STROKE and BLOOD PRESSURE: PREVENTION AND TREATMENT

Cottrell Memorial Lecture

RACP annual Scientific Meeting

Adelaide, May , 2016

John Chalmers
The George Institute for Global Health
The University of Sydney

OUTLINE OF TALK

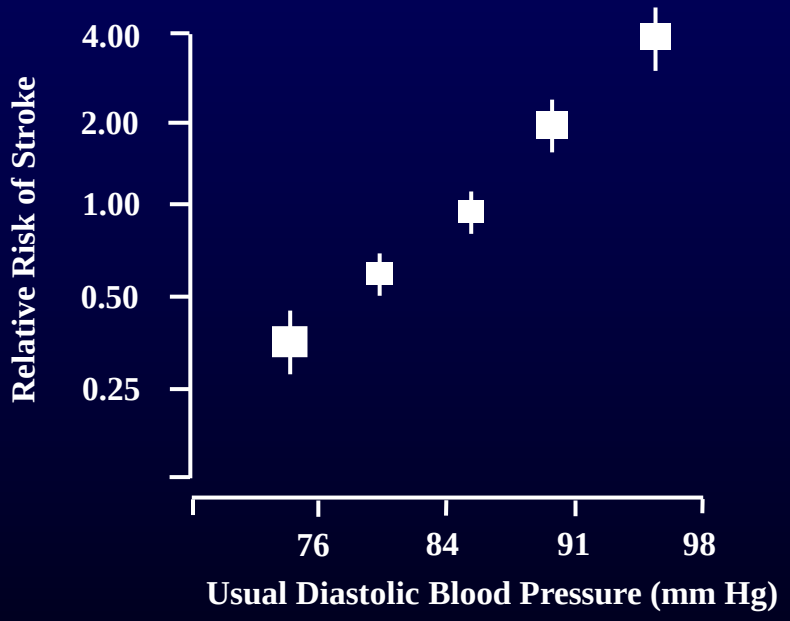
Based on studies conducted with colleagues at George institute in last 20 years

- Association of Stroke and BP
- **PROGRESS trial** : prevention of Recurrent Stroke
- **INTERACT2 trial** : BP Lowering for Acute Intracerebral Haemorrhage (ICH)
- **ENCHANTED trial** in Acute Ischaemic Stroke : dose of rtPA, and BP lowering in first few hours
- Take home messages

BP and Stroke Risk

Primary Stroke

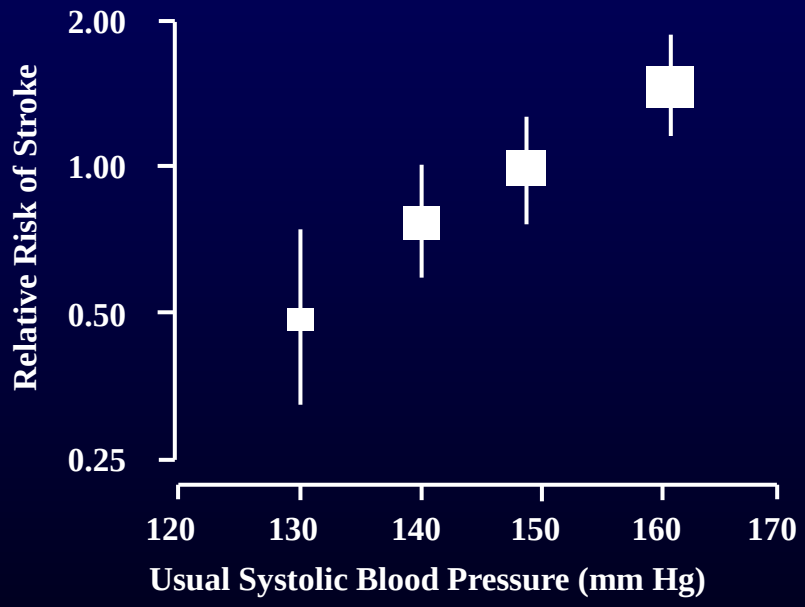
7 Prospective studies



MacMahon et al, Lancet 1990;335:766

Secondary Stroke

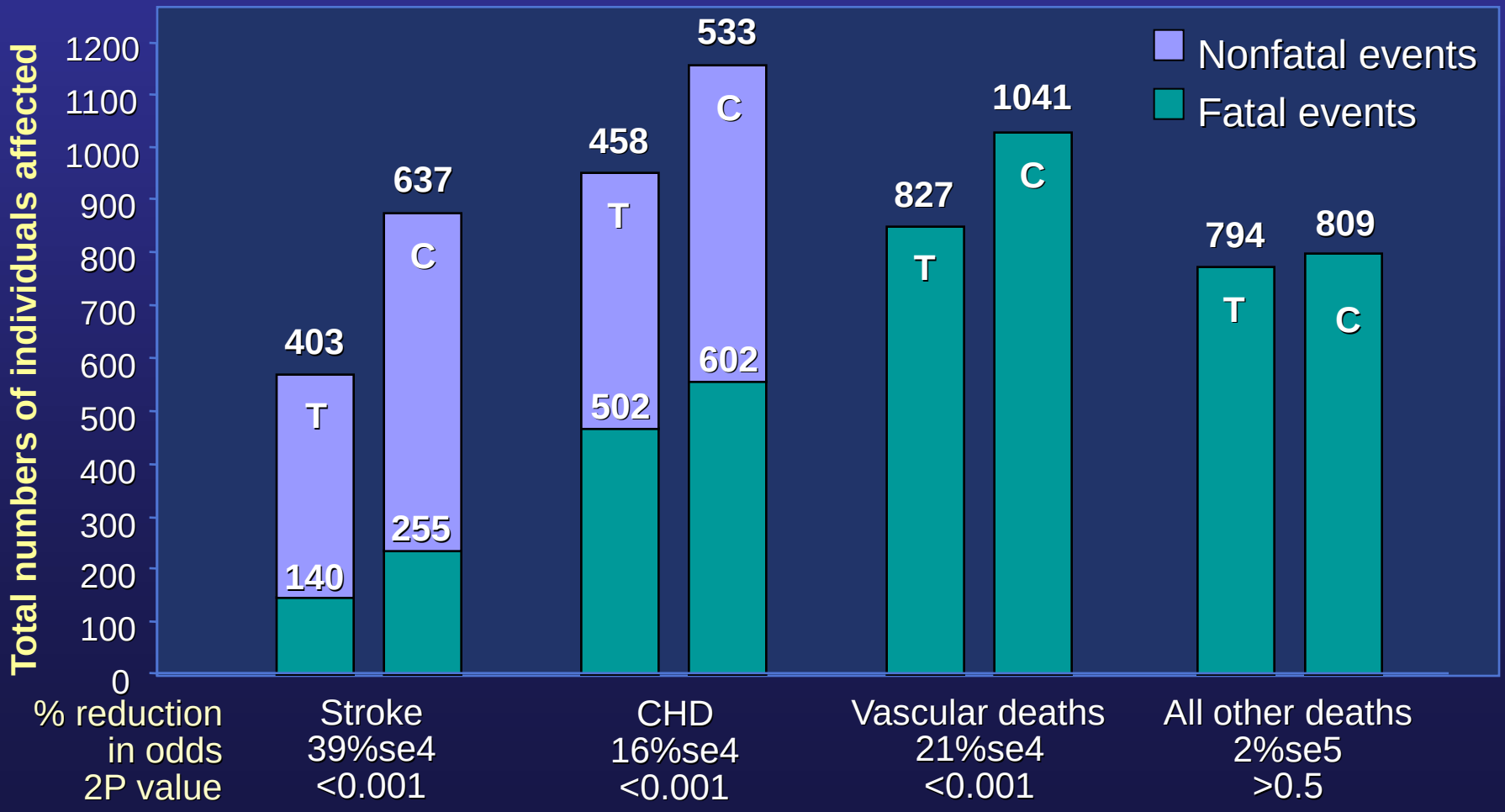
UKTIA study



Rodgers et al. BMJ 1996;313:147

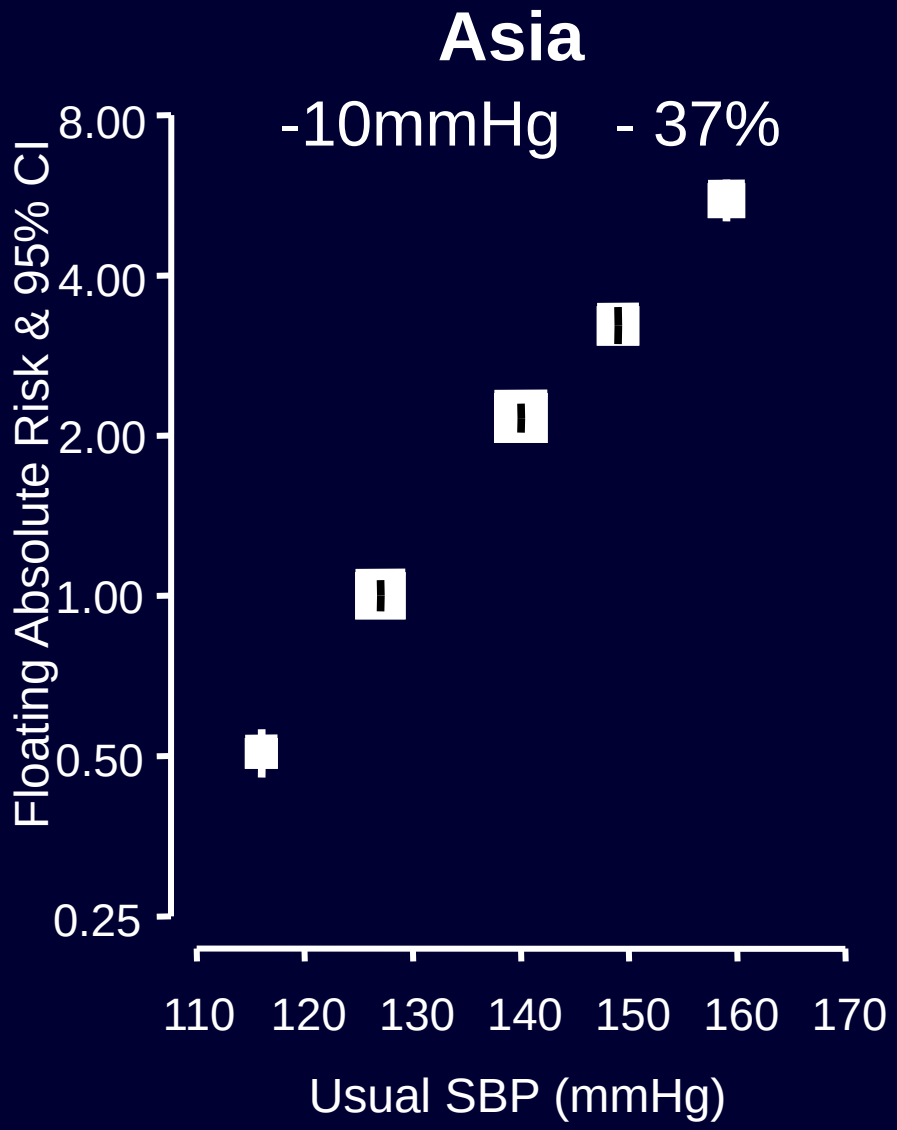
Randomized Trials of Antihypertensive Treatment (Collins, MacMahon et al Lancet 1990)

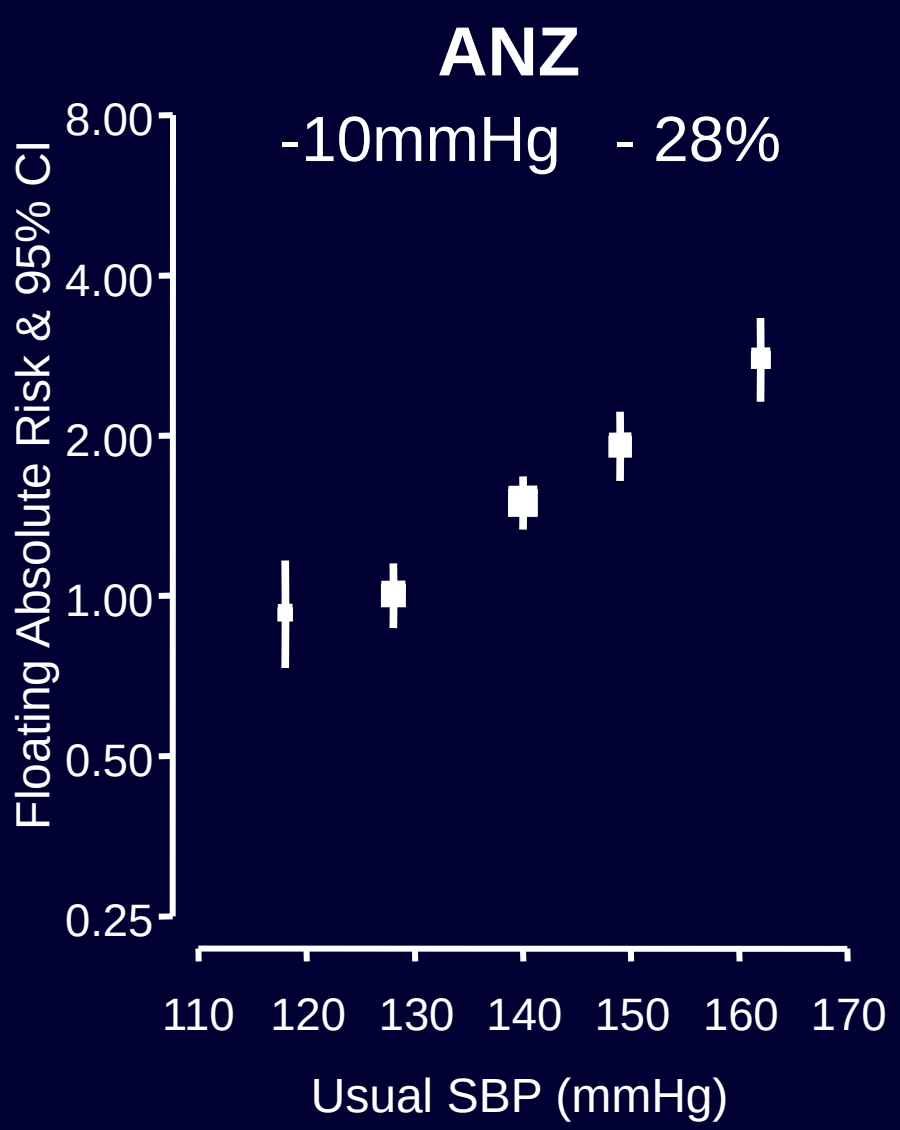
T = treatment **52,348 patients, SBP diff 10–12 mm Hg, DBP diff 5–6 mm Hg**
C = control **Follow-up 5 years**



Asia Pacific Cohort Studies Collaboration (44 cohorts, 9 countries)

