Total cerebral blood flow and mortality in old age

A 12-year follow-up study

Behnam Sabayan, MD
Jeroen van der Grond,
PhD
Rudi G. Westendorp,
PhD
J. Wouter Jukema, PhD
Ian Ford, PhD
Brendan M. Buckley,
PhD
Naveed Sattar, PhD
Matthias J.P. van Osch,
PhD
Mark A. van Buchem,
PhD
Anton J.M. de Craen,
PhD

Correspondence to
Dr. Sabayan:
b.sabayan@lumc.nl

ABSTRACT

Objective: To examine the association of total cerebral blood flow (CBF) with all-cause, noncardiovascular, and cardiovascular mortality in older subjects at risk of cardiovascular disease.

Methods: We included 411 subjects with a mean age of 74.5 years from the MRI substudy of the Prospective Study of Pravastatin in the Elderly at Risk. Total CBF was measured at baseline, and occurrence of death was recorded in an average follow-up period of 11.8 years. For each participant, total CBF was standardized for brain parenchymal volume. Cox regression models were used to estimate risk of all-cause, noncardiovascular, and cardiovascular mortality in relation to CBF.

Results: Mortality rates among participants in low, middle, and high thirds of total CBF were 52.1, 41.5, and 28.7 per 1,000 person-years, respectively. Compared with participants in the high third of CBF, participants in the low third had 1.88-fold (95% confidence interval [CI]: 1.30–2.72) higher risk of all-cause mortality, 1.66-fold (95% CI: 1.06–2.59) higher risk of noncardiovascular mortality, and 2.50-fold (95% CI: 1.28–4.91) higher risk of cardiovascular mortality. Likewise, compared with participants in the high third of CBF, participants in the middle third had 1.44-fold (95% CI: 0.98–2.11) higher risk of all-cause mortality, 1.29-fold (95% CI: 0.82–2.04) higher risk of noncardiovascular mortality, and 1.86-fold (95% CI: 0.93–3.74) higher risk of cardiovascular mortality. These associations were independent of prevalent vascular status and risk factors.

Conclusions: Low total CBF is linked with higher risk of all-cause, noncardiovascular, and cardiovascular mortality in older people independent of clinical cardiovascular status. *Neurology*® 2013;81:1922–1929

GLOSSARY

CBF = cerebral blood flow; **CI** = confidence interval; **FLAIR** = fluid-attenuated inversion recovery; **FOV** = field of view; **ICD-10** = *International Classification of Diseases and Related Disorders*, 10th revision; **PROSPER** = Prospective Study of Pravastatin in the Elderly at Risk; **ROI** = region of interest; **TE** = echo time; **TR** = repetition time.

Structural and functional integrity of the brain depends on adequate supply of nutrients and oxygen through blood flow.¹ The brain is a demanding organ and consumes approximately 20% of the oxygen inspired at rest while accounting for only 2% of the body weight.² This high metabolic demand renders the brain tissue vulnerable to low cerebral blood flow (CBF), as several animal studies have shown that long-standing cerebral hypoperfusion leads to neuronal loss, microvascular abnormalities, and cognitive deficit.^{3,4}

Decreased cerebral perfusion in patients with acute traumatic brain injury and cerebrovascular accidents has been linked to adverse clinical outcomes and shorter survival.^{5,6} Likewise, clinical conditions with a state of chronic reduction in CBF, such as heart failure and carotid stenosis, have been associated with an increased risk of mortality.^{7,8} Despite this evidence, the independent role of CBF in the maintenance of health and survival in old age has not been thoroughly investigated.

From the Departments of Radiology (B.S., J.v.d.G., M.J.P.v.O., M.A.v.B.), Gerontology and Geriatrics (B.S., R.G.W., A.J.M.d.C.), and Cardiology (J.W.J.), Leiden University Medical Center; Netherlands Consortium for Healthy Ageing (R.G.W., A.J.M.d.C.), Leiden, the Netherlands; Robertson Center for Biostatistics (I.F.), and Glasgow Cardiovascular Research Centre (N.S.), University of Glasgow, UK; and Department of Pharmacology and Therapeutics (B.M.B.), University College Cork, Ireland.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

In a cohort of older subjects at risk of cardiovascular disease, we investigated whether lower CBF is linked with a higher risk of all-cause, noncardiovascular, and cardiovascular mortality. We hypothesized that lower total CBF is independently associated with higher risk of mortality in old age.

