Assessment oF FluoxetINe In sTroke recoverY (AFFINITY):

a randomised, double-blind, placebo-controlled trial.

Trial registration: Australian New Zealand Clinical Trials Registry: ACTRN 12611000774921

AFFINITY Trial Collaboration

Funding: National Health & Medical Research Council of Australia

AFFINITY Trial Collaboration

Investigators and nurses as 43 sites

• **Vietnam** (n=10), **Australia** (n=29), **New Zealand** (n=4)

Steering committee

• GJ Hankey (co-Chair), ML Hackett (co-Chair), OP Almeida, L Flicker, GE Mead, MS Dennis, C Etherton-Beer, AH Ford, L Billot, S Jan, T Lung, E Lundström, CS Anderson, V Murray (deceased)

Independent Data Monitoring Committee

• R Herbert (Chair), G Carter, GA Donnan

National co-ordinators

• H.Thang-Nguyen (Vietnam), GJ Hankey (Australia), J Gommans (New Zealand)

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Human Research Ethics Committee (HREC) Liaison lead investigators

• RI Lindley, P New, A Lee, J Gommans

Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
National Health & Medical Research Council (NHMRC), Australia			X					

Aim

To evaluate whether a 6-month course of fluoxetine

is safe and effective, compared to placebo,

for improving functional outcome

after recent stroke

in an ethnically diverse population.

Rationale

- Stroke: 2nd leading cause of Disability Adjusted Life Years (DALYs) globally.
  - GBD 2016 Stroke Collaborators. Lancet Neurol. 2019; 18: 439-458

- Fluoxetine: a SSRI, may reduce disability after stroke.

  - Neuro-protective & neuro-regenerative effects in pre-clinical models of stroke.
    - Lim CM, et al. J Neurosci Res. 2009; 87: 1037-45. Wang et al. J Neurosci. 2008; 28:1374-84.

  - FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial.
    - 118 acute ischaemic stroke patients with moderate to severe hemiparesis
    - Fluoxetine 20 mg daily improved motor recovery (Fugl-Meyer Motor Scale) at 3 months.

Chollet F, et al. Lancet Neurol 2011; 10: 123-30.

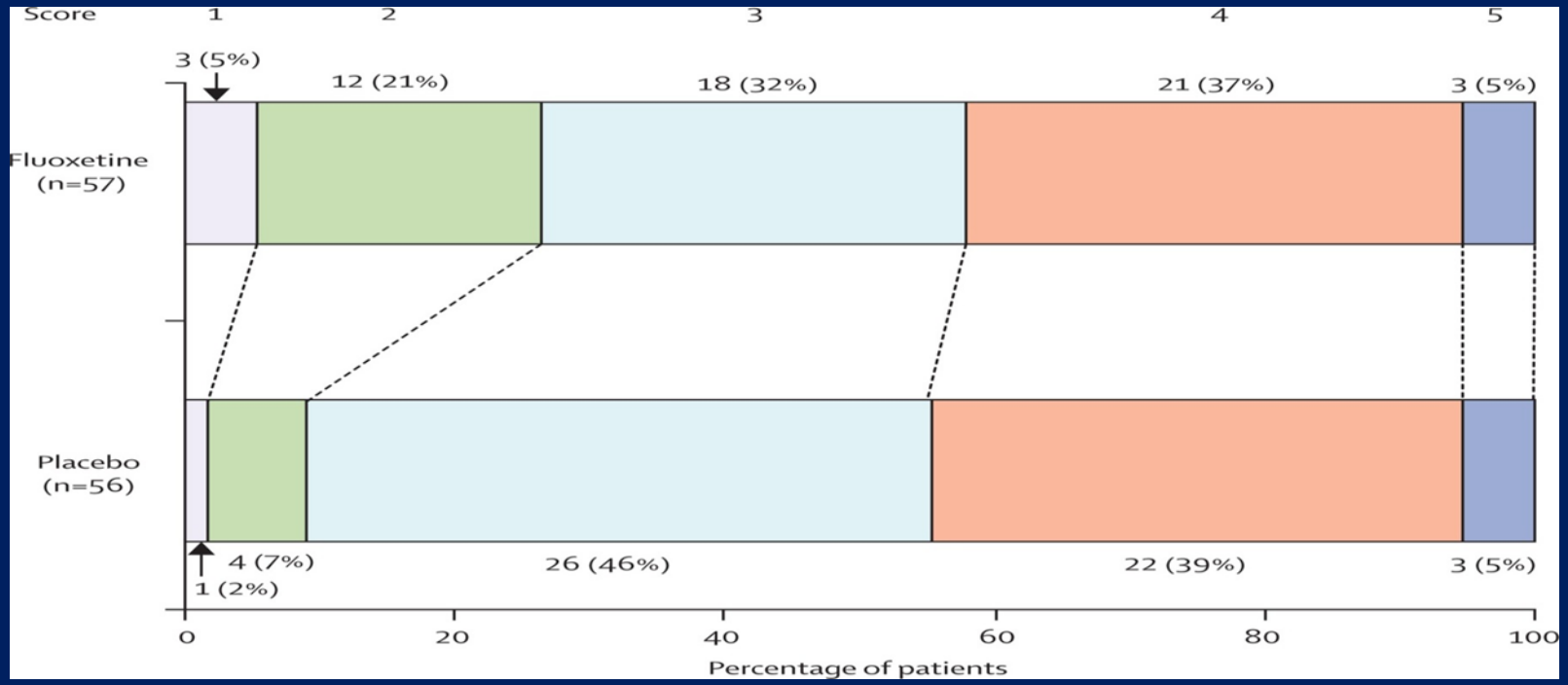
Fluoxetine also improved functional independence (mRS 0-2)* at 90 days

