Individual patient data meta-analysis of the effects of fluoxetine on functional outcomes after acute stroke

Gillian Mead FMed Sci. Usher Institute, University of Edinburgh Room S1642, Royal Infirmary, Edinburgh EH16 4SA

Catriona Graham MSc Wellcome Trust Clinical Research Facility Western General Hospital, Crewe Road, Edinburgh EH4 2XU

Erik Lundström PhD Department of Medical Sciences, Neurology Uppsala University Uppsala University Hospital Ingång 85, 3 trapport SE-751 85 Uppsala, Sweden

Graeme J. Hankey PhD Centre for Neuromuscular and Neurological Disorders, Medical School, The University of Western Australia, Perth, Australia. Perron Institute for Neurological and Translational Science, Perth, Australia

Maree L. Hackett PhD The George Institute for Global Health, Level 18, International Towers 3, 300 Barangaroo Ave, Barangaroo NSW 2000 Australia, PO Box M201, Missenden Rd, NSW 2050 Australia. Professor, Faculty of Medicine, University of New South Wales, Sydney, NSW. Professor of Epidemiology, The University of Central Lancashire, United Kingdom.

Laurent Billot MRes**.** The George Institute for Global Health, Faculty of Medicine and Health, University of New South Wales, Sydney, Australia

Per Näsman PhD KTH Royal Institute of Technology, Stockholm, Sweden

John Forbes PhD University of Limerick Emeritus Full Professor

Martin Dennis MD Centre for Clinical Brain Sciences, Little France Crescent, Edinburgh EH16 4SA

on behalf of the AFFINITY, EFFECTS and FOCUS trialists collaborations

Corresponding author Professor Gillian Mead gillian.e.mead@ed.ac.uk telephone 0131 242 1006

Abstract

Background

We collaboratively designed three large trials of fluoxetine for stroke recovery to facilitate an individual patient data meta-analysis (IPDM).

Methods

We performed fixed effects meta-analyses on the combined data set, for the primary outcome (modified Rankin scale (mRS) at 6 months) and secondary outcomes common to the individual trials. As a sensitivity analysis, summary statistics from each trial were created and combined.

Findings

We recruited 5907 people (mean age 69·5 years (SD 12·3), 2256 (38%) females, 2-15 days post-stroke) from Australia, New Zealand, UK, Sweden and Vietnam; and randomized them to fluoxetine 20mg daily or matching placebo for 6 months. 5833 (98·75%) were available at 6 months. The adjusted ordinal comparison of mRS was similar in the two groups (common OR 0·96, 95% CI 0·87 to 1·05, p=0·37). There were no statistically significant interactions between the minimization variables (baseline probability of being alive and independent at 6 months, time to treatment, motor deficit or aphasia) and pre-specified subgroups (including age, pathological type, inability to assess mood, proxy or patient consent, baseline depression, country). Fluoxetine increased seizure risk (2·64% vs 1·8%, p=0·03), falls with injury (6·26% vs 4·51%, p=0·03), fractures (3·15% vs 1·39%, p<0·0001) and hyponatraemia (1·22% vs 0·61%, p=0·01) but reduced new depression (10·05% vs 13·42%, p<0·0001). At 12 months, there was no difference in adjusted mRS (n=5760; COR 0·98, 95% CI 0·89 to 1·07). Sensitivity analyses gave the same results.

Interpretation

Fluoxetine 20mg daily for six months did not improve functional recovery. It increased seizures, falls with injury, bone fractures but reduced depression frequency at 6 months.

Trial Funding

Stroke Association, National Institute of Health Research, Australian Government National Health and Medical Research Council, Swedish Research Council, Swedish Heart-Lung Foundation, Swedish Brain Foundation, Swedish Society of Medicine, King Gustav V and Queen Victoria's Foundation of Freemasons and STROKE-Riksförbundet

Background

Stroke is a leading cause of adult disability globally; and new treatments are needed to reduce stroke related disability [1,2]. Following the encouraging results of the FLAME trial published in 2011 [3], we collaboratively designed three large trials to test the hypothesis that fluoxetine 20mg given daily after stroke for 6 months would reduce dependency at 6 months [4]. Each trial was neutral with respect to the primary outcome [5-7].

When the collaboration was initiated, we agreed to perform an individual patient data meta-analysis (IPDM) after all three trials had reported their primary results, in order to confirm or refute a smaller benefit of fluoxetine on our primary outcome than the individual trials had been powered to do, either overall or in particular subgroups, and to provide more precise estimates of any harms [8,9].

The primary objective of the IPDM was to determine whether patients with a clinical stroke diagnosis (2 to 15 days after onset) who are prescribed a 6-month course of fluoxetine 20 mg daily have improved functional outcome, as defined by the modified Rankin Scale (mRS) score at 6 months, compared with placebo [8,9].

