Research Article

Can Cardiovascular Risk Management be improved by Shared Care with General Practice to Prevent Cognitive Decline Following Stroke/TIA? A feasibility randomised controlled Trial (SERVED Memory)

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Abstract

Background

Cognitive impairment and dementia following cerebrovascular disease are increasingly common in the UK. One potential strategy to prevent post-stroke cognitive decline is multimodal vascular risk factor management. However, its efficacy remains uncertain and its application in vulnerable patients with incident cerebrovascular disease and early cognitive impairment has not been assessed.

The primary aim of this study was to assess the feasibility of recruitment and retention of patients with early cognitive impairment post-stroke or transient ischaemic attack (TIA) to a trial of enhanced vascular risk factor management combining primary and secondary care.

Methods

In this single centre, open label trial adults with a recent stroke or TIA and mild cognitive impairment (MCI) were randomised 1:1 to a three-monthly multimodal vascular risk factor intervention jointly delivered by the trial team and General Practitioner (GP), or control (defined as usual care from the GP). Chosen risk factors were blood pressure (BP), total cholesterol, blood glucose (HbA1C) in those with diabetes, and heart rate and adequacy of anticoagulation in those with atrial fibrillation (AF). Similar patients with normal cognition

were enrolled in an embedded observational cohort and also received usual care from the GP. All participants underwent repeat cognitive screening after 12 months.

Results

Seventy three participants were recruited to the randomised trial and 94 to the observational cohort (21.8% of those screened). From the randomised trial 35/73 (47.9%) dropped out before final follow-up. In all groups guideline based rates of risk factor control were mostly poor at baseline and did not significantly improve. The observational cohort demonstrated greater decline in cognitive test scores at 12 months, with no difference between the randomised groups.

Conclusions

Recruitment to such a study was feasible, but retention of participants was difficult and rates of risk factor control did not improve with the intervention. Consequently, successful scaling up of the trial would require protocol changes to improve participant retention, perhaps with less reliance on primary care services. Any future trial should include participants with normal cognition post-stroke as they may be at greatest risk of cognitive decline.

Trial Registration

ISRCTN, ISRCTN42688361. Registered 16 April 2015, https://www.isrctn.com/ISRCTN42688361

Keywords: cognitive impairment, dementia after stroke, vascular dementia, stroke, cerebrovascular disease.

Background

Dementia is a significant and increasing health problem in the UK, yet disease modifying treatments are lacking [1], therefore strategies to prevent cognitive decline are desirable. Given that cognitive impairment may affect up to 40% of patients following stroke and TIA [2-4], such strategies may be particularly valuable in this patient group. One potential strategy is multimodal vascular risk factor control as these risk factors contribute to recurrent stroke as well as both vascular dementia (VaD) and Alzheimer's disease [5-7], and their presence also increases the risk of early cognitive decline progressing to dementia [8]. Evidence supports the value of good BP control for reducing the risk of subsequent severe cognitive impairment post-stroke, yet there remains uncertainty about the value of targeting other vascular risk factors that are relevant to secondary stroke recurrence, especially as part of a multimodal risk factor approach [5, 9, 10]. Furthermore, whether targeting such a strategy at patients who already have MCI post-stroke in order to prevent further cognitive deterioration has not been studied [11-13].

SERVED Memory (Screening and Enhanced Risk factor management to prevent Vascular Event related Decline in Memory) was developed to investigate the feasibility of recruiting patients with MCI post-stroke or TIA to a pragmatic intervention trial of enhanced vascular risk factor management. It was hypothesised that enhanced risk factor management with a "treat to target" approach, delivered by a combination of the patient's GP and a trial team, would be safe and effective, potentially reducing the risk of progression of MCI compared to standard GP management alone. The trial also incorporated an embedded non-randomised observational cohort with the aim of providing epidemiological data regarding the natural history of cognitive impairment post-stroke or TIA.

Methods

SERVED Memory was a single-centre, open-label parallel group randomised controlled feasibility trial, with embedded non-randomised observational cohort. The trial was granted ethical approval and was prospectively registered (ISRCTN 42688361). The full trial protocol has previously been published [14].

