Fluoxetine and fractures after stroke: an individual patient data meta-analysis of three large randomised controlled trials of fluoxetine for stroke recovery

Journal:	*International Journal of Stroke*
Manuscript ID	IJS-10-24-12865.R2
Manuscript Type:	Research
Date Submitted by the Author:	06-Jan-2025

Complete List of Authors:	Mead, Gillian; University of Edinburgh, Geriatric Medicine Graham, Catriona; University of Edinburgh, Wellcome Trust Clinical Research Facility Lundström, Erik; Uppsala University, Department of Medical Sciences, Neurology; Uppsala University Hankey, Graeme; Sir Charles Gairdner Hospital, Department of Neurology Hackett, Maree; The George Institute for Global Health, Mental Health, The University of New South Wales; The University of Central Lancashire, Faculty of Health and Care Billot, Laurent; The George Institute for Global Health, ; University of New South Wales, Faculty of Medicine Näsman, Per; KTH, Center for Safety Research Forbes, John; University of Limerick Dennis, Martin; Western General Hospital, 8Dept. of Clinical Neurosciences;

Keywords:	Clinical trial, Stroke, Blood pressure, Intervention, Seizures, Treatment

DOI: 10.1177/17474930251316164

Fluoxetine and fractures after stroke: an individual patient data meta-analysis of three large randomised controlled trials of fluoxetine for stroke recovery

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

Catriona Graham MSc Edinburgh 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, 2 trappor SE-751 85 Uppsala, Sweden

Graeme J. Hankey MD 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

Key words: stroke, fluoxetine, bone fractures, falls

Word count 3826

List of tables and figures

DOI: 10.1177/17474930251316164

Table 4 Multivariable analysis: Any fracture by 6 months in the combined dataset

Table 5 Adjusted ordinal regression analysis of modified Rankin at 6 months, after removal of patients with fractures.

Ethical approval was obtained for all of the original three trials. These analyses used anonymised data.

Data are available on reasonable request.

Funding of the individual trials that make up this individual patient data meta-analysis

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.

There was no specific funding for the current analyses.

Declarations of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. The authors were all investigators in the three fluoxetine trials included in this analysis.

DOI: 10.1177/17474930251316164

Abstract

Background

Observational studies have shown that selective serotonin reuptake inhibitors are associated with an increased risk of bone fractures, but the association can be confounded by indication and other sources of systematic bias that can be minimised in randomised controlled trials (RCTs).

Aim

Our aim was to report the rate, site, context, and predictors of fractures after stroke, and whether the fractures modified the effect of fluoxetine on modified Rankin score (mRS) at six months in an individual patient data meta-analysis of 5907 patients enrolled in three RCTs of fluoxetine (20mg for six months) for stroke recovery.

Methods

We classified fractures by treatment allocation, site (and thus likelihood of osteoporosis) and context, then performed multivariable analyses to explore independent predictors of fractures. We explored whether the trend towards a poorer mRS at 6 months was explained by a fracture excess. Risk of bias was assessed using GRADE.

Results

Among 5907 patients randomised at a mean of 6.6 days (SD3.6) post-stroke onset and followed for six months, the number of fractures at 6 months was 93 (3.15%) in the fluoxetine group vs 41 (1.39%) in the control group (difference 1.76, 95% CI 0.10 to 2.51). 128 patients with fractures were suitable for further analyses. Of these 102 (80%) were in sites typically affected by osteoporosis; 115 (90%) were associated with falls and one (1%) with a seizure. Independent fracture risk factors were female sex (hazard ratio (HR) 1.96; 95% CI 1.37 to 2.81, p=0.0002), age>70 years (HR 2.30, 95% CI 1.52 to 3.49, p<0.001), previous fractures (HR 0.63 for no previous fractures, 95% CI 0.42 to 0.94, p=0.0227), and randomised treatment (fluoxetine) (HR 2.39; 95% CI 1.64 to 3.49, p<0.001). The common odds ratio for the effect of fluoxetine on mRS at 6 months was unchanged after excluding fracture patients. Risk of bias was high for imprecision.

Conclusion

Fractures were more common in the fluoxetine group but the absolute risk of fractures was small and risk estimates were imprecise. Most fractures occurred with a fall, and in osteoporotic locations. Fractures did not modify the effect of fluoxetine on functional outcome.

