Title page

Efficacy and safety of individualized coaching after stroke (the LAST study). A pragmatic randomized controlled trial

Torunn Askim PhD,[1] Birgitta Langhammer PhD,[2,3] Hege Ihle-Hansen MD, PhD,[4] Mari Gunnes MSc,[1] Stian Lydersen PhD,[5] Bent Indredavik MD, PhD[1,6] on behalf of the LAST Collaboration group

1. Department of Neuroscience, Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.
2. Department of Physiotherapy, Oslo and Akershus University College, P.O.Box 4, N-0130 Oslo, Norway.
3. Sunnaas Rehabilitation Hospital, HF, Nesoddtangen, Norway
4. Department of Medicine, Vestre Viken Hospital Trust, Bærum Hospital, P.O.Box 800, N-3004 Drammen, Norway.
5. Regional Centre for Child and Youth Mental Health and Child Welfare, NTNU, P.O.Box 8905, N-7491 Trondheim, Norway.
6. Department of Medicine, Stroke Unit, Trondheim University Hospital, Trondheim, Norway.

Corresponding author: Torunn Askim, NTNU, Faculty of Medicine, P.O. Box 8905, 7491 Trondheim, Norway. E-mail address: torunn.askim@ntnu.no, mobile phone: +47 995 89 235

Cover title: Efficacy of individualized coaching after stroke

Tables 3; Figures 2

Key words: Cerebrovascular disease, Secondary prevention, Rehabilitation, Exercise, Lifestyle, Compliance

Word count: 5000

Abstract

Background and purpose: The evidence for interventions to prevent functional decline in the long term after stroke is lacking. The aim of this trial was to evaluate the efficacy and safety of an 18-month follow-up programme of individualized regular coaching on physical activity and exercise.

Methods: This was a multicentre, pragmatic, single-blinded, randomized controlled trial. Adults (age≥18 years) with first ever or recurrent stroke, community dwelling, with modified Rankin Scale<5 and no serious comorbidities were included 10-16 weeks post-stroke. The intervention group received individualized regular coaching on physical activity and exercise every month for 18 consecutive months. The control group received standard care. Primary outcome was the Motor assessment scale (MAS) at end of intervention (18-month follow-up). Secondary measures were Barthel index (BI), mRS, item 14 from Berg balance scale (BBS), Timed up and go test, gait speed, Six minute walk test and Stroke impact scale (SIS). Other outcomes were adverse events and compliance to the intervention assessed by training diaries and the International physical activity questionnaire (IPAQ).

Results: Three-hundred-and-eighty consenting participants were randomly assigned to individualized coaching (n=186) or standard care (n=194). The mean estimated difference on MAS in favour of control group was -0.70 points (95% CI -2.80, 1.39), p=0.512. There were no differences between the groups on BI, mRS or BBS. The frequency of adverse events was very low in both groups. Results from IPAQ and training diaries showed increased activity levels but low intensity of the exercise in the intervention group.

Conclusions: The regular individualized coaching did not improve maintenance of motor function, nor the secondary outcomes, compared to standard care. The intervention should be regarded as safe. Despite the neutral results, the health-costs related to the intervention should be investigated.

Clinical Trial registration: ClinicalTrial.gov, number NCT01467206.

Introduction

Most patients experience significant improvement in function during the first weeks and months after stroke, and the functional level achieved 3-6 months post-stroke is strongly associated with long term outcome.[1,2] However, stroke survivors are at risk of functional decline in the long term and very few survive for 5 years without hospital readmission.[3]

Task-oriented and intensive exercise in the acute and subacute phases after stroke has been shown to give optimal recovery and a good prognosis for return to an independent life at home.[4] Cardiorespiratory training has also been shown to reduce disability during or after usual stroke care.[5,6] Furthermore, physical activity and exercise are highly recommended in the chronic phase to sustain functions gained in rehabilitation and as part of long term secondary prevention to reduce the risk of recurrent stroke and other vascular events. However, these recommendations are mainly based on expert opinions and extrapolated results from studies in primary prevention.[7] Although little is known about how well community dwelling stroke survivors comply with these recommendations, people with stroke seem less active than their age-matched peers.[8] Hence, development of new interventions is needed to help stroke survivors achieve a more active lifestyle to maintain the functional levels achieved during stroke unit treatment and early post-stroke rehabilitation.

