Medical treatments for ischaemic and haemorrhagic stroke

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Teaching Course
Stroke ABC
WSC Vienna
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World Stroke Academy

Disclosures

- I have been an editor for the Cochrane Stroke Group since 1994
- IST-3 was funded by the UK Medical Research Council and other international governmental and charities. Boehringer Ingelheim donated drug and placebo for the first 300 of the 3035 patients, but thereafter had no role whatsoever in the study
- Lecture fees from BI, Bayer paid to Department.
- Member of DSMB for RELY (BI), REVEAL (Merck), STABILITY/SOLID (GSK) trials

Learning objectives

- Review the clinical trial evidence on treatments for acute stroke
- Evaluate which treatments are supported by strong evidence, and which not
- Consider which of these can be implemented in your own health system
- Consider how to resolve uncertainties about new treatments

Outline

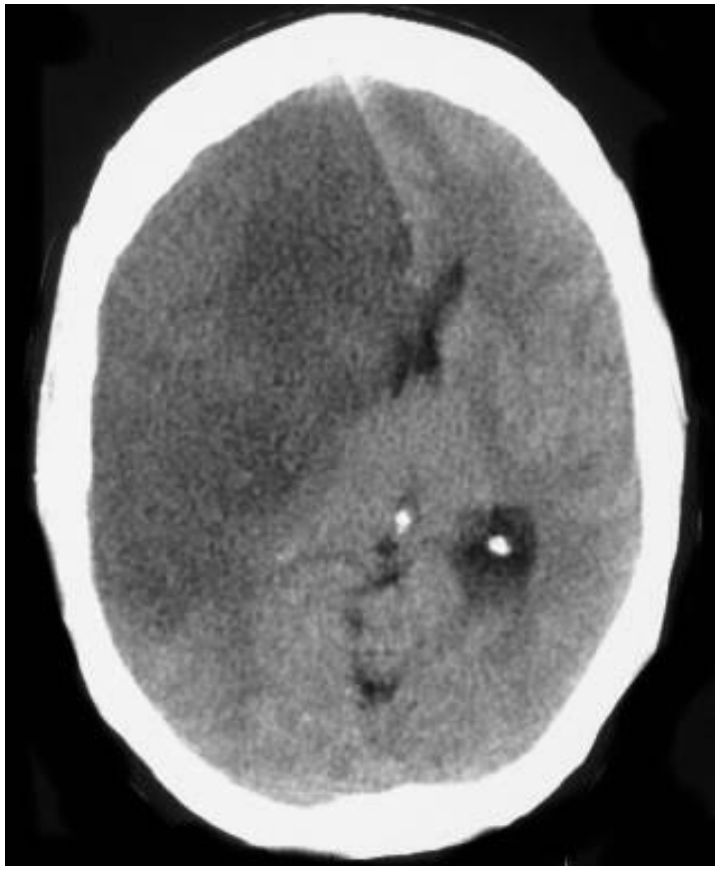
Evidence-based treatments: use routinely

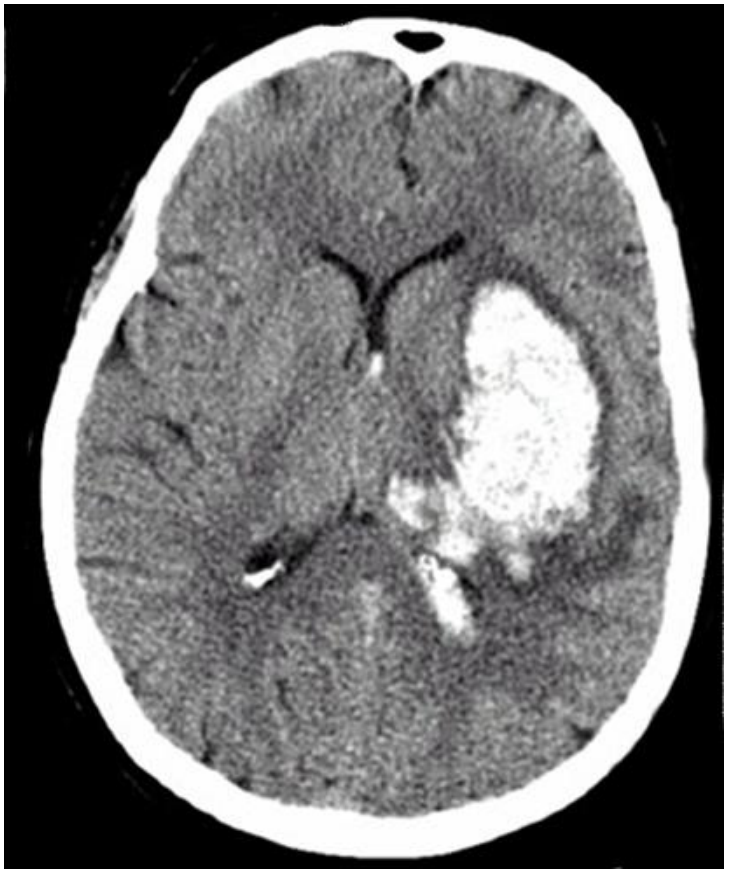
- All stroke types
  - Admit to Stroke Unit
  - Prevent aspiration, DVT, urinary sepsis
- Ischaemic stroke:
  - Immediate aspirin
  - i.v. thrombolysis < 4.5hrs
- Haemorrhagic stroke: BP reduction

Unproven treatments

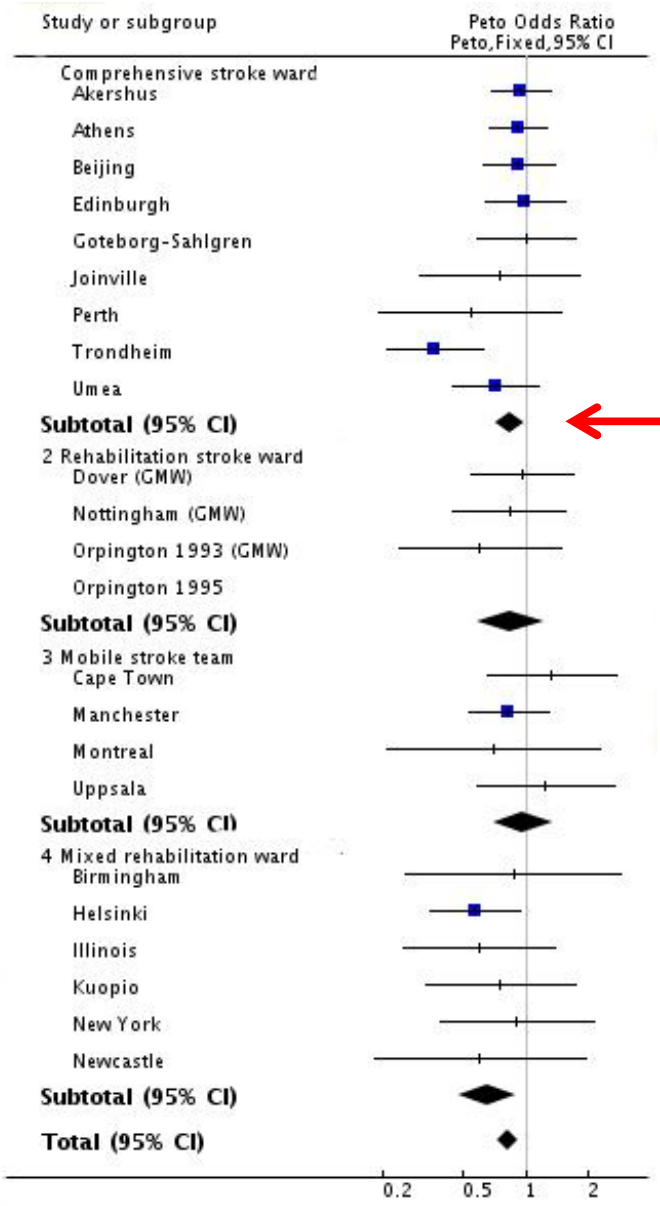
- Don’t use them in routine practice
- Do test them in randomised trials!

