Greater Reduction of Blood Pressure with Exercise Intervention Than Standard Care After Recent Ischaemic Stroke: A Randomized Clinical Trial

Patrice Francis-Emmanuel

University of the West Indies

Michael Boyne

University of the West Indies

Alice Ryan

University of Maryland, Baltimore

Charlene Hafer-Macko

University of Maryland, Baltimore

Richard Macko

University of Maryland, Baltimore

Clive Osmond

University of Southampton

Marilyn Lawrence-Wright

University of the West Indies

Curtis Green

University of the West Indies

Gail Nelson

University of the West Indies

Terrence Forrester (✉ terrence.forrester@uwimona.edu.jm)

University of the West Indies

Research Article

Keywords: blood pressure, stroke, exercise, Low Middle Income Country, body composition, clinical trial

Posted Date: January 5th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1167993/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Greater reduction of blood pressure with exercise intervention than standard care after recent ischaemic stroke: a randomized clinical trial

Patrice M. Francis-Emmanuel^a, Michael S. Boyne^{a,b}, Alice S. Ryan^c, Charlene E. Hafer-Macko^c, Richard F. Macko^c, Clive Osmond^d, Marilyn B. Lawrence-Wright^a, Curtis O. Green^f, Gail A. Nelson^{e,f}, Terrence E. Forrester^f

^a*Department of Medicine, The University of the West Indies, Mona, Jamaica*

^b*Caribbean Institute for Health Research, The University of the West Indies, Mona, Jamaica*

^c*Department of Veterans Affairs and Veterans Affairs Medical Center, Maryland Exercise and Robotics Center of Excellence (MERCE), Geriatric Research, Education and Clinical Center (GRECC) and Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland, USA*

^d*MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK*

^e*Section of Physical Therapy, Department of Basic Medical Sciences, The University of the West Indies, Mona, Jamaica*

^f*UWI Solutions for Developing Countries, The University of the West Indies, Mona, Jamaica.*

Corresponding Author:

Professor Terrence Forrester

UWI SODECO

25 West Road

The University of the West Indies, Mona

Kingston 7

Jamaica

Tel: +1-876-970-3152

Email: terrence.forrester@uwimona.edu.jm

28 Word count: manuscript words, abstract words, 4 tables, 2 figures, references

29

30 Key words: blood pressure, stroke, exercise, Low Middle Income Country, body composition, clinical

31 trial

32

33 Short title: Blood pressure responses after exercise intervention

34

35

ABSTRACT

Context and Objectives: Ischaemic stroke (IS) causes disability and uses massive public health resources. Cumulative disability from recurrence may be reduced with cardiometabolic risk reduction strategies e.g., lowering blood pressure (BP). We hypothesized that intensive exercise plus best available care in adults with recent IS improves fitness, glucose metabolism; muscle protein synthesis in paretic limbs compared to controls. BP changes were compared between intervention (INT) and controls (CON).

Research Design and Setting: A randomised, interventional clinical trial conducted in Jamaican adults

Subjects: We investigate 103 adults with recent IS and residual weakness. Forty-nine subjects (24 women: mean age 61.5; 25 men: mean age 63.8) received task-oriented exercise training (TEXT) plus best available care. Fifty-four subjects (23 women: mean age 60.2; 31 men: mean age 61.3) received best care, including exercise advice.

Measurements: We measured baseline, 3-month and 6-month BP.

Results: After recent IS, TEXT plus best available care reduced systolic BP by 21 mmHg and diastolic by 12 mmHg compared to controls, independent of medication adherence, body composition; stroke severity. Men in the TEXT group had increased lean mass ($P < 0.007$), VO_2 max ($P = 0.03$); 6-minute walk distance ($P = 0.003$). Leg press on paretic ($P = 0.004$) and non-paretic ($P < 0.001$) increased with TEXT vs CON over 6 months, in both sexes (P -values for sex difference > 0.2). Time-to-chair-rise decreased in both sexes who received intervention vs controls ($P < 0.04$)

Conclusions: TEXT results in significant blood pressure reduction in adults with recent ischaemic stroke and residual weakness when compared with best available medical care only.

INTRODUCTION

Ischaemic heart disease and stroke cause more than 27% of worldwide deathsⁱ and are major categories of the non-communicable diseases (NCDs) (7 of 10 leading causes of death in 2019). This equates to 44% of deaths globally. Non-communicable diseases account for 80% of deaths in Jamaicaⁱⁱ; regionally, heart disease, cancer, stroke, and diabetes accounted for 47% of deaths in the Caribbean in 1980. This mortality rate increased to 51% by 2000ⁱⁱⁱ. Globally and in the Caribbean, NCDs are leading causes of death; stroke being a major contributor.

Overall, 20 to 50% of people with incident stroke die within a month^{iv}; survivors are often significantly disabled^v, requiring massive public health expenditures. Up to 50% of survivors are chronically disabled posing a health care burden. Risk factors for stroke include hypertension, diabetes obesity, prevalent globally, in Jamaica and the Caribbean^{vi}.

Risk of recurrent stroke is 30% within 5 years; highest within the first year (13%), 15 times that of the general population^{vii}. Mortality after recurrence is twice that associated with first-time events^{viii}. About 80% of survivors die within 10 years and 50% die from recurrent stroke or cardiovascular (CV) disease^{ix}. Glucose intolerance and CV events increase after thrombotic strokes^x and contribute to the increased mortality. Increased CV risk is largely due to hypertension and diabetes, exacerbated by associated low physical activity^{xi} and high sedentary time^{xii}.

Recurrence can be reduced by optimising cardio-metabolic risk status. Lowering blood pressure (BP), or treating hypertension, reduces recurrence, the effect primarily due to systolic blood pressure (SBP) reduction^{xiii}. In patients with a history of ischaemic stroke (IS) or transient ischaemic attack, 9/4 mmHg BP reduction over 4 years reduces recurrence in patients with and without hypertension^{xiv}. A 5 mmHg

and 10 mmHg BP reduction reduces odds of stroke recurrence by 22% and 31% respectively. Despite the magnitude of the contribution of cerebrovascular disease to stroke-associated mortality/disability, there is little emphasis on secondary prevention.

