

# Long-term effects on survival after a 1-year multifactorial vascular risk factor intervention after stroke or TIA: secondary analysis of a randomized controlled trial, a 7-year follow-up study

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**Background:** Stroke and coronary heart disease share the same risk factors, and a multifactorial intervention after stroke may potentially result in the same reduction in cardiovascular mortality as seen after coronary events. We aimed to evaluate the effect on survival 7 years after a 1-year multifactorial risk factor intervention, and identify clinical predictors for long-term survival in a hospital-based cohort of patients with first-ever stroke or transient ischemic attack (TIA).

**Materials and methods:** We performed a secondary analysis of a randomized controlled trial including patients between February 2007 and July 2008 comparing an intensive risk factor intervention vs usual care the first year poststroke to prevent cognitive impairment. From February 2014 to July 2016, all patients were invited to a follow-up. For patients dying throughout the follow-up period, date of death was obtained from the medical record. Examination at baseline and 1-year follow-up included extensive assessment of vascular risk factors and cognitive assessments.

**Results:** A total of 195 patients were randomized. Mean (SD) age was 71.6 (12.5) years, 53.3% were male, mean (SD) body mass index (BMI) was 25.6 (4.1) kg/m<sup>2</sup>. During follow-up, 35 patients in the intervention group and 41 in the control group died. Kaplan–Meier survival estimates show no significant difference in intention-to-treat (ITT) population or complete case (CC) population (log-rank  $P=0.29$  vs log-rank  $P=0.07$ ). In multivariable Cox proportional hazards regression analyses, lower age and higher BMI was independently associated with long-term survival, adjusted HR (95% CI) 1.08 (1.05–1.11) per year and 0.91 (0.85–0.97) per kg/m<sup>2</sup>.

**Conclusion:** In this post hoc analysis, we found no significant effect on survival after 7 years of a multifactorial risk factor program given during the first year after first-ever stroke or TIA. Higher BMI was an independent predictor for long-term survival in this cohort.

**Keywords:** RCT, stroke, cardiovascular risk, risk factor management, secondary prevention

## Introduction

Stroke remains one of the leading causes of disability and death worldwide,<sup>1</sup> despite a decrease in stroke mortality in the last decades. The substantial long-term risk for recurrent stroke might justify prolonged management strategies for stroke survivors.<sup>2</sup>

After a coronary event, participation in a cardiac rehabilitation program reduces total and cardiovascular mortality, as well as hospital readmissions.<sup>3</sup> Successful programs involve a multifactorial risk-reduction regimen including exercise. In contrast, stroke survivors have limited lifestyle support.<sup>4</sup> Since stroke and coronary heart disease

share many risk factors, a multifactorial intervention after stroke may potentially have beneficial effects on mortality.<sup>5</sup>

In the CAST study (Cognition After Stroke), 227 patients with first-ever stroke or transient ischemic attack (TIA) were randomized to a multifactorial intervention program aimed to preserve cognition. At 1 year poststroke, there were no statistically significant differences between the groups on cognition, but the intervention was associated with a reduction in anxiety and depression.<sup>6</sup> More patients in the intervention group reached the targets for blood pressure and lipid values.<sup>7</sup>

Long-term follow-up of intervention studies poststroke are important. The aim of this follow-up and post hoc analysis was to evaluate the effect on survival after 7 years of the 1-year multifactorial risk factor intervention, and to identify clinical predictors for long-term survival in this hospital-based cohort of stroke survivors.

## Materials and methods

### Trial design and randomization

CAST was a randomized, evaluator-blinded, controlled trial with two parallel groups. Patients with stroke (ischemic stroke or intracerebral hemorrhage) or TIA were randomized to intensive risk factor intervention in the outpatient clinic or standard care in the primary healthcare service. Patients in the intervention group were invited to follow-up at 3 and 6 months, for targeted and individualized multifactorial vascular risk factor management. Details of the intervention and the short-term results have previously been reported,<sup>7</sup> with cognition as the primary endpoint, measured by the trail making test A (TMT-A)<sup>8</sup> and the 10-word test from the Repeatable Battery for the Assessment of Neuropsychological Status.<sup>9</sup> Anxiety and depression as secondary outcomes assessed with Hospital Anxiety and Depression Scale<sup>10</sup> at 12 months and has previously been reported.<sup>6,7</sup>

