

# Blood pressure control to prevent decline in cognition after stroke

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**Background:** Treatment of hypertension post-stroke preserves cognition through prevention of recurrent stroke, but it is not clear whether it prevents cognitive decline through other mechanisms. We aimed to describe changes in blood pressure from baseline to 1 year post-stroke and to evaluate the association between achieved blood pressure targets and cognitive function, mild cognitive impairment (MCI), and dementia.

**Methods:** We included patients with first-ever stroke, and defined achieved blood pressure goals as systolic blood pressure (SBP) in the categories  $\leq 125$  mmHg,  $\leq 140$  mmHg, and  $\leq 160$  mmHg, SBP reduction of  $\geq 10$  mmHg, and diastolic blood pressure (DBP) reduction of  $\geq 5$  mmHg. The main outcome variables were cognitive assessments 1 year post stroke. Secondary outcomes were diagnoses of MCI or dementia.

**Results:** Forty-one of 166 patients (25%) reached SBP  $\leq 125$  mmHg after 1 year, 92/166 (55%) reached SBP  $\leq 140$  mmHg, and 150/166 (90%) reached SBP  $\leq 160$  mmHg. SBP was reduced by  $\geq 10$  mmHg in 44/150 (29%) and DBP by  $\geq 5$  mmHg in 57/150 (38%). We did not find any statistically significant associations between cognitive test performances and different blood pressure goals ( $P=0.070-1.0$ ). Nor was there any significant association between achieved goal blood pressure or blood pressure reduction after 1 year and the diagnoses of MCI or dementia ( $P=0.32-0.56$ ).

**Conclusion:** Treatment of hypertension is important for primary and secondary prevention of stroke. Showing a potential beneficial effect of blood pressure control on cognitive function, however, probably needs longer follow-up.

**Keywords:** cognitive impairment, hypertension, cerebrovascular disease, risk factor management, secondary prevention

## Background

Vascular diseases with and without stroke contribute to cognitive impairment and dementia, and may lead to vascular cognitive impairment, Alzheimer's disease, or a mixed condition of Alzheimer's disease and cerebrovascular disorder.<sup>1,2</sup> Post-stroke cognitive impairments include the continuum from milder cognitive deficits to severe dementia, affect different cognitive domains, and are caused by both degenerative and vascular pathologies. Larger infarct volumes and increased number of infarcts are associated with cognitive problems and dementia.<sup>3</sup> The actual stroke lesion and complications in the acute phase may affect cognition in the early period after stroke, but how a single stroke may lead to progression of cognitive impairment is unclear. One explanation might be that vascular dysfunction progresses and has a large impact over years after the stroke, but this is not likely to be the only explanation.

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Hypertension is a known risk factor for stroke, cardiovascular disease,<sup>4</sup> white matter hyperintensities, and cognitive decline and dementia due to vascular dementia and Alzheimer's disease.<sup>5,6</sup> Antihypertensive drug treatment reduces the risk of stroke and cardiovascular disease,<sup>7,8</sup> and may reduce the risk of dementia, although the evidence for the latter is poor.<sup>9-11</sup> Lowering of blood pressure is effective for prevention of recurrent stroke, but the optimal target or reduction is unknown.<sup>12</sup> Today, guidelines regarding secondary prevention after stroke recommend an individualized blood pressure target and a reduction of approximately 10/5 mmHg or below 140/90 mmHg.<sup>13,14</sup>

Effective measures to slow down the cognitive decline post stroke are urgently needed.<sup>15</sup> There is no clear evidence that lowering the blood pressure post stroke will lead to better cognition or prevent a decline in cognition or development of dementia.<sup>16</sup> The recently published SPS3 study did not report any significant effect of blood pressure reduction on cognition in patients with lacunar stroke.<sup>12,17</sup> The aims of the present study were to describe changes in blood pressure from baseline to 1 year post stroke, and to test the hypothesis that patients who achieve the blood pressure targets have a better cognitive outcome and more rarely develop mild cognitive impairment (MCI) or dementia than patients who do not achieve blood pressure targets.

## Methods

### Study population

Patients with a first-ever stroke admitted to the in-patient stroke unit of Bærum Hospital between February 2007 and July 2008 were invited to participate in a randomized controlled trial (RCT). The study was registered in Clinicaltrials.gov (NCT00506818). Change in cognition was the primary endpoint in the study reported previously.<sup>18</sup> The RCT was negative, and in the present secondary study we evaluate the association between achieved blood pressure and blood pressure reduction on one side and cognitive outcomes on the other, regardless of the allocation in the RCT.