Stroke rehabilitation can improve these adverse sequelae and may ameliorate cardiometabolic risk and future CV or cerebrovascular events. The American Stroke Association (ASA) recommends stroke survivors increase physical activity and participate in aerobic exercise to reduce risk of recurrence and lower CV risk^{xv}. Modifying post-stroke exercise regimens with harness support for body weight allows participants to exercise safely at higher intensity to improve VO_{2max} and cardiometabolic health. Body weight support and task-oriented treadmill TM exercise training [TEXT] cause greater improvement in muscle strength, fitness and reduced inflammatory markers in hemiparetic stroke^{xvi}.

We conducted a randomized trial to investigate the hypothesis that in African-origin Jamaican adults recent (preceding 3 months) hemiparetic stroke, 6 months of specialized exercise intervention across sub-acute into chronic post-event phase will improve cardiometabolic health compared to controls (CON) receiving best available medical care. We report on effects of this intervention on BP response.

METHODS

Study Design:

We conducted a randomized clinical trial of Jamaican stroke survivors by recruiting individuals with hemiparetic stroke from 3 hospitals in metropolitan Kingston: University Hospital of the West Indies (UHWI), Kingston Public and Spanish Town Hospital. Participants were identified by research fellow and chief physiotherapist from admissions to accident & emergency departments and self-referrals from strategically placed flyers. Participants with hemiparetic gait persisting up to 12 weeks post-stroke, not wheelchair-bound were approached for informed consent, medical and neurologic examinations, blood tests, and TM exercise tests to determine eligibility. The Faculty of Medical Sciences/University Hospital of the West Indies Ethics Committee and the University of Maryland Institutional Review Board for Human Research approved study protocol. All methods were performed in accordance with the relevant guidelines and regulations. The research was performed in accordance with the Declaration of Helsinki. Participants gave written informed consent.

Registration:

The trial was registered at clinicaltrials.gov and can be viewed at <https://clinicaltrials.gov/ct2/show/NCT01392391>. The registration was first posted on 12/07/2011 with the ClinicalTrials.gov Identifier NCT01392391.

Eligibility:

Eligibility screening visits included review of medical history, brain imaging, physical examination. Screening visits recorded age, sex, race, medical conditions, medication, family, medical and smoking history, physical activity, and review of screening labs (complete blood count and metabolic panel) while hospitalised during the acute stroke period. Assessments included the Stroke Impact Score, NIH Stroke Scale, Mini Mental Status Examination, Montreal Cognitive Assessment, Centres for

Epidemiological Studies Depression instruments. Patients received head CT scans at stroke diagnosis. Stroke subtypes were categorized according to Oxfordshire nominal classification.

Inclusion criteria included 1) ischaemic stroke <3 months with gait deficits 2) men or women 40-85 with BMI 20-35 kg/m²; 3) adequate language and cognitive function to provide informed consent and participate in tests and training; 4) ability to walk > 3 minutes at 0.09 m/s with TM handrail support, assistive device, or standby aid.

Exclusion criteria included already exercising >20 minutes 3 x/ week, alcohol/drug abuse, cardiac history (unstable angina, myocardial infarction less than 3 months prior, congestive heart failure >NYHA category II, hemodynamic valvular dysfunction), conditions restricting exercise (symptomatic peripheral arterial disease, pulmonary or renal failure, known active cancer, poorly controlled blood pressure, inadequately controlled type 2 diabetes, type 1 diabetes or insulin dependent type 2 diabetes, HIV-AIDS, sickle cell disease), neurological disorders limiting adherence to exercise (dementia, receptive or global aphasia, untreated major depression, etc.).

Baseline measurements:

Cardiometabolic characterization included standardized BP measurements, VO₂ peak (measure of cardiopulmonary fitness), venepuncture (five-point 75g oral glucose tolerance testing); body composition using dual-energy x-ray absorptiometry (DEXA). Body composition tests were performed after overnight fast, before daily training, within 36 hours of the last training session. Dual-energy x-ray absorptiometry was done to determine total fat and lean tissue mass using a GE Lunar Prodigy System; General Electric Inc.).

Functional Tests:

a) Subjects completed 6-minute walk test using the same assistive device and/or orthoses used at home. VO₂ peak exercise test was conducted as previously described^{xvii}. Tests were terminated at participants' request or on signs of cardiopulmonary instability.

Isometric Strength: Bilateral knee extensor (quadriceps) isometric strength was obtained with participants seated with legs hanging freely off table; back at 20 degrees. Seat belt and thigh restraints isolated knee extensors from hip and trunk movement; arms were held across chest. 1-Rep max was done to assess isometric strength.

Randomization:

Subjects were randomized to 6 months 3x/week treadmill exercise and lower limb resistance training accompanied by task oriented physical activity using protocols (TEXT)^{xviii}. Controls (CON) received standardised medical care including advice to engage in 3x/week (30 minutes, 5 days/week) walking at tolerated pace. Randomization was performed using computer-based pseudo-random number generator and Moses-Oakford assignment algorithm to develop allocation schedules and done after participants had completed baseline testing to avoid bias. This process performed done by the clinical research fellow under the supervision of the principal investigator.