SBP and primary stroke

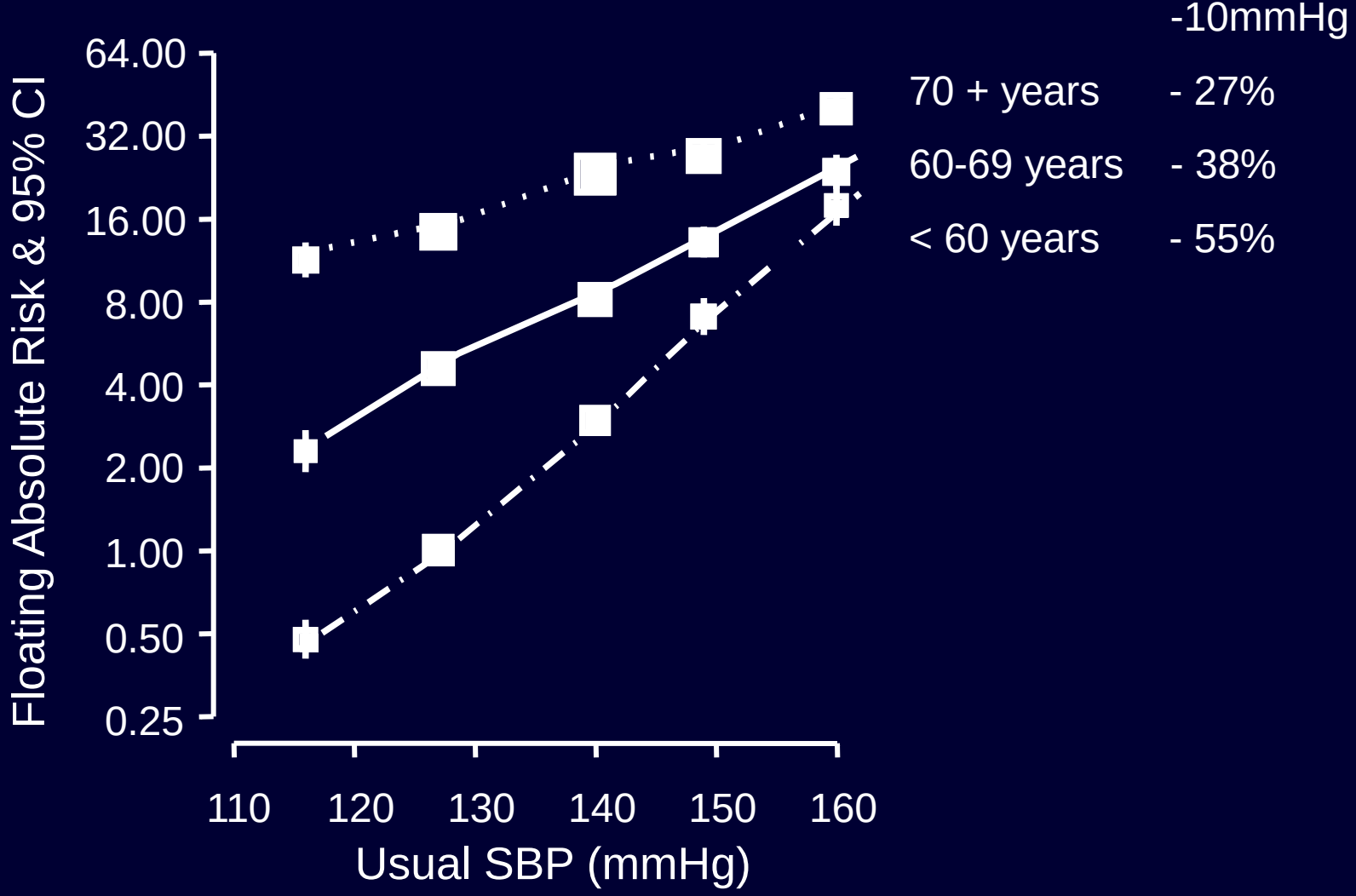




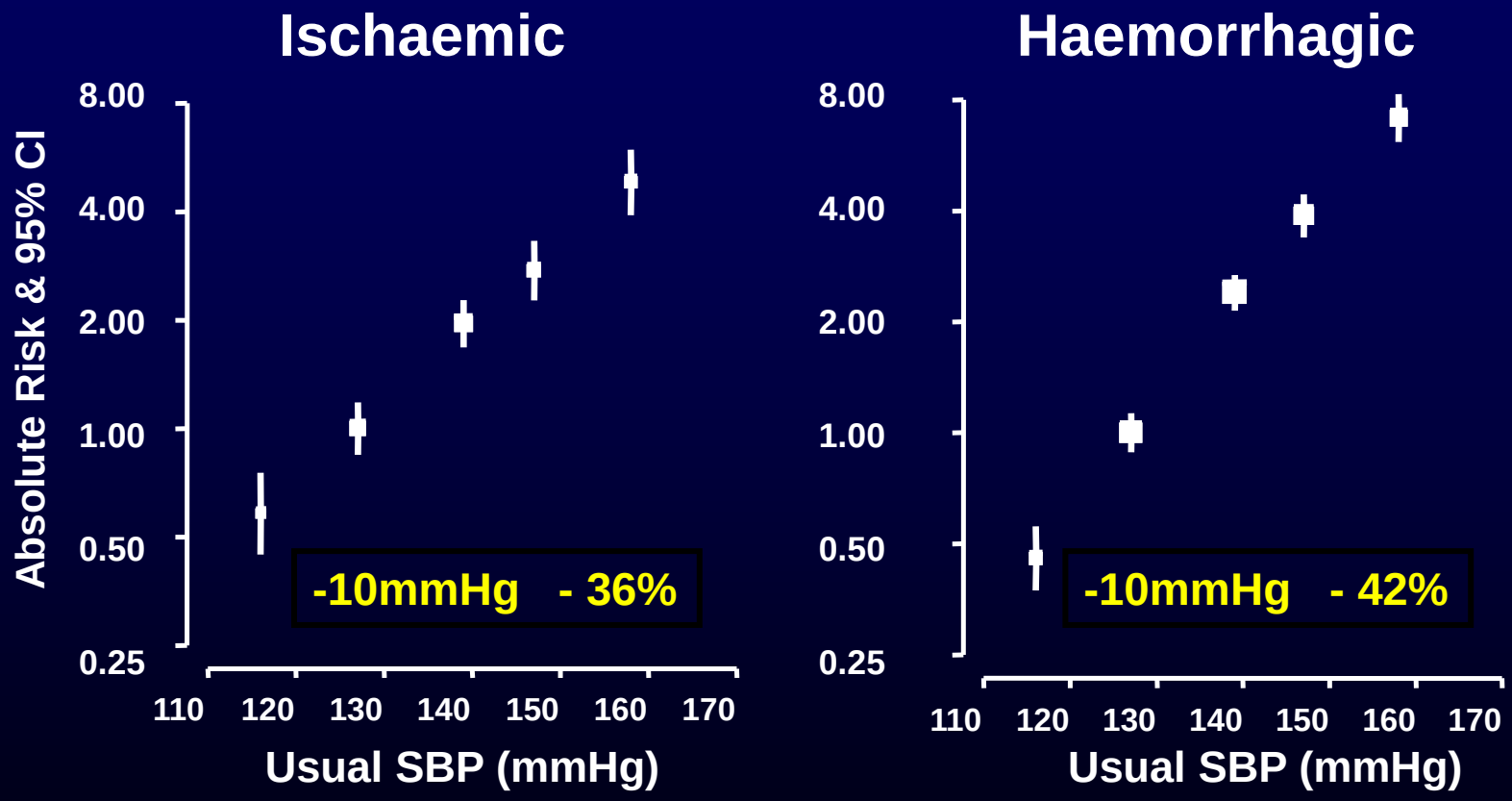
Asia Pacific Cohort Studies Collaboration

SBP and primary stroke

425, 251 participants, 4,708 strokes, 3.2M person-years



BP and Stroke Risk (From APCSC)



APCSC, 2003

Population attributable fractions for stroke

Blood pressure	55-75%
Cholesterol	25-35%
High body mass index	20-30%
Low fruit & vegetables	20-30%
Physical inactivity	10-20%
Tobacco	10-20%
Alcohol	<5%
Urban air pollution	<5%
Lead exposure	<5%

World Health Report 2002

WHO/ISH Hypertension and Stroke

25 May 1993 NARA (JAPAN)

PROGRESS

PERINDOPRIL PROTECTION AGAINST RECURRENT STROKE STUDY

Aim

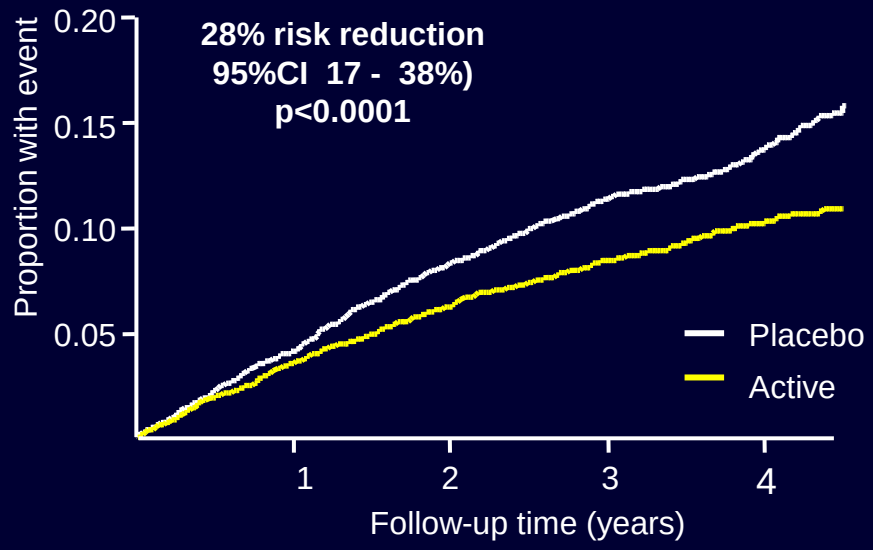
To determine balance of benefits and risks conferred by an ACE inhibitor based BP lowering regimen (perindopril + indapamide) among patients with a history of stroke or TIA and a wide range of BP at entry.

Funded by

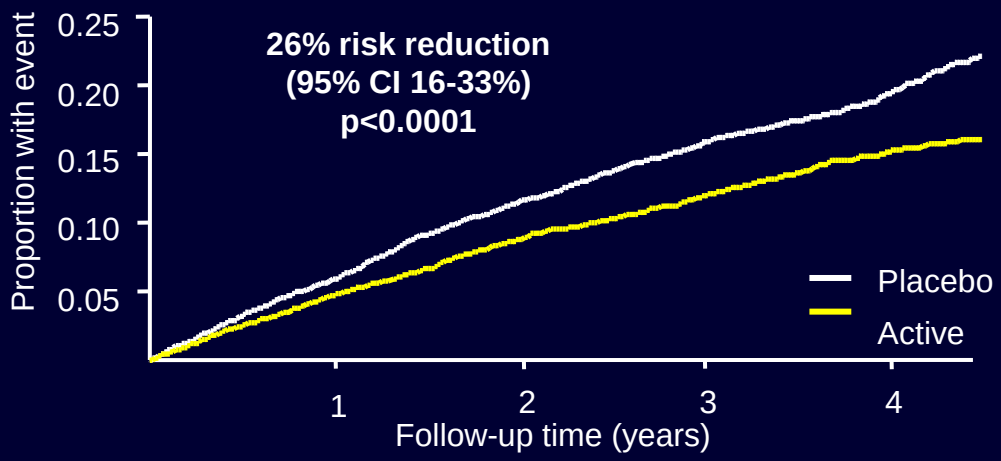
NHMRC and Servier

PROGRESS
Major outcomes

Stroke



Major Vascular Events

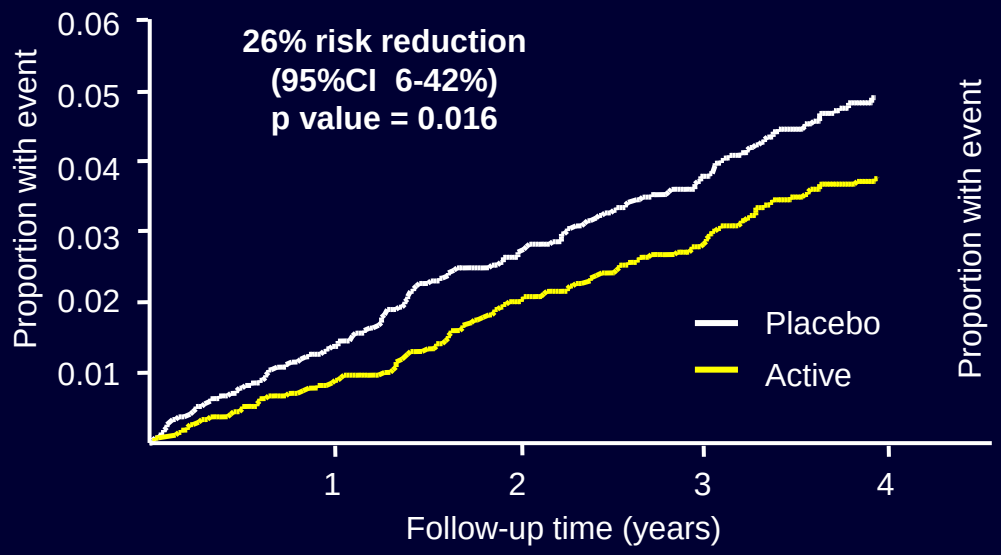


- BP Lowering in patients with previous stroke or TIA
- 6105 patients:10 countries: Europe, Asia, ANZ