### Participants

All patients with a first-ever stroke or TIA, without known cognitive impairment, defined by a score <3.7 on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),<sup>11</sup> admitted to the stroke unit of Baerum Hospital between February 2007 and July 2008, were invited to participate in the study. Patients with a life expectancy of more than 1 year and able to perform cognitive assessments were randomized following the acute phase (day 7–10). From February 2014 to July 2016, surviving participants were invited to a follow-up. For patients who died during follow-up, the date of death was obtained from the patients' medical record

and all-cause mortality was assessed through data from the Norwegian Causes of Death Register. Since this is a follow-up study, power calculation was based on the primary aim of the initial study.<sup>7</sup>

### Assessments

At baseline, recorded vascular risk factors included treated hypertension prestroke, hyperlipidemia (total cholesterol >5.0 mmol/L, low-density lipoprotein [LDL]-cholesterol >3.0 mmol/L), diabetes mellitus (an established diagnosis or hemoglobin A1C [HbA1c]  $\geq 7.0\%$ ), atrial fibrillation (AF), current smoking, and daily alcohol intake. Patients underwent neuroimaging with MRI or computerized tomography. Functional outcome was assessed with the modified Rankin scale (mRS).<sup>12</sup> Neurological impairments were measured by the National Institute of Health Stroke Scale,<sup>13</sup> and activities of daily living (ADL) were assessed using the Bartel ADL index<sup>14</sup> at baseline and follow-up. Cognition was assessed with Mini Mental State Examination (MMSE),<sup>15</sup> TMT-A, and 10-word tests at baseline, after 12 months, and at 7 years follow-up. The same team of physicians and study nurse were used during the study.

Fasting blood samples, electrocardiography, and blood pressure were collected at baseline and 12 months follow-up. At the same time points, weight and height were measured and body mass index (BMI) calculated. Calculated BMI groups: 1: <18.5 kg/m<sup>2</sup> underweight, 2: 18.5–24.9 kg/m<sup>2</sup> normal weight, 3: 25.0–29.9 kg/m<sup>2</sup> overweight, and 4: >30.0 kg/m<sup>2</sup> obese. Self-reported smoking, alcohol use, physical activity, and current medication were recorded.

### Intervention

Patients in the intervention group were invited to the outpatient clinic for a consultation with a study nurse and stroke physician at 3, 6, and 12 months. The intervention was based on the American Heart Association (AHA) 2006 recommendations regarding secondary stroke prevention<sup>16</sup> and included medical treatment and promotion of a healthy lifestyle. Risk factor targets were blood pressure  $\leq 140/90$  mmHg, total cholesterol  $\leq 5.0$  mmol/L, LDL-cholesterol  $\leq 3.0$  mmol/L, HbA1c  $\leq 7.0\%$ , homocysteine  $\leq 15$   $\mu\text{mol/L}$ , and BMI  $\leq 25$  kg/m.<sup>2</sup> The medical treatment was optimized, and patient education was given individually regarding stroke recurrence risk, prognosis, rehabilitation, and how to preserve brain health. Tailored advice regarding lifestyle changes included regular moderate physical activities and possibilities for strength and balance training and smoking cessation courses in groups if necessary. We recommended a diet rich in fruit, vegetables,

and fish, low-fat dairy products, and less sugar in combination with encouragement to avoid excessive use of alcohol.

## Statistical analyses

Baseline characteristics are given in mean  $\pm$  SD or as number and percentage as appropriate. Categorical variables were compared with Pearson's chi-squared test and continuous variables with independent Student's *t*-test. The long-term effect of the intervention upon survival was analyzed using Kaplan–Meier plots and Cox proportional hazard models adjusting for age and BMI. Predictors of survival were assessed using univariable and multivariable Cox proportional hazards regression analyses. The assumptions of proportional hazards were checked by visual inspection of log minus log plots. Variables with  $P < 0.1$  in univariable analyses were included in the multivariable analysis. Finally, as an exploratory analysis, we used Kaplan–Meier plots and log-rank test to study the effect of different BMI categories on survival. Analyses were performed using SPSS Statistic version 23.