Treatments that are effective for both ischaemic and haemorrhagic stroke





Organised inpatient stroke unit care

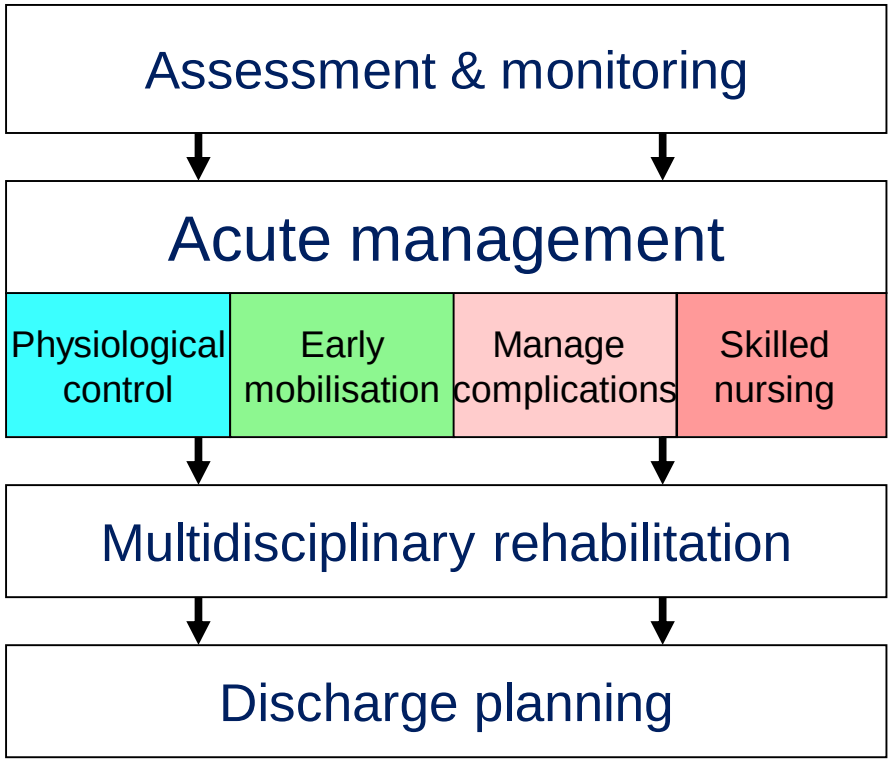


For every 1000 patients admitted to an organised stroke unit, 43 avoid being 'dead or dependent' at 1 year

Greatest benefit from '**Comprehensive stroke unit 'model of care**

Stroke Unit Trialists' Collaboration. Cochrane Database of Systematic Reviews

Comprehensive stroke unit = dedicated area (beds) in acute hospital



Nurse

Doctor

Physiotherapy

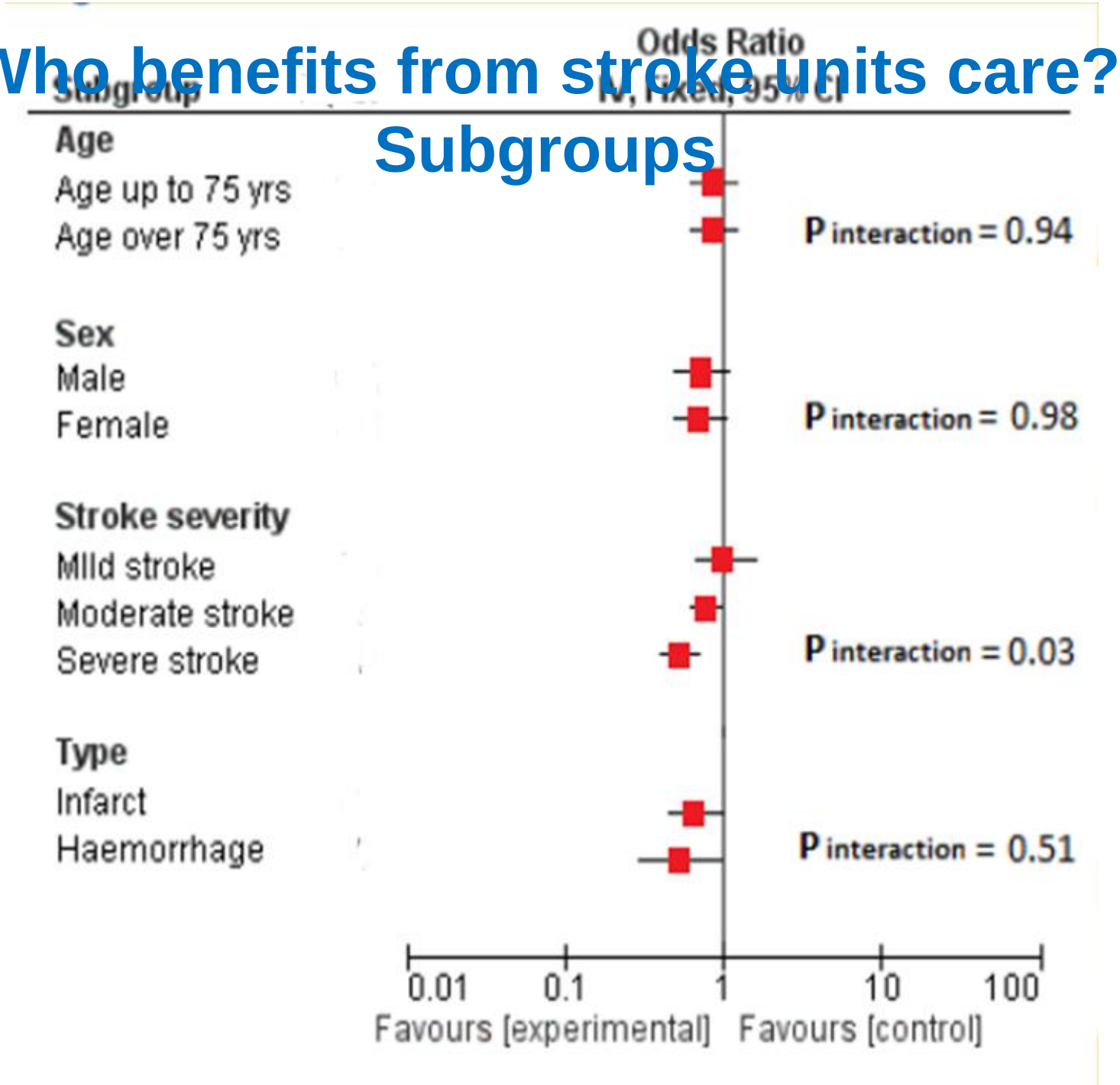
Occupational Therapy

Speech therapy

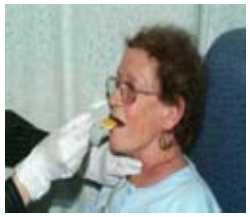
Coordinated multidisciplinary care
= formal multi-disciplinary team meetings 1x per week)

Who benefits from stroke units care?

Subgroups



Beneficial effects of stroke unit care appear to be :



- Independent of patient age, sex, severity, stroke type
- Independent of parent specialty (Neurology, Geriatric Medicine, Internal Medicine)
- Demonstrated in all regions studied (including low- and middle-income countries)
- Not dependent on high technology (benefit even where no access to CT scanning)
- A result of a reduction of stroke complications

Prevent complications

- Assess swallowing on admission
- Avoid use of urinary catheters
- Carefully position paralysed limb
- Mobilise early
- Prevent deep vein thrombosis (DVT) and pulmonary embolism (PE)

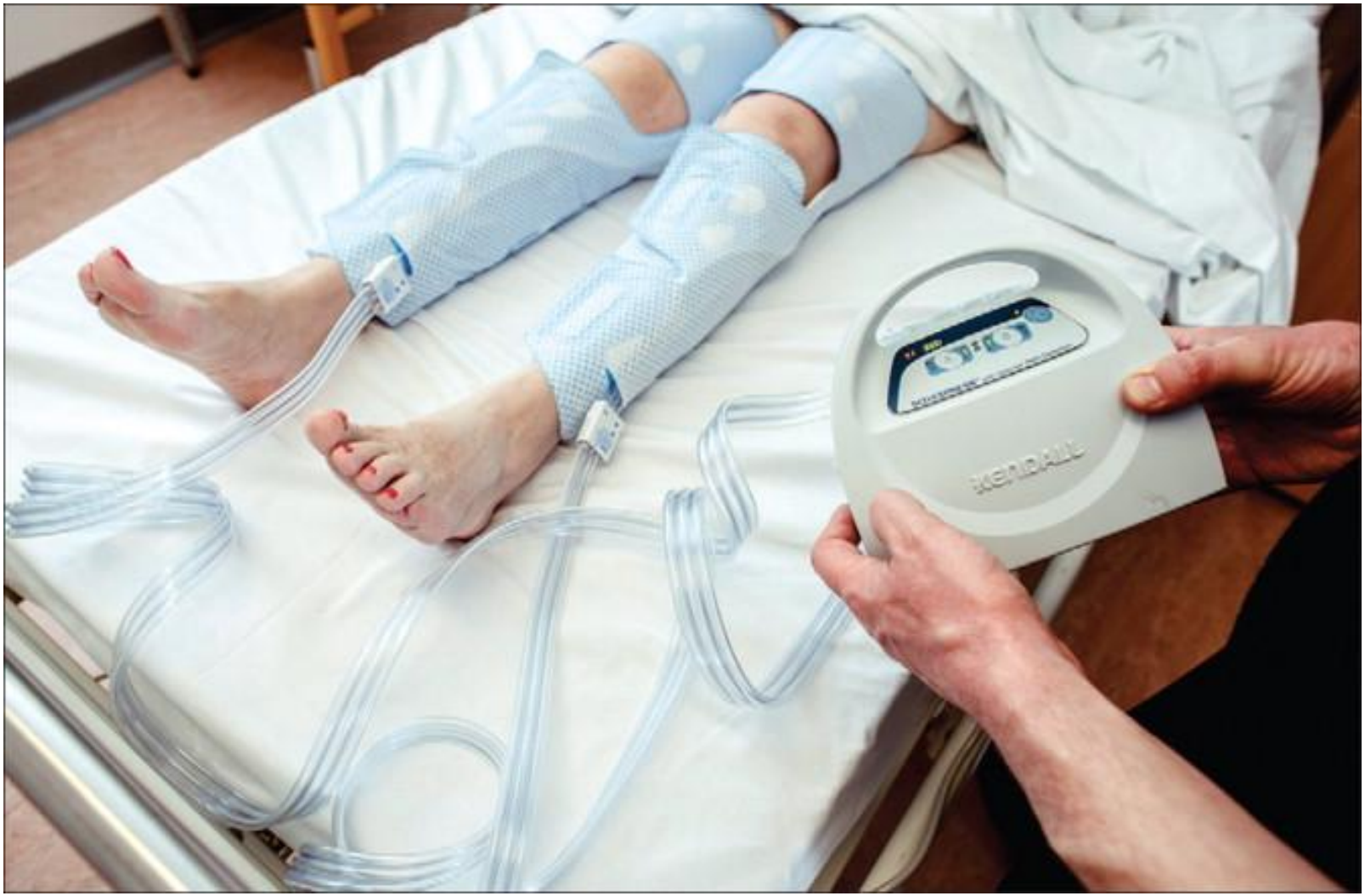
Which of these 4 ways to prevent deep vein thrombosis after stroke does most good and least harm?