after stroke in the FLAME trial

* Secondary endpoint.
* The only significant ($p<0.05$) mRS dichotomy.

15/57 **(26%)** fluoxetine vs 5/56 (**9%**) placebo

OR = **3.8**, 95% CI: **1.2** to **10.7**



Chollet F, et al. Fluoxetine for motor recovery after acute ischaemic stroke (**FLAME**): a **randomised placebo-controlled** trial. **Lancet Neurol. 2011;10:123-30**.

BBC News - Stroke recovery boosted by a course of Prozac - Windows In

http://www.bbc.co.uk/news/health-12135536

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10 January 2011 Last updated at 02:18

Stroke recovery boosted by a course of Prozac

Giving stroke patients Prozac soon after the event could help their recovery from paralysis, a study has found.

Researchers discovered more improvement in movement and greater independence after three months in patients taking the antidepressant (also known as fluoxetine), compared to placebo.

The Lancet Neurology study was based on research on 118 patients in France.

UK stroke experts said the findings were "promising".

Improving motor functions in stroke patients helps their independence

Related stories

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  - FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial,
    - 118 stroke patients with moderate to severe motor deficits,
    - Fluoxetine 20 mg daily significantly improved motor recovery (FMMS) at 3 months.
    - Chollet F, et al. Lancet Neurol 2011; 10:123-30.
  - Cochrane review of RCTs of SSRIs for stroke recovery: 52 RCTs in 4059 pts
    - SSRIs may improve disability but, methodological limitations & heterogeneity of studies, **more definitive trials required**.
    - Mead GE, et al. SSRIs for stroke recovery. Cochrane Database Syst Rev 2012; 11: CD009286

International collaboration

Three trials of fluoxetine for stroke recovery

- United Kingdom
  - Fluoxetine Or Control Under Supervision (FOCUS)
- Sweden
  - Efficacy of Fluoxetine–A Randomised Controlled Trial in Stroke (EFFECTS)
- Australia, New Zealand & Vietnam
  - Assessment oF FluoxetINe In sTroke recoverY (AFFINITY)

- Mead G et al. The FOCUS, AFFINITY & EFFECTS trials of fluoxetine in patients with a recent stroke: a study protocol for three multicentre randomised controlled trials. Trials 2015; 16: 369.
- Graham C, et al. The FOCUS, AFFINITY & EFFECTS trials of fluoxetine in patients with a recent stroke: statistical and health economic analysis plan for the trials and IPD meta-analysis. Trials 2017; 18: 627.