In brief, participants were recruited from stroke services at the Norfolk and Norwich University Hospital (NNUH). Adults with a mild stroke or TIA within the last eight weeks and Montreal Cognitive Assessment (MoCA) score ≥26 were eligible for the observational cohort, and those with a MoCA score consistent with MCI (i.e. 20-25 [11, 12]) were eligible for the randomised controlled trial (RCT). Patients with life expectancy <1 year, diagnosed depression, or MoCA score <20 were excluded. The MoCA has been validated as a screening tool and for assessing change in cognition over time in patients with stroke, and has been shown to be more sensitive than other brief cognitive tests (e.g. Mini Mental State Examination) in assessing MCI [13, 15, 16]. All participants provided written informed consent. RCT participants were randomised 1:1 by computer generated randomisation table, with block size of four, to an intervention or control group. Baseline recording of demographic data, medication use and compliance, and vascular risk factors was completed. Measured risk factors were clinic BP, total cholesterol, blood glucose HbA1c in those with diabetes, and heart rate and anticoagulation adequacy for those with AF. Targets were ideal BP <130/80mmHg and standard <140/90mmHg [17, 18]; total cholesterol <4.0mmol/L (non-fasting); HbA1C 48-53mmol/mol; heart rate 60-80 beats per minute for those in AF. Adequate anticoagulation was defined as taking warfarin with INR 2.5-3.0, or a direct oral anticoagulant, unless contraindicated. Observation and control participants received usual

care from their GP only. Intervention participants were seen in hospital by the trial team at three, six, and nine months post-randomisation for risk factor assessment. Results were passed immediately to the GP for action by phone and letter with the trial team only making treatment alterations when necessary for patient safety. All participants were followed up at 12 months for assessment of risk factors, medication adherence, adverse events and repeat MoCA. Baseline frailty was retrospectively assessed from clinical notes using the Rockwood Frailty Score by a stroke physician blinded to group allocation.

The primary outcome was the assessment of rates of recruitment and retention at 12 months from screening and management logs. Secondary outcomes were (i) rates of risk factor control to the specified targets in each group (ii) differences in the change in MoCA score between the intervention and control groups, (iii) change in MoCA score in the observational arm, and (iv) rates of adverse events (including recurrent stroke) in each group.

A convenience sample size was based on estimates of the prevalence of cognitive impairment in patients with incident stroke/TIA [4], the incidence of dementia post-stroke [19], and estimated cognitive screening rates at NNUH [4]. Based on these estimates target numbers were 100 in the RCT (50 per group) and 100 in the observational cohort.

Statistical Analysis

Data were analysed using SPSS (version 25.0) with descriptive statistics only unless specified. Baseline demographics between the randomised groups were compared using independent samples t test (for normally distributed continuous variables), independent samples median test (for non-normally distributed continuous variables), or Chi-square test (for categorical

variables). Screening logs were assessed to determine the proportion of eligible participants who consented to participate in the trial, including the proportion that would have been eligible for the RCT. Management logs were assessed for retention rates in each trial arm and, where possible, reasons for attrition were identified. Proportions of participants with controlled risk factors in each group were calculated at baseline and follow-up along with the frequency of medication changes that occurred during the trial. Changes in MoCA score from baseline to follow-up for each arm were assessed using a paired samples t test, with further testing of any difference between the intervention and control arms. A general linear model, with a normal error term, was used to estimate the effect of the intervention, with a 95% confidence interval, on the 12 month MoCA values. The model included randomisation group (intervention or control), sex, diagnosis (stroke or TIA) and baseline MoCA value. Differences in rates of vascular risk factor control between randomised goups at 12 months were assessed with a Chi-square test. Post-hoc analysis of the difference in baseline frailty score in retained vs. not retained participants was assessed with a Mann-Whitney U test.