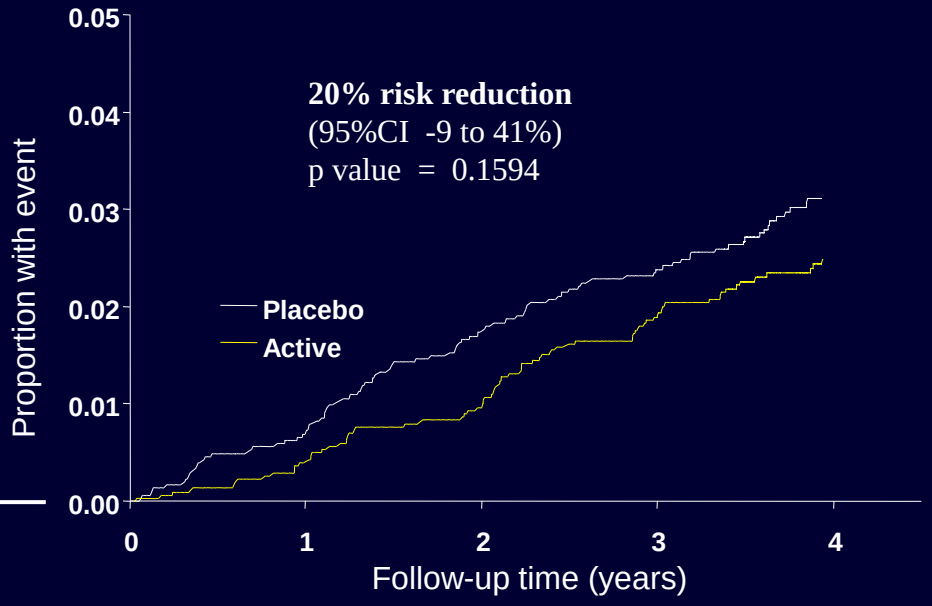
IIH 2001

PROGRESS
Major outcomes

Major Coronary Events

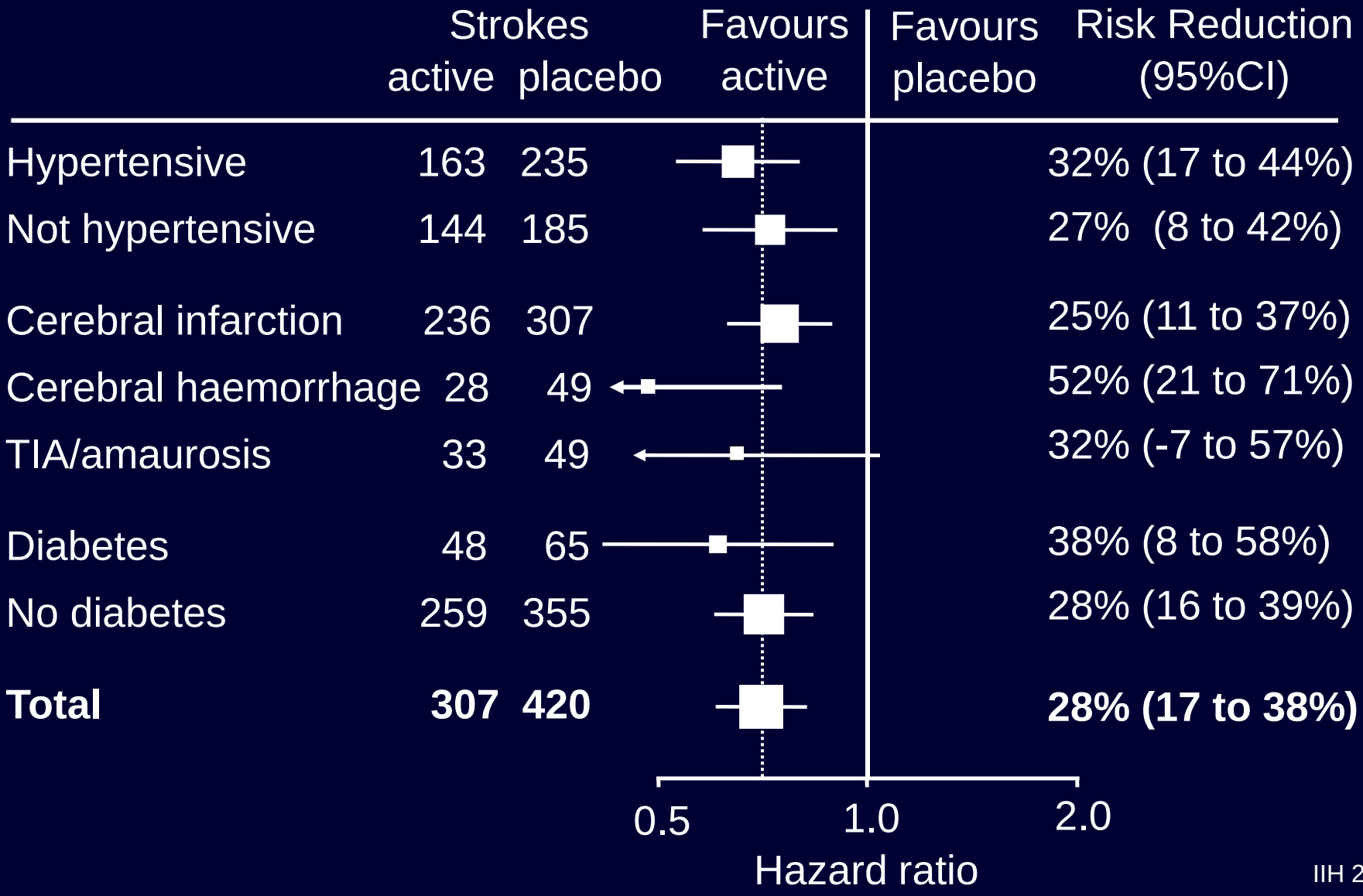


Heart Failure



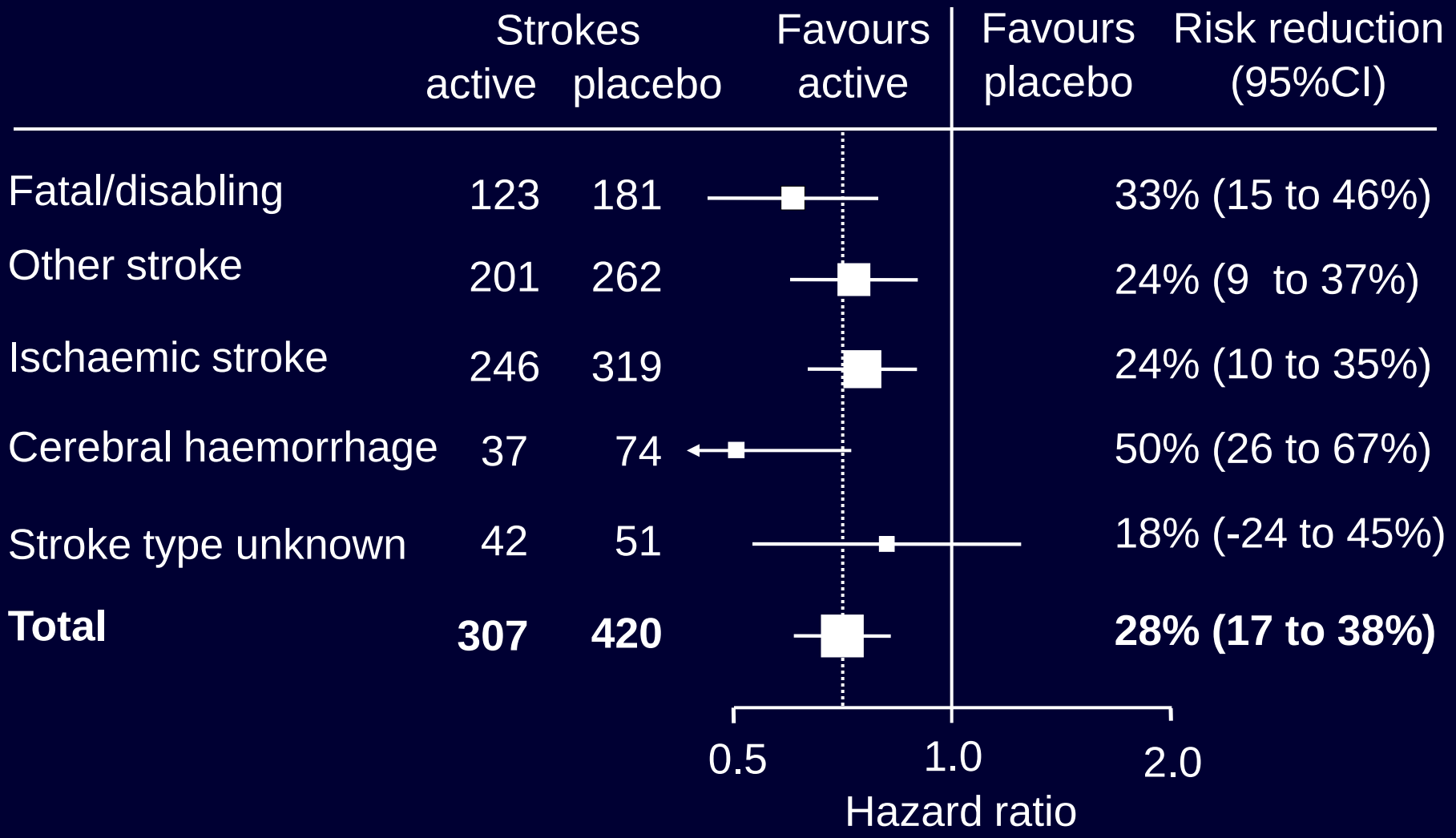
IIH 2001

Stroke by medical history



IIH 2001

Stroke severity and subtype



IIH 2001

Summary of benefits

PROGRESS established benefits of a BP lowering regimen involving ACEI (perindopril) and diuretic (indapamide) among patients with stroke or TIA for the prevention of:

- Secondary stroke
- Primary myocardial infarction
- Total major vascular events

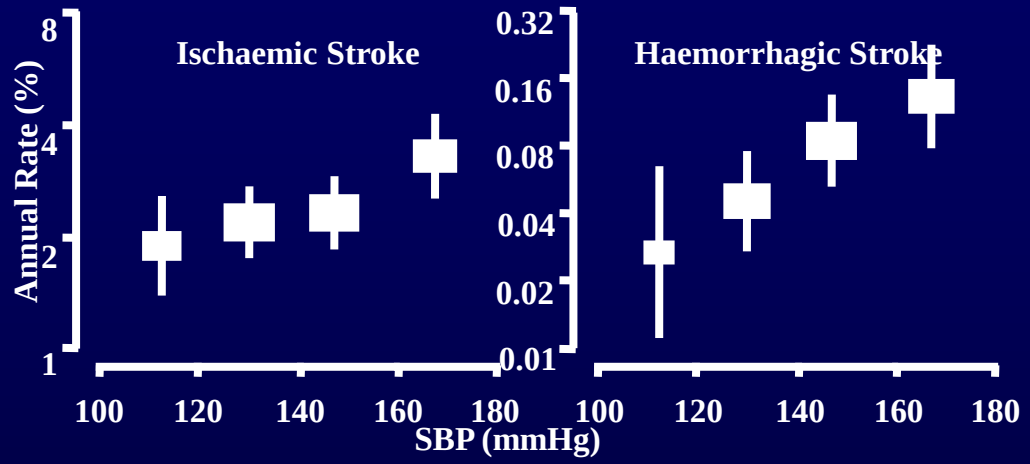
Absolute benefits

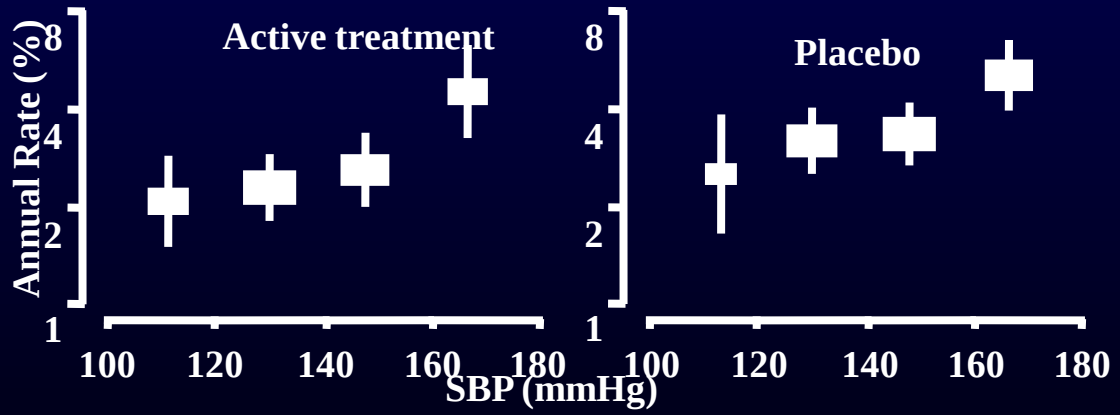
Effects of combination therapy with perindopril and indapamide:

- One fatal or major nonfatal vascular event prevented among every 11 patients (95% CI 9-16) treated for five years (about 2% per year)

PROGRESS

PROGRESS: Risk of recurrent Stroke by Achieved SBP





Arima H et al,
J Hypertens 2006;24:1201-08

PROGRESS

PERINDOPRIL PROTECTION AGAINST RECURRENT STROKE STUDY

PROGRESS Collaborative Group

Institute for International Health
www.iih.org/progress

EPIDEMIOLOGY OF BLOOD PRESSURE IN ACUTE STROKE

EPIDEMIOLOGY OF BLOOD PRESSURE IN ACUTE STROKE

Situation - Early 21st century

1. Early Hypertensive response is v common
2. Concerns re J-shaped curve for BP & and adverse outcomes
3. The J occurs at lower values for ICH than IST
4. Much observational evidence suggested benefit from lower BP in acute stroke
5. Not matched by randomised trial evidence
6. Much more research needed

The early hypertensive response (>140/90) in acute stroke-first 48 hours

70% SBP in Acute Stroke in US National Hospital Ambulatory Care Survey (1)

82% SBP in Isch stroke in Int Stroke trial (2)

75% SBP in Ischaemic Stroke in Chinese CAST Trial (3)

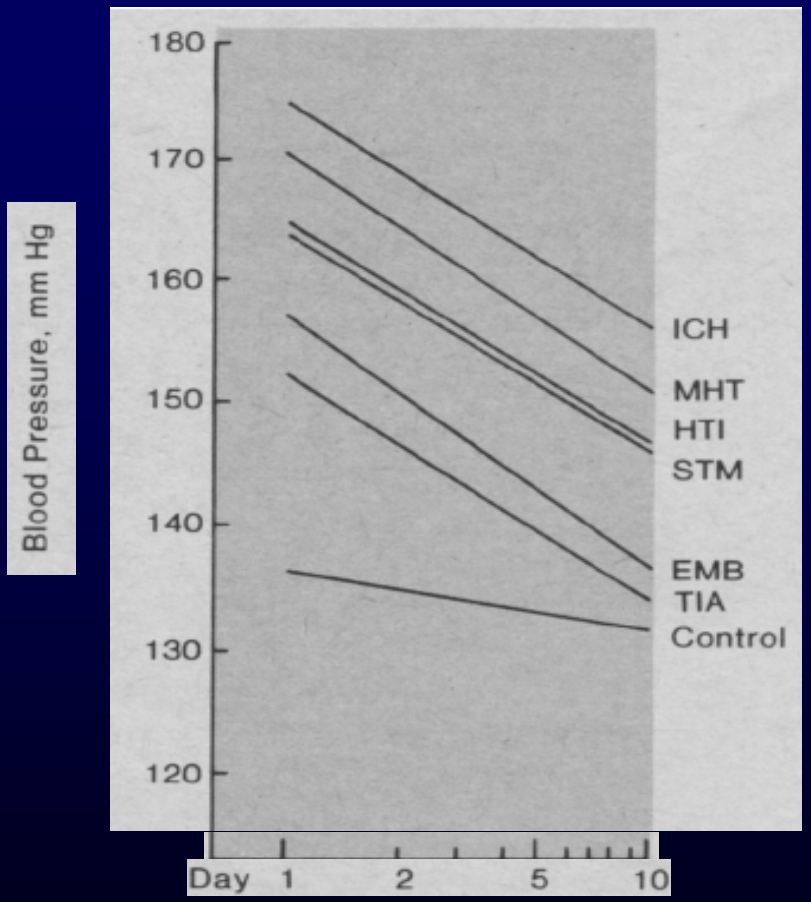
BP settles over a few days

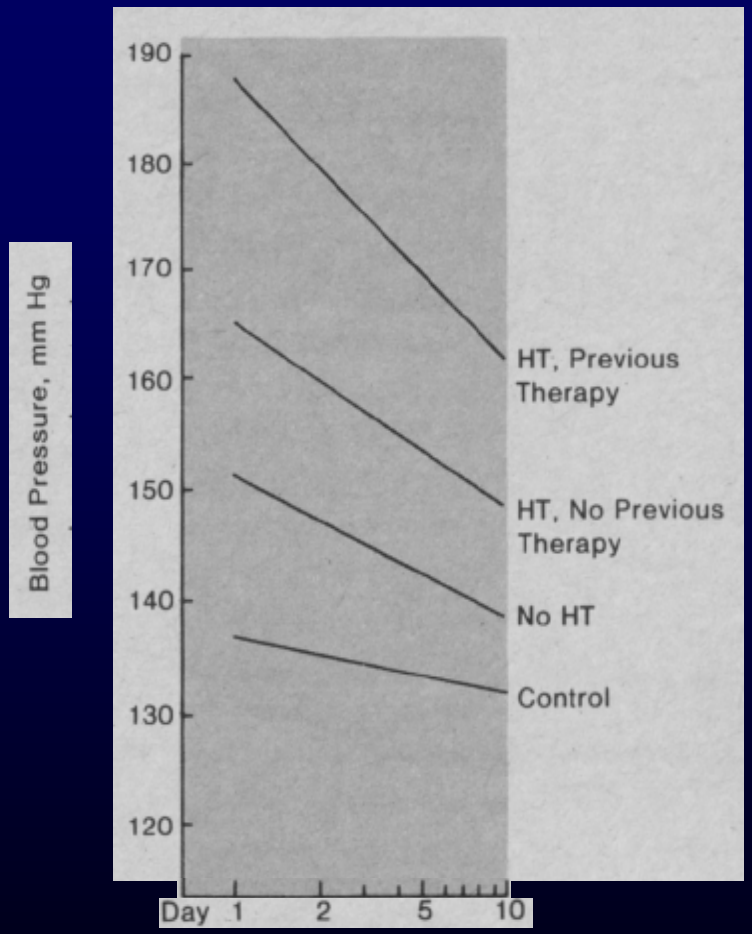
1. Quereshi. Amer J Emerg Med 2007;25:32-38

2 . Leonardi-Bee. Stroke 2002;33:1315-20

3. CAST Collab Gp. Lancet 1997;349:1641-49

SBP Changes in 1st 10 days after Stroke





Wallace and Levy JAMA 1981; 246: 2177-2180

THE GEORGE INSTITUTE
for International Health

Supported by NHMRC program grant

Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial

interact

Pilot phase completed in 2009 in 404 patients in Australia and China, with acute intra-cerebral haemorrhage –established safety and feasibility.

Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial

interact2

The second, main phase, INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial

2839 patients from 21 countries across Europe, N and S America, Asia, Australia

(NEJM 2013;368:2355-65)

for the INTERACT2 Investigators at 144 hospitals in 21 countries

An international collaboration
THE GEORGE INSTITUTE
for Global Health

Funded by NHMRC

Australian Government
National Health and Medical Research Council
NHMRC

Primary Objective—to test the hypothesis

- ***That a management Strategy*** of:
  - **early intensive blood pressure (BP) lowering** (target of <140 mmHg systolic) as compared to the
  - **guideline-recommended 'standard' control** of BP (target of <180 mmHg systolic) improves
  - ***Would improve*** survival free of major disability at 90 days, in acute intracerebral haemorrhage (ICH)

Standardised treatment protocols – locally available intravenous (IV) BP lowering agents of physician's choice

Study plan

(published *Int J Stroke* before unblinding)

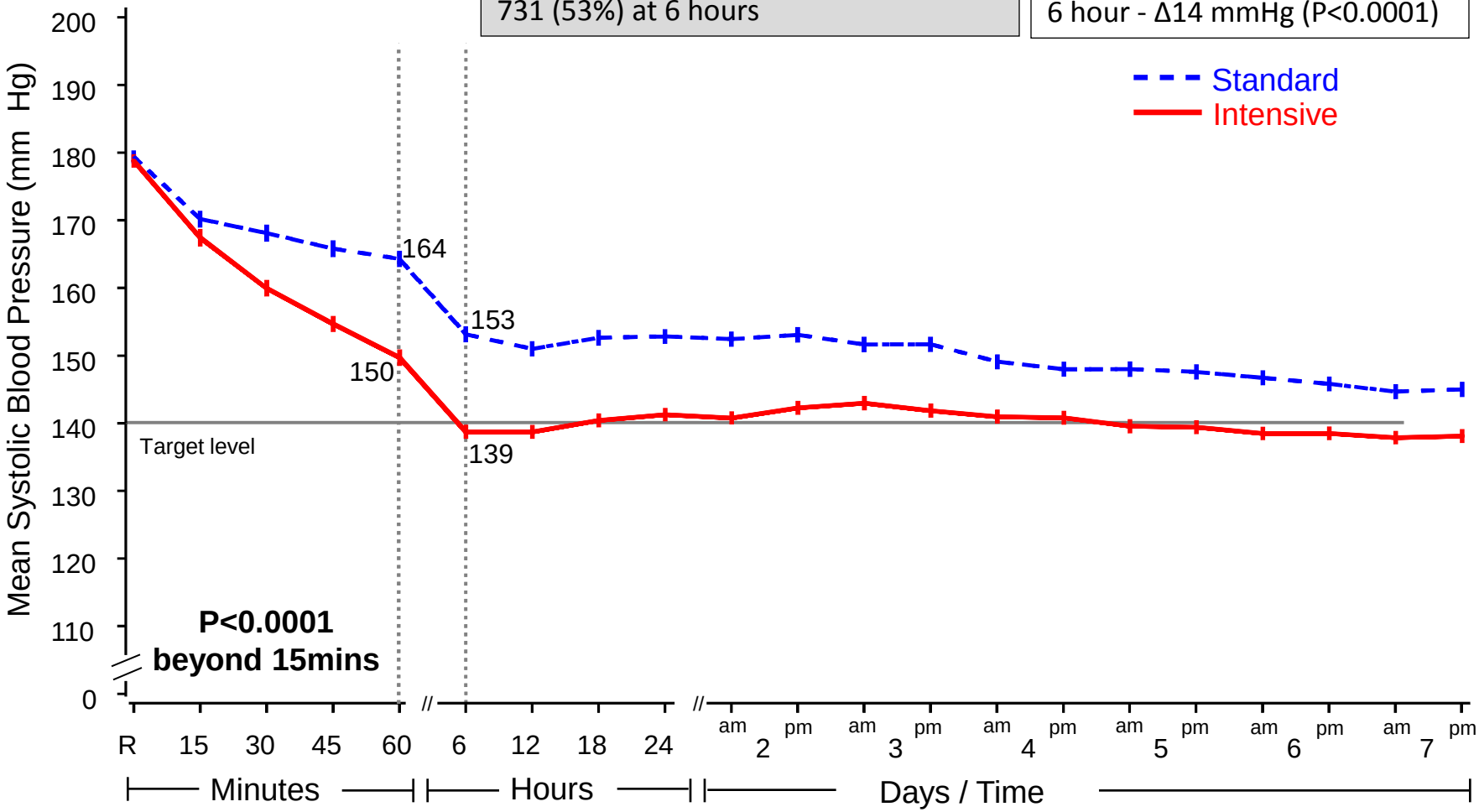
- Patients: Acute ICH, confirmed by CT/MRI, Randomised < 6 hours, SBP 150-220mmHg
- PROBE design
- Primary outcome – mRS 0-2 (Alive and well) vs **3-6 (Dead or disabled)**
- Key secondary outcome- ordinal shift, logistic regression, mRS
- A number of pre-specified Subgroups

Systolic BP control

Median (iqr) time to treatment, hr - intensive 4 (3-5), standard 5 (3-7)

Intensive group to target (<140mmHg)
462 (33%) at 1 hour
731 (53%) at 6 hours

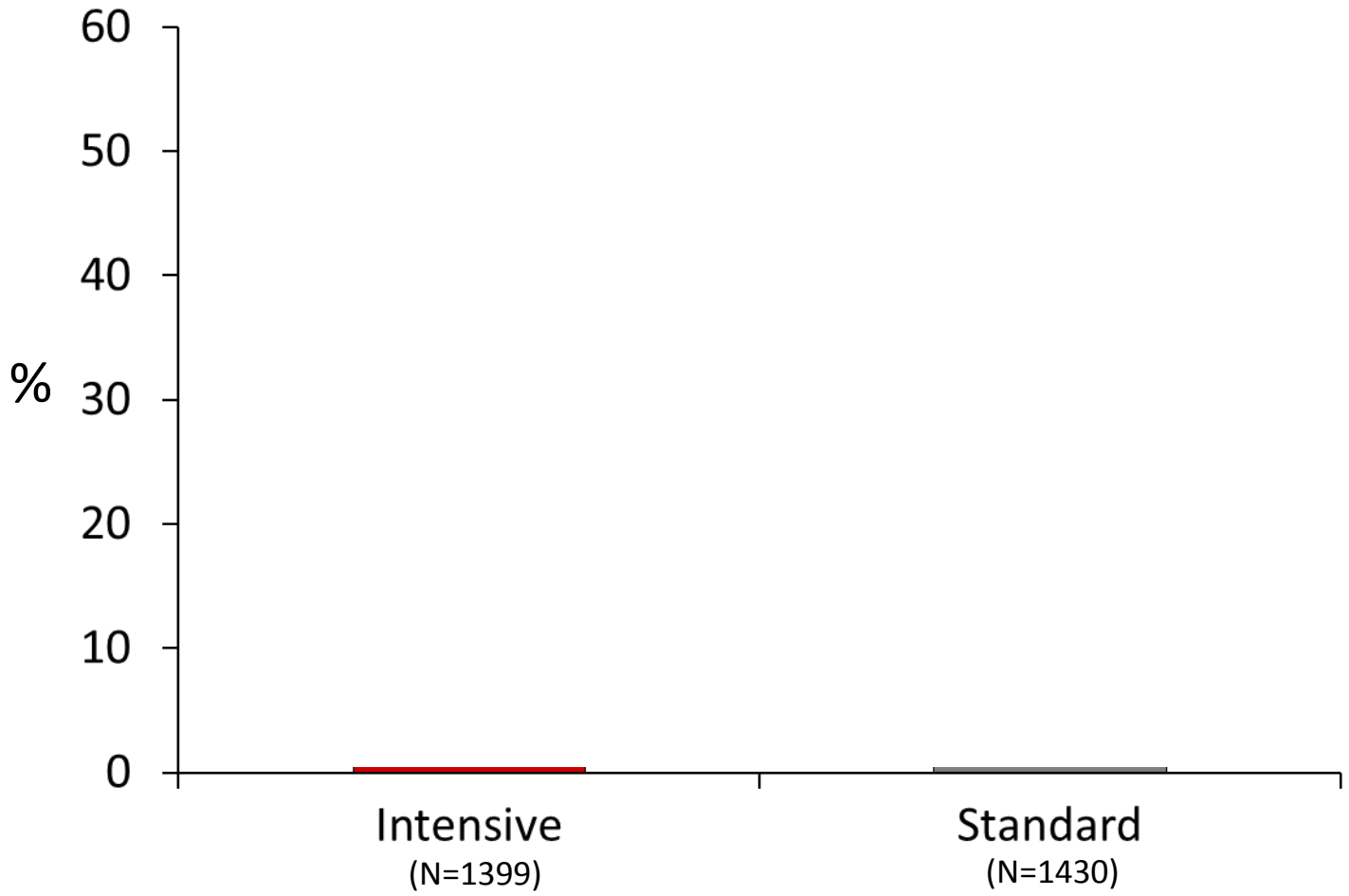
Systolic BP time trends
1 hour - Δ14 mmHg (P<0.0001)
6 hour - Δ14 mmHg (P<0.0001)



Primary clinical outcome

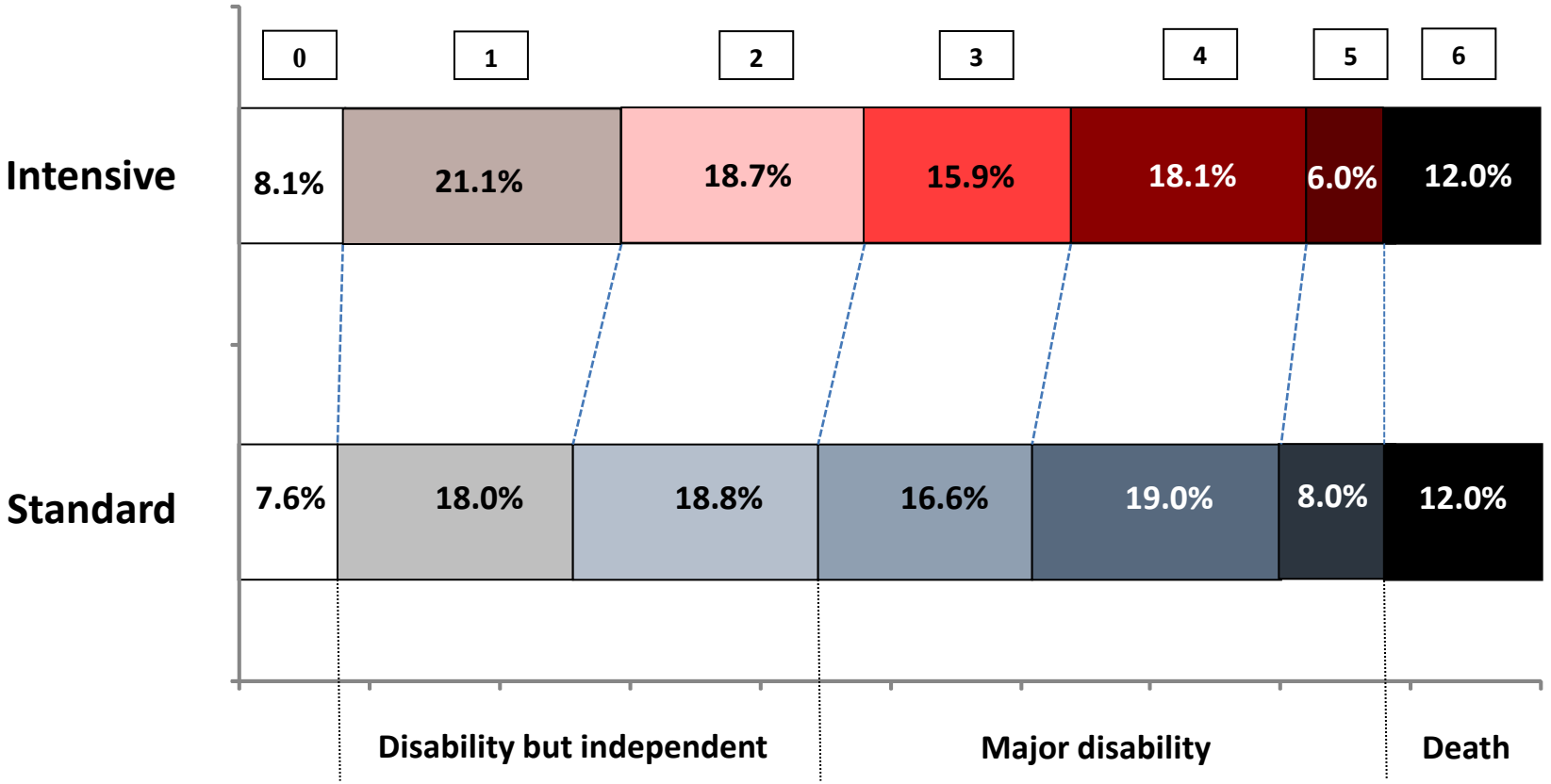
Death or major disability (mRS 3-6) at 90 days

