Basilar Artery Diameter Is an Independent Predictor of Incident Cardiovascular Events

Makiko Tanaka, Manabu Sakaguchi, Kaori Miwa, Shuhei Okazaki, Shigetaka Furukado, Yoshiki Yagita, Hideki Mochizuki, Kazuo Kitagawa

Objective—Basilar arterial (BA) dolichoectasia is associated with cerebral small-vessel disease and stroke. However, the association between moderate dilation of the BA and cerebral small-vessel disease or subsequent cardiovascular events remains unclear. This study aims to clarify the factors related to BA diameter and to clarify whether the BA diameter is an independent predictor of cardiovascular events.

Approach and Results—The study subjects comprised 493 outpatients with atherosclerotic risk factors. BA diameter, lacunar infarct, severity of deep white matter hyperintensities, and intracranial steno-occlusive lesions were assessed with MRI and magnetic resonance angiography. Then, we prospectively evaluated the association between BA diameter and cardiovascular events. The BA diameter ranged from 1.1 to 5.2 mm, and only 0.8% of the patients had dolichoectasia. Male sex, the presence of lacunar infarcts, the severity of deep white matter hyperintensities, the fetal-type variation of the circle of Willis, and intracranial steno-occlusive lesions were independently associated with BA diameter. In the mean follow-up of 6.0 years, 91 patients developed cardiovascular events. BA diameter was independently associated with total cardiovascular events after adjusting for age, sex, and conventional risk factors (hazard ratio, 1.55 per 1 mm increase in BA diameter; \( P=0.009 \)).

Conclusions—Increased BA diameter within the normal range is related to both large-vessel disease and cerebral small-vessel disease, and it could be a new predictor of cardiovascular events. (Arterioscler Thromb Vasc Biol. 2013;33:2240-2244.)

Key Words: atherosclerosis ▪ cardiovascular diseases ▪ cerebral small-vessel disease ▪ magnetic resonance imaging ▪ vertebrobasilar insufficiency

As brain MRI became widely used in the clinical setting, several vascular surrogate markers, such as silent brain infarction, white matter lesions, and cerebral microbleeds, have attracted large attention because of their predictive value for future stroke. Intracranial stenosis or occlusion of major cerebral arteries has been routinely evaluated with brain MRI for the determination of pathogenesis of ischemic stroke, and the predictive value of asymptomatic intracranial artery stenosis has been examined. The vessel diameter of cerebral major arteries can also be evaluated with brain MRI; however, its clinical significance has been rarely examined, except for extreme dilation and elongation, which is called dolichoectasia. Several studies have shown that dolichoectasia is associated with cerebral small-vessel diseases (CSVDs), such as lacunar infarct, état criblé, and white matter lesions. In addition, aging, atherosclerotic risk factors, and some genetic factors that affect connective tissues have been shown to be related to dolichoectasia. Dolichoectasia is most often observed in the basilar artery (BA) and is associated with intracranial bleeding, stroke mortality, and cardiovascular death. Given that (1) BA dolichoectasia is associated with cardiovascular events, (2) BA diameter is the most precise and objective marker of vascular dilation in BA dolichoectasia, (3) BA dolichoectasia is associated with aging and atherosclerosis, and thus mild or moderate BA dilation may gradually become dolichoectasia with aging, and (4) mild or moderate BA dilation is more common than BA dolichoectasia, it is important to assess the relationship between BA diameter and future cardiovascular events. We hypothesize that BA diameter is associated with other cerebral vascular lesions and increased risk of cardiovascular events, even after accounting for underlying known risk factors, such as hypertension, diabetes mellitus, and a history of cardiovascular events.

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In this study, we investigated the association between BA diameter and CSVD and cerebral large-vessel diseases through brain MRI and prospectively investigated the predictive value of BA diameter for subsequent cardiovascular events in patients with atherosclerotic risk factors.