Pre-specified secondary objectives for our IPDM were:

a) Does fluoxetine influence the secondary outcomes at 6 months and 12 months?
b) If fluoxetine improves mRS score at 6 months, does any improvement persist after treatment stops?
c) Does fluoxetine increase the risk of serious adverse events?
d) Is fluoxetine associated with longer-term survival?
e) Is the effect of fluoxetine vs placebo on the primary outcome modified by minimization variables and pre-specified subgroups?
f) In patients with motor deficits at randomisation, does fluoxetine improve motor function?
g) In patients with aphasia at randomisation, does fluoxetine improve communication?
h) Is there a relationship between functional status at 6 months and mood, and is this relationship affected by fluoxetine?
i) How does non-adherence to the study protocol influence outcome?
j) Does the effect of fluoxetine vs placebo vary by country of randomization?
k) Does the effect of fluoxetine vary by ethnicity?
l) Does the effect of fluoxetine vary by trial? [9]

In this paper we present results for all of these aims, except for (h), which will be reported separately as it requires separate statistical analyses.

Methods

We transferred data securely from the AFFINITY and EFFECTS teams to the FOCUS statistician, who combined the data sets.

Where data items were not identical, the chief investigators of each trial decided if/how to combine data. The combined data set included all variables, even if only collected in one or two of the trials.

SAS v9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. We performed descriptive exploratory analyses to display differences in baseline characteristics of patients in the three trials (supplementary table 1 and supplementary table 2).

We reproduced the tables from the published papers [5-7]. We re-analysed each trial's data to ensure that the main results could be reproduced [8-9]. We had intended to describe the duration and type of hospital stays between randomisation and discharge home, discharge to a residential or nursing home or death, but the three trials reported these data were reported in different ways, so this was not possible.

We performed a one stage IPDM by combining all data into one model to produce estimates of treatment effect [8-9]. The minimization algorithms of the three trials had already ensured that patients were allocated to fluoxetine or control in a way which minimized the treatment imbalance with a predefined probability, to ensure allocation was random. We used ordinal logistic regression adjusted for minimization factors but also reported in an unadjusted manner. We conducted ordinal analysis of mRS by treatment allocation (fluoxetine vs placebo), under the assumption of proportional odds in the model, and tested this assumption using the score test for proportional odds assumption. Then, as a sensitivity analysis, we performed a two stage IPDM, which involved the creation of summary statistics from each trial then combining the summary statistics using fixed effects meta-analysis and Forest plots. Had the one stage and two stage IPDD had produced different answers, we would have explored why.

For binary outcomes, we compared treatment groups using a binary logistic regression and adjusted for factors used in the minimisation algorithm. For continuous outcomes we present descriptive statistics categorised by allocated treatment. We used a simple unadjusted analysis comparing the two treatment groups using a Mann–Whitney U-test (i.e. not adjusted for variables in the minimisation algorithm) due to the distribution of the outcomes.

<u>Missing data in IPDD</u>

The mRS, our primary outcome, includes death; therefore, the number of patients with missing mRS at follow-up was small. Those with a missing mRS were not included in any analysis requiring mRS (complete-case analysis). For secondary outcomes for which missing data were expected because

data were not available for patients who did not survive, we presented results for those who were alive at follow-up; and any discrepancies in death rates between groups were taken into account in the interpretation. Missing data for single questions within scores were handled as detailed by each scoring method. Where responses to all questions within a scale or subscale were missing, that patient was not included in that particular analysis.

For secondary outcomes and subgroup analyses we used binomial test for the comparison of proportions, Wilcoxon or Cox proportional-hazard model as appropriate and compared treatment arms.

Subgroup analysis

We performed subgroup analyses by observing the change in log-likelihood when the interaction between the treatment and the subgroup was added into a logistic regression model.

Sensitivity analysis

We sequentially excluded patients from the trials to explore the influence of non-eligible patients being recruited, and compliance with the trial medication as already described in detail in the statistical analysis plan for the individual trials.

Risk of bias across studies

We rated the certainty of the evidence of the IPDM using Cochrane Grades of Recommendation, Assessment, development, and Evaluation (GRADE), for risk of bias, inconsistency, indirectness, imprecision and publication bias, using the criteria high, moderate, low and very low; for our primary outcome.

We did not need to produce a PRISMA IPDM diagram as described in our protocol because data from all three trials were available and analysed [5-7].

Results

Primary results: we randomized 5907 patients (mean age 69·6, SD 12·3, 2256 women, 38·19%) (table 1). Other baseline data are shown in the supplementary table 1; there were expected differences in baseline data for age, NIHSS, predicted outcome and time to randomization between trials; these differences were due to the differences in inclusion criteria (supplementary table 2). There were no differences in the proportion of men and women between trials.