A systematic review of the literature provides some evidence that tailored counselling improves participation in physical activity after stroke.[9] However, only one study has followed patients for more than 12 months, showing that regular phone-calls in addition to counselling of physical activity every 3-6 months did not significantly increase activity levels.[10] The authors hypothesised that the lack of individualized coaching on a more regular basis might explain the neutral result.[10] Therefore, the aim of the present study, was to

investigate whether a long term intervention programme of regular individualized coaching on physical activity and exercise increased activity levels in order to maintain optimal motor function, independence in activities of daily living, balance, walking ability and health-related quality of life. We also aimed to investigate safety and compliance to the intervention. Our primary hypothesis was that individualized coaching would be better than standard care in maintaining motor function at 18 months' follow-up.

Materials and Methods

The LAST study was conducted in accordance with the institutional guidelines and was approved by the Regional Committee of Medical and Health Research Ethics (REC no. 2011/1427). Due to Norwegian regulations and conditions for informed consent, the dataset is not publicly available. The study was registered with Clinicaltrials.gov (NCT01467206). Full details of this study protocol have been published elsewhere.[11]

Study design and participants

This was a pragmatic, single-blinded, parallel-group, randomized controlled trial performed at two centres in Norway: Trondheim University Hospital and Bærum Hospital, in close collaboration with the primary health care service in the municipalities of Trondheim, Asker and Bærum. The study lasted from 18 October 2011 to 15 January 2016.

All patients treated at the stroke unit at the participating hospitals were screened for inclusion and consecutively recruited at the outpatient clinic at 3 months (10-16 weeks) post-stroke. Patients who agreed to participate underwent an initial assessment before randomisation and a follow-up assessment 18 months later.

Eligible participants were aged 18 or older, had confirmed first ever or recurrent stroke (infarction or intracerebral haemorrhage), had been discharged from hospital or inpatient rehabilitation and were community dwelling with a modified Rankin Scale (mRS) score<5, had no serious comorbidities that made it difficult to perform the intervention and were capable of providing consent.

Exclusion criteria were serious medical co-morbidity with short life expectancy, cognitive deficits as evaluated by the Mini-mental state examination (MMSE) (<21 points, or <17 points for patients with aphasia), contraindication to participation in motor training, or inclusion in another study.

Randomisation and masking

Participants were stratified according to stroke severity (mRS>2 points), age≥80 and recruitment site. They were randomly assigned (1:1), in blocks of 2 and 4, to an intervention group receiving regular individualized coaching on physical activity or to a control group receiving standard care. A group of well-trained research assistants, blinded to the treatment allocation, screened patients for eligibility and did all assessments face-to-face at inclusion and at 18 months' follow-up. Randomisation was performed by a web-based randomisation system developed and administered by the Unit of Applied Clinical Research, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Intervention and control

Standard care

All eligible participants underwent evidence-based comprehensive stroke unit treatment in the acute phase and further rehabilitation after discharge from hospital including a three months' follow-up visit at the outpatient clinic in accordance with the Norwegian guidelines on stroke treatment.[12] The rehabilitation after discharge from hospital usually consists of 45 minutes of physiotherapy at moderate intensity per week performed in the patient's home, at an outpatient clinic or during inpatient rehabilitation. Rehabilitation is often limited to the first three months for patients with mild to moderate strokes, but can last for up to six months for patients with the most severe strokes, and for selected patients even longer. After the end of rehabilitation, patients and their families have to take responsibility for further physical activity and exercise. Participants randomized to the control group received standard care.