DOI: 10.1177/17474930251316164

Background

Stroke survivors are at increased risk of fractures, mostly because of physical disability that predisposes to immobility, osteoporosis and falls [1,2]. Observational studies have reported that people with depression who are treated with selective serotonin reuptake inhibitors (SSRIs) are also at increased risk of fracture, perhaps because of cognitive effects of SSRIs [3]. However, observational studies cannot establish whether SSRIs *cause* fractures because the association can be confounded by indication and other sources of systematic bias. Randomised controlled trials (RCTs) are the optimal method of minimising confounding and most other major sources of systematic error.

A 2021 Cochrane review of SSRIs for stroke recovery identified 76 trials recruiting 13,029 patients [4]. Three large, trials of fluoxetine for stroke recovery (FOCUS, The Fluoxetine or Control Under Supervision trial), AFFINITY, Assessment of Fluoxetine in Stroke Recovery, and EFFECTs (Efficacy of Fluoxetine—a Randomised Controlled Trial in Stroke (EFFECTs) contributed almost half the patients [5-7]. These three trials were designed using the same protocol, and included bone fractures as pre-specified outcomes. In the individual patient data meta-analysis (IPDM) of the combined data sets from FOCUS, AFFINITY and EFFECTS, guided by a published protocol [8] we reported that 2956 stroke patients, randomised at a mean of 6.6 days (SD3.6) after stroke onset, allocated fluoxetine were more likely to sustain a bone fracture by 6 months than 2951 patients allocated placebo (93 (3.15%) vs 41 (1·39%)) [9]. This suggests that fluoxetine is a causal factor in fractures after stroke.

When we wrote the protocol for the IPDM [8], we considered whether to include the other trials of SSRIs for stroke recovery identified for the Cochrane review [4], but most other trials were small, had important sources of bias, used SSRIs other than fluoxetine, or did not systematically report adverse events including fractures, so we restricted the IPDM to FOCUS, EFFECTS and AFFNITY.

We have already reported an in-depth analysis of the type, timing and associations of fractures in the FOCUS trial [10]. This current analysis repeats this analysis in the combined dataset.

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Our aims were to determine:

1. What types of fractures occurred? Were they in sites which are associated with osteoporotic fractures?
2. Did the fractures occur as a result of a fall or seizure?
3. Did any excess of fractures in the fluoxetine group appear early after randomization (as one might expect if the mechanism was via falling) or later which one might expect if the mechanism was via an effect of fluoxetine on bone density or strength?
4. What factors are associated with fractures?
5. Was the non-significant trend towards worse mRs in the fluoxetine group due to the excess of fractures?

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Methods

Study selection:

The three data sets from FOCUS, AFFINITY and EFFECTS had already been merged by the FOCUS statistician (Catriona Graham) as described in a statistical analysis plan for the IPDM [8]. We had prespecified that we would include only data from these three large fluoxetine trials, and not include other trials identified in a Cochrane review. The three trials were designed using a common protocol. Eligibility criteria have been prescribed previously; patients with an acute stroke, in the previous 2 to 15 days, were randomised to either fluoxetine 20mg od or matching placebo, for 6 months. The trial drug was prescribed immediately after randomisation. The primary outcome was the modified Rankin Score (mRS) at 6 months. Final follow-up was at 12 months.

This current analysis of fractures was guided by an unpublished protocol which we had developed for analysis of the fractures in FOCUS [10]. This protocol is available on request.

Risk of bias

Risk of bias assessment for the IPD has already been performed using GRADE for the primary outcome (mRS at 6 months) [9]. We repeated this with fractures as the outcome of interest.

Identification of fractures

Data on fractures were obtained from the serious adverse events forms from AFFINITY and from follow-up forms from FOCUS and EFFECTS at six months.

Fractures from AFFINITY and EFFECTS were classified by GEM/CG and FL respectively as they had been for FOCUS (type, side, related to fall or seizure) [5]. Osteoporosis related fractures were defined by fracture site as likely related to osteoporosis (wrist, neck of femur, vertebrae), possibly related (long bone, pelvis, clavicle), unlikely related (rib, other sites). The first fracture event has been considered for each patient and where multiple fractures occurred in the same event, we assigned the highest likelihood first.