Results

Trial recruitment ran from November 2015 to July 2017, with final follow-up completed 12 months later. Seven hundred and sixty-seven patients were screened, with 167 (21.8%) providing consent to participate (**Figure 1**). Ninety-four participants were included in the observational cohort and 73 were allocated to the RCT, 37 being randomised to intervention and 36 to control. Of the remainder screened 362 (47.2%) patients were ineligible and 238 (31.0%) were eligible but declined to participate. Of those declining to participate 18/238 (7.6%) had a MoCA score ≥26, 50/238 (21.0%) had a MoCA score between 20-25, and

170/238 (71.4%) had not completed cognitive testing at the time of screening. Demographic details are presented in **Table 1**. There were no significant differences between the randomised groups.

Over the course of the trial 35/73 (47.9%) randomised participants did not complete follow-up, 14/36 (38.9%) from the control group and 21/37 (56.8%) from the intervention group. Withdrawals accounted for 25/35 (71.4%) of participants not completing the trial and 10/35 (28.6%) were lost to follow-up (i.e. did not respond to telephone calls or written requests to arrange follow-up visits). The trial team took the decision to withdraw six participants before completion (three died and three were hospitalised for significant health issues). The other 19 participants withdrew of their own volition. Participants were not required to provide a reason for dropping out, and 7/19 (36.8%) did not wish to further explain their decision. However, 6/19 (31.6%) reported that their health had deteriorated such that they no longer wanted to volunteer their time and 6/19 (31.6%) withdrew because they did not wish to travel to the hospital for follow-up visits (despite the offer of reimbursement for costs or taxi services).

Average MoCA scores declined significantly in the observation cohort (-1.7 points [95%CI -2.3 to -1.1, $p<0.0001$]), but not in the intervention (-0.6 points [95%CI -2.3 to 1.1, $p=0.45$]) or control groups (-0.5 points [95%CI -2.1 to 1.1, $p=0.45$]). From the general linear model to estimate the effect of the intervention the mean 12 month MoCA for the Intervention group was 0.664 units lower than for Control, with 95% confidence interval for the difference (intervention minus control) being -2.69 to 1.37. Baseline rates of control for all risk factors were low across all trial groups, irrespective of BP threshold value (**Tables 2 and 3**). There were improvements in the rates of control for cholesterol and adequate anticoagulation in

all trial groups at 12 months, however, BP control rates had declined and no changes were seen in relation to heart rate and HbA1C (**Table 4**). The proportions of participants on treatment for the selected risk factors were largely unaltered after 12 months, with the exception of increases in statin use and the prescription of anticoagulants. Rates of adverse events and recurrent stroke were similar between the randomised groups (**Table 5**). Median baseline frailty scores were lower in those who completed the trial compared to those who did not (median 4.0 [IQR 3.0, 6.0] and 5.0 [IQR 4.0, 6.0] respectively, p=0.05).

Discussion

At present it is unclear whether control of multiple vascular risk factors can prevent further cognitive decline in vulnerable patients with a recent cerebrovascular event [5, 9, 20]. Firstly, trials of antihypertensive therapy to prevent cognitive decline have been inconsistent, possibly limited by high rates of treatment in placebo groups, poor participant retention, and short follow-up [5]. However, a large trial in patients with stroke suggested a benefit to treatment, with this finding corroborated by subsequent meta-analysis [5, 9, 10]. Secondly, two randomised controlled trials have assessed the use of statins and found no benefit on cognition despite reduction in cholesterol levels [21]. Thirdly, in the ADVANCE study intensive blood glucose control in type 2 diabetics successfully reduced microvascular complications, but did not reduce rates of dementia [5]. However, given that recurrent stroke is an important factor in the development of post-stroke dementia [2], it remains plausible that multimodal vascular risk factor intervention in this patient group is valuable, with a recent review concluding that such interventions are effective at preventing dementia in the general population [22].