Regular individualized coaching

Participants randomized to the intervention group were given, in addition to standard care, a follow-up programme comprising monthly individualized coaching by a physiotherapist for 18 consecutive months after inclusion. As a starting point, participants were asked to complete a standardised questionnaire to register their individual physical activity preferences[13] and to list one to three individual goals using Goal attainment scaling.[14] Based on the preferences and goals, a schedule for physical activities and exercise was set for the next month. The exercise needed to last 45-60 minutes and include two to three periods of vigorous activity once a week while the physical activity needed to last 30 minutes seven days a week.[15] Vigorous activity was defined as a rating of 15-17 on the Borg scale of perceived exertion.[16] To comply with the weekly exercise, participants were offered participation in a number of existing outpatient, private and community based treatment groups, individual physiotherapy or home training if preferred.

Furthermore, participants were trained in how to complete the training diary and record the amount and intensity of each day's activities. The training diaries were reviewed and the schedule was reassessed according to individual needs including progression for the next month.

The first six meetings were performed face-to-face in the participants' home; in the next six months, every second meeting could take place as a phone meeting and during the final six months, four of the six meetings could take place as a phone meeting.

Outcomes

The primary outcome was motor function at 18 months after inclusion assessed by Motor Assessment Scale (MAS).[17] Developed for persons with stroke, the scale consists of eight functional tasks ranging from rolling from supine to side lying, to advanced hand activities. The advantage of MAS is that it covers all basic motor functions, and has frequently been used in previous stroke trials.[18] MAS has shown good measurement properties, and the reliability and validity of the Norwegian translation of the scale have been ensured.[19]

Secondary outcomes were the Barthel index (BI)[20] and mRS[20] to assess independence in activities of daily living, item 14 from Berg Balance Scale (BBS)[21] and Timed up and go test (TUG)[22] to assess balance, 10 meter maximum gait speed,[23] and the six minute walk test (6MWT)[24] to assess walking ability, and the Stroke impact scale (SIS) 3.0[25] to assess health-related aspects of quality of life at 18 months. Further secondary outcomes were EQ-5D-5L, Fatigue severity scale, one item on fatigue from the HUNT3 questionnaire, Hospital anxiety and depression scale, Mini-mental state examination, Trailmaking A and B and Caregiver strain index.[11]

Adverse events

Information about new cardiovascular and cerebrovascular events, serious falls, fractures or any event of syncope or dizziness with unknown reason, resulting in hospitalisation, was collected from the Norwegian Patient Registry. Information about deaths was collected from the hospital records or next-of-kin.

Compliance

Compliance with the intervention was assessed by combining information from the training diaries with information recorded by the physiotherapists. Participants who performed at least 210 minutes of physical activity (30 minutes 7 days a week) and 45 minutes of exercise every week for 80% of the weeks (19 of 24 weeks) within every 6-month period were considered compliers. Compliance was also calculated for those who complied with the general recommendations, i.e. 150 minutes of physical activity per week.[26] The Borg scale was used to report intensity levels of physical activity and exercise. The proportion of participants who attended at least 50% of the meetings face-to-face within every 6-month period has also been reported.

The amount and intensity of physical activity performed by the participants in both groups were recorded using the International physical activity questionnaire (IPAQ)[27] at 6, 12 and 18 months' follow-up. IPAQ provides information about energy costs (MET, metabolic equivalent task) for walking, moderate intensity and vigorous intensity activity during the last seven days.

Please see Table I and Table II (online-only) at http://stroke.ahajournals.org.

Statistical analyses

Sample size estimation was based on previous data from two comparable populations.[28,29] Difference of 10% between the groups were considered clinically significant. The intervention group was expected to maintain its initial mean MAS score (38.4 points) at 18 months' follow-up, while a 10% reduction was expected in the control group at the same time point (34.6 points). The standard deviation was estimated as 10.6 points. Based on these assumptions, a sample size of 170 in each group was needed to achieve a statistical power of 90% with significance level alpha=0.05. Assuming that 15% of the participants might drop out during the course of the study, a target of 390 participants was set.