Materials and Methods

Materials and Methods are available in the online-only Supplement.
Results

The characteristics of the patients are shown in Table 1. The BA diameter ranged from 1.1 to 5.2 mm (median, 2.7 mm), and the distribution is also shown in Table 1. The variables associated with BA diameter in the univariate analysis were male sex, hypertension, smoking habit, history of ischemic heart disease and stroke, and body height. Also, lacunar infarct, severity of periventricular hyperintensities, deep white matter hyperintensities (DWMH), type of variation of the posterior circle of Willis, intracranial stenotic lesion assessed by MRI, and mean maximum intima-media thickness (IMT) and pulsatility index assessed by carotid ultrasound were associated with BA diameter (Table 2).

In the follow-up study, the mean follow-up period was 6.0 years. Ninety-one patients (18.5%) developed new cardiovascular events, of whom 44 had cerebrovascular events (cerebral infarction in 35, cerebral hemorrhage in 2, subarachnoid hemorrhage in 1, surgical therapy for transient ischemic attack in 6), 39 had coronary events (acute myocardial infarction in 8 and revascularization therapy for ischemic heart disease in 31), and 8...
had peripheral arterial events (arteriosclerosis obliterans in 5 and aortic aneurysm in 3). Of the 35 patients with a cerebral infarction, 11 had lacunar infarction, 8 had large-artery atherosclerosis, 6 had cardioembolism, and 10 had other conditions or unknown pathogenesis. Patients with incident cardiovascular events were more likely to be older, men, and have diabetes mellitus and a history of ischemic heart disease and stroke (Table 1). In the cross-sectional study, BA diameter was markedly associated with cardiovascular events (log-rank test \( P < 0.001 \); Figure). In the Cox proportional hazards models, BA diameter was associated with the risk of total cardiovascular events after adjusting for age and sex (HR, 1.75 per 1 mm increase in BA diameter; \( P = 0.01 \)), and the association remained significant after adjusting for conventional risk factors and other MRI parameters (Table 5). Among the cardiovascular events, BA diameter was associated with coronary heart events after adjusting for age and sex (HR, 1.59 per 1 mm increase in BA diameter; \( P = 0.04 \)) but not with cerebrovascular events (HR, 1.07 per 1 mm increase in BA diameter; \( P = 0.93 \)). However, BA diameter tended to be associated with cerebrovascular events in the vertebrobasilar territory (HR, 1.90 per 1 mm increase in BA diameter; \( P = 0.12 \)) or in noncardioembolic ischemic stroke (HR, 1.76 per 1 mm increase in BA diameter; \( P = 0.09 \)). Concerning the other MRI parameters, lacunar infarct and DWMH were associated with cerebrovascular events. Intracranial stenotic lesions were not significantly associated with the total cardiovascular, cerebrovascular, or coronary heart events.

In the cross-sectional study, BA diameter was markedly influenced by the type of variation of the posterior circle of Willis (Tables 2 and 3). To avoid the effect of anatomic variation, we also assessed the association between BA diameter and cardiovascular events only in patients with adult-type circle of Willis (Table I in the online-only Data Supplement). In 285 patients with adult-type circle of Willis, BA diameter was associated with the risk of total cardiovascular events after adjusting for age and sex (HR, 1.75 per 1 mm increase in BA diameter; \( P = 0.01 \)), and the association remained significant after adjusting for conventional risk factors and other MRI parameters.