1. Heparin?
2. Aspirin?
3. Graded compression stockings?
4. Intermittent pneumatic compression (IPC)?

Evidence-based prevention of DVT after stroke

	No. trials	pts.	Conclusions
Heparin	24	23,748	?PE and ?recurrent stroke =?DVT & EC bleeding **= zero benefit**
Aspirin	12	43,041	Small benefit
Graded compression stockings	2	2615	No benefit
Intermittent pneumatic compression	3	3035	DVT and death reduced

Intermittent pneumatic compression (IPC)



Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial

*CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration**

Summary

Background Venous thromboembolism is a common, potentially avoidable cause of death and morbidity in patients in hospital, including those with stroke. In surgical patients, intermittent pneumatic compression (IPC) reduces the risk of deep vein thrombosis (DVT), but no reliable evidence exists about its effectiveness in patients who have had a stroke. We assessed the effectiveness of IPC to reduce the risk of DVT in patients who have had a stroke.

Methods The CLOTS 3 trial is a multicentre parallel group randomised trial assessing IPC in immobile patients (ie, who cannot walk to the toilet without the help of another person) with acute stroke. We enrolled patients from day 0 to day 3 of admission and allocated them via a central randomisation system (ratio 1:1) to receive either IPC or no IPC. A technician who was masked to treatment allocation did a compression duplex ultrasound (CDU) of both legs at 7–10 days and, wherever practical, at 25–30 days after enrolment. Caregivers and patients were not masked to treatment assignment. Patients were followed up for 6 months to determine survival and later symptomatic venous thromboembolism. The primary outcome was a DVT in the proximal veins detected on a screening CDU or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days of randomisation. Patients were analysed according to their treatment allocation. Trial registration: ISRCTN93529999.

Findings Between Dec 8, 2008, and Sept 6, 2012, 2876 patients were enrolled in 94 centres in the UK. The included patients were broadly representative of immobile stroke patients admitted to hospital and had a median age of 76 years (IQR 67–84). The primary outcome occurred in 122 (8·5%) of 1438 patients allocated IPC and 174 (12·1%) of 1438 patients allocated no IPC; an absolute reduction in risk of 3·6% (95% CI 1·4–5·8). Excluding the 323 patients who died before any primary outcome and 41 without any screening CDU, the adjusted OR for the comparison of 122 of 1267 patients *vs* 174 of 1245 patients was 0·65 (95% CI 0·51–0·84; p=0·001). Deaths in the treatment period occurred in 156 (11%) patients allocated IPC and 189 (13%) patients allocated no IPC died within the 30 days of treatment period (p=0·057); skin breaks on the legs were reported in 44 (3%) patients allocated IPC and in 20 (1%) patients allocated no IPC (p=0·002); falls with injury were reported in 33 (2%) patients in the IPC group and in 24 (2%) patients in the no-IPC group (p=0·221).

Interpretation IPC is an effective method of reducing the risk of DVT and possibly improving survival in a wide variety of patients who are immobile after stroke.

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*See appendix for membership and contributions

This online publication has been corrected. The corrected version first appeared at thelancet.com on June 5, 2013

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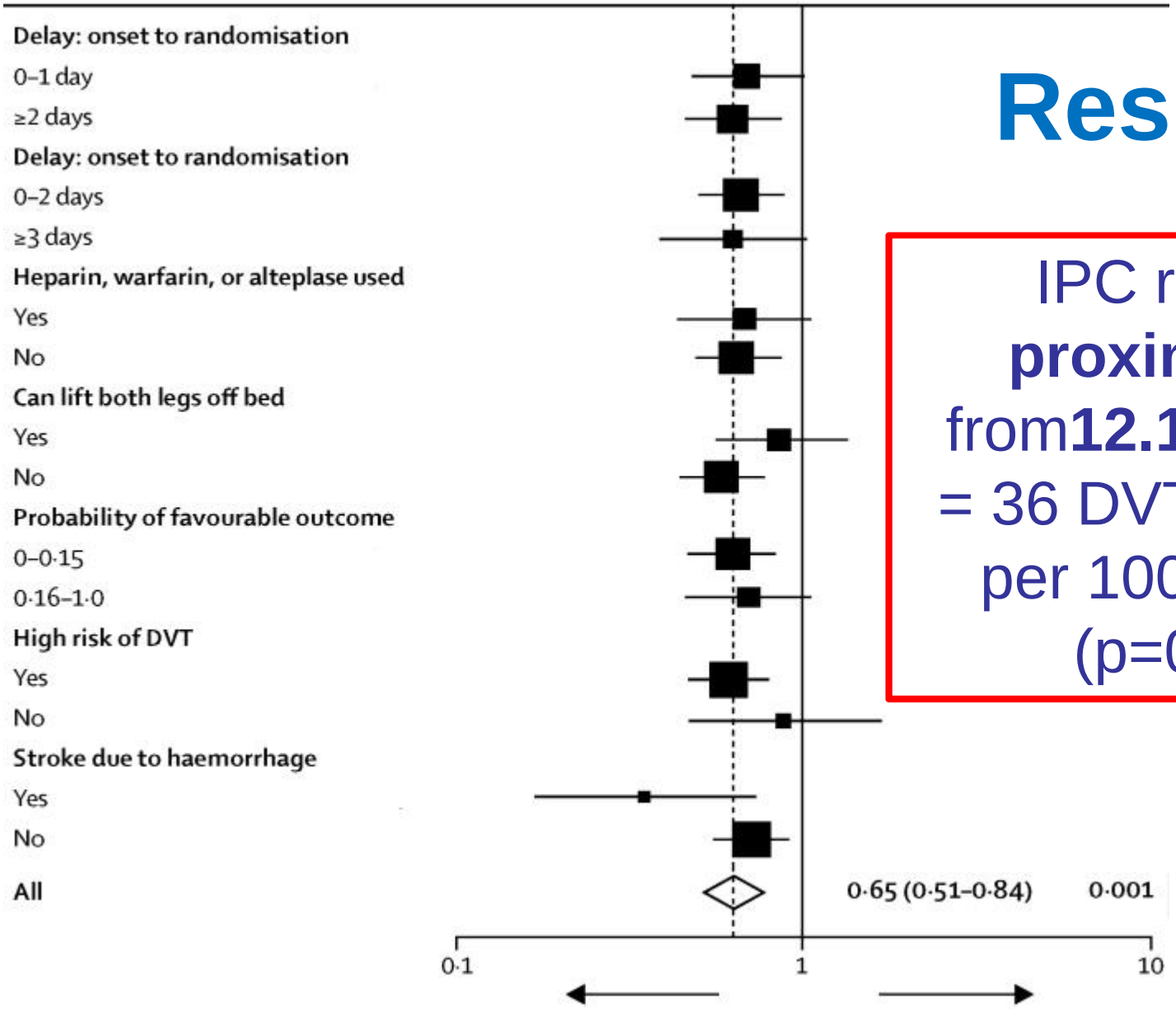
See Online for appendix



