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| Title | Twelve-Month Outcomes of the AFFINITY Trial of Fluoxetine for Functional Recovery After Acute Stroke: AFFINITY Trial Steering Committee on Behalf of the AFFINITY Trial Collaboration |
| Type | Article |
| URL | https://clok.uclan.ac.uk/38051/ |
| DOI | ##doi## |
| Date | 2021 |
| Citation | Hankey, Graeme J., Hackett, Maree orcid iconORCID: 0000-0003-1211-9087, Almeida, Osvaldo P., Flicker, Leon, Mead, Gillian E., Dennis, Martin S., Etherton-Beer, Christopher, Ford, Andrew H., Billot, Laurent et al (2021) Twelve-Month Outcomes of the AFFINITY Trial of Fluoxetine for Functional Recovery After Acute Stroke: AFFINITY Trial Steering Committee on Behalf of the AFFINITY Trial Collaboration. Stroke, 52 (8). ISSN 0039-2499 |
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**MS ID#: STROKE/2020/033070 R2**

# Twelve month outcomes of the AFFINITY trial of fluoxetine for functional recovery after acute stroke.

**AFFINITY Trial Steering Committee on behalf of the AFFINITY trial Collaboration.**

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| Abstract: | 323 words |
| Text: | 2069 words |
| References: | 25 |
| Tables: | 3 |
| Figures: | 1 |
| Total word count: | 5571 words (including title and collaborators listed in the appendix) |

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**Background and Purpose**

The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial reported that oral fluoxetine 20 mg daily for 6 months after acute stroke did not improve functional outcome and increased the risk of falls, bone fractures, and seizures. After trial medication was ceased at 6 months, survivors were followed to 12 months post-randomization. This pre-planned secondary analysis aimed to determine any sustained or delayed effects of fluoxetine at 12 months post-randomization.

**Methods**

AFFINITY was a randomised, parallel-group, double-blind, placebo-controlled trial in adults (n=1280) with a clinical diagnosis of stroke in the previous 2-15 days and persisting neurological deficit who were recruited at 43 hospital stroke units in Australia (n=29), New Zealand (4), and Vietnam (10) between 2013 and 2019. Participants were randomised to oral fluoxetine 20mg once daily (n=642) or matching placebo (n=638) for 6 months and followed until 12 months after randomization. The primary outcome was function, measured by the modified Rankin scale (mRS), at 6 months. Secondary outcomes for these analyses included measures of the mRS, mood, cognition, overall health status, fatigue, health-related quality of life, and safety at 12 months.

**Results**

Adherence to trial medication was for a mean 167 (SD 48) days and similar between randomized groups. At 12 months, the distribution of mRS categories was similar in the fluoxetine and placebo groups (adjusted common odds ratio 0.93, 95% confidence interval 0.76-1.14; p=0.46). Compared to placebo, patients allocated fluoxetine had fewer recurrent ischemic strokes (14 [2.18%] vs 29 [4.55%]; p=0.02), and no longer had significantly more falls (27 [4.21%] vs 15 [2.35%]; p=0.08), bone fractures (23 [3.58%] vs 11 [1.72%]; p=0.05) or seizures (11 [1.71%] vs 8 [1.25%]; p=0.64) at 12 months.

**Conclusions**

Fluoxetine 20mg daily for 6 months after acute stroke had no delayed or sustained effect on functional outcome, falls, bone fractures, or seizures at 12 months post-stroke. The lower rate of recurrent ischemic stroke in the fluoxetine group is most likely a chance finding.

**Key words**

stroke, functional outcome, modified Rankin scale, fluoxetine, placebo, clinical trial

**Clinical Trial Registration Information**

Australian New Zealand Clinical Trial Registry http://www.anzctr.org.au;

number: ACTRN12611000774921

**Non-standard Abbreviations and Acronyms**

AFFINITY trial: Assessment oF FluoxetINe In sTroke recoverY trial

FLAME trial: FLuoxetine for motor recovery After acute ischeMic strokE trial

RCT: randomized controlled trial

SSRI: selective serotonin re-uptake inhibitor

mRS: modified Rankin scale

BDNF: brain-derived neurotrophic factor

GABA: gamma aminobutyric acid

IMP: investigational medicinal product

SIS: Stroke Impact Scale version 3

HRQOL: Health-related quality of life

PHQ-9: Patient Health Questionnaire 9

TICSm: Telephone Interview for Cognitive Status

## Introduction

Stroke is a leading cause of lost disability-adjusted life years globally.[1] Fluoxetine, a selective serotonin re-uptake inhibitor (SSRI), was reported in 2011 to enhance upper and lower limb motor recovery, as measured with the Fugl-Meyer Motor Assessment Scale, after acute ischemic stroke in the FLuoxetine for motor recovery After acute ischeMic strokE (FLAME) trial.[2] Proposed mechanisms included increased expression of brain-derived neurotrophic factor (BDNF), reduced extracellular concentrations of gamma aminobutyric acid (GABA), and augmented activity-dependent plasticity in the brain.[3]