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



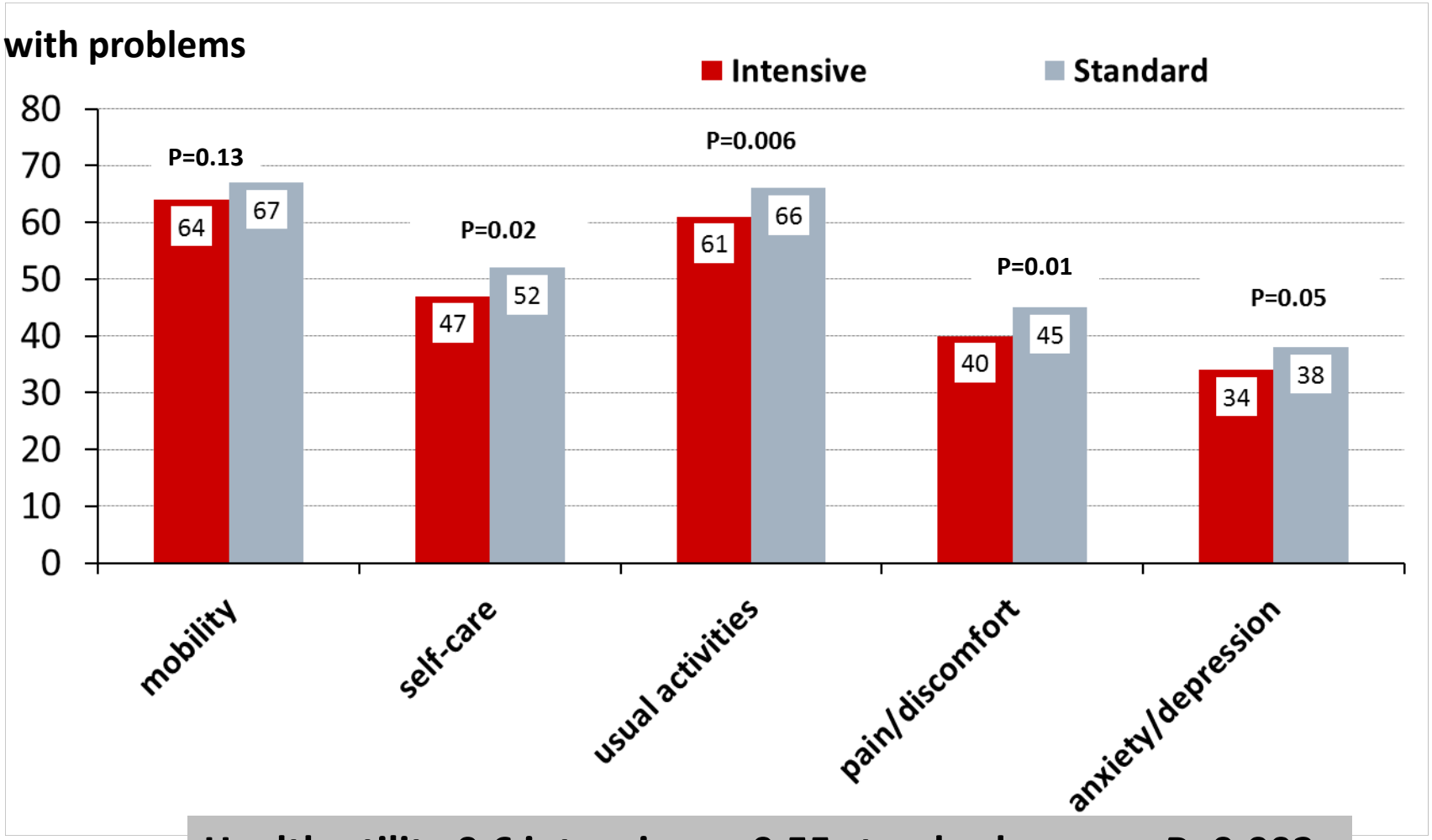
Key 2ry outcome: Global functional recovery
Ordinal shift in mRS scores (0-6)

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



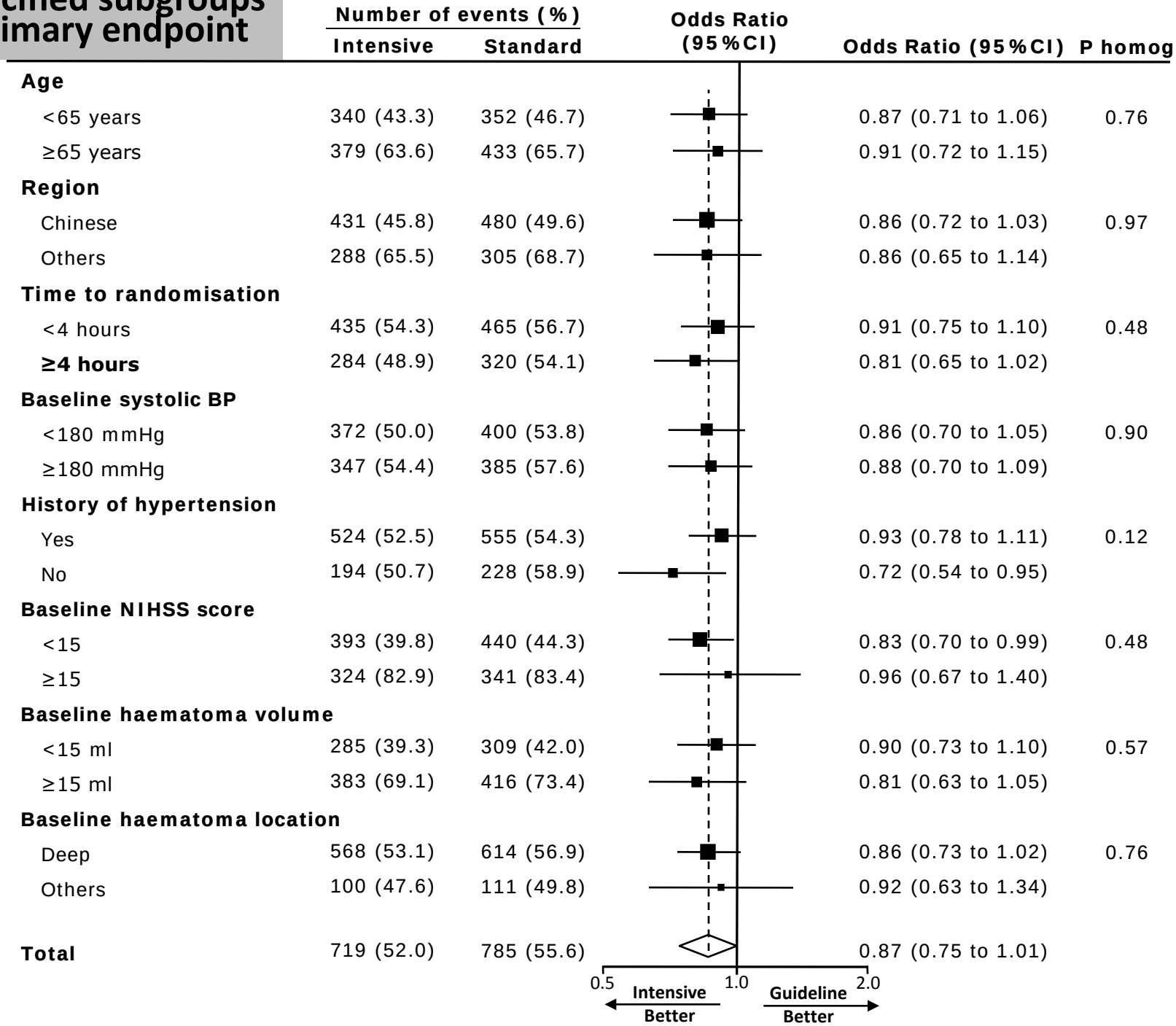
Health-related quality of life

EuroQol EQ-5D domains ‘any problems’ versus ‘no problems’



Health utility 0.6 intensive vs 0.55 standard groups; P=0.002

Pre-specified subgroups and primary endpoint



Other pre-specified clinical and safety outcomes

Parameter	Intensive (N=1399)	Standard (N=1430)	P
Clinical			
Hospital stay, median (iqr)	20 (12-35)	19 (11-33)	0.43
Institutional care at 90 days	9%	9%	0.80
Poor outcome at 28 days	66%	68%	0.22
Safety			
Neurological deterioration in 24 hr	66%	68%	0.22
Deaths from initial ICH	7%	8%	0.67
Non-fatal SAEs	23%	24%	0.92
Severe hypotension	0.5%	0.6%	0.83

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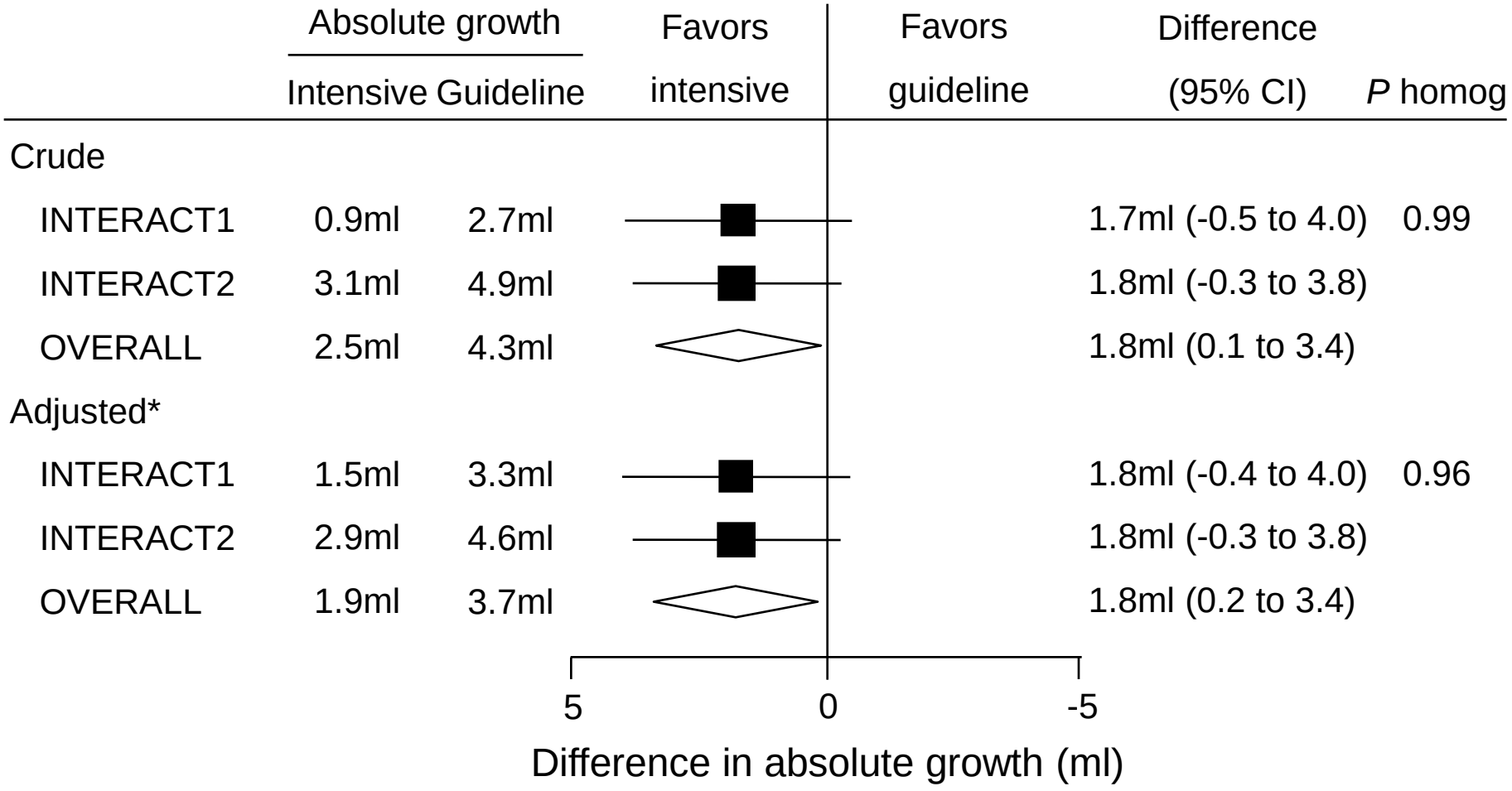
INTERACT1 and 2 CT substudies

Effects of BP lowering on hematoma growth



*Adjusted for baseline volume and location of hematoma, time from onset to CT and trial.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

J. Claude Hemphill III, Steven M. Greenberg, Craig S. Anderson, Kyra Becker, Bernard R. Bendok, Mary Cushman, Gordon L. Fung, Joshua N. Goldstein, R. Loch Macdonald, Pamela H. Mitchell, Phillip A. Scott, Magdy H. Selim and Daniel Woo

Stroke. published online May 28, 2015;

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society

This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on January 28, 2015, and the American Heart Association Executive Committee on February 16, 2015. A copy of the document is available at http://my.americanheart.org/statements by selecting

Recommendations for the control of blood pressure in ICH patients

American Heart Association | American Stroke Association

1. For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe *(Class I; Level of Evidence A)* and can be effective for improving functional outcome *(Class IIa; Level of Evidence B)*. (Revised from the previous guideline)
2. For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring *(Class IIb; Level of Evidence C)*. (New recommendation)

Major findings of INTERACT2

- **BP lowering in acute ICH to target 140mmHg:**
- ***Effective!*** Less disability, better functional outcome & health related QoL
- ***Safe!*** No increase in death or adverse events
- ***Consistent*** effect across patient/disease characteristics
- Effects on haematoma growth – time dependent

Major findings of INTERACT2

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- ***Effective!*** Less disability, better functional outcome & health related QoL
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- ***Consistent*** effect across patient/disease characteristics
- Effects on haematoma growth – time dependent

- **BP lowering most effective when:-**
  - **Early**
  - **Fast**
  - **Sustained**

⇒ Should be considered for all ICH patients

Enchanted

Enhanced Control of Hypertension and Thrombolysis Stroke Study

Presented at European Stroke Organisation Conference Barcelona, 10th May 2016 And NEJM ePub ahead of print

For the ENCHANTED Investigators and coordinators

An international collaborative project of

THE GEORGE INSTITUTE for Global Health

Main funding support

Australian Government National Health and Medical Research Council

NHMRC

Other funding support

the Stroke Association of the United Kingdom

the National Council for Scientific and Technological Development of Brazil

the Ministry for Health, Welfare and Family Affairs of the Republic of Korea

PRIMARY AIMS: to answer reliably 4 major research questions in acute ischaemic stroke

- **Compared to standard-dose (0.9 mg/kg) rtPA,**

  is low-dose (0.6 mg/kg) i.v. rtPA:

  1. *'non-inferior'* - clinical outcome (mRS 2-6) at 90-days
  2. safer - lower risk of *major* sICH?