Results

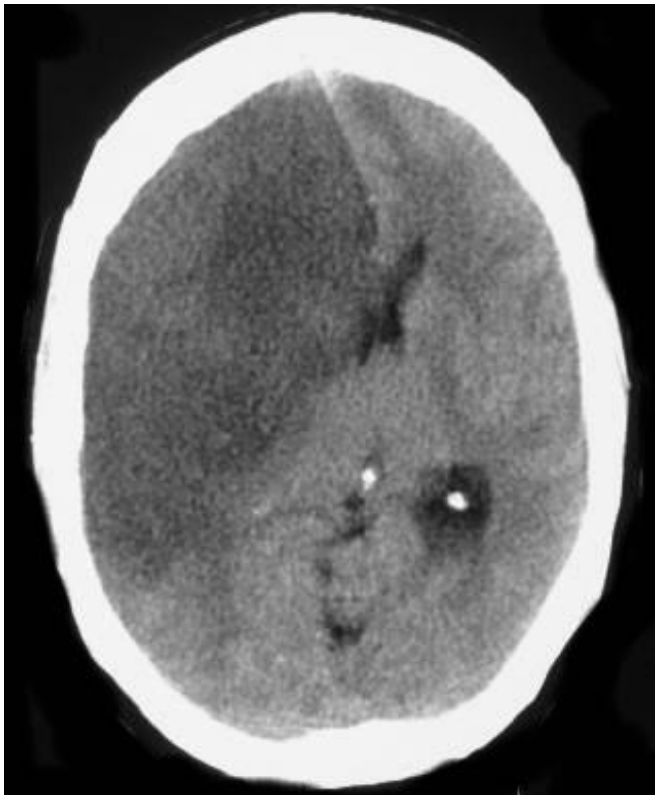
IPC reduced **proximal DVT** from **12.1%** to **8.5%** = 36 DVT's avoided per 1000 treated (p=0.001)

CLOTS-3 trial Lancet 2013

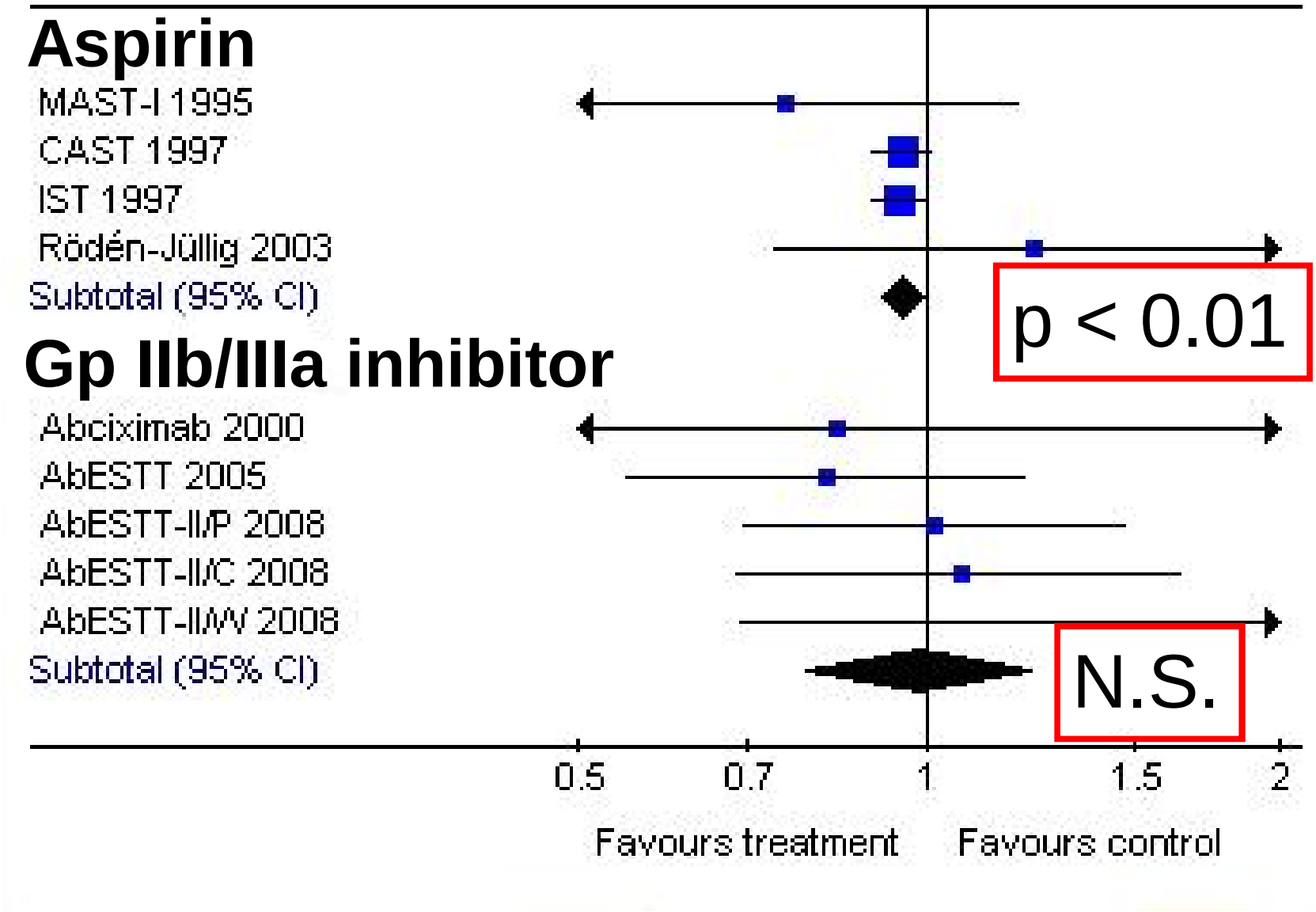
Prevention of DVT after stroke

- Heparin is of no net clinical benefit: reductions in DVT and recurrent ischaemic stroke are offset by increased intra- and extra-cranial bleeds
- Aspirin is of modest benefit
- Compression stockings are ineffective
- Intermittent pneumatic compression
  - prevents DVT PE and may save lives
  - effective in ischaemic and haemorrhagic stroke
  - adds benefit to heparin

Effective treatments for acute ischaemic stroke



Antiplatelet agents in acute ischaemic stroke: effect on ‘death or dependency’



Acute ischaemic stroke: aspirin

- 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
- Should be given immediately after CT/MR has excluded haemorrhage

How to give aspirin immediately.
Ask: can the patient swallow safely?

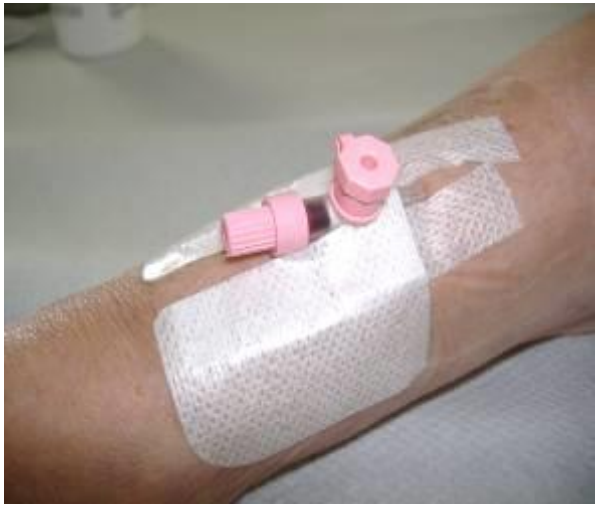
YES !

aspirin by mouth

NO !

aspirin i.v.

aspirin per rectum

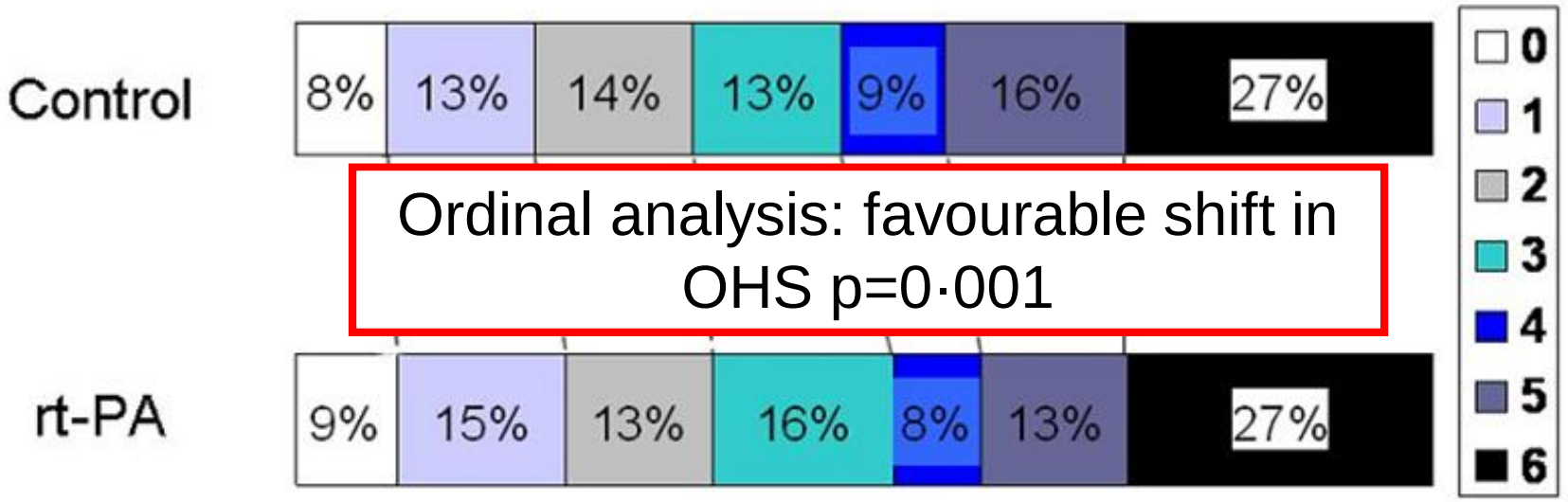


i.v. thrombolysis with rt-PA - act FAST!

