Lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia

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ABSTRACT

Objective: To determine whether strict blood pressure (BP) control is the best medical management for patients with symptomatic carotid artery occlusion and hemodynamic cerebral ischemia.

Methods: In this prospective observational cohort study, we analyzed data from 91 participants in the nonsurgical group of the Carotid Occlusion Surgery Study (COSS) who had recent symptomatic internal carotid artery occlusion and hemodynamic cerebral ischemia manifested by ipsilateral increased oxygen extraction fraction. The target BP goal in COSS was ≤130/85 mm Hg. We compared the occurrence of ipsilateral ischemic stroke during follow-up in the 41 participants with mean BP ≤130/85 mm Hg to the remaining 50 with higher BP.

Results: Of 16 total ipsilateral ischemic strokes that occurred during follow-up, 3 occurred in the 41 participants with mean follow-up BP of ≤130/85 mm Hg, compared to 13 in the remaining 50 participants with mean follow-up BP >130/85 mm Hg (hazard ratio 3.742, 95% confidence interval 1.065–13.152, log-rank $p = 0.027$).

Conclusion: BPs ≤130/85 mm Hg were associated with lower subsequent stroke risk in these patients.

Classification of evidence: This study provides Class III evidence that control of hypertension ≤130/85 mm Hg is associated with a reduced risk of subsequent ipsilateral ischemic stroke in patients with recently symptomatic carotid occlusion and hemodynamic cerebral ischemia (increased oxygen extraction fraction). *Neurology*® 2014;82:1027–1032

GLOSSARY

BP = blood pressure; **CI** = confidence interval; **COSS** = Carotid Occlusion Surgery Study; **ICA** = internal carotid artery; **JNC 7** = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; **OEF** = oxygen extraction fraction.

Patients with symptomatic carotid artery occlusion and hemodynamic cerebral ischemia manifested by increased oxygen extraction fraction (OEF) are at 20%–30% risk for ipsilateral stroke within 2 years.[1–3] Disagreement exists whether strict blood pressure (BP) control is the best medical management for these patients or whether higher BPs are needed to preserve cerebral perfusion and prevent subsequent stroke.[3,4] To address this issue, we analyzed data from the nonsurgical group of the Carotid Occlusion Surgery Study (COSS).[2]

METHODS The COSS was a parallel-group, prospective, 1:1 randomized, open-label, blinded-adjudication treatment trial conducted from 2002 to 2010 to test the hypothesis that extracranial-intracranial arterial bypass, when combined with best medical therapy, could reduce by 40% the subsequent occurrence of ipsilateral ischemic stroke at 2 years in patients with recent symptomatic internal carotid artery (ICA) occlusion and ipsilateral increased OEF measured by PET. COSS was carried out at 49 clinical centers and 18 PET centers in the United States and Canada. The majority were academic medical centers. The trial was terminated early for futility. Details of the trial design and results have been reported.[2,5]

The first follow-up visit was 30–35 days after randomization. Subsequent follow-up visits were at 3-month intervals after randomization until 24 months or the end of the trial. The nonsurgical group remained on the antithrombotic treatment preferred by their physicians. Each follow-up examination included monitoring of the efficacy of risk factor modification: BP, low-density lipoprotein cholesterol, triglycerides, hemoglobin A1C, and smoking. The target goal for BP was ≤130/85 mm Hg. If the BP was greater than this,

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Supplemental data at Neurology.org

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the local COSS investigator was instructed to make recommendations to the primary physician for intervention based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7).[6]

Of the 98 nonsurgical participants, 91 are included in the analysis: 3 had no postrandomization BPs recorded and 4 had ipsilateral ischemic strokes occurring before the first BP recording at the 30–35 days follow-up visit including 1 crossover with a postoperative ipsilateral ischemic stroke. For the 2 other crossovers, we censored data at the time of surgery. Follow-up for the primary endpoint of ipsilateral ischemic stroke until occurrence, 2 years, or the end of the trial was complete in these 91 patients. Ipsilateral ischemic stroke was defined as the clinical diagnosis of a focal neurologic deficit due to cerebral ischemia clinically localizable within the territory of the symptomatic occluded ICA that lasted for more than 24 hours.