METHODS **Setting and participants.** Participants were included from the nested MRI substudy of the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), a large randomized controlled trial assessing the benefits of 40 mg pravastatin daily on vascular outcomes.⁹ Study participants were men or women aged 70 to 82 years with either preexisting vascular diseases or with increased risk of vascular disease because of smoking, hypertension, or diabetes mellitus. Subjects with congestive heart failure (New York Heart Association class III/IV), arrhythmia, and cognitive impairment (Mini-Mental State Examination [MMSE] score <24) were not recruited in the PROSPER study. Inclusion and exclusion criteria of the PROSPER study have been described in detail elsewhere.⁹ A total of 554 Dutch participants who completed the trial underwent MRI scans of the brain. In this study, we included 411 participants for whom data on baseline total CBF, brain parenchymal volume, and mortality were available. There was no significant difference between characteristics of the included participants and subjects with missing values except for higher prevalence of coronary artery disease in subjects with missing values. Because we previously reported that treatment with pravastatin does not influence level of CBF, participants were included from both pravastatin and placebo groups.¹⁰

Standard protocol approvals, registrations, and patient consents. The institutional ethics review boards of all participating centers approved the protocol of the PROSPER study. The protocol was consistent with the Declaration of Helsinki. The institutional ethics review board of the Leiden University Medical Center approved the protocol for the MRI substudy. All participants gave written informed consent.

MRI scanning. All imaging was performed on a magnetic resonance system operating at a field strength of 1.5 tesla (Philips Medical Systems, Best, the Netherlands). Dual fast spin echo (repetition time [TR] = 3,000 milliseconds; echo time [TE] = 27/120 milliseconds; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; field of view [FOV] = 220 × 220 mm; matrix = 256 × 204), fluid-attenuated inversion recovery (FLAIR) (TR = 8,000 milliseconds; TE = 100 milliseconds; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; FOV = 220 × 176 mm; matrix = 256 × 153), and susceptibility weighted images (multislice gradient echo sequence; TR = 2,593 milliseconds; TE = 48 milliseconds; flip angle = 60°; slice thickness = 6 mm; 22 slices; interslice gap = 6 mm; whole-brain coverage; FOV = 220 × 198 mm; matrix = 256 × 176) were obtained from all subjects. The SIENAX (Structural Image Evaluation using Normalization of Atrophy) technique was used to obtain estimates of total brain parenchymal volume and gray matter and white matter volume. In summary, SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to Montreal Neurological Institute 152 space (by using the skull image to determine the registration scaling), done primarily to obtain the volumetric scaling factor to be used as normalization for head size.¹¹ Segmentation of white matter hyperintensities volume

was performed automatically using Software for Neuro-Image Processing in Experimental Research (SNIPER), an in-house-developed program for image processing.¹² This segmentation was based on the T2-weighted and FLAIR images. Cerebral infarcts were defined as parenchymal defects seen on FLAIR images with the same signal intensity as CSF and a surrounding rim of high signal intensity following a vascular distribution. In addition, single slice phase contrast magnetic resonance angiography (TR/TE = 16/9 milliseconds; flip angle = 7.5°; slice thickness = 5 mm; FOV = 250; reduced FOV = 75%; scan percentage = 80%; matrix = 256; 8 signal averages) with a velocity encoding of 100 cm/s was used for flow measurements.¹³ The scans were performed in a plane perpendicular to the left and right internal carotid artery and the vertebral arteries, at the level of the vertical segment of the petrous portion of the internal carotid artery.

