Title: Long-term effect of participation in an early exercise and education program on clinical outcomes and cost implications, in patients with TIA and minor, non-disabling stroke

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Word count: 2,722 words

This is a post-peer-review, pre-copyedit version of an article published in Translational Stroke Research. The final authenticated version is available online at: https://doi.org/10.1007/s12975-016-0510-6.

Abstract

Background: Participation in exercise and education programs following transient ischemic attack (TIA) or minor stroke may decrease cardiovascular disease risk. **Aims:** The purpose of this study was to assess the long-term effect (3.5y) of an exercise and education program administered soon after TIA or minor stroke diagnosis on clinical outcome measures (stroke classification and number, patient deaths, hospital/emergency department admission) and cost implications obtained from standard hospital records. **Methods:** Hospital records were screened for 60 adults (male, n=31; 71±10y), diagnosed with TIA or non-disabling stroke, who had previously been randomized and completed either an 8-week exercise and education program, or usual care control. Follow-up clinical outcomes and cost implications were obtained 3.5±0.3 years post-exercise. **Results:** Participants randomized to the exercise and education program had significantly fewer recurrent stroke/TIAs (n=3 vs. n=13, Cohen's *d*=0.79) than the control group ($P \leq 0.003$). Similar finding were reported for patient deaths (n=0 vs. n=4, *d*=0.53), and hospital admissions (n=48 vs. n=102, *d*=0.54), although these findings were only approaching statistical significance. The relative risk (mean; 95%CI) of death, stroke/TIAs and hospital admissions were 0.11 (0.01 to 1.98), 0.23 (0.07 to 0.72) and 0.79 (0.57 to 1.09), respectively. Hospital admission costs were significantly lower for the exercise group ($9,041 ± 15,080NZD [~$6,000 ± 10,000USD]) than the control group ($21,750 ± 22,973NZD [~$14,000 ± 15,000USD])) during the follow-up period ($P<.05$; *d*=0.69). **Interpretation:** The present study demonstrates the long-term patient benefit and economic importance of providing secondary prevention, exercise and education programs for patients with TIA and minor stroke. **Clinical Trial Registration:** URL: http://www.anzctr.org.au/; Trial Registration Number:ACTRN12611000630910

Key words: Stroke prevention, transient ischaemic attack, physical activity, hospital admissions, secondary prevention, education

Introduction

Stroke is the second most common cause of death, the primary cause of dependency, creates a huge societal burden and costs billions to the global economy in health and social care costs [1,2]. A transient ischemic attack (TIA) is an ischaemic brain attack with focal cerebral or retinal symptoms that last under 24 hours, usually less than 1 hour [3]. Although patients with minor (non-disabling) stroke differ slightly from those with TIA as signs and symptoms last more than 24 hours, minor stroke patients are assessed and treated similarly to TIA patients to prevent a further disabling stroke, myocardial infarction or death [2,4,5]. Approximately 20–40% of people have a warning TIA or minor ischaemic stroke shortly before they have a major disabling stroke.[2] The risk of stroke after TIA is between 3-10 % at 2 days, and 9-17 % at 90 days [2,6-9], and this is placing an ever increasing burden on health care systems. Longitudinal cohort studies have shown that the risk of cardiovascular events remains high (≤ 44%) 10 years post-TIA or stroke [10,11]. In addition to preventative measures, reducing stroke mortality and long-term disability through evidence-based acute and post-discharge treatments is essential to reverse the trend of increasing human, social and economic burden of this disease [12].

Current guidelines for stroke/TIA recommend multifaceted interventions to aid in preventing recurrent events [13-15]. In this regard, short-term exercise and education programs, administered within 2 weeks of TIA or minor stroke diagnosis, have shown to be beneficial in improving systolic blood pressure (≤ 13 mmHg), diastolic blood pressure (≤ 7 mmHg), and blood lipid profile (~0.5 mmol/L for total cholesterol) [16-18]. Longer-term, there is evidence to suggest that these benefits are maintained up to 12 months post-intervention [17,18]. However, there is a paucity of research investigating long-term clinical outcome measures, such as hospital readmission, surgical intervention and recurrent events [14]. A recent study with patients with non-cardioembolic mild ischemic stroke demonstrated that individuals who engaged in a 6 month exercise training, salt restriction and nutrition advice program experienced fewer recurrent vascular events than those in a control group, over a median period of 2.9 years [18].