## Ethical approval and informed consent

Ethical approval for this study was obtained from the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities (2013/1829). Written informed consent was obtained from all subjects or next of kind before inclusion in the study.

## Results

### Study population and intervention

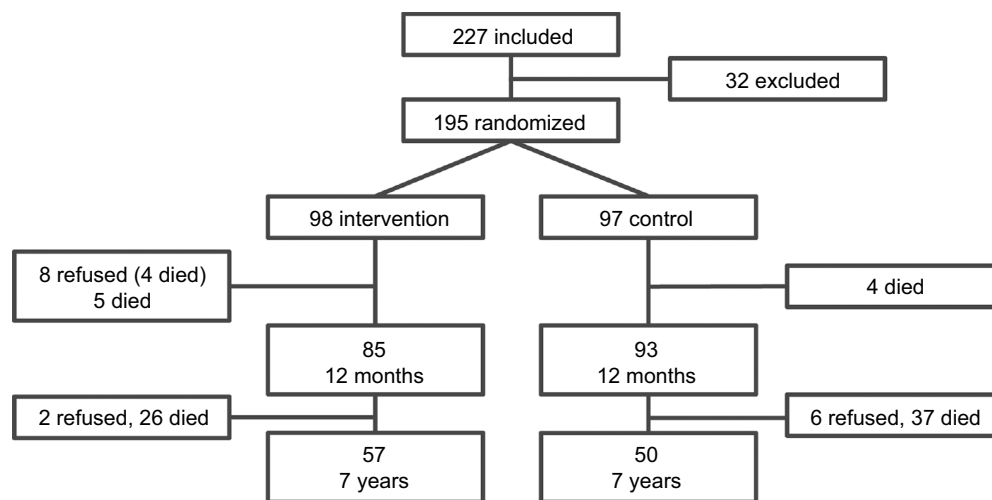
Of the 227 patients included in 2007/2008, a total of 195 patients were randomized. Of the 13 patients who did not complete the

intervention, eight patients discontinued and five died during the first year. Mean follow-up time was 7.3 years (0–9.9), with 76 deaths in total; 35 patients (36 %) in the intervention group and 41 (42 %) in the control group. Thus, the intention-to-treat (ITT) analysis comprised 98 patients in the intervention group and 97 in the control group, and the complete-case (CC) analysis comprised 85 patients in the intervention group and 97 in the control group. Flowchart of the study population is presented in Figure 1.

At baseline there was no significant group differences regarding age, BMI, stroke subtype, risk factors, or MMSE scores. At 12 months, significantly more patients in the intervention group reached the treatment targets for systolic blood pressure and hyperlipidemia. Daily alcohol use and cigarette smoking were reduced in both the groups, but without any significant difference. No significant difference was seen regarding physical activity; mean  $225 \pm 224$  min/week in the intervention group and  $192 \pm 201$  min/week in the control group,  $P = 0.30$ . At 12 months, mean BMI was significantly higher in the intervention group; mean  $26.6 \pm 3.2$  kg/m<sup>2</sup> in the intervention group vs  $25.7 \pm 4.5$  kg/m<sup>2</sup> in the control group,  $P = 0.007$ . After 7 years, mean BMI was  $26.8$  (SD 3.8) kg/m<sup>2</sup> in the intervention group and  $26.7$  (SD 4.0) kg/m<sup>2</sup> in the control group, and ~70% of the survivors had a BMI  $> 25$  kg/m<sup>2</sup>. The baseline characteristics of the study population, including risk factor measurements after 1 year, are presented in Table 1.

### Intervention and long-term effect on mortality

Kaplan–Meier survival curves for the ITT and the CC population, respectively, are presented in Figure 2. Log-rank  $P$ -values are 0.29 (ITT) and 0.07 (CC).



