FOCUS: Fluoxetine Or Control Under Supervision Results

Martin Dennis on behalf of the FOCUS collaborators

Background


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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.

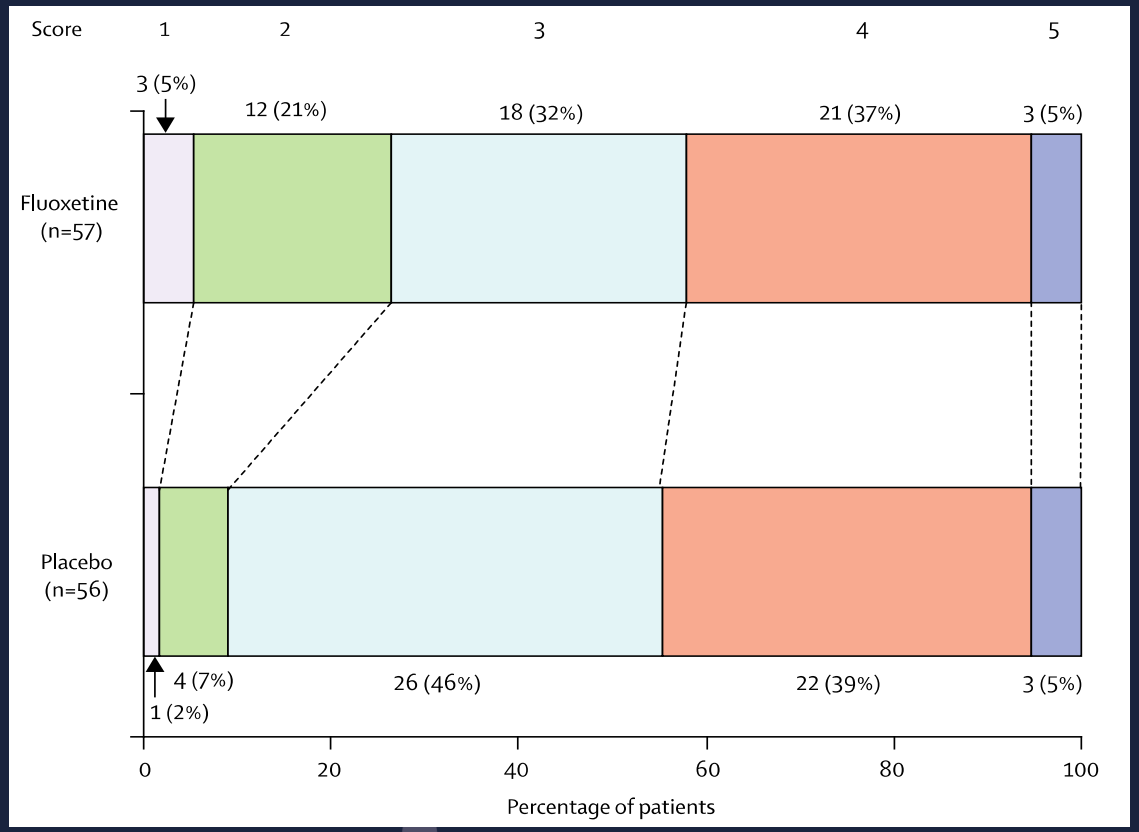
UK stroke experts said the findings were "promising".

Improving motor functions in stroke patients helps their independence

Related stories

- Pre clinical and imaging studies had suggested benefits from fluoxetine (and other SSRIs) in stroke recovery
- FLAME (n=118), ischaemic stroke, a double blind placebo controlled trial of 20mg fluoxetine for 3/12
- Fluoxetine associated with an improvement in their primary outcome - Fugl Meyer motor score (p=0.003) (17 A4 pages)
- Also, proportion with modified Rankin score (mRS) 0-2 increased from 9% to 26% (p=0.015)

The FLAME Trial results
Distributions of mRS ay 90 days



common odds ratio 1·501 [95% CI 0.757–2.974]; p=0.2446).

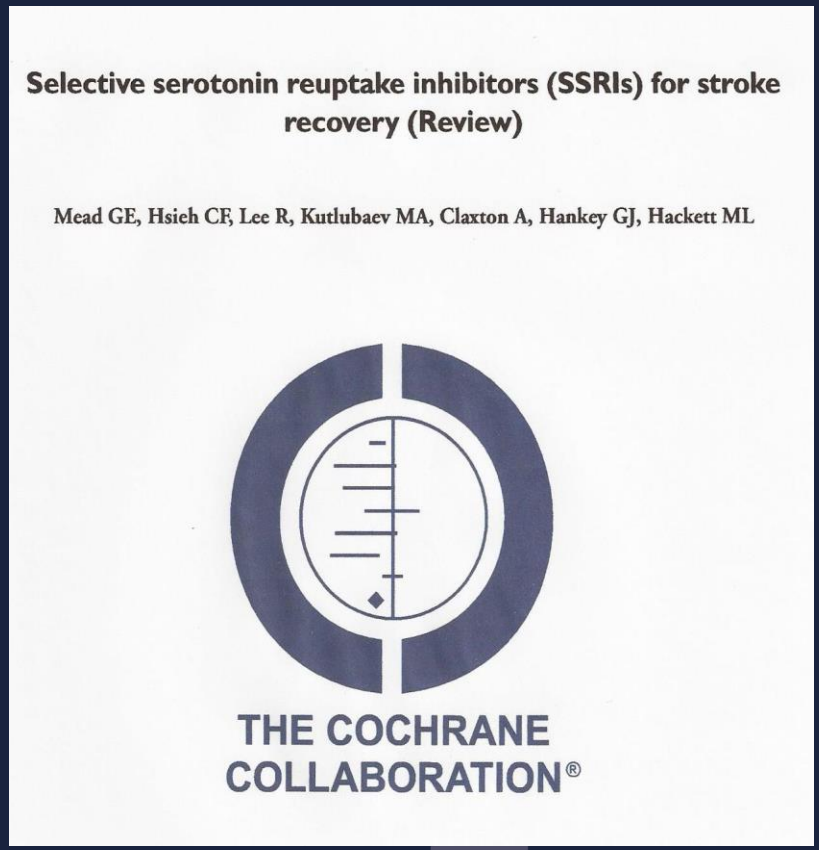
Why might SSRI improve recovery after stroke?