### Discussion

The BA diameter of the present subjects was smaller than that in the previous reports. Marked dilation of the BA, usually defined as >4.5 mm of the vessel size, is defined as BA dolichoectasia.\(^{17,18}\) The prevalence of BA or intracranial dolichoectasia is 3.1% to 13.9% in patients with ischemic stroke\(^{5,11}\) and 1.3% in healthy people.\(^{7}\) In the present study, patients with a BA diameter >4.5 mm made up only 0.8% of the 493 total patients, of whom 24.7% had a history of ischemic stroke. We defined BA diameter as the minor axis of the BA (mean±SD, 3.00±0.70 mm; HR, 1.75 per 1 mm increase in BA diameter; \( P = 0.01 \)) after adjusting for conventional risk factors and other MRI parameters (Table 4). Among the cardiovascular events, BA diameter was associated with coronary heart events after adjusting for age and sex (HR, 1.59 per 1 mm increase in BA diameter; \( P = 0.04 \)) but not with cerebrovascular events (HR, 1.07 per 1 mm increase in BA diameter; \( P = 0.93 \)). However, BA diameter tended to be associated with cerebrovascular events in the vertebrobasilar territory (HR, 1.90 per 1 mm increase in BA diameter; \( P = 0.12 \)) or in noncardioembolic ischemic stroke (HR, 1.76 per 1 mm increase in BA diameter; \( P = 0.09 \)). Concerning the other MRI parameters, lacunar infarct and DWMH were associated with cerebrovascular events. Intracranial stenotic lesions were not significantly associated with the total cardiovascular, cerebrovascular, or coronary heart events.

![Figure](http://atvb.ahajournals.org/)

**Figure.** Cumulative event-free survival for cardiovascular events in patients with basilar artery diameter above or below the median. BA indicates basilar artery; and CVD, cardiovascular disease.
BA dolichoectasia has been extensively studied and shown to be associated with CSVD in previous cross-sectional studies.\(^5^,19–22\) Here, we found that increased BA diameter was associated with CSVD (ie, lacunar infarct and severity of white matter lesions), although most of the patients did not have dolichoectasia. CSVD and BA dilation may have a common pathogenesis. We showed a significant association between BA diameter and the pulsatility index of the carotid artery, which represents the vascular resistance. Large artery stiffening and carotid and intracranial arterial pulsatility have recently been shown to be associated with CSVD.\(^23–25\) Increased arterial stiffness and vascular resistance may underlie both BA dilation and CSVD. We also found that BA diameter was associated with large-vessel atherosclerosis (ie, carotid IMT and intracranial arterial stenosis). Pico et al\(^5\) reported that intracranial arterial dolichoectasia was not associated with carotid IMT in patients with cerebral infarction. However, BA diameter significantly correlated to carotid IMT and intracranial arterial stenosis in our study (Table 2). Only 40% of participants in this study had a history of stroke; thus, the difference in patient backgrounds may explain this discrepancy. The relationship between BA diameter and intracranial arterial stenosis was significant only when the stenosis was localized in the internal carotid arteries. The BA may be dilated as a compensatory response to preserve the cerebral blood flow in case of internal carotid artery stenosis or occlusion.\(^26\) CSVD and large-vessel disease were both related to, although CSVD seems to have a closer association with, BA dilation.

BA dolichoectasia has been shown to be associated with intracranial bleeding and stroke mortality.\(^6,13–16\) However, the clinical significance of BA diameter for incident cardiovascular and cerebrovascular events has rarely been examined. Pico et al\(^6\) investigated the association between BA diameter and 5-year mortality as a result of stroke, nonstroke vascular events, and nonvascular events in 466 patients with brain infarction. They found that BA diameter, especially if \(>4.3\) mm, was independently associated with cerebrovascular mortality. In this prospective cohort study, we showed the predictive value of BA diameter for the total cardiovascular events. Unexpectedly, our results showed that BA diameter had a predictive value for coronary heart events but not for cerebrovascular events. The absence of a relationship between BA diameter and cerebrovascular events may be explained by the fact that stroke is a multifactorial disease with both ischemic and hemorrhagic types. However, we found a borderline significance between BA diameter and cerebrovascular events in the vertebrobasilar arterial territory or in noncardioembolic ischemic stroke. Thus, the relationship between BA diameter and future stroke, especially noncardioembolic ischemic stroke in the posterior circulation, needs to be further examined. In contrast, BA diameter had a predictive value for coronary heart events. BA diameter itself is unlikely to be a causal factor of coronary heart events. However, the association between dolichoectasia and myocardial infarction has also been reported.\(^5,27\) The reasons for the association between intracranial vascular dilation and coronary heart events are unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\) The significant relationship of BA diameter to a history of ischemic heart disease is unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\) The significant relationship of BA diameter to a history of ischemic heart disease is unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\) The significant relationship of BA diameter to a history of ischemic heart disease is unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\) The significant relationship of BA diameter to a history of ischemic heart disease is unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\) The significant relationship of BA diameter to a history of ischemic heart disease is unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\) The significant relationship of BA diameter to a history of ischemic heart disease is unclear. It might be explained by the fact that BA diameter was associated with carotid IMT, which is a strong predictor of myocardial infarction.\(^28\)
DWMH were both related to cerebrovascular events, which have already been shown to be independent predictors of incident stroke. However, intracranial stenosis was not related to cerebrovascular events. The reason may be that most cases of intracranial stenosis were asymptomatic in this study and that the annual stroke rate was low, ≈0.5%, in patients with asymptomatic intracranial stenosis.