- **Compared to guideline recommended BP control (<185 mmHg systolic target before initiation of rtPA),**

  is rapid intensive BP lowering (130-140 mmHg SBP target):

  3. *superior* - clinical outcomes (mRS 2-6) at 90-days
  4. safer - lower risk of *any* ICH

PRIMARY AIMS: to answer reliably 4 major research questions in acute ischaemic stroke

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  1. '*non-inferior*' - clinical outcome (mRS 2-6) at 90-days
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- **BP arm continuing,**
  (1150 patients recruited to date;
  (Completion expected 2018-with presentation in 2019)

Background and rationale for dose arm

- Standard dose (0.9mg/kg) approved after NIH stroke trial vs placebo
- Dose 0f 0.9mg/kg derived from preliminary, non-randomised, dose escalation studies in only 74 patient
- Regulatory approved dose pof 0.6mh/kg approved in Japan, on basis of number of small registry studies
- Variable dose of rtPA used in Asia – due to affordability and IC risk perception

Background and rationale

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- Regulatory approved dose pof 0.6mh/kg approved in Japan, on basis of number of small registry studies
- Variable dose of rtPA used in Asia – due to affordability and ICH risk perception
- **No strong basis for choice of dose**

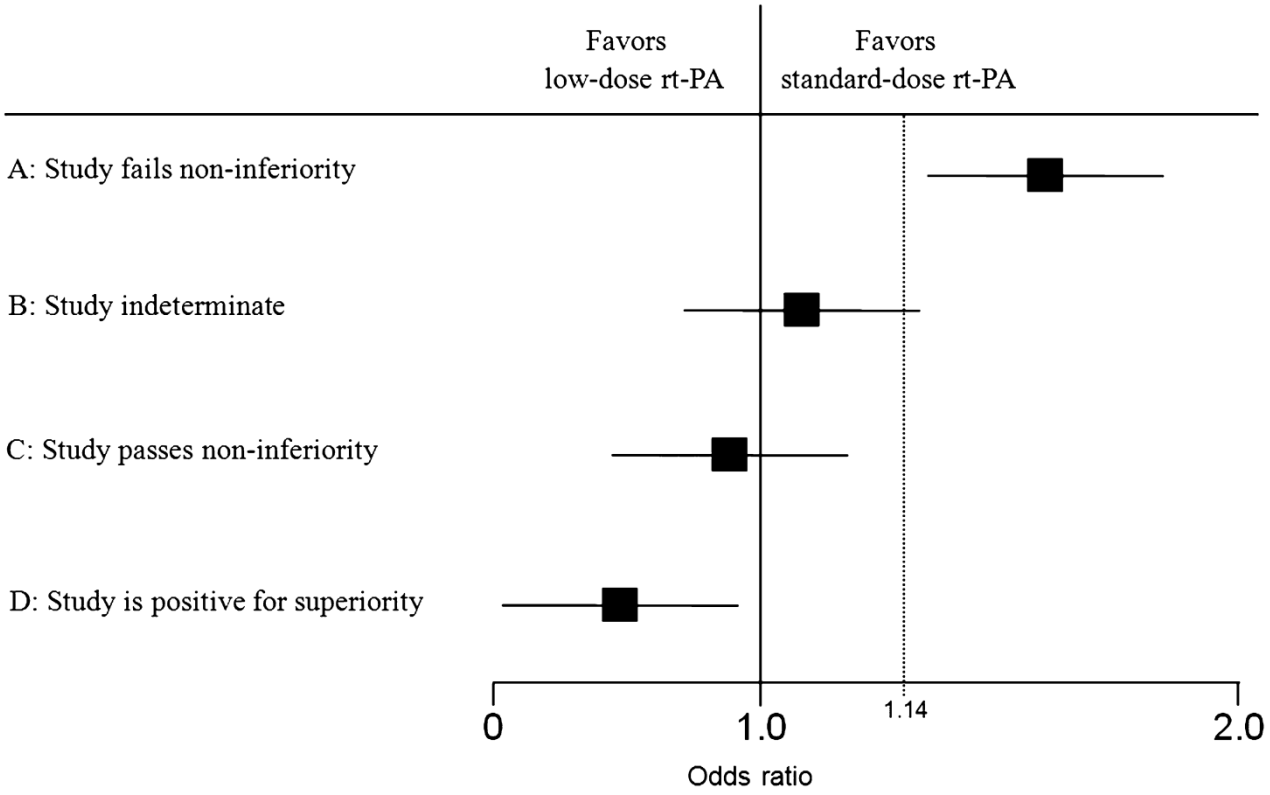
Study plan for dosage arm

Protocol & Analysis plan both published in Int J Stroke

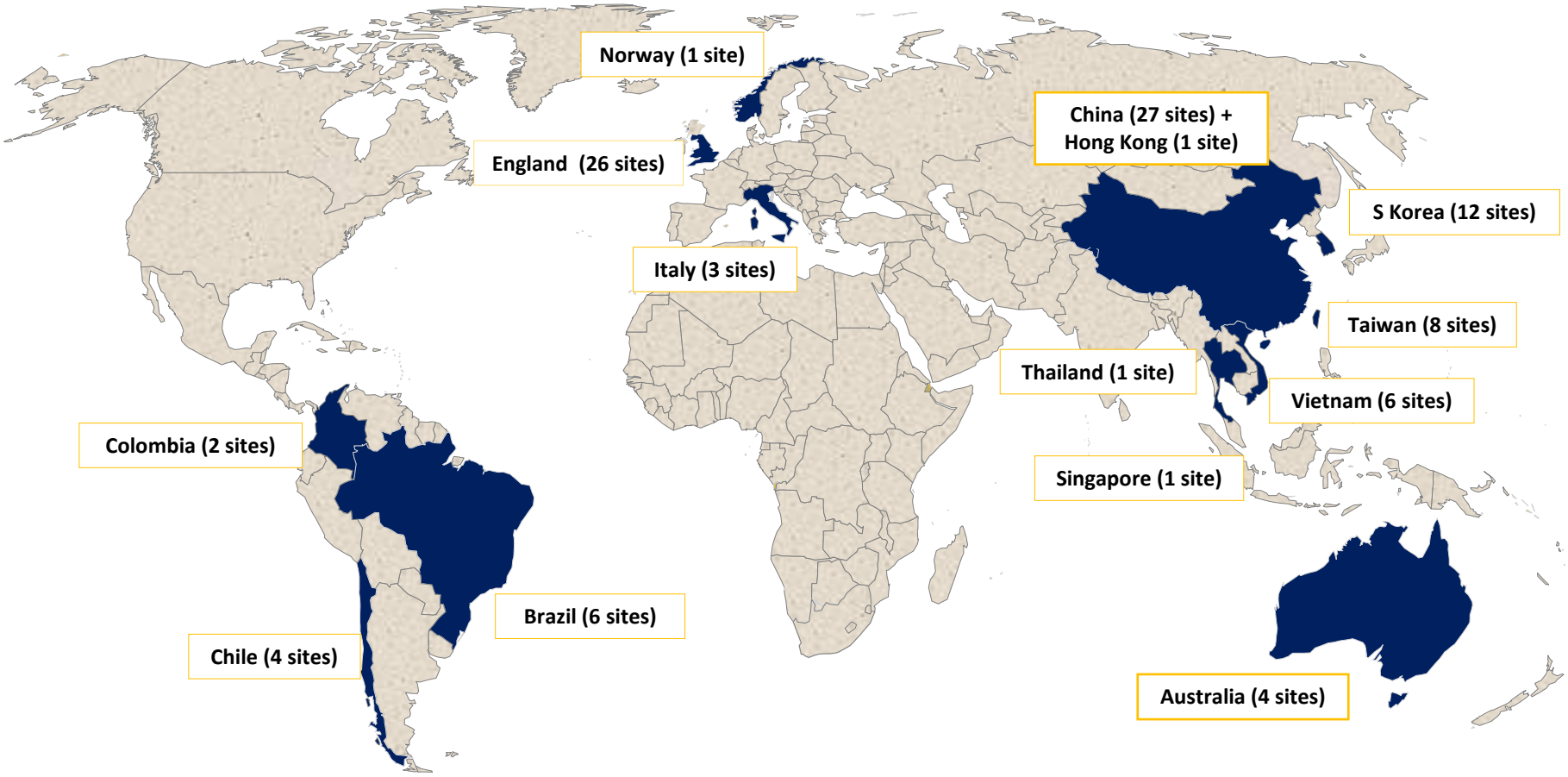
- **Patients**: Acute ischaemic stroke, confirmed by CT/MRI, Randomised within 4.5 hours, SBP ≤185mmH
- **PROBE design** – analysis by ITT
- **Primary outcome** – mRS 0-1 (Alive and well) vs 2-6 (Dead or disabled) – analysed by non-inferiority
- **Key safety outcome** – (ICH by SITS-MOST)
- **Key secondary outcome-** ordinal shift, logistic regression, mRS
- **Pre-specified Subgroups**

Statistical analysis approach for non-inferiority (NB: ITT)

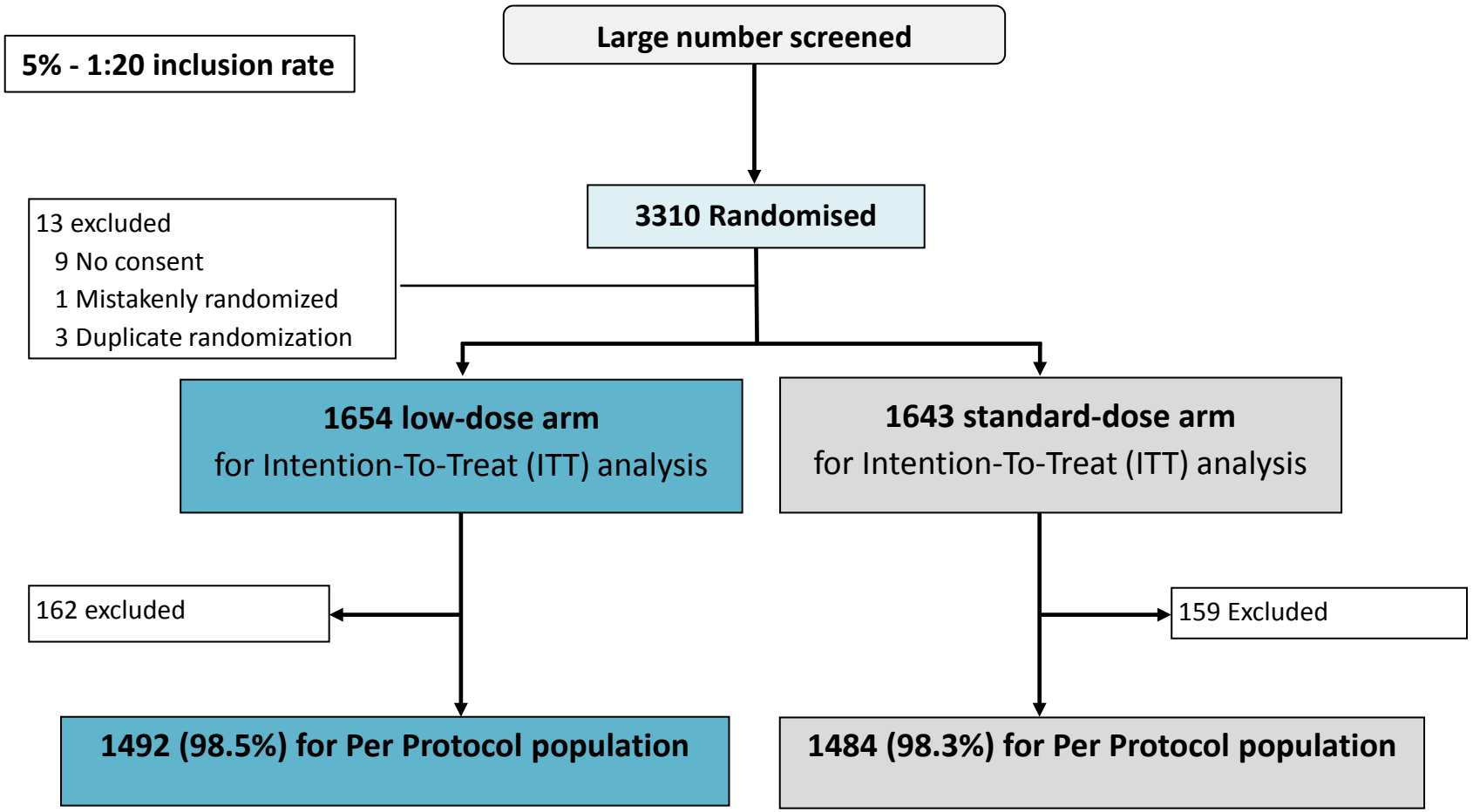
Sample size of N=3300 (1650 per group): estimated to provide >90% power (1-sided α 0.025) to achieve the noninferiority setting, assuming 5% drop-out with the ability to also assess for superiority of low- versus standard-dose r-tPA; and >80% power (2-sided α 0.05) to detect >40% relative reductions in sICH for the low-dose r-tPA group, with 5% of drop-out.



ENCHANTED – network (13 countries worldwide)



Patient Flow



Results

Baseline - Demographic and clinical

Variable	Low-dose N=1654	Standard dose N=1643
Age median (iqr)	68 (58-76)	67 (58-76)
Female	38%	37%
China (origin)	43%	43%
Asian (ethnicity)	63%	63%
History of hypertension	63%	63%
Blood pressure (mmHg)	149/84	150/85
NIHSS median (iqr) score	8 (5-14)	8 (5-14)
GCS median (iqr) score	15 (14–15)	15 (14–15)
Aspirin / Other APT	25%	21%
Large artery occlusion	38%	40%
Cardio-embolism	20%	20%
Small vessel on Lacunar disease	20%	21%