Classification of drugs at baseline

Drugs at baseline in FOCUS had been classified by Martin Dennis. For EFFECTS, Gillian Mead classified these using the same methods. In AFFINITY, drugs had been classified slightly differently: blood pressure (BP) lowering drugs included selective alpha blocker, angiotensin converting enzyme (ACE) inhibitor, Angiotensin II receptor blocker, beta-blocker, calcium channel blocker, combination of atenolol and chlortalidone, diuretic, vasodilator. A 'drug of interest' included drugs that could increase falls risk including through their effect on blood pressure (e.g. drugs for Parkinson's disease,

DOI: 10.1177/17474930251316164

vertigo, or hypertension; antidepressants other than SSRIs, sedatives or tranquilizers) and drugs that might indicate a history of osteoporosis. In AFFINITY, BP lowering drugs and 'any drug of interest' were probably underestimated because we did not have data on whether patients were taking vasodilators, drugs for Parkinson's disease and drugs for vertigo and drugs causing postural hypertension, tranquilizers, sedatives and osteoporosis-related drugs.

Univariable analysis

A univariable analysis (Kaplan-Meier with Log-Rank statistics) was performed to determine the relationship between the following variables of interest at the time of randomisation (also referred to as 'baseline'): sex, age group, required assistance with activities of daily living (ADL) pre-stroke, previous ischaemic stroke/transient ischaemic attack (TIA), diabetes, history of bone fracture, previous depression, able to walk at time of stroke, able to lift both arms off bed, able to talk and not confused, probability of being alive and independent at 6 months, motor deficit, visual field, limb ataxia, current mood (Patient Health Questionnaire 2 (PHQ2)), current BP-lowering drugs and any 'drug of interest' (see above). These variables were selected by the principal investigators of the three trials who are all experts in stroke and/or medicine of elderly, and thus have knowledge of the risk factors for falls and fractures. We did not have data on marital status or living arrangements at time of fracture so we could not include these variables in our analysis. Most of the patients were white and so we did not include ethnicity, and most will have retired so we did not collect data on employment status. The mRS was reported at 6 months after randomisation and we did not have mRS at the time of fracture. We decided not to do multiple-collinearity checks as we did not expect the variables selected to be dependent on each other.

Time to first fracture was presented using Log-Rank statistics and Kaplan-Meier failure plots. Patients who died, or who withdrew without having a fracture were considered to be censored at the time of death or withdrawal.

Multivariable analysis

Multivariable Cox proportional hazard models were generated using the variables identified in the univariate analysis (any variable with a univariate association of p<0.1 was considered for inclusion) after sequential removal of non-significant variables a final model was generated. We pre-specified that we would use a cut-off of p<0.1 rather than a higher p value, to avoid overfitting the model.

We planned to perform a sensitivity analysis was performed by 'on treatment' rather than allocated treatment. Thus, patients who never started any selective serotonin reuptake inhibitor (SSRI) were in the non SSRI group, and those who were taking an SSRI before a fracture were in the SSRI group.

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Results

Risk of bias is shown in Table 1. We downgraded for precision because the Cochrane Handbook states that a 'very wide' confidence interval is 0.5 to 1.10; our point estimate for the absolute difference in fractures between the fluoxetine and placebo group was wider than this [11]. We also downgraded for a small effect size.

We have previously reported the characteristics of the 5907 patients randomized [9]. There were 2256 women (38.2%) and 3651 men (61.8%), mean age 69.6 (SD 12.3), median National Institutes of Health Stroke scale at randomization was 5 (interquartile range 3 to 9).

Rate and timing of fractures occurring by 6 months in the combined data set

There were 93 (3.15%) patients with new fractures in the fluoxetine group compared with 41 (1.39%), difference 1.76% (95% CI 0.10, 2.51, p<0.0001) [9].

Of the 134 patients who had a fracture recorded by 6 months; three had occurred at the time of the stroke and so were excluded, there were insufficient data about timing/type for two fractures and one occurred 185 days from the initial assessment, leaving data about fractures for 128 patients, from a total of 5907 randomised patients. In the fluoxetine group, 89/2956 (3.01%) had a fracture compared with 39/2951 (1.32%) in the placebo group.

Of the 128 patients with fractures, the timing of fractures is illustrated in Figure 1, showing a steady cumulative increase in incidence in both the fluoxetine and placebo groups over the six month follow-up period.