Acute ischaemic stroke: i.v. thrombolysis

- rt-PA should only be administered
  - by personnel trained in its use,
  - with minimal ‘door-to-needle’ time
  - in a centre able to monitor patients adequately
- 3% risk of fatal intracranial haemorrhage
- ‘Time is brain’, i.v. rt-PA is most effective < 3hrs , but benefit up to 4.5 hours of onset
- IST-3 trial showed treatment benefits:
  - people > 80 years,
  - severe stroke
  - Less long-term disability and better quality of life

IST-3: Outcome (OHS) at 6 months



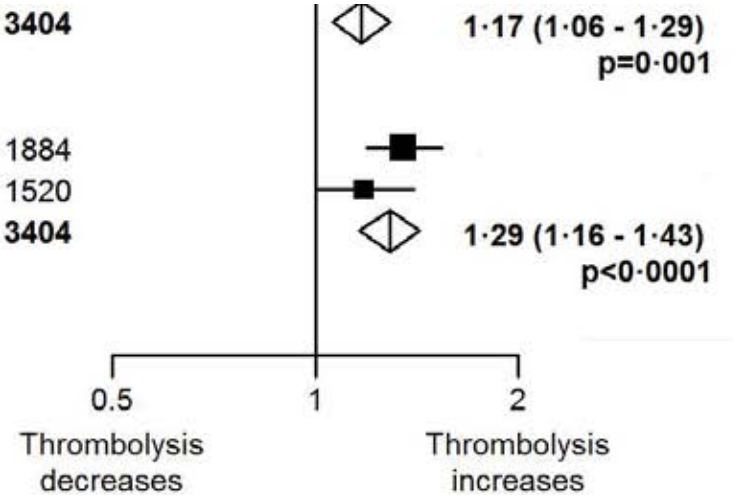
The odds of surviving with less disability were 27% greater for patients treated with rt-PA.

Benefits were:

- greatest < 3 hours
- not less in patients aged > 80 years
- not less in patients with severe stroke

All rt-PA trials: Outcome at end of follow-up

Endpoint	No. trials	Events (No. patients) Thrombolysis	Control	Odds Ratio (95% CI)
All deaths by the end of follow-up				
All trials before IST3	11	271 / 2033	233 / 1944	
IST3	1	408 / 1515	407 / 1520	
All trials	**12**	**679 / 3548**	**640 / 3464**	**1·06 (0·94 - 1·20) p=0·33**
Alive and independent (mRS 0-2) by the end of follow-up *				
All trials before IST3	9	1057 / 1968	900 / 1884	
IST3	1	554 / 1515	534 / 1520	
All trials	**10**	**1611 / 3483**	**1434 / 3404**	**1·17 (1·06 - 1·29) p=0·001**
Favourable outcome (mRS 0,1) by the end of follow-up *				
All trials before IST3	9	848 / 1968	678 / 1884	
IST3	1	363 / 1515	320 / 1520	
All trials	**10**	**1211 / 3483**	**998 / 3404**	**1·29 (1·16 - 1·43) p<0·0001**



Treat 1000 patients with iv rt-PA and:

Among all patients treated < 6h

- 40 more alive and independent
- No increase in deaths at final FU

In patients treated < 3hrs

- 90 more alive and independent

In patients >80 years

- Comparable benefits

Implications for practice.

- Consider thrombolytic treatment for a wider variety of patients,
  - Particularly those aged over 80 years
  - With more severe strokes
- Reinforce efforts to increase the proportion of ischaemic strokes treated < 3 hours
- Have greater confidence that mortality is not increased by treatment

Endovascular treatment?

Clot retrieval, intra-arterial or iv rt-PA? RCTs of interventional vs iv therapy

Trial name	Time from onset (h)	Comparison	Sample size
MR Rescue	0-8	Usual care vs usual care + MERCI	120
SYNTHESIS	0-3	IV vs IA+device	350
IMS-3	0-3	IV vs IV+IA	600

No advantage of interventional treatment over iv therapy. Further trials ongoing (PISTE etc)

The dangers of clinical conviction

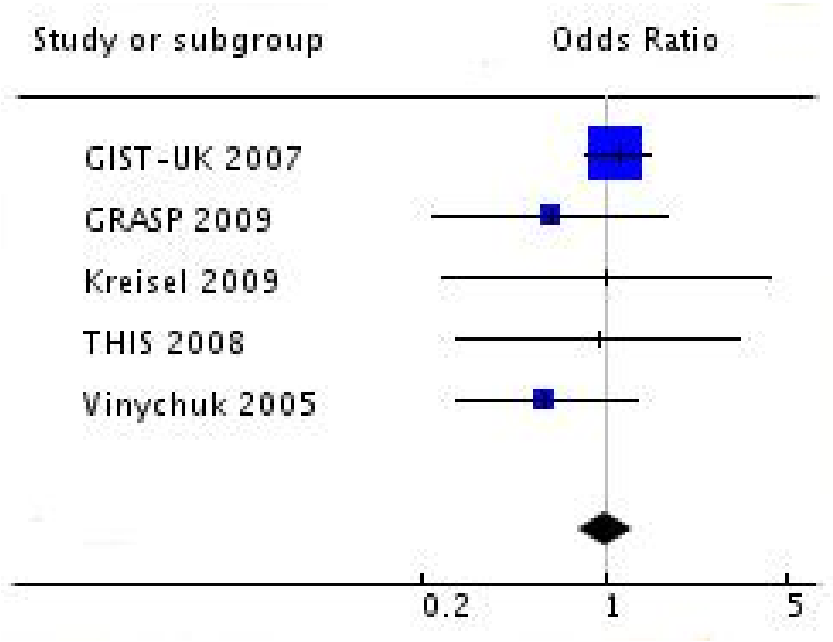
‘We think it is time to stop messing around with the liberal use of endovascular therapies for acute ischemic stroke. It is time to make sure we get better evidence.’

‘The devices have improved, with higher rates of recanalization with the new stent-based retrievers… we should demand randomized data to support their use.’

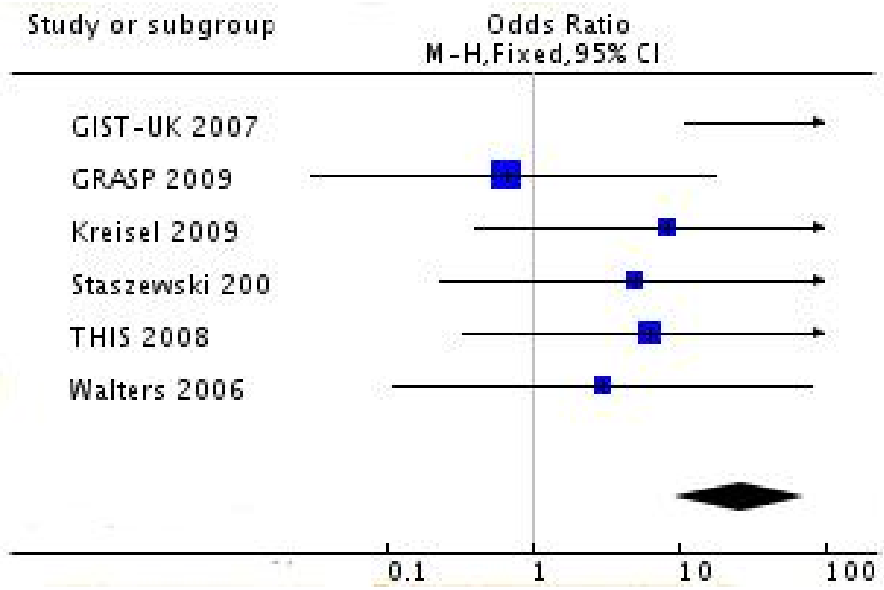
Claiborne Johnston. Ann Neurol 2013

Intensive insulin in acute stroke: no reduction in dead/dependent but increased symptomatic hypoglycaemia