SERVED Memory aimed to test the feasibility of conducting such multimodal, guideline based, risk factor management in a pragmatic trial combining primary and secondary care input. We demonstrated a recruitment rate of >20% of patients screened, suggesting that recruitment of patients with MCI associated with cerebrovascular disease to such a trial is possible. Although short of the recruitment target, the numbers entering the trial support its feasibility, especially given the proportion of patients with a MoCA score 20-25, or unknown at the point of screening, who declined to participate. However, nearly half of participants in the RCT arms did not complete follow-up, with this retention difficulty being partly related to frailty status. Alterations to the protocol may alleviate these difficulties, for example carrying out trial visits in the patients' homes, using online assessments, or treatment changes being made directly by the trial team rather than relaying information to the GP. Such supported self-management strategies are deliverable in this patient population as evidenced by the TEST-BP trial [23], but these changes would inevitably increase the complexity and cost of conducting the trial. With regard to reducing the intervention's reliance on primary care, the data suggests that the increased risk factor monitoring provided by the intervention may not have translated into enhancements in treatment. This may be due to a degree of treatment inertia, but may also relate to additional factors not captured by our data, for example patient choice, treatment side effects, or a more pragmatic approach to treatment in individuals with frailty. Although this trial was supported by a GP applicant, more involvement of primary care in future trial design would be valuable to explore how the intervention as envisaged could be improved.

In terms of the secondary objective of assessing the effect of the intervention we did not show a between-group difference in change in MoCA score over 12 months. Interestingly a greater decline in cognitive scores was seen in the observational cohort. These findings are

in keeping with the results of two similar trials in patients with recent stroke but no evidence of early cognitive decline or MCI. Firstly, Ihle-Hansen et al. (N=195) demonstrated no difference in incident cognitive impairment or dementia at 12 months with a multimodal intervention (including treatment of BP, cholesterol, AF, and diabetes, and cardiovascular lifestyle advice) delivered at three and six months post-randomisation compared to usual GP care [24]. Secondly, Matz et al. (N=202) reported no significant difference in cognitive test scores at 24 months between those treated with a multimodal vascular risk factor intervention (including BP treatment, cardiovascular lifestyle advice, and cognitive training) and usual care [25]. Conversely, the FINGER trial recruited a population of older adults with cardiovascular risk factors (but only 5% with prior stroke) and randomised them to a multimodal intervention (including vascular risk factor monitoring similar to this trial) or usual care. Over a two year follow-up period there was significantly less cognitive decline in the intervention group [26, 27]. Similarly, another primary care based trial of a multimodal intervention aimed at treating cardiovascular risk factors, compared to usual care, demonstrated both improvements in treatment of the relevant risk factors and a reduction in the need for long-term institutional care with the intervention [28]. Given these positive trials, and the small sample sizes and short follow-up duration of existing studies of multimodal vascular risk factor intervention in stroke patients, further trials may be warranted.

The main strength of this trial is the enrolment of patients with early cognitive decline, who are at increased risk of developing dementia, and in whom this preventive strategy has not previously been assessed. A further strength is the use of a pragmatic real-world design, although this also served to highlight challenges in the optimisation of care for secondary stroke prevention that would need addressing in any future trial. An important limitation is

that we did not consult GP's directly as to why treatment targets were not being met, but it may reflect ongoing debate about the most appropriate risk factor targets (especially in older patients) [6, 7, 29], or excessive demands from the existing primary care workload. It is therefore difficult to know whether the lack of impact of the intervention on vascular risk factor control was related to deficiencies in the intervention itself, or was related to other important trial limitations such as small sample size, short duration of follow-up, or the high dropout rate. This is potentially a missed opportunity to glean information that could have helped to improve the intervention in any future trial. The assessment of the secondary trial objectives was also limited by the small sample size and participant dropout. Furthermore, due to the lack of ethnic diversity in the trial population any findings may lack generalisability.

Conclusions

Although the current protocol would not be feasible to deliver a definitive multi-centre trial due to difficulties with participant retention and application of the intervention, a successful further trial may be possible with protocol alterations as discussed. In addition, the findings of the epidemiological observation cohort suggest that such a trial should include patients with normal cognition and MCI following their cerebrovascular event, as all are at risk of further cognitive decline.