The primary endpoint was motor function measured by MAS at 18 months' follow-up. We used analysis of covariance (ANCOVA) for primary and secondary endpoints, with measurement at 18 months as dependent variable, and treatment group, sex, hospital site, stroke severity, age, and measurement at baseline as covariates. The Mann-Whitney U test was used for data that were not normally distributed.

We were aiming for an intention to treat analysis approach. For instrument scales with no more than half of the items missing, the missing values were singly imputed using the expectation-maximation (EM) algorithm on these. In the primary analysis, participants who had died before follow-up were imputed as zero on all scales except mRS, where a score of six means dead. We used multiple imputation to impute all other missing values, with m=100 imputations as recommended by van Buuren S.[30] A sensitivity analysis was done to determine whether participants who were dead at 18 months affected the outcome.

Pre-specified subgroup analyses were performed according to the stratification variables (stroke severity (mRS 0-2 versus 3-4), age<80 and recruitment site) in addition to sex, and cognitive status (MMSE<25), with a separate ANCOVA for each subgroup.

Results

Between 18 October 2011 and 30 June 2014, 1324 individuals were screened for inclusion. The follow-up assessments were completed 15 January 2016. In total, 380 consenting participants were included and randomly assigned to the intervention group (n=186) or to the control group (n=194). The most common reasons for exclusion were refusal (23.6%) or institutionalisation (22.4%). A total of 153 participants in the intervention group and 162 participants in the control group were assessed at 18 months. The flow of participants is shown in Figure 1.

Demographic and baseline characteristics were similar in both groups (Table 1).

Both groups declined on primary outcome, MAS at 18 months, relative to baseline (2 points versus 1.3 points in the intervention group and control group, respectively); however, there were no differences between the groups (adjusted between group mean difference estimate: -0.70 points (95% CI -2.80, 1.39), p=0.512) (Table 2). Regarding secondary outcomes, there were no significant differences between the groups except a greater improvement on TUG in the control group (7.05 seconds (95% CI 2.86, 11.25), p=0.001).

The sensitivity analysis showed that participants who died during follow-up did not affect the outcome.

There was no evidence of effect on the primary outcome for any of the pre-specified subgroups (Figure 2).

Adverse events

The safety measures showed no differences in adverse events between the groups (Table 3). However, there were 39% more hospital admissions because of vascular events, when all cerebrovascular and cardiovascular events were summed up, in the control group compared to the intervention group (28 versus 17 events, p=0.110).

Compliance

Table I (online-only) shows that 43-59% of those who completed the training diaries complied with 210 minutes per week in each 6-month period, while 60-64% complied with 150 minutes per week. The corresponding numbers for compliance to 45 minutes of weekly exercise ranged from 50% to 54% over the 18-month period. The actual number of compliers increased during follow-up.

Table II (online-only) shows that participants in the intervention group were more active in terms of vigorous activity compared to the control group at 6 months' (p=0.009), 12 months' (p=0.016) and 18 months' follow-up (p=0.033). Moderate activity and walking time were only significantly higher at 6 months' (p=0.005) and 12 months' follow-up (p=0.001).

Discussion

Contrary to our hypothesis, we could not demonstrate that individualized coaching was better than standard care in maintaining motor function, as measured with MAS, at 18 months. Nor did the secondary outcomes show any benefit of the intervention. The compliance measures

showed that stroke survivors receiving regular individualized coaching were more active than participants receiving standard care and the safety measures showed no differences in adverse events between the groups.