Location of fractures

There were 131 fractures in 128 patients. The location of the 131 fractures were neck of femur (43, 33%), long bone (20, 15%), wrist (16, 12%), vertebrae (14, 11%), rib (9, 7%), pelvis (8, 6%), clavicle (2, 2%), and miscellaneous sites (19, 15%). Thus 72 (55%) were likely associated with osteoporosis, 30 (23%) possibly, and 26, (20%) unlikely.

Predisposing causes of fractures

Of the 89 patients with fractures in the fluoxetine group, 50 (56%), 21 (24%) and 18 (20%) were judged likely, possibly and unlikely to be related to osteoporosis respectively. Of the 39 patients with fractures in the placebo group, 22 (56%), 9 (23%) and 8 (21%) respectively were likely, possibly, unlikely related to osteoporosis. There was no evidence of a relationship between the fracture being related to osteoporosis and treatment allocation (Chi square test p=0.9978, table 2).

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Context

Cause of fractures

Of the 128 patients with fractures, 115 (90%) fractures were caused by a fall and one (1%) during a seizure. Data on the context were missing for 12 patients.

There was no evidence of a relationship between osteoporosis-related fractures and treatment allocation when we considered fractures occurring up to, and including, 31 days (p=0.7731) separately from fractures occurring after 31 days up to 6 months after stroke (p=0.9384, table 2).

Association between fractures and other factors (tables 3 and 4) at 6 months

On univariable analysis there is a statistically significant relationship between time of fracture and being allocated to fluoxetine, being female, older aged and requiring assistance with ADL prior to stroke, previous ischaemic stroke (TIA), previous bone fracture, not able to walk at the time of stroke and lower probability of being alive/independent at 6 months. BP lowering drugs and 'any drug of interest' had a univariable p value of <0.1 so they were also included in our multivariable model (table 3).

After the sequential removal of the least significant variables, a model with only those variables which remain statistically significant at the 5% level was generated. This contained only sex, older age, previous fracture, able to walk at time of stroke and randomised treatment (fluoxetine) (table 4). After sequential removal of the least significant variables from the model, the final model contained only sex, older age, previous fracture and randomised treatment (fluoxetine).

Effect modification of fractures

Is the trend towards poorer mRS at 6 months related to fracture (table 5)

The common odds ratio (COR) for mRS at 6 months in patients without fractures was 0.96 (0.88 to 1.06). We have previously shown that the COR for the entire group was also 0.96.

Sensitivity analysis according to treatment with fluoxetine or not

There were 15/2956 (0.5%) participants allocated to fluoxetine who received no study medication and 35/2951 (1.2%) participants allocated to placebo who received SSRI within 90 days. We did not perform a sensitivity analysis as there was only one fracture in the placebo arm who received an SSRI within 90 days and none in the group allocated to fluoxetine who did not receive fluoxetine.

DOI: 10.1177/17474930251316164

Discussion

Our IPPD showed that Fractures by 6 months (a secondary endpoint in the three trials) occurred in only 2% of patients with acute stroke followed for 6 months. Although our analyses used data from three high quality RCTs, there were wide confidence intervals for the point estimates of fracture risk. Most fractures were associated with falls and in sites typically affected by osteoporosis. Our multivariable model demonstrated that the independent risk factors for fractures were female sex, increasing age, previous fractures, and exposure to fluoxetine 20 mg once daily for 6 months. Although the absolute percentage of fractures at 6 months was small for statistical analysis, this is still an important number of people who are having fractures that could be potentially avoidable (e.g. by not taking routine fluoxetine).

Why does fluoxetine cause an increased risk of fracture within the first 6 months after stroke? We found no difference in the type of fractures between the fluoxetine and placebo groups (including whether they were likely to be related to osteoporosis or not), suggesting that the predominant mechanism was not because fluoxetine increased the risk of osteoporosis. However, the lack of association could be because our methods of identifying osteoporosis related fractures using the site of the fracture were too insensitive to small effects, or that our analyses were underpowered.

The vast majority (90%) of the fractures occurred in association with falls. Fluoxetine increases falls risk [9], suggesting that the main mechanism of fractures with fluoxetine was through increased falls. In this current analysis, we made the assumption that if increased falls were the mechanism of increased fracture risk, there would be more fractures in the first month of fluoxetine prescription i.e. 'front loading'. But this was not the case, with incident fractures spread evenly across the first six months. Patients may still be undergoing rehabilitation in a hospital setting in the first month, where prevention of falls is an integral aspect of management, and this might mitigate any immediate increased risk of fluoxetine on falls risk. Baseline medication that might increase fall risk (e.g. blood pressuring lowering medication) and those prescribed for osteoporosis were not associated with fractures; this lack of association could be because we were underpowered to identify a small effect. It is likely that the mechanism by which fluoxetine exerts an effect on fracture risk, and on falls risk is more complex than we proposed including confusion, unsteadiness, reaction times, dehydration and hypotension [12].