Primary outcome data (mRS at 6 months) were available for 5833 (98·75%) of the 5907 patients randomised. An ordinal comparison of individual mRS categories at 6 months, adjusted for variables in the minimisation algorithm was similar in the two groups (common OR (COR) 0·96, 95% CI 0·87 to 1·05, p=0·37) where a common OR in favour of placebo is <1·0 (figure 1), and also similar according to pre-specified subgroups. Our two stage meta-analysis gave the same result (COR 0·96, 95% CI 0·87, 1·05, I^2 0%, p=0·98) (figure 2).

Secondary results There was no difference in the secondary outcomes at 6 and 12 months, except for better SIS emotion score in all trials (table 2), a reduced risk of new depression (10·05% vs 13·42%, p<0·0001) and fewer new antidepressants (11·71% versus 15·28%, p<0·001) at 6 months (table 3). At 6 months, fluoxetine was associated with an increased the risk of seizures (2·64% vs 1·8%, p=0·03), falls with injury (6·26% vs 4·51%, p=0·03), fractures (3·15% vs 1·39%, p<0·0001) and hyponatraemia (1·22% vs 0·61%, p=0·01) (table 3).

At 12 months, there was no difference between the fluoxetine and placebo groups for mRS (n=5760; COR 0·98, 95% CI 0·89, 1·07) adjusted for minimization variables, or survival (hazard ratio 0·929, 95% CI 0·756, 1·141, p=0·48) or our secondary outcomes. Twelve month adverse events are reported in the appendix; the trial drug was stopped at 6 months and the trials collected adverse event data slightly differently so we cannot attribute any 12 month differences to treatment allocation.

The effect of fluoxetine on the primary outcome was not modified by baseline probability of being alive and independent at 6 months, time to treatment, motor deficit or aphasia or by pre-specified subgroups (including age, pathological type, inability to assess mood, proxy or patient consent, baseline depression and country) (figure 2). The two stage IPD for subgroups also produced the same results for subgroups.

In patients with motor deficits at randomisation, fluoxetine did not improve motor function (Median (IQR): fluoxetine 64·81 (34·03, 86·16) n=2199 and placebo 64·40 (34·95, 85·30) n=2212; p=0·76). In patients with aphasia at randomization (assessed by the NIHSS aphasia item), fluoxetine did not reduce communication problems (SIS domain) at 6 months (Median (IQR): fluoxetine 75·00 (42·86, 92·86) n=637; placebo78·57 (50·00, 92·86) n=613 p = 0·39). Non-adherence to the study protocol did not influence outcome at 6 months. The effect of fluoxetine vs placebo did not vary by country of

randomization (UK, Australia, Vietnam, New Zealand, Sweden) or ethnicity; or by trial (Figure 2). GRADE quality was high for our primary outcome (table 4).

Discussion:

This IPDM in almost 6000 stroke patients demonstrated that fluoxetine 20mg daily for 6 months did not improve functional outcome, reduced the risk of depression and new antidepressant prescriptions, and improved the 6 month emotion score in the stroke impact scale. However fluoxetine increased the risk of seizures, falls with injury, bone fractures and hyponatraemia at 6 months -though the absolute risks of these events were very low. The evidence is of high certainty for our primary outcome [10]. We had previously calculated that with 6,000 patients in an IPDM there would be 90% power to detect a very small effect size equivalent to a COR of 1·16 [11]. Thus, even if this IPDM has missed a beneficial effect, the effect size would have been extremely small and unlikely to be clinically relevant. Furthermore, the direction of benefit in this IPDM was in favour of placebo. We demonstrated no benefits in our pre-specified subgroups and our minimization variables. The external validity of this IPDM is high, with patients recruited from five countries. Like many stroke trials, more men than women were recruited; but there is no evidence of any difference in treatment effect (fluoxetine versus placebo) in men and women.

The strengths of this IPDM is that we published a protocol in advance and we included three large high quality trials which had been designed to facilitate an IPDM. We were able explore intervention by covariate interactions [12].

This IPDM adds to our Cochrane review by identifying a statistically significant effect on seizures and falls with injuries, and by demonstrating no differences in treatment effects by subgroups, countries, ethnicity, or adherence to study medication. Also, we found no increased risk of bleeding, which had been a theoretical concern based on the pharmacology of fluoxetine. Access to the individual participant data enabled analyses of adjusted treatment effects overall and in pre-specified subgroups, which could not be done with tabulated data in the Cochrane review. The Cochrane review reports the relative and absolute risk of recovery as a group average for the overall trial population, whereas the IPDM used multivariate Cox proportional hazard regression to estimate the baseline risk of recovery from all measured, independent, significant participant prognostic factors and the relative and absolute risk change with fluoxetine vs placebo within each strata of baseline risk to identify which (if any) patient populations derived the greatest benefit/risk of adding fluoxetine to standard care.