Long-term follow-up data on TIA/minor stroke patients are needed to: (i) inform best-practice healthcare guidelines; (ii) identify optimal strategies for reversing the rising economic burden of recurrent events; and (iii) guide further prospective experimental research. Therefore, the purpose of this study was to assess the long-term (3.5 y post TIA/minor stroke) effect of an exercise and education program, employed soon after TIA/minor stroke diagnosis on: i) clinical outcome measures, and ii) the costs associated with inpatient and hospital admissions.

Methods

Participants

This retrospective research study involved 60 patients (male, n = 31; 71 ± 10 y), who had been previously diagnosed with TIA or minor (non-disabling) stroke between February and October 2011, and had been randomized to either an 8 week exercise and education program or to a usual care (pharmacological management) control condition within two weeks of initial diagnosis (see Figure 1 & Supplementary Table) [16,17]. TIA diagnosis was determined by a member of the clinical team, and was based upon criteria from New Zealand's stroke assessment and management guidelines [13]. Clinical diagnosis of TIA was based on an $ABCD^2$ score ≥ 2, while minor stroke was based on the National Institute of Health Stroke Severity Scale (NIHSS) score ≤ 5. A neurologist made a further designation of probable or possible stroke/TIA subtype based on the patient's history, examination, and available imaging and laboratory studies using the TOAST criteria [19].

Participants were eligible to participate in the original randomized controlled trial if they had been diagnosed with their first TIA or minor stroke, if they lived within the local district health board catchment, and if they did not meet exclusion criteria. Exclusion criteria were: unstable cardiac conditions, uncontrolled diabetes mellitus, severe claudication, oxygen dependence, significant dementia, inability to communicate in English or unable to take part in exercise. Participants complied with drug treatment and standardized therapy in accordance with stroke physician recommendations during the period of the intervention. Of the 60 patients recruited to the study, only one participant received intravenous thrombolysis in the form of tissue plasminogen activator (tPA) as a part of their acute treatment.

The trial was approved by New Zealand's Central Regional Health and Disabilities Ethics Committee and registered with the Australian and New Zealand Clinical Trials Registry (Trial Registration Number: ACTRN12611000630910). Written informed consent was obtained prior to participation.

Procedures

The National Health Index number, a unique identifier that is assigned to every person who uses health and disability support services in New Zealand, was used, in December 2014, to access electronic health records for all previously recruited patients. This process was conducted by a Capital and Coast District Health Board (CCDHB) neurologist. Patient data was then coded by a CCDHB employee with no trial involvement to identify the number and type of clinical outcomes that occurred in the CCDHB public hospitals, including both inpatient

and outpatient visits. Clinical outcomes assessed included: stroke classification (major stroke [ischaemic stroke, haemorrhagic stroke], minor stroke, TIA), death, myocardial infarction, unstable angina, vascular surgery (coronary artery bypass graft [CABG], carotid endarterectomy, angiogram), ischaemic heart disease, peripheral vascular disease, congestive heart failure and hospital admissions. The medical records for each clinical outcome were reviewed by a CCDHB neurologist to confirm the diagnosis. A cost analysis was undertaken when a patient was: i) in the emergency department for more than 6 hours, or ii) admitted to the inpatient hospital ward. The cost of each presentation was calculated using the Weighted Inlier Equivalent Separations (WIES) amount, which is a cost unit based on the disease-related group (i.e., stroke disease-related group includes ischaemic stroke, intra-cerebral haemorrhage) and the casemix (complexity of patient illness) used to fund public hospitals in New Zealand.