For the present analysis, we excluded patients with transient ischemic attack (TIA), subarachnoid hemorrhage, pre-stroke cognitive impairment as indicated by a score  $\geq 3.7$  on the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),<sup>19</sup> previous stroke or TIA, patients who did not speak Norwegian, and patients with a remaining life expectancy of less than 1 year as estimated by the treating physician.

### Baseline data

Vascular risk factors recorded at baseline included treated hypertension before hospitalization, hyperlipidemia (total cholesterol  $>5.0$  mmol/L or low-density lipoprotein cholesterol  $>3.0$  mmol/L), diabetes mellitus, atrial fibrillation (permanent or paroxysmal), current smoking, waist and hip circumferences, and calculated waist-to-hip-ratio.

Blood pressure was measured daily during the morning round, with the patient in the supine position, after a minimum 5 minutes' rest. In the analyses, we used the blood pressure measured on day 3 after admittance to the hospital. Pre-stroke cognitive impairment was screened for by the 26-question version of the IQCODE. When possible, the questionnaire was filled in by first-degree relatives. Cognitive function was measured between day 3 and 7 after admittance, with the Mini Mental State Examination,<sup>20</sup> Clock Drawing Test,<sup>21</sup> Trail Making Test (TMT) A and B, and the immediate and delayed recall parts of the 10-word memory test (minimum score 0 and maximum 40).<sup>22,23</sup> Anxiety and depressive symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS).<sup>24</sup> The patients were genotyped for apolipoprotein E (Apo E 4) alleles.

Neurological impairments were measured by the National Institute of Health Stroke Scale (NIHSS) by a stroke physician.<sup>25</sup> Activities of daily living (ADL) were assessed at discharge by stroke nurses using the Barthel ADL index.<sup>26</sup> The stroke was classified according to the Oxfordshire Community Stroke Project classification, and patients with ischemic stroke were classified according to The Trial of Org 10172 in Acute Stroke Treatment classification at discharge.<sup>27,28</sup>

### Follow-up data

Follow-up was performed 12 months after the stroke event. Assessments for cognitive, emotional, neurological, and functional status were repeated. Blood pressure was measured in the supine position after 5 minutes' rest. Self-reported physical activity was recorded.

### Intervention, control conditions, and assessment of the outcome

Hypertension was treated through lifestyle and pharmacological interventions according to guidelines recommending a blood pressure below 140/90 mmHg.<sup>29</sup> All antihypertensive therapeutic agents could be used in the intervention group, and dose adjustments were made and additional antihypertensive drugs were administered when the blood pressure was higher than 140/90 mmHg, unless the patients suffered

from severe large-vessel disease. The controls received care as usual.

The main outcome variables were defined as cognitive functions as measured by one or more of the tests for different cognitive domains 1 year post stroke. The secondary outcomes were diagnoses of MCI or dementia also 1 year post stroke.

## Ethics

The study was approved by the Regional Committee for Ethics in Medical Research and by the Data Protection Authorities. All patients gave their written informed consent before inclusion. First-degree relatives gave consent on behalf of patients with reduced capacity.

## Statistics

The associations between the cognitive test performances (outcome variables) and the explanatory variables achieved blood pressure goals (systolic blood pressure [SBP] in the categories  $\leq 125$  mmHg,  $\leq 140$  mmHg, and  $\leq 160$  mmHg, respectively, SBP reduction of  $\geq 10$  mm Hg, and diastolic blood pressure [DBP] reduction of  $\geq 5$  mm Hg) were studied using linear regression for the outcomes TMT A and B, the 10-word test and Mini Mental State Examination, and logistic regression for the outcome Clock Drawing Test. For each combination of outcome and explanatory variable, two models were fitted: one univariate (unadjusted) model, and one model adjusted for 17 possible confounding variables: age, sex, education, Apo E alleles, hyperlipidemia, diabetes, atrial fibrillation, coronary heart disease, current smoking, hip-waist-ratio, physical activity, neurological deficits as measured by NIHSS day 1, IQCODE, HADS, Oxfordshire Community Stroke Project, Barthel ADL index, and stroke type. Only variables measured at baseline, except physical activity from the follow-up, were included as adjustment variables. The statistical analyses were performed with Stata version 13 (StataCorp LP).