Intervention:

TEXT & CON Groups (TEXT, 6 months, 3x/week): TEXT participants received progressive supervised exercise in our stroke clinic at the University of the West Indies, Mona, with 2 components: 1) Treadmill (TM) training, based on our studies in chronic stroke, using new high intensity formula^{xix}; 2) weight-bearing exercises aimed at improving functional mobility and strength. The latter included a walking course which progressing in duration. The course progressed from simple to complex tasks over time. Subjects engaged in sit-to-stand repeats, dynamic balance, leg-strengthening exercises. These consisted of weight shifting (non-Paretic to paretic), forward, sideways, backward steps, and squats at

ballet bar. Walking course duration was progressed from 3-15 minutes. Sit-to-stand and ballet bar exercises were advanced from 6 repetitions per side x 1 set to 15 repetitions x 2 sets, as tolerated, according to prescribed timeline. Subjects performed mobility exercises at home on 3 non-classroom days per week. Activities were tracked by logbook to facilitate translation of mobility practice into daily lifestyle.

The TM training component was individualized to subject's walking capacity and cardiopulmonary tolerance. Training started conservatively with goal of 8-10 minutes at 40-50% maximal heart rate reserve (HRR) (Karvonen formula)^{xx}. Individuals too deconditioned to walk continuously exercised at intervals. The TM training advanced weekly, as tolerated, by week 6 to target 70-80% HRR; 30 minutes. Exercise testing was repeated at 3 months to adjust training HR parameters. Safety was assured by non-weight bearing harness. The CON and TEXT received the same medical care at Study Stroke Clinic. The CON subjects were given home walking program matching exercise time duration of TEXT and selected to meet/exceed AHA guidelines. Home walking was monitored using interval accelerometric (Actical[®]) recordings to document duration; estimated caloric intensity. Stroke team members contacted each participant monthly to maintain contact, address any concerns and verify home exercise adherence. Walking prescription was customized to initial deficit severity based on baseline 6-minute walking performance, and phone contact at 4-week time-points, and measured walking performance at 3-month interval testing.

All baseline tests were repeated after 3 and 6 months.

Sample size calculations:

Sample sizes were calculated based on comparisons of differences at 6 months between groups and based on mean and SD of the difference between intra-individual measures for V02 Peak in chronic stroke patients (N=17) completing 6 months of treadmill aerobic training. Sample size for change in

fitness levels for CON derive from mean and SD of the difference between repeated intra-individual measures for VO₂ peak across 6 months best medical care + 3x/week non-aerobic stretching exercises in chronic stroke patients. Enrolment of 150 total participants to complete 54/group was adjusted to account for an attrition rate of ~28% based on prior experience.

Statistical analyses

Sample sizes for significance of change in glucose and insulin areas required largest numbers; thus, determined recruitment needs. These were calculated for TEXT using mean and SD of differences between repeated intra-individual measures based on results of 6 months lower intensity TM aerobic training in chronic stroke patients, and for controls from OGTT data for chronic stroke patients completing 6 months best medical care + 3x/week non-aerobic, stretching exercises^{xxi}. Since pilot data showed higher intensity TEXT produced >2 x greater fitness gains than lower intensity TM (37% vs. 17%, Δ VO₂ peak, $p < 0.01$), and we report improved indices of insulin sensitivity were related to change in fitness levels with exercise after stroke, these sample sizes were considered conservative. Sample sizes for fitness for TEXT were based on mean and SD of differences between intra-individual VO₂ peak measures in chronic stroke patients ($n=17$) completing 6 months of higher intensity TM aerobic training in Baltimore; identical to the TM component proposed in TEXT. Sample size for change in fitness for CON derived from mean and SD of differences between repeated intra-individual VO₂ peak measures that we reported across 6 months best medical care + 3x/week non-aerobic stretching exercises in chronic stroke patients^{xxii}. We further considered modest fitness gains reported across 6-month sub-acute stroke recovery period that accompanied conventional rehabilitation care in Canada, the best and only natural history data on the time profile of change in fitness levels across the early to chronic stroke period^{xxiii}.

Sample sizes for paretic muscle CT volume and intramuscular area (IMA) fat derived from mean and SD of differences between repeated intra-individual measures in chronic stroke patients (n=14) completing a 3-month pilot resistive training (RT) study that increased paretic thigh muscle volume by 30% (n=6, p<0.05) and insulin sensitivity by 26% (M/I, p<0.05). TEXT in this proposal combined higher intensity TM with progressive strengthening, dynamic gait and balance exercises that may not be as robust to improve muscle mass as our intensive 3-month resistive training; we anticipated would have significant impact across the longer training time (6 months) and would reduce disuse atrophy across stroke recovery to enhance treatment effect^{xxiv}. Sample sizes for muscle protein synthesis and breakdown were based on studies in non-stroke populations^{xxv}. Enrolment of 150 subjects to complete 54/group was adjusted to account for ~28% attrition based on experience in prior exercise studies of similar duration in hemiparetic stroke patients in 3 countries^{xxvi}, ^{xxvii}.

RESULTS

We recruited 143 subjects, January 2021 to June 2016; 103 completed the study in December 2016 at which time the 5-year study ended. Figure 1 shows randomization and reasons for dropout. Those studied and those who dropped out were not statistically significantly different in age, sex, intervention group, stroke severity or medication adherence at baseline (P -values > 0.2). Baseline BP among dropouts ($n=40$) was not different from those completing TEXT.

At baseline, sample was middle-aged, older, and overweight. Half were men, 39% had diabetes, 3% newly diagnosed with diabetes, 74% had hypertension, 15% newly diagnosed hypertension, 29% had dyslipidaemia, 23% newly diagnosed dyslipidaemia, 5% current smokers: 39% prior smokers. There were no differences in prevalence of these conditions/factors or medications by intervention group.

Table 1 provides the baseline and 6-month data for subject characteristics and metabolic health. Body weight, BMI, waist circumference, fat mass, and pulse did not change. In men, lean mass increased after TEXT ($P=0.007$). Lean mass tended to increase in the combined (women and men) intervention group, compared to CON ($P = 0.05$). VO_2 max ($P = 0.03$), distance walked in 6 minutes ($P= 0.003$), leg press paretic ($P = 0.004$) and non-paretic ($P < 0.001$) increased with TEXT compared to CON over the 6 months, in men and women (P -values for sex difference > 0.2). Time to chair rise decreased in TEXT men and women vs CON ($P < 0.04$) There were no changes in TM time and grip. Stroke severity, depression score and medication adherence did not change between baseline and 6 months in either group.