Statistical analysis

Pearson Chi-squared tests and independent-samples t-tests compared baseline descriptive statistics of exercise and control group participants. Following this, a series of one-way analyses of variance, whereby clinical outcome measures reported at follow-up (e.g., number of strokes, myocardial infarction, hospitalisations) were included as the dependent variable, the group (exercise vs. control) was included as the fixed factor, and potentially pertinent baseline measures (i.e., number of participants with hypertension, high cholesterol, diabetes, heart problems), as presented elsewhere [16], were included as covariates. As the above covariates had no significant bearing on the clinical outcome measures, a series of independent samples *t*-tests were used to compare the number of people who presented at hospital with a clinical outcome measure which was reported during the follow-up period, for each group (exercise vs. control). Levene's test for equality of variance was used to determine whether the assumption of homogeneity of variance had been violated, while a Bonferroni correction factor was used to reduce the risk of Type I error. Cohen's *d* was used to identify the effect size, whereby 0.2, 0.5 and 0.8 represents a small, moderate and large effect [20]. An identical analysis was used to assess the cost implications of patient visits to the hospital during the follow-up period.

The relative risk (RR), standard error of the log relative risk (SE) and 95% confidence interval (CI) were calculated [21]. Although RR does not imply causation, it is a useful measure to demonstrate an intended association between treatment and effect. A RR of 1.0 demonstrates that there is no difference in risk between the treatment (exercise and education) and control groups. A RR < 1 means that the event is less likely to occur in the treatment group than in the control group, while a RR > 1 means that the event is more likely to occur in

the treatment group than in the control group. Lastly, as a marker of clinical significance, the number needed to treat (NNT) was calculated to estimate the number of patients who need to use the new treatment (exercise and education), rather than the standard treatment (usual care control group), to prevent one clinical outcome [22].

Results

As previously demonstrated [16], there were no between-group differences in demographic characteristics, stroke etiology, history of CVD, lifestyle, and medication use at baseline (all $P > .05$; Table 1). Table 2 summarises the number of patients who presented with clinical outcomes within the 3.5 ± 0.3 year follow-up period. During this period of assessment, participants randomised to the exercise and education intervention had significantly fewer recurrent strokes/TIAs, than those in the control group ($P < .05$; Table 2). Moderate to large effect sizes were reported for a number of outcome measures including the prevalence of recurrent strokes/TIAs, deaths, and hospital admissions (Cohen's *d* between 0.53 and 0.80; Table 2, Figure 2). Hospital admission costs were significantly lower for the exercise and education group (n = 18; $9,041 ± 15,080 NZD [~6,000 ± 10,000 USD]) than the control group (n = 23; $21,750 ± 22,973 NZD [~$14,000 ± 15,000 USD]) during the assessment period ($P < .05$; Cohen's $d = 0.69$). As shown in Table 3, the RR for all markers of interest were < 1, demonstrating that adverse events were less likely to occur in those randomized to the exercise and education intervention. In addition, the NNT to ensure a patient benefit was relatively low.

Discussion

This study demonstrated that patients who engaged in an exercise and education program soon after TIA/stroke diagnosis had fewer strokes and/or recurrent TIAs within the follow-up period than those patients who were provided usual care (control) treatment after their initial diagnosis. Furthermore, patients presented at hospital on fewer occasions, and hospital admission costs were, on average, lower for the exercise and education group than the control group during the follow-up period. These findings may be important when considering the long-term patient benefit and decreased economic burden associated with TIA and minor stroke patients engaging in an exercise and education program.