Dead or dependent



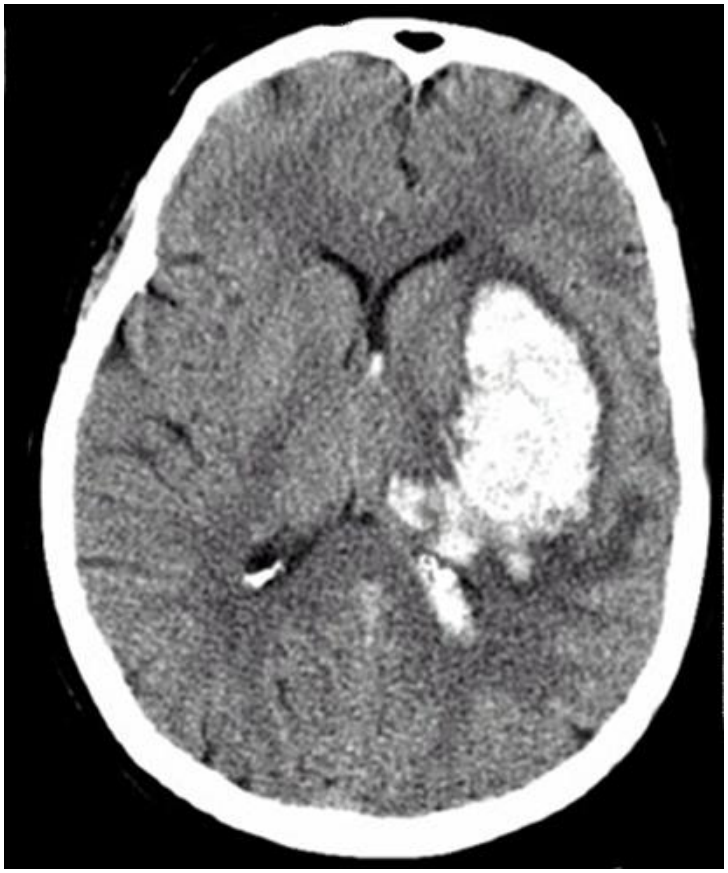
Hypoglycaemia



No net benefit & significant increase in adverse events

Stead CDSR 2011

Treatments for intracerebral haemorrhage



Rapid, intensive blood pressure lowering < 6hrs in ICH (INTERACT-2 trial)

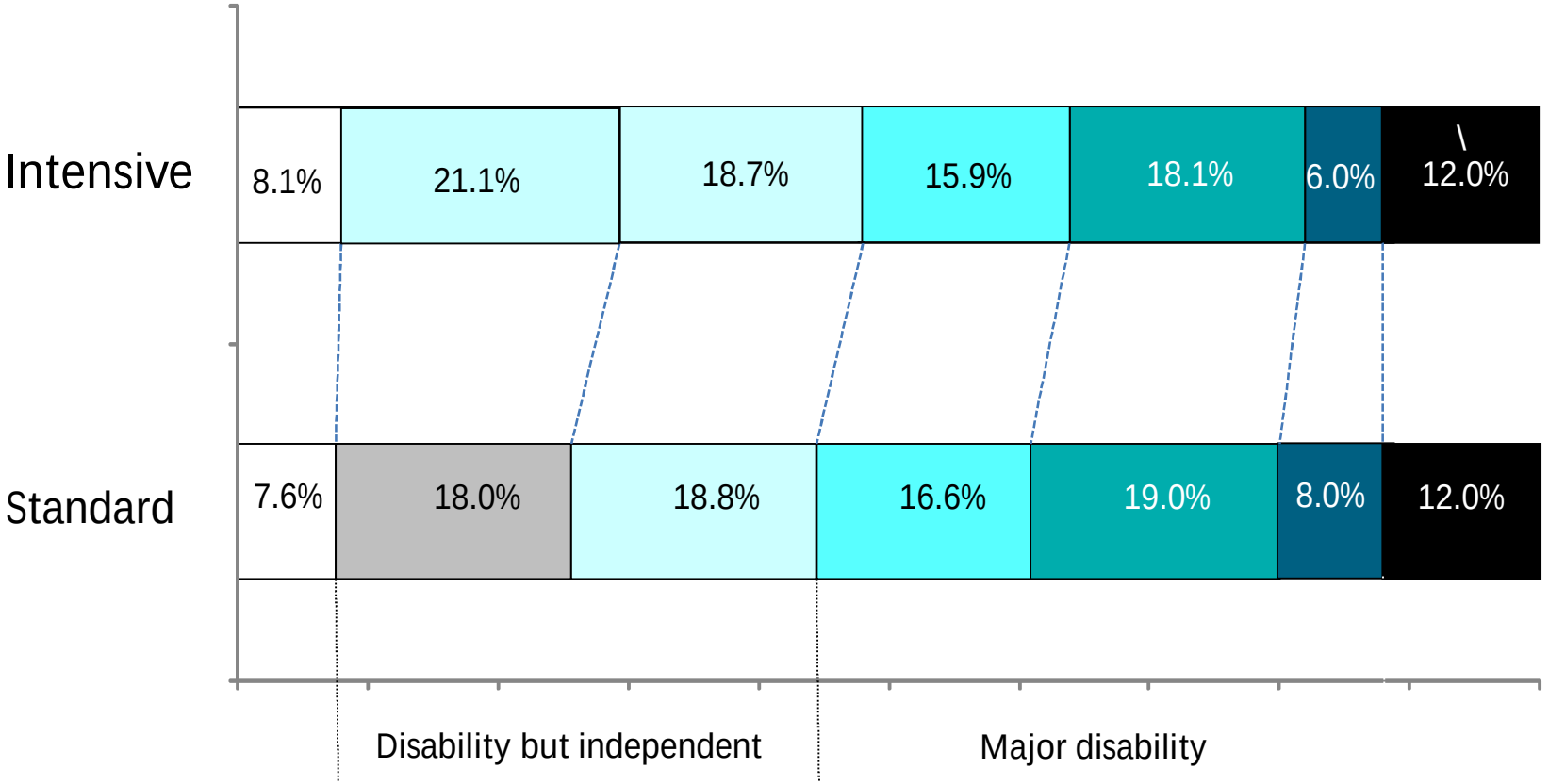
early intensive blood pressure (BP) lowering (target of <140 mmHg systolic)

Versus

guideline-recommended ‘standard’ control of BP (target of <180 mmHg systolic)

INTERACT-2
Ordinal shift in mRS scores

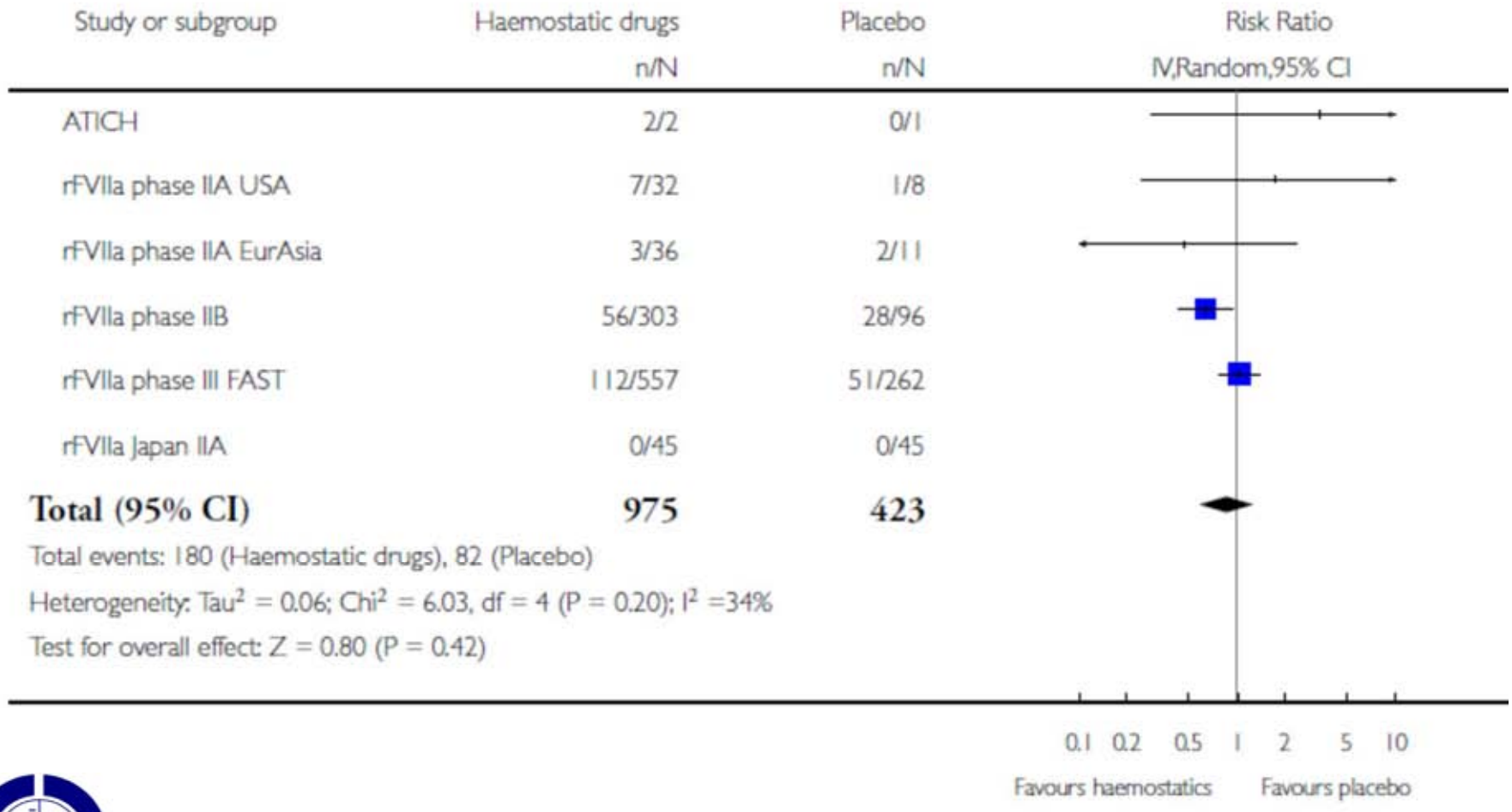
Odds ratio 0.87 (95%CI 0.77 to 1.00); P=0.04