Total CBF. CBF was assessed using an in-house-developed software package (FLOW; Division of Image Processing, Department of Radiology, Leiden University Medical Center) on a workstation (UltraSparc 10; Sun Microsystems, Santa Clara, CA).¹⁴ For this method, a region of interest (ROI) was manually drawn around the vessel in the magnitude image and copied into the phase images. For triggered measurements, a vessel contour was drawn in one heart phase and the software copied this contour to the other phases. Visually, all phases were screened for correct positioning of the ROI. If required, the ROI was adjusted. Flow volume is calculated by integrating the flow velocity values within these contours, multiplied with the areas within the vessel contours. Total CBF was calculated by adding flow from the left and right internal carotid arteries and the flow in both vertebral arteries. Total CBF was expressed in milliliters per minute. We standardized level of total CBF by brain parenchymal volume (mL/min/100 mL) by dividing total CBF (mL/min) by each individual's brain volume (mL) and multiplying the obtained result by 100.

Mortality. Participants were followed for occurrence of mortality until January 1, 2012 in an average follow-up period of 11.8 years. We obtained dates of deaths from the Dutch civic registry and specific data on causes of death from Statistics Netherlands, which assigns codes for all national death certificates according to the *ICD-10*. Death due to cardiovascular mortality was classified as *ICD-10* codes I00–I99 and death due to other reasons was recorded as noncardiovascular mortality.

Other variables. At baseline, a research nurse interviewed all the participants, and data for their demographic characteristics and medication use were obtained. Information about history of vascular diseases was provided by each participant's general practitioner. Diabetes mellitus was defined by self-reported history, a fasting blood glucose concentration of 7.0 mmol/L, or self-reported use of antidiabetic medication. Blood pressure was measured in sitting position using a fully automatic electronic sphygmomanometer (Omron M4; Omron Healthcare, Hoofddorp, Netherlands). Body mass index was measured using standard protocols. Global cognitive function was assessed using the MMSE.

Statistical analysis. Baseline characteristics of the study participants are reported as mean (SD) or median (interquartile range) for continuous variables and number (percentage) for categorical variables. Differences in characteristics of study participants in thirds of CBF were tested by analysis of covariance or Kruskal-Wallis for continuous variables and Pearson χ^2 test for categorical variables. To compare cumulative incidence of all-cause, noncardiovascular, and cardiovascular mortality in thirds of total CBF, Kaplan-Meier graphs were made and strata were compared with

the log-rank test. We used Cox proportional hazard models to estimate risk of all-cause, noncardiovascular, and cardiovascular mortality associated with level of total CBF. Cox regression models were fit with time to death as the outcome variables and total CBF as the determinants. We performed our analyses in 3 steps. In the first step, analyses were performed unadjusted. In the second step, analyses were adjusted for age and sex, and finally analyses were adjusted for age, sex, cardiovascular risk factors, and diseases including body mass index, smoking, serum cholesterol, mean arterial pressure, antihypertensive medication use, diabetes mellitus, statin treatment, and history of vascular disease (coronary, cerebral, or peripheral) at baseline. In the multivariate analyses, body mass index, serum cholesterol, and mean arterial pressure were entered as continuous variables and the other parameters were entered as dichotomous variables. In addition, we performed a series of sensitivity analyses to test whether our results were consistent in different subgroups of participants. In these sensitivity analyses, we separately excluded subjects with diabetes mellitus, hypertension, high body mass index ($>25 \text{ kg/m}^2$), elevated serum levels of N-terminal pro-brain natriuretic peptide ($>400 \text{ ng/L}$)¹⁵ as a marker of impaired cardiac function, coronary artery disease, cerebrovascular accidents (stroke or TIA), brain infarcts, high load of white matter hyperintensities ($>5 \text{ mL}$), and impaired cognitive function (MMSE score <28 points). All

analyses were performed using SPSS software (version 20.0.0; SPSS Inc., Chicago, IL).