The major strength of the present study was the pragmatic randomized controlled study design with few inclusion and exclusion criteria and an intervention applicable in a wide range of settings, strengthening the external validity of the results. The high quality treatment given as part of standard care to participants in both groups should also be regarded as a strength, even though it might have contributed to reducing the ability to achieve significant differences between the groups. The low number of participants lost to follow-up, which was slightly lower than assumed in our sample size estimation, was also a strength.

A weakness of the study was the lack of repeated measurements of motor function and secondary outcomes during follow-up. Another limitation was the lack of detailed and regular information about physical activity and exercise performed by the control group. However, the rationale for not recording such information was to reduce the risk of contamination of the intervention to the control group and because the training diaries were an important part of the individualized coaching given to the intervention group.

The use of a self-reported measure of physical activity and exercise might also be regarded as a weakness. It is well known that people may overestimate their activity levels when self-reported measures are used, and we cannot exclude the possibility that the participants in the intervention group have tended to overestimate their activity levels more than the controls. Objective measures such as activity monitors are recommended for used in future research. However, independent of the choice of method, participants in both groups might be prone to

the Hawthorne effect, i.e. changing their behaviour as a motivational response to the attention received through the assessment.[31]

The neutral results might also be explained by a possible ceiling effect shown by the primary outcome and the large number of participants with mRS score of 0 or 1 at inclusion. There are many pros and cons to consider when choosing a primary measure. MAS was chosen in the present study because it covers the whole range of motor activities and because it was validated in Norwegian.[19] Another advantage of MAS was the very good responsiveness demonstrated for the mobility items (balanced sitting; sitting to standing; walking).[32] However, in future research an instrumental ADL measure, like the Nottingham Extended ADL Scale might be more suitable as a primary outcome in this population.

Despite significantly better TUG score in the control group, this trial should be interpreted as neutral. This difference was probably driven by five extreme cases (TUG>60 seconds) at follow-up.

The frequency of all vascular events was very low in both groups, demonstrating that the intervention was safe. A non-significant trend toward more vascular events in the control group might indicate a possible benefit of the intervention in secondary prevention. This result should be interpreted with caution as a recent systematic review found no effect of lifestyle interventions on cardiovascular event rate after ischemic stroke.[33] However, the follow-up periods were probably too short to reveal such effect. It's important to notice that we only recorded serious adverse events in the present study. We cannot exclude the possibility that the frequency of other events might have been different between the groups.

The results from IPAQ indicate that the participants mainly complied with the intervention, while information from the training diaries indicates that the exercise was not as intensive as intended. This finding was in contrast to the ExStroke Pilot Trial,[10] underscoring the importance of regular individualized coaching that includes systematic goalsetting; agreement on a personalised training programme; and use of training diaries, which were not part of standard care. It is well known that changing lifestyle takes time and it will be of interest in future research to investigate whether this intervention has resulted in a persistent active lifestyle or whether the participants depend on continuous coaching to maintain their activity levels.

Our results do not support the introduction of individualized coaching in the clinic in order to improve motor function in people with minor impairments after stroke. Still, more research is needed to investigate the effect of health coaching after stroke on other outcomes, like the long term risk of new vascular events. To overcome the heterogeneity challenge and improve the compliance, the coaching should probably be even more personalised and multimodal. It is also possible that an earlier commencement of the intervention, increased intensity and a longer follow-up period is needed.

Conclusions

The LAST study has shown that regular coaching did not result in better maintenance of motor function, nor improvement on the secondary outcomes, compared to standard care. The intervention should be regarded as safe. Despite the neutral results, the health-costs related to the intervention should be investigated.

Acknowledgements

We want to thank Christian Sesseng for assistance with the analysis of the compliance data.

Sources of Funding

The LAST study was funded by Norwegian Research Council, Liaison Committee between Central Norway Regional Health Authority and Norwegian University of Science and Technology (NTNU), Joint Research Committee between St. Olavs Hospital and NTNU, Norwegian Fund for Postgraduate Training in Physiotherapy, Stroke Unit Research Fund at St. Olavs Hospital. The funders of the study had no role in study design, data collection, data interpretation, or writing of the report.