- Improves motor cortex plasticity
- Promotion of neuro-regeneration in hippocampus
- Reduce cortisol which is associated with poorer outcomes after stroke
- Reduces blood ‘stickiness’ (and so reduce the risk of ischaemic stroke)
- Lower risk of depression

Meta-analysis of SSRIs for stroke recovery

- Improves disability at end of treatment
- Improves neurological scores
- Reduces depression
- Possibly improves cognition
- BUT possible excess of adverse events
  - Gastrointestinal symptoms
  - Seizures
  - Bleeding

Less effect in high quality studies and in patients without depression



Cochrane Library 2012, JAMA 2013, Stroke 2013

Aims of FOCUS

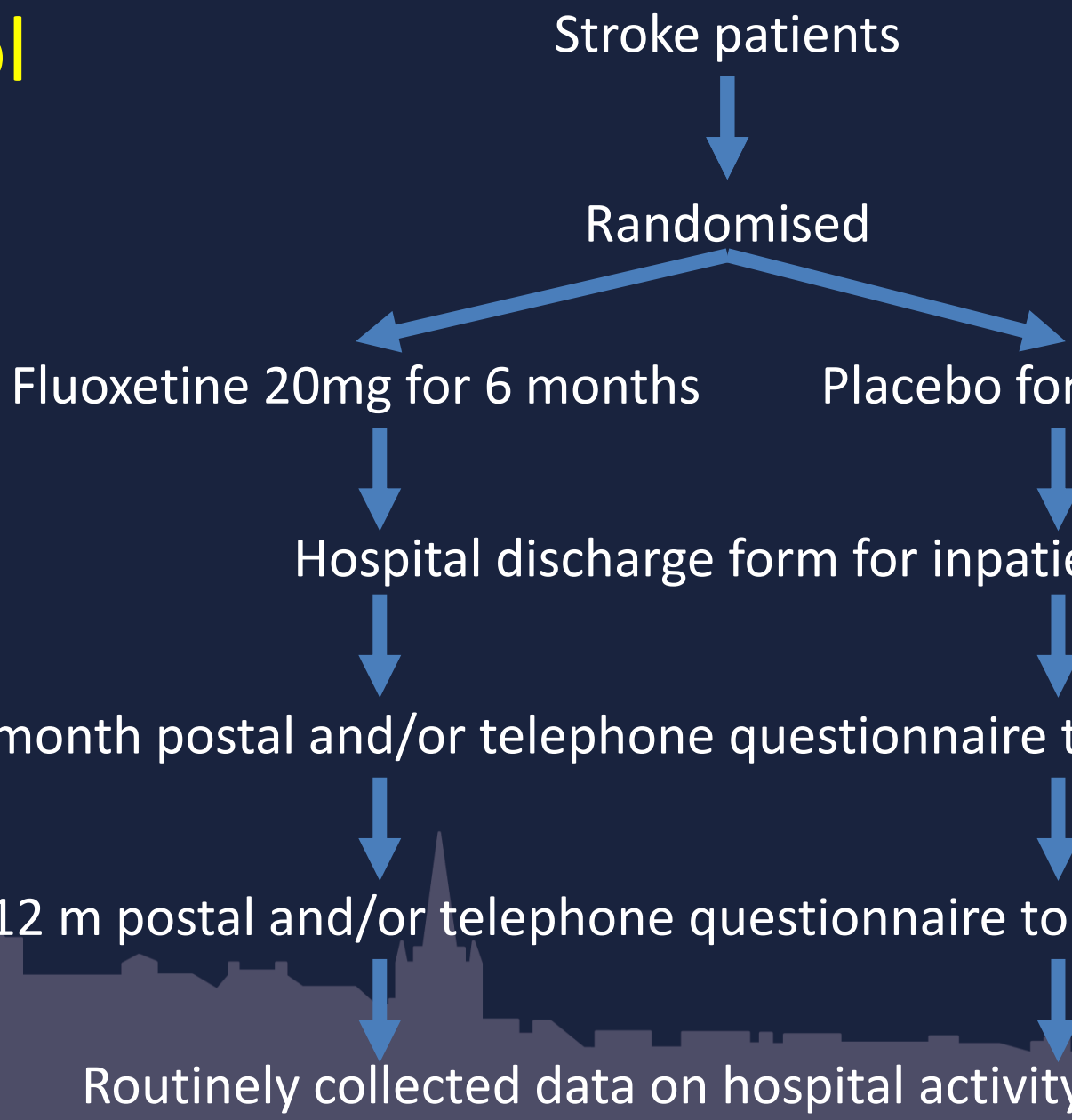
- Determine if fluoxetine 20mg daily for 6 months after stroke
  - Reduces dependency after stroke
  - Reduces other post-stroke problems
  - Whether any improvements persist to 12 months
- Provide robust evidence about benefits vs risks

FOCUS, AFFINITY and EFFECTs

- A family of three trials collaboratively designed
- Very similar protocols
- FOCUS (UK) aimed to recruit > 3000
- AFFINITY (Australasia & Vietnam) >1600
- EFFECTS (Sweden) >1500

- FOCUS is the first to report, the others continue to recruit

Protocol


Stroke patients
Randomised
Fluoxetine 20mg for 6 months
Placebo for 6 months
Hospital discharge form for inpatients
6 month postal and/or telephone questionnaire to patients and GPs
12 m postal and/or telephone questionnaire to patients and GPs
Routinely collected data on hospital activity and survival