We divided participants into 2 groups: 41 with mean BP during follow-up who met the COSS target of ≤130/85 mm Hg and 50 whose BPs were higher than this. Since we were interested in the association between BP and stroke prevention, we only used the BP recorded before the stroke occurred for those 16 who experienced an endpoint ipsilateral ischemic stroke. For all others, we used all recorded BP measurements. Before exclusion of the poststroke BPs, there was no statistically significant difference in the total number of BP recordings during follow-up between the 16 patients who experienced a stroke during follow-up (5.4 ±

Table 1 Baseline characteristics

	Follow-up blood pressure groups				
	≤130/85 mm Hg		>130/85 mm Hg		
	N	Mean ± SD or %	N	Mean ± SD or %	*p* Value
Age, y	41	57.0 ± 8.8	50	58.5 ± 9.0	0.7952
Male	41	58.5	50	64.0	0.6672
Caucasian	41	92.7	49	98.0	0.6006
Hypertension	41	73.2	50	84.0	0.3000
Hyperlipidemia	41	85.4	50	90.0	0.5346
Diabetes mellitus	41	24.4	50	24.0	0.9999
Cigarette smoking	41		50		0.1564
Current		43.9		34.0	
Former		41.5		60.0	
Never		14.6		6.0	
Previous myocardial infarct	41	22.0	50	8.0	0.0745
Previous stroke	40	30.0	50	36.0	0.6542
Entry type	41		50		0.5151
TIA		39.0		32.0	
Stroke		61.0		68.0	
Entry event side	41		50		0.9999
Right		43.9		46.0	
Left		56.1		54.0	
Entry event to randomization, d	41	87.5 ± 33.2	50	66.9 ± 35.8	0.0068
PET OEF ratio	41	1.25 ± 0.13	50	1.26 ± 0.16	0.5985
Contralateral carotid stenosis <50%	37	83.8	41	75.6	0.4132
Modified Barthel Scale (of 20)	41	19.4 ± 1.5	50	19.7 ± 1.0	0.2522
Modified Rankin Scale score	41	1.44 ± 1.05	50	1.30 ± 1.04	0.4856
NIHSS	41	2.32 ± 2.37	50	1.36 ± 1.97	0.0198
SSQoL (summary)	40	3.68 ± 0.84	50	3.72 ± 0.84	0.7422
LDL cholesterol, mg/dL	33	102.0 ± 36.6	34	109.6 ± 35.9	0.2696
Triglycerides, mg/dL	33	166.0 ± 192.8	38	189.3 ± 145.9	0.2173
Hemoglobin A1c, %	33	6.18 ± 0.91	38	6.01 ± 1.22	0.1162

Abbreviations: LDL = low-density lipoprotein; N = number with data; OEF = oxygen extraction fraction; NIHSS = NIH Stroke Scale; SSQoL = stroke-specific quality of life.
Entry type focal ischemic symptoms in the territory of the occluded carotid artery were categorized as TIA (<24 hours duration) or stroke (≥24 hours duration). The summary SSQoL (1–4) asks how self-reported overall quality of life compares to before stroke. A higher score indicates better quality of life.[15,16] LDL cholesterol, triglycerides, and hemoglobin A1c values are from the initial 3-month follow-up visit.

2.8) and the 75 who did not (5.4 ± 2.7, $p = 0.$ 0.97). Once we excluded the poststroke BPs for this analysis, those who experienced a stroke had fewer BP recordings (2.1 ± 1.2, $p < 0.001$).

We compared baseline characteristics using generalized Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Since there was an imbalance at baseline between the 2 groups in time interval from qualifying event to randomization (see Results), a Cox model was used to determine if this time interval was a predictor of the primary endpoint of ipsilateral ischemic stroke.

The primary research question addressed by this study is whether there was an association between lower BPs and the occurrence of ipsilateral ischemic stroke in medically treated patients with recently symptomatic ICA occlusion and hemodynamic cerebral ischemia as manifested by an ipsilateral hemispheric increase in OEF. A Cox regression model with BP group as the predictor and time to first stroke as the outcome was used to estimate the hazard ratio for the 2 groups for the primary analysis. For this primary analysis, the hazard ratio was considered statistically significant if the 95% confidence intervals (CIs) did not include 1.

Usage of antihypertensive drugs was compared between the 2 groups using the method of generalized estimating equations with BP group as the predictor and that accounted for the multiplicity of visits on participants. Since the use of antihypertensive drugs was different between the 2 groups (see Results), we performed subgroup analyses of always treated (taking at least 1 antihypertensive drug at every follow-up visit) participants to address the secondary question of whether treatment of hypertension to ≤130/85 mm Hg was associated with a difference in subsequent stroke.