RESULTS Table 1 shows characteristics of the study participants in the whole study population and in thirds of total CBF. Mean age of participants was 74.5 years and 55.5% of them were female. Mean values for total CBF and total CBF by parenchymal volume were 522.6 mL/min and 49.3 mL/min/100 mL, respectively. There was no significant difference in sociodemographic, cerebrovascular, and cognitive characteristics of the participants in thirds of total CBF except that participants with lower total CBF were more frequently male ($p = 0.016$) and had higher body mass index ($p = 0.041$).

During the follow-up period, 195 subjects (47.4%) died, of whom 129 subjects (66.2%) died due to noncardiovascular reasons and 66 (33.8%) died of cardiovascular causes. Numbers of deaths in low, middle, and high thirds of CBF were 80 (41.0%), 66 (33.8%), and 49 (25.2%) respectively.

Table 1 Characteristics of study participants in the whole study population and in thirds of total CBF

		Thirds of total CBF, mL/min/100 mL			
Characteristics	All (N = 411)	Low, 9.7–45.7 (n = 137)	Middle, 45.8–52.2 (n = 137)	High, 52.3–84.8 (n = 137)	p Value ^a
Sociodemographic factors					
Age, y	74.5 (3.2)	74.6 (3.3)	74.6 (3.2)	74.1 (3.1)	0.307
Men, n (%)	228 (55.5)	86 (62.8)	79 (57.7)	63 (46.0)	0.016
Age left school, y	15.6 (3.0)	15.7 (2.9)	15.5 (3.1)	15.5 (3.0)	0.153
Current smoker, n (%)	84 (20.4)	30 (21.9)	26 (19.0)	28 (20.4)	0.836
Cardiovascular factors					
History of CVD, n (%)	172 (41.8)	64 (46.7)	51 (37.2)	57 (41.6)	0.281
History of stroke or TIA, n (%)	66 (16.1)	21 (15.3)	20 (14.6)	25 (18.2)	0.685
History of CAD, n (%)	48 (11.7)	20 (14.6)	14 (10.2)	14 (10.2)	0.428
NT-proBNP, ^b ng/L, median (IQR)	105 (55.1–211.5)	104 (46.4–199.0)	107 (64.9–235.4)	106 (58.1–197.2)	0.651
Serum cholesterol, mmol/L	5.7 (0.8)	5.6 (0.9)	5.8 (0.8)	5.7 (0.8)	0.153
Body mass index, kg/m ²	26.6 (3.4)	27.2 (3.6)	26.7 (3.3)	26.1 (3.3)	0.041
Diabetes mellitus, n (%)	74 (18.0)	26 (19.0)	24 (17.5)	24 (17.5)	0.936
Antihypertensive therapy, n (%)	254 (61.8)	80 (58.4)	86 (62.8)	88 (64.2)	0.585
SBP, mm Hg	157 (21)	159 (22)	159 (21)	154 (21)	0.089
DBP, mm Hg	86 (11)	87 (10)	86 (10)	84 (11)	0.102
MAP, mm Hg	110 (13)	111 (13)	110 (13)	108 (13)	0.057
MRI findings and cognition					
WMH volume, mL	5.3 (9.9)	5.8 (8.9)	5.9 (12.1)	4.3 (8.4)	0.311
Presence of infarcts, n (%)	135 (32.9)	52 (38)	44 (32.4)	39 (28.5)	0.244
MMSE score, median (IQR)	28 (27–29)	28 (28–29)	29 (27–30)	29 (27–30)	0.441

Abbreviations: CAD = coronary artery disease; CBF = cerebral blood flow; CVD = cardiovascular disease; DBP = diastolic blood pressure; IQR = interquartile range; MAP = mean arterial pressure; MMSE = Mini-Mental State Examination; NT-proBNP = N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure; WMH = white matter hyperintensity.

Data are presented as mean (SD) except as noted.

^aProbability values indicate significant difference in thirds of total CBF.

^bSerum NT-proBNP was measured 6 months after inclusion time.

Figure 1 Mortality rate in relation to cerebral blood flow

All-cause, noncardiovascular, and cardiovascular mortality rates with 95% confidence interval (CI) per 1,000 person-years in thirds of cerebral blood flow.