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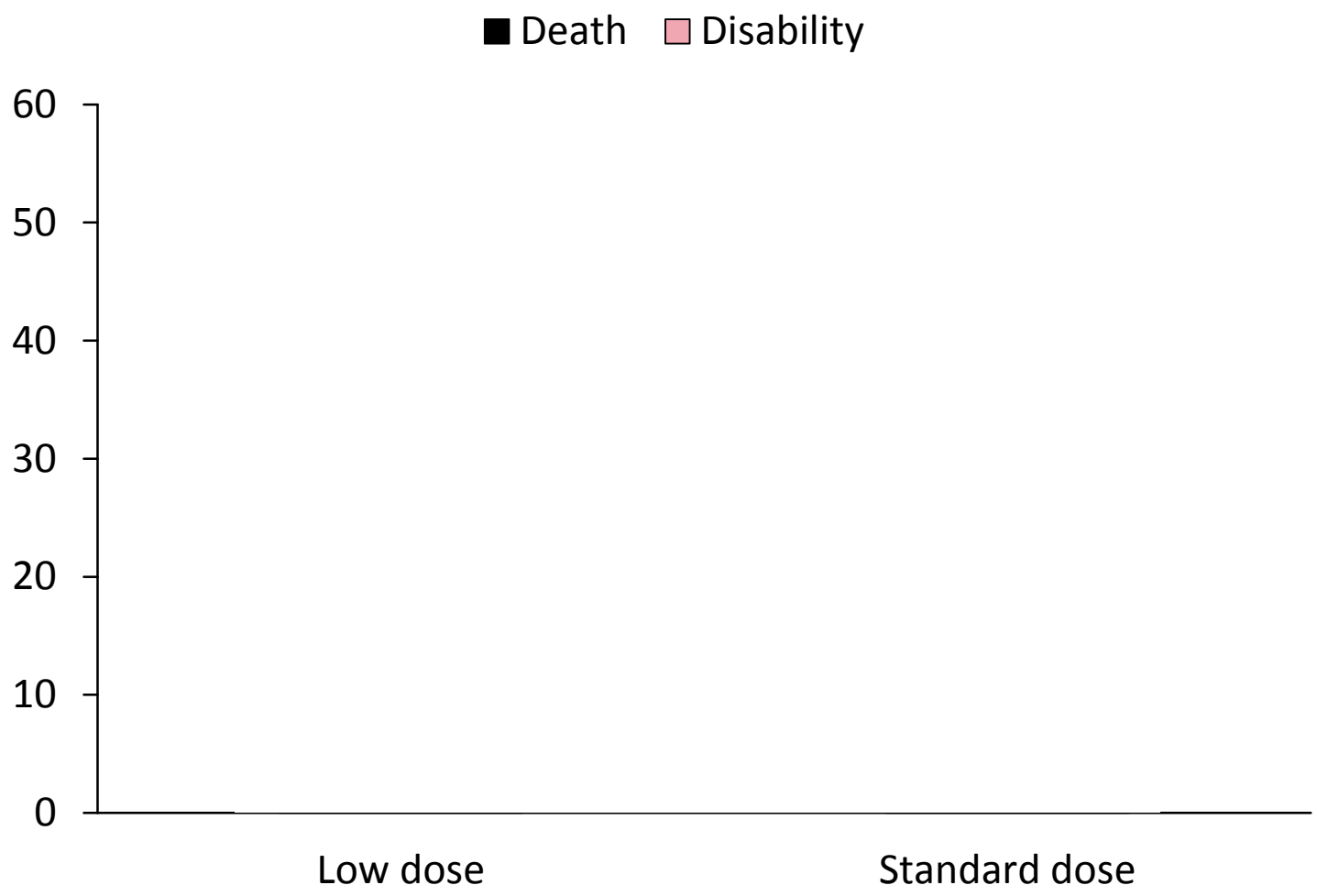
Randomised treatment Timing and dose of rtPA

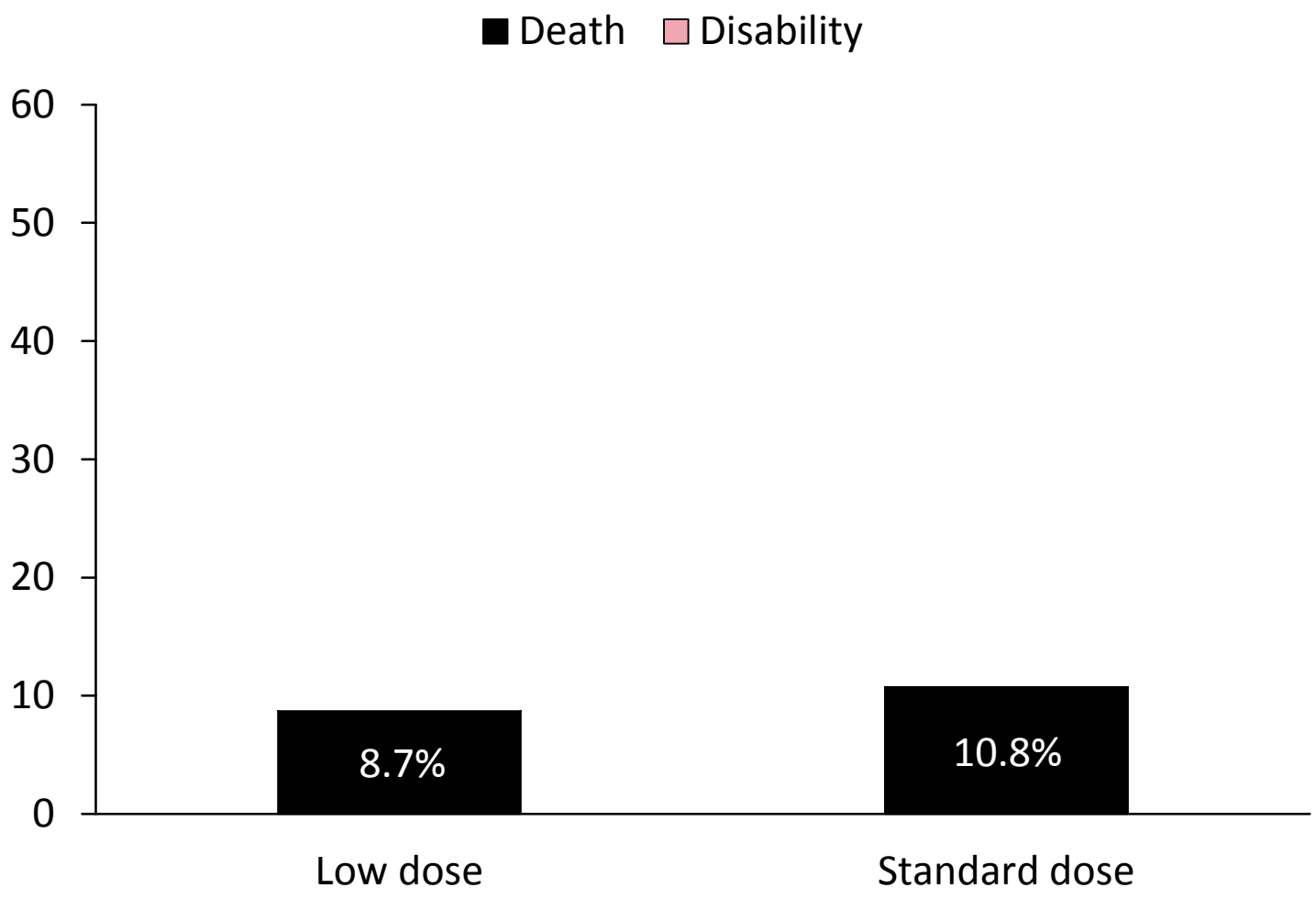
Variable	Low-dose (N=1654)	Standard-dose (N=1643)
Time from onset to treatment – mins		
Median	**170**	**170**
Interquartile range	125-218	127-219
Estimated body weight prior to rtPA	70±14	70±14
Measured body weight after rtPA	1495 (90%)	1475 (90%)
Direct measured body weight after rtPA	69±15	69±14
rtPA given to patients - n (%)	1628 (98%)	1617 (98%)
Bolus infusion dose - mg	6.2±1.2	6.3±2.1*
Maintenance infusion dose - mg	**35.5±7.3**	**56.0±11.3****

*P=0.05 and **P<0.001

Primary clinical outcome
Death or disability (mRS 2-6) at 90 days



Primary clinical outcome
Death or disability (mRS 2-6) at 90 days



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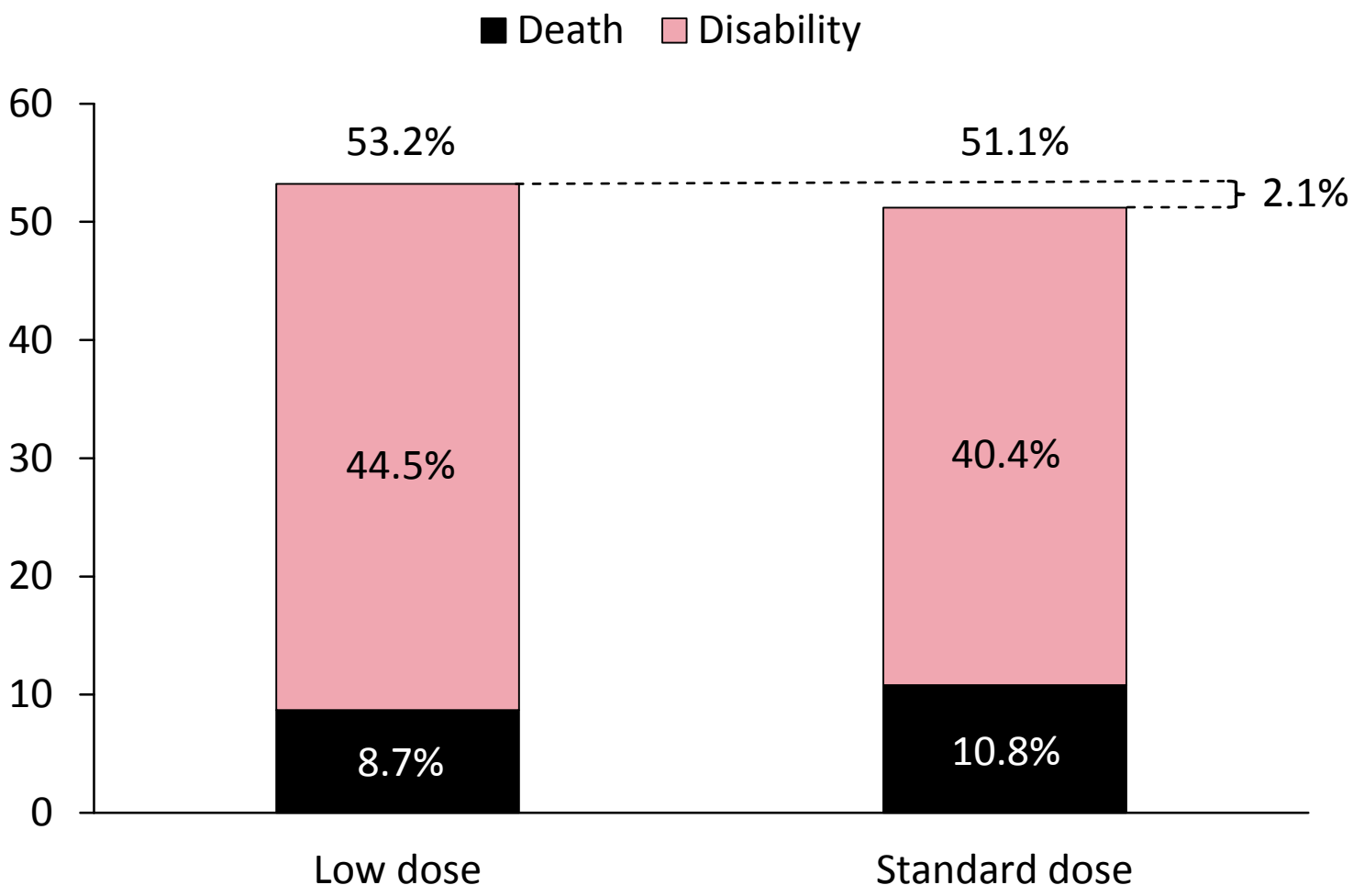
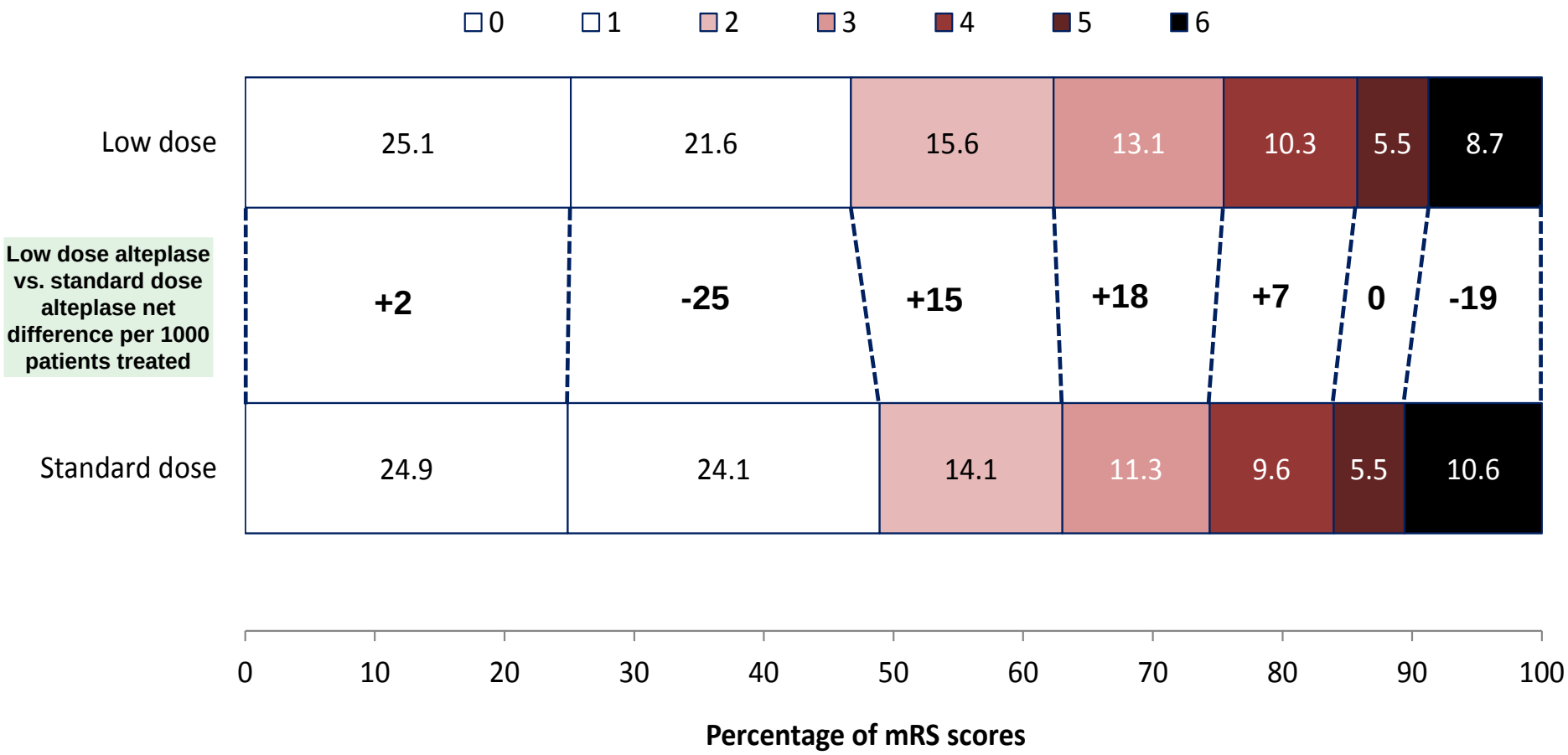