## Clinical trial registration information

ClinicalTrials.gov, number NCT00506818.

## Results

### Baseline characteristics

The initial study population consisted of 250 patients with stroke or TIA. Of these, 59 were excluded from these analyses, 48 did not fulfill the inclusion criteria (36 had a TIA, 6 had an IQCODE score  $\geq 3.7$ , 1 did not speak Norwegian,

1 had an infarction in the spinal cord, 1 had suffered a previous TIA, 2 withdrew their consent, and 1 died before signing the consent), and 11 were diagnosed with other disease than stroke.

Of the remaining 191 patients, 166 completed the follow-up. Of the 25 patients missing, 17 died (three due to a recurrent stroke), six refused to complete follow-up, and two had missing data regarding blood pressure. Of the 166 patients having blood pressure measurements and cognitive screening at follow-up, 149 (90%) had a cerebral infarction and 17 (10%) had a cerebral hemorrhage. Five patients suffered a new TIA during follow-up. Sixteen did not have baseline measures of blood pressure, 13 were already discharged, and three had missing values of unknown causes. Thus, the study sample comprised 166 patients; whereas the analyses on change in blood pressure included 150 patients.

Baseline characteristics of the study population are shown in Table 1. Mean age was  $71.5 \pm 12.4$  (range: 25–94 years) and 56% were men. At baseline, the mean SBP was  $138.0 \pm 24.6$  (range: 79–211 mmHg).

### Blood pressure at 12 months post stroke

Overall, there was a mean increase in SBP from baseline to 1-year follow-up by 0.53 mmHg (95% CI –3.8 to 4.9). Only 64 of 150 patients (43%) had a reduction in mmHg of SBP from baseline to 12-month follow-up, and 88 of 150 patients (59%) had a reduction in DBP.

In all, 41 of 166 patients (25%) reached SBP  $\leq 125$  mmHg after 1 year, 92/166 (55%) reached SBP  $\leq 140$  mmHg, and 150/166 (90%) reached SBP  $\leq 160$  mmHg. SBP was reduced by  $\geq 10$  mmHg in 44/150 (29%) and DBP by  $\geq 5$  mmHg in 57/150 (38%).

### Blood pressure targets and cognitive outcomes

As shown in Table 2, we did not find any significant associations between cognitive test performances (outcome variables) and different blood pressure goals ( $P=0.070$ – $1.0$ ). Forty patients (24%) were diagnosed with MCI and 61 patients (37%) with dementia. There was no significant association between the achieved goal blood pressure or blood pressure reduction after 1 year and the diagnoses of MCI or dementia ( $P=0.32$ – $0.56$ ).

## Discussion

Previous studies have shown that patients suffering from a stroke have an increased risk of a decline of cognitive symptoms

**Table 1** Patient description (n=166)

Assessment	Baseline (N=97)	12 months
Demographics		
Men	93 (56)	
Mean age, years (SD)	71.5 (12.4)	
Less than 9 years of education	37 (22)	
Stroke subtype		
Cerebral infarction	149 (90)	
Cerebral hemorrhage	17 (10)	
Risk factors		
Hypertension	96 (58)	
Hyperlipidemia	92 (55)	
Diabetes	20 (12)	
Cigarette smoking (present)	39 (24)	
Coronary heart disease	39 (24)	
Atrial fibrillation	49 (30)	
Daily alcohol use	32 (24)	
BMI >25	96 (58)	
Physical activity, minutes per week (SD)		183 (206)
Apo E 4 allele	38 (23)	
OCSP classification		
TACI	18 (11)	
PACI	78 (47)	
LACI	46 (28)	
POCI	24 (15)	
TOAST classification		
Large-vessel disease	19 (13)	
Cardio embolic disease	45 (30)	
Small-vessel disease	48 (32)	
Stroke of undetermined etiology	37 (25)	
Precerebral arteries		
Internal carotid artery disease ≥50%	22 (13)	
Vertebral artery occlusion	5 (3)	
Antihypertensive medication		
Betablocker		69 (42)
ACE inhibitor		37 (22)
Angiotensin II receptor blocker		47 (28)
Calcium antagonist		36 (22)
Diuretics		54 (33)
Number of antihypertensive medication		
0		40 (24)
1		51 (31)
2		41 (25)
3		22 (13)
4		12 (7)
Assessments		
Systolic blood pressure, supine position (SD)	138.0 (24.6)*	138.3 (18.8)
Median (IQR)	135.5 (121–157)	137.0 (125–152)
Diastolic blood pressure, supine position (SD)	80.3 (14.4)*	75.4 (10.6)
Median (IQR)	78 (71.0–89.3)	76.0 (67.0–83.0)
NIHSS, median (IQR)	1.0 (0–2)**	1.0 (0–2)
BI, median (IQR)	20 (18–20)	20 (19–20)
mRS, median (IQR)	1 (1–2)	1 (1–2)
IQCODE (SD)***	3.10 (0.22)	3.3 (0.41)