To examine for the possibility of a J-curve relationship between follow-up BP and stroke occurrence, we determined the rate of subsequent stroke when participants were categorized into 5 groups based on their mean systolic BP during follow-up according to the scheme used by Ovbiagele et al.,[7] who found such a relationship in an analysis of the PROFESS trial: <120 mm Hg, 120–<130 mm Hg, 130–<140 mm Hg, 140–< 150 mm Hg, and ≥150 mm Hg.

Standard protocol approvals, registrations, and patient consents. The original COSS study was done with full institutional review board approval of all the participating centers. Written informed consent was obtained from all participants. COSS is registered as NCT00029146 with ClinicalTrials.gov.

This study provides Class III evidence that control of hypertension ≤130/85 mm Hg is associated with a reduced risk of subsequent ipsilateral ischemic stroke in patients with recently symptomatic carotid occlusion and hemodynamic cerebral ischemia (increased OEF).

RESULTS Forty-one participants had mean BP during follow-up of ≤130/85 mm Hg and 50 participants had mean BPs greater than this. The groups were well-matched for baseline characteristics and medical management during follow-up except for the time from entry event to randomization (tables 1 and 2). Time from entry event to randomization was not a significant predictor of subsequent stroke in these 91 patients ($p = 0.3286$).

Of 16 total postrandomization ipsilateral ischemic strokes that occurred within 2 years of randomization, 3 occurred in the 41 participants with mean follow-up BP of ≤130/85 mm Hg, compared to 13 in the remaining 50 participants with mean follow-up BPs >130/85 mm Hg (hazard ratio 3.742, 95% CI 1.065–13.152, log-rank $p = 0.027$) (figures 1 and 2). Estimated 2-year ipsilateral ischemic stroke rates were taken from the Kaplan-Meier curves. For those whose mean BP during follow-up was ≤130/85 mm Hg, the 2-year estimated rate was 0.082 ± 0.046 (SE). For those with mean BP >130/85 mm Hg, the estimated rate was 0.304 ± 0.072 (SE).

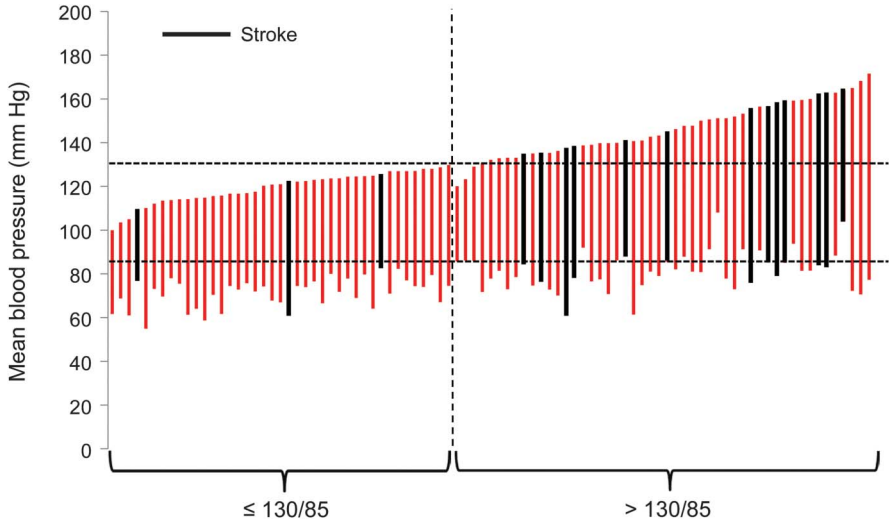
The percent of follow-up visits at which the participants reported the use of antihypertensive drugs was different between the 2 groups: 224/353 (63%) for the ≤130/85 mm Hg group and 356/438 (81%) for the >130/85 mm Hg group ($p = 0.0225$). In the subgroup of always treated participants (taking at least 1 antihypertensive drug at every follow-up visit), there were 2 strokes in 23 patients in the ≤130/85 mm Hg group and 10 strokes in 32 participants in the >130/85 mm Hg group (hazard ratio 3.781, 95% CI 0.827–17.297, log-rank $p = 0.065$). The hazard ratio of 3.781 for this subgroup analysis was essentially identical to that of 3.742 for the primary analysis, indicating no heterogeneity of the association.