Disclosures: None

Appendix

The LAST Collaboration group: Torgeir Engstad, Jon Magnussen, Anne Hansen, Rune Schjørlien, Stian Engen, Randi Moxnes Osmundnes, Anne-Britt Olerud, Camilla Knudsen, Trine Hansen, Walburga Schroeter, Gro Stensrud Fjelldal, Kristin Hovde, Kristine Helen Reneflot, Lisa Wennberg, Ole Petter Norvang, Ailan Phan, John Bjørn Storvoll, Brede Ørjaset, Marianne Syvertsen, Ingvild Berger, Anne Eitrem Dahl, Christine Lundemo Sandø, Veronica Kjølstad, Alexander Hansen, Helene Kværne Vileid, Maren Hjelle Giddal, Julie Bernhardt and Peter Langhorne.

References

1. Slot KB, Berge E, Dorman P, Lewis S, Dennis M, Sandercock P. Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies. *Bmj* 2008;336:376-9.
2. Eriksson M, Norrving B, Terent A, Stegmayr B. Functional outcome 3 months after stroke predicts long-term survival. *Cerebrovasc Dis* 2008;25:423-9.
3. Bravata DM, Ho SY, Meehan TP, Brass LM, Concato J. Readmission and death after hospitalization for acute ischemic stroke: 5-year follow-up in the medicare population. *Stroke* 2007;38:1899-904.
4. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet* 2011;377:1693-702.
5. Saunders DH, Sanderson M, Hayes S, Kilrane M, Greig CA, Brazzelli M, et al. Physical fitness training for stroke patients. *The Cochrane database of systematic reviews* 2016;3:Cd003316.
6. Kendall BJ, Gothe NP. Effect of Aerobic Exercise Interventions on Mobility among Stroke Patients: A Systematic Review. *Am J Phys Med Rehabil*. 2016;95:214-24.
7. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;42:227-76.
8. Rand D, Eng JJ, Tang PF, Jeng JS, Hung C. How active are people with stroke?: use of accelerometers to assess physical activity. *Stroke* 2009;40:163-8.
9. Morris JH, Macgillivray S, McFarlane S. Interventions to promote long-term participation in physical activity after stroke: a systematic review of the literature. *Arch Phys Med Rehabil.* 2014;95:956-67.

10. Boysen G, Krarup LH, Zeng X, Oskedra A, Korv J, Andersen G, et al. ExStroke Pilot Trial of the effect of repeated instructions to improve physical activity after ischaemic stroke: a multinational randomised controlled clinical trial. *BMJ* 2009;339:b2810.

11. Askim T, Langhammer B, Ihle-Hansen H, Magnussen J, Engstad T, Indredavik B. A Long-Term Follow-Up Programme for Maintenance of Motor Function after Stroke: Protocol of the life after Stroke-The LAST Study. *Stroke Res Treat* 2012;2012:392101.

12. Indredavik B, Salvesen R, Næss H, Thorsvik D. Treatment and rehabilitation after stroke (Clinical guidelines). Norwegian Directorate of Health. Publication date: 2010. https://helsedirektoratet.no/retningslinjer/nasjonal-faglig-retningslinje-for-behandling-og-rehabilitering-ved-hjerneslag. Accessed October 27, 2017.

13. Banks G, Bernhardt J, Churilov L, Cumming TB. Exercise preferences are different after stroke. *Stroke Res Treat* 2012;2012:890946.

14. Rockwood K, Stolee P, Fox RA. Use of goal attainment scaling in measuring clinically important change in the frail elderly. *J Clin Epidemiol* 1993;46:1113-8.

15. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public health reports* 1985;100:126-31.

16. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* 1982;14:377-81.