Fractures after stroke probably did not explain the trend towards a poorer mRS in the fluoxetine group; but this analysis could be underpowered, or the effect of fractures could be more subtle-affecting, for example, quality of life rather than dependency [1]. Previous analyses of observational

DOI: 10.1177/17474930251316164

data have shown, that fractures are associated with impaired quality of life, though it is unclear whether relationship is causal [1].

There are several benefits of an IPDM compared with extracting summary (aggregate) data from study publications and performing a meta-analysis of summary effects. For example, IPDM can improve the quality of data and the type of analyses that can be done and produce more reliable results [13]. For these reasons an IPDM is considered to be a 'gold standard' of systematic review. However, IPPD takes longer than a meta-analysis of summary effects, because data needs to be harmonised and combined from different trials, which generally requires additional resource and statistical expertise. This often results in a delay between publication of the primary trials and the IPDM, as there has been for our analyses.

There are some limitations to our study. Despite the experimental design of the three large RCTs, the multivariable analyses of factors associated with fractures are at best only able to report associations not relationships. The number of fractures in the first six months was small and confidence intervals for point estimates were wide. We did not adjust for the mRS prior to the stroke (because we had not collected this information) but we did adjust for the binary variable of independent (or not) in activities of daily living prior to the stroke. Also, we did not collect data on Charleston Comorbidity index. Given that there is an association between multimorbidity and the risk of fractures, this represents a limitation of our study [14], but we did include some important comorbid conditions that we considered to be relevant. We did not record pre-stroke fall history-this was because we did not want to overburden recruiting sites, and because retrospective recall of fall history may not have been accurate-though recent evidence suggest that retrospective recall of falls is reliable [15]. We did, however, record a history of prior fractures. There might also be other unmeasured confounders [12], such as fear of falling, impaired balance, impaired vision and motor-cognitive disorders which are risk factors for falls. We did not record these-though because our three large trials were randomised it is likely that these factors will have been similarly distributed between the fluoxetine and placebo groups, but we could not include them in our univariable and multivariable models.

Fractures after stroke were rare events, and fractures after stroke *not* associated with falls were even rarer. Future studies should consider how to standardise recording of such rare events, and consider how best to analyse the data [16]. Different model specification could be used (e.g. Firth type logistic regression with intercept correction), though effect estimates are likely to be similar. A composite endpoint could be considered but there is overlap between, for example, falls and fractures.

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What are the implications of this research? If prescribing fluoxetine after stroke, clinicians should be aware of the increased risk of fractures; should take into account this risk when balancing the risks and benefits of fluoxetine, and discuss this with patients and their families. For patients already taking fluoxetine at the time of their stroke-clinicians might wish to consider whether this is still needed or whether fluoxetine should be 'deprescribed'. Further analysis of our combined data set to explore reasons, other than fractures, is needed to identify why there is a trend towards poorer mRS at 6 months in those prescribed fluoxetine. Further research is needed to elucidate the mechanisms by which fluoxetine increases both falls and fractures after stroke. Falls risk may be increased via orthostatic hypotension [17], imbalance, dizziness or hyponatraemia [18], and the effect of certain genetic variants might modify antidepressant-related fall risk [19]. A better understanding of how these mechanisms interact could enable new interventions to be developed to reduce fracture risk in people taking SSRIs. The data from this IPDM about absolute risk of fractures-and their type-could be used for power calculations for future mechanistic studies.