In conclusion, BA diameter, easily measured by routine brain MRI, is associated with both CSVD and large-vessel atherosclerosis and could be a new predictive marker of incident cerebrovascular events. Increased vascular resistance, atherosclerosis, and increased flow volume may play a role in BA dilation.

Acknowledgments
We thank C. Kurano and K. Nishiyama for their secretarial assistance.

Disclosures
None.

References

Significance
This study shows the clinical significance of the basilar artery diameter, which can be measured by routine brain MRI. Many studies have reported that extreme dilation of the basilar artery is associated with cerebral small-vessel disease, subsequent stroke, and cardiovascular death. However, the significance of mild or moderate dilation of the basilar artery has not been reported. In this prospective cohort study, we show that the basilar artery diameter is associated with subsequent cardiovascular diseases, including cerebrovascular diseases and coronary heart diseases. We also show that basilar artery dilation is associated with both large-artery atherosclerosis, such as intracranial arterial stenosis and carotid intima-media thickness, and cerebral small-vessel disease, such as lacunar infarction and deep white matter lesion. The basilar artery diameter can be a new predictive marker of incident cardiovascular disease.
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In the article by Tanaka et al, which appeared in the September 2013 issue of the journal (Arterioscler Thromb Vasc Biol. 2013;33:2240–2244. DOI: 10.1161/ATVBAHA.113.301467), reference 12 was incorrect. The correct reference is:


The online version of the article has been corrected and is available at http://atvb.ahajournals.org/content/33/9/2240.full.
Incomplete laboratory data (N = 20)
MRI performed in acute phase of stroke or in the perioperative period (N = 10)
Vasculitis syndromes (N = 7), Vertebrobasilar occlusion, dissection or stenting (N = 4)
Inappropriate MRI sequences (N = 3)

Exclusion

New cardiovascular events
Death (N = 34)
Withdrawal for personal reasons (N = 34)

Enrollment

N = 1106

N = 549

N = 493

N = 91

New cardiovascular events

N = 334

No cardiovascular events (Followed up by June 2011)
**Supplemental Table I. Predictive value of basilar artery diameter for cardiovascular events in patients with adult-type circle of Willis (n = 285)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Model 1</th>
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<th>Model 2</th>
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<th>Model 3</th>
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<td>HR 95% CI</td>
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<td>HR 95% CI</td>
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<td>HR 95% CI</td>
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<tr>
<td>Total cardiovascular events</td>
<td>1.75 1.13–2.69</td>
<td>0.01</td>
<td>1.75 1.11–2.71</td>
<td>0.02</td>
<td>1.97 1.17–3.23</td>
<td>0.01</td>
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<td>events (n = 53)</td>
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<td>Cerebrovascular events</td>
<td>1.29 0.67–2.39</td>
<td>0.44</td>
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<tr>
<td>Coronary heart events</td>
<td>1.65 0.90–2.95</td>
<td>0.10</td>
<td>1.89 0.98–3.58</td>
<td>0.06</td>
<td>1.98 0.99–3.87</td>
<td>0.05</td>
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<td>(n = 27)</td>
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Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, hypertension, diabetes, and history of stroke and ischemic heart disease.
Model 3: adjusted for age, sex, hypertension, diabetes, history of ischemic heart disease, lacunar infarct, DWMH score, and intracranial stenotic lesion.
Materials and Methods