17. Carr JH, Shepherd RB, Nordholm L, Lynne D. Investigation of a new motor assessment scale for stroke patients. *Phys Ther* 1985;65:175-80.

18. French B, Thomas LH, Coupe J, McMahon NE, Connell L, Harrison L, et al. Repetitive task training for improving functional ability after stroke. *The Cochrane database of systematic reviews* 2016;11:Cd006073.

19. Kjendahl A, Jahnsen R, Aamodt G. Reliability of the MAS instrument. *Adv Physiother* 2005;8:12-7.

20. Wolfe CD, Taub NA, Woodrow EJ, Burney PG. Assessment of scales of disability and handicap for stroke patients. *Stroke* 1991;22:1242-4.

21. Alzayer L, Beninato M, Portney LG. The accuracy of individual Berg Balance Scale items compared with the total Berg score for classifying people with chronic stroke according to fall history. *J Neurol Phys Ther* 2009; **33**:136-43.

22. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. *Arch Phys Med Rehabil* 1986; **67**:387-9.

23. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age Ageing* 1997; **26**:15-9.

24. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919-23.

25. Duncan PW, Bode RK, Min LS, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Arch Phys Med Rehabil* 2003;84:950-63.

26. Hanifi R, Lambert V, Fulton J, Hanskell W, Buchner D, Tremblay M, et al. Global Recommendations on Physical Activity for Health. World Health Organisation. Publication date: 2010. Accessed October 27, 2017. http://www.who.int/dietphysicalactivity/publications/9789241599979/en/

27. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381-95.

28. Askim T, Morkved S, Engen A, Roos K, Aas T, Indredavik B. Effects of a community-based intensive motor training program combined with early supported

discharge after treatment in a comprehensive stroke unit: a randomized, controlled trial. *Stroke* 2010;41:1697-703.

29. Langhammer B, Stanghelle JK, Lindmark B. An evaluation of two different exercise regimes during the first year following stroke: a randomised controlled trial. *Physiother Theory Pract* 2009;25:55-68.

30. Buuren Sv. Flexible Imputation of Missing Data. Boca Raton: Taylor & Francis Group; 2012.

31. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672.

32. Scrivener K, Schurr K, Sherrington C. Responsiveness of the ten-metre walk test, Step Test and Motor Assessment Scale in inpatient care after stroke. *BMC neurology* 2014;14:129.

33. Deijle IA, Van Schaik SM, Van Wegen EE, Weinstein HC, Kwakkel G, Van den Berg-Vos RM. Lifestyle Interventions to Prevent Cardiovascular Events After Stroke and Transient Ischemic Attack: Systematic Review and Meta-Analysis. *Stroke* 2017;48:174-9.

Table 1: Baseline demographic and clinical characteristics. Values are n(%) unless stated otherwise.

	Intervention group (n=186)	Control group (n=194)
Age (years), mean(SD)	71.7(11.9)	72.3(11.3)
≥80	44(23.7)	53(27.3)
<80	142(76.3)	141(72.7)
Sex		
Female	82(44.1)	67(34.5)
Male	104(55.9)	127(65.5)
Time from stroke (days), mean(SD)	111.3(24.5)	112.0(17.2)
NIHSS, mean(SD)	1.5(2.3)	1.6(2.5)
<8	181(97.3)	188(96.9)
8-16	5(2.7)	6(3.1)
>16	0	0
mRS, mean(SD)	1.45(1.08)	1.44(1.10)
mRS=0	34(18.3)	38(19.6)
mRS=1	78(41.9)	80(41.2)
mRS=2	36(19.4)	35(18.0)
mRS=3	32(17.2)	34(17.5)
mRS=4	6(3.2)	7(3.6)
Living condition		
Living with someone	130(69.9)	143(73.7)
Living alone	56(30.1)	51(26.3)
Stroke type		