Assessment oF FluoxetINe In sTroke recoverY (AFFINITY):

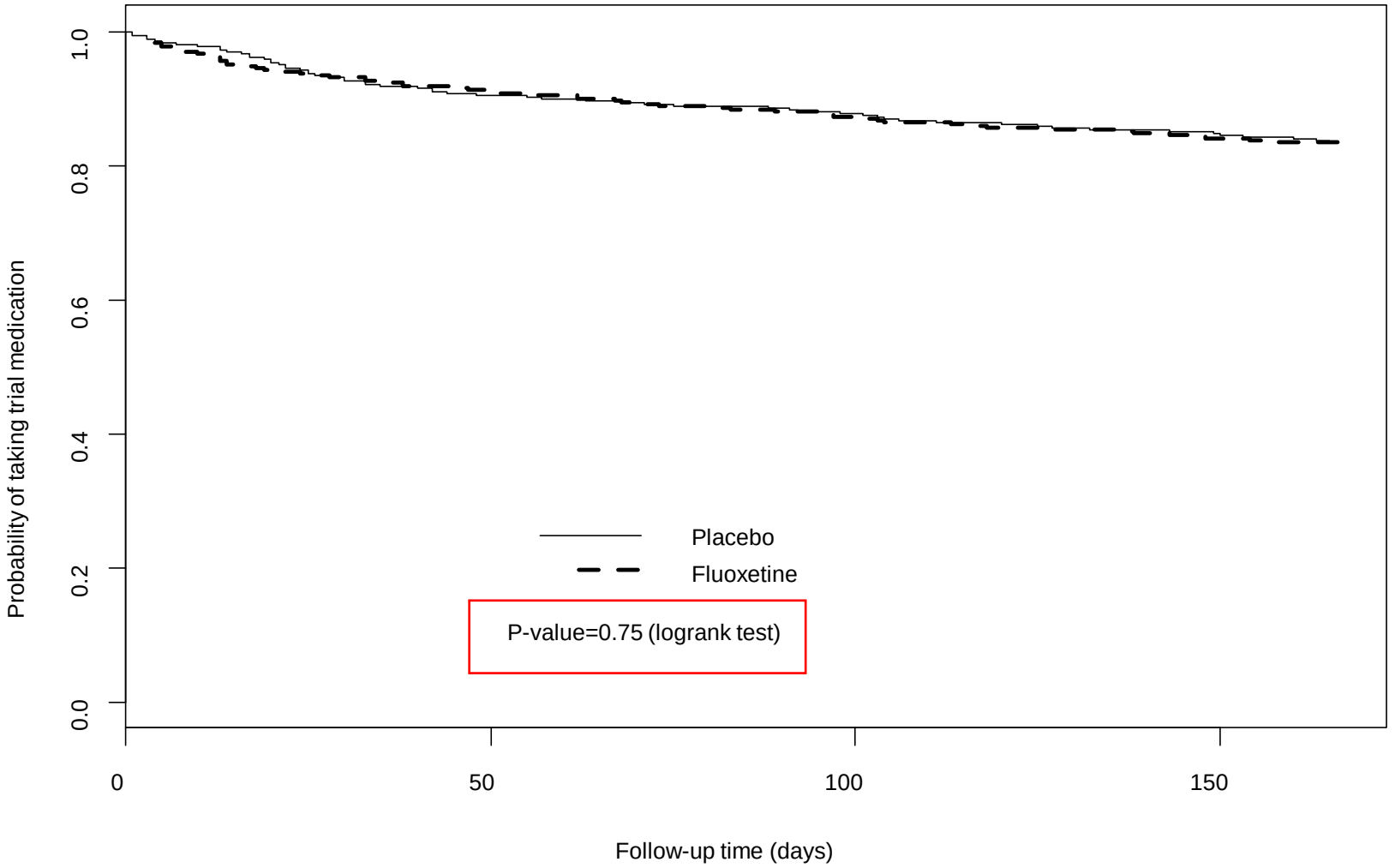
- Design
  - Randomised, parallel-group, double-blind, placebo-controlled trial.
- Setting
  - 43 stroke units in Australia (n=29), New Zealand (n=4), Vietnam (n=10). Recruitment: 11 Jan 2013 to 30 June 2019.
- Patients
  - Clinical diagnosis of recent stroke (2-15 days), persisting neurological deficit (mRS $\geq$ 1); no indication or C/I to SSRI.
- Randomisation
  - Centralised, web-based; minimisation algorithm: time, motor deficit, aphasia, probability mRS 0-2 at 6/12 < > 0.15
- Intervention
  - Fluoxetine 20mg (n=642) or matching placebo (n=638) capsules, orally, once daily, for 6 months.
- Blinding
  - Patients, investigators & outcome assessors were masked to the treatment allocation.
- Primary outcome
  - Functional outcome: modified Rankin scale (mRS), at 6 months.
- Primary analysis
  - Ordinal logistic regression of the mRS at 6 months, adjusted for minimisation variables; intention to treat pop'n.
- Planned sample size
  - 1600 (90% power, mRS 0-2: 42.2% placebo vs 49.4% fluoxetine; OR 1.34; 1440 [90%] with mRS data at 6 months)