A 2023 systematic review and meta-analysis fluoxetine for stroke recovery, published after our Cochrane review, concluded that fluoxetine improved the Fugl Myer Motor score (a score of motor recovery), but this particular analysis was based on only four small trials recruiting 287 patients, some of which were at high risk of bias. Our IPDM clearly shows that in patients with motor deficits, fluoxetine did not improve patient-reported motor recovery.

There are some weaknesses. Although our three trials were collaboratively designed, substantial work was needed to harmonise the datasets because of the slight differences in trial methodology to suit local contexts. Thus it took longer than we had hoped to complete this IPDM. The GRADE assessments were performed by authors of the three trials, and so may have overestimated the certainty of evidence. However, the GRADE assessment performed by the lead author of our Cochrane review of SSRIs for stroke recovery, who had not been involved in the three trials, was similar.

Based on our data, there is no justification for further research exploring the impact of fluoxetine (and by extrapolation-probably other SSRIs too) on functional recovery after stroke. This applies to all stroke types, all severity, and irrespective of baseline deficits. There are, however, unanswered questions about the utility of fluoxetine and other SSRIs for purposes other than functional recovery in patients with stroke e.g. what is their role in *treating* mood disorders, particularly in people with aphasia who are generally underrepresented in trials.

Although there was a very small reduction in the risk of depression at 6 months, the potential benefits of using fluoxetine prophylactically to reduce depression should be outweighed by the risks. An absolute reduction of 3·37% in a diagnosis of depression at 6 months was associated with an absolute increase in new fractures of 1·76%.

In summary fluoxetine should not be given routinely to improve stroke functional recovery or prevent depression, unless the risk of developing depression is considered high and the patient is willing to accept a higher risk of adverse events.

Research in context

Evidence before this study

The three individual trials of fluoxetine showed that fluoxetine did not improve recovery at 6 months when given 2-15 days after stroke but did reduce depression. The 2021 Cochrane review of SSRIs for stroke recovery confirmed this and also demonstrated an increased risk of bone fractures with SSRIs. A subsequent 2023 meta-analysis suggested that fluoxetine improved motor recovery, and recommended further large trials. There have been no further large trials of fluoxetine for stroke recovery published since our three trials (PubMed search using the terms fluoxetine AND stroke on 2nd October 2023).

Added value of this study.

Fluoxetine increases seizure risk, risk of falls with injuries, fractures and hyponatraemia when given to people early after stroke, but does not increase bleeding risk despite theoretical reasons why it could do.

There is no impact of fluoxetine on functional recovery in subgroups.

In patients with motor deficits and aphasia, there is no improvement in motor function and communication respectively.

Compliance with treatment did not affect results.

Further large trials of fluoxetine for stroke recovery are not needed.

Roles of authors

Professor Gillian Mead: conceptualisation, investigation, methodology, project administration, supervision, visualisation, writing original draft.

Catriona Graham: data curation, formal analysis, validation, visualisation, editing draft

Erik Lundström: conceptualisation, data curation, methodology, reviewing and editing draft

Graeme Hankey: conceptualisation, data curation, methodology, reviewing and editing draft

Maree L. Hackett: conceptualisation, data curation, methodology, reviewing and editing draft

Laurent Billot: conceptualisation,data analysis, data curation, methodology, reviewing and editing draft

Per Näsman: conceptualisation,data analysis, data curation, methodology, reviewing and editing draft

John Forbes: conceptualisation,data analysis, data curation, methodology, reviewing and editing draft

Martin Dennis: conceptualisation, investigation, methodology, supervision, visualisation, reviewing and editing original draft.

Declarations and sources of funding

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Data sharing statement

The statistical analysis plan for the IPDM and the main findings from the individual trials have already been published in open access journals.

De-identified participant data and a data dictionary defining each field in the set, will be made available to others, after the planned analyses as described in our statistical analysis plan have been published.

Data will shared only after investigator approval. Researchers requesting the data will need to write a protocol which will be approved by the investigators. Then a signed data access agreement will be produced. The mechanism for sharing the data will be determined by the information governance requirements of the relevant institutions and countries. Requests for data sharing should be made to Professor Gillian Mead in the first instance.

Table 1. Baseline data comparing the characteristics of AFFINITY, FOCUS and EFFECTS trial participants by randomised group