INTERACT- 2 Take home messages

- BP lowering in acute ICH is safe, so
  - Ø treat early
  - Ø treat intensively to target systolic BP 140 mmHg
  - Ø Maintain BP reduction for at least 24 hours
- Treat most patients with ICH
- Remember: BP lowering improves recovery in survivors

Recombinant factor VIIa in ICH: effect on death/dependency



Salman CDSR 2011

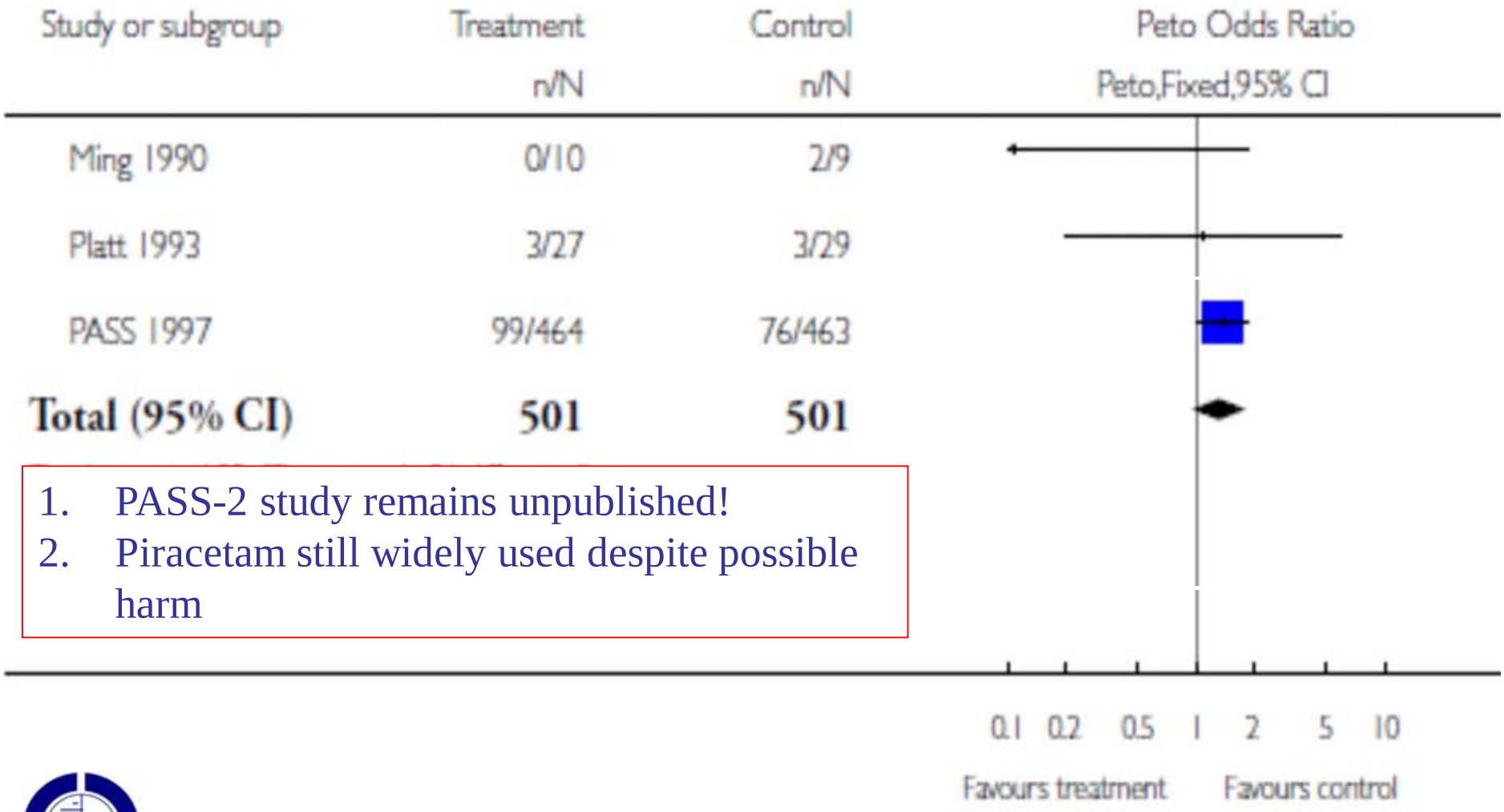
Summary: treatment of ICH

- Intensive BP lowering safe and effective
- Recombinant factor VIIa (very costly):
  - Benefit of reduced haematoma expansion
  - but increased risk of arterial thromboembolism
  - No net benefit
- Tranexamic Acid (TXA)
  - CRASH-2 trial (20,000 pts): TXA after trauma reduced mortality (p= 0.03) & no increase in thrombotic events
  - TICH trial of TXA in primary intracerebral haemorrhage underway

Summary: acute stroke

- Use treatments supported by evidence:
  - stroke unit care,
  - Intermittent pneumatic compression to prevent DVT
  - aspirin,
  - i.v. thrombolysis, selected patients < 3-4.5 hrs
  - BP lowering for acute ICH
- Don’t use these unproven treatments routinely
  - heparin
  - Intensive glucose control with insulin
  - haemodilution with hydroxyethyl starch
  - piracetam, vinpocetine, cerebrolysin
- Recruit into ongoing trials!
- Begin secondary prevention early
  - All stroke: Blood pressure lowering
  - Ischaemic stroke: antiplatelet, statin,