As reported elsewhere [16], two patients in each group (exercise and education vs. control) experienced a recurrent TIA within 8-weeks of being randomized. When considering the longer-term follow-up data, which includes the statistics reported above, of the patients who took part in the exercise and education program, only three patients (10 %) experienced a recurrent stroke or TIA during the 3.5 year follow-up period (Table 2). In

contrast, thirteen (43 %) of the patients who were randomized to the usual care control group presented with a recurrent stroke or TIA. The statistical difference in the prevalence of 'all' strokes in the follow-up period is further supported by the large effect size, the small RR for the treatment (exercise and education) condition and the small number of patients required to demonstrate treatment benefit. When considering the latter, the present study suggests that for every three patients that engage in an exercise and education program rather than usual care, one patient will benefit. Encouraging trends were also evident when assessing the frequency of minor stroke and recurrent TIAs (Table 1 & 2); an interesting finding when considering that previous research has demonstrated high rates of TIA following an initial stroke/TIA episode [8,9]. The findings from the present study are in contrast to a recent meta-analysis which demonstrated no difference in the odds of stroke/TIA re-occurrence when patients engaged in a lifestyle management intervention compared to receiving usual care [14]. The high heterogeneity of the meta-analyses' study sample may offer some reasoning for this difference.

There are a number of reasons as to why those who participated in the exercise program may have a lower risk of reoccurring stroke. Exercise, for example, has been shown to: i) improve functional capacity by increasing aerobic fitness, strength, balance, flexibility and mobility, ii) reduce the risk of cardio- and cerebrovascular disease by reducing blood pressure, and by improving blood lipid profile, glucose regulation, insulin sensitivity and anthropometric profile, and iii) provide psychological benefits through improving quality of life, enabling physical independence and by reducing stress and anxiety [23-26]. Importantly, such physiological and psychological changes may also reduce the risk of other co-morbid conditions such as diabetes, obesity and metabolic syndrome.

The meta-analysis by Lawrence and colleagues [14] has previously shown no significant differences in the odds of death between those partaking in lifestyle management interventions compared to those randomized to a usual care control group. The small number of studies investigated (n = 4), the different lifestyle management interventions employed, and the varying population groups assessed, may be an underpinning reason for this finding. In our study, there does appear to be pragmatic benefit of implementing a secondary prevention exercise and education program soon after initial diagnosis as significantly fewer deaths occurred during the 3.5 year follow-up period (Table 2 and 3). Based on the findings from our study, there is a pressing need for large, multi-site randomized controlled trials, with a significant follow-up period (> 12 months) to ascertain the utility of lifestyle management interventions (i.e., exercise and education) in this population group. Our study emphasises the importance of implementing larger trials as despite the above favourable findings in terms of the prevalence of strokes/TIAs, death and hospitalisations, in total there were slightly more cardiac-

related complications (e.g., myocardial infarction, unstable angina, ischaemic heart disease, peripheral vascular disease, congestive heart failure) for those randomized to the exercise and education group (n = 15) compared to the control group (n = 11).

The present study provides preliminary evidence that early exercise and education engagement could significantly reduce the economic burden associated with recurrent vascular events post-stroke/TIA [2]. This study has shown that the costs associated with hospital admissions were 141% higher in the usual care control group compared to those randomized to the exercise and education program. The difference in cost analysis is strongly associated with the number of hospital admissions during the follow-up period. In this study, 67% of patients in the exercise and education group presented at hospital, of which there were only 48 visits in total over a 3.5 year period. In contrast, 80% (n = 24) of those individuals in the control group presented at hospital, of which there were 102 visits in total (Table 2, Figure 1). The moderate effect size and small number of patients required to demonstrate a treatment benefit (Table 3) provides further support for the implementation of an exercise and education program. When considering the time and cost of consultants, nurses, practitioners and technicians, the cost of imaging and equipment use (CT scans, etc.) and possible medicinal intervention [2], a simple exercise and education intervention employed soon after diagnosis could have significant long-term financial benefit by reducing the number of follow-up hospital admissions.