Inclusion criteria

- Age ≥ 18 years
- Clinical diagnosis of stroke 2-15 days previously
- Brain imaging consistent with intracerebral haemorrhage or ischaemic stroke.
- Persisting focal neurological deficit present at the time of randomisation severe enough to warrant treatment from the patient's or carer's perspective

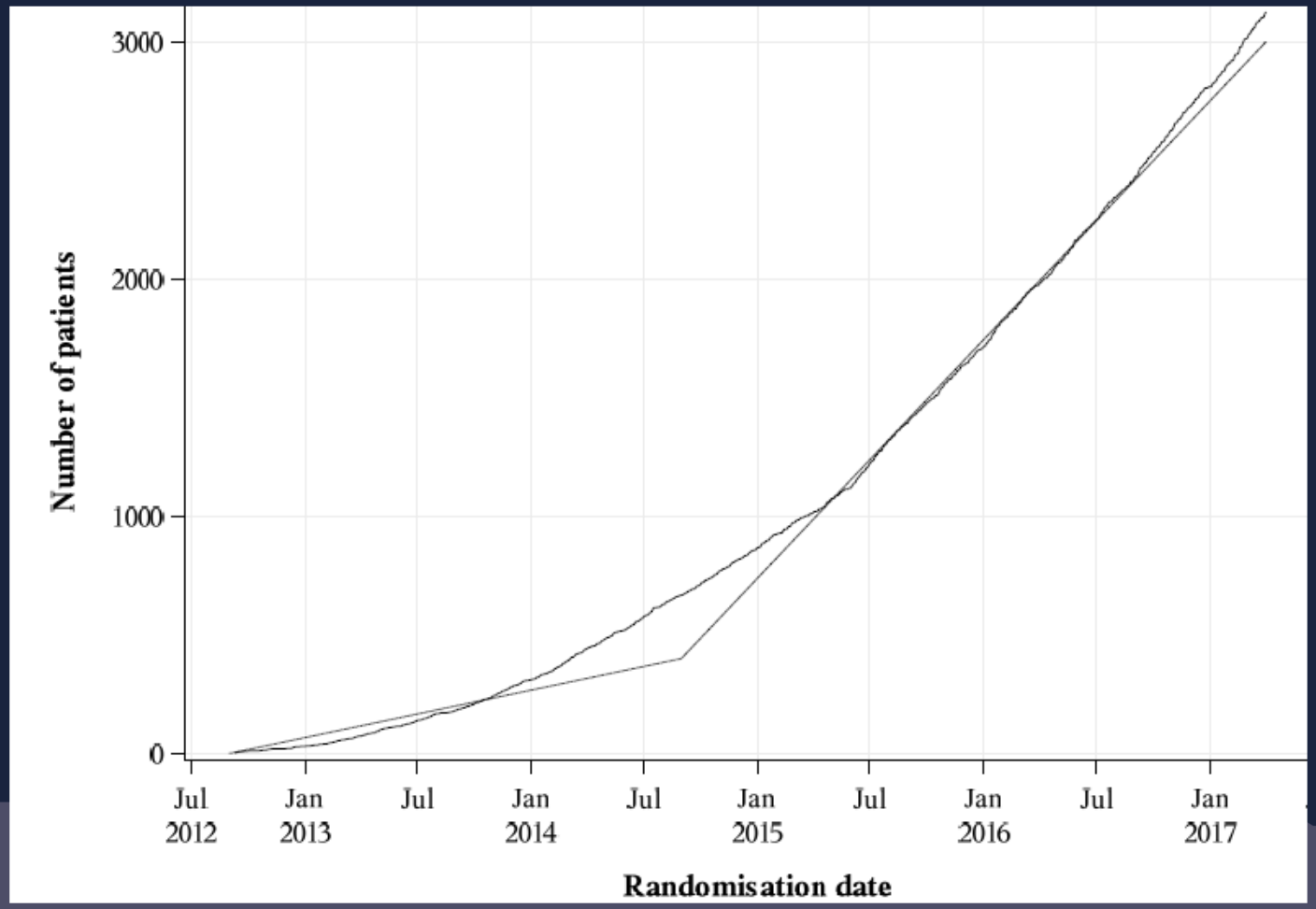
Exclusion criteria

- Stroke due to subarachnoid haemorrhage
- Received SSRI within last 5 weeks
- Epilepsy
- Medications having serious interactions with Fluoxetine
- Pregnant or breast-feeding
- Previous drug overdose or attempted suicide
- Participation in another CTIMP

Outcome measures

- Primary outcome: mRS at 6 months
- Safety: Adverse events within 6 months
- Secondary outcomes
  - mRS at 12 months
  - Stroke Impact Scale (SIS) at 6 & 12 months
  - Mental Heath Inventory (MHI-5) at 6 and 12 months
  - Fatigue (vitality score of SF-36)
  - Health related quality of life (EuroQol 5-D)
  - Survival to 12 months

Recruitment
(Sept 2012 – Mar 2017)



Baseline characteristics (demographics)

	Randomised treatment			
	Fluoxetine		Placebo	
Characteristics of patients randomised	n	%	n	%
All patients	1564	100.0	1563	100.0
Female	589	37.7	616	39.4
Male	975	62.3	947	60.6
Mean age (SD)	71.2	(12.4)	71.5	(12.1)
White	1495	95.6	1493	95.5

Baseline characteristics (stroke type)

	Randomised treatment			
	Fluoxetine		Placebo	
Characteristics of patients randomised	n	%	n	%
All patients	1564	100.0	1563	100.0
Final diagnosis				
Non stroke	2	0.1	2	0.1
Ischaemic stroke	1410	90.1	1406	90.0
Intracerebral haemorrhage	154	9.9	157	10.0
OCSP classification of ischaemic strokes				
Total Anterior Circulation Infarct (TACI)	318	20.3	317	20.3
Partial Anterior Circulation Infarct (PACI)	561	35.9	553	35.4
Lacunar infarct (LACI)	307	19.6	283	18.1
Posterior Circulation Infarct (POCI)	191	12.2	230	14.7
Uncertain	33	2.1	23	1.5