A subsequent Cochrane systematic review of 52 randomised controlled trials (RCTs) of SSRIs for stroke recovery in 4059 patients concluded that SSRIs may improve disability but, given methodological limitations and heterogeneity of the studies, more definitive trials were required.[4]

The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) recently reported that among 1280 patients with acute (2-15 days) stroke, oral fluoxetine, 20 mg daily for 6 months after acute stroke, did not improve functional outcome at 6 months compared to placebo, and increased the risk of falls, bone fractures, and epileptic seizures.[5] The results were consistent with those of two other large trials undertaken concurrently with similar designs.[6,7]

As stated in the trial protocol and statistical analysis plan,[8,9] the AFFINITY trial continued to follow surviving participants for a further 6 months after stopping trial medication, to examine whether any effects of fluoxetine during the first 6 months, were sustained or delayed at 12 months after randomization.

## Methods

The anonymised data that support the findings of this trial are available to other researchers from the corresponding author (GJH) following receipt of a written request and proposal for

use of the data, approval by the AFFINITY trial Steering Committee, and establishment of a data sharing agreement.

The design, methods and primary results of the AFFINITY trial have been published.[5,8,9] Briefly, AFFINITY was a randomised, double-blind, placebo-controlled clinical trial conducted in 43 hospital stroke units in Australia (n=29), New Zealand (4), and Vietnam (10). All participating sites received approval from their ethics committee and institutional review board.

Eligible patients were adults (aged ≥18 years) with a clinical diagnosis of acute stroke within the previous 2-15 days, brain imaging consistent with ischemic or hemorrhagic stroke, and a persisting neurological deficit that produced a mRS score ≥1. Patients were excluded if there was a definite indication for fluoxetine, or contraindication to fluoxetine; if patients were unlikely to be available for follow-up during the subsequent 12 months; if patients had another life-threatening illness that would make 12-month survival unlikely; if women were pregnant, breast-feeding or of child-bearing age and not using contraception; or if patients were enrolled in another clinical trial of an investigational medicinal product (IMP) or device.

Written informed consent was obtained from each patient or, if the patients were unable to provide consent, from their legally approved surrogate.

Randomisation was via a secure, password-protected, centralised, web-based system which used a minimisation algorithm[10] and assigned patients to fluoxetine or placebo in a 1:1 ratio. Placebo capsules were visually identical to the fluoxetine capsules even when broken open. Fluoxetine 20mg capsules or matching placebo capsules were administered orally, once daily, for 6 months. All patients received organised, interdisciplinary care and rehabilitation in stroke units.

Patients recruited in Australia and New Zealand were followed-up at 180 days (6 months) and 365 days (12 months) by postal questionnaire or telephone, by trained staff in the trial coordinating center in Perth, Australia. Patients recruited in Vietnam were assessed by the site investigator at 180 days (6 months) and 365 days (12 months) post-randomization in the

hospital ward or outpatient clinic, or via telephone or email; or, failing that, at the patient's residence. If the patient was unable to complete the assessments, assistance was sought from their proxy (next of kin, close family member or carer). At the 12-month assessment, the mRS (table 1), other secondary outcomes including mood, cognition, overall health status (Stroke Impact Scale), fatigue and health-related quality of life (HRQoL, table 2), safety outcomes (table 3), and all current medications, were recorded. If the patient answered "yes" to any secondary outcome or safety outcome, investigators were asked to complete an outcome event form immediately to verify the diagnosis. Patients and outcome assessors remained masked to the allocated trial treatment at the 12-month assessment.

*Outcomes*

The primary outcome of the trial was functional status, as measured by the mRS,[11] at 6 months after randomization, as previously reported.[5]

Secondary outcomes at 12 months (which are the subject of this report), were the mRS,[11] mood (PHQ-9 score[12]), cognition (Telephone Interview for Cognitive Status [TICSm][13]), communication, motor function, overall health status (Stroke Impact Scale [SIS] version 3.0[14]), fatigue (vitality subscale of the SF-36[15,16]), and HRQoL using the EuroQoL EQ-5D-5L.[17]

Safety outcomes during follow-up included death, recurrent stroke (ischemic or hemorrhagic), acute coronary syndromes, upper gastrointestinal bleeding requiring blood transfusion and/or endoscopy, other major bleeding (subdural, extradural, ocular, lower gastrointestinal) requiring blood transfusion or procedural intervention, epileptic seizures, falls with injury, new bone fractures, new hyponatremia (blood sodium < 125mmol/L), symptomatic hypoglycemia (blood glucose < 3mmol/L), new depression (PHQ-9 score > 15[12]), and attempted or actual suicide or self-harm.