Although the present study has shown favourable changes in specific clinical outcomes in those who engaged in the exercise and education programme, it is pertinent to recognise the potential limitations of the study. First of all, this is a retrospective study with a small sample size. The original study by Faulkner and colleagues [16] was designed and powered to assess the effect of an 8-week exercise and education program on short-term cardiovascular risk factors (e.g., blood pressure, total blood lipid profile), not long-term clinical outcome measures. Secondly, it is difficult to determine an exact cause and effect, as we did not monitor patients consistently during the follow-up period. For example, physical activity participation, nutrition, sleep and psycho-social markers of health were not assessed during the follow-up period. Also, the relative risk data presented in this paper only describes an intended association between treatment and effect, and not causation. In addition, the research team were unable to ascertain pharmacological management during follow-up. Although previous research has shown no differences in medication at 12 months between an exercise and usual care control group [17], we should not necessarily assume that this is the case at 3.5 years. It is also evident, retrospectively, that clinicians found it challenging to provide a specific stroke etiology for a number of the participants (Table 1).

In conclusion, the present study has demonstrated that those patients who engaged in an exercise and education program soon after initial stroke/TIA diagnosis presented at hospital on fewer occasions, and experienced fewer recurrent strokes/TIAs and death, than those who received usual care over the course of a 3.5 year follow-up period. These findings, in combination with the lower financial implications, are highly pertinent when considering the long-term patient benefit and decreased economic burden associated with TIA and minor stroke patients engaging in an exercise and education program.

Compliance and ethical standards:

Funding: This research study was funded by the Massey University Research Fund.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures were in accordance with the ethical standards of the institutional and national research committee (New Zealand Health and Disabilities Ethics Committee) and with the 1964 Helsinki declaration and its later amendments.

Informed consent: All participants provided written informed consent prior to taking part in the study.

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Table and Figure Legend:

Table 1: Demographic and other characteristics for exercise and control groups

Table 2: Clinical outcomes reported for exercise and control groups following a 3.5 year follow-up period.

Values are reported as number of people or events, and as a percentage of the study sample

Table 3: Relative risk and numbers needed to treat (NNT) for key clinical outcomes reported from Table 1

Figure 1 Participant recruitment

Figure 2: Hospital admissions during a 3.5 year follow-up period

Table 1: Demographic and other characteristics for exercise and control groups

		Exercise		Control		*P* value
		n	%	n	%	
Participants (n)		30	50	30	50	
Age (y)		68 ± 11		69 ± 10		0.370
Gender (n)	**Male**	16	53	15	50	0.501
	Female	14	47	15	50	
Descent (n)	**European**	27	90	26	87	0.490
	Maori	1	3	0	0	
	Pacifica	1	3	2	7	
	Asian	1	3	1	3	
	Indian	0	0	1	3	
Stroke subtype	**Small vessel lacunar**	16	53	18	60	0.848
	Large artery atherosclerosis	3	10	1	3	
	Cardioembolic	3	10	3	10	
	Undetermined	8	27	8	27	
Family history of CVD	**Myocardial infarction**	14	47	16	53	0.904
	Heart surgery	4	13	4	13	1.000
	Stent	1	3	3	10	0.068
	Catheter	0	0	3	10	0.171
	Heart defect	3	10	1	3	0.319
	Stroke	12	40	13	43	1.000
Personal history of CVD	**Hypertension**	18	60	23	77	0.451
	High cholesterol	15	50	19	63	0.644
	Diabetes	4	13	7	23	0.411
	Artery diseases	3	10	4	13	1.000
	Thyroid disease	0	0	1	3	0.567
	Lung disease	2	7	2	7	1.000
	Asthma	6	20	5	17	0.561
	Cancer	5	17	8	27	0.439
	Kidney disease	3	10	2	7	0.673
	Hepatitis	2	7	1	3	0.586
Signs & symptoms of CVD	**Chest pain**	10	33	11	37	1.000
	Dyspnea	18	60	17	57	0.492
	Heart palpitations	10	33	9	30	0.624
	Skipped heart beats	9	30	7	23	0.434
	Heart murmur	2	7	4	13	0.498
	Intermittent leg-pain	9	30	12	40	0.640
	Syncope	17	57	12	40	0.068
	Fatigue	12	40	15	50	0.655
	Snoring	10	33	17	57	0.167
	Back pain	12	40	16	53	0.499
Lifestyle factors	**Current Smoker**	2*	7	3†	10	1.000
	Duration smoking (y)	54 ± 8		35 ± 15		0.213
	Previous Smoker	18	60	17	57	0.492
	Quit duration (y)	28 ± 18		28 ± 12		0.992
	Alcohol consumption	20	66	19	63	0.476
	Current Weight Loss Plan	1	3	2	7	0.675
	Everyday Activity: Sedentary	9	30	6	20	0.745
	Light	11	37	17	57	
	Moderate	7	23	7	23	
	Vigorous	1	3	1	3	
Medication	**Statins**	25	83	25	83	
	Antithrombotic	26	87	23	77	
	ACEI	9	30	14	47	
	Diuretics	8	27	11	37	
	Calcium blockers	9	30	7	23	
	Beta blockers	7	23	5	17	
	Anticoagulants	2	7	4	13	
	Other Anti-hypertensives	2	7	1	3	
	Mean medication use	2.87 ± 1.07		2.85 ± 1.01		0.887