Table 2 Medical therapy at last follow-up

	Follow-up blood pressure group		
	≤130/85 mm Hg	>130/85 mm Hg	p Value[a]
Participants, n	41	50	
Duration of follow-up, total days (mean)	23,186 (566)	25,636 (513)	
Number of blood pressure recordings, mean ± SD	5.1 ± 2.9	4.6 ± 2.7	0.403
Use of antithrombotic medication	38/41 (93)	50/50 (100)	0.087
Cigarette smoking (not currently smoking)	23/41 (56)	34/50 (68)	0.295
LDL cholesterol ≤100 mg/dL	15/22 (68)	24/33 (73)	0.797
Triglycerides ≤150 mg/dL	15/24 (63)	22/34 (65)	0.955
Hemoglobin A1c ≤ 7%	19/24 (79)	30/36 (83)	0.702

Abbreviation: LDL = low-density lipoprotein.
Data are N/total N with data (%), unless otherwise noted.
[a] *p* Values from Fisher exact test.

Figure 1 Individual mean systolic and diastolic blood pressures for the 91 participants in the 2 Carotid Occlusion Surgery Study groups

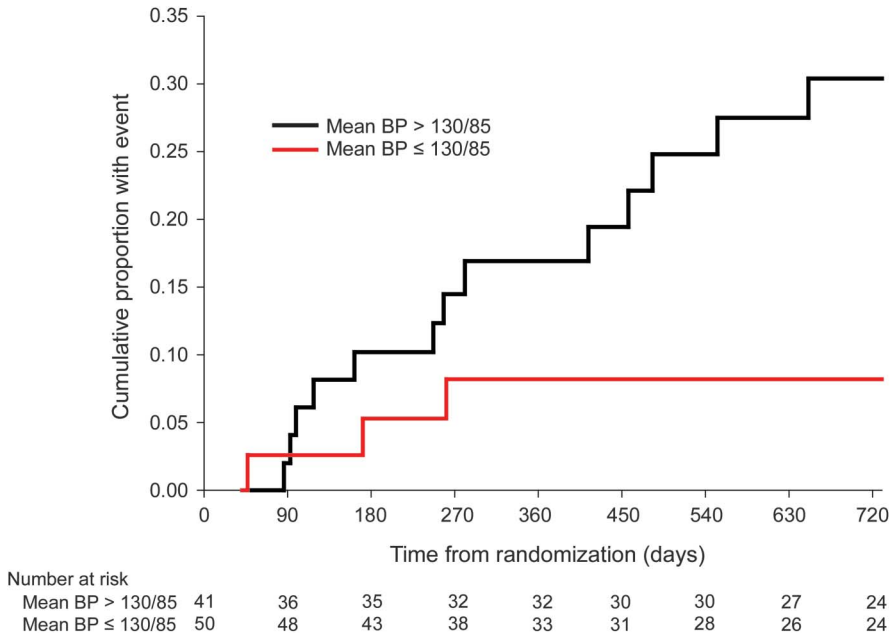


Vertical bars depict the mean systolic (top of bar) and diastolic (bottom of bar) blood pressure of each participant in the study. Those who experienced an ipsilateral ischemic stroke within 2 years of randomization are shown in black. Three participants had mean systolic pressures below 130 mm Hg but diastolic pressures greater than 85 mm Hg. They are just to the right of the dotted vertical line.

Figure 3 shows the categorization into 5 groups based on mean systolic BP during follow-up according to the scheme used by Ovbiagele et al. for the PROFESS trial analysis.

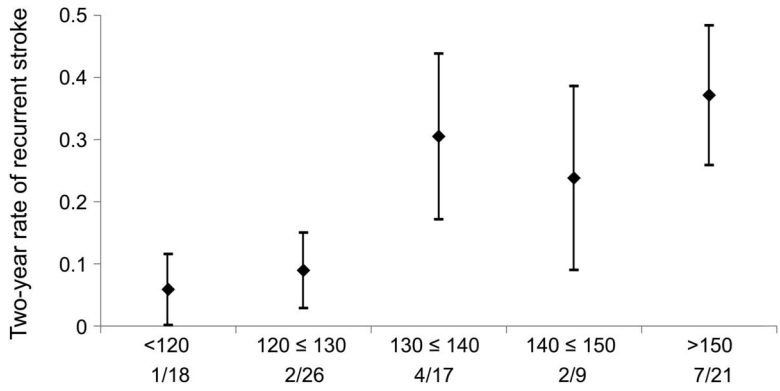
DISCUSSION Prospective observational studies during middle and old age show that usual BP is strongly and directly related to stroke risk down to at least 115/75 mm Hg without any evidence of a threshold effect or J-curve.[8] Treatment of high BP reduces the risk of recurrent stroke, although the optimal level is unknown and a subject of controversy.[6,7,9–12] In the PROGRESS study, the lowest risk of stroke recurrence was among the lowest quartile of achieved systolic BP (<120 mm Hg).[12] In contrast, in the PROFESS study, mean systolic BP <120 mm Hg was associated

Figure 2 Kaplan-Meier cumulative curves for occurrence of ipsilateral ischemic stroke



The number of participants who remained event-free and available for follow-up evaluation at each 90-day interval is shown for each group at the bottom of the graph. BP = blood pressure.