*Statistical analysis*

The statistical analysis plan published before recruitment was completed and without awareness of any unblinded data.[9]

The mRS scores at 12 months in each treatment group were analyzed using ordinal logistic regression before and after adjusting for the baseline factors included in the minimization

algorithm.[5,9] A post-hoc analysis also adjusted for all the baseline covariates listed in appendix table 2. The result was expressed as a common odds ratio (OR less than 1.0 favored placebo) and its 95% confidence interval (CI).

The frequencies of the categorical secondary outcome events in each group were compared using Fisher's exact test. For continuous secondary outcomes, the mean or median in each group, depending on the distribution, were calculated with measures of dispersion (standard deviation [SD] or inter-quartile range [IQR]). The probability that outcomes in the fluoxetine group were significantly different from the placebo group were calculated as p-values.

All analyses were by intention-to-treat, according to the treatment allocation, among patients for whom outcome data were available, and undertaken with SAS, version 9.4. A post-hoc per protocol analysis of the mRS at 12 months in each treatment group was also undertaken which excluded participants who didn't start the allocated trial medication, permanently stopped taking the allocated trial medication, or reported taking open label fluoxetine or another SSRI.

The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000774921.

**Results**

A total of 1280 patients consented and were randomised at 43 sites in Australia, New Zealand and Vietnam between January 11, 2013 and June 30, 2019. Recruitment was terminated before the target of 1600 patients was reached because funding expired on December 31, 2019.

642 patients were randomly allocated to fluoxetine and 638 to placebo (fig 1). The baseline characteristics in the two groups were balanced (Supplementary table I).[5]

The mean duration of trial treatment was 167 days (SD 48.1) days. There was no significant difference between groups in adherence to trial medication.[5]

By 12 months, 26 (2.0%) survivors had withdrawn consent for follow-up, 3 (0.2%) were lost to follow-up, and 1 (0.1%) was followed up at 12 months but the mRS was not recorded.

At the end of the trial treatment period at 6 months after randomization, 42 (3.2%) patients reported that they were taking open label fluoxetine or another SSRI (18 had been randomised to fluoxetine, and 24 to placebo). At 12 months after randomization, 64 (5%) patients were taking open label fluoxetine or another SSRI (32 had been randomised to fluoxetine, and 32 placebo); 29 of these patients had continued to take open label SSRI since the 6 month follow-up (14 randomized to fluoxetine, and 15 placebo), and 35 of these patients had started taking open label SSRI after ceasing study drug at 6 months (18 randomised to fluoxetine, and 17 placebo).

The mRS at 12 months was assessed and analysed in 620 (96.6%) patients allocated fluoxetine and 630 (98.7%) placebo. The distribution of ordinal data from the mRS at 12 months, adjusted for variables in the minimization algorithm, was similar in both groups (common OR 0.93, 95% CI 0.76-1.14; p=0.46; table 1). The unadjusted analysis produced similar results (common OR 0.93, 95%CI 0.76-1.14; p=0.50; table 1). A post-hoc analysis that adjusted for all the baseline covariates listed in appendix table 2, also revealed no significant effect of fluoxetine vs placebo on the mRS at 12 months. A post-hoc per protocol analysis also produced similar results (adjusted OR: 0.88, 95% CI: 0.70-1.10, p=0.25; common OR: 0.87, 95%CI: 0.70-1.09, p=0.24; supplementary table II).

There was no significant difference between treatment groups in any of the other secondary efficacy outcomes at 12 months (table 2).

Table 3 shows that there was also no significant difference between treatment groups in any of the safety outcomes at 12 months, with the exception of a lower incidence of ischemic stroke at 12 months among patients allocated 6 months treatment with fluoxetine compared to placebo (14 [2.18%] vs 29 [4.55%]; p=0.02). At 12 months there was no longer a significant difference in falls (27 [4.21%] vs 15 [2.35%]; p=0.08), bone fractures (23 [3.58%] vs 11 [1.72%]; p=0.054) and epileptic seizures (11 [1.71%] vs 8 [1.25%]; p=0.64) which had been observed at 6 months.[5]

**Discussion**

In this ethnically diverse clinical trial population, fluoxetine 20mg daily for 6 months after acute stroke had no effect on functional outcome at 6 or 12 months. Although exposure to trial fluoxetine for 6 months was associated with increased rates of falls, bone fractures, and

seizures, this difference was no longer statistically significant at 12 months. The only difference between the fluoxetine and placebo groups at this longer time point was a reduction in recurrent ischemic stroke in patients allocated fluoxetine compared to placebo.