In age- and sex-adjusted regression analyses with SBP as outcome variable, baseline BP and treatment effect were independent predictors (Table 2 and Figure 2A-C). TEXT resulted in a 21 mm Hg reduction in SBP compared to CON ($P<0.001$). Similarly, TEXT had an independent effect on DBP with a reduction

268 of 12 mm Hg ($P < 0.001$) compared to CON. Partial correlations of anthropometry, measures of physical
269 performance, depression, stroke severity and medication adherence did not explain the effect on BP
270 at baseline and at 6 months (Table3).

DISCUSSION

In this study of community-dwelling survivors of IS with residual hemiparesis, 6 months of intervention that included regular contact with the team to deliver supervised aerobic and resistive exercise as well as closely supervised management of chronic diseases including hypertension and diabetes, significantly improved BP. Over 6 months, SBP fell by 21 mmHg more in TEXT than CON and DBP fell by 12 mmHg. Effects were independent of medication adherence, body composition, stroke severity, prevalence of depressive symptoms. Changes in fitness did not explain the effect sizes on BP.

There is evidence that moderate intensity, shorter duration exercise training (50%–70% HRR for 30 min per session 3 days a week lowered BP significantly (~10/8 mm Hg) but did not improve cardiorespiratory fitness^{xxviii}. Our intervention confirms this drop in both sexes' BP but by a larger magnitude.

Possible mechanisms:

Mechanisms for the reduction in BP may include modifications in autonomic function, and brain neuropeptides. Cardiovascular autonomic function is impaired for up to 9 months post-stroke^{xxix} and can increase risk of cardiovascular mortality in survivors. Autonomic normalization be one explanation for marked BP differences between TEXT and CON. This is speculative, as pulse rate, limited indicator of autonomic function, was not different between groups.

Brain-derived neurotrophic factor (BDNF), a neurotrophic protein involved in neural plasticity^{xxx}, can influence body fluid balance and cardiovascular regulation. The sub-fornical organ (SFO) which has no blood-brain barrier expresses BDNF mRNA and mRNA for the high-affinity tropomyosin-related kinase B (TrkB) receptor at which BDNF preferentially binds^{xxxi}. In rats, exposure of the SFO to BDNF results

in BP reduction^{xxxii}. BDNF may be essential for development of arterial baroreceptor systems^{xxxiii}, and after injection into the rostral ventrolateral medulla arterial BP increases^{xxxiv}.

Further evidence that BDNF may be important in BP regulation is demonstrated in a Baltimore study^{xxxv}. Low plasma BDNF is implicated in reverse-dipper pattern of nocturnal BP. Aerobic exercise training improves insulin sensitivity and lowers myostatin both of which may improve BDNF.

Limitations

Limitations include lack of ambulatory BP, careful selection criteria (restricting generalizability); absence of mechanistic data explaining BP reduction. Strengths include low dropout (28%), comprehensive, long duration exercise program, BP measured by trained researchers blinded to outcomes; the study of a difficult population (with sub-acute stroke).

Concluding paragraph

Stroke is a leading cause of mortality. Survivors are at high risk of recurrence. Measures to prevent recurrence are paramount in management. Blood pressure control has been shown to reduce risk of recurrence. In this study, TEXT plus best available medical care reduced SBP and DBP by 21 mmHg and 12 mmHg respectively. Neither differences in compliance nor body composition explained these between-group BP changes. Such a BP reduction is expected to result in significant reduction in the risk of recurrent IS.

Task-oriented exercise training is a viable and beneficial tool for risk reduction in patients with recent (<3 months) IS. Education among physicians may allow wider introduction in early post-stroke periods.

Acknowledgements: We would like to acknowledge the hard work of physiotherapists Dr. Dionne Bennett, Ms Kay-Ann Robinson, Ms Kerry-Ann Gordon, and Ms Ronnet Scarlett as well as research nurse Ms. Latiesha Smith and our dedicated drivers who worked tirelessly to ensure the project's success. The administrative team headed by Mrs Sandra Boyne was instrumental in assisting with logistics planning and guided in project execution.

Funding:

PRIME AWARD NUMBER 1 R01 HD 068712-01
SUB AWARD NUMBER TO UWI 7797 OR SR00001751

Summary Table

What is known about the topic
<ul style="list-style-type: none">Up to 50% of stroke survivors are rendered chronically disabled.
<ul style="list-style-type: none">Lowering blood pressure significantly reduces recurrent ischaemic stroke.
<ul style="list-style-type: none">A 5.1 mmHg and 10 mmHg reduction in BP reduces the odds of stroke recurrence by 22% and 31% respectively.
What the study adds
<ul style="list-style-type: none">TEXT resulted in a 21-mmHg reduction in SBP compared to CON ($P<0.001$) and a 12-mmHg reduction in DBP compared to CON ($P<0.001$).
<ul style="list-style-type: none">These effects were independent of changes in medication adherence, body composition, stroke severity and prevalence of depressive symptoms.
<ul style="list-style-type: none">Changes in fitness did not explain these large effect sizes on BP.

TEXT – Task-oriented exercise training
CON – controls
SBP – Systolic blood pressure
DBP – Diastolic blood pressure

Table 1.