List of Abbreviations

TIA	Transient ischaemic attack

MCI	Mild cognitive impairment
GP	General Practitioner
BP	Blood pressure
AF	Atrial fibrillation
VaD	Vascular dementia
NNUH	Norfolk and Norwich University Hospital
MoCA	Montreal Cognitive Assessment
RCT	Randomised controlled trial

Declarations

Statement of ethics: This study was conducted in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects. Ethical approval for the trial was granted by the East of England Cambridge East Research Ethics Committee (ref: 15/EE/0061). All participants provided written informed consent for their involvement.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Author Contributions: PKM, JFP, YKL, CF, DT and LS were involved in the original conception and design of the study. Data acquisition was conducted by GR and WJD under the oversight of PKM and JFP. WJD and LS conducted the statistical analysis for the study. WJD drafted the initial manuscript which has been revised with input from all other listed authors. The final manuscript has been reviewed by all authors and approved for submission/publication.

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Figures and Tables

Figure 1: CONSORT flow diagram

Table 1: Demographic data for each group at baseline.

		Observation	Control	Intervention	P value
N		94	36	37	
Symptom onset to randomisation (days)		25.7 (20.1)	22.6 (20.9)	17.8 (19.7)	0.42
Age (years)		72.1 (10.9)	74.9 (9.2)	75.0 (12.0)	0.97
Gender (male)		59 (62.8%)	23 (63.9%)	27 (73.0%)	0.40
Ethnicity (White British)		94 (100.0%)	36 (100.0%)	37 (100.0%)	-
Smoking status	**Non-smoker**	38 (40.4%)	17 (47.2%)	26 (70.3%)	0.07
	Ex-smoker	29 (30.9%)	14 (38.9%)	10 (27.0%)	
	Current smoker	6 (6.4%)	5 (13.9%)	1 (2.7%)	
Alcohol (units/wk)		0.0 (0.0, 15.8)	3.0 (0.0, 20.0)	2.0 (0.0, 9.0)	0.73
Diagnosis	**TIA**	40 (42.6%)	11 (30.6%)	10 (27.0%)	0.74
	Stroke	54 (57.4%)	25 (69.4%)	27 (73.0%)	
OCSP classification	**LACS**	27 (50.0%)	9 (36.0%)	11 (40.7%)	0.67
	PACS	13 (24.1%)	13 (52.0%)	11 (40.7%)	
	TACS	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	POCS	14 (25.9%)	3 (12.0%)	5 (18.5)	
Past medical history	**AF**	25 (26.6%)	6 (16.7%)	10 (27.0%)	0.29
	Diabetes	19 (20.2%)	7 (19.4%)	5 (13.5%)	0.49
	IHD	11 (11.7%)	4 (11.1%)	6 (16.2%)	0.53
	Stroke	44 (46.8%)	12 (33.3%)	21 (56.8%)	0.05
	TIA	36 (38.3%)	6 (16.7%)	7 (18.9%)	0.80
	Hypertension	53 (56.4%)	20 (55.6%)	25 (67.6%)	0.29
Rockwood Frailty Score		4.0 (3.0, 6.0)	5.0 (4.0, 6.0)	6.0 (4.5, 6.0)	0.33
MoCA		27.4 (1.4)	23.4 (1.4)	23.2 (1.5)	0.61
Clinic BP	**Systolic**	147.3 (20.5)	148.1 (21.0)	145.2 (19.5)	0.54

(mmHg)	**Diastolic**	79.6 (10.5)	78.9 (11.5)	81.8 (12.5)	0.30
Total Cholesterol (mmol/L)		4.9 (1.2)	4.9 (1.2)	4.6 (1.4)	0.34
Heart rate (beats per min)†		76.6 (18.9)	75.9 (16.8)	80.4 (10.2)	0.98
On anticoagulation†		10/25 (40.0%)	3/6 (50.0%)	3/10 (30.0%)	0.42
HbA1C (mmol/mol)‡		52.5 (47.3, 69.5)	49.5 (43.0, 82.3)	73.0 (51.8, 106.3)	0.89

Data presented are mean (SD), median (IQR), or frequency (%). P values represent hypothesis testing for differences between the randomised groups (control vs. intervention).

†Only those with AF

‡Only those with diabetes

Table 2: Rates of control for secondary prevention measures by study group.