These results indicate that routine treatment with fluoxetine for 6 months after acute stroke increased the risk of seizures, falls, and fractures but had no effect on functional outcome at 6 months. After fluoxetine was ceased, the lack of effect on functional outcome persisted and the excess risk of falls, seizures and fractures attenuated.

The mechanisms by which fluoxetine temporarily increased the risk of falls, seizures and fractures within the first 6 months are uncertain but may include orthostatic hypotension[18], increased lower limb spasticity perhaps[19], somnolence[20], sleep disorders[20], heart rhythm disorders[20]; and lowering bone mineral density.[21-23]

It is unclear why the functional outcome of participants was not affected by the increased risk of seizures, falls and fractures at 6 months in the fluoxetine group. One possibility is that the excess proportion of patients who experienced these adverse effects of fluoxetine was too small to impact the overall distribution of the mRS. Another possibility is that participants who experienced adverse effects of fluoxetine had recovered by the time they were assessed by the mRS. A further possibility is that the mRS is insensitive to mild changes in functional capacity of stroke survivors.

Our finding of a lower rate of ischemic stroke at 12 months among patients allocated fluoxetine compared to placebo is probably a chance finding due to random error associated with analyses of numerous secondary outcome measures. Although the result is consistent with a lower 3-year rate of recurrent ischemic stroke reported in another randomized trial of fluoxetine versus placebo, given for 3 months after acute ischemic stroke in a total of 404 patients[24], a lower rate of ischemic stroke at 6 months was not observed among larger populations of acute stroke patients allocated fluoxetine in the FOCUS[6] and EFFECTS[7] trials. The FOCUS trial has also reported no difference in functional outcome or secondary efficacy outcomes at 12 months after exposure to fluoxetine daily in the first 6 months after stroke, but rates of safety outcomes and ischemic stroke at 12 months have not been reported.[25] More reliable estimates of any

effects of fluoxetine will be forthcoming in a planned meta-analysis of the individual patient data from the FOCUS, EFFECTS and AFFINITY trials.

**Conclusions**

Fluoxetine 20 mg daily for 6 months after stroke did not improve functional outcome at 6 or 12 months after randomisation but did increase the incidence of bone fractures, falls and seizures during the 6 month period of treatment with fluoxetine, which attenuated over the 6 months after fluoxetine was ceased. The lower rate of recurrent ischemic stroke at 12 months after randomization in the fluoxetine group is most likely a chance finding.

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**Table 1.**

**Modified Rankin Scale (mRS) score at 12 months after randomisation**

**(6 months after cessation of trial medication)**

| Modified Rankin Scale (mRS) | | Fluoxetine (n=642) N (%) | Placebo (n=638) N (%) |
|---|---|---|---|
| 0 | No symptoms | 89 (14.4) | 104 (16.5) |
| 1 | No clinically significant disability despite symptoms | 267 (43.1) | 258 (41.0) |
| 2 | Slightly disability: unable to do everything | 90 (14.5) | 104 (16.5) |
| 3 | Moderately disability: unable to live independently but can walk | 106 (17.1) | 97 (15.4) |
| 4 | Moderately disability and unable to walk without help from another person | 33 (5.3) | 39 (6.2) |
| 5 | Severe disability: unable to sit up | 8 (1.3) | 7 (1.1) |
| 6 | Dead | 27 (4.4) | 21 (3.3) |
| **Total** | | **620** | **630** |

Ordinal proportional odds model:

Common odds ratio: 0.93, 95%CI: 0.76-1.14, p=0.50

Adjusted odds ratio: 0.93, 95% CI: 0.76-1.14, p=0.46

Covariates adjusted for:

- Delay between and stroke and randomisation (days)
- Probability of being alive and independent at 6 months
- Motor deficit
- Aphasia