Baseline characteristics (stroke severity)

	Randomised treatment			
	Fluoxetine		Placebo	
Characteristics of patients randomised	n	%	n	%
Able to walk at time of randomisation	435	27.8	412	26.4
Able to lift both arms off bed	924	59.1	935	59.8
Able to talk and not confused	1166	74.6	1164	74.5
Probability that alive and independent Median (IQR)	0.3	0.1-0.6	0.3	0.1-0.6
0 to <=0.15	592	37.9	591	37.8
>0.15 to 1	972	62.2	972	62.2
NIHSS Median (IQR)	6	3-11	6	3-11
Presence of a motor deficit	1361	87.0	1361	87.1
Presence of aphasia	457	29.2	449	28.7

Baseline characteristics (depression)

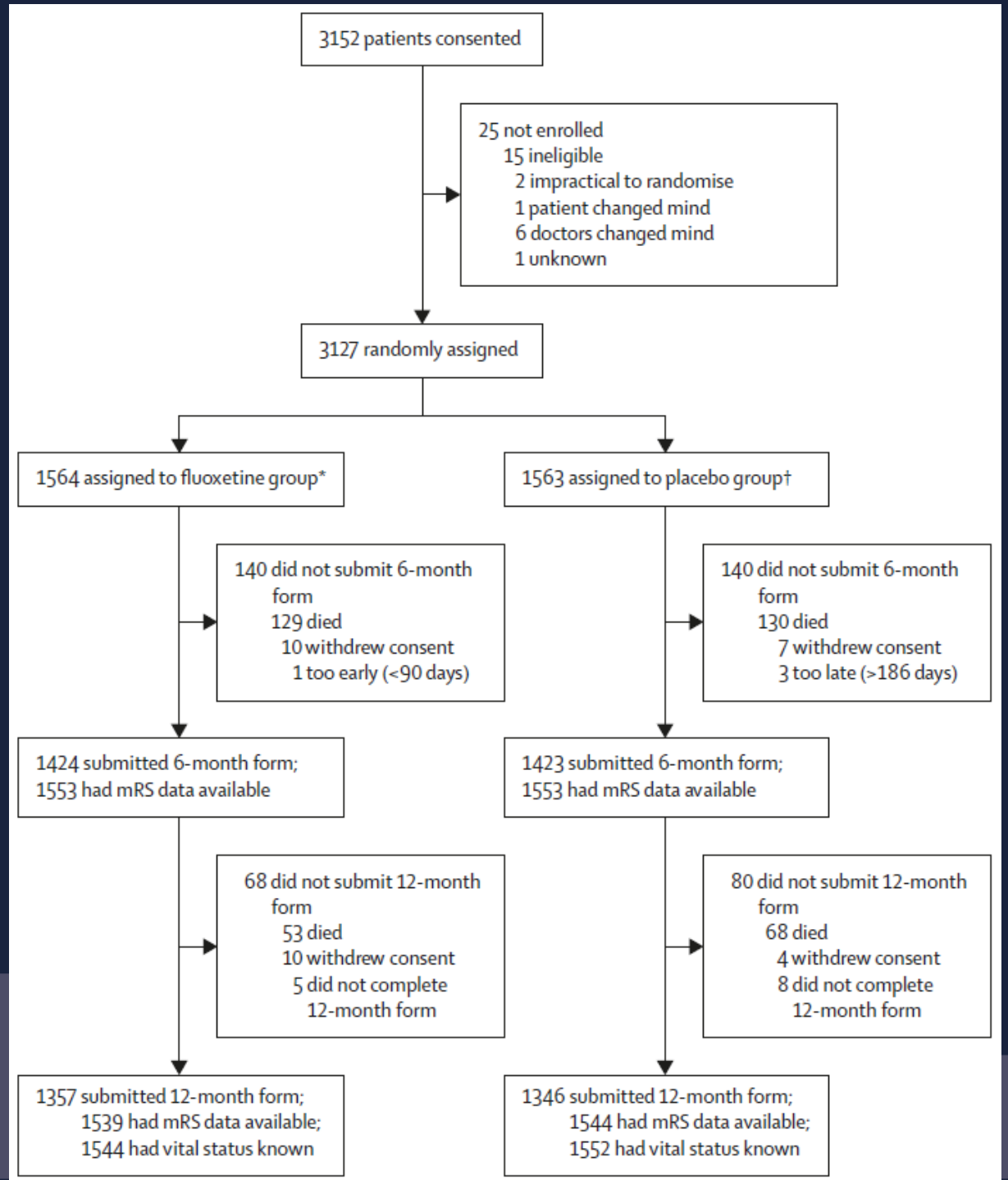
	Randomised treatment			
	Fluoxetine		Placebo	
Characteristics of patients randomised	n	%	n	%
All patients	1564	100.0	1563	100.00
Current diagnosis of depression	26	1.7	18	1.2
Taking a non SSRI antidepressant	65	4.1	77	4.9
Current mood [PHQ] 2				
2 yes responses	81	5.1	60	3.8
1 yes response	136	8.7	130	8.3
0 yes responses	1347	86.1	1373	87.8

Baseline characteristics (timing & consent)

	Randomised treatment			
	Fluoxetine		Placebo	
Characteristics of patients randomised	n	%	n	%
All patients	1564	100.0	1563	100.0
Delay (days) since stroke onset at randomisation				
Delay - Mean (SD)	6.9	3.6	7.0	3.6
2-8 days	1070	68.4	1072	68.6
9-15 days	494	31.6	491	31.4
Enrolled as a hospital inpatient	1544	98.7	1536	98.3
Patient consented	1136	72.6	1118	71.5
Proxy consented	428	27.4	445	28.5