All-cause mortality rates in subjects with low, middle, and high total CBF were 52.1, 41.5, and 28.7 per 1,000 person-years, respectively. Noncardiovascular mortality rates in subjects with low, middle, and high total CBF were 32.6, 27.0, and 21.1 per 1,000 person-years, respectively, and cardiovascular mortality rates in subjects with low, middle, and high total

CBF were 19.5, 14.4, and 7.6 per 1,000 person-years, respectively (figure 1).

Table 2 shows the risks of all-cause, noncardiovascular, and cardiovascular mortality in relation to total CBF. In the multivariate adjusted model, compared with participants in the high third of CBF, participants in the low third had 1.88-fold (95% confidence

Table 2 Risk of mortality in relation to level of total CBF

	Total CBF, mL/min/100 mL			
	Low (9.7-45.7)	Middle (45.8-52.2)	High (52.3-84.8)	p for trend
All-cause mortality				
Unadjusted model	1.98 (1.39-2.83)	1.51 (1.05-2.19)	1 (ref.)	<0.001
Age- and sex-adjusted model	1.82 (1.27-2.61)	1.41 (0.98-2.06)	1 (ref.)	0.001
Multivariate adjusted model ^a	1.88 (1.30-2.72)	1.44 (0.98-2.11)	1 (ref.)	0.001
Noncardiovascular mortality				
Unadjusted model	1.71 (1.11-2.62)	1.35 (0.87-2.11)	1 (ref.)	0.014
Age- and sex-adjusted model	1.57 (1.02-2.42)	1.27 (0.82-1.99)	1 (ref.)	0.040
Multivariate adjusted model ^a	1.66 (1.06-2.59)	1.29 (0.82-2.04)	1 (ref.)	0.026
Cardiovascular mortality				
Unadjusted model	2.74 (1.43-5.25)	1.96 (0.99-3.87)	1 (ref.)	0.002
Age- and sex-adjusted model	2.52 (1.31-4.85)	1.76 (0.89-3.51)	1 (ref.)	0.005
Multivariate adjusted model ^a	2.50 (1.28-4.91)	1.86 (0.93-3.74)	1 (ref.)	0.007

Abbreviations: CBF = cerebral blood flow; ref. = reference.

Data are hazard ratio (95% confidence interval). Number of participants in each third is 13.

^a Adjusted for age, sex, body mass index, smoking, serum cholesterol, mean arterial pressure, antihypertensive medication, diabetes mellitus, statin treatment, and history of vascular diseases (coronary, cerebral, or peripheral).

interval [CI]: 1.30–2.72) higher risk of all-cause mortality, 1.66-fold (95% CI: 1.06–2.59) higher risk of noncardiovascular mortality, and 2.50-fold (95% CI: 1.28–4.91) higher risk of cardiovascular mortality. Likewise, compared with participants in the high third of CBF, participants in the middle third had 1.44-fold (95% CI: 0.98–2.11) higher risk of all-cause mortality, 1.29-fold (95% CI: 0.82–2.04) higher risk of noncardiovascular mortality, and 1.86-fold (95% CI: 0.93–3.74) higher risk of cardiovascular mortality. We found similar associations between

lower CBF and higher risk of mortality when analyses were performed using CBF as a continuous variable (data not shown). The corresponding Kaplan-Meier survival curves showed that subjects with low total CBF had the highest cumulative incidence of all-cause, noncardiovascular, and cardiovascular mortality (figure 2).

We performed a series of sensitivity analyses on the associations of total CBF with all-cause, noncardiovascular, and cardiovascular mortality separately excluding participants who had diabetes mellitus, hypertension, high body mass index, impaired cardiac functioning, coronary artery disease, cerebrovascular accidents, brain infarcts, high load of white matter hyperintensities, and impaired cognitive function (figure 3). We found that exclusion of subjects with cardiovascular risk factors, cerebrovascular diseases, and impaired cognitive function did not essentially change the results. In another sensitivity analysis, to test whether our findings could be attributable to short-term death events, we excluded subjects who died in the first 2 years of follow-up ($n = 12$). This sensitivity analysis showed that the associations were not dependent on short-term death events (data not shown).