**Table 2.**

**Secondary outcomes at 12 months after randomization by allocated treatment group**

| | Fluoxetine (n=642) | | | Placebo (n=638) | | | |
|---|---|---|---|---|---|---|---|
| | **N*** | **Median** | **IQR** | **N*** | **Median** | **IQR** | **P value**** |
| **Mood** (PHQ-9) | 525 | 2.0 | (0.0-4.0) | 516 | 2.0 | (0.0-4.0) | 0.64 |
| **Cognition** (TICSm) | 514 | 24.0 | (20.0-28.0) | 521 | 24.0 | (20.0-28.0) | 0.22 |
| **Stroke Impact Scale (SIS) domains** | | | | | | | |
| Strength | 554 | 75.0 | (62.5-100.0) | 574 | 75.0 | (62.5-100.0) | 0.33 |
| Memory/Thinking | 554 | 92.9 | (78.6-100.0) | 574 | 92.9 | (75.0-100.0) | 0.68 |
| Emotions | 554 | 83.3 | (69.4-91.7) | 574 | 80.6 | (66.7-88.9) | 0.053 |
| Communication | 553 | 100.0 | (92.9-100.0) | 574 | 100.0 | (89.3-100.0) | 0.26 |
| Daily Activities | 554 | 92.5 | (72.5-100.0) | 574 | 90.0 | (72.5-100.0) | 0.67 |
| Mobility | 553 | 91.7 | (69.4-100.0) | 574 | 88.9 | (69.4-100.0) | 0.24 |
| Hand ability | 553 | 90.0 | (60.0-100.0) | 574 | 90.0 | (65.0-100.0) | 0.43 |
| Participation | 553 | 84.4 | (62.5-100.0) | 574 | 84.4 | (62.5-100.0) | 0.92 |
| Recovery (VAS) | 533 | 80.0 | (70.0-90.0) | 557 | 80.0 | (70.0-90.0) | 0.65 |
| Motor† | 554 | 85.9 | (65.7-97.4) | 574 | 84.4 | (65.7-95.8) | 0.31 |
| Physical function‡ | 554 | 87.5 | (67.6-97.4) | 574 | 86.0 | (66.8-96.3) | 0.35 |
| **Vitality (SF-36)** | 540 | 75.0 | (60.0-85.0) | 557 | 70.0 | (60.0-80.0) | 0.48 |
| **EQ-5D-5L** | 545 | 0.85 | (0.66-1.0) | 562 | 0.84 | (0.63-1.0) | 0.39 |

* The number of patients with each of the secondary outcome scores. Data were only available for those who survived and who completed sufficient questions to derive a score.

**Mann-Whitney test

PHQ-9: Patient Health Questionnaire 9 items (higher score indicates more depressive symptoms)

TICSm: Telephone Interview for Cognitive Status (higher scores are better)

SIS: Stroke Impact Scale (where higher scores are better).

†Mean of the Strength, Hand ability, and Mobility domains.

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

VAS: visual analogue scale.

SF-36: 36 item short form questionnaire (higher scores indicate less fatigue, more energy)

EQ-5D-5L: EuroQoL - 5 Dimensions (Mobility, Personal Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) - 5 Levels (where 1 indicates the best health imaginable, and 0 indicates the worst health imaginable).

**Table 3. Safety outcomes at 12 months after randomization by allocated treatment.**

| | Fluoxetine (n=642) | | Placebo (n=638) | | | | |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | Difference % | 95% CI (%) | P-value (Fisher exact) |
| Death | 27 | 4.21 | 21 | 3.29 | 0.91 | -1.17 to 2.99 | 0.46 |
| Any stroke | 25 | 3.89 | 36 | 5.64 | -1.75 | -4.08 to 0.58 | 0.15 |
| All thrombotic events | | | | | | | |
| Ischemic stroke | 14 | 2.18 | 29 | 4.55 | -2.36 | -4.34 to -0.39 | 0.02 |
| Acute coronary events | 3 | 0.47 | 3 | 0.47 | -0.00 | -0.75 to 0.75 | 1.00 |
| All bleeding events | | | | | | | |
| Hemorrhagic stroke | 6 | 0.93 | 2 | 0.31 | 0.62 | -0.24 to 1.48 | 0.29 |
| Upper GI bleed | 2 | 0.31 | 2 | 0.31 | -0.00 | -0.61 to 0.61 | 1.00 |
| Epileptic seizures | 11 | 1.71 | 8 | 1.25 | 0.46 | -0.86 to 1.78 | 0.65 |
| Fall with injury | 27 | 4.21 | 15 | 2.35 | 1.85 | -0.09 to 3.80 | 0.08 |
| New bone fracture | 23 | 3.58 | 11 | 1.72 | 1.86 | 0.10 to 3.62 | 0.054 |
| Hyponatremia < 125mmol/L | 4 | 0.62 | 2 | 0.31 | 0.31 | -0.44 to 1.06 | 0.69 |
| Symptomatic hypoglycemia | 1 | 0.16 | 0 | 0 | 0.16 | -0.15 to 0.46 | 1.00 |
| New depression | 51 | 7.94 | 57 | 8.93 | -0.99 | -4.04 to 2.06 | 0.55 |
| New antidepressant | 51 | 7.94 | 55 | 8.62 | -0.68 | -3.70 to 2.34 | 0.69 |
| Attempted or actual suicide | 0 | 0 | 2 | 0.31 | -0.31 | -0.75 to 0.12 | 0.25 |
| Other safety outcome | 92 | 14.3 | 98 | 15.36 | -1.03 | -4.93 to 2.87 | 0.64 |

GI: gastrointestinal

Footnote:

Only adjudicated events were counted and each event was counted once for each patient.