		Randomised treatment				All	
		Fluoxetine		Placebo			
		N	%	N	%	N	%
Number of patients randomised		2956	100	2951	100	5907	100
Gender	Female	1107	37	1149	38.94	2256	38.2
	Male	1849	63	1802	61.06	3651	61.8
Age	Mean (sd)	69.4 (12.5)		69.9 (12.0)		69.6 (12.3)	
	≤70 years old	1444	49	1412	47.85	2856	48.4
	>70 years old	1512	51	1539	52.15	3051	51.7
Ethnicity	Asian	391	13	412	13.96	803	13.6
	Black	39	1.3	30	1.02	69	1.17
	Other	21	0.7	23	0.78	44	0.74
	White	2505	85	2486	84.24	4991	84.5
Marital status	Divorced	202	6.8	204	6.91	406	6.87
	Married	1736	59	1672	56.66	3408	57.7
	Other	35	1.2	36	1.22	71	1.2
	Partner	222	7.5	206	6.98	428	7.25
	Single	276	9.3	308	10.44	584	9.89
	Windowed	485	16	525	17.79	1010	17.1
Living arrangements	Living alone	829	28	876	29.68	1705	28.9
	Institutional living	10	0.3	6	0.2	16	0.27
	Other	12	0.4	12	0.41	24	0.41
	Living with someone else	2105	71	2057	69.71	4162	70.5
Employment status	Full time	651	22	592	20.06	1243	21
	Other	47	1.6	55	1.86	102	1.73
	Part time	183	6.2	176	5.96	359	6.08
	Retired	1981	67	2035	68.96	4016	68
	Unemployed or disabled	82	2.8	84	2.85	166	2.81
	Voluntary	12	0.4	9	0.3	21	0.36
Independent before stroke		2782	94	2793	94.65	5575	94.4
Past medical history	Coronary heart disease	462	16	468	15.86	930	15.7
	Ischaemic stroke/transient ischaemic attack	477	16	509	17.25	986	16.7
	Diabetes	620	21	609	20.64	1229	20.8
	Current/past hyponatraemia	31	1.1	37	1.25	68	1.15
	Intracranial bleed	56	1.9	56	1.9	112	1.9

	Upper gastrointestinal bleed	59	2	71	2.41	130	2.2
	Bone fractures	533	18	519	17.59	1052	17.8
	Depression	220	7.4	193	6.54	413	6.99
Stroke diagnosis	Not-stroke	7	0.2	4	0.14	11	0.19
	Yes	2920	99	2916	98.81	5836	98.8
	Haemorrhagic	330	11	351	11.89	681	11.5
	Ischaemic	2621	89	2598	88.04	5219	88.4
OCSP classification of ischaemic stroke (shown for ischaemic stroke only)	TACS	544	21	552	21.25	1096	21
	PACS	1138	43	1124	43.26	2262	43.3
	LACS	522	20	491	18.9	1013	19.4
	POCS	371	14	393	15.13	764	14.6
	Uncertain	46	1.8	38	1.46	84	1.61
Causes of ischaemic stroke (modified TOAST classification) (shown for ischaemic stroke only)	Large artery disease	505	19	456	17.55	961	18.4
	Small vessel disease	728	28	673	25.9	1401	26.8
	Embolism from heart	613	23	666	25.64	1279	24.5
	Another cause	72	2.8	59	2.27	131	2.51
	Unknown/uncertain	703	27	744	28.64	1447	27.7
Predictive variables	Able to walk	1109	38	1087	36.83	2196	37.2
	Able to lift both arms	1964	66	1943	65.84	3907	66.1
	Can talk	2357	80	2381	80.68	4738	80.2
Predicted 6-month outcome based on Six simple variables	Median (Q1,Q3)	0.44 (0.12,0.78)		0.42 (0.12,0.77)		0.42 (0.12,0.77)	
	0 to <=0.15	841	28	842	28.53	1683	28.5
	>0.15 to 1	2115	72	2109	71.47	4224	71.5
Neurological deficits	NIHSS: median (Q1,Q3)	5 (3,9)		5 (3,9)		5 (3,9)	
	Motor deficit	2442	83	2434	82.48	4876	82.6
	Aphasia	720	24	704	23.86	1424	24.1
Depression at baseline	Current depression	41	1.4	35	1.19	76	1.29
Current mood [PHQ-2]	2 yes responses	243	8.2	221	7.49	464	7.86
	1 yes responses	306	10	297	10.06	603	10.2
	0 yes responses	2379	80	2402	81.4	4781	80.9
Delay (days) since stroke onset at randomisation	mean (sd)	6.6 (3.6)		6.6 (3.6)		6.6 (3.6)	
	2-8 days	2122	72	2121	71.87	4243	71.8
	9-15 days	834	28	830	28.13	1664	28.2
Details of enrolment	Enrolled as an inpatient	2921	99	2905	98.44	5826	98.6
	Proxy consented	716	24	741	25.11	1457	24.7
	Patient consented	2230	75	2196	74.42	4426	74.9

Abbreviations: Q1=value below which 25% of the distribution lies, Q3=value below which 75% of the distribution lies, sd=standard deviation