Infarction,	172(92.5)	174(89.7)
Haemorrhage	14(7.5)	20(10.3)
MMSE, mean(SD)	27.8(2.3)	27.9(2.6)
≥25	164(88.2)	176(90.7)
<25	22(11.8)	18(9.3)
Comorbidity		
Stroke	29(15.6)	38(19.6)
TIA	20(10.8)	18(9.3)
Myocardial infarction	19(10.2)	28(14.4)
Heart failure	3(1.6)	6(3.1)
Atrial fibrillation	32(17.2)	43(22.3)
Hypertension	90(48.4)	109(56.2)
Diabetes	25(13.4)	29(14.9)
Lung diseases	19(10.2)	25(12.9)

NIHSS = The National Institutes of Health Stroke Scale, mRS = Modified Rankin Scale, MMSE = Mini-Mental State Examination.

Table 2: Baseline and follow-up outcome measures, by group

	Intervention group (n=186)		Control group (n=194)		Between group differences	
	Baseline Mean(SE)	18-month follow-up Mean(SE)	Baseline Mean(SE)	18-month follow-up Mean(SE)	Adjusted coefficient estimate (95% CI)*	P value
Primary outcome						
Motor assessment scale†	41.9(0.50)	39.9(0.88)	41.7(0.53)	40.4(0.81)	-0.70(-2.80, 1.39)	0.512
Secondary outcomes‡						
Barthel index†	96.4(0.05)	90.2(0.18)	96.1(0.066)	90.2(0.16)	-0.41(-4.96, 4.14)	0.860
Modified Rankin Scale	1.45(0.056)	1.28(0.117)	1.44(0.079)	1.33(0.11)	-0.03(-0.30, 0.25)	0.860
Berg balance scale, item 14†	2.55(0.11)	2.63(0.12)	2.52(0.10)	2.71(0.10)	-0.10(-0.33, 0,13)	0.391
Timed up and go test (sec)	12.3(0.57)	19.5(2.16)	16.1(2.25)	12.9(0.69)	7.05(2.86, 11.25)	0.001
Gait speed (m/s)†	1.28(0.04)	1.01(0.06)	1.35(0.05)	1.07(0.07)	-0.03(-0.17, 0.10)	0.625
Six minute walk test	391.1(12.5)	371.6(14.4)	389.1(16.7)	372.2(18.8)	-1.38(-34.6, 31.8)	0.935

(meter)†				
Stroke impact scale, over all recovery	72.8(2.67)	73.5(2.58)	-0.95(-7.58, 5.68)	0.778

*Adjusted estimates after controlling for age, sex, stroke severity (modified Rankin Scale at inclusion), hospital site and baseline Motor assessment scale, Barthel index, modified Rankin scale, Berg balance scale (item 14), Timed up and go test, gait speed and Six minute walk test as appropriate.

† Participants who died before follow-up were given a test score of zero at 18-months follow-up.

‡ EQ-5D-5L, Fatigue severity scale, one item on fatigue from the HUNT questionnaire, Hospital anxiety and depression scale, Mini-mental state examination, Trailmaking A and B and Caregiver strain index showed no differences between the groups. Details will be reported and discussed elsewhere.

Table 3: Safety outcomes. Values are n(%)

	Intervention group (n=186)	Control group (n=194)	p-value
Death	9(4.8)	9(4.6)	0.909
Myocardial infarction	4(2.2)	4(2.1)	0.745
Other cardiovascular events	4(2.2)	10(5.2)	0.120
Recurrent stroke	7(3.8)	12(6.2)	0.279
Transitory ischemic attack	5(2.6)	5(2.6)	0.946
Any vascular event	17(9.1)	28(14.4)	0.110
Unspecific cerebral symptoms	7(3.8)	5(2.6)	0.509
Fracture	11(5.9)	11(5.6)	0.919
Fall	3(1.6)	4(2.1)	0.745

Figure legends

Figure 1: Trial profile

Figure 2: Subgroup analysis for Motor assessment scale at 18 months' follow-up