**Figure 1** Flowchart of the study population.

**Table 1** Baseline characteristics and risk factors at 12 months

Patients characteristics	Baseline		12 months		P-value
	Intervention	Control	Intervention	Control	
N	98	97	85	93	
Male (%)	45 (46)	59 (61)	41 (48)	55 (59)	
Age, years (mean [SD])	72.6 (11.2)	70.6 (13.6)	73.6 (11.2)	71.6 (13.6)	
<b>Stroke subtype (%)</b>					
Cerebral infarction	72 (74)	77 (79)			
TIA	20 (20)	10 (10)			
Cerebral hemorrhage	6 (6)	10 (10)			
<b>Risk factors (%)</b>					
Hypertension*	60 (61)	54 (65)	26 (38)	43 (62)	0.04
Hyperlipidemia	56 (57)	53 (55)	9 (10)	22 (24)	0.04
Diabetes	8 (8)	13 (13)			
Cigarette smoking (present)	18 (18)	24 (25)	8 (9)	18 (19)	0.10
Coronary heart disease	21 (21)	26 (27)			
Atrial fibrillation	34 (35)	24 (25)			
Daily alcohol use	20 (24)	17 (18)	7 (8)	13 (14)	0.36
BMI >25	60 (61)	53 (55)	58 (53)	52 (47)	0.13
BMI, kg/m <sup>2</sup> (mean [SD])	26.0 (3.9)	25.1 (4.4)	26.6 (3.2)	25.7 (4.5)	0.01
<b>OSCP classification (%)</b>					
TACI	3 (3)	7 (7)			
PACI	51 (52)	47 (49)			
LACI	31 (32)	30 (31)			
POCI	12 (13)	13 (13)			
<b>Topography (%)</b>					
Right hemisphere	36 (37)	38 (39)			
Left hemisphere	46 (47)	49 (51)			
Cerebellum/brainstem	16 (16)	10 (10)			
<b>Assessments (SD)</b>					
NIHSS day 1, mean	2.0 (2.2)	3.0 (4.1)			
NIHSS at discharge, mean	1.0 (1.4)	1.6 (2.8)			
BI at discharge, mean	19 (2.6)	18 (3.9)			
mRS at discharge, mean	1.0 (1.1)	1.3 (1.2)			
MMSE, mean	26.5 (3.2)	26.1 (4.0)			

**Notes:** Coronary heart disease, previous myocardial infarction or present angina pectoris; hyperlipidemia = total cholesterol >5 mmol/L or LDL >3 mmol/L. \*Hypertension, use of blood pressure-lowering drugs at baseline, at 12 months: systolic blood pressure >140 mmHg.

**Abbreviations:** blood pressure, Barthel Activities of Daily Living Index; BMI, body mass index; LACI, lacunar circulation infarction; LDL, low-density lipoprotein; MMSE, Mini Mental State Examination; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; OSCP, Oxfordshire Community Stroke Project classification; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; TACI, total anterior circulation infarction; TIA, transient ischemic attack.

In multivariate Cox regression analysis, adjusted for age and BMI, we found no significant difference between the intervention and the control group, neither in ITT analysis (HR 0.92, 95% CI 0.56–1.52) nor in CC analysis (HR 0.71, 95% CI 0.41–1.23). Causes of death during follow-up are presented in Table 3.