Patient characteristics at randomization by allocated treatment: balanced

	Fluoxetine (n=642)	Placebo (n=638)
Sex		
Men	411 (64%)	393 (62%)
Age		
Age ≤ 70 years	450 (70%)	432 (68%)
Mean age, years	63.5 (12.5)	64.6 (12.2)
Ethnicity		
Asian	356 (55%)	371 (58%)
White	267 (42%)	255 (40%)
Other	19 (3%)	12 (2%)
Independent before stroke	634 (99%)	630 (99%)
Previous medical history		
Coronary Heart Disease	58 (9%)	57 (9%)
Ischaemic stroke or TIA	77 (12%)	84 (13%)
Diabetes	143 (23%)	147 (23%)
Bone fractures	71 (11%)	74 (12%)
Depression	30 (5%)	20 (3%)
Stroke diagnosis		
Non-stroke (final diagnosis)	3 (0%)	1 (0%)
Ischaemic stroke	549 (86%)	542 (85%)
Intracerebral haemorrhage	90 (14%)	95 (15%)
Causes of ischaemic stroke		
Large artery disease	123 (22%)	134 (25%)
Small vessel disease	261 (47%)	250 (46%)
Embolism from the heart	95 (17%)	93 (17%)
Another cause	9 (2%)	8 (1%)
Unknown or uncertain cause	61 (11%)	57 (10%)
Neurological deficits		
NIHSS	6 (3-9)	6 (3-9)
Days between stroke onset & randomisation		
Mean delay	6.1 (3%)	6.3 (3%)
2-8 days	486 (76%)	479 (75%)
9-15 days	156 (24%)	159 (25%)