Measurement	Women			Men			All participants
	Intervention (I, n _{max} =24)	Control (C, n _{max} =23)	<i>P</i> -diff I v C	Intervention (I, n _{max} =25)	Control (C, n _{max} =31)	<i>P</i> -diff I v C	<i>P</i> -diff I v C
	Mean, SD, n	Mean, SD, n		Mean, SD, n	Mean, SD, n		
AGE AND ANTHROPOMETRY							
Age (years)	61.5, 12.7, 24	60.2, 11.7, 23	0.7	63.8, 11.6, 25	61.3, 10.1, 31	0.4	0.4
Weight (kg)							
0 months	73.1, 15.4, 24	72.2, 14.5, 23	0.8	77.8, 14.7, 25	74.6, 15.5, 31	0.4	0.5
6 months	73.1, 15.0, 24	72.7, 16.3, 22	0.9	78.5, 14.4, 25	74.0, 14.3, 31	0.3	0.4
6-0 months	0.1, 3.5, 24	0.5, 4.1, 22	0.7	0.7, 4.9, 25	-0.6, 3.9, 31	0.3	0.5
Height (cm)	159.6, 8.2, 24	160.4, 6.7, 23	0.7	173.4, 7.5, 25	170.1, 6.5, 31	0.1	0.3
Body Mass Index kg/m²)							
0 months	28.5, 4.9, 24	27.9, 4.5, 23	0.6	25.8, 4.0, 25	25.7, 4.8, 31	0.9	0.7
6 months	28.6, 4.7, 24	28.2, 5.0, 22	0.8	26.0, 4.0, 25	25.5, 4.3, 31	0.6	0.6
6-0 months	0.1, 1.4, 24	0.2, 1.5, 22	0.7	0.3, 1.7, 25	-0.2, 1.3, 31	0.3	0.5
DEXA Lean Mass (kg)							
0 months	40.9, 8.1, 24	40.7, 5.9, 23	0.9	54.2, 8.6, 24	53.7, 6.8, 30	0.8	0.8
6 months	41.1, 7.2, 24	41.1, 6.6, 22	1.0	55.8, 9.6, 25	52.6, 6.8, 30	0.2	0.3
6-0 months	0.2, 1.7, 24	0.4, 1.8, 22	0.6	1.1, 3.0, 24	-0.8, 1.9, 29	0.007	0.05
DEXA Fat Mass (kg)							

0 months	28.7, 10.0, 24	27.8, 10.3, 23	0.8	17.8, 8.3, 24	17.7, 9.9, 30	1.0	0.8
6 months	27.8, 10.3, 24	27.4, 11.0, 22	0.9	18.3, 8.3, 25	17.2, 8.9, 30	0.6	0.7
6-0 months	-0.8, 3.4, 24	-0.2, 3.2, 22	0.5	0.1, 4.4, 24	-0.4, 2.9, 29	0.6	1.0
Waist circumference (cm)							
0 months	97.1, 11.6, 24	94.7, 9.1, 23	0.4	92.8, 10.3, 25	90.8, 13.1, 30	0.5	0.3
6 months	96.3, 11.0, 24	94.1, 11.4, 21	0.5	92.8, 10.5, 25	91.8, 11.9, 31	0.8	0.5
6-0 months	-0.8, 4.7, 24,	-0.7, 3.8, 21	0.9	0.0, 4.1, 25	0.8, 3.9, 30	0.5	0.6
BLOOD PRESSURE AND PULSE RATE							
Systolic Blood Pressure (mm Hg)							
0 months	153.6, 28.6, 24	158.6, 28.9, 23	0.6	155.0, 18.5, 25	154.8, 25.6, 31	1.0	0.7
6 months	127.8, 21.0, 24	151.2, 28.5, 23	0.002	135.4, 16.8, 25	155.5, 22.4, 31	<0.001	<0.001
6-0 months	-25.8, 24.6, 24	-7.4, 15.1, 23	0.004	-19.6, 20.5, 25	0.7, 27.3, 31	0.003	<0.001
Diastolic Blood Pressure (mm Hg)							
0 months	86.7, 15.1, 24	87.3, 15.2, 23	0.9	88.6, 13.2, 25	87.5, 14.3, 31	0.8	0.9
6 months	71.6, 11.8, 24	82.4, 15.2, 23	0.009	75.3, 9.8, 25	87.9, 11.3, 31	<0.001	<0.001
6-0 months	-15.1, 13.2, 24	-4.8, 9.0, 23	0.003	-13.2, 13.0, 25	0.4, 13.0, 31	<0.001	<0.001
Pulse Rate (bpm)							
0 months	74.7, 14.9, 24	76.6, 12.9, 23	0.6	72.4, 10.4, 25	74.3, 14.7, 30	0.6	0.5
6 months	75.0, 11.8, 24	76.6, 10.8, 23	0.6	68.8, 10.5, 24	72.6, 11.2, 31	0.2	0.2
6-0 months	0.3, 12.8, 24	0.0, 10.7, 23	0.9	-3.6, 11.4, 24	-1.8, 14.7, 30	0.6	0.8
Pulse Pressure (mm Hg)							
0 months	66.9, 20.0, 24	71.3, 24.0, 23	0.5	66.4, 13.8, 25	67.3, 18.1, 31	0.9	0.5
6 months	56.3, 16.8, 24	68.8, 24.2, 23	0.04	60.1, 12.0, 25	67.5, 15.1, 31	0.05	0.005