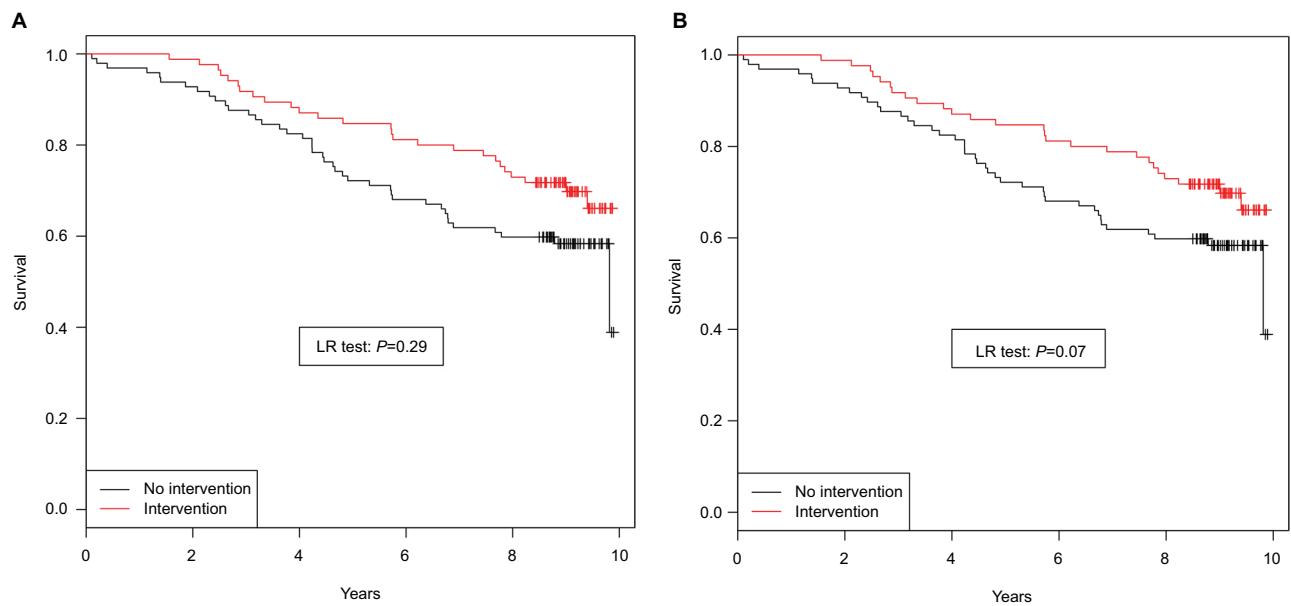
### Predictors for long-term survival

All baseline variables shown in Table 1 were assessed using Cox proportional hazards regression analyses (Table 2). In the univariable models, higher age and higher mRS score were associated with higher mortality, whereas hyperlipidemia, higher BMI, and higher MMSE at discharge were associated

with lower mortality. In the multivariable Cox regression model, including age, hyperlipidemia, AF, BMI, mRS at discharge, and MMSE at discharge, only younger age and higher BMI remained independent predictors for long-term survival over 7 years (HR 1.08, 95% CI 1.05–1.11, and HR 0.91, 95% CI 0.85–0.97, respectively). In a multivariable Cox regression model, without BMI, only age remained independent (HR 1.09, 95% CI 1.06–1.12).

Kaplan–Meier survival curves of calculated BMI groups are presented in Figure 3.

At baseline, seven patients had BMI <18.5 kg/m<sup>2</sup>, 74 between 18.5 and 24.9 kg/m<sup>2</sup>, 72 between 25 and 29.9 kg/m<sup>2</sup>, and 24 patients ≥30 kg/m<sup>2</sup>.



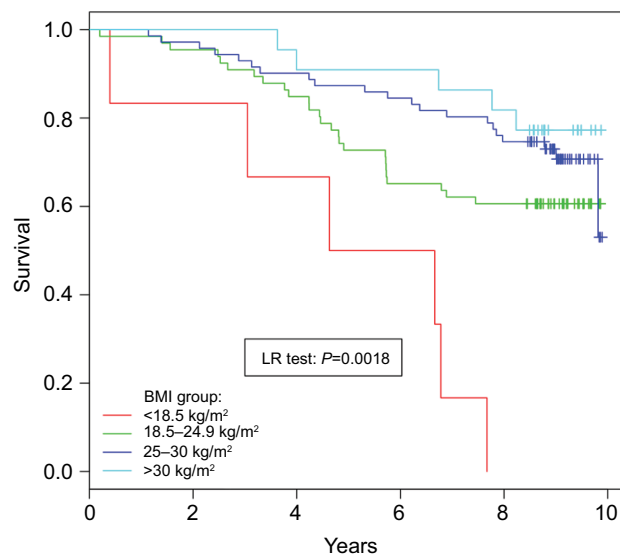
**Figure 2** Kaplan–Meier survival curves for (A) the intention-to-treat and (B) complete case population.