Time to permanent discontinuation of trial medication

Kaplan Meier curve



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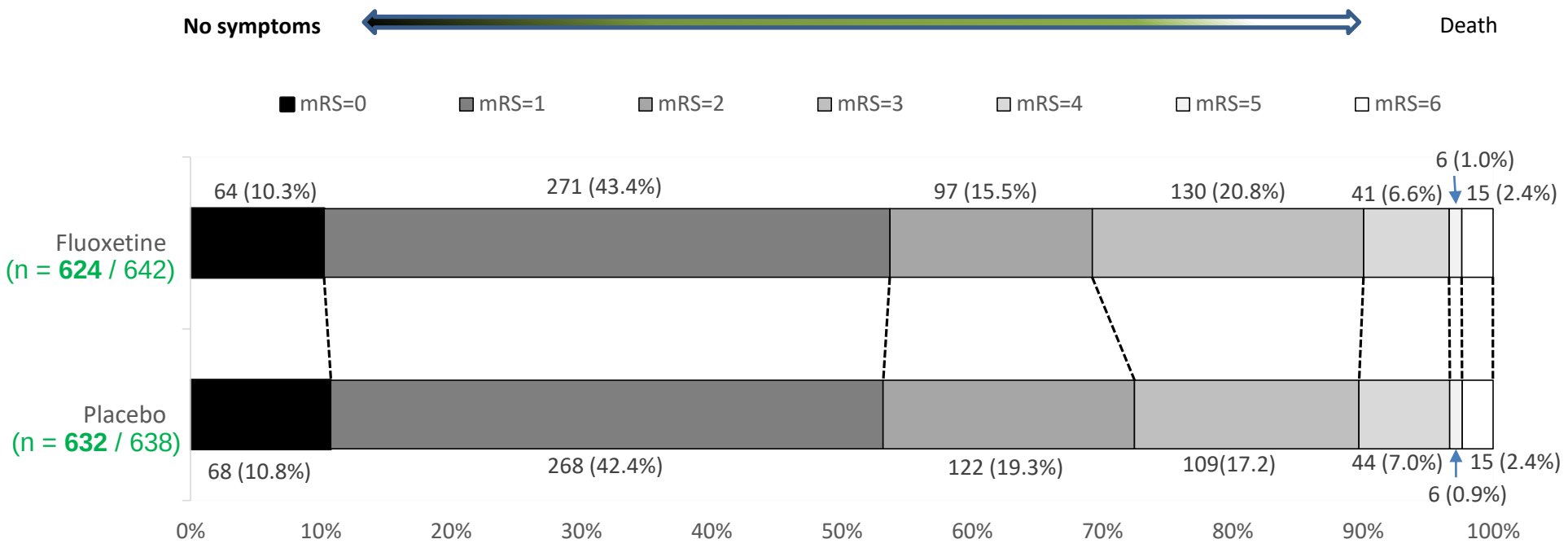
Primary outcome

Distribution of the modified Rankin Scale (mRS) scores at 6 months by treatment group



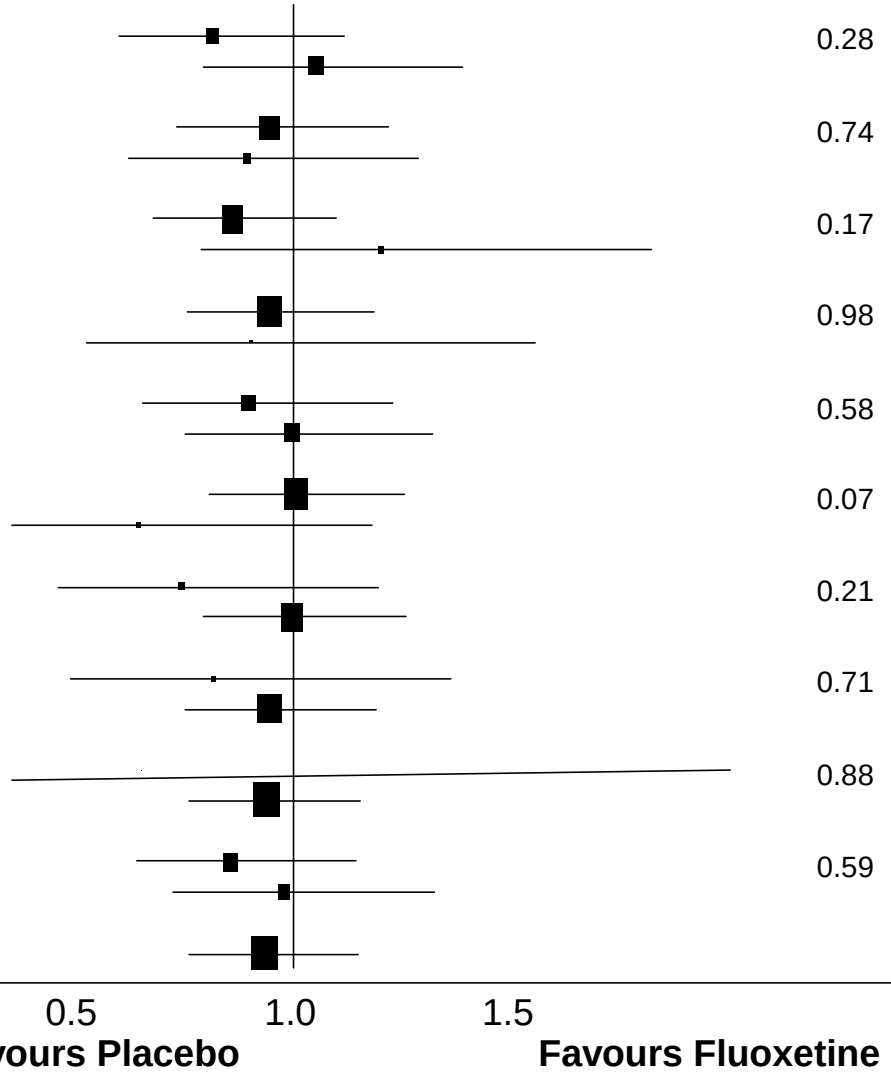
Common odds ratio: 0.94 (95%CI: 0.76 to 1.15), p= 0.53