NIHSS National Institute of Health Stroke Scale

OCSP Oxfordshire Community Stroke Project Classification

TACS Total Anterior Circulation syndrome

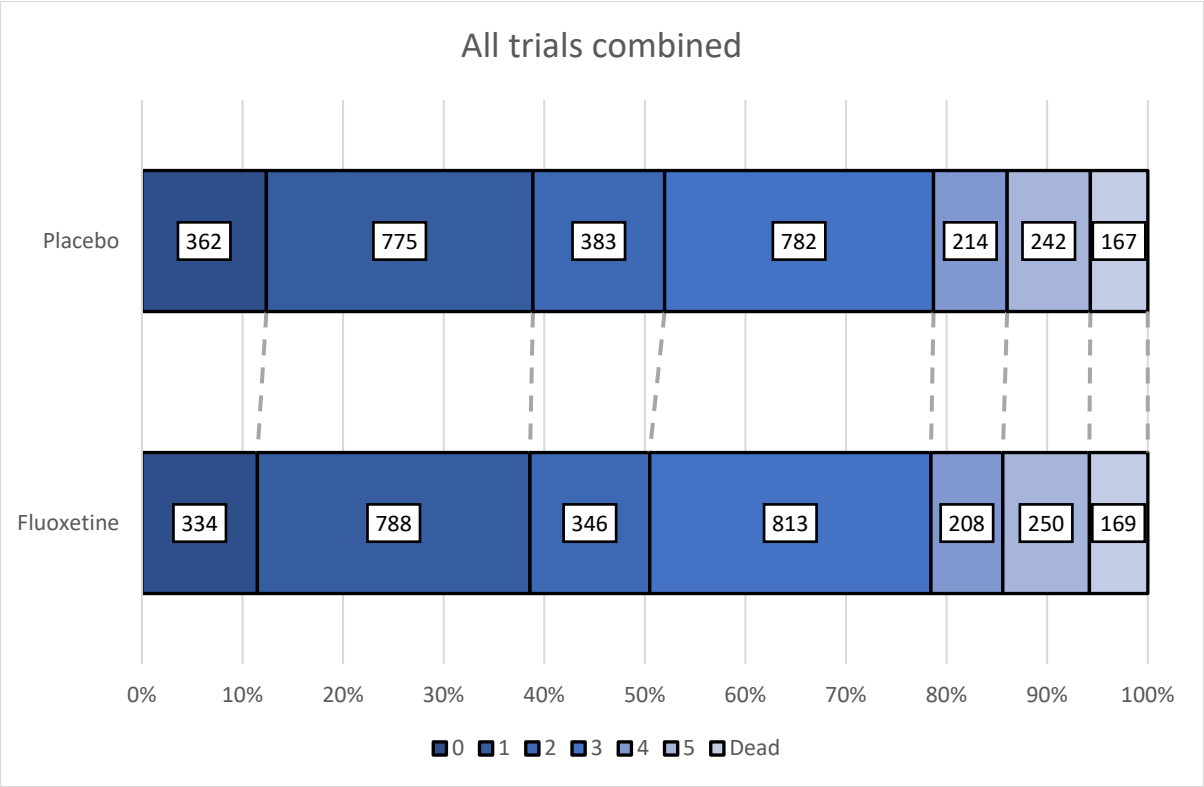
PACS Partial Anterior Circulation syndrome

LACS Lacunar syndrome

POCS Posterior Circulation syndrome

TOAST Trial of Org 10172 in acute stroke treatment

Figure 1 Combined individual participants' mRS scores at 6 months in AFFINITY, FOCUS and EFFECTS



Abbreviations: AFFINITY=assessment of fluoxetine in stroke recovery trial, EFFECTS= efficacy of fluoxetine-a randomised controlled trial in stroke, FOCUS=fluoxetine or control under supervision trial, mRS=modified Rankin scale; 0= no residual symptoms, 1= no significant disability; able to carry out all pre-stroke activities, 2= slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help, 3= moderate disability; requiring some external help but able to walk without the assistance of another individual, 4= moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual, 5= severe disability; bedridden, incontinent, requires continuous care.

Figure 2. Forest plot showing AFFINITY, FOCUS and EFFECTS participants' probability of being alive and independent (mRS score 0-2) in pre-specified subgroups