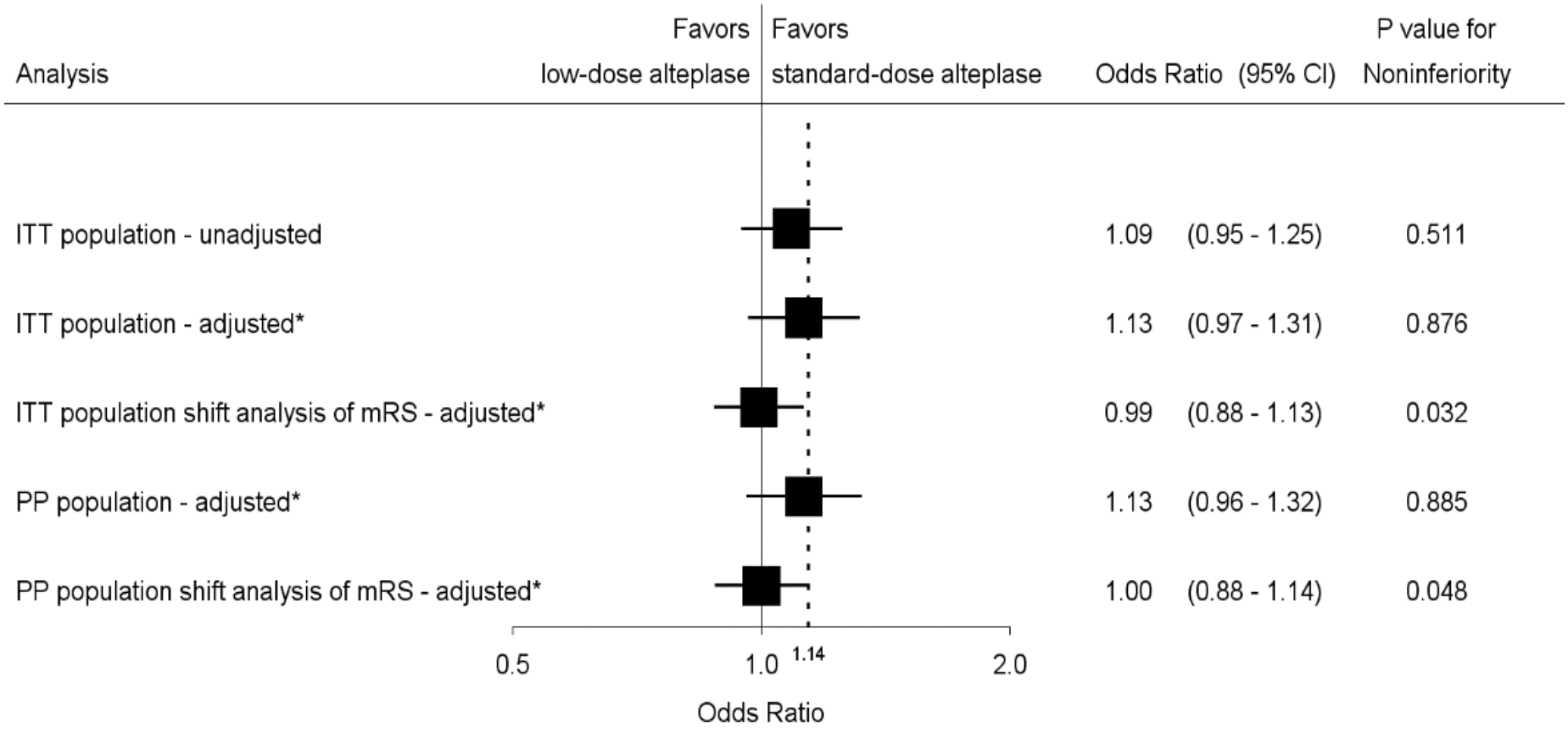
Key secondary outcome

Ordinal shift in mRS scores (0-6)

Odds ratio 0.99 (95%CI 0.88 to 1.13); P=0.032 for noninferiority

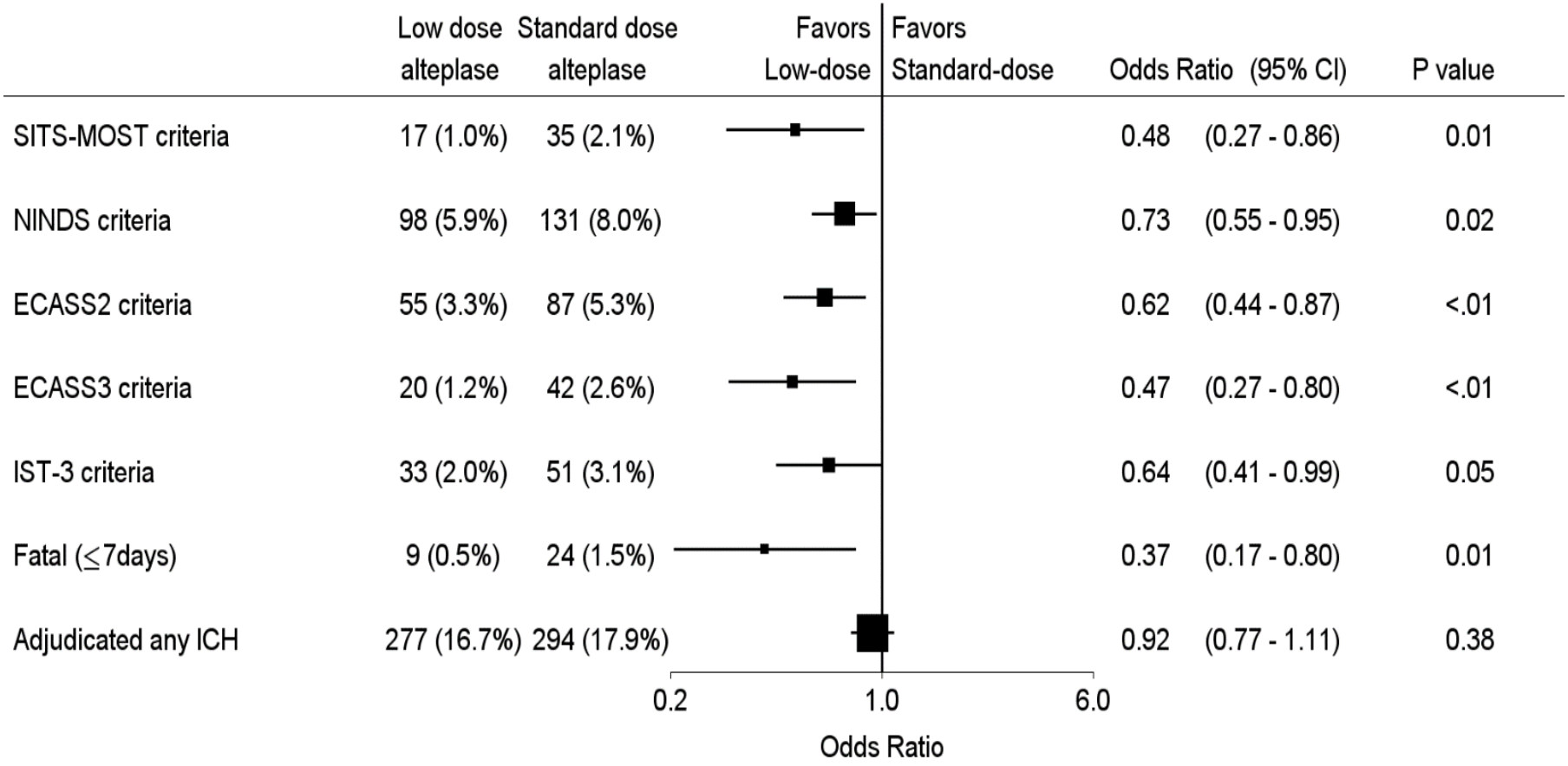


Primary clinical outcome – various analyses
Death or disability (mRS 2-6) at 90 days



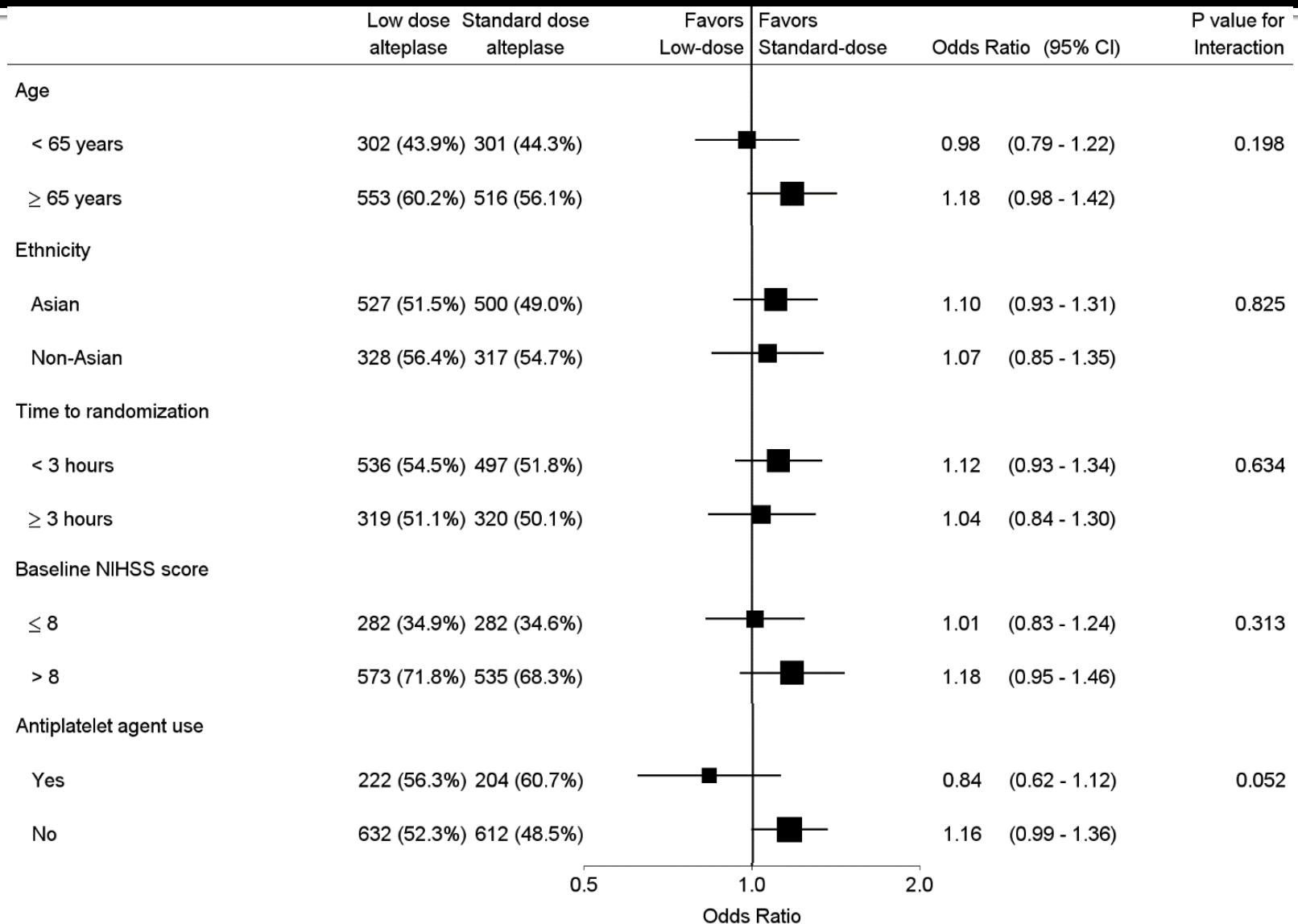
Symptomatic intracerebral hemorrhage

Various standard criteria



Baseline Subgroups

1ry Outcome: death or disability



Other secondary outcomes

Outcome	Low-dose (N=1654)	Standard-dose (N=1643)	Odds Ratio	p
Death/dependency: mRS 3-6	605 (38%)	592 (37%)	1.03	0.15
Death at 90 days	140 (9%)	170 (10%)	0.80	0.07
Health utility - EQ-5D	0.6±0.4	0.6±0.4	0.00	0.86
Living at home	1363 (90%)	1306 (89%)	1.18	0.16
Hospital stay, median (iqr), days	10 (5-17)	10 (5-18)	-0.47	0.53
Death/neuro decline in 24 hr	128 (8%)	141 (9%)	0.89	0.38
Death/neuro decline 7 days	188 (11%)	213(13%)	0.86	0.16
SAE	415 (25%)	448(27%)	0.89	0.16

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Summary of findings

Major findings of ENCHANTED

In thrombolysis-eligible patients with acute ischemic stroke, lower dose (0.6mg/kg) dose rtPA :

- ***Did not meet non-inferiority criteria*** *compared* to standard-dose (0.9 mg/kg) for primary outcome
- ***Did meet non-inferiority criteria*** *compared* to standard-dose for global functional outcome (***shift*** on mRS)
- caused ***fewer deaths, less ICH***, ***and less fatal ICH***
- ***comparable EQ-5D*** and other clinical measures
- ***consistency*** of findings in all pre-specified sub-groups

Implications for Clinicians

In thrombolysis-eligible patients with acute ischemic stroke, low-dose rtPA :

- ***Is safer,*** *with less symptomatic or fatal ICH, and less deaths*
- *Is non-inferior (ie* ***equally effective****) for global functional recovery (****shift****), both ITT and PP*
- *Is especially safer in patients* ***on aspirin or APT***

It should be ***considered for all patients*** *with acute ischaemic stroke who are thought to be* ***at high risk of ICH****, regardless of age and ethnicity, particularly those on anti-platelet treatment.*

Enchanted

Enhanced Control of Hypertension and Thrombolysis Stroke Study

DOSAGE ARM

Presented at European Stroke Organisation Conference

Barcelona, 10th May 2016

And NEJM ePub ahead of print

For the ENCHANTED Investigators and coordinators

An international collaborative project of

THE GEORGE INSTITUTE for Global Health

Main funding support

Australian Government National Health and Medical Research Council

NHMRC

Other funding support

the Stroke Association of the United Kingdom

the National Council for Scientific and Technological Development of Brazil

the Ministry for Health, Welfare and Family Affairs of the Republic of Korea

Enchanted

Enhanced Control of Hypertension and Thrombolysis Stroke Study

BP ARM NOW MAIN FOCUS:

Stepping up recruitment, with support from new NHMRC Project Grant.

Results in 2019—Major issue for all clinicians:

Only ongoing BP trial in acute ischaemic stroke

For the ENCHANTED Investigators and coordinators

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N H M R C

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TRIDENT

Triple therapy prevention of **R**ecurrent **I**ntracerebral **D**isease **E**ve**N**ts **T**rial (TRIDENT)

Multicentre, international, **double-blind, placebo-controlled,** randomised trial to determine the effect of intensive BP control using a **fixed low-dose (half standard dose), combination blood** pressure lowering pill **("Triple Pill")** strategy on top of standard of care, for preventing recurrent stroke in **4300 patients with a history of intracerebral haemorrhage, followed up for 3 years.**

Funded by an NHMRC Project grant, 2016-20

Australian Government
National Health and Medical Research Council
N H M R C

BLOOD PRESSURE & STROKE

Take home message

- Blood pressure & stroke v closely associated
- Benefits of BP lowering established for both 1ry and 2ry prevention
- Little evidence of J-shape for 1ry or 2ry prevention
- More doubts re BP Lowering for acute stroke
- Safety of BP lowering to 140mmHg established for acute ICH (INTERACT2)
- Balance of risks/benefits for ischaemic stroke still an open question (await ENCHANTED)
- Great caution in frail elderly subjects

BLOOD PRESSURE & STROKE

Target blood pressure –A personal view

- Target BP of <140/90 for 1ry prevent in low risk adults <80years
- Target of <130/80 for 2ry stroke prevention and for 1ry prevention in fit, high risk adults <80 yr (NB SPRINT trial)
- Target BP of <150/80 mmHg for 1ry prevention in fit elderly over 80 years (HYVET trial)
- Target SBP of <140mmHg safe for acute ICH
- Target SBP not yet clear for acute ischaemic stroke (await ENCHANTED BP arm)
- More caution in frail elderly in all situations!

STROKE and BLOOD PRESSURE: PREVENTION AND TREATMENT

Cottrell Memorial Lecture

RACP annual Scientific Meeting

Adelaide, May , 2016

John Chalmers
The George Institute for Global Health
The University of Sydney