DISCUSSION In this study, we showed that lower total CBF is associated with higher risk of all-cause, noncardiovascular, and cardiovascular mortality in older subjects at high risk of cardiovascular diseases. These associations were independent of prevalent vascular diseases (coronary, cerebral, or peripheral) and cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, smoking, and hypercholesterolemia.

Despite the fact that multiple systemic and cerebrovascular mechanisms act in concert to maintain optimal CBF, total CBF decreases with increasing age.¹⁶ Decrease in CBF has been implicated in the pathogenesis of neurodegenerative disorders such as dementia and certain cerebrovascular events such as low-flow infarcts.^{17,18} A recent study showed that lower total CBF is an independent risk factor for mortality and adverse clinical outcomes in patients with heart failure.¹⁹ However, little is known about the independent role of CBF in the maintenance of health and survival in older people. In the current study, we observed that lower total CBF in older subjects at risk of cardiovascular disease is associated with higher risk of mortality.

Different explanations can be proposed for the association of lower CBF with higher risk of all-cause, noncardiovascular, and cardiovascular mortality. The first explanation could be that lower total CBF in older subject is related to lower metabolic demand of the brain due to parenchymal atrophy, which independently puts subjects at higher risk of mortality.²⁰ Because we normalized level of total CBF for brain parenchymal

Figure 2 Cumulative mortality in relation to cerebral blood flow

Kaplan-Meier curves for all-cause (A), noncardiovascular (B), and cardiovascular (C) mortality in thirds of total cerebral blood flow (CBF) (mL/min/100 mL).

Figure 3 Subgroup analysis on the association between cerebral blood flow and mortality

Hazard ratios (95% confidence intervals [CIs]) for all-cause, noncardiovascular, and cardiovascular mortality for each third decrease in level of total cerebral blood flow in the whole study population and in subgroups of participants without diabetes mellitus (DM), hypertension (HTN), high body mass index (BMI) >25 kg/m², serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) >400 ng/L, history of coronary artery disease (CAD), stroke or TIA, brain infarcts, high load of white matter hyperintensities (WMH) (>5 mL), and Mini-Mental State Examination (MMSE) score of <28 points. All analyses were adjusted for age and sex.

volume in each participant, this explanation seems unlikely. In addition, we observed that exclusion of participants with impaired cognition, which is closely related to a decrease in number and activity of neurons in the brain,²⁰ did not materially change the associations between CBF and mortality outcomes.

A second explanation might be that lower total CBF reflects the presence of vascular risk factors and preexisting vascular pathologies in the brain and heart^{21–23} and that they, rather than decreased CBF, are responsible for increasing risk of mortality in older subjects. In line with this explanation, we found that subjects with lower CBF tended to have higher blood pressure and body mass index. Previous studies also showed that vascular risk factors such as hypertension can lead to a decline in CBF.²⁴ We observed that the adjustments of the analyses for cardiovascular risk factors and diseases did not essentially change the estimates, and the sensitivity analyses showed that the associations between total CBF and mortality outcomes were not dependent on presence of impaired cardiac functioning, history of coronary artery events, cerebrovascular accidents, cerebral infarcts, and white matter hyperintensities. Nevertheless, the possibility of residual confounding from unmeasured cardiovascular risk factors cannot be excluded. We observed that

correction of all analyses for various well-established cardiovascular risk factors only slightly influenced the associations. Therefore, we expect that if we could account for potential unmeasured confounders, this would result in minor changes of the measures of association between lower CBF and higher risk of mortality.

A third possible explanation involves the critical role of adequate CBF in maintenance of brain structure and function.¹ There are different lines of evidence indicating that lower CBF is associated with structural and functional abnormalities in the brain.¹⁷ Because the brain is a vital organ in regulation of homeostasis,²⁵ it is likely that suboptimal CBF, via neuronal injury and cell death, independently alters normal function of the brain leading to an increased risk of mortality.²⁶ It has been shown that neuronal damage is not only associated with structural and functional changes in the brain but also with disturbances in the immune system, energy homeostasis, autonomic stress response, and endocrine regulation.^{27–30} Because it is not possible to make a causal inference based solely on our observation, this hypothesis needs to be tested in future studies investigating the long-term consequences of suboptimal CBF on major homeostatic mechanisms.