Subjects
The participants were from the Osaka Follow-up Study for Carotid Atherosclerosis, part 2 (OSACA2)—a prospective cohort study in which the risk factors were controlled in high-risk patients for the primary and secondary prevention of cardiovascular disease (CVD).\textsuperscript{1} Outpatients aged >40 years with >1 cardiovascular risk factor, including hypertension, diabetes mellitus, hyperlipidemia, a history of smoking, established arteriosclerosis documented as transient ischemic attack (TIA), stroke, coronary heart disease, or peripheral artery disease, were enrolled. Between January 2001 and June 2007, 1106 outpatients who visited the Department of Neurology and Stroke Center at Osaka University Hospital were enrolled. All participants underwent a baseline clinical assessment that included medical history, inquiry about medications and smoking habits, physical and neurological examination, blood sampling, and carotid ultrasound. Among them, 549 participants aged 50 years or older who underwent brain MRI were included in this study. MRI was mostly performed to examine lesions in cases of a stroke history or suspicious neurological symptoms (e.g., headache, vertigo, dizziness, numbness, syncope, or subjective memory impairment). Patients with incomplete laboratory data (n = 20); those in the acute phase of stroke or in the perioperative period (n = 10); those with vertebrobasilar occlusion, dissection, or stenting (n = 4); those with vasculitis syndromes (n = 7), cancer (n = 5), or moyamoya disease (n = 1); and those with inappropriate MRI sequences (n = 3) were excluded. Patients who were scheduled to have revascularization surgery at the time of enrollment (n = 6) were also excluded. Therefore, a total of 493 patients (284 men and 209 women, 50–89 years old) were included in the study (Supplemental Figure I). This study was approved by the local ethical review board, and all patients gave written informed consent.

MRI protocol and assessment
MRI examinations were performed on a 1.5 T imager (Signa; GE Healthcare, Milwaukee, WI, USA) while the subject was supine, with the neck and head in the neutral position. T1-weighted, fluid-attenuated inversion recovery (FLAIR), and T2-weighted images, and the accompanying magnetic resonance angiograms (MRA) with 3-dimensional time-of-flight images were obtained.
The short axis of the basilar artery (BA) diameter was measured at the midpons level on the axial T2-weighted image (repetition time/echo time, 5000/130 ms; flip angle, 20°; matrix, 256 x 256; field of view, 220 mm; slice thickness, 5 mm). The presence of a stroke lesion (cerebral infarct and cerebral hemorrhage) was assessed on the T1-weighted, T2-weighted, and FLAIR images, and the maximal size of the cerebral infarct was measured on the T2-weighted image. The infarct was classified as lacunar if the maximal size was <15 mm and if it was in the penetrating branch area. The degree of white matter hyperintensity (WMH) was visually rated on the FLAIR images. We used Scheltens' scale, with slight modifications; that is, scores of 0 to 6 were given for deep WMH of the frontal, temporal, parietal, and occipital lobes (deep WMH [DWMH]; range, 0–24), and scores of 0 to 2 were given for the extent of hyperintensity along the frontal horn caps, occipital horn caps, and white matter bands along the lateral ventricles (periventricular hyperintensity; range, 0–6) because it provides more detailed semiquantitative degrees of WMH than the widely used rating scale of Fazekas. Intracranial arterial stenosis or occlusion and the variation in the posterior circle of Willis were assessed on MRA. Intracranial arterial stenosis was defined as a stenosis of >50% on MRA. We categorized the variations in the posterior circle of Willis into 3 types: fetal type when the diameter of the posterior communicating artery (PCoA) was larger than the diameter of the P1 segment of the posterior cerebral artery bilaterally, adult type when the diameter of the P1 segment was larger than that of the PCoA bilaterally, and “other” when the diameter of the P1 was equal to or larger than that of the PCoA ipsilaterally. The presence of a stroke lesion, the degree of WMH, and intracranial arterial stenosis were assessed independently by 2 observers (M.T. and K.M.).