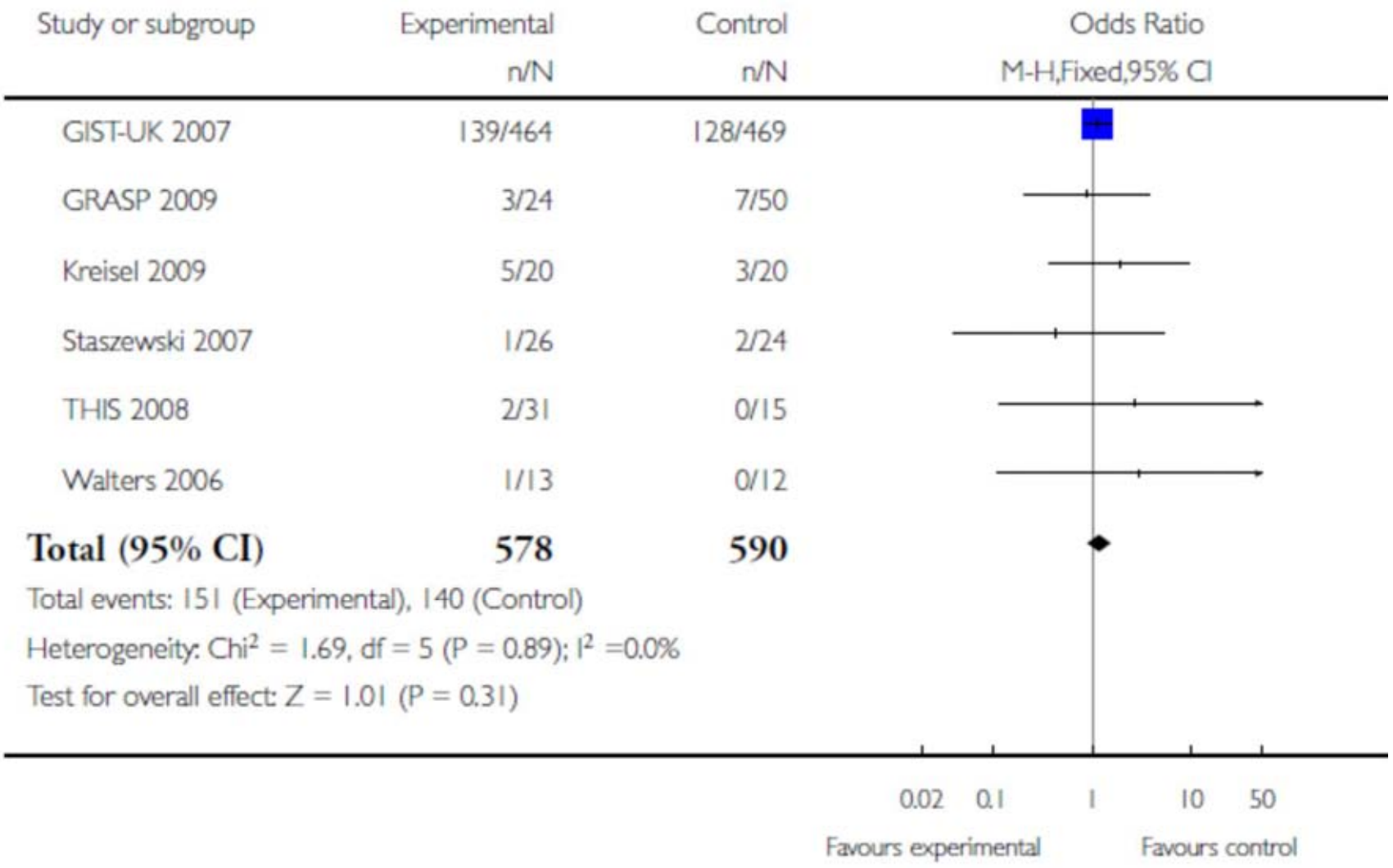
Piracetam: death



1. PASS-2 study remains unpublished!
2. Piracetam still widely used despite possible harm

Ricci. CDSR 2011

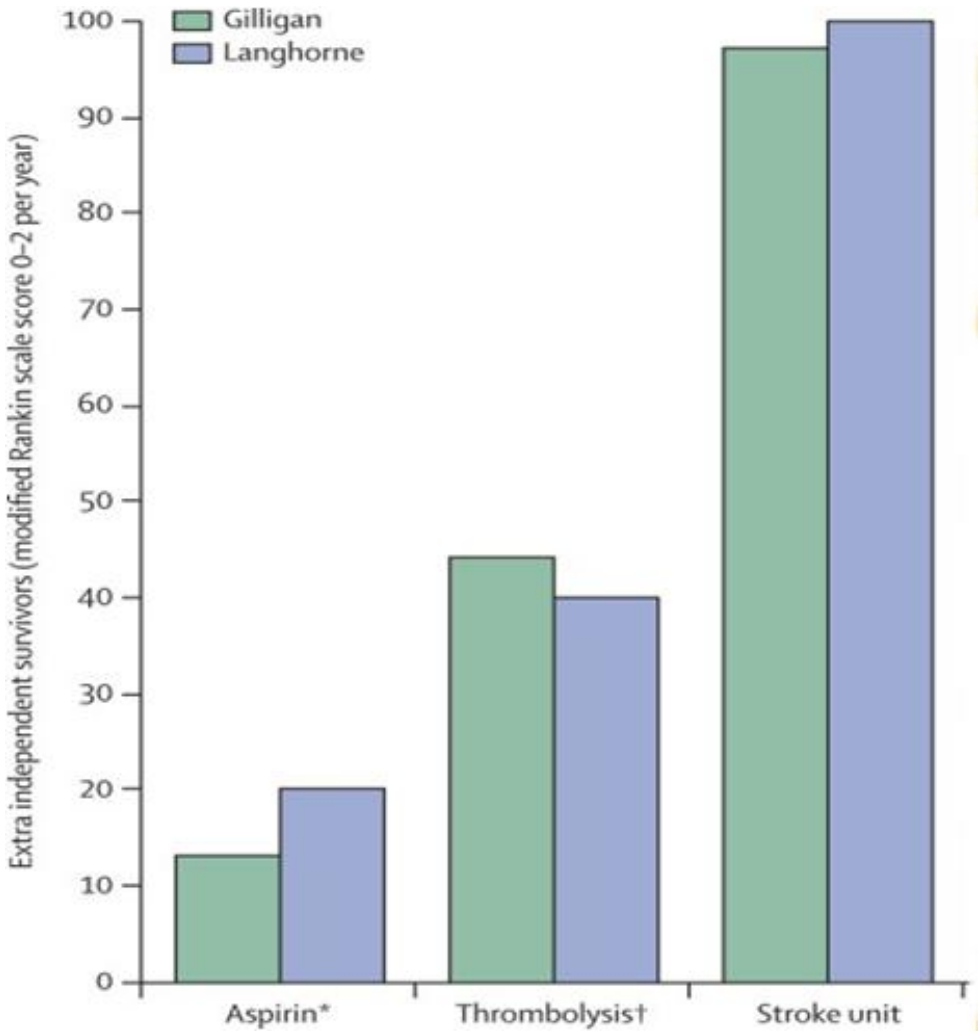
Insulin therapy in stroke: effect on death



Stead CDSR 2011

Good quality stroke unit care does not require ‘high technology’: stroke unit St Petersburg, Russia

Potential population effect of stroke interventions in a population of one million



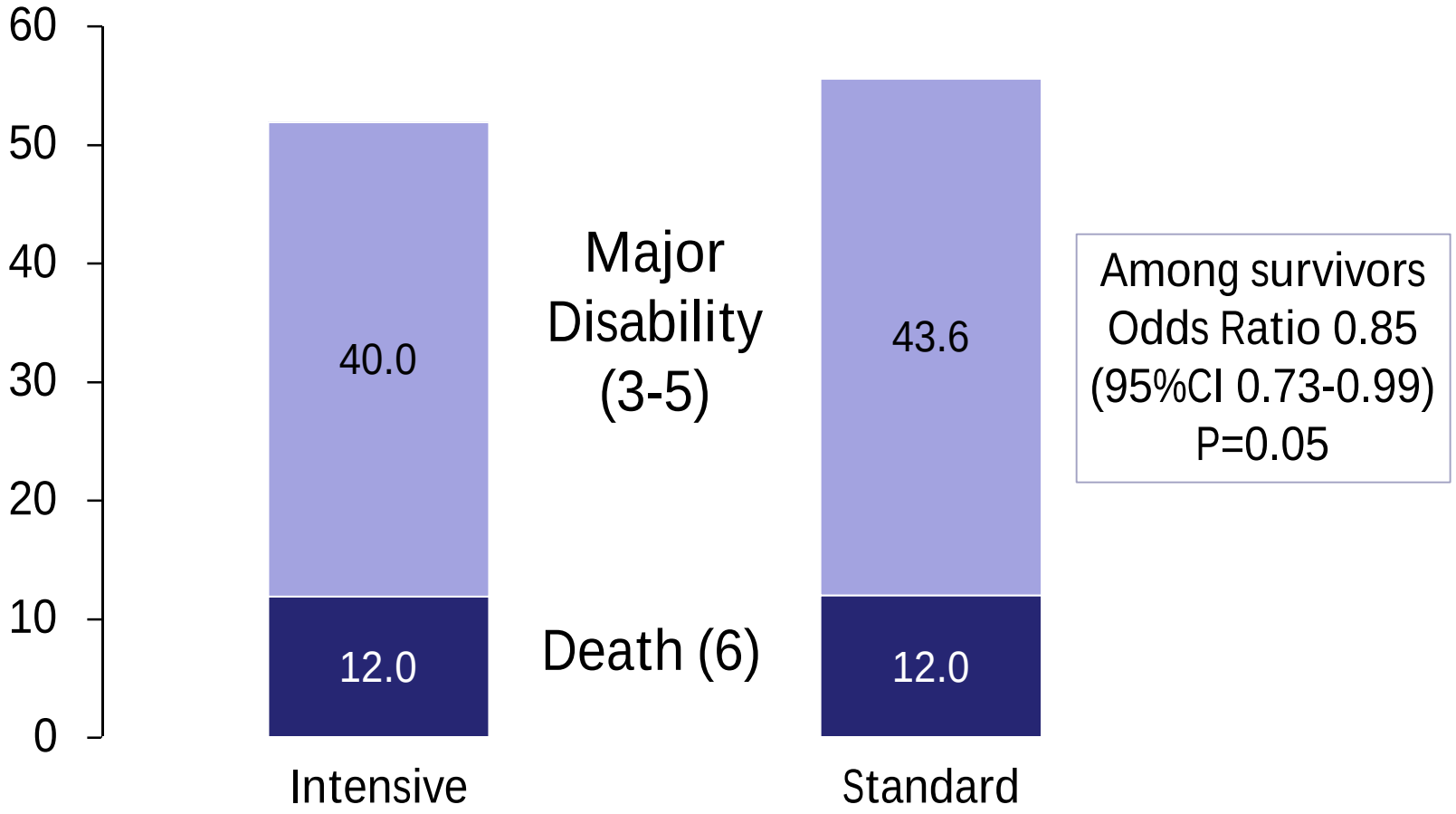
Langhorne, Lancet Neurology 2012; 11; 341-8

Improving your clinical service

- Audit
  - % of patients admitted to stroke unit
  - % with swallow assessment < 24 hrs
  - % aspirin started
- Quality improvement plan
- Participate in research

Death or major disability (mRS 3-6) at 90 days

Odds ratio 0.87 (95%CI 0.75 to 1.01) P=0.06



INTERACT-2 Systolic BP control