Comparison with SSNAP and SSCA data

	FOCUS	SSNAP	SSCA
	3127	74,307	9345
Characteristics of patients randomised	%	%	%
Female	39	50	49
Male	62	50	51
Mean age (years) (SD)	71	77	73
Lives Alone	32		38
Independent before stroke	92	81	82
Prior Ischaemic stroke/TIA	18	27	
Known Diabetes	20	19	
Ischaemic stroke	90	88	87
Intracerebral haemorrhage	10	11	13
Able to walk at enrolment	27		48
Able to lift both arms off bed	59		63
Able to talk and not confused	75		66
NIHSS Median (IQR)	6 (3-11)	4 (2-10)	
Enrolled as a hospital inpatient	98		100



FOCUS TRIAL
Fluoxetine Or Control Under Supervision

Consort Diagram

defines ones intention to treat population

Adherence – duration taking IMP (days) by allocation

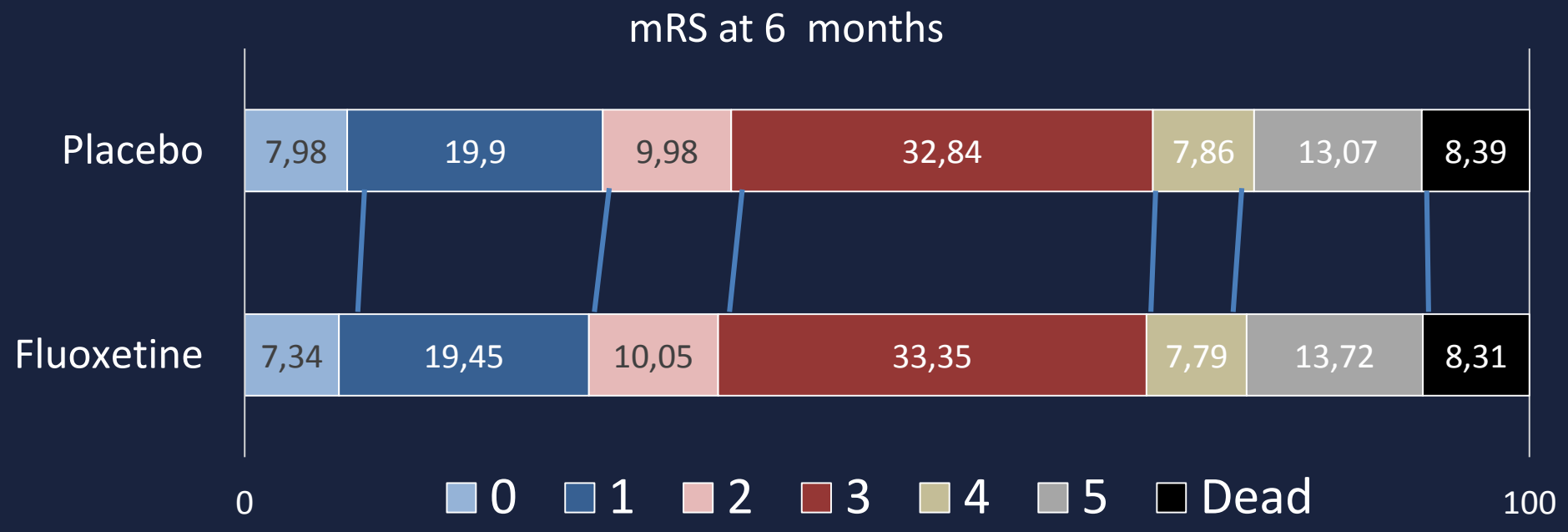
Fluoxetine		Placebo	
Mean	SD	Mean	SD
150.7	59.2	149.0	59.7
Median	IQR	Median	IQR
185	149-186	183.0	136-186

Conduct

- 3127 patients recruited from 103 UK hospitals
  - Sept 2012 to March 2017
- Excellent balance in baseline characteristics between groups
- About 2/3 adhered fully to 6 months treatment
- Emergency unblinding performed in only 3 patients
- Primary outcome available in 99.3% at 6 months
- All analyses based on intention to treat

Result - Primary outcome

Result - Primary outcome



Common Odds Ratio = 0.951 (95% CI 0.839- 1.079; p=0.439)

Safety outcomes at 6 months

	Fluoxetine		Placebo		P value
Outcome event	n	%	n	%	
Epileptic seizures	58	3.7	40	2.6	0.0651
Fall with injury	120	7.7	94	6.0	0.0663
Fractured bone	**45**	**2.9**	**23**	**1.5**	**0.0070**
Hyponatraemia < 125mmol/l	22	1.4	14	0.9	0.1805
Hyperglycaemia	23	1.5	16	1.0	0.2602
Symptomatic hypoglycaemia	23	1.5	13	0.8	0.0940
New depression	**210**	**13.0**	**269**	**16.9**	**0.0033**
New antidepressant	**280**	**17.9**	**357**	**22.8**	**0.0006**
Attempted/actual suicide	3	0.2	2	0.1	0.6550

Safety outcomes at 6 months

	Fluoxetine		Placebo		P value
Outcome event	n	%	n	%	
Any stroke	56	3.6	64	4.1	0·454
Ischaemic stroke	43	2·8	45	2·9	0·826
Acute coronary events	15	1.0	23	1.47	0.191
Other thrombotic events	20	1.3	27	1.7	0.303
All thrombotic events	**78**	**5.0**	**92**	**5·9**	**0·268**
Haemorrhagic stroke	7	0·5	9	0·6	0·615
Upper gastrointestinal bleed	21	1.3	16	1.0	0.409
Other major bleeds	13	0.8	14	0.9	0.845
All bleeding events	***41***	***2·6***	***38***	***2·4***	***0·735***