	Observation (N=71)		**Control (N=22)**		**Intervention (N=16)**		**P value**
	Baseline	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**	
Antiplatelet use	50/71 (70.4%)	51/71 (71.8%)	17/22 (77.3%)	15/22 (68.2%)	10/16 (62.5%)	10/16 (62.5%)	0.72
Systolic BP (mmHg)	147.8 (21.2)	152.1 (18.1)	148.3 (20.3)	152.4 (23.3)	143.7 (14.2)	156.1 (19.4)	
Diastolic BP (mmHg)	80.3 (10.4)	84.5 (10.9)	80.2 (10.8)	81.1 (14.3)	82.7 (10.0)	88.9 (12.5)	
BP <130/80mmHg	7/71 (9.9%)	2/71 (2.8%)	2/22 (9.1%)	1/22 (4.5%)	2/16 (12.5%)	0/16 (0.0%)	0.39
BP <140/90mmHg	24/71 (33.8%)	19/71 (26.8%)	7/22 (31.8%)	5/22 (22.7%)	6/16 (37.5%)	2/16 (12.5%)	0.42
Total Cholesterol (mmol/L)	4.9 (1.1)	4.4 (1.0)	4.9 (1.0)	4.3 (1.0)	4.1 (0.8)	3.9 (1.0)	
Total Cholesterol <4.0mmol/L	16/71 (22.5%)	28/71 (39.4%)	4/22 (18.2%)	10/22 (45.5%)	8/16 (50.0%)	10/16 (62.5%)	0.30
Heart rate (beats per min)[1,]	75.7 (12.1)	74.5 (12.3)	68.4 (13.8)	72.3 (18.9)	78.3 (5.5)	71.1 (10.5)	
HR 60-80bpm[1]	10/21 (47.6%)	12/23 (52.2%)	2/3 (66.7%)	2/6 (33.3%)	3/5 (60.0%)	5/7 (71.4%)	0.72
Adequate anticoagulation[1,2]	8/21 (38.1%)	18/23 (78.3%)	3/3 (100.0%)	5/6 (83.3%)	1/5 (20.0%)	6/7 (85.7%)	1.00
HbA1C mmol/mol[3]	51.0 (44.3, 64.3)	49.0 (44.0, 69.3)	80.0 (-)	66.0 (-)	53.5 (-)	62.0 (-)	

HbA1C 48-53mmol/mol[3]	5/15 (33.3%)	4/17 (23.5%)	0/3 (0.0%)	0/3 (0.0%)	1/2 (50.0%)	1/3 (33.3%)	0.18

Average values and rates of control for secondary vascular prevention measures at baseline and 12 months by study group (restricted to participants who completed follow-up). Data presented are mean (SD), median (IQR), or frequency (%). P values represent testing for differences in rates of control at 12 months between the randomised groups (control vs. intervention).

[1]Only those with AF

[2]INR 2.5-3.0 or on a DOAC

[3]Only those with diabetes

Table 3: Rates of secondary prevention control at baseline in all participants.

	Observation (N=94)	**Control (N=36)**	**Intervention (N=37)**
Antiplatelet use	68/94 (72.3%)	27/36 (75.0%)	24/37 (64.9%)
Systolic BP (mmHg)	147.3 (20.5)	148.1 (21.0)	145.2 (19.5)
Diastolic BP (mmHg)	79.6 (10.5)	78.9 (11.5)	81.8 (12.5)
BP <130/80mmHg	10/94 (10.6%)	6/36 (16.7%)	6/37 (16.2%)
BP <140/90mmHg	35/94 (37.2%)	12/36 (33.3%)	15/37 (40.5%)
Total Cholesterol (mmol/L)	4.9 (1.2)	4.9 (1.2)	4.6 (1.4)
Total Cholesterol <4.0mmol/L	22/94 (23.4%)	7/36 (19.4%)	14/37 (37.8%)
Heart rate (beats per min)[1,]	76.6 (18.9)	75.9 (16.8)	80.4 (10.2)
HR 60-80bpm[1]	11/25 (44.0%)	3/6 (50.0%)	5/10 (50.0%)
Adequate anticoagulation[1,2]	10/25 (40.0%)	3/6 (50.0%)	3/10 (30.0%)
HbA1C mmol/mol[3]	52.5 (47.3, 69.5)	49.5 (43.0, 82.3)	73.0 (51.8, 106.3)
HbA1C 48-53mmol/mol[3]	6/19 (31.6%)	1/7 (14.3%)	1/5 (20.0%)

Average values and rates of control for secondary vascular prevention measures at baseline by study group (all participants). Data presented are mean (SD), median (IQR), or frequency (%).