New depression and new antidepressant were accumulated from all follow-up forms (28, 90, 180 and 365 days).

**Acknowledgements**

We are grateful to all patients and their families who participated in AFFINITY, and the nursing staff who assisted at collaborating sites.

**Sources of Funding and Support**

The AFFINITY trial was funded by the Australian National Health and Medical Research Council (NHMRC) Project Grant 1059094. The minimization algorithm was provided by The Stroke Research Group, Division of Clinical Neuroscience, The University of Edinburgh. The manufacture, storage and distribution of the trial medication was undertaken by Pharmaceutical Packaging Professionals Pty Ltd (Trading as PCI Pharma Services), an Australian Therapeutic Goods Administration-licensed Good Manufacturing Practices facility.

**Disclosures**

Prof. Hankey reports grants from the National Health & Medical Research Council (NHMRC) of Australia, Vetenskapsrådet (The Swedish Research Council), and United Kingdom National Institute for Health Research Technology (NIHR), during the conduct of the study; and personal fees from American Heart Association for serving as an Associate Editor of *Circulation*, outside the submitted work.

Profs. Hackett, Mead, and Dennis report grants from National Health and Medical Research Council of Australia, Vetenskapsrådet (The Swedish Research Council), and United Kingdom National Institute for Health Research Technology (NIHR), during the conduct of the study.

Prof. Etherton-Beer, Prof. Billot, and Dr. Lung reports grants from the National Health and Medical Research Council of Australia during the conduct of the study.

Prof. Anderson reports grants from National Health and Medical Research Council of Australia, grants from Takeda, and personal fees from Takeda, outside the submitted work.

Profs Almeida, Flicker, Ford, Billot, Jan, Lundström, Sunnerhagen, Thang-Nguyen, Gommans, and Yi report no conflicts.

**Supplemental Materials**

Online Supplementary Tables I, II

# APPENDIX

## The AFFINITY trial Collaborators:

| First/Middle Name | Surname |
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| Maree L. | Hackett |
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| Leon | Flicker |
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| Andrew H. | Ford |
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| Stephen | Jan |
| Thomas | Lung |
| Veronica | Murray |
| Erik | Lundström |
| Craig S. | Anderson |
| Robert | Herbert |
| Gregory | Carter |
| Geoffrey A. | Donnan |
| Huy-Thang | Nguyen |
| John | Gommans |
| Qilong | Yi |
| Qiang | Li |
| Severine | Bompoint |
| Sarah | Barrett |
| Anne | Claxton |
| Julia | O'Dea |
| Michelle | Tang |
| Clare | Williams |
| Shenae | Peterson |
| Christie | Drummond |
| Uyen-Ha | Hong |
| Linh-Thi My | Le |
| Tram-Thi Bich | Ngo |
| Yen-Bao | Mai |
| Huyen-Thanh | Han |
| Nhu-Quynh | Truong |
| Huong-Thi | Nguyen |
| Hai-Thanh | Ngo |
| -Thi Binh | Nguyen |
| Oanh-Thi Kieu | Ha |
| Trang-Le Huyen | Nguyen |
| Richard I. | Lindley |
| Peter | New |
| Andrew | Lee |
| Thanh-Trung | Tran |