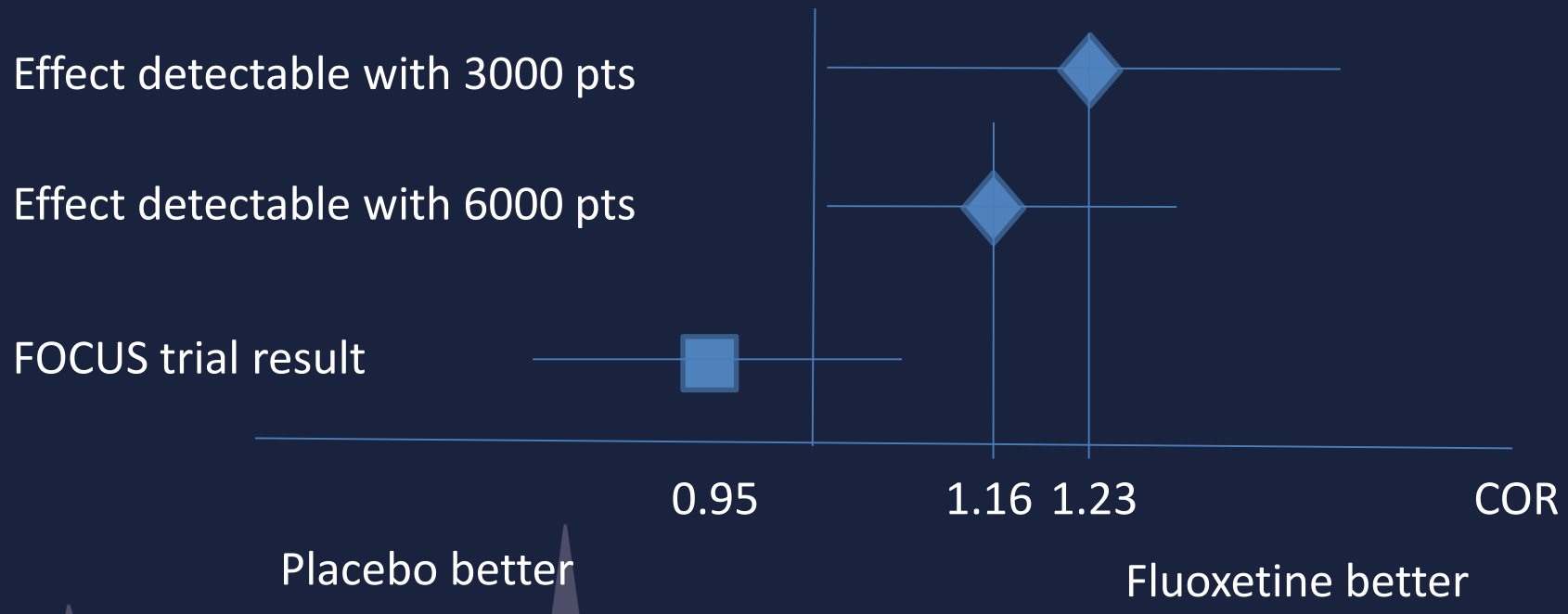
Primary outcome and safety

- Fluoxetine did not improve the functional recovery (mRS) of stroke patients
- It reduced the risk of depression at 6 months
- However, increased risk of bone fractures

Possible explanations for absence of observed effect on primary outcome

- Inadequate power?
- Wrong type of patients?
- Poor adherence?
- Outcomes insensitive to effect?
- Different background setting (e.g. more or less rehab)?
- Functional impact of fractures offset benefits?

Have we missed an effect because insufficient power?



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Primary outcome at Six months in pre-specified subgroups defined at baseline assessment

Subgroup	COR	95% CI		P for interaction
Prob of mRS 0-2 <=0.15	1.026	0.836	1.258	0.326
Prob of mRS 0-2 >0.15	0.905	0.771	1.063	
Delay 2-8 days	0.957	0.822	1.114	0.951
Delay 9-15 days	0.940	0.750	1.178	
No Motor deficit	1.207	0.847	1.721	0.153
Motor deficit	0.919	0.803	1.052	
No aphasia	0.894	0.770	1.038	0.123
Aphasia	1.107	0.874	1.403	
All patients	0.951	0.839	1.079	

Primary outcome at Six months in pre-specified subgroups defined at baseline assessment

Subgroup	COR	95% CI		P for interaction
Ischaemic	0.969	0.848	1.107	0.427
Haemorrhagic	0.816	0.546	1.221	
>= 70 years	0.947	0.780	1.151	0.944
< 70 years	0.952	0.806	1.124	
No depression	0.952	0.836	1.084	0.805
Depression	1.026	0.586	1.798	
Able to assess mood	0.891	0.770	1.031	0.089
Unable to assess mood	1.125	0.871	1.452	
Consent by proxy	0.944	0.741	1.204	0.899
Consent by patient	0.940	0.810	1.090	
All patients	0.951	0.839	1.079	

Secondary outcome at Six months in pre-specified subgroups

	Fluoxetine		Placebo		P value
	Median	IQR	Median	IQR	
Patients with motor deficit at baseline	N=1220		N=1218		
SIS Motor score	48.43	24.98-78.84	52.66	25.28-77.22	0.4714
	N=1220		N=1219		
SIS Physical activity	50.45	26.89-79.70	53.96	27.67-78.68	0.5134
Patients with aphasia at baseline	N=407		N=387		
SIS Communication	64.29	32.14-89.29	64.29	35.71-89.29	0.4971

FLAME trial included only patients with motor deficits and its primary outcome was the Fugl Meier Motor Score

Possible explanations for absence of observed effect on primary outcome

- Inadequate power?
- Wrong type of patients?
- Poor adherence?
- Outcomes insensitive to effect?
- Different background setting (e.g. more or less rehab)?
- Functional impact of fractures offset benefits?