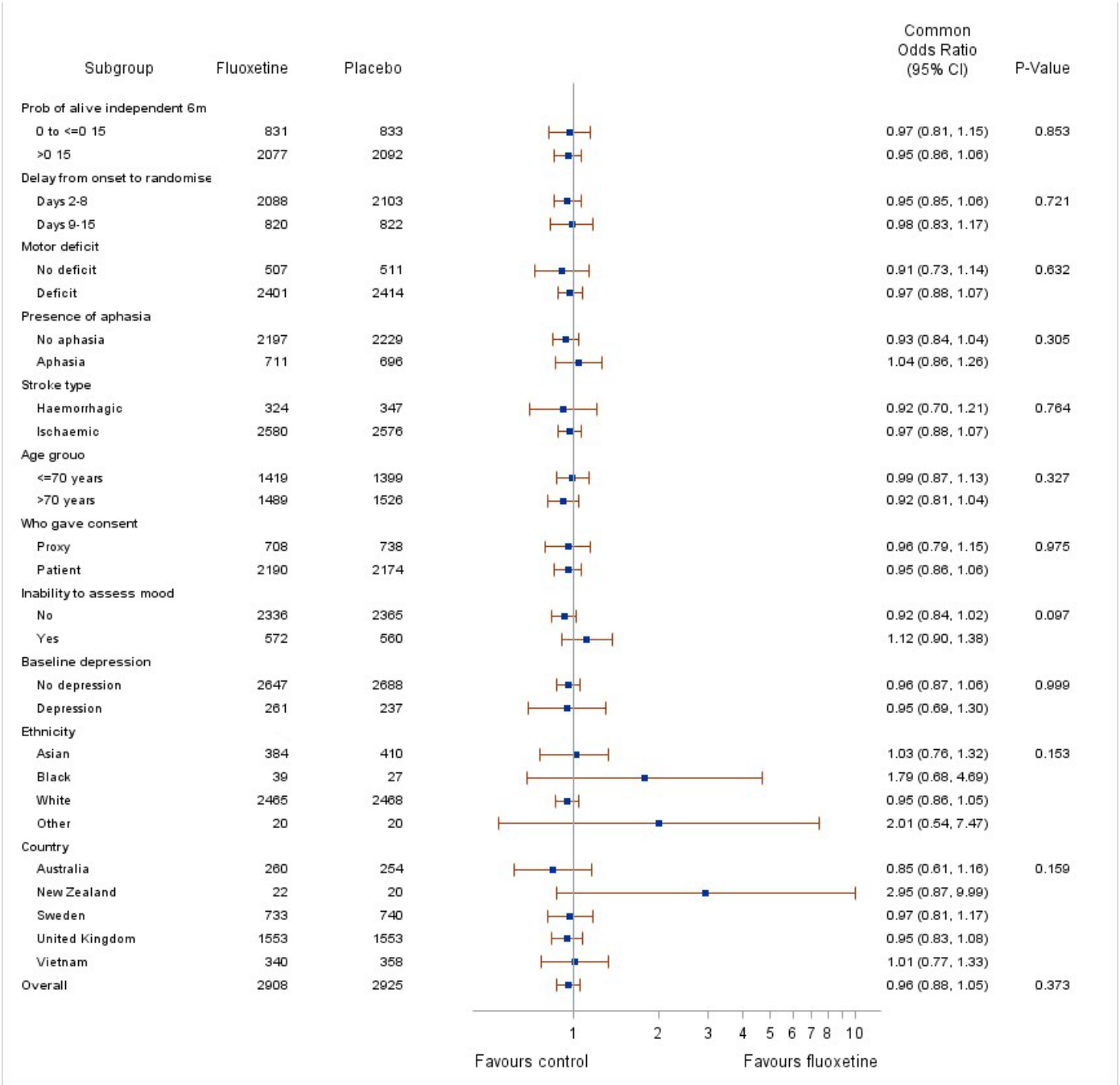


Table 2 Secondary outcomes for participants in AFFINITY, FOCUS and EFFECTS at 6 months

	Fluoxetine		Placebo		
	N	**Score**	**N**	**Score**	**P value for difference between groups**
SIS Strength	2676	68.75 (43.75, 87.50)	2689	68.75 (43.75, 87.50)	0.6719
SIS Hand ability	2671	70.00 (18.75,95.00)	2688	75.00 (20.00, 95.00)	0.9409
SIS Mobility	2681	77.78 (47.22, 94.44)	2705	80.56 (47.22, 94.44)	0.9174
Motor*	2680	71.25 (40.07, 89.81)	2696	71.39 (41.83, 89.58)	0.9335
SIS Daily activities	2680	80.00 (47.50, 95.00)	2698	80.00 (47.50, 95.00)	0.7577
Physical function**	2681	72.71 (42.12, 90.90)	2700	73.00 (43.70, 90.42)	0.984
SIS Memory	2668	85.71 (67.86, 100.00)	2694	89.29 (67.86, 100.00)	0.1194
SIS Communication	2678	92.86 (78.57, 100.00)	2700	92.86 (78.57, 100.00)	0.3438
SIS Emotion	2648	77.78 (63.89, 88.89)	2681	75.00 (61.11, 89.89)	0.0002
SIS Participation	2673	68.75 (43.75, 90.63)	2681	68.75 (43.75, 90.63)	0.4301
Recovery (VAS)	2671	70.00 (50.00, 85.00)	2700	70.00 (50.00, 85.00)	0.7868
Vitality, 5 item scale: (EFFECTS/FOCUS only)	2098	56.25 (43.75, 75.00)	2094	56.25 (43.75, 75.00)	0.5879
Vitality, 6 item scale: (AFFINITY only)	2668	60.00 (43.75, 75.00)	2686	60.00 (43.75, 75.00)	0.6778
EQ5D-5L	2678	0.66 (0.37, 0.84)	2699	0.67 (0.35, 0.84)	0.9174