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|---|---|
| Loan-Tran Truc Mai | Le |
| Thuy-Le Vu | Kieu |
| Sang-Van | Nguyen |
| Thuy-Anh Diem | Nguyen |
| Tam-Nhat | Dang |
| Hanh-Thi Truc | Phan |
| Loan-Thi Ngoc | Vo |
| Mai-Hue | Nguyen |
| Hanh-Cao | Dang |
| Hong-Thi | Tran |
| Linh-Thi Cam | Dam |
| Trinh-Thi Kim | Ngo |
| Thai-Nguyen Thanh | Pham |
| Binh-Nguyen | Pham |
| Nha-Thi Thanh | Dao |
| Huong-Thi Bich | Nguyen |
| Linh-Thi Cam | Le |
| Chi-Minh | Do |
| Huy-Quoc | Huynh |
| Giau-Thi Kim | Tran |
| Oanh-Thi | Le |
| Ly-Thi Khanh | Tran |
| Chinh-Dinh | Duong |
| Duong-Van | Kieu |
| Na | Le |
| Hoa-Ngoc | Nguyen |
| Binh-Van | Le |
| Long-Thanh | Nguyen |
| Long-Van | Nguyen |
| Tuan-Quoc | Dinh |
| Tan-Van | Vo |
| Tram-Ngoc | Bui |
| Uyen-Thi To | Hoang |
| Hien-Thi Bich | Nguyen |
| Ha-Thi Thu | Nguyen |
| Nga-Thuy | Lam |
| Khanh-Kim | Le |
| Phuong-Thanh | Trinh |
| Hop-Quang | Huynh |
| Thao-Thi Thu | Nguyen |
| Huyen-Ngoc | Lu |
| Tham-Hong | Pham |
| Sam-Hoanh | Nguyen |
| Ninh-Hong | Le |
| Giang-Truong | Nguyen |
| Bich-Thi | Doan |
| Sung-Phuoc | Pham |
| Duong-Huu | Luong |
| Ha-Van | Mai |

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| Thuc-Van | Tran |
| Phuong-Thi | Do |
| Hoai-Thi | Le |
| Chi-Van | Nguyen |
| Phuong-Doan | Nguyen |
| Ton-Duy | Mai |
| Phuong-Viet | Dao |
| Dung-Tien | Nguyen |
| Dai-Quoc | Khuong |
| Trung-Xuan | Vuong |
| Lan-Tuong | Vu |
| Ngoc-Duc | Ngo |
| Hanh-Hong | Dang |
| Phuong-Thai | Truong |
| Ngan-Thi | Le |
| Hoa-Van | Hoang |
| Chung-Quang | Do |
| Minh-Thao | Nguyen |
| Anh-Hai | Dam |
| Quynh-Nhu | Le |
| Ngoc-Hoang | Nguyen |
| Tuyen-Van | Nguyen |
| Toan-Dinh | Le |
| Ha-Thi Hai | Dinh |
| Cuong –Van | Pham |
| Khanh-Thi Ngoc | Thach |
| Linh-Hai | Nguyen |
| Loan-Thi | Nguyen |
| Vien-Chi | Le |
| Phuong-Hong | Tran |
| Tai-Anh | Nguyen |
| Tuan-Van | Le |
| Luyen-Van | Truong |
| Tue-Chau | Bui |
| Ngoc-Xuan | Huynh |
| Lap-Van | Dinh |
| An-Gia | Pham |
| Trang-Thi Huyen | Le |
| Vy-Tuong | Nguyen |
| Yen-Hai | Nguyen |
| Thang-Ba | Nguyen |
| Huy | Thai |
| Quyen-Thi Ngoc | Pham |
| Khoa-Duy | Dao |
| Quoc-Nguyen Bao | Pham |
| Thuong-Thi Huyen | Dang |
| Huong-Huynh To | Dinh |
| Trang-Mai | Tong |
| Thuy-Thi | Vu |

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| Si-Tri | Le |
| Tai-Ngoc | Tran |
| Phuong-Hoai | Tran |
| Ngoc-Thuy Nhu | Dinh |
| Binh-Thanh | Nguyen |
| Vinh-Phuong | Do |
| Anh-Ngoc | Nguyen |
| Binh-Thi Thanh | Nguyen |
| Binh-Thanh | Nguyen |
| David | Blacker |
| Lindsey | Bunce |
| Ai Ling | Tan |
| Darshan | Ghia |
| Gillian | Edmonds |
| Nicole | O'Loughlin |
| Megan | Ewing |
| Kerri-Ann | Whittaker |
| Lorralee | Deane |
| Yash | Gawarikar |
| Brett | Jones |
| Maria | Lopez |
| Koushik | Nagesh |
| Emma | Siracusa |
| Stephen | Davis |
| Amy | McDonald |
| Jess | Tsoleridis |
| Rachael | McCoy |
| David | Jackson |
| Gab | Silver |
| Timothy R. | Bates |
| Amanda | Boudville |
| Lynda | Southwell |
| Dennis | Cordato |
| Alan J. | McDougall |
| Cecilia | Cappelen-Smith |
| Zeljka | Calic |
| Shabeel | Askar |
| Qi | Cheng |
| Raymond | Kumar |
| Richard | Geraghty |
| Maree | Duroux |
| Megan | Ratcliffe |
| Samantha | Shone |
| Cassandra | McLennan |
| Ramesh | Sahathevan |
| Casey | Hair |
| Stanley | Levy |
| Beverley | Macdonald |
| Benjamin | Nham |