Primary outcome at 6 months in adherence subgroups NOT intention to treat but Per Protocol

Groups cumulatively excluded	No. meeting each exclusion criteria	Cumulative no. removed from analysis	No. remaining in Fluoxetine group	No. remaining in Placebo group	COR for mRs	95% CI	P value	Likely bias
None – as per Intention to treat analysis	0	0	1553	1553	0.951	0.839-1.079	0.439	+/-
Ineligible – did not meet all inclusion criteria	11	11	1548	1547	0.949	0.837-1.077	0.418	+/-
Received no IMP after randomisation	17	26	1540	1540	0.948	0.835-1.076	0.406	+/-
Received < 90 days of IMP due to failure to follow trial procedures	128	152	1480	1474	0.958	0.842-1.090	0.514	+/-
Received < 90days of IMP due to patient/carer/doctor choice	208	342	1405	1359	0.912	0.797-1.042	0.175	+
Received < 90 days of IMP due to suspected adverse reaction	265	607	1262	1237	0.936	0.813-1.078	0.360	++
Allocated placebo but received SSRI for > 10 days within 90 days	84	628	1262	1216	0.923	0.801-1.064	0.268	++
Allocated fluoxetine and received SSRI for > 10 days within 90 days	52	651	1239	1216	0.927	0.804-1.068	0.294	++
Received < 150 days of IMP unless died earlier still taking IMP	847	892	1122	1092	0.888	0.765-1.032	0.121	++
Received < 150 days of IMP for any reason including death	975	1016	1051	1039	0.921	0.788-1.075	0.296	++

Possible explanations for absence of observed effect on primary outcome

- Inadequate power?
- Wrong type of patients?
- Poor adherence?
- Outcomes insensitive to effect?
- Different background setting (e.g. more or less rehab)?
- Functional impact of fractures offset benefits?

Secondary outcomes at Six months (Stroke Impact Scale)

	Fluoxetine		Placebo		P value
SIS domain	Median	IQR	Median	IQR	
Strength in arms and legs	56.3	31.3-81.3	62.5	37.5-81.3	0.701
Hand ability	45.0	0.0-90.0	50.0	0.0-90.0	0.482
Mobility	63.9	36.1-86.1	63.9	33.3-88.9	0.549
Daily Activities	62.5	37.5-90.0	65.0	35.0-90.0	0.624
Memory	82.1	57.1-96.4	82.1	57.1-96.4	0.307
Communication	89.3	67.9-10	92.9	71.4-100.0	0.192
Emotion	75.0	58.3-88.9	75.0	58.3-88.9	0.469
Participation	62.5	37.5-87.5	65.6	40.6-87.5	0.260
Recovery (VAS)	60.0	40.0-80.0	60.0	40.0-80.0	0.982

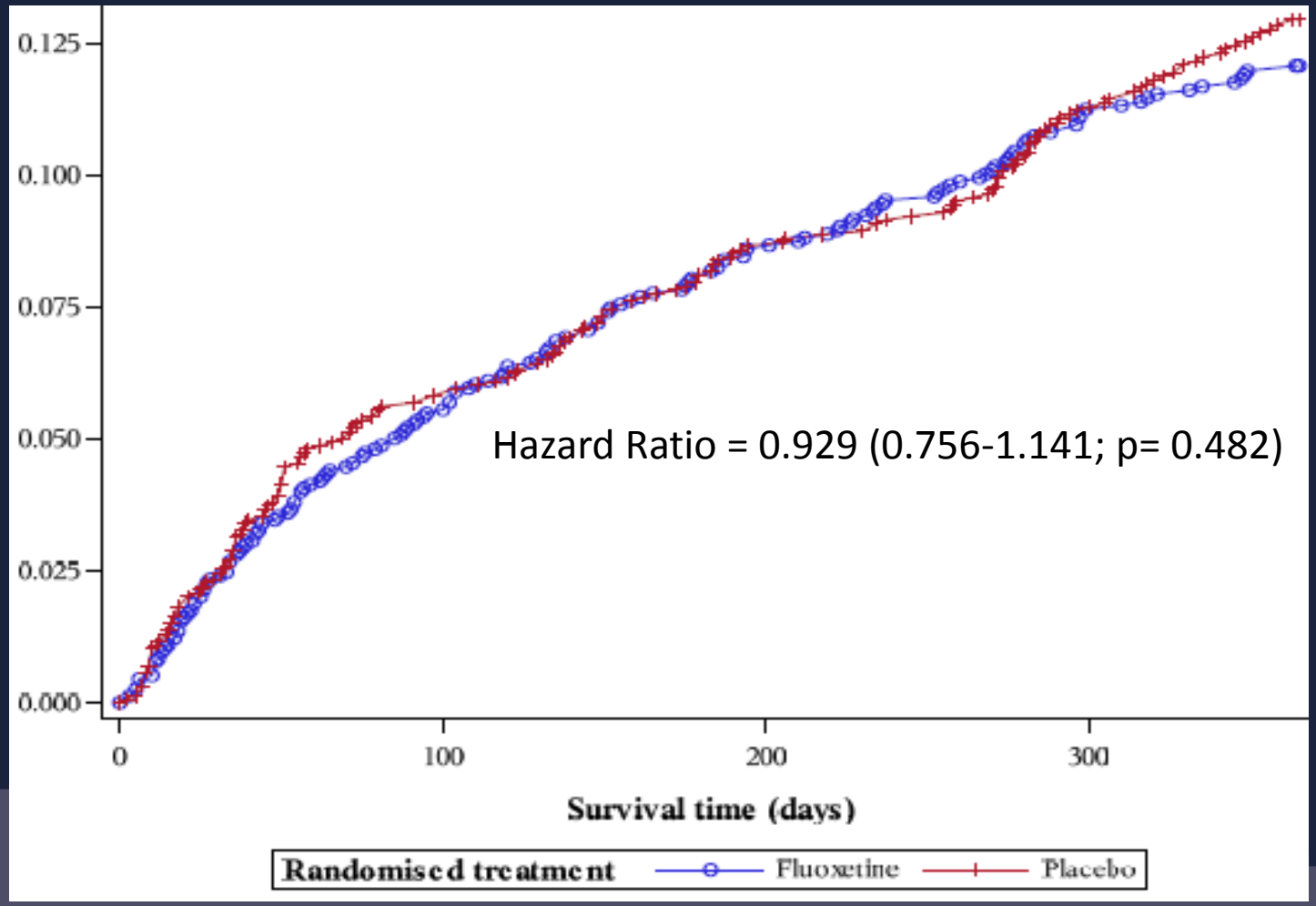
Higher scores reflect better outcomes

Secondary outcomes at 6/12 (Fatigue, Mood and HRQOL)