**Table 2** Cox regression; death in relation to intervention, cardiovascular risk factors, stroke subtypes, and functional and cognitive assessment

Patients characteristics	Univariate HR	95% CI	Multivariate HR	95% CI
Age (years)	1.10	1.07–1.13	1.08	1.05–1.11
Sex, male	1.11	0.71–1.75		
Hypertension	0.96	0.61–1.52		
Coronary heart disease	0.64	0.36–1.12		
Smoking, present	0.99	0.59–1.68		
Hypercholesterolemia	0.45	0.29–0.71	0.68	0.41–1.13
Daily alcohol use	0.52	0.20–1.30		
Atrial fibrillation	0.62	0.37–0.99	1.57	0.92–2.68
Diabetes	0.88	0.43–1.76		
BMI (kg/m <sup>2</sup> )	0.87	0.82–0.93	0.91	0.85–0.97
<b>Stroke subtype, ref: infarct</b>				
TIA	0.74	0.37–1.49		
Hemorrhage	0.91	0.39–2.11		
<b>OCSP, ref: PACI</b>				
LACI	0.88	0.35–2.24		
POCI	0.45	0.26–1.82		
TACI	0.67	0.27–2.32		
<b>Topography, ref: left</b>				
Right	0.95	0.47–1.92		
Back	1.11	0.54–2.26		
NIHSS day 1	1.03	0.97–1.08		
NIHSS at discharge	0.99	0.91–1.10		
mRS at discharge	1.04	1.04–1.48	1.23	0.98–1.53
MMSE at discharge	0.92	0.88–0.96	0.98	0.91–1.05
Intervention	0.79	0.50–1.23		

**Notes:** Univariate and multivariate analyses, intention-to-treat group. Variables with  $P < 0.1$  in univariate analysis were included in the multivariate analysis. Hypertension = use of blood pressure-lowering drugs at baseline, at 12 months: systolic blood pressure  $> 140$  mmHg. Coronary heart disease, previous myocardial infarction or present angina pectoris; diabetes mellitus, an established diagnosis or  $HbA1c \geq 7.0\%$ ; hypercholesterolemia, total cholesterol  $> 5$  mmol/L or LDL  $> 3$  mmol/L.

**Abbreviations:** BMI, body mass index; LACI, lacunar circulation infarction; LDL, low-density lipoprotein; mRS, modified Rankin scale; MMSE, Mini Mental State Examination; NIHSS, National Institute of Health Stroke Scale; OCSP, Oxfordshire Community Stroke Project classification; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; TACI, total anterior circulation infarction; TIA, transient ischemic attack.



**Figure 3** Kaplan-Meier survival curves of calculated body mass index groups.

## Discussion

Although mortality was lower with a maximum difference of ~20% at 7 years, we found no significant effect on survival after 7 years of a multifactorial risk factor program given during the first year after first-ever stroke or TIA. Lower age and higher BMI were independent predictors for 7 years survival in this cohort.

## Intervention and long-term effect on mortality

This is a post hoc analysis and clearly underpowered to detect differences in clinical outcomes. Our findings must be interpreted with caution, but the trend toward better survival in the intervention group is similar to the results of a trial of 70 patients randomized to lifestyle intervention followed for 3 years.<sup>17</sup> Moreover, a recent systematic review and meta-analysis indicated that lifestyle intervention following stroke is significantly associated with lower blood pressure,<sup>18</sup> an important contributor to the general decline in stroke mortality. In our study, significantly more patients in the intervention group reached the treatment targets for systolic blood pressure and hyperlipidemia at 12 months. The intervention in this study included advice regarding diet and encouragement to perform regular moderate physical activity, but no significant differences were observed between the groups at 12 months. Physical activity is associated with reduced cardiovascular mortality,<sup>19</sup> but more specific training programs and strict dietary advices are probably needed to see any difference, as shown in previous studies.<sup>20,21</sup> Our study differs from previous

**Table 3** Causes of death during follow-up

Causes of death	Intervention	Control
Heart disease	4	6
Infectious disease	10	4
Cerebrovascular disease	2	9
Cancer	4	11
Other	5	4
Missing	10	7
<b>Total</b>	<b>35</b>	<b>41</b>

trials in that the study population was older, we included all types of stroke, and the follow-up was longer.