The main strengths of this study include a long follow-up time of 12 years and availability of extensive data on various sociodemographic and cardiovascular factors. A possible limitation is the inclusion of older subjects with or at high risk of cardiovascular disease, which limits the generalizability of our findings to a general population of older subjects. However, the study population represents a substantial part of the aging subjects given the high prevalence of cardiovascular diseases and risk factors in the elderly. As another limitation, we only assessed total CBF and were not able to investigate the association between regional CBF and mortality outcomes. Future studies, using arterial spin-labeling MRI perfusion techniques, might unravel whether there is any association between regional CBF and cause-specific mortality in old age. In addition, we assessed total CBF with an in-house–developed software package that needs further validation in future studies.

Our findings show that lower total CBF standardized for brain parenchymal volume, independent of cardiovascular diseases and risk factors, is linked with higher risk of all-cause, noncardiovascular, and cardiovascular mortality in elderly subjects at high risk of cardiovascular diseases. These findings need to be replicated in future population-based studies with a larger number of participants.

AUTHOR CONTRIBUTIONS

Behnam Sabayan contributed to formulating the research question, analysis and interpretation of data, and drafting the manuscript. Rudi G.J. Westendorp and Mark A. van Buchem contributed to study design, acquisition of subjects and data, interpretation of data, and revising the manuscript. Jeroen van der Grond, Wouter Jukema, Ian Ford, Brendan M. Buckley, Naveed Sattar, and Matthias J.P. van Osch contributed to interpretation of data and revising the manuscript. Anton J.M. de Craen contributed to formulating the research question, interpretation of data, and revising the manuscript.

STUDY FUNDING

The original PROSPER clinical trial was founded by an investigator-initiated grant from Bristol-Myers Squibb, USA. However, the company had no involvement in the formulation of hypotheses, analysis of the data, or in any aspect of the preparation of the manuscript.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received May 15, 2013. Accepted in final form August 27, 2013.

REFERENCES

- Atwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. *Nature* 2010;468:232–243.
- Erecinska M, Silver IA. Tissue oxygen tension and brain sensitivity to hypoxia. *Respir Physiol* 2001;128:263–276.
- Farkas E, Luiten PG, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: a model for chronic cerebral hypoperfusion-related neurodegenerative diseases. *Brain Res Rev* 2007;54:162–180.
- Shin JS, Hyun SY, Kim DH, et al. Chronic hypoperfusion increases claudin-3 immunoreactivity in rat brain. *Neurosci Lett* 2008;445:144–148.
- Downard C, Hulka F, Mullins RJ, et al. Relationship of cerebral perfusion pressure and survival in pediatric brain-injured patients. *J Trauma* 2000;49:654–658.
- Markus HS. Cerebral perfusion and stroke. *J Neurol Neurosurg Psychiatry* 2004;75:353–361.
- Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993;88:107–115.
- Cao JJ, Arnold AM, Manolio TA, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. *Circulation* 2007;116:32–38.
- Shepherd J, Blauw GJ, Murphy MB, et al. The design of a prospective study of pravastatin in the elderly at risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. *Am J Cardiol* 1999;84:1192–1197.
- ten Dam VH, Box FM, de Craen AJ, et al. Lack of effect of pravastatin on cerebral blood flow or parenchymal volume loss in elderly at risk for vascular disease. *Stroke* 2005;36:1633–1636.
- Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 2004;23(suppl 1):S208–S219.
- Admiraal-Behtoul F, van den Heuvel DM, Olofsen H, et al. Fully automatic segmentation of white matter hyperintensities in MR images of the elderly. *Neuroimage* 2005;28:607–617.
- Bakker CJ, Kouwenhoven M, Hartkamp MJ, Hoogeveen RM, Mali WP. Accuracy and precision of time-averaged flow as measured by nontriggered 2D phase-contrast MR angiography, a phantom evaluation. *Magn Reson Imaging* 1995;13:959–965.
- Spilt A, Box FM, van der Geest RJ, et al. Reproducibility of total cerebral blood flow measurements using phase contrast magnetic resonance imaging. *J Magn Reson Imaging* 2002;16:1–5.
- Pfister R, Schneider CA. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: application of natriuretic peptides. *Eur Heart J* 2009;30:382–383.
- van Es AC, van der Grond J, ten Dam VH, et al. Associations between total cerebral blood flow and age related changes of the brain. *PLoS One* 2010;5:e9825.
- Sabayan B, Jansen S, Oleksik AM, et al. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. *Ageing Res Rev* 2012;11:271–277.
- Weiller C, Ringelstein EB, Reiche W, Buell U. Clinical and hemodynamic aspects of low-flow infarcts. *Stroke* 1991;22:1117–1123.
- Kim MS, Kim JS, Yun SC, et al. Association of cerebral blood flow with the development of cardiac death or urgent heart transplantation in patients with systolic heart failure. *Eur Heart J* 2012;33:354–362.
- Kapogiannis D, Mattson MP. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurol* 2011;10:187–198.