**Risk factors**

Information pertaining to medical history of cerebrovascular and coronary artery diseases, current medications, and smoking habits was obtained from the patients’ clinical records at the time of enrollment. Patients were categorized as having CVD if they had a history of coronary heart disease (myocardial infarction, angina, previous coronary artery bypass surgery, or coronary artery angioplasty) or cerebrovascular disease (stroke or TIA). Fasting blood glucose, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined. Proteinuria was measured with urine strip devices. Hypertension was defined as a casual systolic blood pressure of ≥140 mm Hg, a
diastolic pressure of ≥90 mm Hg, or the current use of antihypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of ≥7.0 mmol/L, a glycosylated hemoglobin A1c (HbA1c) concentration of ≥5.8%, or the use of glucose-lowering agents. Dyslipidemia was defined as a fasting total serum cholesterol level of ≥5.7 mmol/L, triglycerides ≥1.7 mmol/L, HDL cholesterol ≤1.1 mmol/L, or the use of cholesterol-lowering agents.

**Carotid atherosclerosis evaluation**
We calculated the mean maximum intima-media thickness (IMT) at 12 sites: the near and far walls of the right and left distal common carotid arteries, bifurcation, and internal carotid arteries. Also, we calculated the mean pulsatility index (PI) at the right and left common carotid arteries.

**Follow-up study**
Patients were followed up to determine the incidence of cardiovascular events by June 30, 2011. Cardiovascular events were defined as vascular death; cerebrovascular events, including stroke and surgical or endovascular treatment for TIA; and coronary heart diseases, including myocardial infarction, hospitalization for unstable angina, and new-onset or worsening peripheral artery disease requiring surgical or endovascular treatment or hospitalization. Investigators blinded to MRI assessment assessed the clinical end points. The participants were examined every 3–6 months at the hospital. For subjects who did not regularly visit the hospital, follow-up information was obtained by telephone interview. Follow-up was terminated when patients died (n = 34) or withdrew from the study for personal reasons (n = 34). However, the follow-up time for each patient was included in the analysis.

**Statistical analysis**
All analyses were performed with JMP 8.0.2 (SAS Institute Inc., Cary, NC, USA). To investigate the association between BA diameter and clinical characteristics, we used Pearson correlation analysis for continuous variables and unpaired t-test or 1-way analysis of variance for categorical variables. Multiple linear regression analyses were performed to evaluate the independent variables associated with BA diameter. The included covariates were conventional risk factors with a P value of <0.2 in the univariate analysis, body height, variations of the posterior circle of Willis, presence of lacunar infarcts on MRI, severity of
white matter lesions, and intracranial steno-occlusive lesion. In the follow-up study, we used an unpaired t-test or the $\chi^2$ test to investigate the difference of clinical variables between patients with and without an incident of a cardiovascular event. Next, we divided the patients into 2 groups according to having a BA diameter above or below the median. The Kaplan-Meier method with log-rank test was used to compare the event-free survival between these 2 patient groups. We used Cox proportional hazards regression to examine the predictors of cardiovascular events. The included covariates were conventional risk factors with a P value of <0.2 in the univariate analysis and MRI parameters such as BA diameter, lacunar infarct, DWMH, and intracranial steno-occlusive lesion. All tests were 2-tailed, and P < 0.05 was considered significant.

References