Pack years; * Current smokers who smoke between 0.5 and 1.0 pack per day

† Current smokers who smoke < 0.5 packs per day

Table 2: Clinical outcomes reported for exercise and control groups following a 3.5 year follow-up period. Values are reported as number of people or events, and as a percentage of the study sample

			Exercise			Control			t	P	ES
			People (n)	%	Total events (n)	People (n)	%	Total events (n)			
Stroke diagnosis	**Major stroke**	**Ischaemic stroke**	0	0	0	0	0	0	-1.439	0.155	3.72
		ICH	0	0	0	2	7	2			
	Minor stroke		1	3	1	5	17	6	-1.764	0.083	0.45
	TIA		2	7	5	6	20	10	1.828	0.074	0.45
	Total (major stroke, minor stroke, TIA)		3^	10	6	13[#]	43	18	-3.099	0.003*	0.80
MI			2	7	2	1	3	1	0.557	0.581	1.38
Unstable Angina			1	3	1	1	3	1	0.000	1.000	0.00
Death			0	0	0	4	13	4	-2.112	0.043[#]	0.53
CEA			4	13	4	1	3	1	1.401	0.167	1.64
Revascularisation			1	3	1	1	3	1	0.000	1.000	0.00
Angiogram			3	10	3	2	7	2	0.460	0.647	0.11
CABG			1	3	1	1	3	1	0.000	1.000	0.00
IHD			7	23		8	27		-0.293	0.770	0.09
PVD			2	7		1	3		0.584	0.561	014
CHF			3	10		0	0		1.795	0.083	0.46
Hospital admissions†			20	67	48	24	80	104	-2.098	0.041[#]	0.54

Abbreviations: CABG, Coronary artery bypass graft; CEA, Carotid endarterectomy; CHF, Congestive heart failure; ICH, Intra-cerebral haemorrhage; IHD, Ischaemic heart disease; MI, Myocardial infarction; PVD, Peripheral vascular disease; TIA, Transient Ischaemic Attack

N.B. *Significant difference between groups ($P \leq 0.003$); ^ Of the three patients in the exercise group who experienced a stroke or TIA, only one of these patients experienced multiple events. [#]Of the thirteen control group patients who experienced a stroke or TIA, two patients experienced multiple events.† ED admissions are analysed in relation to the total number of events.

[#]Approaching a significant difference between groups ($P < .05$)

Table 3: Relative risk and numbers needed to treat (NNT) for key clinical outcomes reported from Table 1

		Relative risk	95%CI	NNT (n)
Stroke diagnosis	**Major stroke (ischaemic stroke, ICH)**	0.20	0.01 to 3.99	16
	Minor stroke	0.20	0.02 to 1.61	8
	TIA	0.33	0.07 to 1.52	8
	Total (major stroke, minor stroke, TIA)	0.23	0.07 to 0.72	3
Death		0.11	0.01 to 1.98	8
Hospital admissions		0.79	0.57 to 1.09	6

Abbreviations: CI, Confidence interval; ICH, Intra-cerebral haemorrhage; NNT, Numbers needed to treat; TIA, Transient Ischaemic Attack