21. Pase MP, Grima NA, Stough CK, Scholey A, Pipingas A. Cardiovascular disease risk and cerebral blood flow velocity. *Stroke* 2012;43:2803–2805.
22. Markus HS, Lythgoe DJ, Ostegaard L, O'Sullivan M, Williams SC. Reduced cerebral blood flow in white matter in ischaemic leukoaraiosis demonstrated using quantitative exogenous contrast based perfusion MRI. *J Neurol Neurosurg Psychiatry* 2000;69:48–53.
23. Ackerman RH. Cerebral blood flow and neurological change in chronic heart failure. *Stroke* 2001;32:2462–2464.
24. Muller M, van der Graaf Y, Visseren FL, Mali WP, Geerlings MI. Hypertension and longitudinal changes in cerebral blood flow: the SMART-MR study. *Ann Neurol* 2012;71:825–833.
25. Lam TK. Neuronal regulation of homeostasis by nutrient sensing. *Nat Med* 2010;16:392–395.
26. Sekhon LH, Morgan MK, Spence I, Weber NC. Chronic cerebral hypoperfusion: pathological and behavioral consequences. *Neurosurgery* 1997;40:548–556.
27. Becher B, Prat A, Antel JP. Brain-immune connection: immuno-regulatory properties of CNS-resident cells. *Glia* 2000;29:293–304.
28. Abizaid A, Horvath TL. Brain circuits regulating energy homeostasis. *Regul Pept* 2008;149:3–10.
29. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci* 2009;10:397–409.
30. Cechetti F, Pagnussat AS, Worm PV, et al. Chronic brain hypoperfusion causes early glial activation and neuronal death, and subsequent long-term memory impairment. *Brain Res Bull* 2012;87:109–116.

Guide the Future of Neurology—Become a Mentor!

The Academy's Neurology Career Center is working to bring experienced members together with members who seek guidance on their career path. AAN Mentor Connect needs volunteer Mentors who are willing to share their expertise, insights, and experiences with Mentees.

This flexible program, available only to AAN members, matches prospective Mentors and Mentees, and enables you to develop a plan with the Mentee that has a mutually agreeable schedule and expectations.

Enjoy the personal satisfaction of making a valued contribution to the career of a fellow AAN member. Visit www.aan.com/view/Mentor to learn more and register to be a Mentor today.

20 Minutes Pack a Punch

Neurology® Podcasts

- Interviews with top experts on new clinical research in neurology
- Editorial comments on selected articles
- Convenient—listen during your commute, at your desk, or even at the gym
- On demand—it's there when you want it
- Fun and engaging
- New topic each week
- FREE

Listen now at www.aan.com/podcast