6-0 months	-10.7, 16.5, 24	-2.6, 8.8, 23	0.04	-6.3, 12.3, 25	0.3, 18.1, 31	0.1	0.01
PHYSICAL PERFORMANCE TESTS							
Vo2 max (ln l/min)							
0 months	-0.05, 0.35, 24	-0.05, 0.29, 22	0.9	0.20, 0.27, 23	0.14, 0.36, 28	0.6	0.6
6 months	0.23, 0.51, 23	0.06, 0.35, 20	0.2	0.36, 0.28, 25	0.21, 0.31, 27	0.08	0.04
6-0 months	0.27, 0.55, 23	0.12, 0.17, 20	0.2	0.16, 0.19, 23	0.02, 0.17, 26	0.009	0.03
Vo2 max (ln (ml/kg/min))							
0 months	2.59, 0.25, 24	2.59, 0.22, 22	0.9	2.78, 0.22, 23	2.76, 0.24, 28	0.7	0.8
6 months	2.75, 0.19, 23	2.70, 0.25, 20	0.4	2.91, 0.20, 25	2.83, 0.20, 27	0.2	0.1
6-0 months	0.16, 0.16, 23	0.11, 0.17, 20	0.3	0.13, 0.16, 23	0.04, 0.16, 26	0.05	0.03
Treadmill time (secs)							
0 months	418, 131, 24	353, 101, 22	0.07	394, 137, 23	377, 100, 28	0.6	0.1
6 months	413, 92, 23	341, 90, 20	0.01	390, 107, 25	365, 81, 27	0.3	0.2
6-0 months	-5, 119, 23	-20, 87, 20	0.6	1, 146, 23	-21, 126, 26	0.6	0.5
Distance walked in 6 mins (m)							
0 months	249, 103, 23	262, 124, 23	0.7	278, 135, 23	254, 121, 29	0.5	0.8
6 months	318, 91, 24	304, 138, 22	0.7	357, 109, 25	279, 124, 30	0.02	0.04
6-0 months	73, 49, 23	49, 41, 22	0.09	81, 79, 23	28, 73, 28	0.02	0.003
Time to 5 chair rises (secs)							
0 months	2.97, 0.41, 21	2.88, 0.53, 23	0.5	2.85, 0.46, 22	2.97, 0.49, 28	0.4	0.8
6 months	2.62, 0.40, 21	2.64, 0.43, 22	0.9	2.60, 0.24, 22	2.91, 0.61, 28	0.03	0.07
6-0 months	-0.35, 0.36, 21	-0.24, 0.33, 22	0.3	-0.26, 0.33, 22	-0.07, 0.38, 28	0.07	0.04
Leg press paretic side (kg)							

0 months	52.6, 20.5, 21	47.6, 29.5, 23	0.5	80.9, 37.8, 22	77.0, 30.3, 28	0.7	0.5
6 months	82.3, 30.9, 22	66.2, 29.8, 21	0.09	98.7, 35.9, 23	76.1, 32.1, 28	0.02	0.004
6-0 months	27.9, 20.8, 21	19.0, 28.9, 21	0.3	20.0, 30.6, 22	-0.9, 17.3, 27	0.004	0.004
Leg press non-paretic side (kg)							
0 months	67.1, 30.4, 21	71.3, 30.3, 23	0.7	111.8, 48.9, 22	107.9, 31.5, 28	0.7	1.0
6 months	94.5, 38.8, 22	88.3, 30.4, 21	0.6	129.1, 44.0, 23	108.6, 32.5, 28	0.06	0.07
6-0 months	26.2, 24.8, 21	15.2, 14.8, 21	0.09	19.1, 17.5, 22	0.0, 18.0, 27	0.001	<0.001
Grip strength paretic side (kg)							
0 months	2.26, 0.88, 21	1.91, 1.04, 23	0.2	2.06, 1.37, 23	2.25, 1.31, 28	0.6	0.8
6 months	2.70, 0.57, 23	2.30, 0.96, 22	0.1	2.69, 1.06, 23	2.49, 1.12, 29	0.5	0.1
6-0 months	0.40, 0.77, 21	0.42, 0.86, 22	0.9	0.62, 0.86, 23	0.24, 0.84, 28	0.1	0.3
MISCELLANEOUS							
Depression score (high more depressed)							
0 months	4.24, 1.51, 23	4.95, 1.63, 23	0.1	4.15, 1.48, 25	4.69, 1.47, 31	0.2	0.05
6 months	3.36, 1.68, 23	4.00, 1.95, 22	0.2	3.34, 2.02, 25	4.49, 1.84, 31	0.03	0.02
6-0 months	-1.00, 1.54, 22	-0.87, 1.48, 22	0.8	-0.82, 1.41, 25	-0.20, 1.51, 31	0.1	0.2
NIH stroke severity score (high more severe)							
0 months	2.42, 1.53, 24	2.96, 2.12, 23	0.3	3.96, 3.16, 25	3.60, 1.77, 30	0.6	0.9
6 months	1.33, 1.09, 24	1.65, 1.92, 23	0.5	2.12, 2.30, 25	2.52, 1.65, 31	0.5	0.3
6-0 months	-1.08, 1.74, 24	-1.30, 1.29, 23	0.6	-1.84, 1.86, 25	-1.03, 1.99, 30	0.1	0.3
Adherence to medication score (high less adherent)							
0 months	2.21, 2.04, 24	2.91, 2.07, 22	0.3	1.56, 2.27, 25	2.35, 2.42, 31	0.2	0.09
6 months	1.63, 1.97, 24	2.43, 2.29, 23	0.2	1.76, 2.05, 25	3.06, 1.95, 31	0.02	0.009

6-0 months	-0.58, 2.34, 24	-0.36, 2.72, 22	0.8	0.20, 1.68, 25	0.71, 2.31, 31	0.4	0.4
------------	-----------------	-----------------	-----	----------------	----------------	-----	-----

Table 2: Regression Analyses

Predictor	Outcome: Systolic Blood Pressure at 6 months (mm Hg)		
	Coefficient	Standard Error	<i>P</i>
Constant	25.2	15.2	0.1
Age (years)	0.15	0.17	0.4
Sex (Female=1; Male=2)	6.3	3.7	0.1
Systolic Blood Pressure at Baseline (mm Hg)	0.48	0.07	<0.001
Treatment (Intervention=1; Control=2)	20.8	3.7	<0.001
Predictor	Outcome: Diastolic Blood Pressure at 6 months (mm Hg)		
	Coefficient	Standard Error	<i>P</i>
Constant	26.2	9.7	0.008
Age (years)	-0.12	0.09	0.2
Sex (Female=1; Male=2)	4.4	1.9	0.03
Diastolic Blood Pressure at Baseline (mm Hg)	0.46	0.07	<0.001
Treatment (Intervention=1; Control=2)	11.7	1.9	<0.001