	Fluoxetine		Placebo		P value
	Median	IQR	Median	IQR	
Fatigue (SF36 Vitality)	56.3	37.5-75.0	56.3	43.8-75.0	0.673
Mood (MHI-5)	**76.0**	**60.0-88.0**	**72.0**	**56.0-88.0**	**0.010**
HRQOL (EQ5D-5L)	0.6	0.2-0.7	0.6	0.2-0.8	0.587

Higher scores reflect better outcomes

Survival to 12 months



Possible explanations for absence of observed effect on primary outcome

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- Outcomes insensitive to effect?
- Different background setting (e.g. more or less rehab)?
- Functional impact of fractures offset benefits?

Possible explanations for absence of observed effect

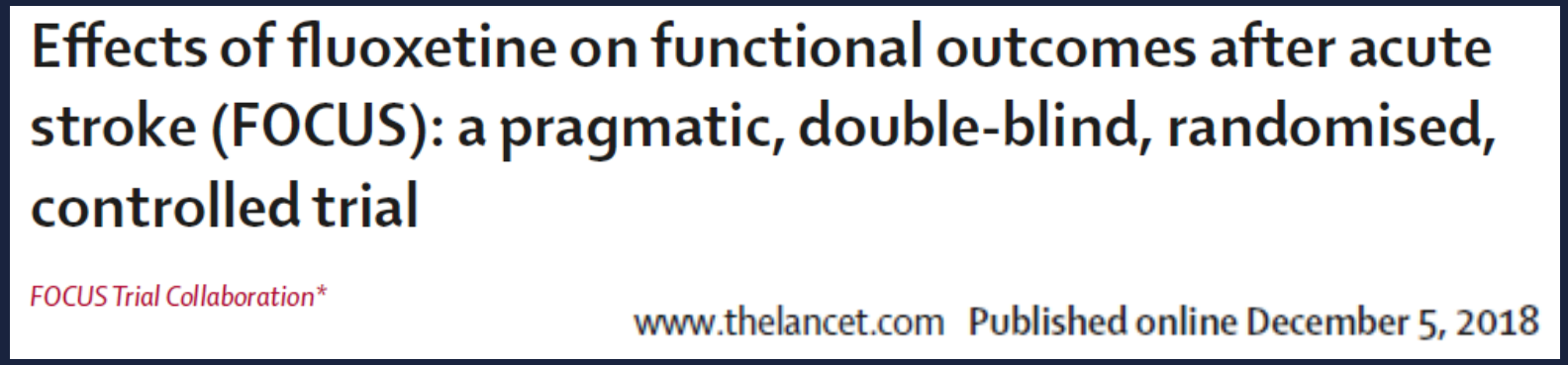
- FOCUS trial results reflect effect in UK NHS
  - Well organised stroke unit care
  - Not very intensive rehabilitation
  - Predominantly (95%) White population
- AFFINITY in Australasia, New Zealand & Vietnam
  - Over 50% Asian population
- EFFECTS in Sweden
  - Milder strokes, better adherence, more intensive rehab

Primary outcome and safety

- Fluoxetine did not improve the functional recovery (mRS), fatigue, SIS or HRQOL of stroke patients
- It reduced the risk of developing depression at 6 months and was associated with improved mood at 6, but not 12 months
- Its use was associated with a significant increased risk of bone fractures

Dissemination

- On 5th Dec 2018
- UKSF presentation on 5th Dec 18



Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial

*FOCUS Trial Collaboration**

www.thelancet.com Published online December 5, 2018

- Trial participants received a newsletter including these results and their allocated treatment

Future

- AFFINITY (Australia, New Zealand and Vietnam) and EFFECTS (Sweden) are ongoing
- They will determine effects in different healthcare systems and different ethnic groups
- Individual patient data meta-analysis will provide more precise estimates of risks and benefits

Depression at 6 and 12 months

	Fluoxetine		Placebo		P value
Outcome event	n	%	n	%	
New depression within 6/12	210	13.0	269	16.9	0.0033
New antidepressant within 6/12	280	17.9	357	22.8	0.0006

	Fluoxetine		Placebo		P value
	n	%	n	%	
New depression within 12/12	292	18.7	327	20.9	0·114
New antidepressant within 12/12	358	22.9	410	26.2	0.030

Randomisation – actually minimisation with a touch of chance

Minimised on 4 factors which are likely to be important determinants of prognosis:

1. Delay – patients improve fastest in first few days
2. Prediction of good outcome on Six Simple Variable model
   - Age
   - Pre stroke independence
   - Living alone
   - Lift arms
   - Walk
   - Talk and not confused
3. Motor deficit
4. Aphasia deficit

Allocated to minimise difference between groups
Not 100% but only 80% of time

Methods of follow up

Method of follow up	Fluoxetine		Placebo	
	n	%	n	%
Completed 6 month postal questionnaire	693	48·6	700	49·1
Required prompting or clarification by phone	312	21·9	276	19·4
Completed 6 month questionnaire by phone	420	29·5	450	31·6
Total completing 6 month questionnaire	1425	100	1426	100
Completed 12 month postal questionnaire	745	54·9	743	55·2
Required prompting or clarification by phone	195	14·4	179	13·4
Completed 12 m questionnaire by phone	417	30·7	424	31·5
Total completing 12 month questionnaire	1357	100	1346	100