[1]Only those with AF

[2]INR 2.5-3.0 or on a DOAC

[3]Only those with diabetes

Table 4: Rates of vascular risk factor treatment at baseline and 12 months.

		Observation (N=71)		Control (N=22)		Intervention (N=16)	
		Baseline	12 months	Baseline	12 months	Baseline	12 months
Antihypertensive medication (at least one agent)	Proportion treated	46/71 (64.8%)	50/71 (70.4%)	14/22 (63.6%)	16/22 (72.7%)	12/16 (75.0%)	14/16 (87.5%)
	Treatment increased	-	12/71 (16.9%)	-	8/22 (36.4%)	-	6/16 (37.5%)
	Treatment decreased	-	12/71 (16.9%)	-	1/22 (4.5%)	-	2/16 (12.5%)
	Treatment unchanged	-	47/71 (66.2%)	-	13/22 (59.1%)	-	8/16 (50.0%)
Statin or other lipid lowering medication	Proportion treated	52/71 (73.2%)	56/71 (78.9%)	20/22 (90.9%)	20/22 (90.9%)	9/16 (56.3%)	10/16 (62.5%)
	Treatment increased	-	14/71 (19.7%)	-	2/22 (9.1%)	-	3/16 (18.7%)
	Treatment decreased	-	7/71 (9.9%)	-	2/22 (9.1%)	-	4/16 (25.0%)
	Treatment unchanged	-	50/71 (70.4%)	-	18/22 (81.8%)	-	9/16 (56.3%)
Rate lowering medication (e.g. beta blocker)	Proportion treated	10/21 (47.6%)	11/23 (47.8%)	0/3 (0.0%)	4/6 (66.7%)	3/5 (60.0%)	5/7 (71.4%)
	Treatment increased	-	0/23 (0.0%)	-	4/6 (66.6%)	-	3/7 (42.9%)
	Treatment decreased	-	2/23 (8.7%)	-	0/6 (0.0%)	-	0/7 (0.0%)
	Treatment unchanged	-	21/23 (91.3%)	-	2/6 (33.4%)	-	4/7 (57.1%)
Warfarin or direct oral anticoagulant	Proportion treated	13/21 (61.9%)	19/23 (82.6%)	3/3 (100.0%)	5/6 (83.3%)	3/5 (60.0%)	6/7 (85.7%)
	Treatment increased	-	8/23 (34.8%)	-	2/6 (33.4%)	-	3/7 (42.9%)
	Treatment decreased	-	2/23 (8.7%)	-	0/6 (0.0%)	-	1/7 (14.2%)
	Treatment unchanged	-	13/23 (56.5%)	-	4/6 (66.6%)	-	3/7 (42.9%)
Oral diabetic medications or insulin	Proportion treated	8/15 (53.3%)	8/17 (47.1%)	2/3 (66.7%)	2/3 (66.7%)	2/2 (100.0%)	3/3 (100.0%)
	Treatment increased	-	0/17 (0.0%)	-	0/3 (0.0%)	-	1/3 (33.4%)
	Treatment decreased	-	0/17 (0.0%)	-	0/3 (0.0%)	-	0/3 (0.0%)
	Treatment unchanged	-	17/17 (100.0%)	-	3/3 (100.0%)	-	2/3 (66.6%)

Rates of vascular risk factor treatment at baseline and 12 months by study group and changes during the trial (restricted to participants who completed follow-up). Data presented are frequency (%).

411

412 **Table 5:** Adverse events.

	Observation	Control	Intervention
Serious adverse events	36	25	24
Deaths	3	1	2
Recurrent stroke/TIA events	7	2	5
Withdrawals due to ill health (other than recurrent stroke/TIA)	2	2	0

413 Rates of serious adverse events, including deaths and recurrent stroke events, by study
414 group.