adjusted for baseline minimization variables.

Common OR < 1.0 favours placebo

Primary outcome by pre-specified subgroups: no heterogeneity.

Subgroup	Sample size Fluoxetine	placebo	Common OR (95%CI)	P-value for Interaction
Country				
AU/NZ	284	274	0.819 [0.602,1.115]	0.28
VN	340	358	1.052 [0.797,1.39]	
Age				
<=70	440	429	0.947 [0.737,1.217]	0.74
>70	184	203	0.896 [0.624,1.286]	
Time from stroke onset to randomisation				
2-8 day	475	473	0.865 [0.682,1.097]	0.17
9-15days	149	159	1.201 [0.793,1.82]	
Stroke pathology				
Ischaemic	534	537	0.948 [0.758,1.185]	0.98
Haemorrhagic	87	94	0.905 [0.528,1.553]	
Stroke severity				
NIHSS 0-5	291	303	0.899 [0.659,1.228]	0.58
NIHSS >5	333	329	0.998 [0.756,1.317]	
Motor deficit (NIHSS)				
Yes	544	543	1.008 [0.809,1.256]	0.07
No	80	89	0.649 [0.357,1.18]	
Aphasia (NIHSS)				
Yes	124	120	0.747 [0.467,1.196]	0.21
No	500	512	1.000 [0.796,1.258]	
Prob. of being alive and independent at 6 months				
0-<=0.15	96	101	0.820 [0.494,1.361]	0.71
>0.15 to 1	528	531	0.948 [0.756,1.189]	
Depression at baseline				
Yes	14	17	0.654 [0.161,2.666]	0.88
No	610	615	0.939 [0.762,1.156]	
Consent given by				
Patient	334	324	0.857 [0.642,1.143]	0.59
Person resposible or Proxy	280	295	0.980 [0.725,1.325]	
Overall	624	632	0.936 [0.762,1.15]	



Secondary outcomes at six months by allocated treatment

	Fluoxetine (n=642)		Placebo (n=638)		P value
New depression N / N (%)	33 (5.1%)		46 (7.2%)		0.13
Mood (PHQ-9)	2.0	(1.0-5.0)	2.0	(1.0-5.0)	0.42
PHQ-9 ≥15 N / N%	4 (0.7%)		6 (1.0%)		0.75
Cognition (TICSm)	24.0	(20.0 -27.0)	24.0	(19.0-27.0)	0.62
Stroke Impact Scale (SIS) domains					
-Strength	75.0	(56.3-93.8)	75.0	(56.3-93.8)	0.26
-Hand ability	85.0	(55.0-100.0)	85.0	(55.0-100.0)	0.39
-Mobility	91.7	(69.4-100.0)	88.9	(66.7-97.2)	0.08
-Motor	83.5	(63.5-94.2)	82.4	(60.4-93.2)	0.28
-Daily Activities	90.0	(72.5-100.0)	90.0	(70.0-97.5)	0.25
-Physical function	85.5	(66.2-94.9)	83.8	(63.4-93.8)	0.24
-Memory	89.3	(78.6-100.0)	89.3	(75.0-100.0)	0.28
-Communication	98.2	(89.3-100.0)	96.4	(85.7-100.0)	0.61
-Mood/Emotions	80.6	(66.7 -88.9)	77.8	(66.7 -86.1)	0.003
-Participation	81.3	(59.4 -96.9)	75.0	(56.3 -96.9)	0.48
-Recovery (VAS)	80.0	(60.0 -90.0)	80.0	(60.0 -90.0)	0.90
Vitality (SF-36)	70.0	(55.0 -80.0)	70.0	(55.0 -80.0)	0.36
Quality of life (EQ5D-5L)	0.81	0.63-1.00	0.78	0.58-0.93	0.08