Table 3: Partial Correlations

Measurement	Systolic blood pressure at 0 months						Systolic blood pressure at 6 months					
	Control Variables						Control Variables					
	Age, sex		Age, sex, intervention		Age, sex		Age, sex, intervention		Age, sex, baseline systolic blood pressure		Age, sex, intervention, baseline systolic blood pressure	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Baseline												
Weight	-.112	.3	-.105	.3	-.155	.1	-.108	.3	-.114	.3	-.061	.5
Height	-.054	.6	-.046	.6	-.184	.07	-.135	.2	-.182	.07	-.131	.2
Body Mass Index	-.113	.3	-.108	.3	-.101	.3	-.073	.5	-.051	.6	-.017	.9
Lean Mass	-.090	.4	-.086	.4	-.104	.3	-.079	.4	-.068	.5	-.039	.7
Fat Mass	-.122	.2	-.119	.2	-.138	.2	-.123	.2	-.088	.4	-.071	.5
Waist Circumference	-.107	.3	-.100	.3	-.057	.6	.003	1.0	-.003	1.0	.069	.5
VO2 max (l/min)	-.047	.6	-.040	.7	-.080	.4	-.030	.8	-.065	.5	-.009	.9
VO2 max(ml/kg/min)	.044	.7	.048	.6	.057	.6	.095	.4	.040	.7	.083	.4
Treadmill time to vo2 max	-.033	.7	-.024	.8	-.082	.4	-.008	.9	-.076	.5	.006	1.0
Distance walked in 6 mins	.081	.4	.086	.4	.028	.8	.066	.5	-.015	.9	.024	.8
Time for 5 chair rises	-.084	.4	-.087	.4	.007	.9	-.016	.9	.058	.6	.037	.7
Leg press – paretic	.176	.09	.186	.08	.015	.9	.083	.4	-.088	.4	-.021	.8
Leg press – non-paretic	.068	.5	.072	.5	.033	.8	.068	.5	-.002	1.0	.035	.7

Grip strength -paretic	.138	.2	.141	.2	.007	.9	.027	.8	-.075	.5	-.060	.6
Depression	-.102	.3	-.119	.2	-.055	.6	-.180	.07	-.003	1.0	-.139	.2
Stroke severity	-.053	.6	-.055	.6	.045	.7	.037	.7	.084	.4	.079	.4
Medication adherence	.080	.4	.070	.5	.226	.02	.162	.1	.216	.03	.148	.1
At 6 months												
Weight	-	-	-	-	-.113	.3	-.049	.6	-.051	.6	.025	.8
Height	-	-	-	-	-.190	.06	-.139	.2	-.192	.06	-.138	.2
Body Mass Index	-	-	-	-	-.049	.6	-.003	1.0	.026	.8	.084	.4
Lean Mass	-	-	-	-	-.083	.4	-.003	1.0	-.059	.6	.031	.8
Fat Mass	-	-	-	-	-.100	.3	-.070	.5	-.029	.8	.009	.9
Waist Circumference	-	-	-	-	.002	1.0	.057	.6	.081	.4	.150	.1
Vo2 max	-	-	-	-	-.048	.6	.092	.4	-.039	.7	.117	.3
Vo2 per max kg	-	-	-	-	.054	.6	.176	.09	-.022	.8	.107	.3
Treadmill time to vo2 max	-	-	-	-	-.054	.6	.065	.5	-.027	.8	.108	.3
Distance walked in 6 mins	-	-	-	-	-.141	.2	-.030	.8	-.200	.05	-.086	.4
Time for 5 chair rises	-	-	-	-	.155	.1	.061	.6	.251	.02	.161	.1
Leg push – paretic	-	-	-	-	-.099	.3	.073	.5	-.122	.2	.064	.5
Leg push – non-paretic	-	-	-	-	-.002	1.0	.129	.2	-.024	.8	.119	.3
Grip strength	-	-	-	-	-.178	.08	-.102	.3	-.185	.07	-.105	.3
Depression	-	-	-	-	.084	.4	-.050	.6	.111	.3	-.033	.7
Stroke severity	-	-	-	-	.166	.1	.132	.2	.234	.02	.207	.04
Medication adherence	-	-	-	-	.268	.01	.180	.07	.195	.05	.090	.4

Figure 1: Enrolment

Figure 2 A

Figure 2B

Figure 2C

References

-
- i 1. Organization WH. WHO Global Health Estimates. 2020.
 - ii 1. Organization WH. Noncommunicable disease country profile, Jamaica, 2018. 2018.
 - iii 1. Organization WHOPH. Overview of the Health situation- Report of the Caribbean Commission on Health and Development 2006.
 - iv 1. Truelsen T, Begg S, C M. Global Burden of Disease 2000 - Cerebrovascular disease 2006.
 - v 1. Warlow C. Epidemiology of Stroke. *Lancet*. 1998;352:1–4.
 - vi 1. Feigin V, Forouzanfar M, Krishnamurthi R, Mensah G, Connor M, Bennett D, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;383(9913):245-55.
 - vii 1. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke*. 1994;25:333-7.
 - viii 1. Hardie K, Hankey G, Jamrozik K, Broadhurst R, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. *Stroke*. 2004;35(3):731-5.
 - ix 1. Hardie K, Hankey G, Jamrozik K, Broadhurst R, Anderson C. Ten-Year Survival After First-Ever Stroke in the Perth Community Stroke Study. *Stroke*. 2003;34(8):1842-6.
 - x 1. Matz K, Keresztes K, Tatschl C, Nowotny M, Dachenhausen A, Brainin M, et al. Disorders of Glucose Metabolism in Acute Stroke Patients; An underrecognized problem. *Diabetes Care* 2006;29 (4):792-7.
 - xi 1. Moore S, Hallsworth K, Plötz T, Ford G, Rochester L, Trenell M. Physical Activity, Sedentary Behaviour and Metabolic Control following Stroke: A Cross-Sectional and Longitudinal Study. *PLOS One*. 2013;8(1).
 - xii 1. Tieges Z, Mead G, Allerhand M, Duncan F, van Wijck F, Fitzsimons C, et al. Sedentary Behavior in the First Year After Stroke: A Longitudinal Cohort Study With Objective Measures. *Archive of Physical Medicine and Rehabilitation*. 2014;96(1):15-23.
 - xiii 1. Lawes C, Bennett D, Feigin V, Rodgers A. Blood Pressure and Stroke. *Stroke*. 2004;35(3):776-85.
 - xiv 1. Group PC. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358(9287):1033-41.
 - xv 1. Billinger S, Ross A, Bernhardt J, Eng J, Franklin B, Johnson C, et al. Physical Activity and Exercise Recommendations for Stroke Survivors; A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2014;45(8):2532-53.
 - xvi 1. Ivey F, Hafer-Macko C, Macko R. Exercise Rehabilitation after Stroke *NeuroRx: The Journal of the American Society of NeuroTherapeutics*. 2006;3:439-50.