The cardiac model of rehabilitation, with pharmacological and lifestyle interventions, has widespread availability, and studies show effect regardless of age.<sup>22</sup> Small studies have indicated that stroke patients can benefit in a similar manner as patients with heart diseases, both in the postacute period and later in the chronic phase.<sup>23–25</sup> A large ongoing trial with multidomain approach after stroke or TIA is the intensified secondary prevention intending a reduction of recurrent events in TIA and minor stroke patients (INSPIRE-TMS),<sup>26</sup> with an estimated completion date of December 2018.

## Predictors for long-term survival

Lower age and higher BMI were independent predictors for long-term survival in this cohort. Taking BMI out of the multivariate Cox regression model, since patients in the intervention group had higher BMI at 12 months, did not change these results. There is an increasing evidence suggesting an inverse relationship between BMI and total poststroke mortality.<sup>27,28</sup> However, there is no prospective data on the effect of weight loss as part of secondary prevention on survival after stroke in adults.<sup>29</sup> The negative association between low weight and mortality may have several explanations. Most importantly, undernourished patients tend to suffer from more stroke complication including infections and gastrointestinal bleedings during their hospital stay.<sup>30</sup> Furthermore, weight loss after stroke may be preceded by poor nutritional status in the early phase, especially due to swallowing problems.<sup>30,31</sup> In the general population, low BMI is an independent risk factor of total mortality in the elderly,<sup>32</sup> and poor outcome in underweight patients could be a contributing factor to our results. At present, AHA guidelines for secondary prevention after stroke or TIA recommend screening for obesity with measurement of BMI, but the usefulness of weight loss among patients with a recent TIA or stroke is uncertain.<sup>33</sup> Our findings support these recommendations, in contrast to



guidelines from 2006 which recommended weight loss in those with BMI >25 kg/m<sup>2</sup>.

The impact of different risks factors of stroke differ according to both age and etiology.<sup>34</sup> Looking at the causes of death, fewer patients in the intervention group died of vascular disease. However, due to small numbers, these results are difficult to interpret. With increasing age conventional vascular risk factors lose their predictive value for stroke, as functional status and cognition being more important.<sup>35</sup> In line with this, and with mean age 71.6 years and all stroke types included at baseline, our findings seem reasonable.

## Strengths and limitations

This is a post hoc analysis of a study originally designed and powered to test whether a multifactorial vascular risk factor intervention could prevent cognitive impairment, underpowered to study survival. Furthermore, the inclusion of both TIA, ischemic and hemorrhagic stroke, with possible different attributable risks by different cardiovascular risk factors, in combination with the limited sample size, makes it difficult to find any group differences. Only patients with life expectancy more than 1 year were included in the study, so our findings might not be applied to most of the stroke patients. In addition, our findings might be biased by comorbidities and age-related complications due to high age at baseline and long-time follow-up. However, the strength of our trial is the randomized controlled design in a representative sample of stroke survivors, with long-term follow-up by the same team of physicians and study nurse, which may produce data of high quality. Long-term follow-up of RCTs after stroke is missing, so our study adds important clinical knowledge.

## Conclusion

We found no significant effect on survival after 7 years of a multifactorial risk factor program given during the first year after first-ever stroke or TIA. Higher BMI is an independent predictor for long-term survival in this cohort.

## Data sharing statement

The data sets are available from the first and corresponding author on reasonable request.

## Acknowledgments

We appreciate the contribution of all our participants. We also thank our dedicated study nurse and the Department of Geriatric, Stroke and Rehabilitation Medicine and Department of Medical Research, Bærum Hospital, Vestre Viken Hospital Trust for their support.

## Author contributions

BF, BT, ARØ, HeIH, TBW, and GH researched literature, conceived the study, and contributed to the statistical analysis plan. HeIH, BF, BT, and GH were involved in protocol development and gaining ethical approval. HåIH, HeIH, and GH were involved in patient recruitment. HåIH, HeIH, ECS, GH, and SN were involved in data analysis. GH wrote the first draft of the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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