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Table 1. Grade assessment for the outcome of fractures 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 ($I^2 = 0\%$), as previously reported in the Cochrane review [4]
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.	Downgraded because the confidence intervals for the difference between fracture risk at 6 months (1.76%, 0.1% to 2.51%) for all fractures identified at 6 months in the IPDM. According to the Cochrane handbook, an example of a 'very wide' confidence interval is 0.5 to 1.10, so we judged our confidence interval as 'very wide'.
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.	The difference between the fluoxetine and control group was small and the confidence intervals for the difference in % of fractures were wide. Downgraded
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 most plausible confounders

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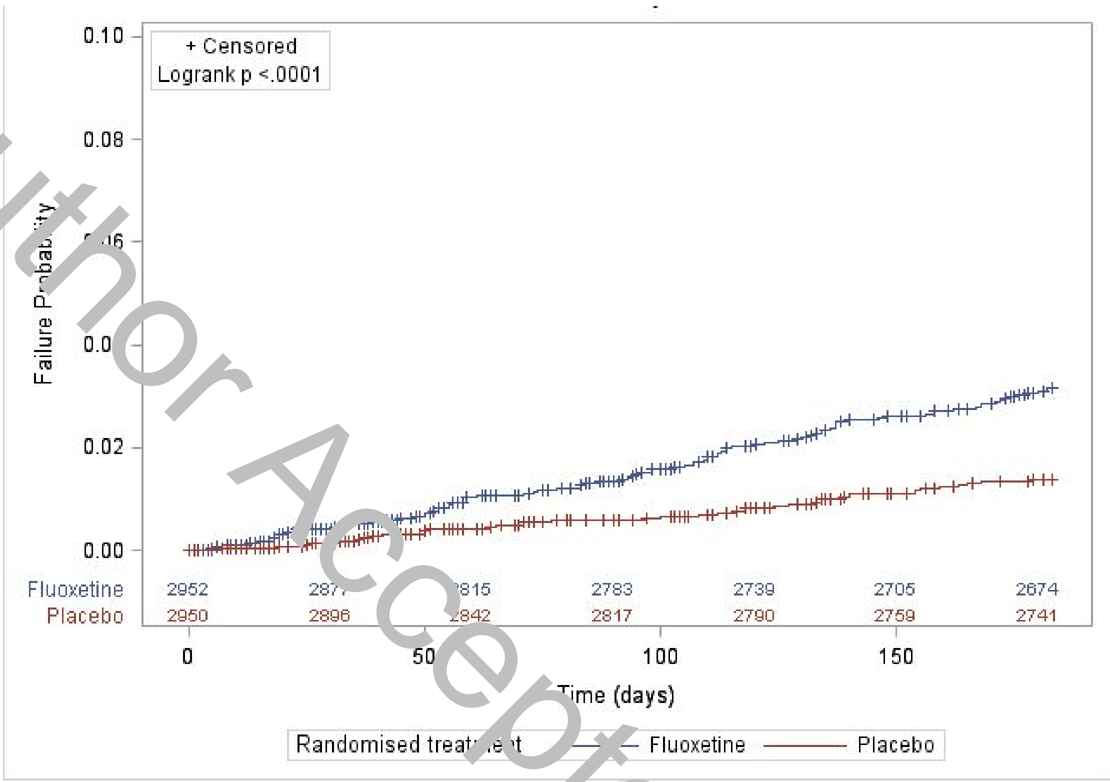
Table 2 Number of fractures by randomised treatment, their timing and their likely relationship with osteoporosis, occurring in the six months after randomisation

	Randomised treatment								**N**	**%**
	Fluoxetine				Placebo					
	>31 days to <=6 months		<=31 days		>31 days to <=6 months		<=31 days			
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Number of patients who had a fracture within 6 months	76	100.00	13	100.00	35	100.00	4	100.00	128	100.00
Relationship with osteoporosis										
Likely	44	57.89	6	46.15	19	54.29	3	75.00	72	56.25
Possibly	18	23.68	3	23.08	9	25.71	.	0.00	30	23.44
Unlikely	14	18.42	4	30.77	7	20.00	1	25.00	26	20.31

There was no evidence of a relationship between osteoporosis in this manner and treatment allocation when we considered fractures occurring up to, and including, 31 days (p=0.7731, using Fishers exact test due to small expected counts) and separately for fractures occurring after 31 days up to 6 months (p=0.9384).

DOI: 10.1177/17474930251316164

Figure 1. Timing of fractures



DOI: 10.1177/17474930251316164

Table 3

Univariable analysis; log-rank statistic (p value) for each variable of interest for fractures up to six months.

'Any drug of interest' is presented for all trials, and each trial individually, but the way that drugs were classified from AFFINITY means that there is likely to be an underestimate of the drugs. Thus we have repeated the combined trial analysis with just EFFECTS and FOCUS.