-
- xvii 1. Macko R, Katzel L, Yataco A, Tretter L, DeSouza C, Dengel D, et al. Low-Velocity Graded Treadmill Stress Testing in Hemiparetic Stroke Patients. *Stroke* 1997;28(5):988-92.
- xviii 1. Macko R, Ivey F, Forrester L. Task-oriented aerobic exercise in chronic hemiparetic stroke: training protocol and treatment effects *Top Stroke Rehabil* 2005;12(1):45-57.
- xix 1. Ivey F, Stookey A, Hafer-Macko C, Ryan A, Macko R. Higher treadmill training intensity to address functional aerobic impairment after stroke. *Journal of Stroke and Cerebrovascular Disease*. 2015;24(11):2539-46.
- xx 1. Ignaszewski M, Lau B, Wong S, Isserow S. The science of exercise prescription: Martti Karvonen and his contributions *BC Medical Journals* 2017;59(1):38-41.
- xxi 1. Ivey F, Ryan A, Hafer-Macko C, Goldberg P, Macko R. Treadmill Aerobic Training Improves Glucose Tolerance and Indices of Insulin Sensitivity in Disabled Stroke Survivors. *Stroke*. 2007;38(10):2752-8.
- xxii 1. Macko R, Ivey F, Forrester L, Hanley D, Sorkin J, Katzel L, et al. Treadmill Exercise Rehabilitation Improves Ambulatory Function and Cardiovascular Fitness in Patients With Chronic Stroke. *Stroke*. 2005;36:2206-11.
- xxiii 1. MacKay-Lyons M, Makrides L. Longitudinal Changes in Exercise Capacity After Stroke. *Arch Phys Med Rehabil* 2004;85:1608-12.
- xxiv 1. Ottenbacher K, Campbell J, Kuo Y, Deutsch A, Ostir G, Granger C. Racial and Ethnic Differences in Postacute Rehabilitation Outcomes After Stroke in the United States. *Stroke*. 2008;39:1514-9.
- xxv 1. Bergström J, Fürst P, Norée L, Vinnars E. Intracellular free amino acid concentration in human muscle tissue. *Appl Physiol*. 1974;36(6):693-7.
- xxvi 1. Macko R, Benvenuti F, Stanhope S, Eng V, Taviani A, Nesi B, et al. Adaptive physical activity improves mobility function and quality of life in chronic hemiparesis . *Journal of Rehabilitation Research & Development*. 2008;45(2):323-8.
- xxvii 1. Stuart M, Benvenuti F, Macko R, Taviani A, Segenni L, Mayer F, et al. Community-Based Adaptive Physical Activity Program for Chronic Stroke: Feasibility, Safety, and Efficacy of the Empoli Model. *Neurorehabil Neural Repair* 2009;23(7):726-34.
- xxviii 1. Rimmer J, Rauworth A, Wang E, Nicola T, Hill B. A Preliminary Study to Examine the Effects of Aerobic and Therapeutic (Nonaerobic) Exercise on Cardiorespiratory Fitness and Coronary Risk Reduction in Stroke Survivors. *Arch Phys Med Rehabil* 2009. p. 407-12.
- xxix 1. McLaren A, Kerr S, Allan L, Steen N, Ballard C, Allen J, et al. Autonomic Function Is Impaired in Elderly Stroke Survivors. *Stroke*. 2005;36:1026-30.
- xxx 1. Binder D, Scharfman H. Brain-Derived Neurtrophic Factor Growth Factors. 2004;22(3):123-31.
- xxxi 1. Tapia-Arancibia L, Rage F, Givalois L, Arancibia S. Physiology of BDNF: focus on hypothalamic function. *Frontiers in Neuroendocrinology*. 2004;25(2):77-107.
- xxxii 1. Black E, Smith P, Mclsaac W, Ferguson A. Brain-derived neurotrophic factor acts at neurons of the subfornical organ to influence cardiovascular function. *Physiological Reports* 2018;6(10).

-
- xxxiii 1. Vermehren-Schmaedick A, Jenkins V, Hsieh H, Brown A, Page M, Brooks V, et al. Upregulation of Brain-Derived Neurotrophic Factor expression in nodose ganglia and lower brainstem hypertensive rats J Neurosci Res 2013;91(2):220-9.
- xxxiv 1. Wang H, Zhou X-F. Injection of brain-derived neurotrophic factor in the rostral ventrolateral medulla increases arterial blood pressure in anaesthetized rats. Neuroscience . 2002;112(4):967-75.
- xxxv 1. Golden E, Emiliano A, Maudsley S, Windham B, Carlson O, Egan J, et al. Circulating Brain-Derived Neurotrophic Factor and Indices of Metabolic and Cardiovascular Health: Data from the Baltimore Longitudinal Study of Aging. PLoS One. 2010;5(4).