Abbreviations: AFFINITY=assessment of fluoxetine in stroke recovery trial, EFFECTS= efficacy of fluoxetine-a randomised controlled trial in stroke, EQ5D-5L=Euroquol 5D 5 level, FOCUS=fluoxetine or control under supervision trial, N=number, P=probability, SIS=stroke impact scale, VAS=visual analogue scale

* Mean of the Strength, Hand ability, and Mobility domains

** Mean of the Strength, Hand ability, Mobility, and Daily activities domains

p-values are from Wilcoxon two-sample test

Table 3 Adverse events for participants in AFFINITY, FOCUS and EFFECTS at 6 months

	Fluoxetine N	**%**	**Placebo N**	**%**	**Difference in % (95%CI)**	**P value**
Further stroke	110	3.72	118	4	-0.28 (-1.26, 0.71)	0.58
Any thrombotic event (acute coronary event, thrombosis, ischaemic stroke)	119	4.03	129	4.37	-0.35 (-1.37, 0.68)	0.51
Ischaemic stroke	74	2.5	71	2.41	0.10 (-0.69, 0.89)	0.81
Other thrombotic events	25	0.85	33	1.12	-0.27 (-0.78, 0.23)	0.29
Acute coronary events	22	0.74	33	1.12	-0.37 (-0.86, 0.12)	0.13
Any bleeding event	55	1.86	48	1.63	0.29 (-0.43, 0.90)	0.49
Haemorragic stroke	12	0.41	10	0.34	0.07 (-0.24, 0.38)	0.67
Upper gastrointestinal bleed	26	0.88	21	0.71	0.17 (-0.29, 0.62)	0.47
Other major bleed	20	0.68	20	0.68	-0.00 (-0.42, 0.42)	1.00
Epileptic seizure	78	2.64	53	1.8	0.84 (0.09, 1.59)	0.03
Fall with injury	185	6.26	133	4.51	1.75 (0.60, 2.90)	0.0029
New fracture	93	3.15	41	1.39	1.76 (0.10, 2.51)	<0.0001
Hyponatraemia	36	1.22	18	0.61	0.61 (0.12, 1.09)	0.01
Hyperglycaemia	26	0.88	17	0.58	0.30 (-0.13, 0.74)	0.17
Symptomatic hypoglycaemia	25	0.85	13	0.44	0.41 (-0.00, 0.81)	0.05
New depression	297	10.05	396	13.42	-3.37 (-5.01, -1.73)	<0.0001
New antidepressant	346	11.71	451	15.28	-3.58 (-5.32, -1.84)	<0.0001
Attempted or actual suicide	4	0.14	5	0.17	-0.03 (-0.23, 0.16)	0.75

Abbreviations: AFFINITY=assessment of fluoxetine in stroke recovery trial, CI=confidence interval, EFFECTS= efficacy of fluoxetine-a randomised controlled trial in stroke, FOCUS=fluoxetine or control under supervision trial, N=number, P=probability

Table 4. Grade assessment for the primary outcome in the combined AFFINITY, FOCUS and EFFECTs trial data set

Domains for assessing certainty of evidence	Results section	Our assessment
Risk of bias	Five domains were evaluated (randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome, selection of reported results)	Not downgraded as all three trials were at low risk of bias
Inconsistency	Describe the degree of inconsistency by outcome using one or more indicators (e.g. I^2 and P value), confidence interval overlap, difference in point estimate, between-study variance.	Not downgraded because the proportion of the variability in effect estimates that is due to true heterogeneity rather than chance is not important (I^2 = 0%).
Indirectness	Describe if the majority of studies address the PICO – were they similar to the question posed?	Not downgraded as all three trials addressed the same PICOs
Imprecision	Describe the number of events, and width of the confidence intervals.	The confidence intervals for the COR of mRS at 6 months (our primary outcome) was narrow
Publication bias	Describe the possible degree of publication bias.	The risk is low as the protocol stated that three trials would be included and they have all been published
Large effects (upgrading)	Describe the magnitude of the effect and the widths of the associated confidence intervals.	Confidence intervals for the COR were narrow
Dose response (upgrading)	The studies show a clear relation with increases in the outcome of an outcome (e.g. lung cancer) with higher exposure levels.	Not relevant
Opposing plausible residual bias and confounding (upgrading)	Describe which opposing plausible biases and confounders may have not been considered.	All three trials controlled for all plausible confounders

Abbreviations: AFFINITY=assessment of fluoxetine in stroke recovery trial, COR=common odds ratio, EFFECTS= efficacy of fluoxetine-a randomised controlled trial in stroke, FOCUS=fluoxetine or control under supervision trial , I^2=statistical measure of study heterogeneity, mRS=modified Rankin scale, P= probability, PICO=patient/population, intervention, comparison and outcomes