Adverse events at 6 months by allocated treatment group

	Fluoxetine (n=642)	Placebo (n=638)	Difference (95% CI)*	P-value
Death	15 (2.34%)	15 (2.35%)	0.01% (-1.64 to 1.67)	1.00
Any stroke	18 (2.80%)	26 (4.08%)	-1.27% (-3.27 to 0.72)	0.22
All thrombotic events				
Ischaemic stroke	11 (1.71%)	21 (3.29%)	-1.58% (-3.29 to 0.13)	0.08
Acute coronary events	1 (0.16%)	2 (0.31%)	-0.16% (-0.69 to 0.37)	0.62
All bleeding events				
Haemorrhagic stroke	3 (0.47%)	1 (0.16%)	0.31% (-0.30 to 0.92)	0.62
Upper gastrointestinal bleed	1 (0.16%)	1 (0.16%)	0.00% (-0.43 to 0.43)	1.00
Epileptic seizures	10 (1.56%)	2 (0.31%)	1.24% (0.19 to 2.30)	0.04
Fall with injury	20 (3.12%)	7 (1.10%)	2.02% (0.45 to 3.59)	0.02
New bone fracture	19 (2.96%)	6 (0.94%)	2.02% (0.51 to 3.53)	0.01
Hyponatraemia < 125mmol/l	3 (0.47%)	2 (0.31%)	0.15% (-0.53 to 0.84)	1.00
Hyperglycaemia	0 (0%)	0 (0%)	0%	
Symptomatic hypoglycaemia	0 (0%)	0 (0%)	0%	
New depression	33 (5.14%)	46 (7.21%)	-2.07% (-4.71 to 0.57)	0.13
New antidepressant	30 (4.67%)	43 (6.74%)	-2.07% (-4.61 to 0.47)	0.12
Attempted or actual suicide	0 (0%)	2 (0.31%)	-0.16% (-0.75 to 0.12)	0.25
Other adverse event	62 (9.66%)	68 (10.66%)	-1.00% (-4.31 to 2.31)	0.56

Summary

- Fluoxetine 20mg daily for 6 months after acute stroke did not improve functional outcome (mRS) at 6 months in an ethnically diverse population.
  - AFFINITY: Common odds ratio: **0.94** (95%CI: 0.76 to 1.15), p = 0.53
  - EFFECTS: Common odds ratio: **0.94** (95%CI: 0.78 to 1.13), p = 0.42
  - FOCUS: Common odds ratio: **0·95** (95% CI 0·84 to 1·08), p = 0·44

- Fluoxetine increased mood and emotional control.

- Fluoxetine increased falls, fractures, & epileptic seizures.

Fractures:

  - AFFINITY: 2.96% (fluoxetine) vs 0.94% (placebo); Absolute increase: **2.02%** (0.51 to 3.53%)
  - EFFECTS: 3.70% (fluoxetine) vs 1.50% (placebo); Absolute increase: **2.20%** (0.06 to 3.90%)
  - FOCUS: 2.88% (fluoxetine) vs 1.41% (placebo); Absolute increase: **1.41%** (0.38 to 2.43%)

Thank you

- Funding: NHMRC, Australia

- Minimisation algorithm: Stroke Research Group, Division of Clinical Neuroscience, The University of Edinburgh.

- Trial medication manufacture, storage & distribution: Pharmaceutical Packaging Professionals Pty Ltd.

- All patients and their families who participated in AFFINITY, and nursing staff who assisted at collaborating sites.

- The Lancet Neurology (in press)

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