		Log-rank statistic (p value)			
Variable		**AFFINITY**	**EFFECTS**	**FOCUS**	**All trials combined**
Treatment allocation		0.0128	0.0053	0.0084	<0.0001
Demographics					
	Sex	0.0022	0.1704	0.0005	<0.0001
	Age group >70 years	0.0001	0.0099	0.0033	<0.0001
	Require assistance with ADL	0.1544	0.1317	0.1762	0.0325
Previous medical history					
	Ischaemic stroke/TIA~	0.0593	0.0200	0.8817	0.0500
	Diabetes~	0.2257	0.5008	0.7603	0.2462
	Bone fracture~	0.1335	0.0200	0.8285	0.0174
	Depression ~	0.2529	0.6306	0.0913	0.1491
Stroke diagnosis					
	Type of stroke (Ischaemic/Intracerebral haemorrhage)	0.3561	0.3802	0.1320	0.3483
	Not able to walk at time of stroke	0.[illegible]691	0.0269	0.0849	0.0064
	Able to lift both arms off bed	0.8[illegible]26	0.2788	0.8704	0.8739
	Able to talk and not confused	0.[illegible]059	0.1264	0.5203	0.6051
	Probability of being alive and independent at 6 months (0 to ≤0.15, >0.15 to 1)	0.17[illegible]8	0.[illegible]650	0.1455	0.0136
	Motor deficit	0.4470	0.[illegible]357	0.7967	0.1731
	Visual field deficit	0.4238	0.49[illegible]8	0.3261	0.8846
	Limb Ataxia *	0.4828	0.8337*	0.8[illegible]23	0.5801*
	Current mood (PHQ2)**	0.6819	0.1104	0.[illegible]222	0.3630
Drugs					
	BP lowering	0.5838	0.7135	0.10[illegible]	0.0880
	Any drug of interest ***	0.6067	0.4604	0.1161	0.0672
	Any drug of interest (EFFECTS and FOCUS only)		0.4604	0.1161	0.0823

~Variable was originally coded as yes, no, unknown. For the purposes of this analysis the no and unknown have been combined to provide an analysis of known to be present yes/no

*EFFECTS have 32 participants with information for this question

**AFFINITY have 59 participants with missing information for this question.

***See explanation in the introduction of document. Any drug of interest does not contain all the drugs which are considered for EFFECTS and FOCUS.

DOI: 10.1177/17474930251316164

Table 4. Multivariable analysis: Any fracture by 6 months in the combined dataset

Parameter	Hazard Ratio	95% Hazard Ratio Confidence Limits		Pr > ChiSq
Sex (female)	1.961	1.372	2.801	0.0002
Age group (>70)	2.299	1.515	3.487	<.0001
Did not required assistance with ADL prior to stroke	0.678	0.357	1.286	0.2339
No previous ischaemic stroke/TIA	0.728	0.478	1.108	0.1386
No previous bone fractures	0.630	0.424	0.938	0.0227
Not able to walk at time of stroke	1.570	1.019	2.417	0.0407
Probably of being alive and independent at 6 months (0-<=0.15, 0.15-1)	0.850	0.550	1.313	0.4638
BP lowering drug (yes, no)	0.924	0.376	2.273	0.8640
Any drug of interest (yes, no)	0.891	0.336	2.366	0.8169
Randomised treatment (fluoxetine, placebo)	2.393	1.641	3.488	<.0001

Cox proportional hazards model including the variables from the univariable analysis that had reached the 10% level of significance

DOI: 10.1177/17474930251316164

Table 5 Adjusted ordinal regression analysis of modified Rankin at 6 months, after removal of patients with fractures.

Ordinal regression Adjusted	Common odds ratio for good outcome	95% CI lower limit	95% CI upper limit	p-value
All trials combined	0.96	0.88	1.06	0.44806
AFFINITY	1.00	0.81	1.23	0.97224
EFFECTS	0.96	0.79	1.15	0.63964
FOCUS	0.96	0.85	1.09	0.54970

These analyses are also adjusted for probability of being alive and independent at 6 months, delay from onset to randomisation, motor deficit and presence of aphasia, as we had done for all patients including those with fractures

DOI: 10.1177/17474930251316164

Acknowledgements

We acknowledge the patients, their families, the patient and public involvement groups, the researcher teams who recruited the patients and the staff employed on each of the three trials.

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

DOI: 10.1177/17474930251316164