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|---|---|
| Louise | Rigney |
| Dev | Nathani |
| Sumana | Gopinath |
| Vishal | Patel |
| Abul | Mamun |
| Benjamin | Trewin |
| Chun | Phua |
| Ho | Choong |
| Lauren | Tarrant |
| Kerry | Boyle |
| Luisa | Hewitt |
| Monique | Hourn |
| Amanda | Masterson |
| Kim | Oakley |
| Karen | Ruddell |
| Colette | Sanctuary |
| Kimberley | Veitch |
| Camelia | Burdusel |
| Lina | Lee |
| Gary | Cheuk |
| Jeremy | Christley |
| Tabitha | Hartwell |
| Craig | Davenport |
| Kate | Hickey |
| Rosanna | Robertson |
| Michelle | Carr |
| Sam | Akbari |
| Hannah | Coyle |
| Megan | O'Neill |
| Cameron | Redpath |
| Caroline | Roberts |
| Marjan | Tabesh |
| Toni | Withiel |
| Kapila | Abeysuriya |
| Andrew | Granger |
| Angela | Abraham |
| Chermaine | Chua |
| Dung | Do Nguyen |
| Vathani | Surendran |
| Melissa | Daines |
| David | Shivlal |
| Mudassar | Latif |
| Noreen | Mughal |
| Patricia | Morgan |
| Martin | Krause |
| Miriam | Priglinger |
| Ehsan E. | Shandiz |
| Susan | Day |
| Lay | Kho |

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|---|---|
| Michael | Pollack |
| Judith | Dunne |
| Helen | Baines |
| Merridie | Rees |
| Jenni | White |
| Monique | Hourn |
| Kimberley | Veitch |
| Aicuratiya | Withanage |
| Colette | Sanctuary |
| Candice | Delcourt |
| Cheryl | Carcel |
| Alejandra | Malavera |
| Amy | Kunchok |
| Elizabeth | Ray |
| Elizabeth | Pepper |
| Emily | Duckett |
| Jenni | White |
| Kimberley | Veitch |
| Luisa | Hewitt |
| Monique | Hourn |
| Kerry | Boyle |
| Sally | Ormond |
| Colette | Sanctuary |
| Andrew | Moey |
| Timothy | Kleinig |
| Vanessa | Maxwell |
| Chantal | Baldwin |
| Wilson | Vallat |
| Deborah | Field |
| Romesh | Markus |
| Kirsty | Page |
| Danielle | Wheelwright |
| Sam | Bolitho |
| Steven | Faux |
| Fix | Sangvatanakul |
| Alexis | Brown |
| Susan | Walker |
| Jennifer | Massey |
| Michael | Pollack |
| Jenni | White |
| Kimberley | Veitch |
| Hillary | Hayes |
| Luisa | Hewitt |
| Monique | Hourn |
| Colette | Sanctuary |
| Pesi | Katrak |
| Annie | Winker |
| Alessandro | Zagami |
| Alanah | Bailey |

| | |
|---|---|
| Sarah | Mccormack |
| Andrew | Murray |
| Mark | Rollason |
| Christopher | Taylor |
| Fintan | O'Rourke |
| Ye Min | Kuang |
| Heike | Burnet |
| Yvonne | Liu |
| Qi | Cheng |
| Aileen | Wu |
| Sam | Akbari |
| Hannah | Coyle |
| Megan | O'Neill |
| Diana | Ramirez |
| Tissa | Wijeratne |
| Sherisse | Celestino |
| Essie | Low |
| Cynthia | Chen |
| Jennifer | Bergqvist |
| Andrew | Evans |
| Queenie | Leung |
| Martin | Jude |
| Rachael | McQueen |
| Katherine | Mohr |
| Latitia | Kernaghan |
| Paul | Stockle |
| Boon L. | Tan |
| Sara | Laubscher |
| Diana | Schmid |
| Melissa | Spooner |
| Bhavesh | Lallu |
| Bronwen | Pepperell |
| John | Chalissery |
| Karim | Mahawish |
| Susan | DeCaigney |
| Paula | Broughton |
| Karen | Knight |
| Veronica | Duque |
| Harry | McNaughton |
| Jeremy | Lanford |
| Vivian | Fu |
| Lai-Kin | Wong |

**Figure 1: AFFINITY trial profile** mRS=modified Rankin Scale

*No. of patients who did not submit form (due to death or withdrawal of consent) between days 180 and 365.