Figure 3 Rate of recurrent stroke within 2 years in the 5 blood pressure groups as defined in the PROFESS study



Kaplan-Meier estimates with vertical bars denoting standard error of the estimates.

with a slight, but statistically significant, increase in stroke risk.[7] Using the same categorization as the PROFESS analysis, we did not find evidence of a J-curve, but this conclusion must be tempered by the wide standard errors for the observed rates due to the small numbers in each group (figure 3).

Patients with severe cerebral arterial occlusive disease may represent a different situation because the hemodynamic effects of the obstruction may require a higher perfusion pressure to maintain cerebral blood flow downstream, thus leading to a higher stroke risk with lower BPs. In the Warfarin-Aspirin Symptomatic Intracranial Disease trial, lower BP during follow-up was associated with lower stroke risk. There was no evidence of an increased stroke risk in those with the lowest BPs (<119 mm Hg systolic or ≤79 mm Hg diastolic).[13] In an analysis of data from the European Carotid Surgery Trial, the North American Symptomatic Carotid Endarterectomy Trial, and the United Kingdom Transient Ischaemic Attack Aspirin Trial, the association of lower BP during follow-up with lower stroke risk was not affected by the presence of a unilateral carotid stenosis or asymptomatic carotid occlusion. However, with bilateral carotid stenosis ≥70%, there was an increased risk of stroke with BPs below 150 mm Hg systolic.[14] Since only 11 nonsurgical participants in COSS had contralateral ≥70% stenosis, we cannot comment on the effect of lower BP in this subgroup. Similarly, we cannot comment on the effect of lower BP on the risk of myocardial infarction. COSS did not record nonfatal myocardial infarction after the first 30 days. None occurred in the nonsurgical group within this period and no fatal myocardial infarctions occurred afterwards.

The patients in our study represent the most extreme case of cerebral hemodynamic compromise, with demonstration by PET of reduced cerebral blood flow relative to oxygen metabolic requirements (increased OEF) in the hemisphere distal to the symptomatic carotid occlusion. Nevertheless, lower BPs were associated with reduced, not increased, stroke risk. This was not simply due to the lower BP group not being hypertensive to begin with as the hazard ratio was the same for the subgroup always treated with antihypertensive drugs as for the entire cohort.

While we cannot definitively conclude from these data that control of BP to these levels will benefit such patients since this was not a randomized trial of different targets for BP control, this study provides Class III evidence that control of hypertension ≤130/85 mm Hg is associated with a reduced risk of subsequent ipsilateral ischemic stroke in patients with recently symptomatic carotid occlusion and hemodynamic cerebral ischemia (increased OEF).

AUTHOR CONTRIBUTIONS

Drs. Powers and Clarke had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Drs. Powers, Clarke, Grubb, Videen, Adams, and Derdeyn. Acquisition of data: Drs. Powers, Clarke, Grubb, Videen, Adams, and Derdeyn. Analysis and interpretation of data: Drs. Powers, Clarke, Grubb, Videen, Adams, and Derdeyn. Drafting of the manuscript: Drs. Powers and Clarke. Statistical analysis: Dr. Clarke. Obtained funding: Drs. Powers and Clarke. Administrative, technical, or material support: Drs. Powers, Clarke, Grubb, Videen, Adams, and Derdeyn. Study supervision: Drs. Powers and Clarke.

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This Week's *Neurology*® Podcast

Lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia (See p. 1027)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the March 25, 2014, issue of *Neurology*. In the second segment, Dr. Andy Southerland talks with Dr. William Powers about his paper on lower stroke risk with lower blood pressure in hemodynamic cerebral ischemia. Dr. Roy Strowd reads our e-Pearl of the week about Déjà vu. In the next part of the podcast, Dr. Maria Farrugia focuses her interview with Dr. Doug Turnbull on the management of mitochondrial disorders. Disclosures can be found at www.neurology.org.

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