechanism
- flying and diving
- *But* low stroke rates & atrial fibrillation and rare complications



The lesson of Ariel Sharon



Population impact of services in 5 million inhabitants (10,000 strokes per year)

Number of extra independent survivors per year

Intervention	Maximum impact Extra independent survivors if all patients were eligible	Proportion eligible for treatment (%)	Actual impact Extra independent survivors per year
Rapid secondary prevention	200	All TIA; 15 stroke	100
Stroke unit (CSU) service	500	80	400
Rehabilitation (ESD) service	500	25	130
Service total	-	-	*630*
Aspirin	100	80	*80*
rtPA within 0-3 hrs rtPA within 3-4.5 hrs	1100 500	10 10	*160*
Mechanical thrombectomy	1200	10	120
Hemicraniectomy	2000	0.5	10
Acute medical total	-	-	*370*
Total	-	-	*1000*

Langhorne 2015

→Treat patients with alteplase as soon as possible at all ages and stroke severities

→No advantage in using lower dose alteplase, unless there are particular concerns about early death from haemorrhage

→ Treat patients with mild symptoms if sure of diagnosis AND deficit is disabling AND small risk of ICH is acceptable

→where BP can be lowered <185mmHg systolic rapidly, then reasonable to do so but prioritise speedy treatment

→ Give aspirin or clopidogrel soon after symptom onset

→ consider dual antiplatelets for 1 month for those with definite TIA or minor stroke with high risk features

→ care for patients on a stroke unit with access to a multidisciplinary team of therapists and specialist nurses

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