(Continued)

**Table 1** (Continued)

Assessment***	Baseline (N=97)	12 months
MMSE (SD)	25.6 (4.6)	25.7 (5.8)
TMT A (SD)	78.3 (71.8)	66.9 (51.0)
TMT B (SD)	157.0 (86.7)	147.0 (85.3)
10-word test (SD)	21.0 (7.3)	23.1 (8.6)
Clock Drawing Test, correct	89 (53.6)	96 (57.8)
HADS total	7.5 (5.8)	6.9 (5.3)

**Notes:** Figures are in n(%) unless specified otherwise. Hyperlipidemia denotes total cholesterol >5 mmol/L or LDL-cholesterol >3 mmol/L. Coronary heart disease means previous myocardial infarction or present angina pectoris. Atrial fibrillation denotes permanent or paroxysmal atrial fibrillation. Anxiety and depressive symptoms were evaluated using HADS. \*n=150; \*\*NIHSS at discharge; \*\*\*n=118–166 due to missing values in cognitive and emotional assessments.

**Abbreviations:** LDL, low-density lipoprotein; BMI, body mass index; Apo E 4, apolipoprotein E alleles; OCSP, Oxfordshire Community Stroke Project; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; LACI, lacunar circulation infarction; POCI, posterior circulation infarction; TOAST, The Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institute of Health Stroke Scale; IQR, interquartile range; BI, Barthel Activities of Daily Living Index; mRS, modified Rankin Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MMSE, Mini Mental State Examination; TMT A, trail making test A; TMT B, trail making test B. HADS, Hospital Anxiety and Depression Scale.

years after the stroke event.<sup>2,30</sup> The mechanisms involved are not fully known, but treating vascular risk has been proposed as a possible measure to prevent a decline in cognition. In this study, we evaluated the association between blood pressure control and cognitive function 1 year after a stroke. We did not find any significant associations on cognitive performance, MCI, or dementia by treating blood pressure. Even in the patients with SBP below 125 mmHg, we found no beneficial effect.

The lack of effect may be explained by the fact that the majority of the patients did not have a very high blood pressure at baseline. Half of them had higher blood pressure 1 year post stroke compared to baseline, and only one-third achieved the recommended individualized reduction of 10 mmHg in SBP. Unfortunately, we had only one measure of blood pressure at every assessment, and not the average of 24 hours. When this study was planned, the recommended goal for blood pressure control was <140/90 mmHg.<sup>29</sup> The guidelines advise individualized blood pressure achievement with reduction of 10/5 mmHg or below 140/90 mmHg.<sup>13,14</sup>

Cognitive impairment post stroke can probably partly be explained as a stable rest phenomenon related to the actual stroke lesion. Treatment of blood pressure post stroke may have little impact in these patients due to minimal reversibility. The potential effect of controlling blood pressure post stroke may be associated with chronic vascular disease and subsequent progressive cognitive impairment. These changes develop over decades, and the effect of good blood pressure management may have potential impact over several years and later in the post-stroke period.

**Table 2** Results of unadjusted and adjusted regression models for associations between achievement of different blood pressure targets and cognitive test performances (outcome variables)

Explanatory variables	Cognitive test performance				
	TMT A	TMT B	10-word test	MMSE	Clock Drawing Test*
SBP ≤ 125					
Univariate	4.20 (−14.6, 23.0)	−12.8 (−47.5, 21.9)	−0.72 (−3.76, 2.32)	0.02 (−2.05, 2.09)	1.06 (0.52, 2.15)
Adjusted**	0.23 (−19.1, 19.6)	−20.2 (−55.1, 14.8)	−0.47 (−3.65, 2.72)	0.56 (−1.20, 2.32)	1.25 (0.44, 3.53)
SBP ≤ 140					
Univariate	1.98 (−14.5, 18.4)	6.91 (−22.8, 36.6)	−0.74 (−3.42, 1.94)	0.09 (−1.92, 1.74)	1.29 (0.69, 2.42)
Adjusted**	2.23 (−15.3, 19.8)	21.3 (−10.8, 53.3)	−1.78 (−4.70, 1.14)	−0.45 (−2.06, 1.16)	1.96 (0.75, 5.09)
SBP ≤ 160					
Univariate	−23.8 (−51.9, 4.30)	−21.3 (−76.9, 34.3)	2.39 (−2.19, 6.97)	2.04 (−0.98, 5.07)	0.69 (0.25, 1.95)
Adjusted**	−21.3 (−47.8, 5.09)	5.74 (−44.9, 56.4)	−1.24 (−5.87, 3.38)	0.005 (−2.47, 2.48)	1.95 (0.45, 8.41)
SBP reduction ≥ 10					
Univariate	11.5 (−8.31, 31.4)	0.83 (−34.6, 36.3)	−0.19 (−3.27, 2.89)	−0.51 (−2.68, 1.66)	1.56 (0.77, 3.17)
Adjusted**	7.32 (−13.7, 28.4)	−11.7 (−49.3, 26.0)	−0.77 (−4.06, 2.51)	0.07 (−1.92, 1.78)	1.79 (0.63, 5.13)
DBP reduction ≥ 5					
Univariate	−1.88 (−18.4, 14.6)	4.64 (−25.1, 34.4)	1.03 (−1.68, 3.74)	0.58 (−1.34, 2.50)	1.10 (0.59, 2.04)
Adjusted**	2.08 (−15.6, 19.8)	12.5 (−18.3, 43.4)	−0.35 (−3.23, 2.52)	−0.29 (−1.88, 1.29)	0.65 (0.25, 1.70)

**Notes:** Data are regression coefficient (95% CI) unless specified otherwise. \*Odds ratio; \*\*adjusted for age, sex, education, Apo E alleles, hyperlipidemia, diabetes, atrial fibrillation, coronary heart disease, current smoking, hip-waist-ratio, physical activity, NIHSS day 1, IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly), HADS, OCSF, Barthel ADL index, and stroke type.

**Abbreviations:** CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; TMT A, trail making test A; TMT B, trail making test B; MMSE, Mini Mental State Examination; NIHSS, National Institute of Health Stroke Scale; HADS, Hospital Anxiety and Depression Scale; OCSF, Oxfordshire Community Stroke Project; ADL, Activities of daily living.

The study has limitations. First, the previously reported RCT regarding intensive risk factor management regarding all modifiable risk factor did not find any effect on cognitive outcome, despite good pharmacological adherence to the program in the intervention group.<sup>18</sup> Second, the findings in the study are from a single center with a limited sample size (and thus a suboptimal statistical power) and a relatively short follow-up period. A larger multicenter study and longer follow-up would have improved generalizability of the findings. Third, blood pressure was measured only once, both at baseline and follow-up, and there is increasing knowledge regarding blood pressure variability. Fluctuations in blood pressure are suggested as a potential risk factor for cognitive decline in patients with degenerative diseases.<sup>31</sup> In addition, treatment of blood pressure was differentiated and managed according to tolerance and indications in relation to comorbid conditions, resulting in many antihypertensive regimes. Therefore, we were not able to investigate the potential relationship between different antihypertensive drug classes and cognitive outcome in this study.<sup>32</sup>

The study has both research and clinical implications. Treatment of hypertension post-stroke preserves cognition through prevention of a recurrent stroke. Strategies for blood pressure control include both pharmacological and nonpharmacological interventions. Increased long-term mortality in stroke survivors with increased risk factor

burden has been observed,<sup>33</sup> and early identification and treatment of vascular risk factors are of importance to improve the prognosis in stroke, both in primary and secondary prevention. Showing a potential beneficial effect of blood pressure control on cognitive function, however, probably needs longer follow-up.

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## Author contributions

HI-H, BT, TBW, MWF, KE, ARØ, and BF were involved in the study design and all part of the preparation of the manuscript; MWF performed the statistical work; and all authors gave the final approval.

## Disclosure

The authors declare no conflicts of interest in this work.

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